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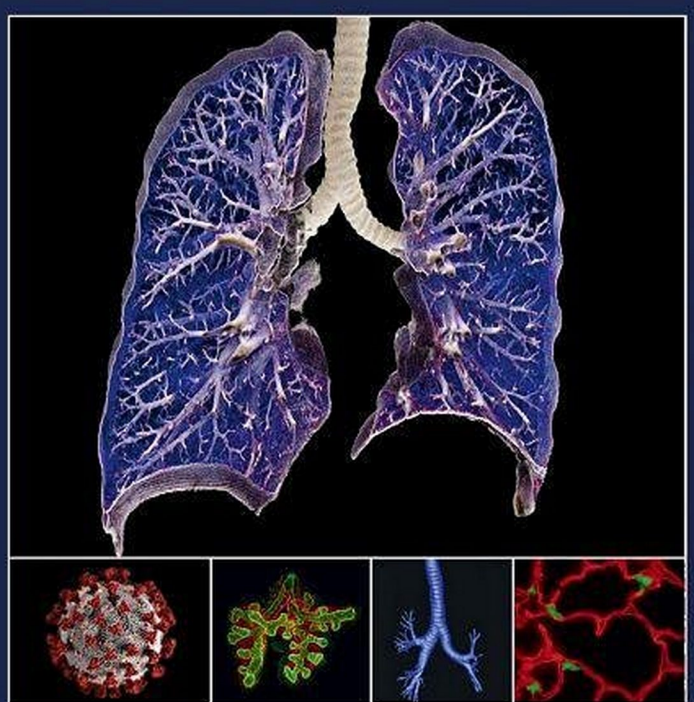

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Murray & Nadel's Textbook of Respiratory Medicine

SEVENTH EDITION

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Elsevier
1600 John F. Kennedy Blvd.
Ste 1600
Philadelphia, PA 19103-2899

MURRAY & NADEL'S TEXTBOOK OF RESPIRATORY MEDICINE, ED 7 ISBN: 978-0-323-65587-3
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Cover images courtesy Michael B. Gotway, MD (images 1 and 4), and U.S. Centers for Disease Control and Prevention/Alissa Eckert, MSMI; Dan Higgins, MAMS (image 2); https://phil.cdc.gov/Details.aspx?pid=23311.

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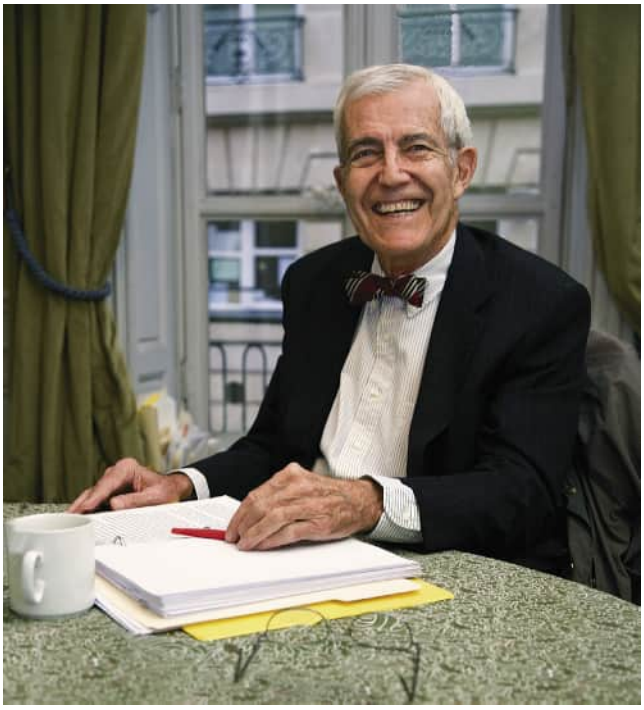
Printed in Canada

Last digit is the print number: 9 8 7 6 5 4 3 2 1





We dedicate this Textbook to Dr. John F. Murray. In 1988, Dr. Murray, together with Dr. Jay A. Nadel, published the first edition of this Textbook. Motivated by his love of teaching, he aimed to create a comprehensive, clear, authoritative, thoroughly annotated compendium of respiratory medicine, always integrated with scientific principles. Over the subsequent years and six more editions, he inspired us to continue his work and to maintain his high standards.
Of all his contributions to respiratory medicine, he was perhaps most proud of the Textbook.

John F. Murray, MD
(1927-2020)

Dedication



To my husband, Chuck, who has been the bedrock.

To the rest of our wonderful family, Chris and Clay, Mary and Lydia, and the grandboys Charlie and Rory.

To my mentors, colleagues and fellow editors for their inspiration and support of my career and of this project.

V. Courtney Broaddus, MD



For my parents, to whom I owe all I have, and to my loving wife and daughter, Mary Pat and Allison, for all the support and inspiration they provide.

Michael B. Gotway, MD



To Vicki, Kristina, and Genevieve, who make everything worthwhile.

Joel Ernst, MD



To my wife, Mozelle D. King

To my children, Consuelo King and Malaika King Kattke

To my grandchildren, Madison and Siena Kattke

To the memories of my mother and father, Almetta and Talmadge King

Talmadge E. King Jr, MD



To my wife, Gail, who makes everything possible, and better; to my daughter, Hillary, and her husband, Andrew, who continue to ask about what I do, and encourage it; to my grandchildren Lola and Axel, who give me hope for the future and joy in the present; and to the many colleagues, students, and trainees, who made my first 49 years at UCSF so enjoyable.

Stephen C. Lazarus, MD, FCCP, FERS



In loving memory of my parents, who were an unwavering source of support and encouragement for everything that I did. They may not have understood why I ran, but they were always at the finish line to cheer me on.

Lynn M. Schnapp, MD



To my parents, Barbara and Barry Brennan, who taught by example the value of hard work, perseverance, and compassion.

Kathleen F. Sarmiento, MD, MPH



To my husband Jonathan; our children Walker, Emmerson, and Orion; my parents Myrna and Ted; and my mentors, colleagues, patients, and trainees for a lifetime of pushing me to learn, grow, and change.

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Preface to the Seventh Edition

This seventh edition of the Textbook represents the first major reorganization since the first edition in 1988. You will notice many changes in structure and content, all aimed to enhance its readability and educational value.

There are two major changes. The first is that the number of chapters has been increased from 106 in the sixth edition to the current 142. This strategic change enabled us to create more focused shorter chapters, which we hope are easier to find and to read. We were able to bring new chapters out of their hiding places under other headings (e.g., Influenza, Idiopathic Pulmonary Fibrosis, and Pneumothorax), to create new chapters on topics not directly covered before (e.g., Hypoxemia, Aspiration, and Air Travel), and to cover entirely new topics (e.g., Microbiome and COVID-19). The second major change was the creation of a new section particularly with our trainees in mind, "The Evaluation of Common Presentations in Respiratory Disease," built on the classic triad of Dyspnea, Cough, and Chest Pain. Seven new chapters were added on topics ranging from Hypercarbia to Hemoptysis to Pulmonary Nodule, which we hope will be a valuable resource for our readers. Other changes to the Textbook are noteworthy: in particular, the sections on Basic Science and on Sleep have been revamped, reflecting the major rethinking of those topics in the last decade.

These changes were spearheaded by our exceptional editorial board, with three new members. The makeup of our editors is now equally women and men, a remarkable change from the time in 2005 when I (V.C.B.) joined as the inaugural woman. Our new editors have brought a fresh outlook and diverse areas of expertise that helped chart this new course. With these new editors have come a slew of new authors. Of our 317 authors, we welcome almost 180 new authors, either to take on new chapters or to take the place of authors who have rotated off. Overall, our authors come from 33 states of the United States and from 18 countries. Here, too, we have increased the participation of women; women now make up 32% of our authors, almost double that in the previous edition (17%).

The printed textbook is a gateway to rich resources online. While there are a whopping 900 figures in the printed text, they are joined by others to make a total of 1650 figures online, all available for download. The text is expanded by an additional 25% online. A total of 190 videos and audio clips are accessible online, popping up with just a click to the link in the text. All the references are online, and each one links to the actual publication. Most importantly, the online textbook will feature regular updates from our editors and authors, with the aim of realizing a "living textbook."

We wish to thank our valuable and skilled colleagues at Elsevier, who made this herculean work possible. In particular, our thanks go to Jennifer Shreiner, who has remained dedicated to the Textbook over the last three editions and made this task a pleasure. In addition, Carrie Stetz had the attention to detail and the high standards necessary to produce a lovely book. Thanks go also to Dolores Meloni and Robin Carter. We also wish to thank the authors and editors who contributed to the past editions.

The COVID-19 pandemic has loomed over us during this project. Much of the book was written and edited during lockdowns and hospital surges, with many of our authors simultaneously juggling heavy frontline clinical and family responsibilities with chapter deadlines. In recognition of this momentous experience, we have added a chapter (46a) devoted to the topic—a chapter that has been updated up to the last moment and will continue to be updated frequently online—and placed an image of the novel coronavirus on our cover. The impact of the pandemic on our lives has made the successful outcome of this project all the more remarkable. A special thanks again to our authors and staff for their outstanding efforts during this particularly difficult time.

Sadly, Dr. Murray, who started this Textbook together with Dr. Jay Nadel and guided it up to this point, died of COVID-19 in March 2020. He remained committed to the textbook until his last days. Over his illustrious career, he taught many of us and inspired all of us to the highest callings of teaching and caring for patients. This Textbook is dedicated to him.

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SECTION **A**

ANATOMY AND DEVELOPMENT OF THE RESPIRATORY TRACT

1 ANATOMY

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INTRODUCTION
GROSS AND SUBGROSS ORGANIZATION
AIRWAYS
BRONCHIAL CIRCULATION
PULMONARY CIRCULATION
TERMINAL RESPIRATORY UNITS
LYMPHATICS
INNERVATION
PLEURAL SPACE AND PLEURAL MEMBRANES
CELLULAR ANATOMY OF THE LUNG
Airway Lining Cells
Alveolar Lining Cells
Mesenchymal Cells
Neural Cells
Hematopoietic and Lymphoid Cells
Pleural Cells
MOLECULAR ANATOMY OF THE LUNG
COMPARISON OF THE LUNG OF HUMANS AND MICE
KEY POINTS

INTRODUCTION

The lung has two essential, interdependent functions. One essential function is ventilation-perfusion matching to deliver *oxygen* (O_2) to the body and to remove the *carbon dioxide* (CO_2) produced by the body (Fig. 1.1). The second essential function is host defense against the onslaught of airborne pathogens, chemicals, and particulates. These essential functions are emphasized through the gross, subgross, histologic, cellular, and molecular determinants of the respiratory gas-exchange process in the normal human lung.[1] Other secondary functions of the lung, which support the essential functions, are important, such as cellular functions of surfactant synthesis, secretion and recycling, mucociliary clearance, neuroendocrine signaling, and synthesis and secretion of myriad molecules by the epithelial and endothelial cells of the lung. The diversity of secondary functions emphasizes the importance of the lung in homeostasis. Finally, the widespread use of murine models in lung research as surrogates for the human lung highlights the need to understand the similarities and differences of the lung between these species. The anatomic features that support the essential and secondary functions and comparative anatomy topics are the focus of this chapter. In addition, online supplemental digital videos linked to this chapter provide views of lung movements related to changes in tidal volume, airway pressures, and respiratory rate. (Videos 1.1 to 1.5).

GROSS AND SUBGROSS ORGANIZATION

The position of the lungs in the chest and in relationship to the heart is shown in Fig. 1.2. Fig. 1.2A shows a midfrontal section through the thorax of a frozen human cadaver. Fig. 1.2B shows a posterior-anterior chest radiograph of a normal human at *functional residual capacity* (FRC). The two illustrations represent the extremes of the approaches to study lung anatomy. On one hand, the cadaver lung (see Fig. 1.2A) shows the gross anatomic arrangements and relationships. The main distortion is that the lungs are at low volume. The height of the lungs is only about 18 cm, which is well below FRC height (see Fig. 1.2A). The diaphragm is markedly elevated in Fig. 1.2A, probably about 5 cm relative to its end-expiratory position in life. Another distortion is the abnormally wide pleural space. However, that fixation shrinkage artifact serves as a useful reminder that the lung is not normally attached to the chest wall. In life, the separation between the parietal and visceral pleurae is only several micrometers.[2,3] On the other hand, the chest radiograph (see Fig. 1.2B) shows that the height of

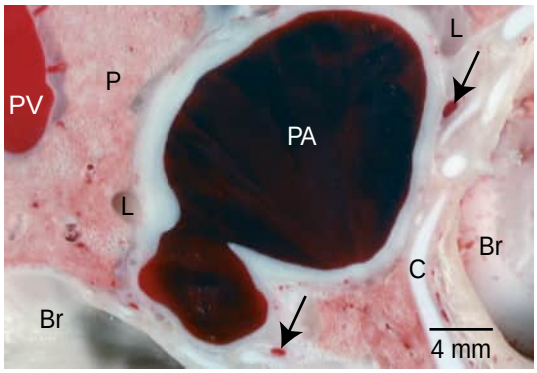

Figure 1.1 Levels of oxygenation of blood in a frozen block of lung tissue. Air is brought into the lung via the bronchus (Br). Pulmonary arterial (PA) blood is dark purple because it is poorly oxygenated. Gas exchange across the lung's parenchyma (P) results in oxygenated pulmonary venous (PV) blood, which is crimson. Also present in the peribronchovascular connective tissue are bronchial arteries *(arrows),* cartilage (C), and lymphatics (L). (Frozen sheep lung, unstained.)

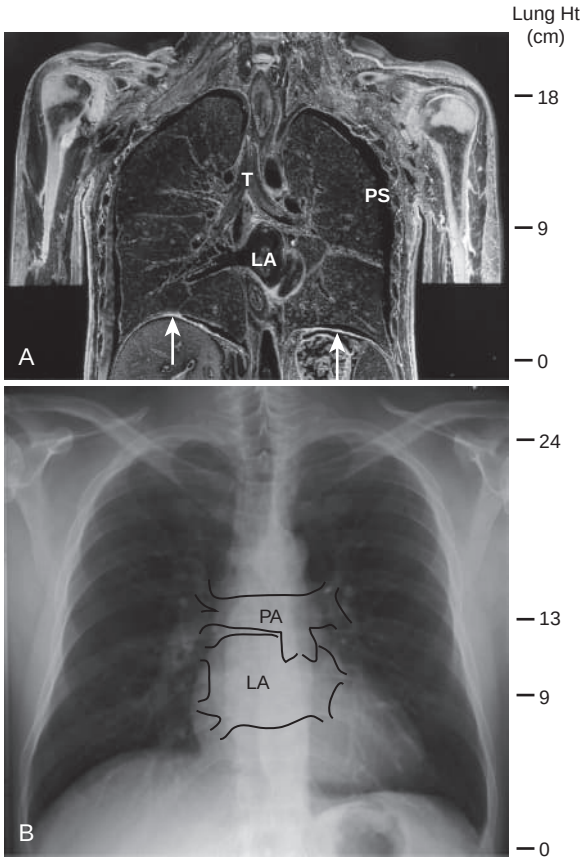

Figure 1.2 Comparison views of the position of the lungs in the chest and their relationship to the heart. (A) Midfrontal section through the thorax of a frozen cadaver of a 35-year-old human. The cadaver was prepared by routine embalming procedures, stored horizontally for 3 months in 30% alcohol, and frozen in the horizontal position for 1 week at −20°C. Frontal sections were cut with a band saw. Because the cadaver was preserved in the horizontal position, the weight of the abdominal organs compressed the contents of the thoracic cavity. The domes of the diaphragm *(arrows)* are elevated about 5 cm relative to their end-expiratory position in life. Pleural space (PS) width is artifactually enlarged; normally, in life it is several micrometers in width. The trachea (T) is flanked on its left by the aortic arch and on its right by the azygos vein. The left pulmonary artery lies on the superior aspect of the left mainstem bronchus. Pulmonary veins from the right lung enter the left atrium (LA), which is located about 7 cm above the lung's base. These structures at the root of the lungs caused the esophagus to be cut twice as it follows a curved path behind them to reach the stomach. (B) Chest radiograph of a normal human adult taken in the upright position at functional residual capacity. The lung height (cm) was measured from the costodiaphragmatic angle to the tubercle of the first rib. The main pulmonary artery (PA) and LA are outlined. The vascular structures, especially the pulmonary veins, are more easily seen near the base of the lung. This is partly because vascular distending pressures are greater near the bottom. The density of the lung is also graded, being higher at the bottom than the top and higher near the hilum than peripherally. (From Koritké JG, Sick H. *Atlas of Sectional Human Anatomy.* vol. 1: *Head, Neck, Thorax.* Baltimore: Urban and Schwarzenberg; 1983:83.)

the lung at FRC is approximately 24 cm, with the level of the bifurcation of the pulmonary artery about halfway up the lungs. The diaphragm is lower and flatter than in the cadaver. However, the radiographic image is only a shadow of dense structures.

In life, the human lungs weigh 900 to 1000 g, of which nearly 40–50% is blood.[4,5] At end-expiration, the gas volume is about 2.5 L, whereas, at maximal inspiration, the gas volume may be 6 L. Thus, overall lung density varies from 0.30 g/mL at FRC to 0.14 g/mL at *total lung capacity* (TLC). However, the density of the lung is not distributed uniformly, being about 1 g/mL near the hilum and 0.1 g/mL peripherally. If one likens each lung to a half cylinder, more than 50% of all the lung's alveoli are located in the outer 30% of the lung radius (hilum to chest wall). This is why the peripheral portion of the lung appears relatively empty in the chest radiograph (see Fig. 1.2). Variability in density also exists from top to bottom. In Fig. 1.2, the blood vessels are more distended in the lower lung fields. The increasing distention of vessels from apex to base also illustrates the increase in vascular distending pressures at the rate of 1 cm H_2O/cm height down the lung.

The composition of the various tissues that comprise the lung is summarized in Table 1.1. An amazing point is how little tissue is involved in the architecture of the alveolar walls.[6,7] However, this is as it should be because the major physical obstacle to gas exchange is the slowness of O_2 diffusion through water.[8,9] Thus, the alveolar walls must be extremely thin. In fact, the thickness of the *red blood cell* (RBC) forms a substantial portion of the air-blood diffusion pathway. Advantage was taken of this fact to separate the carbon monoxide diffusing capacity measurement into two components: the capillary blood volume and the membrane diffusing capacity.[10] (For a discussion of diffusing capacity, see Chapter 31.)

The lung has two well-defined interstitial connective tissue compartments arranged in series, as described by Hayek[11] (Fig. 1.3). These are the parenchymal (alveolar wall) interstitium and the loose binding (extra-alveolar) connective tissue (peribronchovascular sheaths, interlobular septa, and visceral pleura). The connective tissue fibrils (collagen, elastin, and reticulin) form a three-dimensional basket-like structure around the alveoli and airways (Fig. 1.4).[12] This basket-like arrangement allows the lung to expand in all directions without developing excessive tissue recoil. Because the connective tissue fibrils in the parenchymal interstitium are extensions of the coarser fibers in the loose-binding connective tissue, stresses imposed at the alveolar wall level during lung

Table 1.1 Components of Normal Human Lung

Component	Volume or Mass (mL)	Thickness (μm)	Reference
Gas	2400		9
Tissue	900		4, 5
Blood	400		5
Lung	500		9
Support structures	225		6
Alveolar walls	275		6, 7
Epithelium	60	0.18	6, 7
Endothelium	50	0.10	6, 7
Interstitium	110	0.22	6, 7
Alveolar macrophages	55		7

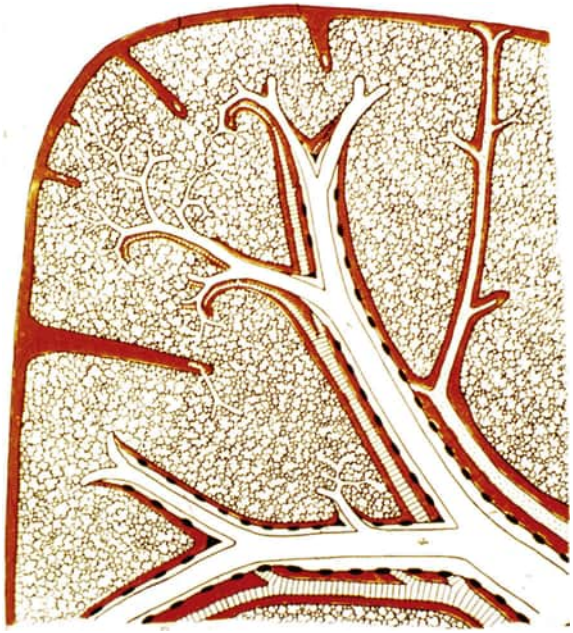

Figure 1.3 General plan depicting the interstitial connective tissue compartments of the lung. All of the extra-alveolar support structures (airways, blood vessels, interlobular septa, visceral pleura) are subsumed under the term, loose-binding connective tissue. The alveolar walls' interstitium comprises the parenchymal interstitium. This organizational plan of the lung follows the general organization of all organs. (From Hayek H. *The Human Lung.* New York: Hafner; 1960:298–314.)

inflation are transmitted not only to adjacent alveoli, which abut each other, but also to surrounding alveolar ducts and bronchioles, and then to the loose-binding connective tissue supporting the whole lobule, and ultimately to the visceral pleural surface (see Fig. 1.3). These relations become more apparent in certain pathologic conditions. For example, in interstitial emphysema,[13] air enters the loose-binding connective tissue and dissects along the peribronchovascular sheaths to the hilum and along the lobular septa to the visceral pleura. Interstitial pulmonary edema fluid enters and moves along the same interstitial pathways (Fig. 1.5).[14]

The bulk of the interstitium is occupied by a matrix of proteoglycans (Fig. 1.6).[15,16] Proteoglycans constitute a complex group of gigantic polysaccharide molecules (≈30

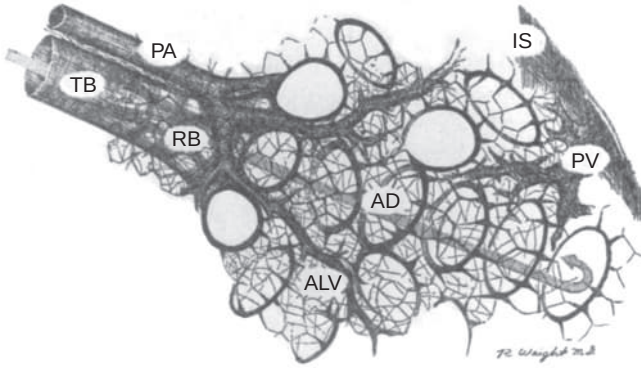

Figure 1.4 Illustration of the connective tissue support of the normal human adult lung lobule. The weave of fibers composing the "elastic continuum" is demonstrated. AD, alveolar duct; ALV, alveolus; IS, interstitial space; PA, pulmonary artery; PV, pulmonary vein; RB, respiratory bronchiole; TB, terminal bronchiole. (From Wright RR. Elastic tissue of normal and emphysematous lungs. *Am J Pathol.* 1961;39:355–363.)

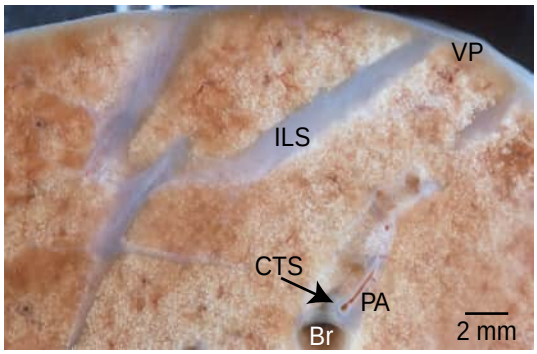

Figure 1.5 Accumulation of interstitial pulmonary edema in the loose-binding interstitial spaces. The edema fluid accentuates the loose-binding (peribronchovascular) connective tissue spaces (CTS) that surround the bronchi (Br) and pulmonary arteries (PA). Interstitial edema also expanded the interlobular septa (ILS) that are contiguous with the connective tissue of the visceral pleura (VP). (Frozen sheep lung, unstained.)

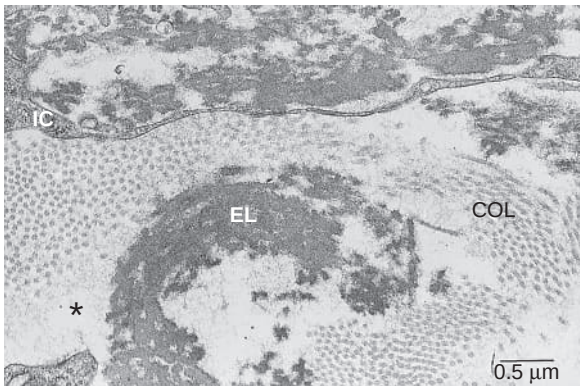

Figure 1.6 Structure of the interstitial compartment. The connective tissue compartment of the lung contains interstitial cells (IC; fibroblasts), fibrils of collagen (COL), and bundles of elastin (EL). The bulk of the interstitium, however, is occupied by matrix constituents (asterisk), such as glycosaminoglycans. (Human lung surgical specimen, transmission electron microscopy.)

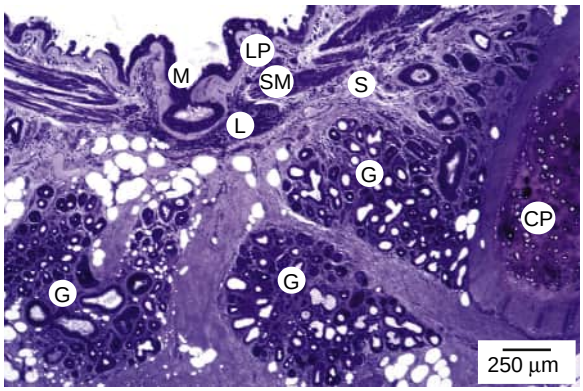

Figure 1.7 Wall structure of a bronchus. The bronchial wall is composed of mucosa (M), lamina propria (LP), smooth muscle (SM), and submucosa (S). Seromucous glands (G) are located between the spiral bands of SM and cartilaginous plates (CP). Diffuse lymphoid tissue (L) has infiltrated the lamina propria and submucosa. (Human lung surgical specimen, right middle lobar bronchus, 2-µm–thick glycol methacrylate section, light microscopy.)

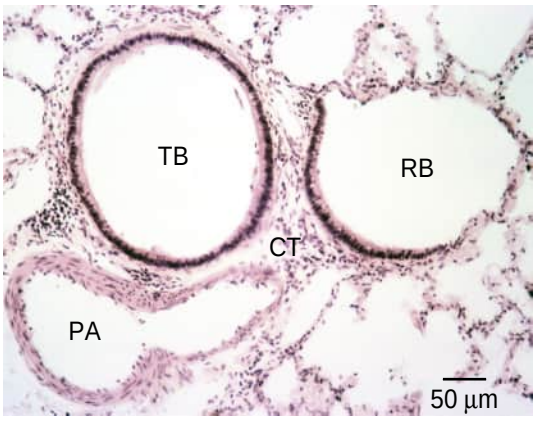

Figure 1.8 Differences in wall structure of terminal bronchioles and respiratory bronchioles. The wall of the terminal bronchiole (TB) is constructed of a single layer of ciliated, cuboidal epithelium that rests over thin, discontinuous bands of smooth muscle and loose areolar connective tissue (CT). In contrast, the wall of the respiratory bronchiole (RB) is only partially lined by ciliated cuboidal epithelium *(lower left)*. The remainder of its wall is lined by squamous epithelium *(upper right)*. The connective tissue also surrounds the adjacent pulmonary arteriole (PA). (Human lung surgical specimen, 10-µm–thick paraffin section, light microscopy.)

different core proteins, with great diversity of glycosaminoglycan side chains) whose entanglements impart a gel-like structure to the interstitium. That structural role, although essential, is not the sole role of these important molecules. A growing view is emerging of the lung's extracellular matrix components as regulators of lung physiology, such as determining epithelial cell phenotype; binding of and subsequent signaling by cytokines; chemokines and growth factors; and cell proliferation, migration, differentiation, and apoptosis.[17–24] In disease states, degradation products of extracellular matrix components may activate the Toll-like receptor pathways (see discussion later), thus the degradation products may serve as endogenous sentinels of tissue damage and initiators of innate immune responses.[19,23–25] Within this gel-like interstitium reside several varieties of interstitial cells (contractile and noncontractile interstitial cells,[26,27] mast cells, plasma cells, and occasional leukocytes). The remainder of the interstitium is composed of laminin, collagens, elastin and reticulin fibrils, fibronectin, and tenascin (see Fig. 1.6). (For more details on the lung mesenchyme see Chapter 5.)

AIRWAYS

The airways, forming the connection between the outside world and the *terminal respiratory units* (TRUs), are of central importance to lung function in health and disease.[28,29] Intrapulmonary airways are divided into three major groups: bronchi (conducting airways with cartilage) (Fig. 1.7), membranous bronchioles (distal conducting airways without cartilage) (Fig. 1.8), and respiratory bronchioles (distal airways participating to some extent in gas exchange) (Fig. 1.9; Table 1.2). Bronchi, by definition, have cartilage in their wall. The trachea, bronchi, and membranous bronchioles peripherally to and including terminal bronchioles (together the *conducting airways*) do not participate in respiratory gas exchange. Respiratory bronchioles serve a dual function as airways and as part of the alveolar volume that participates in respiratory gas exchange.[29]

The anatomic dead space, as measured by the single-breath nitrogen dilution technique, is approximately 30% of each tidal volume. Anatomically, this dead space

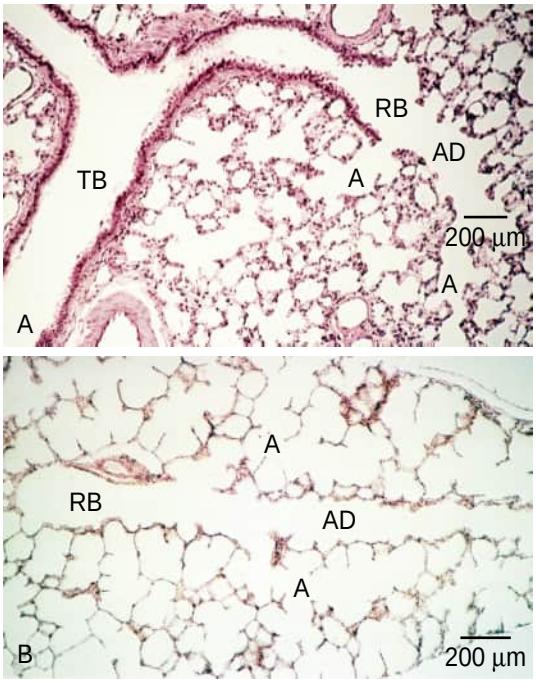

Figure 1.9 Longitudinal sections along membranous bronchioles. (A) Diameter remains relatively constant along the terminal bronchiole (TB), respiratory bronchiole (RB), and alveolar duct (AD). Alveoli (A) communicate with the gas-exchange duct. (B) This longitudinal section along an RB and AD shows that their diameter is relatively constant and that both gas-exchange ducts communicate with clusters of alveoli (A). (Human lung surgical specimen, 10-µm–thick paraffin section, light microscopy.)

is accounted for principally by the volume of the extrapulmonary (upper) airways, including the nasopharynx, trachea, and the intrapulmonary bronchi.[30] The trachea and bronchi are cartilaginous and do not change shape substantially with ventilation. The membranous bronchioles (noncartilaginous airways of ≈1-mm diameter or less), although exceedingly numerous, are short. They

Table 1.2 Characteristics of Airway Generations in Humans

Airway Generation	Generations	Characteristic	Role	TRU	Reference
Trachea	0	Cartilaginous	Conducting		28, 29
Bronchi	1–3	Cartilaginous	Conducting		28, 29
Bronchioles	4–13	Membranous	Conducting		28, 29
Terminal bronchioles	14	Membranous	Conducting		96
Respiratory bronchioles	16–18	Partially membranous	Partially conducting and gas exchange	Yes	96
Alveolar ducts	19–22		Gas exchange	Yes	96
Alveoli	23		Gas exchange	Yes	96

TRU, terminal respiratory unit.

consist of about five branching generations and end at the terminal bronchioles. In contrast to the bronchi, the membranous bronchioles are tightly embedded in the connective tissue framework of the lung and therefore enlarge passively as lung volume increases.[31] Histologically, the bronchioles down to and including the terminal bronchioles ought to contribute about 25% to the anatomic dead space. In life, however, they contribute little because of gas-phase diffusion and mechanical mixing along the distal airways, resulting from the cardiac impulse (refer to the supplemental videos on lung movements). By definition, the respiratory bronchioles and alveolar ducts participate in gas exchange and thus do not contribute to the anatomic dead space. The volume of the respiratory bronchiole-alveolar duct system is approximately one-third of the total alveolar volume, and it is into this space that the fresh-air ventilation enters during inspiration.

Most airway resistance arises from the upper airways and bronchi. Normally, the large airways are partially constricted. The minimum airway diameter in the human lung, about 0.5 mm, is reached at the level of the terminal bronchioles; succeeding generations of exchange ducts (respiratory bronchioles and alveolar ducts) are of constant diameter (see Fig. 1.9).[29,32] The functional significance of centralized resistance is that the TRUs are regionally ventilated chiefly in proportion to their individual distensibilities (compliances) because most of their airway resistance is common. This is demonstrated normally by the finding that regional lung ventilation is dependent primarily upon the initial volumes of the alveoli. TRUs toward the top of the lung, which are more expanded at FRC, do not receive as great a share of the inspiratory volume as do the TRUs near the bottom of the lung.

Airway diameter represents a balance between anatomic dead space volume and airflow resistance. Airway diameter ought to be as small as possible to minimize anatomic dead space and maximize efficient alveolar ventilation by reducing the dead space–to–tidal volume ratio, whereas airway diameter ought to be as large as possible to minimize airway resistance and the work of breathing. In disease, airways are often narrowed (Fig. 1.10), which increases resistance and the work of breathing.

The presence of apical junctional complexes between airway epithelial cells (Fig. 1.11) has important functional implications for metabolically regulated secretion into and absorption of electrolytes and water from the lining liquid.

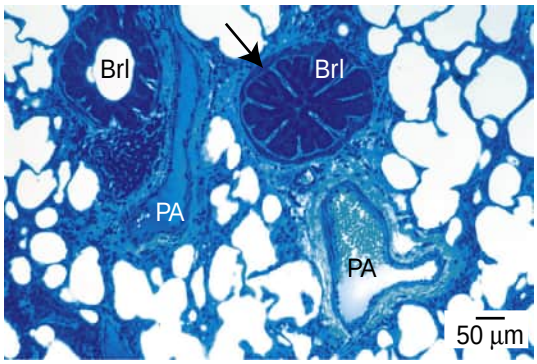

Figure 1.10 Cross-sections of two bronchioles that would contribute to increased airway resistance. On the left is a bronchiole (Brl) that is partially narrowed, evident by the folded and thick epithelium. The bronchiole to the right is completely narrowed. Its lumen is obliterated by the infolded epithelium. This bronchiole's smooth muscle is thick *(arrow)*, suggesting that the narrowing is related to constriction of the smooth muscle. Each bronchiole is flanked by a pulmonary arteriole (PA). (Sheep lung, 5-µm–thick paraffin section, light microscopy.)

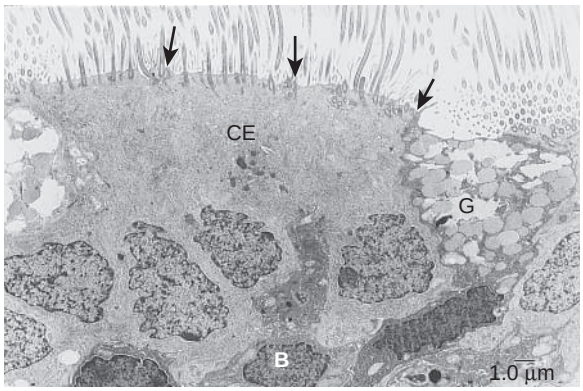

Figure 1.11 Cells constituting the bronchial epithelium. The *arrows* at the apical surface of the airway cells indicate the location of junctional complexes between contiguous epithelial cells. The bronchial epithelium has ciliated epithelial cells (CE), goblet cells (G), and basal cells (B). Goblet cells have abundant mucous granules in the cytoplasm, and their apical surface is devoid of cilia. Basal cells, as their name indicates, are located along the abluminal portion of the lining epithelium, adjacent to the basal lamina. (Human lung surgical specimen, transmission electron microscopy.)

Apical junctional complexes consist of three elements: *zonula occludens* (tight junction), *zonula adherens*, and *macula adherens* (desmosome).[33] Tight junctions serve two important functions: (1) restriction of passive diffusion by

blocking the lateral intercellular space and (2) polarization of cellular functions (ion and water transport) between the apical and basolateral membranes.[34] Polarization of chloride and sodium transport allows the airway epithelium either to secrete or absorb ions, with associated passive water movement (see Chapter 3).

Trapping of foreign material, such as particulates or bacteria, is accomplished by mucins. Mucins are complex glycoproteins that form gels. MUC5AC and MUC5B are the main gel-forming mucins in human airways.[35,36] MUC5AC is produced by surface epithelia in proximal cartilaginous airways.[37] Normally, MUC5B is produced by airway glandular cells[37,38] but, in a variety of pulmonary diseases, its cell source is expanded. Other mucins (e.g., MUC5B, MUC7)[38,39] become expressed by airway epithelial cells in diseases, such as cystic fibrosis. In that disease, MUC5B is produced by airway epithelial cells.[40]

Glands are limited to the submucosa of the bronchi. Airway glands secrete water, electrolytes, and mucins into the lumen. Studies of regulation of secretion in vivo and by explant culture systems in vitro show that secretion can be modulated by neurotransmitters, including cholinergic, adrenergic, and peptidergic transmitters,[41,42] and by inflammatory mediators, such as histamine,[43] platelet-activating factor,[44] and eicosanoids.[45] The absence of airway glands and goblet cells distal to ciliated epithelial cells makes teleologic sense because that arrangement should minimize the flow of mucus backward into alveolar ducts and alveoli.

Although most foreign material and immunologic stimuli are carried up the airways by mucociliary action, some are cleared by the lymphatics. In addition, lymphoid tissue is found within the lungs and referred to as *inducible bronchus-associated lymphoid tissue* (iBALT).[46] These lymphoid aggregates are distributed along the tracheobronchial tree (see Fig. 1.7) and, to a lesser extent, along the blood vessels.[46–48] BALT in the human lung is called inducible because it is not present at birth in humans or in germ-free animals but develops after antigenic stimulation.[47,48] Lymphocytes in these structures are principally B cells, which often form follicles.[49] The presence of lymphocytes along the airways provides a reminder that the respiratory system is constantly challenged by airborne immunologic stimuli. The tracheobronchial lymphoid tissue appears to provide an important locus for both antibody-mediated and cell-mediated immune responses.[50] Another important locus of immune response is provided by the epithelial cells that line the airways and comprise the airway glands. The importance of epithelial cells arises from their expression of *Toll-like receptors* (TLRs), whose role is identification of pathogen-associated molecular patterns.[51] Activation of TLRs leads to downstream signaling cascades involved in mucin production, leukocyte recruitment, antimicrobial peptide production, and wound repair[52–57] (see also Chapter 15).

BRONCHIAL CIRCULATION

The trachea (and esophagus), mainstem bronchi, and pulmonary vessels entering the lung (see Fig. 1.1), as well as the visceral pleura in humans (see "Pleural Space and Pleural Membranes" toward the end of this chapter), are supplied by the bronchial (systemic) blood circulation.[58–60] Measurements of bronchial circulation, by microsphere studies in animals, indicate that flow is 0.5–1.5% of cardiac output and is predominantly to the large airways.[58,59,61–64] The bronchial arteries arborize into bronchial capillaries that form a network in the lamina propria (the underlying connective tissue), in the submucosa, and in the region external to the cartilage of bronchi, as well as in the lamina propria of neighboring pulmonary arteries.[65] Venous blood from the trachea and large airways enters bronchial venules, which converge to form bronchial veins that drain into the azygos or hemiazygos veins. Thus, most bronchial blood flow returns to the right side of the heart. Deeper in the lung, however, bronchial blood passes via short anastomotic vessels into the pulmonary venules, thus reaching the left side of the heart to contribute to the venous admixture. The relationships among the bronchial, pulmonary, and systemic arterial and venous circulations are diagrammed in eFig. 1.1.

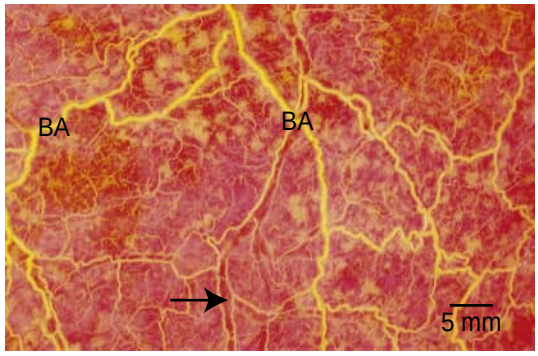

Figure 1.12 Surface view of the visceral pleura. Yellow latex polymer fills the rich network of the bronchial arteries (BA) and subsequent microvascular network. Some bronchial arterioles flank lymphatics *(arrow)* that comprise the superficial lymphatic plexus of the lung. (Sheep lung visceral pleural surface.)

The bronchial circulation has enormous growth potential in contrast to the pulmonary circulation, which, after childhood, is unresponsive to growth signals. As a result, the bronchial circulation is the primary source of new vessels for repair of tissue after lung injury. In long-standing inflammatory and proliferative diseases, such as bronchiectasis or carcinoma, bronchial blood flow may be greatly increased.[59,66] Scar tissue and tumors greater than 1 mm in diameter receive their blood supply via the bronchial circulation.[67,68] As will be discussed near the end of this chapter, the bronchial circulation also supplies the visceral pleura of species that have thick visceral pleura (Fig. 1.12), which includes humans.

PULMONARY CIRCULATION

In humans, the pulmonary artery enters each lung at the hilum in a loose connective tissue sheath adjacent to the main bronchus (see Fig. 1.1). The pulmonary artery travels adjacent to and branches with each airway generation (Fig. 1.13) down to the level of the respiratory bronchiole (see Fig. 1.8). The anatomic arrangements of the pulmonary arteries and the airways are a continual reminder of the relationship between perfusion and ventilation

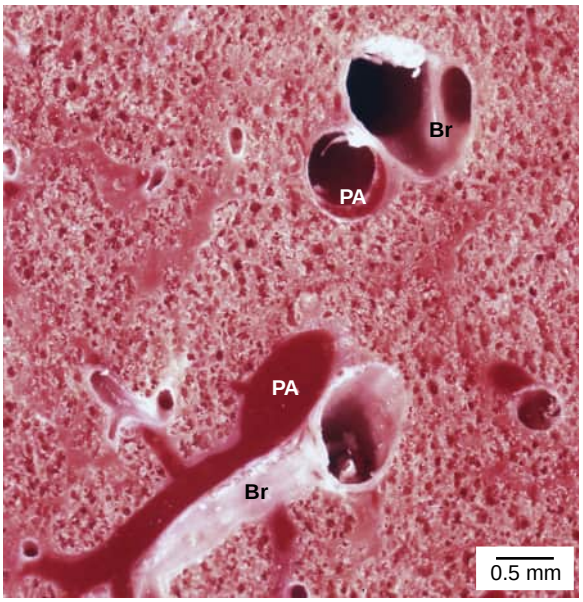

Figure 1.13 Divisions of the pulmonary artery (PA) within the lung. The PA divides and travels beside the bronchi and bronchioles (Br) out to the respiratory bronchioles. Thus, at all airway generations, an intimate relationship exists with pulmonary arterial generations. Note that the loose-binding (peribronchovascular) connective tissue sheaths are not distended, compared to the interstitial edema cuffs in Fig. 1.5. (Frozen normal sheep lung, unstained.)

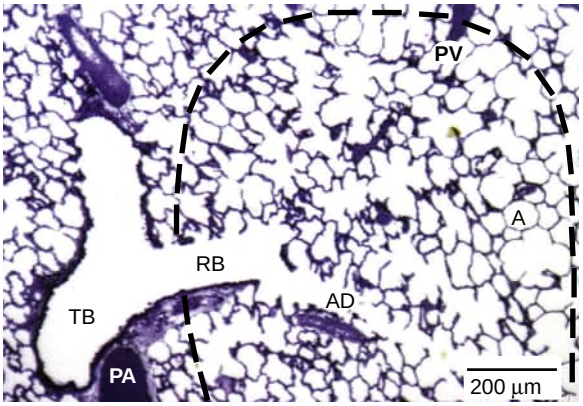

Figure 1.14 Anatomy of terminal respiratory units. Terminal respiratory units (the physiologist's alveolus) consist of the alveoli (A) and alveolar ducts (AD) arising from a respiratory bronchiole (RB). Each unit is roughly spherical, as suggested by the *dashed outline*. Pulmonary venous vessels (PV) are peripherally located. PA, pulmonary artery; TB, terminal bronchiole. (Normal sheep lung, somewhat underinflated, 2-µm–thick glycol methacrylate section, light microscopy.)

that determines the efficiency of normal lung function. Although the pulmonary veins also lie in loose connective tissue sheaths adjacent to the main-stem bronchus and pulmonary artery at the hilum, once inside the lung they follow Miller's dictum that the veins will generally be found as far away from the airways as possible.[58] Peripherally, the pulmonary arteries branch out into the TRU, whereas the veins occupy the surrounding connective tissue envelope (Fig. 1.14). Each small muscular pulmonary artery supplies a specific volume of respiratory tissue, whereas each vein drains portions of several such zones.

Table 1.3 Quantitative Data on Intrapulmonary Blood Vessels in Humans

Vessel Class (With Diameter)	Volume (mL)	Surface Area (m^2)	Reference
Arteries (>500 µm)	68	0.4	69
Arterioles (13–500 µm)	18	1.0	69
Capillaries (10 µm)	60–200	50–70	70
Venules (13–500 µm)	13	1.2	71
Veins (>500 µm)	58	0.1	71

Considerable quantitative data about the pulmonary circulation are available for the human lung (Table 1.3).[69–71] Although most of the intrapulmonary blood volume is in the larger vessels down to approximately 500 µm diameter, nearly all of the surface area is in the smaller vessels. For example, the surface area of arterioles 20 to 500 µm in diameter exceeds that of the larger vessels by a factor of two, and the maximal capillary surface area is 20 times that of all other vessels. Such impressive expansion of surface area maximizes the area for respiratory gas exchange.

Because the vertical height of the lung at FRC is about 24 cm (see Fig. 1.2), the pressure within the pulmonary blood vessels varies by approximately 24 cm H_2O over the full height of the lung. Thus, if pulmonary arterial pressure is taken as 20 cm H_2O (15 mm Hg, 1.9 kPA)* at the level of the main pulmonary artery, which is about halfway up the height of the lung, pressure in the pulmonary arteries near the top of the lung will be about 12 cm H_2O, whereas pressure in pulmonary arteries near the bottom will be about 36 cm H_2O. Pulmonary venous pressure, which is about 8 cm H_2O at the level of the pulmonary artery in midchest (left atrial pressure), would be −4 cm H_2O near the top of the lung and +20 cm H_2O at the bottom. In the normal lung, the blood volume is greater at the bottom because of increased luminal pressure, which expands those vessels and increases their volume. This effect of distention also decreases the contribution of the blood vessels at the bottom of the lung to total pulmonary vascular resistance.

From birth through adulthood, the normal pulmonary circulation is a low-resistance circuit. The resistance is distributed somewhat differently than in the systemic circulation, where the major drop in resistance is across the arterioles. In the pulmonary circulation, although the pressure drop along the pulmonary capillaries is only a few centimeters of water (similar to the pressure drop in systemic capillaries), the pulmonary arterial and venous resistances are low, so a relatively larger fraction of the total pulmonary vascular resistance (35–45%) resides in the alveolar capillaries at FRC.[72,73] (For further information about pulmonary circulation in health and disease see Chapters 6 and 83.)

Vasoactivity plays an important part in the local regulation of blood flow in relation to ventilation.[74,75] Because smooth muscle surrounds the pulmonary vessels on both

*To convert from kPA to cm H_2O, multiply by 10.3; to mm Hg, multiply by 7.5.

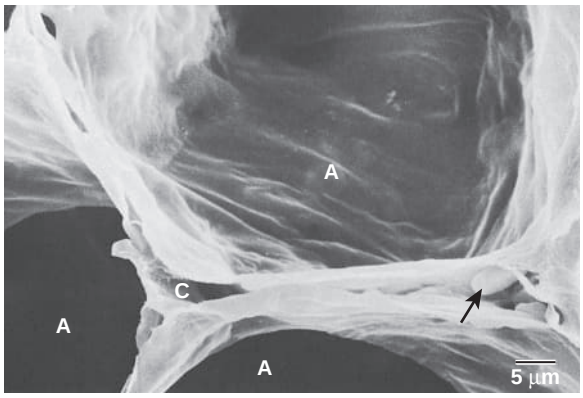

Figure 1.15 Alveolar capillaries are long. An alveolar capillary (C) is shared longitudinally along its path across three alveoli (A). The alveolar walls are flattened, and the wall junctions are sharply curved because the lung is fixed in zone 1 conditions. Some red blood cells remain in the capillary at an alveolar corner *(arrow)*. (Perfusion-fixed normal rat lung; airway pressure = 30 cm H_2O, pulmonary artery pressure = 25 cm H_2O, left atrial pressure = 6 cm H_2O, scanning electron microscopy.)

the arterial and the venous side down to precapillary and postcapillary vessels,[76,77] any segment can contribute to active vasomotion.[78] In pathologic conditions, vascular smooth muscle may extend down to the capillary level.[79,80]

Theoretically, gas exchange may take place through the thin wall of almost any pulmonary vessel. At normal alveolar O_2 tensions, however, little O_2 and CO_2 is exchanged before the blood reaches the true capillaries.[81] In the pulmonary arterioles, because of their small volume (see Table 1.3), blood flow is rapid. As blood enters the vast alveolar wall capillary network, its velocity slows, averaging about 1000 μm/s (or 1 mm/s). Flow in the microcirculation is pulsatile because of the low arterial resistance.[82] Pulsations reach the microvascular bed from both the arterial and the venous sides. In fact, one sign of severe pulmonary hypertension is the disappearance of capillary pulsations.[83]

The capillary network is long and crosses several alveoli (Fig. 1.15) before coalescing into venules. The vast extent of the capillary bed together with the length of the individual paths allows a transit time for RBCs sufficient for gas exchange to take place. The estimate based on anatomy of approximately 0.5- to 1-second average transit time is essentially the same as that found using the carbon monoxide diffusing capacity method, in which one divides capillary blood volume by cardiac output to obtain mean capillary transit time.[84] In the normal lung, there is sufficient time for equilibrium between the O_2 and CO_2 tensions in the alveoli and the erythrocytes in the pulmonary capillaries. Only under extreme stress (heavy exercise at low inspired O_2 tensions) or in severe restrictive lung disease are the RBCs predicted to pass through the microcirculation without enough time to reach diffusion equilibrium.[85]

Normally, capillary blood volume is equal to or greater than stroke volume. Under normal resting conditions, the volume of blood in the pulmonary capillaries is well below its maximal capacity, however. Recruitment can increase this volume by a factor of about three. Thus, the normal capillary blood volume of 60 to 75 mL is one-third of the capacity (200 mL) measured by quantitative histology.[6] This reserve capacity of the capillaries allows them to accommodate rapid increases in cardiac output during times of high demand.

Anatomically, the pulmonary blood vessels can be divided into two groups: extra-alveolar and alveolar. *Extra-alveolar vessels* lie in the loose-binding connective tissue (peribronchovascular sheaths, interlobular septa). Extra-alveolar vessels extend into the TRUs. *Alveolar vessels* lie within the alveolar walls and are embedded in the parenchymal connective tissue. They are subject to whatever forces operate at the alveolar level. They are referred to as alveolar vessels in the sense that the effective hydrostatic pressure external to them is alveolar pressure. Not all of the alveolar vessels are capillaries, however. Small arterioles and venules, which bulge into the air spaces, may also be affected by changes in alveolar pressure. Likewise, not all of the capillary bed is subjected to alveolar pressure under all conditions.[86] The corner capillaries in the alveolar wall junctions are protected from the full effects of alveolar pressure by the curvature and alveolar air-liquid surface tension.[87] This may account for the fact that, even under conditions in which alveolar pressure exceeds both arterial and venous pressure ("zone 1"),[88] some blood continues to flow through the lung.[89] One has to go several centimeters up into zone 1 before blood flow stops completely. (For a discussion of distribution of pulmonary blood flow and lung zones, see Chapter 10.)

An important question is whether the normal human lung contains connections between the pulmonary arteries and veins that permit some portion of pulmonary blood flow to bypass the capillary network. Whereas such vessels may develop congenitally or pathologically,[90] functioning short circuits probably do not exist in the normal lung. (Pathologic arteriovenous communications are discussed in Chapter 88.)

In addition to its function in gas exchange, the pulmonary circulation is involved in a number of other functions important to homeostasis. The pulmonary vascular bed serves as a capacitance reservoir between the right and left sides of the heart. Consequently, the reservoir of blood in the pulmonary circulation is sufficient to buffer changes in right ventricular output for two to three heartbeats. The pulmonary vascular bed also serves as a filter, trapping embolic material and preventing it from reaching systemic vascular beds. For example, during intravascular coagulation or in processes involving platelet or neutrophil aggregation, the predominant site of sequestration is the lung. The main anatomic reason for this is that 75% of the total circulating blood volume is in the venous circuit, and the lung's microvascular bed is the first set of small vessels through which the blood flows. Moderate numbers of microemboli generally produce no detectable dysfunction in the lung because of the huge array of parallel pathways in the pulmonary microcirculation. At most, microemboli temporarily block flow to a portion of or to an entire TRU. The fate of such emboli is not clear. Some are phagocytosed and removed into the lung tissue.[91] Some emboli can be degraded to a small size, pass through into the systemic circulation, and be removed by the reticuloendothelial system. The filtering function of the lung enables such clinical studies as the perfusion scan, in which macroaggregated albumin is trapped by the lung vessels as a measure of perfusion. (Further information about the pathophysiology of thromboembolic disorders is presented in Chapter 81.)

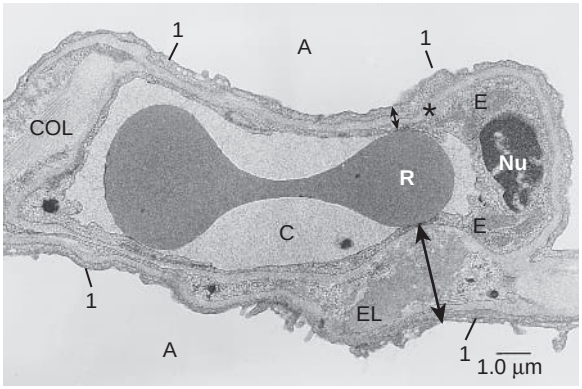

Figure 1.16 Cross-section of an alveolar wall showing the path for oxygen and carbon dioxide diffusion. The thin side of the alveolar wall barrier *(short double-headed arrow)* consists of type 1 epithelium (1), interstitium (asterisk) formed by the fused basal laminae of the epithelial and endothelial cells, capillary endothelium (E), plasma in the alveolar capillary (C), and finally the cytoplasm of the red blood cell (R). The thick side of the gas-exchange barrier *(long double-headed arrow)* has an accumulation of elastin (EL), collagen (COL), and matrix that jointly separate the alveolar epithelium from the alveolar capillary endothelium. As long as the red blood cells are flowing, oxygen and carbon dioxide probably diffuse across both sides of the air-blood barrier. (See also Video 3.1 for a three-dimensional ultrastructural view of alveolar walls.) A, alveolus; Nu, nucleus of the capillary endothelial cell. (Human lung surgical specimen, transmission electron microscopy.)

TERMINAL RESPIRATORY UNITS

The TRU consists of a respiratory bronchiole and all the alveolar ducts together with their accompanying alveolar ducts and alveoli (see Fig. 1.14; see Table 1.2). The TRU has both a structural and a functional existence and was first described in the human lung by Hayek.[11] In the human lung, this unit contains approximately 100 alveolar ducts and 2000 alveoli. At FRC, the unit is approximately 5 mm in diameter, with a volume of 0.02 mL. There are about 150,000 such units in the lungs of normal adult humans.[6]

The functional definition of the TRU is physiologic; namely, gas-phase diffusion is so rapid along patent airways that the partial pressures of O_2 and CO_2 are uniform throughout the unit.[28] Therefore, physiologically, O_2 in the gas phase anywhere along the TRU will diffuse along its concentration gradient across the extremely thin walls into RBCs flowing in the capillaries (Fig. 1.16), where O_2 combines with hemoglobin. CO_2 diffuses in the opposite direction along its concentration gradient. A key point about diffusion is that the process is much faster in the gas phase than in the liquid phase. Thus, the TRU size is defined in part by the fact that gas molecules can diffuse and equilibrate anywhere within the unit more rapidly than they can diffuse across the air-blood barrier into the blood. Of note, the solubility of O_2 in water is low relative to its concentration in gas. CO_2 is much more soluble in water (20 times the solubility of O_2 in water), and therefore CO_2 diffuses rapidly into the gas phase, even though the driving pressure for CO_2 diffusion is only one-tenth that for O_2 entering the blood.

A source of confusion is the term *acinus* in the context of the lung. Historically, the term acinus has been defined differently by different fields. In pathology, the acinus is bigger than a TRU. The pathologists' *acinus* consists of a terminal bronchiole and all of the subsequent respiratory bronchioles together with their accompanying alveolar ducts and alveoli.[92–95] Alas, the term *acinus* also has been used to describe the TRU unit.[96] This chapter uses the physiologists' *alveolus:* the TRU. The physiologists' *alveolus* is the TRU because the unit's definition is functional.

In general, O_2 diffusion is not limiting in the normal lung, except during heavy exercise while breathing gas containing very low O_2 concentrations (e.g., at high altitudes).[85] Even at that, it is not so much diffusion that is limiting, but the fact that the transit time of the RBCs is reduced due to increased cardiac output. However, most disorders of oxygenation are due to ventilation-perfusion inequalities[97] (see also Chapter 44).

All portions of the TRU participate in volume changes with breathing.[98,99] When a unit increases its volume from FRC, the alveolar gas that had been in the alveolar duct system enters the expanding alveoli, together with a small portion of the fresh air. Most of the fresh air remains in the alveolar duct system. This does not lead to any significant gradient of alveolar O_2 and CO_2 partial pressures because diffusion in the gas phase is so rapid that there is equilibrium within a few milliseconds. However, nondiffusible (suspended or particulate) matter remains away from the alveolar walls and is expelled in the subsequent expiration.[100] This explains why it is difficult to deposit aerosols on the alveolar walls and why large inspired volumes and breath-holding are needed for efficient alveolar deposition.

The anatomic alveolus is not spherical (Fig. 1.17, see Fig. 1.15). It is a complex geometric structure with flat walls and sharp curvature at the junctions between adjacent walls. The most stable configuration is for three alveolar walls to join together, as in foams.[6] The resting volume of an alveolus is at 10–14% of TLC. When alveoli go below their resting volume, they must fold up because their walls have a finite mass (see Fig. 1.17). Most of the work required to inflate the normal lung is expended across the air-liquid interface to overcome surface tension; the importance of the air-liquid interface is demonstrated by the low pressure required to "inflate" a liquid-filled lung with more liquid[101] (see Fig. 3.5 and Chapter 3).

The phenomenon of TRU, or alveolar, stability is complex because not only is air-liquid interfacial tension involved but each flat alveolar wall is part of two alveoli, and both must participate in any volume change. Therefore atelectasis does not usually involve individual alveoli but rather relatively large units (Fig. 1.18).[102]

The alveolar walls are composed predominantly of pulmonary capillaries. In the congested alveolar wall the blood volume may be greater than 75% of the total wall volume. Alveoli near the top of the lung show less filling of the capillaries than those at the bottom.[103,104] This affects regional diffusing capacity, which is dependent on the volume of RBCs in the capillaries.

The transition from a cuboidal epithelium of the respiratory bronchiole to the squamous epithelium of the alveolus is abrupt (Fig. 1.19). Little is known about the function, if any, of this transitional junction. Although Macklin[105] speculated that the permeability of the bronchiole-alveolar epithelial junctions might be unique, no definitive difference has been demonstrated.[106] The controversy continues as to whether this region shows unique permeability features that might participate in clearance of particles or leakage of edema.[107–109]

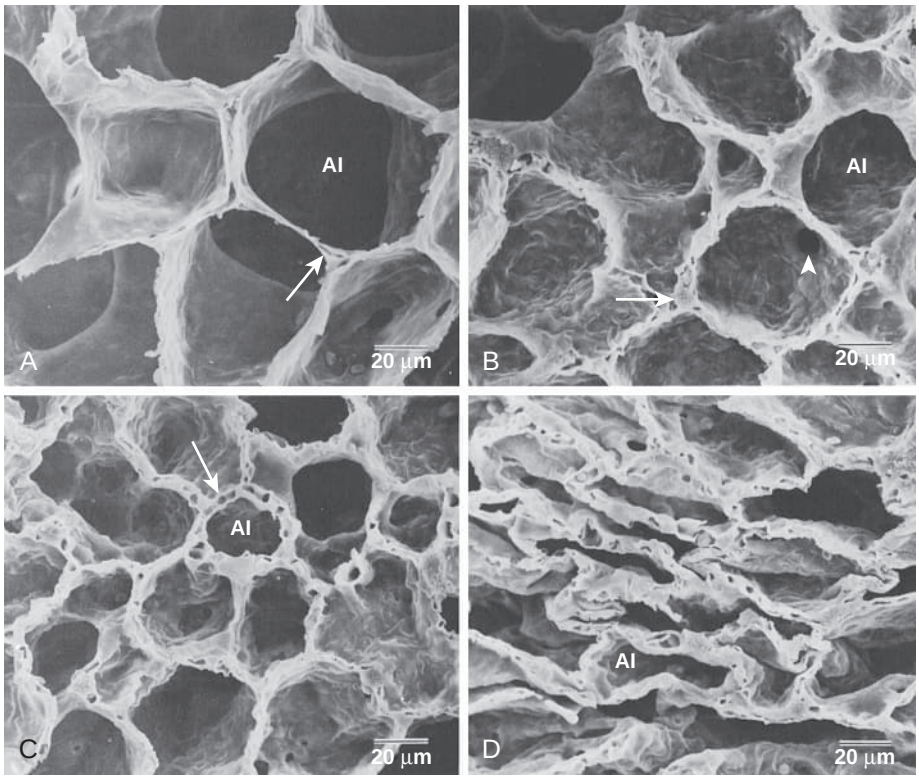

Figure 1.17 Alveolar shape changes at representative points along the air deflation pressure-volume curve of the lung. The four micrographs are at the same magnification. The air deflation pressure points are as follows: (A) airway pressure = 30 cm H_2O (total lung capacity [TLC]); (B) 8 cm H_2O (≈50% TLC); (C) 4 cm H_2O (near functional residual capacity [FRC]); and (D) 0 cm H_2O (minimal volume). Vascular pressures are constant (pulmonary artery presssure = 25 cm H_2O and left atrial pressure = 6 cm H_2O). Intrinsic alveolar shape (AI) is maintained from TLC to FRC (A–C). The alveolar walls are flat, and there is sharp curvature at the junctions between adjacent walls. Note the flat shape of the alveolar capillaries *(arrow)* at TLC ([A] lung zone 1 conditions) compared to their round shape *(arrow)* at FRC ([C] lung zone 3 conditions). The alveolar walls are folded and alveolar shape is distorted at minimal lung volume (D). The *arrow* in (B) identifies an alveolar type 2 cell at an alveolar corner. The *arrowhead* in (B) identifies a pore of Kohn. (Perfusion-fixed normal rat lungs, scanning electron microscopy.)

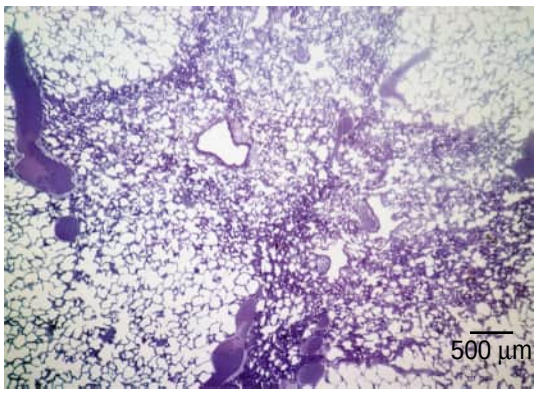

Figure 1.18 Histologic appearance of atelectasis. Atelectasis usually involves relatively large units of lung parenchyma, rather than individual alveoli. Alveolar walls in the atelectatic units are folded, distorting alveolar air space and capillary shape, as shown in Fig. 1.17D. (Sheep lung injured by air emboli, 2 μm–thick glycol methacrylate section, light microscopy.)

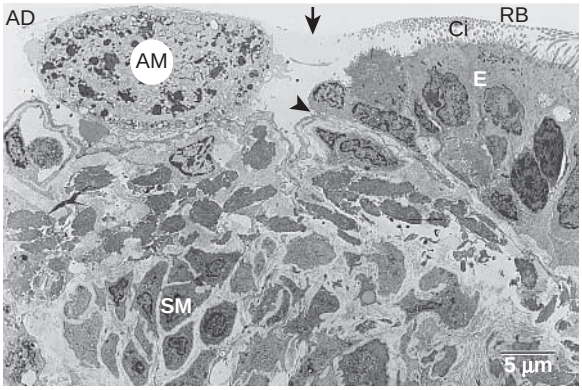

Figure 1.19 The respiratory bronchiole (RB)–alveolar duct (AD) junction is abrupt. The junction is demarcated by an abrupt transition *(arrowhead)* from low cuboidal epithelial cells (E) with cilia to squamous epithelial cells. Submerged in the lining liquid *(arrow)* are an alveolar macrophage (AM) and cilia (Ci). Airway smooth muscle cells (SM) extend to this level of the airway tree. (Human lung surgical specimen, transmission electron microscopy.)

Trapping and clearance of particulate matter impinging on the alveolar surfaces is vital and takes place in the alveolar surface liquid. Within this liquid are suspended alveolar macrophages (see Fig. 1.19).[110] The majority of alveolar macrophages that reach the terminal airways via the slow, upward flow of alveolar lining liquid are expelled with the surface film as it is pulled up onto the mucociliary escalator.[111,112]

LYMPHATICS

Another route for clearance of particulate matter and fluid from the lung is the pulmonary lymphatic system (see Chapter 7). Lymphatics of the lung are subdivided into two principal groups based on their location: a deep plexus and a superficial plexus.[11,58,113,114] Both plexuses are made up of initial and collecting lymphatics, with communications between the two.[11,58,108,113] The *deep plexus* is situated in the peribronchovascular connective tissue sheaths of the lung (see Fig. 1.1).[11,58,108,113] Lymphatics in the deep plexus are distributed around the airways, extending peripherally to the respiratory bronchioles and next to branches of the pulmonary arteries and veins.[11,58,108,113] Lymphatics are not found in the alveolar walls. The *superficial plexus* is located in the connective tissue of the visceral pleura. This plexus is

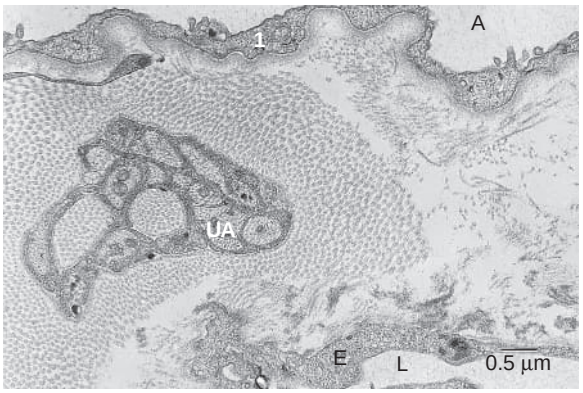

Figure 1.20 Ultrastructure of unmyelinated axons in the lung parenchyma. Unmyelinated axons (UA), known as C fibers, are shown situated in the interstitium of a respiratory bronchiole, between an alveolar type 1 cell (*white 1*) lining an alveolus (A) and an initial lymphatic (L). Although the presence of small clear vesicles is suggestive of cholinergic (autonomic) axons, unequivocal identification as either motor or sensory fibers is not possible in random thin sections. E, lymphatic endothelial cell. (Human lung surgical specimen, transmission electron microscopy.)

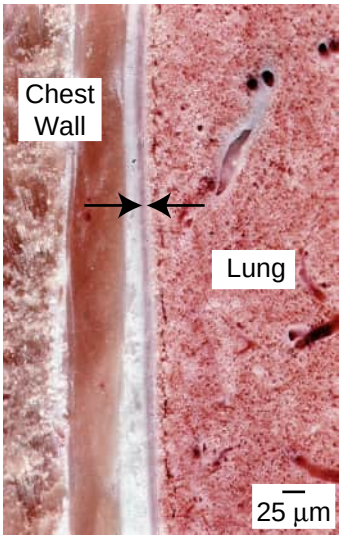

Figure 1.21 The pleural space is a real space. The dark band delimited by the *opposed arrows* is the pleural space, which is located between the chest wall and lung. (Frozen sheep chest wall and lung, unstained.)

prominent in the lung of species with thick visceral pleura, including human lung (see the section "Pleural Space and Pleural Membranes").[11,58,113] Collecting lymphatics have one-way valves and in large species, such as humans and sheep, a discontinuous, thin layer of smooth muscle. Of note, the visceral pleural lymphatics do not open into the pleural space and do not participate in pleural liquid clearance.

Lymph is propelled centripetally toward the lung's hilum or pulmonary ligament by movements of the lungs through the respiratory cycle and by heart pulsations, to reach regional lymph nodes. In the human, pulmonary lymph flows to extrapulmonary lymph nodes located around the primary bronchi and trachea.[11,58,113]

INNERVATION

Innervation of the human lung consists of sensory (afferent) and motor (efferent) pathways.[92,113,115,116] Fibers of the sensory pathway include myelinated, slowly adapting stretch receptors (Hering-Breuer reflex) and irritant receptors, but most sensory fibers are unmyelinated, slow-conducting C fibers located in the TRUs, either along the bronchioles or within the alveolar walls (Fig. 1.20). Investigators have speculated about the function of C fibers since Paintal first suggested that they played a role in sensing parenchymal connective tissue distortion, as during pulmonary vascular congestion and interstitial edema.[117–120] The speculation has neither been proven nor disproven.

The motor pathways reach the lung through the sympathetic and parasympathetic nervous systems. Preganglionic contributions to the sympathetic nerves arise from the upper four or five thoracic paravertebral ganglia, whereas the preganglionic parasympathetic nerves originate in the brainstem motor nuclei associated with the vagus nerves. Postganglionic sympathetic nerve fibers terminate near airways, vascular smooth muscle cells, or submucosal glands. Postganglionic parasympathetic fibers extend from ganglia mainly located external to the smooth muscle and cartilage. Some submucosal ganglia exist, but they are generally smaller and have fewer neurons.

PLEURAL SPACE AND PLEURAL MEMBRANES

As stated earlier, the primary function of the lung is ensuring efficient gas exchange between alveolar air and alveolar capillary blood. This vital function is met, in part, by extensive and rapid movement of the lung within the pleural space and its pleural liquid.[121,122] Online supplemental digital videos linked to this chapter provide a glimpse of the view that surgeons have during dissection through the intercostal muscles: The lungs glide along the deep surface of the translucent endothoracic fascia and parietal pleura (see Videos 1.1 to 1.5). The pleural space also serves as an outlet into which pulmonary edema liquid can escape.[123,124] The pleural liquid also serves to couple the lung to the chest wall.[125] What are the anatomic features of the pleural space and pleurae that contribute to these functions?

An important anatomic fact is that the pleural space is a real space (Fig. 1.21); it is not a potential space.[3,125] The pleural space surrounds the lung, except at its hilum, where the parietal pleura and visceral pleura join.[11,91] Separations are present between the parietal and visceral pleurae along the interlobar fissures and costodiaphragmatic recesses. The normal volume of pleural liquid is 0.1 to 0.2 mL/kg body weight in most mammals.[125,126] This volume is distributed across a pleural surface area of approximately 1000 cm^2/lung and pleural space width of 10 to 20 µm (see Fig. 1.21).[3,125] Normally, there is little or no contact across the pleural space because the microvilli that extend from the parietal and visceral mesothelial cells are only 3 to 5 µm long.[2,3,127,128]

The unique anatomic features of the parietal pleura are the lymphatic stomata.[128–133] The lymphatic stomata are openings (≈1–12 µm in diameter) between parietal and mesothelial cells (Fig. 1.22), which are continuous with

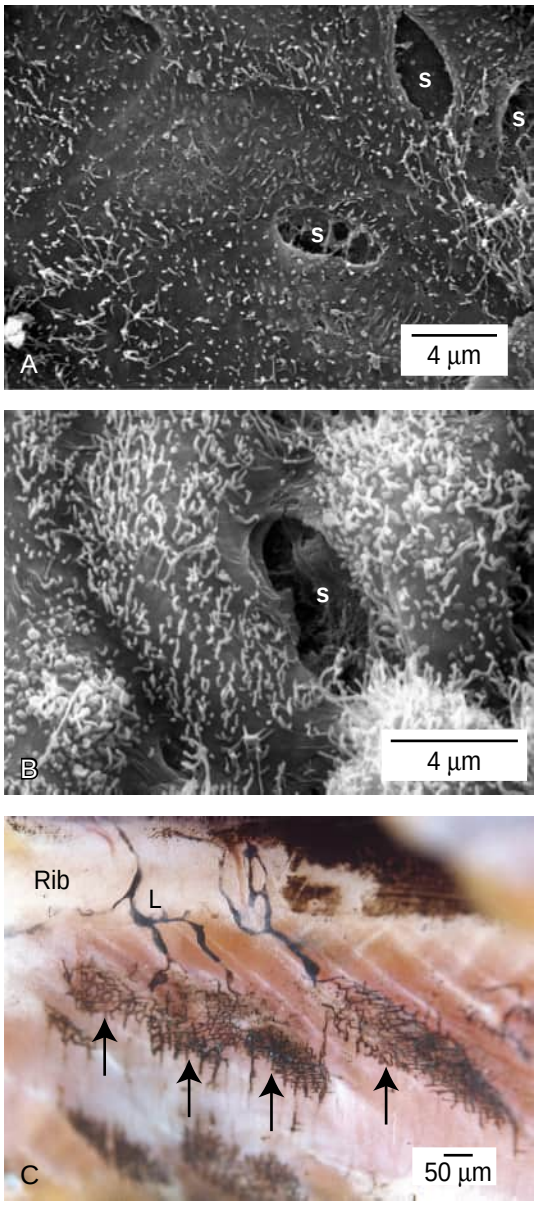

Figure 1.22 Surface view of lymphatics stomata, initial lymphatics, and collecting lymphatics of the parietal pleura. (A–B) Scanning electron micrographs that show the unique structure of lymphatic stomata (S). Stomata are apertures between the pleural space and the initial lymphatics in the parietal pleura. Three stomata are visible in a low-magnification field of view in (A). Stomata are located over intercostal muscles. (B) shows a different stoma at a higher magnification. Microvilli are not present at the aperture of the stomata, which are lined by mesothelial cells. (Sheep parietal pleura, scanning electron microscopy.) (C) shows a portion of the parietal pleura, where colloidal carbon is seen in four beds of initial lymphatics *(arrows)* located over an intercostal space. Colloidal carbon is also in collecting lymphatics (L) that cross a rib, where the collecting lymphatics drain into lymphatic vessels that accompany the intercostal vessels. (Rabbit, macroscopic view of the parietal pleural after colloidal carbon was placed in the pleural space in situ.)

the lumen of lymphatic capillaries. The size likely varies as the chest moves with ventilation. Tracer studies reveal that India ink and chicken RBCs (which are nucleated and therefore easily identifiable) are cleared almost exclusively from the pleural space by the stomata, which are located over the intercostal spaces in the distal half of the thorax, and along the sternum and pericardium of experimental animals that have been studied.[128,134] Physiologic studies showed that protein and particulate matter in the pleural space are cleared almost entirely by the parietal pleural system of stomata and lymphatics.[129,135] The lymphatics transport the cleared pleural liquid (lymph) to regional lymph nodes along the sternum and vertebral column and then, to the thoracic duct and right lymphatic duct. In these regards, normal pleural liquid is cleared by mechanisms consistent with normal interstitial liquid turnover in the peritoneum.

CELLULAR ANATOMY OF THE LUNG

AIRWAY LINING CELLS

The airway epithelium of the human proximal conducting airways contains different types of epithelial cells with specific functions. These cells include basal cells, ciliated cells, and goblet cells, as well as some club cells and a small number of brush cells, single neuroendocrine cells,[136–139] and ionocytes.[140,141] Submucosal gland epithelium, contiguous to the airway surface epithelium, contains serous and goblet secretory cells.[142] The proportion of the different epithelial cell types that form the healthy adult human airways varies along the proximal-to-distal axis, with a decreasing number of submucosal glands and an increasing number of club secretory cells.[137,143]

Basal cells function as progenitor cells within the airway epithelium because these cells are able to self-renew or differentiate into secretory, goblet, and ciliated cells in homeostasis and during injury repair[144,145] (see Chapter 8). In humans, basal cells cover most of the airway basement membrane[146]; however, they do not reach the airway lumen and thereby contribute to the pseudostratified appearance of the airway epithelium. These cells interact with columnar epithelium, basement membrane, and underlying mesenchymal cells, inflammatory cells, lymphocytes, and dendritic cells.[147,148]

Ciliated cells protect the TRUs by filtering the inhaled air for solid particles and removing them by mucociliary clearance. Nearly half of the epithelial cells in the normal human airway are ciliated at all airway generations (Fig. 1.23), down to bronchioles (see Fig. 1.19).[149] Each ciliated cell has multiple cilia (≈200 cilia) that have a specialized capping clawlike structure called a ciliary crown, to make the distal portion stiff to propel the liquid lining layer along the airways and to promote debris clearance from the airways. The cilia have structural and motor proteins that produce coordinated and directional beating at 8 to 15 Hz, which is critical for mucociliary clearance.[136–138,150] As the airway superficial lining liquid moves centripetally, it encounters larger and fewer airways, which have a smaller *total* perimeter. For example, the total perimeter of approximately 150,000 terminal bronchioles is much greater than the total perimeter of the five lobar bronchi.[6] If the lining liquid volume remained constant, the liquid layer ought to grow in thickness, but this does not happen, suggesting that much of the liquid is reabsorbed during its ascent along the airways.

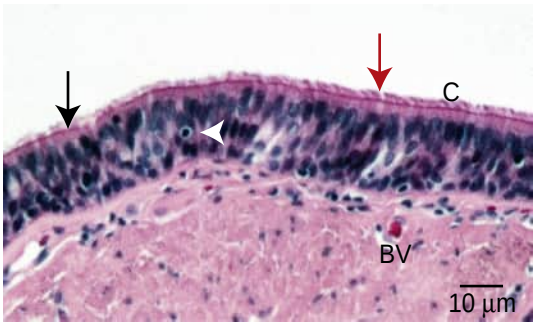

Figure 1.23 Structure of bronchial mucosa. The bronchial mucosa consists of pseudostratified, columnar epithelium with cilia (C) and goblet cells *(red arrow)*. The cilia, which form a thick carpet, move rhythmically and thereby propel liquid, mucus, cells, and debris centrally toward the pharynx. The dark band immediately beneath the cilia *(black arrow)* is produced by the basal bodies. By transmission electron microscopy, basal bodies are recognized as modified centrioles. A lymphocyte *(white arrowhead)* is intercalated among the epithelial cells. A bronchial blood vessel (BV) is located beneath the mucosal layer. (Human lung surgical specimen, 10 µm–thick paraffin section, light microscopy.)

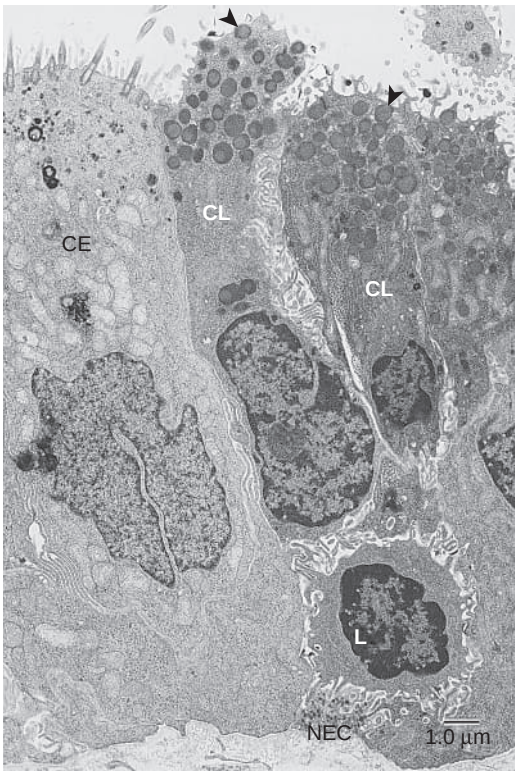

Figure 1.24 Cellular structure of terminal airway epithelium. The epithelium consists mainly of ciliated epithelium (CE) and nonciliated club cells (CL). Club cells have the ultrastructural features of secretory cells; namely, they possess basally located rough endoplasmic reticulum, perinuclear Golgi apparatus, apically located smooth endoplasmic reticulum, and prominent membrane-bound granules *(arrowheads)*. A lymphocyte (L) is intercalated among the epithelial cells. A small portion of a neuroendocrine cell (NEC) containing characteristic dense-cored vesicles is also visible at the base of the epithelial cells. (Human lung surgical specimen, transmission electron microscopy.)

Goblet cells are secretory cells that produce and store mucus in granules of about 800 nm diameter. Secretion of the correct amount of mucus with an optimum viscoelastic profile is essential for maintenance of normal mucociliary clearance.[137,151] Goblet cells also secrete inflammatory mediators that participate in the recruitment and activation of immune cells. Goblet cells are found on the airway surface and in the submucosal glands.[11,58] Furthermore, goblet cells are capable of division and may show stem cell multipotency.[152]

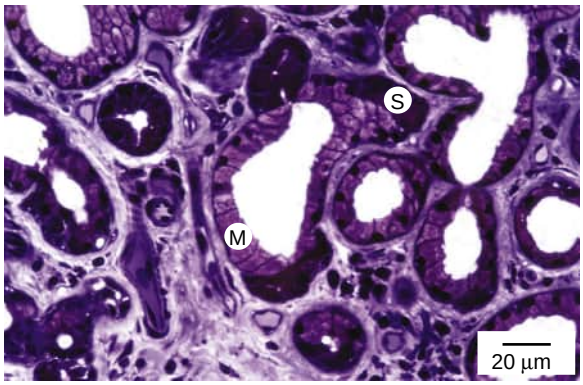

Figure 1.25 Structure of submucosal glands. This figure provides a higher magnification view of a region shown in Fig. 1.7. The mixed, compound tubuloacinar glands contain mucus-secreting cells (M) and serous-secreting cells (S). The latter type form crescentic caps, or demilunes, over the ends of the acini, the rounded secretory units of the gland. Mucous cells are the predominant glandular cell type. (Human lung surgical specimen, right middle lobar bronchus, 2 µm–thick glycol methacrylate section, light microscopy.)

Club cells[153] are dome-shaped cells with dense cytoplasmic granules and microvilli that, in humans, are restricted to terminal and respiratory bronchioles,[154,155] where club cells serve as facultative progenitors for themselves and for ciliated epithelial cells, and they maintain the normal epithelium of the distal conducting airways (see Fig. 1.24).[154,156] Single-cell transcriptome analyses have suggested novel roles for club cells in host defense, antiprotease activity, and physical barrier function.[157] Club cells also secrete secretoglobin 1A1; surfactant proteins A, B, and D; and lipids.[156,158,159]

Submucosal gland epithelial cells line the submucosal glands (Fig. 1.25), which are continuous with the airway epithelium and are located below the airway luminal surface of all of the cartilaginous proximal airways. Submucosal gland epithelial cells secrete mucins, water and electrolytes, and other substances that help protect the lungs from particles and infectious agents. Studies of the regulation of secretion in vivo and in vitro show that secretion is modulated by neurotransmitters, including cholinergic, adrenergic, and peptidergic transmitters,[42] and by inflammatory mediators, such as histamine,[43] platelet-activating factor,[44] and eicosanoids.[45] Submucosal glands are connected to the airway surface by a duct lined by epithelial cells identified as ductal cells.[160] The submucosal gland epithelium contains goblet cells (described earlier) and serous cells. *Serous cells* are the defensive cells of the mucosa because they secrete innate immunity proteins, such as lysozyme, SPLUNC1, β-defensins,[161] mucins, and electrolytes, including chloride and bicarbonate, to control the fluidity of the mucus. These cells, in contrast to goblet cells, have discrete electron-dense granules of about 600 nm diameter. A few serous cells are also present in the surface epithelium of the human bronchioles.[162]

Rare lung epithelial cell types include pulmonary neuroendocrine cells, ionocytes, and brush (tuft) cells. These cell

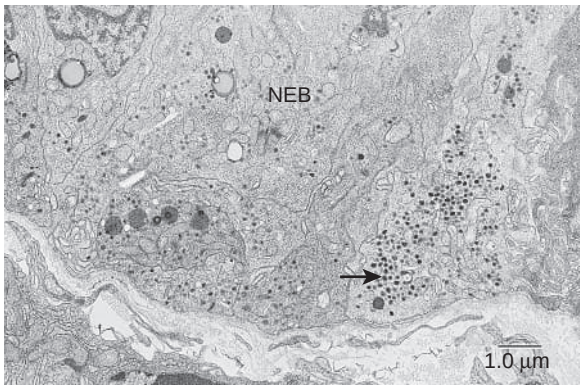

Figure 1.26 Neuroepithelial body (NEB) located in a peripheral airway. Neuroepithelial bodies contain aggregates of neuroendocrine cells. A characteristic ultrastructural feature of neuroendocrine cells is the presence of small (0.1–0.3 µm in diameter) dense-cored vesicles in their cytoplasm *(arrow)*. Each dense-cored vesicle is bounded by a unit membrane. (Human lung surgical specimen, transmission electron microscopy.)

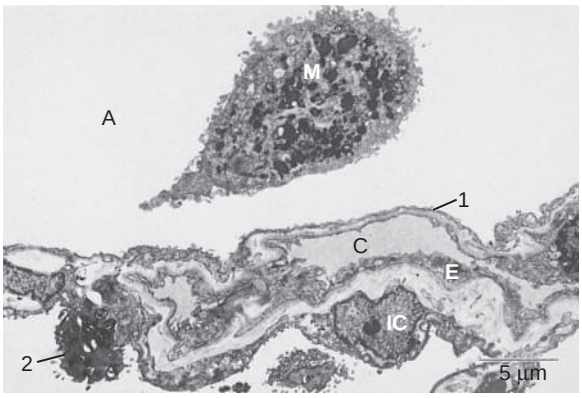

Figure 1.27 Cells of the terminal respiratory unit. An alveolar macrophage (M) is located in an alveolus (A). Alveolar macrophages are the air space scavengers that are cleared either up the mucociliary escalator or into the interstitium. These cells can be activated to express and secrete cytokines, which may interact with other cells. Cells of the alveolar wall are the lining alveolar type 1 and 2 cells (1 and 2, respectively) and the enclosed capillary (C), endothelial cells (E), and interstitial cells (IC; fibroblasts). (Human lung surgical specimen, transmission electron microscopy.)

types are continually and directly replenished by basal progenitor cells.

Pulmonary neuroendocrine cells serve as O_2 sensors[163,164] and release hormones that affect smooth muscle (e.g., vasoactive intestinal peptide[165,166] and substance P).[167–170] Pulmonary neuroendocrine cells represent less than 1% of airway epithelial cells and are a component of the diffuse neuroendocrine system called the amine uptake and decarboxylation system.[171,172] This system is composed of single neuroendocrine cells and clusters of such cells, known as neuroepithelial bodies,[173] distributed along the airway epithelium down to the region of alveolar ducts.[174–177] The neuroepithelial bodies are preferentially located at airway bifurcations. Pulmonary neuroendocrine cells are ultrastructurally characterized by dense-cored vesicles in their cytoplasm (Fig. 1.26). The dense-cored vesicles are the storage sites of amine hormones (serotonin, dopamine, norepinephrine) and peptide hormones (bombesin, calcitonin, leu-enkephalin).[166] Neurons are also associated with neuroendocrine cells.

Ionocytes are a recently identified and rare cell population that serves as the primary source of cystic fibrosis transmembrane conductance regulator activity in the conducting airway epithelium in mice and humans.[140,141] The cystic fibrosis transmembrane conductance regulator is a membrane protein that conducts chloride ions and water across epithelial cell membranes. Mutations in this gene cause cystic fibrosis (see Chapters 67 and 68).

Brush (tuft) cells are pear-shaped cells, with a narrow apex from which extend a tuft of blunt, squat microvilli that stretch their filaments into the underlying cytoplasm. Brush cells also contain numerous intracytoplasmic membrane-bound inclusions and seem to have a chemosensory role, although their function has not been clearly defined.[178]

The complex and diverse cellular composition of the airway epithelium in mammalian organisms has evolved to support the main functions of the airways, namely to connect the outside world to the TRUs, to maintain a balanced secretion and absorption of electrolytes and water from the lining liquid, and to facilitate mucociliary clearance.

ALVEOLAR LINING CELLS

The alveolar epithelial cells that line the anatomic alveoli include *alveolar type 1* (AT1) and *alveolar type 2* (AT2) cells and a minor subpopulation of *alveolar epithelial progenitors* (AEPs), all supported by a shared basal membrane and the subjacent capillaries and fibroblasts.[179,180] AT2 cells outnumber AT1 cells (≈15% vs. 8–10% of total peripheral lung cells, respectively). However, AT1 cells account for approximately 90–95% of the alveolar surface area of the peripheral lung.[181] (See also Video 3.1 for a three-dimensional ultrastructural view of AT1 cells.)

AT1 cells have extensive, attenuated cytoplasmic processes that form a large, thin surface area for gas exchange (Figs. 1.27 and 1.28). AT1 cells express water channels[182] and also epithelial sodium channels and membrane sodium-potassium–adenosine triphosphatase,[183,184] which play a role in pulmonary water flux.[185] Adult rodent and human AT1 cells have a limited proliferative capacity and are sensitive to injury. Under normal conditions, AT1 cells attach via tight junctions to neighboring AT2 cells to form a relatively impermeable seal between alveolar air and alveolar wall interstitial spaces. AT1 cells contain many small, non–clathrin-coated vesicles, or caveolae, that are open either to the alveolar lumen or interstitium or are detached from the surface as free vesicles in the cytoplasm.[186] The vesicles contain caveolin-1 protein, a scaffolding protein that organizes specialized membrane phospholipids and proteins into vesicles. Caveolin-1 can bind free cholesterol and modulate the efflux of cholesterol from the cell when intracellular concentrations rise.[187,188] Caveolae appear to sequester various proteins into the vesicles, such proteins that include growth factor receptors, signaling molecules such as G proteins, calcium ion receptors, and pumps.

AT2 cells are small (≈300 μm^3) cuboidal cells with short stubby apical microvilli (see Figs. 1.27 and 1.29). AT2 cells are specialized in the production and recycling of proteins and phospholipids that form surfactant. Surfactant is stored in cytoplasmic lamellar bodies, which are membrane-bound inclusions (diameter from <0.1–2.5 µm) that are stacked layers of cell membrane-like material (Fig. 1.29) composed

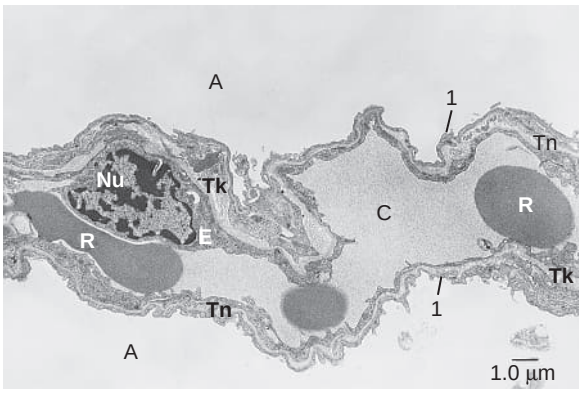

Figure 1.28 Ultrastructure of alveolar walls. The thick (Tk) and thin (Tn) sides of an alveolar capillary (C) change as the capillary crosses between alveoli (A). The basal laminae of the capillary endothelium and alveolar epithelium fuse in the thin regions. The nucleus (Nu) of an endothelial cell (E) is visible above a red blood cell (R). (See also Video 3.1 for a three-dimensional ultrastructural view of alveolar walls.) 1, alveolar type 1 cell. (Human lung surgical specimen, transmission electron microscopy.)

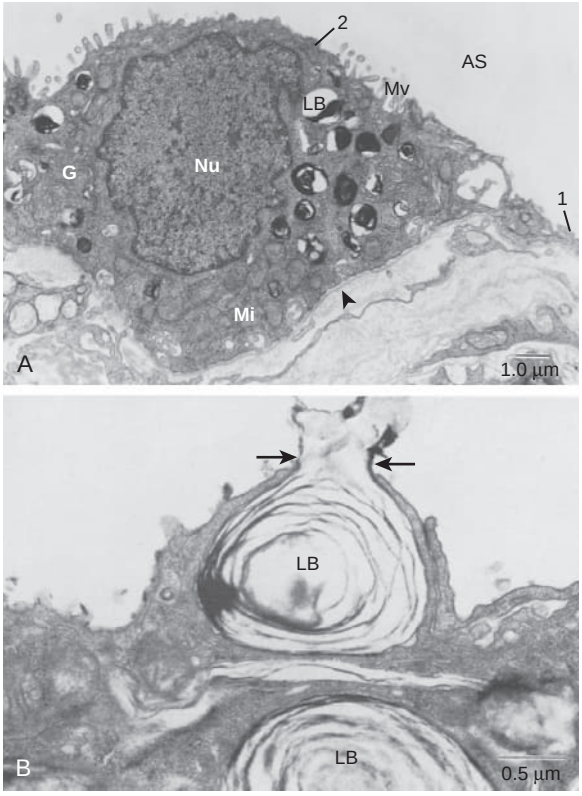

Figure 1.29 Cellular structure of alveolar type 2 cells. (A) Alveolar type 2 (or granular) cells (2) are cuboidal epithelial cells that contain characteristic lamellar bodies (LB) in their cytoplasm and have stubby microvilli (Mv) that extend from the apical surface into the alveolar air space (AS). Other prominent cytoplasmic organelles in alveolar type 2 cells are mitochondria (Mi) and Golgi apparatus (G). Adjacent to the alveolar type 2 cell is a process of an alveolar type 1 cell (1). The abluminal surface of the epithelial cells rests on a continuous basal lamina *(arrowhead)*. Nu, nucleus of an alveolar type 2 cell. (B) The apical region of an alveolar type 2 cell contains two LB, one of which has been fixed in the process of secretion by exocytosis *(arrows)*. The lamellar osmiophilic bodies are the source of surface-active material (surfactant). Alveolar type 2 cells are usually located in the alveolar corners (see Fig. 1.17B). (Human lung surgical specimen, transmission electron microscopy.)

of phospholipids[189] and various proteins, including surfactant proteins A, B, C, and D; lysosomal enzymes; and other molecules.[190,191] Surfactant is secreted to the alveolar space where it decreases the alveolar surface tension.[181] AT2 cells also have immunomodulatory functions. The presence of various ion channels and transporters supports earlier evidence that AT2 cells are actively involved in liquid resorption and transepithelial water fluxes.[192] Studies in mice support a role for AT2 cells as the facultative stem cells of the alveolar epithelium because AT2 cells can both self-renew and differentiate into AT1 cells.[193–195]AEP cells are a subpopulation of AT2 cells that can serve as alveolar epithelial progenitors. AEPs have been identified in adult mouse and human alveoli.[194,195] Human AEPs can be directly isolated by virtue of their expression of the conserved cell surface marker TM4SF1.[194] AEPs are a stable lineage during steady-state turnover in homeostasis but rapidly expand to regenerate the alveolar epithelium after acute lung injury.

The above epithelial cells that line the alveoli are critical for the ultimate function of the lung, which is the gas-exchange process. These cells are shaped and arranged in a way that allows the formation of very thin alveolar septa, where the epithelial cells are in close contact with the capillaries to support the diffusion of gases between air and blood. AT2 cuboidal epithelial cells maintain the integrity of the respiratory units and produce surfactant to control the surface tension of the alveoli.

MESENCHYMAL CELLS

Vascular endothelial cells of both pulmonary and bronchial vessels are continuous (nonfenestrated) endothelial cells (see Fig. 1.16). These flattened cells have an individual area of 1000 to 3000 μm^2 and an average volume of 600 μm^3.[196] The pulmonary capillary bed covers a total surface area of approximately 130 m^2, or the equivalent of one side of a doubles tennis court (260 m^2). Other structural features of capillary endothelial cells are the large number of plasmalemmal vesicles and small number of organelles. Despite having relatively few organelles, capillary endothelial cells have organelles involved in protein synthesis, such as endoplasmic reticulum, ribosomes, and Golgi apparatus, and vesicles, such as caveolae, multivesicular bodies, and lysosomes.[197] The endocytic apparatus participates in receptor-mediated uptake and transport (transcytosis) of albumin, low-density lipoproteins, and thyroxine.[198–202] Vascular endothelial cell functions include O_2 and nutrient transport, control of blood coagulation, interaction with inflammatory cells, and maintenance of epithelial homeostasis.[203] Although all vascular endothelial cells share core properties, there are differences among the endothelial cells in large blood vessels versus capillaries.[204] The large artery endothelium, for example, has a lower barrier strength and angiogenic potential than the capillary endothelium.

Lymphatic endothelial cells share many of the structural and functional characteristics of vascular endothelial cells. The ultrastructural distinction of initial lymphatics (lymphatic capillaries) is that their basement membrane is discontinuous, whereas that of pulmonary and bronchial capillaries is continuous.[205,206]

Fibroblasts are located subjacent to epithelial cell layers of airways or in the interstitium, between the epithelial

and endothelial layers of alveolar walls.[207,208] Fibroblasts produce extracellular matrix components and direct cell growth and differentiation of neighboring cells by cell-cell and cell-matrix interactions. Lung fibroblast populations are highly heterogeneous.[209] For instance, human lung fibroblasts derived from the airway or alveolar regions differ in their gene expression patterns and their phenotype. *Airway fibroblasts* are morphologically and functionally distinct from alveolar fibroblasts, with differences in contractile forces and in gene expression.[210,211] Genes highly expressed in airway fibroblasts are involved in extracellular matrix deposition and organization, whereas genes highly expressed in alveolar fibroblasts participate in actin binding and cytoskeletal organization. Airway fibroblasts synthesize more collagen and eotaxin-1 than alveolar fibroblasts. Also, airway fibroblasts proliferate faster and are more myofibroblast-like, expressing higher levels of α-smooth muscle actin than alveolar fibroblasts. *Alveolar fibroblasts* play an important role during alveologenesis. During lung alveologenesis, two distinct subpopulations of fibroblasts are located in the growing secondary septa: alveolar myofibroblasts and lipofibroblasts.[212] *Myofibroblasts* are considered to be the cell type responsible for secondary septa formation. These cells are located at the tip of growing secondary septa, where they deposit elastin in the apical tip. Myofibroblasts express α-smooth muscle actin and high levels of platelet-derived growth factor receptor-β and contain myofibrils oriented parallel to the alveolar walls. Myofibroblasts differentiate from different precursor cells in disease, being the principal cell in the fibrotic foci.[213,214] *Lipofibroblasts* are characterized by the presence of lipid droplets and specific molecular markers and are located close to AT2 epithelial cells, which is consistent with lipofibroblast support of growth and differentiation of AT2 cells by providing the lipids for surfactant production. Lipofibroblasts are abundant in the late stages of lung development and postnatally. The expression of lipofibroblast marker genes, such as adipose differentiation-related protein, is reduced in the lungs of individuals with interstitial pulmonary fibrosis.[213,215] However, the existence of lipofibroblasts in human lung is still controversial because some electron microscopy studies have not detected lipofibroblasts in developing human lung.[216,217]

Smooth muscle cells in the lung are of two major subtypes[218,219] that differ in their origin and function. *Airway smooth muscle* cells form circular bands around the airway epithelium (see Figs. 1.7 and 1.10) and extend from the trachea throughout the bronchial tree to the terminal bronchioles. Airway smooth muscle cells derive from undifferentiated mesenchymal cells in closest proximity to prodifferentiation signals released from the lung epithelial layer. Newly differentiated airway smooth muscle cells in the embryonic lung are proliferative, but their proliferative capacity decreases with maturation in the fetal and postnatal stages of lung development. The spontaneous phasic contraction of fetal airway smooth muscle cells is important for normal lung development by regulating intraluminal fluid movement. In the adult lung, this phasic contraction is absent and regulation of tonic contraction and airflow is under neuronal and humoral control. Airway smooth muscle responsiveness contributes to the pathophysiology of lung diseases such as asthma.[220] Airway smooth muscle expresses heavy chain α-smooth muscle actin arranged in contractile filaments, along with other contractile proteins.[221,222] *Vascular smooth muscle cells* play an essential physiologic role in regulation of blood flow through the pulmonary and bronchial vasculature. Smooth muscle forming around these vessels derives partly through proliferation/migration of the neighboring airway smooth muscle cell population and de novo differentiation of mesenchymal cells. Airway and vascular smooth muscle cells have differences in phenotype and gene expression that support their distinct structure and function within the lung.[222]

Pericytes are another mesenchymal cell type located along capillary basement membranes in close contact with the endothelial cells.[208,223,224] Pericytes are contractile, sharing characteristics of vascular smooth muscle cells and myofibroblasts. Lung pericytes might serve as myofibroblast progenitors and amplify inflammatory responses by expressing cytokines and adhesion molecules.[225,226]

Chondrocytes are embedded in a collagenous extracellular matrix rich in proteoglycan and elastin fibers that form the C-shaped cartilaginous rings around bronchi.[227,228]

Mesenchymal cells as a group provide the lungs with the structural support, elasticity, and blood supply necessary for sustaining respiratory movements, oxygenation of the lung tissue, and gas exchange at the capillary level in the alveoli.

NEURAL CELLS

Innervation of the lung is mediated by intrinsic neurons, whose cell bodies reside within the lung, and extrinsic neurons, whose cell bodies are located elsewhere. Intrinsic neurons originate in the neural crest and are located asymmetrically around the trachea and primary bronchi.[229] These intrinsic neurons are located close to innervated tissues, including smooth muscle cells in the trachea, airways, and neuroendocrine cells, and their numbers decrease along the proximal-distal axis of the lung.[229]

Extrinsic neuron axons, when found, resemble known sensory endings in other organs (<1 μm in diameter, electron-lucent, and containing microtubules and smooth endoplasmic reticulum).[230] The terminal processes of sympathetic efferent fibers and parasympathetic efferent fibers pierce the epithelial basement membrane, where they initiate airway reflexes, such as bronchoconstriction and cough.[231,232]

HEMATOPOIETIC AND LYMPHOID CELLS

Resident immune cells, including peribronchial and perivascular interstitial macrophages and alveolar macrophages (see Figs. 1.19 and 1.27), control the immune response during homeostasis and disease. Interstitial macrophages and alveolar macrophages, however, have different functional properties. *Interstitial macrophages* are involved in homeostasis and protection against continuous pathogen exposure from the environment. Interstitial macrophages have a high turnover rate and a short life span in the steady state. Interstitial macrophages have been proved to derive from blood monocytes and serve as intermediates for differentiation into alveolar macrophages in primates and in mice.[233]

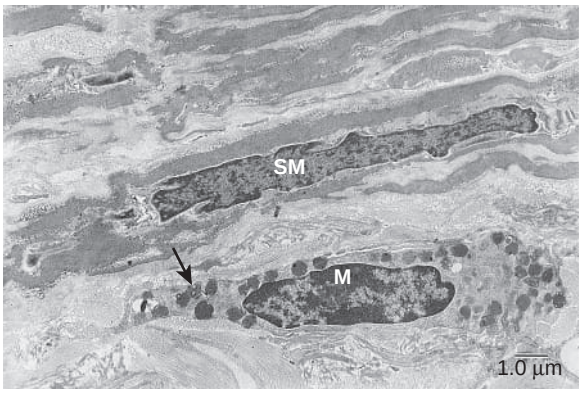

Figure 1.30 Mast cell (M) located adjacent to an airway. The mast cell flanks airway smooth muscle cells (SM). Granules in mast cells demonstrate heterogeneous morphology, including whorled and scrolled contents *(arrow)*. (Human lung surgical specimen, transmission electron microscopy.)

Alveolar macrophages, by comparison, are relatively static under normal conditions, but undergo apoptosis and replacement by interstitial macrophages after exposure to bacterial endotoxin or *Streptococcus* pneumonia.[234,235] Alveolar macrophages actively express and secrete cytokines, such as tumor necrosis factor-α and transforming growth factor-α, and function in surfactant homeostasis and innate immunity.[236] Alveolar macrophages are weak antigen-presenting cells but are active in phagocytosis and production of host defense molecules, such as nitric oxide and cytokines.[237]

Immune response cells, including monocyte-derived macrophages, recruited to the lung during inflammation or infections, migrate through the epithelial basement membrane and pass through to the luminal surface, where some remain intercalated within the surface epithelium. Other immune cells that can be found in the lung, particularly in disease, are mast cells, lymphocytes, eosinophils, neutrophils, basophils, and megakaryocytes.[238] Mast cells in the human lung contain membrane-bound secretory granules (Fig. 1.30) that contain a host of inflammatory mediators, including histamine, proteoglycans, lysosomal enzymes, and metabolites of arachidonic acid.[239] Not only can these mediators induce bronchoconstriction, they can also stimulate mucus production and induce mucosal edema by increasing permeability of bronchial vessels. Lymphocytes are frequently seen intercalated between airway epithelial cells (see Figs. 1.23 and 1.24). These cytotoxic T lymphocytes undergo immunoglobulin A–class antibody responses.[240] T and B lymphocytes also accumulate in the lamina propria beneath the airway epithelium.[240]

The lung is one of the organs in the body in direct contact with the environment. The presence or recruitment of immune cells to the lung is of high importance as a first-line protective mechanism to fight infections, control inflammatory responses, and provide innate immunity.

PLEURAL CELLS

Two types of pleurae exist in the chest: the visceral pleura, which covers the lungs and other chest structures, and the parietal pleura, which is attached to the chest wall.[241] Both visceral and parietal pleurae have a superficial layer of

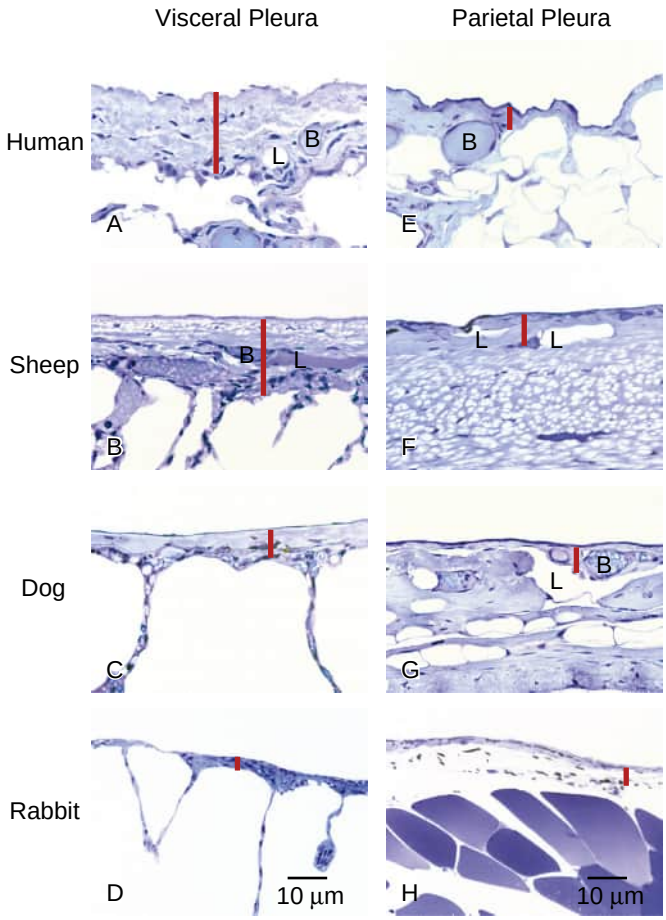

Figure 1.31 Comparative histologic features of the visceral and parietal pleurae among humans, sheep, dogs, and rabbits. The eight panels are shown at the same magnifications. (A–D) Visceral pleura. (E–H) Parietal pleura. The most obvious feature of the visceral pleura is its greater thickness *(longer red vertical bars)* among humans and sheep compared to thinner visceral pleura of dogs and rabbits *(shorter red vertical bars)*. The parietal pleura is thinner and consistently so among species. Both the visceral and parietal pleurae are lined by a single layer of mesothelial cells that have microvilli extending from their surface into the pleural space. Subjacent to the mesothelial cell lining layer is loose areolar connective tissue. Among species with "thick" visceral pleura, the loose areolar connective tissue is traversed by bronchial microvessels (B), lymphatics (L), and nerves. By comparison, among species with "thin" visceral pleura, the loose areolar connective tissue is devoid of microvessels, other than the subjacent pulmonary microvessels at the perimeter of the most superficial alveoli. Lymphatics and nerves are infrequent. In the parietal pleura's loose areolar connective tissue are systemic blood microvessels (B), lymphatics (L), and nerves. This histologic organization is consistent among species. (Human, sheep, dog, and rabbit lung, 2 µm–thick glycol methacrylate sections, light microscopy.)

simple, cuboidal or flattened, mesothelial cells, with various amounts of microvilli on the luminal surface[128,131,132,134] (Fig. 1.31). This mesothelial cell layer is supported by a thin submesothelial connective tissue layer, which includes a basal lamina. Subjacent to this layer is a thin superficial elastic layer, a loose connective tissue layer containing vessels and lymphatics, and a deep fibroelastic layer. Among these layers, thickness of the loose connective tissue layer of the visceral pleura is different across species. For species with thick visceral pleura (human, sheep; see Fig. 1.31), the loose connective tissue layer is much thicker compared to species with thin visceral pleura (dog, rabbit; see Fig. 1.31; rat and mouse; Albertine, unpublished results).

Table 1.4 Comparative Anatomy of Human and Mouse Lungs

Anatomic Feature of the Lung	Human	Mouse
Visceral pleura thickness	25–100 μm	5–20 μm
Visceral pleura arterial supply	Systemic (bronchial)	Pulmonary
Lobes	3 right; 2 left	4 right; 1 left
Airway generations	17–21	13–17
Airway branching pattern	Dichotomous	Monopodial
Main bronchus diameter	≈10–15 mm	≈1 mm
Intrapulmonary airway cartilage	Yes	No
Tracheal epithelium thickness	50–100 μm	11–14 μm
Tracheal club cells	None	≈50%
Tracheal goblet cells	Present	Absent
Tracheal cartilaginous rings	15–20	15–18
Tracheal submucosal glands	Present	Absent
Proximal intrapulmonary airway thickness	40–50 μm	8–17 μm
Proximal intrapulmonary airway club cells	None	≈60%
Proximal intrapulmonary airway goblet cells	Present	Absent
Proximal intrapulmonary airway submucosal glands	Present	Absent
Terminal bronchiole diameter	≈600 μm	≈10 μm
Terminal bronchiole thickness	Not determined	≈8 μm
Terminal bronchiole club cells	≈11%	≈70%
Respiratory bronchioles	Present (≈150,000)	Absent (or 1)
Respiratory bronchiole club cells	≈20%	Absent
Lung parenchyma/total lung volume ratio	≈12%	≈18%
Alveolar diameter	100–200 μm	30–80 μm
Number of alveoli	≈500 million	≈15 million
Alveolar lipofibroblasts	Absent	Present
Blood-air barrier thickness	≈0.68 μm	≈0.32 μm
Pulmonary venule location	Along interlobular septa	Next to bronchioles
Developmental stage at full term	Alveolar	Saccular

Modified from references 154, 155, and 247–249.

The pleural cells provide a smooth tissue surface on the lung and the chest wall. The normal amount of fluid in the pleural cavity facilitates the movement of the lung during breathing.

MOLECULAR ANATOMY OF THE LUNG

Advances in cell isolation and molecular methodologies during the past 3 decades are allowing identification of genes uniquely expressed in the different cell types that form the lung, thus serving as markers to recognize the distinct populations and study their function in health and disease (eTable 1.1). Most markers were first identified in rodents because these models allow genetic manipulation to perform cell lineage tracing to establish lineage and location, as well as cell-specific mutations to study cell-specific function. However, although many markers are common among rodents and humans (see eTable 1.1, uppercase genes), others have been identified only in rodents (see eTable 1.1, lowercase genes) or only in humans (see eTable 1.1, asterisk).

Remarkable technologic advances in the last few years in high-throughput methods for single-cell genomic and transcriptomic analyses and in bioinformatics methodologies have revolutionized the field of lung cell biology. These methods allow studying individual cells within a tissue to classify their cell types, identify new cell types, and characterize variations in their molecular profiles in health and disease.[242] The Human Lung Atlas project[243] is working toward mapping the different structures of the human lung and identifying their cellular and molecular composition. Initial studies show high diversity within each cell population of the lung and emphasize that our knowledge about the number and type of cells that form the human lung in health and disease is incomplete. These single-cell approaches will soon provide a comprehensive cellular composition of the healthy lung[244] and allow dissecting the alterations in cell composition and function associated with the initiation, progression, and resolution of human lung diseases.[245,246]

eTable 1.1 Major Cellular Populations in the Healthy Lung

Structure	Tissue Type	Cell Type	Main Function	Marker Genes (see footnotes)
Bronchi	Epithelium	Ciliated cells (a)	Filtering the inhaled air, mucociliary clearance, ion transport	*FOXJ1, Tubb4,*[260] *Foxa1/a2,*[261] *Sox17, Sox2,*[262] *MUC1, MUC4, MUC16*[263]
		Goblet cells (b)	Mucus production, storage and secretion	*SPDEF,*[264] *MUC5AC, MUC5B, MUC16*[263]
		Basal cells (c)	Stem cell and cell anchor	*ITGA6, NGFR,*[145] *TP63, KRT14,*[265] *KRT5,*[266] *Pdpn,*[267] *LAMB3, LAMC2*[268]
		Serous cells	Secretion of water and antimicrobials	*MUC7*[38]
		Ductal cells	Mucus transport	
		Neuroendocrine cells (single) (d)	Oxygen sensing, chemosensing	*CGRP,*[269] *GRP,*[270] *ASCL1,*[271] *GFI1*[272]
		Ionocyte	Ion transport Chemosensory	*CFTR, FOXI1, V-ATPase*[140,141]
	Mesenchyme (endothelium)	Arterial cells (e)	Blood circulation from heart to lungs	*CD31,*[273] *CDH5,*[274] *EFNB2,*[275,276] *Nrp1, NOTCH 1* and *4, Hey1*[277]
		Venous cells (f)	Return of oxygenated blood to the heart	*CD31,*[273] *Ephb4,*[276] *Nrp2, Nr2f2*
		Lymphatic cells (g)	Fluid maintenance	*CD31,*[273] *Prox1,*[278] *Vegfr3, Lyve1,*[279] *PDPN*[280]
	Mesenchyme (other)	Fibroblasts (h)	Extracellular matrix production Signaling control	*COL1A1, HAS2, ACTA2*[281]
		Smooth muscle cells (i) Airway (ASM) Vascular (VSM)	Contraction-relaxation Air flow control Blood flow control	 ASM = *Gata5, Foxf1, SM-2* and *SM-B*[222] VSM = *LPP, ACTA2, Cnn1, SM-22*[282]
		Chondrocytes	Cartilage production	*Ctrp2, Ctrp3, Sox9*[227,228]
		Neural cells (j)	Reflex control of airway caliber, mucus secretion	*Gfrα3,*[231] *ATP1a3, Vglut1, Vglut2,*[283] *P2RY1, Piezo-2*[284]
Bronchioles	Epithelium	Club cells	Neutralization of inhaled toxins; stem cell	Cyp2f2, SCGB1A1, SCGB3A1, SCGB3A2[285]
		Ciliated cells	See (a) functions	Genes expressed†
		Goblet cells	See (b) functions	Genes expressed†
		Basal cells	See (c) functions	Genes expressed†
		Neuroendocrine cells (clusters)	See (d) functions	Genes expressed†
	Mesenchyme (endothelium)	Arterial cells	See (e) functions	Genes expressed†
		Vein cells	See (f) functions	Genes expressed†
		Lymphatic cells	See (g) functions	Genes expressed†
	Mesenchyme (other)	Fibroblasts	See (h) functions	Genes expressed†
		Smooth muscle cells Airway (ASM) Vascular (VSM)	See (i) functions	Genes expressed†
		Pericytes	Maintain blood vessel wall integrity, control immune response	*PDGFRβ,*[286] *NG2*[208,223]

eTable 1.1 Major Cellular Populations in the Healthy Lung—cont'd

Structure	Tissue Type	Cell Type	Main Function	Marker Genes (see footnotes)
Alveoli	Epithelium	Type 1 cells	Gas exchange	*AGER*,[287] *PDPN*, *AQP5*,[280] *HT1-56**,[288] *Hopx*[289]
		Type 2 cells	Surfactant production and secretion	*HT2-280**,[290] *SFTPC*, *SFTPB*,[291] *ABCA3*,[292] *LAMP3*, *LPCAT1*, *SLC34A2*, *NAPSA*[268,293]
		Progenitor/intermediate cells	Regeneration, homeostasis	*TM4SF1*,[194] *A6-B4 ITGN*,[294] *Sca*, *Sftpc*,[193] *Axin2*[195]
	Mesenchyme (endothelium)	Capillary endothelial cells	Blood flow, gas exchange	*CD31*,[295] *Cdh5*,[274] *CD34*[296]
	Mesenchyme (other)	Fibroblasts Matrix fibroblasts Myofibroblasts (MyF) Lipofibroblasts (LF)	Extracellular matrix production, cell communication MyFs are present in the healthy lung during the postnatal alveolar stage LFs are abundant in the late stages of lung development and postnatally	*PDGFRα*,[208,297] *ACTA2*,[298] *Col1a1*, *NG2*, *VIM*, *DES*, *Pdgfrβ*, *Tbx4*[299] MyF = *ACTA2*, *Eln*, *Col2a1*,[300] *SM-22-α*, *FSP*,[301] *Myh11*[302] LF = *ADRP*,[213] *PPAR-g*,[303] *Fabp1*, *Fabp4*, *Fabp5*, *Lpl*[304]
Pleurae	Mesothelium	Mesothelial cells	Provide a smooth surface for easy sliding of the lung during inhalation and exhalation movements	*DES*, *Cr*,[305] *Wt1*,[306,307] *Msln*[308]
	Submesothelium	Endothelial cells	See (e) functions	Genes expressed[†]
		Fibroblasts	See (h) functions	Genes expressed[†]
		Neural cells	See (j) functions	Genes expressed[†]
Immune	Resident	Interstitial macrophages	Host defense	CD11b, low CD11c[309]
		Alveolar macrophages	Host defense	CD11c, no CD11b[309]

[†]Although the same marker genes are expressed in this cell type in bronchi and bronchioles, or in the pleurae, the cells might not be identical. The heterogeneity of cell types among distinct regions of the lung is being studied by single-cell transcriptomic methods.[243]

Uppercase genes: identified in humans and mice.
Uppercase genes with asterisks: identified only in humans.
Lowercase genes: identified only in mice.

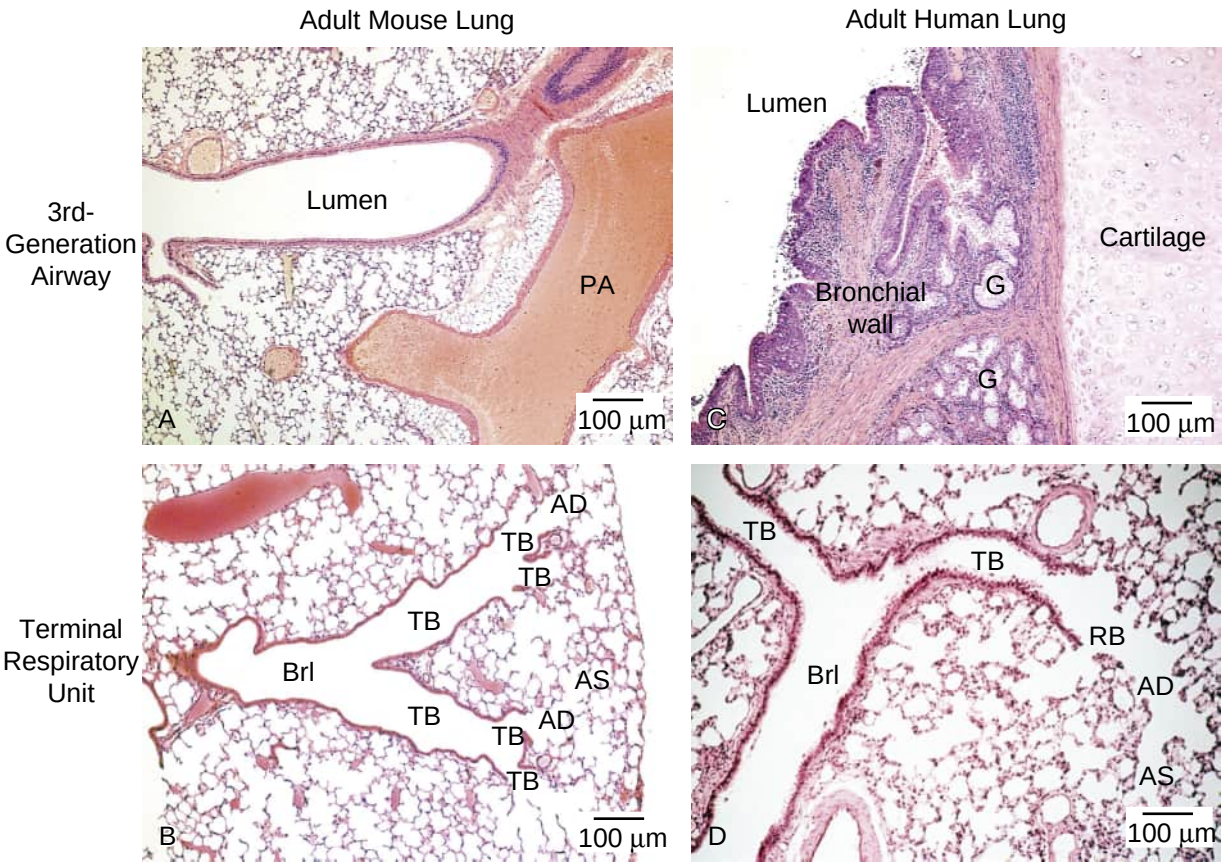

Figure 1.32 Comparison of lung morphology between adult mice *(left column)* and humans *(right column)*. The four panels are the same magnification, as shown by the scale bar in each panel. The upper row compares third-generation, intrapulmonary airways between mouse (A) and human (C). The mouse's airway lumen is narrower than the same generation airway (bronchus) in the human. Absent from the wall of the mouse's airway wall are cartilage and submucosal glands (G), both of which are obvious in the wall of the bronchus of the human airway. The lower row compares terminal respiratory units between mouse (B) and human (D). The mouse's terminal respiratory units do not have respiratory bronchioles; therefore terminal bronchioles (TB) open directly into alveolar ducts (AD). By comparison, the human's terminal respiratory units have respiratory bronchioles, which open into ADs. AS, air space; Brl, bronchiole; PA, pulmonary artery. (Mouse and human lung tissue, 5 µm–thick paraffin-embedded sections, light microscopy.)

COMPARISON OF THE LUNG OF HUMANS AND MICE

A point made in the previous section is that species variations are significant in the visceral pleural structure (see Fig. 1.31) and the blood supply to the lung. This point raises the question of what other species variations are found in the lung. For the purpose of this chapter, comparison is made between human and mouse, owing to the fantastic discoveries about genetic and molecular regulation of lung biology by making mouse constructs to identify normal lung structure and function, as well as to study the impact of disease on lung structure and function. For this discussion, the lung will be divided into the conducting airways (bronchi through terminal bronchioles), which do not participate in respiratory gas exchange, and the lung parenchyma (respiratory bronchioles, alveolar ducts, and alveoli), which do participate in respiratory gas exchange.

Key structural features of human and mouse pulmonary morphology are summarized in Table 1.4.[247–249] This table reveals that many anatomic and developmental differences are present in both the conducting airways and lung parenchyma of the human and mouse lower respiratory systems. Although the general anatomic organization of the human and mouse lower respiratory system is largely similar, important differences also exist, at both the gross anatomy level and in the cellular composition of the lower respiratory system.

Human and mouse lungs have different lobe structures. The human lung has five lobes, with the right lung divided into three lobes by the oblique and horizontal interlobar fissures, whereas the left lung is divided into two lobes by the oblique fissure. The lobe structure of the mouse lung is markedly different, with the right lung divided into four lobes and the left lung consisting of a single lobe. The upper airways in the human lung include the trachea and bronchi, whereas the upper airway in the mouse lung is the trachea alone.[250] In the human lung, airway branching is dichotomous, where the parent airway divides at an approximately 45-degree angle into two daughter segments, generating 17 to 21 generations of branches between the trachea and the lung parenchyma, at which point terminal bronchioles transition into up to three generations of respiratory bronchioles, which are part of the lung parenchyma in humans. In contrast, branching in the mouse lung is monopodial (asynchronous), yielding 13 to 17 generations of airways, with a single axial airway (the central bronchiole) running the entire length of its associated lobe, with lateral branches

forming irregularly along the length of the central bronchiole. The lateral branches (lateral bronchioles) bifurcate repeatedly before terminating into short terminal bronchioles that abruptly give rise to alveolar ducts at the bronchoalveolar duct junctions, which are part of the lung parenchyma in mice. Furthermore, in contrast to the human lung, the walls of intrapulmonary conducting airways in mice do not have cartilage, which may impact the distribution of airway resistance compared to the human lung (Fig. 1.32). A potential impact of the fewer airway generations, as well as narrower conducting airways, in the mouse lung is that the deposition of inhaled particulates may have a different distribution in the lungs of mice compared to those of humans. Also, because the mouse lung has fewer airway generations, the parenchyma makes up a larger proportion of total lung volume (≈18%) compared to humans (≈12%). Furthermore, the different lobar structure of the mouse lung has implications for studies on compensatory lung regrowth after unilateral pneumonectomy. For example, left pneumonectomy in mice allows prominent expansion of the right lung, predominantly of the cardiac (often called the accessory) lobe. Thus, the lobar structure of the mouse lungs facilitates studies on lung regeneration, which may be more difficult in lungs from species with a different lobar structure.

The lung parenchyma of human and mouse lungs also has important differences. In the human lung, the terminal bronchioles transition into respiratory bronchioles, of which the human lung has about 150,000 (see Fig. 1.32). These respiratory bronchioles transition into as many as 11 alveolar ducts, which then subsequently transition into up to six alveolar sacs, which are lined by, in total, approximately 500 million alveoli in the adult human lung.[251] In contrast, in the mouse lung, respiratory bronchioles are essentially absent, and the lung parenchyma encompasses exclusively alveolar ducts and alveoli, with the approximately 15 million alveoli in the adult mouse lung constituting the terminus of the lung parenchyma.[252] Thus, the mouse lung has fewer airway generations than the human lung. In both human and mouse lungs, adjacent alveoli are physically connected through pores of Kohn, which facilitate the maintenance of similar pressures across the alveoli by allowing collateral ventilation. Although these pores are similar in human and mouse lungs, the number of pores increase with age in human lungs, whereas in the mouse the number of pores does not change with age.[253,254]

The cellular structure of human and mouse lungs also has marked contrasts. In the conducting airways, the inner surface of both the human and the mouse trachea is lined by a pseudostratified columnar epithelial layer. In humans, the bulk of the cells lining the trachea are ciliated cells, including columnar, basal, and goblet cells; whereas the mouse trachea is lined largely with nonciliated cells. Indeed, in the upper airways of the human lung, the principal secretory cells are goblet cells (see Fig. 1.32), whereas, in the upper airways of the mouse lung, the principal secretory epithelial cells are club cells. Club cells in the human lung are found in the terminal airways. In addition, in the upper airways of the human lung, additional secretory cells are mucous and serous epithelial cells in submucosal glands, which extend along the trachea and bronchi, whereas in the mouse lung, submucosal glands are limited to the proximal aspect of the trachea. Thus, different cell types contribute to airway secretions, and hence airway defense in the two species. Likewise, the distribution of BALT is different between the two species. In the human lung, BALT is located along bronchi. In the mouse lung, BALT is limited to bronchioles.[255]

Differences in the cellular composition of human *versus* mouse lungs have also been noted in the lung parenchyma, taking the example of the lipofibroblast, a lipid-laden fibroblast subset that has been credited with a key role in lung development and repair. To date, lipofibroblasts remain elusive in human lungs. Lipofibroblasts are present in abundance in mouse lungs.[217] The cellular composition of the conducting vessels of the pulmonary circulation in human *versus* mouse lungs also exhibits differences, notably, cardiomyocytes. In humans, cardiomyocytes are not typically detected in intrapulmonary veins in healthy individuals.[256] Cardiomyocytes are present as part of the pulmonary vein structure in mice, extending along the pulmonary vein beyond the hilum, and surrounding individual intrapulmonary veins, even those of small (<100 μm) diameter. Their presence may lead to misidentification of intrapulmonary veins in mice as intrapulmonary arteries, if the cardiomyocyte layer, which may be substantial, is mistaken for vascular smooth muscle. These differences in cellular composition present some challenges for the extrapolation of experimental studies in mice to human pulmonary physiology. For example, the critical role ascribed to lipofibroblasts during distal lung development cannot be generalized to all mammalian lung development if lipofibroblasts are not present in human lungs.

The lung's developmental stage at full term is different between humans and mice. In humans, lung development at full term is at the beginning of the alveolar stage. In mice, lung development at full term is the saccular stage. This timing difference is helpful to keep in mind when developmental comparisons are made and is particularly relevant to studies addressing lung maturation in preterm-born infants; preterm infants born between the 27th and 36th week of gestational age and mouse pups are both delivered in the saccular stage of lung development. Despite being born at a comparatively earlier stage in terms of lung development, term-born mouse pups in the saccular stage of lung development are fully competent for gas exchange, whereas preterm-born infants in the same stage of lung development may require respiratory and supplemental O_2 support due to a limited capacity for gas exchange. This phenomenon highlights important developmental differences between humans and mice during late lung maturation.[257]

Differences in the structure and cellular composition of lungs are not only evident between species but also between strains of the same species. For example, the apparent size of the alveolar unit in the C3H/He mouse strains is appreciably larger than in four other mouse strains—C57BL/6, BALB/c, FVB/N, and DBA/2—by visual inspection of lung sections, a phenomenon confirmed by the determination of the mean linear intercept,

a very rough surrogate for the distance between adjacent alveolar walls.[258,259] This is important in experimental studies that assess the impact of an intervention (such as genetic interference) on alveolar development or alveolar structure, because mice on a complete or partial C3H/He strain background will have intrinsic differences in the dimensions of their alveoli compared with other mouse strains.

Key Points

- The primary function of the lung is gas exchange, achieved by ventilation-perfusion matching between alveolar air and alveolar capillary blood.
- The anatomic arrangements of the pulmonary arteries beside the airways are a reminder that the relationship between perfusion and ventilation determines the efficiency of normal lung function.
- The major obstacle for gas exchange is the slow rate of oxygen diffusion through water. Thus, the alveolar walls must be extremely thin. Because of that thinness, the thickness of the red blood cell forms a substantial portion of the air-blood diffusion pathway.
- The airways form the connection between the outside world and the terminal respiratory units.
- Smooth muscle cells form circular bands around the airway epithelium as far peripherally as the respiratory bronchioles. Tone in the smooth muscle is altered by the autonomic nervous system and by mediators released from mast cells, inflammatory cells, and neuroendocrine cells.
- Normally, capillary blood volume is equal to or greater than stroke volume and, under normal resting conditions, the volume of blood in the pulmonary capillaries is well below its maximal capacity. Recruitment can increase capillary blood volume threefold.
- The alveolar type 2 cell is the major synthesizing and secreting factory of the alveolar epithelium and implements epithelial repair via its ability to proliferate.
- The terminal respiratory unit consists of all the alveolar ducts together with their accompanying alveoli that stem from the most proximal (first) respiratory bronchiole, and contains approximately 100 alveolar ducts and 2000 alveoli. The functional definition of the terminal respiratory unit is that, because gas phase diffusion is so rapid, the partial pressures of oxygen and carbon dioxide are uniform throughout the unit.
- Genes uniquely expressed in the different cell types that form the lung are serving as markers to recognize the distinct populations and study their function in health and disease.
- Although mouse and human lung share many common characteristics, there are a number of differences in structure, cell composition, and development that need to be considered when using mouse models to study human lung function and structure.

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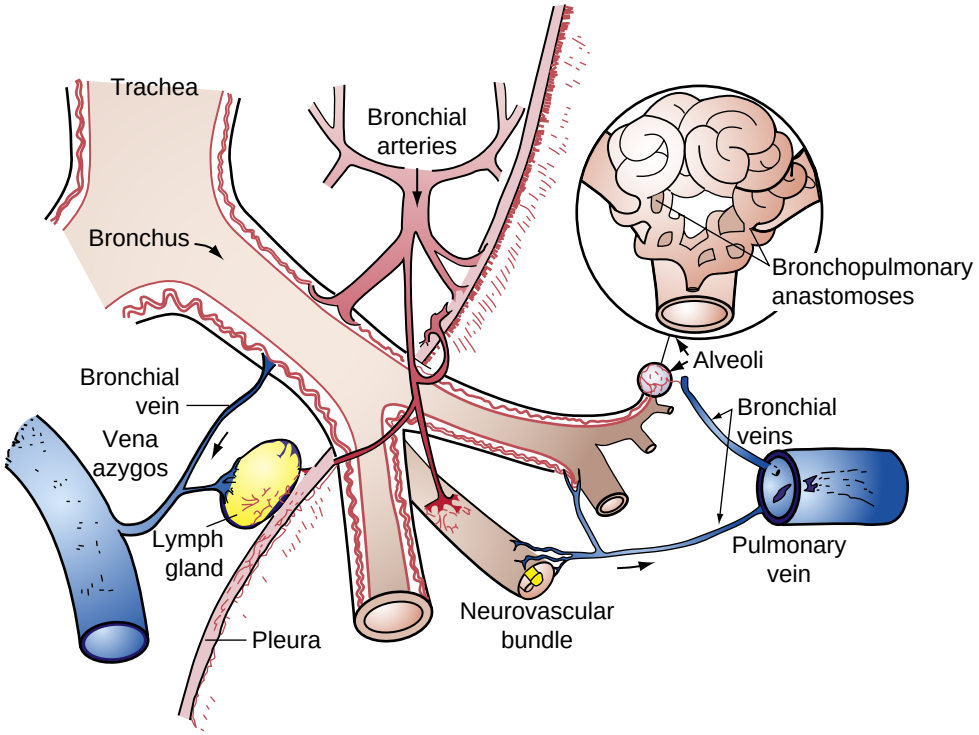
Complete reference list available at ExpertConsult.com.



Acknowledgments

This is my (K.H.A.) final penning of Chapter 1 in *Murray and Nadel's Textbook of Respiratory Medicine*. I am honored to have coauthored the first edition's chapter with my postdoctoral fellowship mentor, Norman C. Staub at the Cardiovascular Research Institute at the University of California, San Francisco (1980–82) and continued uninterrupted as chapter author through this, the seventh edition. A priceless lesson from Norman was always to relate structure to function. I applied this lesson through the seven editions of Chapter 1. I extend special thanks to Jay Nadel and John F. Murray, both of whom served as mentors and coaches while I was a postdoctoral fellow and continuously through my academic career, now spanning 40 years since I started my postdoctoral fellowship. I also say special thanks to V. Courtney Broaddus, who started her clinical fellowship midway into my fellowship in Norman's laboratory. Courtney's focus on the pleura and pleural disease pushed me to complete comparative structural analysis of the pleurae. Finally, appreciation is extended to Dr. Kenneth "Bo" Foreman, Professor of Physical Therapy, College of Health, University of Utah, for videography expertise to create the online supplemental digital videos of lung movements. Portions of this work were supported by grants to K.H.A. from the National Institutes of Health (HL038075, S10-RR004910, S10-RR010489, HL049098, SCOR Grant HL050153, HL062875, and HL110002).

eFIGURE IMAGE GALLERY



eFigure 1.1 Schematic illustration of the components of the bronchial circulation. Flow from capillary beds supplying large airways and lymph glands drains to bronchial veins and into the azygos vein and superior vena cava. Intrapulmonary flow drains into the pulmonary circulation at the level of the alveoli (bronchopulmonary anastomoses) or pulmonary veins (bronchopulmonary veins). (From Deffebach ME, Charan NB, Lakshminarayan S, Butler J. The bronchial circulation. *Am Rev Respir Dis.* 1987;135:463–481.)

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2 LUNG GROWTH AND DEVELOPMENT

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INTRODUCTION

The human lungs, serving as the primary respiratory organ, have an estimated surface area of approximately 130 m.[1,2] The gas-exchange function is carried out by approximately 480 million respiratory units called alveoli.[2] Gas is transported to and from alveoli through an elaborate branched network of conducting airways. Forming in parallel is a network of blood vessels, the pulmonary vasculature, which carries deoxygenated blood to the lungs and oxygenated blood from the lungs, a partnership opposite to other tissues in the body. Because gas exchange is required immediately after birth, developmental patterns leading to a functional lung are key to survival at first breath.

Defects in lung development not only cause mortality and morbidity in the neonatal and pediatric period, they often lead to respiratory deficiency later in life. For example, *bronchopulmonary dysplasia* (BPD), a common consequence of preterm birth, results in poor gas exchange in infancy. This deficiency in respiratory function frequently persists into adulthood and is complicated by increased susceptibility to respiratory infections.[3] It is well established that reduced lung capacity due to abnormalities in early lung growth can lead to premature decline of respiratory function during aging or in chronic conditions such as COPD.[4] Thus understanding and supporting a healthy course of lung development will have long-term benefits.

Human lung development is visible starting at approximately 4 *postconceptual weeks* (PCW 4) of gestation with the appearance of the trachea and paired lung buds. This is followed by an elaborate program of branching morphogenesis. The formation of conducting airways is completed well before birth. In comparison, the gas-exchange regions of the lungs, composed of alveoli, begin to develop relatively late in gestation. It is estimated that 95% of the surface area is added after birth. Although the conventional view suggests that elaboration of gas-exchange surface area is complete by 6 to 7 years of age, a more recent study shows that addition of new alveoli continues into the 20s in humans.[5]

Based on classical morphologic categorization, there are more than 40 resident cell types in a mature lung.[6] An even greater number of cell types is becoming evident from the use of newer technologies, including single-cell RNA sequencing.[7–9] During development, the epithelial cells arise from the endoderm, whereas the mesenchymal or endothelial cells arise from the mesoderm. Lung epithelial cells can be broadly categorized into airway versus alveolar. In the airway epithelium, goblet and club cells are secretory, whereas ciliated cells sport motile cilia that clear inhaled particles and pathogens. Rare airway cells, including pulmonary neuroendocrine cells, ionocytes, and tuft cells, have also been investigated.[10–12] These luminal cells are underlined by basal cells that serve as progenitors and can replace damaged luminal cells after airway injury. Invaginating from the surface airway, submucosal glands are a prevalent and regular feature in the human lung. These glands are lined by serous cells and goblet cells, with myoepithelial cells in the basal layer. In the alveolar epithelium, *alveolar type 2* (AT2) cells produce surfactant and can give rise to *alveolar type 1* (AT1) cells that cover approximately 95% of the surface area and serve as both a barrier and interface for gas exchange. Airway epithelial cells begin to differentiate at midgestation, whereas alveolar epithelial cells begin to differentiate near the end of gestation, in time to support lung expansion and gas exchange at birth.

The lung epithelium is underlined by lung mesenchyme and endothelium. Although both are derived from the mesoderm, the mesenchymal and endothelial lineages become distinct from each other early in lung development. Pulmonary endothelial cells give rise to three distinct vascular networks.

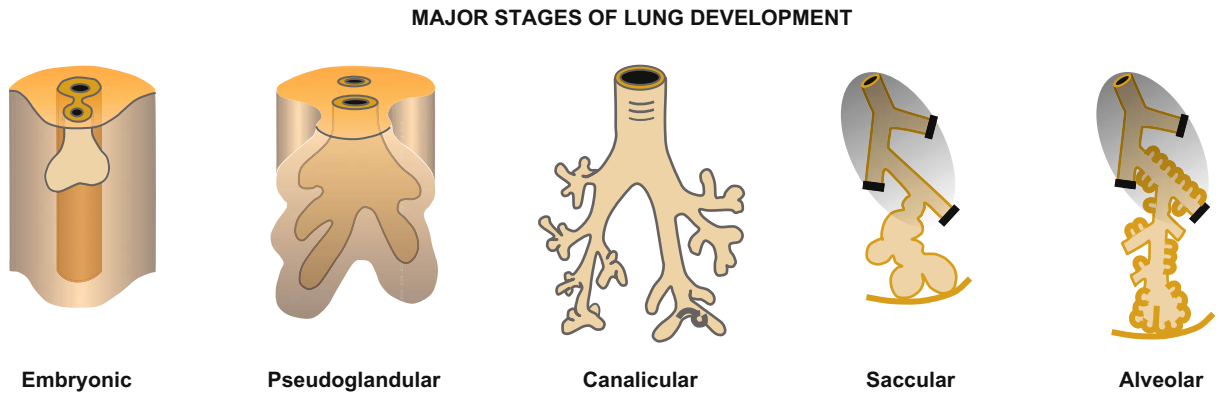

Figure 2.1 Diagrams of key features of the lung at progressive developmental stages, from the embryonic, pseudoglandular, canalicular, saccular, to alveolar stages. See text for stages and details of these events of lung development. (Modified from Swarr DT, Wert SE, Whitsett JA. Molecular determinants of lung morphogenesis. In Wilmott RW, Deterding R, Li A, et al, editors. *Kendig's Disorders of the Respiratory Tract in Children*, ed 9. Philadelphia: Elsevier; 2019.)

The pulmonary vascular network brings deoxygenated blood, via the pulmonary artery, into the lungs for gas exchange before returning oxygenated blood to the heart via the pulmonary veins. In parallel, the bronchial vasculature brings oxygenated blood from the systemic circulation to sustain the survival of lung cell types. Complementing these blood vascular networks, the lymphatic vascular network maintains fluid homeostasis in the lungs and serves as a conduit for antigens and antigen-presenting cells.[13,14] Compared to the epithelium and endothelium, the distinction among lung mesenchymal cell types is more poorly defined. Nevertheless, it is generally agreed that the human lung mesenchyme contains airway smooth muscle, vascular smooth muscle, myofibroblasts, matrix fibroblasts, pericytes, and chondrocytes.

Much of the current knowledge of cellular and molecular control of lung development is gained from animal studies. Among all animal models, mouse models are the most frequently used. Mouse lung development follows a progression that shares many of the same cellular and molecular characteristics as human lung development. With access to tissues with defined genetic backgrounds at any desired stage, the process of mouse lung development has been extensively characterized. Using sophisticated genetic tools in mice, gene networks that control lung development have been elucidated, and progenitor-progeny relationships have been defined in vivo. Furthermore, with CRISPR/Cas9-based genome editing, patient-specific mutations have been engineered into homologous mouse genes, providing patient-specific platforms to study disease etiology and test therapy. Despite the enormous contribution of mouse models to lung development, it should be noted that there are key distinctions between the mouse lung and the human lung, including their size, airway cell type composition, and physiology (reviewed in Chapter 1).[2,15,16] Validation in human cell–based settings is essential and will become more mainstream as new technologies, such as induced pluripotent stem cell–derived lung cell differentiation and single-cell sequencing, are implemented.

In addition to premature birth leading to lung diseases such as BPD, disruptions of lung development can be caused by genetic mutations, early respiratory infections, or exposure to toxic agents, such as pollutants, cigarette smoke, and e-cigarette vapor. With increasing understanding of the normal process of lung growth and development, more avenues are opened for early prevention, treatment, and reversal of developmental defects responsible for pediatric and adult respiratory conditions.

STAGES OF LUNG DEVELOPMENT WITH CELLULAR AND MOLECULAR MECHANISMS

Mammalian lung development can be broadly divided into two major sets of processes: budding and branching morphogenesis responsible for generating the conducting airways, and septation and alveologenesis responsible for generating the surface area in the distal lung for gas exchange.[17] The morphologic changes of lung development have classically been subdivided into five stages: embryonic, pseudoglandular, canalicular, saccular, and alveolar (Fig. 2.1). Although each stage is defined by a distinct period of time, the cellular and molecular processes that direct lung development transition smoothly from one stage to the next.

EMBRYONIC STAGE

The embryonic stage of lung development takes place between PCW 4 and 7 in humans and between embryonic day 8.5 and 11.5 (E8.5–11.5) in mice (Fig. 2.2A–B).[17] At the beginning of this stage, a small number of endoderm-derived ventral foregut epithelial cells become specified to take on the respiratory fate, as demonstrated by their expression of *Nkx2-1*, the earliest known marker of the respiratory epithelium.[18,19] After specification of these respiratory progenitor cells, the first morphologic change is budding of the posterior portion of the nascent respiratory primordium into the surrounding mesenchyme to generate the left and right lung buds.[20] Concurrent with budding, the common foregut tube, anterior to the lung buds, divides into the trachea ventrally and the esophagus dorsally. At the time of budding, the left-right asymmetry of the lung buds is already specified, as part of left-right determination of all visceral organs. After establishment of the respiratory primordium, the lung buds rapidly elongate into the surrounding mesenchyme and initiate branching morphogenesis as they transition into the pseudoglandular stage.

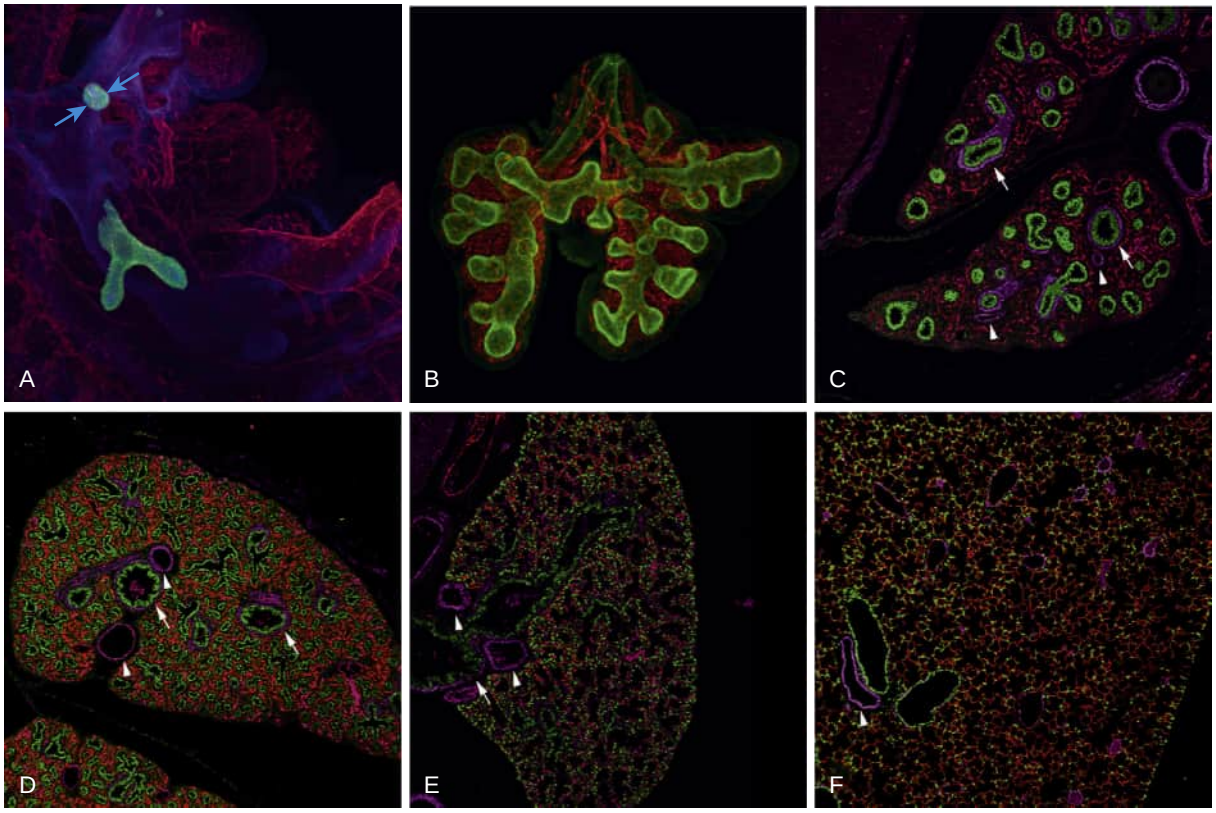

Figure 2.2 Morphology of the stages of lung development. Mouse lungs from the indicated developmental stages were stained with an antibody against Nkx2-1 to identify epithelial cells in the respiratory lineage *(green),* an antibody against endomucin to identify vascular cells *(red),* and an antibody against α-smooth muscle actin to identify smooth muscle cells *(magenta).* An antibody against E-cadherin identifies the foregut endodermal epithelium *(blue).* (A) Lung buds originate as a pair of outpocketings from the ventral foregut endoderm on day E9.5 in the mouse; the lung endoderm stains positive for Nkx2-1, as does the primitive thyroid rudiment *(double arrow).* (B) During the embryonic stage, dichotomous and lateral branching of the lung epithelium continues. Vascular precursors are already present and form a plexus surrounding the epithelium. (C) During the pseudoglandular stage, the lung primarily consists of epithelial tubules surrounded by a relatively thick mesenchyme. Proximal epithelial cells show tall columnar morphologic characteristics, whereas more distal epithelial cells are cuboidal. The vasculature branches in parallel with the epithelium, and smooth muscle cells surrounding airways (*white arrows* in all panels) and vessels *(white arrowheads* in all panels) are evident. (D) During the canalicular stage, epithelial acini appear, and the vasculature becomes more abundant and closely apposed to the epithelium. (E) During the saccular stage, alveolar type 1 cell differentiation increases air space size. The vasculature has continued to expand, fully investing the lung parenchyma. Fusion of the epithelial and endothelial basal laminae brings alveolar type 1 cells and capillaries into close association. (F) During the alveolar stage, the formation, lengthening, and thinning of secondary septa markedly increase the epithelial surface area. All images of sectioned lungs (C–F) are at the same magnification. *Arrows,* airways; *arrowheads,* vessels; *green,* respiratory lineage; *red,* vascular; *magenta,* smooth muscle. (Confocal images generated by Jamie Havrilak, Graduate Program in Molecular and Developmental Biology, Cincinnati Children's Hospital Medical Center.)

All lung lobes are enclosed in pleura, also termed mesothelium, a thin layer of squamous epithelial cells that provide protection and lubrication to allow sliding of lung lobes against the chest wall.[21] By 3 weeks of gestational age, the pleural, pericardial, and peritoneal spaces begin to form from the mesoderm. By 9 weeks, the pleural cavity has become separated from both the pericardial and peritoneal spaces. After lung specification, the lung buds invaginate into the visceral mesoderm, which is covered by pleura. Thus the lungs retain a pleural covering starting at budding.

Findings from mouse models indicate that the site of lung initiation is specified by signaling molecules, including *wingless types* (WNTs). *Wnt2* and *Wnt2b*, two canonical Wnt pathway genes, are both required for lung specification.[18] They act through β-catenin, a downstream nuclear effector, to maintain the expression of *Nkx2-1*, the earliest known marker of respiratory fate.[18,19] In mice, inactivation of Wnts or β-catenin leads to complete failure of trachea and lung development.[18,19] After specification of respiratory progenitor cells, *fibroblast growth factor 10* (FGF10) signaling is essential for lung budding. Inactivation of *Fgf10* leads to lung agenesis, while development of the trachea is maintained.[22,23] Furthermore, retinoic acid signaling has been shown to control budding via regulation of WNT, *transforming growth factor-β* (TGF-β), and FGF10 signaling.[24] In humans, mutations in the WNT pathway gene *RSPO2*, the retinoic acid downstream gene *STRA6*, the FGF pathway gene *FGF10*, and the transcription factor gene *TBX4* have all been tied to lung agenesis or severe hypoplasia.[25–27]

PSEUDOGLANDULAR STAGE

The pseudoglandular stage of lung development takes place during PCW 5 to 17 in humans and E11.5 to E15.5 in mice (see Fig. 2.2C).[17] The primary cellular event in this stage is branching morphogenesis.[28] After lung bud elongation, the epithelial tubules and tips initiate branching with the support and guidance of the mesenchyme. Mapping of lung branching has revealed a largely stereotypic program

composed of three subroutines: domain branching, where side branches emerge from bronchi in proximal-to-distal sequence with regular spacing; planar bifurcation, where distal tips engage in repeated rounds of bifurcation in the same two-dimensional plane; and orthogonal bifurcation, where distal tips bifurcate and then bifurcate again in a plane 90 degrees to the former.[29] In mice, these three subroutines are programmed in a stereotypic sequence, suggesting that they are tightly controlled by genetic circuits.[29,30] In humans, this process is believed to be more variable.[31] Regardless, by the end of the pseudoglandular stage, the majority of proximal airways are formed, and the distal tips are poised to form gas-exchange units in the following stages.

Based on mouse mutants that exhibit lung branching defects and aided by mathematical and computational modeling, the genetic circuits that control branching morphogenesis are beginning to be elucidated.[32] Elegant studies have demonstrated that the mesenchyme provides instructive cues to the airway epithelium to direct the branching pattern.[33] Key among these signals is again *Fgf10*, which is expressed in the lung mesenchyme and concentrated at future sites toward where the epithelial tips grow.[34] FGF10 acts to promote regional proliferation and chemotaxis of the distal tip epithelium toward the signaling source.[35] Bypassing its requirement for earlier budding, conditional inactivation of *Fgf10* in mice during the pseudoglandular stage disrupts branching morphogenesis.[36,37] These data support the notion that the site-specific expression of *Fgf10* establishes the subsequent branching pattern. However, a more recent study showed that lungs with indiscriminate overexpression of *Fgf10* in the mesenchyme still underwent branching morphogenesis. These data suggest that other regulators, including heparin sulfate proteoglycans, may coordinate with FGF activity to coordinate branching.[38]

Multiple models suggest that reciprocal interactions between the mesenchyme and epithelium are required for branching morphogenesis. FGF10 cooperates with other signaling factors in feedback regulatory loops across the epithelium/mesenchyme boundary. For example, FGF10 from the mesenchyme acts through FGF receptor 2 and downstream transcription factors ETV4/5 in the epithelium to promote the expression of sonic hedgehog *(Shh)*.[39] SHH in turn signals to the mesenchyme to inhibit the expression of *Fgf10*. Evidence from genetic, pharmacologic, and mathematical modeling suggests that this feedback regulation may contribute to the repeated bifurcation program.[36,37,39–41]

Concurrent with branching morphogenesis, the overall pattern of the lungs, namely proximal airway versus distal alveolar region, becomes established in the pseudoglandular stage. During this stage, distal tips continue to elongate while undergoing repetitive branching to form the future airways. Molecularly, this distinction between the airways and future air spaces for gas exchange is marked by proximal expression of *Sox2* and distal expression of *Sox9*, two transcription factor genes.[37,42] In mice, *Sox2* and *Sox9* domains are distinct starting from early branching morphogenesis. However, in human lungs, *SOX2* continues to be expressed distally, overlapping with *SOX9* until approximately 20 weeks of gestation, when the *SOX2* expression becomes more restricted to the proximal airway domain.[43–45]

At the end of branching morphogenesis, airway epithelial cells begin to differentiate. Pulmonary neuroendocrine cells, a rare airway cell type with sensory function, are the first cells known to differentiate in the airway epithelium.[46–48] This is followed by basal cells that serve as a prominent source of airway progenitor cells required for airway epithelial cell regeneration in the adult.[49] Concurrently, the adjacent mesenchymal cells differentiate into cartilage and smooth muscle. Elaboration of the pulmonary vascular network continues in parallel to the airway with an increasing number of vessel branches leading into the elaborate capillary network.

CANALICULAR STAGE

The canalicular stage of lung development takes place between PCW 16 and 26 in humans and E15.5 and E16.5 in mice (see Fig. 2.2D).[17] During this stage, there is a transition from the genetic program that directs branching morphogenesis to the program that directs septation of the distal air spaces in preparation for gas exchange. Although the majority of branching morphogenesis happens during the pseudoglandular stage, the distal epithelium undergoes three final rounds of branching during the canalicular stage.[28] In distal tips, canalization of the parenchyma happens as the respiratory air spaces increase in length and width and the capillaries grow in size and complexity.[17] Thinning of the mesenchyme allows a close juxtaposition of the alveolar epithelium and capillaries, establishing the alveolar-blood interface essential for gas exchange. The epithelial cells in the distal lung also begin to differentiate into AT1 and AT2 cells. Production of surfactant by AT2 cells is first detected between PCW 22 and 24.[50] Surfactant production is a key developmental milestone that impacts the survival of premature infants and can be enhanced in utero by the administration of steroids.

SACCULAR STAGE

The saccular stage of lung development happens between PCW 24 and 38 in humans and E16.5 and postnatal day 3 (P3) in mice (see Fig. 2.2E).[17] By this stage, branching morphogenesis is complete and the airways are laid out. During the saccular stage, the major morphologic changes take place in the terminal air spaces that continue to increase in volume, resulting in further compression and thinning of the adjacent mesenchyme.[17] The primary septa that separate the air spaces are covered by an alveolar barrier composed of AT1 cells with interspersed AT2 cells. The alveolar epithelial barrier is underlined by a basket of capillaries. In the thin walls are also fibroblasts and extracellular matrix, which are positioned to support but not to interfere with gas exchange across the epithelium-capillary juxtaposition. During this stage, AT2 cells increase their production of surfactant stored in lamellar bodies.

The timing of sacculation coincides with an increase of amniotic fluid in the fetus that peaks at approximately PCW 34. Experimental evidence in mice suggests that mechanical pressure from the increasing amniotic fluid plays a role in alveolar epithelial cell differentiation during sacculation.[51] Both AT1 and AT2 cells arise from the columnar

distal tip epithelial cells and are present in a near 1:1 ratio by birth. Reduction of amniotic fluid volume in mice led to a decrease in the AT1:AT2 ratio, whereas an increase in the amniotic fluid led to an increase in the AT1:AT2 ratio.[51] These findings suggest that the volume of amniotic fluid and the pressure it exerts on the developing respiratory air space epithelium plays an important role in the differentiation and balance of AT1 and AT2 cell fate. These findings raised the possibility that a similar mechanism may be at play in AT1/AT2 differentiation in humans.

Relatively little is known of the specific genetic control of sacculation due to the paucity of genes specifically required for this process and the lack of genetic tools to target this stage. It is possible that many of the same signaling pathways involved in earlier stages of lung development, such as FGF, *bone morphogenetic protein* (BMP), WNT, SHH, and WNT pathways also function in sacculation. If so, it will be interesting to determine how the same signaling pathway can execute distinct cell morphogenesis programs, such as those that direct branching versus sacculation. Immune regulators, such as nuclear factor kappa B, play a role in the proliferation and thinning of the epithelium and mesenchyme.[52] Hippo signaling, in particular its downstream effector Yap, is central to mechanical force-induced gene expression and cell fate changes.[53–56]

ALVEOLAR STAGE

The final stage of lung development, the alveolar stage, happens between PCW 36 and young adulthood in humans and between P3 and P39 in mice[17,57] (see Fig. 2.2F). The primary goal of alveologenesis (also termed alveolarization) is to expand the surface area for gas exchange. The exact age at which alveologenesis, and thereby lung maturation, ends in humans is debated. As mentioned, although the conventional view suggests that alveologenesis is complete by 6 to 7 years of age, advanced imaging experiments indicate that new septa continue to be added in lungs of early 20-year-olds.[5] Because lung development continues postnatally, exposure of young lung to pollution, secondary smoke, and e-cigarette vapor not only damages existing alveoli but also truncates the program to form new alveoli. This explains why early exposure to toxic aerosols leads to more profound damage than does late exposure, leading to predisposition of adult-onset diseases, such as COPD.

At the beginning of the alveolar stage, each alveolus is a simple balloon-shaped gas-exchange unit extending from an alveolar duct and separated from each other by primary septa. The primary septa remain relatively thick and contain a double-layered capillary network capable of gas exchange, albeit not optimized for efficiency. During alveologenesis, new septa rise from the alveolar wall into the lumen. Each nascent septum is a delicate new gas-exchange surface, with flat AT1 cells and interspersed AT2 cells, overlying a dense capillary network. As mentioned, in humans, an estimated 95% of the final alveolar surface area is constructed by alveologenesis after birth.

The mechanisms that direct alveologenesis are poorly understood. Multiple lines of evidence suggest that smooth muscle actin-positive myofibroblasts are required for septum formation; however, their precise role is debated.[58–60] Conventional studies of alveologenesis relied on two-dimensional sections and depict nascent septa as finger-like protrusions into the lumen, with myofibroblasts frequently found at the tips.[61] These observations led to the hypotheses that septa arise from either repulsion of the myofibroblasts from the alveolar wall into the lumen or growth of the septa along a signaling gradient with FGF at the tip and retinoic acid at the base.[61,62] More recent experiments using confocal microscopy and three-dimensional reconstructions of the alveoli have led to a different view. Instead of the finger-like protrusions, a nascent septum forms a ridge that arises from the walls of the alveolus.[63] Instead of a single point at the tip of a finger-like protrusion, each smooth muscle actin-positive myofibroblast is instead a long, stringlike cell that interconnects with other myofibroblasts, forming a network. This fishnet-like pattern was first described in 1970 by Dr. Embry after analysis of human alveoli.[64] Rather than repulsion or growth to form new septa, the myofibroblasts may guide contraction of this fishnet-like network to form novel septa (Fig. 2.3).[63] Myofibroblasts also produce elastin and elastin cross-linking enzymes to generate the extracellular matrix essential for formation of the septa. In addition to myofibroblasts, other cells within the septa, including alveolar endothelial cells, are required for the formation of this structure. Inactivation of *Vegf-a* and simplification of the capillary network led to alveolar simplification.[65] It remains to be determined how myofibroblasts and the endothelial cells collaborate to establish and maintain the septa.[66]

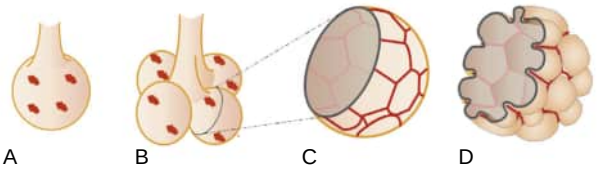

Figure 2.3 Three-dimensional model of septum formation. (A–B) During sacculation, myofibroblast precursors *(red)* proliferate and are evenly spaced in the alveolar mesenchyme. (C–D) During alveologenesis, myofibroblasts differentiate into contractile cells *(red strings),* connect into a network and constrict (D), leading to coordinated rise of septal ridges into the lumen.

DEVELOPMENTAL INSIGHTS INTO LUNG REPAIR AND REGROWTH

Continuing into adulthood, the lung maintains a certain degree of repair and regenerative capacity following injury.[67] For example, upon exposure to pollution or toxic injury, the remaining airway and/or alveolar epithelial cells proliferate and differentiate to replace lost cells (see Chapter 8). Beyond this type of epithelial cell–based repair, the adult lungs are also capable of growing en masse. For example, upon lung resection, also termed pneumonectomy, even though there is no regeneration at the site of the resection, the remaining lobes grow to fill the open space.[68–70] This type of compensatory regrowth is achieved through proliferation and morphogenesis of the alveolar epithelium, mesenchyme, and endothelium, coming together to make new septa.

Growing evidence suggests that after injury there is a general reactivation of the dormant developmental program, leading to repair and regrowth.[67] For example,

bleomycin-induced alveolar injury leads to AT2 proliferation and differentiation into AT1 cells to regenerate gas-exchange capacity.[71] This mimics AT2 behavior during development. Similar AT2 activation is also induced after pneumonectomy. During postpneumonectomy compensatory regrowth, there is also reactivation of secondary crest myofibroblasts, which likely drives the reseptation of enlarged lung lobes.[72]

On the molecular level, there is also reactivation of developmental signals in repair and regrowth. For example, FGFs, WNTs, and TGF-β pathways are reactivated during naphthalene-induced airway repair.[38,73] The Hippo/YAP pathway controls AT2 proliferation and differentiation, similar to its role in alveolar development.[51,53] These findings open the possibility of manipulating these developmental programs to stimulate proper and efficient repair and regrowth.

EMERGING TECHNOLOGIES TO STUDY LUNG DEVELOPMENT

INDUCED PLURIPOTENT STEM CELL–DERIVED LUNG CELLS

An adult skin fibroblast can be erased of its differentiation program and reversed into a pluripotent cell, called an *induced pluripotent stem cell* (iPSC), when it is engineered to express just four transcription factor genes: *OCT4*, *SOX2*, *KLF4*, and *cMYC* (OSKM or Yamanaka factors named after Dr. Shinya Yamanaka's seminal work).[74] The fibroblast-derived iPSCs can then be used to generate individual differentiated cell types. Since the first publication in 2006, iPSCs have been manipulated to generate a kaleidoscope of differentiated cell types, including neurons, cardiomyocytes, intestinal epithelial cells, skeletal myocytes, immune cells, and lung epithelial cells.[75–77] During iPSC differentiation into lung cells, the cells follow a similar sequence as during lung development, that is, transitioning first into endoderm, then foregut endoderm, followed by NKX2-1–positive lung progenitors, and finally into either airway or alveolar lineages.[78–81] Thus this technology can be used to study human lung cell specification and differentiation. Furthermore, it holds tremendous promise for studying disease mechanisms in a human cell context and for generating a sufficient number of corrected, healthy, and mature lung cells for autologous transplantation back into a patient from whom iPSCs are generated.

LUNG ORGANOIDS

Emerging from studies of lung progenitor cells, it was found that adult progenitors, such as airway basal cells and AT2 cells, are capable of forming organoids if given the proper nutrient and extracellular matrix support.[71,82] In the organoids, the progenitors can proliferate and differentiate, often from the origin of an individual cell. Analysis of colony number, size, and proportion of differentiated progeny offers a quantitative measure of progenitor potential. Change of growth factors, addition of agonists and antagonists, and introduction of small interfering RNA agents for gene knockdown have allowed interrogation of the molecular mechanisms that control progenitor cell maintenance and activation. Other cell types, such as mesenchymal cells, have been incorporated into organoid assays to establish tissue niches.[83,84] The prototype of lung-on-a-chip may allow the use of increasingly sophisticated combinations of cells and environmental cues to capture and manipulate the in vivo microenvironment in a dish.[85,86]

CRISPR/CAS9 GENOME EDITING

CRISPR/Cas9-based genome editing technology is a simple yet powerful tool that can target specific stretches of genetic code to edit, allowing investigators to make precise deletions, insertions, nucleotide changes, and other genomic or epigenomic changes in cells.[87–89] These technologies have led to remarkable advances in generating animal models for lung diseases and to investigations of the effects of mutations in human iPSC-derived lung cells.[89,90] Teams are working with the approach to correct disease mutations in patient-derived iPSCs, differentiate them into lung cell types, and engraft these into the same patient from where the cells were derived. In a parallel approach, a recent study succeeded with in utero CRISPR editing of lung cells in animal models, opening the door for in vivo editing of disease mutation somatically in cells in a formed organ.[91] A combination of these technologies holds promise toward bringing cures to patients with congenital diseases such as cystic fibrosis.

SINGLE-CELL SEQUENCING

In 2015, a pair of studies were published on a new, microfluidics-based technology that interrogated the transcriptome at single-cell resolution, at a capacity of thousands of cells at a time.[92,93] This technology, widely known as Drop-seq, has since exploded in its usage and spin-off improvements. Among these, bead-based chemistry improved cell capture efficiency, leading to *single-cell RNA sequencing* (scRNA-seq). More recently, the technology was applied to analyze chromatin accessibility in *single-cell Assay for Transposase-Accessible Chromatin by sequencing* (scATAC-seq), one indicator of the epigenomic state. Several consortia in the lung biology field, including efforts from the *National Heart, Lung, and Blood Institute*–funded LungMAP consortium, have taken advantage of these technologies to reveal the exciting new molecular properties of the lung at single-cell resolution (Fig. 2.4).

Among the explosion of publications with scRNA-seq data are studies of the developing lung[8,9,94–96] The data confirmed all known cell types and added much needed markers for some of these cell types. More important, the data solidified long-suspected heterogeneity within morphologically similar cell types. For example, in published studies and in the LungMAP-generated publicly available datasets, single-cell analysis defined complexity within alveolar mesenchyme with signatures for myofibroblasts, matrix fibroblasts 1 (also known as lipofibroblasts), matrix fibroblasts 2, and pericytes.[8,83,84,97] Single-cell analysis of the trachea uncovered heterogeneity within the basal cell population.[10] A population along the differentiation path of AT2-to-AT1 transition was captured in early postnatal samples.[8] Furthermore, single-cell technology provided the resolution needed to detect rare cell populations, including pulmonary neuroendocrine cells, ionocytes, and tuft cells.[10,98] The importance of these rare cell populations in lung function is just starting to be appreciated.[10,11,46,98] Studies

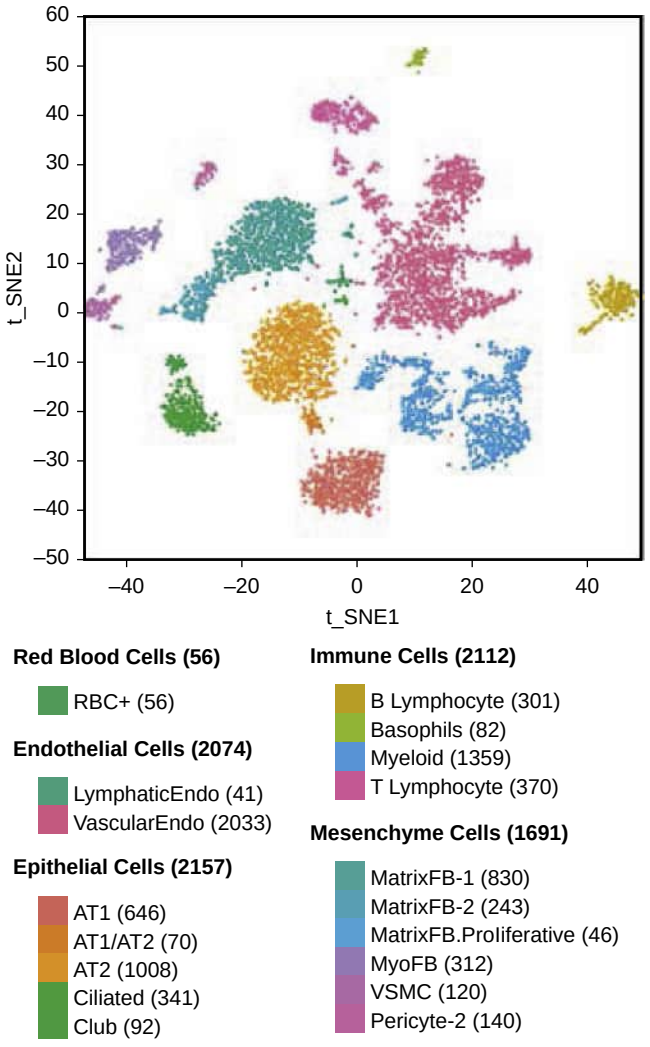

Figure 2.4 Representative single-cell RNAseq *t-distributed stochastic neighbor embedding* (tSNE) plot to demonstrate cell-type–based clustering. Data from single-cell analysis of whole mouse normal lung at postnatal day 3 (beginning of alveologenesis phase). On the tSNE plot, each dot represents a cell placed in in silico space based on its RNA transcript profile. Cells with similar transcriptional profiles are placed near each other. Hence each cluster displayed here represents a cell type, with annotations below. Numbers in the bracket indicate the number of cells captured on this tSNE plot. AT1/AT2, alveolar epithelial type 1/2 cell; MyoFB, myofibroblast; VSMC, vascular smooth muscle cell. (Data from Lung Gene Expression Analysis Web portal, courtesy Dr. Yan Xu, Dr. Jeffery Whitsett, and *National Heart, Lung, and Blood Institute*–funded LungMAP team of the Cincinnati Children's Hospital Medical School. https://research.cchmc.org/pbge/lunggens/mainportal.html.)

of single-cell analysis of the diseased lung are expanding. Examples are emerging on how single-cell resolution analysis has revealed variations in cell populations among patients that may improve the precision of diagnosis of lung diseases.[99,100]

REPRESENTATIVE DEVELOPMENTAL LUNG DISEASES

Developmental defects of the lungs can arise at any stage during their formation. They include abnormalities of the airways, the gas-exchange components of the lungs, and the pulmonary vasculature. Although major structural abnormalities of the lungs are often not compatible with life, many congenital malformations can be detected by prenatal ultrasound and addressed by specialized neonatal care, including surgical treatment in the newborn period. Aside from congenital malformations, preterm birth itself is a significant contributor to lung disease and impacts survival and long-term health outcomes. Although many diseases with disruption of lung development manifest with symptoms soon after birth, there are also many categories of disease that do not become apparent until childhood or even adulthood. Below are described some of the common congenital diseases of the lungs and pulmonary vasculature, organized by the time they arise during development.

DEFECTS IN TRACHEA/ESOPHAGUS SPECIFICATION AND SEPARATION

An abnormal or persistent connection between the airway and the digestive tract, as in tracheoesophageal fistula, develops in approximately 1 in 3500 live births and is frequently accompanied by atresia of the esophagus.[101,102] The fistula can be ligated surgically after birth; however, repair of the esophagus may be complicated depending on the distance between the disconnected proximal and distal esophageal segments. Furthermore, many patients have a spectrum of associated malformations of the *vertebral bodies* (V), *gastrointestinal tract atresia* (A), *cardiac defects* (C), *tracheoesophageal* defects (TE), *renal* and distal urinary defects (R), and *limb* malformations (L) that all make up the VACTERL syndrome.[101] Even more rare, and frequently lethal, is atresia of the trachea.[103] Tracheal atresia may be survivable only if identified before birth or if there is a fistula connecting the lower airways to the esophagus. Tracheal reconstruction using synthetic and stem cell–based approaches is an area that continues to be investigated for these infants and for patients who have tracheal injury or cancer in later life.

DEFECTS IN BRANCHING MORPHOGENESIS

Abnormalities of lung initiation and branching morphogenesis can lead to a variety of congenital lung masses, seen in 1 in 10,000 to 35,000 live births, which include bronchogenic cysts, *congenital pulmonary airway malformation* (CPAM), and pulmonary sequestration.[104,105] Bronchogenic cysts, the result of abnormal budding of the ventral foregut, result in cystic duplications of the proximal airway that frequently do not communicate with the tracheobronchial tree and have a blood supply from either the pulmonary or systemic circulation.[106] Bronchogenic cysts are often not identified until later in life due to recurrent infection; however, they can result in respiratory distress during the newborn period if they rapidly enlarge or cause compression of the normal lungs or heart.[106,107] CPAMs are the most common type of congenital lung mass and are the result of abnormal branching morphogenesis.[108,109] They connect to the normal tracheobronchial tree and have a blood supply derived from the pulmonary circulation. CPAMs are classified according to a variety

of approaches; the most widely adopted scheme includes clinical, macroscopic, and microscopic information.[110] More recently, classification of CPAMs has been based on the size of the abnormal cystic structures as either macrocystic or microcystic. Their treatment includes a wide variety of fetal interventions when the mass impairs development of the normal lungs or the function of the heart.[109,111,112] Due to concern for malignant transformation, CPAMs are typically removed after birth even if they do not cause respiratory distress. This practice is gradually changing, with some practitioners opting to observe patients with CPAMs using serial imaging.[113,114] In contrast, bronchopulmonary sequestrations are another, but rarer, type of congenital lung mass; they do not connect to the tracheobronchial tree and have a blood supply derived from the systemic circulation.[115–117] Sequestrations are subdivided based on their position and characteristics as intralobar, within a normal lobe of the lung; extralobar, outside of the normal lung and separated by an independent layer of visceral pleura; or hybrid, where there are histologic characteristics typical of a CPAM, but blood supply is derived from the systemic circulation. Intralobar sequestrations account for the majority of sequestrations and typically present with infections.

LUNG HYPOPLASIA

Hypoplasia of the lungs and pulmonary vasculature can happen for a variety of reasons. One of the major causes of lung hypoplasia is *congenital diaphragmatic hernia* (CDH), affecting in 1 in 3500 live births.[118,119] Patients with CDH have an opening in the diaphragm allowing the abdominal organs to herniate into the chest. The lungs and pulmonary vasculature are underdeveloped in patients with CDH due to a combination of mechanical compression and intrinsic defects in branching morphogenesis, septation, and vascular development.[120,121] Extrinsic compression of the developing fetal lungs can also result from skeletal dysplasias, pleural effusions, or other structure birth defects such as omphalocele, causing life-limiting lung hypoplasia.[122] Low amniotic fluid levels caused by premature rupture of membranes or bladder outlet obstruction in the fetus, also result in lung hypoplasia.[122] Lack of sufficient amniotic fluid decreases the intrauterine space for lung growth and the volume and pressure of amniotic fluid itself appears to be required for normal lung development and postnatal lung function.[123]

SURFACTANT PROTEIN DEFICIENCIES

In addition to structural lung defects, loss of function of individual molecules can also lead to significant respiratory distress and life-threatening lung disease in the newborn period. Mutations in the genes that encode surfactant proteins B and C (*SFTPB* and *SFTPC*) or in the phospholipid transport protein *ABCA3* gene are among the most common genetic causes of surfactant dysfunction.[124] Surfactant metabolism and function is discussed in Chapter 3. Inadequate pulmonary surfactant production due to preterm birth, gene mutations, or increased surfactant inactivation results in impaired gas exchange in the newborn period with diffuse collapse of the alveoli.

PRETERM BIRTH AND BRONCHOPULMONARY DYSPLASIA

Perhaps the most significant cause of impaired lung development is preterm birth, or birth before 37 weeks of gestation, which complicates 10% of all pregnancies.[125] Infants who are born prematurely are exposed to multiple treatments, including steroids, positive-pressure ventilation, and supplemental oxygen, treatments that improve survival but come at the cost of limiting normal development during the saccular and alveolar stages. The infants who are most commonly and severely affected are those born extremely preterm, or before 28 weeks of gestation. These infants have a high incidence of persistent respiratory distress throughout the newborn period. Preterm infants who require treatment with supplemental oxygen and/or positive-pressure ventilation beyond 36 weeks corrected gestational age are given the diagnosis of BPD.[126] Premature arrest of lung development in these infants is often made worse by inadequate nutrition, recurrent lung infection, and other cardiovascular and inflammatory insults.[126] Despite the association between preterm birth and BPD, the disease itself is very heterogeneous, and it is unclear what treatments improve the outcome. What is clear is that as more and more preterm infants are surviving and technical advances, such as surfactant therapy and better controlled ventilation, have permitted improved survival for infants born at even earlier gestational ages (<24 weeks), care for this group of patients will require specialized management throughout their lifetime.

CHILDHOOD INTERSTITIAL LUNG DISEASES

In addition to preterm birth, there are many other diseases that result from developmental defects arising during the later stages of lung development. Defects in alveolar septation cause a wide variety of interstitial lung diseases presenting in the newborn period or in later life.[127,128] One of the most severe forms of this category of disease is *alveolar capillary dysplasia with misalignment of the pulmonary veins* (ACD/MPV). Infants with ACD/MPV present with respiratory distress, hypoxemia, and pulmonary hypertension during the newborn period.[129,130] Histologic samples from lung biopsies and autopsy specimens show decreased density of pulmonary capillaries, thickening of the alveolar septal walls, hypertrophy of the pulmonary artery smooth muscle, and abnormal positioning of the pulmonary veins. ACD/MPV has been associated with mutations and deletions in the *FOXF1* gene in 40% of patients; however, there are other chromosome and single-gene defects that result in a similar phenotype.[131,132] Historically, the majority of patients with the ACD/MPV did not survive; however, there are increasing reports of patients being identified later in life or of infants who survive despite the disease.[133]

One rare childhood interstitial lung disease whose etiology remains unclear is pulmonary *neuroendocrine cell hyperplasia of infancy* (NEHI), with a frequency of 1 in 10,000 live births.[134] Patients with NEHI are often asymptomatic after birth but develop respiratory deficiency around 6 months of life accompanied by failure to thrive.[135] It has remained an intriguing disease because biopsies show normal alveolar density, unlike many other diseases with gas-exchange defects. Furthermore, computed tomography scans show ground-glass opacities that are not explained by any histologic defects

found in biopsies.[136] The only consistent histologic feature is an increase in the number of pulmonary neuroendocrine cells, thus explaining the name of the disease.[137] However, it remains debated whether changes in an airway cell type can cause the gas-exchange abnormalities manifested in the alveolar region. The first NEHI mutation was identified as a point mutation in *NKX2-1*, the quintessential lung transcription factor gene.[138] These genetic changes provide an entry point to uncovering the mechanism underlying NEHI.

PULMONARY VASCULAR DISEASE

Abnormal development and function of the vasculature in the lungs can result in pulmonary hypertension independent of defects in airway development. The primary mechanisms that contribute to pulmonary hypertension include abnormal or insufficient vascular development causing a decrease in the number of proximal pulmonary arteries, capillaries in the alveolar region, or pulmonary veins. Pulmonary hypertension can also result from hypertrophy or persistent contraction of the pulmonary vascular smooth muscle causing a reduction in the size of vessels in the lungs. Many lung diseases resulting in pulmonary hypertension do so because a combination of these mechanisms causes failure of normal pulmonary vascular smooth muscle relaxation after birth. Mutations in *BMPR2* account for the majority of heritable forms of pulmonary hypertension; however, many other genetic variants have been identified in pediatric and adult patients with pulmonary hypertension, including genes that encode transcription factors, receptor and signaling molecules, and channel proteins.[139,140] In addition, pulmonary hypertension complicates many developmental defects of the airways, including congenital diaphragmatic hernia, alveolar capillary dysplasia, and preterm birth with or without BPD.[141,142]

CONGENITAL OR LUNG DEVELOPMENTAL DEFECTS THAT MANIFEST LATER IN LIFE

Although many congenital lung diseases result in respiratory distress in the newborn period, there are many genetic and developmental diseases that do not become apparent until later life. Among this list are several important diseases that affect large groups of individuals, including cystic fibrosis, primary ciliary dyskinesia, and childhood asthma. These diseases will be discussed in later chapters.

Key Points

- Normal development of the lungs requires complex interactions among cell types across the epithelium, mesenchyme, and endothelium.
- Deviations from normal lung development contribute not only to pediatric lung diseases but also to adult respiratory conditions and the premature decline of respiratory function with aging.
- Lung development is characterized by highly stereotypical programs of branching, sacculation, and alveolar formation.
- Many signaling pathways, involving fibroblast growth factor, wingless type, hedgehog, retinoic acid, bone morphogenic protein, and transforming growth factor-β pathways, play important roles in lung development.
- Airway formation is completed before birth, whereas alveolar development continues after birth.
- There are many contributors to developmental origins of lung diseases, including mutations, premature birth, infections, and early exposures to toxins, such as cigarette smoke and e-cigarette vapor.

Key Readings

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3 ALVEOLAR COMPARTMENT

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INTRODUCTION
CELLULAR COMPOSITION OF THE ALVEOLAR EPITHELIUM
Alveolar Type 1 Cells
Alveolar Type 2 Cells
FUNCTIONAL ROLES OF THE ALVEOLAR UNIT
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KEY POINTS

INTRODUCTION

The major function of the lung is to facilitate gas exchange, a process that takes place in the distal alveolar region. The alveolar compartment comprises greater than 99.5% of the large surface area of the lung,[1,2] estimated in the adult human to be approximately 100 to 150 m^2. The adult human lung contains approximately 480 million alveoli, each about 4.2×10^6 μm^3 in size.[3] In these alveoli, an intricate mixture of epithelial, mesenchymal, and endothelial lineages combine to form a thin air-blood interface for efficient gas exchange[4] (Fig. 3.1), and maintenance of this structure is required to maintain tissue oxygenation.[5] The epithelial cells of the distal lung include *alveolar type 1* (AT1) cells, which share a common fused basement membrane with capillary endothelial cells to facilitate gas exchange, and *alveolar type 2* (AT2) cells, which synthesize pulmonary surfactant components and act as progenitor cells for repair and regeneration of the alveolus (Fig. 3.2). In the mesenchyme, multiple supportive fibroblast lineages participate in alveolar homeostasis, forming niches for both epithelial and endothelial cells. This alveolar unit regulates fluid homeostasis and ion transport; provides protection against inhaled toxins, pathogens, and irritants; and via the biophysical properties of surfactant, prevents atelectasis, alveolar flooding, and severe hypoxemia. The alveolus maintains efficient gas exchange across a large variety of organism sizes, physiologic stresses, and pathologic processes.

This chapter reviews key features of alveolar structure and function, with an emphasis on the functions of alveolar epithelial cells, the physiologic properties and pathophysiologic roles of pulmonary surfactant, and management of ion and fluid homeostasis in the alveolar epithelium. The chapter ends with a brief discussion of diseases of the lung with a primary pathology centered in the alveolus. The topics presented here complement additional discussions found elsewhere focused on the structure of the alveolus (see Chapter 1), lung development (see Chapter 2), and lung mesenchyme (see Chapter 5). The reader is also directed to Chapter 8 for a detailed discussion focused on regeneration of the alveolus. A comprehensive review of *acute respiratory distress syndrome* (ARDS) can be found in Chapter 134.

CELLULAR COMPOSITION OF THE ALVEOLAR EPITHELIUM

ALVEOLAR TYPE 1 CELLS

AT1 cells comprise approximately 10% of the cells in the alveolar region but cover approximately 95% of the internal alveolar surface area,[6] with remarkable conservation of size and function across species.[2] AT1 cells are large squamous cells with a mean volume of 2000 μm^3, whereas AT2 cells are much smaller with a mean volume of 850 μm^3 in the human lung.[6] The average area covered by one AT1 cell is remarkably independent of species and body size, with an estimated area of 5100 mm^2 in humans (76 kg), 4000 mm^2 in the baboon (29 kg), 5300 mm^2 in the rat (0.36 kg), and 5200 mm^2 in the shrew (2.5 g).[2,6–8] Increases in lung size with increased body size thus result from increases in alveolar cell number. Electron microscopy studies demonstrate that the alveolar surface is lined by a continuous epithelium and highlight the complexity of AT1 cell structure.[9,10] AT1 cells contain eccentric nuclei surrounded by perinuclear cytoplasm and attenuated cytoplasmic extensions that come into close contact with the capillaries to form the epithelial component of the air-blood barrier.[10–12] A complex internal structure includes microvilli, mitochondria, Golgi, rough and smooth *endoplasmic reticulum* (ER), small intracellular vesicles, and caveolae,[13,14] suggesting subcellular domains for both metabolic and endocytic functions.[15]

An expanded discussion of the structure and modeling of AT1 cells can be found at ExpertConsult.com.

The basal surface of the AT1 cell is attached to the basement membrane, whereas the apical surface comes into contact with air. Where the epithelium lies directly over the capillary endothelial cells, their two basement membranes can fuse (Fig. 3.3 A–B). AT1 cells are not confined to one alveolus; their cytoplasmic extensions penetrate across several alveolar septa or cross interalveolar pores to

AT1 cells contain abundant caveolae[13,14] and express caveolin-1.[16] Caveolae are smooth-coated or noncoated flask-shaped invaginations of the apical plasma membrane formed by constitutive caveolin and regulatory cavin proteins and are enriched in cholesterol and sphingolipids. Caveolae have diverse functions, including endocytosis, macromolecule transport, and membrane trafficking,[17] and play major roles in modulating cell signaling, although the mechanisms are not entirely clear. Caveolae also protect against mechanical stress at the plasma membrane.[18,19] Studies of AT1 cells injured in vitro have confirmed that membrane repair by lipid recruitment is facilitated by the caveolar endocytic pathway and by the remodeling of the actin cytoskeleton close to the site of wounding extensions. Caveolae can inhibit extracellular components, such as *transforming growth factor-β* (TGF-β) and matrix metalloprotease-1, but can also enhance proinflammatory signaling. The specific functional role of caveolae in alveoli is not well understood.

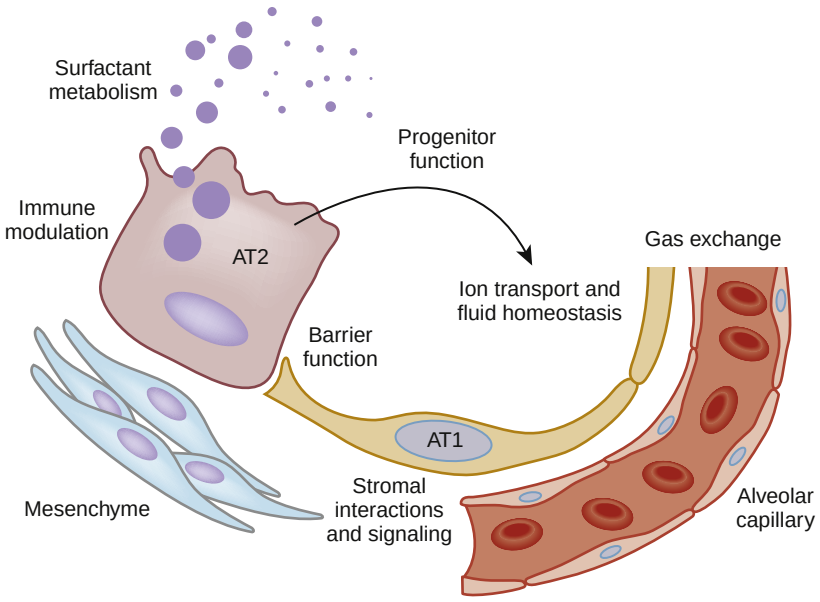

Figure 3.1 The cellular components and functional roles of the lung alveolus. The alveolus is made up of alveolar type 1 (AT1) and alveolar type 2 (AT2) cells that associate closely with supportive mesenchymal lineages and the alveolar capillary endothelium to coordinate major alveolar functions, including gas exchange, surfactant metabolism, ion transport and fluid homeostasis, barrier function, immune modulation, and regeneration.

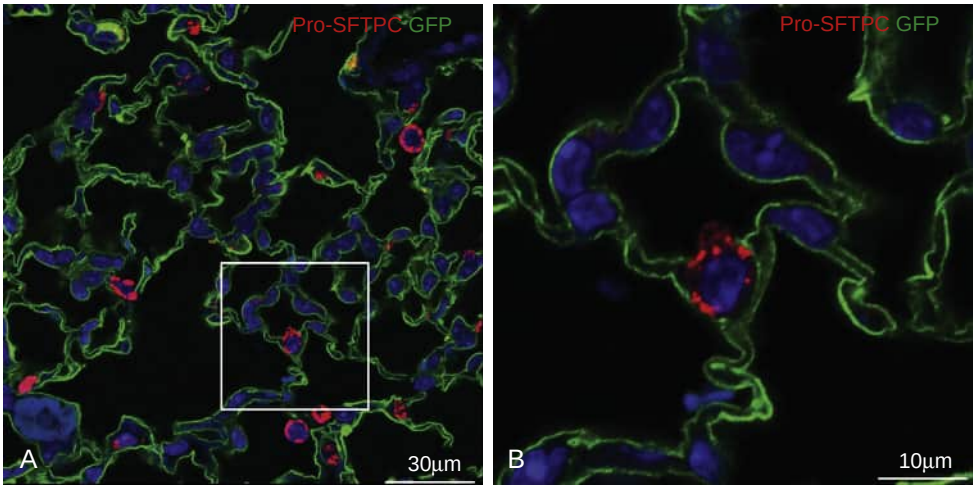

Figure 3.2 Immunofluorescence microscopy of *alveolar type 1* (AT1) and *alveolar type 2* (AT2) cells in adult mouse lung. (A) The majority of the alveolar epithelial surface is lined by AT1 cells. In reporter mice, labeled AT1 cells express green fluorescent protein (GFP, *green*), whereas immunofluorescent staining shows that AT2 cells express prosurfactant protein C (pro-SFTPC, *red*). Panel B shows higher magnification images for the boxed area in panel A. (Courtesy Y. Liu, B. Zhou, and Z. Borok.)

bridge two or three different alveoli.[10,11] AT1 cells also form close contacts with surrounding mesenchymal and inflammatory cells. New volume techniques, such as serial bloc face scanning electron microscopy, which allows for three-dimensional reconstruction, have revealed the morphologic diversity of AT1 cells and their ability to make cell junctions with each other, and have confirmed that entire AT1 cell bodies can cross the alveolar wall, where their cytoplasmic extensions can line both sides of the alveolar septum[20] (Video 3.1). These complex three-dimensional morphologic relationships may complicate simple interpretations of cellular function that assume distinct apical, basal, and lateral membrane domains.

Classically, AT1 cells were thought to play a largely passive role in alveolar homeostasis, serving as an impermeable lining of the alveolar surface and providing the surface area for gas exchange. Although AT1 cells do function in these roles, recent improvements in techniques, including identification of AT1 cell markers,[21–25] methods for AT1 cell isolation and enrichment,[26–32] and generation of novel transgenic mouse models for genetic labeling of AT1 cells,[33–36] have provided new insights (see Fig. 3.2). In vitro and in vivo studies and gene expression profiling[59–67] support an active, important role for AT1 cells in numerous alveolar functions, including ion transport,[26,27,68–70] barrier formation and function,[59-67,71–75] and immunomodulation[30,76] (reviewed in individual sections later).

A number of classical genes and their protein products are enriched in AT1 cells, including *aquaporin-5* (AQP5),[23,77] T1α/podoplanin/*RT140*,[21,78,79] receptor for advance glycation end products,[16,36,61,80,81] caveolin-1,[13,82] and homeodomain-only protein,[35] have been used to identify AT1 cells, facilitate AT1 cell isolation,[28–30,32] and generate AT1 cell–specific lineage tracing and deletion mouse models. However, all have some limitations with regard to cell specificity, and identification of a gene with comparable AT1 cell specificity to that of *surfactant protein C* (*SFTPC* gene) in AT2 cells remains elusive. Although functional or intact AT1 cells are still not highly represented in isolated mixed lung cell populations, recent advances in *fluorescence activated cell sorting* (FACS) and lineage tracing[35,65,83–85] have led to improved yields and purity of sorted AT1 cells.[26,28,29,79,86]

RNA-sequencing analysis[63–67] of these isolated cells has identified novel AT1 cell–enriched proteins[25] and emphasized the role of AT1 cells in fluid handling and signaling interactions in the alveolus. Comparison of AT1 cells from mouse[30] and human lungs[32] demonstrates both

Difficulty in studying AT1 cells in situ and in isolating adequate numbers of viable AT1 cells led to the development of simplified in vitro models for study of AT1 cell function. Considerable information regarding AT1 cell function was obtained using *alveolar epithelial cells* (AECs) in primary culture on inflexible substrata or semipermeable supports, conditions under which isolated AT2 cells undergo phenotypic transition (transdifferentiation) to an "AT1-like cell" phenotype. AT2 cells in primary culture acquire many characteristics of AT1 cells over time,[24,37–40] recapitulating the process in vivo, where AT2 cells serve as progenitors of AT1 cells.[41–44] Although AT1-like cells in two-dimensional culture acquire many, but not all, the properties of AT1 cells, studies of AT1-like cells provided early insights into AT1 cell barrier and transport properties and possible plasticity of AT1 cells.[15,40] Recent studies of AT2 cells in three-dimensional culture show similar acquisition of AT1 cell markers consistent with acquisition of an AT1 cell–like phenotype.[44,45] A challenge for the field was the fact that AT2 cells in culture invariably differentiate toward an AT1 cell phenotype, leading to identification of conditions that could maintain the AT2 cell phenotype to facilitate investigation of AT2 cell function.[46–54] Soluble factors (e.g., serum and growth factors),[46–50] substratum,[51] changes in cell shape,[47,52,53] and growth at air interface,[54] among others, were shown to strongly influence AEC phenotype and function. For example, growth on matrix secreted by Engelbreth-Holm Swarm mouse sarcoma cells (Matrigel)[55] or in the presence of keratinocyte growth factor[47,56] preserved aspects of the AT2 cell phenotype. Furthermore, cells that had already acquired AT1 cell characteristics could be induced to reexpress AT2 cell characteristics,[46,49,57,58] indicating phenotypic plasticity in vitro, a feature that has subsequently been confirmed in vivo (see later).

Challenges to isolation of AT1 cells included their fragility and limited availability of specific AT1 cell markers. The advent of surface markers for AT1 cells and technologic advances in FACS led to the development of techniques for isolation of purified populations of AT1 cells. Initial isolations from rat lung used immunoselection with magnetic beads with or without density gradient centrifugation (purities of 60–98%)[26,28,79] and subsequently FACS (purity >99%).[15,29] Methods have subsequently been developed for isolation of AT1 cells from mouse[30] and human lungs[32] by FACS using combinations of antibodies for positive and negative cell selection, although still with variable contamination by other cell types. Comparisons using microarray platforms revealed both differences[15] and similarities[25] in patterns of gene expression between freshly isolated AT1 and AT1-like cells, as well as between rat and human cells.[25] Use of a fluorescent reporter in lineage-labeled mice facilitated the isolation of $Hopx^{+}$ AT1 cells that could be plated as single cells to form organoids in three-dimensional culture.[87]

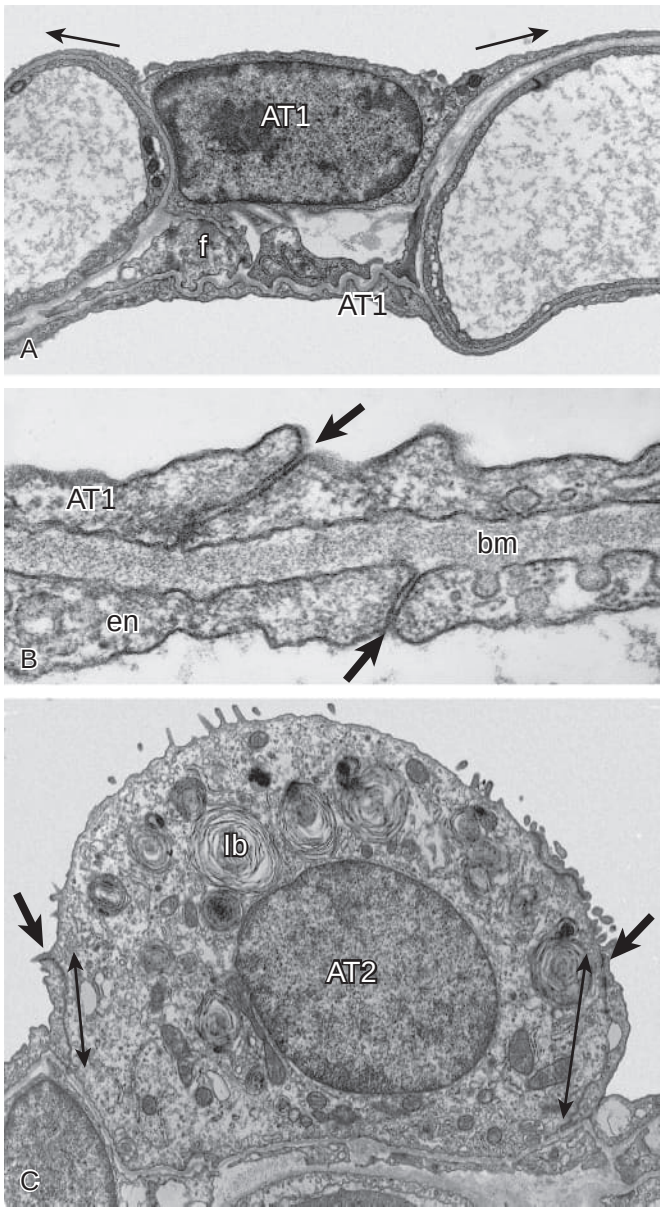

Figure 3.3 Basic features of alveolar epithelial cells. (A) Alveolar type 1 cell (AT1) sitting in a niche of a capillary mesh and extending a thin cytoplasmic leaflet to form the air-blood barrier *(long arrows)*. Interstitial space with fibroblast (f) separates this cell from type 1 cells lining the lower surface. (B) Higher-power view of the cytoplasmic leaflets of type 1 epithelial and endothelial cells (en) separated by fused basement membranes (bm) in thin part of barrier. *Arrows* point to intercellular junctions with tight junction in both cell layers. (C) Alveolar type 2 (AT2) epithelial cell is a cuboidal cell with a cytoplasm rich in organelles related to the production of surfactant elements, such as phospholipids in lamellar bodies (lb) and apoproteins. Note extended lateral membrane *(double-headed arrows)* with junctional complex between AT1 and AT2 cells *(heavy single-headed arrows)*. (A, From Weibel ER, Claassen H, Gehr P, et al. The respiratory system of the smallest mammal. In: Schmidt-Nielsen K, Bolis L, Taylor CR, eds. *Comparative Physiology: Primitive Mammals.* Cambridge, UK: Cambridge University Press; 1980:181–191; B–C, From Weibel ER. On the tricks alveolar epithelial cells play to make a good lung. *Am J Respir Crit Care Med.* 2015;191:504–513.)

conservation[25] and divergence[62] of gene expression in AT1 cells from different organisms and between freshly isolated AT1 cells and cultured AT1-like cells, suggesting both a core AT1 cell gene signature and plasticity of AT1 cells under different conditions. Recent methods allowing isolation and propagation of AT1 cells from three-dimensional lung organoid cultures[35] will likely provide new insights to refine the properties of individual AT1 cells. Advanced techniques, including single cell and single nuclear RNA sequencing, continue to provide new insight into AT1 biology and hold promise to advance our understanding of alveolar biology.

ALVEOLAR TYPE 2 CELLS

AT2 cells (see Fig. 3.3C) are the second major epithelial lineage of the lung alveolus.[88] Although AT2 cells comprise only 3–5% of the alveolar surface area, they constitute 60% of all alveolar epithelial cells and 10–15% of all lung cells. AT2 cells were first comprehensively described by Macklin in 1954[89] before the advent of the electron microscope, and subsequent findings have validated many of the initial predictions about the function of these cells. Starting in 1974 with the seminal report of Kikkawa and Yoneda[90] and continuing over the past 5 decades with pioneering efforts of Dobbs, Williams, Mason, and others,[91–95] a wealth of data from multiple species have been generated implicating AT2 cells in important biosynthetic, secretory, metabolic, host defense, and repair/regenerative functions.[96,97] A combination of robust animal studies and isolation of primary human AT2 cells from both adult and fetal samples[86,98–101] has demonstrated the importance of AT2 cells in the maintenance of alveolar homeostasis and frequently in driving the pathogenesis of parenchymal lung diseases.[85,99,102,103]

The primary role of the AT2 cell is to produce surfactant lipids and proteins and transport them into the alveolar space. AT2 cells of all mammalian species contain specialized cytoplasmic, osmiophilic, lamellated organelles termed *lamellar bodies* (LBs), the storage organelle from which surfactant is released into the alveolar lumen[104] (Fig. 3.4). Biochemically, LBs resemble other lysosomal-related organelles in that they are acidic and express lysosomal markers (CD63, LAMP-1), but LBs also contain surfactant components (phospholipids, surfactant proteins) required for their specialized function. The apparatus for biosynthesis, processing, and exocytosis of surfactant protein is unique to AT2 cells.[88,97,105] AT2 cells are also unique in their exclusive expression and complete processing of one of the *surfactant proteins* (SPs), SP-C (SFTPC)[106,107] (see Fig. 3.2). Both human *(SFTPC)* or murine SP-C *(Sftpc)* promoter elements have been extremely useful for expressing or deleting genes in murine AT2 cells.[108] Of importance, whereas AT2 cells express the surfactant proteins SP-A, SP-B, and SP-D, these proteins are expressed in nonciliated bronchiolar cells, such as club cells, and at low levels in some extrapulmonary tissues.[109–112]

To support the synthesis and secretion of surfactant, which is rich in phospholipids, the lipid metabolism and energy capacity of AT2 cells are highly specialized: (1) the AT2 cell transcriptome is highly enriched in genes involved in lipid metabolism; (2) AT2 cell metabolism is geared toward high glucose and *oxygen* (O_2) consumption; and (3) AT2 cells contain a high density of mitochondria to support lipid biosynthesis, processing of surfactant, and the uptake and reutilization of surfactant.[7,113] Lipogenesis in AT2 cells is up-regulated at the end of gestation and, similar to other lipogenic cells, is regulated by the transcription factors sterol regulatory element binding protein-1c and CCAAT/enhancer-binding protein alpha, as well as dexamethasone, *keratinocyte growth factor* (KGF/FGF7),

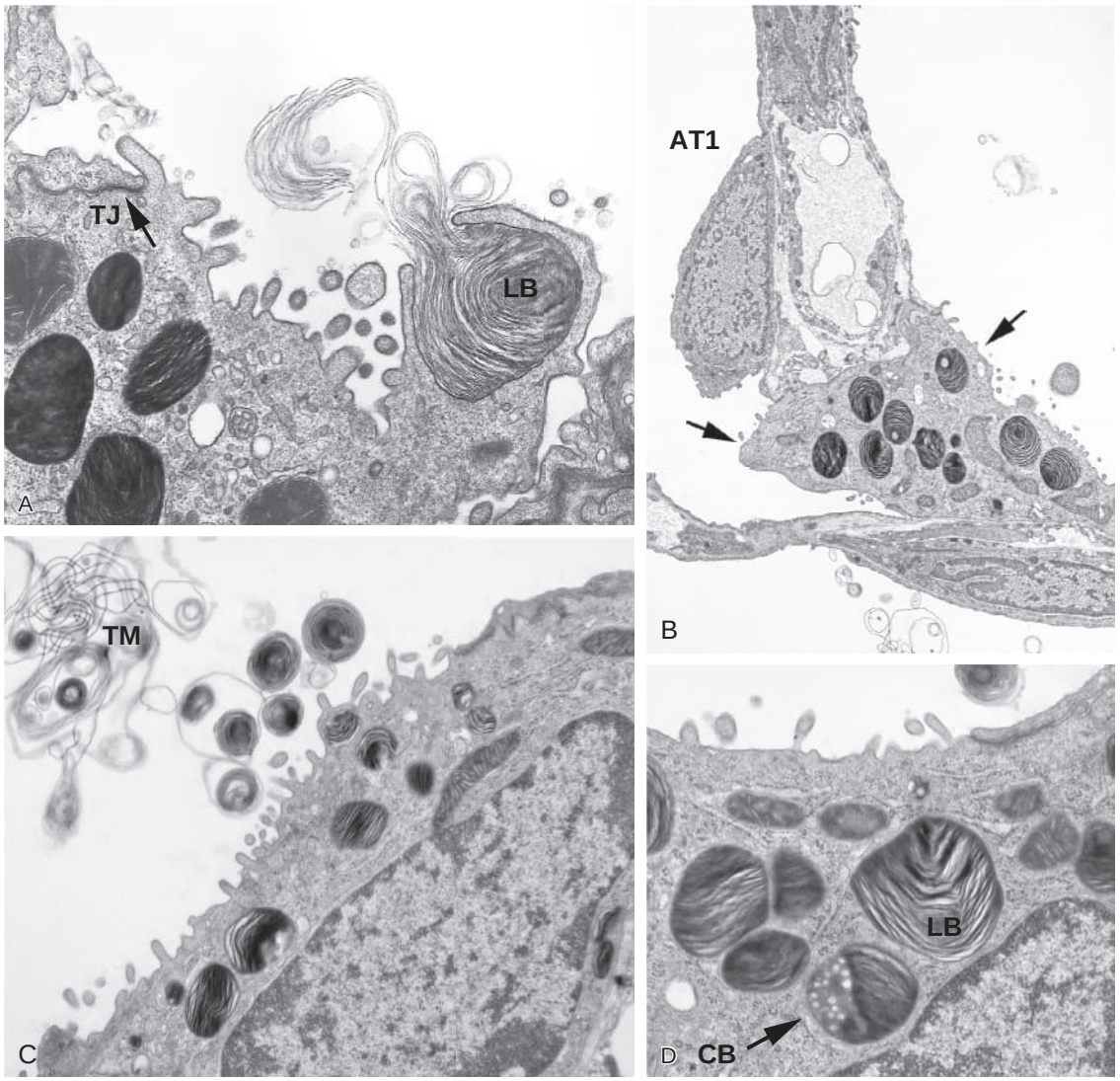

Figure 3.4 ***Alveolar epithelial type 2*** **(AT2) cells.** (A) A portion of an AT2 cell, showing lamellar bodies (LBs), a portion of a tight junction (TJ, *arrow*) between AT1 and AT2 cells, and an LB undergoing exocytosis. (B) Alveolar epithelium showing an AT2 cell bridging two different alveolar surfaces *(arrows)* adjacent to the nucleus of an AT1 cell. (C) A portion of an AT2 cell and secreted LBs and tubular myelin (TM) in the alveolar space. (D) A portion of an AT2 cell with an LB and a composite body (CB), which serves as an intermediate endosomal compartment between the multivesicular body and the LB. (Courtesy Lennell Allen and L. Dobbs.)

and *cyclic adenosine monophosphate* (cAMP).[100,114,115] Lipogenesis is crucial in preparing the alveolus for the first breath of air after birth. AT2 cells are therefore responsible for the biosynthesis, assembly, and complex intracellular trafficking of a diverse and challenging set of cargo. This trafficking requires activation of overlapping processes in multiple subcellular compartments, including the secretory, endocytic, and degradative (lysosomal) pathways.[105] The complexity of this cargo renders AT2 cells highly susceptible to cellular stress, and multiple studies indicate AT2 cell dysfunction is driven by activation of the unfolded protein and impaired cellular quality control pathways[105] (Table 3.1).

In addition to surfactant metabolism, AT2 cells perform critical roles in transporting fluid to prevent the alveoli from flooding and are important participants in innate lung immunity. Finally, AT2 cells function as a progenitor cell during regeneration of the lung alveolus, as discussed in detail later. This extensive secretory burden, other critical roles in the response to and repair from injury, and intrinsic susceptibility to injury highlight AT2 cells as an important participant in lung injury and aberrant repair. Failure of these systems in AT2 cells has been causally associated with a variety of lung diseases and syndromes in both pediatric and adult populations (Table 3.1).

FUNCTIONAL ROLES OF THE ALVEOLAR UNIT

PULMONARY SURFACTANT AND ALVEOLAR SURFACE TENSION

The requirement for an extensive, hydrated, and patent surface for gas exchange presents a challenging bioengineering problem because the surface tension at air-liquid interfaces creates forces promoting alveolar collapse at low lung volumes. Alveolar collapse then results in

ventilation-perfusion mismatch that impairs normal gas exchange. In 1929, von Neergaard[116] discovered that there was a difference in the mechanics and elastic recoil properties of the respiratory system depending on whether the lung was inflated with air or saline (Fig. 3.5). More pressure was required to inflate the lungs with air than with saline, but once inflated, alveoli remained open even at low lung volumes, leading to the hypothesis that the surface tension in the distal lung was lower than predicted for a simple air-water interface due to an "antiatelectasis factor." In the 1950s, Clements[117] and Pattle[118] used lung extracts to demonstrate that surfactant, specifically its phospholipid components, was responsible for lowering alveolar surface tension, decreasing the work of breathing, preventing alveolar collapse, and promoting stability of alveoli of different sizes with different radii of curvature. Soon after these discoveries, Avery and Mead[119] causally demonstrated a deficiency in surface-active material in the lungs of premature infants with neonatal respiratory distress syndrome. This led to the current understanding that the alveolar gas exchange surface is coated with a thin film of *surface active agent* (surfactant), a biochemically heterogeneous complex composed of primarily lipids and protein, that functions to reduce surface tension at the air-liquid interface along the distal lung epithelial lining.

Surfactant Composition

Surfactant is a mixture of lipids and proteins secreted into the alveolar space by AT2 cells. These lipids play a key role in modulating surface tension. The critical lipid component of surfactant is *dipalmitoylphosphatidylcholine* (DPPC), an atypical phospholipid species of phosphatidylcholine in that both fatty acid side chains are saturated. DPPC, along with unsaturated phosphatidylcholine, phosphatidylglycerol, and four surfactant-associated proteins (reviewed later) represent the bulk of the secreted AT2 cell surfactant (Table 3.2). Approximately 50–60% of surfactant lipid is DPPC, which distinguishes it from the composite of phosphatidylcholine species found in cellular membranes. Pulmonary phospholipids are amphophilic (i.e., contain both hydrophilic and hydrophobic parts) and therefore can spontaneously form a monolayer film at air-liquid interfaces to stabilize the surface film at low alveolar volumes.[120] Of note, the

TABLE 3.1 Diseases of the Distal Lung Epithelium

Category	Clinical Diagnosis	Lung Phenotype	Molecular and Cellular Mechanism(s)
SURFACTANT SYSTEM DISORDERS			
Surfactant Deficiencies			
Developmental	Neonatal RDS	Immature lung hyaline membranes Respiratory failure	Decreased surfactant system components Increased surface tension
Inherited	SP-B deficiency	Respiratory failure Alveolar proteinosis PAS-positive staining	Absent SP-B in BAL Dysfunctional surfactant Misprocessed SP-C Increased BAL phospholipids
	ABCA3 mutations (null)	Respiratory failure	Absent lamellar bodies Decreased BAL and AT2 phospholipids Dysfunctional surfactant
Surfactant Dysfunction Syndromes			
Acquired/intrinsic	ARDS	Hyaline membranes Respiratory failure/shunt	Epithelial cell death, barrier dysfunction Surfactant inactivation Inflammatory cell recruitment
	Primary graft dysfunction	Focal pulmonary infiltrates Hypoxic respiratory failure	Epithelial cell death, barrier dysfunction Surfactant inactivation Inflammatory cell recruitment
Extrinsic toxins	Hyperoxic lung injury Nitrogen mustard	Hypoxic respiratory failure	AT2/AT1 cell death Inflammatory cell recruitment Surfactant inactivation
Infectious	*Pneumocystis jirovecii*	Hypoxic respiratory failure Alveolar proteinosis	Defective AT2 surfactant secretion Surfactant inactivation
Altered Surfactant Metabolism			
Pulmonary Alveolar Proteinosis (PAP)			
Autoimmune	iPAP	Alveolar proteinosis PAS (+) alveolar material "Crazy paving" CT scan	GM-CSF autoantibodies
Hereditary	hPAP	Alveolar proteinosis	Recessive variants in GM-CSF receptor common beta chain or alpha chains
Acquired	Secondary PAP	Alveolar proteinosis	Dust exposure: silica, aluminum, titanium Hematologic malignancy Post-allogenic BMT *Pneumocystis jirovecii*

Continued

TABLE 3.1 Diseases of the Distal Lung Epithelium—cont'd

Category	Clinical Diagnosis	Lung Phenotype	Molecular and Cellular Mechanism(s)
INTRINSIC EPITHELIAL CELL DYSFUNCTION			
Mutations in AT2 Cell or Surfactant Component Genes			
SFTPC mutations	Child (children) IPF (adult)	NSIP ± PAP UIP	Epithelial cytotoxicity from protein aggregation or mistrafficking including ER stress. apoptosis, impaired autophagy Cytokine/TGF-β generation
SFTPA mutations	chILD IPF (adult) Lung cancer	NSIP/PAP UIP pathology Adenocarcinoma	Epithelial dysfunction ER stress Cytokine generation
ABCA3 mutations	chILD (children) IPF (adult)	NSIP/PAP UIP (adult)	ER stress Impaired autophagy
Short telomere syndrome	Interstitial lung diseases ± dyskeratosis congenita	IPF/UIP NSIP	Short telomeres Genetic variants: *RTEL1, TERT, PARN, TERC DKC1, NAF1, TINF2*
Organellar Homeostasis			
Hermansky-Pudlak syndrome	Interstitial lung disease	Early-onset UIP	Genetic variants in *HPS1, HPS2*, or *HPS4* Abnormal (giant) lamellar bodies Macrophage-dominant alveolitis
Birt-Hogg-Dubé syndrome	Parenchymal cystic lung disease	Bilateral basolateral lung cysts Pneumothoraces Skin fibrofolliculomas Renal tumors	Variants in *FLCN* (folliculin)
Disorders of AT2 Cell Metabolism			
Macromolecule metabolism	Niemann-Pick disease	Interstitial lung disease Alveolar proteinosis	Mutation in *NPD-A, SMPD1, NPC1, NPC2* Altered LDL cholesterol, sphingomyelin
Ion homeostasis	Pulmonary microlithiasis	CT scan: micronodular "sandstorm" calcifications ± crazy paving pattern	Mutation in *SLC34A2* (Na-PO_4 transporter) Air space accumulation of $CaPO_4$ microliths
BARRIER DYSFUNCTION			
Altered Barrier Integrity			
Genetic	None		
Acquired	Sepsis ARDS	Diffuse alveolar damage Alveolar edema Respiratory failure	Barrier disruption
Transport Dysfunction			
Acquired lower respiratory tract infections	ARDS		Decrease expression of ion transport proteins Proinflammatory cytokines Reactive oxygen and nitrogen species Extracellular nucleotides
Genetic	Multisystem pseudohypoaldosteronism	Recurrent lower respiratory tract infections	Homozygous or compound heterozygous mutations of α-, β-, γ-ENaC subunits

ARDS, acute respiratory distress syndrome; AT1, AT2, alveolar type 1 and 2, respectively; BAL, bronchoalveolar lavage; BMT, bone marrow transplant; chILD, interstitial lung disease of childhood; CT, computed tomography; ENaC, epithelial sodium channel; ER, endoplasmic reticulum; GM-CSF, granulocyte-macrophage–colony-stimulating; hPAP, hereditary pulmonary alveolar proteinosis; iPAP, inspiratory positive airway pressure; IPF, idiopathic pulmonary fibrosis; LDL, low-density lipoprotein; NSIP, nonspecific interstitial pneumonitis; PAP, pulmonary alveolar proteinosis; PAS, periodic acid–Schiff; RDS, respiratory distress syndrome of the newborn; SP-B, -C, surfactant protein B and C, respectively; TGF-β, transforming growth factor-beta; UIP, usual interstitial pneumonitis.

composition of surfactant lipid is important for optimal lung function, and changes are associated with disease; for instance, during ARDS, a reduction in the percentage of phosphatidylglycerol is the earliest alteration detected in the composition of surfactant.[121]



See ExpertConsult.com for more information on the study of composition and measurement of surfactant.

DPPC-enriched phospholipid films reduce surface tension at the air-liquid interface, but these lipids alone demonstrate slow film formation and cannot provide optimal surfactant function. Surfactant proteins play a key supportive role in stabilizing and supporting the lipid monolayer and participate in innate immune functions. Although united by a common nomenclature defined by order of discovery as SP-A, SP-B, SP-C, and SP-D,[131] these surfactant components have both overlapping and distinct functions. The two smaller hydrophobic proteins, SP-B and SP-C, can each improve the rate of delivery (adsorption and spreading) of DPPC and other phospholipids at the air-liquid interface.[132] Of importance, either protein alone or a mixture of the two improves the surfactant-like properties of the phospholipids present in the alveolus and are

Because pulmonary phospholipids are amphophilic, they can spontaneously form a monolayer film at air-liquid interfaces, generating a film pressure that stabilizes the surface film. This is most easily measured in situ and conceptualized using either a pulsating bubble surfactometer[122] or *captive bubble surfactometer* (CBS).[123,124] Analogous to Pattle's original assessment of "bubble instability" in neonatal respiratory distress syndrome samples,[118] these instruments study spherical surfaces similar to those of alveoli. Consistent with the Law of Laplace (surface tension = surface pressure × radius/2), for any spherical structure, DPPC molecules can pack closely together and stabilize the surface monolayer to be able to withstand high film pressures at low alveolar volumes.[120] The CBS dynamically measures the radius and pressure differences across the surface of a bubble and calculates surface tension of the liquid that forms as the bubble is cyclically expanded and contracted at pulsation rates chosen by the operator (0–50 cycles/min). The CBS combines the concepts of Pattle's film bubbles[118] with an improved feasibility over the original Langmuir-Wilhelmy balance used by Clements[117] to produce surface tension–area hysteresis loops using smaller amounts (micrograms) of lipid (surfactant) sample.[123,124] The CBS allows the compression of films to very low and stable surface tensions of 1 to 2 mN/m, in line with results obtained from pressure-volume studies on excised lungs. Further, the CBS has allowed measurement of other essential physical properties of surfactant, including (1) rapidity of film formation and (2) effective replenishment of the surface film on bubble expansion by incorporation of surfactant material from the surface-associated surfactant reservoir. By combining these biophysical techniques with other imaging and morphometric techniques, the behavior of surfactant lipids in the alveolus was defined. The high film pressures squeeze some components of the film, such as unsaturated phospholipids and surfactant-associated proteins, out of the monolayer so that the surface film generated at low lung volumes is felt to be composed of nearly pure (95%) DPPC.[125] Epifluorescence studies with hydrophilic markers have confirmed that there are areas from which aqueous markers are excluded as the film is compressed.

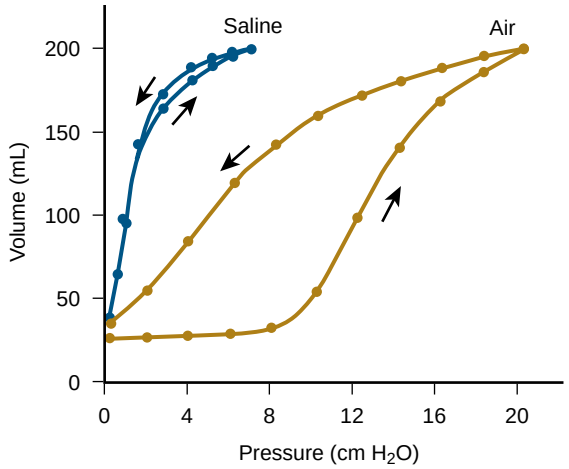

Figure 3.5 Air and saline volume-pressure curves. The classic physiologic observation that led to the discovery of surfactant. It takes more pressure to inflate the lung with air than with saline. However, the pressure difference is much less than would be expected if the alveolar lining had the same surface tension as other biologic fluids, which indicates the presence of a surface-active material. The descending limb of the air volume-pressure curve is highly reproducible and is used to estimate the surface tension of the lung and static compliance. (Modified from Radford EP Jr. Recent studies of mechanical properties of mammalian lungs. In: Remington JW, ed. *Tissue Elasticity*. Washington, DC: American Physiological Society; 1957:177–190.)

TABLE 3.2 Composition of Pulmonary Surfactant

Phospholipids: 85%	**% of Phospholipids**
Phosphatidylcholine	76.3
Dipalmitoylphosphatidylcholine	47.0
Unsaturated phosphatidylcholine	29.3
Phosphatidylglycerol	11.6
Phosphatidylinositol	3.9
Phosphatidylethanolamine	3.3
Sphingomyelin	1.5
Other	3.4
Neutral Lipids: 5%	
Cholesterol free fatty acids	
Proteins 10%	
SP-A	++++
SP-B	+
SP-C	+
SP-D	++
Other	

SP-A, SP-B, SP-C, and SP-D, surfactant protein A, B, C, and D, respectively.
+, relative abundance.

the major protein components in the current surfactant replacement therapies used to treat neonatal respiratory distress syndrome.[133] The other two surfactant proteins, SP-A and SP-D, are hydrophilic and do not appear to have a primary role in modulating surfactant biophysics.[134] They are members of the collectin family of C-type lectins with known host defense functions. Although SP-A coisolates with surfactant phospholipids and can recapitulate some of the biophysical properties of SP-B and SP-C in vitro, its main functions are in innate immunity and homeostasis of surfactant (see also Chapter 15).

After secretion into the alveolus, surfactant can be found in several forms that can be visualized in transmission electron microscopy and freeze fracture images. These include LBs, highly organized structures termed tubular myelin, and phospholipid-rich sheets and vesicles.[135,136] Tubular myelin is a unique extracellular form of surfactant that sediments rapidly on centrifugation and is surface active. Tubular myelin appears as an organized lattice of surfactant bilayers formed at right angles and represents a surfactant intermediate between the LB and the surface monolayer. SP-A, in combination with SP-B, is necessary for the formation of tubular myelin in vitro.[137] However, because SP-A–deficient mice lack tubular myelin but have normal respiratory mechanics at rest, the formation of tubular myelin is not considered absolutely necessary for surfactant function.[138] Overall, this multistage surfactant system promotes a low surface tension in the alveoli and small airways but not in the large airways or trachea.[126–130]

Surfactant Protein A

SP-A was the first surfactant protein identified[139] and is the most abundant of the surfactant proteins. In contrast to SP-B and SP-C, the main role of SP-A in the lung is related to host defense. SP-A is a secreted octadecameric collagenous glycoprotein with a complex tertiary structure similar to serum mannose-binding lectin and the complement component C1q.[134,140] SP-A forms a polarized bouquet-like structure composed of 18 monomers organized as six trimeric units. The SP-A monomer contains a COOH-terminal C-type lectin motif, a triple helical collagen domain, and *carbohydrate recognition domain* (CRD) (Fig. 3.6). The CRD is essential for SP-A host defense function and consists of a globular domain that binds carbohydrate and other ligands recognized by SP-A. In humans, there are two SP-A genes, *SFTPA1* and *SFTPA2*, 4.5 kb each, located on chromosome 10 near the closely related genes SP-D and mannose-binding lectin. The amino acid differences that distinguish SP-A1 from SP-A2 are in general conservative and located mainly in the collagen-like domain, with only one shown to affect protein structure.[141–143]

Greater than 99% of secreted SP-A in lavage fluid is bound to phospholipid.[144] SP-A is localized primarily in the gas exchange units of the lung and small airways.[145] In rodents, SP-A is found in AT2 cells and in nonciliated bronchiolar cells (club cells) lining the conducting airways. In humans, most SP-A is found in the alveoli, with less prominent expression in human tracheal submucosal glands.[146] SP-A is also expressed in extrapulmonary sites, including salivary glands, lacrimal glands, and the female urogenital tract,[147] although the exact physiologic relevance of SP-A in other organs is unknown. At the ultrastructural level, immunogold electron microscopy has detected SP-A in both AT2 cell organelles and intra-alveolar surfactant.[148] A number of factors can increase the synthesis of SP-A, including cAMP, KGF/FGF7, and *interleukin* (IL)-1.[149]

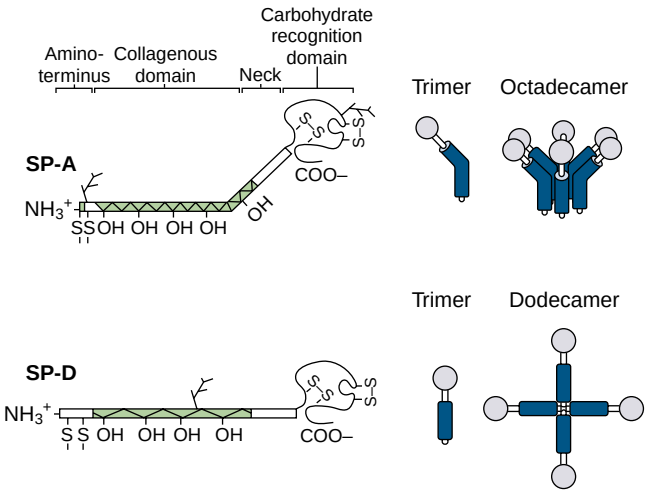

Figure 3.6 Structural organization of *surfactant proteins A and D* (SP-A and SP-D). SP-A *(top)* and SP-D *(bottom)* are collagenous glycoproteins with four important domains. The amino-terminal region contains cysteines for intermolecular disulfide bonding to form covalent oligomeric units. The collagen-like domain imparts structural rigidity and elongated molecular structure to both proteins. In SP-A, the collagen region has a kink, which accounts for the bend in the collagen region and the bouquet-like structure of the octadecamer. In SP-D, the collagen domain is straight and allows formation of a cross-shaped dodecamer. The neck contributes to the trimeric assembly of polypeptide subunits and spacing for the terminal carbohydrate recognition domain (CRD). The CRD is a globular region of the molecule that plays a major role in the recognition of multiple ligands. In SP-A, the CRD accounts for most of the binding to dipalmitoylphosphatidylcholine vesicles, alveolar type 2 cells, macrophages, and inhaled organisms. In SP-D, the CRD unit is responsible for all the reported interactions with viruses and bacteria. (Modified from Kuroki Y, Voelker DR. Pulmonary surfactant proteins. *J Biol Chem.* 1994;269:25943–25946.)

The intracellular trafficking and secretion of nascent SP-A involves both LB-dependent (regulated)[150] and LB-independent (constitutive) pathways.[151] Directly secreted SP-A is newly synthesized, whereas the SP-A found in LBs is likely derived from SP-A recycled via endocytosis and via reincorporation into LBs, which may play an important role in regulation of reuptake of other lipids.[152–154] Beyond the presence of a signal peptide and N-linked glycosylation, structural motifs and signals regulating trafficking of SP-A remain incompletely defined.

The major function of extracellular SP-A appears to be in innate immunity. SP-A binds to a variety of microorganisms and particles, promotes their clearance by phagocytic cells, and directly alters the function of immune effector cells.[155–159] Because SP-A binding is somewhat promiscuous with a low affinity, the physiologic effects of SP-A are likely due to its polyvalent structure and multiple binding sites on cells and organisms. SP-A is capable of binding both the surfactant lipid in alveolar fluid and inhaled organisms or particles. SP-A binds gram-negative bacteria with the rough form of lipopolysaccharide, aggregates these bacteria, and increases their phagocytosis and killing. In contrast, SP-A binds poorly to smooth variant forms of lipopolysaccharide; gram-negative bacteria that colonize the respiratory tract usually express smooth variants that avoid detection. SP-A enhances the adherence and subsequent clearance of mycobacteria,[160] certain fungal pathogens, and the opportunistic pathogen *Pneumocystis jirovecii.*[161] SP-A also binds to a variety of viruses, including influenza and respiratory syncytial virus, and likely aggregates the virus, which may inhibit infection.[162–165]

SP-A suppresses the secretion of inflammatory cytokines by macrophages in the normal lung but enhances cytokine production during infection or lung injury, a duality referred to as the inflammatory paradox of SP-A. The precise receptors on target immune cells mediating this function are unknown. Identifying functional cell receptors for SP-A and SP-D has been challenging because both are polyvalent lectins and can bind to a variety of glycoproteins and glycolipids.[140] Receptors for SP-A exist on AT2 cells[166–168] for surfactant recycling and on macrophages for clearance of apoptotic cells,[169,170] surfactant clearance, and modulation of the innate immune response.[171,172] Currently, the precise role of individual SP-A receptors in normal surfactant metabolism or in disease is unknown.

Surfactant Protein B

SP-B is one of two extremely hydrophobic surfactant proteins (with SP-C) crucial for the biophysical activity of surfactant preparations. As a member of the saposin-like family of peptides that interact with lipids, SP-B avidly associates with phospholipids in surfactant and facilitates their adsorption and surface spreading.[132,173–176] SP-B protein found in lung lavage is a homodimer composed of two 79–amino acid polypeptide chains linked by disulfide bonds. Each monomer has five amphipathic helices that interact with the surface of the surfactant monolayer but do not span the entire monolayer.[177] After a process of posttranslational modification, the mature peptide is secreted into the alveolar space exclusively via regulated LB exocytosis as an 18-kDa disulfide-linked homodimer that is exceptionally hydrophobic due to residues comprised predominantly of valine and leucine.

See ExpertConsult.com for a more detailed discussion of SP-B genetics and processing.

In addition to its role in formation of tubular myelin and generation of a surface film, SP-B is necessary for formation of AT2 cell LBs.[184] Both SP-B–deficient patients with homozygous loss of function mutations and SP-B knockout mice lack LBs.[185–187] In vitro, the interaction of SP-B with lipid vesicles causes lysis and fusion, resulting in the formation of phospholipid sheets,[188,189] a process believed to facilitate transformation of multivesicular bodies into the densely packed lamellae characteristic of the LB. Importantly, SP-B deficiency is uniformly fatal (or requires lung transplantation) due to a lack of both mature SP-B and SP-C. The molecular basis for this double deficiency lies in the critical role of the LB in posttranslational processing of the SP-C propeptide.[105,190,191] Therefore, in contrast to SP-C deficiency (discussed later), loss of functional SP-B protein results in complete loss of all hydrophobic surfactant protein function and very high alveolar surface tension.

There is one 11-kb, 11-exon SP-B *(SFTPB)* gene located on the short arm of human chromosome 2. The SP-B gene is expressed in AT2 cells and in nonciliated bronchiolar epithelial (club) cells. SP-B mRNA, proprotein, proprotein intermediates, and mature protein are present in AT2 cells, whereas only SP-B *messenger RNA* (mRNA) and proprotein are detected in club cells; expression in these cells is unlikely to contribute substantially to surfactant activity. Mature SP-B protein is found in alveolar macrophages without detectable SP-B mRNA or SP-B proprotein, suggesting that macrophages scavenge SP-B from the alveolar space via phagocytosis. Transcription of *SFTPB* results in a 2-kb mRNA, which in turn encodes a 381–amino acid pre-proprotein with a molecular weight of 40 kDa, which is processed to a mature SP-B isoform found in alveolar surfactant.[178–180] Exons VI and VII encode mature SP-B. The structural organization of SP-B mRNA is highly conserved among mammalian species, with 67% cross-species homology throughout the pre-proprotein and 80–85% homology within the mature protein domain. Posttranslation, entry into the secretory pathway by proSP-B is mediated by a 23–amino acid N-terminal signal peptide, which is cleaved in the ER. The 79–amino acid mature SP-B peptide is flanked by 177–amino acid N-terminal and 102-amino acid C-terminal propeptide domains, which are removed by sequential cleavages during transit through the secretory pathway by at least two proteases: napsin A and pepsinogen C.[181–183] Proprotein processing includes glycosylation, modification of N-linked carbohydrates, and proteolytic cleavages giving rise first to a 25-kDa intermediate and subsequently a 9- to 10-kDa intermediate. The final N-terminal cleavage produces the mature, bioactive 8-kDa SP-B peptide. The final processing of SP-B probably takes place within the multivesicular bodies, and the mature SP-B homodimer is formed by the time it arrives in the LB.

Surfactant Protein C

Of all surfactant proteins, only SP-C is made exclusively by AT2 cells; SP-C cooperates with SP-B to enhance the surfactant properties of the lipid monolayer. The mature SP-C protein is an extremely hydrophobic peptide composed of 33 to 35 highly conserved amino acids containing a high content of valine, isoleucine, and leucine (≈60–65% of the primary sequence).[192] The segment between residues 13 and 28 forms a hydrophobic α-helix, which is the membrane-spanning portion of SP-C and is extremely stable in lipids or organic solvents. However, in aqueous solutions, SP-C self-aggregates, adopting a β-sheet conformation and forming amyloid fibrils.[193–195] SP-C is thought to stabilize the surface film and minimize film collapse via insertion into the surface monolayer to organize surfactant phospholipids during the respiratory cycle. Unlike SP-B, SP-C does not appear to interact with SP-A and is not needed for the formation of tubular myelin. SP-C is found in all preparations of natural surfactant, and a recombinant form of SP-C has been used in one version of a surfactant replacement therapy. Both normal posttranslational processing events and the processing of disease-causing *SFTPC* mutants are influenced by four main functional domains and structural motifs contained within proSP-C. Extensive work has led to a detailed understanding of these domains and their relative function in SP-C activity.

More information on these domains can be found at ExpertConsult.com.

Although SP-C is dispensable for surfactant biophysical activity, both loss of function and toxic gain of function mutations in the *SFTPC* gene are implicated in chronic parenchymal lung disease in humans. While autosomal recessive *SFTPC* null mutations have not yet been described in humans, SP-C null mice appear normal at birth but eventually develop a strain-dependent chronic pneumonitis and air space enlargement in adulthood and are more sensitive to bleomycin injury.[209–211] Since 2001, heterozygous expression of more than 60 inherited and sporadic *SFTPC* mutations have been linked with interstitial lung disease in both children and adults.[212–215] Mutations in the COOH-terminus domain produce a misfolded proSP-C protein that accumulates in the ER, self-aggregates, and causes AT2 cell ER stress. Mutations in other regions appear to disrupt other AT2 cell quality control pathways, such as macroautophagy.[105] In familial forms of *SFTPC*-related interstitial lung disease, the age of onset of interstitial lung disease varies from the early perinatal period through older adulthood, indicating that genetic background and other disease-modifying genes contribute to fibrotic pathophysiology in these patients.[215] Recently, expression of either of two clinical *Sftpc* mutations in mice induced a fibrotic lung phenotype, providing proof of concept that *SFTPC* mutations and AT2 cell dysfunction are likely drivers of interstitial lung disease.[216,217] Additional disease associations of alveolar cells and proteins are summarized in Table 3.1.

Surfactant Protein D

Like SP-A, SP-D is a multimeric, calcium-dependent lectin that functions primarily as an important component of innate lung immunity.[155,218,219] SP-D binds the phospholipids of surface-active material weakly and is mostly soluble in alveolar fluid. SP-D is found in ER of AT2 cells and in the secretory granules of club cells, but not in LB of AT2 cells or in tubular myelin, and only sparsely in major conducting airways.[110,145] These characteristics emphasize the immune function of SP-D, a collagenous glycoprotein with a complex but highly ordered tertiary structure (see Fig 3.6). The C-terminal CRD domain contains calcium and carbohydrate binding sites[140,220] and is primarily responsible for multivalent binding to surface ligands on microorganisms. Like SP-A, SP-D binds to a variety of microorganisms to promote clearance from the alveolar space. Full oligomerization of both SP-D and SP-A causes amplification of relatively weak interactions across multiple pathogen binding sites, improving clearance.

In addition to its interactions with microbes, SP-D has both pro-inflammatory and anti-inflammatory signaling functions, which involve posttranslational modifications of the protein. The lectin-like CRD head of SP-D inhibits inflammation, whereas the collagenous tail domain stimulates inflammation.[221,222] S-Nitrosylation results in a disruption of SP-D multimers so that monomers predominate, exposing collagenous tail domains,[223] leading to chemoattraction of macrophages. SP-D is up-regulated in a variety of infectious and inflammatory disease states, including allergic asthma, hyperoxic lung injury, bleomycin injury, and *Pneumocystis* pneumonia.[58,224–230] Up-regulation of SP-D has also been observed in hyperplastic AT2 cells present in interstitial lung diseases. SP-D can be detected in normal serum, and elevation of serum SP-D has been proposed as a diagnostic and/or predictive biomarker in a variety of lung diseases, including idiopathic pulmonary fibrosis, COPD, and post–lung transplant recipients.[231–233]

Surfactant Secretion and Turnover

AT2 cells can synthesize, secrete, and recycle all components of pulmonary surfactant, directing the process of surfactant production and turnover. From 10–20% of the surfactant pool is secreted hourly from AT2 cells.[234] Secretion requires active extrusion of the lamellar body contents,[235] which involves fusion of the lamellar body with the plasma membrane.[236,237] Secretion is highly regulated, and multiple checks and balances likely balance surfactant turnover. In vivo, secretion is stimulated by hyperventilation or even a single deep breath or sigh.[238] Secretion is also stimulated by stretch, an important physiologic stimulus leading to an elevation of intracellular calcium in AT1 cells, which is then propagated to adjacent AT1 and AT2 cells via gap junctions,[239,240] potentiating prosecretory signaling[241] and increasing surfactant secretion. In vitro, secretion is greatly stimulated by tetradecanoyl acetate and *adenosine triphosphate* (ATP)[242–245] and is more modestly increased by other agents, including β-agonists and cholera toxin.

After exocytosis by AT2 cells, the secreted LBs undergo physical rearrangements extracellularly (Fig. 3.7). The initial change is the conversion from the multilamellar state to tubular myelin, which as noted earlier requires SP-A, SP-B, and calcium. In lavage samples, surfactant can be segregated by its sedimentation properties into large and small aggregates. Large-aggregate surfactant contains SP-A and SP-B and is composed of tubular myelin, multilamellar structures, and other loose lipid arrays, which are forms of secreted and unraveling LBs.[246] Large aggregates adsorb rapidly to the air-liquid interface and can be considered

The 2.4-kb *SFTPC* gene located on chromosome 8p of humans is organized into six exons (I–V coding, VI untranslated), which produce a 0.9-kb mRNA encoding either a 191– or 197–amino acid 21-kDa proprotein (proSP-C_{21}).[106,107,192] Key functional domains in SP-C include the following. (1) An NH_2-targeting domain: Mutagenesis studies have identified and characterized a PPxY (PY) motif within the NH_2 propeptide that is crucial for post–ER/Golgi proSP-C trafficking.[196,197] The PPDY motif, which serves as a ligand for tryptophan-tryptophan domains, was shown to interact with two tryptophan-tryptophan domain–containing members of an E3 ubiquitin ligase family, Nedd4, and Nedd4-2 (Nedd4-L).[198] Nedd4-2 was subsequently shown to exert the dominant effect on proSP-C transport catalyzing monoubiquitination, a well-known signal for lysosomal targeting of proteins, of proSP-C_{21} at lysine residue 6 of the cytosolic NH_2 propeptide.[199] (2) Mature SP-C (*transmembrane* [TM]) domain: Functionally, in the context of the propeptide, mature SP-C acts as a noncleavable signal anchor peptide for proSP-C_{21}, facilitating its translocation to the ER.[196,200,201] In addition, a conserved pair of juxtamembrane basic amino acids, lysine and arginine (at positions 34 and 35, respectively, of human proSP-C), play an essential role in the determination of the type II TM topology of proSP-C_{21}.[201] (3) The BRICHOS domain: The distal proSP-C_{21} COOH-terminus (residues 94–197) shares a high degree of structural homology with domains identified in more than 300 proteins.[202] The term BRICHOS was derived from the original disease-associated family members, including *BRI2*, linked to familial British and Danish dementia, chondromodulin-1, and SP-C.[203] The structural similarity of these three is punctuated by the fact that each exists as integral type II TM proteins composed of a cytosolic region, a TM segment, a linker domain, and the BRICHOS domain containing a pair of positionally conserved cysteine residues. Human *SFTPC* encodes for four cysteines in its BRICHOS domain. Cysteines 121 and 189 represent the positionally conserved BRICHOS cysteine residues that are invariant across species and thought to mediate the primary folding function. Mutation of either one of these BRICHOS cysteine residues results initially in proximal (ER) retention and formation of unprocessed polyubiquitinated proprotein aggregates.[204] Functionally, in addition to promoting proSP-C folding, the BRICHOS domain appears to have an intramolecular chaperone-like activity safeguarding the metastable, β-sheet–prone, mature SP-C domain from amyloid fibril formation.[205,206] Amyloid deposits composed of proSP-C have also been observed in lung tissue samples from patients with mutations in the BRICHOS domain.[207] (4) Linker: As the name signifies, the proximal COOH-terminal propeptide (residues 59–93) is linearly positioned between the mature SP-C (TM) and BRICHOS domains, and through formation of a β-hairpin structure facilitates docking of the BRICHOS domain to the TM segment. Of importance, mutations in the linker domain do not induce cytosolic aggregation of proSP-C but instead result in its mistrafficking and accumulation in the plasma membrane and endosomal compartments of AT2 cells.[208]

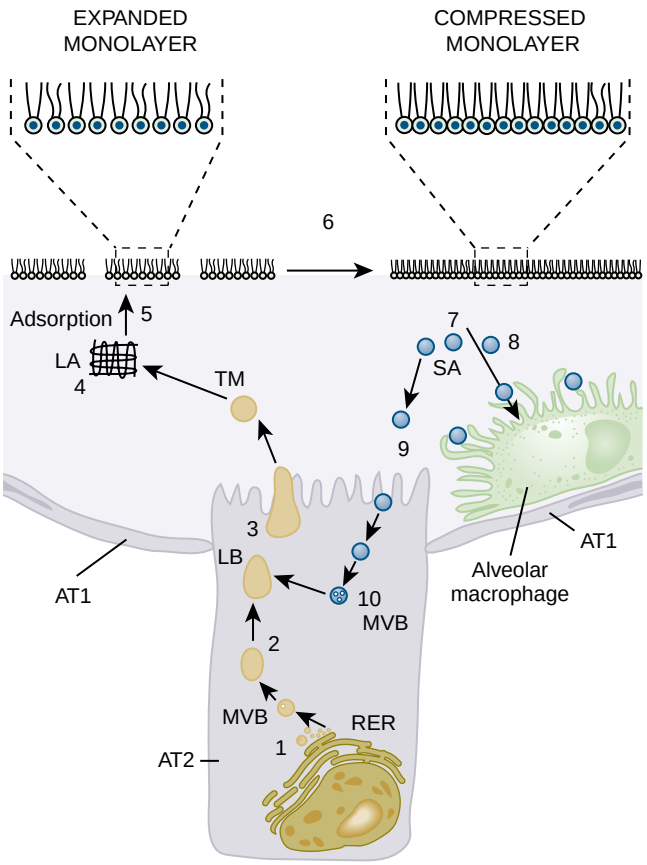

Figure 3.7 Metabolic trafficking of surfactant phospholipids. The phospholipids are synthesized in the rough endoplasmic reticulum (RER) of the alveolar type 2 (AT2) cell (1). They are transported to the multivesicular bodies (MVB) (2), where the first lamellae are formed. These lamellae increase to form lamellar bodies (LB), which are subsequently secreted by exocytosis (3). The secreted LB unfolds to form tubular myelin (TM) (4) and other large aggregates (LA). These forms adsorb into the expanded surface monolayer (5). This is a critical step for producing a low surface tension in the alveolus. During the respiratory cycle, as the film is compressed during exhalation, the film pressure rises, and a compressed, closely packed monolayer of nearly pure dipalmitoylphosphatidylcholine is formed (6). Material is excluded from the monolayer (7) and forms small aggregates (SA). Some of these aggregates are ingested by macrophages (8), but most are endocytosed for reprocessing by AT2 cells (9 and 10). AT1, alveolar type 1 (cell).

an extracellular reservoir of surfactant. Small aggregates, which are much less surface active,[247] are thought to represent surfactant that has left the air-liquid interface and is available to be cleared from the alveolar space.

To maintain steady-state pool sizes of extracellular surfactant, secretion needs to be counterbalanced by surfactant removal. The two dominant routes for the clearance of surface-active material are reuptake by AT2 cells for reprocessing (≈50–85%) and phagocytosis by alveolar macrophages for catabolism.[236,237] Reuptake of extracellular surfactant by AT2 cells can be increased in response to surfactant secretagogues, such as ATP and phorbol myristate acetate.[248] Catabolism of extracellular surfactant is regulated by *granulocyte-macrophage–colony-stimulating factor* (GM-CSF) and its ability to activate macrophages (more details of this pathway can be found in Chapter 98).[249–253] Taken together, these data emphasize that the full complement of surfactant components, the appropriate management of cellular secretion, and regulated surfactant reuptake and removal from the alveolar space are all collectively required to maintain alveolar homeostasis and promote gas exchange.

ALVEOLAR IMMUNE DEFENSE AND INFLAMMATORY MODULATION

The alveolar epithelium forms a thin, single cell surface separating the outside world from the pulmonary circulation. Due to the large amounts of air exchanged during breathing, the distal lung is bombarded with environmental pathogens, particulates, and toxins. To maintain immune quiescence, pulmonary epithelial cells partner with professional immune cells in both the alveolar space and the interstitium to activate adaptive immunity appropriately in the event of barrier breach or infection, while at the same time preventing aberrant inflammatory responses to limit damage. There are three major components of the alveolar immune defense: (1) the surfactant system (reviewed earlier), (2) alveolar epithelial barrier function (reviewed later), and (3) innate host defense in coordination with alveolar cells. This section focuses on the role of the alveolar epithelium in directing immune defense in the alveolus.

Alveolar epithelial cells are constantly exposed to both commensal and pathogenic microorganisms throughout life. Traditional teaching that the alveolus is a sterile space has been supplanted by an understanding, based on modern molecular techniques, that healthy patients harbor a microbiome in the distal lung similar to that in the more proximal airways[254] (see Chapter 17). The resident microbes differ between smokers and healthy patients and vary in multiple lung diseases, including cystic fibrosis and COPD. Antibiotic treatment during late gestation, which limits acquisition of these commensal bacteria, alters the development of pulmonary innate immunity and worsens outcomes of experimental pneumonia, emphasizing the instructive role of commensal bacteria in priming the alveolar immune system.[255]

Alveolar epithelial cells also directly participate in immune defense. AT2 cells express cell surface receptors, including *toll-like receptor* (TLR) family molecules, which allow direct recognition of both commensal and pathogenic bacteria in the alveolar space. TLR2 and TLR4 on AT2 cells are activated in response to viral infections, cigarette smoke, and multiple inflammatory cytokines.[256] Epithelial cells then coordinate with innate immune lineages, especially alveolar macrophages, to balance the immune response. AT2 cells, for example, produce the macrophage growth factor GM-CSF,[257] which is required for proper differentiation of alveolar macrophages in the alveolar space; abnormalities in alveolar macrophage maturation can lead to pulmonary alveolar proteinosis (reviewed in Chapter 98). AT1 cells express high amounts of *receptor for advanced glycation end products* (RAGE),[61] a protein associated with modulation of inflammation in both inflammatory and stromal cells in the lung[258] and a major danger-associated molecular pattern receptor in multiple tissues, including the lung. Finally, as reviewed in detail later, multiple inflammatory stimuli modify the secretion and absorption of fluid in the alveolus during pathologic conditions, directly impacting gas exchange by modifying airway surface-liquid properties. These findings implicate alveolar epithelial cells as direct participants in lung inflammation and immune defense and emphasize the coordinated activity required to maintain functional surface area for gas exchange.

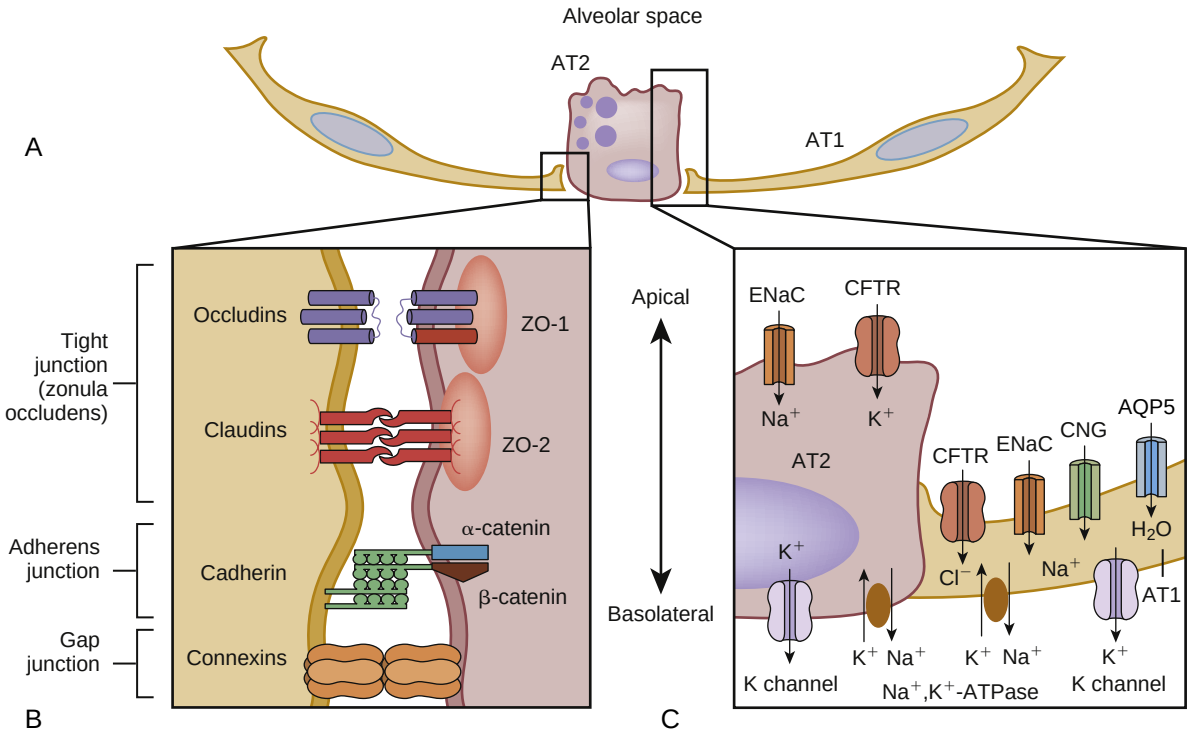

Figure 3.8 Schematic representation of junctions and ion transporters critical to lung epithelial barrier function and fluid handling. (A) Overall schematic showing *alveolar type 1* (AT1) and *alveolar type 2* (AT2) cells in the alveolus. Cell-cell junctions are important to maintain the alveolar epithelial barrier. (B) Schematic of junctional complexes and proteins in the alveolus. Alveolar epithelial cells are connected by tight, adherens, and gap junctions with differential localization of claudins, occludins, cadherins, and connexins. See text for details. (C) Schematic of key apical and basal transporters regulating ion and fluid flow in the alveolar epithelium. See text for detailed discussion of the role of each transporter in alveolar physiology. AT2 cell has been reduced in size to simplify representation. AQP5, aquaporin 5; ATPase, adenosine triphosphatase; CFTR, cystic fibrosis transmembrane regulator; Cl^-, chloride ion; CNG, cyclic nucleotide–gated sodium channels; ENaC, epithelial Na^+ channel; K^+, potassium ion; Na^+, sodium ion; ZO-1, ZO-2, zonula occludens–1 and –2, respectively.

ALVEOLAR EPITHELIAL INTEGRITY AND BARRIER FUNCTION

Alveolar epithelial cells form a barrier separating "external" environmental hazards from the inside of the body. This barrier is constantly challenged. Therefore multiple cellular and extracellular components form a multilayered barrier designed to maintain epithelial integrity without impairing gas exchange. As noted earlier, the first barrier encountered by environmental pathogens is the surfactant system, where SP-A and SP-D bind particulates and pathogens in a pattern-specific manner, augmenting alveolar macrophage function in clearing the alveolar space. Alveolar fluid also contains other defense molecules, including lysozyme, an enzyme that catalyzes the destruction of bacterial cell walls, providing a further barrier above the epithelial surface.

If pathogens and environmental particulates circumvent these barriers, they then reach the epithelial layer. Alveolar epithelial cells are connected by a series of cell-cell junctions that function to coordinate cell behavior and prevent passage of solutes and deleterious molecules between cells (Fig. 3.8). Proper gas exchange is predicated on minimization of fluid in the air space, and the alveolar epithelium contains a host of junctional connections to create one of the tightest epithelial barriers in the human body. The homeostatic function of this barrier is to prevent passive leak of fluid into the air spaces. Thus injury to the junctional proteins and complex leads to alveolar edema and hypoxemia. Barrier damage is a major part of the pathophysiology of ARDS (see Chapter 134), and fluid management in the alveolus is reviewed in detail later.

Tight junctions (also called *zonula occludens* [ZO]) connect adjacent alveolar epithelial cells, where claudins, including Cld3, Cld4, and Cld18,[73] form close connections between AT2 and AT1 cells. Although each of these claudins is expressed in both AT1 and AT2 cells, levels of expression differ between cell types, and AT1-AT1, AT2-AT1, and AT2-AT2 tight junctions have different stoichiometry of these components, as well as other core tight junction proteins, including occludin, tricellulin, junctional adhesion molecule, and ZO-1 and ZO-2.[11] Mouse knockout studies[72,74,239,259] have demonstrated key roles for claudins in both tight junction function and fluid clearance, and injury studies have implicated claudins as key regulators of severity of injury in several human disease and animal models. Within the tight junction, claudins form selective pores allowing regulation of passage of ions and molecules between adjacent epithelial cells.[260] Regulation of formation and degradation of these tight junctions impact both the integrity of the epithelial barrier and the management of fluid and ion transport in the alveolus. Permeability of the alveolar epithelial barrier to ions and solutes is regulated by the precise distribution and interactions of claudins, which are expressed in a cell-specific manner. Recent studies also implicate claudins in regulation of other cellular functions, such as cell proliferation.[261]

Below the tight junction, the adherens junctions, formed of E-cadherin and β-catenin, connect alveolar epithelial cells under homeostatic conditions.[262] Disruption of adherens junctions can potentiate injury to tight junctions after inflammatory injury to the lung,[263] and breakdown in the adherens junctions is also associated with increased

neutrophil infiltration. Both AT1 and AT2 cells also express connexins, form gap junctions, and coordinate cellular signaling in response to stretch and other stimuli. Below the epithelial cell, endothelial cells also form both tight and adherens junctions, forming an additional barrier to passage of fluid, ions, and pathogens.[264] This combination of cellular and extracellular barriers forms a multilayered, resilient, and coordinated system protecting the integrity of the lung.

ALVEOLAR FLUID CLEARANCE AND ION TRANSPORT

An intact barrier is also required to keep the alveolus free of fluid. The close apposition between the alveolar epithelium and the vascular endothelium, in addition to facilitating gas exchange, creates a tight barrier restricting passive movement of liquid, ions, and proteins from the interstitial and vascular spaces, thus assisting in maintaining the relatively dry condition of the alveolar air spaces.[265] Of note, the alveolar epithelium, rather than the endothelium, is believed to be the chief permeability barrier to small, water-soluble molecules.[266,267] Therefore, directed transport of ions, fluid, and proteins across this epithelial layer is essential for maintenance of normal gas exchange and for resolution of both cardiogenic and noncardiogenic pulmonary edema. This transport is made possible via a combination of active and passive transport, mediated by both ion channels and ion pumps.[268] Channels, when open, allow the passive diffusion of ions rapidly down electrical and concentration gradients, which results in the generation of transmembrane electric currents. In contrast, pumps actively transport ions against the electrochemical gradient in an energy-dependent fashion. Ion transporters and other membrane proteins asymmetrically distributed on apical and basolateral surfaces coordinately regulate the directional transport properties of the alveolar epithelium (see Fig. 3.8).[269,270]

For many years, differences in hydrostatic and protein osmotic pressures (Starling forces) were thought to account for the removal of excess fluid from the air spaces of the lung.[270,271] Evidence for the contribution of active ion transport to *alveolar fluid clearance* (AFC) came from extensive in vivo and in vitro experimental studies.[270,272–274] Intratracheally administered fluid is cleared from the alveolus into the interstitium,[275–277] and lymphatic drainage subsequently removes the fluid from the interstitium.[278,279] Clearance is inhibited by amiloride and ouabain, pharmacologic inhibitors of *sodium* (Na^+) channels and Na^+ pumps, respectively,[280,281] emphasizing the importance of Na^+ movement in alveolar fluid clearance. Of interest, there are major species differences in both basal and stimulated rates of AFC, although mechanisms responsible for these differences are not entirely clear.[275,277,281–290]

It is now accepted that the asymmetrical distribution of ion transporters and other membrane proteins on opposing cell surfaces confer directional transport properties to the polarized alveolar epithelium.[270,276] Furthermore, whereas active ion transport was initially thought to be primarily a function of AT2 cells, it is now appreciated that both AT1 and AT2 cells contribute,[26,27,68,70] and it is likely that AT1 cells make a larger contribution to ion transport and fluid clearance than AT2 cells[15,26] due to their extensive surface area. AT1 and AT2 cells express a partially overlapping set of membrane ion channels and pumps, including the *epithelial sodium channel* (ENaC),[270,272,291] *cyclic nucleotide-gated* (CNG) cation channels,[292] *cystic fibrosis transmembrane regulator* (CFTR),[68,293,294] *potassium* (K^+) channels,[295] β-aminobutyric acid type A ($GABA_A$) channels, and voltage-gated *chloride channels* (CLC2 and CLC5) (see Fig. 3.8).[68]

These transporters coordinate to maintain appropriate fluid clearance. Na^+ ions enter *alveolar epithelial cells* (AECs) at the apical membrane and are pumped out at the basolateral membrane by Na^+,K^+-*adenosine triphosphatase* (ATPase).[38,270,276,296] The apical entry step is passive, and Na^+ flows down a chemical potential gradient, whereas basolateral transport requires energy to move ions against the gradient. Because of pump activity, the K^+ electrochemical potential is larger inside the cell, and K^+ leaks through K^+ channels at the basolateral membrane and is then actively transported back into the cell by Na^+,K^+-ATPase to maintain the Na^+ gradient. Mechanisms for Na^+ transport are better understood than are mechanisms for chloride (Cl^-) and K^+ transport.[297] Water channels, including AQPs, participate in passive movement of water through the epithelial barrier, driven by the osmotic gradient created by ion movement. The water channel AQP5, which is localized in the apical plasma membrane of AT1 cells, is thought to be responsible for their extremely high osmotic water permeability,[23,298,299] although, surprisingly, *Aqp5* knockout mice show reduced osmotic water permeability but intact fluid clearance, suggesting that other water channels also participate in fluid clearance by AT1 cells. The molecular basis for water transport across the basal surface of the alveolar epithelium remains unknown.[300,301]

Developmental Ion and Fluid Management

During in utero gestation in mammals (reviewed in Chapter 2), the alveolus is suffused in amniotic fluid and is primarily secretory.[300] During gestation the lung epithelium actively secretes Cl^-, although the precise channel responsible for this activity is unknown. Na^+ is driven across the membrane passively, secondary to high intracellular concentrations and Cl^- flux, and the combined activity of Na^+ and Cl^- provide an osmotic gradient driving water into the alveolar lumen. Absence of appropriate secretion of fluid can lead to development of hypoplastic lungs, a process likely mediated primarily by physical forces, including stretch.[302] At birth, the lung must transition from fluid secretion to fluid absorption.[300,303] Whereas some fluid is mechanically expelled due to compression of the chest wall during labor, the majority of fluid clearance is driven by ENaC; up-regulation of ENaC expression in alveolar epithelium is dependent on the combination of glucocorticoid and thyroid hormone signaling.[304] ENaC activity leads to Na^+ absorption, reversing the gradient for osmotic water flow and helping remove fluid from the alveolus. After this transition, the alveolar surface in the postnatal lung is lined by a thin (average, 0.2 μm) layer of *alveolar lining fluid* (ALF).[305–307] ALF is thought to prevent cells from drying out by preventing direct contact between alveolar epithelial cells and air.[307] The volume, depth, and pH of this fluid are tightly regulated, in part through management of Na^+ flux. Inhibition of ENaC or Na^+, K^+-ATPase reduces fluid clearance in adult lungs by as much as 80%, depending on the species,[270,287,308] and inhibition of either is associated with increased depth of alveolar

TABLE 3.3 Impact of Signaling Pathway Modulation on Alveolar Fluid Clearance

Ion Transport Modulator	Effect on Alveolar Fluid Clearance	Proposed Mechanisms	References
Glucocorticoids	Increased	Up-regulates ENaC expression	370, 409, 410
Thyroid hormone	Increased	Increases Na^+,K^+-ATPase translocation to cell surface	411
Insulin	Increased	Up-regulates ENaC expression	412
Estradiol	Increased	Increases α-ENaC at cell surface	413
Dopamine	Increased	Increases activity of Na^+,K^+-ATPase	414
Leukotriene D4	Increased	Increases activity of Na^+,K^+-ATPase by recruitment of α subunit to membrane	415
Serine proteases	Increased	Activates ENaC	416–418
KGF/FGF7	Increased	Stimulates AT2 cell proliferation and activates ENaC	47, 419–421
EGF	Increased	Increases expression of α and β subunits of Na^+,K^+-ATPase	355, 356
TGF-β	Mixed	Decreases ENaC at membrane and increases Na^+,K^+-ATPase activity	422–424
Purine nucleotides (e.g., adenosine)	Mixed	Regulates ENaC and CFTR activity	374, 425–427
Angiotensin II	Decreased	Decreases cAMP	428
IL-8	Decreased	Decreases cAMP	429
IL-1β	Decreased	Decreases α-ENaC expression and barrier dysfunction	430
TNF-α	Mixed	Mediates barrier dysfunction, but activates ENaC	431–439
Maresins/resolvins	Increased	Stimulates Na^+ channels and Na^+,K^+-ATPase activity	440–442

AT2, alveolar type 2 (cell); ATPase, adenosine triphosphatase; cAMP, cyclic adenosine monophosphate; CFTR, cystic fibrosis transmembrane regulator; EGF, epithelial growth factor; ENaC, epithelial sodium channel; FGF, fibroblast growth factor; IL, interleukin; K^+, potassium ion; KGF, keratinocyte growth factor; Na^+, sodium ion; TGF-β, transforming growth factor-β; TNF-α, tumor necrosis factor-α.

surface fluid. ALF depth influences the diffusion rate for O_2 and carbon dioxide, implying that substantial increases may be deleterious for gas exchange, but limited evidence is available to determine the consequences of changes in ALF volume or composition during more normal conditions.

Roles of Individual Ion Transporters

Epithelial Na^+ channels. The primary pathway for Na^+ entry is via apical amiloride-sensitive ENaC, with basolateral Na^+,K^+-ATPase driving Na^+ into the interstitium to maintain intracellular Na^+ at low levels to allow passive apical transport.[309,310] ENaC channels comprise both *highly selective cation* (HSC) and *nonselective cation* (NSC) channels, with differing cation and amiloride sensitivity. Both AT1 and AT2 cells express the two types of ENaC channels, with HSC exceeding NSC by 10- to 15-fold.[68,311–313] HSC channels have a selectivity for Na^+ over K^+ and are inhibited by amiloride.[68,272] NSC channels are equally selective for Na^+ and K^+ and are inhibited by higher concentrations of amiloride. HSC channels have been proposed to constitute the rate-limiting step for amiloride-sensitive Na^+ absorption.[314] HSC channels are composed of three homologous α, β, and γ subunits.[315–317] A fourth novel δ subunit has been identified in human lungs and most closely resembles the α subunit, but its expression level is low,[318] and its functional role is unclear. The four ENaC subunits have distinct patterns of tissue distribution,[319] and AT1 and AT2 cells express α, β, and γ ENaC subunits.[26,27,68] The composition of NSC channels is less clear; these have been suggested to consist of α-ENaC alone[320] or a combination of α-ENaC with acid-sensing ion channel 1a proteins.[321] ENaC can be regulated at transcriptional and posttranscriptional levels, including by changes in membrane trafficking and altered stability in the apical membrane. Alterations in activity after physiologic and pathologic factors may contribute to impairment of alveolar fluid clearance (Table 3.3).[309,311,319] α-ENaC knockout mice die at birth due to inability to clear fluid from their lungs,[314,322] and α-ENAC knockdown decreases basal AFC and response to β-agonists.[323] The β and γ subunits appear less important.[324–327]

Cyclic nucleotide-gated channels. Apically located amiloride-insensitive CNG channels provide another Na^+ entry pathway in the alveolar epithelium. CNG channels have been observed in cultured, but not freshly isolated, AT2 cells[328] and in both freshly isolated AT1 cells[68] and AT1 cells in lung slices.[292] CNG channels have equal selectivity for Na^+ and K^+, are inhibited by *guanosine monophosphate* (GMP) inhibitors, stimulated by GMP analogues, and variably blocked by pimozide and L-*cis*-diltiazem.[329] Other Na^+ channels implicated in amiloride-insensitive transport in AECs include the sodium-glucose transporter[330,331] and the Na^+-coupled neutral transporter.[332,333] The exact role of these channels is unclear.[334]

Chloride channels. Both AT1 and AT2 cells express a number of Cl^- transport proteins, including CFTR, the CLC2 and CLC5 channels of the CLC family of voltage-gated Cl^- channels, and the $GABA_A$ channel of the ionotropic receptor family of Cl^- channels[68,69,335,336]; however, consensus is lacking as to their role in adult Cl^- absorption versus secretion in the alveolar epithelium. CFTR allows bidirectional

transport of Cl^-, depending on the electrochemical gradient. Activation of CFTR is dependent on intracellular cAMP or GMP.[337] The role of CFTR in Cl^- transport under basal conditions in the adult alveolus is controversial, with some studies demonstrating that CFTR is responsible for Cl^- absorption[293,294,337] and other studies demonstrating that CFTR is responsible for Cl^- secretion.[335,338,339] Under conditions of β-agonist stimulation, Cl^- absorption appears to be important for AFC in whole mouse lungs and human lungs ex vivo. CFTR function in the alveolus is not associated with regulation of lung mucociliary clearance, an important consequence of CFTR function in the airway epithelium. As noted later, the precise role of Cl^- balance remains unclear to date.

Na^+,K^+-ATPase. The activity of the Na^+,K^+-ATPase pump provides the driving force for Na^+ resorption by maintaining low intracellular levels of Na^+. The Na^+ pump exchanges cytoplasmic Na^+ for extracellular K^+ at the basolateral membrane[310] and is inhibited by ouabain. Na^+,K^+-ATPase is a heterodimer composed of two subunits, α and β, and small accessory transmembrane proteins that modulate pump activity.[269,340–342] The existence of four α, three β, and up to seven accessory subunit isoforms leads to extensive isozyme diversity.[343] The specific subunit expression pattern of a cell is a major determinant of overall Na^+ pump activity, based on the differing enzymatic properties of the various isozymes.[344] The α subunit harbors the catalytic domain of the Na^+ pump, is phosphorylated by ATP, and binds ouabain, whereas the β subunit regulates pump activity and localization at the cell membrane.[340,345,346] Na^+ pumps comprised of α_1 and β_1 subunits are the predominant isozymes expressed in freshly isolated AT2 and AT1 cells,[26,27,47,347] although the α_2 isoform was also expressed in AT1 cells in whole lung and in cultured AT2 cells.[348] Activity of Na^+,K^+-ATPase can be regulated by changes in ion affinity and/or abundance.[349] Na^+ pumps are also regulated either indirectly in response to increases in intracellular Na^+[350] or directly by several mechanisms, including β-adrenergic agonists,[351,352] dopamine,[353] corticosteroids,[354] and growth factors,[355,356] among others[343] (see Table 3.3).

Potassium channels. A number of K^+ channels are present on AECs and are important for maintaining membrane potential and the electrochemical gradient required for ion and fluid transport.[295,297,357] It has been suggested that K^+ channels modulate fluid clearance through effects of Na^+ and Cl^- transport.[358] Maintenance of high extracellular K^+ helps maintain Na^+ gradients through the activity of Na^+,K^+-ATPase as noted earlier, and K^+ (ATP) channels have been functionally identified in freshly isolated and cultured AECs.[358] Potassium channels also have been shown to play a role in O_2 sensing. The precise nature of how these channels function and coordinate with other currents is an area of active investigation.

Physiologic Regulation of Ion and Fluid Transport

Directional fluid transport across the distal pulmonary epithelium is regulated by catecholamine-responsive effects on Na^+ channels, Na^+ pumps, and CFTR. Elevated levels of endogenous catecholamines or exogenous administration of β_2-adrenergic receptors can each increase alveolar fluid clearance. Endogenous catecholamines (e.g., epinephrine) stimulate fluid reabsorption from fetal lung at birth[359,360] and increase fluid clearance in conditions such as septic shock[361] and neurogenic pulmonary edema.[362] In most adult mammalian species, stimulation of β_2-adrenergic receptors increases fluid clearance.[284,363–366] Increased fluid clearance in response to β_2-agonists can be inhibited by amiloride or by RNA interference against α-ENaC, indicating that stimulation is related to increased transepithelial Na^+ transport.[323,364] Both AT2[367,368] and AT1 cells express β_1- and β_2-adrenergic receptors, and increased fluid clearance in response to β_2-agonists can also be inhibited by β_2-adrenergic receptor antagonists.

Chloride transport cooperates with Na^+ transport during periods of adrenergic stimulation, with in vitro studies suggesting that CFTR-mediated Cl^- transport[294] is required for cAMP-stimulated fluid Na^+ absorption.[337,369–371] Furthermore, β-agonist stimulation does not increase fluid clearance in Δ508 CFTR mice.[366,372] These results contrast with other studies suggesting Cl^- secretory pathways are active at baseline in rats,[336] mice,[373] and human AT2 cells,[374] and after terbutaline stimulation in rats[375] and rabbits.[376] Furthermore, in hydrostatic pulmonary edema, reversal of transepithelial Cl^- flux via CFTR has been shown to drive alveolar fluid secretion accompanied by inhibition of amiloride-sensitive Na^+ uptake.[339] Therefore the precise role of Cl^- absorption versus secretion during alveolar fluid clearance remains controversial and may depend on the experimental model and specific conditions tested.

Catecholamine-independent mechanisms have also been identified that regulate ion and fluid transport across the distal air spaces of the lung. A number of such pathways are listed in Table 3.3. Effects of many of these modulators, especially growth factors and inflammatory cytokines, are complex because they also affect cell proliferation, barrier function, and resolution of injury independent of effects on ion transport. Several of these modulators provide effects that could potentially be harnessed therapeutically in the future to improve fluid clearance under conditions of alveolar flooding, potentially with additional regenerative effects.

Impaired Fluid Clearance and Resolution of Alveolar Edema Under Pathologic Conditions

Accumulation of fluid in the alveolar air spaces is a common cause of clinically relevant hypoxemia, common to cardiogenic pulmonary edema, usually caused by increases in hydrostatic pressure and conditions of increased vascular and epithelial permeability, such as ARDS. An intact epithelial barrier is crucial for the resolution of alveolar edema in humans.[377] Patients with severe hydrostatic edema generally demonstrate intact fluid clearance.[378] In contrast, most patients with ARDS have markedly impaired fluid clearance, which is associated with worse clinical outcomes.[379] Consistent with the notion that the degree of epithelial injury is an important determinant of outcome in patients with ARDS, elevated levels of RAGE, a marker of AT1 cell injury, correlate with impaired AFC in isolated perfused lungs.[380]

Several conditions coexisting with ARDS also adversely impact fluid clearance and worsen alveolar edema.

Exposure of human AT2 cells to edema fluid from ARDS patients decreased expression of ENaC, Na^+,K^+-ATPase, and CFTR with reduction in net vectorial fluid transport. Respiratory pathogens, including influenza virus, can impair epithelial fluid transport via direct and indirect effects on ENaC, Na^+,K^+-ATPase, and CFTR,[381] thus promoting edema accumulation. Chronic alcohol ingestion exacerbates alveolar edema during ARDS due to inhibitory effects on ion transport. Both hypoxemia and hypercapnia can inhibit transepithelial Na^+ transport through acute and chronic effects on both ENaC and Na^+,K^+-ATPase, further limiting fluid clearance and exacerbating alveolar edema.[382,383] Finally, the overall inflammatory milieu during ARDS includes a number of soluble mediators that also impair AFC, including classical proinflammatory cytokines (e.g., TNF-α and L-1β), reactive O_2 species and reactive O_2-nitrogen species,[384,385] and extracellular nucleotides (see Table 3.3).

Given the impact of decreased fluid clearance on outcomes in ARDS, strategies to increase AFC have been an important focus both experimentally and therapeutically. Although β-adrenergic agonists effectively up-regulate AFC in hydrostatic pulmonary edema and experimental lung injury models,[386–389] two randomized clinical trials of either aerosolized (albuterol) or intravenous selective β_2-agonists (salbutamol) failed to show improved clinical outcomes in patients with ARDS, perhaps because the injury to the alveolar epithelium was too severe[390,391] or because of the challenges in delivering the drug to injured alveoli. Similarly, prophylactic use of corticosteroids and β-agonists in patients at risk of developing ARDS was not effective.[392] Other approaches being explored therapeutically include mesenchymal cells, which, among a variety of effects, improve ion transport in experimental models, with conditioned medium from mesenchymal stem cells restoring Na^+ transport in primary rat AECs.[393] Further studies will be needed to identify patients who may benefit from tailored strategies to improve AFC and to identify the ideal time to provide such therapy to patients with ARDS.

ALVEOLAR EPITHELIAL REPAIR

After acute injury to the alveolar epithelium, restoration of the cellular components, barrier function, and fluid transport are required to restore gas exchange. Under homeostatic conditions, the alveolar epithelium is relatively quiescent, with limited cell renewal.[44,99,394,395] After injury, AT2 cells proliferate rapidly and differentiate to regenerate the epithelial surface. Landmark studies demonstrating the differentiation of AT2 to AT1 cells were performed in rodents using radiolabeling with tritiated thymidine to identify the proliferating cells after oxidant injury; these studies showed labeling first in AT2 cells and later in AT1 cells.[41–43,396] More recent studies of primary AT2 cells in two-dimensional and three-dimensional culture conditions confirm that AT2 cells serve as a progenitor cell for AT1 cells, whereas genetic lineage tracing experiments in mouse models confirm the progenitor role of AT2 cells for repair of the alveolar epithelium—capable of both self-renewal and differentiation into AT1 cells.[41–44,99,397]

A number of signaling pathways and transcription factors have been implicated in the regulation of AT2 to AT1 cell differentiation, including Wnt/β-catenin,[99,398–401] TGF-β,[48,49,66] Hippo (both YAP and TAZ),[402,403] retinoid X receptor,[63] and Notch.[404] There is also evidence of heterogeneity among AT2 cells, with subsets of cells having greater proliferative capacity[99,405] and ability to give rise to AT1 cells.[99,397,406] Furthermore, single-cell RNA sequencing of AT2 cells during regeneration after lipopolysaccharide-induced lung injury has identified distinct populations of AT2 cells in different states, including proliferating, cell cycle–arrested, and transdifferentiating.[66]

In contrast, AT1 cells have been regarded as terminally differentiated cells without significant proliferative potential, although recent data have shown that a small number of AT1 cells exhibit increased plasticity in mouse models[35] or in culture,[46,57,86,407,408] raising the possibility that at least some AT1 cells are not terminally differentiated. Heterogeneity among AT1 cells was further interrogated by single-cell RNA sequence analysis of postnatal AT1 cells,[65] which demonstrated that 95% of AT1 cells did not proliferate after pneumonectomy or form organoids in culture, suggesting these cells were terminally differentiated. Together, these findings indicate that AT2 cells are the predominant progenitor during alveolar repair and highlight the complexity of the regenerative process. Ongoing work continues to identify the factors needed to balance proliferation and differentiation for effective epithelial repair. For a discussion of additional potential progenitor relationships in the lung and their possible contributions to alveolar repair, see Chapter 8.

DISEASES OF THE DISTAL LUNG EPITHELIUM

Consistent with the central role of the alveolus in the maintenance of functional gas exchange and the complex roles reviewed earlier, numerous disease entities have been identified involving alveolar structure and function. Many of the subsequent chapters in this text contain detailed descriptions of lung diseases with a primary or secondary pathogenesis in alveolar injury. A number of diseases, however, specifically relate to dysfunction of the lung epithelium in one of the key roles reviewed earlier. Table 3.1 lists many of the key clinical entities associated with distal epithelial dysfunction. Of note, these diseases present throughout the human life span, with both congenital and acquired alveolar dysfunction often presenting both in childhood and adulthood. Surfactant mutations, for example, are associated with interstitial lung disease in both children and adults and share some common pathophysiology, while also exhibiting distinct characteristics depending on age of presentation. Alveolar proteinosis (reviewed in Chapter 98) can be acquired, hereditary, or autoimmune. Dysfunctional transport of ions and fluids across the alveolar surface is a prominent feature of ARDS (see Chapter 134) but is also present in rare genetic disorders, such as multisystem pseudohypoaldosteronism. This range and spectrum of disorders associated with alveolar function emphasize the important physiologic roles of the alveolar epithelium and provide a number of opportunities to learn more about alveolar function for a better understanding of dysfunction in disease.

Key Points

- The lung alveolus is the primary site of gas exchange.
- Normal function of the alveolar unit requires the combined function of epithelial, mesenchymal, and endothelial cells.
- Alveolar type 1 cells provide the surface for gas exchange and are active participants in maintenance of alveolar fluid homeostasis.
- Alveolar type 2 cells produce, process, and regulate surfactant components; function in ion transport; participate in immune surveillance; and serve as alveolar progenitor cells during regeneration.
- Surfactant lipids and proteins function to maintain appropriate surface tension to prevent alveolar collapse and function as integral members of the alveolar innate immune system.
- Surfactant processing and pool management are crucial for maintenance of alveolar function.
- Epithelial cells lining the alveolus provide a tight barrier to protect the distal air spaces for gas exchange.
- Resolution of alveolar edema requires an intact epithelial barrier and is driven by active ion transport.
- The primary mechanism for reabsorption of excess alveolar fluid is active Na^+ and Cl^- transport driven by basolaterally located Na^+,K^+-ATPase.
- Alveolar fluid transport is impaired in patients with various forms of lung injury, including acute respiratory distress syndrome.
- Many lung diseases originate from disruption of alveolar structure and function.

Key Readings

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4 AIRWAY BIOLOGY

STEVEN L. BRODY, MD • CHRISTOPHER M. EVANS, PhD

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INTRODUCTION

The primary function of the airways is to allow airflow while protecting the alveolar compartment from the hazards in environmental air. The airway is constantly exposed to pathogens, particles, allergens, and toxic pollutants (Fig. 4.1). It is not surprising that airway responses to acute and chronic environmental exposure directly account for a significant proportion of the burden of lung disease in respiratory virus infections, asthma, COPD, bronchiectasis, and *cystic fibrosis* (CF). Airway structure, cellular functions, host response, genetic variants, and the nature of exposure are important factors in pathologic responses. As a platform for understanding the biologic basis of disease, normal human airway structure and function, cellular components, physiologic functions, and the cellular and molecular control of airway functions are described in this chapter. Chapters 70 to 72 cover diseases of the airways, in particular upper airway disorders, large airway disorders, and bronchiolitis.

OVERVIEW

AIRWAY STRUCTURE AND CELLULAR COMPONENTS

Airways are divided anatomically into upper and lower divisions, which can be conceptually separated at the level of the vocal cords (see Fig. 4.1). Airway surfaces possess a continuous layer of epithelial cells with regional differences in morphology, function, and gene expression patterns.

UPPER AIRWAY STRUCTURE AND FUNCTION

The upper airway consists of the nose, paranasal sinuses, posterior pharynx, and larynx, although some sources consider the trachea as part of the upper airway.[1,2] Paranasal sinuses are highly vascularized to provide warming and humidification of air. The nasal mucosa covers 160 cm^2 and secretes 20 to 40 mL/day of mucus.[3] Foreign particles impact on nasal and oropharyngeal surfaces, where they become trapped in mucus or saliva for elimination by expectoration or swallowing. Thus, the upper airway epithelium defends the lung from particles, allergens, and pathogens by mucociliary clearance, swallowing, coughing, and innate barrier function.[4] Particles cleared by the upper airways are typically large (≥10 μm diameter). Smaller particles (particularly <0.5 μm diameter) bypass the mouth and sinuses to deposit in the lower airways[5,6] (see also Chapter 70).

LOWER AIRWAY STRUCTURE AND FUNCTION

The general structure of the lower airway allows movement of inspired gas from the trachea to large airways, then to a very large number of smaller airways, which create a huge cross-sectional surface area. The continuous branching of the airways limits access of particles and pathogens by impaction in large airways and by deposition in smaller airways.[7]

Airway components and cell populations vary with airway generation, from the upper airway to the conducting zone and finally the respiratory zone (Table 4.1) (see also Chapter 1). The large tracheobronchial portion of the airway has greater amounts of airway wall collagen, smooth muscle, and autonomic innervation relative to bronchiolar portions. Within the first 10 to 12 airway generations, smooth muscle, cartilage plates or plaques, and *submucosal glands* (SMGs) are abundant (Fig. 4.2).[8–10] A surrounding structure of incomplete cartilaginous rings and plates, together with smooth muscle, allows airways to remain pliable during breathing while preventing airway collapse.[11] Distal to the

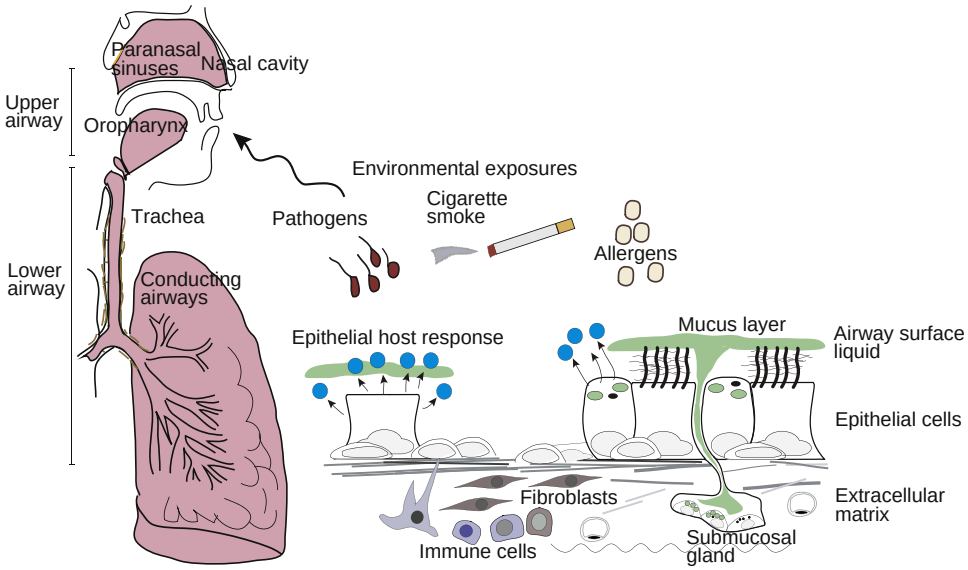

Figure 4.1 Cellular responses of airways to injury. Upper and lower airways are subject to environmental exposures that lead to defensive epithelial responses provided by secreted mucus (*green*) and secreted peptides (*blue*). Upper airway includes the nasal cavity and paranasal sinuses; the lower airway includes the trachea and conducting airways of the lung. Injury and epithelial cell responses are coordinated with responses of the submucosal glands, extracellular matrix, and immune cells.

Table 4.1 Airway Structures

Airway Component (Approximate Generation)	Cartilage	Smooth Muscle	Major Epithelial Cell Types
UPPER AIRWAY			
Nasal and paranasal sinuses	+++	+	Squamous, ciliated and mucous cells; olfactory epithelial cells, SMG
CONDUCTING ZONE			
Trachea (0)	+++	++	Tall columnar ciliated and mucous/goblet cells; SMG
Bronchi (1–3)	++	++	
Small bronchi (4–10)	+	+++	Columnar ciliated and secretory; SMG
Bronchioles (11–14)	0	+	Cuboidal ciliated and secretory cells
RESPIRATORY ZONE			
Respiratory bronchioles (16–18)	0	0	Cuboidal secretory cells
Alveolar ducts (19–22)	0	0	Squamous-like secretory cells
Alveolar sacs (23)	0	0	Alveolar epithelial type 1 and 2 cells

Abundance scored 0 to +++.
SMG, submucosal glands.
Data from Hayward J, Reid LM. Observations on the anatomy of the intrasegmental bronchial tree. *Thorax*. 1952;7(1):89-97.

trachea and mainstem bronchi, airways are embedded within and attached to the lung parenchyma. This "tethering" provides structural and functional interdependence of airways and alveoli during lung inflation and deflation.[12]

Bronchi are primarily lined by ciliated cells and mucin-secreting cells that contribute to the mucociliary escalator for clearance. Mucin refers to the glycoproteins forming a viscoelastic mucus hydrogel for maintaining tissue hydration and supporting host defense (see later). SMG ducts are found along large airway surfaces at a frequency of 0.5 to 1 gland opening/mm^2.[13] Lymph nodes on the outer surface of the trachea and bronchi provide antigen processing for defense in infection, but they may also contribute to metastases in cancer and immune hyperreactivity in asthma.[14]

Bronchioles are lined with ciliated cells and secretory club cells, but they contain few mucin-secreting cells, lack cartilage and submucosal glands, and show progressive decreases in smooth muscle (see Fig. 4.2D). Bronchioles have diameters of less than 2 mm, compared to the 2 mm or greater size of bronchi. Whereas airway diameters provide practical means for identifying "small" and "large" airways, the specific distinction between bronchioles and bronchi are defined by their histologic composition.

See ExpertConsult.com for a discussion of airflow principles.

MICROVASCULATURE

Airway Microvasculature

Airway tissues are supplied with blood by the systemic bronchial circulation.[20] Bronchial arteries branch off from the aorta and extend longitudinally along bronchi to the terminal bronchioles.[21] A plexus of bronchial microvessels in airway walls perfuse tissues while also warming and

AIRFLOW

Upper Airways

The upper airway is primarily a high-flow, low-resistance region. Airflow is affected by inspiratory and expiratory forces and the geometry of conducting airways. Upper airway gas flows at very high rates. Nasal airflow is 18 m/sec during tidal breathing and is greatly increased during sniffing.[6] Airflow in the upper airway is both laminar and nonlaminar, changing as air moves from the nose to the sinus passages.[15]

Lower Airways

In the lower airways, the size and branching of airways determine flow so that successive branching reduces overall airway resistance.[16] Proceeding deeper into the respiratory tract, gas flow properties are also determined by sizes, branching, and numbers of airways. During quiet breathing, airflow through the lower airways is laminar.[17] Increase in airflow velocity during forced inspirations or expirations associated with exercise or cough can induce turbulence.

Airflow Resistance

Airflow efficiency can be expressed as conductance (G) or, more commonly, by its inverse, resistance (R). For laminar flow, R is a function of airway length (l), airway radius (r), and air viscosity (η), which are described by the Poiseuille formula: $R = 8\eta l/\pi r4$. The fourth power of airway radius in the denominator of this formula highlights the importance of airway caliber in determining R. However, while resistance is greatest in individual small airways,[17–19] the total number of small airways past the tenth generation is so large due to successive branching that their contribution to overall airflow resistance in a healthy lung is small.[16]

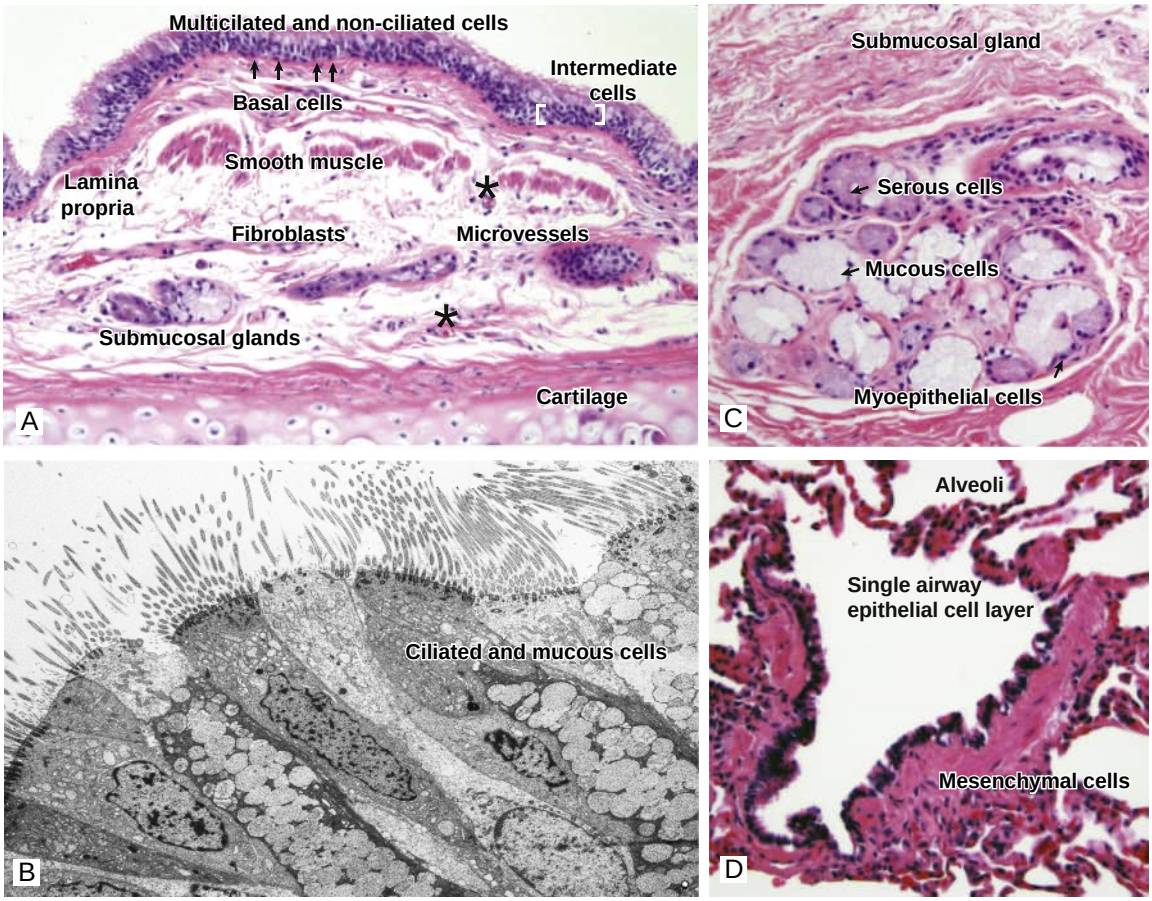

Figure 4.2 Airway structures and cell types. (A) Cellular components and epithelial architecture of bronchi demonstrating a pseudostratified layer. Basal cells are indicated by *arrows,* intermediate cells by *white brackets,* and microvasculature by *asterisks* above vessels. (B) Ultrastructure of bronchial multiciliated and mucous cells by transmission electron microscopy. (C) Epithelial cell types in submucosal glands. (D) Epithelial architecture of terminal bronchiole, demonstrating a single layer of epithelial cells and absence of mucosal glands and smooth muscle. (Hematoxylin and eosin stain.) (Courtesy Dr. Steven L. Brody.)

humidifying large airways.[22] The bronchial arteries drain either to the azygous vein or into the pulmonary veins; the latter route constitutes a small right-to-left shunt as deoxygenated bronchial venous flow enters the oxygenated postcapillary blood.

The airway microvasculature is embedded within the subepithelial matrix and supported by collagen IV in the epithelial lamina propria (see Fig. 4.2). Pericytes that wrap around the capillary and postcapillary venules help maintain endothelial integrity in health. Signals from the endothelium, such as nitric oxide, control vascular tone, while the surrounding extracellular matrix–endothelial interactions maintain normal levels of angiogenesis. Following airway injury, proteolytic extracellular matrix fragments and activated pericytes emit inflammatory signals that can alter endothelial cell function and lead to angiogenesis and remodeling.[23,24]

Mechanisms that regulate flow in the bronchial circulation are extrapolated from animal studies to humans.[22] Bronchial microvessels express α- and β-adrenergic receptors that respond to sympathetic neurotransmission.[25] Adrenergic control of airway vascular tone is dependent on nitric oxide and is sensitive to endothelium-mediated dilation, which, along with histamine, prostaglandin F2α, prostacyclin, and bradykinin, likely play roles in vascular leak and remodeling in airway diseases.

Airway Lymphatic Vessels

Airways also incorporate an extensive network of lymphatic vessels.[26] The importance of lymphatics in fluid homeostasis is especially evident in preterm infants, whose poorly developed lymph networks may contribute to bronchopulmonary dysplasia. Lymph vessels are lined internally by endothelial cells, which, like blood vessels, express the surface protein CD31, but lymphatic endothelial cells also express Prox1 and vascular endothelial growth factor receptor. These and other lymphatic endothelial markers are being used to understand the importance of lung lymphatics in health and disease[27] (see Chapter 7).

Microvascular-Related Inflammation

The airway microvasculature is an important regulator of airway inflammatory responses.[25,28,29] Endothelial cells express cell adhesion proteins, in particular E-selectin, intracellular adhesion molecule-1, and endothelial leukocyte adhesion molecule-1, that facilitate leukocyte attachment. Stimuli such as cigarette smoke, allergens, and viruses cause endothelial cell production of inflammatory mediators. Proinflammatory factors contribute to the disassembly of tight junctions between endothelial cells, allowing leukocytes to migrate into tissues and air spaces. Endothelial cells produce angiogenic growth factors that induce vascular remodeling in airways disease such as asthma, COPD,

and bronchiectasis,[29] potentially through the recruitment of bone marrow–derived endothelial progenitors.[25,30,31]

EXTRACELLULAR MATRIX AND FIBROBLASTS

Structural support and biomechanical properties of lung tissues, including recoil of the airways, is provided by *extracellular matrix* (ECM), consisting of proteins, proteoglycans, and glycosaminoglycans. ECM makes up the thin basal lamina (basement membrane) firmly linked to airway epithelial cells by fibronectin and integrin proteins and also fills the interstitial space (lamina propria) to provide structure and organization to the airway. ECM is produced mainly by the resident fibroblasts, although many other cell types can contribute. (See also Chapter 5.)

ECM is composed of over 300 proteins (collectively called the matrisome), including collagens, elastin, fibrous glycoproteins, fibronectin, laminin, and heparan sulfate proteoglycans.[32] In addition to structural support, integrins relay signals between mucosal epithelia and submucosal microcirculation, lymphatics, fibroblasts, cartilage, and smooth muscle.[32–34] ECM serves as a storage depot for growth factors such as transforming growth factor-β and cytokines, which regulate cell growth, inflammation, repair, and remodeling.[32]

Anatomic Specificity of Extracellular Matrix

ECM composition differs in tracheobronchial, bronchiolar, and alveolar compartments. Across the lung, collagen is the major structural component providing airway elasticity. However, among compartments, the subtypes of collagen, the fibrous nature of collagen structure, and the composition of noncollagen ECM components differ greatly (eTable 4.1).

A discussion of additional protein components is available at ExpertConsult.com.

ECM Alterations in Airway Disease. Remodeling of the ECM is a characteristic of diseases of the airways, including asthma and chronic bronchitis,[45–52] as well as diseases of the lung parenchyma, such as emphysema, pulmonary hypertension, pulmonary fibrosis, and lung cancer,[53–58] that can have etiologic relationships to airway diseases.[32,44,59] Changes in ECM with diseased lungs are related to changes in the production and cross-linking of collagen (eFig. 4.1, and see eTable 4.1), and also to changes in elastin, and other proteins and proteoglycans. Persistent activity of proteases such as *matrix metalloproteinases* (MMPs) and leukocyte-derived elastases further contributes to matrix remodeling and pathology.[32]

SMOOTH MUSCLE

Airway smooth muscle (ASM) surrounds the large airways. In health, the role of ASM contraction is debated.[60] ASM may limit airway distension during normal breathing and cough. ASM may also sequester damaged or infected lung regions to promote ventilation of healthy tissues, and it may compress SMGs to facilitate mucus secretion. Although these homeostatic functions of ASM are unclear, it is well known that ASM contraction causes airway obstruction in asthma and COPD.[61] Accordingly, for maintaining healthy airflow steady state, ASM relaxation is crucial.

ASM normally exists in a relaxed state due to low-level contractile stimulation and to tonic activation of bronchodilatory signals.[62] Contraction is caused by Ca^{2+}-dependent activation of myosin light chain kinase, which stimulates formation of actin-myosin cross-bridges that shorten myocytes. Reversal of myosin light chain kinase phosphorylation and sequestration of intracellular Ca^{2+} are drivers of smooth muscle relaxation.[63]

The main ASM relaxant signal originates from interaction of circulating epinephrine with β_2-adrenergic receptors on ASM.[62,64–67] β_2-receptors stimulate dilation by increasing intracellular cyclic adenosine monophosphate and decreasing intracellular calcium levels (eFig. 4.2). ASM relaxation is also induced by non-adrenergic noncholinergic neurons using *nitric oxide* (NO) and vasoactive intestinal peptide as neurotransmitters[62,68–70] (eTable 4.2).

Steady-state bronchodilation can be overridden by stimuli such as airway surface irritants, chemicals, and inflammatory mediators, leading to ASM contraction and bronchoconstriction. Bronchoconstriction may also be activated by ASM mechanosensory and neural reflex responses[71–73] (eTable 4.2).

INNERVATION

Airway neural control derives from *central nervous system* (CNS) and peripheral nervous system pathways that coordinate breathing,[74–76] airflow, and host defense.[77,78] CNS centers regulate breathing rate and depth by integrating voluntary and involuntary (sensory) inputs from the peripheral nervous system. Efferent signals from the medulla and pons transmit signals that stimulate contraction and relaxation of diaphragm and intercostal muscles during breathing. Additional innervation and muscle contractions control the glottis and larynx during consciously controlled breathing, sneezing, or coughing.[74,75]

To regulate airflow and host defense, CNS and peripheral nervous system pathways exert autonomic control over airway structures (Fig. 4.3). The predominant autonomic control is supplied by the vagus nerves.[72] Neurally mediated bronchoconstriction is mediated by parasympathetic vagal fibers that impinge upon ganglia embedded in tracheobronchial airway submucosal tissues.[72] Inflammatory signals can activate sensory nerves and evoke reflex-mediated bronchoconstriction.

Afferent Autonomic Control of Airway Smooth Muscle

Trachea, bronchi, and bronchioles contain vagal sensory nerve termini.[74,79–81] These nerves have cell bodies in the jugular and nodose ganglia and transmit mechanoreceptive and chemoreceptive signals to synapses in the medulla. The main vagal sensory neurotransmitters in the CNS are gamma-aminobutyric acid and glutamate, and their signals can be potentiated or suppressed by peptide neurotransmitters called tachykinins.[74,76]

Local sensory nerves also terminate in the airway, where the tachykinins, substance P, neurokinin A, and neurokinin B amplify parasympathetic neurotransmission[82,83] independent of CNS-mediated reflexes.[84,85]

Glycosaminoglycans and Proteoglycans. Hyaluronan is an abundant and physiologically important glycosaminoglycan component of ECM. Hyaluronan is found in cartilage, interstitial tissues, and alveolar walls. Hyaluronan is important for maintaining ECM hydration homeostasis. Following injury, degraded hyaluronan fragments bind to CD44 receptor and mediate inflammation, angiogenesis, and cell migration.[35] Proteoglycans such as aggrecan, decorin, perlecan, and versican, and other glycosaminoglycans such as heparan sulfate, are abundant in interstitial compartments, help maintain structure, and are involved in signaling following inflammation or injury.[36]

Collagen. Collagen matrices are three-dimensional mesh networks that form basement membranes, walls of rigid vessels and airways, and molecular scaffolds for maintaining lung structure.[37,38] Collagen can be grouped into two broad categories: fibrillar and nonfibrillar (see eTable 4.1).

Fibrillar collagens in the lungs include types I, II, III, V, and XI, which compose the bulk of lung matrix content.[34] Collagen undergoes cross-linking by enzymes such as lysyl oxidases and transglutaminases, which further strengthen and stabilize ECM networks. Fibers composed of elastin and microfibrils are also present, and they contribute to the stability and elastic recoil of airways.

Non-fibrillar collagens form networks that are abundant in basement membrane and interstitial ECM structures (see eTable 4.1). Among these, collagen IV is a major component of basal lamina, and collagen VI is enriched between basal lamina and interstitial ECM components, where it binds to numerous proteins, proteoglycans, and glycosaminoglycans.

ECM Turnover. ECM components are continually produced and maintained by turnover during homeostasis.[32] ECM turnover is regulated by proteases, including MMPs, and *adamalysins* (ADAMs).[39,40] MMPs comprise over two dozen zinc-dependent endopeptidases that degrade ECM proteins, including collagen and elastin. Since most MMPs are secreted into extracellular spaces, their activities are homeostatically balanced by *tissue inhibitors of metalloproteinases* (TIMPs).

MMPs and TIMPs are primarily produced by fibroblasts, fibrocytes, and endothelial cells within the ECM of the airways, and they are also produced by inflammatory cells. Macrophages in the alveolar and interstitial compartments contribute to MMP activity in the airways.[40] Both MMPs and TIMPs are also expressed by airway epithelial cells, sources that are activated during inflammation and are required for reconstitution, repair, and remodeling of airway basement membranes and interstitial tissues.[39]

Like MMPs, ADAMs can degrade matrix proteins.[32] ADAMs also cleave membrane-associated cytokines and growth factors. The locations of ADAM activities are controlled by their cellular expression since ADAMs are transmembrane, rather than secreted proteins. ADAM targets include tumor necrosis factor, epithelial growth factor, and other inflammatory and growth factor molecules. Accordingly, a significant role for ADAMs in ECM turnover may be related to inflammation, injury, and repair.[40]

ECM Response in Airway Injury and Repair. Airway injury resulting in disruption of the basement matrix leads to deposition of a fibrin and fibronectin–rich structure that forms a transient, provisional matrix.[41,42] Fibroblasts recruited to the injured area then secrete collagen, resulting in protein cross-links that organize and remodel the provisional matrix.[43] Matrix is subsequently degraded by MMPs and proteases, fibroblasts undergo apoptosis, and a scar remains at the newly functional scaffold. Epithelial cells are guided to stretch across the newly formed basement membrane, followed by proliferation of progenitor basal cells, and ultimately epithelial cell differentiation. Dysregulation of MMPs associated with chronic injury can result in exaggerated scarring, resulting in subepithelial cell fibrosis, loss of elastic recoil of the airways, and abnormal epithelial cell differentiation.[44]

eTable 4.1 Airway Matrix Composition

Anatomic Location	Dominant Collagen (Gene) and Other Components	Alterations in Disease
Cartilage	*Collagens:* types II, VI, IX, X, XI *Proteoglycans:* aggrecan, versican, perlecan, decorin, biglycan *Other proteins/glycoproteins:* cartilage oligomeric matrix protein, matrilin, thrombospondin type 1 domain containing protein 4 *Glycosaminoglycan(s):* hyaluronan	Normal[425–427] COPD, chronic bronchitis[428] Relapsing polychondritis[429] Tracheomalacia [430] Rheumatoid arthritis lung disease[431] IPF[425] Bronchiectasis[427] Williams-Campbell[9] Cartilage-hair hypoplasia[432] Cystic fibrosis[433]
Basal lamina	*Collagens:* types I, III, IV, V *Proteoglycans:* bamacan, biglycan, fibromodulin, perlecan, lumican *Other proteins/glycoproteins:* fibronectin, laminins, nidogen/entactin, tenascin, osteopontin	Normal[434,435] COPD[32] Chronic bronchitis[436–438] Emphysema[436] Asthma[437,439] Cystic fibrosis[440]
Interstitial tissue	*Collagens:* types I, III, IV, V, VI, VIII, XIV, XVIII *Proteoglycans:* aggrecan, decorin, lumican, perlecan, versican, biglycan *Other proteins/glycoproteins:* elastin, emilin, fibronectin, fibrillins, fibulin, laminin, nidogen/entactin, osteopontin, thrombospondin, tenascin, vitronectin, von Willebrand factor *Glycosaminoglycan(s):* heparan, hyaluronan	Normal[441] COPD[442] Pulmonary fibrosis[442] PAH[443–444]
Alveoli	*Collagens:* types: I, III, IV *Proteoglycans:* biglycan, decorin, lumican, perlecan, versican *Other proteins/glycoproteins:* elastin, elastin binding protein, fibrillin, fibronectin, fibulin *Glycosaminoglycan(s):* hyaluronan	Normal [32,436,446] COPD[436,446,447] Pulmonary fibrosis[447]

IPF, idiopathic pulmonary fibrosis; PAH, pulmonary artery hypertension.

eTable 4.2 Mediators of Smooth Muscle Activity

		EFFECT (MECHANISM)	
Agonist	**Origin**	**Contraction**	**Relaxation**
Acetylcholine	Parasympathetic cholinergic nerves	M3, M2	M2 (neuronal)
Adenosine		A1	
Adenosine triphosphate	Epithelium	P2X	
Adrenaline	Adrenal chromaffin cells		β2
Bradykinin	Mast cells	β2	
Bitter compounds	Environmental		TAS2R
Endothelin-1	Epithelium, endothelium, inflammatory cells	ETA, ETB	
H^+	Extracellular pH	TRP	
Histamine	Mast cells, basophils	H1	
Cys-leukotrienes	Mast cells, leukocytes, epithelium, platelets	CysLT1	
Neurokinin A	Sensory nerves	NK2	
Nitric oxide	Parasympathetic cholinergic nerves, epithelium		cGMP
Platelet-activating factor	Platelets, leukocytes	PAF receptor	
Prostaglandin E2	Mast cells, leukocytes, epithelium, ASM	EP1, EP3	EP2, EP4
Serotonin	Mast cells (rodent > human)	5HT3	
Thrombin, trypsin	Mast cells	PAR1	

5HT3, serotonin (5-hydroxytryptophan) receptor; A1, adenosine1 receptor; β2, adrenergic β2 receptor; cGMP, cyclic guanine monophosphate; CYsLT1, cysteinyl leukotriene receptor 1; EP1,2,3,4, prostanoid receptors 1–4; ETA and ETB, endothelin A and B receptors; H1, histamine; M2 and M3, muscarinic M2 and M3 receptors; NK2, neurokinin 1 receptor; P2X, purinergic 2X receptor; PAF receptor, platelet activating factor; PAR, protease activated receptor; TAS2R, type 2 bitter taste receptor; TRP, transient receptor potential receptor.
Data from references 63, 81, 192, 448–455.

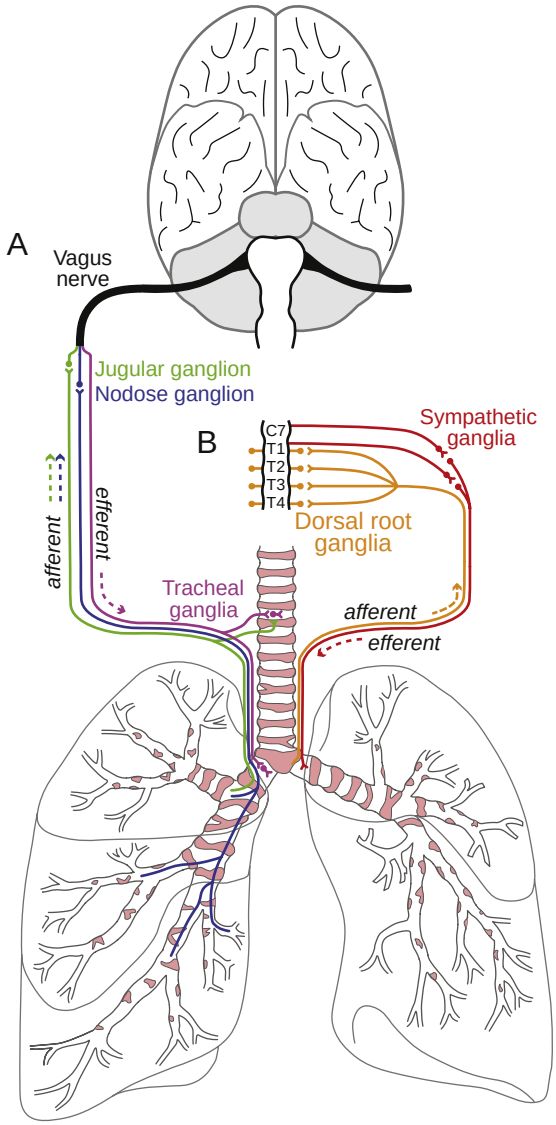

Figure 4.3 Autonomic innervation of the lung. (A) Cranial innervation from the vagus nerve (*black*) includes afferent sensory nerves with cell bodies in jugular (*green*) and nodose (*blue*) ganglia and efferent fibers with cell bodies in tracheal ganglia (*violet*). Postganglionic cholinergic fibers extend into the airways (*violet*). (B) Spinal innervation from afferent fibers (*orange*) with cell bodies in dorsal root ganglia transmit signals to the central nervous system, and efferent fibers (*red*) with cell bodies in the sympathetic ganglia transmit adrenergic signals to the pulmonary vasculature (not shown).

Efferent Autonomic Control of Airway Smooth Muscle

The dominant neural control of ASM contraction is provided by parasympathetic fibers within the vagi.[86–91] Acetylcholine released by parasympathetic nerves stimulates contraction by activating M_3 muscarinic receptors on ASM.[92] In contrast to M_3 receptors, M_2 receptors found on the ASM or on the nerve terminals can have pleiotropic effects. For example, M_2 muscarinic receptor subtypes on ASM facilitate contraction by suppressing β_2-adrenergic receptor signaling.[93,94] Thus, antagonism of the muscarinic receptors on ASM dilates human airways, which can be useful for treating obstructive lung diseases.[95–99] However, M_2 receptors on prejunctional nerve terminals can mediate bronchodilation by suppressing vagally induced acetylcholine release by 80–90%[100,101]; absence of neuronal M_2 inhibitory function causes excessive ASM contraction in animal models of airway obstruction.[102–107] Given the pleiotropic effects of M_2 receptor functions, highly selective M_3 receptor antagonists such as tiotropium have been developed for clinical use as bronchodilators.[95–99]

Other Neural Controls

Additional nonvagal inputs from nerves originating in cervical and thoracic vertebrae and in dorsal root ganglia affect the lower airways (see Fig. 4.3). These include sensory signals involved in airway tone and cough via substance P and efferent signals mediated by norepinephrine and neuropeptide Y that affect SMG secretion.[75,108] Additional sympathetic fibers also regulate vascular flow.

AIRWAY EPITHELIUM

MORPHOLOGY

The tracheobronchial epithelium is pseudostratified, meaning it appears as a multilayered sheet even though it is actually a single layer of cells (see Fig. 4.2). Each cell is firmly attached to the basal lamina, thereby establishing basal-to-apical polarity.[109] From the trachea to the bronchioles, epithelia progressively transition from pseudostratified columnar to simple cuboidal morphologies. Throughout this proximal-distal axis, the heights of individual epithelial cells and thickness of mucosal sheets and submucosal layers also decrease.[17,109,110] Along the distal respiratory bronchioles, the cuboidal epithelial layer becomes discontinuous as conducting airways transition to alveoli.

CELL-CELL JUNCTIONS

Airway Barrier Function

Airway epithelial cells have specialized structures mediating attachment to the ECM and to neighboring cells. In both upper and lower airways, physical barrier function is provided by adhesion of epithelial cells to basal lamina through hemidesmosomes,[111] which are rich in proteins called integrins. The integrin α6β4 facilitates communication between the epithelial cell cytoskeleton and the ECM to provide structural integrity, mechano-coupling, and host defense.[112] The basolateral attachments are also selectively permeable to regulate ion and water flux.

Types of lateral attachments include desmosomes, tight junctions, and adherens junctions (eFig. 4.3).[113–123] These junction complexes provide basolateral barrier strength, cell-cell communication, and control of the selective movements of molecules across cells. Lateral junctions may be disrupted by injury and inflammatory responses following exposure to toxicants, particulates, or pathogens, leading to paracellular leak.[114,120,124,125] In addition, disruption of epithelial junctions triggers epidermal growth factor receptor–mediated repair programs.[125]

Additional junctions are discussed at ExpertConsult.com.

Tight Junction Proteins

Tight junctions are macromolecular complexes that encircle an epithelial cell's apical domain, linking to neighboring cells for apical stability and barrier support. Tight junctions are composed of the following structural, regulatory, and junctional adhesion molecule proteins:

- *Zona occludins* (ZO) family members ZO-1, ZO-2, and ZO-3.[113] ZO proteins interact directly with the actin cytoskeleton, signaling molecules, and the *cystic fibrosis transmembrane conductance regulator* (CFTR).[114,115]
- Claudins provide tight junction size- and molecule-selective paracellular transport. Bronchi and bronchioles are enriched in claudin family members 1 through 5 and 7.[116–119] Heteromeric interactions between claudin members on the same or neighboring cells form functional complexes.[116]
- Junctional adhesion molecule-A and the coxsackie and adenovirus receptor are additional components of tight junctions.[119–121]

Adherens Junction Proteins

Adherens junctions form intercellular links just basal to tight junctions and provide additional barriers to water movement. Adherens junctions also regulate epithelial polarity via E-cadherin (Cadherin-1)-dependent cytoskeletal signaling mediated by p120-catenin, β-catenin, and α-catenin proteins.[122] E-cadherin controls cell morphology and responses to epithelial damage via β-catenin signaling.[123]

CELL POPULATIONS

Upper Airway Epithelial Cells

The majority of the nasal airway epithelium is lined by ciliated respiratory epithelium with numerous interspersed mucous cells. In humans, olfactory cells cover only a small percentage of the epithelium (<5%). Squamous epithelial cells dominate the posterior pharynx, with the exception of specialized cells in the adenoids and tonsils. The luminal aspect of the adenoids is comprised of multiciliated and secretory cells, whereas surfaces of the tonsils have secretory cells.[126]

Lower Airway Epithelial Cell Populations and Frequencies

Major epithelial cell types present within the conducting airway epithelium are basal, intermediate, multiciliated, mucous, club, and pulmonary neuroendocrine cells[127,128] (Fig. 4.4). At the epithelial-lumen surface, approximately equal proportions of ciliated and nonciliated cells can be identified based on morphologies.[129]

In addition to cell appearances, the use of molecular markers and single-cell RNA sequencing reveals a more nuanced and complex view of the lung epithelium in health and disease.[4,130–134] At least a dozen well-defined epithelial cell populations can be found in the upper and lower airways (Table 4.2).[127,128,132–134] Mouse studies have laid the groundwork for understanding each epithelial cell type at molecular and functional levels.

Basal Cells

Airway basal cells are small round cells located on the basal epithelial layer, adherent to the basement membrane throughout the airway, and function as stem cells and barrier components.[110,135] The essential markers of the basal

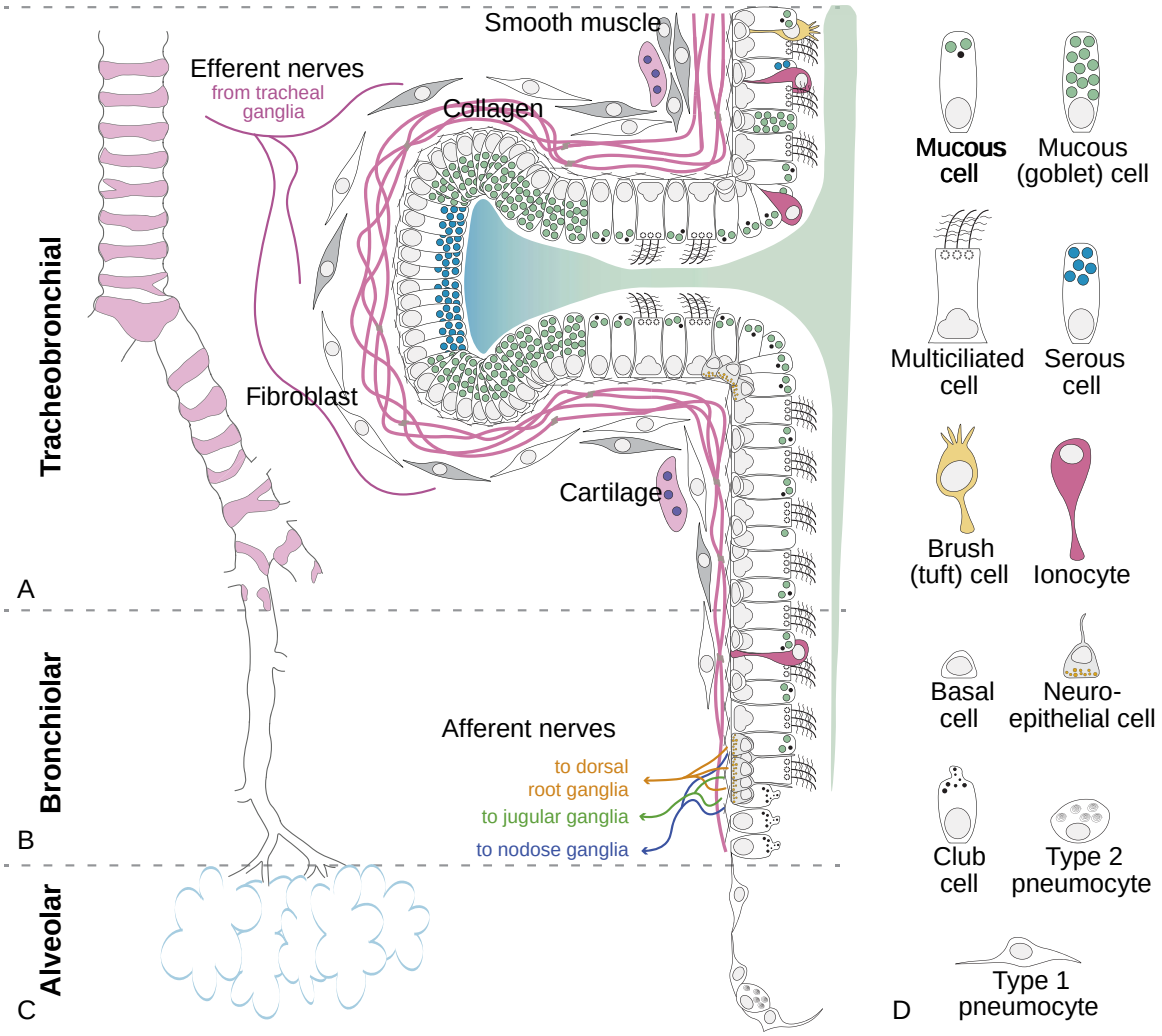

Figure 4.4 Airway cell types. (A) Tracheobronchial airway walls have abundant cartilage, extracellular matrix, and smooth muscle, as well as submucosal glands. Epithelial cells at tracheobronchial surfaces include mucous cells, mucin-packed goblet-shaped mucous cells, serous cells, and multiciliated cells that all contribute to airway surface liquid hydration and mucociliary defense. Hydration and defense properties are strongly enhanced locally by neurally regulated secretions from serous and mucous cells within submucosal glands. Brush cells and ionocytes are rare epithelial types that sense and control the chemical and ionic environments at airway surfaces. (B) Bronchioles have progressively thinner airway walls, with many of the same epithelial cell types found in the tracheobronchial airways, including basal cells. Neuroepithelial cells and club cells are enriched in bronchioles, where they have progenitor, chemosensory, and detoxification functions. Neuroepithelial cells found in clusters called neuroepithelial bodies are innervated by sensory fibers. (C) Distal airways include club cell–lined respiratory bronchioles that terminate at type 1 and type 2 pneumocyte-lined alveoli. (D) Figure key identifying distal airway cell types depicted in A–C.

Table 4.2 Epithelial Cell Types and Features

Cell Type	Morphology and Markers	Major Functions	Location
Basal cells	Small Round Attached to lamina propria *Markers:* TRP63, KRT5	Stem/progenitor	Trachea, bronchi, bronchioles ≈5% in terminal bronchioles
Ciliated cells	Columnar Multiple apical motile cilia *Markers:* Acetylated α-tubulin, FOXJ1	Airway clearance Osmoregulation	Lumen interface in large and small airways
Club cells	Columnar Secretory vesicles Head of cell may protrude into lumen (bronchioles) *Markers:* SCGB1A1, MUC5B	Xenobiotic metabolism Host defense Progenitor Osmoregulation	Bronchioles Absent in trachea and bronchi
Mucous cells	Columnar Large cytoplasmic vesicles varying in numbers and contents Small base (goblet) *Markers:* MUC5AC, MUC5B, CLCA1, SCGB1A1	Host defense Hydration Stem/progenitor Mucin secretion	Submucosal glands Lumen interface in large and small airways <3% in terminal bronchioles
Intermediate cells	Positioned between basal and well-differentiated ciliated, club, and mucous cells. *Markers:* none specific, MYB	Pre-specialized or progenitor	Variable in large airways with multilayered epithelium
Pulmonary neuroendocrine cells	Irregular shaped Dendrites Found in insolation or in clusters (NE bodies) Basolaterally secreted vesicles *Markers:* CGRP, CGA	Chemosensory Stem/progenitor	Rare in all levels Enriched at airway branch points
Ionocytes	Small cells *Marker:* FOXI1, CFTR	Osmoregulation	Very rare Present in bronchi Not well described in humans
Brush (or tuft) cells	Pear-shaped Short apical microvilli *Markers:* ACh-containing vesicles, bitter-taste receptors	Chemosensory Secrete IL-25 postinjury	Very rare Present throughout airways Not well described in humans

ACh, acetylcholine; CFTR, cystic fibrosis transmembrane conductance regulator; CGA, chromogranin A; CGRP, calcitonin gene–related peptide; CLCA1, calcium-activated chloride channel regulation 1; Il-25, interleukin-25; MUC, mucin; NE, neuroepithelial; SCGB1A1, secretoglobin 1A1.
Data from references 132, 133, 135, 161, 177, 423, 424.

cell are the transcriptional regulator transformation protein 63 (p63) and the intermediate filament cytokeratin keratin 5, with its heterodimeric partner keratin 14.[136] In the human airway, basal cells are found in the nasal sinuses and throughout the large and small airways, including the most distal regions. Basal cells are occasionally noted in the bronchoalveolar ducts, the site of transition to the alveoli.[135] The wide distribution of basal cells in human airways is in marked contrast to the mouse, where basal cells are rarely observed distal to the large bronchi.

Intermediate Cells

During repair and regeneration, proliferating basal cells move from the basal lamina toward the lumen, to an intermediate position beneath the well-differentiated luminal cells[135–137] (see Fig. 4.2). These intermediate cells lose typical basal cell markers through down-regulation of p63[136] and lack histologic features of specialized cells, so they are also referred to as parabasal or indeterminant cells. Analysis by single-cell RNA sequencing during differentiation reveals transcriptional features of preciliated or presecretory cells. Specific molecular markers are not known, but transcription factor MYB is expressed in a subpopulation of intermediate cells.[138] Though still poorly understood functionally, intermediate cells may serve as reserve populations for mature types while also serving structural and host defense roles.

Multiciliated Cells. Ciliated cells are the most common type of differentiated cells lining the airway lumen of the bronchi and are present in high proportions in the bronchi and in SMG ducts. The major function of multiciliated cells is airway clearance, which is driven by movements of motile cilia that project apically into air spaces. These cells are referred to as multiciliated cells to avoid confusion with cells that have a single, sensory (nonmotile) cilium.[139] Multiciliated cells are terminally differentiated[140] and have 200 to 300 motile cilia, each 5 to 8 μm in length, that extend into the lumen (Fig. 4.5).[141] Multiciliated cell height and cilia length decrease along the proximal-distal axis of the airways.

In addition to the presence of apical cilia that may be identified by the presence of acetylated α-tubulin, other features of multiciliated cells include the expression of transcription factor FOXJ1, which regulates the assembly of motile cilia.[142,143] The cells also contain hundreds of basal bodies docked in an actin mesh at the apical membrane.[144] Cilia arise from each basal body.

The ultrastructure of the ciliary cytoskeleton or *axoneme* is a circular 9 + 2 arrangement of paired microtubules

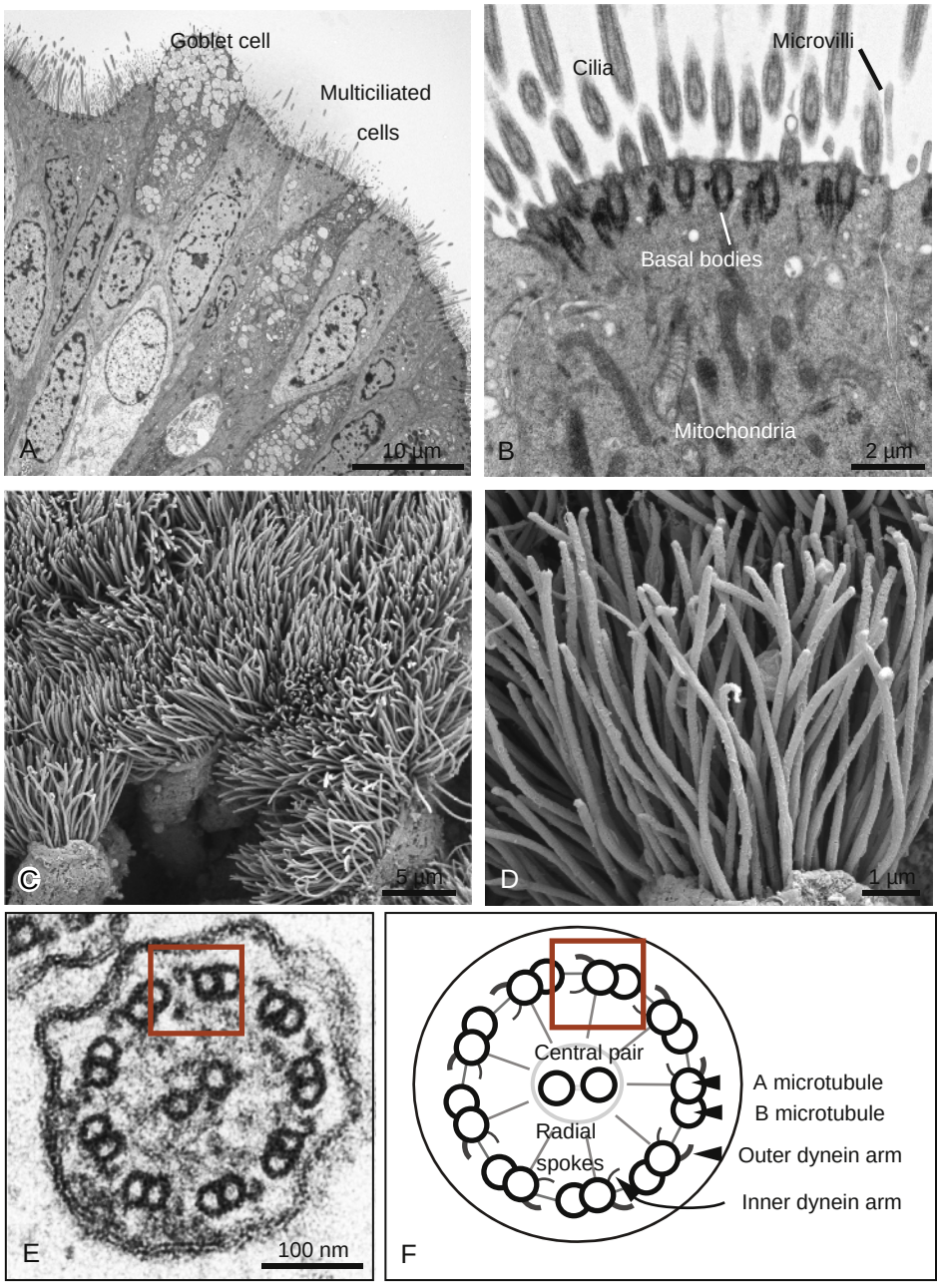

Figure 4.5 Multiciliated airway epithelial cells. (A) Ultrastructure of multiciliated and goblet cells in human bronchi by transmission electron microscopy. (B) Detail of the apical region of a multiciliated cell showing basal bodies with rootlets securing the cilia and relative to the mitochondria. (C) *Scanning electron micrograph* (SEM) of cilia on the surface of a human bronchus. (D) SEM of a single ciliated cell. (E) SEM of transverse section of ciliary axoneme (i.e., cytoskeleton of the cilia). (F) Diagram of part E indicating microtubule organization and the location of dynein motor complexes. Outer doublet A and B microtubules, inner pair, and connecting spokes are shown. Dynein motor complexes appear as arms on the inner and outer portion of the A microtubule. The box shows the same structures in the SEM image and the diagram. (A–E, Courtesy Dr. Steven L. Brody.)

composed of nine outer doublets and a central pair organization (see Fig. 4.5).[141,145] The outer doublets hold dynein motor complexes that power the cilia beating.[146–148] Cilia beat at a frequency of 8 to 15 Hz (8-15 beats/second), as measured ex vivo[149,150] (Video 4.1). Mutations in the genes coding for the motor proteins and ciliary assembly machinery result in abnormal ciliary motility, defining the autosomal recessive disease, primary ciliary dyskinesia[151] (see also Chapter 69).

Secretory Cells

Lumen-facing secretory cells are identified by the presence of cytoplasmic secretory vesicles (or granules) classified based on their numbers, subcellular localization, morphology, and cargo. Secretory cells include mucous cells, serous cells, and club cells. These determinations can be made morphologically by electron microscopy or histochemically by light microscopy and the use of dyes, antibodies, or lectins to identify their secreted products.[152,153] Secretory cells are less numerous than either the ciliated or basal cells.[129] Secretory cells are also present in SMGs.

There is some overlap in secretory cell types depending on whether they are defined by morphologic versus molecular criteria. There is also considerable interspecies heterogeneity in the abundance, distribution, and ultrastructure of secretory cell types in the airways, so experimental studies in nonhuman species must be considered carefully for their relevance to humans.

Mucous Cells

Cells containing abundant granules filled with secreted gel-forming mucin glycoproteins are called mucous cells. Mucous cells can be identified by electron microscopy with

dyes such as Alcian blue and periodic acid–Schiff stain,[154] or with molecular markers for airway mucins such as *mucin 5B* (MUC5B) and MUC5AC.[154–157] Throughout the airways, MUC5B and MUC5AC are the most abundant gel-forming mucins produced in the airways of healthy individuals.[154] In general, MUC5B is the predominant mucin produced in health, and MUC5AC is increased during inflammation.[132–134,154,158–160]

Goblet cells are recognized by their characteristic morphology. When mucous cells accumulate large numbers of granules at their apices, they have a disproportionately small basal lamina attachment site and assume a swollen cuplike morphology or goblet-like appearance (see Fig. 4.5A). Thus goblet cells are a subclass of mucous cells. Historically, "goblet" and "mucous" were terms used to distinguish cells at airway surfaces and at SMGs, respectively. However, these morphologic appraisals are not accurate descriptors of molecular identity. In fact, cells with goblet-shaped morphologies account for the majority of mucous cells in the SMG and also along the surfaces of the large airways.

Although goblet-shaped cells are undetectable in bronchioles by electron microscopy,[129] Alcian blue and periodic acid–Schiff staining, RNA in situ hybridization, and anti-MUC5B antibody labeling reveal that mucin-producing cells are indeed present in bronchioles. These mucous cells account for up to 50% of the luminal epithelia in proximal bronchioles, become less prevalent in terminal bronchioles, and are absent from respiratory bronchioles.[154,161]

Serous cells are secretory cells with electron-dense apical secretory granules that do not stain positively with Alcian blue or periodic acid–Schiff stain. Serous cells are present along large surfaces, but they are most abundant in SMGs. Within the SMGs, serous cells are sources of water and defensive proteins such as lactoferrin, lysozyme, and defensins.[162–164]

Club cells are a subclass of secretory cells with a morphologically distinct clublike or dome-shaped head that may extend into the lumen, a particularly prominent feature in rodent lungs.[152,165] Club cells are defined by the expression of *secretoglobin1A1* (SCGB1A1, also called club cell secretory protein, CC-10, CC16, or uteroglobin), a distinctive secretory protein present only in granules of epithelial cells of the airway and uterus.[152,161,166,167]

In human nonterminal bronchioles, nearly all club cells express both MUC5B and SCGB1A1.[154] In contrast, terminal and respiratory bronchiolar club cells do not express MUC5B. A similar distribution of these club and mucous cell markers is seen in mouse airways.[168–170]

Club cells also produce essential host defense factors, including *surfactant proteins* (SPs) A, B, and D, complement factor C3, and cytochrome P450 enzymes.[171,172] In mouse airways, the P450 enzyme Cyp2f2 is a reliable club cell marker,[173,174] but it is not conserved in human lungs. Club cells are shown experimentally to be highly plastic and capable of differentiating into different types, thus providing progenitor function.[134,168,175,176]

Pulmonary Neuroendocrine Cells

Pulmonary neuroendocrine cells (PNECs) are rare (<1%) airway cells that may be found alone or as clusters of up to 25 cells called *neuroepithelial bodies* (NEBs). PNECs and NEBs are located throughout the entire upper respiratory tract, including the nasal epithelium and lower tract from trachea to the terminal airways. NEBs are frequently present at airway bifurcations and bronchioloalveolar duct junctions.[177]

PNECs and NEBs form contacts with subepithelial nerve terminals.[177,178] The PNEC basal aspect broadly attaches to the basement membrane while the cell has thin apical dendritic-like projections extending across cell layers to the lumen.[179] PNECs contain cytoplasmic secretory granules in the basolateral region for release of contents towards the submucosa, likely signaling to nerves.

PNECs and NEBs are thought to have sensory functions, including detection of environmental hypoxia and allergens.[180,181] PNEC secretory products vary but include combinations of serotonin, calcitonin, calcitonin gene–related peptide, chromogranin A, gastrin-releasing peptide, and cholecystokinin.[179,182] It is suspected that these secreted peptides act as signaling molecules from PNECs and NEBs to sensory nerves.

In mouse models, PNECs proliferate in response to injury, and they have the capacity to differentiate to other cell types.[183–185] Neuroendocrine cell hyperplasia of infancy is a rare pediatric lung disease syndrome in which PNEC numbers are increased, but their role in the etiology of the disease is unclear; increased PNECs are also observed in other pediatric lung diseases.[186] PNECs are considered the cell of origin for malignant neuroendocrine cells, including those of small cell lung cancer.[185,187]

Ionocytes

Although well known for osmoregulation in fish and amphibians,[188,189] ionocytes are a rare epithelial cell recently identified in human airways by single-cell RNA sequencing. Ionocytes are specialized for ion transport, and they have molecular features similar to cells in the kidney collecting duct. Ionocytes are identified by expression of the transcription factor FOXI1. The function of ionocytes in humans is incompletely understood. An intriguing feature of this cell type is its high expression of *cystic fibrosis transmembrane conductance regulator* (CFTR), suggesting that ionocytes may play a role in the pathogenesis of CF[132,133] (see also Chapter 67).

Respiratory Brush (Tuft) Cells

Brush cells, also called tuft cells, are chemosensory cells that express elements of the bitter taste transduction system.[190] In health, they are found in nasal, laryngeal, and tracheobronchial airways, often intertwined with nerve fibers.[190–193] In mice, stimulation of taste receptors results in reduced respiratory rate.[194] Markers that identify brush cells include taste receptors and the signaling molecule α-gustducin. Brush cells may share some chemosensory functions of PNECs.[195] In models of allergic asthma, brush cells secrete the type 2 cytokine *interleukin* (IL)-25,[196] suggesting a role in type 2 inflammation.

Bronchoalveolar Stem Cells

A minute population of cells called *bronchoalveolar stem cells* (BASCs) resides at the bronchoalveolar duct junction in mice. BASCs are marked by dual expression of the club cell protein SCGB1A1 and the alveolar epithelial type 2 cell protein SP-C.[197] It is not clear whether this is a unique cell population or a variant population of SCGB1A1- and SP-C-expressing cells. A proposed function of these cells is

to repopulate airway and alveolar cells following severe injury[198,199]; this feature may promote tumorigenesis in lung adenocarcinoma models.[197] Similar cells have not yet been identified in humans.

SUBMUCOSAL GLANDS

Submucosal glands are invaginations of the airway that are buried within the ECM among the layers of smooth muscle (see Figs. 4.2 and 4.4). SMGs are continuous with the airway epithelium, connected by a ciliated cell–lined duct that terminates in grapelike structures called acini that are lined by mucous and serous cells. SMGs are the major source of airway surface liquid.[108]

SMGs are present in the nasal passages, sinus cavities, trachea, and cartilaginous bronchi. In the nose, SMGs humidify air, provide hydration, and are an important source of airway mucus. Individual glands have volumes of approximately 100 to 150 nL.[200] In the lower airways, SMG ducts can be found at a frequency of 0.5 to 1 gland openings/mm^2.[13] Owing to their multi-acinar structures and frequency across airway surfaces, SMGs support ample fluid production for maintaining airway health.[108] Gland size and duct diameter are increased in cigarette smoking and inflammatory airway diseases, notably chronic bronchitis, COPD, bronchiectasis, asthma, and CF.[13,108,201–204] When ducts are dilated, SMG openings appear as pits that can be easily observed during bronchoscopy.[13,204]

In SMGs, mucous cells produce MUC5B, and serous cells produce peptides that mediate microbial killing and regulate water and ion transport through ion channels to hydrate secretions. SMG secretions pass through ducts to the airway surface.[162–164] SMGs are a major source of mucus supporting hydration of airway surfaces and participating in host defense.[108,162–164] SMGs are embryonically derived from myoepithelial cells,[205,206] and a small population of myoepithelial cells in adult SMGs may serve as progenitor cells during injury repair.[205,207,208]

PROGENITOR CELLS

Airway Epithelial Cell Life Span

Cells within the airway have a very low turnover. Animal studies show that the half-life of ciliated airway epithelial cells is about 6 months in the trachea and 17 months in the bronchioles.[209,210] In the absence of lung disease, about 1% of cells are actively proliferating,[209,211,212] which increases with lung injury.[213–216]

Tissue-Specific Stem Cells of the Airway

Airway epithelial cell proliferation, repair, and regeneration are primarily dependent on basal cells.[136,209,211,212,217–219] The basal cell is considered the major stem cell of the airway and is distinct from a stem cell type in the alveolar epithelial compartment.[128,220–222]

Facultative Progenitor Epithelial Cells

Regionally specific differentiated cells provide a niche for facultative progenitor function through multipotent responses to injury.[175,184,222,223] In fact, nearly all airway epithelial cell types are shown to be highly plastic, so that, in response to injury, differentiated airway epithelial cells may acquire specialized functions of another cell type without proliferation.[134,168,175,224] At least four distinct cell types may have progenitor capacity:

- Club cells. These secretory cells can self-renew and differentiate into multiciliated cells. Club cells may serve as the major progenitor in mice because basal cells, the major progenitor in human airways, are exceedingly rare in mouse bronchioles.[215,225]
- Bronchoalveolar stem cells. The mouse bronchoalveolar duct junction lies where the bronchiole transitions to the alveoli. Within this zone, small numbers of *bronchoalveolar stem cells* (BASCs) are found with the capacity to repair both the airway and alveolar epithelial cells in experimental severe lung injury.[197–199] An analogous BASC population in humans has not yet been identified.
- Cells of SMG ducts and acini. These cells may also function as a rescue progenitor cell population.[207,208] Following severe lung injury, the myoepithelial cells and duct cells proliferate and then migrate to serve as progenitors in the mouse airway surface epithelium.[206,226,227] Evidence for proliferative SMG populations in human glands suggests this is a clinically relevant niche in humans.[206,228]
- Pulmonary neuroendocrine cells. These cells are present as solitary or small clusters throughout the upper and lower airway and can proliferate in human tissues.[177] During severe lung injury, PNECs proliferate and perform progenitor functions to generate differentiated secretory and multiciliated cells.[185]

AIRWAY EPITHELIAL CELL DIFFERENTIATION

Notch Signaling

Notch is the primary signal transduction mechanism that determines whether a basal cell differentiates into a secretory cell or a nonsecretory cell (eFig. 4.4).[137,220,229–231] In the presence of Notch signaling (by engagement of a jagged/delta-like ligand to a Notch receptor), basal cells differentiate into secretory cells. In the absence of Notch signaling and in the presence of other transcription factors, cells differentiate into multiciliated cells,[137,229–234] ionocytes,[133] or PNECs.[230,235,236]

Through this coordinated approach, a balance of secretory and multiciliated, nonsecretory cells is maintained.[230,237,238] In adult cells, interruption of active Notch signaling results in transdifferentiation of secretory to multiciliated cells.[231] Because inhibition of Notch directs mucous cells to multiciliated cells, such an approach could serve as a therapy for COPD.[137]

Differentiation Pathways for Secretory and Ciliated Cells

Following Notch-mediated fate determination, daughter cells undergo secretory cell differentiation and form club cells, serous cells, and mucous cells.[132,133,137,220,230,231,233] Multiciliated cell specification is a default cell fate in the absence of Notch signaling in transgenic animal models.[137,229–234] The transcriptional landscape of multiciliated cells includes the transcription factor MCIDAS early in specification, followed by FOXJ1 later in ciliogenesis.[143,145,239–245] Despite programmatic lineage determinations and defined differentiation pathways, airway

epithelial cells are highly plastic, leading cells to assume different fates and functions, through the influence of multiple other factors, particularly in the setting of injury.[224]

AIRWAY SURFACE LIQUID

The surface of the respiratory system is lined by a thin layer of liquid. This layer differs in thickness in airway and alveolar compartments. Alveolar lining fluid is essential for preventing desiccation, but it is extremely thin (<0.1 μm) to maximize gas-exchange efficiency. The fluid lining the nose, trachea, bronchi, and bronchioles is called *airway surface liquid* (ASL). ASL is essential for maintaining surface hydration throughout the conducting airways. ASL is also crucial for defense and, although thicker than alveolar lining fluid, is ordinarily still thin enough (<10 μm) to permit gas diffusion into underlying epithelia.[108,154]

In tracheobronchial airways, serous and mucous cells in SMGs and on airway surfaces are sources of ASL and macromolecules. The overall volume of ASL is related to numbers of SMGs present (1 to 2 SMGs per mm^2) and stimulation of ASL secretion by homeostatic or neural inputs described above. In bronchioles, which lack SMGs, club cells are the main sources of both mucous and serous components. These secretory cells, along with other surface cells such as ciliated cells and ionocytes, also contribute to ion and water transport.[108]

COMPOSITION

Airway Surface Liquid Layers

ASL comprises a mucus gel, approximately 2 to 5 μm thick, atop a *periciliary layer* (PCL) in which the motile cilia beat.[246,247] Traditionally, mucus was illustrated as a gel-on-liquid model, with mucus above a PCL that was watery and diluted and hence referred to as a "sol" phase. However, microscopic, biochemical, and biophysical measurements show that the PCL is itself a gel.[248] Accordingly, the contemporary view of ASL is a gel-on-gel arrangement, with a mucus gel atop a mesh-like mucin layer in which the cilia beat.

To maintain ASL homeostasis, water is drawn from mucosal and submucosal compartments in a steady-state equilibrium. Along airway surfaces, osmotic pressures across the PCL and mucus layer are driving forces controlled by water diffusion, ion transport, and macromolecule secretions (Fig. 4.6).

Water

Water moves across airway epithelial cells via diffusion between cells and through aquaporin channels located on plasma membranes of basal, ciliated, serous, and club cells. The aquaporins involved in airway epithelial fluid movement are aquaporin 3 on basolateral surfaces and aquaporin 5 on apical membranes.[249–251]

Ions

Cation and anion transporters control fluxes of Na^+, K^+, Cl^-, and HCO_3^- across basolateral and apical surfaces.[252–259] Basolateral transporters maintain the balance of electrolytes supplied from tissues. Apical cation channels also mediate K^+ and Na^+ conductance, with the *epithelial sodium channel* (ENaC) playing a predominant role in Na^+ absorption.[259–261] ENaC is normally inhibited by the anion channel CFTR; however, if CFTR is mutated as in CF, ENaC is unregulated.[259] ENaC overactivity drives CF-like ASL depletion in mice.[262]

Mucins and Other Macromolecules

Proteins and carbohydrates are abundant macromolecules crucial for ASL homeostasis. There are over 130 proteins present in ASL, including mucin glycoproteins that play critical roles in ASL in both the mucus and PCL gel phases.[267]

Mucins are grouped as gel-forming or membrane-associated. Both groups are rich in the amino acids serine and threonine, which are sites of the heavy glycosylation that is a defining characteristic of mucins. In mature mucins, glycans comprise 50–80% of their dry mass and yield strong osmotic potentials.[268]

- *Gel-forming mucins.* MUC5B and MUC5AC are the predominant gel-forming mucins in airway mucus, accounting for approximately one-third of all proteins present. Individually, MUC5AC and MUC5B monomers are very large (>3000 amino acids in length). During synthesis, they multimerize via disulfide bonds formed in the endoplasmic reticuli and the Golgi, resulting in polymers that are tens to hundreds of microns long. MUC5AC and MUC5B are even more massive due to their extensive glycosylation.[268] To fit into secretory granules, mucin glycopolymers form non-covalent interactions with Ca^{2+} and become dehydrated.[266] When secreted into the airway, mucins can hydrate and expand up to 500-fold.[269,270]
- *Membrane-associated mucins.* The surfaces of cilia are coated with three membrane-associated mucins, MUC1, MUC4, and MUC16, which have transmembrane spanning C-terminal domains and extracellular glycosylated domains. Their presence along the apical surfaces of cilia suggests that these mucins play roles in motile cilia structure and function. MUC1, MUC4, and MUC16, also regulate ASL hydration by maintaining osmotic equilibrium between the PCL and mucus gel layer.[248]

Periciliary Layer Contribution to Airway Surface Liquid Hydration

On the extracellular surfaces of multiciliated cells, MUC1, MUC4, and MUC16 absorb water and extend into hydrated brushlike extensions occupying much of the space between individual cilia (see Fig. 4.6). In addition, their glycosylation domains vary in size and carbohydrate mass (MUC16 > MUC4 > MUC1), which causes them to form a mass density gradient from the bases to the tips of cilia.

The smallest of these mucins, MUC1, aggregates against cell surfaces at the bases of cilia projections. The largest, MUC16, concentrates along distal regions of cilia. The intermediate size mucin, MUC4 distributes between cilia bases and tips.[248] This continuum imparts an osmotic force gradient directed towards cilia bases, thereby preventing airway surface desiccation and promoting cilia stability.

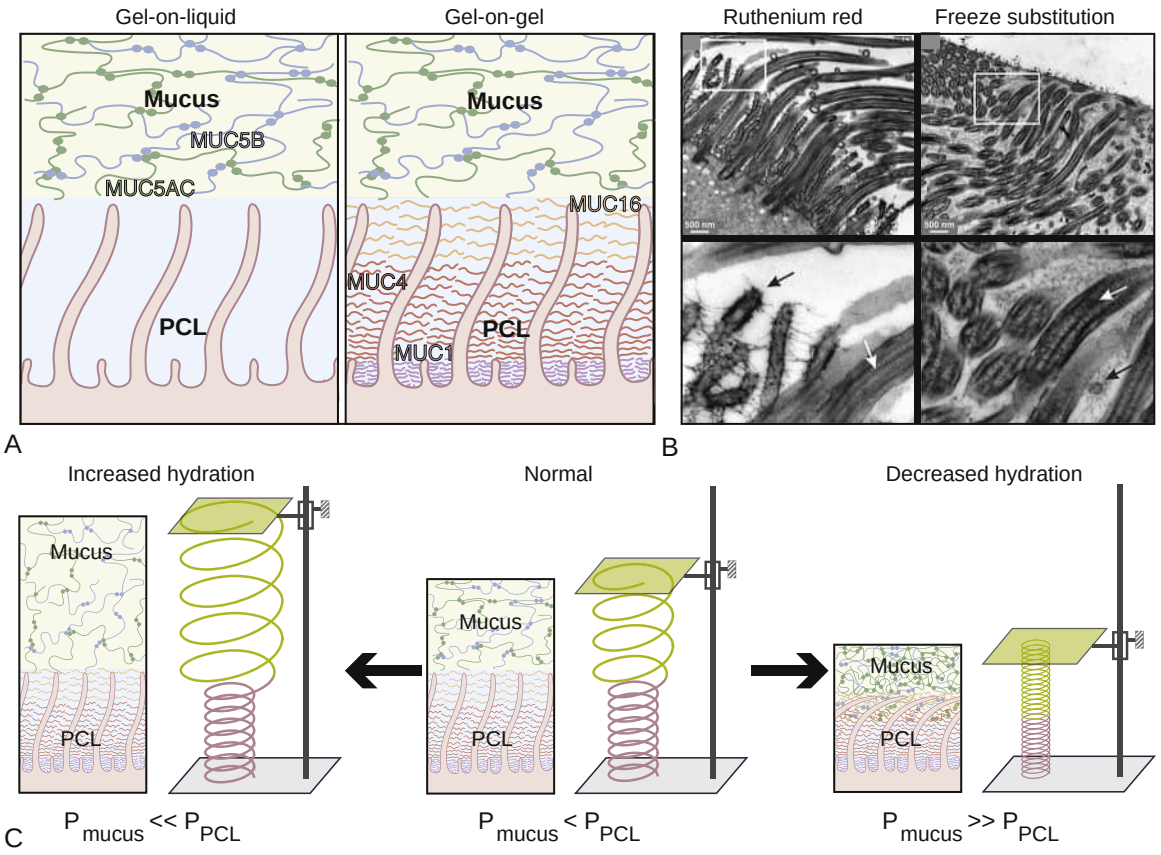

Figure 4.6 Airway surface liquid. (A) Classic gel-on-liquid mucus layer model (*left*) with MUC5AC (*green*) and MUC5B (*blue*) lying on a watery "sol" layer. The revised gel-on-gel model (*right*) shows mucus lying on a periciliary gel comprising hydrated MUC1 (*purple*), MUC4 (*red*), and MUC16 (*orange*) transmembrane mucins. (B) Transmission electron micrographs with cilia (*white arrows*) and periciliary glycans (*black arrows*) shown by ruthenium red staining (*left*) and freeze substitution (*right*). (C) Diagram illustrating mucus and periciliary layer (PCL) osmotic pressure (P) at equilibrium and when concentrations of macromolecules and water change. When P_{mucus} is less than P_{PCL}, mucus is loose and easily cleared. When macromolecules increase or when water decreases in concentration, as in COPD or cystic fibrosis, P_{mucus} exceeds P_{PCL}, and P_{mucus} draws water away from cilia resulting in PCL collapse. (A and C, Modified from Button B, Cai LH, Ehre C, Kesimer M, Hill DB, Sheehan JK, Boucher RC, Rubinstein M. A periciliary brush promotes lung health by separating the mucus layer from airway epithelia. *Science*. 2012;337[6097]:937-941. B, Modified from Kesimer M, Ehre C, Burns KA, Davis CW, Sheehan JK, Pickles RJ. Molecular organization of the mucins and glycocalyx underlying mucus transport over mucosal surfaces of the airways. *Mucosal Immunol*. 2013;6[2]:379-392.)

Mucus Gel Layer

Mucus gels also exert substantial osmotic forces on the ASL. Under healthy conditions, mucus gels contain solid materials at concentrations of approximately 2% weight per ASL volume and, when the percent of solid mass increases, a greater osmotic potential is generated that favors hydration of the mucus gel and drawing of water from the PCL.[248,271] Accordingly, even small increases in the amounts of MUC5AC or MUC5B in the mucus gel can result in strong osmotic forces drawing water away from airway surfaces, resulting in cilia collapse and mucus adhesion (see Fig. 4.6C). In fact, the concentrations of MUC5B and MUC5AC in individuals with cigarette smoke–induced COPD are up to 10 times those of nonsmokers, contributing to reduced airway clearance.[272]

Integrated Effects of PCL and Mucus Gels on ASL Hydration

To explain how mucus and PCL gels regulate airway surface hydration, the ASL can be considered a gel composed of competing osmotic force centers between the mucus and periciliary layers.[248,271,273] A healthy 2% solids mucus gel exerts an osmotic potential of approximately 100 to 200 Pa. At the same time, the graded packing of membrane mucins in the PCL creates an osmotic potential gradient of 300 to 500 Pa that draws water towards epithelial plasma membrane surfaces (see Fig. 4.6).[273]

In equilibrium, sufficient PCL hydration keeps membrane mucins in extended brushlike structures on the apical surface.[248] Small changes can cause water to flow out of the PCL, resulting in cilia collapse and impaired motility. As noted, decreased hydration of the PCL due to excessive mucin polymer concentrations in the mucus gel is one mechanism of impaired clearance in the dehydrated ASL of CF, COPD, and other airway diseases.[248,271,273]

SECRETION

ASL secretion depends on neural mechanisms that regulate bulk release of water and solids from SMGs and on local signaling mechanisms that induce MUC5B and MUC5AC mucin granule exocytosis in airway surface cells (see eFig. 4.2). Water flux is primarily controlled by diffusion. Airway epithelial cells maintain ASL homeostasis by regulating transepithelial ion and water fluxes in large part through

extracellular purinergic signaling pathways. *Adenosine triphosphate* (ATP) and adenosine are released into the ASL as a function of cilia-mucus interactions that result in G protein–coupled receptor activation in SMG and surface mucous cells.

Submucosal Gland Secretion

SMG content release is caused by neuronal inputs, including cholinergic, adrenergic, and neuropeptide-mediated signals such as vasoactive intestinal peptide.[274–278] Additional stimuli include eicosanoids and leukocyte products, as well as NO, nucleotides, and nucleosides, although these latter mediators may have both neuronal and non-neuronal origins.[108] Collectively, these mediators affect mucin exocytosis, fluid flow, and myoepithelial cell contraction during acute secretion.[108,279]

During exit from SMG ducts, bundled strands of mucus become coated and mix with materials from airway surfaces.[280–283] A single SMG can increase mucous secretion 10-fold (from <1 to ≥10 nL/min per gland) within seconds.[275–278] With approximately 100 SMGs per cm^2 of airway surface in bronchi,[108] the rapid release of large amounts of mucus underscores the importance of SMG secretions in acute ASL control and subsequent particle clearance by bulk ASL secretions.

Surface Mucous Cell Secretion

Under healthy homeostatic conditions, mucin is secreted at a low steady-state rate in equilibrium with mucin production. This phenomenon accounts for the apparent paucity of mucous cells in healthy airways.[155,284] Low baseline rate secretion is adequate to support defense against inhaled particles and pathogens while facilitating the elimination of shed epithelial cells or resident leukocytes during normal turnover.[285]

In response to irritant triggers, inflammatory mediators, and pharmacologic or neural stimuli,[286] an exocytic burst results in over a thousand-fold increase in mucin release for brief periods of time (10 to 120 seconds)[284,287–289] (Video 4.2). This allows for localized thickening of mucus to trap particles, which are then transported out of the airways. Steady-state and stimulated secretion are both regulated processes and utilize similar but distinct extracellular ligands, signal transduction pathways, and exocytic machinery.

In the steady state, small deformations in the mucosa can cause shear and compressive stress-triggered ATP release from epithelia. ATP acts on P2Y2 purinergic receptors to cause mucin secretion, and the ATP catabolite adenosine acts on A2b adenosine receptors to control changes in ion and water flux.[247,290–294] ATP is also released during cell injury, inflammation, and in response to neural activation. The precise mechanisms of mucin granule exocytosis in respiratory SMG mucous cells have not been elucidated at a molecular level.

MUCUS AND MUCOCILIARY INTERACTIONS

Mucus is the vehicle used by cilia to transport inhaled particles to the mouth, where they are eliminated by expectoration or swallowing. Mucociliary function requires regulation of cilia and mucus components, including water, ions, and macromolecules, to achieve a composition that falls within biophysical constraints for barrier and transport activities.

MUCOCILIARY CLEARANCE

Establishment of Directional Mucociliary Clearance

Effective *mucociliary clearance* (MCC) is defined by the movement of materials from peripheral air spaces towards the mouth.[271,295] At the tissue level, MCC is controlled by the anatomic distributions of mucous and ciliated cells and the coordinated regulation of mucociliary functions.[129]

Multiciliated cells use highly conserved mechanisms to organize across a directional gradient on tissue surfaces resulting in planar cell polarity.[296,297] In establishing planar cell polarity, signaling along a proximal-to-distal axis results in asymmetric orientation of cytoskeletal cadherins, junction proteins, and cilia basal bodies in sheets of multiciliated cells.[298]

Specific cues for planar cell polarity are being studied, and Wnt signaling pathways are involved in airway surface flow sensing.[297] Planar cell polarity appears to be developmentally programmed and autonomous because surgical removal and reversal of tracheal segments of rabbits or rats does not reverse the direction of cilia beating or mucus transport.[299,300]

Regulation of Cilia Beat Frequency and Motility

Ciliary beating and waveforms are generated by coordinated enzymatic activity. In each cilium, thousands of dynein ATPase motors walk back and forth along the microtubules of the ciliary axoneme (see Fig. 4.5).[147,148,301,302] Rapid, coordinated, asymmetric dynein activity results in ciliary bending.[147,148,303] ATP/adenosine diphosphate–generating enzymes are maintained within the cilia for dynein activity.[304–306]

Several other molecules also control ciliary motility. Intracellular calcium concentration increases cilia motility as regulated by adenosine nucleotide phosphorylation.[149,150,307,308] Increased NO also increases ciliary beat frequency, while imbalanced cell redox state can depress ciliary motility.[309–311] In bronchi, in which multiciliated cell populations are dense, mucociliary transport takes place on coordinated *metachronal* waves, a result of sequential (not synchronized) action of the cilia (Video 4.3). As a result of friction at the margin of the mucus gel layer and the cilia in the PCL, mucus is transported distal to proximal.

Periciliary Layer and Ciliary Beating

In addition to osmoregulation, the gel-on-gel nature of the ASL also optimizes motile cilia function. In health, hydrated membrane mucin extensions from cilia form "grafted brushes" that create lubricative electro-repulsion between cilia.[248] Increased osmotic pressures of mucus gels that draw water away from the PCL cause cilia to collapse, increase friction between cilia, and thereby impair mucociliary transport.[248] It is therefore essential to maintain homeostatic balance among aqueous, ionic, and macromolecular components.[271]

Purinergic Signals Integrate Mucociliary Functions

Adenosine nucleotide and nucleoside signaling mechanisms have well-described roles in mucociliary functions. ATP is released into extracellular spaces in response to tonic or inflammatory signals. ATP activates P2Y2 receptors and drives mucin secretion, ion channel opening, and increased cilia beat frequency.[271,284] Subsequent ATP dephosphorylation activates A2b-dependent hydration signals along with sustained potentiation of cilia beating.[304] Collectively, the physiologic and stimulated release of mucin granule contents in response to ATP-mediated activation of P2Y2 receptors is matched by parallel P2Y2-dependent ion and water fluxes and by potentiated motile cilia functions.

Mucociliary Transport

With gel structure and cilia function in equilibrium in healthy human airways, clearance is approximately 3 to 11 mm/min.[246,312,313] This is validated by measurements of inhaled tracer compounds that are cleared from the human lung in 1 to 2 hours.[312,314,315] Impaired MCC is a primary defect in primary ciliary dyskinesia and CF, and it is a contributing pathophysiologic factor in asthma and COPD.[271,316,317]

MCC does not account for the removal of all particles. Very small particles (<1 μm diameter) can bypass areas of the most efficient MCC.[312] These particles deposit in distal air spaces (including alveoli), where they are ingested by macrophages and may persist for extended periods of time (days to weeks). Because of the anatomic distribution of SMGs in tracheobronchial airways, there are strong correlations between SMG secretion rates, volumes, hydration, and MCC. The absence of SMGs in bronchioles, along with the presence of fewer ciliated cells, likely restrains MCC velocity in small airways.

Cough Clearance of Mucus

In settings of accumulated mucus or overwhelming exposure to particles or irritants, cough becomes another significant means for clearance. Cough efficiency depends on airflows that, in large airways, can reach velocities of 100 to 300 m/sec (approximately 200 mph).[318] If shear forces can overcome adhesive and cohesive forces of mucus, cough can peel mucus from airway surfaces or break the mucus layer, allowing parts of mucus to be cleared. Thus, the efficacy of cough clearance also depends on mucus composition and biophysical properties.[318]

Studies have identified that mucus adhesion and cohesion are key properties determining the effectiveness of cough; both depend on the concentration of mucins in the mucus gel. Efforts to decrease the concentration of mucins by hydration and to decrease the cohesive strength of the long mucin strands with mucolytics may provide additive benefit by improving mucus biophysical properties.[338]

In addition, cough is more effective in clearing thicker mucus gels.[271,318] In large bronchi, high-velocity airflow disrupts thick accumulations of mucus while preserving the thin protective ASL coat. However, in small airways (e.g., 1-mm diameter bronchioles), mucus is less likely to become thick; that fact, coupled with much lower forced airflow velocities, can result in the inability to clear mucus with coughing and, ultimately, small airway obstruction.

Airway mucus gels also function as semi-porous barriers to pathogens and particles. In health, airway mucus has a mean porosity of 100 to 1000 nm, which is sufficient for blocking penetration by most microbes.[319–321] Although mucus may be present as a continuous blanket, there are often insoluble mucin rafts (or "flakes") dispersed across heterogenous mucus strands.[322] In the PCL, the mucins tightly packed along the cilia create a mesh-like region with openings of less than 40 nm diameter, which keeps the mucus gel from penetrating the PCL and maintains the two layers as separate entities.[248] As with ASL hydration, the control of the porosity of mucus gel also requires equilibrium between its aqueous, ionic, and macromolecular components.

MUCOUS CELL METAPLASIA AND HYPERPLASIA

Baseline Mucin Expression

In health, mucous differentiation is controlled by cues that specify secretory lineages (see eFig. 4.4). Signals that promote mucous cell differentiation include Notch, SPDEF, β-catenin, epidermal growth factor, and retinoid receptor pathways.[323–327] Conversely, some factors inhibit mucous differentiation, including NKX2-1, FOXA2, and epigenetic regulation.[328–333] Collectively, these signals determine spatial and temporal patterns that regulate mucous cell differentiation.

Injurious, infectious, or inflammatory responses increase the number of mucous cells and the amounts of MUC5AC and MUC5B they produce. Epithelial cell remodeling leads to excessive mucin production and secretion, which are prominent features in CF, idiopathic pulmonary fibrosis, asthma, and lung adenocarcinoma.[170,330,334–337] The potential importance of MUC5AC and MUC5B in human lung diseases is supported by findings in mouse models.[170,285,338–341]

Mucous Cell Metaplasia

If resident cells transition to a mucous phenotype (i.e., without proliferation), the process is termed *metaplasia.* Metaplasia takes place when mucin is induced in cells, such as serous or club cells, that already possess secretory phenotypes.[168,169] In fact, many of these cells are already "mucous" when defined at the molecular level based on expression of MUC5B.[154–156] In the setting of mild injury or inflammation, metaplastic changes may be transient, resolving within days or weeks.[168,169] Resolution of metaplasia involves down-regulation of *MUC5AC* and *MUC5B* gene expression, coupled with emptying of their contents through secretion, autophagy, or potentially apoptosis.[168,169,342–344]

Mucous Cell Hyperplasia

In contrast to metaplasia, *hyperplasia* involves cell proliferation. In severe or chronic situations, mucous cells arise during proliferation-dependent replacement of epithelia.[168,345] Club cells, serous cells, and basal cells are capable of proliferating, increasing in numbers, and differentiating into secretory cells that synthesize MUC5AC and MUC5B.[132,134,221,346] Resolution of mucous cell hyperplasia may involve secretion, autophagy, and apoptosis.[344,347–349]

Mechanisms of Mucin Overproduction

MUC5AC and *MUC5B* gene expression is regulated by conserved regulatory elements that control baseline and inducible expression.[329,334,350,351] Triggers for mucin gene expression include pathways with proinflammatory, allergic, and innate immune signatures, as well as pathways related to baseline differentiation signals.[352,353] In allergic asthma, type 2 cytokine pathways are major drivers of the transition from normal to pathologic mucin production via signal transducer and activator of transcription 6.[346,354–359]

In addition to allergic stimuli, innate cytokines such as tumor necrosis factor, IL-1β, and IL-17A induce mucin production.[360–362] Inflammatory signals are transmitted by mitogen-activated protein kinases,[363,364] and inducible transcription factors that have been implicated in mucous cell differentiation include CREB, STAT1, STAT3, MyD88, NF-kB, HIF-1, FOXM1, FOXA2, and FOXA3.[324,346,362,365–371] These diverse signals ultimately lead to activation of transcription factor SPDEF, which mediates mucous cell differentiation and induced production of MUC5AC.[372–374]

Current evidence suggests that epidermal growth factor receptor signaling is a parallel pathway involved in mucin overproduction. Epidermal growth factor receptor signaling is necessary for MUC5AC induction in a wide range of settings, including cigarette smoke exposure, viral infection, bacterial infection, and both innate and adaptive immune response signals.[326,354,362,364,375,376]

Mechanisms of Regulated Mucin Secretion

The biosynthesis and secretion of mucins are independent steps. As MUC5AC and MUC5B are synthesized, they are packaged into secretory vesicles that are stored in apical cytoplasmic compartments while they await secretory triggers. Stimuli, such as ATP acting via P2Y2 receptors, result in rapid docking of mucin granules with exocytic machinery present on the inner leaflets of apical plasma membranes[284] (eFig. 4.5).

Mucin granule docking and fusion involve proteins such as vesicle-associated membrane proteins and plasma membrane-associated proteins called syntaxins and SNAPs.[377] Exocytic core complex formation is aided by Munc13 and Munc18 family syntaxin binding proteins.[377–379] In rapid succession, increased cytoplasmic Ca^{2+} levels drive tightening of SNAP receptor complexes, followed by fusion of mucin granule membranes with the plasma membrane mediated by synaptotagmin.[284] After secretory granule fusion, mucin contents become hydrated and expand to form strands that organize into mucus gel layers in the lumen.

INNATE DEFENSE MOLECULES AND MICROBIOTA

INTEGRATION OF BARRIER FUNCTION AND AIRWAY DEFENSE

Components of innate defense include physical, structural, biochemical, and immune factors. As noted, airway branching leads to pathogen impaction and, at the cellular level, an epithelial barrier is provided by the integrity of tight cell–cell junctions. Airway mucus gels are a first-line, essential barrier to pathogens within the lumen.[319–321]

ASL contains many antimicrobial and immunomodulatory proteins secreted by epithelial cells that have broad, nonspecific activity or act as soluble pattern recognition receptors. Important soluble pattern recognition receptors are surfactants and complement.[353,380]

In addition to surfactant proteins and complement, the airways contain many additional antimicrobial factors, including lactoferrin, the bactericidal permeability-increasing protein family, human β-defensins, and cathelicidin (LL37). These members of the innate immune response are produced by airway secretory epithelia and recognize bacteria, viruses, and environmental particles.[381] Resident airway immune cells, including dendritic cells, resident lymphocytes, and interstitial macrophages, are essential participants in airway host defense.

See also Chapter 15 and ExpertConsult.com for a discussion of innate immunity.

SOLUBLE PATTERN RECOGNITION RECEPTOR PROTEINS

Multiple epithelial cell secretory products perform antimicrobial activities, participate in responses to allergens, and clear airway pollutants.

- *Airway complement.* Complements C3 and C5 are broadly expressed in airway epithelial cells, and C3 is particularly high in club cells.[172] Complement cascades activate antibody binding to antigen (classical pathway), mannose-binding lectin binding to bacterial carbohydrates (lectin pathway), and alternative pathways.[392] The active form of complement C3 is cleaved to bind and opsonize bacteria and mediate local inflammation through phagocyte recruitment and bacterial killing.[380] Activated complement can be identified in the airway epithelial cells of individuals with asthma, CF, and obliterative bronchiolitis.[172]
- *Surfactant protein (SP)-A, SP-D, and mannose-binding lectin* are large, hydrophilic glycoproteins categorized as collectins.[393] Collectins can bind to microorganisms and eliminate them by aggregation, complement activation, and activation of phagocytosis, or by inhibiting their growth. SP-A and SP-D are secreted by the nonciliated cells of the bronchioles.[353,380,391] Specific collectins, including mannose-binding lectin on the airway surface or in the serum, bind to oligosaccharides or lipids of bacteria, fungi, and viruses.[380] SP-A and SP-D can effectively inhibit the invasion of respiratory syncytial virus, adenovirus, and influenza A virus and promote neutrophil-mediated phagocytosis. These proteins can also modulate other inflammatory responses.[394,395]
- *Human β-defensins* (hβD-1, -2, -3, and -4) are among the most abundant of antimicrobial factors produced by large airway epithelial cells. These are cationic peptides that bind bacteria and virus, form pores in bacterial membranes, suppress pathogen replication, and induce cytokine expression.[396]
- *Bacterial binding proteins* are another superfamily of epithelial cell defense proteins called the lipid transfer/lipopolysaccharide binding proteins. The proteins share the ability to bind lipid substrates. They can bind lipid A, the lipopolysaccharide region of gram-negative

Airway pathogens can be cleared by three basic responses. First, there may be direct pathogen clearance by a soluble pattern recognition receptor molecule or by interferon production followed by phagocytosis. Second, there is epithelial cell effector recruitment or activation, for example, by CXCL8 (*interleukin* (IL)-8) to mediate neutrophil recruitment. Third is a two-tiered immune response by which epithelial cells secrete cytokines (e.g., IL-1α, -1β, -33 and *interferon* [IFN]-α and -β) to signal innate lymphoid cells, tissue-resident T cells, or natural killer cells. In turn, these cells secrete cytokines (e.g., IL-4, -5, -13, -17, IFN-γ) to activate epithelial cells, monocytes, neutrophils, and others to clear pathogens.[381,382] IFN responses mediate the initial immune response in a potent antiviral transcriptional program.[381]

Cell-bound pattern recognition receptors include receptors that recognize pathogen-associated molecular patterns and damage-associated molecular patterns. Airway epithelial cell pattern recognition receptors include *toll-like receptors* (TLRs), intracellular viral sensors RIG-I-like receptors, Nod-like receptors, and the bitter-taste receptors.[383] TLRs are expressed as extracellular receptors (e.g., TLRs 2, 4, and 6) and within cytoplasmic endosomes (e.g., TLRs 3, 7, 8, and 9) of airway epithelial cells.[384] Upon activation of these receptors, airway epithelial cells secrete antimicrobial and chemotactic factors that may act directly against pathogens and also signal to local tissue and bone marrow immune cells.

RESIDENT IMMUNE CELLS OF THE AIRWAY EPITHELIUM

Conventional and plasmacytoid dendritic cells are normally present in subepithelial and intraepithelial locations to take up and process foreign antigens, including respiratory viruses.[385–388] Small populations of resident lymphocytes localize in subepithelial and interepithelial spaces, where immune-epithelial cell interactions regulate epithelial cytokine and chemokine production in response to pathogens and allergens.[389]

bacteria, to facilitate killing. The *bactericidal/permeability increasing* (BPI) family of antibacterial proteins are enriched in the upper airway epithelial cells. *BPI fold-containing family A1* (BPIFA1; also called SPLUNC1) and *BPI fold-containing family B member 1* (BPIFB1; also called LPLUNC1) are expressed at high levels in epithelia of the nasopharynx, oral cavity, and large airways with high levels in the nasal and respiratory lining fluids.[397,398] These proteins recognize and coat bacteria, while some members also kill. BPIFA1 is reported to regulate ASL hydration through the epithelial sodium channel ENaC.[399]

- *Lactoferrin* is a cationic lipoprotein produced by SMG epithelial cells. A member of the transferrin family, it contains ferrins that chelate iron essential for bacterial function.[400] Lactoferrin also has a broad ability to interfere with both RNA and DNA virus infections by binding virus or receptors.[401,402]
- *Lysozyme* is secreted in abundant amounts by serous cells in the upper airway and in submucosal glands. Lysozyme degrades the polysaccharide capsules of multiple species of bacteria.[403,404]

AIRWAY IMMUNOGLOBULIN A

Dimeric *immunoglobulin A* (IgA) is released by subepithelial B cells and binds the poly Ig receptor on the basal airway epithelial cell surface.[405] The complex of poly Ig receptor and dimeric IgA is transported across the cell in secretory vesicles for apical secretion into the lumen. Secreted IgA then targets and binds viral pathogens or allergens for entrapment in mucus. Evidence suggests a beneficial role of IgA in chronic airway diseases. Patients with COPD, asthma, and chronic rhinosinusitis have impaired poly Ig receptor expression and reduced secretory IgA levels in airway epithelial secretions.[406–409]

NITRIC OXIDE

NO is produced by airway epithelial cells as a stress response through the induction of NO synthases 1, 2, or 3.[410,411] NO acts as an antimicrobial agent by directly causing nitrosative and oxidative damage to pathogens. NO also increases cilia beat frequency.[309,310] Multiple sensors are capable of inducing NO. NO synthase 2 is highly induced in response to infections with respiratory viruses and other pathogens.[412] In the sinuses, *Pseudomonas* can activate the bitter-taste receptors to release NO, increasing cilia beat frequency and airway clearance.[413] Whereas exhaled NO is increased with exacerbations of asthma, nasal NO is decreased in CF, and low levels may support the diagnosis of primary ciliary dyskinesia.[414,415]

AIRWAY MICROBIOTA

The upper and lower airways harbor a microbiome of diverse communities of bacteria, viruses, and fungi that are a component of normal health of the respiratory tract[416,417] (see also Chapter 17). It is proposed that microbes within the respiratory tract prevent invasion and colonization of pathogenic organisms.[416] Acquisition of an upper airway microbiome begins with delivery at birth[416,418] and increases in complexity from birth until stable communities are developed at approximately age 3 years.[416] Bacteria from the upper tract and airway normally enter the lower tract by breathing and micro-aspiration. A hallmark of the airway diseases asthma, CF, non-cystic fibrosis bronchiectasis, and COPD is a change in the microbial diversity or abundance.[419,420]

Key Points

- The major function of the airways is to conduct airflow while also protecting the alveoli from environmental insults. Inspired air is hydrated and diverted into trachea, bronchi, and bronchioles.
- Airways are composed of a mucosal layer lined by epithelium, and a submucosal layer containing smooth muscle, autonomic nerves, and extracellular matrix. Mucosal and submucosal tissues are in constant communication and dynamically respond to environmental challenges.
- Airway structure and function are maintained in part by interactions among matrix, nerves, and smooth muscle. Extracellular matrix provides a rigid support for maintaining airway patency and tissue tensile strength. Smooth muscle provides dynamic changes in airway tone in response to autonomic neural inputs and immune mediators.
- Airway epithelial cells maintain airway barrier function. Basal cells are tightly adherent to the basal lamina by connections between cell cytoskeleton and extracellular matrix by hemidesmosomes and integrins. Cell-cell tight and adherens junctions impart selective movement of paracellular water, proteins, and ions between cells. Specialized epithelial cells lining the lumen provide mucociliary clearance and host defense.
- Airway epithelial cells are a diverse population with specific roles and locations. Multiciliated and mucous cells are the major cell types of the upper tract and large airways. Basal cell populations have progenitor functions. Rarer epithelial cell types include ionocytes, neuroendocrine cells, and tuft cells.
- Airway epithelial cells all survive many months. The basal cell is the major stem cell for maintenance of differentiated epithelial cell types. The dominant pathway for airway epithelial cell differentiation of basal cells is Notch signaling, which generates secretory cells, while an absence of Notch signaling generates multiciliated cells.
- Lumen surfaces are protected by airway surface liquid comprising a gel-on-gel structure, with a mucus gel overlying a periciliary gel layer. Submucosal glands are the major source of airway surface liquid in the healthy lung.
- Mucociliary clearance is the first line of airway host defense. Effective clearance depends on both the mucus gel and the underlying periciliary gel in which the cilia move. Mucus and periciliary layers are in osmotic equilibrium. The mucus gel is composed of roughly 98% water and 2% solid materials, including gel-forming mucins MUC5AC and MUC5B. This composition creates an efficiently transported gel while also imparting homeostatic osmotic forces that support periciliary layer hydration and cilia motility.

Key Readings

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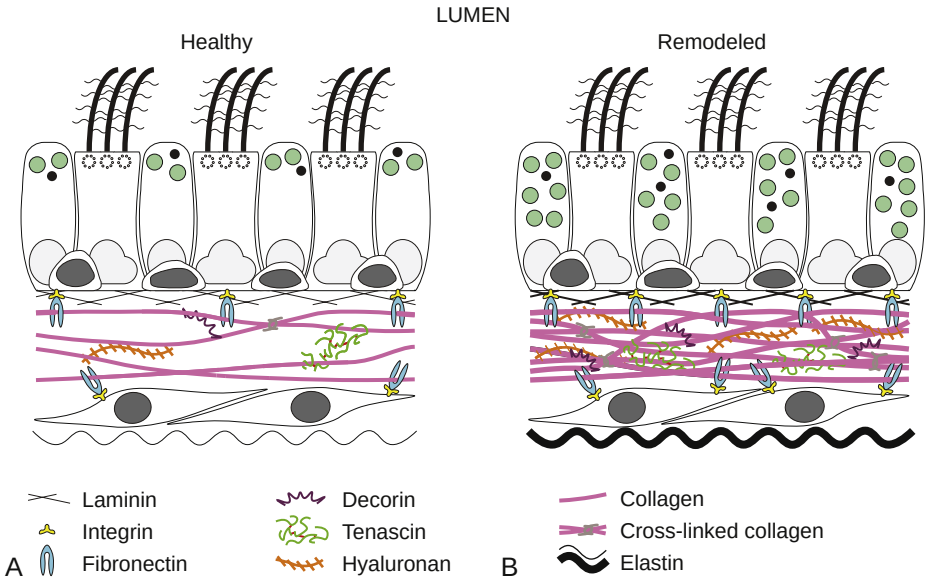
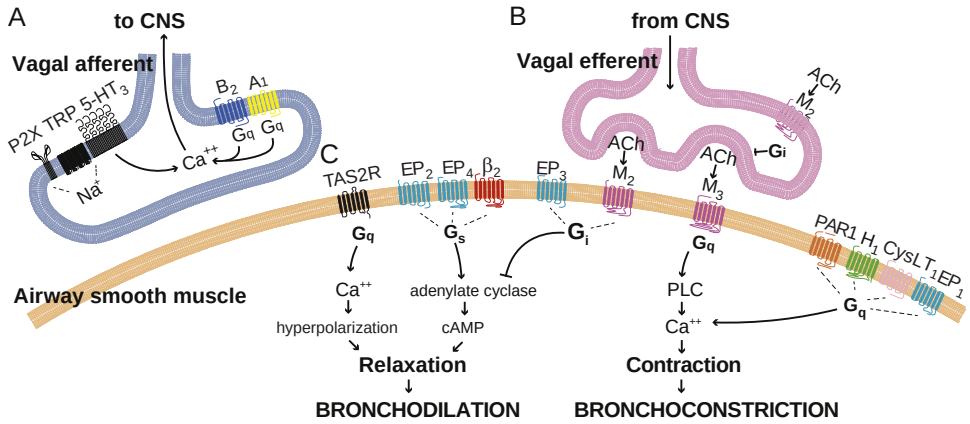
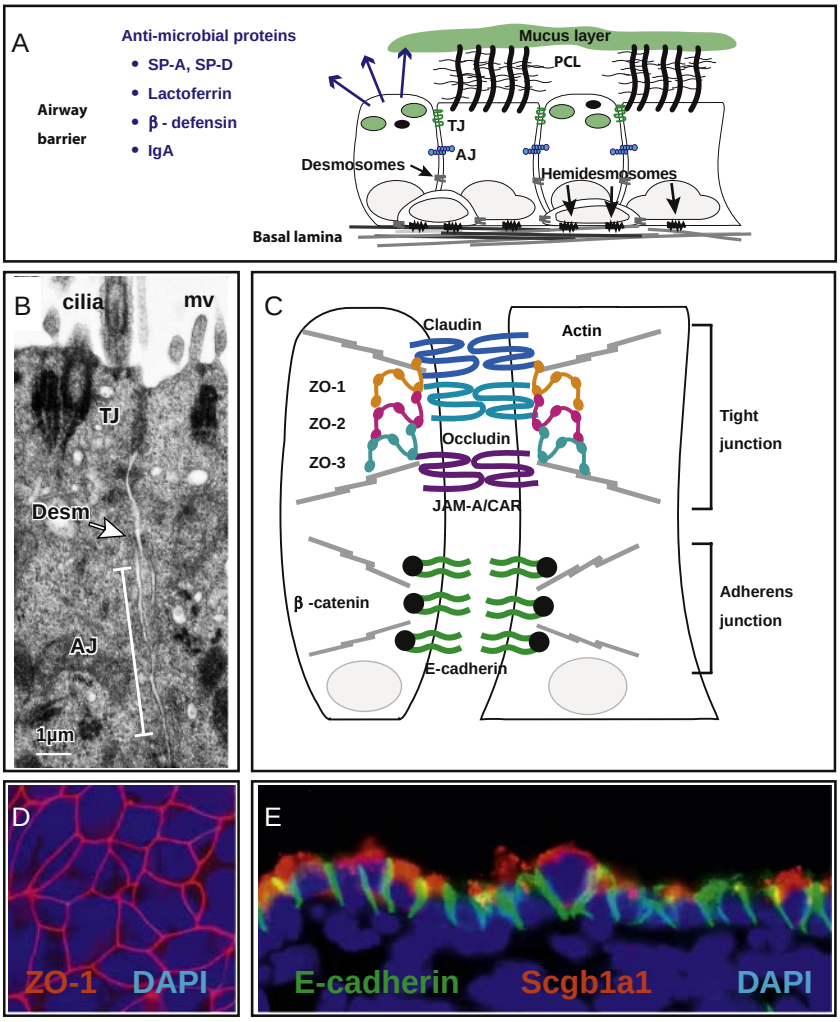
eFIGURE IMAGE GALLERY



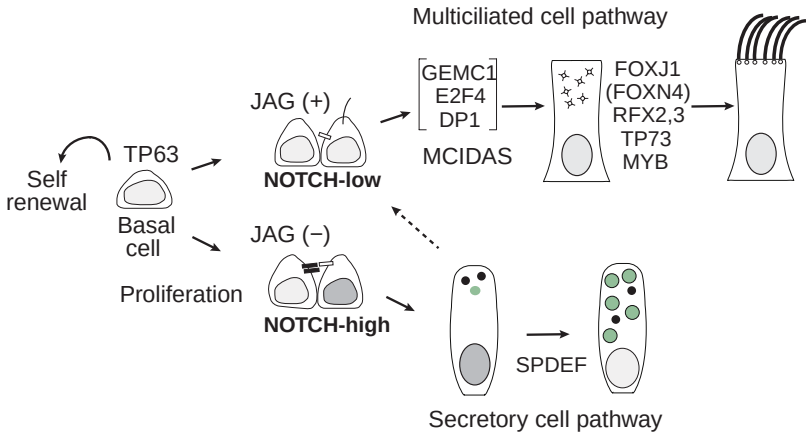
eFigure 4.1 Interaction of epithelial and matrix components in health and following airway remodeling. (A) In health, airway epithelia are positioned on the basal lamina, attached by integrins and fibronectin within extracellular matrix. (B) In disease, aberrant repair results in airway remodeling due to cellular cross-talk, resulting in mucous cell metaplasia characterized by excessive mucin (*green circles*) as well as increased matrix component overproduction, featuring increased collagen and other molecules (e.g., fibronectin and hyaluronan).



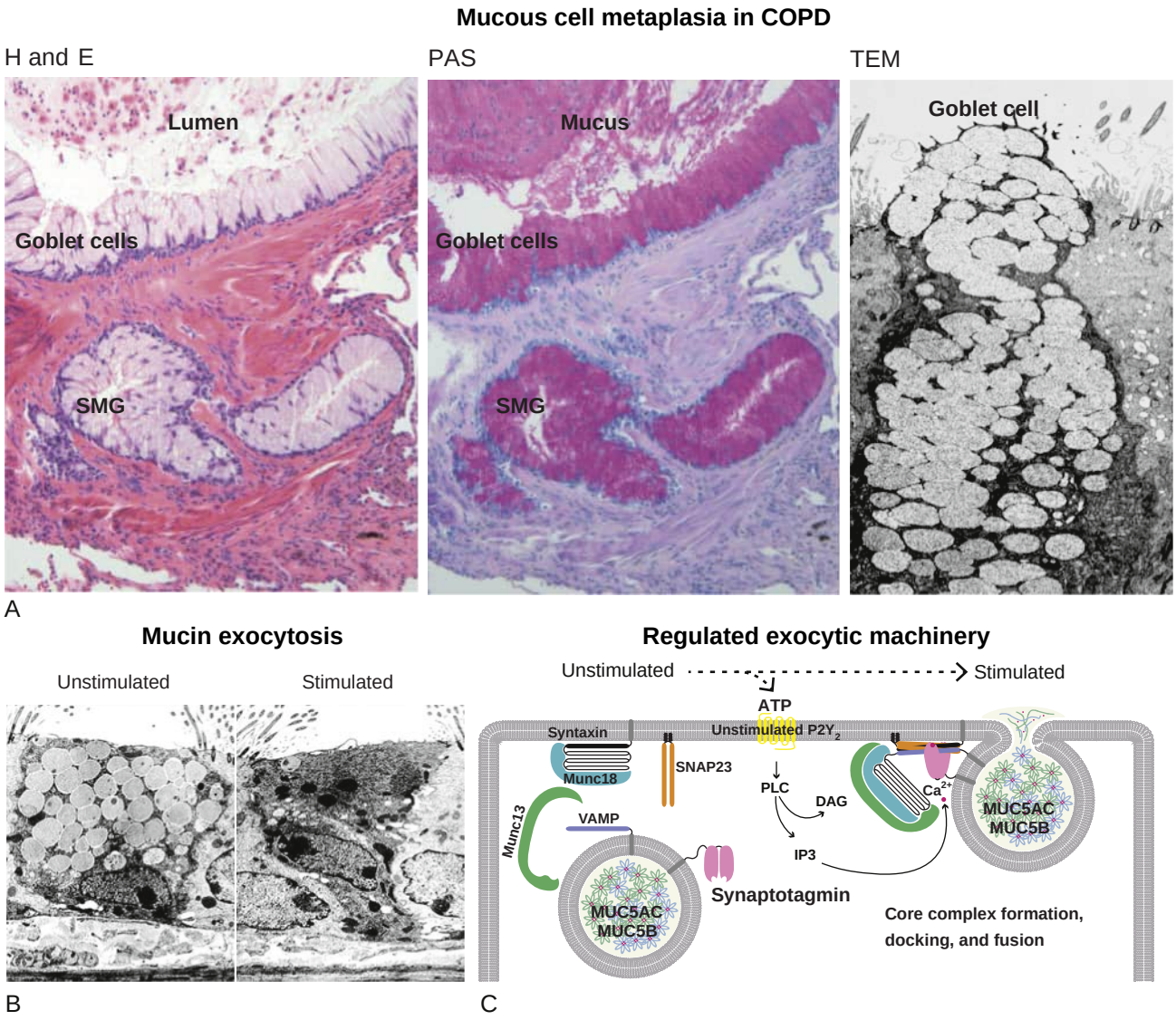
eFigure 4.2 Control of airway smooth muscle. (A) Sensory receptors initiate reflex signals by activating vagal afferent neurons that transmit signals to the *central nervous system* (CNS). (B) Efferent reflex signaling is transmitted from the CNS through tracheal ganglia via nicotinic and M_1 muscarinic receptors (not shown). Postganglionic cholinergic signals are mediated by postjunctional muscarinic M_3 receptors that cause smooth muscle contraction, by postjunctional M_2 receptors that inhibit relaxation, and by prejunctional M_2 autoreceptors that inhibit *acetylcholine* (ACh) release. Additional non-neuronal inflammation-related G protein–coupled receptors also stimulate airway smooth muscle (ASM) contraction. (C) Non-neuronal G protein–coupled receptors are the dominant regulators of ASM relaxation and bronchodilation. A_1, adenosine receptor 1; B_2, bradykinin receptor 2; β_2, β-adrenergic receptor 2; cAMP, cyclic adenosine monophosphate; $CysLT_1$, cysteinyl leukotriene receptor 1; $EP_{1–4}$, prostaglandin E2 receptors 1–4; $5\text{-}HT_3$, 5-hydroxytryptamine receptor 3; H_1, histamine receptor 1; $M_{2–3}$, muscarinic acetylcholine receptors 1–3; PAR1, protease-activated receptor 1; PLC, phospholipase C; P2X, purinergic P2X receptor; TAS2R, taste 2 receptor; TRP, transient receptor potential channel.



eFigure 4.3 Airway barrier, cell-cell junctions, and cellular components. (A) Airway barriers are composed of epithelia, mucus and periciliary layers, cell junctions, desmosomes and hemidesmosomes, basal lamina, and extracellular matrix. Epithelial cells secrete innate defense factors, surfactant proteins A and D (SP-A, SP-D), lactoferrin, human β-defensins, and immunoglobulin A (IgA). (B) Airway epithelial cell ultrastructure of the cell-cell tight junction (TJ), adherens junction (AJ), and desmosome (Desm., *arrows*) complexes by transmission electron microscopy (mv, microvilli). (C) Illustration of TJ and AJ detailing zona occludin (ZO-1 to -3), claudin, junctional adhesion molecule-A (JAM-A), coxsackie and adenovirus receptor (CAR), E-cadherin, and β-catenin components. *Gray lines* connected to TJ and AJ molecules represent links to the cytoskeleton. (D) ZO-1 (*red*) in cultured human airway epithelial cells imaged from the apical surface demonstrating circumferential tight junctions. Nuclei are stained with DAPI (*blue*). (E) E-cadherin (*green*) and SCGB1A1 (club cell secretory protein; *red*) in mouse airway epithelium demonstrate the distribution of AJ in cross-sections. PCL, periciliary layer. (B, D, E Courtesy Dr Steven L. Brody.)



eFigure 4.4 Pathways for airway epithelial cell differentiation. Basal cells, identified by TP63, are capable of self-renewal, proliferation, and differentiation. Basal cell progeny fate is determined by Notch-dependent signaling leading to multiciliated (Notch-low, *top*) and secretory (Notch-high, *bottom*) cell differentiation regulated by indicated factors. Intermediate cell types are shown in the absence or presence of NOTCH signaling. Those fated as multiciliated cells have a solitary, nonmotile, primary cilium present prior to developing motile cilia. Additional transcription factors are required for multiciliated cell differentiation. In the first phase, MCIDAS and a complex of GEMCI-E2F4 and DPI initiate centriole amplification to form basal bodies (indicated by star-shaped cytoplasmic symbols). MCIDAS activates FOXJ1, which in the presence of FOXN4, RFX2,3, TP73, and MYB activates genes required for motile cilia structure and function and controls programs of cilia assembly. Secretory cell differentiation is less well understood. The transcription factor SPDEF activates the program of mucous cell differentiation and mucin MUC5AC production (green cytoplasmic vesicles). Secretory cells demonstrate plasticity with a capacity to become pre-multiciliated, intermediate cells.



eFigure 4.5 Mucous cell metaplasia and secretion. (A) Bronchus from individual with severe COPD showing mucous cell metaplasia and enlarged *submucosal gland* (SMG) stained with hematoxylin and eosin (H and E, *left panel*). Serial tissue section stained with periodic acid–Schiff (PAS) showing mucins in lumen, goblet cells, and SMG (*center panel*). Ultrastructure of a goblet cell in human COPD by transmission electron microscopy (TEM, *right panel*). (B) Ultrastructure of a goblet cell in an airway from a mouse model of mucous cell metaplasia. Shown are cells before (unstimulated) and after (stimulated) ATP-induced secretion of mucin-containing vesicles. (C) Mechanism of regulated secretion of mucin granules showing components of the exocytic machinery before and after secretagogue stimulation (ATP shown). In the presence of increased Ca^{2+}, docked vesicles rapidly fuse with the plasma membrane and release MUC5AC and MUC5B into airway lumen spaces. DAG, diacylglycerol; PLC, phospholipase C; VAMP, vesicle-associated membrane protein. (A, Courtesy Dr. Steven L. Brody. B, From Williams OW, Sharafkhaneh A, Kim V, et al. Airway mucus: From production to secretion. *Am J Respir Cell Mol Biol.* 2006;34[5]:527-536.)

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5 LUNG MESENCHYME

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INTRODUCTION

The lung mesenchyme is a loosely organized mesodermal tissue composed of the cells and connective tissue matrices within the lung interstitium. It includes a few different cell types, including smooth muscle cells, fibroblasts, and pericytes, and contains *extracellular matrices* (ECMs) that occupy the acellular spaces of the lung. Initially considered a compartment containing an inert ground substance solely responsible for providing structural support, the lung mesenchyme is now known to provide key spatial and contextual cues to surrounding cells, thereby exerting roles in physiologic and pathologic processes.[1,2] Proteoglycans, glycoproteins, and collagens make up the lung ECM and, through disulfide bonds and other interactions, connect with each other and with adjacent cells, thereby establishing a vast acellular network of multifunctional molecules that provide support, drive cell behavior, and influence responses to injury.

Pulmonary cells submerged within the lung mesenchyme recognize and interact with individual ECM components through cell surface signaling receptors called *integrins*.[3] Thus the impact of cell-ECM interactions is determined by the relative amount and composition of the ECM in any given compartment and the cellular repertoire of integrins and other matrix binding molecules. Cell-ECM binding allows the transfer of tensile strength, which affects cell phenotypes through mechanotransduction.[4] Embedded within this entangled ECM framework are growth factors and other cell-derived bioactive molecules that lay dormant until the ECM is disturbed (e.g., during lung injury), at which time they are released and activated in the microenvironment, where they interact with adjacent cells.[5]

Considering its distinct ECM components, its ability to influence cell behavior, and its function as a reservoir for extracellular bioactive molecules, the lung mesenchyme is recognized as a dynamic and complex structure necessary to maintain homeostasis during health, while driving repair or disrepair after injury. Most, if not all, pulmonary disorders are associated with alterations in ECM expression, degradation, and turnover. Although it has been difficult to ascertain the exact role of individual ECMs and their cellular receptors in the lung due to the lack of appropriate tools or models, research generated over the past 3 decades has unveiled roles for the mesenchyme in lung morphogenesis and in human disorders, characterized by aberrant tissue remodeling ranging from emphysema and asthma to pulmonary vascular disease, fibrosis, and cancer.[6–10]

This chapter discusses these subjects with a focus on the ECM and emphasizes its roles in the control of cell functions during physiologic processes and lung disease.

THE LUNG EXTRACELLULAR MATRIX

In healthy states, the lung mesenchyme contains few mesenchymal cells (e.g., fibroblasts) surrounded by a vast network of intertwined ECMs. These ECMs are arranged into two types of compartments: *interstitial matrix* and *basement membranes*.[11] The interstitial matrix is a loose meshwork that interconnects cellular structures and maintains the *three-dimensional* (3D) organization and biochemical characteristics of the lung. Even though interstitial matrices represent the main parenchyma of the lung, basement membranes are arranged in thin specialized ECM layers located beneath epithelial and endothelial cell sheets, where they separate distinct cellular structures, thereby allowing the development of specialized and functional pulmonary structures, such as the airways and alveoli.[12]

The composition of the ECM in mouse and human lung has been characterized by isolating the matrix after removing all cellular material (decellularized scaffold), followed by proteinase digestion of the matrix, and analysis of its components by mass spectrometry. The collection of proteins, glycoproteins, proteoglycans, and associated modifying proteins identified by this type of analysis has been termed the *matrisome.* This approach allowed the identification of at least 150 different ECM proteins and modifying enzymes, including some previously unknown, in addition

to collagens, elastin, glycosaminoglycans, and laminin.[13,14] The number of core structural components of the entire mammalian ECM is approximately 300 proteins (also termed the *core matrisome*).[15] The ECM serves as a reservoir for many secreted proteins, including growth factors, ECM-modifying enzymes, and other ECM-associated proteins, together known as the *ECM-associated matrisome.*

The composition and properties of the ECM are heterogeneous among the different regions within the lung (i.e., bronchi, bronchioles, alveoli, vasculature) and among physiologic states (i.e., fetal, adult, aged, injured).[14,16] Each type of ECM component (e.g., proteins, glycoproteins, and proteoglycans) has subcomponents with different physical and biochemical properties. For example, collagen and elastin proteins form fibrils from protein monomers and contribute to the tensile strength and viscoelasticity of the lung.[17] Other proteins, such as *fibronectin* (FN) and laminin, participate in building the matrix network as connectors or linking proteins (Fig. 5.1).[18,19] Individual ECM components might be cross-linked and organized via covalent modifications or undergo further modifications, including glycosylation, that influence cell-ECM interactions and change overall ECM properties, such as stiffness or fiber orientation.[20]

The most abundant proteins in the lung ECM are *collagens*. They provide tensile strength but also regulate cellular communication and developmental functions.[21] Collagen molecules form triple-stranded helices that assemble into complexes called fibrillar (types I, II, III, V, and XI) and nonfibrillar (IV, VI, VIII, and X) forms of collagen (Fig. 5.1B). Fibrillar collagen subtypes I and III predominate in the interstitial matrix and are integral to maintaining the architecture of the lung.[22] Fibrillar collagens are resistant to enzymatic degradation, which is important for limiting the turnover and remodeling of the interstitium during injury. The nonfibrillar form collagen IV is a major constituent of basement membranes.[23] For the most part, collagens are increased in restrictive disorders associated with pulmonary fibrosis.[24]

Another component of the lung ECM is *elastin*, a constituent formed by tropoelastin coalescing to form large polymers[25] (see Fig. 5.1C). Lung compliance and elastic recoil are dependent on the appropriate deposition and alignment of elastin fibers. The production of elastin ceases in the human lung after birth, and elastin has an extremely long half-life under normal conditions. Significant elastin turnover is seen only in pathologic states such as emphysema.[26]

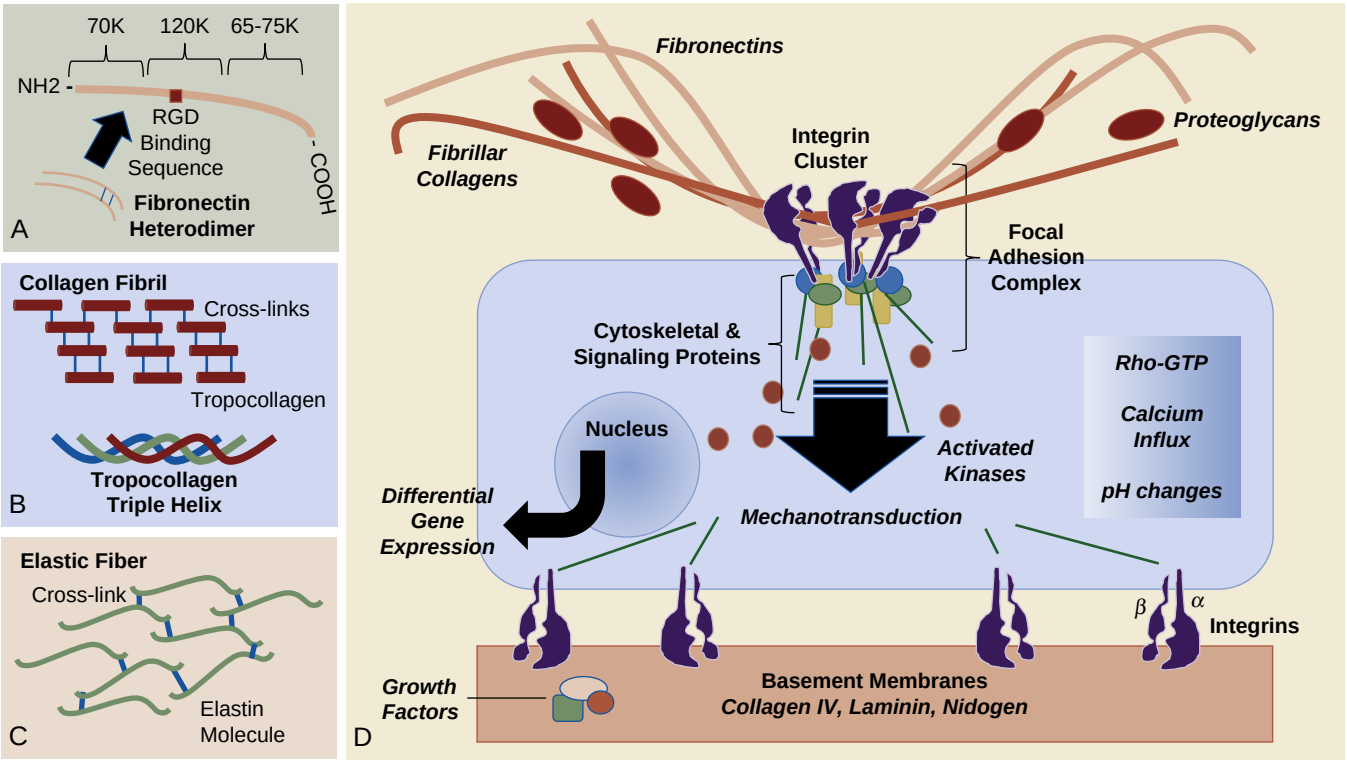

Figure 5.1 Cell–*extracellular matrix* (ECM) interactions via integrins. (A) ECMs assemble and organize into distinct structures that provide support to cells within the mesenchyme. Fibronectin, for example, is expressed as a heterodimer linked at its carboxy terminal end by disulfide bonds and is secreted into the extracellular environment, where it interacts with other ECMs and with cells through its *arginine-glycine-aspartic acid* (RGD) site located in its midsection (the 120K cellular domain), among others, that binds to cell surface integrins. (B) Collagen is initially produced as procollagen, followed by the assembly of a triple helix by three procollagen chains. Once outside, the procollagen ends are cleaved, and tropocollagen molecules form collagen fibrils deposited around cells, where they provide tensile strength. (C) The elastin fiber is formed by microfibrils, along with central cross-linked elastin, and its alignment contributes to lung compliance and elastic recoil. (D) Mesenchymal cells are submerged within a complex mesh of ECM with which they interact through cell surface integrin receptors. Cells interact with ECMs organized within basement membranes (e.g., collagen IV, laminin, nidogen; see *bottom of figure*) or ECMs within the interstitium (e.g., fibrillary collagens, fibronectin, proteoglycans; see *top of figure*). Upon ligand binding, integrin receptors cluster in focal adhesion complexes, where they "integrate" the ECM with cytoskeletal molecules and activate signaling pathways that ultimately impact protein kinase activation, Rho-GTP, calcium influx, and intracellular pH, among other signals. Tension generated through these interactions promotes mechanotransduction, which also stimulates signals that affect differential gene transcription. These interactions can be disrupted by affecting the relative composition of the ECM, disrupting basement membranes (with the release of active growth factors), and impairing integrin signaling. GTP, guanosine triphosphate.

Small peripheral glycoproteins called microfibrils, along with central cross-linked elastin, form the lung's elastic fibers. The glycoproteins fibrillin-1, -2, and -3 represent the major structural components of microfibrils.[27] Elastin–cross-linking *lysyl oxidase* (LOX), elastin microfibril interface-located proteins, and fibulins are associated with microfibrils and elastin.[28]

Laminins are composed of α, β, and γ chains that assemble into approximately 20 distinct cross-shaped high-molecular-weight proteins found in basement membranes. There they serve as bridging molecules with collagen type IV and nidogen (a glycoprotein formerly known as entactin), thereby enabling communication between cells and other ECM proteins, and promoting cell adhesion, migration, and differentiation, which are necessary for appropriate organogenesis.[29–31]

FNs are glycoproteins involved in the organization of the interstitial matrix where they mediate a host of cellular interactions[32] (see Fig. 5.1A and D). A single FN gene results in multiple splicing variants, of which the best studied is the FN *extracellular domain A* (EDA).[32,33] These multifunctional domain molecules have significant roles in matrix assembly, cell adhesion, migration, growth, and differentiation and are increased in embryonic tissues. FN is highly expressed in the developing lung and is assumed to play an important role in lung development. In mice, targeted inactivation of the FN gene leads to death during early embryogenesis.[34,35] FN-EDA expression is reduced in adulthood except in injured tissues, where FNs are involved in tissue repair.

Proteoglycans are the other main constituents of the matrisome. In general, proteoglycans are hydrophilic due to their high polysaccharide content, which enables hydrogel formation and contributes to the viscoelastic properties of the lung. Proteoglycans are composed of *glycosaminoglycan* (GAG) chains linked to a protein core.[36] GAG chains may be sulfated, such as keratin sulfate, heparin sulfate, and chondroitin sulfate, or nonsulfated, such as hyaluronic acid. Based on the GAG chain and the protein core, the three main groups of proteoglycans are *small leucine-rich proteoglycans* (SLRPs), modular proteoglycans, and cell surface proteoglycans. SLRPs are involved in signaling pathways and the activation of *transforming growth factor-β* (TGF-β).[37] Modular proteoglycans in basement membranes include perlecans, agrin, hyalectans, versican, aggrecan, neurocan, brevican, and collagen type XVIII; they have roles in angiogenesis and influence cell adhesion, migration, and proliferation.[38] Cell surface proteoglycans, such as syndecans, have ligand and receptor functions.[39] The SLRPs, decorin, biglycan, and lumican, are among the most abundant proteoglycans found in a matrisome dataset from healthy adult murine lungs and differentially affect TGF-β activation.[40]

DYNAMIC REGULATION OF THE EXTRACELLULAR MATRIX

Throughout the human life span, the lung ECM is remodeled to adapt to mechanical, biochemical, and structural changes that take place during lung morphogenesis, the onset of breathing at birth, injury, repair, aging, and disease.[41] ECM remodeling helps drive lung cell differentiation and tissue organization.[42,43] The remodeling of the ECM is regulated through various mechanisms, including ECM rate of synthesis, deposition, degradation, and posttranslational modifications. These mechanisms control the composition of the ECM, its dynamic organization into 3D structures, and its biomechanical properties.

The main cell type in the interstitial spaces of the lung is the resident fibroblast, which is mainly responsible for the production of the ECM core components (e.g., FN, collagen). Other ECM components (e.g., laminins, thrombospondin-1) are also produced by other mesenchymal cells, such as airway smooth muscle cells, or by endothelial and epithelial cells in close contact to the mesenchyme.[44] The synthesis of collagen, elastin, laminin, FN, proteoglycans, and other ECMs involves multistep mechanisms that are tightly regulated. As an example, there are approximately 30 types of collagen in the human body, which are coded by different collagen genes, with types I, III, IV, and V being the most common.[45] Collagen genes are transcribed in the cell nucleus, where transcription factors and chromatin modifications control the rate of transcription of each collagen gene into pre-RNA. After splicing of the pre-RNA, procollagen *messenger RNAs* (mRNAs) are translated into protein in the cytoplasm. The resulting pre–propolypeptide chains travel to the endoplasmic reticulum, where they undergo posttranslational processing to become procollagen. The latter requires N-terminal signal peptide removal, the addition of hydroxyl groups to lysine and proline amino acid residues by hydroxylase enzymes, and glycosylation of selected hydroxyl groups on lysines. Afterward, three of the hydroxylated and glycosylated procollagen chains assemble by twisting into a triple helix by zipper-like folding. This procollagen molecule moves to the Golgi apparatus for final modification and assembly into secretory vesicles. Once the molecule is in the extracellular space, collagen peptidases cleave and remove the ends of procollagen, and the molecule becomes tropocollagen. Lysyl oxidases then act on lysine and hydroxylysine residues and covalently bond tropocollagen molecules to form the collagen fibril. Although this is an example of a particularly complex process, it is by no means unique, because the production of most ECM components depends on complex synthetic mechanisms.

EXTRACELLULAR MATRIX DEGRADATION AND TURNOVER

The proteins, glycoproteins, and proteoglycans that form the ECM are mostly degraded by proteinases belonging to different families, including *matrix metalloproteinases* (MMPs), adamalysins, and cysteine and serine proteases.[46] The most significant proteinases are the MMPs, a family of more than 30 zinc-dependent endopeptidases expressed in a cell type–specific manner,[47–49] which degrade ECMs and other substrates. MMPs influence several cellular functions, including cell migration, and modulate the activity of molecules by cleavage or release from a storage state. Macrophages, fibroblasts, bronchiolar and alveolar epithelial cells, and other cells express MMPs as well as their inhibitors, the *tissue inhibitors of metalloproteinases* (TIMPs). MMPs are secreted along with their inhibitors in a 1:1 ratio; in consequence, the bioactivity of any given MMP depends on the relative concentration and spatial colocalization of its inhibitor. TIMPs appear to be dysregulated in distinct

lung disorders, such as *idiopathic pulmonary fibrosis* (IPF) and lung cancer.[50,51]

Several MMPs are essential in lung remodeling before and after birth; others are reactivated in response to environmental factors, infection, and injury. Studies performed in null mutant mice indicate that complete absence of MMP2 or MMP14[52] alters lung development, yet mutations of other MMPs do not impair normal lung development. Only after a stimulus or "second hit" do notable differences appear. For example, the absence of MMP9 results in enhanced allergen-induced lung inflammation, whereas the loss of MMP7 and MMP10 results in differential response to *Pseudomonas* infection.[53,54] Like ECMs, MMP expression levels are regulated at the transcriptional, translational, and epigenetic levels.[55] Meanwhile, MMP activity is regulated by vesicle trafficking and secretion, activation of latent pro-forms, deactivation by other proteinases, and complexing with specific TIMPs.

Adamalysins, such as *a disintegrin and metalloproteinases* (ADAMs), and *ADAMs with a thrombospondin motif* (ADAMTs),[56,57] are expressed by many cell types and cleave membrane-bound growth factors, cytokines, proteoglycans, and Fas ligand, leading to the detachment or shedding of mature soluble forms implicated in distinct physiologic and pathologic processes.[58,59] The *serine proteases* include several subfamilies, such as the coagulation proteases, neutrophil serine proteases, and *type II transmembrane serine proteases* (TTSPs), among others. The coagulation proteases play pivotal roles in tissue repair by generating fibrin.[51] However, the coagulation proteinases have functions independent of fibrin formation because they exert profibrotic effects by inducing the expression of potent fibrogenic factors, including platelet-derived growth factors and connective tissue growth factor. The TTSPs are the newest subfamily identified and comprise a large number of proteinases, such as matriptases, hepsin, corin, and human airway trypsin-like protease, which have distinct roles in the lung. The neutrophil serine proteases, such as neutrophil elastase, are found in various chronic inflammatory lung diseases. *Cysteine proteases* degrade ECMs and limit the release of newly synthesized ECM from fibroblasts. Within this subfamily, the cathepsins (i.e., cathepsin K, L, and S)[60] are expressed by epithelial cells and fibroblasts and show elastase and collagenase activities.[61–63]

EXTRACELLULAR MATRIX MODIFICATION AND CROSS-LINKING

ECM components (i.e., collagen and elastin) are cross-linked to form and maintain the 3D structure of the mesenchyme. There are two major groups of cross-links: those initiated by the enzyme LOX and those derived from nonenzymatically glycated lysine and hydroxylysine residues. In contrast, *lysyl hydroxylases* (LHs) reduce the levels of cross-linking between ECMs.[64–66] Thus the balance between LOX and LH regulates the level of cross-linking between collagen and elastin, thereby controlling their biomechanical properties.

Modification and cross-linking enzymes that remodel the ECM (i.e., MMPs, TIMPs, LOX, LHs) are regulated by targeting them to different subcellular locations, by secreting them to the extracellular milieu, or by keeping them tethered to the cell membrane of epithelial and endothelial cells. Furthermore, some ECM modification enzymes exist as inactive precursors, in which their catalytic domain is masked and rendered inactive. Specific proteinases cleave and remove masking peptides, thus activating the modifying enzyme. Posttranslational modifications can further modify the physical properties of the ECM, including glycation and glycosylation, transglutamination, oxidation, carbamylation, and citrullination.[67,68]

CELL–EXTRACELLULAR MATRIX INTERACTIONS VIA INTEGRINS

Integrins are heterodimeric cell surface proteins, members of a large multigene family of receptors involved in cell-cell and cell-ECM interactions. They are characterized by a large α-subunit that noncovalently partners with a smaller β-subunit; both subunits contain large extracellular domains and small intracellular domains[69–71] (see Fig. 5.1D). Mammals express 18 α-subunits and 8 β-subunits capable of forming at least 24 receptors with distinct ligand specificities. The β-subunits can be shared by more than one integrin, whereas the α-subunits typically provide ligand-binding specificity.

The extracellular domain of integrins interacts with ECMs, whereas the intracellular domain interacts with the cytoskeleton. Many ECMs contain an evolutionarily conserved *arginine-glycine-aspartic acid* (RGD) amino acid sequence that mediates binding with specific integrins. Such RGD motifs are found in FN, vitronectin, osteopontin, collagens, thrombospondins, fibrinogen, fibulin-5, and von Willebrand factor, among others.[72] Upon encountering a ligand, integrins cluster at the cell surface, which promotes conformational changes in their cytoplasmic domain that attract cytoskeletal and signaling components. In consequence, ECM ligands, integrins, and cytoskeletal components come together in what has been termed *focal adhesion complexes* (FACs)[73] (see Fig. 5.1D). Signaling molecules assemble within the intracellular aspect of FACs and activate signal transduction through intracellular calcium fluxes, pH changes, and activation of protein kinases, including focal adhesion kinase, integrin-linked kinase, and mitogen-activated protein kinases, among others. These signals, in addition to signals transmitted from cytoskeletal-associated signaling proteins, promote differential gene expression in what is termed *outside-in* signaling. However, intracellular signals may affect integrin activation and ligand binding through *inside-out* signaling. In this fashion integrins bidirectionally "integrate" the extracellular ECM with the intracellular signaling machinery.

By mediating cell-ECM interactions, integrins allow the transfer of tensile strength into cells. The integrin signaling is dependent on ECM composition, its biochemical properties, ligand density, and the way the ligands are spatially displayed.[74] The influence of ECM on cell behavior is demonstrated by in vitro studies showing that fibroblasts align and migrate along ECM fibers and invade areas of reduced matrix rigidity.[75] Aided by the use of atomic force microscopy, matrix stiffening has been confirmed in ECM from human IPF lungs and from animals with experimental lung fibrosis.[76] These studies showed that the normal lung stiffness or Young's modulus (measured in Pascals [Pa]) is about 0.4 to 7.5 kPa, whereas it is on average 16.5 kPa in

idiopathic pulmonary fibrosis. These values are dramatically less than the stiffness of plastic dishes used for in vitro studies, which ranges from 2 to 4 × 10^6 kPa, which may limit the in vivo relevance of these studies.

GROWTH FACTORS WITHIN THE LUNG MESENCHYME

The lung ECM serves as a reservoir for growth factors and other mediators. Insulin-like growth factor, *fibroblast growth factors* (FGFs), *vascular endothelial growth factor* (VEGF), and hepatocyte growth factor, among others, have been found embedded in the lung mesenchyme, where they may associate with ECM proteins or with heparin sulfate.[77] During ECM remodeling observed during lung injury, these growth factors are released and activated and can gain access to cells. TGF-β1, for example, is secreted as a homodimer together with its *latency associated propeptide* (LAP) and binds *latent TGF-β–binding proteins* (LTBPs) that secure it to the ECM. The LAP portion of latent TGF-β1 contains an RGD consensus site for binding of αv integrins. These integrins may bind latent TGF-β1 and activate it through the release of the LTBP via mechanical strain.[78] Newly released TGF-β can also be activated through oxidative stress or via MMP cleavage. In this fashion growth factor activity can be controlled and made available during tissue remodeling or during organ development.[79]

THE LUNG MESENCHYME IN DEVELOPMENT

The lung mesenchyme is mostly derived from the embryonic splanchnic mesenchyme, which provides crucial signals for the progenitor cells that form stromal cells, smooth muscle, cartilage, and ECM-supporting structures. The importance of the mesenchyme in lung development was highlighted in early experiments showing that the transplantation of the lung mesenchyme from one area of the embryonic lung to another led to alterations in morphogenesis with changes consistent with the origin of the transplanted mesenchyme.[80] For example, mesenchyme obtained from distal lung buds induced branching when inserted next to the more proximal tracheal epithelium, whereas branching was prevented when tracheal mesenchyme was inserted in the distal lung bud. Further work revealed that the composition and structure of the ECM within the lung mesenchyme changed during different stages of lung development and served not only as structural support but also as a biomechanical and signaling hub.[81] Reciprocal biochemical and biomechanical signals elicited during epithelial-mesenchymal, endothelial-mesenchymal, and mesenchymal-mesenchymal interactions drive morphogenesis of the distinct structures of the lung. The most studied and critical processes of lung development, which show rapid and precise changes in the composition and organization of the ECM, are branching morphogenesis, vascularization, and alveolarization.

BRANCHING MORPHOGENESIS

Once the lung bud emerges from the foregut during the initial stages of lung development, the organ grows and undergoes branching to form the primitive airway tree through lung *branching morphogenesis*, which consists of iterative rounds of bud formation, extension, and dichotomous bifurcation; this takes place during the pseudoglandular stage of lung development (7–16 weeks of gestation in humans and from embryonic day 9.5–16.5 in mice).[82,83] At the interface of the epithelium and the mesenchyme is the basement membrane, which coordinates branching morphogenesis. Basement membrane components, such as collagen IV, laminin, FN, nidogen, *heparan sulfate proteoglycans* (HSPGs), and netrin, are expressed in a spatially and temporally regulated manner by mesenchymal and epithelial cells.[84–86] Specific signaling molecules, such as FGFs secreted by fibroblasts, induce cell differentiation and budding of the epithelium; conversely, the epithelium expresses the FGF receptors to establish epithelial-mesenchymal communication[87,88]; FGF-10 is considered the main morphogen driving lung branching morphogenesis in mice. During bud bifurcation, FN is found at the site where the epithelium will invaginate to split the epithelial tip. The thinning of the basement membrane at the tip of the buds and the presence of low-sulfated HSPG at the adjacent mesenchyme facilitates branching by allowing the diffusion of FGF-10, whereas highly-sulfated HSPG, with higher affinity for FGF-10, and netrin around the neck, prevents branching by reducing diffusion of FGF-10 and blocking FGF-10 signaling, respectively.[82,89–96] A role for cell-ECM interactions in lung branching morphogenesis is also demonstrated in studies showing that RGD-containing peptides and interventions targeting laminins and other ECMs inhibit this process in embryonic lung explants.[97,98] It must be noted that most of the studies about mesenchymal factors that regulate branching morphogenesis have been performed in mouse models.[94,95] In humans, the importance of the mesenchyme in branching morphogenesis is best demonstrated by the congenital malformations caused by mutations of two transcription factors central to mesenchymal cell functions, FOXF1[99] and TBX4,[100] which result in alveolar capillary dysplasia and acinar hypoplasia, respectively, in newborn infants.

VASCULARIZATION

Overlapping with lung branching morphogenesis is the emergence of vascular structures, which signals the start of the *canalicular stage* of lung development, spanning from 16 to 24 weeks of gestation in humans and embryonic days 16.5 to 17.5 in mice. Mesenchymal cells in the distal parts of the lung coalesce to form vascular structures through the process of vasculogenesis and connect with more proximal vessels through the process of angiogenesis. The distal vascular structures align with alveolar spaces to form the alveolar-capillary unit. Elegant studies in vitro have demonstrated that both vasculogenesis and angiogenesis are driven by ECM composition. Endothelial cells cultured on two-dimensional scaffolds containing basement membrane components, such as laminin, type IV collagen, and nidogen (e.g., Matrigel), undergo vasculogenesis; similar observations were made in collagen-fibrin matrices.[101] FGF and VEGF are required for blood vessel formation. VEGF produced by the airway epithelium is stored within the mesenchyme and released by MMP-mediated cleavage. In turn, FGFs and VEGFs are capable of increasing the expression of MMPs, which are important in vascular biology.[102] Thus the ECM is essential for driving vasculogenesis in the developing lung.

ALVEOLARIZATION

Lung alveolarization spans from 36 weeks of gestation through 3 years of age in humans and from postnatal day 5 to approximately day 30 in mice.[103] During this period, the epithelium, the endothelial capillary network, and the mesenchyme undergo coordinated remodeling to form functional gas exchange units. Early in development, epithelial cells and endothelial cells are separated from each other by two basement membranes and a thick interstitium. During alveolarization, this structure becomes simplified with a reduction in the amount of mesenchymal ECM and focal deposition of elastin, mainly along the sites of the future alveolar septae.[41] The terminal respiratory units are supported by an extensive network of flexible collagen and elastin fibers produced by fibroblasts that support the expansion and recoil mechanisms in each inhaling-exhaling respiratory cycle. Lipofibroblasts store neutral lipids and retinoids to support alveolar epithelial type 2 cell growth, whereas interstitial myofibroblasts confer flexibility to the alveolar septum.[104] Together, these observations suggest that mesenchymal ECMs and cells regulate alveolar septation and, ultimately, the formation of functional alveoli.

THE LUNG MESENCHYME IN AGING

Aging is associated with a number of changes, ranging from mitochondrial dysfunction and oxidative stress to chronic inflammation and stem cell exhaustion.[105] This is also true for the aging lung, where these changes are thought to render the host susceptible to infection and to disrepair after injury in both rodents and humans.[106–114] Although the exact mechanisms responsible for these events remain incompletely elucidated, increasing attention is being paid to the role of the ECM.

Lung aging is associated with physiologic enlargement of air spaces, resulting in the so-called *emphysema of aging.*[115,116] This is thought to be caused by an increased expression and unopposed activity of proteases, leading to the destruction of elastin fibers. Consistent with this idea, a decrease in the number of elastin fibers has been detected via immunohistochemistry within the alveolar walls of aging lungs. These studies also showed increased collagen type III deposition.[117] In other studies, however, decreased collagen and limited changes in elastin were detected in postmortem examinations.[118] Changes in proteoglycans have also been demonstrated with age.[118,119] Although these changes can be measured, their magnitude is typically small, and their clinical significance is unclear.

Early observations made in animal studies, especially rodents, were somewhat inconsistent.[120,121] In more recent studies performed in lungs harvested from young (2-month-old) and aged (24-month-old) mice, increased mRNAs encoding for FN-EDA, collagen type I, and plasminogen activator-1 were detected,[122,123] as were mRNAs and gelatinolytic activity related to MMP-2 and MMP-9. TGF-β1 and its receptor TGF-βRI were also elevated as was the intracellular TGF-β1–dependent transcription factor SMAD3. Primary lung fibroblasts isolated from senescent murine lungs showed decreased expression of Thy-1, a surface protein that regulates TGF-β1 activation and FN expression; animals deficient in Thy-1 show increased fibrosis when exposed to bleomycin.[124]

In addition to increased accumulation of certain ECMs, aging is associated with ECM protein modifications induced by their reaction with reducing sugars; this results in the production of advanced glycation end products.[125,126] Together, these studies suggest that the senescent lung has a "profibrotic" phenotype, resulting in alterations in ECM production and turnover, perhaps driven by altered fibroblasts.

It is well known that the proliferative and migratory capabilities of human lung and skin fibroblasts decrease with age.[127] Loss of fibroblast clonogenicity and progressive myofibroblastic differentiation have been observed in murine lungs and are implicated in the changes described.[128] Oxidative stress has also been proposed as a mechanism responsible for ECM remodeling in the aging lung.[129] Exactly how oxidant stress is generated during aging is not clear, but aging lung fibroblasts are deficient in controlling their redox state; this deficiency is associated with decreased expression of the cystine transporter Slc7a11/xCT, which regulates redox potential for the cysteine/cystine thiol disulfide couple.[130,131]

It should be highlighted that the changes in ECM content and composition noted in aging uninjured lungs are not typically associated with major changes in lung architecture. In fact, except for rare changes suggestive of the so-called emphysema of aging described earlier, senescent lungs appear normal under microscopic examination. It is only under biochemical scrutiny that alterations in ECM, MMPs, and profibrotic growth factors are detected. This "transitional" state between normal and remodeled lung, as traditionally considered, has been termed *transitional remodeling* to denote its transitory state and potential for reversal with appropriate interventions, although the latter requires confirmation.[116] In mice, chronic exposure to nicotine and alcohol also leads to alterations in the expression and relative composition of the lung ECM without causing overt architectural changes.[116,132–134] The role of transitional remodeling in the lung is unclear, but considering the ability of lung cells to recognize specific ECM components that trigger differential intracellular signaling, it is likely that these changes impact the phenotype of resident cells. Furthermore, injuries to the aging lung with transitional remodeling could potentially lead to the rapid upregulation of "maladaptive" pathways resulting in tissue disrepair and loss of organ function, but this requires further exploration.

THE LUNG MESENCHYME IN DISEASE

Essentially every form of lung disease is characterized by alterations in ECM synthesis, deposition, and turnover. In emphysema, destruction of elastin within the alveolar septae leads to enlarged air spaces and fewer gas exchange units. In IPF, the original architecture of the lung is replaced by excessive deposition of collagens and other ECMs, leading to stiffness and inadequate oxygen transfer. In pulmonary vascular disease, the hypertrophy of vascular smooth muscle cells and excess deposition of ECM leads to pulmonary hypertension. In asthma, chronic inflammation and airway wall remodeling are associated with airways hyperreactivity and airflow limitation. In infection, alterations in ECMs may result in fibrosis, bronchiectasis, and cavitation, such as seen in *Mycobacterium tuberculosis* infection.

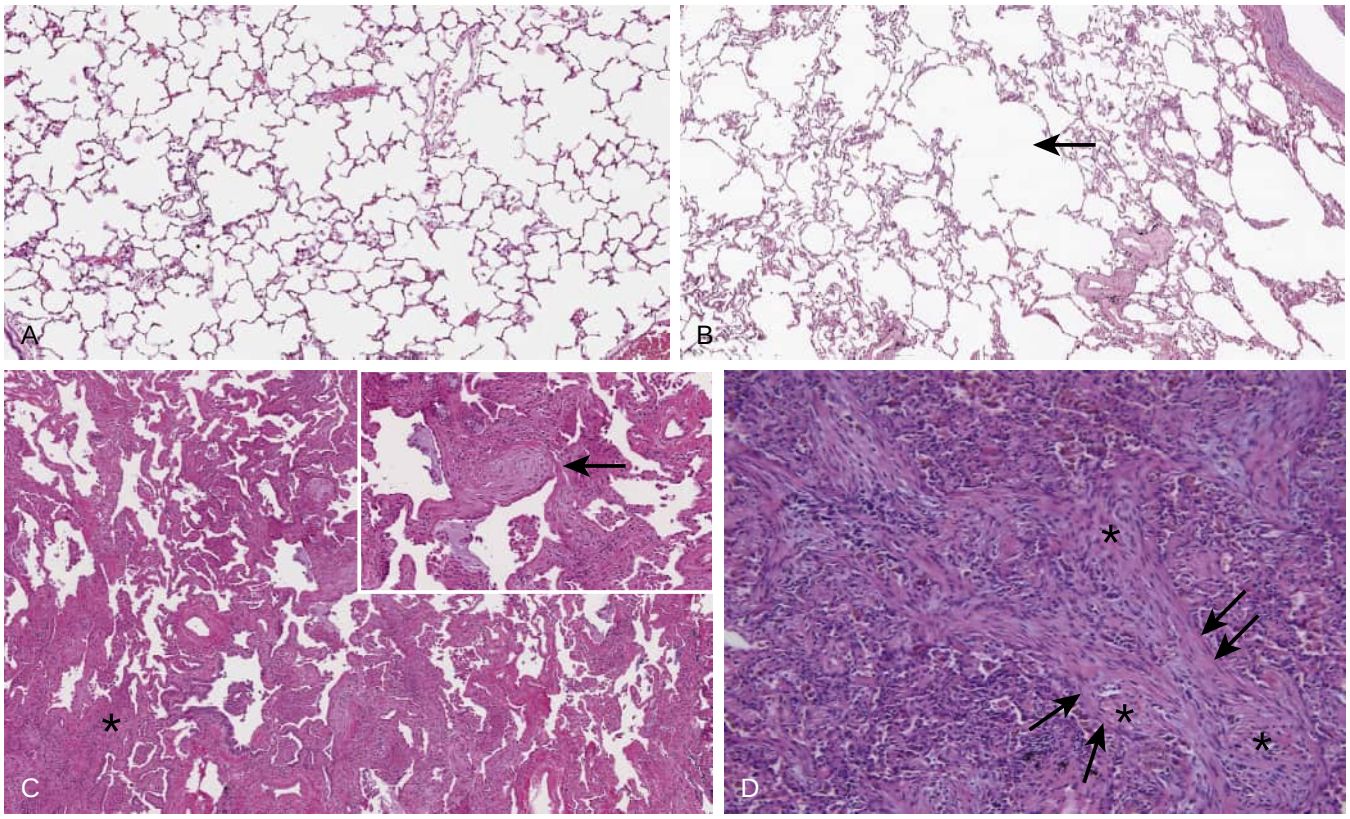

Figure 5.2 ***Extracellular matrix*** **(ECM) deposition in chronic lung disease.** Essentially all forms of chronic lung disease are associated with alterations in ECM expression and turnover resulting in architectural derangements that affect lung function. (A) Normal lung. (B) In emphysema, there is degradation of the ECM resulting in destruction of the alveolar septae leading to enlarged air spaces *(arrow)*. (C) In idiopathic pulmonary fibrosis, there is excessive fibroproliferation and excessive deposition of ECM. These changes result in a heterogeneous pattern with abnormal areas of fibrosis *(asterisk)* located adjacent to normal lung tissue. Fibroblasts organize into fibroblastic foci (insert, *arrow*), which are thought to represent the leading edge of the fibrotic process. In this and related conditions, the basement membranes are disrupted. The disruption of basement membranes is thought to eradicate the original "map" of the tissue, thereby impairing restoration of the original lung architecture after the insult (A–C shown at 40× original magnification; C and inset shown at 200× original magnification). (D) In other conditions, such as in organizing pneumonia, tissue injury leads to the excessive accumulation of ECMs within the air spaces *(asterisk)* without greatly altering basement membranes *(arrows),* which permits adequate tissue repair after the elimination of the initiating injury or by other interventions (D shown at 40× original magnification). (Courtesy Dr. Jeffrey Baliff, Department of Pathology, Thomas Jefferson University.)

Even in cancer, either primary or metastatic to the lung, tumor cell–stromal interactions are believed to influence cancer progression. If uncontrolled, alterations in ECM composition and content in disease states lead to enhanced inflammation, induction of oxidative stress, and phenotypic cellular changes, ultimately resulting in a progressively remodeled structure with impaired organ function.

OBSTRUCTIVE AIRWAY DISEASES

Most components of the lung ECM can be potentially altered in COPD and asthma. In the normal lung, the ECM supports the delicate structure of the lung (Fig. 5.2A). In emphysema, however, inflammation caused by the excess influx of neutrophils leads to the destruction of elastin in alveolar walls[135] (Fig. 5.2B). Early studies pointed to deficiency in alpha$_1$-antitrypsin in the development of the disease.[136] These and other early observations led to the development of the "protease-antiprotease" hypothesis, the idea that imbalances in the production and activity of proteases and antiproteases are responsible for the development of emphysema. This hypothesis is being challenged by new information regarding the immunologic functions of alpha$_1$-antitrypsin and other proteases.[137] In addition, the fact that alpha$_1$-antitrypsin deficiency is uncommon (with <1% of the population affected) suggests that other protease-antiprotease pairs are important, such as MMPs considered pathogenic in COPD.[138]

In one study that compared COPD and IPF, COPD lungs were characterized by increased ECM regulators TIMP3 and MMP-28, whereas IPF lungs were characterized by impaired expression of proteins, such as collagen VI and laminins, involved in cell adhesion.[139] Proteins involved in regulation of endopeptidase activity and serpins were increased in both COPD and IPF. However, the tissues examined included end-stage COPD, which may not be representative of all stages of the condition. In studies using samples harvested from moderate COPD subjects, alterations were noted in elastin, FN, collagens, tenascin-C, and versican.[140] Taken together, these studies demonstrate that COPD is accompanied by substantial changes in ECM composition.

Thickening of collagen fibrils and remodeling also take place in the alveolar walls of emphysematous lungs.[141] A tripeptide fragment containing three to five *proline, glycine, and proline* (PGP) repeats is derived from collagen degradation and induces neutrophil chemotaxis.[142] PGP levels, osteopontin, and FN are elevated in COPD, and PGP levels are highest during COPD exacerbations, indicating increased ECM turnover during periods of increased inflammation.[142–144]

Oxidants produced during the combustion of tobacco not only induce the expression and oxidation of ECMs but may also cleave and inactivate protective molecules, such as alpha$_1$-antitrypsin.[145] Cigarette extract stimulates airway smooth muscle cells harvested from patients with COPD to produce exaggerated amounts of collagen VIII alpha 1 and MMP-1, MMP-3, and MMP-10.[146] Nicotine promotes the expression of FN and collagen type I through induction of protein kinase C and activation of mitogen-activated protein kinases.[134]

In asthma, ECMs accumulate in the submucosal and adventitial areas of large and small airways, with changes in collagens I, III, and V and in FN.[147,148] Decorin and hyaluronan deposition are increased,[149] as are the protease activities of MMP-9 and MMP-12, especially in severe fatal asthma.[150] In long-standing uncontrolled asthma, levels of collagen deposition were found to be increased in the alveolar parenchyma, versican was increased in the central airways, and decorin and biglycan were increased in both.[151]

LUNG FIBROSIS

In IPF and other types of interstitial lung disease, there is an increase in the formation of fibrous tissue, leading to changes in compliance of the lungs. Collagen production, proteoglycans, and glycosaminoglycans are upregulated. Genetic factors and recurrent environmental injuries to the lung epithelium are believed to cause the release of proinflammatory cytokines, proteases, and growth factors. These mediators can activate TGF-β1, which has a central role in fibrosis along with alterations in fibroblast signaling and increased epithelial-mesenchymal transformation and myofibroblast transdifferentiation.[152,153]

Proteomic analysis revealed that the expression of 662 proteins was altered in lung tissue from patients with IPF when compared to controls.[154] Pathway enrichment analysis revealed that these proteins mainly belonged to pathways related to PI3K-Akt signaling, focal adhesion, ECM-receptor interactions, and carbon metabolism. About 229 matrisome proteins were identified: 104 core matrisome proteins and 125 matrisome-associated proteins. Of these, 56 proteins were differentially expressed, including many well-known ECM proteins (e.g., COL1A1) and novel ECM proteins of unknown function. These results illustrate the profound changes in the matrisome found in IPF, which are distinct from those detected in other conditions.

Increased deposition of fibrillar collagen in the ECM around fibroblastic foci and an increase in the expression of cross-linking enzyme LOXL2 are observed in IPF.[155,156] In contrast to emphysema, where elastin levels are reduced by protease enzymes, increased elastin has been seen in mouse models of pulmonary fibrosis, which increases TGF-β1–induced myofibroblast differentiation.[157] FN-EDA and tenascin-C are high, and these molecules promote inflammation and fibrosis.[158] The absence of FN-EDA is protective in the bleomycin model of pulmonary fibrosis in mice,[158] further emphasizing the importance of the ECM.

There is also a significant increase in the turnover and deposition of proteoglycans and glycosaminoglycans. Versican, for example, is increased in concert with collagen in fibroblastic foci.[159] Decorin, which downregulates TGF-β1 and has antifibrotic effects, is decreased in IPF.[91] Membrane-bound hyaluronan synthases accumulate in areas of tissue injury, and these molecules increase ECM production and myofibroblast differentiation. In contrast, low-molecular-weight hyaluronan is also increased, which promotes the release of cytokines and stimulates chemotaxis.[160]

Studies using decellularized normal lungs (declined for lung transplantation) and IPF lungs (explants from patients undergoing transplantation) have allowed the study of the impact of these ECM changes on cellular function. Naive fibroblasts cultured atop fibrotic decellularized lungs show increased expression of α-smooth muscle actin, denoting myofibroblastic differentiation; these changes were not detected when cells were cultured on normal decellularized lungs.[13] Further studies evaluating the transcriptional and translational programs expressed by fibroblasts harvested from normal or IPF-derived lungs or normal fibroblasts cultured atop normal or IPF-derived ECMs show dramatic responses driven by the ECM. In other words, changes in fibroblast gene transcription and translation were primarily driven by the ECM environment rather than being autonomous.[161] Taken in total, the changes in ECM in IPF not only affect the architecture of the lung but also affect cells in ways that promote a profibrotic environment.

OTHER LUNG DISORDERS

Altered ECM structure and function have been demonstrated in bronchopulmonary dysplasia where MMPs have been implicated.[162] Pulmonary hypertension is associated with vasoconstriction and vascular remodeling of the three layers of the pulmonary vasculature (i.e., the intima, media, and adventitia). Increased synthesis of elastin and collagen have been identified in hypoxia-induced pulmonary hypertension.[163] During acute lung injury, a syndrome characterized by noncardiogenic pulmonary edema and refractory hypoxemic respiratory failure,[164] injury to the basement membrane results in increased deposition of FNs, fibrin, collagens, and other ECM proteins within the affected alveolar spaces and interstitium. Newly released fibronectin and collagen fragments promote chemotaxis via integrin-dependent signals, thereby enhancing inflammation.[165] Fibronectin promotes fibroblast proliferation, whereas β_6 integrins serve to activate TGF-β1 after its latent form is released, which further promotes remodeling.[166] The N-terminal peptide of type III procollagen is elevated in acute lung injury, and the excess presence of this peptide is associated with poor outcomes.[167] Chronic alcohol abuse increases susceptibility to acute lung injury in both rodents and humans, perhaps by promoting oxidative stress, epithelial cell dysfunction with increased expression of TGF-β, impairments in macrophage phagocytosis, and surfactant abnormalities. These abnormalities are also associated with increased FN and MMP expression, perhaps highlighting another example of transitional remodeling. Together, these changes result in the "alcoholic phenotype," which is associated with increased incidence of and enhanced mortality from acute lung injury in at-risk individuals (e.g., sepsis).[133,168,169] Chronic tissue rejection is a major cause of limited survival after lung transplantation. Among other things, this process is characterized by the exaggerated deposition of connective tissue matrices, such as collagens

and FN, within the bronchioles resulting in obliterative bronchiolitis. Lack of TGF-β1 and MMP-9 is protective in animal models of tracheal transplantation.[170,171] Thus the matrisome is impacted in essentially every pulmonary disorder studied, and these changes are likely to impact disease development and progression.

In cancer, the role of the lung mesenchyme remains controversial, but most lung cancers emerge in patients with an abnormal lung structure, such as emphysema and pulmonary fibrosis, thereby implicating the ECM. In vitro studies have shown that ECMs influence the proliferation, migration, and invasion of tumor cells.[172] In rodents, the subcutaneous injection of tumor cells silenced for the FN-binding integrin subunit α_5 resulted in reduced lung metastasis.[10] Further studies dissecting the role of the lung mesenchyme in lung cancer are needed.

CURRENT UNDERSTANDING AND GAPS IN KNOWLEDGE

In summary, the lung mesenchyme contains distinct cell types submerged in a mesh of multifunctional ECMs interwoven together to provide structure to the lung, while influencing cellular functions in ways that sustain homeostasis. When disrupted, however, alterations in ECM expression, the release of latent and subsequently activated growth factors, and the generation of ECM fragments by newly released proteases, among other events, promote inflammation, oxidative stress, cell apoptosis, and other actions to rid the lung of the injurious agent, while promoting adaptive tissue repair. Under most circumstances, these events are tightly controlled and lead to the recovery and maintenance of organ function. However, host factors, as well as the type, duration, and severity of the insult, may trigger self-perpetuating mechanisms that drive the aberrant deposition and/or destruction of ECMs, upregulate inflammation, and promote cell death and dysfunction, thereby leading to organ destruction during maladaptive repair or disrepair. In doing so, the distorted ECM does not represent the final stage of injury but contributes to it and becomes an important driver of organ destruction. This nuanced understanding of the complex nature and roles of ECMs in lung health and disease guides current research efforts in this area.

Over the past 2 decades, it has become clear that, although individual ECMs play distinct roles that can be investigated in vitro, the relative concentration, spatial presentation, and physical properties of a combination of ECMs is more likely to be determinant of outcomes in vivo. Technological advances have allowed the identification of the matrisome, but there is still much to be learned about how patterns of ECM expression and turnover exert their influence on cellular functions.

One of the key requirements for tissue healing is the delivery of appropriate physical and biochemical cues for adequate cell reorganization into functional structures. This is mostly driven by ECMs in basement membranes, which provide a map for the reorganization and polarization of epithelial cells into functional units aligned with vascular structures. Diseases characterized by severe basement membrane disruption (e.g., IPF) are typically associated with irreversible organ damage, whereas disorders characterized by the relative maintenance of basement membranes may show recovery of organ function with appropriate interventions (e.g., acute lung injury, organizing pneumonia) (Fig. 5.2C–D).[173,174] This leads to the following obvious question: How can we possibly repair a lung with disrupted basement membranes? Currently, there are very few clues as to how to accomplish this.

Host factors, such as age, genetics, and environmental and occupational factors are undoubtedly important in orchestrating the repair response to injury. How these factors influence inflammation, autophagy, redox stress, mitochondrial function, and other cellular events needs to be defined. In particular, how these events converge with, and are influenced by, signals transmitted from ECMs needs to be elucidated. Lipopolysaccharide, cigarette smoke, and other exposures also have an effect, either through actions on gene transcription or epigenetic control of ECM expression, but the implications of these events to the response to injury remain uncertain. By the same logic, it is likely that medications (e.g., corticosteroids, bronchodilators) also affect ECM composition or integrin signaling in ways that might promote detrimental long-term consequences, such as activation of tissue remodeling.[175] It is also important to understand how such exposures during the perinatal period and childhood affect ECMs in ways that might promote disease susceptibility in the adult.[176]

A major hindrance to advancements in understanding the role of the lung mesenchyme in disease and the impact of interventions is the lack of adequate and sensitive markers of activation of tissue remodeling, which should provide valuable information about disease initiation and progression and about early response to interventions.

Ultimately, it is anticipated that new knowledge in understanding the lung mesenchyme will lead to safer and more efficient therapeutics. Current efforts in lung regeneration focus on the delivery of multipotential cells (e.g., stem cells) capable of differentiating into distinct cells or inducing anti-inflammatory responses.[177] However, emerging data suggest that this approach alone may not succeed in generating a fully functional organ. Because the ECM provides cellular cues that alter cell behavior, aberrant ECMs newly generated and cursorily deposited after injury may not adequately assist in stem cell–induced healing. A better understanding of the mechanisms responsible for these events and the development of interventions that take into consideration both cells and their surrounding ECM are necessary to advance this field.

Finally, it is important to emphasize that, although the complex regulation of the expression, deposition, and turnover of distinct ECMs in diseased states makes it difficult to define effective therapeutic strategies, the complexity also provides diverse opportunities for intervention. Simultaneous multipronged approaches, rather than single specific interventions, are more likely to succeed in halting, and perhaps reversing, the many maladaptive mechanisms triggered during injury. Studies evaluating such approaches targeting ECM and fibroblasts in well-defined experimental models are needed to determine the usefulness of new interventions.

Key Points

- The lung mesenchyme is formed by different cell types, including smooth muscle cells, fibroblasts, and pericytes, and contains *extracellular matrices* (ECMs), including proteoglycans, glycoproteins, and collagens.
- Pulmonary cells submerged within the lung mesenchyme interact with individual ECMs through cell surface signaling receptors called *integrins.* In this fashion the lung mesenchyme provides spatial, contextual, and mechanical cues to surrounding cells, thereby exerting roles in physiologic and pathologic processes.
- Embedded within the ECM framework are growth factors and other cell-derived bioactive molecules that lay dormant until the ECM is disturbed (e.g., during lung injury), at which time they are released and activated in the microenvironment, where they interact with adjacent cells.
- ECM expression, turnover, and distribution are altered in lung development and aging, as well as in pathologic processes related to obstructive airways disease and lung fibrosis, among others. Although the exact role that ECMs play under these circumstances remains incompletely elucidated, information generated over the past 2 decades suggest that they play prominent roles.

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6 VASCULAR BIOLOGY

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INTRODUCTION

The lung is supplied by two different circulations: the pulmonary and the bronchial. The pulmonary circulation is a unique low-pressure, low-resistance circuit that receives the entire cardiac output for gas exchange and yet maintains low perfusion pressures so that fluid filtration is kept low and pulmonary edema does not develop. It is made up of three vascular networks arranged in series: the arterial, capillary, and venous networks. The resistance of each of these networks can change independent of each other, and total *pulmonary vascular resistance* (PVR) is the sum of these three resistances.[1–3] Control of the pulmonary circulation is achieved by complex interactions between endothelial and smooth muscle cells, which include elaboration of vasoactive substances and propagation of signals through direct communications.[4–6] In addition to the key roles of facilitating gas exchange and maintaining barrier function, pulmonary endothelial cells have other functions, including some metabolic functions.[7] The bronchial circulation, which arises from the systemic circulation, supplies nutrients and oxygen to the airways and pulmonary vessel walls.[8,9]

OVERVIEW OF DEVELOPMENT OF THE PULMONARY CIRCULATION

From the earliest stage of development, the lung circulation develops in parallel with the lung parenchyma and airways.[4,10–13] A continuous circulation between the heart and lungs with a pulmonary capillary plexus is formed by the 34th day of gestation in the human fetus, with the artery arising from the outflow tract of the heart and the veins draining into the future left atrium. During the canalicular stage (16–26 weeks of gestation), the number of capillaries increases greatly, and the capillaries grow in close apposition to the epithelium to form the first air-blood barrier. This phase contains the first primitive air sacs. During the saccular stage (24–38 weeks), the terminal air sacs are lined by primary septa that have a capillary on either side separated by mesenchymal tissue. Very premature babies are born with air sacs with this double capillary structure. In the alveolar stage (36 weeks onward), the endothelial layers of the two capillaries fuse to form a single capillary, and the septa become thin and attain the adult form with a single capillary layer.[14] After birth, the arterial walls continue to remodel and thin out with a continued fall in PVR.[15]

In human fetuses at term gestation, pulmonary blood flow is only 11–21% of the combined ventricular output because PVR is very high, and blood is shunted away from the lungs through the foramen ovale and the ductus arteriosus.[16–18] At birth, there is a dramatic fall in PVR. With the first breath and inflation of the lung, the outward tension of the lung parenchyma on the walls of the extra-alveolar vessels leads to a fall in perivascular interstitial pressure, increase in transmural pressure, distention of the vessels, and an immediate fall in PVR.[19] This passive vasodilation increases pulmonary blood flow and increases shear stress on the endothelium, which results in the release of vasodilators from the endothelium, such as *nitric oxide* (NO)[20] and *prostaglandin* I_2 (PGI_2),[21] mediating active vasodilation. In addition, in response to an increase in oxygen tension with breathing, the endothelium releases more vasodilators and inhibits the release of vasoconstrictors, such as platelet activating factor.[4] Thus, during resuscitation of the newborn, it is critically important to inflate and aerate the lungs first, which will immediately lead to an increase in pulmonary blood flow and oxygenation.[19,22] Closure of the foramen ovale and ductus arteriosus after birth directs the entire cardiac output to flow through the lungs. Remodeling of the pulmonary vasculature after birth enables the cardiac output to be accommodated at low perfusion pressures and low PVR, making the lungs ideal organs for gas exchange.[4,10]

PHYSIOLOGIC CONTROL OF THE PULMONARY CIRCULATION

Pulmonary artery pressure in adults is typically one-fifth to one-sixth that in the aorta of the systemic circulation.

PVR in adults is also substantially lower than systemic vascular resistance. A comparison of the characteristics of the pulmonary and systemic circulations is shown in eTable 6.1.[1,6,23–30] PVR can be affected by many passive and active factors. The pulmonary vasculature is highly distensible and not fully recruited and perfused at rest; therefore, various mechanical factors can affect PVR by changing the degree of distension and recruitment of the blood vessels in the lung.[1,6,9,31–33] The pulmonary vasculature is also actively regulated by oxygen tension and various vasoactive factors, in particular those released from the endothelial cells, such as NO, prostacyclin, and *endothelin-1* (ET-1).[4,6,9,34] The current understanding of the influence of mechanical or passive factors on PVR, the active regulation of pulmonary vasomotor tone via various mediators and neural factors, and the important contribution of the veins to total PVR are discussed in this section.

MECHANICAL FACTORS OR PASSIVE REGULATION

The pulmonary vasculature, unlike that in other organs, is unique because it is subject to many mechanical forces that affect the resistances of its three vascular networks.[35] Lung volume increases by approximately 500% when going from residual volume to total lung capacity, which differentially affects the resistances of the three vascular networks within it.[32] Changes in alveolar pressure affect the resistances of the capillaries and corner vessels, vessels that are exposed to alveolar pressure.[35] In addition, other mechanical forces generated by alveolar surfactant and surface tension affect capillary resistance,[36] and the interdependence between parenchymal structures can significantly affect local and total vascular resistance in the lungs. The height of the lungs enables gravity to influence regional pressures and flow within the lungs (see Chapter 10).[31]

Gravity

In the upright position, the pressure in pulmonary vessels increases with increasing distance down the lungs from the hilum due to gravity. Based on the relationship among *pulmonary artery pressure* (PPA), *pulmonary venous pressure* (PPV), and *alveolar air pressure* (PA), the lungs are divided into three zones (eFig. 6.1).[31] In zone 1 (apex), where PA > PPA > PPV, there is no blood flow. In most adult humans at physiologic conditions, zone 1 does not exist. In zone 2 (middle), where PPA > PA > PPV, there is blood flow only when the pressure of PPA exceeds PA, which may happen only in systole. The increase in blood flow in zone 2 results largely from recruitment of vessels that were previously closed. In zone 3 (bottom), where PPA > PPV > PA, the lungs are continuously perfused, and the amount of blood flow is determined by the pressure gradient between PPA and PPV independent of PA. The increase in blood flow in zone 3 results predominantly from distension of patent capillaries (see Chapter 10 for additional details). It should be noted that the zone concept is functional, not anatomic. The borders between zones are fluid and are altered by changes in PPA, PPV, and PA under various physiologic and pathophysiologic conditions, including changes in body position, lung volume, and changes in right ventricular output and left atrial pressure.[1,31,37] In the clinical setting, the measurement of *pulmonary capillary wedge pressure* (PCWP) is only accurate when done in lungs in zone 3, where flow is continuous. In a supine patient, the dorsal, dependent portions of the lungs are in zone 3 but, if the patient is sitting upright or is under high airway pressures on a ventilator, the placement of the Swan-Ganz catheter to measure PCWP correctly becomes very important.[38]

Lung Volume

Changes in lung volume exert opposite effects on the resistance of alveolar (capillary network) and extra-alveolar (arterial and venous networks) vessels. For alveolar vessels, the perivascular pressure is generally slightly lower than alveolar pressure as a result of the elastic recoil of alveolar walls, reflecting both surface tension created by the layer of liquid at the air-liquid interface[39] and traction on membranes surrounding the interstitial space produced by alveolar wall attachments.[40] In effect, surface tension forces tend to collapse alveoli, thereby decreasing perivascular pressure relative to alveolar pressure. During lung inflation, alveolar vessels are compressed and elongated.[41] Therefore, as the lung volume increases from residual volume to total lung capacity, resistance of alveolar vessels progressively increases. In contrast, extra-alveolar vessels are subjected to different stresses. The interstitial pressure surrounding extra-alveolar vessels decreases with lung inflation; the resulting increased transmural pressure causes a decrease in resistance of these vessels. Any increase in perivascular pressure of alveolar vessels or extra-alveolar vessels increases the resistance of these vessels.[9,42] Because the resistances of alveolar and extra-alveolar vessels are in series, their resistances are additive, and the change in PVR forms a U-shaped curve, with the nadir of the curve at approximately functional residual capacity, the end-expiratory lung volume (see Fig. 10.10). Hence, measurement of PVR in patients should be made when lung volume is close to functional residual capacity and the lungs are neither severely underinflated or overinflated.

Shear Stress

In the vasculature, shear stress is defined as the tangential force of blood flow that acts on the endothelium. The magnitude of shear stress (τ) in a straight tube is calculated by the formula: $\tau = 4\mu Q/\pi r^3$, where μ is the blood viscosity, Q the blood flow, π is the ratio of a circle's circumference to its diameter, and r is the radius of the circle. Normally, the shear stress in human blood vessels is approximately 10 to 50 dyne/cm^2 in highly pulsatile arteries and about 10-fold less in the minimally pulsatile veins.[43–45] Pulsatility of flow affects segmental vascular resistances in the lungs, independent of active vasomotion,[46] and abnormalities in flow and shear stress in disease affect local vascular resistances in the lungs.[44,47] Shear stress induces the release of NO and PGI_2 from the endothelium,[48,49] which plays a role in the fall in PVR at birth,[50,51] in the maintenance of a low baseline vasomotor tone, and in the accommodation of the increased cardiac output during exercise.[52] Patients with *pulmonary artery hypertension* (PAH) have been noted to have significantly larger proximal pulmonary arteries than normal, which results in a significant reduction in shear stress in these vessels compared with healthy subjects.[53] In addition, the large pulmonary arteries are stiffer

eTable 6.1 Comparison of the Characteristics of the Pulmonary and Systemic Circulations

	Pulmonary	Systemic	References
Artery pressure (mm Hg)	12–15	80–120	1, 23
Vascular resistance (dyne • sec • cm^{-5})	50–100	~1000	24–26
% of total cardiac output received	■ ~100% ■ At rest: 5 L ■ During exercise: 20–40 L	■ Coronary circulation: ~5% at rest; 3- to 4-fold increase during exercise ■ Cerebral circulation: ~15%, at rest and during exercise ■ Skeletal muscle circulation: <20% at rest, up to 90% during exercise	27–29
Increase in blood flow	Capillary recruitment, vasodilation	Vasodilation	1, 6, 27–29
Response to hypoxia	Vasoconstriction	Vasodilation	1, 6, 30

in *pulmonary hypertension* (PH) patients, and hence wall shear stress is lower.[54] This reduced shear stress may contribute to reduced NO production and thus compromised protection and/or enhanced vascular remodeling and vasoconstriction.

ACTIVE REGULATION

Hypoxic Pulmonary Vasoconstriction

A pulmonary vasoconstrictor response is evoked when alveolar oxygen tension falls below 60 mm Hg, and the response increases proportional to the degree of hypoxia. *Hypoxic pulmonary vasoconstriction* (HPV) is a unique feature of the pulmonary vasculature because systemic vessels generally *dilate* in response to hypoxia. Both pulmonary arteries and veins, but predominantly small arteries and arterioles, constrict in response to hypoxia. Most studies in a variety of species, including humans, indicate that the greatest and most consistent HPV response takes place in small pulmonary arteries.[30]

Underventilation in small defined regions of the lungs, such as develops in patchy pneumonia or segmental atelectasis, results in local HPV due to local alveolar hypoxia.[30,55] The blood is diverted to better ventilated areas of the lungs, and perfusion is matched better with ventilation. However, under conditions of global hypoxia, such as at high altitude, HPV is generalized. With sustained exposure to global hypoxia, there is suppression of HPV.[56]

Perfusion of isolated cat lungs with partially deoxygenated blood increases pulmonary arterial pressure only when the lungs are ventilated with hypoxic gas mixtures and not with atmospheric air, indicating that HPV is driven by alveolar hypoxia.[57] When isolated rat lungs were perfused under alveolar hypoxic conditions, the pulmonary arterial pressure increased only when perfusion was forward (through the pulmonary artery) and not during retrograde perfusion (through the left atrium), indicating that the oxygen sensor for HPV is likely situated at a precapillary site. Both alveolar and perfusate oxygen tensions determine the magnitude of HPV.[58]

It is generally recognized that HPV is an intrinsic property of pulmonary *vascular smooth muscle cells* (VSMCs). Currently there are two major hypotheses regarding the mechanisms underlying HPV: the *redox hypothesis* and the *reactive oxygen species* (ROS) *hypothesis.*[30,55] Both hypotheses propose that the oxygen sensor is located in the mitochondrial electron transport chain in pulmonary VSMCs. The *redox hypothesis* proposes that hypoxia causes decreased generation of ROS by mitochondria, which results in a less oxidized intracellular redox environment. In consequence, the sulfhydryl groups on the voltage-dependent potassium ion (K^+) channel $K_V1.5$ are reduced, causing K^+ channels to close, followed by membrane potential depolarization, opening of voltage-dependent calcium ion (Ca^{2+}), and activation of the contractile apparatus in VSMCs.[56] The *ROS hypothesis* proposes that hypoxia stimulates mitochondrial electron transport chain complex III to generate ROS, which, when released into the cytosol, stimulate Ca^{2+} influx from the extracellular space through nonselective cation channels and promote Ca^{2+} release from the sarcoplasmic reticulum. These events lead to increased intracellular levels of Ca^{2+} ions and vasoconstriction. ROS also activates *Rho kinase* (ROCK), leading to sensitization of myofilaments to Ca^{2+}, and thus augments the contractile response.[59,60] There is experimental evidence in support of both hypotheses, and different methodologies used in the experiments may explain some of the controversy.[61,62]

HPV is modulated by many physiologic variables and by neuronal and humoral factors.[30,55] In anesthetized dogs, HPV is enhanced by metabolic acidosis but attenuated by metabolic alkalosis. HPV is not affected by respiratory acidosis but is blunted by respiratory alkalosis, suggesting that the effect of carbon dioxide is pH independent.[63] Zucker rats have increased sympathetic nerve activity associated with obesity,[64] and they have an enhanced HPV response that may be the result of increased pulmonary sympathetic nerve activity and decreased expression of lung *β_2-adrenergic receptors* (β_2-ARs).[65] Obese humans also have increased sympathetic nerve activity.[66,67] Although hypoxia-induced pulmonary hypertension is enhanced in diabetic mice,[68] and patients with diabetes mellitus exhibit a high prevalence of PH,[69,70] a potential role of an elevated sympathetic activity in the pathophysiologic process of PH in patients with diabetes mellitus remains to be determined. HPV is profoundly affected by a variety of vasoactive substances, in particular those released from endothelial cells such as NO, prostacyclin, and ET-1. Under pathophysiologic conditions, the production and activity of these molecules are often altered, resulting in an exaggerated HPV response.[30,71,72] For example, acute alveolar hypoxia stimulates the production of ET-1,[73,74] which can augment pulmonary vasomotor tone and thus the HPV response. However, ET-1 acts via two receptors: ET_A, with mainly vasoconstrictor activities, and ET_B, with more vasodilatory activities. ET-1 can inhibit HPV by stimulating ET_B receptors on endothelial cells leading to the release of NO and PGI_2.[75] ET-1 can also stimulate the aldosterone system, and hyperaldosteronism can inactivate ET_B receptors on *pulmonary artery endothelial cells* (PAECs) by oxidative modification of cysteinyl thiols, in which case the ET_A-mediated vasoconstrictor effect of ET-1 can prevail, leading to an exaggerated HPV response.[76]

Endothelium-Derived Vasoactive Agents

The endothelium, which is strategically located at the interface between the flowing blood and the vascular smooth muscle of the vessel wall, plays a pivotal role in regulating the pulmonary VSMCs, mainly by the release of a variety of vasoactive agents, specifically NO, PGI_2, and ET-1[34,72,77] (Fig. 6.1).

Nitric Oxide Signaling. Although minor roles for the gaseous molecules carbon monoxide and hydrogen sulfide have been shown in the modulation of HPV[78] and in pulmonary vascular homeostasis,[79–81] NO is the gaseous molecule with the primary role in the regulation of pulmonary vasomotor tone. Endothelial cells synthesize NO from L-arginine by using *endothelial nitric oxide synthase* (eNOS). NO is a highly lipophilic gas that readily diffuses into the underlying VSMCs to exert its vasodilator and antiproliferative actions, primarily by elevating *cyclic 3′,5′-guanosine monophosphate* (cGMP) through activation of *soluble guanylyl cyclase* (sGC) and cGMP-mediated activation of cGMP-dependent protein kinase.[82,83]

In animal models and in humans, inhibition of endogenous endothelial NO production leads to an increase in PVR, suggesting a tonic level of vasodilation induced by

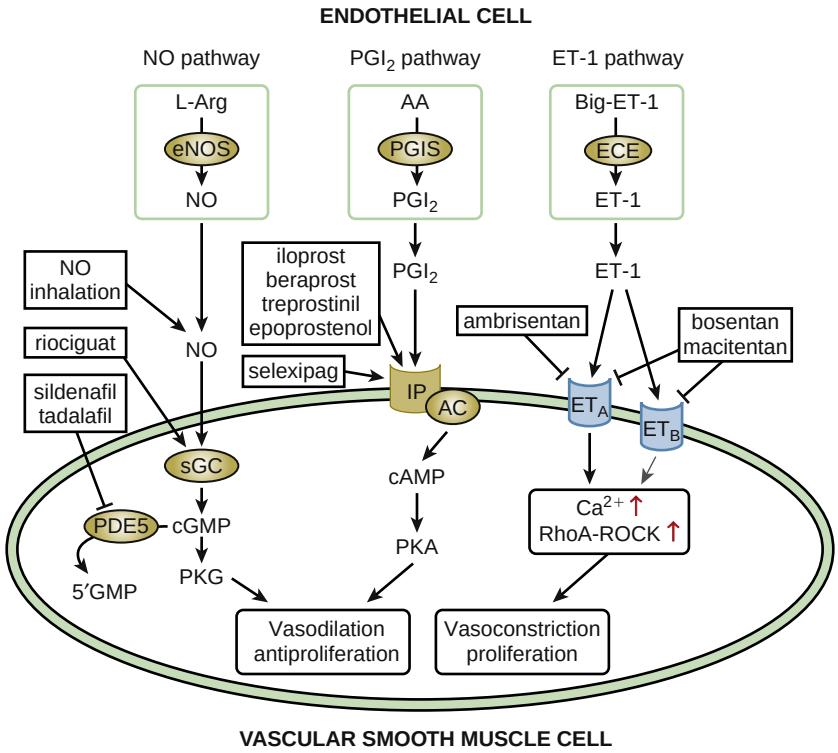

Figure 6.1 Signaling pathways of pulmonary endothelial cells. Shown are the endothelium-derived vasoactive agents *nitric oxide* (NO), *prostacyclin* (PGI_2), and *endothelin-1* (ET-1), which regulate pulmonary *vascular smooth muscle cell* (VSMC) tone and proliferation and the relevant pharmacologic agents used in the treatment of *pulmonary hypertension* (PH). NO is synthesized in *endothelial cells* (ECs) from *L-arginine* (L-arg) by *endothelial NO synthase* (eNOS). It diffuses easily into the underlying VSMCs and stimulates *soluble guanylyl cyclase* (sGC), resulting in increased *cyclic guanosine monophosphate* (cGMP) levels. cGMP then activates *cGMP-dependent protein kinase* (PKG), which leads to relaxation of VSMCs and inhibition of VSMC proliferation. cGMP is degraded by *type 5 phosphodiesterase* (PDE5) into a biologic inactive compound, 3′,5′-GMP. To counteract the impaired NO signaling in PH, NO inhalation, riociguat, an sGC stimulator, and PDE5 inhibitors, sildenafil, and tadalafil, are used clinically. PGI_2 is synthesized in EC from *arachidonic acid* (AA) by cyclooxygenase and *PGI_2 synthase* (PGIS) sequentially. Upon release, it binds to *PGI_2 receptors* (IP), which results in activation of *adenylyl cyclase* (AC), increased *cyclic adenosine monophosphate* (cAMP) levels and activation of *cAMP-dependent protein kinase* (PKA). This results in relaxation of VSMCs and inhibition of their proliferation. Clinically, several synthetic analogs of PGI_2 (iloprost, beraprost, treprostinil, and epoprostenol) and a synthetic IP receptor agonist, selexipag, are in use in the treatment of PH. ET-1 is synthesized in EC by translation from preproendothelin messenger RNA, followed by cleavage to Big–ET-1, which is then converted to ET-1 by *endothelin-converting enzyme* (ECE). ET-1 stimulates VSMC constriction and proliferation via ET_A or ET_B receptors, predominantly the former. ET-1 acts by elevating intracellular Ca^{2+} levels and stimulating *RhoA–RhoA kinase* (RhoA-ROCK) signaling. ET-1 can also stimulate the production of NO and PGI_2 via ET_B receptors present on EC (not shown). Currently, there are three ET-1 receptor antagonists available for the treatment of PH. Ambrisentan is a selective ET_A receptor antagonist, whereas bosentan and macitentan are dual endothelin receptor antagonists (ET_A and ET_B). The *arrow* and T-end lines denote stimulatory and inhibitory effects, respectively.

endothelial-derived NO.[24,26,84] In patients with PAH and other forms of PH, the expression of eNOS, endothelial NO production, and their bioavailability are decreased.[85–88] The expression and activity of sGC is also compromised in PAH, likely due to oxidative stress.[89–91] Net intracellular levels of cGMP are determined by its production via sGC and by its degradation by *phosphodiesterases* (PDEs), in particular the *type 5 PDE* (PDE5).[82,92] In animal models of PH, the expression and/or activity of PDE5 is increased, which leads to augmented cGMP degradation and thus impaired NO-mediated vasodilation.[93–95] PDE5 is highly expressed in lungs, allowing for the use of selective PDE5 inhibitors in the treatment of pulmonary hypertension.[96] Currently, two PDE5 inhibitors, sildenafil and tadalafil, are approved by the *U.S. Food and Drug Administration* (FDA) for the treatment of PAH.[97] In addition to PDE5 inhibitors, inhaled NO is commonly used as first-line vasodilator therapy in persistent PH of the newborn.[98,99] Riociguat, an sGC stimulator, has also been approved by the FDA for the treatment of PAH and chronic thromboembolic pulmonary hypertension.[97]

Prostaglandin I_2/Prostacyclin. Prostaglandin is a potent vasodilator and antiproliferative agent in the pulmonary circulation. PGI_2 is primarily synthesized in endothelial cells by prostacyclin synthase from arachidonic acid. Upon release, PGI_2 binds to *I-prostanoid* (IP) receptors on VSMCs. The IP receptor is coupled to G proteins, which activate adenylate cyclase. This leads to increased generation of *cyclic adenosine monophosphate* (cAMP). cAMP causes pulmonary vasodilation and inhibits vascular proliferation through the activation of protein kinase A.[100,101]

In patients with PAH, the expression of prostacyclin synthase and IP receptors is down-regulated, which contributes to the exaggerated pulmonary vasoconstriction and vascular remodeling seen in this disease.[102,103] Clinically, several synthetic analogs of PGI_2 (epoprostenol, treprostinil, iloprost, and beraprost) have been approved by the FDA for the treatment of PAH and PH related to scleroderma, congenital heart disease, and other causes. Selexipag, a synthetic IP receptor agonist, has been shown to be of therapeutic benefit in PAH.[97,104]

Endothelin-1. ET-1, a 21–amino acid peptide, is a vasoactive agent capable of vasoconstriction and vasodilation and is a pro-proliferation agent of VSMCs. It is synthesized predominantly in endothelial cells, initially as a

212–amino acid precursor prepro–ET-1. It is then cleaved sequentially by a signal peptidase and furin enzymes to generate pro–ET-1 and Big–ET-1, respectively. Big–ET-1 is converted to ET-1 by endothelin-converting enzyme. ET-1 exerts its effect by binding to its receptors—ET_A, which mediates vasoconstriction, and ET_B, which mediates vasodilation. Both receptor types are present in pulmonary VSMCs, with ET_A being dominant. The binding of ET-1 to its receptor ET_A in VSMCs causes vasoconstriction by stimulating the influx of extracellular Ca^{2+} and the release of Ca^{2+} from the sarcoplasmic reticulum into the cytosol. ET-1 also enhances vasoconstriction by increasing the sensitivity of myofilaments to Ca^{2+} through RhoA-ROCK signaling. ET_B receptors are mainly located in pulmonary endothelial cells. Activation of ET_B receptors stimulates the production and release of NO and PGI_2 from the endothelium, resulting in vasodilation. ET-1 has a weak mitogenic effect on VSMCs, which is enhanced by other growth factors, such as transforming growth factor-β1. Under normal conditions, the vasoconstrictive effect of ET-1 via ET_A is balanced by its vasodilatory effect via ET_B. However, when the integrity of the endothelium is compromised, the vasoconstrictive effect of ET-1 prevails.[105–107]

Patients with PH have both increased circulating levels of ET-1 and increased expression of ET-1 in the pulmonary vasculature, which are closely associated with increased PVR and the severity of structural abnormalities in the distal pulmonary arteries.[108–111] Elevated intracellular Ca^{2+} levels and enhanced Ca^{2+} sensitivity of myofilaments induced by ET-1 are implicated in the exaggerated contractility of pulmonary vessels in PAH.[112] Moreover, ET_B-mediated production of endothelial-derived NO is diminished in PAH. NO normally exerts an inhibitory effect on the synthesis and release of ET-1.[113] Decreased NO production would increase the release of ET-1 from the endothelium, thus leading to further vasoconstriction and vascular remodeling.[114] The role of ET-1 signaling in vascular tone has been successfully translated into new therapeutic agents for PAH. Currently, three FDA-approved ET-1 receptor antagonists are available for the treatment of PH. Bosentan and macitentan are dual endothelin receptor antagonists (ET_A and ET_B), whereas ambrisentan is a selective ET_A receptor antagonist.[115,116] In an event-driven study, macitentan significantly reduced morbidity and mortality among patients with PAH.[117] The combination therapy with ambrisentan and PDE5 inhibitor tadalafil was found to have a significantly lower risk of clinical failure events than with ambrisentan or tadalafil monotherapy[118] (see Fig. 6.1).

NEURAL CONTROL

The pulmonary vasculature is innervated by sympathetic, parasympathetic, and sensory-motor nerve fibers but is typically less richly innvervated than the systemic vessels. The density of the nerve fibers is greatest in large vessels and at branch points. Sympathetic activation increases PVR via the release of norepinephrine, which causes vasoconstriction via *α-adrenergic receptors* (α-ARs) and vasodilation via β-ARs, with the vasoconstrictive effect being more dominant.[9,34] Under basal conditions, there is limited sympathetic influence on pulmonary vasomotor tone, but sympathetic activation happens during exercise and hypoxia.[119,120] In PH patients, the sympathetic nervous system is activated and may contribute to increased vasomotor tone.[121] In an animal model of PH, denervation of the large pulmonary arteries significantly reduced pulmonary artery pressure and PVR.[122] Parasympathetic stimulation induces the release of *acetylcholine* (ACh). ACh induces relaxation of isolated human pulmonary arteries through release of endothelial-derived NO, whereas its direct effect on denuded vessels is contraction.[123] Under basal conditions, there is limited parasympathetic influence on pulmonary vasomotor tone.[34,124] In addition to the classic neurotransmitters, a number of neuropeptides and bioactive agents can be co-released from the nerve terminals in the pulmonary vessel wall, such as neuropeptide Y, vasoactive intestinal peptide, calcitonin gene–related peptide, substance P, adenosine triphosphate, and NO. Their roles in regulation of pulmonary vasomotor tone remain to be fully elucidated.[125–127]

ROLE OF PULMONARY VEINS

In the lungs, venous differentiation and patterning are genetically controlled through the coordinated actions of specific transcription factors.[13] In most developing organs, including the lungs, arterial and venous identity is also modulated by hemodynamic forces.[128–131] Arterial fate is acquired by the combined effect of transcription factors FOXC1 and FOXC2 and vascular endothelial growth factor signaling, whereas venous identity is regulated by the orphan nuclear receptor *chicken ovalbumin upstream promoter transcriptional factor-II* (COUP-TFII) through the repression of Notch1.

In the lung, there is now a large body of evidence indicating that the veins are not simple conduits that return blood to the left atrium. Unlike the systemic veins, pulmonary veins play an active role in the regulation of lung blood flow, capillary filtration pressures, and PVR.[4,132,133] Significant vasoreactivity has been described in pulmonary veins in the fetus and newborn[134–139] and in the adult.[140–144] Data from many animal species indicate that, similar to pulmonary arteries, pulmonary veins are reactive to a broad range of vasoconstrictors, such as platelet activating factor, thromboxane and leukotrienes, and vasodilators, such as NO and PGI_2.[4,130,133] Pulmonary veins in the fetus and newborn are exquisitively sensitive to NO and cGMP.[145,146] In the hypoxic environment of the fetus, both pulmonary arteries and veins are constricted. The enhanced responsiveness of veins and arteries in the perinatal period to NO facilitates their relaxation at birth as NO is released from the endothelium with the initiation of respiration.[4]

Although the primary site of resistance to flow in the pulmonary circulation under both normal and hypoxic conditions is the precapillary pulmonary arterioles,[34] numerous studies have shown that hypoxia causes vigorous constriction of pulmonary veins in a variety of species, including rat,[147] guinea pig,[148] ferret,[149] dog,[150] sheep,[132,151] and pig.[152] In dog lungs, acute alveolar hypoxia predominantly constricts pulmonary arteries. However, when the lungs are perfused with histamine, the vasoconstrictor response to acute alveolar hypoxia is in veins.[153] By increasing microvascular pressures, venous constriction can cause distention and recruitment of capillaries with the possibility of better ventilation-perfusion matching; however, venous

constriction can also increase capillary filtration pressures and the likelihood of edema formation.[133,154]

Postcapillary pathology with venous abnormalities as a cause of PH is now recognized in the updated Classification of Pulmonary Hypertension and listed as group 1.6. This group has venous pathology in addition to arterial pathology and therefore is included in group 1. Also, for group 2 patients with PH due to left heart disease, a subcategory of group 2.4 was added to distinguish congenital and acquired pulmonary venous lesions that lead to PH.[155,156] To distinguish patients with both precapillary and postcapillary lesions with venous pathology from those who have isolated postcapillary PH with left heart failure, the hemodynamic definition of PH was updated. Isolated precapillary PH is associated with *mean pulmonary arterial pressure* (mPAP) greater than 20 mm Hg, PCWP less than 15 mm Hg, and PVR greater than 3 Wood units. Isolated postcapillary PH is associated with mPAP greater than 20 mm Hg, PCWP greater than 15 mm Hg, and PVR less than 3 Wood units, and combined precapillary and postcapillary PH is associated with mPAP greater than 20 mm Hg, PCWP greater than 15 mm Hg, and PVR greater than 3 Wood units.[157]

In chronic pulmonary hypertensive disorders, there is vascular remodeling of pulmonary arteries as well as veins[158,159] in a number of species, including rat,[160,161] sheep,[162] and humans.[163–167] In humans, the changes in veins consist of medial hypertrophy and arterialization of bundles of smooth muscle cells within the venous intima.[164] In one study of 19 patients with PAH, intimal and adventitial thickening of pulmonary veins less than 250 μm in diameter was observed in approximately one-half of the subjects studied, suggesting that venous pathology in PAH is underdiagnosed.[165]

COMMUNICATION BETWEEN ENDOTHELIAL AND SMOOTH MUSCLE CELLS

Endothelial cells have an important role in the regulation of pulmonary vasoreactivity, primarily via the release of various diffusible molecules, such as NO, prostacyclin, and ET-1. Increasing evidence indicates that the relationship between the endothelial cells and the underlying VSMCs is bidirectional rather than unidirectional. Paracrine signaling is the primary mechanism by which the endothelium modulates the activity of VSMCs.[168] However, vasoactive agents released from the endothelium can induce the underlying VSMCs to generate diffusible molecules that in turn affect endothelial function. For example, ET-1 can increase VSMC production of hydrogen peroxide, which can then suppress eNOS expression in endothelial cells.[114] In addition to paracrine signaling, additional cross-talk mechanisms exist, including communications via *myoendothelial junctions* (MEJs)[169] and *extracellular vesicles* (EVs).[170] All these mechanisms are crucial to the homeostasis of the pulmonary circulation. Under pathophysiologic conditions, the altered interactions between endothelial cells and VSMCs may promote increased vasoconstriction and hyperproliferation of endothelial cells and VSMCs, the development of pulmonary vascular remodeling, increased PVR, and eventual right ventricular failure.[5,72,169–171]

MYOENDOTHELIAL JUNCTIONS

Functional MEJs are emerging as an important mechanism for communication between vascular endothelial and VSMCs.[172] Abnormal communication via MEJs is implicated in pulmonary vascular disease.[173,174] Located at the boundary between the endothelium and smooth muscle, the MEJs form gap junctions that allow fine tuning of vascular function. MEJs enable the direct transfer of current and small molecules (<1.2 kDa) between the cytoplasm of the adjacent cells. MEJs also provide a microdomain to localize other signaling pathways and proteins involved in intercellular communication and paracrine-based signaling. MEJs are more numerous in small resistance arteries than in larger elastic arteries, which enables a faster endothelial response to signaling from the smooth muscle in these vessels.[172]

The MEJ is composed of two hemichannels termed *connexons,* each composed of six *connexin* proteins. Of the connexin family, only Cx37, Cx40, and Cx43 are found in MEJs.[175] Although ultrastructural localization of MEJs was first described in 1957,[176] functional confirmation of MEJs has lagged behind. Dye transfer studies and comparison of membrane potentials between endothelial cells and VSMCs have provided evidence of functional MEJs. For example, green fluorescent dye loaded in PAECs can diffuse into the underlying *pulmonary arterial smooth muscle cells* (PASMCs). This effect is inhibited by small interfering RNA knockdown of the connexin Cx43, indicating the existence of functional MEJs.[174] There is also evidence that superoxide anion production originating from the VSMCs can diffuse into the endothelial cells to react with NO, leading to inactivation of NO.[5,169] MEJs may facilitate transfer of neurotransmitters between endothelial cells and VSMCs. In pulmonary blood vessels, serotonin is released by endothelial cells and causes pulmonary vasoconstriction by elevating intracellular Ca^{2+} levels and activating ROCK in VSMCs. Serotonin also promotes vascular proliferation via the activation of mitogen-activated protein kinase, Akt, and ROCK.[177–180] Although serotonin acts on VSMC via its cell surface receptors and serotonin transporter, emerging evidence suggests that it can also diffuse from endothelial cells into VSMCs through the MEJs.[177,181,182] For instance, serotonin synthesized in rat PAECs is transferred to PASMCs in a co-culture system when the cells are in contact, but not without contact. The transfer of serotonin between these cell types is suppressed by blockade of the MEJ.[174,177]

EXTRACELLULAR VESICLES

EVs are cell-derived membrane-bound structures that originate from different subcellular membrane compartments. EVs contain *micro-RNAs* (miRNAs), proteins, lipids, and so forth, and they can transmit information to their target cells by delivering their cargo by membrane fusion, endocytosis, or receptor-mediated binding. EVs represent an important mechanism for cell-cell communication. They have been shown to transfer information from one cell to another under physiologic conditions and in disease.[170] However, more is known now about their pathophysiologic role in disease than under normal conditions.[183,184] EVs are classified into three main populations: exosomes,

microvesicles, and apoptotic bodies. *Exosomes* are approximately 40 to 100 nm membrane vesicles of endocytic origin released into the extracellular space after fusion of multivesicular bodies with the plasma membrane. Exosomes contain endosome-specific proteins, such as ALIX and TSG101; components of microdomains in the plasma membrane, such as cholesterol, ceramide, integrins, and tetraspanins; messenger RNA; miRNA; and other noncoding RNAs. The larger *microvesicles* (MVs), sometimes referred to as microparticles, are approximately 100 to 1000 nm in size. They are formed by the outward budding and separation of the plasma membrane and therefore retain surface molecules from parent cells and part of their cytosolic content (proteins, RNA, miRNA). *Apoptotic bodies* are the largest EV (>1 μm). They are formed by outward blebbing of the cell membrane during the late steps of apoptosis and contain cellular organelles, proteins, DNA, RNA, and miRNA. EVs are released from most cell types, including endothelial cells and VSMCs.[5,171,185]

Under physiologic conditions, EVs are actively involved in the maintenance of the hemostasis in various organs, including the lungs.[183,184] Human PAECs can take up PASMC-derived EVs containing *zinc finger E-box–binding homeobox 1* (ZEB1, a well-known gatekeeper for endothelial-to-mesenchymal transition) and transforming growth factor-β superfamily ligands, which may facilitate endothelial-to-mesenchymal transition during normal angiogenesis[186] or during the development of PH[187] and other vascular diseases.[188,189] Pericytes, which are mural cells that wrap around and support the endothelial cells, may be recruited by Wnt5a-containing exosomes released from pulmonary venous endothelial cells, thereby preserving the number of functional vessels within the microcirculation. A lack of Wnt5a production impairs the interaction between endothelium and pericytes, resulting in loss of small vessels and the development of PAH.[190]

The cargo content of EVs has the distinct characteristics of the parental cells. Hence, EVs have a great potential for use as biomarkers in the diagnosis and/or prognosis of various diseases.[191–193] Circulating endothelial MVs are shed from activated or injured endothelial cells. In patients with PAH, the plasma levels of endothelial MVs, as identified by the endothelial markers $CD31^+$ (platelet endothelial cell adhesion molecule) or $CD144^+$ (vascular endothelial cadherin), are significantly increased compared with controls. Moreover, the $CD31^+$ and $CD144^+$ MV levels correlate with mean pulmonary artery pressure, PVR, and mean right atrial pressure in patients with PAH.[194] Endothelial MVs may serve as biomarkers of PAH and be involved in the pathogenesis of PAH.[195–197] Endothelium-dependent relaxation of rat pulmonary arteries is diminished after incubation with MVs obtained from rats exposed to chronic hypoxia, compared to control animals, and is accompanied by decreased eNOS activity and increased production of ROS.[195] Cell migration is an important step in the development of pulmonary vascular remodeling and PAH. The migration of PAECs can be induced by *micro-RNA-143* (miR-143) generated in PASMCs via exosomes. The miR-143–enriched exosomes derived from PASMCs are internalized by PAECs, leading to increased EC migration and angiogenesis.[198] Thus MVs may serve to amplify the pathologic response in PAH.

NONRESPIRATORY FUNCTIONS OF THE PULMONARY CIRCULATION

Although the primary purpose of the pulmonary circulation is gas exchange, it has other functions, such as metabolism.[199] The vast vascular surface area of the lungs and the fact that they receive the entire cardiac output, make them uniquely suited to metabolize and modify blood-borne compounds. Compounds can be either activated or inactivated within the pulmonary circulation.

The relatively inactive polypeptide angiotensin I is converted to the potent vasoconstrictor angiotensin II within the pulmonary circulation by an enzyme, *angiotensin I–converting enzyme* (ACE), located in small pits (caveolae intracellulares) on the surface of the capillary endothelial cells.[200,201] After being converted to angiotensin II by ACE, this potent vasoconstrictor can be converted to a vasodilator, *angiotensin 1-7* (Ang 1-7), by *angiotensin-converting enzyme II* (ACE2),[202] an enzyme abundantly expressed in various organs and tissues.[203,204] Of interest, ACE2 is the key cell receptor for *severe acute respiratory syndrome coronavirus 2* (SARS-CoV-2) to enter human cells and replicate, ultimately leading to the global pandemic of *coronavirus disease 2019* (COVID-19).[205] After binding of SARS-CoV-2 to ACE2, both the virus and ACE2 are internalized, which leads to reduced expression of ACE2 and thus reduced conversion of angiotensin II to Ang 1-7. This results in increased ROS production, increased inflammatory response, vasoconstriction, vascular leakage, a profibrotic response, and eventually severe lung injury.[206] Although COVID-19 is primarily considered a lung parenchymal disease, ACE2 is expressed on both endothelial cells and VSMCs, and the pulmonary vascular system can be infected by the virus.[203,204] The relative resistance of young people to this virus is thought to be in part due to a lower expression of ACE2 because it is developmentally regulated, and its expression is lower the younger the age.[207] In SARS-CoV-2 infection, there is an increased release of von Willebrand factor from the endothelial cells, which may contribute to the hypercoagulable state in COVID-19.[208,209] Currently, there are only a few reported cases of COVID-19 disease in patients with PH. Considering the limited numbers of patients with PH, the relationship between these diseases remains to be explored.[210] Currently there is also no evidence to suggest that PH per se is an independent risk factor for COVID-19.[206]

A number of vasoactive substances are completely or partially inactivated during passage through the lung. Bradykinin is largely inactivated (up to 80%) by ACE. The lung is the major site of inactivation of serotonin (5-hydroxytryptamine), not by enzymatic degradation but by an uptake and storage process. Some of the serotonin is transferred to platelets in the lung or stored and released during anaphylaxis.[199,211] Endothelin, although it is stable in plasma and whole blood, undergoes extensive pulmonary removal after binding to ET_B on the endothelial cells during its passage through the pulmonary circulation.[106,107] Prostaglandins E_1, E_2, and $F_{2\alpha}$ are inactivated in the lung. Norepinephrine is also taken up by the lung to some extent (up to 30%). Histamine appears not to be inactivated by the intact lung but is stored there.[199]

Several vasoactive substances are normally synthesized or stored within the lung but are released into the circulation under pathologic conditions. For example, in anaphylaxis or during an asthmatic attack, histamine, bradykinin, prostaglandins, and leukotrienes are discharged into the circulation. Other conditions in which the lung may release potent chemicals include pulmonary embolism and alveolar hypoxia.[7,199] There is evidence that the lung plays a role in blood clotting under normal and abnormal conditions. There are large numbers of mast cells containing heparin in the interstitium that participate in health and disease.[212] The pulmonary circulation also acts as a filter of blood. Small intravascular thrombi are removed from the circulation before they can reach the brain or other vital organs, in part due to a high fibrinolytic activity expressed in the endothelial cells of pulmonary arteries compared with that of systemic vessels.[213] Abnormal vascular connections in pulmonary arteriovenous malformations bypass the filtering effect of pulmonary capillaries, which may lead to paradoxical septic or nonseptic embolization. In particular, the brain is usually the most frequent target, and any right-to-left shunts would render patients vulnerable to cerebral abscesses or stroke.[214]

Compared with a majority of other organs, there is a higher concentration of neutrophils sequestrated in pulmonary capillaries, which are readily recruitable to serve as important host defense agents.[215,216] In the lung, neutrophils emigrate primarily through capillaries, with about 70% of migrating neutrophils leaving the capillaries at tricellular corners where the margins of three endothelial cells converge (eFig. 6.2).[217]

PERICYTES, ADVENTITIAL CELLS, AND OTHER CELLS

In the pulmonary vessel wall, in addition to endothelial cells and VSMCs, other structures exist, such as the vasa vasorum (the vessels that feed the blood vessel walls), lymphatic vessels, and nerves, as well as fibroblasts, immunomodulatory cells (dendritic cells and macrophages), adipocytes, and vascular progenitor cells.[218]

Pericytes are contractile cells that surround the endothelial cells and are embedded within the basement membrane of the microvasculature, particularly in precapillary arterioles, capillaries, and postcapillary venules.[219] In the process of new vessel formation, although the endothelial cells can form tubelike structures independently, a close interplay between the endothelial cells and pericytes is indispensable for the formation of functional vasculature capable of conducting blood flow.[220–222] For example, when primary human lung pericytes are added to endothelial cells during in vitro microfluidics experiments, the microvessels formed are narrower, less tortuous, and significantly less leaky than vessels formed with endothelial cells alone.[223] The pericytes in microvessels constrict in response to phenylephrine, indicating an active role for pericytes in the regulation of the microcirculation. Pericytes may also act as sentries of the immune system. In response to inflammatory mediators, such as necrotic cell lysates or *tumor necrosis factor-α* (TNF-α), pericytes along arterioles and capillaries upregulate the expression of adhesion molecule intercellular adhesion molecule-1 and release chemoattractant macrophage migration-inhibitory factor. These pericytes can attract and greatly augment leukocyte extravasation and can "instruct" extravasated leukocytes by increasing the expression of toll-like receptors and enhancing the ability of innate immune cells to detect and migrate to their final destination.[224] Increased numbers of pericytes have been observed around lung blood vessels in chronic lung diseases and are thought to be involved in vascular remodeling through pericyte-to-myofibroblast transformation in both humans and rodents.[225] The underlying mechanisms and their role in the development of PH remain to be elucidated.

Fibroblasts are the most abundant cell type in the adventitia of the blood vessel wall. They are the main cell type that synthesizes extracellular matrix to provide structural and biochemical support to the vessel wall. When exposed to hypoxia, ischemia, abnormal mechanical forces, or certain biochemical stimuli, fibroblasts can release a mixture of cytokines, chemokines, adhesion molecules, growth factors, and ROS, which initiate and perpetuate an inflammatory response. The adventitia of the pulmonary vasculature contains innate immune cells, particularly macrophages and *dendritic cells* (DCs). Under various pathophysiologic conditions, macrophages can fight pathogens, promote and restrict T cell responses, promote or resolve fibrosis, regulate angiogenesis, and control homeostasis in local immune networks. The principal role of pulmonary DCs is to encounter putative self and nonself environmental antigens and coordinate appropriate innate and acquired immunity responses. The coordinated actions of fibroblasts, macrophages, DCs, and other resident and recruited cells are essential for initiation, propagation, and resolution of local immune responses. When the response becomes chronic, the dysregulated activities of these cells contribute to the immunopathology of PH.[226–228]

Stem and progenitor cells, both resident and circulating, are present in pulmonary vessels, being most abundant in the adventitia. These cells have the potential to differentiate into various cell types, including endothelial cells, VSMCs, pericytes, fibroblasts, myofibroblasts, and macrophages. Under physiologic conditions, they are inactive and reside in stem cell niches of the vessel wall. When activated, they can be mobilized and migrate to the areas where the stimuli originated. Within the microenvironments surrounding these cells, in addition to soluble factors, the mechanical characteristics of the extracellular matrix exert profound influences on the lineage specification of stem and progenitor cells.[226,229,230]

PULMONARY VASCULAR ENDOTHELIUM AND CONTROL OF ENDOTHELIAL PERMEABILITY

The pulmonary circulation should be viewed as a series of networks from arteries to capillaries and veins. The endothelium in each of these vessels displays unique characteristics, and endothelial phenotypes vary distinctly in terms of origin, morphology, and function along the length of the pulmonary circulation.[231] Whereas pulmonary artery endothelial cells are derived from the pulmonary truncus

through angiogenesis, lung capillary endothelial cells are derived from blood islands via vasculogenesis.[6] Pulmonary artery, capillary, and venous endothelial cells differ in their staining properties, with lectins suggesting differences in glycan composition of their respective glycocalyces. They also differ in their intracellular organelle content (e.g., Weibel-Palade bodies are present only in endothelial cells lining pulmonary arteries and veins, but not in lung capillaries) and in their function because precapillary endothelial cells produce more NO and do not form as tight a barrier as capillary endothelial cells.[6,232] Recent single-cell analytics and cloning identified additional lung endothelial subsets with specific proliferative, angiogenic, and bioenergetic profiles[233] and unique functions specifically in alveolar revascularization after injury.[234] A newly discovered population of pulmonary endothelial cells, called *Car4-high EC,* express a unique gene signature, and ligand-receptor analysis shows that they are primed to receive reparative signals from alveolar type 1 cells. After acute lung injury, they preferentially localize in regenerating regions of the alveolus and contribute to recovery and repair of the lung.[234]

To subserve the function of gas exchange, the overall capillary surface area is extensive (≈60 m^2), and the alveolar-capillary membrane at the gas-exchanging site is only approximately 200 nm thick. On the vascular side, this barrier is composed of approximately 68 × 10^9 endothelial cells[235] covering roughly 300 × 10^9 alveolar capillaries[236,237] (Fig 6.2). Hence each endothelial cell spans an average of four adjoining alveolar capillary segments. On the alveolar epithelial side of the membrane, the alveolar type 1 cell is extremely thin to facilitate gas exchange. At the blood-gas barrier, the endothelial and alveolar epithelial basement membranes fuse into a single one, a phenomenon that is unique to the alveolar-capillary membrane, with the single exception of the similarly fused basement membrane between capillary endothelial cells and podocytes in the kidney glomerulus. At the alveolar-capillary membrane, this results in a thin, yet particularly resilient, basement membrane considered as the major component responsible for the surprising strength of the blood-gas barrier[238,239] (Fig 6.3). This strong fused basement membrane facilitates diffusive gas exchange, while it also provides the tensile strength for this extremely thin membrane to resist rupture, even though it is exposed to constant mechanical stresses from both the vascular and the airspace side, demonstrating the remarkable engineering of the lung[240] (see Video 3.1).

In the intact lung, endothelial barrier function is maintained via restrictive interendothelial junctions composed of *tight junctions* and *adherens junctions*, as well as focal adhesions anchoring the endothelium to the underlying extracellular matrix (Fig. 6.4). For the tight junction, the predominant molecules in the lung endothelium are occludin, zonula occludens-1, and claudin-5, which form band-like structures around the endothelial cells in lung capillaries to ensure intact barrier function.[241,242] Claudin-5 expression is inversely correlated with lung endothelial leak,[243] with various pathogenic stimuli that cause loss of claudin-5.[244] If claudin-5 is silenced, the ability of simvastatin to stabilize the endothelial barrier, either in cultured endothelial cells or in a mouse model of acute lung injury, is decreased, indicating the important role of claudin-5 in maintaining endothelial barrier integrity.[245] For the adherens junctions, the major protein in the vasculature is vascular endothelial–cadherin, which forms homomeric intercellular adhesions linked to the endothelial cytoskeleton at its cytoplasmic tail via β-catenin, p120-catenin, and α-catenin.[246] Disassembly of vascular endothelial–cadherin junctions causes loss of lung endothelial barrier function.[247,248] In lung microvascular endothelial cells, which line alveolar capillaries as well as small nonmuscularized precapillary arterioles and postcapillary venules of up to 18 μm in size,[249] but not in pulmonary artery endothelial cells, expression of activated leukocyte cell adhesion molecules is highly correlated with *N*-cadherin expression.[250] Our understanding of the individual contribution of various cell adhesion molecules to the maintenance of an intact endothelial barrier in the lung is far from complete and may ultimately be crucial for the development of barrier-stabilizing interventions that can specifically target endothelial barrier function in individual vascular subcompartments (e.g., capillaries vs. arteries).

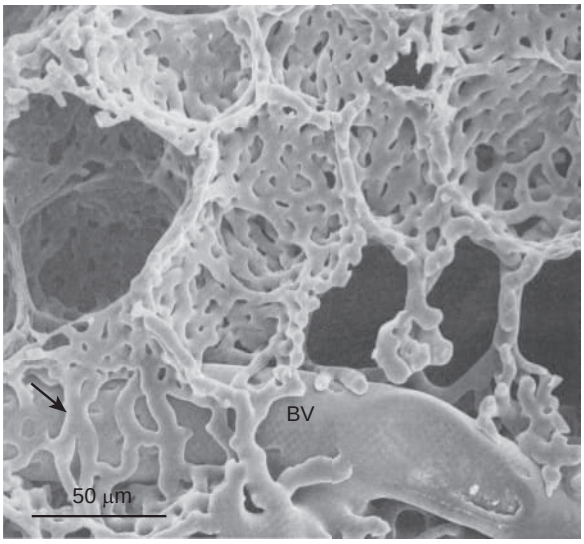

Figure 6.2 A scanning electron micrograph showing alveolar capillaries in a rat lung. Alveolar capillaries are seen as densely matted and intersecting tubules surrounding alveolar spaces. Other less numerous vessels are seen. At the bottom of the micrograph is a large *blood vessel* (BV), and running across this vessel is a nonalveolar capillary (*arrow*). (From Guntheroth WG, Luchtel DL, Kawabori I. Pulmonary microcirculation: tubules rather than sheet and post. *J Appl Physiol Respir Environ Exerc Physiol.* 1982;53[2]:510–515.)

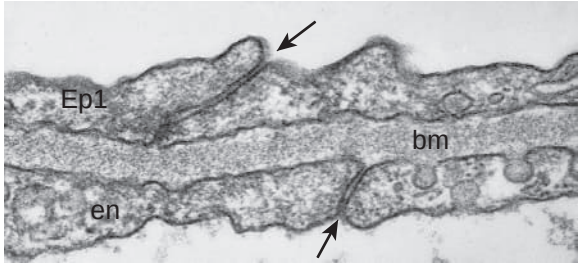

Figure 6.3 The alveolar-capillary barrier. A scanning electron micrograph of diffusion membrane shows the alveolar type 1 cells (Ep1) and *endothelial cells* (en) separated by fused *basement membrane* (bm) in the thin part of barrier. *Arrows* point to intercellular junctions with tight junctions in both cell layers. (From Weibel ER. On the tricks alveolar epithelial cells play to make a good lung. *Am J Respir Crit Care Med.* 2015;191[5]:504–513.)

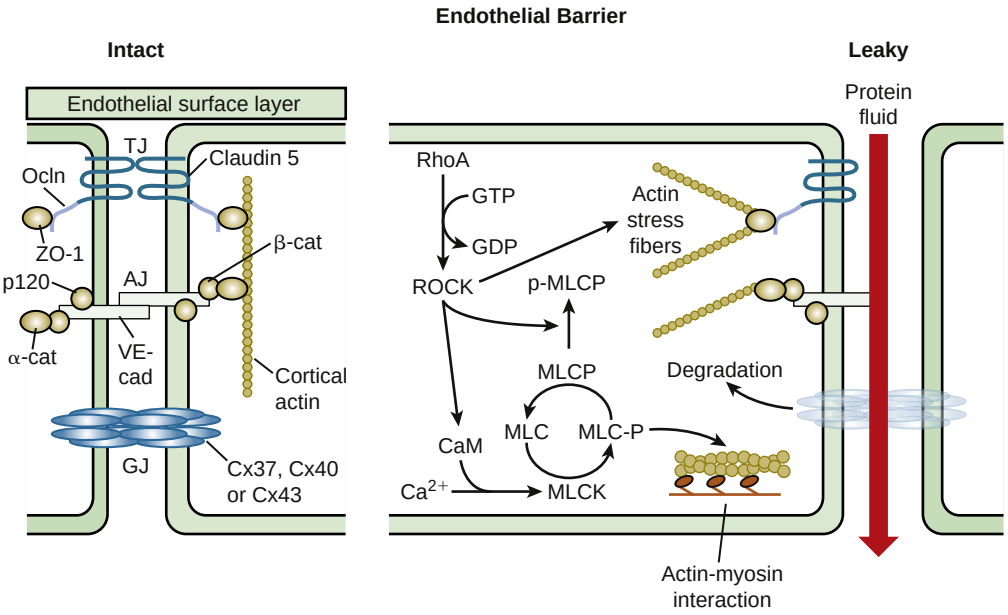

Figure 6.4 Regulation of lung endothelial barrier function. Under normal conditions (at *left*), the intact endothelial barrier restricts fluid and solute exchange due to the presence of an endothelial surface layer hydrogel and intact interendothelial junctions. The latter consist of *tight junctions* (TJs) composed of claudin, which is anchored to the cortical actin cytoskeleton via *occludin* (Ocln) and *zonula occludens* (ZO)-1, and of *adherens junctions* (AJ), which contain *VE-cadherin* (VE-cad) and p120, and α-catenin and *β-catenin* (cat). *Gap junctions* (GJs) composed of *connexins* (Cx) 37, 40, and 43 mediate interendothelial communication. Upon exposure to barrier-disruptive agonists (at *right*), the endothelial barrier can become leaky. The endothelial surface layer is shed and interendothelial gap junctions are degraded. Activation of *RhoA kinase* (RhoA-ROCK) signaling leads to phosphorylation and inhibition of *myosin light chain phosphatase* (MLCP). RhoA-ROCK activation increases Ca^{2+} signaling and by binding to *calmodulin* (CaM) activates *myosin light chain kinase* (MLCK), which leads to myosin light chain phosphorylation and enhanced and prolonged actin-interactions. In parallel, RhoA-ROCK signaling promotes the formation of actin stress fibers in lieu of the cortical actin cytoskeleton. In combination, these effects result in endothelial contraction and disruption of interendothelial junctions, resulting in unrestricted fluid and protein flux across a leaky endothelium.

Gap junctions situated between endothelial cells do not physically stabilize the endothelial barrier but regulate its permeability, in part by creating intercellular communication pathways by the assembly of two juxtaposed hemichannels and in part by direct protein-protein interactions.[251] Analogous to MEJs discussed earlier, interendothelial gap junctions in the lung are composed of connexins, with lung microvascular endothelial cells expressing Cx37, Cx40, and Cx43. There is evidence that connexins play an important role in the regulation of endothelial permeability. Inhibition or genetic deficiency of both Cx40 and Cx43 protects against the increase in endothelial permeability in various lung injury models, which suggests that gap junctions spread local increases in permeability along the pulmonary endothelium.[252,253] A recent study showed that when thrombin or lipopolysaccharide was applied locally to the endothelium of lungs with inhibition or deficiency of connexins, not only was there no spread of increased endothelial permeability, but there was also protection from injury at the site of application of the injurious agent. This finding cannot be explained by intercellular propagation of a permeability signal via gap junctions but, rather, points to additional functions of connexins in barrier regulation at the level of the individual endothelial cell. Of note, connexins seem to up-regulate expression of ROCK and stimulation of its downstream signaling pathway, which plays an important role in endothelial barrier failure.[253,254]

The luminal side of the microvascular endothelium is covered with a two-tiered hydrogel surface layer forming an additional physical barrier for transendothelial fluid and solute flux.[255–258] The lower tier, referred to as the glycocalyx, is approximately 70 nm thick and is anchored firmly in the cell membrane. It consists of proteoglycans with long unbranched *glycosaminoglycan* (GAG) side chains and glycoproteins with short-chain branched carbohydrate side chains. The upper tier, which can exceed 1000 nm in thickness, is formed by a thick layer of GAGs, predominantly hyaluronan, heparan sulfate, and chondroitin sulfate.[216] Degradation of this endothelial surface layer by invading pathogens or inflammatory responses markedly increases endothelial permeability[259,260]; hence, strategies for preservation or reconstitution of the surface layer, such as by GAG fragments[261] or growth factor signaling,[262] may present promising strategies to prevent or limit lung endothelial leak.

The pulmonary endothelium is not impermeable under normal conditions, and there is a constant basal exchange of fluid, electrolytes, and solutes between the vascular lumen and the lung interstitium. This exchange takes place via two main routes: a paracellular and a transcellular route.

The *paracellular* pathway of fluid and solute exchange is via interendothelial junctions and is governed by the variables in the Starling equation:

$$J_v = L_p \times S\,[(P_c - P_i) - \sigma(\pi_c - \pi_i)]$$

where J_v is fluid flux rate, L_p is hydraulic conductivity, S is the vessel surface area, σ is the reflection coefficient for plasma proteins, P is hydrostatic pressure, and π is oncotic pressure. The subscripts c and i refer to the capillary and interstitial compartments, respectively. The product of L_p and S is referred to as the endothelial *filtration coefficient* (K_f). Because K_f can be quantified in isolated perfused lungs, it remains the gold standard parameter for assessing

endothelial permeability in the intact lung.[6] Under basal conditions, this fluid flux is largely driven by the hydrostatic pressure difference. Fluid filtered into the interstitium is rapidly cleared by passive movement of liquid from the filtration site to the initial lymphatics along a hydraulic pressure gradient of approximately 3 cm H_2O.[263] Along with fluid flux, small solutes and particles can extravasate by solvent drag along the paracellular route, yet their ability to permeate across the endothelial barrier decreases exponentially with molecular size. Alveolar epithelial cells also actively secrete solutes and, via the generated osmotic pressure, maintain a fluid layer in the alveolar space.[264] Under normal conditions at rest, the rate of basal paracellular fluid flux across the intact lung microvascular endothelium is relatively low.

Transcellular transport or endothelial transcytosis is the preferred pathway for macromolecules to move across the barrier because they are too big to pass through the paracellular route. Macromolecules move in a receptor-mediated manner via caveolae, clathrin-coated pits, or via clathrin- and caveolin-independent mechanisms, as well as in a receptor-independent manner via fluid-phase uptake. The best studied of these pathways in the lung is caveolar transport. Caveolae are abundant in the lung vasculature and comprise approximately 15–20% of the total endothelial volume.[265] In caveolar transcytosis, macromolecules such as albumin bind to their receptor on the apical endothelial membrane, resulting in activation of downstream kinases, in particular Src. Src phosphorylates both caveolin-1, the structural protein of caveolae, and the small guanosine triphosphatase, dynamin, resulting in "pinching off" of the caveolar vesicle from the cell membrane. Once caveolae reach the abluminal side of the endothelium, they fuse with the plasma membrane, releasing their cargo into the subendothelial space.[266] However, the physiologic significance of endothelial transcytosis across the pulmonary microvascular wall is not certain, and many questions regarding the dynamics and regulation of endothelial transcytosis remain unclear, such as whether caveolar trafficking within endothelial cells is directed or random, or how receptors change their affinity to bind cargo on the luminal side and release it again on the abluminal side. Mice with a genetic knockout of caveolin-1 ($Cav1^{-/-}$) lack endothelial caveolae and develop endothelial hypercellularity and pulmonary hypertension.[267] The $Cav1^{-/-}$ phenotype has fueled the notion that caveolar transport is essential for lung homeostasis, yet the multiple signaling functions of caveolin-1 make it impossible to attribute this phenotype to changes in endothelial transcytosis alone.

A myriad of pathologic and proinflammatory stimuli can impair lung endothelial barrier function and result in an increased permeability-type lung edema, rich in protein and inflammatory cells.[268] Well-established mediators that cause lung endothelial barrier failure are proteins such as thrombin or angiopoietin-2, cytokines such as TNF-α, peptides such as bradykinin, or bioactive lipids such as platelet-activating factor or ceramide.[269] Mediators generally act via two main signaling pathways, namely the RhoA-ROCK pathway and endothelial Ca^{2+} signaling (Fig. 6.4). The downstream effector ROCK is activated by the monomeric Rho guanosine triphosphatase as a result of ligand binding to Gα12/13-coupled receptors. ROCK phosphorylates and inhibits myosin light chain phosphatase, the enzyme that dephosphorylates myosin light chain and thus terminates its interaction with F-actin filaments. ROCK activation enhances and prolongs actin-myosin–driven contractile forces transmitted to the endothelial adherens junctions complex, resulting in disruption of interendothelial junctions and gap formation.[246] With in vitro experiments, barrier-disrupting stimuli, such as TNF-α, cause characteristic ROCK-mediated cytoskeletal remodeling and actin stress fiber formation,[270] which further increases the contractile forces in the endothelium and, in parallel, leads to microtubule dissolution and loss of the cortical actin ring, which anchors interendothelial junction molecules under baseline junctions.[271] The Ca^{2+} pathway represents the other major barrier modification pathway. Barrier-disrupting stimuli, such as thrombin or platelet-activating factor, can increase endothelial Ca^{2+} signaling either by increasing Ca^{2+} release from intracellular stores, typically mediated by Gα12/13-coupled receptors and phospholipase C–dependent formation of inositol trisphosphate, and subsequent activation of store-operated Ca^{2+} channels, or by direct or indirect (e.g., via phospholipase C–derived diacyl glycerol) activation of transmembrane Ca^{2+} channels. The resulting increase in cytosolic Ca^{2+} concentration causes Ca^{2+}/calmodulin-dependent activation of myosin light chain kinase and phosphorylation of myosin light chain, which again increases contractile forces in the endothelium, promoting interendothelial gap formation. Of note, Ca^{2+}-dependent increases in lung endothelial permeability are not restricted to permeability-type lung edema but can also contribute, albeit to a lesser extent, to hydrostatic lung edema formation, which has traditionally been viewed as increased fluid filtration across an intact endothelial barrier with no change in permeability. This paradigm has, however, been revised by the finding that increased vascular pressures stimulate mechanosensitive cation channels, such as transient receptor potential vanilloid 4 on the endothelial plasma membrane, thereby increasing endothelial permeability and contributing to the formation of hydrostatic lung edema.[272]

Whether endothelial barrier disruption is primarily mediated via RhoA-ROCK or via Ca^{2+} signaling depends on the triggering stimulus and its respective receptor on the endothelial cell membrane, and whether the studies have been done under in vitro or in vivo conditions. RhoA-ROCK signaling and stress fiber formation play a key role in virtually all endothelial permeability assays in vitro; in contrast, Ca^{2+} signaling seems to be the dominant regulator in intact lungs, where endothelial stress fiber formation is less prominent or totally absent and inhibition of ROCK signaling does not prevent endothelial hyperpermeability.[269] The reasons for these differences in experimental findings are not fully understood but may relate to the fact that ROCK-dependent formation of stress fibers in endothelial cells becomes more prominent when the cells are on a stiff substrate; the stiffness of plastic or glass used in culture dishes is in the range of 2 to 4 *gigapascals* (GPa) but is a million times less (below 1 kPa) in the intact lung.[273]

Other factors also play a role in barrier function. Paracellular leak of plasma proteins in response to barrier-disruptive stimuli can be amplified by stimulation of protein transcytosis, by mediators such as endotoxin[274] or

thrombin.[266] Finally, a variety of mediators and second messengers can help to reconstitute or preserve endothelial barrier function by attenuating activation of RhoA-ROCK and Ca^{2+} signaling pathways with their effects on cytoskeletal remodeling and contraction. Barrier-protective mediators such as sphingosine-1-phosphate or angiopoietin-1 are potential therapeutic molecules for lung endothelial barrier preservation and repair, but their clinical use awaits definitive clinical trials.

BRONCHIAL CIRCULATION

The bronchial circulation supplies nutrition and oxygenated blood to the conducting airways, walls of the pulmonary arteries and veins, regional lymph nodes, nerves, and the visceral pleura. The bronchial circulation is a high-pressure, low-volume system supplied by the bronchial arteries, which arise directly from the thoracic aorta or one of its branches, although there is significant anatomic variability. Upon entering the lung, the intrapulmonary bronchial arteries travel and branch within the bronchi down to the terminal bronchioles, forming a vast network of capillaries and establishing extensive anastomoses with other bronchial arteries and the pulmonary vasculature. Bronchial blood flow to the lung is estimated to be less than 3% of the cardiac output. A small portion (≈25–33%) of the bronchial arterial supply returns to the right atrium via bronchial veins, and approximately 67–75% flows into the left atrium via pulmonary veins, constituting an intrinsic right-to-left shunt. In consequence, blood in the left atrium is slightly less oxygenated than in the pulmonary capillaries[9,275–277] (eFig. 6.3).

Although often overlooked because of its relatively low blood flow compared to that in the pulmonary circulation, the bronchial circulation is an important contributor to lung homeostasis. For example, although most particulate matter in the airways is cleared by the mucociliary machinery, soluble particles can also be removed by direct uptake into the bronchial vessels.[278,279] Absorption of inhaled drugs by the submucosal bronchial venous system in airways may provide inhaled drugs direct access to the systemic circulation, bypassing hepatic degradation. Such a possibility and its clinical relevance, however, have not yet been evaluated.[280] Compared to the pulmonary circulation, the bronchial circulation also has a much greater capacity to expand and proliferate in response to chronic inflammation. Because the bronchial circulation is a high-pressure system, disruption of the vessels leads to significant bleeding. Indeed, the vast majority of massive and submassive hemoptysis episodes arise from the bronchial circulation.[280,281]

Key Points

- The pulmonary circulation is a low-pressure, low–vascular-resistance circulation functionally different from the systemic circulation.
- Gravity and changes in lung volume during breathing profoundly affect the distribution of blood flow within the lung.
- Pulmonary vessels constrict in response to hypoxia, which leads to improved matching of perfusion to ventilation. However, chronic and global hypoxic vasoconstriction may lead to pulmonary hypertension.
- The pulmonary veins also play an important role in the regulation of pulmonary microvascular filtration pressures and segmental and total pulmonary vascular resistances.
- Endothelial cells play a pivotal role in the regulation of pulmonary vascular contractility and remodeling through the release of nitric oxide, prostacyclin, and endothelin-1.
- Endothelial cells communicate with the underlying vascular smooth muscle cells via paracrine signaling, myoendothelial gap junctions, and extracellular vesicles.
- Pericytes, fibroblast, immune cells, and other cells in the pulmonary vasculature contribute to its vasoreactivity.
- The pulmonary circulation also possesses certain nonrespiratory functions, including activation/inactivation and clearance of various vasoactive agents, anticoagulation and fibrinolytic activity, clearance of particles, and host defense.
- Endothelial cells demonstrate heterogeneity across the arteries, capillaries, and veins.
- Endothelial barrier integrity is maintained by intact interendothelial junctions and an endothelial surface layer hydrogel; barrier-disruptive agents cause shedding of the surface layer, endothelial contraction, and loss of interendothelial junctions, allowing protein and fluid leak into the interstitial space.
- The bronchial circulation is a part of the systemic circulation and is required for the metabolic needs of the lungs. Because it is a high-pressure system, disruption of these vessels can lead to massive hemoptysis.

Key Readings

Dhaun N, Webb DJ. Endothelins in cardiovascular biology and therapeutics. *Nat Rev Cardiol*. 2019;16(8):491–502.
Gao Y, Chen T, Raj JU. Endothelial and smooth muscle cell interactions in the pathobiology of pulmonary hypertension. *Am J Respir Cell Mol Biol*. 2016;54(4):451–460.
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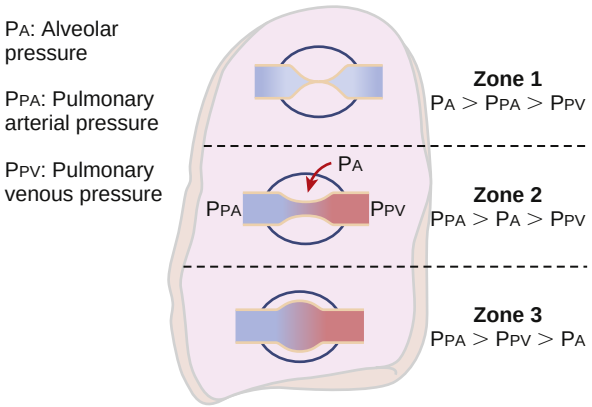
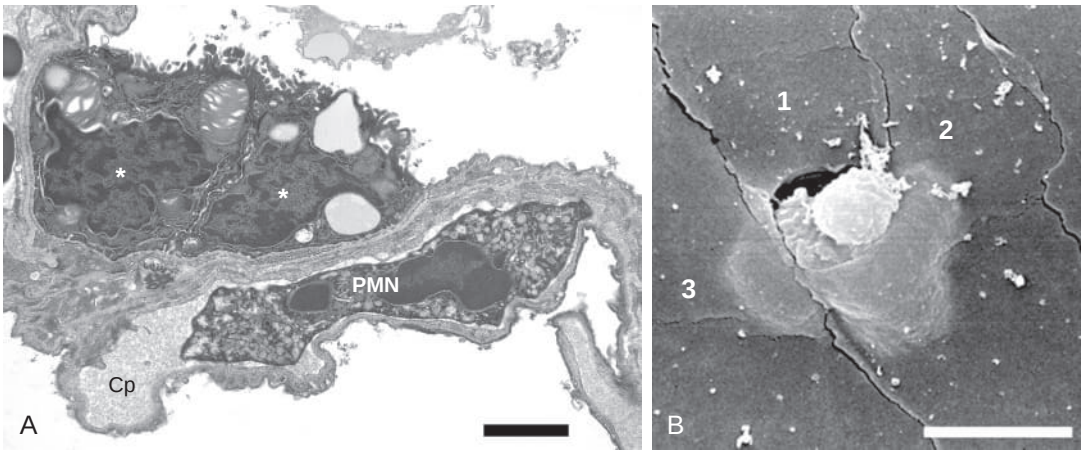
Complete reference list available at ExpertConsult.com.

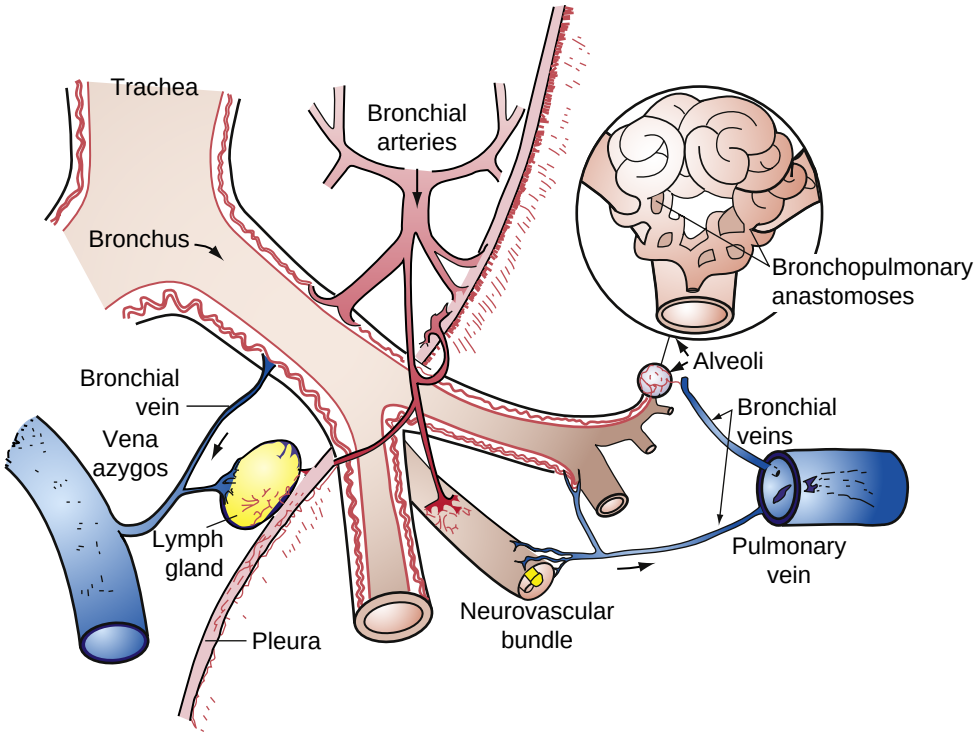
eFIGURE IMAGE GALLERY



eFigure 6.1 Three-zone model of pulmonary blood flow proposed by West and colleagues. In zone 1, the *alveolar pressure* (PA) is greater than *pulmonary arterial pressure* (PPA), which results in capillary collapse and no blood flow. In zone 2, PPA > PA, and blood flow is determined by the difference between them (PPA – PA). In zone 3, PPA > PPV > PA and blood flow is determined by the PPA – PPV pressure gradient. PPV, pulmonary venous pressure. (Modified from West JB, Dollery CT, Naimark A. Distribution of blood flow in isolated lung; relation to vascular and alveolar pressures. *J Appl Physiol.* 1964;19:713–724.)



eFigure 6.2 Neutrophils migrating through a pulmonary capillary. (A) A transmission electron micrograph shows a canine *polymorphonuclear neutrophil* (PMN) within a *capillary segment* (Cp). The neutrophil is deformed into an elongated "sausage" shape to facilitate passage through the narrow capillary segment. Two alveolar epithelial type 2 cells (*asterisks*) are on the thick side of the alveolar-capillary membrane. (B) A scanning electron micrograph of a rabbit neutrophil is shown fixed in the act of migrating across the pulmonary capillary. Note the borders of three endothelial cells (1, 2, and 3) converge on the trailing uropod (tail) of the migrating neutrophil at a tricellular corner. (A, From Burns AR, Smith CW, Walker DC. Unique structural features that influence neutrophil emigration into the lung. *Physiol Rev* 2003;83[2]:309–336. B, From Burns AR, Walker DC, Smith CW. Relationship between tight junctions and leukocyte transmigration. In: Cereijido M, Anderson J, editors. *Tight Junctions.* Boca Raton, FL: CRC Press; 2001:629–652.)



eFigure 6.3 Schematic illustration of the components of the bronchial circulation. Blood flows from bronchial arteries into capillary beds that supply the large airways and lymph glands. The circulation terminates at the level of terminal bronchioles, where it connects with pulmonary capillaries (bronchopulmonary anastomoses) and venules. Most of the bronchial circulation drains into the pulmonary veins, and a small amount drains into the bronchial veins, which drain into the azygos vein and finally the superior vena cava. (From Deffebach ME, Charan NB, Lakshminarayan S, Butler J. The bronchial circulation. *Am Rev Respir Dis.* 1987;135:463–481.)

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7 LYMPHATIC BIOLOGY

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INTRODUCTION

The lymphatic vasculature has long been poorly studied. Over the past 2 decades, the advent of markers that could reliably differentiate *lymphatic endothelial cells* (LECs) from vascular endothelial cells led to important progress in the understanding of lymphatic biology. Lung lymphatics play important roles in lung homeostasis, particularly in the drainage of fluid and macromolecules and immune cell trafficking. The role(s) of lymphatic vessels in lung disease is poorly understood. Most lung diseases are associated with changes in lymphatic distribution and/or density. It is unclear, however, if these changes are secondary to the remodeling process or directly contribute to disease pathogenesis. This chapter focuses on current knowledge regarding the distribution and function of lymphatics in the normal lung and highlights new evidence demonstrating that changes in the lymphatic vasculature play a critical role in lung disease initiation and progression.

ANATOMY OF THE PULMONARY LYMPHATICS

The pulmonary lymphatics drain fluid and traffic leukocytes from the distal lung parenchyma to the mediastinal and hilar lymph nodes. Anatomic studies have defined the relationship of the lymphatics to the other structures in the lung, but historically this was challenging given the lack of specific markers for pulmonary lymphatic endothelium and the fact that, in a normal lung, the lymphatics are thin, collapsed vessels that are difficult to detect. Some of the most detailed early descriptions of the pulmonary lymphatics resulted from casting procedures using resins in rodents in which pulmonary edema was induced to expand and visualize these vessels.[1–3]

These studies described lymphatic structures on the pleural surface (the superficial lymphatic plexus) and within the lung itself (the deep lymphatic plexus); in both cases a network of smaller initial lymphatic capillaries drain into larger conduit or collecting lymphatic vessels.[4] Whole mount imaging techniques using reporter mice in which all LECs are labeled with *green fluorescent protein* (GFP) (Prox1-GFP) have allowed for in-depth imaging of these vessels in the lungs and elsewhere.[5]

Initial lymphatic capillaries are small, thin-walled, blind-ended structures (Fig. 7.1C–D). Initial lymphatics feed into the larger collecting lymphatics containing a series of valves (Fig. 7.1A, B, D). LECs in lymphatic vessels have unique junctions specialized for the uptake of fluid and cells. Initial lymphatic capillaries have discontinuous junctions that form flaps between adjacent areas (called "buttons") and allow cells to enter the lumen of the lymphatic capillary[6,7] (Fig. 7.2). These junctions differ greatly from those of the collecting lymphatics, which have continuous zipper-like junctions that resemble those found between blood endothelial cells in both structure and function (see Fig. 7.2).[8] Collecting lymphatics in the periphery of the lung drain toward the visceral pleura but do not connect to the pleural space, whereas more centrally located lymphatics drain to the mediastinum.

The collecting lymphatics in tissues outside of the lung contain functional subunits known as lymphangions that consist of smooth muscle cell–lined segments of lymphatic vessel separated by valves, which actively pump lymph.[9–11] However, collecting pulmonary lymphatics in humans have only sporadic smooth muscle cell coverage, and collecting pulmonary lymphatics in rodents lack any smooth muscle cell coverage.[12–14] Therefore, collecting pulmonary lymphatics cannot contract robustly,[15] suggesting that extrinsic forces such as changes in thoracic pressure associated with ventilation may play a more central role in driving lung lymph flow.[16–18]

Within the human lung, the vast majority of lymphatic vessels are located either in the interlobular septa or subpleural space rather than within the lobule.[18] Among intralobular lymphatics, nearly all are associated with a blood vessel or in a bronchovascular bundle (Fig. 7.3).[4,19] Casting studies as well as conventional and whole mount immunohistochemistry of lung tissue have failed to identify a significant component of lymphatics in close association with alveoli in humans or rodents.[1–3,20,21]

PULMONARY LYMPHATIC MARKERS

Over the past 2 decades, major advances in the study of lymphangiogenesis were made possible by the identification of

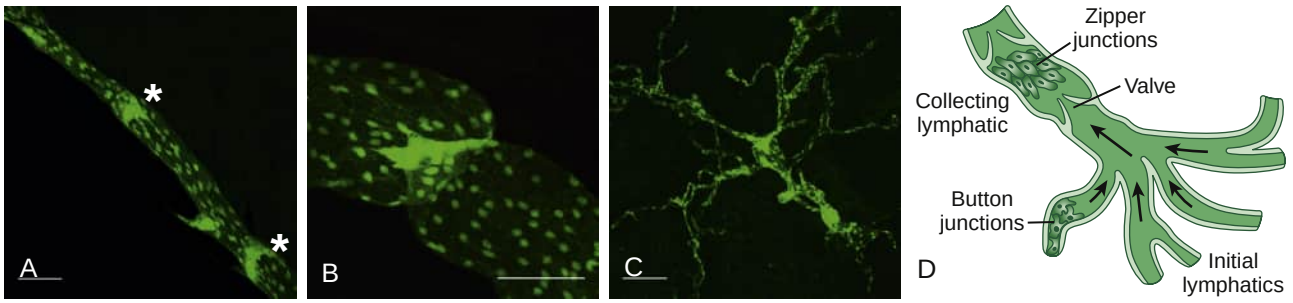

Figure 7.1 Pulmonary lymphatic vessel structure. (A–B) Whole mount imaging of lungs from adult *Prox1-GFP* lymphatic reporter mice shows pulmonary lymphatic vessels in green. (A) Collecting lymphatic vessel, with asterisks indicating areas of Prox1^{hi} endothelial cells that mark lymphatic valves. (B) High-magnification image of collecting pulmonary lymphatic vessel with Prox1^{hi} area demonstrating valve leaflet. (C) Smaller initial lymphatic vessels are blind-ended vessels without valves. (D) Illustration of pulmonary lymphatic vessels. Initial lymphatics begin as blind ends with button junctions. These initial lymphatics drain into larger collecting lymphatics characterized by zipper junctions and a series of valves. Scale bars = 25 μM.

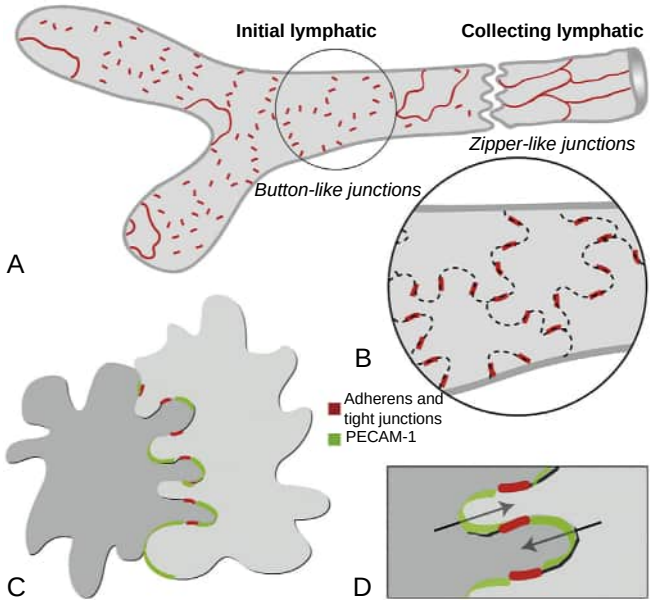

Figure 7.2 Specialized lymphatic junctions. (A) Schematic diagram showing distinctive, discontinuous buttons in endothelium of initial lymphatics and continuous zippers in collecting lymphatics. Both types of junctions consist of proteins typical of adherens junctions and tight junctions. (B) More detailed view showing the oak-leaf shape of endothelial cells (*dashed lines*) of initial lymphatics. Buttons (*red*) appear to be oriented perpendicular to the cell border but are in fact parallel to the sides of flaps. In contrast, most PECAM-1 expression is at the tips of flaps. (C and D) Enlarged views of buttons show that flaps of adjacent oak leaf–shaped endothelial cells have complementary shapes with overlapping edges. Adherens junctions and tight junctions at the sides of flaps direct fluid entry (*arrows*) to the junction-free region at the tip without repetitive disruption and re-formation of junctions. (From Baluk P, Fuxe J, Hashizume H, et al. Functionally specialized junctions between endothelial cells of lymphatic vessels. *J Exp Med*. 2007;204[10]:2349–2362.)

many lymphangiogenic growth factors, including *vascular endothelial growth factor* (VEGF)-C and VEGF-D, which signal through their canonical receptor *VEGF receptor 3* (VEGFR3) present on the surface of LECs.[22] Importantly, the identification of markers of pulmonary lymphatics allows the pulmonary lymphatics to be distinguished from the blood vasculature and capillary network in the lung. While many of these markers are also expressed by LECs in other organs, the repertoire of markers expressed by LECs varies according to the organ in which they are located. Therefore, careful analysis is required to ensure that pulmonary lymphatics are properly identified. In the mouse lung, two commonly used markers of lymphatic endothelium, lymphatic vessel endothelial hyaluronan receptor and podoplanin, are not specific for pulmonary lymphatics because they are highly expressed by blood endothelial cells and the epithelium, respectively.[23,24] Combination of these markers with other more specific lymphatic markers such as PROX1, a transcription factor and master regulator of lymphatic lineage, increase their utility. Expression of VEGFR3 can be used to identify lymphatics in the mouse lung whereas, in the human lung and in other mouse organs, this marker lacks specificity for the lymphatic endothelium. In humans, podoplanin (D2-40 epitope) has good specificity for identifying lymphatic vessels by immunohistochemistry staining.[25] Further complicating the identification of pulmonary lymphatic vessels is the finding that expression of lymphatic markers may change in the setting of lung injury.[26,27] Whenever possible, co-staining using two markers of the lymphatic endothelium should be used to ensure proper distinction of these vessels from the blood endothelium. Commonly used markers of the lymphatic endothelium are detailed in Table 7.1.

ROLE OF LYMPHATICS IN THE LUNG

FLUID UPTAKE AND PREVENTION OF PULMONARY EDEMA

An established role of lymphatic vessels in all organs is uptake of interstitial fluid; therefore, the consequence of a loss of lymphatic function is tissue edema.[28] In the lung, the role of lymphatics for drainage of interstitial fluid and prevention of alveolar edema is essential, because the lungs are exquisitely sensitive to alveolar pulmonary edema, which would negatively affect gas exchange. Accordingly, normal lymphatic function during lung development is required to drain fluid and increase the compliance necessary for neonatal lung inflation.[29,30] However, despite the importance of normal lymphatic development in the clearance of lung fluid immediately after birth, studies in adult large animals have shown that pulmonary lymph flow is relatively minimal even in the presence of lung edema.[16,31,32] In the traditional model by Ernest Starling, fluid balance in the lung

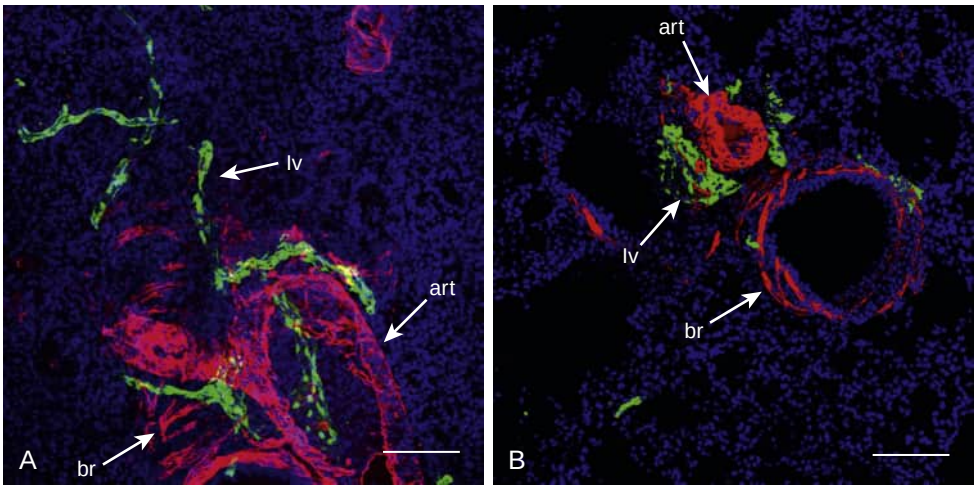

Figure 7.3 Pulmonary lymphatics are closely associated with bronchovascular bundles. (A–B) Immunohistochemistry of thick lung sections from *Prox1-GFP* mice with smooth muscle actin staining (*red*) shows lymphatic vessels (lv, *green*), in close association with arteries (art) and bronchi (br) in bronchovascular bundles. Nuclei stained with DAPI shown in blue. Scale bars = 25 μM.

Table 7.1 Lung Lymphatic Markers

Marker	Species	Comments
VEGFR3	Mouse	Unlike in other tissues, this is a specific marker for pulmonary lymphatics in the mouse lung. Use caution when using this marker in lung injury models because there can be increased VEGFR3 staining of pulmonary capillaries in this setting.
GFP (in *Prox1-GFP* mice)	Mouse	This lymphatic reporter mouse is the best and most specific way to visualize the pulmonary lymphatics in mice. In these mice, the GFP signal expressed from the Prox1 promoter can be detected in fresh or frozen sections, or immunohistochemistry can be used to detect GFP. The Prox1-GFP transgene can be crossed into other backgrounds for use in multiple mouse models. In the mouse lung, Prox1-GFP transgene expression is specific for lymphatic endothelial cells.
tdTomato (in *Prox1-tdTomato* mice)	Mouse	The tdTomato signal can be visualized in fresh or frozen sections, or immunohistochemistry can be used to detect tdTomato. Difficulty breeding these mice and issues with sterility limit their usefulness.
Prox1	Mouse	Nuclear stain labels lymphatic endothelial cells, but also labels other cell types in the lung, limiting its usefulness as a lymphatic marker on its own.
Lymphatic vessel endothelial hyaluronan receptor	Mouse	As opposed to other tissues in mice, this is not a specific marker of lymphatics in the lungs, because it strongly stains much of the blood vascular endothelium. Though it cannot be used on its own, when combined with Prox1 for double staining, it can be used to identify pulmonary lymphatic vessels.
CCL21	Mouse	Provides specific staining of lymphatic endothelial cells in the lungs.
Podoplanin	Mouse/human	Not a specific marker of pulmonary lymphatics in the mouse lung. However, staining for podoplanin (D2-40 clone) in human lungs does provide specific staining and is the best pulmonary lymphatic marker for human tissue.

CCL21, C-C motif chemokine ligand 21; GFP, green fluorescent protein; VEGFR, vascular endothelial growth factor receptor.

is maintained by a balance of hydrostatic forces moving fluid from the blood into the lung interstitium with oncotic forces moving fluid back into the blood capillary system. In this model, lung edema can be considered primarily a consequence of imbalanced Starling forces rather than inadequate pulmonary lymphatic function.[32–34] Nonetheless, lymphatics clearly have a role in the drainage of lung fluid, and pulmonary lymph flow increases in settings of injury and inflammation.[35,36] Genetic mouse models of impaired pulmonary lymphatic flow have been lacking until recently, making testing the role of these vessels in lung biology challenging. Recent work examining a mouse model of impaired lymph flow (from defects in lymphatic-venous separation) has demonstrated that these mice are susceptible to pulmonary edema in the setting of lung injury despite intact lymphatic vessels,[15] though notably these mice did not have evidence of pulmonary edema at baseline. Thus, the role of the pulmonary lymphatics in lung fluid drainage is likely most important in settings of injury and pulmonary edema. These observations are analogous to those of the parietal pleural lymphatics, which drain the pleural fluid (see Chapter 14). At baseline with a normal slow entry rate of pleural fluid, impairment of lymphatic drainage of the pleural space may have little consequence whereas, when entry of fluid into the pleural space increases, the limitation of lymphatic drainage contributes to formation of pleural effusions.

IMMUNE CELL TRAFFICKING

The role of the pulmonary lymphatics goes beyond providing a conduit for excess edema. An additional well-studied

role of the pulmonary lymphatics is regulating the immune response. The lung is constantly exposed to the outside environment and must maintain a quiescent immune state as well as be able to mount a robust immune response to pathogens. Immune cell trafficking to draining lymph nodes via the pulmonary lymphatics plays a central role in coordinating the adaptive immune response.[37,38] At steady state in healthy animals, the migration of antigen-presenting cells from the airways to the mediastinal lymph nodes via the lymphatics takes 1 to 2 days.[39,40] Some studies have shown similar kinetics of the migration of these cells in the setting of infection, while others have shown that the migration of these cells increases in the first few days after infection.[41–44] Of note, the kinetics for upper airway antigen-presenting cells is much faster than for their counterparts in the lung parenchyma, where the migration rate is greater than 7 days in some models.[40,43] Immune cell trafficking via the lymphatics is dependent on signaling between the lymphatic endothelium and antigen-presenting cells, which coordinates their migration. In particular, *C-C motif chemokine ligand* (CCL)21 expressed on the lymphatic endothelium and its receptor CCR7 expressed on T cells and dendritic cells appears to be essential for uptake and migration of these immune cells in pulmonary lymphatic vessels.[45] Immobilized CCL21 on the lymphatic endothelium is also important in directing the leukocytes moving within lymphatic vessels.[46–48] Other factors expressed by the lymphatic endothelium, including S1P, intercellular adhesion molecule-1, and vascular cell adhesion molecule-1, are also important for leukocyte trafficking via lymphatics, particularly in response to inflammation.[26,49,50] Migration of immune cells to draining lymph nodes ensures antigen presentation resulting in either an adaptive immune response or tolerance.

LOCAL IMMUNITY AND INDUCIBLE BRONCHUS-ASSOCIATED LYMPHOID TISSUE

Migration of antigen-presenting cells to the draining lymph node via the lymphatics is essential for proper immune responses. In response to inflammation, the pulmonary lymphatics proliferate and play a role in the local inflammatory environment.[20,51] Lymphatics contribute to the development o*f bronchus-associated lymphoid tissue* (BALT), which is a tertiary lymphoid organ not present in normal lung. Because BALT is induced only in response to a stimulus, the term *inducible bronchus-associated lymphoid tissue* (iBALT) is preferred.[52,53] iBALTs are accumulations of lymphoid cells that resemble lymph nodes in cellular content, organization, and the presence of lymphatic vessels. Chronic inflammation is often associated with the development of iBALT, where antigen presentation and lymphocyte priming can take place in close proximity to the area of inflammation, bypassing the need for antigen-presenting cells to traffic to the draining lymph nodes. However, this can have both favorable and unfavorable consequences. For example, in the setting of infection, iBALT allows for more rapid pathogen clearance and is protective.[54–57] However, in response to cigarette smoke exposure, iBALT may be a source of autoantibodies and destructive inflammatory mediators.[58–61] In mouse models of lung transplantation, iBALT can contribute to rejection through local immune activity,[60] though iBALT may also be a source of regulatory T cells that promote tolerance and acceptance of the graft.[61,62] Although tertiary lymphoid organs are a hallmark of chronic lung disease,[63] the reason they form from such widely differing insults and the role they play in different settings is unclear. Lymphatics are likely to be important in this process, because lymphatic vessels are key features of iBALT[20,52] and, in the setting of inflammation, active lymphangiogenesis is observed in association with these structures.[20] In addition, lymphatic dysfunction can contribute to iBALT formation and alveolar damage, even in the absence of inflammation or insult,[15] suggesting that lymphatic impairment may play a role in the pathogenesis of lung diseases in which iBALT is prominent.

PULMONARY LYMPHATICS IN LUNG INJURY

Apart from iBALT, pulmonary lymphatic function (and dysfunction) likely plays an important role in a variety of lung diseases (Table 7.2). Though lymphangiogenesis is often seen in response to lung inflammation, chronic inflammation leads to impaired lymphatic function,[64–67] perhaps in part due to a change in the LEC junctions that makes them less conducive to leukocyte entry.[6] When lymphatic function is impaired, accumulation of fluid, immune cells, proteins, and hyaluronan leads to inflammation, fibrosis, and changes in immune function.[67–69] However, the precise mechanism of how pulmonary lymphatics play a role in the pathogenesis of lung injury remains elusive. Abnormal lymphatics have been described in association with a variety of lung diseases,[70] but whether they are simply a consequence of the disease or whether lymphatic dysfunction actively contributes to lung injury is not always clear. The current state of knowledge of the role of lymphatics in lung disease is discussed further later.

LYMPHATIC DISORDERS DURING LUNG DEVELOPMENT

The lymphatic vasculature arises mainly from the venous endothelial cells driven by a combination of the expression of lymphatic-specific transcription factors (e.g., Prox1) and response to growth factors such as VEGF-C via VEGFR3 signaling in LECs.[71] LECs undergo a complex maturation program in preparation for birth,[72] which is critically important for the first breath.[32] Thus, disorders of lung lymphatics may be an underrecognized cause of early respiratory failure in preterm infants.[73] Experimental data in genetically engineered mice have shown that VEGF-C overexpression in utero leads to dilated lymphatics, chylous effusions, and respiratory failure, all features of human lymphangiectasia.[74] Importantly, there was a time-dependent response to exposure to VEGF-C overexpression, with worse outcomes with earlier exposures in utero, which was not reversed by stopping VEGF-C overexpression or blocking its receptors (VEGFR2 and VEGFR3) after the development of lymphangiectasia.[74] However, treatment with rapamycin, an inhibitor of the *mammalian target of rapamycin* (mTOR), reversed the aberrant lymphatics without affecting existing normal lymphatics.[75] Even though the mouse phenotype resembled human pulmonary lymphangiectasia, the role of VEGF-C in human disease is unclear.

Table 7.2 Evidence of Lymphatic Involvement in Lung Disease

	Clinical Findings	Experimental Findings
Asthma	Decreased airway lymphatics associated with edema and fibrosis in fatal asthma	Chronic airway inflammation results in lymphangiogenesis in rat and mouse models. Blocking lymphatic vessel formation results in airway edema.
COPD	Increased lymphatic vessel density especially associated with alveolar spaces and in advanced stage COPD	Lymphatic dysfunction alone leads to BALT formation and air space enlargement.
Interstitial lung disease	Increased lymphatic vessel density especially associated with alveolar spaces Fragmented lymphatic vessels Diffuse lymphatic anomalies can manifest as ILD	A decrease in lymphatic vessels after ionizing radiation precedes development of fibrosis. After bleomycin injury, mural cells lining lymphatic lumens result in lymphatic dysfunction.
Lung transplantation	Acute rejection is associated with increased lymphatic vessel density No change in lymphatic vessel density in chronic allograft dysfunction	Stimulation of lymphangiogenesis decreased acute allograft rejection.
Tuberculosis	Elevated serum VEGF-C levels correlate with disease burden	VEGF-C induces lymphangiogenesis. *Mycobacterium tuberculosis* grows in lymphatic endothelial cells.
Sarcoidosis	Elevated VEGF and VEGF-C levels in bronchoalveolar lavage and serum Atypical lymphatics around sarcoid granulomas	

BALT, bronchus-associated lymphoid tissue; ILD, interstitial lung disease; VEGF, vascular endothelial growth factor.

Other diseases characterized by systemic lymphatic malformations such as *Gorham-Stout disease* (GSD) and generalized lymphatic anomaly can affect the lung, causing chylous effusions and respiratory failure.[76] Bone-specific overexpression of VEGF-C in mice results in the bone lymphatic malformations observed in GSD and in the development of chylous effusions, thought to be due to the chyle leakage from aberrant lymphatics in the periosseous chest wall muscles.[77] In GSD, there is an increase in lung lymphatic surface area and in the proliferative capacity of lung LECs.[78] While rapamycin has been shown to be effective in the management of vascular and lymphatic anomalies,[79] precision medicine approaches have recently led to the identification of novel somatic mutations in pathways involved in lymphatic homeostasis leading to rational selection of therapy with either mTOR inhibitors[80] or MEK inhibitors.[81] Additional lymphatic diseases with pulmonary manifestations are listed in Table 7.3.

ASTHMA

Asthma is characterized by airway inflammation leading to mostly reversible airways obstruction. Chronic inflammation, angiogenesis, subepithelial fibrosis, and extracellular matrix deposition are often features of the disease.[82]

There is a paucity of data regarding the fate of the lymphatic vasculature in human asthma. One study showed that, in fatal asthma, there is decreased lymphatic vessel density associated with airway edema and fibrotic changes, despite an increase in VEGF-C and VEGF-D levels,[82] suggesting a link between lymphatics and outcome in severe asthma.[82]

The role of the lymphatic vasculature in chronic airway inflammation has been studied in a mouse model using *Mycoplasma pulmonis*[51,83,84] and in a rat model using house dust mites.[85] Both of these models have yielded important new knowledge in the understanding of chronic airway inflammation. These models showed that inflammation resulted in an increase in lymphatic vessels in the airways. Chronic airway inflammation using *Mycoplasma pulmonis*[51,83,84] in a mouse model resulted in a significant increase in number of lymphatic and blood vessels. VEGF-C/D signaling through VEGFR3 was partially driving the de novo lymphangiogenesis, but not angiogenesis.[51] Critically, blocking lymphangiogenesis resulted in an increase in airway edema,[51] potentially linking lymphatics to the development of airways obstruction. Moreover, while angiogenesis regressed with anti-inflammatory and antibiotic therapy, these treatments did not result in involution of the newly formed lymphatics.

Importantly, LECs isolated from house dust mite–sensitized rats showed increased proliferative, chemotactic, and tubulation properties, which persisted over multiple passages.[85] Although these models have yielded important insights into chronic airway inflammation, the role and contribution of lymphatics to human asthma pathogenesis remains to be elucidated.

CHRONIC OBSTRUCTIVE PULMONARY DISEASE

COPD is characterized by fixed airway obstruction, excess mucus production, and enlarged alveolar spaces, most commonly due to cigarette smoke exposure.[86] The role and fate of the lymphatic vessels in animal models of emphysema and cigarette smoke exposure has not been studied, and the effects of cigarette smoke exposure on LECs are unknown. Lymphoid follicles are increasingly recognized as central to the pathogenesis of COPD.[87] Furthermore, in lung tissues of patients with COPD, there is an increase in lymphatic vessel density, particularly in association with the alveolar spaces, which is associated with worse disease severity.[88,89] These findings are associated with a dysregulation of CCL21 and

Table 7.3 Miscellaneous Lymphatic Diseases With Pulmonary Manifestations

Disorder	Pulmonary Manifestations	Comments
Congenital pulmonary lymphangiectasias[124]	Severe neonatal respiratory distress	▪ Dilated saccular lung lymphatics ▪ Presumed impaired development of the fetal central lymphatic conduction system ▪ Can be associated with other congenital disorders
Diffuse pulmonary lymphangiomatosis[125]	Interstitial infiltrates, chylous effusions	▪ Lymphangiomas within normal lymphatic pathways ▪ Positive staining for endothelial markers such as CD31, factor VIII-related antigen, and D2-40 ▪ Absence of HMB45-positive LAM cells
Gorham-Stout disease[126]	Chylous effusions due to thoracic cage involvement	▪ Primary systemic manifestation is osteolysis ▪ Increased lymphatic and proliferative properties of lung LEC
Lymphangioleiomyomatosis	Pneumothorax, chylous effusions, thin-walled pulmonary cysts	▪ Elevated serum VEGF-D levels ▪ Presence of HMB-45 cells
Yellow nail syndrome[127]	Exudative pleural effusions, bronchiectasis	▪ Impaired lymph transport by lymphoscintigraphy ▪ Possible microvasculopathy

HMB, human melanoma black; LAM, lymphangioleiomyomatosis; LEC, lymphatic endothelial cells; VEGF, vascular endothelial growth factor.

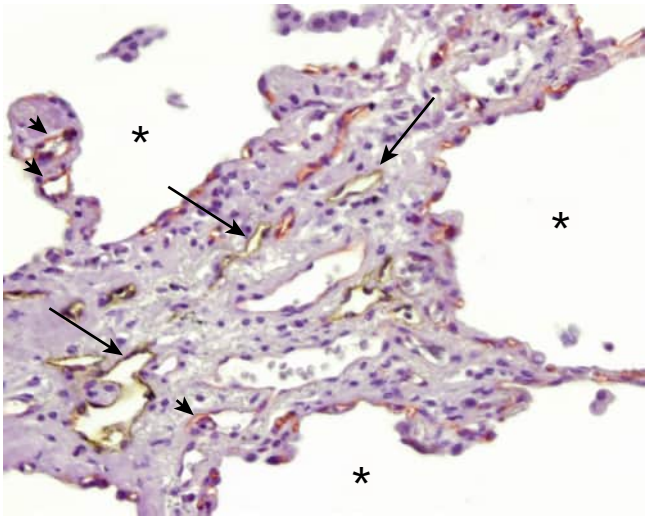

Figure 7.4 Alveolar lymphangiogenesis in *idiopathic pulmonary fibrosis* (IPF). IPF lung tissue section was stained with anti-CD34 (*red*) and anti-D2-40 (*brown*) antibodies. There is an increase in both blood capillary (*red*, *arrowheads*) and lymphatics (*brown*, *arrows*), with lymphatic vessels in proximity to alveolar spaces (*asterisks*). In the normal lung, there is a paucity of lymphatics associated with the alveoli.

chemokine scavenger receptor D6, which may alter transit of immune cells through the lymphatics in COPD.[89] Further evidence of lymphatic involvement in the pathogenesis of COPD is suggested by models of lymphatic impairment in mice that demonstrate that lymphatic dysfunction alone results in development of iBALT and air space enlargement that resembles emphysema.[15] Additional studies are needed to identify the effects of cigarette smoke on LECs, the effects of modulation of lymphangiogenesis on air space enlargement due to cigarette smoke, and whether these newly formed lymphatic vessels are functional.

INTERSTITIAL LUNG DISEASE

Interstitial lung diseases are a heterogenous group of disorders characterized by diffuse parenchymal involvement, with the potential development of fibrosis. Multiple studies have shown an increase in lymphatic vessel density and altered lymphatic distribution in *idiopathic pulmonary fibrosis* (IPF) and other forms of interstitial lung disease[25,90] (Fig. 7.4). These studies have also shown that increased alveolar lymphangiogenesis is associated with worsening fibrosis.[25,90] What remains unclear is the role of these vessels in fibrotic lung disease and whether these newly formed lymphatic vessels are functional or, as one study suggests, whether they are fragmented, and therefore nonfunctional.[91] Intriguingly, diffuse lung lymphatic anomalies can manifest as interstitial lung disease, with pathologic evidence of fibrosis.[92] In a description of three patients with lung lymphatic abnormalities (two cases of pulmonary lymphangiectasia and one case of lymphangiomatosis), CT scan of the chest at the time of presentation showed thickened interlobular septa, and other features of parenchymal lung involvement. However, the main histologic feature was dilated and abnormal lymphatic structures. This report demonstrates that primary lymphatic anomalies may present as interstitial lung disease.

In a mouse model of radiation-induced fibrosis, lung lymphatic vessel density decreased prior to the development of fibrosis,[93] suggesting that these changes are not simply in response to fibrosis. In the bleomycin mouse model of fibrosis, although there were no differences in lymphatic vessel density at day 28, lymphatic vessels were lined with *platelet-derived growth factor receptor* (PDGFR)-β mural cells that blocked the ability of lymphatics to drain hyaluronan, a key regulator of lung injury.[94] Although no preclinical or clinical studies have been undertaken to modulate lymphangiogenesis in fibrotic lung disease, it is important to note that a clinical trial using a PDGFR inhibitor did not improve outcome in IPF, although it is unclear in this study if the target was engaged and whether PDGFR was adequately inhibited.[95] Conversely, nintedanib, a pan–tyrosine kinase inhibitor, has been shown to decrease lung function decline in IPF, and it is tempting to hypothesize that some of the activity of nintedanib is derived from its targeting of LECs.[96]

LYMPHANGIOLEIOMYOMATOSIS

Lymphangioleiomyomatosis (LAM), a rare cystic lung disease that primarily affects women, is characterized by the proliferation of cells carrying inactivating mutations in the tuberous

sclerosis complex gene (see Chapter 97). LAM can be sporadic or in association with the tuberous sclerosis complex. Chylothorax can develop in about 10–30% of patients with LAM.[97] The presence of chylous effusions or ascites in combination with cystic lung disease is diagnostic of LAM.[98]

The origin of LAM cells remains unknown, but some evidence suggests that these cells could be of lymphatic endothelial lineage.[99,100] Further, lymphatic vessels are thought to be the conduit of LAM cell metastasis.[101] VEGF-D, elevated in approximately 70% of women with LAM, is a biomarker used for diagnosis and response to rapamycin, the FDA-approved treatment for LAM.[102]

LUNG TRANSPLANTATION

Lung transplantation carries the worst outcome of any solid organ transplant, with a 60% 5-year survival.[103,104] Acute rejection, which happens in about 30% of recipients,[105] is a major risk factor for the development of chronic lung allograft dysfunction, a driver of poor long-term outcomes.[106,107]

Human studies of transbronchial lung biopsies have shown that acute allograft rejection is associated with an increase in lymphatic vessel density.[108] However chronic lung allograft dysfunction, whether bronchiolitis obliterans syndrome or restrictive allograft syndrome, was not associated with changes in lymphatic vessel density.[109]

Because lymphatic vessels act as a major conduit for immune cell trafficking, they may contribute to graft rejection.[110] In rat models of cardiac transplantation[111] or the orthotopic tracheal transplant model[112] blocking lymphangiogenesis resulted in improved graft survival. However, in a mouse model of orthotopic lung transplantation, enhancing lymphangiogenesis by exogenous administration of VEGF-C decreased acute allograft rejection by increasing the clearance of excess short-fragment hyaluronan, a known alloimmune agonist.[113,114] During lung transplant surgery, lymphatics are severed and not reconnected.[115] This impaired lymphatic drainage has the potential to promote acute allograft rejection by impeding the clearance of proinflammatory molecules. These seemingly contradictory findings may be explained by the different models used.[112] In the mouse orthotopic lung transplant model, recent evidence demonstrates that posttransplant, there is a reestablishment of a functional lymphatic bed, as a result of donor lymphatics sprouting towards the host.[116] Understanding mechanisms of lymphatic regeneration as well as modalities that could enhance lymphangiogenesis posttransplant could result in novel therapies for acute allograft rejection.

TUBERCULOSIS

Mycobacterium tuberculosis (MTB) infection leads to the development of caseating granulomas in the lungs and other infected tissues.[117] Granulomas are composed of a large percentage of $CD11b^+$ macrophages, which produce VEGF-C leading to de novo lymphangiogenesis.[118] The newly formed lymphatic vessels in the granulomatous tissue facilitate the egress of $CD11c^+$ macrophages from the granulomas into the lymph nodes to prime T cells. Blocking lymphangiogenesis in animal models of tuberculosis infection resulted in decreased T cell activation. Although this did not translate to decreased bacterial burden in granulomas in the acute phase, the effects of long-term blockade of lymphangiogenesis in MTB infection are unknown.[118] Moreover, an additional role of lymphatics has recently been identified with the demonstration that lymph node LECs harbor replicating MTB.[119] Interferon-γ is a critical mediator of the interaction between MTB, macrophages, and granuloma formation. LEC stimulation with IFN-γ leads to induction of autophagy and nitric oxide production, which in turn restricts intracellular MTB proliferation.[116] In patients with TB infection, serum levels of VEGF-A, VEGF-C, and VEGFR2 positively correlated with pulmonary involvement and disease burden,[120] suggesting that lymphangiogenesis may be involved in the pathogenesis of human disease, consistent with preclinical model findings. Taken together, these data suggest the importance of lymphatics and LECs in the response to MTB and the persistence of infection.

SARCOIDOSIS

Sarcoidosis is a systemic granulomatous disease with noncaseating granulomas as a hallmark for diagnosis. Sarcoidosis can lead to parenchymal lung involvement as well as hilar lymphadenopathy.[121] The sarcoid granuloma is a source of VEGF and VEGF-C, which are elevated in sera and bronchoalveolar lavage fluid of patients with sarcoidosis.[122] Sarcoid granulomas are surrounded by tubular structures thought to be lymphatics but, in one study, these structures weakly expressed the LEC markers podoplanin and VEGFR2 but not VEGFR3, and were in part connected to afferent lymphatics, suggesting that these structures were likely atypical lymphatic vessels.[122] Evidence shows that mTORC1 signaling in macrophages leads to granuloma formation.[123] Whether these macrophages result in excess production of lymphangiogenic growth factors is unknown. The exact mechanisms driving lymphangiogenesis in sarcoidosis and the contribution of lymphatics to the development of lung granulomas remains unclear.

Key Points

- Lymphatic vessels run along the major airways and the blood vessels. There are very few lymphatics alongside the alveoli in the normal lung.
- Lymphatics are important for fluid homeostasis, macromolecule drainage including hyaluronan, and immune cell trafficking.
- Lymphatic endothelial cells can be identified using a panel of markers, including podoplanin, VEGFR3, and CCL21. Specificity and sensitivity depends on animal species and organ location.
- A functioning lung lymphatic system is essential for proper lung development and for the first breath at birth.
- Lymphatic changes have been observed in almost every lung disease including asthma, COPD, and interstitial lung disease.
- The exact contribution of the lymphatic system to lung disease pathogenesis remains unclear. However, dysfunctional lymphatics are sufficient for the development of air space enlargement mimicking emphysema, blocking lymphatic vessels results in airway edema, and stimulating lymphatic vessel formation leads to decreased transplant rejection.

Key Readings

Alitalo K. The lymphatic vasculature in disease. *Nat Med*. 2011;17(11):1371–1380.

Baluk P, Tammela T, Ator E, et al. Pathogenesis of persistent lymphatic vessel hyperplasia in chronic airway inflammation. *J Clin Invest*. 2005;115(2):247–257.

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8 REGENERATION AND REPAIR

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INTRODUCTION

The pathobiology of many pulmonary diseases involves injury to the lung, followed by delayed, incomplete, or dysfunctional repair. Injury can be viewed at different levels, including at the level of the whole organ or of individual cells or molecules. Repair can be also be viewed at many levels, including restoration of the function of an injured organ (e.g., improvement in the gas exchange function of the lung), of cells (e.g., replacement of terminally injured cells or repair of defects in plasma membranes), or of molecules (e.g., damaged molecules can be degraded in the proteasome and replaced by de novo synthesis). We will emphasize the cellular injury resulting in the dysfunction or death of cells that underlies the pathogenesis of diverse pulmonary diseases. Injury to any of the different cell types residing in the lung can ultimately lead to organ dysfunction (for a review of lung structure, see Chapter 1). A broad concept of lung repair encompasses processes resulting in restoration of the function of the injured lung and in the return to a homeostatic state. This chapter focuses on the cellular and molecular aspects of repair, including replacement of irreversibly damaged cells from endogenous progenitor cells residing in specified niches and restoration of normal cellular function.

The lung is continuously exposed to a diverse array of chemical and biologic agents that are potentially toxic and can cause cellular dysfunction or even death if a threshold is exceeded. The lung frequently undergoes minor damage as a result of viral or bacterial infection or chemical exposures, leading to transient alterations in lung function. *Repair* can be defined as restitution of the cells, and thus the lung, to the preinjury level of structure and function. Normal repair returns the lung to a healthy state capable of responding to subsequent injuries. Aging is manifest by steady and progressive declines in cell number and/or function and decline in overall lung function. The declines are in part due to episodes of recurrent microinjury from environmental toxicants (e.g., pollutants) and decreased capacity of the epithelium or endothelium to heal itself, related to senescence of the lung cells and waning of the ability of the immune system to combat pathogenic microorganisms. Mutations in the genes controlling senescence (e.g., telomerase genes) may impede the ability of lung cells to repair themselves after injury, resulting in prolonged cellular and organ dysfunction. Defective repair leads to episodic decrements in pulmonary function that may ultimately lead to respiratory failure (Fig. 8.1).

LUNG INJURY

LUNG INJURY IN DISEASE PATHOGENESIS

Many pulmonary disorders, such as asthma, COPD, pneumonia, *interstitial lung disease* (ILD), cystic fibrosis, and *acute respiratory distress syndrome* (ARDS), are characterized by cellular injury and faulty repair, resulting in physiologic dysfunction of the lung. The intensity and duration of the insult contribute to the rapidity of onset of symptoms and the chronicity of disease. In ARDS, a severe insult causes widespread lung injury and respiratory failure in hours to days. By contrast, in COPD, years of exposure to the offending agent (usually cigarette smoke in the developed world and smoke from biomass fuels in developing countries) results in slowly progressive loss of respiratory function. Patients with ILD often have a stuttering course with periods of rapidly declining lung function. Dysfunctional repair and "remodeling" contribute to the pathogenesis and clinical course of these and other lung diseases.

The pathogenesis of many lung diseases involves exposure to exogenous toxic agents (e.g., inhaled toxins, allergens, or microbial pathogens) triggering host responses (inflammation or autoimmune responses) that may cause cellular dysfunction or death. In COPD, inhaled toxins, such as those that comprise cigarette smoke, initiate pathologic processes, including inflammation and infection, which culminate in epithelial and endothelial cell death[1–5] and destruction of the scaffolding of the lung.[6] In asthma, allergens, environmental pollutants, pathogens, and the inflammatory response to these agents induce injury to the bronchial epithelium.[7–9] Pulmonary fibrosis/ILD is thought to reflect repetitive injury to the distal lung epithelium interspersed with periods of relative quiescence.[10]

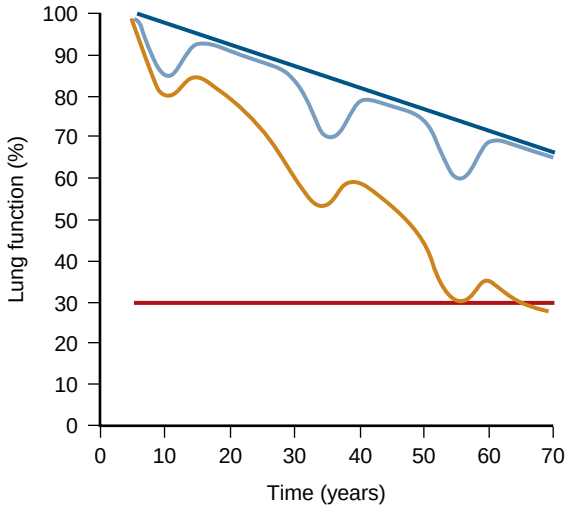

Figure 8.1 Conceptual relationship between lung function and time. Normal aging can be viewed as a process in which steady and progressive declines in cell number and/or function reflect parallel decrements in the capacity of the epithelium or endothelium to heal itself *(straight blue line)*. Acute episodes of injury to the lung and its cellular and structural components, such as viral infection or chemical exposures, result in temporary fluctuations in lung function *(fluctuating blue line)*. Chronic lung disease is associated with a progressive loss of lung function that is exacerbated by environmental exposures. Individuals affected by chronic lung disease may be predisposed to repeated episodes of lung injury and may undergo cycles of injury that result in an accelerated decline in lung function *(orange line)*. Once a hypothetical functional threshold is reached *(red line)*, the lung may no longer have the capacity to repair itself and functionality is irreversibly lost. (Modified from Lazaar AL, Panettieri RA Jr. Is airway remodeling clinically relevant in asthma? *Am J Med.* 115:652–659, 2003.)

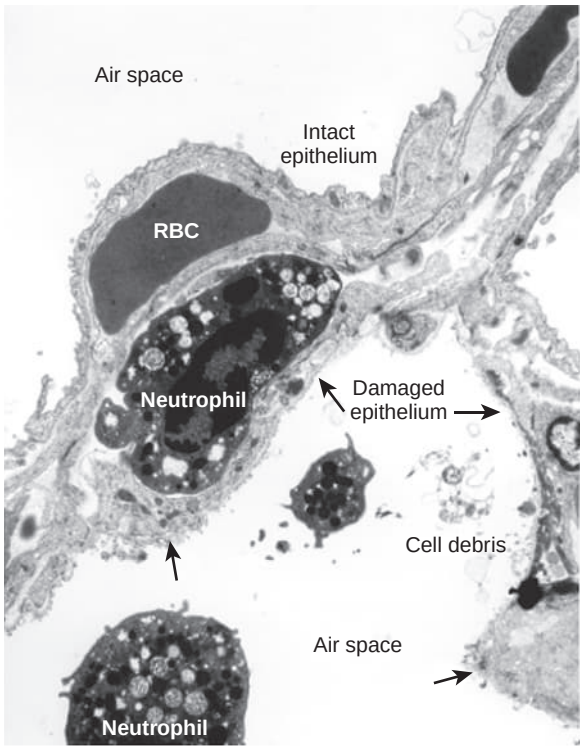

Figure 8.2 Electron micrograph of inflammatory injury in the murine lung. A key contributor to lung injury, from either the vascular or epithelial surface, is the inflammatory process, including the effects of inflammatory mediators and the accumulation and activation of inflammatory cells. This electron micrograph depicts damage to endothelial and alveolar epithelial cells *(arrows)* accompanying sequestration and activation of neutrophils in an acute inflammatory response. The process is usually associated with increased vascular and alveolar permeability, sometimes with sufficient damage to the alveolar wall to result in coagulation (fibrin) and erythrocyte accumulation in the air spaces. RBC, red blood cell.

FACTORS MEDIATING ACUTE EPITHELIAL AND ENDOTHELIAL CELL INJURY

To illustrate the processes involved in lung injury, we will focus on the clinical problem of ARDS, a process that involves inflammatory injury to the lung. An extensive review of the causes, pathogenesis, clinical manifestations, and treatment of ARDS is included in Chapter 134. ARDS is a heterogeneous syndrome rather than a single disease, and predisposing causes include pneumonia, sepsis, inhalational injury, aspiration, injurious (high tidal volume) mechanical ventilation, pancreatitis, trauma, and blood transfusion.[11]

Epithelial and endothelial cells form selective barriers separating the vascular and air space compartments in the lung; the respiratory epithelium also provides a barrier from the environment. This barrier function depends on the presence of an intact layer of viable cells and the intercellular junctions that link adjacent cells, thus restricting the movement of fluid, ions, and macromolecules. In the healthy lung, the epithelium, due to its tight intercellular junctions, prevents fluid from leaking into the alveolar spaces. In addition, there is active removal of fluid, ions, and protein from the alveolar space via the action of channels, ionic pumps, and transporters in the epithelial cells. In ARDS, compromise of the endothelial and/or epithelial barriers, either via disruption of intercellular junctions or via death and sloughing of cells, results in an increase in lung permeability and the influx of protein-rich edema fluid,[12,13] which leads to refractory hypoxemia and bilateral opacities on chest radiographs.[14–17] Impaired fluid, ion, and protein transport[18,19] and decreased surfactant production and function[20,21] further contribute to the impaired lung compliance and gas exchange abnormalities.

In ARDS, structural and functional epithelial and endothelial injury is largely attributable to excessive and dysregulated inflammation[16,22] (Fig. 8.2; see also Chapter 134). During pneumonia, the most common cause of ARDS, microbial products are recognized by resident lung cells, which in turn secrete chemoattractants that recruit inflammatory cells, initially neutrophils, into the lungs.[23–27] During immune surveillance or a normal immune response, neutrophils ingest (phagocytose) microorganisms and release potent antimicrobial compounds, including oxidants, proteinases, and cationic peptides into the phagosome.[28] Thus neutrophil influx into the lungs under most circumstances does not result in tissue injury.[29,30] However, during excessive and dysregulated inflammation in ARDS, large numbers of activated neutrophils release these microbicidal compounds into the extracellular space, causing tissue injury.[31–33] For example, neutrophil elastase, although inherently antimicrobial and critical for host defense,[34,35] can also cause injury to the extracellular matrix in COPD[36,37] and also to the alveolar capillary membrane in ARDS.[38–45] Of importance, neutrophil elastase can cause both a disruption of intercellular junctions[46,47] and death of endothelial[48–50] and epithelial[51,52] cells. ARDS patients have elevated levels of elastase in the bronchoalveolar

lavage fluid and plasma, and these levels correlate with the severity of lung injury.[53–56] Unfortunately, pharmacologic agents that inhibit neutrophil elastase have not proven to be effective in the treatment of ARDS.[57,58] In addition to neutrophil elastase, other serine proteases—*matrix metalloproteinases* (MMPs) and cysteine proteinases—are released by inflammatory cells and contribute to tissue destruction during lung injury.[38] Increased levels of MMPs, derived from both neutrophils and macrophages, are present in patients with ARDS[59–63] and contribute to lung injury.[64–69] The mechanisms by which MMPs cause lung injury have not been fully elucidated. MMPs are able to degrade junctional proteins in both epithelia[70–72] and endothelia[73,74] and induce cell death,[72] although the latter is dependent on the cell type and the specific MMP. Conversely, some MMPs promote survival of the lung epithelium,[75] and others may attenuate injury[76] or even promote repair.[77,78]

In addition to proteinases and antimicrobial peptides such as defensins,[79–86] oxidants, including reactive oxygen and nitrogen species, are released by inflammatory cells during ARDS[87–89] and contribute to tissue injury,[90–98] including epithelial[99–107] and endothelial[108,109] cell death and disruption of tight junctions.[110–112] Although the lung possesses potent endogenous antioxidant mechanisms, which serve to limit injury,[113–121] in ARDS these mechanisms are overwhelmed by the large amount of reactive oxygen and nitrogen species generated. In addition, oxidants can potentiate proteinase-induced lung injury, in part by inactivating antiproteinases.[122] Finally, oxidized phospholipids[98] and another antimicrobial weapon, neutrophil extracellular traps, can cause epithelial and endothelial injury.[123–126]

Although neutrophils and their mediators cause much of the early injury to the alveolar capillary membrane,[31,127–129] they are not the only perpetrators of lung injury, because ARDS can develop even in neutropenic patients.[130] Recruitment of monocytes to the lungs follows the initial neutrophilic response in ARDS.[131] Recruited monocytes gradually acquire the phenotype of macrophages and secrete proinflammatory mediators, including cytokines, chemokines, and lipids, that propagate the inflammatory response. Recruited macrophages also release endogenous toxic and proapoptotic mediators, including reactive oxygen and nitrogen species,[132,133] MMPs,[62,67,68,134] *tumor necrosis factor-α* (TNF-α),[135] vascular endothelial growth factor,[136] *TNF-related apoptosis-inducing ligand* (TRAIL),[135,137] and interferon-β,[138] which may enhance host defense but also induce tissue injury.[139,140] In addition, macrophages also play a critical role in both tissue repair[141–143] and the resolution of inflammation[144,145] (also see later). The role of macrophages in lung inflammation, injury, and repair is further reviewed in Chapter 15. In addition to neutrophils and macrophages, platelets (mostly observed as neutrophil-platelet aggregates) have recently been identified as crucial drivers of the increase in vascular permeability.[146,147] Furthermore, free hemoglobin from red blood cells,[148] angiopoietin-2 released from the pulmonary endothelium,[149] coagulation factors,[150,151] products of infectious agents that directly injure lung cells,[152] inhaled toxins,[153] oxygen,[154] and mechanical forces[155,156] can all contribute to injury to the alveolar capillary membrane. Indeed, a diverse array of mechanisms, mediators, and signaling pathways has been implicated in lung injury.[11,63,157–165] Because the spectrum of injurious agents in ARDS is so broad, and their effects can be modified by preexisting lung disorders and genetic predispositions (Fig. 8.3), it is not surprising that pharmacologic strategies to block a single pathway or class of mediators have been ineffective.

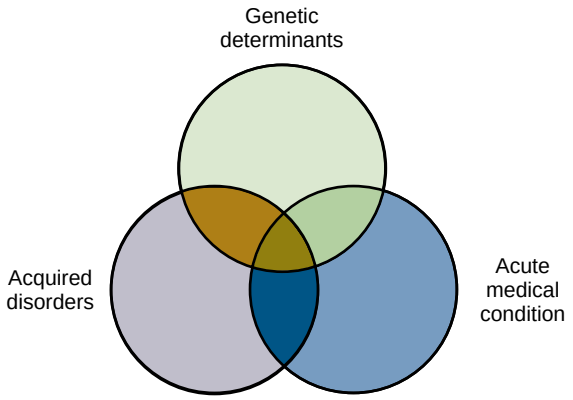

Figure 8.3 Acute lung injury: clinical risk factors. Based on the results of several epidemiologic studies published over the last 2 decades, a variety of factors have been identified that can alter the susceptibility of an individual patient to the development of acute lung injury. These factors can be separated into three general categories: genetic determinants, preexisting acquired disorders, and the acute medical condition. The identification of such patient-specific characteristics could significantly improve both our understanding of the pathogenesis of acute lung injury and our ability to care for these critically ill patients.

HISTOPATHOLOGY AND MECHANISMS THAT CONSTITUTE ALVEOLAR CELL INJURY

Having reviewed the pathogenic agents that induce lung injury, we will now focus on exploring what constitutes lung injury. As mentioned earlier, we define injury as cellular dysfunction or death. Although cellular dysfunction in ARDS includes impaired production of surfactant,[166] which is essential for lung compliance and important in host defense,[167] we focus on the cellular dysfunction and death that contribute to increased lung permeability. In inflammatory lung injury, this includes (1) disruption of intercellular junctions responsible for maintaining the barrier function of the endothelium and epithelium and (2) impaired active ion and fluid transport responsible for fluid reabsorption and maintenance of dry air spaces. Although transient opening and closing of intercellular junctions is necessary for the transmigration of immune cells during immune surveillance or a normal immune response[168] and can take place without compromising barrier function,[30] during ARDS, intercellular junctions of the endothelium[110,169–172] and epithelium[46,112] are disrupted, resulting in enhanced paracellular permeability, which contributes to the flooding of the alveolar spaces with edema fluid. This alveolar flooding is exacerbated by impaired function of the epithelial Na^+/K^+ pumps and epithelial sodium channels responsible for fluid reabsorption.[137,173–179] It should be noted, however, that attempts at stimulating fluid clearance with β-agonists did not improve outcomes in ARDS.[180]

In addition to the disruption of intercellular junctions, severe lung injury in ARDS and other lung diseases[3,181–183] is characterized by cell death. In ARDS, inflammatory

mediators induce death of endothelial cells[184] and *type 1 alveolar epithelial* (AT1) cells, leaving surviving *type 2 alveolar epithelial* (AT2) cells, which are more, but not fully, resistant to injury, for repopulating a largely denuded basement membrane.[13,185–188] This dramatic injury to the alveolar epithelium, together with hyaline membrane formation, protein-rich edema, and hemorrhage, engendered the pathologic term *diffuse alveolar damage* (DAD),[189] which describes the histologic appearance of lungs from patients who died of ARDS. More recent evidence revealed that DAD was only found in some patients with the clinical diagnosis of ARDS, and the pathologic findings were relatively heterogeneous.[190] A study that analyzed postmortem samples reported that 45% of patients who were diagnosed with ARDS according to the Berlin definition revealed DAD, whereas 55% showed an inflammatory pattern consistent with acute pneumonia, and the frequency of the DAD pattern declined in the decade after lung protective ventilation was implemented, suggesting a substantial contribution of ventilator-induced injurious mechanical forces to the DAD pattern.[11,191]

Endothelial Damage

Even in severe DAD, in contrast to epithelial cells, alveolar endothelial cells are often morphologically preserved and, although the endothelial lining remains continuous, there is significant impairment of endothelial function rather than frank cell death and denudation. Homophilic vascular endothelial cadherin bonds between adjacent endothelial cells are crucial for maintaining lung microvascular integrity; loss of these bonds results in functional impairment of the endothelial barrier and increased alveolar-capillary permeability.[11,192]

Epithelial Damage

The extent of epithelial cell loss determines the severity of ARDS. The loss of endothelial and epithelial cells can result from necrotic cell death or programmed cell death, the latter termed *apoptosis*. Originally a morphologic definition, apoptosis might best be defined on the basis of nuclear condensation and characteristic DNA fragmentation and other morphologic alterations; biochemically, it is based on its induction mechanisms and requirement for the action of a series of intracellular proteases termed caspases.[193,194] There are two major pathways leading to apoptosis: the intrinsic pathway, involving signaling from the mitochondria, and the extrinsic pathway, deriving from signals generated from external stimulation of "death" receptors. Mitochondrial regulation of alveolar epithelial apoptosis may be induced by p53[195] or by the proapoptotic Bcl-2 family members BAX or BAK.[99,196] In the extrinsic pathway, death receptors of the TNF receptor family, such as Fas, mediate apoptosis. In animal models of lung injury, Fas[197] and TRAIL[135] induce epithelial cell apoptosis, and inhibition of apoptosis improves survival.[198,199] Apoptotic epithelial cells are engulfed by both professional phagocytes (macrophages) and other epithelial cells.[200,201] Both Fas and Fas ligand levels are elevated in the edema fluid of ARDS patients, induce epithelial cell apoptosis in a manner dependent on their modulation by oxidants and proteases, and predict worse clinical outcomes.[202–204]

In ARDS, cells can also die by necroptosis (programmed cell death leading to necrosis), or direct necrosis, a form of cell death that does not require active participation of cellular processes and generally leads to disruption of the cell membrane with subsequent release of cellular contents that may be additionally injurious. Causes of epithelial necrosis in ARDS include physical effects of acid from inspiration of stomach contents, inhalation of toxic materials or fumes, infection with lytic viruses or bacterial products, hyperoxia,[205] mechanical disruption of cell membranes during mechanical ventilation, and other effects. In summary, cell death is a major mechanism of lung injury, resulting in epithelial denudation and contributing to increased lung permeability and the massive influx of edema fluid into the alveolar space, despite the existence of endogenous protective mechanisms.

LUNG REGENERATION AND REPAIR

The ability of the lung to withstand considerable damage and repair itself enables recovery and survival from a variety of noxious stimuli, independent of containment of pathogens by host defense systems.[206] We define repair broadly as *processes by which the function of the injured lung is restored to normal*. Repair of the lung after acute injury requires coordinated processes to reconstitute the endothelial and epithelial barriers, clear edema fluid,[207–212] and resolve inflammation.[213] In the case of ARDS, survival depends on repair of the injured lung, although some survivors do not completely regain normal lung function.[214]

RESOLUTION OF INFLAMMATION

Inflammation resolution and tissue repair are processes that usually happen in parallel and are closely interrelated: The inflammatory response must resolve to halt ongoing injury to the lung and, vice versa, persistent cell damage will trigger ongoing inflammation due to presence of danger-associated molecular patterns from dead cells and matrix components.

Neutrophils undergo apoptosis as a noninflammatory, nonimmunogenic form of cell death, during which they retain and sequester toxic mediators within their plasma membrane. This is in contrast to a necrotic neutrophil death, in which neutrophils disintegrate and release their intracellular constituents, including toxic and proinflammatory mediators, resulting in prolongation of the inflammatory response. Apoptotic neutrophils are engulfed by macrophages in a phagocytic process termed *efferocytosis* without release of toxic intracellular contents.[144,145] Efferocytosis depends on the recognition by a variety of receptors of "eat me" signals, including phosphatidylserine[215] and calreticulin,[216] displayed on the apoptotic cell surface.[217,218] This is followed by activation of Rho *guanosine triphosphatases* (GTPases), leading to engulfment, which is regulated by the mitochondrial membrane protein Ucp2,[219] as well as high mobility group box-1[220] and urokinase-type plasminogen activator.[221] Efferocytosis results in the release of anti-inflammatory mediators that further promote the resolution of inflammation.[222] In particular, efferocytosis induces an anti-inflammatory, previously termed *M2*, or

alternatively activated phenotype of macrophages that will trigger further resolution and repair processes.[223] Apoptotic neutrophils can also be efferocytosed by myeloid-derived suppressor cells in an *interleukin-10* (IL-10)-dependent manner.[224] Whereas clearance of apoptotic neutrophils is usually highly efficient, yielding a low number of observable apoptotic cells at any given time,[225] if defective or overloaded, apoptotic neutrophils can undergo secondary necrosis or postapoptotic cytolysis.[226] Thus impaired neutrophil apoptosis and efferocytosis prolongs the duration of the inflammatory response, resulting in a chronic inflammatory state.[227] Lipid mediators such as resolvins promote the resolution of inflammation by enhancing neutrophil apoptosis[228] and efferocytosis,[229–231] as well as through other mechanisms.[232–236] In addition to neutrophils, recruited inflammatory macrophages may also be cleared during the resolution of lung injury,[237] or they may replace alveolar macrophages lost during the inflammatory process to regenerate the local tissue-resident pool.[238] Anti-inflammatory, tissue-reparative subsets of T cells (*T regulatory cells* [T_{Regs}]) are additional important cellular players in lung injury resolution, involving *transforming growth factor-β* (TGF-β) and IL-10.[239]

RESORPTION OF EDEMA FLUID

The primary force driving fluid reabsorption from the alveolar space into the interstitium and the pulmonary circulation is active Na^+ transport. Sodium is taken up on the apical surface of the alveolar epithelium by amiloride-sensitive and -insensitive Na^+ channels and is subsequently pumped out of the cell by the *Na^+,K^+-adenosine triphosphatase* (Na^+,K^+-ATPase) on the basolateral side. This process generates an osmotic gradient, which drives passive movement of water from the apical side of the epithelium (the alveolar space) to the basolateral side (the interstitium), mainly paracellularly. Fluid reabsorption requires a widely intact alveolar epithelium and resolution of inflammation.[240] Excess alveolar protein, a hallmark of ARDS, is cleared by active albumin transport via a glycoprotein called megalin.[241–243]

ENDOTHELIAL REPAIR

Given that endothelial cell injury involves disruption of intercellular junctions and, to a lesser extent, cell death, endothelial repair mainly requires reassembly of these junctions. Primary barrier-stabilizing and reparative mechanisms involve adrenomedullin, angiopoietin-1, and sphingosine-1-phosphate, the latter released from activated platelets to stimulate reassembly of endothelial intercellular junctions via Rho- and Rac-dependent cytoskeletal rearrangement.[244–248] This process is dependent on $\alpha_v\beta_3$ integrin.[249] In addition, Slit/Robo stabilizes the endothelial adherens junctions by promoting p120-catenin/E-cadherin association,[250,251] and Rho GTPases stabilize the actin cytoskeleton, thereby enhancing endothelial barrier integrity.[252]

EPITHELIAL REPAIR

The following sections describe basic principles in lung epithelial repair and provide an overview on the current view of epithelial stem cell hierarchies, stem/progenitor cells involved in lung epithelial repair, and the cellular crosstalk and molecular mechanisms involved. To illustrate the underlying basic mechanisms, we will first focus on re-epithelialization of the denuded epithelium by general mechanisms of cell spreading and migration, cell proliferation, and junctional (re)sealing. Re-epithelialization of airways or of the denuded alveolar basement membrane involves different subsets of stem cells, including basal cells, specialized club/secretory cells, and alveolar progenitors, such as specialized AT2 cells, the "defender of the alveolus."[253] Alveolar repair involves AT2 cell proliferation and differentiation into AT1 cells to restore a normal alveolar epithelium. Of note, if the injury is extensive, *bronchioalveolar stem cells* (BASCs) migrate and proliferate to repopulate the injured alveolus (Fig. 8.4; Video 8.1). If these stem/progenitor cell niches are depleted due to extensive injuries, further stem cell niches might be recruited for repair; however, such responses frequently result in aberrant remodeling processes with nonresolving injury or tissue fibrosis. Epithelial injury and repair promotes the activation of resident fibroblast subsets,[254,255] which, although important for physiologic wound repair, can result in fibrotic lung disease. Each of these phenomena is discussed in more detail later.

Basic Principles in Epithelial Repair: Cell Spreading and Migration, Cell Proliferation, and Junctional Resealing

Repair of the epithelium is crucial for clinical recovery, including reestablishment of AT1 cells and resolution of alveolar edema fluid. AT1 cells are flat cells that normally cover the majority of the gas exchange surface and exhibit active ion and fluid transport properties, whereas AT2 cells are cuboidal and synthesize surfactants to prevent the alveoli from collapsing.[256,257] After death of AT1 cells, surviving AT2 cells supposedly spread and migrate onto the denuded basement membrane as an immediate process to reestablish the cellular barrier. Although this has not been directly observed in the lung in vivo, cell spreading and migration is likely to be the initial mechanism for resealing the leaky epithelium[189] based on in vitro observations[258–260] and on the importance of these phenomena in wound repair of other organs.[261] Cell migration depends on a tightly regulated assembly of the cytoskeleton leading to protrusion of "lamellipodia" and "filopodia" from the leading edge, followed by contractile forces that drive release of the rear edge from the extracellular matrix, processes that depend on the Rho GTPases.[262,263] In the lung epithelium, cell spreading and migration after injury are triggered by soluble factors such as *keratinocyte growth factor* (KGF), also known as *fibroblast growth factor 7* (FGF7),[260] TGF-α,[259] TGF-β,[264] *interleukin-1β* (IL-1β),[265,266] and CXC motif chemokine 3.[267] Cell migration is controlled by signaling pathways involving Rac1/Tiam1,[268] *phosphatase and tensin homolog* (PTEN),[269] β-catenin,[270–273] syndecan-1,[274,275] *adenosine triphosphate* (ATP) and dual oxidase 1,[276,277] and vimentin,[264] as reviewed elsewhere.[278] Integrins, which are up-regulated in the alveolar epithelium after injury,[279] contribute to cell migration via interactions with both the actin cytoskeleton[280] and the *extracellular matrix* (ECM).[258,281–283] The production of ECM and MMPs is essential for cell migration.[141,275] MMPs enhance wound healing by cleavage of

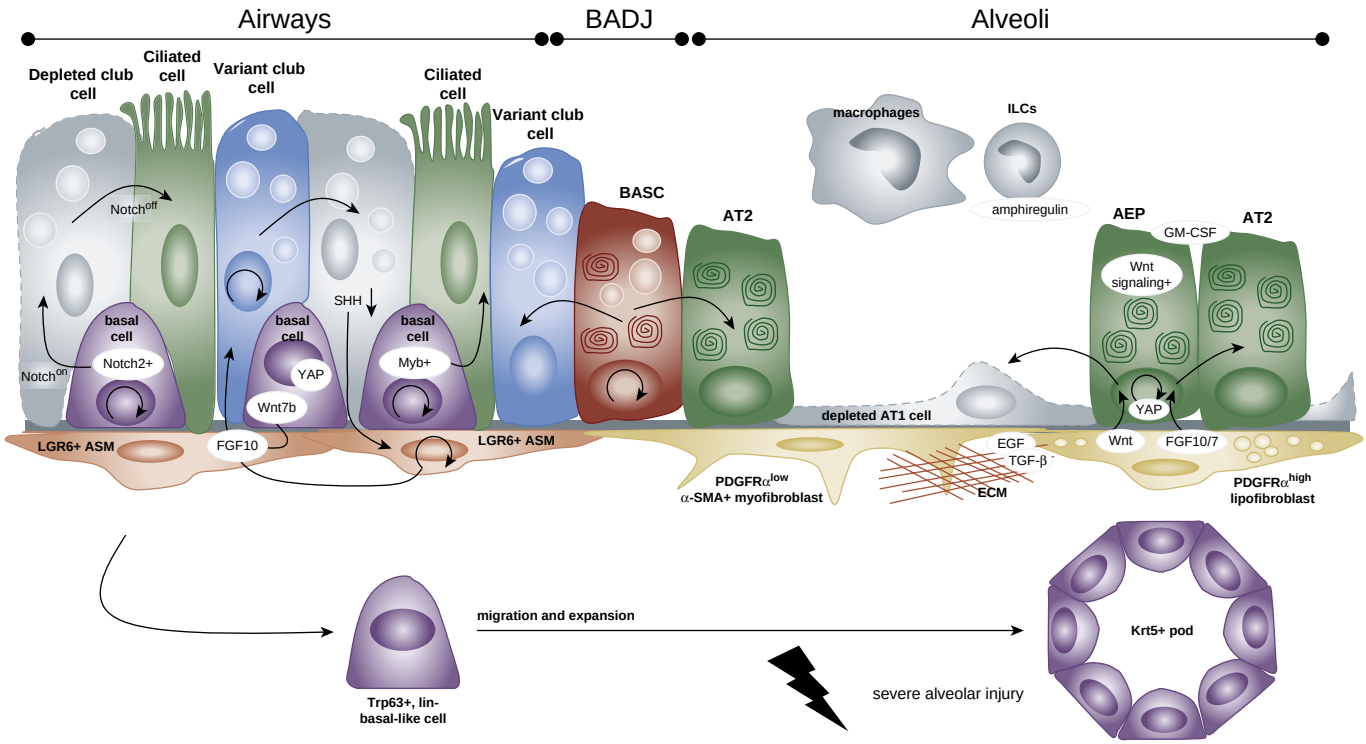

Figure 8.4 Cell types and signaling pathways involved in airway, bronchioalveolar duct, and alveolar epithelial cell repair. In response to ***airway injury***, Notch 2–expressing basal cells give rise to club/secretory cells and Myb-expressing basal cells give rise to ciliated cells. Loss of *sonic hedgehog* (SHH) signaling between the airway epithelium and *airway smooth muscle* (ASM) induces ASM cell proliferation as part of the wound healing response. Upon selected loss of secretory/club cells, remaining "variant club/secretory cells" proliferate and repopulate the lost secretory/club cells. Airway injury causes YAP-mediated epithelial Wnt7b expression, which promotes FGF10 expression in the nearby niche ASM cells, in turn stimulating secretory/club cell proliferation and differentiation. In response to ***alveolar injury***, the Wnt-responsive, bipotent *alveolar epithelial progenitor* (AEP) subset of *type 2 alveolar epithelial cells* (AT2) proliferates and differentiates into *type 1 alveolar epithelial cells* (AT1) and AT2 cells, responses driven by YAP/TAZ and the release of Wnt ligands and FGFs, respectively, from lipofibroblast niche cells. Myofibroblasts are activated to secrete ECM during wound healing. Additional growth factors are released from the matrix (e.g., EGF, TGF-β), by the inflamed AT2 cell pool (e.g., GM-CSF), and by immune cells such as macrophages, *innate lymphocyte cells* (ILC; amphiregulin) and T regulatory cells (TGF-β), and contribute to wound healing. CCSP + SFTPC + BASC residing at the *bronchoalveolar duct junctions* (BADJ) proliferate upon airway and alveolar injury and give rise to both differentiated airway and AT2 cells.[319] Very severe alveolar injury with substantial depletion of endogenous stem cells and facultative progenitors (e.g., after influenza virus infection) can result in a dysplastic (keratinization) wound healing response with generation of abnormal cell clusters ("pods") from basal-like, Trp63+ lineage-negative cells that maintains the tissue barrier but does not result in reestablishment of functional alveolar epithelium. *Arrows* indicate differentiation into or action upon; *circular arrows* indicate proliferation. *Dashed lines* indicate dead cells to be replaced. BASC, bronchioalveolar stem cell; CCSP, club cell secretory protein; ECM, extracellular matrix; EGF, epidermal growth factor; FGF, fibroblast growth factor; GM-CSF, granulocyte-macrophage colony stimulating factor; lin-, lineage negative; Krt5, keratin 5; PDGFRα, platelet-derived growth factor receptor α; SFTPC, surfactant protein C; SMA, smooth muscle actin; TGF, transforming growth factor; Trp63, transformation-related protein 63; YAP, Hippo–yes-associated protein. (Modified from Zepp JA, Morrisey EE. Cellular crosstalk in the development and regeneration of the respiratory system. *Nat Rev Mol Cell Biol.* 2019;20:551–566.)

cell-cell and cell-ECM adhesion molecules, proteolytic activation of chemokines and growth factors, and degradation of the provisional matrix.[142] Of note, cyclic stretch, imposed by mechanical ventilation during the acute and the recovery phase in ARDS, impedes cytoskeletal reorganization during cell spreading.[284]

In addition to cell spreading and migration, the denuded epithelial basement membrane is repopulated through the proliferation of surviving AT2 cells with progenitor cell potential (outlined in more detail later), which accounts for the epithelial cell hyperplasia observed on histologic samples from ARDS patients.[13,188,253,285] In animal models, significant acute lung injury resulting in cell death triggers alveolar epithelial cell proliferation.[286] Factors that promote AT2 cell proliferation after injury include the growth factors KGF, FGF10, *hepatocyte growth factor* (HGF), and *epidermal growth factor* (EGF).[287–294] In animal models of lung injury, exogenous administration of KGF resulted in decreased mortality,[295] although the protective role of KGF may in part be attributable to enhanced epithelial cell survival.[296] Of note, a recently completed phase II trial revealed no improvement when KGF was administered to ARDS patients.[297] Other factors and pathways implicated in AT2 cell proliferation after injury include *granulocyte-macrophage colony stimulating factor* (GM-CSF),[298,299] which is also protective against injury in animal models,[300–302] β-catenin signaling,[303,304] Hippo–*yes-associated protein* (YAP)/*transcriptional coactivator with PDZ-binding motif* (TAZ) signaling,[305] macrophage migration inhibitory factor,[306] and the transcription factor FoxM1.[307]

Although the alveolar epithelial junctions seem more resistant to injury than the endothelial junctions,[308] increased epithelial permeability is a prerequisite for the development of air space edema. Conversely, repair of the alveolar epithelium is critically important for the resolution of edema, restoration of critical lung functions, including surfactant production and ion and fluid transport, and ultimately clinical outcomes.[173,309] In the epithelium, KGF,[112] interferon-γ,[310] PTEN,[311] EGF,[211] and the tyrosine kinase c-Met[312] are protective of tight

junctional integrity during lung injury by a mechanism that involves cytoskeletal reorganization and possibly enhanced expression of junctional proteins,[313] including claudin-4.[314,315]

Stem and Progenitor Cells in the Lung

Replenishment of destroyed lung cells is a key element in repair of the injured lung. A *stem cell* is defined as a reparative cell with the capacity for unlimited self-renewal and with the greatest differentiation potential. A *progenitor* cell is defined as an early descendant of stem cells that can differentiate to form one or more kinds of cells but cannot divide and reproduce indefinitely. In addition, a progenitor cell is often more limited than a stem cell in the kinds of cells it can become. Thus the stem and progenitor cells can be distinguished by the capacity to reproduce (unlimited ability of stem cells vs. limited ability of progenitor cells) and the ability to differentiate into any cell of the body (stem cell) compared to relatively few cell types (progenitor cell).

For the stem cell, the attributes of "stemness" are controlled by interaction with the stem cell microenvironment or niche. The niche serves to protect or sequester stem cells from factors that promote their differentiation. Many of the current concepts about the function of stem and progenitor cells in the lung derive from studies of airway epithelial cells. Comparatively less is known regarding the identity of stem cells in the alveolar region, and even less is known about stem and progenitor cells for the diverse lung mesenchymal cell populations. In addition, most of the studies have been performed in murine models, and it is unknown whether similar progenitor cell populations exist in humans.

Stem Cell Division. Stem cell division produces two daughter cells whose fate is determined by interactions with the stem cell niche. *Symmetrical cell division* results in both daughter cells retaining contact with the niche and maintenance of these nascent cells as stem cells. This mechanism, which results in amplification of stem cell number, takes place in tissues with rapid cell turnover, such as the bone marrow and gut. In contrast, *asymmetrical cell division* results in generation of one daughter cell that maintains contact with the niche and is retained as the stem cell. The second daughter cell is the founding cell for the transit-amplifying cell population. Transit-amplifying cells are temporary constituents of the niche. They proliferate repeatedly over a short time period and then withdraw from the cell cycle as they commit to a differentiation pathway. Thus transit-amplifying cells serve to increase cell number and are destined to produce terminally differentiated cells. Within any organ or tissue the majority of cells are terminally differentiated cells. Terminally differentiated cells are postmitotic. In accordance, turnover of the terminally differentiated cell population acts as a stimulus for differentiation of transit-amplifying cells that resupply this population.

Progenitor Cell. As mentioned earlier, the term *progenitor cell* is a collective term used to describe any cell that has the capacity to proliferate and generate daughter cells, whereas the term *stem/progenitor cells* includes all cells with stem and/or progenitor potential. It is commonly used to indicate a cell in the process of cell division or with the potential to enter the cell cycle. The functional distinctions among lung progenitor cells are defined later.

Tissue-Specific Stem Cells. A tissue-specific stem cell is a rare cell type that is undifferentiated and has the potential to repopulate all of the cell types in their resident tissue,[316] as opposed to embryonic or pluripotent stem cells, which can generate any cell in the body. Due to the relatively quiescent state of the pulmonary epithelium, lung stem cells are mainly identified in various studies as cells activated in response to severe cell depletion.

Tracheobronchial tissue-specific stem cells exhibit a low cuboidal to pyramidal morphology and are termed *basal cells* (Trp63/Krt5-positive) and reside within specialized microenvironments located at the submucosal gland duct junction and in intercartilagenous regions of the trachea and bronchial epithelium.[317] In bronchioles and alveoli, additional tissue-specific stem cells include the BASC, the variant secretory/club cell,[318,319] and the *alveolar epithelial progenitor* (AEP) in the alveoli[320,321] (discussed further later).

Facultative Progenitor Cell Pools. A facultative progenitor cell exhibits defined differentiated features in the quiescent state, yet has the capacity to proliferate for maintenance of normal tissue and in response to injury. Facultative progenitor cells exist in two states: quiescent and reparative. In the quiescent state, facultative progenitor cells are nonmitotic and carry out differentiated functions necessary for tissue homeostasis. In response to injury, facultative progenitor cells dedifferentiate, enter the cell cycle, self-renew, and can differentiate into regionally specific differentiated cell types (e.g., ciliated epithelial cells).[322–325] Examples of facultative progenitor cells in the lung include the club cells in the airway and subsets of AT2 cells in the alveolus.[318,326] In contrast to the bone marrow and gut, the lung epithelium is maintained and repaired under most conditions by an abundant, broadly distributed facultative progenitor cell pool.

Stem/Progenitor Cells Involved in Lung Repair

Airway Repair. In contrast to other mucosal surfaces constantly exposed to external stimuli, such as the gut, the cells of the lung airways and alveoli are relatively quiescent, with a low turnover rate under homeostatic conditions. However, upon injury, several stem and progenitor cells and their niche cells (i.e., adjacent cells that communicate directly or via soluble mediators with stem and progenitor cells) are engaged to repopulate the injured area immediately. In the upper and lower airways, basal cells are located in the basal regions of the pseudostratified epithelium and are considered to be stem cells for the pseudostratified epithelial cells (ciliated cells, secretory cells, club cells) under homeostasis and after injury. As opposed to mice, where basal cells are located in the large conducting airways and the trachea, basal cells in humans are found throughout the proximal and distal airways, suggesting a key role in airway epithelial maintenance and repair.[327] In mice, basal cells preferentially give rise to secretory cells rather than ciliated cells, and this fate decision is regulated by Notch signaling. Secretory cells can then transdifferentiate into

ciliated cells upon Notch inhibition.[328,329] However, upon injury, basal cells are capable of immediately generating both secretory and ciliated cells, with Notch 2–expressing basal cells giving rise to secretory cells, and Myb-expressing basal cells giving rise to ciliated cells.[330] Pathways involved in basal cell-mediated airway repair include FGF10-*FGF receptor 2b* (FGFR2b), bone morphogenic protein, p53, and the Hippo-YAP/TAZ pathway.[327] In addition, so-called "variant" secretory or club cells can repopulate secretory airway cells in mouse models in which secretory cells are depleted by naphthalene.[331] Whether these findings translate to humans remains unclear. A related stem cell population, the BASC, is characterized by coexpression of the AT2 cell marker *surfactant protein C* (SFTPC) and the club cell marker *club cell secretory protein* (CCSP) and is located at the bronchioalveolar duct junctions. The BASC is the only cell that can give rise to both airway and alveolar epithelial cells under homeostasis and after injury in mice[319,332] (see Fig. 8.4).

Alveolar Repair. AT1 and AT2 cells represent the two major epithelial cell types lining the alveoli that function as the gas-exchanging respiratory units of the lung. Alveolar epithelial cells are in close contact with underlying capillary endothelial cells and fibroblasts, and bidirectional communication exists between these cell types that is essential for repair of the injured lung.[257,333,334] Until recently, AT1 cells were considered to be fragile and susceptible to cell death in the setting of acute lung injury. By contrast, AT2 cells were considered to be more resistant to injury, and the surviving AT2 cells were thought to function as alveolar facultative stem or progenitor cells that would proliferate and transdifferentiate to AT1 cells, thus repopulating the alveoli. Recent studies have demonstrated the presence of bipotent alveolar progenitors that can give rise to both AT2 and AT1 cells during development,[321] whereas after birth new AT1 cells derive from rare, self-renewing, long-lived, mature AT2 cells. In this regard a population of AEPs[320,321] that rely on Wnt signaling, a crucial pathway regulating cell fate, was recently described that functions as a major facultative progenitor cell in the distal lung.[320]

During acute lung injury, AEPs express autocrine Wnts that recruit and expand the pool of facultative progenitor AT2 cells to repair the gas exchange surface of the lung.[320,327,335,336] TGF-β is a key regulator of AT2 cell expansion: it halts AT2 cell proliferation and is then inactivated to allow differentiation into AT1 cells during the repair process.[337] Additional important growth factors are released by the alveolar epithelium itself (e.g., GM-CSF)[298,299] or by invading and tissue-resident leukocytes (e.g., amphiregulin by *innate lymphocyte cells* [ILC]; TGF-β by T_{Regs}) (see Fig. 8.4).[239,336] An additional source of alveolar cells is the population of BASC located in the bronchioalveolar duct junctions.[319,332] BASC can give rise to the majority of distal lung epithelial cells after damage but only moderately contribute to homeostatic turnover. Of importance, ablation of BASC impairs regeneration of distal lung epithelia, identifying BASC as crucial components of the lung repair machinery, particularly after severe injury involving the bronchiolar and alveolar compartment[319] (see Fig. 8.4). To date it remains unclear whether an equivalent of the murine BASC exists in the human distal lung.

Loss of Regenerative Potential: Depletion of the Facultative Progenitor Cell Pool

Repeated epithelial injury and repair may deplete the mitotic potential of the facultative progenitor cell pool. Depletion of the facultative progenitor cell pool would leave the epithelium deficient in both regenerative and differentiation functions and contribute to epithelial fragility through loss of cellular autocrine/paracrine protective mechanisms, epithelial hypoplasia, and dysregulation of interactions between the epithelial, mesenchymal, and vascular compartments. In addition, specific properties of pulmonary facultative progenitor cells may limit their ability to repair the injured epithelium. For example, the metabolic pathways that allow the club cell to eliminate lipophilic agents also sensitize it to the toxic effects of excessive amounts of these compounds, leading to depletion of the progenitor pool.[338–340] In addition, the phenotypic plasticity essential to the club cell's ability to detect and eliminate pathogens and toxic agents may compromise the reparative functions of this cell type.[341–343] Thus, even though the progenitor cells are more resistant to injury in most settings, they are also particularly fragile to certain stresses or severe injuries.

In patients with acute lung injury and in chronic lung diseases, there are decreased numbers of club cells, as measured by expression of the club cell marker CCSP. Within small airways of those with COPD and asthma, club cells undergo a metaplastic transition to a mucosecretory phenotype,[344] which removes these cells from the progenitor pool. In addition, a reduction in the number of club cells is associated with tissue remodeling characterized by an increase in the number of an alternative progenitor, the basal cell, and consequent squamous metaplasia.[345–347] Furthermore, increased epithelial proliferation in the lungs of smokers suggests an ongoing injury process and the potential for the facultative progenitor cell pool to undergo replicative senescence, characterized by irreversible arrest of cell proliferation and altered cell functions.[348] Senescent cells persist and consequently inhibit activation of the remaining reparative cells by several mechanisms. Thus senescent cells could compromise differentiated functions while also acting to block cell replacement.

Defects in cellular maturation may also contribute to a failure to establish the facultative progenitor cell pool or to the depletion of the facultative progenitor cell pool after injury. The lung undergoes rapid and extensive maturation during the postnatal period. However, the maturation process can be interrupted by preterm birth and associated oxygen treatment, resulting in bronchopulmonary dysplasia, and can be impaired by postnatal exposure to environmental harms, including ozone and side-stream tobacco smoke in term infants.[349–351] These exposures are associated with depressed protective and reparative functions and morphologic and functional alterations to airway and alveolar facultative progenitor cells. These observations suggest that irritant exposure impairs lung maturation, leading to dysregulation of airway reparative processes. These studies support the concept that failure to establish or maintain an appropriately sized pool of facultative progenitor cells during lung development limits the repair

potential after future injury and fosters chronic injury and dysfunctional repair cycles characteristic of chronic lung disease.

Another important aspect to consider is that the extent and severity of lung injury may determine whether the appropriate stem/progenitor cell type repopulates the lung. In a mouse model of severe influenza lung injury, an alveolar epithelial cell expressing $\alpha_6\beta_4$ integrin and basal cell markers, but not prosurfactant protein C, functioned as alternative AEP cells when local facultative progenitors such as AEP cells (and likely the BASC) were depleted.[352,353] This regenerative response was associated with aberrant remodeling and sustained Notch activation. Likewise, in the same model of severe lung injury, cells expressing basal cell makers migrated to alveolar regions in an attempt to repair the alveolar tissue devoid of facultative progenitor cells and resulted in abnormal repair, forming clusters ("pods") with tissue keratinization (see Fig. 8.4).[353–356] Thus the lung is capable of initiating repair even in settings where the primary progenitor cells are destroyed; however, repair by these "back-up" progenitor cells generally does not restore normal lung architecture. Thus significant depletion or changes in function of the facultative progenitor pool may contribute to the complex pathophysiologic alterations characteristic of acute and chronic lung diseases.

The Mesenchymal Niche in Epithelial Repair

The local microenvironment of a stem or progenitor cell (termed *niche*) is crucial in maintaining or activating repair processes in these cells by direct and indirect crosstalk mechanisms between different cell types. Mesenchymal cells play an important role in this niche, both during normal and abnormal repair. As such, the mesenchyme, comprised of populations of fibroblasts embedded within the extracellular matrix in the interstitium of the lung, represents another area important for consideration of normal and abnormal repair. Normal repair depends on epithelial-mesenchymal interactions, including the proliferation of subepithelial fibroblasts with focal deposition of ECM forming new connective (granulation) tissue that serves to fill in the "wound." We are just beginning to understand the functional heterogeneity of mesenchymal lung cells during these processes. In the airways, smooth muscle cells constitute a niche that harbors *leucine-rich repeat-containing G-protein–coupled receptor 6* (LGR6)-positive *airway smooth muscle* (ASM) cells that surround airway epithelia and drive their repair, involving the Wnt-FGF10 and Hippo pathways.[357,358] Loss of sonic hedgehog signaling between the airway epithelium and ASM induces ASM cell proliferation, thus triggering the wound healing response. During alveolar repair, distinct *platelet-derived growth factor receptor*-α (PDGFRα)-positive mesenchymal cell populations have defined roles in development and regeneration. Lipid droplet-containing "lipofibroblasts" are Wnt-responsive, PDGFRα-high cells that release factors such as HGF and FGFs to drive proliferation and differentiation of AEP cells.[294] In addition, the mesenchyme contains a PDGFRα-low, α-smooth muscle actin–positive profibrotic myofibroblast that releases ECM during the repair process and constitutes a source of growth factors[359,360] (see Fig. 8.4). A leucine-rich repeat-containing G-protein–coupled receptor 5–positive alveolar mesenchymal cell was identified that supports alveolar cell proliferation; however, the lineage relation to the previously mentioned mesenchymal cells remains elusive.[357] Repetitive and/or nonresolving injury can result in fibroblast migration, proliferation, and differentiation into myofibroblasts, with deposition of excessive ECM comprised of collagen and other matrix components.[254,255,273,285,361–363] This is observed in idiopathic pulmonary fibrosis[360,364–367] and many other lung diseases, including ARDS,[13,15,368–370] asthma,[7,8] and COPD.[371–373] Although cytokines and growth factors that induce physiologic repair can prevent fibrosis,[271,273,304,374,375] under other circumstances these same factors, such as TGF-β, may actually promote fibrosis,[303,376–378] underscoring the importance of context in lung repair.

Does Lung Repair Recapitulate Mechanisms of Lung Development?

One of the proposed strategies to assist lung repair is to engage the normal pathways of lung development, at which time the entire lung is generated by the integration of developmental programs. Normal lung development involves the integration of numerous signaling pathways, including Wnt/β-catenin, Notch-delta, sonic hedgehog-patched, Hippo-YAP/TAZ, FGF-FGFR, and bone morphogenetic protein/TGF-β pathways.[305,379,380] These pathways interact to direct the appropriate differentiation of the epithelium, mesenchyme, and vasculature during lung development. During lung injury and repair, many of these pathways are reactivated to drive tissue regeneration and resolution of inflammation.[327] It is unclear, however, how these various signaling pathways are integrated during repair and whether they can be therapeutically exploited to drive productive cell replacement without causing aberrant remodeling or malignant proliferation. Key potential differences between lung development and lung repair include the presence of immune cells and other mediators during injury that might interfere with the normal response to developmental signals and the increased age of the lung, which might not respond the same as a developing lung to the same signals. Hence it is not known if the key regulatory pathways that are dominant during development can ultimately be targeted to improve repair in the adult.

Key Points

- The mechanisms of injury involve changes at the cellular and molecular level that initiate structural alterations and lead to compromised lung function. At the tissue and cellular level, exogenous insults and/or inflammatory stimuli result in increased vascular permeability and loss of alveolar epithelial barrier function due to disruption of intercellular junctions and cell death.
- Susceptibility to lung injury is determined by previous exposures, the level of stem/progenitor cells and their depletion after injury, and the individual's genetic constitution. This "gene-environment interaction" is the cornerstone of research initiatives directed at identification of susceptibility genes and those that modify the response to treatment.
- The pathways leading to injury involve so many mediators and cell types that it is not surprising that pharmacologic strategies to block a single pathway or class of mediators have so far been ineffective.
- Lung repair involves restoration of normal cellular composition, lung architecture, barrier function, and gas exchange.
- The inflammatory response must resolve to halt ongoing injury to the lung and allow reparative processes to proceed. Inflammatory cells undergo apoptosis and are cleared by macrophages in a phagocytic process termed *efferocytosis*, and lung edema fluid and protein are actively cleared from the air spaces.
- In response to cellular injury by noxious stimuli, such as infection and toxic compounds, endogenous stem and progenitor cells undergo rapid proliferation and differentiation to repair and regenerate the injured lung. Under normal circumstances, repair of the alveolar epithelium after injury relies on cell spreading, migration, and proliferation of surviving type 2 alveolar cells, followed by differentiation of specified type 2 cell subsets (or common alveolar progenitor cells) into alveolar type 1 cells. More upstream progenitors, such as the bronchioalveolar stem cells, give rise to both bronchiolar and alveolar cells, depending on the type and extent of injury.
- Repetitive epithelial injury or severe depletion of local stem/progenitor cells can lead to aberrant healing involving basal-like cells and to fibroproliferative responses in the airways and parenchyma, processes which are critically important for the pathogenesis of diseases, including pulmonary fibrosis, COPD, and asthma.

Key Readings

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9 GENETICS OF LUNG DISEASE

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INTRODUCTION

Our genome is a complete set of genetic code. Each genome is unique to an individual; on average, any two people will have approximately 4 to 5 million differences among their 3 billion letters of DNA sequence. Genetics is the study of this inherited variation. One of the first steps in investigating genetics of a trait or disease is to determine whether there is, in fact, a genetic contribution. The relative contribution of genetic factors to disease is called heritability. Formally, it is the fraction of variation of a phenotype—broadly defined as an observable characteristic of an individual, such as lung function—that can be attributed to genetic factors. This measure depends on the population studied and the relative contribution of the environment.[1] Although heritability has traditionally been measured using family studies, more recent methods allow estimation of heritability in unrelated individuals. These studies broadly confirm a significant genetic contribution to most traits and diseases.[2,3]

The field of human genetics has experienced tremendous growth over the last few decades. Technological advances in microarrays and in next-generation sequencing have driven the cost of genome-wide genotyping to less than $50 and whole-genome sequencing to less than $1000. In parallel, bioinformatic platforms and statistical methods have advanced to allow the rapid, efficient, and accurate measurement of this human genetic variation and its association to disease. Large epidemiologic efforts, including recruitment of large populations and biobanks, have enabled larger and better phenotyped samples.

The genome encodes all cellular processes, and genetic variants are assigned at birth. This essentially random assignment has the potential to reveal novel and causal mechanisms of disease pathobiology and confirm existing or uncover new targets for therapeutics. Human genetic evidence for a drug target significantly increases the likelihood of success of a drug trial.[4] Genetic variants also have the ability to identify disease subgroups or subtypes.[5] Complex and polygenic diseases may also be amenable to genetic risk prediction. For example, polygenic risk scores developed using *genome-wide association studies* (GWASs) for obesity and cardiovascular disease have been shown to identify subsets of individuals at a similar risk of disease as those who harbor mendelian variants.[6] These persons may be targets for preventive therapy, including specific pharmacologic treatments or lifestyle modification. The progress made in cystic fibrosis, from the discovery of the causal gene to the development of novel and mutation-specific therapies,[7] serves as a model for precision medicine in other diseases.

HUMAN GENETICS

CHARACTERIZATION OF GENETIC VARIATION

Molecular genetics is elegant in its simplicity. Just four base pairs (two purines [adenine and guanine] and two pyrimidines [thymine and cytosine]) code for 20 amino acids that form the molecular building blocks of complex proteins. However, the assemblage of inherited genes (genotypes), control mechanisms, resultant proteins, and posttranslational modifications have the capacity to create a complex panoply of unique biologic, physiologic, or visible traits of an organism called a *phenotype*. The relationship between these rather simple molecular characteristics and the vast array of complex phenotypes is, in part, explained by a number of seminal discoveries. Gregor Mendel[8] was the first to demonstrate that discrete traits could be inherited as separable factors (genes) in a predictable manner. Mendel's laws established the concept that each gene has alternative forms (alleles). Darwin[9] made the observation that evolution represents a series of environmentally responsive "genomic" upgrades. Thomas Morgan[10] established the concept of linkage to discover that genes were

organized (and inherited) on individual chromosomes, and that genetic material was recombined or exchanged between maternal and paternal chromosomes during meiosis and that the frequency of recombination could be used to establish the relative genomic distance between genes. However, it was not until 1944 that Avery, MacLeod, and McCarty, while working with *Pneumococcus,* discovered that DNA was the essential molecule that transmitted the genetic code.[11] The double-helix structure of DNA was discovered by Watson, Crick, Chargaff, Franklin, and Wilkins in 1953[12] and, since then, genetics assumed a central role in understanding the biologic and physiologic differences between and among species and between states of health and states of disease.

LINKAGE DISEQUILIBRIUM

Over the past several decades, genomic maps have evolved from karyotypes (i.e., microscopic images of chromosomes during metaphase) to maps with specific base-pair sequences. Two major breakthroughs at the end of the 20th and beginning of the 21st centuries changed human genetics forever—the sequencing of the human genome[13,14] and the creation of the International HapMap Project to identify the common sequence differences and similarities between individuals.[15] With the sequencing of the human genome, investigators for the first time had a detailed road map of the human genome that identified the genes, regulatory units, and noncoding sequences with a high degree of resolution. Of the 3.2 billion base pairs in the human genome, fewer than 1% uniquely identify each human being.[16] Although there are several types of variation in the human genome (Table 9.1), the most common types of variation are *single nucleotide variants* (SNVs), which result from the substitution of a single base (e.g., A to G). Common SNVs are referred to as *single nucleotide polymorphisms* (SNPs). To date, more than 450 million SNVs and small insertions or deletions (i.e., indels) have been identified in the human genome. These variants provide much of the genetic diversity that underlies the variable susceptibility to disease development and progression.[16] The 1000 Genomes Project[17] and, more recently, the Trans-Omics in Precision Medicine program,[18] have been developed to expand the catalog of uncommon and rare variation among diverse human populations.

Genetic maps are based on the frequency of recombination events, defined as a specific form of exchange of genetic material between the maternal and paternal chromosomes during meiosis. Genes on the same chromosome that are closer together are more likely to be inherited together (i.e., linked) than genes that are farther apart, which may demonstrate more random and independent assortment. In general, the greater the distance is between genes, the higher the recombination frequency (eFig. 9.1A). A *haplotype* (i.e., haploid genotype) is a set of linked, contiguous genetic variants that are inherited together. The Haplotype Map (HapMap) project leveraged this key concept called *linkage disequilibrium* (see eFig. 9.1B). Linkage disequilibrium exists when two markers in close physical proximity are correlated in a population, when they are in association more than would be expected with random assortment. This "blocky" nature of the genome facilitates genetic discovery because instead of having to interrogate and test all variants in the genome, one achieves nearly the same power by testing a smaller set of variants that are correlated with or "tag" other variants.

Table 9.1 Commonly Used DNA Markers

Single nucleotide variant (SNV)—Individual point substitutions of a single nucleotide that do not change the length of the DNA sequence and are present throughout the genome. Common variants are often referred to as single nucleotide polymorphisms.

Indel—Insertion/deletion variant, leading either to inserted or deleted base pairs. When present in coding regions and not a multiple of three, indels can result in frameshift mutations. Usually short (a few base pairs in length, although can be up to 1000 base pairs in length), and together with SNVs, indels make up the majority of cataloged human variation.

Copy number variant (CNV)—A duplication or deletion of a region of a genome that is 1000 to 5 megabases in length.

PUBLIC DATABASES

Online resources are a major source of information about genetics, such as the Online Mendelian Inheritance in Man (https://www.omim.org) and the Human Gene Mutation Database (http://www.hgmd.cf.ac.uk/ac/index.php).[19] Up-to-date genetic sequence, variant, and other annotation information can be obtained from Ensembl (www.ensembl.org). The University of California at Santa Cruz Genome Browser (genome.ucsc.edu), Ensembl and LDLink (https://ldlink.nci.nih.gov/) provide linkage disequilibrium information across a range of populations, whereas the Genome Aggregation Database (gnomAD; gnomad.broadinstitute.org) and BRAVO (https://bravo.sph.umich.edu) provide resources for interrogating variation across large-scale whole-genome sequencing studies. Resources such the GWAS catalog (https://www.ebi.ac.uk/gwas/) store genome-wide association information.

GENETIC EPIDEMIOLOGY

LINKAGE STUDIES

Genetic epidemiology is the study of genetic factors in families and in populations. Historically, identifying disease regions involved linkage. Linkage analyses use family data, which can be made up by a wide range of pedigree structures from extended pedigrees to affected sibling pairs. There are two broad types of linkage analysis: parametric and nonparametric. Both types of linkage analysis rely on the coinheritance of disease alleles with genetic markers used in the analysis. When a mutation arises on a particular chromosome, initially there is a large shared segment of DNA and hence linkage disequilibrium around it. With each subsequent generation, this region of linkage disequilibrium becomes smaller as a result of meiotic recombination. *Parametric* linkage analysis aims to determine if alleles at a genotyped marker segregate together with the alleles at a putative disease locus more often than one would expect by random assortment, or chance. *Nonparametric* linkage analysis refers to a group of analysis methods that, in contrast to parametric linkage analysis, does not require

assumptions about a particular form of inheritance. This nonparametric approach has been combined with genetic association within the linked region to identify disease susceptibility genes for asthma, Crohn disease, and pulmonary fibrosis.[20–25]

ASSOCIATION STUDIES

Association studies that test for the relationship of a marker to a phenotype are not limited to families and can be an order of magnitude more powerful than linkage analyses.[26] Today genetic association studies are the most commonly used study designs to find disease genes in complex traits and can test for quantitative, binary, or other (e.g., survival) outcomes; contain varying degrees of unrelated and related individuals; and use population-based, case-control, or family studies. Genetic association studies are similar to other epidemiologic study designs and involve identifying genetic markers with significant genotype frequency differences between individuals with the phenotype of interest (cases) and a set of unrelated control individuals.[27] One problem with association studies is that, although genetic data are generally less subject to confounding, differences in genetic background between cases and controls can cause spurious results,[28] termed *population stratification*. Genotyping and adjusting for the effects of a set of randomly distributed markers can address this problem.[29–33] A second problem with early case-control studies has been that often the sample size was too small to allow robust evaluation of the evidence for association. Because of the small genetic effect sizes seen and expected for complex traits, sample sizes at least in the thousands are generally required in addition to replication to generate rigorously validated association results. Thus key considerations when evaluating genetic association studies[34] include (1) accounting for population stratification, (2) assessing nonrandom and evolutionary forces on allele frequencies (i.e., Hardy-Weinberg equilibrium), (3) replicating results, and (4) adjusting for multiple comparisons.

Genetic association tests can also include related subjects. Two main types of models can be used. The first type of statistical model incorporates correlation between samples, such as linear mixed models. Advances in statistical methods have led to faster and more convenient implementations[35,36] that can incorporate sample correlation between family members and correlation due to population substructure (i.e., they can be used to adjust for population stratification). The second type of family-based statistical model is based on the transmission disequilibrium test.[37,38] The test is predicated on the assumption that, if a genetic locus is uninvolved (neither linked nor associated) in the phenotype of interest, one would expect each of the two parental alleles at that locus to be transmitted equally to an affected child (i.e., transmitted 50% of the time). However, if the locus is actually linked and associated with disease, there will be overtransmission (or undertransmission) of one allele at that locus, and its transmission will differ significantly from the expected 50%. These types of tests need to recruit both affected individuals and their parents, which often limits diseases studied and sample size but is immune to population stratification and can be used to identify de novo mutations.

GENOME-WIDE ASSOCIATION STUDIES

GWASs have arguably revolutionized the field of complex trait genetics. In GWASs, single nucleotide variants are selected using linkage disequilibrium information from the population to cover the entire genome; approximately 500,000 variants result in greater than 90–95% coverage of common variants. GWAS have well-accepted approaches to the design, data collection, data cleaning, and data analysis required for these large complex studies. These include proper attention to technical artifacts and batch effects,[39,40] population stratification,[28] and statistical significance, usually a P value of less than 5×10^{-8},[41] although more recent studies may require a more stringent cutoff,[42] ideally with replication in a second study. The number of robustly associated genetic loci for complex diseases has increased dramatically since 2000.[43]

Several important lessons have been learned from the GWAS era. Perhaps the most important lesson is that very few of the candidate genes from previously hypothesized genes have been replicated in large GWASs; nearly all the findings are for genes that have not been studied in the disease of interest. A second is the extensive degree of overlap between genetic association findings among different diseases. This setting, in which a genetic variant has many phenotypic effects, is called *pleiotropy*. Pleiotropy can be horizontal, affecting traits in different causal pathways, or vertical, with different traits mediated by the same pathway. Pleiotropy can lead to insights into gene function or prioritize regions for follow-up.[44] Third is the recognition that the heritability of many traits and diseases appears to be accounted for by common variants, with a smaller proportion of heritability due to rare variants.[45,46] However, these findings do not imply that finding rare variants is unimportant, particularly for understanding disease pathobiology.

GENETIC ARCHITECTURE AND RARE VARIANTS

The specific genetic variants responsible for phenotype exist along a spectrum (Fig. 9.1). This relationship can be illustrated by examining the relationship between two factors. The first, *allele frequency*, represents how common a genetic factor or "version" of a gene (allele) is in the population. The second factor is *penetrance*, or the chance that someone who has the risk allele has disease, and corresponds to *effect size*. For decades, the primary application of human genetics focused on disorders due to these high penetrance, rare variants, and rare diseases, also termed *mendelian*. Examples of these types of diseases include cystic fibrosis and Huntington disease.

At the opposite end of this spectrum are complex, or polygenic diseases. In this setting, no single variant leads to disease; instead, many genetic variants each modestly increase risk. A typical variant in this scenario more commonly lies in the 99% of the genome that is noncoding (does not change a protein amino acid) and has a modest odds ratio in the range of 1.1 to 1.4. Due to these small effect sizes, studying these diseases usually relies on large sample sizes.

These two examples represent opposite ends of what is increasingly being recognized as a spectrum. For mendelian diseases, studies have found that some variants

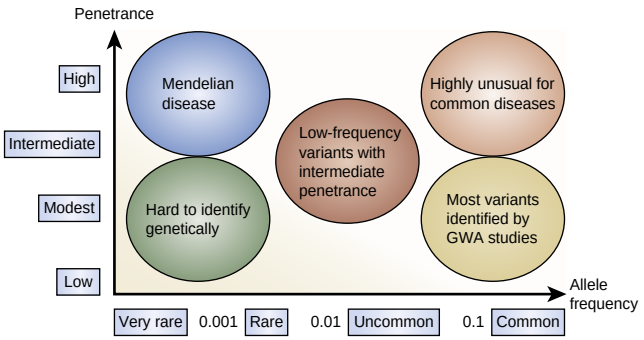

Figure 9.1 The relationship of allele frequency to penetrance. Traditional mendelian diseases harbor very rare genetic variants that have very high penetrance (e.g., large effect sizes); in contrast, most genome-wide association studies identify common variants of weak effect. However, these two contrasting study designs exist on a spectrum, and rare variants can contribute to common disease, whereas common variants can also modify mendelian disease. (From McCarthy MI, Abecasis GR, Cardon LR, et al. Genome-wide association studies for complex traits: consensus, uncertainty and challenges. *Nat Rev Genet.* 2008;9:356–369.)

previously considered fully penetrant do not result in disease,[47] and common genetic variants can also contribute to mendelian disease, as in genetic modifiers of cystic fibrosis.[48] In common diseases, some of the contributing variants are rare coding variants of large effect.[49,50]

Identification of rare variants often requires sequencing. In contrast to genotyping studies—where an individual DNA base pair known to vary in the population is tested—sequencing studies assay all variants in a given region. The advent of *next-generation sequencing* has dropped the cost of sequencing more than a millionfold. This technological advance has led to a revolution in analyzing rare diseases, which formerly required slow and painstaking linkage and mapping. Due to these advances over the past decade,[51] sequencing studies of affected subjects can directly identify the causal gene and variant by screening for very rare, predicted deleterious mutations. Genome centers now routinely perform exome or whole-genome sequencing on patients with rare genetic disorders, with an appreciable rate of success in identifying the likely causal gene.[52]

Sequencing studies are not just limited to very rare diseases. Rare variants can also contribute to the burden of more common diseases. Sequencing studies have identified rare variants in lipid disorders, diabetes, and inflammatory bowel disease.[46,50,53] In pulmonary disease, rare variants are responsible for cases of pulmonary hypertension, allergic diseases, and pulmonary fibrosis, all of which are also due to common variants.[54–57]

Just as there is no true dichotomy between common and rare variant studies, the differences between genotyping and sequencing studies are also less clear. As sequencing studies get larger and more diverse, these data can be used to reconstruct the haplotypes in a population. These population-based "reference panels" allow increasingly accurate genotype *imputation* from genetic microarray data[58] (Fig. 9.2). Imputation refers to a statistical technique of "filling in" variants not covered by genotyping, using sequencing data as a reference. Although imputation is more challenging for rare than for common variants, with the most recent large imputation panels, some rare variants, for example, *BRCA1*, can also be imputed.[18] The decision to perform more economical but less accurate genotyping and imputation, versus more expensive but comprehensive sequencing, depends on the disease and types of analysis to be done. For most complex polygenic diseases, most genetic associations will be identified through genotyping with imputation.[45]

GENE BY ENVIRONMENT INTERACTION

Because both genes and environmental exposures are known to be related to complex traits, performing studies to test both factors in one study design is of great value. The two major challenges for these studies are statistical power and accurate measurement of exposure. Tests for gene-environment interaction require larger sample sizes than tests for the genetic effect alone. Alternative approaches may address some of these limitations. For example, a gene by environment interaction study on lung function and smoking did not find convincing evidence of interaction, but a study using genetic variants in aggregate did find an association.[59,60] Although some environmental factors, such as diet, are hard to measure accurately and require complex techniques, other exposures, such as lifetime cigarette smoking, can be measured with relatively high precision. Accurate and consistent measures of exposure will greatly enhance the ability of these studies to provide new insights into disease pathogenesis.

EPIGENETICS

Epigenetics is the study of changes in gene transcription that are dependent on the molecules that bind to DNA, rather than on the base-pair sequence of DNA.[61,62] This includes both heritable changes in gene expression in the progeny of cells or of individuals and stable, long-term alterations in the transcriptional potential of a cell or tissue that are not necessarily heritable. Because epigenetic processes are highly interdependent and regulate gene expression in an age-, state-, cell-, and tissue-dependent manner, collectively these mechanisms constitute a complex system of molecular controls that affects biologic processes and human diseases.

Although our understanding of the fundamental mechanisms of epigenetics continues to evolve, it is recognized that epigenetic regulation of the genome results in a hierarchy of transcriptional switches that facilitate development and differentiation, normal tissue function, and the ability of the host to respond to stress.[61,62] There are three primary mechanisms that govern gene expression—DNA methylation, histone modifications, and noncoding RNAs—that may be inherited, independent of the sequence of DNA (Table 9.2 and eFig. 9.2). Hypermethylation of cytosine-guanosine motifs, particularly at promoter and enhancer sites, silences gene transcription. Conversely, hypomethylation of these motifs enhances gene transcription. Histones, the building blocks of nucleosomes, undergo numerous posttranslational modifications (methylation, acetylation, or phosphorylation with more than 100 conserved, covalent modifications) that affect chromatin structure and alter gene expression. Noncoding RNAs bind to DNA and interfere with transcription and posttranscriptional regulation

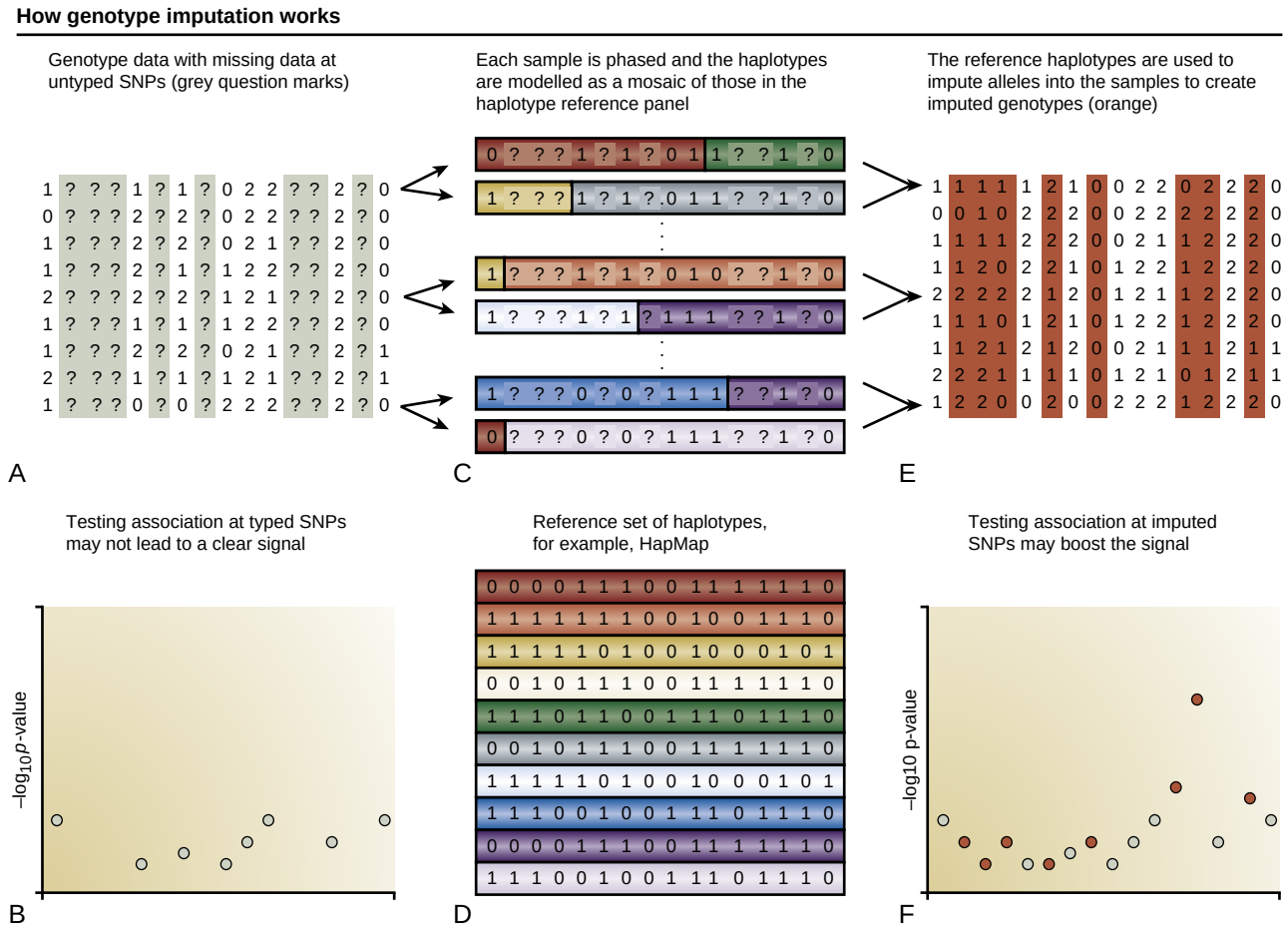

Figure 9.2 The process of genotype imputation. Genotype imputation is a technique by which a reference panel with detailed genetic variation information from a sequencing-based study is used to provide additional information for a study using genotyping arrays. This method increases power of genome-wide association studies and blurs the distinction between rare variant, sequencing-based studies and genome-wide association studies. (A) Genotyping arrays only cover a select set of single nucleotide polymorphisms. (B) Association testing may not show a signal. By computational approaches to phase the data (C) and matching to a reference set (D), these missing values can be filled in (E), leading to a new signal (F). (From Marchini J, Howie B. Genotype imputation for genome-wide association studies. *Nat Rev Genet.* 2010;11:499–511.)

Table 9.2 Known Epigenetic Mechanisms

DNA methylation—The methyl group is transferred from *S*-adenosylmethionine to the C-5 position of cytosine by a cytosine-methyltransferase. Hypermethylation of CpG motifs, particularly at promoter and enhancer sites, silences gene transcription. Alternatively, hypomethylation of these motifs enhances gene transcription.
Histone modification—Histones, the building blocks of nucleosomes, undergo numerous posttranslational modifications (methylation, acetylation, or phosphorylation with >100 conserved, covalent modifications) that regulate chromatin structure and gene expression.
Noncoding RNAs—These RNAs bind to DNA and interfere with transcription and posttranscriptional regulation of gene expression (e.g., miRNA).

CpG, cytosine-guanosine; miRNA, micro-RNA.

of gene expression. In aggregate, these mechanisms serve to regulate the transcriptional activity of specific genes, at specific stages of development, and in response to specific forms of endogenous and exogenous stress. Of importance, these mechanisms are conserved in eukaryotic organisms, from yeast to humans.

Epigenetic mechanisms can have profound effects on cellular, tissue, and whole-organism phenotype, including fundamental mechanisms such as stem cell differentiation[63] and inactivation of the X chromosome.[64] Although epigenetic marks can be inherited, these potent regulators of transcription can also be modified throughout development[65] and by environmental exposures.[66] For instance, although monozygotic twins are genetically identical, as they age, twin pairs develop divergent epigenetic marks associated with differences in gene expression.[65] Environmental endocrine disruptors have been shown to induce transgenerational effects on male fertility as a result of DNA methylation.[66] These findings suggest that the epigenome can be reprogrammed, potentially affecting the risk, cause, and treatment of various disease states.

The technology to measure epigenetic changes is continuing to evolve and, with the advent of methylation sequencing, it will soon be feasible to detect the epigenetic modifications of the entire genome during states of stress and disease. High-quality antibodies have been used to detect known modifications in the amino acid residues of histones. Chromatin immunoprecipitation can be used in conjunction with either microarrays (chromatin immunoprecipitation chip) or next-generation sequencing (ChIP-seq, FAIRE-seq, and ATAC-seq) to evaluate global changes in histone modifications. As the cost of sequencing decreases, these assays will become increasingly accessible.

Considering the importance of the environment in the development of lung disease, it is somewhat surprising that more attention has not been devoted to epigenetic mechanisms that lead to acute and chronic forms of lung disease. Epigenetic mechanisms have been associated with a number of tumors, and the methylation pattern of six genes is associated with the development of lung cancer.[67] However, research is just beginning to demonstrate the relevance of epigenetic changes to nonmalignant forms of lung disease. In patients with *idiopathic pulmonary fibrosis* (IPF), DNA methylation is markedly altered in their lung tissue.[68] In airway diseases such as asthma and COPD, bronchial biopsy specimens and alveolar macrophages have increased histone acetyltransferase activity and reduced histone deacetylase activity,[69–71] thought to be important in the transcriptional regulation of inflammatory mediators.[71] Because cigarette smoke, vitamin supplementation, and other environmental exposures can alter the epigenetic marks along the human genome, studying the importance of changes in DNA methylation, structural changes in amino acid residues of histones, and expression of noncoding RNAs should help us to understand the fundamental mechanisms associated with the etiology and progression of several types of lung disease. Moreover, the epigenome can be modified by a variety of drugs. Of interest, in a murine model of asthma, trichostatin A, a histone deacetylase inhibitor, can decrease ovalbumin-induced allergic airway disease.[72] As we begin to understand the role of epigenetic mechanisms in the development of lung disease, it will become much more obvious how we can modify these mechanisms therapeutically to reduce the burden of lung disease among our patients.

FINE MAPPING AND FUNCTIONAL GENETICS

Genetic association studies, with few exceptions, identify an associated locus, not a causal variant or gene. This result is due to linkage disequilibrium, which, although facilitating discovery, impairs identification of the specific causal variant, a process requiring "fine mapping." Similarly, although an association is often denoted by the closest gene, for instance, *FAM13A*, in most cases the nearest gene is not actually the causal gene,[43,73] nor is the cell or tissue type, the timing of action, or environmental conditions known. This issue is exemplified by one of the strongest genetic associations for obesity, where the most significant variant is located within the *FTO* gene. *FTO* as the causal gene was supported by early studies.[74] However, subsequent work identified a mechanism that did not involve *FTO*; instead, the causal variant disrupted a motif for the *ARID5B* repressor, affecting *IRX3* and *IRX5* expression in preadipocytes and leading to a shift in lipid storage.[75]

Despite hundreds of replicated loci for respiratory disease, the underlying biologic mechanisms are completely unknown for most. In a minority of loci, the associated variant is *nonsynonymous*, which means it results in an amino acid change that can directly affect the function or expression of the encoded protein (e.g., *AGER*, *SFTPD*, or *TERT* variants in COPD and pulmonary fibrosis). However, in most cases, the causal variant is likely regulatory. Although identifying an effect of the identified variant on gene expression can help narrow down the gene of interest, gene expression is pervasive, expression may be condition specific, and directionality may not be consistent.[76,77] To date, most loci have required careful and customized approaches. These examples include *MUC5B*, *ORMDL3*, and *HHIP* in studies of IPF, asthma, and COPD, respectively.[78–80] Methods to perform fine mapping and functional assessment are improving, through increased availability of open chromatin profiling, three-dimensional genome maps, high-throughput functional assays, gene editing, and other methods.[81–84]

INTEGRATIVE GENOMICS AND SYSTEMS GENETICS

The discovery of large numbers of genetic risk factors, most affecting novel genes with unknown mechanisms of action, makes it clear that consideration of single genes in isolation is insufficient. The field of integrative genomics aims to relate genetic variants to other omics. Systems genetics is an approach to understand mechanisms, beginning from genetic variants through intermediate phenotypes, such as transcripts, proteins, and metabolites, and then to determine how these converge on pathways and networks[85] (Fig. 9.3). Network medicine, in turn, is the related concept that diseases arise from perturbations and interactions in a complex intra- and intracellular network, linking tissues and organ systems, and that these processes can be studied using principles of network science.[86]

Although these fields are still emerging, they are already influencing discovery. For example, identification of expression quantitative trait loci—genetic loci that affect gene expression—is a key tool in identifying gene function, as exemplified by *ORMDL3* in asthma (see later). In COPD, specific pathways have been implicated by leveraging gene or protein expression from individual associations.[87]

APPLICATION TO PULMONARY DISEASES

ASTHMA

Asthma has long been known to have a significant genetic component. Although there have been hundreds of reports of associations, many of the studies from the candidate gene era for asthma suffer from the methodologic problems discussed earlier. The first asthma GWAS identified a genome-wide significant locus at 17q21[88] and also was one of the first to integrate gene expression, demonstrating differential expression of *ORMDL3*, a gene involved in the endoplasmic reticulum found to regulate sphingolipid synthesis. The most recent large GWAS include multi-ethnic studies, and studies of adult and childhood asthma,[89–91] the latter of which appears to harbor more genetic susceptibility than adult asthma.[92] Some of the major findings include associations near *interleukin-1 receptor-like 1 (IL1RL1), thymic stromal*

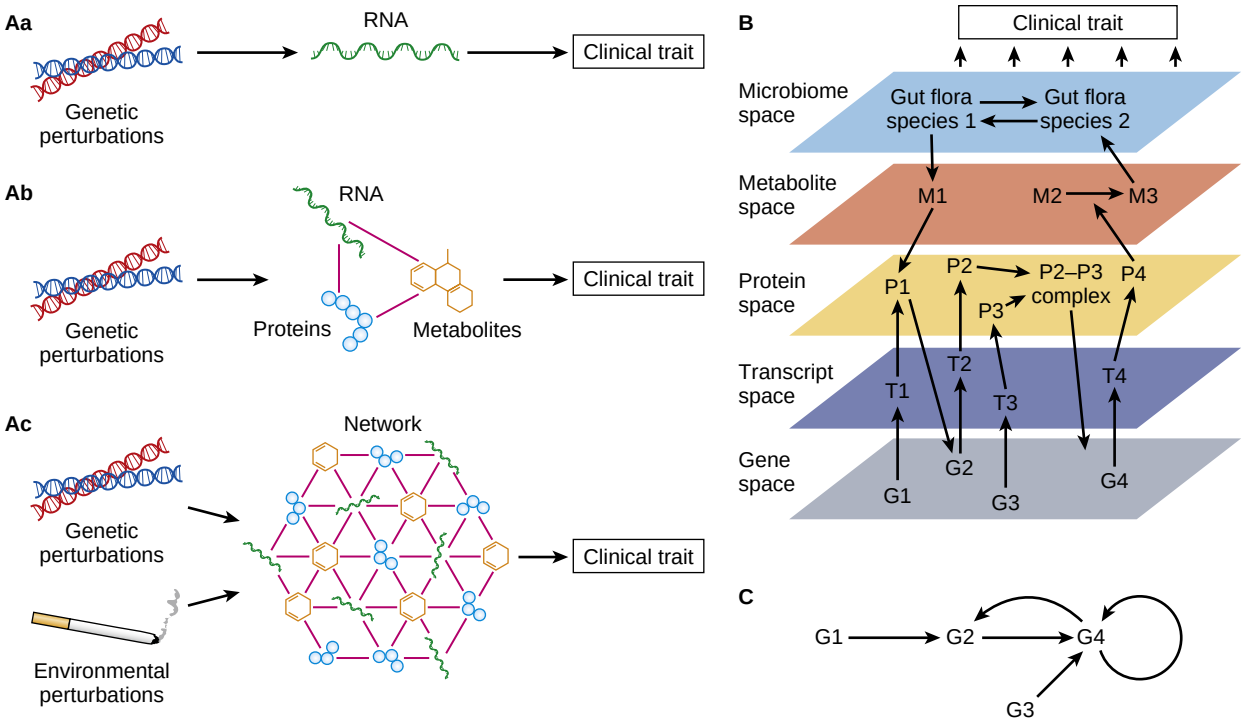

Figure 9.3 Systems genetics. (Aa) A genetic perturbation can have an effect on transcription and a resulting clinical trait; (Ab) or can affect proteins or metabolites; (Ac) or, in conjunction with an environmental perturbation, can affect a network. (B) These interactions can involve multiple genes and molecular phenotypes and (C) result in specifically derived models. (From Civelek M, Lusis AJ. Systems genetics approaches to understand complex traits. *Nat Rev Genet.* 2014;15:34–48; A, Modified from Schadt EE. Molecular networks as sensors and drivers of common human diseases. *Nature.* 2009;461:218–223.)

lymphopoietin (TSLP), and *IL-33 (IL33)*, all genes implicated in type 2 T helper cell–mediated immune responses and genes related to allergy and dysregulated epithelial barrier function. Additional investigations into related traits, such as immunoglobulin E levels and other allergic diseases, have also identified loci that have an influence on asthma.[93,94]

COPD AND LUNG FUNCTION

One of the first genetic causes of COPD was identified more than 50 years ago with the discovery of *alpha$_1$-antitrypsin deficiency* (AATD). However, even after controlling for cigarette smoking exposure and excluding AATD patients, studies in families, twins, and unrelated individuals have found clear evidence of additional genetic contributions. Despite years of candidate gene studies, it has only been with the advance of GWASs that clear, reproducible genetic signals have been identified. The first GWAS for COPD[95] identified a region on chromosome 15q25, and additional studies identified the *hedgehog-interacting protein gene (HHIP)*[96–98] and a *family with sequence similarity 13, member A*[96] *(FAM13A)*. Pulmonary function is also highly heritable. As COPD is defined using lung function, perhaps it is not surprising that GWASs of *forced expiratory volume in 1 second* (FEV$_1$) and the *FEV$_1$ to forced vital capacity* (FEV$_1$/FVC) ratio have a high degree of overlap. Most lung function loci and COPD loci are shared with a consistent direction of effect, and a genetic risk score comprising lung function loci strongly predicts COPD.[99,100] The most recent large studies have identified dozens of loci for COPD[87] and hundreds for lung function.[99,100]

ACUTE RESPIRATORY DISTRESS SYNDROME

Genetic analysis of inbred mouse strains first revealed that acute lung injury susceptibility was strain dependent and therefore may, in part, be genetically determined.[101] Although no studies to date have identified and replicated variants of genome-wide significance,[102] several suggestive associations have emerged. For example, a variant in the *IL-1 receptor antagonist (IL1RN)* reached a predetermined level of significance for coding variants, was replicated, and was associated with an increased IL-1 receptor antagonist response in plasma.[103] Additional bioinformatic analysis in 232 African Americans and 162 control subjects identified a nonsynonymous variant in *selectin P ligand (SELPLG)* as a risk factor for *acute respiratory distress syndrome* (ARDS), with support from preclinical models, including knockout mice.[104] Genetic studies in ARDS still are limited by sample size and heterogeneity; integration of additional omics data, including biomarkers, and identification of more homogeneous phenotypes will likely be helpful.[102]

LUNG CANCER

In a recent pooled analysis from the International Lung Cancer Consortium, first-degree relatives had a 1.5-fold increase in the risk of lung cancer after adjustment for smoking and other confounders, and this relationship seemed to be consistent across histologic subtypes.[105] GWAS have identified several susceptibility loci, including the *CHRNA3/5* and *CYP2A6* loci, both of which are also associated with COPD and cigarette smoking, as well as loci at genes related to telomere maintenance, such as

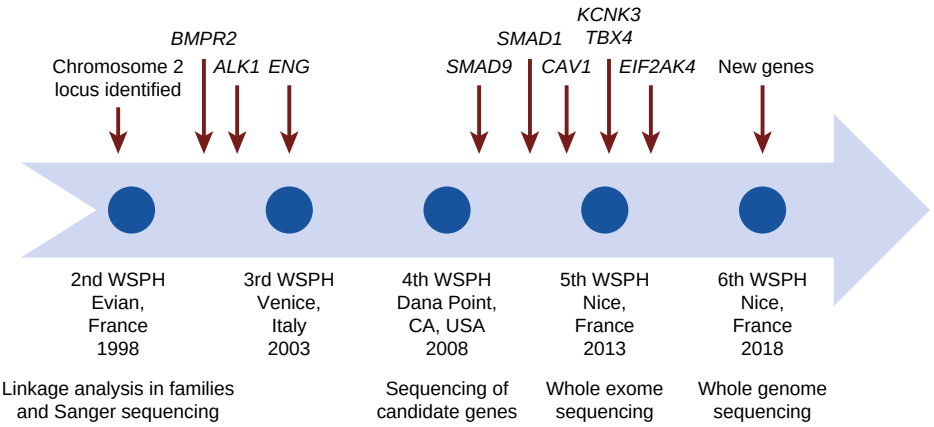

Figure 9.4 Genetics of pulmonary hypertension. The discovery of genes in pulmonary hypertension also traces the development of genetic technology for rare variants to increasingly powerful and unbiased approaches, from linkage analysis and Sanger sequencing, to candidate gene, exome, and whole-genome sequencing studies. WSPH, World Symposium on Pulmonary Hypertension; Sanger sequencing, the standard method of sequencing from 1977 for the next 40 years. (From Morrell NW, Aldred MA, Chung WK, et al. Genetics and genomics of pulmonary arterial hypertension. *Eur Respir J.* 2019;53:1801899.)

TERT, OBFC1, and *RTEL1,* and other genes, such as *HLA, BRCA2, CHEK2, RNASET2, SECISBP2L,* and *NRG1.* This most recent study also identified subtypes as an important consideration in lung cancer association studies; of the 10 novel loci, six appeared to be specific for adenocarcinoma.[106,107] In addition to inherited, germline variation—present in all cells in an individual's genome—another type of genetic variation is important in cancer. Somatic mutations are those that develop in specific tissues during the course of cell division and drive much of lung cancer pathogenesis. These have led to tumor-specific targets,[108–110] an impressive accomplishment of genomic medicine that provided a seamless link between the pathogenesis, prediction of treatment effect, and successful application of treatment (see Chapters 73 and 74).

FIBROSING IDIOPATHIC INTERSTITIAL PNEUMONIA

Fibrosing *idiopathic interstitial pneumonia* (IIP) refers to a group of lung diseases that are characterized by progressive scarring of the alveolar interstitium that leads to significant morbidity and mortality. IPF is the most common and severe form of fibrosing IIP. There is substantial evidence for a genetic basis for IPF.[111–113] Although rare mutations in the *TERT, TERC, SFTPC,* and *SFTPA2* genes have been associated with familial interstitial pneumonia and IPF,[114–119] in aggregate these mutations account for a small proportion of the population attributable risk. One of the most striking findings in respiratory genetics is the identification of a promoter variant in the *MUC5B* gene (rs35705950), found to be present in approximately 50% to 60% of individuals with familial or sporadic forms of IPF. In contrast to most other common variants that are of modest (odds ratio <1.5) effect, the *MUC5B* variant is estimated to increase the risk 6-fold for heterozygotes and 20-fold for homozygotes (eFig. 9.3).[25,120] Of importance, the *MUC5B* promoter SNP also appears to be predictive of early disease; in the Framingham population, the SNP is associated with a threefold to sixfold excess risk per allele for interstitial lung abnormalities that likely represent early radiographic evidence of interstitial lung disease,[121] suggesting that the *MUC5B* promoter SNP could be used to identify individuals with preclinical forms of IPF. Additional loci revealed by GWAS include *TERT/TERC, FAM13A, DSP, OBFC1, ATP11A, DPP9,* and *AKAP13.*[122] Recently, targeted sequencing across the original 10 GWAS loci[123] identified 10 common variants that, in aggregate, account for at least 35% of the risk of IPF.[124] Further characterizing these IIP-associated loci will provide important targets for functional studies that will ultimately allow the development of new prevention and treatment strategies.[113]

PULMONARY HYPERTENSION

In contrast to asthma, COPD, and IPF, where susceptibility appears to be driven primarily by common variants, the genetic susceptibility of pulmonary arterial hypertension (World Health Organization Group 1) appears to be due frequently to rare variants.[125] An overview of discoveries in the genetics of pulmonary hypertension is shown in Fig. 9.4. *Bone morphogenetic protein type II receptor (BMPR2)* variants may account for as many as 80% of familial cases and up to 10–20% of cases without a family history,[126] although only about 25% of carriers actually develop disease. Additional studies have identified *ALK1, ACVRL1,* and *ENG* as associated with hereditary hemorrhagic telangectasia; BMPR pathway genes, including *SMAD1, SMAD4,* and *SMAD9,*[127] and *EIF2AK4,* appear to be relatively specific to pulmonary capillary hemangiomatosis and pulmonary veno-occlusive disease.[128,129] Recent exome sequencing identified rare variants in *ATP13A3, AQP1, SOX17,* and *GDF2* and found approximately 15% also had *BMPR2* mutations. Common variants, identified by GWAS, have loci near *SOX17* and *HLA-DPA1/DPB1.* The identification of causative mutations in pulmonary hypertension has focused research efforts on developing strategies that restore the function and expression of defective pathways.

SARCOIDOSIS

Siblings of those with sarcoidosis are at a relative risk of disease of approximately four- to fivefold.[130,131] Early studies identified a strong association signal in a region of the genome responsible for immune function, the *major histocompatibility complex* (MHC) locus[132]; subsequent studies identified associations at *ANXA11, CCDC88B, RAB23,* and

Table 9.3 Selected Mendelian Syndromes Associated With Pulmonary Disorders

Disorder	Description	Example Gene(s)
Primary ciliary dyskinesia	Also known as *immotile-cilia syndrome;* defect in the cilia resulting in impaired mucociliary clearance, recurrent respiratory tract infections and bronchiectasis, infertility, and situs inversus	*CCDC39, CCDC40, DNAAF1, DNAAF2, DNAH11, DNAH5, DNAI1, DNAI2, DNAL1, NME8*
Neurofibromatosis	Systemic manifestations include café au lait macules, Lisch nodules, neurofibromas, bone abnormalities, cognitive defects, and other tumors. Lung manifestations include pulmonary hypertension, pulmonary artery stenosis, interstitial lung disease, and bullous lung disease	*NF1*
Cutis laxa	Abnormality in elastic fiber resulting in loose, redundant skin, vascular abnormalities, and pulmonary emphysema	*ELN, EFEMP2, FBLN5, LTBP4*
Hermansky-Pudlak syndrome	Lysosomal-related disorder resulting in oculocutaneous albinism, bleeding diathesis, and pulmonary fibrosis	*AP3B1, BLOC1S3, BLOC1S6, DTNBP1, HPS1-6*
Marfan syndrome	Connective tissue disorder resulting in aortic root dilation, arachnodactyly, ectopia lentis, and emphysematous/bullous changes and pneumothorax	*FBN1*
Birt-Hogg-Dubé syndrome	Hamartoma syndrome with skin fibrofolliculomas, renal cancers, and cystic lung disease/pneumothorax	*FLCN*
Familial pulmonary alveolar proteinosis	Diffuse lung disease characterized by lipoproteinaceous material in distal air spaces (*SLC7A7*, in setting of lysinuric protein intolerance)	*ABCA3, CSF2RA, CSF2RB, SFTPB, STPBC, SLC7A7*

IL23R.[133–135] The most recent large association study identified novel associations, but also three independent signals in the MHC,[136] and confirmed and extended the role of IL23/T helper cell type 17 signaling.

RARE DISEASES

In addition to these and other common diseases, many other diseases or syndromes with a primary or a major pulmonary manifestation have been described (Table 9.3). Several panels exist that test for different genes, including the PulmoGene panel that tests for 64 different genes related to cystic lung disease, bronchiectasis (including primary ciliary dyskinesia), fibrosis (including Hermansky-Pudlak syndrome), pulmonary hypertension, and central hyperventilation syndrome (see https://personalizedmedicine.partners.org/Assets/documents/Laboratory-For-Molecular-Medicine/Gene_Disease_Association/PulmoGene_Gene_Assoc_Table.pdf).

THE PATH FORWARD

In the approximately 2 decades since the initial draft of the Human Genome Project was completed, there has been tremendous progress in human genetics, with the development of genotyping and next-generation sequencing, characterization and cataloging of human genetic variation, identification of genes for mendelian diseases and genetic loci for complex diseases, and elucidation of mechanisms of gene regulation.[43,137] Despite tremendous progress, however, less than 10% of the genetic regions responsible for the observed heritability have been identified in most diseases and, of these identified genetic factors, the specific causal variant, gene, cell type, and mechanism are nearly all unknown.[43] Thus, continued investigation is clearly needed. Attention to phenotypic heterogeneity and other ethnicities is important not only to confirm variant effects but can also lead to novel genetic discoveries and elucidate causal variants due to differences in variant allele frequencies.[138–142]

Translating these discoveries into clinical medicine and public health remains challenging. The magnitude of the task of converting a genetic association to functional studies for the correct variant, gene, cell type, and ultimately translational mechanistic insight is only beginning to be realized. The advent of tools such as high-throughput functional studies[84] will help advance what is currently a process that requires bespoke experimental design. Many of these limitations arise from the fact that human diseases are a result of extraordinary complex gene-gene and gene-environment interactions, where exposures affect those that are vulnerable temporally (age), spatially (geographically), and by unique circumstance (comorbid disease, nutritional status, economic status, and ethnicity). Environmental health research and genomic research are logical, even necessary, partners. These concepts are essential to understanding the network relationship of genetics to epigenetics, gene expression, proteomics, metabolomics, and eventually disease phenotypes, all of which reflect a combination of genetics and environment, from the organism down to the single-cell level. The next decade of discoveries that are made in human genetics—incorporating new associations, identification of causal genes and cell types, and environmental genomics—will lead to better diagnosis, treatment, and prevention of these common, complex human diseases.

Key Points

- Heritability is a measure of the contribution of genetic variation to variation in a phenotype.
- Complex genetic disorders account for the majority of lung diseases and are caused by multiple genetic variants and environmental factors.
- The human genome comprises approximately three billion base pairs. There are more than 450 million single nucleotide polymorphisms in the human genome, although the majority of these are rare.
- Genome-wide association studies have emerged as the most commonly used study design to find disease genes in complex disorders. Sequencing provides more detailed characterization of variation and is useful for rare variant studies and enhancing the power of these studies.
- Epigenetics is the study of changes in gene transcription that are dependent on the molecules that bind to DNA, rather than on the base pair sequence of DNA. This includes both heritable changes in gene expression and stable long-term alterations in the transcriptional potential of a cell or tissue that are not necessarily heritable.
- Asthma genetic studies have identified immune cell, epithelial, allergic response genes, and differences between heritability of childhood- and adult-onset disease. As in most complex diseases, only a small portion of the heritability of this disease has been explained.
- COPD risk is largely related to genetic factors independent of smoking, and most of the currently described variants are also determinants of lung function in the population.
- Lung cancer develops in only a minority of smokers, and thus genetic and epigenetic mechanisms need to be considered. Epidemiologic studies have identified germline, inherited risk variants, but somatic mutations, such as those in the *EGFR* and *ALK* families, predict prognosis and response to therapy.
- Interstitial lung disease is caused by environmental and genetic factors. Mutations in surfactant protein C and the telomerase genes enhance the risk for developing this disorder. A common polymorphism in the promoter of the *MUC5B* gene is strongly associated with the development of familial and sporadic forms of idiopathic pulmonary fibrosis. Recently additional novel loci have been found to be associated with the development of pulmonary fibrosis.
- Most familial pulmonary hypertension cases are caused by mutations in *BMPR2*, but other rare variants, including some indicative of specific forms of pulmonary hypertension, and common variants have been identified.
- Sarcoidosis susceptibility is due in part to variants in the human leukocyte antigen A region and other immune-related pathways.
- Rare variants underlie several mendelian syndromes, with pulmonary disease as the primary or commonly associated manifestation, including pulmonary ciliary dyskinesia, cutis laxa, and pulmonary alveolar proteinosis.

Key Readings

Bush WS, Moore JH. Genome-wide association studies. *PLoS Comput Biol*. 2012;8(12):e1002822.

Demenais F, Margaritte-Jeannin P, Barnes KC, et al. Multiancestry association study identifies new asthma risk loci that colocalize with immune-cell enhancer marks. *Nat Genet*. 2018;50(1):42–53.

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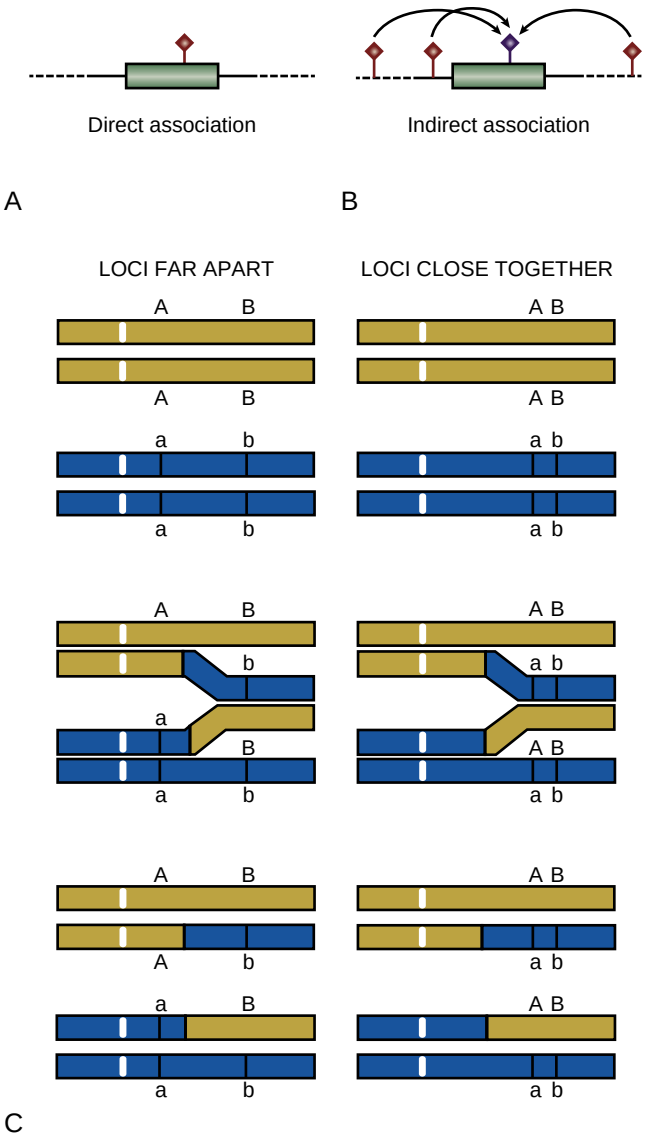
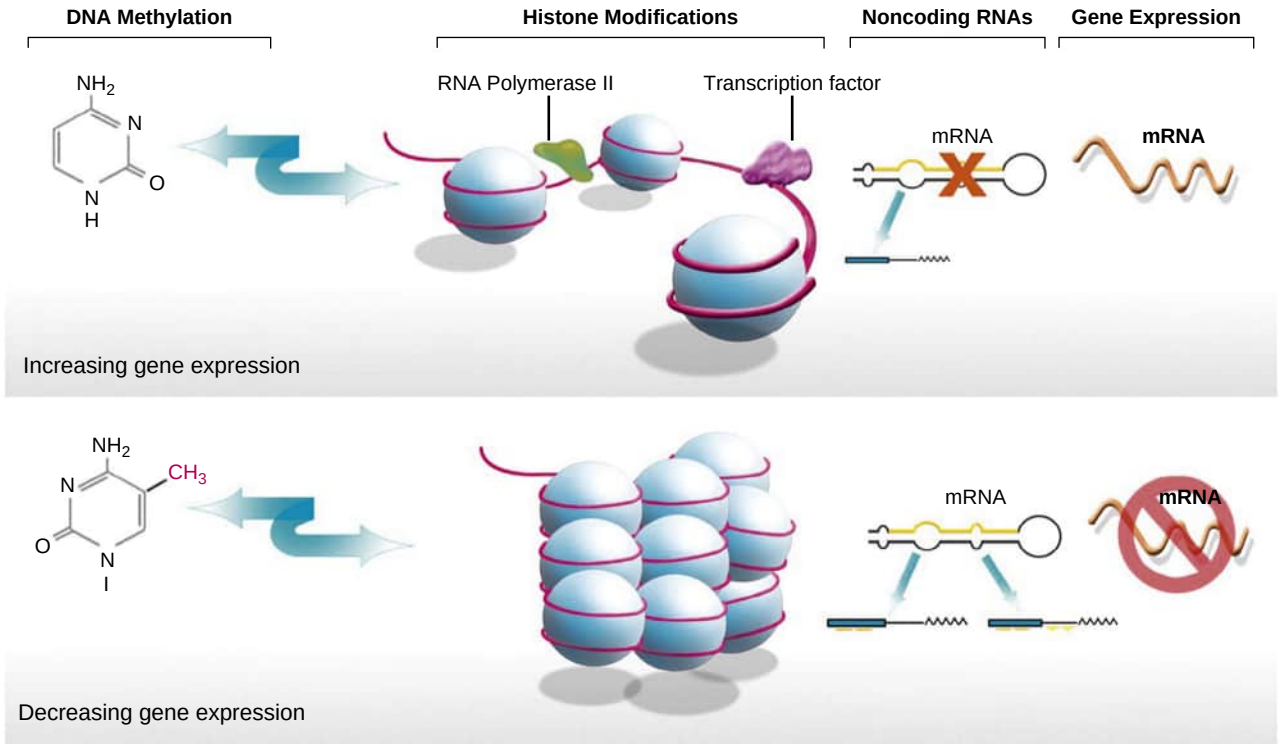
Complete reference list available at ExpertConsult.com.



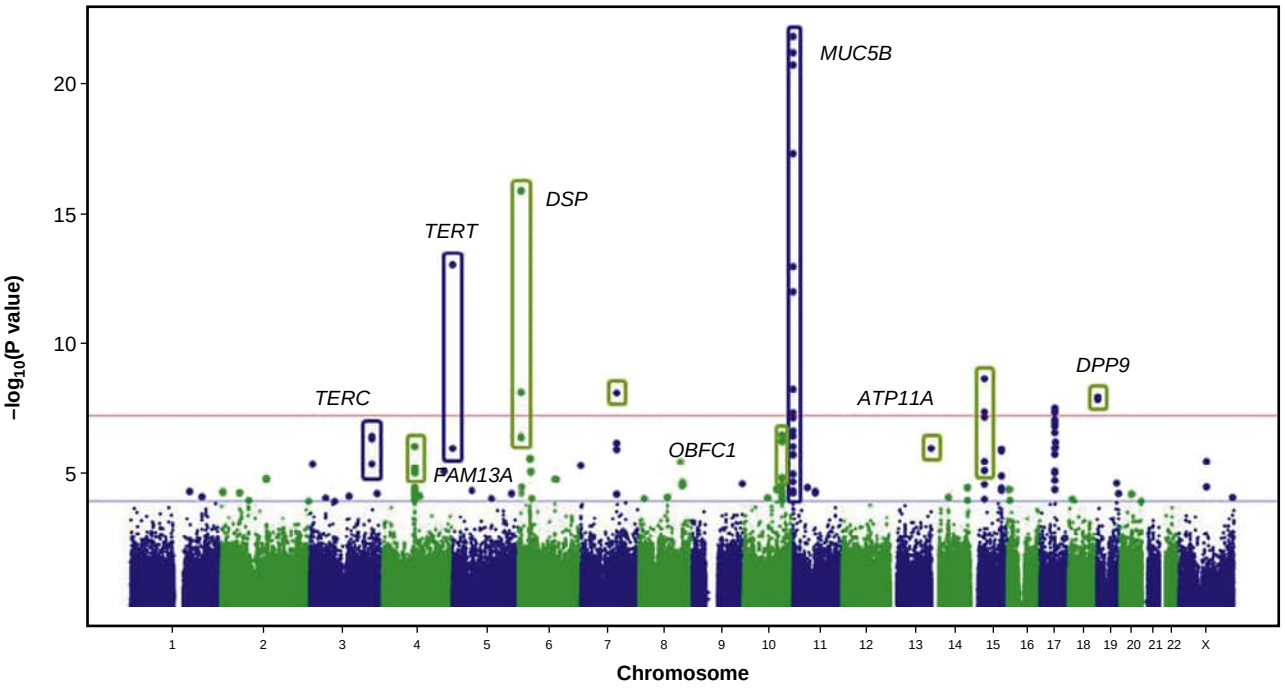
eFIGURE IMAGE GALLERY



eFigure 9.1 Linkage disequilibrium. (A) Crossover between homologous chromosomes in meiosis. On the left is an example in which two loci are far apart on the chromosomes and so remain unlinked. On the right the loci are relatively close to one another and so, after recombination, are more likely to remain together. The loci that are close together will be in linkage disequilibrium. Thus, when testing for an association, an identified genetic association *(red)* can either be the causal variant (B) or markers correlated with the causal variant (C). (B and C, From Hirschhorn JN, Daly MJ. Genome-wide association studies for common diseases and complex traits. *Nat Rev Genet.* 2005;6:95–108.)



eFigure 9.2 Effect of epigenetic marks on gene expression. Epigenetic mechanisms include DNA methylation, modification of histone tails, and generation of noncoding RNAs. Each of these can affect gene expression. The *top panel* shows how these three epigenetic mechanisms can increase gene expression; the bottom panel shows how these three epigenetic mechanisms can decrease gene expression. *Blue arrows* indicate crosstalk between DNA methylation and histone modifications. The relationship between histones and DNA methylation is bidirectional; in addition to histones playing a role in the establishment of DNA methylation patterns, DNA methylation is important for maintaining patterns of histone modification through cell division. mRNA, messenger RNA. (From Yang IV, Schwartz DA. Epigenetic control of gene expression in the lung. *Am J Respir Crit Care Med.* 183:1295–1301, 2011, with permission of the American Thoracic Society.)



eFigure 9.3 *Genome-wide association studies* (GWASs) results for pulmonary fibrosis across 439,828 *single nucleotide polymorphisms* (SNPs), with 1616 cases and 4683 controls under an additive model. GWASs have become the standard approach for identification of common sequence alleles associated with complex diseases and are typically conducted in two phases: discovery across the genome and replication of a smaller set of SNPs in independent samples. For the pulmonary fibrosis example, the results of the first discovery phase are shown in this Manhattan plot. In the second phase, SNPs above the *red line* that were genome-wide significant at $P < 5 \times 10^{-8}$ and the SNPs between the *red and blue lines* (corresponding to $5 \times 10^{-8} < P < 0.0001$) were selected for follow-up in 876 cases and 1890 controls. After considering both phases of the study, seven novel loci for pulmonary fibrosis were identified. (From Fingerlin TE, Murphy E, Zhang W, et al. Genome-wide association study identifies multiple susceptibility loci for pulmonary fibrosis. *Nat Genet.* 2013;45:613–620.)

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SECTION B

RESPIRATORY PHYSIOLOGY

10

VENTILATION, BLOOD FLOW, AND GAS EXCHANGE

MEREDITH C. MCCORMACK, MD, MHS • JOHN B. WEST, MD, PHD, DSC

INTRODUCTION
VENTILATION
Total and Alveolar Ventilation
Inequality of Ventilation
BLOOD FLOW
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Pulmonary Vascular Resistance
Distribution of Pulmonary Blood Flow
Active Control of the Pulmonary Circulation
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INTRODUCTION

This first chapter in the section on respiratory physiology is devoted to the primary function of the lung: gas exchange. Herein, the principles of ventilation and blood flow that underlie gas exchange are reviewed. Although the lung has other functions, such as metabolizing some compounds, filtering unwanted materials from the circulation, and acting as a reservoir for blood, gas exchange is its chief function. Respiratory diseases frequently interfere with ventilation, blood flow, and gas exchange and may ultimately lead to respiratory failure and death.

VENTILATION

The anatomy of the airways and the alveolar region of the lung is discussed in Chapter 1. There we saw that the airways consist of a series of branching tubes that become narrower, shorter, and more numerous as they penetrate deeper into the lung. This process continues down to the terminal bronchioles, which are the smallest airways without alveoli. All these bronchi make up the conducting airways. Their function is to channel inspired gas to the gas-exchanging regions of the lung. Because the conducting airways contain no alveoli and therefore take no part in gas exchange, they constitute the anatomic dead space.

Each terminal bronchiole conducts air to a respiratory unit, or acinus. The acinus is where alveolization, and therefore gas exchange, begins. The acinus can also be termed the terminal respiratory unit, indicating its chief role in gas exchange. The terminal bronchioles divide into respiratory bronchioles that have occasional alveoli budding from their wall, which then transition to the alveolar ducts, structures that are completely lined with alveoli. This alveolated region of the lung where gas exchange takes place is known as the respiratory zone. The distance from the terminal bronchiole to the most distal alveolus is only approximately 5 mm, but the respiratory zone makes up most of the lung in terms of gas volume (some 2–3 L).

The morphologic characteristics of the human airways were greatly clarified by Weibel.[1] He measured the number, length, width, and branching angles of the airways, and he

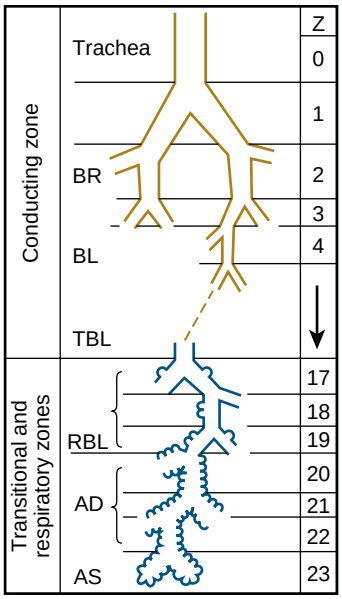

Figure 10.1 Idealization of the human airways according to Weibel's model A. The first 16 generations of airways constitute the conducting zone, the next three generations are the respiratory bronchioles constituting the transitional zone, and the final three generations are the alveolar ducts and alveolar sacs constituting the respiratory zone. Note that the RBL, AD, and AS make up the transitional and respiratory zones. AD, alveolar duct; AS, alveolar sac; BL, bronchiole; BR, bronchus; RBL, respiratory bronchiole; TBL, terminal bronchiole; Z, airway generation. (Modified from Weibel ER. *Morphometry of the Human Lung*. Berlin: Springer-Verlag; 1963.)

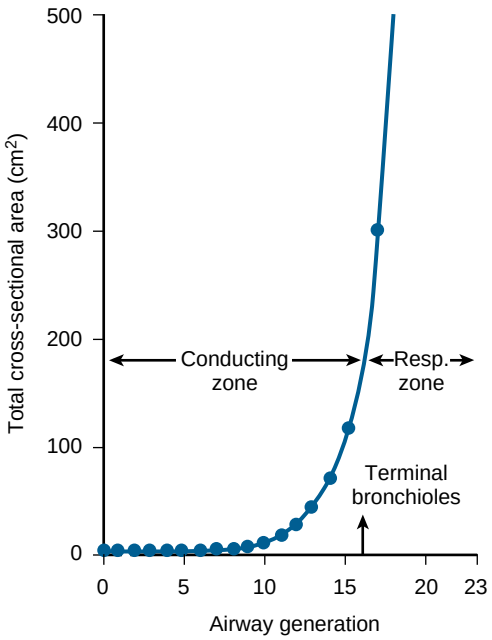

Figure 10.2 Cross-sectional area of the different zones. Diagram showing the extremely rapid increase in total cross-sectional area of the airways in the respiratory (Resp.) zone as predicted from the Weibel model in Fig. 10.1. (Modified from West JB. *Respiratory Physiology: The Essentials*. 9th ed. Baltimore: Lippincott Williams & Wilkins; 2012.)

proposed models that, although they are idealized, make pressure flow and other analyses much more tractable.

The most commonly used Weibel model is the so-called model A, shown in Figure 10.1. Note that the first 16 generations (Z) make up the conducting airways ending in the terminal bronchioles. The next three generations constitute the respiratory bronchioles, in which the degree of alveolation steadily increases. This is called the transitional zone because the nonalveolated regions of the respiratory bronchioles do not have a respiratory function. Finally, there are three generations of alveolar ducts and one generation of alveolar sacs. These last four generations constitute the true respiratory zone.

Other models of the airways have been proposed.[2] However, the Weibel model has been of great value to respiratory physiology, and an example of its use is shown in Figure 10.2. Here the model clarifies the nature of gas flow in all generations of the airways in the lung. Figure 10.2 shows that, if the total cross-sectional area of the airways of each generation is calculated, there is relatively little change in area until we approach generation 16, that is, the terminal bronchioles. Near this level, the cross-sectional area increases very rapidly. This has led some physiologists to suggest that the shape of the combined airways is similar to a trumpet or even a thumbtack.

The result of this rapid change in area is that the mode of gas flow changes in the region of the terminal bronchioles. Proximal to this point, flow is convective, or "bulk," that is, similar to the sort of flow that results when beer is poured out of a pitcher. However, when the gas reaches the region approximating the level of the terminal bronchioles, its forward velocity decreases dramatically because of the very sudden increase in cross-sectional area. As a consequence, diffusion begins to take over as the dominant mode of gas transport. Naturally, there is no sharp transition; flow changes gradually from primarily convective to primarily diffusive in the general vicinity of generation 16.

One implication of this change in mode of flow is that many aerosol particles penetrate to the region of the terminal bronchioles by convective flow, but they do not penetrate further because of their large mass and resulting low diffusion rate. Thus, sedimentation of these particles is heavy in the region of the terminal respiratory bronchioles. This is one reason why this region of the lung is particularly vulnerable to the effects of particulate air pollutants (see Chapters 72 and 102).

Another implication of this dichotomously branching airway tree is that the greater the number of branch points, the greater the potential for nonuniform distribution of airflow among the distal airways and alveoli. In addition, repeated, possibly minor, differences in flow distribution at each branch point will give rise to spatial correlation of flow; in other words, neighboring regions will tend to have more similar flows than regions located far apart, other factors being equal.

Figure 10.3 shows the major divisions of lung volume. Total lung capacity is the volume of gas contained in the lungs at maximal inspiration. The vital capacity is the volume of gas that can be exhaled by a maximal expiration from total lung capacity. The volume remaining in the lung after maximal expiration is the *residual volume* (RV). Tidal volume refers to the normal respiratory volume excursion. The lung volume at the end of a normal expiration is the *functional residual capacity* (FRC). Figure 10.3 also indicates the inspiratory reserve volume and the expiratory reserve volume. These volumes change in characteristic directions with different respiratory diseases, such as COPD and lung

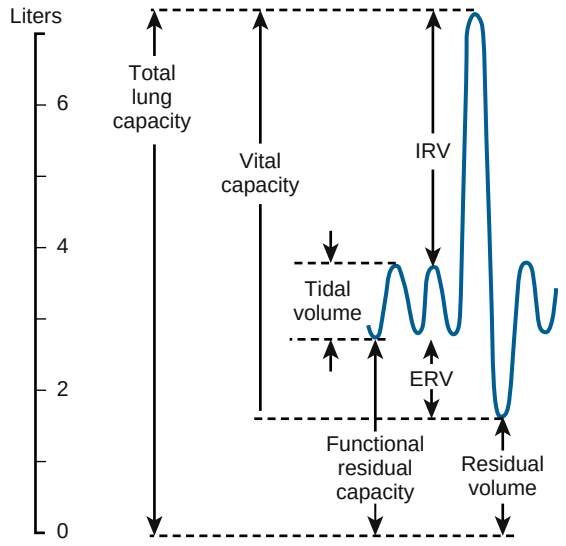

Figure 10.3 Major divisions of lung volumes. Values are illustrative only; there is considerable normal variation. ERV, expiratory reserve volume; IRV, inspiratory reserve volume. (Modified from West JB. *Respiratory Physiology: The Essentials*. 9th ed. Baltimore: Lippincott Williams & Wilkins; 2012.)

fibrosis, so their measurement becomes important (see Chapters 31 and 32).

TOTAL AND ALVEOLAR VENTILATION

Total Ventilation

Total ventilation, also called minute ventilation, is the total volume of gas exhaled per minute. It is equal to the tidal volume times the respiratory frequency. (The volume of inhaled air is slightly greater than the exhaled volume because more oxygen is inhaled than carbon dioxide is exhaled, but the difference is usually less than 1%.) Alveolar ventilation is the amount of fresh inspired air (non–dead-space gas) that enters the alveoli per minute and is therefore available for gas exchange.

Alveolar Ventilation

Because the *tidal volume* (V_T) is made up of the *dead-space volume* (V_D) and the *volume of gas entering (or coming from) the alveoli* (V_A), the alveolar ventilation can be measured from the following equations:

$$V_T = V_D + V_A \qquad \text{Eq. 1}$$

Multiplying by respiratory frequency gives

$$\dot{V}_E = \dot{V}_D + \dot{V}_A \qquad \text{Eq. 2}$$

where $\dot{V}_A$ is the alveolar ventilation, and $\dot{V}_E$ and $\dot{V}_D$ are the expired total ventilation and dead-space ventilation, respectively.

Therefore,

$$\dot{V}_A = \dot{V}_E - \dot{V}_D \qquad \text{Eq. 3}$$

A difficulty with this method is that the anatomic dead space is not easy to measure, although a value for it can be assumed with little error. One milliliter per pound of body weight is a common assumption. This approximation will overestimate dead space in obese subjects and so should be applied using ideal body weight for height.

Another way of measuring alveolar ventilation in normal subjects is to use the alveolar ventilation equation, which expresses mass conservation of carbon dioxide by defining *carbon dioxide production* ($\dot{V}_{CO_2}$), which in a steady state is equal to the amount of CO_2 exhaled in a given time, as the product of *alveolar ventilation* ($\dot{V}_A$) and *fractional alveolar concentration of carbon dioxide* (F_{ACO_2}). Because concentration is proportional to partial pressure, the relationship can be written as:

$$\dot{V}_{CO_2} = \dot{V}_A \times F_{ACO_2} = \dot{V}_A \times P_{ACO_2}/K \qquad \text{Eq. 4}$$

This can then be rearranged as follows:

$$\dot{V}_A = \frac{\dot{V}_{CO_2}}{P_{ACO_2}} \times K \qquad \text{Eq. 5}$$

where $\dot{V}_{CO_2}$ is the volume of carbon dioxide exhaled per unit time, P_{ACO_2} is the alveolar P_{CO_2}, and K is a constant (0.863 when $\dot{V}_A$ is expressed in L/min, $\dot{V}_{CO_2}$ in mL/min, and P_{ACO_2} in mm Hg). In patients with normal lungs, the P_{CO_2} of alveolar gas and that of arterial blood are virtually identical. Therefore, the arterial P_{CO_2} can be used to determine alveolar ventilation from Eq. 5. The equation then becomes

$$\dot{V}_A = \frac{\dot{V}_{CO_2}}{Pa_{CO_2}} \times K \qquad \text{Eq. 6}$$

This equation is often used in patients with lung disease, but the value then obtained is the *effective* alveolar ventilation. This is not the same as the alveolar ventilation as defined in Eq. 3. Because patients with lung disease must increase their total ventilation to overcome the inefficiency of gas exchange caused by ventilation-perfusion inequality just to keep arterial P_{CO_2} normal, $\dot{V}_A$ from Eq. 6 will be less than that from Eq. 3.

Anatomic Dead Space

The anatomic dead space is the gas volume contained within the conducting airways. The normal value is in the range of 130 to 180 mL and depends on the size and posture of the subject. It can be estimated, as described earlier, as 1 mL per pound of ideal body weight. The value increases slightly with large inspirations because the radial traction exerted on the bronchi by the surrounding lung parenchyma increases their size. Anatomic dead space can be measured by Fowler's method,[3] in which a single breath of oxygen is inhaled and the concentration of nitrogen in the subsequent expiration is analyzed, as shown in Figure 10.4.

Physiologic Dead Space

Unlike anatomic dead space, which is determined by the anatomy of the airways, physiologic dead space is a functional measurement based on the ability of the lungs to eliminate carbon dioxide. It is defined by the Bohr equation:

$$\frac{V_D}{V_T} = \frac{P_{ACO_2} - P_{ECO_2}}{P_{ACO_2}} \qquad \text{Eq. 7}$$

where A and E refer to alveolar and mixed expired gas, respectively. In subjects with normal lungs, the P_{CO_2} of alveolar gas and that of arterial blood are virtually the same, so that the equation is often written as

$$\frac{V_D}{V_T} = \frac{Pa_{CO_2} - P_{ECO_2}}{Pa_{CO_2}} \qquad \text{Eq. 8}$$

INEQUALITY OF VENTILATION

Not all the alveoli are equally ventilated, even in the normal lung. There are several reasons for this, related both to gravitational and to nongravitational influences on gas distribution.

Gravitational Influences on Inequality

Hyperpolarized helium and xenon magnetic resonance imaging have been used to measure regional ventilation,[4,5] and more recent studies have used ventilation single-photon emission computed tomography and positron emission tomography scanning techniques.[6–8]

Measurements in upright normal subjects show that the ventilation per unit volume of the lung is greatest near the base of the lung and becomes progressively smaller toward the apex. When the subject lies supine, this difference becomes much less, but the ventilation of the dependent (posterior) lung exceeds that of the uppermost (anterior). In the lateral decubitus position, again, the dependent lung is better ventilated. (These results refer to an inspiration from FRC.)

An explanation of this gravitational inequality of ventilation is shown in Figure 10.5A, which depicts conditions at FRC.[9] The intrapleural pressure is less negative at the bottom than at the top of the lung. This pattern can be attributed to the weight of the lung, which requires a larger pressure below the lung than above it to balance the downward-acting weight forces.[10] There are two consequences of this lower expanding pressure on the base of the lung. First, the resting volume of the basal alveoli is smaller, as shown by the pressure-volume curve. Second, the change in volume for a given change in intrapleural pressure is greater because the alveoli are operating on a steeper part of the pressure-volume curve. Thus, the ventilation (change in volume per unit resting volume) is greater at the base than the apex. However, if a normal subject makes a small inspiration from RV (rather than from FRC), an interesting change in the distribution of ventilation is seen. The major share of the ventilation now goes to the apex of the upright lung, whereas the base becomes very poorly ventilated. Figure 10.5B shows why a different pattern is seen in this case. Now the intrapleural pressures are less negative, and the intrapleural pressure at the base of the lung actually exceeds atmospheric pressure. For a small fall in intrapleural pressure, no gas will enter the extreme base of the lung, and only the apex will be ventilated. Thus, the normal pattern of ventilation is reversed in this early phase of inhalation.

In this way, obesity may change the distribution of ventilation; for example, obesity-associated factors may alter the gravitational distribution of inhaled methacholine, and thus methacholine-induced bronchoconstriction. Findings from studies using two-dimensional and three-dimensional imaging modalities suggest diversion of

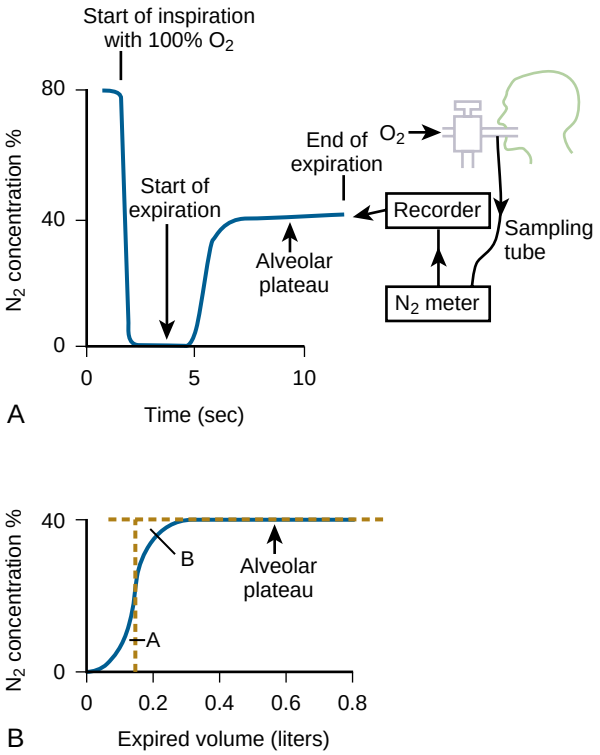

Figure 10.4 Fowler's method of measuring the anatomic dead space with a rapid N_2 analyzer. (A) After a test inspiration of 100% O_2, the N_2 concentration rises during expiration to an almost level plateau representing pure alveolar gas. (B) N_2 concentration is plotted against expired volume, and the dead space is the volume at the vertical dashed line that makes the areas to the left and to the right of the dashed vertical lines (*A* and *B*) equal. In this example, the dead space is ≈150 mL (or 0.15 L). (Modified from West JB. *Respiratory Physiology: The Essentials*. 9th ed. Baltimore: Lippincott Williams & Wilkins; 2012.)

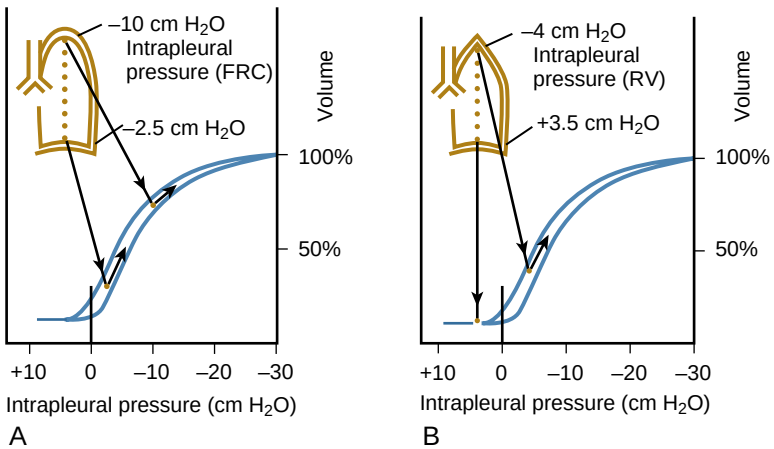

Figure 10.5 The inequality of ventilation down the lung due to gravity. (A) An inspiration from functional residual capacity. (B) The situation at very low lung volumes (see text for details). FRC, functional residual capacity; RV, residual volume. (Modified from West JB. *Respiratory Physiology: The Essentials*. 9th ed. Baltimore: Lippincott Williams & Wilkins; 2012.)

ventilation from the base into the upper lung zone among obese individuals.[6]

Airway Closure

At RV, the compressed region of the lung at the base in Figure 10.5B does not have all its gas squeezed out because small airways, probably in the region of the respiratory bronchioles, close first and trap gas in the distal alveoli. This is known as *airway closure.* In young normal subjects, airways close only at lung volumes below FRC. However, in older normal subjects, the volume at which the basal airways close (closing volume) increases with age and may encroach on the FRC. The reason for this increase is that, with aging, the lung loses some of its elastic recoil, and the intrapleural pressures therefore become less negative, thus approaching the situation shown in Figure 10.5B. Under these conditions, basal regions of the lung may be ventilated only intermittently, with resulting defective gas exchange. A similar situation frequently develops in patients with COPD in whom lung elastic recoil decreases. Airway closure promotes air trapping and hyperinflation characteristic of poorly controlled asthma. Exaggerated airway closure may be a feature of airway hyperresponsiveness in asthma,[11] particularly among obese individuals with asthma.[12,13]

Nongravitational Influences on Inequality

In addition to the inequality of ventilation caused by gravitational factors (Fig. 10.5), nongravitational mechanisms also exist. This is proved by the fact that even astronauts in space, in microgravity, show uneven ventilation.[14,15] This has been confirmed by studies in which labeled small particles in inspired gas demonstrate variability in ventilation at a given horizontal level at which gravitational forces are equal.[4] At least three factors have been proposed to explain the uneven ventilation in the distal, smaller regions of the lung.

One of these factors is the existence of uneven time constants.[16] The time constant of a region of lung is given by the product of its resistance and compliance (analogous to the time constant in electrical circuits, which is the product of electrical resistance and capacitance). Lung units with different time constants inflate and deflate at different flow rates. Depending on the breathing frequency, a unit with a large time constant does not complete its filling before expiration begins and therefore is poorly ventilated; the faster the frequency, the less time for ventilation. In contrast, a unit with a small time constant, which fills rapidly, may receive a high proportion of gas from the anatomic dead space, reducing its effective alveolar ventilation.

Another cause of uneven ventilation in small lung units is the asymmetry of their structure, which can result in a greater penetration of gas by diffusion into the smaller units than into the larger.[17] The resulting somewhat complex behavior is known as diffusion- and convection-dependent inhomogeneity and may play an important role in lung disease.

A third possible reason for uneven ventilation is the presence of concentration gradients along the small airways. This is known as series inequality. Recall that inspired gas reaches approximately the region of the distal terminal or proximal respiratory bronchioles by convective flow, but gas flow over the rest of the distance to the alveoli is accomplished principally by diffusion within the airways. If there is abnormal dilation of an airway, the diffusion process may not be complete within the breathing cycle, and the distal alveoli will be less well ventilated than the proximal alveoli.

Heterogeneity in ventilation can be assessed by single-breath and *multibreath nitrogen washout* (MBNW) methods, which are described in Chapters 31 and 32. Three major indices are derived from the MBNW.[18,19] The *lung clearance index* is a global measure of ventilation heterogeneity but does not allow any specific anatomic localization of the site of heterogeneity. The more uneven the ventilation, the higher the lung clearance index, and abnormalities are apparent in obstructive airways disease, such as asthma, COPD, and cystic fibrosis. Two other indexes, *Scond* and *Sacin*, describe the contribution of convection (driven by pressure gradients, which take place in the conducting airways) and diffusion (driven by concentration gradients, which take place in the extreme periphery of the lung, likely beginning at the entrance to the lung acinus) to overall heterogeneity of ventilation.

BLOOD FLOW

Blood flow is as important for gas exchange as is ventilation. This has not always been appreciated, partly because the process of ventilation is more obvious, especially in the dyspneic patient, and is more accessible to measurement. Much has been learned about the pulmonary circulation in the past few years, especially about its metabolic functions. The anatomy and function of the pulmonary circulation are described in Chapters 1 and 6.

PRESSURES OF THE PULMONARY CIRCULATION

The pressures in the pulmonary circulation are very low compared with those in the systemic circulation, and this feature is responsible for much of its special behavior. The normal pressures in the human pulmonary artery are typically approximately 25 mm Hg systolic, 8 mm Hg diastolic, and 15 mm Hg mean. Normal mean pulmonary arterial pressure is thus six times lower than that in the systemic arterial circulation, which is approximately 100 mm Hg. The evolutionary force keeping the pressures in the pulmonary circulation low is the mechanical vulnerability of the extremely thin blood-gas barrier; higher pressures in the pulmonary capillaries would cause stress failure of the capillary wall.[20]

Pressure Inside Blood Vessels

Because the pulmonary arterial pressure is so low, hydrostatic effects due to gravity within the pulmonary circulation become very important. The adult upright human lung is some 30 cm high, giving a hydrostatic difference in pressure of 30 cm blood between the extreme apex and the base, which is equivalent to approximately 23 mm Hg. As a result, there are very substantial differences in flow within the small pulmonary arteries and the capillaries between the top and bottom of the upright lung. This topic is discussed further in the section "Distribution of Pulmonary Blood Flow."

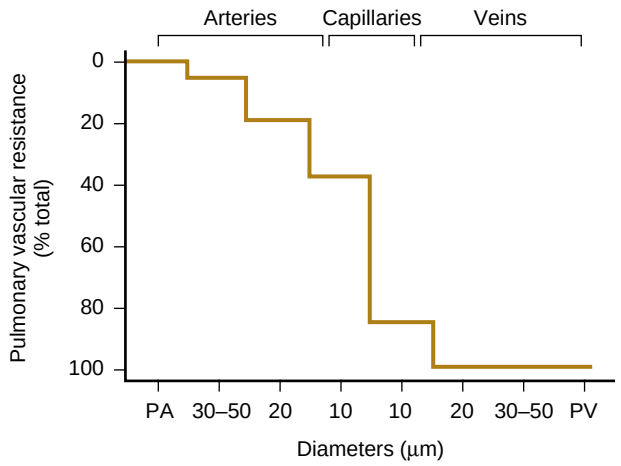

Figure 10.6 Pressure drop along the pulmonary circulation as determined by direct puncture of vessels. The normal pressure drop is greatest at the capillaries, and its mean pressure is approximately halfway between pulmonary artery (PA) pressure and pulmonary vein (PV) pressure. (Modified from Bhattacharya J, Nanjo S, Staub NC. Factors affecting lung microvascular pressure. *Ann N Y Acad Sci.* 1982;384:107–114.)

Various techniques have been used to determine the pattern of pressure drop along the pulmonary blood vessels. These include measurement of the transudation pressure on the pleural surface of isolated lung, measurement of the pressure transient resulting from the injection of a slug of low- or high-viscosity blood into the pulmonary artery,[21] and direct puncture of different-sized vessels along with direct measurement of hydrostatic pressure.[22] The direct puncture measurements indicate that much of the normal pressure drop in the pulmonary circulation probably takes place in the pulmonary capillaries (alveolar vessels), and that the mean capillary pressure is approximately halfway between that in the pulmonary artery and that in the pulmonary vein (Fig. 10.6). The distribution of pressure along the pulmonary blood vessels depends on lung volume. At low states of lung inflation, the resistance of the extra-alveolar vessels (see next section) increases and more pressure drop then takes place across the pulmonary arteries and veins instead of the capillaries. By contrast, there is evidence that, at very high states of lung inflation, the resistance of the capillary bed is increased, and therefore there will be an additional pressure drop in the capillaries.

Of interest, the pressures in the pulmonary circulation are highly pulsatile; indeed, if the normal systolic and diastolic pressures in the main pulmonary artery are 25 and 8 mm Hg, respectively, this is a much greater proportional change than the systolic-diastolic difference in systemic arteries (120 and 80 mm Hg, respectively). There is good evidence that the pulsatility of pressure, and therefore flow, extends to the pulmonary capillaries.[23]

Pressures Outside Blood Vessels

Some pulmonary blood vessels are exposed to alveolar pressure (or very nearly), whereas others are outside the influence of alveolar pressure but are very sensitive to the state of lung inflation. These two types of vessels are known as *alveolar* and *extra-alveolar*, respectively (Fig. 10.7).

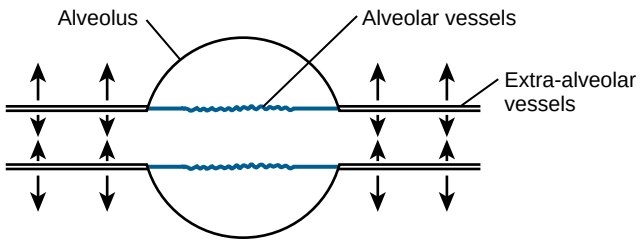

Figure 10.7 Diagram of alveolar and extra-alveolar vessels. The alveolar vessels are mainly the capillaries and are exposed to alveolar pressure. The extra-alveolar vessels have their lumina enlarged by the pull of radial traction (*outward-oriented arrows*) of the surrounding parenchyma. (Modified from West JB. *Respiratory Physiology: The Essentials*. 9th ed. Baltimore: Lippincott Williams & Wilkins; 2012.)

The alveolar vessels are largely capillaries that course through the alveolar walls. The pressure to which they are exposed is very nearly alveolar pressure. However, it can be shown that, when the lung is expanded from a very low lung volume, this pericapillary pressure falls below alveolar pressure because of surface tension effects in the alveolar lining layer.[24] By contrast, during deflation from high lung volumes, surface tension effects are much reduced and the pericapillary pressure is very close to alveolar pressure.

The extra-alveolar vessels are not exposed to alveolar pressure. The caliber of these vessels is determined by the radial traction of the surrounding alveolar walls and therefore depends on lung volume. When the lung inflates, the caliber of these vessels increases; when the lung deflates, their caliber decreases because of the elastic tissue in their walls and also because of a small amount of smooth muscle tone. The important point is that extra-alveolar vessel resistance falls with lung inflation, whereas alveolar vessel (capillary) resistance rises with lung inflation.

The small vessels (≈30 μm diameter) in the corners of the alveolar walls behave in a manner that is intermediate between that of the alveolar capillaries and the extra-alveolar vessels. These corner vessels can remain open when the capillaries are closed. Indeed, this is the normal appearance in zone 1 lung[25] (see later section on the distribution of blood flow). However, the shape and attachments of the corner vessels are very different from those of the larger extra-alveolar vessels, and it is unlikely that the pressure outside them varies in the same way when the lung expands.

The extra-alveolar vessels are surrounded by an interstitial perivascular space, which has an important role in the passive movement of extravascular fluid in the lung. The lymph vessels run in this space, although these lymph vessels do not open into this space or drain this fluid. One of the earliest histologic signs of interstitial pulmonary edema is "cuffing" of the interstitial perivascular space around the extra-alveolar vessels (see Figs. 14.4 and 14.5).[26,27] There is evidence that the perivascular pressure is very low compared with the hydrostatic pressure in the interstitium of the alveolar wall. As a consequence, fluid that moves from the capillaries into the interstitial space of the alveolar wall eventually flows to the perivascular low-pressure region by virtue of the hydrostatic pressure gradient.[28] The interstitial edema fluid then moves toward the hilum or toward the pleural space (see Chapter 14).

PULMONARY VASCULAR RESISTANCE

Pulmonary vascular resistance is given by the following relationship:

$$PVR = \frac{\text{Pulmonary arterial pressure} - \text{Pulmonary venous pressure}}{\text{Pulmonary blood flow}} \quad \text{Eq. 9}$$

Because all three variables vary between systole and diastole, mean values are generally used. This definition is similar to that used for electrical resistance, which is the difference of voltage across a resistor divided by the current. However, whereas the resistance of an electrical resistor is independent of the voltage at both ends and the current, this is not the case for pulmonary vascular resistance. For example, an increase in either pulmonary arterial pressure or pulmonary venous pressure generally results in a decrease in pulmonary vascular resistance because, as capillary pressure rises, there is both capillary recruitment and distention (see later). Similarly, if pulmonary blood flow is increased (e.g., by raising pulmonary arterial pressure), pulmonary vascular resistance usually decreases.

It is important to appreciate that a single number for pulmonary vascular resistance is an incomplete description of the pressure-flow properties of the pulmonary circulation. However, in practice, pulmonary vascular resistance is often a useful measurement because, although the normal value varies considerably, we often wish to compare the value in a normal lung with the higher values in abnormal ones.

Pressure-Flow Relations

If pulmonary blood flow is measured in an isolated, perfused lung, when pulmonary arterial pressure is raised (while pulmonary venous pressure, alveolar pressure, and lung volume are held constant), then flow increases relatively more than pressure. Figure 10.8 shows that pulmonary vascular resistance decreases both when pulmonary arterial pressure is raised and when pulmonary venous pressure is raised (other pressures held constant). The unifying explanation for reduced resistance in both cases is that the increases in intravascular pressure induce vascular recruitment and distension.

The decreases in pulmonary vascular resistance shown in Figure 10.8 help to limit the work of the right heart under conditions of high pulmonary blood flow. For example, during exercise, both pulmonary arterial and venous pressures rise. Although the normal pulmonary vascular resistance is remarkably low (the normal 5 L/min pulmonary blood flow is associated with an arterial-venous pressure difference of only approximately 10 mm Hg), the resistance falls to even lower values when the pulmonary arterial and venous pressures rise, as during exercise.

Two mechanisms responsible for the fall in pulmonary vascular resistance are *recruitment*, the opening up of previously closed blood vessels, and *distention*, the increase in caliber of vessels. Figure 10.9A shows experimental data from rapidly frozen dog lung preparations, indicating the importance of recruitment as the pulmonary arterial pressure is raised from low values.[29] Note that the number of open capillaries per millimeter of length of alveolar wall increased from approximately 25 to more than 50 as pulmonary arterial pressure was raised from zero to almost

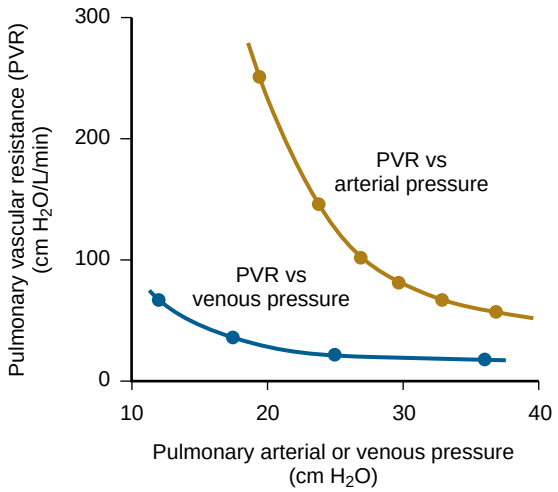

Figure 10.8 The drop in pulmonary vascular resistance seen when the pulmonary arterial or venous pressure is raised in a canine lung preparation. When one pressure was changed, the other was held constant. (Modified from West JB. *Respiratory Physiology: The Essentials*. 9th ed. Baltimore: Lippincott Williams & Wilkins; 2012.)

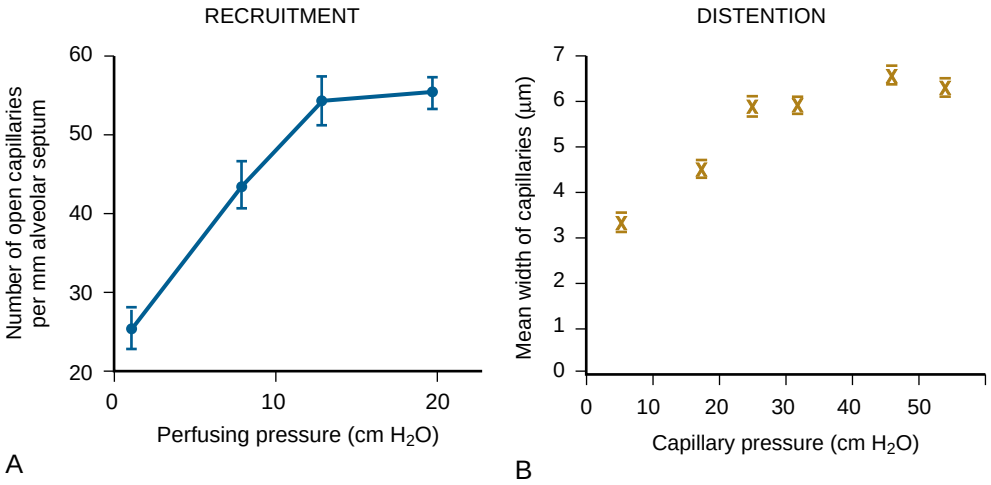

Figure 10.9 Mechanisms responsible for the fall in pulmonary vascular resistance with increases in vascular pressures. (A) Recruitment of pulmonary capillaries as the pulmonary arterial pressure, the perfusing pressure, is raised. (B) Distention of pulmonary capillaries as their pressure is increased. (A, Modified from Warrell DA, Evans JW, Clarke RO, et al. Pattern of filling in the pulmonary capillary bed. *J Appl Physiol.* 1972;32:346–356. B, Modified from Glazier JB, Hughes JMB, Maloney JE, West JB. Measurements of capillary dimensions and blood volume in rapidly frozen lungs. *J Appl Physiol.* 1969;26:65–76.)

15 cm H_2O. Figure 10.9B shows data on the importance of distention of pulmonary capillaries.[25] Note that the mean width of the capillaries increased from approximately 3.5 to nearly 7 μm as the capillary pressure was increased to approximately 50 cm H_2O. Beyond that, there was very little change.

The mechanism of recruitment of pulmonary capillaries is not fully understood. It has been suggested that, as the pulmonary arterial pressure is increased, the critical opening pressures of various arterioles are successively overcome. However, it has been shown that the red blood cell concentration, used as a measure of perfusion, varied within areas supplied by single arterioles, indicating that capillaries, not arterioles, probably accounted for the heterogenous perfusion.[29] This suggests that vessels are recruited at the capillary rather than the arterial level.

The mechanism of distention of pulmonary capillaries is apparently simply the bulging of the capillary wall as the transmural pressure of the capillaries is raised. This behavior is likely caused by a change in shape of the capillaries rather than actual stretching of the capillary wall. Surface tension forces and also longitudinal tension in the alveolar wall associated with lung inflation tend to flatten the capillaries at low capillary transmural pressures; this means that their diameter can then increase when capillary pressure rises. In photomicrographs of rapidly frozen lung preparations, pulmonary capillaries with very high intracapillary pressures show remarkable bulging.[25]

Recruitment and distention also provide mechanisms for increasing both the surface area of the lung microvasculature in contact with alveolar gas and the red cell transit time through the microvasculature, which may facilitate gas exchange.

Effect of Lung Volume

Lung volume has an important influence on pulmonary vascular resistance. Figure 10.10 shows that, as lung volume is increased from very low values, vascular resistance first decreases and then increases. The lung normally operates near the minimal value of vascular resistance, that is, FRC coincides with a low vascular resistance.

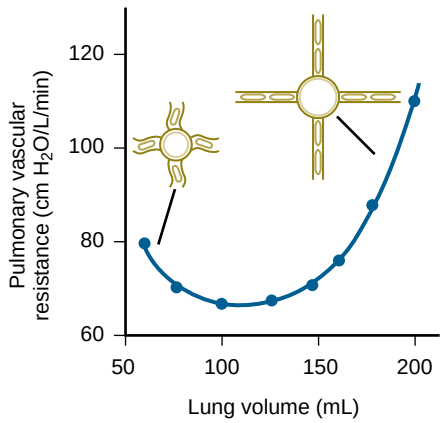

Figure 10.10 Effect of changing lung volume on pulmonary vascular resistance. At low lung volumes, resistance is high because the extra-alveolar vessels are narrowed (central circle) and because pulmonary capillaries become folded and distorted (vessels radiating from central circle). At high lung volumes, capillaries are stretched and their caliber reduced; this is probably the major contributor to increased vascular resistance at high lung volumes. (Data from a canine lung preparation.) (Modified from West JB. *Respiratory Physiology: The Essentials*. 9th ed. Baltimore: Lippincott Williams & Wilkins; 2012.)

At very low lung volume, the increase in pulmonary vascular resistance is caused by the decrease in caliber of the extra-alveolar vessels. Because these vessels are normally held open by the radial traction of the surrounding parenchyma, their caliber is least in the collapsed lung.[30] Another factor that may contribute to the high pulmonary vascular resistance at low states of lung inflation is folding and distortion of pulmonary capillaries.[31,32]

At high lung volume, the increase in pulmonary vascular resistance is probably caused by narrowing of the pulmonary capillaries. An analogy is a piece of thin rubber tubing that narrows considerably when it is stretched sideways, across its diameter. This distortion increases the resistance to fluid moving through it. Direct measurements on rapidly frozen dog lungs show that the mean width of the capillaries is greatly decreased at high states of lung inflation.[25]

In considering the effects of lung inflation, a distinction should be made between "positive" and "negative" pressure inflation. The results shown in Figure 10.10 were found with negative-pressure inflation, that is, when the lung was expanded by reducing pleural pressure and the relationship between pulmonary arterial and alveolar pressures was held constant. If positive-pressure inflation is used (i.e., alveolar pressure is increased with respect to pulmonary arterial pressure), pulmonary vascular resistance increases even more at high states of lung inflation. The reason is that lung inflation is then associated with a decrease in the transmural pressure of the capillaries and they are, in effect, squashed by the increased alveolar pressure.

Other Factors Affecting Pulmonary Vascular Resistance

Various drugs affect pulmonary vascular resistance. In some instances, the effects depend on the species of animal. However, in general, serotonin, histamine, and norepinephrine cause contraction of pulmonary vascular smooth muscle and increase vascular resistance. These drugs are particularly effective as vasoconstrictors when the lung volume is small and the radial traction of surrounding parenchyma on the extra-alveolar vessels is weak. Drugs that often relax smooth muscle in the pulmonary circulation include acetylcholine and isoproterenol. However, normal pulmonary blood vessels have little resting tone, so the degree of potential relaxation is small.

The autonomic nervous system exercises a weak control on the pulmonary circulation. There is evidence that increased sympathetic tone can cause vasoconstriction and stiffening of the walls of the larger pulmonary arteries. Both α- and β-adrenergic receptors are present.[33] Increased parasympathetic activity has a weak vasodilator action. As already indicated, any changes of vascular smooth muscle tone are much more effective at low states of lung inflation, when the extra-alveolar vessels are narrowed or, in the fetal state, when the amount of smooth muscle present is much greater than in the adult.

Pulmonary edema increases vascular resistance by poorly understood mechanisms. It may be that mechanisms

differ depending on the type and stage of edema. Interstitial pulmonary edema causes marked cuffing of the perivascular spaces of the extra-alveolar vessels. Presumably, the edema increases their vascular resistance[34] because the edema widens the perivascular space and thereby reduces the radial traction of the surrounding parenchyma that normally holds the vessels expanded. In addition, however, edema in the interstitium of the alveolar wall may encroach on the pulmonary capillaries to some extent, thus increasing their vascular resistance.[35] Pulmonary edema may also increase pulmonary vascular resistance by reducing ventilation to the most affected regions, thereby reducing the local alveolar P_{O_2} and stimulating hypoxic pulmonary vasoconstriction.

DISTRIBUTION OF PULMONARY BLOOD FLOW

Just as for ventilation, blood flow is not partitioned equally to all alveoli, even in the normal lung. Both gravitational and nongravitational factors affect the distribution of blood flow.

Normal Distribution

The distribution of pulmonary blood flow can conveniently be measured using radioactive materials. In one technique, radioactive xenon is dissolved in saline and injected into a peripheral vein. When the xenon reaches the pulmonary capillaries, it diffuses into the alveolar gas because of its low blood solubility. The resulting distribution of radioactivity within the lung can be measured using a gamma camera and reflects the regional distribution of blood flow. Subsequently, the distribution of alveolar volume is obtained by having the subject rebreathe radioactive xenon to equilibrium. By combining the two measurements, the blood flow per unit alveolar volume of the lung can be obtained. In another technique, the distribution of blood flow can be measured with radioactive albumin macroaggregates and with a variety of radioactive gases, such as ^{15}O-labeled carbon dioxide and ^{13}N. Finally, functional magnetic resonance imaging of the lung can be used to assess distribution of pulmonary blood flow.[36] This noninvasive technique does not expose subjects to radioactivity; therefore, it can be used repetitively and shows great promise for the future.

In the normal upright human lung, pulmonary blood flow decreases approximately linearly with distance up the lung, reaching very low values at the apex.[37] However, if the subject lies supine, apical and basal blood flow become the same, and now blood flow is less in the anterior (uppermost) than posterior (lowermost) regions of the lung. Thus, blood flow distribution is highly dependent on gravitational effects. During exercise in the upright position, both apical and basal blood flow rates increase, and the relative differences are reduced.

The factors responsible for the uneven distribution of blood flow due to gravitational influences can be studied conveniently in isolated lung preparations. These studies show that, in the presence of normal vascular pressures, blood flow decreases approximately linearly up the lung[38] as it does in intact humans. However, if the pulmonary arterial pressure is reduced, blood flows only up to the level at which pulmonary arterial equals alveolar pressures; above this point, no flow can be detected. These observations and others have led to the following model of blood flow.

Three-Zone Model for the Distribution of Blood Flow

Figure 10.11 shows a simple model for understanding the factors responsible for the inequality of blood flow in the lung.[38] The lung is divided into three zones according to the relative magnitudes of the pulmonary arterial, alveolar, and venous pressures.

Zone 1 is that region of the lung above the level at which pulmonary arterial equals alveolar pressures; in other words, in this region, alveolar pressure exceeds arterial pressure. Measurements in isolated lungs show that there is no blood flow in zone 1, the explanation being that the collapsible capillaries close because the pressure outside exceeds the pressure inside. Micrographs of rapidly frozen lung from zone 1 show that the capillaries have collapsed, although occasionally trapped red blood cells can be seen within them.[25] The vertical level of blood flow can also be influenced by the surface tension of the alveolar lining layer, as discussed earlier. If measurements are made on a lung immediately after it is inflated from a near-collapsed state, blood flow reaches 3 or 4 cm above the level at which pulmonary arterial and alveolar pressures are equal.[24] This can be explained by the surface tension, which lowers the pericapillary hydrostatic pressure to below the alveolar pressure and permits flow.

Zone 2 is the part of the lung in which pulmonary arterial pressure exceeds alveolar pressure, but alveolar pressure exceeds venous pressure. Here the vessels behave like Starling resistors,[39] that is, as collapsible tubes surrounded by a pressure chamber. Under these conditions, flow is determined by the difference between arterial and alveolar pressures, rather than by the difference between arterial and venous pressures. One way of looking at this is that the thin wall of the vessel offers no resistance to the collapsing pressure, so the pressure inside the vessel at some point

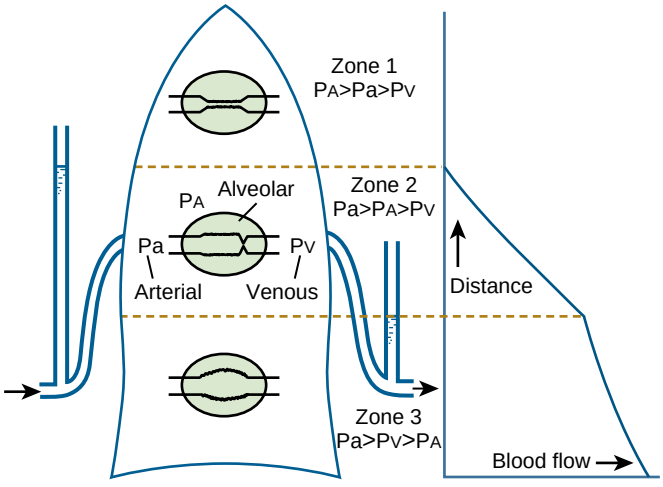

Figure 10.11 Three-zone model designed to account for the uneven gravitational distribution of blood flow in the lung. Pa, pulmonary arterial pressure; PA, pulmonary alveolar pressure; PV, pulmonary venous pressure. (Modified from West JB, Dollery CT, Naimark A. Distribution of blood flow in isolated lung: relation to vascular and alveolar pressures. *J Appl Physiol.* 1964;19:713–724.)

along its length becomes equal to chamber pressure, and the flow is determined by arterial minus chamber pressure. This behavior has been variously referred to as the waterfall[39] or sluice[40] effect and can be demonstrated in rubber-tube models on the laboratory bench. The increase in blood flow down zone 2 can be explained by the increase in hydrostatic pulmonary arterial pressure down the zone, whereas the alveolar pressure remains constant. Thus, the pressure difference determining flow increases linearly with distance down the lung.

Zone 3 is that part of the lung in which venous pressure exceeds alveolar pressure. Radioactive gas measurements show that blood flow also increases as one measures vertically down this zone, although, in some preparations at least, the rate of increase appears less than found in zone 2. Because the pressure difference responsible for flow is arterial minus venous pressure and because these two pressures increase similarly with distance down the zone, the increase in blood flow is not explained by changes in perfusing pressure. Instead, blood flow increases down this zone because vascular resistance falls with distance down the zone, likely because of progressive distention (confirmed histologically[25]) from the increasing transmural pressure (intravascular pressure increasing down the zone while alveolar pressure is constant). However, resistance may also be reduced by recruitment of capillaries.

The Effect of Lung Volume on the Distribution of Blood Flow—Zone 4

The three-zone model of Figure 10.11, based on the effects of pulmonary arterial, alveolar, and venous pressures, accounts for many of the distributions seen in the normal lung. However, other factors play a role; one of these is lung volume. For example, under most circumstances, a zone of reduced blood flow, known as zone 4, is seen in the lowermost region of the upright human lung.[41] This zone becomes smaller as lung volume is increased, but careful measurements indicate that a small area of reduced blood flow is still present at the lung base at total lung capacity. As lung volume is reduced, this region of reduced blood flow extends further and further up the lung so that, at FRC, blood flow decreases in the bottom half of the lung.

These patterns cannot be explained by the interactions of the pulmonary arterial, venous, and alveolar pressures at the alveolar vessels as in Figure 10.11. Instead, we have to take into account the contribution of the extra-alveolar vessels. As pointed out previously (see Fig. 10.10), the caliber of these vessels is determined by the degree of lung inflation; as lung volume is reduced, the vessels narrow. In the upright human lung, the alveoli are less well expanded at the base than at the apex because of distortion of the elastic lung caused by its weight (see Fig. 10.5). As a result, the extra-alveolar vessels are relatively narrow at the base, and their increased contribution to pulmonary vascular resistance results in the presence of a zone of reduced blood flow in that region. As lung volume is reduced, the contribution of the extra-alveolar vessels to the distribution of blood flow increases, and zone 4 extends further up the lung.

Vasoactive drugs and interstitial edema can also modify the contribution of extra-alveolar vessels to pulmonary vascular resistance. With injection of vasoconstrictor drugs such as serotonin, the role of the extra-alveolar vessels can be exaggerated[42] and, under these conditions, zone 4 extends further up the lung. The opposite effect is seen if a vasodilator drug such as isoproterenol is infused into the pulmonary circulation. With interstitial edema, the contribution of the extra-alveolar vessels increases because the edema creates a cuff of fluid around the vessels and the vessels narrow. This is thought to be the cause of the increased pulmonary vascular resistance seen at the base of the human lung in conditions of interstitial pulmonary edema,[34] in which the distribution of blood flow often becomes inverted (e.g., in chronic mitral stenosis).[43] Under these conditions, the blood flow to the apex of the upright lung consistently exceeds the flow to the basal regions. However, the effects of interstitial edema on blood flow distribution are still not fully understood.

Other Factors Affecting the Distribution of Blood Flow

Because the influence of gravity on the distribution of blood flow in the normal lung is so important, it is not surprising that, during acceleration of the body in an upward direction, the distribution of blood flow becomes more uneven.[44] For example, during exposure to $+3g$ acceleration, that is, three times the normal acceleration experienced by someone in the upright posture, the upper half of the lung is completely unperfused.

By contrast, in astronauts at weightlessness in space, the distribution of blood flow becomes more uniform.[45] Because it is not possible to use radioactive gases in this environment, the inequality of blood flow has been determined indirectly from the size of the cardiogenic oscillations for P_{CO_2}. Cardiogenic oscillations are fluctuations in the concentrations of gases such as oxygen, carbon dioxide, and nitrogen during a single expiration. They have the same frequency as the heart rate and are considered to be caused by differential rates of emptying of different parts of the lung due to contraction and dilation of the heart exerting direct pressure on nearby lung parenchyma. For oscillations to be detected, these differentially emptying regions must also have different alveolar P_{O_2} and P_{CO_2} values; this happens when blood flow and ventilation are not uniformly distributed throughout the lung. Weightlessness almost abolishes cardiogenic oscillations, implying greater uniformity in the distribution of blood flow and/or ventilation. Of interest, because these oscillations can still be seen, albeit to a much smaller extent than on Earth, some inequality remains, indicating an effect of nongravitational factors.

Several nongravitational factors may account for an uneven distribution of blood flow. One is that there may be regional differences of vascular resistance, with some regions of the pulmonary vasculature having an intrinsically higher vascular resistance than others. This has been shown to be the case in isolated dog lungs,[46] and there is some evidence for higher blood flows in the dorsal than the ventral regions of the lung in both intact dogs and horses. Another possible factor is a difference in blood flow between the central and peripheral regions of the lung,[47] although this finding is controversial. Some measurements show differences in blood flow along the acinus, with the more distal regions of the acinus being less well perfused than the proximal regions.[48,49] Also, as pointed out earlier, because of the complexity of the pulmonary circulation at the alveolar level, including the very large number of capillary

segments, it is likely that there is inequality of blood flow at this level.[50] There is also work suggesting that the distribution of pulmonary blood flow in small vessels may follow a fractal pattern.[51] The term *fractal* describes a branching pattern of both structure (blood vessels) and function (blood flow) that repeats itself with each generation. This means that any subsection of the vascular tree exhibits the same branching pattern as the entire tree. Were a picture of such a subsection to be enlarged, it would overlie and match the pattern of the whole tree. The repeated branching of blood vessels has implications for how blood flow is distributed independently of gravitational influences. The greater the number of branch points, the greater the likely inequality of perfusion among alveoli. This implies that the finer the spatial resolution of the method used to assess flow distribution, the greater the amount of inequality likely to be detected.

Abnormal Patterns of Blood Flow

The normal distribution of pulmonary blood flow is frequently altered by lung and heart disease. Localized lung disease, such as fibrosis and cyst formation, usually causes a local reduction of flow. The same is true of pulmonary embolism, in which the local reduction in blood flow, as determined from a perfusion scan, is usually coupled with normal ventilation, and this pattern provides important diagnostic information. Lung cancer may reduce regional blood flow, and occasionally a small hilar lesion can cause a marked reduction of blood flow to one lung, presumably through compression of the main pulmonary artery. Generalized lung diseases, such as COPD and asthma, also frequently cause patchy inequality of blood flow.[52,53]

Heart disease frequently alters the distribution of blood flow, as might be expected from the factors responsible for the normal distribution (see Fig. 10.11). For example, patients with increased blood flow through left-to-right shunts or with pulmonary hypertension usually show a more uniform distribution of blood flow because of their higher pulmonary artery pressure.[54] Diseases in which pulmonary arterial pressure is reduced, such as tetralogy of Fallot with oligemic lungs, are associated with reduced perfusion of the lung apices. Increased pulmonary venous pressure, as in mitral stenosis, initially causes a more uniform distribution than normal. However, in advanced disease, an inversion of the normal distribution of blood flow is frequently seen, with more perfusion to the upper than to the lower zones. The mechanism for this shift is not fully understood, but, as indicated earlier, perivascular edema causing an increased vascular resistance of the extra-alveolar vessels is thought to be a factor.

ACTIVE CONTROL OF THE PULMONARY CIRCULATION

The distribution of pulmonary blood flow and the pressure-flow relations of the pulmonary circulation are normally dominated by the passive effects of the hydrostatic pressure gradient described earlier. Thus, the roles of gravity, of variation in vascular lengths and diameters, and of recruitment and distention can account for much of the behavior of the normal circulation. The normal adult pulmonary circulation has a limited amount of smooth muscle in the walls of the vessels, and active control of vascular tone is weak. However, in some conditions there is an increase in the amount of smooth muscle. This is the case in the fetal lung, in long-term residence at high altitude, and in prolonged pulmonary hypertension. In these situations, the tone of the vascular smooth muscle plays a more significant role. However, even in the normal lung, some active control of the circulation is seen.

Hypoxic Pulmonary Vasoconstriction

In a region of a lung with alveolar hypoxia, vascular smooth muscle contracts and raises local vascular resistance, which may reduce blood flow. The precise mechanism of such hypoxic pulmonary vasoconstriction is still not known but, because it can be observed in excised isolated lungs, it clearly does not depend on central nervous system connections. Studies indicate that voltage-gated potassium channels in the vascular smooth muscle cells are involved, leading to increased intracellular calcium ion concentrations.[57–60] Furthermore, excised segments of pulmonary artery can constrict if their environment is made hypoxic, so there appears to be a local action of hypoxia on the artery itself.[55] It is also known that it is P_{O_2} of the *alveolar* gas, not of the pulmonary arterial blood, that chiefly determines the response.[56] This can be proved by perfusing a lung with blood with a high P_{O_2} while keeping the alveolar P_{O_2} low; under these conditions the vasoconstrictive response is still seen. The importance of local factors is supported by observations that hypoxic pulmonary vasoconstriction exists in transplanted lungs, despite the absence of autonomic neural innervation.[55]

For further discussion of the mechanisms of hypoxic pulmonary vasoconstriction, see ExpertConsult.com and Chapter 6.

The major site of vasoconstriction is in the small pulmonary arteries.[67] In the normal human lung, the small arteries have a meager amount of smooth muscle, which may be uneven in its distribution. This may explain why, even in global alveolar hypoxia (e.g., at high altitude), vasoconstriction is uneven. For example, during alveolar hypoxia, the variation in transit times through the pulmonary circulation of a lobe of a dog lung nearly doubles,[68] and the distribution of India ink particles injected into the pulmonary circulation becomes more uneven.[69] This uneven vasoconstriction probably plays a role in the mechanism of high-altitude pulmonary edema[70] (see later).

Hypoxic pulmonary vasoconstriction has the effect of directing blood flow away from hypoxic regions of lung, a redistribution that is beneficial to gas exchange. Other things being equal, this effect reduces the amount of ventilation-perfusion inequality in a diseased lung and limits the depression of the arterial P_{O_2}. An example of this is seen in patients with asthma treated with certain bronchodilators, which can decrease hypoxic pulmonary vasoconstriction. These sometimes reduce arterial P_{O_2} by increasing blood flow to poorly ventilated areas.[71,72]

Probably the most important role for hypoxic pulmonary vasoconstriction is in the fetal period. During fetal life, when the lungs do not undertake gas exchange, pulmonary vascular resistance is very high, partly because of hypoxic vasoconstriction, and only some 15% of the cardiac output

Endothelium-derived vasoactive substances may play a role in hypoxic pulmonary vasoconstriction. *Nitric oxide* (NO) is an endothelium-derived relaxing factor for blood vessels. It is formed from L-arginine and is a final common pathway for a variety of biologic processes. NO activates soluble guanylate cyclase, which leads to smooth muscle relaxation by the synthesis of cyclic guanosine monophosphate. Inhibitors of NO synthesis augment hypoxic pulmonary vasoconstriction in animal preparations, and inhaled NO reduces hypoxic pulmonary vasoconstriction in humans.[61] The required inhaled concentration of NO to see an effect is extremely low (≈20 parts per million). The effects of NO on ventilation-perfusion matching and arterial P_{O_2} in patients with lung disease depends on whether vasodilation increases perfusion of the well-ventilated regions of the lung or the less well-ventilated regions.[62]

Vasoconstrictor peptides, known as endothelins and released by pulmonary vascular endothelial cells, may participate in hypoxic vasoconstriction as well.[63] Their role in normal physiologic processes and disease is still being evaluated, but endothelin antagonists have become important therapeutic agents in pulmonary arterial hypertension.

The stimulus-response curve of hypoxic pulmonary vasoconstriction is very nonlinear (eFig. 10.1). When the alveolar P_{O_2} is altered in the region above 100 mm Hg, little change in vascular resistance is seen. However, when the alveolar P_{O_2} is reduced to approximately 70 mm Hg, vasoconstriction begins and, at a very low P_{O_2} approaching that of mixed venous blood, the local blood flow may be almost abolished. The data shown in eFigure 10.1 are from anesthetized open-chest cats.[64] Different results may be found in different species and different preparations. For example, in the coatimundi (a small South American mammal), there was an almost linear reduction of blood flow found between alveolar P_{O_2} values of 150 and 40 mm Hg.[65] In this study, the chest was closed, and the measurements were made in a very small region of lung. These conditions probably give the best information on the role of the phenomenon in the local regulation of blood flow.

Residence at high altitude results in hypoxic pulmonary vasoconstriction, both in newcomers and in permanent residents. The increase in pulmonary arterial pressure is especially marked during exercise. If 100% oxygen is given to normal subjects after being exposed to hypoxia for as little as 2 weeks, the pulmonary arterial pressure does not immediately return to the normal level.[66] This suggests that hypoxia has already induced some structural change in the pulmonary vessels. There is considerable variation among individuals in the response of pulmonary arterial pressure to alveolar hypoxia, leading some investigators to divide people into "responders" and "nonresponders."

flows through the lungs. The rest bypasses the lungs via the ductus arteriosus. The vasoconstriction is particularly effective because of the abundance of smooth muscle in the pulmonary arteries. At birth, when the first few breaths oxygenate the alveoli, the vascular resistance falls dramatically because of relaxation of vascular smooth muscle, and pulmonary blood flow increases enormously. In this situation, the release of hypoxic vasoconstriction is essential for the transition to air breathing.

DAMAGE TO PULMONARY CAPILLARIES BY HIGH WALL STRESSES

The blood-gas barrier has a basic dilemma. On one hand, the barrier has to be extremely thin to allow efficient gas exchange by passive diffusion. On the other hand, the blood-gas barrier must be strong because of the large mechanical stresses that develop in the capillary wall when the pressure in the capillaries rises or when the wall is stretched by inflating the lung to high volumes. There is evidence that the blood-gas barrier is just strong enough to withstand the highest stresses to which it is normally subjected. Unusually high capillary pressures or lung volumes can result in ultrastructural damage or stress failure of the capillary wall, leading to a high-permeability type of pulmonary edema, or even pulmonary hemorrhage.

When the capillary transmural pressure is raised in animal preparations, disruption of the capillary endothelium, alveolar epithelium, or sometimes all layers of the capillary wall is seen. In the rabbit lung, the first changes are seen at a transmural pressure of approximately 24 mm Hg, and the frequency of breaks increases as the pressure is raised.[73] Although these capillary pressures seem very high, there is now good evidence that the capillary pressure rises to the mid-30s (mm Hg) in the normal lung during heavy exercise.[74] This is largely secondary to the increase in left ventricular filling pressure.[75]

At these increased capillary transmural pressures, the "hoop" or circumferential stresses in the capillary wall become extremely high. The main reason for the very high stresses is the extreme thinness of the wall which, in the human lung, is less than 0.3 μm in some places. It is now believed that the strength of the blood-gas barrier on the thin side comes from type IV collagen in the basement membranes. The thickness of the type IV collagen layer is only approximately 50 nm. The delicacy of the alveoli can be appreciated by scanning electron microscopy, which demonstrates the interface of the alveolar epithelial cells and the alveolar capillary network (see Video 3.1).

Stress failure is the likely mechanism of several clinical conditions characterized by high-permeability pulmonary edema or hemorrhage.[76] Neurogenic pulmonary edema is associated with very high capillary pressures, the edema is of the high-permeability type, and ultrastructural damage to the capillaries is consistent with stress failure. High-altitude pulmonary edema is apparently caused by uneven hypoxic pulmonary vasoconstriction (referred to earlier), which allows some of the capillaries to be exposed to high pressure.[77] Again, the edema is of the high-permeability type, and typical ultrastructural changes in the capillaries have been demonstrated in animal preparations.[78]

A particularly interesting condition is seen in racehorses, which can suffer bleeding into the lungs while galloping. This is a common problem caused by extremely high pulmonary capillary pressures, which approach 100 mm Hg. Direct evidence of stress failure of pulmonary capillaries has been shown in these animals.[79] In fact, there is evidence that elite human athletes develop some ultrastructural changes in their blood-gas barrier during extreme exercise because significantly higher concentrations of red blood cells, total protein, and leukotriene B_4 are seen in their bronchoalveolar lavage fluid compared with sedentary controls.[80] This leakage only happens at extremely high levels of exercise[81]; a similar group of athletes who exercised at submaximal levels for 1 hour showed no changes in the bronchoalveolar lavage fluid.[82]

Overinflation of the lung is also known to increase the permeability of pulmonary capillaries. Stress failure is apparently the mechanism because it has been shown that, for the same capillary transmural pressure, high lung volumes greatly increase the frequency of capillary wall damage.[83] This is because some of the increased tension in the alveolar wall associated with lung inflation affects the capillary wall. Damage to the capillaries by overinflation may be an important mechanism in ventilator-induced lung injury.

BLOOD-GAS TRANSPORT

The partial pressure of a gas is an important concept in any discussion of gas exchange, as described later in the section on gas exchange. The *partial pressure* (P) of a gas is found by multiplying its concentration by the total pressure. For example, the P_{O_2} in dry room air at sea level is 159 mm Hg (0.209 × 760 mm Hg), where oxygen is 20.9% of room air and barometric pressure is 760 mm Hg. However, the relationship between P_{O_2} and its concentration in blood is not linear and is commonly described by an oxygen dissociation curve. Similar considerations apply to carbon dioxide in blood. The physiologic factors that determine the oxygen and carbon dioxide dissociation curves are considered later.

OXYGEN

Oxygen is carried in the blood in two forms. By far the most important component is in combination with hemoglobin. In addition, a small amount of oxygen is dissolved in the blood.

Hemoglobin consists of heme, an iron-porphyrin compound, and a protein (globin) that has four polypeptide chains. There are two types of chains, α and β, and differences in their amino acid sequences give rise to different types of human hemoglobin. There are unique conditions in which alterations in hemoglobin have clinical consequences. Examples include the normal hemoglobin F (fetal), which has a high affinity for oxygen, and hemoglobin S (sickle), which has a reduced affinity for oxygen and, in the deoxygenated form, tends to aggregate and deform the red cell. Methemoglobin, formed as a result of exposure to various drugs or chemicals, is not useful for carrying oxygen and increases the oxygen affinity of the remaining hemoglobin, thus impairing unloading of oxygen in the tissues.

Blood is able to transport large amounts of oxygen because oxygen forms an easily reversible combination with *hemoglobin* (Hb) to give *oxyhemoglobin* (HbO_2):

$$O_2 + Hb \rightleftharpoons HbO_2 \qquad \text{Eq. 10}$$

The relationship between the partial pressure of oxygen and the number of binding sites of the hemoglobin with oxygen attached is known as the *oxygen dissociation curve* (Fig. 10.12). Each gram of pure hemoglobin can combine with 1.39 mL of oxygen and, in normal blood with 15 g Hb/100 mL, the oxygen capacity (reached when all the binding sites are full) is 1.39 × 15, or approximately 20.8 mL O_2/100 mL of blood. The total *oxygen content* of a sample of blood (expressed as mL O_2/100 mL of blood), which includes the oxygen combined with hemoglobin and the dissolved oxygen, is given by

$$O_2\,\text{content} = (1.39 \times Hb) \times \frac{\%\,\text{saturation}}{100} + (0.003 \times P_{O_2}) \qquad \text{Eq. 11}$$

where *Hb* is the hemoglobin concentration and the final term is the oxygen dissolved in the blood (see later).

The characteristic shape of the oxygen dissociation curve has several physiologic advantages. The fact that the upper portion is almost flat means that a fall of 20 to 30 mm Hg in arterial P_{O_2} in a healthy subject with an initially normal value (e.g., ≈100 mm Hg) causes only a minor reduction in arterial oxygen content. However, this also means that noninvasive monitoring of oxygen saturation by pulse oximetry will often fail to indicate substantial falls in arterial P_{O_2} (see Chapter 44). Another consequence of the flat upper part of the curve is that the diffusive loading of oxygen in the pulmonary capillary is enhanced. This results from the large partial pressure difference between alveolar gas and capillary blood that is maintained even when most of the oxygen has been loaded. The steep lower part of the oxygen dissociation curve means that a relatively small drop in capillary P_{O_2} can lead to the unloading of considerable amounts of oxygen. This also maintains the blood P_{O_2} and assists the diffusion of O_2 into the tissue. A useful measure of the position of the dissociation curve is the P_{O_2} for 50% oxygen saturation, known as the P_{50}. The normal value for human blood is approximately 27 mm Hg.

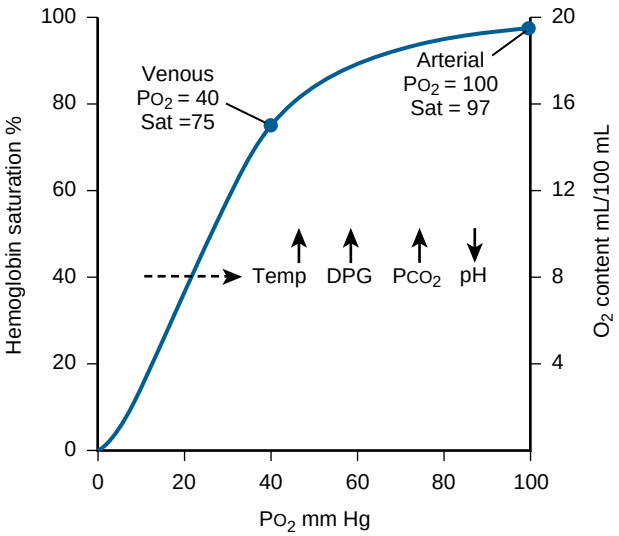

Figure 10.12 Oxygen dissociation curve showing typical values for arterial and mixed venous blood. The curve is shifted to the right by increases of temperature, 2,3-diphosphoglycerate (DPG), P_{CO_2}, and H^+ concentration. P_{CO_2}, partial pressure of carbon dioxide; P_{O_2}, partial pressure of oxygen; Sat, saturation; Temp, temperature. (Modified from West JB. *Respiratory Physiology: The Essentials*. 9th ed. Baltimore: Lippincott Williams & Wilkins; 2012.)

Various factors affect the position of the oxygen dissociation curve (see Fig. 10.12). A rightward shift indicates a decrease in the affinity of hemoglobin for oxygen. The curve is shifted to the right by an increase of temperature, hydrogen ion concentration, the concentration of *2,3-diphosphoglycerate* (2,3-DPG) in the red cell, and the P_{CO_2}. Increased P_{CO_2} reduces the oxygen affinity mainly by the increased H^+ concentration and increases oxygen unloading. The ability of carbon dioxide to reduce the affinity of hemoglobin for oxygen is called the *Bohr effect*. One consequence of the Bohr effect is that, as peripheral blood loads carbon dioxide, the unloading of oxygen is assisted. A rightward shift is also caused by 2,3-DPG, an end product of red cell metabolism.[84,85] The concentration of 2,3-DPG can be increased in the setting of chronic hypoxia.

Leftward shifts of the oxygen dissociation curve mean an increased affinity of hemoglobin for oxygen, as can be caused by a reduced concentration of 2,3-DPG or by the presence of carbon monoxide. The concentration of 2,3-DPG falls in stored blood, which can lead to blood with a high affinity for oxygen but with difficulty releasing oxygen to the tissues. Small amounts of carbon monoxide in the blood increase the affinity of the remaining oxygen for hemoglobin and therefore cause a leftward shift of the dissociation curve. As a result, the unloading of oxygen in the peripheral tissue is hampered. In addition, of course, the oxygen content of the blood is reduced at the same P_{O_2} because some of the hemoglobin is bound to carbon monoxide. This is particularly dangerous because arterial chemoreceptors respond to decreases in P_{O_2} and not to decreases in oxygen content, so the usual physiologic responses to hypoxemia may be absent.

Dissolved oxygen, when compared to oxygen carried by hemoglobin, plays a small role in oxygen transport because the solubility of oxygen is so low (0.003 mL O_2/100 mL blood/mm Hg). Thus, normal arterial blood with a P_{O_2} of approximately 100 mm Hg contains only 0.3 mL of dissolved oxygen per 100 mL, whereas approximately 20 mL is combined with hemoglobin. However, dissolved oxygen can become important under some conditions. The most common is when a patient is given 100% oxygen to breathe. This typically raises the alveolar P_{O_2} to greater than 600 mm Hg, with the result that, if the lungs are normal, the dissolved oxygen may increase from 0.3 to approximately 2 mL/100 mL blood. This dissolved oxygen then becomes a significant proportion of the normal arterial-venous oxygen content difference of approximately 5 mL O_2/100 mL blood.

CARBON DIOXIDE

Carbon dioxide is transported in the blood in three forms: as bicarbonate (≈90%), as dissolved CO_2 (≈5% of the total), and in combination with proteins such as carbamino compounds (≈5%). Because carbon dioxide is some 24 times

more soluble than oxygen in blood, dissolved carbon dioxide plays a more significant role in carbon dioxide transport than dissolved oxygen does in oxygen transport. For example, approximately 10% of the carbon dioxide that diffuses into the alveolar gas from the mixed venous blood comes from the dissolved form.

Bicarbonate is formed in blood by the following hydration reaction:

$$CO_2 + H_2O \xleftrightarrow{CA} H_2CO_3 \rightleftharpoons H^+ + HCO_3^- \qquad \text{Eq. 12}$$

The hydration of carbon dioxide to carbonic acid (and vice versa) is catalyzed by the enzyme *carbonic anhydrase* (CA), present in high concentrations in the red cells but absent from the plasma; some CA is apparently located on the surface of the endothelial cells of the pulmonary capillaries. Because the majority of the CA is in the red cell, carbon dioxide is mostly hydrated there, and bicarbonate ion moves out of the red cell to be replaced by chloride ions to maintain electrical neutrality (the chloride shift). Some of the hydrogen ions formed in the red cell are bound to hemoglobin and, because deoxygenated hemoglobin is a better proton acceptor than the oxygenated form, deoxygenated blood can carry more carbon dioxide for a given P_{CO_2} than can oxygenated blood (Fig. 10.13). In this way, oxygen decreases the affinity of hemoglobin for carbon dioxide, thereby increasing carbon dioxide delivery at the lung. This is known as the *Haldane effect*.

The carbon dioxide dissociation curve describing the relationship between P_{CO_2} and total carbon dioxide concentration is shown in Figure 10.13. Note that the curve is much more linear in its working range than the oxygen dissociation curve (see Fig. 10.12) and that, as we have seen, the lower the saturation of hemoglobin with oxygen, the larger the carbon dioxide concentration for a given P_{CO_2}.

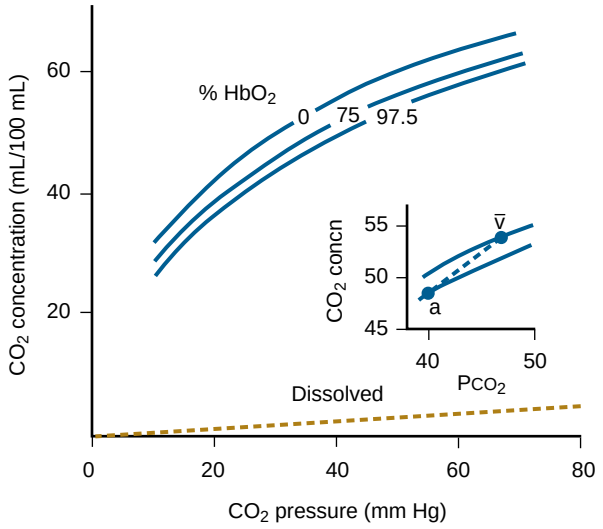

Figure 10.13 Carbon dioxide dissociation curves for blood of different oxygen saturations (oxyhemoglobin [HbO_2]). *Inset*, The physiologic curve between arterial (a) and mixed venous ($\bar{v}$) blood, shown with two dissociation curves representing the %HbO_2 for venous blood (*top*) and for arterial blood (*bottom*). concn, concentration; P_{CO_2}, partial pressure of carbon dioxide. (Modified from West JB. *Respiratory Physiology: The Essentials*. 9th ed. Baltimore: Lippincott Williams & Wilkins; 2012.)

The transport of carbon dioxide by the blood plays an important role in the acid-base status of the body. This topic is discussed at length in Chapter 12.

GAS EXCHANGE

The primary function of the lungs is gas exchange, that is, allowing oxygen to move from the air into the blood and allowing carbon dioxide to move out. It is now established that movement of gas across the blood-gas interface is by simple passive diffusion, that is, random (brownian) motion at a rate determined by temperature. Diffusion results in net transfer of molecules from an area of high to an area of low partial pressure, and active transport is not required. The structure of the lung is well suited to this mechanism of gas exchange. The blood-gas barrier is extremely thin (only 0.3 μm over much of its extent), and its area is between 50 and 100 m^2. Because Fick's law of diffusion states that the amount of gas that moves across a tissue sheet is proportional to its area and inversely proportional to its thickness, the blood-gas barrier is ideal for its gas-exchanging function.

An important concept in any discussion of gas exchange is partial pressure. As described earlier in "Blood-Gas Transport," the partial pressure of a gas is the product of its concentration and the total pressure. For example, $P_{O_2} = 0.209 \times 760$ mm Hg = 159 mm Hg in dry air with 20.9% oxygen at sea level, where the barometric pressure is 760 mm Hg. When air is inhaled into the upper airway, it is warmed and saturated with water vapor. The water vapor pressure at 37°C is 47 mm Hg. Under these conditions, the total dry gas pressure is only 760 − 47 = 713 mm Hg. The P_{O_2} of moist inspired air is therefore (20.9/100) × 713 = 149 mm Hg. In general, the relationship between the *partial pressure* (P) and *fractional concentration* (F) of a gas when water vapor is present is given by $Px = Fx\,(Pb - PH_2O)$, where *Pb* is barometric pressure and *x* is the species of gas.

Figure 10.14 shows an overview of the oxygen cascade from the air that we breathe to the tissues where it is used. The line represents an ideal situation that does not actually exist but does make a useful backdrop for purposes of discussion. One of the first surprises is that, by the time the oxygen has reached the alveoli, its partial pressure has fallen from approximately 150 to 100 mm Hg. The reason for this decline is that the P_{O_2} in the alveolar gas is determined by a balance between two factors. On the one hand, there is the essentially continuous addition of oxygen by the process of alveolar ventilation and, on the other hand, there is the continuous removal of oxygen by the pulmonary blood flow. The net result is that the alveolar P_{O_2} settles out at approximately 100 mm Hg.

It is true that the process of ventilation is intermittent with each breath and not continuous. By the same token, pulmonary capillary blood flow is known to be pulsatile. However, the volume of gas in the lung at FRC is sufficient to dampen both of these oscillations, with the result that the alveolar P_{O_2} varies by only 3 or 4 mm Hg with each breath and by less than that with each heartbeat. Thus, alveolar ventilation and capillary blood flow can be regarded as continuous processes from the point of view of gas exchange. This greatly simplifies consideration of gas exchange.

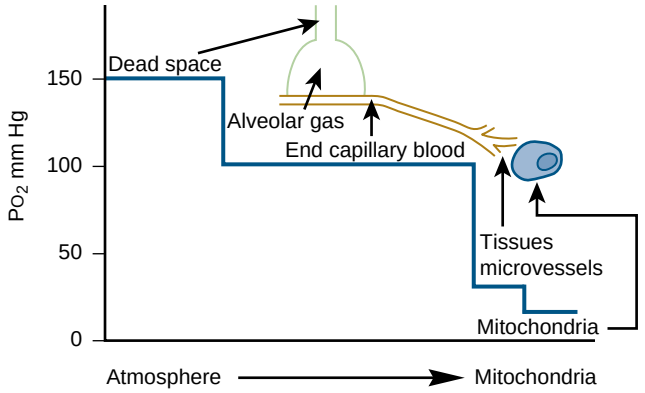

Figure 10.14 Scheme of the oxygen partial pressures from air to tissues. A hypothetically perfect situation. P_{O_2}, partial pressure of oxygen. (Modified from West JB. *Ventilation/Blood Flow and Gas Exchange.* 5th ed. Oxford: Blackwell Scientific; 1990.)

In an ideal lung (see Fig. 10.14), the effluent pulmonary venous blood, which becomes the systemic arterial blood, would have the same P_{O_2} as that of the alveolar gas, namely, approximately 100 mm Hg. This is very nearly the case in the normal lung. However, when the arterial blood reaches the peripheral tissues, P_{O_2} falls substantially en route to the mitochondria. The movement of oxygen in the peripheral tissues is also essentially by passive diffusion, and the mitochondrial P_{O_2} is considerably lower than that in either the arterial or mixed venous blood. Indeed, the P_{O_2} in the mitochondria may vary considerably throughout the body, depending on the type of tissue and its oxygen uptake. Nevertheless, it is useful to bear in mind that the mitochondria are the targets for the oxygen transport system and that any fall in the arterial P_{O_2} caused, for example, by inefficient pulmonary gas exchange must be reflected in a reduced tissue P_{O_2}, other factors being equal.

For carbon dioxide, the process is reversed. There is essentially no carbon dioxide in the inspired air, and the alveolar P_{CO_2} is approximately 40 mm Hg. Under normal conditions, arterial and alveolar P_{CO_2} values are the same, whereas the P_{CO_2} of mixed venous blood is in the range of 45 to 47 mm Hg. The P_{CO_2} of the tissues is probably quite variable, depending, for example, on the state of metabolism. Nevertheless, any inefficiency of the lung for carbon dioxide removal tends to raise the P_{CO_2} of the tissues, other factors being equal.

CAUSES OF HYPOXEMIA (See Chapter 44)

Hypoxemia refers to a reduction in arterial P_{O_2} to below normal values. There are five causes of hypoxemia. Four processes from within the body can impair pulmonary gas exchange and cause hypoxemia when breathing room air at sea level: hypoventilation, diffusion limitation, shunt, and ventilation-perfusion inequality. There is an additional cause from outside the body, namely from a decrease in inspired oxygen concentration. Such a decrease in fractional concentration of oxygen in inspired gas may be found at high altitude or with accidents in which oxygen is consumed or displaced in inspired air.

Hypoventilation

Hypoventilation is used here to refer to conditions in which alveolar ventilation is abnormally low in relation to oxygen uptake or carbon dioxide output (see also Chapter 45). Alveolar ventilation is the volume of fresh inspired gas going to the alveoli (i.e., non–dead-space ventilation), as mentioned earlier. As we shall see, hypoventilation always causes a raised arterial P_{CO_2} and also arterial hypoxemia (unless the patient is breathing an enriched oxygen mixture). It should be noted that other conditions (e.g., ventilation-perfusion inequality) can also result in carbon dioxide retention, and some use the terms *hypoventilation* and *carbon dioxide retention* interchangeably. However, this can be confusing because carbon dioxide can be retained even when a patient is breathing more than normal, so we do not use the terms interchangeably.

As previously mentioned, the P_{O_2} of alveolar gas is determined by a balance between the rate of addition of oxygen by alveolar ventilation and the rate of removal by the pulmonary blood flow to satisfy the oxygen demands of the tissues. Hypoventilation results when the alveolar ventilation is reduced and the alveolar P_{O_2} therefore settles out at a lower level than normal. For the same reason, the alveolar P_{CO_2}, and therefore also arterial P_{CO_2}, are also raised.

Causes of hypoventilation include depression of the respiratory center by drugs, such as opiates, or diseases of the brainstem, such as encephalitis; abnormalities of the spinal cord–conducting pathways, such as high cervical dislocation; anterior horn cell diseases, including poliomyelitis, affecting the phrenic nerves or supplying the intercostal muscles; diseases of nerves to respiratory muscles (e.g., Guillain-Barré syndrome); diseases of the myoneural junction, such as myasthenia gravis; diseases of the respiratory muscles themselves, such as progressive muscular dystrophy; thoracic cage abnormalities (e.g., crushed chest); upper airway obstruction (e.g., thymoma); hypoventilation associated with extreme obesity (obesity hypoventilation syndrome); and other causes, such as metabolic alkalosis and idiopathic states.

Note that, in all these conditions, the lungs are normal. Thus, this group can be clearly distinguished from those diseases in which the carbon dioxide retention is associated with chronic lung disease. In the latter conditions, the lungs are abnormal, and a major factor in the raised P_{CO_2} is the ventilation-perfusion inequality that causes gross inefficiency of pulmonary gas exchange (see later).

The rise in alveolar P_{CO_2} as a result of hypoventilation can be calculated using the alveolar ventilation equation (see earlier section "Total and Alveolar Ventilation" for derivation):

$$\dot{V}_A = \frac{\dot{V}_{CO_2}}{P_{ACO_2}} \times K \qquad \text{Eq. 5}$$

where K is a constant. This can be rearranged as follows:

$$P_{ACO_2} = \frac{\dot{V}_{CO_2}}{\dot{V}_A} \times K \qquad \text{Eq. 13}$$

Because, in normal lungs, the alveolar (P_{ACO_2}) and arterial (P_{aCO_2}) P_{CO_2} are almost identical, we can write:

$$P_{aCO_2} = \frac{\dot{V}_{CO_2}}{\dot{V}_A} \times K \qquad \text{Eq. 14}$$

This very important equation indicates that the level of P_{CO_2} in alveolar gas or arterial blood is inversely related to the alveolar ventilation. For example, if the alveolar ventilation is halved, the P_{CO_2} doubles. Note, however, that this is true only after a steady state has been reestablished and the carbon dioxide production rate is the same as before. In practice, if the alveolar ventilation of a patient is suddenly decreased (e.g., by changing the setting on a ventilator), the P_{CO_2} rises over a period of 10 to 20 minutes. The rise is rapid at first and then is more gradual as the body stores of carbon dioxide are gradually filled.[86]

The same principles used for carbon dioxide can be applied to oxygen to understand the effect of hypoventilation on alveolar, and thus arterial, P_{O_2}. The corresponding mass conservation equation for oxygen is as follows, where $\dot{V}_{O_2}$ is the oxygen uptake:

$$\dot{V}_{O_2} = (\dot{V}_I \times F_{IO_2}) - (\dot{V}_A \times F_{AO_2}) \qquad \text{Eq. 15}$$

Here $\dot{V}_I$ is inspired alveolar ventilation, whereas $\dot{V}_A$ is expired alveolar ventilation. Eq. 15 expresses oxygen uptake as the difference between the oxygen inhaled (volume per minute of inspired gas [$\dot{V}_I$] × *fractional concentration of oxygen* [F_{IO_2}]) and that exhaled (volume per minute of alveolar ventilation [$\dot{V}_A$] × *fractional concentration of oxygen in alveolar gas* [F_{AO_2}]). Normally, because a little more oxygen is taken up per minute than carbon dioxide exhaled, $\dot{V}_I$ exceeds $\dot{V}_A$. However, this difference is usually no more than 1% of the ventilation, and clinically it can most often be ignored. If this is done, $\dot{V}_I$ may then be replaced by $\dot{V}_A$, and Eq. 15 simplifies to

$$\dot{V}_{O_2} = \dot{V}_A \times (F_{IO_2} - F_{AO_2}), \textit{ or}$$

$$\dot{V}_{O_2} = \dot{V}_A \times \frac{(P_{IO_2} - P_{AO_2})}{K} \qquad \text{Eq. 16}$$

where P_{IO_2} is the partial pressure of oxygen in the inspired gas. Thus, as ventilation falls, P_{AO_2} must fall as well to maintain the rate of oxygen uptake necessary for metabolic function.

Eq. 13 (reexpressed as $\dot{V}_{CO_2} = \dot{V}_A \times P_{ACO_2}/K$) and Eq. 16 can be usefully combined. If Eq. 13 is divided by Eq. 16, we get

$$\frac{\dot{V}_{CO_2}}{\dot{V}_{O_2}} = R = \frac{P_{ACO_2}}{(P_{IO_2} - P_{AO_2})} \qquad \text{Eq. 17}$$

Here *R* is the respiratory exchange ratio (volume of carbon dioxide exhaled/oxygen taken up in the same time). Both K and $\dot{V}_A$ cancel out when the division is performed. Rearranging this equation yields

$$P_{AO_2} = P_{IO_2} - \frac{P_{ACO_2}}{R} \qquad \text{Eq. 18}$$

This is called the *alveolar gas equation*, and it uniquely relates alveolar P_{O_2} to P_{CO_2} for given values of inspired P_{O_2} and R. It is the basis of calculations of the *alveolar-to-arterial Po_2 difference,* a commonly used index of efficiency of pulmonary gas exchange. Because we assumed that $\dot{V}_I = \dot{V}_A$ in deriving this equation, it is an approximation. It is possible to account for the difference between $\dot{V}_I$ and $\dot{V}_A$, and, when this is done, the alveolar gas equation contains an additional term:

$$P_{AO_2} = P_{IO_2} - \frac{P_{ACO_2}}{R} + \left[P_{ACO_2} \times F_{IO_2} \times \frac{(1-R)}{R} \right] \qquad \text{Eq. 19}$$

The term in brackets is the correction factor for the difference between inspired and expired volumes. It is generally small during air breathing (1 to 3 mm Hg) and can be ignored in most clinical settings if the patient is breathing air. However, if the patient is being given an enriched oxygen mixture, the correction factor increases. In someone with normal lungs breathing pure oxygen, the factor is approximately 10 mm Hg.

As an example of the use of the alveolar gas equation, suppose that a patient with normal lungs takes an overdose of a barbiturate drug that depresses alveolar ventilation. The patient's alveolar P_{CO_2} might rise from 40 to 60 mm Hg (the actual value is determined by the alveolar ventilation equation). Before the drug, the patient's alveolar P_{O_2} can be calculated assuming R = 1.0, and the small correction factor is neglected:

$$\begin{aligned} P_{AO_2} &= P_{IO_2} - (P_{ACO_2}/R) \\ &= 149 - (40/1) \\ &= 109 \text{ mm Hg} \end{aligned}$$

After the drug, and making the same assumptions, with an increase of P_{CO_2} by 20 mm Hg, the alveolar P_{O_2} will fall by 20 mm Hg:

$$\begin{aligned} P_{AO_2} &= P_{IO_2} - (P_{ACO_2}/R) \\ &= 149 - (60/1) \\ &= 89 \text{ mm Hg} \end{aligned}$$

Hence, when R = 1.0, alveolar P_{O_2} falls by 20 mm Hg, which is the same amount by which the P_{CO_2} rises. If R = 0.8, which is a more typical resting value, and we ignore the small correction factor in Eq. 19, then, when alveolar P_{CO_2} increases by 20 mm Hg, alveolar P_{O_2} decreases by 25 mm Hg, from 99 mm Hg (the P_{AO_2} when the CO_2 is 40 mm Hg and R 0.8) to 74 mm Hg.

Both examples emphasize that, in practical terms, the hypoxemia is generally of minor importance compared with the carbon dioxide retention and consequent respiratory acidosis. This is further illustrated in Figure 10.15, which shows calculated changes in gas exchange as a result of hypoventilation. Note that severe hypoventilation sufficient to double the P_{CO_2} from 40 to 80 mm Hg decreases the alveolar P_{O_2} from only, say, 100 to 50 or 60 mm Hg. Although the arterial P_{O_2} is likely to be a few millimeters of mercury lower than the alveolar value, the arterial oxygen saturation is still approximately 80%. However, at that level of P_{CO_2}, there is substantial respiratory acidosis, with an arterial pH of approximately 7.2. This fact emphasizes that, in pure hypoventilation, the hypoxemia is usually not as important as the carbon dioxide retention and respiratory acidosis.

An important feature of alveolar hypoventilation is that, although the arterial P_{CO_2} is always elevated, the arterial P_{O_2} may be returned to normal very easily by giving supplementary oxygen. Suppose that the patient with barbiturate intoxication just discussed is given 30% oxygen to breathe. If we assume that the ventilation remains unchanged, it can be shown (from Eq. 19) that the alveolar P_{O_2} increases from 74 to approximately 140 mm Hg. Thus, a relatively small increase in inspired P_{O_2} is very effective in eliminating the arterial hypoxemia of hypoventilation.

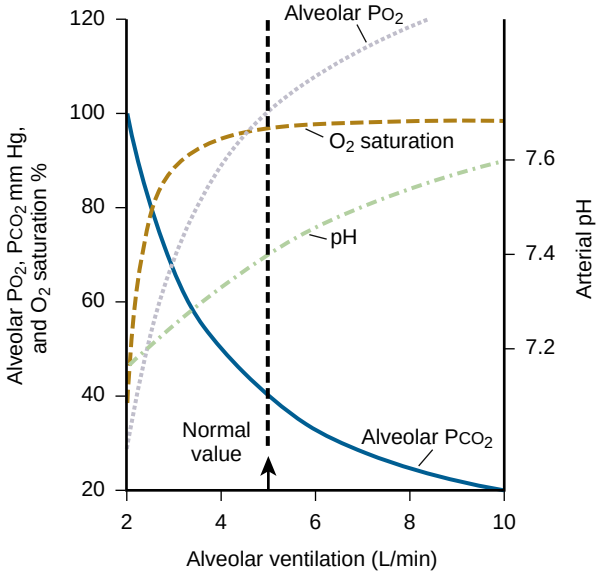

Figure 10.15 Gas exchange during changes in ventilation. With hypoventilation, note the relatively large rise in P_{CO_2} and consequent fall in pH compared with the modest fall in arterial oxygen saturation. P_{CO_2}, partial pressure of carbon dioxide; P_{O_2}, partial pressure of oxygen. (Modified from West JB. *Respiratory Physiology: The Essentials*. 9th ed. Baltimore: Lippincott Williams & Wilkins; 2012.)

Diffusion Limitation

Oxygen, carbon dioxide, and all other gases cross the blood-gas barrier by simple passive diffusion. Fick's law of diffusion states that the rate of transfer of a gas through a sheet of tissue is proportional to the tissue *area* (A) and the difference in partial pressure ($P_1 - P_2$) between the two sides, and it is inversely proportional to the *thickness* (T):

$$\dot{V}gas = \frac{A}{T} \times D \times (P_1 - P_2) \qquad \text{Eq. 20}$$

As we have seen already, the area of the blood-gas barrier in the lung is enormous (50–100 m^2), and the thickness is less than 0.3 μm in some places, so the dimensions of the barrier are ideal for diffusion.

The rate of diffusion is also proportional to a *constant* (D), which depends on the properties of the tissue and the particular gas. The constant is proportional to the *solubility* (Sol) of the gas and inversely proportional to the square root of the *molecular weight* (MW):

$$D \propto \frac{Sol}{\sqrt{MW}} \qquad \text{Eq. 21}$$

This equation can be used to compare the difference of rate of diffusion of oxygen and carbon dioxide. For each millimeter of mercury difference between capillary and alveolar partial pressures, carbon dioxide diffuses approximately 20 times more rapidly than oxygen through tissue sheets because carbon dioxide has a much higher solubility (24:1 at 37°C), whereas the square roots of the molecular weights are not very different (1.17:1). Note that this calculation applies only to tissue sheets and does not fully account for the uptake of oxygen or output of carbon dioxide by the lung because the chemical reactions between these gases and components of blood also play a role (see later discussion).

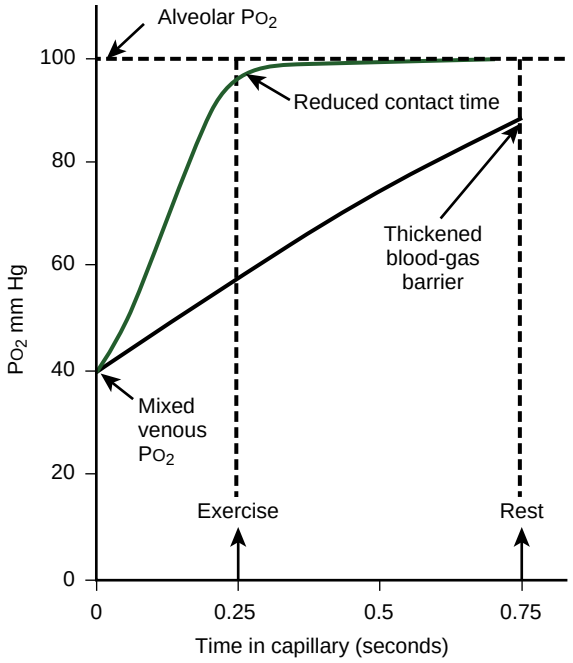

Figure 10.16 Oxygen uptake along the pulmonary capillary. Typical time courses for the change in P_{O_2} in the pulmonary capillary when diffusion is normal (*green line*), when the contact time is reduced as during exercise (*arrow at green line*), and when the blood-gas barrier is abnormally thick (*black line*). P_{O_2}, partial pressure of oxygen. (Modified from West JB. *Respiratory Physiology: The Essentials*. 9th ed. Baltimore: Lippincott Williams & Wilkins; 2012.)

Oxygen Uptake Along the Pulmonary Capillary. Figure 10.16 shows calculated changes in the P_{O_2} of the blood along the pulmonary capillary as oxygen is taken up under normal conditions. The calculation is based on Fick's law of diffusion (see Eq. 20). One of the several assumptions is that the diffusion characteristics of the blood-gas barrier are uniform along the length of the capillary. The calculation is complicated by the fact that the change in the P_{O_2} of the capillary blood depends on the oxygen dissociation curve. This is not only nonlinear, but it is also influenced by the simultaneous elimination of carbon dioxide. The calculation describing this is often known as the Bohr integration because it was first carried out in a simplified form by Christian Bohr.[87] Modern computations take into account reaction times of oxygen with hemoglobin and also reaction rates associated with carbon dioxide elimination (see later discussion).[88]

Figure 10.16 shows that the time spent by the blood in the pulmonary capillary under normal resting conditions is approximately 0.75 second. This number is obtained by dividing the volume of blood calculated to be in the pulmonary capillaries (75 mL) by the cardiac output (6 L/min).[89] The figure shows that the P_{O_2} of pulmonary capillary blood very nearly reaches that of alveolar gas after approximately one-third of the available time in the capillary. This means that there is normally ample time for essentially complete oxygenation of the blood or, as it is sometimes said, the normal lung has substantial diffusion reserves.

If the blood-gas barrier is thickened, the rate of transfer of oxygen across the barrier is reduced in accordance with Fick's law, and the rate of rise of P_{O_2} is slower, as shown in Figure 10.16. Under these circumstances, diffusion may not be sufficient, and a P_{O_2} difference may develop between

alveolar gas and end-capillary blood. This means that there is some diffusion limitation of oxygen transfer. It is important to appreciate that, under most conditions at sea level, oxygen transfer is perfusion limited, meaning that oxygen uptake is entirely dependent on blood flow. Only under unusual conditions, such as severe interstitial lung disease, is there some diffusion limitation. However, at high altitude, diffusion limitation during exercise is universal, even in health. In well-trained athletes with very rapid transit time through the capillaries, diffusion may be limiting during exercise even at sea level.

For further discussion of diffusion and perfusion limitation and diffusion capacity measurements, see ExpertConsult.com and Chapter 31.

Shunt

Shunt refers to the entry of blood into the systemic arterial system without going through ventilated areas of lung. Even the normal cardiopulmonary system shows some depression of the arterial P_{O_2} as a result of this factor. For example, in the normal lung, some of the bronchial artery blood is collected by the pulmonary veins after it has perfused the bronchi. Because the oxygen content of this blood has been reduced, its addition to the normal end-capillary blood results in a reduction of arterial P_{O_2}. Another source of normal shunting is the small amount of coronary venous blood that drains directly into the cavity of the left ventricle through the thebesian veins. Of course, most of the coronary venous blood ends up in the coronary sinus, and only a minute fraction reaches the left ventricle directly. Such shunts depress arterial P_{O_2} only by approximately 1 to 2 mm Hg.

In patients with congenital heart disease, there may be a direct addition of venous blood to arterial blood across a defect between the right and left sides of the heart. In general, this needs an increase in pressure on the right side; otherwise, the shunt would only take place from left to right. In lung disease, there may be gas-exchanging units that are completely unventilated because of airway obstruction, atelectasis, or alveolar filling with fluid or cells. The unoxygenated blood draining from these constitutes a shunt. It could be argued that such units are simply at the extreme end of the spectrum of ventilation-perfusion inequality (see next section), but the gas exchange properties of unventilated units are so different (e.g., in their response to supplemental oxygen) that it is convenient to separate them.

When the shunt is caused by the addition of mixed venous blood (pulmonary arterial) to blood draining from the capillaries (pulmonary venous), it is possible to calculate the amount of shunt flow. This is done using a mixing equation. The total amount of oxygen delivered into the systemic circulation per minute is the *total blood flow* ($\dot{Q}_T$), that is, cardiac output, multiplied by the *oxygen content in the systemic arterial blood* (Ca_{O_2}), or $\dot{Q}_T \times Ca_{O_2}$. This must equal the sum of the amounts of oxygen in the shunted blood ($\dot{Q}s \times C\bar{v}_{O_2}$) and the nonshunted or end-capillary blood [$(\dot{Q}_T - \dot{Q}s) \times Cc'_{O_2}$]. Also, it is assumed that all regions of lung not subject to shunt are normal. Thus,

$$\dot{Q}_T \times Ca_{O_2} = (\dot{Q}s \times C\bar{v}_{O_2}) + (\dot{Q}_T - \dot{Q}s) \times Cc'_{O_2} \qquad \text{Eq. 26}$$

where $\dot{Q}s$ is pulmonary physiologic shunt (in mL/min), Q_T is cardiac output (in mL/min), Cc'_{O_2} is end-pulmonary capillary oxygen content, Ca_{O_2} is arterial oxygen content, and $C\bar{v}_{O_2}$ is mixed venous oxygen content.

Rearranging, this gives

$$\frac{\dot{Q}s}{\dot{Q}_T} = \frac{(Cc'_{O_2} - Ca_{O_2})}{(Cc'_{O_2} - C\bar{v}_{O_2})} \qquad \text{Eq. 27}$$

The oxygen content of end-capillary blood is usually calculated from the alveolar P_{O_2} and the hemoglobin concentration, assuming 100% oxyhemoglobin saturation (Eq. 11), hence the assumption of normalcy of all regions not subject to shunt.

When the shunt is caused by blood that does not have the same oxygen content as mixed venous blood (e.g., bronchial venous blood), it is generally not possible to calculate its true magnitude. However, it is often useful to calculate an "as if" shunt, that is, what the shunt would be if the observed depression of arterial oxygen content were caused by the addition of mixed venous blood.

An important diagnostic feature of a shunt is that the arterial P_{O_2} does not rise to the normal level, which in theory should be 670 mm Hg, when the patient is given 100% oxygen to breathe. The reason for this is that the shunted blood that bypasses ventilated alveoli is never exposed to the higher alveolar P_{O_2}. Its addition to end-capillary blood therefore continues to depress the arterial P_{O_2}. Nevertheless, the arterial P_{O_2} is elevated somewhat because of the oxygen added to the capillary blood of the ventilated lung. Most of this added oxygen is in the dissolved form rather than attached to hemoglobin because the blood that is perfusing lung regions with normal ventilation-perfusion ratios is normally nearly fully saturated.

The administration of 100% oxygen to a patient with a shunt is a very sensitive method of detecting small amounts of shunting. This is because when the arterial P_{O_2} is very high, a very small reduction of arterial oxygen content (or hemoglobin saturation) caused by the addition of the shunted blood causes a relatively large fall in P_{O_2}. This is directly attributable to the almost flat slope of the oxygen dissociation curve in this region.

A patient with a shunt usually does not have an increased P_{CO_2} in the arterial blood in spite of the fact that the shunted blood is rich in carbon dioxide. The reason is that the chemoreceptors sense any elevation of arterial P_{CO_2} and respond by increasing the ventilation. As a consequence, the P_{CO_2} of the unshunted blood is reduced by the hyperventilation until the arterial P_{CO_2} is back to normal. Indeed, in some patients with large shunts caused, for example, by cyanotic congenital heart disease, the arterial P_{CO_2} is low because the arterial hypoxemia increases the respiratory drive.

Ventilation-Perfusion Relationships

The mismatching of ventilation and blood flow is the most common cause of hypoxemia in lung disease. Uneven ventilation and blood flow are also a cause of carbon dioxide retention. Early intimations of the importance of the subject go back to Krogh and Lindhard[94] and Haldane.[95] However, in the late 1940s, our understanding advanced when Fenn and colleagues[96] and Riley and Cournand[97] introduced graphic analysis of gas exchange. This was an important advance because the interrelationships of ventilation, blood

It can be shown[90] that whether diffusive transfer of any gas is perfusion or diffusion limited depends on the ratio of D, the diffusive conductance of the blood-gas barrier, to the product of the solubility of the gas in blood (commonly referred to as beta [β]) and the total pulmonary blood flow rate. For oxygen, β refers to the slope of the oxygen-hemoglobin dissociation curve. Diffusive equilibration is more likely the higher the $D/\dot{Q}\beta$ ratio.

It is clear that for oxygen, the slope of the blood dissociation curve is not a constant, which makes this ratio difficult to apply. It depends on the P_{O_2} and also to a lesser extent on factors that shift the dissociation curve, such as pH, P_{CO_2}, temperature, and red cell 2,3-DPG concentration. Under hypoxic conditions, when the lung is operating on the lower, steeper part of the oxygen dissociation curve, β is much greater than in normoxia, when arterial P_{O_2} is on the flat portion of the curve. Thus, in hypoxia the ratio $D/\dot{Q}\beta$ is lower, and diffusive equilibration becomes less likely. This helps explain why diffusion limitation for oxygen, unusual at sea level, is common at high altitude. eFigure 10.2 shows the extent to which perfusion and diffusion limit the transfer of gas under various conditions.[90] Although the figure is based on a number of simplifying assumptions, it is conceptually valuable.

Note that physiologically inert gases, such as nitrogen and sulfur hexafluoride (right-side end of eFig. 10.2), are completely perfusion limited in their transfer. (*Physiologically inert* means that, being carried in blood only in physical solution, their blood concentration is directly proportional to partial pressure; that is, they obey Henry's law of solubility.) The same perfusion limitation applies to oxygen in hyperoxia because high on the dissociation curve the value of β is very low so that $D/\dot{Q}\beta$ is very high and diffusion limitation is not seen. However, as just described, oxygen transfer under conditions of hypoxia can be partly diffusion limited because the lung is working low on the dissociation curve, where the slope (β) is much higher than normal. This is particularly the case for oxygen transfer during hypoxic exercise and explains why diffusion is limiting in the normal lung during maximal exercise at extreme high altitude, even in well-acclimatized subjects.[91,92] On the summit of Mount Everest, there is apparently diffusion limitation even at rest.

For discussion of diffusion capacity measurements, see also Chapter 31.

Reaction Rates With Hemoglobin. When oxygen (or carbon monoxide) is added to blood, its combination with hemoglobin is quite fast, being close to completion in 0.2 second. Such reaction rates can be measured using special equipment in which deoxygenated hemoglobin and dissolved oxygen are rapidly mixed and the rate of formation of oxyhemoglobin is measured photometrically. Although hemoglobin is oxygenated rapidly within the pulmonary capillary, even this reaction significantly delays the loading of oxygen by the red cell.

The transfer of oxygen from the alveolar gas to the red cell can therefore be regarded in two stages: (1) diffusion of oxygen through the blood-gas barrier, including the plasma and red cell interior, and (2) reaction of the oxygen with hemoglobin (eFig. 10.3A). Although at first sight these two processes appear very different, it is possible to treat them mathematically in a similar way and to regard each as contributing its own resistance to the transfer of oxygen. Such an analysis was carried out by Roughton and Forster,[93] who showed that the following relationship exists:

$$\frac{1}{D_L} = \frac{1}{D_M} + \frac{1}{(\theta \times V_C)} \qquad \text{Eq. 22}$$

where D_L refers to the diffusing capacity of the lung, D_M is the diffusing capacity of the membrane (which includes the plasma and red cell interior), θ is the rate of reaction of oxygen (or carbon monoxide) with hemoglobin (expressed per milliliter of blood), and V_C is the volume of blood in the pulmonary capillaries.

In the normal lung the resistances offered by the membrane ($1/D_M$) and blood reaction components [$1/(\theta \times V_C)$] are approximately equal. If the capillary blood volume is reduced by disease, the measured diffusing capacity of the lung is lowered. In fact, the equation can be used to separate the two components. To do this, the diffusing capacity is measured at both high and normal alveolar P_{O_2} values. Increasing the alveolar P_{O_2} reduces the value of θ for carbon monoxide because the carbon monoxide has to compete with a high pressure of oxygen for the hemoglobin. If the resulting measurements of $1/D_L$ are plotted against $1/\theta$, as shown in eFigure 10.3B, the slope of the line is $1/V_C$, whereas the intercept on the vertical axis is $1/D_M$.

Diffusing Capacity. Carbon monoxide is usually the gas of choice for measuring the diffusion properties of the lung because its transfer is almost entirely diffusion limited. It is true that part of the limitation has to do with the rate of reaction of carbon monoxide with hemoglobin (see eFig. 10.3A), but this is conveniently included in the measurement of diffusion properties. Although it could be argued that we are really more interested in oxygen and the effects of any diffusion limitation on this gas, oxygen uptake is typically perfusion limited under normoxic conditions and partly perfusion and diffusion limited under hypoxic conditions. For this reason, measurements using oxygen are often difficult to interpret, although techniques using isotopes of oxygen have been proposed.[90] However, for the measurement of diffusion properties in the pulmonary function laboratory, carbon monoxide is the best gas.

As indicated earlier, Fick's law states that the amount of gas transferred across a tissue sheet is proportional to the area, a diffusion constant, and the difference in partial pressure, and is inversely proportional to the thickness:

$$\dot{V}gas = \frac{A}{T} \times D \times (P_1 - P_2) \qquad \text{Eq. 20}$$

The actual lung is so complex that it is not possible to determine the area and the thickness of the blood-gas barrier during life. Instead, the equation is written to combine the factors A, T, and D into one constant, D_L, as follows:

$$\dot{V}gas = D_L \times (P_1 - P_2) \qquad \text{Eq. 23}$$

where D_L is the diffusing capacity of the lung and consequently includes the area, thickness, and diffusion properties

of the tissue sheet, as well as the properties of the diffusing gas. Thus, the diffusing capacity for carbon monoxide is given by:

$$D_L = \frac{\dot{V}_{CO}}{(P_1 - P_2)} \qquad \text{Eq. 24}$$

where P_1 and P_2 are the partial pressures of carbon monoxide in alveolar gas and capillary blood, respectively, and $\dot{V}_{CO}$ is defined as the volume of carbon monoxide exhaled per unit time. Because the partial pressure of carbon monoxide in capillary blood is so small, it can generally be neglected. In this case the equation becomes

$$D_L = \frac{\dot{V}_{CO}}{P_{ACO}} \qquad \text{Eq. 25}$$

or, in other words, the diffusing capacity of the lung for carbon monoxide is the volume of carbon monoxide transferred (in milliliters per minute) at the alveolar partial pressure of carbon monoxide (in millimeters of mercury).

Some people, such as cigarette smokers, have sufficient carboxyhemoglobin in their blood that the partial pressure of carbon monoxide in the pulmonary capillaries cannot be neglected. In this case, an estimate of the partial pressure of carbon monoxide in pulmonary capillary blood can be made using a rebreathing technique, and Eq. 24 is used to determine diffusing capacity.

Several techniques are available for measuring the diffusing capacity of the lung for carbon monoxide. For a discussion of the principles of clinical tests, see Chapter 31.

flow, and gas exchange depend on the oxygen and carbon dioxide dissociation curves, which are not only nonlinear but interdependent, and direct solutions to the gas exchange equations that relate the ventilation-perfusion ratio to gas exchange (see later, Eqs. 29 and 30) are not possible.

Later, computers were used to describe the oxygen and carbon dioxide dissociation curves.[98,99] These procedures enabled investigators to answer questions about gas exchange that had been impossibly difficult before that time. The behavior of distributions of ventilation-perfusion ratios was analyzed,[100] and Wagner and colleagues[101] introduced the multiple inert gas elimination technique, which allowed, for the first time, information about the dispersion, number of modes, and shape of the distributions of ventilation, of perfusion, and of their ratio to be obtained.

Gas Exchange in a Single Lung Unit. The P_{O_2}, P_{CO_2}, and P_{N_2} in any gas-exchanging unit of the lung are uniquely determined by three major factors: (1) the ventilation-perfusion ratio, (2) the composition of the inspired gas and the composition of the mixed venous blood, and (3) the slopes and positions of the relevant blood-gas dissociation curves.

Formally, the key role of the ventilation-perfusion ratio can be derived as follows. The amount of carbon dioxide exhaled into the air from alveolar gas per minute is given by Eq. 4:

$$\dot{V}_{CO_2} = \dot{V}_A \times P_{ACO_2}/K$$

where $\dot{V}_{CO_2}$ is the carbon dioxide production, $\dot{V}_A$ is the alveolar ventilation, K is a constant, and there is no carbon dioxide in the inspired gas.

The amount of carbon dioxide that diffuses into alveolar gas from capillary blood per minute is given by:

$$\dot{V}_{CO_2} = \dot{Q}(C\bar{v}_{CO_2} - Cc'_{CO_2}) \qquad \text{Eq. 28}$$

where $\dot{Q}$ is blood flow, and $C\bar{v}_{CO_2}$ and Cc'_{CO_2} are the concentrations of carbon dioxide in mixed venous and end-capillary blood, respectively. Now, in a steady state, the amount of carbon dioxide lost from the alveoli and from the capillary blood must be the same. Therefore,

$$\dot{V}_A \times P_{ACO_2}/K = \dot{Q}(C\bar{v}_{CO_2} - Cc'_{CO_2}), \text{ or}$$

$$\frac{\dot{V}_A}{\dot{Q}} = K \times \frac{(C\bar{v}_{CO_2} - Cc'_{CO_2})}{P_{ACO_2}} \qquad \text{Eq. 29}$$

Thus, the alveolar P_{CO_2} and the corresponding end-capillary carbon dioxide concentration (assuming end-capillary and alveolar P_{CO_2} are identical) are determined by (1) the ventilation-perfusion ratio, (2) the mixed venous carbon dioxide concentration, and (3) the carbon dioxide dissociation curve relating P_{CO_2} to carbon dioxide concentration.

Although this equation looks simple, its appearance is deceiving because, when the ventilation-perfusion ratio, for example, increases, the alveolar P_{O_2} rises. This means that the oxygen saturation of the blood increases, and the relationship between P_{CO_2} and carbon dioxide concentration is altered. Thus, the alveolar P_{O_2} is an implicit variable in the equation. In addition, the relationship between P_{CO_2} and carbon dioxide concentration in blood is nonlinear.

Just as in the context of the alveolar ventilation equation (see "Hypoventilation" earlier), it is possible to write an equation similar to Eq. 29 for oxygen exchange based on the same principles as applied for carbon dioxide. Again, the approximation is made that $\dot{V}_I = \dot{V}_A$ to keep the equation simple but, as for the alveolar gas equation, the fact that $\dot{V}_I$ slightly exceeds $\dot{V}_A$ can formally be taken into account. Using this approximation, the equation for oxygen is

$$\frac{\dot{V}_A}{\dot{Q}} = K \times \frac{(Cc'_{O_2} - C\bar{v}_{O_2})}{(P_{IO_2} - P_{AO_2})} \qquad \text{Eq. 30}$$

Just as for carbon dioxide, the alveolar and end-capillary P_{O_2} values are taken to be identical, implying diffusion equilibrium across the blood-gas barrier. It is seen that the determinants of alveolar P_{O_2}, as for carbon dioxide, are threefold: (1) the ventilation-perfusion ratio, (2) inspired and mixed venous oxygen levels, and (3) the relationship between P_{O_2} and oxygen content in blood (i.e., the oxygen dissociation curve).

Graphic analysis of these relationships is assisted by the use of the oxygen–carbon dioxide diagram, in which P_{O_2} is on the horizontal axis and P_{CO_2} is on the vertical axis. Figure 10.17 is an example of the use of the oxygen–carbon dioxide diagram to show how the P_{O_2} and P_{CO_2} of a lung unit change as the ventilation-perfusion ratio is either decreased below or increased above the normal value. Note that for a given composition of inspired gas (I) and mixed venous blood ($\bar{v}$), the possible combinations of P_{O_2} and P_{CO_2} are constrained to a single line known as the ventilation-perfusion ratio line. Each point on that line uniquely corresponds to a value of the ventilation-perfusion ratio. Note also that, when the ventilation-perfusion ratio is zero, the P_{O_2} and P_{CO_2} of end-capillary blood are those of mixed venous blood and, when the ventilation-perfusion ratio is infinity, the P_{O_2} and P_{CO_2} of alveolar gas are the same as those of inspired gas. In this diagram and in the rest of this section, we assume that there is complete diffusion equilibration between the P_{O_2} and P_{CO_2} of alveolar gas and end-capillary blood. This is a reasonable assumption unless

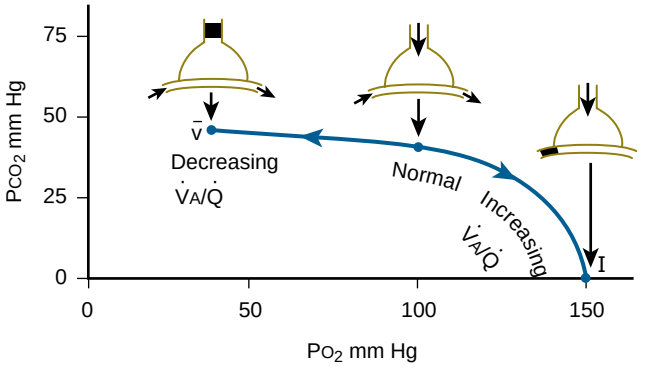

Figure 10.17 Oxygen–carbon dioxide diagram shows how the P_{O_2} and P_{CO_2} of a lung unit change as the ventilation-perfusion ratio ($\dot{V}_A/\dot{Q}$) is changed. I, inspired gas; P_{CO_2}, partial pressure of carbon dioxide; P_{O_2}, partial pressure of oxygen; $\bar{v}$, mixed venous blood. (Modified from West JB. *Respiratory Physiology: The Essentials*. 9th ed. Baltimore: Lippincott Williams & Wilkins; 2012.)

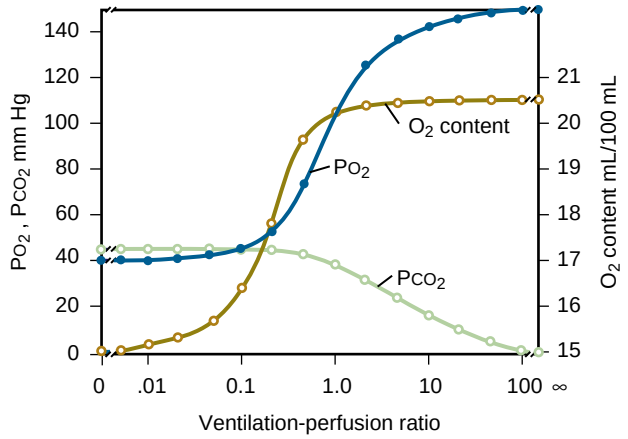

Figure 10.18 Changes in P_{O_2}, P_{CO_2}, and end-capillary oxygen content in a lung unit are shown as its ventilation-perfusion ratio is altered. See text for assumptions. P_{CO_2}, partial pressure of carbon dioxide; P_{O_2}, partial pressure of oxygen. (Modified from West JB. State of the art: ventilation-perfusion relationships. *Am Rev Respir Dis.* 1977;116:919–943.)

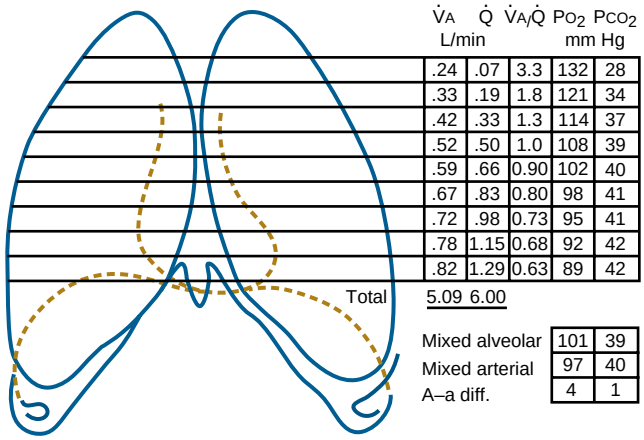

Figure 10.19 Regional differences of gas exchange down the upright normal lung. The lung is divided into nine imaginary slices. $\dot{Q}$, blood flow; $\dot{V}_A$, alveolar ventilation. A–a diff, alveolar-arterial difference. (Modified from West JB. *Respiratory Physiology: The Essentials*. 9th ed. Baltimore: Lippincott Williams & Wilkins; 2012.)

there is marked thickening of the blood-gas barrier or one is considering a subject exercising in hypoxia.

Figure 10.18 shows the P_{O_2}, P_{CO_2}, and oxygen content of end-capillary blood of a lung unit as its ventilation-perfusion ratio is increased from extremely low to extremely high values. The inspired gas is assumed to be air, the P_{O_2} and P_{CO_2} of mixed venous blood are normal (40 and 45 mm Hg, respectively), and the hemoglobin concentration is 14.8 g/100 mL. The normal value of the ventilation-perfusion ratio is in the range of 0.8 to 1. Note that as the ratio is altered either above or below that value, the P_{O_2} changes considerably. By contrast, the oxygen content increases little as the ventilation-perfusion ratio is raised above the normal value because the hemoglobin is normally almost fully saturated. The P_{CO_2} falls considerably as the ventilation-perfusion ratio is raised but rises relatively little at lower ventilation-perfusion ratio values. The quantitative information in this figure is consistent with the graphic analysis of Figure 10.17.

Pattern in the Normal Lung. Both ventilation and perfusion vary throughout the lung. It is thus instructive to look at the inequality of gas exchange in different regions due to gravitational influences in the normal upright lung. As previously stated, both ventilation and blood flow per unit volume decrease from the bottom to the top of the upright lung. However, the changes for blood flow are more marked than those for ventilation. As a consequence, the ventilation-perfusion ratio increases from low values at the base to high values at the apex of the normal upright lung (Fig. 10.19).

Because the ventilation-perfusion ratio determines the gas exchange in any region (see Eqs. 29 and 30), the variation in P_{O_2} and P_{CO_2} in the lung can be calculated. Normal composition of mixed venous blood is assumed. Note that the P_{O_2} increases by some 40 mm Hg from base to apex, whereas the P_{CO_2} falls by 14 mm Hg. The pH is high at the apex because the P_{CO_2} there is low (the base excess is the same throughout the lung). Very little of the total oxygen uptake takes place at the apex, principally because the blood flow there is very low.

Figure 10.19 also helps to explain why ventilation-perfusion inequality interferes with overall gas exchange. Note that the base of the lung has most of the blood flow, but the P_{O_2} of the end-capillary blood is lowest there. As a result, the effluent pulmonary venous blood, which becomes the systemic arterial blood, is loaded with moderately oxygenated blood from the base. The net result is a depression of the arterial P_{O_2} below that which would be seen if ventilation and blood flow were uniformly distributed.

The same argument applies to carbon dioxide. In this case, the P_{CO_2} of the end-capillary blood is highest at the base, where the blood flow is greatest. As a result, the P_{CO_2} of arterial blood is elevated above that which would be seen if there was ventilation-perfusion equality. In other words, a lung with mismatched ventilation and blood flow is less efficient at exchanging gas, be it oxygen or carbon dioxide. In fact, the inefficiency applies to any gas that is being transferred by the lung. The extent of the impairment of gas exchange caused by any given amount of ventilation-perfusion inequality depends mostly on the solubility, or slope of the blood dissociation curve, of the gas. For example, in a lognormal distribution of ventilation-perfusion ratios, gases with medium solubility experience the greatest interference with pulmonary transfer.[104] In the normal lung, the effect of inequality due to gravity on arterial P_{O_2} can be modeled, as shown in Figure 10.19. Of interest, the overall effect of the normal inherent ventilation-perfusion inequality on gas exchange turns out to be very small, reducing arterial P_{O_2} by only approximately 4 mm Hg from that in a homogeneous lung.

Traditional Assessment of Ventilation-Perfusion Inequality. A central question that has engaged the attention of physiologists and physicians for many years has been how best to assess the amount of ventilation-perfusion inequality. Ideally, we would like to know the actual distribution of ventilation-perfusion ratios (see next section), but the

procedure required for this is too complicated for many clinical situations. Traditionally, we rely on measurements of P_{O_2} and P_{CO_2} in arterial blood and expired gas.

The arterial P_{O_2} certainly gives some information about the degree of ventilation-perfusion inequality. In general, the lower the P_{O_2}, the more marked is the mismatching of ventilation and blood flow. The chief merit of this measurement is its simplicity, but a disadvantage is that its value is sensitive to the overall ventilation and pulmonary blood flow, to inspired P_{O_2}, and to other potential causes of hypoxemia already discussed.

Arterial P_{CO_2} is so sensitive to the level of ventilation that it gives little information about the extent of the ventilation-perfusion inequality. However, the most common cause of an increased P_{CO_2} in chronic lung disease is mismatching of ventilation and blood flow, as explained later in the section on ventilation-perfusion inequality and carbon dioxide retention.

Because of these limitations, the alveolar-arterial P_{O_2} difference is frequently measured and is more informative than the arterial P_{O_2} alone because it is less sensitive to the level of overall ventilation. To understand the significance of this measurement, we need to look in more detail at how gas exchange is altered by the imposition of ventilation-perfusion inequality.

Figure 10.20 shows an oxygen–carbon dioxide diagram with the same ventilation-perfusion line as that in Figure 10.17. Suppose initially that this lung has no ventilation-perfusion inequality. The P_{O_2} and P_{CO_2} of the alveolar gas and arterial blood would then be represented by point i, known as the ideal point. This is at the intersection of the gas and blood *respiratory exchange ratio* (R) lines; these lines indicate the possible compositions of alveolar gas and arterial blood consistent with the overall respiratory exchange ratio (carbon dioxide output/oxygen uptake) of the whole lung. In other words, a lung in which R = 0.8 would have to have its mixed *alveolar gas point* (A) located somewhere on the line joining points i and I. A similar statement can be made for the *arterial gas point* (a).

What happens to the composition of mixed alveolar gas and arterial blood as ventilation-perfusion inequality is imposed on the lung? The answer is that both points diverge away from the *ideal point* (i) along the gas and blood R lines. The more extreme the degree of ventilation-perfusion inequality, the further the divergence. Moreover, the type of ventilation-perfusion inequality determines how much each point will move. For example, a distribution containing a large amount of ventilation to units with high ventilation-perfusion ratio especially moves point A down and to the right, away from point i. By the same token, a distribution containing large amounts of blood flow to units with low ventilation-perfusion ratios predominantly moves point a leftward along the blood R line.

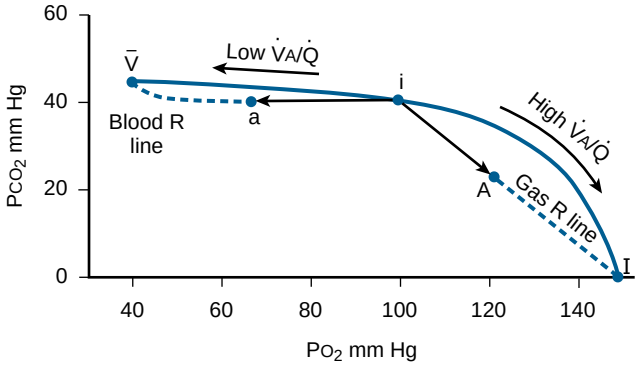

Figure 10.20 Effect of ventilation-perfusion inequality on gas exchange. Oxygen–carbon dioxide diagram showing the ideal point (i) and the points for arterial blood (a) and alveolar gas (A) (see text for details). I, inspired gas; P_{CO_2}, partial pressure of carbon dioxide; P_{O_2}, partial pressure of oxygen; $\dot{Q}$, blood flow; R, respiratory exchange ratio; $\bar{V}$, mixed venous blood; $\dot{V}_A$, alveolar ventilation. (Modified from West JB. *Respiratory Physiology: The Essentials*. 9th ed. Baltimore: Lippincott Williams & Wilkins; 2012.)

It is clear that the horizontal distance between points A and a (i.e., the mixed alveolar-arterial P_{O_2} difference) would be a useful measure of the degree of ventilation-perfusion inequality. Unfortunately, this index is impossible to obtain in most patients because A denotes the composition of *mixed* expired gas, excluding the anatomic dead-space gas. In most diseased lungs the alveoli empty sequentially, with poorly ventilated alveoli emptying last, so that a post–dead-space sample is not representative of all mixed expired alveolar gas. In a few patients who have essentially uniform ventilation but uneven blood flow, this index can be used, and it is occasionally reported in patients with pulmonary embolism. In this instance, the P_{O_2} of end-tidal gas is taken to represent mixed expired alveolar gas.

Because the mixed expired alveolar P_{O_2} is usually impossible to obtain, a more useful index is the P_{O_2} difference between ideal alveolar gas and arterial blood, that is, the horizontal distance between points i and a. The ideal alveolar P_{O_2} is calculated from the full alveolar gas equation:

$$P_{AO_2} = P_{IO_2} - \frac{P_{ACO_2}}{R} + \left[P_{ACO_2} \times F_{IO_2} \times \frac{(1-R)}{R} \right] \qquad \text{Eq. 19}$$

To use this equation, we assume that the P_{CO_2} of ideal alveolar gas is the same as the P_{CO_2} of arterial blood. The rationale for this is that the line along which point a moves (in Fig. 10.20) is so nearly horizontal that the value is close enough for clinical purposes. It is important to note that this ideal alveolar-arterial P_{O_2} difference is caused by units situated on the ventilation-perfusion ratio line between points i and $\bar{v}$, that is, units with abnormally low ventilation-perfusion ratios. This means that a diseased lung may have substantial ventilation-perfusion inequality but a nearly normal ideal alveolar-arterial P_{O_2} difference if most of the inequality is caused by units with abnormally high ventilation-perfusion ratios.

Physiologic shunt is another useful index of ventilation-perfusion inequality. It measures that movement of the arterial point away from the ideal point along the blood R line (see Fig. 10.20). It is therefore caused by blood flow to lung units with abnormally low ventilation-perfusion ratios. To calculate physiologic shunt, we pretend that all of the leftward movement of the arterial point a is caused by the addition of mixed venous blood $\bar{v}$ to ideal blood i. This is not so unreasonable as it might at first seem because units with very low ventilation-perfusion ratios put out blood that has essentially the same composition as that of mixed venous blood (see Figs. 10.17 and 10.18). The shunt equation is used in the following form:

$$\frac{\dot{Q}_{PS}}{\dot{Q}_T} = \frac{(C_{IO_2} - Ca_{O_2})}{(C_{IO_2} - C\bar{v}_{O_2})} \quad \text{Eq. 31}$$

where $\dot{Q}_{PS}$ refers to physiologic shunt, $\dot{Q}_T$ refers to total blood flow through the lung, and C_{IO_2}, Ca_{O_2}, and $C\bar{v}_{O_2}$ refer to the oxygen content of ideal, arterial, and mixed venous blood, respectively. The oxygen content of ideal blood is calculated from the ideal P_{O_2} and the oxygen dissociation curve. The normal value for physiologic shunt as a ratio of total blood flow is less than 0.05.

The last traditional index to be discussed is physiologic dead space (also known as wasted ventilation). Whereas physiologic shunt reflects the amount of blood flow going to lung units with abnormally low ventilation-perfusion ratios, physiologic dead space is a measure of the amount of ventilation going to units with abnormally high ventilation-perfusion ratios. Thus, the two indices provide measurements of both ends of the spectrum of ventilation-perfusion ratios.

To calculate physiologic dead space, we pretend that all the movement of the alveolar point A away from the ideal point i (Fig. 10.20) is caused by the addition of inspired gas I to ideal gas. Again, this is not so unreasonable as it may first appear because units with very high ventilation-perfusion ratios behave very much like point I (see Fig. 10.20). Because, as indicated earlier, it is usually impossible to obtain a pure sample of mixed expired gas, we generally collect mixed expired gas and measure its composition, E. The mixed expired gas contains a component from anatomic dead space, which therefore moves its composition further toward point I. The Bohr equation (see Eq. 8) is then used in the form

$$\frac{V_{D_{phys}}}{V_T} = \frac{(Pa_{CO_2} - P_{ECO_2})}{Pa_{CO_2}} \quad \text{Eq. 32}$$

where $V_{D_{phys}}$ is physiologic dead space, V_T is tidal volume, and P_{ECO_2} is mixed expired P_{CO_2}, and again we exploit the fact that the P_{CO_2} of ideal gas and that of arterial blood are virtually the same. The normal value for physiologic dead space as a ratio of total ventilation is less than 0.3. (For applications of these principles in pulmonary function testing, see Chapter 31.)

Distributions of Ventilation-Perfusion Ratios. The analysis of ventilation-perfusion inequality briefly described in the last section is sometimes known as the three-compartment model because the lung is conceptually divided into an unventilated compartment (shunt), an unperfused compartment (dead space), and a compartment that is normally ventilated and perfused (ideal). This way of looking at the diseased lung, which was introduced by Riley and Cournand,[97] has proved to be of great clinical usefulness in assessing the effects of mismatching of ventilation and blood flow.

However, it was recognized many years ago that real lungs must contain some sort of distribution of ventilation-perfusion ratios and that a three-compartment model is therefore remote from reality. Computer analysis facilitated considerable advances in the understanding of the behavior of distributions of ventilation-perfusion ratios.[100] This allowed the multiple inert gas elimination technique to become the standard research technique for measuring patterns of ventilation-perfusion distributions in normal subjects and patients with lung disease.[101]

For further discussion of measuring the distribution of ventilation-perfusion ratios by the multiple inert gas technique, see ExpertConsult.com.

Distribution in the Normal Lung. Figure 10.21A shows the distribution of ventilation-perfusion ratios in a 22-year-old normal volunteer derived from the multiple inert gas technique.[108] The distribution shows that the plots of both ventilation and blood flow are narrow, spanning only one decade of ventilation-perfusion ratios (i.e., from a ventilation-perfusion ratio of 0.3 to one 10 times higher, of 3). As expected, this range of ventilation-perfusion ratios is slightly greater than the regional differences, which mainly depend on gravity alone (see Fig. 10.19). However, there was essentially no ventilation or blood flow outside this range on the ventilation-perfusion ratio scale. Note also that there was no shunt, that is, blood flow to unventilated alveoli. The absence of shunt was a consistent finding in all the normal subjects studied and was initially surprising. It should be pointed out that this technique is very sensitive, in that a shunt of only 0.5% of the cardiac output approximately doubles the arterial concentration of sulfur hexafluoride. Apparently, young normal subjects are able to ventilate essentially all of their alveoli. One can conclude that bronchial and thebesian shunts are not detected by the method.

In normal subjects, the measured arterial P_{O_2} value is consistent with that modeled for a given ventilation-perfusion distribution and assuming diffusion equilibrium for oxygen. This means that ventilation-perfusion heterogeneity explains all of the difference between ideal alveolar P_{O_2} and arterial P_{O_2} in normal lungs. For example, in older normal subjects the variation of the ventilation-perfusion distribution increases, which explains the gradual fall in arterial P_{O_2} observed with aging. Ventilation-perfusion mismatching must take place between lung units perfused by vessels 150 μm in diameter or larger to have a significant effect on arterial P_{O_2}.[109] This means the functional unit of oxygen exchange in terms of ventilation-perfusion matching is the acinus, or lung units distal to a terminal bronchiole.

Distributions in Lung Disease. Ventilation-perfusion relationships vary by disease state. Figure 10.21B–C and eFigure 10.5 show typical distributions of ventilation-perfusion ratios from patients with COPD, contrasting a patient with an emphysematous phenotype with a patient with a chronic bronchitis phenotype. The distribution typical of the pattern seen in patients with predominantly emphysema shows a broad bimodal distribution, with large amounts of ventilation to lung units with extremely high ventilation-perfusion ratios (alveolar dead space)[110] (see Fig. 10.21B). Note the small shunt of 0.7%. Mild hypoxemia in this patient would be explained mostly by the slight displacement of the main mode of blood flow to the left of normal. Presumably, the high ventilation-perfusion ratio mode reflects ventilation to lung units in which many capillaries have been destroyed by the emphysematous process, reducing their perfusion. Patients with COPD whose predominant lesion is severe bronchitis generally show a different pattern (see Fig. 10.21C). The main abnormality in the distribution

Multiple Inert Gas Elimination Technique. The principles governing inert gas elimination by the lung are identical to those of oxygen and carbon dioxide and are dictated by equations corresponding to Eqs. 29 and 30. When an inert gas dissolved in saline is steadily infused into the peripheral venous circulation, it arrives at the lungs, and some of the gas will be exhaled. The proportion of gas eliminated by ventilation from the blood of a given lung unit depends only on the blood-gas partition coefficient of the gas (λ) and the ventilation-perfusion ratio ($\dot{V}_A/\dot{Q}$).[105,106] The relationship is given by the following equation:

$$\frac{Pc'}{P\bar{v}} = \frac{\lambda}{(\lambda + \dot{V}_A/\dot{Q})} \qquad \text{Eq. 33}$$

where $P_{C'}$ and $P\bar{v}$ are the partial pressures of the gas in end-capillary blood and mixed venous blood, respectively. Eq. 33 looks different from Eqs. 29 and 30 only because inert gases obey Henry's law, allowing concentration to be replaced by the product of solubility and partial pressure. This, in turn, permits the rearrangement of terms ending up with Eq. 33. The ratio of end-capillary to mixed venous partial pressure is known as the retention. This equation is derived from exactly the same considerations of mass balance as applied to carbon dioxide in Eq. 4.

In practice, a mixture of six gases (typically, sulfur hexafluoride, ethane, cyclopropane, isoflurane, ether, and acetone) is dissolved in saline and infused into a peripheral arm vein at a constant rate until a steady state of gas exchange is achieved (10–20 minutes). Samples of mixed expired gas and arterial blood are then taken, and the gas concentrations in each are determined by gas chromatography. At the same time, cardiac output is obtained (e.g., by indicator dilution, echocardiography, or other method), and total ventilation is also measured. From these data, mixed venous concentrations of each inert gas can be calculated and retention determined. In patients who already have an indwelling pulmonary arterial catheter, a sample of mixed venous blood could be taken instead to measure mixed venous inert gas levels directly.

A graph is then constructed, as shown in eFigure 10.4. The upper panel shows the data points of inert *gas retention* (arterial partial pressure divided by mixed venous partial pressure), which are joined for clarity by the broken line. Below this are the data points for *excretion* (mixed expired partial pressure divided by mixed venous partial pressure). Both are plotted against the partition coefficient. Again, the points are joined by a broken line. For comparison, the two solid lines show the values of retention and excretion for a lung with no ventilation-perfusion inequality but with the same overall ventilation and blood flow. Whereas the broken and solid lines are very close together in eFigure 10.4, the differences are more easily seen when the lung is diseased (eFig. 10.5) (see "Distributions in Lung Disease" later).

These plots, called the retention-solubility and excretion-solubility curves, contain information about the distribution of ventilation-perfusion ratios in the lung. The relationship between the distribution of ventilation-perfusion ratios and the retention-solubility and excretion-solubility curves can be expressed formally by a set of simultaneous linear equations.[107] These equations, one for each inert gas, simply reflect the principles of mass conservation and relate the ventilation-perfusion distribution (i.e., the paired set of gas exchange unit blood flows and ventilations) to a measured set of inert gas retention and excretion values. The distribution of ventilation-perfusion ratios that is consistent with the pattern of inert gas retention and excretion is then determined using computer programs that solve these simultaneous equations.

The potential and limitations of this transformation have been explored in great detail.[107] The recovered distribution is not unique, but in most cases the range of possible distributions compatible with the data is small. No more than three modes of a distribution can be recovered, and only smooth distributions can be obtained. In spite of these limitations, however, the technique gives much more information about patterns of distribution of ventilation-perfusion ratios in patients with lung disease than has previously been available.

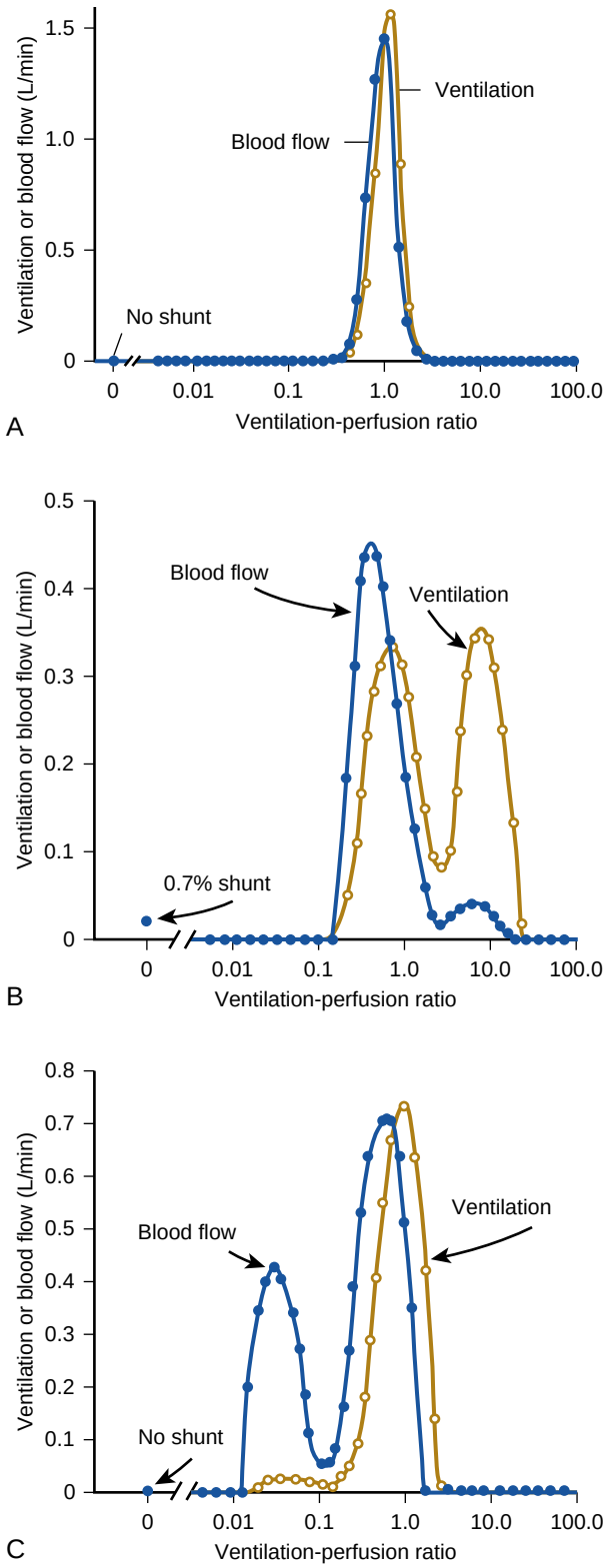

Figure 10.21 Ventilation-perfusion ratios in normal and in patients with COPD of different mechanisms. (A) In a healthy person, the distribution of ventilation (*open circles*) and perfusion (*closed circles*) is narrow, unimodal, and centered around a $\dot{V}_A/\dot{Q}$ of 1. (B) In a person with emphysema-type COPD, the ventilation distribution is bimodal, with areas of high $\dot{V}_A/\dot{Q}$ ratio. (C) In a person with bronchitis-type COPD, the perfusion distribution is bimodal, with areas of low $\dot{V}_A/\dot{Q}$. (From West JB. Causes of and compensations for hypoxemia and hypercapnia. *Compr. Physiol.* 2011;1:1541–1553.)

is a large amount of blood flow going to lung units with very low ventilation-perfusion ratios, between 0.005 and 0.1. This explains the more severe hypoxemia in this type of patient and is consistent with a large physiologic shunt. Presumably, the low ventilation-perfusion ratios in some lung units are the result of partially blocked airways due to retained secretions and airway disease that reduces airway diameter. It should be emphasized that the distributions found in severe chronic bronchitis show considerable variability.

Newer techniques are being developed to image and quantify ventilation-perfusion matching.[111–113] These have the advantage of being less invasive and may be more widely available in the future, providing the ability to detect pathologic changes earlier and to improve the understanding of subgroups of patients.

Ventilation-Perfusion Inequality and Carbon Dioxide Retention. It is important to remember that ventilation-perfusion inequality interferes with the uptake and elimination of all gases by the lung (oxygen, carbon dioxide, carbon monoxide, and anesthetic gases). In other words, mismatching of ventilation and blood flow reduces the overall gas exchange efficiency of the lung. There has been considerable confusion in this area, particularly about the role of ventilation-perfusion inequality in carbon dioxide retention.

Imagine a lung that is uniformly ventilated and perfused and that is transferring normal amounts of oxygen and carbon dioxide. Suppose that the matching of ventilation and blood flow is suddenly disturbed while everything else remains unchanged. What happens to gas exchange? It can be shown that the effect of this "pure" ventilation-perfusion inequality (i.e., with all other factors held constant) is to reduce both the oxygen uptake and carbon dioxide output of the lung.[100] The lung becomes less efficient as a gas exchanger for both gases, and therefore mismatching of ventilation and blood flow must cause hypoxemia and hypercapnia (carbon dioxide retention), other things being equal.

In practice, however, as mentioned earlier for shunt, patients with ventilation-perfusion inequality often have a normal arterial P_{CO_2}. The reason is that whenever the chemoreceptors sense a rising P_{CO_2}, there is an increase in ventilatory drive. The consequent increase in ventilation to the alveoli usually returns the arterial P_{CO_2} to normal. However, such patients can only maintain a normal P_{CO_2} at the expense of this increased ventilation to their alveoli. The ventilation in excess of what they would normally require is sometimes referred to as wasted ventilation and is necessary because the lung units with abnormally high ventilation-perfusion ratios contribute little to eliminating carbon dioxide. Such units are part of the alveolar (physiologic) dead space. Patients with ventilation-perfusion ratio inequality causing carbon dioxide retention are sometimes said to be "hypoventilating," but in fact they may actually be breathing more than normal.

Although patients with mismatched ventilation and blood flow can usually maintain a normal arterial P_{CO_2} by increasing the ventilation to the alveoli, this strategy is much less effective at increasing the arterial P_{O_2}. The reason for the different behavior of the two gases lies in the different shapes of the carbon dioxide and oxygen dissociation

curves. The carbon dioxide dissociation curve is almost straight in the physiologic range, with the result that an increase in ventilation raises the carbon dioxide output of lung units with both high and low ventilation-perfusion ratios. By contrast, the nonlinearity of the oxygen dissociation curve means that not all lung units benefit from increased ventilation by increasing oxygen content in their effluent blood. Those units with high ventilation-perfusion ratios, which operate high on the flat portion of the dissociation curve, increase the oxygen content in blood very little despite large increases in P_{O_2}. In units with a low ventilation-perfusion ratio, P_{O_2} in blood will increase more but some hypoxemia always remains.

In summary, carbon dioxide retention can result from two clearly distinct mechanisms: pure hypoventilation and ventilation-perfusion inequality. The latter is a common cause in clinical practice.

Effect of Changes in Cardiac Output on Gas Exchange in the Presence of Ventilation-Perfusion Inequality. In a lung with no ventilation-perfusion inequality, the cardiac output has no effect on arterial P_{O_2} or P_{CO_2}. This follows from Eqs. 4 and 16, the mass conservation equations for CO_2 and O_2, respectively, which do not contain cardiac output. By contrast, these equations show that the level of total ventilation is very important.

However, in a lung with ventilation-perfusion inequality, cardiac output can have a major effect on arterial P_{O_2} by altering the mixed venous P_{O_2}, which affects the arterial P_{O_2} via shunts through the lung. A reduction in cardiac output reduces the P_{O_2} of mixed venous blood; when this venous blood transits low ventilation-perfusion regions, it exaggerates the hypoxemia. This is sometimes seen in patients with myocardial infarction, in whom the reduction in arterial P_{O_2} seems to be out of proportion to the degree of ventilation-perfusion inequality. The opposite is sometimes seen in patients with bronchial asthma, who may have unusually high cardiac outputs and a high mixed venous P_{O_2}, especially when treated with some β-agonist drugs. The result is that the arterial P_{O_2} is higher than would be expected from the degree of ventilation-perfusion inequality. This important modulating effect of cardiac output on gas exchange is often overlooked in the clinical setting.

OXYGEN SENSING

The responses of the body to hypoxia have been greatly clarified by the discovery of *hypoxia inducible factors* (HIFs). The initial finding was of a protein that bound to the hypoxia response element of the erythropoietin gene under hypoxic conditions.[114] Later it became clear that HIFs are critically important in a large number of responses of cells to hypoxia.

More information on the physiology of hypoxia can be found at ExpertConsult.com.

Acknowledgment

We acknowledge the contributions of Frank L. Powell, PhD, and Peter D. Wagner, MD, who authored this chapter in the previous edition of this text and contributed substantially to the content.

Key Points

- The magnitudes of ventilation and perfusion, as well as their distribution, are key factors determining pulmonary gas exchange.
- Distribution of ventilation and perfusion is predominantly affected by gravity in the normal lung, but intrinsic lung structure also plays a role.
- Distribution of *ventilation-perfusion* ($\dot{V}_A/\dot{Q}$) ratios is nonuniform, with the $\dot{V}_A/\dot{Q}$ ratio being generally higher in nondependent lung regions and lower in dependent lung regions.
- Regional alveolar P_{O_2} and P_{CO_2} are determined principally by the $\dot{V}_A/\dot{Q}$ ratio of each region. Secondary factors are the P_{O_2} and P_{CO_2} of inspired gas and of mixed venous blood and also the shape of the oxygen and carbon dioxide dissociation curves.
- There are five causes of hypoxemia: decreased inspired oxygen, hypoventilation, alveolar-capillary diffusion limitation, shunt, and $\dot{V}_A/\dot{Q}$ inequality.
- There are two principal causes of hypercapnia: hypoventilation and $\dot{V}_A/\dot{Q}$ inequality.
- $\dot{V}_A/\dot{Q}$ inequality is the most important cause of gas exchange abnormalities in most lung diseases.

Key Readings

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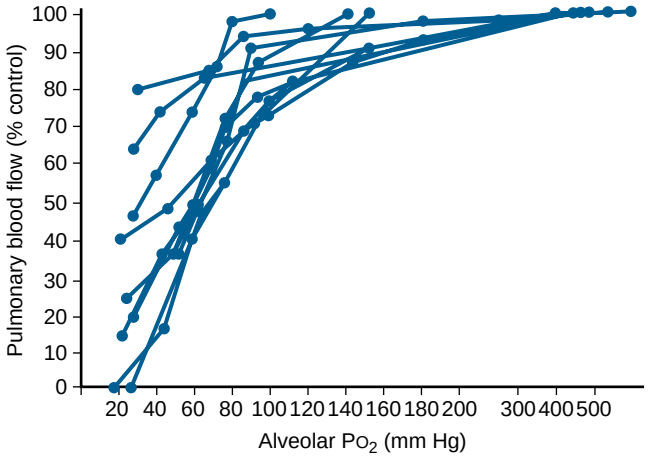
Complete reference list available at ExpertConsult.com.

In fact, it is now known that, in cellular hypoxia, the transcription of over a hundred messenger RNAs is increased, and the expression of an equal number of messenger RNAs is decreased.[115]

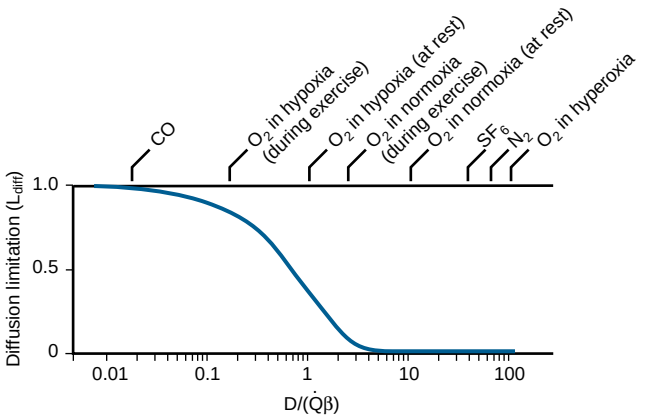
HIFs are heterodimeric transcription factors influenced by the amount of oxygen in the cell. A transcription factor is a protein that binds to specific DNA sequences in a gene and thus controls the flow of genetic information from DNA to messenger RNA. Cellular hypoxia causes an increased concentration of HIF-1α, which then binds to the constitutively expressed HIF-1β, with both binding to the hypoxia response element. It is now known that most oxygen-breathing species express these transcriptional factors, indicating that HIFs have been highly conserved. For example, HIF-1 is expressed in very primitive animals, such as the worm *Caenorhabditis elegans,* without specialized respiratory or circulatory systems. This implies that HIF was most likely developed to enhance the survival of individual cells in low-oxygen environments. After the discovery of HIF-1α, a paralog, HIF-2α, was identified with both overlapping and distinct functions.[116]

Genes regulated by HIFs have many functions throughout the physiologic spectrum. These include mitochondrial genes involved with energy use, glycolytic enzyme genes influencing anaerobic metabolism, genes associated with vascular endothelial growth factor controlling angiogenesis, genes of NO metabolism and ion channels on smooth muscle cells involved with the control of pulmonary blood flow, erythropoietin genes affecting red cell production, and genes controlling the induction of tyrosine hydroxylase, which plays a role in the function of the carotid body chemoreceptor.[117] Of particular interest is cancer, a condition that requires more energy,[118] which can be supplied by a HIF pathway. Furthermore, tumor-associated inflammation causes the induction of glycolytic pathways[119] that use HIF signaling. The role of the HIF pathway has been identified in playing a central role in the adaptive response to chronic hypoxia of high altitude.[120,121] Thus, HIFs constitute a master switch in the general response of the body to hypoxia.

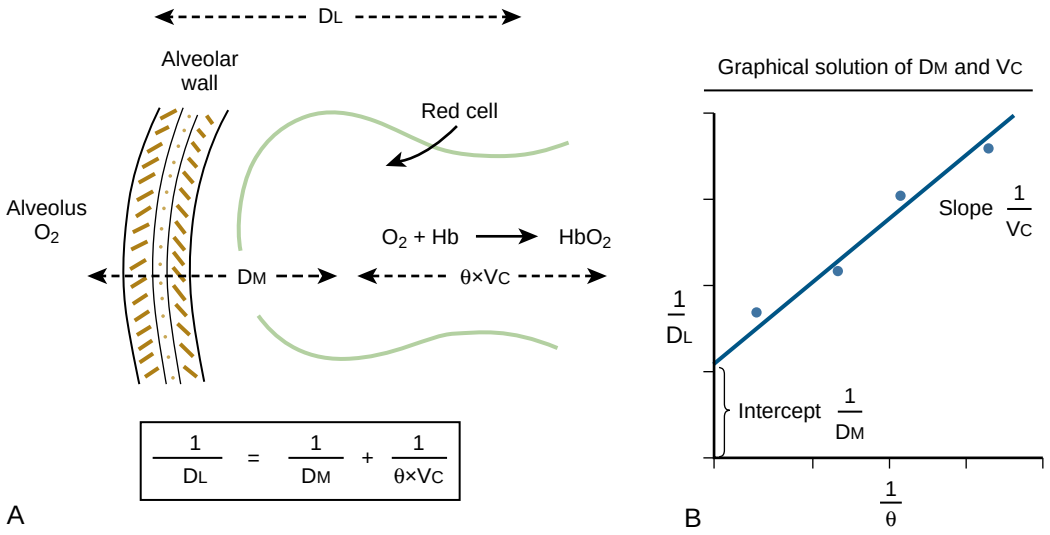
eFIGURE IMAGE GALLERY



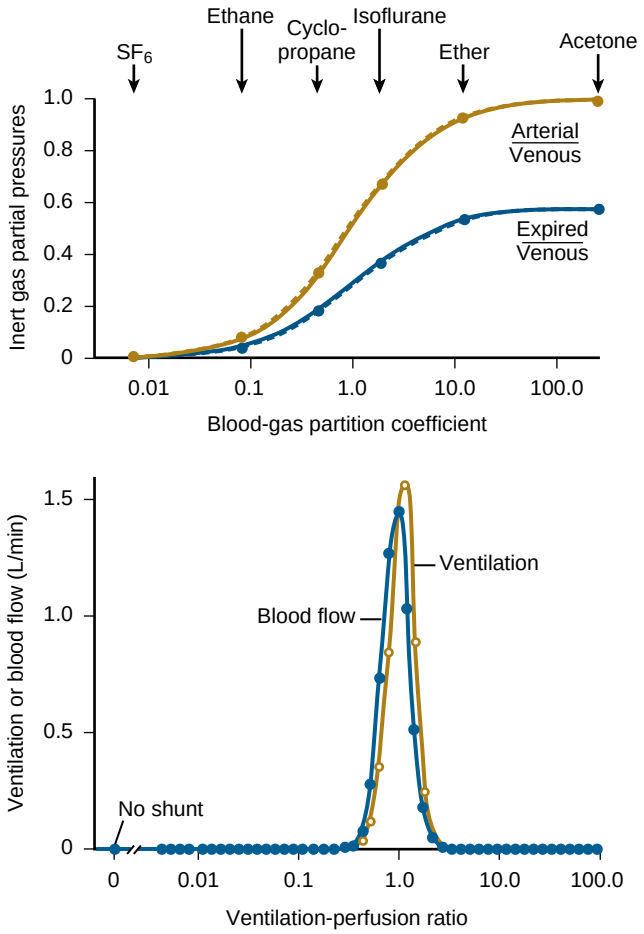
eFigure 10.1 Stimulus-response curves of hypoxic pulmonary vasoconstriction. Pulmonary blood flow is shown in relation to alveolar P_{O_2} in feline lung preparations, each represented by a separate line. P_{O_2}, partial pressure of oxygen. (Modified from Barer GR, Howard P, Shaw JW. Stimulus-response curves for the pulmonary vascular bed to hypoxia and hypercapnia. *J Physiol [Lond]*. 1970;211:139–155.)



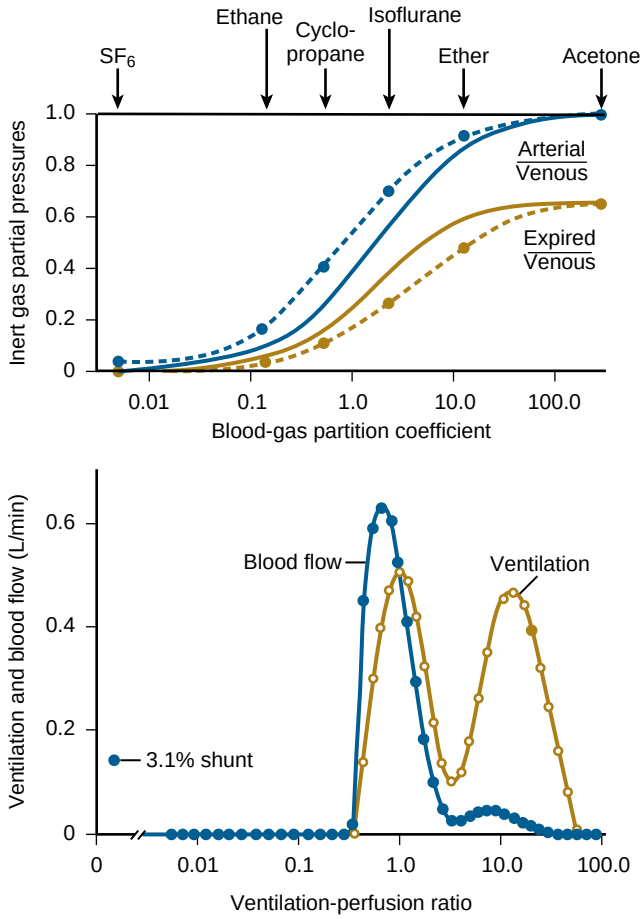
eFigure 10.2 Diffusion-limited transfer of various gases in the lung. Diffusion limitation (L_{diff}) is on a scale of 0 (no limitation) to 1 (complete limitation) (see text for details). $D/\dot{Q}\beta$ ratio, diffusive equilibrium of gas in blood; SF_6, sulfur hexafluoride. (From Scheid P, Piiper J: Blood gas equilibration in lungs and pulmonary diffusing capacity. In: Chang HK, Paiva M, eds. *Respiratory Physiology: An Analytical Approach*. New York: Marcel Dekker; 1989:453–497.)



eFigure 10.3 The components of the diffusing capacity. (A) The two components of the measured diffusing capacity (D_L) of the lung: that due to the diffusion process itself (D_M) and that attributable to the time taken for oxygen (or carbon monoxide) to react with hemoglobin (Hb) ($\theta \times Vc$). (B) $1/D_L$ plotted against $1/\theta$ can be used to derive D_M and Vc. θ is the reaction coefficient that is varied by changing the inspired oxygen to allow separation of the various resistances. Hb, hemoglobin, HbO_2, oxyhemoglobin; Vc, vital capacity.



eFigure 10.4 Use of the multiple inert gas elimination technique to determine the distribution of ventilation-perfusion ratios in a 22-year-old normal patient. *Top panel*, Data points for inert gas retention (*upper curve*) and excretion (*lower curve*). *Broken lines* join the points. The two *solid lines* show the values of retention and excretion for a lung with no ventilation-perfusion inequality. *Bottom panel*, The recovered distribution of ventilation-perfusion ratios. SF_6, sulfur hexafluoride. (Modified from Wagner PD, Laravuso RB, Uhl RR, West JB. Continuous distributions of ventilation-perfusion ratios in normal subjects breathing air and 100% O2. *J Clin Invest.* 1974;54:53–68.)



eFigure 10.5 Distribution of ventilation-perfusion ratios in a 60-year-old patient with COPD, predominantly emphysema. *Top panel*, The retention and excretion solubility curves. *Bottom panel*, The recovered distribution of ventilation-perfusion ratios. SF_6, sulfur hexafluoride. (Modified from Wagner PD, Dantzker DR, Dueck R, et al. Ventilation-perfusion inequality in chronic obstructive pulmonary disease. *J Clin Invest.* 1977;59:203–216.)

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11 RESPIRATORY SYSTEM MECHANICS AND ENERGETICS

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Volume
Pressure
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INTRODUCTION

The movement of gases in and out of the respiratory system may be described by the physical laws that govern pressure, volume, and flow of gas. The study of these relationships is called *respiratory mechanics,* and the study of the energy cost of gas movement is called *energetics.*

This chapter reviews basic terminology, respiratory mechanics under static and dynamic conditions, and energetics, including measurements of the work of breathing. The chapter also highlights how physiologic principles can be applied to specific clinical problems.

TERMINOLOGY

FLOW

Flow is defined as the volume of gas passing a fixed point per unit of time. Flow is usually measured with a pneumotachograph (flowmeter), which consists of a tube with a known fixed resistance. Flow can be calculated by measuring the pressure drop across the resistor.

Gas velocity is the distance moved by a gas molecule per unit of time and should not be confused with flow. At a constant flow, gas velocity will be greater in narrower tubes.

VOLUME

Volume is defined by the space occupied by a gas. The volume occupied by a fixed number of gas molecules is influenced by temperature and pressure.

The volume of gas entering and leaving the lung can be determined by a spirometer that measures volume displacement or by integrating the flow signal measured by a pneumotachograph. The subdivisions of lung volumes are shown in Figure 11.1 (see also Chapters 31 and 32). Some of these subdivisions can be measured by spirometry alone (vital capacity, *tidal volume* [VT]), whereas others require use of helium dilution or plethysmography. *Total lung capacity* (TLC) is the lung volume at the end of a maximal inspiration. *Residual volume* (RV) is the volume at the end of a maximal expiratory effort. *Functional residual capacity* (FRC) refers to the volume in the lung at the end of a normal tidal exhalation, where there is normally relaxation of both inspiratory and expiratory muscles.

Total gas volume in the lung is usually measured using plethysmographic methods or by inert gas dilution methods, and each of these techniques has advantages and disadvantages.[1] In body plethysmography, subjects are completely enclosed in a gas-tight container. Lung volume can be calculated by comparing changes in *alveolar pressure* (Palv) (measured at the mouth while the patient pants against an occluded mouthpiece) with changes in pressure

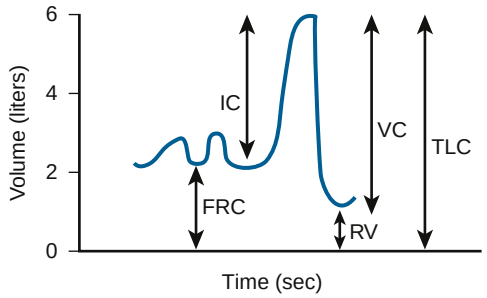

Figure 11.1 Subdivisions of lung volume. Volume-time tracing of a subject taking two normal tidal breaths, inhaling to *total lung capacity* (TLC), and exhaling to *residual volume* (RV). *Vital capacity* (VC) and *inspiratory capacity* (IC) may be measured with a spirometer. The measurement of *functional residual capacity* (FRC), RV, and TLC requires a determination of intrathoracic gas volume by helium dilution, nitrogen washout, or plethysmography.

in the container.[2] Body plethysmography is widely available and accurate but may overestimate lung volumes because it will include measurement of abdominal gas if that gas is compressed and decompressed during the panting maneuver. In addition to using body plethysmography to estimate FRC, inert gas dilution techniques or radiologic assessments can be used. Historically, inert gas methods have usually used helium. For this method, subjects at FRC inhale a known concentration and volume of helium from a bag. The helium mixes with and is diluted by gas already in the lung. A sample of exhaled gas is analyzed for helium concentration, allowing calculation of the FRC thus:

$$C_1 \times V_1 = C_2 \times (V_1 + FRC)$$

Where C_1 is the initial (known) helium concentration in the bag, C_2 is the final (measured) helium concentration, and V_1 is the initial volume of gas in the bag. Therefore:

$$FRC = [(C_1 \times V_1)/C_2] - V_1$$

By the same principle other nonrespiratory gases, such as sulfur hexafluoride, can be used to calculate FRC. In general, inert gas dilution measurements tend to underestimate total lung volume, especially in patients with substantial airway obstruction who may have gas trapped in lung units that do not mix with inspired gas.

Respiratory gases naturally present in a subject's lungs (such as nitrogen) can also be used for FRC determination. Multiple techniques have been described that rely on using nitrogen dilution or "washout." In this test, the subject breathes 100% oxygen, allowing the nitrogen in the respiratory system to "wash out." During this maneuver, the volume of expired nitrogen is calculated and is used to estimate FRC.[3] Similar to inert gas dilution measurements, the nitrogen washout technique may underestimate the lung volume in patients with obstructive lung disease.

Imaging modalities such as chest radiography, computed tomography, and magnetic resonance imaging can provide accurate assessment of FRC.[3–7] Computed tomography may overestimate the volume of alveolar gas available for gas exchange because it measures the entire volume of gas in the lung, whether or not that gas participates in gas exchange.[8] In summary, understanding the advantages and limitations with each method is essential for appropriate interpretation of values.

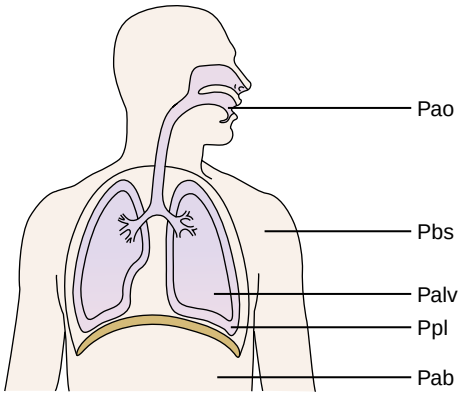

Figure 11.2 Respiratory system pressures. Pao, pressure at airway opening (mouth or nose) in spontaneously breathing patient; Pbs, pressure at body surface; Palv, pressure in alveolus; Ppl, pressure in pleural space; Pab, pressure in abdomen. Trans-pulmonary pressure: Pao – Ppl; trans-lung pressure: Palv – Ppl; trans-chest wall pressure: Ppl – Pbs; trans-respiratory system pressure: Pao – Pbs; trans-diaphragmatic pressure: Ppl – Pab. Under static conditions, when the subject is not on assisted ventilation, Pao = 0 (atmospheric pressure). However, Pao may be positive when the patient is receiving positive-pressure mechanical ventilation. Pbs is equivalent to atmospheric pressure unless the subject is in a negative-pressure device such as an iron lung.

PRESSURE

The pressure of a gas is generated from the momentum of molecules colliding against a surface and is expressed as the force per unit area. Pressure, as opposed to force, is the same in all directions. Respiratory system pressures are usually reported relative to atmospheric pressure.

The pressures relevant to the respiratory system are shown in Figure 11.2. Although it is possible to measure *pleural pressure* (Ppl) directly, esophageal pressure is a less invasive surrogate. Esophageal pressure may be measured using an air-filled balloon inserted into the middle third of the esophagus, approximately 35 to 45 cm from the nares.[9–11] Values obtained by esophageal balloon only reflect the pressure at one level of the lung, adjacent to the esophagus, and can be affected by movement of the neck, weight of the mediastinum from patient positioning, esophageal elastance, and the volume of air in the balloon.[12–14]

Boyle's Law

For an ideal gas at a constant temperature, the relationship between volume and pressure is described by Boyle's law:

$$P_1 \times V_1 = P_2 \times V_2$$

where P_1 is the absolute pressure of the gas and V_1 is the volume. Because the number of particles in an ideal gas remains constant, P_2 and V_2 are the resulting pressure and volume if any parameter is modified. The combined gas law describes how changes in volume of the lung alveoli (through contraction of the respiratory muscles) cause a change in pressure and thus drive ventilation. Although this equation theoretically applies only to an ideal or perfect gas, it is an adequate approximation for clinical purposes.

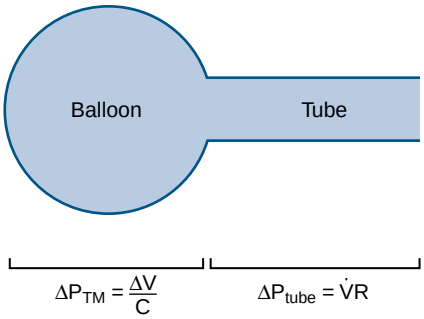

Figure 11.3 Balloon-and-tube analogy of the respiratory system. ΔP_{TM}, change in transmural pressure (inside – outside) of balloon; ΔV, change in volume; C, compliance; $\dot{V}$, flow; R, resistance; and ΔP_{tube}, pressure difference from one end of the tube to the other.

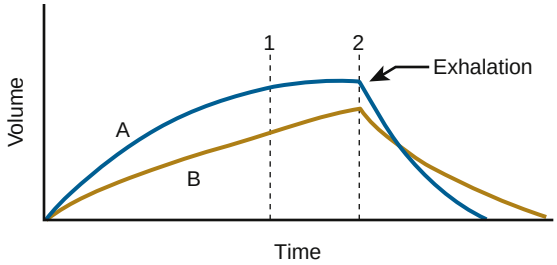

Figure 11.4 Time constants. Shown are two lung units of equal volume, one with a short time constant (A) and one with a long time constant (B). Each is inflated under a constant pressure until point 2 and then exhalation is passive. At point 2, unit A is completely filled but unit B is not. Of note, when time constants are uneven, decreasing inspiration time to point 1 will worsen heterogeneity in ventilation.

COMPLIANCE, RESISTANCE, AND TIME CONSTANTS

The respiratory system can be thought of as a combination of balloons and tubes (Fig. 11.3). As the pressure across the wall of a balloon increases (called transmural pressure, or pressure inside minus pressure outside), the volume inside the balloon increases. The ratio between the change in volume and the change in transmural pressure is the compliance of the balloon. The units of compliance are volume/pressure. A larger compliance indicates that volume changes more for every change in pressure. The inverse of compliance is elastance, with a larger elastance indicating a stiffer system.

Resistance is a measure of the pressure required to generate flow through a tube. The narrower the tube, the greater the pressure needed and the higher the resistance. The units of resistance are pressure/flow. Airway conductance, the inverse of resistance, represents the flow per unit of pressure. Assuming that all other factors are constant, a greater conductance indicates a more dilated airway.

When a pressure is applied to a lung unit (Fig. 11.4), the time required to fill the unit is dependent on its compliance and resistance. That is, it will take longer to fill if resistance is high because the flow will be low. Similarly, it will take longer to fill the unit if compliance is high because it will require more volume to reach the applied pressure. The product of the resistance and compliance of a lung unit is the time constant and represents the time required for the lung unit to fill to 63% of the final volume if a constant pressure is applied. Areas of the lung with small time constants (i.e., low resistance and/or low compliance) will fill more rapidly than areas with larger time constants.

This concept has clinical implications when there are heterogeneous time constants between parallel lung units, as in patients with chronic airflow obstruction or patchy alveolar edema/atelectasis as is found in *acute respiratory distress syndrome* (ARDS). As long as the respiratory rate is low, all units will fill fully. However, if the respiratory rate increases so that the inspiratory time becomes less than the time constant of some units, these units will receive less ventilation and contribute to ventilation-perfusion mismatch.

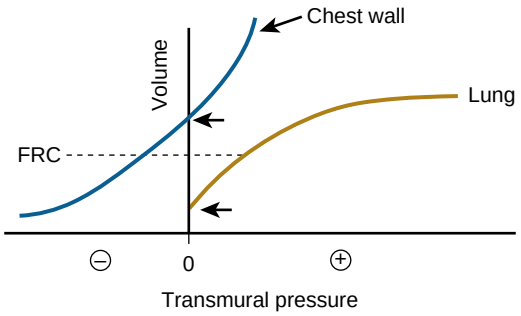

Figure 11.5 Volume-pressure curves of lung and chest wall. The relationship between transmural (inside – outside) pressure of lung and relaxed chest wall volume are shown. At *functional residual capacity* (FRC), outward chest wall recoil is balanced by inward lung recoil. At FRC, transmural pressure for the lung = Pao – Ppl; because Ppl is negative, this yields a positive value. For the chest wall, transmural pressure = Ppl – Pbs, which yields a negative value. The static equilibrium (resting volume) of the chest wall is above FRC whereas that for the lung is below FRC (*arrows*). Pbs, pressure at body surface; Pao, pressure at airway opening; Ppl, pleural pressure.

RESPIRATORY MECHANICS IN STATIC CONDITIONS

We first consider the lung during static conditions, when the respiratory system is maintained at a fixed volume with no gas flow. Even under static or no-flow conditions, pressure gradients are still required to distend the respiratory system. The energy used to distend the respiratory system during inhalation (elastic work) is stored as potential energy. Because of this stored energy, normal exhalation does not require work and is a passive process. The elastic work used to inflate the respiratory system has both lung and chest wall components.

ELASTIC RECOIL OF THE LUNGS

If removed from the body, an isolated lung will deflate to a minimal volume containing only trapped gas, due to its elastic recoil. Because airways close before complete alveolar emptying, application of a negative pressure to the airway opening will not remove the trapped gas. The relationship between lung volume and transpulmonary pressure during inflation is shown in Figure 11.5. Lung compliance is fairly high at the lung volumes associated with normal breathing, but then decreases markedly near TLC. At this volume, very large increases in transmural pressure result in small changes in volume.

Two major factors are responsible for the elastic recoil of the lung: (1) lung connective tissue and (2) surface tension related to the air-liquid interface of the alveolar surface.

Lung Connective Tissue

A network of connective tissue fibers, composed primarily of collagen and elastin, provide the framework for the alveoli and structural integrity for the lung (see also Chapter 5). Collagen fibers exhibit high tensile strength but are relatively noncompliant, whereas elastin, which has a lower tensile strength, is more compliant.[15]

At low lung volumes, elastin fibers are the major contributor to the volume-pressure relationship, facilitating lung inflation and stability, whereas collagen fibers remain curled and unstressed.[16,17] At high lung volumes, collagen fibers uncurl and straighten to have a stiffening effect on the lung. Destruction of lung connective tissue, such as from smoking-induced emphysema, can substantially increase lung compliance.[18]

Alveolar Surface Forces and Surfactant

When a lung is completely filled with water, compliance is much greater than when it is filled with air.[19] This suggests that lung elastic recoil is mostly due to surface tension at the air-liquid interface lining the alveoli rather than from elastin and collagen connective tissue fibers.

Because there are intermolecular forces of attraction between molecules of liquids, the surface of an air-liquid interface is under tension. Whereas molecules in the interior of a liquid are subjected to equal forces in all directions, molecules at the surface are pulled toward each other and pulled down by molecules below the surface. These forces, referred to as surface tension, cause a gas-filled bubble to collapse.

Because of surface tension, a positive pressure must be present to prevent the collapse of a gas-filled bubble of liquid. The pressure of gas within a bubble is related to the *surface tension* (T) and the *radius of curvature* (r) of the bubble by Laplace's law ($P = 2T/r$). The alveolus can be likened to a bubble with a radius of approximately 0.1 mm at FRC. If the surface tension were similar to that of water (72 mN/m), the lungs would be very noncompliant, and ventilation with transpulmonary pressures in the physiologic range (3 to 5 cm H_2O) would be impossible. Furthermore, the high surface tension would lead to alveolar instability. Smaller alveoli with smaller radii of curvature, by the nature of Laplace's law, would generate higher alveolar pressures than larger alveoli. Because gas travels from an area of higher pressure to one of lower pressure, smaller alveoli would tend to empty into larger alveoli, eventually resulting in one large air-filled alveolus.

Many factors contribute to alveolar stability in normal lungs. First, pulmonary surfactant, a mixture of lipids and proteins secreted by type 2 alveolar epithelial cells, reduces surface tension (see Chapter 3).[20] The lipid component of surfactant is amphiphilic, containing both hydrophobic and hydrophilic groups. At an air-liquid interface, the amphiphilic nature of the phospholipids creates a monolayer and displaces water molecules. The saturation of the acyl group allows the phospholipids in surfactant to form ordered monolayers and confers the ability to be compressed (during expiration), which is essential to decreasing surface tension at low lung volumes.[21] Second, alveoli are interconnected (alveolar interdependence) by common walls and structures. Therefore, if one alveolus began to collapse, it would stretch adjacent alveolar walls, creating a tethering effect on the collapsing unit. Third, the connective tissue scaffolding limits overdistention of alveoli.

Hysteresis and Stress Adaptation

During inflation of the lung, the pressure required at any given lung volume is greater than that during deflation (Fig. 11.6). The difference between the inflation and the deflation curves is due to hysteresis and stress adaptation.

Hysteresis refers to changes in mechanical properties due to the volume history of the lung and is caused by several factors. First, the effect of surfactant on surface tension is dependent on volume history, with surfactant less effective at reducing surface tension during inspiration than during expiration. This is due to movement of surfactant molecules from below the surface of the fluid to the liquid surface during inhalation. Second, much higher pressures are required to open collapsed airways or alveoli than are required to keep them open. In disease states characterized by collapse of alveoli (e.g., ARDS), significant hysteresis of the pressure-volume curve can be seen (see Fig. 11.6) and higher inflation pressures are often required for ventilation.[22]

In contrast, *stress adaptation* refers to changes in mechanical properties over time. When lung tissue is stretched to a particular length, the tension required to maintain the length gradually diminishes due to time-dependent properties of surfactant and deformation of viscoelastic tissues of the lung. Therefore, after a sustained lung inflation, the pressure required to keep the lung at that volume will decrease.

ELASTIC RECOIL OF THE CHEST WALL

Movement of the chest wall by the muscles of ventilation generates pressure gradients between the alveoli and the surrounding air, enabling gas to be moved in and out of the lungs.

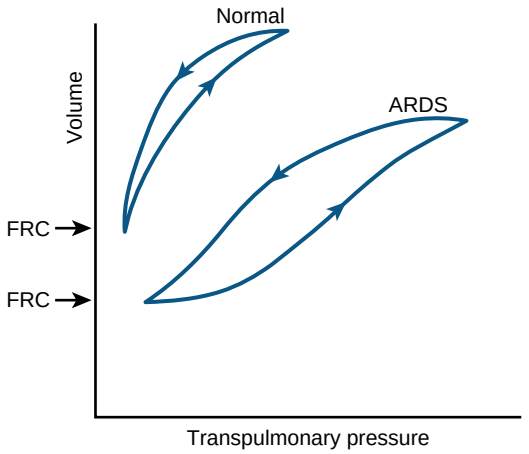

Figure 11.6 Hysteresis in a normal lung and an acutely injured lung. In *acute respiratory distress syndrome* (ARDS) the lung is stiffer than the normal lung and greater inflation pressure is required at any given lung volume. Furthermore, the degree of hysteresis is much greater in ARDS lungs, with a greater separation of the volume-pressure curves on inspiration (*upward arrow*) and exhalation (*downward arrow*). FRC, functional residual capacity.

Chest Wall Compliance

The compliance of the chest wall can be determined by measuring changes in the transmural pressure across the thorax (trans-chest wall pressure, Ppl – Pbs) relative to change in volume (see Fig. 11.5). (Body surface pressure is the pressure acting on the surface of the body, normally atmospheric pressure.) The resting volume of the relaxed chest wall is approximately 1 L above FRC. The difference between the resting volume of the chest wall and that of the lung can be appreciated in patients with a pneumothorax or pleural effusion, when the chest wall recoils outward and the lung recoils inward. When the chest wall is distended to a volume above its resting volume, the chest wall recoils inward; when it is pulled in to a volume below its resting volume, it recoils outward. The compliance of the normal chest wall is approximately 200 mL/cm H_2O, but it becomes progressively stiffer at lower lung volumes. This stiffness predominantly determines RV in normal young subjects.[23]

Factors such as severe kyphoscoliosis, skin eschars from burns, and abdominal distention may reduce chest wall compliance. Chest wall compliance is higher in the sitting position than in the supine position, but the overall effect is usually modest.[24]

INTEGRATION OF LUNG AND CHEST WALL MECHANICS

The chest wall and lung are juxtaposed and, in the absence of pleural disease (e.g., pneumothorax or pleural effusion), changes in chest wall volume are essentially identical to changes in lung volume (Fig. 11.7). An integration of lung and chest wall mechanics can be represented graphically by plotting Ppl against the relaxed volumes of the lung and chest wall (Campbell diagram) (Fig. 11.8A). These plots help to explain the determinants of the commonly measured static lung volumes. At FRC (relaxation volume), the outward recoil pressure of the chest wall is balanced by the inward recoil of the lung. The Ppl at which the recoil pressures are balanced is negative (approximately −3 to −4 cm H_2O) in normal subjects. Changes in the compliance of the lung or chest wall may change the relaxation volume (see Fig. 11.8A).

Increases in lung compliance (e.g., due to emphysema) will tend to shift the volume-pressure curve of the lung upward and to the left. If chest wall compliance remains constant, FRC will increase. In contrast, if lung compliance is reduced (e.g., pulmonary fibrosis), the volume-pressure curve of the lung will shift downward and to the right, leading to a reduction in FRC. Similarly, changes in chest wall compliance can lead to increases or decreases in FRC. FRC is believed to represent the balance of forces in a relaxed state with no muscle activation. However, there is a reduction in FRC with paralysis compared to the relaxed state. This suggests that inspiratory muscle tone of the rib cage muscles and diaphragm may contribute to a "passive" decrease in chest wall compliance and thus to an increase in FRC.[25]

With activation of inspiratory and expiratory muscles, the configuration of the chest wall changes (Fig. 11.8B). Activation of inspiratory muscles effectively shifts the volume-pressure curve of the chest wall, so that at any given Ppl, the volume of the chest wall is increased relative to the relaxed state. The horizontal difference between the relaxed curve and the curve with inspiratory muscle activation represents the net pressure generated by the inspiratory muscles.

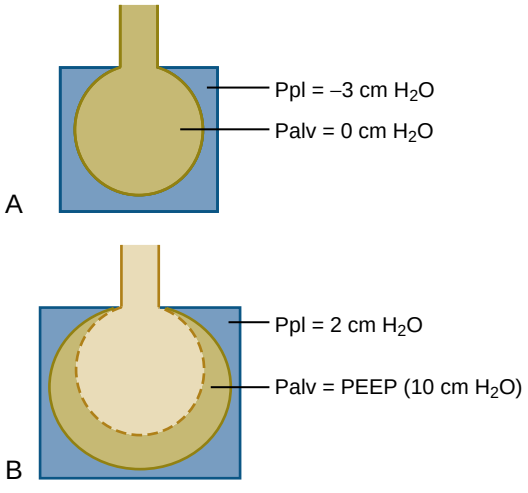

Figure 11.7 Changes in *pleural pressure* (Ppl) with applied *positive end-expiratory pressure* (PEEP). (A) Shown is a lung at end-exhalation with no PEEP. (B) With the application of PEEP, there is an increase in the volume of the respiratory system (lung and chest wall) and an increase in Ppl. The magnitude of the increase in Ppl is dependent on the relative compliances of the lung and chest wall. Palv, pressure in alveolus.

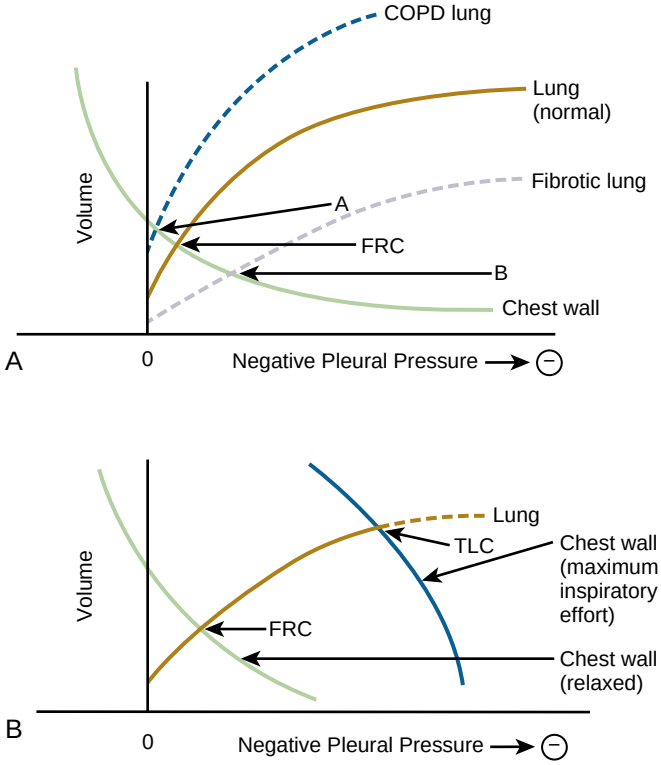

Figure 11.8 Integration of lung and chest wall mechanics. (A) Changes in lung and relaxed chest wall volumes as a function of pleural pressure (Campbell diagram). This is basically the same plot as in Figure 11.5 except that the *x*-axis is pleural pressure rather than transmural pressure for the lung and chest wall. The point at which the two curves meet is the *functional residual capacity* (FRC) (lung recoil balanced by chest wall recoil). If lung compliance is increased (e.g., in COPD), the point at which the two curves meet (FRC) is greater (point A). In contrast, if lung compliance is reduced (e.g., in pulmonary fibrosis), the point at which the two curves meet is less (point B). (B) Maximal inspiratory effort (Campbell diagram). With maximal inspiratory effort, the volume-pressure curve of the chest wall moves to the right. The point at which there is intersection of this curve and the lung volume-pressure curve is the *total lung capacity* (TLC).

TLC is determined by the balance between inward lung recoil plus the inward chest wall recoil and the strength of the inspiratory muscles. However, in normal subjects, TLC is predominantly determined by the increased stiffness of the lung at high lung volume, rather than the recoil of the chest wall or respiratory muscle strength.[26] In support of this concept, inspiratory muscle training in normal subjects increases strength substantially (55% increase in maximal inspiratory pressure) but results in a very modest change in TLC and vital capacity (about 4%).[27] The situation in patients with neuromuscular disease is very different; in such individuals, reduced TLC is largely due to respiratory muscle weakness and can be improved to some extent by inspiratory muscle training.[28]

Activation of expiratory muscles shifts the volume-pressure curve of the chest wall in the other direction, and the degree of shift is a measure of the net pressure exerted by the expiratory muscles. In young subjects, RV is determined by the balance of static forces among the outward recoil of the chest wall, inward lung recoil (small component), and expiratory muscle strength.[26] In older subjects or patients with obstructive lung disease, RV is determined by gas trapping during airway closure upon exhalation before a static balance is achieved.[26]

Calculation of Total Respiratory System Compliance from Lung and Chest Wall Compliance

Mechanical properties of the lungs can be compared to a Newtonian model, which consists of a resistor and capacitor. Airway resistance acts as the resistor and respiratory compliance acts as the capacitor. Because the two components of the respiratory compliance, the chest wall and lung, are arranged in series, the relationship between total *respiratory system compliance* (C_{RS}), *lung compliance* (C_L), and *chest wall compliance* (C_W) is:

$$1/C_{RS} = 1/C_L + 1/C_W$$

Alternatively, because elastance = 1/compliance,

$$\text{Elastance}_{RS} = \text{Elastance}_L + \text{Elastance}_W$$

For example, in a supine paralyzed subject, lung compliance is approximately 150 mL/cm H_2O pressure and chest wall compliance is approximately 200 mL/cm H_2O pressure[29]; the calculated compliance of the respiratory system would thus be approximately:

$$1/(1/150 + 1/200) = 85.7 \text{ mL/cm}H_2O$$

CLINICAL APPLICATIONS

Positive End-Expiratory Pressure and its Impact on Pleural Pressure

Patients with diseases that decrease lung compliance receive positive-pressure mechanical ventilation to maintain positive pressure at the end of exhalation to prevent alveolar collapse.[30] Some—but not all—of this *positive end-expiratory pressure* (PEEP) is transmitted from the alveolar space to the pleural space (see Fig. 11.7B). During mechanical ventilation, changes in both Ppl and transpulmonary pressure depend on the relationships between the *elastance of the chest wall* (E_W), *elastance of the lung* (E_L) and *elastance of the total respiratory system* (E_{RS}, the sum of E_W and E_L), a relationship that can be described by the equation:

$$\Delta Ppl = \Delta Paw \times E_W/E_{RS}$$

where *Paw* represents the airway pressure at the end of the endotracheal tube in a mechanically ventilated patient. In healthy individuals, E_W and E_L are approximately equal, and E_W/E_{RS} has a value of approximately 0.5, within the range of normal ventilation.[31] In this situation, it is reasonable to infer the value of Ppl from Paw. However, in disease, both E_W and E_L demonstrate great variability, so that the ratio of E_W to E_{RS} is unpredictable.[32] In this situation, Ppl cannot be assumed to be directly related to Paw.[33] If lung compliance is much greater than chest wall compliance (e.g., in a patient with emphysema and kyphoscoliosis), a greater proportion of PEEP will be transmitted to the pleural space. In healthy individuals, as described, the chest wall and lung compliances are equal and thus the increase in Ppl is roughly equal to one-half of the applied PEEP (e.g., 5 cm H_2O pressure if the PEEP is 10 H_2O pressure). In contrast, if lung compliance is low and chest wall compliance is high (as in thin patient with severe ARDS), very little of the Palv will be transmitted to the pleural space, and thus Ppl will change minimally with PEEP.

PEEP has two major benefits. PEEP helps to recruit alveolar units and thereby improves ventilation-perfusion mismatch and gas exchange by reducing atelectasis. PEEP also helps reduce the shear stress of repeated alveolar opening and closing (atelectrauma), which can contribute to lung injury.[34] While the addition of PEEP may be beneficial to alveolar recruitment, the amount of PEEP transmitted to each alveolar unit may not be homogenous in disease states (see "PEEP Optimization and Recruitment Maneuvers" later).

PEEP has a number of adverse consequences. First, if PEEP increases Ppl, that can lead to an increase in pericardial pressure and reduce venous return and cardiac output.[35] Second, if PEEP increases Ppl, this will increase central venous pressure and pulmonary artery occlusion pressure to a similar magnitude, which, if not taken into account, may result in errors when using these parameters to asses intravascular volume status. Finally, PEEP acts as an inspiratory threshold load requiring inspiratory muscles to counteract this intrinsic PEEP (see later) to generate airflow.

Plateau Pressures in Patients Receiving Positive-Pressure Mechanical Ventilation

In patients receiving positive-pressure mechanical ventilation, the *plateau pressure* (Pplat) is the distending pressure of the respiratory system at end inspiration when there is no flow. When possible, Pplat should be limited to a maximum of 30 to 35 cm H_2O because higher pressures can damage the lung through overdistention. At TLC in a normal subject, the distending pressure across the lung (Palv − Ppl) is approximately 35 cm H_2O.[36] Therefore, limiting Pplat to less than 35 cm H_2O should limit lung expansion to below TLC and avoid overdistension. Avoiding high Pplat may be even more important in settings where the lung parenchyma is not homogenous because highly compliant lung units may be more at risk of overdistension than less compliant lung units. The use of low V_T during mechanical

ventilation for ARDS has led to improved clinical outcomes, presumably due to decreased alveolar distension and volutrauma, the term referring to injury caused by overdistention of alveoli.[37,38]

During mechanical ventilation, Pplat is often used as a surrogate for transpulmonary pressure (pressure used to distend the lung), when it is actually a measure of transrespiratory system pressure (pressure used to distend both the lung and chest wall). When lung compliance is much less than chest wall compliance (i.e., the lung is quite stiff), this is a reasonable assumption, because during mechanical ventilation most of the pressure will be used to distend the lung, not the chest wall. However, in conditions in which the chest wall is stiff (e.g., obesity, ascites, kyphoscoliosis), Pplat may substantially overestimate the distending pressure of the lung.[39]

Esophageal manometry can be used to separate the contributions of airway pressure into the components that distend the lung (transpulmonary pressure = Paw – Ppl) or chest wall (Ppl). A small air-filled balloon is placed in the midesophagus and attached to a pressure transducer. Assuming that the pressure surrounding the esophagus is properly transmitted, the *esophageal balloon pressure* (Pes) can be used as a surrogate to estimate Ppl at end inspiration.[12] In a mechanically ventilated patient on volume-control mode, Paw is equal to Pplat at end-inspiration. Consider a ventilated patient who develops ascites. In order to maintain the transpulmonary pressure, the increase in Ppl (as measured by Pes) would be matched by an increase in Pplat. In this example, the increase in Pplat is related to reduced chest wall compliance from ascites. An increase in Pplat as in this example may be less injurious to the lung than in a patient with the same Pplat but low Ppl (see later discussion on driving pressure). Thus, the esophageal balloon can provide clinically useful measurements. However, there are limitations to the use of esophageal balloons, including movement of the balloon, inadequate inflation, and patient positioning.[12–14]

STRESS AND STRAIN

A discussion of the mechanics of stress and strain is available at ExpertConsult.com.

THE RESPIRATORY SYSTEM IN DYNAMIC CONDITIONS

The work to distend the chest wall and lung during inhalation is stored as potential energy (elastic work). Work also must be done to overcome the inertia of the gas (which is negligible when breathing air at normal breathing frequency and atmospheric pressures) and nonelastic resistance (resistive work), which cannot be stored but is dissipated as heat. Resistive work has two components that must be considered.

RESISTIVE WORK DUE TO GAS FLOW THROUGH AIRWAYS

When gas flows through an airway, frictional and viscous forces cause energy loss and a pressure drop along the airway. The extent of this pressure drop is dependent on the resistance to gas flow, physical properties of the gas (e.g., density and viscosity), and the nature of flow (laminar versus turbulent).

Laminar versus Turbulent Flow

The pressure drop due to friction is lowest with pure laminar flow, in which gas molecules travel in a straight line. The velocity profile of the gas is parabolic, with the molecules closer to the wall traveling slower than molecules in the center of the airway. When gas flow is laminar, the flow is proportional to the pressure gradient (ΔP) along the airway and inversely proportional to resistance (R).

$$\text{Flow} = \Delta P/R$$

For a straight airway under conditions of laminar flow, resistance of a tube is related to viscosity, length, and radius of the tube by the Poiseuille equation:

$$\text{Flow} = \frac{\pi \times \text{radius}^4 \times \Delta P}{8 \times \text{length} \times \text{viscosity}}$$

Because of this relationship, flow through a tube is dramatically affected by even small changes in tube diameter (i.e., reducing the radius by half causes a 16-fold decrease in gas flow). If the dimensions of a tube are held constant, the most important variable in determining laminar gas flow is viscosity.

In turbulent flow, the orderly movement of gas molecules becomes haphazard. When gas flow is turbulent, the flow is proportional to the square root of the pressure gradient (as opposed to a linear relationship seen with laminar flow)[43]:

$$\text{Flow} = \text{constant} \times (\Delta P)^{1/2}$$

Because resistance is defined as the pressure gradient divided by the flow rate, the "resistance" for turbulent flow is not constant but increases in proportion to flow. In contrast to laminar flow, turbulent flow differs in that (1) a higher ΔP is required for gas flow, (2) gas flow depends on gas density, not viscosity, and (3) ΔP is proportional to the fifth power of the radius of the airway.

Reynolds Number

The Reynolds number is a dimensionless coefficient that predicts whether flow through an unbranched tube will be predominantly laminar, turbulent, or mixed. The equation is as follows:

$$\text{Re} = \rho DV/\mu$$

where ρ is the gas density, D is the diameter of the airway, V is the mean gas velocity, and μ is the viscosity. In general, a Reynolds number of less than 2000 is associated with laminar flow, whereas a value greater than 4000 is associated with predominantly turbulent flow. Intermediate values are associated with mixed flow patterns. Increased gas density, increased gas velocity, and increased tube diameter predispose to turbulent flow.[43]

Air flow through the airways of the lung is more complex than flow through theoretical tubes. The cross-sectional diameter of a small peripheral airway (e.g., bronchiole) is much smaller than that of a central airway (e.g., trachea). However, because of the greater number of peripheral

To an engineer, stress is the net difference between forces acting on a body. From the point of view of lung mechanics, stress reflects the difference between distending forces (e.g., Palv) and collapsing forces (Ppl); stress is therefore represented by the transpulmonary pressure.[40]

The deformation of a structure by stress is called *strain,* which is defined as the change in size or shape compared to the structure's initial shape or volume. That is:

$$\text{Strain} = \Delta V/\text{FRC}$$

For example, if a lung is inflated with a 500 mL VT from an initial FRC of 1500 mL, the strain associated with this is 0.33 (500 mL/1500 mL). The recommendation of a specific VT for lung-protective ventilation is predicated on the assumption that there is a uniform amount of lung able to receive the inspired volume. This volume is the amount of aerated lung at end-expiration: the FRC. Underlying this is the assumption that FRC can be predicted by ideal body weight—an assumption that is not correct in injured lungs.[41] It is therefore understandable that, given the same ideal body weights and VT prescriptions, two patients with ARDS might have significantly different FRCs and thus different lung strains. It therefore may be prudent to attempt to minimize strain during mechanical ventilation by measuring FRC and titrating VT to this assessment rather than to ideal body weight. Indeed, there is some evidence that maintaining strain to less than 1.5 to 2 reduces markers of lung parenchymal injury.[42]

airways, the sum of the entire cross-sectional area of the peripheral airways greatly exceeds that of the central airways. Therefore, as gas moves from the peripheral to the central airways during exhalation, the gas velocity increases. The different flow rates along the airways results in predominantly laminar flow in the periphery and turbulent flow in the larger central airways (except at very low flow rates).

Clinical Effects of Heliox

Heliox is a mixture of oxygen and helium. Heliox has a density less than air because helium has a lower density than the nitrogen it replaces. For instance, a mixture of 20% oxygen and 80% helium has a density of 0.33 relative to air.[44] In patients who have upper airway narrowing (e.g., partial tracheal obstruction),[45] substituting heliox for air reduces gas density, lowers the Reynolds number, and helps to convert turbulent to laminar flow. This reduces the pressure required to move gas and diminishes the work of breathing, unloading the respiratory muscles. Heliox may be useful in patients with asthma or COPD, although this is controversial due to mixed clinical results.[46–48] The clinical benefit of heliox is lost when the gas mixture contains less than 70% helium; thus heliox is not a good option for patients who require more than 30% oxygen supplementation.

Flow Limitation

In a normal subject, increasing expiratory effort will increase air flow until a threshold is reached. Once this effort threshold is exceeded, expiratory flow will not increase with a further increase in effort, resulting in flow limitation (Fig. 11.9).[49] In contrast, patients with very poor effort or marked expiratory muscle weakness may be unable to generate sufficient expiratory pressures to reach flow limitation. If maximum flow was not relatively effort independent, measures such as forced expiratory volume in 1 second would have little utility in monitoring patients because variable effort would result in poorly reproducible results.

The concept of expiratory flow limitation is important and relates to the properties of the airways. For simplicity, the airways are often likened to a rigid tube but, in reality, the airways are partially collapsible. During inhalation, Ppl is negative, and the intrathoracic airways tend to be pulled open. During forced exhalation, Ppl becomes positive, increasing pressure around the intrathoracic airways and predisposing to their collapse.

Several theories have been developed to explain the limitation of flow on expiration, by which a maximal flow cannot be increased even with increasing effort. These theories include the equal pressure point theory, the Bernoulli effect, and the wave speed theory.

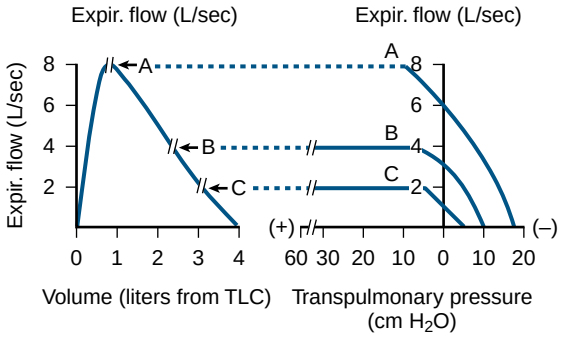

Figure 11.9 Expiratory flow limitation. *Left*, The expiratory flow volume curve for a normal subject. Maximal flow rates are plotted against their corresponding volumes at A, B, and C and define the maximal expiratory flow-volume curve. *Right*, Three isovolume pressure-flow curves for the same subject. Once a threshold transpulmonary pressure is achieved, no increase in flow is seen. (From Hyatt RE. Forced expiration. In: Macklem PT, Mead J, eds. *Handbook of Physiology. Section 3. The Respiratory System. Vol III: Mechanics of Breathing [part 1].* Bethesda, MD: American Physiological Society; 1986:295–314.)

Equal Pressure Point Theory. Consider the respiratory system depicted as a balloon (lung) inside a box (chest wall) connected by a tube that extends through the box (intrathoracic airway) (Fig. 11.10). The pressure inside the lung is equal to the Ppl (created by expiratory muscle activation) plus the recoil pressure of the lung. As air travels down the airway, pressure in the airway decreases, predominantly due to frictional losses. A point is eventually reached where the Ppl in the box is equivalent to the pressure inside the tube, termed the *equal pressure point* (EPP).[50,51] Downstream (mouthward) of this EPP, the pressure outside the airway exceeds the pressure within the airway, and the airway tends to collapse. Further increases in effort increase Ppl, but this simply causes greater narrowing of the airway downstream of the EPP so that flow remains constant. Under these conditions, the airway acts as a Starling resistor; flow is now not proportional to the difference between Palv and mouth pressure, but rather is proportional to the difference between Palv and pressure at the EPP. In this case, the pressures downstream from the EPP have no effect on expiratory flow.

This concept can be mathematically expressed as follows:

Because

$$\text{Palv} = \text{Ppl} + \text{Lung recoil pressure}$$

and

$$\text{Pressure at EPP} = \text{Ppl}$$

and

$$\text{Driving pressure} = \text{Palv} - \text{Pressure at EPP}$$

therefore

$$\text{Driving pressure} = \text{Lung recoil pressure}$$

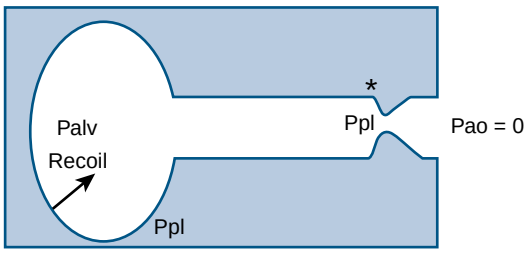

Figure 11.10 Equal pressure point theory. At the *equal pressure point* (EPP; asterisk), pressure inside the tube is equal to the pressure outside the tube (pleural pressure, Ppl) due to pressure drop related to flow-resistive losses from alveolus to the asterisk. Downstream (mouthward) from the EPP, the airway is compressed. Once an EPP develops, increasing expiratory effort, although increasing the *alveolar pressure* (Palv), also increases the downstream compression and causes no increase in flow. Pao, airway opening pressure.

Therefore, further increases in effort will increase both Palv and pressure at the EPP equally, resulting in no difference in driving pressure and airflow.

The Bernoulli Effect and Wave Speed Theory. The Bernoulli effect provides an alternative explanation for flow limitation.[52] As gas flows through a tube, the intraluminal pressure decreases, and the lateral pressure exerted by the gas is less than the pressure driving flow by an amount proportional to the velocity of the gas. If the tube is collapsible, as gas velocity increases, there is a tendency for the tube to collapse, leading to a reduction in airflow.

The wave speed theory is yet another explanation for expiratory flow limitation.[53] When fluid is pushed through a collapsible tube, a pressure wave is propagated along the wall of the tube. The speed of this pressure wave is dependent on the characteristics of the tube and the density of the gas rather than the driving pressure. The velocity of the gas in the tube cannot exceed the velocity of the pressure wave; thus the velocity of this wave represents a "speed limit" for the gas in the tube.

Interestingly, the maximal flow of gas derived using the Bernoulli effect and wave speed theory are identical, as shown by the following formula:

$$\text{Maximal flow} = A\sqrt{\left(\frac{A}{\text{gas density}}\right) \times \frac{dP}{dA}}$$

where A represents the cross-sectional area of the airway wall and dP/dA represents the slope of the relationship between changes in transmural pressure of the tube and changes in tube area. Therefore, maximal flow should increase if the tube area increases, gas density decreases, or tube stiffness increases.

Different mechanisms for flow limitation may predominate at different lung volumes. As lung volume increases, there is a proportional decrease in airway resistance and an increase in volume of the airways. Air flow in larger airways is often turbulent and is affected by changes in gas density, not viscosity (see earlier discussion of laminar versus turbulent flow). At high lung volumes, the Bernoulli effect may be more important in flow limitation because it is also related to gas density. Conversely, flow in smaller airways is laminar and influenced by gas viscosity, not density. Thus at low lung volumes, the wave speed effect may be less significant, whereas the EPP mechanism may be more important in determining flow limitation.[54]

OTHER RESISTIVE WORK

Besides the elastic work done by the respiratory muscles on the lung and chest wall, an additional component of work is expended to overcome what is sometimes called "tissue resistance." This is energy required to distort the lung and chest wall during inhalation and is dissipated as heat.

Equation of Motion

During ventilation, gas moves down a pressure gradient (ΔP). This pressure difference must be created by either the patient's own muscular efforts (Pmus) or a mechanical ventilator (Paw). The energy loss represented by this pressure drop is used to overcome resistance to airflow and tissue deformation, to expand the lungs and chest wall, and to overcome gas inertance (resistance to changes in velocity or direction of gas flow). The first-order linear equation of motion describes the relationship between these variables as:

$$\Delta P = \text{Paw} + \text{Pmus} = \left(\dot{V} \times R\right) + V_T/C + \left(I \times \ddot{V}\right) + (\text{PEEPi} + \text{PEEPset})$$

The work done to overcome airflow and tissue resistance is represented by $\left(\dot{V} \times R\right)$, where $\dot{V}$ is gas flow and R is resistance; the work done to expand the respiratory system is represented by V_T/C, where V_T is tidal volume and C is compliance; and the work done to overcome gas inertance is represented by $\left(I \times \ddot{V}\right)$ where I represents inertance and $\ddot{V}$ represents acceleration of gas flow. *PEEPi* represents intrinsic PEEP above PEEPset, and *PEEPset* represents PEEP provided by the ventilator. In most practical situations involving adults, inertance is ignored because it makes such a small contribution to work.

INTRINSIC PEEP DURING POSITIVE-PRESSURE VENTILATION OF COPD

An appreciation of the dynamics of the respiratory system aids in understanding clinical scenarios, such as for patients with COPD who are treated with positive-pressure ventilation for respiratory failure. Because lung resistance and compliance are variable in these patients, heterogeneity of time constants will result in variable emptying times. If insufficient time is allowed for complete emptying of lung units, the result will be a positive mean Palv in the alveoli at the end of exhalation or *intrinsic PEEP* (PEEPi; also known as auto-PEEP). High end-expiratory Palv acts as an inspiratory threshold load. In order to generate a negative pressure great enough to trigger the ventilator and initiate inspiratory flow, the inspiratory respiratory muscles must exert adequate pressure to counteract the PEEPi and reduce Palv to a subatmospheric value before inspiratory flow can be initiated.[55] PEEPi can also develop in the absence of airflow obstruction if the expiratory time is too short (e.g., in the setting of high minute ventilation).

As mentioned, high PEEPi may lead to inspiratory efforts that are ineffective in triggering the ventilator if the respiratory muscles cannot reduce Palv to less than the applied PEEP (Fig. 11.11).[56] This may lead to patient

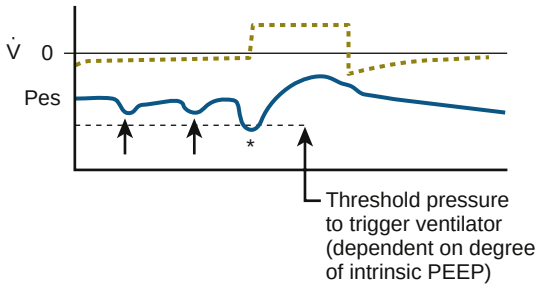

Figure 11.11 Failure to trigger the ventilator in a COPD patient. Graph of flow ($\dot{V}$) and esophageal pressure (Pes) over time in a patient with COPD and intrinsic positive end-expiratory pressure receiving positive-pressure mechanical ventilation. The patient has made two attempts (*up arrows*) at triggering inspiration but could not due to the positive end-expiratory alveolar pressure. When pleural pressure is sufficiently negative to exceed the ventilator's threshold (*dotted line*), this triggers the ventilator (asterisk) and a breath is provided. Note the failure of expiratory flow to reach 0 prior to a triggered breath.

ventilator dysynchrony and places the inspiratory muscles at a mechanical disadvantage,[57] which can lead to failure of weaning from mechanical ventilation.

Management of PEEPi should include treatment of the underlying contributing disorder, such as an acute COPD or asthma exacerbation, as well as efforts to decrease minute ventilation and ventilator maneuvers to increase expiratory time. In patients with expiratory flow limitation, dynamic airway collapse acts as an equal pressure point causing flow limitation and an inability to increase expiratory flow at end-expiration (see earlier discussion on flow limitation). Increasing expiratory effort raises pleural and alveolar pressure but does not improve expiratory air flow. If a patient is unable to expire to FRC because of flow limitation, end-expiratory lung volume increases and leads to dynamic hyperinflation, or PEEPi.

If expiratory flow limitation results in the development of PEEPi, then increasing PEEPset to match the PEEPi should decrease the gradient between the mouth and alveoli at end-expiration (i.e., the inspiratory threshold load). This may improve ventilator synchrony.[58] Pressures downstream from the equal pressure point will not have any effect on expiratory flow, thus the application of PEEPset will not produce further hyperinflation or reduce the expiratory flow if the PEEPset is less than or equal to the PEEPi.[59]

Conversely, PEEPi may not be due to expiratory flow limitation, for example at very high respiratory rates, if the lungs simply do not have enough time to empty to FRC. In this instance, there is still a pressure difference between the mouth and alveoli to allow for expiratory flow. If PEEPi is present, without evidence of expiratory flow limitation, additional application of PEEP will worsen respiratory mechanics.[60]

The end-expiratory occlusion method is commonly used to measure static PEEPi (Fig. 11.12A). The expiratory line in the ventilator is occluded at the end of an exhalation; with flow now at zero, the pressure can be measured.[60] If PEEPi is present, Paw will increase until a plateau is reached, usually in 2 to 4 seconds. Given sufficient time for lung units to equilibrate, this represents the "average" measure of PEEPi because volume will redistribute from some alveoli to others depending on regional compliance.

Alternatively, PEEPi can be measured under dynamic conditions. This can be done by determining the change in pressure required to initiate lung inflation, or the difference between Paw at zero flow and at end-expiratory pressure. Dynamic PEEPi, which is measured just prior to the initiation of inspiratory flow, is usually less than that measured under static conditions, that is, at end-expiration. Inspiratory flow starts when airway pressure exceeds end-expiratory alveolar pressure; air flows first to the lung regions with the shortest time constants. Dynamic PEEPi therefore corresponds to the lowest PEEPi in regional lung tissue with the shortest time constants as opposed to the average amount of PEEPi.[60]

PEEPi is not limited to patients on mechanical ventilation. Spontaneously breathing patients who have COPD can develop PEEPi, especially when they increase their inspiratory rate during exertion, a phenomenon that has been termed dynamic hyperinflation. PEEPi and hyperinflation increases the work of breathing (see later) and contributes to exercise limitation in these patients.

MEASUREMENT OF STATIC COMPLIANCE AND RESISTANCE DURING MECHANICAL VENTILATION

In the intensive care unit, measurement of respiratory system compliance and resistance can be helpful in assessing weaning from mechanical ventilation. Normal C_{RS} in a supine subject is approximately 100 mL/cm H_2O. A markedly decreased compliance should prompt a search for causes of reduced C_L (e.g., edema) and/or C_W (e.g., abdominal distention) that might be potentially reversible. Similarly, a markedly increased resistance should prompt a search for reversible causes, including bronchospasm, or partial obstruction of the endotracheal tube from kinking or secretions.

Calculation of compliance and resistance should be performed with a square wave flow pattern after an inspiratory pause. Patients need to be relaxed or paralyzed to obtain accurate measurements. If respiratory efforts are present, Paw may not reflect transmural pressures across the respiratory system.

Consider a paralyzed sedated patient treated with positive-pressure mechanical ventilation in the assist-control mode. The changes in flow, volume, and pressure over time are shown in Figure 11.12B. Assume a constant inspiratory flow rate (1 L/sec) and a V_T of 500 mL (0.5 sec inspiratory time). Because flow is constant, volume increases linearly over time. Peak pressure is 40 cm H_2O, Pplat is 35 cm H_2O, and PEEP is set at 5 cm H_2O.

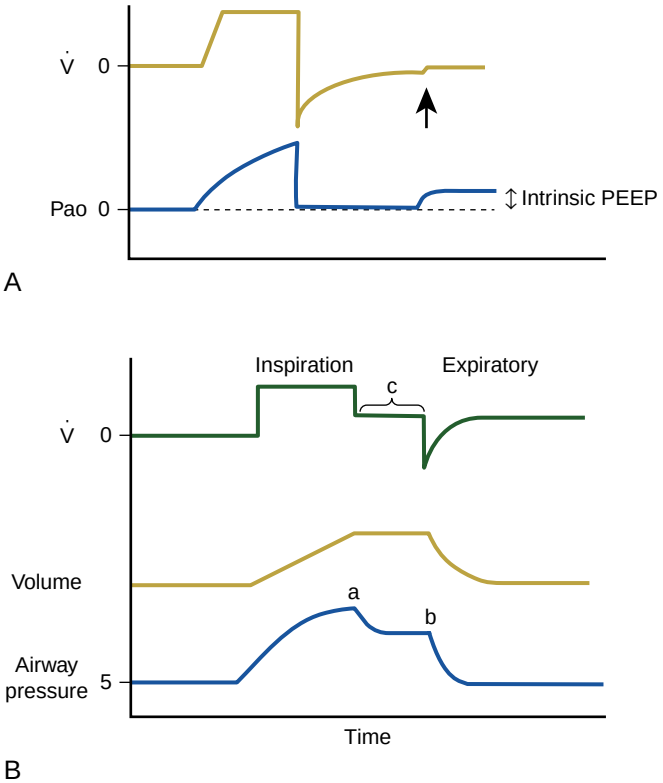

Figure 11.12 Pressures measured in a patient on mechanical ventilation. (A) Measurement of intrinsic *positive end-expiratory pressure* (PEEP), flow (V) and airway pressure over time. *Arrow* represents the point at which the expiratory line is occluded, leading to an increase in measured pressure that represents the degree of intrinsic PEEP. (B) Ventilator mechanics. Point a is the peak pressure (40 cm H_2O). Point b is the plateau pressure (35 cm H_2O). The bracket at *c* indicates the inspiratory pause.

Using the balloon and tube analogy of the respiratory system (see Fig. 11.3), the components of pressure required to ventilate are as follows:

$$\begin{aligned}\text{Total pressure} &= \text{Pressure to distend respiratory system}\\ &+ \text{Pressure to maintain gas flow}\\ &+ \text{Inertial pressure losses}\end{aligned}$$

Because the inertial component can be ignored at the respiratory rates commonly used:

$$\begin{aligned}\text{Total pressure} &= \text{Pressure to distend respiratory system}\\ &+ \text{Pressure to maintain gas flow}\\ &= \Delta\ \text{Volume/compliance}\\ &+ \text{Flow} \times \text{resistance}\end{aligned}$$

The difference between Pplat (measured during an inspiratory hold) and PEEP represents the pressure required to distend the respiratory system at 0 flow.

Therefore,

$$\text{Pplat} - \text{PEEP} = \Delta\text{Volume/Compliance} + \text{Flow} \times \text{Resistance}$$

Because flow = 0, rearranging the equation yields:

$$\text{Compliance} = \Delta\text{Volume}/(\text{Pplat} - \text{PEEP}) \qquad [1]$$

The difference between peak pressure (a) and Pplat (b) represents the pressure required to overcome resistance of the respiratory system. This predominantly represents flow resistance, but also includes contributions from tissue resistance, stress relaxation, and time constant heterogeneity within the lung (i.e., pendelluft). Therefore,

$$\begin{aligned}\text{Peak pressure} - \text{PEEP} &= \Delta\text{Volume/Compliance}\\ &+ \text{Flow} \times \text{Resistance}\end{aligned} \qquad [2]$$

Rearranging Equations 1 and 2:

$$\text{Peak pressure} - \text{Pplat} = \text{Flow} \times \text{Resistance}$$

Because flow is known:

$$\text{Resistance} = (\text{Peak pressure} - \text{Pplat})/\text{Flow}$$

Going back to the patient:

$$\text{Compliance} = 500\ \text{mL}/(30\ \text{cm}\ H_2O) = 16.7\ \text{mL/cm}H_2O$$

$$\text{Resistance} = \frac{40 - 35\ \text{cm}\ H_2O}{1\ \text{L/sec}} = 5\ \text{cm}\ H_2O/\text{L/sec}$$

In other words, the patient's resistance is relatively low but the compliance is severely reduced, suggesting an extremely stiff respiratory system (as mentioned above, normal respiratory system compliance in a supine subject is approximately 100 mL/cm H_2O).

RESPIRATORY MECHANICS IN ARDS

ARDS is an inflammatory disease state resulting in heterogenous parenchymal changes, poorly compliant lung units, a reduction in FRC from atelectasis, and shunting from airspace filling resulting in profound hypoxemia.[61] In order to maintain viable gas exchange, mechanical ventilation is required, but it is associated with potential for *ventilator-induced lung injury* (VILI).[62]

Conceptually, the term *baby lung* has been coined to reflect the small volume of lung parenchyma relatively spared from disease which demonstrates relatively normal mechanics.[63] Although the mechanics of this small lung may be normal, the potential for VILI is possible if it is inadvertently ventilated with high volumes (see later). Lung injury is also possible because aerated lung in ARDS demonstrates altered permeability and susceptibility to inflammation. The use of lung protective ventilation in ARDS is predominantly to spare the baby lung from additional injury while maintaining adequate gas exchange (see Chapter 135 for more details).

PEEP OPTIMIZATION AND RECRUITMENT MANEUVERS

At low lung volumes, atelectrauma and repetitive sheer forces from recruitment-derecruitment likely contribute to VILI.[64] In patients with recruitable lung, PEEP can improve oxygenation and promote homogenous ventilation by preventing alveolar collapse.[65] Esophageal pressure is a surrogate for Ppl and has been used to separate contributions of the lung and chest wall to the reduced respiratory system compliance in ARDS patients.[66] While PEEP titrated by use of an esophageal balloon has been shown to improve oxygenation, a recent study found no difference in death or ventilator-free days in ARDS patients when esophageal balloon-titrated PEEP was compared to PEEP titrated according to FiO_2.[67]

Trials examining low versus high levels of PEEP in ARDS have failed to show improvements in mortality, possibly due to unrecognized variation in the amount of recruitable lung.[30,68–70] Previously collapsed alveoli may become newly recruited, whereas PEEP applied to previously functional alveoli may cause added stress and strain.[65] The degree of recruitment or overdistention could be assessed by the stress index.

STRESS INDEX

A discussion of the stress index is available at ExpertConsult.com.

RECRUITMENT MANEUVERS IN ARDS

ARDS is also thought to lead to surfactant dysfunction. The dysfunction of surfactant increases surface tension at the air-liquid interface of the alveoli, leading to collapse, intrapulmonary shunting, and hypoxemia.[74]

Recruitment maneuvers with high pressure to open alveoli have been used in ventilated patients with ARDS who remain hypoxemic despite moderate levels of PEEP.[75–79] A recruitment maneuver consists of a sustained inflation

One method to evaluate the degree of recruitment or overdistention is to utilize the pressure-time curve during volume-controlled ventilation. Assuming the flow is constant, a relationship between pressure (P) and time exists, $P = a \times \Delta t^b + c$ and can be described using a coefficient (b) called the stress index.[71] A convex pattern at the terminal portion of the pressure-time curve indicates a stress index less than 0.9 or intratidal recruitment. A linear pattern represents a stress index of 1, whereas a concave pattern with a stress index greater than 1.1 represents overdistention (eFig. 11.1).[72] Caution must be exerted when interpreting the stress index in the presence of extrapulmonary abnormalities such as pleural effusions and obesity; it requires the use of software, and concave patterns may simply relate to progressive derecruitment.[22,73]

at a constant high pressure, which opens collapsed alveoli. Because closing pressures are much less than opening pressures, the alveoli stay open (at least temporarily) after the sustained inflation is ended as long as the lung is not allowed to return to a low volume. Although recruitment maneuvers may be useful at treating hypoxemia, frequent and aggressive recruitment with high PEEP has led to respiratory and hemodynamic complications.[80]

VENTILATING ARDS USING PLATEAU PRESSURE, TIDAL VOLUME, AND DRIVING PRESSURE

A landmark study in ARDS concluded that lung protective ventilation using small V_T (6 mL/kg predicted body weight) and minimizing Pplat (<30 cm H_2O) improved clinical outcomes, presumably due to decreased alveolar distention and volutrauma of the more normal areas of lung (see Chapter 135 for further discussion).[37,38,81] Although limiting Pplat and V_T during mechanical ventilation has demonstrated benefit in decreasing ventilator-associated lung injury, it is not known whether additional reduction will improve outcomes even further.[82] There may not be a safe level of pressures or tidal volume in patients with ARDS.

Driving Pressure

Driving pressure (DP) is the difference between Pplat and PEEP following a mechanically delivered V_T. It reflects the distending pressure of the lung. In mechanically ventilated patients, C_{RS} is a ratio between V_T/(Pplat – PEEP) or, alternatively, DP = V_T/C_{RS}. DP thus describes the relationship between V_T and functional lung available for ventilation. An excessive Pplat, and thus excessive DP, increases the risk of lung injury whereas potential benefits of high levels of PEEP depend on lung recruitability and resulting change in compliance.[83] Reexamination of randomized clinical trials of ARDS patients demonstrated that DP was the pulmonary mechanical variable most predictive of 60-day mortality.[84] Limiting DP to 14 cm H_2O or less may reduce lung injury.[85]

It is important to recall that C_{RS} reflects the distending pressure of the lung but does not represent the true stress on the lung, which is represented by the transpulmonary pressure. Transpulmonary pressure represents Paw – Ppl. Remembering that esophageal balloons can be used to measure pleural pressure, then *transpulmonary driving pressure* (TPDP) equals

$$(\text{Pplat} - \text{PEEP}) - (\text{Esophageal plateau pressure} - \text{End-expiratory esophageal pressure})$$

Unlike DP, TPDP considers the effect of chest wall elastance.[86] A patient with high chest wall elastance and normal pulmonary elastance (as in chest wall edema) will have a large DP and low TPDP with minimal stress across lung parenchyma. This patient may be less susceptible to lung injury than a patient with a large DP and high TPDP who has high lung and chest wall elastance (e.g., ARDS with chest wall edema). This may explain why DP was not associated with mortality reduction in obese ARDS patients.[87] Other limitations of DP include the underestimation in spontaneously breathing patients, overestimation in prone patients, and the lack of randomized control trials supporting the benefit of DP to guide ventilator strategies.[88–89]

ENERGETICS AND WORK OF BREATHING

When a force is applied to an object over a distance, energy is required; the work done is equal to:

$$\text{Work} = \text{Force} \times \text{Distance}$$

Similarly, because pressure is force over an area and volume is an area multiplied by a distance, work in a fluid system may be defined as the integral of applied pressure over a change in volume:

$$\text{Work} = \int P dV$$

During inspiration, work must be performed to distend the respiratory system (elastic work), which is stored as potential energy. Also, nonelastic work must be done to generate flow through the airways (to overcome resistance to gas flow), to overcome lung and chest wall tissue resistance, and to accelerate gas (to generate the inertial component). This work cannot be stored as potential energy and is dissipated as heat. The inertial component is minimal and is usually ignored in measuring total work.

MEASURING WORK OF BREATHING DONE BY A POSITIVE-PRESSURE VENTILATOR IN A PARALYZED PATIENT

Consider a paralyzed patient receiving positive-pressure mechanical ventilation, for whom the entire work of breathing is performed by the ventilator (Fig. 11.13A). On a volume-pressure plot, pressure applied to the airway will track to the right of the static volume-pressure curve of the respiratory system because additional pressure is required to overcome resistive forces. In Figure 11.13A, the blue shaded area represents the elastic work done by the ventilator during one inhalation, whereas the gray shaded area represents the resistive work expended to generate flow and overcome tissue resistance. With exhalation, the stored elastic energy can be used to deflate the lungs so that exhalation is normally a passive process. Increases in resistance or decreases in compliance can increase the work of breathing significantly.

MEASURING WORK OF BREATHING IN A SPONTANEOUSLY BREATHING PATIENT

In a spontaneously breathing patient, work is performed by the inspiratory muscles rather than by a ventilator. Graphing the pressure-volume characteristics of the lung and chest wall against Ppl illustrates the work performed by inspiratory muscles (Fig. 11.13B). During inspiration, Ppl decreases to expand the lungs (see Fig. 11.13B). The distance between the two curves at any given lung volume represents the pressure the inspiratory muscles must exert to overcome elastic forces of the lung and chest wall. In Figure 11.13B, the blue shaded area thus represents the elastic work of breathing against the lung and chest wall. To overcome the resistive forces, additional pressure and work are required, as indicated by the gray shaded area.

Under normal conditions, exhalation is passive, because the stored potential energy from elastic work is more than sufficient to overcome resistive work. However, in the presence of severe airflow obstruction (e.g., an asthma

attack), the necessary resistive work may exceed this stored energy, requiring active generation of force by expiratory muscles and additional work for exhalation.

OXYGEN COST OF BREATHING

The oxygen cost of breathing is an indicator of the total amount of energy required by the respiratory muscles for ventilation. At rest, the oxygen cost of breathing is low at 0.25 to 0.5 mL/L of ventilation, or 1–2% of total body oxygen consumption. However, at maximal exercise in normal subjects, the oxygen cost of breathing represents approximately 10–15% of total oxygen consumption.[90] The oxygen cost of breathing can increase markedly as minute ventilation increases (eFig. 11.2).

Patients with COPD have an increased oxygen cost of breathing as a function of ventilation (see eFig. 11.2). This may be related to a combination of increased work of breathing and decreased efficiency of the respiratory muscles due to dynamic hyperinflation. Dynamic hyperinflation is an increase in end-expiratory lung volume seen when patients with airflow obstruction develop PEEPi. PEEPi is caused when there is incomplete expiration of air from the lungs due to long time constants for gas distribution and an increased respiratory rate.[91] Dynamic hyperinflation can be exacerbated by tonic inspiratory muscle activity at end-expiration.

Although the dynamic increase in lung volume can have a beneficial effect by dilating intraparenchymal airways to decrease the resistive work, the end-expiratory alveolar pressure acts as an inspiratory threshold load, which increases the work of breathing. Furthermore, the mechanical efficiency of the inspiratory muscles is compromised by hyperinflation because the zone of diaphragmatic apposition is reduced and the inspiratory muscles are shorter than the optimal length for force generation. The efficiency of breathing (defined as the ratio between the rate of mechanical work accomplished and the rate of energy consumed) may be further diminished if postural or other stabilizing muscles (trunk, neck, shoulder) need to be recruited.

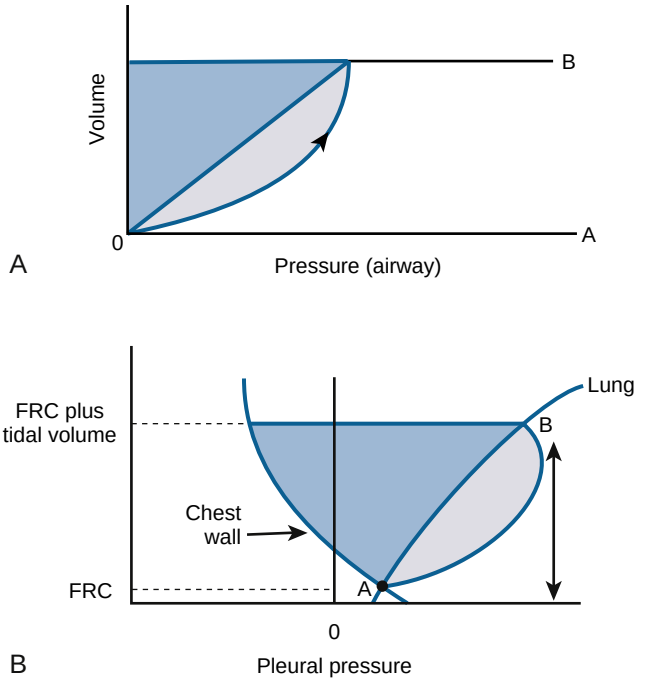

Figure 11.13 The work of breathing. (A) Work of breathing during mechanical ventilation. Consider a paralyzed patient receiving one tidal breath while on positive-pressure mechanical ventilation (point A to point B). The *diagonal blue line* represents the volume-pressure curve of the static respiratory system; the *shaded dark blue area* to the left of this line thus represents the elastic work done during the inflation. This work can be stored as potential energy and can be used during exhalation. The *gray shaded area* to the right of the line represents the resistive work done. (B) Work of breathing during spontaneous breathing (Campbell diagram). Consider a patient taking a spontaneous breath from *fuctional residual capacity* (FRC; point A) with a volume equal to the height of the *double-headed arrow* (point B). In order to overcome elastic forces of the lung and chest wall, the inspiratory muscles must exert a force equal to the horizontal distance between the chest wall and lung volume pleural pressure curves. Thus, the entire elastic work done will be equal to the *blue shaded area*. Resistive work must also be done, requiring the inspiratory muscles to generate an even greater negative pleural pressure. This is indicated by the *gray shaded area*. The total work done will be the sum of both areas.

Key Points

- Under conditions of laminar flow, flow is directly proportional to the pressure difference along the path of flow. Under conditions of turbulent flow, flow is directly proportional to the square root of the pressure difference. Turbulent flow, such as with partial upper airway obstruction, can be reduced by using a less dense gas mixture like heliox.
- The majority of the elastic recoil of the lung is due to surface forces generated by fluid lining the alveoli. The unique properties of surfactant help to reduce surface tension and stabilize alveoli at low lung volumes, preventing their collapse.
- At functional residual capacity (relaxation volume), the outward recoil pressure of the chest wall is balanced by the inward recoil of the lung. Total lung capacity is determined by the balance between the maximal inspiratory pressure generated by the respiratory muscles and the opposing pressure generated by the inward recoil of the lungs and chest wall.
- Measuring respiratory system resistance and compliance can be easily accomplished in ventilated patients and is useful for assessing reasons for difficulty weaning from the ventilator.
- In ventilated patients, the proportion of the applied airway pressure transmitted to the pleural space is dependent on the ratio of lung and chest wall compliance.
- In patients with airflow obstruction who are treated with positive-pressure ventilation, intrinsic positive end-expiratory pressure can lead to hemodynamic compromise, increased work of breathing, an inspiratory threshold load, mechanical inefficiency of the diaphragm, and patient-ventilator asynchrony.
- Patients with acute respiratory distress syndrome benefit from a ventilation strategy using low tidal volume, low plateau pressures, low driving pressures and positive end-expiratory pressure.

Key Readings

Akoumianaki E, Maggiore SM, Valenza F, et al. The application of esophageal pressure measurement in patients with respiratory failure. *Am J Respir Crit Care Med*. 2014;189:520–531.

Amato MBP, Meade MO, Slutsky AS, et al. driving pressure and survival in the acute respiratory distress syndrome. *N Engl J Med*. 2015;372:747–755.

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Writing Group for the Alveolar Recruitment for Acute Respiratory Distress Syndrome Trial (ART) Investigators, Cavalcanti AB, Suzumura ÉA, et al. Effect of lung recruitment and titrated positive end-expiratory pressure (PEEP) vs low PEEP on mortality in patients with acute respiratory distress syndrome: a Randomized. *JAMA*. 2017;318:1335–1345.

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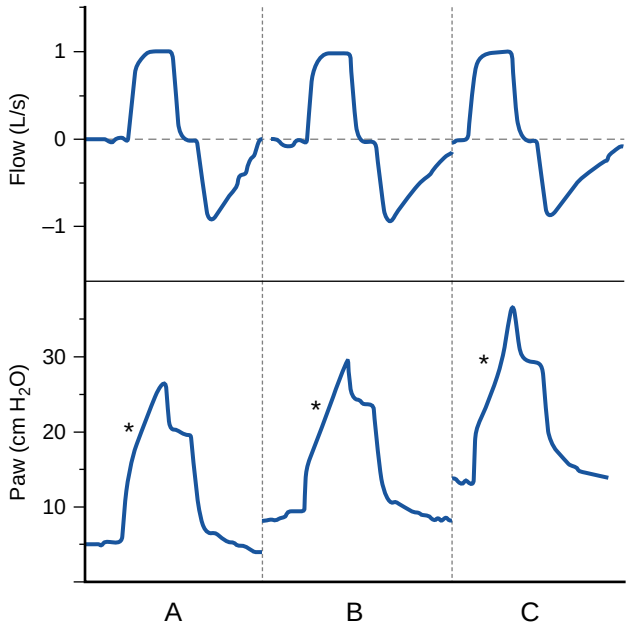
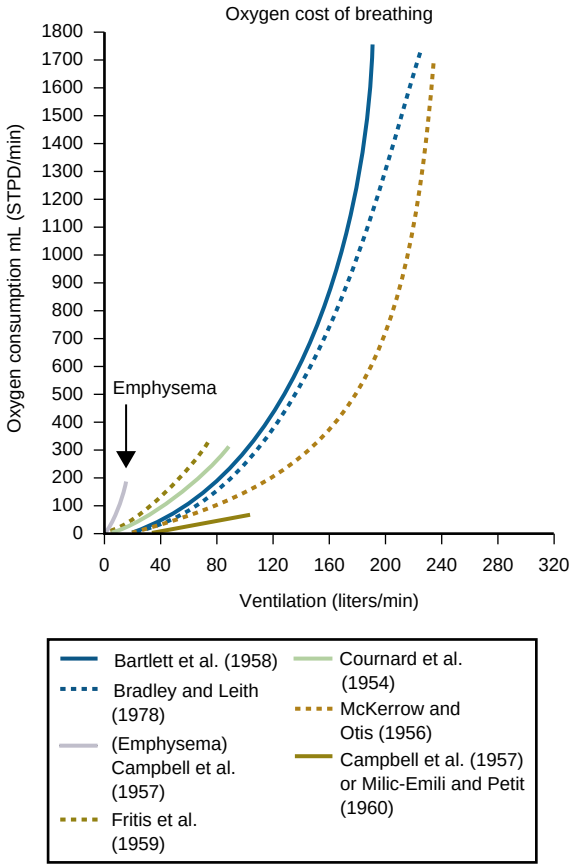
Complete reference list available at ExpertConsult.com.



eFIGURE IMAGE GALLERY



eFigure 11.1 Stress index. Examination of the late portion of the inspiratory pressure–time curve may provide information on the effect of *positive end-expiratory pressure* (PEEP) on tidal recruitment (*asterisks*). (A) Demonstration of a convex shape, consistent with a stress index < 1, on a PEEP of 5 cm H_2O. (B) Demonstration of a flat shape, consistent with a stress index of 1, on a PEEP of 10 cm H_2O. (C) Demonstration of a concave shape, consistent with a stress index > 1, on a PEEP of 15 cm H_2O. These patterns are correlated with intratidal alveolar recruitment, stable alveolar mechanics, and tidal hyperinflation, respectively. Paw, airway pressure. (From Henderson WR, Chen L, Amato MBP, Brochard LJ. Fifty years of research in ARDS. Respiratory mechanics in acute respiratory distress syndrome. *Am J Respir Crit Care Med*. 2017;196[7]:822–833.)



eFigure 11.2 Oxygen cost of breathing. Oxygen cost of breathing at varying levels of ventilation. Note the variability among studies and the steeper slope in patients with emphysema. (From Roussos C, Zakynthinos S. Respiratory muscle energetics. In: Roussos C, ed. *The Thorax [Part A]*. New York: Marcel Dekker; 1995:681–749.)

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12 ACID-BASE BALANCE

SARAH SANGHAVI, MD • TYLER J. ALBERT, MD • ERIK R. SWENSON, MD

FUNDAMENTAL CONCEPTS
Acid-Base Chemistry
Carbon Dioxide and Bicarbonate
Arterial and Venous Blood Gas Analysis
Nomenclature of Acid-Base Disorders
Role of Ventilation: Arterial P_{CO_2}
Role of the Kidneys
Compensation
METABOLIC ACIDOSIS
Anion Gap Concept
Causes of Anion Gap Acidosis
Hyperchloremic Acidosis
Clinical Manifestations
Therapy
METABOLIC ALKALOSIS
General Considerations
Chloride-Responsive Alkalosis
Chloride-Resistant Alkalosis
Excessive Intake of Alkali
Clinical Manifestations
Therapy
RESPIRATORY ACIDOSIS
General Considerations
Causes
Clinical Manifestations
Therapy
RESPIRATORY ALKALOSIS
General Considerations
Causes
Clinical Manifestations
Therapy
KEY POINTS

In all things you shall find everywhere the Acid and Alcaly.
OTTO TACHENIUS, HIPPOCRATES CHEMICUS (1670)

FUNDAMENTAL CONCEPTS

The care of critically ill patients requires a thorough understanding of acid-base balance. Maintenance of normal arterial pH (7.35–7.45 in plasma) is a critical factor in maintaining stable extracellular fluid and intracellular acid-base homeostasis. Arterial pH is kept under tight control by both pulmonary and renal mechanisms, each of which also regulate other processes, such as gas exchange in the lungs and fluid and electrolyte balance by the kidneys. Although, in most cases of acid-base disorders, deviations of arterial pH are moderated by specific compensatory responses to maintain acid-base homeostasis, other physiologic priorities may intervene. For example, hypoxemia stimulates the carotid bodies, resulting in hyperventilation and respiratory alkalosis. In the case of metabolic alkalosis generated by severe vomiting, alkalosis will be maintained by the overriding need for the kidneys to maintain extracellular volume. What follows is a review of some of the more important concepts and disorders of acid-base balance.

ACID-BASE CHEMISTRY

pH, the logarithmic function of H^+ concentration ($[H^+]$, normally 35–45 nanomole/L [nmol/L or nM] in plasma; Eq. 1), is used to represent a broad range of concentrations in body fluids from 1 in gastric acid to 8 in alkaline urine and pancreatic and biliary fluid.

$$pH = -\log_{10}[H^+] \quad [1]$$

Using the Henderson-Hasselbalch equation (Eq. 2), pH can be calculated from two variables, *partial pressure of carbon dioxide* (P_{CO_2}) and *bicarbonate* (HCO_3^-), without consideration of other acid-base pairs in the plasma.

$$pH = pK_a + \log\left[\frac{[HCO_3^-]}{\alpha P_{CO_2}}\right] \quad [2]$$

The Kassirer-Bleich approximation (Eq. 3) is a more practical tool that allows determination of pH when P_{CO_2} and HCO_3^- are known.

$$H^+ = 24\ P_{CO_2}/[HCO_3^-] \quad [3]$$

In this equation, the units of H^+, P_{CO_2}, and HCO_3^- are nmol/L, mm Hg, and mEq/L, respectively. The calculated $[H^+]$ can then be converted to pH, with $[H^+]$ of 25, 40, and 63 roughly correlating to a pH of 7.6, 7.4, and 7.2, respectively. It is a useful check for internal consistency of laboratory-reported values.

CARBON DIOXIDE AND BICARBONATE

Buffer systems minimize changes in pH upon the addition of acid or alkali and are therefore paramount to normal enzymatic function and protein structure. The HCO_3^- buffer system is extremely important in maintaining arterial pH at approximately 7.4 (Eqs. 4 and 5).

$$CO_2 + H_2O \underset{CA}{\overset{CA}{\rightleftharpoons}} H_2CO_3 \rightleftharpoons H^+ + HCO_3^- \quad [4]$$

$$CO_2 + OH^- \underset{CA}{\overset{CA}{\rightleftharpoons}} HCO_3^- \quad [5]$$

Gas exchange by the lungs keeps HCO_3^- concentration 20 times greater than that of dissolved *carbon dioxide* (CO_2), favoring H^+ consumption and CO_2 production. A low P_{CO_2} is a prerequisite for optimal function of the HCO_3^- buffer system. The predominant pathway to form HCO_3^- from CO_2 is shown in Eq. 4, with an alternative pathway shown in Eq. 5. However, generation of HCO_3^- through either pathway is slow in the absence of the catalyst *carbonic anhydrase* (CA), which is present in erythrocytes, vascular endothelium, alveolar epithelium, and in most other organs, including the kidney.[1–3]

pH Versus H^+, Conjugate Acids and Bases

In aqueous solutions, "free" hydrogen ions (protons) are associated with clusters of water molecules, but for convenience these are designated as H^+ or H_3O^+. As established by Brønsted- Lowry, an acid is a proton (H^+) donor, whereas a base is an H^+ acceptor. Because the pH of the extracellular fluid is normally approximately 7.4, some interpretations of acid-base chemistry categorize many organic acids (with dissociation constants below ≈4.0) as "strong" acids because greater than 99.9% of these acids are dissociated at an extracellular pH of 7.4.

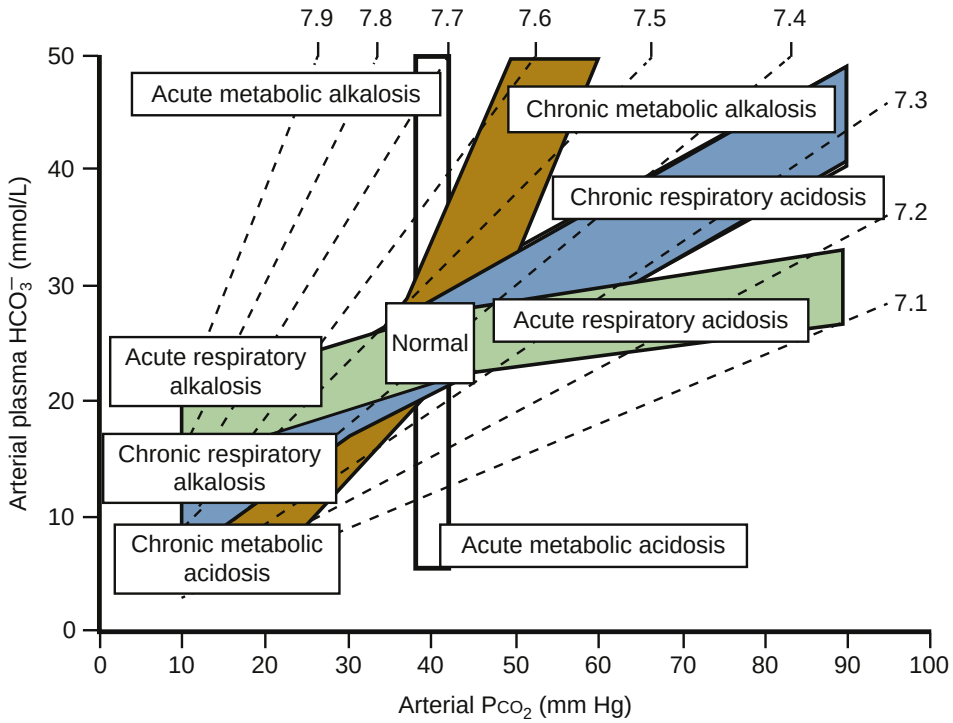


Figure 12.1 The relation between bicarbonate (HCO_3^-) and P_{CO_2} in a variety of clinical disorders. For discussion, see text. The 95% confidence levels for acute and chronic respiratory and metabolic abnormalities are denoted by the colored boxes. The *vertical transparent bar* indicates the absence of any change in arterial P_{CO_2} with acute changes in HCO_3^-. However, the respiratory response to the onset of metabolic acidosis and alkalosis is rapid, and the metabolic band rotates clockwise toward the chronic metabolic position within a matter of minutes to hours. Compensatory metabolic responses to respiratory changes in arterial P_{CO_2} are much slower, making it easier to observe the acute respiratory bands before metabolic compensation.

Base Excess

Although HCO_3^- is the most commonly used metabolic parameter in assessing acid/ base status, it underestimates the amount of acid (or base) that must be used to titrate samples of blood, plasma, or the body as a whole to a pH of 7.4. This reflects the presence of other buffer pairs that are titrated by the addition of strong acids and bases. The second problem with using HCO_3^- as a metabolic parameter is that it is influenced by changes in arterial P_{CO_2}.

The *base excess* (BE) is a complex equation developed in response to these limitations. It estimates how much strong acid or alkali must be added to titrate fully oxygenated blood to a pH of 7.4 at 37°C and at the hemoglobin concentration in that sample. The term *base deficit* is simply the negative of BE. Standard BE is provided by most *arterial blood gas* (ABG) machines and is commonly used as an indicator of metabolic acidosis in the setting of trauma.

ARTERIAL AND VENOUS BLOOD GAS ANALYSIS

Arterial blood gas (ABG) analysis is the standard for assessing oxygenation and the concentration of CO_2 in arterial blood. *Partial pressure of oxygen* (P_{O_2}), P_{CO_2}, and pH are directly measured with electrodes in blood and plasma samples, whereas HCO_3^- is calculated from pH and P_{CO_2} values. *Acidemia* and *alkalemia* refer to the deviations in arterial plasma pH from normal plasma pH. *Acidosis* and *alkalosis* refer to processes pushing the pH in the acid or alkaline direction but do not designate the actual pH.

The pH and P_{CO_2} of blood are prone to error if blood samples are exposed to air, inadvertently diluted, or measured without temperature correction for hypothermia or hyperthermia. Exposure to air decreases P_{CO_2}, raises pH, and more gradually decreases CO_2 content. Dilution of samples by saline or other fluids in indwelling catheters causes both P_{CO_2} and HCO_3^- to fall equally. Failure to temperature correct for hypothermia leads to spuriously higher P_{CO_2}, lower pH, and higher P_{O_2}; the opposite is seen with hyperthermia.[4]

Venous blood gas (VBG) measurement is less invasive than ABG measurement and may be used in its place if the clinician does not require an arterial P_{O_2} measurement. On average, compared to arterial values, venous pH is lower by 0.05 units, and venous P_{CO_2} is higher by 5 mm Hg. In states of low cardiac output, high CO_2 production or inhibition of red cell carbonic anhydrase, the arteriovenous differences can increase by as much as 10-fold.[5]

Alternatively, $[HCO_3^-]$ can be estimated from the total CO_2 content measured as part of a basic metabolic profile in venous blood. It tends to run approximately 5% higher (2–3 mmol/L) than arterial HCO_3^- because venous blood includes CO_2 produced from cellular metabolic activity not yet excreted by the lung. It also includes carbonic acid (H_2CO_3), dissolved CO_2, carbonate, and CO_2 bound to amino acids (carbamates).

NOMENCLATURE OF ACID-BASE DISORDERS

Procedures for naming acid-base disorders become quite simple if CO_2 and HCO_3^- are used as the respiratory and metabolic parameters. An additional assumption is made that compensation is incomplete, especially with severe acid-base disturbances. If arterial pH is low, the primary disorder must be an acidosis and, if high, the primary disorder is an alkalosis. Based on this approach, abnormal combinations of pH, P_{CO_2}, and HCO_3^- can be designated in terms of a primary disorder and any compensation that might be present.

Figure 12.1 indicates the ranges in which HCO_3^- and P_{CO_2} changes have been observed in normal persons subjected to acute or chronic respiratory or metabolic changes.

Figure 12.1 is based on the simple assumption that changes in P_{CO_2} reflect respiratory events, whereas changes in HCO_3^- reflect metabolic events. Note that if respiratory and metabolic parameters change proportionately, pH does not change. Baseline patient values for both P_{CO_2} and HCO_3^- are helpful in understanding compensatory responses. When no baseline values are available, a lack of appropriate compensation for a primary metabolic acidosis may suggest an underlying respiratory disorder; of note, these patients may appear to be breathing comfortably without tachypnea. Similarly, a lack of renal response after 48 to 72 hours may indicate a concurrent renal disorder. "Triple disorders" may also be encountered, involving an anion gap acidosis, non–anion gap acidosis or metabolic alkalosis, and a primary respiratory disorder.

Several caveats should be noted in the interpretation of acid-base status. The distinction between primary and compensatory disorders is based simply on which alteration is proportionately greater at the time the blood was drawn rather than on the sequence of events involved. For example, it is common for patients with COPD to be admitted to the hospital with compensated respiratory acidosis. With therapy, P_{CO_2} may decrease, revealing what might be interpreted as "a primary metabolic alkalosis with secondary respiratory compensation" if the clinical history is unknown.

ROLE OF VENTILATION: ARTERIAL P_{CO_2}

Arterial P_{CO_2} is determined by the rate of CO_2 production relative to the rate of alveolar ventilation. If arterial P_{CO_2} exceeds the normal range (35–45 mm Hg), then the patient is hypoventilating; conversely, if the arterial P_{CO_2} is lower, the patient is hyperventilating. These terms are distinct from hyperpnea and hypopnea, which refer to the increases or decreases of ventilation (high and low minute ventilation) to meet respiratory requirements, and from tachypnea and bradypnea, which indicate rapid and slow respiratory rates, respectively. Thus arterial P_{CO_2} can be interpreted as a "ventilatory" parameter that reflects the adequacy of ventilation relative to the rate of CO_2 production.

The utility of arterial P_{CO_2} as a ventilatory parameter is readily illustrated by a few brief examples. Arterial P_{CO_2} is usually normal during moderate exercise, and the subject is neither hyperventilating nor hypoventilating, despite obvious hyperpnea and tachypnea. Patients with severe lung disease frequently hypoventilate despite both hyperpnea and tachypnea at rest because much of the inhaled air is delivered to an enlarged physiologic dead space because of both shunting and regions of low $\dot{V}_A/\dot{Q}$ ratio. Regardless of the reason that ventilation fails to keep pace with CO_2 production, the concomitant increase in arterial P_{CO_2} is classified as hypoventilation.

ROLE OF THE KIDNEYS

The kidney is essential in maintaining acid-base balance under physiologic conditions and correcting deviations under pathologic conditions. In general, to maintain homeostasis, the kidney reclaims filtered HCO_3^- in the proximal tubule and excretes dietary acid in the cortical collecting tubule (Fig. 12.2).

Metabolic Alkalosis

As much as 80–90% of the filtered HCO_3^- is indirectly reclaimed in the proximal tubule by secretion of H^+ via the *Na^+, H^+–exchanger 3* (NHE3) on the luminal membrane. The driving force for this exchanger is the low intracellular Na^+ concentration generated by the basolateral Na^+, K^+-*adenosine triphosphatase* (ATPase) pump. The distal nephron is responsible for the reabsorption of a small quantity of HCO_3^-. In states of alkalosis, the capacity of the proximal tubule to reclaim HCO_3^- is overwhelmed, and HCO_3^- is excreted in the urine, aiding in the resolution of the metabolic alkalosis.

Metabolic Acidosis

In conditions of acidosis, the increased acid load is excreted predominantly as *ammonium chloride* (NH_4Cl) in the collecting duct. NH_4^+ is produced from glutamine by the proximal tubular cells; this process can be stimulated by chronic acidosis and hypokalemia. Through a complex pathway of secretion and reabsorption, *ammonia* (NH_3) is present in the cortical collecting tubule, where it may accept protons secreted by the cortical collecting tubule cells. Because the collecting duct fluid tends to be very acidic, NH_3 becomes "trapped" as NH_4^+ and is excreted in the urine.[11,12] Distal tubular acid secretion is mediated by K^+, H^+-ATPase and H^+-ATPase on the luminal surface of cortical collecting tubule cells.

COMPENSATION

Respiratory Acidosis

Although the acute increase in HCO_3^- is relatively modest after onset of hypercapnia, HCO_3^- continues to rise if hypercapnia persists and reaches a peak value after approximately 5 days (Table 12.1). An increase in HCO_3^- of approximately 4 mEq/L may be expected when P_{CO_2} is increased in steps of 10 mm Hg. Increases in plasma HCO_3^- require an initial net loss of H^+, which is made possible by the loss of increased quantities of NH_4^+ in the urine. Mechanisms mirror those that arise with an increase in exogenous acids. Chronic respiratory acidosis may down-regulate activity of the apical HCO_3^-, Cl^--exchanger pendrin in the distal tubule.[13] Once plasma HCO_3^- has reached a new steady state, H^+ secretion need only be sufficient to reabsorb HCO_3^- from the tubular fluid, and NH_4^+ and H^+ excretion usually return to normal.

Respiratory Alkalosis

Hypocapnia results in a decrease in renal acid excretion and a fall in HCO_3^- that becomes fully evident within 2 to 3 days. As indicated in Table 12.1, HCO_3^- decreases by 2.5 mEq/L for each decrease of 10 mm Hg in P_{CO_2}[14] and does not generally fall much below 16 mEq/L in respiratory alkalosis unless there is an independent metabolic acidosis present. Confidence bands for chronic compensation are indicated in Figure 12.1.

Metabolic Acidosis

Respiratory compensation for metabolic disorders is quite fast (within minutes) and reaches maximal values within 24 hours. In metabolic acidosis, a decrease in P_{CO_2} of 1 to 1.5 mm Hg should be observed for each mEq/L decrease of HCO_3^-.[15] A simple rule for deciding whether the fall in P_{CO_2} is appropriate for the degree of metabolic acidosis is that the P_{CO_2} should be equal to the last two digits of the pH. For example, compensation is adequate if the P_{CO_2} decreases to

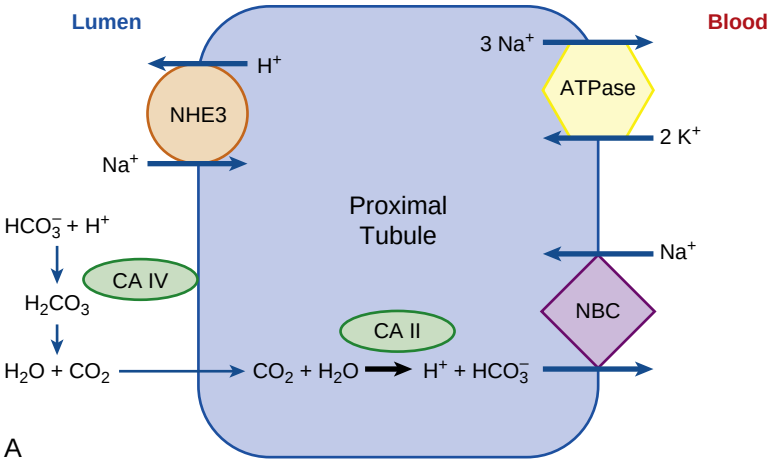
Strong Ion Difference

Stewart and, subsequently, Constable analyzed acid-base disorders on the basis of the concentrations and dissociation constants of each of the strong and weak acids and bases present in the plasma, thereby avoiding either titration or the use of some of the approximations associated with earlier approaches. They modified a method that has long been used by chemists to estimate the effect of multiple acids and bases on arterial pH. Stewart and Constable calculated the arterial plasma pH and HCO_3^- from (1) the difference between total concentrations of strong cations and strong anions in the plasma (*strong ion difference* [SID], which is normally 40–42 mEq/L), (2) the total concentration and dissociation constants of all nonvolatile weak acids and bases (primarily albumin and phosphates), and (3) the PCO_2. The SID is normally close to the difference between Na^+ and Cl^- concentrations, and albumin usually accounts for much of the weak nonbicarbonate anions in the SID. Stewart assumed that all of the constituents in the plasma other than H^+, CO_2, HCO_3^-, and CO_3^{2-} were conserved and that the solution remained electroneutral. Furthermore, he included organic anions, such as lactic acid, with pK_a below 4 among the "strong" ions because these molecules are largely ionized at physiologic pH. The simultaneous equations for pH and HCO_3^- were then solved iteratively as a fourth-order polynomial using a computer program. Stewart concluded that "metabolic" changes in acid-base balance are due to alterations in either SID or the total concentration. If serum albumin concentrations are normal, then an increase in SID indicates a metabolic alkalosis, and a decrease in SID indicates a metabolic acidosis.

In principle there is merit in defining the effects of each of the acid-base pairs upon the plasma pH. However, it is difficult to make sufficiently precise measurements of the constituents of the SID and the concentrations of weak acids and bases in the plasma, many of which have not been identified or properly quantified, especially in patients with liver or kidney disease.[6,7] Furthermore, the assumption that a single dissociation constant can be assumed for all of the weak acids is questionable. Stewart's distinctions between "independent" and "dependent" variables, as well as his assumption that H^+ and HCO_3^- transport do not alter compartmental pH, have also been challenged.[8–10] Nor does the SID approach distinguish between acute and chronic disorders. The original suggestion that pH and HCO_3^- can be calculated rather than measured is particularly unfortunate because these two variables can be much more easily and reliably measured than indirectly estimated from concentrations of all of the nonvolatile acids and bases in the blood, all of which have their own measurement errors.

It can be concluded that none of the three most popular metabolic parameters (HCO_3, BE, and SID) provides a completely reliable estimate of the quantity of nonvolatile H^+ or OH^- that has been added to the blood or plasma samples, as judged by actually titrating the samples. Nor is it clear that either in vitro titration or SID calculations would provide a reliable guide to the in vivo acid-base status of patients. In consequence, frequent monitoring of arterial blood is essential in patients with metabolic acid-base disorders who are receiving infusions of acidic or alkaline fluids.

In conclusion, it remains unproven that any of the alternative approaches yields more reliable information than the conventional practice of using PCO_2 as a respiratory parameter, HCO_3^- as a metabolic parameter, and the "anion gap" to interpret the effects of changes in concentrations of nonvolatile constituents in the blood (see later). The conventional approach will therefore be retained in the remainder of this chapter.



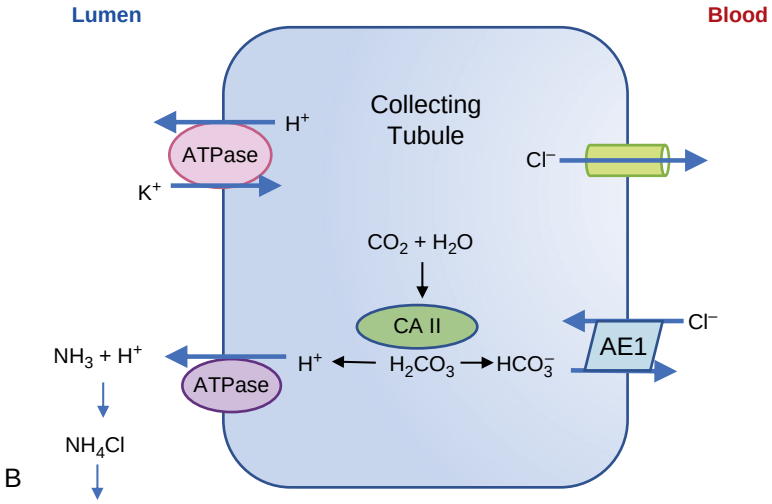


Figure 12.2 Acid-base handling by the kidney. (A) Reclamation of bicarbonate (HCO_3^-). In the proximal tubule, the Na^+, H^+–exchanger 3 (NHE3) secretes H^+ into the lumen. H^+ combines with filtered HCO_3^- producing carbonic acid (H_2CO_3), which is then catalyzed to H_2O and carbon dioxide (CO_2) by membrane-bound carbonic anhydrase (CA) type IV. CO_2 is recycled back into the proximal tubule cell, where it is hydrated to H_2CO_3 by carbonic anhydrase type II and subsequently dissociates into HCO_3^- and H^+. The HCO_3^- is reabsorbed into the blood via the sodium-bicarbonate cotransporter (NBC), and the H^+ enters the lumen to continue the cycle of HCO_3^- reclamation. No net acid is excreted in this process. (B) Acid excretion and generation of HCO_3^-. In acidosis, the acid load is excreted predominantly as ammonium chloride (NH_4Cl) in the collecting duct. Ammonia (NH_3) in the lumen combines with H^+ secreted by K^+, H^+–adenosine triphosphatase (ATPase) and H^+-ATPase on the luminal side of the collecting duct cells. NH_4Cl is excreted in the urine, and HCO_3^- is reabsorbed via a chloride-bicarbonate exchanger. AE1, anion exchanger 1.

Table 12.1 Rules of Chronic Compensation

		EXAMPLES	
Primary Disorder	**Secondary Compensation**	**Primary Change**	**Compensation**
↑ P_{CO_2}	↑ HCO_3^-: 4 mEq/L for each 10 mm Hg increase in P_{CO_2} (±3 mEq/L)	P_{CO_2}: 40 → 80	HCO_3^-: 24 → 40 pH: 7.1 → 7.32
↓ P_{CO_2}	↓ HCO_3^-: 2.5 mEq/L for each 10 mm Hg decrease in P_{CO_2} (±3 mEq/L)*	P_{CO_2}: 40 → 20	HCO_3^-: 24 → 19 pH: 7.70 → 7.60
↓ HCO_3^-	↓ P_{CO_2}: 1–1.5 mm Hg for each mEq/L decrease in HCO_3^-	HCO_3^-: 24 → 9	P_{CO_2}: 40 → 25 pH: 7.00 → 7.20
↑ HCO_3^-	↑ P_{CO_2}: 0.5–1.0 mm Hg for each mEq/L increase in HCO_3^-	HCO_3^-: 24 → 34	P_{CO_2}: 40 → 50 pH: 7.56 → 7.46

*HCO_3^- seldom falls below 18 mEq/L in acute and 16 mEq/L in chronic respiratory alkalosis.

28 when the pH is 7.28. Another helpful formula is Winter's formula (Eq. 6),[15] which can be used provided pH > 7.1.

$$\text{Expected } P_{CO_2} = 1.5\,(HCO_3^-) + 8 \pm 2 \qquad [6]$$

Metabolic Alkalosis

Compensation for metabolic alkalosis results in a decrease in tidal volume, resulting in a rise of P_{CO_2} by approximately 0.6 to 0.7 mm Hg for each mEq/L increase in HCO_3^-. This compensatory hypoventilation generally does not exceed a P_{CO_2} of 55 mm Hg because the accompanying fall in arterial P_{O_2} evokes increased ventilation to defend body oxygenation. This general rule may not apply in severe metabolic alkalosis, where compensatory values of P_{CO_2} greater than 60 mm Hg have been documented.[16] Respiratory compensation for metabolic alkalosis, such as that for metabolic acidosis, can have a counterproductive effect on renal H^+ transport: increases in P_{CO_2} associated with metabolic alkalosis decrease intracellular pH in the kidney, thereby promoting acid secretion and further increasing serum HCO_3^- levels.[17]

METABOLIC ACIDOSIS

ANION GAP CONCEPT

The most useful classification of metabolic acidosis is based on the concept of the anion gap, which is calculated by subtracting the sum of plasma concentrations of Cl^- and HCO_3^- from that of Na^+ (eFig. 12.1). This difference provides a convenient index of the relative concentrations of plasma anions other than Cl^- and HCO_3^-. Normally the anion gap is between 8 and 16 mEq/L, although somewhat lower values (5–11 mEq/L) have been observed when newer techniques for measuring ion activities rather than total concentrations are used.[6,18] The anion gap accounts for anions present in plasma that are not included in the equation, including albumin (which normally constitutes approximately half of the gap), lactate, pyruvate, sulfate, and phosphate.

Elevations of the anion gap are generally accompanied by a similar decrease in HCO_3^- ("anion gap acidosis"). In contrast, loss of *sodium bicarbonate* ($NaHCO_3$) results in acidosis without a rise in the anion gap (hyperchloremic acidosis). The mnemonic GOLDMARK may be used to remember many of the causes for an anion gap acidosis: ***g***lycols including ethylene glycol and propylene glycol, 5-***o***xoproline [pyroglutamic acid], ***l***actic acidosis, ***D***-lactic acidosis, ***m***ethanol, ***a***spirin, ***r***enal failure, and ***k***etoacidosis.[7]

Once the presence of an anion gap has been established, the next step is to assess for other metabolic disturbances. This is achieved by calculating the delta gap, which is the difference in the anion gap from the patient's baseline value or from a normal value of 12. In a pure anion gap acidosis, the delta gap should equal the deficit in HCO_3^-. Thus, when the delta gap is added to the total CO_2, the sum is 24. If the sum is much greater than 24, a concurrent metabolic alkalosis exists. If the sum is lower than 24, then a coexisting hyperchloremic acidosis exists. The actual value is approximate because either the H^+ or the conjugate base may leave the extracellular space, altering this 1:1 relationship. For example, in lactic acidosis, the delta gap often exceeds the decrease in HCO_3^-, whereas the opposite is true in diabetic ketoacidosis (see later sections).

A low anion gap reflects an increase in cations other than Na^+ (e.g., *calcium* [Ca^{2+}], *magnesium* [Mg^{2+}], *lithium* [Li^+], and abnormal cationic proteins, such as in multiple myeloma) or a decrease in unmeasured anions, typically albumin. Hypoalbuminemia decreases the anion gap by approximately 2.5 mEq/L for each decrease in albumin concentration of 1 g/dL.[18] Alkalemia tends to decrease H^+ binding to albumin, thereby increasing the number of negatively charged groups and the anion gap.

CAUSES OF ANION GAP ACIDOSIS

Lactic Acidosis

Approximately 1400 mEq of lactate are normally produced each day.[8] At rest, production is balanced by consumption and precisely regulated so that serum levels are kept at approximately 1 mEq/L. Most lactate is produced by skeletal muscle contraction but, with various stresses, such as ischemia, profound hypoxemia, sepsis, and high sympathetic tone, other tissues may also generate lactate due to anaerobic metabolism. In resting healthy individuals, the liver and, to a lesser extent, the kidneys are responsible for most of its consumption,[8] with oxidation in red skeletal muscle accounting for the remainder. In states of acidosis, renal lactate metabolism increases, and hepatic lactate metabolism decreases.[9]

As noted earlier, the delta gap in lactic acidosis may exceed the decrease in HCO_3^-. Lactate is poorly cleared by the kidney and tends to stay in the extracellular space, whereas H^+ moves intracellularly and is buffered by non-HCO_3^- buffers. This difference may be more profound in severe acidosis because the capacity for intracellular buffering increases as the serum HCO_3^- decreases.[10] Thus, when the delta gap is added to the total CO_2, the sum can be greater than 24. This is frequently seen in lactic acidosis and should not be misinterpreted as evidence for a coexisting metabolic alkalosis.[18] Also, lactic acidosis may cause hyperkalemia due to concomitant renal dysfunction and cellular ischemia.

Lactic acidosis can be divided into two types: type A, in which tissue hypoxia is evident, and type B, in which the tissue P_{O_2} appears to be adequate for aerobic metabolism.[19] Type A disorders include all forms of shock, acute hypoxemia, and a variety of conditions that impair oxygen delivery, such as carbon monoxide poisoning and severe anemia. Type B disorders include illnesses such as liver disease, a variety of drugs and poisons, and congenital metabolic enzyme deficiencies (Table 12.2).

In diabetic patients, low insulin levels reduce the metabolism of pyruvate by pyruvate dehydrogenase, resulting in an increased lactate concentration. Accumulation of ketones in the plasma may inhibit the monocarboxylic acid pump responsible for hepatic uptake of lactate.[20] In some patients with *diabetic ketoacidosis* (DKA), elevated lactate may be caused by extracellular fluid volume depletion due to the osmotic diuresis induced by hyperglycemia.

Malignancies, particularly lymphoproliferative and myeloproliferative disorders, may result in overproduction of lactic acid, which may impair normal immune tumor surveillance. This phenomenon results from the reliance of cancer cells on aerobic glycolysis as an ATP source rather than mitochondrial oxidative phosphorylation, the so-called Warburg effect, as a means to generate carbon intermediates necessary for rapid cell growth.[21] Renal or hepatic failure may impair metabolism of lactate, delaying its clearance once perfusion has been restored.

Although L-lactate is usually the cause of lactic acidosis, D-lactate accumulation due to intestinal bacterial metabolism has been documented in patients with short bowel syndrome, bowel ischemia, or obstruction. Bacteria in the colon metabolize carbohydrates to D-lactic acid, which is absorbed systemically. Because D-lactate cannot be converted into pyruvate by L-lactate dehydrogenase, it may accumulate. It may be treated by avoiding foods that contain lactobacilli (e.g., yogurt and sauerkraut), by decreasing dietary carbohydrates, and by the administration of oral antibiotics.

Of interest, lactic acidosis is not frequently observed in patients with severe respiratory insufficiency or cyanotic heart diseases. Lactic acidosis is much more likely to develop when tissue perfusion is impaired than when arterial blood oxygen content is moderately reduced. Several compensations for chronic arterial hypoxemia help minimize tissue hypoxia: cardiac output rises, the hematocrit rises and, if pH declines in those with CO_2 retention, hemoglobin oxygen affinity falls because of increased 2,3-diphosphoglycerate

Lactic Acidosis Biochemistry

From a strict biochemical standpoint, it is lactate and not lactic acid that is generated at the terminal point in glycolysis when pyruvate is reduced to lactate by lactate dehydrogenase, a step that consumes rather than produces a proton (eFig. 12.2).

$$\text{Pyruvate} + \text{NADH} + \text{H}^+ \rightleftharpoons \text{Lactate} + \text{NAD}^+$$

The hydrogen ion formed in states of "lactic acidosis" arises from the hydrolysis of *adenosine triphosphate* (ATP) and other yet unknown reactions, forming H^+ under states of metabolic stress. When *adenosine diphosphate* (ADP) is not rephosphorylated, H^+ will accumulate.

$$\text{ATP} + \text{H}_2\text{O} \rightleftharpoons \text{ADP} + \text{PO}_4^- + \text{H}^+$$

Table 12.2 Causes of Anion Gap Acidosis

LACTIC ACIDOSIS
Type A: Tissue Hypoxia
Poor tissue perfusion: distributive shock, cardiogenic shock, obstructive shock
Severe hypoxemia: pulmonary disorders, acute respiratory distress syndrome, carbon monoxide poisoning
Exercise above anaerobic threshold, seizures, shivering
Rhabdomyolysis
Severe anemia
Type B: Altered Lactate Metabolism Without Hypoxia
Liver disease, renal failure, diabetes mellitus, malignancies (especially hematopoietic), SIRS, HIV
Drugs: acetaminophen, β-agonists, biguanides, cocaine, cyanide, ethanol, diethyl ether, fluorouracil, halothane, iron, methanol, salicylates, ethylene and propylene glycol, isoniazid toxicity, linezolid, nalidixic acid, niacin, zidovudine (azidothymidine [AZT]), metformin, chemotherapy, propofol, total parenteral nutrition, valproic acid
Hereditary: glucose-6-phosphatase deficiency, fructose-1,6-phosphatase deficiency
D-Lactic acidosis
KETOACIDOSIS
Diabetes mellitus
Starvation
Ethanol
Inherited errors of metabolism
UREMIA
TOXIC ANIONS
Salicylates
Ethylene glycol (glyceraldehyde, oxalate)
Methanol (formaldehyde, formate)
Paraldehyde (acetoacetate)
Aminocaproic acid

HIV, human immunodeficiency virus; SIRS, systemic inflammatory response syndrome.

production, permitting more oxygen to be released at the tissue level.

Diabetic Ketoacidosis

Ketoacidosis refers to the accumulation of acetoacetate, β-hydroxybutyrate, and acetone ("ketone bodies") in the body. Development of ketoacidosis requires both increased mobilization of free fatty acids from lipid stores and their excessive conversion within hepatocytes to ketone bodies (eFig. 12.3). Triglycerides within fat are normally broken down by lipase into free fatty acids and glycerol. Lipase activity is enhanced by low concentrations of insulin and increased concentrations of glucagon, catecholamines, and growth hormone. Free fatty acids released from adipocytes are taken up by the liver and linked to *coenzyme A* (CoA) to form acyl CoA. Acyl CoA is either transformed by esterification to triglycerides and lipoproteins or transferred into the mitochondria, degraded to form acetyl CoA, and then metabolized to CO_2 and water via the Krebs cycle or converted to ketone bodies. In DKA, the acetyl CoA produced exceeds the capacity of handling by the mitochondria and is converted to ketone bodies. Ketoacids are normally taken up and metabolized to CO_2 and water by muscle and kidney rather than by the liver, but this process may be reduced in DKA.[22]

In normal subjects, the ratio of β-hydroxybutyrate to acetoacetate is 2:1. With DKA, this ratio increases to 2.5:1 to 3:1 and, with poor tissue perfusion and associated lactic acidosis, it can exceed 8:1.[23] The urine nitroprusside test detects acetoacetate but not β-hydroxybutyrate. Therefore, as patients improve with appropriate therapy, conversion of β-hydroxybutyrate to acetoacetate may be misinterpreted as worsening of the ketoacidosis.[23] Serum and point-of-care capillary blood assays are now available that directly measure β-hydroxybutyrate levels.

The decrease in HCO_3^- may be lower than the delta gap during the treatment of DKA. During volume resuscitation, ketoacid anions are renally excreted with Na^+ and K^+. The excretion of ketoacids removes conjugate anions from the extracellular space, thereby decreasing the anion gap. Thus, when the delta gap is added to the total CO_2, the sum can be less than 24. As noted earlier, this should not be interpreted as an additional acid-base disorder.

The observed hyperkalemia in DKA is due to cellular insulin deficiency preventing cellular uptake of K^+. Hyperosmolarity also causes water efflux from cells, a process that moves K^+ extracellularly by solute drag. However, despite hyperkalemia at presentation, most patients with DKA have total body depletion of potassium and require potassium supplementation during treatment, as acidosis and hyperosmolarity resolve and potassium shifts intracellularly.

Starvation Ketoacidosis

Starvation often leads to ketoacidosis within 1 or 2 days, particularly after exercise, but HCO_3^- levels seldom decline below 18 mEq/L. Starvation ketoacidosis may decrease insulin concentrations, but the insulin does not fall to levels as low as those encountered in DKA. Furthermore, there is evidence that ketosis stimulates insulin secretion in those with normal pancreatic function. Alcoholics who binge and then abruptly stop drinking and eating may develop severe ketoacidosis,[24,25] which may be underestimated because of a disproportionate rise in β-hydroxybutyrate. They usually become dehydrated from vomiting before hospital admission, and they may develop severe acidosis, frequently with concomitant lactic acidosis. Glucose concentrations are frequently low, and glucose (given with thiamine to avoid the Wernicke-Korsakoff syndrome of cerebral beriberi) stimulates insulin secretion and corrects the ketoacidosis. Supplementation with K^+, phosphate, and Mg^{2+} is frequently required.

Uremic Acidosis

Acute kidney injury does not usually produce an anion gap acidosis until the *glomerular filtration rate* (GFR) falls below 20 mL/min. However, because of differences in diet and sites of renal damage, there is some variation in the filtration threshold at which anion gap acidosis develops.[23] The loss of nephrons is accompanied by a decrease in the ability to excrete both NH_4^+ and anions. Numerous anions normally kept low by renal clearance contribute to the anion gap, including sulfate, phosphate, and lactate.

Toxic Forms of Anion Gap Acidosis

Salicylates. Large ingestions of salicylates, such as aspirin, cause a mixed disorder with both an anion gap metabolic acidosis and a primary respiratory alkalosis due to *central nervous system* (CNS) stimulation. Although salicylates are themselves anions, most of the acidosis observed after an overdose is related to formation of organic acids, particularly lactic acid and ketones.[26] Associated symptoms include tinnitus, nausea/vomiting, and vertigo. The most severe consequence is neurotoxicity, which may manifest as altered mental status, seizures, and cerebral edema. Salicylates lower cerebral glucose concentrations, resulting in neuroglycopenia despite normal serum glucose concentrations.[27] Salicylate levels above 40 mg/dL are associated with increased toxicity, and levels above 100 mg/dL are associated with increased morbidity and mortality. First-line therapy is intravenous $NaHCO_3^-$, which promotes salicylic acid excretion in the urine and flux from the CNS into plasma by ionic trapping of salicylate anion.

Volatile Alcohols. Methanol, isopropyl ethanol, and ethylene glycol ingestions are frequent causes of anion gap metabolic acidoses. Methanol (rubbing alcohol) is converted to formic acid, and ethylene glycol (antifreeze, radiator fluid) is converted to glycoxalic acid and oxalic acid by alcohol dehydrogenase. Both methanol and ethylene glycol contribute to serum osmolarity but are not represented in the calculated osmolarity (Eq. 7):

$$\text{Serum osmolality} = 2\times[Na^+]+\text{BUN}/2.8+\text{glucose}/18 \quad [7]$$

In acute ingestions, the difference in measured serum osmolarity and calculated serum osmolarity (osmolar gap) is greater than 10. However, as these alcohols are metabolized to acids, the osmolar gap may decrease as the anion gap increases. Ethanol consumption will also increase the osmolar gap. In addition, any severe critical illness may raise the osmolar gap to greater than 10 due to increased membrane permeability and leakage of intracellular solutes.[31] Nonetheless, an unexplained, large osmolal gap is highly suggestive of toxic volatile alcohol ingestion.

Treatment with fomepizole,[28] an alcohol dehydrogenase inhibitor, prevents the accumulation of toxic metabolites, such as formic acid, glycoxalic acid, and oxalic acid. The parent drugs are ultimately cleared by the kidney. Hemodialysis is a very effective method to remove parent drug and toxic metabolites, particularly in the setting of end-organ damage.

HYPERCHLOREMIC ACIDOSIS

Metabolic acidosis in the absence of an elevated anion gap is usually associated with hyperchloremia. The first step in the workup of a hyperchloremic acidosis is determining if the kidneys are handling acid excretion appropriately. The normal response to a metabolic acidosis is increased excretion of urinary NH_4^+, which can be estimated using the urine anion gap (Eq. 8).

$$\text{Urine Anion Gap} = U_{NA^+} + U_{K^+} - U_{Cl^-} \quad [8]$$

The normal urine anion gap is greater than 20. When the kidneys are excreting more acid, because the majority of NH_4^+ is excreted with Cl^- as NH_4Cl, the U_{Cl^-} should increase and the urine anion gap should decrease. Therefore, in the setting of an acidosis, a urine anion gap greater than 20 suggests that the kidneys are not excreting the excess acid and thus a renal tubular acidosis is the cause of the hyperchloremic acidosis. The cardinal feature of all types of renal tubular acidosis is a low rate of NH_4^+ excretion in the setting of a chronic metabolic acidosis, out of proportion to the GFR.[29]

Type 1 Renal Tubular Acidosis

Type 1 (distal) *renal tubular acidosis* (RTA) involves defects in distal tubular acid secretion, resulting in a urine pH > 6.5. Hypokalemia is also a prominent feature of type 1 RTA. As indicated in Table 12.3, many disorders are associated with type 1 RTA, which most commonly affects the activity of carbonic anhydrase II or the proton pump (H^+-ATPase) of the renal cortical collecting duct. Amphotericin B may induce an RTA by making pores in luminal cell membranes allowing leak of H^+ from the tubular fluid back into the intercalated cells.

Chronic acidosis leads to osteopenia with Ca^{2+}, Mg^{2+}, and PO_4^{2-} loss in the urine. Decreased tubular citrate secretion promotes precipitation of Ca^{2+} and PO_4^{2-}, which contributes to the development of nephrolithiasis and nephrocalcinosis in patients with type 1 RTA.

If untreated, the acidosis progresses relentlessly because the normally generated acids cannot be excreted at their rate of production. Correction of hypokalemia and treatment with 1 mEq/kg $NaHCO_3^-$ daily (roughly the rate of bodily fixed acid generation) is usually sufficient to normalize acid-base status in adults.

Type 2 Renal Tubular Acidosis

In type 2 (proximal) RTA, HCO_3^- reabsorption is impaired because of a defect in the proximal tubule apical membrane NHE3. Normally, HCO_3^- is completely reabsorbed from glomerular filtrate, and maximal reabsorption rates are not observed until concentrations are approximately 28 mEq/L. In proximal RTA, maximal reabsorption values may top out at a serum concentration of approximately 18 mEq/L. The distal tubules cannot absorb more than 15–20% of the filtered load of HCO_3^-, so bicarbonaturia ensues. If the serum HCO_3^- level falls below the HCO_3^- recovery threshold, then urinary HCO_3^- loss ceases, urine pH falls, and the acidosis does not progress. A typical patient will have a steady-state serum HCO_3^- value in the range of 12 to 20 mEq/L. When serum HCO_3^- is normalized to 24 mmol/L by HCO_3^- infusion, more than 15% of the filtered HCO_3^- is lost in the urine in type 2 RTA, compared with less than 5% in normal subjects and in those with type 1 RTA. Therefore, patients with type 2 RTA tend to have a urine pH of 5 to 6 under chronic steady-state conditions, with a rise to close to 7 with $NaHCO_3$ infusion.

Table 12.3 Causes of Hyperchloremic Acidosis

RENAL TUBULAR ACIDOSIS
Type 1 (Distal) Hypokalemic
Congenital defects without systemic disease (anion exchanger, AE1 deficient) or with systemic disease (e.g., Ehlers-Danlos syndrome, sickle cell anemia, Southeast Asian ovalocytosis)
Autoimmune disorders (e.g., Sjögren syndrome, thyroiditis, systemic lupus erythematosus, autoimmune hepatitis/biliary cirrhosis, rheumatoid arthritis)
Drug toxicity (e.g., amphotericin B, analgesics, lithium, ifosfamide)
Nephrocalcinosis (e.g., primary hyperparathyroidism, vitamin D intoxication, hyperoxaluria, Fabry disease, Wilson disease)
Tubular and interstitial renal disease (e.g., pyelonephritis and obstructive renal disease, renal transplant rejection)
Type 2 (Proximal) Hypokalemic
Selective carbonic anhydrase inhibitors: topiramate, acetazolamide, methazolamide
Genetic (e.g., cystinosis, Wilson disease, tyrosinemia, galactosemia, Lowe syndrome)
Dysproteinemias (e.g., multiple myeloma, amyloidosis)
Drug or chemical toxicity (e.g., lead, cadmium, ifosfamide, tenofovir)
Secondary hyperparathyroidism with hypocalcemia (e.g., vitamin D deficiency or resistance)
Renal interstitial disease (e.g., medullary cystic disease, Sjögren syndrome, renal transplant)
Combined Type 1 and 2 RTA
Carbonic anhydrase II deficiency
Type 4 Hyperkalemic
Mineralocorticoid deficiency: Addison disease, tuberculosis, autoimmune, adrenal hemorrhage, AIDS, critically ill patients,
Hyporeninemic states: diabetes mellitus, AIDS
Mineralocorticoid resistance: pseudohypoaldosteronism (congenital, spironolactone)
Medications: potassium-sparing diuretics (amiloride, triamterene), angiotensin-converting enzyme inhibitors, trimethoprim, pentamidine, nonsteroidal anti-inflammatory drugs, cyclosporine A, β-adrenergic inhibitors, α-adrenergic agonists, heparin, digitalis overdose, lithium, insulin antagonists (diazoxide, somatostatin), succinylcholine drugs (ketoconazole, phenytoin, rifampin)
NONRENAL HYPERCHLOREMIC ACIDOSIS
Excessive intravenous saline administration
Diarrhea
Pancreatic drainage
Ureterosigmoidostomy
Cholestyramine (diarrhea)
Hyperalimentation with amino acid infusions
Administration of NH_4Cl or $CaCl_2$
Toluene exposure (hippurate production)
Loss of ketones with Na^+ or K^+

AE1, anion exchanger 1; AIDS, acquired immunodeficiency syndrome; RTA, renal tubular acidosis.

Type 2 (proximal) RTA may be an isolated tubular lesion, but it is more frequently associated with other proximal tubular defects that lead to loss of glucose, phosphate, amino acids, and low-molecular-weight proteins (Fanconi syndrome) (see Table 12.3). If the acidification defect is associated with calcium and phosphate loss, patients are susceptible to osteomalacia and rickets. In contrast to distal RTA, nephrolithiasis and nephrocalcinosis are not characteristic of proximal RTA. Treatment of proximal RTA requires much more $NaHCO_3$ (10–15 mEq/kg/day) to correct the acidosis than treatment of distal RTA. In addition, large amounts of $NaHCO_3$ exacerbate losses of K^+, and potassium supplements and/or potassium-sparing diuretics are commonly required.

Type 4 Renal Tubular Acidosis

Type 4 RTA is distinguished from other RTAs by the presence of hyperkalemia and a less severe acidosis. It is classically associated with hypoaldosteronism, but newer data suggest hyperkalemia-induced inhibition of ammoniagenesis may also be causative.[30] Aldosterone increases the number of open *epithelium sodium channels* (ENaCs) in the luminal membranes of cortical collecting tubule cells, which stimulates distal secretion of H^+ and K^+. Hyperkalemia itself also suppresses proximal NH_3 production, resulting in low NH_4^+ excretion. Because NH_3 cannot buffer H^+ secreted by H^+-ATPase, urine pH may still be less than 5.5. A wide variety of disorders lead to low aldosterone production (see Table 12.3) but, in clinical practice, it is most commonly seen in diabetic kidney disease due to hyporeninemic hypoaldosteronism. Potassium-sparing diuretics, angiotensin-converting enzyme inhibitors, and heparin, which can inhibit aldosterone production, may also cause hyperkalemia and type 4 RTA.

Acidosis of Progressive Renal Failure

Hyperchloremic RTA without hyperkalemia is characteristic of many chronic renal diseases associated with loss of renal tissue and a decrease in the GFR. Acid retention in these patients is attributable to a decrease in the ability of the kidneys to excrete NH_4^+. Although the decline in serum HCO_3^- is relatively modest, it is recommended that serum HCO_3^- concentrations should be maintained above 22 mEq/L, with $NaHCO_3$ supplementation to minimize bone reabsorption, protein catabolism, and progression of chronic kidney disease.[31]

Gastrointestinal Causes of Hyperchloremic Acidosis

Diarrhea is a common cause of hyperchloremic acidosis. In the bowel, Cl^- is selectively absorbed in exchange for HCO_3^-. In the setting of diarrhea, significant amounts of HCO_3^- can be lost: each liter of diarrheal fluid can result in the loss of 200 mEq of HCO_3^-. Acidosis is exacerbated by absorption of NH_4^+ generated by gut bacteria. Ureterosigmoidostomy or ureteroileostomy can also produce hyperchloremic acidosis because the Cl^- in the urine diverted to the bowel tends to be absorbed instead of the HCO_3^-. Severe losses of pancreatic or biliary fluids, which contain 50 to 100 mEq of HCO_3^- per liter, can cause a severe hyperchloremic acidosis. Finally, extracellular volume depletion promotes aldosterone secretion, which in turn enhances urinary K^+ loss. Chronic acidosis increases renal NH_4^+ secretion, distinguishing it from RTA. A nonrenal cause of acidosis may be inferred from a urinary anion gap less than 20.

Miscellaneous Causes of Hyperchloremic Acidosis

A common cause of hyperchloremia in hospitalized patients is the administration of large amounts of normal saline. Other causes of hyperchloremia causes include some hyperalimentation fluids and administration of NH_4Cl, or $CaCl_2$. Because chronic respiratory alkalosis is normally

compensated by a decrease in proximal HCO_3^- reabsorption, the correction of an underlying respiratory alkalosis may transiently produce a hyperchloremic acidosis. Toluene inhalation can also cause hyperchloremic acidosis due to its conversion to benzoic acid and hippurate, which are rapidly excreted renally with cations.[32]

CLINICAL MANIFESTATIONS

A classic sign of metabolic acidosis is Kussmaul respiration, which consists of slow, deep breaths. Kussmaul respiration is particularly effective because the dead-space fraction and its contribution to ventilation is minimized. However, most patients with chronic metabolic acidosis are often asymptomatic, and their hyperventilation may not be clinically obvious. With more severe acidosis, patients may complain of dyspnea with exertion, along with headache, nausea, and vomiting. Although acidosis decreases myocardial contractility and inotropic responsiveness in vitro and in animal models,[33] there are no convincing data that acidosis decreases total peripheral resistance or vasoconstrictor response to vasopressors.

THERAPY

Treatment of metabolic acidosis should focus on correcting the underlying metabolic disorder responsible for its emergence and the hemodynamic, oxygenation, and electrolyte derangements that ensue, rather than the acidemia itself.

$NaHCO_3$ administration is indicated in patients with chronic metabolic acidosis, such as those with significant hyperchloremic acidosis (e.g., RTA) to prevent bone and muscle catabolism, relieve exertional dyspnea, and promote growth in children. In acute severe metabolic acidosis (especially the endogenous anion gap acidoses), HCO_3^- administration is not always helpful or effective. In severe DKA, even with an arterial pH as low as 6.8, HCO_3^- administration does not alter rates of glucose correction or ketoacid clearance when compared with equivalent NaCl administration. Likewise, there are no clear benefits of HCO_3^- administration for sepsis, severe hypoxemia, and cardiogenic shock, and even suggestions of worse outcomes in HCO_3^--treated patients (for review, see Swenson[35]). Although it is often claimed that when the pH is lower than 7.2, $NaHCO_3$ infusions may be lifesaving by enhancing cardiac contractility and response to vasopressors, the supporting data are unconvincing. Any transient hemodynamic benefits of HCO_3^- administration may simply be the result of volume expansion by any sodium-containing fluid. Potential downsides of serum alkalization in these conditions include a left-shift of the oxygen-hemoglobin dissociation curve that may impair oxygen delivery in already hypoxic tissues, a decrease in ionized calcium, and nonmetabolic generation of CO_2 from HCO_3^- with paradoxical intracellular acidosis.[36–38] As the underlying disorders improve, both ketone bodies and lactate may be metabolized to HCO_3^-, resulting in the development of posttherapeutic alkalosis.

Alkalinizing agents may be indicated to treat associated severe hyperkalemia or to enhance excretion of acid metabolites of certain toxins.[39] $NaHCO_3$ infusions should be kept as low as possible (usually <200 mmoL) to avoid volume overload, which may alternatively be managed by hemodialysis against a $NaHCO_3$ solution. If $NaHCO_3$ is indicated acutely, determinations of arterial blood P_{O_2}, P_{CO_2}, HCO_3^-, pH, glucose, and electrolytes must be repeated at frequent intervals to monitor the response to therapy.

METABOLIC ALKALOSIS

GENERAL CONSIDERATIONS

For both diagnostic and therapeutic reasons, it is helpful to divide the causes of metabolic alkalosis into those associated with a decrease in the extracellular volume or chloride (chloride-sensitive) and those associated with a normal or increased extracellular volume (chloride resistant)[40] (Table 12.4). In general, maintenance of a metabolic alkalosis requires the presence of increased aldosterone *and* distal Na^+ delivery. Severe chloride depletion and hypokalemia may also independently contribute to the maintenance of a metabolic alkalosis.[41] Urine chloride values less than 20 mEq/L suggest a chloride-responsive process, whereas levels greater than 40 mEq suggest a chloride-resistant process. Bicarbonaturia may be present in metabolic alkalosis, which can pull cations such as Na^+ in the urine, so urine Na^+ is not useful in determining volume status in this setting. Metabolic alkalosis may be associated with an elevated anion gap due to an increase in the negative anion charges on albumin, but the anion gap is not helpful in determination of the cause.

CHLORIDE-RESPONSIVE ALKALOSIS

Gastrointestinal Losses

Upper gastrointestinal tract acid losses generate an alkalosis that is initially associated with increased renal Na^+ excretion. *Extracellular fluid* (ECF) volume depletion causes the GFR to fall and is associated with increased aldosterone secretion. This enhances HCO_3^- reabsorption, and alkalosis persists even after all initiating factors (e.g., protracted vomiting and continuous nasogastric suction) have abated. In these patients, Cl^- is avidly reabsorbed from the tubules, and urine concentrations remain less than 10 mEq/L. Although diarrhea usually generates a hyperchloremic acidosis (see earlier discussion), alkalosis may rarely be seen with Cl^--HCO_3^- exchange across the ileal mucosa[42] and in a minority of patients with villous adenomas of the colon. In general, correction of the metabolic alkalosis depends on replacement of Cl^- losses, given as saline in the setting of volume depletion.

Diuretics

These agents are the most common cause of excessive renal fluid losses. When Na^+ delivery to the distal nephron persists despite ECF depletion (e.g., after diuretic therapy), H^+ secretion by this segment is enhanced. In these conditions, Cl^- concentrations in the urine may be appreciable. Both loop diuretics (furosemide, bumetanide, ethacrynic acid) and thiazides can promote H^+ and K^+ secretion from the more distal segments of the nephron. This frequently results in severe hypokalemic alkalosis.

Mechanisms of Hyperkalemia During Metabolic Acidosis

Hyperkalemia often develops in the setting of metabolic acidosis due to various mechanisms. In nonorganic acidosis, low extracellular pH reduces the activity of the Na^+, H^+-exchanger 1 (NHE1) in skeletal muscle. The lower intracellular Na^+ concentration then decreases activity of the Na^+, K^+-ATPase, resulting in less intracellular movement of K^+. In organic acidoses such as ketoacidosis and lactic acidosis, the monocarboxylate transporter shuttles organic acids intracellularly, resulting in low intracellular pH. The low intracellular pH increases activity of NHE1 so there is no effect on K^+ movement by this mechanism.[34] As a rule, respiratory acidosis causes much smaller changes in potassium than nonorganic metabolic acidosis.

Table 12.4 Causes of Metabolic Alkalosis

LOSS OF H^+ FROM THE BODY
Chloride-Responsive With Urine Cl^- < 20 mEq/L
Gastrointestinal losses of chloride: stomach (vomiting), some villous adenomas, congenital chloride-wasting diarrhea, high-volume ileostomy drainage
Renal losses of chloride with volume depletion: recent use of loop and thiazide diuretics
Sweat losses of chloride: cystic fibrosis
Posthypercapnia: elevated HCO_3^- after resolution of chronic respiratory acidosis
Chloride-Resistant With Urine Cl^- > 40 mEq/L With Hypertension
Hyperaldosteronism: primary adrenal hyperplasia, aldosterone producing adenoma, Cushing syndrome, 11-β-hydroxysteroid dehydrogenase type 2 deficiency, glycyrrhetinic acid (licorice)
Liddle syndrome: increased epithelial sodium channel expression in collecting duct
Chloride-Resistant with Urine Cl^- > 40 mEq/L Without Hypertension
Bartter syndrome: impaired reabsorption of sodium ions (Na^+) and chloride ions (Cl^-) in the thick ascending loop of Henle (variants)
Gitelman syndrome: impaired thiazide-sensitive Na^+/Cl^- transporter in the distal convoluted tubule
Administration of poorly absorbed anions (e.g., penicillin)
EXCESSIVE INTAKE OF HCO_3^-
Milk-alkali syndrome
Bicarbonate dialysis in end-stage renal disease
Recovery from ketoacidosis or lactic acidosis after bicarbonate administration
Massive blood transfusions (citrate)
EXTRACELLULAR FLUID VOLUME REDUCTION

Sweat

Metabolic alkalosis is reported in patients with cystic fibrosis, who lose proportionately more Cl^- than HCO_3^- in their sweat.

Mechanical Ventilation

In patients with chronic respiratory acidosis and chronic metabolic compensation, initiation of mechanical ventilation with an acute increase in minute ventilation to "normalize" the P_{CO_2} may result in life-threatening metabolic alkalosis. The arterial pH and plasma levels of HCO_3^- of these persons may remain high and inhibit spontaneous ventilation unless Cl^- is restored, generally in the form of KCl. An additional consideration is that normalizing the CO_2 while on mechanical ventilation can result in reversal of chronic metabolic compensation. Once patients are liberated from the ventilator and assume their baseline CO_2, the serum pH will be much lower than at their baseline.

CHLORIDE-RESISTANT ALKALOSIS

Metabolic alkalosis may be associated with either normal or increased ECF volume, particularly in the presence of excessive aldosterone secretion. Mineralocorticoids increase Na^+ retention by the distal nephron, resulting in H^+ and K^+ wasting. Unlike situations in which the ECF is decreased, Cl^- is lost in the urine with metabolic alkalosis caused by excessive mineralocorticoid secretion (urine Cl^- > 40 mEq/L). Maintenance of the metabolic alkalosis is a result of persistent excess mineralocorticoid secretion as well as hypokalemia.

Any alteration in the renin-angiotensin-aldosterone axis that promotes aldosterone secretion also causes a metabolic alkalosis (see Table 12.4). Patients with edema due to liver disease, nephrotic syndrome, or congestive heart failure may secrete excessive aldosterone because their effective arterial blood volume is reduced, even though their total ECF volume is increased. The development of hypokalemic alkalosis is particularly likely when they receive diuretics.

The pathogenesis of several forms of congenital hypokalemic, hypochloremic metabolic alkalosis not associated with hyperaldosteronism (Bartter and Gitelman syndromes) has been traced to abnormalities in renal tubular transporters.[43] In patients who are volume depleted, sodium salts of penicillin or other anions that cannot be reabsorbed by the renal tubules pulls sodium distally, which causes acid and K^+ losses and results in a metabolic acidosis.

EXCESSIVE INTAKE OF ALKALI

Although the kidneys normally can excrete large quantities of HCO_3^-, metabolic alkalosis may occasionally be generated by excessive intake of HCO_3^- or other anions metabolized to HCO_3^-, especially in patients with renal insufficiency. For example, metabolic alkalosis may be observed after ingestion of extremely large amounts of HCO_3^- and milk (milk-alkali syndrome, which is associated with renal calcification, reduced GFR, and reduced ability to filter HCO_3^- for excretion), after fasting (due to conversion of ketones to HCO_3^-),[44] and after transfusions of large amounts of blood (conversion of citrate to HCO_3^-).[45] In the absence of volume depletion or renal disease, alkalosis due to increased HCO_3^- intake rapidly resolves once intake is restricted.

Extracellular Fluid Contraction

Water loss from plasma may induce a modest alkalemia that is sometimes referred to as a "contraction" alkalosis and is related to the relatively greater increase of HCO_3^- compared with P_{CO_2}. It would probably be more appropriate to designate this as a *concentration alkalosis* to distinguish it from the alkalosis of contraction caused by ECF fluid depletion, which promotes renal acid excretion and alkalemia.

CLINICAL MANIFESTATIONS

Metabolic alkalosis frequently remains asymptomatic and is often untreated even after discovery. Nevertheless, it may be associated with significant mortality, particularly when pH > 7.5 and $[HCO_3^-]$ > 45 mmol/L.[46–48] Alkalosis increases the affinity of hemoglobin for oxygen, thereby reducing oxygen delivery to the tissues. It also decreases ventilation by suppressing the carotid body and may constrict the peripheral vasculature, further limiting oxygen supply to tissues. Neuromuscular hyperirritability may be observed in alkalosis and has been attributed in part to

increased calcium binding to albumin. Twitching and tetany may be preceded by the Chvostek and Trousseau signs, and seizures can ensue. The myocardium may also become irritable, leading to ventricular arrythmias.[47] Thus prompt recognition and treatment is important.

THERAPY

Treatment of metabolic alkalosis depends on the status of the ECF volume. Patients with ECF volume loss can be distinguished from those with excess volume on the basis of urine Cl^-. For patients who have sustained severe volume losses, fluids that contain Na^+, Cl^-, K^+, and Mg^{2+} are frequently indicated.

Fluid administration to edematous patients with alkalosis is usually inappropriate, and KCl may resolve the metabolic alkalosis without the administration of Na^+.[41] Spironolactone is useful in the presence of excessive mineralocorticoid secretion. The carbonic anhydrase inhibitor, acetazolamide, may be helpful in patients with post-hypercapnic alkalosis, although it may increase loss of K^+ and occasionally cause hepatic encephalopathy in those with cirrhosis by interfering with NH_4^+ detoxification to urea and CO_2 retention in patients with severe lung disease.

Infusions of HCl (at a concentration of 100–200 mEq/L) may be safer than NH_4Cl in patients with liver and kidney disease, but these infusions require central access confirmed radiologically by location of the catheter tip in the superior vena cava to minimize the likelihood of tissue necrosis and hemolysis caused by the acid infusion. Alternatively, intubation and intentional hypoventilation to increase the P_{CO_2}, thereby reducing arterial pH, may be used.

RESPIRATORY ACIDOSIS

GENERAL CONSIDERATIONS

Respiratory acidosis is common in patients with severe respiratory insufficiency, generally when lung function falls below 25% of the predicted value. Chemoreceptors located in the medulla (central chemoreceptors) and in the carotid bodies (peripheral chemoreceptors) normally keep P_{CO_2} within narrow limits. Normally, arterial P_{CO_2} is controlled primarily by the central chemoreceptors, which may have increased sensitivity because of concomitant hypercapnic peripheral chemoreceptor input. However, central chemoreceptors may be suppressed by chronic hypercapnia because compensatory renal generation of HCO_3^- increases the cerebrospinal fluid pH and reduces the magnitude of a pH change with fluctuations in arterial P_{CO_2}. This blunting of the central chemoreceptor response is seen mostly in patients with severe COPD. When this happens, ventilation is maintained by the carotid bodies responding to alterations in P_{O_2} and pH. In this setting, if P_{O_2} is raised excessively, carotid body output may be suppressed, leading to progressive hypercapnia and narcosis.

Acute increases in P_{CO_2} are buffered by non-HCO_3^- buffers to form HCO_3^-, but HCO_3^- concentrations seldom exceed 30 mEq/L during the first 24 hours of hypercapnia. Increases in P_{CO_2} also result in an intracellular acidosis within the renal tubular cells that favors acid excretion and, over the next few days, acid excretion is accelerated by a rise in NH_4^+ formation, as compensation for respiratory acidosis.

CAUSES

Any process interfering with ventilation can lead to respiratory acidosis (Table 12.5). COPD is the most frequent cause of this problem, related primarily to mechanical conditions that decrease alveolar ventilation and lead to respiratory muscle weakness, either from reduced intrinsic strength or effective weakness as hyperinflation puts the respiratory muscles at a disadvantageous position in their length-tension relationship. Interstitial lung disease is less likely to increase P_{CO_2} until it becomes severe and the increased work of breathing cannot be maintained. Extensive infiltrative processes, including pneumonias and all forms of pulmonary edema, and large pleural effusions can decrease alveolar ventilation. With significant acute pulmonary artery embolic obstruction, wasted ventilation due to increased alveolar dead space can explain sudden increases in ventilation; hypercapnia may ensue if ventilation cannot be increased sufficiently. In such situations, the dead-space ventilation to tidal volume ratio (V_D/V_T) may be measured by sampling both arterial blood and mixed expired gases. A paralyzed diaphragm or extensive rib fractures that lead to a unilateral flail chest can produce an inefficient mode of ventilation and lead to hypoventilation.

Hypoventilation is the most serious complication of a wide variety of neuromuscular disorders. The central respiratory centers may be depressed acutely or chronically by narcotics or by any process that injures the brainstem, including chronic hypoxemia and hypercapnia. A complex disturbance of the respiratory center may be encountered in patients with the obesity-hypoventilation syndrome. Apneic episodes during sleep are common in these persons and are related to airway obstruction or to a central failure to initiate ventilation, or both.

Rarely, if cardiac output is low, if anemia is severe, and/or if certain drugs are used that interfere with the normal high efficiency of red cell CO_2 transport and exchange, CO_2 retention in the tissues may develop and yet not be reflected in the arterial P_{CO_2}.[49] In fact, as CO_2 rises in the vicinity of the central chemoreceptors, ventilation may be stimulated sufficiently to cause a paradoxical arterial hypocapnia that can be mistaken as evidence of a primary respiratory alkalosis. If P_{CO_2} is measured in the venous circulation (mixed venous P_{CO_2}), one will find an elevated P_{CO_2} and lower pH, revealing the true state of CO_2 homeostasis.

CLINICAL MANIFESTATIONS

If hypoventilation is caused by neuromuscular or mechanical problems, the patient will be dyspneic and tachypneic. In contrast, if the respiratory center is impaired, ventilation may be reduced without any sensation of dyspnea.

Table 12.5 Causes of Respiratory Disorders

RESPIRATORY ACIDOSIS

Central Nervous System Depression

Drugs: opiates, sedatives, anesthetics
Excessive administration of oxygen in COPD
Obesity-hypoventilation syndrome
Central nervous system disorders

Neuromuscular Disorders

Neurologic: multiple sclerosis, poliomyelitis, phrenic nerve injuries, high spinal cord lesions, Guillain-Barré syndrome, botulism, tetanus, amyotrophic lateral sclerosis
End plate: myasthenia gravis, succinylcholine chloride, curare, aminoglycosides, organophosphorus
Muscle: hypokalemia, hypophosphatemia, muscular dystrophy, polio

Airway Obstruction

COPD
Acute aspiration, laryngospasm

Chest Wall Restriction

Pleural: effusions, empyema, pneumothorax, fibrothorax
Chest wall: kyphoscoliosis, scleroderma, ankylosing spondylitis, extreme obesity

Severe Pulmonary Restrictive Disorders

Pulmonary fibrosis
Parenchymal infiltration: pneumonia, edema

Abnormalities in Blood Carbon Dioxide Transport

Decreased perfusion: heart failure, cardiac arrest with cardiopulmonary resuscitation, extensive pulmonary embolism, severe anemia
Carbonic anhydrase inhibition—high-dose acetazolamide

RESPIRATORY ALKALOSIS

Central Nervous System Stimulation

Hyperventilation syndrome, anxiety
Pregnancy
Cerebrovascular disease, subarachnoid hemorrhage
Meningitis, encephalitis
Septicemia, hypotension
Hepatic failure
Drugs: salicylates, nicotine, xanthines, quetiapine, progestational hormones

Pulmonary Disease

Pneumonia, interstitial fibrosis, pulmonary fibrosis, embolism, edema
Right-to-left shunt

Hypoxia

High altitude
Severe anemia, hemoglobinopathy
Decreased cardiac output

Excess Carbon Dioxide Removal

Mechanical ventilation
Acetate hemodialysis, heart-lung machine, extracorporeal membrane oxygenation

Decreased Carbon Dioxide Production

Myxedema, hypothermia

The physiologic and clinical consequences of respiratory acidosis tend to be more serious in acute than in chronic states. Elevations in P_{CO_2} cause systemic vasodilation that is particularly evident in the cerebral circulation. Cerebral blood flow and intracerebral pressures increase and may lead to a picture of pseudotumor cerebri with papilledema, retinal venous distention, and retinal hemorrhages. The patient may complain of dyspnea and manifest myoclonic jerks, asterixis, tremor, restlessness, and confusion. Coma may be observed at P_{CO_2} values of 70 to 100 mm Hg when the onset of hypercapnia is abrupt. Significantly higher levels may be well tolerated in patients with chronic respiratory acidosis, who have much higher HCO_3^- concentrations from renal compensation. Peripheral vasodilation and increased cardiac output promote warm, flushed skin and a bounding pulse. Arrhythmias are observed occasionally. Mild increases in serum phosphate and K^+ and decreases in lactate and pyruvate have been described in acute respiratory acidosis, and serum Na^+ may increase modestly in both acute and chronic hypercapnia.

THERAPY

Treatment of respiratory acidosis depends on the restoration of adequate ventilation. In COPD, attention must be focused on bronchodilation, adequate oxygen supplementation, and relief of anxiety or other causes of an increased metabolic rate. Judicious use of supplemental oxygen to correct hypoxemia is warranted to avoid the phenomenon of oxygen-induced hypercapnia in these patients. Sudden correction of arterial hypoxemia causes further hypercapnia by a combination of three mechanisms: (1) by relief of hypoxic pulmonary vasoconstriction in poorly ventilated lung regions that further reduces the ability of the lung to eliminate CO_2 because local perfusion to poorly ventilated regions increases, (2) by saturation of hemoglobin with oxygen that causes previously buffered protons on deoxyhemoglobin to be released with subsequent generation of new CO_2 from HCO_3^- stores (Haldane effect) and from hemoglobin carbamate, and (3) by depression of the hypoxia-driven peripheral chemoreceptor drive that causes more hypoventilation. Low-flow oxygen generally suffices to increase P_{O_2} to satisfactory levels (60 mm Hg and arterial oxygen saturation [arterial SO_2] approximately 90%); greater elevations are neither needed nor advisable. If mechanical ventilation becomes necessary, care must be taken that P_{CO_2} is not decreased by more than 10 mm Hg each hour to avoid life-threatening metabolic alkalosis. If opiates are responsible for central respiratory depression, the respiratory acidosis may be relieved by naloxone. Aminophylline acts as a respiratory center stimulant, but blood levels must be monitored carefully. Bicarbonate is generally contraindicated because it tends to decrease respiratory drive and increases CO_2 levels in the tissues.

"Permissive hypercapnia" with gradual increases in P_{CO_2} of 10% per hour to levels as high as 100 mm Hg may help mitigate lung damage by barotrauma associated with mechanical ventilation. This approach is frequently used in patients with acute respiratory distress syndrome, neonatal respiratory failure, or asthma by hypoventilation with tidal volumes less than 7 mL/kg and plateau pressures less than 30 to 35 cm H_2O. The value of HCO_3^- infusions to reverse acidosis in these patients remains uncertain. Permissive hypercapnia should be avoided in those with head trauma, increased intracerebral pressure, acute renal insufficiency, or cardiac dysfunction.

RESPIRATORY ALKALOSIS

GENERAL CONSIDERATIONS

Respiratory alkalosis is a common disorder, but it seldom has a significant impact on the clinical status of patients. Changes in pH related to hyperventilation are quickly moderated by tissue buffering and, to a lesser extent, by generation of lactic acid, as described earlier. However, HCO_3^- concentrations do not usually fall below 18 mEq/L acutely and, even with renal compensation, a HCO_3^- concentration below 16 mEq/L should raise the possibility of an independent metabolic acidosis. Although respiratory alkalosis may have prognostic implications, it generally requires little in the way of specific therapy to reverse the hyperventilation directly.

CAUSES

It is convenient to divide the causes of respiratory alkalosis into three major categories: CNS stimulation, pulmonary diseases, and hypoxia (see Table 12.5).

CNS stimulation is among the most common cause of respiratory alkalosis. Anxiety can provoke hyperventilation (hyperventilation syndrome). Central stimulation of respiration is also common in a wide variety of intracerebral injuries. Many drugs and hormones (notably salicylates, theophylline, thyroxine, and progesterone) stimulate ventilation, and hyperventilation may be an early sign of both sepsis and hepatic insufficiency due to the accumulation of ammonia and amines known to be responsible for respiratory center stimulation.

Many pulmonary disorders are associated with hyperventilation. Hypoxia certainly plays a role but, in addition, receptors have been described in lung tissue that are activated by local irritant stimuli and fluid accumulation and remain activated even after hypoxemia has been corrected.

Both central (arterial) and peripheral (capillary) hypoxia are causes of hyperventilation. Decreases in arterial P_{O_2} stimulate the carotid bodies directly. In contrast, tissue hypoxia caused by decreased cardiac output, shock, severe anemia, or excessive hemoglobin oxygen affinity results in the production of lactic acid and other stimuli, which are sensed in blood by the carotid chemoreceptors and by other less well-defined chemoreception in the affected tissues themselves. Acute ascent to altitudes greater than 8000 feet predictably leads to hypocapnia as a result of hypoxic stimulation of breathing.

CLINICAL MANIFESTATIONS

Many manifestations of respiratory alkalosis may be related in part to a fall in free serum Ca^{2+} due to increased calcium binding to serum proteins. Phosphate may also decline slightly and sometimes fall to rather low concentrations in patients who have prolonged severe respiratory alkalosis. The decline in phosphate may be related to activation of glycolysis and phosphorylation of the produced glucose metabolites. Some of the CNS changes of acute respiratory alkalosis may be caused by hypocapnic cerebral vasoconstriction leading to reduced blood flow and tissue hypoxia. Often, deliberate hyperventilation is used to reduce cerebral blood flow in states of impending brain herniation from high intracranial pressure, but evidence is mounting that it is useful only for a few hours as a temporizing measure to allow more definitive pressure relief by other means.

Panic, weakness, and a sense of impending doom are common, as are paresthesias and muscle weakness or cramping. As in metabolic alkalosis, Trousseau and Chvostek signs can often be elicited, and overt tetany or seizures may follow, particularly in patients with previous seizure diatheses. Vision and speech may become impaired, and syncope can follow. Transient electrocardiographic changes can resemble those of myocardial ischemia; this finding can be particularly misleading because it is not uncommon for hyperventilating patients to complain of chest discomfort. Indeed, acute hypocapnia, for example with mechanical ventilation, can induce coronary artery vasospasm, angina, ominous cardiac arrhythmias, and ST elevations in patients with coronary artery disease. Acute respiratory alkalosis can increase lactate and reduce serum K^+ concentrations.

THERAPY

Reassurance and rebreathing in a small paper bag are frequently all that is needed to control hyperventilation associated with anxiety attacks. In more severe cases, β-adrenergic inhibitors have proved useful, and specific therapy for anxiety may be indicated. Correction of respiratory alkalosis in other conditions, such as hepatic coma and pulmonary disorders, depends on treatment of the primary disorder. CO_2 inhalation by patients with hepatic coma has not been helpful.

Key Points

- Arterial P_{CO_2} provides a suitable criterion for determining whether alveolar ventilation is appropriate for the rate at which CO_2 is produced in the body. Abnormalities in arterial P_{CO_2} may be "primary" causes of abnormal pH or "secondary" responses, which act to compensate for pH disturbances.
- Changes in total CO_2 reflect net accumulation or loss of nonvolatile acids and bases from the body and can be primary or secondary. Both the kidneys and other organs, including the gastrointestinal tract and skin, may be involved.
- Incorporation of electrolyte concentrations into the analysis permits calculation of the anion "gap" and identification of various processes involved in both metabolic acidosis and alkalosis. However, these measurements must always be accompanied by measurement of conventional acid-base parameters (pH_a, arterial P_{CO_2}, and HCO_3^-).
- Correction of the underlying metabolic or respiratory disorder represents the most effective way to treat any acid-base disorder but, in specific circumstances, judicious direct manipulation of P_{CO_2} and HCO_3^- may be considered.

Key Readings

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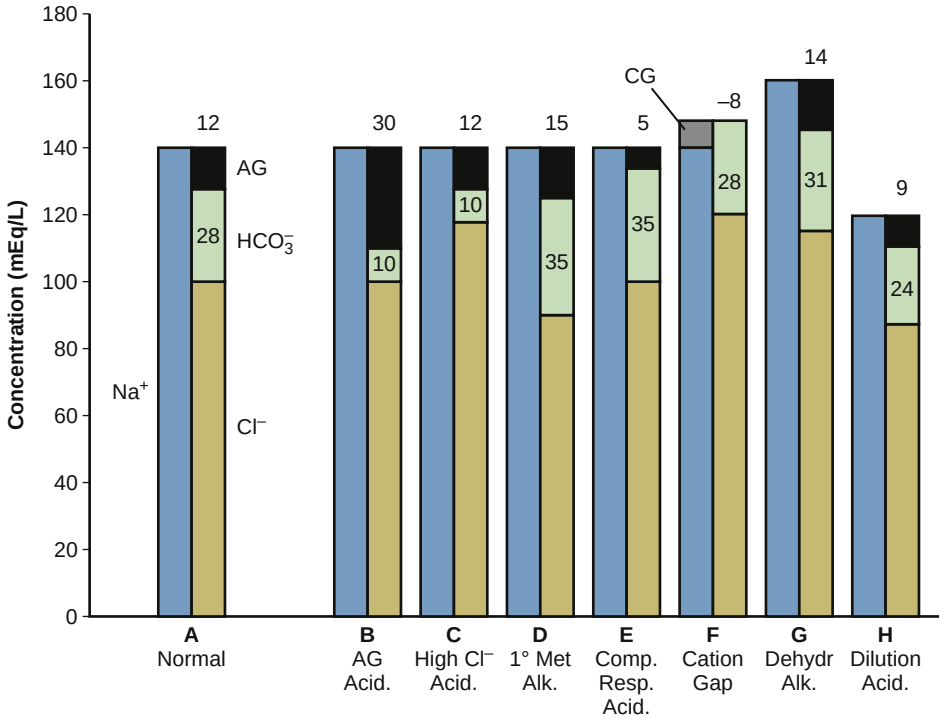
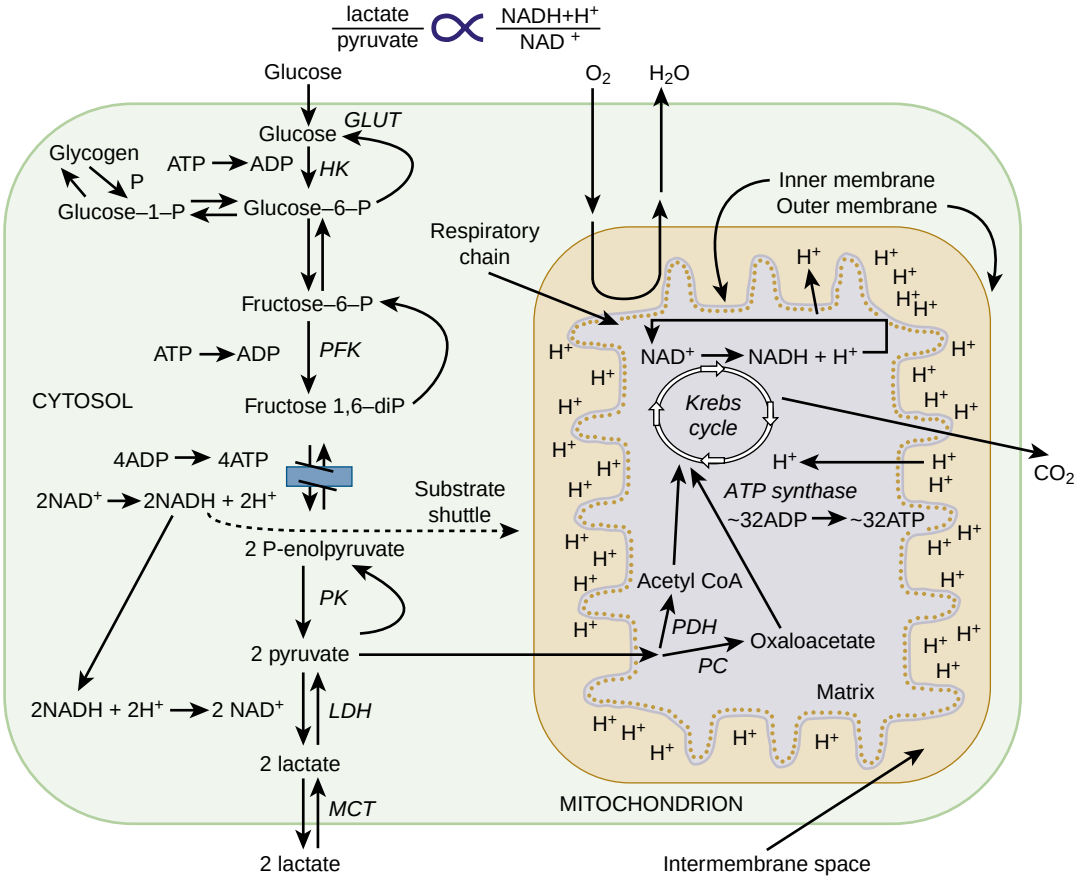
Complete reference list available at ExpertConsult.com.



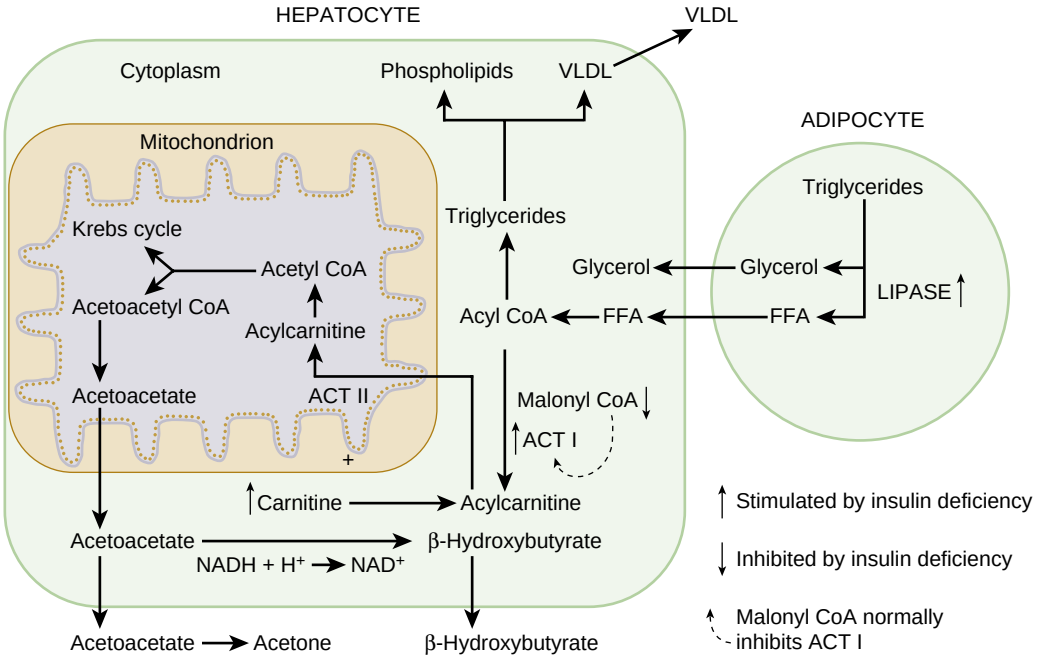
eFIGURE IMAGE GALLERY



eFigure 12.1 Typical *anion gap* (AG) profiles are shown for eight different acid-base conditions (see text). Because these histograms do not show pH, $[H^+]$, or P_{CO_2}, they do not indicate whether acidemia or alkalemia is present, but they do provide useful information about the nature of these disorders. The value of the AG is shown above each bar, and the bicarbonate concentrations are indicated (mEq/L). (A) Normal. (B) AG acidosis. (C) Hyperchloremic acidosis. (D) Primary metabolic alkalosis. (E) Compensated respiratory acidosis. (F) Excess cations other than Na^+ creating a cation gap (CG). (G) Contraction alkalosis. (H) Dilutional acidosis.



eFigure 12.2 The metabolic events responsible for the development of lactic acidosis during hypoxia. Both enhancements and reduction of metabolic reactions that produce lactic acid are shown (see text). Factors affecting the balance between lactate and pyruvate are indicated in the equation at the top of the figure. Stoichiometry is not shown for most of the reactions within the mitochondrion, other than ADP and ATP. ADP, adenosine diphosphate; ATP, adenosine triphosphate; CoA, coenzyme A; GLUT, glucose transporter; HK, hexose kinase; *k,* constant; LDH, lactate dehydrogenase; MCT, monocarboxylate transporter; NAD^+, nicotinamide adenine dinucleotide (oxidized); NADH, nicotinamide adenine dinucleotide (reduced); P, phosphate; PC, pyruvate carboxylase; PDH, pyruvate dehydrogenase; PFK, phosphofructokinase; PK, pyruvate kinase.



eFigure 12.3 Factors encouraging ketoacidosis. Some reactions are stimulated by insulin deficiency *(up arrow),* whereas others *(down arrow)* are inhibited by insulin deficiency and increased glucagon. The *open curved arrow* indicates that *acylcarnitine transferase* (ACT) I is normally inhibited by *malonyl coenzyme A* (CoA). FFA, free fatty acid; NAD^+, nicotinamide adenine dinucleotide (oxidized); NADH, nicotinamide adenine dinucleotide (reduced); VLDL, very-low-density lipoprotein.

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13 AEROSOLS AND DRUG DELIVERY

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INTRODUCTION

The human lung has a large surface area, which for an average-size person approximates half a doubles tennis court, thus maximizing the approximation and apposition of capillaries to the epithelial surface. Although this design optimizes gas exchange, it also has the intrinsic risk of exposing the delicate alveolar tissues to potentially noxious particles present in the ambient air. There are various safeguards against the danger posed by inhaled particles. The first line of defense is the configuration of the nasopharynx and serial branching of the airways, which causes particles to deposit proximal to the more vulnerable alveolar structures.[1,2] Second, if an insoluble particle deposits in the lung, there are processes by which it can be cleared from the airways or alveoli. Clearance of insoluble particles that deposit in the ciliated airways is achieved by mucociliary clearance.[3] The particles are trapped in a mucus blanket, which is then transported proximally by beating cilia. If the cilia are not functioning optimally or if the quantity or quality of the airway mucus is abnormal, the mucus and its entrapped particulates can be cleared by cough. Particles that deposit distal to the ciliated airways are removed by alveolar clearance, mainly by macrophages ingesting the particles and transporting them to regional lymph nodes.

The branching structure of the airways is a barrier not only to noxious environmental aerosols but also to therapeutic aerosols. However, the application of the principles of deposition facilitates the design of therapeutic aerosols.[4] For the most part, therapeutic aerosols are "targeted" to the lungs; that is, they are designed to treat lung diseases directly and avoid systemic toxicity. Theoretically the large surface area of the lungs can facilitate the systemic delivery of nonrespiratory drugs via the lung as aerosols, usually proteins, such as insulin, that cannot be given by the oral route. However, to date the use of this pathway has not had a major impact on clinically successful systemic therapeutic drugs.

DEFINITION AND DESCRIPTION OF AN AEROSOL

An *aerosol* can be defined as a system of solid particles or liquid droplets that can remain dispersed in a gas, usually air. Naturally occurring aerosols and those emitted by clinical aerosol generators almost always contain a wide range of particle sizes. Because the aerodynamic behavior of an aerosolized particle is critically influenced by its mass, it is important to be able to describe precisely the size distribution of aerosolized particles. In clinical studies, the *mass median aerodynamic diameter* (MMAD) and the geometric standard deviation are often used to characterize the dimensions of an aerosol. When the mass distribution of particles in an aerosol is fractionated and the cumulative particle distribution plotted as a lognormal distribution, it often approximates a straight line. However, recent studies of clinical aerosols have indicated that nebulized particles are often not lognormal in distribution.[5] The MMAD represents the point in the distribution above which 50% of the mass resides, expressed as the diameter of a unit density (1 g/mL) sphere having the same terminal settling velocity as the aerosol particle in question, regardless of its shape and density.

The lognormal plot is convenient because, if linear, it defines a statistically "normal" distribution and the data can be described accurately by the MMAD and the standard deviation alone. For a lognormal distribution, one standard deviation is called the *geometric standard deviation* (σg). The σg is the ratio of the size at 84% (or 16%) to the MMAD and is an indicator of the variability in particle diameters. If the particle size varies over a wide range (σg > 1.2), it is described as having a *polydisperse* particle distribution; if the particles are of similar size (σg < 1.2), the particle distribution is described as *monodisperse.* Monodisperse aerosols are usually encountered only in research studies where specialized generators are used to create such an aerosol.[6] For clinical aerosols that are not lognormal and are widely polydisperse, it is best to relate deposition studies to the entire distribution of particles and avoid focusing on simple descriptive terms, such as the MMAD and σg.[5,7]

PRINCIPLES OF DEPOSITION

The fraction of inhaled particles that deposit (as opposed to being exhaled) is called the *deposition fraction.*[1,2] The likelihood that a particle will deposit in a particular airway depends on the interaction of three factors: the physical characteristics of the particle (e.g., mass, shape), the gas flow in which the particle is transported (the patient's breathing pattern[8] and any velocity provided to the particle by a propellant), and the airway anatomy (especially the presence of airway obstruction[9]). Particles deposit in the lung by three primary mechanisms: inertial impaction, gravitational sedimentation, and Brownian diffusion.

Inertial impaction is the dominant mechanism by which particles deposit in the nasopharynx and more proximal airways. In general, the greater the mass, the faster the velocity, and the narrower the airway, the greater the likelihood that the particle will deposit by impaction. Impaction describes the process by which a particle fails to follow the air stream in which it is suspended, thereby impacting on an obstacle instead of circumventing it. The probability of a particle undergoing inertial impaction can be estimated using Equation 1[1]:

$$I = \alpha\,(V_t V_a \sin\theta / gR) \qquad \text{[Eq. 1]}$$

where I is inertial impaction, V_t is the settling velocity of the entrained particle, V_a is the air stream velocity, θ is the angle required to circumvent the obstacle, g is the acceleration due to gravity, and R is the airway radius. The settling velocity (defined in Equation 2) increases as particle size increases. This equation applies to situations in which laminar flow predominates. The presence of turbulent nonlaminar flow will tend to increase impaction further. Particles that fail to deposit in proximal airways by inertial impaction can deposit in peripheral airways and alveoli by a process called gravitational sedimentation.

Gravitational sedimentation is the process by which a particle accelerates under gravity until it reaches a terminal settling velocity (V_t), which is determined by Equation 2[1]:

$$V_t = (\rho - \sigma)\, gd^2 / 18\gamma \qquad \text{[Eq. 2]}$$

where ρ is the density of the particle, σ is the density of air, g is the acceleration due to gravity, d is the diameter of the particle, and γ is the viscosity of air. Therefore, for a given velocity, the greater the aerodynamic mass of an aerosol, the shorter the time it will remain suspended in the air stream. Gravitational sedimentation is the main mechanism by which particles between 0.5 and 5.0 μm in diameter deposit in the peripheral regions of the lung. Sedimentation is critically dependent on the patient's breathing pattern.[8] If there is a breath-hold before exhalation, particles are more likely to sediment; without a breath-hold, particles are more likely to be exhaled rather than deposited. It has also been suggested that alveolar volume may affect deposition fraction (larger air spaces require more time for sedimentation).

Brownian diffusion describes how very small particles (<0.2 μm) can deposit. The diffusion coefficient of a particle (D) reflects the rate of diffusion of the particle in air and can be expressed as in Equation 3:

$$D = kT / 3\pi\eta d \qquad \text{[Eq. 3]}$$

where k is the Boltzmann constant, T is the temperature in Kelvin, η is the gas viscosity, and d is particle diameter.[2] These tiny particles are rarely important in therapeutic aerosols but can be produced by combustion and may be clinically relevant, even though they tend to be transient because of the tendency to agglomeration. In addition, human-made nanoparticles, which are of increasing interest in electronics and biomedical research, would, if inadvertently inhaled, likely deposit by diffusion. Particles between 0.2 and 0.5 μm in diameter tend to be too small to deposit efficiently by sedimentation and yet too large to deposit efficiently by Brownian diffusion and tend to be exhaled rather than deposited in the lung.[1,2]

MEASUREMENTS AND APPLICATIONS OF AEROSOL PARTICLE SIZE

Particle size is an important factor in determining whether a particle will undergo nasopharyngeal deposition, airway deposition, or alveolar deposition.[10] Particle size is usually measured by light scattering or cascade impaction. Light scattering is based on the principle that there is differential scattering of polarized light by particles of different sizes; cascade impaction is based on a different trajectory of particles of different mass. In cascade impaction, particles at a set flow rate go through a series of apertures of decreasing diameter and impact on a series of plates if they fail to follow the air stream. Cascade impactors with high flow rates (e.g., 28 L/min) were originally designed for environmental sampling of ambient air to collect 100% of the emitted dose. They have been adopted as the method of choice for monitoring quality control in manufacturing plants for aerosol delivery. Cascade impaction has an advantage over light scattering in that it facilitates the correlation of different methods of quantifying the distribution of the active drug (e.g., chemical analysis of drug on each plate compared with radioactive label or weight). However, measuring the emitted dose of aerosol using a high-flow cascade impactor is not ideal for predicting how an aerosol will perform in clinical practice. Although low-flow cascade impactors sample only some of the output, they more closely duplicate in vivo conditions.[5,11–13]

Particle size measurements using different techniques are not necessarily interchangeable. Meaningful comparisons of the sizes of clinical aerosols, especially those produced by

a pressurized *metered-dose inhaler* (MDI), can be made only if obtained with identical techniques. Nevertheless, despite the technical difficulties, some investigators have established that, when used with appropriate caution, data obtained by in vitro measurement of particle size provide useful predictive information for subsequent clinical studies.[5,7,11,13]

The classic studies of the influence of particle size on lung deposition were performed with monodisperse aerosols consisting of particles that would not absorb moisture from the air (nonhygroscopic).[6] In contrast, pharmaceutical aerosols tend to be polydisperse liquid droplets, with the active pharmaceutical ingredient and, in some cases, pharmaceutically inactive ingredients, such as preservatives and hydrofluoralkane, being either in solution or suspended as micronized particles. Droplets can change size by exchanging water with either the dry carrier gas or the humid environment of the upper airway.[2,14] In addition, some drug ingredients are hygroscopic, and some diluent solutions are hypertonic, both of which could lead to an increase in particle size due to an increase in aqueous content of the particle; the clinical significance of such changes is not clear.[15] Thus measuring the particle distribution of droplet aerosols is difficult because the particles can be affected by ambient humidity. The predictive value of cascade impaction data from droplet aerosols for in vivo deposition (e.g., for upper airway deposition as measured by gamma scintigraphy) is strongly dependent on the specific technique used for cascade impaction.[12]

GENERATION OF THERAPEUTIC AEROSOLS

Therapeutic aerosols can be generated in three ways. First, the patient's inspiratory airflow can aerosolize a micronized dry powder (*dry powder inhalers* [DPI]). Second, micronized particles can be suspended in a volatile pressurized liquid that vaporizes when at atmospheric pressure, thus imparting velocity to the emitted particles (MDIs). Third, a dispersal force can be applied to a liquid to generate droplets, which are then inhaled by tidal breathing. The generation of the dispersal force can be as simple as using a compressed air source attached to a narrow orifice to generate a Venturi effect (i.e., jet nebulizer) or by more complex vibrating membranes and meshes. In addition, a novel delivery system, Soft Mist, a metered liquid aerosol that does not use a propellant, is briefly described below.

DRY POWDER DEVICES

Because DPI aerosols are generated by the patient's inspiration, they are by definition coordinated with inspiration, a feature that enhances drug deposition (Fig. 13.1A).[4,16–19] The need to trigger the aerosol generation by an inspiratory effort makes them unsuitable for infants and for patients with severe cognitive impairment, who may be unable to comprehend the instructions. The design of DPI devices has evolved over several decades to meet the key objective that the emitted dose should not vary significantly within the clinically relevant range of inspiratory flow. By so doing, the DPI intersubject dosing remains consistent and meets stringent regulatory standards for the quality and reproducibility of the emitted aerosol. For dry powder devices to maintain reproducible dosing over time, it is essential that the powder be protected from moisture. The design of DPIs has greatly improved, and the devices approved in major markets now perform at high levels of efficiency and reproducibility.[20] Devices can be single-dose devices in which a capsule of powder is perforated in the device (HandiHaler, Boehringer Ingelheim), a multidisk with individual doses wrapped in foil blisters[17] (Diskus and Ellipta, GlaxoSmithKline), or a multidose metered reservoir (Turbuhaler and Flexhaler, AstraZeneca).

A DPI device (Trelegy Ellipta, GlaxoSmithKline) has recently been developed that can deliver three medications simultaneously (an inhaled corticosteroid, a long-acting β_2-agonist, and a long-acting muscarinic antagonist) and is used once daily, making this a more convenient device for patients with COPD to use.[18] Clinical trials in patients with COPD demonstrate that the three-drug combination as a single inhaler was superior to a two-drug combination single-inhaler therapy and was noninferior to the three drugs being administered in two inhalers.[18,19]

PRESSURIZED METERED-DOSE INHALERS

Pressurized MDIs (pMDIs) using chlorofluorocarbon propellants were developed 60 years ago to treat obstructive lung disease. Chlorofluorocarbon-containing pMDI formulations have been replaced by formulations that use hydrofluoroalkane as a propellant.[21–23] pMDIs remain the most popular method of administering short-acting rescue inhalers and are an alternative to DPIs in delivering controller medications to patients with asthma and COPD. They are portable and discreet, but many patients have difficulty with inhaler technique, which can contribute to poor control of disease. For adequate lung deposition, there must be precise coordination with a patient's ventilation. Even with optimal technique, 80% of the emitted dose may deposit on the pharynx and cause local irritation (see Fig. 13.1B). In addition, some orally bioavailable medications cause significant systemic exposure from swallowed medication. Valved holding chambers ("spacers") reduce pharyngeal deposition because high-velocity particles impact on the inside of the chamber; use of these devices decreases the need for precise coordination with respiration.[21] For young children, a

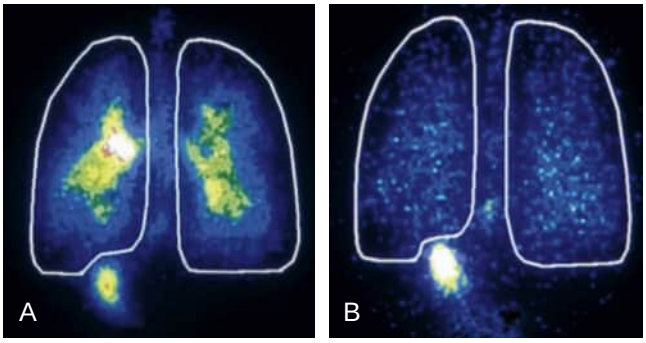

Figure 13.1 Comparison of drug deposition using common aerosol delivery systems. Deposition images after inhalation of radiolabeled aerosols using a dry powder inhaler (A) or a *metered-dose inhaler* (MDI) (B). The dry powder inhaler provided more lung deposition than the MDI. With the MDI, most of the inhaled dose was deposited in the oropharynx due to inertial impaction and detected in the stomach after being swallowed.

face mask can be used in conjunction with a valved holding chamber. Pivotal studies of novel MDI medications undertaken for regulatory approval are almost always performed without a holding chamber because manufacturers do not want their product's prescription tied to a specific holding chamber. To make the chambers more acceptable to patients, small-volume chambers (140 mL) and collapsible chambers have been developed.

As an alternative to using a holding chamber, pMDIs have been developed that are actuated during inspiration and have similar performance characteristics as an optimally used conventional pMDI (Qvar RediHaler, Teva Respiratory).[24]

Increasing frequency of rescue inhaler use may be a sign of worsening control of asthma. As a result, electronic monitoring devices have been attached to these devices to measure their use in real time. Electronic monitoring devices are also being developed for controller medications given via pMDI or DPI in efforts to encourage improved adherence and facilitate early intervention during exacerbations.[25,26]

JET NEBULIZERS

The ubiquitous small-volume jet nebulizer is the mainstay of bronchodilator delivery in hospitalized patients and patients at the extremes of age. These devices are inexpensive and require little patient cooperation. In addition, they are useful for delivering medications with a relatively large mass, such as antibiotics. Generation of the driving pressure requires either a tank of pressurized gas or an electric compressor. Although the manufacturers of compressors have made these devices more portable, they are far from convenient for ambulatory patients. In addition, conventional nebulizers take 10 to 20 minutes to deliver a single treatment, which may decrease adherence. Most generic nebulizers are inefficient and deliver less than 10% of the drug to the lung. The remainder is left in the nebulizer chamber as so-called dead volume (droplets and dried particles left on the nebulizer walls), lost through the expiratory port because the device generates aerosol throughout the respiratory cycle, or deposited in the extrapulmonary upper airway because most of the emitted dose is contained in large, poorly respirable particles. Recent enhancements of jet nebulizers include addition of internal recycling baffles to reduce emitted particle size and addition of expiratory filters to trap potentially hazardous aerosols and reduce collateral exposure.[27]

During the COVID-19 respiratory virus pandemic of 2020, concerns regarding exposure of health care workers to potentially contaminated aerosols during nebulization of bronchodilators led hospital clinicians to switch from using jet nebulizers to MDIs with spacers (https://www.cdc.gov/coronavirus/2019-ncov/hcp/infection-control-recommendations.html).

Increased drug delivery by nebulizers is possible by the use of breath actuation, which coordinates nebulization with inspiration and essentially turns the nebulizer off during expiration, or by the use of breath enhancement, which uses the patient's inspiratory flow through the nebulizer to increase drug delivery (e.g., LC Star, Pari; Medicaid Ventstream, Medicaid, Ltd.).[28]

VIBRATING MESH NEBULIZERS

These devices provide an alternative to jet nebulizers for delivery of larger quantities of drugs such as antibiotics or proteins. Instead of bulky compressors, the devices use either vibrating mesh or crystal, extrude the liquid through tiny holes (microextrusion), or use a combination of both vibration and microextrusion.[29] Vibrating mesh systems vary in durability, cost, and the relative ease with which they can be cleaned between treatments. They usually have a lower dead volume in the nebulizer chamber than the conventional jet nebulizers, resulting in increased efficiency and shorter treatment times.[30] The increased efficiency increases the risk of overdosage if a patient has previously been using a less-efficient device. Some aerosol devices are customized for specific drug approval; for example, different iterations of the eFlow device (Pari) deliver specific aerosolized antibiotics to *cystic fibrosis* (CF) patients more rapidly than conventional nebulizers. The Aerogen vibrating mesh nebulizers are used to deliver bronchodilators more rapidly than conventional nebulizers and to deliver novel medications (insulin, Dance Biopharm Holdings) now in clinical trials. Another vibrating mesh device (I-neb) has been adapted to administer inhaled prostacyclin (Ventavis, Actelion), a drug with a relatively narrow therapeutic index, to treat pulmonary hypertension. The I-neb device uses adaptive aerosol technology, monitors the breathing pattern of a patient, and provides feedback to the patient to facilitate a more consistent inhaled dose. As discussed earlier, a "slow" inspiration reduces inertial impaction and thus decreases oropharyngeal deposition, allowing distal delivery of particles that would otherwise deposit in the oropharynx during tidal breathing. "Smart" nebulizers that provide feedback to patients can help patients adjust their breathing pattern to achieve more consistent dosing.[30,31]

SOFT MIST AEROSOLS

The Respimat Soft Mist (Boehringer Ingelheim) device is approved for delivery of short-acting and long-acting bronchodilators. It is a small hand-held device significantly different in design from a conventional pMDI or DPI.[32] The drug is stored in a liquid reservoir, and an aerosol is generated when a precisely calibrated volume of liquid is forced through a nozzle to produce two jets of liquid that converge at a defined angle. The velocity of the resulting aerosol mist is much slower than that generated by a pMDI and is thus both less likely to impact on the upper airway and easier to coordinate with a patient's inspiration. The efficiency is higher than with a conventional DPI. For example, the nominal dose of tiotropium is 18 μg by DPI but only 5 μg with the Respimat.

The challenge of demonstrating clinical equivalence of the same drug from two devices is illustrated by a regulatory requirement to perform a 17,000-patient head-to-head safety study comparing the safety of DPI to Respimat in patients with COPD. No difference in mortality was observed in this large study, which was performed to evaluate a potential mortality signal with soft mist aerosols in earlier smaller studies.[33] Improved drug delivery by soft mist aerosols will decrease the amount of drug needed per dose. However, the small metered volume limits this device to high-potency drugs.

PRINCIPLES OF ASSESSMENT OF DELIVERY SYSTEMS

Assessing effects of an aerosolized drug requires the understanding of three major factors: the characteristics of the aerosol delivery system, the quality of the aerosol produced, and the quantification of deposition within the lungs.[34] Quantification of deposition is performed in vivo, is time consuming and costly, and involves some degree of risk and uncertainty to the patient. The other two components of the aerosol delivery process can be well characterized and studied in vitro. The field of aerosol delivery has advanced significantly in the last 10 years so that aerosol delivery characteristics and the quality of the aerosol can be significantly optimized on the bench before exposure to patients.

THE INHALED MASS

The term *inhaled mass* has been coined to represent the amount of drug that passes the lips of the patient, that is, *drug delivery* to the patient, to distinguish this quantity from drug *dose* or drug *deposition* (see later). Bench models are useful in identifying the parameters that define the inhaled mass for different devices and experimental conditions[11] (eFig. 13.1). A mouthpiece is replaced by a filter that captures the aerosolized particles, and a breathing device (piston ventilator) can duplicate conditions such as routine tidal breathing and mixing of ambient air with the nebulized particles. The quantity of drug captured on the inspiratory filter represents the inhaled mass. The setup can be modified to incorporate a ventilator circuit and endotracheal tube to duplicate aerosol delivery in the setting of mechanical ventilation and determine the impact of the brand of nebulizer, humidification, ventilator settings, and nebulizer fill volume on drug delivery before proceeding to clinical studies.[35,36]

DEPOSITION

The term *deposition* implies a "dose" to the patient. The term *deposition* needs to be further refined in a given situation (e.g., oropharyngeal vs. parenchymal deposition, or central vs. peripheral deposition within the lung). Each of these terms may be important depending upon the disease entity to be treated. Obviously, the measurement of the actual deposition requires an in vivo experiment. However, deposition can be estimated based on parameters measured in vitro as shown in Equation 4:

$$\text{Deposition} = \text{Inhaled mass} - \text{Exhaled mass} \quad [\text{Eq. 4}]$$

Clinical deposition studies using gamma scintigraphy can be used to assess the regional distribution of drug deposited in the patient.[37] Deposition can be divided into extrapulmonary deposition versus pulmonary deposition, whereas pulmonary deposition can be further subdivided into deposition in central airways versus in peripheral air spaces. A radiotracer (usually technetium) is mixed with the study drug and aerosolized and inhaled. It is important to confirm that the size distribution of the radiotracer and the drug are identical.[35] The drug deposition images on the gamma camera are superimposed on an outline of the patient's lung, obtained by a separate radioactive gas study,[38,39] or a transmission image from an external standardized radioactive source.[30,40] Quantification of lung deposition can be obtained by expressing the radioactivity detected in the lungs as a percentage of the radioactivity initially placed in the nebulizer (see Fig. 13.1).

Several other methods can be used to assess deposition. A mass balance technique uses filters placed near a patient's mouth to measure the amount inhaled and, in a separate experiment, the amount exhaled, with the difference being what was deposited in the patient.[38,39] However, this technique does not provide information on the specific compartment in which the material was deposited. Pharmacokinetic approaches include comparison of blood levels of aminoglycosides obtained after an intravenous calibration standard to blood levels obtained after inhalation[41] or the urinary concentrations of pentamidine after inhalation.[42,43] Oral charcoal can be used to block the absorption of swallowed pharyngeal deposited drug so that blood levels will be due entirely to drug absorbed through lung deposition and absorption.[16]

STRATEGIES TO OPTIMIZE DEPOSITION OF THERAPEUTIC AEROSOLS

The determinants of aerosol deposition apply to both therapeutic and environmental inhaled particles. To optimize deposition of therapeutic aerosols, a number of strategies have been developed.

GETTING PARTICLES PAST THE OROPHARYNX

In clinical studies, predicting penetration of aerosol beyond the oropharynx and subsequent lung deposition is a major criterion for device selection. Deposition estimations are often based on particle size measurements defined by in vitro characterization of the aerosol produced by a given device. During tidal breathing, most investigators would expect aerosols with particles smaller than 5 μm to be deposited primarily in the lungs (the fine particle fraction). Conventional aerosol delivery devices (DPI, pMDI, and jet nebulizer) emit particles with a wide range of sizes and velocities (i.e., polydisperse particles). It is estimated that the combined effect of particle size, particle inertia, and the geometry of the oropharynx result in upper airway deposition ranging from 30–90% of the total deposition in the patient. Only nebulizers producing particles with particularly small MMAD (e.g., AeroTech II, Biodex; MMAD, 1.0 μm) bypass the upper airways (5% oropharyngeal deposition in adults).[44] In children, the smaller oropharyngeal airways make the task more difficult.[45] In children, compared to adults, significantly more drug may be deposited in the oropharynx and less in the lung (Fig. 13.2).

CONTROL OF BREATHING PATTERN AND AEROSOL DEPOSITION

In normal subjects, the pattern of breathing is the most important factor affecting aerosol delivery and deposition.

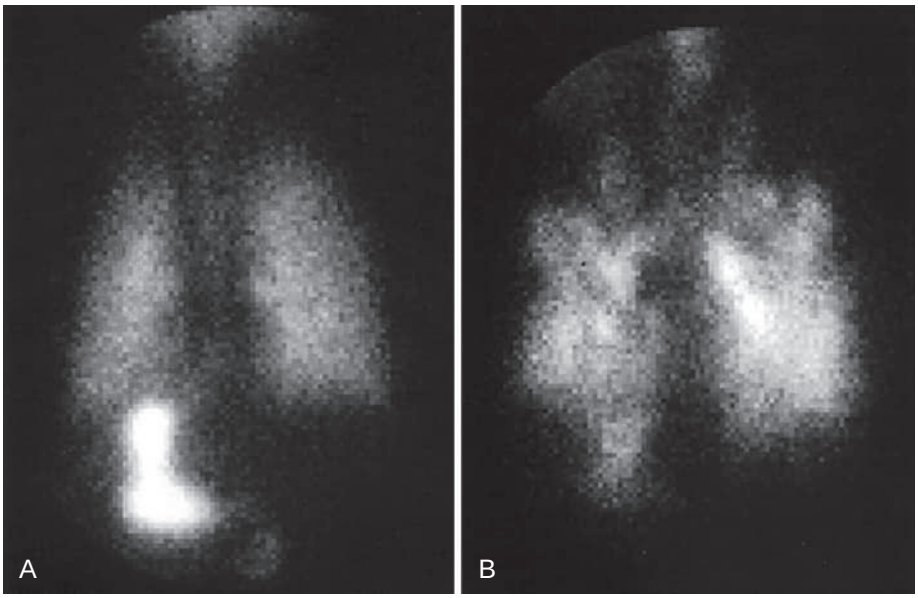

Figure 13.2 Differences in aerosol deposition between adults and children illustrated by deposition scans from patients with cystic fibrosis breathing the same aerosol. (A) A 9-year-old boy with 48% upper airway deposition, which appears in the stomach after a drink of water. (B) A 31-year-old woman demonstrating a more peripheral but patchy distribution but minimal activity in stomach. Aerosols that can readily bypass the upper airways of an adult frequently deposit in the oropharynx of a child. (From Diot P, Palmer LB, Smaldone A, et al. RhDNase I aerosol deposition and related factors in cystic fibrosis. *Am J Respir Crit Care Med.* 1997;156:1662–1668.)

How the patient breathes can affect the performance of the device, the particle distribution, the penetration of particles past the oropharynx, and the deposition within the parenchyma. Earlier studies suggested that much of the variation in parenchymal deposition was related to differences in airway geometry among subjects. However, variability in deposition among subjects appears well controlled if the pattern of breathing is controlled. As tidal volume increases and breathing frequency decreases, the time of inspiration is prolonged (e.g., slow and deep inspiration). As demonstrated in Figure 13.3, changes in the deposition fraction can largely be accounted for by changes in the tidal volume and breathing frequency.

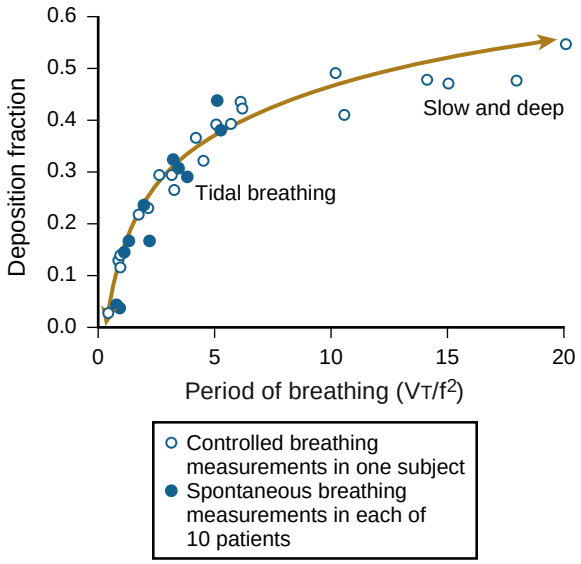

Figure 13.3 Deposition in the lungs is primarily determined by the pattern of breathing. Deposition fraction of 2.6-μm monodisperse particles from one subject during controlled breathing (*open circles*) and from 10 patients during spontaneous breathing (*solid circles*). The deposition fraction is the fraction of inhaled particles that deposited in the subject; breathing pattern is illustrated by the period of breathing (tidal volume divided by breathing frequency squared [V_T/f^2]). Typical tidal breathing is found near the origin; slow and deep inspirations appear away from the origin. The deposition fraction varied over a wide range, but changes in the deposition fraction were accounted for by changes in the breathing parameter. (Modified from Bennet WD, Smaldone GC. Human variation in the peripheral airspace deposition of inhaled particles. *J Appl Physiol.* 1987;62:1603–1610.)

EXPIRATION AND PROBLEMS WITH AEROSOL DEPOSITION

Particles that pass through the oropharynx during inspiration enter the central airways and traverse them without difficulty because lobar and segmental bronchi are generally widely patent during inspiration. Then the particles enter alveoli, with a few depositing by sedimentation and, like cigarette smoke, the bulk of the aerosol is exhaled. Deposition is controlled by sedimentation in small airways and is influenced by local geometry and, to a strong degree, by the residence time (period of breathing). In normal subjects the particles that do not deposit during inspiration are largely exhaled completely.

In obstructive lung disease, maximal expiratory flows are diminished. With moderate disease, maximal flows can be superimposed on tidal breathing; as the disease progresses, maximal flows can be reduced even further. Therefore, it is common to observe that patients are often breathing on their maximal expiratory flow-volume curves even during quiet, tidal breathing[46] (eFig. 13.2). In these patients, the flow-limiting segments exist in the same airways as in normal subjects during forced expiration but, in patients with obstructive lung disease, they form during every tidal breath. Therefore, in patients with obstructive lung disease, deposition in the peripheral

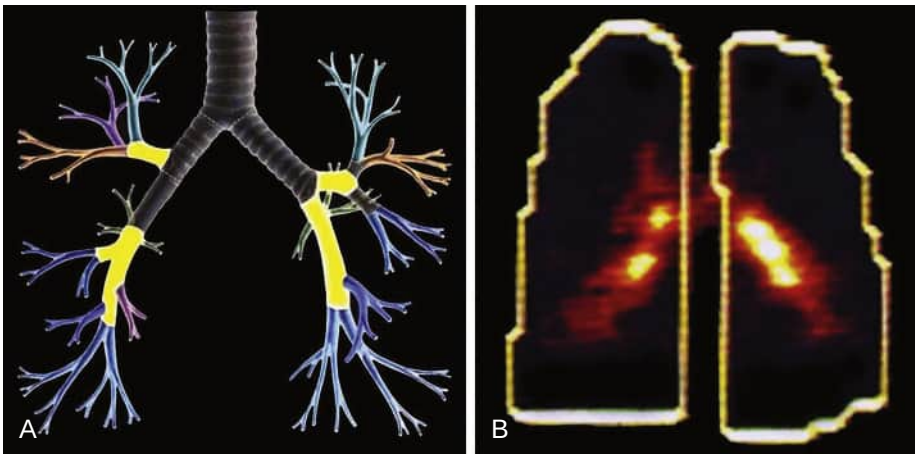

Figure 13.4 Particles are deposited preferentially at sites of flow-limiting segments in patients with COPD. Sites of flow-limiting segments (A, *yellow*) and the corresponding deposition image (B) in a patient with severe COPD (*posterior view*). (Modified from Smaldone GC. Advances in aerosols: adult respiratory disease. *J Aerosol Med*. 2006;19:36–46.)

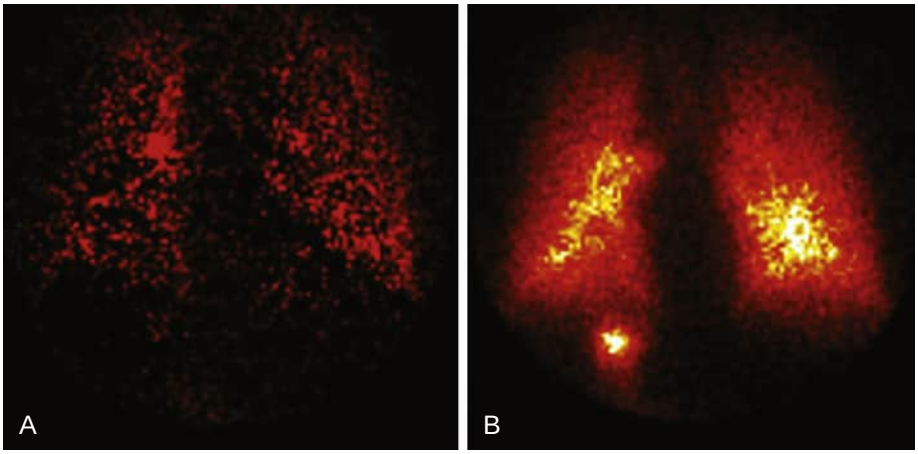

Figure 13.5 Slow and deep breathing improves aerosol delivery and deposition. Deposition scans from a normal subject after breathing from I-neb, a breath-actuated vibrating mesh nebulizer in which particles are generated only during inspiration. (A) After 20 breaths of normal tidal breathing. (B) Scan repeated after 3 breaths of very slow and deep inspiration (~7 sec/breath). For slow and deep breathing, deposition was 50 times more efficient per breath, a combination of enhanced delivery and more efficient deposition. (Courtesy G.C. Smaldone, unpublished data.)

lung poses a significant challenge because deposition of aerosol is enhanced during expiration at sites of flow limitation (Fig. 13.4). Based on these physiologic considerations, peripheral deposition of aerosol in these subjects would be favored by a slow prolonged inspiration with a breath of sufficiently long duration to promote deposition by settling and to minimize the particles available to the airways during expiration.

For many aerosol applications, inhaling particles slowly and deeply solves the problems outlined previously. A slow inhalation will minimize oropharyngeal deposition. Slow inspiration reduces particle inertia and allows inhalation of larger particles that would have deposited in the oropharynx during tidal breathing. Subsequently, commercial applications of these principles have combined slow and deep inspiration with direct mechanical feedback to the patient for particles of relatively large MMAD, resulting in more efficient delivery to the more distal airways (Fig. 13.5).[47]

ADDITIONAL FACTORS INFLUENCING DEVELOPMENT OF THERAPEUTIC AEROSOLS

In addition to efforts to bypass the oropharynx and optimize lung deposition, other factors influence the design of therapeutic aerosols. Some of these factors are disease related and others relate to specific patient populations.

INHALED PROTEINS

Most approved inhaled products are small molecular chemical entities. Larger molecules can also be inhaled, such as proteins,[48] including inhaled recombinant DNase for CF, *granulocyte-macrophage colony-stimulating factor* (GM-CSF) for alveolar proteinosis,[49] interferon-γ for pulmonary fibrosis,[50] and recombinant alpha$_1$-antitrypsin for emphysema.[51] Development programs of inhaled proteins face

additional challenges. Preclinical evaluation is important to ensure that the nebulization process does not denature these agents. In addition, the structure of these proteins may be modified to decrease risk of being denatured by the proteolytic enzymes present in airway secretions. In addition to their use as therapeutic agents for pulmonary disease, the inhaled route of administration can be used to take advantage of the large alveolar surface area of the lung to facilitate systemic absorption. To date, the most extensively studied class of inhaled protein has been inhaled insulin,[52,53] based on the rationale that patients may prefer the inhaled administration to subcutaneous injection. Despite two products achieving U.S. regulatory approval, inhaled insulin has not been widely adopted by prescribers or patients. Some patients, especially those with preexisting airways disease, complained of cough after inhalation. Hypoglycemia was observed particularly in smokers in whom systemic absorption appeared to be accelerated. In rare cases, there was evidence of a decline in diffusion capacity, an observation that may result in requirements for extensive testing of future inhaled proteins. There are also theoretical concerns that exposure to insulin could accelerate the growth of lung cancer in populations at increased risk for cancer.

Despite these concerns, with the rapid progress in development of new biologic treatment modalities (fusion proteins, RNA silencing, gene therapy, etc.), it is likely that many of these agents will be evaluated for their potential to be delivered by inhalation.

ASTHMA

It is important that commercial formulations of inhaled corticosteroids, the mainstay of maintenance therapy for asthma, have a low oral bioavailability.[54–56] Because many delivery systems for inhaled corticosteroids have high levels of oropharyngeal deposition (up to 80% with pMDIs and DPIs), it is crucial that, when this oropharyngeal-deposited drug is subsequently swallowed, its systemic exposure be kept as low as possible. The oral bioavailability of beclomethasone, one the oldest of the inhaled corticosteroids, is approximately 20%, fluticasone is approximately 1%, and mometasone less than 1%, whereas ciclesonide does not become activated until it deposits in lung tissue.[56] However, even if there is no oral bioavailability, there can still be systemic exposure when inhaled corticosteroids are absorbed from the lung itself, either from the alveoli or airways. Alveolar deposition may give rise to more systemic exposure than airway deposition because particles depositing in the alveoli are not removed by mucociliary clearance and because the alveoli may be more permeable to diffusion than the airway. There are some pharmacodynamic data that, when fluticasone is administered to both normal subjects and asthmatics, the asthmatic subjects have less systemic absorption, likely due to the more proximal deposition in the asthmatic subjects because of reduced airway caliber.[57] Most pharmaceutical manufacturers have therefore tried to target airway deposition while avoiding alveolar deposition. This appears reasonable because asthma is thought to be an airways disease. Some investigators, however, have suggested that there may be an alveolar inflammatory component in asthma, thus suggesting that alveolar deposition may be beneficial.[58] Nonetheless, this remains a minority viewpoint.

Targeting the airways in asthma is complicated by the polydisperse nature of therapeutic aerosols. Making the average aerosol diameter smaller reduces oropharyngeal deposition but increases the amount of alveolar deposition. A low oral bioavailability is more important for polydisperse aerosols with larger MMADs to minimize systemic exposure from swallowed drug. Systemic exposure to inhaled corticosteroids can lead to short-term growth suppression in children, decreases in bone mineral density, and possibly an increase in cataracts.[54–56] The potential role of inhaled corticosteroids in cataract development is confounded by concomitant use of intermittent systemic corticosteroids, smoking, and ultraviolet light exposure.[58,59] However, an epidemiologic study from Australia that controlled for use of systemic and ocular steroid use found an association between inhaled steroids and the prevalence of cataracts.[60] Theoretically, cataracts could also be due to inadvertent spraying of aerosol into the eyes in addition to systemic exposure.

Although the search continues for the ideal method of delivery for inhaled steroids to patients with asthma, advances in drug design, formulation, and delivery now provide a wider array of options to the clinician. However, no delivery system can be considered to be intrinsically superior to all others. The delivery system should be judged instead by its ability to optimize the pharmacokinetic properties of the drug, most notably oral bioavailability, and by its suitability for the target subpopulation of asthmatics.[4]

CYSTIC FIBROSIS AND NON–CYSTIC FIBROSIS BRONCHIECTASIS

CF, the most common fatal single-gene genetic disease in Europe and North America, is associated with severe bronchiectasis.[61,62] Antibiotics such as tobramycin, aztreonam, and polymyxin are commonly inhaled for treatment. Antibiotics usually require the aerosolization of several hundred milligrams of medication. Jet nebulizers or vibrating mesh devices are usually needed to deliver such a large mass of drug. However, only approximately 10% of the dose is deposited in the lungs because of inefficiencies of the delivery systems. Nevertheless, inhalation can be effective at targeting the drug to the lung and avoiding systemic side effects and toxicity. For example, aminoglycosides, when given systemically, have poor airway penetration and are limited by renal and ototoxicity. Inhalation of tobramycin, on the other hand, can result in sputum levels two orders of magnitude higher than those associated with systemic delivery. For the purposes of inhalation, tobramycin was reformulated without the preservative present in the intravenous preparation.[63] Aztreonam was reformulated with a lysine side chain for inhalation instead of the methionine side chain found in the intravenous formulation, to reduce the risk for airway irritation.[64]

In addition to antibiotics, inhalation of mucolytics (recombinant DNase) and osmotic hydrating agents (hypertonic saline and mannitol) are of benefit in patients with CF.[65] The multiplicity of inhaled treatments, however, is likely to reduce patient adherence[66] and therefore creates the need to explore the use of devices with shorter treatment duration.

Because the key physiologic finding in the lungs of patients with CF is bronchiectasis with chronic bacterial infection, inhaled antibiotics effective in treating CF (tobramycin, aztreonam) were also evaluated in non-CF bronchiectasis. However, the antibiotics were much less effective in demonstrating efficacy, and the primary end points were not met in most trials. Recently, randomized trials evaluating a novel formulation of inhaled ciprofloxacin produced inconsistent evidence of efficacy.[67] The reasons for the disappointing outcomes in non-CF bronchiectasis are not understood but may include greater heterogeneity of disease severity, lower bacterial load, lower frequency of exacerbation, and more localized lobar distribution of disease in the non-CF patients.[68–72]

IDIOPATHIC PULMONARY FIBROSIS

Idiopathic pulmonary fibrosis (IPF) is a progressive interstitial lung disease with a peak incidence of onset in the sixth decade. Although there are two approved orally administered agents (pirfenidone and nintedanib) demonstrated to slow the rate of decline in lung function, there remains an unmet need for more effective and better tolerated medications.[73] There has been a recent increase in interest in exploring the inhaled route for IPF therapeutics.

In addition to the challenges facing all development programs in IPF (an incomplete understanding of the pathogenesis and requirement for relatively large and prolonged trials), an inhaled agent faces additional challenges: the need to target alveolar deposition rather than airway deposition, a requirement for a well-tolerated aerosolized drug in patients prone to debilitating cough, and a need to address marked regional variation in distribution, given that IPF is usually more severe in the lower lobes. Current inhalational strategies under development include an agent already approved through the systemic route (e.g., inhaled pirfenidone[74]), agents that were not effective by systemic administration (e.g., interferon-γ[50]), and agents not previously evaluated (e.g., galectin).[75]

PULMONARY MYCOBACTERIAL INFECTIONS

The emergence of resistance to first-line antibacterial agents has prompted a search for novel therapeutic approaches for pulmonary mycobacterial diseases, including tuberculosis and nontuberculous mycobacterial lung disease.

Several candidate aerosolized agents for treating multidrug-resistant tuberculosis have been formulated, with the majority of new formulations being dry powders.[76,77] Most antitubercular drugs require high doses (tens to hundreds of milligrams), rendering them unsuitable for many conventional DPIs, necessitating development of high-volume DPI systems.[77] Administration of aerosolized drugs to patients with multidrug-resistant tuberculosis may induce cough and increase risk of infecting other individuals in the vicinity of the treatment area. Several novel formulations have advanced to Phase I tolerability studies in healthy volunteers but, to date, none has advanced to registration trials of tuberculosis. In addition to development of direct antimicrobial agents, there was a preliminary evaluation of adding inhaled interferon-γ as adjunctive therapy with evidence of increased clearance of infection, but this has not been further advanced.

For treatment of nontuberculous mycobacterial infection, aerosolized amikacin as a liposomal formulation received preliminary approval from the U.S. Food and Drug Administration for treatment of *Mycobacterium avium* complex, to be used as an adjunct with standard oral combination therapy. The rationale for the use of a liposomal formulation is that airway macrophages are believed to ingest liposomes, which could potentially enhance intracellular killing of organisms.[77]

DELIVERY OF INHALED MEDICATIONS TO YOUNG CHILDREN

See ExpertConsult.com for a brief discussion of pediatric considerations.

DELIVERY OF THERAPEUTIC AEROSOLS TO THE NASAL MUCOSA

Diseases of the nasal mucosa are now being treated by an increasing list of aerosolized medications, including corticosteroids, anticholinergics (ipratropium bromide), antihistamines, cromoglycate, saline, and decongestants. In general, these formulations use large particle sizes to maximize nasal deposition. Manual pumps that produce large, relatively low-velocity particles are being used as an alternative to high-velocity pMDIs. There are isolated reports of nasal perforation with high-velocity inhalers,[86] and patients should be advised to direct the spray in the direction of the ipsilateral ear and away from the nasal septum. In addition, directing the inhaler against the lateral wall of the nares reduces the risk for epistaxis (caused by irritating the septum by delivery in a medial direction) or headache (caused by stimulating the olfactory nerve by delivery in a vertical direction). In severe allergic sinusitis, the mucosa may be so congested that a short course of systemic corticosteroids may be needed to allow penetration of aerosolized therapy. Prolonged use of topical decongestant sprays may lead to rebound hyperemia and intractable nasal congestion. In certain cases, systemic administration of decongestants may be preferable. For children who use inhaled corticosteroids for perennial rhinitis, formulations with low oral bioavailability, such as fluticasone, mometasone, and ciclesonide, are preferable and reduce the risk for growth suppression.[87,88]

Nasally inhaled mometasone is an effective topical treatment for chronic rhinosinusitis with nasal polyps.[89] However, obstruction of the nasal passages with large polyps can impair delivery, and surgical implants of topical corticosteroids have been developed as adjuncts to nasal inhalation.[90] In addition, a novel device for fluticasone (Xhance, Optinose) has been approved to treat chronic rhinosinusitis with nasal polyps. This device has a mouthpiece and a nasal piece for drug delivery. Delivery of corticosteroids to the nasal mucosa is achieved when the patient *exhales* through the device. Exhalation releases drug from the device and directs it to the nose. With exhalation, the soft palate also separates the nasal cavity from the mouth, and the drug is sent into one nostril, filling the nasal cavity and exiting via the other nostril.[91]

Asthma is common in children, and delivery of aerosols poses special challenges. There is a need for cooperation and coordination with breathing pattern and a need to generate a threshold inspiratory flow. Thus those younger than 4 years cannot use a DPI. At this age, children may benefit from face masks with either holding chambers or jet nebulizers. Children between 4 and 6 years of age can use a pMDI, but it should be used with a valved holding chamber (spacer) because they will have difficulty coordinating with the respiratory cycle.[78] After age 6 years, children can be taught how to use a pMDI without a spacer, although the use of spacers should continue to be encouraged.

For young children with asthma, nebulized treatment with a suspension of budesonide is an effective and well-tolerated alternative.[79] It should be noted that nebulizers tend to be less effective at aerosolizing suspensions than solutions, and clinicians are advised to prescribe budesonide only with the brand of nebulizers used in the clinical trials of this product.

Physicians should be aware that face masks affect MDI–valved holding chambers differently than they affect nebulizers. For masks used with MDI–valved holding chambers, there should be a tight seal between the face mask and the face. Leaks around the face mask limit the exchange of tidal air with air in the chamber, thereby reducing the inhalation of aerosol by the patient. For face masks used with nebulizers operated with compressors, the face mask can be kept filled with particles in spite of leaks because the compressor flow can exceed the minute ventilation of the child.[80] When used with a mask, nebulizers result in less variability in inhaled mass than does the MDI with valved holding chambers.[80] Because of these nuances with drug delivery in children, clinically relevant in vitro modeling should include mimicking a child's breathing pattern and placing the face mask on a model of a child's face.[78]

It is impossible to seal a mask perfectly to the face. Small leaks, particularly along the nasal-labial fold, create high-velocity jets of aerosol directed to the eyes. Deposition of drugs in the eye may be clinically relevant.[81] Using breathing manikin models and radioactive aerosols, as shown in eFig. 13.3A, nebulized drug can be directed into the eyes using tight-fitting face masks. This effect can be reversed if masks are designed so that linear velocity in the region of the leaks near the bridge of the nose is reduced (see eFig. 13.3B).[78] Although we commonly think that the face mask is a simple conduit for aerosol particles, human deposition studies in young children have confirmed that face masks commonly cause facial deposition, consistent with the findings outlined earlier using the pediatric manikin. In eFig. 13.4, all the commercial face masks were associated with facial deposition.[82] Even though the incidence of cataract in children receiving inhaled corticosteroids is very low, there is epidemiologic evidence linking inhaled steroid use in adults to an increased risk for cataract.[83]

Finally, children often will not cooperate with face mask therapy. An MDI–valved holding chamber combination will fail to deliver aerosol unless the mask is pressed and sealed to the face. A nebulizer combined with a mask may not be tolerated (Video 13.1). Jet nebulization affords the possibility of blow-by therapy, in which the mask is held away from the face and the aerosol directed toward the patient, often in an attempt to minimize patient irritation. Blow-by has been criticized as ineffective,[83] but recent studies demonstrated that drug delivery can be maintained using properly tested combinations of nebulizer and face mask[84] (eFig. 13.5). A newer mask called the soother mask incorporates a pacifier in the mask (Video 13.2) that can relax some children.[85] The physician must work with the patient to decide on the proper device-drug combination when prescribing aerosolized drugs.

AEROSOL DELIVERY DURING MECHANICAL VENTILATION

Bronchodilators, either delivered by nebulizer or pMDI, are commonly used to treat patients with airway obstruction while they undergo mechanical ventilation.[92] The use of a pMDI is feasible provided certain conditions are met.[93] For example, delivery during mechanical ventilation must be synchronized with inspiration, and a spacer/holding chamber must be used with a pMDI. Not all holding chambers are equivalent in efficiency, and different brands are not necessarily interchangeable. For a therapeutic effect, it is essential that a dose-escalation protocol be used because it may be necessary to use doses far in excess of those used in ambulatory patients. Hence, objective evidence on response to treatment (e.g., peak airway pressure, dynamic compliance) and toxicity (tachycardia, arrhythmias) should be sought. In endeavoring to maximize delivered doses, however, it must be remembered that the efficiency of pMDI delivery decreases significantly if there is no pause between serial actuations and if the synchronization with inspiration is suboptimal.[94] Nebulizers are less dependent on timing or technique; modeling has shown similar delivery from nebulizers or pMDIs when both are optimally used.[94] Despite limitations, delivery of bronchodilators through ventilator circuitry is a mainstay of treatment of patients with obstructive diseases.

There is also interest in delivering aerosolized antimicrobial therapy via nebulizers in patients with purulent tracheobronchitis and ventilator-associated pneumonia.[92,95,96] The dose delivered in this setting can be highly variable, and delivery can be subtherapeutic if certain factors are not optimized. Similar to drug delivery in spontaneously breathing patients, drug delivery in intubated patients is highly dependent on the breathing pattern.[92] Delivery can be improved by reduced humidification (temporary discontinuation of humidification doubles the delivered dose by reduced rainout of medication), coordination with inspiration, and the appropriate selection of delivery system. If these factors are optimized, delivery can be consistently achieved at doses that approximate those delivered in spontaneously breathing subjects.[35,36] Single-center studies suggested that use of aerosolized antibiotics decreased rate of ventilator-associated pneumonia and other signs and symptoms of respiratory infection, facilitated weaning, reduced bacterial resistance, and decreased use of systemic antibiotics.[92,95–97] However, recent large-scale clinical trials of aerosolized antibiotics in the intubated critically ill patient have failed to reach clinical end points. These trials did not disclose how the delivery of the test drugs was ensured. Controlling drug delivery during mechanical ventilation is a requirement for the success of any future studies.

In conclusion, once technical factors have been identified and optimized, efficient delivery of aerosolized medications to patients undergoing mechanical ventilation is readily attainable.[36]

DIAGNOSTIC RADIOAEROSOLS

The radiolabeled ventilation-perfusion scan is an important clinical tool for detection of pulmonary emboli. Perfusion is measured by injecting radiolabeled macroaggregates of protein that impact in capillaries, whereas ventilation is evaluated by inhalation of a radioactive gas or aerosol. Discrepancies between perfusion abnormalities and ventilation abnormalities are used to assess the probability of pulmonary emboli. The measurement of ventilation should ideally be performed by using a radioactive gas (e.g., xenon-133). However, xenon-133 has a relatively long half-life and needs to be trapped after exhalation. In response to these concerns, aerosols labeled with technetium were developed on the assumption that aerosols would distribute similarly to the gas. In general, that assumption is true if submicron aerosols are inhaled, but it must be remembered that aerosol behavior is not identical to that of a gas.[98] For example, patients who are tachypneic with high inspiratory flows and who have airway obstruction will have central "hot spots" (see Fig. 13.5). This limits the use of the aerosol techniques in certain patient groups.

MUCOCILIARY CLEARANCE AND DISEASE

Mucociliary clearance is the primary mechanism to remove inhaled insoluble particles in the normal host. Inhaled particles that deposit in the ciliated airways are trapped in a blanket of mucus. This free-floating mucus gel overlies the respiratory epithelium. The equilibrium between the osmotic modulus of the gel and brush layers maintains an adequate periciliary depth to facilitate optimal movement of cilia. Mucus is transported proximally by the rhythmic beating of the cilia (a fast, forward-power stroke and slower, backward-recovery stroke) to the pharynx, where it is swallowed, a process called mucociliary clearance.[3] Mucociliary clearance in healthy subjects is usually completed within 24 hours of deposition.[3] The mucus path can be followed using radiolabeled aerosols (Video 13.3).

Ciliated respiratory epithelial cells are most numerous in the tracheal and lobar bronchi and decrease progressively in more distal airways. Secretory cells are also more numerous in proximal airways; goblet cells produce thick carbohydrate-rich secretions, whereas other cells produce more serous secretions. In diseases such as chronic bronchitis and bronchiectasis, the number of goblet cells increases in more distal airways. Airway secretions are also produced by submucosal glands. The latter are lined by mucinous and serous epithelial cells and become hypertrophic and hyperplastic in chronic bronchitis and other types of chronic airway inflammation.

Mucociliary clearance can be impaired by intrinsic defects in ciliary function, which can be congenital (primary ciliary dyskinesias[99]) or acquired (tobacco smoking, influenza).[3] Mucociliary clearance impairment can also be due to changes in the quantity and composition of airway secretions (chronic bronchitis, CF).[3] If the mucociliary apparatus is significantly impaired, secretions are cleared predominantly by coughing. If both mucociliary clearance and cough clearance become ineffective, retained secretions produce both physical obstruction of the airway lumen and amplification of the underlying inflammatory processes.

Primary ciliary dyskinesia is a genetically heterogeneous disorder of the dynein arms or other components of the cilia, resulting in loss of ciliary movement[99] (see Chapter 69).

In the absence of ciliary movement, these patients will have mucus stasis and develop bronchiectasis and sinusitis. In males, ciliary dyskinesia is also associated with infertility due to immotile spermatozoa. Patients may also have abnormalities of visceral organs, such as situs inversus and dextrocardia due to the role of monociliated cells during embryogenesis.[99]

CF management is complicated by impaired mucociliary clearance.[61,62] The mucus becomes dehydrated and less easy to clear because of an impaired chloride channel (*cystic fibrosis transmembrane conductance regulator* [CFTR]), which leads to reduced secretion of chloride into the airway lumen.[62] In addition, an increase in epithelial sodium channel activation due to inflammatory proteases promotes absorption of sodium from the lumen, further exacerbating the dehydration of mucus. Adequate hydration of airway secretions is essential for optimal mucociliary clearance. Hypertonic saline, when administered to the airways of patients with CF, creates an osmotic gradient that draws water into the airway lumen; this treatment is associated with decreased rates of acute exacerbation.[100] Inhaled mannitol is another inhaled osmolyte for patients with CF and has been approved by some regulatory authorities.[101] The airway secretions in CF not only contain mucus secreted by the airway but also consist of DNA and actin from dead neutrophils. Inhaled recombinant DNase can facilitate clearance of secretions and destroy neutrophil extracellular traps, the extracellular DNA released by neutrophils at sites of infection.[102] The development of drugs that modulate CFTR receptor function has significantly improved the clinical course of CF.[103] In addition to demonstrating improvements in standard clinical end points, such as lung function and exacerbation frequency, modulation of CFTR function improves the homogeneity of aerosol deposition and increases clearance of radiolabeled mucus[104,105] (see also Chapter 68).

In chronic bronchitis, there is hypertrophy and hyperplasia of the submucosal glands as well as an increase in the number of goblet cells and the presence of goblet cells in more distal airways, compared to normal. The resultant mucus has an increase in the mucous component relative to the serous component, which means that the mucus layer is relatively dehydrated.[106] In addition, chronic airway inflammation is associated with an increase in secretion of the mucin MUC5AC, which may have proinflammatory properties promoting a positive feedback cycle of inflammation and hypersecretion.[107] Both of these mechanisms contribute to impaired mucociliary clearance in chronic bronchitis.

In patients who die of status asthmaticus, the airways at autopsy are filled with inspissated mucus.[3] The mucus in patients with status asthmaticus has abnormal viscoelastic static properties that may be due in part to excessive cross-linking of mucus glycoproteins.[108,109] In addition, increases in the type 2 cytokine interleukin-13 in asthma promotes a hypersecretory phenotype and impairment of mucus transport.[110,111] Mucociliary clearance is severely impaired acutely in patients with status asthmaticus but can recover within weeks.[112]

In conclusion, mucociliary clearance is impaired in asthma, chronic bronchitis/COPD, CF, bronchiectasis, and primary ciliary dyskinesia and may be an index of disease severity.[113–115] Serial measurements of mucociliary clearance by tracking radiolabeled particles can be useful in measuring pharmaceutical enhancement of mucociliary clearance as, for example, in the sustained effects of hypertonic saline in CF[100] and CFTR modulation.[104] In addition to addressing the primary pathophysiologic defect, such as inflammation, CFTR dysfunction, or dehydration, efforts are being undertaken to develop novel inhaled agents to optimize rheologic properties of airway mucus and improve clearance.[116]

ALVEOLAR CLEARANCE

Particles deposited in the alveoli are cleared by alveolar rather than mucociliary clearance.[117,118] Particle solubility affects clearance in alveoli. Soluble particulates may be absorbed through the thin membrane of the peripheral air spaces. Insoluble particulates, however, tend to be phagocytosed by alveolar macrophages. Their metal content influences the free radical–generating properties of the particle and can promote inflammation, especially when the particle is delivered to the lysosomes. Lysosomes have a very low pH designed to kill microorganisms, but the low pH may promote solubility of transition metals, such as ferrous iron, and therefore be proinflammatory.[119]

Cells primed by one type of inflammation (e.g., by tobacco smoke or endotoxin) may be more reactive to a second stimulus from an inhaled particulate. Excessive particulate exposure can lead to overloading of alveolar macrophages, which can be proinflammatory even with relatively nonreactive particulates. Macrophages migrate to regional lymph nodes, and inhalational exposure to certain particles can be characterized by a distinctive adenopathy (e.g., silicosis and its eggshell calcifications).

The alveolar deposition and clearance of nanoparticles (<100 nm diameter) differ from the clearance of larger but fine particles that deposit in alveoli.[120,121] Nanoparticles are more likely to be absorbed through the alveolar epithelium, resulting in systemic exposure. Environmental nanoparticles arising from combustion tend to be unstable and aggregate into larger particles. However, engineered nanoparticles may be less likely to aggregate and may pose an increased risk of systemic exposure and potential health hazards.

Key Points

- The likelihood that a particle will deposit in an airway depends on the physical characteristics of the particle, the gas flow transporting the particle, and the airway anatomy. The greater the mass, the faster the flow, and the more narrow the airway, the greater is the potential for inertial impaction. For the clinician, forces that define inertial impaction are most important in determining upper airway deposition and the passage of aerosol into the lungs.
- Once particles pass through the upper airways, deposition in the lungs is largely defined by sedimentation. This process is dependent on a subject's breathing pattern, both the depth and the duration of the breath.
- Holding chambers ("spacers") reduce pharyngeal deposition and reduce the need for precise coordination to get the full dose.
- Face mask seal and design can be important factors in the delivery of clinical aerosols in pediatric populations.
- The design of dry powder inhaler devices has evolved to meet the key objective that emitted dose should not vary significantly within a clinically relevant range of inspiratory flow so that intersubject delivery remains consistent and thereby meets stringent regulatory standards for the quality and reproducibility of the emitted aerosol.
- Compared to systemic therapy, medicines can be delivered by aerosol in greater concentration to the target organ, the lung, with fewer side effects, but most traditional jet nebulizers are inefficient and deliver less than 10% of the drug to the lung.
- Directing the jet of high-velocity nasal sprays laterally avoids the side effects of epistaxis when directed medially, and headache when directed vertically.
- Serial measurements of mucociliary clearance may be of value in evaluating novel medications.

Key Readings

de Boer AH, Hagedoorn P, Hoppentocht M, Buttini F, Grasmeijer F, Frijlink HW. Dry powder inhalation: past, present and future. *Expert Opin Drug Deliv*. 2017;14(4):499–512.

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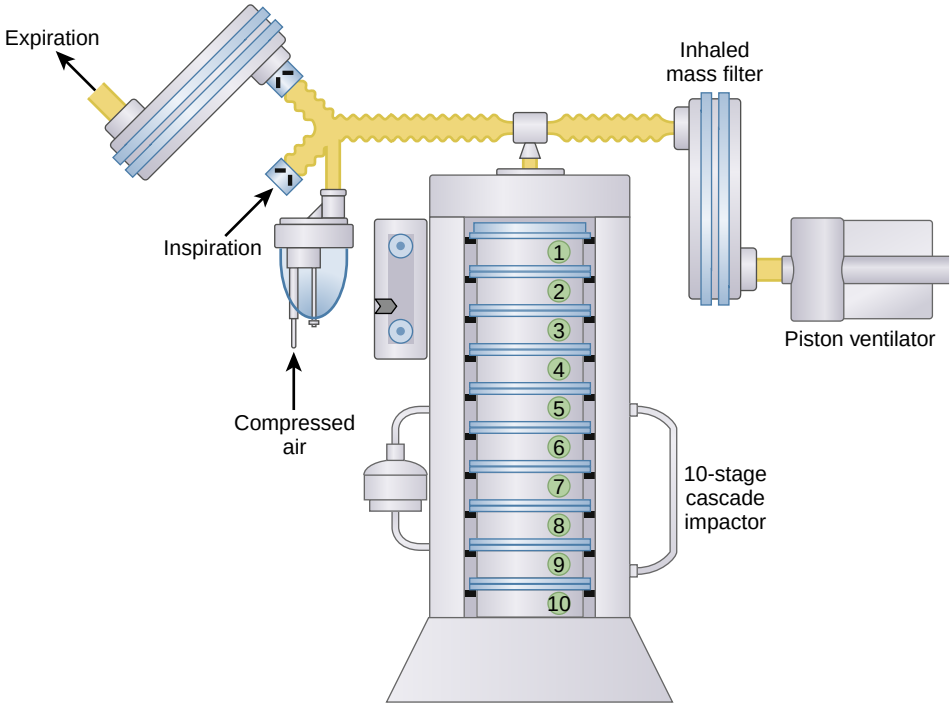
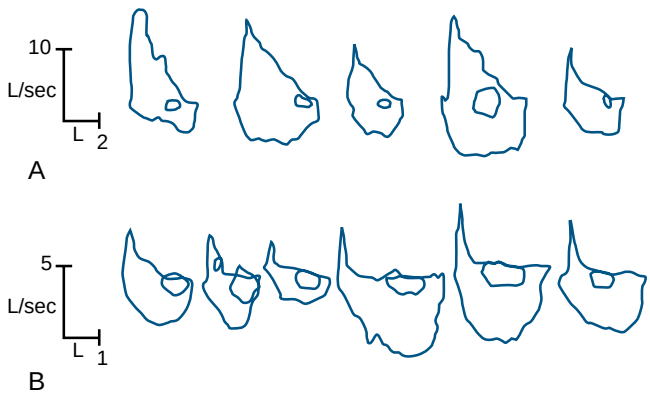
Complete reference list available at ExpertConsult.com.

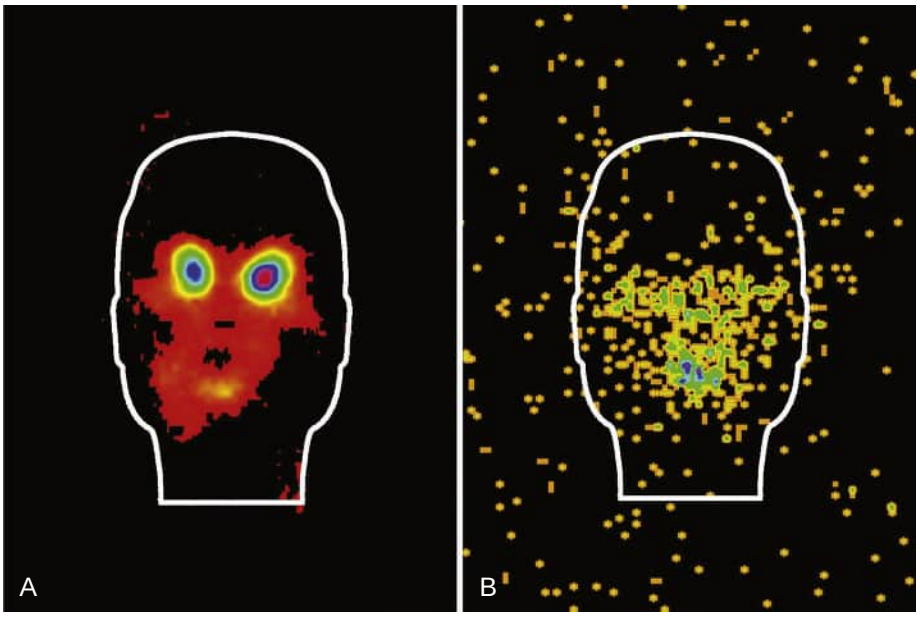
eFIGURE IMAGE GALLERY



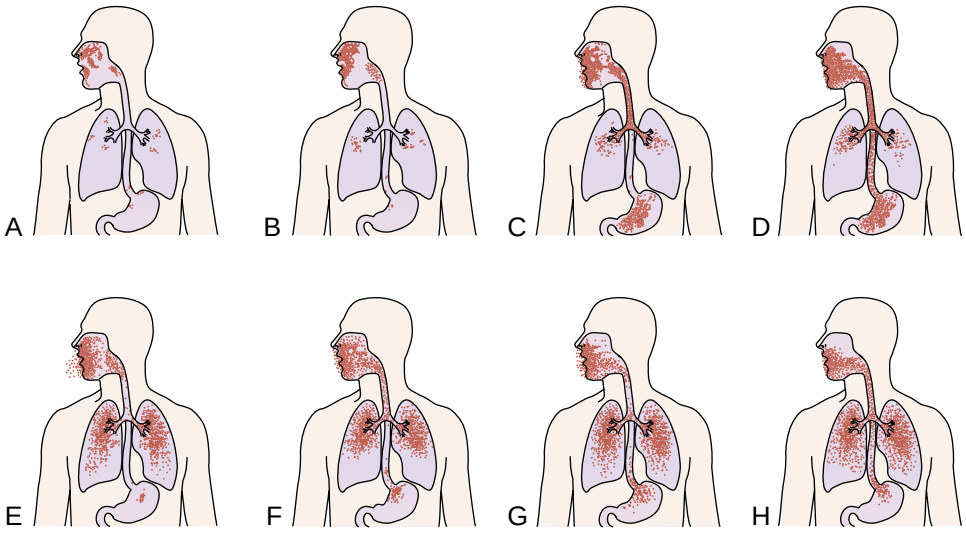
eFigure. 13.1 Modern testing of aerosol delivery systems can measure inhaled mass and particle distribution for a nebulizer. Breathing patterns are defined by settings on the piston ventilator. Particles presented to the "patient" (the ventilator) are captured on the inhaled mass filter. In separate experiments, the cascade impactor measures inspired aerosol. These methods have been useful in simulating patient exposures. (Modified from Smaldone GC. Drug delivery via aerosol systems: concept of "aerosol inhaled." *J Aerosol Med.* 1991;4:229–235.)



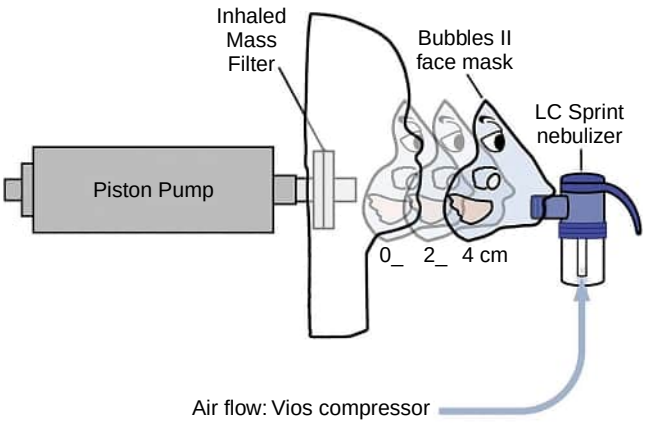
eFigure 13.2 Tracings of maximal flow and tidal flow versus volume for normal subjects (A) and patients with severe obstructive lung disease (B). Note the difference in size of the axes for the two panels (*y*-axis: flow range from 0–10 or 0–5 L/sec; *x*-axis: volume range from 0–2 or 0–1 L, respectively). (B) Tidal loops are superimposed on maximal flow-volume curves. (Modified from Smaldone GC, Messina M. Flow-limitation, cough and patterns of aerosol deposition in humans. *J Appl Physiol.* 1985;59:515–520.)



eFigure 13.3 Serial gamma camera images of a breathing pediatric manikin face after a nebulizer treatment with a face mask. (A) Facial and eye deposition after nebulizer treatment with a Pari nebulizer and tight-fitting face mask. In this study, more drug was deposited on the face than was delivered to the lungs. (B) Reduced deposition with the same nebulizer and prototype face mask designed to reduce particle acceleration in the region of the eyes. The face mask was modified by opening the area near the nasolabial fold, preventing a tight seal and reducing the jet of aerosol directly into the eyes. (Modified from Smaldone GC. Assessing new technologies: patient-device interactions and deposition. *Respir Care.* 2005;50:1151–1160.)



eFigure 13.4 Drug deposition of radiolabeled salbutamol in young children. For all combinations of devices and face masks, the images clearly show facial deposition. This figure illustrates in vivo the important principles demonstrated in the manikin study described in eFig. 13.4. Efficient lung delivery requires quiet breathing. Coaching is an important part of nebulized therapy. (A) Inhaling from a pressurized *metered-dose inhaler* (MDI)/spacer through a non–tightly fitted face mask. (B) Inhaling from a nebulizer through a non–tightly fitted face mask. (C) Inhaling from a pressurized MDI/spacer through a tightly fitted face mask, crying during inhalation. (D) Inhaling from a nebulizer through a tightly fitted face mask, crying during inhalation. (E–F) Inhaling from a pressurized MDI/spacer through a tightly fitted face mask, quietly inhaling. (G–H) Inhaling from a nebulizer through a tightly fitted face mask, quietly inhaling. Deposition on the face is apparent, especially for the tight-fitting masks (C–H). These principles apply to all patients treated with face masks. (Modified from Erzinger S, Schuepp KG, Brooks-Wildhaber J, et al. Face masks and aerosol delivery in vivo. *J Aerosol Med.* 2007;20[suppl]:S78–S84.)



eFigure 13.5 A blow-by system can be used for drug delivery with children who cannot cooperate. A ventilated pediatric manikin face is shown during a nebulizer treatment using a face mask. The mask is held away from the face in an attempt to prevent patient withdrawal seen in Video 13.1. Although blow-by is controversial, recent studies have shown that reasonable quantities of aerosol can be delivered (e.g., to the inhaled mass filter) using this technique, provided the proper device-mask combination is used. (From Mansour MM, Smaldone GC. Blow-by as potential therapy for uncooperative children: an in-vitro study. *Respir Care.* 2012;57:2004–2011.)

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14 PLEURAL PHYSIOLOGY AND PATHOPHYSIOLOGY

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INTRODUCTION

The pleural space is bounded by two membranes, the visceral pleura covering the lung and the parietal pleura covering the chest wall and diaphragm. Pleural pressure is subatmospheric and ensures inflation of the lung. In the normal state, it is now believed that liquid moves into the pleural space along the pressure gradient and across a leaky mesothelium; the low protein concentration suggests that the liquid originates as a filtrate from a systemic circulation, as opposed to a pulmonary filtrate which has a higher protein concentration. The liquid normally exits via the parietal pleural lymphatics, which open directly onto the pleural space. These lymphatics can increase their rate of liquid clearance approximately 30-fold and thus can accommodate large variations in the entry of pleural liquid without allowing accumulation. Therefore, the most likely explanation for the accumulation of an abnormal volume of pleural liquid (i.e., a pleural effusion) is if *both* the pleural liquid entry rate increases and the pleural liquid exit rate decreases. The pleural liquid may originate from a wide variety of sources and reach the pleural space because of (1) the subatmospheric pleural pressure, (2) the leaky pleural membranes, and (3) the high capacitance of the pleural space. Depending on the protein and *lactate dehydrogenase* (LDH) concentrations of the liquid, these effusions can be categorized initially as transudates or exudates. This chapter covers these points in more detail, focusing on how liquid normally moves into and out of the pleural space and how disturbances of the normal pattern allow the accumulation of a pleural effusion.

Other related chapters cover the anatomy of the pleural membranes (see Chapter 1) and the embryology of the pleural space (see Chapter 2) and the clinical information about pleural effusions in general (see Chapter 108), pleural infections (Chapter 109), and pleural malignancy (Chapter 114). In addition, pneumothorax, chylothorax, pleural fibrosis, and hemothorax are covered in Chapters 110 through 113.

FUNCTION

The visceral and parietal pleural membranes cover the lung and the chest wall, respectively, and meet at the hilar root of the lung. In the sheep, an animal with a pleural anatomy similar to humans, the surface area of the visceral pleura of one lung, including that invaginating into the lung fissures, is similar to that of the parietal pleura of one hemithorax, approximately 1000 cm^2.[1] The normal pleural space is approximately 10 to 30 μm in width, although it widens more at its most dependent areas.[1] It has been shown that the pleural membranes do not touch each other and that the pleural space is a real, not a potential, space (see Fig. 1.21).[1]

It is likely that the primary function of the pleural membranes is to allow extensive movement of the lung relative to the chest wall. If the lung adhered directly to the chest wall, its expansion and deflation would be more limited. Encased in its slippery coat, the lung, although still coupled mechanically to the chest wall, is able to expand across a breadth of several intercostal spaces. Nonetheless, in clinical and experimental studies, obliteration of the pleural space by pleurodesis via talc or surgical procedures has not been associated with abnormalities in overall lung function,[2–4] although there may be minor differences in regional lung function with changes in the distribution of air flow.[5] When there is pleural thickening, there may be measurable decreases in lung ventilation or blood flow to the affected lung and also, to some degree, to the opposite lung as well.[6] Thus, abnormalities of lung function may result more from pleural fibrosis than from obliteration of the pleural space alone (see Chapter 112).

The visceral pleura may also provide mechanical support for the lung: contributing to the shape of the lung, providing a limit to expansion, and contributing to the work of deflation. Because the submesothelial connective tissue is continuous with the connective tissue of the lung parenchyma, the visceral pleura may help to distribute the forces produced by negative inflation pressures evenly over the lung. In this way, overdistention of alveoli at the pleural

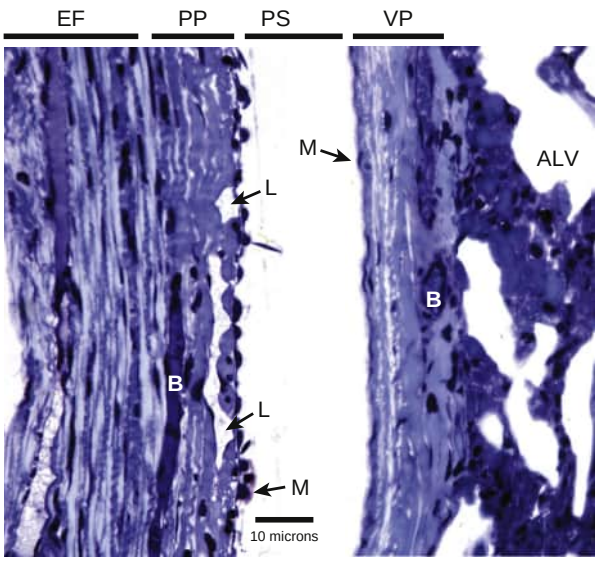

Figure 14.1 Light micrograph showing the parietal and visceral pleurae of the sheep, an animal with a pleural anatomy similar to that of humans. The two pleural membranes are positioned side by side at a distance of 20 μm, which represents an average width of the pleural space (PS).[1] On the left, the parietal pleura (PP) lies between the pleural space and the endothoracic fascia (EF). Within the loose connective tissue of the parietal pleura are blood microvessels (B) from the intercostal arteries and lymphatic lacunae (L), which open into the pleural space via stomata. On the right, the visceral pleura (VP) lies between the pleural space and the alveoli (ALV). The blood supply is via the bronchial arteries (B), which drain into pulmonary veins. (From Staub NC, Wiener-Kronish JP, Albertine KH. Transport through the pleura: physiology of normal liquid and solute exchange in the pleural space. In: Chrétien J, Bignon J, Hirsch A, eds. *The Pleura in Health and Disease*. New York: Marcel Dekker; 1985:174-175.)

surface may be avoided, lessening the chance of rupture and pneumothorax.

Another function of the pleural space may be to provide a route by which edema can escape the lung.[7] As has been shown in several experimental studies of either hydrostatic or increased-permeability lung edema[8,9] and summarized in this review,[10] edema fluid can and does move from the lung into the pleural space. In this way, the pleural space can function as an additional safety factor protecting against the development of alveolar edema. Seen in this way, the formation of transudative effusions in patients with *congestive heart failure* (CHF) reflects the movement of edema from the lung to a space where its effects on lung function are relatively small (see discussion of effusions from CHF later).

ANATOMY

PLEURAL MEMBRANES

The pleural membranes are smooth glistening coverings for the constantly moving lung. Overlying each pleural membrane is a single cell layer of mesothelial cells. These cells, the most numerous cell of the pleural space, have a variety of functions important to pleural biology.[11] Mesothelial cells can secrete and organize extracellular matrix proteins, phagocytose particles, produce fibrinolytic and procoagulant factors, and secrete neutrophil and monocyte chemotactic factors that may be important for inflammatory cell recruitment into the pleural spaces. The mesothelial cells also produce cytokines such as transforming growth factor-β, epidermal growth factor, and platelet-derived growth factor, cytokines important in pleural inflammation and fibrosis.

On the mesothelial cell surface are microvilli. Although microvilli presumably exist to increase surface area for metabolic activity, the function of these prominent features is unknown. Mesothelial cells produce hyaluronan but not mucin, express keratin microfilaments, stain positively for calretinin and mesothelin, and fail to stain with epithelial-specific antibodies (Ber-EP4, B72.3, Leu.M1, and CEA), all features important for histochemical and immunohistochemical identification of the cells in pleural effusions.[12,13]

The mesothelial cells lie on a thin basement membrane overlying a region of connective tissue containing mostly collagen and elastin. The parietal pleural thickness is relatively constant in an individual and among species, whereas the visceral pleural thickness varies greatly. In a single individual, the visceral pleura varies from a thinner layer at the cranial region to a thicker layer at the caudal region.[14] Among mammalian species, the visceral pleura thickness also varies, from a "thin" pleura without a separate blood supply, as seen in small mammals, to the "thick" pleura with a bronchial arterial circulation, as seen in humans (see Fig. 1.31). Analysis of the constituents of the visceral pleura has shown that there is more collagen relative to elastin than is found in the lung parenchyma, a finding consistent with a structural role for the pleura.[15] This connective tissue layer contains blood vessels and lymphatics and joins with the connective tissue of the lung. The submesothelial tissue has been shown to have mechanical strength and to contain various growth factors supporting cell growth, suggesting that mesothelium could function as a repair and regenerative platform.[16] There is also evidence that mesothelial cells floating freely in the pleural liquid are viable and can adhere to denuded areas of the pleura to contribute to repair.[17]

BLOOD SUPPLY

The parietal pleura is supplied by intercostal arteries (Fig. 14.1).[18] In humans as well as in other large mammals with a "thick" visceral pleura, the visceral pleura is supplied by the bronchial circulation, which drains, not into systemic veins, but into pulmonary veins (Fig. 14.1).[14] The drainage route via pulmonary veins may have contributed to earlier confusion about whether the visceral pleural blood supply was from a systemic (bronchial) or pulmonary circulation. Thus, both pleuras in humans have a systemic circulation, although the visceral pleural circulation may have a slightly lower perfusion pressure than the parietal pleural intercostal circulation because of its drainage into a lower pressure venous system.

LYMPHATICS

If one injects carbon particles into the pleural space as a visible tracer of lymphatic drainage pathways, one later finds that the carbon has been taken up into lymphatics on the parietal side, not the visceral side (Fig. 14.2; also see Fig. 1.22C). The visceral pleura has extensive lymphatics, but they do not connect to the pleural space.[14] The parietal

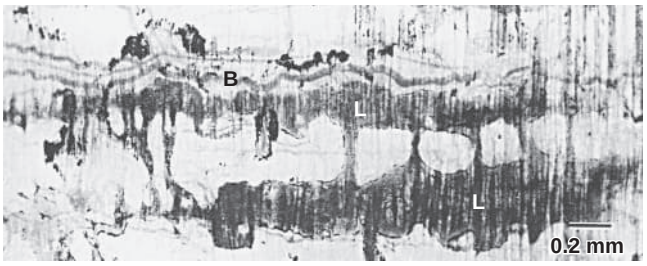

Figure 14.2 Macroscopic photograph of lymphatic lacunae in the parietal pleura over an intercostal space. Carbon particles were instilled into the pleural space to label the draining lymphatics. When looking down on the pleura, the lymphatic lacunae (L) appear as broad cisterns. (Original magnification ×39.) B, blood vessel. (From Albertine KH, Wiener-Kronish JP, Staub NC. The structure of the parietal pleura and its relationship to pleural liquid dynamics in sheep. *Anat Rec*. 1984;208:406.)

pleural lymphatics connect to the pleural space via stomata, openings of 2 to 12 μm in diameter formed by discontinuities in the mesothelial layer where mesothelium joins to the underlying lymphatic endothelium (see Fig. 1.22A–B).[19–21] Although lymphatics were known for some time to be important in drainage of liquid, protein, and cells from the pleural space,[22] the connection between the pleural space and the lymphatics could not be identified until the advent of scanning electron microscopy, at which time the existence of stomata was confirmed in rabbits and mice.[19] Lymphatic stomata have since been demonstrated in many other species, including monkeys[23] and humans.[24] Although their size has been reported to vary from 1 to 6 μm in rabbits, mice,[19] and sheep[18] to 3 to 12.5 μm in monkeys[23] and humans,[24,20] the reported size is probably a minimum and likely increases with expansion of the chest with ventilation. From the stomata, which can accommodate particles as large as erythrocytes, liquid drains to lacunae (spider-like submesothelial collecting lymphatics) and then to infracostal lymphatics, to parasternal and periaortic nodes,[25,26] to the right lymphatic duct and thoracic duct,[27] and into the central veins. The right lymphatic duct empties near the junction of the right internal jugular and right subclavian veins; the thoracic duct empties near the junction of the left internal jugular and left subclavian veins. The right lymphatic and the thoracic ducts likely drain all the lymph from the two hemithoraces. In animal studies, Courtice and Simmons showed that all the labeled protein introduced into the pleural space was drained by these ducts.[27] Interference with the drainage of lymph at these sites can be important clinically, as when large persistent transudative effusions arise when the brachiocephalic veins are thrombosed, stenosed, or otherwise compressed.[28–30]

NERVE SUPPLY

The parietal pleura contains sensory nerve fibers, supplied by the intercostal and phrenic nerves, and has long been thought to be the major site of pain sensation in the pleura. The costal and peripheral diaphragmatic regions are innervated by the intercostal nerves, and pain from these regions is referred to the adjacent chest wall. The central diaphragmatic region is innervated by the phrenic nerve, and pain from this region is referred to the ipsilateral shoulder. The visceral pleura has more recently been shown to have sensory nerve fibers that may participate in pain or other sensations such as dyspnea.[31] In addition, pleural adhesions may become innervated with pain fibers and contribute to postthoracotomy or postpleurodesis pain[32] (see also Chapter 38).

PLEURAL PRESSURE

The pleural pressure in humans is approximately −5 cm H_2O at midchest at functional residual capacity and −30 cm H_2O at total lung capacity.[33] If the compliance of the lung were to decrease, pleural pressures at the same lung volume would be more negative. In one study of patients undergoing thoracentesis, those with more negative pleural pressures had a smaller improvement in lung volume than those with less negative pressures, presumably reflecting the presence of underlying noncompliant lung.[34]

The pleural pressure is the lowest pressure of the body and can explain how liquids accumulating elsewhere can move along pressure gradients toward the pleural space. Combined with a leaky mesothelium (see later), this pressure gradient can pull liquid into the pleural space. The pressure can become more negative if the lung collapses or can become more positive if liquid or air enters the pleural space. However, as long as the lung is inflated, even partially, the pleural pressure must be subatmospheric. A corollary to that is, as long as the aerated lung is partially inflated, a large pneumothorax even with some mediastinal shift cannot be a tension pneumothorax.[35]

Although the pleural space pressure is subatmospheric, gases do not normally accumulate there. The sum of all partial pressures of gases in capillary blood is approximately 700 mm Hg, or 60 mm Hg below atmospheric (P_{H_2O} = 47, P_{CO_2} = 46, P_{N_2} = 570, and P_{O_2} = 40 mm Hg). The subatmospheric pressure of dissolved gases in capillary blood helps to maintain the pleural space free of gas and facilitates absorption of any gas that does enter the pleural space. Of note, to increase the gradient favoring absorption of gas from the pleural space (e.g., pneumothorax), the partial pressure of nitrogen in the blood can be lowered by having a patient breathe higher concentrations of inspired oxygen. The oxygen displaces alveolar nitrogen, thereby lowering the partial pressure of nitrogen in capillary blood; at the same time, the increased inspired oxygen does not increase the oxygen tension in capillary blood due to the threshold of absorption demonstrated by the plateau of the oxygen-hemoglobin dissociation curve. The net result is a decrease in the partial pressure of gases in capillary blood and an accelerated absorption of pleural gas.

PHYSIOLOGY OF THE PLEURAL SPACE

A consensus currently exists that the normal pleural liquid arises from the systemic pleural vessels in both pleurae, flows across the leaky pleural membranes into the pleural space, and exits the pleural space via the parietal pleural lymphatics[36,37] (Fig. 14.3). In this way, the pleural space is analogous to other interstitial tissues of the body, such as muscle or subcutaneous tissue.[22,36] Knowing how the

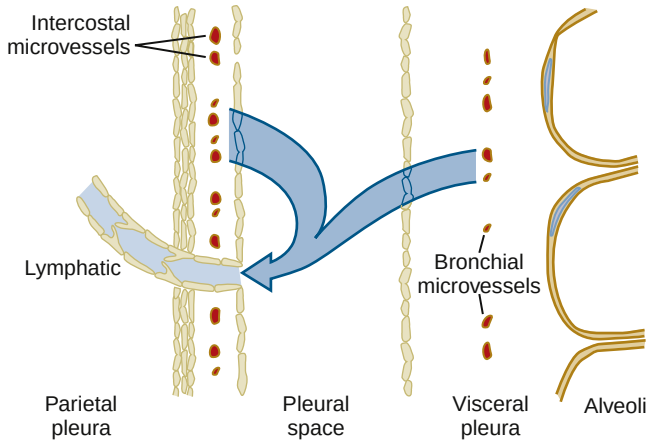

Figure 14.3 Schema showing normal pleural liquid entry and exit. The microvascular filtrate from the systemic microvessels in the parietal and visceral pleura flows across the leaky pleural mesothelial layers into the pleural space. The pleural liquid exits the pleural space via the parietal pleural lymphatic stomata. (From Staub NC, Wiener-Kronish JP, Albertine KH. Transport through the pleura: physiology of normal liquid and solute exchange in the pleural space. In: Chrétien J, Bignon J, Hirsch A, eds. *The Pleura in Health and Disease*. New York: Marcel Dekker; 1985:182.)

pleural liquid enters and exits is helpful in understanding how things go awry to allow effusions to form. This understanding also removes some of the mystery about how the pleural space functions, a mystery that arose in large part because of the difficulty of studying the narrow space without introducing inflammation or injury.

ENTRY OF NORMAL PLEURAL LIQUID

A Systemic Microvascular Source

There are two main lines of evidence that normal pleural liquid originates from the systemic circulation of the pleural membranes. For one, the low protein concentration of pleural liquid is more in keeping with systemic filtrate and is quite unlike pulmonary filtrates. For another, the protein concentration changes in concert with changes in systemic pressures, not pulmonic pressures.

Protein Concentration is Similar to Systemic Filtrates. The protein concentration of normal pleural liquid is low in sheep[38] and probably in humans, which implies sieving of the protein across a high-pressure, low-permeability microvascular barrier, as would be expected in systemic capillaries.[36] The protein concentration of sheep pleural liquid (1.0 g/dL) and pleural-to-plasma protein concentration ratio (0.15) is also much lower than found in filtrates from the low-pressure pulmonary vessels (protein concentration [4.5 g/dL] and ratio [lymph-to-plasma protein concentration ratio 0.69]).[39]

Protein Concentration Changes With Changes in Systemic Hydrostatic Pressures. With increases in filtration rates across a semipermeable membrane, proteins are retarded relative to liquid and electrolytes, and the protein concentration of the filtrate decreases. Therefore, if the systemic circulation is the source of pleural liquid, an increase in filtration pressure in the systemic circulation should manifest as a decrease in protein concentration of pleural liquid. Two studies demonstrate this concept. In the first study, spontaneously hypertensive rats were found to have pleural liquid with lower total protein and albumin concentration ratios (pleural/serum) than in the control, normotensive rats.[40] In the second study, sheep were studied at different stages of development. As mammals grow from fetuses to newborns to adults, systemic arterial pressure increases while pulmonary arterial pressure decreases. Thus, if pleural liquid arose from the systemic circulation, pleural liquid protein concentrations would be expected to decrease; if they arose from the pulmonary circulation, it would be the opposite. Indeed, pleural liquid protein concentration ratios decreased from fetuses (ratio 0.50) to newborns (ratio 0.27) to adults (ratio 0.15).[41] These physiologic observations support the concept that the systemic circulation is the source of normal pleural liquid.

The Parietal Pleura Is the Major Source

The pleural space is sandwiched between two adjacent systemic circulations: the intercostal arterial circulation of the parietal pleural and the bronchial arterial circulation of the visceral pleura. Although both likely contribute to normal pleural liquid, the major source is likely the parietal pleura, for the following reasons:

1. The parietal pleural circulation is constant among species, with an anatomy nearly interchangeable from small mammals to humans. However, the visceral pleura changes dramatically depending on whether the visceral pleura is "thick" as in humans, sheep, and most large animals or is "thin" as in smaller mammals like dogs, rabbits, and mice (see Fig. 1.31).[14] Thick visceral pleura has a systemic bronchial blood supply, whereas the thin visceral pleura has no circulation of its own and is fed by the underlying pulmonary circulation. Interestingly, the measured rates of pleural entry are similar among different species, even when their visceral pleurae are strikingly different.[53] Thus, the parietal pleura is the likely constant and major source of normal pleural liquid.
2. The parietal pleura microvessels are closer and have a higher microvascular pressure. Although both pleurae have a systemic circulation, as in sheep and humans, the systemic arteries of the parietal pleura are closer to the pleural space (10–12 μm) than are the systemic arteries of the visceral pleura (20–50 μm).[14,18,36] The parietal pleural vessels also likely have a higher microvascular pressure due to their drainage into systemic venules, whereas the visceral bronchial vessels drain into lower resistance pulmonary venules.[36]

Pleural Membranes Are Leaky

The pleural membranes are leaky, at least compared with the very tight membranes of the alveolar epithelium. Whether tested in vitro[42,43] or in situ,[44,45] the pleura offers little resistance to liquid or protein movement. Indeed, the peritoneal membrane, a closely related mesothelial structure, is leaky enough to permit peritoneal dialysis, with a relatively free movement of solutes and water. Studies of peritoneal transport have concluded that the barrier to flow into the peritoneal space is primarily the vascular endothelium; the peritoneal mesothelial surface is not a significant barrier.[46]

In addition, the mesothelium, although it may exhibit microvilli and express various transporters and aquaporins, has not been shown to participate in active fluid transport.[47,48] Such a function would not be expected in a cell without tight cell-cell junctions providing a barrier to the movement of ions. Nonetheless, one argument for active transport has been that the pleural liquid contains more bicarbonate than does the plasma.[49,50] However, this bicarbonate difference is likely explained by a passive phenomenon called the Donnan equilibrium, which describes how ions move to achieve electroneutrality. In a Donnan equilibrium, differences in protein concentrations (and their negative charges) alter ionic balances passively between two electrolytic solutions separated by a semipermeable membrane. With the lower protein concentration in pleural liquid than in plasma, there is less of a negative charge; the distribution of bicarbonate allows for a balance of negative charge across the pleural membrane.[51]

Entry From the Interstitium into the Pleural Space

Once the liquid filters across the systemic microvessels, it can then flow along the pressure gradient toward the pleural space and across the mesothelial layer into the pleural space. The pressure gradient exists from the high-pressure pleural systemic microvessels into the surrounding interstitial tissue and from there into the subatmospheric pleural space.[52]

The entry of pleural liquid is slow, as shown by radiolabeled albumin studies in which the equilibration into the pleural space of mammals was calculated without instrumenting the pleural space. As mentioned, the rates were surprisingly similar among different species, at approximately 0.01 mL/kg/hr. Such a rate would be equivalent to an entry of 0.5 mL/hr, or 12 mL/day in a 50-kg person.[38,53] Much higher rates previously reported were most likely due to the disturbance of the pleural space by the placement of catheters that led to inflammation and injury, thereby increasing the entry of liquid.

The Pleural Space Is Vulnerable to Liquid Entry

The pleural space is susceptible to the entry of liquid from any source of excess liquid in the body. The subatmospheric pressure in the space establishes a gradient for liquid entry. The leaky mesothelium allows the entry of the liquid and protein into the pleural space. The large surface area of the pleural space provides a large area for liquid flow. Finally, the space itself can accommodate a large amount of liquid without a rapid elevation in pressure (i.e., the space is compliant). Thus, perhaps the interesting question is why there are not more effusions. The key must lie in the mechanisms that remove liquid from the pleural space.

EXIT OF NORMAL PLEURAL LIQUID

Lymphatics Are the Major Exit Route

The majority of liquid exits the pleural space by bulk flow, not by diffusion or active transport. This is evident because the protein concentration of pleural effusions remains constant as the effusion is absorbed, as is expected with bulk flow.[54] If liquid were absorbed by diffusion or active transport, proteins would diffuse at a slower rate, and the protein concentration would progressively increase. (In fact, in *alveolar* liquid, protein concentration does increase as ions and water are actively absorbed across the alveolar epithelium, with protein absorbed more slowly by other routes.[55])

As a demonstration of the route of exit, sheep erythrocytes instilled into the sheep pleural space are absorbed intact and in almost the same proportion as the liquid and protein.[54] This indicates that the major route of exit is via holes large enough to accommodate sheep erythrocytes (~4.5 μm diameter). In addition, when chicken erythrocytes (identifiable because avian erythrocytes contain a nucleus) were instilled into a sheep pleural space, they could later be seen intact in the parietal pleural lymphatics.[18] The only possible exit for these particles is via the parietal pleural stomata into the pleural lymphatics. To visualize the lymphatic route of exit, ink, which consists of tiny particles of carbon, can be instilled into the pleural space, allowed to dwell for several hours, and then washed out. The absorbed carbon can be seen within the parietal pleural lymphatics, outlining them (see Fig. 14.2). Thus, a lymphatic route of clearance explains how protein can be absorbed without a change in concentration and how erythrocytes can be removed intact.

Lymphatics Have a Large Reserve Capacity

Importantly, the pleural lymphatics have a large reserve capacity for absorption. When artificial effusions were instilled into the pleural space of awake sheep, the measured exit rate (0.28 mL/kg/hr) was nearly 30 times the baseline exit rate (0.01 mL/kg/hr).[54] A reserve capacity of lymphatic absorption is a feature of lymphatics throughout the body; baseline lymphatic flow is slow, handling the normal low filtrate from microvessels, but increases briskly when faced with a higher filtration load.[56] Pleural lymphatics likely increase their flow for at least two reasons: because more liquid reaches them and because the pleural pressure rises slightly with the presence of more liquid. The ability of lymphatics to increase their rate of absorption and their large reserve capacity is probably a key feature in limiting the accumulation of excess liquid in the pleural space and anywhere in the body.

In earlier theories of pleural liquid absorption, it was postulated that the liquid diffused into the lung. However, as discussed earlier, diffusion cannot play a major role in absorption given the unchanging protein concentration of pleural effusions as they are absorbed. In addition, the pleural space has a pressure less than that of the lung, thereby inflating the lung. Thus, for liquid to enter the lung, the liquid would be moving against the pressure gradient, in effect flowing "uphill." Lymphatics, by virtue of their active pumping and one-way valves, perform the function of returning extravascular, interstitial liquid and protein to the venous system, for pleural liquid and also for interstitial liquids throughout the body. Both the intrinsic pumping of the collecting lymphatics and the extrinsic contractions of the chest wall muscles with ventilation can propel the lymph[27,57]; certain studies have attempted to distinguish the intrinsic and extrinsic mechanisms.[58]

Despite the large reserve capacity of lymphatic clearance, there is ultimately a maximum rate that limits absorption. Perhaps over time, when faced with increased loads, the lymphatics can increase their maximum absorption rate, as

by increases in the number of lymphatics or in their contractility. However, the maximal lymphatic capacity will establish an upper limit to the exit rate of pleural liquid.

PATHOPHYSIOLOGY OF THE PLEURAL SPACE

WHAT IS REQUIRED TO PRODUCE A PLEURAL EFFUSION?

Based on the understanding of the normal turnover of pleural liquid, we can consider what is required to create a pleural effusion. For sufficient pleural liquid to accumulate to form an effusion, it is most likely that both the entry rate of liquid must increase and the exit rate must decrease. If only the entry rate increased and the exit rate could increase normally, it would require a sustained entry rate more than 30 times normal to exceed the reserve lymphatic absorptive capacity and allow excess liquid to accumulate.[54] Alternatively, if the exit rate was completely stopped and the entry rate did not change, it would take more than a month at the normal entry rate of 12 mL/day to accumulate an effusion detectable by chest radiograph.[37] Thus, for the creation of persistent and clinically relevant pleural effusions, it is most likely that changes in both the entry and exit rates are required.

WHAT DISEASES COULD ACCOUNT FOR THIS?

Of course, one disease can simultaneously increase the entry rate of liquid and decrease the exit rate. For example, a pleural infection could increase liquid entry from leaky pleural vessels and could also interfere with the exit of liquid by obstructing the parietal pleural lymphatics with fibrin. As another example, central venous obstruction could increase liquid entry by increasing parietal systemic capillary pressures and also decrease the exit of liquid by increasing the downstream venous pressure into which the parietal pleural lymphatics must drain.

But then, one could imagine that two different disease processes might cooperate to form an effusion; these disease processes could also take place at different times. For example, one disease might first interfere with lymphatic function, thereby decreasing the lymphatic reserve. This could happen gradually without notice because there would still be enough reserve to handle the slow entry rate. Then, if a second disease led to an increase in the liquid entry rate, the increased liquid could then exceed the reduced lymphatic capacity and accumulate as an effusion. The concept that different diseases can cooperate to form an effusion has some clinical support; in a prospective study, as many as 30% of effusions could be shown to have more than one etiology.[59] The concept can also explain how one pleural effusion could have multiple etiologies,[60] especially if one condition renders the pleural space more susceptible to liquid accumulation from other causes. For example, the interaction of different disease entities may account for the presence of transudates in the setting of pleural malignancy, especially when another transudative process like CHF coexists with malignancy.[61–63]

MECHANISMS OF INCREASED ENTRY OF LIQUID

Liquid is constantly filtered out of the microvessels, entering the interstitial (i.e., the peri-microvascular) space and then being returned to the vascular space by lymphatics. There are three mechanisms by which flow of liquid out of microvessels is governed: the hydrostatic pressure gradient, the osmotic pressure gradient, and the permeability or leakiness of the microvascular barrier. These forces are classically described by the Starling equation:

$$\dot{Q} = Kf[(P_{mv} - P_{pmv}) - \sigma(\pi_{mv} - \pi_{pmv})]$$

where $\dot{Q}$ is the net liquid filtration rate, Kf is the filtration coefficient or the leakiness of the barrier to water and electrolytes, P_{mv} is microvascular hydrostatic pressure, P_{pmv} is peri-microvascular hydrostatic pressure, σ is the protein reflection coefficient describing the leakiness of the barrier to protein, π_{mv} is microvascular osmotic pressure, and π_{pmv} is peri-microvascular osmotic pressure. Mechanisms of increased liquid entry due to changes in these Starling forces and other mechanisms are shown in Table 14.1. Relevant clinical examples including hypothetical ones are listed.

Increased Filtration Pressure

Hydrostatic Pressures. An increase in microvascular pressure (i.e., capillary pressure) will increase the filtration

Table 14.1 Mechanisms of Increased Liquid Entry Into the Pleural Space

Mechanism	Starling Symbol	Relevant Clinical Examples
Increased filtration pressure	↑ P_{mv}	Increased systemic venous pressure, increased pulmonary venous pressure
	↓ P_{pmv}	Atelectasis, trapped lung, (chest tube suction)
	↓ π_{mv}	Hypoalbuminemia, plasmapheresis
	(↑ π_{pmv})	(Hemothorax, iatrogenic tube feeding instillation)
Increased microvascular permeability	↑ Kf, ↓ σ	Inflammation, injury, malignancy
Entry of other biologic liquids		Chyle, bile, urine, pancreatic secretions, cerebrospinal fluid, hemothorax
Entry of nonbiologic liquids		Intravenous fluids, tube feedings, peritoneal dialysis fluids

Hypothetical examples are shown in parentheses.
Kf, filtration coefficient or the leakiness of the barrier to water and electrolytes; P_{mv}, microvascular hydrostatic pressure; P_{pmv}, peri-microvascular hydrostatic pressure; σ, protein reflection coefficient describing leakiness of the barrier to protein; π_{mv}, microvascular osmotic pressure; π_{pmv}, peri-microvascular osmotic pressure.

across the microvascular barrier. The microvascular pressure is particularly sensitive to elevations of venous pressure and is less likely to increase with elevations of arterial pressure because of the regulation of precapillary resistance. (Note: actual precapillary sphincters have been described only in the mesentery.[64])

A decrease in the peri-microvascular pressure (i.e., the pressure around the capillaries) also increases the hydrostatic gradient for liquid filtration. In the case of pleural microvessels, the peri-microvascular pressure of pleural microvessels is influenced by the nearby pleural pressure. Thus, a decrease in pleural pressure decreases peri-microvascular pressure and increases filtration.

Osmotic Pressures. A decrease in the osmotic pressure of the blood within microvessels would be expected to increase filtration. The osmotic pressure of blood is driven mostly by serum protein, comprised primarily of albumin. However, the effects of hypoalbuminemia are likely minimal, because hypoalbuminemia usually develops gradually and is accompanied by a decrease in the peri-microvascular osmotic pressure and the osmotic gradient as filtration of low-protein liquid dilutes the interstitial protein concentration. Nonetheless, a low serum osmotic pressure likely decreases the threshold for other factors, such as the hydrostatic forces, to increase filtration. Lowering the threshold for filtration may explain why, although it is not commonly a sole cause for effusions,[65] hypoalbuminemia is commonly found in patients with effusions of all causes; it may increase the likelihood of effusions[66,67] and increase their size.[68]

In comparison to the gradual scenario just described, a rapid decrease in microvascular osmotic pressure could be expected to swing the balance quickly toward increased filtration and the formation of pleural effusions. Such a picture has been described in an interesting case in which plasmapheresis of a patient with Waldenstrom macroglobulinemia dropped the serum osmotic pressure rapidly and was quickly followed by the appearance of large bilateral pleural effusions.[69] Again, the effusions would be expected to be transient until a new osmotic balance reestablished itself.

An increase in peri-microvascular osmotic pressure would also be expected to increase filtration, although this phenomenon has not been described in the clinical setting. One could speculate that pleural and secondarily peri-microvascular osmotic pressure could increase following a hemothorax or the intrapleural instillation of a hyperosmolar or high-protein liquid such as a tube feeding solution. Of note, there has been a modification of the Starling equation in recent years, which has deemphasized the role of the peri-microvascular osmotic force.[70]

Table 14.2 Mechanisms of Decreased Liquid Exit via Parietal Pleural Lymphatics From the Pleural Space

Mechanism	Examples*
Decreased lymphatic stomata patency	Inflammation (granulomas, empyema, fibrin), malignancy
Decreased lymphatic contractility	Hypothyroidism, drug effect
Infiltration of lymphatics or lymph nodes	Malignancy
Increased venous (downstream) pressure	Central venous pressure elevation
Blocked lymphatic drainage	Central venous thrombosis
Reduced pleural (upstream) pressure	Atelectasis, trapped lung
Lymphatic disorders	Yellow nail syndrome

*Many of these examples also increase entry; see Table 14.1.

Increased Microvascular Permeability

Filtration Coefficient (Kf) and Reflection Coefficient (σ). When the permeability of the microvascular barrier increases due to inflammation, infection, or malignancy, the resistance to the filtration of liquid and electrolytes and to protein is lowered (i.e., there is an increase in Kf and a decrease in σ). With an increase in microvascular permeability, the rate of filtration of liquid, electrolytes, and protein increases even without any change in hydrostatic pressures. However, in addition to the change in permeability, inflammation may also increase the hydrostatic pressure by relaxing the precapillary resistance.[71] The combination of an increase in hydrostatic pressure in the setting of a leakier barrier greatly enhances filtration.

Other Biologic Liquids and Iatrogenic Sources. As mentioned, the Starling factors discussed above are relevant to all the circulations of the body, systemic and pulmonary, and increases in filtration anywhere can lead to increased interstitial liquid that can then migrate to the pleural space. In addition, pleural effusions can be composed of other biologic liquids, such as blood, urine, chyle, pancreatic secretions from a pseudocyst, bile, and cerebrospinal fluid. In addition, pleural effusions can be composed of nonbiologic liquids such as intravenous fluids or tube feedings (see Table 14.1).

MECHANISMS OF DECREASED EXIT OF LIQUID

As postulated earlier, the accumulation of an effusion likely requires not only an increase in the entry of liquid, but also a decrease in the exit rate by interference with lymphatic function. Otherwise, if lymphatic function was normal, the exit rate could increase approximately 30-fold rapidly and, in most cases, handle the increased entry of liquid.[54]

Lymphatic function may become impaired in many ways. There may be reduced patency of the parietal pleural stomata, inhibition of lymphatic contractility,[56] infiltration of the lymphatics or their draining parasternal lymph nodes, an increase in the downstream central venous pressure, a complete obstruction of the central vein into which they drain, a decrease in the pleural pressure against which they must pump, or primary lymphatic disorders (Table 14.2).[37] There are few studies on the rate of removal of liquid in humans; however, decreases in lymphatic clearance have been confirmed in patients with tuberculous and malignant effusions,[72] and in those with the yellow-nail syndrome, a disease of lymphatic function.[73]

As previously stated, for either transudates or exudates, interference with lymphatic function may contribute to the accumulation of the effusion. Nonetheless, because the exit of pleural liquid via lymphatics does not alter the

pleural liquid protein concentration, the protein concentration gives insight into the *formation* of the liquid, not its *removal*.[37]

CATEGORIES OF PLEURAL EFFUSIONS

Effusions can be categorized based on their protein concentration. Because the protein concentration is not altered by its removal by the lymphatics, the protein concentration of pleural effusions stays relatively constant during the life of the effusion. This feature allows protein concentration to be a useful biomarker; the protein concentration and its ratio with that of serum give information about the formation of the liquid. It is for this reason that effusions can be divided into transudates (protein concentration ratio (pleural/serum) < 0.5) and exudates (protein ratios > 0.5), which constitute part of Light's criteria.[74] Of course, LDH is also used as a biomarker for effusions but, because LDH is at high levels intracellularly, this marker is more useful as a marker of cell turnover and inflammation (see Chapter 108).[74]

Transudates

Transudates form by filtration of liquid across an intact microvascular barrier owing to increases in hydrostatic pressures or decreases in osmotic pressures across that barrier. Transudates generally indicate that the pleural membranes and their microvessels are not themselves diseased. Transudates may form from increased filtration across either the systemic or the pulmonary circulations. However, if the protein concentration is very low (pleural/serum ratio <0.1–0.2), the effusion is likely caused by either (1) liquids formed from CSF or urine that normally have very low protein and have migrated to the pleural space or (2) nonbiologic liquids such as intravenous fluids.

Exudates

Exudates arise from inflamed or injured microvessels in the pleura, the lung, or other tissues. Many exudates arise from direct pleural injury due to inflammation, infection, or malignancy. Other exudates, such as those associated with pneumonia, may arise from inflammation or injury to the lung, creating a high-protein lung edema that leaks into the pleural space. Exudates can also form when exudative liquid in the mediastinum (esophageal rupture or chylothorax), retroperitoneum (pancreatic pseudocyst), or peritoneum (ascites with spontaneous bacterial peritonitis or Meigs syndrome) enters the pleural space.

Pseudoexudates

Pseudoexudate refers to an effusion that presumably starts as a transudate and develops exudative characteristics following diuresis. Although a common concern, the creation of a pseudoexudate is likely uncommon.[75] By removing protein-free liquid, diuresis will increase the concentration of protein in all liquids of the body. However, that does not mean that the *ratio* of pleural protein to serum will necessarily increase. Studies of this phenomenon show that only a few effusions move from a transudative to an exudative category,[75] and these studies did not always control for the effect of multiple thoracenteses that themselves might have increased pleural protein concentrations.[76]

An effusion may be considered a possible pseudoexudate if the diuresis has been effective in removing salt and water, particularly if it has reduced the size of the effusion. Even then, diuresis should only account for a small change in protein ratio (pleural/serum). In other words, pleural effusions with clearly exudative pleural characteristics should be considered exudative and not readily labeled pseudoexudative. Dismissing a true exudate as a pseudoexudate might lead to missing diagnoses such as cancer, pulmonary embolism, and other serious clinical conditions. When there is doubt, these effusions should undergo a thorough workup for underlying causes of exudates.

Indeterminate Effusions

Indeterminate is an acceptable term to use when the protein ratio and/or LDH ratios are near their cutoff values, making it difficult to determine if the effusion is clearly a transudate or an exudate. In such a case, which can arise frequently, it is better to avoid categorizing the effusion, especially if it would be categorized as a transudate and falsely reassure the clinician about the absence of serious exudative conditions. It is worth remembering that protein concentration ratios described in Light's criteria are most accurate at the extremes, when they are clearly high or low. Ratios in the middle are less helpful.

One possible reason for ambiguity is worth keeping in mind—there may be more than one thing going on. In fact, there could be an underlying transudative process (e.g., CHF, hypoproteinemia) and a secondary exudative process (e.g., pneumonia, viral pleuritis). One could imagine then that the protein values could reflect contributions from both processes.[59]

MECHANISMS BY WHICH SPECIFIC DISEASES CAUSE PLEURAL EFFUSIONS

Congestive Heart Failure

The cause of most transudates, and likely the cause of most effusions, is CHF.[77] Thus it is particularly important to understand how these effusions develop.

These transudates now are thought to form from leakage of interstitial edema across the leaky visceral pleura into the pleural space.[8,10] It is worth noting that once interstitial edema reaches the interstitial spaces of the lung, collecting around the bronchovascular bundles to form what are called "cuffs," the edema is not in contact with the pulmonary lymphatics and is not cleared by them (Fig. 14.4).[78] This extravascular interstitial edema flows along the interstitial spaces to the mediastinum, where lymphatics are available, or to the pleural space.[52] In edematous lungs, subpleural interstitial pressure rises steeply, enhancing the gradient for edema flow into the pleural space.[79] Once at the visceral pleura (Fig. 14.5), the edema can cross a leaky mesothelium to enter the pleural space. Such flow from the edematous lung into the pleural space has been described in a variety of animal models of lung injury,[9,10] showing that this route of movement of edema is not specific to any particular type of edema.

The protein concentration of pleural effusions in the setting of CHF is around 3 gm/dL with a ratio of 0.3 to 0.4 to that of serum. Such a protein concentration is higher than the normal pleural liquid (ratio 0.15) and is more consistent with a pulmonary filtrate than a systemic filtrate.[8] The

movement of edema from the lung has been estimated in sheep experiments to account for up to 30% of the edema formed.[8] The pleural space may thus serve as a "safety factor" for clearance of interstitial edema from the lung, reducing the risk of alveolar edema.



Figure 14.4 A frozen edematous sheep lung cut in cross section and dissected to show bronchovascular cuffs. Interstitial edema in the lung first collects in interstitial spaces around the bronchi and vessels. (A) A cross section showing a bronchovascular "cuff" of interstitial edema. Note the surrounding alveoli are air-filled, showing that there is no alveolar edema. (B) A dissection of a cuff showing its extent along the bronchovascular bundle. Interstitial edema in this location is not accessible to pulmonary lymphatics and flows either to the mediastinum or to the pleural space. When these "cuffs" are sampled, the protein concentration matches that of the pleural effusion.[8] (Courtesy V. Courtney Broaddus, MD.)

When there are bilateral effusions, the right-sided effusion is often larger than the left. Given that the origin of the effusion is the edematous lung, a possible explanation may be that the right lung is larger and has more surface area for edema to move across than the left. In support of this idea, in studies in sheep, the lymphatic exit rate for pleural liquid was the same from the two hemothoraces[54]; however, the entry of liquid from the edematous lungs was greater on the right.[8]

By itself, central venous pressure elevation due to pulmonary hypertension may be associated with either no effusions[80] or with small effusions.[81,82] However, elevated central venous pressure may act cooperatively with CHF in the formation of effusions, although this has not been confirmed.

Malignancy

Malignancy can cause effusions by its effects either outside the pleural space or inside the pleural space. Outside the pleural space, malignancy can infiltrate lymphatics and lymph nodes and interfere with lymphatic absorption; it can obstruct a lung leading to collapse and to a decrease in pleural pressure. These mechanisms could explain the formation of transudative effusions. Inside the pleural space, the malignancy increases the permeability of the pleural microvasculature by cytokine production[83,84]; less commonly, it can invade vessels leading to a hemothorax. In their studies of liquid and protein turnover in pleural effusions of patients with different diseases, Leckie and Tothill reported that malignant effusions had an elevated entry of protein and a slow exit, suggesting both an increased permeability and decreased lymphatic flow.[72] In one interesting case, a young patient without other illnesses developed a transudate with negative cytology; within a short time, this effusion changed to an exudate with positive cytology and a biopsy showing malignant infiltration of the subpleural lymphatics. One interpretation of this case is that the malignancy induced a transudate by lymphatic obstruction outside the pleural space and then induced an exudate when the malignant cells invaded the pleural space.[62] Although one cannot be certain, this case illustrates what might be found if one is alert to the different ways malignancy may cause effusions. In addition, malignancy can induce many abnormalities

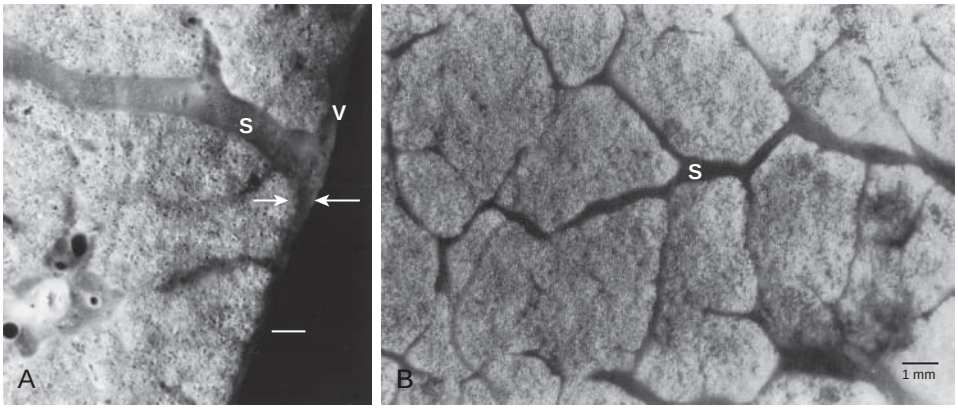

Figure 14.5 The interstitial edema seen at the visceral pleural surface. (A) A frozen edematous sheep lung cut to show the edema in the interlobular septum (S) and the subpleural space (V, visceral). The arrows indicate the width of the edema. (B) En face view of the lung showing interlobular septae (S) expanded by interstitial edema. The edema is only separated from the pleural space by a leaky visceral pleura. (A, From Broaddus VC, et al. Clearance of lung edema into the pleural space of volume-loaded anesthetized sheep. *J Appl Physiol*. 1990;68[6]:2627. B, From Wiener-Kronish JP, Broaddus VC, Albertine KH, et al. Relationship of pleural effusions to increased permeability pulmonary edema in anesthetized sheep. *J Clin Invest*. 1988;82[4]:1422-1429.)

that can lead to effusions, such as central venous thrombosis[61] or pulmonary embolism, among others.

Pulmonary Embolism

Pulmonary embolism (PE) is associated with exudative effusions.[85] PE may increase liquid entry in several ways: by increasing pulmonary and pleural vascular permeability (via bradykinin or VEGF), increasing central venous pressures thereby increasing pleural microvascular hydrostatic pressures, and creating atelectasis thereby decreasing pleural pressure. All these changes would tilt the balance toward increased entry of liquid into the pleural space. PE could also decrease liquid exit by increasing central venous pressure. Interestingly, it is not entirely clear that PE is the direct cause of effusions or whether it is merely associated with them. In three *computed tomography* (CT) studies, patients presenting with symptoms and signs suggestive of PE were studied by CT pulmonary angiography; effusions were common in all patients but not different in those found to have PE or not.[86–88] In the three studies, effusions were found in 50% to 58% of patients, without regard to the presence of PE. Thus, it appears that patients suspected of PE are highly likely to have effusions, although the exact cause of these effusions is not clear.

Tuberculosis

Tuberculosis is discussed here as representative of an infection targeted to the pleural membranes. In pleural tuberculosis, the intense granulomatous infiltration of the pleural membranes both increases the entry of a high-protein liquid into the pleural space and interferes with the exit of the liquid from the pleural space by lymphatics in the infiltrated parietal pleura. The study of effusions by Leckie and Tothill found that lymphatic flow from patients with TB was low, about 50% of that in patients with CHF.[72]

PLEURAL EFFUSION EFFECTS ON LUNG AND CARDIAC FUNCTION

In the presence of space-occupying liquid in the pleural space, the lung recoils inward, the chest wall expands outward, and the diaphragm is depressed inferiorly and is sometimes inverted.[89] If the lung and chest wall have normal compliances, the decrease in lung volume accounts for approximately one-third of the volume of the pleural effusion, and the increase in the size of the hemithorax accounts for the remaining two-thirds. As a result, lung volumes are reduced by less than the pleural effusion volume.

These mechanical abnormalities may explain dyspnea, exercise intolerance, and diaphragm dysfunction. All may be improved with thoracentesis. Dyspnea is most likely caused by the mechanical inefficiency of the respiratory muscles stretched by the outward displacement of the chest wall and the downward displacement of the diaphragm.[89] After the removal of large amounts of pleural liquid, dyspnea is generally relieved promptly, although the reduction in pleural liquid volume is associated with only small increases in lung volume. In one study, nine patients underwent removal of over 1800 mL of pleural liquid and, despite increases in vital capacity of only 300 mL, all patients experienced immediate relief of dyspnea.[90] Although the vital capacity changed little, patients could generate a more negative pleural pressure at the same lung volume after thoracentesis than before, indicating an improved efficiency of the respiratory muscles following the return of the chest wall and diaphragm to a more normal position after thoracentesis. A related explanation is that dyspnea is due to the inversion of the diaphragm caused by the weight of the pleural effusion, and that dyspnea is promptly relieved when thoracentesis allows the restoration of a dome-shaped diaphragm.[91] A mechanical explanation for the relief of dyspnea is supported by a case of a man with chronic absent lung perfusion on the side of a large effusion who nonetheless experienced significant relief of dyspnea with thoracentesis.[91a] Thoracentesis of a unilateral effusion (mean value 1.5 L) has also been shown to improve exercise tolerance.[92] Thoracentesis of an effusion in a ventilated patient has been shown to improve diaphragmatic function.[93] It appears that mechanical effects of a pleural effusion account for dyspnea and related symptoms.

If the lung is otherwise normal, there is no evidence that an effusion causes significant hypoxemia, presumably because ventilation and perfusion decrease similarly and remain reasonably matched. In fact, in one study, mild hypoxemia present before thoracentesis worsened *after* thoracentesis,[94] when perfusion presumably was restored while ventilation lagged behind. In another study using multiple inert gas techniques to quantify ventilation-perfusion distributions, pleural effusion was associated with a small intrapulmonary perfusion shunt (6.9%) that did not change significantly when measured again 30 minutes after thoracentesis of approximately 700 mL (6.1%).[95] Draining pleural effusions in patients with refractory hypoxemia on mechanical ventilation may improve oxygenation,[96] although there is no consensus on the indications for thoracentesis in this setting.[97] It appears therefore that the effects of pleural effusion and thoracentesis on oxygenation are variable and may depend on the underlying lung function.

Less well appreciated is the fact that large pleural effusions may impair cardiac function, most likely by decreasing the distending pressures of the cardiac chambers and thereby reducing cardiac filling. In a study of 27 patients with large effusions occupying more than half the hemithorax, clinical and echocardiographic findings of cardiac tamponade were identified in most patients. These findings, including elevated jugular venous pressure, pulsus paradoxus, right ventricular diastolic collapse, or flow velocity paradoxus, resolved in all patients when studied again 24 hours after thoracentesis of more than 1.0 L.[98] Large pleural effusions should be considered as potentially reversible causes of cardiac dysfunction.[99]

Understanding the physiology of the pleural space, liquid and protein turnover and the mechanics of pleural pressure lend themselves to understanding the abnormalities that commonly arise.

Key Points

- At baseline, pleural liquid entry is slow and balanced by an equal rate of pleural absorption (0.01 mL/kg/hr, or 12 mL/day in a 50-kg person).
- Normal pleural liquid enters from the pleural systemic microvessels and represents a filtrate from these high-pressure, low-permeability vessels, explaining the low protein concentration (1 gm/dL or ≈15% of serum protein).
- Normal pleural liquid exits via bulk flow through lymphatics which open directly onto the pleural space at the parietal pleura. This explains why pleural liquid protein concentration remains relatively constant even as liquid is absorbed.
- Lymphatics have a large reserve capacity and can normally accommodate increases in liquid entry into the pleural space without the development of an effusion.
- Pleural effusions develop when a disease or a combination of diseases increases liquid entry into the pleural space and decreases its exit from the pleural space; both changes are likely necessary for formation of a clinically relevant effusion.
- Because the protein concentration does not change with absorption via bulk flow through lymphatics, the protein concentration of pleural effusions gives information about the formation of the pleural liquid, not its removal.
- Transudates usually result from changes in hydrostatic and/or osmotic pressures that lead to increased filtration and accumulation of a protein concentration (pleural/serum protein ratio <0.5) lower than that of exudates.
- Transudates with a very low protein concentration (protein ratio <0.1–0.2) are most likely caused by entry of cerebrospinal liquid, urine, or intravenous fluids into the pleural space.
- Exudates result from pleural or extrapleural injury that can be due to a multitude of inflammatory, infectious or malignant diseases, leading to an effusion with a relatively high protein concentration.
- Excess liquid anywhere in the body can move to and enter the pleural space due to (1) its subatmospheric pleural pressure (−5 to −30 cm H_2O), (2) the leaky mesothelial layer, and (3) the high capacitance of the pleural space.

Key Readings

Bintcliffe OJ, Hooper CE, Rider IJ, et al. Unilateral pleural effusions with more than one apparent etiology. *Annals ATS*. 2016;13:1050–1056.

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SECTION C

DEFENSE MECHANISMS AND IMMUNOLOGY

15 INNATE IMMUNITY

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INTRODUCTION

The immune system is broadly conceptualized as having two separate but interconnected arms. In evolutionary terms, the innate immune arm is an older and more primitive system that has developed to provide early host defense against viruses, fungi, and bacteria. The fundamental basis of innate immunity is a system for pathogen detection that relies on the recognition of *pathogen-associated molecular patterns* (PAMPs), which include complex lipids, carbohydrates, unmethylated cytosine-guanosine DNA sequences, and double-stranded RNAs. PAMPs are recognized by a series of secreted, cell surface, and intracellular *pattern recognition receptors* (PRRs). These PRRs promote the recognition, phagocytosis, antigen presentation, and killing of microbial invaders. In addition, recognition of PAMPs by PRRs initiates inflammation, which in turn leads to the recruitment of phagocytes that kill and degrade microbes, promote the repair of damaged tissues, and assist in the restoration of tissue function. Although some organisms, such as sea urchins, have evolved a system of host defense based exclusively on the innate immune system,[1] mammals and higher animals have evolved an adaptive immune system that differs from the innate immune system in its exquisite antigenic specificity and the ability to develop immunologic memory, allowing a more rapid response to previously encountered microbes and antigens. Both the innate and adaptive immune systems operate together and exist in a classic symbiotic relationship to provide optimal defense of the lung and other organs and tissues (see Chapter 16).

The broad concepts of innate and adaptive immunity outlined previously have evolved to protect most organs and tissues from microbes, a term that includes bacteria, yeasts, fungi, protozoa, multicellular parasites, and viruses. However, most organs and tissues, including the lung, have evolved additional mechanisms to tailor the immune system to their own specific needs. The lung epithelium has a surface area approximately the size of one side of a doubles tennis court and represents the largest epithelial surface in the body (see Chapter 1). With an average respiratory rate of 10 to 12 breaths/min and an average tidal volume of 600 mL, the lungs are exposed to more than 10,000 L of ambient air per day. The air we breathe is a complex mixture of gases and particulates containing pollutants, oxidants, inorganic and organic dusts, pollens, toxins, bacteria and their constituents (e.g., bacterial endotoxin, *lipopolysaccharides* [LPSs]),

and viruses. In addition, the airways and gas-exchange surfaces of the lung can be exposed by aspiration to acidic gastric contents and to infected mucus from the nasal sinuses. Thus, all surfaces of the respiratory tract from the nasal passages to the alveoli are constantly exposed to a spectrum of harmless and harmful agents, raising the key question of how the lung differentiates between what is harmful and what is essentially harmless.

Like the gut, the lung has evolved discriminative mechanisms both to suppress unwanted and potentially harmful responses to harmless materials and to retain the ability to activate a vigorous innate and adaptive immune response when encountering harmful microbes and stressors. The overall goal of this chapter is to review current concepts of lung innate immunity and its fundamental underlying mechanisms. Multiple cell lineages participate in innate protection of the lung, and many share similarities in the way they recognize and respond to microbes and other harmful agents. Therefore, this chapter is organized into four broad sections: (1) an overview of lung innate immunity and its fundamental components, (2) a general mechanism of innate immune recognition, (3) a review of innate lung cells and their effector mechanisms, and (4) an outline of how these systems and mechanisms are integrated. Throughout the chapter we also discuss how the innate immune system primes the adaptive immune system as a prelude to the chapter on adaptive immunity (Chapter 16).

OVERVIEW OF THE COMPONENTS OF LUNG INNATE IMMUNITY

The long-held view that the lower respiratory tract of healthy individuals is sterile has now been invalidated through the application of culture-independent methodologies, especially bacterial 16S ribosomal RNA sequencing. Based initially on a single-center study with a modest number of subjects,[2] the National Heart, Lung, and Blood Institute–sponsored multicenter Lung HIV Microbiome Project analyzed bronchoalveolar lavage fluid and provided indisputable data that bacterial DNA is present in the lower respiratory tract of healthy subjects. Furthermore, the bacterial sequences found in bronchoalveolar lavage closely resembled the diversity seen in the mouth,[3,4] although the bacterial load was estimated to be approximately 0.1% of that found in oral washes.[5] Whether the DNA found in the lower respiratory tract was derived from reproducing bacterial colonies or represented bacteria that may have been inhaled or aspirated remains to be determined. These groundbreaking studies have ignited interest into how dysbiosis of the lung microbiome may contribute to susceptibility or to the pathogenesis of multiple lung diseases. Thus, as knowledge of the lung microbiome continues to grow, it will become increasingly important to integrate emerging information into our understanding of how the innate immune system interfaces with these potentially commensal bacteria.[6–8] For more information, see Chapter 17.

The innate immune system provides protection against a diverse spectrum of resident microbes, in addition to inhaled particles and antigens, ranging from harmless nonmicrobial particles (e.g., dusts and pollens) to harmful pathogenic microbes (e.g., *Mycobacterium tuberculosis*). To accomplish this range of protection, the lungs have evolved multiple mechanisms to survey and respond to inhaled particles based on their size, physicochemical properties, and especially the presence or absence of PAMPs. As illustrated in Figure 15.1, innate immune protection in the lung can be broadly divided into considerations of the conducting airways and the alveoli. At the cellular level, innate protection is afforded by the coordinated functions of airway and alveolar epithelial cells, *innate lymphoid cells* (ILCs),[9,10] resident macrophages (alveolar and interstitial macrophages), monocytes, *dendritic cells* (DCs), and recruited neutrophils (*polymorphonuclear leukocytes* [PMNs]).

Although often underestimated, an important component of airway host defense resides in the anatomic structure and epithelial cell lineages of the tracheobronchial tree. Air turbulence created by the nasal passages and the cartilaginous segmentation of the trachea and large airways ensures that particles in excess of 10 μm in diameter are deposited on the mucus-coated surfaces of the nose, pharynx, trachea, and descending airways. In turn, mucus, with its ensnared particulates and dissolved solutes, is constantly wafted toward the pharynx by the coordinated beating of ciliated airway epithelial cells, where its removal is aided by coughing, sneezing, and swallowing. In addition to the biophysical properties of mucus in innate host defense of the airways, the gel and pericellular liquid phases also contain an array of antimicrobial peptides, proteins, antioxidants, antiproteases, and specific *immunoglobulin* (Ig) A antibodies, all of which are maintained at a modestly acidic pH (pH 6.6).[11] Principal among airway antimicrobial peptides in humans are salt-sensitive cysteine-rich cationic β-defensins and the cathelicidin LL37/hCAP18.[12–16] β-Defensin-1 is constitutively secreted by airway epithelia and accumulates in airway surface liquid at μg/mL concentrations.[17] Expression of other β-defensins and LL37/hCAP18 is induced after exposure to LPS and other proinflammatory mediators.[18–20] Antimicrobial proteins, including lactoferrin and lysozyme, are also present in airway epithelial secretions.[21,22]

The conducting airways are lined with ciliated and secretory epithelial cells that serve a key role in the initial evaluation of large particles with which they come into contact. In addition, a network of DCs resides throughout the airway epithelium and continuously samples the airway lumen (see Fig. 15.1). DCs are particularly abundant in the trachea and large conducting airways, where most large particulates are deposited. In the absence of PAMPs, DCs and trafficking monocytes capture airway antigens and migrate to regional lymph nodes, where they process and present foreign and self-antigens to cognate T cells.

In contrast to large particles, particles smaller than 5 μm in diameter are able to descend the entire tracheobronchial tree and lodge at bronchiolar-respiratory duct junctions or deposit onto the surfactant-rich surfaces of the alveoli. Although sharing many similarities with innate protection of the airways—for example, the presence of antioxidants, antiproteases, and antimicrobial enzymes—additional innate protection of the alveoli is afforded by the presence of alveolar macrophages and the lung-specific collectins *surfactant protein A* (SP-A) and *surfactant protein D* (SP-D) (see Fig. 15.1). In addition to expressing *toll-like receptors* (TLRs), alveolar macrophages express *scavenger receptors* (SRs) that participate in the phagocytosis of microbial and

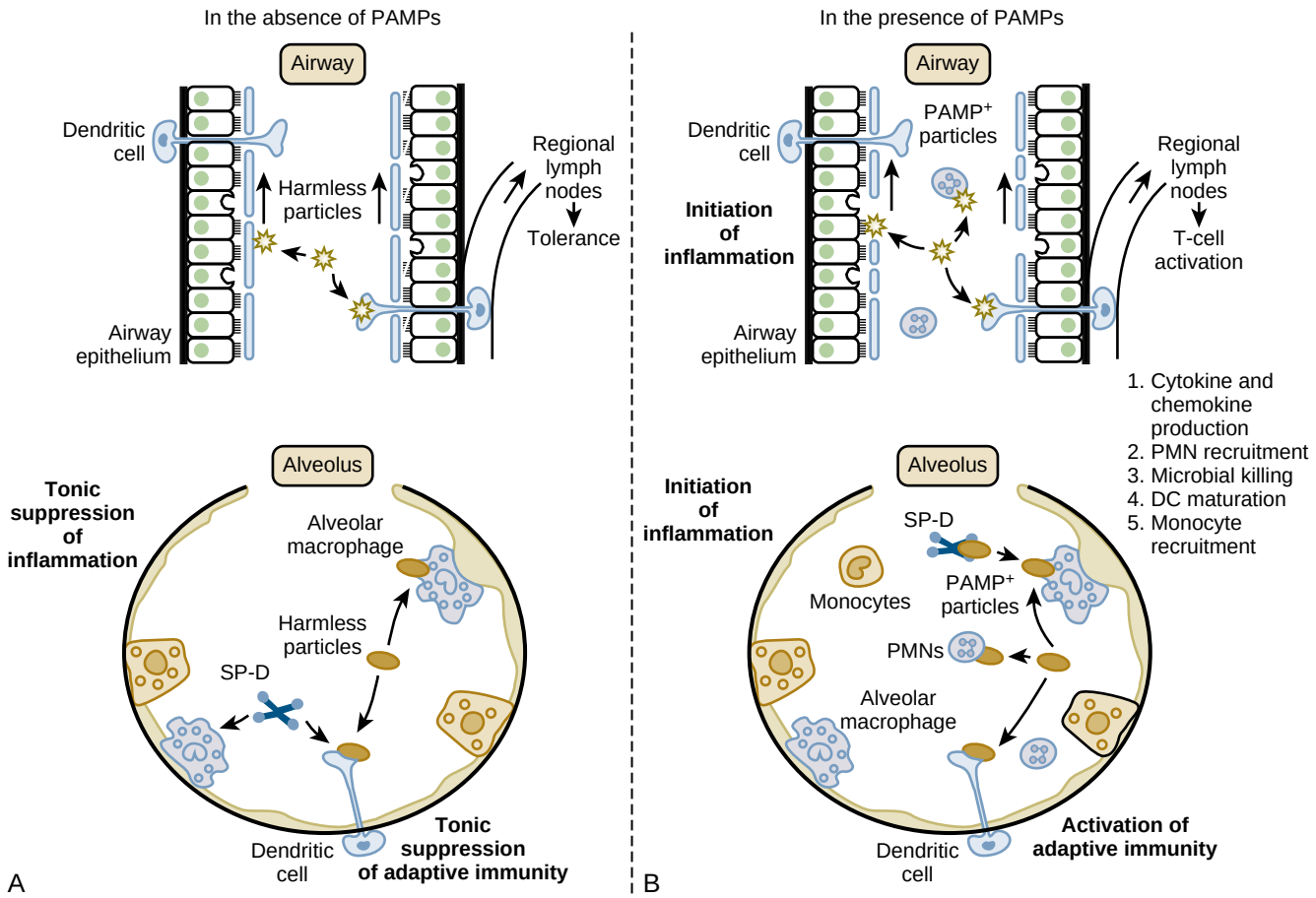


Figure 15.1 Overview of innate immune protection in the conducting airways (*upper*) and alveoli (*lower*) of the lung. (A) In the absence of *pathogen-associated molecular patterns* (PAMPs), that is, in the steady state, the airways are protected by mucus that captures harmless particulates and transports them along the mucociliary escalator. *Dendritic cells* (DCs) also capture particles, traffic to regional lymph nodes, and promote tolerance to commonly inhaled antigens. Also, in the absence of PAMPs, the alveoli are maintained in an anti-inflammatory and immunosuppressed state to prevent unwanted inflammation and immune activation toward commonly inhaled particles and antigens. (B) In the presence of PAMPs, innate immunity is activated. PAMPs stimulate airway epithelial cells to express chemokines, cytokines, and lipid mediators that attract neutrophils (polymorphonuclear leukocytes), which in turn kill PAMP-expressing microbes. Airway DCs respond to PAMPs by maturing, migrating to regional lymph nodes, and stimulating T cell proliferation. A similar program is activated in the alveoli upon PAMP detection by alveolar macrophages, alveolar epithelial cells, and DCs, resulting in the initiation of inflammation and activation of adaptive immunity. PMN, polymorphonuclear leukocytes; SP-D, surfactant protein D.

nonmicrobial particles, such as *macrophage receptor with collagenous structure* (MARCO). SP-A and SP-D are secreted PRRs and are capable of binding to microbial PAMPs, leading to opsonization and phagocytosis by alveolar macrophages and by intraseptal DCs, which then crawl into the airways and move up the mucociliary escalator or migrate to regional lymph nodes, respectively. In the absence of PAMPs, alveolar macrophages also play an important role in suppressing inflammation and adaptive immunity, thereby protecting the alveoli from unwanted responses to harmless inhaled particulates. SP-A and SP-D have a key role in suppressing inflammation through tonic signaling effects on alveolar macrophages. Thus, the innate immune system not only protects the lungs from harmful microbes but also prevents inflammation, injury, and activation of the adaptive immune system in the steady state and in response to harmless inhaled particulates.

How, then, do the airways and alveoli respond to the presence of potentially harmful microbes? As illustrated in Figure 15.1, resident airway and alveolar macrophages, DCs, and airway and alveolar epithelial cells are capable of recognizing different PAMPs through their repertoires of cell surface and intracellular PRRs and by the interaction of PAMP-bound secreted PRRs with specific receptors on epithelial cells, macrophages, and DCs. In turn, these interactions induce signaling responses that promote the expression of an array of innate response genes (Table 15.1). These gene products collectively promote the migration of PMNs and monocytes from the pulmonary circulation into the air spaces, facilitate changes in endothelial and epithelial permeability to enhance inflammatory cell transmigration into the air spaces, and initiate the expression of specific genes involved in microbial killing. In addition, DCs and monocytes phagocytose PAMP-expressing microbes, mature, and migrate to regional lymph nodes (see Fig. 15.1).[23] During this process, ingested microbial products are digested, captured by *major histocompatibility complex* (MHC) class II and I molecules, and displayed on the plasma membrane together with co-stimulatory molecules, such as CD40, CD80, and CD86, for effective presentation to naive $CD4^+$ and $CD8^+$ T cells. After activation

Table 15.1 Representative Genes Activated by Pattern Recognition Receptors

CXCL CHEMOKINES
CXCL1, CXCL2, CXCL4, CXCL9, CXCL10, CXCL11
CCL CHEMOKINES
CCL1, CCL2, CCL7
CYTOKINES
TNF-α, IL-1β, TGF-β, IL-10
TOLL-LIKE RECEPTORS
TLR2, TLR4, TLR9
PROSURVIVAL
BCL2, cIAP1, cIAP2, BCL10
ANTIMICROBIAL
β-Defensins, cathelicidins
DC MATURATION
CD40, CD80, CD86, MHC class II, class II

Transcription of most of these genes is initiated by the activation of NF-κB and/or AP1. NF-κB activation is initiated by most PRRs.

AP1, activator protein-1; BCL, B-cell lymphoma; CCL, CC chemokine ligand; CD, cluster of differentiation; cIAP, cellular inhibitor of apoptosis; CXCL, CXC chemokine ligand; DC, dendritic cell; IL, interleukin; MHC, major histocompatibility complex; NF-κB, nuclear factor-κB; PRR, pattern recognition receptor; TGF, transforming growth factor; TLR, Toll-like receptor; TNF, tumor necrosis factor.

and expansion in regional lymph nodes, effector $CD4^+$ and $CD8^+$ T cells then migrate back to the site of microbial infection to augment specific host defense through their ability to activate macrophages and other effector cells. In addition, long-term central and resident memory T cells become resident in the lung and lymph nodes for future pathogen encounters.[24,25]

In summary, innate immune mechanisms involving the airway and alveolar epithelium, secreted antimicrobial enzymes, PRRs and peptides, mucus and mucociliary transport, and resident macrophages and DCs protect the lung against inhaled microbial and nonmicrobial particulates to maintain lung homeostasis. During steady-state conditions, the innate immune system actively suppresses inflammation and promotes tolerance to commonly inhaled harmless particulates. However, above a certain threshold and/or upon sensing the presence of PAMPs, additional mechanisms are activated to protect the lungs by promoting inflammation and adaptive immunity and by establishing communication and cooperation between these systems. Although it is convenient to think of these events separately, innate host responses both to harmless nonmicrobial particulates and to harmful microbes take place simultaneously and silently to maximize lung health and protection.

INNATE RECOGNITION IN THE LUNG

With this broad overview of the key elements in innate host defense of the lung and their connections to adaptive immunity, we now consider how microbes are recognized by resident and recruited lung cells. For this purpose, we specifically focus on the mechanisms of recognition by PRRs expressed by epithelial cells, macrophages, and DCs or that are present in airway or alveolar surface liquids.

SECRETED PATTERN RECOGNITION RECEPTORS

Secreted PRRs have evolved to serve as bridges between certain PAMPs and specific receptors for these molecules. In the lung, secreted PRRs have particularly important roles in innate protection of the alveolar surfaces.

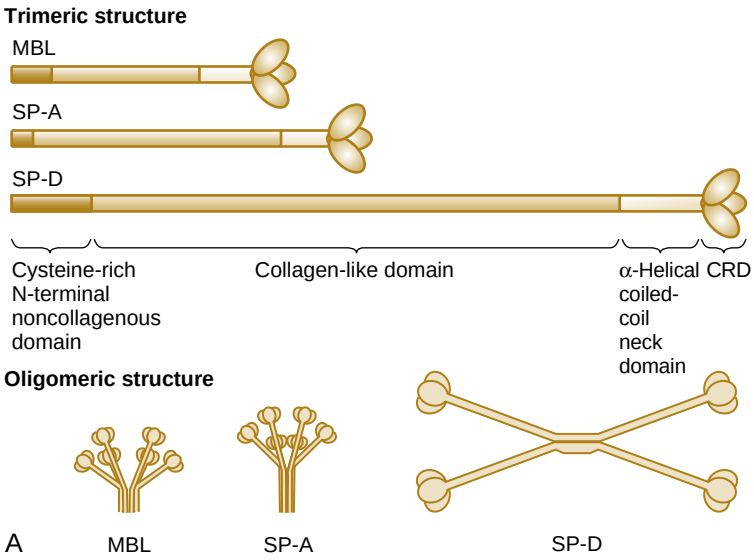
Collectins

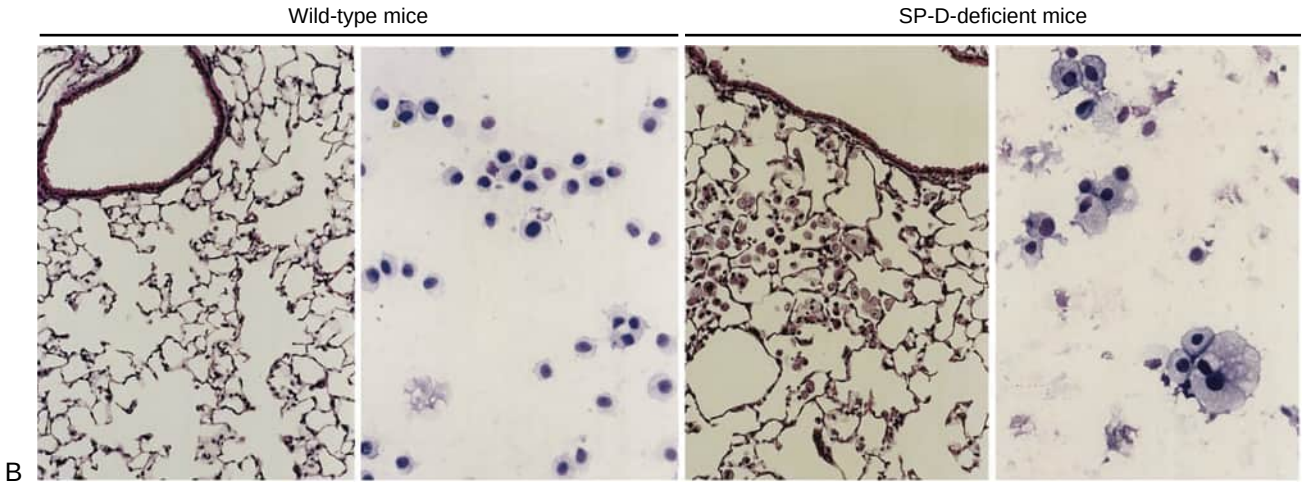
The collectins are a family of secreted PRRs; SP-A and SP-D are collectins uniquely expressed in the distal lung.[26] All members of the collectin family are characterized by the presence of a cysteine-rich N-terminal noncollagenous domain, a collagen-like domain, an α-helical coiled-coil neck domain, and a globular C-type lectin domain, also called the carbohydrate recognition 2 domain, that interacts with microbial PAMPs (Fig. 15.2A). At baseline, SP-A and SP-D suppress inflammation (see later; shown for SP-D in Fig. 15.2B); in the presence of a variety of PAMPs, SP-A and SP-D stimulate microbial phagocytosis, the production of reactive oxidant species, and the expression of proinflammatory cytokines (see Fig. 15.2C).[27,28] A proinflammatory response is activated when PAMP-bound SP-A and SP-D interact with macrophages via their collagenous tails through a multifunctional protein made of calreticulin bound to CD91[29–31] (see Fig. 15.2C). Consistent with these findings, SP-A–deficient and SP-D–deficient mice have increased susceptibility to pulmonary infection with *Pseudomonas aeruginosa* and *Staphylococcus aureus,*[32,33] emphasizing the important contribution of these lung-specific collectins to innate lung host defense. Additional information on SP-A and SP-D can be found in Chapter 3.

The lung is remarkable in that it is capable of eliminating harmful pathogens from the alveolar surfaces while actively suppressing unwanted and potentially harmful inflammatory responses to harmless inhaled materials. Several studies have shed new light on this dichotomy by revealing an additional role for SP-A and SP-D in the tonic suppression of lung inflammation. When initially created, SP-D–deficient mice were found to have increased numbers of foamy, activated alveolar macrophages, suggesting that SP-D may somehow tonically suppress lung macrophage activation and lung inflammation (see Fig. 15.2B).[34] As illustrated in Figure 15.2C, in the steady state (i.e., in the absence of PAMPs), SP-D and SP-A interact with alveolar macrophages via their globular head groups and signal via *signal-inhibitory regulatory protein-α* (SIRPA) to suppress proinflammatory responses.[29] Thus, SP-A and SP-D, through their ability to interact under different circumstances with SIRPA and with calreticulin/CD91, play a pivotal role in the maintenance of the anti-inflammatory environment of the alveoli under steady-state conditions, while promoting an inflammatory and innate response when microbes are sensed. Other studies suggest that lipid and phospholipid constituents of surfactant also contribute to maintenance of the anti-inflammatory environment of the alveoli.[35]

Complement

The complement system functions as a pattern recognition system and a bridge to adaptive immunity through its ability to recognize repetitive structures on some microbes and





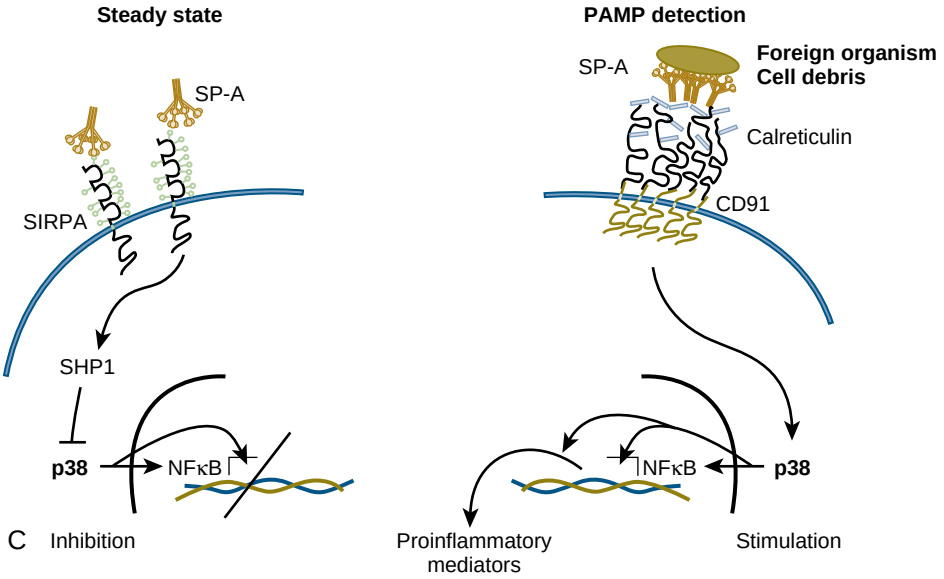


Figure 15.2 Pulmonary collectins, especially *surfactant protein A* (SP-A) and *surfactant protein D* (SP-D), play a key role in suppressing inflammation in the absence of *pathogen-associated molecular patterns* (PAMPs) while stimulating inflammation in the presence of PAMPs. (A) Structure of pulmonary collectins. (B) The importance of SP-D in tonic suppression of lung inflammation is illustrated by the spontaneous proinflammatory phenotype of SP-D–deficient mice. (C) Tonic suppression of inflammation is mediated by the binding of collectins to signal-inhibitory regulatory protein α (SIRPA) via their head groups, whereas activation of inflammation is mediated when PAMP-bound collectins interact with calreticulin/CD91 via their collagenous tail regions. CRD, carbohydrate recognition domain (C-type lectin domain); MBL, mannose-binding lectin; NFκB, nuclear factor-κB; SHP1, Src homology 2 domain-containing protein tyrosine phosphatase-1. (A, Modified from Wright JR. Immunoregulatory functions of surfactant proteins. *Nat Rev Immunol.* 2005;5:58–68. B, Modified from Fisher JH, Sheftelyevich V, Ho YS, et al. Pulmonary-specific expression of SP-D corrects pulmonary lipid accumulation in SP-D gene-targeted mice. *Am J Physiol Lung Cell Mol Physiol.* 2000;278:L365–L373. C, Modified from Gardai SJ, Xiao YQ, Dickinson M, et al. By binding SIRPalpha or calreticulin/CD91, lung collectins act as dual function surveillance molecules to suppress or enhance inflammation. *Cell.* 2003;115:13–23.)

on the Fc region of IgG and IgM antibodies. Complement activation is important in lung innate immunity because it promotes the opsonization of microbes and the generation of the potent chemotactic factor C5a, which in turn assists in the recruitment of phagocytic cells. Complement components of the classical, alternative, and mannose-binding lectin activation pathways are present in the lung airway and alveolar fluids[36–38] and are synthesized by alveolar epithelial type 2 cells, macrophages, and DCs.[22,39–41] Many microbes can directly activate the alternative complement pathway, resulting in the covalent attachment of C3b to the microbial cell wall. Microbes expressing cell wall–associated mannose-rich polysaccharides can also bind mannose-binding lectin and activate the mannose-binding lectin pathway to promote C3b attachment to the microbial cell wall. Phagocytic cells, especially macrophages, PMNs, and DCs, express various receptors for C3b and C3bi and, together with other receptors, phagocytose and kill complement-opsonized microbes. Moreover, the top genes expressed by three recently identified interstitial macrophages are *C1qa, C1qb,* and *C1qc,* which form the C1q complex required to initiate the classical complement pathway.[42]

Pentraxins and Other Secreted Pattern Recognition Receptors

The pentraxins, including C-reactive protein, serum amyloid P, and pentraxin 3, also recognize PAMPs on microbes and activate the complement system to assist in microbial removal by phagocytic cells.[43,44] Similarly, ficolins promote phagocytosis and complement activation by binding to the gram-positive bacterial cell wall components *N*-acetylglucosamine and lipoteichoic acid.[45]

CELLULAR PATTERN RECOGNITION RECEPTORS

Different families of PRRs have evolved to enable the host to sense the presence of PAMPs in extracellular, endosomal, and cytoplasmic compartments in each of the lineages involved in lung innate immunity (Fig. 15.3). Transmembrane cell surface and endosome-associated PRRs include the TLRs widely

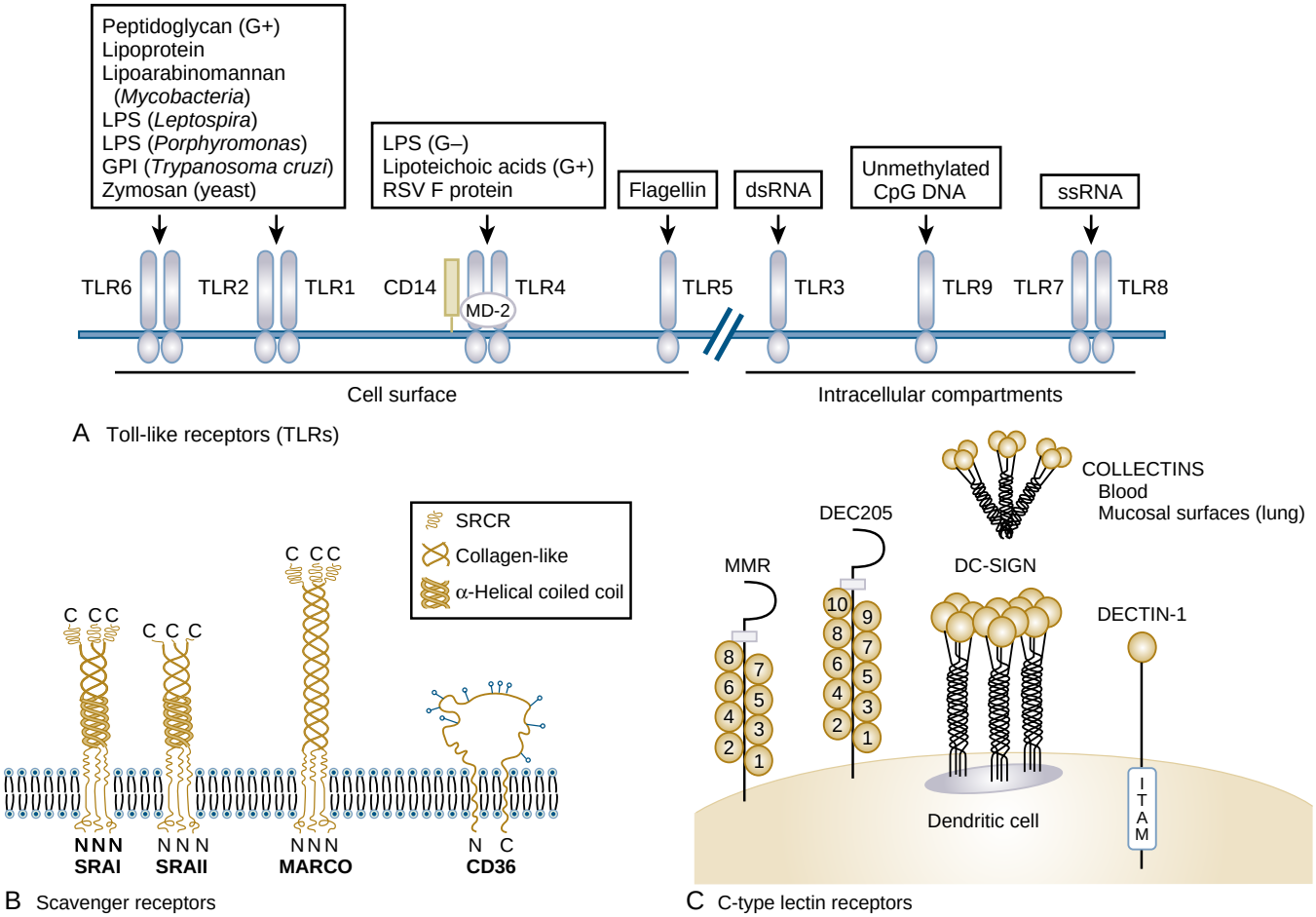


Figure 15.3 Major classes of transmembrane cell surface pattern recognition receptors expressed by lung cells. (A) Toll-like receptors. (B) Scavenger receptors. (C) C-type lectin receptors. CpG, cytosine-guanosine; DC-SIGN, dendritic cell–specific intercellular adhesion molecule–grabbing nonintegrin; DEC205, dendritic and thymic epithelial cell-205; dsRNA, double-stranded RNA; GPI, glycosylphosphatidylinositol; ITAM, immunoreceptor tyrosine-based activation motif; LPS, lipopolysaccharide; MARCO, macrophage receptor with collagenous structure; MD2, myeloid differentiation protein-2; MMR, macrophage mannose receptor; RSV, respiratory syncytial virus; SRAI, scavenger receptor AI; SRAII, scavenger receptor AII; SRCR, scavenger receptor cysteine-rich domain; ssRNA, single-stranded RNA. (A, Modified from Medzhitov R. Toll-like receptors and innate immunity. *Nat Rev Immunol.* 2001;1:135–145. B, Modified from Taylor PR, Martinez-Pomares L, Stacey M, et al. Macrophage receptors and immune recognition. *Annu Rev Immunol.* 2005;23:901–944. C, Modified from Gijzen K, Cambi A, Torensma R, Figdor CG. C-type lectins on dendritic cells and their interaction with pathogen-derived and endogenous glycoconjugates. *Curr Protein Pept Sci.* 2006;7:283–294. D, Modified from Geddes K, Magalhães JG, Girardin SE. Unleashing the therapeutic potential of NOD-like receptors. *Nat Rev Drug Discov.* 2009;8:465–479.)

expressed on epithelial cells, macrophages, PMNs, and DCs (see Fig. 15.3A); SRs primarily expressed on macrophages (see Fig. 15.3B); and C-type lectin receptors mainly expressed on DCs (see Fig. 15.3C). Cytoplasmic PRRs are composed of *nucleotide-binding and oligomerization domain (NOD)-like receptors* (NLRs) and RNA helicases of the *retinoic acid–inducible gene* (RIG) family. Each of the cytoplasmic PRRs has evolved as a strategy to alert the host to the presence of PAMPs within the cytoplasm, as often happens during the intracellular replication of facultative bacteria and viruses.

Plasma Membrane and Endosomal Pattern Recognition Receptors

Toll-like Receptors. TLRs are expressed on airway and alveolar epithelial cells, macrophages, PMNs, and DCs.[46–49] There are 10 TLRs in humans (TLR 1–10) and 12 TLRs in mice (TLR 1–9, 11–13).[50] TLR2, TLR4, TLR5, TLR7, TLR8, and TLR13 are expressed by most macrophages, with TLR4 being part of a core macrophage signature gene,[51] and TLR1 and TLR5 are highly expressed by interstitial macrophages.[42] Significant progress has been made in understanding the functions and downstream signal transduction pathways of TLRs.[52–55] TLRs can be divided into those expressed on the cell surface (TLR1, TLR2, TLR4, TLR5, TLR6, and TLR12) and those expressed in intracellular compartments (TLR3, TLR7, TLR8, TLR9, and TLR13) (see Fig. 15.3A).[50] TLRs also recognize endogenous ligands called *danger-associated molecular patterns* (DAMPs), including heat shock proteins, low-molecular-weight hyaluronan, heparin sulfate, fibronectin, high-mobility-group box-1 protein, and low-density lipoproteins. Recognition of DAMPs by TLRs and other PRRs is usually associated with the initiation of sterile inflammation. Surface TLRs recognize a wide variety of PAMPs, whereas intracellular TLRs mainly recognize nucleic acid–based PAMPs. TLRs not only recognize their individual cognate PAMPs but also combine with other TLRs to form heteromeric complexes that recognize a broader range of PAMPs.[55–58] For example, TLR1 associates with TLR2 to recognize microbial lipopeptides,[58] TLR2 and TLR4 recognize the LPS-binding protein/myeloid differentiation protein-2 complex when presented by CD14, and TLR2 recognizes broad patterns of lipoproteins in concert with either TLR1 or TLR6.[59] CD14 is a PRR that exists in membrane and soluble forms and recognizes both PAMPs and DAMPs and greatly amplifies signaling through TLR2, TLR3, and TLR4.[60] Of importance, soluble CD14 can present PAMPs to cells that do not respond to direct stimulation, such as endothelial and epithelial cells, thereby broadening inflammatory responses.[61] TLR5 recognizes flagellin and is particularly important in the response of airway epithelial cells to *P. aeruginosa* infection. Similarly, TLR6 can functionally associate with TLR2 to recognize a variety of microbial lipopeptides and peptidoglycans from gram-positive bacterial cell walls.[62] TLR3, TLR7, TLR8, and TLR9 are expressed intracellularly in endosomal and endoplasmic reticulum membranes, where they sense nucleic acids released from ingested and digested microbes.[52–55] TLR3 recognizes viral double-stranded RNA and induces the production of type I *interferons* (IFNs; IFN-α/IFN-β),[63] which in turn play a vital role in antiviral immunity and in the maturation of the cross-presenting Batf3+ DC, also known as DC1.[64–66] TLR7 recognizes single-stranded RNA from viruses and is highly expressed by DC2, monocytes, and *plasmacytoid DCs* (pDCs),[67] whereas TLR9, which recognizes unmethylated cytosine-guanosine motifs in microbial DNA, is highly expressed by pDCs.[68,69] Of note, pDCs were previously thought to be myeloid derived. However, recent findings have shown them to be derived from lymphoid progenitors.[70]

Scavenger Receptors. The first macrophage SR was described by Goldstein and colleagues and Brown and associates[71,72] and was shown to bind and internalize acetylated low-density lipoprotein. Since then, multiple SRs have been identified and shown to play diverse roles in the phagocytosis of a variety of particles and molecules ranging from bacteria to lipids (see Fig. 15.3B). The SR family comprises eight classes (A–H), of which class A (SR-A) and class B (SR-B) are primarily involved in innate immunity through their ability to recognize and promote phagocytosis of a wide range of bacteria. Members of the SR-A and SR-B subfamilies are abundantly expressed on macrophages but do not appear to be expressed by airway or alveolar epithelial cells. The lack of expression on epithelial cells is in keeping with the notion that, during exposure to inhaled microbes and particles, the lung epithelium has evolved mechanisms to respond to PAMPs by promoting inflammation but not to engage in phagocytosis, leaving this activity to professional phagocytes.

Class A SRs are homotrimeric type II transmembrane proteins (extracellular C-terminal). SRA exists as two splice variants (SRAI and SRAII) of a single gene whose primary function is to promote the phagocytosis of a range of non-opsonized bacteria, including *S. aureus*, *Streptococcus pneumoniae,* and *Escherichia coli*.[73] SRA-deficient mice have increased susceptibility to systemic infections with *S. aureus* and *Listeria monocytogenes*[74,75] and to pulmonary infections with *S. pneumoniae*.[76] MARCO is an additional SRA involved in innate pulmonary host defense against *S. pneumoniae*.[77] Down-regulation of MARCO by IFN-γ increases susceptibility to *S. pneumoniae* in mice and may contribute to the development of pulmonary bacterial pneumonias after influenza infections.[78] MARCO may also play a role in dampening pulmonary inflammation because MARCO-deficient mice exhibit increased lung inflammation in response to inhaled silica and oxidants.[79,80] There is a notable difference in MARCO expression when alveolar macrophages are derived from embryonic monocytes compared to monocytes replenished postnatally. (Alveolar macrophages only replenish after birth if there is a significant loss of alveolar macrophages, such as by experimental depletion after intranasal delivery of liposome-encapsulated clodronate.) Postnatal-derived alveolar macrophages express significantly less MARCO than embryonic-derived alveolar macrophages,[81] and the lack of MARCO expression could be disadvantageous during certain infections, as described earlier.

Class B SRs are primarily represented in the lung by CD36. CD36 is expressed on monocytes, macrophages, DCs, and vascular endothelium.[82–84] Like class A SRs, CD36 has been implicated in PAMP recognition[85] and in the phagocytosis of *S. aureus*.[86,87] However, whereas CD36 deficiency in mice results in impaired host defense against *S. aureus*,[85] the absence of CD36 in humans, via a natural genetic deficiency, is not associated with a pulmonary phenotype.[88]

C-Type Lectin Receptors. *C-type lectin receptor* (CLR) domains are also present in a family of cell surface receptors that plays an important role in the function of DCs and macrophages (see Fig. 15.3C). CLRs recognize high-density carbohydrate-based PAMPs on microbial cell walls and viral coats. Carbohydrate binding can be divided into mannose and galactose specificity.[89] Type I CLRs include macrophage mannose receptor and *dendritic and thymic epithelial cell-205* (DEC205), and type II CLRs include DC-specific *intracellular adhesion molecule 3* (ICAM3), *DC–specific intercellular adhesion molecule–grabbing nonintegrin* (DC-SIGN), and *DC-specific receptor-1* (DECTIN1). As will be discussed later, studies in mice bearing targeted disruptions of CLR genes have emphasized their importance in innate host defense and particularly in DC maturation and antigen presentation.

DEC205 is a type 1 transmembrane receptor protein found on alveolar macrophages and the cross-presenting Batf3$^+$ DC1 subset in humans and mice.[90,91] The natural carbohydrate ligands remain largely uncharacterized, although the receptor has been shown to induce the endocytosis of experimental antigen–anti-DEC205 receptor complexes and promote their delivery to endosomes before antigen processing and presentation. When DCs are treated with the antigen–anti-CD205 fusion protein alone, they induce tolerance to the antigen by deleting specific CD4$^+$ and CD8$^+$ T cells and by promoting the development of T regulatory cells.[92] In the presence of an inflammatory stimulus, DCs exposed to the antigen–anti-DEC205 fusion proteins promote long-lived immunity mediated by antigen-specific CD4$^+$ and CD8$^+$ T cells.[93,94] Antigens delivered by targeting DEC205 may be presented in association both with MHC class II molecules and by cross-presentation with MHC class I molecules.[95–98] Furthermore, a recent study showed that DEC205 mediates the uptake of self-antigens via the endocytosis of apoptotic cells, thereby providing a plausible mechanism for the cross-presentation of self-antigens, resulting in the induction of both central and peripheral tolerance.[99]

DECTIN1 is expressed on DCs, macrophages, monocytes, PMNs, and some T cell subsets.[91,100–102] DECTIN1 specifically recognizes β-(1,3)-linked glucans and β-(1,6)-linked glucans[103] and is thought to play a key role in the nonopsonic phagocytosis of a number of pathogenic yeasts, fungi, and bacteria by macrophages and DCs.[104] Ligation of DECTIN1 also stimulates the production of an array of proinflammatory cytokines, oxidants, and lipid mediators.[105–109]

DC-SIGN is also a type II CLR[110,111] but differs from DECTIN1 by its specificity for microbial mannose-rich carbohydrates.[110,112–114] DC-SIGN is important in DC trafficking and DC–T cell interactions through its ability to interact with ICAM3 and ICAM2, respectively.[102] DC-SIGN is also expressed on the surface of a subset of peripheral blood and lung BDCA-2$^+$ pDCs and alveolar macrophages.[115] Of interest, increased expression of DC-SIGN by alveolar macrophages has been reported in response to stimulation with *interleukin-13* (IL-13), suggesting a possible role for DC-SIGN$^+$ cells in the pathogenesis of *type 2 T helper* (Th2)–mediated lung diseases.[115]

Cytoplasmic Pattern Recognition Receptors

Nucleotide-Binding and Oligomerization Domain–like Receptors (NLRs). In humans, NLRs are a family of intracellular PRRs that have evolved to sense PAMPs in the cytoplasm of most cells. Cytoplasmic PAMPs recognized by NLRs include bacterial peptidoglycans and flagellin from gram-positive and gram-negative bacteria, as well as microbial toxins, such as *Bacillus anthracis* lethal factor.[116–118] Earlier, we briefly introduced DAMPs as a collection of nuclear and cytoplasmic molecules, including high-mobility-group box-1 protein, adenosine triphosphate, *nicotinamide adenine dinucleotide* (NAD$^+$), and adenosine, which are released after tissue injury.[119] Studies have also shown that, although not technically DAMPs, uric acid and crystalline silica are also sensed by NLRs and, like PAMPs, initiate sterile inflammatory responses.[120–122] In turn, the recognition of cytoplasmic PAMPs and DAMPs by NLRs activates an array of signal transduction pathways that lead to the production of proinflammatory cytokines. Inflammasomes,[123–126] which are large protein-protein complexes comprising an NLR, an *apoptosis-associated speck-like protein containing a caspase activation and recruitment domain* ([CARD], ASC) adaptor protein, and procaspase-1, are important in the development of the inflammatory response. *Nucleotide-binding oligomerization domain, leucine-rich repeat and pyrin domain–containing protein 3* (NLRP3) is particularly relevant because it promotes the cleavage of pro–IL-1β and pro–IL-18 and the subsequent release of mature IL-1β and IL-18.[127] Inflammasomes also initiate several different forms of programmed cell death, including apoptosis, necrosis, pyroptosis, and pyronecrosis.[128] NLRs may also play a role in the maturation of immature DCs after exposure to PAMPs or cytokines.[125] The precise mechanisms by which NLRs signal is an area of intense investigation, but studies show that NLRs participate in the formation of three distinct inflammasomes, including the NLRP1 and NLRP3 inflammasomes and interleukin-1β–converting enzyme protease–activating factor–containing inflammasomes.[116,124] Although the role of NLRs in a variety of human disorders has been characterized, the complete role of these molecules in lung homeostasis and defense is not yet fully understood. More information about NLR structure and function is available in several revi ews.[116,118,124,128–134]

Retinoic Acid–Inducible Gene-1–like Receptors. The last group of cytoplasmic PAMP sensors is the RIG-I–like receptors that have evolved to detect the presence of RNA from RNA viruses (as recently reviewed[135]. Recent studies have also revealed that host-derived RNA can trigger these sensors in herpesvirus (a double-stranded DNA virus) infected cells.[136] Three family members—RIG-I, myeloma-differentiation–associated gene 5, and laboratory of genetics and physiology 2—have been identified. RIG-I has been shown to recognize viral RNA sequences from several viruses and is involved in the response of lung epithelial cells to influenza virus.[137,138] In contrast, myeloma-differentiation–associated gene 5 has been shown to respond to polyriboinosinic-polyribocytidylic acid and picornoviruses.[139] Upon sensing viral RNA sequences, RIG-like family members promote the expression of type I IFNs and proinflammatory cytokines,[140] thereby inducing and augmenting host and lung innate immunity.

SUMMARY

Secreted, plasma membrane, endosomal, and cytosolic PRRs provide remarkable flexibility in innate protection

of the lung. In the descending airways, plasma membrane PRRs, especially TLRs, are poised to sense PAMPs but are generally unable to phagocytose PAMP-containing microbes. However, TLR signaling in airway epithelial cells results in the production of proinflammatory mediators, especially chemokines and cytokines, which call in PMNs and macrophages to the site of PAMP detection to enable microbial clearance. In addition, intraepithelial DCs constantly sample the airway lumen to maintain immunologic tolerance to commonly encountered antigens that do not express PAMPs, while remaining poised to activate the adaptive immune system once PAMPs are sensed. The alveoli are also protected by epithelial cells, DCs, resident memory T cells, ILCs, and alveolar macrophages that also sense PAMPs via alveolar PRRs. However, in the alveoli, two additional levels of protection exist. First, secreted PRRs, especially SP-A and SP-D, protect the alveolar surfaces by tonically suppressing unwanted inflammation in the steady state, while remaining poised to stimulate innate responses in the presence of PAMPs. Second, alveolar macrophages express an additional array of PRRs, especially SRs that promote the phagocytosis of microbes and other particulates. It seems reasonable to suggest that, in the steady state, the innate immune system responds to inhaled particulates and microbes continuously, but silently. In the next section we discuss how ligation of these various PRRs activates and regulates innate host defense responses in lung cells.

EFFECTOR MECHANISMS

The cell types primarily responsible for innate protection of the lung in the steady state are airway and alveolar epithelial cells, macrophages, monocytes, and DCs and ILCs. In addition, in response to the initial activation of these cells, PMNs, although not an abundant cell type in the steady state, are rapidly recruited to augment lung phagocyte numbers once the presence of PAMPs is detected. In the following section, we review the origin and functions of these resident and recruited cells in innate protection of the lung.

EPITHELIUM

The lung epithelium has an important role in host defense against microbes that pass through the glottis and reach the conducting airways and gas-exchange parenchyma. The conducting airways of the lower respiratory tract are lined by ciliated columnar epithelial cells down to the terminal airways; these cells become nonciliated in the respiratory bronchioles. In contrast, the alveolar epithelium consists of flattened type 1 epithelial cells forming most of the alveolar surface and type 2 cuboidal epithelial cells that project into the subepithelial structures of the lungs, produce surfactant and surfactant-related proteins, and serve as both self-renewing stem cells and progenitors of type 1 epithelial cells. The classic antimicrobial defense mechanism in the conducting airways is the mucociliary system, which moves microbes deposited on the airway epithelial surface upward and out of the lungs. In addition to this physical removal system, the airway and alveolar epithelium participate actively in the innate defense of the lungs, with the major goal of protecting the critical gas-exchange surface from microbial invasion.[141] The mucociliary system provides for the removal of all particles that deposit on the airway epithelium, and the clearance times in the trachea and proximal airways are measured in minutes (see Video 13.3). The cilia on the epithelial surface beat in coordinated waves, directing the movement of particles upward toward the larynx. Epithelial cell activation is not required for optimal ciliary beating, although beat frequency can be increased by β-agonists and slowed by opiates and other drugs.[142] Additional information on mucociliary clearance can be found in Chapter 13.

The mucociliary system and antimicrobial constituents of airway epithelial fluid discussed in the "Overview of the Components of Lung Innate Immunity" section (see Table 15.1) can be thought of as constitutive host defenses because they do not depend on specific microbial recognition mechanisms and do not need activation. However, the airway and alveolar epithelium also participate in innate immune mechanisms in that they express bacterial recognition molecules (PRRs) common to innate immune cells and can produce an array of proinflammatory mediators that recruit leukocytes into the airways directly through the airway and alveolar epithelial walls. Bacterial products stimulate the airway epithelium to produce chemotactic signals that recruit inflammatory cells into the airways. Endogenous cytokines also stimulate airway and alveolar epithelial cells to amplify leukocyte migration. Bacterial LPS stimulates ciliated airway epithelial cells to produce CXC and CC chemokines, which recruit PMNs and monocytes, respectively, into the airway lumen.[143] Airway epithelial cells also produce IL-1β, IL-6, IL-8, *regulated on activation, normal T cell expressed and secreted* (RANTES), *granulocyte-macrophage colony-stimulating factor* (GM-CSF), and *transforming growth factor-β* (TGF-β).[141] As with other cells involved in innate immunity, airway epithelial cells produce cytokines via the activation of transcription factors, including *nuclear factor-κB* (NF-κB), activator protein-1, and nuclear factor IL-6.[144] Of interest, noninfectious environmental agents, such as ozone,[145] asbestos,[146] diesel exhaust particles,[147] and air pollution particles,[148] all lead to NF-κB activation in airway epithelial cells under experimental conditions, which is typically followed by IL-8 production and release. Airway epithelial cells also recognize unmethylated bacterial DNA via TLR9, leading to NF-κB activation and production of IL-6, IL-8, and β_2-defensin in the airways.[149] Unlike airway epithelial cells, alveolar epithelial cells do not respond directly to LPS but do produce chemokines in response to the *tumor necrosis factor-α* (TNF-α) and IL-1β produced by alveolar macrophages in response to PAMPs.

The critical role of the lung epithelium in innate immunity and microbial defense has been supported by studies using transgenic mice. When a dominant negative IκB construct was expressed in the distal airway epithelial cells of mice, thereby preventing NF-κB activation, airway PMN recruitment in response to inhaled LPS was impaired.[150] This finding supports the importance of bacterial recognition by distal airway epithelial cells in vivo and shows that epithelium-derived cytokines produced by the NF-κB pathway probably are just as important as macrophage-derived cytokines in driving innate inflammatory responses in the

airways and alveolar spaces. Hajjar and colleagues[151] created bone marrow chimeras in which either myeloid (leukocytes) or nonmyeloid (epithelial) cells lacked Myd88, a key adapter molecule required for signaling via all TLRs except TLR3. Unexpectedly, nonmyeloid deficiency of Myd88 impaired bacterial clearance more than myeloid deficiency. Specifically, mice lacking Myd88 (and therefore lacking TLR signaling) in nonmyeloid cells, including the airway and alveolar epithelium, had markedly impaired clearance of *P. aeruginosa*, whereas mice with or without Myd88 in myeloid cells had normal bacterial clearance. This surprising result further supports the important role of the airway and alveolar epithelium in bacterial recognition and clearance from the lungs, a role perhaps equivalent to that of resident and recruited leukocytes.

Innate immune responses in the airway epithelium can generate or influence adaptive responses. For example, recognition of β-(1,3)-glucan in house dust mites stimulates the production of CCL20, a chemokine that recruits immature DCs into the airways.[152] The airway epithelium can directly influence the function of lung DCs, inducing adaptive Th2 responses thought to be important in the pathogenesis of asthma, and LPS responses in the airway epithelium involved in some DC-driven Th2-cell responses.[153] Airway epithelial cells produce thymic stromal lymphopoietin, GM-CSF, IL-1β, IL-25, IL-33, and osteopontin, all of which activate DCs.[154]

An emerging concept is that deliberate stimulation of innate immunity in the airways and air spaces produces broad enhancement of antimicrobial defenses. Exposure of mice to a crude extract of nontypeable *Haemophilus influenzae* bacteria via aerosol initially stimulated innate immunity and then protected the mice from lethal infection with *S. pneumoniae*.[155] This was associated with enhanced production of lysozyme, lactoferrin, and defensins in the lungs. Similarly, exposure to this crude bacterial extract protected mice from *S. aureus*, *P. aeruginosa*, and the fungus *Aspergillus fumigatus*.[156] Thus, prestimulation of innate immune mechanisms in the airway and perhaps alveolar epithelium enhances antimicrobial activity and host defense of the lungs against a broad array of bacteria and fungi. The implication is that deliberate low-level stimulation of innate immunity in the lungs could be used as a protective strategy; however, the recognition of the important role of lung epithelial innate immunity in stimulating and regulating adaptive immune mechanisms raises the possibility that such a strategy might have unexpected effects, such as promoting a hyperinflammatory state.

Thus, innate immune mechanisms in the airways stimulate endogenous defenses by enhancing production of airway defensins and other antimicrobial products, by stimulating PMN and monocyte recruitment into the airways to augment antimicrobial defenses, and by setting the stage for DCs and Th2-mediated adaptive immune responses that could be important in the pathogenesis of allergic lung diseases.

POLYMORPHONUCLEAR LEUKOCYTES

PMNs serve as the immediate effector arm of the innate immune system.[157,158] PMNs are produced from progenitor cells in the bone marrow, circulate for a short time in the bloodstream, and migrate to sites of tissue inflammation in response to signals produced by local innate immune mechanisms. Mature PMNs are released from the marrow in response to granulocyte colony–stimulating factor and other stimuli and circulate for up to 6 to 8 hours.[159] The bone marrow releases between 10^9 and 10^{10} PMNs each day, and marrow release can increase several fold in response to acute signals from the lungs and other tissues. PMNs contain several different kinds of cytoplasmic granules, containing an array of proteins (Fig. 15.4). Small specific granules serve as a source of new membrane during cell migration. Primary (azurophilic) granules contain myeloperoxidase, which accounts for the green color of pus, bacterial permeability–increasing protein, neutrophil elastase, matrix metalloproteinases, other proteinases, and defensins.

Circulating PMNs are spherical, with a diameter of approximately 8 μm, and must deform to make their way through the capillary microcirculation in the lungs and other organs.[160] Under normal circumstances, this migration is not associated with injury to the endothelial or epithelial barriers. PMNs bear surface adhesion molecules that recognize carbohydrate and protein moieties expressed on activated endothelial cells. In the systemic circulation, PMNs migrate into tissue through postcapillary venules in a four-step process by (1) weakly adhering to the venular endothelium, (2) rolling along the endothelial surface, (3) arresting on the endothelial surface, and (4) migrating between endothelial junctions into tissue in response to local chemotactic gradients.[160,161] In addition, the

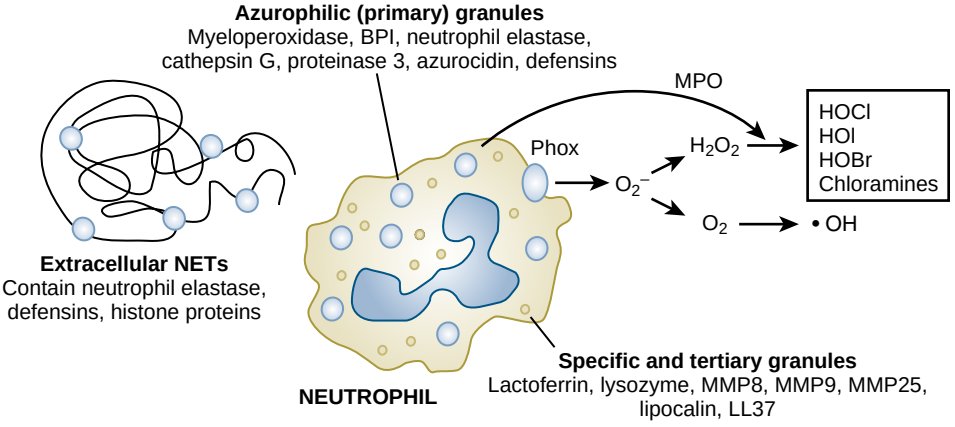


Figure 15.4 Neutrophils use several mechanisms to kill microbes. BPI, bacterial permeability–increasing protein; HOBr, hypobromous acid; HOCl, hypochlorous acid; HOI, hypoiodous acid; LL37, cathelicidin; MMP, matrix metalloproteinase; MPO, myeloperoxidase; NET, neutrophil extracellular trap; Phox, phagocyte oxidase. (Modified from Nathan C. Neutrophils and immunity: challenges and opportunities. *Nat Rev Immunol.* 2006;6:173–182.)

endothelial cells undergo reversible contraction in response to thrombin and other inflammatory stimuli, thereby opening endothelial junctions and allowing the passage of leukocytes. The alveolar barrier is much tighter, and yet PMNs reach the air spaces with only minor and transient changes in epithelial permeability.[162,163] Within the lungs, the small cross-sectional size of the pulmonary capillaries slow the transit of PMNs, producing a reservoir of capillary PMNs poised to respond directly to signals from the innate immune system in the air spaces.[164,165]

When bacteria or their products, such as gram-negative LPS, circulate in the bloodstream, PMNs undergo activation with cytoskeletal rearrangements that cause stiffening,[166] promoting increased entrapment of PMNs in the pulmonary capillaries. During migration, specific granules fuse with the leading edge of the cell membrane, providing new membrane material bearing specific adhesion molecules initiating the migratory process. Metabolic studies of PMNs in rabbits with pneumococcal pneumonia and humans with bronchiectasis have shown that most PMNs become fully activated in the air spaces and not during their migration into the lung.[162,167,168] However, when endothelial activation is intense or when PMN activation signals are present within the circulation, PMNs become preactivated, and migration can be associated with damage to the endothelial and epithelial barriers, with the development of increased-permeability pulmonary edema.[169]

When innate immunity is activated in the lungs, chemotactic factors are produced by alveolar macrophages and activated epithelium, which create complex, combinatorial, soluble, and tissue-fixed gradients that recruit PMNs into the alveolar spaces.[170] Leukotriene B_4 is a product of arachidonic acid metabolism in alveolar macrophages that produces an immediate and short-lived soluble gradient that recruits PMNs into the air spaces but dissipates within minutes.[171,172] Release of leukotriene B_4 is closely followed by the release of IL-8, a chemokine that binds to heparin residues on tissue matrix, creating a tissue reservoir promoting long-lived gradients that guide PMNs sequestered in the pulmonary capillaries into the airspaces.[173,174] IL-8 is the dominant member of a group of CXC chemokines, which also include GRO-α, GRO-β, and GRO-γ, and ENA-78. The CXC chemokines have a C-X-C sequence at the N-terminus, which provides PMN specificity, and an N-terminal Glu-Leu-Arg peptide sequence, which is important in chemotactic receptor binding. The CXC chemokines recruit PMN to sites of inflammation, whereas chemokines with the CC N-terminal sequence recruit monocytes. Whereas PMNs bear a single receptor for leukotriene B_4, they express two different receptors with differing affinity for IL-8. The low-affinity receptor (CXCR2) is thought to recruit PMNs to sites of inflammation, whereas the high-affinity receptor (CXCR1) is thought to guide PMN migration into the tissues. The low-affinity receptor is shed from the surface of circulating PMNs in sepsis, leaving the high-affinity CXCR1 receptor as the dominant IL-8 receptor.[175] This suggests that a CXCR1 receptor–targeted strategy could be effective in limiting PMN inflammation in patients with sepsis. PMNs also have receptors for the complement component C5a and for formylated peptides produced by bacteria in the air spaces so that endogenous and exogenous signals attract PMNs to sites of inflammation.

PMN migration into most tissues depends on the integrin CD11/CD18 on the PMN surface recognizing the counterligand ICAM1 on the endothelial surface. In the lungs, however, both CD18-dependent and CD18-independent mechanisms exist, and the signals that determine the dependence on CD18 are not clear.[176] For example, PMN migration into the lungs in response to *E. coli* and *P. aeruginosa* is CD18 dependent, whereas PMN migration in response to *S. pneumoniae* does not require CD18. TNF-α and IL-1β appear to direct CD18-dependent migration, whereas IFN-γ is more important for CD18-independent migration.

Once in the air spaces, PMNs ingest bacteria and fungi opsonized by complement and immunoglobulins that accumulate in the air spaces at sites of inflammation. PMNs contain a series of effector mechanisms to kill bacteria and fungi, including oxidant production, microbicidal proteins in primary azurophilic granules, and extracellular traps (see Fig. 15.4). As microbes are recognized, they are enveloped by plasma membrane to form the phagosomes. The phagosome is the intracellular compartment where digestion and killing of ingested particles takes place in a tightly regulated manner.[177] Within the phagosome, the subunits of a *nicotinamide adenine dinucleotide phosphate, reduced form* (NADPH) oxidase are assembled in the cell membrane, and the cell undergoes a respiratory burst; a superoxide anion is formed and reduced to form hydrogen peroxide. This happens on the invaginating phagosomal membrane. As the phagosome forms, the primary granules fuse with the phagosomal membrane, adding myeloperoxidase and cationic antimicrobial peptides to the phagolysosome. Myeloperoxidase catalyzes the formation of hypochlorous acid from hydrogen peroxide and a halide, typically *chloride* (Cl^-), because of its high concentration in the cellular environment. Hypochlorous acid is a highly reactive oxidant that oxidizes methionines, tyrosines, and other amino acids on proteins, facilitating the killing of the microbes.

When α-defensins or human neutrophil protein 1, 2, and 3 (present in the primary azurophilic granules) are added to the phagolysosomal space, they attach to negatively charged microbial membranes via electrostatic interactions and are thought to form lytic pores in the microbial cell wall.[178,179] PMN defensins have antimicrobial activity for gram-positive and gram-negative organisms, fungi, and some viruses. Defensins are most active under conditions of low ionic strength and lose activity with increasing concentrations of salt or plasma proteins, which interfere with electrostatic interactions between the cationic defensins and the anionic microbial surface.[178] The loss of defensin activity in higher salt concentrations has been proposed as a contributing factor for the pathogenesis of chronic airway infection in cystic fibrosis.[180] In addition to their antimicrobial activity, defensins participate directly in innate and adaptive immunity because they stimulate IL-8 production by epithelial cells and modulate the responses of T cells and immature DCs.[179,181]

When phagocytosis is appropriately regulated, microbes are killed within the protected environment of the PMN phagolysosome. However, at sites of intense inflammation, PMNs release superoxide anions, hydrogen peroxide, and granular contents directly into the extracellular environment, leading to oxidant formation in the alveolar spaces with oxidation of structural proteins in the alveolar walls and intracellular proteins in leukocytes, and the

accumulation of defensins and other granular contents in the alveolar spaces.[182] These extracellular products contribute to tissue injury by PMNs.

In addition to killing intracellular microbes using oxidants, chlorination, and antimicrobial peptides, as a final act, PMNs can project uncoiled nuclear DNA into the surrounding environment to form *neutrophil extracellular traps* (NETs) that ensnare and destroy bacteria.[183,184] NET formation depends on the initial respiratory burst of the PMN and leads to the death of the PMN in a process distinct from apoptosis and necrosis.[185] The PMNs of patients with chronic granulomatous disease, which lack a functional membrane NADPH oxidase, do not form NETs after appropriate stimulation.[185] A variety of proinflammatory stimuli activate NET formation, including LPS and IL-8. C5a triggers NET formation in PMNs after priming with IFNs or GM-CSF. Some microbes, including *S. aureus*, *E. coli*, *P. aeruginosa*, and *M. tuberculosis*, directly stimulate NET formation by PMNs.[186] The extracellular DNA mesh contains cationic proteins embedded in the negatively charged DNA net, including histones, defensins, and cathelicidin, which kill enmeshed bacteria. NET formation thickens secretions at sites of inflammation, creating a viscous pus with enmeshed microbes. As might be expected, some bacteria produce extracellular enzymes that degrade DNA NETs, including *S. pyogenes* (DNase Sda1/2) and *S. pneumoniae* (DNase EndA).[187,188] The mechanisms by which NETs are cleared from the air spaces during resolution of inflammation are not clear. Recent evidence suggests that NETs contribute to disease pathology in several immune-mediated diseases, including cystic fibrosis, where clinical isolates of *P. aeruginosa* are resistant to NET-mediated killing.[189–193]

PMNs have an important role in signaling the activation of adaptive immunity.[194] In rabbits with tuberculous pleurisy, PMNs are the first cells that migrate into the infected pleural space, where they produce chemotactic factors that direct the subsequent wave of monocyte recruitment, which characterizes the full inflammatory reaction to *M. tuberculosis.*[195] PMN granule proteins cathepsin G and azurocidin are chemoattractants for mononuclear cells, which mature into macrophages and DCs at sites of inflammation, and neutrophil-derived CC chemokines recruit DCs.[196,197] PMNs release limited amounts of TNF-α and IFN-γ, which regulate macrophage, T cell, and DC activation and maturation; however, the large numbers of PMNs at sites of inflammation can bring the concentrations of these PMN-derived cytokines into biologically relevant ranges. PMNs also produce CXC chemokine ligand 10 (IFN-γ inducible protein-10), which is a chemoattractant for natural killer cells and Th1 cells.[198] They also produce the lipid mediators prostaglandin E2 and leukotriene D4, which are potent activators of ILCs.[199,200]

At the same time that PMNs participate in and intensify inflammation in tissue, they also produce signals that control and begin the resolution of inflammation. PMNs, like macrophages and endothelial cells, release the secretory leukocyte protease inhibitor, which inhibits neutrophil elastase.[201] After migration into tissues, PMNs produce lipoxins from membrane arachidonic acid, which inhibit PMN recruitment, superoxide anion generation, and NF-κB activation, and enhance the uptake of apoptotic PMNs by macrophages.[202] PMN-derived oxidants inactivate proteases and other proteins at sites of inflammation.

PMNs and their products are cleared largely by macrophages during the resolution of inflammation. PMNs die primarily by apoptosis, necrosis, or NET formation. PMNs undergoing apoptosis express phosphatidylserine on the outer leaflet of the cell membrane and undergo nuclear chromatin condensation and cell shrinkage. Apoptotic PMNs are recognized by macrophages via the class B SR, CD36, and are rapidly ingested, so that large numbers of apoptotic PMNs are usually not seen. Macrophages that ingest apoptotic PMNs produce TGF-β and IL-10, which have anti-inflammatory effects. This process results in the clearance of PMNs and their residual intracellular contents and the dampening of inflammation.

However, in some cases inflammation may not be appropriately dampened. PMNs not ingested by macrophages undergo secondary necrosis with loss of membrane integrity, cytoplasmic swelling, and release of remaining intracellular contents into the inflammatory environment. Intracellular components are recognized as danger signals by macrophages, some of which function as "alarmins," or DAMPs.[203] DAMPs include the nuclear protein high-mobility-group box-1, granular antimicrobial peptides, and other intracellular products. Macrophages recognizing these danger signals produce IL-1β, TNF-α, IL-8, and other proinflammatory cytokines, initiating or perpetuating inflammatory responses. Some PMNs recovered from the lungs of patients with the acute respiratory distress syndrome have features of apoptosis, with small cytoplasmic features and nuclear pyknosis, whereas many have features of necrosis, including severe degranulation, membrane blebbing, and cytoplasmic swelling. The signals that govern the balance between apoptosis and necrosis, and therefore the balance between controlled or sustained inflammation, are incompletely understood.

Thus PMNs are important effector cells in innate immunity, ideally designed to circulate through the body and accumulate rapidly at tissue sites during acute inflammation. Under normal circumstances, they arrive in tissue ready to ingest and kill microbes, then quietly go away by programmed cell death. PMN-derived signals regulate local inflammation and stimulate adaptive immune responses, providing a broader role for PMNs in host defense.

INNATE LYMPHOID CELLS

ILCs are a newly identified class of lymphoid cells that are $CD45^+$ $Thy1^+$ but do not have antigen specificity, either through recombination of antigen receptors or through clonal selection.[204–206] ILCs are found within mucosal tissues, including the respiratory tract, and respond to pathogens through PRRs.[207] Once they are activated, they secrete immunoregulatory cytokines associated with Th1, Th2, or Th17 responses.[208] An important feature of IL-17–mediated diseases is the regulation of PMNs, both during homoeostasis and inflammation, thus making ILCs a potent influencer of neutrophil trafficking.[209] Additional information on ILCs can be found in Chapter 16.

MONONUCLEAR PHAGOCYTES

The concept of the mononuclear phagocyte system as a functionally and phenotypically heterogeneous system

distributed throughout the body was developed in the 1960s and 1970s through a series of insightful studies pioneered by van Furth and Cohn[210] and Volkman and Gowans.[211] The central concept was that the resident macrophages of all organs and tissues were derived from progenitor cells in the bone marrow. In turn, the progenitor cells gave rise to circulating blood monocytes that were recruited into organs and tissues, where they differentiated into macrophages, to maintain macrophage homeostasis and to respond during inflammation or infection.[212–214] Fate-mapping studies involving lineage-tagged mice and other genetic models have refuted this notion by showing that there is a pool of "primitive" F4/80-high resident macrophages located within tissues derived from the yolk sac beginning on *embryonic day 8* (E8) (Fig. 15.5A).[215–217] In addition to expressing high levels of F4/80, these yolk sac–derived macrophages express CX3CR1, macrophage mannose receptor, and *colony-stimulating factor 1 receptor* (CSF1R; *c-fms* [gene]) and are dependent upon IL-34, CSF1, and the transcription factor PU.1 for their development (see Fig. 15.5A).[216,218–221] By E10.5, yolk sac–derived macrophages reside in most tissues, including the lung, and are able to undergo self-renewal.[212,214,216,222–230]

At E10.5, the fetal liver becomes the major site of hematopoiesis[231] and, with its development, a unique "definitive" macrophage population derived from the hematopoietic stem cell can also be found.[216,220] These cells express low levels of F4/80, high levels of CD11b, and, in contrast to the yolk sac–derived macrophages, are dependent on the transcription factor c-Myb for development.[216] During liver hematopoiesis, macrophages constitute up to 15% of the total cells in many organs,[220] and their importance in embryonic development has been definitively shown in studies using *c-fms*–, colony-stimulating factor 1–, CX3CR1-, c-Myb–, and PU.1-deficient mice.[216,232–235] These studies also showed that adult Langerhans cells, the prominent antigen-presenting cells of the skin, are produced by the fetal liver and that their development is dependent on IL-34 and CSF1. In studies using these and other models, macrophages have been shown to play important roles in bone morphogenesis, ductal branching in the mammary gland, neuronal patterning, angiogenesis, vascular remodeling, and kidney and endocrine development.[234,236,237] Analysis of embryonic tissue has shown that the lungs basally contain macrophages of fetal liver and hematopoietic stem cell origin.[216,238]

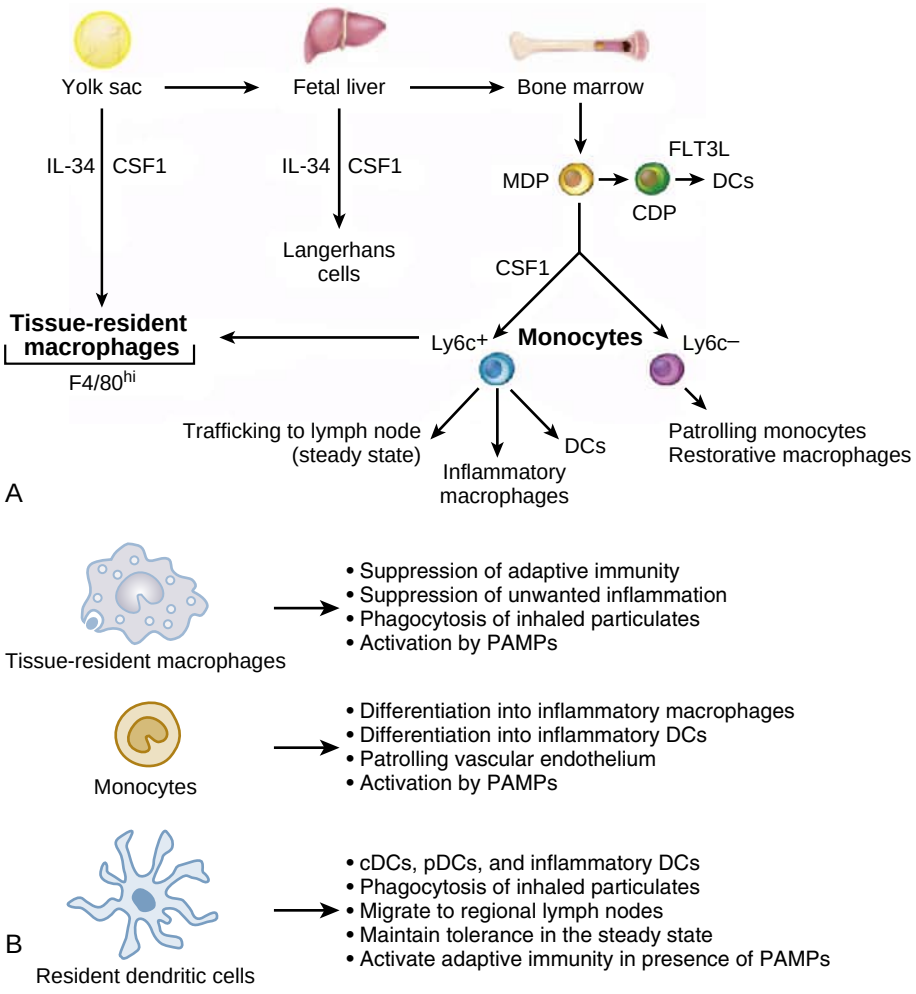


Figure 15.5 Pathways of development of tissue-resident macrophages and blood monocytes. (A) During embryogenesis, macrophages derived from the yolk sac populate most tissues, including the lung. Later, the fetal liver and the bone marrow become sites of hematopoiesis. (B) In the steady state, lung mononuclear phagocytes can be considered to include (1) tissue-resident macrophages of the alveoli and interstitium, (2) marginating monocytes of the lung microvasculature, and (3) resident DCs. Each of these subsets exhibits overlapping and unique functions. cDC, conventional DC; CDP, common DC precursor cell; CSF1, colony-stimulating factor 1; FLT3L, FMS-like tyrosine kinase 3 ligand; IL, interleukin; MDP, macrophage and DC precursor; PAMP; pathogen-associated molecular pattern; pDC, plasmacytoid DC. (A, Modified from Wynn TA, Chawla A, Pollard JW. Macrophage biology in development, homeostasis and disease. *Nature.* 2013;496:445–455.)

In addition to macrophages, DCs play a fundamental role in lung innate immunity. Steinman[239] published the first report on a population of antigen-presenting cells in mouse spleen and, based on their morphologic characteristics, coined the name dendritic cells. This work was recognized in 2011 with the posthumous award of the Nobel Prize in Physiology or Medicine. Since the late 1980s, a vast array of monoclonal antibodies against monocytes, macrophages, and DC cell surface antigens, together with lineage-tracing mice, have been developed and used to classify monocytes/macrophages and DCs.[42,240] With the onset of single-cell RNA sequencing technology, the ability to classify and define macrophages, monocytes, and DCs has been greatly expanded.[81,241–244] Cell surface molecules that help distinguish mononuclear phagocytes in humans and mice are FcgR1/CD64 and C5aR1/CD88, which are highly expressed on monocyte/macrophages and not DCs. F4/80 and CD11c, originally thought to distinguish monocytes/macrophage and DCs, are expressed on all mononuclear phagocyte classifications. In addition, much of our initial understanding of the functions of lung mononuclear phagocytes has come from studies conducted without the use of extensive cell surface marker panels or lineage-tracing technologies or using in vitro systems. Thus, although it is clear that the cells described in many studies are mononuclear phagocytes, it is sometimes difficult to classify them further without the use of multiple antibody markers combinations.[245] As illustrated in Figure 15.5B, pulmonary mononuclear phagocytes can be broadly thought of as three overlapping subpopulations: (1) *resident macrophages* of alveoli and interstitium; (2) *monocytes*, which marginate in the lung microvasculature, survey the lung environment, and can be recruited into the air spaces in response to innate activation; and (3) *resident and recruited DCs* of the airways and lung parenchyma. In this section, we discuss the localization and innate immune functions of each group of cells.[239,242,246]

Resident Macrophages

Tissues have two classes of resident macrophages: one that is *tissue specific*—in the lungs, the alveolar macrophage—and one that is *common* among all tissues—in the lungs, the interstitial macrophage.

Alveolar macrophages are distinguished from interstitial macrophages by several factors. The first is origin, with alveolar macrophages being derived from the yolk sac embryogenesis and interstitial macrophages derived from the fetal liver and circulating monocytes.[238] However, it is still unclear how origin dictates the functional outcome of a macrophage population.[247] The second is transcriptional signatures. There are major transcriptional differences between alveolar and interstitial macrophages.[51,248–251] All tissue-resident macrophages share core macrophage signature genes, but each tissue-specific macrophage displays their own unique transcriptional signature adapted to a given environment.[51] Tissue-specific macrophages also differ functionally, in parallel with the variation in their transcriptomes. By contrast, interstitial macrophages from the skin, heart, intestine, and lung have transcriptionally overlapping profiles independent of their local tissue environment.[248–251] The conserved transcriptional profile across multiple organs, also observed in DCs,[42] suggest that interstitial macrophages may have a similar function in different organs.

ALVEOLAR MACROPHAGES

The primary functions of alveolar macrophages are to (1) dispose of inhaled microbes and particulates, (2) clear pulmonary surfactant, and (3) suppress the development of inappropriate inflammatory and immune responses. Alveolar macrophages are capable of phagocytosing a wide spectrum of harmless and harmful microbes and other particulates. Under basal conditions, most ingested phagocytosed particulates are enclosed within phagosomes, which ultimately fuse with lysosomes, leading to their degradation by an array of acid-pH optimum hydrolytic enzymes. Some inhaled microbes (e.g., *M. tuberculosis*) and some environmental particulates (e.g., crystalline silica) are resistant to this process and become sequestered in secondary lysosomes, where they remain for the life span of the macrophage. Most of these latter cells probably crawl into the airways and are cleared via the mucociliary escalator.[252,253] Some particle-laden macrophages may remain in the lung for extended periods of time before either dying and releasing their particle burden, thereby rendering it available for phagocytosis by other macrophages, or undergoing apoptosis and being cleared by other phagocytes.

Alveolar macrophages reside in the mixed environment of epithelial lining fluid and ambient inhaled air,[42,254–256] where they actively contribute to the normal homeostasis of pulmonary surfactant. This point is most clearly emphasized in patients with pulmonary alveolar proteinosis, a disorder characterized by the accumulation of proteinaceous and lipid-rich surfactant in the alveoli, leading to impaired gas exchange. A fundamental characteristic of the disorder is the finding that alveolar macrophage numbers are reduced, and those present are inefficient in clearing pulmonary surfactant.[257,258] Several studies have shown that pulmonary alveolar proteinosis can be associated with the development of autoantibodies against GM-CSF,[257–259] emphasizing the importance of GM-CSF in the activities of alveolar macrophages. Additional information about alveolar proteinosis syndromes can be found in Chapter 98.

Last, alveolar macrophages play a critically important role in tonic suppression of alveolar inflammation and adaptive immunity. Based in part on studies by MacLean and associates,[260] the concept has evolved that the lung can deal with inhaled microbes and particulates until a certain threshold burden is reached. The threshold is in part determined by the phagocytic capacity of alveolar macrophages. Once the threshold is exceeded, microbes and other particulates are phagocytosed by resident DCs that "snorkel" through tight junctions of the alveolar epithelium to sample the alveolar compartment. Consistent with this concept, studies have shown that depletion of alveolar macrophages with liposome-encapsulated clodronate augments antigen presentation by pulmonary DCs, which in turn augments adaptive immune responses to intranasal delivered antigens.[261,262]

INTERSTITIAL MACROPHAGES

There are three *interstitial macrophage* (IM) subtypes: Two IMs, IM1 ($CD206^{hi}MHCII^{+}$) and IM2 ($CD206^{hi}MHCII^{lo}$), display classical macrophage characteristics, whereas the third IM, IM3 ($CD206^{lo}MHCII^{+}$), although containing macrophage properties, has a higher rate of turnover and expresses proinflammatory mediators, monocytic and DC genes.[42,248–251] Furthermore, all IMs express high levels of standard macrophage markers, such as MerTK, CD64, CD11b, and F4/80, while differing in their expression of CX3CR1, Lyve-1, CCR2, CD11c, and MHC class II.[42,248–251] Interstitial macrophages have been observed to interact with lymphatic vessels and sympathetic nerves in the bronchovascular bundle.[42,263,264] With the advent of single-cell RNA sequencing and identification of interstitial macrophage subtypes, new questions can now be addressed to determine their functional properties and relationship to cells in close proximity (i.e., blood vessels, lymphatic vessels, fibroblasts, nerves, and epithelial cells).

Monocytes

After birth and postnatal bone formation, liver hematopoiesis declines and is replaced by bone marrow hematopoiesis, which then becomes the exclusive source of circulating monocytes. Circulating monocytes have the potential to differentiate into macrophages or DC-like cells.[265–270] In 1989, Passlick and associates reported heterogeneity among human macrophages based on the differential expression of CD14 and CD16.[271] *Classical* $CD14^{hi}CD16^{-}$ monocytes make up approximately 95% of circulating monocytes in the steady state, and *nonclassical* $CD14^{lo}CD16^{+}$ monocytes constitute the remaining 5%.[272,273] Similar to human monocytes, mouse monocytes have been classified into *classical* ($Ly6C^{hi}$) and *nonclassical* ($Ly6C^{lo}$) monocyte subsets.[269,274,275] During steady state, $Ly6C^{lo}$ monocytes patrol the lung vasculature; they express high levels of the fractalkine receptor CX_3CR1, which interacts with fractalkine CX_3CR1L, expressed on the luminal face of vascular endothelial cells, and promotes adherence.[274,276] The $Ly6C^{hi}$ monocytes enter tissue in a CCR2-dependent manner in steady-state and inflammatory conditions. In the steady state, circulating $Ly6C^{hi}$ monocytes continuously traffic into the lung and lymph nodes without differentiating into resident macrophages, unless there is a macrophage niche to fill.[277] $Ly6C^{hi}$ monocytes survey the tissue environment and can acquire antigen and traffic to regional lymph nodes for antigen presentation (see Fig. 15.5A).[277,278] During inflammation, monocytes can differentiate into inflammatory and resolving macrophages, which display distinct properties from resident macrophages,[241,244,279,280] or monocyte-derived DCs. In lymphoid tissue, even though lymph node monocytes are highly present, their role in adaptive immunity is less defined than DCs. Last, $Ly6C^{hi}$ monocytes are a short-lived obligatory precursor intermediate for $Ly6C^{lo}$ monocytes under steady-state conditions.[223] Additional information about the mechanisms of monocyte, macrophage, and DC migration can be found in other reviews.[278,281,282]

Functions of Recruited Monocytes and Macrophages

In contrast to alveolar macrophages, recruited monocytes and macrophages have important proinflammatory and host-defense activities, including (1) microbial killing and (2) amplification of inflammation. Monocytes and macrophages kill microbes with *reactive oxygen species* (ROS) and reactive nitrogen species. *Superoxide anion* (O_2^-) is mainly produced by the phagocyte NADPH oxidase.[283] Like PMNs, monocytes subsequently convert O_2^- into additional ROS in a myeloperoxidase-dependent fashion[284] but, as they differentiate into macrophages, intracellular myeloperoxidase content declines, and additional ROS (e.g., hydroxyl radical [OH^-]) are formed by the Fenton reaction.[285]

The generation of ROS is critical to host defense against commonly encountered and pathogenic bacteria. Patients with chronic granulomatous disease and mice bearing a targeted disruption of the $p47^{phox}$ component of the NADPH oxidase[286,287] are deficient in their ability to control pulmonary and other infections.[286–289] Thus, whereas ROS play a vital role in the protection of the lung against microbes, inappropriate production in response to nonmicrobial particulates and pollutants, including cigarette smoke,[290] can result in a spectrum of injury to the airway and alveolar epithelium. *Nitric oxide* (NO) produced by *inducible nitric oxide synthase* (iNOS or NOS2) also contributes to macrophage-mediated microbial killing and epithelial injury after condensation with O_2^- to form peroxynitrite.[291,292] Whereas the importance of NO in microbial killing of *L. monocytogenes* and *M. tuberculosis* has been clearly demonstrated in mice,[293] the role of NO in host defense in humans is less clear.

Recruited monocytes that develop into macrophages are also capable of further differentiation. Based on earlier work in which different PAMPs were found to induce distinct patterns of macrophage gene expression,[39,294–296] the concept evolved that different patterns of gene expression could be induced in response to the conditions or stimuli prevailing at the sites to which macrophages have been recruited.[297–299] Much of the initial work describing macrophage programming subtypes was conducted using in vitro studies and macrophage cell lines. The diversity, complexity, and flexibility of macrophage programming in homeostasis and disease is now recognized, and the simple classification of macrophages into "classical" and "alternative" programming is being redefined because there are often overlapping patterns of gene expression in response to multiple stimuli.[300,301] Macrophages have the capacity to respond to a diverse range of environmental stimuli, and it may be more appropriate to think about these adaptive responses as points on a continuum in which the response generated is purely an adaptation to the microenvironment that macrophages encounter.[297,299,302,303]

In summary, macrophages play key roles in the maintenance of lung homeostasis through their abilities to suppress unwanted inflammation and immune responses to harmless, commonly encountered inhaled materials. However, they remain constantly poised to respond to harmful inhaled microbes and other substances. Part of this response involves calling in additional support through

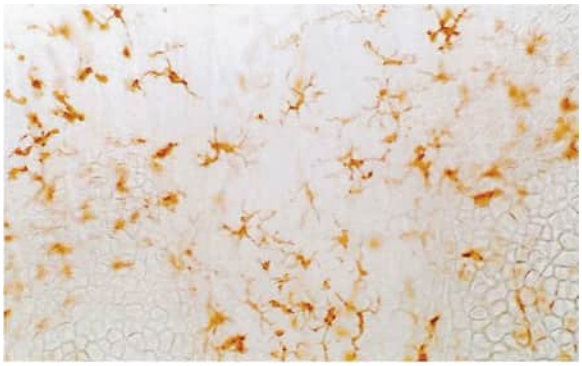


Figure 15.6 Airway dendritic cells exist as an interdigitating network within the epithelium and below the basement membrane. This population requires specific tissue preparation techniques for visualization. This whole-mount section of a mouse trachea was stained for major histocompatibility complex class II. (From Vermaelen K, Pauwels R. Pulmonary dendritic cells. *Am J Respir Crit Care Med.* 2005;172:530–551.)

the recruitment of circulating blood PMNs and monocytes. In turn, recruited monocytes can differentiate into macrophages or DCs, which can then express appropriate responses to microenvironmental cues at the site to which they have been attracted.

Resident and Recruited Dendritic Cells

DCs are the "professional" antigen-presenting cells of most tissues. DCs represent an important group of phagocytic and antigen-presenting cells acting as a bridge between the innate and the adaptive immune systems. In the lung, DCs have been shown to form an extensive intraepithelial and subepithelial network throughout the respiratory tract (Fig. 15.6).

DCs differ from alveolar macrophages in their (1) ontogeny, (2) antigen processing (macrophages rapidly degrade exogenous antigen), (3) expression of the receptor CCR7 mediating lymphatic migration, and (4) presentation of antigen to naive T lymphocytes in the lymph nodes and initiation of their maturation into effector cells. In the mouse, a division of labor by the two migratory DCs has been demonstrated in part on the basis of their transcription factors Batf3$^+$ versus Irf4$^+$ or integrins CD103$^+$ versus CD11b$^+$, respectively.[24,64,251,304–306] Both DCs migrate to the draining lymph node and present antigen to lymphocytes[307,308] but differ in a number of other important ways.[64,65,309–322] The *Batf3$^+$ CD103$^+$ DC* (DC1) selectively takes up apoptotic cells and cross presents cell-associated antigens on class 1 MHC to CD8 T cells in vivo, and mediates their subsequent differentiation to cytotoxic CD8$^+$ T cells, processes important for combating intracellular pathogens and cancer.[64,306,310,323] In fact, most studies have suggested that DC1s are the dominant cross-presenting DCs in the lung. On the other hand, the *Irf4$^+$ CD11b$^+$ DC* (DC2) cannot ingest apoptotic cells (i.e., is less likely involved in immune responses to cell-associated antigens), and is inefficient at cross-presentation to CD8 T cells but is highly efficient in presenting to CD4 T cells.[64,313]

Studies of human lung DC subsets are limited by difficulties in the availability of tissue samples, as is the case for interstitial macrophages. Human lung DCs are distinguished from alveolar macrophages by their expression of CD1c and CD1a.[324,325] Human lung DCs can be distinguished from other myeloid and lymphoid cells by the elimination of T cell, B cell, natural killer–cell, monocyte/macrophage, and granulocyte lineage markers. MHC class II$^+$ DCs are found in normal human airway epithelium, lung parenchyma, and visceral pleura,[326] and a langerin$^+$ DC subset is present in bronchioles.[327] Large numbers of DCs are present in alveolar septa.[328,329] Many subsets of DC have been identified in the lung.[330–333] As multiple unique DC subsets are identified and found to be associated with specific lung tissue structures, further studies can be conducted to understand the functional division of labor of DCs and how they contribute to the maintenance of lung homoeostasis and response to a harmful challenge.

SYSTEM INTEGRATION

The innate and adaptive immune systems have evolved to protect the lungs from harm by environmentally acquired microbes and other inhaled substances, as well as from host-derived harmful stressors, such as unwanted inflammation and inappropriate activation of adaptive immunity. Several core concepts emerge from considering innate immune mechanisms in the lungs. The first is that innate immune protection in the lungs is not a consequence of individualized responses of individual cells but represents coordinated responses and collective cooperation between many resident and recruited lung cell types. These coordinated events result in homeostasis of the airways and gas-exchange units, tolerance to harmless inhaled substances and self-antigens, and vigilance to respond to harmful microbes and substances. In addition, innate immune mechanisms assist in the rapid resolution of injury and restoration of lung function.

A second core concept is that from the nose to the alveolus, the respiratory epithelium, interdigitating DCs, and resident and recruited macrophages have evolved exquisite, diverse, and overlapping mechanisms to distinguish between the harmful and harmless. In its simplest form, this distinction is achieved by sensing the presence of microbial PAMPs. In the absence of PAMPs the epithelium remains largely ignorant of inhaled particulates, whereas "snorkeling" DCs continuously sample the airways and alveoli for particles, antigens, and apoptotic cells to phagocytose and to present antigen to lymph node resident naive CD4$^+$ and CD8$^+$ T cells, thereby maintaining tolerance to harmless commonly encountered antigens and self-antigens. Similarly, resident macrophages phagocytose and dispose of particulates that reach the alveoli, while tonically maintaining an anti-inflammatory and immunosuppressive environment through the production of anti-inflammatory cytokines, especially TGF-β and IL-10, and eicosanoids, such as prostaglandin E_2.

A third core concept is that integration of innate functions is dependent on cell-cell communication. In some settings, communication is fostered by proximity: DCs exist as a network within the airway epithelium and contact each other through tight junctions, whereas alveolar macrophages use integrins to communicate with alveolar epithelial cells. In other settings, cell-cell communication is mediated through

the secretion of a vast array of cytokines and lipid mediators, which can act in autocrine or paracrine fashions. Thus, different cell lineages can communicate with each other and among themselves. Communication between different cell types also plays an important role in the coordination of innate immunity and in the activation of adaptive immunity. For example, depletion of alveolar macrophages reduces tolerance to inhaled antigens and induces alveolitis and lung injury, emphasizing the importance of alveolar macrophages for suppressing inflammation. Integration of innate immunity in the lung is also associated with "coordinated burden sharing." Airway goblet cells and submucosal glands produce mucus, whereas ciliated epithelial cells propel mucus and entrapped particulates toward the pharynx. Similar coordinated burden sharing is exhibited by airway epithelial cells, which are poorly phagocytic but are highly capable of sensing PAMPs and calling in PMNs and monocytes, which in turn are highly phagocytic, microbicidal, and able to eliminate an array of microbes.

A final core concept is that the clinical symptoms and consequences of innate immunity in the lungs depend on where in the respiratory system innate immunity is triggered—nasopharynx, airways, or alveoli. For example, streptococci that deposit on the posterior pharynx and stimulate innate immunity trigger acute tonsillitis, and rhinoviruses trigger initial symptoms in the nasopharynx. In contrast, adenoviruses, influenza viruses, and some bacteria, such as *Haemophilus* and *Moraxella* species, attach to cellular receptors in the ciliated airway epithelium and typically cause severe acute airway inflammation with cough, bronchospasm, and airway mucus production, leading to exacerbations of asthma or COPD in susceptible individuals. Yet other pyogenic bacteria, such as staphylococci, pneumococci, *E. coli*, *Klebsiella pneumoniae*, and others, reach distal airways and alveolar spaces and cause localized or severe lobar pneumonia. Viruses such as severe acute respiratory syndrome CoV-1 and -2 attach to alveolar epithelial and capillary endothelial cells via the angiotensin-converting enzyme-2 receptor, triggering an initial wave of innate immunity that leads to the acute respiratory distress syndrome with few if any upper respiratory symptoms (see Chapter 46a).

Taken together, innate immunity in the lungs involves a number of integrated systems that have evolved to provide the lungs with maximum protection against harmful microbes, while minimizing harmful responses against harmless inhaled substances. The net result is an exquisite system for protecting the delicate and critically important gas-exchanging parenchyma of the lungs from harm.

Key Points

- A primitive host defense system is broadly based on the recognition of repetitive structures on microbes called *pathogen-associated molecular patterns* (PAMPs) by pattern recognition receptors expressed on lung cells.
- Airway epithelium of the trachea and large airways is protected by (1) airway surface liquid, which contains antibacterial proteins; (2) mucus, which traps large inhaled particulates and transports them to the pharynx by mucociliary transport; and (3) immune cells, which produce chemokines, cytokines, and lipid mediators in response to PAMPs.
- Alveolar epithelium is protected by surfactant proteins A and D, which serve the dual purpose of (1) opsonizing microbes and (2) suppressing unwanted inflammation and adaptive immune responses to commonly encountered antigens.
- Polymorphonuclear leukocytes (i.e., neutrophils) are recruited to the airways and alveoli when airway and alveolar epithelial cells detect PAMPs. Neutrophils phagocytose and kill microbes by combined oxidative and nonoxidative mechanisms.
- Macrophages are resident phagocytic cells of the alveolar lumen involved in the removal of a wide range of microbial and nonmicrobial inhaled particulates. Macrophages also suppress unwanted alveolar inflammation and adaptive immunity in the steady state but can be activated by PAMPs to amplify inflammation.
- Dendritic cells are the primary antigen-sensing and -presenting cells of the innate immune system. In the absence of PAMPs, immature dendritic cells traffic to regional lymph nodes and promote tolerance to inhaled antigens. In the presence of PAMPs, dendritic cells mature, express co-stimulatory molecules, and promote T cell development into T helper cells type 1, 2 and 17, or T regulatory effector cells.
- The cell lineages of innate lung immunity collaborate to promote optimal responses to perceived danger signals (primarily PAMPs) while maintaining tolerance to inhaled antigens in the steady state.
- The clinical consequences of innate immune reactions in the lungs depend on where and how microbial pathogens deposit in the respiratory system.

Key Readings

Barlow JL, McKenzie ANJ. Innate lymphoid cells of the lung. *Annu Rev Physiol*. 2019;81:429–452.

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16 ADAPTIVE IMMUNITY

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INTRODUCTION

The human immune system consists of many cell types and organs that have evolved to destroy or control potentially harmful foreign substances. The immune response is essential for survival because it constitutes the principal means of defense against infection by pathogenic microorganisms, including those that enter and reside in the respiratory tract. The immune response is also critically involved in pathologic processes of the lung and upper respiratory tract. This chapter provides an understanding of the adaptive (or acquired) immune response, which depends on the specific recognition of antigens by T and B lymphocytes. Immune recognition is highly specific for a particular pathogen, and yet an individual's immune cells can collectively respond to an almost unlimited number of foreign antigens. The molecular mechanisms underlying this specificity and diversity are unique to the immune system. The adaptive immune response also changes after successive encounters with the same pathogen. For example, memory of an antigen allows the immune system to respond faster and in greater magnitude compared with the initial encounter. This chapter also describes how primary and secondary immune responses are regulated by complex cellular interactions and the release of particular types of soluble mediators. Antigen-specific immune responses are also regulated and augmented by nonspecific inflammatory cells of the immune system, such as dendritic cells, macrophages, monocytes, neutrophils, eosinophils, innate lymphoid cells, and mast cells. Defects in the development of adaptive immunity are discussed in Chapter 124. Innate immunity is covered in Chapter 15.

COMPONENTS OF THE IMMUNE SYSTEM: OVERVIEW

Cells of the immune system arise from pluripotent hematopoietic stem cells through two main lines of differentiation that give rise to the lymphoid lineage and the myeloid lineage.[1] Specificity within the immune system is primarily provided by lymphocytes. The two major categories of lymphocytes are T cells,[2] which are derived from bone marrow stem cells and primarily develop in the thymus, and B cells, which develop in the bone marrow in adult humans.

Lymphocytes and other cells of the immune system express a large number of different molecules on their surfaces. Some of these can be used as markers to separate cells with different functions or to distinguish cells at particular stages of differentiation. Monoclonal antibodies to many different cell surface markers have been produced, and a systematic nomenclature has been developed. The CD (cluster of differentiation, or cluster determinant) system provides a basis by which monoclonal antibodies that bind to the same surface molecule are grouped together, and the CD number is used to indicate the specific molecule recognized. Tables 16.1 to 16.3 provide a partial list of surface antigens, particularly those mentioned in this chapter. The markers are grouped based on the cell type expressing them. It may be necessary to refer to this list of molecules throughout this chapter.

T cells are distinguished by the presence of the *T cell receptor* (TCR).[3–5] Most T cells express a receptor composed of an α and a β chain, whereas a much smaller subset expresses a structurally similar receptor composed of a γ and a δ chain. Both receptors are associated with a complex of polypeptides, the CD3 complex, which provides a transmembrane signaling function and allows TCR engagement to be coupled to cellular activation. T cells expressing αβ TCRs can be divided into $CD4^+$ and $CD8^+$ T cell subsets. $CD4^+$ T cells primarily recognize antigens presented by *major histocompatibility complex* (MHC) class II molecules expressed on antigen-presenting cells. $CD8^+$ T cells primarily recognize antigens presented by MHC class I molecules expressed by all nucleated cells.

Functionally, T cells can be divided into several major subsets. For example, T helper cells may interact with B cells and help them to survive and divide, make antibody, and become

Table 16.1 Selected Cell Surface Markers of Human T Cells

Cell Surface Markers	Identity/Function
TCR	Interacts with peptide/MHC complex on antigen-presenting cells
CD2	Binds to LFA-3; involved in co-stimulation and adhesion
CD3	T cell signaling complex
CD4	T cell subset with helper function; interacts with MHC class II molecule
CD8	T cell subset with cytotoxic function; interacts with MHC class I molecule
CD25	α chain of IL-2 receptor; expressed on activated T cells and on a subset of regulatory $CD4^+$ T cells
CD28	Binds B7-1 (CD80) and B7-2 (CD86); co-stimulatory molecule involved in T cell activation
CD45	Phosphatase involved in cellular activation and differentiation; different isoforms (CD45RA, CD45RO) mark naive versus previously activated T cells and stages of activation
CD62L	L-selectin; involved in lymphocyte adhesion; levels mark naive versus memory cells
CD69	Activation marker
CD95 (FAS)	FAS; receptor involved in apoptosis
CD95L (FAS ligand)	Ligand for FAS; involved in T cell–mediated killing
CD152 (CTLA4)	Binds to B7-1 (CD80) and B7-2 (CD86); involved in down-regulation of TCR signaling
CD154 (CD40 ligand)	Ligand for CD40; important for T cell activation and T cell–dependent B cell activation
CD134 (OX40), CD137 (4-1BB), ICOS, PD1	Additional co-stimulatory molecules in the TNF or CD28 family; involved in T cell activation and regulation

CTLA4, cytotoxic T lymphocyte antigen-4; ICOS, inducible co-stimulator; IL-2, interleukin-2; LFA-3, lymphocyte function–associated antigen-3; MHC, major histocompatibility complex; PD1, programmed cell death-1; TCR, T cell receptor; TNF, tumor necrosis factor.

memory B cells. T helper cells also may interact with cytotoxic T cells or with phagocytic cells and help them destroy intracellular pathogens. Different subsets of T helper cells can be distinguished by the presence of specific transcription factors and the pattern of cytokines that they secrete during an immune response. T helper cells are generally encompassed within the $CD4^+$ T cell subset. Another subset of T cells is responsible for destruction of cells that have become infected by virus or other intracellular pathogens. These cells are called *cytotoxic T cells* and usually express the CD8 phenotypic marker. Although not clearly distinguished by phenotypic markers, separate subsets of T cells, within both the CD4 and CD8 subsets, have been termed *T regulatory (or suppressor) cells* because they down-regulate immune responses.

B cells are identified by the expression of surface *immunoglobulin* (Ig) or antibody molecules, which represent their specific *B cell receptor* (BCR) for antigen. Analogous to the CD3 complex on T cells, BCRs are also linked to accessory molecules, Ig-α (CD79a) and Ig-β (CD79b), which are required for cellular activation after antigen interaction.[6] After differentiation, B cells can develop the ability to produce high levels of antibody (soluble Ig). B cells also express

Table 16.2 Selected Cell Surface Markers of Human B Cells

Cell Surface Markers	Identity/Function
BCR	Immunoglobulin molecules; recognizes antigen
CD5	Binds to CD72; regulation of cell proliferation/activation; identifies B1a cell subset
CD19	B cell coreceptor subunit; involved in co-stimulation
CD20	B cell marker
CD21	Complement receptor type II; B cell coreceptor subunit; marks certain B cell subsets; EBV receptor
CD22	Adhesion molecule; involved in B cell activation
CD23	Identifies B cell subset; low-affinity receptor for IgE
CD40	Binds CD40L; involved in T cell–dependent B cell activation
CD79a (Ig-α)	Involved in B cell activation; signaling through BCR
CD79b (Ig-β)	Involved in B cell activation; signaling through BCR
CD80 (B7-1)	Binds CD28 and CD152 (CTLA4) on T cells
CD86 (B7-2)	Binds CD28 and CD152 (CTLA4) on T cells

BCR, B cell receptor; CD40L, CD40 ligand; CTLA4, cytotoxic T lymphocyte antigen-4; EBV, Epstein-Barr virus; Ig, immunoglobulin.

a large number of other surface markers that are critically involved in their function and interaction with T cells. For example, most B cells express MHC class II molecules that allow them to present antigen to T helper cells. Other B cell surface molecules are listed in Table 16.2.

A third population of lymphocytes recently classified as *innate lymphoid cells* (ILCs) seed the peripheral tissues early in life and modulate tissue-specific immunity and barrier homeostasis.[7] ILCs are characterized by expression of the interleukin-7 receptor but are devoid of other immune cell lineage markers.[8] They are grouped into three distinct subsets (ILC1, ILC2, and ILC3) and resemble different T helper cell subsets based on their differential expression of key transcription factors and cytokines.[9,10] However, unlike T helper cells, ILCs do not express a classical antigen receptor like TCR or Ig, and, as a result, ILCs do not undergo antigen-specific expansion upon activation. Instead, these innate lymphocytes sense alterations in the local tissue microenvironment caused by tissue damage. Because ILCs are tissue resident, they can rapidly respond to these tissue cues (often in the form of cytokines or alarmins) by proliferating as well as by secreting effector cytokines in much the same way that memory T cells quickly respond to reinfection.[11] In addition to their role as early tissue sentinels, ILCs help to educate adaptive immune responses via regulation of dendritic cells and B cells as well as to modulate $CD4^+$ T cells through expression of MHC class II molecules.[12–16] In sum, ILCs serve three key functions: (1) modulate tissue homeostasis, (2) serve as an early line of innate defense against infection and promote tissue repair after sensing tissue damage, and (3) instruct the adaptive immune response after barrier insult.

The myeloid lineage consists primarily of monocytes, macrophages, dendritic cells, and neutrophils, which

Table 16.3 Other Cell Surface Markers of General Interest

Cell Surface Markers	Distribution	Identity/Function
CD1	Thymocytes, subset of lymphocytes, antigen-presenting cells	MHC class I–like molecule; involved in presentation of nonpeptide antigens
CD11a	Leukocytes	α chain of LFA-1; associates with CD18; interacts with ICAM1; involved in adhesion and migration
CD11b	NK cells, monocytes, granulocytes	α chain of CR3; adhesion molecule
CD11c	Monocytes, granulocytes	α chain of CR4; adhesion molecule; identifies dendritic cells
CD14	Granulocytes, monocytes	Receptor for LPS/LPB complex; myeloid differentiation antigen; cell activation
CD16	NK cells, monocytes	Receptor for Fc domain of IgG, type 3 (FCGR3); low-affinity receptor for IgG; involved in ADCC
CD18	Leukocytes	β chain of β_2 integrin molecules, including LFA-1, CR3, and CR4
CD29	Leukocytes	β chain of β_1 integrin molecules, including VLA1-VLA6
CD32	B cells, monocytes, granulocytes	Receptor for Fc domain of IgG, type 2 (FCGR2)
CD35	B cells, subset of NK cells, monocytes, granulocytes	CR1
CD45	Leukocytes	Leukocyte common antigen; phosphatase; involved in cell signaling
CD46	Broad distribution	Membrane cofactor protein; regulates complement activation
CD54 (ICAM1)	Broad distribution	Binds LFA-1; adhesion molecule
CD56	NK cells	Neural cell adhesion molecule
CD58 (LFA-3)	Broad distribution	Binds CD2; adhesion molecule; involved in cell signaling

ADCC, antibody-dependent cellular cytotoxicity; CR, complement receptor; ICAM1, intercellular adhesion molecule-1; IgG, immunoglobulin G; LFA, lymphocyte function–associated antigen; LPB, LPB binding protein; LPS, lipopolysaccharide; MHC, major histocompatibility complex; NK, natural killer; VLA, vascular leukocyte adhesion molecule.

provide nonspecific inflammatory mediators and phagocytic function. These cells are critically involved in the nonspecific component of the inflammatory response (see Chapter 15). In addition, macrophages and dendritic cells are specialized to present antigens to T cells, thus contributing to specific immune responses.

The cells involved in the immune response are organized into tissues and organs. Primary lymphoid organs are the major sites of lymphopoiesis, in which stem cells and their committed precursor cells differentiate into lymphocytes and acquire specific functions. In humans, T lymphocytes mainly develop in the thymus, and B lymphocytes develop in the fetal liver and adult bone marrow. In the thymus, T cell differentiation also includes acquiring the ability to recognize foreign antigens in the context of self-MHC molecules and the elimination of self-reactive cells (self-tolerance). B cell acquisition of self-tolerance during development appears to take place in the bone marrow.

Differentiated lymphocytes migrate to secondary lymphoid organs, which include lymph nodes, spleen, and mucosa-associated lymphoid tissues, such as the tonsils, lymph nodes of the respiratory tract, and Peyer patches of the gut. These tissues provide an environment for lymphocytes to interact with each other, with antigen-presenting cells and other accessory cells, and with foreign antigens. The immune response is generated mostly within these secondary lymphoid organs, and lymphocytes migrate through the blood and lymph from one lymphoid organ to another and to nonlymphoid tissues. For example, foreign antigen exposure in the lung usually involves the movement of antigen to surrounding lymph nodes, where the specific immune response by T and B cells takes place. Generation of a cell-mediated immune response or antibody response allows antigen-specific effector T cells or specific antibodies, respectively, to circulate to lung tissue for a direct assault on foreign antigens.

Under normal conditions, there is a continuous active flow of lymphocyte traffic through the lymph nodes. About 1–2% of the lymphocyte pool recirculates each hour, allowing a large number of antigen-specific lymphocytes to come into contact with their appropriate antigen. Recirculating lymphocytes leave the blood and enter the lymph node through specialized postcapillary venules, known as *high endothelial venules* (HEVs). Specific interacting receptors on lymphocytes and HEV cells facilitate this homing process. Lymphocytes return to the circulation by way of afferent lymphatics that pass via the thoracic duct into the left subclavian vein. Lymphocytes also enter mucosa-associated lymphoid tissues, such as the tonsils and Peyer patches, via HEVs. The recirculation and trafficking of memory and effector T and B cells is tightly regulated, determined by unique combinations of adhesion molecules and chemokines.[17] For example, certain lymphocytes may preferentially migrate across HEVs into intestinal lymphoid tissues (either Peyer patches or mesenteric lymph nodes) or into respiratory tract tissues or may specifically home to the peripheral lymph nodes or the spleen.

Separate combinations of cell-surface adhesion molecules and chemokines allow activated lymphocytes and other leukocytes to migrate into nonlymphoid tissues, especially during inflammation and in response to the release of inflammatory cytokines.[17] The difference in trafficking patterns for nonactivated (resting) versus activated lymphocytes is striking and emphasizes the importance of particular adhesion molecules in the control of lymphocyte migration.

IMMUNE RECOGNITION

B CELLS AND ANTIBODIES

Structure of Immunoglobulin and the B Cell Receptor for Antigen

Ig molecules, or antibodies, are glycoproteins that act as BCRs. These molecules can also be secreted in large quantities by activated B cells and plasma cells. Figure 16.1 shows the basic structure of an Ig molecule. Each Ig molecule is bifunctional, consisting of an antigen binding region (Fab) and a constant region (Fc) that mediates various effector functions, such as binding to host tissues and activating the first component of the complement system.

The basic structure of Ig molecules involves two identical light polypeptide chains and two identical heavy polypeptide chains linked together by disulfide bonds (see Fig. 16.1A). The isotype (class or subclass) of an Ig molecule is determined by its heavy chain type. There are five Ig classes—IgG, IgM, IgA, IgD, and IgE—corresponding to the γ, μ, α, δ, and ε heavy chain types. In humans, there are four IgG subclasses, IgG1 to IgG4. There are major differences in the structure and main functions of these different Ig classes and subtypes.

In Figure 16.1B, the IgG molecule is shown as an example of basic antibody structure. Each chain is composed of a series of globular regions or domains, and each domain encompasses about 60 to 70 amino acids connected via an internal disulfide bond. The site of antigen binding is the amino (NH_2)-terminal domain for both the *heavy* (H) and *light* (L) chains. This domain is characterized by remarkable sequence variability and is referred to as the variable region of the heavy and light chains (V_H and V_L region, respectively). The combination of V_H and V_L forms the antigen-binding site, and there are two such sites per IgG molecule (see Fig. 16.1B). The remainder of each polypeptide has a relatively constant structure. The constant domain of the light chain is termed the C_L region, whereas the heavy chain has three constant domains: C_H1, C_H2, and C_H3. The hinge region, located between the C_H1 and C_H2 domains, provides flexibility and independence to the two antigen-binding sites. In both μ and ε heavy chains, there is an additional constant domain between C_H1 and C_H2, resulting in a total of four constant domains.

The greatest variability in antibody molecules takes place in the V_H and V_L domains, and these domains are responsible for the specificity in antigen binding.[18] Within the variable domains (see Fig. 16.1C), certain short segments show exceptional variability and are called *hypervariable* regions. These regions are also referred to as *complementarity-determining regions* (CDRs) because they are directly involved in the binding to antigen. In both the V_H and V_L regions, there are three CDRs (CDR1 to CDR3) with intervening segments referred to as framework regions (see Fig. 16.1C). CDR3 (a component of the polypeptide V region) is formed by parts of the V (*variable*), D (*diversity*), and J (*joining*) gene segments. Variation within the V_H and V_L regions distinguishes one antibody molecule from another and is referred to as idiotype or idiotypic variation. Additional information on heavy chain rearrangement is shown in eFig. 16.1.

Formation of the B Cell Receptor Repertoire

The BCR repertoire and the Ig molecules are characterized by enormous diversity. The principal genetic mechanisms that are used to generate this diversity include (1) genetic

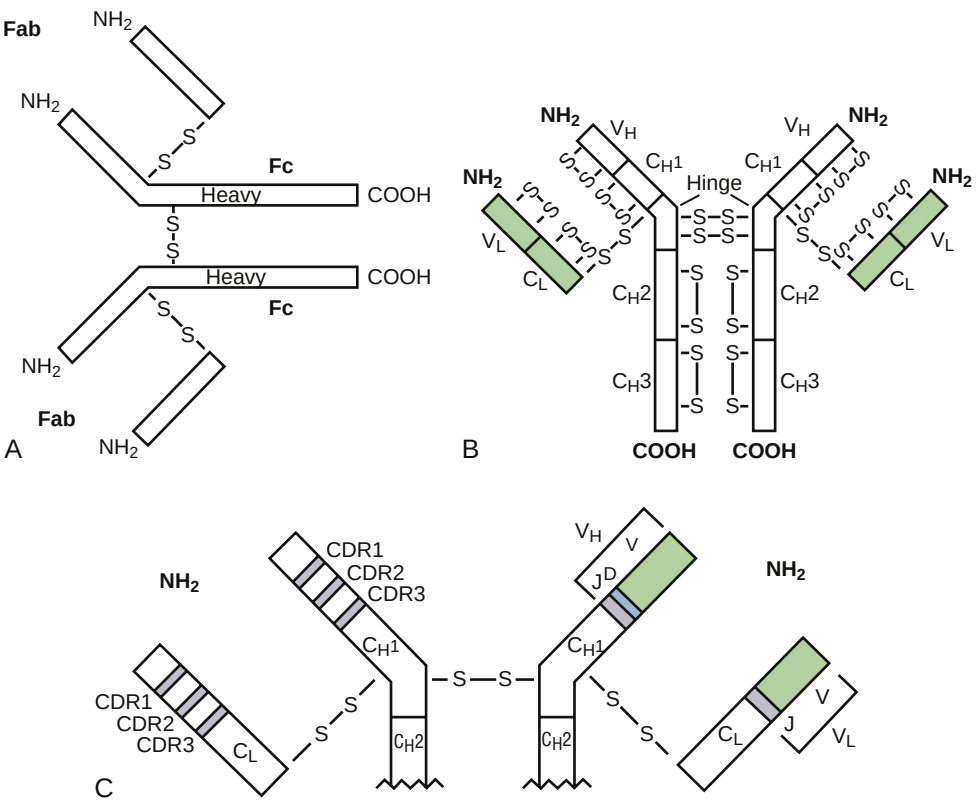

Figure 16.1 The structure of *immunoglobulin* (Ig) molecules. (A) Basic Ig structure with two heavy chains and two light chains linked together by disulfide bonds. The Fab region is involved in antigen binding, whereas the Fc region mediates various effector functions. (B) Increasing detail of IgG molecule showing domains of both heavy and light chains. Each domain has an internal disulfide bond. The sites of antigen binding involve the NH_2-terminal domains of both the heavy and the light chains and are referred to as the variable regions (V_H and V_L, respectively). The rest of each chain has a relatively constant structure (C_H and C_L domains). (C) Close-up of the antigen-binding variable regions. On the left, the complementarity-determining regions (CDRs) are shaded because they are the most variable components (i.e., hypervariable regions) and are involved in actual antigen binding. The CDRs are separated by intervening segments referred to as framework regions. On the right, the Ig polypeptide regions are correlated with the Ig gene segment (exons) that encode the variable region. Note that CDR3 corresponds to parts of the V/D/J junctional region of the rearranged heavy chain gene and the V/J junctional region of the rearranged light chain gene. D, diversity region; J, joining region; V, variable region.

recombination of gene segments to form a functional Ig gene, (2) combinatorial diversity of heavy and light chain matching, and (3) somatic hypermutation of rearranged genes.[19] Another major force in shaping the antibody repertoire has been termed *receptor editing*, which allows receptors with self-reactive potential to be modified by additional recombination events during B cell differentiation.[20,21]

Figure 16.2A illustrates the principle of genetic recombination for an Ig gene.[18] In this case, one of several V region gene segments (normally separated upstream from the *constant* [C] region gene segments on the same chromosome) can be linked to a single C region gene segment by genetic recombination. The combining of gene segments, rather than the existence of a single gene coding for every individual antibody molecule, considerably reduces the amount of genetic information required to encode many different antibody molecules. In Figure 16.2B the different gene segments that encode a κ light polypeptide chain are shown. Note that, in this case, a V region rearranges proximal to a J segment, which is linked to the C region segment. Rearrangement of κ or γ light chain genes involves V, J, and C region gene segments (see Fig. 16.2A; see also Fig. 16.1C). In the formation of a functional heavy chain gene, a successful rearrangement of gene segments includes one V, one D, and one J region segment linked to a C region segment (compare Figs. 16.1C and 16.2B).

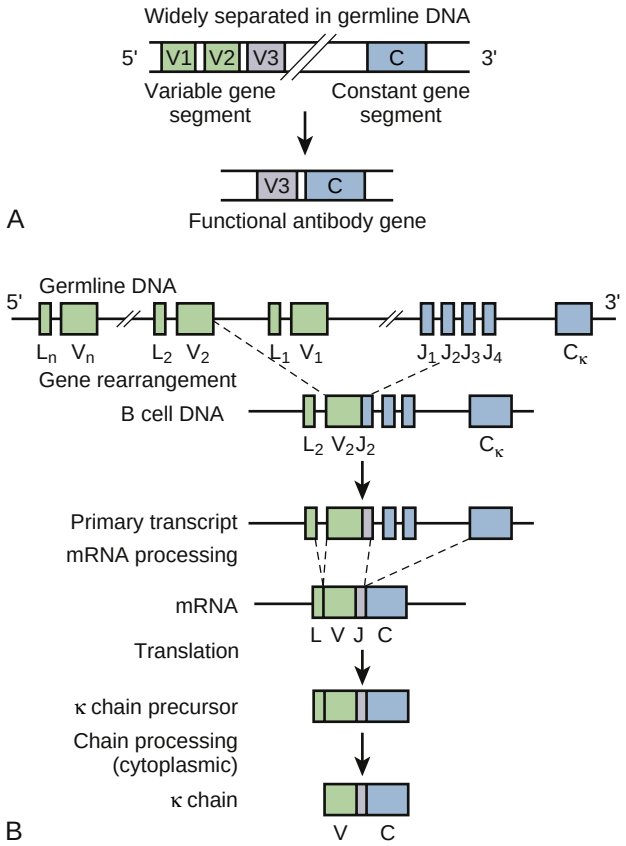

Figure 16.2 Principles of genetic recombination. (A) In the germline DNA, the V region segments are located upstream from the D, J, and C segments on the same chromosome. Recombination, which takes place only in lymphocytes, brings the V gene segments in proximity to the downstream segments. (B) In the B cell, rearrangement of gene segments separated in the germline DNA allows for the formation of a functional immunoglobulin light chain gene (compare with Fig. 16.1C) in this case, a κ light chain. mRNA, messenger RNA.

During genetic recombination, additional variability is generated by a process known as junctional diversification. When two gene segments are brought together during rearrangement, linking is not precise. Instead, some nucleotides are randomly inserted or deleted at the junctional site. This introduces new codons, and therefore new amino acids, into the junctional sequence. If an incorrect number of junctional nucleotides are added or deleted, functional molecules will not be encoded because the rest of the gene will be "out of frame" or a "stop" sequence will be introduced. Junctional diversification takes place in the hypervariable CDR3 region of the molecule (see Fig. 16.1C).

In general, a single B cell usually expresses an Ig molecule of only one antigen specificity, composed of one heavy chain molecule and one light chain molecule. Even though there are two chromosomal copies of the heavy chain genes in each cell, only one is usually functionally expressed. This phenomenon of using genes on only one parental chromosome is known as allelic exclusion. Once there has been a functional rearrangement of heavy chain genes on one parental chromosome, rearrangement of heavy chain genes on the other chromosome is mostly prevented. If the first rearrangement is not successful, the second one can take place. All of the genetic events described earlier happen before the B cell encounters antigen. The B cell (or antibody) response further diversifies after interaction with antigen by a process known as *somatic hypermutation*, primarily involving point mutations in the hypervariable regions of the V genes.[22] Somatic hypermutation can be viewed as fine tuning of the antibody response, taking place after the primary response to a stimulus and during the development of memory B cells. It is, therefore, mostly observed during a secondary immune response. Somatic hypermutation allows for the production of antibodies with higher affinity for antigen, that is, the ability to bind more strongly to an antigen. Although the mutations are random, B cells with high affinity are selectively expanded (referred to as affinity maturation) because the stronger binding allows preferential stimulation by the target antigen. Somatic hypermutation is closely tied to isotype switching, and T cell help is required. Somatic hypermutation usually takes place at the site of T cell–B cell interaction in the germinal centers of lymph node or spleen.

Isotype Switching and Function of the Different Immunoglobulin Classes

One B cell usually makes antibody of a single specificity that is fixed by the nature of V_LJ_L and $V_HD_HJ_H$ rearrangements. During the lifetime of this cell, however, it can switch from making an IgM molecule to producing a different class of antibody, such as IgG or IgA, while retaining the same antigenic specificity. This phenomenon is known as class switching or *isotype switching*.[19]

Figure 16.3 shows the predominant mechanism by which a B cell switches from production of surface IgM to secretion of an IgG, IgA, or IgE molecule. The mechanism involves further DNA rearrangement (a process unique to Ig heavy chain genes), linking rearranged VDJ gene segments with a different heavy chain C region gene segment downstream. The *switch* (S) region is a stretch of repeating sequences 5′ to

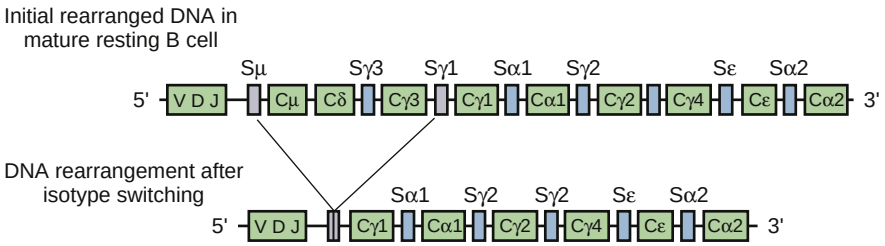

Figure 16.3 Genetic mechanisms involved in *immunoglobulin* (Ig) isotype switching. *Top,* The initial rearrangement of Ig heavy chain gene segments has already taken place in the B cell to put the V region proximal to the D, J, and Cμ segments. This latter genetic region contains other constant region gene segments farther downstream, including Cδ, various Cγ and Cα gene segments, and Cε. In the process of T cell–dependent B cell activation in the germinal centers, the B cell is signaled to undergo isotype switching to allow high-rate secretion of an IgG1 antibody. *Bottom,* This is accomplished by additional DNA rearrangements that put the VDJ unit adjacent to the Cγ1 segment downstream. The intervening DNA is deleted. S, switch region.

Table 16.4 Properties and Functional Characteristics of Immunoglobulin Classes and Subclasses*

Effector Function	IgM	IgD	IgG1	IgG2	IgG3	IgG4	IgA	IgE
Mean serum levels (mg/mL)	1.5	0.04	9	3	1	0.5	2.1	0.00003
Opsonization	—	—	+++	—	++	+	+	—
Complement fixation	+++	—	++	+	+++	—	—	—
Binding of Fc receptor on phagocytic cells	—	—	++		++	+	—	—
Induction of mast cell degranulation	—	—	—	—	—	—	—	+++

*Activity levels of immunoglobulin classes and subclasses: +++ high; ++ moderate; + low; =/— minimal; — none.
Ig, immunoglobulin.

the C region that allows a VDJ unit (previously linked to the Cμ region gene segment) to rearrange to another C region downstream. In the process the intervening DNA is deleted. The B cell, therefore, cannot return to IgM production. Class switching generally follows stimulation of the B cell by antigen and frequently is dependent on factors released by T helper cells and pathogen-associated molecular patterns present in surrounding microenvironment.

Each class of secreted Ig has a different set of functions (Table 16.4).[23] IgG is the major antibody of secondary immune responses and is most important for obtaining effective immunization to various toxins, toxoids, and certain extracellular pathogens. IgG accounts for 70–75% of the total Ig pool and is the major Ig class in the blood. It also crosses the placenta and confers immunity to newborns and neonates for the first few months of life. The interaction of IgG antibodies with antigen can have diverse consequences, including precipitation, agglutination, neutralization, complement activation, and various cellular effector functions via IgG receptors.[23–26] There are four IgG subclasses, with IgG1 and IgG3 being most effective at fixing complement and activating complement-mediated effector functions.

IgM is the predominant early-secreted antibody, frequently seen in primary immune responses. IgM is important for effective responses to antigenically complex infectious organisms, especially those with polysaccharide-containing cell walls. IgM antibodies may also be extremely effective at precipitation, agglutination, and complement activation after binding to antigen. Secreted IgM is usually found as a pentamer of the basic (four-domain) Ig unit. Polymerization is facilitated by the binding of the heavy chain tailpieces to a J peptide.

IgA plays a major role in mucosal immunity and is the predominant Ig in saliva and tracheobronchial secretions. Secretory IgA exists mainly in dimeric form and contains a secretory component, which is synthesized by epithelial cells and facilitates transport into secretions as well as protection from proteolysis. Secretory IgA is involved in the prevention of microbial adherence to mucosal cells and in the agglutination of microorganisms. IgA provides the first line of defense against a variety of pathogens.

IgE is scarce in serum. Its major importance relates to its ability to bind to FcεR1 receptors on mast cells and basophils, and cross-linking of IgE bound to these cells results in cellular activation, degranulation, and release of mediators involved in allergic responses, such as histamine and various leukotrienes.[27] IgE plays a role in immunity to parasites but, in developed countries, it is more commonly associated with allergic responses and allergic diseases, such as hay fever and asthma (see Chapters 60, 61, and 62).[28] IgE interaction with FcεR1 also promotes anti-tumor immunity by enhancing antigen cross presentation by DCs.[29]

B Cell Development

B cells are produced in the specialized microenvironments of the fetal liver and the adult bone marrow.[30] After migration from the bone marrow, the life span of mature naive B cells is limited unless there is contact with antigen. B cells interact with foreign antigen in the peripheral lymphoid tissues, particularly in germinal centers of lymph nodes and spleen.[31] The interaction with antigen, in the setting of T cell help, results in the generation of memory B cells and cells that secrete large amounts of Ig. This frequently involves class switching and somatic hypermutation, which allows a secondary antibody response to generate antibodies of a different isotype with higher affinity for the stimulating antigen. An additional view of B cell development is shown in eFig. 16.2.

The formation of the B cell repertoire in the bone marrow is mostly random, and B cells with self-reactivity are generated. Negative selection of cells capable of strongly

binding to self-antigens is an important part of B cell development. This process of B cell self-tolerance involves both deletion (elimination) and functional inactivation (anergy) of self-reactive cells.[32] In addition, as mentioned, B cells with specificity for self-antigens can modify their receptors through receptor editing.[20,21] These self-reactive B cells undergo a reversible arrest of development and reinitiate light chain gene rearrangements to alter their BCR. If a B cell fails to edit its BCR, it is destined for cell death (apoptosis). Immature B cells in the bone marrow are capable of receptor editing, whereas mature B cells in the peripheral lymphoid tissues normally lose this ability to initiate a new round of Ig gene rearrangements.

Immunoglobulin Interactions with Antigen

An antigen is a molecule or molecular complex recognized by B cells or T cells. The term *immunogen* usually refers to a substance capable of eliciting an immune response, and therefore it must also be capable of being recognized as an antigen. An antigen (e.g., a protein molecule) is usually much larger than the small region fitting into the binding site of an Ig molecule or the processed peptide recognized by a TCR. This smaller region is frequently referred to as an antigenic determinant or *epitope*. In a protein, a B cell epitope can theoretically be constructed in two ways—as a continuous or a discontinuous epitope. In a continuous epitope, the amino acid residues are part of a single uninterrupted sequence, whereas, in a discontinuous epitope, residues are not contiguous in the primary structure but are brought together by the folding of the polypeptide chain. Because this kind of epitope requires a special conformation of the antigen, it is frequently referred to as a conformational epitope.

B cells and T cells usually recognize different parts of an antigen. B cells and their secreted Ig molecules most commonly recognize unprocessed or "native" antigens. These antigens have maintained their native configuration, and most of the epitopes are usually of the discontinuous or conformational type. In general, only a minor component of a B cell response is directed to small linear peptide regions of the antigen. Studies indicate that epitopes recognized by B cells are not randomly distributed throughout the antigen but rather reside in regions with particular structural features. One important feature is accessibility because epitopes normally must be on the outer surface of a protein and may protrude from an antigen's globular surface to be able to interact with the BCR.

T CELLS AND ANTIGEN-PRESENTING CELLS

In contrast to B cells, T cells recognize processed pieces of a protein antigen, which are presented to the TCR by MHC molecules on the surface of antigen-presenting cells.[3–5,33]

T Cell Receptors

The TCR shows important structural similarities with Ig molecules (Fig. 16.4).[3–5] The αβ TCR is expressed by at least 90% of peripheral blood T cells. Essentially, all $CD4^+$ T cells and most $CD8^+$ T cells express this form of TCR. A small percentage of αβ-expressing T cells have a double-negative ($CD4^-$ and $CD8^-$) phenotype. As shown in Figure 16.4, each chain consists of two extracellular Ig-like domains

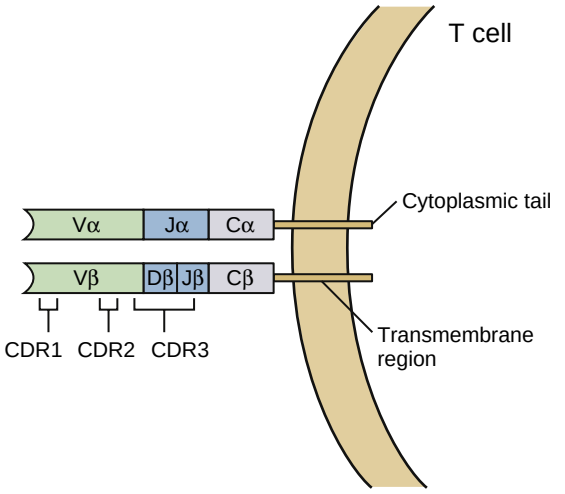

Figure 16.4 The *T cell receptor* (TCR) α and β chains indicate the regions encoded by different TCR gene segments. The positions of the *complementarity-determining regions* (CDRs) of both the β and the α chains are also shown. These are the most variable parts of the TCR and the most important for TCR binding to the peptide/major histocompatibility complex. CDR1 and CDR2 of both the α and the β chains are encoded within the variable region genes. CDR3 is formed by the rearrangement of V, D, and J gene segments of the β chain and V and J segments of the α chain and is encoded by the distal part of the V region segment through part of the J segment. The different parts of the TCR are not drawn to scale.

anchored into the plasma membrane by a transmembrane region and a short cytoplasmic tail. Similar to Ig molecules, the outer NH_2-terminal domain of each chain constitutes the variable region. Outside of the transmembrane region, the two chains are covalently linked together by disulfide bonds. Due to the short cytoplasmic tail, the αβ heterodimer is not capable of transmitting an intracellular signal after TCR engagement. This function is accomplished by the CD3 complex of polypeptides and other signaling proteins that are associated with the TCR.

The γδ TCR is an alternative form of TCR that is similar in overall structure to the αβ receptor.[34] Although some γδ cells express CD8, most are $CD4^-$ and $CD8^-$ (double negative). CD8 expression is largely confined to those γδ cells residing in the small intestine. The γδ TCR is also expressed in association with the CD3 complex. Although γδ T cells form a minor proportion of the T cells in the thymus and secondary lymphoid organs, they are abundant in various intraepithelial locations, such as in the skin, intestines, and lung.[35]

T Cell Receptor Structure and T Cell Receptor Repertoire Formation

Genes encoding the TCR are organized similarly to Ig genes[5,36] (eFig. 16.3). In a manner similar to that described previously for B cells, rearrangement of gene segments, junctional diversity, and combinatorial joining of the two chains are responsible for the diversity of the TCR repertoire. However, in contrast to B cells, TCR genes do not undergo somatic hypermutation. Thus, nearly the entire TCR αβ repertoire is formed during T cell development in the thymus and before any interaction with antigen. It is believed that extrathymic somatic hypermutation might result in the generation of deleterious self-reactive T cells.

The components of the αβ TCR heterodimer are shown in Figure 16.4, and the ribbon backbone structure of the Vα and Vβ portions of a human TCR are shown in Figure 16.5.[3–5,37,38] The upward-pointing loop structures are the CDRs. These regions are the most variable part of the TCR α and β chains and are most important for binding of the TCR to the MHC/peptide complex. The CDR1 and CDR2 regions of the α chain and β chain are encoded within the germline *TCRAV* and *TCRBV* gene segments, and variability in their sequences distinguishes the different V region subfamilies. The most diverse part of the α and β chains is the CDR3, which directly interacts with peptide in the binding groove of the MHC molecule.

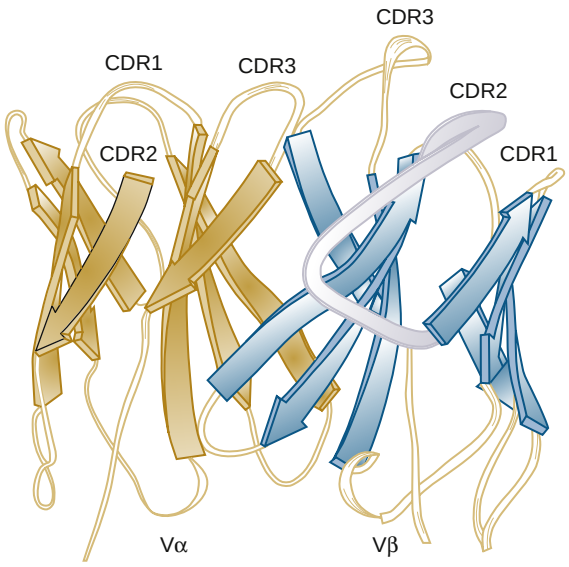

Figure 16.5 A ribbon backbone structure of the Vα and Vβ portions of a human *T cell receptor* (TCR). The upward-pointing loop structures are the *complementarity-determining regions* (CDRs). These regions are the most variable part of the TCR α and β chains and are most important for TRC binding to peptide/major histocompatibility complex. The CDR1 and CDR2 regions of the α chain and β chain are encoded within the germline *TCRAV* and *TCRBV* gene segments, respectively. The highly variable CDR3 region is formed by the rearrangement of V, D, and J gene segments. Junctional nucleotide substitutions and deletions at the margins of rearrangement add to the potential diversity of the CDR3 region. (Modified from Kotzin BL, Kappler J. Targeting the TCR in rheumatoid arthritis. *Arthritis Rheum.* 1998;41:1907.)

Antigen-Presenting Cells and the Major Histocompatibility Complex

There are two major varieties of MHC molecules (and genes) involved in the presentation of antigens to T cells. MHC class I molecules include *human leukocyte antigen* (HLA)-A, HLA-B, and HLA-C molecules. MHC class II molecules include the HLA-DR, HLA-DQ, and HLA-DP molecules. MHC class I molecules are expressed on nearly all nucleated cells. In contrast, MHC class II molecules have a limited distribution and are normally present only on cells involved in antigen presentation to T cells, including dendritic cells, macrophages, B cells, and thymic epithelial cells. The limited expression of MHC class II molecules in different tissues may be extremely important in preventing various types of autoimmune reactions. After activation or exposure to certain cytokines, such as *interferon-γ* (IFN-γ), other human cell types, such as activated T cells and epithelial cells, can express MHC class II molecules.

The general structures of the two classes of MHC molecules are shown in Figure 16.6. For MHC class I antigens, the α chain (encoded within the MHC) is complexed to beta$_2$-microglobulin (encoded outside the MHC). The α chain is highly polymorphic (variable between individuals), whereas beta$_2$-microglobulin is invariant. The extracellular portion of the α chain is divided into three domains: α1, α2, and α3. The outer α1 and α2 domains represent the polymorphic components of the molecule, and the α3 domain is relatively constant. MHC class II molecules are composed of an α and a β chain, both of which are encoded within the MHC. The NH_2-terminal domains of each chain (α1 and β1 domains) represent the polymorphic regions of the molecule and are important in antigen presentation, whereas the α2 and β2 domains are relatively constant.

The structures of MHC class I and class II molecules have provided remarkable insight into how antigenic peptides are bound and presented to T cells.[4,39–42] In Figure 16.7A, the peptide-binding groove of a class I molecule is viewed from the top, showing the surface that is contacted by a TCR. MHC class I pockets can usually bind only peptides of 8 to 10 amino acids, which are bound in a typical extended conformation with both the NH_2 terminus and the carboxy terminus anchored in the peptide-binding groove. In the case of MHC class II, the peptide-binding groove is formed by the interaction of the NH_2-terminal domains of the α and β chains (see Fig. 16.7B). The structure of MHC class

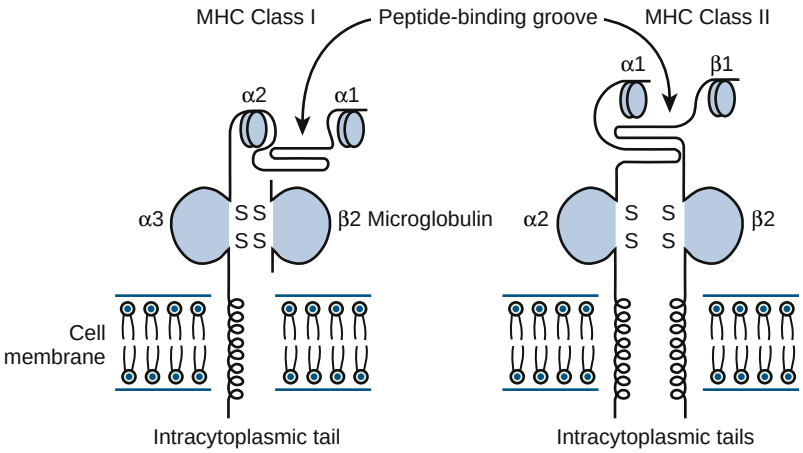

Figure 16.6 Comparison of the composition of *major histocompatibility complex* (MHC) class I and II molecules. The MHC class I α chain is variable (polymorphic) among different individuals. It is expressed with beta$_2$-microglobulin, which is encoded outside the MHC region and does not differ among different individuals. The MHC class II molecules are composed of α and β chains. *For human leukocyte antigen* (HLA)-DR molecules, only the β chain is variable, whereas for the HLA-DQ and HLA-DP molecules, both the α and the β chains are encoded by polymorphic alleles. In MHC class I molecules, the peptide-binding region is formed between the α1 and the α2 domains, which are polymorphic. The peptide-binding region of MHC class II is formed between the α1 and β1 domains of the α and β chains, respectively.

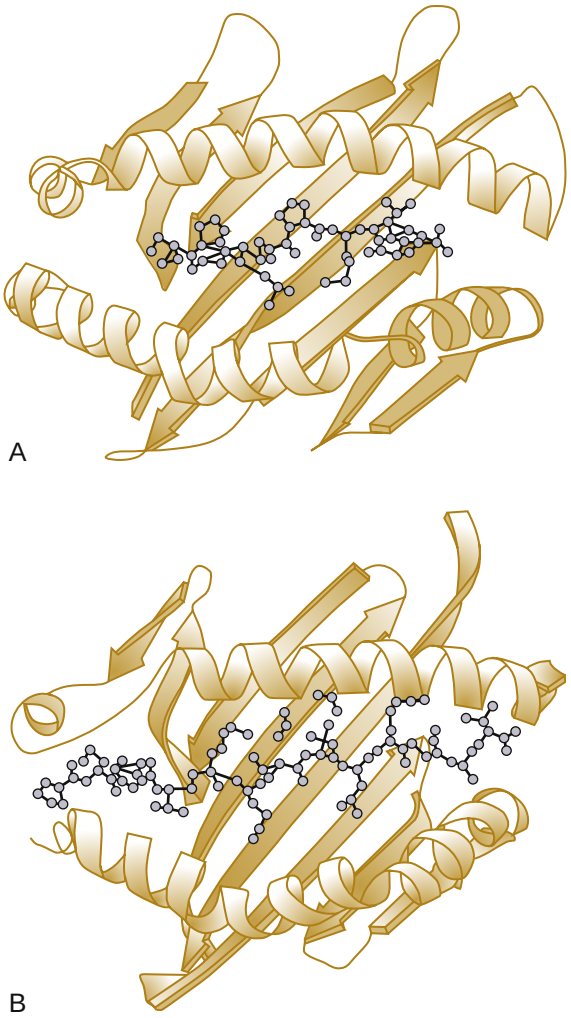

Figure 16.7 Structure of the *major histocompatibility complex* (MHC)/peptide complexes. (A) A schematic view of an MHC class I binding groove with peptide. The peptide is shown in ball-and-stick representation. In class I molecules, the peptide is usually of fixed length (8–10 amino acids) and bound so that both the NH_2 and carboxy termini are anchored in the peptide-binding groove. (B) A schematic view of an MHC class II (human leukocyte antigen–DR1) molecule with bound peptide in the groove. The peptide is shown in ball-and-stick representation. The peptide has the typical polyproline extended helical conformation seen in all class II bound peptides. The structure of class II allows peptides of varying lengths to bind because both ends of the peptide are free and can extend out of the groove on both sides. (From Jones EY. MHC class I and class II structures. *Curr Opin Immunol.* 1997;9:76-77.)

II allows peptides of varying lengths to bind because both ends of the peptide are free, and the peptide shown in Figure 16.7B has the typical polyproline-like extended helical conformation seen in all MHC class II-bound peptides.

Presentation and T Cell Recognition of Antigens

In contrast to B cells, T cells recognize processed peptides of a foreign antigen that are complexed to MHC molecules on antigen-presenting cells. Because of the process of thymic selection for self-MHC recognition, there is little capability for T cells to recognize intact or native protein antigens. $CD4^+$ T cells generally recognize peptides complexed to MHC class II molecules, whereas $CD8^+$ T cells interact with peptide/MHC class I molecules.[3–5,43] The purpose of this relatively complex antigen-presentation process may

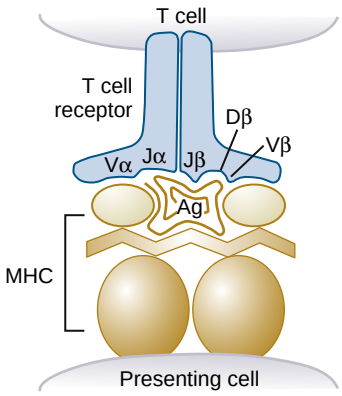

Figure 16.8 T cell recognition of a conventional peptide antigen. The *major histocompatibility complex* (MHC) molecule on the antigen-presenting cell (*brown*) shows the peptide-binding groove with a peptide in it. The interacting *T cell receptor* (TCR) is shown as a *blue* structure. Note that the junctional regions of the TCR α chain (Vα/Jα) and β chain (Vβ/Dβ/Jβ) are depicted so that they appear to have the most important interaction with the peptide. These junctional regions form the *complementarity-determining region* (CDR) 3 of the α and β chains, which is the most variable component of the TCR. The CDR1 and CDR2 loops are encoded within the Vα and Vβ regions and may have more interaction with the MHC parts of the complex compared with CDR3. A ribbon diagram of the TCR CDR loops is depicted in Figure 16.5. (Modified from Drake CG, Kotzin BL. Superantigens: biology, immunology, and potential role in disease. *J Clin Immunol.* 1992;12:140.)

be to focus the T cell response onto cells. For example, it is much easier for a T cell to kill a virus-infected cell before the pathogen has the opportunity to multiply than it is to kill individual virus particles. The MHC class I molecules therefore focus the cytotoxic T cell response on cells infected with intracellular organisms, whereas free infectious particles are the targets of antibodies. MHC class II molecules similarly focus the delivery of T cell help on the relevant antigen-specific B lymphocytes that eventually produce antibodies. Recognition of antigen only on the surface of MHC class II–expressing cells also allows for a system by which the activation of $CD4^+$ T cells can be closely regulated.

Peptide-containing MHC class I and class II molecules on the surface of antigen-presenting cells serve as ligands for TCRs of $CD8^+$ and $CD4^+$ T cells, respectively. To present antigenic peptides effectively, antigen-presenting cells must be capable of performing at least two functions: (1) processing and displaying parts of antigens in the peptide-binding groove of MHC molecules on their cell surface and (2) providing the other accessory signals necessary for T cell activation. *Antigen processing* refers to the series of steps that generate these peptide fragments, load them onto MHC molecules, and allow expression of the peptide/MHC complex on the cell surface.[44–48] Major differences exist in the manner in which endogenous and exogenous foreign antigens are processed and presented to T cells, which are beyond the scope of this chapter.

Figure 16.8 shows a schematic view of antigen recognition by a $CD4^+$ T cell. A foreign peptide is contained within the antigen-binding groove of an MHC class II molecule, and the TCR simultaneously recognizes the complex of peptide and MHC class II molecule. Thus, residues of the variable region of the TCR interact with the peptide and MHC residues extending out from the peptide-binding groove. The highly variable CDR3 region of the αβ TCR is frequently

most important in the binding of peptide, whereas other parts of the variable regions are more involved in interactions with MHC residues.[33,49]

Development and Selection of the TCR Repertoire

Stem cells precommitted to the T cell lineage arise in the bone marrow and migrate to the thymus. See eFig. 16.4 for additional information on T cell development and maturation. These cells do not express TCR molecules and do not express CD4 or CD8 molecules. These cells develop by rearranging TCR α and β chain genes and generating a functional αβ TCR. In the thymus, two major processes modify this repertoire.[50,51] One process positively selects cells that have some TCR affinity for self-MHC molecules. Evidence suggests that an interaction with thymic cortical epithelial cells is involved in this positive selection step. This process allows mature cells to recognize foreign antigens in the context of self-MHC antigens (a phenomenon termed self-MHC restriction). Cells that are not positively selected undergo programmed cell death (apoptosis) within the thymus. The other process deletes cells that have a high level of self-reactivity (termed negative selection or self-tolerance). This deletion process primarily involves an interaction with bone marrow–derived cells (macrophages, dendritic cells, B cells) that have migrated to the thymus and specialized cells within the thymic medulla (medullary epithelial cells) that express a variety of organ-specific antigens.[52] The transcriptional regulator, Aire, plays an important role in T cell tolerance induction in the thymus, mainly by promoting ectopic expression of a large repertoire of transcripts encoding proteins normally restricted to differentiated organs in the periphery.[52] Only a small percentage (≈1–3%) of thymocytes actually survive positive and negative selection and become mature thymocytes that have a relatively high level of TCR expression and express either $CD4^+$ or $CD8^+$ markers. In general, cells that are positively selected by an interaction with MHC class II molecules mature into the CD4 population, whereas cells that are positively selected on MHC class I molecules become the CD8 population.[53] Mature thymocytes subsequently migrate to peripheral lymphoid tissues, where they maintain these surface characteristics.

T Cell Tolerance: Prevention of Self-Reactivity

Tolerance at the T cell level is critically important for the prevention of autoimmunity. Clonal deletion of self-reactive T cells in the thymus is a major process for eliminating T cells that are reactive to non–organ-specific cellular proteins and to circulating proteins because these self-antigens are likely to be in the thymus during T cell development. Some organ-sequestered antigens (e.g., certain uveal tract, brain, and endocrine organ antigens) are also expressed in the thymus.[52,54] However, studies have clearly shown that T cells to various self-antigens, including many organ-sequestered and posttranslationally modified antigens, are not completely deleted in the thymus. Therefore, self-tolerance must also involve the prevention of activation of these autoreactive T cells after they migrate from the thymus to the peripheral lymphoid tissues.[55,56]

Studies have shown that T cells with self-reactive TCRs are present in the peripheral lymphoid organs and the circulation of healthy individuals, but they are not sufficient for the development of autoimmune disease. Different peripheral mechanisms appear to help prevent the generation of autoimmune responses. One process appears to prevent the self-antigen from being effectively presented to a self-reactive T cell, which maintains that T cell in an ignorant state. For example, resting T cells with self-reactive potential may not be able to traffic to the tissue that expresses the antigen, or the antigen may not be presented by antigen-presenting cells. Some studies have suggested that inappropriate expression of MHC class II antigens in a tissue can lead to autoimmunity, perhaps by circumventing this protective mechanism. T cell activation triggered by a separate process (e.g., an infectious agent) may also bypass this protective mechanism by allowing cells with self-reactive potential to traffic to tissues inappropriately. T cells that do recognize antigen without effective antigen-presenting cells and co-stimulation may also be functionally deactivated (or anergized)[57] and prevented from any subsequent stimulation by that self-antigen. These cells continue to be present in the peripheral T cell repertoire, but their prior contact with self-antigen prevents any subsequent response. Current evidence indicates that anergic T cells activate some but not other signaling pathways after TCR engagement.[57] There is also evidence that the encounter of self-reactive T cells with antigen, but without effective presentation, sometimes leads to death of the autoreactive T cell rather than just anergy.

A final mechanism to prevent activation of self-reactive T cells involves regulatory (suppressor) T cells. In experimental animal models, there is evidence that $CD4^+$, $CD8^+$, and γδ T cells may be involved in the down-regulation of certain immune responses, and their absence may be associated with pathologic autoimmune responses. At least two subsets of regulatory $CD4^+$ T cells have been described that can inhibit cell-mediated immune responses and autoimmune pathologic responses: naturally occurring cells with suppressive activity and those induced by stimulation.[58,59] The naturally occurring regulatory $CD4^+$ T cells are characterized by constitutive CD25 expression and constitute 5–10% of the circulating $CD4^+$ population.[58–61] In murine models, depletion of these $CD4^+CD25^+$ T cells results in the spontaneous onset of multiorgan autoimmunity. These cells mediate their suppressive effects in a contact-dependent, antigen-independent manner in the absence of *interleukin-10* (IL-10) or *transforming growth factor-β* (TGF-β). A novel member of the forkhead box/winged-helix family of transcription regulators, designated FOXP3, has been identified as a specific molecular marker for this type of regulatory T cell, and its expression is essential for programming both thymic development and function of these T cells.[59,62] In sarcoidosis, FOXP3-expressing regulatory T cells accumulate at the periphery of the granuloma in subjects with active disease.[63] However, despite suppressing mitogen-induced T cell proliferation, the regulatory T cells in lung could not completely suppress *tumor necrosis factor-α* (TNF-α) and IFN-γ secretion, suggesting that the activity of this regulatory T cell subset was incapable of controlling granulomatous inflammation. The other type of regulatory $CD4^+$ T cell is activation induced, and these cells lack CD25 and FOXP3 expression.[59] Much of the suppression from this group of regulatory cells can at least in part be attributable to cytokines such as TGF-β, because TGF-β is capable

of suppressing both *type 1* (Th1) and *type 2* (Th2) *T helper* cell responses (see Th1 and Th2 responses, later). It is relevant to note that mice deficient in TGF-β show evidence of progressive inflammation and autoimmunity involving multiple organs.[64] In some cases, regulatory CD4+ T cells appear to release cytokines, such as IL-10 or even IL-4, that modulate the development and activation of Th1-type cells involved in a cell-mediated response.[58,65,66]

GENERATION OF AN IMMUNE RESPONSE

T CELL ACTIVATION AND CO-STIMULATION

Most immune responses depend on the activation of T cells and, normally, immune responses to foreign antigens are carefully orchestrated by a reciprocal communication between antigen-specific T cells and antigen-presenting cells. To be activated, naive T cells must receive several signals. One signal is antigen specific and is provided by engagement of the TCR. Additional signals are provided by co-stimulatory molecules and their interactions (Fig. 16.9). Resting antigen-presenting cells, such as resting B cells, frequently do not express significant levels of co-stimulatory molecules, and their interaction with T cells does not lead to T cell activation. Two of the most important co-stimulatory systems involve the interaction of CD28 with B7-1 (CD80) and B7-2 (CD86) and the interaction of CD40 ligand with CD40.[67] These two systems of interacting molecules also affect each other.

CD28 is constitutively expressed on CD4+ T cells. Early in the immune response, B7-1 and B7-2 are up-regulated on the antigen-presenting cells. Binding of CD28 to B7 co-stimulates T cell activation, leading to increased T cell production of IL-2 and other cytokines, increased cytokine receptor expression, increased cell survival, and increased T cell proliferation.[68-70] Occupation of the CD28 receptor alone, without TCR engagement, has little effect on T cells; therefore, signaling through CD28 is clearly a co-stimulatory event. The intracellular signaling that follows CD28 co-stimulation may overcome certain negative signals generated when the TCR is activated alone.[67,71,72]

Presentation in an inflammatory setting also leads to up-regulation of CD40 ligand (CD154) on the CD4+ T cell.[73] CD40 ligand interacts with its counter-receptor, CD40, on B cells and other antigen-presenting cells, also inducing up-regulation of B7-1 and B7-2 as well as certain adhesion molecules and cytokine production by the presenting cell.[74] The interaction of CD40 ligand with CD40 is clearly bidirectional in that it provides signals important for T cell and B cell activation. CD40 ligand is a member of the TNF receptor family, and a variety of other TNF receptor family members, such as CD134 (OX40), CD137 (4-1BB), and CD27, have also been shown to possess co-stimulatory function following T cell activation.[67,75] In chronic beryllium disease, CD137 has been shown to be a critical co-stimulatory molecule for the induction of T cell proliferation and for the prevention of activation-induced cell death in effector CD4+ T cells in lung.[76]

Following activation, T cells express *cytotoxic T lymphocyte antigen-4* (CTLA4) on their surface, which also binds B7-1 and B7-2 on the antigen-presenting cell and with stronger affinity than CD28.[77] This interaction sends a negative signal to down-regulate the T cell response after its initial activation. CTLA4 appears to be involved in the development of anergy and the generation of peripheral tolerance. CTLA4-deficient mice develop a lymphoproliferative disorder and die early, and alterations in the gene encoding CTLA4 have been associated with autoimmune endocrine diseases, further emphasizing the role of CTLA4 in the control of lymphocyte homeostasis.[78,79] *Programmed cell death 1* (PD-1) is another activation-induced inhibitory receptor that is expressed by T cells and binds the B7 family members PD-L1 and PD-L2.[80] Similar to CTLA4, PD-1 engagement by its ligands results in down-regulation of the

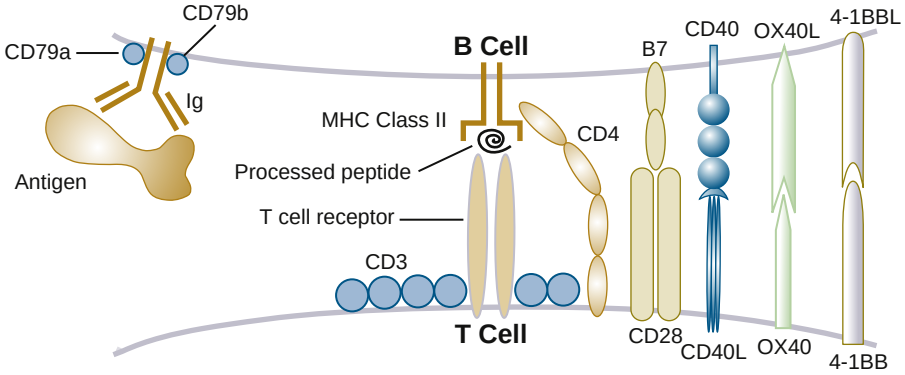

Figure 16.9 T helper cell–B cell interactions important for T cell–dependent antibody production. Antigen cross-links membrane *immunoglobulin* (Ig) on the *B cell receptor* (BCR), which provides the first signal for the B cell. CD79a (Ig-α) and CD79b (Ig-β) are Ig-accessory molecules necessary for transmitting the signal intracellularly. The antigen is internalized into an intracellular compartment in the B cell, processed to peptides, and combined with *major histocompatibility complex* (MHC) class II molecules for expression and presentation to the T helper cell. *T cell receptor* (TCR) binding to the peptide/MHC provides the first signal for the T cell. The CD3 complex allows for the TCR signal to be transmitted intracellularly. Activation of the T cell results in expression of CD40 ligand (CD40L), OX40, and 4-1BB. Interaction with CD40 provides the most important second signal to the B cell and is involved in T cell activation. In addition, B7-1 (CD80) and B7-2 (CD86) are up-regulated on the B cell. Interaction with CD28 provides an important co-stimulatory signal to the T cell. This figure does not show the release of cytokines from the T helper cell that are necessary for full activation and differentiation of the B cell. In addition, this figure does not show other cellular interactions mediated by adhesion molecules. For example, the lymphocyte function-associated antigen (LFA)-1 integrin (CD11a, CD18) on the T cell interacts with intercellular adhesion molecule-1 (CD54) on the B cell. This interaction appears to be enhanced once the TCR and BCR have been engaged. CD2 on the T cell also interacts with LFA-3 on the B cell, which provides additional cell-cell adhesion.

immune response. Deficiencies of this gene have been associated with autoimmune diseases in animals and may be a possible gene contribution to human lupus.[81,82] In contrast, blockade of CTLA4 or PD-1 signaling can activate cytolytic T cells in tumors and provides highly effective immunotherapy for a subset of patients with certain tumors, including non–small cell lung cancer.[83] In addition to these negative signals, down-regulation of the T cell response may be further ensured by decreases in surface expression of CD40 ligand, OX40, and 4-1BB after T cell activation.[70,75]

As discussed earlier in the context of self-tolerance, engagement of the TCR on a naive T cell in the absence of co-stimulation can result in different outcomes.[67] In some situations, the outcome is a failure to stimulate, and the T cell is oblivious to this encounter. At other times, recognition can induce death (apoptosis) of the responding T cells or anergy, in which case the T cells are unable to respond to a subsequent encounter with the same antigen (tolerance). Memory T cells appear to be less dependent on co-stimulatory molecules. However, antagonists that interrupt co-stimulatory interactions have been shown to have profound effects even later in the course of an established immune response. Blockers of the CD28-B7 interaction (with CTLA4-Ig, anti-B7, or anti-CD28 monoclonal antibodies) or of the CD40 ligand-CD40 interaction (with anti-CD40 ligand monoclonal antibodies), separately and together, are being investigated as therapies to treat autoimmune diseases and alloreactive responses after transplantation.[84–87] However, the development of cytokine storm in healthy volunteers receiving an anti-CD28 monoclonal antibody demonstrates the potential risk of immunotherapy.[88]

SUBSETS OF T HELPER CELLS

Although more sharply defined in mice than in humans, it is clear that T cells after activation may evolve into at least four major subsets of T helper cells, distinguished by their secreted cytokines (Fig. 16.10).[65,66] Th1 cells are defined as a unique T helper lineage by their expression of the transcription factor T-bet and mainly synthesize IL-2, IFN-γ, and TNF-α as well as other inflammatory cytokines, such as lymphotoxin. *T follicular helper* (Tfh) cells are characterized by the ability to secrete CXCL13, IL-21, and IL-4. Th2 cells are defined by expression of the Th2 lineage-determining factor GATA-3 and are primarily distinguished by secretion of IL-4, IL-5, and IL-13. Th17 cells represent a distinct lineage of T cells from either Th1 or Th2 cells and express IL-17A, IL-17F, and IL-22 as well as the transcription factor RORγt.[89–92] These major types of T helper cells serve very different functions. Th1 cells primarily enhance cell-mediated immune responses, such as delayed-type hypersensitivity reactions, which involve activation of macrophages and effector T cells. Th2 cells appear to be important for immune responses, especially against helminths.[20] Th2 cells also drive allergic responses, such as IgE production and eosinophil activation in asthma (see Chapter 60).[20] The ability to mediate an effective immune response against certain intracellular pathogens and the pathogenesis of certain diseases

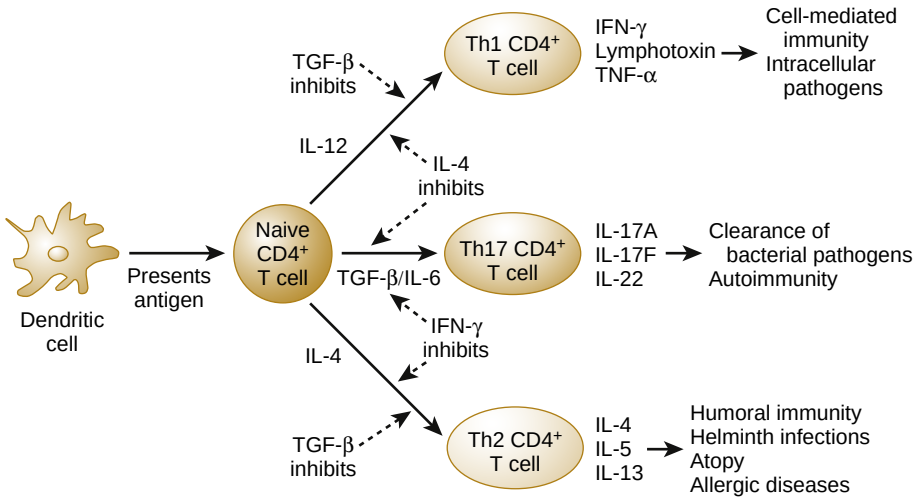

Figure 16.10 Regulation of T helper cell activation and responses. Naive CD4+ T cells can develop into *type 1 T helper* (Th1) cells if they are activated in the presence of *interleukin* (IL)-12, produced mostly by macrophages and other non–T cells. *Interferon*-γ (IFN-γ), increased by IFN-γ–inducing factor (IL-18), also enhances the development toward a Th1 response. IFN-γ appears to increase the production of IL-12 and also the expression of receptors for IL-12. The generation of a Th1 response leads to the production of IL-2, IFN-γ, lymphotoxin *tumor necrosis factor*-β (TNF-β), and TNF-α. These inflammatory cytokines are important for a successful immune response to intracellular pathogens. Inappropriate Th1 responses have also been implicated in organ-specific autoimmunity, such as in type 1 diabetes, multiple sclerosis, and rheumatoid arthritis. The early presence of IL-4 in the activation of a helper cell prevents Th1 responses and enhances the development of a type 2 T helper cell (Th2) response. The source of the early IL-4 is not clear, but it may come from Th2 cells already present, natural killer 1+ T cells, or non–T cells, such as mast cells and eosinophils. The Th2 response results in production of IL-4, IL-5, IL-10, and IL-13 and enhances humoral immunity. Although the Th2 cells are critical for the immune response to helminths, in the developed world, Th2 cells are probably most singled out for their important role in allergic disease and asthma. IL-4 and IFN-γ inhibit the development of a Th17 response that promotes bacterial clearance and may play a role in the development of autoimmunity. IL-6 and *transforming growth factor*-β (TGF-β) promote the development of Th17 cells, whereas IL-23 expressed by macrophages augments expression of Th17 cytokines by memory but not naive CD4+ T cells. Various regulatory CD4+ T cells have also been described. Regulatory CD4+ T cells secreting IL-10 have been shown to suppress Th1 responses. Regulatory T cells secreting TGF-β have the capability to suppress both Th1 and Th2 responses. Evidence suggests that, in addition to the cytokines present at the time naive CD4+ T cells are stimulated, the type of dendritic cell may regulate the differentiation of CD4+ T cells into Th1, Th2, or Th17 subsets.

are strongly influenced by the type of T helper cells involved. For example, in leishmaniasis and leprosy, the development of a response polarized toward the Th1 pathway is important for successful immune defense. The development of an early Th2 response may result in the inability to clear the pathogen. Inappropriately developed and activated Th1 cells have been implicated in the pathogenesis of certain autoimmune diseases, such as type 1 diabetes, multiple sclerosis, and rheumatoid arthritis. Th17 cells function at the interface between the innate and adaptive immune response, secreting cytokines that are important in bacterial clearance and in the pathogenesis of autoimmunity. Evidence suggests that in collagen-induced arthritis, T cell–mediated colitis, and experimental autoimmune encephalitis, Th17, as opposed to Th1, cytokines are critically important for the induction and maintenance of inflammation.[93–95] Although Th2 cells were initially described to provide help to B cells by promoting class switching and enhancing the production of certain IgG isotypes and production of IgE, it is now clear that this role is largely performed by a different subset of IL-4-expressing Tfh cells that reside in the B cell follicles.[96-98] Tfh cells are classified by expression of the follicular homing chemokine receptor CXCR5, and by PD-1 and IL-21 expression.[99–101] Tfh cells lack high expression of the T helper lineage-determining factors T-bet, GATA-3, and RORγt. Instead, this population of $CD4^+$ T cells expresses the Tfh lineage-determining factor BCL6.[102–104] Like classical Th1, Th2, and Th17 subsets, Tfh cells in humans and mice can express IFN-γ, IL-4, and IL-17, respectively, but secretion of these cytokines by Tfh is largely confined to B cell follicles and germinal centers and can be repressed by BCL6.[96,104–106] The directed secretion of these cytokines induces class switching toward distinct isotypes as discussed.

Th1, Th2, and Th17 subsets develop from the same T cell precursor, which is a naive $CD4^+$ T lymphocyte producing mainly IL-2 after stimulation with antigen. Considerable evidence indicates that the cytokine microenvironment is the primary determining factor for Th1, Th2, or Th17 differentiation (see Fig. 16.10).[65,66,90,91] IL-12 and IFN-γ are most important in directing the development of Th1 cells that then produce IFN-γ and TNF-α. IL-12 is produced by antigen-presenting cells (e.g., macrophages and dendritic cells) in response to Toll-like receptor stimulation by pathogens. IL-12 drives Th1 differentiation through signal transducer and activator of transcription 4 and the activation of a unique Th1 transcription factor known as T-box expressed in T cells (T-bet).[107,108] Certain microbial products induce macrophages and natural killer cells to release IFN-γ, which is involved in driving development of Th1 cells from their naive precursors. IFN-γ up-regulates a component of the IL-12 receptor on naive and differentiating T cells.[109] However, some pathogens, such as the measles virus, have the ability to down-regulate IL-12 production by macrophages and therefore possibly evade destruction by cell-mediated immune responses. Early production of IFN-γ by Th1 cells and natural killer cells has been related to the production of IFN-γ-inducing factor (IL-18), and this cytokine may synergize with IL-12 for maximal early production of IFN-γ and Th1 development.

In a similar but opposite manner, the presence of IL-4 early in the immune response promotes Th2 cell development from naive precursors through signal transducer and activator of transcription 6, which leads to activation of the transcription factor GATA3 and up-regulation of IL-4, IL-5, and IL-13.[88,90] The effects of IL-4 in promoting Th2 development are dominant over Th1- and Th17-polarizing cytokines.[56,57,91] Thus, if IL-4 levels exceed a threshold, Th2 commitment ensues, which leads to additional IL-4 production. Th2 cells do not respond to IL-12, which may be related to the ability of IL-4 to down-regulate expression of a component of the IL-12 receptor.

TGF-β and IL-6 are necessary for the differentiation of naive $CD4^+$ T cells into Th17 cells.[110–113] The orphan nuclear receptor, RORγt, is the master transcription factor in the differentiation of Th17 cells.[114] Expression of RORγt is TGF-β and IL-6 dependent and is both necessary and sufficient to induce Th17 development in most $CD4^+$ T cells.[91] The ligand of RORγt remains unknown. Using an IL-6–independent pathway, IL-21 and TGF-β can induce Th17 cells. IL-21 is also highly expressed by Th17 cells, and IL-21 production creates a positive feedback loop to amplify Th17 responses in vivo.[110] Despite the finding that IL-23 signaling is not required for Th17 commitment and early IL-17 secretion, IL-23 is important in amplifying and/or stabilizing the Th17 phenotype.[91]

The cytokines produced by Th1, Th2, and Th17 subsets cross-regulate one another's development and function. For example, IFN-γ produced by Th1 cells inhibits the development of Th2 and Th17 cells and certain humoral responses.[65,66,107] In a similar manner, IL-4 produced by Th2 cells inhibits Th1 and Th17 development and activation as well as macrophage activation by Th1 cytokines. IL-4 and IL-10 inhibit IL-12 production by dendritic cells and macrophages. In addition, the transcription factors GATA3 and T-bet expressed in T cells may antagonize the development of the opposite T cell subset by directly opposing each other's expression.[107,115] TGF-β also inhibits the development of Th1 and Th2 phenotypes.[107] However, separation of T cell differentiation into Th1, Th2, and Th17 phenotypes is not absolute. For example, in BAL fluid and mediastinal lymph nodes from patients with active sarcoidosis, increased proportions of T cells expressing markers consistent with Th17 and Th1 phenotypes (designated Th17.1 cells) have been defined as compared to patients undergoing disease resolution within 2 years.[116]

Following antigen exposure, naive T cells become activated, proliferate, and migrate to sites of inflammation. Although the majority of antigen-primed cells die, a population of memory T cells develops, which allows for a more rapid and effective secondary immune response upon reexposure to antigen.[117–121] There are at least three subsets of memory T cells, possessing different functional and migratory capabilities compared with naive lymphocytes. The effector memory T cell represents a terminally differentiated cell that immediately produces cytokine following antigen exposure and lacks the lymph node homing receptors L-selectin and CCR7. Conversely, central memory T cells express L-selectin and CCR7 and can differentiate into effector memory cells after subsequent antigen exposure. A third subset of tissue-resident memory T cells persists at the nonlymphoid site of infection.[122–125] These memory T cells are long-lived and do not transit back into the circulation or migrate into lymphoid tissues. Tissue-resident memory cells

can be distinguished from effector memory T cells found in nonlymphoid tissues by their high expression of CD103 and CD69.[126–128] Functionally, these tissue-resident memory cells act as key early sentinels against reinfection.

CD4+ T CELL–B CELL COLLABORATION AND REGULATION OF ANTIBODY PRODUCTION

A central event in the immune response is the antigen-specific interaction between a T helper lymphocyte and a B lymphocyte, which leads to their mutual activation. Although some antigens (usually nonproteins derived from bacteria) can activate B cells in a T cell–independent fashion, the antibody response to most protein antigens requires the relevant B cell to recognize antigen with its surface Ig receptor and receive activation signals from a specialized subset of $CD4^+$ T helper cells that reside largely in Tfh cells. These signals include both secreted T cell–derived lymphokines and those resulting from cell-cell contact. T cell recognition of antigenic peptides bound to MHC class II molecules on the B cell surface, with co-stimulatory signals, leads to T cell activation and secretion of T helper lymphokines. Secretion is directed toward the site of contact with the B cell. Thus far, no combination of known T cell–derived factors can fully replace contact with the T helper cell, indicating that the interaction of surface molecules provides additional signals to the B cell that promote its activation. Numerous interacting molecules have been identified that could transmit signals in the T cell–B cell interaction (see Fig. 16.9).

Similar to the process of effective T cell stimulation, which requires interaction of TCR with MHC/peptide and co-stimulatory signals, B cells also need more than one signal for activation to take place. The first signal is provided by antigen binding to surface Ig (BCR), and cross-linking of multiple receptors is usually required. The B cell then processes and presents the antigen via its MHC class II molecule to a cognate T helper cell that is specific for that MHC/peptide complex. A major second signal to the B cells is provided via CD40 on its surface through interaction with up-regulated CD40 ligand on the T helper cell. After receiving additional co-stimulatory signals from up-regulated B7-1 and B7-2 on the B cells, the activated T helper cell delivers cytokines in a focused manner to the antigen-specific B cell it is helping. Although many reciprocal receptor-ligand pairs are expressed on T cells and B cells, the signaling between CD40 ligand and CD40 is an obligatory and nonredundant interaction for functional T cell–dependent B cell activation.[87] The signals transduced by CD40 are essential for the prevention of apoptosis of antigen-specific B cells in the germinal center and required for B cell proliferation and differentiation, isotype switching, and formation of memory B cells. Mutations in the CD40 ligand gene cause X-linked hyper-IgM syndrome, characterized by absent or low levels of IgG, IgA, and IgE (Ig isotypes that require T cell help) but normal or elevated levels of IgM. Because T cell activation also requires co-stimulatory signals through CD40 ligand, these individuals demonstrate defects in T cell-mediated immunity and defective T cell activation.[129]

T cell help is required for effective antibody responses, especially those involving specific high-affinity antibodies of the IgG, IgA, and IgE isotypes. However, as emphasized earlier, T cell–B cell signaling is clearly bidirectional. After resting T cells are activated, which frequently requires specialized antigen-presenting cells such as dendritic cells, they migrate to the follicular border where they recognize cognate antigen presented by antigen-specific B cells. B cells may be the most efficient presenters of determinants of a specific antigen.[130] The helper $CD4^+$ T cell recognizes a processed antigen presented on the B cell in the context of MHC class II. The B cell focuses antigen for antigen-specific help by binding antigen through its Ig receptor, internalizing and processing the antigen, and presenting the derived peptides with MHC class II molecules (see Fig. 16.9). It is important to emphasize that the epitope on the native antigen recognized by the B cell is almost always different from the peptide epitope recognized by the Tfh cell. After interacting with B cells at the follicular border, Tfh cells undergo follicular migration where they are required for productive germinal center development and high-affinity B cell selection and antibody production.[131,132]

Subsequent to recognition, the T cell is activated to provide help for B cell proliferation and differentiation. T cell help is critically dependent on the T cell release of various cytokines, as described earlier. These cytokines have marked effects on B cell maturation, especially in determining which Ig isotypes will be produced by the B cell. The reciprocal surface molecular interactions, the directed nature of T cell cytokine release, and the controlled local action of these molecules result in "focused T cell help" without generalized bystander activation of surrounding B cells.

GENERATION AND REGULATION OF CELL-MEDIATED IMMUNE RESPONSES

Cell-mediated cytotoxicity is an essential defense against intracellular pathogens, including viruses and certain bacteria and parasites. Cytotoxic T cells are stimulated by presented antigens, predominantly derived from intracellular pathogens and bound to MHC class I molecules. In contrast to most helper cells that express CD4, cytotoxic T cells are usually $CD4^-CD8^+$. The recognition of the antigen presented by MHC class I molecules triggers the T cell to express receptors for IL-2. Although some cytotoxic lymphocytes are able to produce their own IL-2, most depend on IL-2 produced by helper $CD4^+$ T cells of the Th1 type. The binding of IL-2 and possibly other cytokines leads to some proliferation and to the development of cytotoxic function. $CD4^+$ T helper cells (Th1 type) provide additional signals and cytokines for the generation of a maximal cytotoxic response.

Activated effector cells are capable of delivering a lethal message to a target cell, separating from their dying target, and moving on to strike a new target. This creates a very efficient system of killing unwanted cells. Several mechanisms are involved in the actual killing process.[133–136] For example, cytotoxic T cells can directly signal their targets to undergo apoptosis through the interaction of FAS ligand, expressed on the surface of activated T cells, with FAS on the target cell. The cytotoxic T cell also produces substances such as lymphotoxin (also known as TNF-β), trimers of which bind to receptors on the cellular targets and signal for apoptosis. During binding to the target cell, the cytotoxic $CD8^+$ T cells also release the contents of their granules, which include perforins and granule-associated

serine esterases (granzymes), toward the adjacent membrane of the target cell. Released perforins assemble on the surface of the target cell and perforate the target cell plasma membrane, resulting in lysis and the entry of enzymes. The transmembrane channel created by the perforins resembles the membrane attack complex of the complement cascade. After entry into the target cell, activated granzymes released from the cytotoxic T cell activate proteins that mediate apoptosis and cause other types of cell damage.

INNATE LYMPHOID CELL SUBSETS AND FUNCTION

ILCs seed peripheral tissues during fetal development and early in neonatal life.[137,138] ILCs in the fetal liver and later the bone marrow develop from a common lymphoid progenitor.[139,140] At this stage, they lose natural killer cell potential and progress through an early helper ILC precursor and finally to a common ILC progenitor that expresses the transcription factor PLZF.[139-142] However, some ILC progenitors maintain natural killer cell progenitor potential.[143] ILC progenitors give rise to ILC1/3 and ILC2 progenitors that fully mature into ILC1, ILC2, and ILC3 subsets.[144-146] Once in the peripheral tissues, ILCs acquire tissue-specific identities that modulate tissue homeostasis and act as sentinels for barrier integrity.[147,148]

The ILC1 subset secretes IFN-γ and encompasses classical natural killer cells.[7,149,150] A large proportion of natural killer cells contains numerous electron-dense granules and is recognized morphologically as large granular lymphocytes. Markers on these cells are frequently shared with T cells (e.g., CD2 and CD8) or cells of the myelomonocytic series, for example, the integrin molecule CD11b or the low-affinity receptor for IgG (FCGR3 or CD16). Natural killer cells appear to play an important role in the initial (innate) host defense against infection and tumor cells. Similar to certain phagocytes, they have the capability to destroy target cells or pathogens that have been coated with specific antibody via a process known as antibody-dependent cellular cytotoxicity. While ILC1 share expression of T-bet and IFN-γ with natural killer cells, these two cell types are distinct in a number of ways. ILC1 arise during fetal development and require GATA-3 and IL-7 receptor while natural killer cells do not depend on these factors and arise after birth.[151] Another difference relates to the dependence of ILC1 and natural killer cells on the transcription factors T-bet and Eomes.[152] While natural killer cells depend on Eomes expression, they can develop in the absence of T-bet. Conversely, ILC1 depend on T-bet but not Eomes. Lastly, natural killer cells and ILC1cells differ in their cytotoxicity and expression of perforin. Natural killer cells mediate effector function through the release of IFN-γ to promote macrophage activation and phagocytosis. Natural killer cells are directly cytotoxic via their release of perforin. In contrast, ILC1-mediated killing is largely confined to promoting macrophage engulfment of infected cells. ILC1 cells exhibit little direct cytotoxicity because they express low amounts of perforin. Despite these differences, both natural killer cells and ILC1 cells are important in type-1 immunity against intracellular pathogens such as viruses and bacteria and antitumor immunity.

The ILC2 subset modulates barrier integrity and tissue repair at mucosal sites.[153–155] ILC2 cells, similar to T helper 2 cells, depend on the transcription factor GATA-3 during development and for ultimate commitment to the ILC2 fate.[145,156,157] These cells can be distinguished from other ILC subsets through their high expression of the surface receptor KLRG1 and cytokine receptors for IL-33, IL-25, and thymic stromal lymphopoietin.[153–155,158] Human ILC2 can be additionally identified by the expression of the chemokine receptor CRTH2 and the c-type lectin receptor CD161.[159,160] Their effector function depends on the production of IL4, IL-5, and IL-13. ILC2-derived cytokines are critical for mucosal barrier homeostasis. This is most evident in the small intestine where resident ILC2 cells sense IL-25 produced by intestinal tuft cells and in turn produce IL-13 to regulate intestinal goblet and tuft cell differentiation.[161–163] In addition, ILC2 cells are important in orchestrating early type 2 immune responses to large extracellular pathogens such as parasitic helminths. In the intestine, the presence of helminths increases IL-25 production by tuft cells, initiating a feed-forward circuit promoting ILC2-derived IL-4 and IL-13, which leads to goblet and tuft cell hyperplasia. As a result, the generation of IL-13 by ILC2 cells leads to enhanced mucus production, smooth muscle contractility, and ultimately worm clearance. In addition to their role in antiworm immunity, ILC2 cells express both arginase-1 and amphiregulin, which are important effector molecules involved in innate defense and tissue repair.[160,164–166] In combination, ILC2-derived IL-4, IL-5, IL-13, arginase-1, and amphiregulin promote the differentiation of reparative or alternatively activated macrophages, eosinophil mobilization, and tissue repair. Lastly, neuropeptide receptors are also expressed by subsets of ILC2 cells, allowing these cells to sense signals from the neuroendocrine systems of both the lung and intestine.[167–170] These neuropeptides work with alarmins to enhance ILC2 cytokine production in these mucosal tissues. This suggests that, like alarmins released by damaged epithelial cells, neuropeptides and neurotransmitters released by the neuroendocrine system may represent signals of barrier damage. When sensed by ILC2 cells, this initiates the recruitment of other immune cells for enhanced mucosal immunity and tissue repair.

ILC3 cells, like ILC2 cells, are found primarily in mucosal tissues and modulate barrier tissue homeostasis.[171–174] The ILC3 subset, like ILC1 cells, is heterogeneous. Two distinct subsets can be distinguished based on their surface expression of natural cytotoxicity receptors NKp46 (mouse) or NKp44 (human).[172,174,175] ILC3 cells produce IL-17 and/or IL-22, and *granulocyte-macrophage colony-stimulating factor* (GMCSF). All ILC3 cells in mice depend on the expression of the transcription factor RORγt similar to committed T helper 17 cells.[173,175,176] This is more variable in humans where IL-17-producing ILC3s require RORγt but IL-22-producing cells can exist in its absence.[144] Like other ILC subsets, ILC3 cells respond to various signals in the tissue microenvironment. These consist of both host-derived signals like retinoic acid, IL-1β, and IL-23, as well as exogenous, environmental signals such as microbial and dietary metabolites.[177–182] As these various tissue-specific cues suggest, ILC3 cells serve various functions in both tissue homeostasis and immunity. First, ILC3-derived IL-22 modulates intestinal stem cell differentiation and epithelial cell survival.[183–185] Second, ILC3 and IL-22 aid in modulating commensal bacteria and homeostasis at barrier tissues.[16,186–189] Third, ILC3 subsets

promote mucosal immunity by promoting phagocytosis of infected cells, regulating CD4 T cell responses, and inducing epithelial cells to produce antimicrobial peptides to protect against pathogens that may breech the epithelial barrier.[12,190,191] Lastly, like ILC2 cells, ILC3 cells also recognize signals derived from the nervous system, suggesting an important role for this innate lymphocyte in neuroimmune cell communication.[192,193]

SPECIFIC IMMUNE RESPONSES IN THE LUNG

LYMPHOCYTE POPULATIONS AND TRAFFICKING IN THE LUNG

The lung in healthy individuals usually harbors only a small number of lymphocytes.[194,195] The location of $CD4^+$ and $CD8^+$ αβ T cells can be arbitrarily separated into four compartments: bronchoalveolar space, *bronchus-associated lymphoid tissue* (BALT), lung interstitial tissues, and intravascular space. Although lymphocytes from these different positions may be involved in lung immune responses, there is no clear indication that these cells represent a resident lymphocyte population in the lung in humans. In contrast, γδ T cells have been localized to intraepithelial positions in the lung, and these cells may selectively reside in the lung.[35]

In a normal nonsmoking individual, lymphocytes account for approximately 10–15% of the bronchoalveolar cells obtained during bronchoalveolar lavage.[195] The number of bronchoalveolar lymphocytes can increase markedly in inflammatory diseases involving the alveoli and the interstitium, such as in hypersensitivity pneumonitis and sarcoidosis (see Chapters 91 and 93). Most bronchoalveolar lymphocytes are T cells, and essentially all of these cells express memory cell markers (e.g., CD45RO and low CD62L), indicating previous activation.[196] In disease, a significantly increased percentage of these T cells compared with those in peripheral blood also express markers of recent activation, such as HLA-DR, IL-2 receptor (CD25), and CD69.

BALT is a localized collection of lymphocytes in the subepithelial area of bronchi, analogous to gut-associated lymphoid tissue (e.g., Peyer patches).[197] These lymphoid aggregates are separated from the airway lumen by a lymphoepithelium composed of flattened epithelial cells, which lack cilia. BALT also contains HEVs facilitating the recirculation of lymphocytes between blood and lymph. However, unlike gut-associated lymphoid tissues in the form of Peyer patches, which are present in all mammals, BALT is found only in some mammalian species. Indeed, it is usually absent in humans as long as there is no respiratory tract infection. Evidence suggests that BALT may appear in patients after chronic airway inflammation and COPD.[198,199]

The interstitium of the normal lung contains few lymphoid cells, and most of these are not T cells. The majority of interstitial lymphocytes are natural killer cells, which belong to the ILC1 subset and constitute 10–15% of circulating lymphocytes. These cells do not express TCR or Ig but express markers characteristic of both T cell and myelomonocytic lineages.[200] Natural killer cells recognize and kill tumor cells and virus-infected cells in a nonspecific manner.[200] These cells also kill targets coated with antibodies via surface receptors for IgG (FCGR3 or CD16) in a process known as antibody-dependent cellular cytotoxicity. Furthermore, natural killer cells can also be an important source of cytokines (e.g., INF-γ, TNF-α, and GM-CSF) early in the immune response.

γδ T cells constitute only 0.5–10% of the peripheral blood lymphocyte population in humans.[35] However, they represent an enriched T cell population in the pulmonary epithelium, intestinal epithelium, and skin. Unlike αβ T cells, epithelial γδ T cells do not recirculate and appear to represent resident pulmonary lymphocytes. The population of γδ T cells in the lung of normal adult C57BL/6 mice is approximately 2 to 5×10^4 cells, with the majority being either $V\gamma4^+$ or $V\gamma1^+$.[201] Importantly, the different γδ T cell subsets are thought to have different functional capabilities. For example, in a murine model of asthma, $V\gamma1^+$ γδ T cells enhance airway hyperresponsiveness, whereas $V\gamma4^+$ γδ T cells suppress this response.[202] The pulmonary γδ T cells preferentially interact with $F4/80^+$ macrophages and MHC class II–expressing dendritic cells, suggesting that γδ T cells represent a primitive line of defense evolved to protect epithelial integrity and provide a possible bridge between innate immunity and acquired immune responses. γδ T cells have also been implicated in the regulation of various immune responses in the lung through IL-22 expression.[203]

The distribution and trafficking of lymphocytes is governed by interactions between molecules on the lymphocyte surface and ligands present on vascular endothelial cells. The migration of lymphocytes from the bloodstream is not a random event, and this migration appears to be restricted to lymphoid tissue and areas of inflammation.[17] Naive T cells lack the ability to initiate an antigenic response until they are activated within a secondary lymphoid organ. Evidence indicates that their initial interaction with an antigen entering through the lung takes place in the surrounding lymphoid tissues and not in the lung directly. Naive and resting lymphocytes represent the major population that recirculates from blood to lymph via HEVs,[204] with the initial attachment mediated by the homing receptor L-selectin (CD62L) to peripheral lymph node addressin and glycosylation-dependent cell adhesion molecule-1 on the surface of endothelial cells.[17] This interaction results in lymphocyte tethering and rolling along the endothelial surface. Subsequent binding of chemokines (e.g., stromal cell–derived factor-1α, 6-C-kine, and macrophage inflammatory protein-3b) to G protein–coupled receptors on the lymphocyte surface leads to activation of integrin molecules (*lymphocyte function–associated antigen-1* [LFA-1]).[17] After activation, LFA-1 binds to intercellular adhesion molecule-1 on the vascular endothelium, resulting in firm adhesion.[17] This is followed by transendothelial migration of the lymphocyte into the lymphoid tissue. A second family of G protein–coupled receptors, known as sphingosine-1-phosphate receptor-1, is required for lymphocyte egress from the lymph node.[205] As stated earlier, BALT consists of diffuse lymphoid aggregates found in the bronchial mucosa of most mammals.[197] In contrast to HEVs in other secondary lymphoid organs, BALT HEVs express high levels of vascular cell adhesion molecule-1, which binds $\alpha_4\beta_1$ integrin on T cells. Thus, an adhesion cascade exists involving

L-selectin/peripheral lymph node addressin, $\alpha_4\beta_1$ integrin/vascular cell adhesion molecule-1, and LFA-1/intercellular adhesion molecule-1, which targets specific lymphocyte populations to BALT and other bronchopulmonary tissues.[17,197]

Effector and memory T lymphocytes have distinct pathways of lymphocyte recirculation compared with naive lymphocytes.[17] Effector T cells, especially after activation in the lymphoid tissues, travel to regions of inflammation where chemokines and other chemotactic molecules are generated by the underlying inflammatory process.[17] Expression of adhesion molecules on the lymphocyte and binding to their appropriate molecular targets expressed on inflamed vascular endothelium allow cells to enter sites of inflammation.[17] The expression of intercellular adhesion molecule-1, P-selectin, and vascular cell adhesion molecule-1 on the surface of inflamed vascular endothelium is involved in lymphocyte entry into areas of inflammation.[17] Tissue tropism is established by the expression of different combinations of adhesion molecules that allow a different subset of effector cells to home to different sites. For example, circulating memory lymphocytes specific for skin-associated antigens express the cutaneous lymphocyte antigen.[17] Conversely, memory for intestinal antigens has been localized to circulating lymphocytes expressing high levels of $\alpha_4\beta_7$ integrin.[17] Thus, memory T cells display selective homing to the tissue type where antigen was first encountered.

ILC2 and ILC3 cells represent important populations of lymphocytes in the lung. These are rare cells that acquire a lung-specific identity based on tissue-specific and environmental cues. The majority of turnover among ILC2 and ILC3 populations in the lung is a result of local homeostatic proliferation.[11,137,206] However, these cells can quickly proliferate in response to inflammation and tissue damage. In addition to local proliferation of the tissue-resident ILC2 population, a transient population of ILC2 cells migrates to the lung early after mucosal barrier disruption.[158] Unlike the tissue-resident population that is responsive primarily to IL-33, this circulating ILC2 population responds preferentially to IL-25. The small intestine has been described as one source for this migratory ILC2 population, and it has been suggested that this population can convert to a tissue-resident phenotype upon entry into the lung tissue.[207] It should be noted that IL-33 has also been shown to induce the migration of ILC2 cells to the lung from the bone marrow, indicating that migratory IL-33-responsive ILC2 cells may also play a role in immunity in the lung.[208]

ANTIBODY-MEDIATED IMMUNE RESPONSES IN THE LUNG

Immune Response to Extracellular Pathogens

The humoral immune response is adapted for elimination of extracellular pathogens. An example of an antibody-mediated immune response is that which takes place after exposure to *Streptococcus pneumoniae.* This bacterium frequently colonizes the nasopharynx and is the most common bacterial cause of community-acquired pneumonia.[209] Pneumococci gain access to the lower respiratory tract via aspiration. The upper airway is equipped with clearance mechanisms (e.g., mucociliary clearance and cough) that effectively eliminate most inhaled or aspirated bacteria from the airways (see Chapter 4). If aspirated pneumococci evade the upper airway defenses, the pathogen first encounters the mucosal humoral immune system. IgA provides the first line of defense against infectious agents, with IgG and IgM being less important in the bronchial secretions. The major functions of secretory IgA include the prevention of microbial adherence to the epithelial surface and the promotion of the agglutination of microorganisms. The combination of inhibition of adhesion and microbial agglutination favors the clearance of pneumococci via mechanical forces. Unlike IgG, IgA is unable to activate complement and is not an effective opsonin.

The first exposure of the host to the pneumococcus generates a primary humoral response. Bacteria in the lung are bound by antigen-presenting phagocytes, which migrate to secondary lymphoid organs, where antigens are processed and presented with MHC class II molecules to $CD4^+$ T cells (Fig. 16.11). After TCR binding and effective co-stimulation enhanced by an inflammatory environment, antigen-specific T cells are activated and multiple T helper cytokines are elaborated. During this process, naive B cells in the lymph node bind unprocessed antigen via surface IgM and present peptide fragments to specific T helper cells via MHC class II molecules. T cell–B cell interactions in the germinal centers lead to additional T cell and full B cell activation, characterized by clonal proliferation, isotype switching, and differentiation of B cells into antibody-secreting plasma cells and memory cells. Subsequently, specific antibody, activated T cells, and perhaps some activated B cells circulate back to the lung to combat the pneumococcal infection.

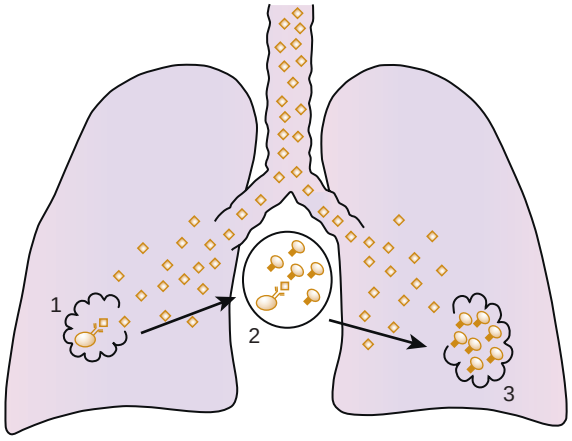

Figure 16.11 Immune responses in the lung. Antigen (e.g., bacterial pathogen) enters the lung. Microbial products create an inflammatory environment. *1,* Antigen is taken up by nonspecific phagocytic cells and transported to regional lymph nodes. *2,* In the lymph nodes, a primary immune response is generated. Antigen-specific T cells are stimulated, and initial T helper cell–B cell interactions and antibody production take place in the germinal centers. *3,* Antibodies, T helper cells, and effector cells circulate back to the lung for the immune response to target the pathogen. Trafficking of inflammatory cells is enhanced by the production of chemokines and other chemotactic factors and involves interactions of leukocytes with endothelial cells in the area of inflammation. In the process of the initial immune response, memory T cells and B cells are generated. This allows for the generation of a more effective secondary immune response if the same pathogen is encountered at a later time.

In the area of infection, IgG1, IgG3, and IgM specific for intact pneumococcal antigens activate the complement system, resulting in some bacterial cell lysis. More important, antibody and complement act as opsonins, enhancing phagocytosis of encapsulated microorganisms. The release of mediators from activated T cells also enhances the antibacterial capacity of recruited nonspecific inflammatory cells in the lung. These events take place over a 4- to 7-day period and characterize the initial phase of a primary response. The time needed for peak response is approximately 7 to 10 days. The presence of memory B and T cells ensures that repeat exposure to *S. pneumoniae* results in a secondary immune response, which is characterized by a shorter lag phase, resulting in a more rapid response of greater magnitude and longer duration. Clinically, pneumococcal vaccination, which induces a primary humoral response, has decreased the rates of invasive pneumococcal disease in both children and adults.[210]

Immune Response to Autoantigens

Autoimmune disorders result when the normal mechanisms of immune self-tolerance fail. Essentially all autoimmune diseases, including antibody-mediated autoimmune diseases, appear to be dependent on the inappropriate activation of autoreactive $CD4^+$ T cells as well as on the autoreactive B cells responsible for the pathogenic autoantibodies. One example of an autoimmune disease involving the lung is anti-*glomerular basement membrane* (GBM) disease (also known as Goodpasture syndrome) (see also Chapter 94). This syndrome is characterized by pulmonary hemorrhage and glomerulonephritis, which are associated with elevated levels of IgG antibodies directed against basement membrane antigens. In various studies, pathologic damage has been shown to be dependent on the binding of these autoantibodies, which are primarily directed against the noncollagenous domain (α3 chain) of type IV collagen in basement membrane.[211–213] Immunofluorescent staining with anti–human IgG antibodies usually reveals a linear deposition of IgG in the glomerular and alveolar basement membranes. Despite the widespread distribution of type IV collagen in the body, disease expression is mostly limited to the lungs and kidneys. This limited disease expression suggests the possibility that other factors allow exposure of this autoantigen selectively in alveolar or glomerular basement membranes. In this regard, influenza A infection, hydrocarbon inhalation, and cigarette smoking have been associated with the initial episode of diffuse alveolar hemorrhage and exacerbation of disease in the setting of elevated levels of anti–basement membrane antibodies. Much is known regarding how autoantibodies cause damage in an autoimmune disease such as anti-GBM disease. More recently, HLA associations and the B- and T cell epitope have been identified.[214] *HLA-DRB1*15:01* is strongly associated with the development of anti-GBM disease, whereas *HLA-DRB1*07:01* and *DRB1*01:01* confer protection against development of this disease. In addition, the T cell epitope has been mapped to the amino-terminal region of the α3 chain of type IV collagen.[215] As noted earlier, activation of both autoreactive $CD4^+$ T cells and autoreactive B cells appears to be necessary for a pathologic autoimmune response. These autoreactive $CD4^+$ T cells require CD28 co-stimulation, because blockade of this co-stimulatory molecule reduces anti–basement membrane antibody production and prevents the development of experimental autoimmune glomerulonephritis.[216]

Studies have identified an autoimmune cause underlying the development of acquired pulmonary alveolar proteinosis.[217] This disorder is characterized by the accumulation of a periodic acid–Schiff staining, granular, eosinophilic material within the alveolar space (see Chapter 98). Based on the development of pulmonary alveolar proteinosis in mice rendered deficient in GM-CSF, a fundamental role of this factor in surfactant homeostasis has been discovered.[218] In addition, the presence of neutralizing IgG autoantibodies directed against GM-CSF has been identified in the bronchoalveolar lavage fluid and serum of all patients with acquired pulmonary alveolar proteinosis, but not in individuals with the congenital or secondary form of the disorder or in normal control subjects.[219] The detection of this IgG autoantibody is highly sensitive and specific and thus useful in the diagnosis of the acquired form of this disease. More recently, mutations in the ligand-binding α chain of the GM-CSF receptor have been identified in pediatric patients with pulmonary alveolar proteinosis.[220]

Immune Response in Allergic Disease

Atopic asthma results when an immune response and IgE antibodies are directed against normally harmless proteins present in the environment (see Chapter 60). Numerous cell types, including mast cells, eosinophils, macrophages, and $CD4^+$ T lymphocytes, as well as IgE-secreting B cells, are important in the development of allergy and asthma. The $CD4^+$ T cells, which accumulate in the lungs of asthmatics, display a Th2 phenotype,[221] and studies using murine asthma models have shown that allergic airway inflammation is dependent on Th2-type $CD4^+$ T cells. As discussed earlier, the development of a Th2 response is prompted by exposure of naive $CD4^+$ T cells to IL-4 at the beginning of an immune response.[65,66,107,109] In the presence of high expression of IL-4 and low IFN-γ, these IL-4–producing $CD4^+$ T cells induce isotype switching in antigen-specific B cells to IgE.[222] The elevated levels of IgE in asthma are essential for the immediate hypersensitivity response. The presence of IL-4 and IL-5 and the production of various chemokines during T cell activation also enhance accumulation of eosinophils and basophils in the airways. Studies in murine models of allergic asthma have suggested an important role for another Th2 cytokine, IL-13, which is capable of inducing the pathologic features of asthma independent of IgE and eosinophils.[223] Related to the Th2 dependence of asthma in humans, susceptibility to disease has been linked to loci on chromosome 5q, which contains the genes for IL-4 and IL-13.[224] Studies also suggest that genetically determined abnormalities in antigen-presenting cells may also play a role in the development of allergic reactions. In atopic individuals, antigen-presenting cells were shown to underproduce IL-12 or overproduce prostaglandin E_2, which favors a Th2 response.[225]

CELL-MEDIATED IMMUNE RESPONSES IN THE LUNG

Granulomatous Lung Disease

Granulomas are characteristic of persistent infections caused by organisms that reside intracellularly, such

as *Mycobacterium tuberculosis* and *Mycobacterium leprae*. There is considerable evidence to suggest that $CD4^+$ T cells and the elaboration of Th1 cytokines are required for maximal granulomatous inflammation in the response to these infections. The triggering event in the development of noninfectious granulomatous lung disease is the deposition of antigen in the lung parenchyma. In the case of chronic beryllium disease[226,227] and hypersensitivity pneumonitis (see Chapter 91), the antigenic stimulus is known. In sarcoidosis, the inciting agent is unknown, although the immunopathogenic events are believed to be similar (see Chapter 93).[228] Thus, the unknown antigen is likely to be engulfed by antigen-presenting cells (i.e., dendritic cells and macrophages) in the lung parenchyma and presented to naive $CD4^+$ T cells in peripheral lymphoid organs. In the absence of IL-4, exposure of these activated naive $CD4^+$ T cells to IL-12 released by macrophages directs the T cell toward a Th1 response.[65,66,107,109] The development of a Th1 response is also influenced by early release of IFN-γ through the up-regulation of IL-12 production by macrophages and through the up-regulation of receptors for this cytokine on Th1 cells.

Production of chemokines and other chemotactic factors at the site of inflammation in the lung directs migration of activated effector $CD4^+$ T cells to the lung. The Th1 cytokines and other mediators produced by these T cells are responsible for the recruitment and activation of macrophages and other inflammatory cells. The accumulation of inflammatory cells within the alveolus (alveolitis) appears to be the initial lesion characterizing sarcoidosis and other granulomatous lung diseases. In sarcoidosis, the accumulated $CD4^+$ T cells (obtained at bronchoalveolar lavage) include expanded subsets, identified by expression of particular TCR Vβ and Vα regions. Within these subsets are expansions of T cell clones, each with a unique αβ TCR. The presence of these oligoclonal expansions indicates a T cell response to conventional peptide antigens, and the presence of different T cell clones with related TCRs indicates a response to the same antigen. Both the HLA allotype (the presenting MHC class II molecule) in an individual and the stimulating antigen(s) will determine the TCRs used in these T cell responses. In chronic beryllium disease, particular HLA-DP alleles (e.g., *HLA-DPB1* alleles expressing a glutamic acid residue at the 69th position of the β-chain) are the most important in the presentation of antigen to beryllium-specific T cells,[229] and this explains the increased disease susceptibility in individuals with the same HLA-DP alleles.[230] $CD4^+$ T cell clones expressing similar TCRs (with the same V regions and highly similar CDR3 regions) have been noted to be expanded in the lungs of different individuals with chronic beryllium disease, reflecting similarities in presenting MHC class II molecules and the same stimulating antigen (beryllium).[231] In sarcoidosis, an association between the TCR usage of Vα2.3 and HLA-DR17 (DR3) expression has been reported.[232] It is important to emphasize that the pathologic T cell responses in these diseases are compartmentalized to the lung because the same T cell clones are either absent or rare in the peripheral blood.[196] Recent evidence suggests that increased expression of inhibitory receptors (e.g., PD-1) on $CD4^+$ T cells in sarcoidosis results in an exhausted phenotype and that this exhaustion reverses with clinical resolution of pulmonary sarcoidosis.[233,234]

The major effector cells of inflammation in chronic beryllium disease, sarcoidosis, and other granulomatous diseases appear to be macrophages primarily derived from circulating monocytes during the process of inflammation. Activated alveolar macrophages express MHC class II molecules and may contribute to antigen presentation. Noncaseating granulomas form by coalescence of activated macrophages, which can also fuse to form multinucleated giant cells. $CD4^+$ T cells predominate in the center of the noncaseating granuloma, with $CD8^+$ T cells located at the periphery of the granulomatous response.

Cytotoxic T Cell Reactions in the Lung

Cytotoxic T lymphocytes (CTLs) are critical in the recognition and elimination of virus-infected cells and tumor cells as well as in allograft rejection. These cells predominantly express CD8, although $CD4^+$ CTLs and natural killer cells may also be involved in cytotoxic responses. $CD4^+$ T helper cells are almost always required for full expression of a cytotoxic T cell reaction. CTL responses have been detected in humans after infection with numerous viruses, including respiratory syncytial virus, parainfluenza, and influenza A and B. Once a $CD8^+$ CTL recognizes a respiratory syncytial virus–infected cell, there are at least three distinct mechanisms by which the CTL can induce cell death.[133-136] As discussed earlier, CTLs can secrete cytotoxic cytokines such as TNF-α and IFN-γ in the vicinity of the target cell. In addition, CTLs can release granule enzymes, including perforin and granzymes, which cause pore formation in the membrane of the target cell and enzyme-mediated apoptosis. Finally, CTLs can induce cell death via the interaction of FAS ligand on its surface with FAS on the target cell. $CD4^+$ CTLs do not have cytotoxic granules and primarily use FAS-mediated apoptosis as their mechanism of cytotoxicity.

Natural killer cells have a role complementary to that of CTLs in combating virus-infected cells or tumor cells.[200] Natural killer cells appear to form the first line of defense against viral infection, providing cytotoxic activity to kill virus-infected cells. These cells differ from CTLs in their lack of TCRs, and they recognize their targets in a non–MHC-restricted fashion. However, the mechanism of natural killer cell killing appears to be similar to that employed by $CD8^+$ CTLs. In addition, natural killer cells have receptors for IgG (FCGR3; CD16) and can bind to the Fc region of antibody attached to the surface of a target cell and mediate antibody-dependent cellular cytotoxicity.

Innate Lymphoid Cell Responses in the Lung

ILC2 cells in the lung play a role in the protective immunity against parasitic helminth infection.[154,155] After parasitic larvae enter the lung via capillaries, they migrate into the air spaces before eventual entry into the intestine. It is here that the larvae mature into adult worms and produce eggs. The migration of the larvae through the lung causes extensive damage and release of tissue alarmins such as IL-25, IL-33, and thymic stromal lymphopoietin. ILC2 cells recognize these alarmins and rapidly produce type 2 cytokines to initiate innate cell recruitment, mobilization of

eosinophils from the bone marrow, and promote the mucosal response in the small intestine to eliminate worms. In addition, ILC2 cells express MHC class II molecules and promote dendritic cell generation of T helper 2 responses, which are required for protective type 2 immunity.[13,14] Lastly, ILC2 cells express factors such as amphiregulin and arginase-1, which, in addition to type 2 cytokines, promote the differentiation of reparative macrophages and tissue repair.[160,164,166,235]

In addition to their protective capacity in the context of parasitic helminth infection, ILC2 cells have been described to have a pathogenic role in other settings of type 2 inflammation. In particular, ILC2 cells have been described to play a pathogenic role in various lung diseases. These cells have been best studied in the context of allergic asthma.[14,236–239] Furthermore, ILC2 cells have been implicated in the exacerbation of asthma as it relates to respiratory viral infections. These include asthma exacerbations driven by respiratory syncytial virus, rhinovirus, and influenza.[240–245] Lastly, although less well characterized, ILCs have been implicated in driving inflammation associated with many other chronic respiratory diseases, including COPD, pulmonary fibrosis, and cystic fibrosis.[246]

Key Points

- Although a functional immune system is essential to protect against microbial invasion, dysregulated immune responses contribute to pathogenesis of diverse lung diseases.
- Protective immunity against microbial pathogens is provided by humoral immune responses and a variety of cell-mediated responses that result in activation and accumulation of leukocytes.
- T helper cells are central to all of these immune responses for their full expression and maximal effect.
- The capacity for defense against widely diverse pathogens is achieved through unique molecular mechanisms of the B cell receptor and the T cell receptor repertoire formation, which are fundamental to the adaptive immune response.
- The end results of specific immune responses depend on cytokine expression and interactions of regulatory T cells with effector T cell subsets.
- In some individuals, the defense system may break down and, in others, aberrant immune responses contribute to pathologic conditions involving the lungs.
- Granulomatous lung diseases (e.g., sarcoidosis and chronic beryllium disease) are characterized by exuberant type 1 T helper CD4$^+$ T cell responses, whereas allergic diseases (e.g., asthma) are characterized by excessive type 2 T helper responses.
- Type 17 T helper polarized immune responses contribute to defense in bacterial pneumonia and to pathology in subjects with severe, corticosteroid-unresponsive asthma.
- Innate lymphoid cells are tissue-resident immune cells that regulate mucosal barrier homeostasis and serve as early sentinels against infection and tissue damage.

Key Readings

Barry M, Bleackley RC. Cytotoxic T lymphocytes: all roads lead to death. *Nat Rev Immunol.* 2002;2:401–409.

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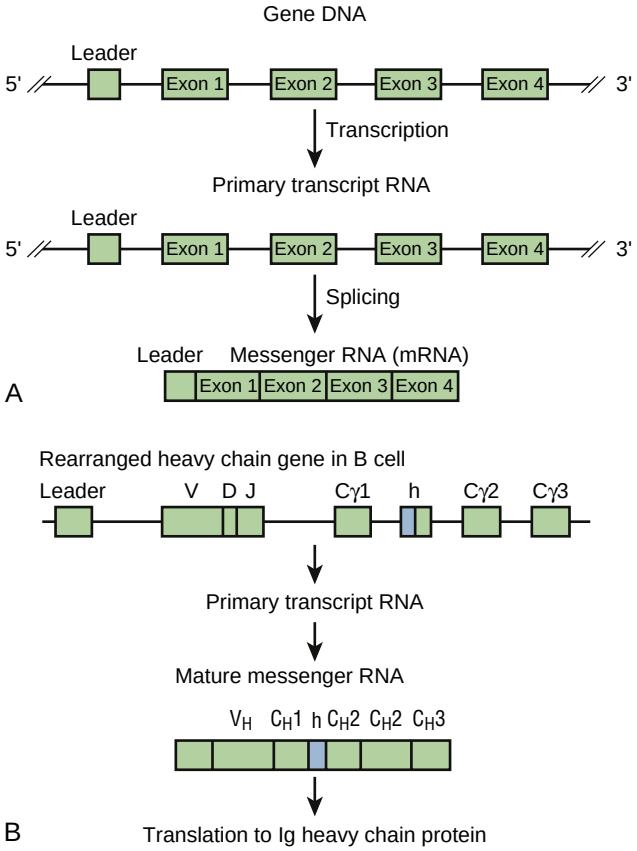
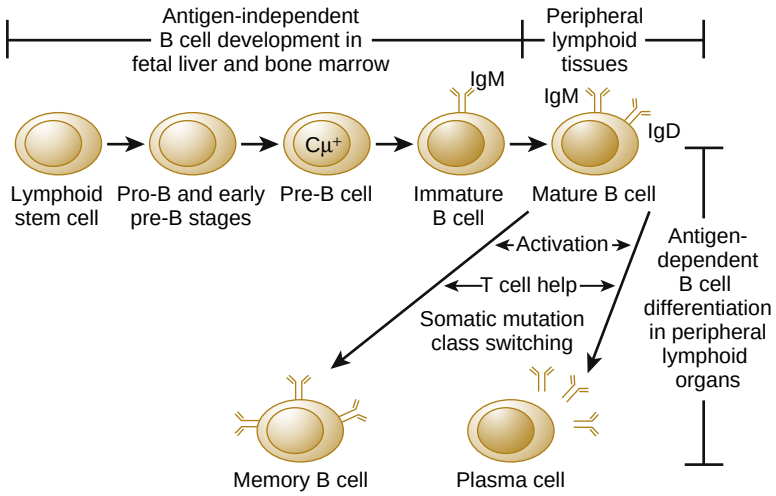
Complete reference list available at ExpertConsult.com.

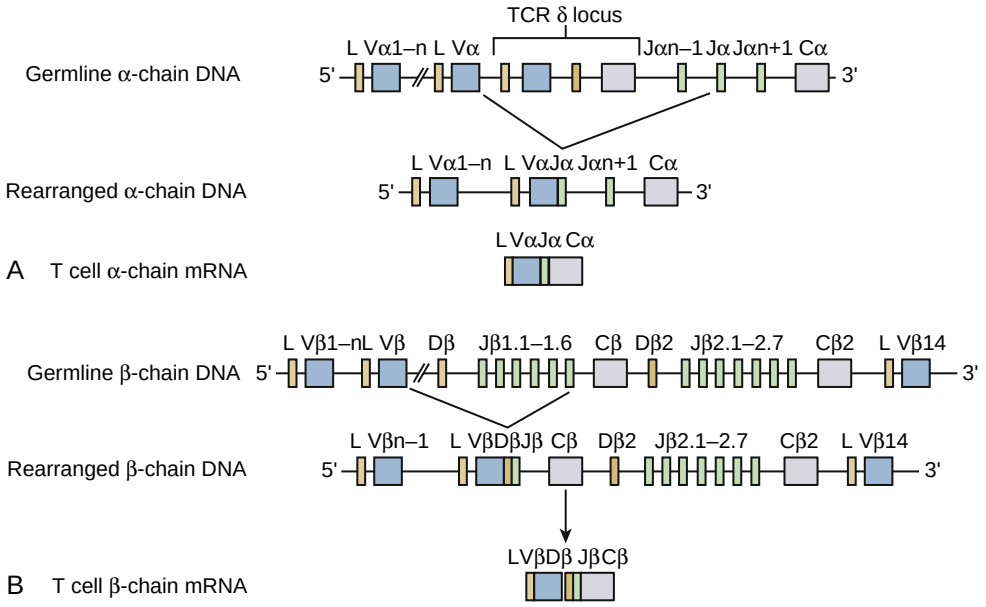
eFIGURE IMAGE GALLERY



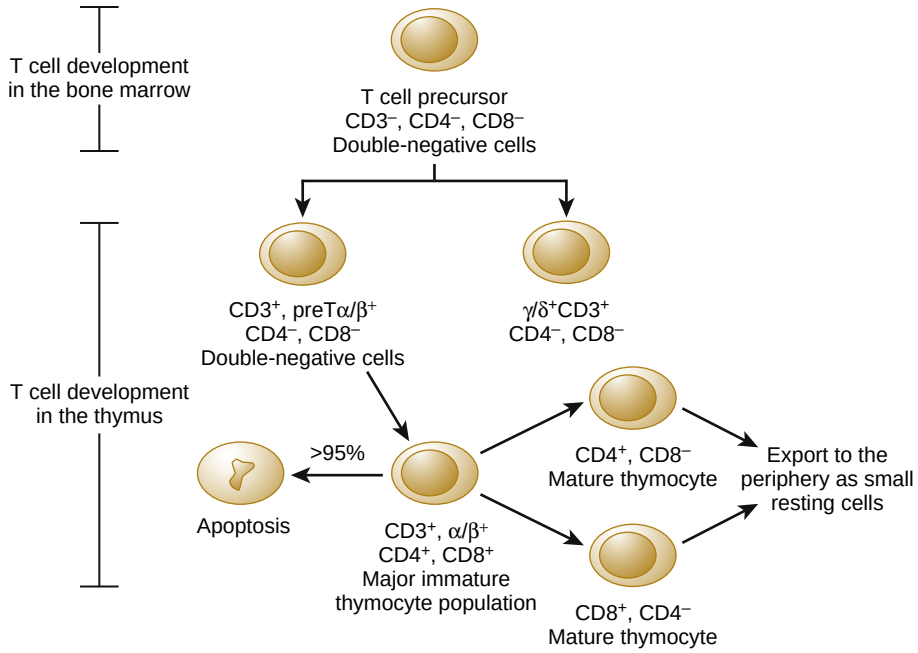
eFigure 16.1 Genes encoding immunoglobulin molecules. (A) Corresponding structure of a rearranged *immunoglobulin* (Ig) G heavy chain gene. The leader–V region segment of DNA was initially located upstream on the same chromosome and has rearranged proximal to the DJ segment, which is proximal to the IgG Cγ exons. Processing of the primary transcript brings all of the coding regions together in the messenger RNA molecule for translation of the protein.



eFigure 16.2 B cell development. Antigen-independent differentiation of the B cell in the adult bone marrow is shown from left to right. Pro-B and early pre-B stages involve the rearrangement of *immunoglobulin* (Ig) heavy chain D-J and V-DJ gene segments and transient expression of a pre–*B cell receptor* (BCR). Subsequent rearrangement of Ig light chain genes in the later pre-B cell allows for the development of a BCR-expressing immature B cell. The interaction of the mature naive B cell with antigen in the germinal centers of peripheral lymphoid organs and in the presence of T cell help allows for somatic hypermutation of the Ig genes (affinity maturation), isotype switching, generation of B cells that are capable of high-rate IgG secretion, and generation of memory B cells.



eFigure 16.3 Rearrangement of genes encoding the *T cell receptor* (TCR). (A) In the germline TCR α chain gene complex, before any rearrangement in T cells, approximately 40 to 50 Vα gene segments are located upstream of the multiple Jα and Cα gene segments. Within the TCR α chain locus is the TCR δ gene complex (expressed in γδ T cells), which is deleted when Vα genes are rearranged. During T cell development, Vα genes are rearranged to downstream Jα gene segments to form a functional α chain gene. This process is similar to that described for immunoglobulin gene rearrangements. Expression of RNA and RNA processing allows for generation of TCR α chain mRNA. (B) A similar process allows for rearrangement of TCR β chain genes in the pre-T cell during T cell development. In both A and B, nucleotide additions and deletions at the margins of the rearranging segments are not shown.



eFigure 16.4 T cell development and maturation in the thymus. The rearrangement of the *T cell receptor* (TCR) β chain genes in the pre-T cell and then TCR α chain genes results in generation of a remarkably diverse TCR repertoire, expressed at the stage of the major immature thymocyte. These cells express TCR at relatively low density and are double positive for both CD4 and CD8. The repertoire is positively selected for (low) affinity to self–*major histocompatibility complex* (MHC) (self-MHC restriction). Cells with TCR that do not undergo positive selection die in the thymus by apoptosis. Immature and mature thymocytes with high affinity for self-MHC/peptide complexes are negatively selected and undergo apoptosis (deleted). Overall, greater than 95% of immature thymocytes fail to mature for export to the peripheral lymphoid organs. As immature thymocytes mature, they maintain CD4 expression and down-regulate CD8 (MHC class II restricted) or maintain CD8 expression and down-regulate CD4 (MHC class I restricted).

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17 MICROBIOME

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INTRODUCTION

The recent discovery of diverse microbial communities present in the human respiratory tract, collectively termed the *lung microbiome,* is reshaping our understanding of respiratory physiology and disease pathogenesis. Propelled by technological innovations of *next-generation sequencing* (NGS), culture-independent studies have reproducibly demonstrated the existence of a lung microbiome, which is detectable in health and altered in disease. Such findings overturned a long-standing dogma of presumed lung sterility that the normal lungs were free from bacteria and introduced new conceptual models in pulmonology. The human lung can no longer be viewed as a sterile organ, and theories of disease need to address not only host cell biology but also complex host-microbe interactions.

The lung microbiome field is nascent and rapidly evolving in scope and volume. Early observations of disease-associated microbiota and proposed mechanisms of actions will have to stand the tests of time and replication. Lung microbiome research is only a few years old, and many of the methodologies continue to develop, suggesting that our understanding of the lung microbiome and its role in health and disease will evolve in upcoming years. For these reasons, this chapter does not provide an exhaustive catalog of reported microbiota associations with lung disease. Instead, we review basic principles and important lessons learned in the first wave of lung microbiome research; provide an accessible overview of commonly used terminology, experimental and analytic approaches, and prevailing ecologic theories; and review key findings in the healthy lung microbiome and major lung diseases.

Table 17.1 provides definitions of commonly used terms necessary for understanding the lung microbiome literature.[1–5]

THE GENESIS OF THE LUNG MICROBIOME FIELD

Since the introduction of the germ theory and Koch's postulates,[6] our view of human-associated microbes has been formed primarily through the lens of a microscope focused over ex vivo cultured bacteria. After completion of the Human Genome Project, technological innovations in massive parallel sequencing of nucleic acids (via NGS) allowed a culture-independent revolution in microbiology.[7,8] With NGS studies of 18 body site specimens, the first phase of the Human Microbiome Project revealed microbial communities with enormous diversity, functional capacity, and interpersonal variability in all examined loci.[9,10] Mainly composed of bacteria, but also including fungi, viruses, and archaea, the microbiota of the entire human body are estimated to amass a total of 3.8×10^{13} cells with more than 2 million genes.[11] The human microbiome is emerging as a major contributor to human health, conceptualized as an internalized organ that helps modulate immune responses, host metabolism, mucosal barrier homeostasis, and colonization resistance against pathogens.[1] Microbiome disruptions can lead to disease via loss of commensal physiology, pathogen invasion, production of bacterial metabolites, and dysregulation of the host inflammatory response.[2,12]

The lungs were not included among the 18 body sites examined in the Human Microbiome Project published in 2012,[9,10] perhaps as a reflection of a belief of lung sterility, in addition to practical difficulties in sampling the lower airways of healthy individuals. This omission contributed to a considerable delay in systematic investigations. Early reports of culture-independent bacterial identification in bronchoscopic samples from healthy lungs were met with skepticism.[4] The detected bacterial DNA was attributed to procedural contamination of the bronchoscope during passage through the high biomass oropharynx. However,

Table 17.1 Commonly Used Terms in the Microbiome Literature

GENERAL TERMS	
Human microbiome	The collection of all genomes of microbes (including bacteria, viruses, fungi, archaea, and protozoa) in the human body
Microbiota	The assemblage of microbes in a defined ecosystem
"Meta-omics": Metagenome Metatranscriptome Metaproteome Metabolome	The total content of a microbial community in terms of: Genomic DNA Transcribed RNA Entire protein complement Metabolite pool
Commensal bacteria	Bacteria that provide benefits to the human host without being affected by it
Symbiotic bacteria	Bacteria in a mutually beneficial relationship with the human host
Dysbiosis	Disruption of the normal structure and function of the microbiome that is detrimental for the host
TERMS FOR SEQUENCING TECHNOLOGIES	
Culture-independent technique	Molecular technique that analyzes biologic material directly from a sample and not from cultured microbes
Marker	A DNA sequence that identifies the genome that contains it
Amplicon sequencing	Amplification (with polymerase chain reaction) and sequencing of specific markers
16S ribosomal RNA gene	16S ribosomal subunit gene, unique to prokaryotic cells, with highly preserved sequence and specific hypervariable regions used as markers for bacterial identification
Metagenomic shotgun sequencing	Sequencing of short, random DNA/RNA fragments in an undirected whole-genome fashion
BIOINFORMATICS/ECOLOGY TERMS	
Operational taxonomic units	Classification for amplicon sequences clustered based on a similarity threshold (e.g., >97%) as a proxy for species-level taxonomic assignment.
Abundance	Prevalence of a particular taxonomic group in a microbial community
Richness	Number of taxonomic groups in a microbial community
Evenness	Relative abundance of different taxonomic groups
Alpha diversity	Within-sample taxonomic diversity (including richness and evenness) as a summary statistic of a single population
Beta diversity	Between-sample taxonomic diversity describing absolute or relative taxonomic overlap between samples

carefully designed, multicenter studies from the Lung HIV Microbiome Project identified bacterial DNA sequences from the *lower respiratory tract* (LRT) across different cohorts, with a minimal effect of pharyngeal carryover contamination.[13–15] After these seminal observations the field has been growing rapidly.[16] In retrospect the notion of lung sterility appears a rather implausible one. Given that bacterial communities can be found even in the most extreme environmental niches on earth,[17] it is now counterintuitive to theorize that no bacteria should be expected to be found in the warm and moist mucosal surfaces of the lower airways, centimeters away from the bacteria-rich oropharynx and subject to an influx of bacteria with breathing and with subclinical microaspiration.[18] With the concept of the lung microbiome now widely accepted, the roles of lung microbes are being examined in a wide spectrum of diseases.

TECHNOLOGIES FOR MICROBIOME STUDIES

High-throughput, culture-independent technologies have allowed comprehensive microbiota analyses that were not possible using culture-based methods. Cultures are inherently selective, identifying only the living microbes at the time of sampling that are able to grow in the specific media and incubation conditions used. Although recent methodologic developments with combinations of multiple growth conditions and prolonged incubation have increased the scope of culture-based approaches (culturomics),[19–21] such methods are laborious and not possible in large-scale lung microbiome studies. By using assays for specific molecules of interest (e.g., nucleic acids, proteins, or metabolites), culture-independent methods allow for organisms in a sample to be detected regardless of viability or specific growth conditions.[7,8,22] Such methods are advantageous in terms of comprehensiveness (capturing organisms without the need for ex vivo growth) and efficiency (ability to analyze millions of multiplexed sequences in a single experiment). An overview of the available -omics approaches for microbiome studies, moving from DNA to RNA to protein-based approaches, is provided in Fig. 17.1. DNA approaches offer information on the composition of the microbial community, whereas RNA, protein, and metabolite approaches provide functional insights about the community of interest (e.g., revealing which pathways are expressed or what metabolic products are being produced). Because most of the available literature has used the efficient and highly reproducible DNA-based methods,[16] we provide a brief overview of the two main DNA-based approaches and refer to additional resources for further details on other techniques.[7,23–26]

Amplicon sequencing methods rely on marker DNA sequences in the genome that can be used as molecular fingerprints for the organisms of interest. The most commonly used method for bacteria involves 16S *ribosomal RNA* (rRNA) gene sequencing (16S).[27] *Polymerase chain reaction* (PCR) primers amplify conserved regions of the 16S gene common to all bacteria that flank interspersed hypervariable regions (regions 1–9). These hypervariable regions are the molecular fingerprints that can allow categorization of bacteria (Fig. 17.2). With PCR amplification of the hypervariable regions, millions of short genome sequences (typically <250 base pairs) can be generated and then aligned, sorted, and classified according to publicly available databases. Sequences that are similar above a certain threshold (often >97%) are grouped together into *operational taxonomic units* (OTUs or taxa) as a proxy for bacterial species, although often these OTUs can only be identified to

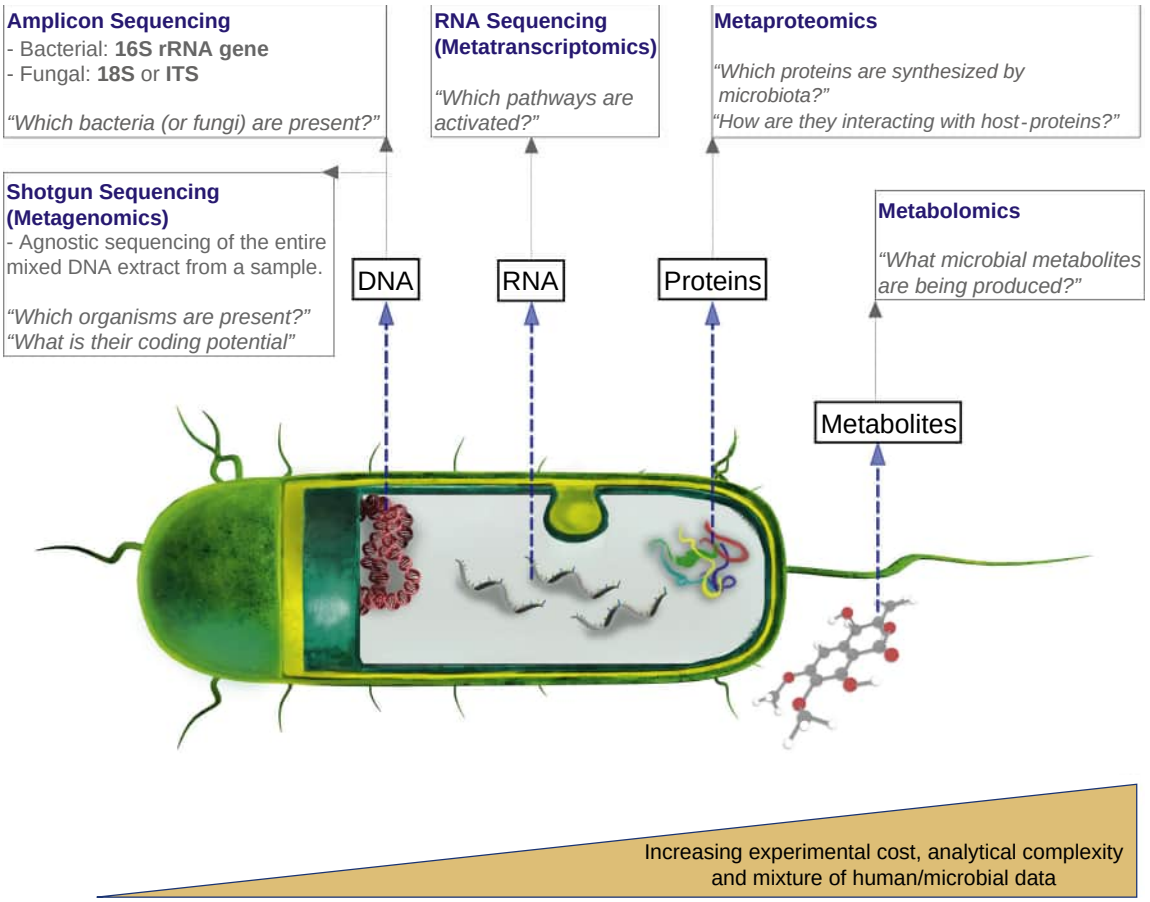

Figure 17.1 Overview of available -omics approaches for culture-independent studies of microbiota. Available technologies are structured according to the central dogma of biology, that is, from DNA- to RNA- to protein/metabolite-based approaches. DNA-based approaches are the most widely used due to the stability of DNA molecules and standardization of experimental and analytic pipelines. DNA methods include both amplicon sequencing (e.g., 16S ribosomal RNA gene sequencing for bacteria) and metagenomic shotgun sequencing for community-wide agnostic microbial detection. Metatranscriptomics, metaproteomics, and metabolomics approaches can offer more functional insights about the community of interest but are associated with higher experimental costs, analytic complexity, and difficulties in disentangling human from microbial data. ITS, internal transcribed spacer.

a genus level.[28] The end result of this approach is a population census for each sample, that is, how many times each taxonomic group was encountered, that can then be used for further analytic processing. *Quantitative PCR* (qPCR) of the 16S rRNA gene can approximate the absolute bacterial load present in each sample but, because there may be more than one 16S gene copy per bacterium, precise bacterial counts are not possible.[29] The 16S approach is reproducible and cost-effective and has become the workhorse method for large-scale microbiome studies. Drawbacks of 16S include the narrow scope (capturing only bacteria and not viruses or fungi), limited resolution (only genus-level taxonomy can be predicted accurately), lack of information on the full bacterial genome, and sensitivity to potential biases in the experimental pipeline (primer selection, amplification biases, etc.).[16] Similar amplicon sequencing approaches are available for fungi, by sequencing the 18S rRNA subunit or an internal transcriber spacer region, but not for viruses.[30]

Metagenomic shotgun sequencing techniques sequence the entire mixture of DNA present in a sample (see Fig. 17.2). The derived sequences are compared against reference genomes or gene catalogs for assignment to specific organisms and pathways. This approach allows improved taxonomic resolution (e.g., ability to distinguish a sequence belonging to *Staphylococcus aureus* vs. *Staphylococcus epidermidis* when 16S can only identify the genus *Staphylococcus*) and can offer insights into the functional capability of a community (e.g., abundance of specific genes and pathways).[8] Metagenomics can capture DNA from all successfully extracted organisms and thus reveal comprehensive microbial profiles. However, the high abundance of human DNA present in low microbial biomass samples, such as those from the lung, makes metagenomic experiments impractical and expensive because the vast majority of sequences detected are of human origin.[31] Several methods have been developed to deplete human genomic DNA from clinical samples,[32–34] but given current technical challenges and associated costs, the lung microbiome literature contains few metagenomic studies.[16]

Regardless of the sequencing approach used, culture-independent methods are vulnerable to contamination risks in every step of the experimental pipeline.[35] Reagent contamination is a threat for generating false-positive results (type I errors) when working with low microbial biomass samples, and thus close attention is needed to minimize, identify, and account for effects of contaminating DNA in sequencing experiments.[26,35,36]

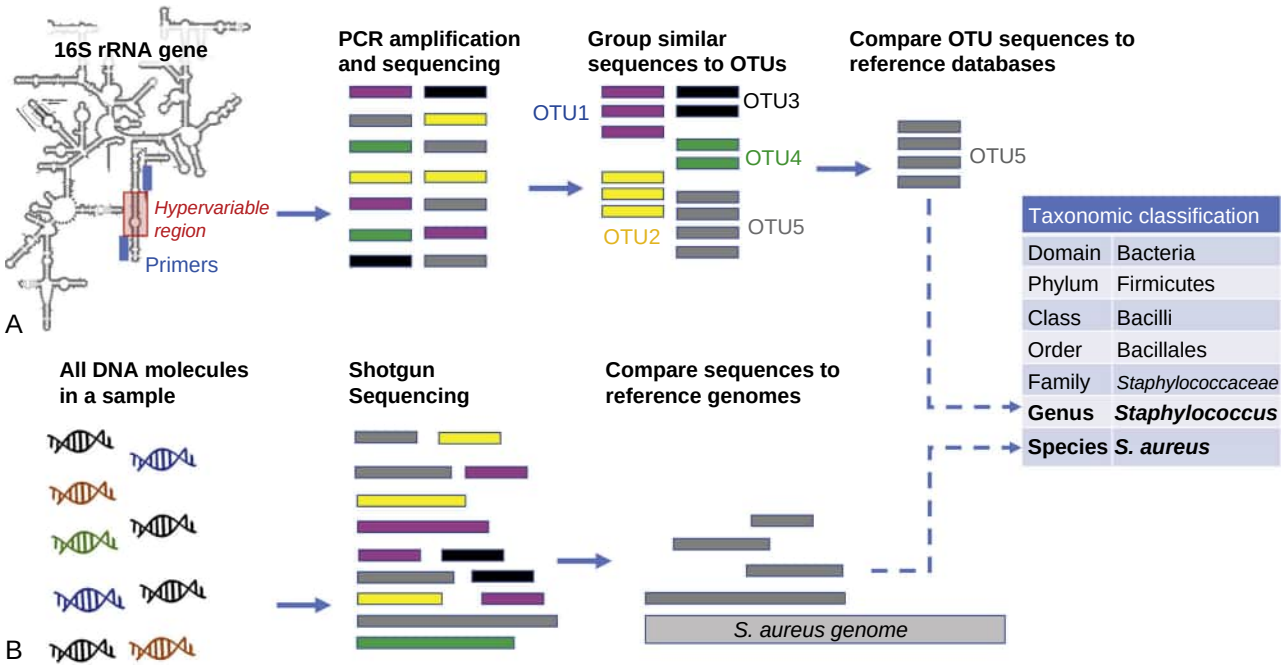

Figure 17.2 Amplicon sequencing vs. metagenomic shotgun sequencing. (A) Amplicon sequencing of the 16S *ribosomal RNA* (rRNA) gene for bacteria. Highly conserved regions in the 16S gene allow the design of *polymerase chain reaction* (PCR) primers *(blue vertical bars)* for amplification of interspersed hypervariable regions with informative genomic variation *(red vertical shaded bar)*. The PCR amplicons are sequenced in parallel with barcoding methods to allow multiplexing of many samples, and then they are grouped together based on similarity thresholds to *operational taxonomic units* (OTUs) as proxies for bacterial taxa. An alternative method to OTU similarity thresholds applies individual comparisons between sequences for distinguishing sequence variants and inferring bacterial origin (amplicon sequencing variants). Regardless of approach used, the taxa (OTUs) are compared against reference databases to obtain taxonomic information for this group of sequences, which can typically be reliably predicted at the genus level of taxonomic classification. (B) Metagenomic shotgun sequencing involves agnostic sequencing of all DNA molecules in a sample. The derived sequences are then compared against reference genomes (or gene catalogs) to obtain more detailed, species- or strain-level identification of the organism of interest (bacterial, fungal, or viral) and protein coding potential.

SEQUENCING DATA ANALYSIS

After the completion of a sequencing experiment and appropriate bioinformatic data processing[37,38] (see Fig. 17.2), the final output consists of a taxonomic table, that is, a population census expressed as either absolute number or relative abundance of taxa for each sample. Although analyses of such multidimensional data can be undertaken at many different levels of complexity and sophistication, widely used approaches are based on main principles of microbial and environmental ecology theory.[27,39,40] Microbiome sequencing data lend themselves to analyses of diversity measures within (alpha) and between (beta) samples, as well as comparisons of taxonomic abundance, as illustrated in the example analysis in Fig. 17.3.

STUDY DESIGN APPROACHES FOR MICROBIOME STUDIES OF THE RESPIRATORY TRACT

HUMAN STUDIES

Multiple different sampling approaches have been used for direct study of *upper respiratory tract* (URT) and LRT microbiota in humans, including nasopharyngeal or oropharyngeal swabbing, induced or expectorated sputum, endotracheal aspirate, *bronchoalveolar lavage* (BAL), bronchoscopic protected specimen brushing, and surgical lung biopsy (eFig. 17.1). Although no gold-standard approach exists, and different samples can offer complementary information, attention to procedural sterility and collection of procedural experimental controls (e.g., sterile saline, bronchoscope rinse before insertion) is essential to minimize, detect, and control procedural contamination, especially for LRT samples.[26]

ANIMAL MODEL STUDIES

Animal modeling is a powerful tool for mechanistic interrogations of lung microbiota in respiratory diseases.[41–44] This approach allows controlling microbial exposure in ways that are impossible for human studies, such as with germ-free animals, microbiota depletion with intensive antibiotic treatments, introduction of specific bacteria (e.g., gnotobiotic animals),[45] or microbial replacement (e.g., with fecal transplant or oral gavage).[16] Of note, with mice, LRT sampling is most reproducibly achieved by using whole-lung homogenate instead of BAL.[46,47] Nonetheless, animal studies are not free from confounding, because studies have shown the influences of cage and cohousing on lung microbiota of coprophagic mice, and such factors need to be taken into account in study designs.[46,48] Mice are the most commonly used animal models in this literature, but given the anatomic and ecologic differences of the mouse and human respiratory tracts, mice also present challenges in providing information relevant to human biology. In this regard,

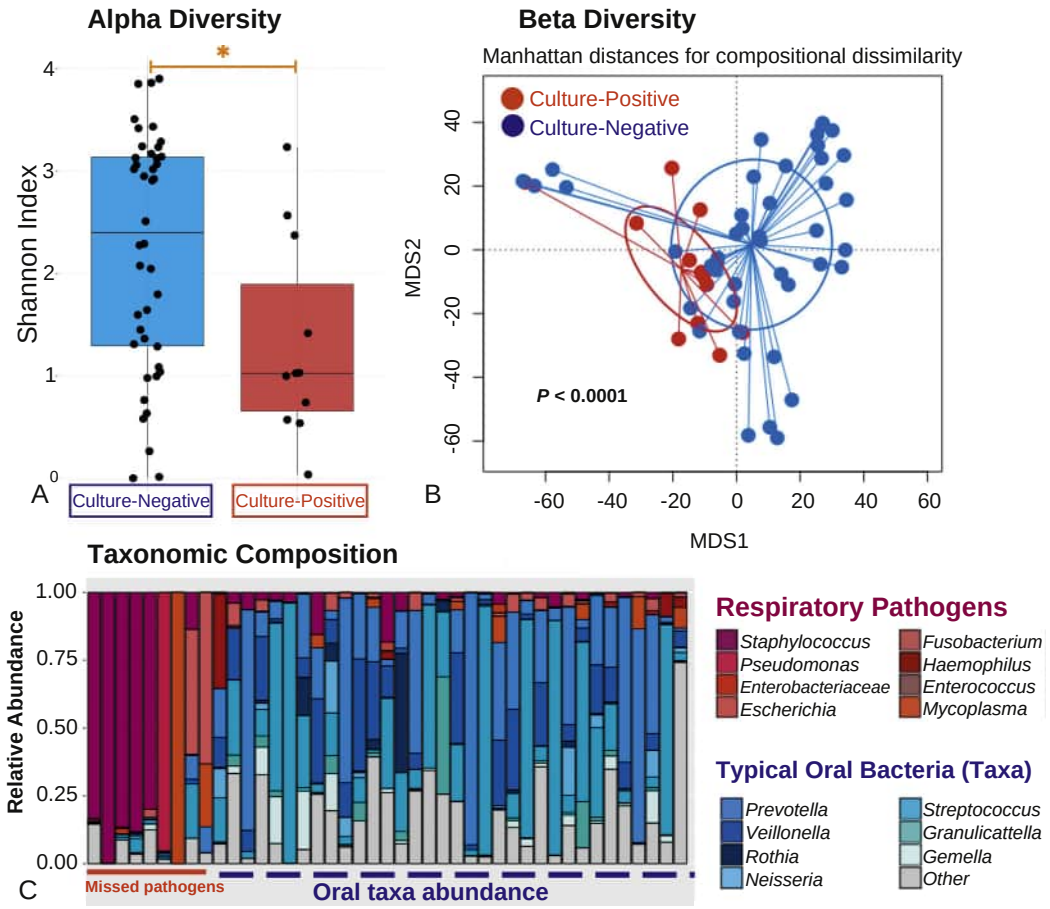

Figure 17.3 Common analytic approaches for microbiome data. Analyses applied in a study example of microbial communities analyzed with 16S sequencing from culture-positive and -negative endotracheal aspirate samples obtained from critically ill mechanically ventilated patients. (A) *Alpha diversity* examines the organismal richness of an individual sample (i.e., *How many different OTUs [i.e., taxa] are present?*) and the evenness of the organisms' abundance distribution in the sample (i.e., *How are the microbes balanced to each other, are they similar in abundance, or do some species dominate others?).* Commonly used metrics include Chao1, Shannon, Simpson, or Faith's index.[27,40] In general, for respiratory microbial communities, high alpha diversity is considered a marker of community fitness and often, but not always, associated with health. In the example of a study of mechanically ventilated patients with culture-positive and -negative endotracheal aspirates,[113] culture-positive samples had much lower alpha diversity (Shannon index) compared to culture-negative samples, indicating that culture-positive communities were dominated by fewer (pathogenic) bacterial taxa. (B) *Beta diversity* compares taxonomic dissimilarity between each pair of samples, generating a matrix of beta diversity distances between all pairs of samples in a study. Many different beta diversity metrics are available, assessing either relative abundance (e.g., Bray-Curtis, weighted UniFrac, or Manhattan) or presence/absence of taxa (e.g., Jaccard or unweighted UniFrac). With available software, beta diversity metrics can be statistically compared for differential clustering between groups of interest (e.g., *Do communities in patients with asthma differ from healthy controls?*) and can also be used for visualizing compositional differences with ordination techniques that reduce the dimensionality of data into interpretable plots, such as the *principal coordinates analysis method* (PCoA). In panel B, the PCoA plot illustrates different clustering of culture-positive versus culture-negative samples, suggesting differences in underlying taxonomic composition. Each circle represents a microbial community, and distance between individual communities on this two-dimensional plot depicts compositional dissimilarities. Formal statistical comparison with *permutation analysis of variance* (PERMANOVA) showed statistically significant differences in beta diversity by culture positivity ($P < 0.0001$). (C) *Taxonomic composition* and *differential abundance* describe individual samples in terms of their component taxa (genera or species) expressed in relative or absolute abundance. Comparisons for differentially abundant taxa or functional elements (e.g., genes or pathways) between groups of interest can reveal important organisms or other features that explain differences in communities. Nonetheless, microbiome data are compositional and interdependent in nature, requiring dedicated analytic methods for robust assessment of differential abundances.[40] In panel C the relative abundance at the genus level for culture-negative samples is shown. Each bar represents a separate sample, and the relative height of each component color represents the relative abundance for each taxon. Twenty percent of culture-negative samples were dominated by common respiratory pathogen taxa (e.g., *Staphylococcus* or *Pseudomonas*) (see "Missed pathogens" on *x*-axis), whereas the remaining 80% had high abundance of typical members of the oral microbiome (e.g., *Prevotella*, *Veillonella* and *Streptococcus*) (see "Oral taxa abundance" on *x*-axis). Overall, the analytic considerations described above apply not only to DNA sequencing data but also to functional -omics approaches, although analytic pipelines and software platforms are less standardized.

nonhuman primates can offer important experimental insights (see also Chapter 1 for comparison of human and mouse lungs).

THE HEALTHY LUNG MICROBIOME

A key question before studying the role of the microbiome in disease is its composition in health. Multicenter NGS studies of BAL from healthy individuals reveal significant interpersonal variability in lung microbial communities,[13,14] but with some common, recognizable features.

1. *Low biomass:* BAL fluid from healthy subjects analyzed by 16S rRNA gene qPCR has a much lower bacterial load (estimated bacterial density approximately 10^{2-3} bacteria/mL of BAL fluid[3,49–52]) compared to oral wash fluid (density estimates in range of 10^{5-6} bacteria/mL of oral wash).[49,50,52] The differences are considered to be

much greater than would be accounted for by differences in dilution.

2. *High alpha diversity:* Although specific estimates of alpha diversity vary among studies based on experimental and analytic differences, BAL communities from healthy subjects are generally characterized by higher alpha diversity indices[13] compared to diseased subjects[53,54] (see Fig. 17.3).
3. *Oral similarity:* The higher compositional similarity of lung communities with corresponding oral and not nasal communities is a reproducible finding in many studies,[13,50,52,55,56] which has reinforced the notion of the mouth (and not the nose) as the source of bacteria in healthy lungs.
4. *Limited regional heterogeneity:* In healthy subjects who underwent bronchoscopic sampling of multiple sites, microbial communities differed more between than within subjects, that is, a given individual's right middle lobe community more closely resembles the same individual's left upper lobe than another individual's right middle lobe.[57]

Firmicutes and Bacteroidetes are the two dominant phyla in healthy individuals, with lower abundance of Proteobacteria phylum organisms, Actinobacteria, and Fusobacteria.[13,52,55,58,59] The number of reported unique taxa (community richness) present in BAL samples is in the range of approximately 50 taxa per sample.[13,50,56,60] Bacteria recovered by culture comprise 61% of the taxa detected by 16S sequencing, indicating that NGS-profiles in BAL specimens provide representations of viable bacterial communities.[60]

Although typical oral-origin bacteria are predominantly found in the lung microbiome, their presence is not always detected in healthy individuals. Based on unsupervised clustering techniques, there appear to be two main profiles, referred to as *pneumotypes*, with similar frequency: a supraglottic pneumotype with higher bacterial load that contains typical members of the oral microbiome, such as *Prevotella, Veillonella,* and *Rothia*, and a background pneumotype that is enriched for taxa found in background controls (i.e., experimental noise), such as *Acidocella*, *Pseudomonas,* and *Sphingomonas*.[52,55] A notable exception to the predominance of supraglottic bacteria is the case of *Tropheryma whipplei*, a bacterium that is detected in up to a quarter of BAL samples from healthy subjects.[13,61–63] *T. whipplei* is associated with the gut microbiome (and the pathogenesis of Whipple disease) and is generally not detected in the mouth; its presence in the lungs may indicate site-specific reproduction and selective growth.

The lung *mycobiome* has been the subject of only a few studies in healthy individuals. Nonetheless, fungal DNA has been reproducibly detected and sequenced with amplicon approaches, with distinct and variable communities between individuals.[30,64–66] Predominant fungal taxa include members of the family Davidiellaceae, and the genera *Cladosporium, Eurotium, Penicillium,* and *Aspergillus,* whereas *Pneumocystis* colonization is also found in a small proportion of healthy individuals.[49,64]

The lung virome has not yet been characterized in detail because of methodologic challenges. Amplicon sequencing has been constrained because there is no conserved genomic region in DNA or RNA viruses to enable the design of primers. With metagenomic shotgun sequencing, high prevalence of members of the *Anelloviridae* family and bacteriophages have been detected.[67,68]

DERIVATION OF THE LUNG MICROBIOME

Multiple theories have been proposed to explain the formation of the lung microbiome in health and its disruption with disease.[26] Whether the relatively low microbial population density in the LRT is resident and reproducing in the lungs or whether it represents the net result of continuous population renewal from influx and efflux of microbes from the high biomass URT is not completely established. According to the widely cited *adapted model of island biogeography*,[12,26,57,69] the URT is the primary source of microbes in the lungs (Fig. 17.4). The lungs are conceptualized as microbial islands whose members are influenced by the rates of microbial immigration from the URT "mainland" (through inhalation, microaspiration, or mucosal dispersion) and elimination from the lung "island" (through mucociliary clearance, cough, and host mucosal defense mechanisms).[12,26,57,69,70] The net balance of these opposing forces determines the formation of a highly diverse, but low biomass, lung microbiome in health. Subclinical microaspiration even in healthy asymptomatic individuals is a well-established phenomenon that likely accounts for a continuous low-grade influx of bacteria in the lungs (see Chapter 43).[56] Changes in the rates of immigration and elimination (e.g., oropharyngeal dysphagia, diminished cough reflex) could reset this equilibrium and alter the lung microbial community. The lung microbiome may also be impacted by regional reproductive rates of microbes in the lungs as determined by nutrient availability, immune defenses, and environmental conditions (see Fig. 17.4). Whereas environmental conditions may not be conducive to bacterial proliferation in health, the altered ecosystem of diseased lungs with anatomic distortion and aberrant physiology (e.g., with stagnant nutrient-rich mucus in inflamed cystic fibrosis airways) can lead to bacterial overgrowth, further mucosal injury, inflammation, and a vicious cycle for establishment of *dysbiosis*—the disruption of the normal microbiome leading to harm to the host.[69] Finally, the concept of a gut-lung axis for microbiota has been proposed, with lung communities being influenced by gut microbiota by direct translocation of intestinal organisms to the lungs in states of abnormal gut permeability,[44] by shaping of the systemic immune response from the gut microbiome, by remote effects of gut microbe-derived components and metabolites on airway physiology and microbiota, or a combination of these mechanisms.[71,72]

THE EARLY LIFE ORIGINS OF THE HUMAN LUNG MICROBIOME

From birth and delivery to the outer microbial world and throughout early childhood development, there is evidence of dynamic adaptation of respiratory communities.[73]

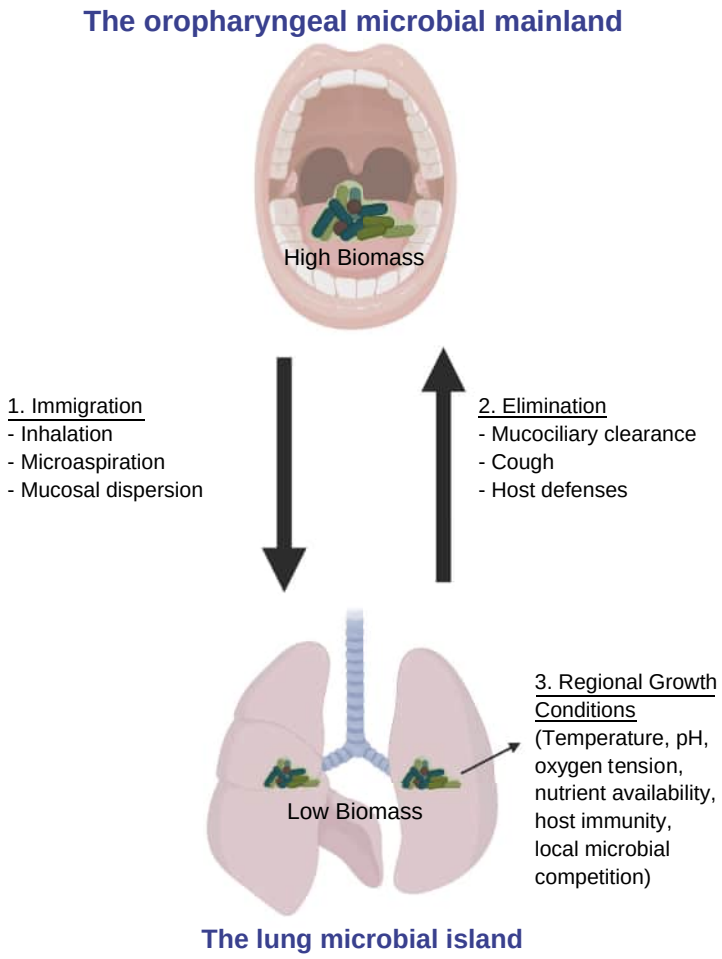

Figure 17.4 The adapted model of island biogeography for the formation of the lung microbiome in health and its disruption in disease. This model explains key features of the oral-lung axis: the large differences in microbial density, the taxonomic similarity of communities, and their gravitational relationship in humans, the only primates walking upright. According to the model, there is continuous influx and efflux of microbes in the lungs, with immigration from the high biomass oropharyngeal mainland (microbial source) to the low biomass lung islands (via microaspiration, inhalation, or direct mucosal dispersion) and elimination via cough, mucociliary escalator clearance, or phagocytosis. In health, the net balance between immigration and elimination determines the composition and load of microbes in the lungs. In disease, altered environmental growth conditions are expected to have a larger impact on shaping the lung microbial communities by creation of specific niches and enabling selective growth.

Vaginally born children are seeded with maternal gut/urogenital microbiota, whereas caesarean-born children carry typical skin bacteria.[74,75] Although the effects of such initial colonization appear to be transient, children who are born vaginally and/or are breastfed demonstrate more swift and predictable transition to stable microbial profiles associated with lower risk of respiratory illnesses (e.g., higher abundance of URT *Moraxella*, *Corynebacterium*, and *Dolosigranulum* taxa and lower abundance of *S. aureus*).[75,76] The "maturation" process of the respiratory microbiome in childhood is subject to multiple environmental influences, including infections and antibiotics, vaccination, dietary changes, daycare or school exposures, and pets in the household.[3] Although the gut microbiota matures into an adult-like profile by the first 3 years of life,[77] the time required to establish an adult-like pneumotype is unknown. Changes in the lung microbiome beyond childhood have not been defined.

THE LUNG MICROBIOME IN DISEASE

An expanding body of literature has reported associations between alterations in microbial profiles and disease. Compared with the healthy LRT, lung diseases can be associated with a high bacterial load by 16S qPCR, lower alpha diversity of LRT communities, and higher abundance of Proteobacteria phylum organisms (instead of the normal Firmicutes and Bacteroidetes composition). However, it remains to be determined whether such microbiome perturbations are disease specific, causally related, and clinically relevant. Most evidence consists of single-center, cross-sectional, observational surveys of LRT samples with 16S sequencing.[16] Cross-sectional study designs do not allow examination of longitudinal dynamics or determining temporality and directionality of effects, that is, "Does the microbiome change before disease onset and lead to disease or vice versa?" With few exceptions,[13,14,61] the small datasets collected in different centers have not yet been synthesized in multicenter analyses to examine the robustness and generalizability of findings across populations. In addition, the descriptive nature of 16S-based studies may miss informative species-level information or functional disruptions, detection of which would require more sophisticated meta-omics approaches. Thus interpretation for much of the available evidence needs to be cautious and viewed as hypothesis-generating for subsequent studies.

In the next sections we review key findings of selected human and animal model lung microbiome studies of obstructive airway diseases, interstitial lung diseases,

infectious diseases, lung cancer, lung transplantation, *acute respiratory distress syndrome* (ARDS) and other conditions.

OBSTRUCTIVE DISEASES

Asthma

Research efforts in asthma have broadly focused on two different phases of disease pathogenesis: first, on early-life interactions between microbiota (gut and URT) with risk of asthma development, and second, on associations between LRT microbiota with disease severity and response to treatment in adults.[78,79] Studies of the nasopharyngeal microbiome in children have shown associations between altered microbial communities, recurrent viral illnesses, and subsequent risk of asthma development. Alpha diversity of URT communities has been inversely associated with sensitization to house dust mites.[80] Similarly, a seminal study comparing Amish children (raised on traditional farms with low prevalence of asthma) with Hutterite children (raised on highly industrialized farms with high prevalence of asthma) found that differences in dust microbial composition and endotoxin load from the two housing environments were associated with very different innate immunity responses and with protection from asthma in Amish children.[81] Patterns of gut microbiome composition in young children have also been associated with increased risk for asthma.[82] In adults with established asthma, features of dysbiosis, including reduced alpha diversity and higher proteobacteria abundance (mainly due to enrichment for *Moraxella* and *Haemophilus*), have been associated with neutrophilic inflammation, degree of airflow obstruction, and resistance to corticosteroids.[83–86] Different microbial profiles found in different asthma subphenotypes (e.g., low bacterial load in patients with high type 2 inflammation)[87] suggest potential microbial contributors (and thus treatment targets) for observed clinical heterogeneity in asthma.

Chronic Obstructive Pulmonary Disease

Unlike asthma, where dysbiosis has been associated with future risk of disease development and severity across the entire spectrum, few differences in microbiomes have been observed among smokers, nonsmokers, and those with mild-to-moderate COPD.[79] Instead, dysbiosis in COPD has been more consistently detected in patients in severe disease by *Global Initiative for Chronic Obstructive Lung Disease* (GOLD) criteria,[4,79] with an increase of the Proteobacteria (mainly *Haemophilus* enrichment) and a decrease of the Bacteroidetes phylum.[59,88,89] Patients with acute exacerbations have shifts in the sputum microbiome, including low alpha diversity and increased abundance of *Staphylococcus*,[90,91] which may predict long-term adverse outcomes after hospital discharge.[92]

Cystic Fibrosis

Cystic fibrosis (CF) is the lung disease with the largest number of published microbiome studies in adult and pediatric populations.[16] Culture-independent methods have revealed a far greater microbial complexity than detected by cultures, and microbiome profiles are associated with host inflammation. Through early adulthood, diversity decreases and dominance develops of typical CF pathogens of the Proteobacteria phylum (*Pseudomonas, Burkholderia,* and *Achromobacter*) or *Staphylococcus* taxa.[53,54,93–95] With longitudinal analyses, a complex, multidirectional relationship between disease progression and airway microbiota has emerged: Airways progressively obstructed with mucus create niches for characteristic microbiota, which relate to host inflammation and infectious exacerbations, triggering repeated antibiotic exposures that further select for resistant bacteria, thereby establishing a vicious cycle of dysbiosis and inflammation.[79,96]

Non–Cystic Fibrosis Bronchiectasis

The microbiome of non-CF bronchiectatic diseases is not as well studied. Among patients with established bronchiectasis, the lung microbiome remains relatively stable over time, with separate clusters of *Pseudomonas* or *Haemophilus* dominance.[97] Of importance, patients with low-diversity communities may experience worsening airway obstruction.[97]

INTERSTITIAL LUNG DISEASES

Idiopathic Pulmonary Fibrosis

The lung microbiome has been implicated in *idiopathic pulmonary fibrosis* (IPF) pathogenesis based on the results of two cohort studies from patients with early stage IPF, in which high bacterial burden by 16S qPCR was independently associated with shorter patient survival.[43,98] Additional features of BAL microbial communities correlated with systemic and local innate immune responses and inflammation.[43,99,100] In murine models of bleomycin-induced fibrosis, lung dysbiosis preceded peak lung injury, whereas germ-free mice had longer survival.[43] These provocative findings have provided a rationale for studies of chronic antibiotic treatments in early IPF.[101,102] Nonetheless, the exact location of lung microbiota in IPF remains to be defined, with tissue-based examination suggesting that areas of end-stage honeycombing are devoid of bacterial loads above the detection threshold.[103,104]

Sarcoidosis

Despite long-standing hypotheses about potential microbial triggers and perpetuators of sarcoid-related granulomatous inflammation,[105] no reproducible microbial profile has emerged in available studies to date,[105–109] with sensitive metagenomic analyses revealing no clearly associated microbial lineages.[108]

INFECTIOUS DISEASES

Pneumonia

In multiple observational studies, NGS techniques have been leveraged for better understanding of the molecular microbiology of infectious pneumonia,[110] as well as for development of diagnostics to overcome the limitations of cultures.[31,111,112] Individual microbial profiles vary depending on the causative pathogen(s) in cases of community- or hospital/ventilator-acquired pneumonia.[32,113–125] In cases caused by a single pathogen, diversity collapses, and the community is dominated by the pathogen. However, NGS studies have also revealed more complex profiles, that is, by

identifying abundant organisms not frequently considered typical respiratory pathogens, organisms that are difficult to culture, and oral bacteria, routinely dismissed as nonpathogenic contaminants of LRT samples in clinical microbiology.[113,120,123,126,127] With integration of host responses and microbial profiles,[113,125] NGS studies in pneumonia can help redefine concepts of "pathogenicity" and "colonization versus infection" for respiratory microbiota.

Nontuberculous Mycobacteria Infection

The microbial profiles of samples from patients with *nontuberculous mycobacteria* (NTM) have disclosed an ecologic profile distinct from other bacterial infections: The causative NTM DNA has low abundance, near or below the limit of detection of dedicated molecular methods,[128] suggesting that NGS approaches may have inadequate sensitivity compared to cultures for NTM.[129]

Tuberculosis

Despite the global burden of tuberculosis, very limited knowledge of LRT microbiota is available for patients with or at risk for *tuberculosis* (TB).[130–132] High abundance of oral anaerobes (*Prevotella*) and elevated serum short-chain fatty acids have been associated with diminished production of protective antituberculous cytokines (e.g., interferon-γ and interleukin-17) and increased risk for TB infection.[131] In a macaque model, TB infection led to modest shifts of lung microbiota composition with enrichment for typical oral taxa, and not with the Actinomycetales order to which the *Mycobacterium* genus belongs. Important interactions with the gut microbiome have been reported,[133–135] with risk of *Mycobacterium tuberculosis* infection and progression modified by intestinal *Helicobacter* coinfection.[136]

Human Immunodeficiency Virus Lung Disease

Systematic examination of LRT microbiota with NGS was first performed in *persons with human immunodeficiency virus* (PWH). In initial studies, no major differences in microbial communities were found between generally healthy PWH and uninfected individuals, although *T. whipplei* was more common in PWH.[13,137,138] In PWH studied before and after initiation of antiretroviral therapy, their oral taxa abundance in BAL progressively increased.[139] Systems biology approaches have identified significant correlations between BAL metabolites, microbiota, and peripheral CD4 counts in PWH, suggesting a functional impact of the lung microbiome.[140]

LUNG CANCER

Compared to animals with a normal microbiome, germ-free animals demonstrate a lower risk of spontaneous or induced carcinogenesis, suggesting a potential role for the microbiome in cancer.[141] However, analyses of microbial communities in tumors or adjacent tissue in lung cancer patients have not disclosed a clear signal.[142–146] *Streptococcus* and *Veillonella* taxa have been associated with up-regulation of carcinogenic signaling pathways (*extracellular signal-regulated kinase* [ERK] and *phosphatidylinositol-3-kinase* [PI3K]) both in vivo and in vitro, suggesting a potential mechanistic link.[145] The microbiome may also play a role in response to therapy. For example, gut microbiota appear to modulate the response to immune checkpoint inhibitor therapy for non–small cell lung cancers, suggesting potential to improve clinical response rates by targeting the gut microbiome.[147]

LUNG TRANSPLANT

Given the intensive immunosuppressive therapy and associations of prior allograft infections with rejection, the role of lung microbiota in transplant recipients is actively investigated in both short-term (primary graft dysfunction) and long-term (*chronic lung allograft dysfunction* [CLAD]) outcomes.[148,149] Lung transplant recipients with clinical suspicion of pneumonia have low lung microbial community diversity and elevated alveolar cytokine and catecholamine levels, indicative of host inflammation and injury.[150,151] Both culture-based and culture-independent studies have shown that bacterial (mainly *S. aureus* and *P. aeruginosa*), viral (cytomegalovirus), and fungal (*Aspergillus*) detection in lung allografts are associated with risk for CLAD.[148,149,152,153] BAL microbiota are also associated with proinflammatory myeloid-derived suppressor cells and catabolic lung remodeling gene expression, potentially contributing to CLAD pathogenesis.[154,155]

ACUTE RESPIRATORY DISTRESS SYNDROME

The markedly altered ecosystem of the flooded alveolar space in ARDS, with nutrient-rich edema and intense host inflammation, may support increased microbial growth and further propagation of alveolar injury.[2,156] This hypothesis is reinforced by animal models of lipopolysaccharide-induced lung injury, where bacterial load increased fivefold in BAL samples due to a bloom of proteobacteria capable of metabolizing the alveolar nutrients.[42] In the few studies available in humans, enrichment of the lung microbiome with gut-associated bacteria (e.g., *Bacteroides*[44] or Enterobacteriaceae[157]) was associated with ARDS development and increased host inflammation. Antibiotic-mediated depletion of microbiota in mice leads to more severe ventilator-induced lung injury, suggesting that a healthy microbiome may also protect the host.[158]

OTHER LUNG DISEASES

The potential role of respiratory microbiota has also been investigated in other disease entities, including obstructive sleep apnea,[159] allergic bronchopulmonary aspergillosis,[160] pulmonary complications posthematopoietic cell transplant,[161] pulmonary hypertension,[162] and bronchopulmonary dysplasia,[163] among others. The reader is referred to the primary literature referenced for discussion of these emerging associations.

FUTURE DIRECTIONS FOR LUNG MICROBIOME RESEARCH

The transition of the lung microbiome field from its current, largely descriptive, hypothesis-generating studies into more mechanistic and targeted interventional studies will be necessary for clinical translation of related discoveries.[2,16]

Multi-omics data integration approaches, including deep phenotyping of host responses with detailed profiling of microbiota, supplemented by rigorous animal modeling experiments, can uncover new mechanisms of respiratory disease pathogenesis. With the evolution of rapid NGS platforms, real-time lung microbiome profiles may offer important diagnostic or prognostic information in clinical practice, such as improved accuracy for etiologic pathogen diagnosis in pneumonia [32,112,113,125,127] or risk stratification for patients with acute exacerbations with COPD.[92] Finally, there is potential for new therapeutic interventions targeting lung microbiota, either with direct manipulations (e.g., aerosolized drug delivery or URT community decontamination/reconstitution) or with indirect mediation via the gut-lung axis (e.g., use of probiotics or dietary interventions).[164] Although formidable challenges exist for advancing the lung microbiome research agenda, methodologic rigor and transparency in this nascent research field is expected to catalyze its maturation into a transformative new frontier of pulmonary medicine.

Key Points

- The study of the lung microbiome was made feasible by the introduction of culture-independent next-generation sequencing techniques of microbial DNA.
- The lung has a detectable microbiome even in healthy individuals, which is highly diverse, has a low bacterial biomass, and resembles the oral cavity microbiome in composition.
- Continuous microaspiration and elimination of microbes via the oropharynx are considered to be the main forces shaping the lung microbiome in health.
- Fungi and viruses are also detectable in the lung, but their communities and importance are less well understood.
- Studies of the lung microbiome are susceptible to contamination because of the low biomass in the lower respiratory tract.
- The lung microbiome may impact disease via infection, metabolite production, or modulation of host inflammatory pathways.
- Common alterations of the normal communities seen in various lung diseases include increase in bacterial biomass, loss of biodiversity, and shifts in community composition favoring pathogenic proteobacteria.
- The potentially causative role of microbiome changes in disease remains to be elucidated.

Key Readings

Biesbroek G, Tsivtsivadze E, Sanders EAM, et al. Early respiratory microbiota composition determines bacterial succession patterns and respiratory health in children. *Am J Respir Crit Care Med*. 2014;190(11):1283–1292.

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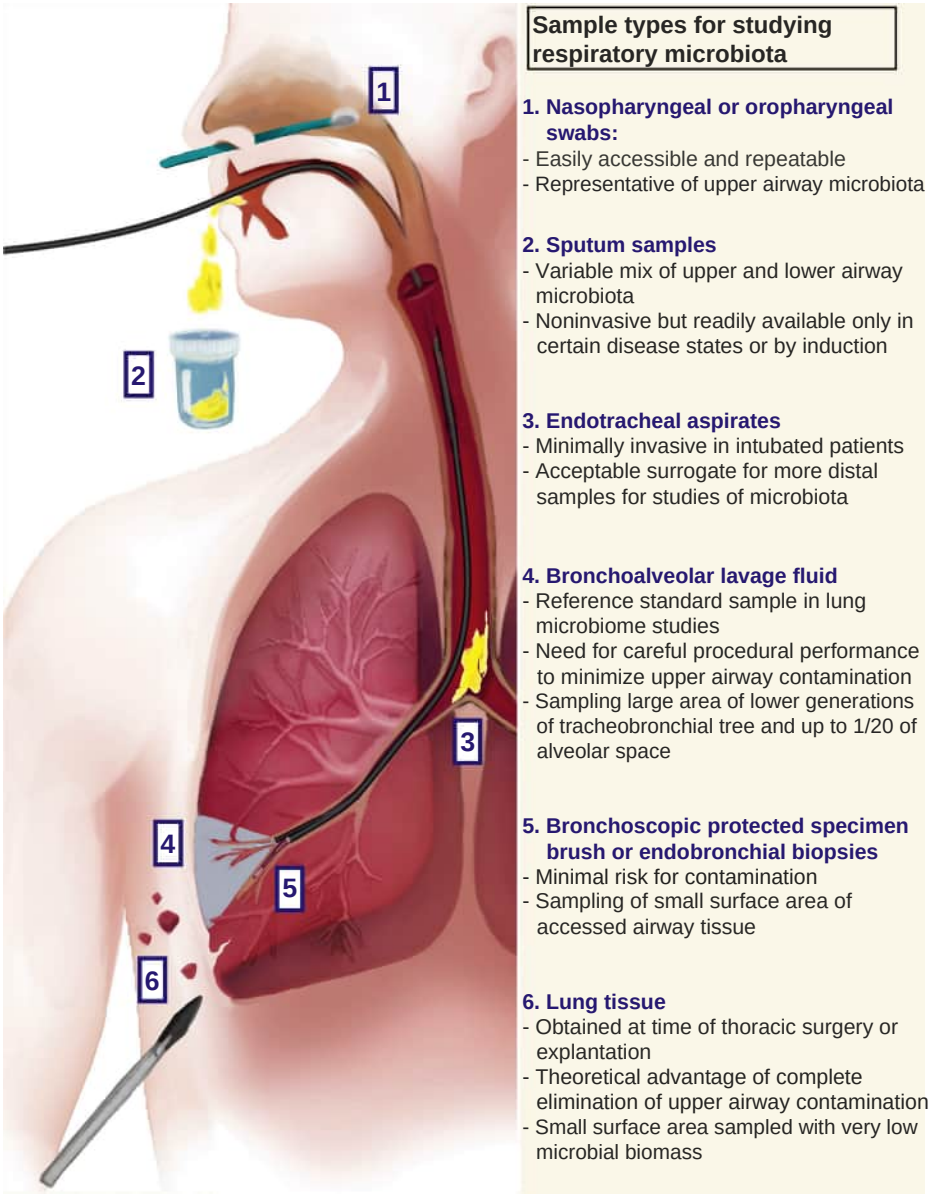
Complete reference list available at ExpertConsult.com.

eFIGURE IMAGE GALLERY



eFigure 17.1 Sampling methods for culture-independent studies of respiratory microbiota. Available sample types are shown in descending order from the *upper* to the *lower respiratory tract* (URT and LRT, respectively). No gold standard method for sampling respiratory tract microbiota is suggested, but there are important anatomic, ecological, and technical/procedural parameters to be taken into account in sample type selection.[16,26] Physiologic gradients from the URT to the LRT (in terms of surface area, pH, temperature, humidity, and partial pressure of exchanged gases) translate into microbial density gradients, from high bacterial biomass in the URT to several orders of magnitude lower biomass in the LRT.[3] Thus, albeit LRT samples are more directly representative of the lung microbiome, they are also more sensitive to contamination and experimental noise.[26] Anatomic specificity of sampling (as in the case of protected brushing or lung tissue specimens) needs to be balanced against maximizing the area sampled to increase recoverable microbial signal (e.g., *bronchoalveolar lavage* [BAL] samples capture much larger areas, including lower generations of the tracheobronchial tree and up to 5% of the alveolar space). Sputum and BAL are the most commonly used sample types,[16] and BAL has been validated as a reliable technique for studying LRT microbiota, with negligible effect of whether a trans-oral or nasal approach is used for bronchoscope insertion.[56]

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SECTION D

DIAGNOSIS

18 HISTORY AND PHYSICAL EXAMINATION

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INTRODUCTION
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INTRODUCTION

Today, medical technology is thoroughly integrated into medical practice, including all aspects of evaluation. The electronic medical record prepopulates much of the history with clinical problems, the past medical history, and medications. The electronic medical record often serves as the primary source of information about a patient's medical, social, and family history, thereby replacing one of the most personal aspects of the medical interview and taking away an early opportunity to establish a relationship with the patient. In many settings, laboratory and imaging tests are preemptively ordered before the medical interview and examination. Today a conscientious clinician can generate lists of differential diagnoses before the patient interview with help from various computer resources. Artificial intelligence is already entering the process of medical evaluation.[1–3] Yet, despite our adoption of technology in every aspect of everyday practice, the ancient and fundamental skill of constructing a history and performing a thorough physical examination remains the defining art of the clinician.

Inevitably, both the practice of medical interviewing and physical diagnosis, as well as the underlying goals and philosophy, have evolved significantly. One principal influence is the biopsychosocial model, which postulates that to provide comprehensive care, clinicians must consider not only the diagnosis and prognosis of the underlying condition but also how the patient experiences it. Although initially proposed in the 1970s, it is only in recent years that the tenets of the biopsychosocial model have begun to shape the way the medical interview is conceived and taught.

For example, while building a history, the physician faces the challenge of separating out the "illness"—how a patient experiences his or her condition—from the "disease"—the pattern of symptoms and signs that are observed and expected to manifest themselves in the patient's body. There are many benefits to considering the illness and disease first individually and then together. Consider a patient with locally advanced lung cancer intially experiencing the illness simply as mild dyspnea. Without significant functional limitations, the patient may feel reluctant to accept that the prognosis is life-threatening. Risky or uncomfortable treatments, including chemotherapy and surgery, could appear unnecessary in this context. Conversely, consider a patient with undifferentiated cough in whom the clinician has already excluded the most common concerns such as laryngopharyngeal reflux and sinusitis, as well as more serious ones such as asthma, interstitial lung disease, and cancer. In this scenario, the provider may feel reassured that there is no important disease present, yet the patient is left without relief for the unexplained and perhaps debilitating cough. The conventional maxim may then be reversed so that only when the illness is understood can the disease be diagnosed and treated.[4]

Providers who adopt this more holistic approach may experience higher patient satisfaction and adherence, fewer lawsuits, less doctor-shopping, and improved health outcomes.[5] The premise of this chapter is that high-quality care requires the full integration of the patient and provider perspectives into the history-building and physical examination.

COMMUNICATION SKILLS

Physicians are often better at obtaining medical information than at understanding how that information affects the patients.[6] The legendary internist Sir William Osler used to tell students "Listen to the patient, he [or she] will tell you the diagnosis." The ability to listen attentively and to communicate with the patient clearly and empathetically is the foundation for the physician-patient relationship. This can be challenging, particularly in today's environment, where long-term physician-patient relationships are less common and time pressures are ubiquitous.

Patients may communicate through both verbal and nonverbal means.[7] For example, when embarrassing or personal symptoms are discussed, patients may change topics, exhibit avoidance, or engage in spontaneous associations.[8] There may be shifts in posture, a loss of eye contact, fidgeting with the hands, or tapping of the feet, each hinting at emotional concerns and personal reactions. Taking these forms of communication into account is one way that clinicians can begin to place the medical context of the disease within the human context of the illness that the patient is experiencing.

The physician's communication should be objective, nonjudgmental, and empathetic. The clinician should also be mindful that her/his posture, gestures, and words should convey transparency and help make the patient feel secure. More directly, the clinician can acknowledge the patient's emotions and inquire about beliefs.[9] Clinicians should be aware that patients may guard or conceal certain symptoms or concerns when the physician, ignorant of these fears, takes the lead. Time constraints may pressure physicians to control or accelerate the pace of the conversation. These pressures may contribute to misjudgments and cognitive traps that are more likely to lead to medical errors. The average physician interrupts the patient's initial history in as little as 16 seconds and frequently thereafter.[10] Explicitly setting expectations at the opening of the meeting may help patients and physicians alike change this dynamic. Specifically, physicians should note the time available for the session, encourage the patient and any other attendees to begin by sharing a list of concerns, and then jointly set priorities and plans for follow-up on other matters. Facilitation techniques such as sharing silence, summarizing the concerns stated by the patient, echoing, making open-ended requests, nodding, and making neutral utterances are other ways to keep the session productive without interrupting.

CLINICAL REASONING

There is both an art and a science to clinical reasoning, and today's paradigm draws from both medieval philosophy and modern decision science.[11,12] The maxim "uncommon presentations of common diseases are more frequent than common presentations of uncommon diseases" is likely true. More than one disease may be present, and rare diseases are diagnosed only if they are considered. Thus it is important to continue to gather information and to be open to revising diagnostic hypotheses as more information becomes available. Premature judgment or failing to consider reasonable alternatives after making an initial diagnosis is the single most common diagnostic error.[13–15] In the field of "human factors engineering," these failures are postulated to arise from "cognitive dispositions to respond" and include several of the biases in judgment or reasoning defined in Table 18.1.[16] Making clinicians more aware of these common errors of reasoning and encouraging the use of checkpoints to facilitate "cognitive debiasing" could reduce their frequency.[17] Another complementary approach is to use decision-support software to expand the differential diagnosis and consider unusual or severe conditions.[18] Finally, patient-centered conversations have the potential to empower the patient to hold the clinician accountable when the proposed diagnosis does not fully explain all symptoms or concerns.

Bayes' theorem implies that diagnostic tests can be more efficiently used if the probability of the diagnosis before testing (also called pretest probability) is considered. Specific details from the history may then raise or lower the probability of different diagnoses and help direct selective testing toward the most important diagnostic possibilities. The added value of further investigations depends on the history.

Table 18.1 Selected Biases in Judgment or Reasoning

Bias	Definition
Anchoring	Tendency to lock onto salient features in the patient's initial presentation too early in the diagnostic process, with failure to adjust initial impression in light of later information.
Confirmation bias	Tendency to look for confirming evidence to support a diagnosis rather than for evidence to refute it, despite the latter often being more persuasive and definitive.
Framing effect	Tendency to be influenced by how the available clinical information is framed or presented using a recognizable rubric (e.g., presenting a patient with fever and tachycardia as having sepsis rather than a viral syndrome may lead to initiation of potentially harmful resuscitative care).
Premature closure	Tendency to accept a diagnosis before it has been fully verified. The consequences of the bias are reflected in the maxim "When the diagnosis is made, the thinking stops."
Search satisfying	Tendency to call off a search once something is found. This may lead the clinician to overlook critical comorbidities, second foreign bodies, other fractures, and coingestants in poisoning. Also, if the search yields nothing, diagnosticians should be sure that they have been looking in the right place.
Unpacking principle	Failure to elicit all relevant information (unpacking), which may result in missing important diagnostic possibilities.

Modified from Croskerry P. The importance of cognitive errors in diagnosis and strategies to minimize them. *Acad Med.* 2003;78:775–780.

Table 18.2 Comparison of Physician-Directed and Patient-Centered Approaches to the Medical Interview

	Physician-Directed Approach	Patient-Centered Approach
Philosophy and objectives	Identify the biomedical cause of disease	Elicit the psychosocial causes and consequences of the illness
History and physical (H&P)	Take a history 1. Ask questions to characterize symptoms: location and radiation; quality; intensity; onset, frequency, and duration; aggravating or alleviating factors and associated symptoms 2. Complete all components of the H&P in the first sitting	Build a history 1. Prompt the patient to tell you how the symptoms and signs impact the patient's experiences (e.g., misses work, cannot sleep) 2. Establish rapport and return as needed for additional data collection
Tests and imaging	Order in advance to save time for physicians	Order only after discussion with patient about the goals of the testing in order to engage the patient in the diagnostic process
Assessment strategies	Redirect the patient to the clinician's agenda Provide a diagnosis and prognosis	Allow the patient to set the agenda Summarize the patient's concerns
Plan	Write prescriptions to treat the disease and to treat the symptoms	Educate and empower the patient to manage the illness

CLINICAL HISTORY

"Medical interviewing is the process of gathering and sharing information in the context of a trustworthy relationship that takes into account both disease, if present, and illness."[9] Although traditionally conceived as an interview of the patient by the clinician, we will argue here that constructing the clinical history should be framed as a patient-centered collaboration between the clinician and the patient. Its main purposes are to (1) gather useful information, (2) develop rapport between the patient and the clinician, (3) respond to patient concerns, and (4) educate the patient. Some of the differences between the physician-directed and patient-centered approaches to the clinical history are outlined in Table 18.2.

The process of building a clinical history with the patient establishes rapport and understanding. It is "a purposeful conversation…[that] reflects the respective needs of both participants—patient and physician."[8] To start, the patient is encouraged to take the lead in expressing his or her symptoms and experiences related to these symptoms.[19] There are clear benefits for both parties: Patients find satisfaction in having their problems heard and understood, whereas physicians learn which symptoms are of greatest concern.[20] In addition, the patient's adherence to diagnostic and treatment plans depends on the physician's ability to win the patient's trust.[8] In the subsequent phase of the interview, most patients want to be informed about their condition and to be involved in the deliberations and decision making.[21] The physician assists this process when he or she explains symptoms, provides a plan for physical and mental recovery, and comforts.[8] Collaborating on the care plan is another way of emphasizing the importance of the patient perspective in building the clinical history.

The physician sets the stage for the discussion by welcoming the patient, introducing herself or himself to the people in the room, and clarifying the relationship of each person present to the patient.[9] This technique helps ensure that the environment is comfortable for the patient and family and free of barriers to communication, a goal that can be emphasized by providing adequate seating and removing obstructing objects from the room. Expectations are established by setting a time limit for the visit and an agenda for the meeting. The patient's concerns should have a central place on this agenda, although it may be necessary to ask the patient to prioritize the two or three most important items, while committing to addressing other questions at a later time. The physician should then encourage the patient to talk about himself or herself, using nonfocusing communications skills, such as open-ended questions and supportive gestures. Subsequently, focusing skills can guide the patient to elaborate further. Physicians can echo the patient (e.g., "You can't breathe?") or make requests ("Can you tell me more about how your walking has changed?") to fill in missing details about the present illness, past medical history, social history, family history, and review of systems. At this point in the meeting, the physician has likely assimilated enough data to establish and explore one or more working diagnoses. It is important that the physician remain attentive to the personal and emotional context of the patient's responses, even while directing the conversation. The medical session closes with the physician summarizing the patient's concerns and explaining how they might be further explored or addressed.

CHIEF COMPLAINT AND PRESENT ILLNESS

The medical history includes the chief complaint; the present, past, social, and family histories; and the review of systems. Ideally, the chief complaint should be written in the patient's own words, lest the physician's assessment be prematurely substituted for the patient's actual concerns. After being asked about the chief complaint, the patient should be allowed a few moments to mention any other ailments. Multiple concerns are common,[22] and inviting patients to enumerate them up front does not extend the length of the session[23] but does reduce the frequency of last-minute requests.[24] As each chief complaint is explored in detail, the resulting aggregate of information constitutes the history of the present illness. The clinician should organize the information into a cogent, chronological story that incorporates all the facts that support the preliminary diagnosis and differential diagnoses. At the end of the clinical history, the

review of systems is a series of questions designed to cover previously unexamined territory, especially by probing topics that may help narrow or expand the differential diagnosis.[25,26] It is also sometimes useful to ask what the patient thinks may be causing the condition under evaluation, to expose previously unexplored avenues for inquiry.

MAJOR PULMONARY SYMPTOMS

Dyspnea, cough, and chest pain are among the most common reasons for patients to visit physicians, and may portend serious underlying intrathoracic disease. Careful questioning is warranted to establish their etiology and significance. The anatomic and pathophysiologic basis of these cardinal symptoms is provided in Part 3 of the textbook. In general, an adequate assessment of any symptom takes into consideration seven basic characteristics: (1) location, (2) quality, (3) intensity, (4) temporality, (5) aggravating factors, (6) alleviating factors, and (7) related symptoms. To aid the interviewer in obtaining a medical history, a brief overview of these three common presenting symptoms is provided as follows.

Dyspnea

When a healthy person increases his or her level of physical activity sufficiently, an awareness of breathing emerges; if the intensity of activity increases further, the sensation becomes progressively more unpleasant, until it ultimately compels the individual to slow down or stop.[27] Although dyspnea, shortness of breath, and breathlessness are often used interchangeably, some purists use the term *dyspnea* only when the symptom is abnormal. Many patients describe their breathing discomfort as "tightness," "choking," "feeling unable to take a deep breath," "suffocating," "feeling unable get enough air," or occasionally even "feeling tired."

The mechanisms underlying the sensation of dyspnea remain poorly understood and are reviewed in Chapter 36. Unlike pain and cough, for which specific receptors and neural pathways have been identified, such information is lacking for dyspnea, although evidence is mounting that links the symptom with pain.[27,28] Studies of the neurophysiology of dyspnea are further complicated by the lack of objective tools to quantify a subjective sensation with interindividual variation. Rating instruments, such as the Borg scale,[29] and questionnaires, such as the British Medical Research Council questionnaire[30] and the Pulmonary Functional Status and Dyspnea Questionnaire,[31] have been validated as useful in measuring dyspnea.

Clinical Features. Patients with respiratory, cardiac, hematologic, metabolic, and neuromuscular disorders may all complain of dyspnea, which may worsen with disease progression. Others say their dyspnea has not worsened, but probing reveals that this is because they now walk more slowly or no longer climb stairs. Sometimes this slowing down is so gradual that patients are unaware of it or attribute it to aging. Thus accurately assessing the activity required to bring about dyspnea is important. How many stairs can be climbed before stopping? How far can someone walk on level ground at her or his own pace without stopping? Does talking on the phone, getting dressed, or eating cause dyspnea? Is the patient short of breath at rest?

The course of dyspnea over time should be noted. Dyspnea may be triggered by cigarette smoke, dusts, molds, and perfumes, or alleviated by staying indoors or albuterol use. Associated features, such as wheezing, productive cough, fever, or lower extremity edema, may help differentiate among the causes of dyspnea, such as airways disease, pulmonary infections, and pulmonary vascular congestion.

Special types of dyspnea are distinctive and warrant separate designations. Episodes of breathlessness that wake persons from sleep, *paroxysmal nocturnal dyspnea,* usually denote left ventricular failure. This symptom may also be described by patients with chronic lung disease because of pooling of secretions in the airways, in patients with gravity-induced decreases in lung volumes, in patients with sleep-induced increases in airflow resistance, or in those with nocturnal aspiration. *Orthopnea,* the onset or worsening of dyspnea on assuming the supine position, such as paroxysmal nocturnal dyspnea, is found both in patients with heart disease and in those with chronic lung disease.[32] The inability to assume the supine position *(instant orthopnea)* is characteristic of paralysis of both diaphragms. Dyspnea soon after assuming the supine position may also be associated with other conditions, such as arteriovenous malformation, bronchiectasis, and lung abscess. *Platypnea,* which denotes dyspnea in the upright position, and *trepopnea,* an even rarer form of dyspnea that develops in either the right or the left lateral decubitus position, suggest pulmonary vascular shunting. Both the terms *hyperpnea,* an increase in minute ventilation, and *hyperventilation,* an increase in alveolar ventilation in excess of carbon dioxide production, indicate that ventilation is abnormally increased, without any implication about the presence or absence of dyspnea.

Cough

As described in Chapter 37, coughing is an essential mechanism that protects the airways from inhaled noxious substances and from excess secretions.[33] The daily quantity of bronchial secretions produced by a nonsmoking healthy adult is not precisely known, but it is sufficiently small to be removed by mucociliary action alone: Healthy persons seldom cough.[34] Coughing can be occasional, transient, and unimportant. By contrast, it may indicate the presence of severe intrathoracic disease.

Clinical Features. Most episodes of coughing are short lived, and patients, recognizing this, seldom visit their physicians for this type of cough. Nevertheless, cough is the most common complaint for which patients seek medical attention and the second most common reason for having a general medical examination.[35] Physicians should realize that when patients seek their help for cough, it is often out of concern for something new, different, and alarming about the symptom. The evaluation of cough begins with categorizing the duration of cough as acute, less than 3 weeks; subacute, 3 to 8 weeks; and chronic, greater than 8 weeks of cough symptoms. Next, the physician must exclude any red flags that may signify severe illness: hemoptysis; a new cough in an active smoker older than 45 years; a change in the characteristics of an existing cough or a change in voice; any cough in a 55- to 80-year-old with a history of smoking of 30 pack-years or greater; and any cough in association with any of the following symptoms—prominent dyspnea at rest or at night, hoarseness, fever, weight loss, dysphagia, or vomiting—with a history of recurrent pneumonia, or with any abnormality on physical examination or imaging.

Any of these findings should prompt further investigation beyond the common causes of cough into potential underlying conditions, such as interstitial lung disease or malignancy. In endemic areas, tuberculosis should be considered during every cough evaluation. Also, environmental and occupational exposures should also be reviewed as potential culprits.[36]

Acute coughing is frequently associated with respiratory tract infections, often viral, and exacerbations of underlying illnesses, such as asthma or COPD and pneumonia.[36] Less commonly, cough may be the chief manifestation of pulmonary embolus, heart failure, or inhalation of allergenic or irritating substances. Subacute coughing can be due to postinfectious cough, exacerbations of underlying illnesses, and upper airway cough syndrome due to rhinosinus disease. Chronic coughing is often due to upper airway cough syndrome, asthma, nonasthmatic eosinophilic bronchitis,[37] and gastroesophageal reflux disease.[35,36] Other important, though less common, etiologies include the use of angiotensin-converting enzyme inhibitors[38] and sitagliptin, a dipeptidyl peptidase-4 inhibitor used to treat diabetes.[39] Of interest, dipeptidyl peptidase-4 inhibition in the mucosa promotes inflammation, and manifests as rhinorrhea, postnasal cough, and fatigue. An unsuspecting patient or physician may erroneously assume these symptoms are due to a cold or seasonal allergies. Less well known is that cough may be the sole presenting manifestation of asthma[40] or gastroesophageal reflux disease.[41] It is noteworthy that, of the various components of the workup used by the authors of a systematic anatomic investigation to determine the causes of chronic cough, the medical history alone led to the correct diagnosis in 70% of patients.[35] A careful history of patients with cough lasting at least 3 months revealed that nearly all patients misdiagnosed as "psychogenic" had one of the conditions listed previously for chronic cough.[42] Even cough made worse with psychological stress is often caused by underlying lung disease. Patients with exaggerated cough responses or habitual cough may have a "psychogenic" component; therefore, even when chronic cough has a pulmonary cause, behavioral modification may be effective.[43]

Among the many complications of persistent or recurrent cough that may present concurrently are tussive syncope; retinal vessel rupture; persistent headache; chest wall and abdominal muscle strains, including the development of abdominal wall hernia[44]; subcutaneous emphysema; pneumothorax; and even rib fractures. Severe chronic cough may create devastating personal distress, causing patients to restrict their social and professional activities.

Chest Pain

Various types of chest pain are extremely common; their mechanisms and clinical patterns are described in Chapter 38. Because there is no clear relationship between the intensity of the discomfort and the importance of its underlying cause, all complaints of chest pain must be carefully considered.[45]

Clinical Features. Pleurisy, or acute inflammation of the pleural surfaces, has several distinctive features. Pleuritic pain is usually localized and unilateral, and it tends to be distributed along the intercostal nerve zones. Pain from diaphragmatic pleurisy is often referred to the ipsilateral shoulder and side of the neck. The pain may be variously described as "sharp," "burning," or simply as "a catch." The most striking and defining characteristic of pleuritic pain is its clear relationship to respiratory movements. It typically worsens by taking a deep breath, and coughing or sneezing causes intense distress. Patients with pleurisy frequently experience dyspnea because the aggravation of their pain during inspiration makes them conscious of every breath.

Acute pleuritic pain can be found in patients with spontaneous pneumothorax, pulmonary embolism, and pneumonia, especially bacterial pneumonia, whereas a gradual onset over several days is observed in patients with tuberculosis; an even slower development is characteristic of primary or secondary malignancies. Chronic pleuritic pain is characteristic of mesothelioma. It may be difficult to distinguish pleuritic pain from the pain of a rib fracture, although point localization favors the latter. Pericardial pain is typically sharp, retrosternal in location, and relieved by sitting up and leaning forward.

The distribution and superficial knifelike quality of the pain of intercostal neuritis or radiculitis may resemble pleural pain because it is worsened by vigorous respiratory movements but, unlike pleurisy, not by ordinary breathing. A neuritic origin may be suggested by the presence of lancinating or electric shock–like sensations unrelated to movements, and hyperalgesia or anesthesia over the distribution of the affected intercostal nerve provides confirmatory evidence. In many instances of new-onset neuritic chest wall pain, the diagnosis becomes clear a day or two later when the typical vesicular rash of herpes zoster appears.[46] Among the most important types of chest pain is myocardial ischemia. Typical anginal pain is induced by exercise, heavy meals, and emotional upsets; the pain is usually described as a substernal "pressure," "constriction," or "squeezing" that, when intense, may radiate to the neck or down the ulnar aspect of one or both arms.[47] Pain from variant or Prinzmetal angina is similar in location and quality to typical anginal pain but is experienced intermittently at rest rather than during exertion.[48] Acute myocardial infarction should be considered when the pain is greater than that of angina in intensity and duration, when the pain arises without exertion or is not alleviated by rest or nitroglycerin, or when the pain is accompanied by profuse sweating, nausea, hypotension, and arrhythmias. Pain similar to that of myocardial ischemia can also be experienced by patients with aortic valve disease, especially aortic stenosis, and other noncoronary heart disease.

Inflammation of or trauma to the joints, muscles, cartilages, bones, and fasciae of the thoracic cage is a common cause of chest pain.[49] Redness, swelling, and soreness of the costochondral junctions is called Tietze syndrome. All of these disorders are characterized by point tenderness over the affected area.

Most pulmonary thromboemboli are not associated with chest pain; the hallmark of pulmonary infarction, however, is typical pleuritic pain, presumably because the infarction irritates the visceral and then the parietal pleural membranes. (The visceral pleura is now known to contain pain fibers, but most pain is still thought to arise from the parietal pleura.) Both acute and chronic causes of pulmonary hypertension may be associated with episodes of chest pain that resemble myocardial ischemia in its substernal location and pattern of radiation and in its being described as "crushing" or "constricting."[49] This type of chest pain is believed to result from right ventricular ischemia owing to impaired coronary blood flow secondary to increased right

ventricular mass and elevated systolic and diastolic pressures or to compression of the left main coronary artery by the dilated pulmonary artery trunk.

FAMILY HISTORY AND SOCIAL HISTORY

The family history provides important clues to the presence of heritable pulmonary diseases, such as cystic fibrosis, alpha$_1$-antitrypsin deficiency, hereditary hemorrhagic telangiectasia, immotile cilia syndrome, and immunodeficiency syndromes, among others. Careful history taking also can uncover even more common familial disease associations, which are polygenic or in which the exact mode of genetic transmission has not yet been established. As genomic surveillance uncovers more genetic linkages, the family history assumes greater importance. The family history should encompass at least three generations to account for sex-linked traits. Family history also can identify relevant prior exposures, such as to tuberculosis or other contagious diseases.

Of course, no evaluation of pulmonary symptoms is complete without a detailed history of smoking habits. The physician should ask, "Have you ever smoked?" If a negative answer returns, this should prompt a confirmatory question such as, "So you are a lifelong nonsmoker?" If the patient has smoked, the next questions should be, "When did you start?" "When did you quit?" and "How much did you smoke when you were smoking?" Ask also about different forms of tobacco and exposure at home or workplace to other people's tobacco smoke. A history of exposure to environmental smoke is also important.[50] A separate inquiry into electronic cigarette use or vaping should be made. In many developing countries, smoke from indoor cooking and heating fires is a major cause of lung disease, especially in women. Risk factors for *human immunodeficiency virus* (HIV) infection, such as unprotected sexual activity and injection drug abuse, should be specifically queried. Finally, the amount and frequency of any alcohol or illicit drug use should be recorded.

Medications and Allergies

A complete list of medications is essential to a thorough history. Ideally, the patient should bring in all his or her medications, and the physician should carefully go through each one, checking that the prescription has been properly written and filled and that the patient understands the benefits and possible side effects of each medicine. A complete listing of supplements and herbal medications should also be recorded and reviewed for potential interactions with conventional medications. It is essential to note whether the patient has ever had an allergic or toxic reaction and what these reactions were.

Occupational History

The occupational history, which is often included as part of the social history, is an integral part of a thorough medical interview. Identifying a relevant occupational exposure may provide the only opportunity to remove the patient from the exposure and prevent progressive and irreversible lung damage. Moreover, identifying injurious occupational exposures can facilitate justifiable compensation for the patient and removal of the hazardous materials from the workplace by the industry.

The evaluation of possible occupational lung disease is discussed in Chapters 100 to 103. Although only a few questions are asked in most initial medical interviews, if occupational illness is seriously being considered, a detailed inquiry about each industry, profession, and job the patient has held needs to be performed.[51,52] Environmental exposures and associated illnesses are constantly changing; it can be valuable to consult online resources from federal agencies such as the Centers for Disease Control and Prevention's National Center for Environmental Health (https://www.cdc.gov/nceh/) or National Institute for Occupational Safety and Health (https://www.cdc.gov/niosh/index.htm), and to involve occupational health specialists to identify and learn more about possible environmental toxins.[53,54] Individual state health department occupational safety and health contacts can also be found online (https://www.cdc.gov/niosh/statosh.html).

Travel History

A review of prior places of residence can expose the possibility of endemic fungal diseases, especially histoplasmosis and coccidioidomycosis. A history of recent travel may help establish the possibility of exposure to infectious diseases restricted to specific geographic regions.[55] The physician should inquire about duration of travel. Long trips by air or car increase the risk for deep venous thrombosis and venous thromboembolism, which are reported in up to 10% of passengers on long-haul flights.[56] Of importance, these may present at variable times after the inciting event. Finally, the epidemic of severe acute respiratory syndrome in Southeast China in 2002 and the pandemic of COVID-19 in 2019 and their rapid spread throughout the world by airline passengers emphasizes the importance of obtaining a careful travel history.

PAST MEDICAL HISTORY

Previous illnesses may recur (e.g., tuberculosis), and new diseases may complicate old ones (e.g., bronchiectasis as a sequela of necrotizing pneumonia). Information about previous illnesses, operations, intubations, and trauma involving the respiratory system may be essential to understanding the current problem. Although such data may be gathered as part of the past medical history, it may also emerge while obtaining the history of present illness in chronological sequence. Prior chest radiographs are an important aid in the evaluation of any abnormal chest radiograph because of the insights they provide into the duration and trajectory of illness. Patients should be asked to bring in previous films but, if they are unavailable, physicians should make every effort to obtain them because old radiographs may save needless, costly, and sometimes risky interventions.

QUESTIONNAIRES, COMPUTER-ASSISTED AND NURSING HISTORY

Printed or computer-based questionnaires and histories taken by nurses or allied health professionals are often used to expedite history taking. Occupational questionnaires have been shown to enhance recognition of occupational illness and correlate well with the findings of an industrial hygienist.[57] Computer-based interviews can gather more

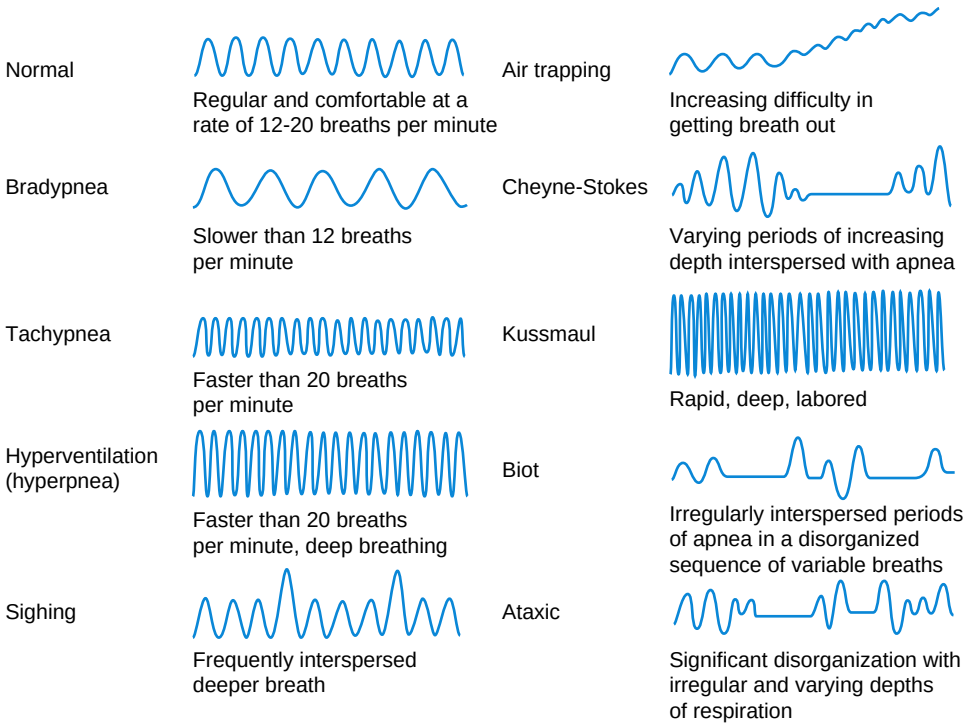

Figure 18.1 Waveforms in different patterns of breathing. (Modified from Wilkins RL, Hodgkin J, Lopez B. *Lung and Heart Sounds Online.* St. Louis: Mosby; 2011.)

information, allow more time to complete the interview, uncover sensitive information, and may be adaptable to the hearing impaired and to persons speaking a language different from that of the physician.[58] These forms of information gathering should be considered as adjuncts to and not as substitutes for the thorough history taken by the physician.

For monitoring the course of certain disorders such as asthma, daily recording of symptoms such as wheezing and breathlessness and objective assessments of disease severity using peak expiratory flow are preferable to a single questionnaire because recall of symptoms may be faulty, and one-time measurements may not be representative. Electronic monitors embedded within home noninvasive ventilation devices give the date and time of the respiratory events and use time of these devices. Increasingly, patients agree to real-time transmission of such measures to physicians' offices to improve routine management and early recognition of danger signs.

PHYSICAL EXAMINATION

Sadly, the declining emphasis on proficiency in physical examination during medical school and residency training and the ever-increasing reliance on technology-based diagnosis have led to a decreased interest in, some say even in the "demise" of, the physical examination.[59] However, the old observation that 88% of all diagnoses in primary care were established by taking a thorough medical history and performing a complete physical examination[60] probably still holds true today. At the very least, a carefully executed history and physical examination leads to more intelligent and cost-effective use of diagnostic testing. Moreover, a physical examination can be performed virtually anywhere, lends itself to serial observations, and increases the confidence patients have in their physicians.

EXAMINATION OF THE CHEST

Physical examination of the chest uses the four classic techniques of inspection, palpation, percussion, and auscultation. Each is described subsequently, as are the patterns of abnormalities. Apart from inspection, which may be both a visual and an olfactory tool, the other three modalities depend on the generation and the perception of sound or tactile sensations and vibrations. The optimal conditions to perform the physical examination therefore allow privacy, warmth, good light, and a quiet atmosphere.

Inspection

The physical examination begins the moment the clinician first sees the patient. Keen observations and the ability to pursue and interpret these observations are the keys to skilled clinical diagnosis. Inspection of the chest is carried out after sufficient clothing has been removed and the patient has been suitably draped to permit observation of the entire thorax. Ordinarily, inspection is performed with the patient sitting. Observing the shape and symmetry of the chest allows such abnormalities as kyphoscoliosis, pectus excavatum, pectus carinatum, ankylosing spondylitis, gynecomastia, and surgical scars or defects to become obvious. The pattern of breathing can provide immediate clues to the nature of the illness; several classic patterns of ventilation are described in Fig. 18.1.[61] Inspection, including the sense of smell, may be a clue to habits or addictions. Tobacco leaf stains may be visible on teeth, lips, fingers, or clothing, and tobacco or cannabis smoke may leave a characteristic odor on hair and clothing. The odor of ethanol or other toxic alcohols may be detected on the breath, as is the odor of ketones during diabetic crisis. Characteristic odors may also arise from certain infections, such as the foul smell of an anaerobic lung abscess, or the sweet smell of a skin and soft tissue infection caused by *Pseudomonas aeruginosa*.

Palpation

Palpation of the thorax can detect bony abnormalities, such as a cervical rib, and subcutaneous calcinosis seen with systemic sclerosis. It is essential in evaluating pain to test for point tenderness and thoracic spinal tenderness. It can detect fluctuant areas associated with *empyema necessitans* and crepitant areas associated with subcutaneous emphysema. Palpation of the trachea deviant from the suprasternal notch suggests shifts of the mediastinum. A spastic, extra-firm-feeling back muscle recognized by palpation may identify the cause of thoracic pain. A lag in movement of the chest wall can be confirmed by placing the two hands over opposite portions of each hemithorax and both feeling and observing whether or not the thorax moves symmetrically[61]; assessing symmetry is as important in palpation as it is in inspection.

A palpable vibration felt on the body, usually over the chest, is called *fremitus.* Vocal fremitus is elicited by having the patient speak "one, two, three," while the examiner's palms or sides of the hands are moved from top to bottom of the two hemithoraces. Vocal fremitus is increased over regions of lungs where there is increased transmission of sound, for example, consolidation from pneumonia. Conversely, fremitus is decreased in conditions in which sound transmission is impaired, for example, pleural effusion.

In examining the heart, the examining physician should always search for an apical impulse, heaves and lifts, thrills, and palpable valve closure. In patients with severe COPD, the abnormal cardiac movements are often better felt in the subxiphoid region than over the precordium.

Percussion

Skillful percussion depends on a uniform free and easy stroke of the striking finger (plexor) on the finger being struck (pleximeter), the ability to sense minor changes in pitch, and a keen sense of vibration; although the percussion note is heard, it is predominantly felt. Percussion of the thorax over normal air-containing lung produces a resonant note.

Pathologic processes may impair or enhance the resonating quality of the thorax. For example, the percussion note over a large pneumothorax is hyperresonant and becomes tympanitic when tension is present; in contrast, percussion over a pleural effusion or pneumonia produces dullness, which has been defined as a low-intensity sound of short duration, feeble carrying power, and rather high pitch.[62] Flatness is the nonresonant sound obtained by percussing over the liver. Three different tonal zones can thus be detected when percussing large pleural effusions: normal resonance above the fluid, dullness in the middle, and flatness when completely below the fluid.

Auscultation

A stethoscope draped around the neck has long been the badge of the medical professional, and it is worn with pride by physicians, nurses, and respiratory therapists, despite predictions such as "it, too, will someday be relegated to a museum shelf."[63] This will not happen for a long time, however, according to Murphy,[64] who mounts a spirited defense of stethoscopes backed up by analyses of breath sounds obtained by respiratory acoustic recording. The fundamentals of lung auscultation in physical examination are also covered in this review.[65]

Stethoscopes are also helpful in identifying pathology when chest radiograph findings are normal, such as detecting wheezes in asthmatic patients or crackles in patients with interstitial lung disease. Moreover, patients with cardiorespiratory complaints expect their physicians to listen to their heart and lungs.

Like any piece of medical equipment, there are a number of available choices, and the design and care of the stethoscope may have a substantial impact on performance. Electronic models promise ambient noise reduction and audio amplification, features shown in randomized trials to provide statistically significant improvements in acoustics, especially in noisy environments.[66,67] However, the magnitude of improvement is small relative to the best acoustic stethoscopes, and electronic stethoscopes have not been shown to improve trainee performance.[68] Sound quality with any stethoscope can be substantially degraded by failure to maintain the integrity of the rubber fittings, and prolonged contact of the tubing with the skin when worn around the neck can lead to hardening of the tubing and decreased performance. In any case, the stethoscope must be kept clean because it is increasingly recognized as a vector of nosocomial infection.[69] Glycerin-free isopropyl alcohol wipes are gentler on rubber and preferred to chlorine bleach except when *Clostridium difficile* colitis is possible; soap and water is an alternative, provided all internal pieces are allowed to dry.

The terminology of breath sounds has been standardized and simplified to enhance understanding and communication (Table 18.3). Although standardized nomenclature has been proposed by the American Thoracic Society[70] and the Tenth International Conference on Lung Sounds,[71] communication at the bedside often strays from recommended terminology. Although a number of other nonstandard terms (e.g., vesicular breath sounds, coarse breath sounds, rales, crepitations, sibilant and sonorous rhonchi, and high- and low-pitched wheezes) may be encountered based on historical usage, on homologies with terms used in languages other than English, or on common usage, we encourage adherence to this standard classification.[72]

The basic technique of auscultation with an ordinary stethoscope is well known to most physicians: The diaphragm detects higher-pitched sounds, and the bell detects lower-pitched sounds, although if the bell is tightly pressed against the body, the taut underlying skin itself may serve as a "diaphragm" and improve perception of higher pitches. Conversely, the bell should be applied very lightly to hear low-pitched sounds, for example, the low-pitched rumble of mitral stenosis. Full contact with the skin is necessary for best listening, which may pose a problem in a patient whose intercostal spaces are sunken from weight loss. In addition, the skin or hairs may brush against the diaphragm and produce a sound that resembles a pleural friction rub. As with examiners' hands, a warm stethoscope head is appreciated by patients. The importance of a quiet room and of applying the stethoscope directly to the skin rather than through clothing has recently been reemphasized.[73]

Table 18.3 Classification of Major Lung Sounds

Lung Sounds	Acoustic Characteristics	American Thoracic Society Nomenclature	Significance (Examples)
Normal	200–600 Hz; decreasing power with increasing Hz; soft, nonmusical sound heard on inspiration	Normal breath sounds*	
	75–1600 Hz Flat until sharp decrease in power (900 Hz); hollow, nonmusical sound heard in both inspiration and expiration just below the sternal notch	Tracheal breath Sounds	
Adventitious (abnormal)	Same as tracheal breath sounds but heard in periphery of lung; louder than normal breath sounds; equal on inspiration and expiration	Bronchial breath sounds†	Indicate airless air spaces around patent airway (e.g., atelectasis, consolidation)
	Discontinuous, interrupted explosive sounds (softer, higher in pitch, and shorter in duration than coarse crackles or crackles), middle to late inspiratory	Fine crackles	Indicate opening of collapsed distal airways (e.g., atelectasis, fibrosis)
	Discontinuous, interrupted explosive sounds (loud, low in pitch), early inspiratory or expiratory	Coarse crackles	Indicate opening of distal airways, may change after cough (e.g., distal secretions)
	Continuous sounds (>250 msec, high-pitched; dominant frequency ≥ 400 Hz, hissing in quality)	Wheezes	Indicate airway narrowing (e.g., asthma/COPD if diffuse, airway lesion if focal)
	Continuous sounds (>250 msec, low-pitched; dominant frequency < 200 Hz, a snoring sound)	Rhonchi	Indicate secretions in large airways (e.g., may clear with cough or suctioning)
Extrapulmonary	Continuous high-pitched sound mainly inspiratory, high-pitched, best heard over neck	Stridor	Indicates extrathoracic variable or fixed obstruction; needs urgent attention (e.g., anaphylaxis, epiglottitis)

*The label "vesicular" has now been shown to be inaccurate because normal breath sounds do not arise from the opening of vesicles (i.e., alveoli) but from turbulent airflow within distal airways.
†Associated with voice-generated sounds, such as egophony (Audio 18.8), bronchophony (Audio 18.9), and whispered pectoriloquy (Audio 18.10).

Careful auscultation of both front and back of the patient's chest is required for a comprehensive examination. The sections that follow include links to audio clips of many of the most important lung sounds; **these are best appreciated by listening through a stethoscope, while holding the diaphragm near your audio speaker.**

Normal Lung Sounds

Normal lung sounds, as shown in Table 18.3, are categorized as normal breath sounds (Audio 18.1) and tracheal breath sounds. Normal breath sounds were previously termed vesicular breath sounds because they were incorrectly assumed to represent air entering the alveoli or vesicles; we now know that air enters the alveoli via diffusion, a silent process. Instead, the inspiratory component arises from sounds generated by turbulent airflow within the lobar and segmental bronchi, whereas the expiratory component arises within the larger airways.[70] During normal breathing, inspiratory sounds are louder, and expiratory sounds are softer or even inaudible. Compared to inspiratory sounds, expiratory sounds are softer because the sounds are generated in the larger, more central airways, where they are dampened by the large volume of the lungs' air spaces. The intensity of normal breath sounds varies with regional ventilation and, like percussion notes, diminishes with increasing thickness of the chest wall. There is considerable variation among persons in the quality of breath sounds, which makes it essential to compare breath sounds from one hemithorax with those heard over the same location on the opposite hemithorax. Tracheal breath sounds (Audio 18.2) are tubular, nonmusical sounds heard in both phases of the respiratory cycle; their frequency pattern resembles "white noise." It is best heard below the suprasternal notch. Auscultation of tracheal breath sounds implies open central and upper airways.

In pathologic conditions, the transmission of normal breath sounds to the chest wall may be either attenuated or exaggerated. When the lung parenchyma is consolidated, breath sounds are well transmitted to the chest wall and *bronchial breath sounds* (Audio 18.3) become audible in the peripheral areas. Bronchial breath sounds are loud, medium-pitched, tubular sounds that are as loud as or louder during expiration as during inspiration. Bronchial breath sounds are similar to *tracheal breath sounds*, but their presence in the periphery is the classic auscultatory sign of consolidation, which could be from pneumonia, pulmonary edema, or hemorrhage. The presence of this sign assumes that the sounds originate centrally at the trachea and reach the chest wall only through amplification within airways surrounded by consolidated lung.[74] Furthermore, detecting bronchial breath sounds indicates that the airway to this region is patent.

Interposition of a sound barrier between the central airways, where sounds originate, and the chest wall, where they are heard, also attenuates or interrupts transmission of normal lung sounds. In accordance, normal breath sounds are diminished or absent over a pleural effusion, pneumothorax, or peripheral bulla, or distal to an obstructing mass lesion. Conversely, they may be increased if chest wall deformity or bronchial or tracheal derangement allows movement of air to be closer than usual to the stethoscope.

Adventitious (Abnormal) Lung Sounds

The major types of adventitious, or abnormal, lung sounds are classified in Table 18.3. Two generic categories of adventitious sounds have been documented by high-speed

recording techniques, and each of these has two subdivisions: discontinuous sounds, including fine crackles and coarse crackles, and continuous sounds, including wheezes and rhonchi.[75] This categorization emphasizes the relevance of noting the timing of breath sounds. Abnormal breath sounds generally have a strong expiratory component; loud expiratory sounds should raise special concern, and their type and origin should be clarified.

Fine and Coarse Crackles (Discontinuous Sounds)

Crackles, still often referred to as "rales" in the United States and "crepitations" in Great Britain, consist of a series of short, explosive, nonmusical sounds that punctuate the underlying breath sound; fine crackles (Audio 18.4) are softer, shorter in duration, and higher in pitch than coarse crackles (Audio 18.5). There is general agreement that the brief recurrent pops that characterize fine crackles are caused by the explosive openings of small airways that had closed owing to the surface forces within them.[70,76] This is also compatible with the presence of crackles in healthy elderly or obese persons in whom dependent airways close at resting lung volumes. Crackles therefore are best heard during the first deep breaths at the lung bases posteriorly. After several such breaths or intentional coughing, these fine crackles will disappear if the small airways remain open throughout the time the patient is being examined.[76] Coarse crackles are lower-frequency sounds transmitted to the mouth that indicate intermittent airway opening, such as found with secretions.[77] Coughing or deep inspiration may also change the quality of coarse crackles, but the crackles rarely disappear entirely.

The timing of crackles is also important. Fine crackles are much more common during inspiration than during expiration, which is why they are best heard over dependent lung regions—where airways are more likely to close—than over the uppermost regions. Nath and Capel[78] have shown that fine crackles heard late in inspiration are more often found in restrictive lung disease rather than in alveolar filling processes. This suggests that more tension is required to open individual airways in fibrosis than in lungs with secretions or edema. As inspiration progresses, radial traction on airway walls increase until suddenly they pop open.[78] Thus crackles heard later in inspiratory time imply that the tension required to open individual airways is greater. Expiratory crackles are much less frequent than inspiratory crackles and are often seen in obstructive lung disease.[75]

Wheezes and Rhonchi (Continuous Sounds)

The American Thoracic Society Committee on Pulmonary Nomenclature has defined wheezing as high-pitched (dominant frequency > 400 Hz) continuous adventitial lung sounds.[74] Continuous sounds are longer than 250 msec in duration. Wheezes are usually louder than the underlying breath sounds and frequently noted by patients. A leading theory is that wheezes are produced by fluttering of the airway walls and air together, induced at or above a critical flow velocity.[79] The pitch of the wheeze is dependent on the mass and elasticity of the airway walls and the flow velocity. The degree of bronchial obstruction is proportional to the amount of the respiratory cycle it occupies. There is no relationship to the intensity or pitch of the wheeze and pulmonary function. Wheezes are well heard over the trachea, and listening over the trachea may be superior to listening over the lung in most asthmatic patients[79] (Audio 18.6). Wheezing with forced expiration can sometimes be provoked in healthy subjects[70] and does not establish a diagnosis of asthma. A more specific technique for detecting pathologic wheezes is to elicit wheezing and/or coughing *without* forced expiration by having the patient breathe slowly to end-expiration. Because several disease states are associated with wheezing, additional information should be obtained to make the correct diagnosis.

Rhonchi are low-pitched continuous sounds with a dominant frequency of approximately 200 Hz or less (Audio 18.7). These sounds are likely to originate from rupture of fluid films and airway wall vibrations.[70] Rhonchi may clear with cough or with suctioning in intubated patients. Some have questioned whether the term rhonchi is needed at all, finding the substitute "low-pitched wheezes" more parsimonious.[80] However, the term retains its place in classification systems and in clinical usage.[70,71,77]

Voice-Generated Sounds

Another way of generating sounds for auscultation is to have a patient speak certain sounds (e.g., "one, two, one, two," "ninety-nine, ninety-nine," or "eee-eee.") in a quiet voice while the examiner listens to his or her chest. If enhanced responses are heard, the patient repeats the words while whispering. Because sounds of central origin are attenuated as they are transmitted peripherally through normal air-filled lung, voice-generated sounds have a muffled quality and the words are indistinct. In the presence of consolidation, the characteristics of the sounds are remarkably different. The term *egophony* (Audio 18.8) indicates sounds with a high-pitched, bleating quality; a change in sound-filtering properties of consolidated lungs accounts for the change in transmitted frequency. The classic way to identify egophony is with the "E" to "A" test. When a patient says "E" and the sound is transmitted along a patent airway through an area of consolidation, its frequency drops so that the "E" sounds more like an "A." *Bronchophony* (Audio 18.9) and *pectoriloquy* (Audio 18.10) both mean that spoken sounds are transmitted with increased intensity and pitch; when each syllable of every word, especially when whispered, is distinct and easily recognized, pectoriloquy is the preferred description. Each of these auscultatory findings is a manifestation of the same acoustic property of consolidated lungs, such as would be present in pneumonia or atelectatic lung with a patent airway.

Pleural Friction Rub

The small amount of liquid normally present in the pleural space separates the visceral and the parietal pleural layers and allows the lungs to expand and contract freely during breathing. In contrast, when the pleural surfaces are thickened and roughened by an inflammatory or neoplastic process, sliding is impaired and a pleural friction rub (Audio 18.11) may be produced. These sounds vary in intensity but often have a leathery or creaking quality that may be exaggerated by pressure with the stethoscope. Typically rubs are heard during both inspiration and expiration, but they are evanescent and variable and may be heard in only one part of the respiratory cycle. The terminology "rub" implies that friction between pleural surfaces generates the

sounds. In actuality, rubs may be generated simply by the change in shape of the thickened pleura itself, because a small amount of fluid is likely always present between the pleural surfaces, preventing their direct contact. This would also explain why rubs are occasionally audible even in the presence of large pleural effusions.

Extrapulmonary Sounds

Stridor is a high-pitched continuous sound produced by turbulent flow in the extrathoracic airway, which is louder and longer during inspiration than expiration (Audio 18.12). Stridor has many causes,[81] some of which are life-threatening and demand immediate attention (see also Chapter 39). At the patient's peril, stridor is occasionally mistaken for wheezing. Wheezing is an exclusively expiratory sound that is loudest over the chest. Auscultation over the upper trachea with attention to the timing in the respiratory cycle will help identify stridor and differentiate it from wheezing. Stridor may be heard only during inspiration if the causative lesion is functional or dynamic, or in both inspiration and expiration if the lesion is fixed.

The presence of air or other gas in the mediastinum may be associated with crunching, crackling sounds that are synchronous with cardiac contraction and are audible when breathing is momentarily stopped. This association with cardiac rather than respiratory motion differentiates a crunch from a rub, and pitch is lower for crunch than a rub. The finding of a mediastinal crunch by auscultation usually signifies mediastinal emphysema, even when the chest radiograph shows no abnormalities.

Various sounds may originate from the chest wall itself. Some of these have pathologic significance; others do not. Rubbing hairs between the skin and the stethoscope produce intermittent crackling sounds that may be confused with crackles (Audio 18.13). Variable crackles are also produced when the stethoscope is placed over an area of subcutaneous emphysema and is rocked back and forth (Audio 18.14). Contracting chest wall muscles may generate sounds that have a muffled, distant, low-pitched, and rumbling quality. On occasion, it is possible to hear a snapping sound during breathing from motion of a newly fractured rib, a sound called bone crepitus (Audio 18.15).

Interpretation

When abnormalities are discovered on physical examination of the chest, it is useful to identify them by their anatomic location in the involved lung. This requires knowledge of the surface projections of the underlying bronchopulmonary lobes, which are shown in Fig. 18.2. In the presence of either distortions of pulmonary anatomy or the shape of the rib cage, the surface projections of the underlying lung also change.

The classic findings on physical examination of the chest in some common pulmonary disorders are shown in Table 18.4. Ordinarily, consolidation must be within 1 or 2 cm of the costal surface to be reliably detected. Even then, physical examination alone cannot be relied upon to diagnose or exclude pneumonia.[82] Some pneumonias, such as *Mycoplasma* pneumonia, typically cause surprisingly few physical abnormalities despite extensive radiographic involvement (see eFig. 33.9) but, even in patients with classic lobar pneumonia, the findings may

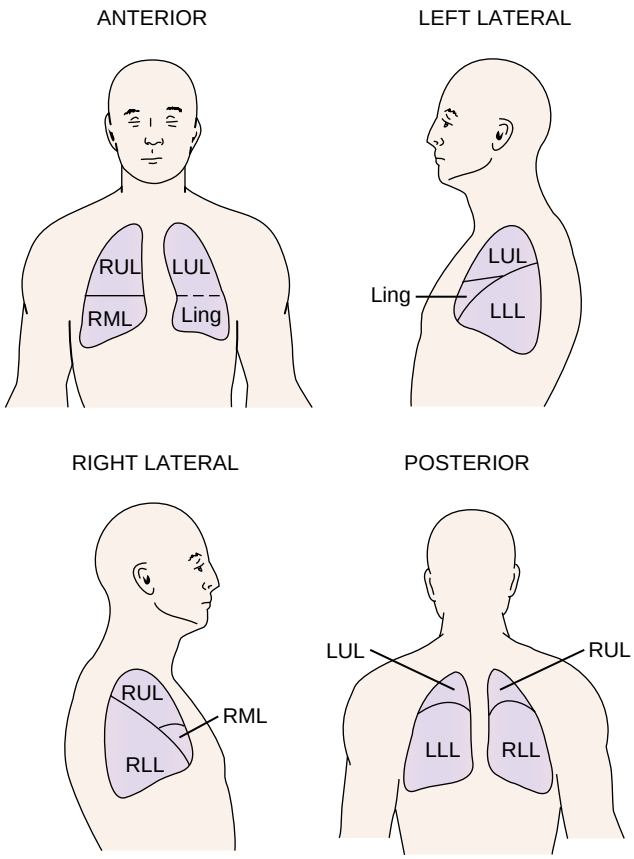

Figure 18.2 Surface projections of underlying lobar anatomy of a healthy man. The upper and lower lobes of both lungs are separated by the two oblique fissures, which course from the spinous process of the third thoracic vertebra posteriorly to the level of the 6th rib in the midclavicular line anteriorly. On the right side anteriorly, the upper and middle lobes are separated by the horizontal fissure, which lies at about the level of the 4th costal cartilage. Ling, lingular division of left upper lobe; LLL, left lower lobe; LUL, left upper lobe; RLL, right lower lobe; RML, right middle lobe; RUL, right upper lobe.

be nonspecific. Although unable to distinguish reliably between new-onset pneumonia and other pulmonary diseases, the findings from physical examination, including vital signs and mental confusion, are extremely important in assessing severity and in deciding whether or not to hospitalize patients with pneumonia.[83] The distinction between pleural effusion and atelectasis can be made on physical examination by determining whether the heart and mediastinal contents shift toward or away from the abnormal side, a finding that can usually be made only if the effusion is large or the atelectasis involves at least one lobe. However, the absence of these findings does not exclude an abnormality, and a chest radiograph or ultrasound image should be obtained to complete the pulmonary workup.

EXTRAPULMONARY MANIFESTATIONS

The examination of the lungs and pleura unlock only some of the clues to the presence of lung disease. Looking for extrapulmonary signs can often point toward a specific pulmonary disease or toward systemic diseases, such as lupus erythematosus, or toward diseases arising elsewhere in the

Table 18.4 Classic Physical Findings in Selected Common Pulmonary Disorders

Disorder	Inspection	Palpation	Percussion	Auscultation
Bronchial asthma (acute exacerbation)	Hyperinflation; use of accessory muscles of respiration	Impaired excursion; decreased fremitus	Hyperresonance; low diaphragm	Prolonged expiration: inspiratory and expiratory wheezes
Pneumothorax (complete)	Lag on affected side, increased size of hemithorax	Absent fremitus on affected side	Hyperresonant or tympanitic	Absent breath sounds
Pleural effusion (large)	Lag on affected side, increased size of hemithorax	Decreased fremitus, trachea and heart shifted away from affected side	Dullness or flatness	Absent breath sounds
Atelectasis (lobar obstruction)	Lag on affected side	Decreased fremitus; trachea and heart shifted toward affected side	Dullness or flatness	Absent breath sounds
Consolidation (pneumonia)	Possible lag or splinting	Increased fremitus on affected side	Dullness	Bronchial breath sounds; bronchophony, pectoriloquy, crackles

Modified from Hinshaw HC, Murray JF, eds: *Diseases of the Chest*. ed 4. Philadelphia: WB Saunders; 1980:23.

body that secondarily involve the lung. Certain extrapulmonary manifestations are particularly useful.

Clubbing

The association of clubbing of the fingers or toes with disease has caught the attention of physicians since the time of Hippocrates. Clubbing is easy to recognize when severe (Fig. 18.3), but subtle changes are more common and less reliable. The hallmarks of clubbing are (1) an increase of the normal 165-degree angle that the nail makes with its cuticle, in effect flattening it; (2) a softening and periungual erythema of the nail beds, where the nails to seem to float; (3) an enlargement or bulging of the distal phalanx, which may be warm and erythematous; and (4) a curvature of the nails themselves. Of these features, the straightening of the nail cuticle angle appears to be the most sensitive measurement.[84] The main pathologic finding in clubbing is increased capillary density stimulated by hypoxia, which intensely produces vascular growth factors.[85] With histochemical staining, Atkinson and Fox[86] showed increases in vascular endothelial growth factor, platelet-derived growth factor, hypoxia-inducible factor-1α, and hypoxia-inducible factor-2α, along with increased microvessel density in the stroma of clubbed digits. The second common characteristic of patients with digital clubbing is shunting of blood past the capillary bed of either the lung or the liver, which suggests that lack of metabolism of angiogenic factors that bypass a critical organ may be involved. Several of the conditions associated with clubbing have inflammation and shunting, such as bronchiectasis and liver cirrhosis.

Clubbing may develop rapidly, about 2 weeks in patients with new-onset empyema, and similarly reverse, also about 2 weeks in patients after corrective cardiac surgery. Clubbing was found in 1% of all admissions to an internal medicine department and was associated with "serious disease" in 40% of afflicted patients[87]; therefore new-onset clubbing always warrants a chest radiograph and, if unrevealing, a CT scan to look for a pulmonary neoplasm or other lesion, which may still be localized and curable. Clubbing has been found in many diverse conditions, such as in children with HIV[88] and in patients with hepatopulmonary syndrome[89] or with benign asbestos pleural disease[90] (eTable 18.1).

Patients with clubbing may also have *hypertrophic osteoarthropathy:* subperiosteal formation of new cancellous bone at the distal ends of long bones, especially the radius and ulna and the tibia and fibula. Hypertrophic osteoarthropathy (eFig. 18.1) is almost always associated with clubbing, particularly in patients with bronchogenic carcinoma, other intrathoracic malignancies, and cystic fibrosis. It occasionally develops in patients with bronchiectasis, empyema, and lung abscess but is rare in patients with most of the other conditions in which clubbing has been observed. Both clubbing and hypertrophic osteoarthropathy can be idiopathic, familial, or drug induced (e.g., voriconazole); the familial form is often transmitted as a dominant trait.

Other Extrapulmonary Associations

Besides clubbing, thoracic neoplasms may cause extrathoracic abnormalities that may become evident on physical examination, including anemia, Cushing syndrome, gynecomastia, and other paraneoplastic syndromes (eTable 18.2). Wasting, hoarseness, adenopathy (especially supraclavicular), and hepatomegaly are additional common extrathoracic manifestations. When evaluating patients with dyspnea, a thorough examination of the neck for increased jugular venous pressure should be performed to exclude right heart failure.[91] The extremities should also be examined for peripheral edema, venous thrombosis, chronic venous stasis, and scars that suggest injection drug abuse.

Lung disease is associated with abnormalities in other organ systems. Important lesions associated with various primary lung disorders are listed in tables available in the electronic version of the text. Included are lists of the lung diseases associated with skin and subcutaneous abnormalities (eTable 18.3); eye involvement (eTable 18.4); renal involvement (eTable 18.5); bone, joint, nerve, or muscle involvement (eTable 18.6); and gastrointestinal or hepatic involvement (eTable 18.7).

eTable 18.1 Causes of Clubbing (Partial Listing)

NOT ASSOCIATED WITH OVERT DISEASE
Hereditary clubbing
Sporadic clubbing
Pachydermoperiostosis
THORACIC NEOPLASMS
Lung cancer (the most common cause of clubbing)
Benign and malignant pleural tumors
Other thoracic neoplasms, including esophageal cancer, and lymphoma
HEART AND VASCULAR DISEASE
Cyanotic congenital heart disease
Subacute bacterial endocarditis
Infected aortic graft
Aortic surgery
Takayasu's arteritis
Behçet syndrome
PULMONARY ARTERIOVENOUS SHUNTING
Cyanotic congenital heart disease
Acquired heart disease
Pulmonary arteriovenous fistula
Hereditary hemorrhagic telangiectasia
INTERSTITIAL LUNG DISEASE
Asbestosis
Idiopathic pulmonary fibrosis
Collagen vascular disease
Lipoid pneumonia
Pulmonary Langerhans cell histiocytosis
CHRONIC INFECTIONS
Bronchiectasis
Bronchiectasis from sarcoidosis or tuberculosis
Lung abscess
Empyema
Cystic fibrosis
GASTROINTESTINAL AND LIVER DISEASE
Inflammatory bowel disease
Crohn disease
Ulcerative colitis
Polyposis coli
Infectious bowel disease
Amebic colitis
Bacillary dysentery
Liver disease
Hepatoma
Hepatopulmonary syndrome
Biliary cirrhosis
Esophageal stricture
HEMOGLOBINOPATHY
Hemoglobinopathies
Congenital methemoglobinemia
OTHER
Thyroid acropachy
Secondary hyperparathyroidism
HIV-related
Lymphoid interstitial pneumonia
Other infections
Prostaglandin infusion
Fabry disease
Toxic exposure to arsenic, mercury, or beryllium
UNILATERAL CLUBBING
Vascular disorders
Subclavian artery aneurysm
Brachial AV fistula
Subluxation of the shoulder
Median nerve injury
Local trauma
Hemiplegia

AV, atrioventricular; HIV, human immunodeficiency disease.

eTable 18.2 Paraneoplastic Syndromes (Partial Listing)

PARANEOPLASTIC SYNDROMES
Acanthosis nigricans
Clubbing
Hypertrophic osteoarthropathy
Intravascular thrombosis
Muscle weakness
Neuropathy
Pemphigoid
Polymyositis-dermatomyositis
Raynaud phenomenon
ENDOCRINE SYNDROMES ASSOCIATED WITH LUNG NEOPLASMS
Acromegaly (growth hormone)
Diarrhea (vasoactive intestinal peptide)
Hypercalcemia (parathyroid-like substance)
Hyponatremia (inappropriate antidiuretic hormone)
Carcinoid syndrome (serotonin)
Cushing syndrome (ACTH)
Gynecomastia (gonadotropins) (prolactin)
Hyperglycemia and hypoglycemia (insulin)
Skin pigmentation (melanocyte-stimulating hormone, ACTH)

ACTH, adrenocorticotropic hormone.

eTable 18.3 Skin and Subcutaneous Lesions Associated With Lung Disease

SKIN LESIONS

Diffuse pigment change
- Acanthosis nigricans—lung neoplasm
- Albinism—Hermansky-Pudlak syndrome
- Bronze pigmentation—hemosiderosis
- Gray-brown—Whipple disease

Cutaneous draining sinus
- Fungal infections (especially histoplasmosis)
- Mycobacterial infections (especially tuberculosis)
- Necrotizing vasculitis
- Neoplasms (especially mesothelioma)
- Other bacterial infections (especially actinomycosis)

Cutaneous ulcers
- Chronic beryllium disease
- Chronic venous insufficiency
- Fungal infections (especially histoplasmosis)
- Mycobacterial disease
- Necrotizing vasculitis
- Parasitic disease
- Polycythemia
- Sickle cell disease
- Tularemia

Cutaneous vasculitis
- Behçet syndrome
- Collagen vascular disease
- Eosinophilic granulomatosis with polyangiitis
- Granulomatosis with polyangiitis
- Sarcoidosis

Erythema multiforme
- Drug reactions
- Fungi (especially coccidiomycosis)
- *Mycoplasma* and other infectious agents
- Neoplasms

Exfoliative dermatitis
- Adverse drug reactions
- Chemotherapy
- Disseminated malignancy
- Graft-versus-host disease
- Radiation therapy

Flushing
- Bronchial carcinoid, pheochromocytoma, other neoplasms
- Carbon dioxide, cyanide, and other toxins
- Drugs
- Foods and vasodilatory substances
- Hormones
- Mastocytosis
- Metabolic states (e.g., hyperthyroidism, fever)

Macular rash
- Anti–glomerular basement membrane disease
- Anti–synthetase syndrome
- Café-au-lait spots (neurofibromatosis)
- Coal miner's scars
- Collagen vascular disease
- Idiopathic pulmonary fibrosis
- Rose spots (psittacosis)
- Sarcoidosis
- Syphilis
- Viral pneumonia

Maculopapular rash
- Amyloidosis
- Birt-Hogg-Dubé disease
- Drug-induced lung disease
- Collagen vascular disease
- Gaucher disease
- Kaposi sarcoma
- Lung neoplasm
- Lymphoma
- Lymphomatoid granulomatosis
- Parasites
- Sarcoidosis
- Syphilis
- Vasculitis
- Viral pneumonia

Sicca syndrome (dry mouth and eyes)
- Gaucher disease
- Lymphocytic interstitial pneumonia
- Sjögren syndrome

Telangiectasia
- Arteriovenous malformation
- Ataxia-telangiectasia
- Carcinoid syndrome
- Cushing disease
- Hepatopulmonary syndrome and other chronic liver diseases
- Hereditary hemorrhagic telangiectasia
- Mastocytosis
- Systemic sclerosis and other collagen vascular diseases

Urticaria
- Asthma
- Drug reactions
- Cystic fibrosis
- Exercise-induced urticaria
- Food allergy
- Hereditary angioneurotic edema
- Infectious agents, such as *Mycoplasma* and *Helicobacter*
- Inhaled antigens
- Insect bites and stings
- Mastocytosis
- Occupational sensitization
- Parasites
- Vasculitis

NAIL CHANGES WITH LUNG DISEASE

- Color changes
- Cigarette smoking discoloration
- Splinter hemorrhages
- Yellow nail syndrome

Beau lines (any severe illness)
- Dermatomyositis
- Sarcoidosis
- Seronegative arthropathies
- Systemic sclerosis

LUNG DISEASE WITH SUBCUTANEOUS INVOLVEMENT

Adenopathy
- Environmental mycobacteria
- Fungal infections
- HIV infections
- Metastatic neoplasm
- Leukemia
- Lymphoma
- Sarcoidosis
- Tuberculosis

eTable 18.3 Skin and Subcutaneous Lesions Associated With Lung Disease—cont'd

Calcinosis
- Dermatomyositis
- Metastatic osteosarcoma
- Mixed connective tissue disease
- Scleroderma
- Tuberculosis
- Uremic metastatic calcification

Erythema induratum (Bazin disease)
- Aortic stenosis
- Cryoglobulinemia
- Nodular vasculitis
- Panniculitis
- Peripheral neuropathy
- *Streptococcus* infection
- Takayasu's disease
- Tuberculosis and other mycobacterial disease
- Weber-Christian disease

Erythema nodosum
- Neoplasm
- Other infectious and inflammatory diseases
- Primary coccidiomycosis, histoplasmosis
- Primary tuberculosis
- Psittacosis
- Sarcoidosis

Subcutaneous nodules
- Amyloidosis
- Neoplasm
- Neurofibromatosis
- Rheumatoid arthritis
- Tuberous sclerosis (angiofibromas)
- Weber-Christian disease

LUNG DISEASE WITH SALIVARY GLAND ENLARGEMENT
- Bulimia and aspiration
- Gaucher disease
- Lymphatic carcinoma
- Lymphoid interstitial pneumonitis
- Lymphoma
- Other causes of lymphadenopathy
- Sarcoidosis
- Sjögren disease

HIV, human immunodeficiency virus.

eTable 18.4 Eye Disorders Associated With Lung Disease

BLINDNESS

Amaurosis fugax
- Antiphospholipid syndrome
- Aspergillosis
- Eosinophilic granulomatosis with polyangiitis
- Granulomatosis with polyangiitis
- Temporal arteritis

Giant cell arteritis
Late stage of many diseases
Sarcoidosis

CHOROID

Histoplasmosis
Lupus erythematosus
Toxoplasmosis

CONJUNCTIVA

Allergic reaction
Chlamydia
Granulomatosis with polyangiitis
Herpes
Kaposi sarcoma
Sarcoidosis

CORNEA

Chlamydia
Granulomatosis with polyangiitis
Herpes
Syphilis

IRIS

Neoplasm
Neurofibromatosis

LENS

Cataracts
- Steroid use
- Tobacco smoking

Marfan syndrome (dislocated)

LIDS

Proptosis
- Graves disease
- Leukemia
- Neoplasm

Ptosis
Myasthenia gravis
Muscular dystrophy

OPTIC NERVE

Cryptococcosis
Granulomatosis with polyangiitis
Graves disease
Leukemia
Neurofibromatosis
Sarcoidosis
Syphilis

eTable 18.4 Eye Disorders Associated With Lung Disease—cont'd

RETINA

Antiphospholipid syndrome
Behçet disease
Candidiasis
Chronic ocular histoplasmosis
Cytomegalovirus, herpes, and other viruses
Diabetes
Disseminated intravascular coagulation
Dysproteinemia
Ehlers-Danlos syndrome
Embolic disease
Endocarditis
Fat emboli
Fungemia
Genetic metabolic deficiencies
Granulomatosis with polyangiitis
HIV disease
Leukemia, lymphoma
Lupus erythematosus
Macroglobulinemia
Marfan syndrome
Neoplasm (especially melanoma)
Polycythemia
Sarcoidosis
Sickle cell disease
Subacute bacterial endocarditis, sepsis (Roth spots)
Syphilis
Temporal arteritis
Toxoplasmosis
Trauma
Tuberous sclerosis

SCLERA AND EPISCLERA

Granulomatosis with polyangiitis
Inflammatory bowel disease
Rheumatoid arthritis
Sarcoidosis
Scleroderma
Systemic lupus erythematosus
Systemic vasculitis

SICCA

Graft-versus-host disease
Rheumatoid arthritis
Sjögren syndrome

UVEA

Ankylosing spondylitis
Behçet disease
Crohn disease
Granulomatosis with polyangiitis
Herpes zoster
Inflammatory bowel disease
Reactive arthritis
Rheumatoid arthritis
Sarcoidosis
Syphilis

HIV, human immunodeficiency disease.

eTable 18.5 Renal Disorders Associated With Lung Disease

GLOMERULONEPHRITIS

Anti–glomerular basement membrane disease
Sarcoidosis
Collagen vascular disease
Systemic vasculitis

NEPHROTIC SYNDROME

Amyloidosis
Disseminated Langerhans cell histiocytosis
Drug-induced lung disease
Paraneoplastic syndrome
Posttransplantation
Pulmonary hydatid disease
Systemic lupus erythematosus
Vasculitis
Venous thrombosis

RENAL MASS

Granulomatosis with polyangiitis
Lymphangioleiomyomatosis
Metastatic neoplasm
Renal carcinoid
Tuberous sclerosis

NEPHROLITHIASIS

Alveolar proteinosis
Cystic fibrosis
Hypercalcemic syndromes
Osteolysis from mycobacteria or fungi
Sarcoidosis

SYSTEMIC HYPERTENSION

Collagen vascular disease
Diffuse alveolar hemorrhage
Neurofibromatosis
Pulmonary renal syndromes
Sleep apnea

eTable 18.6 Bone, Joint, Nerve, and Muscle Disorders Associated With Lung Disease

ARTHRITIS

Ankylosing spondylitis
Collagen vascular diseases
Reactive arthritis
Sarcoidosis
Systemic vasculitis
Tuberculosis

BONE LESIONS

Ankylosing spondylitis
Blastomycosis and other fungal disease
Collagen vascular diseases
Eosinophilic granulomatosis
Fibrous histiocytoma
Gaucher disease
Hypertrophic osteoarthropathy
Neoplasm
Sarcoidosis
Tuberculosis

MUSCLE DISEASE

Collagen vascular disease
Diabetes insipidus
Eosinophilic granulomatosis
Polymyositis
Sarcoidosis

NEUROLOGIC DISEASE

Acute inflammatory polyneuropathy
Amyotrophic lateral sclerosis
Aspiration
Botulism
Eosinophilic granulomatosis with polyangiitis
Granulomatosis with polyangiitis
Lambert-Eaton myasthenic syndrome
Myasthenia gravis
Organophosphate poisoning
Polio and postpolio syndrome
Sarcoidosis

eTable 18.7 Gastrointestinal or Hepatic Disorders Associated With Lung Disease

ESOPHAGEAL REFLUX
Aspiration pneumonia
Asthma
Bronchiectasis
Bronchitis
Cough
Mycobacterial disease
Pulmonary fibrosis
Scleroderma
INFLAMMATORY BOWEL DISEASE
Adverse reactions to drug treatments
Bronchiectasis
Bronchiolitis
Bronchitis
COLOBRONCHIAL FISTULA
Desquamative interstitial lung disease
Eosinophilic lung disease
Interstitial lung disease
Necrobiotic nodules
Obstructive lung disease
Organizing pneumonia
Sarcoidosis
Serositis affecting pleura or pericarditis
Tracheal stenosis
LIVER
$Alpha_1$-antitrypsin deficiency
Chronic active hepatitis
Hepatopulmonary syndrome
Portopulmonary hypertension
Primary biliary cirrhosis
Hepatosplenomegaly
Amyloidosis
Collagen vascular disease
Eosinophilic granulomatosis
Lymphocytic interstitial pneumonia
Sarcoidosis



Figure 18.3 Clubbing of the digits as seen in severe diffuse interstitial pulmonary fibrosis. (From Cashman MW, Sloan SB. *Nutrition and nail disease. Clin Dermatol.* 2010;28:420–4225.)

Acknowledgment

We acknowledge Professor John F. Murray for his major contributions to earlier versions of this chapter, many of which have been retained in the current edition.

Key Points

- An integrated approach to the history and physical examination balances the concerns of patients and clinicians so that the experience of the patient's illness receives as much attention as the quest for a diagnosis for any underlying disease.
- Physical examination can be performed virtually anywhere, provides important information, lends itself to serial observations, and increases patients' confidence in their physicians.
- After the clinician arrives at a tentative diagnosis, selected radiographic, laboratory, and other tests are ordered for further and confirmatory evaluation.
- Careful questioning and further workup of patients with dyspnea, cough, and chest pain is mandatory because these symptoms are among the most common reasons for patients to visit physicians and can indicate serious underlying chest disease.
- Stridor, a high-pitched continuous sound louder and longer during inspiration than expiration, can indicate a life-threatening upper airway obstruction and requires immediate attention.
- New-onset clubbing of the digits warrants further investigation owing to its frequent association with serious underlying disease.
- After collecting high-quality data during the history and the physical examination, it is essential to remain vigilant against common errors in clinical reasoning, which are among the most common causes of diagnostic error.

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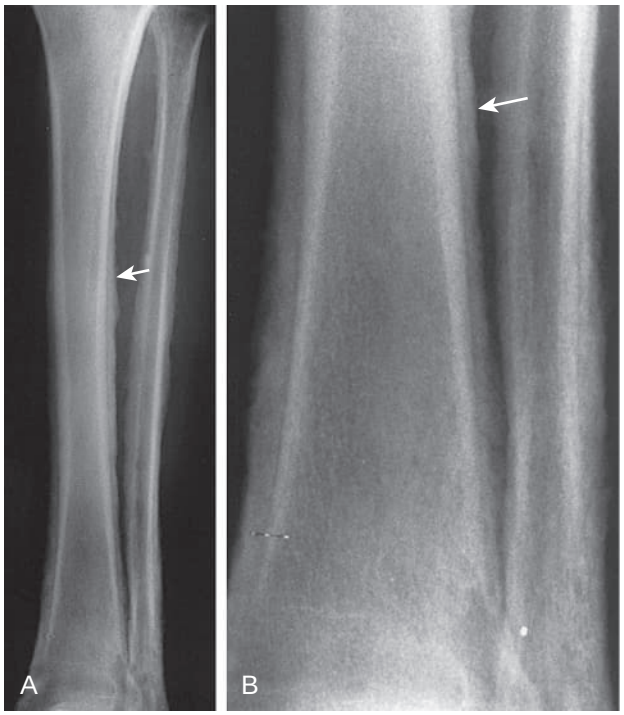
eFIGURE IMAGE GALLERY



eFigure 18.1 Hypertrophic osteoarthropathy. Radiographs of the leg show marked subperiosteal new bone formation *(arrows)* that is diagnostic of hypertrophic osteoarthropathy. (A) View of most of the tibia and fibula. (B) Detailed view near the ankle.

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19 MICROBIOLOGIC DIAGNOSIS OF LUNG INFECTION

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INTRODUCTION

The clinical microbiology laboratory plays a critical role in diagnosis and management of patients with *lower respiratory tract* (LRT) infections. By providing pathogen detection and identification and susceptibility testing, the laboratory provides the basis of optimal empirical antimicrobial therapy and individually tailored regimens.[1] The microbiology laboratory also provides data that assist the hospital epidemiologist in the prevention, detection, investigation, and termination of nosocomial outbreaks.[2] When correctly and promptly used, the information provided by the clinical microbiology laboratory improves clinical outcomes, reduces unnecessary use of antibiotics, and prevents nosocomial transmissions.[3,4]

The primary aim of this chapter is to assist clinicians in efficient and effective use of the clinical microbiology laboratory in diagnosis and management of infections of the LRT. This chapter assumes that clinical laboratories are using validated methods and reporting quality-assured results and does not delve into technical or operational aspects of the clinical microbiology laboratory. For additional information on laboratory operation, the reader is referred to the latest edition of the *Manual of Clinical Microbiology* (American Society for Microbiology).[5]

PREANALYTIC PRINCIPLES

PRINCIPLES OF TESTING

The decision to order a diagnostic test should hinge on whether the result is likely to affect the clinician's treatment decisions. If the clinician is convinced that the patient has a particular disease based on clinical presentation and prevalence (high pretest probability), then the decision to treat will likely not be altered by the test result and testing may not be indicated. Similarly, testing should not be ordered if the clinician has a high degree of a priori certainty that the patient does not have a disease because the decision not to treat will likely not be altered by the test result. Testing is most useful when the clinician is uncertain about the probability of disease and the result can sway the physician's decision about treatment. In addition to the pretest probability, several factors affect this decision. For example, if therapy comes at a low harm (in terms of toxicity, financial cost, and selection of resistance), then treating all patients without testing may be appropriate. If the diagnostic test has a low sensitivity (i.e., it is positive in a low percentage of patients with disease), then testing may lead to an inappropriate decision not to treat. Similarly, if a diagnostic test has a low specificity (i.e., it is positive in a high percentage of patients without disease), then testing may lead to unnecessary treatment. The determination that clinical suspicion is uncertain enough to benefit from a particular diagnostic test involves the interplay of the cost and accuracy of the test, pretest probability of the disease, and benefit and harm of treatment.

INFECTION PREVENTION

The clinician plays a critical role in notifying the microbiology laboratory (and the hospital infection control epidemiologist) when virulent and transmissible agents are suspected as the cause of disease. Alerting laboratory staff reduces the risk of exposure of laboratory staff handling specimens and cultures harboring highly virulent pathogens (listed in Table 19.1). Not all specimens from patients with infectious diseases should be handled by the on-site laboratory. According to guidelines developed by local and national public health officials, specimens potentially containing high-risk agents, such as *Bacillus anthracis* spores, *Francisella tularensis, Yersinia pestis,* variola major, hemorrhagic fever viruses, or *Clostridium botulinum* toxin, are directly sent to the public health laboratories, where appropriate containment facilities and diagnostic tools are applied to make a diagnosis.[6] Other pathogens that are handled by the on-site laboratory, but still require laboratory notification, include *Coccidioides* and *Brucella* species because cultures of these are associated with a high risk for

Table 19.1 Pathogens That Require Laboratory Notification When Suspected Clinically

Bacillus anthracis
Brucella sp
Burkholderia pseudomallei
Clostridium botulinum
Coccidioides sp
Francisella tularensis
Hemorrhagic fever viruses
Yersinia pestis
Variola major

laboratory-associated infection. Although the technologists are expected to handle all specimens and microbiologic cultures using universal precautions, accidental exposures can happen, especially if the findings are unexpected. Therefore laboratory notification alerts the staff to protect themselves from exposure to highly transmissible agents.

SYNDROMIC ORDER SETS

The diversity of etiologic agents of LRT infection poses a number of diagnostic challenges for the clinician. First, the provider must formulate a comprehensive yet pragmatic differential diagnosis that takes into account the clinical presentation, immune status, and the exposure history of the patient. Then the clinician must order the correct set of laboratory tests and ensure collection of the appropriate specimens and their placement in correct transport containers for transport to the laboratory under preestablished conditions for testing. Because improper test selection and specimen collection could reduce the analytic sensitivity and specificity of assays performed in the laboratory, syndromic order sets have been designed that consider the most common pathogens for the specific syndrome. Syndromic order sets incorporate general guidelines for the types of specimen required, collection and transport, and available assays for pathogens expected in a given clinical setting or syndrome. By prioritizing diagnostics that maximize yield and avoiding the need to repeat invasive procedures, these order sets also serve to minimize risk to the patient and to lower health care costs. However, it is the responsibility of the clinician to ensure that specimen requirements are met and the most critical tests are prioritized, especially when the amount of specimen material obtained is limited and multiple tests are ordered. Tables 19.2 to 19.4 show syndromic order sets for *community-acquired pneumonia* (CAP), hospital-acquired and ventilator-associated pneumonia, and immunocompromised host pneumonia, respectively. Order sets developed to address local epidemiologic characteristics and preanalytic practices may be tailored to serve each institution. Finally, clinicians should also familiarize themselves with local sample storage practices in case additional tests need to be performed.

SPECIMEN SELECTION, COLLECTION, AND TRANSPORT

In general, sterile specimens such as tissue samples and aspirates are the most valuable diagnostically because the absence of contamination with commensal organisms ensures that any organism detected likely represents a true pathogen. Histopathologic examination of tissue also provides information on the immunopathologic characteristics of the infectious process. However, a major diagnostic challenge of LRT infection is that LRT secretions are usually obtained through the oropharynx, which normally contains 10^{10} to 10^{12} *colony-forming units* (CFU) of aerobic and anaerobic bacteria per milliliter. Therefore LRT secretions collected for microbiologic examination are commonly contaminated with diverse bacteria (Table 19.5),[7] some of which, such as *Streptococcus pneumoniae, Haemophilus influenzae, Moraxella catarrhalis,* and *Neisseria meningitidis,* can also be pathogens of the LRT.[8–10] The oropharynx can also contain *Mycoplasma pneumoniae*[11] and aerobic actinomycetes, including *Nocardia* and nontuberculous mycobacteria, in the absence of disease.[12] Aspiration of even minute amounts (0.1–1 μL) of oropharyngeal secretions can deliver 10^9 CFU to the tracheobronchial tree. The distinction in such cases between colonization of the *upper respiratory tract* (URT) and pneumonia cannot be easily made by sputum examination and culture. Another challenge is that oropharyngeal secretions, which normally contain only a few gram-negative bacilli, such as Enterobacteriaceae, *Pseudomonas,* and *Acinetobacter*, may become colonized with as many as 10^7 CFU of gram-negative bacilli per milliliter in seriously ill patients requiring intensive care,[13] patients treated with antibiotics after hospitalization for acute pulmonary inflammatory disease,[14] chronic alcoholic and diabetic patients,[15] institutionalized older adults and chronically ill patients,[16] and hospitalized patients with acute leukemia.[17] Last, *Aspergillus* spores present in the environment are commonly deposited in the LRT and may be recovered from sputum in the absence of disease, although in immunocompromised patients it is best to consider this finding seriously.[18] In summary, because LRT secretions collected through the oropharynx are nearly always contaminated with resident microflora of the oral cavity, and definitive diagnosis would require sterile lung tissue with demonstration of parenchymal invasion, appropriate steps must be taken to obtain specimens of highest quality for microbiologic testing.

Expectorated sputum is the specimen most frequently obtained for the laboratory diagnosis of LRT infection.[5] The importance of proper sputum collection was documented by Laird[19] 100 years ago in studies on the yield of *Mycobacterium tuberculosis* according to the appearance and cellular composition of the sputum examined. The first requirement for collection of a good-quality sputum specimen is an alert and cooperative patient who can be instructed to rinse out his or her mouth with water or even brush his or her teeth before producing an LRT specimen. The patient then must be encouraged to cough deeply to expectorate a sample of LRT secretions. With some infections such as *tuberculosis* (TB), a larger sputum volume (i.e., minimum of 5 mL) can improve the sensitivity of culture.[20] Specimens are to be collected in sterile, leakproof, screw-capped containers. Containers should be transported in a watertight plastic biohazard bag.

Although a single sputum specimen may be sufficient for establishing the diagnosis of an acute bacterial process, collection of a series of three sputum specimens obtained in 1 or 2 days is recommended by the *Centers for Disease Control and Prevention* (CDC) in the United States for patients

Table 19.2 Community-Acquired Pneumonia Order Set

Syndrome/Organisms	Testing Uses/Indications	Appropriate Specimens	Available Testing
TYPICAL BACTERIA			
Haemophilus influenzae *Moraxella catarrhalis* *Staphylococcus aureus* *Streptococcus pneumoniae* *Streptococcus pyogenes* Aerobic gram-negative bacilli	Outpatients: microbiologic studies optional Inpatients: ■ Sputum studies for those with defined risks, complications, and/or severity ■ Blood culture for defined risk factors, including ICU admission	Sputum Bronchoscopic specimen Tissue Blood	Gram stain Aerobic culture Aerobic culture
LESS COMMON BACTERIA			
Chlamydophila pneumoniae *Chlamydia psittaci* *Coxiella burnetii* *Legionella pneumophila* serogroup 1 *Legionella* sp—other *Mycobacterium tuberculosis* *Mycoplasma pneumoniae*	*Mycoplasma* and *C. pneumoniae:* outbreaks and familial transmission *C. psittaci:* exposure to psitaccines	Nasopharyngeal swab, throat swab or washings Sputum Bronchoscopic specimen Bronchoalveolar lavage Tissue (including FFPE) Serum	NAT (species specific): *M. pneumoniae; C. pneumoniae; C. psittaci* NAT: 16S rRNA sequencing (tissue only) DFA: *C. pneumoniae* IgM, IgG: *M. pneumoniae; C. pneumoniae; C. psittaci* IgM, IgA, IgG: *C. burnetii*
	Legionella: outbreaks, travel-associated, lack of response to cell wall–active antibiotics, severe illness	Sputum Bronchoscopic specimen Tissue (including FFPE) Urine	BCYE culture NAT: *Legionella* sp NAT: 16S rRNA sequencing (tissue only) DFA: *L. pneumophila* *L. pneumophila* serogroup 1 antigen
	M. tuberculosis complex: appropriate epidemiology	Sputum Bronchoscopic specimen Tissue Pleural fluid	Acid-fast stain Mycobacterial culture NAT
VIRUSES			
Influenza A/B Adenovirus Parainfluenza 1/2/3 Respiratory syncytial virus Human metapneumovirus Varicella-zoster virus Hantaviruses Novel coronaviruses Novel influenza viruses SARS-CoV-2	Viral testing may provide justification for discontinuing antibiotics Seasonal epidemiology Known outbreak, epidemic, or pandemic	Nasopharyngeal swab Nasal aspirates or washes Bronchoscopic specimen Tissue	NAT
ASPIRATION PNEUMONIA			
Mixed anaerobic infections	Anaerobes typically already covered by broad-spectrum antibiotics; anaerobic culture rarely changes management	Pleural fluid Bronchoscopic specimen using protected specimen brush Tissue Pleural fluid Tissue	Gram stain Aerobic culture Anaerobic culture NAT
INVASIVE FUNGI			
Dimorphic Molds			
Blastomyces dermatitidis *Coccidioides immitis* *Coccidioides posadasii* *Histoplasma capsulatum* *Paracoccidioides brasiliensis*	From area of high endemicity	Sputum Bronchoscopic specimen Tissue Tissue Tissue (including FFPE) Pleural fluid Serum Urine	Fungal stain Fungal culture Histology NAT: species specific NAT: rRNA locus sequencing Antigen: *H. capsulatum; B. dermatitidis; C. immitis/posadasii* IgG (complement fixation, EIA): *H. capsulatum; C. immitis/posadasii; B. dermatitidis* IgM (immunodiffusion, latex agglutination, EIA): *C. immitis/posadasii* Antigen: *H. capsulatum*

Table 19.2 Community-Acquired Pneumonia Order Set—cont'd

Syndrome/Organisms	Testing Uses/Indications	Appropriate Specimens	Available Testing
Cryptococcus *C. neoformans* C. gattii		Serum Tissue Tissue (including FFPE) Pleural fluid	Cryptococcal antigen test Fungal stain Culture NAT: species specific NAT: rRNA locus sequencing
PARASITES			
Strongyloides stercoralis *Paragonimus* sp	From area of high endemicity	Sputum Bronchoscopic specimen Tissue	Microscopic examination Histology NAT: species specific

BCYE, buffered charcoal yeast extract; DFA, direct fluorescent antibody; EIA, enzyme immunoassay; FFPE, formalin-fixed paraffin-embedded; ICU, intensive care unit; Ig, immunoglobulin; NAT, nucleic acid test; rRNA, ribosomal ribonucleic acid; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2.

Table 19.3 Hospital-Acquired and Ventilator-Associated Pneumonia Order Set

Syndrome/Organisms	Testing Uses/Indications	Appropriate Specimens	Available Testing
TYPICAL BACTERIA			
Aerobic Gram-Positive Cocci *Staphylococcus aureus* *Streptococcus pneumoniae* **Aerobic Gram-Negative Bacilli** *Acinetobacter* sp *Enterobacter* sp *Escherichia coli* *Klebsiella pneumoniae* *Pseudomonas aeruginosa* *Stenotrophomonas maltophilia* **Anaerobes** Mixed anaerobic species	Refractoriness to antibiotics Clinically ill patients with suspicious respiratory or chest radiograph findings Anaerobes typically already covered by broad-spectrum antibiotics; anaerobic culture rarely changes management	Sputum Endotracheal aspirate Bronchoalveolar lavage Bronchoscopic specimen using protected specimen brush Tissue Tissue (including FFPE) Blood	Gram stain Aerobic culture Anaerobic culture NAT: 16S rRNA sequencing Aerobic culture
ATYPICAL BACTERIA			
Legionella pneumophila serogroup 1 *Legionella* sp—other	*Legionella* outbreaks Refractory to β-lactams or AGs Immunocompromised Pneumonia plus GI symptoms	Induced sputum Bronchoscopic specimen Urine Tissue (including FFPE)	BCYE culture *Legionella* sp NAT: *Legionella* PCR DFA *L. pneumophila* serogroup 1 urine antigen NAT: 16S rRNA sequencing
VIRUSES			
Influenza A, B Adenovirus Parainfluenza 1, 2, 3 Respiratory syncytial virus	Circulating in community/seasonality Unvaccinated host Outbreak/cluster Pneumonia despite broad-spectrum antibiotics	Nasopharyngeal swab Nasal aspirates or washes Endotracheal aspirate Bronchoscopic specimen Bronchoscopic specimen using protected specimen brush	NAT
INVASIVE FUNGI			
Aspergillus sp *Mucorales* Mold species—other	Pulmonary cavity disease Environmental exposure/outbreak Immunocompromised	Endotracheal aspirate Bronchoalveolar lavage Bronchoscopic specimen using protected specimen brush Tissue Plasma Tissue (including FFPE) Bronchoalveolar lavage Serum	Fungal stain Fungal culture NAT: species specific NAT: rRNA locus sequencing (tissue only) NAT: metagenomics sequencing (plasma) Histology NAT: 18S rRNA sequencing Galactomannan (1→3) β-D-glucan

AGs, aminoglycosides; BCYE, buffered charcoal yeast extract; DFA, direct fluorescent antibody; FFPE, formalin-fixed paraffin-embedded; GI, gastrointestinal; NAT, nucleic acid test; rRNA, ribosomal ribonucleic acid; sp, species.

Table 19.4 Immunocompromised Host Pneumonia Order Set

Syndrome/Organisms	Testing Uses/Indications	Appropriate Specimens	Available Testing
BACTERIA			
CAP and HAP/VAP bacteria	See Tables 19.2 and 19.3	See Tables 19.2 and 19.3	See Tables 19.2 and 19.3
Burkholderia cepacia complex	Cystic fibrosis, CGD	Sputum Bronchoscopic specimen	Aerobic culture
Aerobic Actinomycetes			
Nocardia sp *Rhodococcus* sp Actinomycetes—other	Soil/environmental exposure	Sputum Bronchoscopic specimen Tissue (including FFPE)	Gram stain Modified acid-fast stain Aerobic culture including BCYE plate NAT: 16S rRNA sequencing (tissue only)
MYCOBACTERIA			
M. tuberculosis complex *M. avium-intracellulare* complex *M. kansasii* *M. xenopi* *M. haemophilum*	From area of high endemicity Known exposure/outbreak Bronchiectasis Appropriate epidemiology	Expectorated sputum Bronchoscopic specimen Tissue (including FFPE)	Cytology Acid-fast stain Mycobacterial culture NAT: *M. tuberculosis*–specific NAT: nontuberculous mycobacteria–specific NAT: 16S rRNA sequencing (tissue only)
M. abscessus *M. chelonae*—other		Tissue	Histology
VIRUSES			
CAP and HAP/VAP viruses Cytomegalovirus Herpes simplex virus Varicella-zoster virus	See Tables 19.2 and 19.3 CMV 1–4 months after transplant Serodiscordant donor/recipient Skin lesions	See Tables 19.2 and 19.3 Bronchoscopic specimen Tissue Tissue (fresh and FFPE) Plasma	See Tables 19.2 and 19.3 Cytology NAT Shell vial culture: CMV; HSV Histology Immunohistochemistry: CMV; HSV NAT NAT
FUNGI			
Pneumocystis jirovecii		Sputum Bronchoalveolar lavage Bronchoscopic specimen	DFA Fungal stain NAT
Cryptococcus neoformans *C. gattii*		Serum Tissue	Cryptococcal antigen test Fungal stain Culture
Monomorphic molds *Aspergillus fumigatus* Other *Aspergillus* sp		Sputum Bronchoscopic specimen Tissue Tissue (fresh and FFPE) Pleural fluid Plasma Serum	Fungal stain Fungal culture Histology NAT: species specific NAT: rRNA locus sequencing; metagenomics sequencing (plasma) Antigen: galactomannan Antigen: (1→3) β-D-glucan
Dimorphic molds	See Table 19.2	See Table 19.2	See Table 19.2
PARASITES			
Toxoplasma gondii	Cat exposure Raw meat consumption From area of high endemicity Lymphadenopathy	Induced sputum Bronchoscopic specimen Tissue Serum	Giemsa stain NAT IgM
Strongyloides stercoralis	From area of high endemicity	Induced sputum Bronchoscopic specimen Stool Tissue	Microscopy for larvae Strongyloides culture Histology

BCYE, buffered charcoal yeast extract; CAP, community-acquired pneumonia; CGD, chronic granulomatous disease; CMV, cytomegalovirus; DFA, direct fluorescent antibody; FFPE, formalin-fixed paraffin-embedded; HAP, hospital-acquired pneumonia; HSV, herpes simplex virus; IgM, immunoglobulin M; NAT, nucleic acid test; rRNA, ribosomal ribonucleic acid; VAP, ventilator-acquired pneumonia.

Table 19.5 Oropharyngeal Bacteria That Can Be Present Without Causing Disease

Commonly Present	Less Commonly Present, Transiently Present, or Present Only in Specific Contexts
Actinomyces, Corynebacterium, Eikenella corrodens, Enterococcus, Haemophilus, Moraxella catarrhalis, Neisseria, Staphylococcus, Streptococcus, Candida	Enterobacteriaceae, *Pseudomonas aeruginosa, Acinetobacter baumannii,* nontuberculous mycobacteria

suspected of having TB and nontuberculous mycobacterial infections.[21,22] In patients with nonproductive cough or suspected mycobacterial, fungal, or *Pneumocystis jirovecii* infections,[23] it may be helpful to induce sputum production with an inhaled aerosol of hypertonic salt solution (3–10%).

Once collected, the specimens should be delivered rapidly to the laboratory for processing to avoid overgrowth by contaminating flora, which can compromise microscopic detection and isolation of pathogenic bacteria.[24,25] Penn and Silberman[25] found that organisms observed microscopically on Gram-stained smears of sputum specimens and their relative numbers in cultures changed dramatically between processing within an hour of collection and processing after overnight refrigeration. Although there were no significant differences in the culture results between the immediate and delayed cultures in this study, the loss of reliable microscopic features had a significant impact on the interpretation of culture results. Processing delay is particularly important for culture recovery of slow-growing mycobacteria.[26] Specimens not sent to the laboratory for processing within 2 hours should be refrigerated for no more than 5 days.[27] If refrigeration is not possible, samples should be treated first with equal volume of 0.6% cetylpyridinium bromide or 1% cetylpyridinium chloride in 2% sodium chloride, which reduces the survival of contaminating microorganisms while preserving the viability of *M. tuberculosis* for up to 8 days.[26,28–30] Although the recovery of fungi is optimal from cultures of fresh specimens, most clinically significant fungi survive storage of 16 days or longer.[31] Specimens for viral cultures should be shipped refrigerated but not frozen, whereas specimens for chlamydial culture should be placed into sucrose phosphate medium and shipped frozen.

Although there is no universal agreement on the value of anaerobic culture,[32] protected catheter brushes may be used to obtain samples for culture and identification of organisms causing anaerobic pleuropulmonary disease.[33] It is essential to transport samples in an anaerobic vial to preserve the viability of anaerobic organisms.

For detection of respiratory viruses, nasopharyngeal specimens are preferred, although LRT specimens may be necessary to detect viral infection of the LRT.[34] There are a number of methods for the collection of nasopharyngeal specimens, which includes the use of flocked and traditional swabs, as well as aspirates and washes. Flocked swabs contain perpendicular arrangements of fibers with an open structure, to create a highly absorbent thin layer capable of efficient uptake of respiratory samples and elution into viral transport media. Nasopharyngeal flocked swabs have been shown to be more sensitive for the detection of respiratory viruses than traditional swabs.[35,36] In turn, nasopharyngeal aspirates or washes have been shown to be more sensitive than nasopharyngeal flocked swabs.[37–39] However, the modest gains in sensitivity for detection of most respiratory viruses using aspirates or washes may be offset by the ease of nasopharyngeal specimen collection using flocked swabs. Oropharyngeal specimens are less sensitive for the diagnosis than nasopharyngeal specimens, although the combination may increase respiratory virus detection.[40–43] Oropharyngeal swabs may also be used for detecting *Chlamydophila pneumoniae,*[44–47] *M. pneumoniae,*[44,48,49] and *Legionella* sp.[44]

In patients who are critically ill or immunocompromised, or who cannot expectorate, one or more invasive approaches may be necessary to obtain diagnostic samples. Specimens may include endotracheal aspirates, pleural fluids, *bronchoalveolar lavage* (BAL), percutaneous lung aspirate, or lung biopsies.[5,50] The use of BAL has also been expanded to include diagnosis of bacterial pneumonia, especially for nosocomial cases.[51–53] In patients with CAP requiring admission to the hospital, use of protected catheter brush and BAL has been shown to provide microbiologic diagnoses not obtainable by noninvasive means,[54] although there is little support for using these procedures to diagnose CAP.[55] Although the results of cultures from protected catheter brushes and BAL specimens are quantitatively similar, Meduri and Baselski[54] concluded that BAL specimens provided a larger and more representative sample of LRT secretions than the protected catheter brushes, allowing microscopic analysis of the cytocentrifuged BAL fluid to identify the type of bacteria present and to demonstrate the presence of neutrophils with intracellular organisms. These procedures may also yield additional pathogens not obtainable by noninvasive approaches. Much work has also been done with the use of BAL for the diagnosis of ventilator-associated pneumonia[53–56] (see Chapter 49).

In children younger than 7 years with suspected TB, gastric aspirate is used as a surrogate for respiratory samples. Historically, it has been recommended that the pH of gastric aspirate be neutralized with sodium bicarbonate before transport to the laboratory; however, a more recent study suggests that neutralization of gastric aspirate may reduce the recovery of *M. tuberculosis.*[57] Nasopharyngeal aspirates have also been used for diagnosis of TB, although the sensitivity for culture-confirmed TB is lower than with induced sputum.[58] Stool samples in children with pulmonary TB may become the specimen of choice if processing methods can be optimized to concentrate the tubercle bacilli.[59,60]

Other specimen types that may aid in diagnosis of LRT infection include whole blood for blood culture, serum for antibody and antigen testing, urine for antigen testing, and plasma for detection of pathogen *cell-free DNA* (cfDNA). Blood culture is recommended in cases of severe pneumonia[61] but is positive only up to 37% in CAP and in less than 25% in nosocomial pneumonia.[61–65] It is important to note that a large blood volume (60 mL or three sets of blood culture bottles in adults) is necessary to maximize sensitivity of blood culture.[66,67] Although routine blood culture systems have been shown to be highly sensitive for detection of candidemia and cryptococcemia, automated blood culture systems are insensitive for cultivation of monomorphic and dimorphic

molds. Isolation of molds (and fastidious bacteria) from blood requires the lysis-centrifugation method (Isolator)[68–70] or the use of enriched fungal medium bottles.[71,72]

S. pneumoniae can be recovered from urine cultures in as many as 38% of patients with pneumococcal pneumonia.[73] Urine may be tested for the presence of pneumococcal[74] and *Legionella pneumophila* serogroup 1[75] antigens. Fungal antigen tests of urine are also available for diagnosis of histoplasmosis, blastomycosis, and coccidioidomycosis.[76–78] Antigen assays are discussed later in this chapter.

Detection of cfDNA in the acellular fraction of blood (i.e., plasma) and urine has recently emerged as a promising new modality for noninvasive testing for infectious diseases.[79–81] Several different blood collection tubes and urine preservatives are commercially available. Studies are starting to define best practices for sample collection and processing to maximize accuracy.[82]

SPECIMEN ADEQUACY

Clinical laboratories are mandated by accrediting agencies to monitor specimen quality and quantity and to enforce rejection criteria when sample requirements are not met. Common causes for rejection include insufficient sample quantity, poor sample quality, and mislabeling of samples. For bacterial cultures, microscopic examination of sputum and endotracheal aspirate with Gram stain is used to screen samples for adequate quality.[19,83] The presence of excessive squamous epithelial cells (>10–25 per low-power field) is indicative of oropharyngeal contamination and therefore grounds for rejection for bacterial culture (Fig. 19.1). Although earlier criteria for the adequacy of sputum specimens for bacterial cultures also required the presence of polymorphonuclear leukocytes (neutrophils), the number of neutrophils in a sample is no longer used to evaluate specimen adequacy.[84] Endotracheal aspirates are rejected if the screening Gram-stained smears show no organisms.[83,85] Inclusion of microscopic sputum quality characteristics, such as a high number of white blood cells and or a low number of squamous epithelial cells, was not shown to be associated with diagnostic yield (i.e., smear microscopy) of *M. tuberculosis*.[86] For mycobacterial, fungal, and viral cultures, cytologic screening to determine specimen acceptability is not enforced because contamination with commensals does not interfere with interpretation of the culture results. However, the presence of respiratory columnar epithelial cells has been shown to improve respiratory virus detection by *direct fluorescent antibody* (DFA) testing.[87]

MICROBIOLOGIC ASSAYS

The clinical microbiology laboratory offers a broad range of assays for diagnosis of LRT infection. For any particular pathogen, multiple assays may be available, and therefore it is the responsibility of the clinician to choose the assay with the best performance characteristic for a particular specimen type. eTable 19.1 summarizes the accuracy of assays used in the diagnosis of LRT infections caused by bacteria, fungi, and parasites. In addition, the clinician must be familiar with the turnaround time for each assay to optimize use of the results in managing the patient.

MICROSCOPY

Microscopic examination of LRT specimens offers a rapid approach to detection and identification of many pathogens. However, microscopic examination cannot distinguish between infection, colonization, and contamination when the specimen is collected through the oropharynx.[88–90] In addition, microscopy lacks sensitivity in specimens with less than 10^4 CFU per milliliter. Microscopy does routinely provide valuable information on the quality of specimen and the type of inflammatory response present. Specimens demonstrating a preponderance of polymorphonuclear leukocytes, ciliated columnar epithelial cells, or alveolar macrophages with few, if any, squamous epithelial cells (<10 per low-power field) represent LRT secretions. The presence of alveolar macrophages is a more specific marker of LRT secretions than neutrophils and is more likely to be associated with a significantly lower incidence of oropharyngeal contamination.[91] The finding of neutrophils with intracellular organisms is considered indicative of an active infectious process.[92–94]

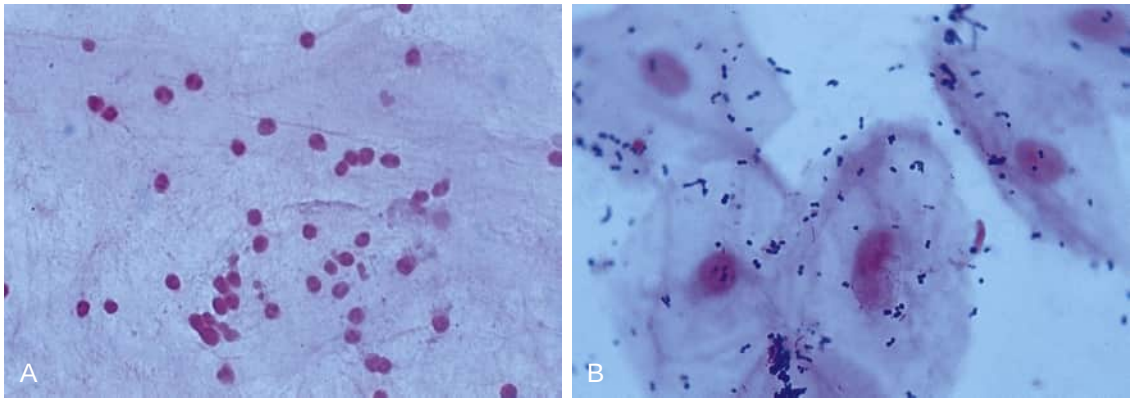

Figure 19.1 Gram stain of sputum specimens. (A) This specimen contains numerous polymorphonuclear leukocytes and no visible squamous epithelial cells, indicating that the specimen is acceptable for routine bacteriologic culture. (B) This specimen contains numerous squamous epithelial cells and rare polymorphonuclear leukocytes, indicating an inadequate specimen for routine sputum culture. (From Tille P. *Bailey & Scott's Diagnostic Microbiology,* ed 13. Philadelphia: Elsevier; 2014.)

eTable 19.1 Accuracy of Assays Used in Diagnosis of Lower Respiratory Tract Infections Caused by Bacteria, Fungi, and Parasites

Organism	Diagnostic Target	Testing Method	Sample Type	Sensitivity (%)	Specificity (%)	References
BACTERIA						
Chlamydia sp (excluding *C. trachomatis*)	Antibody (IgG)	Microimmunofluorescence	Serum	65–92	30–51	293
	Antibody (IgM)	Microimmunofluorescence	Serum	43–75	67–84	293
	Antibody (IgG and IgM)	Microimmunofluorescence	Serum	87–100	22–40	293
	Antibody (IgM)	Enzyme immunoassay	Serum	100	92.9	294
	DNA	PCR—enzyme immunoassay	Nasopharyngeal swab	55–83	91–99	293, 296
Coxiella burnetii	Antibody (IgG, IgA, and IgM)	Microimmunofluorescence	N/A	N/A	N/A	*
	DNA	PCR	N/A	N/A	N/A	*
Francisella tularensis	DNA	PCR	Swab/tissue	73–78	97	296
	Antibody	Enzyme immunoassay	Serum	93.9	96.1	297
	Antibody	Latex microagglutination	Serum	81.8	98.0	297
Legionella sp	Antibody	Direct fluorescent antibody	Respiratory samples	25–66	94	105
	Antigen	Enzyme immunoassay	Urine	37.9–85.7	N/A	298
	Antigen	Lateral flow immunoassay	Urine	80	97–100	299
Legionella pneumophila serotype 1	Antigen	Immunoassay	Urine	74	99.1	219
	DNA	PCR	Urine/serum	64–73	100	300
	DNA	PCR	Throat swab	88.2	100	301
Mycoplasma pneumoniae	Antibody	Complement fixation	Serum	65	97	302
	Antibody (IgG and IgM)	Enzyme immunoassay	Serum	35–77	49–100	302
	DNA	PCR	Throat swab	62	96	303
Nocardia asteroides group	DNA	PCR	Tissue/sputum/BAL	100	100	304
Streptococcus pneumoniae	Antigen	Lateral flow immunoassay	Urine	67–82	93–99.8	216
	DNA	PCR	Plasma or sputum	26–100	58–99	305
Streptococcus pyogenes	Antigen	Enzyme immunoassay	Throat swab	70–90	90–100	306
MYCOBACTERIA						
M. tuberculosis complex	DNA	NAT	Smear negative	33.3–92.9	N/A	101, 153
	DNA	NAT	Smear positive	85.7–94.6	98	101, 153
	Organism	Microscopy	Carbolfuchsin	32–94	N/A	100
	Organism	Microscopy	Fluorochrome (HIV–)	52–97	N/A	100
	Organism	Microscopy	Fluorochrome (HIV+)	26–100	N/A	100

Continued

eTable 19.1 Accuracy of Assays Used in Diagnosis of Lower Respiratory Tract Infections Caused by Bacteria, Fungi, and Parasites—cont'd

Organism	Diagnostic Target	Testing Method	Sample Type	Sensitivity (%)	Specificity (%)	References
INVASIVE FUNGI						
Aspergillus sp	DNA	PCR	Serum	80	100	307
	Antigen	Galactomannan enzyme immunoassay	Serum	71	89	236
Blastomyces dermatitidis	Antigen	Enzyme immunoassay	Urine	80.7–92.9	77–79[†]	308, 309
	Antigen	Enzyme immunoassay	Serum	81.8	100[†]	309
	Antibody	Immunodiffusion	Serum	28	100	310
	Antibody	Enzyme immunoassay	Serum	77–100	86–96	310
	Antibody	Complement fixation	Serum	9	100	310
	Organism	Microscopy	Body fluid/tissue	38–97	N/A	311
Coccidioides sp	DNA	Real-time PCR	Respiratory sample	92.9–100	98.1–98.4	312
	Antibody (IgG)	Complement fixation	Serum	67–75	N/A	272
			Serum (IC patients)	33–100	N/A	272
	Antibody (IgG and IgM)	Immunodiffusion	Serum	53–73	N/A	272
			Serum (IC patients)	0–75	N/A	272
	Antibody (IgG and IgM)	Enzyme immunoassay	Serum	75–92.6	84.6–98.3	313
			Serum (IC patients)	25–90	N/A	272
Cryptococcus neoformans (and *Cryptococcus gattii*)	Antigen	Latex agglutination	Serum	83–91.1	92.9–100	314, 315
	Antigen	Latex agglutination	Urine	N/A	100	314
	Antigen	Latex agglutination	CSF	93–100	93–98	315
	Antigen	Lateral flow assay	Serum	97.6 (CI, 95.6–98.9)	98.1 (CI, 97.4–98.6)	224
	Antigen	Lateral flow assay	Urine	85.0 (CI, 78.7–90.1)	Not estimatable	224
	Antigen	Enzyme immunoassay	Serum	94.1–100	93–100	315, 316
	Antigen	Enzyme immunoassay	Urine	92	Unknown	316

Organism	Diagnostic Target	Testing Method	Sample Type	Sensitivity (%)	Specificity (%)	References
Histoplasma capsulatum	Antibody (IgG)	Complement fixation	Serum/urine	72.8–94.3	70–80	317
	Antibody (IgM)	Microimmunodiffusion	Serum	70–100	100	317, 318
	Antibody (IgG)	Enzyme immunoassay	Serum	91–100	66–97	317, 318
			Serum (AIDS, disseminated)	69.2	N/A	230
			Serum (other IC patients, disseminated)	84.2	N/A	230
			Serum (non-IC patients, disseminated)	85.7	N/A	230
			Serum (pulmonary subacute infection)	92.3	N/A	230
	Antigen	Enzyme immunoassay	Urine	79 (CI, 76–82)	99 (CI, 98–100)	232
			Urine (AIDS, disseminated)	92.1	N/A	230
			Urine (other IC patients, disseminated)	93.5	N/A	230
			Urine (non-IC patients, disseminated)	63.6	N/A	230
			Urine (pulmonary subacute infection)	38.9	N/A	230
			Serum	82 (CI, 79–85)	97 (CI, 96–98)	232
	Antibody	Latex agglutination	Serum	65–97	39	317
Pneumocystis jirovecii	DNA	PCR	BAL	98.3 (CI, 91.3–99.7)	91 (CI, 82.7–95.5)	247
	Organism	Microscopy with silver stain	Induced sputum/BAL	86–92	92–97	108
	Antigen	Direct fluorescent antibody	Induced sputum/BAL	90–97	85–90	108
	Antigen	Indirect fluorescent antibody	Induced sputum/BAL	86–97	100	108
	Organism	Diff-Quik stain	Induced sputum/BAL	81–92	97–100	108
	Antigen	β-D-glucan assay	Serum/plasma	90.8–97.1	81.7–89.9	319
Other (fungi excluding *P. jirovecii*)	Antigen	β-D-glucan assay	Serum/plasma	76.8	85.3	252
PROTOZOA						
Toxoplasma gondii	Antibody (IgG)	Sabin-Feldman dye test Enzyme immunoassay Immunofluorescence antibody IgG avidity	Serum	N/A	N/A	*
	Antibody (IgG and IgM)	Agglutination	Serum	N/A	N/A	*
	DNA	PCR	Serum/CSF/aqueous humor/BAL	15–85	95	320

*Testing for acute Q fever and toxoplasmosis should be done using a battery of tests that must be interpreted together because sensitivity and specificity of individual tests are not available.
†Cross reaction is seen with *Histoplasma capsulatum*.
AIDS, acquired immunodeficiency syndrome; BAL, bronchoalveolar lavage; CI, 95% confidence interval; CSF, cerebrospinal fluid; HIV, human immunodeficiency virus; IC, immunocompromised; Ig, immunoglobulin; N/A, not available; NAT, nucleic acid test; PCR, polymerase chain reaction.

Table 19.6 Laboratory Criteria for Reporting Gram Stain Results to the Ordering Physician

Number of Bacteria Found per Field Under Oil Immersion 100× Objective	Bacterial Quantity Reported to Clinician
0	Negative
<1	1+ (rare)
1–5	2+ (few)
6–30	3+ (moderate)
>30	4+ (heavy)

Table 19.7 Pathognomonic Gram Stain Patterns

Pattern Reported	Pathogen or Entity Suggested
Intracellular organisms	Active infection
Gram-positive cocci in pairs (lancet-shaped diplococci) and short chains	*Streptococcus pneumoniae*
Pleomorphic gram-negative coccobacilli	*Haemophilus influenzae*
Gram-negative diplococci	*Moraxella catarrhalis**
Gram-positive cocci in clusters	*Staphylococcus aureus*
Mixed morphotypes of gram-positive and gram-negative rods, cocci, and coccobacilli	Aspiration pneumonia
Beaded gram-positive or gram-variable rods	Actinomycetales order, which includes genera *Mycobacterium*, *Actinomyces*, *Corynebacterium*
Filamentous branching gram-positive or gram-variable rods	*Nocardia*, *Actinomyces*

*Cannot be distinguished from *Neisseria meningitidis*.

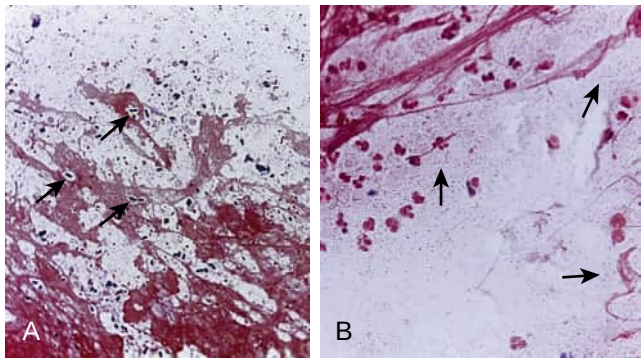

Figure 19.2 Gram stains of bacteria in sputum. (A) Lancet-shaped diplococci in Gram-stained sputum from a case of *Streptococcus pneumoniae* pneumonia. The clear "halo" surrounding some of the diplococci *(arrows)* is the consequence of the thick polysaccharide capsule. (B) Gram stain of *Haemophilus influenzae* in sputum. The small gram-negative bacilli *(arrows)* can be difficult to distinguish from debris. (From Tille P. *Bailey & Scott's Diagnostic Microbiology,* ed 13. Philadelphia: Elsevier; 2014.)

The Gram-stained smear is an essential and necessary part of the evaluation of sputum and tracheal aspirates for determining the quality and acceptability of specimens for bacterial culture[83,85] and for providing a rapid assessment of the most likely etiologic agent of the pneumonia. Although Gram stains might also suggest the presence of mycobacteria, fungi, and parasites, special stains should be ordered when those pathogens are suspected. Table 19.6 shows criteria used by the laboratory to interpret findings on Gram stain and report them to the physician. Although it is impossible to correlate every staining pattern to a particular pathogen, several Gram stain patterns are pathognomonic for a particular pathogen or clinical entity (Table 19.7).

The accuracy of Gram stain for detection of infection depends on the stringency of criteria. In assessing patients with acute CAP, Rein and colleagues[95] found that three or more gram-positive lancet-shaped diplococci (Fig. 19.2A) correctly predicted the presence of pneumococci in corresponding cultures in 90% of cases, with a sensitivity and specificity of 62% and 85%, respectively. As expected, improving the sensitivity of the Gram stain examination by lowering the criteria for positivity resulted in reduced specificity in the diagnosis of pneumococcal infection. Similar levels of sensitivity of Gram-stained smears have been reported by others in identifying pneumococci as well as *H. influenzae* (see Fig. 19.2B) in sputum specimens from patients with acute CAP.[96,97] For the diagnosis of pneumococcal pneumonia, a combination of Gram-stained smear and culture of sputum can yield the correct diagnosis in greater than 80% of patients who received less than 24 hours of effective antibiotic therapy.[98]

Direct examination of sputum for the identification of other organisms that can either be commensals or causes of acute bacterial pneumonia in adults, such as *H. influenzae, M. catarrhalis,* and *N. meningitidis,* may also be challenging.[8,88,90,99] Their role as etiologic agents of pneumonia is strongly suggested by the finding of large numbers of gram-negative coccobacilli *(H. influenzae)* and diplococci (*M. catarrhalis* and *N. meningitidis*) located within and outside of neutrophils in sputum specimens.[92–94] Because sputum microscopy (and subsequent culture) can give misleading results, the diagnosis of *Haemophilus, Moraxella,* or meningococcal pneumonia can be confirmed only by invasive techniques. Because invasive techniques are infrequently performed to identify the etiologic agents of acute CAP, the sensitivity and specificity of sputum Gram-stained smears cannot be determined reliably in such cases. A similar challenge is faced when trying to distinguish between colonization and infection by gram-negative bacilli. For example, up to 10^8 CFU of gram-negative bacilli per milliliter may be found in respiratory secretions of patients on mechanical ventilation in intensive care units without evidence of pneumonia.[13]

Acid-fast staining is the method of choice for visualization of mycobacteria in respiratory specimens. Laboratories may use either carbolfuchsin or fluorochrome to stain mycobacteria. Table 19.8 shows criteria used by the laboratory to report findings on the acid-fast stain. In most studies the carbolfuchsin-based stain has a sensitivity of 60% or lower compared to culture.[100] The fluorochrome stain, which uses a fluorescent dye such as auramine or auramine-rhodamine to highlight mycobacteria, is on average 10% more sensitive than carbolfuchsin[100] and is therefore the method recommended by the *World Health Organization* (WHO) for screening sputum smears for mycobacteria. The sensitivity of acid-fast microscopy depends on the bacillary burden, sample volume, host immune status,

Table 19.8 Laboratory Criteria for Reporting of Acid-Fast Stain Results

No. of AFB Found Under Oil Immersion 100× Objective (Carbolfuchsin Stain)	No. of AFB Found Under 10× Objective (Fluorochrome Stain)	Bacterial Quantity Reported to Clinician
0 per 300 fields	0 per 30 fields	Negative
1–2 per 300 fields	1–2 per 30 fields	± (suspicious)
1–9 per 100 fields	1–9 per 10 fields	1+
1–9 per 10 fields	1–9 per field	2+
1–9 per field	10–90 per field	3+
>9 per field	>90 per field	4+

AFB, acid-fast bacilli.
Modified from David HL. *Bacteriology of the mycobacterioses*. Publication No. CDC 76-8316. Atlanta: Department of Health, Education, & Welfare. 1976:153.

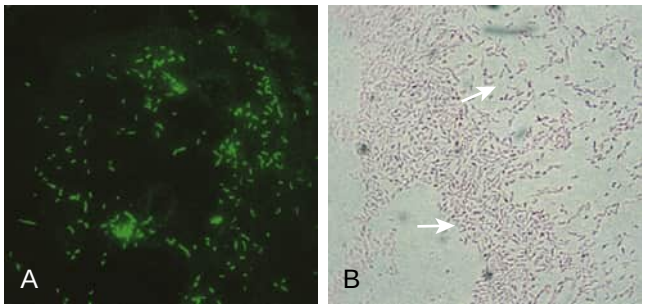

Figure 19.3 *Legionella* pneumophila detection by microscopy. (A) Direct fluorescent antibody stain. (B) Gram stain of a colony grown on agar. The organisms are thin gram-negative bacilli *(arrows)*. (From Tille P. *Bailey & Scott's Diagnostic Microbiology*, ed 13. Philadelphia: Elsevier; 2014.)

staining method, and other variables.[101] The major limiting factor is that approximately 10^4 acid-fast bacilli per milliliter of sputum must be present to be visualized under light microscopy using an acid-fast stain.[101] The insensitivity of smear microscopy for TB therefore necessitates the use of more sensitive methods, such as culture and *nucleic acid tests* (NATs).[102,103] In addition, although acid-fast stains have high specificity, they cannot distinguish between *M. tuberculosis* complex and nontuberculous mycobacteria, and carbolfuchsin stains also stain *Legionella micdadei* (also known as *Tatlockia micdadei*).[104] Modified acid-fast stain, a modified carbolfuchsin stain, is used for direct staining of partially acid-fast–positive organisms, such as *Nocardia, Tsukamurella, Rhodococcus,* and *Gordonia*.[5]

Immunofluorescence examination by DFA staining is an alternative method for direct visualization of organisms. The diagnosis of legionellosis is usually made by a combination of direct immunofluorescence examination and culture of respiratory specimens, and antigen and antibody testing. DFA staining can be performed on sputum, endotracheal aspirate, bronchial washing, and lung tissue specimens, with sensitivities ranging from 25–66% and specificities of greater than 94% for the diagnosis of *L. pneumophila* pneumonia[105] (Fig. 19.3). Both clinical and technical variables account for the broad range of sensitivity of this test, and the accuracy of this method for detection of pneumonia due to other *Legionella* sp is less precisely known. In the absence of other supporting evidence, a positive DFA result is generally not accepted as sufficient for the diagnosis of *Legionella* infection, and other confirmatory measures should be undertaken.

DFA testing is sensitive and specific in detecting *Chlamydia trachomatis* in nasopharyngeal specimens from infants with pneumonia and has also been applied to sputum and BAL for detection of *P. jirovecii,* the agent of *Pneumocystis* pneumonia.[106,107] Silver stain, direct immunofluorescence, indirect immunofluorescence, and Diff-Quik (a modified Giemsa stain) have all been found to have greater than 90% sensitivity for detecting *P. jirovecii* in induced sputum and BAL samples from *human immunodeficiency virus* (HIV)-infected patients[108] (Fig. 19.4A). All of these staining techniques have lower sensitivity in patients who are not infected with HIV, but DFA is consistently more sensitive than the other staining techniques.[109,110]

DFA has also been applied to respiratory secretions for the diagnosis of respiratory virus infections. DFA testing can be performed in 1 to 4 hours and is typically more sensitive than rapid antigen tests.[87,111] However, DFA testing for respiratory viruses requires a high level of technical and interpretive expertise, is difficult to adapt to the high throughput required for pandemic or high-volume testing, and remains less sensitive than real-time *polymerase chain reaction* (PCR).[87,112] DFA for viral detection has been phased out in many clinical laboratories as rapid, sensitive, multiplexed molecular diagnostic respiratory virus tests have become available.

The visualization of fungal elements in respiratory secretions requires the use of special stains. Historically, potassium hydroxide was used to degrade host tissue and visualize fungal elements, such as *Blastomyces* (see Fig. 19.4B–C). Calcofluor white stain, a fluorochrome that binds to chitin and cellulose present in the fungal cell wall, is now commonly added to potassium hydroxide or used alone to provide better delineation of fungal elements, including *Histoplasma capsulatum* (see Fig. 19.4D).[113,114] Table 19.9 lists staining patterns suggestive of certain fungal pathogens. It is important to note that identification of fungi based on microscopic appearance of fungal elements in lung tissue or secretions is subject to error, and definitive identification must be deferred to culture or NATs.[115]

The identification of pulmonary parasites, such as *Strongyloides stercoralis* and *Paragonimus* sp, is typically made by microscopic examination of respiratory secretions. *S. stercoralis* larvae and rarely eggs can be seen on most stains but are sufficiently large that they are more likely to be found using a low-power objective (Fig. 19.5).[116] The diagnosis of microfilariae causing tropical pulmonary eosinophilia requires peripheral blood parasite examination of nightly blood samples because these parasites typically

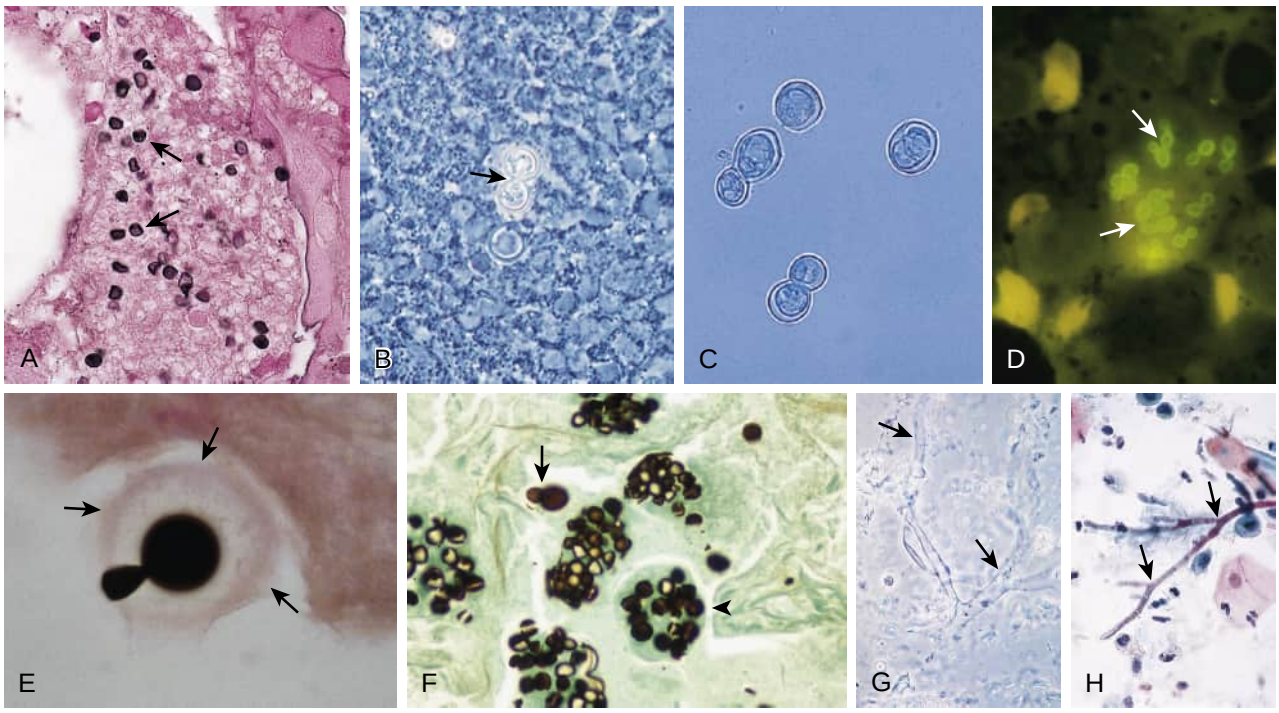

Figure 19.4 Microscopic identification of fungal pathogens. (A) Cyst forms of *Pneumocystis jirovecii (arrows)* stained with methenamine silver and hematoxylin and eosin stain (×500 original magnification). (B) *Blastomyces dermatidis*. Potassium hydroxide preparation of exudate shows a large budding yeast cell with a distinct broad base *(arrow)* between inflammatory cells (phase-contrast microscopy). (C) Thick-walled, oval to round, single-budding, yeast-like *Blastomyces dermatidis* cells from culture. (D) *Histoplasma capsulatum (arrows)* seen with calcofluor white stain of sputum showing 2- to 5-μm-diameter intracellular organisms. (E) *Cryptococcus neoformans* with narrow-based bud; silver stain. The faintly staining capsule is also visible *(arrows).* (F) *Coccidioides immitis* spherules in a tissue biopsy. Spherules can also be found in fresh sputum samples. The internal endospores stain with silver *(arrowhead),* whereas the external wall of the spherule does not. The endospores that have been released from a spherule resemble budding yeast *(arrow)* (GMS stain; ×400 original magnification). (G) *Rhizopus* sp in a potassium hydroxide preparation of sputum showing broad, predominantly nonseptate hyphae *(arrows).* Phase-contrast microscopy. (H) Branching septate hyphae *(arrows)* of *Aspergillus fumigatus*. Papanicolaou staining of sputum. GMS, Gomori methenamine silver. (A–D and F–H, From Tille P. *Bailey & Scott's Diagnostic Microbiology,* ed 13. Philadelphia: Elsevier; 2014; E, From Mandell GL, Bennett JE, Dolin R. *Principles and Practice of Infectious Diseases,* ed 7. Philadelphia: Elsevier; 2010.)

Table 19.9 Microscopic Descriptions Suggestive of Certain Fungal Pathogens

Key Patterns Reported From Respiratory Specimens	Pathogens the Findings Suggest
Broad-based budding yeast (see Fig. 19.4B–C)	*Blastomyces dermatitidis*
Narrow-based budding yeast (Fig. 19.4D–E)	*Candida, Cryptococcus, Histoplasma capsulatum, Sporothrix schenckii*
Spherule (Fig. 19.4F)	*Coccidioides immitis, Coccidioides posadasii*
Nonseptate hyphal element (Fig. 19.4G)	Zygomycetes (cannot be predicted from formalin-fixed paraffin-embedded tissue)
Septate hyphal element (Fig. 19.4H)	Monomorphic hyaline and dematiaceous molds, including *Aspergillus*



Figure 19.5 *Strongyloides stercoralis* rhabditiform larva; iodine stain. When examined under low power, staining of sputum may be unnecessary. Unfixed preparations can also show larval mobility. (From Tille P. *Bailey & Scott's Diagnostic Microbiology,* ed 13. Philadelphia: Elsevier; 2014.)

circulate in the blood only at night, which coincides with activity of its insect vector.[117] *Echinococcus* cysts may be detected in pulmonary cyst fluid, and *Entamoeba histolytica* may be seen in association with pleural disease, if an amebic liver abscess erodes through the diaphragm.

CULTURE

Microbiologic culture of respiratory specimens allows definitive identification of the suspected pathogens and permits determination of susceptibility to antimicrobial agents for bacteria, mycobacteria, and yeast. For cultivation of particular groups or species of microorganisms, laboratories must inoculate processed samples on one or more culture media supplemented with nutrients suitable for cultivation of the desired

Table 19.10 Semiquantitative Scheme for Grading Bacterial Growth on Streaked Agar Plates

	NO. OF COLONIES PRESENT IN CONSECUTIVE STREAKED QUADRANTS		
Grade	**First**	**Second**	**Third**
1+	<10	0	0
2+	>10	<5	0
3+	>10	>5	<5
4+	>10	>5	>5

Data from Waites KB, Saubolle MA, Talkington DF, et al. *Cumitech 10A: Laboratory Diagnosis of Upper Respiratory Tract Infections*.Washington, DC: American Society for Microbiology Press; 2006.

microorganisms and inhibitors for selective inhibition of undesirable organisms. The clinician must therefore be aware that, although many organisms do grow on routine aerobic and anaerobic cultures, a number of respiratory pathogens, such as *Mycoplasma, Legionella, Mycobacterium, Nocardia, Rhodococcus,* and *H. capsulatum,* require pathogen-specific growth conditions (growth supplements, temperature and carbon dioxide requirements, and incubation times), which have to be specified when fastidious pathogens are part of the differential diagnosis.[5] For example, *Legionella* sp require culture media supplemented with L-cysteine and α-ketoglutarate (buffered charcoal yeast extract),[105] slow-growing mycobacteria require media enriched with a lipid extract and antimicrobials to limit the growth of oral commensals,[101] and *H. capsulatum* requires extended incubation time up to 4 weeks.[118] Although most *Nocardia* sp grow well on mycobacterial culture media and on ordinary bacterial and fungal culture media, optimal recovery from clinical specimens is obtained by using the same buffered charcoal yeast extract culture medium as that for the isolation of *Legionella.*[119]

Laboratories commonly use a semiquantitative culturing method and report the number of colonies present in consecutive streaked quadrants using a 1+ to 4+ grading system. Table 19.10 lists criteria for reporting of semiquantitative cultures. It is important to note that with the semiquantitative culture method, the volume of specimen cultured is not standardized. Quantitative cultures are also performed on certain respiratory specimens, such as protected catheter brush specimens and BAL fluid.[120] Nonetheless, a randomized trial found that in mechanically ventilated patients with pneumonia, the use of quantitative BAL and nonquantitative endotracheal aspirate cultures resulted in similar clinical outcomes, although patients known to be colonized or infected with *Pseudomonas aeruginosa* or methicillin-resistant *Staphylococcus aureus* were excluded, and antibiotics were withheld until the results of culture were available.[56] Bacteria present in quantities greater than 10^3 CFU/mL in cultures of protected catheter brushes[52] and in quantities greater than 10^4 CFU/mL in cultures of BAL fluids[54] are defined by the laboratory as positive and identified and tested for their susceptibility to appropriate antimicrobial agents.[121] The diagnostic value of break points of bacterial growth (i.e., 10^3–10^5 CFU/mL) depends not only on the type of microbiologic processing used but also on the relationship of two variables: The concentration of pathogens present in the BAL fluid and degree of contamination of the bronchoscopic channel through which lavage fluid was injected and aspirated. Other variables affecting the sensitivity of BAL specimens include antibiotic administration and the volume of lavage fluid injected and volume of fluid retrieved.[122] Diagnostic specificity depends greatly on techniques used to minimize contamination of the specimen by upper respiratory flora, such as discarding the first aliquot of aspirated fluid.[123]

Because many pathogens of the LRT are also members of the oropharyngeal flora, culture results must be correlated with the Gram stain findings, including the presence or absence of polymorphonuclear leukocytes. Respiratory pathogens seen to be predominant on Gram stain with typical morphologic characteristics within and outside polymorphonuclear leukocytes are reported and identified to the species level. Upper respiratory colonization with potentially pathogenic microorganisms, such as gram-negative bacilli, may not be related to the actual etiologic agents of LRT infection. Sputum specimens contaminated with Enterobacteriaceae or *S. aureus* from oropharyngeal secretions may obscure the diagnosis of pneumococcal pneumonia, anaerobic pleuropulmonary infection, or even TB.[124–127] With the exception of *Cryptococcus,* yeasts are considered to be of upper respiratory origin and are not routinely identified.[127]

The sensitivity and specificity of cultures depend on the pathogen burden, specimen type, collection method, the cytologic screening criteria applied to ensure sampling of LRT secretions, and the threshold of colony count to distinguish infection from contamination. In 1971, Barrett-Connor[124] showed that only 45% of patients with bacteremic pneumococcal pneumonia had pneumococci isolated from their sputum cultures, whereas 27% of patients had moderate to heavy growth of another potential pathogen in these cultures. In contrast, fungal cultures of respiratory specimens were positive in approximately 85% of cases with disseminated or chronic pulmonary histoplasmosis.[128,129] Careful specimen collection, cytologic screening of specimens to discard those contaminated with oropharyngeal secretions, and use of the results of the Gram-stained smear to guide identification of isolates in culture all contribute to the diagnostic value of sputum culture in acute pneumococcal pneumonia.

It is also important for the clinician to have knowledge of the turnaround time of all tests, including cultures. The time to detection of positive culture results is dependent on the number of organisms in the inoculum and the replication rate of the pathogen.[118] Table 19.11 shows typical turnaround times for LRT pathogens.

Bacterial cultures can also assist with diagnosis of certain parasitic infections. Fecal *Strongyloides* culture may be useful in cases of suspected pulmonary involvement with *S. stercoralis* when sputum cytologic examination fails to identify larvae. The agar plate method, which looks for tracking of bacteria by the motile larvae, is a useful adjunct to standard microscopic fecal examination and may be up to six times more sensitive.[130–133]

Viral culture techniques previously played an important role in the diagnosis of respiratory virus infections.[134] However, traditional viral culture is laborious, requires significant technical and interpretive expertise, allows the isolation of only a limited range of disease-causing viruses, and has a long turnaround time that limits clinical utility.[135] Shell vial culture is an improved method in which a sample is centrifuged onto a layer of cells, with subsequent detection of viral

Table 19.11 Time to Detection of Respiratory Pathogens in Culture

Key Respiratory Pathogens	Time to Detection in Culture
Acinetobacter baumannii, Aspergillus, Coccidioides immitis, Coccidioides posadasii, Cryptococcus, Escherichia coli, Haemophilus influenzae, Klebsiella pneumoniae, Moraxella catarrhalis, Mycobacterium abscessus group, Mycobacterium chelonae, Neisseria meningitidis, Nocardia, Pseudomonas aeruginosa, Staphylococcus aureus, Streptococcus pneumoniae, Zygomycetes*	1–3 days
Actinomyces, Legionella Sporothrix schenckii*	3–5 days
Blastomyces dermatitidis, Histoplasma capsulatum, Mycobacterium avium-intracellulare complex, *Mycobacterium tuberculosis* complex, *Mycoplasma pneumoniae*	1–4 weeks

*May take longer.
Modified from Hove MG, Woods GL. Duration of fungal culture incubation in an area endemic for *Histoplasma capsulatum*. *Diagn Microbiol Infect Dis.* 1997;28:41.

antigen. Shell vial cultures, particularly those using a mixture of mink lung and A549 cells, provide equivalent to improved sensitivity compared to traditional culture, with more rapid turnaround time.[136–138] Similar to respiratory virus DFA, routine respiratory viral cultures are being phased out in many clinical laboratories with the widespread availability of respiratory virus molecular diagnostic tests. However, in BAL samples from transplant recipients and other immunocompromised patients, shell vial cultures using human fibroblast cell lines may be clinically useful for detection of *cytomegalovirus* (CMV),[139,140] and traditional viral cultures may be useful for recovery of herpes simplex virus.[141–143]

ANTIMICROBIAL SUSCEPTIBILITY TESTING

Antimicrobial susceptibility testing is performed to assist clinicians with the selection of appropriately targeted antibiotic therapy to optimize clinical outcomes. There are several aspects of this in vitro testing that are important to understand. First, testing methods and interpretation of results must be done according to accepted standards, such as the *Clinical and Laboratory Standards Institute* (CLSI), the *US Food and Drug Administration* (FDA), or the *European Committee on Antimicrobial Susceptibility Testing* (EUCAST) for the various categories of organism. Second, the selection of antibiotics to test and report is determined in collaboration with CLSI/EUCAST guidelines, the hospital formulary, infectious disease specialists, the pharmacy, and the infection prevention committee. Third, antimicrobial susceptibility testing should not be performed when the pathogen has a predictable susceptibility profile (e.g., all *Streptococcus pyogenes* are currently susceptible to penicillin), nor is susceptibility testing needed for a specific antibiotic when an organism has intrinsic resistance to that antibiotic (e.g., *Enterobacter* sp, *Klebsiella* sp, *Citrobacter* sp, and *Serratia* sp are all intrinsically resistant to ampicillin). The bacterial pathogens from the LRT for which the susceptibility profile is not predictable, and thus antimicrobial susceptibility testing is commonly performed, are *S. pneumoniae, S. aureus, H. influenzae, M. catarrhalis,* the Enterobacteriaceae, *P. aeruginosa,* and other nonfermenting gram-negative rods. Fourth, because antimicrobial susceptibility testing measures in vitro activity, other factors must be considered when determining in vivo activity, including antimicrobial pharmacokinetics and pharmacodynamics and patient-specific factors such as immune status.

Phenotypic susceptibility testing methods used by the clinical laboratory consist of the disk diffusion method, which generates a qualitative result based on the zone size of bacterial growth inhibition, and the dilution method, which generates a quantitative result: the *minimum inhibitory concentration* (MIC). Results generated by each method are reported as "susceptible," "susceptible–dose-dependent," "intermediate," or "resistant." Susceptible implies the organism will likely respond to treatment with the antibiotic at a standard dosage. Susceptible–dose-dependent implies likely response to treatment with a higher and more frequent dose than the standard dosage. Intermediate may be effective if higher dosing can be used (e.g., β-lactams) or if the antibiotic has high concentrations at the site of infection (e.g., fluoroquinolones for urinary tract infections). Resistant implies the organism is not likely to respond to therapy with that antibiotic. The interpretation criteria (susceptible, intermediate, resistant) are specific to each organism-drug combination and to the pharmacokinetics (e.g., peak serum levels, protein binding, and clearance rate of the drug) and the pharmacodynamics (e.g., whether the rate of bacterial killing is concentration dependent) of each drug. Therefore, because the measurement of the MIC alone does not capture these multiple considerations, simply choosing a drug on the basis of the lowest MIC in a susceptibility report is not recommended.

Genotypic susceptibility testing is also possible for certain pathogen-drug combinations when a monogenic mutation accurately predicts a resistant phenotype. Examples include the *mecA* gene for methicillin resistance in *Staphylococcus,*[144] *vanA* and *vanB* for vancomycin resistance in *Enterococcus,*[145] and specific *rpoB* mutations in rifampin resistance in *M. tuberculosis.*[146]

Not all pathogens isolated in the laboratory can be reliably tested for antimicrobial susceptibility. For organisms such as *Chlamydophila, Mycoplasma, Legionella,* nontuberculous mycobacteria, and molds, there are currently no standard test methods or interpretive criteria. For these pathogens, clinical experience, use of consensus guidelines, and careful assessment of patient response to antimicrobial therapy is most valuable for optimal patient management.

NUCLEIC ACID TESTS

In recent years, technological advances in NATs and instrument automation have revolutionized the simplicity, speed, and accuracy of detecting fastidious pathogens directly from respiratory specimens.[146–148] In many laboratories, these tests have replaced conventional, less sensitive, more laborious methods for routine use. With the unique capabilities of molecular diagnostic tests and the need for rapid, sensitive detection of respiratory pathogens, molecular assays will continue to gain an increasing role in the diagnosis and management of patients with opportunistic

pneumonia and CAP. Most NATs are based on amplification and detection of nucleic acid targets specific to the pathogens of interest. NATs offer several advantages over conventional direct examination, microbiologic cultures, and serologic assays. First, NATs have the ability to detect and identify pathogens rapidly (in hours). Second, NATs provide the only means of direct detection for some microorganisms that are difficult or impossible to grow in culture. Certain viruses, for example, are very difficult to cultivate by conventional culture-based methods, and NATs enable detection of these organisms in clinical specimens.[149] Third, NATs make possible detection of pathogens, such as *M. tuberculosis,* in resource-limited settings where laboratory infrastructure for culture is lacking.[150,151] Finally, for some pathogens, NATs allow determination of antimicrobial susceptibility directly from respiratory tract specimens.

A number of commercial and in-house NATs are available for direct detection of *M. tuberculosis* in sputum, BAL, pleural fluid, lung tissue, and lymph node. These assays can yield results in 2 to 8 hours. For example, in comparison to conventional cultures for *M. tuberculosis,* NATs have high sensitivities (86–97%) and specificities (98%) in smear-positive respiratory samples.[101] In smear-negative, culture-positive specimens, NATs can confirm the presence of *M. tuberculosis* in 33–96% of samples, weeks earlier than culture.[101] The Xpert MTB/RIF (Cepheid) assay is a *sample-to-answer* assay, meaning it is a self-contained system that can process the sample and provide the answer without intervening steps from the laboratory personnel. The Xpert MTB/RIF has a pooled sensitivity of 98% and 67% in smear-positive and smear-negative TB, respectively.[152] The pooled specificity is 99%. Compared to Xpert MTB/RIF, the Xpert Ultra assay, designed to have higher sensitivity, has higher pooled sensitivity (88% vs. 83%) but slightly lower specificity (96% vs. 98%).[153] For smear-negative sputa, the sensitivity of NATs further improves if the assay is performed on one to two additional samples.[146] Detection of *M. tuberculosis* susceptibility to first- and second-line drugs can also be accomplished directly from sputum.[154,155] Commercial NATs detect rifampin and isoniazid resistance with sensitivity of 94–99% and 88–95%, respectively.[101,155–157] Xpert MTB/RIF has a pooled sensitivity of 95% and specificity of 98% for rifampin resistance detection.[153] Based on the improved performance of NATs over smear microscopy and the rapid turnaround time compared to culture, the CDC has recommended that NAT "testing should be performed on at least one respiratory specimen from each patient with signs and symptoms of pulmonary TB for whom a diagnosis of TB is being considered but has not yet been established, and for whom the test result would alter case management or TB control activities."[103] Further, based on a multicenter study in US patients, FDA approved the use of either one or two negative Xpert MTB/RIF result(s) as an alternative to three negative smears to remove patients from respiratory isolation.[158] In addition, WHO has recommended the use of Xpert assay as the initial diagnostic test in all individuals with presumed pulmonary TB.[159,160]

Diagnostic methods have also been described for detecting the nucleic acids of *C. pneumoniae,*[8,45,46] *M. pneumoniae,*[44,48,49] *L. pneumophila,*[44] dimorphic fungi,[161] monomorphic fungi,[162–165] *P. jirovecii,*[166] *Toxoplasma gondii,*[167,168] respiratory viruses,[149] herpes simplex virus,[142] and CMV[169–172] directly in respiratory specimens of normal and immunocompromised hosts. Accuracy studies have indicated that most of these assays are at least comparable to, if not better than, conventional culture, direct antigen, and/or serologic detection methods, especially when examining respiratory specimens that contain low numbers of pathogens. For example, a rapid PCR assay has been applied for the diagnosis of an outbreak of *Chlamydia psittaci* that resulted from transmission to humans from birds purchased in stores; in this outbreak, PCR detected 50% more cases than did culture.[173] Compared to culture and serologic tests, PCR was also shown to be the most sensitive method for detection of *C. pneumoniae* during an outbreak of CAP.[174] For *P. jirovecii,* pooled sensitivity and specificity of PCR in BAL fluid was 98.3% and 91.0%, respectively.[166] However, NAT results should be interpreted with caution because NATs currently cannot differentiate between organisms that inhabit the upper airway without causing disease and those that are responsible for the patient's illness. For example, as mentioned, *S. pneumoniae, C. pneumoniae,* and *M. pneumoniae* may inhabit the upper airway without causing disease.[7,11] Similarly, the lowered diagnostic specificity of *P. jirovecii* NATs is likely due to the detection of *P. jirovecii* nucleic acid from cysts that are present in low numbers and in a latent state in pulmonary tissues of asymptomatic patients.[175–177]

In patients with infection with negative culture results or when cultures were not performed on a tissue biopsy sample before fixation, a broad-range PCR assay coupled with amplicon sequencing can be used for detection and identification of bacterial and fungal DNA from fresh or *formalin-fixed paraffin-embedded* (FFPE) specimens.[178–182] The bacterial 16S ribosomal RNA gene and the fungal ribosomal RNA operon (encoding 5.8S, 18S, 28S ribosomal subunit genes with the internal transcribed spacer regions [ITS1 and ITS2]) are the most reliable and frequently used targets for identifying bacterial and fungal sequences, respectively.[183] As with all NATs, sensitivity is higher from fresh tissue than from FFPE specimens. For example, fungal sequencing was successfully completed on 97% of specimens when performed on fresh specimens compared to 63–70% when performed on FFPE specimens.[180,182] Despite the many advantages of direct bacterial and fungal identification by sequencing, clinicians must be aware that the success of this method is dependent on the amount of specimen submitted (e.g., open biopsy vs. needle biopsy), the pathogen burden, and whether fresh versus FFPE tissue is tested.[182] It is imperative that testing is strictly limited to samples obtained from sterile sources because contamination of the sample with commensal organisms or environmental spores could yield false-positive results and lead to mismanagement of the patient.[180,181] Sequence results must always be correlated with clinical, histopathologic, and ancillary test results (antibody or antigen detection) to ensure the clinical accuracy of sequence results.

The diagnosis of respiratory virus infections (Table 19.12) has been revolutionized by NATs.[149] These tests are now considered more sensitive than all other current methods of respiratory virus detection, including viral culture and DFA testing, discussed earlier, and rapid antigen tests, discussed later. Two major groups of respiratory virus NATs are currently in widespread clinical use, with different technical

Table 19.12 Respiratory Viruses

STANDARD RESPIRATORY VIRUS TEST PANEL
Influenza A, B
Respiratory syncytial virus
EXPANDED RESPIRATORY VIRUS TEST PANEL
Parainfluenza 1, 2, 3, 4
Human metapneumovirus
Adenovirus
Human coronavirus (229E, HKU1, OC43, NL63)
Rhinovirus
Enterovirus*
ADDITIONAL VIRUSES TO CONSIDER IN THE IMMUNE COMPROMISED
Cytomegalovirus
Herpes simplex virus
Varicella-zoster virus
Human herpesvirus 6
OTHER VIRUSES THAT CAUSE LOWER RESPIRATORY TRACT INFECTION
Hantavirus
Measles virus
SEVERE ACUTE RESPIRATORY SYNDROME VIRUSES
Avian influenza (H5N1, H7N9)
SARS coronavirus
SARS-coronavirus-2 (COVID-19)
MERS coronavirus

*Commercial multiplex nucleic acid amplification tests may not distinguish between Rhinovirus and Enterovirus.
MERS, Middle Eastern respiratory syndrome; SARS, severe acute respiratory syndrome.

and personnel requirements. These requirements are defined by the test complexity, which is divided into nonwaived and waived testing according to the *Clinical Laboratory Improvement Amendments* (CLIA). Nonwaived tests include moderate- and high-complexity testing and must be performed in accredited clinical laboratories, whereas waived tests are under less stringent regulation and can be performed outside of the clinical laboratory setting, including at the point-of-care. Previous commonly used laboratory-developed and commercial FDA-cleared high-complexity, *real-time reverse-transcriptase PCR* (rRT-PCR) assays, which require separate extraction and amplification steps before nucleic acid detection,[184–187] are being phased out as laboratories implement various automated systems to detect respiratory viruses.

The first group of respiratory virus NATs include the nonwaived panels performed on FDA-cleared sample-to-answer platforms (eTable 19.2). Standard panels typically target influenza A, influenza B, and *respiratory syncytial virus* (RSV), whereas extended panels add influenza A subtyping (including H1, 2009 H1, and H3); parainfluenza virus 1, 2, 3, and 4; human metapneumovirus; adenovirus; coronaviruses; and rhinovirus/enterovirus. These expanded panels may also include bacterial targets, such as *M. pneumoniae, Chlamydophila pneumoniae, Bordetella pertussis, and Bordatella parapertussis.*

A majority of the available respiratory virus tests are only approved for URT specimens, such as nasopharyngeal swabs and aspirate/washes, so it is important to verify that the local laboratory has validated the use of LRT specimens in their test system before sending such samples for testing. Currently, one nonwaived system is approved for lower tract specimens, the Biofire FilmArray Pneumonia Panel (Biofire Diagnostics). This test is approved for expectorated/induced sputum, tracheal aspirates, and BAL fluid. This panel includes qualitative detection of viruses (influenza A, influenza B, RSV, human metapneumovirus, parainfluenza virus, adenovirus, coronaviruses, rhinovirus/enterovirus), atypical bacteria, and antimicrobial resistance genes (methicillin resistance, carbapenamases, and extended-spectrum β-lactamases), as well as semiquantitative detection of 15 bacterial causes of pneumonia. The prospective study carried out by the manufacturer to obtain FDA approval demonstrated positive percent agreements ranging from 75–100%, and negative percent agreements ranging from 89–100%, depending on the target.[187a–d]

The second group of respiratory virus NATs include the CLIA-waived panels, also performed on various FDA-cleared sample-to-answer platforms (eTable 19.3). These tests include the Alere i (Abbott),[187–197] cobas Liat (Roche),[188,196,198–205] and Xpert Xpress (Cepheid)[197,201–210] rapid influenza A/B NAT assays, among several others. Rapid detection of influenza may be essential to allow prompt treatment with antiviral agents, to reduce the risk for further transmission through implementation of infection control practices, and to reduce inappropriate use of antibiotics.[211,212] Meta-analysis revealed that these rapid NATs have pooled sensitivities of 92% for influenza A and 95% for influenza B, with pooled specificities of greater than 99%.[213] Given these test characteristics, facilities using respiratory virus tests at the point-of-care no longer need to compromise performance for simplicity, ease of use, and rapid test turnaround.[214,215] Currently, one extended panel, the BioFire Respiratory Virus Panel EZ has received a CLIA waiver. This test detects influenza A (including H1, 2009 H1, and H3 subtyping), influenza B, RSV, human metapneumovirus, parainfluenza virus, adenovirus, coronaviruses, rhinovirus/enterovirus, *B. pertussis, C. pneumoniae, and M. pneumoniae.* The waived version of this test uses identical test pouches to the nonwaived version; only the software and interpretation differs.

Given the variety of NATs currently available for the diagnosis of respiratory virus infection and the ongoing development of new NATs, it is important to communicate with the laboratory to confirm the viruses included in the local panel, the expected turnaround time, and local test performance characteristics.

ANTIGEN TESTING

The diagnosis of LRT infections can be aided by detection of pathogen-specific antigens in serum or other body fluids. Antigen detection offers an alternative to direct examination of infected tissue and may play a role in the detection of pathogens that grow poorly, or not at all, in culture.

Urinary antigen assays may have value for adults with *S. pneumoniae* and *L. pneumophila* infections. In a meta-analysis of 27 studies using a composite of culture tests as the reference standard, the pooled sensitivity for direct antigen detection of *S. pneumoniae* in the urine of adults with

eTable 19.2 Selected FDA-Cleared Respiratory Virus NATs: Non-Waived

Manufacturer	Product	Platform/Instrument	Panel Size	Approved Specimens
BioFire Diagnostics	BioFire FilmArray Respiratory Panel 2	BioFire FilmArray	Extended	NPS
BioFire Diagnostics	BioFire FilmArray Respiratory Panel	BioFire FilmArray	Extended	NPS
BioFire Diagnostics	BioFire FilmArray Pneumonia Panel	BioFire FilmArray	Extended	IS, TRA, BAL
Cepheid	Xpert Flu/RSV XC	GeneXpert	Standard	NPS, NPA, NPW
Cepheid	Xpert Xpress Flu	GeneXpert	Standard	NS, NPS
Cepheid	Xpert Xpress Flu/RSV	GeneXpert	Standard	NS, NPS
Diasorin	Simplexa Flu A/B + RSV Direct	Liason MDX	Standard	NPS
GenMark Diagnostics	ePlex Respiratory Pathogen Panel	ePlex	Extended	NPS
Hologic	Panther Fusion Flu A/B/RSV Assay	Panther Fusion	Standard	NPS
Hologic	Panther Fusion AdV/HMPV/RV Assay	Panther Fusion	Standard	NPS
Hologic	Panther Fusion Paraflu Assay	Panther Fusion	Standard	NPS
Luminex	ARIES Flu A/B + RSV Assay	ARIES	Standard	NPS
Luminex	VERIGENE Respiratory Pathogens *Flex*	VERIGENE Reader/ Processor *SP*	Extended	NPS
Qiagen	QIAstat-Dx Respiratory Panel	QIAstat-Dx	Extended	NPS
Quidel	Solana Influenza A/B Assay	Solana	Standard	NS, NPS
Quidel	Solana Influenza RSV + hMPV Assay	Solana	Standard	NS, NPS

BAL, bronchoalveolar lavage; FDA, United States Food and Drug Administration; hMPV, human metapneumovirus; IS, induced/expectorated sputum; NATs, nucleic acid tests; NPA, nasopharyngeal aspirate; NPS, nasopharyngeal swab; NPW, nasopharyngeal wash; NS, nasal swab; RSV, respiratory syncytial virus; TRA, tracheal aspirate.

eTable 19.3 FDA-Cleared Respiratory Virus NATs: CLIA Waived

Manufacturer	Product	Platform/Instrument	Approved Specimens
Abbott	Alere i Influenza A/B2	Alere i (ID NOW)	NS direct, NPS direct, NS, NPS
Abbott	Alere i Influenza RSV	Alere i (ID NOW)	NPS direct, NPS
BioFire Diagnostics	BioFire FilmArray Respiratory Panel EZ	BioFire FilmArray	NPS
Cepheid	Xpert Xpress Flu	GeneXpert Xpress	NS, NPS
Cepheid	Xpert Xpress Flu + RSV	GeneXpert Xpress	NS, NPS
Mesa Biotech	Accula Flu A/Flu B	Accula Dock	NS
Mesa Biotech	Accula RSV	Accula Dock	NS
Roche	cobas Liat Influenza A/B Assay	cobas Liat	NPS
Roche	cobas Liat Influenza A/B + RSV Assay	cobas Liat	NPS
Sekisui Diagnostics	Silaris Influenza A/B Test	Silaris Dock	NS direct

CLIA, Clinical Laboratory Improvement Amendments; FDA, United States Food and Drug Administration; NATs, nucleic acid tests; NPS, nasopharyngeal swab; NS, nasal swab; RSV, respiratory syncytial virus.

CAP was 74%, and specificity was 97%.[216] In children, pneumococcal antigen in urine is less specific for invasive infection because it was detected in 43% of children with only nasopharyngeal colonization.[217] Similarly, in children with pneumonia, detection of *H. influenzae* type B antigens in urine is of potential diagnostic value, but transient antigenuria may follow immunization with *H. influenzae* type B conjugate vaccine.[218] In the evaluation of adults for Legionnaires' disease, urine *L. pneumophila* serogroup 1 antigen has a high negative predictive value with pooled sensitivity of 74% and specificity of 99%.[219] Urine antigen for *L. pneumophila* is detectable in 80–89% of patients with Legionnaires' disease, beginning with the first 3 days of symptoms and continuing for at least 14 days; the duration of antigenuria was reduced by antibiotic therapy but was detectable for up to 42 days, especially in immunocompromised patients.[220] The urinary antigen assays are limited to detection of infections due to *L. pneumophila* serogroup 1 and not other *Legionella* serogroups or species.[104]

Detection of urinary *lipoarabinomannan* (LAM), a major lipoglycan in the *M. tuberculosis* cell wall, with *lateral flow urine LAM assay* (LF-LAM) is recommended by WHO for diagnosis and screening of TB in HIV-positive individuals with a CD4 count less than or equal to 100 cells/μL.[221] In a meta-analysis of five studies, pooled sensitivity and specificity of LF-LAM were 56% and 90%, respectively, in patients with a CD4 count less than or equal to 100 cells per μL versus 26% and 92%, respectively, and in those with a CD4 count greater than or equal to 100 cells per μL.[222]

Detection of fungal antigen in serum, urine, and other body fluids is used as an aid in the diagnosis of infections due to *Cryptococcus neoformans, Aspergillus, H. capsulatum, Coccidioides immitis*, and *P. jirovecii*. Assays to detect capsular polysaccharides of *C. neoformans* in serum, urine, or cerebrospinal fluid are essential for rapid diagnosis of cryptococcosis. Commercially available latex agglutination assays show sensitivity ranging from 83–97% and specificity from 93–100%.[223] More recently, a simpler lateral flow immunoassay (Immuno-Mycologics) has been introduced, which shows pooled sensitivity and specificity of 98% and 98%, respectively, on serum and sensitivity of 85% on urine.[224] Cryptococcal antigen may also be detectable in pleural fluid and BAL fluid of patients with cryptococcal pneumonia.[225,226] Serial measurement of serum antigen titers over time is not useful for management of patients with pulmonary cryptococcosis.[227] Cryptococcal antigen may be falsely positive in patients infected with *Trichosporon* sp[228] or due to the presence of rheumatoid factor or heterophile antibodies (i.e., antibodies produced to poorly defined antigens with weak affinity and multispecific activities) and falsely negative due to the prozone effect (antigen excess), localized infection, infection with a poorly encapsulated strain, or low organism burden.[229]

Two commercial *H. capsulatum* antigen assays include MiraVista Diagnostics *Histoplasma* Quantitative EIA and IMMY ALPHA *Histoplasma* Antigen EIA. These tests have variable accuracies for diagnosis of histoplasmosis.[230,231] The polysaccharide antigen of *H. capsulatum* can be detected in urine in approximately 90% of patients with disseminated disease and in 75% with diffuse acute pulmonary histoplasmosis.[128,129] A meta-analysis on the performance of *Histoplasma* antigen showed pooled sensitivity and specificity of 79% and 99%, respectively, in urine and 82% and 97%, respectively, in serum.[232] Urinary *Histoplasma* antigen levels persist during ongoing active infection, become undetectable with successful therapy, and rise with relapse of infection. The specificity of the *Histoplasma* antigen assay was 99% in patients with nonfungal infections and in healthy controls[230]; however, the assay is known to yield positive results in patients with disseminated infections caused by *Blastomyces dermatitidis, C. immitis, Paracoccidioides brasiliensis, Aspergillus,* and *Penicillium marneffei.*[233,234] Cross reactivity of the assay has not been observed in patients with invasive candidiasis, cryptococcosis, or other opportunistic systemic mycoses.[233]

At least one commercial laboratory offers antigen tests for the diagnosis of coccidioidomycosis and blastomycosis, but both tests exhibit significant cross reaction with *H. capsulatum.*[235] The *Coccidioides* antigen test was 93% sensitive and 100% specific on cerebrospinal fluid in patients with coccidiodal meningitis. The performance is not characterized for pulmonary infection.

Aspergillus galactomannan is a major cell wall component of the fungus, and detection of this antigen has been studied in many different clinical situations. Galactomannan detected in serum by enzyme immunoassay can aid in the early diagnosis of invasive pulmonary aspergillosis, with pooled diagnostic sensitivity of 71% and specificity of 89% and positive predictive value of 25–62% for proven invasive aspergillosis.[236] The reported sensitivity and specificity ranges are 40–100% and 56–100%, respectively, in various patient groups.[18,162,237–239] The Platelia *Aspergillus* test (Bio-Rad Laboratories), a commercially available assay that detects galactomannan from *A. fumigatus, A. flavus, A. niger, A. versicolor,* and *A. terres,* has been shown to yield positive results at an early stage of infection, with positive and negative predictive values of greater than 90% in high-risk patients who were tested biweekly.[237] A modeling study showed an increase in mortality of 25% per galactomannan unit increase and 22% decrease per unit decline per week.[240] However, this assay may cross-react with *Histoplasma, P. brasiliensis, Penicillium, Paecilomyces, Alternaria,* and *Cryptococcus,*[239,241,242] and false-positive galactomannan antigen assay results were observed in earlier formulations in patients receiving certain foods or intravenous piperacillin-tazobactam, amoxicillin, or ticarcillin.[242–245] Cross reactivity with *Listeria monocytogenes* has also been reported.[246] Meta-analysis of BAL fluid specimens in patients with proven or probable invasive aspergillosis showed an overall sensitivity of 87% and specificity of 89%.[247] Of note, the Plasma-Lyte (Baxter International) solution commonly used to perform BAL has been found to yield false-positive results with the Platelia *Aspergillus* test.[248] Assays for galactomannan show promise, but their utility is currently greater in hematopoietic stem cell transplant patients than in other groups (see Chapter 57).

Another fungal antigen used for the diagnosis of invasive fungal infection is (1→3)-β-D-glucan, which is a component of the outer cell wall of saprophytic and pathogenic fungi except Zygomycetes (*Mucor* and *Rhizopus* sp) and *Cryptococcus* sp.[237,249] This antigen has been detected in serum or other body fluids of patients with invasive aspergillosis, invasive candidiasis, and infections caused by *Fusarium, Acremonium, Trichosporum, Scedosporium,*

Saccharomyces, and *P. jirovecii*.[164,250,251] A meta-analysis for diagnosis of invasive fungal infection showed a pooled sensitivity of 77% and specificity of 85%.[252] Similar performance was reported in a more recent meta-analysis.[253] Use of different assay cutoff values may result in differences in sensitivity and specificity among the various commercially available assays for detecting this antigen.[249,253,254] For the diagnosis of *Pneumocystis* pneumonia, a meta-analysis showed pooled sensitivity and specificity of 95% and 86.3%, respectively. In HIV-positive patients the sensitivity of the (1→3)-β-D-glucan assay was 92% and specificity was 65%.[255] In *Pneumocystis* pneumonia, β-D-glucan levels do not correlate with organism burden, severity of illness, or response to therapy.[255] Cross reactivity of β-D-glucan assays has been reported with the use of cotton gauzes, swabs, packs, pads, or sponges for wound care or surgery; cellulose filters in hemodialysis patients; and various antimicrobial agents, including piperacillin-tazobactam.[249,256]

Antigen tests are commonly used for the rapid diagnosis of influenza A and B, although CLIA-waived rapid NAT tests (discussed earlier) have begun to replace antigen testing in outpatient and emergency room settings. Rapid antigen tests for influenza demonstrate poor to moderate sensitivity, depending on the particular assay and the circulating strain. Meta-analysis of conventional influenza rapid antigen tests, typically lateral flow immunoassays with visual detection of a colloidal gold reporter, revealed pooled sensitivities of 65% for influenza A and 52% for influenza B, with a combined pooled specificity of 98%. In a subsequent meta-analysis more recently developed digital antigen immunoassays, such as the Quidel Sofia and BD Veritor (Becton Dickinson) systems that use lateral flow immunoassay readers, were shown to have pooled sensitivities of 80% for influenza A and 77% for influenza B, with combined pooled specificity greater than 98%.[213] In the same meta-analysis, conventional rapid antigen immunoassays showed pooled sensitivities of 54% for influenza A and 53% for influenza B, with similarly high pooled specificity. Higher pooled sensitivity of digital antigen immunoassays compared with conventional rapid influenza antigen tests has also been observed in an additional meta-analysis.[257] Due to the overall limited sensitivity of antigen testing, the CDC recommends that patients presenting with a syndrome consistent with influenza and who have a negative rapid antigen test should receive a confirmatory NAT or be treated as if they have influenza. Influenza rapid antigen tests have been reclassified by the FDA to meet minimum performance standards.[258] Rapid antigen tests for RSV are also available and may similarly aid in patient triage, infection control, antibiotic management, and the administration of RSV passive immunization (palivizumab), particularly in high-risk pediatric patients. Meta-analysis of RSV rapid antigen tests that included digital immunoassays with automated readers revealed a pooled sensitivity of 80% and pooled specificity of 97%.

SEROLOGIC TESTING AND INTERFERON-γ RELEASE ASSAYS

Apart from assays that detect pathogens or their products, the cause of LRT infections can be suggested by detection and quantitation of humoral (e.g., antibody) responses to pathogens. In addition, *latent TB infection* (LTBI) can be diagnosed by detection of cellular immune responses to *M. tuberculosis* antigens, such as the *interferon-γ release assays* (IGRAs). Serologic testing is used commonly to identify infections due to pathogens that are difficult to detect directly by other conventional methods, to evaluate the course of an infection, and to determine the nature of the infection (primary infection vs. reinfection, acute vs. chronic infection). Serologic testing and IGRAs are less sensitive in patients with compromised immune systems and therefore cannot be used to rule out infection.[259–261] When possible, microbiologic culture and NATs on respiratory secretions or lung tissue should be performed to detect and confirm the presence of pathogens in immunosuppressed patients who may not be able to mount antibody or cell-mediated immune responses (see Chapter 42).

The serologic methods commonly used in diagnostic laboratories include enzyme immunoassay, immunoprecipitation, *immunodiffusion* (ID), *complement fixation* (CF), immunoblotting (including Western blot), agglutination, hemagglutination inhibition, and indirect immunofluorescence assay. Serologic results are often expressed as a titer, which is the inverse of the greatest dilution, or lowest concentration of a patient's serum that retains measurable specific antibody-antigen reactivity (e.g., dilution of 1:16 = titer of 16). A fourfold or greater rise in antibody titer between acute and convalescent sera is usually required for diagnosis. An elevated pathogen-specific *immunoglobulin* (Ig)M antibody titer in a single serum sample suggests recent infection, and a falling titer provides further support for the etiologic significance of this organism. However, false-positive IgM antibody tests are not rare. Thus serologic testing of pathogen-specific IgG antibody in acute and convalescent sera remains the accepted approach to establish a specific microbial cause of the infection.[262]

Various commercial assays are available for detection of specific IgM and/or IgG antibodies to respiratory tract pathogens.[263] These assays are useful for supporting or confirming the diagnosis of bacterial infections caused by *C. pneumoniae, Legionella* sp, *F. tularensis, Y. pestis, C. trachomatis, C. pneumoniae, C. psittaci,* and *Coxiella burnetii.* Although antibody testing is commonly used for the detection of infection with *M. pneumoniae*, it is not possible to distinguish between infection and asymptomatic colonization with this organism.[11] The diagnosis of *C. pneumoniae* infection can also be a problem. In some additional instances, such as infection with *M. tuberculosis,* commercial serologic tests have been shown to be inconsistent and imprecise, which is the basis of WHO policy statement advising against use of existing serologic tests in TB.[264]

M. pneumoniae infection is often diagnosed by the presence of specific antibodies in serum.[265] Cold agglutinins, detected by agglutination of type O Rh-negative red blood cells at 4°C, are present in the sera of approximately 50% of patients with *M. pneumoniae* infection, and levels decline to baseline within 6 weeks after acute infection.[266] However, cold agglutinins are nonspecific. Antibodies to a chloroform-methanol glycolipid extract of *M. pneumoniae* are detected by a CF test in greater than 85% of culture-positive patients; a single elevated titer

of greater than 80 or a greater than fourfold rise in titer between acute and convalescent sera is required to establish a diagnosis. Enzyme immunoassays to detect IgM and IgA antibodies that specifically recognize *M. pneumoniae* membrane proteins have been developed with improved sensitivity and specificity over the CF assay.[265] Specific IgM antibodies appear during the first week of illness and reach peak titers during the third week. However, the IgM antibodies to *M. pneumoniae* are not consistently produced in adults because of prior sensitization so that a negative IgM result does not rule out acute *M. pneumoniae* infection, particularly in older adults. False-positive IgM in pediatric patients also has to be considered.[267] Detection of specific IgA antibodies in the serum has been shown by one group to be a reliable approach for diagnosis because these antibodies are also produced early in the course of disease and more reliably present in the infected individuals regardless of age.[265] Others, however, found them of little value.[11]

Serologic testing plays an important role in the diagnosis of fungal respiratory tract infections due to *C. immitis* and *H. capsulatum*.[266] For *C. immitis* a diagnosis of infection can be based on detection of antibodies to antigens derived from the coccidioidal mycelia or spherules, although there may be cross reactivity with other yeasts and dimorphic fungi. Antibodies to *C. immitis* were conventionally detected by ID and CF. Enzyme immunoassays have been shown to be as sensitive and specific as ID and CF for detection of IgG antibodies.[268] A new immunoassay was shown to be 88% sensitive and 90% specific for active disease and was also more sensitive than ID and CF.[269] Complement-fixing IgG antibodies appear later and persist in relation to the severity of disease but decline with disease remission. Titers of 32 or higher suggest the possibility of disseminated infection.[270,271] The sensitivity of serologic testing drops 8–20% in immunocompromised hosts compared to immunocompetent patients.[272]

For *H. capsulatum,* serum antibodies are detected by CF using yeast and mycelial antigens and by an ID assay, which show increased titers in greater than 90% of patients with pulmonary histoplasmosis and approximately 80% with disseminated disease.[129] The CF test is more sensitive but less specific than the ID test for the diagnosis of subclinical and acute pulmonary histoplasmosis.[273] Antibodies become detectable first by CF at 2 to 6 weeks after *Histoplasma* infection and then by ID 2 to 4 weeks later. However, the ID test remains positive longer than the CF test after resolution of infection, becoming negative 2 to 5 years later. Antibody levels remain high in those with chronic pulmonary infection, progressive disseminated disease, or fibrosing mediastinitis. Commercially available serologic tests for blastomycosis exist but have limited accuracy and are of minimal value in patient care.[274]

Serologic testing is also useful for diagnosis of parasitic infections, especially *Paragonimus*, *T. gondii*, and *S. stercoralis*,[275,276] and for diagnosis of extraintestinal *E. histolytica* disease. Serologic testing plays an especially important role for screening prospective organ transplant recipients and other patients considered for immunosuppressive therapies.

Serologic testing plays a limited role as an aid to the diagnosis of respiratory viral infections. Although detection of recent respiratory virus infection, for example with influenza A, may be determined via seroconversion or a fourfold or greater rise in antibody titer in a convalescent relative to an acute serum sample, the requirement for two temporally distinct specimens makes serologic results unlikely to factor into clinical decision making.[277] In contrast, routine CMV serologic testing in transplant donors and recipients provides valuable information about the risk for subsequent CMV-related sequelae, including the development of respiratory disease.[278]

IGRAs are in vitro assays used to measure T cell responses to *M. tuberculosis*–specific antigens, such as *early secretory antigenic target-6* (ESAT-6) and *culture filtrate protein-10* (CFP-10).[279] Two FDA-approved commercial IGRAs are currently available: the *QuantiFERON-TB Gold Plus* assay (QFT-Plus; Qiagen) and the *T-SPOT.TB* assay (Oxford Immunotec). IGRAs were developed as an alternative to the *tuberculin skin test* (TST) for diagnosis of LTBI.[279] Compared to the TST, IGRAs have improved specificity for distinguishing between the responses due to *bacillus Calmette-Guérin* (BCG) vaccination and LTBI because the antigens used in IGRAs, ESAT-6 and CFP-10, are absent from all strains of BCG. Otherwise, the specificity of IGRA in BCG-unvaccinated individuals is 98–99% for QFT and 86–92% for T-SPOT.TB.[280,281] Also, compared to the TST, IGRAs offer logistical advantages because they do not depend on accurate intradermal injection, and patients do not have to return to a health facility for the result to be read.[279] However, like TSTs, IGRAs cannot distinguish between LTBI and active disease and are not able to predict which patients with positive results develop active TB.[282–284] The sensitivity of IGRAs in culture-positive active TB cases has ranged from 65–100%,[285,286] and the sensitivity in patients with LTBI who progressed to active TB ranged from 40–100%.[287] Both IGRAs and the TST have been shown to have similar sensitivity in adults in low- and middle-income countries.[288] The accuracy of IGRA testing appears to falter at the borderline levels of positivity due to random sources of variability.[289] Studies conducted in health care workers in low-incidence settings have shown highly variable IGRA results with serial testing. The rate of conversions (negative to positive result using the manufacturer- and CDC-recommended cutoff) ranged from 2–14%, and the rate of reversions (positive to negative result) ranged from 22–77%.[290,291] Those with borderline results around the assay cutoff are more likely to revert or convert. Standardizing QFT preanalytic and analytic steps, and including an indeterminate zone bordering the cutoff, has improved the prognosis of individuals with definite conversion.[292] IGRA results have not proven useful for monitoring response to TB treatment. In summary, IGRAs are most useful as an alternative to the TST, especially in subject populations with a high incidence of BCG vaccination (see also Chapter 42).

Acknowledgment

We thank former Stanford Pathology residents Natalia Isaza, Albert Tsai, and Lee Frederick Schroeder for contributing to this chapter.

Key Points

- Diagnostic testing should be ordered only if the result will alter treatment decisions.
- The clinician plays a critical role in preventing accidental laboratory exposure by notifying the microbiology laboratory when highly virulent and transmissible agents are suspected as the cause of disease.
- Syndromic order sets can improve the accuracy and efficiency of test selection and thus facilitate accurate diagnosis of infectious diseases.
- Lower respiratory tract secretions collected through the oropharynx are nearly always contaminated with resident microflora of the oral cavity, and therefore microscopy, culture, and nucleic acid test results must be interpreted in the context of other clinical evidence and diagnostic findings.
- Nucleic acid tests can facilitate rapid and accurate diagnosis of lower respiratory tract infections, especially those caused by viruses and pathogens that are difficult to culture.

Key Readings

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20 THORACIC RADIOLOGY: NONINVASIVE DIAGNOSTIC IMAGING

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KEY POINTS

An expanded version of this chapter (see italicized headings in the above outline) is available at ExpertConsult.com.

INTRODUCTION

Imaging plays a major role in the detection, diagnosis, and serial evaluation of thoracic disease. The appropriate use of imaging requires a basic understanding of the technical aspects of different imaging modalities, including the diagnostic accuracy and limitations of each technique. It is not the intent of this chapter to provide a complete description of the techniques involved or an encyclopedic catalogue of radiographic abnormalities of thoracic diseases; these issues are detailed in subsequent chapters dedicated to specific disorders. Rather, this chapter is intended to provide a general survey of the imaging methods available, their most common indications, and certain principles concerning their use.

Since the late 1990s, there have been remarkable advancements in the effectiveness of cross-sectional imaging techniques for the diagnosis of thoracic diseases, particularly with the development of multislice *computed tomography* (CT), as well as improvements in *magnetic resonance imaging* (MRI) and ultrasonography (see Chapters 23 and 24). In many instances, cross-sectional methods have supplanted radiography for the diagnosis of chest diseases. As with any imaging method, the decision to use cross-sectional imaging should be based on consideration of the patient's clinical problem and the results of other imaging and laboratory testing.

Chest radiography still plays a fundamental role in the diagnosis of thoracic disease. Chest radiography is usually the initial imaging procedure performed when chest disease is suspected. Despite the proliferation of other imaging methods, chest radiography remains one of the most frequently performed imaging examinations in the United States.

The thorax is difficult to image because of large regional differences in tissue density and thickness. For example, with standard radiography, the number of x-rays passing through the lungs is more than 100 times greater than the number of x-rays penetrating the mediastinum.[1] The dynamic contrast range of conventional film-screen radiography is insufficient to demonstrate this range of x-ray transmission properly; with standard radiographic techniques, the use of exposure high enough to display the mediastinum and the subdiaphragmatic regions usually results in overexposure of the lungs (Fig. 20.1A). Conversely, an exposure designed to provide the best visualization of the pulmonary parenchyma (see Fig. 20.1B) is normally too underexposed to visualize mediastinal anatomy. One of the advantages of digital imaging is that displayed contrast and brightness are largely independent of the *peak kilovoltage* (kVp) and milliamperage values used to obtain the examination; both contrast and brightness can be manually adjusted by the user after the image has been obtained.[2] Furthermore, the dynamic contrast range (i.e., latitude) of digital radiographic techniques exceeds that of film-screen methods by a factor of 10 or more.[2]

Meticulous attention to technique is essential. Regardless of the method of recording the image, whether through standard film-screen radiography, image intensification, or digital recording, poor quality control leads to degradation of diagnostic information. Unfortunately, many technically inadequate radiographs are produced, leading either to

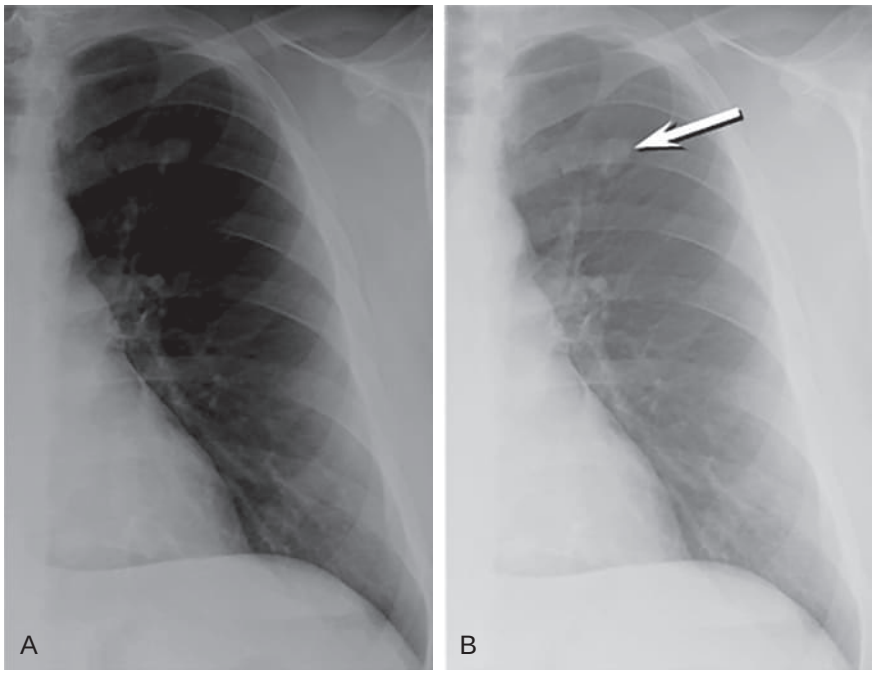

Figure 20.1 Overexposed versus properly exposed chest radiograph. (A) Frontal chest radiograph performed with overexposed technique shows relatively good visualization of the mediastinum, but the lungs are abnormally "black," which obscures fine detail. (B) Repeat frontal chest radiograph performed with proper exposure shows slightly reduced ability to "see through" the mediastinum compared with the overexposed chest radiograph, but lung parenchymal detail is clearly superior in the properly exposed image. The proper exposure allows visualization of a left upper lobe nodule *(arrow)*. (Courtesy Michael B. Gotway, MD.)

repeat studies with additional patient radiation exposure or to interpretation of the poor images, increasing the chance of diagnostic errors.

Indications for the use of chest radiography are protean and include the assessment of both acute (e.g., pneumonia) and chronic (e.g., COPD) lung diseases; assessment of dyspnea or other respiratory symptoms; evaluation of treatment success for patients with acute lung disease; follow-up of patients with a known chronic lung disease; monitoring of patients in *intensive care units* (ICUs); confirmation of life-support device placement, such as central *intravenous* (IV) lines and endotracheal tubes; diagnosis of pleural effusion; screening for asymptomatic diseases in patients at risk; monitoring patients with industrial exposure; preoperative evaluation of surgical patients; and as the initial imaging study in patients with known or suspected lung cancer or other tumors, vascular abnormalities, or hemoptysis. However, abnormal radiographic findings can be quite subtle and, in many circumstances, the sensitivity and specificity of chest radiography are limited. In such situations, other imaging modalities, especially chest CT, are performed to investigate abnormalities visible on radiographs or to evaluate patients considered high risk for a particular condition but with equivocal chest radiographic results.

The utility of chest radiography has been studied in a number of clinical settings, and the appropriate criteria for its use have been determined by the *American College of Radiology* (ACR; https://www.acr.org/Clinical-Resources/ACR-Appropriateness-Criteria). A detailed analysis of the diagnostic accuracy of chest radiography in all situations is beyond the scope of this chapter; however, for illustrative purposes, their utility and limitations in several specific clinical settings are reviewed.

A discussion of the major technical aspects that may affect image quality is available at ExpertConsult.com.

CHEST RADIOGRAPHY: TECHNIQUES

RADIOGRAPHIC VIEWS AND TECHNIQUES

Routine Examination

A routine chest radiographic examination in an ambulatory patient usually consists of *posteroanterior* (PA) and left lateral projections. However, the utility of routine lateral radiographs has been questioned. After analyzing more than 10,000 radiographic chest examinations obtained routinely in a hospital-based population, Sagel and associates[20] concluded that the lateral radiograph could be safely eliminated in the routine examination of patients 20 to 39 years of age. Conversely, they and others[21] have concluded that the lateral radiograph should be obtained in patients with suspected chest disease and in screening examinations of patients 40 years of age or older (Fig. 20.2).

Expiratory Views

Conventional radiographs are made at total lung capacity (i.e., full inspiration), thereby permitting the greatest volume of lung to be evaluated for possible pathology and providing the most contrast between intrapulmonary

MAJOR FACTORS AFFECTING IMAGE QUALITY IN STANDARD FILM-SCREEN RADIOGRAPHY AND DIGITAL RADIOGRAPHY

The goal of chest radiography is to maximize diagnostic information through optimal image quality while limiting radiation exposure. Although there are minor disagreements among experts, virtually all definitions of image quality include three general factors: radiographic contrast, spatial resolution, and image noise.[1,3] These are interrelated, and the ultimate quality of the radiograph is determined by the most limited of the factors involved in its production.

With film-screen radiography, an x-ray photon is absorbed in a screen containing a photostimulable coating, resulting in the production of multiple light photons that, in turn, expose the actual film. This method differs from that used by digital radiographic techniques for image creation[2]; the differences between film-screen and digital radiographic techniques are reviewed later. Nevertheless, the following discussion of technical factors impacting imaging quality applies to both methods.

Radiographic Contrast

Radiographic contrast, or *contrast resolution,* may be defined as the magnitude of signal difference between the imaged object and its surroundings in the displayed image.[2] It is principally determined by components of the system, chiefly the energy of the x-rays, and the degree to which secondary radiation (scatter) is eliminated. A film-screen combination possessing an intermediate or wide gray scale is preferable to one producing extreme contrast[1,3]; such wide dynamic range, or "latitude," is intrinsic to digital radiographic production methods and, as will be discussed, is one of the advantages digital imaging enjoys over older film-screen techniques. Although very "black-and-white" radiographs appear to demonstrate excellent detail, differentiation of structures differing slightly in density, such as the pulmonary vessels and the background lung, is better achieved with a wide-latitude film-screen combination or digital radiography. Wide-latitude film-screen combinations or digital radiography also better display the wide range of densities present in the thorax, that is, more "shades of gray."[1]

When an object is radiographed, some photons are absorbed and some are scattered, whereas others are transmitted unaffected through the object (eFig. 20.1A). If the object is close to the detector, exposure from scattered radiation degrades image contrast and detail.[1,3] Because production of scatter radiation varies with the volume of tissue being imaged, the use of devices referred to as "collimators" (lead or tungsten plates), to restrict the beam size to the area being studied, reduces scatter radiation. The further addition of filtration to the x-ray tube in the area of the collimator prevents low-energy (low-kiloelectron volt) photons from reaching the patient. These low-kiloelectron volt x-rays cannot penetrate through the body and only contribute to skin dose without affecting image creation; filtering them out reduces the radiation absorbed by the patient without compromising diagnostic information.

Scattered radiation can also be removed by placing an antiscatter grid between the patient and the x-ray cassette with film-screen systems (eFig. 20.2A, see eFig. 20.1B)[1,3–5] and digital systems.[2] Such grids permit the passage of the parallel primary x-rays to expose the detector while absorbing x-rays scattered at an angle to the primary beam. The grid also absorbs some primary x-rays, making it necessary to increase the exposure technique to maintain the correct image density. Care must be taken to ensure that the grid is of the proper type and is properly aligned to the x-ray beam. Off-center placement, angulation, or the use of a grid focused at the wrong distance may affect the symmetry of radiograph exposure or even render it uninterpretable. Scatter radiation may also be reduced by increasing the distance between the detector and the patient, a process referred to as "creating an air gap" (see eFigs. 20.1C and 20.2B). Some digital imaging systems, such as scanned-slot digital radiography detectors, have intrinsic scatter rejection capability and therefore do not require the use of a grid.[2]

Spatial Resolution

Spatial resolution reflects the ability of an imaging system to resolve two adjacent structures as distinctly separate.[2] Spatial resolution of film-screen combinations is about 10 to 12 line pairs/mm and is primarily determined by the thickness of the screen used (thicker screens are associated with poorer spatial resolution).[2] Other technical factors are responsible for spatial resolution in digital radiography systems.[2] A number of additional factors may contribute to the reduction of the final resolution achieved on a chest radiograph produced by either film-screen or digital techniques. The use of large focal spots (the point on the anode from which x-rays are emitted), particularly in thick body parts such as the thorax, degrades spatial resolution by producing "edge unsharpness" or blur due to penumbra effects. Conversely, the limited heat capacity of a very small focal spot requires a long x-ray exposure, increasing time for the patient to move, which degrades spatial resolution and causes edge unsharpness as well. A compromise in choice of x-ray focal spot size of 1 mm or less is recommended. Lengthening exposure duration degrades spatial resolution due to insufficient power of the x-ray generator or deficiency of the heat capacity of the tube as well as to increased time for motion. Ideally, exposure duration should not exceed 25 msec and for frontal projections should be considerably less. A tube-detector distance of at least 6 feet (1.8 m) is usually used to reduce magnification and image blurring (see eFig. 20.2).

Noise

All imaging systems are limited by noise, or "quantum mottle,"[3] which, in radiography, may be defined as random fluctuations within the image that do not correspond to variations in x-ray attenuation in the imaged object.[2] Noise is primarily determined by the number of x-ray photons used to produce the image, although factors intrinsic to the imaging system also contribute to image noise.[2] The fewer the number of photons, the noisier the image will be. With a given film-screen or digital system, attempts to increase speed generally result in increased noise, which degrades resolution.

X-ray screens have been developed that use rare earth phosphors; these have the property of converting x-ray

photons to light more efficiently. When used with properly matched films, these rare earth screens double or triple the speed at which a properly exposed radiograph can be made. They do not increase the noise of the system significantly and enable reduction of radiation exposure to the patient by one-half or more.

American College of Radiology Standards

The ACR standards for performing adult chest radiography[6] specify the use of at least a 72-inch tube-film distance, a tube focal spot not to exceed 2 mm (0.6–1.2 mm recommended), rectangular collimation and beam filtration, a high-kVp technique (120–150 kVp) appropriate to the characteristics of the film-screen combination, a film-screen speed of at least 200, an antiscatter technique (grid or air gap) equivalent to at least a 10:1 grid (preferably 12:1), and a maximum exposure time of 40 msec. The ACR also specifies a maximum mean skin entrance radiation dose (0.3 mGy/exposure). Guidelines for the production of digital chest radiographs have been published.[2]

Portable Radiography

The proliferation of ICUs and the increased use of patient monitoring for life-support devices have significantly increased the number of portable radiographs obtained.[1,7,8] As indicated earlier, these examinations are necessary to determine whether catheters, endotracheal tubes, intra-aortic balloons, and various other devices have been correctly placed (eFigs. 20.3 through 20.7).[9,10] Portable radiographs are also essential for assessing responses to therapy and surveying for the presence of new thoracic disease.

Even under ideal circumstances, the quality of the radiographs obtained with portable techniques does not approach the standard of those made in the radiology department (eFig. 20.8). Portable examinations are generally made at a focal spot–detector distance of less than 72 inches, resulting in penumbral blurring, edge unsharpness, and degradation of spatial resolution.[3] The routine use of the *anteroposterior* (AP) projection, with the image detector against the patient's back, increases the distance of the heart and other anterior structures from the detector, resulting in magnification of the cardiac silhouette. When possible, the radiograph should be obtained with the patient sitting upright, but this is frequently not feasible for ill patients tethered to multiple life-support devices. Images obtained with the patient supine or even semi-upright compromise the detection of pleural effusions and pneumothorax as well as the assessment of the gravitational distribution of pulmonary blood flow based on vessel size and lung zone opacification.

Mobile x-ray generators used for portable radiography are somewhat limited compared to their fixed unit counterparts. Exposure duration is difficult to control and is relatively long, and motion blurring degrades the image. Because of these limitations and the frequent need for immediate viewing of chest radiographs, storage phosphor–computed digital units are widely used for ICU radiography (see later discussion).[10] The storage plate phosphor's ability to provide relatively even density for overexposed and underexposed films and its ability to adjust the images digitally to visualize mediastinal or pulmonary parenchymal areas are well suited for ICU portable radiography.

The ACR standards for performance of portable chest radiographs are relatively forgiving.[6,11] A tube-film distance of 40 to 72 inches is recommended, the latter preferred. From 70 to 100 kVp is recommended if a grid is not used, whereas more than 100 kVp may be used in conjunction with a grid. Exposure times should be as short as feasible to reduce motion artifacts.

Digital Radiographic Techniques: Computed Radiography and Direct Radiography

The development of reusable radiation detectors, along with advances in electronics and computer technology, enabled the development of new digital radiographic imaging techniques: *computed radiography* (CR) and *direct radiography* (DR).[1,12] These systems are fundamentally different from film-screen radiography in that image detection can be completely separated from the method of image display[2] and, because the images are digital in format, they can be subjected to significant postprocessing to improve diagnostic information.[2] Also, digital image receptors have a much wider dynamic range, or latitude, compared with standard film-screen combinations (10,000:1 rather than 100:1), and their response to radiation is linear over this entire range.[1,2] Within these large limits, image contrast is independent of exposure. Furthermore, digital images can be displayed, transmitted, and stored electronically,[2,3] and digital systems allow faster patient throughput, increased dose efficiency, and reduced x-ray exposure compared with film-screen techniques.[2,12] These advantages have allowed digital radiography to supplant film-screen radiography in many radiology facilities.[12] Indeed, the Consolidated Appropriations Act of 2016 imposes a Medicare reimbursement penalty for claims for imaging examinations performed with traditional film-screen techniques.

Computed Radiography Storage Phosphor Systems

CR is a commonly used system of digital radiographic imaging that uses plates exposed by conventional radiographic equipment and can be used like any x-ray cassette.[1,3] The reusable plates are coated with a photostimulatable phosphor (a form of scintillator) that absorbs energy and retains a latent image when exposed to x-rays. The stored energy of the latent image is released as light when the plate is scanned by a laser in an image plate reader.[2] The light produced is measured and digitized, yielding an image that can be subjected to contrast and spatial frequency enhancement and can be stored on magnetic or optical disks, viewed on monitors, or printed on film with a laser printer (eFig 20.9). The imaging plates are erased by exposure to light and may be reused almost immediately. Note that the term CR is relatively generic and may refer to a number of systems that vary considerably in performance, depending on the detector type and read-out system used. Although initial versions of CR were characterized by relatively high noise and limited dose-reduction capability compared with film-screen techniques, relatively recent improvements in detector material and read-out technology have led to marked improvements in dose efficiency that now rival flat-panel detector systems and greatly exceed sensitivity of traditional film-screen techniques. Nevertheless, CR techniques are being replaced with true digital acquisition

systems that use solid-state detectors. In fact, the aforementioned Consolidated Appropriations Act of 2016 also imposes penalties for claims for imaging examinations performed with CR techniques and the traditional film-screen methods noted previously.

Direct Radiography

DR refers to a system whereby the transmitted x-ray signal is *immediately read* by a detector system after exposure; the image capture and read-out processes are combined. Approaches to DR imaging may be broadly categorized as cassette based, with the associated workflow more or less analogous to film-screen techniques, or "cassette-less," whereby by the x-ray signal is acquired by a detector system without the need for a cassette, and the x-ray signal is transformed into an image at a local workstation for review.[4] Methods for processing the DR x-ray signal vary and may be categorized as *direct*, in which the x-ray signal is directly transformed by the detector into an electrical charge, or *indirect*, which uses an intermediary step, commonly the conversion of the x-ray signal into light by a scintillator, which then is transformed into an electrical charge for digital storage.[4] Ultimately, all DR detector systems take an input signal, either x-ray energy or light, and convert it to an output signal, usually in the form of electrons, with the amount of charge associated with the electrons proportional to the number of x-rays absorbed by the detector elements.[4] This charge is digitally stored and can be converted to an image at a workstation for review. A number of approaches for reading the output signal are available, using either direct or indirect DR techniques, each associated with particular advantages and disadvantages.

The resolution of digital images depends on the matrix size used. Spatial resolution may be less than that of film-screen combinations (2.5 to 5 line pairs/mm), depending on the size and type of detector used to capture the image,[1] but with detectors using larger matrix sizes, spatial resolution of some digital systems exceeds film-screen chest radiography. The unit can be set to perform automatic processing by preprogramming parameters for certain examinations or may be postprocessed manually by the radiologist to enhance various specific image features.[13] The contrast scale can be altered, and the optical density of the entire image, or of various areas, can be changed. Edge enhancement can be obtained by amplifying high frequencies to visualize minute pulmonary detail. For the thorax, the automatic processing can be preset to produce a pair of images: one resembling a conventional film-screen radiograph and the other exhibiting varying amounts of edge enhancement (eFig. 20.10).

An obvious advantage of digital imaging systems is that the images can be immediately transmitted electronically and viewed at a workstation in the emergency department, ICU, operating room, or other area where online viewing is required.[1,3] In fact, imaging data acquired with some digital systems may be wirelessly transmitted from the acquisition point, commonly the bedside, to the imaging department, which is a major benefit for the radiologic technologist's workflow, particularly with regard to mobile chest radiography performed in ICUs. Because the images are stored electronically, they may be recalled for comparison with subsequent studies and can be printed for conventional display at any time. High-resolution display units (2000-line) allow display of images with excellent spatial resolution. Other advantages of digital imaging include improved dose efficiency compared with film-screen radiography; enhanced workflow with increased patient throughput; imaging processing options, such as digital subtraction radiography (electronic removal of opaque structures, particularly bones, from the image) and computer-aided diagnostic capabilities; and digital tomosynthesis (a form of limited-angle tomography that uses a flat-panel detector coupled with a conventional x-ray tube that moves along a predefined path, producing an arbitrary number of section images of a patient. This technique is most commonly applied to breast imaging but has been used for chest imaging. Digital radiographic flat-panel detector systems have been shown to produce image quality equivalent to, but at a lower exposure level than, film-screen combinations.

Clinical Efficacy

A large number of studies have compared digital imaging systems with conventional film-screen radiographs in both measured physical performance and interpretive accuracy. It is generally agreed that the denser portions of the thorax and the lung in front of or behind these dense areas are significantly better visualized with digital systems. Early in the development of digital imaging techniques, limited visualization of fine lung detail, line shadows, pneumothoraces, and *interstitial lung disease* (ILD) had been noted,[14–18] but subsequent work[19] has shown that digital flat-panel detector systems are equivalent or even superior to conventional film-screen systems for clinical chest imaging in practice. An important consideration is that digital recording systems have a very wide exposure latitude, and adequate images can be obtained from a wide range of exposures, reducing the need for repeat imaging.[4]

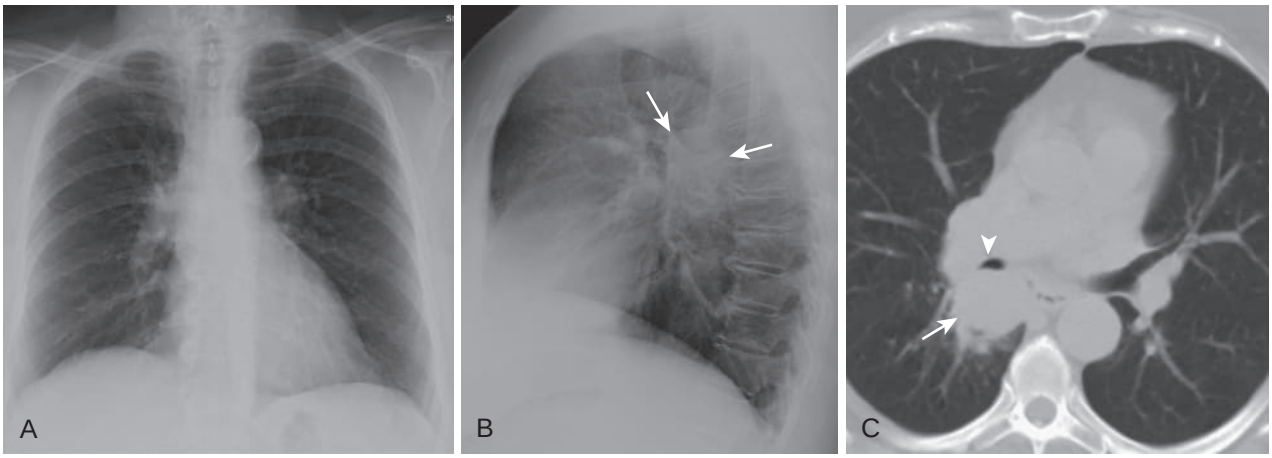

Figure 20.2 The utility of the lateral radiograph. (A) The posteroanterior radiograph shows no specific abnormalities. (B) The lateral radiograph identifies a mass (*arrows*) projected over the hilum. (C) Axial chest computed tomography confirms the presence of a mass (*arrow*) in the right lower lobe posterior to the bronchus intermedius (*arrowhead*). The lesion was found to represent bronchogenic carcinoma. (Courtesy Michael B. Gotway, MD.)

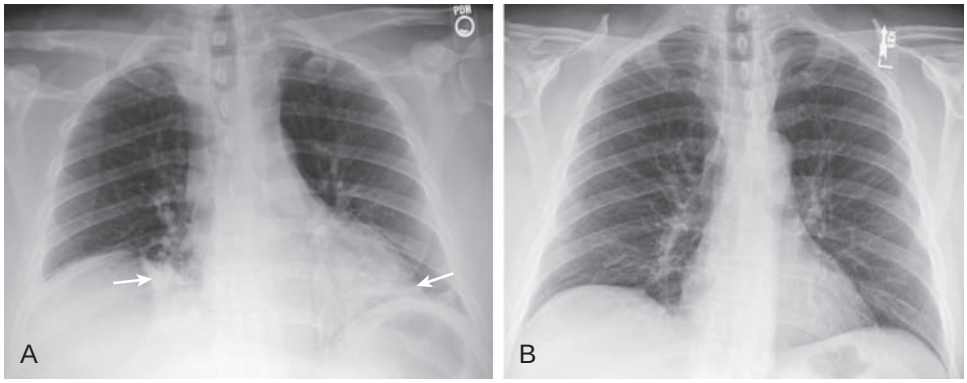

Figure 20.3 Comparison of radiographic appearances of thorax between expiratory and inspiratory radiographic techniques. (A) Frontal chest radiograph performed with expiratory technique shows basal opacities (*arrows*) bilaterally. The mediastinum is wide, and the heart size is difficult to assess. (B) Repeat frontal chest radiograph performed at full inspiratory volume made shortly after (A) now shows clearing of the basal opacities; the heart size is clearly normal, and the mediastinum now shows normal width. (Courtesy Michael B. Gotway, MD.)

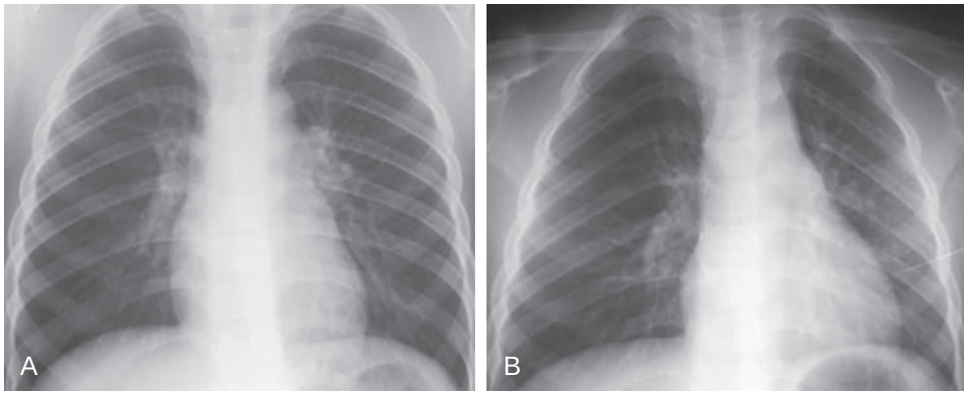

Figure 20.4 Unilateral hyperlucent lung in an 8-year-old boy with a foreign body in the right main-stem bronchus. (A) The inspiration radiograph shows mild hyperlucency of the right lung. (B) The expiration film shows that the right hemidiaphragm remains fixed in a low position, the right lung remains lucent, and the mediastinum is shifted to the left (air trapping). A foreign body was removed. (Courtesy Michael B. Gotway, MD.)

air and normal and abnormal intrathoracic structures (Fig. 20.3). However, localized or generalized air trapping in the lung or pleural space is more readily, and occasionally exclusively, detected on a radiograph made during expiration. The normal lung diminishes in volume and increases in density with expiration. Areas of air trapping retain their lucency and volume regardless of the phase of respiration. With unilateral or localized air trapping, mediastinal shift (Fig. 20.4) and failure of normal elevation of the hemidiaphragm on the affected side are frequently apparent only on expiration. Small pneumothoraces, difficult to visualize and frequently

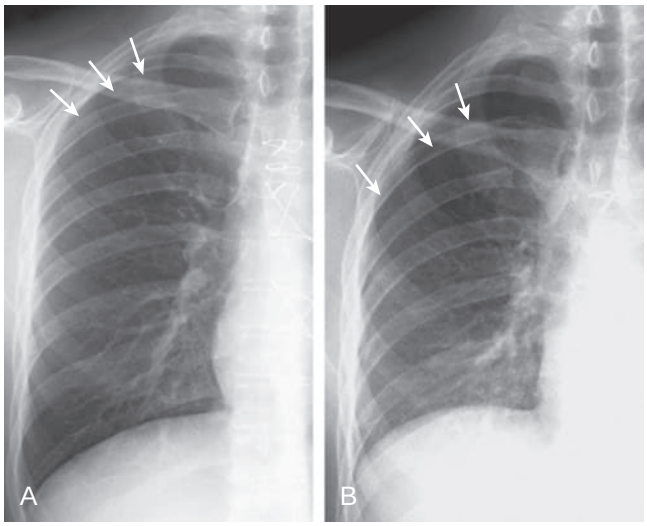

Figure 20.5 Inspiration and expiration chest radiography of pneumothorax. (A) On the inspiratory image, the right pneumothorax is difficult to visualize but is faintly seen in the right upper thorax (*arrows*). (B) On the expiratory image, the right pneumothorax (*arrows*) is outlined against denser lung and appears larger than on the inspiration study. (Courtesy Michael B. Gotway, MD.)



Figure 20.6 Unilateral hyperlucent lung simulating air trapping. Frontal chest radiograph shows lucency throughout the left thorax compared with the right, simulating air trapping (compare with Fig. 20.4B). Note, however, that the left thorax shows neither abnormally increased (unlike Fig. 20.4B) nor decreased lung volume. The left axillary surgical clips are a clue to the cause of left lung hyperlucency: left mastectomy for previous breast malignancy. The removal of left chest soft tissue creates less tissue density along the path of travel of the x-ray photons through the patient's left side relative to the right, resulting in relative lucency of the left thorax compared with the right. (Courtesy Michael B. Gotway, MD.)

overlooked on inspiratory radiographs, appear larger and more apparent on the expiratory study. As the thorax and underlying lung diminish in volume, the lung becomes denser, whereas the pneumothorax remains essentially unchanged in size and attenuation, thus occupying a greater proportion of the deflated hemithorax and outlined more clearly by the adjacent higher-attenuation pulmonary parenchyma (Fig. 20.5).

Localized or unilateral lucency on the radiograph may be seen without air trapping on the expiratory study. Among these are technical causes, such as patient rotation (eFig. 20.11), miscentered x-ray beam or grid, or the "anode heel" effect (i.e., an artifact of asymmetrical transmission of x-rays by the anode of the x-ray tube). Other causes of lucency without air trapping are chest wall abnormalities, either congenital or postsurgical (Fig. 20.6); areas of atelectasis with compensatory overexpansion of other portions of the lung; and primary vascular disease, such as pulmonary embolus (see eFig. 81.9). None of these causes of pulmonary lucency will show trapped air on the expiratory radiograph.

Expanded discussions of decubitus, lordotic and oblique views, fluoroscopy, bronchography, pulmonary angiography, aortography, ultrasonography, computed tomography (principles, techniques, protocols and indications) and magnetic resonance imaging (principles, techniques) are available at ExpertConsult.com.

MEDICAL IMAGING AND RADIATION

The major drawback of the increasing use of CT is radiation exposure. In 1980–82, radiation from medical imaging accounted for approximately 18% of the per capita effective radiation dose in the United States, but this value increased to 54% by 2006, largely due to increased radiation doses resulting from CT scanning and, to a much lesser extent, nuclear medicine procedures. It was recently reported that CT represents about 17% of all radiologic procedures in the world but accounts for greater than 40% of the collective dose.[27] Given the continued increased use of CT since 2006, it is likely that these numbers are now even greater.[28]

Effective doses (scanner outputs) for CT are given in Table 20.1 and compared with nonmedical radiation exposures.

Additional material regarding radiation exposure from medical sources and on radiogenic cancer risk is available online at ExpertConsult.com.

Although conflicting interpretations are difficult to reconcile and data on both sides of the argument can be compelling, in practice, medical radiation should be used in amounts as low as reasonably achievable to answer relevant clinical questions and only in cases where other radiation-free imaging options will not suffice. Such decisions should provide an optimal approach to balancing the immediate need for diagnostic information with patient safety.

APPLICATIONS OF CONVENTIONAL CHEST RADIOGRAPHY

SCREENING AND "ROUTINE" CHEST RADIOGRAPHS

It is now generally agreed that screening chest radiographs are not indicated except in specific high-risk populations.[52] Estimates of iatrogenic disease caused by ionizing radiation from screening examinations, forecasts of possible genetic consequences, and financial concerns outweigh the medical value of such examinations. In 1973, the Department of Health, Education, and Welfare, in conjunction with the ACR and the American College of Chest Physicians, recommended the discontinuation of screening examinations. In 1985, recommendations of the ACR were more explicit:

Decubitus Views

Decubitus radiography is performed by placing the patient in the recumbent position, usually lying on one side, followed by the contralateral side. The x-ray exposure is made with a horizontal beam in either the AP or PA projection.

The technique is useful for determining the presence or absence of free fluid in the pleural space or parenchymal cavities, for estimating the size of effusions, and for diagnosing pneumothorax in patients who are unable to sit or stand. Free fluid gravitates to the dependent portion of the thorax, which in the decubitus patient lies against the lateral rib cage of the dependent hemithorax (eFig. 20.12) or the mediastinum of the contralateral side; pneumothorax behaves in the opposite fashion. In the typical AP supine chest radiograph, free fluid will layer posteriorly and manifest as an increase in density involving the entire hemithorax. Air within the pleural space will collect anteriorly and is often difficult to detect. The proper use of decubitus radiography will demonstrate the presence of free fluid, pneumothorax, or both (eFigs. 20.13 and 20.14). When a portable study must be performed with the patient in bed, it may be technically difficult to obtain high-quality radiographs of the dependent portion of the hemithorax due to the underlying bed, clothes, or other inconveniences. For this reason, bilateral decubitus studies may be obtained. Even in patients in whom PA and lateral erect radiographs can be performed, subpulmonic effusions may be difficult to detect, and no fluid meniscus may be visualized. Unless the fluid is completely loculated, a decubitus study will demonstrate its presence and size (see eFig. 20.14). As little as 20 mL of fluid can be seen in the decubitus position.

Lordotic Views

Radiographs made in the lordotic position can be of value in demonstrating lesions in the immediate subclavicular region or partially hidden by the clavicle (eFig. 20.15). This is particularly true if these lesions are located posteriorly. In the lordotic view, which is most frequently obtained in the AP projection, the clavicle, being an anterior structure, is projected above the lung apex, and the subclavicular lung regions are well visualized (see eFig. 20.15). The lordotic view may also be used to confirm middle lobe or lingular atelectasis: A lordotic view centered over the lower portion of the chest will project the atelectatic lobe or segment so that it directly faces the x-ray beam, and it will be easily visualized as a dense triangular shadow.

Oblique Views

On occasion, shallow oblique views are valuable in sorting out superimposed shadows and in visualizing pulmonary parenchymal opacities obscured by superimposition from the heart, mediastinum, or portions of the bony thorax (eFig. 20.16). In general, it is more rewarding to study these opacities with CT. Oblique views can also be helpful when attempting to localize the tip of a central venous catheter because the slight rotation helps move the catheter tip away from the spine, which can otherwise obscure the line tip.

FLUOROSCOPY

Fluoroscopy at one time was commonly used either as the primary method of radiologic examination of the chest or as an adjunct study to standard radiographs. Its use over the past several decades has diminished considerably. However, there remain a few situations in which fluoroscopy can provide information that is difficult to obtain by other means, such as for the detection of abnormalities of diaphragmatic motion that result from conditions affecting the phrenic nerve (Video 20.1). The major use of chest fluoroscopy in current medical practice is as a guide for interventional procedures, such as catheter angiography and needle or transbronchial biopsies.

BRONCHOGRAPHY

Contrast bronchography, formerly a fairly common thoracic examination, has been replaced by the performance of fiberoptic bronchoscopy or by imaging via either CT or *high-resolution CT* (HRCT) of the lungs. In patients with suspected bronchiectasis, HRCT and CT are as sensitive and are safer, more easily obtained, and much more pleasant to undergo than bronchography.

PULMONARY ANGIOGRAPHY (see Chapter 21)

Pulmonary angiography has traditionally been used primarily for the detection or exclusion of *pulmonary embolism* (PE) (Video 20.2, eFig. 20.17). Although it has been traditionally regarded as the gold standard for establishing the diagnosis of PE, it has limitations and tends to be underutilized. Other situations in which pulmonary angiography has been used include the diagnosis and embolization of pulmonary arteriovenous malformations (eFig. 20.18, see eFig. 21.14 and Chapter 88); pulmonary arterial foreign body retrieval; pulmonary vasculitis (eFig. 20.19, see Chapter 87); occasionally for the delineation of the anatomy of pulmonary vessels before lung surgery, such as for sequestration resection; and, more recently, as part of catheter-based therapy for PE (see Chapters 82 and 86). The study is performed by rapidly injecting IV contrast material through a catheter and imaging the lung while the contrast material traverses the arteries and veins. Most frequently, the catheter is inserted into the femoral vein percutaneously and then guided into the pulmonary artery under fluoroscopic control.

Angiograms may be done with the catheter in a main branch of the pulmonary artery or more selectively in distal vessels. The radiographic contrast material is injected at the rate of approximately 10 to 25 mL/sec, depending on the vessel size. The volume of contrast depends on the location of the catheter. Between 20 and 30 mL of contrast material is usually injected into the right or left main pulmonary artery using digital subtraction techniques. Selective injections in the more distal pulmonary arteries require smaller volumes. If the angiogram is performed for the detection or exclusion of PE after an abnormal but nondiagnostic perfusion scan, the location of the perfusion defect on the scan may act as a road map for the angiographer, and selective or superselective

injections proximal to the area of perfusion deficit may be performed.

Unless the angiogram is done using a balloon occlusion technique, serial recording is necessary. Imaging is usually carried out for several seconds after injection to permit visualization of the pulmonary veins, the left side of the heart, and the thoracic aorta.

It is frequently necessary to image in several different projections to confirm or exclude PE. Oblique or lateral projections may be desirable. If the angiographic suite contains biplane equipment, the number of necessary contrast material injections can be diminished by imaging in two orthogonal planes after a single injection of contrast medium. Magnification angiography may show emboli in vessels that are too small to be seen clearly on standard studies.

For a definite diagnosis of PE, it is necessary to visualize the embolus as either a filling defect (see eFig. 20.17) within a vessel or obstruction of the vessel with the embolism protruding into the enhanced vessel proximal to the obstructing embolism. Other abnormalities should not be regarded as diagnostic of embolism.

Complications and death are rare, fortunately. Significant complications are seen in less than 5% of patients, and 0.1–0.5% of patients die undergoing angiographic studies to evaluate suspected PE,[22] although others have noted that catheter pulmonary angiography is a safe procedure owing to advancements in technology.[23] Minor arrhythmias are not infrequent when the catheter tip traverses the right ventricle. Ventricular fibrillation has been reported, as has refractory shock. Electrocardiographic monitoring and immediate availability of defibrillating equipment are mandatory. Reactions to contrast material are most frequently minor and primarily consist of urticaria and vasovagal responses. However, patients can occasionally suffer major reactions, with bronchospasm and cardiopulmonary collapse. Preexisting renal disease manifested by elevated serum creatinine levels represents a relative contraindication to angiography. In all circumstances, the amount of contrast material injected should be the minimum required to produce diagnostic opacification of the pulmonary vessels. The use of nonionic or low-osmolar contrast material, now routine in most practices, diminishes the number of minor reactions and increases patient comfort during the procedure.

AORTOGRAPHY AND BRONCHIAL ANGIOGRAPHY (see Chapter 21)

Aortography is generally accomplished by the retrograde passage of a catheter from the femoral artery to the aorta or its branches after percutaneous insertion (eFig. 20.20). The study of the aorta and its branches plays a limited role in diseases of the lung. The imaging modalities of choice for diagnosing suspected aortic abnormalities, including aortic dissection, are CT, MRI, and, in acute cases, transesophageal ultrasonography; aortography is seldom required. The diagnosis of pulmonary sequestration once depended on the demonstration of anomalous systemic blood supply by aortography, but in modern practice, CT angiography of the aorta and *magnetic resonance angiography* (MRA) are often diagnostic and easily demonstrate the abnormal vascular supply (eFig. 20.21). Patients with severe hemoptysis may require bronchial arteriography and embolization of the bronchial artery or arteries supplying the bleeding site (eFig. 20.22). These studies require selective catheterization of the bronchial arteries. Angiographic technique is, for the most part, individualized to fit the particular clinical condition being studied.

Digital subtraction angiography can be used with angiography to improve the image and reduce the contrast needed. With digital subtraction angiography, an early image from the angiogram is recorded with an image intensifier and a high-resolution television camera and is digitized and stored. A later image in which vessels are opacified is handled in a similar manner. The first image is then subtracted from the second, and the resulting image is displayed. The background body structures are subtracted, leaving an image of the contrast-filled vessel (see eFigs. 20.20 and 20.22). Because the body background does not obscure the final image, angiography can be accomplished with smaller amounts of contrast than otherwise necessary. Motion of structures in the area being studied may make complete subtraction of images difficult.

ULTRASONOGRAPHY

Ultrasonography, which is also discussed in Chapters 23 and 24, has been traditionally regarded as having limited utility in thoracic imaging because the ultrasound beam is reflected at the air–soft tissue interface around the lungs; however, it has been recognized as useful for an increasing number of thoracic applications. It is useful for studying vascular, cardiac, and some mediastinal abnormalities, for the localization of pleural fluid and air collections, and for directing interventions (see eFig. 21.1 and Chapter 21). Transesophageal sonography can allow imaging of some mediastinal structures and is often performed to assess the thoracic aorta and heart. Endobronchial ultrasound has become the standard approach for imaging the mediastinal lymph nodes and directing biopsies for staging lung cancer (see Chapter 27) The use of transthoracic ultrasonography in lung imaging is largely limited to the pleura and immediate subpleural areas or to areas of consolidated lung or masses contacting or invading the chest wall. It is most commonly used for the detection, localization, and characterization of pleural effusions and to guide thoracentesis (eFig. 20.23).

Ultrasonography is also valuable in differentiating effusion from pleural thickening. Effusion is usually anechoic or hypoechoic, whereas pleural thickening results in an echogenic stripe within the enclosing rib margin. When free-flowing or layering fluid is not demonstrated on decubitus radiographs in the presence of a thickened pleural stripe, ultrasound may show collections of loculated fluid surrounded by pleural adhesions. Septations may be visualized within pleural collections, and their shape may change during the breathing cycle, confirming the presence of low-viscosity fluid. A complex echogenic fluid collection indicates the presence of exudate, empyema (eFig. 20.24), or hemothorax, but an echo-free collection does not exclude these diagnoses. Ultrasound is also effective in differentiating subphrenic fluid from pleural effusion because the two hemidiaphragms are excellent reflectors of the ultrasound beam and therefore provide a visible boundary distinguishing intrathoracic from subdiaphragmatic spaces (eFig. 20.25). The presence of a hypoechoic area caudal to the echogenic diaphragmatic stripe but cranial to the liver or spleen indicates ascites.

Ultrasound-guided thoracentesis is frequently performed when loculated fluid is suspected or after attempts at unguided thoracentesis have failed. The use of real-time equipment permits the performance of this procedure at the bedside (see eFig. 20.23). After locating the apparent fluid collection, the appropriate depth to which the needle should be inserted is displayed on the screen, and the aspiration is performed in the usual manner. Placement of catheters for drainage can be accomplished in a similar fashion.

Pleural neoplasms, mediastinal masses, or parenchymal masses that abut the pleural surface may be biopsied under ultrasonic guidance, provided that no aerated lung intervenes between the lesion and the pleura. The tip of the needle can be guided and identified within the mass, thus confirming appropriate placement before aspiration or biopsy. However, CT (see Figs. 21.1, 21.2, and 21.6) or fluoroscopic guidance is more frequently used for this purpose.

COMPUTED TOMOGRAPHY

PHYSICAL PRINCIPLES

CT is based on the precise measurement of attenuation of a thinly collimated x-ray beam from a variety of different projections, a technique allowing a reconstruction of a "slice" of the body. The imaging of a slice is known as tomography (*tomos* in Greek means slice or section). Differential x-ray beam attenuation by different tissues forms the basis of image contrast on CT images. The advantages of CT are its axial tomographic ("slice-like") format and its high sensitivity to differences in attenuation between different tissues, yielding excellent contrast resolution.

To obtain CT images, x-rays—produced by a modified standard x-ray tube—are passed through the patient, and the transmitted photons are measured by a series of x-ray detectors. The detectors produce an electric current that is proportional to the intensity of the incident x-ray beam. The strength of this current is measured and digitized by an analog-to-digital converter and thus is available for computer manipulation. The reduction in the intensity of the beam as it passes through the patient's body is termed *attenuation* and is due to scattering and absorption of the x-ray photons by tissue. The attenuation (more precisely, the linear attenuation coefficient) of each point within the body can be calculated by the scanner's computer, provided that multiple measurements of x-ray attenuation can be made from different angles. The details of the x-ray beam and detector motion by which these multiple measurements are obtained vary considerably among scanners.

Because the x-ray attenuation measurements are stored in a computer, the image can be enhanced or manipulated mathematically with specific reconstruction algorithms. For example, HRCT combines narrow collimation/thin-slice thickness (≈1 mm) and image reconstruction with a high-spatial-frequency algorithm to produce increased sharpness in the final image.

IMAGE DISPLAY

The reconstructed CT image is made up of a matrix of picture elements, or pixels. The x-ray attenuation of each pixel is normalized to that of a test object containing pure water. The CT number is the ratio of tissue attenuation minus water attenuation relative to water attenuation multiplied by 1000 and is expressed in *Hounsfield units* (HU). The CT number for normal lung ranges from −700 to −900 HU, whereas soft tissues have CT numbers ranging from −100 (fat) to +100 HU (blood clot), with water measuring 0 HU and most soft tissues in the 20 to 60 HU range. The range of CT numbers encountered in patients is approximately 2000, ranging from −1000 (air) to +1000 (bone). However, although the computed image contains 2000 number levels, which could correspond to 2000 shades of gray, the human eye can perceive only about 16 to 20 distinct shades of gray. It is thus necessary when displaying CT images to restrict the image display to a small fraction of the actual range of attenuation values.

This restriction is done first by combining similar CT numbers into a single gray shade and second by setting the window width and window level display settings. The window *width* is the range of densities that will be displayed as shades of gray; all higher pixel values are shown as white, and all lower ones are shown as black. The window *level* is simply the median pixel value about which the display range is centered. Thus, to view the lungs, which are low attenuation due to the presence of air, an appropriate window level is −700 HU, with a window width of approximately 1200 HU, which may be adjusted depending on user preference. For viewing soft tissues, pleural space, mediastinum, or hila, a window level of 20 to 40 HU with a width of approximately 400 HU is preferred. These are usually referred to, respectively, as lung window and mediastinal or soft tissue window settings, and both should be displayed for a chest CT study.

VOLUMETRIC IMAGING VIA HELICAL AND MULTISLICE COMPUTED TOMOGRAPHY

Volumetric CT refers to the ability of modern CT scanners, either helical/spiral or multislice, to acquire scan data continuously between two points (in the thorax, typically from the cervical-thoracic junction to the diaphragm), rather than, as with older CT technology, using a "step-and-shoot" method. With the older technique, individual images could be summed to create a volume of imaged tissue but were limited by misregistration between the individual image slices/slabs, particularly between successive individual breath-holds. Owing to the rapid acquisition times of modern CT scanners, the entire thorax can now be imaged completely in a single breath-hold, leading to a single "block" of anatomic data that can be reconstructed into practically any desired slice thickness and imaging plane orientation.

Helical or spiral CT are essentially equivalent terms; they refer to the path the rotating x-ray beam describes as a result of its continuous rotation around the longitudinal axis of the patient as the patient is transported though the CT gantry on a continuously moving table. This continuous tube rotation during simultaneous table movement allows a continuous spiral acquisition of data. In many patients the entire thorax can be scanned during a single breath-hold. Compared to the older techniques of step-and-shoot, helical/spiral CT has the advantages of (1) volumetric imaging, which ensures contiguous image reconstruction and allows multiplanar or three-dimensional reconstructions to be performed, (2) more rapid scanning, and (3) more rapid contrast infusion with denser opacification of vessels.

Multislice CT (MSCT) markedly improves on the advantages offered by single-slice helical CT. MSCT scanners acquire information using *multiple channels* during a single

tube rotation, thereby dramatically increasing the data acquisition rate. Current MSCT scanners may acquire up to 320, even 920, images per tube rotation for a given slice thickness, whereas routine single-slice helical CT scanners generally only acquire one image per tube rotation for a given slice thickness. The speed advantage of MSCT scanning is obvious; this tremendous speed allows rapid imaging of large volumes of tissue in practically any phase of IV contrast enhancement. The image datasets provided by MSCT scanners also allow improved-quality reformatted images (eFig. 20.26, Videos 20.3 and 20.4). Furthermore, the imaging data acquired with MSCT scanning allow retrospective reconstruction of narrow-section images (e.g., thin sections or high-resolution images) after scan completion, a process that has transformed nodule characterization, for example.

With MSCT the ability to reconstruct narrow-section images retrospectively has transformed the process of nodule characterization. In the era of single-slice CT scanning, when narrow-section imaging was used to characterize a pulmonary nodule, particularly by the detection of calcium or fat within the nodule, either the patient would be held within the department and the radiologist contacted to review the scan to determine if narrow-section imaging was required (with the associated detrimental effect on departmental throughput), or the patient would be called back at a later time for further imaging (with the associated patient and referring physician inconvenience). With MSCT scanning, CT protocols that acquire narrow sections (often on the order of 1 mm or less) are devised but are reconstructed using wider sections (often 3 mm) for routine interpretation, which allows optimized computer performance and data handling; however, the narrow sections have been acquired and are available for review. In the foregoing example, if narrow sections are needed for pulmonary nodule characterization, the narrow-section data may be retrospectively reconstructed and reviewed (Fig. 20.7). In fact, many radiology departments prospectively reconstruct both wider section widths for routine viewing and narrow-section widths for specialized applications and save both series to the picture archiving communication system; such an approach strikes an excellent balance between the need for smaller datasets to facilitate routine data handling, while still allowing specific questions to be addressed later through the use of thin-section imaging without having to reimage the patient.

COMPUTED TOMOGRAPHY SCAN PROTOCOLS

CT scans can be obtained with a variety of differing parameters that can be adjusted depending on the indication of the examination (eTable 20.1). Variables include scanning range, field of view, patient position, scan section thickness, table transport speed/pitch, breath-hold instructions, and IV contrast injection rate, timing, and volume. These parameters are briefly reviewed later. The influence of table transport speed/pitch on CT protocols has evolved with the proliferation of MSCT scanners. Consideration of these variables is more relevant to cardiovascular imaging and is not discussed here. The interested reader is referred to excellent reviews on the topic of MSCT scan parameters and the technical aspects of MSCT scanning in the Key Readings list at the end of this chapter.

Owing to MSCT's rapid scan capability and ability to reconstruct narrow-section data retrospectively, in recent years there has been some degree of CT protocol simplification compared with the single-slice CT era. For example, with single-slice CT scanning, the imager often had to choose between thicker, low-resolution but contiguous slices to cover the entire anatomy of the lungs versus thinner, noncontiguous but high-resolution slices that "skipped" 1 to 2 cm of intervening lung due to the time constraints imposed with single-slice scanning. For example, scanning 30 10-mm-thick slices can cover 30 cm of lung contiguously, but with poor spatial resolution due to partial volume averaging, whereas covering the same 30 cm of lung with contiguous 1-mm-thick slices would require 300 slices, taking 10 times as long and probably longer, given the limited ability of early CT systems to deal with tube overheating. As such, HRCT protocols in the era of single-slice scanning included noncontiguous supine and prone 1-mm inspiratory scans, as well as noncontiguous supine expiratory scanning. Using such a protocol, it was not uncommon to mistake a pulmonary vessel for a lung nodule because of the inability to review adjacent sections immediately cranial and caudal to the vessel. This HRCT protocol was distinct from the "routine" single-slice CT chest protocol, using contiguous imaging required to clarify the nature of this potential abnormality. Current multislice HRCT protocols, however, use a helical technique to obtain contiguous 1-mm supine imaging in a single breath-hold; additional prone inspiratory and supine expiratory images are obtained separately. These additional acquisitions complete the typical high-resolution chest CT protocol and are performed to survey for both air trapping and fibrotic lung disease. MSCT avoids the difficulties associated with noncontiguous imaging techniques while simultaneously maintaining the benefits of thin-section imaging in the characterization of diffuse lung diseases.

Scanning Range

In most instances a chest CT study should encompass the entire thorax, from the lung apices to the posterior costophrenic angles. This is easily accomplished in a matter of a few seconds with MSCT. In patients with lung cancer, chest CT done for staging purposes may include the adrenal glands and liver, although the liver acquisition should be timed properly to obtain images in the correct phase of liver enhancement. In practice, lung cancer staging studies are typically performed as dedicated examinations of the entire chest, abdomen, and pelvis.

Patient Position

Normally, patients are scanned in the supine position. However, decubitus positioning or prone positioning may be used to elucidate whether pleural fluid collections are free or loculated, distinguish dependent atelectasis from parenchymal fibrosis, demonstrate findings partially obscured by dependent atelectasis, or position lung lesions optimally for biopsy. Images are normally obtained at total lung capacity to obtain maximum air-tissue contrast and to spread anatomic structures and lesions over a larger area, thus minimizing volume averaging. Prone images are usually obtained with HRCT studies. Technical advances now permit the acquisition of CT images during, rather than after, forced expiratory vital capacity maneuvers (see Videos 140.1 to 140.3), a technique often referred to as dynamic expiratory imaging. This approach

eTable 20.1 Common Chest Computed Tomography Scanning Protocols and Indications

Scan Protocol	Intravenous Contrast Use?	Common Indications	Notes
"Routine" chest CT* (including helical and multislice technology)	Possibly, depending on specific application	Initial and repeat cancer staging (may be performed with IV contrast, depending on tumor type), nonspecific chest pain, cough, or shortness of breath, pleural disease, mediastinal or chest wall mass evaluation, suspected thoracic lymphadenopathy, investigation of focal chest radiographic abnormalities, suspected infection, lung cancer screening	IV contrast injection often beneficial for suspected lymphadenopathy, pleural disease, bronchogenic malignancy staging. Used for fever of unknown origin—often when chest radiography is unrevealing, particularly for immunosuppressed patients. Often used for evaluation before solid- or hollow-organ transplant to assess for asymptomatic findings that could represent malignancy. Aggressive radiation dose reduction frequently used for unenhanced lung cancer screening studies
CT pulmonary angiography	Yes	Assessment of suspected acute or chronic thromboembolic disease, pulmonary artery aneurysm, or pulmonary artery anomaly, arteriovenous malformation	IV contrast injection timing scaled for optimal pulmonary artery enhancement. Initial evaluation of arteriovenous malformation may include initial unenhanced imaging
CT aortography	Yes	Assessment of suspected aortic dissection or aneurysm	IV contrast injection timing scaled for optimal aortic enhancement
Coronary calcium scoring	No	Evaluation for presence of calcified coronary artery atherosclerosis for heart disease risk stratification	Volume of acquisition limited to heart, ECG-gated
Coronary CT angiography	Yes	Evaluation for coronary artery atherosclerosis, aneurysm, or anomaly	Scan performed with ECG gating for motion-free images. Volume of acquisition typically limited to heart
Cardiac CT	Yes	Evaluation for congenital or acquired structural cardiac disease, pericardial disease, or assessment of specific mediastinal or lung pathology impacting on heart	Scan performed with ECG gating for motion-free images. Volume of acquisition typically extended slightly beyond heart to include great vessel anatomy. Contrast injection timing may be adjusted to suit particular indications
Pulmonary vein CT	Yes	Assessment for pulmonary venous and left atrial anatomy before electrophysiologic ablation	Contrast injection timing optimized for left heart enhancement. Some facilities ECG gate. Delayed or prone imaging to assess for left atrial appendage thrombus
High-resolution CT	Typically not required, although in the case of initial evaluation of suspected sarcoidosis may be of benefit	Diffuse lung disease at chest radiography or suspected by clinical evaluation—initial diagnostic assessment, biopsy site selection, serial evaluation of treatment efficacy; small airway diseases, bronchiectasis, tracheobronchomalacia, chronic dyspnea or progressive exercise intolerance, assessment of abnormal pulmonary functions testing, lung transplantation evaluation	Thin-section imaging with prone and postexpiratory imaging as well. Expiratory imaging can be end-exhalation or dynamic. Dynamic exhalation also considered for suspected tracheobronchomalacia
Contrast-enhanced chest CT for solitary nodule evaluation	Yes	Evaluation of an indeterminate solitary pulmonary nodule (typically >1 cm, <3 cm)	Specific, weight-based contrast injection protocol with structured timing of image acquisition to assess for nodule enhancement. Lack of nodule enhancement strongly suggests an indeterminate nodule is benign

*"Routine" chest CT section thickness (collimation) varies depending on scanner manufacturer but typically approximates 3–5 mm. Narrower sections are routinely automatically obtained with modern multislice CT scanning protocols (on the order of ≤1 mm); however, these images may or may not be reconstructed and archived in the picture archive and communications system (PACS), depending on individual radiology departmental protocols. Even when such images are routinely reconstructed and archived to PACS, often an additional series of images using a wider reconstruction interval (typically ≈3–5 mm) is saved to PACS to facilitate day-to-day interpretation and data handling and storage efficiency.

CT, computed tomography; ECG, electrocardiogram; IV, intravenous.

is useful for the detection of gas trapping and for revealing tracheobronchomalacia.

Multislice Computed Tomography Detector Configuration and Scan Section Thickness

In the era of single-slice helical CT, the thickness of an individual CT section was set to a predetermined value before scanning by setting the x-ray beam to a certain thickness, a process referred to as collimation. Typical slice thicknesses for single-slice helical CT ranged from 1 to 10 mm, with 5- to 7-mm collimation used for most routine chest CT applications. With the development of MSCT systems, although various collimation choices are still possible, most MSCT protocols use certain detector configurations that either favor narrow detector width (to promote optimal spatial resolution) or wider detector widths (to facilitate rapid coverage). As systems with greater numbers of detectors are developed, the choice of high spatial resolution at the expense of volume

of coverage and total length of exposure—an age-old compromise in the era of single-slice helical CT—is becoming less of a quandary. Modern MSCT systems now allow the entire thorax to be scanned with a narrow detector configuration (≤1 mm) in a matter of a few seconds or less. Once such images are acquired, they may be combined in various ways for optimal viewing. For example, a chest CT study obtained on an MSCT system with detector elements arranged in a manner resulting in 1-mm detector configuration would produce several hundred 1-mm images for the thorax of an averaged-sized patient. However, these 1-mm images can be "combined" to generate 5-mm images, and these images can be displayed for routine review; this results in about 100 images for a typical chest CT. Should the radiologist desire to view the high-resolution 1-mm images, these images can be reconstructed from the original dataset as long as the original scan data are saved.

An additional benefit realized by the development of MSCT is the ability to image using isotropic voxels. The term *isotropic voxel* indicates that the resolution of the scan in the *x*-, *y*-, and *z*-planes is equal. In other words, MSCT scanning using isotropic voxels allows the CT data to be reconstructed in any plane with resolution equal to that of the axial scans. Most single-slice CT examinations did not possess this capability, and therefore nonaxial reformatted images suffered from degraded quality compared with that of the axial scans. MSCT's ability to scan using isotropic voxels allows creation of images that are equal in resolution to the axial scans in any desired plane (see eFig. 20.26 and Videos 20.3 and 20.4); this multiplanar capability was previously an advantage that MRI and ultrasound had over CT.

Contrast Enhancement

The injection of IV iodinated contrast material during chest CT is important in many situations. Administration of contrast material is not routine except for the diagnosis of vascular abnormalities, such as aortic dissection, aneurysm, PE, when using a specific protocol in selected patients with pulmonary nodules, or for examinations performed for lung cancer staging or assessment of pleural or chest wall diseases. If possible, iodinated contrast materials should be avoided because they are expensive and associated with a small but definite risk of serious reactions and toxicity. Although contrast infusion can be helpful in distinguishing vessels and soft tissue masses in the mediastinum and hila, it is not considered necessary for diagnosis by all radiologists. For routine CT of the lungs (e.g., to rule out metastases), contrast material is rarely required, although it can be quite helpful for certain highly vascular malignancies such as melanoma and renal cell carcinoma. In the past there was concern regarding CT-related iodinated contrast-media administration resulting in delays performing whole-body scans or radioiodine ablation for thyroid carcinoma patients after total thyroidectomy. However, it has been recognized that water-soluble iodinated contrast agents are typically eliminated in 4 to 8 weeks in most patients, so radioactive iodine scanning and therapy can be adequately performed within 1 month of contrast-enhanced CT.[24]

Nonionic and low-osmolar contrast materials have proved to have a lower incidence of adverse reactions than high-osmolar agents.[25] Patients with a prior history of contrast reaction should be treated with extreme care because they are at higher risk for subsequent serious reactions, particularly those rare patients that have experienced contrast reactions despite proper premedication with corticosteroids and antihistamines.[25,26] If vascular pathology is of interest in such patients, MRI may be the preferred modality. If CT with contrast enhancement is necessary, pretreatment with corticosteroids is advisable.

Peak opacification of the structures of interest is desirable when administering IV contrast; thus the timing and technique of administration are important. To achieve this, a bolus of contrast material must be administered, preferably via a calibrated mechanical power injector, and the area of interest must be scanned rapidly and at the appropriate time during the initial transit of the contrast agent. For example, chest CT protocols designed for the detection of PE generally use rather short delays from the time of the beginning of contrast injection to the start of imaging (usually ≤20 seconds) due to the short transit time between an upper extremity vein (usually where the IV catheter is placed) and the pulmonary arteries, whereas chest CT protocols designed for the evaluation of the aorta and coronary arteries require a longer contrast injection delay due to the longer transit time between the IV catheter and the aorta.

Optimal timing of CT acquisition after the beginning of contrast administration is often achieved via bolus tracking, in which a single tracking slice is obtained and a trigger region of interest is placed on the desired vascular compartment (pulmonary artery or aorta) within that slice. The contrast is injected, and the scanner repeatedly scans the tracking slice until the attenuation within the trigger reaches a certain threshold, such as 100 HU. This signals the impending arrival of the contrast bolus into the vascular compartment of interest, at which point the scan starts.

Radiation Exposure and Cancer Risk

The two primary terms for describing the radiation imparted by a CT scan are *adsorbed* and *effective dose.* The adsorbed dose, measured in *grays* (Gy), is the energy absorbed per unit mass of a specific organ. In other words, it is the radiation imparted to a specific organ and thus accounts for the future risk of developing a malignancy at that site. Effective dose, measured in *Sieverts* (Sv), is an overall estimate of total-body radiation exposure; this unit attempts to provide a measure of the overall potential harm caused by radiation exposure. Effective dose is defined as the radiation dose that must be delivered to the whole body to yield the same biologic consequences (specific for cancer induction only) as the dose actually received by the exposed organs.[29] This is calculated by summing the individual adsorbed doses to each organ, each of which is multiplied by a weighting factor reflecting individual organ radiosensitivities. Effective dose is useful for gross comparisons between different modalities and techniques. It should be understood that effective dose is *not* an actual measure of the radiation imparted to a patient during a given CT examination, although many published articles use this unit (often expressed as *milliSieverts* [mSv] or in the form of the older unit, *millirems* [mrem]) in this fashion.[30] This misconception is compounded by the recording of a "patient dose report" as part of the CT scan report (eFig. 20.27). Rather, the actual radiation dose imparted to a patient during a CT examination depends directly on the size and shape of the patient.[30] The units reported by

the CT scanner, often the *CT dose index* (usually expressed as the $CTDI_{vol}$, reported as an absorbed dose, in mGy) or the dose-length product (reported as an effective dose, in mSv, and equal to the $CTDI_{vol}$ multiplied by the irradiated scan length), are measures of scanner radiation output, not patient dose. Calculating the radiation dose imparted to a patient during a given CT scan requires complex equations that take into account patient size, shape, body composition, and the organs irradiated, as well as scanning range. With knowledge of the patient size, body region scanned, CT scanner output, and scan length, a reasonable approximation of patient dose for a given CT scan is possible, but it remains imperative to understand that the units of scanner output—the CTDI and dose-length product—are not measures of patient radiation dose.[30] Therefore these parameters should not be used to estimate potential cancer risk or radiation-related deterministic effects (e.g., skin injury) for individual patients undergoing medical imaging procedures.[30]

Approximate effective doses (scanner outputs) for CT are given in Table 20.1 and compared with nonmedical radiation exposures.[31] Of note, the values given are representative measurements but, in fact, there is a wide range of exposures dependent on CT technique and method of estimation. Also, indications such as PE, which require narrower sections, may involve a relatively greater amount of radiation exposure compared with standard chest CT protocols. In recent years, concerted efforts to curtail medical radiation exposure have resulted in a number of advances that have significantly reduced the amount of radiation delivered to the patient, chiefly through reduction of CT-related exposures. In general, exposure reduction is approached in several ways: (1) increasing public and provider awareness through efforts such as the ImageGently campaign conducted by the Alliance for Radiation in Safety in Pediatric Imaging and the ACR's ImageWisely (radiation safety in adult medical imaging) effort; (2) technical advances in CT scanner equipment (e.g., with new reconstruction algorithms and automated exposure controls that more efficiently apply the radiation exposure to the patient); (3) encouraging the use of nonionizing radiation imaging alternatives for selected disorders; and (4) active interventions by radiologists, including limiting scanning range and reducing x-ray tube current and voltage. It is now relatively commonplace that exposures associated with newer CT protocols are significantly less than the values reported in Table 20.1 (Video 20.5).

Considerable controversy regarding the genesis and magnitude of adverse effects resulting from radiation exposure in humans exists and has been the subject of debate for decades.[29] The rapid rise in the use of CT scanning in recent years and several well-publicized patient overexposure events at CT scanning have fueled this debate.[29] Nevertheless, several points can be agreed on by investigators on both sides of this debate.

1. Radiation is potentially harmful to biologic systems and exposure can induce cancer, among other effects.[32]
2. There is relatively clear evidence for radiation-induced carcinogenesis for exposures exceeding 100 mSv.[29,32]
3. Radiation is a relatively weak carcinogen, and excess radiogenic cancer risk, if any, is considerably less than spontaneous cancer risk.[27]
4. There are no parameters that allow a radiation-induced malignancy to be distinguished from one arising naturally.[34]
5. The risk of radiation-induced malignancy is generally inversely related to age[32] and relatively higher in women compared with men.[27,35]
6. The risk for radiation-induced carcinogenesis from a CT scan is generally far less than the benefit of the information gained from appropriately indicated CT studies.[31,36]

The primary source of controversy between those who believe low-level radiation exposures—exposures less than 100 mSv, which are typical for the exposures associated with medical imaging—may result in the development of malignancy and those who claim no such evidence exists lies with the *linear nonthreshold* (LNT) model for radiation-induced carcinogenesis. The LNT theory holds that a linear and proportional relationship between radiation dose and cancer risk exists, and there is no threshold dose below which radiation is not carcinogenic.[29,31] Proponents of the LNT theory hold that a linear model best describes the relationship between radiation exposure and cancer induction[37,38]; by contrast, critics of the LNT model for radiation-induced carcinogenesis risk prediction insist that the LNT model was developed to establish standards for protection of occupationally exposed individuals and overestimates the incremental risk for cancer development at low-level radiation exposures, and therefore it is inappropriate to project individual cancer risks from medical radiation exposures using this model.[29] Nevertheless, many of the widely publicized reports[32,39–41] estimating the number of cancer-related deaths resulting from CT scanning have used the LNT methodology.

Estimates for the risk of radiation-induced carcinogenesis in humans primarily stem from epidemiologic studies of exposed patient cohorts, particularly Japanese survivors of the atomic bombings in 1945; other data sources include occupational radiation exposures and radiation accidents, such as the Three Mile Island and Chernobyl accidents.[29,31,32,42] The LNT model is often used to extrapolate the elevated rate of malignancy found among these exposed cohorts to patients receiving the relatively low-level radiation exposures typical of medical imaging in the effort to estimate individual cancer risks. However, such extrapolation is not advised by either the National Council on Radiation Protection and Measurements or the International Commission on Radiological Protection.[35] Furthermore, it should be understood that the LNT model does not provide for the ability to "sum" separate radiation exposures from temporally separated radiation-utilizing procedures into a "cumulative" cancer risk. In other words, regardless of the patient's previous radiation exposures, the imaging study the patient is about to undergo only adds the potential incremental risk for cancer development attributable to that examination[35]; the radiation exposures from separate examinations are not additive.[35,43–45] This notion carries significant implications regarding the recent trend toward the development of radiation "dose registries,"[46] whereby patient medical imaging radiation exposures are tracked in a database with the intention of using such information to make future medical imaging decisions.

Low-Level Radiation-Induced Malignancy: Evidence for and Against

Investigators who assert that low-level radiation has carcinogenic potential cite the elevated incidence of malignancy noted in many large epidemiologic cohorts of exposed patients, particularly the Japanese atomic bomb survivors in the Life Span Study. This argument relies on the LNT model to extrapolate the experience of these cohorts, exposed at relatively higher rates, to estimate the risks associated with the lower-level radiation exposures typical of medical imaging.[38] These investigators assert that a linear relationship (e.g., the LNT model) best describes the relationship between cancer rates and radiation exposures over a wide range of exposures; moreover, this relationship is consistently observed not only in the Life Span Study but in the analysis of other large epidemiologic studies of individuals exposed to radiation,[38] and that linearity best describes the responses of biologic systems to radiation exposure. Furthermore, experimental evidence can directly show cellular damage induced by radiation.[32] Finally, a large epidemiologic study focusing on younger patients undergoing CT scanning has shown a significant linear association between radiation dose to the brain and bone marrow and subsequent development of brain tumors and leukemia, respectively.[36,47] This study evaluated 180,000 patients younger than 22 years undergoing nearly 280,000 CT scans in the United Kingdom between 1985 and 2002 who were subsequently followed for cancer development; the investigation specifically focused on brain tumors and leukemias, which are the cancers expected to appear first in irradiated pediatric patients.[36,47] The risks for brain tumor and leukemia development in this patient cohort were small; it was estimated that one head CT may result in one excess brain tumor, for every 10,000 patients undergoing CT, in the first decade after the exposure.[36,47] However, an editorial[36] also noted that the relatively short follow-up time in this study (average, 10 years)[47] is insufficient to detect all potentially radiation-induced malignancies in this patient cohort, given that the latency of some radiation-induced malignancies may be as long as 20 to 40 years. Extrapolating the 10-year risk for radiation-induced carcinogenesis for the patients studied to lifetime carcinogenic risks for the exposed individuals yields estimates for cancer induction that are roughly similar to those asserted by the Life Span Study.[36] Note that this study[47] focused on pediatric patients, in whom the individual risks for radiation-induced malignancy are higher than for adults, but greater than 90% of CT scans are performed in adult patients.[36]

Investigators who challenge the notion that low-level radiation poses significant carcinogenic potential note the difficulties resulting from the reliance on the LNT model, as discussed previously, but also point to significant differences among the patients in the Life Span Study compared with those undergoing procedures utilizing medical radiation. Such differences include the fact that cancer incidence in Japan today is substantially different than in the United States, and cancer incidence in both countries today is likely substantially different from in Japan in 1945.[42] Medical imaging radiation exposure sources include relatively low-energy x-rays and γ-rays, whereas atomic bomb explosions exposed patients to high-energy γ-rays, neutrons, and other charged particles[42]; medical imaging typically uses *fractionated* doses (radiation doses delivered intermittently over a period of time, as in the context of repeated imaging studies), whereas atomic bomb blasts exposures are instantaneous[42]; and Japanese atomic bomb survivors suffered uniform, whole-body exposures and radioactive fallout, whereas patients undergoing medical imaging procedures typically have nonuniform radiation exposure to limited body regions, the exception being some nuclear medicine procedures.[42] Furthermore, the health of Japanese atomic bomb survivors was relatively compromised compared with patients undergoing medical imaging, owing to the limited resources for medical care, food, and shelter in Japan after the atomic bomb blasts.[42] Thus it seems clear that these substantial population differences limit the ability to extrapolate radiation-induced cancer incidence from one cohort to another.

In contrast to other investigators,[32] those who challenge the belief that low-level radiation has carcinogenic potential assert that the results of epidemiologic studies of radiation-induced carcinogenesis show no, or much smaller, health effects from radiation exposure than the data from the Life Span Study.[42] In addition, these investigators have called attention to serious limitations in the manner in which radiation-induced malignancy rates are calculated through the generation of lifetime attributable risk modeling.[42]

Lines of biologic evidence also call into question the simple notion that the rate of cancer induction is proportional to the amount of radiation exposure. For example, it has been suggested that a 0.1-Sv radiation dose, which is at the upper limit of what is referred to as "low-level radiation," is estimated to cause 0.004 long-term mutations per cell, which is a minor addition to the 1 mutation per cell per day that results from natural processes.[48] Furthermore, a number of in vivo experiments have shown a reduced rate of chromosomal aberrations after the use of priming low-level radiation exposure before exposure to high-dose radiation because of the stimulated production of DNA repair enzymes and immune system activation—the so-called adaptive response.[33,48] Finally, the same survival curves plotted for Japanese atomic bomb survivors and other large-scale epidemiologic investigations of radiation effects, interpreted by some investigators as supporting the notion of a linear-dose response relationship between radiation exposure and carcinogenesis, are interpreted by others as showing a threshold effect, below which cancer is not induced, or in some cases, below which cancer risk actually decreases. The latter concept has been referred to as hormesis and is thought to be due to upregulation of protective mechanisms within cells and tissues induced by low-level radiation.[33,48]

MAGNETIC RESONANCE IMAGING

PHYSICAL PRINCIPLES

MRI is performed by magnetizing the protons within a patient's tissues and then manipulating them with a combination of magnetic gradients and radiofrequency pulses to create and spatially map signal from the tissues. This signal carries information about the tissues. MRI does not

require mechanical motions of the scanner and therefore can image directly in nonaxial planes, including, but not limited to, sagittal and coronal imaging.

Although MRI uses electromagnetic radiation, the energy levels used in MRI are quite low, typically falling in the radiofrequency range (i.e., nonionizing). MRI appears to be free of significant bioeffects. Potential safety hazards in MRI relate to the extremely strong static magnetic field and rapidly switched gradient magnetic fields used and to the possibility of tissue heating from radiofrequency energy absorbed by the body. Tissue heating is a theoretical concern but, in practice, is not significant when conventional MRI techniques are used. Theoretically, the rapidly varying gradient magnetic fields could stimulate electrically excitable tissue, but this is not a problem with routine MRI techniques. In contrast, the powerful static magnetic field is a major safety hazard because the magnetic forces near a whole-body *magnetic resonance* (MR) imager are strong enough to cause significant projectile hazards. For example, an ordinary steel oxygen cylinder brought into an MRI examination room will fly into the bore of the magnet with a terminal velocity of about 45 mph. The possibility of displacements or torques on metallic implants within patients also must be considered. Although the margin of safety is high, there are rare documented instances of harm to patients from dislodging intracranial aneurysm clips or intraocular metallic foreign bodies. Finally, it is possible the magnetic field could induce movement, programming changes, and lead currents, resulting in heating and cardiac stimulation, in patients with cardiac pacemakers. Furthermore, the powerful electromagnetic fields created by MR imagers could potentially produce asynchronous pacing, activate tachyarrhythmia therapies, or inhibit demand pacemakers. In accordance, strict security around MRI facilities is essential to prevent patients with certain types of metallic implants from entering the scanner and to prevent medical personnel from carrying into the scan room objects that could become projectiles. Although beyond the current scope of discussion, it is now recognized that, with the appropriate caution, MRI examinations may be safely conducted in a number of patients with cardiac pacemakers and implantable defibrillators.[49]

MRI produces extremely high contrast between different types of soft tissue. This soft tissue contrast is based on intrinsic properties of the tissues, but it can be modified and exploited by appropriate use of operator-selectable imaging techniques. The tissue properties normally used in MRI are as follows: the concentration of protons available to produce an MR signal (proton density), the presence of motion or blood flow (phase contrast), and two properties known as T1 and T2, which are time constants. The T1 property of a tissue is a measure of the speed at which it is able to relax back into a low-energy state after having been excited. In general, tissues containing fluid (and most pathologic processes) have long T1 times and appear dark; whereas fat, certain proteins, and certain blood products have a short T1 time and appear bright on imaging whose image contrast is primarily determined by T1 effects (T1-weighted imaging). The T2 property of a tissue is a measure of how quickly the initial coherence of the MR signal within a tissue degrades. Usually, fluid-containing tissues (and most pathologic processes) have long T2 times and appear bright on T2-weighted images. Fat also has a long T2 time and will be high signal, masking fluid signal on T2-weighted imaging, unless the fat signal can be suppressed (fat saturation). Flowing blood can appear either bright or dark on MR images depending on the examination technique used.

The art of performing an MRI examination depends on appropriate manipulations of imaging techniques to capitalize on differences in proton density, flow, T1, and T2 between normal and pathologic tissues. In addition, the use of gadolinium-based MRI contrast materials, which alter the T1 and T2 relaxivity of tissues semiselectively, has become important for many clinical applications, particularly MRA. MRI also can display other tissue properties, such as molecular self-diffusion, temperature, pH, and metabolites (MR spectroscopy), but these are less important for thoracic applications, although diffusion imaging and MR spectroscopy have recently shown some promise in lung cancer evaluation and staging and mediastinal mass characterization.[50]

TECHNIQUES

Motion during MRI causes artifacts that can degrade image quality severely. Motion compensation techniques, such as electrocardiographic gating and respiratory compensation, are widely used in chest MRI. High-speed techniques permit imaging in a matter of seconds and, in some instances, in a few milliseconds, fast enough to freeze cardiac motion.

Direct MRI in sagittal, coronal, and oblique planes can provide superior depiction of structures oriented in the long axis of the body, such as the aorta, and edges of structures that lie within the axial plane, such as lesions in the aortopulmonary window or lung apex.[51]

Flow has profound effects on the MR image. The manifestations of flow effects in MR images strongly depend on the type of flow and on the specific MRI techniques. Using different techniques, one can make the MR image of blood either bright (white-blood images) or dark (black-blood images). Most types of vascular pathology can be demonstrated with either white-blood or black-blood images, but there are usually clinical advantages to using one approach or the other. Flow and peak velocity can be estimated with phase-contrast MRI techniques; thus noninvasive estimates of blood flow and velocity are potentially available.

Although high-speed imaging techniques are now available, MRI remains a largely inappropriate method to use for wide-ranging screening examinations of the entire trunk, such as in the search for metastatic disease, save perhaps for whole-body screening examinations for patients with certain hereditary cancer syndromes.

MR effectiveness for imaging lung tissue is limited mostly by the relative lack of protons in the air-filled lungs. The earlier concern about motion artifacts has been alleviated with cardiac and respiratory gating and techniques allowing rapid image acquisition. Nevertheless, most screening examination applications of the lung are best performed with modern CT scanners and MR could be considered in selected circumstances when CT is not available or appropriate.

Table 20.1 Typical Radiation Doses Associated With Background Sources and Common Thoracic Imaging Applications and Environmental Exposures

Radiation Exposure	Effective Dose (mSv)
U.S. annual per capita effective radiation dose, 2006 (background/medical/total)	2.4/3.0/5.6[27]
Posteroanterior chest radiograph*	0.02[328]
Ventilation/perfusion scan*	1.4–2[328,329]
Standard chest CT	5–8[328,329] (exposures now commonly less than this value)
"Low-dose" chest CT	2
High-resolution chest CT (1-cm noncontiguous intervals)*	1
Catheter pulmonary angiography*	2.3–4.1
Whole-body PET*	14[329]
Coast-to-coast U.S. flight (≈3000 miles)†	0.03
Living near coal-fired power plant†	0.0003
Proximity to x-ray (e.g., luggage inspectors)	0.00002
Living within 50 miles of a nuclear power plant†	0.00009
Living in Denver for 1 year	1.8
Airport backscatter device (body scanner)	0.000015–0.00088[330]
Smoking, 1 year‡	2.8

Additional comparisons are available in McCollough CH, Guimaraes L, Fletcher JG. In defense of body CT. *Am J Roentgenol* 2009;193(1):28–39.
*Values may vary according to individual equipment manufacturers, patient size, duration of study, use of dose-reduction techniques, and individual institutional protocols. Exposure for axial acquisition now similar to "standard CT," given volumetric acquisition; additional dose also from prone and postexpiratory imaging.
†Data from http://www.ans.org/pi/resources/dosechart/.
‡Data from http://web.princeton.edu/sites/ehs/osradtraining/backgroundradiation/background.htm.
CT, computed tomography; mSv, millisievert; PET, positron emission tomography.

chest radiographs obtained for routine examination, preemployment screening, prenatal or obstetric screening, and hospital admission, as well as repeated examinations of patients with positive tuberculin tests and a negative initial chest radiograph, should be eliminated. From their analysis of more than 10,000 chest radiographic examinations obtained in a hospital-based population, Sagel and associates[20] concluded that routine screening examinations done solely because of hospital admission or scheduled surgery are not warranted in patients younger than 20 years. Even in selected high-risk populations, radiographic screening for carcinoma of the lung has failed to increase longevity.

The value of the routine hospital admission chest radiograph is still controversial. Although the yield is low in asymptomatic patients, the examination can be extremely valuable as a baseline study for comparison with radiographs taken during or after the course of hospitalization in patients who develop pulmonary symptoms. In general, hospital admission chest radiographs are not recommended unless there is evidence of acute or unstable chronic cardiopulmonary disease or for elderly patients unable to provide an accurate history or undergo a reliable physical assessment.[52]

DETECTION OF LUNG CANCER AND ASSESSMENT OF SOLITARY PULMONARY NODULES

Although chest radiographs are clearly useful in the initial evaluation of patients suspected of having lung cancer, they are of limited accuracy in showing small or early cancers. At the time of their initial diagnosis, it is not uncommon for lung cancers to be visible retrospectively on prior radiographs.[53] Additional radiographic studies, such as oblique views, are cost-effective for the initial evaluation of "nodular opacities" (see eFig. 20.16) that do not clearly represent a lung nodule and are often of value in determining that a "nodular opacity" is not a true nodule. That being said, CT is superior for the detailed evaluation of a known lung nodule.[54]

EVALUATION OF INTENSIVE CARE UNIT PATIENTS

Chest radiography is generally the most common imaging study performed in the ICU. ICU radiographs are taken with portable, and therefore suboptimal, technique. Regardless, the information they provide is useful and may alter patient management.[9]

A further discussion of the indications for chest radiography in the ICU is available at ExpertConsult.com.

INDICATIONS IN ACUTE LUNG DISEASE

Dyspnea

Two studies suggest that chest radiography should be used routinely in patients with acute or chronic dyspnea.[64,65] In one study, new, clinically important radiographic abnormalities requiring acute intervention or follow-up evaluation were identified in 35% of 221 symptomatic patients.[64] Another study found that acute dyspnea was a strong predictor of a radiographic abnormality, but mainly in patients older than 40 years.[66] In this group, 86% of dyspneic patients had abnormal chest radiographs, whereas radiographs were abnormal in only 31% of patients younger than 40 years. Only 2% of patients younger than 40 years with a normal physical examination had abnormal radiographs indicative of an acute abnormality. The ACR[66a] has previously recommended chest radiography when dyspnea is chronic or severe or when additional risk factors are present, such as age older than 40 years and when there is known cardiovascular, pulmonary, or neoplastic disease, or abnormal physical findings. The ACR further suggests that chest radiography is usually an appropriate first investigation for patients with dyspnea suspected to be due to obstructive or *interstitial lung disease* (ILD), central airway disease, or diseases of the pleura, chest wall, or diaphragm.[67]

Acute Respiratory Symptoms

Opinions are also divided about the utility of chest radiographs in patients with suspected acute lung disease and symptoms other than dyspnea. In a study of 1102 outpatients with acute respiratory disease, Benacerraf and coworkers[66] found patient age, results of physical examination, and presence or absence of hemoptysis to be important factors in predicting the value of radiographs. Only 4% of patients younger than 40 years, without hemoptysis and without detectable abnormalities on physical examination, had

Indications for Chest Radiography in the ICU

The overall incidence of abnormalities found on chest images in ICU patients is quite high; in a study of more than 1000 consecutive medical or surgical ICU images obtained routinely or after a change in clinical status, malposition of a monitoring device or a marked change in apparent cardiopulmonary status was found in 65%.[8] In a study of patients in a respiratory ICU,[55] chest radiographs demonstrated at least one new, clinically unsuspected finding in 35% of patients, which, in turn, lead to a subsequent change in management for 29% of these patients. Significant findings are even more likely when the study is obtained to assess a change in clinical status. In intubated patients in a medical ICU, 43% of radiographs showed significant worsening of a known process or development of a new abnormality.[56] The value of obtaining chest radiographs on a daily basis in ICU patients is less clear. Strain and colleagues[57] found that routine morning radiographs revealed unsuspected abnormalities, leading to a change in management in only about 15% of medical ICU patients, although this percentage was considerably higher (57%) in patients with pulmonary or unstable cardiac disease. Graat and coworkers[58] prospectively assessed the value of 2457 routine chest radiographs performed on patients in a combined medical and surgical ICU and found only 5.8% of routine chest radiographs showed new or unexpected findings; only 2.2% of patients required a change in management. Hall and colleagues[59] found that 18% of mechanically ventilated patients in a medical/surgical ICU had at least one radiograph that showed a clinically significant and unsuspected finding. The value of daily chest radiography in patients who have undergone thoracotomy and pulmonary resection has also been challenged. Daily chest radiography in nonhypoxemic patients who had recently undergone thoracotomy and pulmonary resection changed care in only 27% of patients, whereas chest radiography altered management in 79% of such patients who were hypoxemic.[60] Finally, a meta-analysis of eight studies totaling 7078 patients found that elimination of daily routine chest radiography did not affect hospital or ICU mortality, and there was no difference in length of stay in either the ICU or hospital, or the period required for mechanical ventilation, between patients undergoing routine daily chest radiography and those receiving on-demand imaging.[61] Similarly, Hejblum and associates[62] concluded that an on-demand strategy for ordering chest radiographs for mechanically ventilated patients in the ICU is associated with a 32% reduction in the use of chest radiography compared with a routine daily strategy, but both strategies result in a similar rate of therapeutic or diagnostic intervention.

The ACR has recommended that portable chest radiography should be obtained only for clinical indications, not routine assessment, when monitoring a stable patient or for a patient undergoing mechanical ventilation in the ICU.[63] Furthermore, routine chest radiography is not recommended for stable patients admitted to the ICU for cardiac monitoring or for stable patients admitted to the ICU for extrathoracic disease only.[63] Chest radiography is still recommended for the assessment of patients after initial support-device placement, including endotracheal intubation, central venous catheter insertion, pulmonary arterial catheter placement, nasogastric tube placement, and thoracostomy tube insertion.[63]

acute radiographic abnormalities, whereas a much higher incidence of radiographic abnormalities was present if the patient was older than 40 years, had hemoptysis, or had abnormal physical findings. Heckerling,[68] in a study of 464 patients with acute respiratory symptoms, found a low incidence of pneumonia (3%) in patients with a negative physical examination, except in those with dementia. Whenever pneumonia is suspected in adults, the *American Thoracic Society* (ATS) recommends PA (and lateral when possible) chest radiography, although the impact of chest radiography on clinical outcomes in patients with lower respiratory tract infections remains unclear.[69] In this setting, chest radiography may be useful to determine which patients should be hospitalized and which patients should be classified as having "severe" pneumonia.[70] The ACR considers chest radiography appropriate in immunocompetent patients with acute respiratory illnesses when physical examination findings or vital signs are abnormal, or other risk factors or comorbidities are present, or in patients 60 years or older.[71] It has previously been thought that patients younger than 40 years with normal vital signs and physical examination findings presenting with an acute respiratory illness may not require chest radiography, but a review by the ACR[71] suggests that nearly 5% of such patients will have pneumonia, and chest radiography should therefore be deferred in this context only when reliable follow-up is ensured and there is a low likelihood of morbidity if the diagnosis of pneumonia is delayed.

Acute Asthma

In asthma, chest radiographs are often normal, and visible abnormalities in this disease are usually nonspecific.[72] Although Petheram and associates[73] reported that 9% of 117 patients with severe acute asthma had unsuspected radiographic abnormalities affecting management, and the usefulness of radiography in both adult and pediatric[74] patients with an established diagnosis of asthma who experience an acute attack is limited. Correlation between the severity of radiographic findings and the severity or reversibility of an asthma attack is generally poor,[72,73,75] and radiographs provide significant information that alters treatment in 5% or fewer patients with acute asthma.[68,76,77] Although it is difficult to generalize regarding the role of radiographs in both adults and children with acute asthma, chest imaging should be used to exclude the presence of associated pneumonia or other complications when significant symptoms and/or appropriate clinical or laboratory findings are suggestive.[72,75,77] The ACR considers chest radiography warranted in adult patients with asthma when a clinical suspicion for pneumonia or pneumothorax is present,[71] but the utility of chest radiography in otherwise uncomplicated adult acute asthma exacerbations remains controversial.[71]

Exacerbation of COPD or Cystic Fibrosis

Chest radiographs are often used in the initial assessment of patients with suspected COPD; however, they are of limited value in patients with known COPD who present with worsening of their disease.[77,78] In a study of 107 patients with COPD presenting with an exacerbation of symptoms, only 17 (16%) had an abnormal chest radiograph, and in only half of these did the radiographic findings result in a significant alteration in management.[77] In another study, including patients with both COPD and asthma, the management of 21% of patients was altered by radiographic findings.[78] The ACR indicates that chest radiography is generally appropriate for immunocompetent patients with suspected COPD exacerbations, particularly when chest pain, fever, leukocytosis, a history of coronary artery disease, or heart failure is present.[71] When such criteria are used as a guide, nearly all patients with significant findings will have radiographs performed; moreover, it should be noted that more than two-thirds of patients in one study met inclusion criteria for performing radiography.[78]

In most patients with an established diagnosis of cystic fibrosis, clinical findings and chest radiographs are often sufficient for clinical management. Conversely, it should be recognized that patients with cystic fibrosis can have a significant exacerbation of their symptoms with little visible radiographic change.

APPLICATIONS OF CROSS-SECTIONAL IMAGING TECHNIQUES

SOLITARY PULMONARY NODULES (see Chapter 41)

Assessment of a *solitary pulmonary nodule* (SPN) seen on chest radiography is a common indication for CT.[54,79] CT is used to confirm that the SPN is real, confirm that the SPN is solitary, attempt further noninvasive characterization of the lesion, guide percutaneous biopsy of the lesion, and provide staging information if the SPN is found to represent cancer.

In general, CT of a patient with an SPN should be performed with thin-section volumetric imaging to provide detailed analysis of nodule morphology and to allow identification of the presence of fat or calcium (Video 20.6, see Fig. 20.7) within the nodule, and, when the latter is present, the pattern of calcification; this is now fairly routine in the era of *multislice CT* (MSCT) technology.

In up to 20% of instances, a "lung nodule" visible on a chest radiograph actually represents an artifact, chest wall lesion (eFig. 20.28), or pleural abnormality; in some cases, CT is essential to determine the true nature of the opacity. CT can be useful to define the morphology of the SPN and suggest whether it is benign, likely malignant, or indeterminate (i.e., having neither benign nor malignant characteristics). In some patients a specific diagnosis of lesions, such as rounded atelectasis (Fig. 20.8, Video 20.7), a mucous plug, or arteriovenous malformation (Video 20.8) can be made on the basis of CT findings, indicating the benign nature of the lesion.[54,79] Other CT appearances suggest the presence of malignancy (eFig. 20.29).[54] Malignant features include spiculated (see eFig. 20.29D) or irregular margins; air bronchograms within the nodule (see eFig. 20.29A); bubbly air collections (pseudocavitation, eFig. 20.29E); cavitation; and larger size, such as diameter larger than 2 cm (Fig. 20.9, see eFig. 20.29A).[54,79] Benign features include several patterns of calcification (eFig. 20.30), such as diffuse, central, laminated, and chondroid, or "popcorn," calcification patterns (Fig. 20.10, see eFig. 20.30).[54,79] In about 30% of benign nodules, the calcium is not readily visible on chest radiographs but can be seen on thin-section CT (eFigs. 20.31 and 20.32).

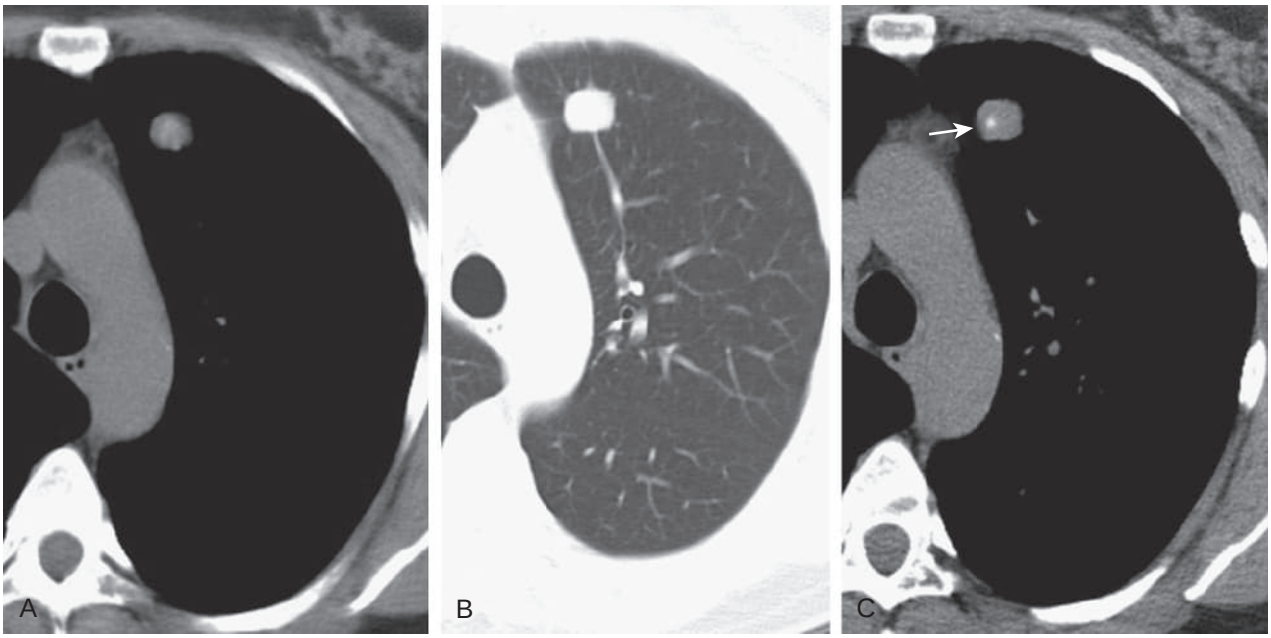

Figure 20.7 Volumetric multislice *computed tomography* (CT) imaging of a pulmonary nodule detected at chest radiography. (A) "Routine" axial 5-mm CT image shows a soft tissue nodule in the left upper lobe. Vaguely increased attenuation is seen within the nodule, suggesting calcification, but the finding is not well seen. (B) Lung window images show that the nodule is circumscribed. (C) Retrospectively reconstructed thin-section (1-mm) soft tissue image more clearly shows a small focus of calcification *(arrow)* within the lesion, suggesting a benign etiology. Coccidioidomycosis titers were elevated, and the patient is being followed. (Courtesy Michael B. Gotway, MD.)

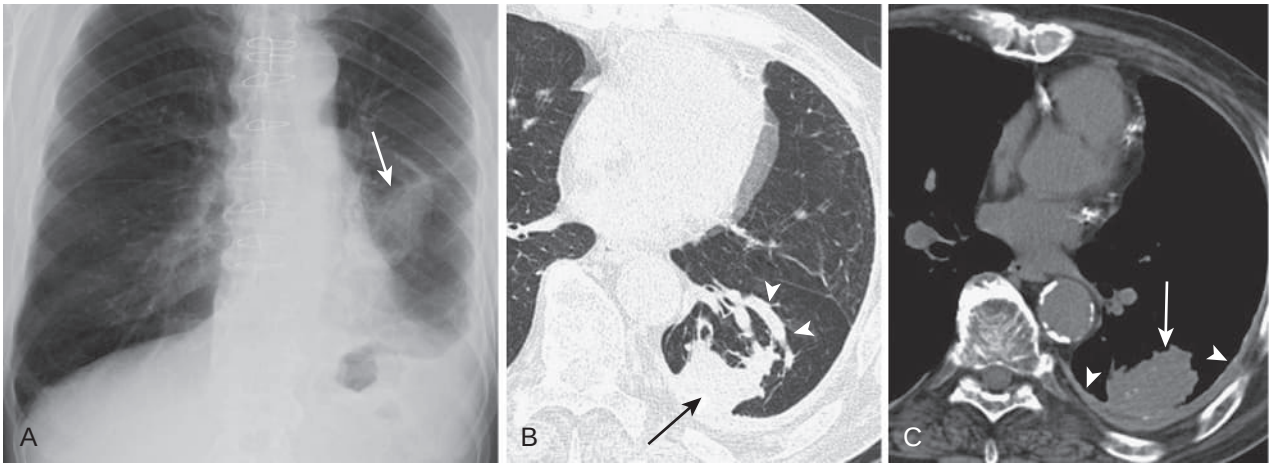

Figure 20.8 Chest *computed tomography* (CT) image shows typical findings of rounded atelectasis. (A) Frontal chest radiograph shows volume loss in the left lower lobe associated with an oblong mass (*arrow*) and left-sided pleural abnormality. (B) Axial chest CT in lung windows shows a subpleural left lower lobe mass (*arrow*) associated with left lower lobe volume loss (posterior displacement of left major fissure, small volume in the left lower lobe). Note "spiraling" appearance of left lower lobe bronchovascular bundles as they extend into the mass (*arrowheads);* this is the so-called comet-tail sign. (C) Axial chest CT displayed in soft tissue windows shows other features consistent with rounded atelectasis including abnormally thickened pleura (*arrowheads*) and contact of the mass (*arrow*) with the abnormal pleura. (Courtesy Michael B. Gotway, MD.)

Carcinomas may occasionally show calcification (eFig. 20.33), although often in an eccentric or stippled pattern. The presence of fat within an SPN, indicated by a low CT attenuation coefficient (Fig. 20.11), strongly suggests the presence of hamartoma[54,79] or lipoid pneumonia (eFig. 20.34); such nodules can be safely followed with serial radiographs.

Malignant tumors tend to show greater enhancement than benign nodules after the rapid injection of iodinated contrast material.[80–83] Because the degree of enhancement depends on the amount and rapidity of contrast infusion, it is important to use a consistent technique. Using a specific contrast enhancement CT protocol, a threshold for enhancement of 15 *Hounsfield units* (HU) or more is typically seen with malignancy, hamartoma, and some inflammatory lesions. Enhancement of less than 15 HU almost always indicates a benign lesion, usually a granuloma. Therefore, whereas positive results (enhancement of >15 HU at any time point during the study) are nonspecific, negative results are quite useful (eFig. 20.35). This technique has been shown to have a sensitivity of 98% and a specificity of 58% in diagnosing carcinoma. More important, the negative predictive value of this technique is approximately 96%.[82] CT nodule enhancement studies are most appropriately used for patients with *indeterminate* nodules (i.e., those without typical benign or malignant appearances). A

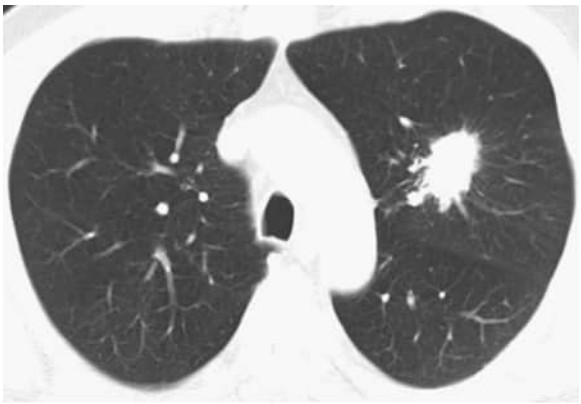

Figure 20.9 Chest computed tomography of bronchogenic carcinoma. Axial computed tomography displayed in lung windows shows a spiculated lesion within the left upper lobe. (Courtesy Michael B. Gotway, MD.)

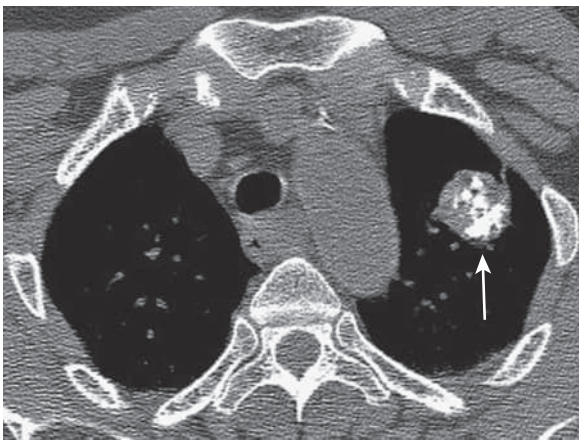

Figure 20.10 Chest computed tomography of hamartoma. Chest computed tomography showing "popcorn" (chondroid) calcification within a left upper lobe nodule (*arrow*), consistent with hamartoma. (Courtesy Michael B. Gotway, MD.)

similar use for dynamic, contrast-enhanced MRI has been reported, although data are limited.[84] Fluorodeoxyglucose *positron emission tomography* (PET) imaging (see Chapter 25) has also been shown to be useful for distinguishing benign from malignant nodules (see Fig. 25.1)[85] and is generally favored over contrast-enhanced CT for additional imaging characterization of indeterminate lung nodules. In a meta-analysis,[84] PET was shown to be 94% sensitive and 83% specific for the differentiation of benign from malignant solid nodules 1 to 3 cm in size, although specificity decreases in regions with a high prevalence of granulomatous infections. The addition of PET-CT tends to increase sensitivity with no change in specificity compared with PET alone.[86] False-positive PET results may be seen with inflammatory processes, particularly granulomatous diseases[84] such as tuberculosis, histoplasmosis, and sarcoidosis. Tumors that may be PET negative include minimally invasive adenocarcinoma (see Fig. 25.2), carcinoid tumors,[84] and some metastases (e.g., renal cell carcinoma).[87] In addition, small nodules may not be large enough to produce a positive result on PET scanning. The sensitivity of PET imaging significantly decreases with nodules measuring less than 8 to 10 mm in diameter. As with any imaging modality, the correlation of the PET results with morphologic features on

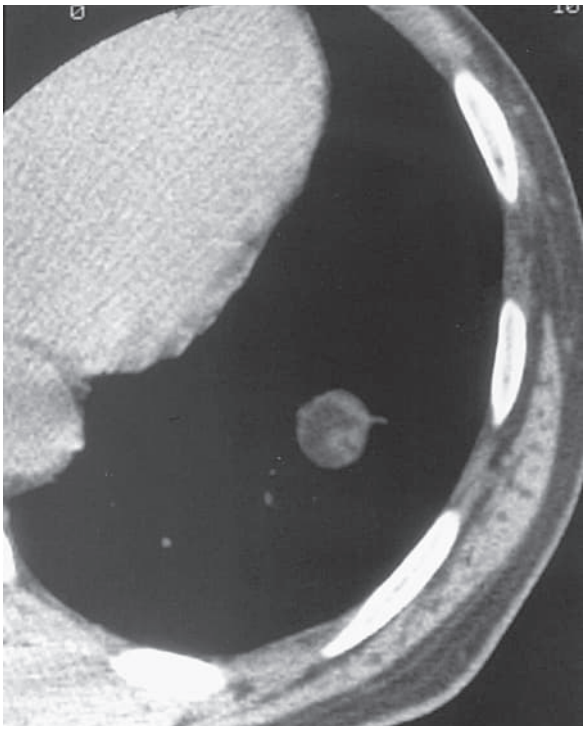

Figure 20.11 Chest *computed tomography* (CT) of a hamartoma. CT shows a low attenuation within the solitary pulmonary nodule (typical CT numbers within the lesion ranged from −90 to −100 Hounsfield units), consistent with fat. (Courtesy Michael B. Gotway, MD.)

CT, prior radiographic examinations, and the clinical presentation will improve the determination of the likelihood of malignancy.

MULTIPLE PULMONARY NODULES

CT is the favored procedure for identifying multiple pulmonary nodules or masses. It detects more and smaller metastases (Fig. 20.12, Video 20.9) than any other imaging technique, and 2- to 3-mm nodules are routinely visible.[88–90] This is most relevant for patients with extrathoracic malignancies, in whom the detection of metastatic disease has a major impact on initial staging and assessment of response to therapy. The major sources of controversy regarding the use of CT for evaluation of possible metastases have been its limited specificity and cost/benefit ratio,[89] although CT is nevertheless widely accepted for this application.

CT is clearly more sensitive than chest radiographs in diagnosing multiple pulmonary nodules in patients with suspected metastasis.[88–90] Although exquisitely sensitive for small nodule detection, CT is not infallible, and nodules, particularly small nodules, can be overlooked. Although it is likely that older reports suffer from biases, such as the possibility that surgical palpation will detect benign nodules, and may overlook some malignant nodules that subsequently manifest as growing nodules at chest CT, as well as the inherent difficulties correlating the location of nodules detected at chest CT with pathologic specimens, there are limitations of chest CT for small nodule detection and characterization.[90]

In accordance, CT results must be interpreted in light of the clinical characteristics of the patient. Primary tumors that commonly spread to the lungs, more advanced

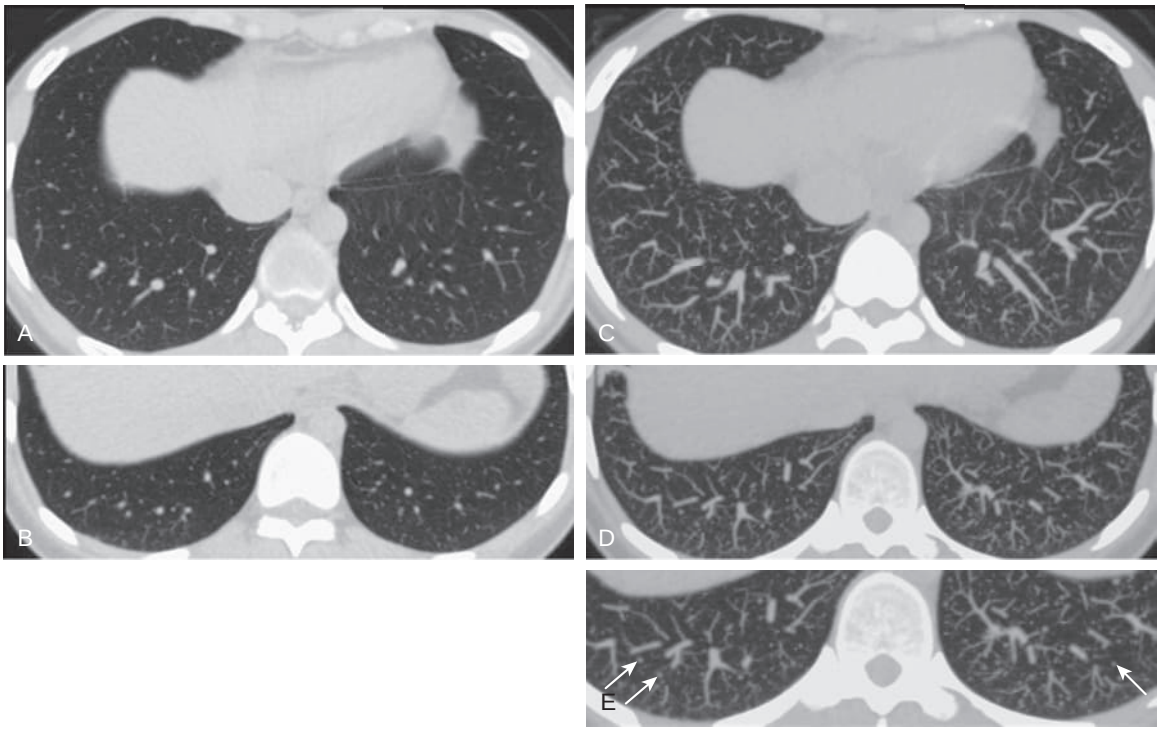

Figure 20.12 Multiple nodules representing pulmonary metastases from papillary thyroid carcinoma in a 28-year-old woman. (A–B) Axial "standard" chest *computed tomography* (CT) images (3-mm reconstruction increment) show little abnormality; some very faint nodularity may be evident in the posterior lung bases. (C–D) Maximum-intensity projected CT images (E magnified image of D) enhance the visualization of very tiny basal pulmonary nodules (*arrows*) representing metastatic disease. These nodules are difficult to visualize at "standard" chest CT (A–B) and were not visible on chest radiography. CT is more sensitive than radiography for detection of small nodules of any cause. (Courtesy Michael B. Gotway, MD.)

malignancies, and the absence of any simulators of metastases (silicosis, sarcoidosis, and prior granulomatous infection) would favor malignancy in pulmonary nodules detected by CT. Furthermore, smaller and less numerous nodules are more likely to be benign. The findings on CT are in themselves not specific, however, and follow-up may be necessary to demonstrate the growth or stability of small nodules.

LUNG CANCER STAGING

In patients with lung cancer, accurate anatomic staging is essential for planning the therapeutic approach.[91,92] CT is used in both assessment of primary tumor extent and detection of lymph node metastases. However, its accuracy in both situations is limited.[91,92] Lung cancer staging is reviewed in detail in Chapter 76.

Computed Tomography

The primary goal of CT is to help distinguish patients who likely have resectable (i.e., potentially surgically curable) tumors from those who do not.[93] Pulmonary malignancy is considered to be likely unresectable (T4) if the primary tumor (1) involves the trachea (eFig. 20.36) or carina; (2) invades the mediastinum (eFig. 20.37) with involvement of mediastinal structures (see eFig. 20.37); (3) invades the heart or great vessels (eFig. 20.38), brachial plexus (C8 or above), recurrent laryngeal nerve, esophagus, diaphragm, or vertebral column (eFig. 20.39); (4) measures more than 7 cm; or (5) is accompanied by separate tumor nodule(s) in a *different* lobe from the primary tumor but still within the *ipsilateral* lung. The tumor is also generally considered unresectable (N3 or M1) when there is (6) contralateral hilar, peribronchial, or mediastinal lymph node involvement; (7) ipsilateral or contralateral scalene or supraclavicular lymph node involvement; (8) tumor nodules present in the lung *contralateral* to the primary tumor, (9) malignant pleural (eFig. 20.40) or pericardial effusion; (10) involvement in nonregional lymph nodes (i.e., those lymph node stations not considered among the N descriptors); and (11) metastatic disease outside the thorax or involving the osseous thorax.[93–97] Note, however, that acceptable morbidity and mortality have been reported after en bloc vertebral body resection with reconstruction for neoplasms invading the spine, particularly after induction chemotherapy, but such extensive surgeries are usually restricted to larger academic or high-volume centers. The presence of satellite nodules in the same lobe as the primary tumor is designated as T3 in the *Eighth Edition of the TNM Classification of Malignant Tumors* (TNM-8) and does not preclude surgical resection.[93–97]

Tracheal (see eFig. 20.36) or carinal invasion (eFig. 20.41) can be suggested with CT but often requires biopsy confirmation. The CT diagnosis of chest wall or mediastinal (see eFig. 20.37) invasion can sometimes be a problem, and many CT scans suggesting chest wall invasion are relatively nonspecific and can be seen with a number of inflammatory disorders. The sensitivity and specificity of CT for diagnosing T4 mediastinal or chest wall invasion are about 60% and 90%,[98,99] respectively, although some findings (e.g., vertebral body destruction, encasement of mediastinal structures, mediastinal fat infiltration) are virtually diagnostic.[98–103] Chest wall invasion is surgically resectable, and even limited mediastinal invasion is considered

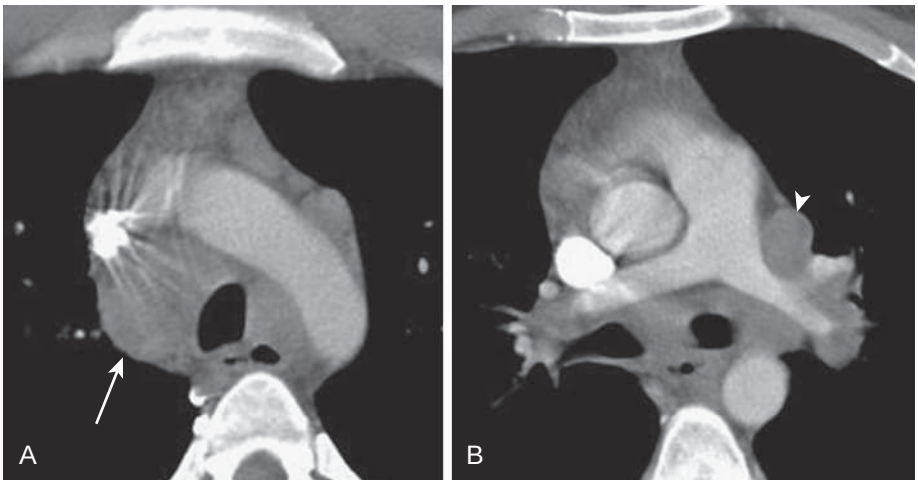

Figure 20.13 Chest computed tomography performed for staging in a patient with non–small cell lung cancer. (A) The primary tumor was present at another level in the right lung. Right paratracheal lymphadenopathy is present (*arrow*); left mediastinal nodes also appear enlarged. (B) Axial chest computed tomography at a slightly lower level shows left hilar and subaortic lymph nodes (*arrowhead*), which measure greater than 1 cm in short-axis diameter, the most widely accepted size threshold for abnormality, and would be considered suspicious for metastasis. Sampling of the left node confirmed metastatic nodal disease. (Courtesy Michael B. Gotway, MD.)

potentially resectable by many surgeons, but knowledge of tumor extent is nonetheless an important factor when planning therapy. Thoracic MRI, either without or with IV contrast, is often considered superior to chest CT for the assessment of local tumor extent when chest wall, spinal, or mediastinal invasion is suspected, particularly in the context of superior sulcus (Pancoast) tumors.[93,96]

CT findings suggesting mediastinal invasion[99,101] include (1) replacement of mediastinal fat by soft tissue attenuation; (2) compression or displacement of mediastinal vessels by tumor; (3) tumor contacting more than 90 degrees of the circumference of a structure, such as the aorta or pulmonary artery (the greater the extent of circumferential contact, the greater the likelihood of invasion); (4) more than 3 cm of contact between tumor and the mediastinum; and (5) obliteration of the mediastinal fat plane normally seen adjacent to most mediastinal structures (eFig. 20.42, see eFig. 20.37). However, individually these findings are unreliable for differentiating mediastinal invasion from anatomic contiguity.[101] Note that invasion of the mediastinal pleura, previously classified as a T3 descriptor in TNM-7, was deleted as a "T" descriptor in TNM-8 because this finding was rarely used as a descriptor in clinical staging. The presence of mediastinal pleural invasion is difficult to determine in practice, and commonly when mediastinal pleural invasion is found at pathologic staging, the primary tumor has already extended beyond the mediastinal pleura and invaded the mediastinum proper (a T4 descriptor in TNM-8).[97]

CT is often of limited value in the diagnosis of malignant pleural effusion because this diagnosis requires cytologic confirmation.[104] However, in some patients CT may show diffuse or nodular pleural thickening with or without (see eFig. 20.40) pleural liquid.[104,105] PET may show tracer uptake in patients with malignant pleural effusion, even when CT does not show evidence of nodular pleural thickening and when cytologic analysis is negative.[106]

The diagnosis of mediastinal lymph node metastasis by CT is determined largely by node size, although the preservation of fat within lymph nodes often reflects the absence of pathologic infiltration, whereas necrosis may imply pathologic infiltration even within normal-sized lymph nodes.[92,96] By convention, a nodal short-axis diameter of greater than 1 cm is considered to be abnormal in all node stations (Fig. 20.13),[92,96] except perhaps in the subcarinal space.[107,108] In general, a tumor cannot be reliably detected in normal-sized lymph nodes by CT, nor do mildly enlarged lymph nodes always harbor tumor[96]; essentially, there are no characteristic appearances that confidently allow benign and malignant causes of nodal enlargement to be distinguished.[108–110] Pooled information from 35 studies published between 1991 and June 2006 evaluating the performance of CT scanning for noninvasive staging of the mediastinum has shown that this size threshold has a sensitivity of only about 51% and a specificity of 86% for diagnosing mediastinal lymph node metastases in patients with lung cancer.[97,111,112] Furthermore, the accuracy of CT for detecting involvement of individual node groups is low (hilar, paratracheal, subcarinal, etc.), perhaps as low as 40%.[111] In a more recent review[92] of the accuracy of mediastinal lymph node staging using CT, a combination of studies evaluating 7368 patients found the median sensitivity and specificity for mediastinal lymph node metastases detection at chest CT of 55% and 81%, respectively.

Despite its limited accuracy, CT, particularly in conjunction with PET, is useful in determining the need for preoperative invasive mediastinal lymph node staging. Furthermore, findings at CT may also be useful in deciding on the choice for a particular preoperative mediastinal staging procedure, such as endobronchial ultrasound, endoscopic ultrasound, mediastinoscopy, anterior mediastinotomy (e.g., the Chamberlain procedure), video-assisted thoracoscopy, or transthoracic needle biopsy.

Perhaps the most important contribution of CT to intrathoracic staging is precise mapping of nodes likely to be involved by tumor and directing additional diagnostic procedures required for accurate lung cancer staging.

Positron Emission Tomography and Positron Emission Tomography–Computed Tomography

The role of PET imaging in the staging of bronchogenic malignancy is explored in detail in Chapters 25 and 76.

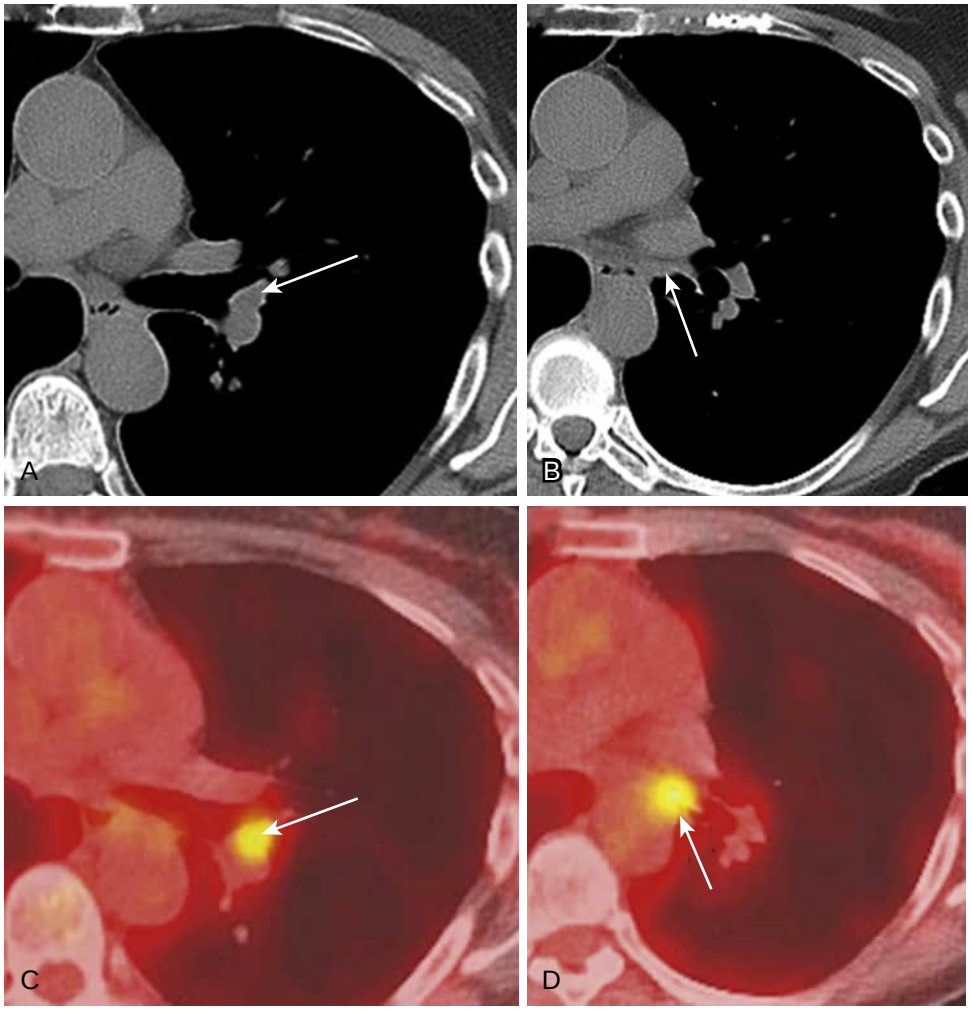

Figure 20.14 Utility of *positron emission tomography–computed tomography* (PET-CT) in the staging of pulmonary malignancy. This patient was diagnosed with left lung non–small cell lung cancer, and CT and PET-CT were performed for staging. (A–B) Axial unenhanced chest CT shows subcentimeter left peribronchial lymph nodes *(arrows).* (C–D) Axial ^{18}fluorodeoxyglucose-PET scan images at the same level as the CT images shows hypermetabolism within the subcentimeter left peribronchial lymph nodes, suggesting tumor involvement. Neoplastic infiltration within left peribronchial lymph nodes was confirmed at surgery. (Courtesy Michael B. Gotway, MD.)

The primary value of PET is to increase the sensitivity for the detection of local and distant malignancy to spare patients with unresectable disease from undergoing unnecessary surgery, thereby reducing the rate of futile thoracotomies.[93,96] PET and PET-CT are most useful for evaluating the N (Fig. 20.14) and M (eFig. 20.43) components of staging,[95] although PET activity in the primary tumor (T component) may provide insight into biologic aggressiveness and the chance of future spread of early localized tumors.[113]

Magnetic Resonance Imaging

There are few situations in which MRI is the preferred imaging modality for patients with primary lung cancer. The extent of chest wall, mediastinal, and great vessel invasion adjacent to a lung tumor sometimes may best be shown by MRI, and there may be some advantage to MRI over CT for assessment of mediastinal invasion, vertebral body invasion, and involvement of the chest wall.[92,93,96] Sagittal or coronal MR images can be advantageous in delineating the extent of tumors at the lung apex.[92,114] As a consequence, MRI may be more accurate than CT for determining chest wall involvement in superior sulcus tumors, and certainly tumor involvement of the neurovascular bundle[114] is better shown with coronal and sagittal MRI than with axial or even reformatted CT images.

In most patients with primary lung cancer, MRI has little additional information to offer, and CT is the preferred imaging procedure.[92] MRI is generally similar to CT in its ability to identify mediastinal lymph nodes[92] and diagnose mediastinal metastases. Although it has been reported that MRI is more accurate than CT in detecting mediastinal[97,115] cardiac or vascular invasion by lung cancer, the reported differences in accuracy are small. In general, the MR properties of benign and tumor-bearing mediastinal lymph nodes do not differ significantly in most patients and, as with CT, node size is usually the main diagnostically useful discriminator. However, recent data with newer MR sequences—particularly diffusion-weighted imaging,[96,116] short-tau inversion recovery imaging,[117,118] and recent observations regarding findings at T2-weighted chest MRI[119]—may allow discrimination between benign and malignant lymph node involvement, even for lymph nodes with short-axis dimensions less than 1 cm. A recent meta-analysis of the performance of MR imaging for peribronchial and mediastinal lymph node status in patients with non–small cell lung carcinoma

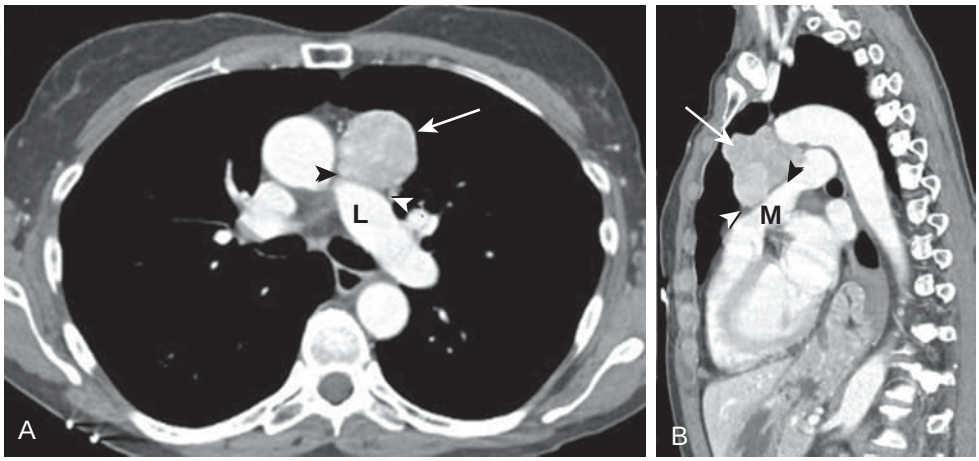

Figure 20.15 ***Computed tomography*** **(CT) for mediastinal mass detection and characterization.** Axial (A) and coronal (B) enhanced chest CT shows a mildly heterogeneous anterior mediastinal mass (*arrows*) subsequently shown to represent a thymoma. The CT image clearly shows a preserved fat plane (*arrowheads*) between the mass and the main (M) and left (L) pulmonary arteries. (Courtesy Michael B. Gotway, MD.)

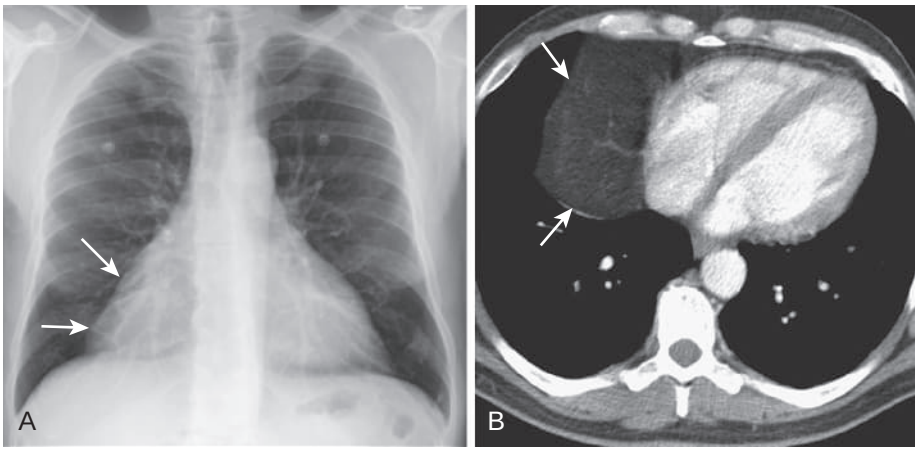

Figure 20.16 **Chest** ***computed tomography*** **(CT) characterization of fatty mediastinal masses.** (A) Frontal chest radiograph shows a contour abnormality (*arrows*) along the right inferior mediastinum. (B) Axial chest CT image shows a fatty right paracardiac mass (*arrows*), consistent with thymolipoma. The diagnosis was confirmed by biopsy. (Courtesy Michael B. Gotway, MD.)

indicates that the per-patient (86.5%) and per-node (87.9%) sensitivity for metastatic involvement is at least comparable to PET-CT at equivalent specificity values.[120] Furthermore, the recent development of hybrid PET-MR scanners could combine the anatomic and physiologic information available from both modalities, further improving noninvasive lung carcinoma staging (eFig. 20.44).

LUNG CANCER SCREENING

Lung cancer screening is discussed in detail with attention to technical aspects of low-dose CT at ExpertConsult.com.

HILAR AND MEDIASTINAL MASSES

CT is indicated as the primary imaging modality in most patients with suspected hilar or mediastinal masses. The cross-sectional display and tissue discrimination of CT have revolutionized diagnostic imaging of the hilum and mediastinum.

Lesions can be detected with high sensitivity and located precisely to a particular region of the mediastinum (see Fig. 20.15, see Chapter 115). By localizing a mass to a particular region of the mediastinum,[147,148] the differential diagnosis can be more specific and biopsy procedures can be planned with greater accuracy and safety. In addition to the information gained from the location of the mass, the density discrimination of CT enables soft tissue abnormalities, fluid collections, and fatty tissue to be distinguished accurately (Fig. 20.16).[149–151] With use of IV contrast material, masses and vascular anomalies (see eFigs. 115.47B, 115.48B–D, and 115.49B) can be accurately discriminated. CT is useful in further evaluating a mass initially detected on chest radiography, for demonstrating pathology suspected on the basis of the clinical setting (but not visible on conventional imaging studies), and for precisely delineating the location of lesions for planning therapy.

MRI may be indicated as the primary imaging modality in patients with a suspected mediastinal mass in many situations: for differentiating thymic neoplasia from thymic hyperplasia, for displaying lesions at the thoracic inlet in the coronal plane, for distinguishing cystic from solid masses (see eFigs. 115.27B–C and 115.42C–D),[152] for detecting hemorrhagic components within a mediastinal lesion (see eFig. 115.35D–E), for distinguishing between surgical (see eFigs. 115.16D–G and 115.23C–D) and nonsurgical (see eFig.

LUNG CANCER SCREENING: TECHNICAL ASPECTS OF LOW-DOSE COMPUTED TOMOGRAPHY EXAMINATIONS AND NODULE REPORTING AND MANAGEMENT

The results of the *National Lung Screening Trial* (NLST) and accumulated experience since that trial were published in 2011[125] have changed the approach to the early detection of primary lung malignancy and have greatly enhanced the understanding of the biologic behavior of early lung malignancy. Furthermore, the results of the NLST and numerous other lung screening studies have highlighted the need for an organized and evidence-based approach to the management of screen-detected nodules. The details of the evidence for CT screening for lung carcinomas and issues related to the institution of a program for early detection of lung cancer, eligibility for screening, and so forth, are reviewed in Chapter 75; the discussion that follows focuses on the technical aspects of CT for lung cancer screening and the reporting and management of screen-detected findings.

Technical Aspects of Computed Tomography Performed for Lung Cancer Screening

In modern practice there is relatively little difference between a "routine" unenhanced chest CT and a "low-dose" CT performed for lung cancer screening purposes. Facilities that perform lung cancer screening are required to perform *low-dose CT* (LDCT) with a volumetric $CTDI_{vol}$ of less than or equal to 3 mGy, with some allowance for variability in patient size (see eFig. 20.27).[126] Although such a requirement may have previously required some active intervention on the part of radiologists to ensure this exposure level is not exceeded, widespread awareness of the need for dose-reduction measures with CT scanning and the myriad tools available on modern CT scanners enabling exposure reduction have made relatively low-dose CT imaging the norm.

Although not mandated as part of the coverage requirements for lung cancer screening as determined by the Centers for Medicare and Medicaid Services, tools that facilitate nodule detection and characterization are valuable adjuncts for LDCT interpretation. One such tool, *maximum intensity projection* (MIP) imaging, has been shown to enhance nodule detection compared with review of the axial CT data alone.[127] When a reconstructed CT slice is thicker than the size of the CT detector, the HU values of the detectors within that slice are averaged and that average HU value is displayed in the corresponding pixel. For example, if a CT scanner has 0.5-mm detectors, a 5-mm-thick slice will contain HU data averaged from 10 detectors. The MIP technique, rather than averaging the HU data from all contributing detectors, displays the highest value only. For the 5-mm slice referenced earlier, the data from the detector with the highest HU value will be displayed. The result is a relatively thick slice that accentuates blood vessels (by displaying them longitudinally for a portion of their course) and nodules, making it easy to differentiate between the two (eFig. 20.45, see Fig. 20.12).[127] The optimal MIP slab thickness for solid-nodule detection at CT is approximately 10 mm.[127]

The Centers for Medicare and Medicaid Services requires that LDCT studies be interpreted using a standardized nodule identification, classification, and reporting system.[126] The ACR's *Lung (CT) Screening Reporting and Data System* (Lung-RADS) has been widely adopted to fulfill this requirement. Lung-RADS is a tool designed to provide a common lexicon and definitions for reporting LDCT results; to standardize practice among radiologists regarding LDCT reporting and management recommendations; to define what constitutes a positive LDCT study; and to facilitate lung cancer screening program quality assurance, improvement, and outcomes.[126,128,129] Having undergone its first revision since its original release in April 2014, Lung-RADS was modeled after the standardized reporting system used in breast imaging, the Breast Imaging Reporting and Data System, also commonly referred to as BI-RADS. The Lung-RADS assigns an overall assessment as a two-part score, which includes a category and, potentially, a modifier (see Fig. 41.3).[128,129] The category classifies a nodule (or the most suspicious nodule when multiple nodules are present) using a score of 0 to 4 on the basis of the presence or absence of specific findings, primarily the combination of (1) nodule size, (2) nodule attenuation, (3) nodule morphology, and (for serial studies), (4) time point (baseline prevalence scan vs. interval or subsequent scan).[128] The possible modifier is coded as S or X. The S modifier is applied when additional significant or potentially clinically significant findings unrelated to lung cancer are present.[128,129] Such findings often include extensive coronary artery calcification, mediastinal masses, thyroid nodules, and abdominal abnormalities, such as renal lesions or abdominal aortic aneurysms (see Fig. 75.2).[129] The X modifier may be used when there are additional features or imaging findings that increase the suspicion for lung cancer, such as nodule spiculation, rapid growth of a nodule, or lymphadenopathy.[128] Each Lung-RADS assessment category includes specific recommendations for patient management (see Fig. 41.3).

Nodule Size

Although there is no specific nodule size below which malignancy is completely excluded, cumulative experience over a number of studies has shown a strong relationship between nodule size and the prevalence of malignancy. The NLST study used greater than or equal to 4 mm as the threshold for a positive LDCT result, with just over half of "positive" LDCT studies across all three screening time points due to nodules in the range of 4 to 6 mm, yet the prevalence of malignancy for nodules in this size range was less than 1%.[125] The initial version of Lung-RADS increased the solid-nodule size required for a positive LDCT screen result from the ≥4 mm greatest transverse diameter threshold used in the NLST[125] to a ≥6 mm bidirectional average. The change was based on accumulated evidence that such a shift would result in far fewer positive results without a substantial loss in sensitivity; this size threshold has been maintained in the most recent iteration of Lung-RADS (version 1.1, see Fig. 41.3). For nonsolid nodules, a ≥20 mm bidirectional average diameter threshold was indicated in the first iteration of Lung-RADS; this threshold has been increased to ≥30 mm in the most recent revision of Lung-RADS (see Fig. 41.3), reflecting the indolent nature of nonsolid nodules compared with solid or part-solid nodules.

With the increase in the threshold for a positive screen result from 4 to 6 mm, investigators have shown a decrease in false-positive results. Pinsky and colleagues[130] showed

that increasing the threshold for a positive screen result from 4 to 6 mm decreased the rate of false-positive LDCT studies from 26.6% to 12.8% at baseline and from 21.8% to 5.8% for interval studies, at the expense of a decrease in sensitivity from 93.5% to 84.9% at baseline and from 93.8% to 78.6% for interval studies. These results were echoed by McKee and colleagues,[131] who found that the application of the original version of Lung-RADS (with the ≥6-mm threshold) reduced the overall positive LDCT study rate compared with NLST criteria from 27.6% to 10.6% while increasing the positive predictive value of a LDCT examination to 17.3% from 6.9% without any false-positive results.

A "negative" baseline LDCT result (Lung-RADS version 1.1, see Fig. 41.3), that is, solid, part-solid, and nonsolid nodules less than 6 mm, 6 mm, and 30 mm, respectively, entails annual screening LDCT, allowing malignant solid nodules less than 6 mm (or nonsolid nodules less than 30 mm) to be detected by the demonstration of growth on the subsequent annual LDCT study. Therefore, for screen-detected solid nodules not yet shown to be stable for more than 2 years (longer for subsolid nodules, see later), caution is required when lung cancer screening participants approach the end of screening eligibility; such patients may require continued CT follow-up to ensure stability of pulmonary nodules detected during screening.[129] A similar assessment applies to interval nodules detected at the end of screening eligibility. An example of the use of the Lung-RADS for the interpretation of LDCT results is shown in eFig. 20.46. Because it is clear that accurate measurements of nodules detected at CT are critical for appropriate management, the Fleischner Society has published guidelines regarding the proper measurement and characterization of pulmonary nodules.[132] Note that the authors of this document have specifically cautioned that the use of their recommendations must be dictated by clinical circumstances, and that these recommendations are not intended to replace other measurement approaches, such as Lung-RADS. Note that there are slight differences between the Fleischner Society recommendations and Lung-RADS version 1.1, particularly regarding the handling of the first decimal place when measuring pulmonary nodules. Nevertheless, this document is a valuable resource for those with interest in the reporting and management of screen-detected pulmonary nodules.

Nodule Attenuation

Nodule attenuation may be classified as *solid* or *subsolid*, the latter further subdivided into *nonsolid* and *part-solid* nodules (eFig. 20.47). *Solid* nodules are nodules that appear as relatively homogeneous soft tissue attenuation. *Nonsolid* nodules, sometimes also referred to as *ground-glass* nodules, are relatively discrete focal parenchymal areas of increased density that do not obscure underlying structures, such as vessels, interlobular septa, and bronchial walls, on ≤1 mm section thickness at lung windows.[54] *Part-solid* nodules consist of a mixture of both nodule types, commonly a larger nonsolid region with internal solid elements; a nodule is often considered part-solid when the solid element comprises less than 50%,[133] or perhaps ≤80%[134] of the nodule. Distinguishing among these nodule morphologies is important because the prevalence of solid nodules is far greater than subsolid nodules at both baseline and interval LDCT studies,[134] the frequency of malignancy is greater for subsolid nodules compared to solid nodules for a given nodule size,[134,135] and the subsolid nodule morphology in general is associated with more indolent lesions along the adenocarcinoma spectrum: atypical adenomatous hyperplasia, adenocarcinoma in situ, minimally invasive adenocarcinoma, and lepidic-predominant adenocarcinoma. Furthermore, subsolid lesions are often associated with slower growth and are less frequently fluorodeoxyglucose avid for a given size compared with solid lesions,[54] and therefore follow-up recommendations tend to differ for these three nodule morphologies for both LDCT screening (see Fig. 41.3) and incidentally detected nodules.[135] Indeed, the reported volume doubling times in one lung cancer screening study for nonsolid and part-solid nodules were 813 and 457 days, respectively, whereas the doubling time for adenocarcinomas manifesting as solid nodules was 149 days.[136] Finally, it is well documented that lung carcinoma presenting as subsolid nodules is associated with very high survivorship, a fact that may influence the management of lung carcinomas with this morphology.[134,137]

Nodule Morphology

Certain morphologic features of nodules, particularly the border (or edge) characteristics, and the presence of calcification or fat, influence the likelihood of malignancy in a pulmonary nodule. Smoothly circumscribed nodules are more likely benign, whereas irregular lobulated or spiculated nodule margins are associated with lung malignancy. In the Dutch-Belgian Randomized Lung Cancer Screening Trial (NELSON) study, compared with smoothly marginated nodules, lobulated and spiculated nodules were associated with likelihood ratios for malignancy of 11 and 7, respectively.[138] However, nodule border characteristics are incompletely discriminatory for differentiating benign from malignant lesions, and for the comparatively small sizes of nodules detected at LCDT, the edge characteristics of a nodule are often difficult to appreciate. One particular morphologic characteristic of a screen-detected nodule that can be considered a benign finding is a nodule that meets the description of an *intrapulmonary lymph node*. Such nodules are recognized as lentiform-, triangular-, or polygonal-shaped, positioned in contact with or within 10 mm from the visceral pleural surface, and when not directly abutting the visceral pleura, possessing linear opacities, or septa, connecting the nodule to the visceral pleural surface, and commonly infracarinal in location[129,138–140] (eFig. 20.48). These nodules, commonly also referred to as perifissural nodules, often represent benign intrapulmonary lymph nodes and are usually less than 10 mm in size (typically 3–6 mm), although perifissural nodules as large as 13 mm have been reported.[140] When these imaging criteria are met, such nodules are virtually always benign, a situation recognized in the most recent version of Lung-RADS.[129] Nodules meeting the definition of an intrapulmonary lymph node are consistent with "negative" findings at LDCT screening and are merely followed at an annual screening of LDCT. When "atypical" imaging features of perifissural nodules are present, such a shape not conforming to the aforementioned description, or lack of visualization of a septum connecting a peripheral nodule to the adjacent visceral pleural surface, an intrapulmonary lymph node remains a possibility but the diagnosis is less certain. Nodules with features

inconsistent with perifissural lymph nodes include irregular shape, spiculation, poorly circumscribed margins, and fissural distortion[139] (eFig. 20.49). Note that nodules meeting the strict definition of perifissural nodules can show growth on follow-up CT scans, sometimes quite rapidly, and therefore the growth of such nodules is not an absolute indicator of malignancy.[141]

Nodule Growth Rate

In addition to nodule size, attenuation, and morphology, nodule growth, defined as an increase in nodule size between two given CT examinations,[132] is used by Lung-RADS version 1.1 to assign the probability of malignancy for a screen-detected pulmonary nodule at LDCT. Nodule growth at CT has traditionally been defined as an increase in diameter, which presumably reflects an increase in nodule volume.[132] With the increasing sophistication of computer software and tools applied to CT imaging, it is now becoming common to measure nodule volume direc tly,[54,126,133,142] and Lung-RADS version 1.1 now incorporates volumetric measurements, in addition to mean diameters, for its nodule assessment categories (see Fig. 41.3), although nodule sizes are still more commonly reported as a mean diameter in clinical practice. Nodule growth on serial CT scans is often approached using the concept of *doubling time*. Assuming a nodule is spherical, the formula for the volume of a sphere indicates that a nodule has doubled in volume when the diameter of the nodule has increased by 26%.[135] Malignant solid pulmonary nodules show doubling times between 20 and 400 days[54,129,133]; nodules growing at a faster or slower rate are commonly benign lesions. Pulmonary malignancies presenting as subsolid nodules, typically lesions along the adenocarcinoma spectrum as discussed previously, are known to have longer doubling times, often more than 400 days and even as long as 1436 days.[129] The doubling times of nodules on serial CT scans are easily determined by entering the mean diameters into a variety of online calculators (eFig. 20.50).[143,144] The notion of using diameter measurements to determine nodule growth begs the question of the accuracy of such measurements. The Fleischner Society recommendations[132] on nodule measurement cite evidence of the relative inaccuracy for the detection of slight changes in diameter for small nodules, particularly those less than 10 mm, a notion echoed by other investigators.[54,133,142] For example, a 4-mm nodule that doubles in volume will barely exceed 5 mm, a change very difficult to detect reliably with CT scanning.[142] The Fleischner Society suggests a 2-mm threshold to define growth of a nodule and further suggests that this threshold be applied to both solid nodules and the solid components of part-solid nodules.[132] This 2-mm threshold reflects rounding up from the 1.5-mm threshold, pursuant to the Fleischner Society recommendations to report nodule measurements to the nearest millimeter,[132] which is consistent with the recommendations in the original iteration of Lung-RADS. Note, however, that Lung-RADS version 1.1 suggests a 1.5 mm change in nodule size to define interval growth and does not round this 1.5-mm threshold to 2 mm as previously (see Fig. 41.3). Lack of demonstrable growth for more than 2 years (doubling time of >730 days)[142] is generally consistent with a benign etiology for solid nodules,[133,142] although protracted surveillance to ensure stability is required for subsolid nodules. Such protracted surveillance is automatic in the LDCT screening context as long as the patient remains eligible for screening. However, when subsolid nodules are encountered incidentally or found in a patient previously enrolled in a lung cancer screening program now "aging out" of screening eligibility, stability should be documented for at least 3 to 4 years,[135,145] possibly even 5 years (see eFig. 20.50),[145] before regarding such nodules as benign.

Although Lung-RADS was enacted to standardize reporting and management for lung cancer screening CT and to facilitate the monitoring and outcome of lung cancer screening programs, it is clear that a number of situations remain unaccounted for in the application of this system. For example, the term "slowly growing" is a descriptor used for nonsolid and part-solid nodules across a number of assessment categories (see Fig. 41.3) but, without precise definition, such descriptors contribute to significant interobserver variability in the application of Lung-RADS to lung CT screening results.[146] Therefore, whereas the use of structured assessments such as Lung-RADS for lung cancer screening CT represents an important advance for improving patient care, additional experience will be required to clarify the impact of such assessments and allow further refinement.

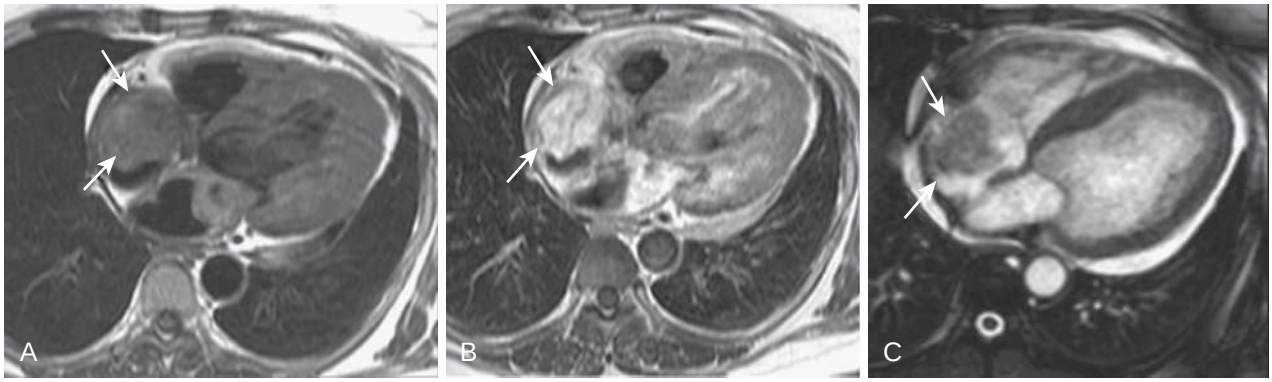

Figure 20.17 ***Magnetic resolution imaging*** **(MRI) characterization of cardiac masses.** (A) Axial T1-weighted image shows a soft tissue–intensity mass (*arrows*) within the right atrium. (B) Contrast-enhanced axial T1-weighted MRI shows intense enhancement of the mass (*arrows*), excluding thrombus as the diagnosis and suggesting neoplasm. (C) Balanced fast-field echo image (obtained for function) shows the mass as a low-signal lesion (*arrows*) within the right atrium. Resection confirmed right atrial myxoma. Most intracardiac right atrial tumors turn out to be thrombus (often catheter/lead related), in which case anticoagulation would be the therapy of choice, and an invasive resection would add unnecessary risk for the patient. Thus, in this case, preprocedural MRI confirmation that the right atrial lesion is indeed neoplastic is critical for guiding patient management. (Courtesy Michael B. Gotway, MD.)

115.15B–D) mediastinal masses,[153] and for evaluation of posterior mediastinal masses (see eFigs. 115.14 and 115.40D–E) and neurogenic tumors (see eFig. 115.14), which may have intraspinal components.[152,154,155] Early experience with mediastinal MRI suggested that this modality may be capable of distinguishing between a tumor mass and a benign fibrous mass[156–158] after radiation therapy, a distinction that can be difficult with CT. However, in practice the differentiation of tumor from associated inflammation or posttreatment changes is difficult with any imaging technique,[156,157] and PET is generally preferred for this distinction.

MRI is rarely indicated for imaging hilar masses; contrast-enhanced CT is usually preferred for this application. Traditionally, contrast-enhanced MR would be considered as an alternative to contrast-enhanced chest CT for the assessment of hilar or mediastinal lesions in patients with impaired renal function, however, in patients with impaired renal function, gadolinium may predispose to fibrosing dermopathy (referred to as nephrogenic systemic fibrosis).[159] Nevertheless, unenhanced MR, due to its inherent high-contrast resolution (see eFig. 115.15), may still provide valuable information regarding hilar and mediastinal masses.

Primary and metastatic cardiac tumors are often detected initially by echocardiography, but MRI is also an accurate method of delineating such lesions.[160–162] It is thus appropriate as a problem-solving technique for patients with inconclusive echocardiographic examinations, but it is also emerging as a first-line examination for a number of cardiovascular applications. Both MRI and CT can specifically demonstrate fat within cardiac lesions and fluid within pericardial cysts (see eFig. 115.42B–D). Intracardiac tumor (Fig. 20.17) and thrombus can be differentiated by MRI, particularly after contrast administration.

DIFFUSE LUNG DISEASE

The clinical assessment of a patient with suspected *diffuse ILD* (DILD) can be a difficult and perplexing problem. Imaging studies are often important in reaching a final diagnosis, suggesting appropriate diagnostic procedures, and assessing the patient's course and prognosis.

In clinical practice, the imaging studies most frequently used to evaluate patients with suspected DILD are chest radiographs and *high-resolution CT* (HRCT). HRCT is a technique that combines narrow collimation/thin-slice thickness (≈1 mm) and image reconstruction with a high-spatial-frequency algorithm to maximize sharpness in the final image—often accompanied by prone and postexpiratory imaging—and is typically used when the diagnosis is uncertain at chest radiography and clinical evaluation and further assessment is considered warranted, as well as to assess treatment response in patients with established diagnoses.

HRCT findings have been described in a wide variety of parenchymal diseases, including the idiopathic interstitial pneumonias,[163] sarcoidosis,[164–167] diffuse neoplasms, pneumoconioses,[168–172] infections, and numerous other disorders.[173–185] These studies have shown that HRCT delineates both normal anatomic structures (Fig. 20.18) and pathologic alterations in lung morphology more clearly than chest radiographs or routine CT.[167,181,186,187] Much of the basis of HRCT interpretation rests on recognition of the anatomy of the secondary pulmonary lobule (see Fig. 20.18) as reflected on HRCT images; in particular, the histopathologic patterns of disease involvement of the secondary pulmonary lobule are often reflected in HRCT images, and recognition of the HRCT correlates of these disease facilitates noninvasive diagnosis. This approach is particularly useful for the anatomic localization of small nodules at HRCT, described later.

In general, HRCT findings of lung disease can be divided into *increased* lung opacity, including reticular, linear, and nodular opacities, consolidation, and *ground-glass opacity* (GGO), and *decreased* lung opacity, including cysts, cavities, emphysema, and mosaic perfusion.[188]

Increased Lung Opacity

Linear and Reticular Opacities. Thickening of the interstitial fiber network of lung by fluid, fibrous tissue, or interstitial infiltration by cells results in an increase in both linear and reticular opacities as seen on HRCT.[188] Interlobular septal thickening is seen in patients with a variety of ILDs, but most typically with increased pressure pulmonary edema, lymphangitic spread of tumor (Fig. 20.19A),[188] and sarcoidosis,[166] in addition to a small number of rarer causes.[171,189,190] Septal thickening is not common in patients with interstitial fibrosis, except for those with sarcoidosis and

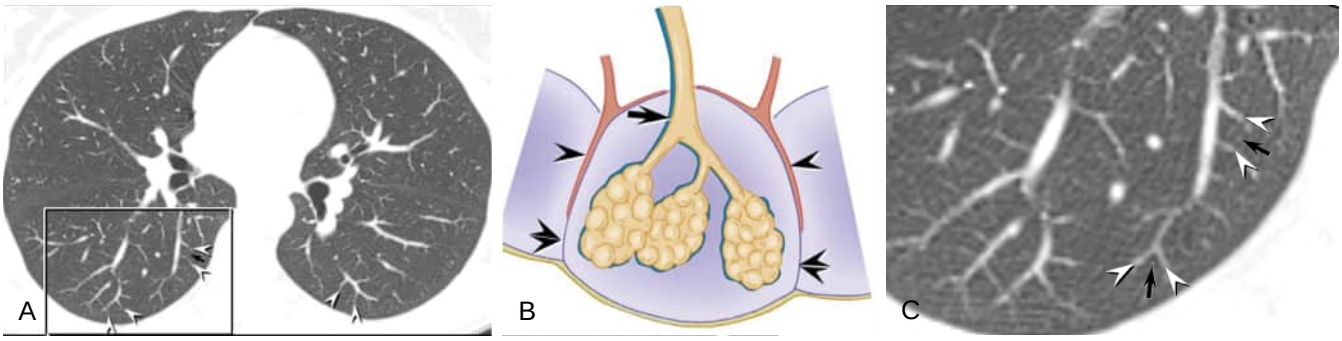

Figure 20.18 Normal high-resolution chest computed tomography (HRCT): secondary lobular anatomy. (A) Axial HRCT image through the level of the right lower lobe bronchus shows normal major (oblique) fissures, central airways, and pulmonary vessels. (Inset C is a detailed image of the area of interest in the right lower lobe.) Small peripheral pulmonary veins (*white arrowheads*) are visible. Pulmonary veins travel within interlobular septa and therefore may outline secondary pulmonary lobules (lung parenchyma between *white arrowheads*). On occasion, the centrilobular artery (*black arrows*), the artery entering the center of the pulmonary lobule, may normally be visible. An understanding of secondary pulmonary lobular anatomy underlies the anatomic approach for localization of small nodules detected at HRCT, which provides the basis for differential diagnosis of such nodules. (B) Illustration of the normal secondary pulmonary lobule. Pulmonary veins (*single arrowheads*), travel within interlobular septa (*double arrowheads*). The centrilobular artery and bronchus (*arrow*) enter the secondary lobule and branch sequentially, eventually extending to the level of gas-exchange units—respiratory bronchioles, alveolar ducts, alveolar sacs, and alveoli and the capillary network associated with these structures. (A and C, Courtesy Michael B. Gotway, MD.)

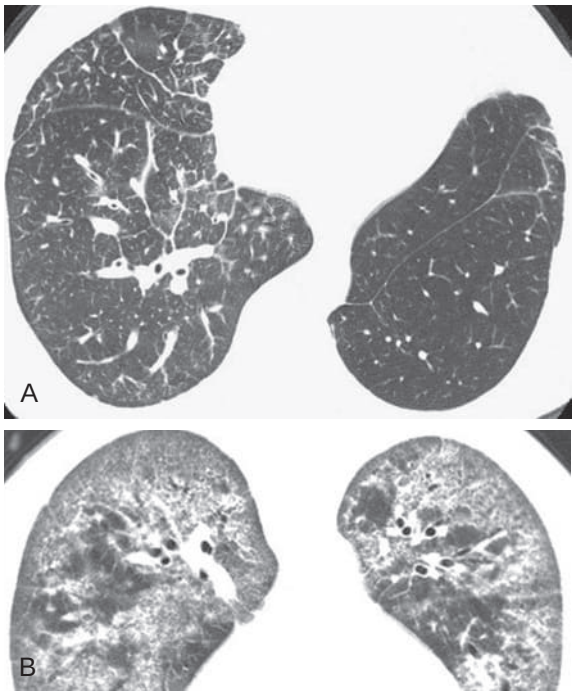

Figure 20.19 Both *interlobular* septal thickening and *intralobular* interstitial thickening. (A) Axial high-resolution computed tomography image shows smoothly thickened interlobular septa (*arrowheads*) in a patient with metastatic breast carcinoma; note asymmetry of the process. (B) Prone high-resolution computed tomography image in a patient with scleroderma shows reticular opacity resulting from numerous intralobular lines, manifesting as small, fine lines separated by a few millimeters, creating a fine, lace- or netlike pattern. Mild peripheral bronchiolectasis (*arrow*) is present. (Courtesy Michael B. Gotway, MD.)

asbestosis.[191] The term *intralobular lines* refers to a pattern of small lines within the secondary lobule separated by a few millimeters creating a reticular or netlike pattern. This finding is commonly seen in the context of fibrotic lung diseases (see Fig. 20.19B) but may also be encountered with interstitial inflammation in the absence of fibrosis. Pathologically, intralobular lines, or intralobular interstitial thickening, reflect infiltration of the distal peribronchovascular interstitium and the interstitium within the secondary lobule.

Nodules. Nodules can be classified as *perilymphatic, random*, or *centrilobular*, according to their distribution within the secondary pulmonary lobule (see Fig. 20.18).[188,192] Recognition of one of these distributions is fundamental to the generation of differential diagnoses.[192,193]

- *Perilymphatic* nodules affect the peribronchovascular, interlobular septal, subpleural, and, to a lesser extent, centrilobular interstitial compartments and are typical of sarcoidosis, which tends to have a peribronchovascular and subpleural predominance (Fig. 20.20, Video 20.10)[166,192–194]; silicosis and coal workers' pneumoconiosis, which predominate in the subpleural and centrilobular regions[171,176,189]; and lymphangitic spread of tumor, which is usually peribronchovascular and septal.[188]
- *Random* nodules are found both in perilymphatic and in centrilobular locations, and are defined by a broad diffuse and fairly even pattern in the lung. They are most typical of miliary infections (Fig. 20.21)[195] and hematogenous metastases.[188]
- *Centrilobular* nodules are predominantly located in the bronchovascular location in the center of the secondary lobule. They can be either well-defined or poorly defined. *Well-defined centrilobular* nodules can be seen in silicosis and coal workers' pneumoconiosis,[169] asbestosis,[168] and *pulmonary Langerhans cell histiocytosis* (PLCH).[196] *Poorly defined centrilobular* nodules often reflect bronchiolar or peribronchiolar abnormalities[193] and can be seen in silicosis and coal workers' pneumoconiosis,[169] endobronchial spread of infection,[195] pulmonary hemorrhage (Fig. 20.22), hypersensitivity pneumonitis,[197,198] and pulmonary edema.[199]

A comparison of the three nodular distributions using HRCT is shown in Fig. 20.23.

Consolidation and Ground-Glass Opacity. Air space consolidation, by definition, is seen when alveolar air is replaced by fluid, cells, or other material.[200] On HRCT, consolidation results in an increase in lung opacity associated with obscuration of underlying vessels. Among patients with chronic DILD, common causes of this pattern include chronic eosinophilic pneumonia and cryptogenic organizing

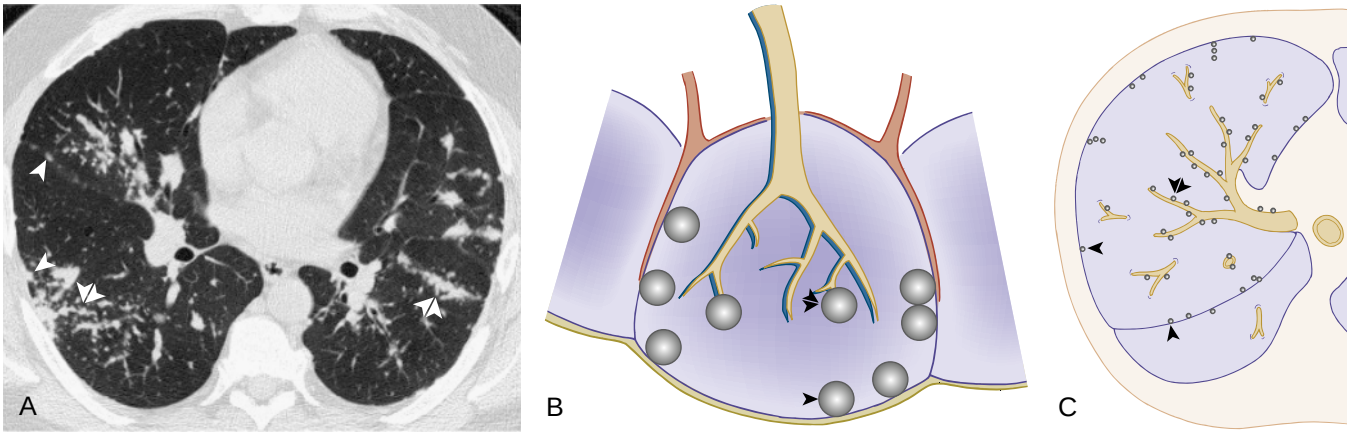

Figure 20.20 ***High-resolution computed tomography*** **(HRCT) illustration of perilymphatic nodules: sarcoidosis.** (A) Axial HRCT image of a patient with sarcoidosis shows numerous subpleural nodules in relation to costal and fissural visceral pleural surfaces (*single arrowheads*), and nodules are also clearly visible along bronchovascular bundles (*double arrowheads*). These findings, along with the patchy distribution of the nodules, are diagnostic of sarcoidosis in the appropriate clinical setting. (B) Perilymphatic nodule distribution in the secondary pulmonary lobule and (C) anatomic localization. Small nodules are primarily distributed along the visceral pleural surfaces (*single arrowhead*) and interlobular septa; to a lesser extent, they may also appear in the centrilobular area, at the bronchovascular bundles (*double arrowheads*). (A, Courtesy Michael B. Gotway, MD.)

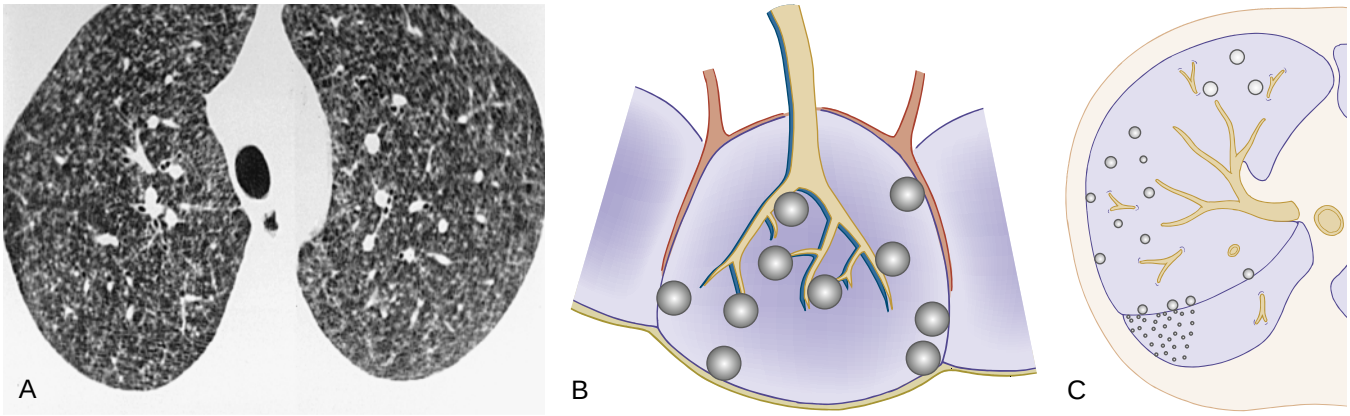

Figure 20.21 ***High-resolution computed tomography*** **(HRCT) illustration of random nodules: miliary tuberculosis.** (A) Axial HRCT image shows numerous small circumscribed nodules equally distributed throughout the lungs bilaterally, with nodules seen in contact with fissural pleural surfaces, as well as sparing the fissural surfaces. (B) Random nodule distribution in the secondary pulmonary lobule. Small nodules are seen along the visceral pleural surfaces, interlobular septa, and bronchovascular bundles. (C) Anatomic localization of small nodules at HRCT. Random nodules are distributed in a fairly even, diffuse distribution bilaterally. (A, Courtesy Michael B. Gotway, MD.)

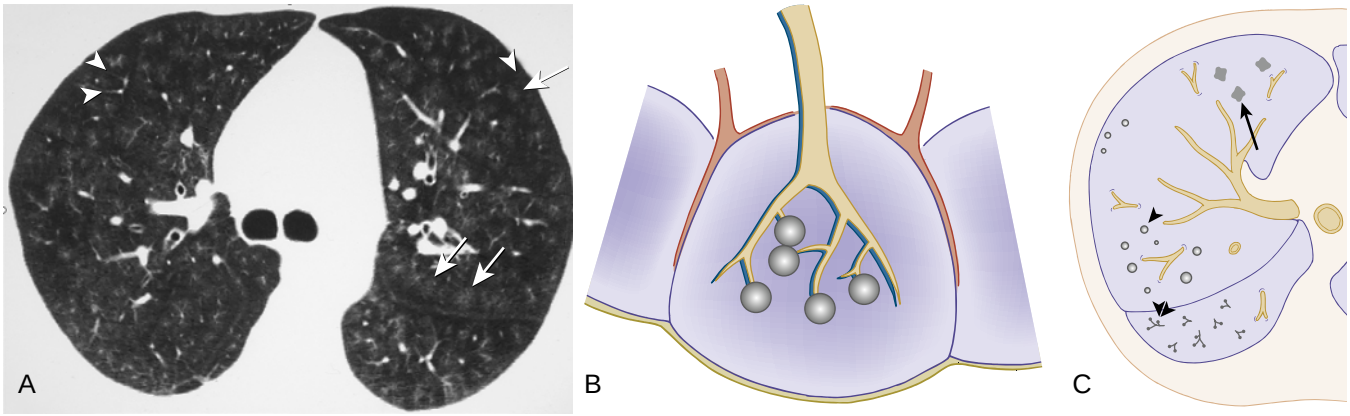

Figure 20.22 ***High-resolution computed tomography*** **(HRCT) illustration of centrilobular nodules: diffuse pulmonary hemorrhage.** (A) Axial HRCT image shows numerous bilateral poorly defined, ground-glass opacity nodules (*arrows*). Note that the nodules approach, but generally do not touch, costal and fissural visceral pleural surfaces; this relationship is particularly evident along the left major fissure. Also note that occasionally the relationship of the nodules to adjacent pulmonary veins (*arrowheads,* right upper lobe) and interlobular septa (*arrowhead,* left upper lobe) is apparent; the nodules have a small amount of "spared" lung separating them from the interlobular septa and small pulmonary veins, a key indicator of the centrilobular distribution. (B) Centrilobular nodule distribution in the secondary pulmonary lobule. Small nodules are seen primarily in the center of the lobule, along the bronchovascular bundles, largely sparing the interlobular septa, pulmonary veins, and visceral pleural surfaces. (C) Anatomic localization of small nodules at HRCT. Centrilobular nodules typically approach, but do not contact, the costal and fissural visceral pleural surfaces and interlobular septa. Centrilobular nodules may be well defined and round (*single arrowhead*) or poorly defined and irregular in shape (*arrow*), or they may show ground-glass attenuation. When centrilobular nodules show branching configurations (*double arrowhead*), the nodule morphology is often described as tree-in-bud opacity. (A, Courtesy Michael B. Gotway, MD.)

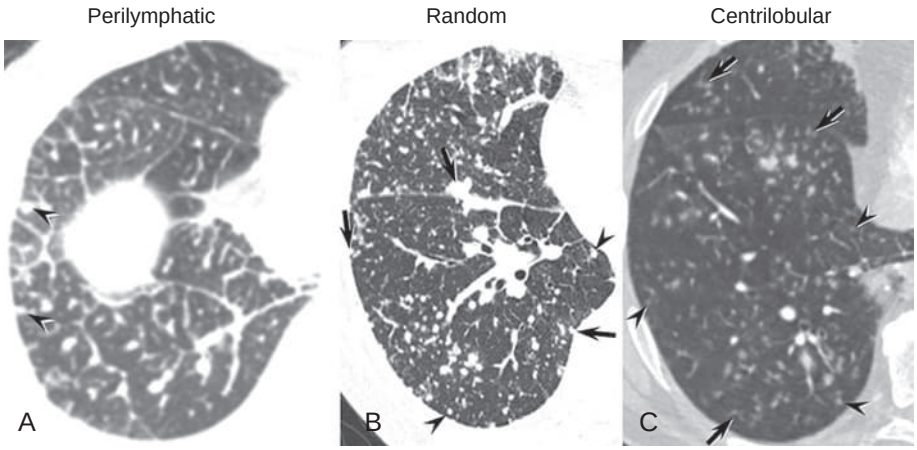

Figure 20.23 Comparison of nodule distribution patterns on *high-resolution computed tomography* (HRCT). (A) Axial HRCT image in a patient with lymphangitic carcinomatosis illustrates the perilymphatic small nodule distribution. Note how many of the small, circumscribed nodules are in contact with visceral pleural surfaces (*arrowheads*). Also note the presence of prominent interlobular septal thickening. (B) Axial HRCT image in a patient with metastatic malignancy illustrates the random small nodule distribution. Many nodules approach, but do not contact, the visceral pleural surfaces (*arrowheads*), consistent with a centrilobular localization, whereas other nodules (*arrows*) clearly contact the visceral pleural surfaces. Critically, the small nodules characteristic of the random distribution pattern are *diffusely distributed*—present throughout the lung parenchyma in a roughly equal manner—as opposed to the *patchy distribution* characteristic of perilymphatic processes. (C) Axial HRCT image in a patient with bronchopneumonia and centrilobular small nodule distribution shows numerous, bilateral, poorly defined nodules, most of which approach, but generally do not touch, costal and fissural visceral pleural surfaces (*arrowheads*). Several nodules also show a branching configuration—so-called tree-in-bud morphology (*arrows*)—typical of inspissated mucous and pus within small airways.

pneumonia.[201,202] GGO refers to a hazy increase in lung opacity that is not associated with obscuration of underlying vessels.[200] This finding can reflect the presence of a number of diseases and can be seen in patients with either minimal interstitial thickening or minimal air space filling.[180,182,203–206] It often reflects the presence of an active process, such as pulmonary edema (see eFig. 98.7G); alveolitis associated with some idiopathic interstitial pneumonias (see Chapters 89 and 90); pulmonary hemorrhage (see Fig. 20.22 and Chapter 94); infectious pneumonias, particularly *Pneumocystis jirovecii* pneumonia (see eFigs. 123.12B, 123.14C, 123.15B, 123.18); lipoid pneumonia (see eFigs. 43.2B and 98.7B); alveolar proteinosis (see Fig. 98.3 and eFigs. 98.5, 98.6, 98.9A–D, 98.10, and 98.11); hypersensitivity pneumonitis (see Fig. 91.4), often with a centrilobular nodular appearance (see Fig. 20.23 and eFig. 91.3C–D); and sarcoidosis.[207] However, GGO may reflect the presence of fibrosis below the resolution of HRCT, particularly when the GGO is associated with other findings of fibrotic lung disease, such as coarse reticulation, architectural distortion, traction bronchiectasis, and honeycombing.[204] Because of its potential reflection of active lung disease, the presence of GGO may lead to surgical lung biopsy depending on the clinical status of the patient.

Decreased Lung Opacity

Emphysema. Emphysema is accurately diagnosed with HRCT, and HRCT is more sensitive for the detection of emphysema than is routine CT or chest radiography.[143,183] Emphysema results in focal areas of low attenuation easily contrasted with surrounding, higher-attenuation, normal lung parenchyma (Fig. 20.24). In patients with centrilobular emphysema (see Fig. 20.24A), areas of lucency can be seen surrounding the centrilobular artery and have a patchy, upper lobe distribution. In panlobular emphysema, focal areas of lucency are usually not present, but a diffuse simplification of lung architecture and a decrease in lung attenuation are present (see Fig. 20.24B). Paraseptal emphysema is readily diagnosed at HRCT (see Fig. 20.24C), appearing as thin-walled cystic spaces of variable size forming a single layer, usually predominating in the upper lobes. In clinical practice, HRCT is not commonly used to diagnose emphysema; usually, the combination of a smoking history, a low diffusing capacity, airway obstruction on pulmonary function tests, and an abnormal chest radiograph showing large lung volumes is sufficient to make the diagnosis. HRCT is useful for evaluating patients with COPD being considered as candidates for lung volume–reduction procedures, bullectomy, or lung transplantation. In addition, some patients with early emphysema can present with clinical findings more typical of infiltrative lung disease or pulmonary vascular disease, namely shortness of breath and low diffusing capacity, without evidence of airway obstruction on pulmonary function tests.[208] In such patients, HRCT can be valuable for detecting the presence of emphysema and excluding an interstitial abnormality. If significant emphysema is found on HRCT, no further evaluation is necessary.[209] A growing area of interest for the application of HRCT in COPD is the quantification of imaging features of obstructive pulmonary disease. Quantitative assessment of emphysema and CT measures of bronchial wall thickness in patients with COPD independently predict airflow obstruction severity at pulmonary function testing and the risk of COPD exacerbations.[210] Furthermore, the quantitative assessment of emphysema in patients with COPD is also associated with increased all-cause mortality.[210]

Further discussion of functional imaging and quantification in COPD and fibrotic lung disease is available at ExpertConsult.com.

Cystic Pulmonary Diseases. Lymphangioleiomyomatosis (see images associated with Chapter 97, eFig. 97.2, and Fig. 20.25A–B) and PLCH (see Chapter 95) often result in multiple lung cysts (see Figs. 95.1B and 20.25C), which have a distinct appearance on HRCT.[196,211–217] The cysts have a thin but easily discernible wall, ranging up to a few millimeters in thickness. Associated findings of fibrosis are usually absent or much less conspicuous than they are in patients

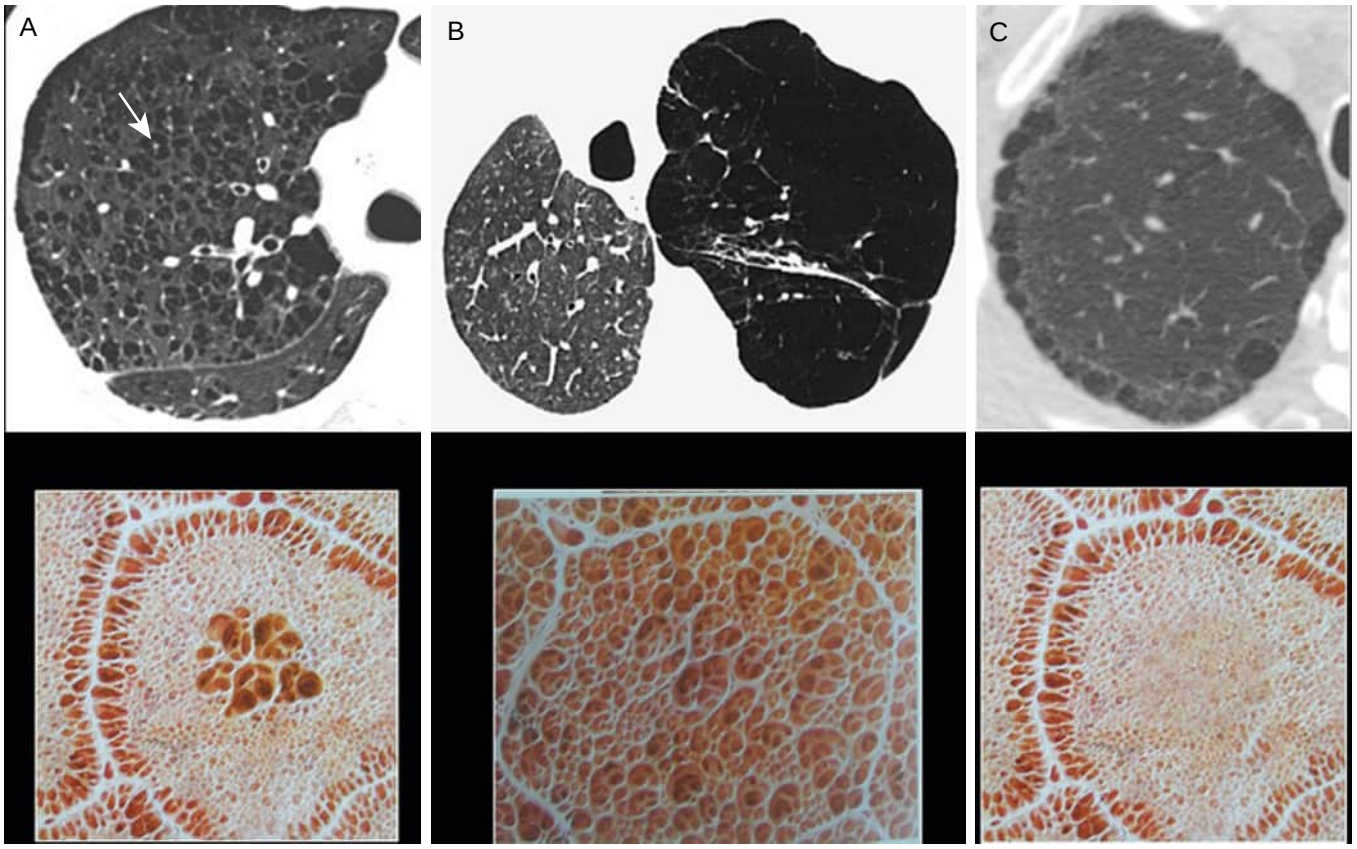

Figure 20.24 ***High-resolution computed tomography*** **(HRCT) appearance of emphysema and accompanying illustrations of the secondary lobule.** (A) Axial HRCT image in a patient with centrilobular emphysema shows upper lobe, well-defined, "punched-out" cystic spaces without definable walls. Note the centrilobular "dot" (*arrow*) in the center of many of the cystic spaces, representing the centrilobular artery. (B) Axial HRCT image in a patient with panlobular emphysema who underwent right lung transplantation shows the emphysematous left lung contrasted with the normal-appearing right lung. The left lung is less dense, is larger in volume, and contains fewer and smaller vessels, with "simplified" pulmonary architecture. (C) Axial HRCT image in a patient with paraseptal emphysema shows upper lobe, well-defined, thin-walled cysts lining the subpleural regions in the upper lobes, forming a single layer. Lower panels illustrate the changes at the lobular level. (Courtesy Michael B. Gotway, MD.)

with honeycombing. In these diseases, the cysts are usually interspersed within areas of normal-appearing lung. In patients with PLCH (see Fig. 95.1B–D), the cysts can have bizarre shapes and an upper lobe predominance. Numerous causes of cystic and cavitary pulmonary lesions are recognized (eFig. 20.51, see Fig. 20.25).[218,219]

Mosaic Perfusion. Decreased lung attenuation not reflecting the presence of cystic lesions or emphysema can sometimes be recognized on HRCT in patients who have diseases that produce air trapping, poor ventilation, or poor perfusion (Fig. 20.26A).* The areas of decreased lung attenuation seen on HRCT can be focal, lobular (see Fig. 20.26C),[222] lobar, or multifocal. The term *mosaic perfusion* has been used to refer to patchy decreased lung attenuation resulting from perfusion abnormalities (see Figs. 20.25K and 20.26A).[200] In patients with air trapping, this appearance can be enhanced with expiratory HRCT (see Fig. 20.26C).[183,221,223,224]

Honeycombing

The Fleischner Society defines honeycombing (Fig. 20.27A–C and G) as "the appearance of clustered cystic air spaces, typically of comparable diameters on the order of 3 to 10 mm but occasionally as large as 2.5 cm. Honeycombing is usually subpleural and is characterized by well-defined walls. It is a CT feature of established pulmonary fibrosis and is an important criterion in the diagnosis of usual interstitial pneumonia."[200] Although seemingly a straightforward imaging finding, the CT diagnosis of honeycombing is surprisingly subject to significant interobserver variability, even among experts.[225] Honeycombing is an important imaging feature for the diagnosis of the usual interstitial pneumonia pattern at CT, and hence it must be distinguished from other findings that may mimic the appearance of honeycombing (see Fig. 20.27D–F and H), particularly paraseptal emphysema (see Fig. 20.27D and H), cystic lung diseases, and traction bronchiectasis.

Important imaging features that suggest the diagnosis of honeycombing include cystic spaces with relatively thick, shared walls arranged in concentric layers, often in the subpleural regions of lung; perhaps most important, these findings should be seen in the context of other features of fibrotic lung disease, such as traction bronchiectasis, intralobular lines, and architectural distortion.

Diagnostic Utility

CT, in particular HRCT, has essentially replaced chest radiography for the detection and assessment of the treatment response for numerous causes of DILD, owing to the

*References 183, 201, 203, 205–209, 213–215, 220, 221.

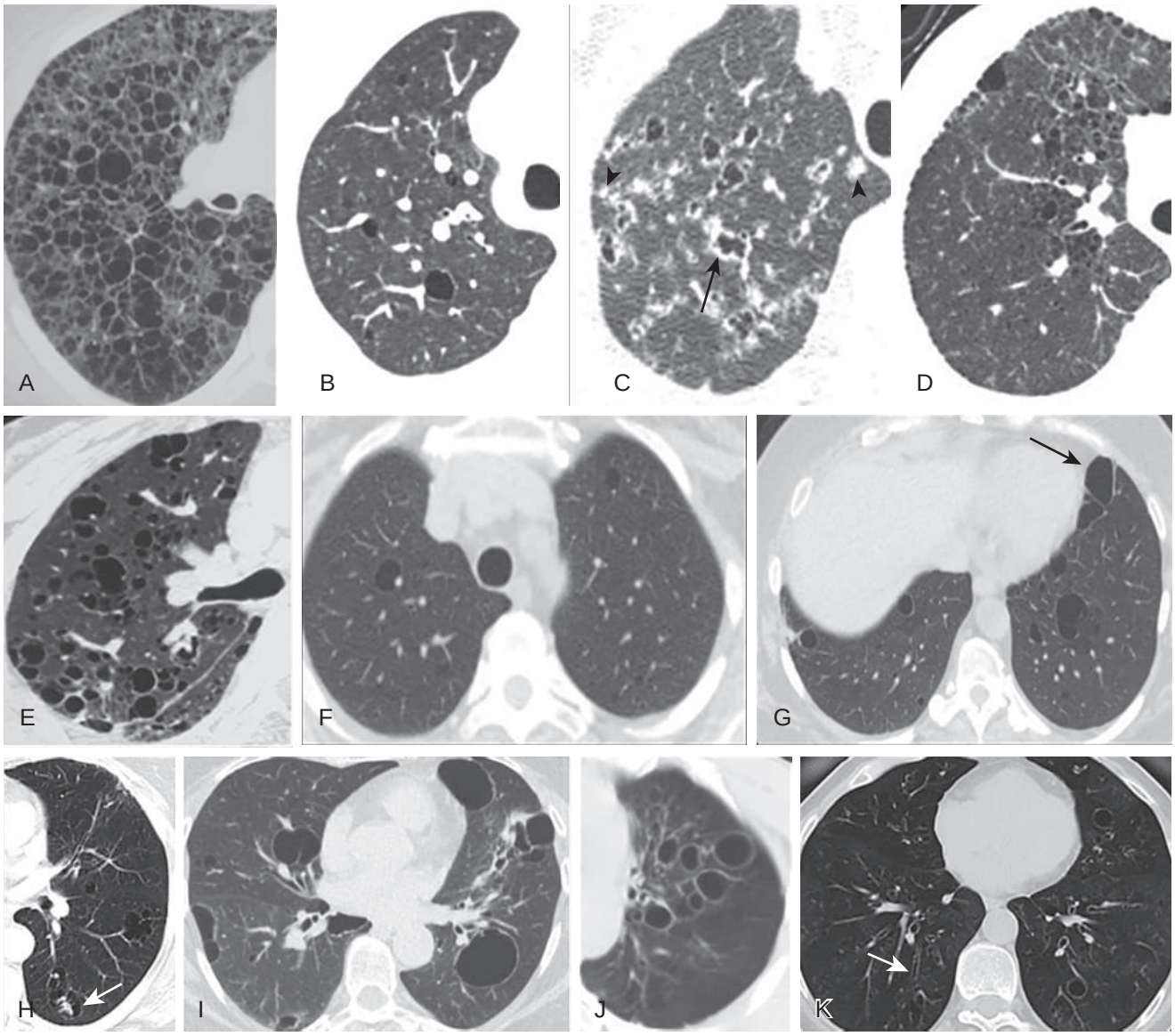

Figure 20.25 ***High-resolution computed tomography*** **(HRCT) appearances of diffuse cystic pulmonary diseases.** (A–B) Axial HRCT images in two patients with lymphangioleiomyomatosis, one with extensive disease (A) and the other with a paucity of cysts (B), show multiple cystic areas having clearly definable walls, in contrast to the appearance of emphysema. (C) Axial HRCT image in a 19-year-old patient with pulmonary Langerhans cell histiocytosis shows upper lobe irregular (bizarre-shaped), somewhat thick-walled cysts (*arrow*) and small nodules (*arrowheads*). (D) Axial HRCT image in a nonsmoking patient with juvenile rheumatoid arthritis and biopsy-proven follicular bronchiolitis shows uniform, thin-walled cysts in the subpleural regions of lung and more centrally located cysts. (E) Axial HRCT image in a patient with Sjögren syndrome and lymphocytic interstitial pneumonia shows uniform, thin-walled cysts in the midlung. (F–G) Axial HRCT image in a patient with Birt-Hogg-Dubé syndrome shows lower lobe predominant cysts, some with an oblong, septated appearance in a subpleural, paramediastinal location (*arrow*). (H–I) Axial HRCT images in two patients, one with amyloidosis (H) and the other with biopsy-proven pulmonary light chain deposition disease (I), show multiple pulmonary cysts. One cyst in the patient with amyloidosis shows a calcified nodule within the cyst (*arrow*). (J–K) Axial HRCT image in two patients with constrictive bronchiolitis shows multiple thin-walled cysts in addition to large airway thickening (*arrow*) and inhomogeneous lung opacity representing mosaic perfusion due to severe airflow obstruction. (Courtesy Michael B. Gotway, MD.)

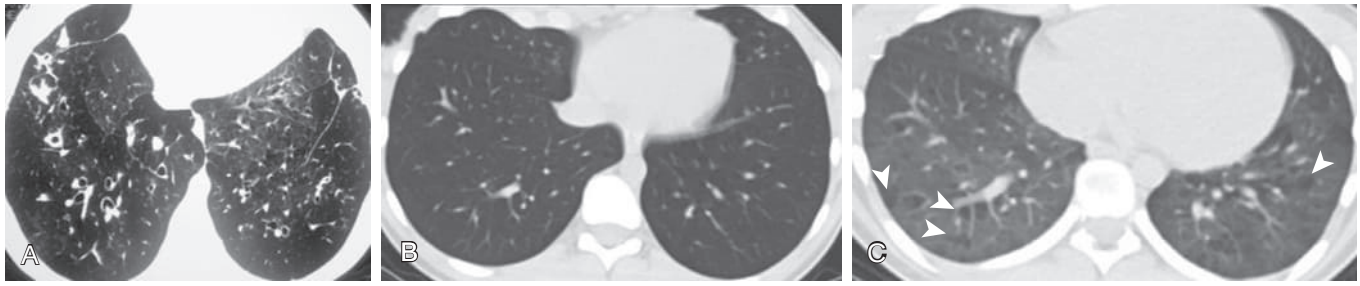

Figure 20.26 Mosaic perfusion and lobular gas trapping at ***computed tomography*** **(CT) imaging.** (A) Axial high-resolution CT image in a patient with cystic fibrosis and mosaic perfusion shows inhomogeneous opacity in the lung bases bilaterally. The areas of decreased attenuation represent mosaic perfusion, in this patient resulting from a combination of regional air trapping due to large airway disease and hypoperfusion in the affected areas of lung. Axial inspiratory (B) and postexpiratory (C) CT images through the lower lungs in a 19-year-old patient with asthma shows relatively normal findings at inspiratory imaging (B) but, at postexpiratory imaging (C), numerous small lobular areas of low attenuation (*arrowheads*) develop, consistent with small airway obstruction. (Courtesy Michael B. Gotway, MD.)

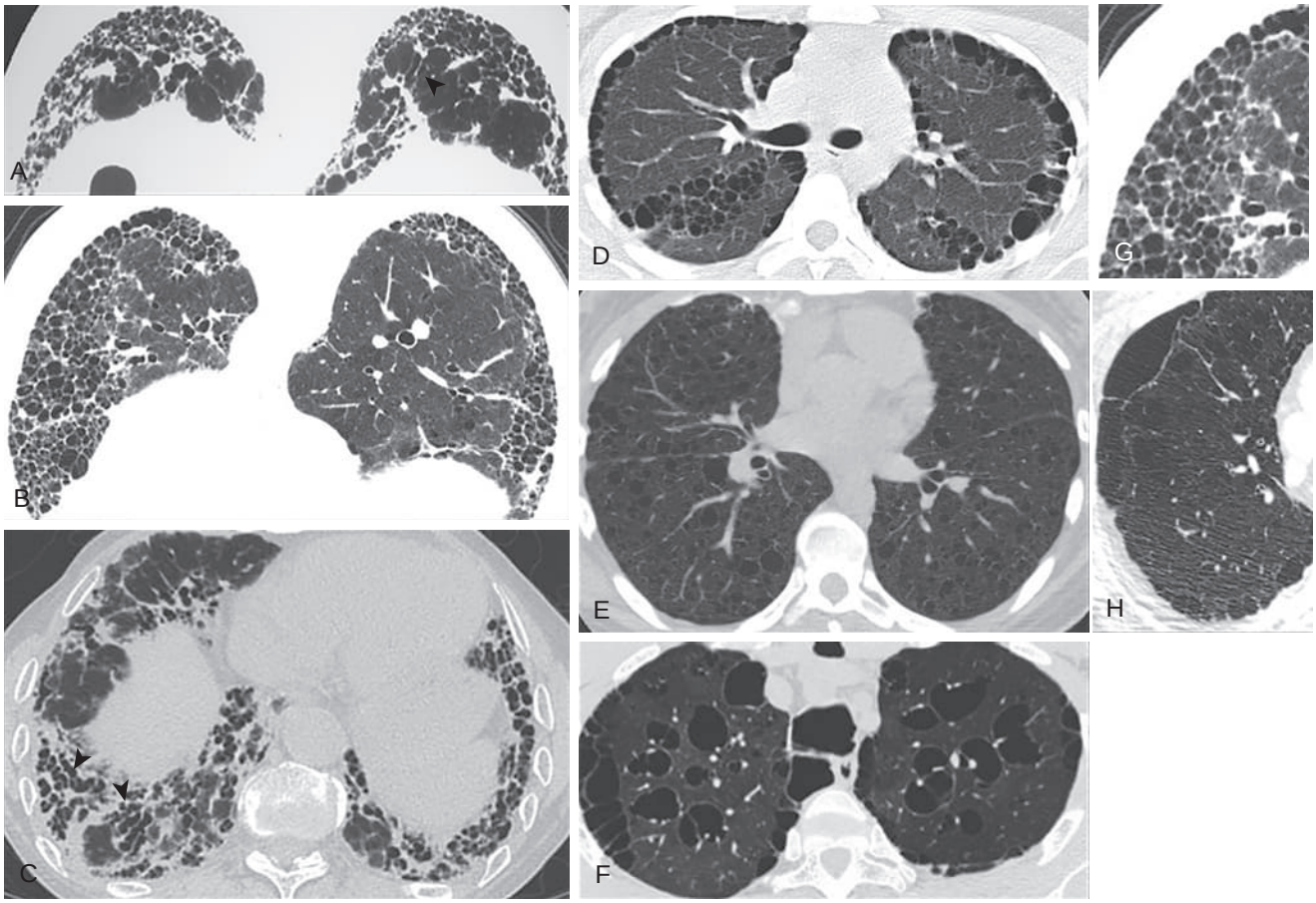

Figure 20.27 ***Computed tomography*** **(CT) appearance of honeycombing compared with several mimics.** Axial prone (A–B) and supine (C) CT images of honeycombing show subpleural cysts on the order of 1 to 3 mm with relatively thick walls located in the subpleural regions of lung. Note how the cysts appear to share walls and form concentric layers. Of importance, other features of fibrotic lung disease are present, such as traction bronchiectasis (*arrowheads*) and architectural distortion. (D–F), Several mimics of honeycombing. (D) Idiopathic paraseptal emphysema in a nonsmoking 17-year-old woman. Although the cysts are peripheral and even appear to stack upon themselves along the major fissures, they are all uniformly thin-walled and unassociated with other features of fibrotic lung disease. (E) Cystic lung disease due to lymphangioleiomyomatosis. Note lack of fibrotic features and normal-appearing lung intervening between the cysts. The cysts are randomly scattered throughout the lungs and do not predominate in the subpleural regions. (F) Tracheobronchomegaly (Mounier-Kuhn disease). Note how some cysts are thin walled, located centrally, along vessels, typical of cystic bronchiectasis. Paraseptal emphysema, forming a single layer of thin-walled cysts unassociated with features suggesting fibrosis, is also present. Detailed images of honeycombing (G) and paraseptal emphysema (H) illustrate the imaging differences between the two findings. Honeycomb cysts (G, prone image near the lung base) tend to be relatively thick-walled and may form stacked layers, whereas paraseptal emphysema cysts (H) are comparatively thin walled and form a single layer in the subpleural regions of lung. Of importance, honeycomb cysts will invariably be accompanied by other features of fibrotic lung disease, such as traction bronchiectasis, intralobular lines, and architectural distortion, whereas isolated paraseptal emphysema is typically unassociated with such findings. (Courtesy Michael B. Gotway, MD.)

ability of CT to detect the presence of lung disease (sensitivity and specificity), characterize its nature, assess disease activity, and guide lung biopsy. It is now widely recognized that CT is integral for the characterization of DILD, assessing disease activity and therapy response, and directing tissue sampling procedures. The evolution of the role CT has assumed in the evaluation of one of the most important DILDs—*usual interstitial pneumonia/idiopathic pulmonary fibrosis* (UIP/IPF)—is reviewed below as an example of how CT imaging has revolutionized DILD assessment.

CT has been widely used for the assessment of fibrotic lung disease, and it had been recognized for a number of years that the CT pattern of lower lobe–predominant honeycombing, in combination with upper lobe linear opacities,[226] is a strong predictor of the pathologic diagnosis of UIP in the proper clinical context. The 2011 ATS, *European Respiratory Society* (ERS), *Japanese Respiratory Society* (JRS), and *Latin American Thoracic Association* (LATA) statement[227] recognized that CT alone can be used to diagnose UIP without the need for tissue sampling by classifying the imaging certainty into one of three levels: definite UIP, possible UIP, and inconsistent with UIP.[227,228] A tissue sampling procedure was recommended only for the latter two patient groups. Compared to the previous clinical practice, the central role CT assumed in the diagnosis of UIP was a new approach[227] and reflected the collective accumulation of knowledge regarding the ability of the CT pattern of basal subpleural–predominant honeycombing, architectural distortion, traction bronchiectasis, and upper lobe reticulation to predict the pathologic presence of UIP.[228] Despite these advancements, a significant number of patients with UIP, particularly patients with CT findings interpreted as possible UIP, were subjected to tissue sampling procedures with the morbidity, mortality, and expense attendant to such procedures. Further

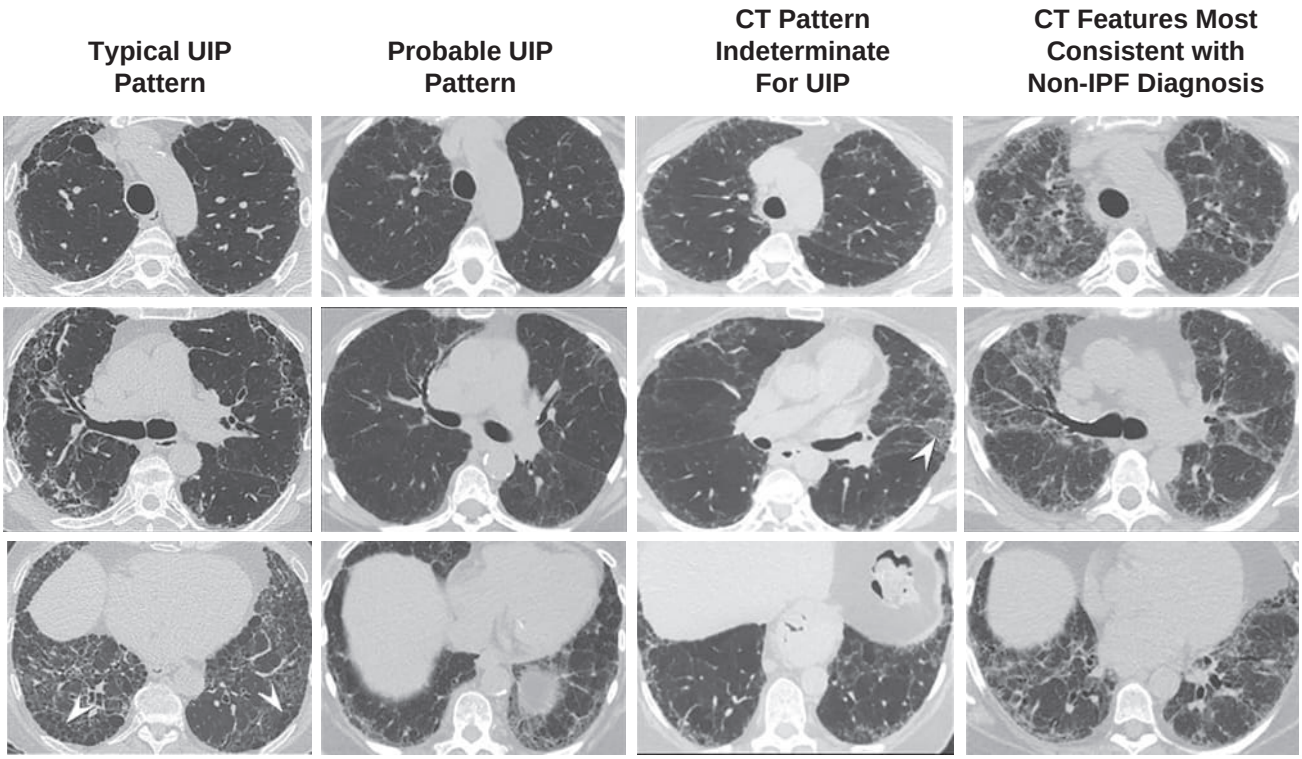

Figure 20.28 Fleischner Society diagnostic categories of usual interstitial pneumonia based on *computed tomography* (CT) patterns. *Typical usual interstitial pneumonia* (UIP) pattern: basal predominant (occasionally diffuse), subpleural and heterogeneous distribution. A reticular pattern with peripheral traction bronchiectasis or bronchiolectasis is present and honeycombing (*arrowheads*) is seen. No features to suggest an alternative diagnosis are present. *Probable UIP pattern:* basal predominant (occasionally diffuse), subpleural and heterogeneous distribution. A reticular pattern with peripheral traction bronchiectasis or bronchiolectasis is present, but honeycombing is absent. No features to suggest an alternative diagnosis are present. *CT pattern indeterminate for UIP:* diffuse or variable distribution. Evidence of fibrosis with some inconspicuous features suggestive of non-UIP pattern. In this example, some peribronchovascular ground-glass opacity extending centrally (*arrowhead*) is present, and there is slight relative basal sparing of the fibrotic findings. Surgical lung biopsy showed pathologic features characteristic of usual interstitial pneumonia. *CT features most consistent with a non–idiopathic pulmonary fibrosis (IPF) diagnosis:* Distributions atypical for usual interstitial pneumonia, such as upper lung or midlung predominant fibrosis or a peribronchovascular predominance with subpleural sparing. Any of the following findings (when they are conspicuous or predominate): consolidation, extensive pure ground-glass opacity (without acute exacerbation), extensive mosaic attenuation with extensive sharply defined lobular air trapping on expiratory CT, diffuse nodules or cysts. In this example, central peribronchovascular ground-glass opacity is present in the upper lobes, and there is basal sparing of the infiltrative lung findings, possibly with some lobular low attenuation suggesting air trapping. Surgical lung biopsy showed features consistent with hypersensitivity pneumonitis.

investigation into patients undergoing evaluation for suspected UIP lead to even greater refinements in CT interpretation; in particular, it has become widely recognized that the reliance on honeycombing to establish the presence of a UIP pattern at CT is both fraught with interobserver variability (see previous discussion regarding honeycombing and Fig. 20.27) and ultimately unnecessary, because honeycombing is a late-stage fibrosis finding, and other features of fibrosis at CT can provide equal predictive value for the pathologic diagnosis of UIP.[228] This realization lead to additional refinements in the interpretation of CT for suspected UIP/IPF, now classifying the imaging certainty into one of four levels[229,230] (Fig. 20.28): (1) typical UIP pattern, (2) probable UIP pattern, (3) CT pattern indeterminate for UIP, and (4) CT features most consistent with a non-IPF diagnosis.

These refinements have allowed tissue sampling procedures to be avoided for the first two categories—the typical UIP pattern and the probable UIP pattern—because it has been recognized that both of these CT patterns predict the pathologic diagnosis of UIP.[228,229] Although tissue sampling is still considered by some for patients with the probable UIP pattern in the proper clinical context,[230] tissue sampling is not mandatory for every patient that fits this category.[231] Furthermore, the fourth CT category of features most consistent with a non-IPF diagnosis may indicate an alternative non-IPF diagnosis and thereby direct management in an entirely different direction. This latest refinement in the CT approach to the diagnosis of UIP has significantly narrowed the number of patients with imaging that falls into the "uncertain" category (pattern indeterminate for UIP).

In addition to refining the clinical approach to the diagnosis of patients with suspected IPF, certain CT imaging findings have been shown to be important prognostic biomarkers for patients with fibrotic lung disease. In particular, the presence and severity of traction bronchiectasis[228,229] and honeycombing[228,229] have been shown to correlate with a poor prognosis in patients with IPF, and honeycombing has been further shown to be associated with a high mortality across a diverse set of non-IPF ILDs.[232] This observation suggests that the CT finding of honeycombing represents a progressive fibrotic ILD phenotype regardless of the underlying diagnosis.[232]

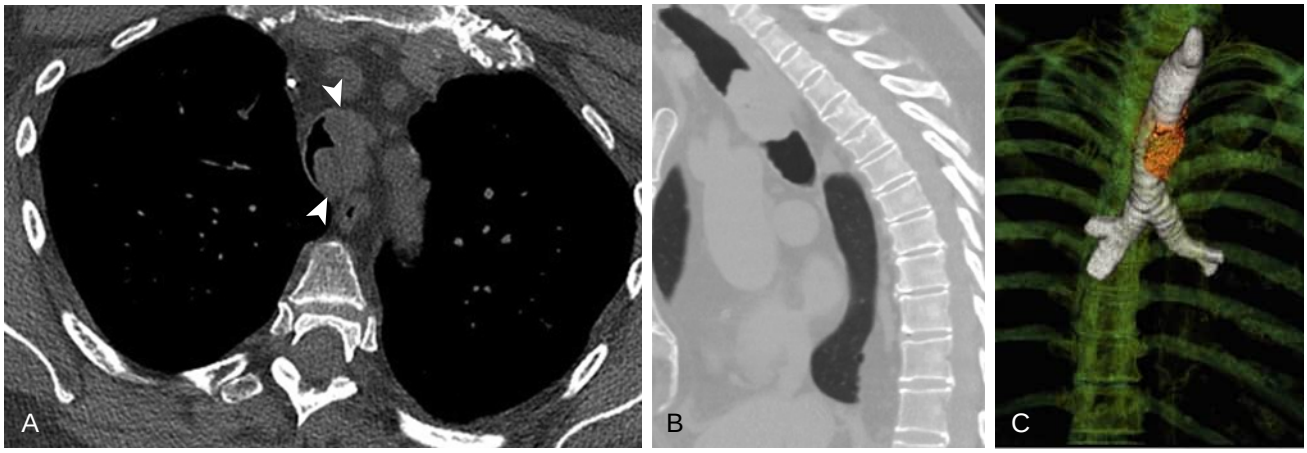

Figure 20.29 Utility of *computed tomography* (CT) for central airway lesions. (A) Axial unenhanced CT image shows a lobulated, noncalcified mass (*arrowheads*) arising from the left aspect of the trachea compromising a substantial portion of the tracheal lumen. (B) Sagittal reformatted image shows the lobulated morphology and full cephalocaudad extent of the lesion. (C) Coronal oblique volume-rendered image highlights the relationship of the lesion to the entire extent of the trachea in a single image. The diagnosis was tracheal MALT lymphoma. (Courtesy Michael B. Gotway, MD.)

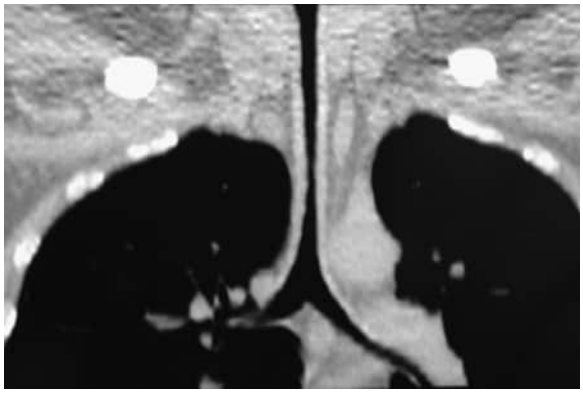

Figure 20.30 Multislice *computed tomography* (CT) for central airway evaluation. With rapid volumetric high-resolution imaging, multislice CT allows detailed three-dimensional analysis of the airways. In a patient with relapsing polychondritis, coronally reconstructed image shows diffuse thickening and narrowing of the trachea. (Courtesy Michael B. Gotway, MD.)

See ExpertConsult.com for additional discussions on the historical data addressing the development of HRCT for the characterization of DILD, assessing disease activity and therapy response, and directing tissue sampling procedures.

INTRATHORACIC AIRWAY DISEASE

With the development of MSCT, volumetric HRCT is now routinely performed for dedicated CT assessment of the large airways, which allows simultaneously optimized evaluation of the central airways combined with HRCT technique for evaluation of the peripheral airways in a single examination.

Central Airways

CT can effectively evaluate lesions of the trachea (Fig. 20.29) and central airways,[261] including strictures and stenoses, inflammatory diseases such as polychondritis (Fig. 20.30), some cases of extrinsic versus intrinsic obstruction,[262] aspirated foreign objects, tracheobronchomalacia (see Chapter 71), and neoplasms (Video 20.11).[261] MSCT, with its ability to acquire images rapidly with equal resolution in all planes, is particularly useful in this assessment and can provide detailed three-dimensional analysis of the central airways (see Video 20.11B). The ability to produce excellent quality three-dimensional images aids in the evaluation of subtle airway stenoses and complex airway lesions, particularly when they are oblique with respect to the imaging plane. In the assessment of tracheal and central bronchial neoplasms, CT does not substitute for bronchoscopy and biopsy, but it can be useful to determine the extent of invasion and to direct the bronchoscopist to a particular segment or to a precise location of peribronchial disease. The major value of CT imaging is its ability to visualize the luminal contents, the airway wall, and the surrounding soft tissue. Thus, CT has the most value in circumstances that require all three of these capabilities.

Bronchiectasis

CT should be the initial investigation in all patients with suspected bronchiectasis, as discussed further in Chapter 69.[263–266] The sensitivity and specificity of HRCT for diagnosing bronchiectasis to the segmental level are 95–98% (Fig. 20.31), which is superior to thicker-section CT scans. In current medical practice, CT has replaced bronchography, and a review of the CT criteria for diagnosing bronchiectasis and the technical pitfalls that may be encountered has been published.[267] Volumetric CT scanning with narrow collimation (on the order of 1 mm) provides a larger volume of coverage and the creation of exquisite reformatted images, including volume rendering, and is now the reference standard for the diagnosis of bronchiectasis. Although there are numerous causes of bronchiectasis, certain imaging features of bronchiectasis at CT, particularly the distribution of the airway abnormalities, may suggest a specific etiology for bronchiectasis in a number of patients (eFig. 20.52, also see Fig. 69.5).[268]

Small Airway Disease

HRCT has the ability to demonstrate abnormalities of small airways having a diameter of a few millimeters or less.*

*References 163, 193, 199, 201, 221, 223, 224, 246, 269.

History of the Use of HRCT for DILD: Diagnosis, Assessing Activity and Directing Biopsy

Sensitivity and Specificity. It is well documented that chest radiographs are limited in both their sensitivity and specificity in patients with DILD.[203–209,211–218,220–224,233–235] For example, Gaensler and Carrington[234] reported that nearly 16% of patients with pathologic proof of ILD had normal chest radiographs. The sensitivity of CT for detecting lung disease has been compared with that of chest radiography in a number of studies; without exception, these have shown that CT, and particularly HRCT, is more sensitive than chest radiography for detecting both acute and chronic diffuse lung diseases.[165,172,177,197,236,237] The average results of several studies show that the sensitivity of HRCT for detecting DILD is approximately 94% compared with 80% for chest radiographs.[235] The sensitivity of HRCT has also proved superior to that of routine CT obtained with wider collimation.[168,206,207]

It is important to note that the increased sensitivity of HRCT is not achieved at the expense of decreased specificity or diagnostic accuracy.[173,176,235] A specificity of 96% for HRCT compared with 82% for chest radiographs was reported by Padley and colleagues[235] in patients with DILD. In other studies of patients with suspected DILD on chest radiographs, normal biopsy results have been proven in 10–20% of patients.[203,234] Although HRCT is clearly more sensitive than chest radiographs, its sensitivity in detecting lung disease is not 100%, and a negative HRCT cannot generally be used to rule out DILD. For example, in one study, although HRCT had high sensitivity and specificity values, 4% of subjects with biopsy-proven lung disease were interpreted as having a normal HRCT.[235]

Diagnostic Accuracy. Even in the presence of definite abnormalities, chest radiographs have limited diagnostic accuracy for patients with DILD.[238] Numerous reports have shown that HRCT is significantly more accurate than are chest radiographs in diagnosing both acute and chronic diffuse lung disease, usually allows a more confident diagnosis, and is subject to considerably less interobserver variation in its interpretation.[173,175,176,183,191,206,239–245]

In an attempt to refine diagnostic accuracy, Grenier and coworkers[174] used Bayesian analysis to determine the relative value of clinical data, chest radiographs, and HRCT for patients with chronic DILD. For this study, two samples from the same population of patients with 27 different diffuse lung diseases were consecutively assessed: an initial retrospectively evaluated set of "training" cases ($n = 208$) and a subsequent prospectively evaluated set of "test" cases ($n = 100$) for validation. The results showed that for the test group an accurate diagnosis could be made in 27% of cases based on clinical data only, increasing to 53% ($P < 0.0001$) with the addition of chest radiographs and to 61% ($P = 0.07$) with the further addition of HRCT scans. In some situations, HRCT findings are sufficiently diagnostic to obviate biopsy.[163,188,246]

Assessing Disease Activity. In addition to being more sensitive, specific, and accurate than chest radiographs, HRCT may also play a critical role in the evaluation of disease activity in patients with diffuse lung disease.[163,188,246] Available data suggest that, in certain cases, HRCT may be used to determine the presence or absence, and extent, of reversible (acute or active) lung disease compared with irreversible (fibrotic) lung disease. Furthermore, because HRCT may accurately identify subtle "active" lung disease, it can be used to study patients being treated to monitor the success or failure of the treatment.[163,164,188,246–251]

Although a number of HRCT findings have been described as being indicative of active or reversible lung disease in patients with different disease entities, most attention has focused on the potential significance of GGO in patients with chronic DILD.[180,204] This finding has been reported in a wide range of DILDs, including UIP, desquamative interstitial pneumonitis, lymphoid interstitial pneumonia, sarcoidosis, hypersensitivity pneumonitis, alveolar proteinosis, cryptogenic organizing pneumonia, respiratory bronchiolitis, and chronic eosinophilic pneumonia.[180] GGO has also been described in patients with premalignant lesions and pulmonary neoplasms, in particular atypical adenomatous hyperplasia and adenocarcinoma in situ (formerly referred to as *bronchoalveolar carcinoma*), respectively, as well as a wide variety of acute lung processes, such as acute interstitial pneumonia; bacterial, fungal, viral, and parasitic infections; pulmonary hemorrhage syndromes; and congestive heart failure and other causes of pulmonary edema.

Although GGO is a nonspecific finding and can reflect various histologic abnormalities, in patients with chronic DILD, GGO may represent active parenchymal inflammation. In a study of 26 patients with DILD in whom histopathologic correlation was obtained, biopsy specimens demonstrated that GGO corresponded to inflammation in 24 cases (65%), and in eight additional cases (22%) inflammation was present but fibrosis predominated[180,204]; in only five cases (13%) was fibrosis the sole histologic finding. Similarly, Leung and associates,[203] in a study of 22 patients with a variety of chronic DILDs and evidence of GGO as either a predominant or an exclusive HRCT finding, showed that 18 (82%) had potentially active disease identified on lung biopsy.

GGO may also be seen in the presence of interstitial fibrosis without active inflammation.[180,203,204] For GGO to indicate active disease, this finding should generally be unassociated with HRCT findings of fibrosis.[180,203,204] In patients with IPF, a significant correlation has been found between the presence of HRCT findings of GGO and pathologic findings of active inflammation, the development of pulmonary fibrosis, the patient's prognosis,[184,248,249,251–258] and the likelihood of response to therapy.[248,249,251] HRCT has also been used to assess disease activity and the likelihood of response to therapy in patients with sarcoidosis.[164,167,194,205,250] In most series of patients with sarcoidosis, the main HRCT determinant of disease activity has been the presence and, to a lesser degree, the extent and distribution of small nodules.[167,205]

Guiding Tissue Sampling Procedures. Among the many indications for HRCT, an important one is as a potential guide for surgical lung biopsies. Many "diffuse" lung diseases are quite patchy in distribution, with areas of abnormal lung frequently interspersed among relatively normal areas of lung parenchyma. Furthermore,

both active and fibrotic disease can be present in the same lung.[144,146,163,184,194,199,201,202,246,257,258] To establish a specific diagnosis and assess the clinical significance of the abnormalities present, it is critically important to sample those portions of the lung that are most likely to be active. Optimal sampling sites can be selected with HRCT. Also, as a direct consequence of its ability to visualize, characterize, and determine the distribution of parenchymal disease, HRCT also provides a unique insight into the likely efficacy of transbronchial biopsy, cryobiopsy, or surgical lung biopsy in patients with either acute or chronic diffuse lung disease. Surgical lung biopsy is often diagnostic, with accuracies greater than 90% generally reported,[188,234,246,259,260] but this procedure is also subject to sampling error. HRCT is of considerable value in determining the most appropriate sites for biopsy.[164,188,240,246]

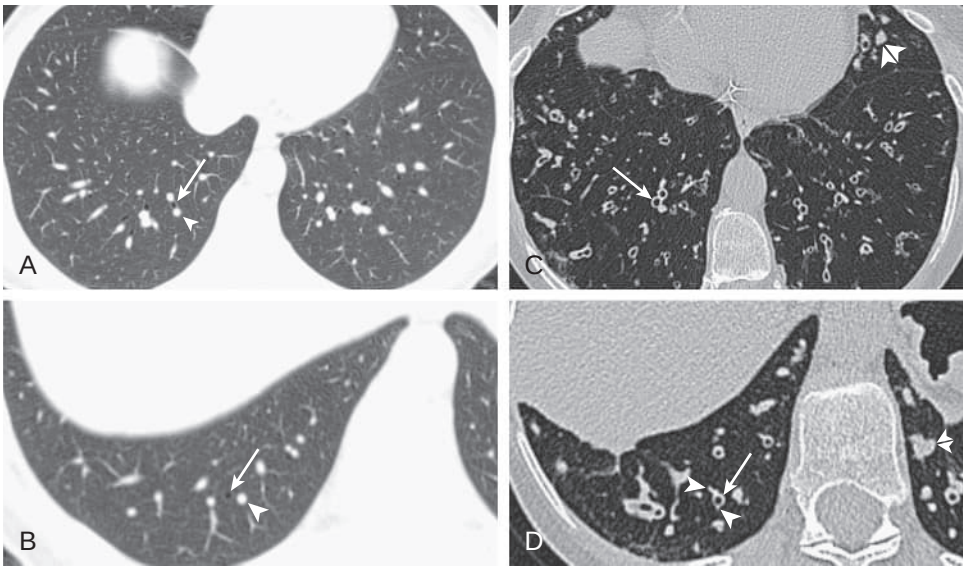

Figure 20.31 Normal appearance of bronchi at chest *computed tomography* (CT) compared with bronchiectasis. (A–B) Axial chest CT images show the appearance of normal peripheral bronchi; the internal diameter of the bronchus (*arrows*) is similar to the adjacent pulmonary artery (*arrowheads*), and the bronchi are patent and uniformly thin walled. (C–D) Detailed images through the lung bases showing CT features of bronchiectasis and large airway disease. The bronchi are abnormally dilated—the internal diameter of the bronchi (*arrows*) clearly exceeds the size of the adjacent pulmonary arteries (*single arrowheads*). The bronchi are also clearly visualized more peripherally than is normal (compare with images A and B, where peripheral bronchi are largely not visible). Finally, the bronchi (*arrows*) are visibly thick walled, and several airways show intraluminal secretions and impaction (*double arrowheads*). (Courtesy Michael B. Gotway, MD.)

Abnormalities that can be diagnosed include (1) inflammatory forms of bronchiolitis, such as cellular bronchiolitis (usually due to infection [Fig. 20.32A], aspiration, or hypersensitivity pneumonitis [see Figs. 20.23 and 20.32B]), respiratory bronchiolitis (see Fig. 20.32C), follicular bronchiolitis, and panbronchiolitis (see Fig. 20.32D), and (2) small airway diseases associated with airflow obstruction (e.g., constrictive bronchiolitis; see Fig. 20.32E–F).[269] (Cryptogenic organizing pneumonia has been previously classified as a disease of the small airways but is now considered an idiopathic interstitial pneumonia.[163,246,269]) The use of postexpiratory HRCT is particularly important in the diagnosis of small airway diseases because air trapping may be visible in the absence of other abnormalities (see Fig. 20.26B–C and eFig. 140.3).[223,224] Postexpiratory HRCT may be performed by imaging after a forced vital capacity maneuver (Video 20.12, see Videos 140.1 and 140.3)[270] or with lateral decubitus CT.[271] Compared to CT performed at a single time point, a cine CT performed during a forced vital capacity maneuver, called dynamic expiratory CT, is a more effective technique for the demonstration of subtle or transient air trapping.[270,272,273]

CARDIOVASCULAR DISEASE

Pulmonary Thromboembolism

Chest MSCT, performed with IV contrast injection using a specific *CT pulmonary angiography* (CTPA) technique, has emerged as the test of choice for the imaging evaluation of suspected *pulmonary embolism* (PE) (Fig. 20.33A, Video 20.13). Ventilation-perfusion scanning has long been used as the initial test for such patients. Its strengths and its limitations are well known and reviewed in Chapters 81 and 82. The test is extremely safe, widely available, and exceedingly sensitive; a normal perfusion scan effectively excludes PE. A high-probability scan is quite specific (97% in the *Prospective Investigation of Pulmonary Embolism Diagnosis* [PIOPED] I study).[274] However, a substantial fraction of perfusion scans yield results that are abnormal but nonspecific, which has contributed to the widespread adoption of CTPA as the first-line test for suspected thromboembolic disease.

The evolution of the adoption of CTPA for the assessment of suspected thromboembolic disease is complex and punctuated by major developments in CT technology. The brief discussion that follows focuses on several specific issues related to the use of CTPA for thromboembolic disease assessment: the negative predictive value of CTPA and the risk of "overdiagnosis" of PE at CTPA.

See ExpertConsult.com for additional discussions on the historical evolution of CTPA from single-slice CTPA to the MSCT era.

Ultimately, the main question when patients suspected of thromboembolic disease undergo CTPA is, "Can anticoagulation be safely withheld in patients with a negative result?" In other words, what is the negative predictive value of CTPA for thromboembolic disease? Several studies have addressed this question, and the negative predictive value of CTPA ranges from 95–99%.[275,276] Of importance, it has been suggested that further diagnostic testing should be pursued when CTPA results (with or without indirect CT venography, see later) are discordant with the clinical probability for PE, particularly when CTPA results are negative and the clinical probability of PE is considered high.[275]

The development of MSCT technology allowed the routine use of narrow detector configurations, resulting in improved visualization of small pulmonary arteries that were largely unapparent with single-slice CT. Although this improved resolution was initially heralded as an advance,

Evolution of Single-Slice CTPA to Multislice

Single-slice helical CTPA in pooled data from a number of studies showed an overall sensitivity and specificity for PE approaching 90% and 96%, respectively. Regardless, criticisms regarding the methodology used in single-slice CTPA studies, as well as the long-held faith in the diagnostic accuracy of catheter pulmonary angiography for suspected PE, led to relatively slow adoption of the use of CTPA for this application in some centers. Once MSCT technology became available, however, it became clear that multislice CTPA scans could demonstrate smaller vessels and therefore, by inference, should be more sensitive than single-slice CTPA for the detection of thromboembolic disease. Several studies investigating the incremental value of multislice CTPA over single-slice CTPA for the diagnosis of thromboembolic disease (Video 20.13) were conducted shortly after the introduction of this technology, including the PIOPED II trial,[275] the results of which were published in 2006. In PIOPED II the sensitivity of multislice CTPA for the diagnosis of PE was 83% (95% confidence limits, 76–92%), and the specificity was 96%. The positive predictive value of a positive multislice CTPA study was 86%, and the negative predictive value was 95%. The suboptimal sensitivity of multislice CTPA in the PIOPED II trial has led some investigators to question the utility of CTPA for the evaluation of suspected PE; nevertheless, currently multislice CTPA is widely used as the first-line diagnostic modality for the investigation for such patients all across the world.

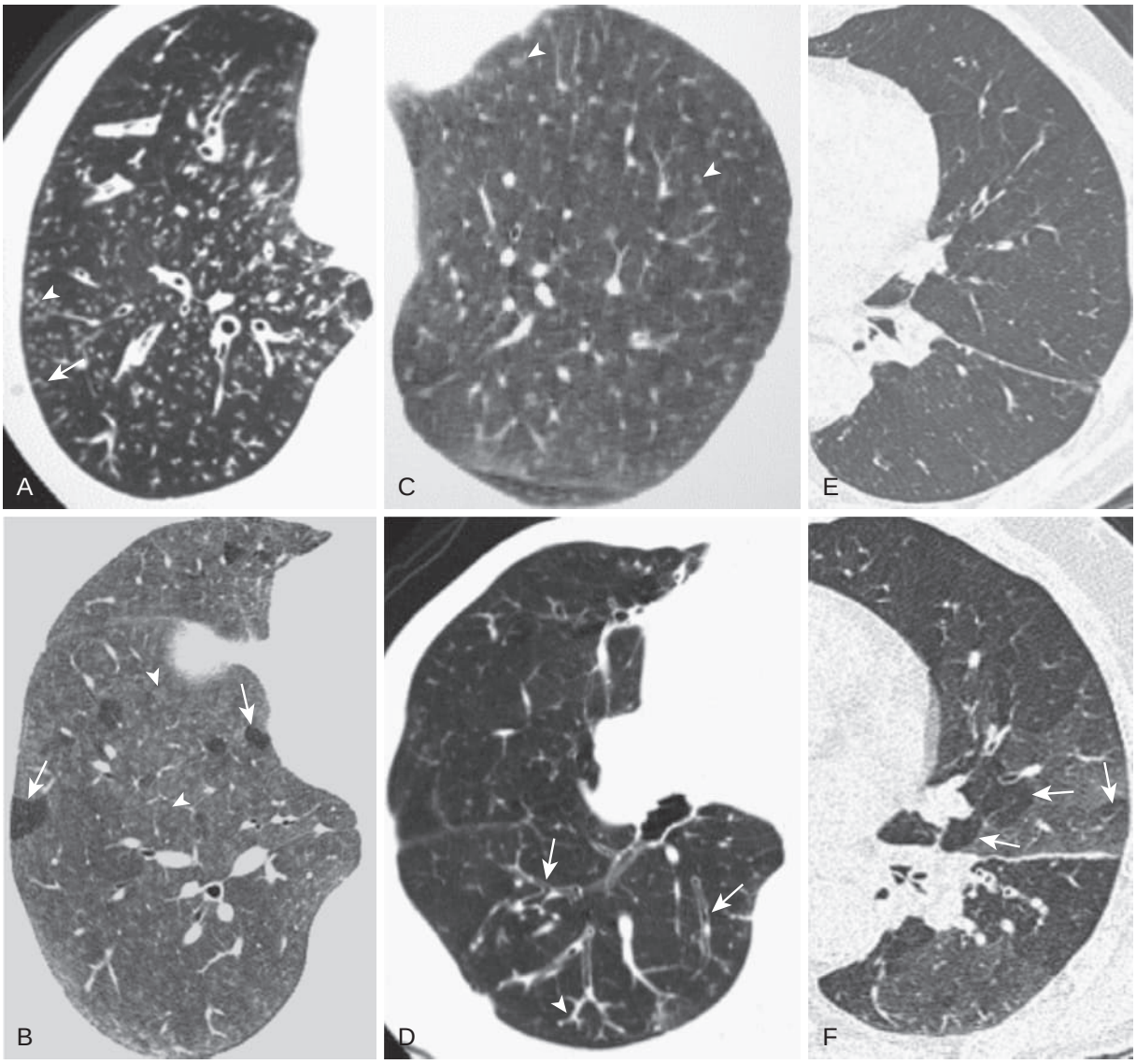

Figure 20.32 ***High-resolution computed tomography*** **(HRCT) manifestations of small airway disease.** (A) Bronchopneumonia and bronchiolitis. Axial chest CT image through the right lower lobe shows numerous small, solid centrilobular nodules (*arrow*), some with branching configurations (*arrowhead*), the latter consistent with tree-in-bud opacity, representing bronchiolar impaction. (B) Cellular bronchiolitis in hypersensitivity pneumonitis. Axial chest CT image through the right lower lobe shows poorly defined ground-glass opacity centrilobular nodules (*arrowhead*). Areas of lobular low attenuation (*arrows*), representing air trapping resulting from inflammatory bronchiolitis, are present. (C) Respiratory bronchiolitis. Axial chest CT image through the left upper lobe shows faintly detectable ground-glass attenuation nodules (*arrowheads*). (D) Panbronchiolitis. Axial chest CT image through the right lower lobe shows large airway thickening and dilation (*arrows*), associated with intraluminal material and small airway impaction (*arrowhead*). (E–F) Constrictive bronchiolitis (bronchiolitis obliterans). Axial chest CT image through the left lung shows normal inspiratory scan findings (E). Postexpiratory imaging (F) shows the development of numerous areas of low attenuation consistent with air trapping, in some areas with a lobular configuration (*arrows*) due to small airway obstruction. (Courtesy Michael B. Gotway, MD.)

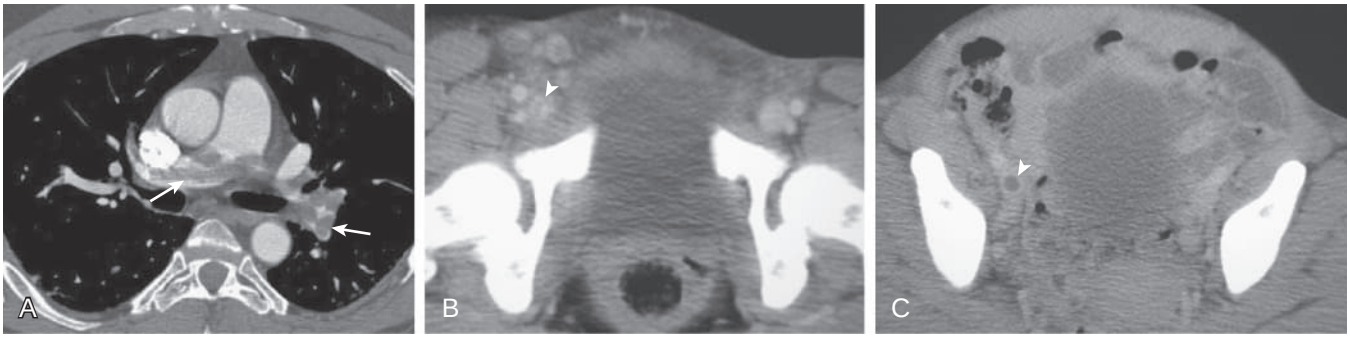

Figure 20.33 ***Computed tomography pulmonary angiography*** **(CTPA) and indirect CT venography images demonstrate pulmonary emboli and deep vein thrombosis.** (A) CTPA image shows bilateral large filling defects (*arrows*) consistent with pulmonary emboli. (B–C) Axial indirect CT venography image (i.e., without additional contrast material injection) shows filling defects in the right common femoral and iliac veins (*arrowheads*) consistent with venous thrombi. (Courtesy Michael B. Gotway, MD.)

thereby mitigating concerns regarding insufficient sensitivity of CTPA for the diagnosis of thromboembolic disease, concerns regarding the "overdiagnosis" of pulmonary emboli soon followed. The term overdiagnosis can be interpreted to encompass two entities. On the one hand, CTPA examinations can be incorrectly interpreted as positive for pulmonary emboli, largely because of various artifacts at CT, including motion artifacts, noise, and volume averaging causing suboptimal pulmonary arterial enhancement simulating intraluminal filling defects, among others.[277] On the other hand, and possibly more important, CTPA may lead to increased detection of small, isolated subsegmental PE of uncertain clinical significance.[278] Indeed, a meta-analysis showed that that the rate of isolated subsegmental PE was twice as high for MSCT-CTPA (9.4%) compared to single-slice CT (4.7%), and there was no clear difference in the 3-month incidence of venous thromboembolism between untreated patients with negative results by single-slice CT versus MSCT.[279] Data indicating that PE-related mortality changed only minimally after the widespread adoption of CTPA for PE diagnosis (1998–2006); yet the incidence of PE increased dramatically (81%) during this time period compared with the pre–MSCT-CTPA era (2003–08),[280] which furthered this concern. Complications related to anticoagulation treatment for PE also increased in the later time period, as may be expected given the rise in number of PE diagnoses, suggesting that the possibility of overdiagnosis is not an innocuous one.[280] The conundrum of PE overdiagnosis may be multifactorial, including possible relative inexperience with the intricacies of thoracic anatomy and PE diagnosis on the part of some radiologists compared with dedicated thoracic imaging experts, overinterpretation of technically inadequate studies, and incompletely evaluated patients or frankly inappropriately ordered CTPA examinations, potentially stemming from lack of guideline adherence and from inappropriate pretest risk stratification.

However, perhaps most important among these potential causes for PE overdiagnosis is the problem of the isolated subsegmental PE.[277] Note that the term *isolated subsegmental PE* often refers to the potential identification of a single pulmonary embolus on a study that results in a positive interpretation, a situation perhaps better referred to as solitary PE,[277] but others have used this term to denote PE in the absence of deep venous thrombosis.[281] A solitary pulmonary embolus, particularly when small (distal segmental or subsegmental), is recognized as having significant potential for contributing to PE overdiagnosis because this finding is subject to significant interobserver variability (eFig. 20.53), even among experienced thoracic radiologists.[277,281] Therefore, to mitigate the potential for PE overdiagnosis, a number of measures may be undertaken[277,282]:

1. Appropriate pretest risk stratification should be used before CTPA examinations are ordered.
2. CTPA examinations should be conducted using optimized technique, and radiology reports should provide some indication of study quality. When a remark regarding study quality is lacking, it is advisable for referring clinicians to speak with the interpreting radiologist regarding their confidence in the examination interpretation, particularly when the study is rendered positive due to a solitary PE or the pretest probability is discordant with the CT interpretation.
3. When the patient's pretest probability for PE is discordant with the CTPA results, or the CTPA study is rendered positive due to a solitary PE, obtaining a second interpretation by either a dedicated thoracic radiologist, or at least a different experienced observer, is appropriate.
4. Lower extremity ultrasound examination for a potential deep venous source for thromboembolism, or an alternative study for PE, such as ventilation-perfusion scintigraphy (eFig. 20.54), may be pursued in difficult, indeterminate cases.

Various investigations also suggest that CTPA may also be able to detect deep venous thrombosis in the proximal leg and pelvic veins without injection of additional contrast material (see Fig. 20.33), a technique known as indirect CT venography.[283–285] The addition of CT venography to CTPA studies obtained for the evaluation of suspected PE allows for the simultaneous evaluation of deep venous thrombosis and PE with a single test. Combining CTPA with CT venography increased the sensitivity for the diagnosis of PE to 90%, and the negative predictive value of the combination of the examinations was 97% in the PIOPED II trial.[275] Despite these encouraging data and the appeal of a single test capable of addressing both PE and deep venous thrombosis simultaneously, indirect CT venography is not widely used, and lower extremity venous thrombosis is typically assessed with lower extremity venous ultrasound in most centers.

As for CTPA, MRI can demonstrate PE directly as intravascular filling defects on cross-sectional images (Fig. 20.34, Video 20.14).[286–298] Experience with MRI in patients suspected of having PE is more limited than that with CTPA. The two techniques are probably overall roughly similar in accuracy for the detection of PE, although MRI may show more pronounced interobserver variability than CTPA and may show slightly decreased sensitivity compared with CTPA at the segmental and subsegmental vascular levels.[296,299] The diagnostic accuracy of MRI for PE assessment is enhanced through the use of multiparametric protocols that include a combination of real-time steady-state free precession imaging (noncontrast white-blood imaging), perfusion imaging, low flip angle, three-dimensional gradient-echo imaging (a contrast-enhanced technique that allows better visualization of the vessel wall compared with MRA), and contrast-enhanced MRA (see Video 20.14)[286,287,290,293,294,300]; not all studies reporting the diagnostic accuracy of MRI for acute PE diagnosis have used a multiparametric approach.[296] In addition, MRI has been shown to be highly accurate for detecting deep venous thrombosis.[301,302]

The potential advantages of MRI are the lack of need for iodinated contrast material or ionizing radiation, ability to image the pulmonary arteries and deep venous system in a single examination, ability to assess right ventricular function simultaneously, and ability to perform perfusion imaging. The latter point is of particular significance in light of the

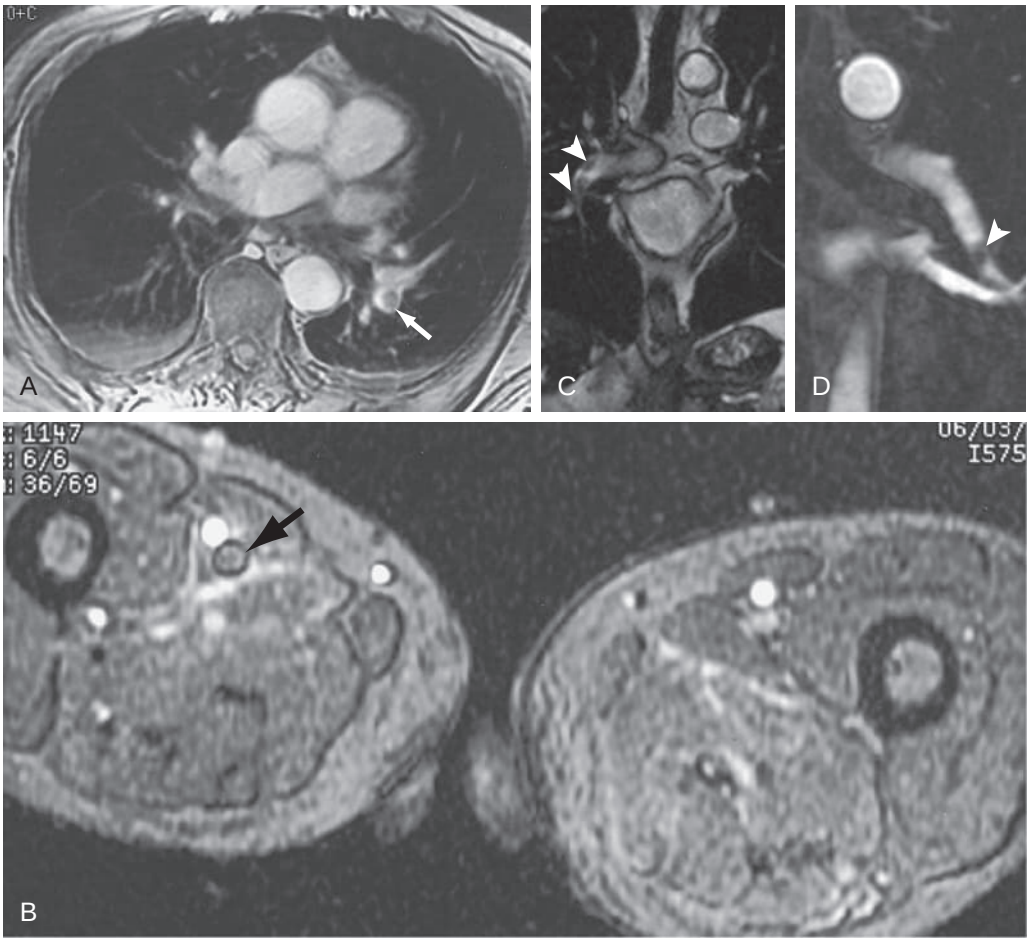

Figure 20.34 Multiparametric *magnetic resonance imaging* (MRI) demonstrating pulmonary embolism and deep vein thrombosis. (A) Contrast-enhanced fast gradient recalled-echo MRI shows a filling defect consistent with pulmonary embolus in the left lower lobe artery (*arrow*). (B) This MRI made without intravenous contrast material shows a filling defect in the right superficial femoral vein consistent with venous thrombus (*arrow*), whereas the contralateral vein is patent and without filling defects. (C) Coronal steady-state free precession image in a different patient, performed without the use of intravenous contrast, shows an intraluminal filling defect within the right interlobar and lower lobe arteries (*arrowheads*), consistent with pulmonary embolism. (D) Coronal MR angiography examination of a third patient shows a low-signal filling defect in the left lower lobe pulmonary artery (*arrowhead*) consistent with pulmonary embolism (Courtesy Michael B. Gotway, MD.)

imperfect sensitivity of CTPA. The advantages of CTPA are higher spatial resolution, wider availability, fewer artifacts, faster examination time, and simpler, more robust technology, as well as, of importance, the generation of alternative diagnoses for patients with negative results. Currently, CTPA is a realistic option in the clinical management of patients with suspected PE. The clinical use of MRI has been traditionally limited to medical centers with personnel who are highly skilled with advanced MRI technology, in part a result of the PIOPED III[296] experience; however, the data from PIOPED III[296] were limited to gadolinium-enhanced MRA only and did not use a multiparametric approach. Furthermore, MR technology has advanced significantly since the publication of PIOPED III,[300] and MRI has been successfully used for the assessment of suspected thromboembolic disease in some academic centers.[300]

See ExpertConsult.com for additional discussions on imaging acquired cardiovascular diseases and congenital anomalies of the thoracic great vessels.

PLEURAL DISEASE

Many pleural processes, as discussed further in Chapters 108 to 114, can be imaged accurately and cost-effectively with conventional radiography or ultrasonography. However, CT can be useful in evaluating several clinical problems relating to the pleura.[104,315,316] These include differentiation of pleural and parenchymal disease, including the distinction between lung abscess and empyema; detection of subtle pleural abnormalities, such as early pleural plaques or small pneumothoraces; location of pleural fluid collections and pleural tumors, including localization for interventional purposes (e.g., tube drainage, biopsy); determination of the extent of pleural tumors, in particular, metastases and mesothelioma; and on occasion, characterization of pleural lesions (Figs. 20.35 and 20.36, see Fig. 20.8) or paradiaphragmatic lesions. MRI currently has a limited role in the evaluation of pleural abnormalities, in general, but has been shown to be useful for assessment of malignant pleural mesothelioma.

CARDIOVASCULAR DISEASE AND THORACIC GREAT VESSELS

Acquired Cardiovascular Disease

Acquired cardiovascular diseases, especially acquired aortic diseases, such as aortic dissection and aneurysm, can be imaged with aortography, CT aortography, echocardiography, and MRI.[303,304] Transthoracic echocardiography can assess the ascending aorta, but its limited field of view restricts its utility. Transesophageal echocardiography has produced definitive results,[305] but this technique requires sedation and carries the risk of esophageal injury. Catheter aortography is invasive and can produce both false-positive and (more commonly) false-negative results.[303] It has largely been replaced by cross-sectional imaging methods for the evaluation of aortic pathology.

CT aortography can accurately identify the intimal flap, the true and false lumens (eFig. 20.55), the vessels involved by dissection, and the presence of end-organ perfusion impairment; thus CT aortography is used routinely for evaluating aortic dissection.[306] Complications of dissection, such as mediastinal hematoma, hemothorax, and hemopericardium, can also be detected. The mild relative limitations of CT aortography include the need for iodinated contrast material and its limited ability to assess aortic valve function (information that some surgeons require and others do not), but this latter concern has been alleviated with the development of retrospectively electrocardiographic-gated CT aortography. With this technique the imaging acquisition is conducted simultaneously with the electrocardiographic tracing, and data can then be reconstructed to show relevant anatomy at any time during the cardiac cycle. Images reconstructed during late diastole often are motion free and allow assessment of the coronary arteries and aortic valve (eFig. 20.56).

MRI has several advantages in suspected aortic dissection. No iodinated contrast material is required (eFig. 20.57), and MRI does not require ionizing radiation. Certain MR sequences can assess aortic valve and left ventricular function. However, MRI also has limitations in the assessment of dissections. Some patients are excluded from MRI for safety reasons. MRI examinations usually require more time than CT aortography studies for dissection. Artifacts lead to nondiagnostic studies more often with MRI than with CT aortography. Greater experience is required to interpret MR images accurately.

The relative accuracy of aortography, transesophageal echocardiography, CT aortography, and MRI for detecting and characterizing dissections has not been established by definitive prospective clinical trials. For practical reasons, such a trial is not likely to be conducted. In accordance, which technique is superior is arguable, and judgment is required for individual cases. Aortography is invasive and known to be inaccurate, particularly in cases with thrombosed false lumens, and has largely been replaced by cross-sectional methods. Extensive data indicate that both CT aortography and MRI are accurate in evaluating dissections.[306,307] However, no single technique always fulfills all of the requirements for characterization of dissections. Several reports suggest that hemodynamically unstable patients with suspected aortic dissection should be studied with transesophageal echocardiography, whereas stable patients should be evaluated by CT aortography or MRI.[305,308] MRI is also recommended for serial studies of patients with chronic dissection.

Both CT aortography and MRI have advantages over aortography for evaluating thoracic aortic aneurysms. Both are noninvasive, can document that a mediastinal mass is an aneurysm, can assess the thickness of the aortic wall, and can measure accurately the diameter and longitudinal extent of the aneurysm.[306] In most situations, CT aortography is sufficient for diagnosis, and because it is less expensive and faster than MRI, it is the preferred study. MRI is particularly useful for patients with contraindications to iodinated contrast material.

In suspected traumatic aortic rupture, CT aortography has replaced catheter aortography for initial diagnosis.[309] Catheter aortography is generally reserved for indeterminate CT aortography studies, problem-solving cases, or percutaneous interventional therapy, such as during endovascular stent placement. Although MRI has been reported in this setting, it is not normally used because the problems of monitoring and sustaining the trauma patient are greater with MRI; in addition, CT aortography examinations are substantially faster than MR examinations, and time is of the essence in traumatically injured patients. Chronic pseudoaneurysms (eFig. 20.58) in survivors of traumatic or iatrogenic aortic injury can be evaluated with either MRI or CT aortography.

Numerous other cardiovascular conditions can be assessed with CT angiography and MRI. In particular, valvular disease can be well assessed with both techniques. MRI is particularly useful for quantifying valvular regurgitation and stenosis and can provide quantitative data regarding the need and timing of corrective interventions. CT angiography has become the reference standard for preprocedural planning for percutaneous valve implantation, particularly the aortic valve. CT coronary angiography has gained wide acceptance as an appropriate imaging modality for the assessment of suspected coronary arterial atherosclerosis and other coronary artery conditions, such as coronary anomalies.

Congenital Anomalies of the Thoracic Great Vessels

Echocardiography, MR and CT angiography, and catheter angiography are commonly chosen modalities for demonstrating great vessel anomalies, associated cardiac malformations, and their physiologic sequelae. CT angiography usefully can demonstrate both simple vascular anomalies, such as an aberrant subclavian artery and persistence of the left superior vena cava, and more complex congenital and developmental cardiovascular abnormalities. The vascular supply of sequestrations can be identified by MRI or CT angiography, and angiography is rarely necessary (see eFig. 20.21). In adults with congenital anomalies of the great vessels, MRI is often the procedure of choice because its field of view is wider than that of echocardiography and it is noninvasive, but in complex lesions these techniques often are complementary. CT angiography is also an effective tool for the investigation of adult and pediatric congenital cardiovascular abnormalities.

Published experience with MRI in developmental anomalies of the great vessels has focused on aortic coarctation and pulmonary artery obstruction, but extensive investigations of the utility of MR techniques for other vascular abnormalities, including extracardiac shunts and partial anomalous pulmonary venous return, have been performed. Coarctation is detected accurately by MRI (eFig. 20.59) or CT angiography. Complications of treatment, including restenosis and aneurysm, can be detected,[310,311] and the degree of collateral vascular supply, which affects the risk of surgery, can be established with either technique. The pressure gradient across the coarctation and the relative increase in blood flow distal to the coarctation (due to collateralization around it) may be quantified by MRI. Such calculations also provide quantitative data regarding the efficacy of operative and percutaneous interventions.

Both MRI and gated CT angiographic studies are highly useful for detecting central pulmonary artery obstruction,[312] evaluating the potential for palliative shunts,[313] and assessing the results of surgery and percutaneous interventions.[310,314] Comparisons of MRI with transthoracic echocardiography usually have shown MRI to be superior for demonstration of great vessel anomalies. Diagnosis of a variety of other congenital vascular anomalies by MRI and MSCT angiography also has been reported.

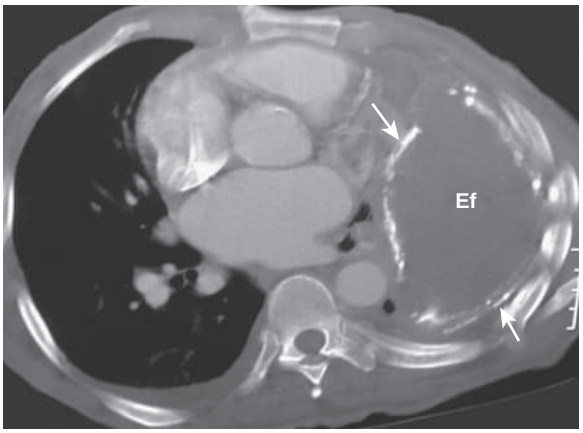

Figure 20.35 Chest *computed tomography* (CT) for pleural disease. Chest CT performed in a patient with a history of tuberculosis shows pleural thickening and calcification (*arrows*) and a residual pleural effusion (Ef) indicative of empyema. (Courtesy Michael B. Gotway, MD.)

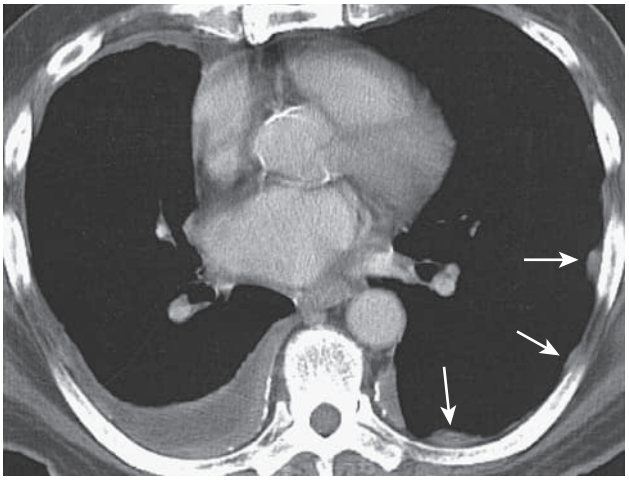

Figure 20.36 Chest computed tomography for pleural disease. A patient with prior asbestos exposure has focal areas of pleural thickening or pleural plaques within the left hemithorax (*arrows*). Pleural thickening on the right is associated with pleural effusion. This reflected the presence of early malignant mesothelioma. (Courtesy Michael B. Gotway, MD.)

Type of Fluid

Most effusions have an attenuation near to that of water; in accordance, CT numbers cannot be used to predict the specific gravity of the fluid or its cause. Exceptions include (1) acute or subacute hemothorax, which can sometimes appear inhomogeneous in attenuation, with some areas having an attenuation value higher than that of water, and (2) chylothorax, which can sometimes appear decreased in attenuation relative to water due to high fat/triglyceride content.

The presence of pleural thickening is often of value in predicting the nature of the effusion. In patients with effusion (see Chapter 108), the presence of pleural thickening on CT strongly suggests that the effusion is an exudate.[104] By definition, the pleura is considered thickened if it is visible on a contrast-enhanced or unenhanced CT. Transudative causes of pleural effusion typically do not produce pleural thickening. Conversely, the absence of pleural thickening on contrast-enhanced CT is less helpful. In this situation, the effusion can be an exudate or transudate. Only about 60% of exudates are associated with visible pleural thickening. However, the absence of pleural thickening on a contrast-enhanced scan rules out empyema; empyema is always associated with parietal pleural thickening on contrast-enhanced CT.

Pleural Versus Parenchymal Disease

Opacities detected at chest radiography can frequently be localized as either parenchymal or extraparenchymal (pleural or chest wall) in location. Chest radiographic features that favor a parenchymal location for a pulmonary opacity include a relative rounded contour, relatively acute angles between the opacity and the chest wall (Fig. 20.37, see (Figs. 50.1 to 50.6), and air-fluid levels (when present) relatively similar in length in both frontal and lateral projections (Fig. 20.38). In contrast, opacities that are extraparenchymal in location often show an elliptical or lenticular contour; the opacity forms obtuse angles at the point of contact with the chest wall (see Figs. 20.37A and 38), and air-fluid levels commonly show significantly different lengths in the frontal and lateral projections (see Fig. 20.38). However, on occasion, chest radiography may not be able to distinguish between parenchymal disease, pleural disease, and pathology affecting both compartments. CT can be useful in this setting. Pleural lesions typically have obtuse tapering margins and sharp interfaces with adjacent lung parenchyma (see Fig. 20.37 and eFig. 50.7B–E), whereas parenchymal lesions tend to blend with lung parenchyma and have acute, irregular margins (see Figs. 20.37 and 20.38, see eFigs. 50.4B–E, 50.13A, and 50.26A). One of the more common and therapeutically important problems in this category is differentiating lung abscess from empyema. Empyemas typically have smooth outer and inner margins, a lenticular shape (see Figs. 20.37 and 20.38), and a sharp interface with underlying lung; they tend to displace pulmonary vessels around them (see eFig. 50.7B–E) and often display prominent rim enhancement (the "split pleura sign") after IV administration of iodinated contrast material. Lung abscesses are characterized by spherical or polygonal shape, a thick wall with a shaggy or irregular inner margin, and destruction, not displacement, of adjacent structures (see Figs. 20.37 and 20.38). None of these features is unique but, when considered together, they permit categorization of the abnormality in most cases.

Early Detection

The contrast resolution and cross-sectional format of CT make it highly sensitive and accurate in detecting pleural thickening and early pleural plaques in patients with asbestos-related pleural disease (see Fig. 20.36).[168,316] Circumscribed plaques often are overlooked on chest radiographs unless they are calcified or attain a thickness of about 5 mm or more. Furthermore, normal extrapleural soft tissues and fat can be misinterpreted as plaques when they are prominent on chest radiography.

CT has also been shown to be accurate and more sensitive than conventional radiographs in detecting pneumothoraces. This can be of particular importance in trauma patients, who may require intubation and positive-pressure ventilation.

See ExpertConsult.com for a discussion of recent advancements and future directions.

RECENT ADVANCEMENTS AND FUTURE DIRECTIONS

Artificial Intelligence, Machine Learning, and Deep Learning

Artificial intelligence (AI) is a broad term that can be construed to mean a focus in computer programming and development designed to train machines to perform tasks as well as, or better than, humans. *Machine learning* is a related application of artificial intelligence, in which a computer is provided programming and large amounts of data to learn its own patterns, rather than the patterns and limits set by a human programmer, and thereby improve from experience. *Deep learning* is a class of machine learning techniques that uses multilayered neural networks. The application of AI to medical tasks is not new[317] but has exploded in recent years owing to advances in computing power, hardware capabilities, and software advances. In essence, AI algorithms attempt to provide classifications.[317] As applied to medical imaging, cardiopulmonary imaging in particular, a given AI algorithm may attempt to determine if a lung nodule is present or not, or determine the amount of reticular abnormality in a patient with fibrotic lung disease compared to normal lung. One prominent application of AI in pulmonary imaging is lung nodule detection and characterization of lung malignancies called radiomic analysis (i.e., the quantification of the phenotypic features of a lesion from medical imaging),[318] particularly for genomic prediction. Additional cardiopulmonary applications for AI include pneumonia detection, detection and quantification of obstructive pulmonary disease, and the CT determination of fractional flow reserve for atherosclerotic coronary disease, among others. Artificial intelligence methods have been applied to the assessment of ILDs at CT and have shown the ability to predict pulmonary function in patients with IPF better than visual scoring,[319] potentially identifying nonvisual CT parameters that may predict the severity of functional impairment.

The applications of AI are expanding rapidly and growing immensely in sophistication. The translation of AI methods into clinical practice has been somewhat slow; issues regarding integration into workflow, cost, and reimbursement for applications must be addressed. Nevertheless, it seems clear that AI will play a large role in medicine, and imaging in particular, in the years to come.

Functional Imaging and Quantification: COPD and Fibrotic Lung Disease

CT has been increasingly recognized as providing valuable insight into structural and pathophysiologic pulmonary indices, particularly as regards obstructive pulmonary disease. As discussed previously, emphysema phenotypes are easily visually recognized at CT,[210] but manual quantification of emphysema through visual scoring is time consuming. Automated densitometry methods allow quantification of emphysema on inspiratory CT scans obtained at total lung capacity by calculating the percentage of lung voxels at, or less than, a given attenuation, typically −910 HU[320] or −950 HU[320,321] for mild and severe emphysema, respectively. These methods have shown to be independent predictors of mortality in patients with alpha$_1$-antitrypsin deficiency and can be used to document the effectiveness of therapy in these patients by showing a slowed rate of decline in lung density.[321] Lung densitometry methods do not yet adequately discriminate among the types of emphysema, and therefore visual quantification of emphysema is still valuable.

The large airways can be readily investigated with CT down to approximately the sixth generation.[320] A number of measures have been used to assess segmental and subsegmental airway wall thickness, including direct measurement of the thickness of the airway wall, calculation of the airway wall percent area (Outer area of airway − Lumen area × 100%), and measurement of Pi10—a measure of the linear relationship between the square root of the airway wall area and the internal perimeter of the airway.[320,321] This measure is a predictor of the presence of COPD at lung cancer screening CT[21] and correlates with forced expiratory volume in 1 second, bronchodilator responsiveness, and respiratory morbidity independent of emphysema.[320]

With the recognition that terminal bronchioles become narrow and are lost before the development of emphysema and the understanding that the small airways (<2 mm) are the main site of airflow obstruction in COPD,[320,321] interest in small airway imaging has grown rapidly. Because the small airways are very difficult to image directly, the focus has turned to an indirect measure of small airway function—gas trapping. Density mask assessment of expiratory scans demonstrates gas trapping by showing increased gas, and hence lower lung density, at end-expiration, reflecting the reduced elastic recoil due to emphysema and small airway obstruction.[320] Although a threshold of −856 HU or lower has been used to demonstrate the presence of gas trapping at expiratory CT, the use of this threshold cannot distinguish between low-attenuation lung due to emphysema and that due to gas trapping from small airway disease. Therefore the assessment of gas trapping at CT has been approached in several ways, including calculating the ratio of expiratory to inspiratory mean lung density, determining the relative change of voxels with attenuation coefficients between −860 and −950 HU between expiratory and inspiratory scans, and calculating the percentage of voxels with attenuation less than −856 HU on expiratory imaging. Among these methods, parametric response mapping has gained some attention. This method matches each voxel on inspiratory and expiratory CT and classifies each voxel as normal lung, emphysematous lung, and functional small airway disease. In this fashion, parametric response mapping provides a measure of nonemphysematous gas trapping and has been shown to correlate with lung function independent of emphysema.[320,321] Computational methods for obstructive lung disease may also have some ability not only to demonstrate the presence of disease before visual detection is possible but also to reveal the parenchymal heterogeneity of obstructive disease, unlike spirometry, which is a global measure of lung volume change from inspiration to expiration.[320] This latter consideration may play an important role for directing therapies such as lung volume reduction.[320]

As with obstructive lung disease, efforts are underway to quantify and characterize ILDs. It has been noted that *interstitial lung abnormalities* (ILAs) are often detected in large asymptomatic CT screening patient cohorts and may be present in up to 7–10% of the general population.[322,323]

The significance of these ILAs is uncertain, as they may remain stable in some patients but may progress in others and have been associated with an increased risk of death.[323] However, the prevalence of ILAs is substantially higher than IPF, and therefore it is clear that not all patients with ILAs progress to overt fibrotic lung disease. Because these ILAs represent a preclinical phenotype[323] and the visual assessment of early ILD is both highly subjective and time consuming when conducted on a large scale, there has been substantial interest in applying computational models to this effort. Quantitative CT densitometry can detect *high-attenuation areas* (HAAs), below the threshold of visual inspection, that represent subtle increases in lung attenuation, which are more prevalent in smokers and patients with reduced lung function, are associated with biomarkers of pulmonary inflammation and the visual identification of ILAs, and are associated with all-cause mortality.[322,323] Recently, HAAs have also been shown to be associated with increased odds of being subsequently diagnosed with ILD, having an increased rate of respiratory and ILD-related hospitalizations, and death due to ILD.[322,323] Of interest, the study by Podolanczuk and colleagues,[322] showed that the association between HAAs and ILAs was weak, suggesting that these two findings are distinct entities, and HAAs may represent a derangement not detectable by visual inspection.[323] Furthermore, the use of computational tools to identify HAAs, rather than visual assessment for ILAs, has the advantage of automation, reproducibility, ease, and perhaps less expense.[322] Of importance, HAAs may be detected before ILAs, which may offer the advantage of earlier intervention for at-risk patients.[322] Although computational techniques such as those described are still primarily research applications, the data and experience these efforts yield will ultimately penetrate into the realm of clinical medicine and alter medical practice substantially.

Dual-Energy/Spectral Computed Tomography Imaging

Although the concept of using multiple energy levels to create images is not new, until fairly recently CT scanning was limited to creating images with a single tube producing x-rays at a single energy level (or, more accurately, a polychromatic x-ray beam with a single average x-ray energy level). The term dual energy, as applied to CT, refers to the ability of a CT scanner to create nearly simultaneous acquisition of CT images at two x-ray energies. This ability has been made possible by a number of fairly recent technical advances in CT scanning. The manner in which dual energy scanning is conducted is beyond the scope of this brief discussion, but, for the purposes of this brief review, it is sufficient to understand that CT manufacturers have approached the process of dual-energy acquisitions differently[324]:

1. Scanning using two x-ray sources perpendicular to each other, one tube with a high kilovoltage (140–150 kV), the other lower kilovoltage (70–100 kV)
2. Scanning using a single x-ray tube that rapidly switches between x-ray beam energies during the same x-ray tube rotation (80–140 kV)
3. Scanning using a separate x-ray tube rotation, acquiring a low-energy image, followed by a second rotation to acquire a higher energy image
4. Scanning using a dual-layer detector, with the superficial layer absorbing low-energy x-rays and the deeper layer absorbing higher-energy x-rays

The physical principles that underlie dual-energy image creation are rather technical. Suffice to say that single-source high- kV CT scanning using a polychromatic x-ray beam is incapable of distinguishing the material composition of the substance scanned. However, scanning with two x-ray energy spectra using lower and higher average kVs has the ability to demonstrate changes in attenuation of a voxel due to relative changes in the ratio of Compton scatter versus photoelectric effect at low versus high kVp. Scanning using two x-ray energy spectra using a monochromatic x-ray beam has the ability to favor a more specific interaction—the photoelectric effect—between the incident x-ray energy and the substance scanned, and this interaction is specific to the atomic number of the material scanned, thus providing characterization and even quantification of the imaged material.[324]

Dual-energy CT scanning allows for the decomposition of a variety of materials, such as water, iodine, silicone, uric acid, and calcium. By examining the changes in attenuation at different kVp within a given voxel, these substances can be specifically identified and one "subtracted" from the other to create images that highlight features of interest. For example, subtracting the iodine component from a dual-energy contrast-enhanced study creates a "virtual unenhanced" study, without the need to acquire a dedicated unenhanced scan before iodinated IV contrast is injected. This virtual unenhanced dataset can be used to assess intrinsically hyperattenuating substances, such as calcium and hemorrhage, without the interference of hyperintense iodinated IV contrast; this potential has some advantages for vascular imaging. Similarly, the water component of a dual-energy scan can be subtracted from an enhanced acquisition, leaving the iodine component, which can provide a map of the iodine-enhanced blood volume of an organ of interest, allowing quantification of the distribution and absolute iodine content of a structure.[324]

The applications of dual-energy CT in the thorax include assessment of PE (eFig. 20.60A and C), assessing regional lung perfusion in patients with COPD, prediction of postoperative lung function, malignancy characterization, and chest wall abnormalities (see eFig. 20.60D–I). Dual-energy techniques have been applied to PE detection improving the quality of otherwise suboptimal examinations and demonstrating regional pulmonary perfusion. The latter ability functions in a manner analogous to the perfusion scan of a ventilation-perfusion study—pulmonary emboli create "perfusion defects" (see eFig. 20.60C) on dual-energy images. The ability to demonstrate a perfusion defect within the lung in a patient suspected of PE has been suggested as allowing improved detection of small emboli[325]; the perfusion defect may draw the reader's attention to an otherwise overlooked small embolus and or even suggest embolic disease not directly visualized at CTPA. Note, however, that the effort to detect even smaller emboli conflicts with the concept of overdiagnosis in PE imaging discussed previously. Therefore it has been suggested that dual-energy embolic-related perfusion defects could give context to small emboli; conceivably, a small embolus could reflect

overdiagnosis, but one creating a perfusion defect may be significant enough to warrant therapy. This concept, however, remains conjecture. Note also that, similar to ventilation-perfusion scintigraphy, some emboli are unassociated with substantial perfusion defects, whereas not all perfusion defects are due to embolic disease (see eFig. 20.60B). Finally, dual-energy CT scanning in patients with pulmonary emboli has been suggested as an adjunct to risk stratification and outcome prediction, with pulmonary blood volume measurements in some studies showing variable correlation with arterial obstructive indices and measures of right ventricular strain.[326,327]

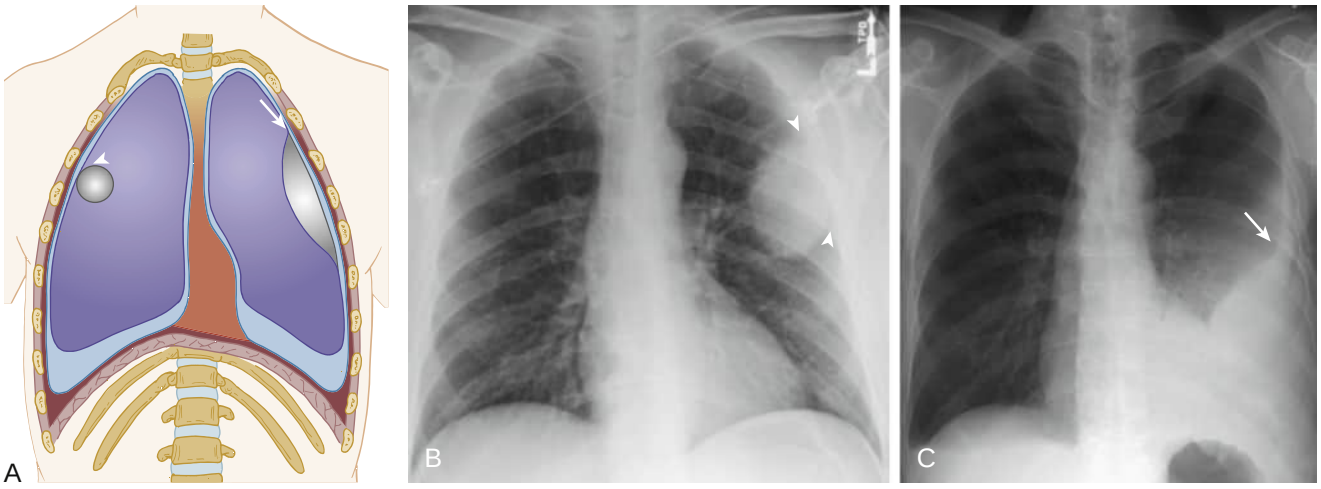

Figure 20.37 Chest radiographic localization of an opacity as parenchymal or extraparenchymal: angle of the opacity with the chest wall. (A) Illustration showing the typically *acute* angles (*arrowhead*) formed by a parenchymal process, such as a lung abscess, with the chest wall, compared with the *obtuse* angles (*arrow*) usually formed with the adjacent chest wall by an *extraparenchymal* process, such as empyema. (B) Frontal chest radiograph in a patient with a lung abscess shows the typically *acute* angles (*arrowheads*) formed with the chest wall by a *parenchymal* process. (C) Frontal chest radiograph in a patient with empyema shows the usual *obtuse* angles (*arrow*) formed with the chest wall by an *extraparenchymal* process. (B–C, Courtesy Michael B. Gotway, MD.)

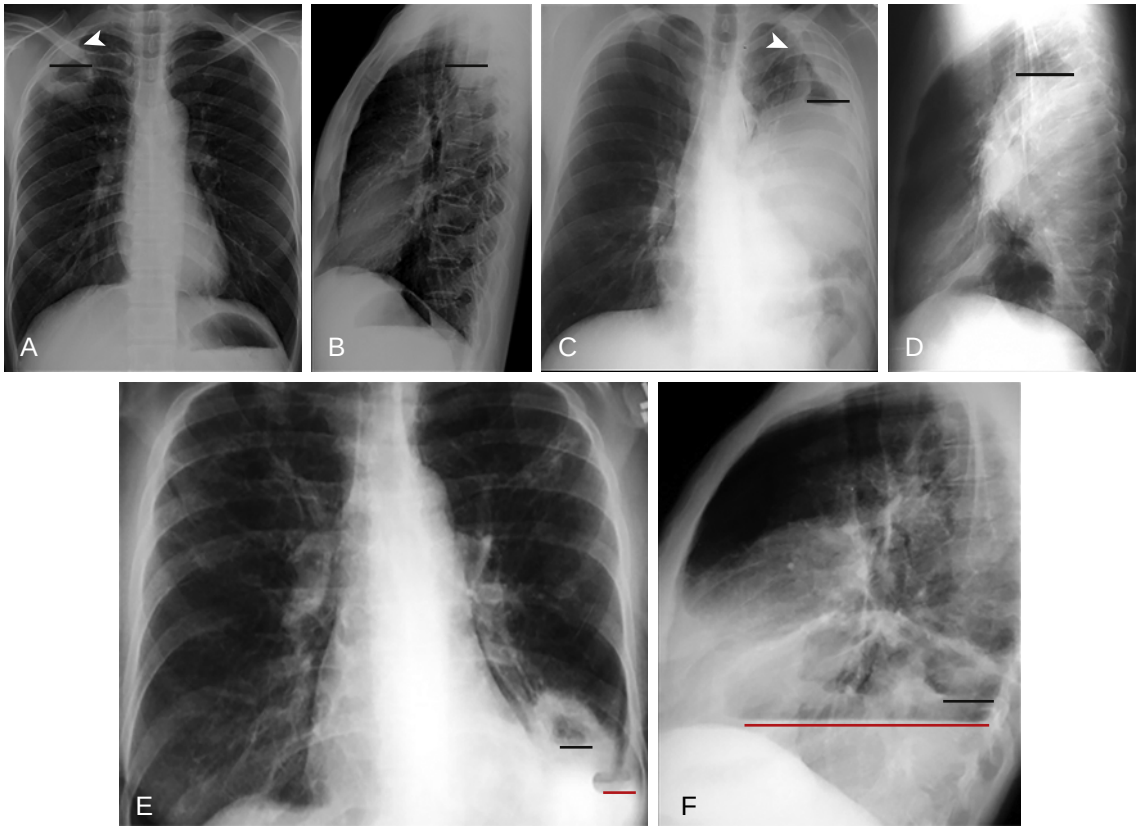

Figure 20.38 Chest radiographic localization of an opacity as parenchymal or extraparenchymal: differential air-fluid length. (A) Frontal and (B) lateral chest radiograph in a patient with lung abscess (same patient as Fig. 50.1) shows an opacity with an air-fluid level (*line*) that is roughly the same length in both projections. The typical acute angle formed by the parenchymal process with the chest wall (*arrowhead*) is evident. (C) Frontal and (D) lateral chest radiograph in a patient with empyema shows an opacity creating the obtuse angles with the chest wall characteristic of an extraparenchymal process (*arrowhead*). An air-fluid level is present (*line*) and shows a different length in both projections, which suggests extraparenchymal localization of the process. (E) Frontal and (F) lateral chest radiograph in a patient with lung abscess creating a bronchopleural fistula shows an opacity with an air-fluid level (*black line*) of roughly the same length in both projections, representing a lung abscess. Another process with air-fluid levels that differ in length markedly between the frontal (E) and lateral (F) projections (*red line*) represents empyema. (Courtesy Michael B. Gotway, MD.)

Key Points

- After the medical history and physical examination, radiography is the most commonly used technique in the evaluation of patients with known or suspected thoracic disease.
- High-quality frontal and lateral chest radiographs can address many clinical questions. Currently available techniques of digital recording of images offer many interpretive and logistical advantages.
- Helical (or spiral) *computed tomography* (CT) technology allows the entire chest to be scanned during a single breath-hold, thereby permitting volumetric imaging, which generates a continuous block of data (rather than slices) that can be reconstructed to produce images in different slice thicknesses or orientations. Multislice CT uses multiple channels during the helical acquisition, thereby dramatically increasing the amount of data acquired and the speed of acquisition.
- Multislice CT, with its rapid acquisition time and greatly improved resolution, has become the imaging method of choice for further evaluation of pulmonary nodule(s), lung cancer, mediastinal abnormalities, diffuse lung diseases, airway diseases, and suspected pulmonary embolism.
- *High-resolution CT* (HRCT) is a technique combining narrow collimation/thin-slice thickness (1 mm) and image reconstruction using a high-spatial-frequency algorithm to maximize sharpness in the final image. HRCT is best suited for analysis of the lung parenchyma in patients with diffuse lung diseases, where its findings are based on the anatomy of the secondary pulmonary lobule. HRCT findings relevant to lung disease can be broadly divided into *increased opacity*, including nodule, linear, and reticular opacities; ground-glass opacity and consolidation; and *decreased lung opacity*, including cysts, cavities, emphysema, and mosaic perfusion.
- Small nodules can be classified as perilymphatic, random, or centrilobular at HRCT, according to their distribution in the secondary pulmonary lobule. Recognition of the distribution is fundamental for generating differential diagnoses of lung disease.
- Radiation is a relatively weak carcinogen, and the risk for radiation-induced carcinogenesis from a CT scan is generally more than offset by the benefits of the information gained from an appropriately indicated study.
- Magnetic resonance imaging is useful in evaluating superior sulcus lesions, brachial plexopathy, and certain cardiac and mediastinal abnormalities. It is also useful, although less often used than multislice CT, for evaluating suspected aortic dissection and pulmonary embolism.

Key Readings

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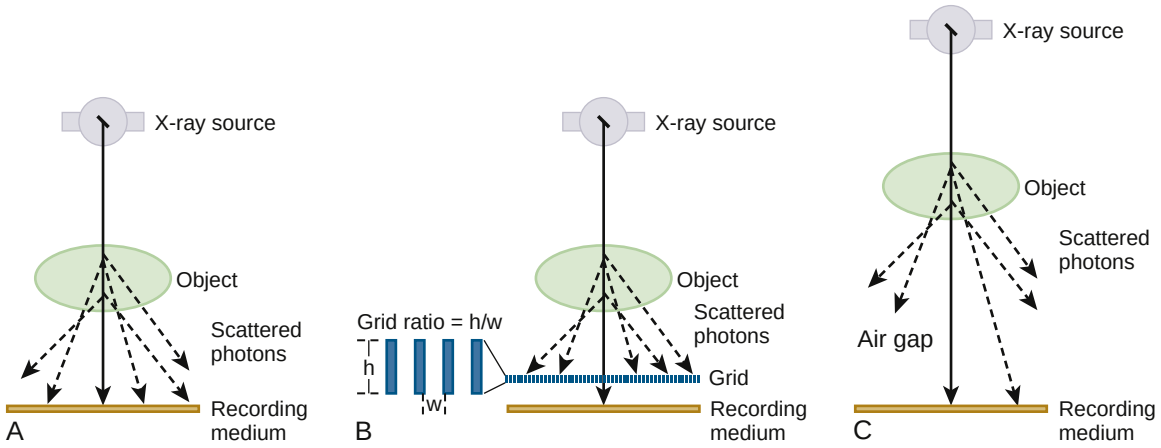
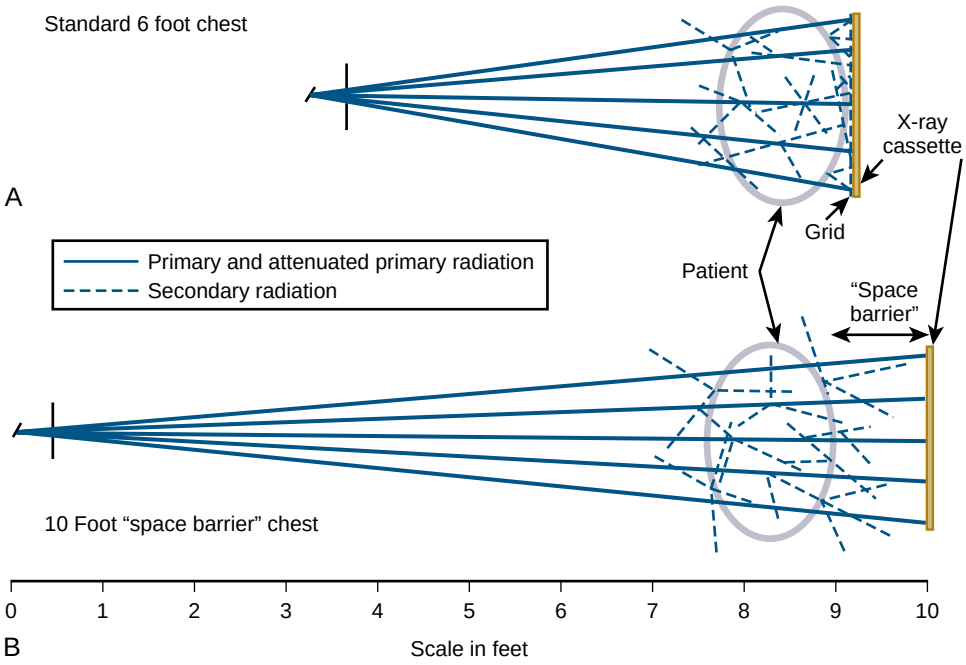
Complete reference list available at ExpertConsult.com.

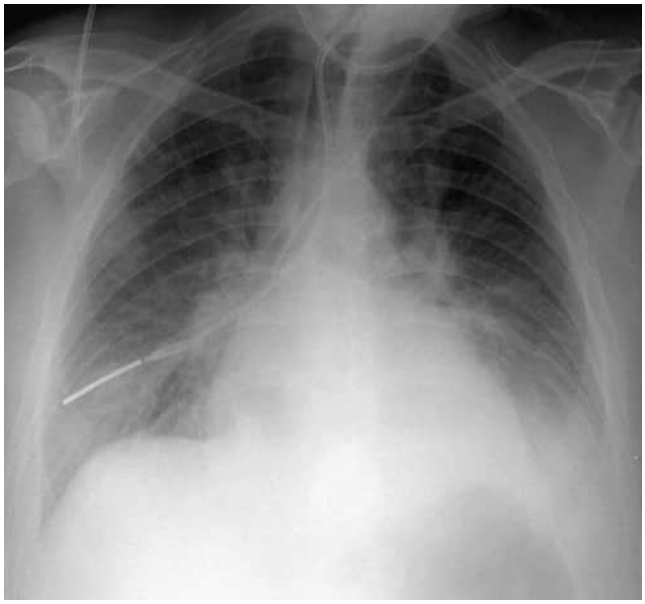
eFIGURE IMAGE GALLERY



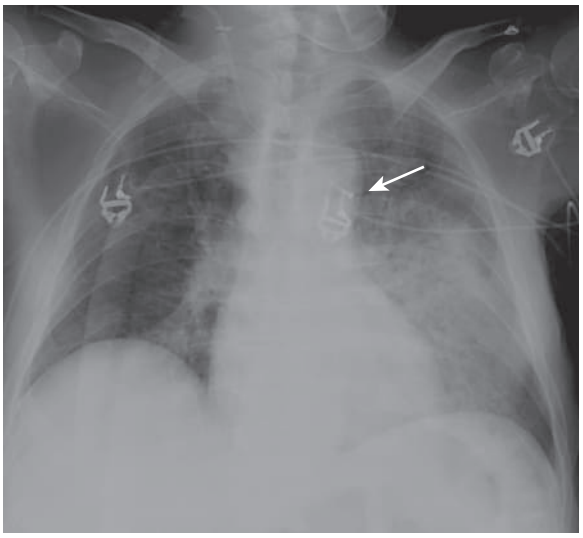
eFigure 20.1 Scattered radiation and scatter reduction. (A) When an object is radiographed, some photons (the primary x-ray beam) (*solid line*) pass unaffected through the patient. Scattered or secondary radiation *(dashed lines)* arises at various angles to the primary beam and may expose the recording medium, reducing image contrast and detail. (B) Scatter can be reduced with a grid. An antiscatter grid placed between the object and the recording medium reduces exposure due to scattered radiation. A grid is made of thin layers of radiation absorber (e.g., lead). Scattered radiation traveling at an angle to the grid layers is absorbed, although some scattered radiation at shallow angles may pass through. The grid ratio is equal to the height of the radiation absorber strips divided by the distance between them. (C) Scatter can be reduced with an air gap. When the distance between the object and the recording medium is increased, an air gap is created. With an air gap, scattered photons at sufficiently great angles miss the recording device.



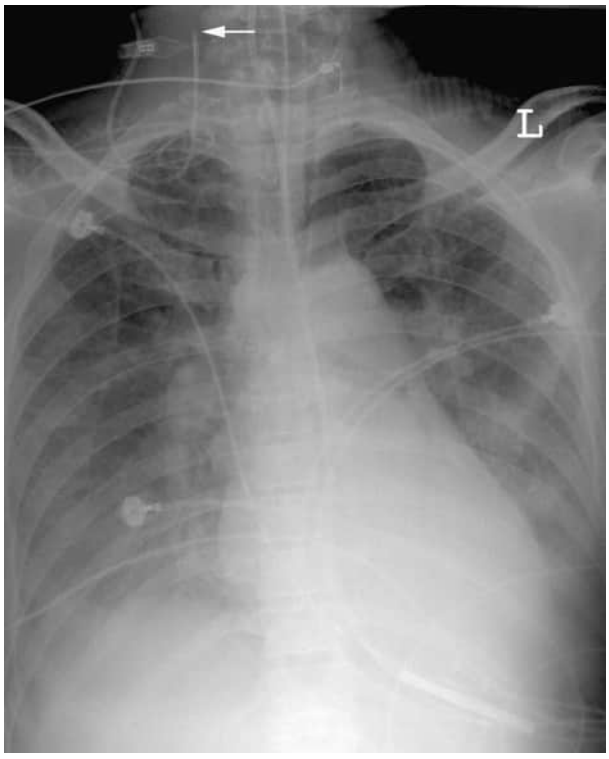
eFigure 20.2 Use of grid or space barrier in radiography. (A) The geometry of a standard 6-foot chest radiograph. For beam energies in the recommended range (>120 kVp), a grid is necessary between the patient and the detector to diminish scattered radiation. (B) A 10-foot air gap, or "space barrier," can also be used. The air gap obviates the need for a grid. The 10-foot tube-to-detector distance helps to minimize geometric enlargement. The avoidance of the grid diminishes patient radiation exposure.



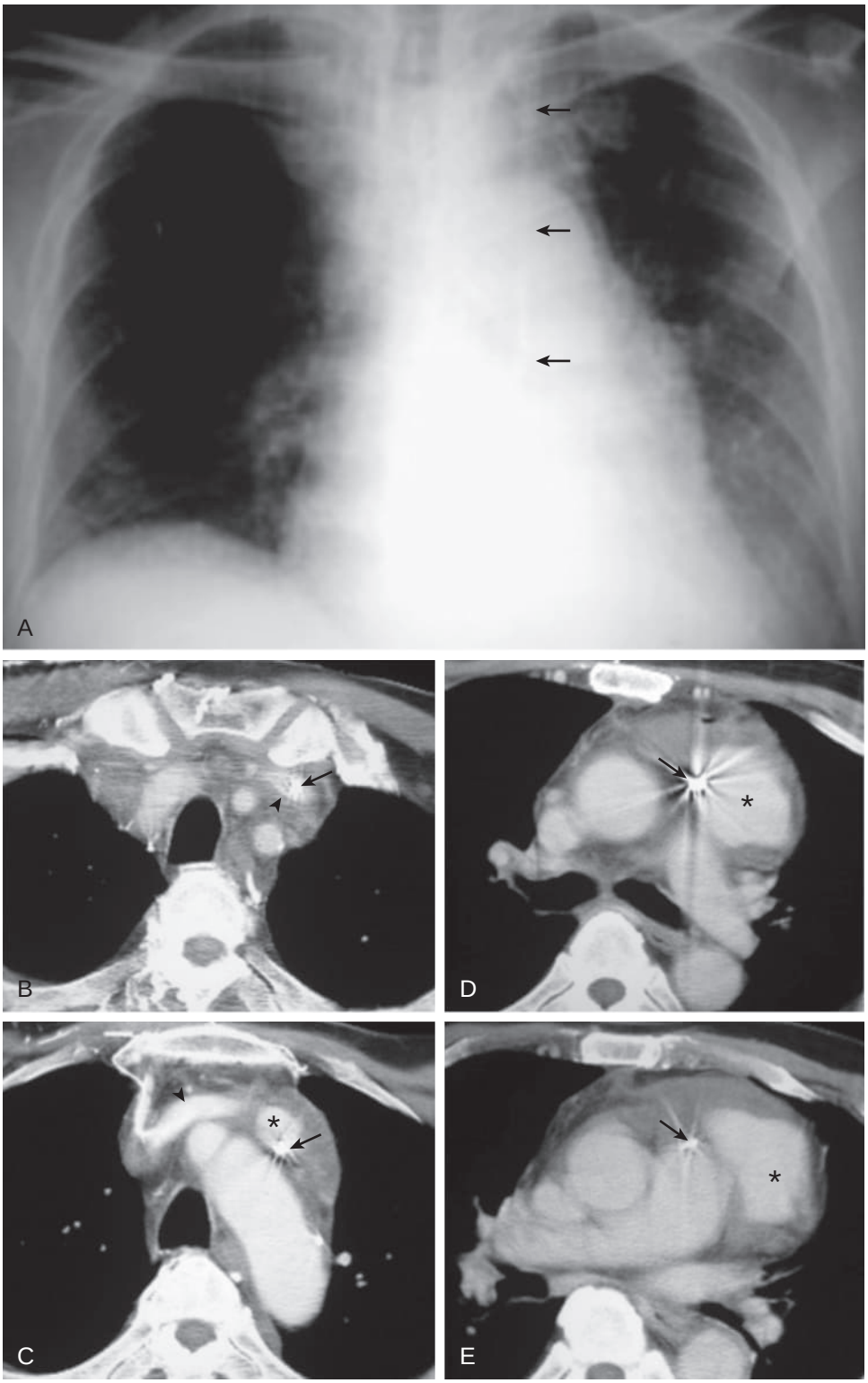
eFigure 20.3 Portable chest radiograph shows malposition of an enteric tube. Frontal chest radiograph shows placement of an enteric tube in the right lower lobe bronchus. (Courtesy Michael B. Gotway, MD.)



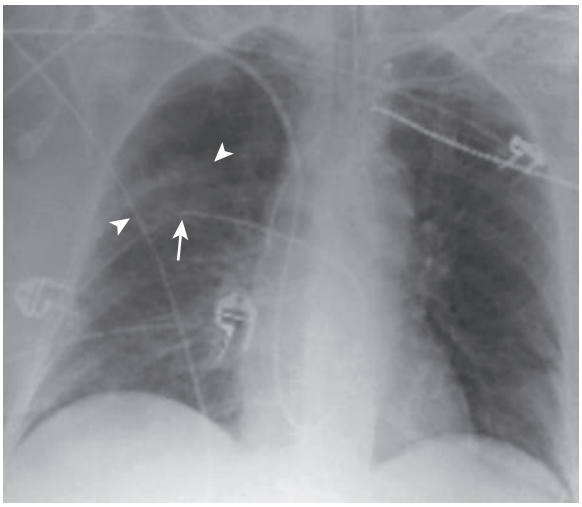
eFigure 20.5 An intensive care unit portable radiograph demonstrates malposition of a right central venous catheter. The catheter has been inadvertently inserted into the right carotid artery; the tip (*arrow*) resides in the aortic arch. A large area of consolidation is seen in the left lung. (Courtesy Michael B. Gotway, MD.)



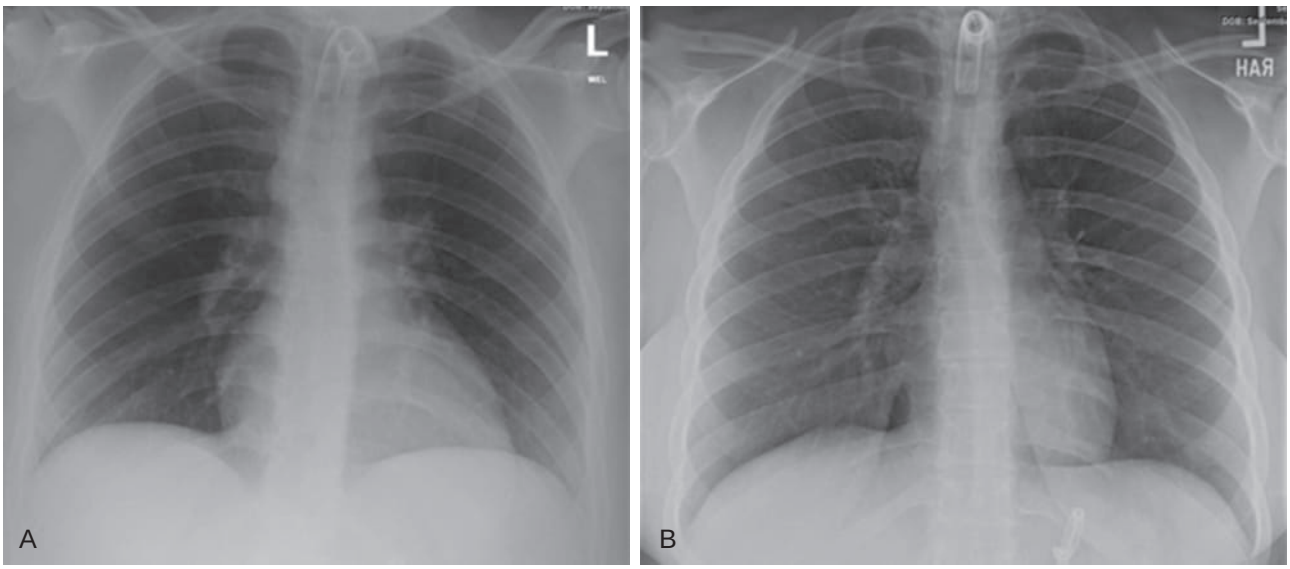
eFigure 20.4 A portable radiograph shows a misplaced central venous line. Note that the right external jugular venous catheter tip (*arrow*) is within the right internal jugular vein, rather than the superior vena cava. Extensive opacities (pulmonary edema) are present in both lungs. (Courtesy Michael B. Gotway, MD.)



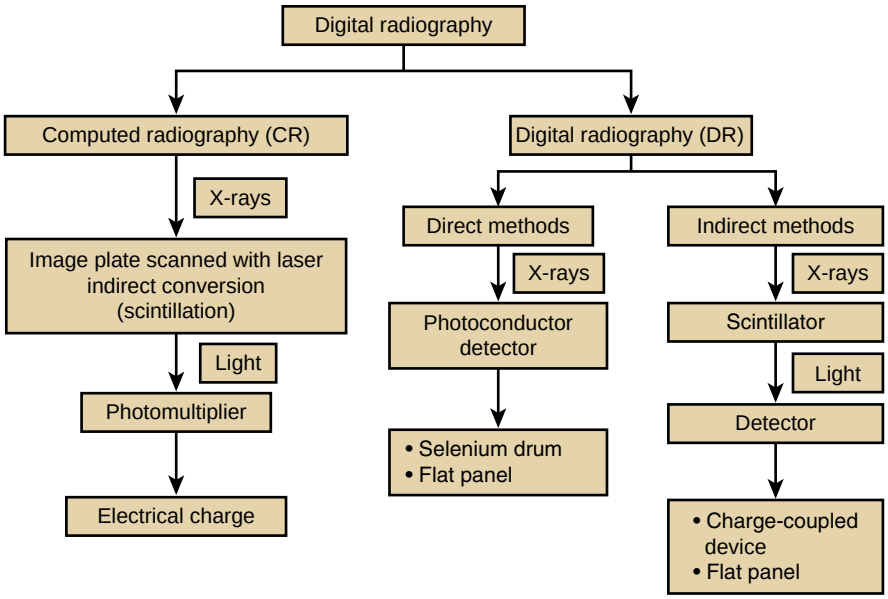
eFigure 20.6 Portable intensive care unit radiography is useful in several situations. (A) Chest radiograph performed after insertion of a left internal jugular central venous catheter shows the catheter (*arrows*) follows a more medial and inferior course than expected for left internal jugular and brachiocephalic vein catheter placement. Sequential axial contrast-enhanced chest computed tomography images near the thoracic apex (B), at the thoracic aortic arch (C), at the level of the left pulmonary artery (D), and at the level of the main pulmonary artery (E) show the catheter (*arrow*) extending through the inferior margin of the left brachiocephalic vein (*arrowhead,* B–C) into an extravascular location more inferiorly, with surrounding active contrast extravasation (*asterisk*) and hematoma resulting from venous perforation and pulmonary artery laceration. (Courtesy Michael B. Gotway, MD.)



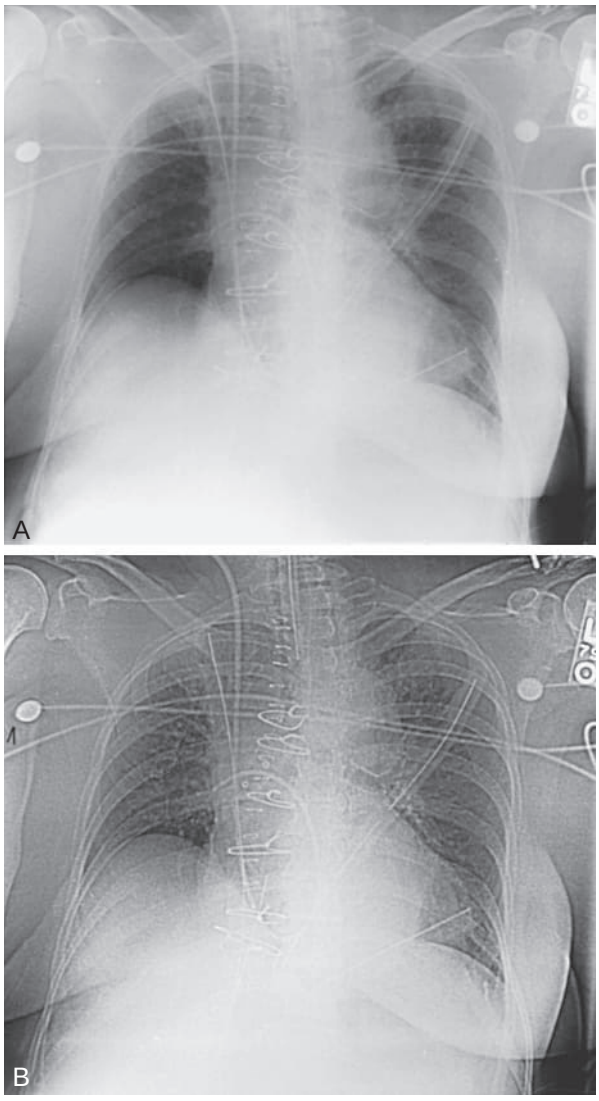
eFigure 20.7 Sequelae of a malpositioned pulmonary artery catheter. The catheter (*arrow* denotes the tip) extends too far peripherally into the segmental vessels of the right upper lobe artery. The catheter had been in this location for a number of hours. Note the opacity in the right upper lobe (*arrowheads*), representing pulmonary hemorrhage or infarction secondary to vessel obstruction by the pulmonary artery catheter. (Courtesy Michael B. Gotway, MD.)



eFigure 20.8 Portable radiography has limitations. (A) This anteroposterior supine portable radiograph was made in the intensive care unit. The energy of the beam was 100 kVp, and the focal spot–film distance was 40 inches. The pulmonary vasculature is poorly visualized because of a long exposure with motion blurring and a short focal spot–film distance with magnification and detail degradation. (B) This radiograph was obtained from the same patient shortly after that shown in (A) but in the main radiology department. The energy of the beam was 130 kVp, with a focal spot–film distance of 72 inches. Radiograph in (B) shows much better detail than radiograph (A) and also has less magnification. (Courtesy Michael B. Gotway, MD.)



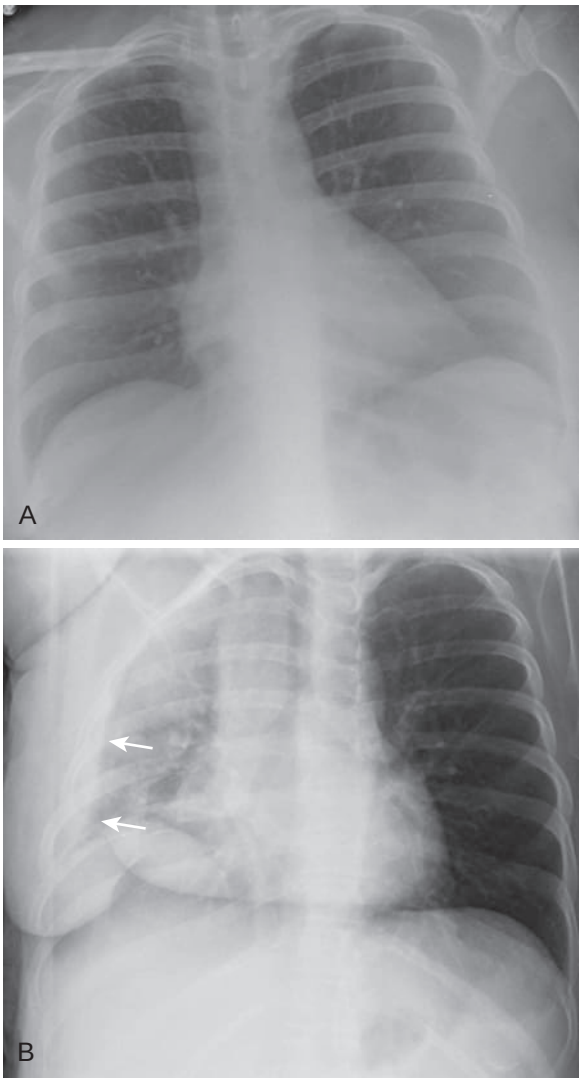
eFigure 20.9 Digital radiographic methods. Computed radiography uses imaging plates exposed by conventional radiographic equipment. The reusable plates are coated with a photostimulatable phosphor that absorbs energy and retains a latent image after x-ray exposure. The stored energy of the latent image is released as light when the plate is scanned by a laser in an image plate reader. Pixel content is developed for each raster line by changes in the strength of the light signal. DR approaches are broadly categorized as either *direct* or *indirect* methods. Indirect DR methods are by far the most commonly used for chest imaging. Indirect methods first convert incident x-ray energy into light through the use of a photostimulable material (usually cesium-iodide [CsI]) referred to as *scintillator*. These light energy photons are then converted into an electrical charge in the underlying absorbing material, usually amorphous silicon (aSi), whose pixelated size determines the resolution. The charge developed in the aSi is proportional to the amount of incident x-ray energy, which is read out to form the image. Direct DR techniques do not have any intermediate scintillating material; thus x-ray energy incident on the detector is immediately converted to an electrical charge proportional to the amount of x-ray energy detected. Direct DR devices are not currently used for chest imaging as this detector is expensive to manufacture. Indirect DR methods are predominantly used for chest imaging, and imaging plates are available in various sizes and resolutions and allow various processing capabilities. Portable indirect (CsI-aSi) plates can use blue-tooth connectivity for chest examinations. Other indirect DR devices use a scintillator with a charge-coupled device, but such devices are less frequently used.



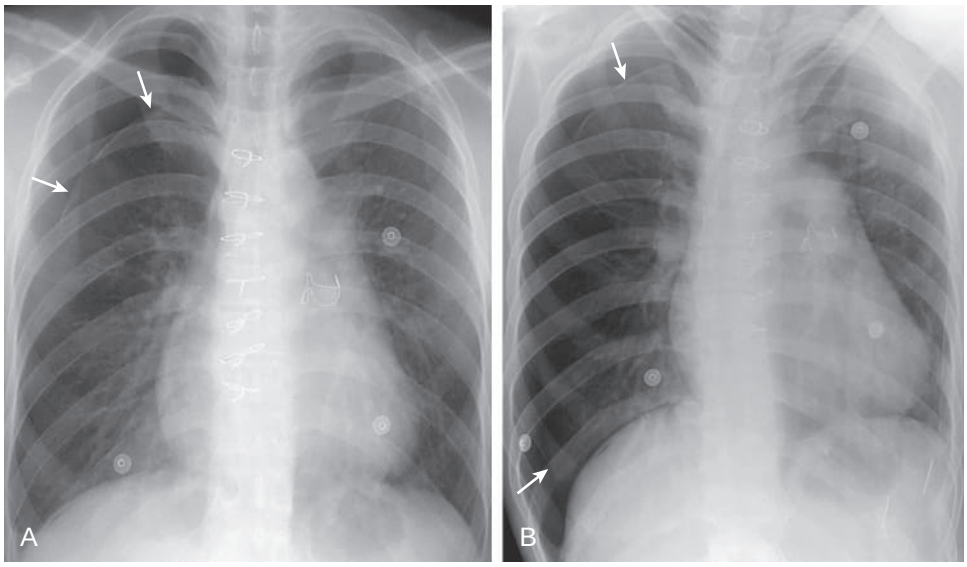
eFigure 20.10 Digital (computed radiographic) study of the chest made in an intensive care unit. (A) This view resembles a "conventional" film-screen radiograph. (B) This view was processed for edge enhancement. (Courtesy Michael B. Gotway, MD.)



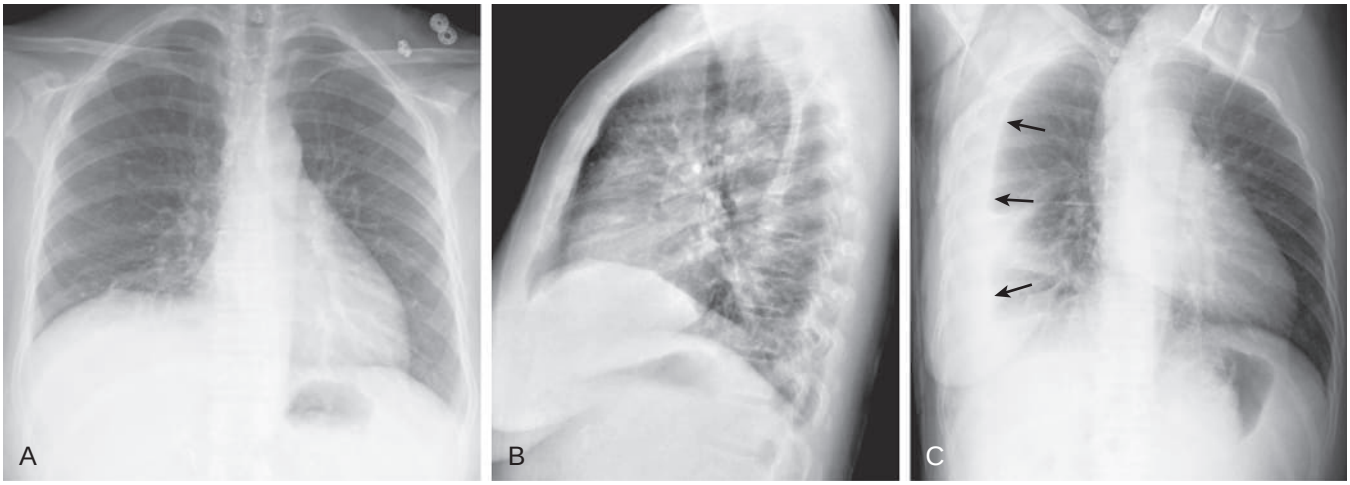
eFigure 20.11 Unilateral hyperlucent lung due to patient rotation. Frontal chest radiograph rotated to a right anterior oblique position shows diffuse lucency affecting the left thorax. Focal lucency can result from air trapping due to obstructive lung disease or endobronchial obstruction, or, rarely, vascular obstruction (see eFigs. 78.15, 81.6, and 81.8), or chest wall disorders, such as mastectomy or Poland syndrome (a birth defect of underdeveloped chest muscle on one side of the body), but is most commonly the result of technical factors. (Courtesy Michael B. Gotway, MD.)



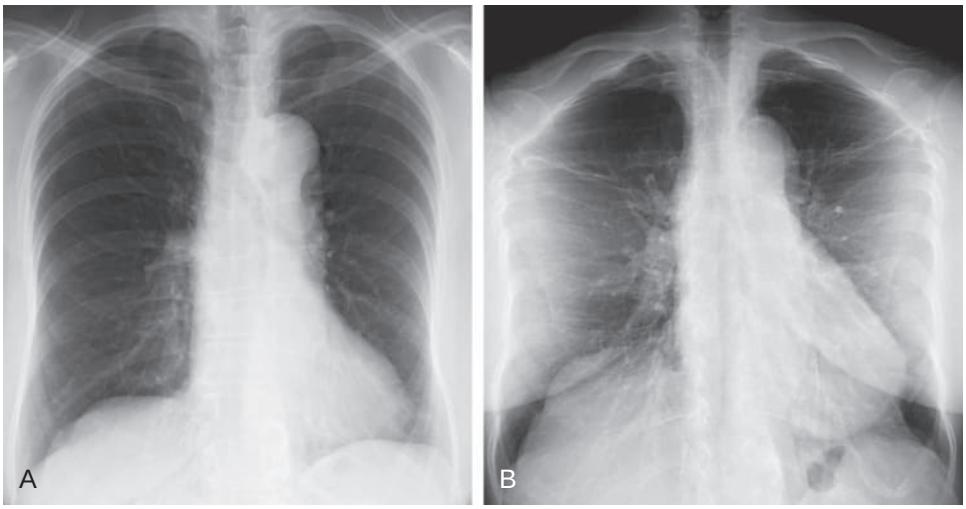
eFigure 20.12 The value of decubitus radiography. This patient had right pleuritic chest pain. (A) A frontal chest radiograph shows no specific abnormalities; the right costophrenic angle is sharp. (B) A right lateral decubitus radiograph shows a small right pleural effusion (*arrows*). Note that decubitus imaging causes collapse of the ipsilateral lung. (Courtesy Michael B. Gotway, MD.)



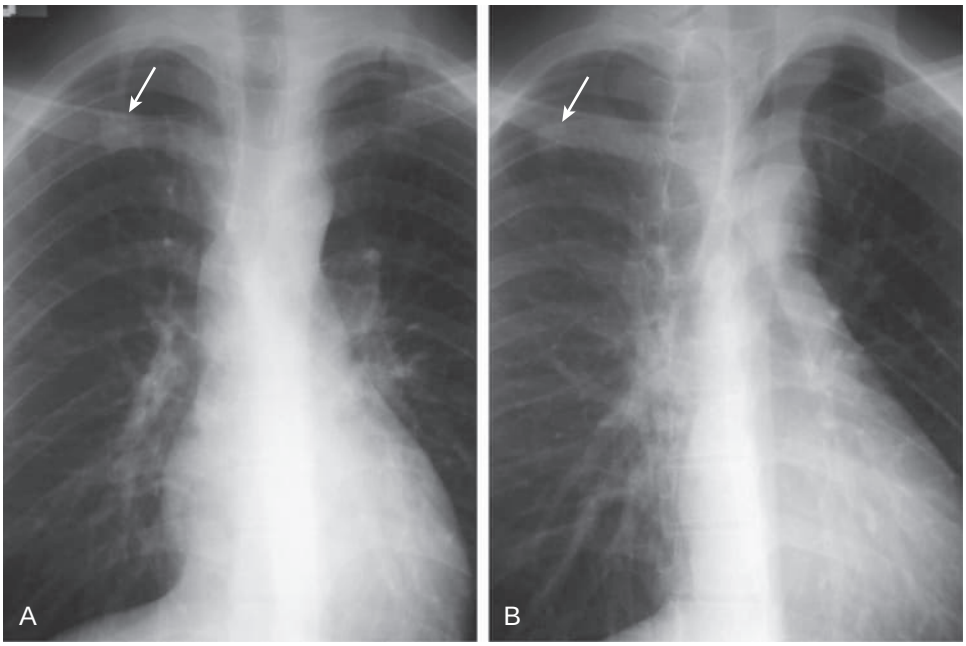
eFigure 20.13 Comparison of pneumothorax appearance at upright and lateral decubitus chest radiography. (A) Upright inspiratory frontal chest radiograph shows the typical appearance of a pleural line (*arrows*) over the apex of the right lung, representing pneumothorax. (B) Left lateral decubitus chest radiograph shows the gas in the pleural space has migrated in a nondependent fashion over the entire peripheral right thorax, creating a pleural line (*arrows*) over both the apical and costophrenic regions. (Courtesy Michael B. Gotway, MD.)



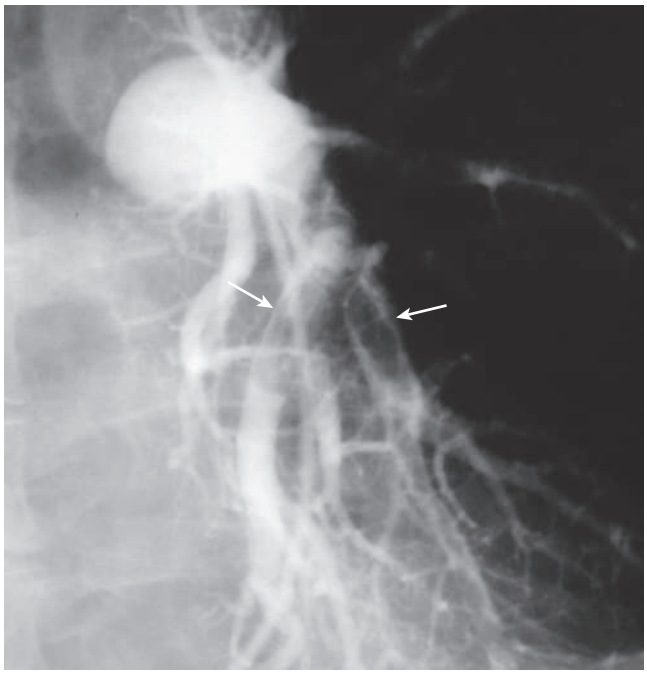
eFigure 20.14 The value of decubitus radiography in a patient with right chest pain. (A) Frontal chest radiograph shows apparent elevation of the right hemidiaphragm, but the right costophrenic angle is sharp. (B) Lateral chest radiograph reveals obscuration of the posterior portion of the right hemidiaphragm, but a clear meniscus indicating right pleural effusion is not seen. (C) Right lateral decubitus radiograph reveals the presence of a large, free pleural effusion (*arrows*). The apparent elevation of the hemidiaphragm on the conventional posteroanterior and lateral radiographs is due to subpulmonic effusion. (Courtesy Michael B. Gotway, MD.)



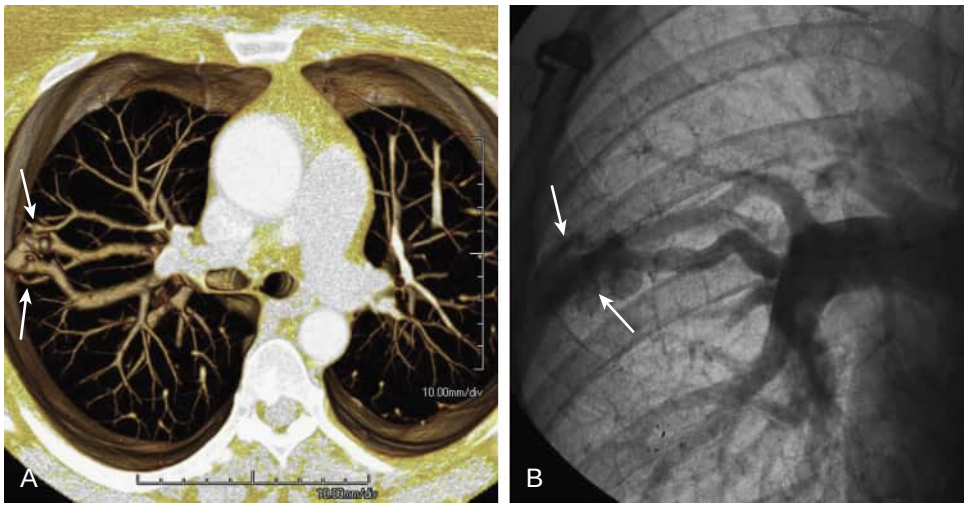
eFigure 20.15 Lordotic chest radiography. (A) Frontal chest radiograph shows how the anterior and posterior cranial ribs overlap with the clavicles, creating superimposition that often obscures abnormalities in the apices. (B) Lordotic chest radiograph shows that the clavicles are now projected cranial to the first ribs, and the anterior and posterior portions of the ribs nearly overlap with one another, improving visualization of the pulmonary parenchyma in the lung apices. (Courtesy Michael B. Gotway, MD.)



eFigure 20.16 Value of oblique chest radiography. (A) Frontal posteroanterior radiograph shows a possible nodular opacity (*arrow*) at the right apex, obscured by overlap of the right clavicle and anterior first rib. (B) Five-degree right anterior oblique chest radiograph shows that the possible opacity (*arrow*) "moves" relative to the clavicle and first rib, indicating that the lesion is unrelated to the anterior chest wall and resides within the lung. (Courtesy Michael B. Gotway, MD.)



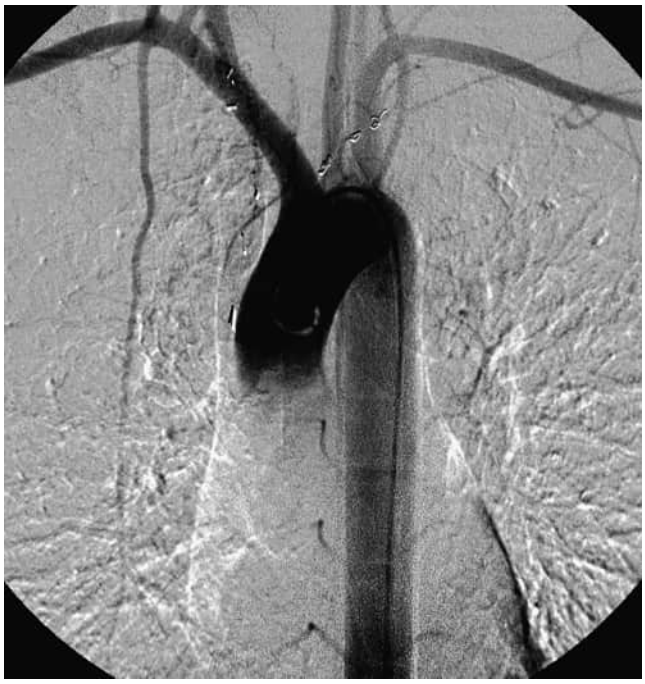
eFigure 20.17 Catheter pulmonary angiography of acute pulmonary embolism. Pulmonary angiography image shows multiple emboli. Intraluminal filling defects *(arrows)* are present within the left pulmonary arterial vasculature, consistent with pulmonary emboli. (Courtesy Michael B. Gotway, MD.)



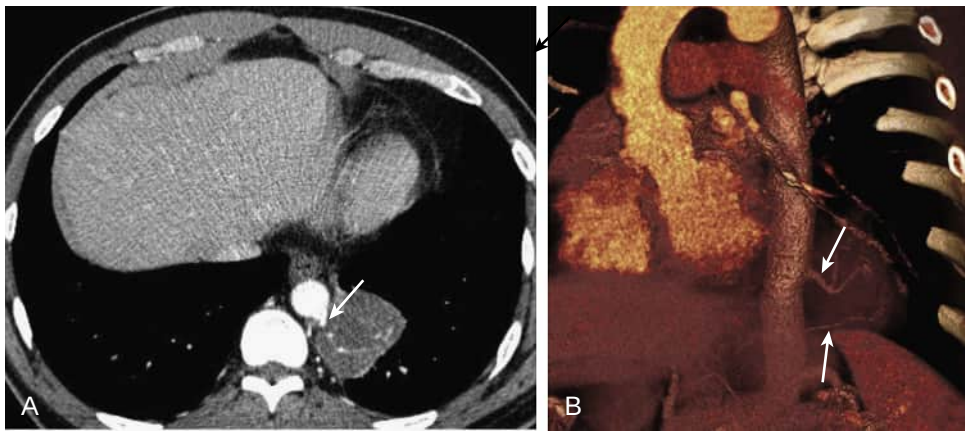
eFigure 20.18 Arteriovenous malformation. (A) Axial volume-rendered chest computed tomography image shows an arteriovenous malformation (*arrows*) in the peripheral right lung. (B) Coronal pulmonary angiogram before embolization shows the arteriovenous malformation (*arrows*). (Courtesy Michael B. Gotway, MD.)



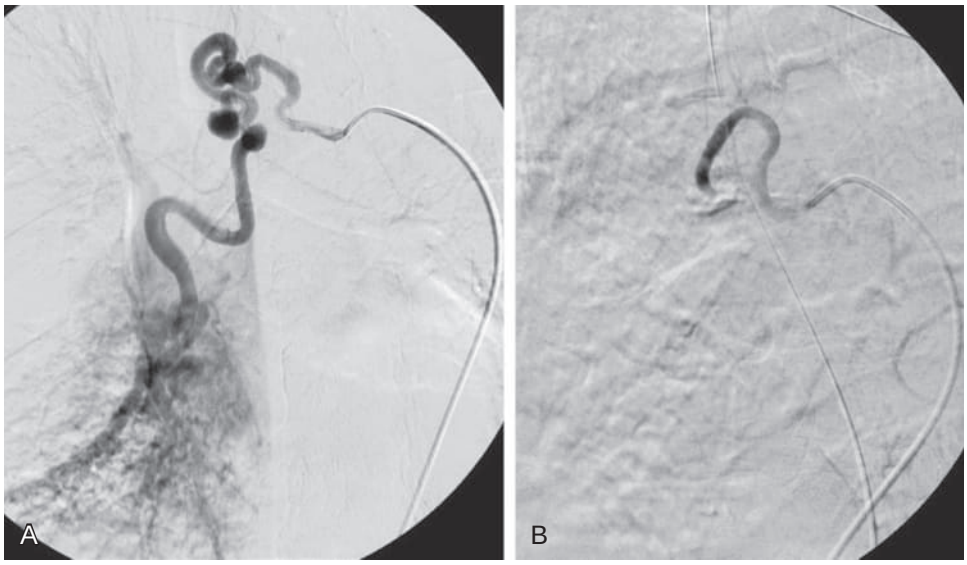
eFigure 20.19 Catheter pulmonary angiography of pulmonary artery vasculitis. Pulmonary arteriogram in a patient with Takayasu arteritis shows a high-grade stenosis *(arrow)* of the right upper lobe pulmonary artery. (Courtesy Michael B. Gotway, MD.)



eFigure 20.20 Catheter aortography. Oblique coronal image from an aortogram shows the typical appearance of the aorta and great vessels. (Courtesy Michael B. Gotway, MD.)



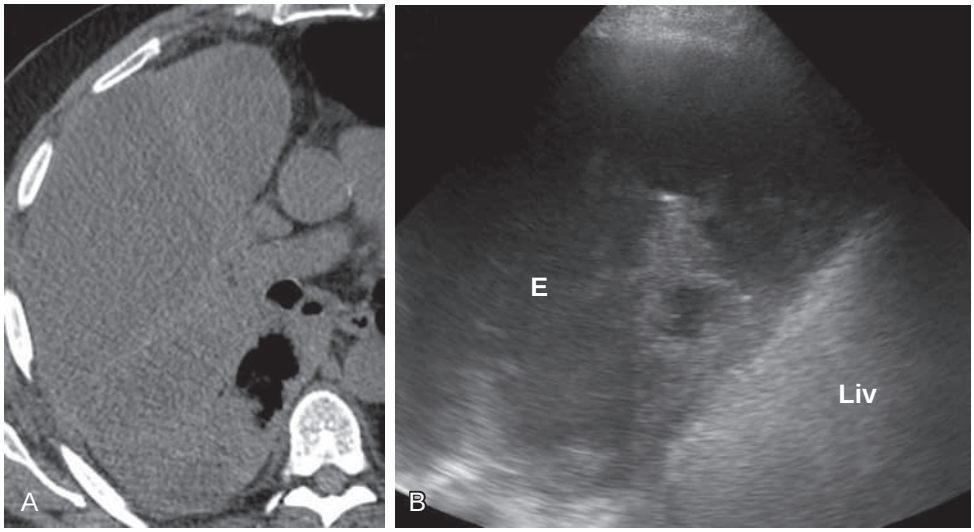
eFigure 20.21 Intralobar bronchopulmonary sequestration. (A) Axial chest computed tomography image in a 24-year-old man with recurrent pneumonia shows a masslike opacity in the posterior basilar left lower lobe. Note the prominent aberrant vessel originating from the descending thoracic aorta (*arrow*) supplying the mass. (B) Oblique coronal volume-rendered image shows the posterior basilar left lower lobe mass and two aberrant vessels (*arrows*) supplying the lesion. (Courtesy Michael B. Gotway, MD.)



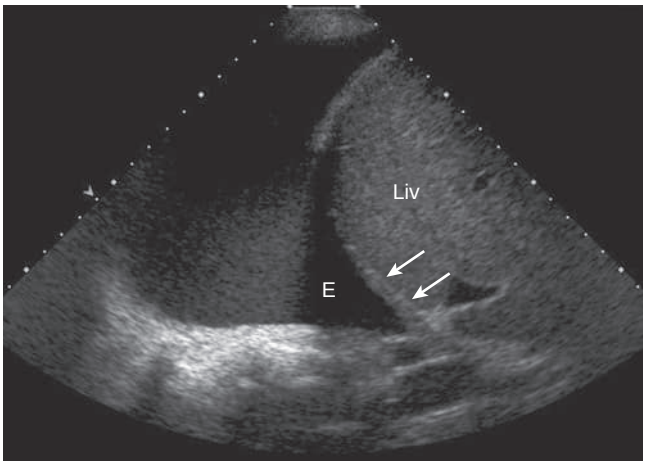
eFigure 20.22 Bronchial arteriography in a patient with right lower lobe bronchiectasis and hemoptysis. (A) Initial contrast injection into a hypertrophied bronchial artery. (B) Injection into the same artery as in (A) shows significantly decreased blood flow after coil embolization. (Courtesy Michael B. Gotway, MD.)



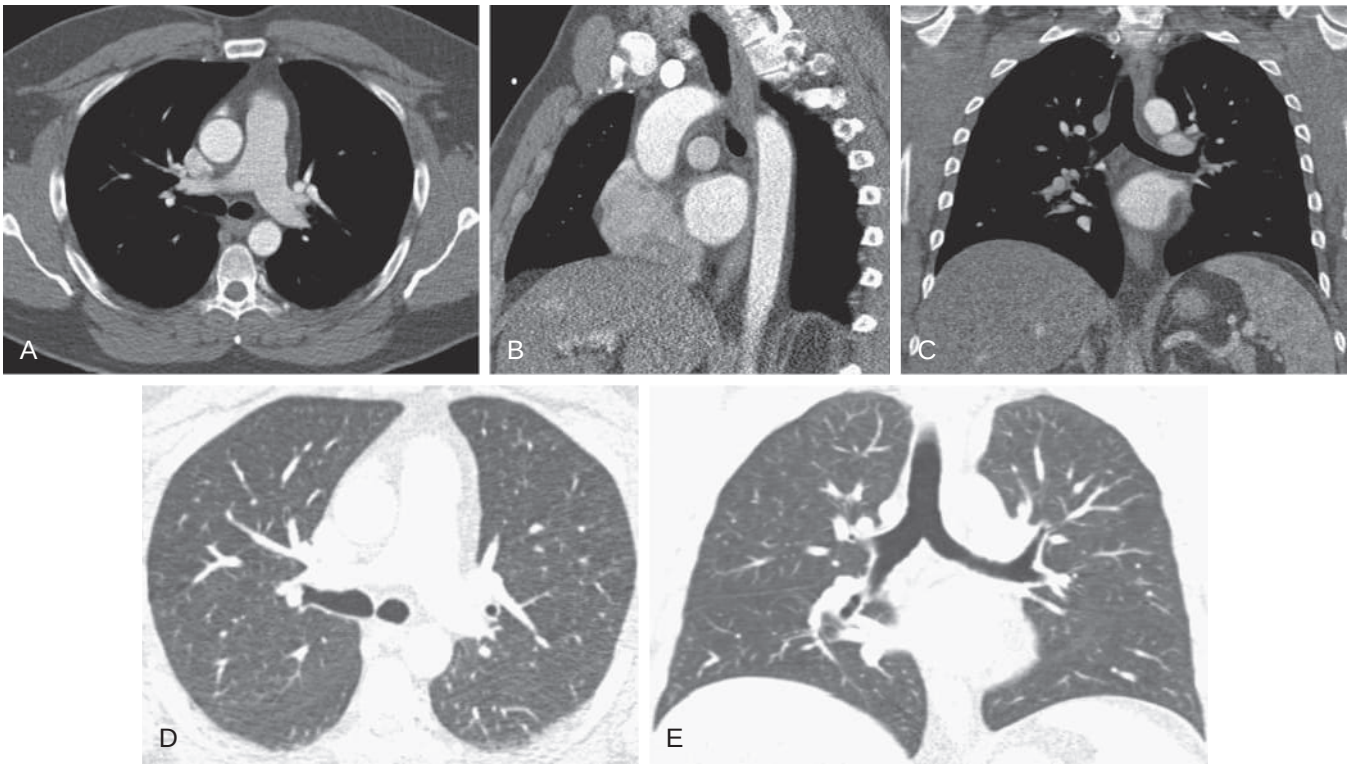
eFigure 20.23 The position of a patient for ultrasound-guided thoracentesis. (Courtesy Michael B. Gotway, MD.)



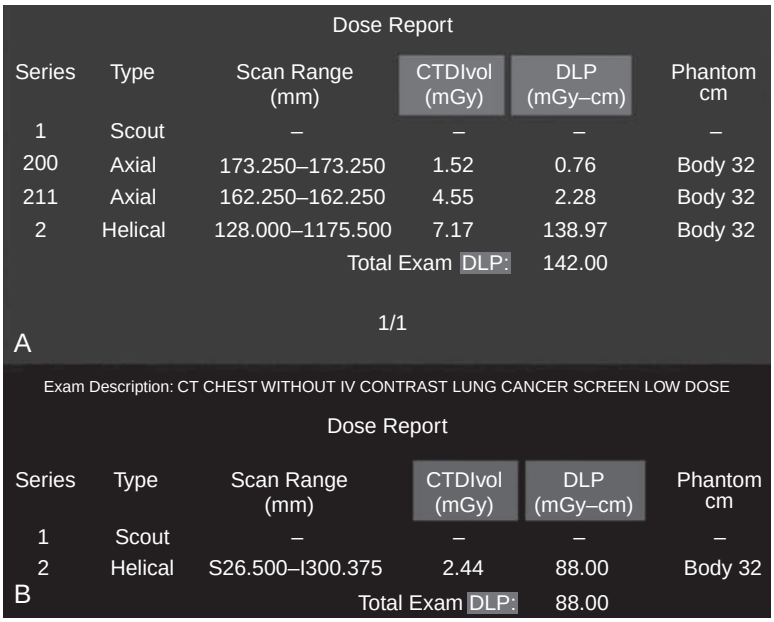
eFigure 20.24 Ultrasound of empyema. (A) Axial unenhanced chest computed tomography image shows a multiloculated complex right pleural space collection. (B) Ultrasound of the right thorax shows a complex, echogenic collection (E) in the right pleural space. The patient was a 60-year-old man with a history of severe asthmatic bronchitis presenting with a 6-week history of intermittent fever, productive cough, shortness of breath, and decreased appetite and treated with amoxicillin for presumed community-acquired pneumonia and corticosteroids for possible COPD exacerbation, without improvement. The patient was seen by his pulmonologist, who noted decreased breath sounds over the right thorax and referred the patient to the emergency department. Ultimately, empyema due to *Streptococcus intermedius* was proven. Liv, liver. (Courtesy Michael B. Gotway, MD.)



eFigure 20.25 Ultrasound of pleural effusion. Ultrasound examination of the lower left chest shows effusion (E) cranial to the right hemidiaphragm (*arrows*). Liv, liver. (Courtesy Michael B. Gotway, MD.)



eFigure 20.26 Isotropic multiplanar imaging with multislice computed tomography of the thorax. Axial (A), sagittal (B), and coronal (C) soft tissue images from a pulmonary computed tomography angiography study show that the resolution and diagnostic quality of the sagittal and coronal imaging is identical to that of the source axial images. Axial (D) and coronal images (E) displayed in lung windows also show equivalent diagnostic quality. (Courtesy Michael B. Gotway, MD.)



Dose Report

Series	Type	Scan Range (mm)	CTDIvol (mGy)	DLP (mGy–cm)	Phantom cm
1	Scout	–	–	–	–
200	Axial	173.250–173.250	1.52	0.76	Body 32
211	Axial	162.250–162.250	4.55	2.28	Body 32
2	Helical	128.000–1175.500	7.17	138.97	Body 32
			Total Exam DLP:	142.00	

1/1

A

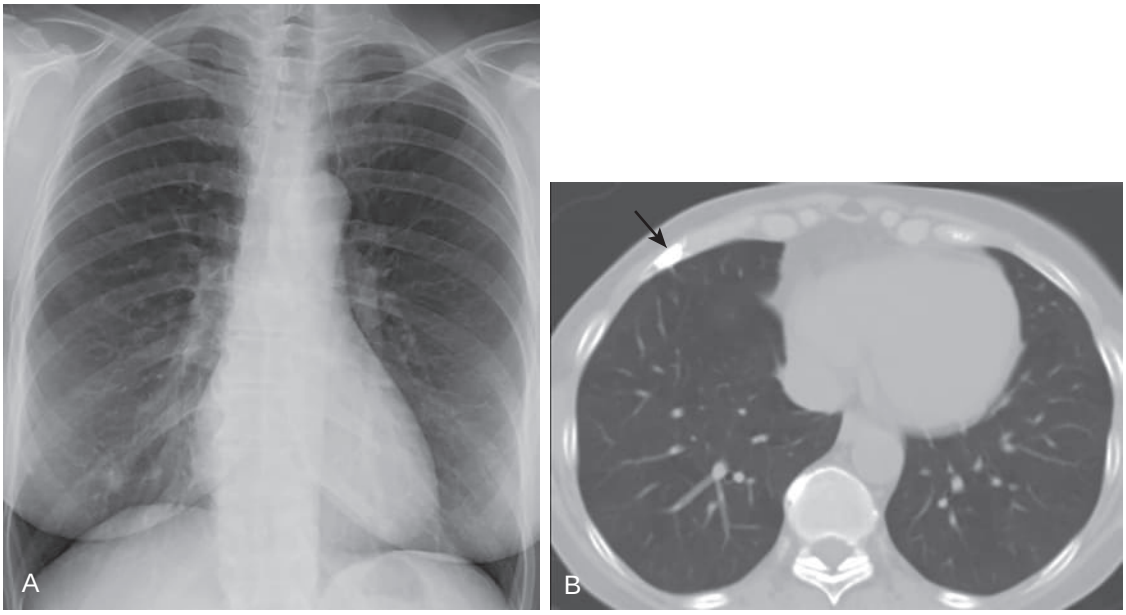
Exam Description: CT CHEST WITHOUT IV CONTRAST LUNG CANCER SCREEN LOW DOSE

Dose Report

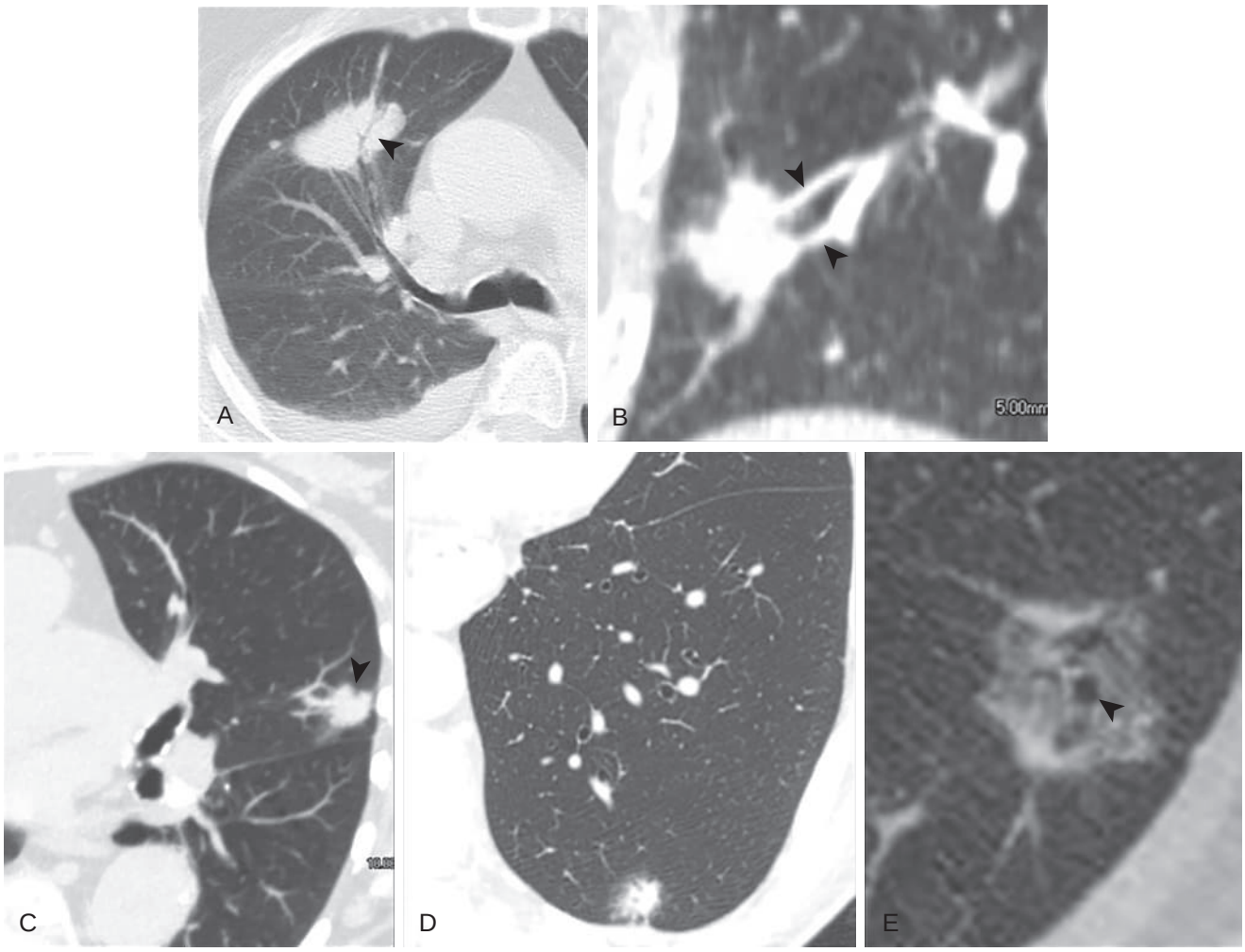
Series	Type	Scan Range (mm)	CTDIvol (mGy)	DLP (mGy–cm)	Phantom cm
1	Scout	–	–	–	–
2	Helical	S26.500–I300.375	2.44	88.00	Body 32
			Total Exam DLP:	88.00	

B

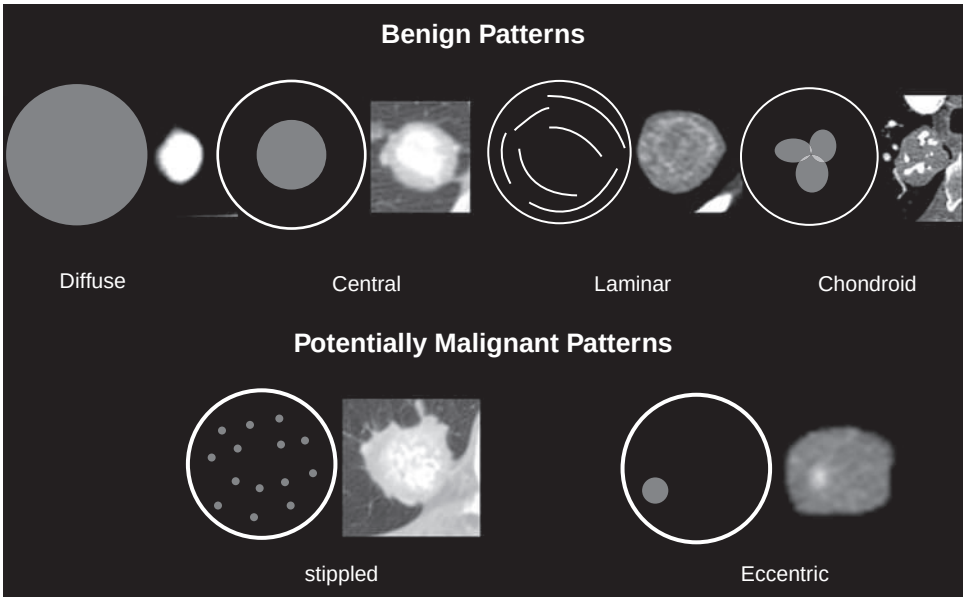
eFigure 20.27 ***Computed tomography*** **(CT) dose reports.** (A) The total radiation exposure associated with the "routine" CT examination is shown as both the *CT dose index* ($CTDI_{vol}$) and the *dose-length product* (DLP). Such dose reports are often recorded as *digital imaging and communications in medicine* (DICOM) images and archived as part of the CT examination in the radiology database, typically a *picture archiving and communication system* (PACS) or electronic medical record. (B) A dose report from a low-dose CT examination performed for lung cancer screening. Note that the $CTDI_{vol}$ = 2.44 mGy, less than the exposure of ≤3 mGy specified for low-dose CT screening examinations. (Courtesy Michael B. Gotway, MD.)



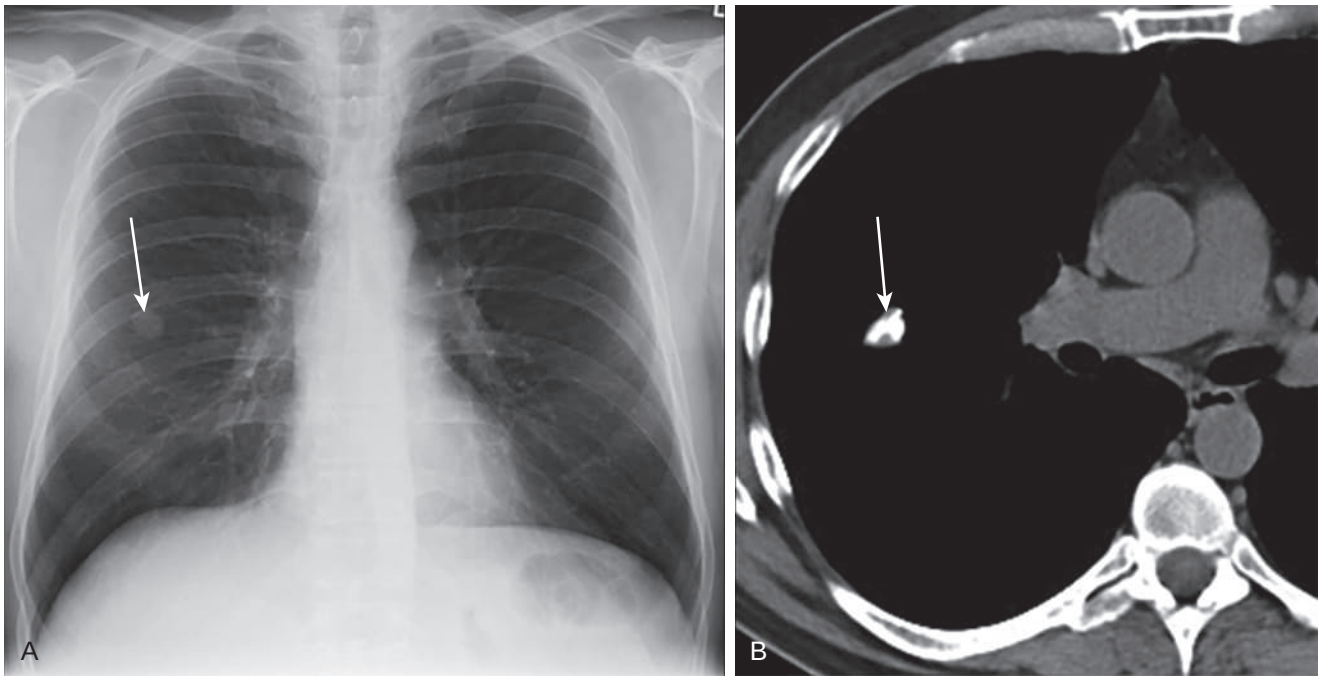
eFigure 20.28 **Chest wall lesion simulating a solitary pulmonary nodule at chest radiography: value of chest computed tomography.** (A) Frontal chest radiograph shows a right lower lobe opacity simulating a pulmonary nodule. (B) Axial chest computed tomography image displayed in lung windows shows a sclerotic lesion (*arrow*) within an anterior rib, which accounts for the chest radiographic abnormality; no lung nodule is present. (Courtesy Michael B. Gotway, MD.)



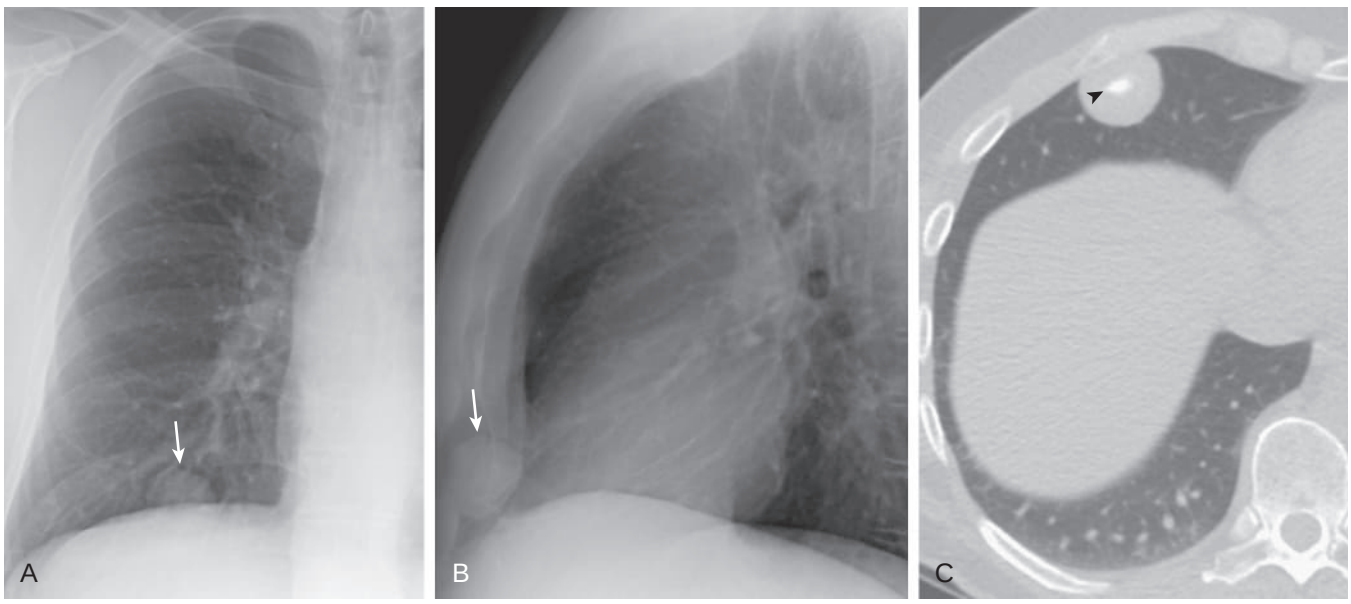
eFigure 20.29 Computed tomography features of malignant pulmonary nodules. (A) Air bronchogram (*arrowhead*) within a solitary pulmonary nodule. (B) Vascular convergence sign: note pulmonary vessels (*arrowheads*) appearing to "converge" on the poorly defined pulmonary nodule. (C) Notch sign: note the lucent defect within the anterior portion of the lingular nodule (*arrowhead*). (D) Spiculation: note that this nodule also shows a notch or small air bronchogram anteriorly. All four nodules show a pleural "tail"—linear opacities extending from the nodule to the visceral pleural surface. Once thought to be a feature suggesting a malignant etiology for a solitary pulmonary nodule, the pleural tail is actually a nonspecific finding. (E) Internal cystic lucency (*arrowhead*), also often referred to as "cystification"or pseudocavitation within a part-solid invasive adenocarcinoma. (Courtesy Michael B. Gotway, MD.)



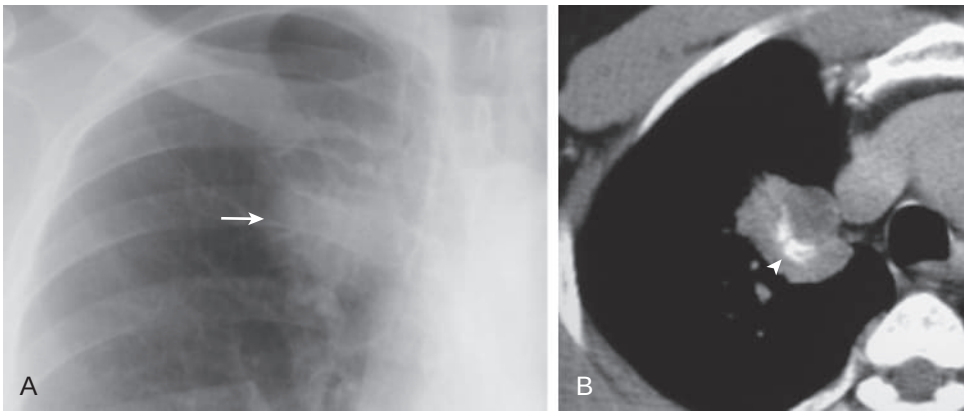
eFigure 20.30 Patterns of nodule calcification: illustrations and computed tomography examples. Benign patterns of calcification within a solitary pulmonary nodule include *diffuse*, or homogenous, nodule calcification; *central* ("bull's-eye"), *laminar,* or "target" calcification (presenting as concentric rings of calcification); and *chondroid,* or "popcorn," calcification. When calcification is found within a pulmonary malignancy, it usually manifests in either a *stippled* or *eccentric* pattern; the latter is thought to result from a pulmonary malignancy engulfing a granuloma. (Courtesy Michael B. Gotway, MD.)



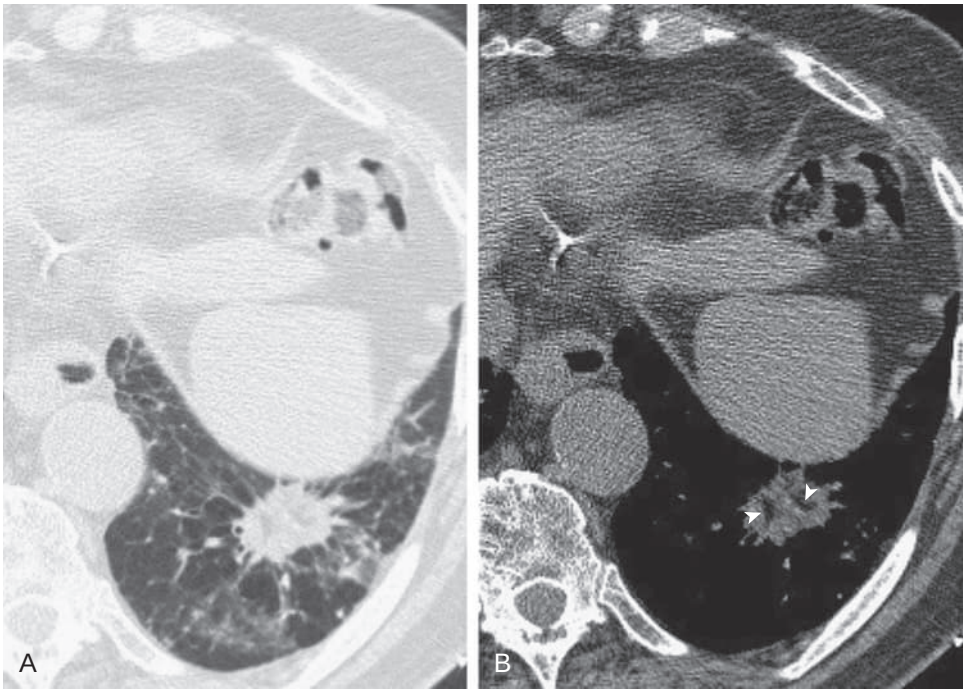
eFigure 20.31 Failure of detection of calcification within a solitary pulmonary nodule at chest radiography: value of chest computed tomography. (A) Frontal chest radiograph shows a solitary pulmonary nodule (*arrow*) in the right lung. The nodule may be calcified, but the absolute determination of calcification within a nodule at chest radiography can be both difficult and occasionally inaccurate. (B) Unenhanced chest computed tomography image displayed in soft tissue windows shows that the nodule (*arrow*) is almost entirely calcified. (Courtesy Michael B. Gotway, MD.)



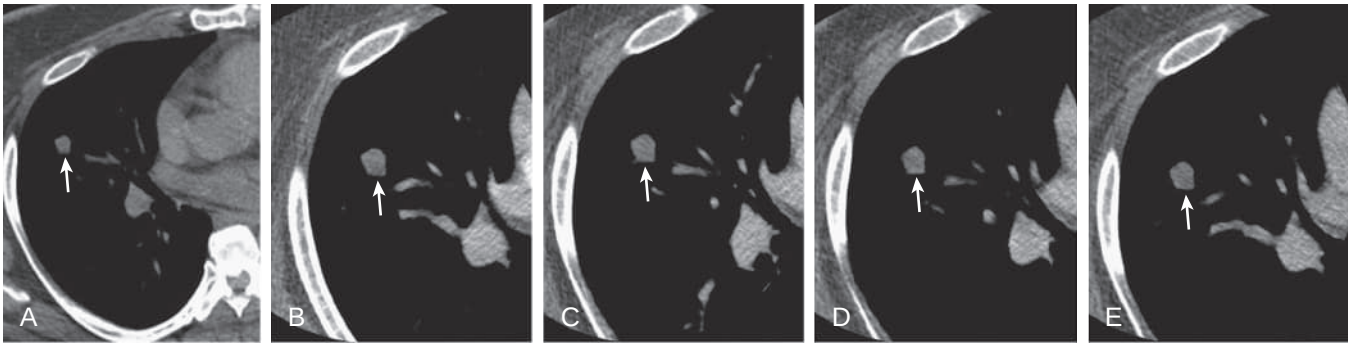
eFigure 20.32 Failure of detection of calcification within a solitary pulmonary nodule at chest radiography: value of chest computed tomography. (A) Frontal and (B) lateral chest radiograph in a patient with a right middle lobe, solitary nodule (*arrow*) does not clearly show calcification within the nodule. (C) Axial chest computed tomography image displayed in lung windows shows a small focus of calcification *(arrowhead)* within the center of the nodule. This lesion was growing slowly and was resected; it proved to be a necrotic granuloma. (Courtesy Michael B. Gotway, MD.)



eFigure 20.33 Calcification in a bronchogenic carcinoma. (A) Detailed frontal chest radiograph shows a right upper lobe nodule (*arrow*), but calcification is not clearly seen within the lesion. (B) Enhanced chest computed tomography image displayed in soft tissue windows shows calcification (*arrowhead*) within the nodule. Note the heterogeneous appearance of this nodule; biopsy subsequently confirmed adenocarcinoma. (Courtesy Michael B. Gotway, MD.)



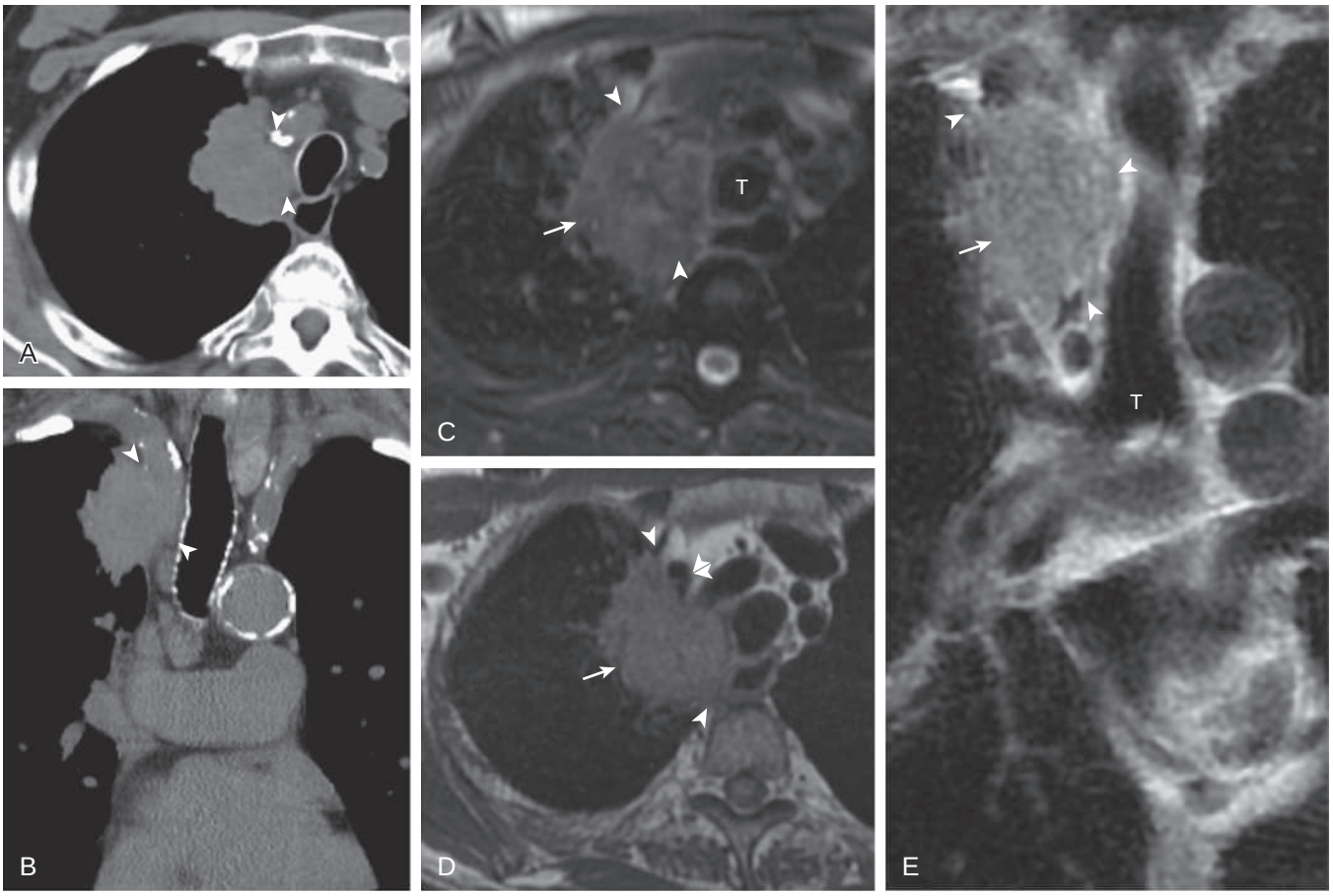
eFigure 20.34 Detection of fat within a nodule at chest *computed tomography* (CT): lipoid pneumonia. (A) Axial chest CT image displayed in lung windows shows a spiculated left lower lobe opacity associated with surrounding inhomogeneous lung opacity. The appearance resembles bronchogenic carcinoma. (B) Axial chest CT image displayed in soft tissue windows shows that the nodule contains low-attenuation material consistent with fat (*arrowheads*), consistent with lipoid pneumonia. The patient was subsequently discovered to be using mineral oil as a laxative. (Courtesy Michael B. Gotway, MD.)



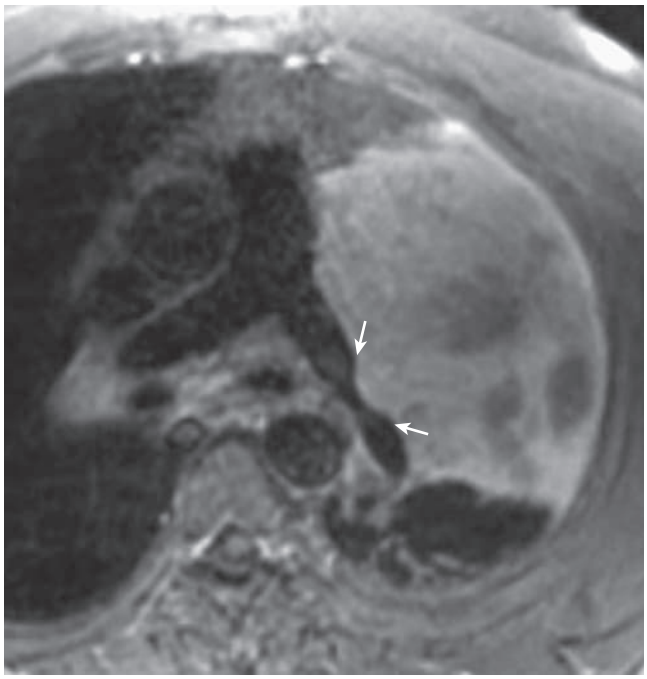
eFigure 20.35 Chest *computed tomography* (CT) solitary-nodule enhancement study: negative results. Axial chest CT imaging (A) before intravenous (IV) contrast injection, (B) at 1 minute, (C) at 2 minutes, (D) at 3 minutes, and (E) at 4 minutes after IV contrast injection shows an unenhanced nodule (*arrow*) attenuation coefficient of 18 Hounsfield units (HU), and after IV contrast injection of 20, 24, 21, and 23 HU at 1, 2, 3, and 4 minutes, respectively. The lack of significant IV contrast enhancement (i.e., >15 HU) at any of the four time points after IV contrast injection strongly suggests that the nodule is benign. (Courtesy Michael B. Gotway, MD.)



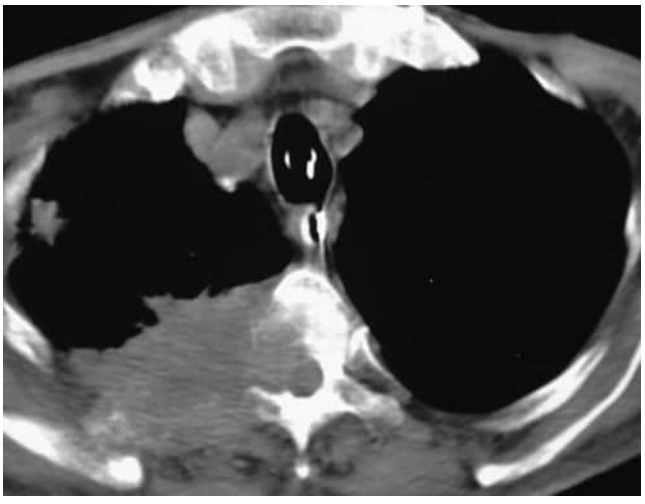
eFigure 20.36 Chest *computed tomography* (CT) for lung cancer staging: tracheal involvement. Enhanced chest CT image displayed in soft tissue windows shows a large right lung mass invading the mediastinum and clearly extending into the trachea. (Courtesy Michael B. Gotway, MD.)



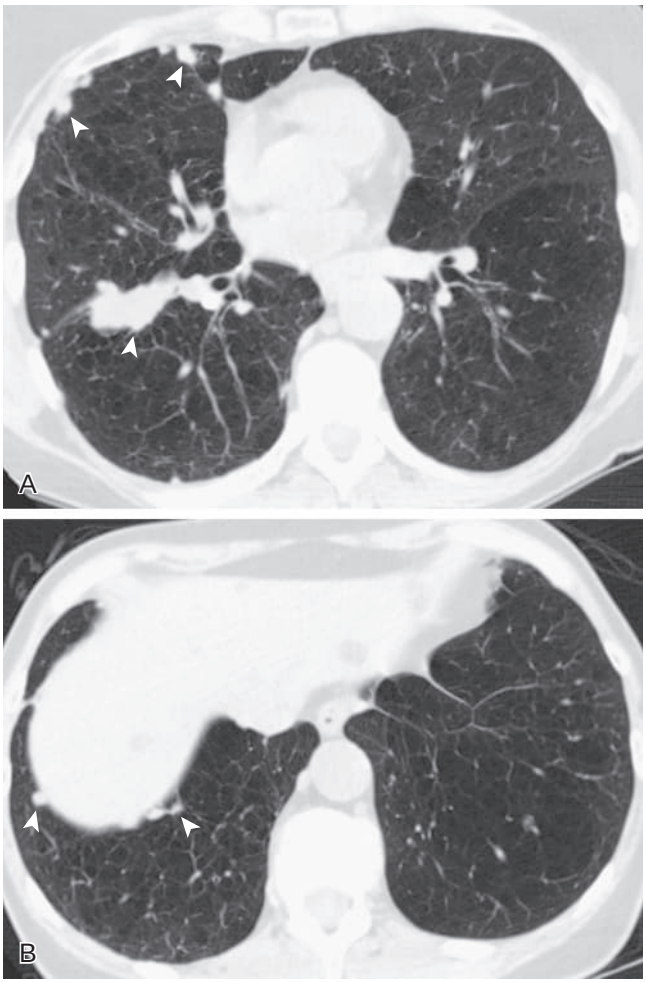
eFigure 20.37 ***Computed tomography*** **(CT) and magnetic resonance imaging for lung cancer staging: mediastinal invasion.** Axial (A) and coronal (B) unenhanced chest CT image displayed in soft tissue windows shows a medial right upper lobe bronchogenic carcinoma invading the mediastinum; note the obliteration of mediastinal fat planes by the tumor (*arrowheads*) and the tumor's close approach to the right brachiocephalic artery. Axial T2-weighted (C), unenhanced axial T1-weighted (D), and enhanced coronal T1-weighted (E) magnetic resonance images show the intermediate to low-signal intensity tumor (*arrows*) extending into the mediastinal fat (the hyperintense, white stripe between the tumor and the trachea [T] in images C and E). The tumor show extensive contact with the mediastinum (margins of the tumor—mediastinal contact is indicated by *arrowheads*). The tumor also shows extensive contact with the right brachiocephalic artery (***double arrowheads,*** D). (Courtesy Michael B. Gotway, MD.)



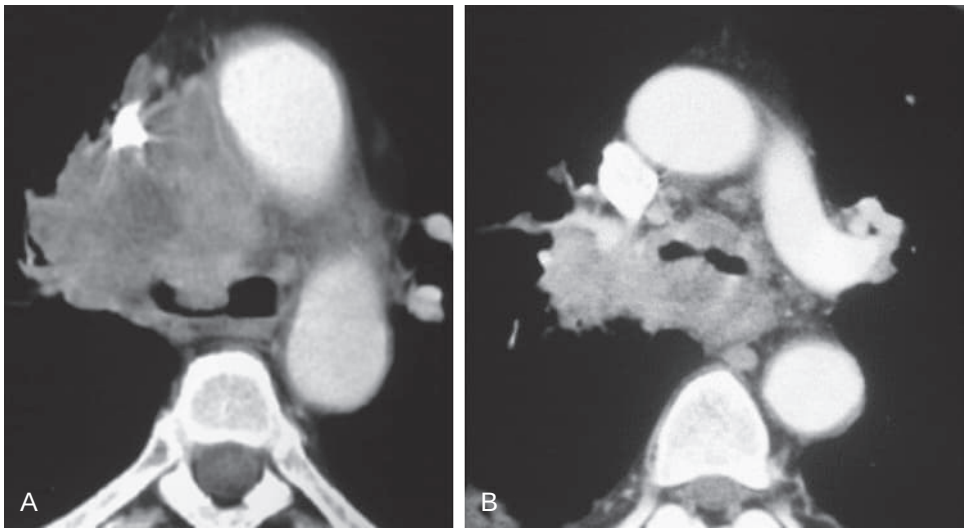
eFigure 20.38 Chest magnetic resonance imaging for lung cancer staging: mediastinal vascular invasion. Enhanced, T1-weighted fat saturation magnetic resonance image shows a heterogeneously enhancing left lung mass clearly invading the left pulmonary artery *(arrows).* (Courtesy Michael B. Gotway, MD.)



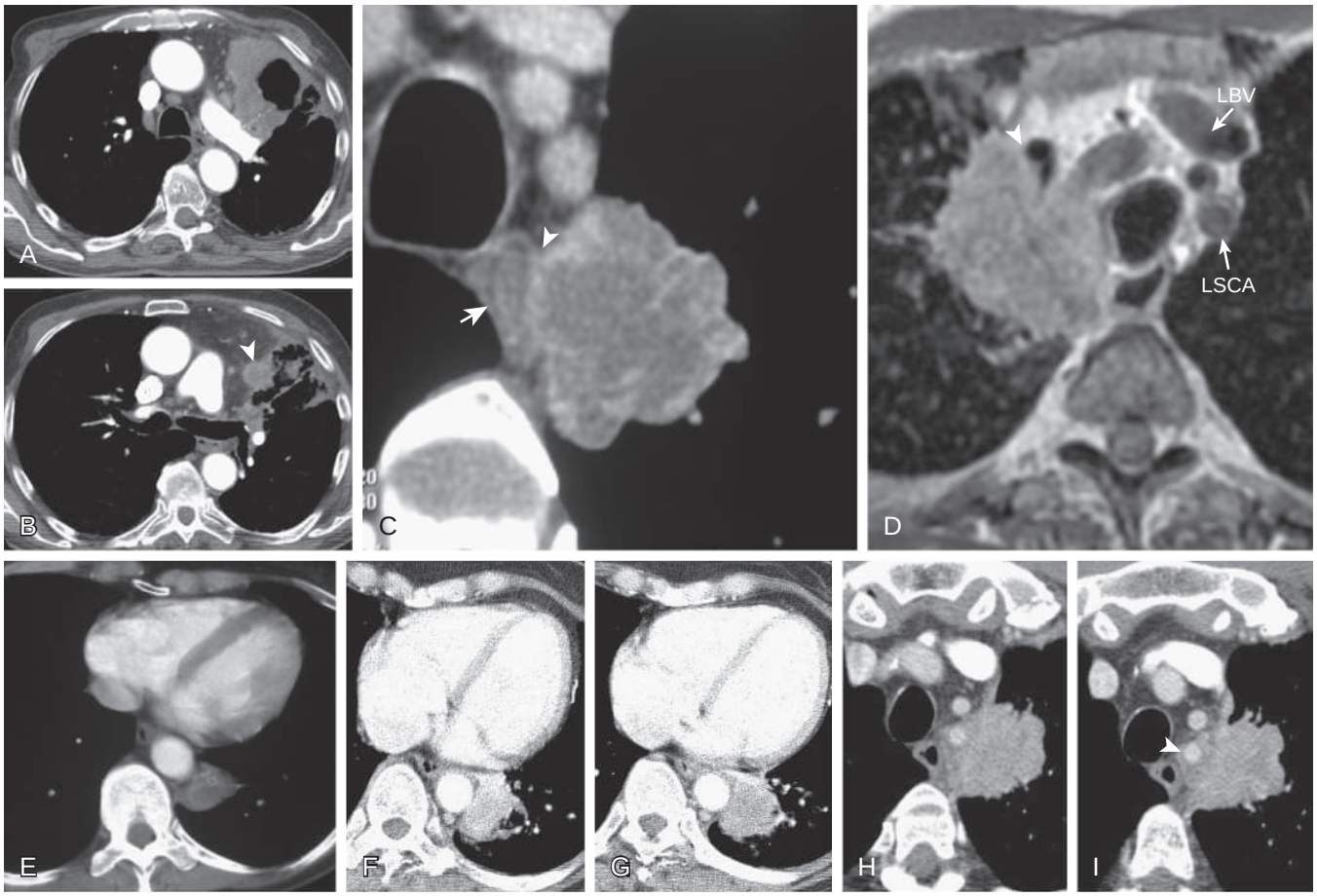
eFigure 20.39 Computed tomography for lung cancer staging: chest wall and vertebral body invasion. Unenhanced axial chest computed tomography image displayed in soft tissue windows shows an extensive right apical neoplasm invading the posterior chest wall and vertebral body. (Courtesy Michael B. Gotway, MD.)



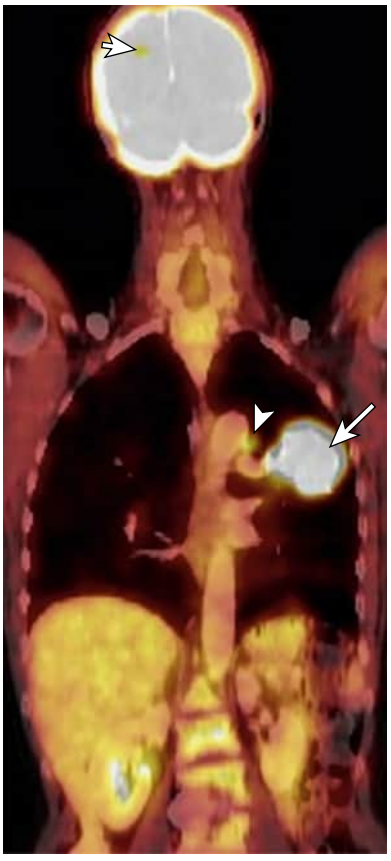
eFigure 20.40 Computed tomography for lung cancer staging: pleural dissemination. (A–B) Axial chest computed tomography image displayed in lung windows shows extensive pleural nodularity (*arrowheads*) representing pleural metastatic disease from bronchogenic malignancy. (Courtesy Michael B. Gotway, MD.)



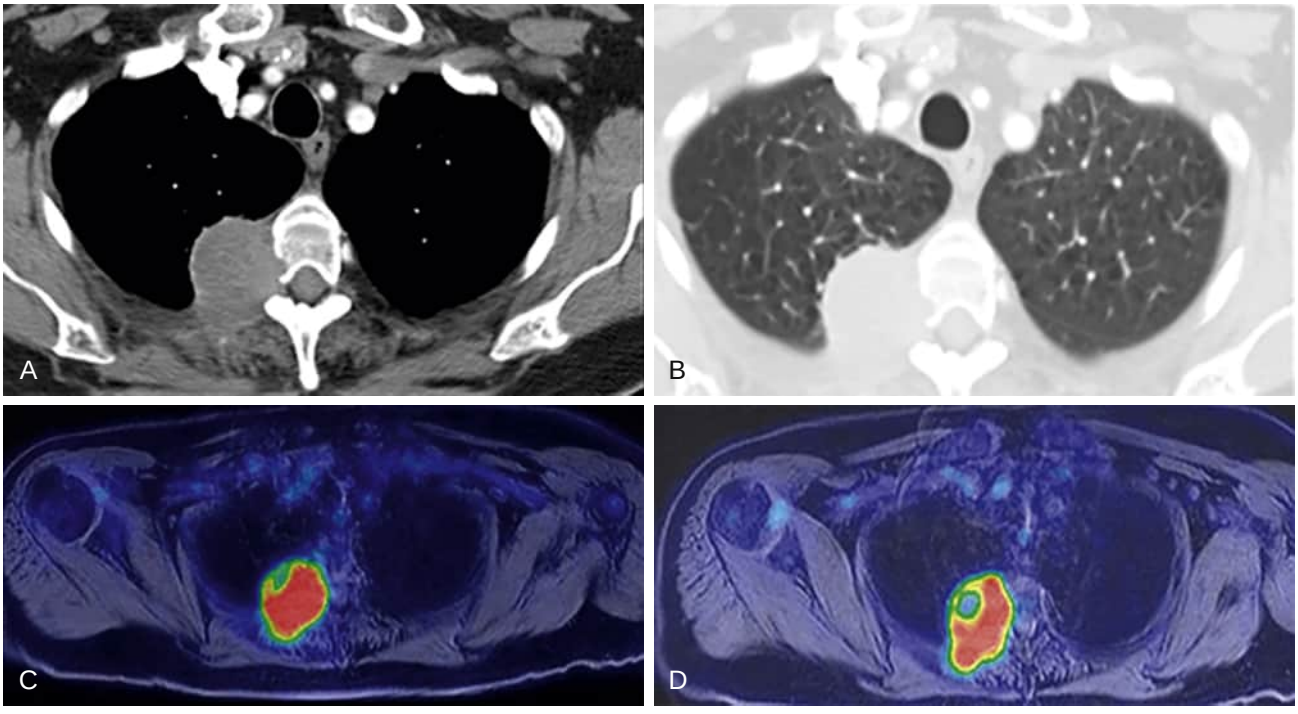
eFigure 20.41 *Computed tomography* (CT) for lung cancer staging: tracheal carinal invasion. (A) Axial contrast-enhanced chest CT image shows extensive tumor involvement of the mediastinum with invasion of the tracheal carina. (B) Axial contrast-enhanced chest CT image in another patient shows tumor surrounding both main-stem bronchi at the level of the inferior margin of the carina. (Courtesy Michael B. Gotway, MD.)



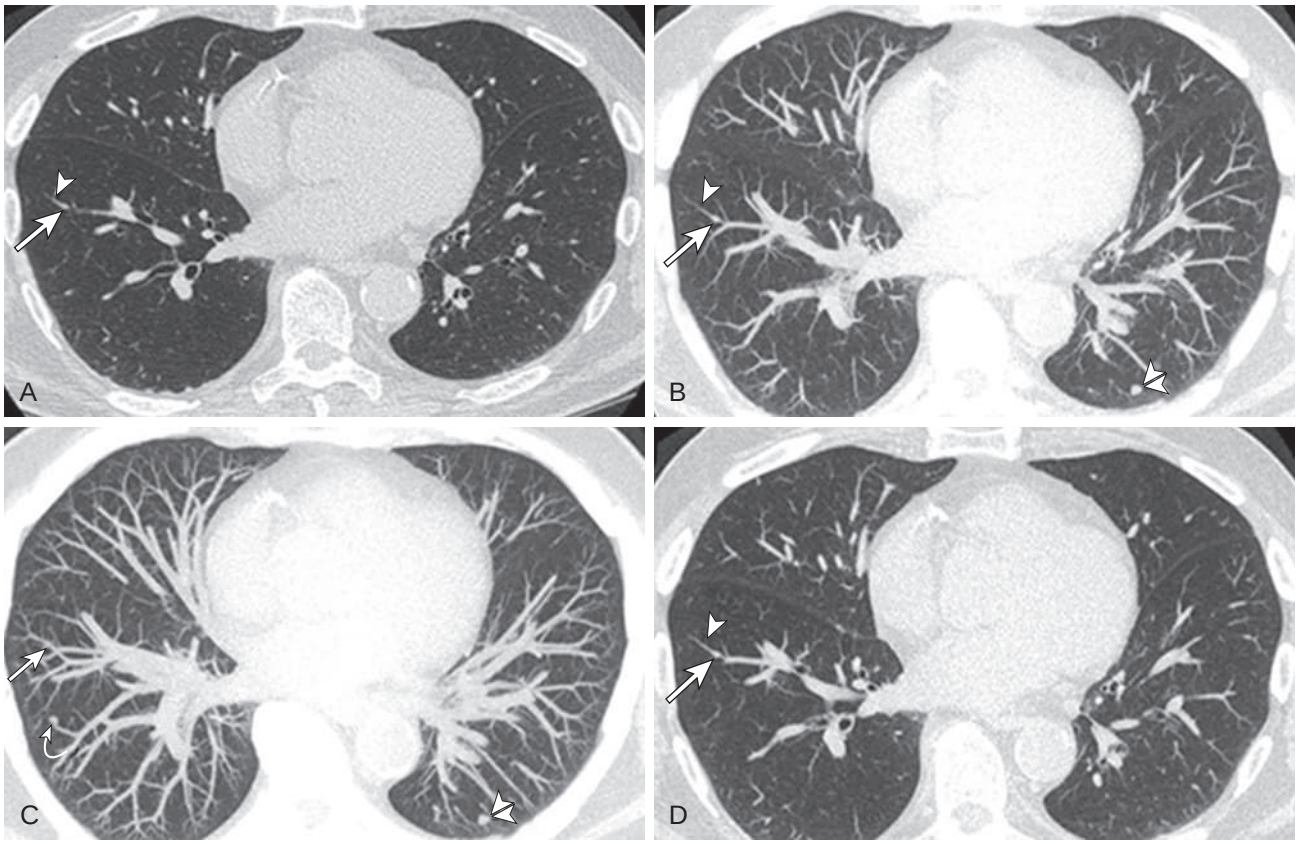
eFigure 20.42 Chest *computed tomography* (CT) for lung cancer staging: summary of the CT approach to possible mediastinal invasion by bronchogenic carcinoma. (A–B) Axial chest CT image displayed in soft tissue windows shows extensive mediastinal tumor contact (>3 cm) and clear tumor nodules invading mediastinal fat (*arrowhead*). (C) Axial enhanced chest CT image displayed in soft tissue windows shows a medial left upper lobe neoplasm exerting mass effect on the adjacent mediastinal fat and obliterating the fat plane (*arrowhead*) normally surrounding the esophagus (*arrow*); endoscopic ultrasound confirmed invasion of the esophagus. (D) Axial enhanced, T1-weighted magnetic resonance image shows invasion of the hyperintense mediastinal fat; note the signal characteristics of normal mediastinal fat surrounding the left subclavian artery (LSCA) and left brachiocephalic vein (LBV). The tumor invades the right brachiocephalic artery (*arrowhead*); note the mass effect deforming this vessel and the small intraluminal soft tissue focus, representing tumor thrombus. (E) Axial enhanced chest CT image displayed in soft tissue windows shows a medial left lower lobe bronchogenic neoplasm contacting the mediastinum and descending thoracic aorta; the tumor contacts less than 90 degrees of the descending thoracic aortic circumference, which generally predicts the *absence* of vascular invasion. (F–G) Axial enhanced chest CT images displayed in soft tissue windows shows a medial left lower lobe bronchogenic neoplasm contacting the mediastinum and descending thoracic aorta; this tumor contacts greater than 90 degrees but less than 180 degrees of the descending thoracic aortic circumference, which is indeterminate as regards vascular invasion. (H–I) Axial enhanced chest CT images displayed in soft tissue windows show a medial left upper lobe bronchogenic neoplasm contacting the mediastinum and left subclavian artery (*arrowhead*); this tumor contacts greater than 180 degrees of this vessel, suggesting the presence of vascular invasion. (Courtesy Michael B. Gotway, MD.)



eFigure 20.43 Value of *^{18}F-fluorodeoxyglucose–positron emission tomography* (^{18}FDG-PET) imaging for lung cancer staging: detection of metastatic disease. Coronal whole-body ^{18}FDG-PET scan shows a hypermetabolic left upper lobe non–small cell carcinoma (*arrow*) associated with increased tracer utilization within aortopulmonary window lymph nodes (*arrowhead*). A hypermetabolic focus within the brain (*short arrow*) represents distant metastatic disease. This whole-body ^{18}FDG-PET scan provided effective staging in a single study. (Courtesy Michael B. Gotway, MD.)

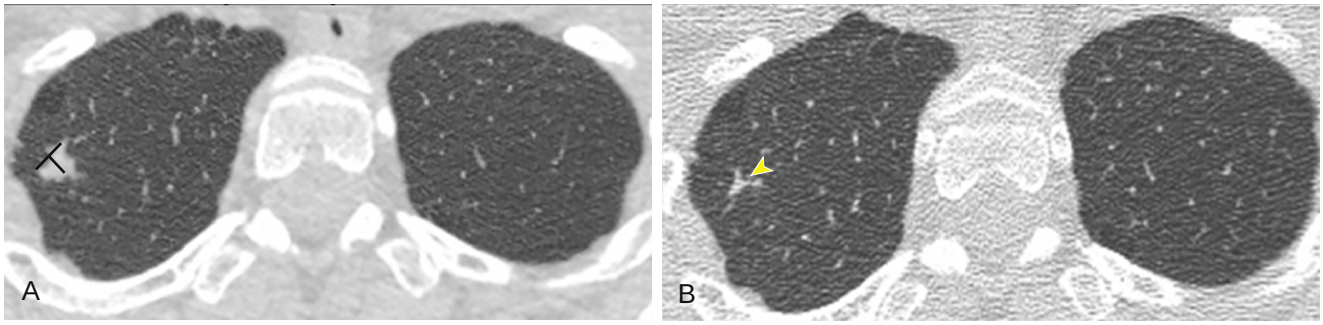


eFigure 20.44 *Positron emission tomography–magnetic resonance imaging* (PET-MRI) for lung cancer staging. Axial soft tissue (A) and lung window (B) computed tomography images show a medial right upper lobe mass with extensive chest wall contact. (C–D) Axial hybrid PET-MRI shows marked tracer uptake within the primary lung malignancy and extensive uptake of the tracer utilization into the posterior chest wall, consistent with chest wall invasion.

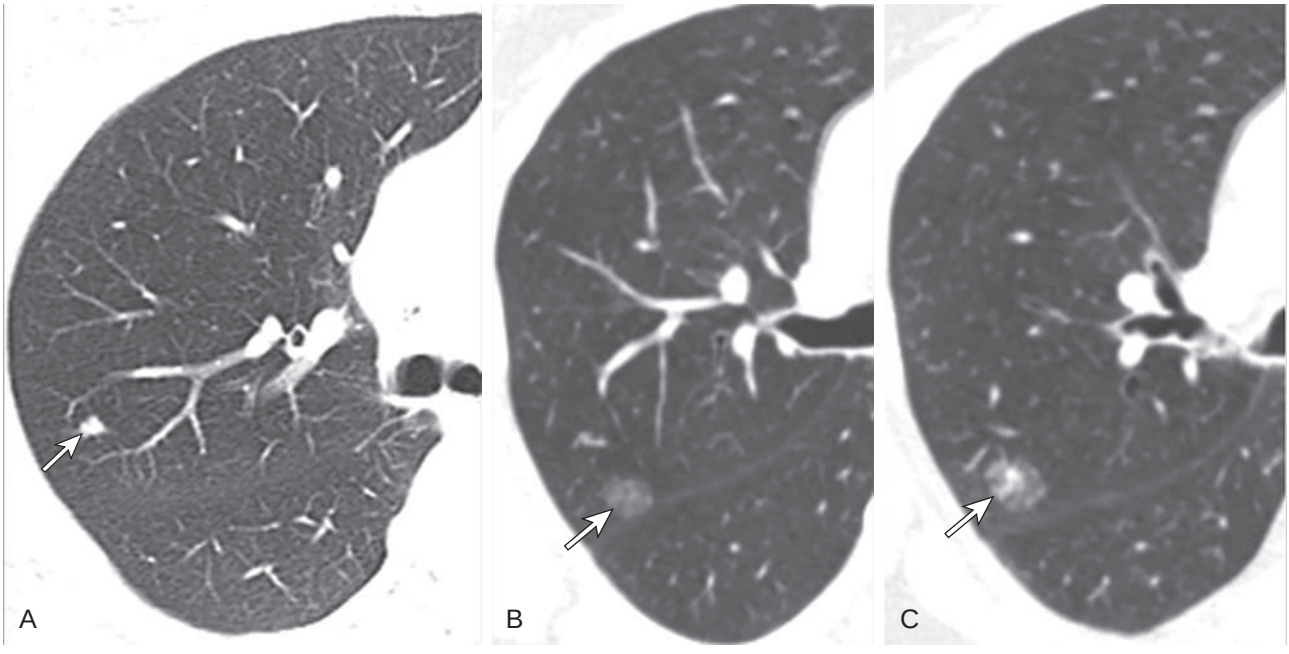


eFigure 20.45 Value of *maximum-intensity projection* (MIP) imaging for lung nodule detection. (A) Axial chest computed tomography dataset reconstructed at 0.625 mm shows a barely detectable nodule (*arrow*) in the right lower lobe, obscured by a close association with an adjacent vessel (*arrowhead*). (B) Axial MIP reconstructed with a 10-mm slab thickness makes the perivascular right lower lobe nodule (*arrow*) more conspicuous and more clearly displays the longitudinal course of the closely associated vessel (*arrowhead*). Note that a nodule (*double arrowhead*) in the left lower lobe has now been "collapsed" into view. (C) Axial MIP reconstructed with a 25-mm slab thickness shows that the right lower lobe nodule (*arrow*) has been rendered less conspicuous compared with the 10-mm slab (B) because "too much" tissue has been collapsed into view, resulting in lung parenchymal obscuration by the presence of numerous pulmonary vessels. Note that now a third nodule, in the right lower lobe (*curved arrow*) has been collapsed into view. The left lower lobe nodule remains visible (*double arrowheads*). (D) Axial MIP reconstructed with a 3.1-mm slab thickness shows the small right lower lobe nodule (*arrow*) adjacent to a vessel (*arrowhead*), but now the left lower lobe nodule seen at the 10-mm (B, *double arrowheads*) and 25-mm (C, *double arrowheads*) slab MIPs, and the right lower lobe nodule visible only on the 25-mm slab MIP (C, *curved arrow*), are no longer visible. (Courtesy Michael B. Gotway, MD.)

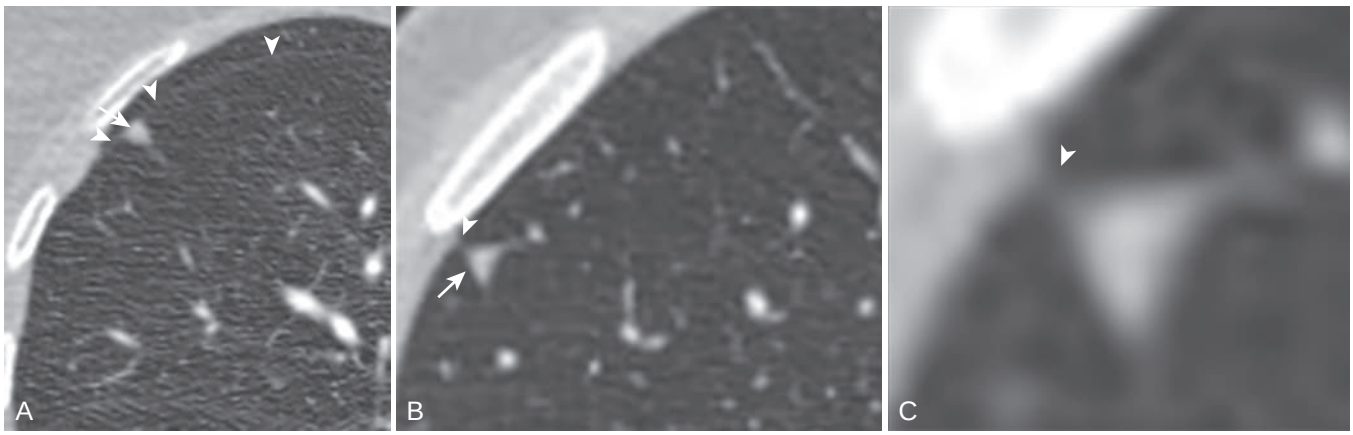
Category Descriptor	Lung-RADS Score	Findings	Management	Risk of Malignancy	Est. Population Prevalence
Probably Benign Probably benign finding(s) - short term follow up suggested; Includes nodules with a low likelihood of becoming a clinically active cancer	3	Solid nodule(s): ≥6 to < 8 mm (≥ 113 to < 268 mm^3) at baseline OR new 4 mm to < 6 mm (34 to < 113 mm^3)	6 month LDCT	1-2%	5%
		Part solid nodule(s) ≥ 6 mm total diameter (≥ 113 mm^3) with solid component < 6 mm (< 113 mm^3) OR new < 6 mm total diameter (< 113 mm^3)			
		Non solid nodule(s) (GGN) ≥ 30 mm (≥ 14137 mm^3) on baseline CT or new			



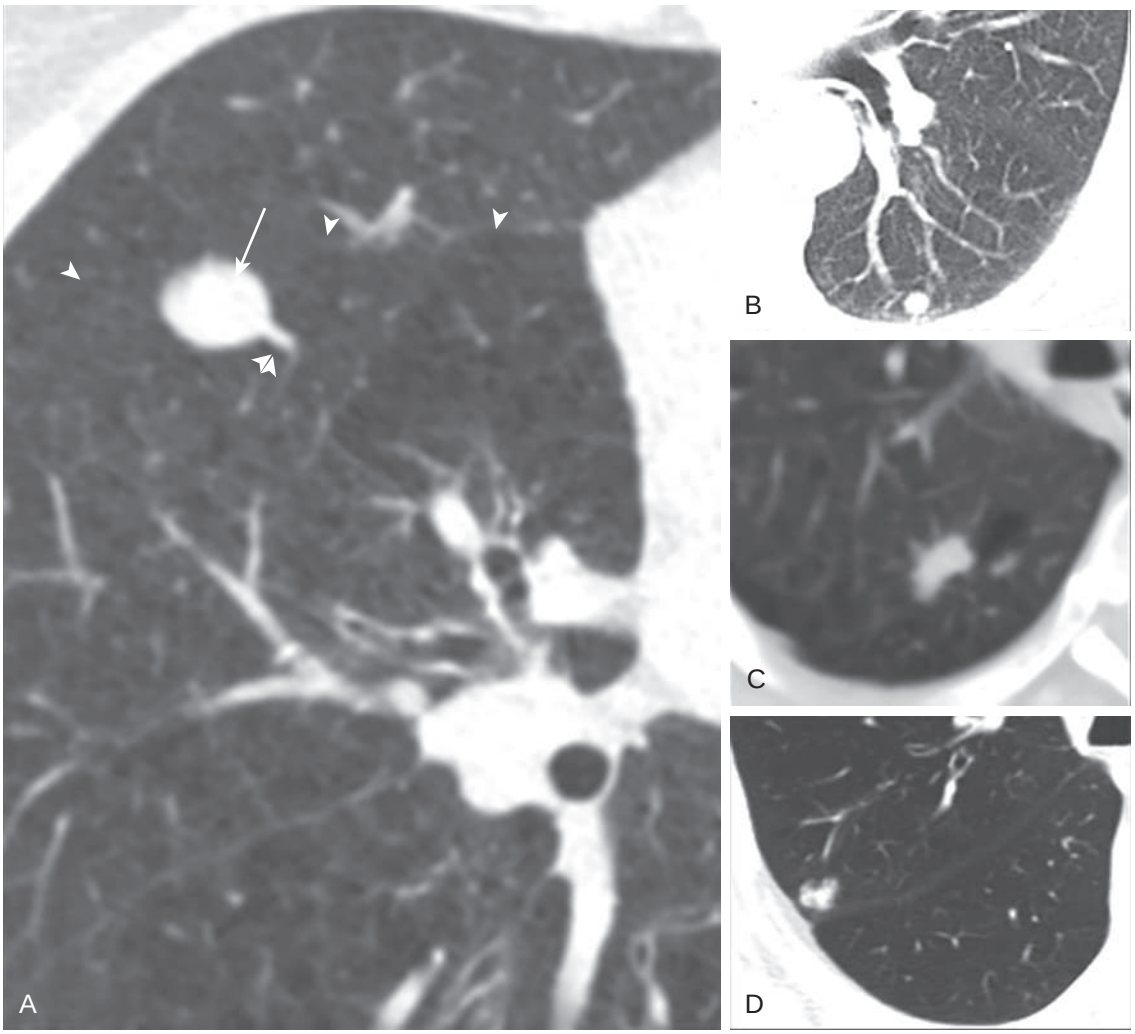
eFigure 20.46 Application of the *Lung (CT) Screening Reporting and Data System* (Lung-RADS) to *low-dose computed tomography* (LDCT) screening results. (A) Axial chest CT image displayed in lung windows shows a right upper lobe nodule (note bidirectional measurement bars) measuring 8.3 mm × 6.3 mm, for an average bidirectional measurement of 7.3 mm, which, for a solid lesion at baseline LDCT, is consistent with Lung-RADS assessment category 3, or a "probably benign" lesion with an estimated prevalence of malignancy of 1–2%, and a recommendation for follow-up LDCT in 6 months. Note that the irregular margins of this lesion could prompt an interpretation of the Lung-RADS assessment category as 4X: category 3 or 4 nodules with additional features or imaging findings that increases the suspicion for malignancy. (B) Axial chest CT image displayed in lung windows performed 2 years earlier than (A) shows that the right upper lobe nodule was present (*arrowhead)* but clearly has grown on the LDCT study (A). This behavior suggests a higher likelihood of malignancy and the revised Lung-RADS assessment category changes from 3 to 4B: a growing nodule greater than or equal to 8 mm, with an estimated prevalence of malignancy of 15%. The management recommendations for Lung-RADS category 4B nodules include repeat chest CT with or without contrast, ^{18}F-fluorodeoxyglucose–positron emission tomography scanning, or tissue sampling. GGN, ground-glass density nodule. (Courtesy Michael B. Gotway, MD.)



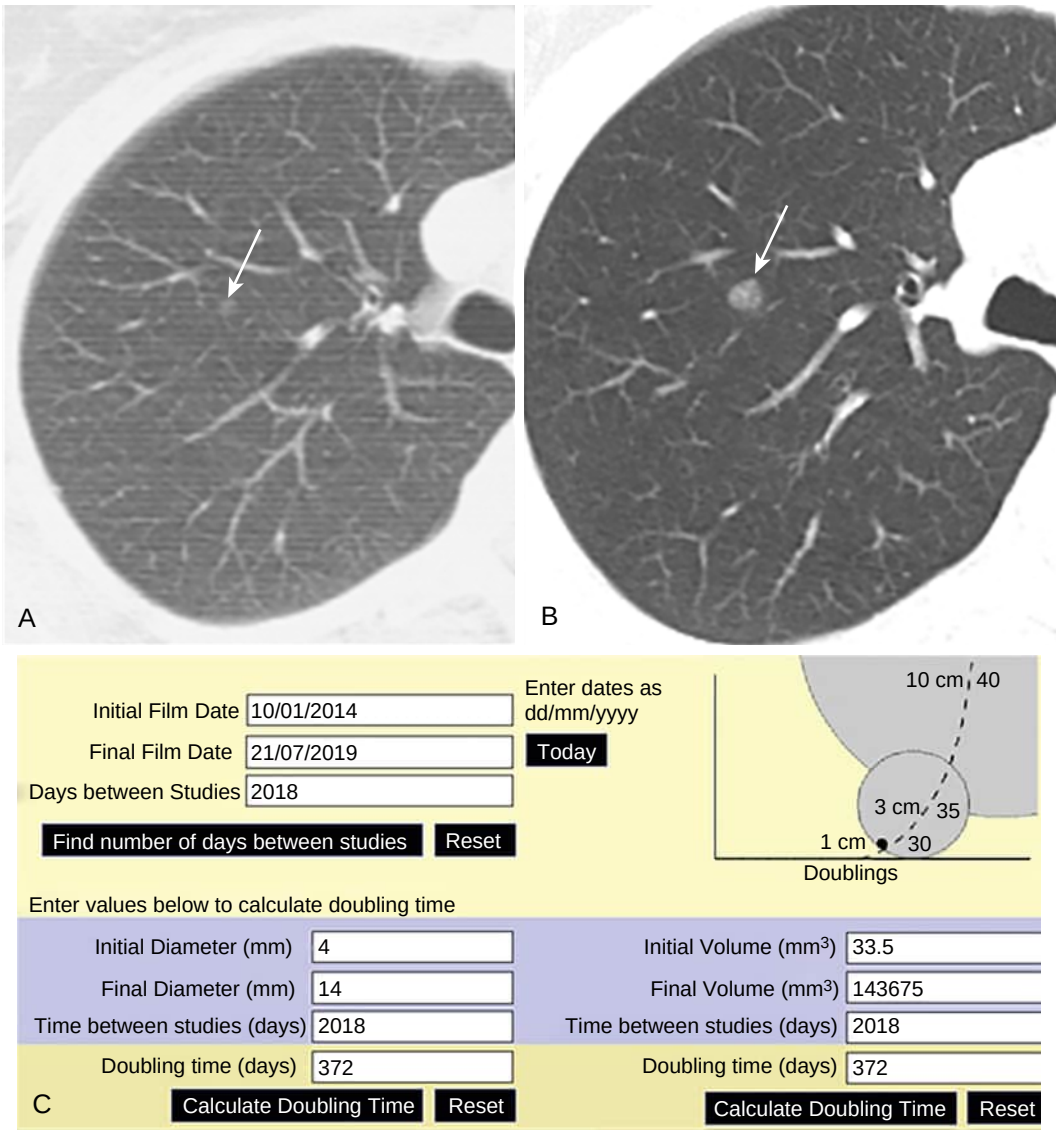
eFigure 20.47 Classification of nodule attenuation at computed tomography. (A) Solid nodule, (B) nonsolid nodule, (C) part-solid nodule (*arrows*). The solid component of part-solid nodules is often associated with invasive malignancy, particularly when this component shows growth on subsequent computed tomography scans. When measuring part-solid nodules, it is important to address the solid component of the lesion as the solid component most closely correlates with invasive carcinoma. (Courtesy Michael B. Gotway, MD.)



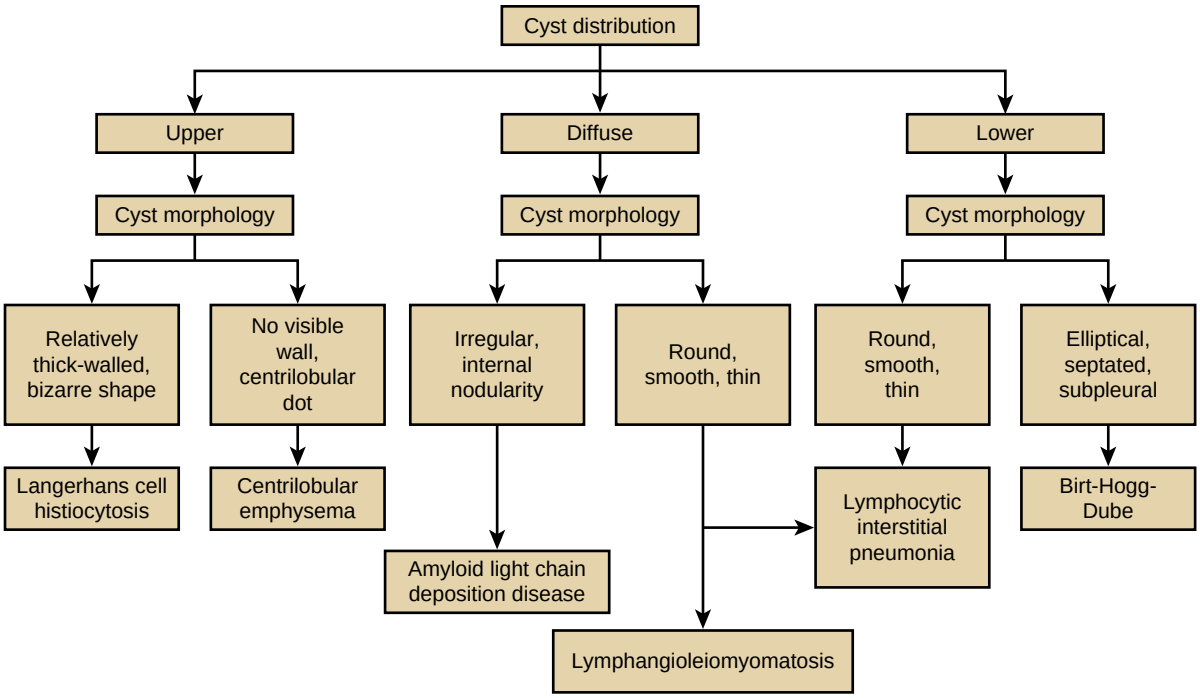
eFigure 20.48 Benign intrapulmonary lymph nodes (perifissural nodule). (A) Axial focused *computed tomography* (CT) image displayed in lung windows shows a circumscribed, triangular-shaped nodule (*arrow*) broadly contacting the minor (horizontal) fissure (*arrowheads*). (B) Axial focused CT image displayed in lung windows shows a circumscribed, triangular-shaped nodule (*arrow*) slightly removed from the visceral pleural surface but connected to the visceral pleura by a thin septum (*arrowhead*). (C) The thin septum (*arrowhead*) is more appreciable on the magnified inset image (Courtesy Michael B. Gotway, MD.)



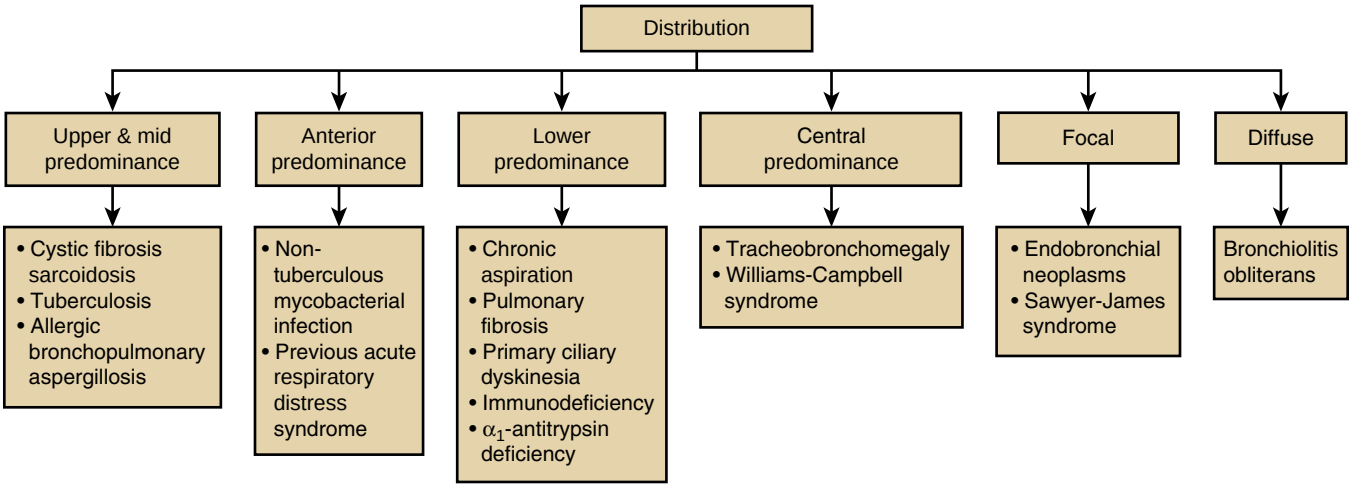
eFigure 20.49 Four nodules not meeting criteria for perifissural nodules and representing primary pulmonary malignancies. (A) Axial focused *computed tomography* (CT) image displayed in lung windows shows a nodule (*arrow*) measuring 13 mm abutting the minor fissure (*arrowheads*). The lesion is larger than typically encountered for perifissural nodal tissue; note that *Lung (CT) Screening Reporting and Data System* (Lung-RADS) version 1.1 describes a perifissural nodule—an assessment category 2 nodule, defined as "a nodule with a benign appearance or behavior"—as "a solid nodule with smooth margins, an oval, lentiform or triangular shape, and maximum diameter less than 10 mm (or 524 mm^3)." Therefore, based on size, this nodule is difficult to dismiss as a benign intrapulmonary lymph node. A vessel entering the lesion (*double arrowhead*) was identified as a pulmonary vein, which does suggest that the nodule may indeed reflect a large intrapulmonary lymph node. (B) Axial focused CT image displayed in lung windows shows a finely lobulated nodule that does not contact the visceral pleural surface. (C) Axial focused CT image displayed in lung windows shows a nodule in contact with the major fissure, but the nodule visibly distorts and "puckers" the visceral pleura of the right major fissure. (D) Axial focused CT image displayed in lung windows shows a clearly lobulated peripheral nodule, rather than the smooth, oval or lentiform shape expected for perifissural nodules representing benign intrapulmonary lymph nodes. The lesions shown in (B–D) were adenocarcinomas. (Courtesy Michael B. Gotway, MD.)



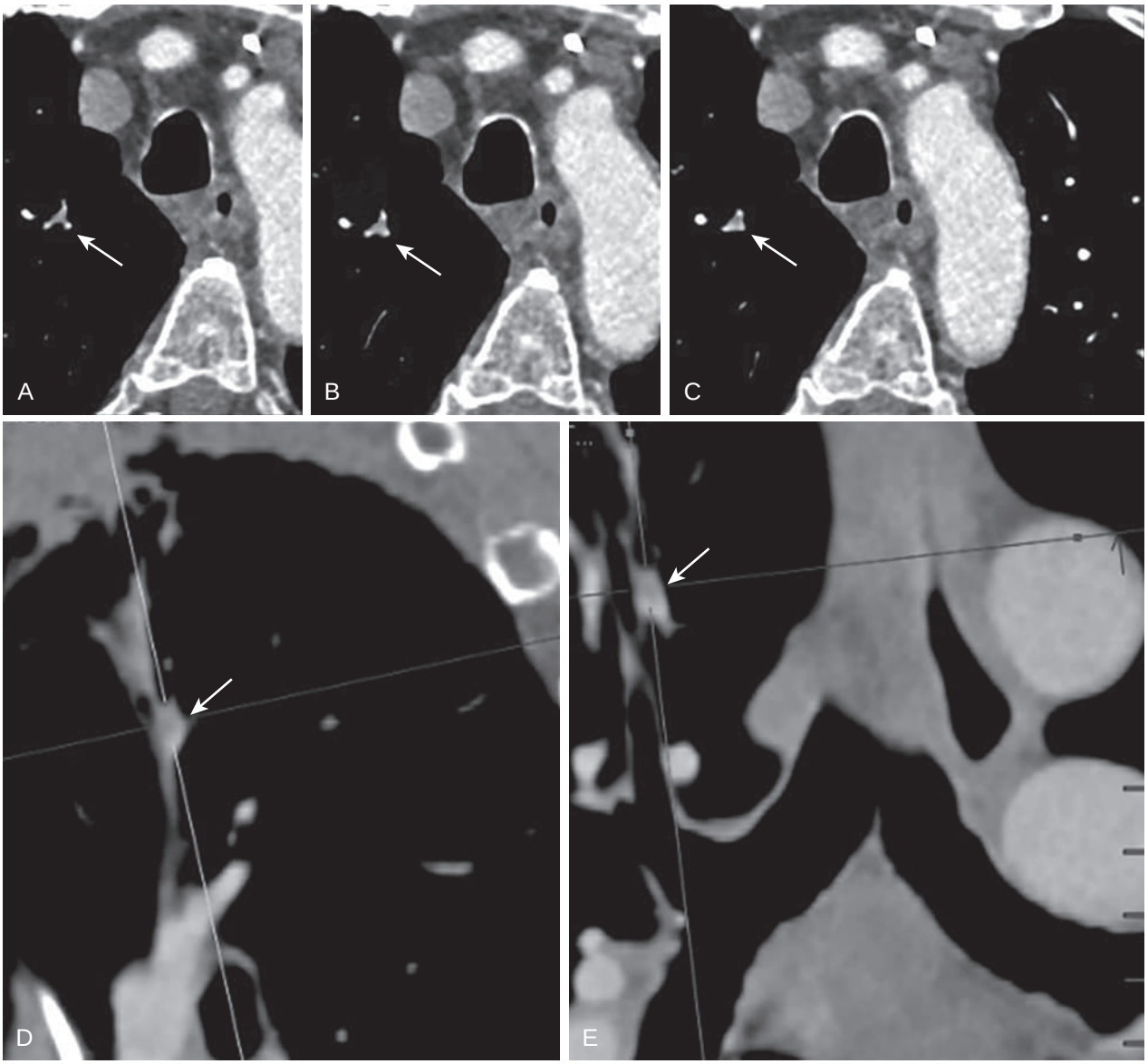
eFigure 20.50 Adenocarcinoma manifesting as a slowly growing nonsolid nodule. (A) Focused axial *computed tomography* (CT) image displayed in lung windows shows a 4-mm nonsolid nodule (*arrow*) in the right upper lobe, not detected prospectively. (B) Focused axial CT image displayed in lung windows obtained 5 years later shows the nodule (*arrow*) has grown, now measuring 14 mm, possibly with a tiny solid component. (C) Use of an online calculator for determining nodule doubling time (http://www.chestx-ray.com/index.php/calculators/doubling-time). The initial imaging date and follow-up dates are entered, yielding a time between studies of 2018 days. The maximum diameter (or volumetric measurements) of the nodule at the initial and follow-up CT are entered, and, using the time integral between the two studies and the formula for a sphere, the nodule doubling time is calculated automatically. (Courtesy Michael B. Gotway, MD.)



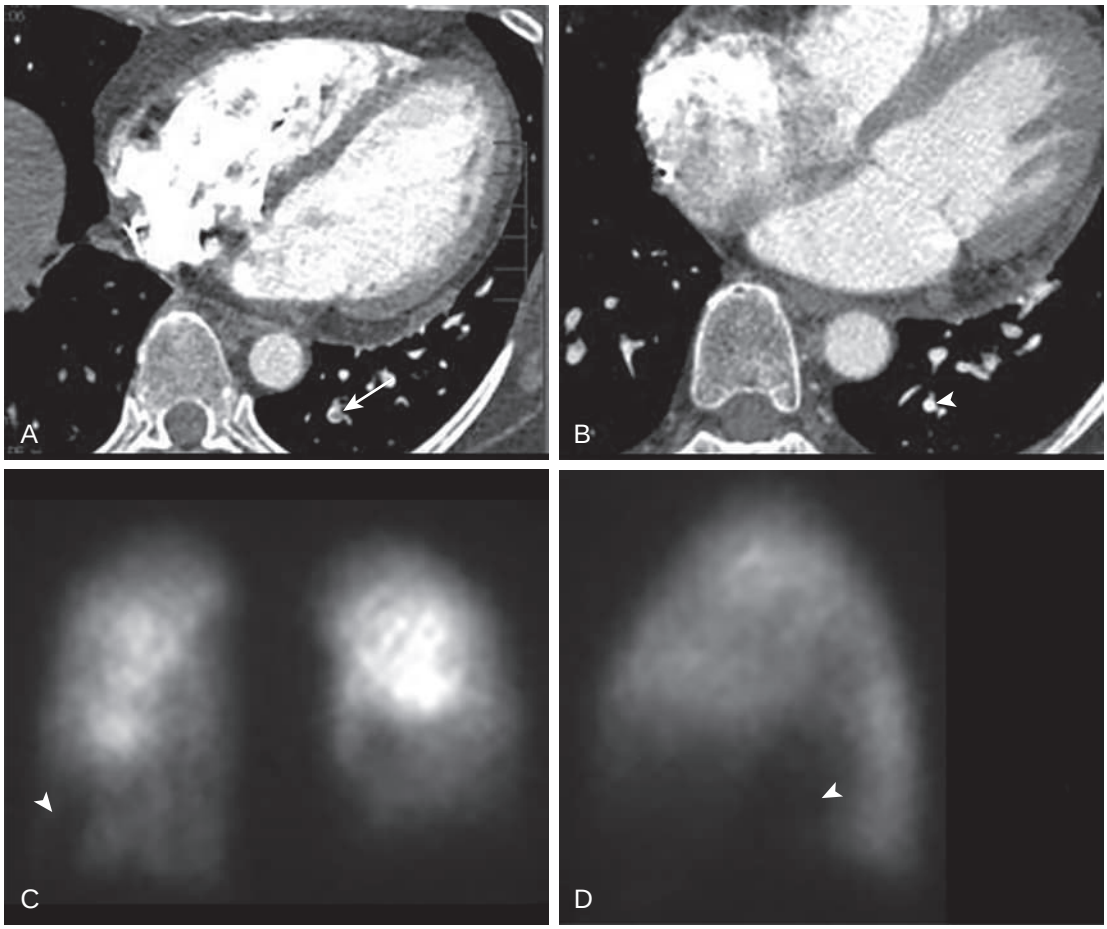
eFigure 20.51 High-resolution computed tomography evaluation of the major etiologies of diffuse cystic pulmonary disease. The algorithm begins with clinical assessment. Patients with neoplasms known to produce thin-walled cysts, such as metastatic angiosarcoma and genitourinary system malignancies, and patients with acute presentations suggesting infection (i.e., septic pulmonary emboli) must be evaluated individually. Furthermore, certain historical features, such as patient sex, tobacco use, or the presence of tuberous sclerosis, strongly influence the relative likelihood of certain pulmonary cystic disorders. The imaging algorithm begins with the distribution of cysts, to which as assessment of the cyst morphology is added; often these two features alone may significantly allow the differential diagnostic possibilities when diffuse cystic pulmonary disorders are encountered. The presence of small nodules can be occasionally helpful also, as such findings are commonly seen in patients with pulmonary Langerhans cell histiocytosis, but small nodules may be encountered incidentally or in patients with tuberous sclerosis-lymphangioleiomyomatosis complex as well. Note that, although lymphocytic interstitial pneumonia has a tendency to show lower lobe predominant cysts, a diffuse distribution may be seen as well. (Courtesy Michael B. Gotway, MD.)



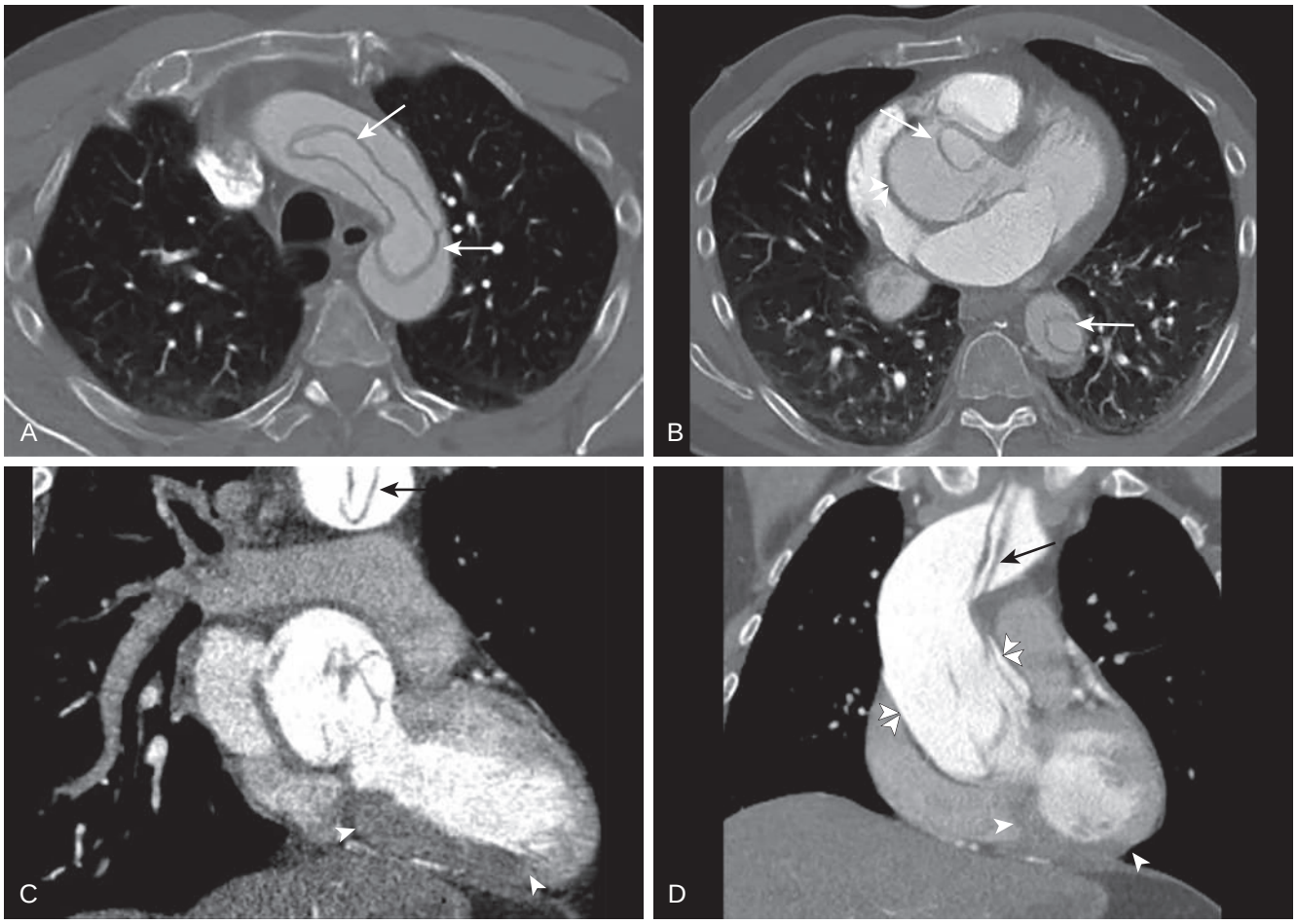
eFigure 20.52 Differential diagnostic considerations for bronchiectasis based on the distribution of findings at computed tomography.



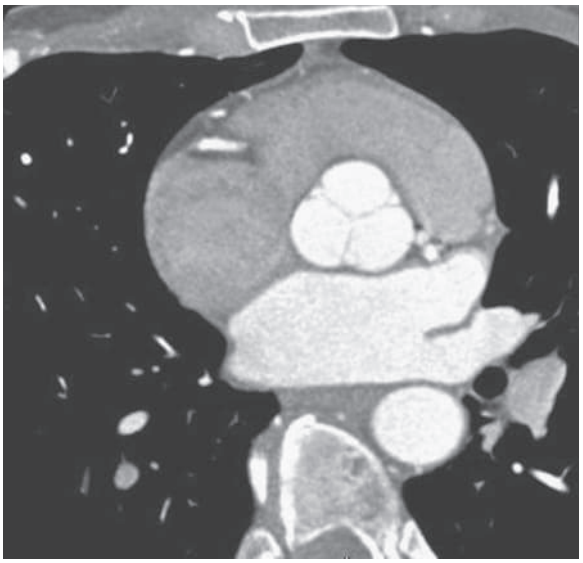
eFigure 20.53 Overdiagnosis of *pulmonary embolism* (PE) at *computed tomography* (CT) pulmonary angiography: the identification of solitary PE resulting in a false-positive examination. (A–C) Axial, (D) sagittal reformatted, and (E) coronal reformatted images through a small subsegmental right upper lobe pulmonary artery (*arrow*) show poor opacification of this vessel, leading to the diagnosis of acute PE based entirely on this finding. The examination was prospectively interpreted as positive by a board-certified radiologist and subsequently over-read as negative by a chest radiologist. No other potentially suspicious intraluminal pulmonary arterial filling defects were identified elsewhere on the scan. Upon further investigation, the patient presented fever and cough. The CT was obtained primarily to evaluate for pulmonary infection, given the history of fever and cough, but was ordered by the emergency department personnel as a CT pulmonary angiogram. Therefore the overdiagnosis of PE in this example is the result of both an inappropriate CT pulmonary angiography request and overinterpretation of a solitary, poorly opacified, upper lobe pulmonary artery as PE. Anticoagulation was withheld, and follow-up at 6 months revealed no evidence of thromboembolic disease. (Courtesy Michael B. Gotway, MD.)



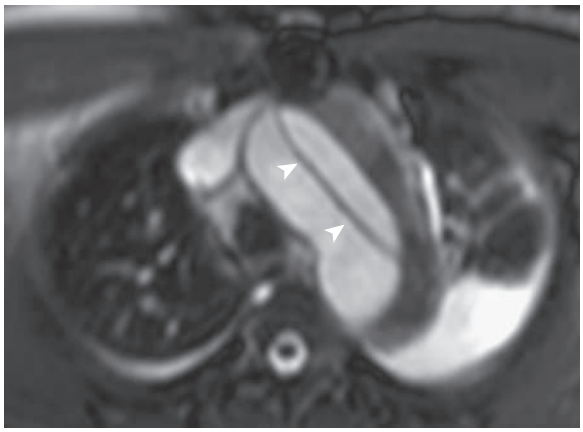
eFigure 20.54 Solitary subsegmental pulmonary embolism at *computed tomography pulmonary angiography* (CTPA). (A) Axial CTPA image shows a small intraluminal filling defect (*arrow*) in a posterior subsegmental left lower lobe pulmonary artery. This finding was the only filling defect suspicious for pulmonary embolism (PE) detected at this study. (B) Axial CTPA study performed more than 1 year earlier for suspected PE shows the affected vessel in (A) to be widely patent (*arrowhead*). (C–D) Given that only a solitary, third-order subsegmental PE was identified, and lower extremity venous ultrasound was negative for deep venous thrombosis, ventilation-perfusion scintigraphy (C, posterior projection; D, left lateral projection) was performed and showed a perfusion defect (*arrowheads*) in the left base. (Courtesy Michael B. Gotway, MD.)



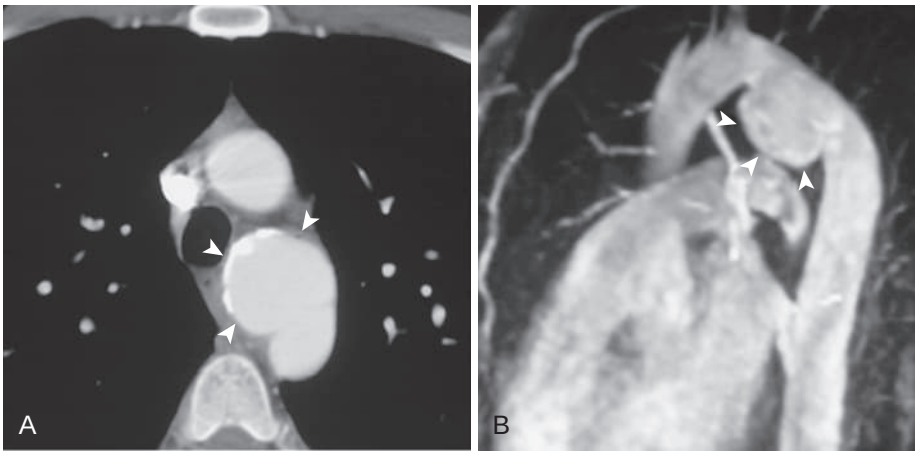
eFigure 20.55 *Computed tomography* (CT) angiography of aortic dissection with right coronary artery involvement and myocardial infarction. (A–B) Axial, (C) coronal, and (D) oblique coronal chest CT angiography images in a patient with Stanford type A aortic dissection show an intimal flap (*arrows*) in the ascending and descending thoracic aorta. Note dilation of the ascending aorta (*double arrowheads*). The intimal flap extends anteriorly at the root of the aorta (*arrow* in B) and involved the right coronary artery, leading to myocardial infarction in the right coronary artery distribution, evidenced by segmental left ventricular hypoperfusion, manifesting as hypoattenuation involving the left ventricle (*single arrowheads*). (Courtesy Michael B. Gotway, MD.)



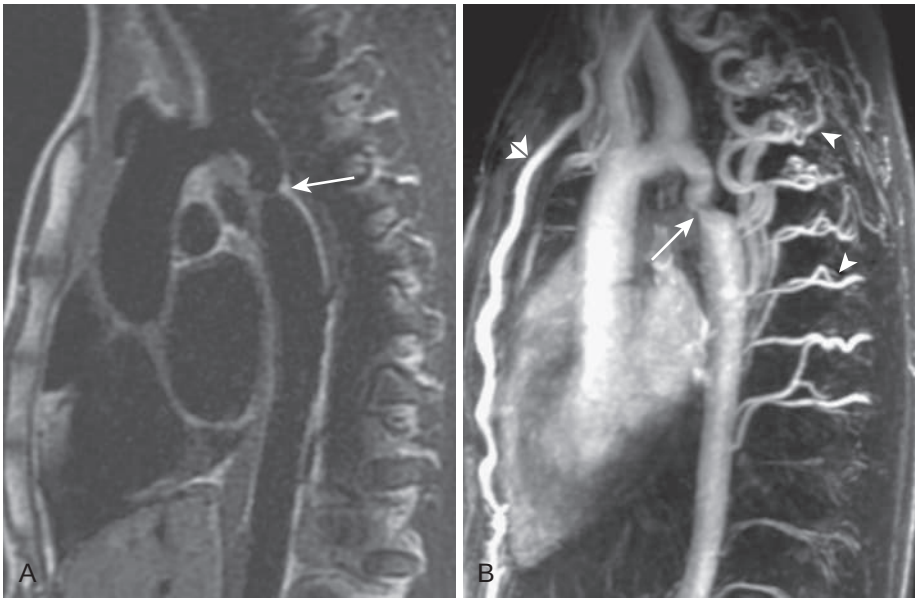
eFigure 20.56 Value of retrospectively gated chest *computed tomography* (CT) aortography for the evaluation of the aorta. Axial CT aortography image obtained with retrospective electrocardiographic gating (image reconstructed during diastole) shows a motion-free image. Note clarity of the aortic valve cusps. (Courtesy Michael B. Gotway, MD.)



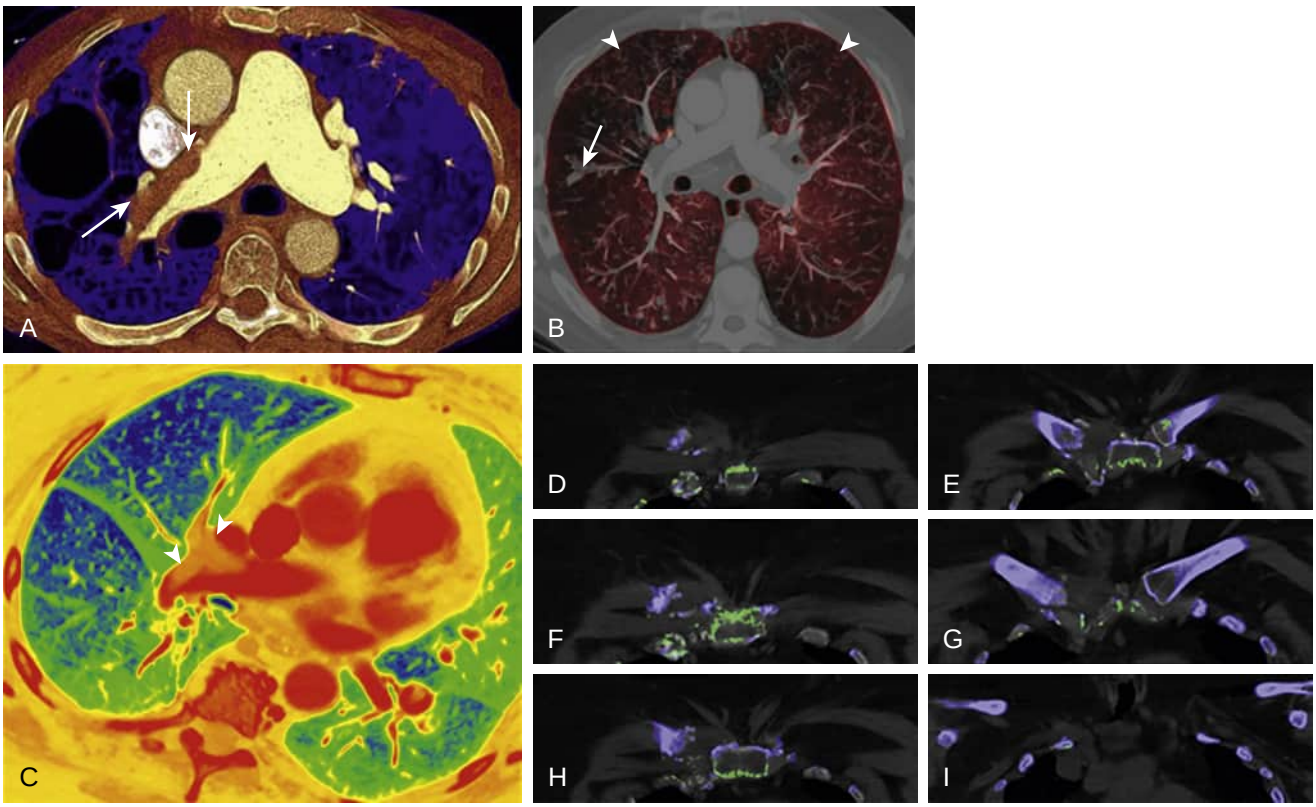
eFigure 20.57 Patient with symptoms classic for aortic dissection. Bright-blood cine–magnetic resonance images show an intimal flap within the aortic arch (*arrowheads*), consistent with aortic dissection. (Courtesy Michael B. Gotway, MD.)



eFigure 20.58 Chronic pseudoaneurysm in a long-term survivor with undiagnosed traumatic aortic injury 17 years earlier. (A) Chest computed tomography aortogram at the level of the aortic arch reveals a pseudoaneurysm (*arrowheads*); note calcification along the medial wall of the lesion. (B) Oblique sagittal three-dimensional magnetic resonance angiography image shows the pseudoaneurysm (*arrowheads*) to advantage. (Courtesy Michael B. Gotway, MD.)



eFigure 20.59 Value of magnetic resonance imaging in the assessment of congenital cardiovascular diseases: aortic coarctation. (A) Oblique sagittal T1-weighted spin-echo image of the thoracic aorta shows focal, severe narrowing of the proximal descending thoracic aorta (*arrow*) consistent with aortic coarctation. (B) Oblique sagittal volume-rendered image shows coarctation (*arrow*) and collateral vessel formation. The latter derive from intercostal *(single arrowheads),* internal mammary (*double arrowheads*), and chest wall arteries and indicate the presence of a significant pressure gradient across the coarctation. (Courtesy Michael B. Gotway, MD.)



eFigure 20.60 Dual-energy (spectral) *computed tomography* (CT). Dual-energy CT imaging applications in the thorax. (A) Dual-energy CT pulmonary angiogram shows eccentric thrombus (*arrows*) within the right pulmonary artery in a patient with chronic thromboembolic pulmonary hypertension. (B) Dual-energy CT pulmonary angiogram without evidence of pulmonary embolism shows heterogeneous lung perfusion (*red*) due to bronchiectasis (*arrow*) and bronchiolitis (*arrowheads*); the altered pulmonary perfusion is due to extensive airflow obstruction. (C) Dual-energy CT pulmonary angiogram in a patient with acute pulmonary embolism shows a filling defect (*arrowheads*) in the right interlobar pulmonary artery extending in the right middle and lower lobe arteries (*orange*), accompanied by hypoperfusion within the distribution of the emboli (lung parenchyma coded as *blue*. Lung parenchyma coded as *green* is relatively normally perfused lung parenchyma). (D–I), Coronal dual-energy thoracic CT examination shows right sternoclavicular joint space widening and fragmentation with clavicular head irregularity and erosion; the *green* color coding indicates the presence of monosodium urate crystal deposition. (Courtesy Michael B. Gotway, MD.)

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21 THORACIC RADIOLOGY: INVASIVE DIAGNOSTIC IMAGING AND IMAGE-GUIDED INTERVENTIONS

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INTRODUCTION

Interventional thoracic radiology can assist in the diagnosis and increasingly in the treatment of common thoracic problems. This chapter describes the indications and practical aspects of the most clinically useful procedures.

Image-guided *transthoracic needle biopsy* (TNB), which is typically performed with guidance by *computed tomography* (CT), is a minimally invasive procedure that can provide a definitive cytologic, histologic, or microbiologic diagnosis in more than 90% of patients with localized thoracic lesions.[1]

Interventional radiologists also help manage intrathoracic air and fluid collections using cross-sectional imaging to guide catheter placement and monitor response to drainage and treat massive hemoptysis by embolization of bronchial or systemic arteries. More recently, CT-guided thermal ablation of early-stage lung cancer and limited pulmonary metastatic disease has shown efficacy as a minimally invasive alternative to surgical management and external-beam radiation therapy in selected patients.

TRANSTHORACIC NEEDLE BIOPSY

INDICATIONS AND CONTRAINDICATIONS

The decision to perform TNB in lieu of alternative invasive diagnostic procedures or imaging follow-up, particularly for indeterminate lung lesions, is usually made after a multidisciplinary review of relevant clinical, laboratory, imaging, and pathologic material and requires consideration of local expertise, the availability of alternative invasive diagnostic procedures, including bronchoscopy and *video-assisted thoracic surgery* (VATS), and the needs of the referring physician and patient.

TNB is most commonly used for the diagnosis of a solitary pulmonary nodule (Fig. 21.1). Additional indications include diagnosis of a mediastinal mass,[2] enlarged hilar or mediastinal lymph nodes, chest wall mass, or a pleural mass or thickening.[3] Most often the primary diagnostic concern is malignancy, but the diagnosis of opportunistic lung infection producing focal lung lesions in immunocompromised patients is an additional indication for image-guided TNB. In these latter patients, the primary purpose for TNB is to obtain material for microbiologic stains and cultures.[4] In selected patients with suspected extensive stage *non–small cell lung cancer* (NSCLC), core tissue TNB can be performed for immunohistochemical analysis to determine if the lesion is a primary lung (squamous cell carcinoma vs. adenocarcinoma) or metastatic disease. Immmunohistochemistry can also be used to perform prognostic markers (e.g., breast cancer metastases assessed for the presence of estrogen and progesterone receptors and HER2/Neu)[5] or molecular testing for genetic alterations (e.g., epidermal growth factor receptor mutations or amplifications, echinoderm microtubule-associated protein-like 4–anaplastic lymphoma kinase fusions)[6] to help guide therapy. On occasion, a lesion thought likely to be benign, based on clinical and imaging analysis, is sampled using TNB to confirm a benign diagnosis.

The only absolute contraindication to TNB is the inability of a patient to cooperate for safe and successful sampling of the thoracic lesion in question. Most adults, even those with compromised pulmonary function, can undergo successful image-guided TNB using local anesthesia and either

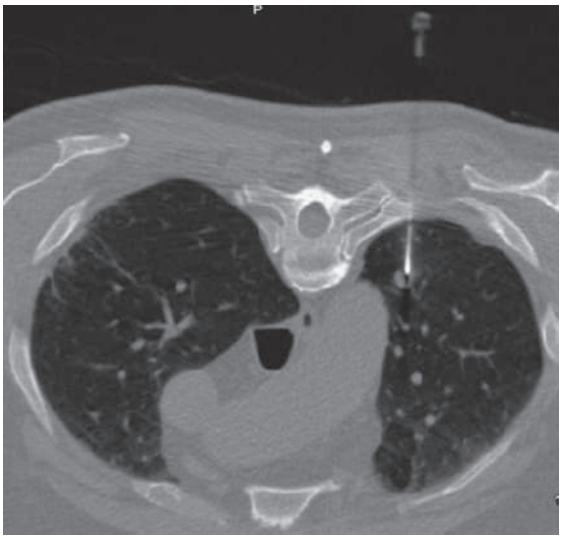

Figure 21.1 Transthoracic needle biopsy of a solitary pulmonary nodule. Computed tomography with patient prone during transthoracic needle biopsy showing the vertical course of the coaxial needle with its tip at the edge of a 1-cm left upper lobe nodule.

conscious sedation or monitored anesthesia care. For sampling of small lesions (<15 mm in diameter), the patient must be able to hold his or her breath when instructed to allow the operator to position the needle accurately within the lesion for successful retrieval of cytologic material. Precise breath-holding is less important for sampling larger lesions, particularly those at the lung periphery, or for upper lobe lesions, which move less than lower lobe lesions with normal breathing.

A bleeding diathesis is the only relative contraindication to TNB and, if identified, can usually be corrected before the procedure. Although no objective data exist showing an increased risk for bleeding from TNB in patients with abnormal clotting parameters, such as elevated international normalized ratio higher than 1.5 or a platelet count less than 50,000 cells/μL, most operators and published guidelines recommend preprocedure correction of abnormal bleeding parameters.[7] Patients receiving antiplatelet agents, including aspirin and/or P2Y12 inhibitors (e.g., clopidogrel), for prophylaxis after myocardial infarction, stroke, or recent coronary artery stent placement and who require TNB should have an assessment of the relative risks and benefits of discontinuing these agents compared with the potential bleeding complications induced by TNB. Published guidelines recommend discontinuing antiplatelet agents at least 5 days before TNB.[7] Patients considered to be at risk for thrombosis if anticoagulation or antiplatelet agents are withdrawn before biopsy can be bridged to receive intravenous heparin, which can be discontinued several hours before TNB, thereby providing a brief periprocedural window off anticoagulation. For large mediastinal masses or large peripheral lung or pleural/chest wall lesions, biopsy can be safely performed while the patient remains on anticoagulation or antiplatelet agents. Patients who have had a prior pneumonectomy are at greater risk for respiratory compromise if they develop bleeding or pneumothorax from lung biopsy. However, because these complications can usually be anticipated and managed successfully, prior pneumonectomy does not preclude TNB for evaluation of a suspicious lesion in the residual lung.

PATIENT-LESION SELECTION AND PREPROCEDURE CLINICAL AND IMAGING EVALUATION

The decision to perform a TNB follows a thorough imaging evaluation and clinical assessment of the patient (see Chapter 76). For patients younger than 35 years without significant risk factors for malignancy who have focal lung lesions, imaging follow-up is typically used because the likelihood of malignancy in such patients is very low. Conversely, for patients with localized lesions who have a high prebiopsy likelihood of NSCLC, direct referral for surgical evaluation for possible resection is reasonable and more cost-effective because the result of TNB is unlikely to obviate resection of the lesion. In patients with stage I NSCLC who are older than 75 years, sublobar resection using segmentectomy or extended wedge resection may be an effective and potentially beneficial alternative to lobectomy, particularly for patients with smaller (<2 cm in diameter) peripheral lesions (particularly if subsolid on CT) and significant medical comorbidities, such as severe COPD.[8] Nevertheless, biopsy of likely malignant nodules can be useful in several situations: for patients who are poor surgical candidates, for those whose lesion is not amenable to VATS resection, and for those with a history of prior malignancy in whom metastatic disease is a consideration but who would not be a candidate for surgical metastatectomy. For anterior mediastinal masses, core biopsy is almost always necessary for the initial diagnosis of lymphoma, particularly if diagnosis would preclude unnecessary sternotomy and resection, because these lesions are treated with radiation therapy and/or systemic chemotherapy.

All patients referred for image-guided TNB should have a recent (optimally within 4 weeks of the procedure) thin-section (<2-mm slice thickness) CT examination of the lesion to be sampled. For TNB of mediastinal masses, enlarged mediastinal nodes, or pleural and chest wall masses, a recent contrast-enhanced CT or magnetic resonance imaging study helps determine the vascularity of the lesion and its proximity to critical vascular structures.

Informed consent for TNB should include a detailed explanation of the procedure itself, the expected length of time in the department (typically 1 hour for the procedure and 3 hours of postprocedure observation), the risk of adverse events (see "Complications" section), and the benefits of the image-guided transthoracic approach compared with alternative noninvasive diagnostic options, including the option of not undergoing any further diagnostic procedures.

CHOICE OF IMAGING GUIDANCE

Although TNB can be performed under fluoroscopic, CT, or ultrasonographic guidance, most operators use standard CT-fluoroscopic or C-arm cone-beam CT guidance[9] to perform the vast majority of biopsies. CT provides rapid and precise information regarding lesion and needle location. It is the only imaging modality that allows TNB access to small central lesions and enlarged mediastinal nodes (Fig. 21.2). The ability to visualize intervening structures allows the operator to avoid bullae or large vessels in the projected needle path. Precise needle tip localization allows a more confident assessment of adequacy of needle placement, particularly for placement

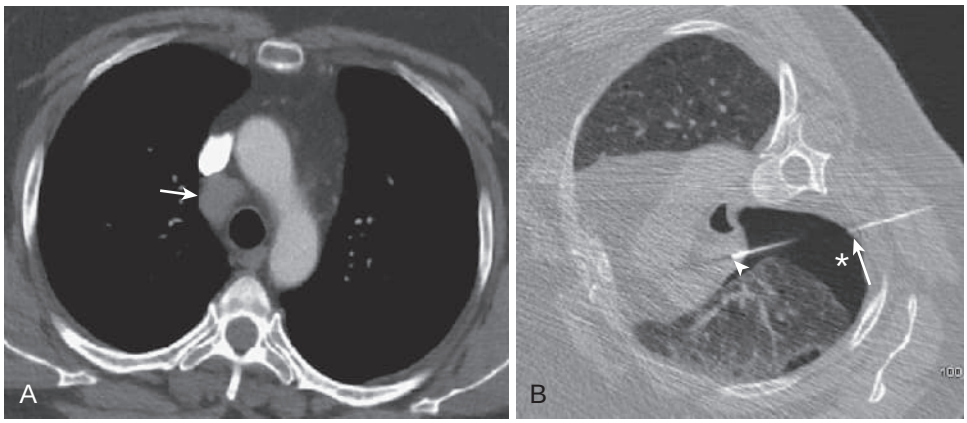

Figure 21.2 Transthoracic needle biopsy of mediastinal lymphadenopathy. (A) Contrast-enhanced computed tomography just below the level of the aortic arch shows an enlarged right lower paratracheal (4R) node *(arrow)*. The patient had a left upper lobe mass (not shown). (B) Computed tomography with the patient in the right lateral decubitus position showing the coaxial needle tip *(arrowhead)* within the enlarged right lower paratracheal node. The pneumothorax was created by a second, blunt-tipped needle *(arrow)* placed into the pleural space to inject air, allowing the coaxial needle to access the lesion without traversing the lung. Aspiration and core biopsy of the nodes confirmed the presence of contralateral (N3) nodal metastases from primary adenocarcinoma of the left upper lobe.

within small lesions or within the wall of those with central necrosis or cavitation. Complications such as bleeding or pneumothorax are readily identified and can be expeditiously managed.

Ultrasonography can be used to guide TNB in selected cases.[10] Compared to CT, its primary advantage is that it allows the operator to visualize needle placement and lesion sampling in real time. Intervening vascular structures are easily identified using Doppler ultrasonography so that they may be avoided. Although the technique is operator dependent, most radiologists have experience with diagnostic ultrasound probes and biopsy techniques that are easily applied to TNB. The use of ultrasonography to guide TNB is limited to lesions with an adequate acoustic window, such as anterior mediastinal masses and peripheral lung lesions with pleural contact (eFig. 21.1).

PROCEDURE

For CT-guided TNB, the patient is placed recumbent and positioned to provide the shortest distance from the anticipated skin puncture site to the lesion, typically with the skin puncture site nondependent, allowing a vertical needle trajectory (see Fig. 21.1). For patients unable to lie prone for the procedure because of breathing difficulties, the patient can be placed in the lateral decubitus position and a puncture performed with the needle oriented horizontally. Most patients receive local lidocaine only or conscious sedation using short-acting and readily reversible analgesic and amnestic agents, such as fentanyl and midazolam; a minority of patients require monitored anesthesia care or general anesthesia. The use of local lidocaine helps patients cooperate more consistently with breathing commands and allows the operator to position the biopsy needle accurately into smaller lesions. For TNB performed using conscious sedation, the patient should ideally be able to cooperate with consistent breath-holding, which is necessary to position the biopsy needle accurately into small lesions for successful sampling; this is particularly important for lesions near the diaphragm, which move craniocaudally even with tidal breathing.

Once the patient has been properly positioned, a scout view (a planar image of the thorax analogous to a frontal radiograph used to plan for the axial scans) is obtained at functional residual capacity (at normal end-expiration). All scans obtained through the region of interest are likewise obtained at normal end-expiration, which is a comfortable and reproducible lung volume for the patient to achieve, even when sedated. For TNB of small lung nodules, a reconstructed scan thickness of no greater than half of the diameter of the lesion should be obtained for identifying and marking the needle puncture site. This provides a detailed view of the ribs and intercostal space, helps visualize the anticipated needle path and any intervening large vessels or bullae to be avoided, and minimizes partial volume averaging when assessing the position of the needle tip relative to the lesion being sampled. Thin sections are particularly important when sampling lesions with subsolid attenuation because it is important to identify and target any solid components within the lesion to provide a more confident cytologic diagnosis of malignancy. Once the thin sections encompassing the lesion have been obtained, an electronic grid is superimposed on the image at the desired level for needle entry at the technologist's console. Measurements are then made on the console from the axis closest to the desired entry point; this point is marked on the patient's skin using a ruler and an indelible marker.

The area is then prepared and draped with a sterilizing solution, and local 2% lidocaine is administered subcutaneously to the entry site and also to the parietal pleural surface, which is heavily innervated and therefore best anesthetized before pleural transgression of the biopsy needle. In muscular or obese patients in whom the lidocaine needle may not be long enough to reach the parietal pleura, lidocaine can be administered to the pleural surface through the coaxial needle inserted to the edge of the lung. The coaxial approach involves use of an outer thin-walled guide needle, 18- or 19-gauge in diameter, placed through the chest wall and adjacent pleura and positioned with its tip at the edge of the lesion. Once positioned at the edge of the lesion, samples are obtained by placing thin 20- to 22-gauge aspiration or core biopsy needles through the outer

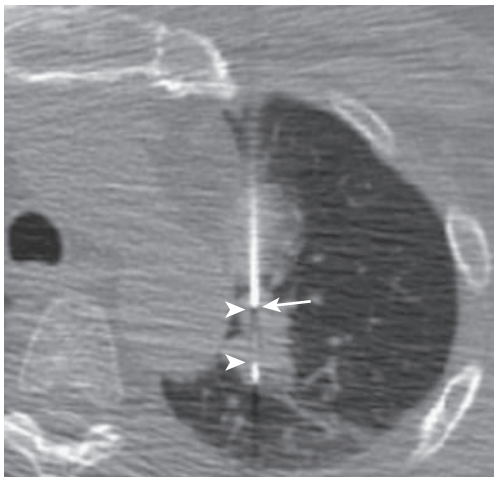

Figure 21.3 Core biopsy for molecular analysis. Computed tomography performed at the level of the aortic arch shows the coaxial guide needle *(arrow)* with its tip at the anterior edge of a lobulated left upper lobe nodule, with the receptacle stylet of the inner cutting needle (between *arrowheads*) within the nodule. Core specimens were obtained for subsequent molecular analysis of this known pulmonary adenocarcinoma.

Table 21.1 Indications for Core Needle Biopsy in the Thorax

- To obtain tissue as needed for a diagnosis of:
  - Anterior or posterior mediastinal mass
  - Probable benign lesion (hamartoma, granuloma)
  - Mesothelioma
  - Subsolid lung lesions
- To obtain sufficient tissue for molecular markers in non–small cell lung cancer
- To maximize yield for diagnosis when rapid cytolopathologic review is unavailable

coaxial guide needle and into the lesion. Patient breath-holding during needle placement and repositioning at the same end-expiratory volume as directed for the preliminary scans is crucial for accurate needle placement. Rapid assessment of needle position after advancement and repositioning can be obtained by repeated axial images through the region or by using CT fluoroscopy or cone-beam CT, which allows the operator to obtain several quick, contiguous, low-dose, thin-section images through the lesion and needle without having to leave the room.

Aspiration biopsy is performed by using a rapid, rotatory, and to-and-fro motion with the inner needle attached to a syringe to which suction is applied. The needle-syringe combination is removed and handed to a cytotechnologist who expresses the contents onto glass slides that are then fixed in alcohol. The slides are then stained using a rapid stain, examined with a microscope, and assessed for adequacy by a pathologist.[11] Additional aspiration samples are typically obtained for immunocytochemical analysis, cell block, molecular studies, or stains and cultures when necessary. Core tissue biopsy specimens are performed through the same coaxial needle used for the aspirates with 20-gauge or larger automated 1- to 2-cm cutting needles and are reserved for situations when histologic analysis is deemed necessary or when molecular genetic analysis is desired (Fig. 21.3; Table 21.1). A common error in sampling is to neglect to send material for culture in cases where malignancy is not found on the initial on-site interpretation by the pathologist. Aspirates should be obtained and processed for microbiologic stains and cultures, even when infection is only remotely suspected.

The initial approach to the pathologic evaluation of a TNB specimen obtained from a lung nodule or mass is to determine whether the lesion represents a small cell lung cancer or a NSCLC. This distinction is typically made using light microscopic examination of the stained specimen.[12] In the majority of biopsy specimens showing an epithelial malignancy, additional immunocytochemical tests performed on aspirated specimens are needed for definitive determination of type and the primary site of disease (see Chapters 76 and 22 and eFigs. 21.2 and 21.3.

Neuroendocrine markers, including chromogranin and synaptophysin, are used to help confirm the diagnosis of small cell carcinoma, typical and atypical carcinoid tumors, and large cell neuroendocrine carcinoma. The markers most often used to determine the primary site of adenocarcinoma include thyroid transcription factor 1 (positive in lung and thyroid carcinoma; see eFig. 21.2), cytokeratin 7 and 20 (positive in lung and colorectal carcinoma, respectively), CDX2 (positive in colorectal carcinoma; see eFig. 21.3), and GATA3 and estrogen receptors (positive in some breast carcinomas).[13] Increasingly, core specimens for epidermal growth factor receptor, anaplastic lymphoma kinase, and programmed death ligand-1, as well as other potential molecular mutational analysis in patients with NSCLC, are obtained in patients who might benefit from targeted or immunologic therapies.

POSTPROCEDURE PATIENT MANAGEMENT

After a lung biopsy has been completed, most operators inject a pleural sealant through the coaxial needle. The most commonly used pleural sealants are an autologous blood clot obtained immediately before the biopsy, which is then injected through the coaxial needle as it is withdrawn from the chest, or a hydrogel plug that is pushed through the coaxial needle and placed at the pleural surface and hydrated before the coaxial needle is removed. These pleural sealants have been shown to reduce the rate of biopsy-induced pneumothorax and need for chest tube placement.[14] The patient is then moved by radiology personnel from the biopsy table to a stretcher, with the biopsy side placed dependently. The patient receives supplemental oxygen as a precaution while recovering from conscious sedation and also to help promote resorption of any pneumothorax (see Chapter 110).

An upright chest radiograph is obtained 2 to 3 hours after the completion of the biopsy to assess intraparenchymal or pleural hemorrhage and to exclude a pneumothorax. If no pneumothorax is detected, the patient can be safely discharged home.[15] If a small (<2 cm from chest apex to pleural line of upper lobe) pneumothorax is present and is not growing, and the patient is asymptomatic, the patient can be discharged safely. Otherwise, the patient is observed for an additional 1 to 2 hours to confirm that the pneumothorax is stable in size. Any symptomatic, moderate-sized (2–4 cm), large (>4 cm), or enlarging pneumothorax should be evacuated with placement

of a pleural drainage catheter. The drainage catheter is attached to a pleural evacuation system placed on suction until the air leak ceases and resolution of the pneumothorax is confirmed on upright radiography or CT. In selected patients who have drainage of a biopsy-induced pneumothorax, the catheter can be attached to a Heimlich valve and safely managed on an outpatient basis; these patients should have no air leak, minimal to no dyspnea or pain, oxygen saturations greater than 92% or at preprocedure baseline, and have support at home with close proximity to a health care facility should symptoms worsen. The remainder of patients with pneumothorax drains are admitted for inpatient management.

DIAGNOSTIC YIELD

TNB has proven highly sensitive for the cytologic diagnosis of malignancy, with sensitivities exceeding 90% in multiple published series.[1,2] The distinction between NSCLC and small cell lung cancer is made with high accuracy (>85%).[12] A number of factors have been shown to affect sensitivity, including the patient's ability to lie still and cooperate sufficiently, the presence of underlying emphysema, operator experience, lesion size and location, lesion density, and availability of expert cytopathologic analysis. Even for lesions smaller than 10 mm, the sensitivity rate of TNB is high.[16] Certain lesions, particularly large mediastinal lymphomas, such as nodular sclerosing Hodgkin lymphoma, and certain forms of non-Hodgkin lymphoma that contain significant fibrosis, localized fibrous tumors of pleura, and neurogenic lesions can be more difficult to diagnose cytologically; core needle biopsies are typically obtained for definitive diagnosis of these lesions. For sampling of subsolid lung nodules, the yield of TNB approaches that for solid nodules.[17]

Precise cytologic diagnosis of benign pulmonary lesions, particularly granulomas, is more difficult than that of malignant lesions because their relatively small size and typically hypocellular, fibrotic matrix makes retrieval of diagnostic material from TNB difficult. Core needle biopsy as an adjunct to cytologic analysis alone can increase the diagnostic yield from TNB of benign lesions to approximately 80%.[18] Pulmonary hamartomas, particularly those with a significant cartilaginous component, can be difficult to aspirate, and core needle biopsy may be necessary for these lesions. Nevertheless, a skilled cytopathologist can make the diagnosis of a pulmonary hamartoma if provided adequate cytologic material (eFig. 21.4).

The diagnostic yield of TNB for infection is somewhat lower than for malignancy. However, TNB can identify the causative microorganisms, diagnosing focal lesions in 80% of immunocompromised patients with suspected lung infection.[19]

COMPLICATIONS

The most common complications of TNB include pneumothorax and bleeding. Pneumothorax develops in approximately 18–29% of patients undergoing TNB, of whom 4–6% require catheter or tube drainage.[20] Factors that may be associated with an increased rate of TNB-induced pneumothorax include operator inexperience, advanced patient age, smaller lesion size, greater lesion depth from the pleural surface, the presence of underlying emphysema or obstructive lung disease, larger outer coaxial needle diameter, prolonged needle dwell time, and greater obliquity of the angle between the biopsy needle and the transgressed visceral pleural surface.[21]

Hemorrhage (eFig. 21.5) with or without hemoptysis develops in approximately 6–18% of patients undergoing TNB[20,21] but is rarely the cause of prolonged observation, hospitalization, or need for transfusion. Biopsy-induced hemorrhage can preclude successful completion of TNB if it leads to intractable coughing or if blood in the lung obscures the lesion being sampled, thereby rendering further attempts at accurate sampling impossible.

Rare complications of TNB include hemothorax (0.1%) from intercostal artery damage (see eFig. 21.5), air embolism (0.06%) (eFig. 21.6), malignant seeding of the biopsy path (0.01–0.06%), and, rarely, death.[22]

CATHETER DRAINAGE OF INTRATHORACIC COLLECTIONS

Image-guided catheter or tube drainage of intrathoracic collections is an effective, minimally invasive method for treating a spectrum of intrapleural and intrapulmonary collections. This section reviews the common indications, imaging considerations, catheter placement, and postprocedure management of intrathoracic collections.

PARAPNEUMONIC EFFUSIONS: EMPYEMA

Selected patients with complicated parapneumonic effusions, defined as those unlikely to resolve spontaneously with treatment of the underlying pulmonary infection, or frank empyema can benefit from image-guided drainage, thereby avoiding prolonged hospitalization, VATS, or open surgical drainage and/or decortication procedures. Although deciding between image-guided drainage versus surgical intervention will vary by institution, there has been an overall increase in an initial trial of percutaneous drainage in recent years to treat unilocular and more complex parapneumonic effusions, typically accompanied by subsequent intrapleural fibrinolytics and DNAse[23] (see Chapter 109).

According to the American College of Chest Physicians consensus statement on the medical and surgical management of parapneumonic effusions, the anatomy of infected pleural fluid collections, the presence or absence of bacteria within the parapneumonic effusion, and pleural fluid chemistry have prognostic utility and can help determine the need for drainage.[24] Assessment of pleural fluid with ultrasonography has become the initial imaging modality of choice given its bedside utility for detection, characterization, and sampling of pleural collections.[25] Ultrasonographic findings that predict the likelihood of successful catheter or tube drainage include small to moderate size and presence of free-flowing, nonloculated fluid lacking internal echoes or septations. Alternatively,

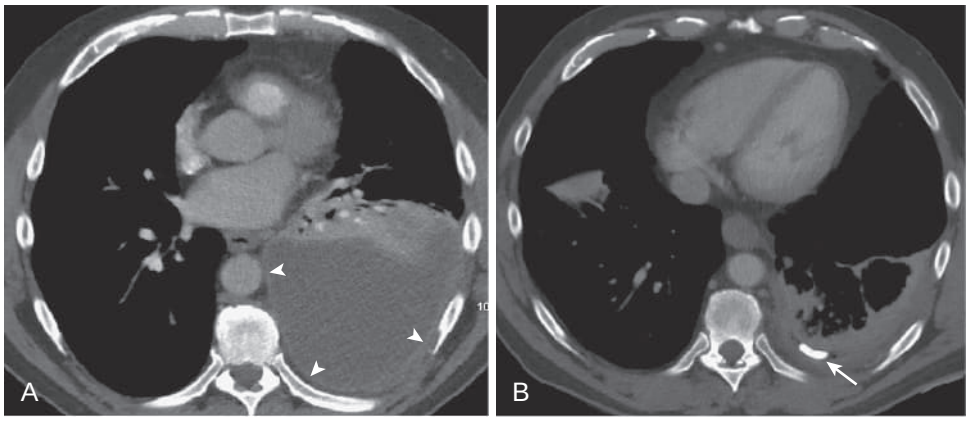

Figure 21.4 ***Computed tomography*** **(CT)-guided catheter drainage of loculated empyema treated with intrapleural fibrinolytics.** (A) Contrast-enhanced CT through the level of the left atrium showing a unilocular collection in the lower posterior left pleural space found to represent empyema. Note subtle enhancement of the parietal pleural surface *(arrowheads),* suggesting presence of an exudative effusion. (B) Repeat contrast-enhanced CT scan performed through the lower lobes after placement of a 14-French pigtail drainage catheter and intrapleural instillation of recombinant tissue plasminogen activator for 5 days shows the catheter *(arrow)* in the posterior pleural space with evacuation of the pleural fluid.

ultrasonographically detected septations and multiple loculations make it more likely that a longer duration of chest tube drainage, surgical intervention, and longer hospital stay will be necessary. Similar findings can be seen with contrast-enhanced CT, which is superior to sonography for assessing the extent of pleural and parenchymal disease for planning drainage. CT findings suggesting a higher likelihood of successful percutaneous drainage include dependent meniscoid or unilocular collections; success rates were as high as 93% using small-bore (<14 French) image-guided catheter placement in one case series.[26] The presence of enhancing visceral and parietal pleural layers encompassing a loculated pleural fluid collection is relatively specific for the presence of an empyema, although the identification of this "split pleura" sign does not preclude successful catheter drainage. Selected patients with unilocular empyema or multiloculated collections can be successfully managed with one or more image-guided catheters, either as definitive therapy or as a bridge to definitive surgical treatment. Early pleural drainage is indicated for pleural fluid analysis demonstrating pus, positive Gram stain or culture or, if the effusion is associated with a pneumonia, a pH less than 7.2 or glucose less than 40 mg/dL.[24] Additional pleural fluid analysis, such as lactate dehydrogenase greater than 1000 IU/L, can also be used to guide management decisions (see Chapter 109).

After ultrasonographic or CT localization, either a Seldinger technique using a 19-gauge thin-wall coaxial needle, guidewire, and dilators or trocar catheter placement using a 14- or 16-French drainage catheter can be performed for drainage of free-flowing or unilocular, nonseptated parapneumonic collections. If a trocar placement technique is chosen, it is important to ensure that the collection has an adequate area of contact with the costal pleural surface and sufficient width of the collection to allow safe placement of the sharp-tipped trocar/catheter combination into the dependent part of the collection (Fig. 21.4). For treatment of frank empyema or large collections with septations on imaging, we prefer a 16-French pigtail drain placed with a Seldinger technique and subsequent intrapleural therapy (discussed later). If the viscosity of the pleural fluid does not allow aspiration through the 19-gauge coaxial access needle, a larger 28-French tube is placed using a Seldinger technique. If necessary, multiple catheters or tubes can be used to drain different locules within the chest as depicted on CT, particularly for patients believed to be poor candidates for primary surgical drainage. Large-volume aspiration or an attempt at evacuation of the pleural fluid using a 60-mL syringe and a three-way stopcock or a Y-connector with a nonreturn valve at the time of catheter placement can be helpful to assess the likelihood of drainage response and need for an additional catheter placement into separate locules.

Once catheters and tubes have been placed under imaging guidance, the patient's clinical status, tube output, and radiologic studies are reviewed daily to determine the effectiveness of treatment. The tube or catheter should be flushed with saline (10 mL) three times a day to maintain patency of the lumen and prevent occlusion of the drainage holes located in the distal aspect of the device by fibrin and debris. An inadequate response to treatment is defined as a lack of improvement in fever, peripheral white blood cell count, and oxygenation, with persistent dyspnea or pain. In addition, a persistent or enlarging collection on radiography or CT warrants a reevaluation of the patient, with consideration of additional maneuvers to improve drainage or a determination to proceed to surgical management. Assuming radiologic evaluation and management demonstrates adequate positioning and functioning of the drainage catheter or tube within the collection(s), inadequate drainage in the setting of a poor clinical response may require increasing the size of the tube and/or the use of intrapleural fibrinolytic agents to promote drainage. Contrast-enhanced chest CT evaluation is helpful to detect undrained locules, to guide tube exchange when necessary, or to detect progressive pulmonary infection. Once there has been clinical and radiographic resolution of the collection and drainage has diminished to less than 100 mL/day, the catheter is removed.

Lastly, it should be reinforced that early consultation with a surgeon and consideration of surgical management (VATS or open thoracotomy) of parapneumonic

effusions and empyemas are recommended in the setting of highly complex and loculated pleural collections. Early surgical management can also be considered for patients who have had documented pleural fluid or pulmonary symptoms for more than 3 weeks, have extensive pleural thickening on CT, and/or do not respond to initial percutaneous drainage (see Chapter 109 for considerations in the treatment of patients with nonresolving pleural infection).

MALIGNANT PLEURAL EFFUSIONS

A malignant pleural effusion is defined by the presence of positive cytologic results on pleural fluid analysis or positive pleural biopsy in a patient with malignancy. Malignant pleural effusion is most commonly due to lung or breast cancer, although in 10–15% of patients with malignant effusions, no primary tumor can be identified.[27] Before indwelling catheter drainage or pleurodesis is considered, the patient should be shown to be symptomatic due to the effusion by showing that symptoms of dyspnea or cough improve after a large-volume thoracentesis. Postdrainage chest radiographs and pleural manometry can be used during the evacuation of the fluid to assess for unexpandable ("trapped") lung. Catheter drainage of a malignant effusion, followed by either chemical pleurodesis or the use of an indwelling tunneled catheter, can be used to provide prolonged drainage of symptomatic malignant effusions in patients with a limited life expectancy and is a reasonable alternative to thoracoscopic or open surgical drainage and sclerosis (eFig. 21.7).[28] Patients with symptomatic malignant effusion with expandable lung may undergo talc pleurodesis or placement of an indwelling pleural catheter, whereas those with nonexpendable lungs, failed pleurodesis, or pleural loculations should be offered indwelling pleural catheters only.[29]

A drainage catheter is inserted via a lower intercostal approach to place the tip in a dependent location to facilitate drainage of dependent fluid no matter what position (i.e., supine or upright) the patient maintains. Optimally, the catheter is placed through the junction of the serratus anterior and latissimus dorsi muscles along the lower posterolateral chest wall, where it traverses the least amount of muscle and will not be compressed or kinked when the patient lies on his or her back, typically along the sixth or seventh intercostal space. For serous or thin serosanguineous effusions, a 10- or 12-French catheter allows adequate drainage, whereas a larger diameter (12- or 14-French) is used if talc slurry is to be administered for subsequent pleurodesis after adequate drainage of the pleural space and reexpansion of the underlying lung. Loculated collections can benefit from intrapleural fibrinolytics to lyse adhesions before attempts at chemical sclerosis.[30]

An indwelling pleural catheter is designed for longer-term outpatient drainage. If symptoms improve with thoracentesis, even if the lung fails to reexpand, an indwelling catheter can be useful. Of note, if the lung does reexpand, additional instillation of talc after placement of an indwelling pleural catheter has shown greater rates of pleurodesis than drainage alone.[31]

To place an indwelling pleural catheter, the patient is positioned in an oblique or decubitus position with the effusion side up. Using ultrasound, an appropriate entry site to access the pleural space and place the drain posteriorly is marked on the skin. Two skin incisions are then made—one at the aforementioned pleural insertion site and one at 5- to 8-cm lateral and caudal to the first incision for the catheter exit. The fenestrated end of a 15.5-gauge pleural catheter is then tunneled subcutaneously from the caudal lateral (catheter exit) to the cranial medial (pleural entry) incision. Using ultrasound guidance, an 18-gauge coaxial needle is used to access the pleural space through the superior skin incision, and a J-tip wire is placed under fluoroscopic guidance. The needle is removed, and a peel-away introducer is passed over the guidewire, and the guidewire is removed. The subcutaneously placed fenestrated end of the catheter is then inserted into the peel-away introducer and pleural space while the peel-away introducer is removed. The tube is connected to a drainage bag. Once patency is confirmed, both incisions are sutured, the catheter sutured to the skin, and sterile dressing placed.

If talc slurry is used for chemical pleurodesis, 4 g of talc mixed with 50 mL of normal saline is injected into the evacuated pleural space and left to dwell for 1 hour. Suction is then reinstituted, with the catheter removed once drainage has diminished to less than 150 mL/day and the patient has shown symptomatic and radiographic improvement. Complete response rates of 70% and higher have been reported for use of small-bore catheters and talc pleurodesis in selected patients.[32]

PNEUMOTHORAX (See Chapter 110)

Fluoroscopy- or CT-guided small-bore (<12-French) catheter drainage of pneumothorax can be used for management of moderate to large or enlarging pneumothoraces, or any pneumothorax that is symptomatic. Today, most often image-guided catheter drainage of pneumothorax is performed for pneumothorax that develops as a complication of TNB or thermal ablation of localized thoracic malignancy, although catheter drainage has been traditionally used to treat spontaneous pneumothorax and pneumothorax related to traumatic causes (eFig. 21.8).[33]

For pneumothorax resulting from a CT-guided procedure, catheter placement is typically performed using CT. Otherwise, fluoroscopy provides real-time visualization of catheter placement and is the preferred guidance modality. An approach via the anterior second intercostal space in the midclavicular line is typically used, although in women a lateral approach via the fifth to sixth intercostal space in the midaxillary line can be used to avoid traversing breast tissue. Conscious sedation and local anesthesia are used, with adequate numbing of the heavily innervated parietal pleura with lidocaine being the key to patient comfort during catheter placement. Similar to pleural fluid drainage, either a trocar or Seldinger techniques may be used, each with its own advantages and disadvantages. For the trocar technique, after successful pleural anesthesia, a drainage catheter with a self-retaining pigtail tip configuration loaded onto a stiffening cannula and inner sharp-tipped trocar is placed into the pleural space and positioned into the pleural apex under direct visualization. Once the catheter tip is confirmed to lie within the apex of the pleural space,

the pigtail tip is "locked" into position by use of a string that opposes the catheter tip to a more proximal portion of the catheter. Lidocaine is injected, although the catheter lumen to provide local anesthesia to the apical pleura, which if contacted by the catheter, can produce significant ipsilateral shoulder pain. Alternatively, the catheter can be introduced into the pleural space in a stepwise fashion, whereby a hollow needle is initially used to access the pleural space, followed by placement of a guidewire and then progressive dilation of the track to the diameter of the catheter to be placed for drainage.

Once the catheter has been successfully placed, it is affixed to the skin using an adhesive ostomy-type dressing with ties surrounding the catheter and is attached to a chest drainage system.

Success rates for small-bore catheter drainage of iatrogenic pneumothorax exceed 85% in multiple series,[34,35] but drainage is also successful in the majority of patients when used in emergency settings for noniatrogenic traumatic and spontaneous pneumothoraces.[36]

LUNG ABSCESS (See Chapter 50)

Although postural drainage and antibiotics are the standard methods for medical management of lung abscess, collections that do not readily communicate with an airway or for which medical management is unsuccessful can be treated with catheter drainage under CT guidance. Patients who do not improve clinically or radiologically with antibiotic therapy are candidates for percutaneous drainage; those presenting with an abscess greater than 4 cm should also be considered for drainage because they have a higher rate of failure with conservative management.[36] Because most of these collections are pleural based, with intrapleural adhesions typical at the site of pleural contact, the risk for development of a pneumothorax is low. As with drainage of complex pleural collections, image-guided catheter drainage can be definitive or can be used as a bridge to surgical management.

Drainage of lung abscess or an infected bulla is best performed under CT guidance to visualize the catheter course and minimize traversal of normal intervening lung. The principles of catheter placement are similar to those for drainage of abscesses elsewhere in the body. The patient is positioned to allow access to that part of the abscess closest to a pleural surface. If possible, it is best to avoid placing the patient in the decubitus position with the unaffected side dependent because pus or blood can spill from the abscess cavity into the dependent lung during catheter placement, producing respiratory compromise. We typically use a Seldinger technique for catheter placement into the abscess, using a 19-gauge thin-wall coaxial needle, guidewire, sequential dilators, and a pigtail drainage catheter (typically 12 or 14 French). Trocar placement technique is also a reasonable option in experienced hands. The pigtail-shaped tip should be placed into the dependent part of the collection to facilitate dependent drainage of the infected fluid. Once properly positioned, we recommend attempting to aspirate as much fluid as possible with a 60-mL syringe to assess viscosity of the fluid and document residual fluid remaining in the cavity while the patient is on the table. Due to the risk of a bronchopleural fistula, we try to aspirate and remove the tube while the patient is on the table or leave the catheter in for less than 24 hours. If the drainage catheter is to remain, it is affixed to the skin and attached to suction until fluid drainage ceases and there is evidence of clinical and radiologic improvement (eFig. 21.9).

There are only limited case series describing the success rate and complications from percutaneous catheter drainage of lung abscess. A summary of results from 21 studies showed a success rate of 84%, with a complication rate of 16%.[35] Clogging of smaller drainage tubes, pneumothorax, hemothorax, hemoptysis, and bronchopleural fistula formation are the most frequent complications after catheter abscess drainage.

BRONCHIAL ARTERIOGRAPHY

INDICATIONS AND CONTRAINDICATIONS

The most common indication for urgent or emergent bronchial arteriography is massive hemoptysis. The most commonly used criterion for massive hemoptysis is 500 mL of expectorated blood in a 24-hour period, although it has been defined variably from as low as expectoration of 100 mL to greater than 1000 mL of blood in a 24-hour period.[37] The need for emergent intervention is most commonly determined by a sudden onset of hypoxemia; hemoptysis rarely causes life-threatening exsanguination.

Massive hemoptysis most commonly results from chronic inflammatory lung diseases due to bronchiectasis, cystic fibrosis (eFig. 21.10), or complicating fungal infection.[37] Neoplasm, such as bronchogenic carcinoma or vascular metastatic disease, can also cause hemoptysis. Less common causes of hemoptysis include lung abscess, pneumonia, chronic bronchitis, ruptured bronchial artery aneurysm, pulmonary arteriovenous malformations, and traumatic or inflammatory pulmonary artery aneurysms. In resource-poor countries, pulmonary tuberculosis is by far the most common cause of massive hemoptysis.

Indications for nonemergent bronchial arteriography and intervention include patients with non–life-threatening chronic hemoptysis unresponsive to medical therapy.[38] Less frequent indications for bronchial arteriography include bronchial artery aneurysms or pseudoaneurysms and arteriovenous fistulas. Bronchial arteriography and intervention have been used for patients with lung cancer and other intrathoracic malignancies that can produce significant bleeding, such as hypervascular metastases to the chest. Relative contraindications to bronchial arteriography include severe iodinated contrast allergy and acute or chronic renal disease. Severe aortoiliac or upper extremity occlusive disease may also pose a challenge in accessing the origins of the bronchial arteries.

Conservative management of massive hemoptysis is associated with a mortality rate of 50–100%.[39] Moreover, reported mortality rates for surgery performed for massive hemoptysis are as high as 35%. Bronchial artery embolization is a safe and effective alternative to medical or surgical management of hemoptysis, with successful control of acute life-threatening hemoptysis in 73–98% of patients,

although hemoptysis may recur.[38–40] Recurrence rates are 2–27% at 1 month and 10–52% at 46 months, emphasizing the point that bronchial embolization is a temporizing or palliative measure to control the bleeding but does not treat the underlying causative pathology. A preprocedure CT angiogram and/or bronchoscopy is recommended to determine laterality of the bleed, assess for hypertrophied bronchial arteries (eFig. 21.11), or exclude the rare pulmonary arterial source of the bleed.

The procedure involves obtaining aortic access and performing a descending thoracic angiogram to identify origin, number, and course of the bronchial arteries. Selective catheterization of a bronchial artery with a 5-French catheter and arteriogram is performed. A microcatheter is then advanced further to the region of presumed bleed to reduce the chance of nontarget embolization. Embolization to near stasis is performed with particulates greater than 350 μm. During bronchial artery embolization, the culprit bleeding bronchial artery or branch is typically not identified on angiography, and empirical embolization is performed to the suspected site of bleeding. Therefore, having a reasonable estimation of the source or region of bleeding via a bronchoscopy showing asymmetrical airway blood or a CT showing localized alveolar hemorrhage or other abnormalities is often needed to direct appropriate therapy.

The bronchial arteries have variable anatomy with multiple different combinations of origins, branching patterns, and vessel course (eFig. 21.12). There may also be anomalous and collateral bronchial arteries; the latter typically supply the lung after directly crossing diseased pleura (eFig. 21.13) or via the pulmonary ligament. Unlike the bronchial artery collaterals, these systemic collaterals do not follow the course of bronchi from the hila. An alternative systemic source should be considered in two main settings: when the bronchial artery supply to a known and often peripheral parenchymal abnormality is not demonstrated during angiography or when massive hemoptysis persists despite recent bronchial artery embolization. In these instances, investigating for the presence of anomalous or collateral blood supply may be necessary; unfortunately, this search for an alternative systemic source of hemoptysis can be difficult and time consuming.

PULMONARY ARTERIOGRAPHY

INDICATIONS AND CONTRAINDICATIONS

Multidetector CT pulmonary angiography has largely replaced conventional pulmonary angiography in the localization and diagnosis of pulmonary arterial pathologic conditions, particularly for pulmonary embolism (see Chapter 81). Therefore diagnostic pulmonary angiography is rarely performed in modern practice for purely diagnostic purposes.

Nevertheless, the most common indications for conventional pulmonary angiography are acute pulmonary embolism and diagnosis of pulmonary arteriovenous malformations[41] (eFig. 21.14) as discussed further in Chapter 88. Although there are no randomized trials demonstrating improved clinical outcomes, there is increasing use of catheter-directed thrombolysis and mechanical thrombectomy for patients presenting with massive pulmonary embolism. Fibrinolytic therapy administered directly into the clot has been shown to increase the rate of lysis alone or in combination with simple mechanical techniques, such as fragmentation of the thrombus with catheter rotation or angioplasty balloons. Newer devices using different mechanisms of thrombectomy and thrombolysis include rheolytic, rotational, and ultrasonic fragmentation and aspiration may have a larger and emerging role in treating massive acute pulmonary emboli in the future.[42]

Less common indications for pulmonary arteriography include the diagnosis of chronic pulmonary embolism, pulmonary sequestration, pulmonary artery stenosis, pulmonary aneurysm or pseudoaneurysm, and pulmonary artery neoplasms.[41–43] Relative contraindications for pulmonary arteriography include severe contrast allergy, severe pulmonary hypertension, and left bundle-branch block.

THERMAL ABLATION OF LOCALIZED LUNG CANCER AND PULMONARY METASTATIC DISEASE

INDICATIONS AND CONTRAINDICATIONS

Thermal ablation of lung nodules using *radiofrequency* (RF) waves, microwaves, or a cryoprobe has been used to obtain local control of malignancy in the chest for more than 15 years.[44–46] All three minimally invasive techniques involve image-guided targeting of lung nodules or masses with needles that induce tumor necrosis via either coagulation necrosis (*radiofrequency ablation* [RFA], microwave) or freezing and thawing of tissues (cryoablation). The most extensive experience with thermal lung ablation has been with RFA. When used in the chest, the needle probes are usually placed via CT guidance, with the patient under conscious sedation or, less often, general anesthesia.

Two primary groups of patients are considered for thermal ablation of the lung: (1) those with small, stage Ia (T1 lesions ≤3 cm) NSCLC in whom surgery is contraindicated or has been declined and (2) patients with malignancy and limited (three or fewer) pulmonary metastases who are not candidates for surgical metastasectomy and have documented control of the primary tumor. For those with limited pulmonary metastases, a potential survival benefit from successful treatment of their metastases should exist to consider thermal ablation. Because many of these same patients are also candidates for external-beam radiation using stereotactic techniques, the decision for nonsurgical candidates to use one or both techniques, if available, is made by a multidisciplinary group in consultation with the patient.

There are several relative or absolute contraindications to performing image-guided thermal ablation of the lung. A patient's inability to cooperate for a prolonged (1.5 hours) procedure on the CT table despite the use of conscious sedation can be managed by the use of general anesthesia with airway maintenance. Coagulopathy is a particular concern with cryoablation, which tends to

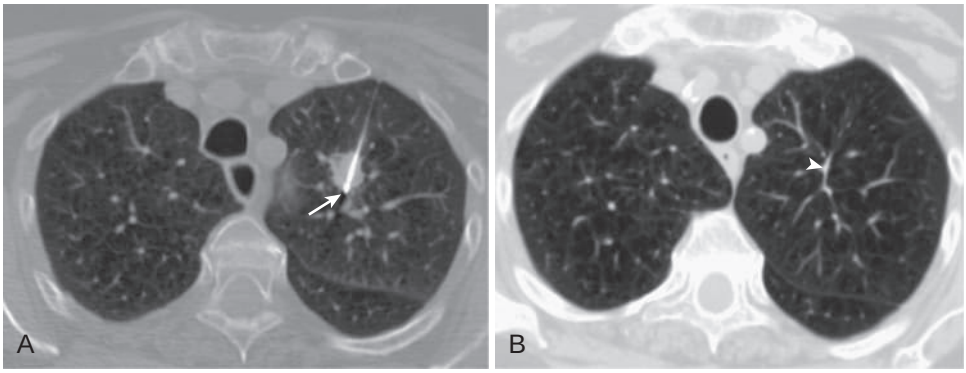

Figure 21.5 Long-term success of radiofrequency ablation for T1a non–small cell carcinoma of lung. (A) Unenhanced computed tomography performed through the upper lobes during radiofrequency ablation shows the electrode *(arrow)* placed through the left upper lobe nodule known to reflect a non–small cell lung carcinoma. (B) Computed tomography scan 5 years after ablation shows a linear scar *(arrowhead)* at the site of the previous nodule.

induce local bleeding as a result of the freezing and thawing of tissue inherent to this technique. For these reasons, any bleeding diathesis should be corrected before thermal ablation. Lesions immediately adjacent to the heart, aorta, superior vena cava, trachea, or esophagus are not amenable to thermal ablation due to concern for damage to these structures. In addition, lesions adjacent to large intrathoracic vessels may not be adequately heated (RFA, microwave) or frozen (cryoablation) because flowing blood in these vessels produces a "heat sink" effect. As a result, temperatures in the part of the lesion nearest the flowing blood may not reach the required cytotoxic temperature, and thus this component of the tumor may remain viable after ablation.

The procedure of performing RFA is similar to the other two approved thermal treatment methods. The patient is positioned as if undergoing CT-guided TNB, with the anticipated puncture site placed nondependently. Because RFA involves electrical current extending from the probe into the surrounding tissues and through the body, grounding pads are placed on the patients' thighs before the procedure to prevent the potential for skin burns by allowing safe egress of electrical current from the body.

For most lung lesions, a single needle probe is used and placed through to the center of the lesion along its long axis. For lesions smaller than 2.5 cm, a standard 14-gauge probe ablates approximately a 3- to 4-cm zone of tissue, which provides effective treatment of the lesion, and a 1-cm zone of normal lung surrounding the lesion, which should treat any microscopic disease at the margin of the tumor. For lesions larger than 2.5 cm, microwave ablation may be preferable because the ablation zone created with microwave probes tends to be larger and more spherical than with RF probes.

Successful RFA or microwave ablation produces a zone of ground-glass opacity surrounding the lesion and needle electrode on CT scans obtained immediately after ablation (eFig. 21.15). With cryoablation, CT obtained after ablation shows a decrease in attenuation of solid nodules because ice generated from pressurized, infused argon gas encompasses the lesion.

Multiple series detailing CT-guided RFA of unresectable early-stage lung cancer and limited pulmonary metastatic disease have shown the procedure to be safe with an acceptable complication rate.[44–46] The most common complications include pneumothorax in approximately 30–40% of patients, with 10–20% of all patients requiring catheter drainage.[47,48] For lesions situated along the outer edge of the lung, pain typically develops either during the ablation procedure or within 5 days of treatment because RFA induces significant tissue infarction and secondary parietal pleural irritation. Twenty percent of patients, usually those with peripheral lesions, will develop a pleural effusion, with most remaining small and asymptomatic.

Although there are no randomized controlled trials comparing thermal ablation with standard therapies, such as surgery and radiation, multiple studies have shown 2-year survival rates of approximately 70% for the treatment of stage I NSCLC (Fig. 21.5) and for RF-treated colorectal metastases when lesions are 3 cm or smaller in diameter.[49–52] In comparing RFA to microwave ablation for lung cancer and pulmonary metastases, a recent meta-analysis showed that RFA was associated with superior 1-, 2-, 3-, 4- and 5-year survival rates compared to microwave ablation.[53] The majority of lung cancer recurrences are local and are more likely with a larger tumor, with lesions greater than 3 cm in diameter showing significantly higher recurrence rates and lower overall and disease-specific patient survival than those 3 cm or smaller.[54]

PREOPERATIVE COMPUTED TOMOGRAPHY–GUIDED LOCALIZATION FOR VIDEO-ASSISTED THORACIC SURGERY NODULE RESECTION

INDICATIONS AND CONTRAINDICATIONS

With the increased detection of small pulmonary nodules on multidetector chest CT examinations, there is a concomitant increase in the need for pathologic diagnosis of those lesions too small to characterize as definitively benign or to sample accurately with TNB. The most common clinical scenario is the patient with a small lung nodule or nodules and a known primary thoracic or extrathoracic malignancy in whom the diagnosis of metastatic disease must be excluded. A patient with a solitary small lung nodule in whom wedge resection would provide both diagnostic

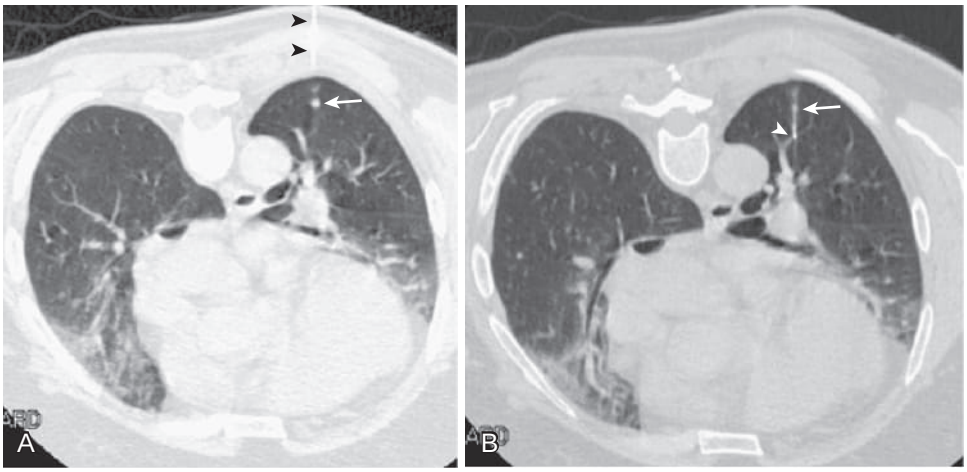

Figure 21.6 Computed tomography–guided needle localization of small peripheral nodule for video-assisted thoracic surgery resection. (A) Computed tomography performed through the mid-chest with the patient in prone position shows a 3-mm left lower lobe nodule *(arrow)* with the guide needle in the posterior chest wall *(black arrowheads)*. (B) Repeat scan after deployment of hook wire shows the wire with its tip *(arrowhead)* deep to the nodule *(arrow)*. The lesion was successfully identified and resected intraoperatively.

information and potential therapeutic benefit may also be considered for VATS resection.

Most solid nodules 1.5 cm or smaller in the lung periphery (i.e., within 1.5 cm of the costal or diaphragmatic pleural surface) can be successfully identified and resected at VATS. In certain patients with lesions smaller than 10 mm or with subsolid nodules, preoperative needle localization may aid the surgeon in identifying nodules intraoperatively. This facilitates successful intraoperative resection of these lesions, particularly if the nodule is greater than 1 cm from the visceral pleural surface and will be difficult to identify intraoperatively.

The preoperative patient preparation and basic technique of marking subpleural nodules for VATS resection is similar to that for TNB. The procedure is typically performed under CT guidance and is coordinated with the operating room so that the patient proceeds directly from radiology to the preoperative holding area and operating room immediately after image-guided localization.

The patient is positioned as if for a CT-guided TNB, with the planned needle approach being the shortest distance between the nodule and the costal pleural surface. This aids the surgeon in using the localizing needle or wire to palpate the subpleural nodule intraoperatively and resect the least amount of normal lung along with the lesion to be removed. Rarely, a biopsy of a small nodule is attempted before the localizing procedure so that a VATS planned for diagnosis can be canceled if the TNB recovers a specimen with positive cytologic results or can proceed if the TNB is nondiagnostic. For patients in whom the VATS resection will be performed regardless of the preoperative diagnosis, only a localization procedure is performed. Ordinarily, conscious sedation is used as for TNB.

Although several differential techniques have been detailed for marking small peripheral nodules to aid VATS resection, most describe placing a needle through the nodule with a hook wire deployed through the needle and positioned with the hook deep to the nodule and left in position to aid resection in the operating room (Fig. 21.6).[55] A dressing is then applied to the skin and the patient transferred to the operating room for VATS.

Additional methods include methylene blue dye injection into the nodule through the coaxial needle with or without autologous blood to reduce rapid dye diffusion. Microcoil and fiducial markers can be placed using a similar technique to the hookwire deployment, with the release of a platinum microcoil or gold fiducial marker. These markers can then be visualized with fluoroscopic guidance during the VATS procedure without the need for external wires. Instead of metallic objects, water-insoluble contrast medium, such as barium or lipiodol, have be used, also visualized by the surgeon with fluoroscopy. Radiotracer-guided localization is performed with injection of technetium-99m tagged to macroaggregated albumin into the nodule, with postprocedure scintigraphy to confirm appropriate placement and intraoperative localization with a gamma probe. Last, if the patient can tolerate complete lung deflation, an intraoperative ultrasonography for localization of lung nodule can be performed for small solid nodules; this approach is not useful for ground-glass lesions.[56]

Published success rates from multiple series detailing preoperative localization before successful VATS resection of peripheral nodules are generally around 90%.[57] Even when a wire or marker becomes displaced after deployment, the puncture site at the visceral pleura is usually visible intraoperatively and helps guide the surgeon to successful resection. Pneumothorax develops in approximately 10% of patients but rarely leads to wire displacement and is easily managed because the patients invariably proceed to thoracoscopy where a pneumothorax is induced as part of the operative procedure.

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Key Points

- The most common indications for performing transthoracic needle biopsy include the definitive pathogenic diagnosis of a solitary pulmonary nodule, mediastinal mass, enlarged lymph node, chest wall mass, or pleural mass or thickening.
- Early-stage parapneumonic effusions, particularly when free flowing or unilocular, are amenable to successful image-guided catheter drainage using computed tomographic or ultrasonographic guidance; intrapleural fibrinolytic agents are considered if the patient fails to improve with drainage and antibiotics.
- Indwelling pleural catheter drainage, with or without pleurodesis, provides effective treatment of symptomatic, recurrent malignant pleural effusions, whether or not the lung reexpands.
- Small-bore catheter drainage is a particularly effective treatment for iatrogenic pneumothorax, with success rates exceeding 85%.
- When indicated, catheter drainage for lung abscesses should be performed under computed tomographic guidance, placing the catheter in that part of the abscess closest to the pleural surface, ideally avoiding traversal of normal lung.
- Image-guided thermal ablation of lung tumors is most effective for lesions less than 3 cm in diameter, with higher recurrence rates and lower overall survival for patients with lesions exceeding 3 cm.
- Needle-wire localization of lung nodules before video-assisted thoracoscopic surgical resection is most useful for lesions 1 cm or smaller and more than 1 cm from the pleural surface.

Key Readings

Bargellini I, Bozzi E, Cioni R, et al. Radiofrequency ablation of lung tumours. *Insights Imaging*. 2011;2(5):567–576.

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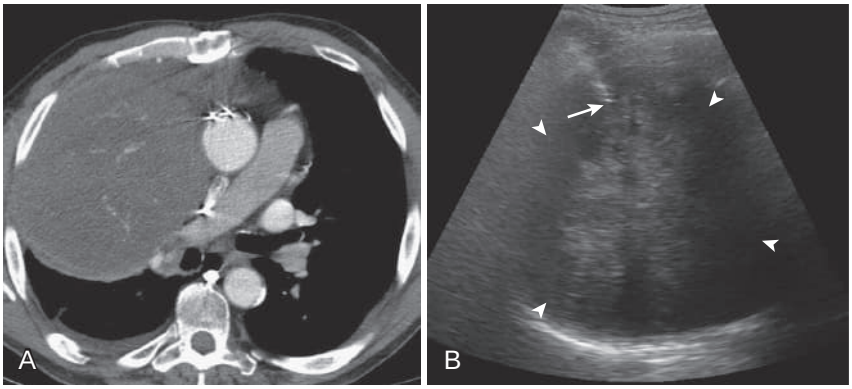
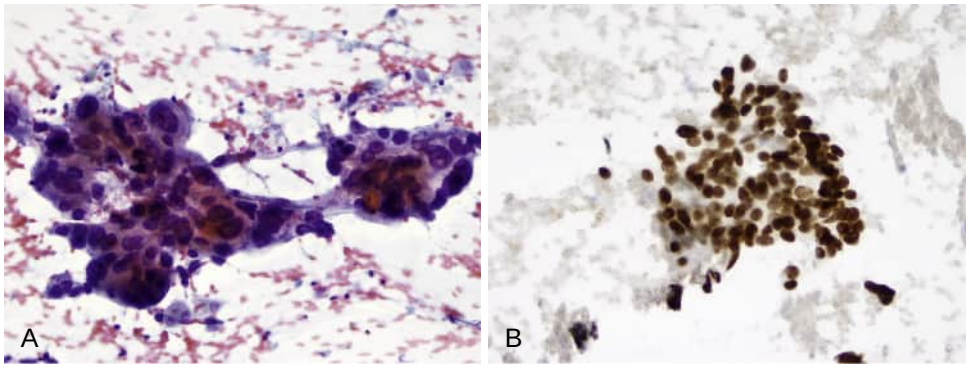
Complete reference list available at ExpertConsult.com.

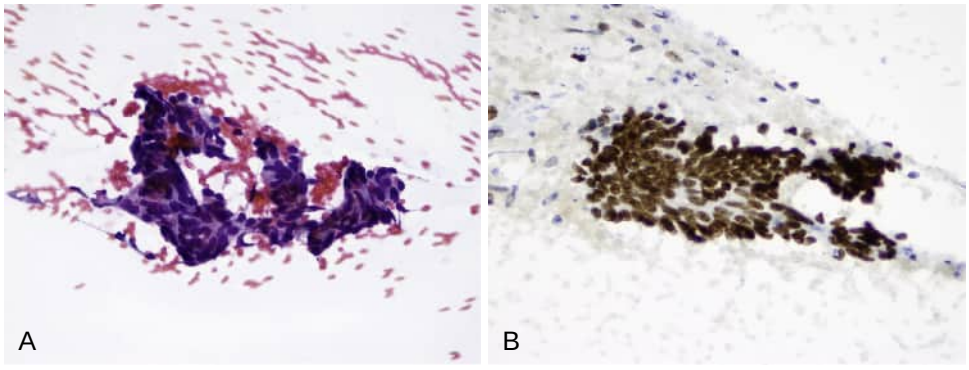
eFIGURE IMAGE GALLERY



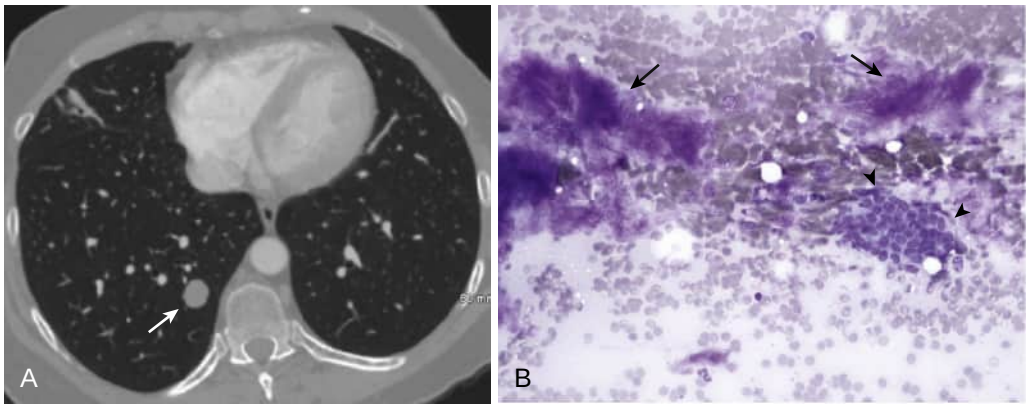
eFigure 21.1 Ultrasonographically guided biopsy of large lung mass. (A) Contrast-enhanced computed tomography at the level of the right pulmonary artery showing a large right chest mass that has a broad area of contact with the pleural surface anteriorly and laterally. (B) Transverse ultrasonographic image through the right anterior chest during core biopsy shows the mass *(arrowheads)* with an irregular echogenic region centrally. The biopsy needle is seen with its tip *(arrow)* within the mass. Histologic diagnosis was rhabdomyosarcoma.



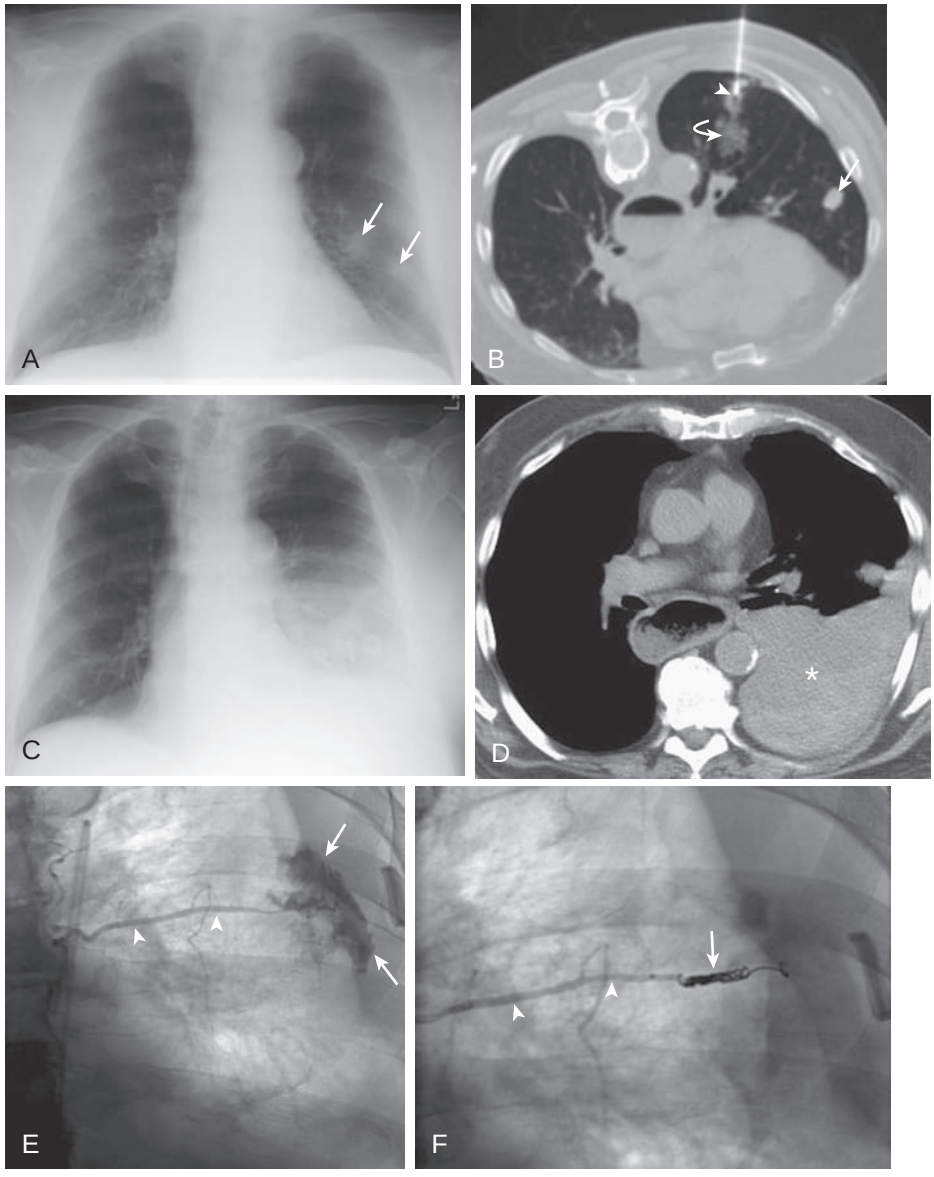
eFigure 21.2 Immunocytochemical diagnosis of primary pulmonary adenocarcinoma. (A) Photomicrograph of aspirated specimen from a 71-year-old patient with a spiculated 15-mm upper lobe lung nodule showing cohesive clusters of large pleomorphic tumor cells with irregular nuclear contours and somewhat vacuolated cytoplasm. (Papanicolaou stain; ×20 original magnification.) (B) Thyroid transcription factor 1 immunocytochemical stain shows strong nuclear positivity, supporting pulmonary origin for this adenocarcinoma. (×20 original magnification.) (Courtesy Sharon Mount, MD, Department of Pathology, University of Vermont College of Medicine.)



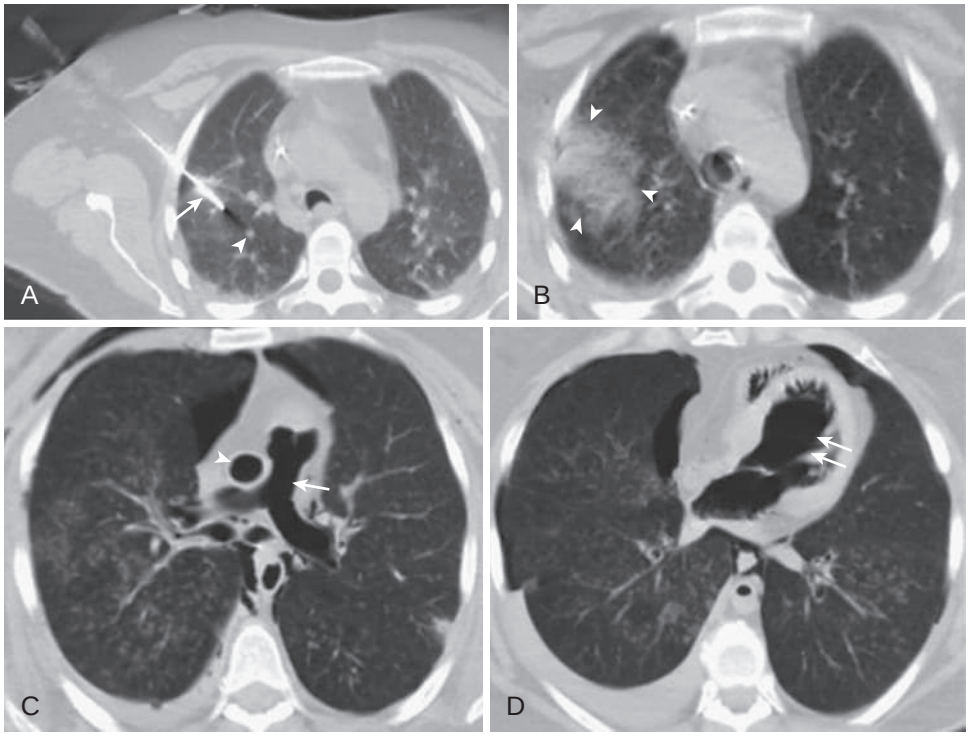
eFigure 21.3 Immunocytochemical diagnosis of metastatic colorectal adenocarcinoma to lung. (A) Photomicrograph of aspirated specimen from a patient with a history of stage III colorectal carcinoma and a solitary pulmonary nodule showing a cohesive cluster of tumor cells with rather uniform oval-shaped nuclei and delicate cytoplasm. (Papanicolaou stain; ×20 original magnification.) (B) Immunocytochemical stain for CDX2 shows nuclear immunoreactivity, supporting the diagnosis of metastatic adenocarcinoma of gastrointestinal origin. (×20 original magnification.) (Courtesy Sharon Mount, MD, Department of Pathology, University of Vermont College of Medicine.)



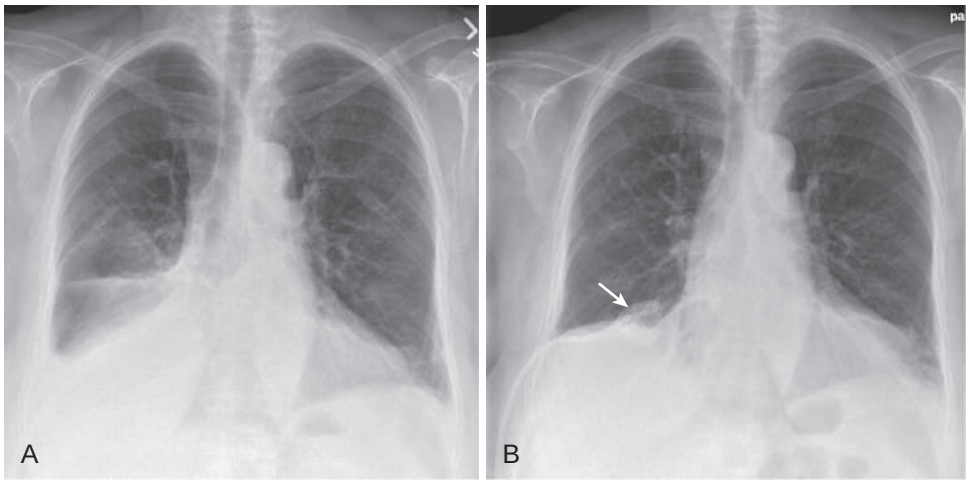
eFigure 21.4 Pulmonary hamartoma on transthoracic needle biopsy. (A) Computed tomography scan through the lower lobes showing a lobulated 13-mm right lower lobe nodule without obvious fat or calcium *(arrow).* (B) Photomicrograph of aspirated specimen shows chondroid fragments *(arrows)* with adjacent normal bronchial epithelial cells *(arrowheads),* consistent with a chondroid hamartoma. (Giemsa stain; ×20 original magnification.) (Courtesy Gladwyn Leiman, MD, Department of Pathology, University of Vermont College of Medicine.)



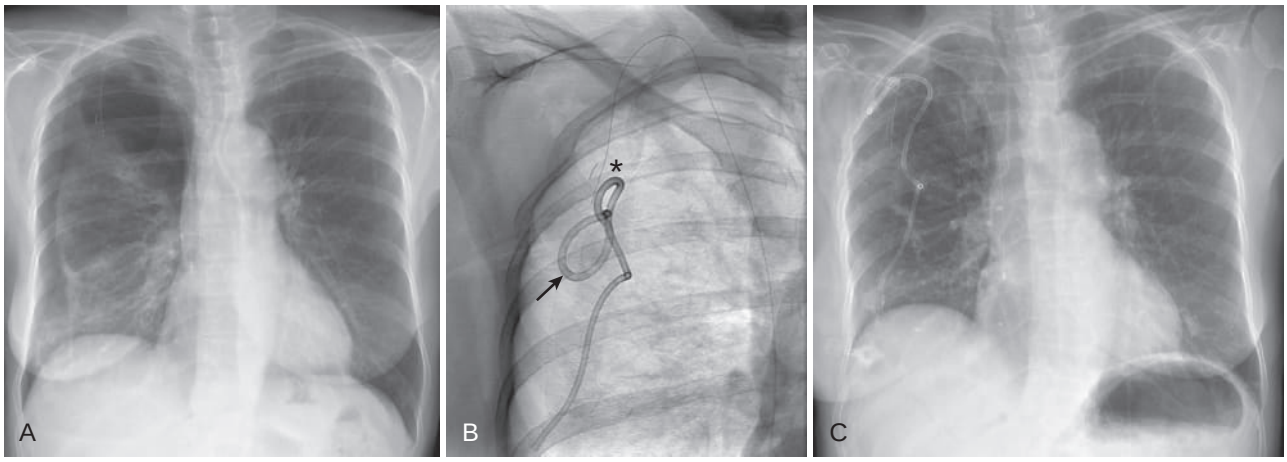
eFigure 21.5 Transthoracic needle biopsy complication: intercostal artery laceration resulting in hemothorax. (A) Frontal chest radiograph shows two nodular opacities *(arrows)* projected over the left lung base. (B) Axial prone chest computed tomography during percutaneous needle biopsy shows the needle tip within a left lower lobe nodule *(single arrowhead).* The other nodule seen at chest radiography (also in part A) is visible in the lingula *(arrow).* Hemorrhage is seen *(curved arrow)* deep to the lesion undergoing biopsy. (C) Frontal chest radiograph performed several hours after the biopsy was completed, when the patient began to complain of chest pain and shortness of breath, shows extensive new left base opacity consistent with a combination of pleural effusion and adjacent consolidation. (D) Axial unenhanced chest computed tomography performed to assess the new chest radiographic findings shows high-attenuation material in the left posterior thorax *(asterisk)* consistent with hemothorax. These findings suggested the possibility of intercostal artery laceration. (E) Selective intercostal artery angiogram shows the intercostal artery *(arrowheads)* that was injured and documents the presence of active extravasation *(arrows)* from this vessel. A pigtail catheter is visible at the far image right, and the catheter in the aorta is visible at the far image left, projected over the left paraspinous region. Note the relationship of the intercostal artery on this image—midway between the posterior thoracic ribs. (F) Selective intercostal artery angiogram after intercostal artery coil embolization *(arrow)* shows cessation of active extravasation from the injured vessel *(arrowheads).* (Courtesy Michael B. Gotway, MD.)



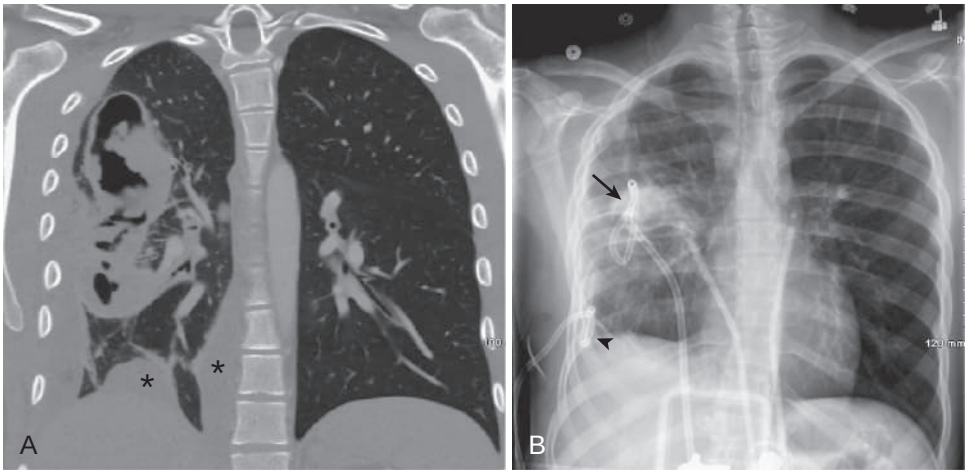
eFigure 21.6 Transthoracic needle biopsy complication: massive air embolism. (A) Axial chest computed tomography (CT) during percutaneous needle biopsy shows the biopsy needle tip *(arrow)* slightly short of the targeted small nodule *(arrowhead).* (B) Axial chest CT performed after the development of severe cough shows rounded ground-glass opacity *(arrowheads),* representing pulmonary hemorrhage. Axial chest CT performed after cardiopulmonary collapse (C–D) shows extensive air embolism, with gas lucency now occupying the ascending aorta (*arrowhead*, C), main pulmonary artery (*arrow*, C), and left ventricle (*double arrows*, D). Numerous small centrilobular nodules bilaterally represent aspirated blood after pulmonary hemorrhage. The patient subsequently died. (Courtesy Michael B. Gotway, MD.)



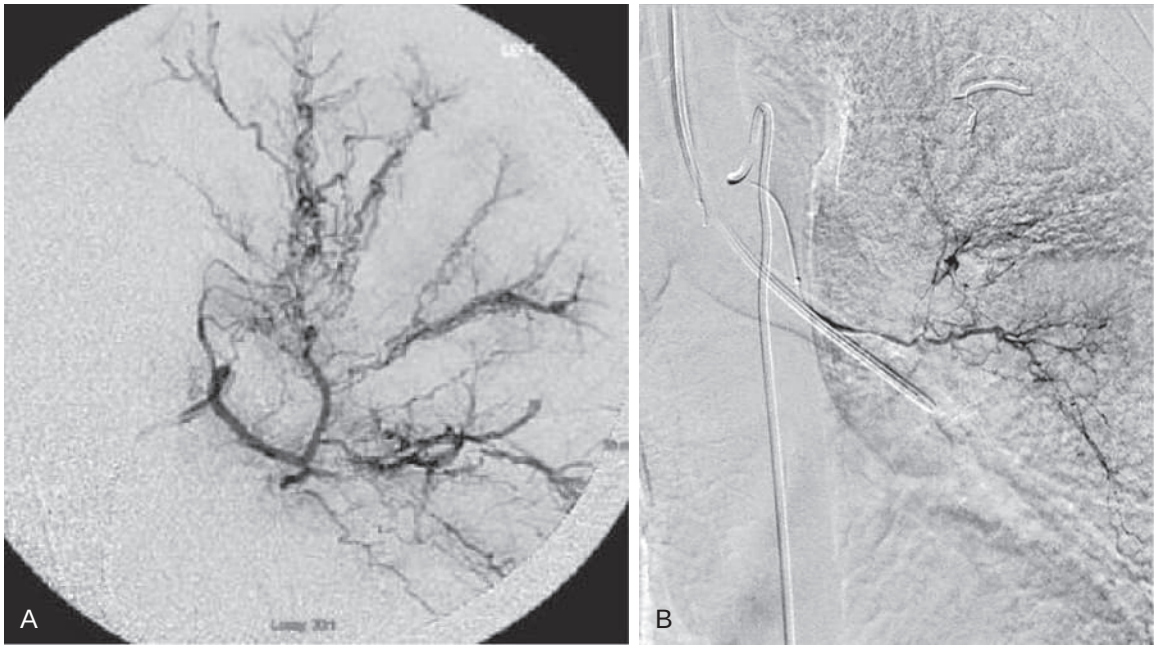
eFigure 21.7 Ultrasonographic-guided drainage of a malignant pleural effusion. (A) Frontal chest radiograph in a 68-year-old woman with a malignant right pleural effusion from metastatic ovarian carcinoma showing a right pleural effusion with passive right lower lobe atelectasis. (B) Repeat radiograph after ultrasonographically guided placement of a 10-French pigtail catheter shows the catheter *(arrow)* in the dependent aspect of the right pleural space with evacuation of the effusion and reexpansion of the lower lobe.



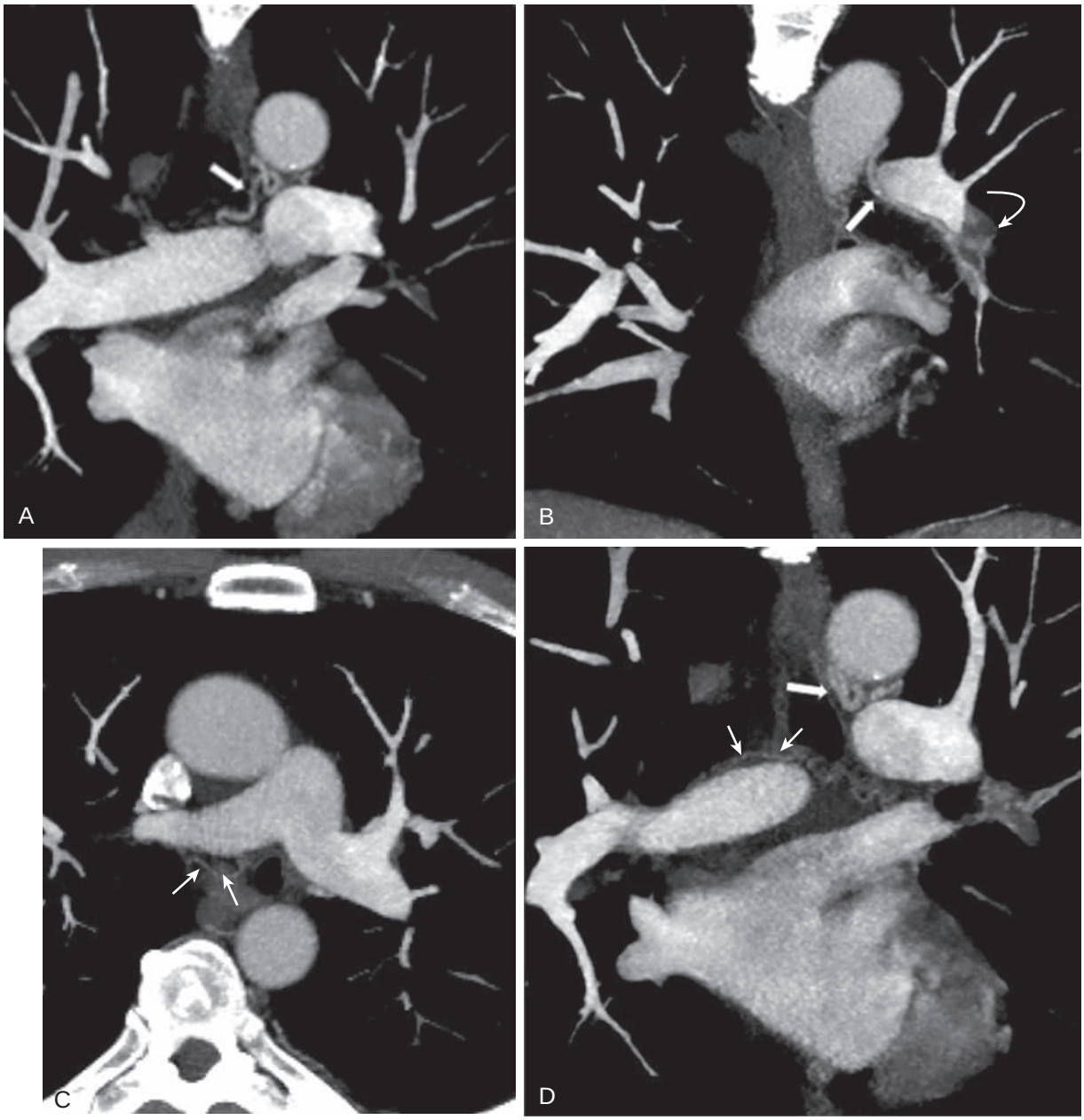
eFigure 21.8 Catheter drainage of a biopsy-induced pneumothorax. (A) Upright frontal chest radiograph obtained 2 hours after computed tomography–guided biopsy of a cavitary metastasis to the right lung showing a large right pneumothorax. (B) Spot radiograph during drainage catheter placement shows the catheter *(arrow)* placed via the second anterior intercostal space with the catheter coursing over the right pleural apex *(asterisk)*. (C) Repeat frontal radiograph obtained the following morning shows the catheter over the right lung apex and complete evacuation of the pneumothorax.



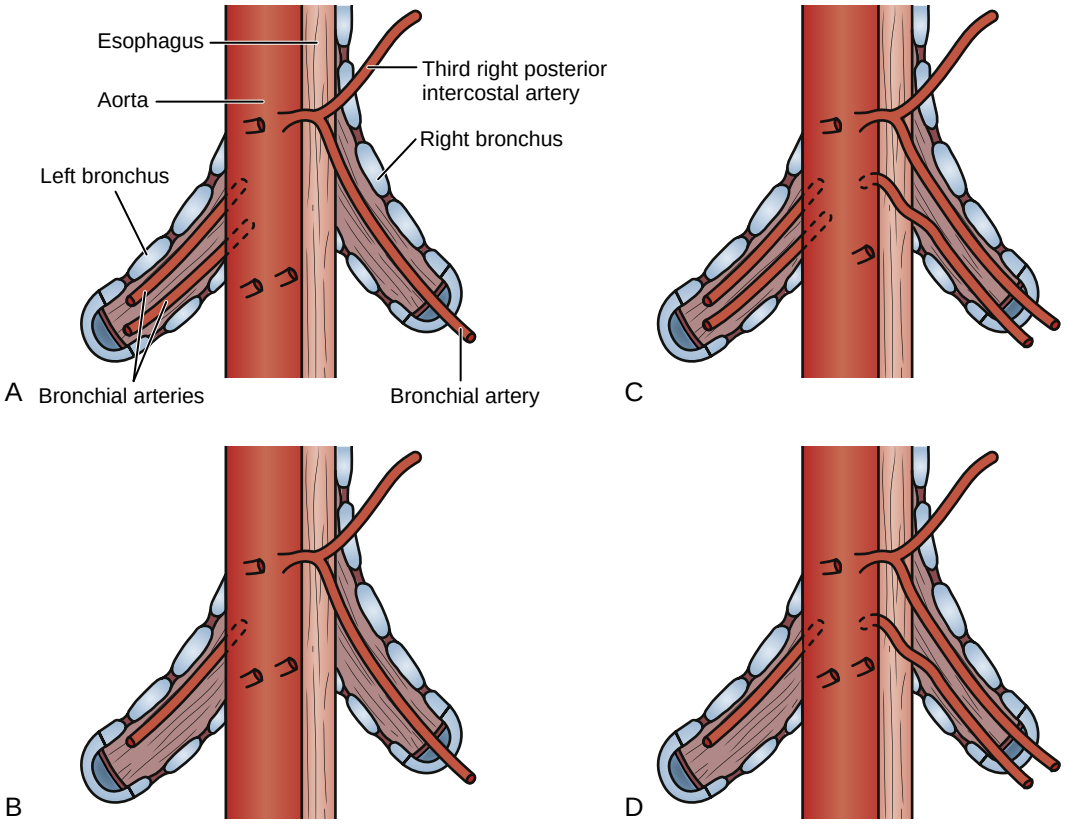
eFigure 21.9 *Computed tomography* (CT)-guided drainage of right lung abscess. (A) Coronal-reformatted CT scan through the posterior thorax in a 19-year-old man showing a large cavitary lesion extending from the upper to the lower lobe, representing an abscess. There is a multiloculated right parapneumonic effusion *(asterisks)*. (B) Upright frontal chest radiograph after CT-guided placement of a 16-French curved drainage catheter *(arrow)* into the abscess and a 12-French pigtail catheter *(arrowhead)* into the lower lateral right pleural fluid collection shows improvement in the abscess and pleural collection. The patient showed significant clinical improvement after the drainage.



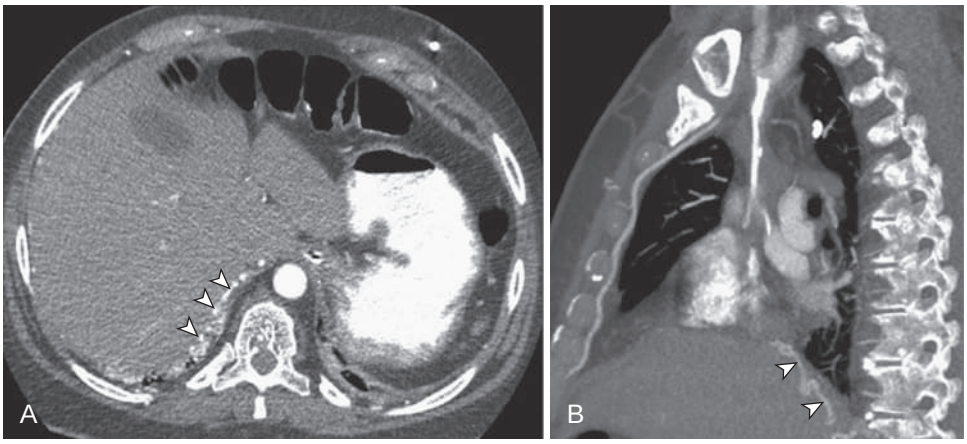
eFigure 21.10 Bronchial arteriography. (A) Left bronchial arteriography shows an enlarged and tortuous left bronchial artery with irregular luminal caliber, typical of hypertrophy in the presence of chronic pulmonary inflammation due to cystic fibrosis. (B) Selective catheterization of a left bronchial artery shows a normal caliber vessel without excessive tortuosity or irregularity. (B, Courtesy Michael B. Gotway, MD.)



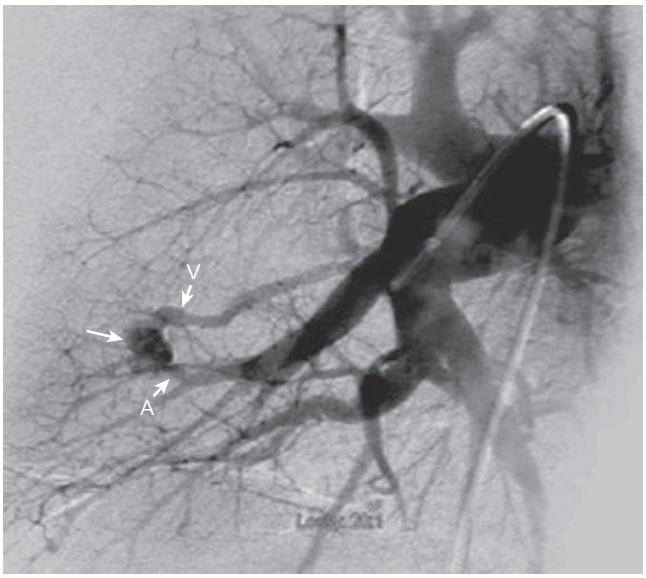
eFigure 21.11 Hypertrophied left bronchial arteries in patient with chronic thromboembolic disease. Coronal (A–D) and axial maximum intensity projected (C) contrast-enhanced chest computed tomography images show enlarged left bronchial arteries *(thick arrows)* secondary to chronic occlusion of the left lower lobe pulmonary artery (*curved arrow,* B). Note the normal-size right bronchial arteries (*thin arrows,* C–D).



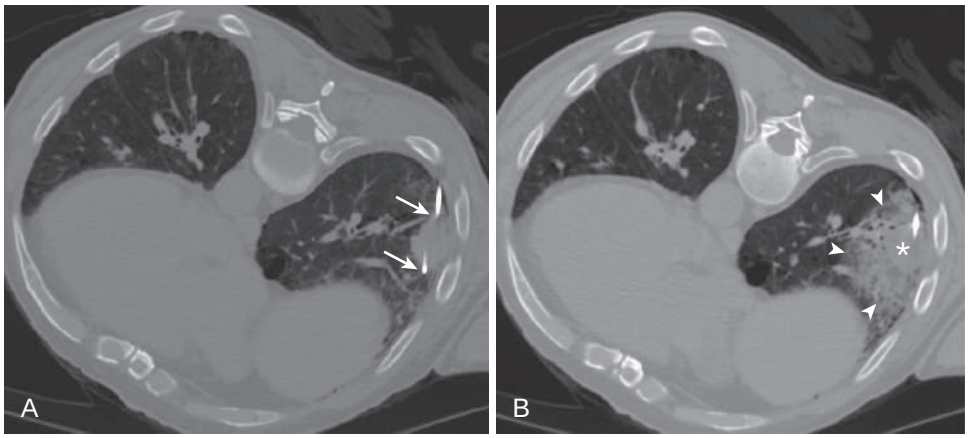
eFigure 21.12 The four most common bronchial artery branching patterns (viewed from posterior). (A) Two left vessels and one right vessel that represent an intercostobronchial trunk. (B) One left vessel and one intercostobronchial trunk vessel on the right. (C) Two left and two right (one intercostobronchial trunk and one bronchial artery) vessels. (D) One left and two right (one intercostobronchial trunk and one bronchial artery) vessels. (Modified from Cauldwell EW, Siekert RG, Lininger RE, Anson BJ. The bronchial arteries: an anatomic study of 105 human cadavers. *Surg Gynecol Obstet.* 1948;86:395–412.)



eFigure 21.13 Transpleural systemic-to-pulmonary collateral vessels. Axial (A) and sagittal maximum intensity projected (B) contrast-enhanced chest computed tomography images from a patient with chronic right pleural inflammation show prominent transpleural collateral vessels *(arrowheads).* (Courtesy Michael B. Gotway, MD.)



eFigure 21.14 Pulmonary arteriovenous malformation on pulmonary angiography. A selective right descending pulmonary arteriogram in a 64-year-old woman with hereditary hemorrhagic telangiectasia demonstrates a pulmonary arteriovenous malformation *(arrow)* in the middle lobe. Note characteristic feeding artery (A) and early draining vein (V).



eFigure 21.15 *Computed tomography* (CT) appearance immediately after radiofrequency ablation of a pulmonary lesion. (A) Chest CT with the patient prone during radiofrequency ablation of a solitary 3.5-cm metastasis from urothelial carcinoma shows two ablation probes *(arrows)* used to create a large ablation zone. (B) Repeat CT scan after ablation shows a large halo of ground-glass opacity *(arrowheads)* encompassing the treated lesion *(asterisk)*.

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22

PATHOLOGY: NEOPLASTIC AND NON-NEOPLASTIC LUNG DISEASE

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INTRODUCTION

The diagnosis of both neoplastic and non-neoplastic lung disease relies heavily on pathologic evaluation of lung tissue. This chapter first reviews the types of biopsy specimens most commonly encountered by pulmonary pathologists, how these different specimens are used in specific clinical scenarios, and how the biopsy tissues are processed for histologic evaluation. The remainder of the chapter is devoted to a summary of the most common neoplastic and non-neoplastic lung lesions encountered in lung biopsies. The discussion is meant as an introduction to lung pathology, with a focus on the general approach to histologic diagnosis and emphasis on the most important clinical and radiologic correlates.

TYPES OF LUNG TISSUE SPECIMENS

Pathologic evaluation of lung tissue plays a critical role in the diagnosis of lung disease. The types of lung specimens evaluated by pathologists vary depending on the diagnostic question, type of lesion, and its accessibility for various biopsy techniques (Table 22.1).

Localized lung lesions such as consolidations or nodules (>5 to 10 mm) can be sampled using percutaneous transthoracic image-guided (most often *computed tomography* [CT]-guided) techniques. Both *fine-needle aspiration* (FNA) and/or needle core biopsy are performed via the percutaneous approach and produce samples only a few millimeters in size but sufficient for histologic classification and additional ancillary studies in many cases. Alternatively, bronchoscopic biopsy techniques can be used to target mass lesions, particularly those located in the peritracheal or hilar regions. For example, endobronchial ultrasound–guided transbronchial FNA is often used to sample perihilar tumors as well as hilar lymph nodes for possible metastases. Lesions involving the bronchial mucosa that extend into the lumen are readily sampled by endobronchial forceps biopsy.

Diffuse parenchymal lung lesions can be targeted by transbronchial biopsy, including traditional forceps biopsy or more recently developed cryobiopsy techniques. Although transbronchial biopsy can be helpful in classifying some forms of *interstitial lung disease* (ILD), particularly acute lung injury patterns and sarcoidosis, definitive classification of interstitial fibrosis usually requires a more invasive surgical lung biopsy due to the patchy nature of the disease. At present, most surgical lung biopsies are performed via video-assisted thoracoscopic surgery and remain the gold standard for diagnosis of ILD. Although the risk of the procedure is significantly less than that of open lung biopsy, the potential risk of serious complications remains a significant barrier, particularly in patients with advanced disease.[1] More extensive procedures performed for mass lesions, most often tumors, can range in size from subsegmental wedge resections to pneumonectomies. Entire lungs are also evaluated by pathologists following lung transplantation and during autopsy.

Rapid histologic evaluation (frozen section) of tissue samples obtained during surgery is sometimes performed to guide surgical decisions. For example, an intraoperative biopsy of a solid nodule without a prior histologic diagnosis may be performed to determine whether the process is neoplastic or infectious. With this information, the surgeon is made aware of the need for further resection or staging and whether additional material is needed for flow cytometry

Table 22.1 Types of Lung Tissue Specimens Used for Pathologic Evaluation

Specimen Type	Size	Typical Use	Advantages	Limitations
Percutaneous needle ■ FNA ■ Core	1–15 mm	Localized mass lesions targetable by imaging	Safe, no need for general anesthesia	Challenging for small or central lesions
Bronchoscopic ■ Transbronchial ■ Endobronchial ■ EBUS-FNA	1–5 mm	Localized and some diffuse lung lesions, endobronchial and hilar lesions	Less invasive than surgical techniques	Low sensitivity for most diffuse interstitial processes
Surgical biopsy ■ Open lung ■ Thoracoscopy	1–5 cm per site	Diffuse ILD classification	Gold standard in diagnosis of ILD	Higher complication risk than nonsurgical techniques
Surgical resection ■ Wedge ■ Segmentectomy ■ Lobectomy ■ Pneumonectomy	From >5 cm to entire lung	Localized lesion, with or without a prior histologic diagnosis	Allows complete resection; more tissue for diagnosis and additional studies	Increased risk of complications
Autopsy	Entire lung	Evaluation of cause of death	Entire organ available for diagnosis	Postmortem preservation artifacts

EBUS, endobronchial ultrasound; FNA, fine-needle aspiration; ILD, interstitial lung disease.

for diagnosis and classification of hematolymphoid malignancies or for microbial cultures. Tissue samples requiring rapid intraoperative evaluation are snap-frozen and sections are cut in a cryostat while frozen, then briefly fixed in alcohol and stained with *hematoxylin and eosin* (H&E). The entire process is typically performed in less than 15 minutes. Other applications of intraoperative frozen sections include assessment of surgical margins to ensure complete tumor resection and confirmation that sufficient or intended target tissue is obtained. If the sampled tissue is not sufficient for diagnosis, additional diagnostic tissue can be obtained. Evaluation of frozen sections can be challenging due to freezing and sampling artifacts inherent in the method, which results in higher diagnostic uncertainty and higher frequency of misinterpretation when compared to routine histologic evaluation.[2,3] Therefore, unused frozen tissue "remnants" are formalin-fixed and processed using routine histologic techniques. These "permanent sections" have fewer histologic artifacts and allow additional special stains to be performed to help establish the final diagnosis.

TISSUE PROCESSING AND HISTOLOGIC EVALUATION

Lung tissue samples obtained via bronchoscopic biopsy and tissue cores collected by percutaneous biopsy are immediately placed in formalin to ensure optimal preservation of the tissue. Additional tissue is sometimes collected for microbial cultures or other testing such as flow cytometry or electron microscopy; these tissue samples should not be put in formalin and require special transport media for processing. Because bronchoscopic and core samples are small (<15 mm), they are generally properly fixed by formalin within hours and can be histologically examined the day after the procedure. Lung tissue samples obtained during surgical resections are generally larger (>1 cm) and are usually delivered to the pathology department for formalin fixation. Large specimens require longer fixation times for optimal penetration of formalin, which may delay histologic examination compared to small biopsies. Large specimens, once fixed, are dissected and evaluated grossly to identify the most representative or diagnostic areas, from which sections are taken for histologic evaluation. In tumor resection specimens, in addition to sampling the tumor, sections are also taken to evaluate the margins and to assess tumor stage (e.g., invasion into adjacent structures or lymph node involvement).

The tissue sections are placed in cassettes for processing, which is usually automated and includes dehydration (with alcohol), clearing (with xylene), and paraffin wax infiltration steps. The processed *formalin fixed paraffin embedded* (FFPE) tissue blocks are then cut into 3- to 5-μm thick tissue sections, which can be stained by various histochemical techniques (Table 22.2). H&E is the mainstay of microscopic evaluation used by pathologists and is the only stain required for diagnosis in many cases. However, additional special histochemical stains may be needed to highlight specific histologic structures or cellular or extracellular components (e.g., mucin, basement membranes, collagen, elastic fibers, amyloid), elements or minerals (e.g., calcium or iron), or microbial cell wall components (e.g., mycobacteria or fungi).

Over the last several decades, *immunohistochemical* (IHC) stains targeting specific cellular proteins have been developed to aid in the diagnosis of diverse neoplastic and non-neoplastic lesions.[4] These stains employ antibodies directed against defined cellular components such as various cytokeratins, transcription factors, or surface glycoproteins. A histologic section is first incubated with a primary antigen-specific antibody, and bound antibodies are then detected by a secondary antibody conjugated to an enzyme that catalyzes a chromogenic (color-producing) chemical reaction. The resulting stable brown (or sometimes red) staining pattern can be visualized under a regular light microscope. Hundreds of IHC markers are currently used by pathology practices and are a critical component of the diagnostic workup to determine the neoplastic or infectious nature of a pathologic process. Common IHC markers used in diagnosis of lung cancer are listed in Table 22.3.

Table 22.2 Common Histochemical Stains

Stain	Purpose	Appearance
Hematoxylin and eosin	Primary histologic evaluation	Nuclei/chromatin: blue Cytoplasm, collagen, fibrin: pink
Verhoeff-Van Gieson	Highlight elastic fibers	Elastic fibers: brown-black (silver stain)
Trichrome	Highlight areas of fibrosis	Collagen fibers: blue
Periodic acid–Schiff	Highlight basement membranes, glycoproteins, mucin	Basement membranes, mucin: pink-purple
Congo red	Identify tissue amyloid deposits	Amyloid: orange-red under routine light microscopy, changes to apple-green (birefringence) under polarized light
Perls Prussian blue	Highlight ferric iron in ferritin and hemosiderin, and ferruginous bodies	Iron deposits: dark blue
Mucicarmine	Highlight mucin; identify polysaccharide capsule of *Cryptococcus* species	Mucin: pink-purple
Grocott-Gomori methenamine silver	Identify fungi (stains fungal cell walls)	Fungi: brown-black (silver stain)
Acid-fast bacilli (e.g., Kinyoun or Fite)	Identify mycobacteria (stains mycobacterial cell walls)	Pink-red
Gram (e.g., Brown-Brenn)	Identify bacteria (stains bacterial cell walls)	Gram-positive: purple-blue Gram-negative: pink

Table 22.3 Common Immunohistochemical Stains Used in Diagnosis of Lung Cancer

Target Protein	Pulmonary Cell Type	Cellular Localization	Common Diagnostic Use
Cytokeratins (multiple)	All epithelial cells	Cytoplasmic	Carcinoma (positive) vs. sarcoma (negative) Pulmonary adenocarcinoma (CK7)
TTF-1	Bronchiolar epithelial cells, alveolar epithelial type 2 cells	Nuclear	Pulmonary adenocarcinoma
Napsin A	Alveolar epithelial type 2 cells, alveolar macrophages	Cytoplasmic	Pulmonary adenocarcinoma
p63 or p40	Bronchial epithelial basal cells, squamous cells	Nuclear	Squamous cell carcinoma, other
Synaptophysin	Neuroendocrine cells	Cytoplasmic	Neuroendocrine tumors
Chromogranin A	Neuroendocrine cells	Cytoplasmic	Neuroendocrine tumors
Ki-67	All dividing cells	Nuclear	Proliferation index (% dividing cells)

Additional ancillary studies performed on tissue sections include RNA-directed in situ hybridization (e.g., to detect RNA transcripts of Epstein-Barr virus or human papillomavirus), fluorescence in situ hybridization (e.g., to detect common gene fusions or translocations in numerous malignancies), and increasingly other molecular techniques.[5] For example, tissue sections are used as starting material for isolation of nucleic acids for downstream sequencing applications, including detection of genetic alterations, evaluation of mRNA expression or DNA methylation profiles of specific genes, and detection of various pathogens. Mass spectrometry–based proteomic techniques that utilize FFPE tissue are also being developed (e.g., amyloid subtyping).[6] Many of these techniques can be applied retrospectively on archival FFPE blocks in both research and clinical applications. Further development and widespread adoption of molecular techniques are anticipated to transform the practice of pathology over the next decades and will have a major impact on how we diagnose, subclassify, and treat both neoplastic and nonneoplastic lung disease.

CYTOLOGY SPECIMENS

Cytology is a subfield of pathology that uses cells obtained from fluids or removed from tissues to determine a diagnosis. Common thoracic cytology specimens include sputum samples, pleural fluid aspirates, bronchoalveolar lavage fluid, and FNA samples collected using bronchoscopic or transcutaneous techniques. Clinicians collecting these samples must consider the differential diagnosis and plan accordingly if a sample needs to be apportioned for multiple tests in addition to the routine microscopic cytologic evaluation (e.g., microbial cultures, flow cytometry, or molecular assays).

The cytologic evaluation of fluid samples, such as pleural or bronchoalveolar aspirates, begins with sample

centrifugation to concentrate the cells, after which a variety of techniques can be used to prepare slides for microscopic evaluation. Traditionally, a direct smear from the cell pellet is made, followed by air drying or alcohol fixation and staining. However, over the past 2 decades, several commercial systems for liquid-based cytology have been developed to automate the entire process of cell centrifugation, slide preparation, and staining.[7] In addition to the cytologic slide preparations, large volumes of fluid can be centrifuged into cell pellets to make FFPE histologic blocks. These so-called cell blocks have the advantage of the traditional FFPE tissue blocks because they allow the full range of conventional sectioning and staining techniques (including histochemical and immunohistochemical stains), molecular nucleic acid-based tests, and long-term archival storage.[8] However, in general, histologic sections prepared from cell blocks do not provide information about the tissue architecture.

FNA biopsies are typically more cellular than body fluid samples, and smears can be prepared directly from the aspirated material without centrifugation. A small portion of the aspirate is spread on a glass slide, which is then air dried or alcohol fixed and stained for cytologic evaluation. The remaining aspirate is typically used to prepare an FFPE cell block and used for other testing modalities (e.g., microbial cultures or flow cytometry) if needed.

Cytopathologists and trained cytology technicians often perform rapid on-site evaluation of FNA samples at the time they are being acquired by radiologists or interventional pulmonologists.[9] Rapid on-site evaluation ensures that a target lesion is adequately sampled and allows real-time decision making about sample handling. For example, if an inflammatory lesion is encountered, a portion of the sample is sent for microbial cultures. Rapid on-site evaluation has been shown to decrease the number of nondiagnostic FNAs and to reduce the need for repeat procedures.[10]

Table 22.4 World Health Organization Classification of Tumors of the Lung (2015)[20]

Adenocarcinoma ■ Lepidic adenocarcinoma ■ Acinar adenocarcinoma ■ Papillary adenocarcinoma ■ Micropapillary adenocarcinoma ■ Solid adenocarcinoma ■ Invasive mucinous adenocarcinoma ■ Colloid adenocarcinoma ■ Fetal adenocarcinoma ■ Enteric adenocarcinoma ■ Adenocarcinoma in situ ■ Minimally invasive adenocarcinoma
Squamous cell carcinoma ■ Keratinizing squamous cell carcinoma ■ Nonkeratinizing squamous cell carcinoma ■ Basaloid squamous cell carcinoma ■ Squamous cell carcinoma in situ
Neuroendocrine tumors ■ Small cell carcinoma ■ Large cell neuroendocrine carcinoma ■ Carcinoid tumor ■ Diffuse idiopathic pulmonary neuroendocrine cell hyperplasia
Large cell carcinoma
Adenosquamous carcinoma
Sarcomatoid carcinoma
Salivary gland–type tumors
Papillomas
Adenomas
Mesenchymal tumors
Lymphohistiocytic tumors
Tumors of ectopic origin
Metastases to the lung

EVALUATION OF NEOPLASTIC LUNG LESIONS

Pathologic evaluation continues to be a critical component in the diagnosis, staging, prognostication, and treatment of lung cancer. This discussion focuses on the most common subtypes of primary lung cancer. Other less common lung neoplasms are discussed in Chapters 78 through 80.

A histologic (and increasingly a molecular) classification of a suspected lung neoplasm is the main objective of the initial diagnostic evaluation. Small samples, such as image-guided core biopsies or bronchoscopic FNAs, are most frequently used for this purpose.[11] In contrast, most surgical resections (both primary and post–neoadjuvant therapy) may be curative but also serve to confirm and refine the initial histologic diagnosis, determine the pathologic tumor stage, assess resection margins, and evaluate response to pre-resection therapy (when applicable).

The three most common histologic subtypes of lung cancer are adenocarcinoma and squamous cell carcinoma (comprising *non–small cell lung carcinomas* [NSCLCs]), and *small cell lung carcinoma* (SCLC), which together account for approximately 85% of all lung cancer cases.[12] Other histologic subtypes encompass a diverse list of tumors (Table 22.4), some relatively common (e.g., carcinoid tumors) and some exceedingly rare. The classification of lung neoplasms continues to evolve, with molecular diagnostic techniques playing an increasingly important role in defining subcategories relevant to prognosis, treatment selection, and response to therapy (see also Chapter 73).

Historically, the most important distinction in the diagnosis of lung cancer was between SCLC and NSCLC, because SCLC often presents at advanced stage, is resistant to treatment, generally does not benefit from surgical resection, and has markedly worse prognosis compared to NSCLC.[13] However, over the past 2 decades, in addition to this distinction, more precise histologic subclassification of NSCLC has become critically important in the evaluation of lung cancer, prompted by the advances in systemic therapy for specific histologic subtypes and the introduction of targeted therapies.[14]

ADENOCARCINOMA

Adenocarcinomas account for approximately 40% of all lung cancer cases in the United States.[12] A large portion of pulmonary adenocarcinomas are thought to arise from components of the terminal respiratory unit (i.e., acinus).[15,16] These tumors arise in the peripheral lung parenchyma, and the tumor cells transcriptionally resemble

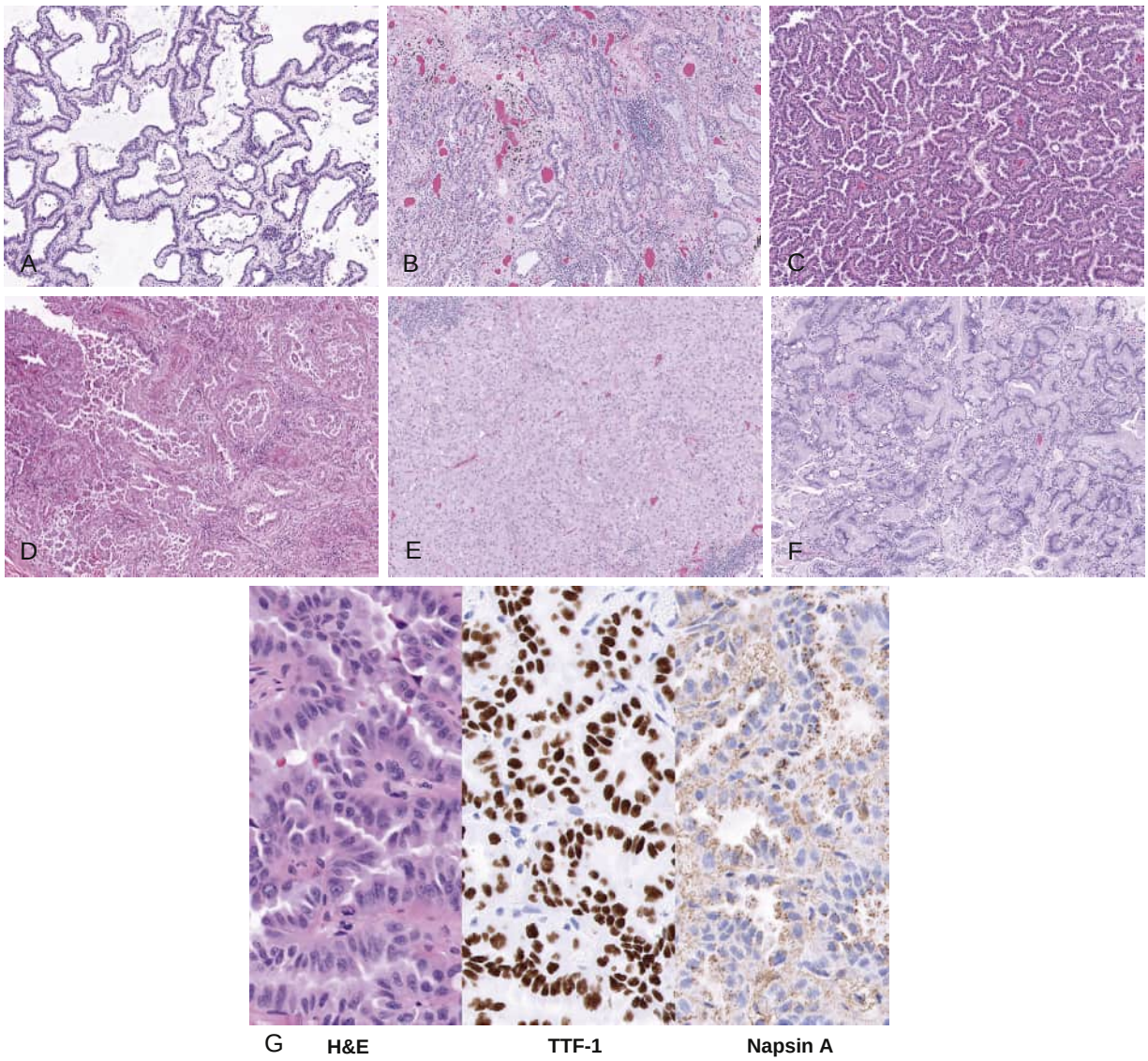

Figure 22.1 Pulmonary adenocarcinoma. Architectural patterns of growth are the basis of histologic grading of adenocarcinoma and include the following types. (A) Lepidic: neoplastic cells grow along preexisting alveolar septa without stromal invasion. (B) Acinar: neoplastic cells form irregular glands with stromal invasion. (C) Papillary: neoplastic cells line branchlike structures called papillae that grow from preexisting alveolar septa and contain fibrovascular bundles at their cores. (D) Micropapillary: neoplastic cells form small papillary-like tufts that lack a central fibrovascular core and shed extensively into alveolar spaces. (E) Solid: neoplastic cells grow as sheets or solid nests that are often invasive into the stroma. (F) Mucinous: alveoli, papillae, or acini are lined by characteristic columnar pseudostratified cells with abundant mucinous cytoplasm and basal ovoid nuclei (hematoxylin and eosin [H&E]; ×100 original magnification). (G) Immunohistochemical stains useful in diagnosis of pulmonary adenocarcinoma (×200 original magnification). TTF-1, thyroid transcription factor 1.

alveolar epithelial type 2 cells (i.e., express *thyroid transcription factor 1* [TTF1] and napsin A). In addition, adenocarcinomas can arise throughout the bronchoalveolar tree, including in association with larger caliber airways (i.e., non–terminal respiratory unit tumors). These tumors often lack expression of TTF1 and napsin A and histologically resemble bronchial columnar epithelial or mucinous cells.[17]

Conventional non-mucinous pulmonary adenocarcinoma (also called adenocarcinoma not otherwise specified) may exhibit several architectural patterns of growth such as lepidic (along the alveolar septa), acinar, papillary, micropapillary, or solid (Fig. 22.1). The predominant architectural pattern is an important predictor of survival in adenocarcinoma. Therefore, the 2011 International Association for the Study of Lung Cancer/American Thoracic Society/European Respiratory Society lung adenocarcinoma classification recommends that the diagnosis of adenocarcinoma should include the predominant histologic pattern, and enumeration of all patterns within a tumor (as percent of total in 5% increments) is encouraged in all resection specimens.[18] Tumor grading schemes use histologic features such as degree of cell differentiation (or similarity to benign counterparts) as predictors of tumor behavior. Although no universally accepted tumor grading system for adenocarcinoma has been developed, a simple system largely based on the predominant architectural pattern is in wide use today (Table 22.5). Some authors also advocate the use of mitotic count in grading pulmonary adenocarcinoma.[19]

In addition to pulmonary adenocarcinoma not otherwise specified, several distinct histologic adenocarcinoma variants are recognized by the 2015 *World Health Organization* (WHO) classification,[20] including invasive mucinous (formally mucinous bronchioloalveolar carcinoma), colloid, enteric, and fetal adenocarcinoma. These rare variants have characteristic architectural and cytologic appearance and appear to represent biologically distinct categories. For example, invasive mucinous adenocarcinomas often exhibit oncogenic *KRAS* mutations, frequently present with multifocal lung involvement which can mimic pneumonia on CT scan, and may show aggressive clinical behavior.[21]

Staging of adenocarcinoma follows the general tumor-node-metastasis guidelines for lung tumors (see later and Chapter 76). However, two categories deserve a special mention. Adenocarcinoma *in situ* (is) is defined as a tumor 3 cm or less in size and composed of lepidic growth pattern only. Minimally invasive adenocarcinoma is defined as a lepidic-predominant tumor of up to 3 cm in size, wherein the invasive component cannot exceed 5 mm. Both adenocarcinoma in situ and *minimally invasive* (mi) adenocarcinoma have excellent prognosis, with near 100% 5-year survival, and are given the pathologic stage of pT0is and pT1mi, respectively. Both adenocarcinoma in situ and minimally invasive adenocarcinoma are thought to be precursor lesions for higher-grade adenocarcinomas.[18]

Molecular profiling studies of lung adenocarcinoma have identified recurrent activating genetic alterations in several driver oncogenes, including mutations in *KRAS* (30% of cases), *EGFR* (15–30%) and *BRAF* (5–10%); and rearrangements of *ALK* (5%) and *ROS1* (<2%), among others.[22]

Table 22.5 Adenocarcinoma Grading System Based on the 2011 IASLC/ATS/ERS International Multidisciplinary Classification of Lung Adenocarcinoma[18]

Predominant Architectural Pattern	Tumor Grade
Lepidic	Low grade (G1, well-differentiated)
Acinar, papillary	Intermediate grade (G2, moderately differentiated)
Solid, micropapillary	High grade (G3, poorly differentiated)

IASLC/ATS/ESR, International Association for the Study of Lung Cancer/American Thoracic Society/European Respiratory Society.

Specific inhibitors targeting many of these oncogenes are now available and have transformed the treatment options of patients with lung adenocarcinoma. As a result, routine testing for the most common actionable mutations in adenocarcinoma is now standard practice, particularly in advanced-stage cases requiring systemic therapy.[23,24] Although single-gene testing for common genetic alterations is still in use, targeted multiplex gene sequencing panels using next-generation sequencing are now preferred. The next-generation sequencing multiplex panels provide more comprehensive coverage of known genetic alterations, do not require division of the sample for multiple tests, and offer turnaround times approaching those of single-gene assays. Both biopsy tissue blocks and cytology preparations (cell blocks or smears) are compatible with next-generation sequencing panels as long as there is sufficient tumor cellularity (at least 20%).[23]

SQUAMOUS CELL CARCINOMA

Squamous cell carcinoma (SCC) accounts for approximately 25% of all lung cancer cases in the United States.[12] Chronic smoking continues to be the most important risk factor for SCC. Smoking is thought to promote transformation of bronchial epithelial lesions from squamous metaplasia to dysplasia, to carcinoma in situ, and finally to invasive carcinoma.[25,26] Historically, up to two-thirds of SCC presented as central lung tumors in association with hilar airways.[27] However, over the past 2 decades, there has been an increase in the proportion of peripheral SCC, which also coincided with a declining proportion of SCC relative to adenocarcinoma in smokers.[28,29] Although the reasons for these trends are not well understood, the shift from unfiltered to filtered cigarettes in the 1960s and 1970s has been proposed as a possible contributor.[30]

The morphologic features of squamous cell differentiation include intercellular bridges, keratinization of individual cells, and formation of keratin pearls (Fig. 22.2). These features are readily apparent in well-differentiated tumors, can be subtle or focal in moderately differentiated tumors, and may be entirely absent in poorly differentiated tumors. The diagnosis of SCC is supported by nuclear expression of p63 (or its splice variant p40) and the lack of expression of pulmonary adenocarcinoma markers (TTF1 and napsin A) by IHC.[31] Next-generation sequencing of SCC has identified recurrent alterations in *TP53* (65%), *PIK3CA* (30%), *CDKN2A* (25%), *SOX2* (15%), and *CCND1*

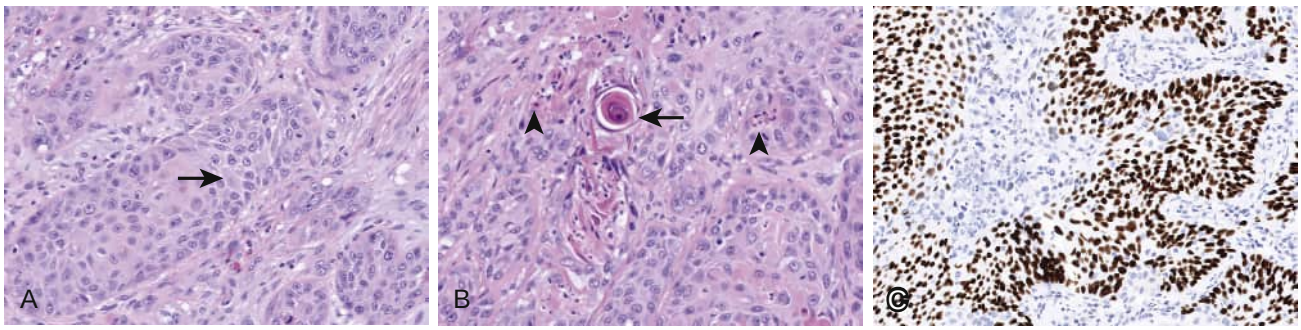

Figure 22.2 Squamous cell carcinoma. Histologic features include (A) intercellular bridges (*arrow*), (B) intracellular keratinization (*arrowheads*), and keratin pearls (*arrow*) (hematoxylin and eosin; ×100 original magnification). (C) Brown staining demonstrates expression of p40, helpful in confirming squamous differentiation, particularly in poorly differentiated tumors (×200 original magnification).

(15%), none of which are currently actionable for targeted therapy.[32,33] Although *FGFR1* amplification is observed in up to 20% of SCC, FGFR inhibitors alone have been largely ineffective.[34]

The 2015 WHO classification recognizes three histologic subtypes of SCC (keratinizing, nonkeratinizing, and basaloid), but there appears to be little prognostic significance to the three subtypes.[20] Similarly, although several grading systems (which categorize SCC as well differentiated, moderately differentiated, or poorly differentiated) have been proposed, none is uniformly accepted.

SMALL CELL CARCINOMA

SCLC accounts for 10–15% of lung cancer cases in the United States.[12] Most cases present with a perihilar mass, and over 80% of cases are at an advanced stage (III or IV) at presentation.[35] Importantly, current studies on the utility of low-dose CT screening in heavy smokers suggest that, unlike NSCLC, screening may not significantly improve the rate of detection of early-stage tumors or reduce mortality in SCLC.[36] The diagnosis is most often made using transbronchial biopsy or FNA. Surgical resections are rare and most often performed for small solitary lesions, where surgery in the context of multimodality therapy may have a role in improving survival.[37]

Histologically, SCLCs are solid neoplasms with very cellular sheetlike or nested growth architecture.[38] The tumor cells characteristically have scant pale cytoplasm, which gives an impression of "small" cell size. However, the overall cell size is still two to three times that of a lymphocyte. The nuclei usually show high pleomorphism, fragile nuclear envelopes (manifest as nuclear "smudging" and "molding"), finely granular nuclear chromatin, and absent or inconspicuous nucleoli (Fig. 22.3). Mitotic activity is characteristically high, and necrosis is usually extensive. Although not required, immunohistochemical staining is helpful in confirming the diagnosis. SCLC cells are often positive for neuroendocrine markers (e.g., synaptophysin and chromogranin A) and show a high (usually >80%) Ki-67 *proliferation index*, that is, the percentage of the malignant cells that are undergoing division, as measured by IHC staining for Ki-67, a nuclear protein expressed during cell division. Next-generation sequencing of SCLC has revealed a highly characteristic bi-allelic inactivation of *TP53* and *RB1* in approximately 90% of the tumors.[39,40]

Rarely, SCLC can present in combination with other types of NSCLC such as large cell carcinoma, adenocarcinoma, squamous cell carcinoma, or other less common histologic types. To date, no significant difference in clinical features, prognosis, or response to therapy has been demonstrated in these combined tumors compared with pure SCLC.[41,42]

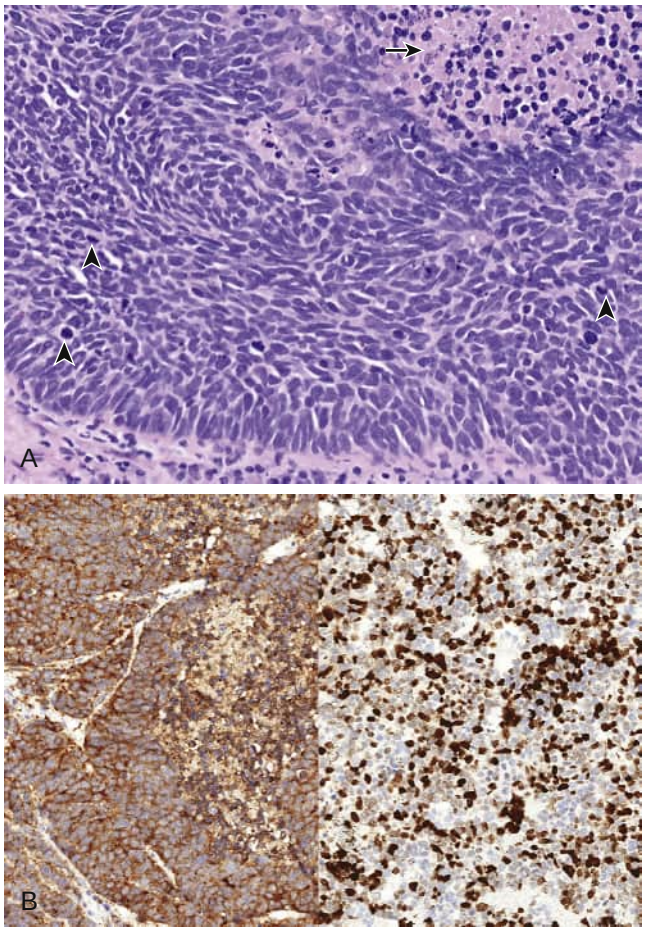

Figure 22.3 Small cell lung carcinoma. (A) Cells appear "small" due to high nucleus to cytoplasm ratio. Nuclei contain finely granular chromatin and lack prominent nucleoli. Note scattered mitotic figures (*arrowheads*) and focal necrosis (*arrow*) (hematoxylin and eosin, ×400 original magnification). (B) Expression of synaptophysin by immunohistochemical staining is helpful in confirming neuroendocrine differentiation (×200 original magnification). Ki-67 stain shows a high (>80%) proliferation rate (×200 original magnification).

LARGE CELL NEUROENDOCRINE CARCINOMA

Large cell neuroendocrine carcinoma (LCNEC) accounts for approximately 3% of resected lung cancer cases.[43] LCNEC is a high-grade neuroendocrine carcinoma that shares some morphologic and molecular similarities with SCLC.[44] However, like other types of NSCLC, LCNEC has a better prognosis than SCLC.[45] The common histologic features include nested or trabecular (cord-like) pattern of growth, frequently with peripheral palisading, and abundant central necrosis within the tumor nests (Fig. 22.4). The tumor cells are large and polygonal, with abundant cytoplasm, and nuclei with frequent prominent nucleoli and neuroendocrine-like coarse or vesicular chromatin. The mitotic rate is high (11 or more per 2 mm^2 with a mean of 60 per 2 mm^2). The diagnosis is confirmed by the presence of at least one immunohistochemical marker of neuroendocrine differentiation, such as synaptophysin, chromogranin A, or neural cell adhesion molecule (CD56). Molecular profiling of LCNEC has identified two major molecular subtypes: SCLC-like group with high frequency of *TP53* and *RB1* co-mutation or loss, and NSCLC-like group with genetic alterations characteristic of NSCLC (including *STK11*, *KRAS*, and *KEAP1*). However, no significant differences in clinical characteristics, including survival, have been identified between the two groups.[46]

CARCINOID TUMORS

Carcinoid tumors account for less than 5% of all invasive lung neoplasms.[12] Although SCLC, LCNEC, and carcinoid

tumors are grouped together under the general category of neuroendocrine neoplasms in the 2015 WHO classification of lung tumors, it is clear that carcinoid tumors (also known as well-differentiated neuroendocrine tumors) have major biologic differences compared with the high-grade LCNEC and SCLC (Table 22.6).[47,48] Carcinoid tumors in younger patients do not have a strong association with smoking and have a significantly better prognosis than either LCNEC or SCLC.[49]

Carcinoid tumors may arise centrally, often in association with a large airway where they may have a significant luminal component, or less commonly in the distal subpleural parenchyma.[47,50] The tumors have smooth lobulated borders on imaging and may bleed during biopsy owing to their extensive vascular supply. A classic pattern shows organoid (nested) growth of cytologically uniform cells with neuroendocrine appearance (Fig. 22.5). The cells have round or ovoid nuclei with smooth nuclear envelopes, finely granular ("salt and pepper") chromatin, and moderate-to-abundant eosinophilic or granular cytoplasm. However, a variety of other growth patterns (trabecular, papillary, or rosette-like, among others) and cell features (e.g., spindle cell, acinic cell-like, signet-ring, mucin-producing, or melanocytic) have been described. These patterns do not have prognostic significance but are important for pathologists to recognize to avoid misclassification.

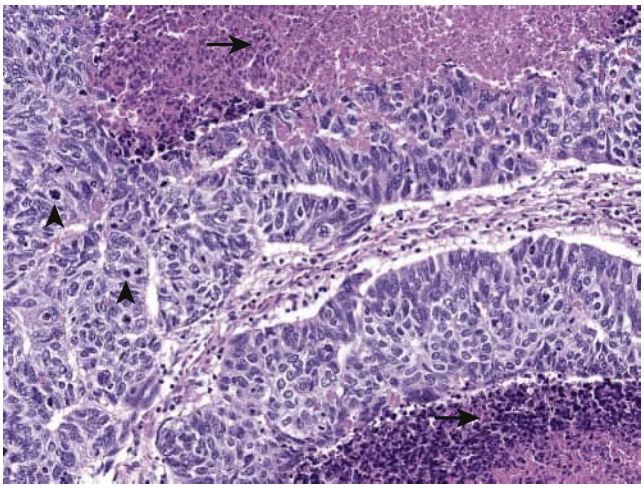

Figure 22.4 Large cell neuroendocrine carcinoma. Large cell neuroendocrine carcinoma cells have more ample cytoplasm and more frequent nucleoli than in small cell lung carcinoma. Note the ribbon-like architecture, areas of necrosis (*arrows*), and frequent mitotic figures (*arrowheads*) (hematoxylin and eosin; ×200 original magnification).

Lung carcinoid tumors are traditionally classified as either typical carcinoid (≈90%) or the more aggressive atypical carcinoid (≈10%). According to the 2015 WHO diagnostic criteria, typical carcinoids have low mitotic rates (<2 per 2 mm^2) and lack tumor cell necrosis, whereas atypical carcinoids have higher mitotic counts (2 to 10 per 2 mm^2) and/or demonstrate tumor cell necrosis, which may be focal or punctate.[20] Typical carcinoids tend to be smaller at presentation, less frequently metastasize, and have a better prognosis than the atypical carcinoids (5-year survival is approximately 90% for typical compared to 60% for atypical carcinoids). Importantly, regional lymph node involvement should not be used to distinguish between the two types of carcinoid tumors because it is present in approximately 10% of typical carcinoid as well as 50% of atypical carcinoid cases.[47,50]

Carcinoid tumors stain strongly for neuroendocrine markers such as synaptophysin, chromogranin, and CD56. The Ki-67 proliferation index in typical carcinoid is low (<5%) compared with atypical (5–20%). Ki-67 staining is particularly helpful in small biopsies for separating either of the carcinoid tumors from high-grade neuroendocrine carcinomas (LCNEC and SCLC), which have much higher proliferation rates (typically >40% and >60%, respectively).[47,51]

OTHER LESS COMMON TUMOR TYPES

Adenosquamous carcinoma accounts for 1% of lung cancer cases in the United States. It is defined by the presence of both adenocarcinoma and squamous cell carcinoma when each component comprises at least 10% of the entire tumor. This diagnosis is difficult to make definitively in small biopsies and is usually reserved for resected specimens. Molecular testing of these tumors often reveals genetic alterations commonly found in adenocarcinoma, including mutations in *EGFR* and *KRAS*.[52,53]

Large cell (undifferentiated) carcinoma is a subtype of NSCLC. It is a diagnosis of exclusion reserved for undifferentiated

Table 22.6 Lung Neuroendocrine Tumors

	Typical Carcinoid	Atypical Carcinoid	Large Cell Neuroendocrine Carcinoma	Small Cell Lung Carcinoma
WHO grade	Low (grade 1)	Intermediate (grade 2)	High (grade 4)	High (grade 4)
Morphology/cytology	Well-differentiated/ neuroendocrine cells	Well-differentiated/ neuroendocrine cells	Poorly differentiated/non-small cells	Poorly differentiated/small cell
Mitoses (per 2 mm^2)	<2	2–10	>10	>10
Necrosis	No	May be present (focal, punctate)	Yes (extensive)	Yes (extensive)
Ki-67 index (%)	<5	5–20	40–90	60–96
Neuroendocrine markers by immunohistochemistry	Yes	Yes	Yes (required)	Absent in 10–15% of cases (not required)

WHO, World Health Organization.

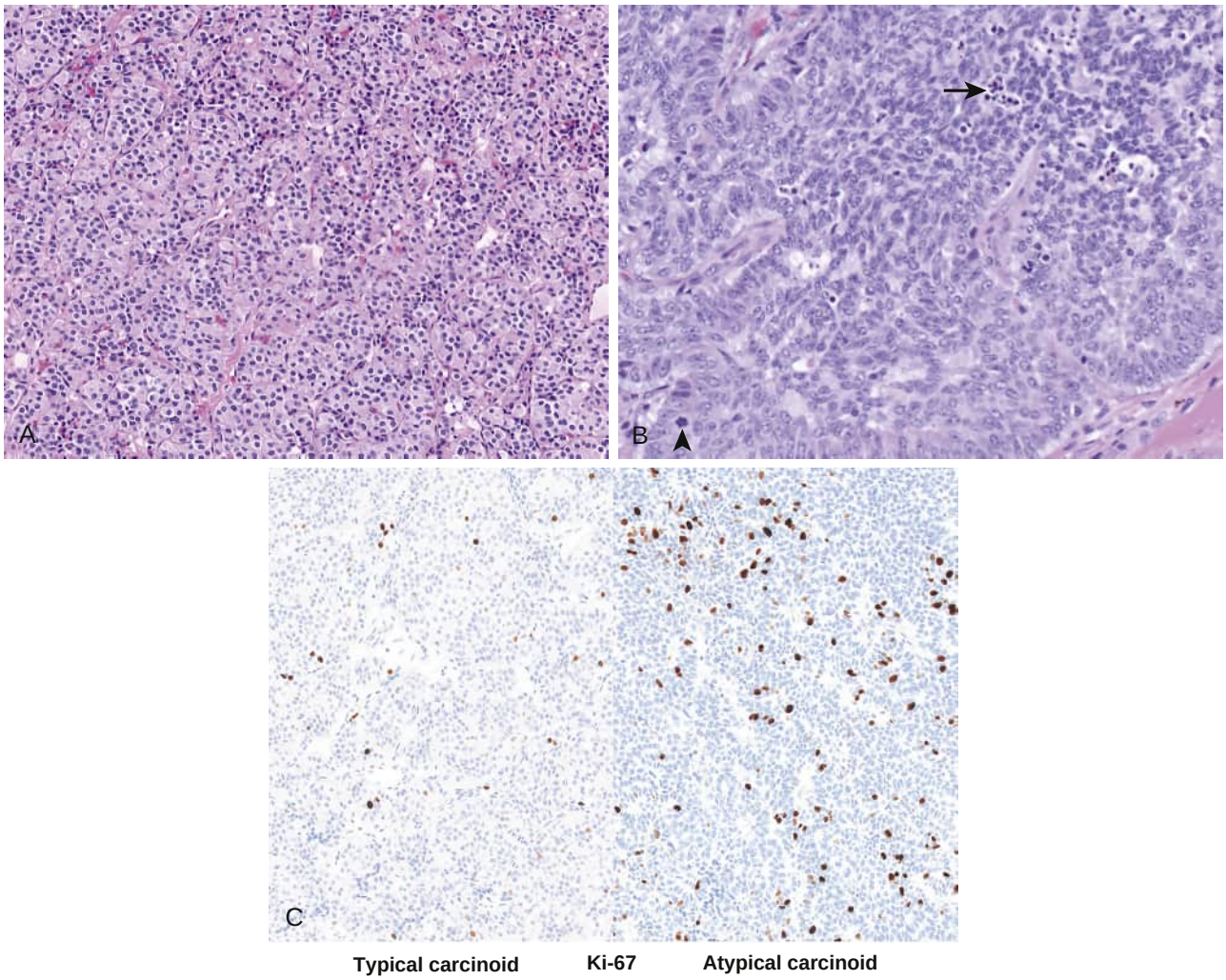

Figure 22.5 Carcinoid tumors. (A) Typical carcinoid with classic organoid architecture and cytologically uniform cells; no mitosis or necrosis is seen (hematoxylin and eosin [H&E]; ×200 original magnification). (B) Atypical carcinoid with increased nuclear pleomorphism, occasional mitoses (*arrowhead*), and small foci of necrosis (*arrow*) (H&E; ×400 original magnification). (C) Immunohistochemical staining for Ki-67 shows a lower proliferation index in typical carcinoid than in atypical carcinoid (×200 original magnification).

tumors that lack features of adenocarcinoma, squamous cell carcinoma, or neuroendocrine carcinoma. In the past 2 decades, the widespread use of IHC markers to help distinguish poorly differentiated cases of adenocarcinoma and squamous cell carcinoma has significantly reduced the number of cases diagnosed as large cell carcinoma, from about 9% of all lung cancer cases in the 1980s to less than 2% at present.[12,54] Recent molecular evidence also parallels this trend. Up to one-third of large cell carcinoma tumors that cannot be further classified histologically harbor molecular alterations characteristic of adenocarcinoma, and up to one-fourth harbor those typical of SCC. Importantly, at least 20% of the tumors do not reveal any recognizable lineage-specific genetic profiles, suggesting that large cell carcinoma will likely remain a rare histologic subtype in need of further characterization.[55]

Sarcomatoid carcinomas are the rarest histologic subgroup of the major types of lung cancer and account for 0.5% of all invasive lung malignancies in the United States. These poorly differentiated tumors histologically resemble sarcomas and may have pleomorphic, sarcomatoid, or sarcomatous elements. They are often bulky and have aggressive invasive clinical behavior. Immunohistochemical expression of epithelial markers, particularly keratins, is helpful in confirming epithelial rather than mesenchymal origin, thus confirming the diagnosis of carcinoma rather than sarcoma. Peripheral tumors can be challenging to distinguish from sarcomatoid mesothelioma. In these cases, IHC stains for tissue-specific antigens such as TTF1 and mesothelial markers may be helpful.[56,57]

PATHOLOGIC STAGING

Staging of lung tumors is performed using guidelines provided by the American Joint Commission on Cancer in the United States and by the Union for International Cancer Control internationally.[58,59] Pathologic staging considerations are relevant to both resection specimens and some small biopsies. In resection specimens, tumor size is measured either grossly or microscopically, and the largest dimension is reported with millimeter precision. Surgical resection margins (i.e., edges of the specimen that have tissue transected by the operation, which most often include

lung parenchyma, bronchi, and pulmonary vessels) are evaluated for the presence of tumor. The distance from tumor to the closest margin is measured, both grossly and microscopically, and recorded in the report. Tumor invasion into mediastinal structures, pleura, or chest wall is assessed grossly and in histologic sections. All surgically sampled lymph nodes, as well as lymph nodes identified within the resection specimen, are evaluated for the presence of metastases. Microscopic evaluation may also reveal lymphovascular or perineural invasion, both of which are markers of more aggressive tumor behavior.

Small biopsies of presumed metastatic sites (e.g., hilar lymph nodes or extrathoracic sites) may be used to stage and identify the histologic subtype of lung cancer and to provide tissue for molecular marker analysis. Similarly, sampling of two (or more) simultaneously identified lung masses may be used to distinguish between metastatic disease and synchronous primaries.

Most pathology practices follow standardized cancer reporting protocols, also known as *tumor synoptics*, such as those available from the College of American Pathologists.[60] These protocols are regularly updated and are available for the entire range of cancer types, including lung cancer. Standardized reporting facilitates data collection by local and national cancer tracking databases and enables longitudinal studies of cancer trends. Lung cancer staging is further discussed in Chapter 76.

EVALUATION OF NON-NEOPLASTIC LUNG DISEASE

Transbronchial biopsies are most useful in diagnosis of acute lung injury patterns, pulmonary sarcoidosis, some localized processes (particularly when aided by endobronchial ultrasound or electromagnetic navigation), and in evaluation of lung allograft rejection. Nodules and sometimes more diffuse consolidative processes can also be sampled by percutaneous CT-guided biopsy. However, small transbronchial biopsies are not sufficient for definitive diagnosis of most diffuse chronic patterns of ILD, particularly those with interstitial fibrosis, due to their non-uniform distribution in the lung and the difficulty in sampling subpleural parenchyma.[61,62] Recent experience from several centers shows that transbronchial cryobiopsy has improved sensitivity for ILD classification compared to conventional transbronchial biopsy and has the potential to be used as an alternative to surgical lung biopsy.[63] However, surgical lung biopsy continues to be the gold standard in ILD diagnosis. Therefore, the discussion later is focused largely on histopathologic evaluation of surgical lung biopsies.

In patients with ILD, histologic evaluation of surgical biopsies may show distinct histologic patterns useful in generating a differential diagnosis of possible etiologies or associated conditions. Liebow and Carrington published their classification of interstitial pneumonias in 1969.[64] While their classification continues to be refined by new knowledge about the underlying mechanisms and by newly recognized clinicopathologic entities,[62,65,66] the major histologic patterns of ILD (Table 22.7) have remained unchanged over several decades and continue to serve as the foundation of histologic evaluation. There are several methods of evaluating lung biopsies according to pattern of injury and distribution of disease.[67–69] The following set of questions is provided as a conceptual framework for understanding how findings in a lung biopsy can help define the disease process.

Table 22.7 Histologic Patterns of Interstitial Lung Disease

Acute lung injury
■ Diffuse alveolar damage
■ Organizing pneumonia
■ Acute fibrinous and organizing pneumonia
Consolidation of alveolar spaces
■ Eosinophilic pneumonia
■ Desquamative interstitial pneumonia
■ Pulmonary alveolar proteinosis
Interstitial fibrosis
■ Usual interstitial pneumonia
■ Nonspecific interstitial pneumonia (fibrosing NSIP)
Interstitial inflammation
■ Nonspecific interstitial pneumonia (cellular NSIP)
■ Lymphocytic interstitial pneumonia
■ Hypersensitivity pneumonitis

IS THERE ACUTE LUNG INJURY?

The acute lung injury patterns traditionally included *diffuse alveolar damage* (DAD) and *organizing pneumonia* (OP). *Acute fibrinous and organizing pneumonia* (AFOP) is a more recently described pattern.[70] Recognition of these patterns of lung injury is important because they are most often associated with severe acute or subacute respiratory illness. A unifying feature of acute lung injury patterns is the presence of cellular or proteinaceous exudates in the alveolar spaces, which are likely recognized on high-resolution CT as areas of consolidation.

Diffuse Alveolar Damage

The *acute phase* of DAD (Fig. 22.6A) is histologically characterized by diffuse injury of the alveolar septa.[71,72] Both alveolar epithelial and endothelial cells show changes ranging from swelling to necrosis. The alveolar septa show interstitial edema and scattered inflammatory cells in the alveolar septal capillaries. The alveolar spaces accumulate proteinaceous exudate containing serum, fibrin, scattered macrophages, and occasional neutrophils. Within several days, the fibrin-rich exudate and necrotic cellular debris form compacted linear aggregates lining the alveolar walls called hyaline membranes, a diagnostic feature of DAD.[73,74]

Over days to weeks following the injury, tissue repair mechanisms are activated. In this *organizing phase* of DAD (see Fig. 22.6B), the alveolar septa become thickened by fibroblast-rich granulation tissue and sparse chronic inflammation. Proliferation of alveolar epithelial cells (alveolar epithelial type 2 cell hyperplasia) results in re-epithelialization of the injured alveolar septa. The alveolar exudates first become more cellular, with an influx of macrophages and fibroblasts, and are then consolidated into rounded plugs of granulation tissue that resemble organizing pneumonia. Over weeks to months, there may be

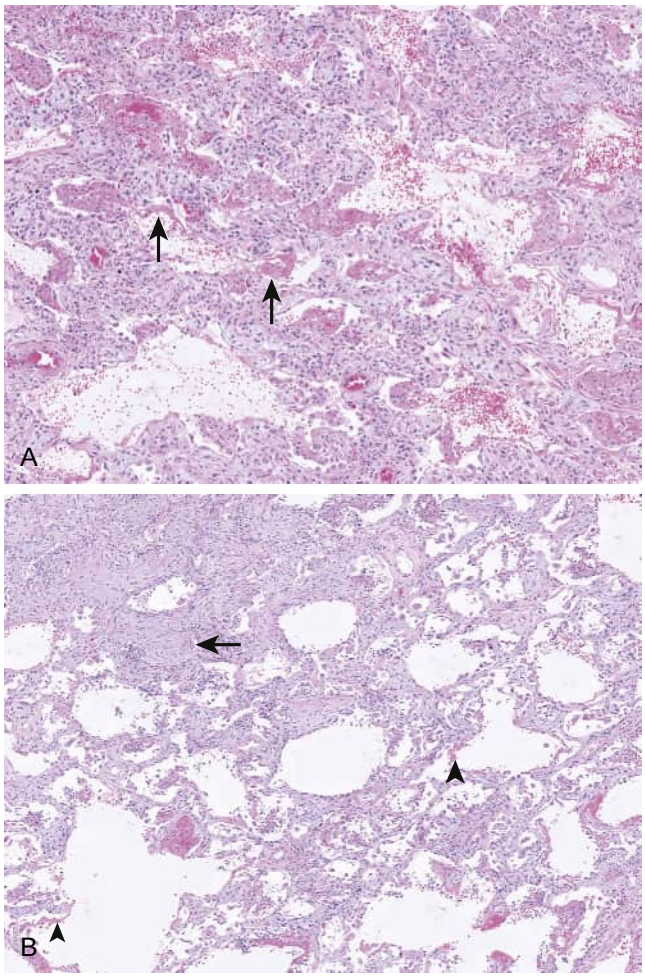

Figure 22.6 Diffuse alveolar damage. (A) Acute phase of *diffuse alveolar damage* (DAD) with prominent alveolar septal thickening by edema and early granulation tissue, alveolar epithelial type 2 cell hyperplasia, air space filling by fibrinous exudate, and occasional hyaline membranes (*arrows*). (B) Organizing phase of DAD with alveolar septal consolidation by granulation tissue and replacement of air space exudates by fibroblast-rich plugs of granulation tissue resembling organizing pneumonia (*arrow*); residual hyaline membranes are still present (*arrowheads*) (hematoxylin and eosin; ×100 original magnification).

complete or near-complete resolution or variable degrees of persistent fibrosis and alveolar septal loss.

While most cases of DAD show nonspecific histologic findings that cannot differentiate between multiple possible etiologies, biopsies may occasionally reveal histologic clues suggestive or even diagnostic of the underlying process. Examples of such findings include viral cytopathic changes in viral pneumonia, aspirated food particles in aspiration pneumonia, or characteristic lipid-filled or foamy macrophages in some drug toxicities.

Organizing Pneumonia

OP is characterized histologically by polypoid plugs of granulation tissue filling the alveolar spaces (Fig. 22.7). The plugs are bound by the surrounding alveolar septa, which gives them the characteristic rounded and branching shapes. The plugs are rich in fibroblasts, loose myxoid matrix, and often contain admixed inflammatory cells. Alveolar epithelial type 2 cell hyperplasia can be prominent in many cases.[75,76]

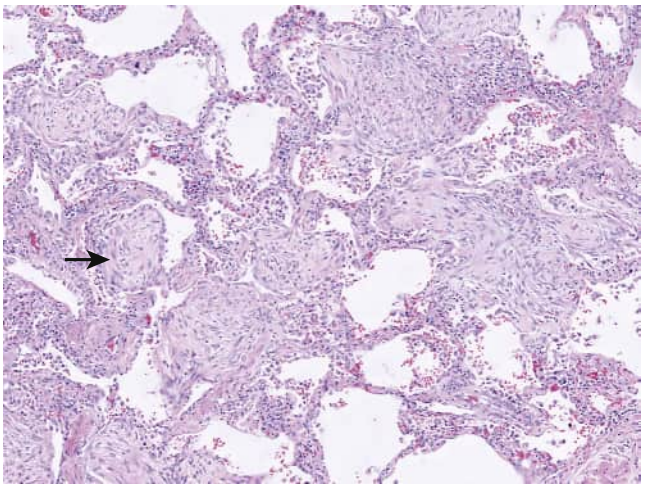

Figure 22.7 Organizing pneumonia. The air spaces contain rounded plugs of fibroblast-rich granulation tissue (*arrow*) (hematoxylin and eosin; ×100 original magnification).

As with DAD, most cases of OP lack histologic features to suggest a specific etiology. However, if present, histologic clues such as viral cytopathic changes or aspirated food material are very helpful in establishing or confirming the cause. If clinical evaluation does not reveal a specific etiology, cryptogenic organizing pneumonia is used as the diagnosis of exclusion.[77]

Acute Fibrinous and Organizing Pneumonia

AFOP is an acute lung injury pattern with histologic features resembling both DAD and OP (Fig. 22.8). Well-developed hyaline membranes are not present in AFOP, but rather the air spaces contain prominent plug-like aggregates of fibrin. Both the clinical presentation and differential diagnosis are essentially the same as those of DAD, although some of the patients appear to have a less severe clinical course compared to DAD. Therefore, AFOP is considered a variant of DAD by some authors.[78]

IS THERE CONSOLIDATION OF ALVEOLAR SPACES?

Acute lung injury is just one of the many causes of filling of air spaces. Consolidation of the air spaces may be secondary to accumulation of edema, blood, proteinaceous fluid, or various cells (e.g., neutrophils, eosinophils, or macrophages). Several of these diverse air space–filling clinicopathologic entities are briefly described later.

Eosinophilic Pneumonia

Eosinophilic pneumonia is characterized by numerous eosinophils within the air spaces (Fig. 22.9) and is divided clinically into acute and chronic forms. Like other acute lung injury patterns, acute eosinophilic pneumonia shows features of alveolar injury, including alveolar epithelial type 2 hyperplasia, interstitial edema, and alveolar accumulation of fibrin and macrophages. Chronic cases typically show findings of air space consolidation by eosinophils and plugs of granulation tissue similar to those of OP and may show variable associated fibrosis. Known etiologies include initiation of or a change in smoking habits, exposure to

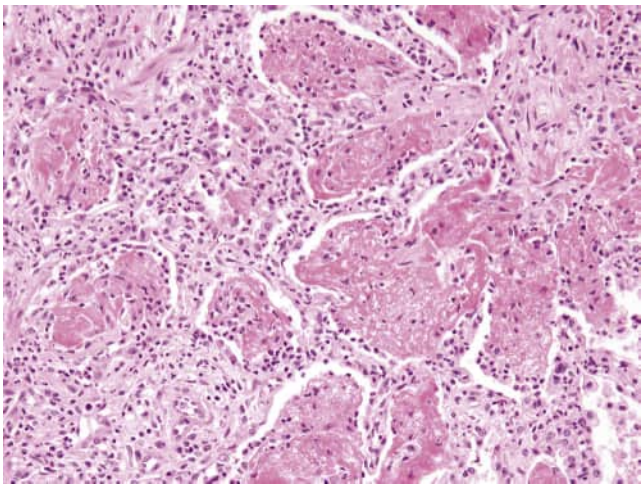

Figure 22.8 Acute fibrinous and organizing pneumonia. The alveolar septa show diffuse edema and sparse lymphocytic and neutrophilic inflammation. The air spaces are filled by fibrin with occasional inflammatory cells (hematoxylin and eosin; ×200 original magnification).

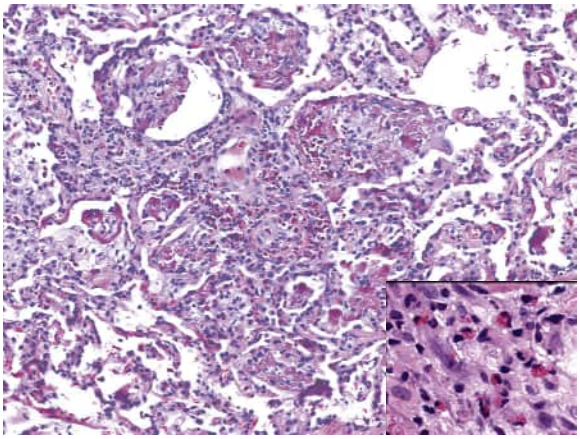

Figure 22.9 Eosinophilic pneumonia. Numerous eosinophils are seen in the fibrin-rich air space exudates and focally within the alveolar septa (hematoxylin and eosin; ×200 original magnification). *Inset,* Eosinophils at high magnification (×400 original magnification).

other inhaled substances, drug- or toxin-induced reactions, systemic hypereosinophilic syndromes, and rare infections (e.g., parasitic).[79,80]

Desquamative Interstitial Pneumonia

Desquamative interstitial pneumonia is characterized by dense alveolar filling with alveolar macrophages (Fig. 22.10). Although the term desquamative interstitial pneumonia is a misnomer because the primary process is neither desquamative nor interstitial, it nevertheless has stuck since first being coined by Liebow in the 1960s. The most common cause is smoking, and therefore desquamative interstitial pneumonia is often discussed in the context of smoking-related lung diseases. Other findings of smoking are often present, including respiratory bronchiolitis (peribronchiolar accumulation of smoker's macrophages), emphysema, and variable alveolar septal fibrosis. Smoker's macrophages characteristically have fine gray-brown and sometimes coarse black pigment in the cytoplasm. Less common causes of desquamative interstitial pneumonia include other inhaled substances,

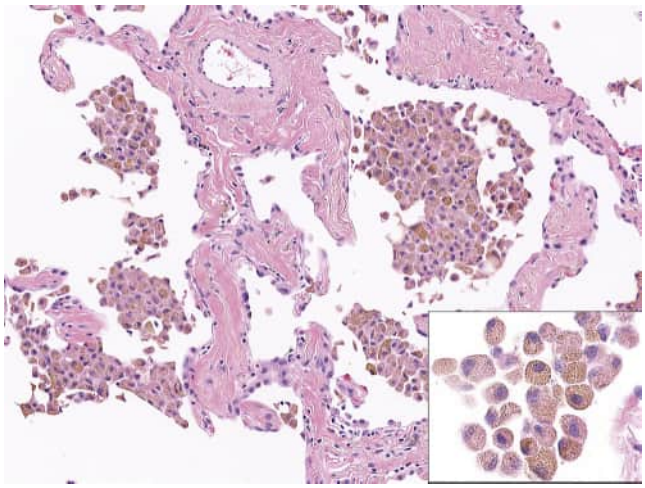

Figure 22.10 Desquamative interstitial pneumonia. The alveolar spaces are filled by large clusters of variably pigmented "smoker's" macrophages. The alveolar septa are thickened by acellular fibrosis, without significant inflammation (hematoxylin and eosin; ×200 original magnification). *Inset,* Smoker's macrophages at high magnification (×400 original magnification).

drug reactions, and rarely autoimmune connective tissue diseases.[81,82]

Pulmonary Alveolar Proteinosis

Pulmonary alveolar proteinosis is characterized by alveolar filling and expansion by granular eosinophilic proteinaceous material. There are frequent acicular (needle-like) cholesterol clefts, rare macrophages, and scattered hyereosinophilic protein globules (Fig. 22.11).[83] The proteinaceous fluid is classically described as periodic acid–Schiff positive, but this staining may be weak to absent in some cases. Electron microscopy is used in some cases but is usually not necessary for diagnosis; it may show extracellular and macrophage accumulation of surfactant with characteristic lamellar bodies.[84,85] The most common cause of pulmonary alveolar proteinosis is acquired antibodies to granulocyte macrophage colony stimulating factor in adults. Rarer causes include genetic deficiencies of granulocyte macrophage colony stimulating factor or surfactant in neonates[86,87] (see also Chapter 98).

IS THERE INTERSTITIAL FIBROSIS?

ILD encompasses many different entities that are characterized predominantly by increased fibrosis (fibrosing interstitial pneumonias), inflammation (cellular interstitial pneumonias), or both. Fibrosing ILD patterns are characterized by accumulation of collagen in the lung interstitium. When classifying these patterns histologically, it is helpful to note the distribution of fibrosis within the pulmonary lobule (Fig. 22.12).

Usual Interstitial Pneumonia

Usual interstitial pneumonia (UIP) is the most common pattern of fibrosing ILD.[88,89] Although its most frequent clinical correlate is idiopathic pulmonary fibrosis, this pattern is also observed in some cases of familial ILD, autoimmune connective tissue disease, chronic *hypersensitivity*

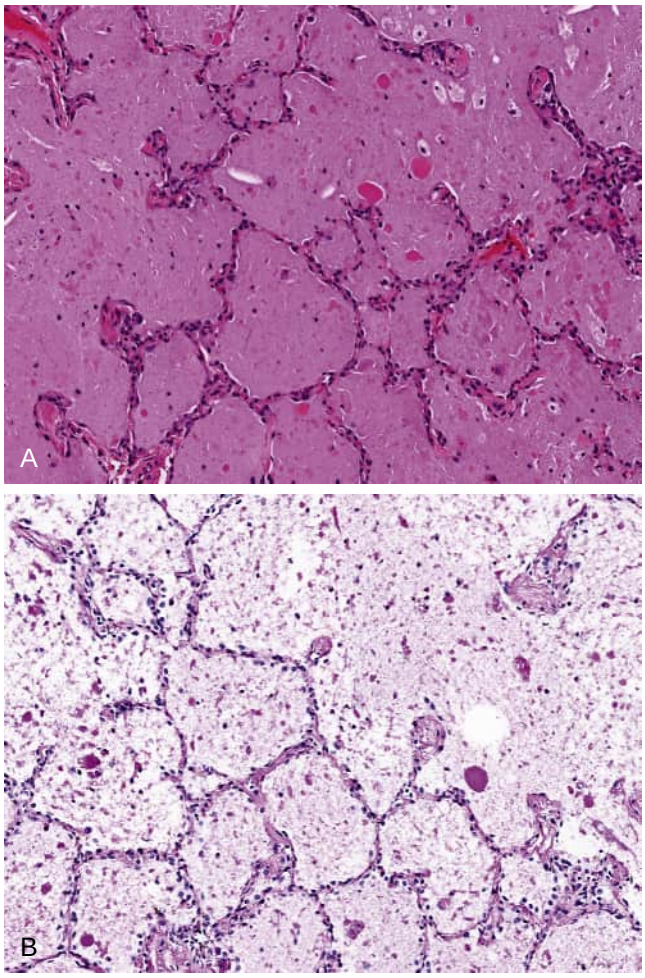

Figure 22.11 Pulmonary alveolar proteinosis. (A) The alveolar spaces are filled by brightly eosinophilic proteinaceous fluid; the alveolar septa appear normal (hematoxylin and eosin; ×200 original magnification). (B) Occasional periodic acid–Schiff (PAS)-positive precipitates (*dark pink*) are seen in the alveolar spaces (PAS; ×200 original magnification).

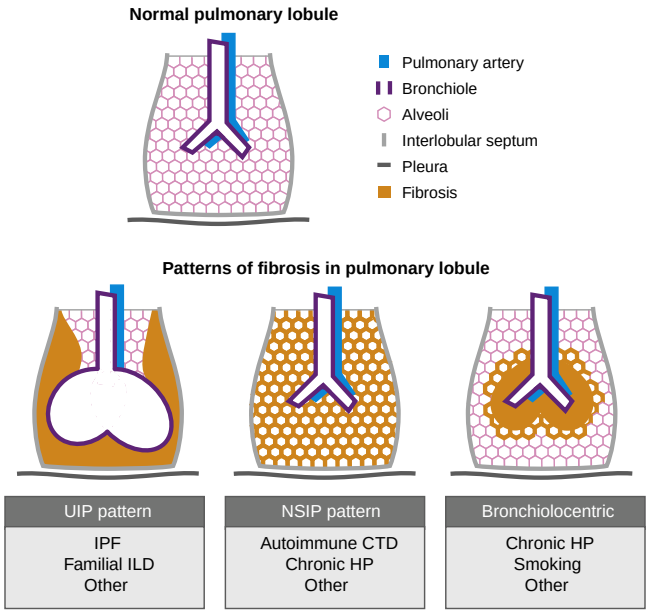

Figure 22.12 Patterns of pulmonary lobule involvement by fibrosis. The distribution of fibrosis in affected pulmonary lobules helps classify fibrosis into three histologic patterns: usual interstitial pneumonia (UIP) pattern (subpleural and interlobular septal fibrosis with microscopic honeycombing), nonspecific interstitial pneumonia (NSIP) pattern (diffuse alveolar septal fibrosis), and bronchiolocentric fibrosis (peribronchiolar fibrosis). Recognition of these patterns aids in formulating a differential diagnosis for the underlying etiology or associated condition. CTD, connective tissue disease; HP, hypersensitivity pneumonitis; ILD, interstitial lung disease; IPF, idiopathic pulmonary fibrosis.

pneumonitis (HP), some pneumoconioses (e.g., asbestosis), and rare drug toxicities (e.g., nitrofurantoin).[90] It is important to distinguish UIP from other patterns because it has the worst prognosis among all fibrosing ILD, independent of the underlying cause.[91,92] Classical high-resolution CT findings of UIP include basilar and subpleural-predominant fibrosis, honeycombing, and traction bronchiectasis. When present, these findings have approximately 90% specificity for UIP, and biopsy is usually deferred. However, in patients with less certain findings on high-resolution CT, surgical biopsy is usually sought for definitive diagnosis and to rule out other causes of ILD.[93]

Histologically, UIP is characterized by fibrosis most notable along the pleura and interlobular septa (periphery of the pulmonary lobules). Affected lobules are replaced by fibrosis from outside in, which eventually leads to cystic dilation of the distal airways surrounded by dense fibrosis. This so-called microscopic honeycombing is most notable in the distal subpleural parenchyma (Fig. 22.13).[94,95] Areas of fibrosis are juxtaposed with areas of normal lung in the more central parenchyma, producing the distinctive feature of spatial heterogeneity. Another feature of UIP is temporal heterogeneity, which refers to the coexistence of old collagenous fibrosis as well as new fibrosis in the form of fibroblast foci. These fibroblast-rich areas are found at the interface of fibrosis with normal lung and are thought to be the sites of active collagen deposition. Fibroblast foci should not be confused with the plugs of granulation tissue in OP. Although both feature numerous fibroblast or myofibroblast-like cells within a loose myxoid matrix, fibroblast foci are located in the interstitium, while plugs of OP develop in the air spaces.

Nonspecific Interstitial Pneumonia

The term *nonspecific interstitial pneumonia* (NSIP) was initially coined to describe a histologic pattern of ILD distinct from UIP, which later was shown to have different epidemiologic and clinical features.[96] Patients with NSIP tend to be younger, are more often female, and overall have a better prognosis compared to those with UIP.[82,97]

The histologic pattern of NSIP is defined by diffuse alveolar septal involvement that lacks the temporal heterogeneity of UIP and instead appears to be more uniform (Fig. 22.14). The alveolar walls are thickened by variable proportions of chronic interstitial inflammation and fibrosis. Although areas of relative accentuation and sparing may be present, the transitions between them are more gradual, and completely normal parenchyma is most often absent. NSIP cases are a spectrum ranging from those dominated by interstitial inflammation and lacking significant fibrosis to those marked by prominent fibrosis. NSIP can be classified into three groups: cellular NSIP (with predominance of interstitial inflammation), cellular and fibrotic NSIP (with a mixture of inflammation and fibrosis), and fibrotic NSIP

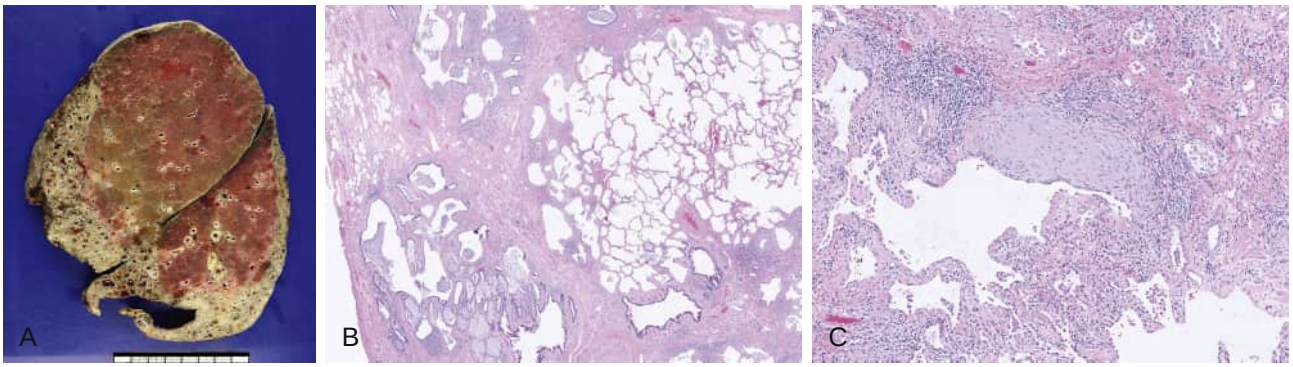

Figure 22.13 Usual interstitial pneumonia. (A) Pneumonectomy specimen from a patient who underwent lung transplantation demonstrates subpleural and lower lobe predominant fibrosis (1 cm scale at bottom). (B) A histologic section from the same specimen shows fibrosis with subpleural and interlobular septal distribution, areas of microscopic honeycombing, and abrupt transition to more central nonfibrotic parenchyma (hematoxylin and eosin [H&E]; ×20 original magnification). (C) A fibroblast focus in an area of fibrosis is seen at a higher magnification (H&E; ×100 original magnification).

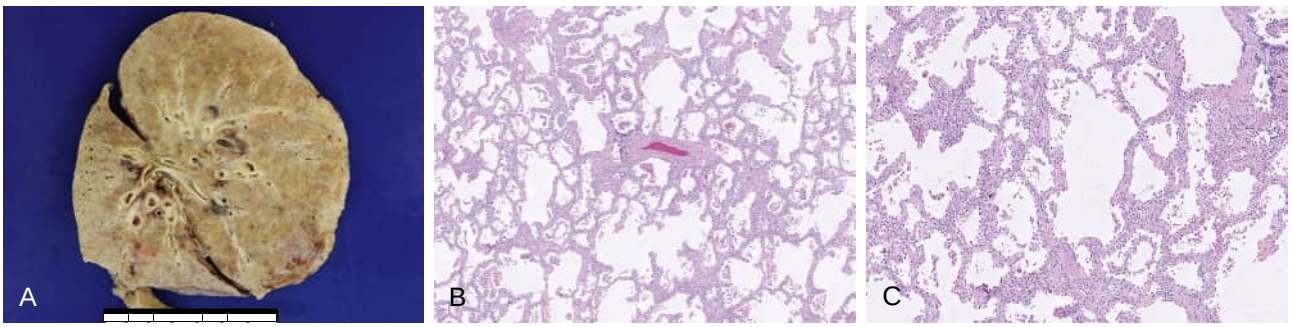

Figure 22.14 Fibrosing nonspecific interstitial pneumonia. (A) Transplant pneumonectomy specimen from a patient with autoimmune connective tissue–associated interstitial lung disease shows diffuse involvement by fibrosis (1 cm scale at bottom). (B) A histologic section from the same specimen shows diffuse widening of the alveolar septa (hematoxylin and eosin [H&E]; ×20 original magnification). (C) At higher magnification, the alveolar septa appear diffusely thickened by fibrosis (fibrosing nonspecific interstitial pneumonia) and contain occasional lymphocytes (H&E; ×100 original magnification).

(with predominance of interstitial fibrosis).[96] As one would predict, NSIP cases with a predominance of fibrosis have more advanced disease, are less responsive to treatment, and have less favorable prognoses compared to those dominated by inflammation.

A significant proportion of the patients with NSIP have identifiable associated conditions (Table 22.8), most importantly autoimmune connective tissue disease, chronic HP, viral or atypical bacterial infections, some immunodeficiency conditions, and rare drug toxicities.[98–101] Several useful histologic clues can aid in the identification of an associated condition.[102] For example, cases of autoimmune connective tissue disease more often show frequent large lymphoid follicles (sometimes with germinal centers) and involvement of other compartments such as pleura and blood vessels. Conversely, cases of chronic HP with NSIP pattern tend to have more prominent bronchiolocentric accentuation of both inflammation and fibrosis; the presence of peribronchiolar interstitial poorly formed granulomas is highly suggestive of this etiology. However, many biopsies with NSIP pattern lack distinct histologic features to implicate a specific cause. In these instances, careful correlation with the clinical features, laboratory findings, and exposure history is recommended and is best accomplished in a multidisciplinary discussion setting.[62,103] Cases without identifiable cause or associated condition are classified clinically as idiopathic NSIP.[104]

Table 22.8 Conditions Associated with Nonspecific Interstitial Pneumonitis Pattern

Autoimmune connective tissue diseases
Chronic hypersensitivity pneumonitis
Infection (e.g., viral or atypical bacterial)
Inherited or acquired immunodeficiency
Drug toxicity
Idiopathic

IS THERE INTERSTITIAL INFLAMMATION?

The distribution of interstitial inflammation can vary from diffuse involvement of the alveolar septa (as in cellular NSIP) to more variable distribution with accentuation around bronchioles, to strictly bronchiolar involvement. If inflammation is associated with interstitial fibrosis, then fibrosing ILD patterns should be the primary focus in the evaluation. On the other hand, if the inflammation is largely restricted to bronchioles, primary patterns of bronchiolitis should be considered.

Cellular Nonspecific Interstitial Pneumonia Versus Lymphocytic Interstitial Pneumonia

As discussed earlier, cellular NSIP refers to a subset of cases with an NSIP pattern in which interstitial inflammation is

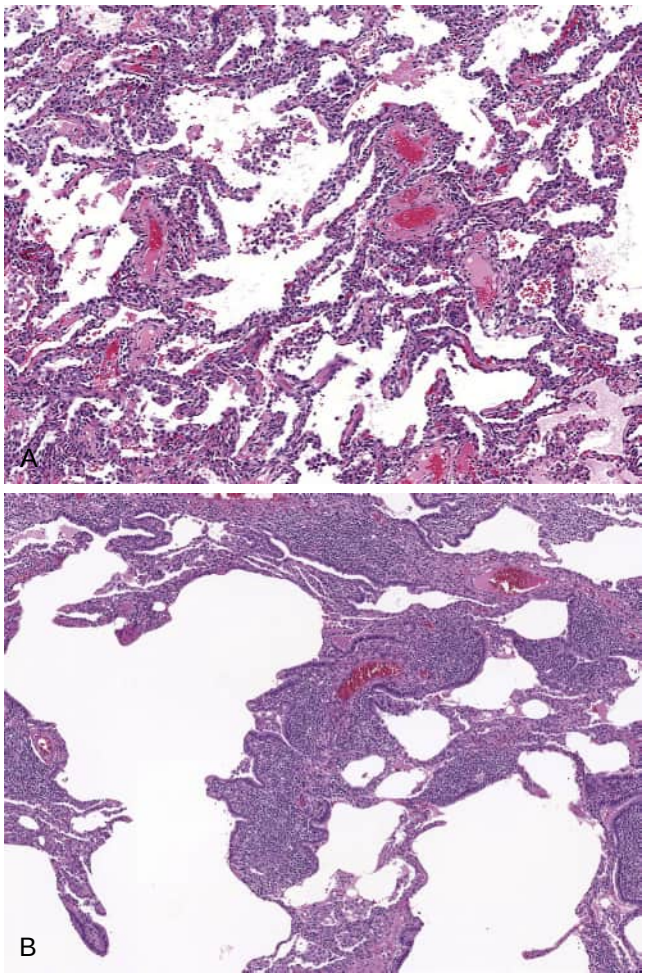

Figure 22.15 Cellular nonspecific interstitial pneumonia and lymphocytic interstitial pneumonia. (A) Cellular nonspecific interstitial pneumonia pattern is characterized by diffuse alveolar septal inflammation, most often composed of lymphocytes and occasional plasma cells, without significant fibrosis (hematoxylin and eosin [H&E]; ×100 original magnification). (B) In lymphocytic interstitial pneumonia pattern, the inflammatory infiltrate is much more prominent, resulting in marked thickening of the alveolar septa and formation of frequent lymphoid follicles (H&E; ×80 original magnification).

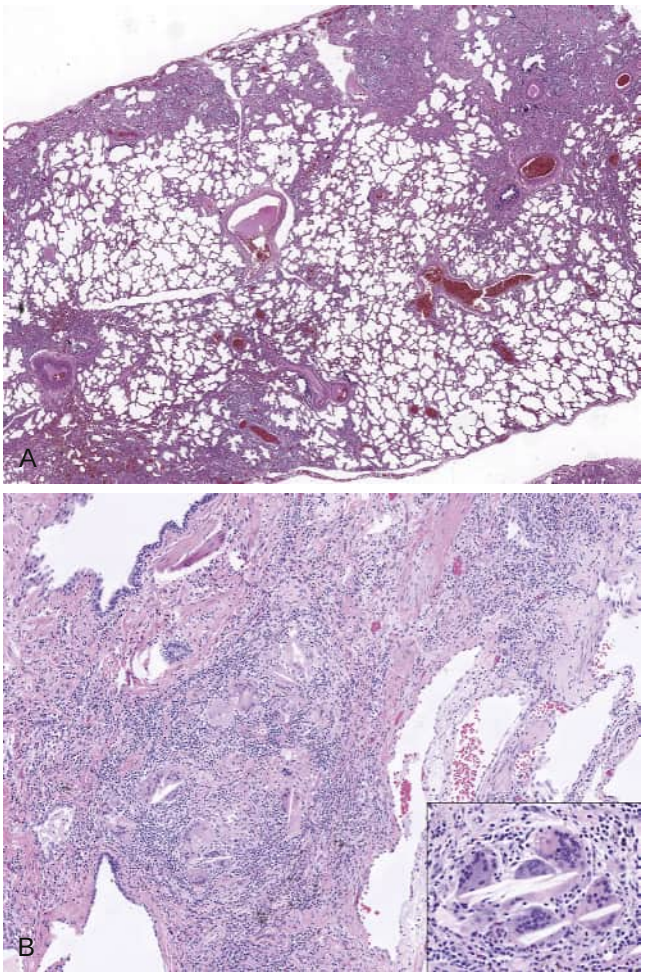

Figure 22.16 Hypersensitivity pneumonitis. (A) A low-magnification view shows a patchy parenchymal involvement with peribronchiolar accentuation (hematoxylin and eosin [H&E]; ×10 original magnification). (B) At higher magnification, peribronchiolar interstitium is expanded by fibrosis, chronic inflammation, and contains several poorly formed granulomas with giant cells and cholesterol clefts (H&E; ×100 original magnification). *Inset,* Poorly formed granuloma at high magnification (×400 original magnification).

present without significant interstitial fibrosis (Fig. 22.15A). These cases tend to represent early or less advanced disease, are more responsive to treatment, and have better long-term prognoses than fibrotic NSIP. However, the clinical differential diagnosis is essentially the same for both NSIP subtypes.[82,96,104]

Lymphocytic interstitial pneumonia is a term reserved for cases that have particularly prominent interstitial inflammation that leads to dramatic widening of the alveolar septa by a lymphocyte-predominant infiltrate (Fig. 22.15B). Some of the alveolar septa become obliterated by the inflammation, which may result in formation of parenchymal cysts (a helpful radiologic correlate of lymphocytic interstitial pneumonia). Frequent lymphoid aggregates, usually with germinal centers, are another feature of lymphocytic interstitial pneumonia. The main differential diagnosis of lymphocytic interstitial pneumonia is autoimmune connective tissue disease or immunodeficiency syndromes (e.g., congenital HIV or common variable immunodeficiency), but rare cases of lymphoma can also present with similar histologic findings.[105–107]

Hypersensitivity Pneumonitis

The inflammatory infiltrates in HP tend to be bronchiolocentric with sparing of more distal lobular parenchyma, particularly early in the disease. However, in more advanced cases, the distribution of inflammation and fibrosis can be difficult to distinguish from fibrotic NSIP. Bronchiolocentric accentuation of inflammation remains a helpful feature, and the presence of poorly formed granulomas is highly suggestive of HP. The HP-type granulomas (Fig. 22.16) are most commonly found in the interstitium surrounding the bronchioles and are composed of epithelioid macrophages and multinucleated giant cells. The giant cells often contain needle-shaped *cholesterol clefts* likely derived from the breakdown of cellular membranes and sometimes dystrophic calcifications called Schaumann bodies.[108–110]

ARE THERE NODULES OR MASSES?

Pathologic processes that manifest as lung nodules or larger masses are sometimes considered together due to

Table 22.9 Histopathologic Entities Characterized by Lung Nodules

Malignancy ■ Solid primary lung or metastatic ■ Hematolymphoid
Infection ■ Granulomas ■ Abscess or necrobiotic nodule ■ Miliary (hematogenous)
Infarct
Pulmonary Langerhans cell histiocytosis
Sarcoidosis
Beryllium lung disease
Vasculitis
Amyloidosis

their characteristic appearance on imaging studies and an overlapping clinical differential diagnosis. However, this group is a collection of very diverse histopathologic entities (Table 22.9). Aside from neoplasms that include both primary lung and metastatic tumors, nodules can arise in multiple infectious processes, pulmonary sarcoidosis, *pulmonary Langerhans cell histiocytosis* (PLCH), and other less common conditions.

Pulmonary Sarcoidosis

The histologic hallmark of sarcoidosis in any organ is the presence of non-necrotizing granulomas.[111,112] In the lung parenchyma, sarcoidal granulomas form nodules that have a characteristic distribution along the lymphatic routes (Fig. 22.17A). This "lymphangitic" distribution of the nodules is apparent both histologically and on high-resolution CT and includes involvement of the bronchovascular bundles, interlobular septa, and the pleura.[113,114] Mediastinal lymph node involvement is also present in most cases. The granulomatous inflammation is associated with variable amounts of fibrosis, which can be very prominent, in some cases leading to the clinical manifestations of an ILD.[115] Unlike most types of ILD that require surgical lung biopsy for diagnosis, transbronchial biopsies are often sufficient for evaluation of sarcoidosis.[116–118]

Sarcoidal granulomas are composed of well-formed rounded aggregates of epithelioid macrophages, occasional multinucleated giant cells, and few scattered lymphocytes (Fig. 22.17B). The granulomas are often numerous and coalesce to form larger aggregates. Early granulomas may show more prominent lymphocytic inflammation without much fibrosis, while more established ones are embedded in collagenous or sclerotic stoma. Importantly, sarcoidal granulomas should lack significant necrosis. If necrosis is detected, an infectious process is much more likely.[111,112]

Pulmonary sarcoidosis continues to be a diagnosis of exclusion requiring careful consideration of other possible etiologies and mimics. No immunohistochemical or molecular testing is currently available to confirm the diagnosis, and therefore the efforts are largely directed towards excluding other causes. Acid-fast and Gomori methenamine silver stains are routinely obtained to exclude mycobacterial and fungal infections, respectively. Careful correlation with the exposure and medication history is helpful in ruling out other mimics such as beryllium lung disease and drug-induced sarcoidal reaction.[112,119]

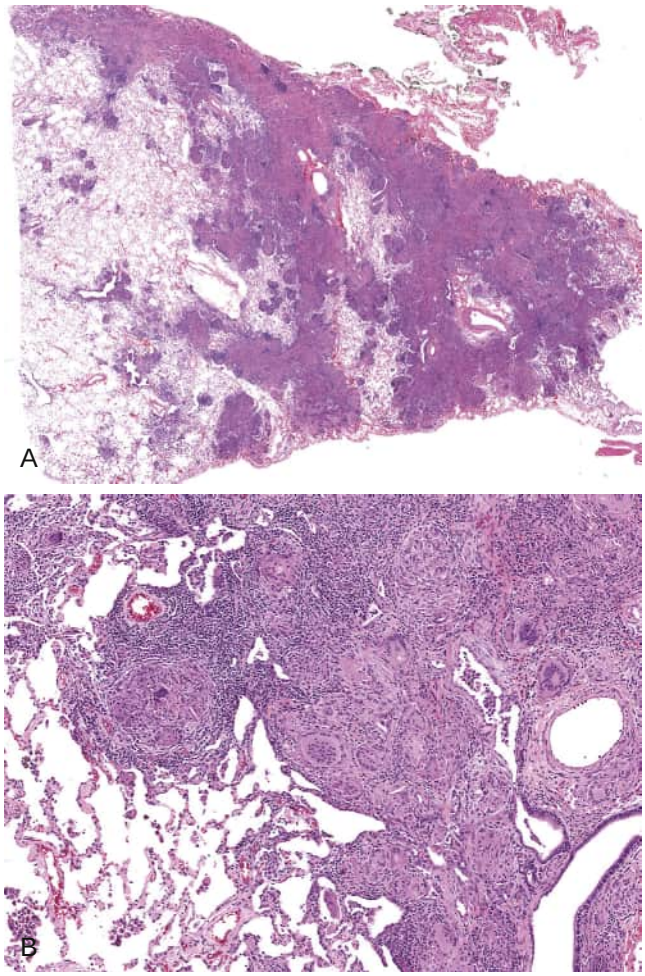

Figure 22.17 Pulmonary sarcoidosis. (A) At low magnification, the perilymphatic distribution of parenchymal nodules is apparent (hematoxylin and eosin [H&E]; ×6 original magnification). (B) The nodules are composed of well-formed granulomas, which are numerous and coalescing; they lack necrosis and are surrounded by fibrosis and chronic inflammation (H&E; ×100 original magnification).

Infectious Granulomas

Numerous infectious pathogens can produce single or multiple granulomas in the lung parenchyma. The most important examples include mycobacterial species such as *Mycobacterium tuberculosis* and *Mycobacterium avium* complex, and fungal species such as *Coccidioides*, *Aspergillus*, *Histoplasma*, *Cryptococcus*, and many others. The histologic appearance of the granulomas and changes in the surrounding lung tissue may vary, but most infectious granulomas show prominent central necrosis (Fig. 22.18). When encountered grossly, the granulomas are often described as caseating, referring to their cheese-like appearance when transected. However, when evaluated histologically, the term necrotizing granuloma is preferred to describe the presence of central necrosis more specifically. Acid-fast and Gomori methenamine silver stains are very helpful in highlighting the microorganisms but, in cases where a pathogen is not readily identified, additional immunohistochemical

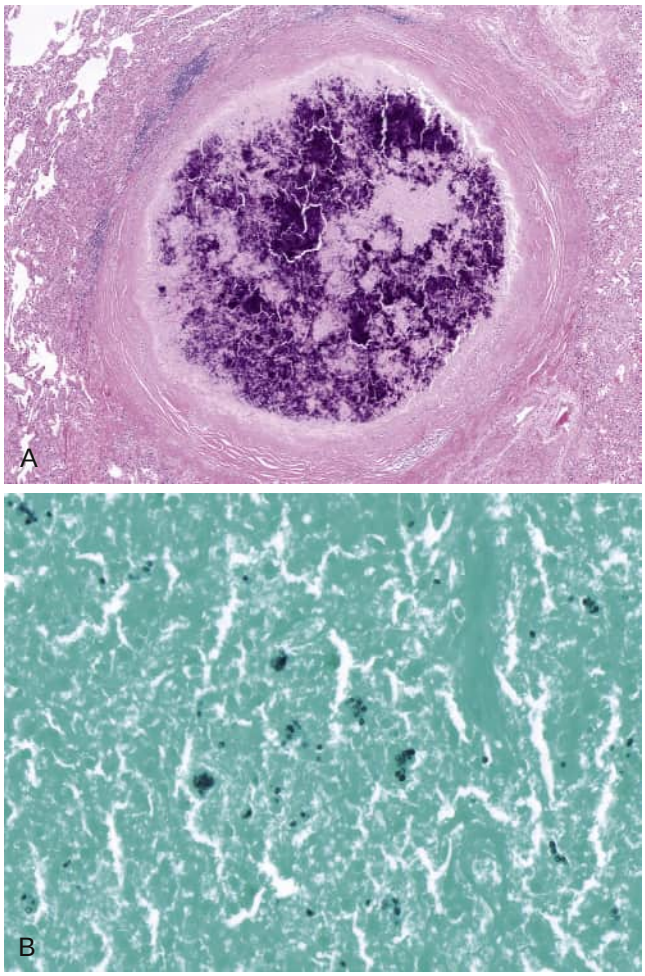

Figure 22.18 Infectious necrotizing granuloma of pulmonary histoplasmosis. (A) This granuloma forms a round solid nodule with a fibrotic rim and a partially calcified necrotic core (hematoxylin and eosin; ×50 original magnification). (B) Gomori methenamine silver stain highlights clusters of *Histoplasma capsulatum* yeast forms in the cytoplasm of macrophages within the necrotic core of the granuloma (×600 original magnification).

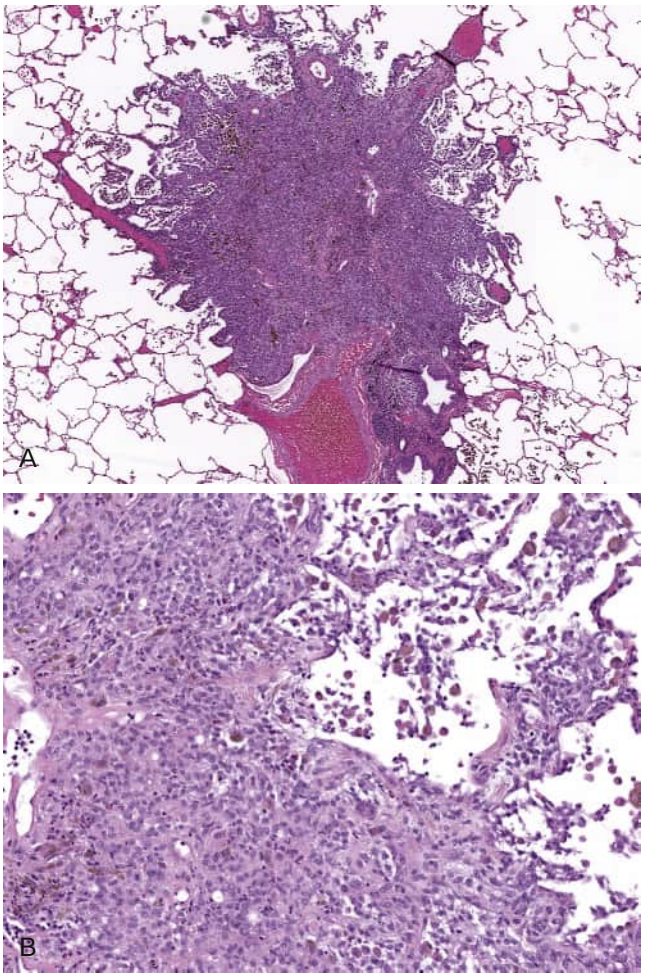

Figure 22.19 Pulmonary Langerhans cell histiocytosis. (A) At low magnification, a peribronchiolar irregularly shaped fibroinflammatory nodule is easily recognized (hematoxylin and eosin [H&E]; ×40 original magnification). (B) The nodule is composed of a cellular proliferation of Langerhans cells, pigmented smoker's macrophages, scattered eosinophils, and associated fibrosis (H&E; ×200 original magnification).

and molecular techniques (e.g., universal bacterial 16S RNA or targeted polymerase chain reaction) can be performed on the FFPE blocks.[120–122]

Pulmonary Langerhans Cell Histiocytosis

PLCH is another process that may show a nodular appearance on imaging. Histologically, it is defined by interstitial aggregates of Langerhans cells (Fig. 22.19), often with associated eosinophils.[123] Most cases are associated with cigarette smoking and resolve with smoking cessation. The lesions can be replaced by fibrosis (forming characteristic stellate scars), particularly with persistent smoking.[124] Destruction of the alveolar walls by the lesions often leads to formation of parenchymal cysts that can be an important radiologic clue to the diagnosis of PLCH.[125] Significant associated fibrosis and pulmonary hypertension can develop in rare cases. Similar lesions have been described in multiple organs, including the skin, bones, lymph nodes, brain, liver, spleen, and other sites. Most of these lesions are now known to be neoplasms of Langerhans cells or their progenitors with frequent genetic alterations involving genes of the MAPK signaling pathway.[126,127] These extrapulmonary cases should be distinguished from those of PLCH. While cases of single-organ bone and skin disease tend to have a benign clinical course, disseminated multiorgan disease carries a poor prognosis[128,129] (see also Chapter 95).

WHAT IF THE LUNG PARENCHYMA LOOKS NORMAL?

While assessment of small airways and blood vessels is part of any surgical biopsy evaluation, it is particularly important not to overlook these compartments when the lung parenchyma appears to be normal. Some of the important entities to consider in this setting are obliterative (constrictive) bronchiolitis and vascular diseases such as pulmonary arterial hypertension and pulmonary veno-occlusive disease. The diagnosis of both small airway and vascular diseases can be challenging due to their patchy distribution in the lung. Special stains, such as Verhoeff-Van Gieson, are often helpful in identifying subtle lesions by highlighting the elastic fibers within the walls of small airways and vessels.[102,130,131]

FUTURE OUTLOOK

Pathology as a field, including thoracic neoplastic and non-neoplastic pathology, is in the process of transformation from strictly morphologically defined entities to those increasingly augmented or even redefined by molecular phenotypes. With the continued evolution of gene sequencing and protein-based detection technologies, we expect to see a shift from larger to smaller, less invasive biopsies and, in some cases, from tissue samples to liquid biopsies, such as from bronchoalveolar lavage fluid or peripheral blood. Continued developments in digital pathology and automated image analysis will reshape ways in which pathologists examine and report their findings and will revolutionize the ways in which practitioners, patients, researchers, and educators access and share pathologic imaging.

Key Points

- Histopathologic evaluation of lung tissue specimens is an integral component in the diagnosis of both neoplastic and non-neoplastic lung diseases.
- Neoplastic lung disease is evaluated either by small biopsies, to provide a histologic and/or molecular diagnosis, or by resections, which may be curative but also confirm and refine the initial histologic diagnosis, determine the pathologic tumor stage, assess resection margins, and evaluate response to preresection therapy (if any).
- Small biopsies are increasingly used for the diagnosis, staging, and molecular typing of lung neoplasms.
- Molecular characterization is used for diagnosis and therapeutic planning for both malignant (e.g., *EGFR*, *BRAF,* and rearrangements of *ALK* and *ROS1)* and nonmalignant diseases (e.g., MAPK signaling pathway in pulmonary Langerhans cell histiocytosis).
- Non-neoplastic lung disease is evaluated by considering whether there is presence of the following pathologic patterns: acute lung injury, consolidation of alveolar spaces, interstitial fibrosis, interstitial inflammation, nodules/masses, or normal lung.
- The histologic diagnosis of most diffuse patterns of interstitial lung disease, particularly usual interstitial pneumonitis, continues to be challenging in small transbronchial biopsies and often requires surgical lung biopsy.
- Correlation of a histologic pattern of interstitial lung disease encountered in a lung biopsy with clinical and radiologic findings is key to identifying the most likely etiology or underlying condition and is best accomplished in a multidisciplinary discussion setting.

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23

ULTRASONOGRAPHY: PRINCIPLES AND BASIC THORACIC AND VASCULAR IMAGING

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INTRODUCTION

Point-of-care ultrasound (POCUS) is routinely used for pulmonary and critical care procedures and diagnostic applications in pulmonary and critical care medicine. POCUS differs from comprehensive ultrasound examinations performed by technicians and interpreted by radiologists or cardiologists in at least two important ways. First, POCUS is often used to answer urgent clinical questions when comprehensive imaging may not be available, practical, or necessary. Second, POCUS is best targeted to specific questions for which a dedicated examination of a single or limited number of structures might be obtained to provide a dichotomous "yes or no" answer. An adept clinician will use POCUS in these settings, understanding that appropriate follow-up may require a traditional comprehensive diagnostic ultrasound study to address nuanced or complex questions.

This chapter covers the principles underlying thoracic ultrasound and basic thoracic and vascular applications. The following chapter, Chapter 24, covers advanced ultrasound, including cardiac evaluation.

PHYSICS OF ULTRASOUND

Humans hear sounds in the frequency range of 20 to 20,000 Hz. Ultrasound imaging uses sound pressure waves generated in a handheld transducer with frequencies of 2 to 15 MHz. In conventional ultrasound transducers, sound waves are generated by the application of an electrical current across a crystal lattice, which induces vibration and sound wave formation, a phenomenon known as the reverse piezoelectric effect.

The transducer is placed on a patient's skin with a layer of conductive gel to facilitate transmission of the sound waves into the body. Waves then travel through the tissues and are reflected back to the transducer by the underlying structures. Returning sound waves are translated by the transducer crystals into electrical signals (i.e., the piezoelectric effect), which then generate images on the ultrasound screen. The depth of structures in the body is computed using the time required for waves ("echoes") to return to the skin surface from these structures.

Acoustic impedance is the resistance to propagation of sound waves. Tissues have variable degrees of resistance to propagation and, as sound waves travel through the body, they encounter differences in acoustic impedance between adjacent tissues. These interfaces cause scatter, refraction, or reflection of sound waves. The cumulative pattern of reflected waves returning to the transducer translates into detailed images of tissue structure. For example, a wave may pass through a layer of subcutaneous fat before reaching the surface of an organ. The difference in acoustic impedance between these tissues results in increased reflection of sound waves at that depth, which appears on the ultrasound screen as the edge of that structure.

Attenuation is the loss of wave energy via absorption by the tissue as the ultrasound waves pass through the body. This results in a decrease in amplitude and the generation of a small amount of heat. Higher frequency (shorter wavelength) waves experience more attenuation and therefore exhibit less tissue penetration.

The focal zone of an ultrasound transducer is the regional distance from the transducer that allows the greatest image resolution for a given frequency and crystal/transducer diameter. On the ultrasound screen, areas proximal or distal to the focal zone are known, respectively, as the near and far fields. In general, the distance from the skin surface to the focal zone is shorter with higher frequency and narrower transducers. Resolution in the focal zone is generally sharper than in near and far fields.

Axial resolution is the ability to distinguish two structures in a line parallel to the course of the ultrasound beam (e.g., a superficial structure overlying a deeper one). Axial resolution is generally greater at higher sound frequencies. *Lateral resolution* is the ability to distinguish two structures aligned perpendicular to the ultrasound beam (side by side) (Fig. 23.1). Lateral resolution is generally better with wider ultrasound transducers. For any frequency or transducer size, lateral resolution is greatest within the focal zone.

In combination, these principles result in a tradeoff for imaging characteristics inherent to ultrasound at higher versus lower frequencies. As a rule, higher frequency, shorter wavelength transducers provide superior imaging of superficial structures, whereas lower frequency, longer wavelength transducers provide better imaging of deeper structures (see Table 23.1 for terminology used in ultrasound and the clinical applications).

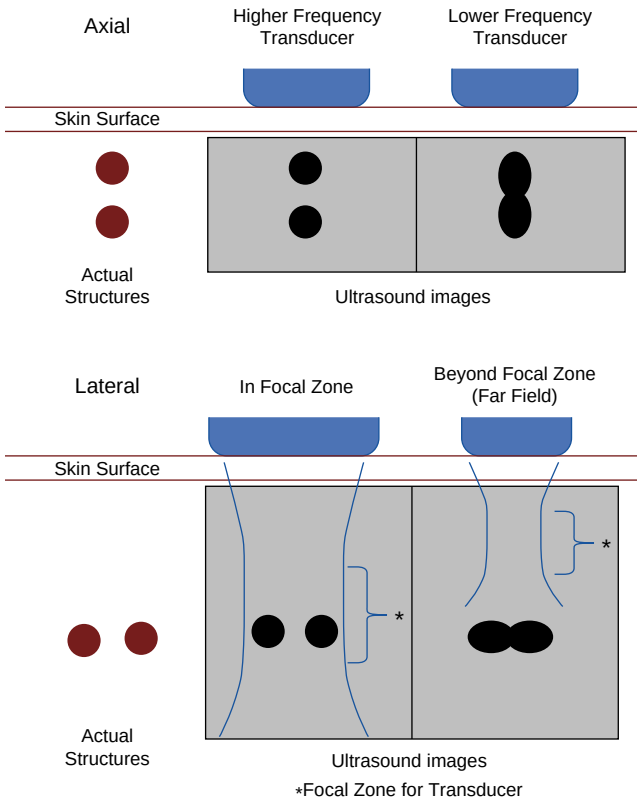

Figure 23.1 Axial and lateral resolution in ultrasound. Axial resolution is the ability to distinguish structures in a line parallel to the ultrasound beam and is greatest with higher frequency transducers. Lateral resolution is a property of the transducer to distinguish structures perpendicular to the axis of the beam and is dependent on frequency and crystal size. Lateral resolution is greatest within the focal zone of the transducer, often the mid-screen zone of the default settings. Distal to the focal zone, it may be more difficult to distinguish neighboring structures.

TRANSDUCER SELECTION

Transducers differ primarily in frequency and mode of crystal excitation. The optimal frequency choice for a given examination is the highest available that also provides the appropriate tissue penetration for the structure of interest. Beyond frequency, the mode of crystal excitation is relevant primarily for cardiac imaging. *Linear* transducers operate by activating crystals in a sequential fashion along the width of the transducer from one side toward to the other. *Phased array* transducers use simultaneous excitation of an array of crystals that span the transducer width to generate multidirectional, overlapping ultrasound beams. This produces *two-dimensional* (2D) imaging that is superior for the evaluation of motion and flow (see "Doppler Imaging" later). A typical configuration for a POCUS machine includes a high-frequency (5–13 MHz) linear transducer for superficial structures and at least one lower frequency (1–8 MHz) transducer for deeper structures. Ideally, for the lower frequency transducers, users will have both a phased array transducer with a small square footprint for cardiac imaging and a linear array with a curved shape to facilitate a wide field of view (*convex* or *curvilinear* transducer) (Fig. 23.2). Transducer selection for specific examinations is discussed later.

Vascular Imaging

Vascular POCUS is most often procedural in nature, to guide peripheral or central vascular access (see "Vascular Imaging" later). A high-frequency (5–13 MHz) linear array transducer provides high-resolution images of superficial structures. This transducer also is used for diagnostic imaging of the deep veins of the lower extremities to evaluate for thrombosis. In contrast, to reach an adequate depth for imaging of the *inferior vena cava* (IVC), a lower frequency (1–5 MHz) phased array or curvilinear transducer is used.

Thoracic Imaging

A phased array (1–5 MHz) transducer is used to examine the heart and great vessels (see Chapter 24). In pulmonary imaging, sliding of the parietal and visceral pleura can be evaluated with either a phased array or high-frequency linear transducer, but for deeper evaluation of pleural effusion or lung parenchyma, a low-frequency transducer, either curvilinear or phased array, is preferred.

Abdominal Imaging

Examining deeper structures, such as the liver, spleen, kidneys, or bladder, is typically performed with a low-frequency (2–5 MHz) curvilinear transducer, with a linear crystal array and a convex shape for a wide field of view. In addition to better penetration, this transducer type has a wider beam that affords greater lateral resolution than narrower phased array transducers.[1]

ULTRASOUND MODES

Two-Dimensional Mode, or B-Mode

The mode most commonly used in POCUS is 2D mode, also called B- (for "brightness") mode, in which pixel brightness is proportional to the intensity of the reflected sound waves, and a 2D image is displayed on the screen. Tissues

Table 23.1 Point-of-Care Ultrasound Terminology

Term	Definition	Clinical Application
PHYSICS OF ULTRASOUND		
Echogenicity	Interpretation of returning sound wave energy by the ultrasound machine that results from differences in tissue impedance, attenuation, reflection, and scatter of sound waves	Tissues are described as isoechoic when similar in intensity or brightness, hyperechoic when brighter than reference, hypoechoic when dimmer, and anechoic when black
Frequency	The physical property of sound waves indicating the time elapsed between wave peaks passing a specific point	Higher frequency, shorter wavelength waves attenuate more quickly in body tissues, so are best for imaging structures close to the skin surface
Focal zone	A property of the beam emitted from the transducer where it is most narrow	Lateral resolution, or the ability to distinguish objects side by side, is best for any transducer within its focal zone
Acoustic impedance	Property of a tissue that influences sound wave propagation, including transmission, reflection of waves, and energy loss over distance	Physical basis for visualizing distinct tissues with ultrasound
Acoustic enhancement	Region of increased echogenicity immediately distal to a tissue with low acoustic impedance relative to surrounding tissues, such as a cyst or blood vessel	May facilitate identification of vessels and cysts compared to soft-tissue masses or nodules, such as lymph nodes
Acoustic shadowing	Region of hypoechoic or anechoic signal immediately distal to a tissue with very high impedance relative to surrounding tissues, such as a bone	Allows identification of bones, calcifications, and certain stones
TRANSDUCER NOMENCLATURE		
Linear transducer	Transducer in which crystals are activated in a sequential, linear fashion along the length of the array. Narrow rectangular footprint	Best for examining static structures throughout the field, or motion within a single vertical line from the transducer
Phased-array transducer	Transducer in which crystals are activated in a simultaneous, sweeping fashion through the field of view	Ideal for detecting motion across an entire field of view, such as in echocardiography
Convex/curvilinear transducer	Transducer in which crystals are activated in a linear fashion but with a curved footprint; usually lower frequency for imaging deeper structures	Creates a wider field of view than linear transducer, used for imaging the abdomen or, less common, the thorax
Transducer indicator	Marker on the ultrasound screen and on the transducer that allows for orientation of image direction	Standard orientation in lung ultrasound is cephalad left on the ultrasound screen
MODES		
B-mode or two-dimensional	"Brightness" mode, or two-dimensional imaging, wherein pixel intensity corresponds to the strength of the returning sound wave energy	The most commonly used modality in point-of-care ultrasound
M-mode	"Motion" mode of imaging, wherein a signal intensity along a single line within the transducer beam is evaluated over time	Often used to detect and measure movement of structures, such as the pleura, diaphragm, vessel walls, or heart structures
KNOBOLOGY		
Depth	Distance from the transducer; shallow structures appear at the top of the ultrasound screen; deeper structures appear lower	Depth is often adjusted so that the region of interest is in the middle of the screen; in procedural ultrasound, depth may be set to maximize the operative field of view for needle passage
Far field/near field	Region distal (far) or proximal (near) to the focal zone within the ultrasound beam, a property of the transducer	Lateral resolution, or the ability to distinguish objects side by side, is poorer for any transducer outside its focal zone
Gain	Factor by which all signals received from the transducer are multiplied as to make an image appear brighter or darker	Makes the image brighter or darker
Time gain compensation	Application of increasing gain inversely proportional to the timing of signal return to the transducer so as to compensate for sound wave attenuation due to distance traveled through the tissues	Used to make a tissue appear homogeneous through the depth of the image, whereas would otherwise appear darker at increasing depth due to ultrasound attenuation

that transmit sound waves well, and therefore generate less reflected sound, appear dark. For example, simple fluid reflects very little sound and therefore appears black (anechoic) on the monitor. This includes vessels, simple pleural effusions, or urine in the bladder. Solid structures that strongly reflect and attenuate sound waves appear as bright, hyperechoic edges with deeper structures obscured by dark anechoic shadows (see "Ultrasound Artifacts" later). All other tissues appear hypoechoic, or as shades of gray, on the ultrasound screen.

M-Mode

M- (for "motion") mode surveys a single point in the ultrasound beam over time. This mode is useful for evaluating changes in size or shape over time, such as change in diameter of the IVC with respiration (Fig. 23.3).

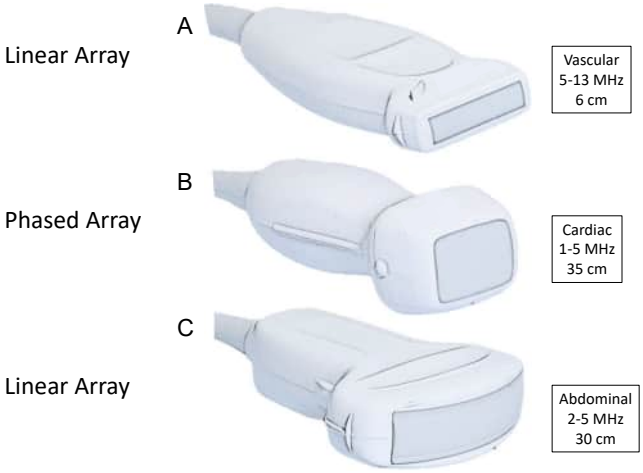

Figure 23.2 Transducers frequently used in point-of-focus ultrasound. A typical configuration for a point-of-focus ultrasound machine includes (A) a high-frequency (5–13 MHz) linear transducer for superficial structures, (B) a phased array transducer with a small square footprint for cardiac imaging, and (C) at least one lower frequency (2–5 MHz) transducer with a curved shape for deeper structures to facilitate a wide field of view (convex or curvilinear transducer).

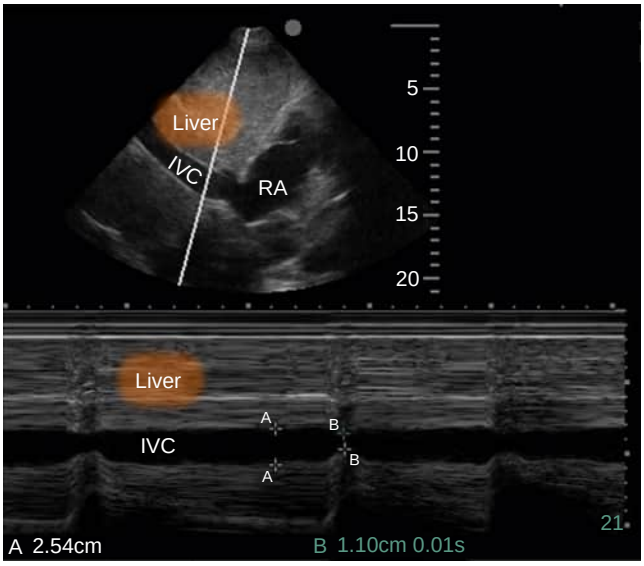

Figure 23.3 Two-dimensional image and associated M-mode. In the two-dimensional image at the top of the screen, a subcostal view of the inferior vena cava (IVC) is seen coursing through the liver to empty into the right atrium (RA). The white M-mode line indicates the location to be followed over time on the bottom half of the screen. The diameter of the IVC changes over time due to respiratory variation, fluctuating between 2.54 cm (measurement A) and 1.10 cm (measurement B).

Doppler Imaging

In POCUS, color flow Doppler is most often used to evaluate blood flow in vessels. Flow toward or away from the transducer is color coded on the ultrasound machine in response to the Doppler shift during 2D imaging (Video 23.1). Spectral Doppler, particularly pulse wave Doppler, is used in POCUS to detect flow velocity over time within a specific region. In this mode a sampling gate is placed over the area of interest and the angle of the gate

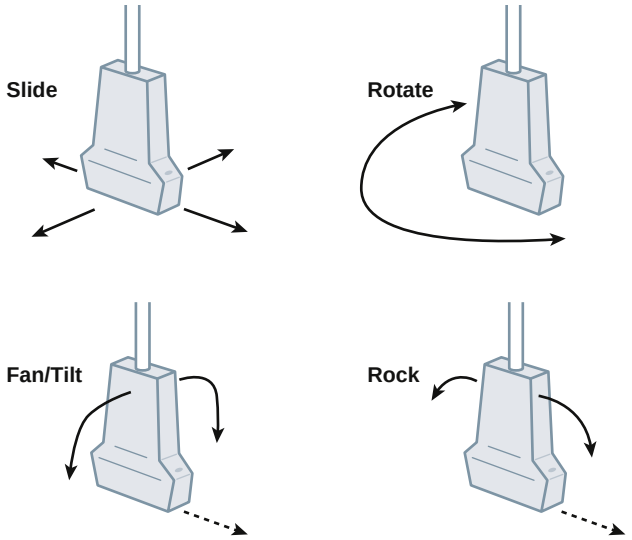

Figure 23.4 Conventional terms for movement within planes of examination in point-of-focus ultrasound. Sliding indicates movements across the body surface. Rotation is movement around a single point on an axis perpendicular to the skin surface. Fanning or tilting is the side-to-side movement of the distal end of the transducer in a vector perpendicular to that of the orientation marker of the transducer (*dashed line*), while maintaining the same position at the skin surface. Rocking is the side-to-side movement of the distal end of the transducer in a vector parallel to that of the orientation indicator (*dashed line*), while maintaining the same position at the skin surface.

adjusted to be parallel with flow. Pulse wave Doppler can be used to examine blood flow velocity over time within a vessel or at the left ventricular outflow tract to estimate cardiac output (see Chapter 24).

KNOBOLOGY

Knobology refers to machine settings that are adjusted by the user to optimize image quality for every ultrasound examination.

Depth, gain (essentially "brightness" control), and orientation are essential knobology functions that are discussed in detail at ExpertConsult.com.

IMAGING PLANES AND TRANSDUCER MOVEMENT

POCUS terminology includes the conventional terms for sagittal, coronal, and transverse body planes, as well as terms for planes specific to the structure being imaged. The *longitudinal* axis refers to imaging with the ultrasound beam parallel to the long axis of the structure. *Cross-sectional* or *short axis* images refer to imaging with the beam perpendicular to the long axis of the structure. Transducer movements are described in Figure 23.4.

When acquiring ultrasound images, it can be helpful to isolate transducer movements to one plane or direction at a time. Transducer movements in the *x*, *y*, and *z* axes are rocking, fanning, and rotation, respectively. *Sliding* refers to translocation of the transducer to a new acoustic window. *Rotation* around the *z*-axis is pivoting the transducer on the current point, such as when maneuvering between the long and short axis of a structure. *Fanning* is moving the

Depth

By convention, the most superficial structures (usually skin and subcutaneous tissue) are at the top of the ultrasound screen, whereas deeper structures, further away from the transducer, appear progressively lower on the screen. The optimal depth for a given examination depends upon the goal of the examination and the patient's body habitus. The operator first selects the appropriate transducer for the examination (see "Transducer Selection" earlier) and then adjusts the depth within the range of that transducer. For most examinations, depth should be set such that the object of interest appears near the center of the screen. Image resolution is generally sharpest mid-screen because it coincides with the focal point of the ultrasound beam on most default machine settings which, on many POCUS machines, is not adjustable. For real-time needle guidance it may be preferable to maximize the operative field by setting the depth such that the target structure appears closer to the bottom of the screen, giving the operator a greater area in which to view the progress of the needle through tissue.

Gain

Gain is the degree of amplification applied to the ultrasound signal returning to the transducer. By adjusting the gain, the operator is adjusting "brightness," or pixel intensity, displayed on the screen for a given ultrasound signal strength. When gain is low, some returning ultrasound signal will drop out altogether, resulting in an overall darker image. When gain is increased, the machine will amplify more of the returning signal, resulting in an overall brighter image. On most machines, gain can be adjusted for the overall image or for various depths individually. This is known as time gain control in reference to the machine's use of time to signal return to calculate depth. Because sound wave energy attenuates over distance, ultrasound machines use time gain compensation to avoid images appearing too dark in the far field. Even the simplest machines do this automatically to some degree and allow the operator to adjust near (superficial) and far (deep) gain independently.

When gain has been set correctly, simple fluid, such as blood, appears anechoic (black) on the screen, whereas highly reflective structures, such as bone or the diaphragm, appear hyperechoic (bright). Ideal gain amplifies enough reflected signal for the operator to distinguish tissue planes, but not so much that excess artifactual signal obscures the structures of interest (eFig. 23.1). Gain settings for a given examination will depend upon the indications for the study, the specific tissues being scanned, and the body habitus of the patient. Fine gain adjustments may be used to highlight specific aspects of visualized anatomy to answer the clinical question at hand.

Orientation

The orientation marker on an ultrasound transducer is usually a palpable dot or ridge or possibly a visual marker. Traditionally, in most diagnostic ultrasound examinations the transducer marker is oriented toward the patient's head or right side, and the corresponding indicator on the ultrasound machine is located on the left side of the screen. The exception to this rule is echocardiography, wherein the transducer marker is oriented as needed to obtain the standard views, and the screen indicator appears on the right of the screen. In POCUS, the sonographer and interpreter are the same, and therefore orientation standards may be less tightly followed. There are standard views in the most commonly acquired POCUS images. For example, when investigating a pleural effusion, it is routine to orient the transducer so that the marker is cephalad, whether in a sagittal or coronal plane. In this way, lung and effusion will appear on the left side of the ultrasound screen, whereas the diaphragm and liver or spleen are seen on the right (eFig. 23.2).

For procedural guidance, it is advised to align the orientation marker on the transducer to the same side as the indicator on the screen to facilitate hand-eye coordination. For example, when standing at the head of the bed to place an ultrasound-guided central venous catheter into a patient's *internal jugular vein* (IJV), the transducer orientation marker points toward the operator's and patient's left. The ultrasound machine is placed next to the bed within the operator's line of sight, with the marker on the left side of the screen. With this arrangement, if the operator sees that the needle is off-target and must redirect, hand movements can easily be adjusted in the appropriate direction.

Measurements

POCUS is often used to answer simple dichotomous questions that do not require precise measurement, such as whether a sliding lung sign is present or absent (see "Pneumothorax" later). When more precise assessment is required, it is often for distance or area, such as in determining the depth or dimensions of a structure or fluid pocket. Even the simplest POCUS machines provide measuring tools in 2D or M-mode settings, either during a live scan or with the image frozen and scrolled to the time frame of interest. Measurements may be relevant to static structures, such as an abscess, or dynamic structures, such as the diameter change of the IVC during respiration (see Chapter 24).

plane of view (ultrasound beam) in either direction perpendicular to the rocking motion. *Rocking* is a tilting motion of the transducer along the plane of view to extend the image in either direction within the same plane.

ULTRASOUND ARTIFACTS

The term *artifact* typically connotes an undesirable effect within a measurement system; however, in POCUS, certain artifacts associated with image generation can provide useful clinical information. Commonly encountered artifacts include acoustic attenuation and enhancement, reverberation, and mirroring.

ACOUSTIC ATTENUATION AND ENHANCEMENT

Acoustic *attenuation,* or shadowing, is a reduction of signal deep to structures that strongly reflect or absorb sound waves. In thoracic ultrasound, ribs have a bright hyperechoic curved surface, casting a shadow that may impede desired imaging of other structures, such as the heart or diaphragm (Fig. 23.5, Video 23.2).

Acoustic *enhancement* is the apparent increase in signal when sound energy is minimally attenuated as it passes through a structure with less impedance than the surrounding tissues. Tissue deep to this area appears hyperechoic, as if a bright "tail" emanates from the low-impedance structure. Acoustic enhancement can be useful to differentiate fluid-filled structures, such as cysts, which can show enhancement, from solid masses, which will not (see Fig. 23.5).

REVERBERATION

Reverberation artifacts are caused by the reflection of sound waves between two locations of tissue interface at which there is a large difference in acoustic impedance. In simple terms, the ultrasound beam "bounces" between two strong reflection points. *A-lines* represent a clinically useful example of this phenomenon. Ultrasound beams leave the transducer and travel through the skin and soft tissues to reach the pleural surface. There is large acoustic impedance difference between soft tissue and aerated lung just deep to this location, so the sound wave is strongly reflected back to the transducer, where it again encounters a strong reflector at the skin-transducer interface. Ultrasound signal reflects repeatedly between these two locations, and each time it returns to the transducer it is interpreted as another tissue plane. Because the time from beam emission to return is interpreted as distance, the ultrasound machine displays an image of equally spaced horizontal lines, representing the distance between skin and pleura (Fig. 23.6, Video 23.3).

A-lines represent either aerated lung deep to the pleura (a normal finding) or air alone (i.e., a pneumothorax). Either will

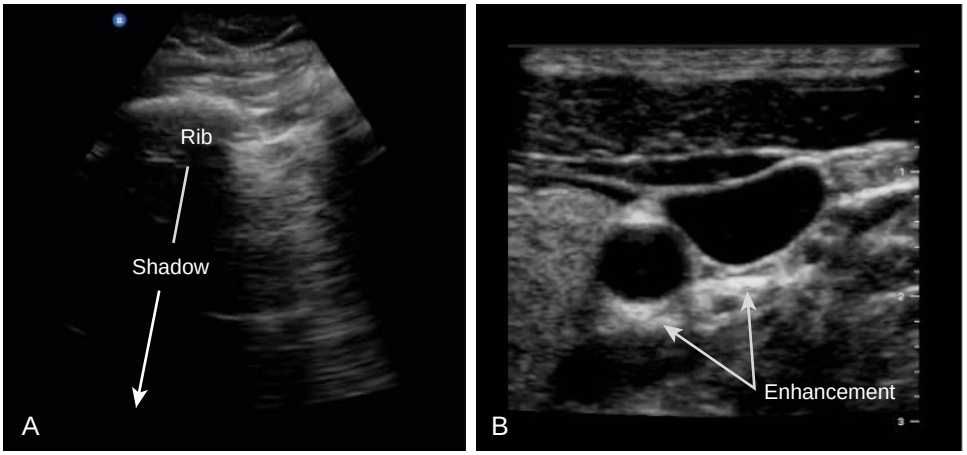

Figure 23.5 Acoustic attenuation and enhancement. (A) Acoustic attenuation, or shadowing, is seen in this thoracic image. The prominent rib casts an acoustic shadow deep to the bony cortex. Also present is a mixed pattern of horizontal A-lines and vertical ray-like B-lines in the intercostal space. (B) Acoustic enhancement is the result of sound energy passing through low-attenuation fluid, such as the blood, in this carotid artery and internal jugular vein, before encountering adjacent tissue with greater impedance. Here the tissues deep to these vessels appear as a hyperechoic "tail."

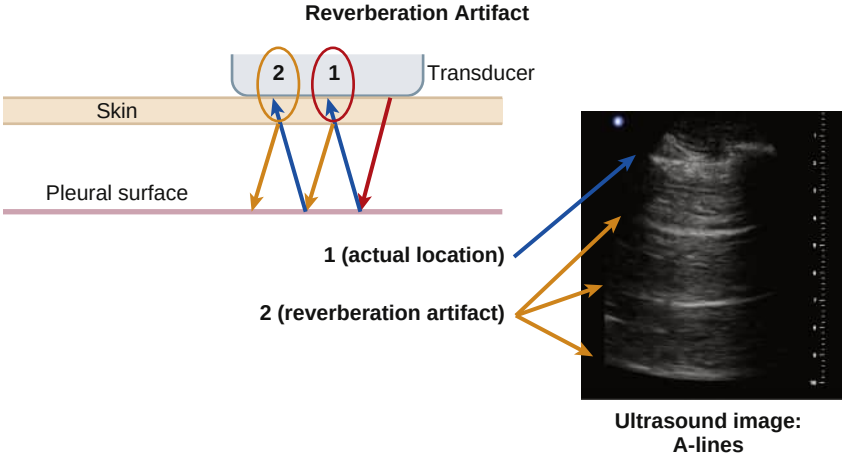

Figure 23.6 Reverberation artifact: A-lines. An ultrasound beam (*red arrow*) leaves the transducer and reaches the pleural surface. The beam is reflected back to the transducer (*blue arrows*) and is interpreted as a bright line corresponding to the depth of the pleura relative to the skin surface (*point 1; blue arrow* on ultrasound image). Some of this reflected energy is, in turn, reflected off the inner surface of the skin (*orange arrows*) and back toward the pleural line. It takes twice as long as the first signal to return to the transducer, so it is interpreted as a second hyperechoic structure exactly twice the depth of the pleural line (*point 2*). This is the first A-line. This pattern repeats with each signal reflecting, generating multiple A-lines at equidistant depths on the ultrasound screen (*orange arrows* on ultrasound image).

produce the same pattern of reflection between skin and pleural surface (see Fig. 23.6). The presence of other normal findings, such as pleural sliding, can exclude pneumothorax and reassure the examiner that the lung parenchyma at the scanned location is normal (see "Pneumothorax" and "Use of Ultrasound in the Clinical Evaluation of Respiratory Failure" later).

B-lines are generated via complex mechanisms but are most easily understood as another type of reverberation artifact. However, B-lines represent abnormal lung. Unlike normal air-filled lung, thickened intralobular septa near the visceral pleura allow ultrasound waves to penetrate into lung tissue. Ultrasound signal will continually reverberate between the abnormal intralobular septa and collapsed or fluid-filled alveoli over small distances within the lobule below the spatial resolution of the ultrasound machine. This leads to a near-continuous stream of signal returning to the transducer that is portrayed on screen as a B-line, an uninterrupted ray of hyperechoic signal emanating from the pleural line[2] (Fig. 23.7, Videos 23.2 and 23.4). B-lines move with pleural sliding, extend to the bottom of the screen, and obliterate any A-lines they cross.

Dependent lung regions in normal patients may have small amounts of intralobular fluid or microatelectasis causing occasional thin B-lines; one or two narrow, discrete B-lines in an intercostal space can be a normal finding if it is not a widespread pattern.[2] With alveolar interstitial processes, such as pulmonary edema, interstitial fibrosis, or early pneumonia, the number of B-lines (both in a given intercostal space and distribution across lung fields) and their width increase (Video 23.5). Differentiating a predominantly A-line or B-line pattern and assessing the focality of any B-lines can be helpful in determining the cause of respiratory impairment in the acute setting (see "Use of Ultrasound in the Clinical Evaluation of Respiratory Failure" later).

MIRRORING

Mirroring artifacts may be seen in thoracic ultrasound, typically when a field of view captures structures immediately above and below the diaphragm. It is important to recognize this artifact so that "mirrored" images of abdominal structures that appear to lie superior to the diaphragm are not confused for abnormal lung tissue (Fig. 23.8).

ARTIFACTS AND IMAGE PROCESSING FEATURES

Many bedside ultrasound machines use imaging processing software that can influence the appearance of images and artifacts.[3] Tissue harmonic imaging is essentially a filter that limits certain reverberation artifacts, improves lateral resolution, and decreases beam thickness. Decreased beam slice thickness reduces speckle artifact (bright dots throughout the image) and increases acoustic enhancement, enhancing the appearance of some artifacts that are useful in thoracic ultrasound, such as B-lines.[4] Other features, such as image compounding via spatial compound imaging, reduce B-lines.[1] A detailed discussion is beyond the scope of this chapter, but POCUS providers should be familiar with these features on the machines used in practice and their impact on the obtained images.

THORACIC ULTRASOUND

NORMAL PLEURA AND LUNG

By using 2D imaging with the ultrasound transducer oriented cephalad-caudad, the pleura is visualized as a hyperechoic line in the intercostal space just deep to the ribs. When the two pleural layers are normally apposed, the movement of visceral pleura against the relatively stationary parietal pleura creates a shimmering effect on the ultrasound screen. This is the pleural "sliding" or "gliding"

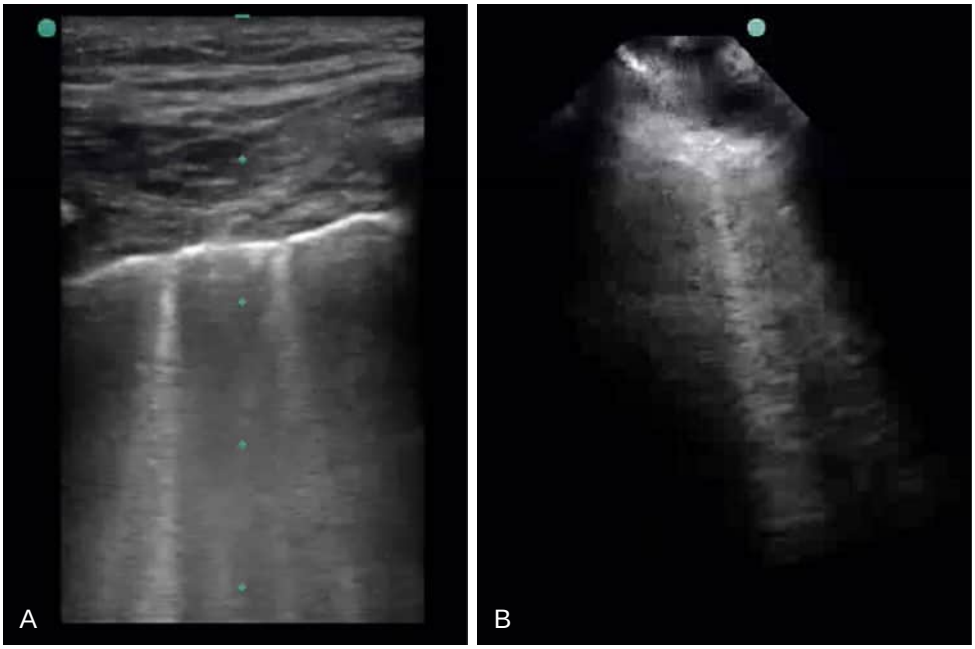

Figure 23.7 B-lines. B-lines are a type of reverberation artifact, as seen with a linear transducer (A) and phased array transducer (B). Pleura and B-lines often appear less distinct with the lower frequency, phased array transducer (B), but their recognition is the same: B-lines are hyperechoic vertical rays that extend from the pleural line all the way to the bottom of the ultrasound screen, obliterating any A-lines along the path.

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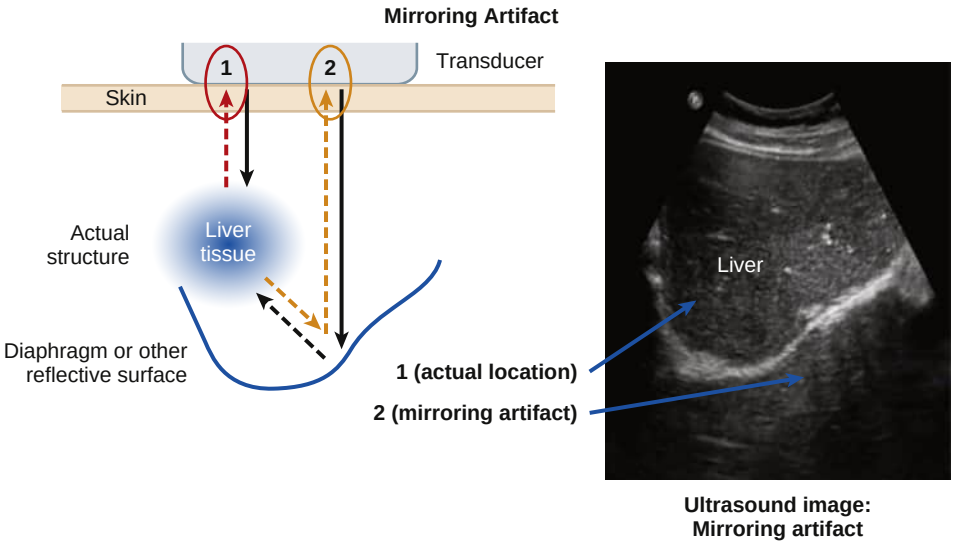

Figure 23.8 Mirroring. Mirroring is an ultrasound artifact in which duplicate structures are seen on either side of a curved, highly reflective surface. Some ultrasound waves travel to and from a structure along a direct path, reflecting off the structure (*dashed red line*) to produce an image corresponding to the depth of the structure (*point 1*). At the same time, sound wave energy from a different part of the transducer will reflect off the reflective surface at an angle, where the waves are directed to the structure (*dashed black line*) and back again (*dashed orange line*) to the reflector and then the transducer (*point 2*). The machine assumes returning echoes have traveled a direct path, and therefore, because these waves took longer to return than the direct echoes, they are interpreted as representing structures deep to the reflector. A common example in thoracic imaging is the appearance of hepatic structures both above and below the diaphragm when imaging from the abdomen. Mirroring can be mitigated by decreasing gain.

sign (also called lung sliding) (Video 23.6). Below the pleural line, normal lung is not visible, because it is fully aerated. Instead, an A-line reverberation pattern is seen on the ultrasound screen, as described earlier. In M-mode imaging of normal lung, the linear pattern seen with stationary subcutaneous tissues is interrupted at the pleural level due to pleural sliding, creating an appearance likened to lines of waves at the top of the screen meeting a sandy beach below the pleural line (the "seashore" sign; see below). Normal and abnormal ultrasound findings are listed in Table 23.2.

PNEUMOTHORAX

Because the appearance of pleural sliding represents the apposition of both pleural layers, this sign effectively excludes the presence of a pneumothorax at the imaged location.[5,6] The absence of sliding suggests either that the pleural layers are no longer in apposition at the imaged location, as seen in pneumothorax or pleural effusion, or that the pleural layers are not moving relative to each other, as seen in apnea or pleural adhesions (Video 23.7).

M-mode images may supplement B-mode evaluation of pleural sliding. In M-mode, stationary tissue has a uniform linear appearance over time. This means that the soft tissues of the chest wall create an image with a uniform linear pattern. Normally, this linear pattern is interrupted at the pleural level due to pleural sliding, creating the seashore sign as just described[7] (Fig. 23.9A). When pleural movement is absent, as in pneumothorax, apnea, or pleural adhesions, this linear pattern extends from the top to the bottom of the screen as a result of A-line reverberation artifact beyond the parietal pleura (i.e., a series of horizontal lines throughout the depth of the ultrasound screen), an appearance known as the "bar code" or "stratosphere" sign (see Fig. 23.9B).

Although the presence of pleural sliding excludes pneumothorax at the imaged location, a lack of sliding does not by itself confirm a diagnosis of pneumothorax because there may be alternative explanations for its absence.[8] When sliding is absent, POCUS providers can exclude pneumothorax by identifying other findings suggesting the pleural layers are in apposition. For example, the presence of B-lines indicates there is abnormal lung tissue immediately below the pleural line (see "B-Lines" earlier).[3,5,8,9] Similarly, a *lung pulse* represents the transmission of cardiac pulsations through the lung parenchyma and also indicates that lung is immediately underneath the pleura[10,11] (Video 23.8).

Although the absence of pleural sliding is not specific for pneumothorax, a "lung point" is highly suggestive of this diagnosis.[12] This finding has the appearance of sliding on one side of the ultrasound image and an absence of sliding on the other side, where the lung has fallen away from the parietal pleura. A lung point therefore represents the edge of the pneumothorax[13] (Video 23.9). The transition point from presence to absence of sliding moves with breathing. Identification of a lung point at multiple locations can allow for estimation of pneumothorax size.[14]

In practical terms, ultrasound is most easily used to exclude pneumothorax at a given location by confirming the presence of pleural sliding. Using ultrasound to diagnose pneumothorax is a more complex multistep process (Fig. 23.10). The clinical context is important in deciding how to act upon the finding of absent pleural sliding, especially if the lung point cannot be identified. For example, the pretest probability that this represents a pneumothorax is much higher in a trauma patient compared to one without

Table 23.2 Common Ultrasound Findings in Thoracic Imaging

Term	Definition	Clinical Interpretation
PLEURA		
Pleural sliding (i.e., lung sliding)	Appearance of movement in the horizontal direction along the pleural line in thoracic ultrasound.	Results from the movement of visceral pleura against the relatively stationary parietal pleura. Indicates that the two pleural layers are apposed (i.e., pneumothorax is not present).
Seashore sign	M-mode finding of normal lung and pleura in thoracic ultrasound.	M-mode correlate of pleural sliding. Indicates normal apposed pleura.
Stratosphere sign	M-mode finding in pneumothorax with exclusively horizontal lines through the field of view.	M-mode correlate of absent pleural sliding and A-line reverberation pattern. Consistent with, although not diagnostic of, pneumothorax.
Lung point	A transition involving the appearance of sliding in part of the field of view and absence of sliding in an adjacent area.	Represents the point at which inflated lung contacts the visceral pleura at the edge of a pneumothorax. Has high specificity for pneumothorax.
LINE ARTIFACTS		
A-lines	Reverberation artifact in which ultrasound beams "bounce" between two strong reflectors. Repeated signal return is interpreted by the machine as multiple equidistant structures deep to the reflector.	Seen at the interface of tissues with markedly different impedance, in thoracic ultrasound this refers to signal reverberation between the skin surface and pleura, resulting in a pattern of repeating horizontal A-lines deep to the pleural line. Present in normal lung and with pneumothorax.
B-lines	Continuous, long vertical lines that appear to move with the pleura that result primarily from reverberation artifacts near the lung surface.	Indicates lung tissue is present beyond the pleura, and is not fully aerated. B-lines increase in number and width with increased septal thickness or alveolar filling as in interstitial lung diseases, early pneumonia, pulmonary edema, and other conditions.
OTHER ARTIFACTS		
Mirroring	Interpretation by the ultrasound machine of returning sound wave signals as two images instead of one due to alternate paths of sound wave reflections returning to the transducer.	Commonly seen with the liver and spleen adjacent to the diaphragm, wherein these organs may appear both above and below the diaphragm due to its reflective properties and the limited returning signal from the lung.
Shred or fractal sign	An irregular linear interface between collapsed or consolidated lung and aerated lung within a lobe.	Diagnostic of partially collapsed or consolidated lung.

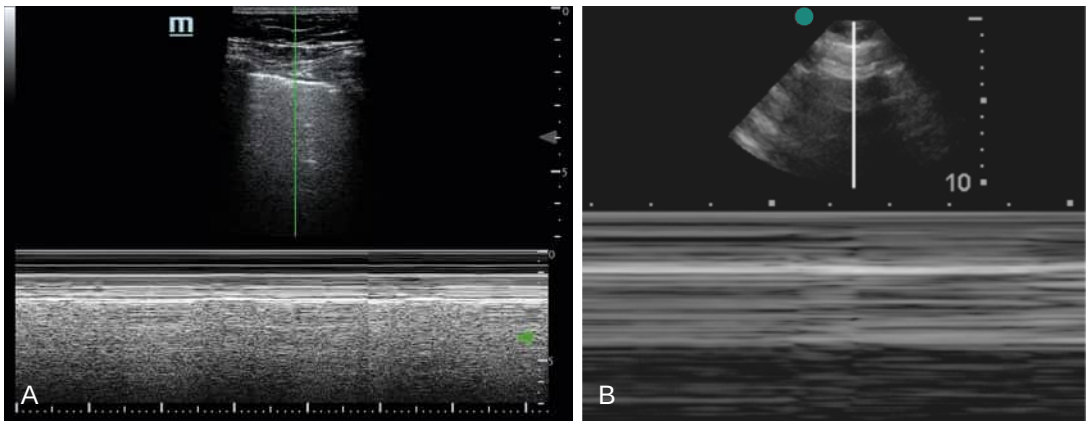

Figure 23.9 M-mode appearances of pleural sliding: normal and absent. (A) Normal pleural sliding in M-mode: "seashore" sign. Immobile soft-tissue structures of the chest wall appear as horizontal lines at the top of the image, whereas sliding at the pleural surface creates a white noise pattern lower down, in the far field. (B) Absent pleural sliding: "stratosphere sign." In comparison, when the visceral parietal pleura layers are not in apposition (as in a pneumothorax) or are affixed together (as after a pleurodesis), the M-mode panel will demonstrate a lack of movement at all depths, appearing as fixed lines in a "bar code" or "stratosphere" sign.

that history. Overall, ultrasound has been shown to have a sensitivity of 79–91% for the diagnosis of pneumothorax in meta-analyses, performing considerably better than portable chest radiographs, which have a sensitivity of 28–75%.[15–19] These studies noted that the test performance characteristics of ultrasound in the diagnosis of pneumothorax are operator dependent.

PLEURAL EFFUSION AND THORACENTESIS

Simple pleural fluid appears as an anechoic (black) space between the parietal and visceral pleura. On 2D imaging, atelectatic lung may be visible as hypoechoic tissue, often triangular in shape, moving within the pleural fluid (Videos 23.10 and 23.11). In M-mode, the respiratory motion of

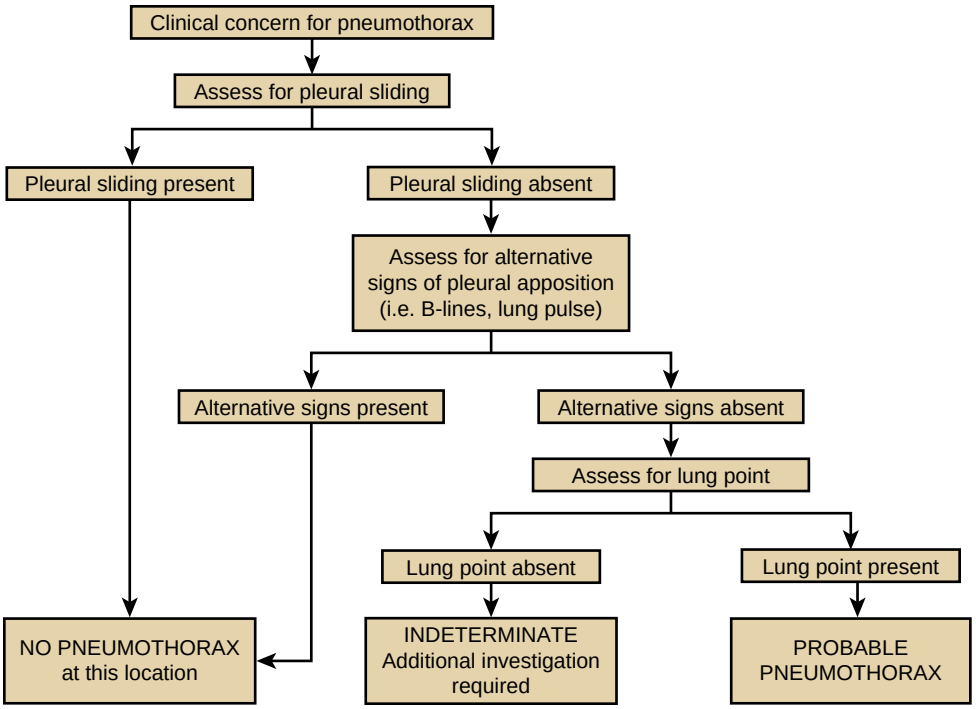

Figure 23.10 Sample algorithm for evaluation of suspected pneumothorax using ultrasound. The presence of pleural sliding rules out this diagnosis at the scanned location, but its absence is not confirmatory of that diagnosis. When pleural sliding is absent, one can look for alternative findings to suggest pleural apposition, such as B-lines or a lung pulse. Absent these, finding a lung point is highly suggestive of a pneumothorax; otherwise the examination is indeterminate at that location. As shown in this algorithm, it is easier to use ultrasound to exclude a pneumothorax than to make the diagnosis.

visceral pleura relative to parietal pleura creates an undulating pattern referred to as the "sinusoid" sign.[20] Pleural fluid should be distinguished from ascites by confirming that the anechoic space lies superior to the diaphragm.[21] In the absence of pleural effusion, aerated lung lies directly cephalad to the diaphragm and liver or spleen and will descend with respiration to obscure the view of these structures; a normal finding known as the "curtain" sign (Video 23.12).

Ultrasonography is more sensitive than chest radiograph but less sensitive than *computed tomography* (CT) for detecting pleural effusion.[22,23] Pleural effusion volume may be estimated using several formulas, the simplest of which involves multiplying the distance between the pleural surfaces by a constant.[24,25] Estimates are likely more accurate when the patient is upright.

The sonographic appearance of pleural fluid can help characterize the nature of an effusion; ultrasound is superior to CT for characterizing the internal structure of pleural effusions and may be more useful for following evolution over time.[26,27] Echogenic material within an effusion may indicate septations in a complex exudative process[28,29] (Videos 23.13 and 23.14). The presence of septations suggests that the fluid may be loculated and may require a different management approach than would simple pleural effusions[30,31] (Video 23.15). Pleural thickening of more than 3 mm also suggests an exudative effusion.[28,29]

Ultrasound guidance improves the success rate and safety of thoracentesis.[32,33] *Static guidance* refers to preprocedure imaging to mark the insertion site, ideally immediately before and with the patient in the same position as during the procedure. *Dynamic guidance* is used to direct needle movement in real time. In either technique, the needle insertion site should be selected to maximize the depth of pleural fluid, avoid lung and other structures, and allow the needle to pass over the top of a rib to avoid the intercostal neurovascular bundle. The sonographer should note the limits of downward excursion of the lung and upward excursion of the diaphragm during respiration to avoid injury to this structure. If using static guidance, the operator should hold the transducer at the anticipated angle of needle insertion and note the distance from skin to pleural fluid and the depth of pleural fluid. The depth of fluid indicating a safe volume for thoracentesis depends on the skill level of the operator and the patient's clinical circumstances. British Thoracic Society guidelines suggest a minimum of 10 mm of pleural fluid depth, although other authors suggest 20 mm.[34,35] Dynamic guidance may be required for very small or loculated pleural effusions and should be performed by operators with appropriate experience.

The addition of color Doppler imaging to determine the location and course of the intercostal artery may reduce the risk of bleeding complications with thoracentesis.[36,37] A high-frequency linear array transducer is used to scan the anticipated needle course to identify any aberrant vessels within the intercostal space. As compared with CT imaging, POCUS can rule out such a vessel with a sensitivity of 0.86.[36]

PLEURA AND PLEURAL BIOPSY

Normal pleura is a thin hyperechoic line on ultrasound. Pleural irregularities may be seen in areas of inflammation, such as acute respiratory disease syndrome or pneumonia.[38,39] Pleural thickening, however, has a different significance. Pleural thickening has been defined as a focal lesion greater than 3 mm in width arising from either pleural surface.[40] Thickened pleura is typically hypoechoic and may be difficult to distinguish from pleural fluid. Because respiratory or cardiac motion will be transmitted to pleural fluid, but not to pleural thickening, the presence of a Doppler

color signal may help to differentiate the two.[41] In the presence of a pleural effusion, the findings of pleural thickening greater than 1 cm, pleural nodularity, or diaphragmatic thickening greater than 7 mm all suggest the presence of malignancy[42] (Video 23.16).

Thoracoscopy is increasingly considered the gold standard for pleural biopsies but is not universally available. Closed pleural biopsy is the traditional alternative, and the widespread availability of ultrasound has improved the diagnostic yield and safety of this approach. Because it is a blind procedure, closed pleural biopsy is typically only performed in the presence of at least a moderate effusion or pneumothorax to minimize the risk of lung injury, with a diagnostic yield of less than 60% for pleural malignancy and 80–90% for tuberculous pleural effusion.[43,44] The use of ultrasound to guide the location of closed pleural biopsies to thickened areas can increase the yield for pleural malignancy and may allow performance even in the absence of a large pleural effusion.[45–47]

LUNG PARENCHYMA

Ultrasound evaluation of the lung can be a useful addition to the physical examination in the urgent evaluation of dyspnea and respiratory failure to aid in diagnostic and therapeutic decision making.[48,49] Imaging findings from multiple locations in both lungs should be interpreted together rather than relying on a single lung image. Key parenchymal findings include artifact patterns, such as B-lines, and abnormalities within the lung parenchyma, including consolidation and air bronchograms.

B-Lines

The appearance and generation of B-line artifact were described earlier. One or two individual B-lines may be seen in an intercostal space of a normal lung, particularly in more dependent regions. However, if multiple scanned locations demonstrate this pattern, it may represent pathology. As parenchyma becomes increasingly abnormal with interstitial thickening or alveolar filling, B-lines become more numerous, widen, and may coalesce into broad beams extending from the pleural line (see Video 23.5). B-lines correlate with extravascular lung water and can be quantified to follow dynamic changes, such as increases in pulmonary edema.[50,51] Of importance, B-lines are not specific to a single diagnosis; early pneumonia, pulmonary edema, interstitial fibrosis, or acute respiratory disease syndrome will all cause B-line artifacts. The term *alveolar interstitial syndrome* originally described a nonspecific chest radiograph finding of alveolar filling and interstitial thickening that correlated well with the presence of B-lines, and this term is similarly used by point-of-care sonographers.[2] Clinicians must interpret B-line patterns in light of the full clinical context, including history, physical examination, and additional studies, such as echocardiography, to make a clinical diagnosis.

Consolidation

When B-lines are seen, there is at least some air in the lung. However, when air spaces become completely fluid filled (consolidated) or degassed (atelectasis), the lung is easily penetrable to ultrasound and appears as a solid organ with a similar echogenic texture as the liver. It is therefore described as "hepatized" on ultrasound. Air bronchograms may be visible as branching shapes of hyperechoic signal that move with respiration (Video 23.17). In the absence of any aerated lung, B-lines are not seen.

At the interface between normally aerated lung and an area of dense consolidation or atelectasis, there may be a transition zone of partially air-filled lung. This area is sometimes visualized as a "fractal" or "shred" sign: an irregular hyperechoic border with B-lines emanating from it. This finding may be seen in pneumonia or atelectasis (Video 23.18).

DIAPHRAGM

The diaphragm is best imaged with a high-frequency linear transducer at the point of diaphragm apposition with the chest wall. This is typically at approximately the tenth rib interspace along the midaxillary line. The diaphragm appears as two hyperechoic parallel lines deep to the ribs and intercostal muscles. The diaphragm thickens during inspiration from 1.6 to 2.9 mm at functional residual capacity to approximately 4.5 mm at total lung capacity[52,53] (Video 23.19). Paralyzed hemidiaphragms are thinner at rest, demonstrate little change during inspiration, and may move paradoxically cephalad with inhalation.[54] The contralateral working hemidiaphragm typically thickens even more than in normal subjects.

Increased diaphragm thickness during inspiration correlates with the pressure generated during a maximal inspiratory pressure maneuver in normal subjects and with respiratory effort in ventilated patients.[52,55] Diaphragm thickening and excursion, particularly in combination with other measures of readiness, has been shown to improve prediction of successful extubation in some studies[56–58] but not in others.[59]

In patients with neuromuscular disease, diaphragm thickness on inspiration correlates closely with other measures of respiratory muscle strength. In patients with amyotrophic lateral sclerosis, diaphragm thickening correlated with forced vital capacity, maximal inspiratory pressure, and sniff nasal inspiratory pressure.[60] Decreased diaphragm thickening, measured as a fraction of the resting thickness, may predict the need for noninvasive ventilation in patients with amyotrophic lateral sclerosis, performing similarly to measurements of forced vital capacity.[61]

USE OF ULTRASOUND IN THE CLINICAL EVALUATION OF ACUTE RESPIRATORY FAILURE

Diagnostic POCUS may be used to answer isolated questions or can be applied using a systematic approach to aid in the assessment of seriously ill patients with a broad differential diagnosis. POCUS does not replace a careful physical examination but can greatly augment the traditional bedside evaluation to narrow the differential diagnosis or confirm a specific diagnosis and direct further evaluation and urgent clinical intervention.

Several algorithmic approaches have been developed to evaluate patients with acute respiratory failure alone

or as part of multisystem critical illness. The *Bedside Lung Ultrasound in Emergency* (BLUE) protocol is one of the best-known examples.[48,62] This and other published protocols use the recognition of thoracic ultrasound patterns at a standard set of examination points on the thorax to determine likely clinical diagnoses (Fig. 23.11). A thorough thoracic ultrasound protocol can be performed with a lower frequency (1–8 MHz) phased array or linear transducer that allows imaging depths up to 17 cm, but some providers also choose to use a higher frequency linear transducer for better resolution of the pleura. Published protocols and consensus guidelines call for a minimum of three or four scanned intercostal spaces per hemithorax.[63] The BLUE protocol includes one upper anterior location just caudal to the clavicle in the mid-clavicular line, one anterolateral location at the fifth intercostal space between the mid-clavicular and anterior axillary lines, and a third dependent location as far posterior as possible.

At each examination point, the operator first identifies the pleural line and examines for sliding. If absent, additional evidence will be sought to evaluate for pneumothorax (see "Pneumothorax" earlier and Fig. 23.10). The clinician then determines whether the lung parenchyma in each examination location has only A-lines throughout (A-pattern), B-lines in all locations (B-pattern), a combination of only A-lines in some fields and B-lines in others (A-B pattern), or consolidated lung in any location. When a B-line pattern is present in a single field, the full assessment should include the patterns identified in the other fields also examined (e.g., B-lines localized to some, but not all fields, or widespread) and severity (e.g., few or many B-lines, narrow/discrete or coalescent).

In some cases, these elements alone may be enough to solidify a clinical diagnosis (see Fig. 23.11). For example, a dyspneic patient who has a history of both heart failure and obstructive lung disease, with intact pleural sliding and a widely distributed B-line pattern, likely has pulmonary edema and not an isolated COPD exacerbation. Among patients with acute hypoxemic respiratory failure, the finding of B-lines in all six locations has been reported to have a positive predictive value of 87% for acute cardiogenic pulmonary edema.[48] In contrast, the same patient with intact pleural sliding and a normal aerated A-line pattern in all locations more likely has an exacerbation of underlying obstructive lung disease.

In other situations, the clinical context may necessitate further investigation. For a dyspneic patient with diffuse B-lines but no history of heart failure, echocardiography should be considered. Similarly, hypoxemia in a postoperative patient with intact pleural sliding and a diffusely normal A-line pattern should prompt further evaluation for pulmonary embolism. The presence of a widespread A-line pattern and a deep venous thrombosis has a positive predictive value of 94% for pulmonary embolism.[48] The combination of A-lines only in some areas and B-lines in others (mixed A-B pattern) requires further investigation and can

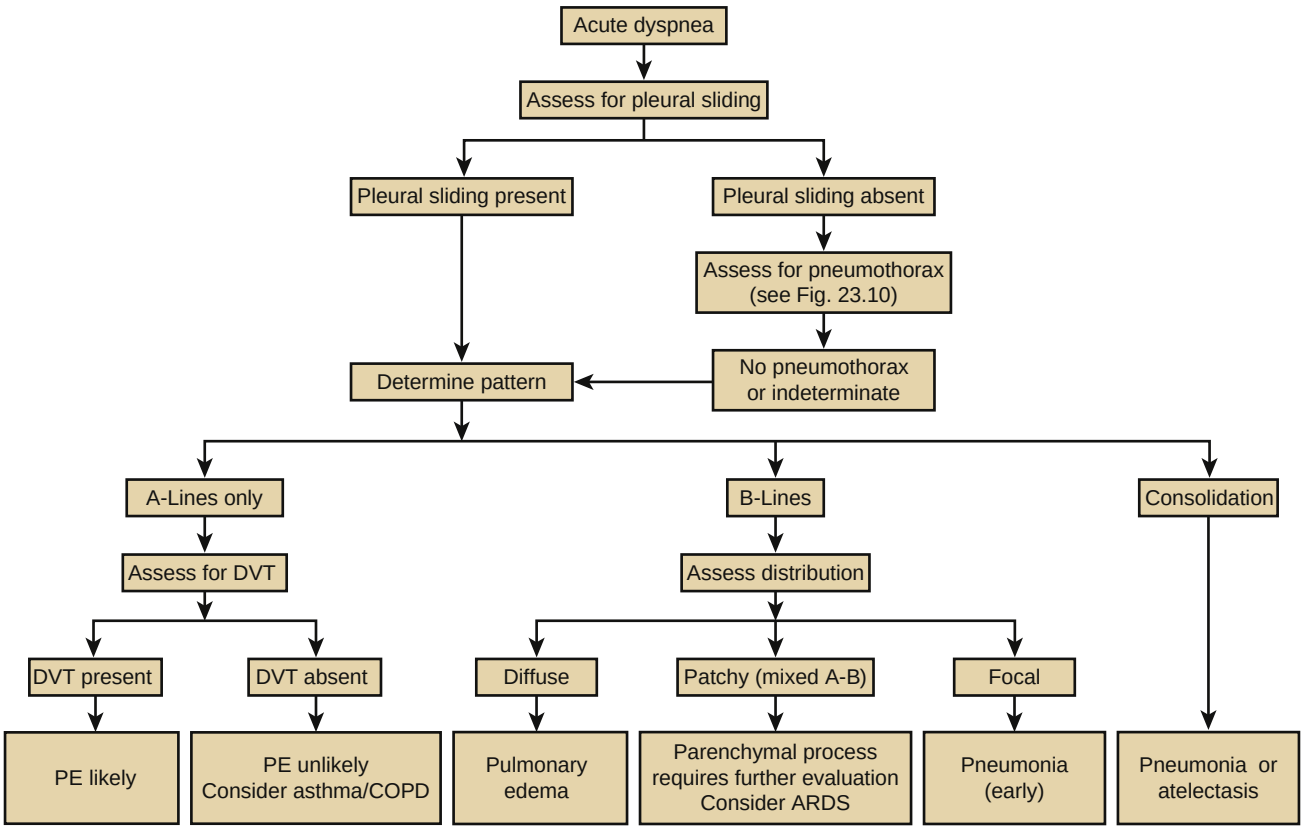

Figure 23.11 Sample algorithm for the use of ultrasound to evaluate a patient with acute dyspnea. After evaluating for pleural sliding (see Fig. 23.10), ultrasound can be used to differentiate between A-lines, B-lines, or mixed A-B line patterns and to identify areas of consolidation. The overall pattern identified in multiple scanned areas can guide the operator toward additional investigations, if needed, and direct early treatment. ARDS, acute respiratory distress syndrome; DVT, deep venous thrombosis; PE, pulmonary embolism.

be seen in pneumonia, acute respiratory distress syndrome, or limited cardiogenic pulmonary edema, for example.

In all of these cases, a thorough history and detailed physical examination provide context for the findings of a protocolized ultrasound examination to narrow the differential diagnosis for the presenting complaint and to guide clinical decision making.

VASCULAR IMAGING

CENTRAL VENOUS CATHETER PLACEMENT

The use of ultrasound to guide central venous catheterization is a recommended standard practice endorsed by many professional society guidelines.[64–70] It has been demonstrated to improve the success rate and decrease the complications of this procedure, particularly for less-experienced practitioners, in both adult and pediatric patients.[71–75]

Because the *internal jugular vein* (IJV) overlies the carotid artery in greater than 50% of patients, the increased safety provided by the use of ultrasound is at least partly related to visualization of the adjacent artery.[76–79] The position of the subclavian vein posterior to the clavicle is less easily amenable to ultrasound guidance, but this technique can be used by experienced providers in a supraclavicular or infraclavicular approach.[75]

Technique

Before the procedure, a preliminary scan of the relevant vascular structures should be performed to assess vessel patency. For IJV and subclavian vein catheters, it may be helpful to document the presence of sliding lung in the anterior thoracic field in the event of patient deterioration raising the question of pneumothorax (see "Pneumothorax" earlier). The operator should choose the insertion site based on external patient anatomy and imaging because the IJV often appears largest inferiorly on the neck, where it is also closest to the lung apex. Dynamic ultrasound guidance is recommended over a static approach.[65,66,71,75] The vessel and needle may be visualized using a short-axis (transverse, or out of plane) or long-axis (longitudinal, or in plane) approach; neither is conclusively superior.[80–82] The short-axis view allows visualization of the vein and accompanying artery but requires the operator to translocate, or fan, the transducer (see Fig. 23.4) in small movements, alternating with advancement of the needle, to visualize the needle tip throughout the procedure. The longitudinal approach does not require alternating movements of the ultrasound and needle, but the needle must remain precisely in plane with the ultrasound beam, which may be more challenging for novices. A short neck length or inguinal crease, in the case of femoral vein catheterization, may not allow a longitudinal approach.

Despite ultrasound guidance, arterial puncture and occasionally cannulation happen rarely.[74,75] To avoid malposition, the operator should visualize the guidewire in the short and long axis to confirm venous placement before dilation and catheter insertion (Fig. 23.12). After the procedure is completed, chest radiography is traditionally used to confirm catheter position, but ultrasound can also be used with a combination of vascular and cardiac views.[83,84]

PERIPHERAL VASCULAR ACCESS

Ultrasound may be used to facilitate catheterization of the peripheral venous and arterial system. The relative ease of compressibility of the venous lumen with gentle pressure aids in the differentiation of peripheral veins and arteries. In patients with difficult venous access, ultrasound guidance reduces the number of attempts and the time to successful placement of peripheral intravenous catheters compared to traditional blind technique. Improved success with ultrasound-guided peripheral intravenous catheter placement may reduce the need for central venous catheters.[85–89] In addition to traditional antecubital fossa and forearm locations, the use of ultrasound allows providers to access brachial or proximal basilic vessels. However, these locations require careful consideration because standard 3 to 5 cm length catheters have a high rate of dislodgement and early failure.[90] As in central venous catheter guidance, providers may use a short- or long-axis approach to peripheral vessels.

DEEP VENOUS THROMBOSIS ASSESSMENT

Limited sonography of the lower extremity deep veins is a useful adjunct in the assessment of dyspnea when pulmonary embolism is suspected. Clinicians can diagnose deep venous thrombosis by performing a two-point compression examination at the femoral and popliteal locations with a sensitivity and specificity of 96% and 97%, respectively, compared to gold-standard formal duplex examinations or

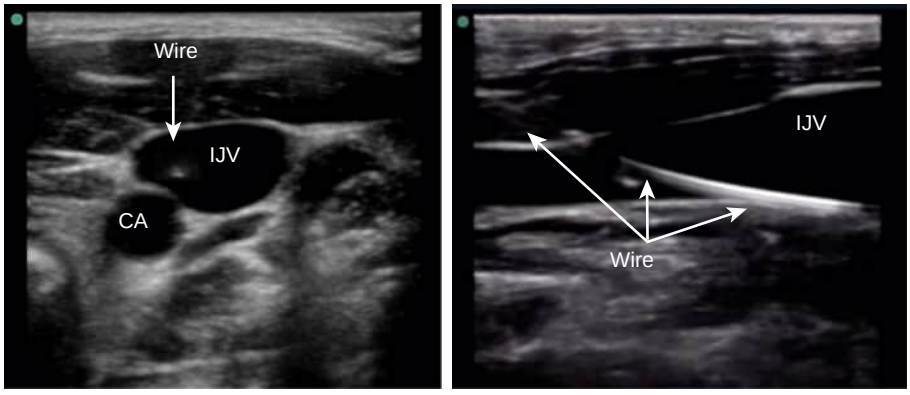

Figure 23.12 Central venous catheter placement. To ensure proper placement before dilating and catheter insertion, visual confirmation of the wire within the target vessel should be confirmed as shown in both the short (A) and long (B) axes. CA, carotid artery; IJV, internal jugular vein.

venography.[91,92] To perform the examination, the supine patient's leg is externally rotated slightly at the hip and flexed at the knee. The common femoral vein is identified above the inguinal ligament using a high-frequency linear transducer in the transverse plane. The operator follows its course to the bifurcation into the superficial and deep femoral veins, compressing every 2 cm along the course of the veins. This is repeated for the popliteal vein from just above the popliteal fossa to its distal trifurcation.

Normal veins are easily completely collapsed with light pressure (Video 23.20). If adequate pressure is applied to deform the accompanying artery slightly and the vein is *not* completely collapsed, even if no material is visible in the lumen, it suggests the presence of a fresh acute thrombus that is not yet organized and therefore less echogenic (Video 23.21). Absence of Doppler signal at this location, with or without augmentation by calf compression, may help confirm presence of thrombosis. Larger and older, organized thrombus may be visible within a vein as an echogenic structure (Video 23.22).

Key Points

- Point-of-care ultrasound is increasingly used for diagnostic purposes in pulmonary and critical care medicine and is the standard of care for several common procedures.
- Ultrasound signal travels through the body, reflects off internal structures, and returns to the transducer, where it is interpreted as images. The time required to complete this journey is interpreted as depth.
- Tissues have variable acoustic impedance, which determines how ultrasound signal travels through the body and the echogenicity, or brightness, with which they appear on screen.
- Lung ultrasound images are often generated by artifacts, but these patterns can provide useful information even if they are not a true picture of the underlying tissues.
- The presence of pleural sliding rules out pneumothorax at the imaged location with high accuracy.
- B-lines, which indicate the underlying lung parenchyma is not normally aerated, can be seen in pulmonary edema or interstitial fibrosis but are not specific for any one diagnosis.
- Ultrasound guidance for thoracentesis, pleural biopsy, and central venous catheter placement increases the success and safety of these procedures and is the standard of practice.

Key Readings

American Society of Anesthesiologists Task Force on Central Venous Access, Rupp SM, Apfelbaum JL, Blitt C, et al. Practice guidelines for central venous access: a report by the American Society of Anesthesiologists Task Force on Central Venous Access. *Anesthesiology*. 2012;116(3):539–573.

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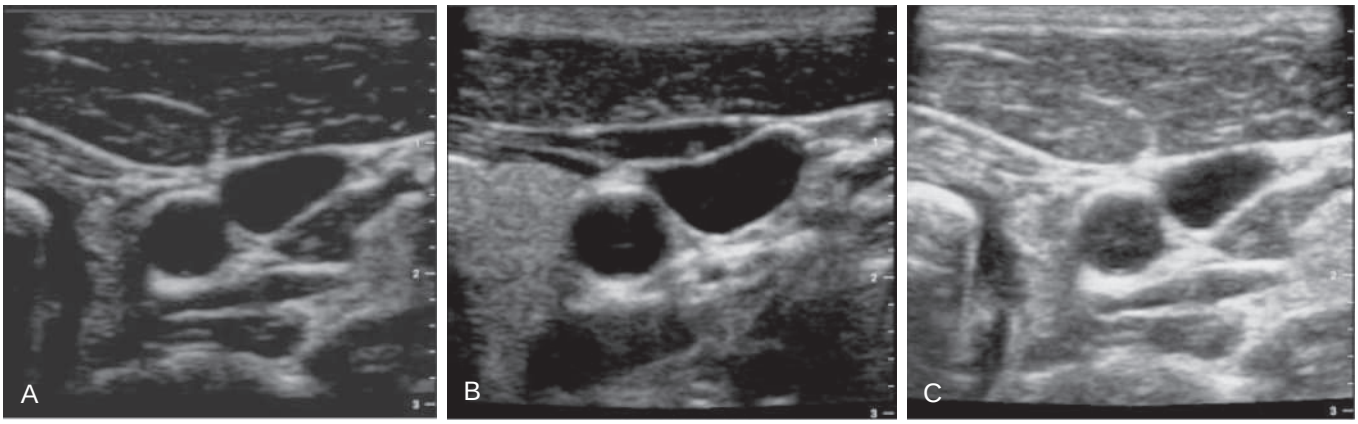
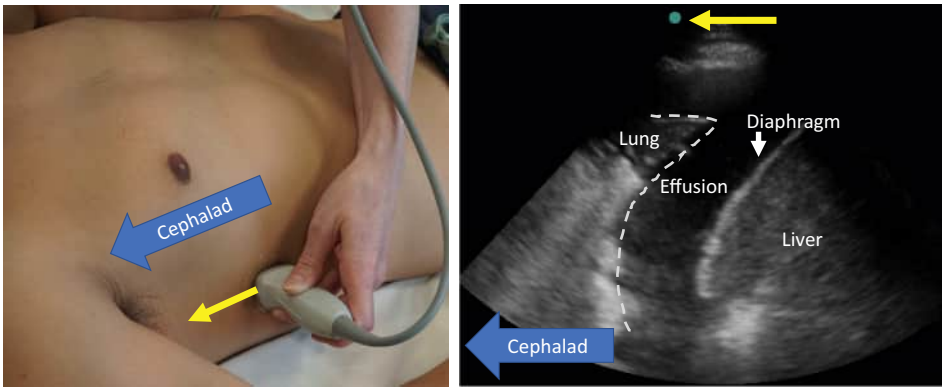
Complete reference list available at ExpertConsult.com.

eFIGURE IMAGE GALLERY



eFigure 23.1 Gain adjusts pixel intensity for any given signal strength, making the image brighter or dimmer. (A) Gain set too low: note the difficulty in discerning superficial tissue planes. (B) Just right: anechoic structures (vessels at center screen) appear black; relatively hyperechoic structures, such as the fascia and vessel walls, appear bright white; and the observer can distinguish between the remaining hypoechoic tissues, such as the thyroid at screen left. (C) Too high: everything in the screen appears "snowy," and it is difficult to differentiate between fascial planes. The carotid artery and internal jugular vein are centered in these images.



eFigure 23.2 Transducer orientation. The orientation marker on the transducer corresponds to the orientation marker on the screen (*yellow arrows* indicate the orientation marker direction and the orientation indicator mark on the ultrasound screen), allowing the operator to recognize relevant structures more easily. This image shows a pleural effusion that includes anechoic and more echogenic material dependently, typical of cellular debris within the fluid. The *dashed line* approximates the edges of the lung.

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24 ULTRASONOGRAPHY: ADVANCED APPLICATIONS AND PROCEDURES

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INTRODUCTION

The use of ultrasound machines in *intensive care units* (ICUs) is common. Noncardiologists can learn to acquire images and interpret them rapidly and correctly to answer common clinically relevant questions, such as determining a patient's left ventricular systolic function. The answers to these questions can alter treatment and optimize patient care. This chapter reviews the data to support training in critical care echocardiography for noncardiologists. It then reviews how to acquire basic views and how to interpret these images to be used in clinical decision making. The chapter concludes with a suggested approach to combining all of the ultrasound assessments described in Chapter 23 and this chapter for use in the evaluation and management of a patient with shock.

Critical care ultrasound (CCU), defined as point-of-care ultrasound performed by intensivists, has become a widely embraced technology in the ICU to aid with procedures, diagnosis, and treatment. *Critical care echocardiography* (CCE), a subdivision of CCU, can be further divided into basic and advanced skill sets. Basic CCE is largely limited to B- and M-mode imaging, addresses specific clinical questions (e.g., whether pericardial effusion is present), and generates qualitative findings (e.g., the systolic function is hyperdynamic, nearly normal, reduced, or severely reduced). Basic CCE has lent itself to the development of a number of systematic approaches (with acronyms such as FEEL, FATE, and RUSH) for addressing specific critically ill groups of patients, including, most notably, patients with shock.[1–3] Advanced CCE, conversely, is quantitative and goes beyond basic CCE to include Doppler ultrasound for the purpose of evaluating valvular function, cardiac output, and left heart diastolic function. Advanced CCE is beyond the scope of this chapter. In contrast, basic CCE has been promoted by the Accreditation Council for Graduate Medical Education and is quickly becoming an expected skill set for all intensivists.[4]

CRITICAL CARE ECHOCARDIOGRAPHY AS A DIAGNOSTIC TOOL FOR INTENSIVISTS

Noncardiologist physicians from different specialties (emergency medicine, internal medicine, and surgery) at different levels of training (resident or attending) can perform and accurately interpret focused cardiac ultrasound examinations.[5–9] Shared characteristics across studies support the diagnostic use of basic CCE. In most studies, training was limited to 1 day and included both didactic and hands-on sessions. Most of these studies, using complete or formal echocardiographic examinations as the comparator, demonstrated that noncardiologists are able to use a portable

or handheld ultrasound device to make a qualitative assessment of left ventricular function, identify the presence or absence of a pericardial effusion, and evaluate the size of the *inferior vena cava* (IVC) with good interrater agreement. Basic CCE estimations of left ventricular function can be performed in less than 15 minutes.[7,9] Moreover, the basic CCE examination is almost always performed in conjunction with a pulmonary ultrasound examination. When the findings of these two examinations are integrated, a more complete clinical picture can be achieved, especially in cases of undifferentiated shock or when there is concern for heart failure with pulmonary edema.[10]

Judging whether a hypotensive patient would be responsive to fluids is an ongoing challenge for critical care practitioners. The use of central venous pressure, a static measure, to predict fluid responsiveness is inferior to dynamic measurements, such as assessing the changes of IVC diameter with breathing.[11] Nonetheless, even when performed in sedated, mechanically ventilated patients, measurements of IVC diameter variation are imperfect in predicting fluid responsiveness.[11] Advanced CCE skills such as measuring stroke volume variation have been shown to be superior to assessing IVC variation in some studies, although this examination requires more time at the bedside and can be technically challenging.[12] In addition, the practitioner of advanced CCE should be cautious when assessing valvular disease because this can be demanding even for experienced echocardiographers.[13]

IMPACT OF CRITICAL CARE ECHOCARDIOGRAPHY ON THE MANAGEMENT OF CRITICALLY ILL PATIENTS

The impact of CCE on the management of critically ill patients has been studied, with mixed results. In one study, CCE evaluation changed the working diagnoses and the corresponding management plans in 37% (33 of 90) of critically ill patients.[7] Typical management changes after the CCE examination included starting or stopping diuretic agents, fluid resuscitation, or inotropic therapies. In a study of trauma patients (n = 240), CCE assessment led to a decrease in intravenous fluid administration, a quicker time to the operating room, and a trend toward a lower mortality rate (11% vs. 19.5%; $P = 0.09$).[14] In a retrospective study of patients with subacute septic shock (N = 220), CCE led to less fluid administration, increased use of inotropic therapies, and improved 28-day survival (66% vs. 56%; $P = 0.04$) compared with historic control subjects.[15] Unfortunately, not all studies of point-of-care ultrasound in critically ill patients have shown benefit, including one retrospective report (n = 5441) that found care delays and a higher in-hospital mortality rate (29% vs. 22%; $P < 0.001$) if bedside ultrasound examination was performed before initiating a fluid bolus or a vasoactive medication.[16]

CRITICAL CARE ECHOCARDIOGRAPHY TRAINING, COMPETENCY, AND CERTIFICATION

Various education and clinical care regulatory bodies, along with surveyed critical care fellowship directors, have acknowledged the importance of point-of-care ultrasound in the care of critically ill patients. However, there is no consensus on how best to train intensivists, determine competency, and ultimately award certification for CCU.[3,4,17] In general, most CCU training includes a short focused course (1 to 2 days), with the majority of the time dedicated to CCE. Typically, didactic lectures constitute 50% of the training time, with the other 50% of the course dedicated to hands-on training using task trainer simulation, ultrasound simulation, and live ultrasound scanning of volunteer individuals. Hands-on training is generally performed in small groups usually consisting of one model, one instructor, and five or fewer learners.[18] For critical care fellows in training, a comprehensive CCU program also entails regular image review sessions and documentation by the trainee of successfully performed point-of-care ultrasound examinations and ultrasound-guided procedures.

Despite recognition of the importance of all of these elements, it is rare that a fellowship program can achieve such a comprehensive CCU educational experience. In a 2014 survey of critical care program directors, 42% (25 of 60) lacked a formal curriculum.[19] Limited numbers of faculty proficient in point-of-care ultrasound and limited time to teach CCE are among the barriers to developing a CCU program.[17] Despite these shortcomings in training, multiple societies have produced position papers establishing standards for CCU, including CCE training and competency.[20–22] Beginning in 2019, The National Board of Echocardiography began offering an Examination of Special Competence in Critical Care Echocardiography. The examination was developed with input from the National Board of Medical Examiners and representation from eight medical societies, with the aim of establishing an objective means of identifying individuals with expertise in CCE.[23]

IMAGE ACQUISITION AND INTERPRETATION OF THE CRITICAL CARE ECHOCARDIOGRAM

The following sections describe the four standard cardiac views that we suggest should be obtained during a cardiac critical care echocardiogram. We then share the approach that we recommend for use in interpreting the images obtained. We favor a simple subjective evaluation of the images that can be easily performed without additional image processing. Acquiring CCU skills requires adequate training. Professional society guidelines vary; however, we recommend a structured program of didactic and hands-on instruction followed by a longitudinal curriculum that incorporates proctored ultrasound examinations and image interpretation.[24]

DATA QUALITY, CONFIDENCE OF INTERPRETATION, AND RESPONSIBILITY FOR UNEXPECTED FINDINGS

Similar to the physical examination, cardiac ultrasound image acquisition and interpretation are subjective, and the value of the interpretation is markedly affected by the quality of the data acquired. Operators should incorporate an assessment of the quality of the data and confidence in their

interpretation into the report of their findings. For example, during assessment of left ventricular function, if only two of four recommended assessments can be performed, it should be clearly noted that the data were inadequate to perform a complete evaluation and the interpretation may be adversely affected. These limitations should then be considered when making patient care decisions. At times, it is appropriate to conclude that the data from the ultrasound examination are of poor quality, cannot be interpreted, and should not be used for clinical decisions. Assessment of the data quality is an important skill that must be learned and practiced and will improve as operators accumulate experience.

Another important aspect of data collection and interpretation is recognizing when an acquired image shows an unexpected finding that may have clinical significance but that the operator does not know how to interpret.[25] We recommend that, in this setting, the operator immediately contact an imaging expert to review the stored images or to perform a complete examination.

PREPARATION FOR THE CRITICAL CARE ECHOCARDIOGRAM

Similar to other ICU procedures, spending adequate time to gather all needed equipment and prepare for the ultrasound examination will increase the possibility of successful image acquisition and greater likelihood that the examination will be useful in patient care. Needed equipment includes ultrasound gel, towels for removing ultrasound gel at the completion of the examination, the ultrasound machine with ultrasound probes needed for the planned examination, a wedge or pillows to position the patient and, ideally, an assistant who can manage the controls on the ultrasound machine during the examination so the operator can focus on image acquisition and interpretation.

Less experienced operators will benefit if the ultrasound machine is positioned so that the patient and ultrasound probe are in the same line of sight as the ultrasound machine. Typically, this means that the machine will be positioned on the side of the patient opposite to the position of the operator. The patient's bed should be raised or lowered so that the operator can acquire images without bending or reaching. Sometimes this is best accomplished with the operator sitting on a chair or standing on a step. The bed height should be adjusted during the examination as needed to optimize patient positioning with respect to the operator.

For acquiring parasternal long, short, and apical views, patients should be in the left lateral decubitus position (eFig. 24.1). Although it may be possible to acquire these images in the supine patient, it is often much more difficult and may significantly degrade data quality, particularly when acquiring an apical view in which foreshortening (see later for a description of foreshortening) can go unnoticed. Echocardiography laboratories often use beds with a breakaway panel to facilitate imaging of the patient in a decubitus position. Although this is not possible in an ICU bed, wedges, pillows, or towels can all be used to provide space for the probe. In contrast, the subcostal view requires the patient to be supine. When possible, having patients bend their knees can result in relaxation of abdominal muscles and improved imaging.

PROBE MANIPULATION

Familiarity with how to manipulate the ultrasound probe and the terminology that describes these maneuvers can markedly improve the ability of the operator to acquire high-quality ultrasound images. It is important that the operator analyze the image on the screen, determine how image quality can be optimized, and then carefully and deliberately manipulate the probe to achieve the desired image.

Four basic probe movements can be described using agreed-upon terminology (eFig. 24.2). When the foot (the part of the probe in contact with the patient's skin) of the ultrasound probe is moved to a new location on the chest (e.g., when moving from a parasternal to an apical view, or moving along a rib space in the parasternal view), this is referred to as "sliding." All other movements should be performed while keeping the foot of the probe anchored in place on the patient's chest. "Rocking" is changing the angle of the probe along the long axis of the probe foot while maintaining contact with the patient in a fixed position. "Fanning" is changing the angle of the probe interface along the short axis of the probe foot while maintaining contact with the patient in a fixed position. "Rotating" is turning the probe clockwise or counterclockwise while keeping the foot of the probe in contact with the skin. In general, these maneuvers should be performed sequentially rather than simultaneously (i.e., fan only; do not also rock or tilt in the same maneuver) to obtain and optimize an image in a stepwise fashion.

BASIC CRITICAL CARE ECHOCARDIOGRAM VIEWS

Basic CCE uses four ultrasound views to answer clinically relevant questions (Fig. 24.1). These four views exclude significant portions of the heart, such as segments of the anterior and inferior wall, that would be seen in a complete echocardiogram.

Obtaining images of the heart in all four views is important for several reasons. First, not all cardiac structures are present in all views, so all of the views described here are needed to view all relevant cardiac structures. Second, it is often difficult to see all of the cardiac structures expected in a view because of the limitations of ultrasound physics (see Chapter 23 for a discussion of basic ultrasound physics) or because of a patient's anatomy. For example, the endocardial borders (where the cardiac wall ends and the left ventricular cavity starts) are better visualized when the ultrasound beam is perpendicular to the cardiac walls versus when the ultrasound beam is parallel to cardiac walls. Third, it is necessary to confirm findings in multiple views because images may be affected by artifact or other imaging errors that are recognized only when the same structure is seen in a different view.

Obtaining high-quality images and recognizing normal cardiac structures and function require proctored ultrasound scanning and repetitive scanning of many patients with normal hearts. Comparison with gold standard images, hands-on instruction, and review of saved images with an expert are all approaches that we recommend so

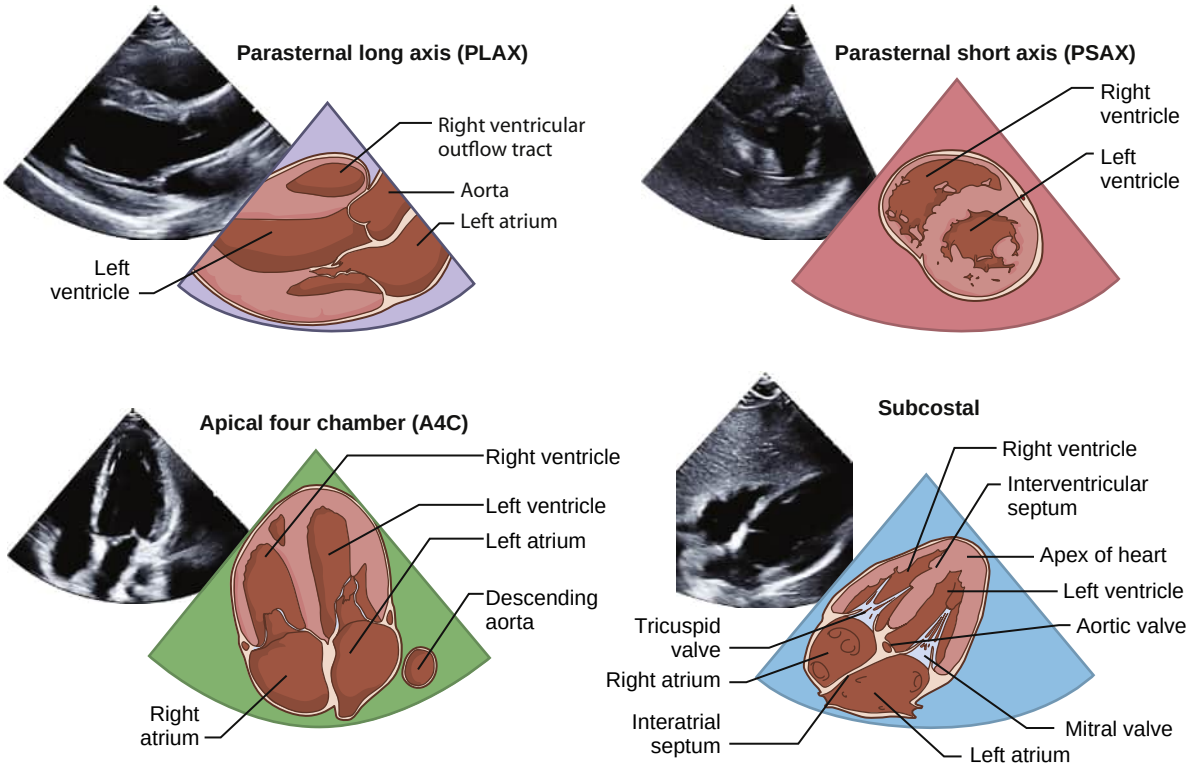

Figure 24.1 The four basic critical care echocardiography views. Careful attention should be paid to the ultrasound images to ensure that only good-quality data are incorporated into clinical decision making. If image quality is not adequate, the image should be discarded and other ultrasound views should be obtained. Multiple views should be interrogated in all patients to ensure that findings are consistent across views and do not represent artifact or result from poor data quality.

learners will come to recognize what a healthy heart looks like and therefore will recognize abnormalities. To achieve proficiency in identifying healthy and abnormal hearts, we recommend 50 or more proctored cardiac examinations; however, skills will continue to improve with additional practice.

Although a few high-quality images obtained from these four basic views are typically adequate to answer the clinically relevant questions posed by an intensivist, for complete assessment of cardiac structure and function, a complete echocardiogram requires between 70 and 125 images.

PARASTERNAL LONG-AXIS VIEW

The *parasternal long-axis* (PLAX) view is obtained by placing the foot of the ultrasound probe in the third or fourth intercostal space adjacent to the sternum with the long axis of the probe in line with the patient's right shoulder (Video 24.1). Sliding the probe laterally along the rib space may improve image quality. The probe is sequentially rotated and fanned until all of the desired structures are optimally viewed. A good-quality image of the heart in the PLAX view has the following characteristics: (1) the heart will appear horizontal on the screen; (2) the walls of the myocardium will be parallel; (3) the two leaflets of the mitral valve along with the posterior papillary muscle and two of three leaflets of the aortic valve will be seen; and (4) the complete left atrium will be seen. Frequently, the heart will appear to point up to the top of the screen. This is an indication that the probe is too low on the chest, thus placing the apex too close to the transducer. To remedy this issue, the probe should be moved up an intercostal space.

In this view, segments of the anteroseptal and posterior walls are seen perpendicular to the ultrasound beam, so this view is useful to assess for wall thickening. This view is frequently the optimal view for assessment of mitral valve opening and mitral annular excursion, which are important for determining left ventricular systolic function.

PARASTERNAL SHORT-AXIS VIEW

The *parasternal short-axis* (PSAX) view is a view through the midwalls of the myocardium at the level of the papillary muscles (Video 24.2). An optimal PSAX view is obtained by starting with an optimal PLAX view and then rocking the probe so a line dropped from the apex of the image intersects perpendicularly with both walls of the myocardium and passes through the papillary muscle. Many ultrasound machines can display a line on the screen that can be turned on to facilitate this maneuver. The probe is then rotated clockwise 90 degrees with care not to rock or fan. The resulting image of the left ventricle is a circle with the papillary muscles in the short axis evident at approximately the 3 and 7 o'clock positions. Because there are few asymmetric structures in the PSAX view useful to guide probe movement for image optimization, we recommend returning to a PLAX view as needed to optimize the image, then using the same rock-then-rotate maneuver, returning to the PSAX view.

The PSAX view shows the midsegments of all of the myocardial walls. Because the mitral valve is not visualized, the view is of limited utility in assessing left ventricular dysfunction. The PSAX view provides important clues to the presence of right ventricular dysfunction because it is the best view to identify flattening of the septal wall of the left ventricle caused by right ventricular abnormalities.

APICAL FOUR-CHAMBER VIEW

The *apical four-chamber* (A4C) view is obtained by positioning the ultrasound probe as close as possible to the apex of the heart, which can be located by palpation of the point of maximum impulse (Video 24.3). The probe is then rotated and fanned until both ventricles, both atria, and the mitral and tricuspid valve leaflets can be seen fully opening and closing.

It is important to recognize and avoid foreshortening of the left ventricular image in the A4C view (Fig. 24.2). Foreshortening results when the ultrasound beam does not pass through the left ventricular apex but instead passes through a wall of the left ventricle. The apex of the left ventricle is normally thin, and it thickens only minimally during ventricular systole. If the apex appears thick in an A4C view, then the image is likely foreshortened. If an image is foreshortened, abnormalities of the left ventricular apex will not be seen. Foreshortening can also make left ventricular systolic function appear better than it actually is, thereby leading to misinterpretation of data. Additionally, a foreshortened A4C results in artifactual enlargement of the right ventricle, so a normal, healthy right ventricle may appear dilated with reduced function. To obtain a proper image of the right ventricle in the A4C view, a non-foreshortened image of the left ventricle must first be obtained, and then the probe should be rotated until the right ventricle is as large as possible.

This view shows the basal, middle, and apical segments of the septal and lateral walls, as well as the right ventricular chamber, which is not seen in the parasternal views. This view also provides another view of the mitral valve annulus, which is important in the evaluation of left ventricular dysfunction.

SUBCOSTAL VIEW

The subcostal view (or the subxiphoid view) is obtained by placing the probe inferior to the xyphoid process and slightly lateral (right) to the midline with the probe foot in a horizontal position (Video 24.4). The ultrasound probe is oriented so the beam passes through the liver, and the probe is then rotated, fanned, and rocked until the heart can be identified.

As in the A4C view, both ventricles, both atria, and the tricuspid and mitral valves should be seen on the subcostal view. The IVC can be imaged by manipulating the probe so the right atrium is in the center of the screen. The probe is then rotated counterclockwise and manipulated to be perpendicular to the abdominal wall.

The structures seen in the subcostal view are the same as the structures seen in the A4C view. At times, these structures are better visualized from the subcostal view. The subcostal view is often the best view for assessing right ventricular function because the ultrasound beam is perpendicular to the right ventricular free wall.

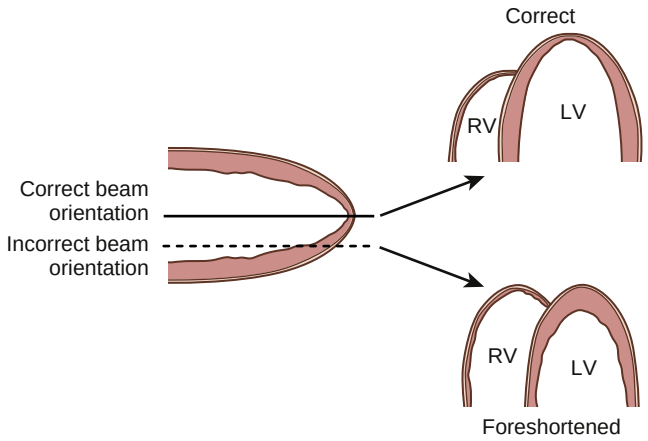

Figure 24.2 Foreshortening. Foreshortening results when the ultrasound beam does not pass through the left ventricular apex but instead passes through a wall of the left ventricle (LV). With foreshortening, the true apex of the left ventricle is not imaged, and the right ventricle (RV) falsely appears enlarged; this may lead to incorrect image interpretation and inappropriate patient care decisions.

INTERPRETATION OF ULTRASOUND IMAGES

LEFT VENTRICULAR FUNCTION

For evaluation of the left ventricular systolic function, we recommend combining four subjective assessments into an overall impression and suggest that each of the four assessments should be performed as completely as possible in each of the four basic ultrasound views. Furthermore, we recommend grading systolic function into one of three broad categories: (1) normal or hyperdynamic, (2) reduced systolic function, or (3) severely reduced systolic function (Videos 24.5 through 24.8).

1. The first assessment is an evaluation of the change in the size of the cavity of the ventricle. This is a subjective assessment of the ejection fraction that is made by simply examining the left ventricular cavity during systole and diastole and noting whether the cavity decreases in size and by how much (Table 24.1).
2. The second assessment is an evaluation of wall thickening. Even though the term *wall motion* is in common use, it is important to understand that myocardial segments are functioning normally when the myocardium thickens. (Dysfunctional myocardial segments may "move" because they are adjacent to other normally functioning myocardial segments.) The visible walls should be examined to determine whether the wall is thickening.
3. The third assessment is an evaluation of the motion of the anterior leaflet of the mitral valve in the PLAX view. This is a subjective assessment of the E-point septal separation, a measure commonly used to assess systolic function before the availability of two-dimensional echocardiographic imaging.[26] In a heart with normal systolic function, the mitral valve should open wide

Table 24.1 Assessments of Left and Right Ventricular Function*

LEFT VENTRICULAR FUNCTION
1. Change in the size of the left ventricular cavity
2. Thickening of the walls of the myocardium
3. Opening of the mitral valve
4. Movement of the mitral valve annulus toward the apex
RIGHT VENTRICULAR FUNCTION
1. Movement of the tricuspid annulus toward the apex
2. Motion of the right ventricular free wall
3. Change in the size of the right ventricular cavity
4. Flattening of the interventricular septum

*Recommended assessments to use for evaluating ventricular systolic function. Each of these assessments should be performed in as many of the four views as possible and integrated for a final conclusion about ventricular function.

during diastole so the anterior mitral leaflet is close to the interventricular septum.

4. The final assessment is evaluation of the motion of the mitral valve annulus; this is best assessed in either the PLAX view or the A4C view. The movement of the myocardium at the point that it joins the posterior mitral valve leaflet is assessed. In a heart with normal systolic function, the mitral valve annulus moves vigorously from the base of the heart toward the apex. In a complete echocardiographic evaluation of this function, the equivalent objective measurement is referred to as the *mitral annular plane systolic excursion.*

Because no single view and no single assessment are reliable, all four of these assessments should be performed in all four basic views (with the exception of the PSAX view, in which only two of the assessments are possible). For example, in a patient with mitral valve disease, the mitral valve may not appear to open fully, but the provider can conclude that systolic function is normal on the basis of the other three assessments.

There are several technical pitfalls in assessing left ventricular systolic function. As previously discussed, a foreshortened view may cause systolic function to appear better than it actually is because the cavity size appears smaller during systole. A similar problem arises if the heart moves out of the ultrasound imaging plane during image acquisition.

There are also pitfalls in interpretation of left ventricular systolic function when other pathologic conditions are present. For example, hypovolemia may falsely create the appearance of normal systolic function because there is little intracavitary volume. Another potential pitfall is the presence of severe mitral valve regurgitation. Assessment of mitral valve disease is beyond the scope of this chapter; however, when there is severe mitral regurgitation, left ventricular systolic function may appear normal because much of the blood ejected during systole is ejected into the low-pressure left atrium. Nonetheless, there may still be significant myocardial dysfunction. In fact, a patient may present in cardiogenic shock resulting from severe mitral regurgitation, but myocardial function on the standard views as described earlier will appear normal.

RIGHT VENTRICULAR FUNCTION

Right ventricular systolic function is evaluated using a set of assessments similar to those used for left ventricular systolic function. Because right ventricular function is more difficult to evaluate, we recommend grading the right ventricle as "normal" or "not normal." In the PSAX and PLAX views, the right ventricle is typically not well visualized, and only a portion of the right ventricular outflow tract can be seen. The A4C and subcostal views are therefore needed for a meaningful evaluation of right ventricular function (Video 24.9).

1. The first assessment is evaluation of the motion of the tricuspid valve annulus in the A4C or subcostal views. The movement of the myocardium at the point that the right ventricular free wall joins the tricuspid valve leaflet is assessed. In a heart with normal systolic function, the tricuspid valve annulus moves vigorously from the base of the heart toward the apex. In a complete echocardiographic evaluation of this function, the equivalent objective measurement is referred to as the *tricuspid annular plane systolic excursion*[27] (see Table 24.1).
2. The second assessment is an evaluation of the motion of the right ventricular free wall. However, the right ventricular free wall is often not well visualized, especially in a healthy right ventricle, so this assessment cannot always be incorporated into the final conclusions about right ventricular function.
3. The third assessment is an evaluation of the change in the size of the cavity of the ventricle. This assessment is made by examining the right ventricular cavity during systole and diastole and noting whether the cavity decreases in size and by how much. Given the shape of the right ventricle, it is not possible to calculate an ejection fraction without three-dimensional imaging. The analogous objective assessment performed in the echocardiography laboratory is the *fractional area change.*
4. The fourth assessment is an evaluation of the shape of the interventricular septum. In the PSAX view, the left ventricle should appear round. Flattening of the septum (so the left ventricle appears D-shaped) suggests that there may be an abnormality of the right ventricle. Evaluation of the right ventricle in other views is needed to confirm and characterize the abnormality more clearly.

RIGHT ATRIAL PRESSURE

Determining the IVC diameter and the change in diameter with breathing is a useful technique for estimating right atrial pressure.[28] There are several approaches to obtaining this view. We recommend starting with a good-quality subcostal view of the heart. The probe is then rotated counterclockwise and manipulated so the probe is perpendicular to the abdominal wall. During this motion, the right atrium is kept in the center of the screen. As

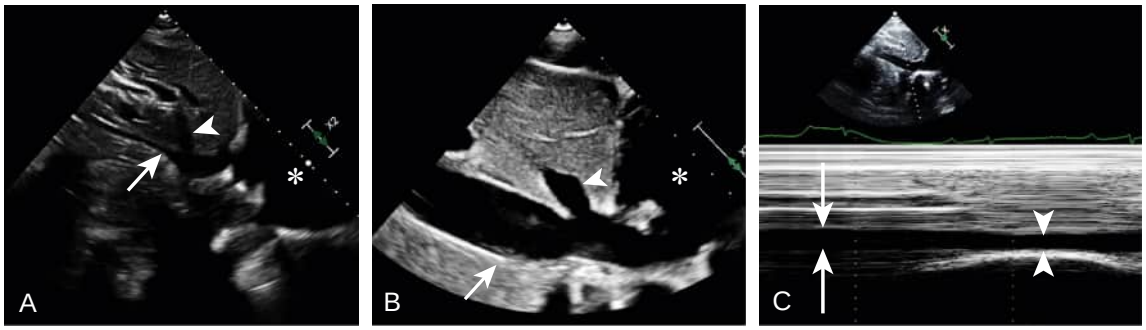

Figure 24.3 Images of the inferior vena cava. These images show (A) a small, nearly completely collapsed inferior vena cava compared with (B) a large, dilated inferior vena cava. (C) Application of M-mode imaging just distal to the hepatic vein to visualize inferior vena cava diameter over time and identify maximum (*arrows*) and minimum (*arrowheads*) inferior vena cava diameter. The appearance of the inferior vena cava reflects right atrial pressure. An inferior vena cava that is less than 2 cm in diameter and collapses by 50% (to a diameter of 1 cm) corresponds to a right atrial pressure of approximately 5 mm Hg, which is normal. The relationship between right atrial pressure and inferior vena cava diameter is lost in patients treated with positive-pressure ventilation. The assessment of inferior vena cava diameter may be used to make predictions about hemodynamic response to fluid administration for patients in shock and is addressed in the text. *Arrow,* inferior vena cava; *arrowhead,* hepatic vein; *asterisk,* right atrium.

the probe is rotated, the image of the IVC in long axis will come into view. The aorta lies just medial to and can easily be confused with the IVC. Definitive identification of the IVC requires seeing it enter the right atrium and seeing it connect with the hepatic vein. The diameter of the IVC and the change in diameter with breathing are used to assess right atrial pressure (Fig. 24.3). The significance of right atrial pressure depends on the clinical scenario, which must be carefully considered when using IVC imaging to make patient care decisions (see the later discussion of assessment of volume status).

PERICARDIAL EFFUSION AND CARDIAC TAMPONADE

Pericardial tamponade is a life-threatening emergency typically identified by findings on echocardiography interpreted in combination with the clinical status. A complete echocardiographic hemodynamic assessment for pericardial tamponade is beyond the scope of this chapter; however, it is reasonable for intensivists to identify a pericardial effusion, as well as features suggestive of pericardial tamponade. Pericardial fluid usually appears as an echo-free (hypoechoic) space around the heart. Identifying fluid anterior to the aorta in the PLAX view is useful as a way to differentiate pericardial from pleural and peritoneal fluid; fluid seen anterior to the aorta in the PLAX view is pericardial, and fluid seen posterior is pleural or peritoneal. Fat in the pericardial space is common, but it is typically seen primarily anterior to the heart and is bright in appearance (hyperechoic). It is important to remember that the size of a pericardial effusion is not necessarily related to the risk of pericardial tamponade. Small amounts of fluid accumulating quickly may cause tamponade, whereas large pericardial effusions accumulating slowly typically do not (Video 24.10).

Several findings suggest a diagnosis of pericardial tamponade. In tamponade physiology, the pressure inside the pericardial space exceeds the diastolic pressure inside the cardiac chambers. This results in compression of the right ventricle and right atrium during diastole. Because the heart rate is typically high during pericardial tamponade, the compression may be difficult to appreciate and may not be visible in all cardiac cycles and in all portions of the respiratory cycle. We recommend recording long clips with multiple cardiac cycles and then reviewing these clips slowly to look for evidence of right heart chamber diastolic collapse (Video 24.11). Although not always present, the associated finding of a plethoric IVC that does not collapse with breathing would further support the diagnosis of cardiac tamponade. In this context, the high right atrial pressure indicated by assessment of the IVC is caused by the elevated pericardial pressure.

THE USES OF CRITICAL CARE ULTRASOUND

Perhaps the most studied and validated role for CCE is its use in detecting the cause of undifferentiated shock. It is often difficult to determine the reason for undifferentiated shock with traditional invasive monitoring and physical examination alone. Furthermore, transporting unstable patients to remote locations for imaging studies is not always feasible or safe. Ultrasound has the advantage of being portable, noninvasive, and repeatable, and it allows critical care physicians to make rapid assessments of pulmonary and cardiac physiology. Focused CCE has been shown to be reliable in providing rapid assessments of volume status, left ventricular function, the presence or absence of pericardial effusion, and right ventricular size and function and thereby aids in the diagnosis of undifferentiated shock.[25,29,30]

ASSESSMENT OF VOLUME STATUS

Determining volume status in critically ill, hemodynamically unstable patients is complex, and volume responsiveness (defined as a 10–15% increase in stroke volume or cardiac output with a crystalloid or colloid bolus of 250 to 500 mL[31]) is often difficult to predict. Although optimization of volume status improves outcomes, excessive fluid administration can lead to increased morbidity and mortality.[32–34] In addition, studies have shown that only one-half of hemodynamically unstable patients will respond to a fluid challenge.[11,35] Historically, intensivists have used a variety of invasive monitors, laboratory

studies, diagnostic studies, and physical examination maneuvers to predict volume responsiveness. In more recent times, IVC measurements, both static and dynamic, have emerged. Measured at one time point, IVC diameter, a surrogate for central venous pressure, is a static measure. Measuring the respiratory variation in the IVC diameter over time is a dynamic measure that has been found to have some success as a means of estimating fluid responsiveness in critically ill patients.[11,36,37]

Inferior Vena Cava Diameter and Collapsibility and/or Distensibility

When imaging the IVC for the purpose of estimating fluid responsiveness, both the absolute greatest diameter and the change in diameter with breathing should be assessed. IVC diameter and collapsibility (decrease in diameter of the IVC) in spontaneously breathing patients can be used to estimate right atrial pressure and, by extrapolation, central venous pressure. If the IVC is small (<2.0 cm) and collapses more than 50% with inspiration, the central venous pressure is low or normal. If the IVC is large (>2.0 cm) and does not collapse, the central venous pressure is elevated. Three indices have been studied with regard to respiratory variation of the IVC and prediction of fluid responsiveness: the IVC collapsibility index, the IVC distensibility index, and IVC diameter variation (Table 24.2). All three of these dynamic IVC measurements have been studied in mechanical ventilation; only the IVC collapsibility index has been studied in spontaneously breathing patients.[35,38–41]

Inferior Vena Cava and Volume Status

There is extensive literature on the accuracy of the IVC examination (in both spontaneously breathing and mechanically ventilated patients) in predicting volume responsiveness. Early studies on mechanically ventilated patients showed that an IVC distensibility index greater than 15% was suggestive of fluid responsiveness.[38,41] However, patients in these studies were receiving large tidal volumes (10 mL/kg) and were heavily sedated and/or paralyzed, which is uncommon in current critical care management. In some small studies of spontaneously breathing patients, higher values of the IVC collapsibility index (>40%) have been predictive of fluid responsiveness.[39,40] The change in IVC diameter with assisted ventilation (continuous positive airway pressure, bilevel positive airway pressure, supportive mechanical ventilation modes, high-flow nasal cannula) is much more difficult to predict and standardize given multiple confounding factors, including patient effort, chest wall compliance, and degree of positive end-expiratory pressure. In addition, there are many pitfalls associated with measuring the IVC and interpreting the examination. For example, movement of the IVC during inspiration can lead to misalignment of the scanning plane and overestimation of collapsibility. Imaging the aorta instead of the IVC can lead to the mistaken conclusion that there is an absence of respiratory variability. Finally, in several clinical conditions, IVC size and respiratory variability may not accurately predict preload or volume responsiveness.[42,43]

Because of inconclusive existing evidence on the accuracy of predicting volume responsiveness and the potential for misinterpretation, it is paramount to recognize the limitations of the IVC examination and to interpret images accordingly.[44] IVC examination is more useful with serial examinations and at the extremes (i.e., very collapsible or very dilated). In this context, we recommend the following approach for specific clinical scenarios:

- *Large IVC that does not collapse with respiration (patient not undergoing mechanical ventilation):* The patient is unlikely to benefit from additional fluid (except in the case of cardiac tamponade). Obtain cardiac views to evaluate for tamponade or obstructive shock. Perform a pulmonary ultrasound examination to evaluate for prominent B-lines suggestive of pulmonary edema. Consider diuresis if concern exists for decompensated heart failure or pulmonary edema causing respiratory failure.
- *Small IVC that collapses with respiration (patient not undergoing mechanical ventilation):* The patient may benefit from a fluid bolus. Evaluate the patient for deep breathing, which may exaggerate IVC collapsibility. If the patient is in shock, consider fluid administration.
- *Large IVC that does not collapse with respiration (patient undergoing mechanical ventilation)*: In this scenario it is unclear whether the patient will benefit from additional fluid or whether additional fluid will be harmful. Do not use an IVC examination alone to determine whether the patient will be volume responsive. We recommend performing a full CCU examination and using other clinical data to help determine volume status.
- *Small IVC that collapses with respiration (patient undergoing mechanical ventilation):* The patient is likely to be volume responsive. We recommend administering a fluid bolus if the patient is in shock if the respiratory status allows.

Table 24.2 Three Different Dynamic Inferior Vena Cava Measurements*

Measure	Formula	Study Patients
IVC collapsibility index (cIVC)	$\frac{(IVC_{max} - IVC_{min})}{IVC_{max}} \times 100$	Spontaneously breathing, mechanically ventilated
IVC distensibility index (dIVC)	$\frac{(IVC_{max} - IVC_{min})}{IVC_{min}} \times 100$	Mechanically ventilated
IVC diameter variation (ΔD_{IVC})	$\frac{(IVC_{max} - IVC_{min})}{(IVC_{max} + IVC_{min})/2} \times 100$	Mechanically ventilated

*Multiple different cutoff values have been reported for each of the measurements above in defining which patients in shock are more likely to respond favorably to administration of fluids. However, all of these measures have limited predictive utility.

IVC, inferior vena cava; max, maximum; min, minimum.

OTHER CRITICAL CARE ULTRASOUND EXAMINATIONS TO EVALUATE SHOCK AND ASSESS VOLUME STATUS

Basic Critical Care Echocardiography

Assessment of left ventricular function, presence or absence of pericardial effusion, and assessment of right ventricular size and function are all useful measurements

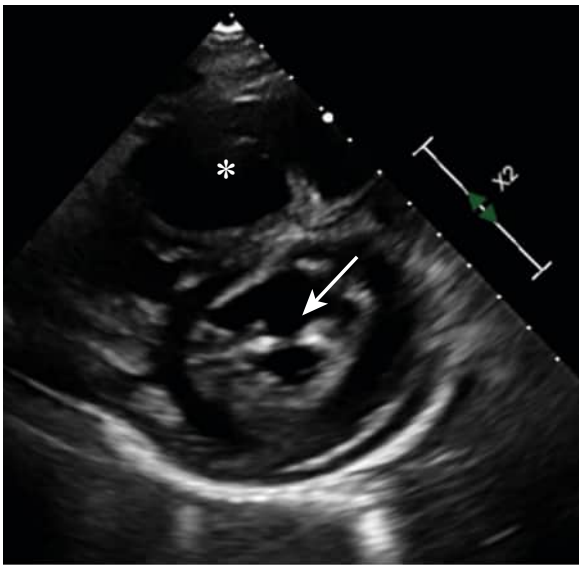

Figure 24.4 Underfilled left ventricle. The heart seen in a parasternal short axis view shows "kissing" papillary muscles (*arrow*) suggestive of an underfilled left ventricle. *Asterisk,* right ventricle.

to help determine the etiology of undifferentiated shock. A hyperdynamic left ventricle with complete obliteration of the left ventricular cavity in systole ("kissing" papillary muscles on the PSAX view) may be suggestive of an underfilled left ventricle and predict that a patient would benefit from fluid administration (Fig. 24.4). In the setting of hemodynamic instability, hemorrhagic shock from blood loss and distributive shock from sepsis should be considered as potential causes. Alternatively, decreased left ventricular function and/or the presence of obvious wall motion abnormalities may suggest that cardiac dysfunction is contributing to shock. This can be seen in the setting of myocardial infarction, myocarditis, chronic heart failure, and various other clinical settings such as sepsis-induced cardiomyopathy. Detecting the presence of left ventricular dysfunction can help guide decisions about using inotropic agents and vasopressors, withholding fluids to avoid volume overload, or obtaining more definitive diagnostic studies (e.g., complete echocardiography, cardiac catheterization). If a pericardial effusion is present in a patient with hemodynamic instability, the diagnosis of tamponade should be considered (Fig. 24.5). Depending on the clinical scenario, further imaging with complete echocardiography and consultation with cardiology or emergency pericardiocentesis may be indicated. An enlarged right ventricle seen in the A4C and/or subcostal view or flattening of the intraventricular septum in the PSAX view may indicate right ventricular dysfunction. When coupled with a positive deep venous thrombosis ultrasound examination in a patient with shock, these findings are highly suggestive of an acute pulmonary embolism (Fig. 24.6 and eFig. 24.3; see also Fig. 81.2).

Advanced Critical Care Echocardiography

Basic CCE can answer many questions about a patient in shock, but some cardiac causes of shock and/or respiratory failure may not be identified by this limited approach. For example, as mentioned, a patient with cardiogenic shock resulting from severe acute valvular regurgitation

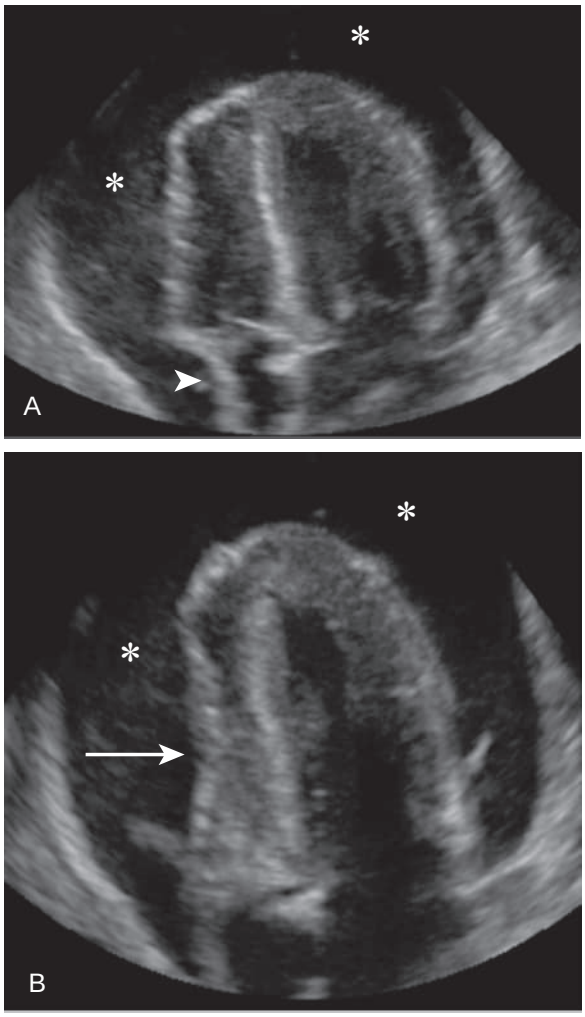

Figure 24.5 Cardiac tamponade. The heart is seen in an apical four-chamber view. The images show a large pericardial effusion with diastolic collapse of the (A) right atrium (*arrowhead*) and (B) right ventricle (*arrow*) suggestive of tamponade. *Asterisk,* pericardial fluid.

may show normal left ventricular function on a basic CCE examination. Advanced CCE can address some of these shortcomings. For example, using advanced CCE, one can perform cardiac ultrasound examinations to obtain quantitative measures such as cardiac output that can be repeated over time to assess the efficacy of therapeutic interventions.[45,46] Additional applications of advanced CCE include evaluation for severe valvular disease, noninvasive cardiac output measurement, identification of regional wall motion abnormalities, and measurement of pulmonary artery systolic pressure. A detailed description of these applications is beyond the scope of this chapter. It is important to recognize that competence in advanced CCE requires significantly more training and experience than required for basic CCE.[22]

Pulmonary Ultrasound

The pulmonary ultrasound examination is an important, simple, and sometimes underused tool for evaluating the patient in shock and/or respiratory failure. Pneumothorax is common in the ICU and can be related to trauma, underlying lung disease, mechanical ventilation, or procedural complications. The pneumothorax examination is fast and easy to

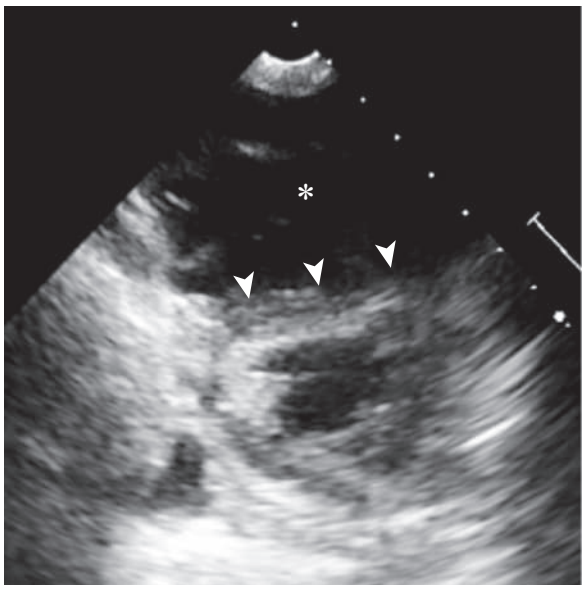

Figure 24.6 Flattening of the interventricular septum. The heart in the parasternal short-axis view shows a flattened or D-shaped septum (*arrowheads*) suggestive of right ventricular pressure or volume overload. *Asterisk,* right ventricle.

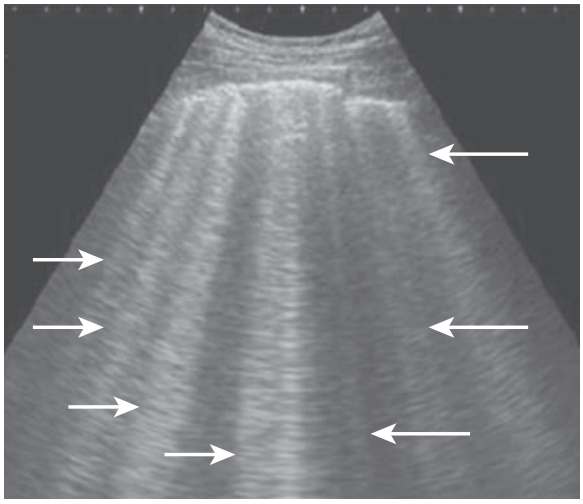

Figure 24.7 Lung ultrasound showing multiple B-lines (*arrows*) suggestive of interstitial edema. (From Blum M, Ferrada P. Ultrasound and other innovations for fluid management in the ICU. *Surg Clin North Am.* 2017;97:1323–1337.)

perform, and it can lead to an immediate intervention with chest tube placement, with resolution of shock. As detailed in Chapter 23, pneumothorax would be suspected if there is an absence of lung sliding and/or an absence of B-lines on pulmonary ultrasound examination. If a lung point is seen during the examination, then pneumothorax can be definitively diagnosed. Diffuse B-lines emanating from the lung parenchyma can aid in the diagnosis of respiratory failure and guide diuresis in patients with significant pulmonary edema (Fig. 24.7). The use of ultrasound to assess for pleural fluid in the setting of respiratory failure can lead to potential therapeutic interventions such as thoracentesis to improve clinical status. In the setting of shock, diagnostic sampling of

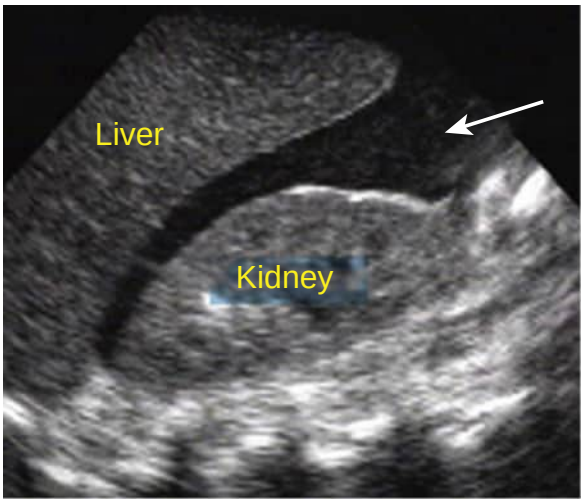

Figure 24.8 Examination of the right upper quadrant demonstrating free fluid between the liver and kidney. The potential space between the liver and the kidney, known as Morison's pouch, is the most common place for fluid to accumulate in the right upper quadrant view. If there is no fluid, there will be no space between the liver and the kidney. Free fluid appears either anechoic (*arrow*, as demonstrated in this figure) or hypoechoic (clotted blood, ascites). In an unstable trauma patient, a positive result of a *focused assessment with sonography in trauma* (FAST) examination is extremely sensitive and specific for intra-abdominal bleeding. In the intensive care unit setting, a positive result of a FAST examination is less specific and sensitive for acute hemorrhage (ascites and normal postsurgical changes may appear similar).

pleural fluid may yield the source of infection in sepsis and lead to source control with drainage of infected fluid. Finally, consolidations viewed on lung ultrasound examination suggest respiratory failure from pneumonia and, in the patient with shock, potential sepsis from a pulmonary source.

Abdominal Ultrasound

Abdominal ultrasound can detect the presence of intra-abdominal hemorrhage, aortic abnormalities, and potential sources of septic shock. The *focused assessment with sonography in trauma* (FAST) examination has been used and validated extensively in trauma to detect the presence of free fluid suggestive of active bleeding in hemodynamically unstable patients with blunt injury.[47] Although a "positive" FAST examination result in the ICU is much less specific, some findings can be helpful. Serial abdominal ultrasound examinations showing increasing size of fluid pockets in an unstable patient suggests intra-abdominal hemorrhage as a cause of shock (Fig. 24.8). Abdominal ultrasound with examination of the aorta may reveal an enlarged abdominal aorta or aortic dissection. Finally, in patients with suspected septic shock, abdominal ultrasound may reveal hydronephrosis or other fluid collections concerning for abscesses when looking for sources of infection (Fig. 24.9).

PUTTING IT ALL TOGETHER: A SYSTEMATIC APPROACH

Given the limitations and pitfalls of using any one measurement to elucidate the etiology of shock in critically ill patients, we recommend completing a comprehensive

CCU examination on patients in shock. This includes not only cardiac ultrasound, but pulmonary ultrasound, abdominal ultrasound, and the deep venous thrombosis examination when indicated. Each of these examinations has unique findings depending on the etiology of shock and, when combined, will provide a clearer clinical picture and help yield a diagnosis (Table 24.3). For example, a patient with cardiogenic shock may have decreased left ventricular function and a dilated, noncollapsing IVC on cardiac ultrasound and prominent B-lines on pulmonary ultrasound. A patient with hemorrhagic shock may have hyperdynamic left ventricular function, a small and collapsible IVC, and free fluid on abdominal ultrasound.

Numerous protocols for ultrasound in shock and critical illness have been developed as CCU has become more ubiquitous in critical care. Each protocol uses some combination of the core ultrasound examinations described previously (e.g., cardiac, pulmonary, abdominal) to create a fast and systematic way to use ultrasound to aid in diagnosis and guide resuscitation in shock.[48] In addition, each protocol prescribes the order in which the different ultrasound examinations should be performed. Because of the complex nature of critically ill patients across different ICUs (e.g., cardiac, medicine, surgical), we do not recommend a single protocol for CCU.[48] Instead, we suggest tailoring each CCU examination to the patient's real-time clinical scenario and adding additional ultrasound examinations as needed to enhance clinical understanding. For example, in a patient with acute respiratory distress, hypotension, and high peak pressures immediately after a central line was placed in the internal jugular vein, the highest priority and most appropriate ultrasound examination to perform would be the lung ultrasound to evaluate for pneumothorax. In a more complex patient with hypoxemia, hypotension, elevated lactate, and fever who has just had major abdominal surgery, a more comprehensive examination, including cardiac, IVC, FAST, and potentially deep venous thrombosis examinations, would be appropriate.

When performing CCU, it is important to know the limitations of each component of the ultrasound examination. Findings should always be interpreted in the context of the patient's entire clinical picture. Examinations should be repeated as indicated to evaluate for both the efficacy of therapeutics and the need for further interventions. Any unclear or clinically relevant findings should prompt more complete diagnostic studies. Guidelines for the use of ultrasound in the critical care setting have been developed by professional societies with expert consensus.[49–51] It is essential that training programs adhere to these guidelines and establish robust, longitudinal ultrasound curricula that ensure competency of trainees. CCU is a valuable tool to improve patient care when used in the appropriate scope of practice by competent providers. As this section has described, CCU is vital in the setting of undifferentiated shock and/or respiratory failure, and it should be incorporated into daily practice in the critical care setting.

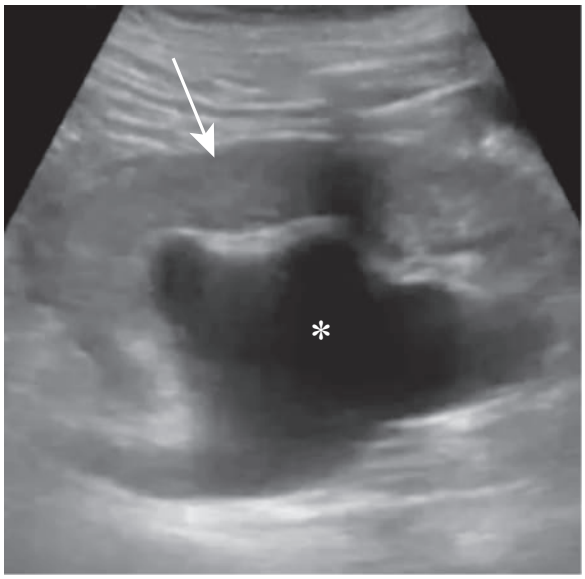

Figure 24.9 Hydronephrosis. Left kidney ultrasound examination shows severe hydronephrosis with a severely dilated renal pelvis. In a patient with sepsis, this finding could suggest a urinary source of infection. *Arrow,* renal parenchyma; *asterisk,* renal pelvis.

Table 24.3 Patterns of Findings on Critical Care Ultrasound in Shock

Parameter	Cardiogenic	Hypovolemic or distributive	Obstructive*
Cardiac function	Abnormal	Normal or hyperdynamic	Hyperdynamic LV RV dysfunction
Cardiac filling	Full	Underfilled RV and LV	Underfilled LV
Other cardiac findings	Wall motion abnormalities Valvular disease	—	Pericardial effusion
Inferior vena cava	Enlarged, noncollapsible	Collapsible	Enlarged, noncollapsible
Pulmonary	Pulmonary edema	Consolidation or pleural effusion (source of sepsis)	Pneumothorax
Vascular	—	—	Deep venous thrombosis
Abdominal or FAST	—	Free fluid Hydronephrosis	—

*Ostructive shock is considered to be mostly extracardiac, usuallly due to pulmonary vascular obstruction but also tamponade or pneumothorax.
FAST, focused assessment with sonography in trauma; LV, left ventricle; RV, right ventricular.

Key Points

- Noncardiologists can learn to acquire and interpret cardiac ultrasound images and use their findings to make patient management decisions.
- Critical care echocardiographic images should be carefully evaluated and, if image quality is not adequate for interpretation, the data should be discarded and not incorporated into patient care decisions.
- The four assessments used to determine the left ventricular systolic function are (1) change in the left ventricular cavity size, (2) thickening of the left ventricular myocardium, (3) opening of the mitral valve, and (4) motion of the mitral annulus.
- Foreshortening of the left ventricle in the apical four-chamber view is important to recognize and avoid because it can lead to overestimation of left ventricular systolic function and to underestimation of right ventricular systolic function.
- The clinical meaning of right atrial pressure determined by imaging of the inferior vena cava varies depending on the clinical context. For example, elevated right atrial pressure is a feature of both decompensated heart failure and cardiac tamponade.
- Ultrasound examination of the inferior vena cava has limitations for use in predicting which patients will improve hemodynamically following fluid administration. Our approach is to emphasize the value of either a very collapsed or a dilated inferior vena cava, serial inferior vena cava examinations, and incorporation of other clinical data into clinical decision making about fluid administration.
- When assessing a patient in shock, examinations of multiple body areas (critical care echocardiography, pulmonary ultrasound, abdominal ultrasound) should be combined to make the correct diagnosis and treatment decisions.
- It is important to know the limitations of critical care ultrasonography. Complete imaging or consultation with specialty services should be considered to evaluate further or to clarify clinically significant or unexpected findings or when critical care ultrasonographic images are not adequate for diagnosis.

Key Readings

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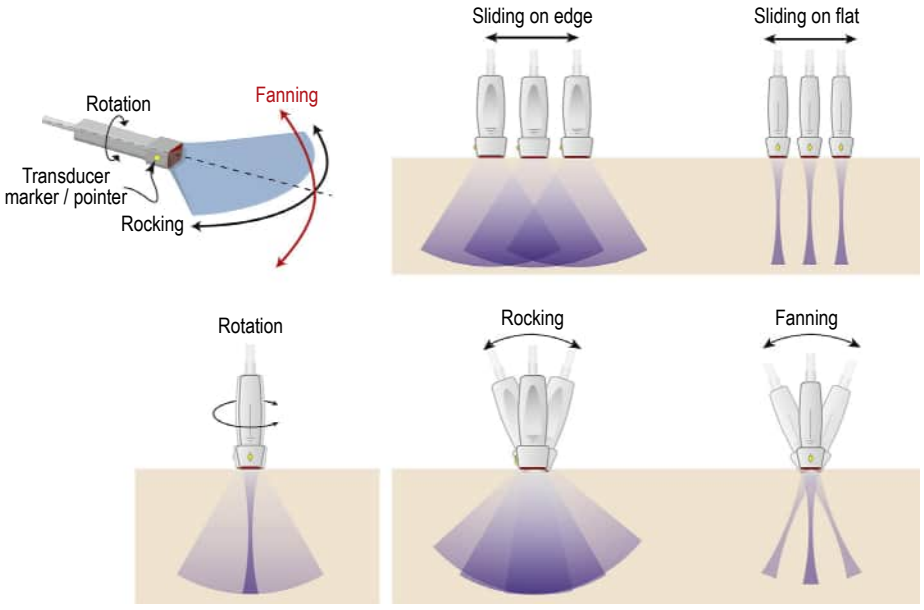
Complete reference list available at ExpertConsult.com.

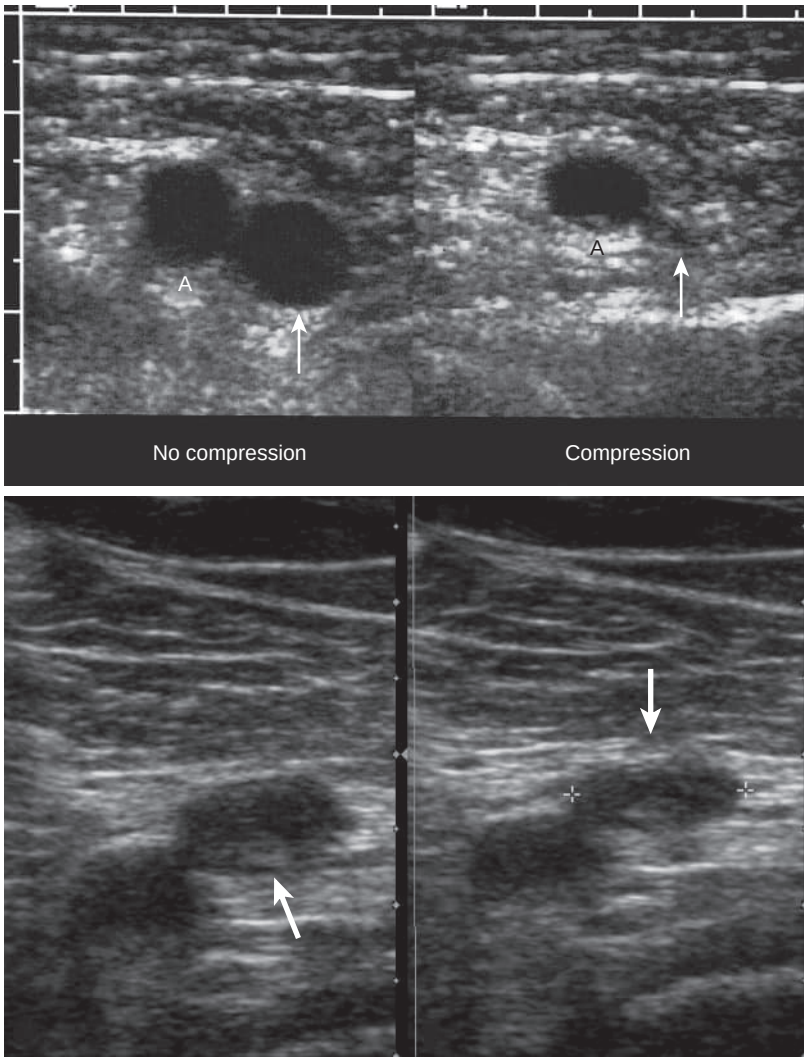
eFIGURE IMAGE GALLERY



eFigure 24.1 Optimal patient positioning for the cardiac ultrasound examination. The optimal position to obtain the parasternal long-axis (PLAX), short-axis (PSAX) and apical views is with the patient in the left lateral decubitus position (*center image*). Even in sick intubated patients, some degree of left lateral decubitus positioning can be achieved, which markedly increases the likelihood that good-quality, interpretable images can be obtained. Optimal positioning for the subcostal view is with the patient flat on the back with knees flexed. (Courtesy Bernard E. Bulwer, MD, FASE.)



eFigure 24.2 Nomenclature of transducer motions. These maneuvers should be performed sequentially rather than simultaneously (e.g., fan only; do not also rock in the same maneuver) to obtain and optimize an image in a stepwise fashion. (From McLean A, Huang S. *Critical Care Ultrasound Manual.* Churchill Livingstone; 2012.)



eFigure 24.3 Normal and abnormal collapse of the femoral vein with compression during ultrasound examination. *Top*, Transverse image of the femoral artery (*A*) and vein (*thin arrow*) before compression (*left*) and after compression (*right*) with the sonographic transducer, demonstrating normal vein collapse with compression. *Bottom*, In a patient with deep venous thrombosis, the femoral vein does not collapse normally. With no compression (*left*), the femoral vein is shown (*arrow*); with compression (*right*) (in the direction of *arrow*), the vein fails to collapse. (*Top,* From Rumack CM, Wilson SR, Charboneau JW, Levine D. *Diagnostic Ultrasound*. 4th ed. Philadelphia: Mosby; 2011.)

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25 POSITRON EMISSION TOMOGRAPHY

CHRISTOPHE M. DEROOSE, MD, PHD • CHRISTOPHE DOOMS, MD, PHD

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INTRODUCTION

Positron emission tomography (PET) is a noninvasive imaging technique allowing depiction of molecular targets or metabolic processes. Its main clinical applications are in the field of respiratory medicine, where PET has evolved from a tool for in vivo research to a routine imaging test for patients with lung tumors at many different stages of disease. The main use currently is for staging of lung cancer, where it is a crucial tool for determining the *tumor, nodal, and metastatic* components of cancer stages. However, it has important applications for other cancers, such as small cell lung cancer, mesothelioma, and neuroendocrine tumors. It is increasingly used to follow response to therapy and monitor patients in follow-up after therapy with curative intent. New tracers are also being developed. Because ^{18}*F-fluorodeoxyglucose* (^{18}F-FDG) is by far the most commonly used tracer for this purpose, the term PET refers to ^{18}F-FDG-PET unless stated otherwise.

PRINCIPLES

POSITRON EMISSION TOMOGRAPHY CAMERA

A PET camera produces tomographic images that represent the three-dimensional distribution of radioactivity within the body of a patient. Any molecule labeled with a positron-emitting radionuclide can be used to generate PET images. The PET camera consists of a number of rings containing several thousands of scintillation detectors that detect high-energy photons resulting from the annihilation of the emitted positrons when the radionuclide decays. To identify the direction of the incoming rays, a conventional gamma camera uses lead collimators that block photons from directions. A PET camera does not need physical collimators to generate an image and uses a complex algorithm to trace the high-energy photons back to their source in the body, an "electronic" collimation. As a result, instead of losing more than 99% of the emitted photons to absorption from the collimators, PET has higher sensitivity (counts per unit of radioactivity) and higher spatial resolution. The spatial resolution of contemporary PET cameras is about 3 to 4 mm, allowing characterization of lesions larger than 6 to 8 mm. Smaller lesions cannot be accurately depicted except for strongly FDG–avid lesions. Images can be acquired with or without respiratory gating.[1]

Modern PET cameras are hybrid systems in which a PET camera is combined with a morphologic imaging modality, either *computed tomography* (CT)[2] or a *magnetic resonance* (MR) camera. The morphologic imaging modality adds the following to the PET image: (1) increased accuracy of the exact position of the lesion and morphologic characterization of the underlying correlate, reducing equivocal findings; (2) increased confidence of the reporting physician; (3) in the case of PET/CT, CT-based attenuation correction, which corrects for absorption of signal by the body of the patient. To match the respiratory phase of PET, which is expiration dominated, the CT is often performed in expiration, which can lead to limited depiction of small lesions and increase in density of ground-glass lesions compared to inspiratory CT.

PET/MR imaging and PET/CT show an equivalently high diagnostic and *tumor-node-metastasis* (TNM) staging performance in *non–small cell lung cancer* (NSCLC).[3] The main disadvantages of PET/MR are its higher cost, lesser availability, smaller bore size, more difficult imaging of lung parenchyma, and typically longer scan times. On the other hand, it offers better assessment of thoracic wall and diaphragmatic invasion than PET/CT, and MR of the brain, the test of choice for detecting brain metastasis, can be performed simultaneously. Due to current limited availability of PET/MR (one system for each 20 to 50 PET/CT scans performed[4]), PET/CT is the current modality used to evaluate lung cancer patients.

In a recent trend, the PET camera rings are increased, leading to a larger *field of view* (FOV) and allowing shorter scan times, less injected activity, or both. Typical scan times are 10 to 15 minutes for PET/CT cameras with an FOV of approximately 20 cm and skull-to-thigh imaging. Total-body PET scanners, using cameras with a very large FOV, up to greater than 190 cm,[5] allow acquisition of a whole-body image (skull-to-toe) and completion of imaging within 1 minute. PET is preferably combined with a high-dose, contrast-enhanced diagnostic CT for more precise TNM staging, because localization and interpretation of the CT is superior compared to that of low-dose CT.[6]

METABOLIC TRACER: ^{18}F-FLUORODEOXYGLUCOSE

For clinical cancer imaging, the glucose analog FDG is by far the most common tracer. Its use is based on the observation that cancer cells have an increased cellular uptake of glucose, due to an increased expression of facilitative *glucose transporters* (GLUTs), and a much higher rate of glycolysis.[7] FDG is a glucose analog in which the oxygen molecule in position 2 is replaced by a positron-emitting fluorine-18 atom, undergoes the same uptake as glucose, but it is metabolically trapped and accumulated in the neoplastic cell after phosphorylation by hexokinase.[8] The radiation dose for a typical examination is in the order of 5 to 8 mSv.[9]

The image units with FDG-PET can be quantitative in nature (expressed in mmol glucose used per minute per gram of tissue), but this requires time-consuming dynamic scanning (continuous imaging of a lesion for about 60 minutes). In clinical practice, FDG uptake is expressed as the *standardized uptake value* (SUV), a semiquantitative measure of tracer uptake that normalizes the uptake within a lesion by the injected activity per unit of body weight. The SUV is thus the ratio between the observed radioactivity concentration in a specific tissue (e.g., primary tumor) and the virtual concentration that would be observed if the full amount of the injected tracer spread evenly in the entire body. SUV can be determined in the voxel (i.e., a volume unit of information, a volumetric pixel) with the *highest value of a volume of interest in the image* (SUV_{max}) or on the whole lesion (SUV_{mean}).

INTERPRETATION OF PET IMAGES

For tumor detection, visual analysis focuses on the detection of lesions with activity higher than background not caused by physiologic processes, both for the discrimination of nodules and for the evaluation of mediastinal involvement. Non–attenuation correction images should be examined to detect small lung lesions because they have a higher contrast than corrected images. High physiologic FDG uptake is present in the brain (cortex > white matter), kidney, and urinary tract (due to urinary excretion) and can be present in the heart.[10] There is a low degree of physiologic uptake of FDG in the other thoracic structures. The high uptake in the brain interferes with lesion detection in the brain, which is one of the weaknesses of PET.

False-positive findings can be anticipated because FDG uptake is not tumor specific. Uptake of FDG can be found in all active tissues with high glucose metabolism, particularly in those with inflammation. Therefore, clinically relevant FDG–positive findings, especially if isolated and decisive for patient management, require confirmation. The differentiation between metastasis, a benign[11] or inflammatory lesion, or even an unrelated second malignancy should be made by other tests or tissue diagnosis. The major causes of false-positive results in chest pathology are infectious, inflammatory, and granulomatous disorders (Table 25.1) and recent iatrogenic procedures.[12] An emerging class of nonmalignant uptake is seen in patients treated with immuno-oncologic drugs, where immune-related side effects can cause inflammation in a range of organs and be detected by FDG-PET imaging.[13]

Table 25.1 Reasons for False-Positive and False-Negative PET Findings.

FALSE-POSITIVE FINDINGS
Infectious/Inflammatory Lesions
(Postobstructive) pneumonia/abscess
Mycobacterial or fungal infection
Granulomatous disorders (sarcoidosis, granulomatosis with polyangiitis)
Chronic nonspecific lymphadenitis
Rheumatoid arthritis
Occupational exposure (anthracosilicosis)
Bronchiectasis
Organizing pneumonia
Reflux esophagitis
Iatrogenic Causes
^{18}F-FDG embolus
Invasive procedure (puncture, biopsy)
Talc pleurodesis
Radiation esophagitis and pneumonitis
Bone marrow expansion postchemotherapy
Colony-stimulating factors
Thymic hyperplasia postchemotherapy
Benign Mass Lesions
Salivary gland adenoma (Whartin)
Thyroid adenoma
Adrenal adenoma
Colorectal dysplastic polyps
Focal physiologic ^{18}F-FDG-uptake
▪ Gastrointestinal tract
▪ Muscle activity
▪ Brown fat
▪ Unilateral vocal cord activity
▪ Atherosclerotic plaques
FALSE-NEGATIVE FINDINGS
Lesion Dependent
Small tumors (<8–10 mm)
Ground-glass opacity neoplasms
Carcinoid tumors
Lower lobe lesions (with greater respiratory motion)
Technique Dependent
Hyperglycemia
Paravenous ^{18}F-FDG injection
Excessive time between injection and scanning

FDG, fluorodeoxyglucose; PET, positron emission tomography.

False-negative findings are less common and may be due to lesion-dependent or technical factors (Table 25.1). Early lesions in the development of lung adenocarcinoma can rely on intracellular glucose transport mediated by the *sodium-glucose cotransporter* (SGLT), not GLUT, resulting in low FDG avidity.[14] Certain tumors are also known to have decreased FDG uptake, such as small-sized very well-differentiated adenocarcinoma, adenocarcinoma with lepidic growth, or carcinoid tumors (see eFig. 78.6). Small lesions, less than 5 mm, may be falsely negative due to the limitations in spatial resolution. Lesions in the lower lung fields, where respiratory motion exceeds that in the apices, may be more difficult to detect due to motion, and the detection limit may even be 10 mm.[15] High blood glucose levels can reduce ^{18}F-FDG uptake through competitive inhibition of GLUT and hexokinase, and blood glucose should be measured and confirmed to be within an acceptable range (typically 60–180 mg/dL) before tracer injection.

DIAGNOSIS

Noncalcified *solitary pulmonary nodules* (SPNs) are a common finding on radiograph or CT in clinical practice and have become even more common with the increasing use of low-dose spiral CT for early lung cancer detection.[16] FDG-PET/CT is a routine technique in the determination of a malignant etiology of these nodules[17] (see also Chapters 41 and 75).

Initial PET studies in the diagnosis of SPNs used a threshold value of greater than 2.5 for the SUV_{max} for the diagnosis of malignancy. With this criterion, overall sensitivity, specificity, and positive and negative predictive values of 96%, 78%, 91%, and 92%, respectively, were reported in a meta-analysis based on series with nodules larger than 1 cm[18] (Fig. 25.1).

The use of SUV_{max} of less than 2.5 to exclude malignancy has been challenged. Solid malignant lesions of at least 1 cm will usually have an SUV_{max} greater than 2.5, but smaller cancers, lesions with ground-glass appearance on CT (e.g., the lepidic type of adenocarcinoma[19,20]; Fig. 25.2), or tumors with low metabolic activity (e.g., typical carcinoid tumors[21,22]) may be missed. Early lesions in pulmonary adenocarcinoma development, such as adenocarcinoma in situ, minimally invasive adenocarcinoma, mucinous adenocarcinoma, and lepidic adenocarcinoma, can have SUV_{max} values less than 2.5, with a stepwise increase in SUV from adenocarcinoma in situ to micropapillary invasive adenocarcinoma.[23,24] A large prospective study with PET/CT scanning in indeterminate SPNs

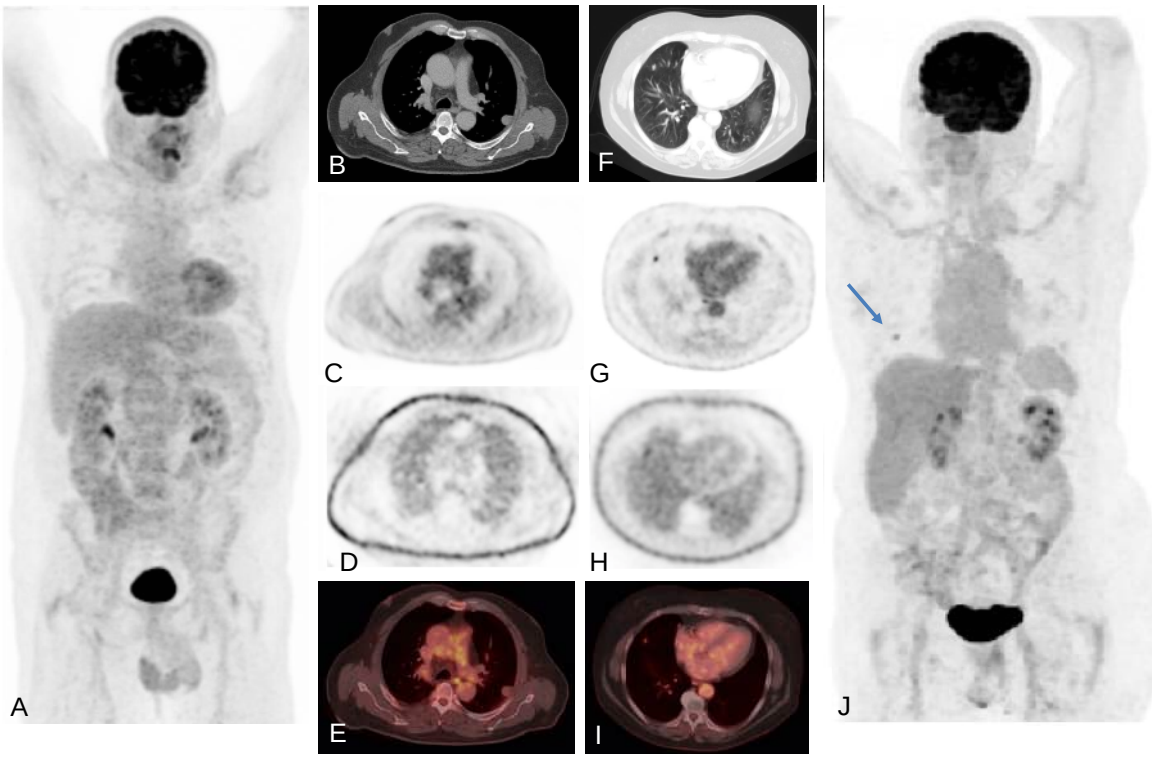

Figure 25.1 Solitary pulmonary nodules in two patients: value of *positron emission tomography* (PET) in diagnosis. Two patients with a solitary pulmonary nodule lesion differentiated by ^{18}F-*fluorodeoxyglucose* (FDG) PET/*computed tomography* (CT). (A–E) The first patient, a 60-year-old man, presented with a smooth juxtapleural nodule in the left upper lobe on CT (B), with limited growth over a 4-month period up to 19 mm. Both the attenuation-corrected and non–attenuation-corrected transverse FDG-PET images (C and D, respectively) show absence of increased FDG uptake, with a maximum standardized uptake value of 2.1. The fusion image shows uptake within the lesion lower than in the mediastinal vessels (E). Histology after wedge resection demonstrated a pulmonary fibrous hamartoma. (F–J) The second patient, a 69-year-old woman, had a history of chemoradiation treatment for a bronchial squamous cell carcinoma 6 years before presentation with a slowly growing 7 mm large, irregularly delineated lesion on CT (F). FDG-PET/CT showed focal increased uptake, on both the attenuation-corrected (G) and non–attenuation-corrected (H) images, corresponding to the nodule on the fusion images (I). The maximum standardized uptake value was 3.9, and the lesion was clearly visible on the maximum intensity projection images (J, *arrow*). Pathology after right middle lobe lobectomy showed bronchial adenocarcinoma.

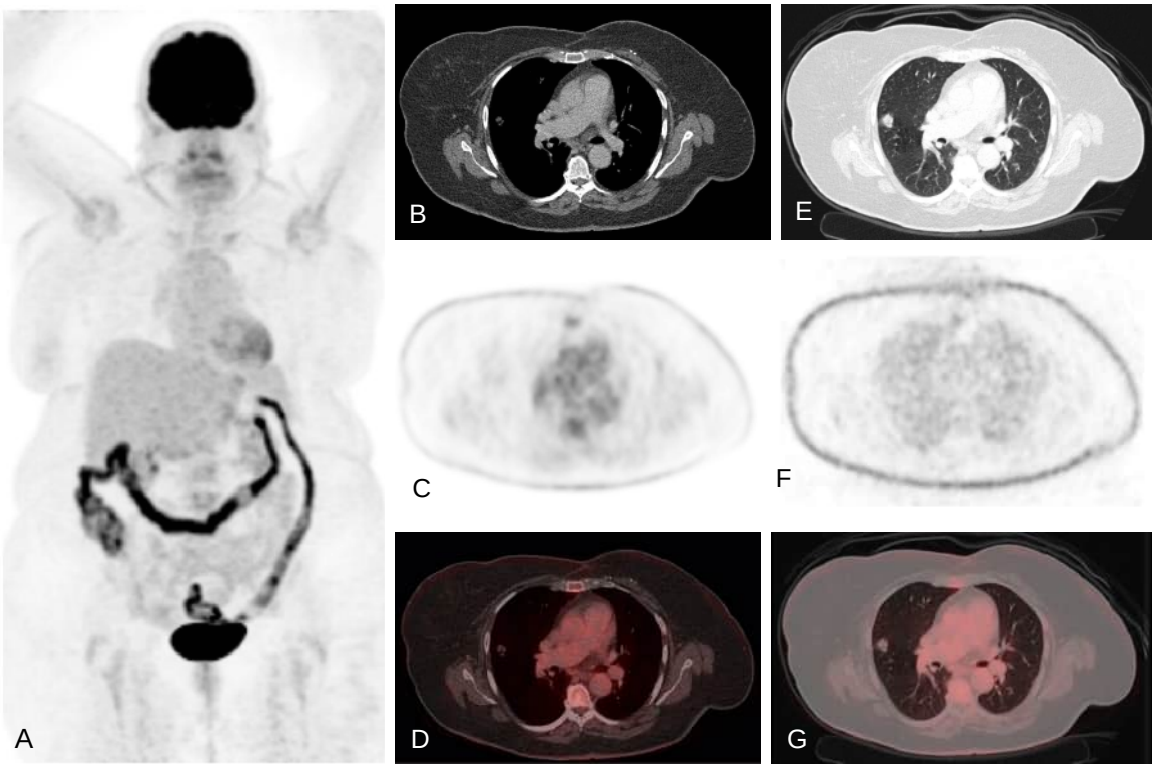

Figure 25.2 False-negative ^{18}F-*fluorodeoxyglucose* (FDG) positron emission tomography finding. (B and E) A 65-year-old woman with a 17-mm part-solid nodule with central lucency in the right upper lobe. There is absence of FDG uptake in the lesion on the maximum intensity projection image (A), attenuation-corrected (C) and non–attenuation-correction image (F), confirmed by the fusion images (D and G). The maximum standardized uptake value was 0.84. Pathology after lobectomy showed a bronchial mucinous adenocarcinoma with lepidic growth pattern.

less than 2.5 cm reported a 24% chance of a malignant nodule when SUV_{max} was between 0 and 2.5, 80% if between 2.6 and 4.0, and 96% if 4.1 or more.[25]

Rather than using the SUV_{max} criterion as a threshold, the visual information from PET images (lesions with any increased FDG-uptake being potentially malignant) should be added to the comprehensive nodule assessment based on clinical characteristics (smoking and age being core factors), imaging characteristics (aspect and margins on CT), and growth pattern if available. With this approach, PET improves standard prediction models to estimate the chance of malignancy in an SPN. The added benefit of PET in this setting was examined in a series of 106 radiologically indeterminate SPNs (61 malignant).[26] PET improved the accuracy over a clinical and radiographic prediction model[27] by 13.6% when measured as improvement in area under the receiver operating characteristic curve. This so-called Herder model, which uses FDG-PET information in addition to clinical and radiologic data, is recommended by several guidelines, including those from the British Thoracic Society.[28]

Recent meta-analyses have shown that the positive predictive value of FDG-PET evaluation of SPNs is dependent on the incidence of known causes of false positives, in particular endemic infectious lung disease. In a large meta-analysis including 70 studies (of which 10 were in areas of endemic fungi) evaluating 8511 nodules (60% cancer incidence), there was a 16% lower average- adjusted specificity for malignancy in regions with endemic infectious lung disease (61%) compared with nonendemic regions (77%).[29] As expected, sensitivity was not influenced by endemic infections (88% in nonendemic vs. 94% in endemic regions).

STAGING

According to the extent of the primary *tumor* (T), the spread to locoregional *lymph nodes* (N) and the presence of distant *metastasis* (M), lung cancer patients of different TNM subsets with similar prognosis are grouped into stages. Stage is the most important factor in prognosis and choice of treatment[30,31] (see also Chapter 76). Therefore, reliable noninvasive methods for accurate staging are very important. CT scan, endoscopic techniques, and surgical staging procedures are key players, but addition of PET to these conventional methods has been shown to improve the staging process substantially by distinguishing patients who are candidates for curative approaches, such as surgical resection or intense multimodality treatment, from those who are not.[32]

For the T factor, detailed images of modern multislice CT allow the reviewer to evaluate the relationship of the tumor to fissures, mediastinal structures, and the pleura and chest wall, determining the type of resection most appropriate, if any. Integrated PET/CT images may allow more precise evaluation of chest wall and mediastinal infiltration or correct differentiation between tumor and peritumoral inflammation or atelectasis[33–35] (Fig. 25.3).

For the N factor, initial studies[36,37] indicate the addition of PET to CT results in more accurate lymph node staging than CT alone, with an overall sensitivity of 80–90% and specificity of 85–95%.[38–40] The absence of mediastinal lymph node

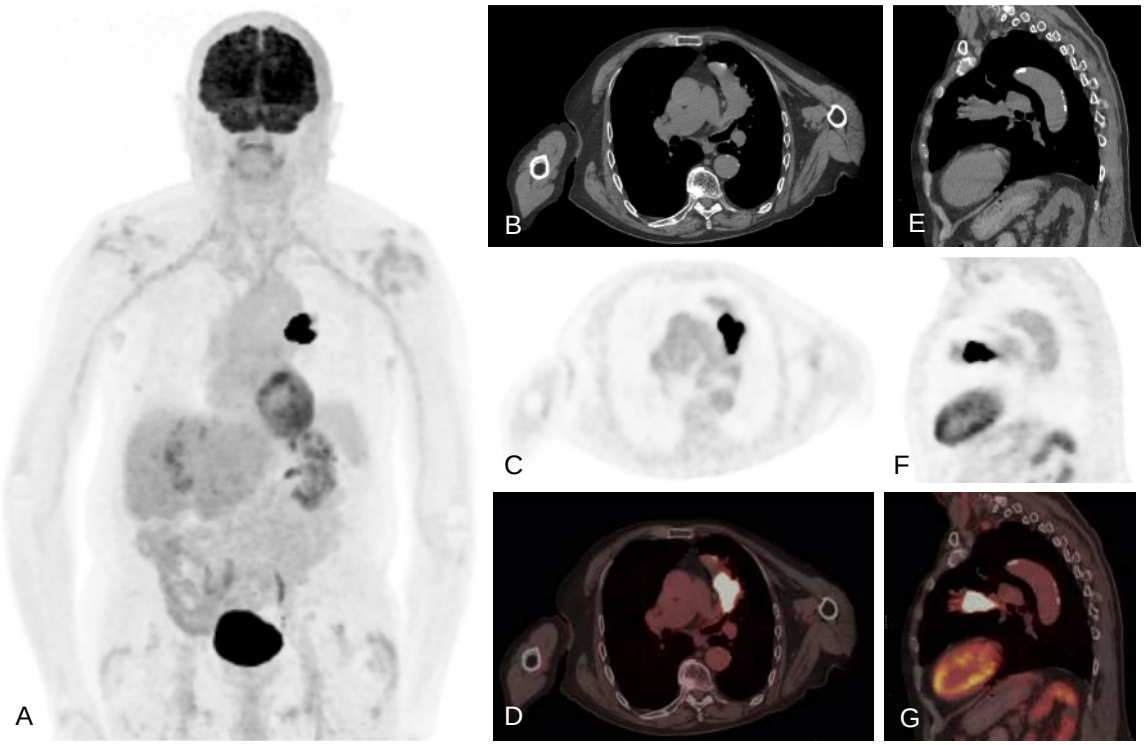

Figure 25.3 Usefulness of ^{18}F-*fluorodeoxyglucose* (FDG) *positron emission tomography* (PET)/*computed tomography* (CT) in determination of T stage. An 84-year-old man presented with an increasing consolidation (81 mm longest diameter) in the left upper lobe visualized on unenhanced CT (B and E). On FDG-PET/CT, the mass showed very intense FDG avidity (maximum standardized uptake value of 59.4) in the central part, with only very limited uptake in the more distal part, in line with the mediastinal blood pool (A, C, D, F, G). The distal part was caused by postobstructive mucus plugging. The longest diameter of the FDG-avid part was 48 mm, leading to a T2B stage instead of a T4. Biopsy showed bronchial squamous cell carcinoma.

disease on PET/CT has a high negative predictive value; invasive lymph node staging tests may thus be omitted in these patients, who can proceed straight to surgical resection. Exceptions to this include a primary tumor greater than 3 cm, insufficient FDG-uptake in the primary tumor, hilar nodal disease (N1), or a centrally located tumor that may obscure coexisting N1 or N2 disease on PET. When PET/CT is suggestive of lymphatic spread, images may direct tissue sampling procedures, such as *endobronchial ultrasound* (EBUS)-guided or *esophageal ultrasound* (EUS)-guided transbronchial needle aspiration or cervical mediastinoscopy. Because there may be false-positive images in lymph nodes (based on the conditions listed in Table 25.1), pathologic proof of lymph node involvement should be sought in most patients with positive mediastinal nodes on PET, except those with obvious bulky nodes on imaging.

For the M factor, PET added to CT is almost uniformly superior to CT alone, except for brain imaging, where sensitivity is unacceptably low due to the high glucose uptake of normal cortical brain tissue. For detecting extrathoracic metastases, the pooled sensitivity and specificity for PET/CT were 77% (95% confidence interval [CI], 47 to 93) and 95% (95% CI, 92 to 97), respectively, in a recent meta-analysis.[41] MRI remains the method of choice for brain imaging.

For bone metastases, which are actually bone *marrow* metastases not necessarily affecting the mineral content of bone tissue, PET is more accurate than *technetium-99m–methyl diphosphonate* (^{99m}Tc-MDP) bone scintigraphy; sensitivity is at least as good (90–95%), and specificity is far superior (95% vs. 60%).[42,43] Limitations are the limited FOV when PET images only from the head to just below the pelvis, and possible false-negative findings in osteoblastic lesions, which are nonetheless rare in untreated lung cancer. A series of PET/CT-guided bone biopsies has shown very high diagnostic yields (>95%) and confirmed bone metastases in 48 out of 51 patients, with other non-NSCLC malignant lesions confirmed in the remaining three patients.[44]

For adrenal gland metastases, PET has a high sensitivity of detection so that an equivocal lesion on CT without corresponding FDG uptake on PET has a low probability of being metastatic. PET may also be of help in evaluating hepatic lesions that remain indeterminate by conventional studies. PET may reveal metastases in sites that escape attention or are outside the FOV in conventional staging (Fig. 25.4), including soft tissue lesions, retroperitoneal lymph nodes, hardly palpable supraclavicular nodes, and painless bone lesions. Exclusion of malignancy requires caution in case of smaller lesions (<1 cm) (see Table 25.1). A particular example is the finding of small contralateral lung nodule(s), common in the era of spiral multislice CT, where PET/CT often does not give certainty so that invasive sampling by, for instance, thoracoscopy or rigorous follow-up, is still needed.

For pleural metastases, the use of PET/CT has shown promising results[45–47] because small pleural deposits, especially without an associated pleural effusion, can be missed on CT imaging alone due to low tumor load and/or partial volume effects. Inflammatory pleural lesions can cause false-positive findings, such as pleurodesis-induced inflammation. A recent meta-analysis of 323 lung cancer patients has shown an acceptable diagnostic accuracy, with a sensitivity

of 86% and specificity of 80%.[48] If pleural abnormalities determine the choice for curative treatment, pathologic verification with cytology or thoracoscopy is needed.

INFLUENCE ON TREATMENT CHOICES AND PLANNING WITH CURATIVE INTENT

PET has a significantly complementary role to CT for two reasons. First, unexpected lymph node or distant organ metastatic spread (see Fig. 25.4) may be detected. After a negative conventional staging, unknown metastases are found on PET/CT in 5–20% of the patients, in increasing numbers from clinical stage I to III tumors.[49–57] Second, PET is able to determine the nature of some equivocal lesions on conventional imaging.[49,50,52,53] Interpretation is indisputable when whole-body PET shows multisite metastases, but an isolated suspect lesion that would exclude candidacy for curative treatment should always be verified by other tests or tissue sampling because of the risk of a false-positive finding (see Table 25.1) or a second primary tumor. In one large retrospective series of NSCLC patients, solitary extrathoracic lesions were documented in about 20% of the patients.[53] About half of these were metastatic, whereas the other half were not related to lung cancer; they were either inflammatory, other benign lesions, or second primary tumors. In nonrandomized studies, PET induced a change of stage in 27–62% of NSCLC patients, in general more often upstaging than downstaging, mainly due to the detection of unexpected distant lesions.

The effect of adding PET or PET/CT to a standard lung cancer staging algorithm has been investigated in several randomized controlled trials.[58,59] In an early Dutch trial,[58] patients with stages IIIA and IIIB were included (29% of total) and the end point of "futile thoracotomy" (a surgical procedure deemed not to result in benefit to the patient) was clearly defined (i.e., benign disease, explorative thoracotomy, pathologic stage IIIA–N2/IIIB, or postoperative relapse or death within 12 months). In the PET arm of this trial, a reduction in futile thoracotomies of 20% in all patients was observed. Selection of surgical candidates using PET reduced the frequency of futile thoracotomies by 50% in those who underwent surgery.

Three later trials used PET/CT imaging in addition to standard workup, two of which were in the surgical setting. The study by Fischer and colleagues[60] largely reproduced the Dutch experience, with a significant reduction of futile thoracotomies (42% of all patients in the control group underwent a futile thoracotomy vs. 21% in the PET/CT group; 52% of performed thoracotomies in the control group were futile vs. 35% in the PET group). The study by Maziak and colleagues[61] mainly looked at improved correct upstaging in resectable stage I to III NSCLC and met this primary end point. Overall, there was a 4–11% increased detection rate of stage IV disease.[60,61] The use of PET/CT led to a positive change in patient management, both in intent (curative vs. palliative) and modality (chemotherapy vs. other modalities). In a study in unresectable stage III NSCLC, upstaging was correct in 21 of 140 (15%) patients with PET/CT versus 4 of 149 (2.7%) with CT only ($P = 0.0002$). Thus, the evidence shows significantly more accurate TNM staging with PET/CT compared to conventional imaging alone, influencing treatment decisions (e.g., the avoidance of futile surgery) and goals of therapy (curative or palliative intent). Although more accurate staging and resulting treatment recommendations are recognized benefits of PET/CT,[62] improved overall outcomes[63,64] have

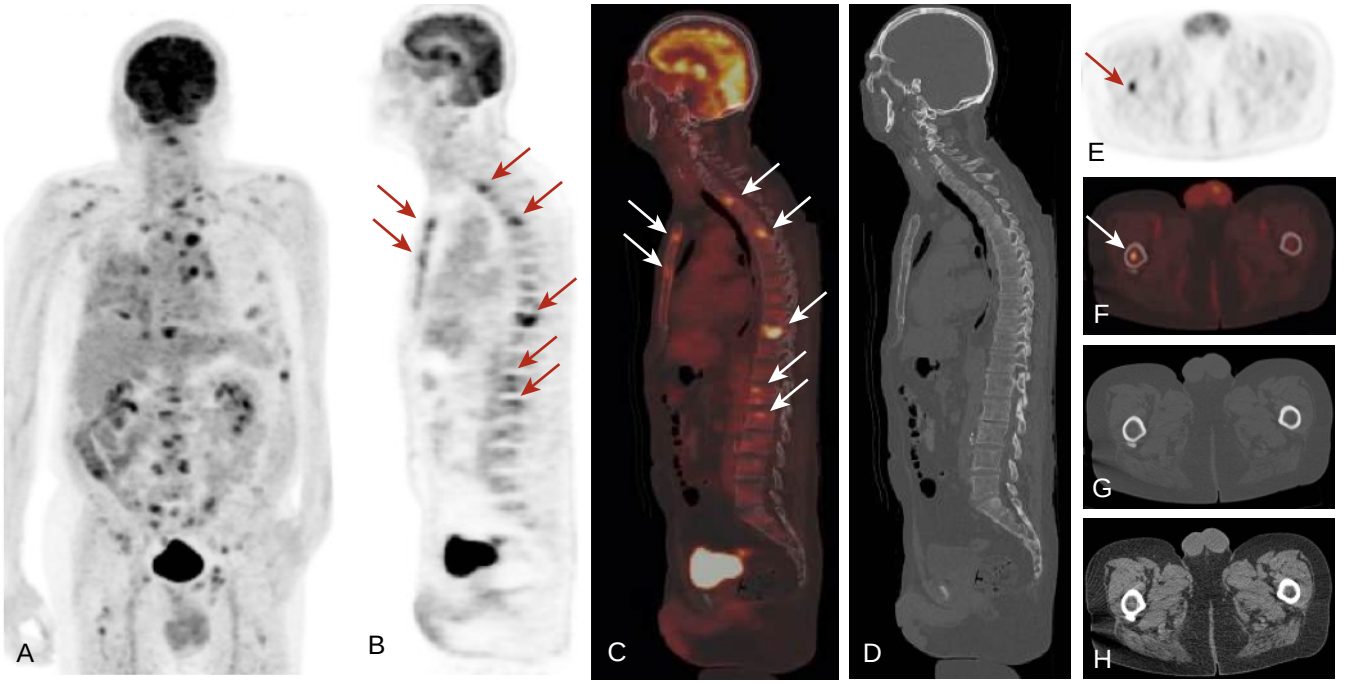

Figure 25.4 Detection of radio-occult bone marrow metastases. A 72-year-old man underwent a ^{18}F-*fluorodeoxyglucose* (FDG) *positron emission tomography* (PET)/*computed tomography* (CT) scan for an adenocarcinoma of the right lung. (A) In addition to strong uptake in the central primary tumor, the maximum intensity projection image showed multiple skeletal foci with pronounced FDG avidity. Sagittal PET image (B, *red arrows*) shows multiple lesions in the thoracic and lumbar vertebrae and in the sternum, confirmed by the fusion image (C, *white arrows*). (D) The corresponding CT image does not show alterations of the bone mineral content (no osteolysis, no sclerosis). (E–H) Similar findings are seen in the proximal left femur, where PET imaging showed a focus of increased FDG uptake (E and F, *arrows*) without abnormalities on CT (G and H).

yet to be observed because randomized controlled trials were underpowered to assess this end point.

It has been shown in many radiotherapy planning studies that PET/CT influences the accurate delineation of target volumes for radiotherapy.[65–67] The PET-based volume delineations were in general smaller than those with CT alone, mainly due to the possibility of more selective nodal irradiation.[65] The more selective radiation field allowed for an escalation of the radiation dose to the tumor in a substantial number of patients. Prospective clinical trials using PET/CT-based selective nodal irradiation reported isolated nodal failures in less than 5% of patients treated with (chemo)radiotherapy.[66,67] PET/CT-based delineation may also be crucial to avoid geographical misses (i.e., misses of the target) leading to treatment failures. Because of the possibility of false-positive lymph nodes on PET, invasive nodal staging using EBUS or mediastinoscopy may be warranted if malignant involvement of the nodes concerned would have a major impact on the radiation treatment field. We recently proposed an algorithm on how to incorporate EBUS findings in patients staged with PET/CT (Fig. 25.5).[69]

For the primary tumor, the gain of PET-based delineation compared to CT-based delineation is in general smaller, except in situations with postobstructive atelectasis. The optimal method of delineation still remains to be defined. In recent studies, automated PET/CT delineation reduced the interobserver variability in treatment planning compared to CT alone.[70] PET may also identify radio-resistant areas within the primary tumor (e.g., areas with higher FDG uptake requiring higher radiation doses) before and during treatment with high accuracy.[71,72] Guidance on using this information to plan higher radiation doses to these areas to improve outcomes is under investigation. Radiation dose escalation using an integrated boost to the high FDG-uptake region inside the primary tumor proved to be safe and feasible in a small cohort of a randomized phase II study.[73] A recent update on the toxicity of this integrated boost strategy in 107 patients showed increased toxicity compared to standard treatment but lower than the study predefined stopping rules.[74]

PROGNOSIS AND SURVIVAL

Several studies clearly demonstrated stage migration (i.e., reclassification into different prognostic groups based on recognition of disease or disease manifestation) when PET

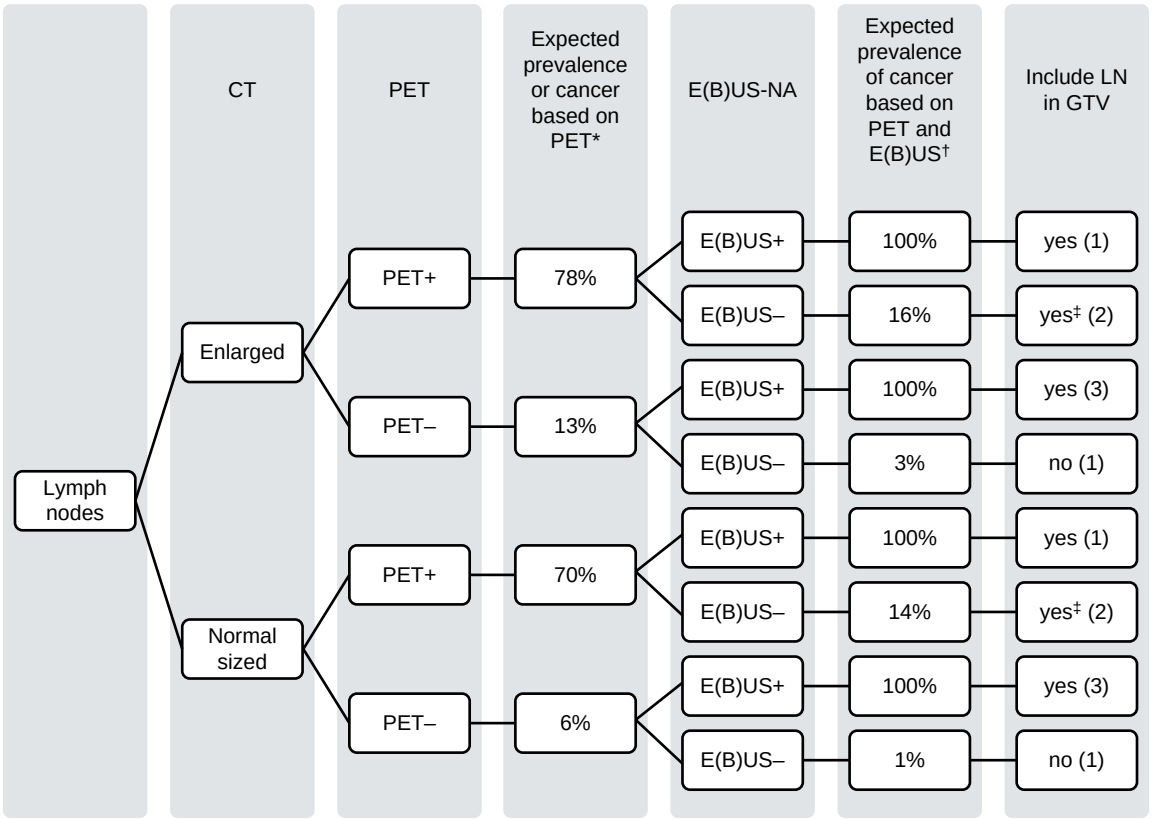

Figure 25.5 Inclusion of lymph nodes in radiotherapy target volume based on ^{18}F-*fluorodeoxyglucose* (FDG) *positron emission tomography* (PET)/*computed tomography* (CT) and *endobronchial/esophageal ultrasound* (E[B]US) findings. Expected prevalence of cancer for different findings on CT, FDG-PET, and E(B)US needle aspiration (NA). The last column indicates whether the lymph node (LN) should be included in the gross tumor volume (GTV) for radiation planning: (1) E(B)US does not change GTV compared to PET-CT only; (2) E(B)US sometimes changes GTV; and (3) E(B)US increases GTV.
*Based on Hellwig and colleagues.[169]
†Prevalence of cancer, taking into account a false-negative rate of E(B)US of 20%.
‡With the exception of symmetrical FDG-PET–positive LN with a nonmalignant diagnosis (anthracosis, silicosis, granulomatous disease, etc.) after adequate E(B)US mapping.
(From Peeters ST, Dooms C, Van Baardwijket A, et al. Selective mediastinal node irradiation in non–small cell lung cancer in the IMRT/VMAT era: how to use E(B)US-NA information in addition to PET-CT for delineation. *Radiother Oncol.* 2016;120[2]:273–278.)

was used.[62] The effect of stage migration in part accounts for improvements in survival of treated patients both in early and in advanced disease stage cohorts, widely referred to as the "Will Rogers phenomenon" of the PET scan era.[75] Will Rogers, the American humorist, was believed to have said, "When the Okies left Oklahoma and moved to California, they raised the average intelligence level in both states." This phenomenon suggests that, if patients are moved from one group, where their survival is below the average, to another, where their survival is above the average, they can increase the average survival of each group. Examples can be found in the prospective multicenter trials on the use of PET in patients with stage III NSCLC, where 25–30% of patients had upstaging confirmed and where there was a significantly longer overall survival ($P = 0.006$) in patients staged by PET than in those without PET. However, the randomized controlled trials in NSCLC were underpowered to evaluate the potential individual patient survival benefit attributable to PET. Smaller studies in *small cell lung cancer* (SCLC) have shown similar stage migration effects to those observed in NSCLC.[76]

PET has also been shown to predict the prognosis of patients with NSCLC.[77] SUV of the primary tumor at diagnosis may predict outcome in NSCLC, especially in earlier stages.[78] Recent meta-analyses on individual patient data have confirmed that SUV_{max} has prognostic value in stage I to III NSCLC.[79] These studies consistently found a better overall survival among patients with a metabolic activity lower than the threshold SUV value, which itself is determined by post hoc analysis and thus varies from study to study. Although SUV may be a way to assess prognosis, there is no true cutoff point suitable for broad clinical use. Instead of a true cutoff point, there is a continuous SUV spectrum of a gradually worsening prognosis. Baseline SUV, incorporated as a continuous variable in a Cox proportional hazards model, showed a 7% increase in hazard of death after a one-unit increase in SUV in resected stage I to III NSCLC[80] and a 6% increase in hazard of death after a one-unit increase in SUV in inoperable NSCLC patients treated with radiotherapy.[81] In patients treated with surgery, SUV_{max} is similarly prognostic, but a recent meta-analysis points to potential superior (and potentially complementary) prognostic value of the determination of the volume with increased FDG uptake (*metabolic tumor volume* [MTV]) and the total glucose consumption of tumoral tissue (*total lesion glycolysis* [TLG]).[82] Recent studies have confirmed the utility of TLG assessment, with a markedly different prognosis in stage III patients based on whole-body TLG.[83] Similar effects have been observed in other tumor types, and this is a very active area of research.[84]

INDICATIONS BEYOND INITIAL EVALUATION OF NON–SMALL CELL LUNG CANCER

SMALL CELL LUNG CANCER

SCLC typically shows very high FDG accumulation. The data on the use of PET in the management of SCLC are less robust than in NSCLC because the emphasis on systemic and radiation therapy provides less histologic data to serve as the gold standard. Furthermore, most studies are rather small (mean, $n = 40$) and retrospective in nature. A review of 14 studies comparing FDG-PET with conventional staging procedures found an overall cumulative staging concordance between PET and conventional imaging in 84%.[85] Based on PET, limited-stage SCLC was upstaged to extensive-stage SCLC in 18%, and extensive-stage SCLC was downstaged to limited stage in 11%. The information on PET could result in considerable changes in patient management, ranging from 27%[86] to 47%[87] across studies. A recent meta-analysis in SCLC[88] concluded that PET/CT is more sensitive for detecting bone metastases than bone scintigraphy or CT alone and is more sensitive for detecting any distant metastases. Another meta-analysis, focusing on detection of extensive disease, showed a sensitivity of 97.5% and specificity of 98.2% for extensive disease, based on a pooled analysis of 369 patients.[89]

The use of PET/CT resulted in changes to the three-dimensional conformal radiation therapy plan in 58% of patients with SCLC in a small pilot study, mainly by decreasing the target volume (in case of atelectasis) or detecting unsuspected nodal or pulmonary foci.[90] Complete metabolic response on posttreatment PET/CT was associated with better outcome in retrospective analyses.[91]

MESOTHELIOMA

Integrated PET/CT imaging has an increasing role in the assessment of suspected or known *malignant pleural mesothelioma* (MPM; Fig. 25.6) (see also Chapter 114). PET/CT is an effective tool in differentiating malignant (mainly MPM) and benign pleural diseases in asbestos-related CT findings with an overall accuracy of greater than 90% and a high negative predictive value of greater than 90%.[92,93] PET/CT is significantly more accurate in baseline TNM staging of patients who are appropriate candidates for multimodal therapy based on CT scan alone.[94–96] Although PET/CT does not provide additional information about the primary tumor compared to CT alone, it identifies a higher number of metastatic mediastinal lymph nodes and/or unknown distant metastatic disease in up to two-thirds of patients, resulting in a significant clinical impact on treatment planning. Because of the greater accuracy of MRI than CT for T staging, MPM is a disease entity where PET/MRI could outperform PET/CT, as shown by small pilot studies.[97,98] One particular pitfall in MPM is chronic iatrogenic inflammation after talc pleurodesis on FDG-PET[99] (see Fig. 114.2).

Early evidence also suggests that PET/CT may have a role in evaluating response to therapy in MPM,[100] with changes in MTV and TLG correlated with overall survival. This is interesting because the assessment of response in patients with MPM according to standard response criteria on CT is far from simple, with potential for PET/CT to outperform *response evaluation criteria in solid tumors* (RECIST)[101] imaging criteria[102] commonly used to evaluate treatment responses in oncology clinical trials and clinical practice. More work to define response criteria for MPM on PET is needed. Furthermore, a prospective study in patients with nonsarcomatoid malignant pleural mesothelioma observed that baseline MTV on PET was more predictive of survival than CT-assessed TNM stage in a multivariate analysis.[103] These observations of prognostic potential show considerable promise but still require prospective validation.

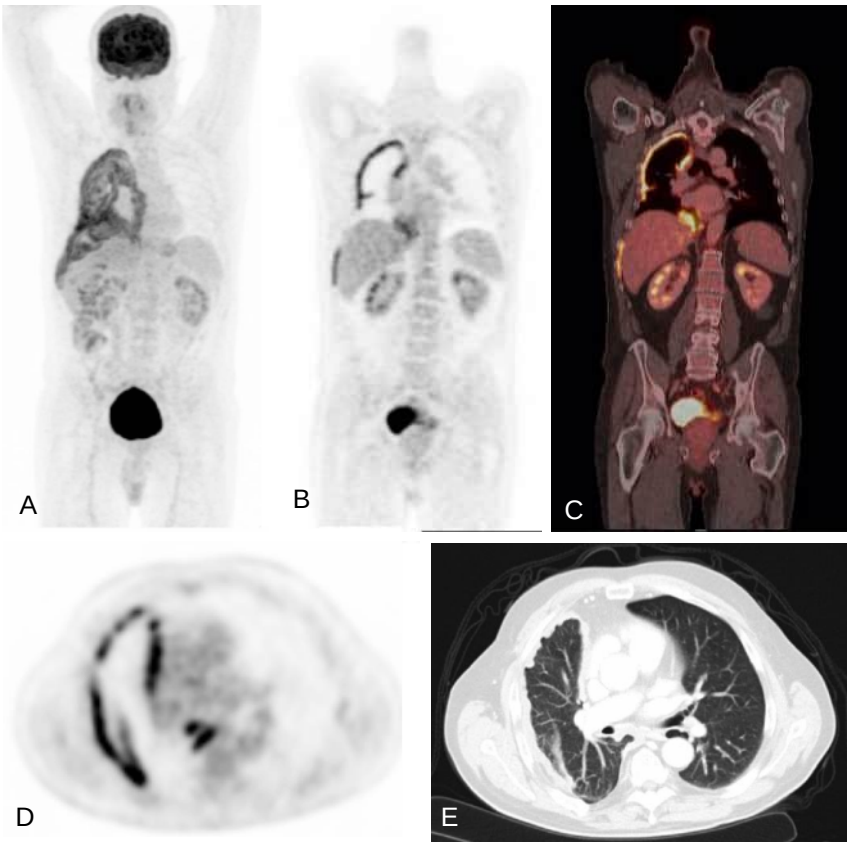

Figure 25.6 ^{18}F-*fluorodeoxyglucose* (FDG) *positron emission tomography* (PET)/*computed tomography* (CT) in mesothelioma. A 67-year-old patient underwent FDG-PET/CT for staging of a primary epithelioid pleural mesothelioma. (A) The maximum intensity projection images show diffuse strong uptake in the right chest cavity. (B–C) Coronal sections show linear strong uptake on a large portion of the lateral and medial pleura, with a small area on the lateral side without increased uptake. (D) Transverse section shows increased uptake of most of the pleura, corresponding to tumoral irregular thickening of the pleura (E).

NEUROENDOCRINE TUMORS

Neuroendocrine tumors (NETs) arise in cells of the diffuse neuroendocrine system, also known as the amine precursor uptake and decarboxylation system. NETs of the lung are divided into four categories: *typical carcinoid* (TC), *atypical carcinoid* (AC), *large cell neuroendocrine carcinoma* (LCNEC), and small cell neuroendocrine carcinoma (i.e., SCLC).[104] FDG uptake is often low in TC and is known as a cause of false negatives on FDG-PET. In contrast, in higher-grade NETs (AC, LCNEC), the FDG-uptake can be similar to NSCLC and SCLC.[105] (See Chapter 78.)

Alternative tracers have been studied for the detection and staging of the NETs with low FDG avidity. Neuroendocrine cells synthesize and secrete a range of peptide hormones. The molecular substrate of this hormone production has been harnessed to provide imaging targets. The most studied target is the *somatostatin receptor* (SSTR), a seven-transmembrane G-coupled peptide receptor that plays a role in the control of hormone secretion and cell growth[106] and is internalized upon ligand binding.[107] Synthetic peptides derived from the somatostatin hormone have been derived with chelators and radiolabeled with a range of different radionuclides, of which the most interesting for PET are the so-called *gallium-68–dodecanetetraacetic acid* (^{68}Ga-DOTA) peptides labeled with the generator-derived gallium-68.[108] They consist of a positron-emitting radionuclide (^{68}Ga), a chelator (DOTA), and a *somatostatin analog* (SSA) vector molecule binding the SSTR (e.g., *d-Phe^1-Tyr^3-octreotide* [TOC], *Tyr^3-octreotate* [TATE], *^{1}-Nal^3-octreotide* [NOC]). Three of these are currently in clinical use: ^{68}Ga-DOTA-TOC, ^{68}Ga-DOTA-TATE, and ^{68}Ga-DOTA-NOC. These tracers all have a high affinity for subtype 2 of the SSTR, the SSTR2A (in the low nanomolar range), varying affinity for subtypes 3 and 5, and low affinity for subtypes 1 and 4.[109]

Many studies have documented the increased diagnostic performance of these ligands for detection of NETs in general.[110,111] A recent study documented expression of SSTR2A, the prime target for these radioligands, in more than 80% of patients with bronchial carcinoid, with similar mean immunohistochemistry scores for SSTR2A in TC and AC.[112] There are very high uptake rates in TC and AC, with median SUV_{max} of about 15, 20, and 25, respectively, for ^{68}Ga-DOTA-TATE,[105] ^{68}Ga-DOTA-TOC,[113] and ^{68}Ga-DOTA-NOC[114] (Fig. 25.7). Somatostatin-based tracers may have advantages compared to FDG tracers in imaging of NETs. In a large series of 207 patients, FDG-PET showed a sensitivity for mediastinal lymph nodes of 33%.[115] SSTR-PET, on the other hand, has been shown to provide additional information for staging compared to CT in 37% of patients, with impact on patient management, including 21% of patients in which occult metastatic disease was detected.[116] Also, in 16% of early postsurgical patients, metastatic disease was detected. Comparing FDG and ^{68}Ga-DOTA-TATE uptake, an interesting observation has been made regarding central bronchial carcinoids,[117] which often present with postobstructive atelectasis. ^{68}Ga-DOTA-TATE consistently showed low uptake in the area of atelectasis, whereas FDG could yield moderate to even very high uptake due to postobstructive inflammation or infection, and low uptake in the primary tumor.[105] Based on these data, international guidelines recommend the use of ^{68}Ga-DOTA-SSA PET

if available.[118] A recent review of seven studies concluded that somatostatin analogs and FDG gave complementary information in patients with NETs.[118a] Further strategies for increasing availability include commercial kit development and use of longer–half-life radionuclides, such as fluorine-18 and copper-64.[119] This tracer is also used to select patients for radionuclide therapy with SSA that include beta- or alpha-emitters, a concept called peptide receptor radionuclide therapy; selecting patients for therapy using imaging with very similar radiopharmaceuticals is referred to as *theranostic* use.

RESPONSE TO THERAPY

FDG uptake in tumors is related to (1) the number of viable cancer cells, (2) their metabolic activity and proliferation capacity, and (3) the presence of inflammatory cells.[120] In many clinical settings, the metabolic changes caused by cancer therapy precede morphologic changes. The discrimination of viable tumor from nonviable tumor is the basis for the use of PET for the determination of response to therapy. Whenever PET scans will be compared at different time points, it is crucial to perform the entire PET procedure using the same methodology (interval from last therapy, patient preparation, camera setting, reconstruction parameters, image analysis).[121,122]

For early-stage NSCLC, the assessment of response and prediction of outcome after *stereotactic ablative radiotherapy* (SABR) have become very important. Retrospective data regarding the value of pretreatment FDG uptake on PET in the prediction of response to SABR are too conflicting to be used in clinical practice.[123–125] On the other hand, the potential of semiquantitative FDG uptake on posttreatment PET at 3, 6, and 9 months after SABR for stage I NSCLC has been evaluated in both retrospective and prospective studies. For posttreatment follow-up, CT is the standard and, if suspicious findings are observed, PET/CT should be performed.[126] A systematic literature review suggests that recurrent disease is highly likely if these high-risk CT changes correlate on PET with an SUV_{max} of 5 or greater or an SUV_{max} higher than the pre-SABR value in tumors with low FDG avidity. If the SUV values are below these values, there is a low suspicion of recurrence, and close follow-up or biopsy should be used.[126] PET/CT has a high specificity of 94% and complements CT.[127] Further studies are, however, needed to validate these findings.

For potentially resectable stage III NSCLC, the evaluation after induction chemo(radio)therapy is crucial in deciding whether to resect. Several studies addressed restaging after induction therapy. In the restaging of mediastinal lymph nodes, integrated PET/CT has a sensitivity of up to 70%, with a specificity of up to 90%. Mediastinal restaging with PET/CT thus reaches an accuracy level of some clinical value, but tissue confirmation is still mandatory to certify the real nodal status. New positive lesions, especially lymph nodes, need to be interpreted carefully because new findings in this setting have a high false-positive rate.[128] The findings of the value of PET/CT on prediction of outcome after induction therapy are even more interesting. The classical prognostic parameters for surgery in these patients are obtained from the resection specimens: (1) downstaging of mediastinal nodes and (2) the pathologic response in the primary tumor. These histologic features are poorly predicted by clinical symptoms or evolution of CT findings during induction therapy. In these prospective studies, both the residual FDG uptake in the primary tumor after induction, as well as the change in FDG uptake when comparing preinduction and postinduction values, had strong power to predict outcome after combined modality treatment (Fig. 25.8). With the advent of minimally invasive EBUS/EUS baseline mediastinal staging to confirm N2/N3 disease, the postinduction assessment can be based on

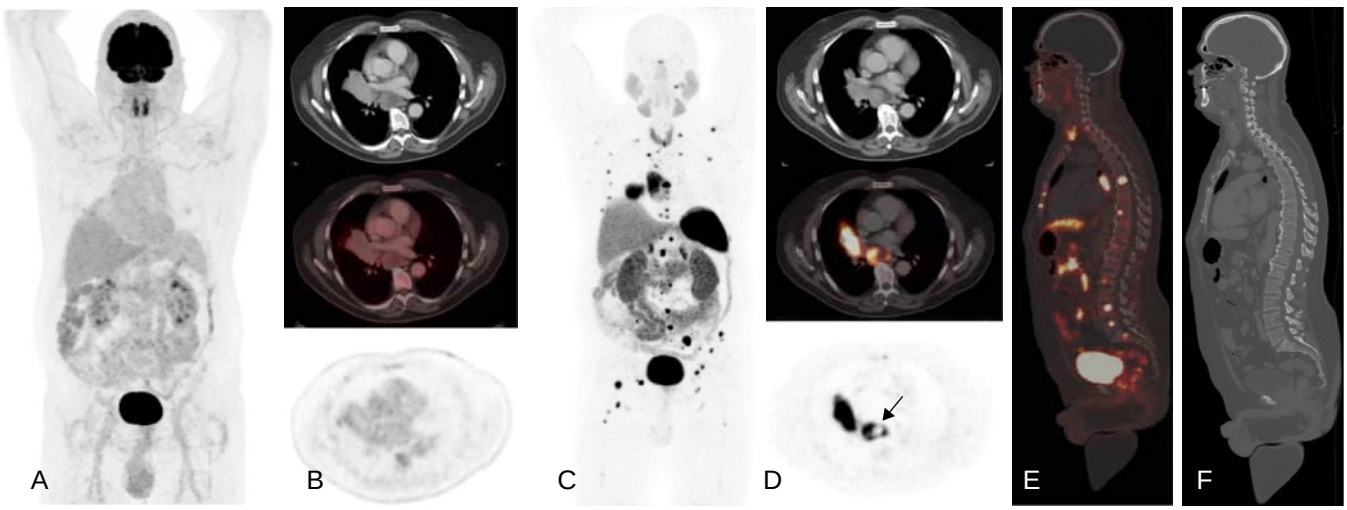

Figure 25.7 Additional value of ^{68}Ga-DOTA-TATE *positron emission tomography* (PET)/*computed tomography* (CT) in bronchial neuroendocrine tumor. A 62-year-old man, a former smoker with 20 pack-years, was treated for a right-sided pulmonary infection. Chest radiography and CT showed a mass in the right lung hilum associated with hilar and subcarinal lymphadenopathy. (A–B) *^{18}F-fluorodeoxyglucose* (FDG)-PET/CT showed consolidation adjacent to the right hilum and lymphadenopathy with only faint FDG uptake, similar to the mediastinal blood pool (B). Transbronchial biopsies showed a bronchial neuroendocrine tumor, positive for synaptophysin and chromogranin A, with a Ki-67 index less than 2% and without necrosis or mitosis figures, compatible with a typical carcinoid. Based on these findings, ^{68}Ga-DOTA-TATE PET/CT was performed. (C) The maximum intensity projection image shows intense uptake in the tumor in the right middle lobe and the subcarinal lymph nodes, with necrosis-induced central photopenia in the latter (D, *arrow*), as well as multiple foci with strong to intense uptake in the skeleton (E), with no changes on the corresponding CT to indicate osseous metastases (F). Based on these findings, no surgery was performed, contrary to the initial CT and FDG-PET/CT–based treatment plan.

primary tumor response information on serial comparison of PET or lymph node assessment by EBUS/EUS or mediastinoscopy. In one model, the combination of lymph node involvement and primary tumor response on PET could discriminate "good prognosis" patients (5-year survival, 62%) from "poor prognosis" patients (only 6%; hazard ratio, 0.18).[129] Other studies have shown a similar separation in prognosis based on similar cutoff values in a setting of induction chemoradiotherapy, with 5-year survival of approximately 70% in the group with good PET response and approximately 22% survival in the group with poor PET response.[130] Thus, PET/CT can be regarded as a key tool for the planning of preoperative induction therapy, for following response to treatment, and for determining overall prognosis.

For nonresectable stage I to III NSCLC treated with curative radiotherapy, the data are in line with the findings described earlier for operable disease.[131] Indeed, patients undergoing radiotherapy alone or sequential/concurrent chemoradiotherapy had a markedly different prognosis based on their metabolic response status 2 weeks into radiotherapy[132] (e.g., 2-year survival 92% for responders vs. 33% for nonresponders in one study).[133] PET obtained after completion of (chemo)radiotherapy also allows for strong discrimination of prognosis, with complete metabolic responders having a median survival of 31 months versus 11 months for incomplete metabolic responders.[134] When compared to CT alone, PET enables more accurate determinations of response to treatment and is a better predictor of survival than baseline stage response on CT or performance status.[135] In locally advanced patients treated with concurrent chemoradiotherapy, PET after completion of treatment has an accuracy of approximately 90% for predicting subsequent tumor response after treatment.[136] PET has also been used to predict recurrent tumor growth and spread after radiotherapy or chemotherapy, enabling a more personalized approach by guiding the need for and timing of supplemental therapy on an individual basis.[137] One study suggests improved outcomes when the decision to perform salvage lung resection after curative-intent radiation in patients with locally advanced NSCLC is guided by abnormal FDG-PET findings rather than the more traditionally used obvious relapse by CT (overall median survival, 43 vs. 12 months).[138]

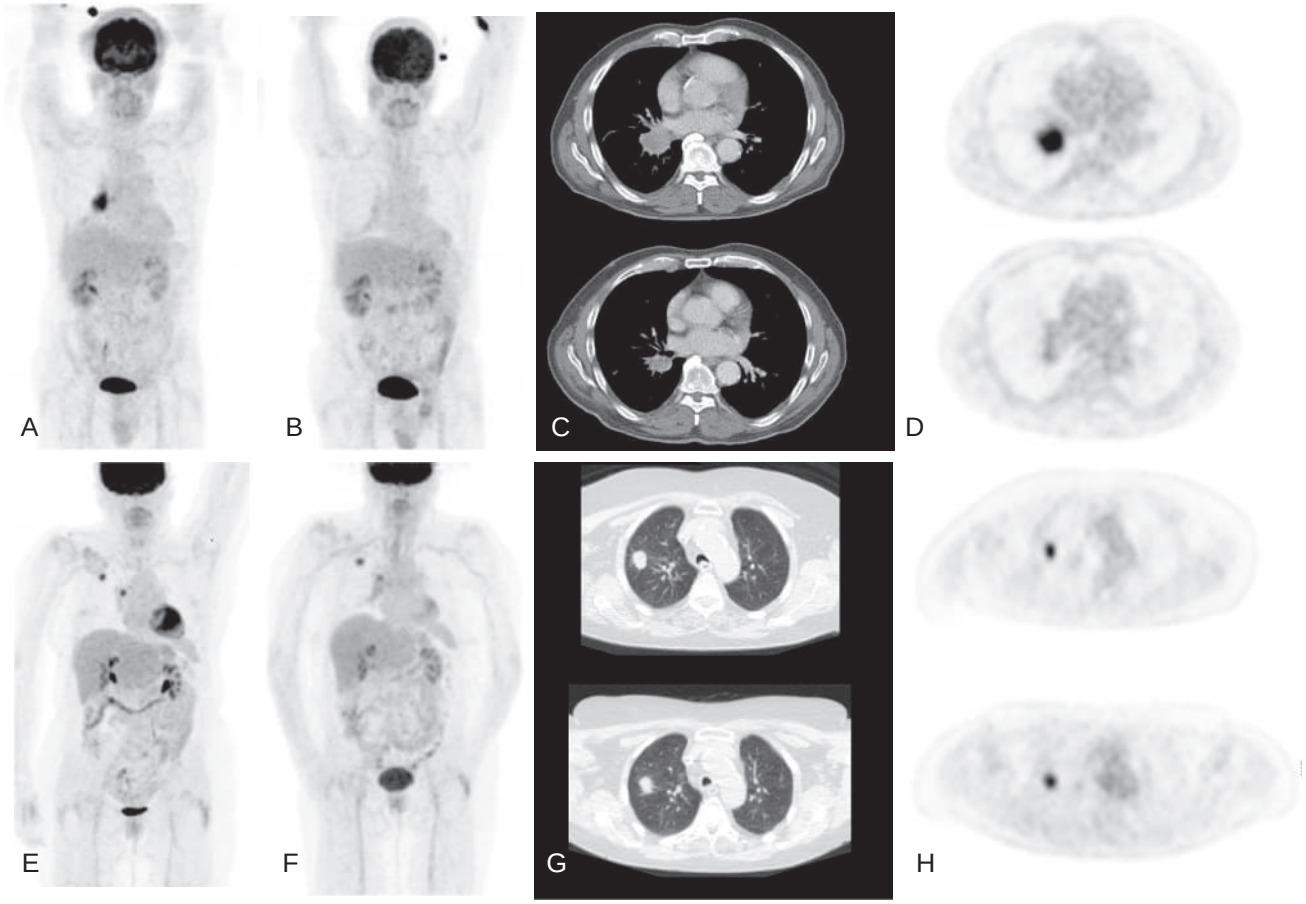

Figure 25.8 ^{18}F-*fluorodeoxyglucose* (FDG) *positron emission tomography* (PET)/*computed tomography* (CT) after induction chemotherapy. Two patients with histologically proven N2 disease treated with induction chemotherapy and surgery are shown. (A–D) The first patient was a 67-year-old man with a cT2N2M0 adenocarcinoma. Baseline images (A; C–D *upper row*) showed intense uptake in the tumor in the right lower lobe (SUV_{max}, 13.5). Images after three cycles of cisplatinum-gemcitabine doublet (B; C–D *lower row*) showed a near normalization of FDG uptake in the primary tumor (*maximum standardized uptake value* [SUV_{max}], 3.45; ΔSUV_{max}, −74.5%), compatible with a metabolic response. Surgery showed ypTisN1M0 disease. He was alive 7 years later with no evidence of recurrence. (E–H) The second patient is a 73-year-old woman with a cT1aN2M0 tumor in the right upper lobe. Baseline images (E; G–H, *upper row*) showed intense uptake in the tumor in the right upper lobe (SUV_{max}, 9.80) and in hilar lymph nodes. Images after three cycles of cisplatinum-pemetrexed doublet (F; G–H, *lower row*) showed a persistent elevated uptake in the primary tumor (SUV_{max}, 8.12; ΔSUV_{max}, −17%), compatible with metabolic nonresponse. Mediastinoscopy demonstrated persistent multilevel N2 disease after which she was treated with radiotherapy. She died from progressive disease 7 months after the initial PET/CT scan.

In patients with stage IV NSCLC, effective systemic chemotherapy causes a rapid decrease in FDG uptake during the first cycle and therefore could potentially identify chemotherapy responders and nonresponders at an early treatment stage.[139] Targeted therapies are a cornerstone of modern respiratory oncology and conceptually PET might be of great interest in the assessment of these agents. Two independent studies have shown that early PET can predict progression-free and overall survival in patients treated with erlotinib, even in the absence of a response based on imaging criteria (RECIST).[140,141] A systematic review of *epidermal growth factor receptor* (EGFR) inhibitors showed that patients who were responsive to this therapy presented with a metabolic response within the first 2 weeks and had a durable response to treatment. Patients without early response had a low probability of benefit.[142] In a small study evaluating the role of PET/CT versus CT in determining tumor response to anaplastic lymphoma kinase inhibitors, PET/CT detected progression earlier than CT in almost half of progressive events and simultaneously with CT for the other events.[143] PET/CT could be of benefit in the detection of oligoprogressive disease, where disease is stable at some sites but progresses in others, in oncogene-addicted NSCLC. A recent study showed that patients with oligoprogressive disease detected by PET/CT could be treated with ablative therapies in a higher fraction, leading to greater progression-free survival and overall survival.[144] PET/CT can be of particular value in the follow-up of patients with disease burden difficult to assess with CT alone (e.g., patients with predominant bone [marrow] involvement) with few target lesions for imaging-based (RECIST) follow-up.

The rapid advent of immuno-oncologic treatment in both nonmetastatic and advanced-stage lung cancer provides promising opportunities for FDG-PET/CT, such as assessment of response to neoadjuvant treatment, discrimination of pseudoprogression, or the detection and characterization of immune-related adverse events.[13,145–147]

FOLLOW-UP AFTER CURATIVE-INTENT TREATMENT

After curative therapy of NSCLC, early detection of recurrence is important because salvage therapies can be rewarding, especially in asymptomatic locoregional recurrences.

Selective use of PET can be recommended for the evaluation of a suspect local recurrence on conventional radiologic imaging in lung cancer patients previously treated for early stage NSCLC with curative intent. Two prospective studies compared the differential diagnostic performance of PET and CT in the early detection of local recurrence.[148,149] In both, the accuracy of PET was better than that of CT (93% vs. 82%; 96% vs. 84%). Several prospective series in patients with a residual thoracic abnormality after treatment addressed the value of PET to differentiate between local recurrence versus residual nonspecific posttreatment changes.[148–153] A cutoff for SUV of 2.5, differentiating benign from malignant lesions, just as suggested for newly diagnosed lung lesions, had a sensitivity ranging from 97–100% and a specificity ranging from 62–100%.

Surveillance by PET/CT every 6 to 12 months after a treatment with curative intent (surgery or SABR) for early-stage NSCLC cannot be recommended. Despite several reports of a better sensitivity to detect disease recurrence on PET/CT in asymptomatic patients compared to chest CT scan alone, no survival benefit has been demonstrated in the postoperative follow-up setting.[154,155] However, PET/CT can be used in patients showing suspicious findings on follow-up CT in patients treated with SABR.[126]

HEALTH ECONOMICS

As respiratory oncologists, we aim for the best-quality health care for our patients, while acknowledging the need for financial prudence. The major cost of modern oncology practice, however, does not lie in the baseline diagnostic process but in the delivery of expensive treatments and in caring for morbidity related to side effects. Therefore, application of economic modeling to the use of PET has to be based on both diagnostic and therapeutic aspects of health care expenditure within a routine clinical setting.

In a recent overview of all economic evaluations on PET in oncology performed between 2005 and 2010, it was concluded that the strongest evidence for cost-effective use of PET was the staging of NSCLC, where there may be a benefit for patients in terms of a slight increase in life expectancy and for the health care system in terms of avoiding invasive procedures.[156] Taking into account the superior accuracy of PET/CT compared to PET alone in lung cancer staging, the cost-effectiveness can probably be extended to PET/CT. Since the introduction of PET/CT technology in 2001, additional studies in respiratory oncology have confirmed the cost-effectiveness of this integrated scanning method.[157,158] Furthermore, PET was shown to be cost-effective for characterizing SPNs and the most cost-effective diagnostic strategy for nodules of low to moderate pretest probability of malignancy on CT.[159]

NEW TRACERS

The vast majority of PET imaging in pulmonary medicine is performed with FDG. However, many new tracers are being developed to expand the uses of PET (eTable 25.1). One recently developed category of tracers could potentially outperform FDG as a general cancer detection tracer: radiolabeled *fibroblast-activation protein inhibitors* (FAPIs). These tracers, for instance, ^{68}Ga-FAPI-04, target fibroblasts in the tumoral stroma. They have very low background uptake in lung, mediastinum, liver and, in contrast with FDG, normal brain, which can improve staging in NSCLC patients.[160] Initial studies in 25 lung cancer patients have shown high tumoral SUV values,[161] and comparison with FDG has shown significantly higher SUV values in 14 lung cancer patients compared to FDG-PET (12.0 vs. 4.5, respectively).[162] The increased lesion to background of ^{68}Ga-FAPI-04 compared to FDG might be one advantage of this tracer but, similar to FDG, this tracer also shows uptake in inflammatory processes, so little improvement in specificity is expected. The low background in virtually all normal organs will allow for development of therapeutic radiopharmaceuticals and theranostics imaging.

PET tracers have been developed for a whole range of biologic and pathophysiologic processes.[163]

These tracers are described at ExpertConsult.com and in eTable 25.1.

eTable 25.1 Positron Emission Tomography Tracers Beyond ^{18}F-Fluorodeoxyglucose

Tracer	Category	T½	Target	Status and Potential Clinical Use
^{68}Ga-DOTA-TATE ^{68}Ga-DOTA-TOC ^{68}Ga-DOTA-NOC	Somatostatin analogs	68 min	Somatostatin receptor	*In clinical use* Staging/restaging/therapy monitoring/theranostic indications.
Methyl 4-deoxy-4-[^{18}F]fluoro-alpha-D-glucopyranoside (Me4FDG)	Glucose analog	109.8 min	Sodium-dependent glucose transporter 2	*Experimental* Detection of early stage lung adenocarcinoma (when still not ^{18}F-FDG avid)
^{68}Ga-FAPI-04	Quinoline derivative	68 min	Fibroblast activation protein	*Experimental, proof of concept in established patients* Staging/restaging/therapy monitoring/theranostic indication
4-[^{18}F]fluorobenzyl-triphenylphosphonium (^{18}F-BnTP)	Phosphonium derivative	109.8 min	Mitochondrial membrane potential	*Experimental* Monitoring of tumor bioenergetics. Selecting patients for treatment with metabolic inhibitors (biomarker)
^{18}F-fluoromisonidazole (^{18}F-FMISO) ^{18}F-fluoroazomycin arabinoside (^{18}F-FAZA) ^{18}F-flortanidazole (^{18}F-HX4)	Nitromisonidazole derivates	109.8 min	Hypoxia	*Established concept in patients, used in clinical trials* Modulation of dose to tumoral target Assessment of antihypoxic therapies
[^{64}Cu] copper(II)-diacetyl-bis(N^4-methylthiosemicarbazone (^{64}Cu-ATSM)	Bisthiosemicarbazone complex	12.7 hr		
^{18}F-MPG	Tyrosine kinase inhibitor	109.8 min	Mutant epidermal growth factor receptor (EGFR)	*Experimental, proof of concept in established patients* Select patients for anti-EGFR therapy (biomarker)
^{89}Zr-Atezolizumab	Monoclonal antibody	74.4 hr	Programmed death-ligand 1 (PD-L1)	*Experimental, proof of concept in established patients* Imaging of PD-L1 expression Selection of patients for anti–PD-L1 therapy (biomarker)
^{18}F-BMS986192	Adnectin (10th type III domain of human fibronectin derivate)	109.8 min		
^{89}Zr-Nivolumab	Monoclonal antibody	74.4 hr	Programmed death 1 (PD-1)	*Experimental* Imaging of PD-1 expression Selection of patients for anti-PD-1 therapy (biomarker)
^{89}Zr-Ipilimumab	Monoclonal antibody	74.4 hr	Cytotoxic T-lymphocyte–associated protein 4 (CTLA4)	*Experimental, evaluated in clinical trials* Imaging of CTLA4 expression Selection of patients for anti-CTLA4 therapy (biomarker)
^{89}Zr-Df-IAB22M2C	Minibody (single-chain antibody fragment)	74.4 hr	CD8 (cluster of differentiation 8)	*Experimental, evaluated in clinical trials* Imaging of cytotoxic lymphocytes (CD8 positive) Baseline determination of immune status Monitoring early effect of immune therapy

Besides FDG as a tracer for glucose metabolism, other tracers that detect tumor metabolic activity have the potential to be of clinical value. Methyl 4-deoxy-4-[^{18}F] fluoro-α-D-glucopyranoside (Me4FDG) is a substrate for SGLTs.[14] SGLTs are present on precursor lesions (atypical adenomatous hyperplasia) and early forms of lung adenocarcinoma (adenocarcinoma in situ and minimally invasive adenocarcinoma), when GLUT expression can be still low. This tracer could allow detection of adenocarcinoma early in its biologic development. Other tracers, such as *4-[^{18}F] fluorobenzyl-triphenylphosphonium* (^{18}F-BnTP), allow in vivo visualization of the mitochondrial membrane potential and the extent and spatial heterogeneity of mitochondrial bioenergetics (synthesis of adenosine triphosphate by oxidative phosphorylation) in lung cancers.[164]

Hypoxia within lung tumors can be depicted using tracers that accumulate in tissue based on lower oxygen tension, such as ^{18}F-fluoromisonidazole (FMISO) and *^{64}Cu-diacetyl-bis(N^4-methylthiosemicarbazone* (^{64}Cu-ATSM).[165] Both tracers undergo reduction under hypoxic conditions and subsequently bind to intracellular macromolecules. Because tumor hypoxia is an important factor in resistance to radiotherapy, noninvasive measurement of hypoxic areas would allow dose escalation strategies with modern irradiation techniques.

Noninvasive detection of EGFR mutation status and mapping of the heterogeneity among metastases is possible by using PET tracers based on *tyrosine kinase inhibitor* (TKI) backbones, such as ^{18}F-MPG, which is based on the molecular structure of the EGFR-TKI PD153035.[166] Evaluation of ^{18}F-MPG PET in patients with primary and metastatic NSCLC demonstrated 84% concordance between EGFR activation as detected by PET and shown by tissue biopsy. There was a strong difference in response to EGFR-TKIs (82% vs. 6%) and longer progression-free survival in NSCLC patients with ^{18}F-MPG PET/CT SUV_{max} above the optimal threshold. These findings suggest a potential novel noninvasive strategy to detect EGFR mutation status.

One of the most exciting promises of PET is molecular imaging of the immune system. *Programmed cell death 1* (PD-1) and *programmed cell death ligand-1* (PD-L1) targeting monoclonal antibodies can be radiolabeled with long-lived PET radionuclides (e.g., zirconium-89; half-life, 78.4 hr) and can quantify expression within the entire tumor burden in lung cancer patients. ^{89}Zr-atezolizumab, an anti–PD-L1 PET tracer, has been shown to reach high uptake in NSCLC (SUV_{max} up to 20), with higher uptake correlating with imaging-based (RECIST) response and substantially longer overall survival, outperforming immunohistochemical evaluation of PD-L1 expression.[167] The presence of CD8 cytotoxic T cells within tumors, at baseline or after checkpoint blockade, can be assessed with CD8-binding PET probes, such as ^{89}Zr-Df-IAB22M2C, an anti-CD8 minibody (i.e., single-chain antibody fragment binding to human CD8).[168] Molecular imaging could allow early assessment of immuno-oncology therapies in a noninvasive manner in all tumor sites of the patient.

Key Points

- ^{18}*F-fluorodeoxyglucose* (FDG) is the most common tracer used for clinical cancer *positron emission tomography* (PET) imaging and reflects cellular uptake of glucose.
- FDG-PET/*computed tomography* (CT) results in better *tumor-node-metastasis* (TNM) staging in *non–small cell lung cancer* (NSCLC) than conventional imaging alone and may alter treatment choice or intent in a substantial proportion of patients.
- Limitations to FDG-PET should be well understood. False-negative PET findings can result from slow-growing tumors, small tumors (<8–10 mm), or hyperglycemia. False-positive PET findings can result from increased metabolic activity from inflammation, infection, autoimmune processes, sarcoidosis, talc pleurodesis, or some benign tumors.
- Higher uptake of FDG by NSCLC is often associated with greater aggressiveness and poorer prognosis.
- FDG-PET is useful in assessments of response to therapies, particularly in patients with locally advanced NSCLC, with combined modality treatment. PET/CT should not be used for surveillance after curative intent in early-stage NSCLC but can be useful to characterize abnormal findings detected on conventional imaging during follow-up.
- PET/*magnetic resonance imaging* (MRI) and PET/CT have equivalent staging performance for NSCLC. PET/MRI offers superior assessment of disease involving the chest wall or diaphragm but is suboptimal for imaging of the lung parenchyma and is less widely available.
- PET imaging may be similarly useful in the assessment of small cell lung cancer and mesothelioma (using FDG) and bronchial carcinoid tumors (using radiolabeled somatostatin analogs).
- Other tracers beyond FDG are emerging to detect tumor metabolic activity based on sodium-dependent glucose transporters, mitochondrial membrane potential, tumor hypoxia, epidermal growth factor receptor mutation status, and immune system imaging, which may potentially guide immuno-oncologic therapy.
- The most cost-effective role of PET is in staging NSCLC, where PET reduces the number of invasive procedures and improves staging accuracy of disease. Use of FDG-PET in NSCLC patients with a potential for cure is evidence based and cost effective.

Key Readings

Aide N, et al. FDG PET/CT for assessing tumour response to immunotherapy: report on the EANM symposium on immune modulation and recent review of the literature. *Eur J Nucl Med Mol Imaging*. 2019;46(1):238–250.

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26 DIAGNOSTIC BRONCHOSCOPY: BASIC TECHNIQUES

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Sedation and Anesthesia
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INTRODUCTION AND HISTORICAL BACKGROUND

Flexible bronchoscopy (FB) is one of the most frequently performed invasive procedures in pulmonary medicine. It is increasingly being performed for its diagnostic and therapeutic potentials. Recently, the introduction of novel technologies, such as electromagnetic navigation and robotic bronchoscopy, has further increased the reach of the instrument and increased the diagnostic yield. This chapter deals with the basics of the FB procedure; the advanced diagnostic techniques and therapeutic applications are presented in the successive chapters of this textbook.

Gustav Killian performed the first bronchoscopy in 1897 to extract a piece of a pork bone from the right main bronchus.[1] From that meager beginning, the technology in bronchoscopy has advanced exponentially. In 1966 the flexible bronchoscope was introduced into clinical practice by Shigeto Ikeda.[2] Currently, this instrument is one of the most important tools for diagnosis and treatment of pulmonary diseases.

FB can be performed in an outpatient setting, under moderate sedation and local anesthesia. Compared with FB, rigid bronchoscopy is now primarily used for selective indications, such as massive hemoptysis and therapeutics.[3–6]

INDICATIONS

The indications for diagnostic FB are broad and growing (Table 26.1). Nonetheless, certain conditions are not considered indications for FB. For example, FB is not indicated to evaluate patients with cough unless the cough fails to respond to conventional treatment or if there is a change in its character. Similarly, bronchoscopy is not indicated to evaluate patients with isolated pleural effusion or atelectasis,[7–9] and its use to remove secretions during acute exacerbations of chronic obstructive lung disease is also considered inappropriate.[10] FB also has little role in finding synchronous lesions in patients undergoing lung resection of a solitary pulmonary nodule suspected to be primary bronchogenic carcinoma.[11] Absolute and relative contraindications to performing FB are presented in Table 26.2.

PROCEDURE

The nasal and oral routes provide excellent access to the lower airways. By either route, attention should be given to the upper airway. In particular, bronchoscopy performed for the evaluation of hemoptysis or wheezing should also include a careful evaluation of the upper airway, including the nasopharynx, oropharynx, and vocal cords. FB is often performed via the nasal route.[12] The nasal route is avoided in patients suspected to have foreign body aspiration, to have sufficient room to remove the object, and among those with coagulopathies, because of the risk of epistaxis.

SEDATION AND ANESTHESIA

The need for sedation during FB remains a matter of some debate in the literature.[13–15] The purpose of sedation is to improve patient comfort and add to the ease of the procedure for the bronchoscopist.[16,17] Although bronchoscopy can be carried out without sedation,[18,19] most are performed under moderate sedation.[20–23] Of interest, according to some surveys, 16% to 21% of physicians use deep sedation or general anesthesia for FB.[20,22]

Intravenous (IV) preparations of various sedatives, such as diazepam, midazolam, lorazepam, morphine sulfate, fentanyl, and hydrocodone, have been used either alone or in combination based on the bronchoscopist's preference and the availability of the drug.[24–29] Fentanyl has a greater analgesic potency than morphine.[25] Hydrocodone has a greater antitussive property than codeine but less than that of morphine.[30] Due to its rapid onset and anxiolytic and amnestic properties, midazolam is one of the most commonly used sedatives; sedation with midazolam in FB improves the patient's comfort and decreases recall without causing significant hemodynamic compromise. It should be offered to the patient on a routine basis.[31,32]

TABLE 26.1 Indications for Diagnostic Flexible Bronchoscopy (Adult)

Hemoptysis
Wheeze and stridor: suspected stricture, upper airway obstruction
Lung opacities of unknown cause ▪ Suspected pulmonary infections not responding to conventional treatment Localized Diffuse ▪ Lung opacities in an immunocompromised host ▪ Recurrent or unresolved pneumonia ▪ Cavitary lesion ▪ Interstitial opacities ▪ New pulmonary nodule
Unexplained lung collapse without air bronchograms
Suspected or known bronchogenic carcinoma ▪ Positive or suspicious sputum cytologic findings ▪ Staging of known bronchogenic carcinoma ▪ Follow-up after endobronchial treatments
Mediastinal and hilar lymphadenopathy and masses
Lung transplantation ▪ Inspect airway anastomosis ▪ Rejection surveillance
Esophageal cancer evaluation
Endotracheal intubation ▪ Confirm tube position ▪ Evaluate for tube-related injury
Evaluation for foreign body aspiration
Chest trauma ▪ Rule out rupture of central airways ▪ Examine for aspirated contents
Evaluation following burns or chemical injury to the airways
Unexplained superior vena cava syndrome
Unexplained vocal cord paralysis or hoarseness
Suspected fistulas ▪ Bronchopleural ▪ Tracheoesophageal and bronchoesophageal ▪ Tracheoaortic or bronchoaortic ▪ Iatrogenic (postsurgical)

Table 26.2 Contraindications for Flexible Bronchoscopy

ABSOLUTE
Uncorrectable hypoxemia Lack of patient cooperation Lack of skilled personnel Lack of appropriate equipment and facilities Unstable angina Uncontrolled arrhythmias
RELATIVE
Unexplained or severe hypercarbia Uncontrolled asthma Uncorrectable coagulopathy Unstable cervical spine Need for a large tissue specimen for diagnosis Debility, advanced age, malnutrition

The combination of a benzodiazepine and an opioid has been shown to be safe and synergistic for the purposes of sedation during FB.[28,33] Because the combination of benzodiazepines and opiates may cause hypoventilation, particularly in patients with preexisting respiratory failure, patients should be appropriately monitored.[34] The combination of hydrocodone and midazolam reduces cough during FB without causing significant desaturation and improves the patient's tolerance for the procedure.[28,33] Dexmedetomidine (Precedex, Dexdomiror) also has favorable properties of sedation, sympatholysis, analgesia, and a low risk for apnea. These properties suggest that dexmedetomidine may be useful in procedural sedation. However, it has been shown that dexmedetomidine as a sole agent is unable to provide adequate sedation for awake diagnostic FB without the need for rescue sedation in a large proportion of patients.[35] Dextromethorphan can also be given orally 90 minutes before the procedure to improve cough suppression during the procedure.[36]

Propofol has come into use, both alone and in combination. For conscious sedation, propofol alone has been shown to be as effective and safe as combined sedation in patients undergoing FB, thus representing an appealing option if timely discharge is a priority.[37] Deep sedation with propofol for bronchoscopy has gained popularity in recent years, although concern has been raised regarding its potential to induce severe respiratory depression. In one prospective study, the use of small boluses of propofol at short intervals, with monitoring of transcutaneous carbon dioxide level, was found to be safe; the authors concluded that propofol used in this manner does not cause excessive respiratory depression and represents an excellent alternative to traditional sedation agents.[38] In another prospective study, the combination of propofol and hydrocodone was safe and better for cough suppression than propofol alone during FB.[39] Fospropofol disodium is a water-soluble prodrug of propofol. In a subset analysis among elderly patients (≥65 years) undergoing FB, fospropofol provided safe and effective sedation, rapid time to fully alert status, and high satisfaction, outcomes which were comparable to those in younger patients.[40]

Higher-than-usual doses of sedatives are usually required for patients with human immunodeficiency virus infection, recipients of stem cell transplantation, lung transplant recipients for cystic fibrosis, and drug users.[31–43] In addition, because protease inhibitors used in patients with human immunodeficiency virus infection have been shown to extend the half-life of benzodiazepines significantly, many institutions in the United States instead encourage the use of deep sedation in these patients.

Local Anesthesia

Although nerve blocks can be used to provide excellent analgesia to the airway, physicians generally rely on topical administration of local anesthetic agents. Lidocaine is the most commonly used drug for providing topical anesthesia.[44] It offers a relatively wide margin of safety, with a rapid onset and sufficient duration of action to allow completion of most bronchoscopic procedures. The gel preparation of lidocaine is preferred over the spray for nasal anesthesia.[45–47] Given that sensory anesthesia is not dependent on the concentration of lidocaine, 1% is preferred because larger volumes can be instilled to cover a greater surface area of the mucosa before toxic dosages are reached.[48,49] The oropharynx can be anesthetized with 2–4% lidocaine applied as a spray, nebulized solution, or gargles.

The vocal cords and the endobronchial tree are anesthetized by direct instillation of lidocaine via the working channel of the bronchoscope. The total dose of lidocaine should be limited to 8.2 mg/kg in adults, with extra caution in the elderly or those with liver, renal, or cardiac impairments.[24]

Anticholinergic agents, such as atropine and glycopyrrolate, have been commonly used as premedication for FB,[50,51] with the aim to reduce the bronchial secretions and suppress vagal overactivity. Several studies have shown that anticholinergics offer little advantage as premedications, and their use should be abandoned.[52–54]

MONITORING

To ensure adequate oxygenation (oxygen saturation of >92%) and hemodynamic stability, pulse oximetry, heart rate, and blood pressure are monitored throughout the procedure. There should be IV access and equipment for resuscitation readily available. Supplemental oxygen should be administered to all patients undergoing bronchoscopy. In October 2010, the American Society for Anesthesiology updated their statement on basic anesthesia monitoring to include capnography in addition to clinical assessment to monitor ventilation during moderate sedation. It has been realized that sedation to anesthesia is a continuum, and patients can slip into a deeper-than-intended plane of sedation without any prior warning. In fact, it has been shown that the majority of patients undergoing moderate sedation may enter a state of deep sedation, at least for a short duration, and the use of capnography can improve safety[55] (see also Chapter 44). All FB procedures are performed observing universal precautions. After each procedure, the instrument is thoroughly disinfected or sterilized according to published consensus statements.[56–59]

Approach

The standard procedure for FB involves a thorough examination of the entire tracheobronchial tree in a systematic fashion, from the upper airway and vocal cords to the trachea and carina, major bronchi, and the segmental bronchi in each of the five lung lobes. A thorough understanding of normal features can allow detection of abnormalities in anatomy (e.g., missing or duplication of bronchi), shape (e.g., narrowing or distortion), changes in the anatomy with breathing (e.g., collapse), or endobronchial mucosa (e.g., induration, friability, erythema, lesions). A bronchoscopy of a patient with a relatively normal tracheobronchial tree is shown in Video 26.1. The bronchoscopist aims to maintain the bronchoscope in the center of the airway to avoid cough and endobronchial trauma, which can also obscure airway lesions, and away from major and minor carinae where the cough fibers are concentrated.

Inspection

Examination of the upper airway can be instructive. The vocal cords may be involved with infections (Fig. 26.1) or malignancy; the cords may be paralyzed as a result of interruption of the recurrent laryngeal nerve or be erythematous or edematous due to gastroesophageal reflux. The trachea may be abnormal owing to either congenital or acquired conditions (Fig. 26.2A–B). The endobronchial mucosa exhibits characteristic changes due to infiltrative or systemic conditions (Fig. 26.2C–D). Endobronchial lesions may be caused by a multitude of conditions, including inflammatory, malignant, or infectious disease, or by foreign bodies (Fig. 26.3). Attention should also be paid to the normal expiratory collapse of the central airway as well as to the presence of excessive dynamic airway collapse/tracheobronchomalacia.[60–65]

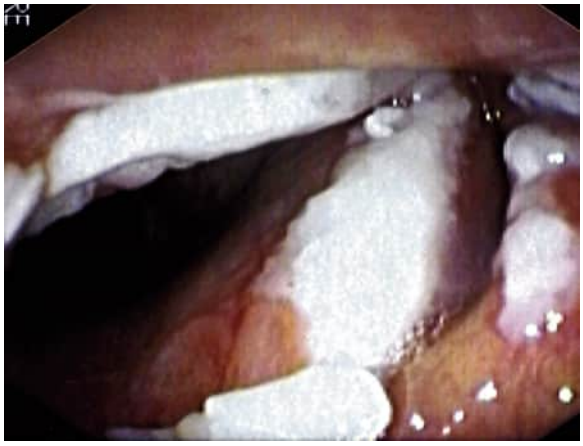

Figure 26.1 Vocal cord abnormality on inspection. Vocal cord candidiasis in an immunocompromised host.

During the inspection of the airways, the bronchoscopist should remain vigilant for any endobronchial anomalies, such as tracheal bronchus (Fig. 26.4). The bronchial wall mucosa should be thoroughly inspected for neovascularization, submucosal infiltration, or depigmentation. Yellowish pigmentation of the mucosa may suggest endobronchial amyloidosis, whereas black pigmentation may suggest tuberculosis (Fig. 26.5). Cobblestoning involving the bronchial mucosa, resembling a "pebbly mural," is nearly pathognomonic for endobronchial sarcoidosis[66–69] (Fig. 26.2C).

Narrow-band imaging, a feature often supplementing videobronchoscopy, lacks both specificity and sensitivity in detecting carcinoma in situ and hence is not a part of routine airway examination.

BASIC TECHNIQUES

BRONCHOALVEOLAR LAVAGE

Bronchoalveolar lavage (BAL) is an important clinical and investigational tool.[70,71] It is a standard diagnostic procedure in all patients with diffuse lung abnormalities of unknown cause, whether an infectious, noninfectious, immunologic, or malignant cause is suspected.[72,73] BAL allows the recovery of both cellular and noncellular components of the epithelial (alveolar) lining fluid and epithelial surface of the lower respiratory tract. Components of the BAL fluid represent the inflammatory and immune status of the lower respiratory tract and the alveoli[70,74] (Fig. 26.6). BAL, which samples the distal air spaces, differs significantly from a bronchial washing, which samples the large airways via aspiration of small amounts of instilled saline.[73,75,76] BAL should be considered a standard procedure in the evaluation of diffuse lung diseases, suspected infection, or malignancy, especially when the bleeding risk

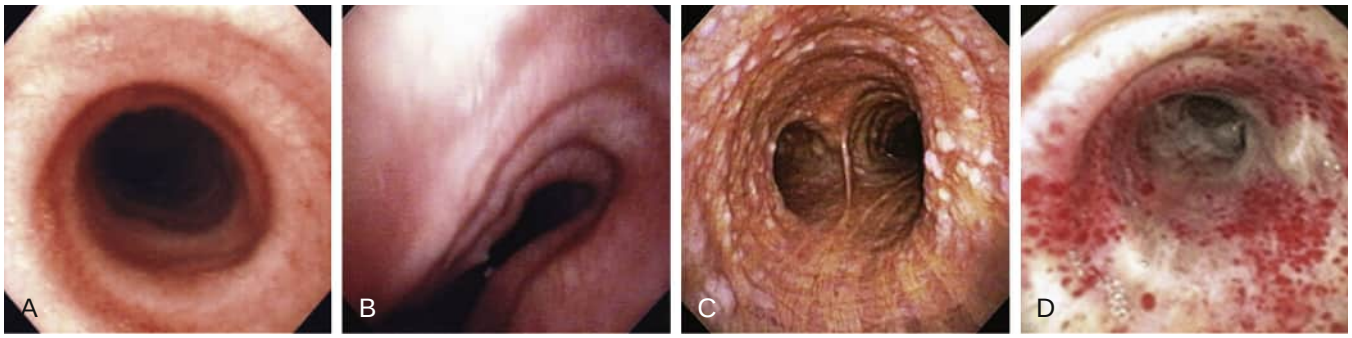

Figure 26.2 Tracheal abnormalities on inspection. (A) Complete tracheal ring, also called a "stovepipe trachea." Note the absence of the posterior membrane. (B) A "saber-sheath" trachea in a patient with emphysema. (C) Diffuse "pebbly mural" appearance of endobronchial sarcoidosis. (D) Endobronchial petechiae in a patient receiving clopidogrel. (A, Courtesy Dr. James Stoller.)

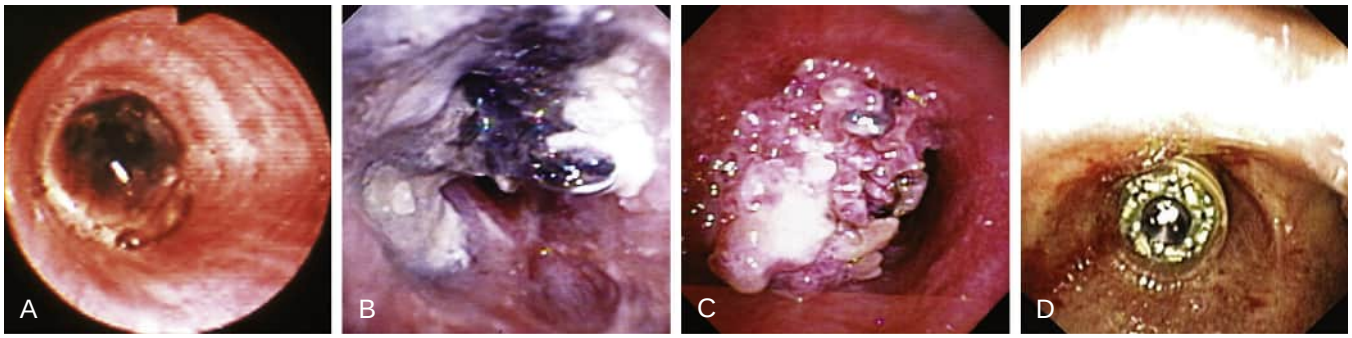

Figure 26.3 Endobronchial lesions. (A) Metastatic melanoma involving the left main bronchus. Note the black pigmentation of the tumor. (B) *Aspergillus niger* infection in a lung transplant recipient. The black pigment indicates the fungus, and the white pigment indicates calcium oxalate crystals produced by the fungus. (C) Recurrent respiratory papillomatosis involving the trachea. Note the typical mulberry appearance. (D) A foreign body in the left main bronchus. The object is a camera used for capsule endoscopy that was aspirated into the lungs. (D, Courtesy Dr. Thomas Gildea.)

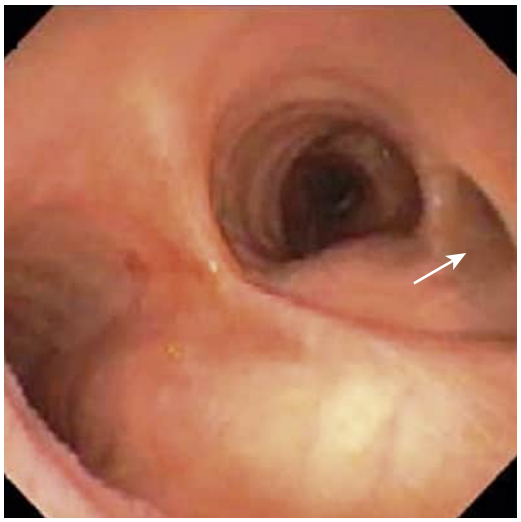

Figure 26.4 Tracheal bronchus. The view from a bronchoscope at a level above the major carina *(center)*. Note right upper lobe bronchus arising from the right lateral tracheal wall *(arrow)*. (From Mehta AC, Thaniyavarn T, Ghobrial M, Khemasuwan D. Common congenital anomalies of the central airway in adults. *Chest.* 2015;148:274–287.)

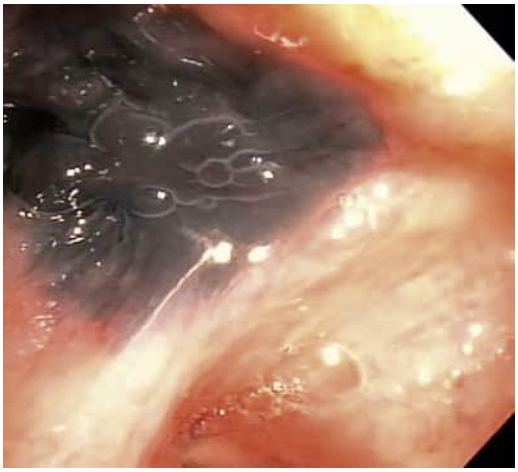

Figure 26.5 Appearance of endobronchial tuberculosis. Black, velvety, irregular mucosa involving the superior segment of the left lower lobe from *Mycobacterium tuberculosis*.

prohibits either bronchial brushing, *transbronchial biopsy* (TBB), or *transbronchial needle aspiration* (TBNA).

For diffuse opacities, any area can be chosen for BAL; however, in such cases, either the right middle lobe or the lingula is preferred because, in a supine patient, gravity assists the recovery of a maximal amount of BAL fluid return.[70,72,77] In the case of localized disease, lavage should be performed in the area of focal radiographic abnormality[73,75,77] and, for maximal recovery, the patient can be positioned appropriately to improve recovery from the desired segment. For example, the patient's head can be elevated to improve recovery from the upper lobes, or the patient can be turned sideways to improve recovery from the lateral segments. "Good wedge" position usually means that the bronchoscope is advanced as far as possible without losing

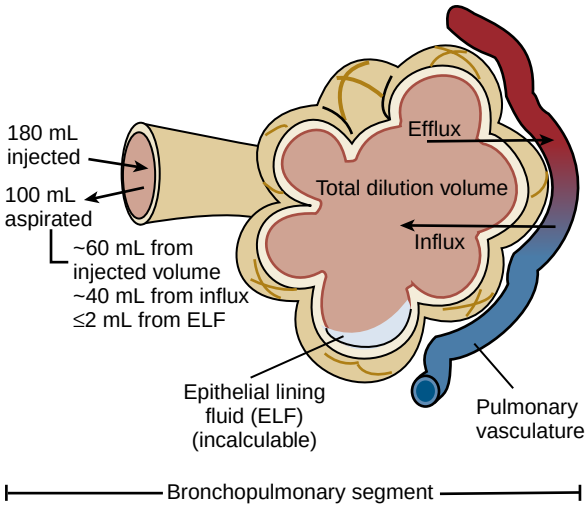

Figure 26.6 Schematic presentation of the constituents of the bronchoalveolar lavage fluid. The fluid samples the cellular and noncellular components of the lower respiratory tract. (From Kuvuru MS, Dweik RA, Thomassen MJ. Role of bronchoscopy in asthma research. *Clin Chest Med.* 1999;20:153–189.)

the view of the distal lumen. In this optimal position, a slow, manual gentle aspiration, without allowing the airway walls to collapse, tends to maximize the lavage return.[78]

BAL has significantly improved the diagnostic workup of lung diseases, whether diffuse or localized. In pulmonary alveolar proteinosis, it has both diagnostic and therapeutic values.[72,79–82] In an international statement on the major interstitial lung diseases, BAL is considered to be helpful in strengthening the diagnosis of sarcoidosis in the absence of a tissue diagnosis, by finding a lymphocytosis (>25%) and a CD4/CD8 ratio greater than 4.[83,84] BAL may be a useful tool in the diagnosis of peripherally located primary lung cancer, with an overall diagnostic yield range of 33–69%, being exclusively diagnostic in 9–11% of cases.[85–92] Numerous case reports confirm the ability of BAL to diagnose leukemia and lymphomatous pulmonary involvement, as well as plasma cell dyscrasia.[93–95] Finding asbestos bodies in BAL fluid may correlate with occupational exposure, yet in itself, it is not proof of an asbestos-related lung disease.[96,97] The presence of greater than 25% eosinophils in the BAL fluid confirms the diagnosis of eosinophilic lung diseases, and the presence of greater than 4% $CD1^+$ Langerhans cells confirms a diagnosis of pulmonary Langerhans cell histiocytosis, albeit with low sensitivity.[98] In chronic beryllium disease, lymphocytes from the BAL proliferate when stimulated in vitro with soluble beryllium salts, with a sensitivity and specificity approaching 100%; this lymphocyte stimulation test has become a valuable diagnostic tool for this condition and has replaced open-lung biopsy.[99,100]

In patients with ventilator-associated pneumonia, a positive quantitative culture ($>10^4$ *colony-forming units* (CFU)/mL) on BAL fluid may be clinically useful, with a sensitivity of 22–93% and a specificity of 45–100%, depending upon the clinical status of the patient.[101–108] BAL is also a useful tool in the diagnosis of pulmonary infections in immunocompromised patients, with the reported yield as high as 93%[109–116] (Fig. 26.7). Thus, in certain conditions, BAL findings can be diagnostic and thus avoid the need for either TBB or open-lung biopsy (Table 26.3). In other settings, although not diagnostic, BAL can be used as an adjunct to



Figure 26.7 Bronchoalveolar lavage can be diagnostic for infection. Bronchoalveolar lavage specimen reveals a larva of *Strongyloides stercoralis.* (Courtesy Dr. Suhail Raoof.)

TABLE 26.3 Diseases in Which Bronchoalveolar Lavage Can Be Diagnostic

Opportunistic infections (*Pneumocystis jirovecii,* fungi)
Invasive aspergillosis (via galactomannan levels)
Pulmonary alveolar proteinosis
Diffuse alveolar hemorrhage
Malignant opacities (solid tumors, lymphoma, leukemia)
Eosinophilic lung disease
Chronic beryllium disease
Pulmonary Langerhans cell histiocytosis

the diagnosis when interpreted in the context of the entire clinical picture and can be used to exclude infection before starting immunosuppressive therapy.

While performing BAL in an immunocompromised host and if invasive *Aspergillus* infection is suspected, the fluid should be submitted for galactomannan cell wall antigen detection using an enzyme immunoassay. The sensitivity and specificity of elevated galactomannan levels in BAL fluid are of value in immunocompromised patients; according to two meta-analyses in immunosuppressed populations, the sensitivity ranged from 71–92%, and the specificity was 89–98%.[117,118] It needs to be pointed out that concomitant use of certain antibiotics, such as piperacillin-tazobactam, amoxicillin, or amoxicillin-clavulanate, may produce false-positive results. Besides, the test may also have cross reactivity with *Histoplasma capsulatum* and *Penicillium* species cell wall antigens. Hence the results should be interpreted in the context of the total clinical picture and rechecked if clinically indicated.[119]

The most common complications associated with BAL are fever, which can be seen in up to 30% of patients, and transient hypoxemia, which is readily handled with supplemental oxygen. Rare cases of pneumothorax after BAL have also been reported.[120]

BRONCHIAL WASHINGS

Bronchial washings are obtained by advancing the bronchoscope into an airway, instilling 10 to 20 mL of sterile saline, and then quickly aspirating the instilled saline into a

specimen trap. The utility of bronchial washings is largely for the diagnosis of airway diseases, including primary or metastatic lung carcinoma and fungal or mycobacterial infection. Of the various bronchoscopic procedures, bronchial washing is the easiest to perform but has the lowest yield (sensitivity, 27–90%),[121–126] with a higher yield for central lesions.[124,127–129] Bronchial washings are an inexpensive adjunct and should be collected during a diagnostic bronchoscopy when appropriate because, even though by a small percentage, they can increase the overall diagnostic yield of the procedure.[124,130,131]

BRONCHIAL BRUSHINGS

Bronchial brushings were analyzed for the first time in 1973 and showed highly suspicious cytologic findings in most cases with lung cancer.[132] In general, bronchial brushings provide diagnostic material in 72% (44–94%) of patients with central lung cancers and 45% of patients with peripheral lesions, when obtained under fluoroscopic guidance.[133] When bronchial brushing is combined with *endobronchial biopsy* (EBB) of central lesions, the diagnostic yield of FB increases to between 79% and 96%.[134] We usually perform brushing after obtaining all the other bronchoscopy specimens because the bleeding caused by the brushing can interfere with obtaining or interpreting subsequent samples. The diameter or the length of the brush has not been shown to affect the diagnostic yield from the bronchial brushing.

Protected Specimen Brush

Protected specimen brush was first described in 1979 by Wimberley and coworkers[135] as a technique to establish an accurate diagnosis in patients with suspected pneumonia. Brushing specimens are collected using a brush that is enclosed within a double catheter sheath, capped at its distal end by a wax plug that can be easily dislodged before obtaining the specimen. The purpose of the catheter sheath and wax plug is to prevent contamination of the brush with oropharyngeal flora inside the working channel of the bronchoscope.

In patients with ventilator-associated pneumonia, the sensitivity of protected specimen brush sampling ranges from 58–86% and the specificity from 71–100%.[136,137] For now, the procedure appears to have lost popularity against empiricism for the diagnosis of ventilator-associated pneumonia; however, when it is used, protected brush samples should be analyzed using quantitative cultures with a cutoff value of greater than 10^3 CFU/mL.

ENDOBRONCHIAL BIOPSY

EBB is an essential and technically simple technique in the diagnosis of endobronchial neoplasms and for inflammatory conditions involving the airways, such as sarcoidosis and amyloidosis. For tissue sampling using EBB, the cusps of the forceps are opened, advanced onto the target and closed, thereby gripping the target. The forceps are then briskly pulled back, taking a sample of the endobronchial lesion 2 to 4 mm in diameter. The forceps and biopsy specimen are then pulled out through the working channel, and the tissue sample is collected in saline or fixative. EBB is used for lesions directly visualized during bronchoscopy. It provides histologic specimens, whereas bronchial washing provides only cytologic samples. The reported diagnostic yield of EBB is 80%, with a range of 51–97%, depending upon the patient population.[121,122,133,138–140] The number of biopsy specimens required for optimal diagnostic yield varies according to the suspected diagnosis. Three biopsy specimens of an endobronchial lesion suspected to be bronchogenic carcinoma can provide a diagnostic yield of greater than 97%.[141] Care should be taken to prevent excessive bleeding after an endobronchial biopsy of a lesion that appears very vascular, such as carcinoid. One can instill a small amount of ice cold saline before obtaining the biopsy or may consider performing TBNA instead. A deep biopsy of a necrotic-looking tumor is essential to obtain a viable and diagnostic tissue. On the contrary, biopsy of a lesion exhibiting vascular hue and pulsation should be avoided (i.e., Dieulafoy lesion of the bronchus). Endobronchial ultrasound can be helpful in identifying an increased risk of bleeding after EBB.

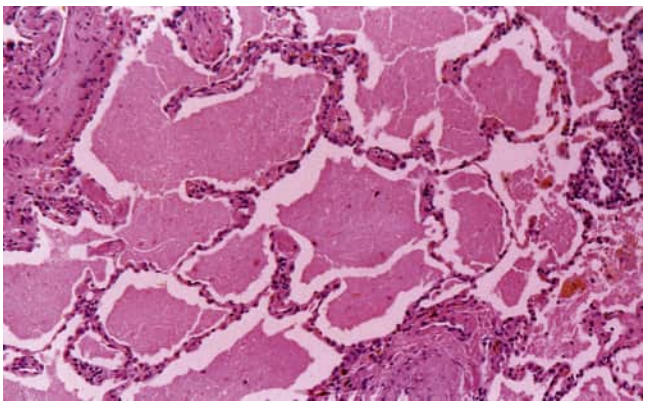

Figure 26.8 Transbronchial biopsy specimen confirms the diagnosis of pulmonary alveolar proteinosis. Note periodic acid–Schiff stain–positive material filling up the alveolar spaces.

TRANSBRONCHIAL BIOPSY

TBB is the technique by which a piece of lung parenchyma is obtained using flexible forceps positioned distally via FB. TBB specimens can be obtained blindly or with guidance by fluoroscopy, computed tomography, or radial-probe endobronchial ultrasonography. In many instances TBB can obviate the need for an open-lung biopsy; however, certain conditions, such as interstitial lung diseases, generally require larger tissue samples than those that can be obtained bronchoscopically. TBB is diagnostically useful in 38–79% of patients (average sensitivity, 52%), depending upon the underlying disease.[142–146] For example, in sarcoidosis, TBB has a diagnostic yield of 40–90%,[147,148] although later studies have indicated that endobronchial ultrasound–guided TBNA of mediastinal/hilar nodes may have a greater diagnostic yield.[149] TBB has also been shown to be diagnostic in up to 10–40% of cases of pulmonary Langerhans cell histiocytosis,[150] 88–97% in *Pneumocystis jirovecii* pneumonia,[111,151] and 57–79% in lung infections caused by *Mycobacterium tuberculosis.*[152] In patients suspected of having pulmonary alveolar proteinosis, its diagnostic yield has been reported to be as high as 100% (Fig. 26.8).

The diagnostic yield of TBB increases with the number of biopsy specimens obtained.[153] Usually, 6 to 10 biopsy specimens are obtained under fluoroscopic guidance. However, the use of fluoroscopy is not mandatory in patients with diffuse parenchymal disease, and biopsy specimens can be obtained by assessing the proximity to the pleura as guided by the patient's perception of chest pain. It is highly recommended that a large (7.3-mm cusp size), fenestrated, crocodile-type biopsy forceps should be used to obtain tissue of an adequate size without crush artifact. Compared to cutting forceps, crocodile forceps are considered to provide larger pieces of tissue by tearing rather than cutting. The yield of TBB for malignant peripheral lesions more than 2 cm in diameter was also reported to be 70% in one study, even without fluoroscopic guidance.[154] When performed in association with bronchial brushings and TBNA, TBB adds to the diagnostic yield of FB for peripheral lung cancers.[128,133,155–160]

The success of lung transplantation cannot be imagined without the contributions from FB and especially TBB. In lung transplant recipients, TBB helps in diagnosing or ruling out acute cellular rejection. It also helps establish the diagnosis of antibody-mediated rejection and chronic rejection, albeit with lower yield. To date, however, there are no gold standard findings for diagnosing rejection in the lung transplant population.

Pneumothorax and hemorrhage are the most feared complications after TBB, with an incidence of up to 5% of cases. Renal insufficiency (blood urea nitrogen level >30 mg/dL [10.7 mmol/L] and creatinine level >3 mg/dL [0.27 mmol/L]) and other coagulopathies are considered risk factors for bleeding after TBB.[161,162] Although there are no scientific data, there is a prevailing notion among bronchoscopists that IV vasopressin (desmopressin, DDAVP [1-deamino-8-D-arginine vasopressin]) 3 to 4 hours before TBB in patients with uremia or those who are on dialysis may reduce the risk of bleeding. Bleeding after the TBB is from the bronchial circulation, and moderate pulmonary hypertension is not a contraindication for the procedure.[163]

TBB can be safely performed while patients are receiving aspirin or nonsteroidal anti-inflammatory drugs; however, clopidogrel bisulfate should be withheld for at least 5 to 7 days before the procedure.[164–166] Wedging the tip of the bronchoscope in the segment of interest before obtaining a TBB is highly recommended to prevent spilling of the blood in other areas and resultant hypoxemia. A 4-minute wait before dislodging the bronchoscope allows enough time for clot formation and adds to the safety of the procedure. Other management of hemoptysis is discussed in Chapter 40.

Use of fluoroscopy during TBB may reduce the rate of pneumothorax. After the procedure, a repeat fluoroscopy is sufficient to rule out pneumothorax. A chest radiograph is not essential unless the complication is suspected. A thoracic ultrasound can be used for the confirmation, yet could be redundant.

CONVENTIONAL TRANSBRONCHIAL NEEDLE ASPIRATION

Conventional TBNA (C-TBNA) is a sensitive, accurate, safe, and cost-effective technique in the diagnosis and staging of lung cancer.[160,167–172] It can also be applied for the diagnosis of nonmalignant diseases, such as sarcoidosis[173–178] (Video 26.2). Despite proven advantages, C-TBNA remains underutilized.[179–181] Needless to say, the advantages of the C-TBNA have been heavily overshadowed by the introduction of endobronchial ultrasound–guided TBNA. There are no absolute, specific contraindications for C-TBNA.

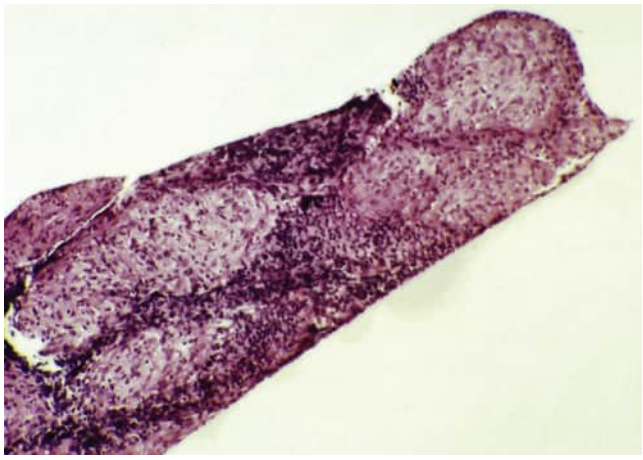

Figure 26.9 Transbronchial needle aspiration specimen in sarcoidosis. A tissue sample obtained using a 19-gauge histology needle reveals noncaseating granulomas under high-power magnification (×200 original magnification) after hematoxylin and eosin stain.

Diagnosis and staging of bronchogenic carcinoma, lymphoma, and sarcoidosis can be established using 21- or 22-gauge cytology needles.[149,180,182,183] For the diagnosis of lung cancer, the reported sensitivity, specificity, and accuracy of C-TBNA are 60–90%, 98–100%, and 60–90%, respectively.[182–187,193] For mediastinal staging of lung cancer, the overall sensitivity, specificity, and accuracy of C-TBNA are 50%, 96%, and 78%, respectively.[133] Judicious use of C-TBNA can thus reduce the need for surgical staging. In the diagnosis of involvement of mediastinal or hilar lymph nodes by sarcoidosis or tuberculosis, C-TBNA can be useful as well[173–177] (Fig. 26.9). In cases with pulmonary nodules, C-TBNA increases the diagnostic yield of FB by 25%.[149] C-TBNA can also be safely performed in mechanically ventilated patients.[187]

The procedure of C-TBNA is safe, with an overall major complication rate of approximately 0.26%. Complications include fever, bacteremia, bleeding from the puncture site (Fig. 26.10), and damage to the working channel of the bronchoscope.[155,160,180] Use of computed tomography, fluoroscopy, and ultrasonographic guidance has been shown to improve the yield of C-TBNA.[190–195]

Low-grade postbronchoscopy fever has been reported in up to 50% of patients within first 24 hours. It is more frequent when a BAL specimen is obtained. It is postulated that the release of cytokines, such as tumor necrosis factor and interleukins (IL-1, -6, and -8), into the bloodstream from the alveolar cells is responsible for the phenomenon. There are no data to suggest that the postbronchoscopy fever is related to transient bacteremia, and hence there is no indication for prophylactic antibiotics.[196]

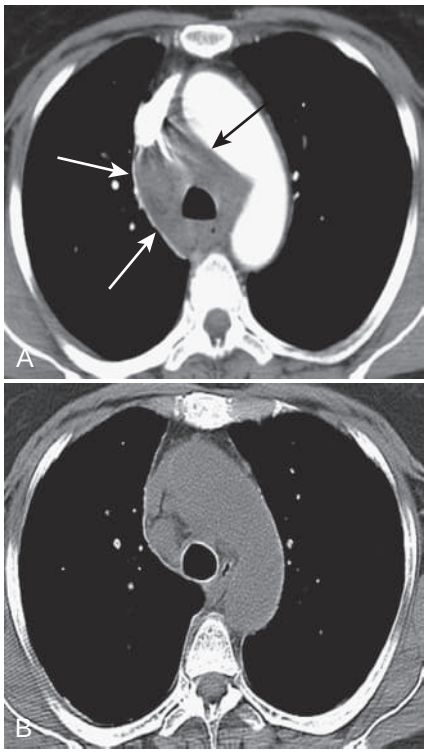

Figure 26.10 Complication of transbronchial needle aspiration. (A) On day 1 mediastinal hemorrhage is noted *(arrows)*. (B) By day 6 the abnormality has resolved. (Courtesy Dr. Stefano Gasparini.)

Key Points

- Since its introduction in 1966, flexible bronchoscopy has replaced rigid bronchoscopy for most diagnostic and therapeutic indications; rigid bronchoscopy has a continued role for unique indications, such as massive hemoptysis and removal of large foreign bodies.
- Bronchoalveolar lavage, which samples the distal air spaces, can be used to diagnose several diseases that involve the air spaces, including opportunistic infections, eosinophilic pneumonia, and pulmonary alveolar proteinosis.
- Bronchial brushing can add to the diagnostic yield of bronchoscopy, particularly for the diagnosis of endobronchial neoplasms.
- Endobronchial biopsy is a high-yield procedure for all types of airway neoplasms and for infiltrative processes.
- Transbronchial biopsy has value in the diagnosis of diffuse pulmonary diseases. With the advent of novel guidance techniques, such as electromagnetic navigation, transbronchial biopsy may also become accurate at sampling distal focal lesions.

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DIAGNOSTIC BRONCHOSCOPY: ADVANCED TECHNIQUES (EBUS AND NAVIGATIONAL)

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INTRODUCTION
ENDOBRONCHIAL ULTRASOUND
Convex
Radial
CONFOCAL BRONCHOSCOPY
ELASTOGRAPHY
THIN AND ULTRATHIN BRONCHOSCOPY
VIRTUAL BRONCHOSCOPY
ELECTROMAGNETIC NAVIGATION
Electromagnetic Navigational Transthoracic Needle Aspiration
BRONCHOSCOPIC TRANSPARENCHYMAL NODULE ACCESS
AUGMENTED FLUOROSCOPY NAVIGATION
CONE BEAM CT FOR BRONCHOSCOPY
ROBOTIC BRONCHOSCOPY
CRYOBIOPSY
KEY POINTS

INTRODUCTION

Gustav Killian performed the first bronchoscopy in 1897 to extract a piece of a pork bone from the right main bronchus. From that meager beginning, the technology in bronchoscopy has advanced exponentially. In 1966, the flexible bronchoscope was introduced into clinical practice by Shigeto Ikeda. Currently, this instrument is one of the most important tools for diagnosis and treatment of pulmonary diseases.

Following publication of the National Lung Screening Trial[1] and the increasingly common use of *computed tomography* (CT) scans in general, more pulmonary nodules are found and the requirement for biopsy, especially for peripheral nodules, has increased.[2] Likewise, bronchoscopy is often performed to investigate lung opacities in immunocompromised patients, search for sources of hemoptysis, and evaluate interstitial lung disease and mediastinal/hilar adenopathy.

Previously, the diagnostic yield for peripheral nodules with bronchoscopy ranged from 20–80%. Historically, these biopsies used a bronchoscope with an outer diameter of 5 to 6 mm, often under fluoroscopic guidance. Limitations included the restricted depth of bronchoscope insertion due to a relatively large diameter, difficulty in guiding the bronchoscope and biopsy instruments to smaller peripheral lesions, and lack of real-time confirmation of target localization.[3,4] This chapter reviews the many advances in diagnostic bronchoscopy. More "basic" bronchoscopic procedures and therapeutic bronchoscopy are discussed in other chapters.

ENDOBRONCHIAL ULTRASOUND

Endobronchial ultrasound (EBUS) is a bronchoscopic approach that offers sonographic assessment of parenchymal lesions and tumors compressing/invading the central airways as well as real-time localization and sampling of mediastinal, hilar, or parenchymal lesions. There are two forms: convex EBUS evaluates the mediastinum, hilum, and central pulmonary lesions, and radial EBUS evaluates lesions that involve the airway itself or peripheral pulmonary lesions.

CONVEX

The convex EBUS bronchoscope, introduced in 2004, has a convex ultrasound probe at the tip of the bronchoscope and provides sonographic, real-time visualization during *transbronchial needle aspiration* (TBNA) of lymph nodes and peribronchial lesions.[5] Convex EBUS has revolutionized the diagnosis and staging of lung cancer and extrathoracic malignancies. EBUS has become standard of care with such widespread acceptance that it has largely replaced conventional TBNA and even mediastinoscopy as the gold standard for lung cancer staging.[6,7]

Other entities commonly diagnosed with convex EBUS include lymphoma and nonmalignant diseases such as sarcoidosis. The *American College of Chest Physicians* (ACCP) has published guidelines and evidence-based recommendations regarding the technical use of EBUS.[8] A needle-based approach (EBUS-TBNA) is recommended in the 2013 ACCP Guidelines for Lung Cancer as a first-line intervention for

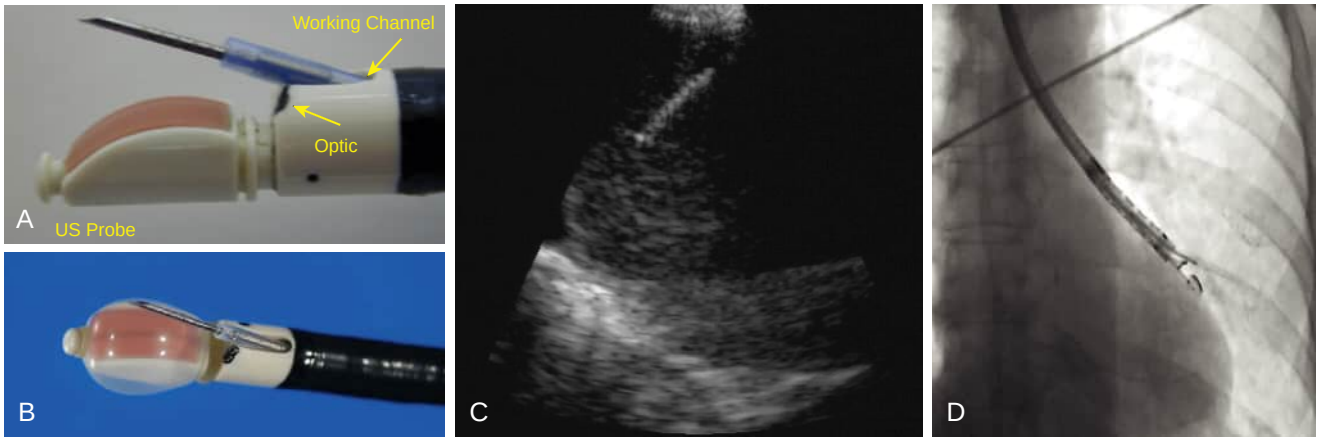

Figure 27.1 Convex *endobronchial ultrasound* (EBUS). (A) EBUS scope is shown with the probe, working channel and optic portions labeled. (B) EBUS scope shown with balloon filled with saline, used to improve probe contact with airway wall for better image quality. (C) EBUS *transbronchial needle aspiration* (TBNA) of a mediastinal lymph node showing needle within node. (D) Fluoroscopic view of EBUS-TBNA of a central pulmonary lesion. (A–B, Courtesy Olympus Medical.)

invasive mediastinal staging of *non–small cell lung cancer* (NSCLC).[9,10]

Convex EBUS incorporates a 7.5 MHz ultrasound transducer on the tip of a bronchoscope used to guide TBNA (Fig. 27.1). The EBUS sonographic footprint lies parallel to the long axis of the bronchoscope and provides a 50-degree field of view. Depending on the location of the lymph node or lesion, the ultrasound may not have adequate contact with the airway wall, a technical problem that can substantially affect the ultrasound image quality. In that case, a latex balloon at the tip of the ultrasound probe can be inflated with saline to assist in probe contact and improve image acquisition. However, it is unclear if the balloon tip improves diagnostic yield. Its use should be avoided in patients with a latex allergy.[8]

Diagnostic Yield for Lung Cancer

Many studies, systematic reviews, and meta-analyses have demonstrated a pooled sensitivity of EBUS for mediastinal staging of lung cancer of approximately 90%,[6,7,11,12] which is comparable to that from video mediastinoscopy.[9] However, it should be noted that after neoadjuvant chemotherapy and radiation, the sensitivity of EBUS-TBNA is only approximately 67%, and thus a nondiagnostic EBUS in that setting may need to be followed by surgical restaging.[13] Additionally, EBUS-TBNA has also been found to have a high yield for intrathoracic lymph node metastases from extrathoracic malignancies with a pooled sensitivity of 85%, though with a sensitivity of only 55% for occult metastatic disease (pathologic disease without suggestive radiographic findings such as a lung mass or lymphadenopathy that is pathologic by radiographic criteria).[14] Therefore, minimally invasive mediastinal and hilar lymph node investigations should be considered for both intrathoracic and extrathoracic disease.

Many techniques and factors can affect results and improve diagnostic yield with EBUS:

- *Number of passes:* The diagnostic yield for detection of malignant cells does not increase above three passes.[15] If *rapid on-site evaluation* (ROSE) by cytology is available, a reasonable approach is to perform aspirations until adequate cell material (i.e., sufficient for a specific diagnosis or a good recovery of lymphocytes) is obtained or a minimum of four to five passes are completed to ensure a diagnosis and adequate material for specific molecular testing.[6,16,17]
- *Size of needles:* EBUS needles of several sizes are currently commercially available. Guidelines recommend the use of either a 21- or 22-gauge needle as acceptable, though newer studies would suggest that 19- and 25-gauge options are equally effective. In selected cases, additional tissue obtained with a 19-gauge needle may increase the diagnostic yield.[18–24]
- *Suction:* One prospective, single-blinded, randomized control trial looked at 115 patients who underwent EBUS-TBNA with passes taken with or without suction. Results showed no difference in diagnostic yield regardless of the size of lymph node (greater or less than 1 cm).[25]
- *Use of stylet:* The EBUS needle stylet helps reduce needle contamination with airway epithelial debris and mucosa. It can also be used to assist in providing suction via capillary action when it is withdrawn from the needle during sampling. Another study evaluated TBNA samples with and without the stylet using an EBUS-TBNA needle for a prospective, single-blind, randomized control trial with 121 patients and 194 lymph nodes sampled. Results reported no difference in sample adequacy or diagnostic yield.[26]
- *Sedation:* Several studies have looked at different sedation strategies for EBUS (moderate sedation vs. general anesthesia using either a laryngeal mask airway or endotracheal tube), and the data are conflicting without a significant benefit to any one strategy. The EBUS guidelines therefore recommend that either sedation strategy can be used, based on operator comfort level and institutional preferences.[27–30]

Central lesions (within the inner one-third of the lung) in a peribronchial location can often be sampled using EBUS-TBNA. Two studies retrospectively evaluated the yield of EBUS for centrally located pulmonary lesions and found the diagnostic yield to be greater than 84%, even when there

was no visible airway leading into the lesion (i.e., a bronchus sign).[31,32]

Additionally, performing concurrent *endoscopic ultrasound* with fine-needle aspiration via the esophagus using an EBUS scope or a gastrointestinal endoscope has demonstrated improved diagnostic yield.[9,33]

Ultrasound Features That Predict Malignancy

EBUS ultrasound characteristics of lymph nodes have been shown in several studies to be predictive of malignancy.[34,35] Fujiwara et al.[34] reported that several signs were independent risk factors for malignancy: round shape, distinct margin, heterogeneous echogenicity, and the coagulation necrosis sign. When all four signs were absent, there was a 96% negative predictive value for metastases. Another cohort by Memoli et al.[35] showed that increased size and a round or oval shape are risk factors for malignancy. Also, increased vascularity in specific patterns may be useful in identifying malignant lymph nodes.[36,37] Finally, the absence of a central nodal vessel on ultrasound may also be predictive of malignant involvement.[38] However, despite such ultrasound imaging characteristics, tissue diagnosis is still necessary.[8]

Molecular Markers

Molecular marker testing is considered standard of care and necessary for the consideration of tailored therapy in every locally advanced or metastatic NSCLC (see also Chapter 73). Since EBUS is increasingly used for the diagnosis and staging of lung cancer, many studies have now emerged demonstrating the ability of EBUS-TBNA to acquire samples with enough cellularity to perform all of the necessary immunohistochemistry, molecular, and next-generation sequencing required, including PD-L1 testing. In several studies, PD-L1 expression in NSCLC was compared from different biopsy samples (cytology, small biopsy, and surgical biopsy) and found to be adequate with comparable results among all specimen types.[39–51]

Diagnostic Yield for Diagnoses Other Than Lung Cancer

Lymphoma. For diagnosing and subtyping lymphoma, the yield for EBUS has been around 70%, though with considerable variation reported.[52–54] Despite the lower diagnostic yield, EBUS-TBNA is still recommended as an initial minimally invasive evaluation.[8] EBUS has been reported to have a lower sensitivity for Hodgkin lymphoma compared with non-Hodgkin based on sample size along with cytopathology expertise and comfort level.[54,55] Reed-Sternberg cells within the needle aspirates are usually scarce, and the evaluation of lymphoid background architecture is often difficult. It is noted that recurrence of lymphoma is more easily diagnosed by EBUS than a de novo diagnosis (91% vs. 79%).[54]

Sarcoidosis. The sensitivity of EBUS-TBNA for pulmonary sarcoidosis is 85–90% as opposed to transbronchial biopsy and endobronchial biopsy, which have a combined diagnostic yield of only 35%. Combining all three modalities of biopsy can increase the yield to 93–95%.[8,56–59]

Infection. Although EBUS-TBNA is suggested for evaluation of patients with mediastinal or hilar adenopathy concerning for tuberculosis or possible histoplasmosis, the value in respiratory infection is unproven but understudied. In one retrospective study, routine microbiologic results of EBUS-TBNA samples from 82 patients showed very little evidence of infection. The authors concluded that EBUS did not have sufficient sensitivity to rule out infectious causes of adenopathy.[60] Another study demonstrated that polymerase chain reaction for *M. tuberculosis* using EBUS-TBNA samples is a useful laboratory test for evaluating intrathoracic granulomatous lymphadenopathy. Moreover, this technique can prevent further invasive evaluation in patients whose histologic and microbiologic tests are nondiagnostic.[61] Dhooria et al. reported that a cartridge-based nucleic acid amplification test has good specificity and positive predictive value in the diagnosis of tuberculosis and is a useful investigation in separating tuberculosis from sarcoidosis.[62]

More sensitive methods of detection will be needed to improve the usefulness of EBUS in this population of patients.

Rapid On-Site Evaluation

Multiple conflicting studies have been published on the utility and importance of ROSE, whereby a pathologist/cytopathologist or cytotechnologist prepares slides for immediate visualization and interpretation during the procedure. In the setting of traditional TBNA, ROSE has been performed routinely to ensure adequate sampling by confirming location within a lymph node.[8] With EBUS-TBNA, because the needle is visualized within the target lesion in real time, this benefit of ROSE is not as clear cut. Though ROSE may not improve the diagnostic yield of EBUS-TBNA, it does reduce the number of aspirations or passes required, can reduce overall procedure time, and may reduce the need for other procedures such as transbronchial biopsy of a parenchymal lesion, thus decreasing complications such as bleeding and pneumothorax. Notably, if ROSE is available, it can help determine the sample adequacy for immunohistochemistry, molecular, and next-generation sequencing testing. Thus, the value of ROSE with EBUS-TBNA lies in a timely and accurate diagnosis with streamlined care and a decrease in unnecessary procedures, thereby minimizing complications and cost.[63–67]

Complication Rate and Safety

A large systematic review of more than 1500 patients identified no serious adverse events with EBUS-TBNA and only agitation, cough, and blood at the puncture site as minor complications.[68] Prospective database analyses report complication rates of EBUS to be approximately 1%, though there are individual reports of more serious complications such as mediastinitis, pericarditis, and death.[69,70]

With respect to EBUS and anticoagulation, only two studies have evaluated the safety of performing EBUS in patients taking clopidogrel. The first was a retrospective review of 12 patients on clopidogrel who underwent EBUS-TBNA, 67% of whom were also taking aspirin; there were no bleeding complications. The more recent study accrued 42 patients for a prospective, multicenter cohort, all of whom were unable to stop therapy with clopidogrel and aspirin for

5 days. Only 1 of the 42 patients had significant bleeding; this was controlled with instillation of 30 mL of cold saline at the needle insertion site. No long-term or serious complications were reported.[71,72] Convex EBUS can be considered in a patient taking clopidrogel and aspirin if the patient is at high risk for discontinuation.

Cost

There are cost data to support the use of EBUS for mediastinal sampling. A large retrospective database review compared EBUS-TBNA with mediastinoscopy using claims data. Of 30,570 patients, 49% underwent EBUS. Severe adverse events were similarly low between the groups. Compared with mediastinoscopy, EBUS was associated with less vocal cord paralysis (odds ratio, 0.57) and less expense.[73] Another study looked at the cost of performing EBUS-TBNA under monitored anesthesia care versus moderate sedation. They found no difference in diagnostic yield, significant complications, or procedure duration, but the cost was $245 more for the monitored anesthesia care cases.[74] Finally, Steinfort et al. proposed a minimally invasive staging strategy in which patients are first biopsied using EBUS and, if they have a negative result, proceed to mediastinal staging with mediastinoscopy. This EBUS/mediastinoscopy strategy was compared to performing EBUS without surgical confirmation of negative results, conventional TBNA alone, and mediastinoscopy alone. The costs were AU$2691, AU$3344, AU$3754, and AU$8859, respectively, demonstrating cost-effectiveness of a thoughtful, minimally invasive approach to staging of patients with NSCLC.[75]

Education and Competency

Because the safety and value of EBUS are now well known, more Pulmonary and Critical Care fellowship programs are aiming to have their trainees certified in EBUS prior to graduation. The number of procedures required to perform EBUS competently is unknown, though 50 supervised procedures has been cited by the ACCP.[76] Previous data have shown that the number of procedures needed to reach this level of proficiency is variable from person to person and can take up to 120 procedures or more depending on the operator and his or her experience and training.[77–81] A key factor, however, is not merely acquiring "minimal competency," but rather mastery; in addition, as with any other procedure, key knowledge as well as procedural competence determine procedure success. A recent study, for example, found that interventional pulmonologists have a much higher rate of "appropriate mediastinal staging" than general pulmonologists,[82] presumably because of their greater procedural experience and competence.

There has been increased interest in simulation-based learning and the development of combined cognitive and skills assessments validated for EBUS.[83,84] These tools may assist in the development and assessment of the detailed anatomic knowledge and procedural skills required to evaluate and sample using EBUS-TBNA to ensure standardization and ability. Such skills are particularly important when staging for cancer because this requires diligence and precision and should not be performed without the necessary expertise.

In sum, convex EBUS is a minimally invasive, safe tool that has revolutionized the evaluation of mediastinal, hilar, and central pulmonary disease for a variety of both benign and malignant conditions. Successful use is dependent on operator training and skill.

RADIAL

Introduction

Radial EBUS was first described in 1992 and was initially used to locate mediastinal lymph nodes and guide conventional TBNA as well as to distinguish tumor invasion from compression in the central airways.[5] Radial EBUS provides a circumferential or 360-degree ultrasound image around a small probe inserted through the working channel of a bronchoscope and allows the bronchoscopist to characterize the tissue densities surrounding the probe in real time (Fig. 27.2). A standard frequency of 20 MHz is used, providing a spatial resolution of less than 1 mm and penetration depth up to 5 cm. Unfortunately, it is currently not possible to biopsy with direct visualization using the radial EBUS image because the probe must be removed from the working channel to allow the biopsy instrument to be introduced.

Imaging Techniques

When radial EBUS is used to evaluate the multiple layers of the bronchial wall, the probe has an integrated water-filled balloon sheath to ensure "acoustic coupling." This approach allows evaluation of the depth of central lesions in the tracheobronchial wall.[85] Distinguishing central tumor invasion from compression was the initial use of radial EBUS and, for this use, radial EBUS was found to be more accurate than chest CT imaging.[86]

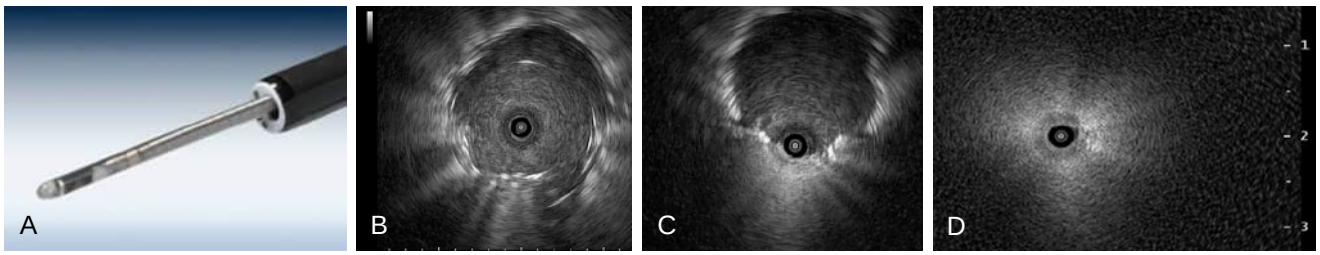

Figure 27.2 Radial *endobronchial ultrasound* (EBUS). (A) Radial EBUS probe extended through a bronchoscope channel showing circumferential imaging surface at tip. (B) Radial EBUS concentric view of peripheral lesion. (C) Radial EBUS eccentric view of a peripheral lesion. (D) Radial EBUS "blizzard" appearance of an area of a ground-glass opacity. (A, Courtesy Olympus Medical.)

More recently, radial EBUS is used for localization and to guide sampling of peripheral pulmonary lesions. Radial EBUS is typically directed to the lesion in conjunction with navigation modalities including virtual bronchoscopic navigation, *electromagnetic navigation bronchoscopy* (ENB), or robotic bronchoscopy, which are all discussed in further detail later in this chapter. Normal lung parenchyma has a "snowstorm" appearance due to air-filled alveolar tissue, whereas nodules and masses appear as hypoechoic lesions with a bright and well-defined border. Even ground-glass opacities can be visualized using radial EBUS because they are now recognized to create a "blizzard sign," which is an enlarged hyperintense acoustic shadow.[4,87]

There are two methods of utilizing the radial EBUS ultrasound. Either the probe can be advanced through the working channel of a bronchoscope directly or through a separate sheath, also known as a guide sheath. The value of the guide sheath is that, once the radial probe is removed, the sheath secures the location for subsequent biopsies of the lesion.

Utilizing ultrathin bronchoscopes may obviate the need for a guide sheath because such bronchoscopes can be advanced much deeper into the periphery of the lung (discussed in more detail later in this chapter). Although radial EBUS can provide real-time imaging, it cannot provide actual real-time biopsy visualization because the probe is withdrawn from the bronchoscope or guide sheath before sampling.[4]

Diagnostic Yield

A randomized trial comparing radial EBUS-guided transbronchial biopsy for malignancy by Paone and colleagues demonstrated a sensitivity of 79% compared with 55% using conventional transbronchial biopsies.[88] Another prospective study utilizing radial EBUS for small peripheral pulmonary lesions, which were invisible on fluoroscopy, demonstrated an 89% localization and 70% diagnosis for lesions averaging 2.2 cm in size.[89] The overall sensitivity of radial EBUS for the diagnosis of peripheral lung lesions is around 70%.[90]

Localization and diagnostic yield of radial EBUS is dependent on several factors, including lesion location, size, the presence of a "CT bronchus sign" (i.e., an airway that goes directly to the target lesion), and location of the probe relative to the lesion. Based on a multivariate analysis in a retrospective study, Tay and colleagues concluded that lesions less than 2 cm and more than 5 cm from the hilum were significantly less likely to be localized by radial EBUS.[91] Kurimoto and colleagues demonstrated that diagnostic yield was significantly higher when the radial probe was within a lesion (87%, concentric view) compared with when the probe was adjacent to it (42%, eccentric view).[92] Of note, a concentric view may not guarantee a high diagnostic yield in a malignant nodule because the malignant cells may not be homogeneously present in the lesion. Other studies have demonstrated that the diagnostic yield with radial EBUS increases with nodule size and the presence of a CT bronchus sign.[93–95]

The diagnostic yield is lower for ground-glass opacities compared with solid lesions despite using radial EBUS for localization. One retrospective study evaluated 67 patients with ground-glass opacities with a mean diameter of 21 mm who underwent radial EBUS with a guide sheath and fluoroscopy. This study found a 57% diagnostic yield using this radial EBUS method.[96] Another retrospective study of 40 patients with ground-glass opacities with a mean diameter of 22 mm (90% were partly solid) undergoing radial EBUS bronchoscopy and tomosynthesis guidance found a diagnostic yield of 65%.[97] Tomosynthesis refers to the technique by which a limited-angle image reconstruction is performed from images acquired from a two-dimensional method such as fluoroscopy or cone beam, thereby improving the appreciation of three-dimensional anatomy.[98]

Complications

The complication rate of radial EBUS is low, with one meta-analysis reporting a pneumothorax rate of 1% and only 0.4% requiring a chest tube.[90] Additionally, the guide sheath may be used to tamponade biopsy-related bleeding.[4]

Conclusion

In summary, radial EBUS has helped improve peripheral bronchoscopic evaluation and diagnostic yield of biopsies of peripheral pulmonary lesions. Notably, a certain amount of skill and learning are required to utilize and interpret the information gathered from this tool.

CONFOCAL BRONCHOSCOPY

Fibered confocal fluorescence microscopy is a technique that produces microscopic imaging of living tissue via a small probe introduced through the working channel of a conventional bronchoscope. Fibered confocal fluorescence microscopy can analyze human airway wall architecture and endobronchial abnormalities with near-histologic detail in vivo.[99] Thiberville and colleagues used fibered confocal fluorescence microscopy to examine two bronchial specimens ex vivo and in vivo for 29 individuals at high risk for lung cancer.[100] Alterations of the microstructure were observed in 19 of 22 metaplastic or dysplastic samples, 5 of 5 carcinomas in situ, and 2 of 2 invasive lesions. The authors suggest this could potentially be a minimally invasive method to study specific basement membrane alterations associated with premalignant bronchial lesions in vivo.

Another prospective, observational study evaluated ex vivo transbronchial biopsy samples of 36 patients using a 1.4-mm diameter confocal mini-probe.[101] Once the biopsy samples were obtained, they were placed in formalin for fixation, then removed and placed on gauze for assessment with the confocal probe. The stroma and parenchyma were examined and the carcinoma samples were found to have a highly fluorescent field penetrated by dark hollows. The sensitivity for malignancy was 91%, and the specificity was 77%. Both interobserver and intraobserver agreement was moderate. The authors concluded that this method could be used as a form of ROSE because it could be used to provide immediate feedback on specimen adequacy and preliminary diagnosis.

This technology continues to be evaluated as a form of "optical biopsy" that can help direct appropriate sampling in the future.

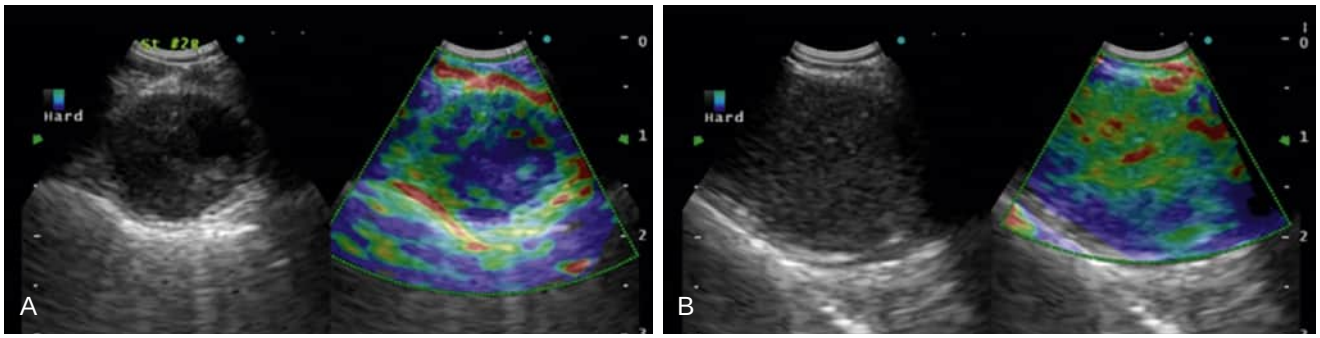

Figure 27.3 Elastography added to standard endobronchial ultrasound. (A) A lymph node demonstrating a malignant elastography pattern showing areas of stiffness (blue predominant). (B) A lymph node demonstrating a benign elastography pattern (green and red predominant). (From Fujiwara T, Nakajima T, Inage T, et al. The combination of endobronchial elastography and sonographic findings during endobronchial ultrasound-guided transbronchial needle aspiration for predicting nodal metastasis. *Thorac Cancer*. 2019;10[10]:2000–2005.)

ELASTOGRAPHY

Elastography is an ultrasonic technique that measures tissue compressibility and is an add-on feature to standard EBUS bronchoscopy. Because pathophysiologic processes such as malignancy generally make tissues more stiff, detecting stiffness can assist tumor location. With elastography, the stiffness of tissue is translated into a color signal overlaid onto the B-mode image. The colors associated with stiff, intermediate, and soft tissue are blue, green, and yellow/red, respectively. Normal and inflammatory lymph nodes have been shown to have a deformable medulla and hilum, with stiffness localized to the cortex. In early metastatic infiltration of a lymph node, stiffness can be detected in localized areas of the node; such imaging characteristics may help direct biopsies to the more abnormal areas. In advanced-stage cancer, stiffness will be increased throughout the lymph node (Fig. 27.3).[102]

Early endoscopic ultrasound elastography studies used a combination of color and color pattern homogeneity to differentiate benign from malignant lesions; however, better results have been obtained when the strain ratio is calculated (see below). Combining elastography with EBUS-TBNA may allow for the lymph node(s) most affected and even small areas within individual nodes to be targeted for optimal results.[103]

Various studies have evaluated the usefulness of elastography. In a study of 94 patients, 206 lymph nodes were evaluated by EBUS-TBNA and elastography. B-mode and elastography patterns were used to distinguish between benign and malignant nodes; sensitivity for malignancy was found to be 91%.[102]

Another study published in 2015 by He et al. performed EBUS-guided elastography of lymph nodes prior to EBUS-TBNA.[104] Elastography data were given a grading score of 1 to 4, with higher values being more likely to represent malignancy. Strain ratio was then calculated by quantifying the strain value of the target lymph node and comparing it to a similar area of normal tissue. Pathologic determination of malignant or benign lymph nodes was used as the gold standard. Results of this study showed that elastography images and strain ratio are well correlated and, when verified against pathologic data, the sensitivity, specificity, positive predictive value, negative predictive value, and accuracy were 88% (37/42), 81% (21/26), 88% (37/42), and 85% (58/68), respectively. The authors thus determined that elastography and strain ratios can be used effectively to predict mediastinal and hilar lymph node metastases.

Finally, Fujiwara et al. published their experience with lung cancer or suspected lung cancer patients undergoing EBUS-TBNA.[105] Sonographic, B-mode, and elastography findings were independently evaluated for each lymph node. Benign features on EBUS included oval shape, indistinct margins, and homogeneous echogenicity. Lack of coagulation necrosis on B-mode and less than 31% of the lymph node appearing malignant on elastography were also considered benign features. The results of these imaging interpretations were compared with a final pathologic diagnosis. B-mode predicted benign lymph nodes 96% of the time, and elastography predicted malignant lymph nodes 72% of the time. The combination of sonographic evaluation, B-mode, and elastography predicted malignant nodes 83% of the time and benign lymph nodes 96% of the time, showing benefit of a combined approach.[105]

Pitfalls when using elastography are anatomic location and pathologic changes that create significant artifact of the ultrasound image and compromise compressibility.[106]

THIN AND ULTRATHIN BRONCHOSCOPY

The thin bronchoscope has an outer diameter of 4 mm and a working channel of 2 mm. The most recent ultrathin bronchoscope on the market has a distal tip outer diameter of 3 mm and a working channel diameter of 1.7 mm (Fig. 27.4). This device has been developed to overcome the low diagnostic yield of bronchoscopy for peripheral lesions less than 20 mm in diameter.[107–110] Complexities of the distal airway anatomy often requires fluoroscopic, electromagnetic/virtual bronchoscopic navigational, or CT guidance to direct the bronchoscope to peripheral lesions.[111] Given the 1.7-mm working channel on the new ultrathin bronchoscope, radial EBUS can also be inserted and used for real-time confirmation of location within the lesion.



Figure 27.4 Ultrathin and thin bronchoscopes. *Left to right,* ultrathin, thin, and regular bronchoscopes. The outer diameters are 3 mm, 4.2 mm, and 6.2 mm, respectively.

Ultrathin bronchoscopes allow greater penetration into the lung. Whereas a conventional bronchoscope can navigate to the fourth-generation airways, the ultrathin bronchoscopes can navigate to a median of the fifth and up to the ninth-generation airways.[112] Oki and colleagues reported a diagnostic yield for peripheral nodules of 59% with a thin (4 mm) bronchoscope versus 70% using the ultrathin (3 mm) bronchoscope in combination with virtual bronchoscopy and fluoroscopic guidance.[113]

Aside from the ability to navigate more distally in the airways, the thin and ultrathin bronchoscopes can be used to evaluate the nature and extent of central airway obstruction where there is a risk for completely obstructing the airways with standard-sized bronchoscopes.[107] An ultrathin bronchoscope can define the distal extent of endobronchial tumor because it is more easily able to traverse the lesion, even when the lesion causes significant airway obstruction.[111] These smaller bronchoscopes can also be used for mechanically ventilated patients despite small endotracheal tubes.

Although most reports show these bronchoscopes to be safe, there have been case reports of visceral pleural perforation caused by the ultrathin bronchoscope. Care should be taken to monitor the location of the scope at all times when in the distal bronchi.[114]

VIRTUAL BRONCHOSCOPY

Virtual bronchoscopy uses a thin-slice CT scan to create a three-dimensional map of the airways using proprietary software that enables the user to create a virtual pathway through the tracheobronchial tree. The software is mainly limited by the quality of the CT scan used to create the three-dimensional airway model as well as the ability to differentiate distal airway and emphysematous lung. Ideally, CT slices should be less than 1 mm in thickness with some overlap (slice spacing <0.625 mm). The virtual images of the proposed pathway can be displayed during bronchoscopy and synchronized with the endoscopic images in real time (Fig. 27.5).

Asano et al. published their series on 38 peripheral pulmonary lesions measuring less than 30 mm using a combination of virtual bronchoscopy, ultrathin bronchoscopy, and fluoroscopic guidance. Virtual bronchoscopic images were generated to a median of sixth-generation bronchi. The ultrathin bronchoscope could be inserted into 95% of the planned airways, and diagnostic yield was 82%.[115] The diagnostic yield in a meta-analysis was found to be 74% for lesions less than 3 cm and 67% for lesions less than 2 cm.[116]

Finally, another study compared the use of radial EBUS with and without virtual bronchoscopy. Virtual bronchoscopy increased the diagnostic yield from 78% to 94% in patients who had lesions smaller than 2 cm located in the outer third of the lung where an airway could be seen leading to the nodule (CT bronchus sign) but invisible on fluoroscopy.[117]

ELECTROMAGNETIC NAVIGATION

Like virtual bronchoscopy, *electromagnetic navigation* (EMN) utilizes CT data to reconstruct the tracheobronchial tree and identify a lung nodule. However, with EMN, the patient lies in an electromagnetic field and a sensor can be tracked during the bronchoscopic procedure in space and time, with the goal of improving navigation to the target lesion. In principle, the device is similar to the global positioning system used in automobiles.

Two systems are currently available in the United States: SuperDimension (Medtronic) and SPiNDrive (Veran Medical Technologies).[118] To date, there have been no comparative efficacy trials between these systems.

Preprocedure planning differs slightly between the two systems. The SuperDimension system uses a chest CT scan obtained while the patient is in an inspiratory hold for preprocedure planning, and the movement of target related to breathing is estimated by a preprogrammed algorithm. The magnetic field is generated by a board placed underneath the patient. The SPiNDrive System uses both inspiratory and expiratory chest CT images. Respiratory motion is accounted for by using fiducial pads on the chest during the procedure. The magnetic field is generated by a pad over the patient.

The instruments used by the two systems are also different. SuperDimension uses a sensor placed within a locatable guide loaded into an extended working channel passed through the working channel of a therapeutic bronchoscope. The locatable guide and extended working channel are then steered to the target and the locatable guide is removed, leaving the extended working channel in place through which standard bronchoscopic sampling tools (i.e., needle, brush, forceps) are passed. In contrast, the SPiNDrive sensor is located on the tip of its instruments and allows for "always on" tracking during navigation as well as during the sampling process[5] (Fig. 27.6).

ENB may have a better yield for the diagnosis of peripheral lung lesions, especially when combined with radial EBUS. Eberhardt et al. compared the use of radial EBUS alone, ENB alone, and the combination of radial EBUS with ENB in 118 patients followed by surgical resection.[119] The diagnostic yield of the combination of radial EBUS/ENB was 88% as opposed to radial EBUS alone (69%) or ENB only (59%) ($P = 0.02$).

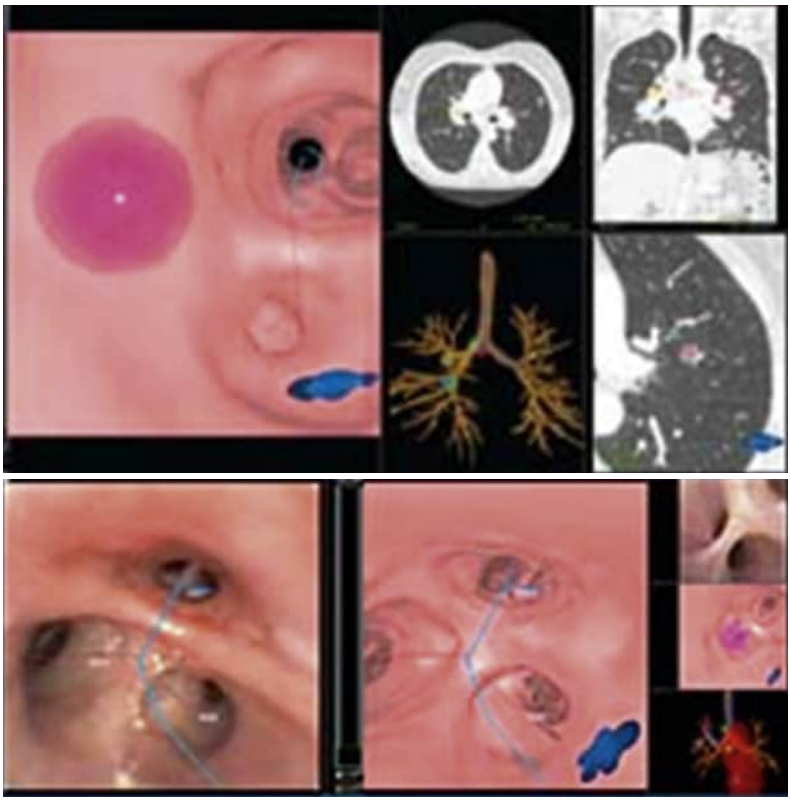

Figure 27.5 Virtual bronchoscopy platform. The bronchoscopic navigation pathway was created to access the lesion (*shown in pink*). This platform shows a virtual endoscopic view and three views of the patient's uploaded computed tomography scan (axial, coronal, and sagittal), followed by a pathway (*blue line*) superimposed upon the virtual endoscopic image.

In 2012, a large meta-analysis of more than 3000 cases found that the diagnostic yield of all advanced bronchoscopic techniques, including radial EBUS and ENB for peripheral lung nodules (malignant or nonmalignant), was roughly 70%.[121] A more recent meta-analysis with inclusion of 15 trials reported an overall diagnostic yield of ENB to be 65%.[120] Analysis of a prospectively gathered, multicenter registry indicates a considerably lower diagnostic yield of only 39% for EMN.[122] Another prospective, multicenter (academic and community centers) registry of 1092 patients reported an overall diagnostic yield of 73% for EMN cases at 12 months.[123] Such widely divergent diagnostic yield is unexplained but may relate to various factors.

Predictors of improved diagnostic yield include operator experience (independent of lesion size and location),[124] presence of a CT bronchus sign (i.e., a visible airway leading into the lesion), the addition of TBNA, and larger size of nodule.[125,126]

Many hypotheses for the relatively poor diagnostic yield have been suggested. There could be a bias for using ENB only for the smaller or more difficult to localize lesions or lesions without a CT bronchus sign. In addition, several studies have demonstrated the variability in nodule location during breathing.[127,128] Protocols for mechanical ventilation during bronchoscopy have been published to minimize nodule motion and atelectasis, both of which can significantly alter the location of the nodule to be sampled.[129] Navigation without real-time guidance certainly limits the chances of adjustment for changes in nodule location. Finally, on occasion, nodules have been shown to regress or resolve between the time of CT scan and bronchoscopy.[130]

Overall, ENB is a safe procedure. A meta-analysis reported complications of ENB including pneumothorax in 3.1% (1.6% requiring chest tube insertion) as well as bleeding in 0.9% that was either minor or moderate.[121] In the NAVIGATE study, the pneumothorax rate requiring either admission or chest tube placement was found to be 2.9%. Grade 2 or higher bleeding was 1.5% and grade 4 or higher respiratory failure was 0.7%.[123]

ENB is also used to place fiducial markers to guide stereotactic body radiation therapy, to mark with dye to guide video-assisted or robotic-assisted thoracoscopic resection of lesions not palpable by the surgeon, such as ground-glass nodules/carcinoma in situ,[131,132] and to retrieve foreign bodies.[133]

ELECTROMAGNETIC NAVIGATIONAL TRANSTHORACIC NEEDLE ASPIRATION

In combination with ENB, *electromagnetic navigational transthoracic needle aspiration* (ETTNA) has been introduced as an application of the EMN (SPiNDrive) system. This procedure uses a sensor-tipped ("always-on") transthoracic needle guided within the same electromagnetic field generated for ENB to provide guidance for transthoracic biopsy. A single-center, prospective pilot study examined safety, feasibility, and diagnostic yield of combined EMN and ETTNA. A total of 24 patients underwent EBUS for staging

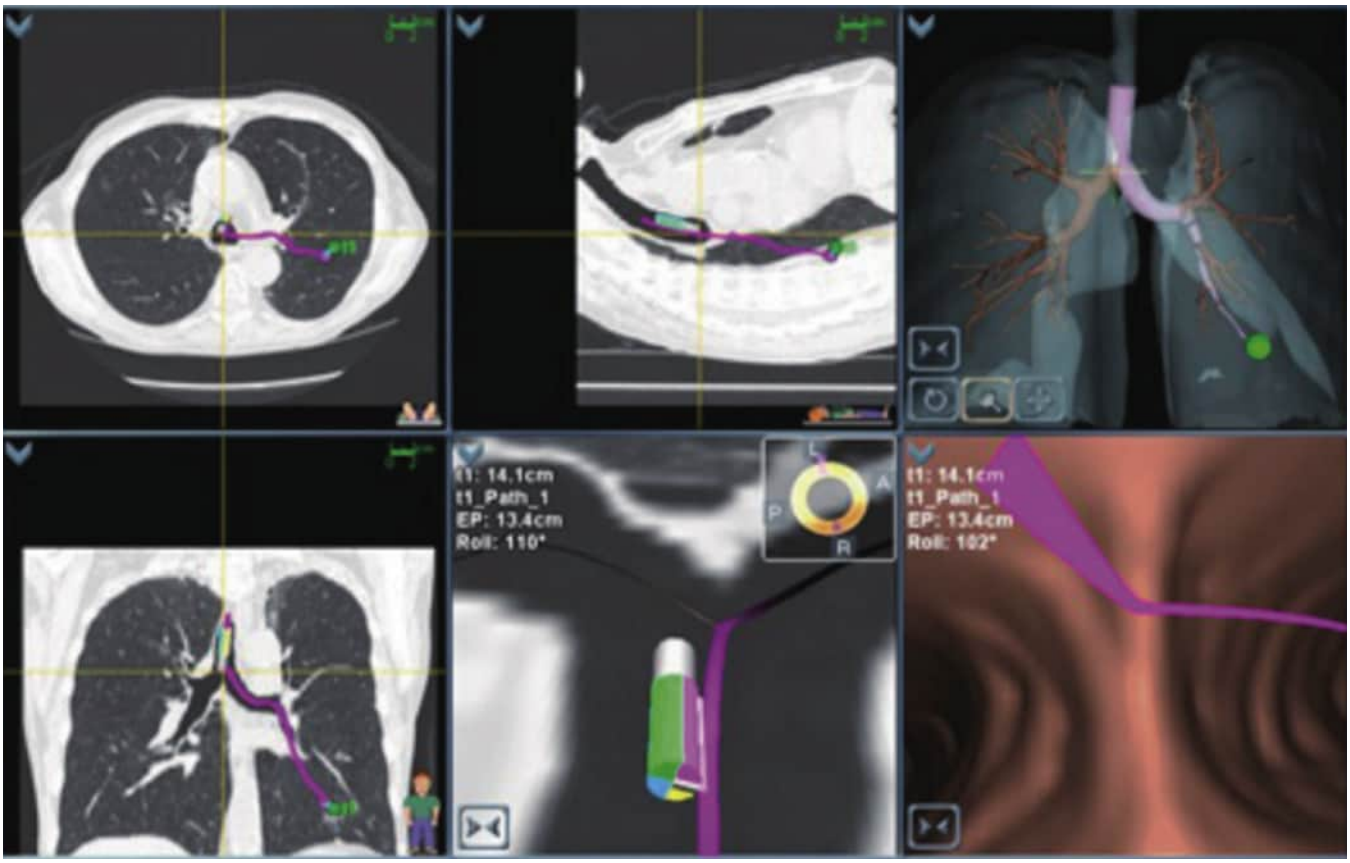

Figure 27.6 Electromagnetic navigation bronchoscopy. This system demonstrates preprocedural planning with computed tomography in three views (axial, coronal, and sagittal) with a three-dimensional airway reconstruction overlay and a pathway to the lesion (*pink line*). (From Arias S, Yarmus L, Argento AC. Navigational transbronchial needle aspiration, percutaneous needle aspiration and its future. *J Thorac Dis*. 2015;7[S4]:S317–S328.)

followed by EMN with ETTNA for sampling of a peripheral lesion. The diagnostic yield for ETTNA alone was 83% and increased to 87% when combined with EMN. With all three modalities combined, the diagnostic yield increased to 92%[134] (Fig. 27.7). A multicenter randomized study is currently underway to validate these results (All in One Study: A Prospective Trial of Electromagnetic Navigation for Biopsy of Pulmonary Nodules; NCT03338049).[5,135]

BRONCHOSCOPIC TRANSPARENCHYMAL NODULE ACCESS

Bronchoscopic transparenchymal nodule access (BTPNA) uses virtual bronchoscopy to identify and create a pathway from the central airways to a peripheral pulmonary lesion based on a preprocedure CT scan. The previously discussed navigational platforms help guide biopsy of lesions that have a CT bronchus sign but, for those without a bronchus leading directly into the lesion, the Archimedes system (Broncus Medical, Inc.) allows biopsy via a BTPNA. The system will identify the target nodule as well as the pulmonary vasculature to plan a safe biopsy pathway.[4] Once the target has been selected, the proprietary software calculates two suitable points of entry with straight-line access to the targeted lesion. The path is then fused to a fluoroscopic image. Users are able to "visualize" the blood vessels, points of entry, and target lesion on the virtual pathway. A needle is then used to create a hole in the airway, and a balloon catheter is inserted to dilate the hole. A sheath with a blunt-tipped stylet is advanced under fused fluoroscopic guidance through the lung parenchyma to the lesion. Once in the lesion, as seen on fused fluoroscopy in multiple views, needle aspirates, brushings, and biopsies are taken (Fig. 27.8). The feasibility study for BTPNA showed that tunneled pathway creation was successful in 10 of 12 (83%) patients with peripheral pulmonary lesions. The inaccessible lesions were in the left apex, and the process was limited by bronchoscope angulation. No complications were noted in these procedures. These patients then underwent surgical resection of their lesions, and there was no evidence of hemorrhage or parenchymal laceration.[136] A subsequent report of BTPNA showed that after successful biopsy in 5 of 6 (83%) patients, 2 patients developed iatrogenic pneumothoraces (only 1 required chest tube insertion).[137]

Although this approach is helpful for lesions without a CT bronchus sign, there are still lesions out of reach, particularly in the lung apices or superior segments, due to limitations in bronchoscope angulation.[135]

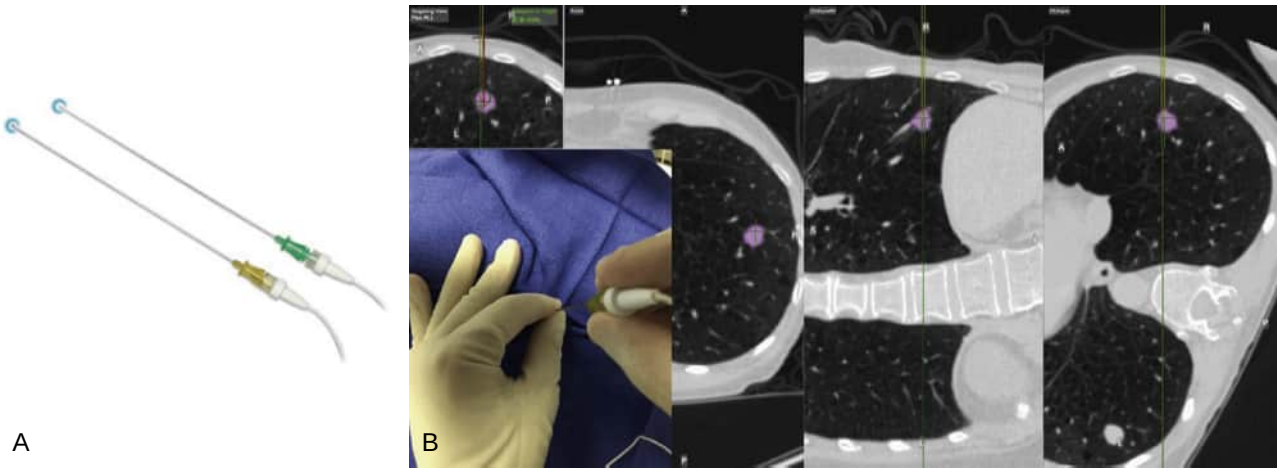

Figure 27.7 ***Electromagnetic navigational transthoracic needle aspiration*** **(ETTNA).** (A) ETTNA needle with the sensor-tipped needles. (B) ETTNA procedure showing the needles directed using an electromagnetic navigation system. (A, Courtesy Veran Medical Technologies. B, From Arias S, Yarmus L, Argento AC. Navigational transbronchial needle aspiration, percutaneous needle aspiration and its future. *J Thorac Dis*. 2015;7[S4]:S317–S328.)

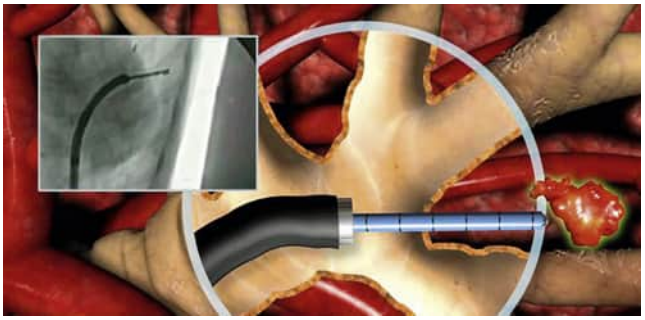

Figure 27.8 **Bronchoscopic transparenchymal nodule access.** Based on a preprocedure computed tomography scan, virtual bronchoscopy is used to create a pathway from the central airways to a peripheral lesion. The path through the airway wall is opened and dilated to allow access for the biopsy. *Inset,* Fluoroscopic view. (From Herth FJF, Eberhardt R, Sterman D, et al. Bronchoscopic transparenchymal nodule access [BTPNA]: first in human trial of a novel procedure for sampling solitary pulmonary nodules. *Thorax*. 2015;70[4]:326–332.)

AUGMENTED FLUOROSCOPY NAVIGATION

Augmented fluoroscopic navigation enhances nodule as well as airway visualization in an attempt to improve sensitivity of navigation-guided bronchoscopy. As discussed above, the diagnostic yield of guided bronchoscopy (via radial EBUS, virtual bronchoscopy, or ENB) is approximately 50–70%. This is significantly worse than CT-guided biopsy (sensitivity of ≈90%), though the latter is associated with a higher pneumothorax rate (approximately 15%).[2,138] The reduced diagnostic yield of guided bronchoscopy is likely secondary to the reliance on preoperative CT planning and virtual navigation as opposed to real-time image guidance. As a result, there can be significant divergence between the CT and the body. Suggested possibilities contributing to divergence include the difference in lung volume at the time of CT scan compared with the time of the procedure, influence of general anesthesia, and the development of atelectasis.[127] Augmented fluoroscopic navigation is designed to minimize these problems. There are three available augmented fluoroscopic platforms currently available.

The first and most established is Fluoroscopic Navigation (SuperDimension-Medtronic), which utilizes digital tomosynthesis by conventional fluoroscopy to visualize and reregister the target nodule location. As described, tomosynthesis refers to a sweep arc of a fluoroscopic C-arm around the chest wall with continuous image acquisition, obtaining multiple image projections. The goal is to improve positional accuracy of the navigation catheter due to real-time changes and assist with path correction if the nodule has changed locations during the procedure. One retrospective study utilizing this technology demonstrated a 25% absolute increase in diagnostic yield (79%) compared with using standard navigation bronchoscopy (54%). In this study, the majority of nodules (64%) were less than 20 mm in diameter and only 22% had a CT bronchus sign.[139]

Another augmented fluoroscopy platform, LungVision (BodyVision), enables enhanced fluoroscopic visualization of airways with predetermined pathways as well as target lesions. These enhanced views are obtained by utilizing preoperative CT planning software along with fluoroscopic registration; the platform has demonstrated improved diagnostic yield in small case series.[140]

Finally, a third system by SONIALVISON (Shimadzu) was studied in 40 patients with radial EBUS with sheath guide combined with preprocedural chest tomosynthesis to serve as a map. The nodules were ground-glass opacities with a mean average diameter of 22 (±10) mm. Overall diagnostic yield was 65%, which improved to 79% if a radial EBUS view of the lesion was obtained. The ability to detect the nodule on tomosynthesis was not predictive of improved diagnostic yield.[141]

CONE BEAM CT FOR BRONCHOSCOPY

Cone beam CT (CBCT) is another imaging modality that may improve the diagnostic yield for bronchoscopic lung biopsy. It is a compact CT system with a moving C-arm

that can be used during bronchoscopy to provide real-time confirmation of biopsy device location. This modality has previously been widely adopted in many fields of interventional radiology, including intravascular and hepatobiliary interventions. Similar to the aforementioned fluoroscopic tomosynthesis approach, the C-arm of the CBCT performs a single rotation around a stationary patient to obtain volumetric data. After image acquisition, the biopsy device location can be reviewed and adjusted to a new target location as needed with repeat scans.[142]

A prospective study of bronchoscopy with a thin bronchoscope, radial EBUS, and CBCT in 20 patients demonstrated that by redirecting sampling tools to the lesion based on CBCT images, the diagnostic yield increased from 50% to 70%.[143] In a prospective study of 20 patients, Casal and colleagues concluded that CBCT-guided bronchoscopy demonstrated a 25% absolute increase in navigation yield and 20% absolute increase in diagnostic yield of peripheral lung nodules. Additionally, they noted that the use of CBCT was associated with acceptable radiation doses (11 to 29 mSv).[144] Hohenforst-Schmidt and colleagues conducted a prospective feasibility study combining CBCT with conventional bronchoscopy without radial EBUS. In the 33 patients with peripheral pulmonary lesions, the overall diagnostic yield was 70%.[145]

Adoption of CBCT may be difficult given its cost, lack of availability in most endoscopy suites, and increased radiation exposure when compared to other enhanced navigation technologies.

ROBOTIC BRONCHOSCOPY

Robotic bronchoscopy has better maneuverability, enabling navigation further into the periphery of the lung, and can remain static once a desired position is reached. There are currently two companies in the market: the Monarch (Auris), which was approved by the U.S. Food and Drug Administration in 2018, and the Ion (Intuitive), which was approved in 2019. Research is underway to demonstrate diagnostic yield and peripheral reach of these systems. Large prospective data, however, are lacking.[146,147]

The Monarch system robotic arms are operated with a small handheld controller similar to that for a videogame. The controller guides an outer sheath that is wedged in a proximal position and then steers an inner scope to the biopsy site. Chen et al. evaluated this robotic platform using human cadavers to compare how far the scope could reach compared to a thin scope driven by expert bronchoscopists.[148] The robotic bronchoscope was able to be advanced farther into the lung periphery compared to a thin bronchoscope despite the scopes having the same outer diameter. The outer sheath design provides support for the inner scope and allows for improved maneuverability. A subsequent cadaver study reported that lesional tissue was able to be acquired in 65 of 67 (97%) human cadavers when using the robotic platform with EMN guidance and radial EBUS confirmation.[149]

The Ion platform uses an ultrathin robotic catheter with a 3.5-mm outer diameter. EMN is not required because the catheter is fitted with shape-sensing technology to provide accurate positional information. The catheter is advanced with a trackball and wheel controller. In order to have such a small outer diameter, the optic is removed once the target is reached, and the catheter (with shape-sensing technology) is used as a guide sheath through which various sampling instruments are introduced.

The early data using these systems are encouraging. A pilot study of 15 patients with the Monarch system reported safety and feasibility with no major bleeding events or pneumothorax despite biopsies having been performed in 93% of patients.[147] The first human study for Ion robotic bronchoscopy by Fielding and colleagues[150] was performed in 30 patients with small peripheral nodules (12.5 mm mean diameter). Radial EBUS was used to confirm the location of the target lesion, and flexible TBNA needles, forceps, and brushes were used for sampling. The overall diagnostic yield was 83%, and there were no device-related adverse events.

CRYOBIOPSY

Cryobiopsy has emerged as a technique for sampling tissue in diffuse parenchymal lung disease. Cryobiopsy has been shown to obtain larger pieces of tissue than standard transbronchial biopsies and minimize crush artifact, thereby leaving intact parenchymal architecture and a potentially higher overall diagnostic yield than standard bronchoscopic techniques. Unfortunately, complications such as pneumothorax and massive hemorrhage have been reported in up to 20% of cases. For years, the technique of cryobiopsy varied widely among practitioners, including whether they used fluoroscopy or bronchial blockers, the duration of freeze time, and other factors. A recent consensus statement has been published with the goals of standardizing the procedure and minimizing complications.[151]

The technique requires a cryotherapy probe, for which there are currently two sizes: 1.9 mm and 2.4 mm. The probes are introduced through the working channel of a bronchoscope and extended into the periphery of the lung, ideally 1 to 2 cm from the pleural surface, as seen on fluoroscopy. The cryoprobe is then cooled for 3 to 6 seconds, causing lung tissue to adhere to the tip. Finally, the probe is removed en bloc along with the adherent tissue and the bronchoscope to obtain a large piece of lung tissue (Fig. 27.9). Ideally, the

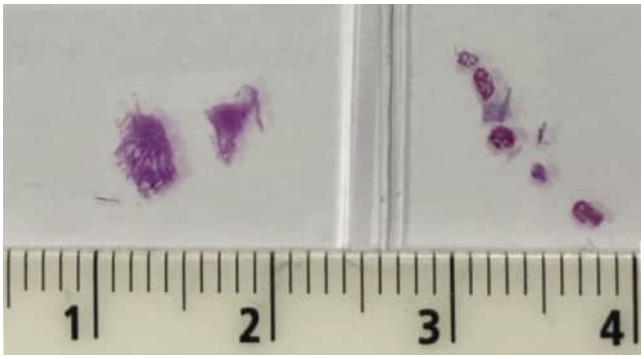

Figure 27.9 Cryobiopsy. Cryobiopsies *(left)* are larger than transbronchial biopsies *(right)*. Measurements are in centimeters. (From Lentz RJ, Argento AC, Colby TV, Rickman OB, Maldonado F. Transbronchial cryobiopsy for diffuse parenchymal lung disease: a state-of-the-art review of procedural techniques, current evidence, and future challenges. *J Thorac Dis*. 2017;9[7]:2186–2203.)

patient is intubated and under general anesthesia for the procedure. A bronchial blocker should also be positioned into the target airway ahead of time and, once the biopsy, probe, and bronchoscope are removed, the blocker is inflated in case bleeding results. When the sample is collected and the bronchoscope is back in the airway, the blocker can be deflated and bleeding can be assessed. Pneumothorax and significant bleeding are reported to range from 9–10% and from 14–20%, respectively. For these reasons, cryobiopsy should only be performed in experienced centers with the ability to manage these complications.[152–154]

In 2018, an international conference on transbronchial cryobiopsy published an expert statement on safety, utility, and the need for standardization of this procedure.[151] They report that despite a substantial and expanding body of literature, the technique has not yet been standardized and its place in the diagnostic algorithm of diffuse parenchymal lung disease remains to be defined. A meta-analysis of 27 studies demonstrated a yield of 73% for cryobiopsy in the diagnosis of diffuse parenchymal lung disease, together with a lower complication rate than for surgical lung biopsy.[155] They concluded that cryobiopsies have a good diagnostic yield but a significant risk for complications and that outcomes vary markedly across institutions, indicating that standardization of the procedure is required. Romagnoli et al. published a prospective two-center study comparing specimens obtained in a single setting: cryobiopsy and surgical biopsy obtained by video-assisted thoracic surgery for patients with interstitial lung disease. Their pathologic results were compared to consensus from a multidisciplinary discussion that demonstrated poor concordance between cryobiopsies and surgical biopsies, with surgical biopsy results more frequently consistent with the multidisciplinary conference diagnosis. The group concluded that surgical biopsies should remain the gold standard for interstitial lung disease.[156] Thus, cryobiopsy in its current form is not ready for routine use outside of the research setting. In addition to interstitial lung disease, information about the utility of cryobiopsy in cancer, post–lung transplant, and immunocompromised hosts is emerging.[157–160]

Finally, in a recent study using an animal model, a mini-cryoprobe that can acquire samples through the working channel of a bronchoscope showed preservation of histologic quality with the promise of improved safety. Clinical trials are underway.

Key Points

- Endobronchial ultrasound, both convex probe and radial probe, has revolutionized the diagnosis and staging of lung cancer and replaced surgical mediastinoscopy as first-line approach for this indication.
- Certain techniques, such as confocal bronchoscopy and elastography, may help direct biopsy to areas of the tumor or lymph node based on imaging characteristics.
- Thin and ultrathin bronchoscopes offer advantages for deeper penetration into the lung, for evaluating obstructing lesions, and for use in mechanically ventilated patients with small endotracheal tubes.
- Recent advances in technology, including radial probe endobronchial ultrasound and virtual and electromagnetic navigation, have increased the diagnostic yield for peripheral pulmonary nodules to approximately 70%.
- Robotic bronchoscopy shows promise because it allows for improved localization and stability of the bronchoscope for biopsy of peripheral lung nodules.
- Cryobiopsy needs to be standardized to benefit from improved diagnostic yield for diffuse parenchymal lung disease while avoiding a greater risk of complications.

Key Readings

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28 THERAPEUTIC BRONCHOSCOPY: INTERVENTIONAL TECHNIQUES

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INTRODUCTION AND HISTORICAL BACKGROUND
REMOVING FOREIGN BODIES
Indications
Contraindications, Procedure, Results, and Complications
MANAGING CENTRAL AIRWAY DISORDERS
Electrocautery
Argon Plasma Coagulation
Laser Photoresection
Stent Placement
Microdébrider
Cryotherapy
Photodynamic Therapy
Brachytherapy
MANAGING OTHER INDICATIONS
Bronchoscopic Lung Volume Reduction
Bronchial Thermoplasty for Severe Asthma
Endobronchial Valve Placement for Persistent air Leaks
KEY POINTS

INTRODUCTION AND HISTORICAL BACKGROUND

Gustav Killian performed the first rigid bronchoscopy in 1897 to extract a piece of a pork bone from the right main bronchus.[1] Because this was in the preantibiotic era, this innovation resulted in a dramatic decrease in the mortality from aspiration pneumonia. In 1966 the flexible bronchoscope was introduced into clinical practice by Shigeto Ikeda.[2] Currently, the majority of pulmonologists are trained in *flexible bronchoscopy* (FB), whereas only a minority have been trained in rigid bronchoscopy.[3,4] With the advent of formalized fellowship training programs in interventional pulmonology, training in rigid bronchoscopy has made a comeback. The rigid bronchoscope is an extremely valuable instrument in the management of central airway obstruction[5] (Video 28.1). Whereas FB remains invaluable for the diagnosis of lung masses, parenchymal disease, and mediastinal/hilar adenopathy, the rigid bronchoscope offers the ability to provide an airway allowing oxygenation and ventilation, as well as the passage of large-bore suction catheters and a variety of tools, including the flexible bronchoscope, that can aid in the destruction and excision of tumor. In addition, because silicone stents can be placed only via the rigid bronchoscope, rigid bronchoscopy allows the physician more options and therefore the ability to place the "best" stent in a selected patient as opposed to being limited to stents that can be placed solely via FB.

Central airway obstruction, from both malignant and nonmalignant causes (Table 28.1), is associated with significant morbidity and mortality and often presents a great challenge to physicians. It is estimated that 20–30% of patients with lung cancer will develop complications associated with airway obstruction, and the incidence of nonmalignant causes, such as postintubation/posttracheostomy stenosis, is likely to increase due to the increasing use of artificial airways in an ever-aging population.[6]

It should be noted that designing large randomized trials to investigate comparative treatment efficacy is extremely difficult and potentially unethical in patients with central airway obstruction. Limitations include selecting patients with comparable disease and comorbidities, as well as the fact that many of these patients present in respiratory distress. Double blinding is also clearly impossible. Therefore the literature supporting therapeutic bronchoscopy is primarily based on large case series/registries and retrospective analyses. That being said, the impact of therapeutic bronchoscopy on quality and length of life is impressive.[7–12] In addition, improvements in dyspnea and health-related quality of life are maintained long term.[11] Therapeutic bronchoscopy has also been associated with immediate reductions in the level of care required for patients with acute respiratory failure from central airway obstruction.[13]

Training in advanced diagnostic and therapeutic bronchoscopy tends to be limited to the centers that have dedicated interventional pulmonology training programs.[14] Over the last decade, however, dedicated training in interventional pulmonology has become more popular, with 37 dedicated programs currently available in the United States, adding more than 40 interventional pulmonologists into the workforce annually[15,16] (aabronchology.org). With this expansion, standardized interventional pulmonology fellowship training requirements, curricula, and in-service examinations have been developed.[5,17,18]

Even with the recent increase in training in rigid bronchoscopy, the flexible bronchoscope remains an essential tool in therapeutic bronchoscopy. It is used in almost every rigid bronchoscopic procedure and, when rigid bronchoscopy is not available, can also be used as the only bronchoscope for foreign body removal, tumor excision/tumor destruction, bronchial thermoplasty, bronchoscopic lung volume

reduction, and balloon dilation. There are several therapeutic techniques, each with its own associated risks and benefits, advantages, and disadvantages (Table 28.2). Because comparative data are lacking, the technique of choice often depends on equipment availability and the bronchoscopist's expertise. Two of the most important considerations in the care of patients with central airway obstruction are assessing the stability of the patient for the planned procedure and having a realistic understanding of the local resources and skill set. Clearly, all efforts should be made to ensure that a patient with a relatively stable airway does not develop an unstable airway during the procedure because such patients can deteriorate quickly. These patients are often best cared for in a multidisciplinary approach in centers of excellence that routinely evaluate and manage such complex patients.[6]

Table 28.1 Causes of Central Airway Obstruction

Nonmalignant	Malignant
Vascular Sling Cartilage Relapsing polychondritis Lymphadenopathy Infectious (e.g., histoplasmosis, tuberculosis) Sarcoidosis Granulation tissue associated with: Artificial airways Airway stents Aspirated foreign bodies Surgical anastomosis Inflammatory lesions Granulomatosis with polyangiitis Amyloidosis Papillomatosis Tracheobronchomalacia Other: Goiter Secretions/blood clot	Primary airway tumors Bronchogenic Mucoepidermoid Adenoid cystic Carcinoid Tumors metastatic to the airway Bronchogenic Renal cell Breast Melanoma Thyroid Colon Esophageal Lymphadenopathy from any malignancy Mediastinal tumors Thyroid Thymus Germ cell Lymphoma

REMOVING FOREIGN BODIES

INDICATIONS

Foreign body aspiration is one of the most common indications for therapeutic bronchoscopy. There is a bimodal incidence of airway aspiration, peaking in children 1 to 2 years of age and in adults older than 70 years. Risk factors for aspiration in adults include alcohol intoxication, sedative and hypnotic drug use, poor dentition, senility, seizure, trauma, swallowing impairment, parkinsonism, and general anesthesia. In adults foreign bodies are most commonly found in the right-sided airways but in children are found equally in the left and right owing to the equal size and angulation of the main bronchi. Because a history

Table 28.2 Advantages and Disadvantages of Therapeutic Modalities

Modality	Time to Achieve Results	Advantages	Disadvantages	Comments
Electrocautery	Immediate	Inexpensive Multiple accessories	Often need to couple with mechanical débridement	Need to deactivate pacemaker/AICD Keep F_{IO_2} <0.4
Argon plasma coagulation	Immediate	Inexpensive Can treat at an angle to electrode	Risk for gas embolization with higher flow rates Often need to couple with mechanical débridement	Need to deactivate pacemaker/AICD Depth of penetration 2–3 mm Keep F_{IO_2} <0.4
Laser photoresection	Immediate	Extensive data supporting its use	Need laser safety precautions	Depth of penetration up to 10 mm Keep F_{IO_2} <0.4
Stent	Immediate	Only bronchoscopic modality for extrinsic compression	All stents have associated complications of granulation tissue formation, infection, and migration	Metallic stents should be used with caution in patients with nonmalignant disease
Microdébrider	Immediate	Can use in high-F_{IO_2} environments Can provide tissue for pathology	May need additional tools to provide hemostasis	Cannot reach distal airways
Cryotherapy	48–72 hr	Normal airway is cryoresistant Can use in high-F_{IO_2} environments	Delayed maximal effect Requires "cleanout" bronchoscopy	Cryoadhesion can remove organic foreign bodies
Photodynamic therapy	48–72 hr	Can destroy submucosal tumor Can use in high-F_{IO_2} environments	Delayed maximal effect Requires "cleanout" bronchoscopy Systemic photosensitivity Need laser safety precautions	Swelling of tumor can cause obstruction
Brachytherapy	Delayed: days to weeks	Can destroy submucosal tumor	Coordination with radiation oncology	Radiation bronchitis Risk for erosion into vessels Swelling of tumor can cause obstruction

AICD, automatic internal cardiac defibrillator; F_{IO_2}, fractional concentration of oxygen in inspired gas.

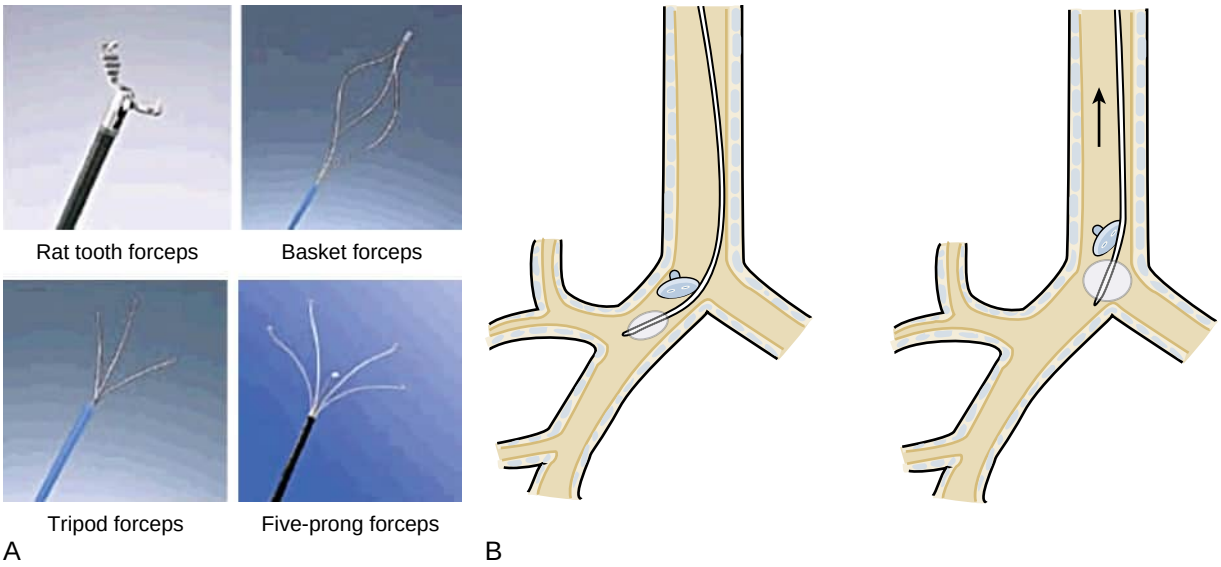

Figure 28.1 Tools and schematic diagram of the method used for foreign body removal. (A) Examples of foreign body retrieval tools: rat tooth forceps, basket forceps, tripod forceps, five-prong forceps. (B) The use of a balloon catheter for dislodging a foreign body by a retrograde pull *(arrow)*. (B, Courtesy Dr. Eric Folch.)

of aspiration is obtained in less than 50% of patients, and visible foreign bodies can be identified on chest radiography in less than 10% of cases, a high index of suspicion is required.[19–22]

CONTRAINDICATIONS, PROCEDURE, RESULTS, AND COMPLICATIONS

All contraindications that apply to routine FB also apply to the removal of a foreign body. Lack of experience and lack of availability of all necessary endobronchial accessories are the more important considerations. Removal of a foreign body using FB should be attempted only by or under the supervision of an expert bronchoscopist. The removal of foreign bodies can be performed successfully with either the flexible or rigid bronchoscope. Flexible bronchoscopy is successful in 86–91% of cases, whereas rigid bronchoscopy is successful in 99.9%.[20,21,23–29] If available, rigid bronchoscopy should be used in all cases of acute respiratory distress caused by foreign body aspiration, given the near 100% success rate. The benefits of FB include its widespread availability and its lack of a requirement for general anesthesia. Despite these benefits, however, in the setting of acute respiratory distress or large foreign body aspiration, the extraction of the foreign body is much more efficient with rigid bronchoscopy because it can be accomplished often on a first attempt, using rigid graspers and removal through the large lumen of the rigid scope.

Foreign body removal using FB is carried out in stages: first, dislodging the foreign body; then, grasping or securing the object; and finally, removing it along with the flexible bronchoscope as a single unit. A variety of ancillary accessories (forceps, grasping claws, snares, baskets, and magnets) are available for foreign body extraction (Fig. 28.1). A cryoprobe passed through the flexible bronchoscope can be especially useful for the removal of blood clots, mucous plugs, and organic material because the extreme cold can cause immediate and strong adherence ("cryoadherence") to the biologic materials.[30] Once the object is grasped and secured, care must be taken to avoid losing it at the level of the vocal cords. If necessary, the patient can also be asked to cough to expel the foreign body once it has been brought into the mid-upper trachea.

Serious complications can accompany removal of a foreign body, including central airway obstruction, hypoxemia, bronchospasm, and bleeding. Objects can also migrate, and their fragments can impact in distal airways resulting in postobstructive pneumonia.

MANAGING CENTRAL AIRWAY DISORDERS

A variety of techniques have been developed for managing central airway obstructions usually due to malignant or benign tumors. Each technique has its own advantages and disadvantages, and special considerations for its use (see Table 28.2). Of course, only some of these techniques may be used at any one institution. The indications for the use of therapeutic bronchoscopy for central airway disorders include malignant airway obstruction, postintubation tracheal stenosis and other nonmalignant etiologies of central airway strictures and stenosis, massive hemoptysis with or without central airway tumors, and foreign body extraction as discussed earlier. The specific indications and complications of these procedures are discussed in turn.

ELECTROCAUTERY

Endobronchial electrocautery is the application of heat produced by high-frequency electrical current to cut or destroy tissue. It involves the use of special accessories, such as blunt probes, forceps, knives, and snares introduced through the bronchoscope. These function as an active electrode that focuses energy at the point of contact, leading to tissue cutting, coagulation, or

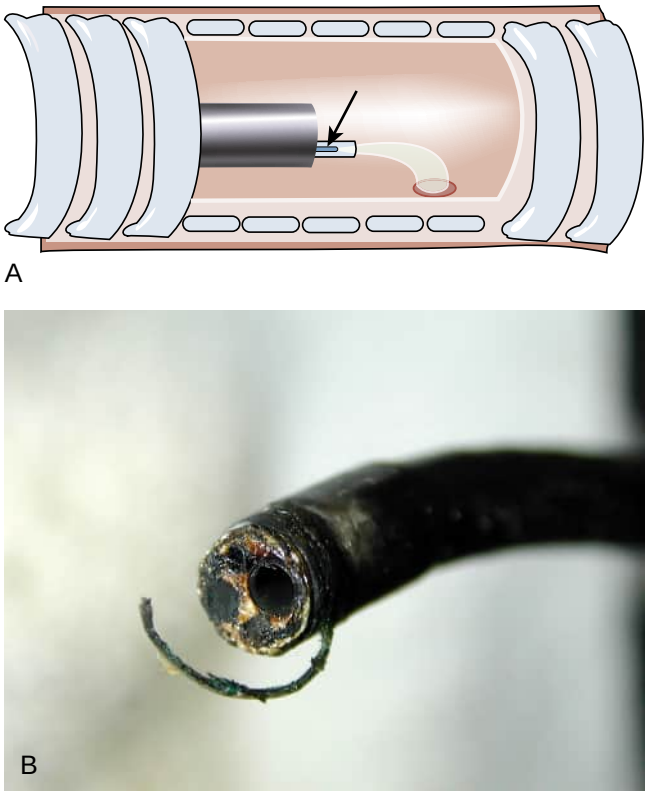

Figure 28.2 Argon plasma coagulation and a complication. (A) Argon plasma coagulation can be used to treat lesions tangential to the bronchoscope. *Arrow* shows the tungsten carbide electrode. Positively charged argon gas automatically flows radially to the negatively charged bleeding tissue. (B) Damage to the tip of the bronchoscope caused during argon plasma coagulation by having the catheter too close to the tip of the bronchoscope during activation. Note the charred tip along with the frayed rubber sheath. (A, Courtesy Dr. Eric Folch.)

vaporization. The degree of tissue destruction depends on the power used, duration of contact, surface area of contact, and water content of the tissue. Use of the snare device is especially suited for the removal of a pedunculated airway lesion because cauterization of the stalk can allow removal of the majority of the tumor for pathologic review (Video 28.2).

To avoid endobronchial ignition, the *fractional concentration of oxygen in inspired gas* (FIO_2) should be kept less than 0.4, requiring active communication with the anesthesiologists. Insulated bronchoscopes, compatible with electrocautery, are used to prevent leakage of electrical current, avoiding burns or electrical shock to the patient and the bronchoscopist.

Indications and Contraindications

Electrocautery is used for either coagulation or vaporization of malignant or nonmalignant disease within the airways and may be curative in patients with carcinoma in situ. Coagulation is achieved by gently touching the tumor tissue and applying 1- to 2-second bursts of 20- to 40-W energy until blanching or destruction of the mucosa becomes apparent. Additional contact time can result in vaporization of the tissue as desired. The tumor area should be kept free of blood or mucus by continuous suctioning to prevent dissipation of the electric current. The coagulated tissue can then be removed using biopsy forceps or suction. The use of electrocautery is considered a relative contraindication in patients with pacemakers and/or defibrillators because of the potential for electrical interference with these devices.[31]

Results and Complications

Electrocautery has been used effectively and safely as an ablative modality in both malignant and nonmalignant airway obstruction. In several studies electrocautery has been shown to achieve luminal patency and symptomatic improvement at rates similar to *laser* (light amplification by stimulated emission of radiation) and other ablative airway modalities.[32–36] Moreover, electrocautery is a cost-effective bronchoscopic intervention due to the low cost of the unit and the reusable nature of its accessories.[32] In a selected group of patients with small, polypoid endobronchial lesions, Coulter and Mehta[37] showed that electrocautery had a high success rate (89%) under local anesthesia, thereby eliminating the need for the more costly laser therapy. Complications are rare in experienced hands: The most common ones are bleeding (2–5%), endobronchial fire in a high-FIO_2 environment, and electrical shock to the operator should the cautery probe touch an ungrounded bronchoscope. It should be noted, however, that in a multicenter study, Ost and colleagues[38] showed that, after multivariate analysis of many factors, electrocautery use was associated with increased likelihood of requiring escalation in the level of care.

ARGON PLASMA COAGULATION

Argon plasma coagulation (APC) is a noncontact form of electrocautery that uses ionized argon gas (plasma) to conduct electrical current from the probe to the tissue. Because positively charged argon gas flows toward the negatively charged tissue, treatment can be directed in an axial or tangential fashion (Fig. 28.2A). As the tissue becomes desiccated, it offers more resistance to the electrical current, limiting its penetration to approximately 2 to 3 mm.[31,32] APC probes can be passed via a rigid or flexible bronchoscope.

Indications and Contraindications

APC is frequently used for palliation of malignant airway obstruction as part of multimodality therapy, including mechanical débridement. APC is also extremely useful for the control of bleeding in the central airways and has been used for the treatment of excess granulation tissue (including stent-related granuloma), postinfectious airway stenosis, and endobronchial papillomatosis (Video 28.3).[31,32] The most important advantages of this technique are the ability to treat lesions tangential to the tip of the probe, to treat lesions in close proximity to airway stents, and to achieve hemostasis. The major limitation of APC is the depth of penetration of less than 3 mm; however, this also may reduce the risk for airway perforation. Its only absolute contraindication is the presence of a pacemaker or implantable defibrillator susceptible to electrical interference. As with electrocautery and laser use in the airway, APC requires that the FIO_2 be less than 0.4.

Results and Complications

In properly selected cases, APC in conjunction with other modalities, such as mechanical tumor debulking, provides symptomatic relief in almost 90% of patients with central airway obstruction.[31,32] It is also portable, less expensive than laser, and typically available in most operating rooms, although the bronchoscopic probes that carry the current through the bronchoscope to the endobronchial tumor at the desired location may need to be purchased. Potential complications include gas embolization,[39] airway fire, postprocedure stenosis, and injury to deeper structures or to the flexible bronchoscope (see Fig. 28.2B). The observed mortality and overall complication rates are 0.4% and 3.7% of cases, respectively.[40,41]

LASER PHOTORESECTION

Laser light has three unique characteristics—monochromaticity, coherence, and collimation—that permit controlled delivery of a well-defined energy. Laser light causes thermal, photodynamic, and electromagnetic changes in living tissue. Laser energy can cut, coagulate, or vaporize endobronchial lesions in a predictable manner, depending on the wavelength used. Although many types of laser systems exist, the *neodymium:yttrium-aluminum-garnet* (Nd:YAG) and *neodymium:yttrium-aluminum-perovskite* (Nd:YAP) lasers are most commonly used in the airways because of their ability to coagulate and vaporize tissue, with a depth of penetration of 5 to 10 mm.[32] Another laser, the carbon dioxide laser, provides minimal hemostasis but is extremely precise (depth of penetration of <1 mm). Such precision can permit fine procedures, such as those needed to incise weblike stenoses or to remove granulation tissue surrounding airway stents.

Indications

The main indications for *laser photoresection* (LPR) are relief of central airway obstruction from exophytic obstructive neoplasms and from tracheal stenosis (Video 28.4). An ideal lesion for LPR is an endobronchial tumor that arises from a single wall of a central airway and has a visible distal lumen, with a duration of distal lung collapse of less than 4 to 6 weeks. LPR can be performed using either a rigid or flexible bronchoscope. The end results and the complication rates are similar with both types of instruments. The selection of the scope mainly depends upon personal preference, availability of the instruments, and training. Bronchoscopists proficient in rigid bronchoscopy typically prefer to use the rigid scope because of the ease of mechanical debulking and superior suction capabilities.

Contraindications

Lesions not amenable to LPR are extrinsic or submucosal, primarily involving lobar or segmental bronchi, and those for which the operator is unable to identify a patent airway distal to the obstruction. As with other forms of heat therapy, laser is contraindicated in patients with a high oxygen requirement.[32]

Results and Complications

LPR can restore airway patency with immediate symptomatic improvement in 93% of cases (Fig. 28.3).[32,42] It can be combined with other techniques, such as mechanical debulking, using the rigid bronchoscope, microdébrider, APC, or stent placement to achieve full patency of major airways. This technique palliates symptoms of cough, dyspnea, and hemoptysis along with documented benefits in radiographic, spirometric, and quality-of-life parameters.[11] LPR is generally a very safe procedure; however, bleeding, endobronchial ignition, pneumothorax or barotrauma, bronchopleural or bronchoesophageal fistula, and hypoxemia have been reported.[43] Extensive knowledge of the anatomy of the tracheobronchial tree is mandatory before performing the procedure. Accumulation of blood and secretions can lead to rapid desaturation. Tracheobronchial tree perforation can be fatal owing to the close proximity of the airways to the great vessels. While performing the procedure, one must take precautions to avoid airway fires, activating the laser only when the FIO_2 is less than 0.4. Laser safety precautions for the bronchoscopist and operating room personnel are also required.[43]

STENT PLACEMENT

Stents are devices used for the internal splinting of luminal structures. The first stents that were used in the trachea were silicone T-tubes developed by Montgomery.[44] Although they require a tracheostomy for their placement, these stents are still widely used, primarily in patients with high tracheal stenosis and/or tracheomalacia. Westaby and colleagues[44a] modified this stent and designed a T-Y prosthesis, which enabled splinting of the distal trachea and carina. Dumon[45] later developed the first stents that could be inserted through a bronchoscope without a tracheostomy. Over the years, several other stents have been developed, including "dynamic" stents made to mimic the airway with a "posterior longitudinal membrane," stents made of steel or nitinol (a nickel-titanium alloy), and newly developed (although not commercially available) bioabsorbable and drug-eluding varieties (Fig. 28.4).[46] Unfortunately, there is no perfect stent. The ideal stent would be easy to insert and remove, strong enough to support the airway yet flexible enough to mimic normal airway physiology and promote secretion clearance, biologically inert to minimize the formation of granulation tissue, and available in a variety of sizes and shapes. Self-expanding metallic stents can be placed with flexible bronchoscopy. However, silicone stents require rigid bronchoscopy because the silicone stent is thick walled and requires manual folding and loading into a stent loader, which can only fit within the lumen of a rigid bronchoscope. Many bronchoscopists feel that metallic stents are also best placed via rigid bronchoscopy because the larger rigid forceps allow easier stent manipulation, and the patients are under general anesthesia. All currently available stents have their own advantages and disadvantages, and thus it is most important to select the best stent for the individual patient. This requires the bronchoscopist to be familiar with and be able to place a variety of stents.

Indications and Contraindications

Airway stents may be indicated for (1) counteracting extrinsic compression from tumors or lymph nodes (Video 28.5), (2) preventing regrowth of intraluminal tumor that will compromise an airway, (3) maintaining airway patency in patients with significant and symptomatic malacia, or (4) sealing

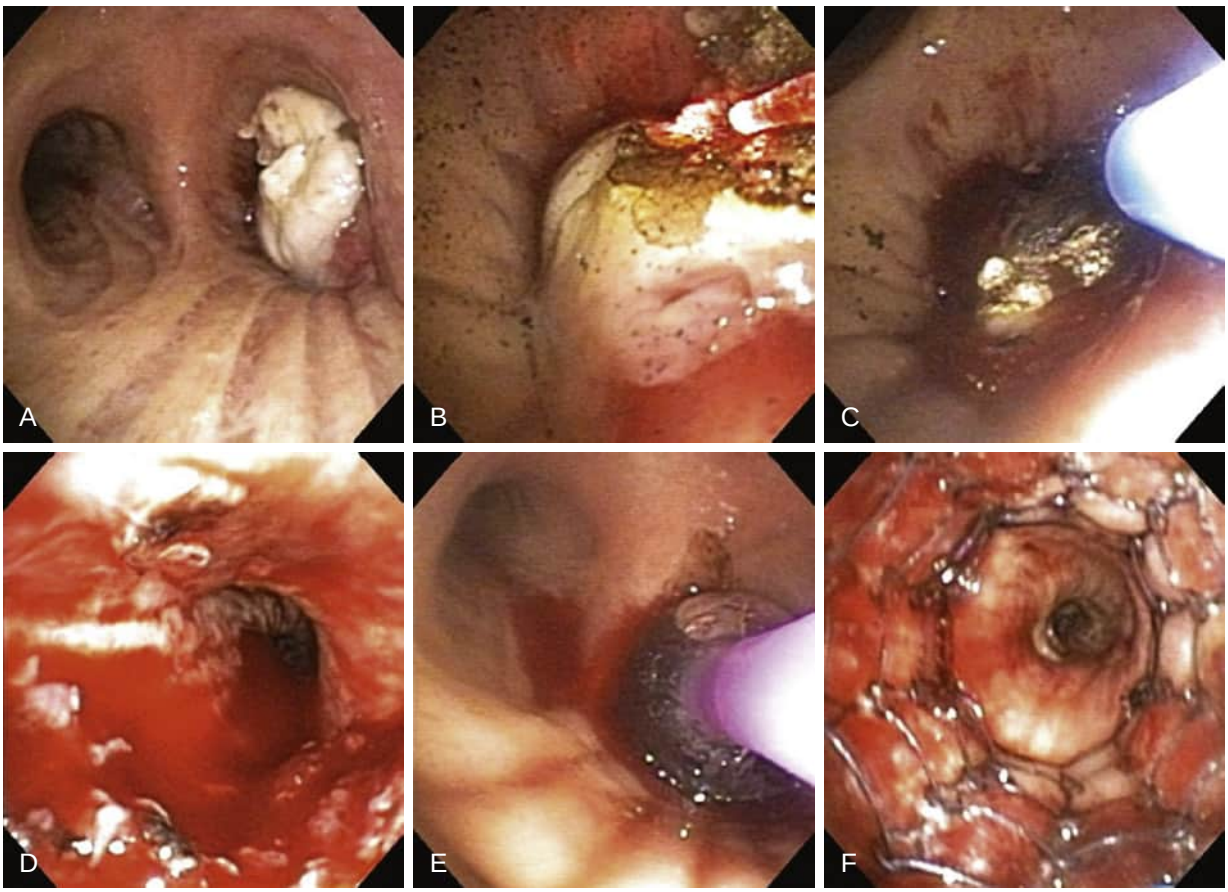

Figure 28.3 Bronchoscopic images of multimodality palliative therapy for a patient with a malignant lesion obstructing the right mainstem bronchus. (A) Pretreatment. (B) Laser photoresection (note the laser fiber). (C) Argon plasma coagulation (note the blue argon plasma coagulation catheter). (D) After mechanical débridement. (E) Balloon dilation. A silicone balloon is fully inflated in the right mainstem bronchus location. (F) Stent placement. Note the self-expanding metallic stent in place. (Courtesy Dr. Eric Folch.)

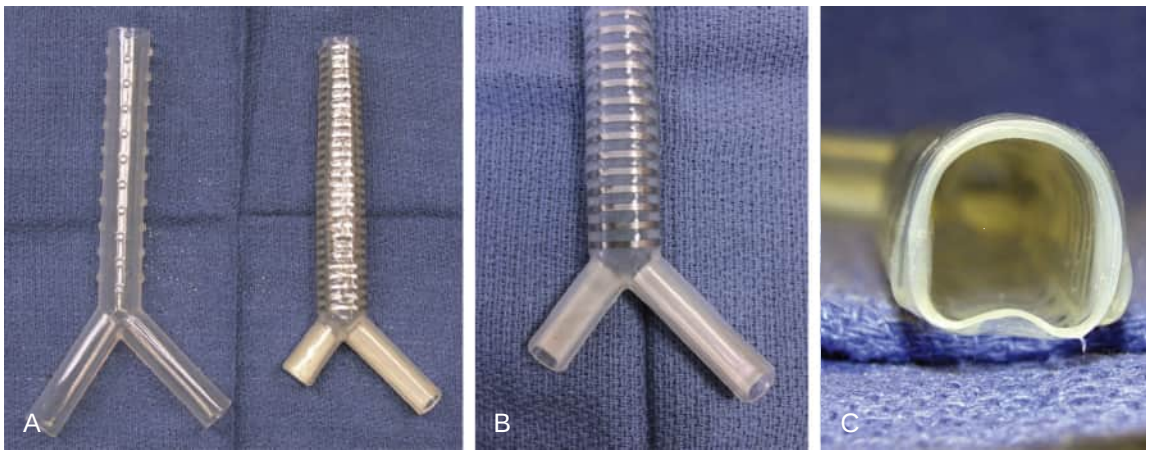

Figure 28.4 Various airway stents. (A) Silicone Y stent and Rusch Y stent. (B) Rusch Y stent (with metal anterior rings to mimic the normal trachea). (C) Rusch Y stent on end. Note the dynamic nature of the stent with a "posterior membrane."

malignant fistulas.[32] Because one of the major complications of metallic stents is epithelialization, which makes removal extremely difficult, the *U.S Food and Drug Administration* (FDA) has issued a warning against the use of metallic stents in patients with benign conditions until all therapeutic options, including use of silicone stent and surgery, have been explored. Although many of the other modalities described in this chapter can be used to treat patients with intraluminal or transmural disease, airway stents are the only bronchoscopic modality that can treat extrinsic airway compression.

Results and Complications

Airway stenting has been associated with improved quality and length of life in patients with malignant airway obstruction[11,32,47,48]; improved quality of life in patients with tracheobronchomalacia[49]; an increased ability to be liberated from

the ventilator, even in patients with nonmalignant disease[50]; and improved lung function and pulmonary infection rates in patients with airway stenosis after lung transplantation.[51]

Retained secretions, bacterial colonization, migration, stent fractures, and development of granulation tissue are frequent complications, and all can be seen with any type of stent. Silicone stents tend to have a higher incidence of migration, whereas covered metallic stents are more prone to infection.[52–54] Silicone stents and the presence of lower respiratory tract infections were also found to increase the risk for granulation tissue formation. Although typically requiring rigid bronchoscopy, removal of silicone stents is a relatively easy procedure. Removal of metallic stents on the other hand, especially the uncovered/partially covered varieties, can be extremely difficult and associated with significant complications and cost.[55,56] Surveillance bronchoscopy within 4 to 6 weeks of stent placement may be useful for early detection of complications and their subsequent management because the complications, if present, are often easier to manage earlier rather than later after the patient develops symptoms.[57]

MICRODÉBRIDER

The microdébrider is a form of "powered instrumentation" that uses a spinning blade contained within a rigid suction catheter to cut tissue while providing suction to remove blood and tumor/granulation tissue[58,59] (Video 28.6). We generally use a 45-cm-long, 4-mm-wide angle-tip blade, allowing it to reach lesions in the trachea, mainstem bronchi, and bronchus intermedius. Advantages of the microdébrider are that it can be used in high-FIO_2 environments, and because it does not vaporize tissue, a specimen trap can be connected in line so that tissue can undergo pathologic analysis. The continuous suction also provides a clean operating environment. Because the microdébrider does not use any thermal energy, it is often necessary to use additional modalities, such as APC, to achieve complete hemostasis. When used by skilled operators, adverse events are rare but can include airway perforation and bleeding.

CRYOTHERAPY

Cryotherapy relies on repeated freeze-thaw cycles to cause tissue damage. Maximal cellular damage results from rapid and deep cooling and a relatively slow thaw. The Joule-Thompson effect describes the drop in temperature that develops as a gas expands from a high-pressure to a low-pressure environment. The most commonly used cooling agents (cryogens) available are nitrous oxide and carbon dioxide. The cryoprobe can be used through rigid or flexible bronchoscopes. When nitrous oxide is used, the temperature at the tip of the probe falls to −89°C within several seconds. The temperature increases approximately 10°C per mm from the tip ("warming effect"), so the effective killing zone is approximately 5 to 8 mm. Because freezing and recrystallization depend on cellular water content, cartilage and fibrous tissue are relatively cryoresistant, making it more difficult to damage the normal airway with this therapy than with other forms of thermal energy. Repeated cycles of freezing and thawing are applied to the endobronchial tissue in a contiguous fashion to cover the entire surface of the lesion. Tissue necrosis and sloughing take place within 24 to 48 hours, and a "cleanup" bronchoscopy is usually required to remove necrotic tissue. This delayed tissue effect is one of the shortcomings of cryotherapy.[60]

Indications and Contraindications

Cryotherapy has been used for the destruction of endobronchial lesions when immediate results are not mandatory and "hot" therapies are contraindicated (Video 28.7). For example, cryotherapy is ideal for treating stent-related granulomas when the stent is made of a flammable material.[32,60] Cryotherapy can be used with excellent results in removing organic foreign objects, blood clots, and mucous plugs by cryoadhesion, as described earlier. Advantages of cryotherapy include its ability to be used in a high-oxygen environment and its limited bronchial wall damage.[60] Cryoextraction describes the related technique in which tumor in the central airways is frozen to the cryoprobe and removed en bloc with the bronchoscope.[61,62]

Results and Complications

In most cases cryotherapy offers a safe and inexpensive alternative for ablation of endobronchial tumor, with success rates up to 80%.[63,64] Kuo and colleagues[62] noted that reobstruction after cryotherapy was significantly associated with nonsquamous cell carcinoma (65.7 vs. 16.7%, $P = 0.001$). As mentioned, tumor sloughing requiring a repeat bronchoscopy and delayed maximal effect are the two major downsides of using cryotherapy for tumor excision. As a result, in the setting of acute central airway obstruction, cryotherapy should be used in conjunction with other modalities. Moderate bleeding, mediastinitis, and fistula formation after cryotherapy have also been encountered in few cases, although the risk for bleeding is likely less than with other therapies due to the vasoconstrictive and platelet-aggregating properties of cryotherapy.[11,60,62] Likewise, the risk for airway fire is nonexistent. It should be noted that the risk for bleeding may be higher when the tumor is removed by cryoextraction than when the tumor is destroyed by cryotherapy.

PHOTODYNAMIC THERAPY

Photodynamic therapy (PDT) refers to a process by which a photosensitizing drug is activated by a nonthermal laser light to induce a phototoxic reaction leading to cell death. PDT is a three-step process. On day 1 a photosensitizing agent (typically porfimer sodium) is administered intravenously. Forty-eight hours after injection, when the drug has been preferentially retained by tumor cells and cleared from most healthy tissues, the tumor is exposed to a nonthermal laser light introduced via a flexible bronchoscope. Exposure of the drug to light of wavelength 630 nm results in a photochemical reaction, including generation of oxygen radical species, direct damage to cells and organelles, indirect ischemic effects, apoptosis, and inflammatory effects. One to 2 days later, a cleanup bronchoscopy is necessary to remove the devitalized tissue, which can be difficult to expectorate and cause complications, such as postobstructive pneumonia, respiratory distress, or respiratory failure.[32]

Indications and Contraindications

PDT is indicated for the palliation of advanced non–small cell lung cancer obstructing the tracheobronchial tree and appears to be effective for superficial and submucosal disease. Curative treatment for early lung cancer/carcinoma in situ is another indication for PDT. On occasion, it is also

used preoperatively to reduce the extent of surgical resection by rendering the line of resection free of disease.

Owing to its delayed effect and to possible edema after the therapy, PDT is relatively contraindicated for treatment of tracheal and carinal lesions or lesions in postpneumonectomy patients (i.e., lesions for which any swelling might precipitate total lung obstruction).[65] PDT is also contraindicated if the tumor invades vascular structures or if there is a history of porphyria and/or porphyrin hypersensitivity.

Results and Complications

PDT has been used to treat advanced lung cancer,[66] to treat multiple malignancies alone or in combination with surgery,[67] and to pretreat to reduce the extent of the surgical resection.[68] In superficial tumors a complete remission rate between 64% and 98% with PDT has been described, and balloon-sheath endobronchial ultrasonography can be invaluable in determining lack of transmural spread.[66,67,69]

Compared to other therapies, PDT is not immediately effective and therefore should not be used for acute central airway obstruction. In addition, cleanup bronchoscopy is required, and the induced systemic photosensitivity mandates that the patient avoid sunlight for 4 to 6 weeks, a potentially major drawback for those with limited life expectancy.[65,70] The most common complications include photosensitivity, local airway edema, strictures, hemorrhage, and fistula formation.[32]

BRACHYTHERAPY

Brachytherapy refers to a technique in which the radiation source is placed within or in close proximity to the target to deliver the maximum dose of radiation to the tumor while sparing the normal surrounding tissues. The radiation dose to the surrounding tissue is dictated by the inverse square law, according to which the radiation dose decreases as a function of the inverse square of the distance from the center of the source. Thus this mode of radiation therapy allows the tumor to receive significantly higher radiation doses than the surrounding healthy tissues, such as lung parenchyma and mediastinal vasculature.

For central airway lesions, a polyethylene catheter is placed adjacent to the lesion via FB and its position verified by fluoroscopy. The catheter is then loaded with the radioactive source while it is secured in position adjacent to the tumor. Low-dose-rate, intermediate-dose-rate, and high-dose-rate treatments imply a dose of less than 2 Gy/hr, 2 to 12 Gy/hr, and greater than 12 Gy/hr, respectively, to a target at a distance of 10 mm. High-dose-rate brachytherapy, which uses iridium-191 as the radiation source, is the most common form of brachytherapy and is typically applied in three treatment sessions over a week in the outpatient setting.[71] Brachytherapy requires close collaboration between the bronchoscopist and the radiation oncologist. The role of the bronchoscopist is to identify appropriate patients and place a catheter into the tracheobronchial tree, whereas the radiation oncologist calculates the radiation dose and guides the actual delivery of radiation to the tumor. The catheter may be removed after each treatment session, as in high-dose-rate brachytherapy, or left in place for the few days of treatment, as in low-dose-rate brachytherapy, an approach that often requires inpatient care.

Indications

Brachytherapy is most useful for endobronchial tumors with a component of submucosal/peribronchial disease. Brachytherapy is also useful for recurrent tumors after maximally tolerated external beam radiation. The primary goal of brachytherapy is palliation of tumor symptoms, such as cough, dyspnea, and hemoptysis. Because it requires up to 3 weeks for the tumor to regress, brachytherapy is not suitable for immediate relief of obstructive symptoms.[71] Brachytherapy is a therapeutic option for occult early-stage central lung cancers when surgery cannot be performed. Brachytherapy has also been used in management of excessive granulation tissue at the site of anastomosis in lung transplant recipients.[71]

Contraindications

Few absolute contraindications for endobronchial brachytherapy exist; one of these is the presence of fistulas involving the airways. To avoid life-threatening complications, one should exclude tumors directly involving the major vessels. Patients with endotracheal carcinoma causing high-grade obstruction should not be treated with brachytherapy because of the delayed effects and potential postradiation edema that could lead to total airway obstruction.

Results and Complications

When compared to external beam radiation, brachytherapy produced similar symptom relief but no survival benefit; thus the role of brachytherapy is mainly for palliation.[72] Brachytherapy is reported to improve cough in 20–70%, dyspnea in 25–80%, and hemoptysis in 70–90% of patients.[73] For patients who have not yet received radiation, external beam radiation therapy offers improved duration of response and survival compared with brachytherapy alone; thus external beam radiation therapy should be selected as first-line therapy instead of brachytherapy for lung cancer patients with central lesions.[72] In patients with inoperable early-stage cancer of the central airways, brachytherapy has been reported to produce a complete endoscopic response in up to 60–90% with 5-year survival rates of 30–80%.[71,74,75]

Complications include respiratory compromise, massive hemoptysis, fistula formation, radiation bronchitis, and airway stenosis. Fatal hemoptysis has been reported in up to 5–10% of patients.[74,75] The risk for late exsanguination has been found to be highest in patients receiving brachytherapy to the right upper lobe, owing to its close proximity to the pulmonary artery.[71,74]

MANAGING OTHER INDICATIONS

Bronchoscopy has emerged as a therapeutic option for some of the most common respiratory diseases, such as COPD and asthma. The emergence of new technology and its utility in small obstructive airway disease management is supported by ongoing research focused on appropriate patient selection, and short- and long-term outcomes.

BRONCHOSCOPIC LUNG VOLUME REDUCTION

Until recently the only options for patients with advanced emphysema in the United States were the use of supplemental oxygen, lung volume-reduction surgery, and lung transplantation.[76] The National Emphysema Treatment Trial demonstrated that, in patients with heterogeneous emphysema with upper lobe predominance and low exercise capacity, lung volume-reduction surgery significantly improves lung function, exercise tolerance, quality of life, and survival.[77] Unfortunately the associated morbidity and mortality of the procedure have limited its widespread application. Bronchoscopic treatments of emphysema were introduced to achieve the beneficial physiologic changes seen with surgical lung volume reduction. In June 2018 the FDA approved endobronchial Zephyr valves manufactured by Pulmonx, as the first bronchoscopic treatment in the United States for patients with heterogeneous emphysema and minimal collateral ventilation.

Indications and Contraindications

Endobronchial treatment of severe emphysema has been studied for over a decade and has been approved in several countries around the world. Due to the lack of data on long-term and clinically meaningful benefits of bronchoscopic lung volume reduction, endobronchial treatment was not approved for use by the FDA until recently.[76] Various devices and chemical agents have been used via the endobronchial route to reduce lung volumes in a relatively noninvasive fashion.[78–83] The majority of studies have focused on patients with heterogeneous (i.e., upper lobe predominant) emphysema, although some have also investigated patients with homogeneous disease. Due to scarcity of long-term outcome data for most of these techniques and devices, the ideal patient population for each specific approach will need to be defined. The following section provides a brief review of current knowledge related to concepts of bronchoscopic lung volume reduction.

Endobronchial Valves

Endobronchial valves are one-way valves designed to allow air to exit the targeted lung segment without allowing reentry of the inspired air, thus leading to deflation of the emphysematous portion of the lung and volume reduction (Fig. 28.5). Two different types of valves, the Zephyr valve and *intrabronchial valve* (IBV; Olympus), have been recently approved by the FDA. For either of these valves, the ability to deflate the lung, and thus the benefit of their use, may depend on the lack of collateral ventilation to the abnormal segment (Videos 28.8 and 28.9).

The *Pulmonx Endobronchial Valves Used in Treatment of Emphysema Study* (LIBERATE) randomized, multicenter, international study was conducted in patients with severe heterogeneous emphysema. Before randomization, all patients were shown to have little or no collateral ventilation by use of a bronchoscopic system (Chartis; Pulmonx) that has an effectiveness of approximately 75% in predicting clinical improvement after lobar occlusion.[83] LIBERATE examined the safety, efficacy, and durability of benefits of Zephyr endobronchial valves for 12 months in comparison to optimal medical care without valves.[84] Compared to those without valves, patients with endobronchial valves were more likely to have at least a 15% improvement in postbronchodilator *forced expiratory volume in 1 second* (FEV_1) (47.7% endobronchial valve and 16.8% control, $P < 0.001$). The endobronchial valve group also showed significant improvements in secondary outcomes, including absolute changes in postbronchodilator FEV_1, 6-minute walk distance, and St. George's Respiratory Questionnaire scores. Pneumothorax, the most common serious adverse event, was seen only in the endobronchial valve group (26.5%, all during the first 45 days).

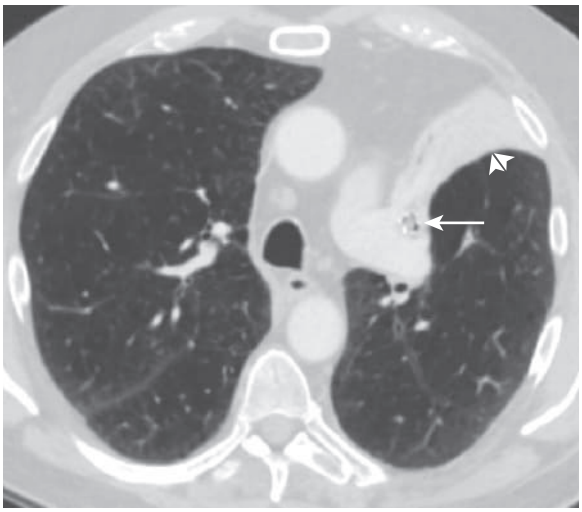

Figure 28.5 Complete left upper lobe collapse after endobronchial valve placement. The valve was placed in a patient with COPD for lung volume reduction. Axial chest computed tomography displayed in lung windows shows complete collapse of the left upper lobe *(arrowheads)* after placement of left upper lobe endobronchial valves *(arrow)*. (Courtesy Steve Tseng, DO, Pulmonary and Critical Care Medicine, University of Arizona College of Medicine—Phoenix.)

The IBV Valve for Emphysema to Improve Lung Function Study (EMPROVE) was another randomized multicenter study in emphysema patients with heterogeneous emphysema and no evidence of collateral ventilation via a chest computed tomography assessment of fissure integrity. The results of EMPROVE achieved the primary end point, and the valve was also approved by the FDA in December 2018.[85]

Bronchial Lung Volume-Reduction Coils

The bronchial lung volume-reduction coil (PneumRx) is made of nitinol wires that, when deployed by advancing into the bronchus via the bronchoscope, retract and fold the parenchyma, thus reducing lung volume in abnormal areas. The benefit of this approach is that the presence of collateral ventilation does not affect its efficacy. A single-center open-label pilot study in Germany using lung volume-reduction coils showed improved quality of life, pulmonary function, and 6-minute walk distance.[86] The *Lung Volume-Reduction Coil for Treatment in Patients with Emphysema Study* (RENEW), a multicenter, randomized phase III trial, was conducted in patients with severe emphysema and evidence of severe air trapping.[87] The primary outcome was the difference in absolute change in 6-minute walk distance between baseline and 12 months. The study showed that among patients with emphysema and severe hyperinflation treated for 12 months, the use of endobronchial coils compared with usual care resulted in an improvement in

median exercise tolerance that was modest and of uncertain clinical importance, with a higher likelihood of major complications, such as pneumonia, requiring hospitalization and other potentially life-threatening or fatal events. As such, this device was not approved by the FDA for use in the United States; however, it is available in Europe.

Biologic Sealant

Bronchoscopic lung volume reduction using direct application of a biologic sealant to collapse areas of emphysematous lung has been reported. Initial tests of a synthetic polymeric foam sealant (emphysematous lung sealant, AeriSeal; Aeris Therapeutics) have shown improvements in pulmonary function, exercise capacity, and quality of life.[81] It should be noted that fissure integrity may not be as important with this method of achieving bronchoscopic lung volume reduction because the sealant may block sites of collateral ventilation.[88] A pivotal trial, study of the *AeriSeal System for Hyperinflation Reduction in Emphysema* (ASPIRE), was terminated for financial reasons.[76]

Bronchoscopic Thermal Vapor Ablation

Bronchoscopic thermal vapor ablation involves delivery of a precise dose of steam water vapor at a precise temperature directly into the targeted lung segments via a specialized catheter. The thermal reaction produces a localized inflammatory response leading to fibrosis and atelectasis. This results in complete and permanent lung volume reduction. Improvements in pulmonary function and quality of life have been reported with this technique in preliminary studies.[89] As with the coils and biologic sealants, a potential advantage of bronchoscopic thermal vapor ablation is that success is independent of the presence or absence of collateral ventilation.[90]

Complications

Because these procedures are performed in patients with severe underlying emphysema, complications can be expected. The more common complications include transient reductions in lung function, flares of bronchitis or pneumonia, and pneumothorax. Whereas placement of valves is reversible, the placement of coils, instillation of sealant, and ablation via bronchoscopic thermal vapor are irreversible.

BRONCHIAL THERMOPLASTY FOR SEVERE ASTHMA

Bronchial thermoplasty (BT) is a novel bronchoscopic treatment for patients with severe asthma aiming to reduce the airway smooth muscle mass, therefore diminishing bronchial constriction and improving asthma symptoms.[91] This is accomplished by delivering controlled heat to the airway walls via a radiofrequency electrical generator and a disposable catheter with an expandable four-electrode basket at its distal tip (Fig. 28.6). BT is performed in three bronchoscopy sessions, 2 to 3 weeks apart. The first two sessions treat each lower lobe separately, and the third session treats both upper lobes; the right middle lobe is not treated because it was not included in the original study protocols, although inclusion of the right middle lobe has been shown to be feasible.[92] Radiofrequency energy is delivered in a systematic fashion at 5-mm intervals, starting from just beyond the endoscopic visual limit sequentially to the proximal lobar bronchi.

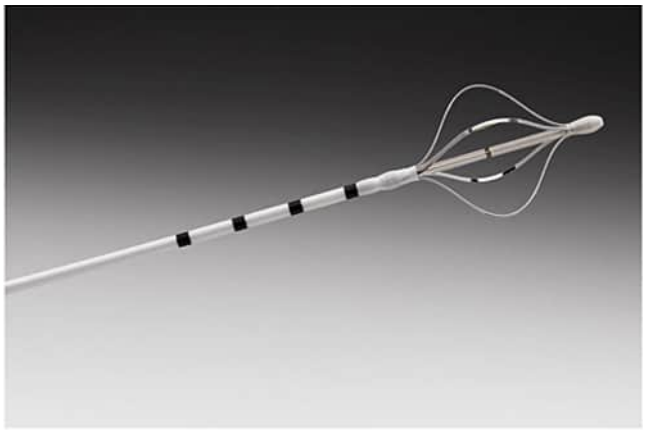

Figure 28.6 Catheter used for bronchial thermoplasty. The disposable catheter contains a four-electrode basket that delivers controlled heat to the airways.

Indications and Contraindications

BT is indicated in adult patients with severe persistent asthma who remain symptomatic despite maximal medical treatment. Concomitant medical conditions that can contribute to asthma symptoms should be sought and treated before resorting to this treatment. In addition, BT should not be used as a substitute for medication compliance. Contraindications for BT include the presence of an implantable electronic device and severe comorbid conditions that increase the risk of the procedure. In children (age < 18 years), the procedure has not been studied and is not approved.

Results and Complications

In multiple studies performed in patients with asthma of various severity, BT has been shown to reduce asthma exacerbations and improve quality of life.[93–97] Adverse events were limited to an increase in asthma exacerbations in the perioperative period.[93–97]

The definitive study of BT, which led to FDA approval, used a randomized double-blind, sham-controlled design of 288 subjects with severe persistent asthma.[97] Patients receiving BT had improvement in quality of life based on a questionnaire but, most important, had a 30% reduction in severe exacerbations, an 80% reduction in emergency department visits, and a decrease in days missed from work or school. The short-term adverse events included airway inflammation and upper respiratory infections that resolved with conventional treatment. There was a higher rate of hospitalization in the BT group in the post-procedure period. In a 5-year follow-up of 162 patients enrolled in the study, the procedure was shown to be safe and its benefits durable.[98] In a similar multicenter study of 279 patients, the findings were reproduced; at the 3-year follow-up, there was a 45% reduction in severe exacerbation, 55% decrease in emergency department visits and 40% decrease in hospitalization rate compared to the control group.[99]

No comparative data between BT and biologic therapy, such as targeted monoclonal antibodies, are currently available.[100]

ENDOBRONCHIAL VALVE PLACEMENT FOR PERSISTENT AIR LEAKS

Persistent air leaks after thoracic surgery are a common complication, reported in up to 18% of patients undergoing lobectomy or lesser resections, and are associated with prolonged hospitalizations, morbidity, and considerable health care costs.[101–103] The usual management of these patients includes prolonged tube thoracostomy drainage, pleurodesis, or attempts at surgical repair. The IBV endobronchial valve, initially developed as an approach to achieve bronchoscopic lung volume reduction in patients with emphysema, has received FDA approval as a humanitarian use device for the treatment of persistent leak after lobectomy, segmentectomy, or lung volume-reduction surgery. The procedure is performed under deep sedation/general anesthesia and begins with selective balloon occlusion of the suspected airways; when the culprit airway is occluded, a significant reduction or cessation of the leak can be visualized in the water-seal chamber of the chest drainage system. A calibrated balloon is used to select the proper-sized valve, which is then placed under bronchoscopic control. It is common that multiple valves are used in each case because many patients have a degree of collateral ventilation. After 6 weeks the valves are removed. IBV use in this patient population has been associated with cessation of the air leak as soon as 1 day after placement and hospital discharge within 3 days in the majority of patients. Although complications can theoretically include postobstructive pneumonia, hypoxemia, and valve migration, these seem to be quite rare. In a recent systematic review of available literature in the form of case reports and case series comprising 208 patients, the most common underlying etiologies were emphysema and cancer, and valves were used most often in postlobectomy and other causes of persistent air leak.[104] In their analysis, upper lobes were found to be the most frequent location of air leaks. Complete resolution was gained within less than 24 hours in the majority of patients, and no deaths were reported due to valve implantation. The most common complications were migration or expectoration of valves, moderate oxygen desaturation, and infection of the treated lung. More data are required before the use of endobronchial valves can be recommended for other causes of persistent air leaks, such as in the setting of secondary spontaneous pneumothorax.

Key Points

- Rigid and flexible bronchoscopy are essential tools for the interventional pulmonologist.
- Therapeutic bronchoscopy can improve quality and length of life in patients with central airway obstruction.
- Each therapeutic bronchoscopic modality has its own advantages and disadvantages; it is hoped that, with ongoing research, the best use of these techniques will be determined.
- Patients with central airway obstruction are best served by a multidisciplinary team of an interventional pulmonologist, thoracic surgeon, head and neck surgeon, anesthesiologist, and medical and radiation oncologist.
- Central airway obstruction with tumor can be approached by immediate (e.g., laser, stent) or delayed approaches (e.g., cryotherapy, photodynamic therapy). Techniques with immediate action should be selected when urgent therapy is needed or when any swelling would compromise ventilation.
- The hot techniques (electrocautery, argon plasma coagulation, laser photoresection) have immediate effects but cannot be used in a high-FIO_2 environment because of the risk for fire. For immediate therapy in a high-FIO_2 setting, a stent or microdébrider can be considered.
- Stent placement is the only technique that can treat extrinsic airway compression.
- Lung volume reduction can now be achieved via bronchoscopic techniques, including one-way endobronchial valves. One-way valves are reversible and affected by collateral flow; lung volume-reduction coils, biologic sealants, and thermal vapor ablation are irreversible and may be useful even in the presence of collateral air ventilation.
- Bronchial thermoplasty is indicated only in adult patients with severe persistent asthma who remain symptomatic despite maximal medical treatment and consideration of other causes of asthma exacerbation, such as acid reflux or chronic respiratory infections.

Key Readings

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29 THORACOSCOPY

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INTRODUCTION

Biopsy procedures play an essential role in the diagnostic evaluation of patients with respiratory diseases. Most of the techniques used today were developed and refined during the 20th century. Recently, significant advances in endoscopic technology have provided sophisticated endoscopic instruments and endoscopic telescopes with extremely high optical resolution and small diameters. In addition, developments in anesthesiology offer a wide range of alternatives, from procedures performed under local anesthesia to selective double-lumen intubation under general anesthesia.

As with all medical procedures, the risk/benefit ratio of invasive methods must be considered for each individual patient by weighing the risk for morbidity and mortality against the benefit of obtaining the diagnosis either to guide correct therapy or to provide clarity on prognosis and clinical trajectory. More invasive procedures are used if less invasive methods have failed and if therapeutic options can be combined with a diagnostic modality.

This chapter reviews the more invasive procedures associated with pleural disease, performed thoracoscopically and by pulmonologists. Other invasive pulmonary methods, including bronchoscopic biopsies, thoracentesis, needle biopsy of lung lesions, and nonthoracoscopic biopsy of the pleura, are described in other chapters.

THORACOSCOPY (PLEUROSCOPY/ MEDICAL THORACOSCOPY)

A brief history of the use of thoracoscopy is available at ExpertConsult.com.

The terms *thoracoscopy, medical thoracoscopy,* and *pleuroscopy* are used interchangeably in the literature. To avoid confusion, this chapter uses the term *thoracoscopy* for the procedure performed by the pulmonologist, and consequently the terms *thoracoscopist* and *thoracoscope,* whether rigid or semirigid. For the thoracoscopic procedure performed by a surgeon, the term *video-assisted thoracic surgery* (VATS) is used. This procedure is technically very similar to thoracoscopy, with some important differences. First, the surgeon can perform procedures on the lung, whereas the pulmonologist usually, but not always, confines the biopsies and interventions to the pleura. Second, VATS is usually performed with the patient under general anesthesia and intubated and ventilated using a double-lumen endotracheal tube that allows selective blockage of a main bronchus and thus collapse of the lung. Although VATS has significant advantages, producing a pneumothorax cavity in which to operate regardless of the state of the lung, it is associated with the normal risks of general anesthesia and may not be suitable in all patients.

In both Europe and the United States, thoracoscopy is part of the training program of interventional pulmonary medicine.[15] According to a national survey in 1994, thoracoscopy was used frequently by 5% of all pulmonary physicians.[16] The interest in the technique seems to be increasing.[17] However, training is lagging: In an American College of Chest Physicians survey of U.S. pulmonary/critical care fellowship programs in 2002–03, only 12% of the directors stated that thoracoscopy was offered in their programs.[18] In the United Kingdom, where thoracoscopy has been increasing compared with the rest of Europe, there is also growing interest, with a doubling in the number of centers offering thoracoscopy over a 5-year period.[19–21] In 2010, the *British Thoracic Society* (BTS) published a guideline on thoracoscopy using local anesthetic, which has driven further interest and quality standards.[22] In this guideline, three levels of competence in thoracoscopy are defined, of which level 1 includes basic diagnostic and therapeutic techniques and level 2 including the more advanced techniques, whereas level 3 covers all VATS techniques (e.g., lung resection) and is considered the province of the thoracic surgeon.[22]

Meanwhile, the technique has been introduced successfully in many Asian countries and in other parts of the

HISTORICAL CONTEXT

As early as 1866, F.R. Cruise in Ireland was possibly the first to perform a thoracoscopy, examining the pleural space of a pediatric patient with empyema through a pleurocutaneous fistula that had developed after spontaneous pleural drainage.[1] However, the first report of thoracoscopy as would be recognized today was in 1910 by Hans-Christian Jacobaeus, who at that time worked as an internist in Stockholm, Sweden. He published his first experiences in a paper entitled "On the Possibility to Use Cystoscopy in the Examination of Serous Cavities."[2] In this pioneering paper, Jacobaeus mentions two cases of "pleuritis exudative" (tuberculous pleurisy), in which he studied the pleural surfaces after replacing the fluid with air. Although not able to obtain a clear impression of the pleural changes, he was confident that the method would be successful in the future and might eventually yield prognostic information. Jacobaeus[3] himself initiated the therapeutic application of thoracoscopy for the lysis of pleural adhesions by means of thoracocautery to facilitate pneumothorax treatment of tuberculosis, which was known as the Jacobaeus operation. During the ensuing 40 years, his technique of using a single entry site for the thoracoscope and another for the electrocautery device, under local anesthesia, was applied worldwide for this specific therapeutic purpose, until antibiotic therapy of tuberculosis was introduced and made the procedure obsolete.[4] Between 1950 and 1960, a generation of chest physicians familiar with the therapeutic application of thoracoscopy began to use the technique for biopsy diagnosis of pleural and pulmonary disease.[5] Today, thoracoscopy is considered to be an integral part of interventional pulmonology.[6]

In parallel, the excellent results of laparoscopic surgery and the tremendous advances in endoscopic technology stimulated many thoracic surgeons simultaneously in Europe and the United States to develop minimally invasive techniques, which were termed "therapeutic" or "surgical thoracoscopy," as well as video-controlled or videothoracoscopic surgery, or as VATS.[7,8]

Definitions of techniques are important in this area, although somewhat fluid. The term medical thoracoscopy[9,10] is generally used to refer to thoracoscopy performed under local anesthesia or conscious sedation, via one or two entry ports, and using nondisposable instruments.[5] Prior definitions have suggested that the instruments must be rigid, although the development of semirigid thoracoscopy has rendered this part of the definition obsolete.[11] In addition, although previous definitions have suggested that these techniques are performed by pulmonologists in an endoscopy suite, we suggest that the operator and place of procedure are less important than the technique itself.

The main indications for thoracoscopy are the diagnosis and treatment of recurrent pleural exudative effusions and the treatment of spontaneous pneumothorax. However, because the term *thoracoscopy* is used for both the medical and surgical procedures, a degree of uncertainty has arisen that may lead to unnecessary surgical interventions for what are, in fact, medical indications. As a result, the old term pleuroscopy[10] has been reintroduced mainly for thoracoscopy with the semirigid (semiflexible) instrument, sometimes referred to as the pleuroscope.

Finally, in some countries, interventional pulmonologists have broadened their field of expertise to include more elaborate interventions (e.g., sympathectomy, splanchnicectomy, treatment of empyema)[12–14] and to perform thoracoscopy in the operating theater under total intravenous anesthesia and spontaneous ventilation, with a laryngeal mask or simple endotracheal tube protecting the airway, or mechanical ventilation. These techniques arguably are more similar to VATS, and there is thus a gray area between medical and surgical practice.

world, particularly with the introduction of the semirigid (semiflexible) thoracoscope.[11,23–25]

TECHNIQUES

Thoracoscopy is an invasive technique that should be used to obtain a diagnosis when other simpler methods are nondiagnostic, in case of pleural exudates, or to achieve pleurodesis, in case of recurrent pleural effusion or pneumothorax.[26] As with all technical procedures, there is a learning curve before full competence is achieved,[27–29] and appropriate training is mandatory.[10,29,30] The technique involves insertion between the ribs into the pleural space of a rigid or semirigid trocar, through which fluid is aspirated and air is allowed to enter. The thoracoscope is then inserted to visualize the pleural cavity and conduct biopsies or other interventions. Insertion of the trocar is conducted with a thorough local anesthetic technique and then blunt dissection, using an incision in the skin of no more than 1 cm; as such, this part of the technique is very similar to insertion of a "surgical" or large-bore chest tube. Once the scope is in the pleural space, the thoracoscopist can visualize and obtain biopsies as appropriate from all areas of the pleural cavity, including the chest wall, diaphragm, mediastinum, and lung, under direct visual control. When indicated, talc poudrage can be performed.

There are two different techniques of diagnostic and therapeutic thoracoscopy, as performed by the pulmonary physician.[10,27,31–33] In the first technique, a single entry site is usually produced with a trocar for a thoracoscope with a working channel for accessory instruments and optical biopsy forceps.[5] This approach can be modified for use of a semirigid thoracoscope, also called the pleuroscope.[11,23] In the other technique, two entry sites are used: one with a trocar for the examination telescope and the other with a smaller trocar for accessory instruments, including the biopsy forceps. For both techniques, adequate local anesthesia and conscious sedation are used, with some operators preferring deep sedation or general anesthesia.[12,27] In some countries the use of heavily sedating medications, such as propofol, even in the absence of intubation, requires the presence of an anesthesiologist.

With increasing data on the use of thoracic ultrasound, it is generally agreed that ultrasound should be performed "live" just before the procedure to identify the best entry site and the presence of septations and adhesions.[22,31,34,35]

EQUIPMENT

Rigid

Rigid instruments are still used for thoracoscopy,[32] although more recently the semirigid thoracoscope has become an attractive option. The requirement for full sterilization of the equipment had been a limitation in the use of semirigid tools until the development of a modified semirigid thoracoscope with a flexible tip that could tolerate sterilization.[23,24]

The single entry site technique is usually performed via a 7 or 9 mm diameter trocar and a cannula. Trocars are available with diameters of 5 and 3.75 mm for performing thoracoscopy in children. Optical devices exist with various fields of view (0, 30, and 90 degrees) (Fig. 29.1).

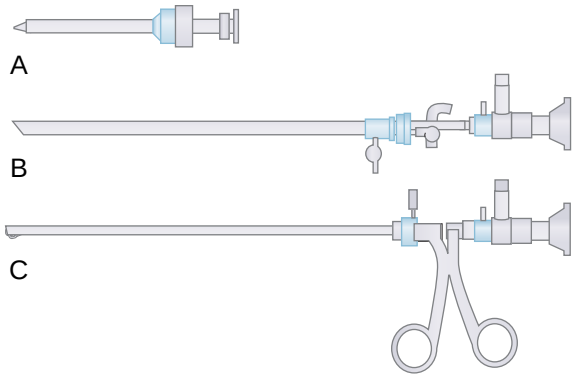


Figure 29.1 Instruments for thoracoscopy. (A) Trocar and cannula with valve. (B) Single-incision thoracoscope (9 mm diameter). (C) Biopsy forceps with straight optics. (Modified from Loddenkemper R. Thoracoscopy—state of the art. *Eur Respir J.* 1998;11:213–221.)

Alternatively, a mini-thoracoscope is available, requiring two ports for biopsy, with the use of a rigid optical telescope of 3 mm and a trocar with a diameter of 4 mm, providing somewhat limited views but a similar size to a needle aspiration catheter.[33] This instrument is particularly helpful in the initial evaluation of small pleural effusions or in the presence of a narrow intercostal space. A second port of entry is necessary in these cases to obtain biopsy specimens. For talc pleurodesis, a talc atomizer is used.[27]

The two-entry-site technique uses a 7-mm trocar for the first site of entry for appropriate telescopes and forceps and similar accessory instruments. For the second site of entry, a 5-mm trocar is used for insertion of instruments designed for its smaller bore, including a loop for dividing adhesions and a double-lumen insufflator.[27]

Semirigid

The semirigid (semiflexible) thoracoscope offers several useful features.[11,23,24] The design, including the handle, is similar to that of a standard flexible bronchoscope; however, the proximal 22 cm is stiff, and the distal 5 cm is bendable with an angulation of 160 and 130 degrees (Fig. 29.2). The outer diameter of the shaft is 7 mm, and a working channel of a diameter of 2.8 mm allows the use of standard instruments available for flexible bronchoscopy. The scope is inserted using a dedicated, soft trocar/cannula of approximately the same size as that used for a rigid procedure. The skills involved in operating the instrument are already familiar to the practicing bronchoscopist. Because the shaft is rigid, it can be moved like the rigid thoracoscope without losing the orientation, and it is compatible with the video processors and light sources of the same manufacturer. The flexible tip permits easier visualization of the entire pleural cavity and permits a homogeneous distribution of talc on all surfaces.[11] The potential easier navigation technique around the pleural space, using the flexible tip, may put less pressure on the surrounding ribs and thus result in a more comfortable procedure. In addition, more advanced imaging techniques, such as narrow band imaging, are feasible through the semirigid thoracoscope, which may have the potential to increase diagnostic yield by better identification of early malignant change,[36,37] although prospective data are currently lacking.



Figure 29.2 The semirigid (semiflexible) thoracoscope (Olympus Corporation). The control section allows handling as with the flexible bronchoscope. (Copyright Olympus SE & Co. KG.)

There are some disadvantages of the semirigid instrument compared to more traditional rigid scopes. The flexible scope is more costly and there may be smaller biopsy specimens, although the diagnostic yield in pleural disease has been shown to be comparable with that of the conventional rigid thoracoscope.[11,38] It should be noted that the only direct randomized trial of the two techniques showed a higher diagnostic yield using the rigid scope in the intention-to-treat population,[39] although there were methodologic issues with this study. In some cases, the flexible forceps used with the thoracoscope may not have the mechanical strength to obtain pleural biopsy specimens of sufficient depth, which may reduce the diagnostic yield in mesothelioma. This technical problem can be overcome by the use of a various techniques (diathermic knife, cryobiopsy),[40–42] which may also have a role in lysing pleuropulmonary adhesions.

Environment

The procedure suite should be equipped with monopolar or bipolar electrocoagulation (in units where adhesion division is practiced, with bipolar electrocautery having the advantage of not requiring grounding unlike monopolar), as well as equipment for resuscitation and assisted ventilation; electrocardiography; blood pressure monitoring; and a defibrillator, an oxygen source, and vacuum generators.[22,27]

Thoracoscopy can be performed in the operating room or in an environment dedicated to invasive procedures.[10,24] Besides the physician, there should be an endoscopy nurse (or an endoscopy assistant) to assist with the instrumentation and an additional assistant outside the sterile field to bring necessary equipment.[22,29] Ideally, an additional person sits at the patient's head end and monitors his or her overall condition. In an emergency, thoracoscopy can be performed with only a physician and a nurse, but this is less efficient and prolongs the procedure. There is now increasing evidence that medical thoracoscopy can be performed safely in an entirely outpatient setting.[43,44]

INDICATIONS

Thoracoscopy today is primarily a diagnostic procedure but can also be applied for therapeutic purposes (Table 29.1).[10,12,45] Thoracoscopy is mainly used for diagnosis of exudates of unknown cause, for staging of diffuse malignant mesothelioma or lung cancer, and for treatment by talc pleurodesis of malignant or other recurrent effusions.[46] Thoracoscopy is also a possible technique for diagnostic biopsies from the diaphragm, lung, mediastinum, and pericardium, and for more elaborate procedures; although, because of the increased risk of complications, these applications should be restricted to highly expert individuals.[13,14] As mentioned earlier, there is an overlap of indications between thoracoscopy and VATS (see later discussion and Table 29.1). In addition, thoracoscopy offers a remarkable tool for research in the study of pleural effusions.

Diagnostic thoracoscopy has its main and oldest use for the diagnosis of pleural effusions, as described by Jacobaeus himself in his earliest articles.[2] The diagnostic value of thoracoscopy grew to include evaluation and diagnosis of spontaneous pneumothorax, focal pulmonary disease, diseases of the chest wall, mediastinal tumors, diseases of the heart and great vessels, and thoracic trauma. Later, these indications were expanded to include performing biopsies for localized and diffuse lung diseases.[10] Today the use of thoracoscopy for diagnosis of lung diseases has decreased owing to the improvements in less invasive pulmonary biopsy techniques, such as flexible bronchoscopic biopsy and *computed tomography* (CT)-guided biopsy, as well as higher confidence in diagnosis of interstitial lung disease from CT imaging and clinical features alone.

In the past, *therapeutic* thoracoscopy was used extensively for collapse treatment of *tuberculosis* (TB) to sever adhesions that prevented a complete artificial pneumothorax.[3,47] This indication disappeared after the successful introduction of chemotherapy for TB. Today the main indication for therapeutic thoracoscopy is talc poudrage in malignant or other chronic and recurrent pleural effusions.[48] The first report on *talcage* was published in 1935[46] and, in 1963, it was first used for treating recurrent effusions.[47] Since then, talc poudrage performed during thoracoscopy for pleurodesis in malignant pleural effusions has been widely applied, especially in Europe. Talc pleurodesis via thoracoscopy has been thought to have advantages over pleurodesis with talc slurry via a thoracostomy tube: simultaneous drainage of pleural fluid, visualization of the visceral pleura to ensure that the lung is not encased by pleural thickening or tumor that could prevent reexpansion (Video 29.1), and guidance of chest tube placement.[49]

However, increasing data, including high-quality randomized studies, demonstrate that the overall pleurodesis success rate in malignant pleural effusion is not higher via poudrage than slurry and, in our view, should not be preferred over talc slurry as a stand-alone therapeutic procedure (see later for a review of the data). The main advantage of talc poudrage via thoracoscopy is the single-procedure approach, whereby, if there is clear macroscopic evidence of tumor, the malignant effusion can be fully drained, high-yield biopsies obtained, and talc poudrage performed at one time. In addition, talc pleurodesis can be used to prevent recurrent pneumothorax, although it should be noted

Table 29.1 Indications for Thoracoscopy (Medical Thoracoscopy) vs. VATS (Surgical Thoracoscopy)

Thoracoscopy	Thoracoscopy or VATS (Gray Area)	VATS
PLEURAL EFFUSIONS ■ Pleural effusions of unknown cause ■ Staging of lung cancer ■ Staging of tumor in diffuse malignant mesothelioma ■ Pleurodesis by talc poudrage	**SPONTANEOUS PNEUMOTHORAX** ■ Inspection/evaluation ■ Pleurodesis by talc poudrage **EMPYEMA (STAGE I/II)** ■ Drainage **DIFFUSE PULMONARY DISEASES** ■ Biopsy **LOCALIZED LESIONS** ■ Chest wall, diaphragm ■ Sympathectomy ■ Splanchnicectomy	**LUNG PROCEDURES** ■ Lung biopsy ■ Lobectomy ■ Lung volume-reduction surgery **PLEURAL PROCEDURES** ■ Pleurectomy (pneumothorax) ■ Drainage/decortication (empyema stage III) **ESOPHAGEAL PROCEDURES** ■ Excision of cyst, benign tumors ■ Esophagectomy ■ Antireflux procedures **MEDIASTINAL PROCEDURES** ■ Resection of mediastinal mass ■ Thoracic lymphadenectomy ■ Thoracic duct ligation ■ Pericardial window ■ Sympathectomy

VATS, video-assisted thoracic surgery.

that the presence of normal parietal pleura in these cases means that the procedure is potentially very painful, and deep sedation or general anesthesia should be considered for these cases.[50]

Other indications for therapeutic thoracoscopy are the drainage of early empyema[12] or dorsal sympathectomy in patients with hyperhidrosis.[14] Anecdotal reports describe its use for removal of foreign bodies,[51] for removal of benign tumors, and for the production of pericardial fenestrations, although we believe that these techniques are best conducted in the highly controlled environment of VATS.

CONTRAINDICATIONS

Contraindications to thoracoscopy are few and rarely absolute.[22] The main limitation is the size of the free pleural space. If extensive adhesions prevent the lung from collapsing away from the chest wall, thoracoscopy can still be performed, using *extended thoracoscopy*, where manual dissection is used to create a pleural space to conduct biopsies, but this requires special skill and should not be undertaken without appropriate training.[52]

Although the majority of thoracoscopy cases are performed in patients with pleural effusion, the technique is possible in cases with small or no pleural effusion, for example, where there are pleural nodules or thickening in the absence of pleural fluid. This technique requires induction of a pneumothorax, which is performed using a pneumothorax induction needle, known as the Boutin needle, in which there is a front- and side-facing opening to allow entrainment of air. Increasing evidence demonstrates that the use of preprocedure ultrasound can predict the presence of a freely moving lung and therefore a nonadhered pleural space.[35]

Several factors are relative contraindications to thoracoscopy; these include a persistent cough, hypoxemia, hypocoagulability (prolonged international normalized ratio or platelet count <40,000–60,000/μL), and cardiac abnormalities. Hypercarbia indicative of respiratory failure may prove to be an absolute contraindication, except in patients with a tension pneumothorax or massive pleural effusion, in whom it can be anticipated that thoracoscopy would provide therapeutic benefit in addition to a possible diagnosis. Under these conditions, premedication should be administered judiciously to minimize respiratory center depression. In cases of respiratory compromise, consideration should be given to conducting VATS in preference, with the advantage of full anesthetic control, but with the understanding that this will require complete single-lung ventilation and general anesthesia.

Concerning lung biopsy via thoracoscopy, contraindications include suspicion of arteriovenous pulmonary aneurysm, vascular tumors, hydatid cysts, or a stiff fibrotic lung because of a higher risk for persistent bronchopleural fistulae. After lung biopsy in patients with interstitial lung disease, Vansteenkiste and coworkers[53] found that the pleural drainage time was on average 5.3 ± 4.7 days and was related to the total lung capacity, which mirrors the severity and stiffness of interstitial lung disease. Relative contraindications for lung biopsy include previous systemic steroid or immunosuppressive therapy because, under these circumstances, bronchopleural fistulas resulting from lung biopsy may heal poorly. However, due to increased risk of fistula and the increased need to handle complications such as bleeding, we do not recommend lung biopsy via thoracoscopy be performed by physicians except in specific circumstances and by specific operators.

COMPLICATIONS

Thoracoscopy is a safe and effective modality in the diagnosis and treatment of several pleuropulmonary diseases if certain standard criteria are fulfilled.[22,55] In the most thorough review, there was only one death among 8000 cases, for a mortality rate of 0.01%.[54] In another series reviewing 4300 cases, the mortality rate was 0.09%.[27] The reported mortality rate of thoracoscopy is thus roughly equivalent to or less than that of transbronchial biopsies. The major

complication rate in a series of 102 patients was 1.9% and included ventricular tachycardia responding to resuscitation, subcutaneous emphysema, and persistent air leak.[56] The minor complication rate was 7.5%, including transient air leak, fever, and minor bleeding at biopsy sites. Another large series including 360 patients reported morbidities of fever in 9.8%, empyema in 2.5%, pulmonary infection in 0.8%, and malignant invasion of the scar in 0.3%.[57] Major uncontrollable bleeding requiring thoracotomy was not reported in any of these large series and appears to be extremely rare. In case of persistent bleeding, electrocoagulation may become necessary,[27] and operators should have a plan of escalation in case of uncontrolled bleeding, such as involvement of interventional radiology or surgery.

Reexpansion pulmonary edema from the removal of large pleural effusions is infrequent; this is likely to be because immediate equilibration of the pleural pressure is provided by direct entrance of air through the cannula into the pleural space, with the lung allowed to expand only at procedure end. Bronchopleural fistulas may follow lung biopsies; if the lungs are stiff, a fistula may require longer to heal than the usual 3- to 5-day period of chest tube drainage.[27] Local site infection is uncommon, and empyema has been reported rarely.[54] In cases of mesothelioma, the late complication of tumor growth at the site of entry has been observed after thoracoscopy and also after thoracentesis or closed-needle biopsy. Radiation therapy 10 to 12 days after thoracoscopy has been used to prevent this late complication,[58] although adequately powered randomized trials indicate that the routine use of prophylactic radiation therapy in these cases is not required.[59] After talc poudrage, any postprocedure fever, such as a nonspecific inflammatory reaction, and pain can be treated symptomatically.

In the studies reviewed in the evidence-based BTS medical thoracoscopy guideline review of 2010,[22] the mortality from thoracoscopy was low and, for diagnostic procedures only (i.e., not using poudrage), was close to 0%. The reported mortality rate in this review was largely driven by the large randomized trial of thoracoscopy poudrage[60] in which small-particle talc was used; small-particle talc has been shown to be associated with lung inflammation and acute respiratory distress syndrome, most likely because of dissemination of the smaller talc via the lymphatics to the circulation.[61] Studies have demonstrated that use of large-particle (graded) talc is not associated with lung inflammation[62]; thus, if poudrage is conducted, graded talc should be used. With the use of graded, larger-particle talc, the mortality rate from thoracoscopy should be quite low, nearly 0%.

In conclusion, the overall mortality rate with thoracoscopy is extremely low. Morbidity, which is mainly due to benign postprocedural fever, is minimal.

PATIENT PREPARATION

Before planning thoracoscopy, the patient should provide informed consent and receive information on major and minor complication rates; diagnostic sensitivity and the rationale for treatment should also be discussed. Radiologic tests should have confirmed the presence of pleural effusion or thickening and, in the presence of fluid, a previous pleural aspiration without a definitive diagnosis is often required. Because thoracoscopy in this situation is an elective procedure, the clinician should consider stopping anticoagulation and antiplatelet agents as long as this does not risk other complications, including considering low-molecular-weight heparin bridging if required. It is our practice to stop clopidogrel for 7 days before such procedures and aspirin for 5 days, but this is not based on evidence.

Evaluation of the patient's respiratory status requires basic observation and consideration of arterial blood gas analysis in cases where hypercarbia is considered possible. An electrocardiogram should be obtained to exclude recent myocardial infarction or significant arrhythmia. The clinical laboratory will provide the coagulation parameters, serum electrolyte levels, and blood glucose level, as well as blood group typing, platelet count, results of liver function studies, and serum creatinine level. We would recommend a platelet transfusion if the platelet count is less than 50×10^9 cells per milliliter and that the international normalized ratio be corrected to below 1.5. Patients with renal dysfunction can safely undergo thoracoscopy, but caution must be used with sedative drugs, and it should be noted that there is a higher risk of bleeding; the risk benefit of biopsy should be openly discussed with the patient.

Immediately before the procedure, ultrasonography for localization of the pleural fluid and for diagnosis of potential fibrinous membranes or adhesions in the pleural space is now considered mandatory (see Chapter 23). In an observational study, thoracic ultrasonography localized a safe site for thoracoscopy, when not clinically apparent, in 11 of 80 cases (14%) and detected unexpected septations in 7 (9%).[63] According to the guidelines of the BTS on pleural procedures and ultrasonography, thoracic ultrasonography is strongly recommended before all pleural procedures to localize the site of pleural fluid.[64] A CT scan is not mandatory before thoracoscopy but is usually performed. CT scans can be helpful to localize abnormalities, such as loculated empyema or localized lesions (tumors) of the chest wall or diaphragm.

ANESTHESIA

Thoracoscopy by the single-entry-site technique is usually done under local anesthesia with premedication, together with an antianxiolytic, a narcotic, or both (e.g., midazolam and hydrocodone).[32] If necessary, additional pain medication should be given during the procedure, as required. With the use of conscious sedation, an anesthesiologist is usually not needed. However, there are circumstances where the presence of an anesthesiologist is very helpful as, for example, with rare idiosyncratic or allergic sensitivities to typical anesthetics, very anxious patients or patients unable to cooperate, including children, and patients with severe hypercarbia. An alternative is sedation by propofol with or without premedication[65]; however, the use of propofol for moderate sedation is not approved in some countries, including the United States, without the supervision of an anesthesiologist.[66] General anesthesia with intratracheal intubation and ventilation is used in some centers, as it is for VATS, but is not generally necessary for thoracoscopy.

Monitoring devices such as a cardiac monitor, oxygen saturation monitor, and automatic blood pressure monitor are applied. Some advocate the simultaneous measurement

of cutaneous or exhaled carbon dioxide tension because sedation may lead to significant hypoventilation.[67] An intravenous line is maintained, both for intravenous sedation and for possible resuscitation medications.

ACCESS TO THE PLEURAL SPACE

Because it is impossible to perform the procedure if the pleural cavity is completely obliterated, a sufficiently large pleural space is an essential prerequisite, allowing the introduction of the trocar and thoracoscope without injuring the lung or other organs.

The simplest access is available in the setting of a preexisting complete pneumothorax or large pleural effusion, in which the trocar can be introduced directly into the pleural space without risk of injuring the lung. In the setting of a small or moderate-size pleural effusion, a needle puncture should be performed at the level of greatest opacification/dullness or, ideally, under ultrasonographic guidance. After pleural fluid is aspirated, the syringe is removed from the needle, and air enters the pleural space either spontaneously or after the patient takes a few deep breaths. The entry of air causes the lung to collapse away from the chest wall and creates a larger pleural space for safe trocar insertion. Alternatively, if the needle is well positioned in the pleural fluid (e.g., not in the lung), air can be injected into the pleural space by syringe. Most often, a few milliliters of air are sufficient to create a good separation of the lung from the chest wall. Greater safety is provided under ultrasonographic guidance, which allows the operator to localize the pleural effusion and to exclude thick septations/adhesions, which may prevent a sufficient collapse of the lung and thus may cause possible complications, such as bleeding and injury to the lung, diaphragm, and other thoracic structures, when introducing the trocar at the site of the septations/adhesions.[68] Another option is fluoroscopy of the patient "on the table," which can show the air-fluid level caused after injection of air and the presence of any adhesions.

If neither effusion nor pneumothorax is present, an artificial pneumothorax must be created either by the blunt dissection technique using the finger[52] or by the technique of pneumothorax induction. The blunt dissection technique (i.e., extended thoracoscopy) involves gentle dissection of the pleural adhesions with a finger to advance the thoracoscope into the pleural space.[52] Some operators introduce carbon dioxide, which is absorbed more rapidly than air, and would maximize absorption rates in the unlikely event of air embolism. If so, the pneumothorax should be induced immediately before undertaking thoracoscopy, because the pneumothorax will be absorbed rapidly. Some thoracoscopists induce a pneumothorax the day before the procedure, allowing more time to obtain pressure measurements and to determine if the pleural space is patent, as indicated by a fluctuation of pressure with breathing between −15 and −5 cm H_2O (1 cm $H_2O \cong 1$ mbar). A direct ultrasound-guided technique to induce pneumothorax can also assist in prediction of where the lung will fail to collapse.[35] In cases where the ultrasound predicts that thoracoscopy will not be possible, a real-time image-guided cutting-needle biopsy is an alternate approach, and can provide high diagnostic yields. This allows the pulmonologist to obtain tissue without the patient needing to reattend for a further procedure.[69]

POSITION AND ENTRY SITE

Thoracoscopy is usually performed with the patient in the lateral decubitus position with the intended procedural site facing upward.[5,27,45] The site of introduction of the thoracoscope should be chosen to access the location of presumed abnormalities and to avoid potentially hazardous areas, such as the midanterior line, where the internal mammary artery lies; the axillary region with the lateral thoracic artery; and the infraclavicular region with the subclavian artery. The region of the diaphragm is unsuitable, not only because adhesions are frequent there but also because the liver or spleen may be injured.[5,27] For general applications, the trocar is introduced in the lateral thoracic region between the midaxillary and the anterior axillary line in the fourth to seventh intercostal space (i.e., the triangle of safety); for pleural effusions, in the sixth or seventh intercostal space; and for pneumothorax, in the fourth intercostal space. After preparation with a surgical disinfectant and local anesthesia, using 1% or 2% lidocaine, a small skin incision is made, and blunt dissection using scissors or a blunt pair of forceps is used to create a tract. The trocar is advanced with a corkscrew motion until the detectable resistance of the internal thoracic fascia has been overcome. The cannula of the trocar should lie at least 0.5 cm within the pleural space. Pleural effusions should be removed by using a suction tube that does not occlude the cannula so that air may rapidly enter the pleural space and avoid generating large negative pleural pressures. After complete removal of the effusion or, in cases without effusion, the optical device is then introduced through the cannula, and the pleural space is inspected (eFig. 29.1). A second trocar can be safely placed using direct vision via the thoracoscope once a suitable position has been found (Video 29.2).

THORACOSCOPIC TECHNIQUE

The pleural space can be inspected directly through the thoracoscope or indirectly by viewing the image on a screen via videothoracoscopy. The advantages of videothoracoscopy over direct thoracoscopy are multiple: the view is better when projected on a screen and the other participants of the procedure (fellow, nurse, anesthesiologist) can watch the thoracoscopy, which is also important for teaching purposes.

Anatomic relationships and intrathoracic structures are usually well recognized (Video 29.3). Biopsies of the pleura and, if needed, the lungs, can be performed easily and safely by means of the biopsy forceps (Video 29.4). In the presence of undiagnosed pleural effusions, biopsy specimens should be taken from macroscopic lesions at the anterior chest wall, the diaphragm, and the posterior chest wall for histologic evaluation and, usually, for mycobacterial culture. If no macroscopic abnormalities are visible, several biopsy specimens should be taken from different sites of the parietal pleura. Pleural biopsies should be taken down to the fat, because this is helpful for the pathologist to comment on invasion.

Biopsy specimens are not routinely taken from the lung because of the risk of creating a fistula but may be necessary when abnormalities are seen only on the lung surface. The likelihood of creating a bronchopleural fistula can be reduced by the use of an electrocautery biopsy forceps. In cases of inflammatory pleural exudates or when several therapeutic thoracenteses have already been performed, fibrinous membranes or adhesions may be present that hinder examination. If so, these can be severed by using blunt forceps or by cutting with electrocautery.

Although a single site of entry is generally sufficient, a second site may be useful for biopsies or to coagulate.[27] A second port of entry is mandatory to introduce a biopsy forceps in case of mini-thoracoscopy, in which the scope is too small to accommodate a forceps.[33] The position of the second site of entry can be determined by viewing through the 50-degree scope while depressing the possible entry site with the index finger. It may be helpful to insert a needle through the same site while viewing its precise location through the thoracoscope. After administration of a local anesthetic, a 5-mm incision is made, and the 5-mm trocar is inserted directly. Its cannula will accommodate many instruments designed for its smaller bore.

The semirigid technique is very similar to the earlier description and usually does not require a second port. Using a combination of the flexible tip and angular movements of the entire scope, the entire pleural cavity can be visualized. A flexible large-jaw biopsy forceps (2.2–2.6 mm diameter) is introduced via the working channel of the scope to perform biopsies of visualized abnormalities or of thickened parietal pleura.

TALC POUDRAGE PLEURODESIS

Talc poudrage is the most widely reported method of talc instillation into the pleural space.[46] It is mainly used for pleurodesis in malignant or recurrent pleural effusions[46,48] but also in persistent or recurrent spontaneous pneumothorax.[50] Thoracoscopic talc pleurodesis can be performed under local anesthesia but generally requires additional pain medication.[32]

Talc poudrage is conducted during thoracoscopy under a number of circumstances. Most commonly, poudrage is conducted when there is evidence during thoracoscopy of macroscopically obvious malignancy, usually manifested as multiple and different-sized pleural nodules. In cases where there is no evidence of macroscopic malignancy, but the pleura is not normal (e.g., diffuse pleural thickening, which can be caused by either benign or malignant conditions), the decision is more challenging. In our practice, we tend to use poudrage in cases where any further pleural intervention is not an option (e.g., the elderly, in whom thoracic surgery is not possible), but this does risk introducing talc in those who are subsequently shown to have a benign cause of their effusion. This decision is now somewhat more complex, because there is also the possibility of insertion of an indwelling pleural catheter (as a definitive pleural intervention) during thoracoscopy.

Before poudrage, it is important to confirm that the lung can completely expand because contact of the lung with the chest wall is necessary for a successful pleurodesis.[46,48,49] Failure to expand fully may indicate a trapped lung caused by thickening of the visceral pleura, which can be suspected at thoracoscopy, although blinded video studies have shown that this is not detected reliably by expert operators.[70] Most reliably, lung expansion is confirmed with a large-volume pleural aspiration before the thoracoscopy, conducted to obtain samples for cytology.

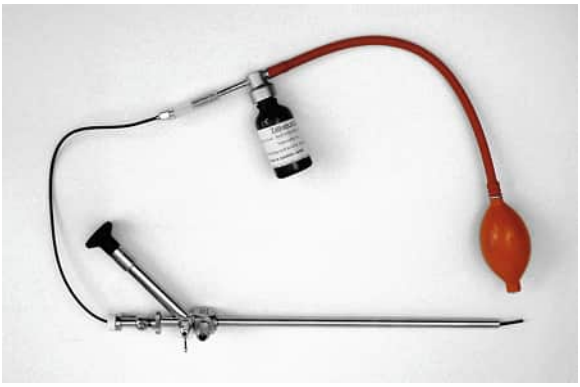


Figure 29.3 Apparatus for talc poudrage. The flexible catheter, connected to a small bottle containing talc and to a pneumatic atomizer (manual insufflator), is introduced through the working channel of the rigid thoracoscope. This allows talc to be sprayed on the pleural surface under direct vision during thoracoscopy.

The optimal dose of talc for poudrage is not known, but usually a dose of 4 g is recommended for malignant or recurrent effusions,[48,49] whereas, for pneumothorax patients, 2 g is usually sufficient.[50] The pleural cavity should be inspected during insufflation of the talc to ensure that the talc is uniformly distributed (Video 29.5). For this purpose, one can use a thoracoscope with an angled optical device and a flexible suction catheter connected to a small bottle containing talc and to a pneumatic atomizer introduced through the working channel of either the thoracoscope[27] (Fig. 29.3) or the semirigid thoracoscope.[11,17]

After talc poudrage, a 10- to 24-French chest tube should always be inserted. We recommend a tube of at least 20-French size to ensure that air leak does not result in the creation of subcutaneous emphysema leaking around the chest tube and the port site. The use of suction postprocedure is controversial, and no clear data exist to demonstrate its utility. If suction is applied, the use of high-volume, low-pressure systems is recommended, with a gradual increment in pressure to about −20 cm H_2O.[48] The introduction of digital suction, which is more accurate and highly portable, may be an important direction in the future, but more data demonstrating utility are required.

After the procedure, chest tube removal has been recommended when the daily amount of fluid production is less than 150 mL, but there is little evidence to support this practice.[48] One report suggests that the chest tube can be removed within 24 hours after talc slurry pleurodesis without regard to daily fluid production; however, this was an underpowered study.[71]

Talc is inexpensive and highly effective.[72] Its most common short-term adverse effects include fever and pain. Cardiovascular complications, such as arrhythmias, cardiac arrest, ischemic chest pain, myocardial infarction, and hypertension, have been noted. Acute respiratory distress syndrome, acute pneumonitis, and respiratory failure have also been reported after talc poudrage and slurry, especially

in the United States, where only talc including small-particle sizes was available. The use of graded, larger-size talc appears to be absolutely safe, both in the treatment of recurrent pleural effusions and spontaneous pneumothorax.[62,73] More recently, large-particle size-calibrated talc has been approved for use in the United States.

RESULTS

Pleural Effusions

Even after extensive diagnostic workup of the pleural fluid, the cause of a number of pleural effusions may remain undetermined. Blind needle biopsies may establish the diagnosis in some additional cases, particularly in tuberculous pleurisy. In a 1981 series by Boutin and colleagues[74] of 1000 consecutive patients with pleural effusion, 215 cases remained undiagnosed after repeated pleural fluid analysis and performance of pleural biopsies. This has been supported by the results of several other authors who, without the use of thoracoscopy, report that at least 20–25% of pleural effusions remain undiagnosed, although this certainly depends strongly on the particular patient populations.[10] Because of the higher diagnostic yield and ability to induce pleurodesis in a single setting, it has been estimated in a theoretical cost analysis in the United Kingdom that medical thoracoscopy may save considerable costs in the evaluation of unexplained pleural effusions compared with other tests, including transthoracic image-guided pleural biopsy.[75]

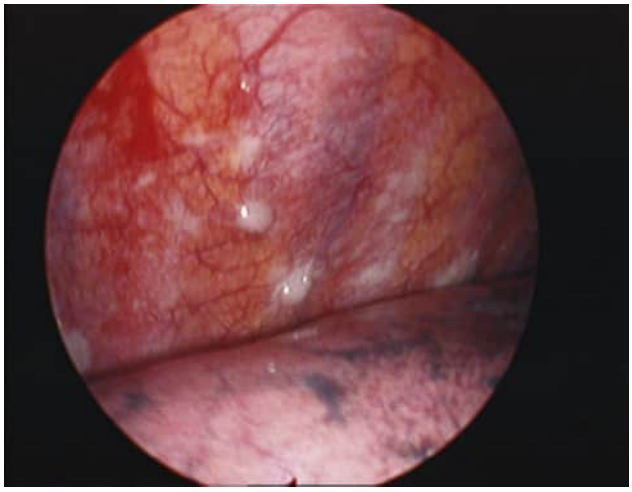
Several studies have tried to determine the diagnostic accuracy of thoracoscopy in the setting of undiagnosed pleural effusion, but the results vary, with a range of 60–90%, as is well summarized in the evidence-based BTS guidelines of 2010.[22] One well-designed study of thoracoscopy in 102 patients reported by Menzies and Charbonneau,[56] with follow-up periods between 1 and 2 years, found a sensitivity of 91%, a specificity of 100%, accuracy of 96%, and a negative predictive value of 93%. Boutin and colleagues[74] reported a false-negative rate of 15% within 1 year of follow-up. In a retrospective study of 709 patients who underwent thoracoscopy for diagnosis of unexplained exudative effusions, Janssen and Ramlal[76] also found a 15% false-negative rate in a long-term follow-up (minimum, 24 months) of 208 patients with initial negative results; the overall sensitivity of thoracoscopy was 91%, the specificity was 100%, the positive predictive value was 100%, and the negative predictive value was 92%. This finding has been replicated in several other well-designed studies since.[77–80]

Of note, even surgical thoracotomy can "miss" the diagnosis. In a study of the results of thoracotomy in patients with pleural effusion of undetermined cause, even after a pathologic diagnosis of a benign pleural process, 25% of patients were diagnosed with a malignancy over a period of follow-up. The diagnoses most often missed were malignant pleural mesothelioma and lymphoma.[76,81] We believe that a certain small proportion of such patients are, in fact, not diagnosable using any form of biopsy or histologic analysis, requiring further follow-up and later biopsy; whether these cases are truly false-negative rather than "undiagnosable" at the time is not clear.

Because of its high diagnostic accuracy, diagnostic thoracoscopy is an excellent option in cases of exudates in which the cause remains undetermined after pleural fluid analysis and radiology (usually CT).[22,48] The procedure allows fast and more definite biopsy diagnosis, including a high yield for TB cultures, and determination of hormone receptors and molecular targets in malignancies. Furthermore, staging in lung cancer and diffuse mesothelioma is possible. The exclusion of an underlying malignancy or of TB is provided with high probability. Surgery, including surgical thoracoscopy, not only is more invasive and expensive but also does not produce better results than thoracoscopy.

Malignant Pleural Effusions

Diagnosis. Malignant pleural effusions are the leading diagnostic and therapeutic indication for thoracoscopy[82] (Fig. 29.4A and eFig. 29.2). In a prospective comparison of diagnostic tests, each performed in every patient, the diagnostic yield of nonsurgical biopsy methods in malignant pleural effusions was studied simultaneously in 208 patients, including 116 metastatic pleural effusions (from 28 breast cancers, 30 cancers of various other organs, and 58 cancers of undetermined origin), 29 cancers of the lung,



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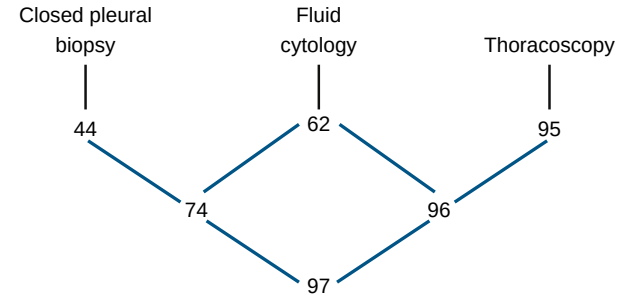

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Figure 29.4 Thoracoscopy for diagnosis of malignancy. (A) View through the thoracoscope in a patient with a malignant pleural effusion due to breast cancer. Small whitish tumor nodules are present on the parietal (chest wall) pleura (*top of photograph*). The lung surface (*bottom of photograph*) demonstrates some anthracosis. (B) Sensitivity of different biopsy methods (cytologic and histologic results combined) for the diagnosis of malignant pleural effusions. Numbers represent sensitivity (%) of tests, either alone or combined, in a prospective intrapatient comparison of 208 patients. Thoracoscopy alone has 95% sensitivity for the diagnosis of malignancy; cytology and closed pleural biopsy contribute little to the total sensitivity of 97% for all three tests. (A, From Loddenkemper R, Mathur PN, Noppen M, Lee P. *Medical Thoracoscopy/Pleuroscopy: Manual and Atlas.* New York: Thieme; 2011. B, Modified from Loddenkemper R, Boutin C. Thoracoscopy: present diagnostic and therapeutic indications. *Eur Respir J.* 1993;6:1544–1555.)

58 diffuse malignant mesotheliomas, and 5 malignant lymphomas.[54] The diagnostic yield of pleural fluid cytologic examination was 62%, of closed pleural biopsy was 44%, and of thoracoscopy was 95%. The sensitivity of thoracoscopy was higher than that of cytologic examination and closed pleural biopsy combined (95% vs. 74%; $P < 0.001$). The combined methods were diagnostic in 97% of malignant pleural effusions (see Fig. 29.4B). In 6 of the 208 cases (2.9%), an underlying neoplasm was suspected at thoracoscopy but confirmed only by thoracotomy or autopsy. Similar results have been reported by other investigators.[77–79]

The diagnostic sensitivity of thoracoscopy is similar for all types of malignant effusion. In one study, the overall yield in 287 cases was 62% for cytologic examination and 95% for thoracoscopy; the relative yields for cytologic examination and thoracoscopy did not vary greatly for lung carcinomas ($n = 67$), at 67% and 96%, respectively; for extrathoracic primaries ($n = 154$), at 62% and 95.5%, respectively; or for diffuse malignant mesotheliomas ($n = 66$), at 58% and 92%, respectively.[54]

Staging. Thoracoscopy may be useful in staging lung cancer, diffuse malignant mesothelioma, and metastatic cancer. In lung cancer patients, thoracoscopy can help to determine whether the effusion is malignant or paramalignant.[54] As a result, it may be possible to avoid exploratory thoracotomy for tumor staging. Canto and associates[83] found no thoracoscopic evidence of pleural involvement in 8 of 44 patients with lung cancer and pleural effusion; 6 proceeded to resection, where the lack of pleural involvement was confirmed.

In diffuse malignant mesothelioma (Videos 29.6 and 29.7), thoracoscopy can provide an earlier diagnosis and better histologic classification than closed pleural biopsy because of larger and more representative biopsy specimens and more accurate determination of the extent of tumor.[84,85] Earlier diagnosis and staging may have important therapeutic implications either for surgery or for local immunotherapy or local chemotherapy because better clinical outcomes have been observed for patients detected in earlier stages; thoracoscopy provides information on T stage, although this technique cannot be used to assess lymph node involvement.[85]

Thoracoscopy is also helpful in the diagnosis of benign asbestos-related pleural effusion by excluding mesothelioma or malignancies. Fibrohyaline, or calcified, thick, and pearly white pleural plaques, may be found (Video 29.8), indicating possible asbestos exposure.

A further advantage of thoracoscopy in metastatic pleural disease is that biopsies of the visceral and diaphragmatic pleura are possible under direct observation. In addition, the larger size of thoracoscopic biopsy specimens may provide easier identification of primary tumor, including hormone receptor determination in breast cancer,[86] and improved morphologic classification in lymphomas.[87]

The assessment of specific mutations in lung cancer cells can increasingly direct targeted therapy. In pleural biopsy specimens, Guo and colleagues[88] found a rate of 70% of epidermal growth factor receptor mutations and concluded that pleural biopsy specimens, in this case obtained by VATS, provided better material than other techniques. Adequate tissue may be important for these assays; however, the reliability of cytologic examination for demonstration of epidermal growth factor receptor mutations does have a growing evidence base and is recommended in guidelines.[89,90]

Therapy. The relative utility of thoracoscopic talc poudrage pleurodesis has been mentioned above. In summary, despite high success rates reported in case series using poudrage, which will suffer from selection bias, randomized trials have failed to demonstrate a consistent benefit of talc poudrage over talc slurry, with overall success rates of 70–80%.[60] Thus, we suggest that talc poudrage is an effective method of pleurodesis in malignant effusion but should not be promoted in isolation (i.e., where a biopsy is not required) as a therapeutic procedure over talc slurry, which is less invasive.

In chylothorax due to lymphoma, Mares and Mathur[91] showed excellent results of talc poudrage, all in cases refractory to chemotherapy or radiation therapy. All 19 patients with 24 hemithoraces involved had no recurrence after 30, 60, and 90 days (8 patients died during the 90 days of follow-up).

The development of "tunneled" or *indwelling pleural catheters* (IPC) has challenged the position of talc pleurodesis as the first option of treatment for malignant pleural effusion.[92–94] The primary goal of an IPC is symptom relief by repeated drainage of pleural fluid in the home setting. In addition, the IPC can induce a spontaneous pleurodesis at mean rate of 46%,[95] although this rate is less in randomized studies.[96–98] Spontaneous pleurodesis is increased by active management of the indwelling catheter, including daily drainage,[96,98] and the administration of talc through the indwelling catheter.[97] However, the drainage bottles are expensive, and reimbursement by health insurance companies is not provided in many countries. Reported complications include malfunctioning of the catheter (9.1%), pneumothorax requiring chest tube (5.9%), pain (5.6%), and blocked catheter (3.7%). Less common complications are catheter fracture, empyema, cellulitis, and tumor metastasis along the catheter tract.[95]

No randomized studies are yet available comparing thoracoscopic talc poudrage and IPC placement. In a randomized controlled trial, talc slurry pleurodesis and an IPC were compared with a primary end point of patient-reported relief of dyspnea; in this study, no significant difference between the two methods was found in dyspnea or in quality of life. Twelve patients (22%) in the talc slurry group required further pleural procedures, compared to three patients (6%) in the IPC group. On the other hand, fewer patients in the talc group had adverse events (13%) than in the IPC group (40%).[93] In a cost-analysis study, talc slurry pleurodesis was found to be more cost-effective than the IPC if the patient survived for more than 6 weeks,[99] and a number of other analyses have supported the relative cost-effectiveness of indwelling catheters in the absence of long survival.[100,101]

In a noncomparative study, thoracoscopic talc poudrage and IPC placement were combined in 30 patients.[102] Successful pleurodesis was obtained in 92%; the IPC could be removed at a median of 7.5 days. The authors stated that both length of hospital stay and duration of IPC use could be reduced significantly compared to either procedure alone.

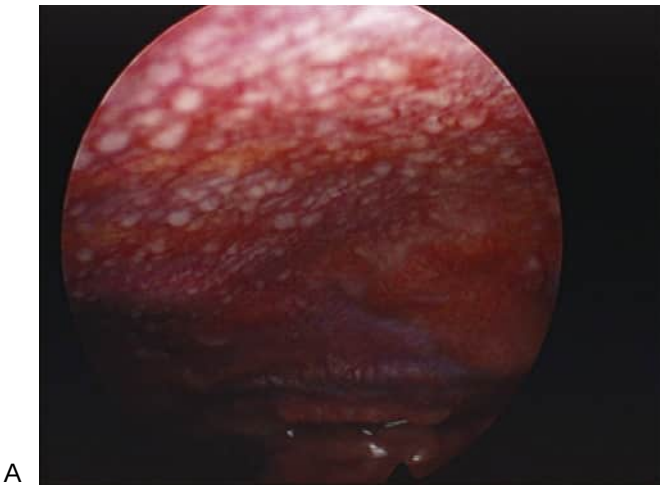
This finding has since been replicated in a similar observational study.[103]

An IPC placement is a better treatment option in patients with a trapped lung.[104] For all other patients, the advantage of placement of an IPC as opposed to thoracoscopic talc pleurodesis, or the combination of both, remains to be established. A major advantage of thoracoscopic talc pleurodesis is the possibility of obtaining a histologic diagnosis of the pleura in the same session. In future studies comparing IPC and thoracoscopic talc pleurodesis, assessment of this advantage should be included in the design of the study.

In real-life practice, if a patient requires fluid control in a case of established malignant effusion, patient choice is crucial when deciding between talc- and IPC-based treatment. We tend to discuss patient preference in terms of "outpatient" or "inpatient" treatment and proceed accordingly. It is also, of course, perfectly feasible to place an IPC at the completion of a thoracoscopic biopsy procedure; we tend to follow this procedure in patients who do not wish to stay in the hospital and in those with a known or recognized trapped lung.[70]

Tuberculous Pleural Effusions. Although the diagnostic yield of pleural fluid culture combined with closed-needle biopsy for the diagnosis of TB is quite high, there may be indications for thoracoscopy in otherwise uncertain pleural effusions (Fig. 29.5). The diagnostic accuracy of thoracoscopy is almost 100% because the pathologist is provided with multiple selected biopsy specimens, and there is a higher likelihood of obtaining the tubercle bacilli on culture. In a prospective comparison in which diagnostic procedures were compared in each patient, an immediate diagnosis of *Mycobacterium tuberculosis* infection in 100 cases was established histologically in 94% with thoracoscopy but in only 38% with needle biopsy.[54] This may be of clinical importance because a proper histopathologic diagnosis allows antituberculous chemotherapy to be started without delay. The combined yield of histologic diagnosis and bacteriologic culture was 99% for thoracoscopy and 51% for needle biopsy, increasing to 61% when culture results from effusions were added (see Fig. 29.5B). The percentage of positive *M. tuberculosis* cultures from thoracoscopic biopsies (78%) was twice as high as that from pleural fluid and needle biopsies combined (39%), allowing bacteriologic confirmation of the diagnosis and, importantly, drug susceptibility testing. In 5 of the 78 positive cases (6.4%), resistance to one or multiple antituberculous drugs was found and influenced therapy and prognosis.

Closed-needle biopsy can have high yield in areas with a high prevalence of TB but, even then, thoracoscopy can have benefits. In a prospective study of 40 cases from South Africa, thoracoscopy had a diagnostic yield of 98% compared with an 80% diagnostic yield from pleural biopsies performed with an Abrams needle.[105] In addition, thoracoscopy can allow complete drainage of the effusion; initial complete drainage of the effusion, performed during and after thoracoscopy, has been associated with greater symptomatic improvement than subsequent pleural therapy.[106] The positive role of early removal of the pleural fluid has also been shown in a double-blind, randomized, placebo-controlled trial from Taiwan.[107] No studies are known that compare the potential benefits of thoracoscopy, allowing early diagnosis, complete drainage, and early drug treatment with those of empirical drug treatment alone.



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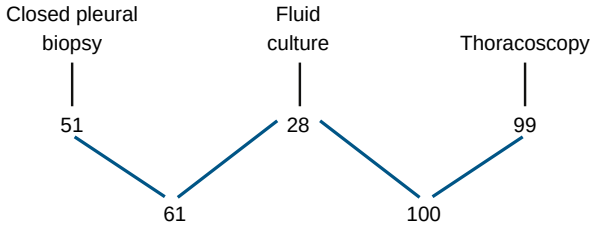

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Figure 29.5 Thoracoscopy for diagnosis of tuberculosis. (A) View through the thoracoscope in a patient with a tuberculous pleural effusion. Note the numerous small whitish nodules on the parietal (chest wall) pleura. The histologic examination revealed florid exudative tuberculous pleurisy with epithelioid cell granulomas, numerous multinucleated giant cells, and necrosis. *Mycobacterium tuberculosis* cultures from the biopsy specimens were positive, whereas those from the effusion were negative. (B) Sensitivity of different biopsy methods (histologic and bacteriologic results combined) for the diagnosis of *M. tuberculosis* infection. Numbers represent sensitivity (%) of tests, either alone or combined, in a prospective intrapatient comparison of 100 patients. Thoracoscopy alone has 99% sensitivity for the diagnosis of tuberculosis. (A, From Loddenkemper R, Mathur PN, Noppen M, Lee P. *Medical Thoracoscopy/Pleuroscopy: Manual and Atlas.* New York: Thieme; 2011. B, Modified from Loddenkemper R, Boutin C. Thoracoscopy: present diagnostic and therapeutic indications. *Eur Respir J.* 1993;6:1544–1555.)

It is debatable whether to treat patients with antituberculous medication merely on the suspicion of tuberculous pleurisy if they present with a high lymphocyte count in the pleural fluid and a positive skin test. In countries with a low prevalence of TB, supportive tests such as for adenosine deaminase have low specificity and should not be used for the diagnosis of TB pleuritis. In these circumstances, pleural biopsy (thoracoscopic or blind) is indicated. The high yield for *M. tuberculosis* cultures from thoracoscopic biopsy specimens increases the possibility of obtaining susceptibility tests, which, in cases of drug resistance, may influence therapy and prognosis.[105]

Other Pleural Effusions. For diagnosis in cases with effusions that are neither malignant nor tuberculous, thoracoscopy may give visual clues to the cause, such as revealing thick white fibrin deposits seen in rheumatoid effusions, calcifications in effusions after pancreatitis, dilated veins

in liver cirrhosis, or signs of trauma.[54] Although for these entities the history, pleural fluid analysis, and physical and other examinations are usually helpful, thoracoscopy may be indicated to confirm the clinical suspicion. Thoracoscopy is well suited for determining that a patient with a history of asbestos exposure likely has benign asbestos-related pleural effusion, which, by definition, is a diagnosis of exclusion of other causes, in particular malignancies.[84]

For diagnosis in the setting of other undiagnosed pleural effusions, the main diagnostic value of thoracoscopy lies in its ability to exclude malignant and tuberculous disease.[108] By means of thoracoscopy, the proportion of so-called idiopathic pleural effusions usually falls below 10%, whereas, in studies that have not used thoracoscopy, failure to obtain a diagnosis can exceed 20% of cases. However, this certainly also depends on the selection of patients and on the definition of "idiopathic." Even after surgical exploration—the gold standard—there are still undiagnosed effusions.[79]

For treatment, talc pleurodesis can be considered in some cases of nonmalignant pleural effusions that are recurrent and symptomatic and do not respond to medical therapy. Such effusions may include those due to hepatic and renal hydrothorax, chylothorax, yellow nail syndrome, and systemic lupus erythematosus.[109–111] In such patients with recurrent benign undiagnosed effusions, Vargas and colleagues[112] achieved successful pleurodesis in 20 of 22 patients by using talc poudrage.

Empyema

Thoracoscopy can also be used in the management of early empyema, mainly to achieve early and complete drainage[12,27] (Video 29.9). As a procedure intermediate between tube thoracostomy and VATS, thoracoscopy has the potential to be effective and, compared with surgical drainage, is less costly and avoids general anesthesia; however, choice of patients at an early stage of pleural infection is likely a key factor for success. In cases with multiple loculations, it is possible to open these spaces to remove the fibrinopurulent membranes by forceps and to create a single cavity that can be successfully drained and irrigated.[113] If performed for this indication, thoracoscopy should be carried out early in the course of empyema, before the adhesions become too fibrous and adherent to perform thoracoscopy. As mentioned, adhesions can be evaluated before the procedure by ultrasonography; thick dense adhesions may preclude thoracoscopy or talc pleurodesis.[31] In fact, ultrasonographic imaging before thoracoscopy significantly reduces the number of pleural access failures; it helps locate the optimal site for thoracoscopy and, in case of complete adhesion of the pleura, indicates the need for another procedure, such as VATS or a CT-guided biopsy.[31]

If the indication for placement of a chest tube is present and if the facilities are available, thoracoscopy can be performed at the time of chest tube insertion. In effect, thoracoscopy is a procedure similar to chest tube placement but one that enables the creation of a single pleural cavity, allowing potentially more effective drainage.[34,113] In a retrospective study of 41 patients, thoracoscopy was successful without further intervention in 35 (85%)[114]; this was mainly successful in free-flowing fluid (100%) and multiloculated empyema (92%), but in only 4 of 8 patients with an empyema in the organizational stage. However, prospective comparative studies on the role of thoracoscopy in the treatment of early empyema in adults are currently lacking, and the evidence from retrospective case-selected noncomparative studies should be interpreted cautiously. We suggest that only early-stage pleural infection should be considered for thoracoscopic intervention because later-stage disease may require decortication of the lung surface, which can only be performed surgically. In addition, there are now other nonthoracoscopic options in pleural infection treatment, such as combined tissue plasminogen activator/DNAse and saline irrigation,[115,116] which are proven in randomized trials to improve outcomes and, in our view, should be used preferentially.

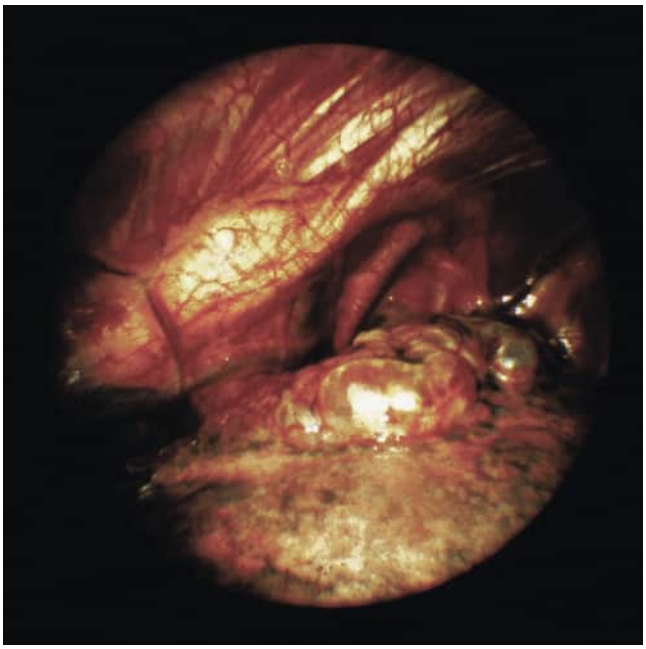

Figure 29.6 View through the thoracoscope in a patient with a spontaneous pneumothorax. On the surface of the lung (*lower part of image*), large apical blebs are visible.

Spontaneous Pneumothorax

In spontaneous pneumothorax, thoracoscopy has both diagnostic and therapeutic purposes[5,27,54,117–119] (Fig. 29.6). Whenever a chest tube is introduced by the trocar technique, it is easy to use an optical device for visual inspection of the lung and pleural cavity before insertion of the chest tube. Special techniques, including fluorescence thoracoscopy, have been used to identify blebs and other porosities (Video 29.10).[120] By inspection during thoracoscopy, the underlying lesions can be directly assessed for the presence of bullae and blebs.[117] In 1047 cases of pneumothorax in which thoracoscopy was used by three different teams, pathologic lesions were detected in approximately 70%.[10]

Treatment by thoracoscopy may include electrocautery of blebs and bullae and pleurodesis using talc poudrage (Video 29.11).[10] Talc poudrage achieves excellent results, with recurrence rates reported as less than 10%.[50] A prospective study showed that, for complicated pneumothorax, defined as recurring or persistent pneumothorax, simple talc poudrage under local anesthesia prevented recurrence in a large proportion of patients.[121] In a prospective,

randomized, multicenter comparison, talc poudrage for primary spontaneous pneumothorax proved more efficient (only 1 of 61 patients with talc poudrage had a recurrence, compared with 10 of 47 with simple pleural drainage) and more cost-effective than drainage alone.[122] The recurrence rate after thoracoscopic talc poudrage is 5%, which is similar to the recurrence rate after VATS.[123] An important disadvantage of VATS is long-term postoperative pain, which may develop in more than 30% of patients and may last for 3 to 18 months.[124] Currently there is no study directly comparing efficacy and complication rates of VATS and thoracoscopy for pneumothorax management.[123]

Other types of pneumothorax treated successfully by thoracoscopy have included those due to *Pneumocystis jirovecii* pneumonia, metastatic osteosarcoma, pleural endometriosis, lymphangioleiomyomatosis, and cystic fibrosis.[125]

In talc poudrage for pneumothorax, 2 to 4 g of talc can be sufficient for effective pleurodesis.[50] The short-term safety of insufflation of large particle size talc in patients with spontaneous pneumothorax has been shown in a prospective multicenter study.[62] In a study of patients 22 to 35 years after talc poudrage, there were no long-term sequelae; total lung capacity averaged 89% of the predicted value in 46 patients, whereas it was 97% of the predicted value in 29 patients treated with tube thoracostomy alone.[126] In this long-term follow-up, none of the poudrage group developed mesothelioma. Although talc poudrage may result in minimally reduced total lung capacity, as well as pleural thickening on chest radiography, these changes appear to be clinically unimportant.[127,128] Talc poudrage may be relatively contraindicated for patients who may become candidates for lung transplantation, although it is not considered an absolute contraindication to lung transplantation.[129]

In some centers, apical bullectomy followed by mechanical abrasion or resection of the pleura is considered the procedure of choice for treatment of recurrent spontaneous pneumothorax, if apical blebs or bullae are present. It is important to add pleurodesis, chemical or mechanical, to a VATS procedure because the recurrence rate after bullectomy alone is unacceptably high—27.5% after 10 years of follow-up in one study.[130] Mechanical pleurodesis can include abrasion or a partial parietal pleurectomy. There are a few studies comparing these approaches. When talc pleurodesis was added to the VATS procedure, Bridevaux and colleagues[73] found a significantly lower recurrence rate of 1.8% compared to 9.2% after partial parietal pleurectomy. In a review by Sepehripour and associates,[131] recurrence rate after VATS pleurectomy was demonstrated to be lower than after pleural abrasion; however, there were slightly better results with talc pleurodesis than with either of the mechanical techniques.

Therefore, if the facilities are available, thoracoscopy may be performed in patients with spontaneous pneumothorax, but, as mentioned earlier, thought should be given to adequate heavy sedation during the poudrage procedure.

Diffuse Pulmonary Diseases

Previously, diagnosis of diffuse lung diseases has been considered an indication for diagnostic thoracoscopy[5,27,54,53,132,133] (Fig. 29.7). An overview of the entire lung surface, assisted by the magnification of the thoracoscope, allows harvesting of representative samples of abnormal areas of parenchyma. In a review of the literature, the sensitivity of thoracoscopic lung biopsy specimens was 93% in 1031 cases with varying causes.[27] In a large series of 419 patients with diffuse lung diseases, the overall sensitivity was 85%, with different yields depending upon the underlying disease: 98% in sarcoidosis stage II and III, 88% in malignant diseases, 85% in diffuse pulmonary fibrosis/interstitial pneumonia, and 42% in pulmonary Langerhans cell histiocytosis.[54] Thoracoscopy has also been used with a high diagnostic yield in immunocompromised patients.[133]

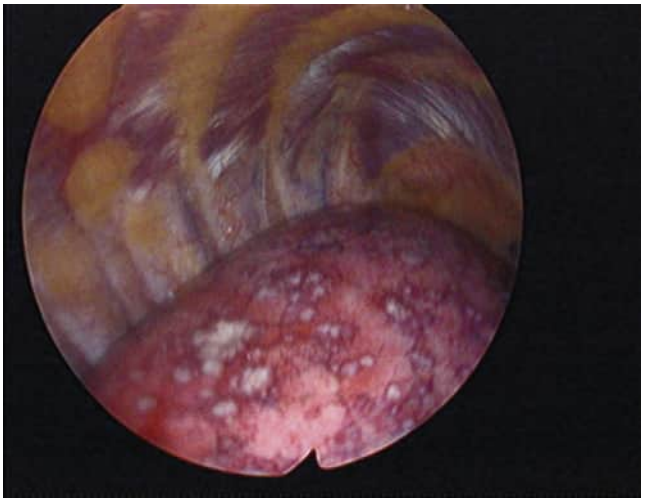

Figure 29.7 A view through the thoracoscope in a patient with diffuse lung infiltration. The abnormalities were found to represent multiple pulmonary metastases due to ovarian cancer (*lower part of image*).

In comparison with bronchoscopy, thoracoscopy is more invasive (see "Contraindications" section) but presents several advantages. It provides significantly larger samples and allows the physician to choose the biopsy site. Unlike transbronchial biopsy, thoracoscopy enables electrocautery so that bleeding after a thoracoscopic parenchymal biopsy can be managed without difficulty.

With regard to diagnostic sensitivity and invasiveness, thoracoscopy ranks between transbronchial biopsy and open-lung biopsy.[54] In an experimental animal study, subpleural and deep-lung biopsy specimens were taken during thoracoscopy in six sheep.[134] No significant differences were found between subpleural and deep biopsies regarding the mean quality scores of the tissue obtained. According to this study, subpleural biopsy specimens obtained during thoracoscopy might be sufficient for establishing an accurate diagnosis in diffuse parenchymal lung disease, where the subpleural layers are involved.

With better radiologic techniques and reclassification of interstitial lung disease, the reliance on lung biopsy in general has waned in the last few years, meaning that this biopsy technique is required less often. The innovation of transbronchial cryobiopsy to obtain lung parenchymal tissue for diagnosis of interstitial lung disease[135] may well decrease the need for thoracoscopic lung biopsy even further.

Localized Diseases

Localized abnormalities of the chest wall, diaphragm, and thoracic spine may be diagnosed using thoracoscopy if the pleural space is not obliterated.[5,54] Hyaline pleural plaques,

localized pleural mesothelioma, lipoma, neurinoma, rib metastasis, rib erosions, and the like can be examined and, if necessary, biopsied. Very discrete metastases are sometimes found in the region of the diaphragm and the posterior chest wall, with or without associated pleural effusion. Chest wall lesions may be easier to diagnose than lung lesions. In a retrospective study in which 109 cases with chest wall lesions of different causes were analyzed, the diagnostic sensitivity was 83%,[54] whereas, in solitary lung lesions, the overall diagnostic sensitivity was only 46%.

Currently, the application of thoracoscopy has decreased substantially for localized disease because of better imaging techniques, such as CT, magnetic resonance imaging, and ultrasonography, which allow image-guided biopsies. Alternatively, VATS will now be used for these indications because the technique not only is diagnostic but also allows the complete resection of benign or malignant lesions.

DIFFERENCES BETWEEN THORACOSCOPY AND VIDEO-ASSISTED THORACIC SURGERY

As described in the preceding sections, thoracoscopy is used mainly for diagnosis of pleural diseases. The most common indications for thoracoscopy are diagnosis of pleural effusion with inspection of the pleural cavity, combined with biopsy specimens from the parietal pleura, as well as treatment of malignant or other therapy-refractory effusions by talc poudrage. It is a relatively simple and inexpensive technique because it can be performed in an endoscopy room, under local anesthesia or conscious sedation, and through a single-entry site with nondisposable instruments.

VATS, conversely, has now been technically developed to the point that it can replace thoracotomy for most indications, if certain limitations, such as dense pleural symphysis, are not present. VATS requires an operating room, general anesthesia with single-lung ventilation, more than two (usually three) entry sites, and complex instruments. Overall, it is a more invasive and expensive technique with a higher risk than thoracoscopy; however, in experienced hands and in the proper setting, VATS is less invasive, is less expensive, and has a lower risk than thoracotomy.

The different clear-cut indications for either thoracoscopy or VATS are listed in Table 29.1. However, there remains a gray area of indications for which method can be used (see Table 29.1). Gray areas include treatment of pneumothorax, drainage of early empyema, biopsies in diffuse parenchymal lung diseases, and sympathetic nerve interventions. For these indications, the choice of the medical or the surgical approach depends on local expertise, availability of the technique, and performance status and prognosis of the patient.

Key Points

- Thoracoscopy (medical thoracoscopy/pleuroscopy) is less invasive than video-assisted thoracic surgery (surgical thoracoscopy) because it is performed under local anesthesia and conscious sedation, most commonly through a single entry port; it is less expensive because it can be performed in an endoscopy suite and usually does not require an anesthesiologist.
- Thoracoscopy is used mainly for diagnostic purposes, in particular in pleural effusions of otherwise indeterminate origin, with very high sensitivity and specificity for the diagnosis of malignancy and tuberculosis.
- Thoracoscopy is the investigation of choice in patients with cytology-negative undiagnosed effusion, either by obtaining a diagnosis or by providing reassurance with negative biopsies in benign disease.
- Thoracoscopy allows definitive pleural intervention to prevent fluid recurrence by the use of talc poudrage, used in malignant and recurrent pleural effusions, or by the placement of an indwelling catheter.

Key Readings

Ali MS, Light RW, Maldonado F. Pleuroscopy or video-assisted thoracoscopic surgery for exudative pleural effusion: a comparative overview. *J Thorac Dis*. 2019;11(7):3207–3216.

Bridevaux PO, Tschopp JM, Cardillo G, et al. Short term safety of thoracoscopic talc pleurodesis for recurrent primary spontaneous pneumothorax. *Eur Respir J*. 2011;38:770–773.

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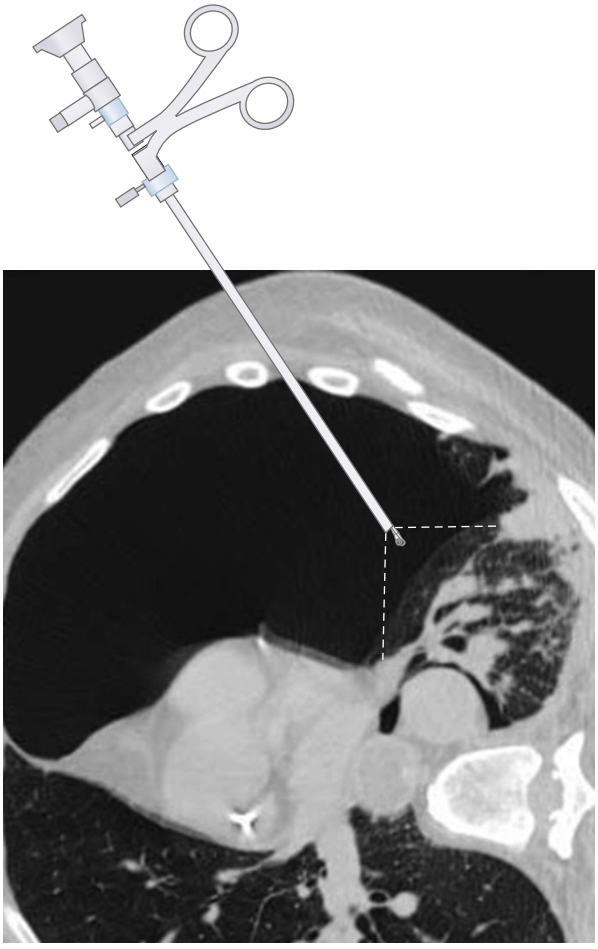
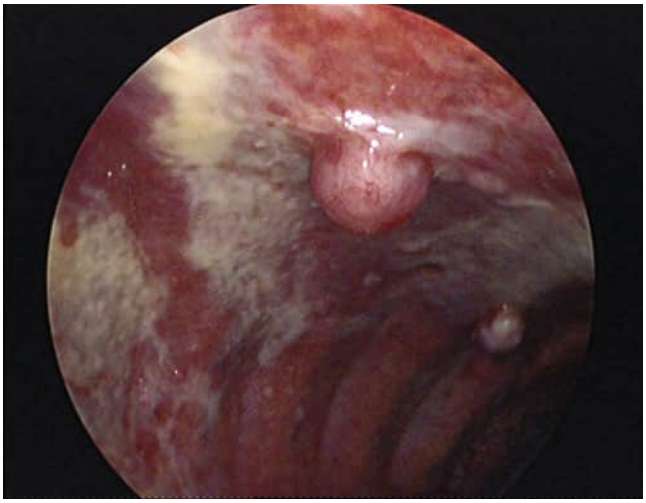
Complete reference list available at ExpertConsult.com.

eFIGURE IMAGE GALLERY



eFigure 29.1 Computed tomography representation of thoracoscopy in the left thoracic cavity with the patient in the right lateral decubitus position. Visualization of the chest wall, pleura, diaphragm, lung, and anterior (and part of posterior) mediastinum is possible.



eFigure 29.2 View through the thoracoscope in a patient with diffuse malignant mesothelioma after occupational asbestos exposure. Tumor nodules and whitish areas with pleural thickening are present on the parietal (chest wall) pleura. Histologic examination revealed a sarcomatoid cell type. (From Loddenkemper R, Mathur PN, Noppen M, Lee P. *Medical Thoracoscopy/Pleuroscopy: Manual and Atlas.* New York: Thieme; 2011.)

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30 THORACIC SURGERY

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PREOPERATIVE EVALUATION
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KEY POINTS

PREOPERATIVE EVALUATION

Before thoracic surgery where pulmonary resection will be performed, all patients should be seen by a thoracic surgeon. In addition to recent axial imaging (i.e., *computed tomography* [CT] scan), all patients should have a cardiopulmonary workup and examination. This will almost always include *pulmonary function testing* (PFT). In patients with cardiac issues, obtaining consultation with a cardiologist can be of benefit in determining the cardiac risk to the patient. Additional testing, such as *positron emission tomography* (PET) scans, magnetic resonance imaging, *ventilation-perfusion* (V/Q) scans, and other tests (e.g., echocardiogram), are ordered on a case-by-case basis.

LUNG RESECTION: PULMONARY FUNCTION TESTING

Because the majority of pulmonary surgeries involve anatomic lung resections, such as a lobectomy for lung cancer, the pulmonary workup is essential before surgery. The initial, and often sole, component of this evaluation is PFT that includes both spirometry and diffusion. On the spirometry side, the *forced expiratory volume in 1 second* (FEV_1) has the most predictive value for the ability to tolerate a resection. In general, a patient with an FEV_1 greater than 2 L should be able to tolerate any resection. A patient with an FEV_1 greater than 1.5 L should be able to tolerate a lobectomy.[1,2] In addition to predicting if a patient will tolerate a resection, these tests are predictive for postoperative complications. Studies have shown pulmonary complications are more frequent when the preoperative FEV_1 is less than or equal to 60% and *diffusing capacity for carbon monoxide* (D_{LCO}) is 50% or less, and when the estimated postoperative FEV_1 or D_{LCO} is 50% or less.[3]

To calculate a postoperative predictive FEV_1 from PFT is relatively straightforward. As discussed elsewhere in this textbook, the lung is made up of lobes that are further subdivided into segments. In general, there are 9 to 10 segments in each lung, for a total of 19. The clinician needs to determine how many segments will be resected (e.g., three from the right upper lobe) and use this as a fraction to calculate the predictive postoperative value.

The following equation is most commonly used to calculate estimated postoperative FEV_1:

$$\text{epoFEV}_1 = \text{preFEV}_1 \times \frac{19 - \text{segments to be removed}}{19}$$

where $epoFEV_1$ is estimated postoperative FEV_1 and $preFEV_1$ is preoperative FEV_1. Segments include right (upper 3; middle 2; lower 5) and left (upper 3; lingula 2; lower 4).

Using this equation, the following example is given. A patient with an FEV_1 of 1.3 L is planning to undergo a right upper lobectomy. Resection of the right upper lobe will result in removal of three segments. Therefore, at the conclusion of the resection, the patient will retain 84% of the original lung parenchyma ([19 – 3]/19 = 84%). Thus, the expected postoperative FEV_1 should be about 1.1 L, and thus the patient should be able tolerate the resection.

When PFTs are marginal, judgment is required when determining a patient's candidacy. A commonly encountered scenario is one in which a patient with marginal PFTs would require an upper lobectomy. Such a patient is likely to have emphysematous changes in the lungs, which, if homogeneous, would mean the patient would likely have inadequate lung function after surgery. If, however, the patient has heterogeneous distribution of emphysema, with compressed parenchyma in the bases and overt bullous disease in the upper lobe, the patient might tolerate an upper lobe resection that would be contraindicated by the calculations just listed. Embarking on these high-risk cases that rely on a "lung volume reduction effect" requires mature judgment.

Previously, it was accepted that an epoFEV$_1$ less than 800 mL was a contraindication to surgery.[4] This value has been called into question because extrapolating from studies on lung volume reduction surgery, such as the National Emphysema Treatment Trial,[5] and calculating *maximal oxygen consumption* ($\dot{V}O_{2max}$) and quantifying split lung function (while taking into account the area of the lung to be resected) has allowed surgery to be performed on patients who previously would have been considered inoperable. Nonetheless, although there is no set "lower limit," care must be exercised when operating on patients for whom the epoFEV$_1$ is likely to be less than 800 mL.

In these cases of marginal PFTs, the quantitative V/Q scan may also contribute useful information. Quantitative V/Q scans can allow the clinician to calculate postoperative values more accurately. Using the perfusion portion of the scan, preferably done with both anterior-posterior and posterior-oblique views, an estimate can be made of the exact amount of perfusion to each lobe of the lung. This test can complement the PFTs to help render a more accurate prediction of postoperative predicted lung function. An example would be a patient with moderate COPD with significant disease only in the upper lobes. It is not uncommon to see perfusion to the upper lobes less than 5% of the overall perfusion. Thus, if the patient has a tumor that requires resection of the upper lobe, it can be expected that the overall PFTs will decrease by only 5% after a right upper lobectomy. In addition, it is known that after some resections, such as a pneumonectomy, the final decrease in pulmonary function testing is less then would be predicted, likely due to increased inflation of the remaining lung parenchyma.[6,7]

Quantitative V/Q scan is most commonly used when the estimated postoperative predictive value for either FEV$_1$ or D_{LCO} is less than 40%. This does not mean that surgery cannot be performed but that the plan must be highly individualized. When the estimated values are less than 40%, studies show minimally invasive surgery can be used to perform lung resections with complication risks that are the same as patients with values closer to 60% done by open thoracotomy.[8] In patients with a value less than 40% or when there are other concerns about suitability for surgery, additional testing should be performed.[9] Cardiopulmonary testing with measurement of the $\dot{V}O_{2max}$ has been shown to be helpful; in a prospective study, patients with a $\dot{V}O_{2max}$ less than 16 mL/min/kg were significantly more likely to suffer complications and death.[10]

In patients where there is concern about postoperative lung function, another option is for surgeons to limit the amount of lung resected. Whereas lobectomy currently remains the gold standard for lung cancer resections, there are two potentially appropriate parenchymal-sparing approaches: anatomic segmentectomies and nonanatomic wedge resections.

Anatomic segmentectomy allows preservation of lung parenchyma and, in the appropriate setting, has been shown to be equivalent to a lobectomy in oncologic outcomes.[11,12] Although lobectomy is currently the standard of care for an early stage *non–small cell lung cancer* (NSCLC), anatomic segmentectomy may prove an appropriate option for a patient with compromised pulmonary function, by providing equivalent oncologic outcomes. A clinical trial evaluating this issue has recently closed to accrual. It will be a few more years before these prospective results are available. The results will hopefully show what role exists for anatomic segmentectomy and whether perhaps it will be considered the standard of care for some lung cancers.

A retrospective review of patients who had PFT, before and between 6 and 36 months after surgery, demonstrated that parenchymal-sparing resection results in better preservation of pulmonary function at a median of 1 year. However, the benefit appeared to be greatest when only one to two segments were resected.[13]

TABLE 30.1 Common Complications for Different Lung Resections

	Wedge Resection*	Lobectomy/ Segmentectomy	Pneumonectomy
Atrial fibrillation	1.2%	7.3–12.3%	19.9–34%
Air leak > 5 days	1.9%	7.6–8.7%	1–4%
Bleeding	0.5–1.9%	1.1–4.7%	2%
Any pulmonary complication	5.6%	6.8–12.6%	23%
Any complication	12–19%	26.2–36.6%	48.2%
Mortality (30 day)	0.5–1.5%	0.9–1.8%	2.4–11.1%

*Wedge resection includes lung biopsy for interstitial lung disease.
Data from references 3, 6, 30, 31, 39, and 40.

LUNG RESECTION: ADDITIONAL WORKUP AND EVALUATION

In addition to the standard PFTs that should be done for all patients undergoing lung resection, any additional testing should be tailored to each individual patient's physiologic and oncologic circumstances. This can vary considerably for benign and malignant conditions. If there are any concerns about a patient's cardiac status, in addition to an electrocardiogram, an echocardiogram and/or stress test can be obtained along with cardiac risk stratification by a cardiologist. Some refer to this as "cardiac clearance." This term should, arguably, be abandoned because the cardiologist provides insightful risk stratification, but the onus for "clearance" ultimately lies with the surgeon taking the patient to the operating room. In general, common rates of complications are known for most pulmonary operations (Table 30.1).

For cases of malignancy, a PET scan is a standard preoperative test to screen for metastatic disease throughout the body, except the brain. Although some surgeons obtain magnetic resonance imaging of the brain with contrast for all patients with lung cancer, others only get it for tumors greater than 3 cm or in cases with concern for neurologic symptoms.[14] For lung tumors greater than 3 cm, there is an increased incidence of spread beyond the lung to both mediastinal lymph nodes and distant sites, such as the liver, adrenal glands, bone, and brain.[15] Staging of the mediastinum before surgery is mandatory when a PET scan shows increased uptake in mediastinal lymph nodes. Studies demonstrate that mediastinoscopy and *endobronchial ultrasound*

(EBUS) with transbronchial fine-needle aspiration, in the hands of a skilled bronchoscopist, are essentially equivalent.[16] Some surgeons, particularly since the emergence of EBUS, tend to obtain invasive staging by EBUS on most patients, to avoid the very small, but real, risk of false-negative radiographic staging. A current trend, where navigational bronchoscopy is used to diagnose lung nodules, is to perform mediastinal staging with EBUS at the same setting if intraoperative cytology reveals the lung nodule to be malignant. Staging the mediastinum is essential whenever there is concern for stage 3A(N2) disease because this may serve as an indication for nonoperative therapy in a marginal surgical candidate or as an indication for neoadjuvant chemotherapy or chemoradiotherapy in a good surgical candidate who understands the potential risks and benefits of the proposed operation.[17]

The need for biopsy of the primary lung tumor is to be considered on a case-by-case basis. The role for CT-guided biopsy has decreased with the advent of navigational bronchoscopy, where it is available. Compared to CT-guided biopsy, navigational bronchoscopy does have a slightly lower overall diagnostic yield (88% vs. 69%). However, the risk of complications is lower with navigational bronchoscopy.[18] Instead of thinking of the two modalities as competitive, it is better to think of them as complementary. In central lesions or when a fissure is likely to be crossed using CT-guided biopsy, navigational bronchoscopy may be a better choice. However, when nodules that are within 2 cm of the visceral pleura, the reverse may be true, and CT-guided biopsy is likely preferable. The current success of navigational bronchoscopy, to a great extent, hinges on having the target nodule in proximity to a navigable airway. Even peripheral nodules, if favorably located, can sometimes be accessed with navigational bronchoscopy. As previously noted, another potential advantage of navigational bronchoscopy is that that it can be combined with EBUS, at the same setting, both to establish a diagnosis and stage the mediastinum (see Chapters 21 and 27).

Establishing a tissue diagnosis before consideration for surgery is not mandatory. Clinical suspicion of a nodule growing on serial imaging with increased uptake on PET scan should be considered highly suspicious for malignancy in most patients. When nodules are near the visceral surface, a frozen section via a wedge resection at the time of surgery carries very low morbidity and mortality with far greater accuracy of establishing a diagnosis compared to preoperative biopsy techniques, such as CT-guided biopsy or navigational bronchoscopy. Concerns have also been raised about whether CT-guided biopsy leads to pleural dissemination.[19] A meta-analysis[20] concludes that CT-guided biopsy does not increase overall risk of total recurrence compared to other strategies; however, in the subgroup of patients with subpleural lesions compared to those without subpleural lesions, there was an increase in pleural recurrence. The researchers concluded that CT-guided biopsy should not be performed for subpleural lesions and only on non-subpleural lesions where a pathologic diagnosis is necessary. Further studies are needed on this issue. The final point in considering foregoing a CT-guided diagnostic test depends on the pretest probability of cancer. The context of the evolution and appearance of the mass needs to be considered but, in some cases, it is completely appropriate to proceed to surgery without a diagnosis if the lesion is highly suspicious for a cancer and, especially, if a negative biopsy result would be considered likely to be a false negative. In either case, the patient would still require surgery: for an excisional biopsy if malignancy is not proven preoperatively or for resection if the diagnosis is established. In either case, surgery would be an appropriate step without subjecting the patient to the risk and discomfort of a preoperative invasive diagnostic procedure.

The argument that a diagnosis must be established to "rule out small cell cancer" is passé. In a patient with a solitary pulmonary nodule that is PET avid and without radiographic findings concerning for either distant or lymphatic spread, surgery for small cell lung cancer treated with lobectomy has been retrospectively shown in large databases to have superior overall survival compared to chemoradiotherapy alone.[21,22] Therefore, in patients who are clinically stage 1 with pulmonary nodules that can be localized, surgical resection carries certain advantages, such as decrease in the time from clinically finding the tumor to treatment.

SURGICAL PROCEDURES ON THE LUNG

Multiple different surgical procedures can be performed on the lung for a variety of reasons, both oncologic and nononcologic. The appropriate procedure to perform is based upon the underlying disease process and the patient's physiologic status. Some of these factors include, but are not limited to, the indications (e.g., oncologic vs. benign), the intent (e.g., diagnostic and/or therapeutic), the pulmonary status (e.g., PFTs or on a ventilator), and the location of a nodule. Clearly communicating the decision making and the details of the operation is important for the surgeon in working together with the pulmonologists and other specialists, and in educating the patient and the family.

When pulmonary surgery is performed for cancer, it is important to understand if it is for primary disease (e.g., lung cancer) or secondary disease (e.g., pulmonary metastasis). For both, the first principle is to achieve negative margins. In addition, resection of primary lung cancer requires an anatomic resection and resection of the lymph nodes that drain the lung and evaluation of mediastinal lymph nodes. Anatomic resections (e.g., segmentectomy, lobectomy, and pneumonectomy) all remove associated lymph nodes both individually and en bloc with the resected lung parenchyma. As for mediastinal lymph nodes, a prospective trial of sampling versus complete resection only demonstrated equivalence.[23] For primary lung cancer, it is generally accepted that at least five separate stations need to be evaluated and greater than 14 total lymph nodes need to be examined by pathology for it to be considered an adequate resection.[24] In contrast, resection of pulmonary metastases generally does not require a lobectomy, pneumonectomy, or removal of lymph nodes.

WEDGE

Wedge resection is a nonanatomic resection of lung (Fig. 30.1A). It is considered therapeutic when it includes a

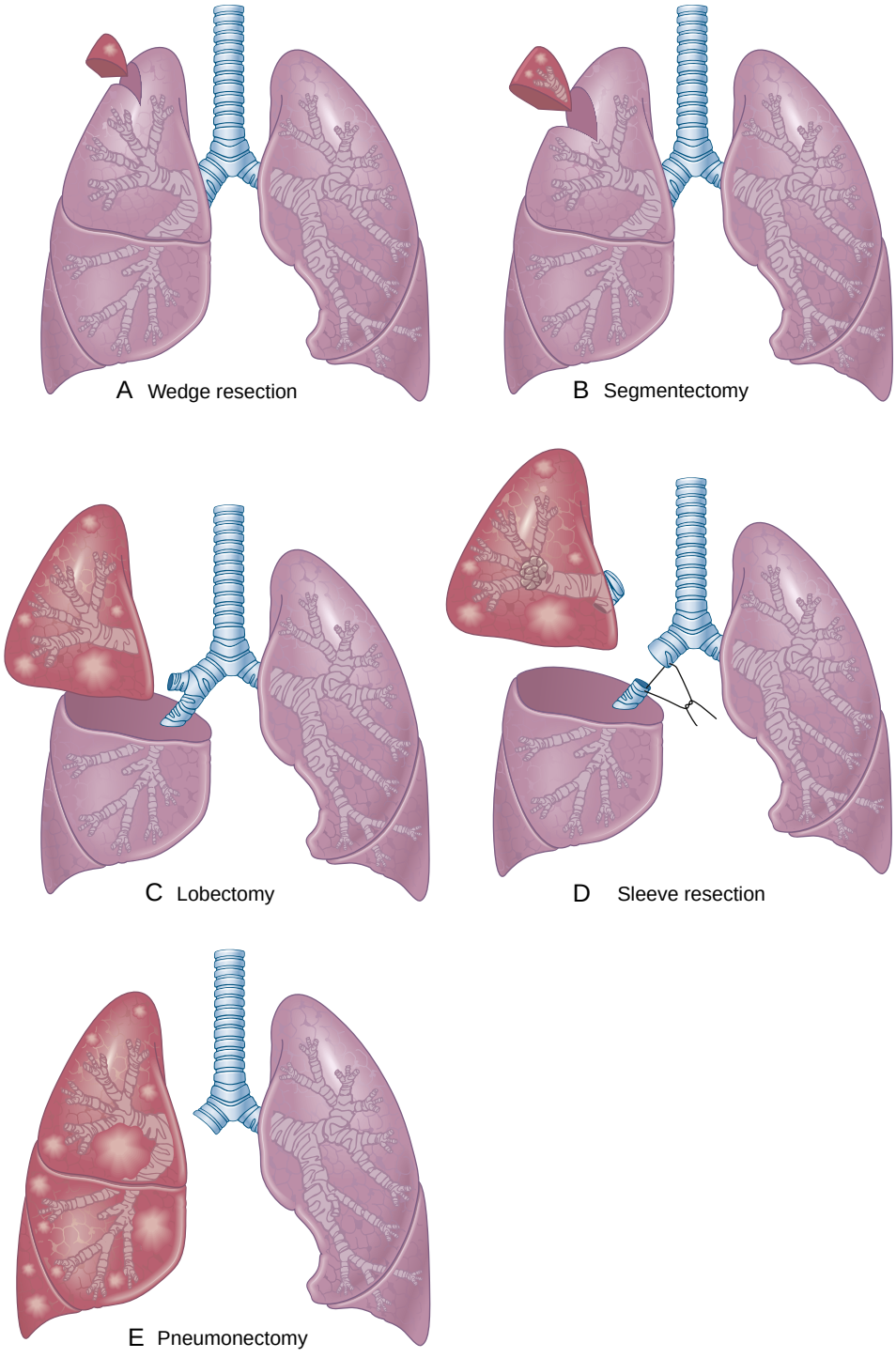

Figure 30.1 Standard lung resections. (A) Wedge resection. A nonanatomic resection, usually used for diagnosis of diffuse lung disease. (B) Segmentectomy. An anatomic resection of one of the 19 pulmonary segments, increasingly used for lung-sparing resections of lung cancer. (C) Lobectomy. An anatomic resection of one of the five pulmonary lobes. It remains the standard for curative lung cancer surgery. (D) Sleeve resection. A reconstruction of the bronchus to spare a lobe not involved in tumor, thereby avoiding a pneumonectomy. (E) Pneumonectomy. Resection of an entire lung. (Modified from Chabner DE. *The Language of Medicine,* 11th ed. St. Louis: Elsevier; 2017.)

nodule that is sent for diagnosis. It is considered diagnostic when performed for a diffuse or localized process, such as for interstitial lung disease. This is generally done near the periphery of the lung and has a very low complication rate, and air leaks are generally not expected. This is almost always performed with a specialized stapler that staples and cuts simultaneously. There is another technique known as a Perelman resection.[25] This technique uses electrocautery dissection to perform a nonanatomic resection in certain circumstances in which the location of the lesion makes a stapled wedge resection difficult or impossible. In the Perelman technique, the raw surface of the lung is left charred and allows minimum to no air leak after the procedure.

SEGMENTECTOMY

Each of the five lobes of the lungs is made up of a number of individual segments. Each lobe has a unique number of segments, discussed earlier. A segmentectomy is an anatomic resection where both the bronchus and pulmonary artery are individually divided, similar to a lobectomy (see Fig. 30.1B). The pulmonary vein is occasionally divided independently but can also be resected

as part of the intersegmental fissure. Segmentectomy, like wedge resection, is a parenchymal-sparing operation. As opposed to wedge resection, segmentectomy is anatomically based with resection of the pulmonary vessels and airway at their respective origins and, depending upon the scenario, has been shown to be both equivalent to a lobectomy for both cancer-specific and overall survival. As opposed to wedge resection, which may still be appropriate in highly selected situations, a proper segmentectomy adheres to the same oncologic principles of lobectomy or pneumonectomy.[11]

LOBECTOMY

This is the most common oncologic resection performed by thoracic surgeons. It has been the backbone of lung cancer surgery since publication of the Lung Cancer Study Group results in 1995.[26] This operation consists of complete and independent division of all bronchovascular structures leading to one of the five anatomic lobes of the lung, and separation of the operative lobe from those around it by dissection of any incomplete intralobar fissures (see Fig. 30.1C).

BILOBECTOMY

Bilobectomy is a right-sided operation that consists of removal of either the upper or lower lobe, along with the middle lobe. Preservation of only the middle lobe is typically considered ill advised because the middle lobe is small and would be unable to fill the hemithoracic space; as such, it would be prone to significant complications, such as torsion.

SLEEVE RESECTION

A sleeve resection may be indicated to spare lobes not involved in tumor to avoid pneumonectomy (see Fig. 30.1D). This can become useful when the tumor involves the main bronchus or is too close to the lobar bronchial orifice to close and maintain a negative airway margin. In such situations, the option is typically to go more proximally on the airway and perform a pneumonectomy, or to perform a sleeve resection by removing that part of the airway (which looks like a short tube or "sleeve" of bronchus) and to reattach the distal airway from the remaining lobe(s) to the divided end of the proximal airway. The most common is a right upper lobe sleeve resection. In this operation, the distal divided bronchus intermedius is anastomosed to the proximal right mainstem bronchus. Any lobe can be "sleeved." In addition, there are more complex operations involving sleeve resections involving the carina. In addition to a sleeve resection of the airway, sometimes it is necessary to perform sleeve resections of the pulmonary artery or to remove a portion of the pulmonary artery and reconstruct it to maintain a normal caliber. These can be complex operations, sometimes requiring advanced reconstructive techniques on both the artery and airway to preserve a lobe. In general, the pulmonary veins will not tolerate reconstruction, and whatever portion of the lung is supplied by invaded veins will need to be removed.

PNEUMONECTOMY

Pneumonectomy, that is, complete removal of a lung, was the first successful operation for NSCLC and was performed by Dr. Evarts Graham in 1933 on a physician from Pittsburgh. This operation involves individual ligation and division of all bronchial and vascular structures to the resected lung (see Fig. 30.1E). One of the key technical points of this procedure is to ensure that the bronchial stump is as flush as possible to the carina, to prevent pooling of secretions that can lead to infection and possible stump breakdown leading to bronchopleural fistula. Bronchopleural fistula and the resultant empyema, after pneumonectomy, is a devastating complication and accompanied by a significant mortality rate. Pneumonectomy is also the main thoracic operation in which the remaining lung is most vulnerable to hydrostatic edema from volume overload, for which fluid restriction during and immediately postsurgery is thought to be protective. This complication is rare but is likely the genesis of the misperception that all "thoracic surgical patients" be run very dry. Diuresis and volume depletion is rarely indicated for patients other than pneumonectomy patients and can, in some thoracic surgical patients, such as those having nonpulmonary surgery, actually be harmful.

INTUBATION AT THE TIME OF SURGERY

The overwhelming majority of pulmonary operations require lung isolation, that is, the ability to ventilate one lung while allowing the other to collapse. There are two standard ways to isolate the two lungs during general anesthesia.

DOUBLE-LUMEN ENDOTRACHEAL TUBE

This approach is the same as a standard endotracheal intubation, except that the endotracheal tube is divided into two separate channels. One of the channels, the bronchial side, is longer and seats in either the right or left mainstem airway (Fig. 30.2). The shorter channel terminates in the distal trachea. The most commonly used *double-lumen tube* (DLT) is a left-sided DLT, owing to the greater length of the left mainstem airway, which makes it easier to maintain the tube in position while the lung is manipulated during surgery. A right-sided double-lumen tube can be much harder to position and maintain and is typically only used for left pneumonectomy or left-sided sleeve resections. There are two separate cuffs on the DLT, with the more proximal cuff referred to as the tracheal balloon. There is a separate cuff to inflate on the bronchial lumen that allows isolation of the left lung from the right. By opening either the tracheal or bronchial lumen to the atmosphere, while ventilating the other lumen, one lung can be allowed to collapse while the other is maintained on positive-pressure ventilation. Because most thoracic surgery cases are performed with the patient in the lateral decubitus position, the isolated lung will be the "up" lung, the

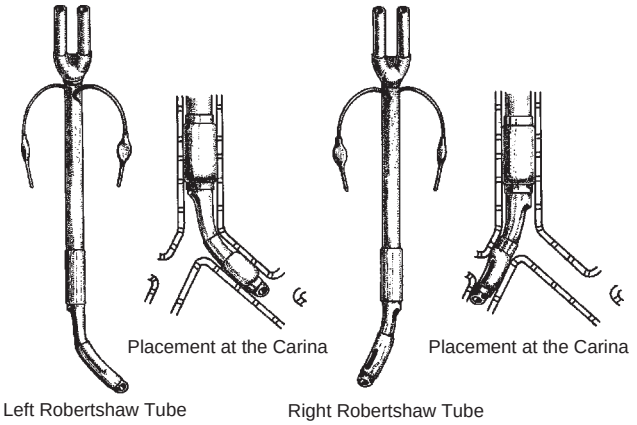

Figure 30.2 Left- and right-sided double-lumen endotracheal tubes. The left-sided double-lumen tube is easier to insert because it can be seated in the longer left main bronchus. The right-sided double-lumen tube is more difficult to position because it sits in the shorter right main bronchus and must be aligned so its side hole faces the orifice of the right upper lobe. (Modified from Benumof JL. *Anesthesia for Thoracic Surgery*. Philadelphia: WB Saunders; 1987.)

lung facing the ceiling, and the ventilated lung will be the "down" lung, the lung facing the floor. A DLT must always be placed under bronchoscopic visualization to confirm that the tube is in the correct position. This is accomplished after the patient is intubated and still in the supine position. The bronchoscope is passed down the tracheal lumen; the carina should be clearly seen and the bronchial lumen should be seen in the left mainstem bronchus. Then the right upper lobe orifice, with its classic appearance, should be identified. The tube placement position should be rechecked after the patient is placed in lateral decubitus position because the tube can migrate.

The right-sided DLT is placed in exactly the same way as just described, except that the bronchial lumen is placed in the right mainstem bronchus, with a side hole cut into the lumen to allow the right upper lobe to be ventilated. This tube requires a more fastidious placement to avoid obstructing the right upper lobe orifice. It is important to recall that some patients may have a *bronchus suis*, an accessory bronchus sometimes supplying the entire right upper lobe, which originates from the trachea. A patient with *bronchus suis* can present a challenge for DLT placement.

BRONCHIAL BLOCKERS

The other option for isolation of the lungs is with a bronchial blocker. There are two types: the conventional single-balloon bronchial blocker (Cook) (Fig. 30.3) and dual-balloon blocker (EZ-Blocker, Teleflex Medical) (Fig. 30.4).

The blocker is placed via a *single-lumen endotracheal tube* (SLT), which must be at least an 8.0 endotracheal tube. The conventional blocker is placed under direct visualization into the mainstem to be isolated (see Fig. 30.3). The dual blocker is designed with two separate lumens, with one branch going down each mainstem bronchus (see Fig. 30.4). Once in place, a cuff is inflated and the selected lung is isolated. The lung isolation can be confirmed with either bronchoscopy or auscultation.

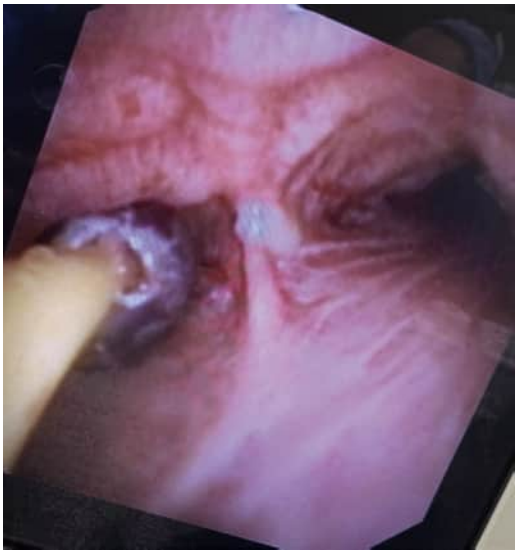

Figure 30.3 Single-balloon blocker in place in the left mainstem bronchus.



Figure 30.4 Dual-balloon blocker in place in the airway. Once placed in the airway, with one balloon in each major bronchus, the blocker can be used to isolate each lung separately.

SEGMENTECTOMY VERSUS LOBECTOMY

Any lung resection results in a decrease in lung capacity due to resection of lung parenchyma, with the exception of those done for volume reduction. Although it seems obvious, the larger the resected section of lung, the greater the decrease in lung function for a patient. However, there are certain situations when this is not the case, such as when the resection is for a patient with apical-predominant heterogeneous emphysematous lungs who would be eligible for lung volume reduction surgery. But in general, for those with marginal lung function, sublobar resections are considered, to avoid damaging the quality of life or causing a major pulmonary disability. In addition, sublobar

resections are considered in patients with excellent lung function if they have disease that appears likely to recur and may require more surgery in the future. Sublobar is generally defined as less than lobar but can either be wedge resection, which is nonanatomic, or segmentectomy, which is anatomic (see earlier).

As of this writing, the current standards of care for surgical treatment of NSCLC are still dictated by the results of the Lung Cancer Study Group[26] published in 1995. This is the trial that established lobectomy as the appropriate oncologic operation for lung cancer. Although there are many limitations of this prospective, randomized controlled trial, the conclusion was that local recurrence rates were significantly higher after sublobar resection than anatomic lobectomy. Unfortunately, in this trial both nonanatomic wedge resections and anatomic segmentectomies were combined as sublobar resections, which together were found to be inferior to lobectomy. In the more than 25 years since this publication, many investigators have sought to understand the role of anatomic segmentectomy.[11,27–29]

In one of the largest series, a single-institution retrospective review demonstrated equivalent recurrence and survival for segmentectomy compared to lobectomy for patients with NSCLC less than 3 cm in size, when all lymph nodes were negative.[11] In a separate study, a previously unrecognized variable that independently influences recurrence rate was the ratio of the margin (i.e., the distance from the tumor to the stapled bronchovascular margin) to the tumor diameter (M:T). In segmentectomy patients, when M:T was greater than 1, patients had significantly lower local recurrence rates compared to those with M:T less than 1.[12] Although all currently published studies are observational, a prospective randomized controlled trial, CALGB 140503, has completed enrollment of 701 patients who were randomized to either lobectomy or sublobar resection, which could have been either a wedge or a segmentectomy. The primary end point is to determine whether disease-free survival after sublobar resection is noninferior to that after lobectomy in patients with small peripheral NSCLC less than or equal to 2 cm in size. The results of this trial are not yet available but are eagerly anticipated.

MINIMALLY INVASIVE SURGERY VERSUS OPEN THORACOTOMY

Essentially any thoracic surgery procedure can be performed either by open or minimally invasive approaches. The benefits of minimally invasive surgery are essentially the same, no matter the operation, and may include shorter length of stay, less postoperative pain, quicker recovery, and, possibly, decreased cost.

In thoracic surgery, minimally invasive surgery can be done in one of two different ways: *video-assisted thoracoscopic surgery* (VATS) or *robotic-assisted thoracoscopic surgery* (RATS). At the present time, there are no prospective trials comparing the two; however, there is currently an international trial looking into that question (*Robotic Approach for Lobectomy or Anatomical Segmentectomy* [ROMANS] Trial; estimated completion date in 2023).



Figure 30.5 Traditional video-assisted surgery port sites on right chest. Access port is near axilla *(arrow),* camera port is at the level of the eighth intercostal space *(arrowhead),* the third port is to allow the assistant to aid with retraction *(thick arrow).* This third port is posterior and at about the same level at the anterior camera port and is usually in line with the tip of the scapula.

This trial is randomizing patients to either of the two minimally invasive techniques and assessing both short- and long-term outcomes, except disease-free survival, for which the studies are not adequately powered.

However, there are several studies that support the purported benefits of either minimally invasive platform compared to open procedures.[30–33] Currently the recommendation from the Society of Thoracic Surgeons is that all early stage lung cancers should be performed in a minimally invasive fashion. The decision of VATS versus RATS is deferred to the surgeon in discussion with the patient.

In general, a patient who undergoes VATS surgery will have three incisions. (Fig. 30.5) There will be an access incision near the axilla that is set at the level of the hilum. This incision is normally between 2 to 5 cm in length. The other two incisions are smaller, both less than 10 mm, because they are used for the camera and assistant ports. They are at about the same level in approximately the eighth intercostal space, with one anterior and the other posterior, usually in the line of the tip of the scapula. A newer technique for VATS, preferred by some surgeons, involves using just one incision, "uniportal" VATS.[34] This technique is only practiced in very few centers and seems to have a steep learning curve. With the wider adoption of robotic approaches, which are easier to learn, the future of uniportal VATS is unclear.

RATS normally requires five incisions. There are four incisions to accommodate the individual arms of the robotic platform. There is also an assistant port to aid with

retraction, passing of surgical sponges, and suction. All the robotic ports are placed in the same intercostal space to minimize pain. One of these ports is enlarged, if needed, at the end of the procedure to retrieve the specimen.

In comparing VATS to open lobectomy, a propensity-matched analysis of the Society of Thoracic Surgeons General Thoracic Surgery Database[31] demonstrated a reduction in length of stay by 2 days and in duration of chest tube by 1 day. Later studies continue to demonstrate the same results. Regardless of the particular minimally invasive approach, it is the prevailing opinion of thoracic surgeons and a consensus opinion by the Japanese Association of Chest Surgery[35] that all early stage lung cancers be resected in this manner. Although multiple studies and case reports have been published on successful completion of essentially every thoracic surgical operation in a minimally invasive fashion, experience and clinical judgment should help guide which cases should go "straight to open." Some very experienced thoracic surgeons are able to do sleeve resections either by VATS or on the robotic platform. However, one should accrue significant experience with less complex operations before attempting highly technically advanced cases.

INTRAOPERATIVE LOCALIZATION OF NODULES

Palpation of the lung during surgery can generally identify most nodules in the lung. One of the drawbacks of robotic surgery is the lack of haptic feedback, which makes the ability to find subpleural nodules harder. In addition, due to nodule size, sometimes even manual palpation of the lung is not successful in finding the nodule. In cases where these concerns exist, there are a few options for helping to identify the pulmonary nodule so that a therapeutic wedge resection can be performed to secure a diagnosis on frozen section.[36–38]

Needle localization with a wire placed by radiology under CT imaging, similar to wire localization for breast cancer, has been performed for many years. Although this technique is not new, it does still have a few limitations. The biggest limitation is that it can be dislodged, especially when the chest is opened with the patient on single-lung ventilation. At this point the lung collapses, and the wire can be pulled from the lung parenchyma. Although it may provide an idea of the area to evaluate the lung for the nodule, the wire then does not actually locate the lesion.

Navigational bronchoscopy is being used more often now either to place a fiducial radiographic marker or inject dye for visualization. When a fiducial marker is used, it can be placed at the time of the initial navigational biopsy, and surgery can be on a different day. The use of a marking dye can be either methylene blue or indocyanine green. Either dye must be placed at the beginning of the surgical case. Then, once the chest is entered, the area with the nodule can be visualized. Indocyanine green is a fluorescent dye that requires use of a near-infrared light with a wavelength of around 800 nm to visualize (Fig. 30.6). Of note, if the injection breaches the visceral pleura, it can dye the entire pleural space and interfere with localization.

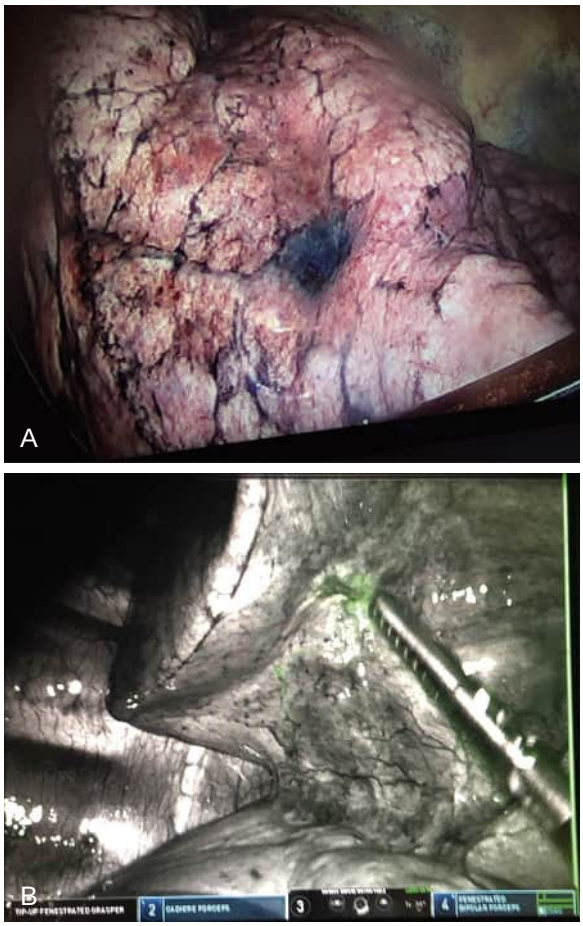

Figure 30.6 Methylene blue and indocyanine green dye marking for a pulmonary nodule. These dyes were placed at the site of a pulmonary nodule via navigational bronchoscopy. (A) Methylene blue can be detected with white light. (B) Indocyanine green requires near-infrared light to visualize.

WEDGE RESECTION FOR INTERSTITIAL LUNG DISEASE

There are times when a patient has a diffuse lung process that cannot be diagnosed by any means other than a surgical biopsy. This operation is historically, and still commonly, referred to as an open lung biopsy. However, an open procedure should be extremely rare. Indeed, there are dire circumstances where a patient is unstable and cannot be moved from the intensive care unit or will not tolerate any element of decreased ventilation from intrathoracic gas insufflation during VATS and, in these situations, an open biopsy through an inframammary incision with the patient supine may be all that can be offered. However, the vast majority of these operations should be performed using a VATS approach.

In attempting to predict if an intubated patient will tolerate single-lung ventilation, it is our practice to place an intubated patient on 100% F_{IO_2} and, after about 15 minutes, obtain an arterial blood gas. If the arterial P_{O_2} is greater than 120 mm Hg, patients will usually tolerate single-lung ventilation long enough to allow a biopsy.

The procedure is relatively straightforward. After a patient is intubated, the two lungs are isolated. As long as

the disease process is equally distributed to both lungs and the patient will tolerate having the right lung collapsed, then the right side is generally preferred because there is more space to operate in the right chest. A 5-mm incision is made, and a port is introduced through the seventh intercostal space at the anterior axillary line. Carbon dioxide is insufflated to 8 mm Hg pressure. This initial port site can be used for a chest tube at the conclusion of the case. The second port site is posterior near the level of the diaphragm in line with the tip of the scapula. The stapler can be introduced through this port. On occasion, an additional 5-mm port needs to be inserted anteriorly to allow insertion of an instrument to manipulate the lung. Ports are placed for two reasons. First, they allow instruments to be inserted and removed quickly and easily, thus speeding up the operation. The second reason is that with instrument ports in place and the hemithorax insufflated with carbon dioxide, the patient can by placed back on two-lung ventilation if needed, without complete visual loss of the operative field. The positive pressure of the insufflated gas allows the lung to be inflated and ventilated partially, thereby allowing the procedure to be completed in a minimally invasive fashion.

Separate biopsies of each lobe are performed that are each about 1 × 3 cm in size. This allows plenty of tissue for both pathology and microbiologic studies while allowing ease of extraction from the chest. Review of the imaging with radiology and pulmonary medicine before surgery allows directed biopsies of the lung that correspond to areas of concern for active disease. At the conclusion of the case, a 24-Fr chest tube can be placed and attached to a chest drainage unit, commonly known as a Pleur-evac (Teleflex Medical). As long as the lung remains expanded, the chest tube can be left on water seal.

Lung biopsy entails some risks of complications. In a review of the Society of Thoracic Surgeons General Thoracic Database, the overall complication rate was less than 10%. The composite rate of postoperative respiratory failure, defined as pneumonia, initial ventilator support of more than 48 hours, acute respiratory distress syndrome, reintubation, or tracheostomy, was 2.9%. The rate of any pleural complication was 5.6%. In this database, the operative mortality was 1.5% at 30 days after an operation.[39,40] Risk factors for morbidity and mortality were pulmonary hypertension, preoperative corticosteroid use, and low diffusion capacity. Although all patients are different, careful consideration and multidisciplinary discussion can result in a safe procedure that provides answers to allow optimal treatment of the patient. The utility of lung biopsies is a question that generates debate. Discussion with pulmonary medicine and radiology of the radiographic findings with the clinical picture generally narrows the differential diagnosis. When the results of the biopsy can change treatment and help to provide a guide to prognosis, lung biopsy can be extremely helpful.

POSTOPERATIVE MANAGEMENT

The management of patients after surgery is as critically important as good surgical technique and preoperative decision making. This can even begin before surgery with the application of *enhanced recovery after surgery* (ERAS) protocols. After pulmonary resections, there are particular issues to manage. For one, all patients will have a chest tube. For another, pain control allows patients to take deep breaths, ambulate, and clear secretions with coughing. How these two issues are managed can have a profound impact on patient outcomes. In some situations, a patient may remain intubated after surgery. In these instances, ventilator management strategies focusing on airway pressures need to be considered.

CHEST TUBE MANAGEMENT

Overall, the management of chest tubes after surgery does have some individual variations, but there is literature to support an overall approach. Some practice variation concerns different views about the use of a clamp trial to ensure that there is no air leak and different end points for the appropriate output before removing the tube.

First, after surgery, placing a chest tube to water seal initially is ideal, regardless of whether or not there is an air leak.[41,42] This begs the question: when should the chest tube be on suction?

For all patients after thoracic surgery, a chest radiograph should be obtained in the recovery area. If the lung is not full expanded, and it is the expectation of the surgeon that the residual lung should fill the entire pleural space, then suction should be applied. A repeat radiograph can then confirm that the lung is expanded. At that point, suction should be applied until at least the next day and then placed back to water seal. A follow-up radiograph can confirm that the lung remains expanded. The underlying principle behind the preference for water seal is that it minimizes the pressure gradient across fresh staple lines and bronchial stumps. Thus, in deciding to apply suction for a pneumothorax, one cannot refer to an algorithm. The decision is based on the degree of postoperative air leak, the lobe removed and the expected lung volume loss (e.g., lower lobectomy patients can often have some residual space), and the patient's pulmonary status. Most current pleural evacuation systems have a regulator to titrate the suction from none (water seal) to −10, −20, −30, or −40 cm of water suction. If the goal is to reexpand the lung in the immediate postoperative setting, then one should use the least amount of suction necessary to accomplish this.

The other immediate postoperative indication for placing the chest tube to suction is to deal with increasing amounts of subcutaneous air. Although this is very rarely dangerous to the patient, it does cause discomfort and, when extreme, is reversibly disfiguring and often quite disconcerting to the patient, the patient's family, or even medical staff unfamiliar with this condition. Patients can, literally, inflate from head to toe. One of the only scenarios where this can be life threatening is if the air actually dissects into the oropharynx, compressing the tissue and limiting air flow through the trachea. The subcutaneous air can cause a condition known as Hamman syndrome and creates the characteristic crackling feeling, or subcutaneous crepitation, under the skin of the patient to the examiner's touch. Changes in voice normally manifest as an increase in pitch. Without placing the chest tube to suction, the air can continue to accumulate until the eyes swell shut. Even this degree of subcutaneous air is almost never dangerous. Development of subcutaneous emphysema in the setting of an indwelling chest tube is the result either of the chest tube not able to access the air (by perhaps being

clogged, kinked, or walled off by expanded lung), the chest tube unable to handle a massive air leak, or often the chest tube with one of the ports outside the pleural space and providing access of the pleural air to the subcutaneous tissue. The initial steps are to ensure the tube is patent and functioning and has all ports within the pleural space. Then suction is gradually increased until the process appears to arrest. If maximal suction is reached and the situation is progressive, then another tube will be required. It is much more common in the perioperative period for there to be an issue with the tube than for it to be functioning perfectly and overwhelmed by the size of the leak. If an additional tube is required, a CT scan might be helpful in determining the optimal location. Once the air leak stops, in general it takes about 7 to 10 days for the subcutaneous air to resolve.

Starting on postoperative day 1, the indications for chest tube removal are the same: no air leak and appropriate chest tube output.

To check for an air leak, drain all the fluid from the tubing into the collection chamber and then have the patient perform a vigorous cough. There should be no bubbles coming through the water-seal chamber. The tube can then be safely removed. If there is an air leak, the tube should not be removed. On occasion a patient may generate a cough that moves a bubble or two across the water seal. This generally happens only on the first cough and a series of coughs can help to determine if there is or is not an air leak.

If there is any concern, a clamp trial may be of benefit. This is done by clamping the chest tube and getting serial radiographs. Individuals may want a different protocol, but in general a tube is clamped for 4 to 6 hours and, if there is no change in radiographs compared to the one before clamping, the chest tube can be removed. If the radiographs appear equivocal, then leaving the tube clamped longer, typically 24 hours, may be advised. It is important to emphasize that, when a chest tube is clamped, the patient should remain closely monitored. If there are any concerns, such as increasing subcutaneous air, hypotension, acute tachycardia, or hypoxia, the tube should be unclamped immediately.

The recent advancement of digital pleural drainage systems may change the need for clamp trials.[43,44] They provide real-time objective measurements and digitally track both fluid output rates and air leaks. The precise time when the air leak resolves can be identified with the digital readout, thus decreasing unexpected pneumothorax after removal of the chest tube caused by a failure to appreciate a small air leak.

The appropriate chest tube output acceptable for removal is not certain.[45–47] Most thoracic surgeons use an amount between 250 and 400 mL per day. Studies looking at correlating chest tube output with weight and body mass index have not shown that using the amount of output as a ratio to another variable adds anything to the actual output.

Pneumonectomy Patients

There are some unique postoperative concerns for patients who undergo pneumonectomy. First, chest tube management differs. Although chest tubes are not usually removed until the output decreases to an appropriate level, after a pneumonectomy, the chest tube is removed relatively early to allow the pleural space to fill completely with fluid. The chest eventually needs to fill with fluid that will then form a fibrothorax and allow the mediastinum and heart to remain in their appropriate anatomic position. Issues can come up when the chest fills too fast, too slow, stops filling up, or fully empties.

When the chest fills too fast, this can cause a tension hydropneumothorax because the fluid has nowhere to go, and the air is not able to be reabsorbed fast enough by the body. Just like a tension pneumothorax, it presents clinically with tachycardia, hypotension, and shift of the mediastinum away from the side of the pneumonectomy. This complication can be treated by placing a central venous catheter directly into the pleural space to "balance the mediastinum." This is done normally through the second or third intercostal space anteriorly at the midclavicular line. Then the air and some fluid are withdrawn until the symptoms are relieved. The benefit is nearly instantaneous. The catheter is left in place for a few days to provide access for repeated treatment, if necessary. Repeat radiographs will demonstrate return of the heart to the center of the chest.

When the chest takes an excessive length of time to fill up completely (>2 weeks), one must consider a possible mechanism limiting fluid accumulation. The diagnosis of greatest concern to thoracic surgeons is the development of a bronchopleural fistula at the bronchial stump staple line. If not diagnosed and treated immediately, it can result in a postpneumonectomy empyema. This should be considered when the fluid forms a horizontal line on radiograph at the level of the carina. Confirmation is made with bronchoscopy and evaluation and interrogation of the staple line stump. If this diagnosis is suspected or confirmed, thoracic surgery should be consulted immediately.

Rarely after a pneumonectomy, when the pleural space does not fill up with fluid or the fluid is slowly reabsorbed over years, a patient can develop a postpneumonectomy syndrome. With this syndrome, the mediastinum shifts to that side, leading to partial or complete obstruction of the contralateral airway and/or pulmonary venous system. This can acutely or progressively cause significant cardiopulmonary impairment (Fig 30.7). If this should happen, management involves surgery to recenter the mediastinum. We prefer to use adjustable saline breast implants in the pleural space to maintain the position of the heart and allow relief of the obstruction of the bronchus and/or pulmonary veins[48,49] (Fig. 30.8).

PAIN

Postoperative pain can lead to various serious complications, including atelectasis, mucous plugging, pneumonia, blood clots, and pulmonary embolism. Pain also interferes with deep breathing, coughing, and mobility. Atelectasis is a particular issue for thoracic surgery patients, all of whom experience single-lung isolation during surgery and thus decruitment of alveoli. Mucous plugging can lead to hypoxia and increased risk of cardiac arrhythmias. If a patient is unable to cough and clear the plug, bronchoscopy is then routinely performed. Certain operations, such as sleeve resection, typically have higher rates of patients requiring postoperative bronchoscopy, both because of plugging and ciliary dysfunction after the resection. Thus postoperative pain control is paramount in a thoracic surgery patient.

Various steps to prevent or treat postoperative pain are used, and more are under investigation. If an open thoracotomy is being planned, before induction of anesthesia, the placement of a thoracic epidural is highly encouraged. This

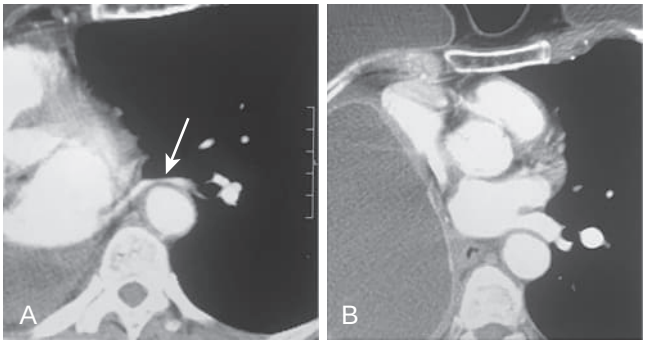

Figure 30.7 *Computed tomography* (CT) scans demonstrating change in the caliber of the inferior pulmonary vein before (A) and after (B) placement of adjustable implants. (A) Two years after a right pneumonectomy, the patient had progressive dyspnea, dysphagia, and reflux. CT scans showed a gradual shift of the mediastinum to the right with increasing compression of the left inferior pulmonary vein *(arrow)* and left lower lobe bronchus. During thoracotomy, two saline implants were placed, and their volume was adjusted to move the mediastinum medially. Upon recovery, the patient's symptoms were completely resolved. (B) Six months later, repeat CT scan shows significant increase in size of the inferior pulmonary vein. (From Encarnacion CO, Deshpande SP, Mondal S, Carr SR. Surgical correction of postpneumonectomy syndrome with adjustable saline implants and transoesophageal echocardiography. *Eur J Cardiothorac Surg.* 2020;57:1224–1226.)

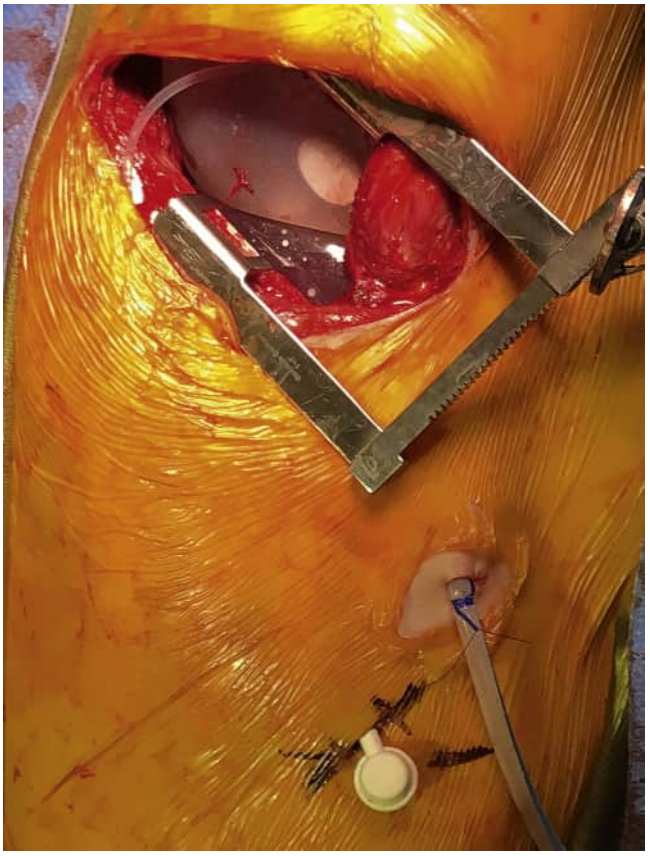

Figure 30.8 Intraoperative picture of the implants and adjustable access reservoir. An adjustable saline breast implant is seen through the incision in the right hemithorax. The access port for postoperative adjustments is the white-colored structure next to the pleural drain. (From Encarnacion CO, Deshpande SP, Mondal S, Carr SR. Surgical correction of postpneumonectomy syndrome with adjustable saline implants and transoesophageal echocardiography. *Eur J Cardiothorac Surg.* 2020;57:1224–1226.)

allows excellent pain control for patients without oversedating them, which aids in their ability to ambulate and participate in maneuvers for improving their pulmonary toilet. However, these can cause issues with hypotension, epidural headaches, and urinary retention. When a patient experiences hypotension, decreasing the epidural analgesic flow rate can allow improvement in blood pressure but may come at the cost of pain control. In a prospective study in thoracic surgery patients from the Mayo Clinic, leaving Foley catheters in place until the epidural was removed resulted in few complications, which generally runs counter to most hospital policies of removing Foley catheters within 24 hours of surgery to decrease the risk of catheter-associated urinary tract infections. In this study, the opposite was seen, mainly thought to be because, in the setting of urinary retention, maintaining the Foley catheter in place avoided multiple instrumentations of the bladder.

Paravertebral blocks are becoming more popular. Although more challenging to place than an epidural, they can provide equivalent pain relief without the side effects of hypotension and spinal headache commonly seen with epidurals. Hypotension, the most common side effect with an epidural, is due to a bilateral effect on the sympathetic nerves. This is uncommon with paravertebral blocks because they only affect the sympathetic nerves on the side of the block. Spinal headache from an epidural is due to its intrathecal location; this is also less common with the paravertebral block because the catheter is extrathecal.

Recently, the use of cryoablation has been proposed. In this procedure a cryoprobe is used to freeze the intercostal nerves at their emergence from the spine. Early nonrandomized preliminary data suggest that this may be effective, but this has not been demonstrated in a conclusive way.[50] Studies are ongoing. Of note, the effect does not start until 24 to 48 hours after cryoablation, so early pain control measures are needed, but the hope is that this approach could allow decreased use of postoperative narcotics and early recovery.

There has been a recent push to adopt ERAS protocols.[51,52] In addition to early mobilization, the protocols support the use of adjuvants for pain control to include nonsteroidal anti-inflammatory drugs, acetaminophen, and gabapentin. Studies of ERAS protocols have shown decreased use of opiates after surgery. There are a few studies on this topic in thoracic surgery patients, but all are favorable. In addition to ERAS protocols, a current study is underway at the University of Maryland School of Medicine, the WINNERS Trial, that, in addition to using ERAS protocols, helps to educate patients on what to expect and set goals and expectations for after discharge. The aim is to determine if preoperative education can also help to decrease hospital readmission rates.

Patients who are mobilized early and often decrease their risks for blood clots and pulmonary embolism. Pulmonary embolism is generally poorly tolerated in this population and, particularly after pneumonectomy, is accompanied by a significant mortality rate. Mobilization allows increased ventilation and recruitment of lung.

VENTILATOR MANAGEMENT

In general, every attempt is made to extubate thoracic surgery patients at the conclusion of the operation. Patients

who undergo decortication are sometimes the exception, where the patient is left on positive-pressure ventilation to help reexpand a lung that has been entrapped for a significant period of time. Even when a significant air leak is present while a patient is on positive-pressure ventilation, extubation greatly reduces the air leak. It is rare for a patient to require reintubation for an air leak. The main reason to strive for extubation is to decrease the pressure on the bronchial stump, staple lines, and/or airway anastomosis.

When a patient must remain intubated, it is imperative to minimize airway pressure. Pressure-control modes of ventilation are generally preferred to volume-controlled modes. Although there are no data providing exact target values, we generally aim for peak airway pressures of less than 24 cm H_2O and plateau pressures in the teens. We have unpublished data demonstrating that the peak inspiratory pressures are most damaging to a fresh staple line and therefore recommend ventilator management geared toward limiting peak inspiratory pressures. Permissive hypercapnia is tolerated and worth trying to keep airway pressures low, as long as the arterial blood gas pH remains greater than 7.30. Allowing for spontaneous ventilation with minimal pressure support to provide adequate ventilation should be the goal. On occasion, a patient may develop acute respiratory distress syndrome after pulmonary surgery. In this type of scenario, extracorporeal membrane oxygenation may provide the only option to support gas exchange while minimizing ventilation and airway pressures.

Patients who undergo decortication are occasionally left intubated for 24 to 48 hours after surgery to help with alveolar recruitment from a lung that has been very atelectatic for a long period of time. Providing a patient with a low level of pressure support and setting the positive end-expiratory pressure at 8 to 10 cm H_2O helps with lung expansion in the immediate postoperative period.

Key Points

- Minimally invasive surgery should be the initial approach for nearly all thoracic surgery pulmonary resections because the risk of complication and recovery time are usually less compared to open surgery.
- Whereas lobectomy is the gold standard for oncologic resections, anatomic sublobar resection (e.g., segmentectomy) appears to have a role in early stage lung cancer by preserving pulmonary parenchyma.
- Thoracoscopic wedge resections for interstitial lung disease are safe and provide high diagnostic yield compared to other approaches.
- Postoperative pain management is paramount to helping decrease complications after surgery.
- Chest tubes in patients after thoracic surgery should ideally be on water seal, with the exception of patients where achieving pleural to pleural apposition is essential (e.g., decortications and pleurodesis).
- In patients requiring ventilation after pulmonary resection, pressure-control modes of ventilation are preferred to decrease overall airway pressure on surgical staple lines.

Key Readings

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SECTION E

EVALUATION

31 PULMONARY FUNCTION TESTING: PHYSIOLOGIC AND TECHNICAL PRINCIPLES

NIRAV R. BHAKTA, MD, PHD • DAVID A. KAMINSKY, MD

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INTRODUCTION

Pulmonary function tests (PFTs) permit accurate, reproducible assessment of the functional state of the respiratory system. PFTs do not diagnose specific diseases. Different diseases cause different patterns of abnormalities in a battery of PFTs. These patterns allow us to quantify the severity of respiratory disease, which enables us to detect disease early and characterize the natural history and response to treatment. The accuracy of interpretation depends on a complete knowledge of the physiologic basis of the functions tested, properly validated equipment, and appropriate protocols. The purpose of this chapter is to describe these PFTs, reviewing briefly their physiologic basis, their equipment and protocol requirements, and their clinical implications. The next chapter, Chapter 32, covers the clinical interpretation and application of PFTs in more detail.

This chapter has an extended online version. A wealth of details of procedures, normal and predicted values, equations, and descriptions of techniques can be found at ExpertConsult.com.

MECHANICAL PROPERTIES OF THE RESPIRATORY SYSTEM

The physiologic determinants of airflow during quiet breathing, maximal airflow, lung volumes, and elastic recoil are introduced in Chapter 11. Figure 31.1 reviews the equal pressure point theory for limitation of maximal airflow in more detail.

FORCED SPIROMETRY

Spirometry is the measurement of the volume of air inhaled or exhaled. Spirometry is commonly performed with a pneumotachometer that measures flow rates and integrates flow to obtain the volume of air inhaled and exhaled during a series of ventilatory maneuvers. Lung volumes and capacities are defined in Figure 31.2. Recommended criteria for acceptable performance standards for equipment have been published, as well as criteria for an acceptable maneuver.[1] Although the maneuver appears quite simple, the initial 25–30% of the maximal expiratory maneuver is effort dependent, and these measurements depend heavily on patient understanding and

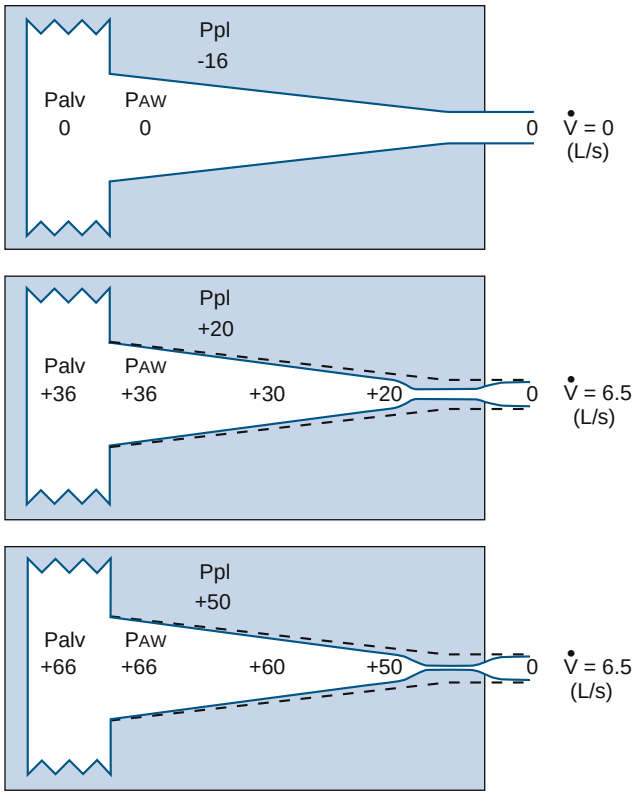

Figure 31.1 Model of expiratory flow limitation. *Top:* The static relationships of pleural pressure (Ppl), alveolar pressure (Palv), intraluminal airway pressure (PAW), and airway dimensions at a fixed lung volume. *Middle and bottom:* Conditions at the onset of maximal flow and with increased expiratory effort, respectively. *Dotted lines* show static airway dimensions for comparison with the dynamic state. All three panels show pressures (cm H_2O) at the same lung volume: 60% of total lung capacity where lung elastic recoil pressure is +16 cm H_2O and equals the transpulmonary pressure (PL): (PL = Palv – Ppl). *Top:* When conditions are static, Palv is zero (i.e., atmospheric) and flow ($\dot{V}$) at the mouth is zero. *Middle:* The subject makes a forced expiratory effort at the same lung volume. Now $\dot{V}$ is 6.5 L/sec driven by Palv of +36 cm H_2O. Because of the resistances down the airways from alveolus to mouth, PAW decreases to the point where PAW = Ppl (+20 cm H_2O, which is called the equal pressure point [EPP] because Ppl = PAW). Between the alveolus and the EPP, the airways are not compressed, but distal to the EPP there is compression and airway narrowing because Ppl exceeds the pressure within the airways. For this lung volume, 6.5 L/sec is the maximal flow possible. *Bottom:* The subject makes a forced expiratory effort starting at the same volume as in the top and middle panels (PL = Palv – Ppl = +16). In this instance, the expiratory effort is markedly increased, reflected by the increased Ppl (+50 cm H_2O) and Palv (+66 cm H_2O). However, the flow generated is still only 6.5 L/sec because the increased effort succeeds only in compressing the airways more, dissipating the increased driving pressure across the increased resistance offered by the more narrowed airways; thus, flow is maximum for this particular lung volume. (Modified from Rodarte JR: Respiratory mechanics. In: Rodarte JR, Hyatt RE. *Basics of Respiratory Disease.* New York: American Thoracic Society; 1976.)

cooperation and must be conducted by a well-trained technician able to communicate instructions clearly.

Comparison of the resulting tracings of volume versus time and flow versus volume, as well as the numbers derived from these tracings, to expected values from healthy reference populations, determines whether the subject has a normal ventilatory reserve or an abnormal pattern characteristic of obstructive, restrictive, or mixed ventilatory abnormalities. None of these patterns is specific, although most diseases cause a predictable type of ventilatory defect. Spirometry alone cannot establish a diagnosis of a specific disease, but it is sufficiently reproducible to be useful in following the course of many different diseases. In addition, the results of

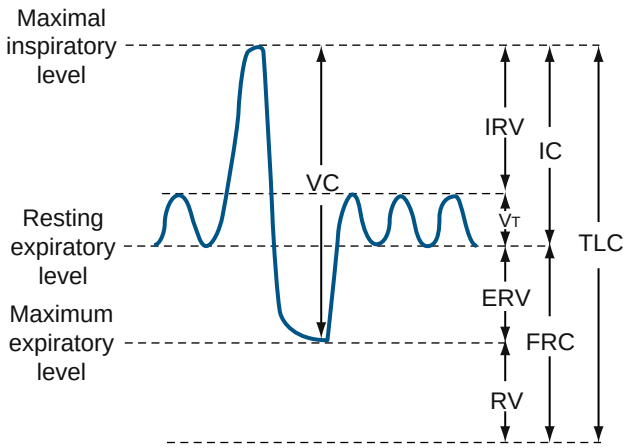

Figure 31.2 Lung volume and capacity. *Volumes:* There are four volumes, which do not overlap: (1) tidal volume (VT) is the volume of gas inhaled or exhaled during each respiratory cycle; (2) inspiratory reserve volume (IRV) is the maximal volume of gas inspired from end inspiration; (3) expiratory reserve volume (ERV) is the maximal volume of gas exhaled from end expiration; and (4) residual volume (RV) is the volume of gas remaining in the lungs after a maximal exhalation. *Capacities:* There are four capacities, each of which contains two or more primary volumes: (1) total lung capacity (TLC) is the amount of gas contained in the lung at maximal inspiration; (2) vital capacity (VC) is the maximal volume of gas that can be expelled from the lungs after maximal inspiration, without regard for the time involved; (3) inspiratory capacity (IC) is the maximal volume of gas that can be inspired from the resting expiratory level; and (4) functional residual capacity (FRC) is the volume of gas in the lungs at resting end expiration.

spirometry make it possible to estimate the degree of exercise limitation due to a ventilatory defect (e.g., *maximal voluntary ventilation* [MVV] can be predicted from the *forced expiratory volume in 1 second* [FEV_1])[2] and to identify the type of patient likely to develop ventilatory failure after pneumonectomy.[3,4]

Indications for spirometry are reviewed at ExpertConsult.com and in society guidelines.[1] Definitions are reviewed at ExpertConsult.com.

Maximal-Effort Expiratory Vital Capacity

To obtain a maximal-effort expiratory *vital capacity* (VC), the subject inhales maximally to *total lung capacity* (TLC) and then exhales as rapidly and forcefully as possible. When volume is recorded on the *y*-axis and time on the *x*-axis, the resulting curve is called the *forced vital capacity* (FVC) curve (Fig. 31.3). Analysis of this curve permits computation of the volume exhaled during the time after the start of the maneuver (*forced expiratory volume over time* [FEV_t]), the ratio of FEV_t to total FVC, and average flow rates during different portions of the curve. The terms used in clinical spirometry, including these different components, are summarized in Table 31.1.[7]

Forced Expiratory Volume Over Time

The FEV_1 is the measurement of dynamic volume most often used in conjunction with the FVC in analysis of spirometry (see Fig. 31.3). The measurement incorporates the early, effort-dependent portion of the curve and enough of the midportion to make it reproducible and sensitive for clinical purposes. The *forced expiratory volume exhaled in 6 seconds* (FEV_6) approximates FVC, and FEV_1/FEV_6 ratio has been shown to be a valid alternative to the conventional FEV_1/FVC ratio and is easier for patients with severe airflow obstruction to attain.[8] In addition, the end of the test is more clearly defined, permitting more reliable correspondence between measured and referenced values.[9]

There are several reasons to perform spirometry.

1. In any occupation that is potentially hazardous to the lungs, individual workers should be monitored periodically by spirometry to detect and quantify evidence of pulmonary problems.
2. Spirometry can indicate the statistical risk of specific surgical procedures for a group of patients but is usually not useful for the individual patient except for lung resection. Arterial oxygen desaturation is a much better indicator of the probability of a high risk associated with a surgical procedure (e.g., the need for prolonged postoperative mechanical ventilation) than is spirometry.[5]
3. Many government agencies (e.g., the Social Security Administration) require results of spirometry to quantify impairment in patients who claim disability caused by chronic bronchitis or emphysema, as well as pneumoconioses, pulmonary fibrosis, and other pulmonary disorders.
4. Spirometric results, including peak flow rates, are extremely useful in assessing the effectiveness of treatment in asthmatic patients. These simple tests are equally valuable for quantifying the effects of treatment in patients with other forms of chronic airflow obstruction and many forms of restrictive disorders.
5. Spirometry can be very sensitive for evaluating progression of disease, especially if baseline values or results obtained early in the course of the illness are available for comparison. Variation in the range of normal is so large that changes in serial test results are much more sensitive than a single value for detecting abnormal function. For example, changes in forced vital capacity were found to be predictive of survival time in idiopathic pulmonary fibrosis.[6]
6. Spirometry is an excellent test for detection of chronic airflow obstruction, localizing and grading a critical orifice in the central airways, and may also be useful in detecting restrictive disorders.

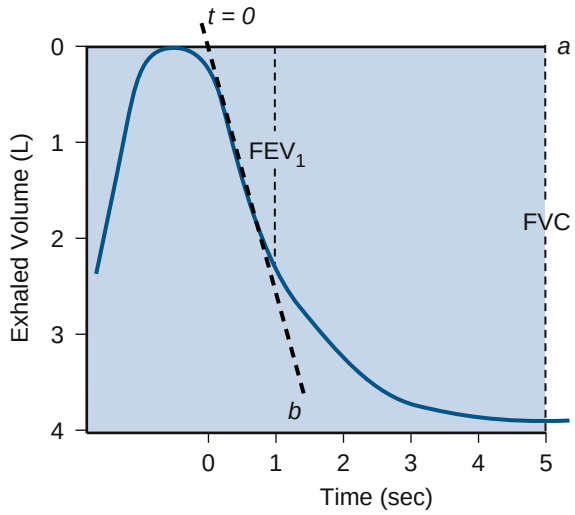

Figure 31.3 Measurement of *forced expiratory volume in 1 second* (FEV_1). This diagram illustrates measurement of FEV_1 using the back-extrapolation method to define time zero (i.e., the point during the forced vital capacity [FVC] maneuver when the subject began to blow as hard and as fast as possible). A solid horizontal line (*a*) indicates the level of maximal inhalation. A heavy dashed line (*b*) passes through the steepest portion of the volume-time tracing. The intersection point of these two lines becomes time zero, from which timing is initiated, as indicated; 1 second after time zero, the vertical dashed line is drawn, indicating FEV_1, and 5 seconds later, another vertical dashed line is drawn, indicating FVC.

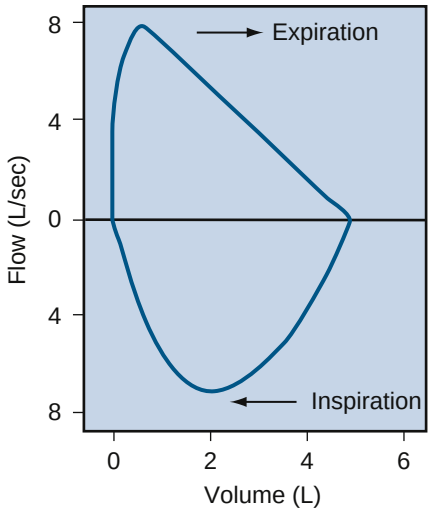

Figure 31.4 The flow-volume curve. The tracing of the flow-volume curve is recorded during maximal inspiration and expiration in a normal subject.

Table 31.1 Terms Used for Spirometric Measurements

Term	Description
Vital capacity (VC)	Largest volume measured on complete exhalation after full inspiration
Forced VC (FVC)	VC performed with forced expiration
Forced expiratory volume with subscript indicating interval in seconds (FEV_t) (e.g., FEV_1)	Volume of gas exhaled in a given time during performance of FVC
Percentage expired in time (seconds) (FEV_t%) (e.g., FEV_1%)	FEV_t expressed as percentage of FVC
Forced midexpiratory flow ($FEF_{25\%–75\%}$)	Maximal midexpiratory flow
Forced expiratory flow with subscript indicating volume segment ($FEF_{V1–V2}$) (e.g., $FEF_{200–1200}$)	Average rate of flow for a specified segment of FVC, most commonly 200–1200 mL in adults
Maximal voluntary ventilation (MVV)	Volume of air a subject can breathe with voluntary maximal effort for a given time

Modified from Kory RC. Clinical spirometry: recommendation of the Section on Pulmonary Function Testing, Committee on Pulmonary Physiology, American College of Chest Physicians. *Dis Chest.* 1963;43:214.

Forced Expiratory Volume Over Time as a Percentage of Forced Vital Capacity

The ratio of FEV_1 to total FVC has been defined precisely in healthy subjects.[10] It declines with age, but abnormally decreased ratios indicate airway obstruction; normal or increased ratios do not reliably exclude airway obstruction, particularly in the presence of a decreased FVC. When the FVC is decreased by an interstitial process or by chest wall restriction and the airways are normal, the FEV_1/FVC ratio is increased. (The FEV_1/FVC ratio may also be increased in subjects who are not able to sustain a maximal effort throughout the expiratory maneuver.) The absence of an increased ratio in patients in whom one would expect the ratio to be increased suggests the presence of concomitant airway obstruction.

Average Forced Expiratory Flow Between 25% and 75% of Forced Vital Capacity

The average *forced expiratory flow between 25% and 75%* ($FEF_{25\%–75\%}$) of FVC was introduced as the maximal mid-expiratory flow rate (eFig. 31.1). This measurement was intended to reflect the most effort-independent portion of the curve and a portion more sensitive to airflow in peripheral airways, where diseases of chronic airflow obstruction are thought to originate.[11] These properties have gained support from clinical experience and theoretical analysis.[12] However, the $FEF_{25\%–75\%}$ shows marked variability in studies of large samples of healthy subjects, and the 95% confidence limits for normal values are so large that they limit its sensitivity in detecting disease in an individual subject.[4,13]

Maximal Voluntary Ventilation

The *maximal voluntary ventilation* (MVV) measurement is defined as the maximal volume of air that can be moved by voluntary effort in 1 minute. Subjects are instructed to breathe rapidly and deeply for 12 seconds, ventilatory volumes are recorded, and the maximal volume achieved over 12 consecutive seconds is expressed in liters per minute. Lung volumes are reported at the largest size possible within the chest and at body temperature (37°C) and standard pressure fully saturated with water vapor (760 mm Hg). MVV in L/min can be estimated as FEV_1 (L) × 40, and in the absence of inspiratory airflow obstruction, neuromuscular weakness or morbid obesity, is a reasonable alternative.

For additional information, see ExpertConsult.com.

FLOW-VOLUME RELATIONSHIPS

Most commonly, spirometry data are visualized by plotting flow versus volume data obtained while a subject inspires and expires fully with maximal effort (Fig. 31.4). As summarized in Figure 31.1, analysis of these curves has

The observer should demonstrate the test; then the subject should choose his or her own respiratory rate and perform several practice runs. The respiratory frequency used in the MVV should be noted and recorded as a subscript (e.g., MVV_{90} or MVV_{110}). Maximal levels are usually achieved between 70 and 120 breaths/min, but the choice of frequency does not greatly affect the test.[14]

This test is heavily dependent on subject cooperation and effort. Loss of coordination of respiratory muscles, musculoskeletal disease of the chest wall, neurologic disease, and deconditioning from any chronic illness, as well as ventilatory defects, decrease MVV, so the test is nonspecific. The MVV is decreased in patients with airway obstruction but less so with mild or moderate restrictive defects because rapid, shallow breathing can compensate effectively for the decreased lung volume.

Despite these caveats, MVV can be useful in special circumstances. It correlates well with subjective dyspnea and is useful in evaluating exercise tolerance. It appears to have prognostic value in preoperative evaluation, possibly because the extrapulmonary factors to which it is sensitive are also important for recovery from a surgical procedure.[15] It also provides a measure of respiratory muscle endurance that may be important in the evaluation of respiratory muscle fatigue, whether from obstructive or restrictive ventilatory defects or from specific neuromuscular diseases.[16] In myasthenia gravis, for example, the patient can often produce maximal efforts for a short time so that FVC and maximal inspiratory and expiratory pressures are normal. However, the effort cannot be sustained, so the MVV or repeated FVC values decrease, even within 12 to 15 seconds. The respiratory crisis of myasthenia gravis may happen rapidly and lead to respiratory failure. As a result, some investigators have suggested that MVV should never be measured in patients with myasthenia gravis, except under carefully controlled circumstances when it may be useful in evaluating treatment.[4]

contributed to the basic understanding of the mechanical events that limit maximal exhalation. Maximal flow clearly depends on lung volume: for every point on the lower two-thirds of VC, a maximal flow exists that cannot be exceeded regardless of the effort exerted by the subject. Thus maximal flow must depend on mechanical characteristics of the lungs. Flow-volume curves also provide a useful way to display ventilatory data for diagnostic purposes.

On forced exhalation, the flow-volume curve has a characteristic appearance. The curve shows a rapid ascent to peak flow and subsequently a slow linear descent proportional to volume. The curve over the initial quarter to one-third of vital capacity exhaled depends on effort. As a subject exerts increasing effort during exhalation, associated with increasing intrathoracic pressure, increasing flow is generated. This portion of the curve has limited diagnostic use because its appearance depends primarily on the subject's muscular effort and cooperation rather than on the mechanical characteristics of the lung.

Shortly after development of peak flow, the curve follows a remarkably reproducible, effort-independent envelope as flow diminishes in proportion to volume until *residual volume* (RV) is reached. For each point on the volume axis, a maximal flow exists that cannot be exceeded regardless of the pressure generated by the respiratory muscles. Although this portion of the curve is very reproducible in a given patient from time to time, it is altered in a characteristic manner by the effect of diseases on the mechanical properties of the lungs. In most subjects older than 30 years and in patients with pulmonary disease, RV is determined by airway closure, so the flow-volume curve shows a gradual downward slope in flow until RV is reached. In some young individuals, however, and perhaps in some patients with chest wall disease, RV is determined by chest wall rigidity, which limits maximal exhalation. In such cases, expiratory flow abruptly decreases to zero at low lung volumes.

On forced inhalation, the flow-volume curves are normally entirely effort dependent. The shape of the inspiratory portion is symmetric with flow, increasing to a maximum midway through inspiration and then decreasing as inhalation proceeds to TLC. It is less influenced by diffuse airway or parenchymal disease. When central airway obstruction is suspected, however, the inspiratory limb of the flow-volume curve has great diagnostic usefulness, whereas ordinary spirometry reveals a nonspecific pattern. See the section on "Large Airway Obstruction: Stenosis and Malacia" in Chapter 32.

See ExpertConsult.com for discussion on other measurements derived from the flow-volume curve.

LUNG VOLUMES

Vital Capacity and Other Static Lung Volumes

The measurement of VC requires the subject to inhale as deeply as possible and then to exhale fully, taking as much time as required. Figure 31.2 illustrates the subdivisions of lung volume.[20] The measurement can also be obtained by adding two of its components: the *expiratory reserve volume* (ERV), obtained by having the subject exhale maximally from the resting end-tidal level; and the *inspiratory capacity* (IC), obtained by having the subject inspire fully from the resting end-tidal level. The sum of these two measurements yields the "combined VC"; as long as the resting end-tidal lung volume is the same for the two component maneuvers, the combined VC and the VC are equal. In patients with severe airflow obstruction, the combined VC appears to be larger than the VC, suggesting the presence of poorly ventilated regions of lungs, or so-called trapped gas. This result probably reflects increased transmural pressure, which tends to cause airway closure during a large portion of the single maneuver—but only in the portion near RV during the combined VC maneuver.

A similar inference can be made by comparing the "slow VC" (performed without regard to time) and FVC, or by comparing inspired VC (maximal volume inhaled from RV to TLC) with the expired VC maneuver just described. Except for those subdivisions involving RV, each of the defined volumes can be recorded and measured by simple spirometry. The RV can be measured only by indirect methods (e.g., nitrogen [N_2] washout, helium (He) dilution, or body plethysmography). Figure 31.2 illustrates the fact that VC can be decreased in two different ways: by a decrease in TLC or by an increase in RV. Only by measuring RV and TLC can these two causes be differentiated.

Gas Dilution Methods

The two most commonly used gas dilution methods for measuring lung volume are the open-circuit N_2 method and the closed-circuit He method. Both methods rely on the use of a physiologically inert gas that is poorly soluble in alveolar blood and lung tissues. These methods most often make a primary measurement of *functional residual capacity* (FRC), the volume of gas remaining in the lung at the end of a normal expiration. Other lung volumes are subsequently derived by asking the subject to breath out to RV and in to TLC in linked maneuvers through a spirometer.

In the original open-circuit method, all exhaled gas is collected while the subject inhales pure oxygen. By assuming values for the initial concentration of N_2 in the lungs (alveolar N_2 fraction varies slightly with the respiratory quotient but is assumed to be approximately 0.81) and, for the rate of N_2 elimination from blood and tissues (about 30 mL/min, or estimated from a formula based on body surface area), measurement of the total amount of N_2 washed out from the lungs permits the calculation of the volume of N_2-containing gas present at the beginning of the maneuver, usually FRC (Fig. 31.5). In the modern era of rapid N_2 analyzers, the total amount of N_2 washed out is calculated as the sum of the within-breath product of tidal volume and the fraction of exhaled gas that is N_2, across all breaths until the fraction of N_2 is below some threshold (e.g., <1.5%) for at least three breaths.[21] With rapid analyzers, rather than assuming a value, the initial concentration of N_2 in the lungs is measured.

In the closed-circuit He dilution method (Fig. 31.6), the theory is similar. The subject rebreathes a gas mixture containing He, a physiologically inert tracer gas, in a closed system until equilibration is achieved. If the volume and concentration of He in the gas mixture rebreathed are known, measurement of the final equilibrium concentration of He permits calculation of the volume of gas in the lungs at the start of the maneuver, usually FRC.

See ExpertConsult.com for further details on gas dilution methods.

Peak Expiratory Flow Rate

Expiratory flow reaches a transient peak early in the forced expiratory maneuver. Peak expiratory flow manifests during the most effort-dependent portion of the expiratory maneuver, so decreased values can result from even slightly submaximal effort rather than from airway obstruction. Nevertheless, the ease of measuring peak flow with an inexpensive, small, portable device[17] has made it a popular means of following the pattern of airflow obstruction on an ambulatory basis. For example, the test is used to monitor patients suspected of having occupational asthma and those who seem insensitive to the severity of bronchospasm. When a maximal effort is made, peak flow is largely a function of the caliber of large airways; it is also influenced by the transient flow caused by expulsion of air from compressed central airways. For these reasons, peak flow is abnormally decreased only in moderate to severe airway obstruction.

Gas Density

Comparison of flow-volume curves obtained when the subject is breathing air and breathing low-density gas mixtures, such as "heliox" (80% helium, 20% oxygen), has been advocated to detect early airway obstruction[18] or localize the site of obstruction.[8] During a forced exhalation, when flow limitation develops in large central airways where flow is turbulent, a low-density gas, such as heliox, increases maximal flow (defined by the increased maximal flow at 50% VC, or $\Delta\dot{V}max_{50\%}$). As lung volume decreases, the flow-limiting segment moves into small peripheral airways, where flow is laminar and density independent. At this lung volume, air and heliox flow-volume curves can be superimposed; the lung volume at which flow becomes density independent is called the volume of isoflow. Thus, if maximal flow increases when breathing heliox compared to air, maximal flow limitation is presumed to be located in larger, more central airways. Clinical application of heliox in detecting airflow obstruction is generally not performed because of technical variation between patient efforts and lack of large data sets from which to infer the structural pathology and clinical implications.[19]

Open-Circuit Method. An advantage of the open-circuit method is that it also permits an assessment of the uniformity of ventilation of the lungs by analyzing the slope of the change in N_2 concentration over consecutive exhalations, by measuring the end-expiratory concentration of N_2 after 7 minutes of washout,[19] or by measuring the total ventilation required to reduce end-expiratory N_2 to less than 2%.[23] The open-circuit method is sensitive to leaks anywhere in the system (especially at the mouthpiece) and to errors in measurement of N_2 concentration and exhaled volume. If a pneumotachygraph is used to measure volume, attention must be paid to the effects of viscosity changes in the exhaled gas because it contains a progressively decreasing concentration of N_2. The open-circuit method shares several disadvantages with the closed-circuit method: It does not measure the volume of gas in poor communication with the airways (e.g., lung bullae); it assumes that the volume at which the measurement was made corresponds to the end-expiratory point on the spirometry tracing used to calculate ERV and IC (needed for the computation of RV and TLC from the measured FRC); and it requires a long period of reequilibration with room air before the test can be repeated. Measuring spirometric volumes immediately before measuring FRC as a combined, linked sequence, instead of on a separate maneuver on the mouthpiece, allows for calculation of ERV, RV, inspiratory capacity, and TLC without the need to assume a constant and reproducible end-expiratory volume. This can be achieved with appropriate valves connected to the mouthpiece, which are available in many commercial systems.

Closed-Circuit Method. In a closed-circuit method, a thermal-conductivity meter measures the He concentration continuously, permitting return of the sampled gas to the system. Because the meter is sensitive to carbon dioxide, and because carbon dioxide must in any case be removed from a closed system, a carbon dioxide absorber is added. The removal of carbon dioxide results in a constant fall in the volume of gas in the closed circuit, as oxygen is consumed and the subject produces carbon dioxide. An equivalent amount of oxygen is therefore introduced as an initial bolus or as a continuous flow. In either case it is important that the subject be "switched into" the system at the end-tidal point. It is possible to calculate the correction for an error in this point, but only if the subject is able to relax and exhale reproducibly to the actual end-tidal point while breathing from the circuit. In a cooperative subject the closed-circuit method also permits the measurement of IC, ERV, and VC from maneuvers recorded on the spirometer while the subject is switched into the system.

Like the open-circuit method, the closed-circuit method is sensitive to errors caused by gas leaks and alinearity of the gas analyzer. It also fails to measure the volume of gas in lung bullae, and it cannot be repeated at short intervals. The test nevertheless gives reproducible results (the *standard deviation* [SD] of repeated measurements is 90 to 160 mL),[24] and normal values are available from several studies of healthy subjects.[4,25]

Other Gas Dilution Methods. Two other measurements of lung volume can be obtained from the dilution of gases used in standard tests of lung function. In the single-breath N_2 washout test for distribution of ventilation, lung volume can be calculated by measuring the mean concentration of N_2 in the air exhaled after the VC inspiration of pure oxygen.[26] In the single-breath measurement of the *diffusing capacity for carbon monoxide* (D_{LCO}), lung volume can be calculated by measuring the change in concentration of the neon, helium, or methane used as the inert tracer gas.[27] Indeed, the alveolar volume achieved during performance of the standard diffusing capacity maneuver is approximately TLC (expected to underestimate TLC by an amount equal to the anatomic dead space) and must be calculated to measure D_{LCO}. Although the lung volume calculated from the single-breath N_2 washout test of distribution is rarely reported, the TLC calculated from measurement of D_{LCO} is used commonly in many pulmonary function laboratories. The ratio of alveolar volume to TLC is expected to be 0.85 or greater in healthy subjects.[28] Because the time for dilution of the tracer gas is short (10 seconds), true TLC is underestimated in patients with airway obstruction

or uneven distribution of ventilation. In healthy subjects and in patients with mild airflow obstruction, the values obtained correspond well with those obtained by body plethysmography.[4,29]

Radiographic Methods

TLC and FRC can be estimated from chest radiographs, although what is measured is the combined air and tissue volume of the lungs; this is in contrast to the communicating gas volume measured by gas dilution methods and the compressible gas volume measured by body plethysmography.[30] Lung volumes assessed by computed tomography scans use segmentation methods to improve the measurement of air instead of tissue and are increasingly used in clinical research.[31–33]

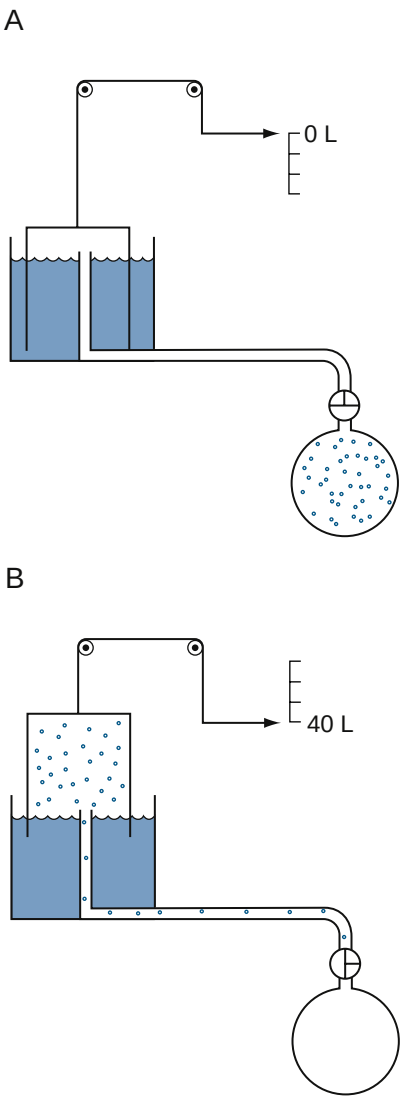

Figure 31.5 Open-circuit nitrogen method to measure functional residual capacity. Dots represent nitrogen (N_2) molecules. (A) Initially, all the N_2 molecules are in the lungs (as 80% N_2). (B) When N_2-free oxygen ("pure O_2") is breathed, the N_2 molecules are washed out of the lungs and collected with the O_2 as expired gas in the spirometer. The spirometer contains 40,000 mL of mixed expired gas with a N_2 concentration of 5%. Thus, the spirometer contains 0.05 × 40,000 = 2000 mL of N_2; the remaining 38,000 mL of gas is mainly O_2 used to wash the nitrogen out of the lungs, plus some carbon dioxide. The 2000 mL of N_2 was distributed within the lungs at a concentration of 80% N_2 when the washout began; therefore, the alveolar volume in which the N_2 was distributed was 2000 mL/0.8 = 2500 mL. (Corrections must be made for the small amount of N_2 washed out of the blood and tissue when O_2 is breathed and for the small amounts of N_2 in "pure O_2.")

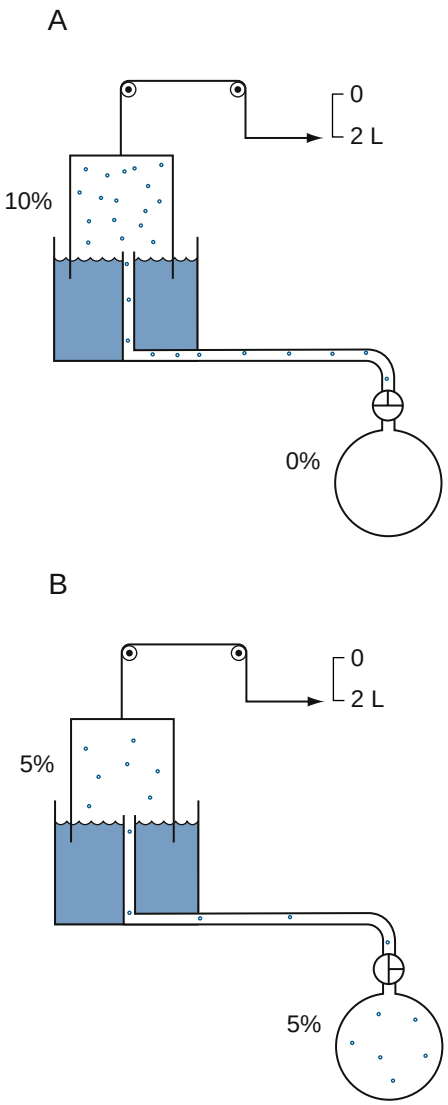

Figure 31.6 Closed-circuit helium method to measure functional residual capacity. Dots represent molecules of helium (He). (A) Initially, all He molecules are in the spirometer and tubing (as 10% He), and no molecules are in the lungs. If the spirometer and tubing contain 2000 mL of gas, of which 10% is He, then 2000 mL × 0.1, or 200 mL, of He is present in the spirometer and tubing before rebreathing. (B) Rebreathing results in redistribution of the He molecules until equilibrium develops, at which time lung volume can be calculated. At the end of the test, the same amount of He (200 mL) must be redistributed in the lungs, tubing, and spirometer, assuming that He is inert and not soluble in blood or tissues. At equilibrium, the concentration of He is 5%. The spirometer and tubing then account for 0.05 × 2000 mL = 100 mL He; the lung accounts for the remainder of the He: 200 − 100 mL = 100 mL. Therefore, the lung volume is 100 mL/0.05 = 2000 mL.

Body Plethysmography

There are three types of plethysmographs: pressure (most commonly used in clinical practice), volume, and pressure-volume.

Pressure (Closed-Type) Plethysmograph. This type of plethysmograph has a closed chamber with a fixed volume in which the subject breathes the gas in the plethysmograph (or body box) (Fig. 31.7). Volume changes associated with compression or expansion of gas within the thorax are measured as pressure changes in gas surrounding the subject within the box. Volume exchange between lung and box does not directly cause pressure changes, although thermal, humidity, and carbon dioxide–oxygen exchange differences between inspired and expired gas do cause pressure changes. Thoracic gas volume and airway resistance are measured during rapid maneuvers, so small leaks are tolerated; in fact, small leaks may be introduced to allow the pressure to equalize to the outside as air warms in the body box. This device is best suited for measuring small volume changes because of its high sensitivity and excellent frequency response. It need not be leak-free, absolutely rigid, or refrigerated because the measurements are usually brief and are used to study rapid events.

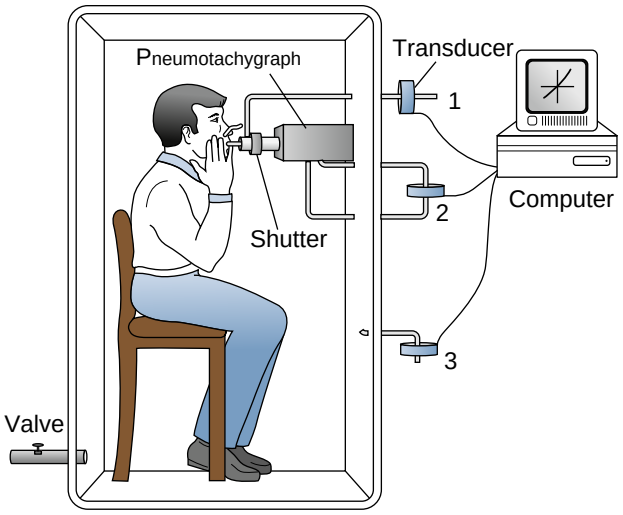

Figure 31.7 Pressure (closed-type) plethysmograph. The subject breathes through a shutter/pneumotachygraph. The shutter is open during tidal breathing and for measurements of airway resistance and closed for measurements of thoracic gas volume. When the shutter is closed, mouth pressure (equal to alveolar pressure at no flow) is measured by a pressure transducer (*1*). The pneumotachygraph measures airflow with another transducer (*2*), and the flow signal is integrated to volume electronically. The plethysmograph pressure is measured by a third transducer (*3*). The signals from the three transducers are processed by a computer. Excess box pressure caused by temperature changes when the subject sits in the closed box is vented through a valve.

Volume (Open-Type) Plethysmograph. This type of plethysmograph (eFig. 31.2) has constant pressure and variable volume. When thoracic volume changes, gas is displaced through a hole in the box wall and is measured either with a spirometer or by integrating the flow through a pneumotachygraph (or flowmeter). This device is suitable for measuring small or large volume changes. For a good frequency response, the impedance to gas displacement must be very small. This requires a low-resistance pneumotachygraph, a sensitive transducer, and a fast, drift-free integrator, or meticulous use of special spirometers; in consequence, this form of plethysmography is challenging and is used in the research setting only.

Pressure-Volume Plethysmograph. This device (eFig. 31.3) combines features of both the closed and open types. As the subject breathes from the room, changes in thoracic gas volume compress or expand the air around the subject in the box and also displace it through a hole in the box wall. The compression or decompression of gas is measured as a pressure change; the displacement of gas is measured either by a spirometer connected to the box or by integrating airflow through a pneumotachygraph in the opening. At every instant, all of the change in thoracic gas volume is accounted for by adding the two components (pressure change and volume displacement) (eFig. 31.4). This combined approach has a wide range of sensitivities, permitting all types of measurements to be made with the same instrument (i.e., thoracic gas volume and airway resistance, spirometry, and flow-volume curves). The box has excellent frequency response and relatively modest requirements for the spirometer. The integrated flow version dispenses with water-filled spirometers and is tolerant of leaks.

Measurement of Thoracic Gas Volume in a Pressure (Closed-Type) Plethysmograph. The *thoracic gas volume* (V, also often referred to as TGV) is the compressible gas in the thorax, whether or not it is in free communication with airways. In the process of determining the V, the airway is occluded, and the subject makes small inspiratory and expiratory efforts against the occluded airway. The thoracic gas volume usually measured is slightly larger than FRC unless the shutter is closed precisely after a normal tidal volume is exhaled. Connecting the mouthpiece assembly to a valve and spirometer (or pneumotachygraph and integrator), or using a pressure-volume plethysmograph, makes it possible to measure TLC and all its subdivisions in conjunction with the measurement of thoracic gas volume.

During inspiratory efforts against the closed shutter, the thorax enlarges (ΔV) and decompresses intrathoracic gas, creating a new thoracic gas volume ($V' = V + \Delta V$) and a new pressure ($P' = P + \Delta P$), where P is atmospheric pressure. A pressure transducer between the subject's mouth and the occluded airway measures the new pressure (P'). It is assumed that the *mouth pressure* (Pmouth) equals *alveolar pressure* (Palv) during compressional changes as long as there is no airflow at the mouth because pressure changes are equal throughout a static fluid system (Pascal's principle). By Boyle's law, pressure multiplied by the volume of the gas in the thorax is constant if its temperature remains constant ($PV = P'V'$). In accordance,

$$PV = P'V' = (P + \Delta P)(V + \Delta V) \quad \text{Eq. 1}$$

$$0 = P\Delta V + \Delta PV + \Delta P\Delta V \quad \text{Eq. 2}$$

$$\text{If } \Delta P \ll P, \text{ then } \Delta P\Delta V \approx 0 \quad \text{Eq. 3}$$

$$V = -\frac{\Delta V}{\Delta P}P \quad \text{Eq. 4}$$

where P equals atmospheric pressure minus water vapor pressure (in mm Hg), assuming that alveolar gas is saturated with water vapor at body temperature; ΔV equals change in thoracic gas volume; and ΔP equals change in Pmouth, which is equal to the change in alveolar pressure (ΔPalv). Note that ΔP is a negative value during inspiratory efforts. Then the thoracic gas volume is calculated as follows:

$$V = -\frac{\Delta V(\text{mL})}{\Delta \text{Palv}(\text{cm H}_2\text{O})} \times (P - 47\ \text{mm Hg})(1.36\ \text{cm H}_2\text{O/mm Hg}) \quad \text{Eq. 5}$$

If a closed plethysmograph is used, ΔV is detected by measuring plethysmographic pressure with a sensitive pressure transducer. If plethysmographic pressure is displayed on the x-axis and Pmouth = Palv is displayed on the y-axis (Fig. 31.8), the slope of the line (α) can be measured during panting efforts against the closed airway. In the following equations, the term *box calibration* refers to an empirically derived constant relating how changes in box volume reflect proportional changes in box pressure.

$$V = \frac{(P - 47\ \text{mm Hg})(1.36\ \text{cm H}_2\text{O/mm Hg}) \times \text{box calibration}(\text{mL/cm H}_2\text{O})}{\alpha} \quad \text{Eq. 6}$$

$$V = \frac{970 \times \text{box calibration}}{\alpha} \quad \text{Eq. 7}$$

Technical issues are discussed at ExpertConsult.com.

Technical Issues

As might be expected, several problems may complicate these measurements. The most important are the following.

- Effects of heat, humidity, and respiratory gas exchange ratio cause difficulties in obtaining stable baselines.
- Outside pressure changes can make it difficult to detect the "signal" relative to "noise."[34]
- Refrigeration is required for many of these boxes, but it can cause a variety of problems related to vibration and localized cooling (e.g., a cool body and a warm head may result because of poor circulation currents).

Underestimation of Mouth Pressure

Stanescu and colleagues[35] have reported that, in patients with asthma, lung volume measured by plethysmograph may be overestimated owing to an underestimation of Palv by measurements of Pmouth.

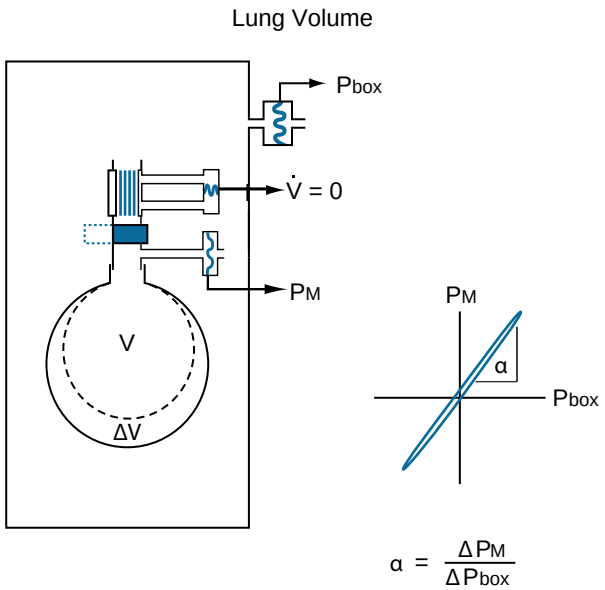

Figure 31.8 A closed, constant-volume, variable-pressure whole-body plethysmograph. As described in eFig. 31.4, at end-expiration airflow ($\dot{V}$) is zero, thoracic gas volume (V) = functional residual capacity, and alveolar pressure (Palv) = mouth pressure (P_M) = barometric pressure (Pbar). The rectangle represents the plethysmograph. When the subject inhales against an occluded shutter in the airway, airflow remains zero, but V increases by ΔV to V′ and P_M (= Palv) changes by ΔP (P + ΔP) to equal P′. When P_M is plotted against box pressure (Pbox), the slope of the line (α) yields ΔPalv/ΔPbox, and V is derived, as indicated in the text. $\dot{V}$, airflow. (Modified from Comroe JH Jr, Forster RE 2nd, DuBois AB, et al. *The Lung: Clinical Physiology and Pulmonary Function Tests*. 2nd ed. Chicago: Year Book; 1962.)

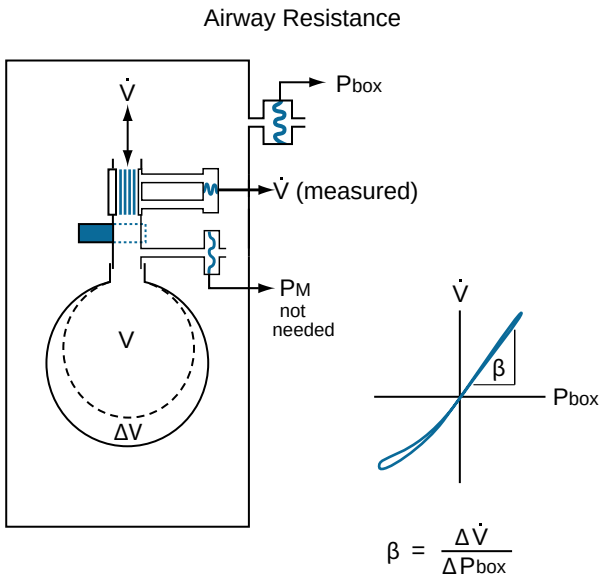

Figure 31.9 Measurement of airway resistance by plethysmography. The rectangle represents a closed, constant-volume, variable-pressure, whole-body plethysmograph. The subject is represented by a single alveolus and its conducting airway. The top pressure transducer measures pressure within the plethysmograph, or box pressure (Pbox). The middle pressure transducer measures the pressure drop across the pneumotachygraph connected in series with the open shutter to the airway, which yields airflow ($\dot{V}$). During inspiration, the alveolus enlarges by ΔV from the original volume (*dashed line*) to a new volume (*solid line*); during expiration, the alveolus returns to its original volume. Throughout inspiration, alveolar gas (previously at atmospheric pressure) is subatmospheric and therefore occupies more volume. This is the same as adding this increment of gas volume resulting from decompression of the alveolar gas to the plethysmograph, so Pbox increases and is recorded by the sensitive Pbox transducer. The reverse happens during expiration when alveolar gas is compressed. Thus alveolar pressure can be monitored throughout the respiratory cycle. When $\dot{V}$ is plotted against Pbox, the slope of the line (β) yields the ratio of $\Delta\dot{V}/\Delta F$ as indicated in the text. (Modified from Comroe JH Jr, Forster RE 2nd, DuBois AB, et al. *The Lung: Clinical Physiology and Pulmonary Function Tests*. 2nd ed. Chicago: Year Book; 1962.)

AIRWAY RESISTANCE

General Principles

Airway resistance (RAW) is always related to the lung volume at which it is measured. It is useful to detect diseases such as asthma, which are associated with increased airway smooth muscle tone, as well as diseases such as COPD, in which there is a loss of airways or narrowing of airways due to secretions or edema. Increased tone can be shown by demonstrating that RAW is abnormally increased relative to lung volume and can be significantly reduced by administration of bronchodilator drugs. The measurement of RAW can also detect increased airway smooth muscle tone induced by provocative stimuli such as exercise, cold air, or specific agents, including allergens and chemicals (e.g., isocyanates) associated with occupational asthma (see "Bronchial Provocation" section).

RAW is measured during airflow and represents the ratio of the driving pressure (between the alveoli [Palv] and mouth [Pmouth]) and instantaneous airflow ($\dot{V}$). In a closed plethysmograph, inspiration of gas from the box into the lungs increases plethysmographic pressure, because to reduce Palv to subatmospheric pressure and drive air into the lungs, the expansion of the lungs slightly exceeds the volume of air drawn into the lungs from the box. This decompression of thoracic gas is equivalent to adding a small volume of gas to the plethysmograph around the thorax, so its pressure increases, as measured by a sensitive pressure transducer. The reverse results during exhalation, when alveolar gas is compressed. Thus $\dot{V}$ is measured continuously with a pneumotachygraph, Pmouth is measured with a pressure transducer connected to a side tap in the mouthpiece, and Palv is estimated continuously with the body plethysmograph (Fig. 31.9).

In practice, RAW is determined by measuring the slope (β) of a curve of plethysmograph pressure (*x*-axis) displayed against airflow (*y*-axis) on a computer monitor during rapid, shallow breathing (panting) through a pneumotachygraph within the plethysmograph. Air is exchanged between the lungs and the box without communication to the air outside the box. Then a shutter is closed across the mouthpiece, and the slope (α) of plethysmographic pressure (*x*-axis) displayed against Pmouth (*y*-axis) is measured during panting under static conditions. Because Pmouth equals Palv in a static system, the closed shutter step serves two purposes. First, it relates changes in plethysmographic pressure to changes in Palv in each subject. Palv is thus effectively calculated from plethysmographic pressure changes with the shutter open, provided that the ratio of

lung to plethysmographic gas volume is constant; this is true because Palv for a given plethysmographic pressure is the same whether or not flow is interrupted. Second, it relates RAW to a particular thoracic gas volume.

$$\begin{aligned} RAW &= (Palv - Pmouth)/\dot{V} = (Palv - 0)/\dot{V} \\ &= Palv/\dot{V} = \Delta Palv/\Delta\dot{V} \end{aligned} \quad \text{Eq. 8}$$

For Δ Palv, substitute $\Delta Palv_{open} = \dot{V}box_{open} \times (\Delta Pmouth_{closed}/\Delta\dot{V}box_{closed}) = \Delta\dot{V}box_{open} \times \alpha$.

$$\begin{aligned} RAW &= \Delta\dot{V}\, box_{open} \times \alpha/\Delta\dot{V} \\ &= \alpha/(\Delta\dot{V}/\Delta\dot{V}\, box_{open}) \\ &= \alpha/\beta \end{aligned} \quad \text{Eq. 9}$$

The resistance of breathing through the mouthpiece and pneumotachygraph is subtracted from the result above. The units of RAW are cm H_2O per L/sec. The inverse of RAW, 1/RAW, is airway conductance, GAW. GAW increases, and RAW decreases, as lung volume increases. Therefore a value that is normalized for and independent of lung volume is made by dividing GAW by the thoracic lung volume at which it was measured and is called specific airway conductance: sGAW = GAW/TGV. The inverse of sGAW is specific airway resistance, sRAW, which can be interpreted as the work of breathing through a fixed resistance.[36,37] Although there is no universally accepted method by which to measure the slope β on the panting loops, common approaches have been described.[36,37] Inspiratory and expiratory resistance, and hence slope β, can differ in some obstructive airway diseases, further complicating the determination of a single β.

See ExpertConsult.com for physiologic factors that affect the measurement of airway resistance.

Forced Oscillation Methods

DuBois and colleagues[42] described an oscillatory method to measure the mechanical properties of the lung and thorax. In contrast to the methods already described, the *forced oscillation techniques* (FOT) use an external loudspeaker or similar device to generate and impose flow oscillations on spontaneous breathing, rather than using the respiratory muscles, and is measured during quiet tidal breathing. The FOT measures *respiratory system impedance* (Zrs),[45] which is the sum of all forces that must be overcome to cause airflow.[46] These forces include resistance and reactance, the latter of which is composed of elastance and inertance. Sound waves at various frequencies (typically 4–35 Hz) are applied to the entire respiratory system (airways, lung tissue, and chest wall). With computer methods, the slow frequency changes in pressure, flow, and volume generated by the respiratory muscles during normal breathing are subtracted from the raw data, permitting analysis of the pressure-flow-volume relationships imposed by the oscillation device (eFig. 31.6). Clinically, the FOT is mostly used for the assessment of pulmonary function in children, but it is expected to have expanded use in adults as research increasingly shows a value for the detection of abnormal function in this group. The European Respiratory Society recently released updated technical standards for oscillometry covering hardware, software, testing protocols, and quality control.[47]

Technical details are reviewed at ExpertConsult.com.

LUNG ELASTIC RECOIL

Lung elastic recoil is an important physiologic characteristic of the lungs, which may change in qualitatively different ways in various diseases. In general, elastic recoil is increased in a restrictive ventilatory defect associated with decreased lung volumes. Conversely, in almost all forms of airflow obstruction, elastic recoil is decreased. Testing for elastic recoil is time consuming, difficult to perform, expensive, and invasive. Thus the test may not be practical for the routine evaluation of patients with restrictive ventilatory defects but may be of great value in the assessment of various obstructive ventilatory defects, including those with isolated bullae or advanced emphysema, to determine whether patients will benefit from resection of nonfunctioning or very poorly functioning lung tissue. In other patients, it may be useful to differentiate emphysema from asthma or bronchitis. In evaluating patients with mixed ventilatory defects (e.g., emphysema plus fibrosis), the test may confirm the presence of both disorders.

Principles, protocols, and analysis of the measurements are presented at ExpertConsult.com.

EXPIRATORY FLOW LIMITATION

Obstructive airway disease is associated with a reduced reserve between maximal flow rates and those achieved during tidal breathing. This reduced flow reserve often presents as a superimposition of tidal breathing loops on the maximal expiratory limb of the flow-volume curve. In the research setting, this overlap has been quantified as shown in Figure 31.10 and termed *expiratory flow limitation* (EFL). EFL has also been quantified by a reduced augmentation of flow during tidal breathing with applied negative pressure at the mouth (eFig. 31.9).[63]

Further details regarding comparison of tidal and maximal flow-volume curves are given at ExpertConsult.com.

The degree of expiratory flow limitation has been found to be associated with dyspnea in obstructive airway diseases independent of FEV_1. Expiratory flow limitation may develop with exercise even if not present at rest. An important physiologic consequence of expiratory flow limitation is the inability to exhale the inhaled tidal volume completely as respiratory rate and tidal volume increase during exercise, a phenomenon known as *dynamic hyperinflation.*

Dynamic hyperinflation is a progressive increase in *end expiratory lung volume* (EELV, synonymous with FRC), typically during exercise, although it may also manifest with any increase in respiratory rate or tidal volume, such as from pain, anxiety, or hypoxemia. Assuming TLC does not change, an increase in EELV is linked to a decrease in IC, which can be easily measured during exercise to infer changes in EELV. There are a number of negative consequences of dynamic hyperinflation with exercise, including increased work of breathing due to increased elastic load at higher lung volumes, increased dyspnea, early ventilatory limitation to exercise, reduced maximum oxygen consumption, *carbon dioxide* (CO_2) retention, and potential adverse cardiac consequences. Although airway resistance decreases slightly at higher operating lung volumes, this change is usually not enough to prevent expiratory flow limitation. Of importance, dynamic hyperinflation

Physiologic Factors

Several physiologic factors affect the values obtained during plethysmographic measurement of RAW.

Airflow. RAW relates to a particular flow rate during continuous pressure-flow curves, so the slope may be read at any desired airflow rate. In general, RAW is measured at low flows, at which transmural compressive pressures across the airways are small and the relation to Palv is linear. RAW will be increased transiently with forced respiratory maneuvers in which airflow rates become limited by large transmural compressive pressures across the airways, by maximal dynamic airway compression, and by possible alterations in airway smooth muscle tone. Thus, to avoid artifacts, the standard approach is to measure RAW at low flows.

Volume. Near TLC, resistance is small, but near RV, resistance is large. Lung volume may be changed voluntarily to evaluate RAW at larger or smaller volumes in health and disease.

Transpulmonary Pressure. RAW is related directly to lung elastic recoil pressure at any lung volume. Subjects with increased lung elastic recoil have a lower RAW at a given lung volume than normal subjects because of increased tissue tension pulling outward on airway walls. In contrast, loss of elastic recoil results in loss of tissue tension and decreased traction on airway walls, so RAW is increased. This relationship may be used to analyze the mechanism of airflow limitation in various obstructive ventilatory defects (e.g., bullous lung disease).[38,39]

Airway Smooth Muscle Tone. The airways are affected markedly by smooth muscle tone, depending on the state of inflation and the subject's previous pattern of breathing (referred to as volume history).[40] These relationships are relevant to diseases in which smooth muscle tone is increased (e.g., asthma) or low lung volumes are encountered (e.g., during cough). Thus bronchoconstriction is not demonstrable temporarily after a deep breath or at TLC in healthy subjects. Similarly, RAW in healthy subjects may be greater when a given lung volume is reached from RV than from TLC.

Panting. Panting minimizes changes in the plethysmograph caused by thermal, water saturation, and carbon dioxide–oxygen exchange differences during inspiration and expiration; hence these factors may be neglected if measurements are made during panting. Panting also improves the signal-to-drift ratio because each respiratory cycle is completed in a fraction of a second; gradual thermal changes and small leaks in the box become insignificant compared with volume changes attributable to compression and decompression of alveolar gas. The low volume fluctuations with panting make the contribution of elastance to the relationship between pressure and flow negligible; inertance is already low at breathing frequencies up to approximately 8 Hz. The glottis stays open during panting, rather than varying its position as it does during tidal breathing. Abdominal pressure changes are also minimized.

Increasingly, laboratories are using commercial plethysmographs that estimate RAW during so-called quiet breathing, relying on computer software rather than panting to compensate for the effects of humidity, temperature, and gas exchange. In fact, the subject must breathe at higher-than-normal frequencies and tidal volumes to estimate RAW using this software. The limitation to this approach is that the average resistance values tend to be slightly higher than those observed during panting because the glottis is often partially closed during the measurement.

Stanescu and Rodenstein[41] have demonstrated that, to avoid overestimation of thoracic gas volume, as described previously, closed shutter panting must be done at 1 Hz; however, to measure RAW and avoid the temperature artifact, panting must be done at approximately 2 Hz, as advocated originally by DuBois and colleagues.[42] Alternatively, both artifacts may be avoided if the subjects breathe quietly at *body temperature (37°C) and standard pressure fully saturated with water vapor (760 mm Hg)* (BTPS) or may be compensated for electronically.[43]

RAW measured plethysmographically is not the average of unequal resistances throughout the lungs; rather, it is the average Palv per unit volume divided by average airflow rate at the mouth. It corresponds to average GAW. $GAW = G_1 + G_2 + \ldots + G_n$, which is equivalent to adding resistances in parallel according to reciprocals: $1/RAW = (1/R_1) + (1/R_2) + \ldots + (1/R_n)$.

Controlling these physiologic influences is often essential in determining specific factors that influence GAW (or RAW) in a particular subject (e.g., loss of lung elastic recoil or airway smooth muscle spasm).

The elastic forces (pressures) of the lungs and chest wall oppose the volume changes induced by the applied pressure and decrease as the frequency of oscillation increases. Zrs is a complex number calculated by using Fourier analysis to relate changes in pressure and flow in the frequency domain, and it represents a combination of the resistance and reactance. The reactance reaches a minimum at frequencies of approximately 3 to 8 Hz, where the resistance produces the only opposing force. The frequency is the resonant frequency of the respiratory system.

Values for total lung resistance primarily reflect RAW (≈50%). The portion due to lung tissue resistance is about 40% of the pulmonary resistance in healthy subjects, with the remainder due to resistance in the small airways (10%). The total resistance of the respiratory system (airway + lung + chest wall, or RT = RAW + RL + RCW) usually is about 25% greater than the resistance of the airways in healthy subjects or not much greater than pulmonary resistance. It is increased in patients with pulmonary fibrosis or kyphoscoliosis[48] but rarely to a level of clinical importance where it becomes the limiting resistance.

If the airways, lungs, and chest wall behaved as if they were a single bellows with frictional resistance, elasticity, and inertia, then the oscillations in airflow into and out of the lungs caused by the driving pressure produced by the loudspeaker across the respiratory system could be described as a function of the applied frequency by the following equations. At any frequency, the magnitude and

phase shift of the reflected waves give a measure of impedance (Z) and reactance. The impedance is described by

$$Z = \sqrt{R^2 + \left(2\pi fL - \frac{1}{2\pi fC}\right)^2} \qquad \text{Eq. 10}$$

where Z is mechanical impedance (cm H_2O per L/sec) and is analogous to electrical impedance, R is resistance (cm H_2O per L/sec), L is inertance (cm H_2O per L/sec^2) and is analogous to electrical inductance, C is compliance (L/cm H_2O) and is analogous to electrical capacitance, and f is the frequency of the driving pressure applied by the loudspeaker (Hz, or cycles per second).

Eq. 11 describes the phase angle or lag (Θ) of the flow with respect to the applied pressure wave:

$$\text{Tan}\Theta = \frac{X}{R} = \frac{2\pi fL - \frac{1}{2\pi fC}}{R} \qquad \text{Eq. 11}$$

The inertial reactance ($2\pi fL$) corresponds to the electrical inductive reactance, which increases with frequency and leads flow. The elastic reactance ($2\pi fC$) corresponds to the electrical capacitance, which decreases with increasing frequency and lags flow. The resistance of the system is in phase with flow.

The frequency at which the absolute values of these reactances are equal and opposite is called the resonant frequency. According to Eq. 10, the impedance (Z) becomes equal to the resistance of the respiratory system at the resonant frequency, which can be calculated from the following equation:

$$\text{Resonant frequency} = \frac{1}{2\pi\sqrt{LC}} \qquad \text{Eq. 12}$$

The part of impedance that reflects pressure in phase with flow is the *resistance* (Rrs). Rrs is typically flat above 5 Hz in healthy subjects but tends to increase at lower frequencies approaching breathing frequency (≈0.2 Hz). This frequency dependence of resistance is likely due to inhomogeneities of resistance, with some component of tissue viscoelasticity seen at very low frequencies (<1 Hz). In general, lower frequencies (<1 Hz) reflect peripheral lung mechanics, and higher frequencies (>5 Hz) reflect central lung mechanics. Therefore resistance at 5 Hz (R5) and above typically reflects RAW as measured by body plethysmography.

Landser and coworkers[49] developed a device based on multiple frequencies (pseudorandom noise) in contrast to Dubois and colleagues[42] and Michaelson and coworkers,[50] who used a random noise signal. The technique requires little of the subject but to simply breathe quietly on a mouthpiece for 30 seconds; the computer does the complete analysis, yielding values for respiratory resistance at different frequencies. (The same device simultaneously estimates respiratory inertance and dynamic compliance.) This approach is fast, noninvasive, and reproducible; moreover, it seems to yield clinically meaningful results in healthy subjects before and after use of a bronchodilator, as well as in the evaluation of airflow obstruction in COPD, asthma, and congestive heart failure.[51–53]

It should be noted that the lungs and chest wall rarely respond to a driving pressure with diverse frequencies in the same way as a simple model assumed to be composed of single values of resistance, compliance, and inertance, as described earlier. The resonant frequency of the ribs is 7 to 10 Hz, whereas the resonant frequency of the abdomen and diaphragm is about 3 Hz. The air in the trachea, bronchi, and bronchioles has an inertial reactance that is significant at relatively high frequencies (≈6 Hz or greater). In consequence, when the whole system appears to be at resonant frequency, the impedance is probably not a pure resistance at all, but rather an admixture of other forces of the lungs and chest wall, as described earlier.[54–57]

Lung elastic recoil pressure, or *transpulmonary pressure* (P_L), is the difference between the pressure inside the lungs (the alveolar pressure) and the pressure outside the lungs (the *pleural pressure* [Ppl]): P_L = Palv − Ppl. To maintain a sustained inspiration at a volume of three-fourths of TLC with the mouth and glottis open, the muscles of inspiration must maintain a pleural pressure of approximately 12 cm H_2O below atmospheric pressure (Ppl = −12 cm H_2O). During conditions of no flow and when pressures at the mouth, alveoli, and atmosphere are equal, P_L = 0 − (−12 cm H_2O). If the muscles of inspiration relax, allowing the chest wall to recoil inward, Ppl rises from −12 to 0 cm H_2O and Palv from 0 to +12 cm H_2O at the instant before flow begins. This example illustrates two of the principles that underlie measurement of lung recoil: (1) The pressure required to expand a lung to any volume is equal to the recoil pressure at that volume, and (2) under conditions of no flow, with the glottis open, Palv and Pmouth are identical. It is easy to measure Pmouth, absolute lung volume can be measured by any of a variety of methods already discussed, and the change in volume can be measured easily with a spirometer. All that is needed to measure lung elastic recoil pressure and lung compliance is a measurement of Ppl in relation to lung volume.

Because the esophagus passes through the pleural space, it seems reasonable to assume that pressure within the esophagus approximates Ppl. This assumption works as long as the sphincters of the upper and lower esophagus are competent and there is no force compressing the esophageal lumen, such as active contraction of the esophageal muscles or passive compression by surrounding mediastinal structures. Most of these conditions are met in subjects without esophageal disease who are sitting or standing upright.

Protocol for Measurement of Lung Elastic Recoil

To preserve the patency of a tube placed in the esophagus to measure esophageal pressure, it is necessary to cover the end of the tube with a balloon. This complicates the situation, for now intraballoon pressure is assumed to reflect intraesophageal pressure, which in turn is assumed to reflect the surrounding Ppl. The artifacts caused by the balloon generally cause the measured pressure to be too positive, owing to the compression of the balloon by the walls of the esophagus (eFig. 31.7). A long (10 cm), narrow (2.5 cm perimeter), thin-walled (0.04 cm), highly compliant latex balloon containing a small amount (0.2–0.4 mL) of air can reduce these artifacts. The volume of air that minimizes this artifact varies slightly for different balloons. The volume can be determined for each balloon by suspending it vertically in water, with the top (proximal end) of the balloon at the surface, allowing it to empty before the tube is closed with a stopcock.[58]

Ppl changes along a vertical gradient, with pressures being most negative at the base of the thoracic space. It is

customary to measure pressure in the lower third of the esophagus, to estimate the pressure necessary to expand the greater proportion of the lungs. The balloon is advanced to the gastroesophageal junction (identified easily by the positive pressure caused by an inspiratory sniff) and then pulled back 10 cm.

Analysis

Compliance. When the balloon is in place, the relationship between changes in lung volume and changes in Ppl can be measured.

Dynamic lung compliance refers to the ratio of the change in volume to the change in pressure over a tidal breath, with the pressure measured at moments of zero flow during breathing. Measurement of dynamic lung compliance at increasing respiratory frequencies allows estimation of the frequency dependence of compliance. A fall in dynamic lung compliance as frequency increases implies narrowing of some of the distal airways. Thus, in the absence of abnormalities in total RAW or FEV_1 (which, as described previously, are largely determined by resistance in large airways), decreased dynamic lung compliance suggests possible narrowing of small peripheral airways.[59]

Static lung compliance is the slope of the pressure-volume curve of the lung obtained during deflation from TLC.

Having the subject inhale to TLC three times standardizes the volume history and ensures minimization of the changes due to the dynamics of entry of surface-active material into the air-liquid interface. On the third inhalation the subject pauses at TLC for 3 to 5 seconds and then exhales slowly, while flow is interrupted by closing the mouth shutter for 2 to 3 seconds at each of several volumes. Repeating this maneuver four or five times provides enough data to characterize the relationship between the change in lung volume and the change in PL over the entire VC (eFig. 31.8). To fix the resultant curve on the volume axis requires knowing absolute lung volume at some PL. This is easily measured directly if the curve is obtained with the subject in a body plethysmograph. Alternatively, but less accurately, lung volume (TLC, FRC, or RV) measured at another time by a gas dilution technique, for example, may be assumed to be the same at the time of measurement of lung compliance.

The data obtained are conveniently expressed in terms of lung compliance: the ratio of the change in lung volume to the change in PL. However, it is clear that lung compliance changes with lung volume, with the highest values observed at volumes around FRC and lower values prevailing as the lungs are expanded more nearly to TLC (see eFig. 31.8). Compliance therefore is usually reported as the chord slope from FRC to 0.5 L above FRC. However, when this convention is used, the value expressed for lung compliance is influenced by the determinants of FRC, rather than simply by the relationship between lung volume and distending pressure. Another value commonly calculated is the *coefficient of retraction* (CoeffR: lung elastic recoil pressure at TLC divided by TLC). Normal values are available for both compliance and CoeffR (compliance ≈0.12–0.28 L/cm H_2O and CoeffR ≈4–8 cm H_2O/L),[60] although the great variability of these measurements limits their utility in individual patients. Because lung compliance is so dependent on lung volume (compliance can fall by 50% with resection of one lung, for example, even though the elastic properties of the remaining lung are unaltered), its variability can be somewhat reduced by correcting it for height, predicted TLC, or measured FRC.[61]

Maximum information about lung elastic recoil can be derived by analyzing the whole curve when, for example, static lung elastic recoil pressure is plotted against lung volume expressed as a percentage of predicted TLC.[62] Such a plot often makes it obvious whether a reduction in TLC is a function of the inability to generate an adequate lung elastic recoil pressure due to neural, muscular, or chest wall disease or is caused by a true loss of lung compliance. If lung compliance is reduced, it can still be difficult to determine whether the abnormality is due to a true increase in elastic forces or to a decrease in the number of alveoli communicating with the airways (see later discussion).

Expiratory Flow Limitation Assessed by Comparison of Tidal and Maximal Flow-Volume Curves

1. Tidal and maximal flow curves are usually aligned on the assumption that TLC does not change during exercise and hence that changes in IC reflect changes in end-expiratory lung volume. Most reports indicate that TLC does not change with exercise in individuals with COPD or without lung disease,[64,65] although one small study found that TLC does increase in normals.[66] This approach assumes that the patients can make a truly maximal inspiratory effort during exercise. In fact, some COPD patients are not able to perform these maneuvers during exercise. In addition, any concern for respiratory muscle weakness should lead to caution in interpreting changes in IC as changes in EELV.
2. Maximal expiratory airflow depends on the volume and time history of the preceding inspiration.[67,68] However, the previous volume and time history always differ between tidal breathing and maximal inspiration. Therefore assessment of flow limitation by comparison of tidal and maximal flow-volume curves may lead to erroneous assumption of abnormal airway collapsibility, even if the measurements are made plethysmographically.
3. In nearly all reports, the tidal and forced flow-volume loops were obtained from measurements of expired gas volume at the mouth. The assumption is made that both loops develop at the same lung volume when, in fact, the forced loop may be at a smaller volume due to gas compression during the forced maneuver. Such gas compression artifacts can be avoided by measuring volume with a body plethysmograph, as suggested by Ingram and Schilder.[69]
4. Exercise may result in bronchodilation and other changes in the mechanical properties of the lungs, which may affect both the tidal and maximal flow-volume curves.[64]
5. Evaluation of expiratory flow limitation has also been studied by comparison of tidal flow-volume curves with partial flow-volume curves, thereby keeping the previous volume history constant. Although theoretically appealing, this approach often neglects the effect of the previous time history (which affects both partial and maximal forced flow-volume curves)[67,70] and is not

practical in most patients with COPD at rest, let alone during exercise.

Thus it appears that study of expiratory flow limitation on the basis of comparison of tidal with maximal flow-volume curves can have problems. An alternative approach, called the negative expiratory pressure method, has been developed by Koulouris and associates[71] (see eFig. 31.9). This method does not require flow-volume maneuvers by the subject, nor must it be performed in a body plethysmograph. A negative pressure is applied at the mouth during a tidal expiration, and the ensuing expiratory flow-volume curve is compared with that of the previous tidal expiration. With this method the volume and time history of the standard and test breath are the same. The negative expiratory pressure method has been validated in mechanically ventilated patients by direct comparison with isovolume pressure-flow curves.[72] It has also been used to study stable COPD patients at rest and during exercise.[73,74]

Ninane and associates[75] have offered another approach to the technical issues associated with comparing tidal breathing with maximal flow curves. They described a method to detect expiratory flow limitation by manual compression of the abdominal wall. In healthy subjects, abdominal compression causes decreased abdominal diameter, increased gastric and pleural pressures, and increased expiratory flow. This method has been used successfully to study expiratory flow limitation in neonates, but in adults with COPD abdominal compression fails to increase expiratory flow despite increased gastric and pleural pressures.[75]

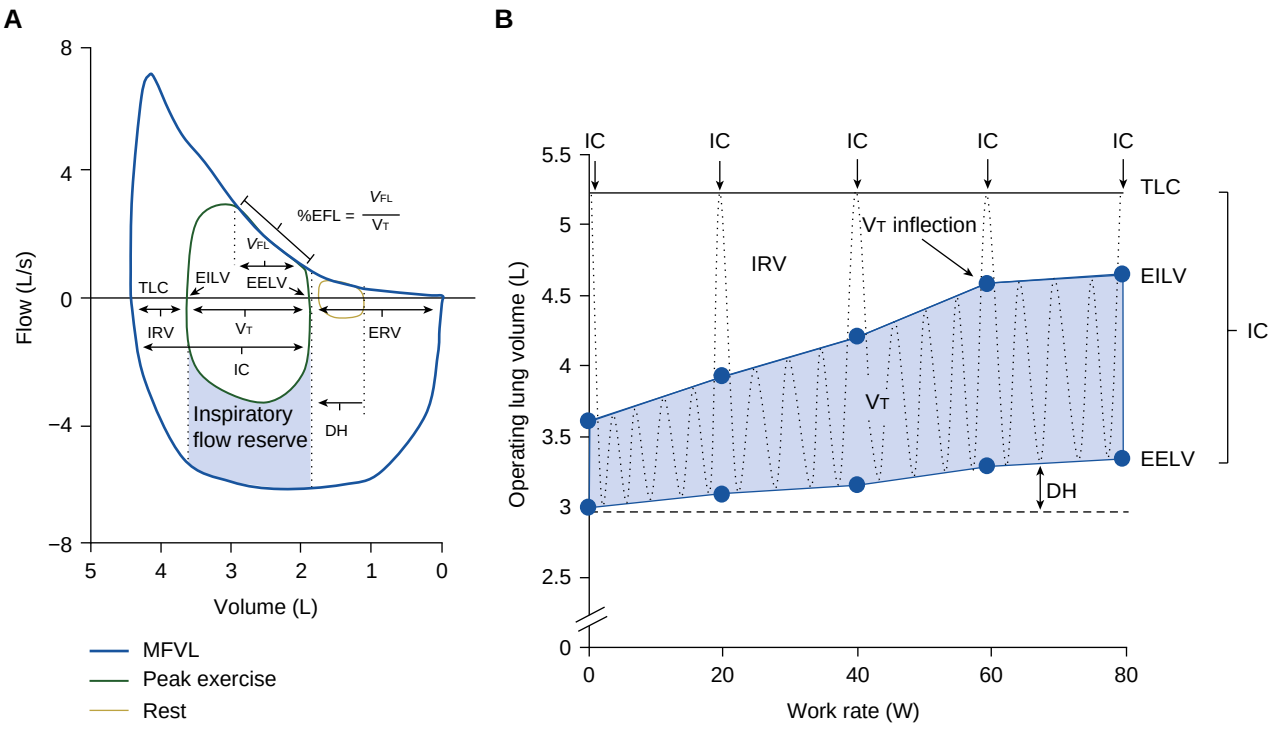

Figure 31.10 ***Dynamic hyperinflation*** **(DH) with exercise, showing the** ***expiratory flow limitation*** **(EFL) and decrease in** ***inspiratory capacity*** **(IC).** (A) Example of a resting (*lighter line*) and peak exercise (*darker line*) tidal breath superimposed within a maximum flow-volume loop (*thick black line*). The position of the tidal breaths along the x-axis is based on the measurement of end-expiratory lung volume as determined from inspiratory capacity maneuvers. (B) Operating lung volume plot versus cycle work rate. IC maneuvers are performed at rest (0 W) and every 20 W throughout exercise. Note how the IC decreases with DH. EELV, end-expiratory lung volume; %EFL, percentage of expiratory flow limitation; EILV, end-inspiratory lung volume; ERV, expiratory reserve volume; MFVL, maximum flow-volume loop; V_{FL}, volume of the tidal breath that is flow limited on expiration; V_T, tidal volume. (From Guenette JA, Chin RC, Cory JM, et al. Inspiratory capacity during exercise: measurement, analysis, and interpretation. *Pulm Med*. 2013;2013:956081.)

may even be present in mild COPD, causing dyspnea and reduced exercise tolerance independent of the severity of airflow obstruction as assessed by other parameters such as FEV_1. Supplemental oxygen, via a reduction in respiratory rate, and bronchodilators, via an increase in expiratory flow, have been shown to improve exercise capacity in COPD in part through reduced dynamic hyperinflation.

DISTRIBUTION OF VENTILATION

For discussion of ventilation, blood flow, and gas exchange, see Chapter 10.

Tests that measure distribution of ventilation are very sensitive to abnormalities in lung structure and function but are nonspecific. Thus they are useful for detecting the presence of abnormal function early when other test results are normal or to confirm the presence of airflow obstruction when other test results are only mildly abnormal. They may be very useful in epidemiologic studies, such as evaluation of the effects of smoking or air pollution in large populations.

Measurements of Distribution Of Ventilation

The physiologic determinants of distribution of ventilation are reviewed in Chapter 10. eFigure 31.10 illustrates the concept of uneven distribution of inspired gas.

Additional information on the single-breath N_2 washout test is available at ExpertConsult.com.

Multiple-Breath Nitrogen Washout

The measurement of residual N_2 after *multiple-breath, open-circuit N_2 washout* (MBNW) is used to assess the uniformity of the distribution of ventilation.[82] In the MBNW, continuous breath-by-breath measurement of N_2 concentration at the mouth during tidal breathing of pure oxygen is performed until end-tidal N_2 concentration falls to less than 1%. The fall in end-tidal N_2 concentration on a breath-by-breath basis is related to the cumulative volume of ventilation or breath number. By extending the N_2 washout time to 30 minutes or more in subjects with severe chronic airway obstruction, estimates of lung volume may be obtained that compare favorably with those calculated by plethysmographic or radiographic methods.[83]

There are three major indexes derived from the MBNW.[84] The *lung clearance index* (LCI) is the total number of FRC-sized breaths (termed lung turnovers) that are required to reduce the N_2 concentration down to 1/40 of its starting value. As ventilation becomes more uneven, the measured LCI increases, because more lung turnovers are required to dilute the ambient N_2. The LCI is abnormal in obstructive airways disease, such as asthma, COPD, and *cystic fibrosis* (CF). The LCI is a global measure of ventilation heterogeneity but does not allow any specific anatomic localization of the site of heterogeneity. Two other indices, S_{cond} and S_{acin}, attempt to do this, based on modeling the lung in terms of the two types of mechanisms of gas transport. The first mechanism is gas transport due to convection, driven by pressure gradients, which takes place

Resident Gas, Single-Breath Test

The *single-breath N_2 washout test* (sometimes called the *single-breath oxygen test*) is designed to assess the uniformity of gas distribution in the lungs and the behavior of the dependent airways.[76] It can be important in the evaluation of patients with suspected upper airway obstruction to determine if there is associated disease of the airways distal to the trachea. At present, the most clinically useful aspect of the test is the measurement of the slope of the phase III (the alveolar gas plateau; see eFig. 31.10) to determine the uniformity of gas distribution. The single-breath N_2 washout test has abnormal results in both restrictive and obstructive ventilatory defects. Presumably, this reflects its sensitivity to abnormalities in the mechanical properties of the lungs. Even though interstitial pulmonary fibrosis or emphysema may affect the lung diffusely, the process is never distributed homogeneously. Thus some regions of lung fill and empty more slowly than others, resulting in abnormal single-breath N_2 test results.

Protocol. The subject inspires a single breath of pure oxygen from RV to TLC (inspiratory VC maneuver); nitrogen concentration at the mouth during exhalation is measured with a N_2 analyzer or mass spectrometer. At end inspiration, the dead space is filled with oxygen that has just been inspired (see eFig. 31.10). At the beginning of the subsequent expiratory VC maneuver, the N_2 meter continues to record 0% N_2 because the first gas to leave the lungs is from conducting airways—the so-called anatomic dead space (phase I) (see eFig. 31.10). Subsequently, the N_2 concentration increases in a sigmoid curve upward and reflects mixing of gas from dead space and alveoli (phase II). The slightly sloping plateau in phase III reflects the almost constant nitrogen concentration in alveolar gas. If inspired oxygen is distributed evenly to all alveoli so each has the same N_2 concentration, then phase III of the N_2 tracing is almost horizontal (alveolar plateau). However, if inspired oxygen is distributed unevenly, as happens to a small extent even in healthy subjects, then the end-inspiratory N_2 concentrations are not equal throughout the lung. The concentrations of exhaled N_2 from different alveoli are not recorded as a horizontal line; the first portion of phase III usually contains a lower N_2 concentration than the last portion.

The analysis of these curves is not entirely objective. When the same observer reads such curves twice under "blind" conditions, agreement between the two measurements is poor. This variability appears to be due to differences between individual lungs; when a subject generates such a curve, usually all curves produced by that subject are difficult to analyze. On the other hand, if a subject generates a curve that is easy to analyze, most curves produced by that subject are reproducible. Obviously, analysis of these curves requires good judgment; some curves, although conforming to the criteria of acceptability, are unreadable and therefore should be ignored. It appears difficult, if not impossible, at present to establish a uniform set of criteria for this analysis.[77]

Normal Values. The slope of phase III (percentage of N_2 per liter) is determined as the line of best fit (by least-squares linear regression) between 70% of VC and the onset of phase IV. In most cases, the range about the mean of three measurements of the slope of phase III should not be greater than ±0.5% N_2/L.[78] The variations appear to be independent of the time of day at which the test is performed, but the slope of phase III does depend on inspiratory flow.[79]

A lung clearance index can be measured not only by resident N_2 but also by exogenous tracer gas using a mass spectrometer or, more recently, a novel gas analyzer (Innocor), thus providing a potentially useful clinical tool as an early marker for disease in children and adults.[80] With the use of exogenous tracer gases not found in normal air, patients can perform the washout tests while breathing air and not pure oxygen, as is needed for N_2 washout. By breathing air, the patient avoids the unwanted changes in ventilation related to oxygen breathing. Sulfur hexafluoride, an inert gas, is a tracer used for this purpose.[81]

in the conducting airways; this is quantified by S_{cond}. The second mechanism is gas transport due to diffusion-convection flow driven by concentration gradients, which takes place in the extreme periphery of the lung, likely beginning at the entrance to the portion of lung distal to a terminal bronchiole (the last purely conducting airway), also called an acinus; this is quantified by S_{acin}. During MBNW, the slope of the phase III (alveolar gas plateau; see eFig. 31.10) of each breath is measured, normalized by the N_2 concentration in that breath, and plotted against the number of lung turnovers. The slope of the regression of the normalized phase III slopes between 1.5 and 6 lung turnovers is thought to represent convection-dependent ventilation heterogeneity in the conducting airways, and is termed S_{cond}. This value (S_{cond}) is subtracted from each measurement of normalized phase III slope to derive the contribution of the diffusion-convection–dependent heterogeneity of ventilation, termed S_{acin}. The clinical significance of S_{cond} and S_{acin} is just beginning to be appreciated, particularly as they relate to asthma severity and control.[85]

DIFFUSION

Tests for measuring diffusing capacity permit diagnosis of an impaired surface area for the transfer of gases from the alveoli to the pulmonary capillaries, sometimes even during early stages of disease. Many pulmonary diseases may manifest by a diffusion defect when there is no abnormality apparent in other routine PFTs. These include interstitial lung diseases, asbestosis, scleroderma, lupus erythematosus, emphysema, pulmonary thromboembolism, diffuse metastatic cancer of the lungs,[86] *Pneumocystis jirovecii* pneumonia, and rejection of a transplanted lung. There is now considerable evidence correlating the diffusing capacity and its subdivisions (*membrane diffusing capacity* [DM] and *pulmonary capillary blood volume* [VC]) with the morphometric study of normal lungs.[87] Similar correlative studies of the lungs of patients with emphysema[38] document the structural basis for the abnormal alveolar-capillary interface as a result of decreased numbers of patent pulmonary capillary segments.[88] Finally, the tests are relatively simple (as far as the patient is concerned) and easy to repeat, making it practical to study the diffusing capacity frequently and to evaluate the effects of therapy or the natural history of the disease.

GENERAL PRINCIPLES

The measurement of pulmonary diffusing capacity (also known as transfer factor) requires the use of a gas that is more soluble in blood than in lung tissues. Oxygen and carbon monoxide are two such gases, and their chemical reaction with hemoglobin is responsible for this unusual pattern of "solubility." Both molecules measure the same process, and estimates of D_{LO_2} can be made by multiplying the *diffusing capacity for carbon monoxide* (D_{LCO}) by 1.23. However, the more difficult and time-consuming method of measurement by oxygen has been displaced by the carbon monoxide method.

For the standard D_{LCO} method, a low concentration of carbon monoxide is added to inspired air. Molecules of carbon monoxide diffuse across the alveolar capillary membrane, dissolve in the plasma, cross the *red blood cell* (RBC) membrane, and then combine with hemoglobin. The D_{LCO} is often thought of as a measure of gas exchange or the ability of the lungs to oxygenate blood. In Europe, the test is called the transfer factor for carbon monoxide. The term transfer factor is actually more accurate because the movement of gas from air to blood depends not only on diffusion but also on hemoglobin concentration. The measurement is typically measured at rest, thus yielding a result much less than the maximal capacity for transfer. *Carbon monoxide* (CO) was chosen as the test gas nearly 100 years ago because it has a high affinity for hemoglobin, 210 times that of oxygen; thus CO in the vicinity of a hemoglobin molecule binds avidly to it, and the partial pressure of dissolved CO remains very low. With such a high affinity, it was assumed that CO instantaneously combined with hemoglobin, maximizing the gradient for diffusion. In that case, changes in the D_{LCO} would only reflect changes in the total surface area and thickness of the alveolar-capillary membrane. Unfortunately, the noninstantaneous reaction between CO and hemoglobin makes interpretation of the test more complicated. In fact, some studies estimate that less than 50% of the measured D_{LCO} is determined by the surface area the lung provides to diffusion. The remainder is determined by the limited hemoglobin reservoir: As CO diffuses, it accumulates in the plasma during the maneuver. The more hemoglobin available to bind CO, the lower the accumulation of soluble CO concentration in the plasma during the test and the higher the concentration gradient for diffusion across the barrier. The hemoglobin reservoir is determined by pulmonary capillary blood volume and hemoglobin concentration. The extent to which the membrane affects the measured D_{LCO} is determined principally by the available capillary surface area exposed to the test gas; the membrane itself is very thin and likely affects CO diffusion minimally in health or disease. The transfer of carbon monoxide therefore can be considered a measure of the surface area and volume of blood-containing capillaries available for gas exchange.

D_{LCO} is calculated as follows:

$$D_{LCO} = \frac{\text{CO transferred from alveolar gas to blood (mL/min)}}{\text{Mean alveolar CO pressure} - \text{Mean capillary CO pressure (mm Hg)}} \quad \text{Eq. 13}$$

To determine the amount of carbon monoxide transferred from alveolar gas to blood per minute, it is necessary to measure the mean alveolar carbon monoxide pressure and the mean pulmonary capillary carbon monoxide pressure. The technical factors that can affect the measurement of D_{LCO} are in Table 31.2. There are several tests available.

The standard single-breath D_{LCO} test is probably the most widely used and the best standardized of the various methods described. It has been used in the largest number of normal subjects and has been corrected for the effects of age, body size, sex, ethnic background, cigarette smoking, and physiologic factors.

Table 31.2 Technical Factors That Affect Measurement of D_{LCO}

Factor	Effect on D_{LCO}	Mechanism
Incomplete maximal inspiration	Reduced*	Reduced alveolar surface area and capillary blood volume
Incomplete exhalation before maximal inspiration	No change	
Valsalva maneuver during breath hold	Reduced	Less capillary blood volume
Mueller maneuver during breath hold	Increased	More capillary blood volume
Carboxyhemoglobin (without adjustment)	Reduced	Fewer heme sites available to bind CO
Anemia (without Hb adjustment)	Reduced	Fewer heme sites available to bind CO
Polycythemia	Increased	More heme sites available to bind CO
Altitude (low inspired partial pressure of oxygen)	Increased	More heme sites available to bind CO
Supine position, exercise, left-to-right shunt	Increased	Capillary recruitment/filling

Although changes in D_{LCO} during the menstrual cycle, independent of hemoglobin concentration, have been reported, the results are inconsistent. Reports of diurnal variation and the effect of β_2-agonists (in health and in patients with airflow obstruction) on D_{LCO} and V_A are also inconsistent. ATS/ERS guidelines conclude that the weight of evidence is against a significant effect of β_2-agonists on the D_{LCO}. Some carbon monoxide sensors may be affected by exhaled ethanol and ketones.

*The effect of incomplete inspiration is nonlinear, with small changes in D_{LCO} near TLC. This nonlinear relationship between lung volume and D_{LCO} likely reflects the complex effects of alveolar and capillary unfolding and stretching as lung volume increases.

ATS, American Thoracic Society; CO, carbon monoxide; D_{LCO}, diffusing capacity for carbon monoxide; ERS, European Respiratory Society; Hb, hemoglobin; TLC, total lung capacity; V_A, alveolar volume.

SINGLE-BREATH METHOD

In the single-breath method the patient inhales a gas mixture containing 0.3% carbon monoxide and a low concentration of inert gas (0.3% neon, 0.3% methane, or 10% helium), then holds his or her breath for approximately 10 seconds. During the breath-hold, carbon monoxide leaves the air spaces and enters the blood. The larger the diffusing capacity, the greater the amount of carbon monoxide that enters the blood in 10 seconds. In the single-breath test, alveolar P_{CO} is not maintained at a constant concentration, because carbon monoxide is absorbed during the period of breath-holding.

The equation used in the single-breath method is as follows:

$$D_{LCO} = \frac{V_A \times 60}{(Pbar - 47) \times t} \ln \frac{FACO_0}{FACO_t} \qquad \text{Eq. 14}$$

where $FACO_t$ is fractional alveolar carbon monoxide concentration at time (t), *t* is breath-hold time in seconds, *Pbar* is barometric pressure (in mm Hg), V_A is alveolar volume (in mL, in *standard temperature, pressure, and dry* [STPD]) obtained from the ratio of inspired and expired inert gas concentrations and inspired volume, $FACO_0$ is the inspired carbon monoxide concentration corrected for dilution by the RV as estimated by the ratio of inspired and expired inert gas concentrations, and *60* is the conversion factor for seconds to minutes.

Analyses are performed with an infrared analyzer or gas chromatograph, and no blood samples are needed. An inert gas such as helium, methane, or neon must be inhaled with carbon monoxide to correct for dilution of inspired carbon monoxide.

Factors such as inhalation time, breath-holding time, breath-holding lung volume, exhalation time, and the size and portion of alveolar gas sampled have all been shown to affect the single-breath D_{LCO}. Ogilvie and colleagues[89] recognized that these discrepancies could exist either because diffusing capacity is not distributed homogeneously within the lung or because the single-breath equation ignores the fact that carbon monoxide uptake takes place during inhalation and exhalation as well as during breath-holding. They tried to circumvent these problems by standardizing the test.

Jones and Mead[90] showed that, because the diffusion equation was valid only for breath-holding, there are errors in calculation of single-breath D_{LCO} owing to the nature of carbon monoxide uptake during inhalation and exhalation. Because delay in collection of the alveolar sample has been shown to cause an apparent increase in D_{LCO}, the *American Thoracic Society* (ATS) Epidemiology Standardization Project[14] developed a variation of the Jones and Mead method that took this problem into account and placed strong emphasis on an automated system, which standardized the procedure and is available in most commercial systems.

Standardization of the Single-Breath Methods

The ATS has recommended standardization of the test using acceptability criteria, including rapid inspiration, inspired volume at least 90% of largest VC, breath-hold time between 8 and 12 seconds, sample collection completed within 4 seconds of the start of exhalation, and adequate washout and sample volumes.[91] At least two acceptable D_{LCO} measurements within 2 mL/min per mm Hg are required to meet criteria for repeatability (at STPD). The mean of the acceptable tests is reported. Calculations are standardized for breath-hold time and adjusted for dead space, gas collection conditions, and carbon dioxide concentration.

Refer to ExpertConsult.com for three additional methods to measure the diffusing capacity (steady-state, rebreathing, and intrabreath).

TECHNICAL AND PHYSIOLOGIC FACTORS

Hemoglobin. Adjustment for hemoglobin is not mandatory but is desirable. Unadjusted values must always be reported even if the adjusted values are also reported. The adjustment should be made on the observed, not the predicted, value. Hemoglobin is reported in grams per deciliter, and the method of Cotes and associates[123] should be used to

Other Protocols for Measurement of Diffusing Capacity

Steady-State Method. In the steady-state method, the patient breathes a mixture of 0.1% carbon monoxide in air for several minutes through a one-way valve system. During the last 2 minutes, exhaled gas is collected in a plastic bag and analyzed for oxygen, carbon dioxide, and carbon monoxide concentrations (requiring rapidly responding gas analyzers). During collection, an arterial blood sample is drawn and analyzed for P_{CO_2}.[92] The *amount of carbon monoxide transferred from the air spaces to capillary blood per minute* ($\dot{V}_{CO}$) can be calculated from the inspired and expired gas concentrations and the *volume of gas exhaled per minute* ($\dot{V}_E$) at standard conditions (i.e., STPD, where the "ideal gas" is corrected to standard pressure dry [760 − 47 mm Hg] and 0°C or 273°K, where 1 mole of ideal gas occupies 22.4 L). The mean *alveolar fractional concentration of carbon monoxide* (F_{ACO}) is estimated from the Bohr equation for *dead space volume divided by tidal volume* (V_D/V_T). Assuming that V_D/V_T for carbon dioxide and carbon monoxide are the same, F_{ACO} can be calculated with the following equation, using the *fractional concentrations of mixed expired carbon monoxide* (F_{ECO}), mixed *expired carbon dioxide* (F_{ECO_2}), *alveolar carbon dioxide* (F_{ACO_2}), and *inspired carbon monoxide* (F_{ICO}):

$$F_{ACO} = F_{ICO} - \frac{F_{ACO_2}}{F_{ECO_2}}(F_{ICO} - F_{ECO})$$
$$P_{ACO} = F_{ACO}(Pbar - 47) \qquad \text{Eq. 15}$$

This value (*alveolar carbon monoxide* [P_{ACO}]) can now be used to calculate pulmonary diffusing capacity:

$$D_{L_{CO}} = \frac{\dot{V}_{CO}}{P_{ACO}} \qquad \text{Eq. 16}$$

Steady-state $D_{L_{CO}}$ can be measured during tidal breathing, anesthesia, sleep, and exercise. Nevertheless, the method is not used widely because its results are more subject to error than those of the single-breath technique, especially in patients with uneven distribution of ventilation or with ventilation-perfusion abnormalities. In these conditions a decreased $D_{L_{CO}}$ (steady state) may reflect impairment of the ventilation-perfusion ratio $\dot{V}_A/\dot{Q}_C$, where $\dot{V}_A$ is alveolar ventilation and $\dot{Q}_C$ is pulmonary capillary blood flow, or an alteration of pulmonary gas transfer. A major problem is the estimation of alveolar carbon monoxide concentration. In addition, the method requires obtaining an arterial blood sample and is extremely sensitive to changes in breathing pattern. The "end-tidal" modification[86] of the steady-state method does not require arterial blood samples but suffers from even more sources of error. Both approaches to the estimation of diffusing capacity really reflect ventilation-perfusion abnormalities in the lungs more than characteristics of the alveolar-capillary surface and functioning pulmonary capillaries. Marshall[93] has reported another modification of this method, in which mixed venous P_{CO_2} was computed by an equilibration method that avoids arterial puncture but may be too imprecise for use in the equations (Eqs. 15 and 16) at rest.

Rebreathing Method. In the rebreathing method[94] the patient rebreathes the test gas (air plus a low concentration of CO) from a reservoir, the volume of which equals the patient's FEV_1. The patient exhales to RV before a valve is turned, then rebreathes from the reservoir, which should be emptied with each inspiration. Rebreathing continues for 30 to 45 seconds at a controlled rate of 30 breaths/min to ensure mixing between lung and reservoir. The volume of RV plus reservoir, multiplied by the change in CO concentration, equals the CO volume transferred. Mean capillary P_{CO} is neglected. Mean alveolar P_{CO} is calculated from the same equation used in the single-breath method. Compared to the single-breath and the steady-state methods, the rebreathing method for measuring $D_{L_{CO}}$ is more variable and requires considerable patient cooperation, but it is less influenced by abnormalities in distribution of ventilation and is easier to use during exercise. The rapid respiratory rate may be difficult for some patients to maintain and is not physiologic.

Intrabreath Method. In the intrabreath (within-breath or exhaled) $D_{L_{CO}}$ method, $D_{L_{CO}}$ is measured at increments of the exhaled volume using a method devised by Newth and associates[95] and modified by Hallenborg and colleagues.[96] The intrabreath method requires a special, very rapid infrared analyzer, but this is also commercially available. Because this method does not require a breath-hold and expiratory flow can be controlled by a critical orifice, the intrabreath method is probably the easiest for sick patients to perform of the four methods (i e., single-breath, steady-state, rebreathing, and intrabreath). With proper filters the same analyzer can be used to measure methane, acetylene, and carbon monoxide simultaneously. Diffusing capacity can be measured during exercise to define distensibility of the capillary bed using the intrabreath or three-gas iteration method, but this also requires extensive validation and establishment of predicted normal values.[97–99]

Intrabreath Protocol. As originally described, the subject performs two VC maneuvers, then exhales to RV and rapidly inhales a mixture containing 0.3% carbon monoxide, 15% helium, 21% oxygen, and the remainder N_2 from a bag-in-box. After a 3-second breath-hold, the subject exhales while watching a flow signal to maintain a constant flow of 0.5 L/sec. Carbon monoxide concentrations are measured continuously with a rapidly responding infrared meter, and helium concentrations are measured with a mass spectrometer. Airflow is measured with a pneumotachygraph and integrated electrically to obtain volume. Data are converted from analog to digital form at 30 points per second and recorded by a digital computer to adjust carbon monoxide and helium recordings for time lags and to remove cardiac oscillations using a sliding 30-point curve-averaging technique. The exhaled VC is divided into 2% decrements, and the corresponding exhaled carbon monoxide and helium values are used for calculations. The initial part of the VC, until the onset of phase III of the helium curve, is discarded as dead space. The lower portion of the VC, after the onset of phase IV of the helium curve, is also discarded because of uncertainties regarding contributions by dependent regions to expired gas concentrations. Approximately 40 data points are obtained over the lower 80% of the exhaled VC, and the rate of carbon monoxide uptake is calculated over 10% intervals of the exhaled VC (e.g., 20–30%, 22–32%). Alveolar volume is calculated at the midpoint of each 10% interval by subtracting the

exhaled volume from TLC (measured by the single-breath helium dilution method). Intrabreath D_{LCO} is calculated in each interval by the Krogh equation[100] and plotted against exhaled volume.

Although more complicated than the standard single-breath method, this technique makes no assumptions about the initiation of carbon monoxide uptake or the volume at which carbon monoxide uptake manifested, measures carbon monoxide uptake directly during the entire maneuver, and can be used during exercise as well as at rest. The method does require a rapidly responding carbon monoxide meter or special modification of a mass spectrometer to make the number of measurements of carbon monoxide concentration required during the single exhalation. The intrabreath method has been useful in detecting pulmonary hemorrhage[96] and pulmonary vascular obstruction.[101] The method is now available commercially using a rapidly responding infrared analyzer. With appropriate filters, the device can measure not only carbon monoxide but also methane (to measure tracer gas dilution) and acetylene (to measure pulmonary capillary blood flow to ventilated lung units), and the response to all three gases is linear.[102–105]

Three-Equation Method for Calculating the Single-Breath D_{LCO}. Graham and associates[106] have described a method of calculating D_{LCO} that uses separate equations for the inhalation, breath-hold, and exhalation phases of the single-breath maneuver rather than trying to force them to fit the breath-hold equation. The method is now available commercially using a rapidly responding infrared analyzer. This method has been reported in a theoretical paper,[107] analyzed in a lung model, and compared with three conventional methods for determining the size and timing of the alveolar sample and the breath-hold time: standard Ogilvie method,[89] the Jones-Mead modification,[90] and the ATS epidemiology standardization modification of the Ogilvie method.[14] It has also been reported during exercise.[97–99]

Although D_{LCO} values calculated using the three conventional methods showed large changes with variations in inspiratory flow rates, inspiratory volumes, and collection times, the three-equation method yielded calculations of D_{LCO} that were minimally affected by these changes.[106] These results agree with previous results obtained in the lung model, support the hypothesis that diffusing capacity is independent of lung volume, and indicate that the three-gas iteration method significantly improves the accuracy and precision of single-breath measurements.[108] The three-gas iteration method may be more reproducible and is unaffected by a wide variety of factors that alter the single-breath or intrabreath methods, especially by abnormalities in distribution of ventilation. More normal data are needed, as is validation in other laboratories, but the method is commercially available.

Subdivisions of the Total Diffusing Capacity. It is possible to separate the pulmonary diffusing capacity into its two components: the *membrane diffusing capacity* (DM) and the component related to the *volume of blood in the pulmonary capillaries exposed to alveolar air* (Vc). Nonetheless, it has been shown that almost all decreases in diffusing capacity are due to decreases in the Vc (eTable 31.1 and Hughes and colleagues[109]).

$$1/D_{LCO} = 1/\theta Vc + 1/DM \qquad \text{Eq. 17}$$

A number of reasonable assumptions were made to distill the complex diffusion reaction of CO in the lung to Eq. 17 that separates the D_{LCO} into the sum of two resistances.[110] The resistance $1/DM$ represents passive diffusion through an alveolar-endothelial membrane barrier of less than 0.6 μm and plasma around the RBCs. In normal lungs, D_M is very large, so most of the resistance is a result of CO binding to hemoglobin. It is important to note that $1/D_M$ is independent of alveolar O_2 concentration. The resistance of non-instantaneous binding of CO by hemoglobin is represented by $1/\theta V_C$, where θ is the rate in mL/min/mm Hg/mL blood of chemical combination, and V_C is the volume of capillary blood exposed to alveolar air. Note that $1/\theta V_C$ changes with alveolar O_2 concentration because O_2 competes with CO for the same Hb binding sites, causing θ to decrease with increasing O_2 concentration. Anemia reduces θ. The success in applying this equation to predict the relationship between D_{LCO} and hemoglobin concentration, and in relating structure to function across disease states, is remarkable considering that the D_{LCO} on the left side is computed using Eq. 14, which incorrectly assumes capillary CO gas tension is zero.

The method of separation depends on measurement of D_{LCO} at different alveolar oxygen pressures. When alveolar oxygen is increased by breathing enriched oxygen mixtures, oxygen molecules compete with carbon monoxide molecules for reactive sites on hemoglobin, thereby decreasing carbon monoxide uptake by the RBCs. However, even at the higher oxygen concentration, transfer of carbon monoxide across the alveolar-capillary membranes is presumed to be unaffected. Thus measurements of D_{LCO} at 21% oxygen and at several higher concentrations of oxygen permit separation of the two components of the D_{LCO} (eFig. 31.11).[111] The assumptions that were made to derive Eq. 17, the method of separation, and values for θ have been challenged.[112]

Diffusing Capacity for Nitric Oxide

The *diffusing capacity of the lung for nitric oxide* (D_{LNO}) is a relatively new PFT and similar in many ways to the more established D_{LCO}.[113] It differs from the latter in being independent of P_{O_2} and the hematocrit. It has been suggested that D_{LNO} can be used to describe pulmonary DM directly.[114]

Diffusion properties of nitric oxide are similar to those of carbon monoxide; however, its rate of reaction with RBCs is much greater.[115] This higher affinity between nitric oxide and hemoglobin strengthens the assumption that the concentration of nitric oxide on the capillary side of the membrane remains nearly zero during diffusion and thereby markedly reduces the dependence of D_{LNO} on Vc. Therefore D_{LNO} primarily reflects DM, whereas D_{LCO} depends on both DM and Vc.[113,115] In combination with D_{LCO}, Vc and DM can be determined in a single maneuver, based on the equation for the serial connection of resistances.[116] Using the combined D_{LNO}/D_{LCO} method, patients with COPD,[117] pulmonary arterial hypertension,[118] and parenchymal lung diseases[119,120] have been studied, as well as the effects of exercise.[115,116,121] In addition, reference values have been published.[122] The clinical utility of the D_{LNO}/D_{LCO} method remains to be determined by studies of healthy subjects under various experimental conditions and by studies of diverse patients by various laboratories.

make the adjustment, where D_M is the membrane diffusing capacity and V_C is the pulmonary capillary blood volume.

Carboxyhemoglobin. Heavy smokers may have as much as 10–12% carboxyhemoglobin in their blood, and therefore the back-pressure of carbon monoxide in mixed venous blood entering the pulmonary capillaries cannot be assumed to be zero in such individuals. The steady-state method is more sensitive to errors caused by this problem than the single-breath technique. Carbon monoxide back-pressure may be estimated, and D_{LCO} calculations may be corrected for back-pressure of carbon monoxide using the Haldane equation.[123,124] Alternatively, carboxyhemoglobin may be measured directly.[125] In either case, the measured D_{LCO} is adjusted, and both the unadjusted and the adjusted values are reported. D_{LCO} measurements should not be performed on patients who have been breathing oxygen-enriched mixtures immediately before the test; at least 20 minutes of breathing room air should be allowed before measurement of D_{LCO}.

Graham and associates[126] demonstrated that carbon monoxide back-pressure has a more complex effect than suggested in the ATS standardization statement. To adjust properly for the effect of carbon monoxide on the diffusing capacity, not only must the direct effect of carbon monoxide back-pressure build-up be corrected, but also the indirect anemia effect of increasing carboxyhemoglobin.

Altitude. As altitude increases and *fractional concentration of inspired oxygen* (F_{IO_2}) remains constant, *pressure of inspired oxygen* (P_{IO_2}) decreases and D_{LCO} increases approximately 0.35% for every 1-mm Hg decrease in alveolar P_{O_2}.

If alveolar P_{O_2} is not available, adjustments may be made for interpretative purposes, assuming a mean P_{IO_2} of 150 mm Hg at sea level and assuming $P_{IO_2} = 0.21(Pbar - 47)$.

Lung Volume. Adjustment of the D_{LCO} for lung volume is a controversial issue. A primary measurement from the single-breath D_{LCO} is K_{CO} (the CO transfer coefficient), the portion of equation (Eq. 14) that is multiplied by the computed V_A, which is reported at *body temperature (37°C) and standard pressure fully saturated with water vapor (760 mm Hg)* (BTPS) but converted to STPD to calculate D_{LCO}. K_{CO} can be computed from reported data as D_{LCO}/V_A, which leads to the suggestion that D_{LCO} can be corrected or normalized for the lung volume accessible to test gas. However, D_{LCO}/V_A fails to correct for inadequate inspired vital capacity because D_{LCO} decreases far less than the amount of lung volume below TLC. This finding may be due to the complex relationship between increasing lung volume, alveolar-capillary surface area, and capillary blood volume as the membrane unfolds and stretches.[91] In disease states, the intent of the D_{LCO} is to quantify the capability of the lung as a whole—healthy and diseased portions together—to participate in gas exchange. One cannot assume that areas of lung inaccessible to test gas have a normal capillary bed. The variability in V_A and K_{CO} within diseases[127] and the low predictive value of K_{CO} for hypoxemia[128] further limit the clinical utility of K_{CO}. Even after lung resection, changes in blood flow make an abnormal K_{CO} an unreliable parameter by which to detect disease in the remaining lung tissue. Examination of K_{CO} and V_A separately may aid in interpretation of the pathophysiology behind a reduced or increased D_{LCO}, but as of yet the evidence base for its clinical utility is not robust.[129,130] A somewhat related parameter, $FVC\%/D_{LCO}\%$, has promise as part of a multivariate screening tool for pulmonary hypertension in scleroderma[131] but may increase cost of screening compared to echocardiography alone. A method to adjust D_{LCO} and K_{CO} to actual lung volume has been derived from healthy humans, but its role in clinical decision making remains to be established.[132]

Additional physiologic factors affecting the diffusing capacity are discussed at ExpertConsult.com.

REGULATION OF VENTILATION

Ventilatory regulation may be assessed by measuring the ventilator response to hypoxia or hypercapnia or by measuring the overall respiratory drive. The response to hypoxia and hypercapnia has been assessed using rebreathing methods, which are less time-consuming and tiring than classic steady-state methods. In one rebreathing method described by Severinghaus and associates,[144] rapid step changes in the patient's P_{O_2} while P_{CO_2} is stabilized offer the advantage of a brief stable period of hypoxia. Respiratory drive can be assessed by measuring the *inspiratory occlusion pressure* at 100 msec (0.1 second), which is thought to reflect the entire neural output of the respiratory center. It is not influenced by conscious muscle effort and is less influenced by abnormal mechanical properties of the respiratory system than is measurement of ventilation. Other methods, including electromyographic measurements of the diaphragm, the measurement of isometric inspiratory loads, and the use of drugs that stimulate the carotid body, have not been used often enough to establish their clinical utility.[145]

See ExpertConsult.com for protocols for the measuring of regulation of ventilation.

VENTILATION-PERFUSION RELATIONSHIPS

For discussion of ventilation, blood flow, and gas exchange, see Chapter 10.

MEASUREMENTS OF VENTILATION-PERFUSION RELATIONSHIPS

Inhaled air and pulmonary capillary blood flow are not distributed uniformly or in proportion to each other, even in the normal lung. Distributions of ventilation and blood flow are altered by posture, lung volume, and exercise not only in healthy subjects but even more so in patients with respiratory disease. The most common cause of arterial hypoxemia is increased mismatching of ventilation and perfusion, resulting in regional hypoventilation relative to perfusion (eTable 31.1). Whereas samples of alveolar gas and pulmonary capillary blood cannot be obtained to analyze gas exchange, inspired and expired gas (gas entering and leaving the alveoli), mixed venous (blood entering the pulmonary capillaries), and arterial blood can be obtained and analyzed.

Specific measurements of ventilation-perfusion measurements are discussed at ExpertConsult.com.

eTable 31.1 Causes of Hypoxemia: The Effect on Alveolar-Arterial P_{O_2} Differences

Cause	Effect on Alveolar P_{O_2}	Effect on (A–a)P_{O_2}
Normal lungs/inadequate oxygenation		
Deficiency of oxygen in atmosphere	↓	↔
Hypoventilation (neuromuscular disorder)	↓	↔
Pulmonary disease		
Hypoventilation (airway/parenchymal disorder)	↓	↔
Diffusion abnormality	↔*,†	↑*,†
Ventilation-perfusion imbalance	↓† or ↔	↑†
Right-to-left shunts	↔†	↑
Inadequate transport/delivery of oxygen		
Anemia	↔	↔
General/localized circulatory insufficiency	↔	
Inadequate tissue oxygenation (abnormal tissue demand/poisoned enzymes/edema)	↔	↔

*Infrequently observed at rest but more likely during exercise in patients with pulmonary fibrosis, elite athletes at very high levels of exercise, and exercise in general at altitude. In all these cases the diffusion limitation arises from inadequate time spent by red blood cells in gas-exchanging units of the lung in the setting of increased cardiac output ± reduced pulmonary capillary cross-sectional area, rather than thickening of, or a problem with diffusion across, the alveolar-epithelial capillary-endothelial membrane.

†Unless patient is hyperventilating.

↑, increased; ↔, no change; ↓, decreased; P_{O_2}, partial pressure of oxygen.

Modified from Arterial blood oxygen, carbon dioxide and pH. In: Comroe JH Jr, Forster RE 2nd, DuBois AB, et al. *The Lung: Clinical Physiology and Pulmonary Function Tests* 2nd ed. Chicago: Year Book; 1962:140–161.

Body Size. Body size is one of the factors that probably affect normal values[4]; diffusing capacity has been found to vary with *body surface area* (BSA, in square meters) according to the following equation, derived by Ogilvie and colleagues[89]:

$$D_{L_{CO}} = 18.85\ BSA - 6.8 \qquad \text{Eq. 18}$$

A better prediction[133] is based on *height* (H, in centimeters) and *age* (A, in years):

$$\text{Males}: D_{L_{CO}} = 0.416(H) - 0.219(A) - 26.34 \qquad \text{Eq. 19}$$

$$\text{Females}: D_{L_{CO}} = 0.256(H) - 0.144(A) - 8.36 \qquad \text{Eq. 20}$$

Values for $D_{L_{CO}}$ measured by analyzing the gases with a chromatograph are approximately 6% higher than values obtained with infrared meters.[134]

Age. Maximal $D_{L_{O2}}$ (i.e., $D_{L_{O2}}$ during maximal exercise) has been found to decrease with increasing age according to the following equation:

$$\text{Maximal } D_{L_{O2}} = 0.67(H) - 0.55(A) - 40.9 \qquad \text{Eq. 21}$$

Age also affects $D_{L_{CO}}$ at rest (see previous discussion).

Exercise. Despite the important effect of a noninstantaneous reaction rate between CO and hemoglobin, carbon monoxide transfer is surprisingly not limited by pulmonary blood flow per se.[135] Instead, exercise raises $D_{L_{CO}}$ and $D_{L_{O2}}$ by enlarging the surface area of functioning alveoli in contact with pulmonary capillaries (eFig. 31.12). This is due primarily to recruitment of capillaries. Exercise causes an approximate doubling of pulmonary diffusing capacity and pulmonary capillary blood volume.[136,137] Huang and coworkers[102] studied 105 healthy subjects with the intrabreath method and reported reference equations for diffusing capacity at rest and during exercise based on age, sex, and height. Hsia and associates[137] found that $D_{L_{CO}}$ increased normally as cardiac output increased during exercise in patients who had undergone pneumonectomy compared with normal subjects. Although an upper limit to $D_{L_{CO}}$ with respect to oxygen uptake during exercise was observed by Stokes and colleagues,[138] using the intrabreath carbon monoxide method, no upper limit to $D_{L_{CO}}$ was found in normal subjects or in pneumonectomy patients with respect to cardiac output during exercise.[97,137,139] Maximal values attained during exercise in patients who had undergone pneumonectomy were less than those attained by normal controls, as might be expected because the patients had been chronic smokers and probably had emphysema in the remaining lung.

As reviewed by Ceretelli and DiPrampero,[140] whether $D_{L_{CO}}$ reaches a true plateau during exercise appears to depend on the method used and the level of exercise attained by the subjects. Kinker and associates[141] used a modified steady-state method to determine breath-by-breath $D_{L_{CO}}$ during exercise. They found that the rise of $D_{L_{CO}}$ with increasing work was attenuated at high levels of exercise (maximal oxygen uptake, or $\dot{V}O_{2max}$ approximately 4 L/min) in most subjects, suggesting that alveolar-capillary surface area tends to approach a maximum.[141] These findings are consistent with studies of capillary perfusion patterns in single alveolar walls visualized through a transparent thoracic window implanted in anesthetized dogs.[142] Results of this study agreed with a computer model of capillary flow developed by West and associates.[143]

Body Position. $D_{L_{CO}}$ is 15–20% greater in the supine than in the sitting position and 10% to 15% greater in the sitting than in the standing position because of the effects of changes in posture on pulmonary capillary blood volume.

Alveolar Oxygen Pressure. Alveolar P_{O_2} affects $D_{L_{CO}}$ because of the former's effect on the carbon monoxide reaction with hemoglobin. For example, diffusing capacity values measured at alveolar P_{O_2} values of 40 and 600 mm Hg are approximately 45 and 18 mL/min per mm Hg, respectively (see eFig. 31.11). ATS/European Respiratory Society guidelines recommend that supplemental oxygen be stopped for at least 10 minutes, if it is safe to do so, before measuring $D_{L_{CO}}$. Changes in $D_{L_{CO}}$ caused by variations in alveolar P_{O_2} in the physiologic range are much smaller. In patients with severe hypoxia (arterial P_{O_2} < 40 mm Hg), increased pulmonary blood flow and dilation of the pulmonary capillaries may increase the $D_{L_{CO}}$. Hypoxia may also increase $D_{L_{CO}}$ as a result of its effect on the reaction rate between carbon monoxide and hemoglobin.

General and Specific Protocols for the Measurement of Regulation of Ventilation

The subject should be prepared for these tests according to the recommendations of the ATS Workshop on Assessment of Respiratory Control in Humans.[146] To minimize distractions, the subject should be positioned so as to be screened from the meters, monitors, and manipulators; preferably, the subject's eyes should be closed during the test procedure.

The ventilatory responses to hypoxia and hypercapnia vary considerably even in normal individuals. To prevent extraneous influences from further increasing this variability, the following recommendations are made: (1) studies should be performed in the fasting state with the bladder empty, (2) the subject should be comfortable and should rest for at least 30 minutes before the test, (3) the room should be quiet, (4) body temperature should be determined, (5) tests may be performed in either the sitting or semisupine position, (6) consideration should be given to preliminary evidence suggesting that normal subjects may have greater hypoxic responses when using a nose clip and mouthpiece than when using a mask, and (7) tests should be performed in duplicate with at least 10 minutes of rest between tests.

Ventilatory responses to hypoxia and hypercapnia are potentially hazardous. The clinical condition of the patient should be considered when evaluating the potential hazardous effects of the test procedure, and the usual precautions for safety of the patient used in any stress test should be taken.

Breath-Holding Time

With nose clips in place, the subject exhales to RV, inhales to TLC, and holds his or her breath as long as comfortably possible. Analyses of expired gases can be made to estimate end-tidal carbon dioxide concentrations. Breath-holding time equals the average time in seconds from the end of inspiration to TLC until the first expiration. The test is repeated until the breath-holding times or end-tidal carbon dioxide concentrations are reproducible. The mean value for predicted breath-holding at TLC is 78 seconds.[147] In six normal subjects studied by Davidson and colleagues,[148] reproducibility of the test at TLC was 75 ± 3 seconds at sea level (mean ± *standard error* [SE]); subjects were trained until the expired end-tidal carbon dioxide was reproducible within 2 mm Hg.

Hypercapnic Response

As suggested by Read,[149] a reservoir bag is filled with a volume equal to the subject's V_C plus 1 L with a mixture containing 7% carbon dioxide and 93% oxygen. The subject breathes room air and exhales into the room. Expired flow and end-tidal carbon dioxide are recorded. After a period to establish a stable baseline, valves are turned so the subject breathes in and out of the reservoir bag. The test is continued until the subject stops because of dyspnea, until the end-tidal P_{CO_2} equals 9%, or until 4 minutes have elapsed.

The *ventilation in liters per minute* (BTPS) ($\dot{V}_E$), either breath-by-breath or averaged over 5 to 10 breaths, is plotted on the ordinate, and the mean end-tidal carbon dioxide (in mm Hg) is plotted on the abscissa for the same periods (eFig. 31.13). The slope change in $\dot{V}_E$ $\Delta\dot{V}_E$/change in end-tidal P_{CO_2}) is determined for all of the periods, preferably by linear least-squares regression analysis, eliminating the first 30 seconds of rebreathing.

The variability among normal subjects is large.[4,149] The hypercapnic response has been shown to correlate with weight, height, and V_C.[150] Although short-term reproducibility is high, there is variability over longer time periods.

Hypoxic Response

Following the method of Rebuck and Campbell,[151] a reservoir bag is filled with a volume equal to the VC of the subject plus 1 L with a mixture containing approximately 7% carbon dioxide, 70% N_2, and the balance oxygen (≈23%). The subject breathes from and exhales into the room. Values for expired volume, end-tidal P_{O_2}, end-tidal P_{CO_2}, and oxygen saturation are recorded. When the end-tidal P_{CO_2} values become stable, appropriate valves are then turned so the subject rebreathes from the bag. The subject then takes three deep breaths to facilitate mixing; after these three breaths, the carbon dioxide value is recorded. Carbon dioxide is maintained at this level by manually adjusting flow through the carbon dioxide absorber. Rebreathing is continued until end-tidal P_{O_2} decreases to 45 mm Hg, oxygen saturation decreases to 75%, or the subject becomes distressed. If ventilation increases too rapidly, addition of oxygen at a rate of 125 to 200 mL/min will slow the rate of change.

Ventilation, in liters per minute BTPS (breath-by-breath or averaged over 5–10 breaths), is plotted on the ordinate and the mean oxygen saturation (percentage) on the abscissa for the same periods (eFig. 31.14). The slope ($\Delta\dot{V}_E$/1% desaturation) is calculated, preferably by linear least-squares regression analysis. These values are reported in terms of the mean end-tidal P_{CO_2} during the test.

The variability of the hypoxic response during eucapnia in normal subjects is large. The difference in slopes indicates that the hypoxic response is very sensitive to the level of end-tidal P_{CO_2} selected. According to Rebuck and Campbell,[151] repeated measurements in five subjects from day to day showed a variance within individuals of 0.76 and between individuals of 7.75.

Inspiratory Occlusion Pressure

When the patient is breathing room air or while the hypercapnic or hypoxic response is being tested, Pmouth at 100 msec (0.1 second), $P_{0.1}$, or the *maximum rate of inspiratory pressure change* ([dP/dt]max), can be measured. Brief inspiratory occlusion should be performed randomly, always preceded by three or more tidal breaths.[152] Out of view of the subject, the operator uses a syringe during expiration to close a Starling resistor arranged in series with the inspiratory channel so the channel is occluded. The syringe is decompressed as soon as possible after the inspiratory attempt is initiated. Recorder speed should be 50 mm/sec during the subject's inspiratory attempt. Alternatively, Pmouth and its differential (the change in pressure) can be measured in the 10 to 50 msec before the inspiratory valve opens. This approach takes advantage of the inherent resistance of the valve and can be measured at a slow recording speed for every breath without requiring use of a Starling resistor or other maneuvers by the operator.[153] $P_{0.1}$ should be measured every minute and at

the same time after the inspiratory effort begins (e.g., 100 ± 10 msec).

The $P_{0.1}$ measured during single partially occluded breaths, or the average (dP/dt)max of several breaths, is determined directly from the recording and plotted on the ordinate. Mean $\dot{V}E$ (ventilation in liters per minute) calculated from three or more breaths preceding inspiratory occlusion, end-tidal P_{CO_2}, or arterial oxygen saturation is displayed on the abscissa (eFig. 31.15).

Clinical Applications

Carbon Dioxide Responses. In general, there are three clinical conditions associated with abnormal carbon dioxide responses: decreased central chemoreceptor response to carbon dioxide, neuromuscular disease preventing a normal response to carbon dioxide, and abnormalities of the mechanical properties of the respiratory system.

Patients with decreased central chemoreceptor response to carbon dioxide may have varied defects. Decreased responsiveness may result from congenital abnormalities or may be acquired after trauma or inflammatory lesions in the central nervous system. Decreased responsiveness may also result from chronic carbon dioxide retention with associated increased bicarbonate levels and increased buffer capacity of blood and other tissue fluids.

Patients with neuromuscular disease have normal chemoreceptor responses from the ventilatory centers but an inadequate peripheral response. Thus patients with myasthenia gravis cannot respond because of the defective neuromuscular junction, and patients with poliomyelitis cannot respond because of damaged anterior horn cells. These patients have decreased inspiratory work and diminished maximal inspiratory force in response to inhaled carbon dioxide and can be diagnosed using tests of respiratory muscle strength.

Patients with chronic airflow obstruction, pulmonary restriction, or deformities of the chest wall have mechanical limitations to thoracic expansion in response to inhaled carbon dioxide. These patients have normal chemoreceptor responses from the ventilatory centers, a normal peripheral response, but a mechanical limitation that prevents the respiratory muscles from increasing ventilation normally. Thus the ventilatory response to inhaled carbon dioxide may be reduced, but the response reflected by diaphragmatic *electromyography* (EMG), the $P_{0.1}$, is appropriate for the carbon dioxide.

Hypoxic Responses. There are few clinical indications for evaluation of hypoxic responses. The response to alveolar hypoxia has been used in patients with carotid body denervation to test the degree of depressed sensitivity to oxygen. Patients born at high altitude and patients with cyanotic congenital heart disease may have diminished response to hypoxia.

In patients with chronic carbon dioxide retention, it may be worthwhile to test hypoxic responses because ventilation may be driven primarily by hypoxia. This possibility can be assessed by measuring the level of ventilation when the patient breathes room air and again with breathing oxygen. Whereas normal subjects show a small decrease in ventilation, some patients with chronic carbon dioxide retention show a more marked decrease in ventilation. However, the increased hypercarbia in response to supplemental oxygen in the minority of patients with chronic carbon dioxide retention is mostly driven by increased ventilation-perfusion mismatching from alteration of hypoxic pulmonary vasoconstriction and the Haldane effect rather than decreased ventilation.[154]

The Bohr Equation for Respiratory Dead Space

The Bohr equation, applied to a particular gas X, is as follows. Expired gas is the total volume of gas leaving the nose and mouth between the beginning and the end of a single exhalation (V_E). V_A indicates the volume of alveolar gas contributed to the exhaled gas and does *not* refer to the total volume of gas in the alveoli. The amount of gas X in V_E, V_A, or V_D is the product of its fractional concentration (F_x) and the volume in which gas X is contained. Therefore

$$F_{E_X} V_E = F_{A_X} V_A + F_{D_X} V_D \qquad \text{Eq. 22}$$

If the gas in question is carbon dioxide, this equation is simplified because inspired air contains practically no carbon dioxide (*fractional concentration of* CO_2 [F_{ICO_2}] = 0.0005), and the Bohr equation becomes

$$V_D = \frac{[F_{ACO_2} - F_{ECO_2}]}{F_{ACO_2}} V_E \qquad \text{Eq. 23}$$

"Physiologic" Dead Space (Also Called Wasted Ventilation)

In the Bohr equation for respiratory dead space, F_{ECO_2} and V_E can be measured easily, but the *fractional alveolar concentration of* CO_2 (F_{ACO_2}) is difficult to obtain, and V_D cannot be calculated unless the correct value for F_{ACO_2} is known. Because there is almost always complete equilibrium between alveolar P_{CO_2} and end-pulmonary capillary P_{CO_2}, arterial P_{CO_2} represents a mean alveolar P_{CO_2} over several respiratory cycles, provided that arterial blood is sampled over this same period and the patient does not have a significant venous-to-arterial shunt. Thus, arterial P_{CO_2} can replace alveolar P_{CO_2}, and the Bohr equation becomes the Bohr-Engoff equation:

$$V_D = \frac{[P_{aCO_2} - P_{ECO_2}]}{P_{aCO_2}} V_E \qquad \text{Eq. 24}$$

By substituting arterial P_{CO_2} for alveolar P_{CO_2} in the Bohr equation, it is possible to calculate physiologic dead space. This includes anatomic dead space and alveolar dead-space ventilation. Alveolar dead-space ventilation includes several conditions with increased $\dot{V}A/\dot{Q}C$ ratios: ventilation of alveoli without perfusion; alveoli with decreased perfusion and increased, normal, or slightly decreased ventilation, and alveoli with normal perfusion and marked overventilation. Because it is technically impossible to distinguish the various conditions generating increased $\dot{V}A/\dot{Q}C$ ratios, we assume that part of alveolar ventilation to regions with diminished perfusion goes to regions without any blood flow. In this situation the physiologist simplifies by assuming two compartments: one with and one without

perfusion. Overventilation relative to perfusion wastes ventilation with respect to oxygen transfer because of the shape of the oxygen-hemoglobin dissociation curve. Little oxygen is added to blood by increasing alveolar P_{O_2} from 100 to 140 mm Hg. However, this excess ventilation is not wasted with respect to carbon dioxide elimination because increased ventilation decreases arterial carbon dioxide. Regions with excess ventilation are usually accompanied by other regions with diminished ventilation and increased P_{CO_2}. Ventilation is still "wasted" with respect to carbon dioxide because it is not distributed proportionately to perfusion.

Assessment of wasted ventilation is essential for the proper management of critically ill patients in the intensive care unit and for the diagnosis of patients with pulmonary vascular obstruction in the pulmonary exercise laboratory. In the ideal lung, anatomic and "physiologic" dead spaces are equal. However, in patients with uneven ventilation–blood flow ratios in the lung, the physiologic dead space is larger than the anatomic dead space because regions with decreased blood flow in relation to ventilation act as regions of wasted ventilation or respiratory dead space.[155] A consequence of the substitution of arterial P_{CO_2} for alveolar P_{CO_2} is that areas with low ventilation will increase arterial P_{CO_2} and therefore artifactually increase physiologic dead space at high levels of shunt.[156,157] Interpretation of the wasted ventilation depends on the volume of anatomic dead space. The anatomic dead space is often assumed be 1 mL per pound of actual body weight, an estimate that agrees poorly with directly measured dead space and is somewhat improved by use of ideal body weight.[158]

Alveolar Gas Equation

The measurement of alveolar P_{O_2} and P_{CO_2} from analysis of a single sample of exhaled alveolar gas is subject to considerable error, but effective alveolar P_{O_2}, as an average over the whole lung and over the respiratory cycle, can be calculated accurately. The underlying principle is based on mass conservation of oxygen—oxygen consumption rate is equal to the amount of inhaled oxygen minus the amount exhaled from the alveolar space—and on the relationship between alveolar ventilation, alveolar carbon dioxide tension, and rate of carbon dioxide excretion in steady state.[159,160] Arterial P_{CO_2} is used to represent mean alveolar P_{CO_2} because arterial blood coming from all the alveoli approaches an integrated value of alveolar P_{CO_2} with respect to different regions of the lung and to different times during the respiratory cycle.[161,162] The precise formula (assuming inspired P_{CO_2} is zero) is

$$P_{AO_2} = P_{IO_2} - \frac{P_{ACO_2}}{R} + \left[F_{IO_2} \times P_{ACO_2} \times \left(\frac{1-R}{R}\right)\right] \quad \text{Eq. 25}$$

P_{IO_2} (moist) at sea level is calculated as 20.93% × (760 − 47) = 149 mm Hg. Water vapor pressure at 37°C is approximately 47 mm Hg, and R is the respiratory exchange quotient (ratio of carbon dioxide excretion to oxygen consumption). Note that with an $F_{IO_2} = 1$ or R = 1, the equation simplifies to:

$$P_{AO_2} = P_{IO_2} - P_{aCO_2} \quad \text{Eq. 26}$$

The *alveolar gas equation* is often approximated to estimate alveolar-arterial oxygen differences for clinical purposes:

$$P_{AO_2} = P_{IO_2} - \frac{P_{aCO_2}}{R} \quad \text{Eq. 27}$$

The third term in Eq. 25 is small and accounts for the fact that the oxygen removed per minute is greater than the amount of carbon dioxide added at rest, with a typical value for the respiratory exchange quotient of:

$$R = \frac{200 \text{ mL } CO_2/\text{min}}{250 \text{ mL } O_2/\text{min}} \cong 0.8 \quad \text{Eq. 28}$$

The *alveolar-arterial P_{O_2} difference* ($[A–a]P_{O_2}$) has been shown to be larger in older subjects than in younger ones.[163] According to Mellemgaard,[164] the regression with age is expressed as $(A–a)P_{O_2} = 2.5 + 0.21 \times$ age (in years). Mellemgaard's study was performed on 80 healthy, seated subjects whose ages ranged from 15 to 75 years. Lack of steady-state breathing and the use of an assumed rather than measured R can limit the accuracy of $(A–a)P_{O_2}$ in clinical situations. The $(A–a)P_{O_2}$ is often inappropriately referred to as a "gradient," thereby incorrectly suggesting that a physical difference in oxygen tension between alveoli and their associated end-capillary blood exists or is calculated (see Staub[165] and Finley and colleagues[166] for evidence against an alveolar–end-capillary oxygen difference at normal or elevated inspired oxygen concentration).

Calculation of Alveolar Ventilation

Carbon dioxide in exhaled gas must all come from alveolar gas. As derived in Chapter 10, this equation is as follows:

$$\dot{V}_A\,(\text{mL}) = \frac{\dot{V}_{CO_2}\,(\text{mL}) \times 863}{P_{ACO_2}} \quad \text{Eq. 29}$$

Relation of Alveolar Ventilation to Pulmonary Blood Flow

Eq. 30 relates the factors that determine the adequacy of alveolar ventilation:

$$\frac{\dot{V}_A}{\dot{Q}_C} = \frac{863\left(C\bar{v}_{CO_2} - Cc'_{CO_2}\right)}{P_{ACO_2}} \quad \text{Eq. 30}$$

where $\dot{Q}_C$ is pulmonary capillary blood flow, $C\bar{v}_{CO_2}$ is the carbon dioxide concentration in mixed venous blood, Cc'_{CO_2} is the carbon dioxide concentration in the end-pulmonary capillary blood, $\dot{V}_A$ is alveolar ventilation, P_{ACO_2} is alveolar carbon dioxide tension, and *863* is a constant to correct for changes from alveolar fraction to alveolar pressure of carbon dioxide. In any individual the mixed venous blood distributed to all pulmonary capillaries has the same carbon dioxide concentration, and end-pulmonary capillary blood has the same P_{CO_2} as alveolar gas; therefore alveolar P_{CO_2} is determined by the ratio $\dot{V}_A/\dot{V}_C$.

Calculation of Quantity of Venous-to-Arterial Shunt

For a more detailed discussion of intrapulmonary shunts, see Chapter 88, which discusses pulmonary arteriovenous malformations and other pulmonary vascular abnormalities.

When a patient has a venous-to-arterial shunt, arterial blood contains some mixed venous blood that has bypassed the lungs and some well-oxygenated blood that has passed through the pulmonary capillaries. The equation that expresses this relationship for blood is analogous to the Bohr equation for calculation of respiratory dead space:

$$\dot{Q}S = \frac{Cc'O_2 - CaO_2}{Cc'O_2 - C\bar{v}O_2} \times \dot{Q} \qquad \text{Eq. 31}$$

where $\dot{Q}S$ is shunt blood flow, $Cc'O_2$ is the oxygen content of end-capillary blood, CaO_2 is the oxygen content of arterial blood, $C\bar{v}O_2$ is the oxygen content of mixed venous blood, and $\dot{Q}$ is total blood flow.

Arterial and mixed venous blood can be obtained, so the arterial concentration of oxygen and $C\bar{v}O_2$ can be measured. The quantity of blood flowing through the shunt can be determined by having the patient breathe pure oxygen for a sufficient time to wash all of the N_2 from the alveoli. Alveolar P_{O_2} is then equal to 760 − alveolar P_{H_2O} − alveolar P_{CO_2}, or approximately 673 mm Hg. Under these conditions there is no alveolar-to-end-capillary difference, and end-capillary blood can be assumed to contain an amount equal to the oxygen capacity of hemoglobin plus 2.0 mL of dissolved oxygen per 100 mL.

"Venous admixture" or "physiologic shunt" can be estimated by the method of Lilienthal and associates.[167] Physiologic shunt includes several conditions associated with decreased $\dot{V}A/\dot{Q}C$ ratios: unventilated alveoli with perfusion; very poorly ventilated alveoli with normal, increased, or slightly decreased perfusion; and ventilated alveoli with markedly increased perfusion. In this situation the physiologist simplifies by assuming two compartments: one with and one without a complete shunt.[168]

If a patient is given pure oxygen to breathe, it is possible to distinguish a right-to-left shunt from a ventilation-perfusion abnormality; the high alveolar P_{O_2} corrects the ventilation-perfusion imbalance. Alveolar and arterial P_{O_2} values expected in an ideal lung, with $\dot{V}A/\dot{Q}C$ ratio imbalance and with right-to-left shunt, are given in eTable 31.1.

Pure oxygen replaces N_2 with oxygen in all gas-exchange units that have patent airways, even in the presence of severe airway obstruction or pulmonary restriction; this leaves only oxygen, carbon dioxide, and water in the air spaces.

Total pressure ($P_{A_{TOTAL}}$) and *water vapor pressure* (P_{AH_2O}) are the same in all patent gas-exchange units. In this idealized two-compartment model, the shunt fraction that the calculation yields is the proportion of blood flow from right to left that would need to be pure shunt (i.e., no contact with alveoli) to quantitatively explain the observed oxygenation defect, after removing nonzero low $\dot{V}A/\dot{Q}C$ by breathing 100% oxygen, to the extent possible dictated by communication of airspaces to the conducting airways.

In most normal subjects the existing right-to-left shunts are distal to the gas-exchange units (so-called postpulmonary shunts). These shunt vessels include bronchial veins, mediastinal-to-pulmonary veins, and thebesian vessels (i.e., vessels draining from the left ventricular muscle into the left ventricular cavity). In some patients, pulmonary shunts are caused by intracardiac shunts, pulmonary arteriovenous malformations, or perfusion of nonventilated alveoli. In patients with pulmonary disorders, most shunts involve perfusion of nonventilated alveoli.

Some laboratories have estimated the amount of right-to-left shunt from the fall in arterial P_{O_2} below the expected value of 673 mm Hg, as long as the P_{O_2} is sufficient to saturate hemoglobin (i.e., >200 mm Hg). For every decrease in P_{O_2} of 35 mm Hg, shunt increases by 2%. We use the following equation in our laboratory to compute the shunt fraction from a single arterial blood gas drawn while a patient breathes 100% oxygen; the equation adjusts for carbon dioxide tension and assumes an arterial-venous oxygen content difference of 5 mL O_2 per dL of blood[169]:

$$\frac{Q_s}{Q_t} = \frac{0.003 \times (P_{AO_2} - Pa_{O_2})}{0.003 \times (P_{AO_2} - Pa_{O_2}) + 5} \qquad \text{Eq. 32}$$

where P_{AO_2} is calculated using Eq. 27.

An alternative approximation to the above also used in our laboratory is $\dot{Q}S/\dot{Q}T$ = [A–a difference]/20 expressed as a whole number percentage value.

Distribution of Ventilation-Perfusion Ratios

Distribution of perfusion in relation to ventilation of the lung may be analyzed on the basis of a region or lobe or for the lung as a whole and expressed in terms of physiologic shunt, physiologic dead space, or in terms of ventilation-perfusion ratios. In an approach developed by Wagner and colleagues,[170] the lung is assumed to consist of a large number of homogeneous compartments in parallel, each with its own ventilation, blood flow, and appropriate gas concentrations. Distribution of ventilation-perfusion ratios is evaluated with six inert gases of varying solubility dissolved in saline and infused intravenously and concurrently at a constant rate. Under these circumstances in the steady state, the amount of any gas exchanging between the pulmonary capillary blood and the alveoli is identical to that exchanging between alveoli and atmosphere. For each compartment the quantity of gas is a function of the ventilation-perfusion ratio and the blood-gas partition coefficient for the gas in question, expressed as a fraction of that in the mixed venous blood. For the lung as a whole, the mixed arterial concentration is a blood flow–weighted mean of the values for several compartments, and the mean expired level is similarly a ventilation-weighted mean of the compartmental values. These parameters are measured directly, together with the cardiac output and the minute volume of ventilation. They are used to calculate the corresponding mixed venous and alveolar concentrations and then a distribution of ventilation-perfusion ratios that is compatible with the arterial and alveolar concentrations of all gases concurrently (eFigs. 31.16 and 31.17).

The limitations of the method include the limited accuracy of current chromatographic techniques for gas analysis. In addition, it does not provide a unique solution because the same arterial and alveolar gas concentrations could result from other distributions of ventilation and perfusion in the lung. Wagner and associates[171] also reported a modification of the multiple inert gas method that permits estimation of the levels of inert gases in peripheral venous blood, rather than arterial blood, which may prove to be of considerable clinical interest.

Clinical Applications

The various methods of measuring ventilation-perfusion relationships have been used widely in the diagnosis and management of patients with various pulmonary disorders. This is not surprising because almost every pulmonary disease affects the delicate match between ventilation and perfusion early in the process, with the matching becoming worse as the disease progresses.

Understanding ventilation-perfusion mismatching may be essential to proper diagnosis and management. For example, measurement of physiologic dead space has provided insights into the gas exchange defects of the patient in the intensive care unit and of the patient with chronic pulmonary embolism who presents with the complaint of exertional dyspnea. Measurement of intrapulmonary shunts by having a patient breathe pure oxygen can be used to estimate the size of shunts and assess efficacy of therapeutic embolization of shunt vessels.

Although the measurement of distribution of ventilation-perfusion ratios has taught us a great deal about the pathophysiology of ventilation-perfusion matching in pulmonary disease, it has not been useful as a clinical tool. On the other hand, radioisotope lung scans are critically important in the management of many of our patients, not only those with pulmonary vascular problems, but also patients who have undergone a single-lung transplant, in whom we can understand the role played by the native lung as well as the graft.

Arterial Blood Gases

The physiologic determinants of arterial oxygen levels and acid-base balance are reviewed in detail in Chapters 10 and 12, respectively.

The technical aspects of these measurements are discussed at ExpertConsult.com.

OTHER PULMONARY FUNCTION TESTS

BRONCHIAL PROVOCATION

Provocation tests may be extremely useful in the diagnosis and management of patients with asthma or occupational asthma and in the differential diagnosis of patients with chronic cough, wheezing, or intermittent dyspnea. Although most laboratories use spirometry to evaluate the airway response, the measurement of RAW in a body plethysmograph is more sensitive, more specific for abnormalities in airway tone, and usually easier for the patient to perform than spirometry, which depends on inspiration to TLC followed by a forced exhalation. In limited numbers of patients, tests with exposure to specific allergens may be helpful in the evaluation of allergic asthma. Similarly, in a small number of patients suspected of having occupational asthma, specific challenge with agents found in the workplace may be useful in the diagnosis. However, the referring physician should be aware that these challenge tests are dangerous and tedious, usually require hospitalization for observation, and may not be useful if the patient is exposed to multiple agents in the workplace.

TESTS OF NONSPECIFIC AIRWAY RESPONSIVENESS

Abnormal airway responsiveness is viewed by many as a characteristic feature of asthma. It may also be found in patients with chronic bronchitis and CF. Although a variety of stimuli have been used to induce airway response, including exercise and eucapnic ventilation (see later in discussion of indirect tests), the most common stimulus is methacholine.

Methacholine is an acetylcholine agonist that causes constriction of airway smooth muscle through direct stimulation of M3 receptors. The test begins with baseline measurement of spirometry and in some cases sRAW.[216] Next, the patient is asked to inhale a control aerosol consisting of the diluent, and responses are reported relative to the diluent value. Then the patient inhales a methacholine aerosol at increasing doses, starting from a low dose to avoid an inordinately severe reaction. Inhalation should take place through tidal breathing, avoiding deep inhalations, and over a period specified by the aerosol characteristics of the nebulizer. Approximately 1 minute of tidal breathing is recommended for each dose. Spirometry is then measured at 30 and 90 seconds after completion of the inhalation period, and FEV_1 recorded. If the requisite 20% or more fall in FEV_1 is not seen, then the next dose is prepared and administered, maintaining a consistent 5 minutes between doses. A dose-response plot is constructed depicting the dose of agonist on the logarithmic abscissa as amount of agonist (in micromoles) delivered from the nebulizer, and the response as the FEV_1 on the ordinate. The end point for the test is the dose causing a decrease in FEV_1 of 20% or causing a doubling of sRAW.

FEV_1 is the most common test used to evaluate the outcome of this procedure, although sRAW may be more sensitive. Medications, baseline airway function, respiratory infections, and exposure to specific allergens and chemical sensitizers influence responses. Bronchodilators, antihistamines, and other agents that decrease bronchial responsiveness should be withheld before the test.[217]

Compared to methacholine, which has *direct* effects on airway smooth muscle to cause airway narrowing, so-called *indirect* challenge tests, which cause airway narrowing indirectly by triggering mast cell degranulation by osmotic stimuli, or mediator release from inflammatory cells, may have an important place in the assessment of asthma.[218] Such indirect challenge tests, including exercise-induced bronchoconstriction, eucapnic voluntary hyperpnea, hypertonic and hypotonic aerosols, and mannitol, are useful for monitoring treatment with inhaled corticosteroids.[219] Indirect tests identify subjects with the potential for exercise-induced bronchoconstriction and therefore are useful for members of the armed services, firefighters, police, and elite athletes. A positive indirect test result suggests that inflammatory cells and their mediators are present in sufficient numbers and concentration to indicate that asthma is active at the time of the test. A negative test result in a known asthmatic patient means good control or mild disease. Healthy subjects do not experience significant bronchoconstriction during indirect tests.[219]

More information on the advantages of indirect tests and specific airway responsiveness is available at ExpertConsult.com.

RESPIRATORY MUSCLE FUNCTION TESTS

Respiratory muscle function may be tested clinically by measuring muscle strength or endurance. Common measurements include maximally negative inspiratory and positive expiratory airway pressure, sniff nasal inspiratory pressure, maximum transdiaphragmatic pressure, maximum voluntary ventilation, diaphragmatic electromyography, and fluoroscopy.

For more details about these measurements of muscle function, see ExpertConsult.com.

For a discussion about pulmonary function testing in children, see ExpertConsult.com.

PULMONARY FUNCTION LABORATORY MANAGEMENT

GENERAL STRUCTURE: PERSONNEL, EQUIPMENT, AND QUALITY CONTROL

The pulmonary function laboratory is an essential component of any diagnostic laboratory service. Surprisingly, at the present time, a pulmonary function laboratory is not overseen for quality by any formal accreditation body, unlike any other diagnostic laboratory. Many of the following general principles are outlined in detail in such references as the ATS Pulmonary Function Laboratory Manual (http://store.thoracic.org/product/index.php?id=a1u33000000ye1TAAQ).

The PF laboratory must have a medical director who oversees the proper management of the laboratory, supervises

Invasive Measurements

pH. The pH of blood is now measured almost entirely by the use of the pH electrode (eFig. 31.18). This device takes advantage of the discovery that an electrical potential difference exists across some types of glass membranes placed between solutions of different pH. By maintaining one side of the membrane at a known pH with a buffer solution (pH = 6.84), the pH of the solution placed on the other side of the membrane can be calculated from the potential difference generated, using the Nernst equation. The modern pH electrode is made up of two cells. The measurement half-cell consists of a fine capillary tube of pH-sensitive glass separating the introduced sample (as little as 25 μL) from the buffered solution and a silver/silver chloride electrode to conduct the generated potential difference to the electronic circuitry. The reference half-cell usually contains a calomel (mercury/mercurous chloride) electrode in an electrolyte solution to provide a constant reference voltage and is connected to the measurement half-cell by a contact bridge to complete the circuit. These two cells are enclosed together in a sealed jacket and are maintained at a constant temperature (see eFig. 31.18).

The potential difference generated across the glass membrane is a linear function of the pH. Thus it is usually adequate to calibrate the electrode with two buffered solutions of known pH that span a significant portion of the range expected in the samples to be measured. The normal range for arterial pH at sea level is 7.35 to 7.45 units. Even preliminary deviations from this range can be interpreted only by also examining the P_{CO_2}, making use of the Henderson-Hasselbalch equation, to infer whether the deviation in pH is due primarily to a metabolic or a respiratory cause and whether it is due to an acute or chronic disturbance. In clinical use the pH meter has proved to be a rugged, dependable device. Repeated measurements of a single sample by the same instrument fall within a narrow range of ±0.02 unit (±2 SD). Generally there is good agreement among the values obtained on unknown samples by the different instruments used by laboratories enrolled in quality-control programs (SD = 0.014 pH unit has been obtained in more than 800 laboratories).[172] This remarkable accuracy depends on the integrity of the differential permeability of the glass membrane to hydrogen ions. The permeability may be altered by the deposition of protein or by the development of cracks on the membrane surface. Proper quality control requires that pH calibration be checked at one point before each series of pH determinations and at two major points every 4 hours. A number of standard phosphate buffer solutions are suitable for routine calibrations and are available commercially. Protein contamination of the membrane can be minimized by flushing the electrode with a cleaning solution at regular intervals (every 10 samples) and by taking care to follow injections of blood with injections of saline (not distilled water).

Carbon Dioxide. Early chemical methods for measuring gas concentrations in blood were laborious and demanding. They involved liberating chemically bound oxygen and carbon dioxide in blood by adding chemical agents to a sample kept in a closed vessel. The quantity of gas released was then measured by a manometric[173] or volumetric[174] method. Carbon dioxide was then selectively absorbed, and the change in volume permitted calculation of the content of the blood sample of the two gases. These tedious and technically demanding methods gave accurate values for the content of the two gases in blood. Determination of pressure required measurement of the content of the gases in plasma alone after separating plasma from RBCs in a closed system. Alternatively, back-calculation of pressure could be made by measurement of blood hemoglobin content combined with measurements and calculations of the quantities of the gases transported in the cells and proteins of blood.

The breakthrough in the measurement of carbon dioxide came with the development of the membrane-covered carbon dioxide electrode (eFig. 31.19). This device exploits the principles of the pH electrode and the known relationship between P_{CO_2} and pH in a buffered solution. The sample to be analyzed is separated from a buffer solution by a membrane permeable to carbon dioxide. The carbon dioxide molecules that diffuse through the membrane alter the concentration of carbonic acid and therefore the concentration of hydrogen ion in the buffered solution:

$$CO_2 + H_2O \leftrightarrow H_2CO_3 \leftrightarrow H^+ + HCO_3^- \qquad \text{Eq. 33}$$

A pH meter reads the resulting change in pH with the output scaled in terms of P_{CO_2}. The time for response of the carbon dioxide electrode depends on the concentration and volume of the buffered solution, the diffusion properties of the artificial membrane, and the thickness of a second "stabilizing membrane" placed over the pH-sensitive glass. With silicone-rubber membranes, the 95% response time has been reduced to as little as 10 seconds (see eFig. 31.19).

Perhaps because it incorporates a pH electrode in its design, the P_{CO_2} electrode also has the advantages of precision and dependability if calibrated regularly. As with the pH electrode, a one-point calibration should be checked before each series of blood-gas measurements, and two-point calibrations every 4 to 8 hours or whenever the one-point calibration indicates the need for readjustment of more than 2 mm Hg P_{CO_2}. The range of repeated measurements of samples of blood equilibrated under controlled conditions to P_{CO_2} of 20 to 60 mm Hg is ± 3.0 mm Hg, and tests with commercially available, sealed buffer solutions with different P_{CO_2} values show similar reproducibility with a variety of blood-gas measuring devices. The agreement among devices of laboratories enrolled in quality-control programs is also good.

The normal range of values for P_{CO_2} varies with altitude. At sea level, it ranges from 36 to 44 mm Hg.[175] In Salt Lake City, Utah (elevation, 1340–1520 m), the range is reported to be 30 to 40 mm Hg.[176]

Oxygen

Oxygen Pressure. As with the measurement of P_{CO_2}, the development of an accurate, stable electrode has almost entirely supplanted the use of older chemical methods for measuring total blood oxygen content and then back-calculating P_{O_2}. The principle of the oxygen electrode differs from that of the pH and P_{CO_2} electrodes in that the oxygen electrode measures a current generated by the presence of the relevant molecule, rather than a potential difference. The device consists of platinum and silver electrodes placed

in potassium chloride solutions, a polarizing voltage of 0.5 to 0.6 volt, and an electrolyte bridge to complete the circuit. Oxidation takes place at the silver electrode, where silver reacts with chloride ions to form silver chloride. This reaction produces electrons, which are consumed by the reduction of oxygen at the platinum electrode. The flow of electrons (current) is thus proportional to the concentration of oxygen at the platinum electrode (eFig. 31.20).

Clark[177] developed a useful electrode based on this principle. The important features of the Clark electrode are that it minimizes oxygen consumption by the use of a thin platinum electrode and ensures a constant diffusion distance between the surface of the electrode and the sample by covering the electrode with an oxygen-permeable membrane. The surface area of the platinum electrode and the permeability of the membrane to oxygen determine the sensitivity and response time of the electrode. However, the larger the electrode and the more permeable the membrane, the more rapidly oxygen is consumed, causing P_{O_2} to fall in small samples as the measurement is made. For most available devices, the compromises made result in a 95% response time of about 50 seconds.

A peculiarity of the oxygen electrode is that slightly different currents are generated when gases and liquids at the same P_{O_2} are introduced. The magnitude of the difference is usually 3–4%, depending on the electrode diameter, the nature and thickness of the membrane, and the flow of the sample around the electrode. A correction factor is sometimes introduced into the calculation of arterial P_{O_2} when gases are used for calibration. These factors, however, may not be related linearly to P_{O_2}, resulting in errors when high oxygen pressures are measured, as in samples obtained from a patient to whom pure oxygen is given to estimate the magnitude of a right-to-left shunt. The simplest approach would seem to be calibration of the electrode with solutions, rather than gases. This is probably true, but large differences have been found for the same instrument using samples of different test solutions equilibrated to the same P_{O_2}.[178] In general, the more the oxygen-carrying capacity of the solution approximates that of blood, the smaller is the error. Thus the large interinstrument variability of oxygen pressure values reported for blind samples tested in a quality-control program may not reflect the variability that would be achieved if all tests were run with blood equilibrated to the appropriate oxygen tensions. For a single machine, the range of repeated measurements of P_{O_2} in blood is 3.0 mm Hg for P_{O_2} values from 20 to 150 mm Hg.[175] In normal seated adult subjects, the predicted arterial P_{O_2} can be obtained from Mellemgaard's data[164] with a SD around the regression line of approximately 6.0 mm Hg:

$$P_{O_2} = 104.2 - 0.27 \times \text{age (years)} \qquad \text{Eq. 34}$$

A final problem for some highly automated blood-gas machines appears only when samples of very high or very low P_{O_2} are tested. This is due to the error introduced by "contamination" of the sample chamber by the rinsing fluid.[149] If the P_{O_2} of the rinsing fluid is similar to that of room air, then the persistence of a small amount of fluid does not much alter the P_{O_2} measured for blood samples with oxygen pressures between 60 and 100 mm Hg. The P_{O_2} of the rinsing fluid affects the values recorded for samples with oxygen pressures at either extreme. If the design of the machine permits, this source of error can be reduced by flushing the sample chamber with a fluid that has a P_{O_2} near the estimated value of the sample or by introducing consecutive specimens without flushing the chamber.

Oxygen Content. Assessment of the adequacy of oxygen delivery requires not only measurement of the P_{O_2} in plasma but also measurement of the oxygen content in blood. Oxygen content, the sum of the oxygen bound to hemoglobin and that dissolved in plasma, can be measured directly by chemical or galvanic cell methods and can be estimated from the P_{O_2}, the total hemoglobin concentration, and the percentage of oxyhemoglobin. The measurement or estimation of oxygen content of arterial and venous blood is required for calculating cardiac output by the Fick equation and for estimating the shunt-like effect in hypoxemic patients.

The chemical method for measuring total oxygen content involves liberating chemically bound oxygen and carbon dioxide from blood by adding ferricyanide, measuring the total quantity of gas displaced, and then absorbing the carbon dioxide with sodium hydroxide. This is the basis of the Van Slyke method, which served as the reference method for many years but is now used infrequently because of its demands on time and technical skill.[173]

Another method is the galvanic cell method, in which oxygen is chemically liberated from blood and transferred to a fuel cell, where a current is generated in proportion to the amount of oxygen delivered. This device yields values with an accuracy and precision similar to those obtained by the Van Slyke method.[179]

The method used most commonly for calculating oxygen content is measurement of the total hemoglobin concentration by the cyanmethemoglobin method,[180] the percentage of oxyhemoglobin by a spectrophotometric method, and the dissolved oxygen as the product of arterial P_{O_2} and oxygen's solubility coefficient (0.003 mL/100 mL blood).

Spectrophotometry is based on the discovery that substances differentially absorb various wavelengths of light. In the absence of other materials that absorb light at the same wavelength, the concentration of a substance in a solution is proportional to the amount of light absorbed. This method is especially applicable to hemoglobin analysis because the various forms of hemoglobin (e.g., oxyhemoglobin, reduced hemoglobin, carboxyhemoglobin, sulfhemoglobin, methemoglobin) have characteristic spectra of light absorption. A simple two-wavelength spectrophotometer developed in 1900 could relate the amount of oxyhemoglobin to total hemoglobin but gave falsely high values when carboxyhemoglobin or methemoglobin was present. Three-wavelength instruments can simultaneously measure total hemoglobin, oxyhemoglobin, and carboxyhemoglobin; and a four-wavelength device is now marketed that enables measurement of methemoglobin as well.[180]

The importance of measuring carboxyhemoglobin lies not just in quantifying correctly the proportion of nonreduced hemoglobin that is actually available for carrying oxygen but also in identifying a cause of a shift in the position of the oxygen-hemoglobin dissociation curve. The presence of carboxyhemoglobin increases the affinity of adjacent hemoglobin molecules for oxygen, so the curve is shifted to the left (i.e., less oxygen is unloaded from oxyhemoglobin at normal tissue P_{O_2}). Similar disorders may result

from inherited abnormalities in hemoglobin structure, as with hemoglobin Chesapeake, for which 50% desaturation does not develop until the P_{O_2} is lowered to 19 mm Hg, as opposed to the normal 50% unloading point of 27 mm Hg.

Direct measurement of the P_{O_2} at which 50% of the binding sites on hemoglobin are saturated (P_{50}) requires measurement of hemoglobin saturation after the blood sample is equilibrated at three oxygen pressures spanning the expected range (P_{O_2} values from 20 to 35 mm Hg are typical). Alternatively, a close estimate of P_{O_2} can be drawn from single measurements of P_{O_2} and hemoglobin saturation.[180]

Measurement of P_{50} is rarely needed in clinical practice. With the important exception of conditions in which carboxyhemoglobin is likely to be present in appreciable quantities (as in victims of fires or of exposure to closed-space combustion, or in heavy cigarette and cigar smokers), the estimation of blood oxygen content from measurements of arterial P_{O_2} and hemoglobin concentration usually provides sufficient information for decisions about clinical management.

Errors in the values used for such decisions arise most often from failures in the methods used for obtaining, transporting, and storing the sample of blood to be analyzed. For validity of the measurement, care must be taken to avoid contamination with room air or an excessive amount of anticoagulant when the sample is obtained, as well as leakage, diffusion, or consumption of gases while the sample is being transported and stored. For clinical utility, it is important that the sample be obtained with minimal discomfort and hazard. Syringes for *arterial blood gas* (ABG) collection are now designed to reduce the chance of a needle stick and to contain the optimal concentration of heparin.

Because of the adequacy of collateral flow in the event of occlusion of the sampled artery, the radial artery is the preferred site for obtaining the blood sample. However, in elderly patients and in patients with arteriosclerotic vascular disease, the adequacy of ulnar flow should be confirmed by the Allen test (appearance of palmar flush when the ulnar artery alone is decompressed). In infants, samples are most safely collected from the temporal or umbilical arteries. If radial and femoral arterial cannulation cannot be accomplished, then the brachial, axillary, and dorsalis pedis arteries should be considered. Sometimes physicians have been advised to avoid percutaneous cannulation of the brachial artery because of a lack of collateral vessels and the anatomic proximity to the median nerve. Aneurysm formation, thrombosis with loss of radial arterial pulse, and permanent median nerve neuropathy caused by hematoma have all been reported as complications of brachial cannulation. On the other hand, the literature associated with left heart catheterization states that percutaneous cannulation of the brachial artery is as "safe and effective" as surgical cutdown and arteriotomy.[181]

Venous blood gases (VBG) are increasingly used as alternative samples to estimate systemic carbon dioxide and pH that do not require ABG sampling. Using VBG in the intensive care unit is particularly attractive because most critically ill patients have a central venous catheter from which it is easy to obtain VBG quickly.

VBG analysis can be performed on a central venous sample (central venous catheter), mixed venous sample (pulmonary artery catheter), or peripheral venous sample (venipuncture).

Central venous samples have been well correlated with ABGs. Venous pH, serum HCO_3^-, and P_{CO_2} are used to assess ventilator and acid-base status and arterial oxygen saturation to guide resuscitation during septic shock, but partial oxygen pressure in mixed venous blood has no practical value because the tissues have already extracted oxygen before reaching the venous system.

The difference between VBG and ABG depends on the site of venous sampling: Central venous pH is usually 0.03 pH units lower than ABG, P_{CO_2} 4 to 5 mm Hg higher than ABG, and little or no difference in serum HCO_3^-.[82,183] Mixed venous blood results are similar to central venous blood samples.[184,185] Similar comparisons have been published for peripheral venous pH and ABG.[186–190] These comparisons represent group differences, and there is wide variability in differences at the level of individual patients, especially for P_{CO_2}.

In clinical studies there is good agreement for pH and HCO_3^- between ABG and VBG in COPD patients, but not for P_{CO_2} or P_{O_2}. To avoid misleading results, clinicians should avoid VBG in hemodynamically unstable patients and rely on ABGs instead.[191–193] If serial monitoring of critically ill patients is done routinely, VBG and ABG should be compared periodically. Widespread clinical use of VBG is limited because of the lack of validation studies on clinical outcomes.[194]

An alternative to arterial puncture is to obtain a sample of "arterialized" capillary or venous blood. The assumption is that the vasodilation produced by heat or by application of vasodilator cream to a region with low metabolic activity will result in delivery of such an excess of arterial blood that local metabolism causes only small changes in P_{O_2}, P_{CO_2}, and pH. Under these circumstances, analysis of capillary or venous blood should provide close estimates of arterial values. The sites most commonly used for capillary sampling are the earlobe in adults and children and the lateral margin of the foot in infants; for sampling of arterialized venous blood, a dorsal hand vein is most commonly used. From any of these sites, the values obtained correlate well with arterial pH and P_{CO_2}.[195] The values for P_{O_2} are also accurate, except in patients with arterial hypotension or local reductions in flow to the sample site (as may develop with the vasoconstrictive response to severe hypoxemia), in newborns, and in patients with high arterial P_{O_2} (i.e., breathing oxygen-enriched gas mixtures).

Once the sample is obtained, it should be analyzed promptly or placed on ice to minimize the effects of continued cell metabolism on oxygen consumption. This is especially important for samples with very high white blood cell or platelet counts and in samples with P_{O_2} greater than 100 mm Hg.

However the sample is obtained, clinical interpretation of blood-gas values is possible only if the condition of the patient at the time of sampling is noted. Most important is a description of the oxygen pressure of the inspired gas mixture, but position, activity level, habitus, diet, and other factors can also influence arterial blood-gas values. Clearly, an excited or frightened patient may hyperventilate or breath-hold during arterial puncture. However, comparison with the values obtained from indwelling catheters shows that pain caused by arterial sampling does not routinely cause a change in alveolar ventilation.

NONINVASIVE MEASUREMENTS

The appeal of an accurate, noninvasive means of assessing arterial blood-gas pressures is compelling, and several devices have been developed for transcutaneous measurement of oxygen saturation and pressure. Some devices already provide sufficiently accurate data on oxygen pressure to have been put into widespread clinical use. However, important physiologic and technologic barriers must be overcome for the development of a useful device for measuring carbon dioxide content and pressure.

Oxygen

Oximetry. It was recognized more than 50 years ago that the principles of spectrophotometry could be applied to transcutaneous measurement of oxygen saturation in capillary blood by measuring the quantities of light at different wavelengths transmitted through or reflected from the earlobe. With dilation of local arterial vessels through application of heat or a vasodilating chemical (e.g., nicotine, alcohol), capillary oxygen saturation should approximate arterial oxygen saturation. Early ear oximeters were reported to give accurate data but were not widely accepted because of the practical difficulties in operating cumbersome instruments that were hard to calibrate, sensitive to changes in position, and likely to give unpredictable, unstable values.

The principle of oximetry depends on Beer's law, by which the amount of light absorbed by a solute in solution is related to the concentration of the unknown solute:

$$\text{Log}\frac{I_{IN}}{I_{TR}} = C_A \times d \times \varepsilon_A \qquad \text{Eq. 35}$$

where I_{IN} is the quantity of incident light, d is the distance through which light passes, C_A is the concentration of the solute (e.g., hemoglobin), ε_A is the absorption coefficient, and I_{TR} is the amount of light transmitted through A, the substance containing the solute.

When light is passed through tissue from the oximeter, the tissues absorb most of the light, and the amount of light absorbed does not vary with the cardiac cycle. During the cardiac cycle, however, there is a small increase in arterial blood, causing an increase in absorption of light. By comparing absorption at the peak and trough of the arterial pulse, the nonarterial sources of absorption become irrelevant (eFig. 31.21).

The probe consists of two light-emitting diodes that emit light at specific wavelengths, usually 660 nm and 940 nm (eFig. 31.22). At these wavelengths the light absorption by oxyhemoglobin and by reduced hemoglobin is markedly different. A photodetector is placed across a vascular bed (finger, nose, or earlobe) from the light source. When the *ratios* (R) of pulsatile and baseline light absorption are compared at these two wavelengths, the ratio of oxyhemoglobin to reduced hemoglobin may be calculated:

$$R = \frac{\dfrac{\text{pulsatile absorbance (660)}}{\text{baseline absorbance (660)}}}{\dfrac{\text{pulsatile absorbance (990)}}{\text{baseline absorbance (990)}}} \qquad \text{Eq. 36}$$

The relationship between R and oxygen saturation was determined experimentally because there is no known function relating these two variables. A calibration curve was created by having healthy subjects with previously measured amounts of methemoglobin and carboxyhemoglobin breathe various hypoxic gas mixtures designed to produce oxygen saturations from 70–100%.[196] A sample of arterial blood was obtained with each gas mixture, oxygen saturation was measured using a co-oximeter (spectrophotometric hemoximeter), and the R value measured by the pulse oximeter was compared.

Because only two wavelengths are used, the pulse oximeter can measure only two substances, so it determines "functional saturation":

$$\text{Functional saturation} = \frac{\text{oxyhemoglobin}}{\text{oxyhemoglobin} + \text{reduced hemoglobin}} \qquad \text{Eq. 37}$$

Pulse oximeters are accurate when oxygen saturation is from 70–100%,[197] but they may be inaccurate below that range. These devices may be misleading in the presence of abnormal hemoglobins (methemoglobin, carboxyhemoglobin, fetal hemoglobin), dyes (methylene blue, indocyanine green), increased bilirubin level, low perfusion states, anemia, increased venous pulsations, and external light sources.[198]

Continuous monitoring of oxygen saturation is considered the standard of care in operating rooms and recovery rooms.[199] The limitation of oximetry is that it measures oxygen saturation, and the flattened shape of the upper portion of the oxygen-hemoglobin dissociation curve means that large changes in P_{O_2} result in small changes in arterial oxygen saturation. Oximetry is thus inherently insensitive to changes in P_{O_2} from the normal range that have diagnostic and clinical significance even if they do not result in important falls in oxygen delivery. The actual 95% confidence limits of ±5% for arterial oxygen saturation reported for oximetry make this limitation all the more important.

Transcutaneous Oxygen Electrode. The basic idea of the transcutaneous electrode is that a small polarographic electrode can measure the oxygen pressure in a bubble of gas trapped over the skin. Because the P_{O_2} at the surface of unwarmed skin is near zero, the success of the transcutaneous oxygen electrode depends on producing enough local vasodilation to compensate for the arterial-capillary gradient and also for the further loss of oxygen due to skin metabolism and imperfect diffusion of oxygen through the skin layer. This degree of vasodilation is achieved by warming the skin to 42°C. The increase in temperature causes local vasodilation and displaces the hemoglobin dissociation curve to the right. Thus the oxygen pressure is increased for any blood oxygen pressure, partially correcting for the losses of oxygen between the arterioles and the skin surface.

The skin surface electrode developed by Huch and associates[200] in 1973 has proved accurate in continuous measurement of transcutaneous P_{O_2} in both healthy and sick newborns. Not surprisingly, transcutaneous P_{O_2} most severely underestimates arterial P_{O_2} when skin perfusion is decreased from hypotension. Arterial P_{O_2} was also underestimated in infants treated with tolazoline for pulmonary hypertension, possibly because the general peripheral vasodilation caused by the drug exceeded the effect of the preferential local vasodilation intended from local heating of the skin. These

problems have not prevented the application of this noninvasive device for regulating oxygen therapy or ventilatory assistance to infants with neonatal respiratory distress syndrome, for monitoring apnea, for sleep studies, or for analyzing the impact of nursery procedures on oxygenation. The technique is not as well accepted for estimating P_{O_2} in adults, in whom the greater thickness of skin impairs oxygen diffusion. Carter and Banham[201] reported that transcutaneous electrodes for measuring P_{O_2} and P_{CO_2} during exercise in adults with a variety of pulmonary disorders were reliable, provided the electrodes were kept at a slightly higher temperature (45°C) and the work rate intervals were gradual to allow the slow response time. Unfortunately, most other workers have failed to confirm these findings,[202] although the technique appears reliable for measuring the direction of change in arterial P_{O_2} in adult patients performing exercise[203,204] or during sleep studies.

Carbon Dioxide

Capnography. The noninvasive measurement of P_{CO_2} is as important as the measurement of P_{O_2}, especially in critical care units and operating rooms. The measurement of carbon dioxide during the respiratory cycle is called capnometry, and the display of the analog waveform is called a capnogram (eFig. 31.23). This measurement can be made using an infrared spectrometer, which is widely available. Care must be taken to calibrate the instrument regularly and to avoid interference by nitrous oxide, acetylene, and carbon monoxide.[205] A mass spectrometer can be used to measure all the respiratory gases (carbon dioxide, oxygen, and N_2) and many anesthetic gases. This device is very rapid but very expensive. It is used most commonly in pulmonary and exercise laboratories and in operating rooms where sample gases from several patients may be tested in sequence. Capnography is valuable in detecting successful tracheal intubation versus esophageal intubation and in monitoring cardiopulmonary resuscitation. Capnography is also useful in detecting a variety of problems in ventilated patients, including an obstructed endotracheal tube, a disconnected airway, ventilator malfunction, severe pulmonary hypoperfusion, and pulmonary embolism.[206–208]

The end-tidal carbon dioxide may decrease suddenly in a life-threatening situation, such as ventilator malfunction or a disconnected airway, as illustrated in eFigure 31.24. The end-tidal carbon dioxide data may be misleading when dead space is increased (increased anatomic dead space, dead space added in series to the airway of the patient, abnormally increased respiratory rate). In these situations there is an increased difference between arterial and end-tidal carbon dioxide, and the end-tidal level does not plateau. When wasted ventilation is increased because of regional increased ventilation relative to perfusion (e.g., restrictive or obstructive ventilatory defects, parallel dead space, or pulmonary vascular obstruction), differences between arterial and end-tidal carbon dioxide are also increased. In these situations the alveolar plateau is present but abnormally reduced. The shape of the waveform may be diagnostic of pulmonary vascular obstruction (eFig. 31.25).

Colorimetric End-Tidal Carbon Dioxide. In some centers, colorimetric measurement is used instead of capnography or other devices to monitor end-tidal carbon dioxide in critical care units, recovery rooms, and operating rooms. The method appears to be as accurate and sensitive as capnography. Both techniques appear useful in the management of critically ill patients.[209]

Transcutaneous Carbon Dioxide Electrode. A device for transcutaneous measurement of P_{CO_2} has been developed. It also involves trapping gas above the skin layer and measuring carbon dioxide pressure by photometric analysis with infrared light.[210] The device has a long time constant, and skin preparation requires stripping of the stratum corneum. Although the values for transcutaneous P_{CO_2} correspond closely to those for arterial P_{CO_2} in healthy subjects, erroneous values manifest with decreased skin perfusion, edema, and obesity.[201] This electrode does appear useful in long-term monitoring,[211] and its use in evaluating carbon dioxide transfer and wasted ventilation during exercise in adults is growing.[202,212,213] Sensor temperature and placement are important to control to get readings that agree with invasive measurements.[214]

Potential Advantages of Indirect Challenge Tests. Although histamine and methacholine are well-established agents for identifying airway hyperresponsiveness, the response to these agonists is not specific for the diagnosis of asthma. Both agents are better at excluding the diagnosis of asthma than making the diagnosis. Furthermore, neither agonist can establish or exclude the diagnosis of exercise-induced asthma, so they are not appropriate for assessment of persons at occupational risk or of athletes. Many asthmatic patients remain reactive to histamine and methacholine long after treatment, so airway hyperresponsiveness is not useful as a guide to withdrawal from steroid treatment.

According to Anderson and Brannan,[219] dry powder mannitol can identify those patients with exercise-induced asthma who will respond to inhaled corticosteroids. A positive response to mannitol depends on activation of mast cells secondary to osmotic changes in the airways, release of leukotrienes and other mediators, and development of active inflammation in the airways.[219] If the mannitol response is positive, sufficient numbers of inflammatory cells are present to release enough mediators to cause bronchoconstriction. The response to mannitol is reduced by corticosteroid therapy and may disappear within 6 to 8 weeks. Thus mannitol responsiveness may be able to predict the risk for a clinical flare during reduction of the corticosteroid dose.

Tests of Specific Airway Responsiveness

Incremental allergen concentrations are given sequentially until the desired pulmonary function change develops. The response to inhaled allergen depends on both allergic sensitivity, as reflected by skin test, and nonspecific airway responsiveness, as reflected by histamine or methacholine responsiveness.

Most commercial allergens are obtained as lyophilized extracts or as concentrated solutions. These retain potency indefinitely when stored at −20°C. Thus the original guidelines of a starting concentration of *ragweed pollen extract* (AgE) that produces a 2+ reaction (larger than a 5-mm wheal) after intradermal injection is probably safe but may result in many doses having to be delivered in some

patients. With a 2+ skin test at 0.0005 μg AgE/mL, an aerosol of 0.025 μg AgE/mL is used; with a 2+ skin test at 0.005 μg AgE/mL, an aerosol of 0.05 μg AgE/mL is used; and with a 2+ skin test at 0.05 μg AgE/mL, the same concentration of AgE is used in the aerosol challenge.

Aerosol delivery in North America is usually by (1) intermittent generation of aerosol during inspiration from a DeVilbiss 646 nebulizer connected to a dose-metering device that controls flow of compressed air at 20 psi for a fixed time, at a flow rate of 750 mL/min or less,[220] or (2) by a Wright nebulizer with aerosol delivered to a face mask with a nebulizer output of 0.13 to 0.16 mL/min.[221] Respiratory rate, tidal volume, and inspiratory flow rate are kept constant for a fixed time interval, and the volume of aerosol solution administered is 3 mL.

Maximal Inspiratory and Expiratory Pressure. *Minimal inspiratory pressure* (MIP) is measured during a maximal inspiratory effort against an occluded airway. In this test the subject inspires maximally from RV against an obstructed mouthpiece with a small leak (1 mm in diameter) to prevent closure of the glottis or development of pressure above the glottis by the muscles of the cheeks. A plateau pressure should be maintained for at least 1 second. The measurement of *minimal expiratory pressure* (MEP) is similar to that of MIP except the patient exhales forcefully against a brief occlusion from near TLC. There is a wide range of normal predicted values for MIP and MEP, which generally fall with age. Reproducible maximal values are difficult to obtain; the coefficient of variation is about 9% for duplicate tests for MIP and MEP.[222] Because MIP and MEP are recorded near RV and TLC, respectively, they also include contribution of the respiratory system recoil.

Sniff Nasal Inspiratory Pressure. One of the limitations of measuring inspiratory muscle function by MIP is the need to provide a tight seal around the mouthpiece and performing a relatively unnatural maneuver from near RV. In contrast, maximal inspiratory muscle pressure may also be assessed by the somewhat more natural sniff test, which involves measuring peak nasal inspiratory pressure through one nostril during a maximal sniff starting from the end of normal exhalation (FRC).[223] The measured pressure is thought to approximate esophageal pressure and thus reflect inspiratory muscle strength, without significant contribution of respiratory system recoil. *Sniff nasal inspiratory pressure* (SNIP) and MIP are not identical, as SNIP often exceeds MIP in healthy people, perhaps due to more complete neuromuscular activation. There may be a substantial learning effect, with the best SNIP typically achieved after 10 to 20 trials. Like all noninvasive tests of muscle function, SNIP should probably be used in conjunction with other measures for more complete functional assessment of respiratory muscle strength.[224]

Peak Cough Flow. Although not a muscle pressure per se, peak cough flow is thought to reflect underlying expiratory muscle strength. It is the highest flow recorded during a vigorous cough, and the best of four to seven trials is recorded. Peak cough flow may be useful for monitoring expiratory muscle strength, predicting cough efficacy, and evaluating patients for extubation during mechanical ventilation.[225]

Maximum Transdiaphragmatic Pressure. *Maximum transdiaphragmatic pressure* (Pdi_{max}) is measured during the same maneuver as MIP by determining the difference between intragastric and esophageal pressures. These pressures should be measured at RV because maximally negative airway pressure is reduced at larger lung volumes. Conversely, MEPs are greatest at TLC. Because it is difficult to obtain cooperation from patients to exhale to RV, MIP, MEP, and Pdi_{max} are often measured at FRC, which probably accounts in part for the reported variability. Healthy persons can sustain respiratory patterns requiring 40% of Pdi_{max} for long periods without fatigue. When a patient must increase the Pdi/Pdi_{max} ratio to overcome a resistive load, endurance decreases in proportion to the resistive load (eFig. 31.26). Normal subjects can inspire with varying degrees of diaphragm and rib cage contraction. Thus Pdi_{max} may be decreased because of marked recruitment of the rib cage during the test. The range reported is accordingly large: 18 to 137 cm H_2O. Training results in improved coordination and reproducible values with a coefficient of variation of 19%.[226]

Similowski and colleagues[227] have reported the use of *cervical magnetic stimulation* (CMS) as a method of phrenic nerve stimulation. They reported the results of comparisons of stimulated Pdi, with the maximal Pdi obtained during the static combined expulsive-Mueller maneuver (Pdi_{max}) and with the Pdi generated during a sniff test. Their results were comparable to those obtained in other studies using transcutaneous phrenic stimulation. They were highly reproducible in all the subjects. EMG data provided evidence of bilateral maximal stimulation. CMS is a nonspecific method and may stimulate various nervous structures. Co-contraction of neck muscles, including the sternomastoid, was present, but its influence in the CMS-induced Pdi appeared minimal. The method appears to avoid the pain of transcutaneous phrenic stimulation and the potential danger of needle stimulation of the phrenic nerves. However, subsequent studies showed that CMS stimulated many muscles of the upper thoracic cage and the diaphragm. Investigators have used chest wall electrodes to record the diaphragm compound action potential to assess the extent of stimulation of other muscles.[228]

Although initially promising, these studies have demonstrated difficulty in obtaining surface signals of acceptable quality.[229] The variable shape and latency of the action potential induced by magnetic stimulation plus the shorter phrenic nerve conduction times with CMS compared with electrical stimulation indicate that diaphragm EMG after CMS is potentially unreliable, perhaps because chest wall electrodes also record electrical activity from other muscles. As demonstrated by Luo and associates,[230] the method also appears unreliable for the measurement of phrenic nerve conduction time.

Maximum Voluntary Ventilation. MVV measurements can also be used to assess endurance. Endurance decreases as V_E/MVV increases in a pattern similar to that observed with increasing Pdi/Pdi_{max} ratio. In the absence of an

external resistance, the largest ventilation that can be sustained more than 15 minutes is approximately 60% of the MVV.

Diaphragmatic Electromyography. This is another technique used to evaluate respiratory muscle strength and endurance. Changes in respiratory muscle electrical activity appear to reflect closely other aspects of muscle contraction. Normally the phrenic nerve stimulates the diaphragm at a mixture of frequencies between 20 and 400 Hz. A graphic display of the EMG signal strength against frequency is called the power spectrum. When the EMG is analyzed over two limited frequency ranges (<50 Hz and >150 Hz), the power spectrum shifts to the low-frequency range as the diaphragm fatigues. This change precedes failure of contraction, and it therefore may be useful to predict decompensation of the respiratory muscles. Phrenic nerve conduction time may also be used to assess diaphragmatic paralysis or weakness. With recording electrodes placed over the rib cage above the diaphragm, the phrenic nerve is stimulated in the neck. Normal conduction time is 7.7 ± 0.8 msec.

Fluoroscopy. Fluoroscopy may be used to evaluate diaphragmatic function. Decreased excursion should be evaluated with a lateral view using the sniff test. Decreased excursion alone is nonspecific, but decreased excursion associated with paradoxical motion during the sniff test is very specific. False-negative findings may result during spontaneous breathing because of contraction of abdominal muscles during exhalation, which produces a normal-appearing downward motion of the diaphragm when the abdominal muscles relax at the beginning of inspiration. False-positive results may be produced by paradoxical motion limited to the anterior portion of the diaphragm.

Events Precipitating Respiratory Failure

Any one of three events may precipitate respiratory failure: increased work of breathing, decreased energy supply, and decreased muscular efficiency.

Increased Work of Breathing. Higher airflow resistance or greater elastic recoil of lung or chest wall, or both, may increase the work of breathing and the energy required of the respiratory muscles.

Decreased Energy Supply. Reduction in the supply of vital metabolic substrates may limit the efficiency of respiratory muscles under certain circumstances. Reduction in cardiac output, arterial oxygen content, or extraction of oxygen from the blood (or a combination of these factors) may impair aerobic metabolism and compromise respiratory muscle function. Decreased oxygen delivery may be critically important under conditions that increase respiratory work. Oxygen consumption by respiratory muscles may rise 25-fold above baseline under conditions of high ventilatory requirement and increased RAW, and it may exceed supply. Forceful muscle contraction alone impedes blood flow to respiratory muscles in animals breathing against increased respiratory workloads. Other variables related to metabolism (e.g., hypercapnia, malnutrition, acidosis, electrolyte disorders) may also limit endurance.

Decreased Muscular Efficiency. The number and distribution of fiber types determine inspiratory reserve. Disease processes and inactivity may alter the number and relative proportions of fibers in the diaphragm. Under certain conditions, changes in the distribution of fiber types or the loss of fibers may play an important role in the development or maintenance of respiratory failure. For example, atrophy of respiratory muscles is a potentially important problem in patients undergoing long-term mechanical ventilation.[231]

Muscular efficiency depends on mechanical factors and on structure.[232] The position and configuration of the diaphragm at the beginning of inspiration determines the resting length of the muscle fibers. As FRC increases, the contour of the diaphragm flattens, and muscle fibers are not stretched to their optimal length. Acute hyperinflation (as in asthma) may cause a mechanical disadvantage of the diaphragm by shortening muscle fibers. In addition to changing muscle fiber length, hyperinflation also causes a mechanical disadvantage by changing the shape of the diaphragm. The Pdi_{max} is determined by the radius of curvature of the diaphragm at any value of muscle tension (Laplace's law). Thus increasing the radius of curvature of the diaphragm (i.e., flattening the diaphragm) greatly reduces its capacity to develop Pdi and to change lung volume.

Although abdominal muscles are usually regarded as expiratory, abdominal muscle tone may be needed to maintain the mechanical advantage of the diaphragm. Thus flaccidity of abdominal muscles contributes to the inefficient ventilation seen in paraplegic patients, especially when these patients are in the upright position.

VC is a useful test of respiratory muscle weakness because normally a small fraction of the muscle strength is required to inflate the lung. Furthermore, the curvilinear relationship between pressure and volume means that a greater loss of muscle strength (pressure) is required to produce a loss of volume; for example, a 50% decrease in MIP is associated with only a 15% decrease in VC. Although MIP may be reduced markedly before lung volume decreases, most patients with respiratory muscle weakness have decreased VC and decreased lung compliance. The latter finding is thought to result from atelectasis, which may be detectable in chest radiographs. FRC, IC, ERV, and TLC may also be decreased in association with decreased lung elastic recoil, suggestive of decreased outward recoil of the chest wall.

According to Rochester and Esau,[233] substantial respiratory muscle strength can be lost without a change in spirometric values or ABG levels. There is a moderate decrease in MVV and increased RV, and MIP and MEP may be 50% of predicted normal. In advanced chronic disease, patients still may not have symptoms because they are not exercising. When patients reach the stage of poor cough, scoliosis, absent gag reflex, and MIP and MEP less than 50% of predicted normal, MVV is decreased more and RV enlarges further. Overt respiratory failure may develop abruptly, so it is important to follow these patients serially with VC and MIP/MEP studies.

PEDIATRIC TESTING

SPECIAL TESTS AND CONSIDERATIONS IN PEDIATRIC PULMONARY FUNCTION TESTING

It is important to realize that pulmonary physiology in children does not simply reflect a smaller version of pulmonary physiology in adults. In particular, the airways, lung parenchyma and chest wall continue to grow and develop until the early to mid-20s. In accordance, lung function varies over this time period in a way not predicted by lung function in adults. The best example of this is consideration of the FEV_1/FVC ratio. The normal lower limit in young children is substantially higher than that in adults, and particularly higher than the fixed cut-off ratio of 0.7 advocated by the Global Initiative for Chronic Obstructive Lung Disease guidelines. The main reason for this is the enhanced elastic recoil of the lung at younger age.

Common clinical pulmonary function testing with spirometry may be performed in children as young as 3 to 5 years. Because of their increased lung recoil and smaller lung volume, children may reach an end-of-test criterion sooner than adults, and FEV less than 1 second may be more clinically significant, such as $FEV_{0.75}$. However, both the $FEV_{0.75}$ and the popular $FEF_{25\%–75\%}$ have been shown to be no more useful in general than the FEV_1/FVC ratio for diagnosing obstruction in both children and adults.[234] Similarly, bronchodilator responsiveness may be significant at 10% change in FEV_1. The Global Lung Function Initiative reference equations have been published for children as young as 3 years of age.

Other tests of respiratory mechanics performed in children include the forced oscillatory technique and measurement of respiratory resistance by the interrupter technique. Both of these methods have been discussed previously and may be useful in children with asthma, CF, or bronchopulmonary dysplasia.[235] Another test commonly performed in children is the MBNW, primarily to measure FRC and lung volumes, and also LCI as a measure of ventilation heterogeneity. The LCI has become popular as a measurement in children with CF as it appears more sensitive than spirometry to detection of early bronchiectasis.

There are a few highly specialized lung function tests that are performed in infants.[236] One is the use of forced deflation to assess for obstruction by means of the rapid thoracic compression technique. This is performed by rapidly inflating a rubber bladder that surrounds the chest of the sedated infant when lung volume is close to FRC. A modification of this technique is also used, called the raised volume rapid thoracic compression technique, where the infant's lung is first inflated to close to TLC before rapid compression. Lung volumes in infants may be measured by gas dilution or body plethysmography. Lung mechanics can be assessed during muscle relaxation after the induction of the Hering-Breuer reflex to elicit a brief apnea. During this apneic period, the passive deflation pressure and flow at the mouth is recorded to calculate respiratory system compliance. Ventilation heterogeneity can be measured in infants using tidal breathing of an inert gas rather than 100% oxygen as is used in the MBNW technique. Predicted values for all of these methods in infants are limited, but the methods are used in specialized centers to evaluate infants with chronic lung disease or unexplained symptoms and signs of respiratory illness.[237]

laboratory personnel, develops policies and procedures, maintains ongoing quality control, and ensures timely and accurate reporting and interpretation of results. Working closely with the medical director will be a laboratory manager, who typically has direct experience in pulmonary function testing and equipment, as well as supervising personnel and maintaining standard operating procedures. The laboratory manager and all laboratory personnel must be familiar with policies and procedures, including all facility procedures related to safety, hygiene, and infection control, and those related to scheduling and billing. The PF laboratory technologists must be certified as competent in performing PFTs, typically through accredited respiratory care training and credentialing by the National Board for Respiratory Care. All equipment must be in good working order and pass regular calibration checks and quality control for accuracy and safety.[1,238] Quality control should be performed both mechanically, to test the accuracy of equipment, and by testing of healthy, normal biologic controls to check the entire testing process. Quality control analysis should be as rigorous as that found in any laboratory, including careful logs and plotting of longitudinal data to inspect for "out-of-control" conditions.[239]

SAFETY AND CONTRAINDICATIONS TO TESTING

The physical demands and potential hemodynamic consequences of forced exhalation can be challenging for patients with selected conditions. Expert opinion lists recent myocardial infarction, pneumothorax, abdominal surgery, eye surgery, brain surgery, and sinus or middle ear surgery or infection as contraindications; suggested recovery periods before testing vary.[238,240,241] Other safety concerns include pregnancy with cervical incompetence, severe hypertension or hypotension, and history of syncope with forced exhalation or cough. A sensitivity to develop tachyarrhythmia may increase the risk of bronchodilator administration. Interrupting supplemental oxygen for the recommended greater than or equal to 10 minutes before measurements of D_{LCO} may not be tolerated by patients with certain conditions; oxygen saturation should be monitored during the wait time and during testing with a minimum value protocolized at which time testing is aborted. Of note, for the few cases where evidence has accumulated, such as with aortic aneurysms, prior concerns with testing that arose from expert opinion have been tempered.[242]

INFECTION CONTROL

When patients with communicable infectious diseases are referred for PFTs, they always present a potential risk for transmission of infectious diseases to the technical and administrative staff, as well as to other patients who may be in the laboratory for studies at the same time. Pulmonary laboratory directors are familiar with the risk for spreading tuberculosis by aerosols produced by sputum-positive patients. There has also been the more theoretical possibility of transmitting tuberculosis from one patient to another via infected secretions, which may contaminate pulmonary function equipment. The increasing number of immunosuppressed patients in cancer treatment and transplantation programs has raised the possibility of increased risk for transmission of infection to such patients. In most circumstances, testing of patients with active communicable respiratory infection is delayed until the risk of transmission no longer poses a significant threat.

All studies are performed with the patient breathing through a filter that traps particles as small as 0.2 μm in diameter without affecting the results of the physiologic tests performed. It is assumed that infectious particles, whether bacterial, fungal, parasitic, or viral, will be carried in respiratory secretions of such a large size that all of them will be trapped by these filters. However, not all such filters are perfect, and it should not be assumed that they remove the need for regular decontamination.[238] For testing patients with CF, who are at risk of being colonized with multidrug-resistant organisms, special protocols are followed, including circulation of air through a high-efficiency particulate air filter before and after testing; use of gloves, gown, and mask by technical staff; and external cleaning of equipment.

Key Points

- Because pulmonary function testing is effort dependent, technicians must be trained and laboratories must adhere to high standards to obtain the most accurate and reproducible results possible.
- Measurements from spirometry alone, including the flow-volume curve, can be useful in patients whose main physiologic impairment is airway obstruction. The findings from spirometry can provide clues that concomitant restriction is present; however, for assessment of restriction, lung volumes must be measured.
- Gas dilution methods to measure lung volumes are accurate except in patients with airflow obstruction in whom lung volumes may be underestimated. If airflow obstruction is suspected, body plethysmography will yield more accurate measures of functional residual capacity, reserve volume, expiratory reserve volume, and total lung capacity.
- In patients with reversible mild airway disease, the results of pulmonary function tests may be normal. Assessment of spirometry and airway resistance (e.g., by body plethysmography or forced oscillation) before and after bronchodilation may be needed.
- Tests of the distribution of ventilation can provide additional evidence of abnormal structure of the airways or lung parenchyma. They may be more sensitive than spirometry or lung volumes but less specific.
- Methacholine provocation testing is used to identify abnormal airway responsiveness. Usually this indicates a diagnosis of asthma, but the clinician must understand that other conditions that involve airway inflammation may also show abnormal airway responsiveness.
- The diffusing capacity measurement is used to determine defects of the alveolar-pulmonary capillary unit. An abnormal diffusing capacity alerts the physician that the alveolar-capillary membranes and/or pulmonary capillaries may not be normal, and further evaluation of the underlying cause of this defect should be pursued.

Key Readings

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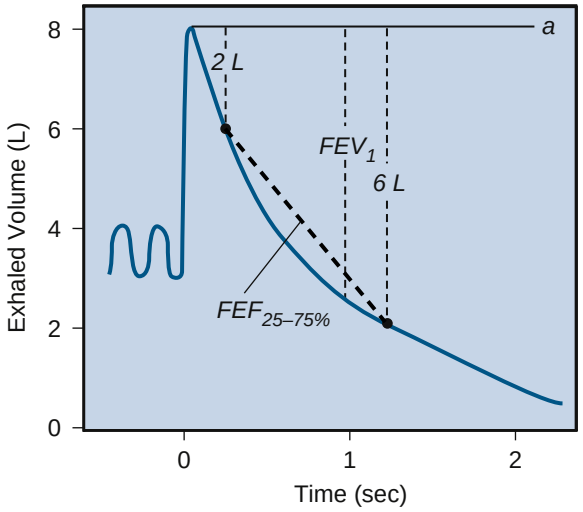
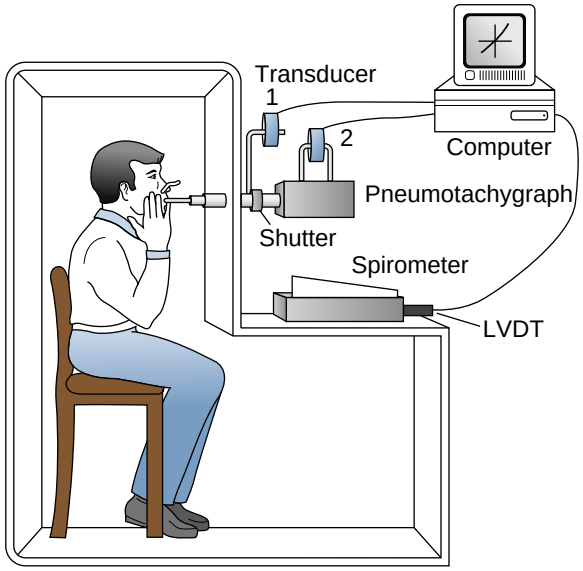
Complete reference list available at ExpertConsult.com.

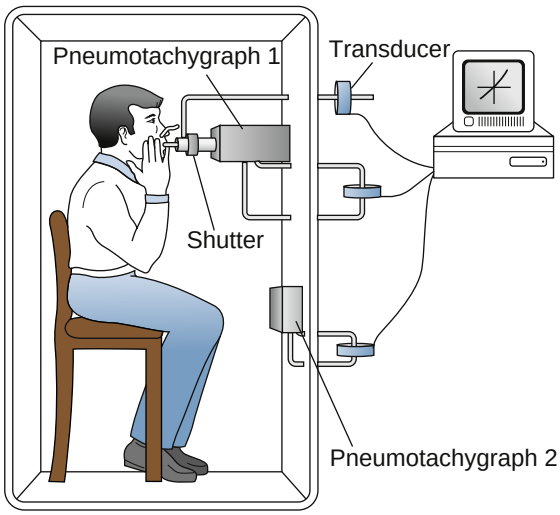
eFIGURE IMAGE GALLERY



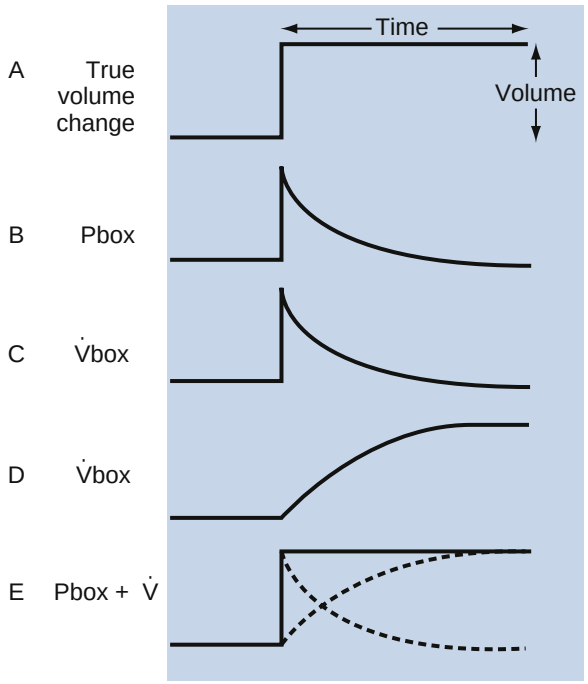
eFigure 31.1 Determination of forced expiratory flow (FEF) between 25% and 75% of total lung capacity ($FEF_{25\%–75\%}$). A *heavy dashed line* connects two points on the volume-time curve of the forced vital capacity (FVC) maneuver. One point is marked when 25% of the FVC has been exhaled (2 L); the other point is marked when 75% of the FVC (6 L) has been exhaled from the level of maximal inhalation indicated by the *solid line* (*a*). In this example, the elapsed time between these two points is 1 second; thus the calculated $FEF_{25\%–75\%}$ is 4 L/sec. FEV_1, forced expiratory volume in 1 second.



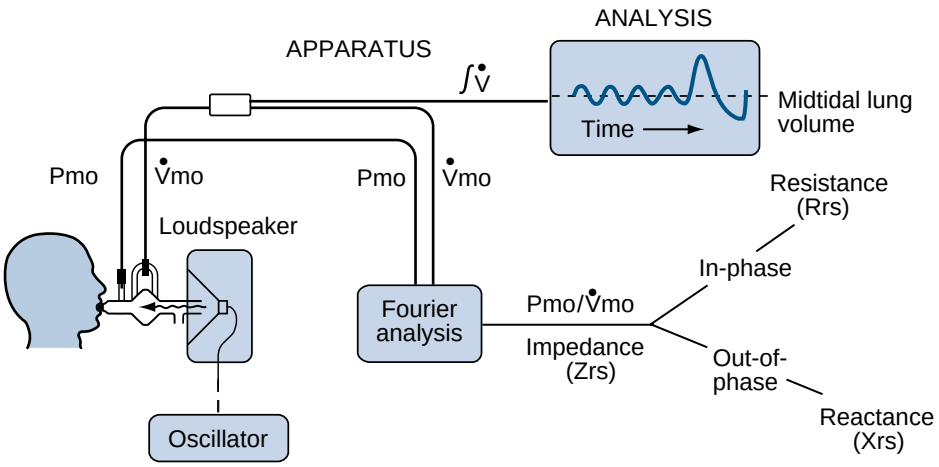
eFigure 31.2 Volume (open-type) plethysmograph. In this constant-pressure, variable-volume type of plethysmograph, the subject also breathes through a shutter/pneumotachygraph apparatus, which usually is located outside the plethysmograph itself. The shutter is open for tidal breathing, measurement of airway resistance, and spirometry. It is closed for measurement of thoracic gas volume. In the closed-shutter mode, mouth pressure is measured by a transducer (*1*) and approximates alveolar pressure with no flow and small volume changes. The pneumotachygraph measures flow via another transducer (*2*, above the pneumotachygraph). Flow is integrated electronically to obtain volume. Changes in volume of the plethysmograph, reflecting movement of the chest wall, are measured with a spirometer and a linear volume-displacement transducer (LVDT). The spirometer illustrated is a Krogh water-sealed spirometer with good frequency response and very small impedance to gas displacement. A low-resistance pneumotachygraph (flowmeter) with a fast, drift-free integrator may be used instead. Processing is usually performed by computer and permits slow and forced vital capacity maneuvers as well. However, neither approach is routine.



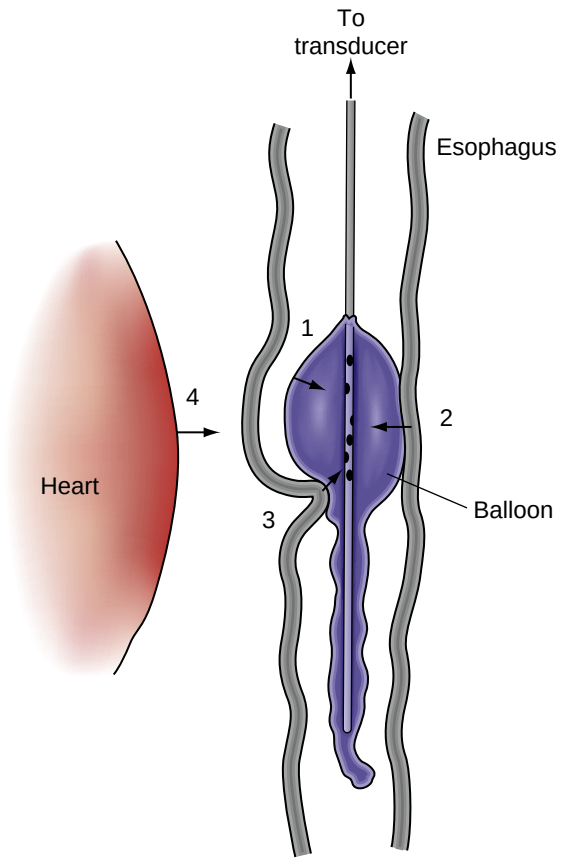
eFigure 31.3 Pressure-volume (or flow) plethysmograph. This type of plethysmograph combines features of the closed and open types. The subject breathes through a shutter/pneumotachygraph apparatus. The shutter is open for tidal breathing, measurement of airway resistance, and spirometry. It is closed for measurement of thoracic gas volume. In the closed position, mouth pressure (alveolar pressure) is measured by a transducer (*top*). The pneumotachygraph at the mouth (pneumotachygraph 1) measures airflow with another transducer (*middle*). This airflow at the mouth is integrated to obtain volume inhaled and exhaled at the mouth. Changes in plethysmograph or box volume resulting from movements of the chest wall are measured by a pneumotachygraph in the wall of the plethysmograph (pneumotachygraph 2) with a third transducer (*bottom*), and this signal is integrated to obtain volume change of the thorax. The signals from all three transducers usually are processed by computer to obtain slow and forced vital capacities, as well as resistance and thoracic gas volumes.



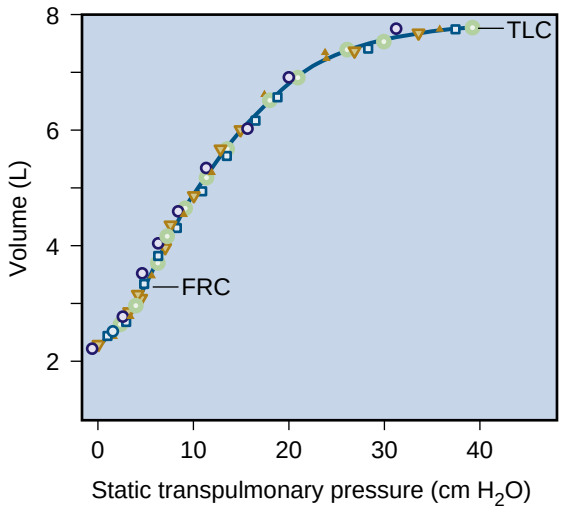
eFigure 31.4 Physical principles underlying pressure-volume plethysmography. (A) The theoretical "true" instantaneous volume event. During this event, plethysmographic pressure increases rapidly and then actually decays exponentially (B). If the plethysmographic pneumotachygraph is linear, the flow signal has a shape similar to that of the pressure transducer (C). This flow signal is integrated to obtain volume (D), which reaches the same level as the true volume event, but the shape does not conform to the "true" event. The difference is a result of the compression of a large volume of gas in the plethysmograph and is directly proportional to the plethysmograph pressure. Therefore, by adding a portion of the plethysmograph pressure to the integrated plethysmograph flow (E), the true volume event is reconstructed accurately: $\Delta V = Pbox + \int \dot{V}box$. Thus the true volume is obtained by adding the plethysmographic compression volume (Pbox) and the displacement volume ($\int \dot{V}box$). More precisely, (1) box pressure (Pbox) is multiplied by a constant (Kbox), a factor to correct pressure to volume that is proportional to the gas volume in the box (total box volume − patient volume); and (2) Pbox is also divided by the box flowmeter resistance (Rbox) to yield box flow ($\int \dot{V}box$), and integrated to obtain volume ($\dot{V}box$.). These two signals are added together to yield the change in lung volume: $\Delta V = PboxKbox + Pbox / Rbox \int \dot{V}box$.



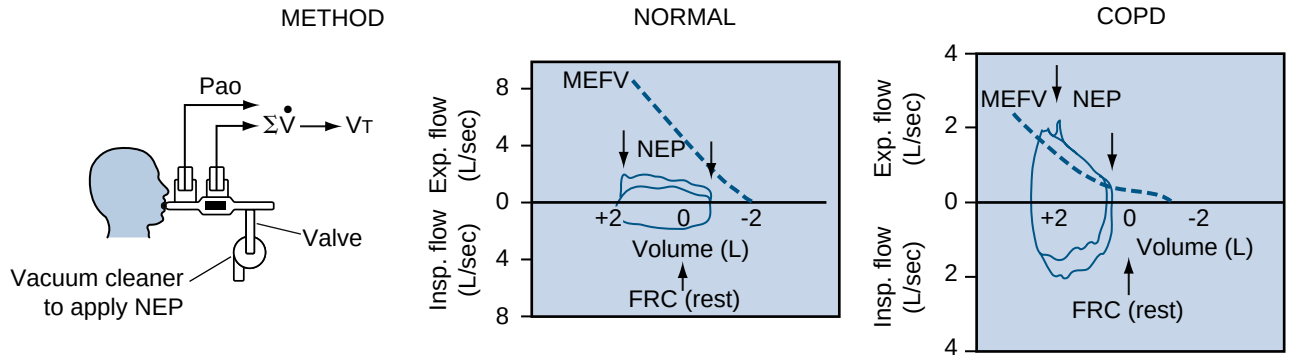
eFigure 31.6 Measurement of respiratory resistance by forced oscillation. A loudspeaker or piston may be driven to produce a sinusoidal oscillation at a single frequency, a sequence of sinusoidal oscillations at diverse single frequencies, or a random noise signal. The flow signal is integrated to yield tidal volume or, at the end of the study, inspiratory capacity. The recorded signals for mouth pressure (Pmo) and flow ($\dot{V}$mo) are directed to a Fourier analyzer, and the component of each signal caused by the applied oscillation is differentiated from changes caused by tidal breathing. Impedance (Zrs) is the sum of all forces that must be overcome to effect flow and includes resistance, elastance, and inertance. Zrs may be calculated at single frequencies over a wide range of frequencies. The impedance is subdivided into the in-phase and out-of-phase components of the primary signals. The in-phase signal is the resistance of the total respiratory system (Rrs), and the out-of-phase signal is the reactance (Xrs), sometimes called the imaginary part of the impedance. The reactance is related to the compliance and inertance of the respiratory system (see text). (Modified from Hughes JMB, Pride NB. *Lung Function Tests*. London: WB Saunders; 1999:35.)



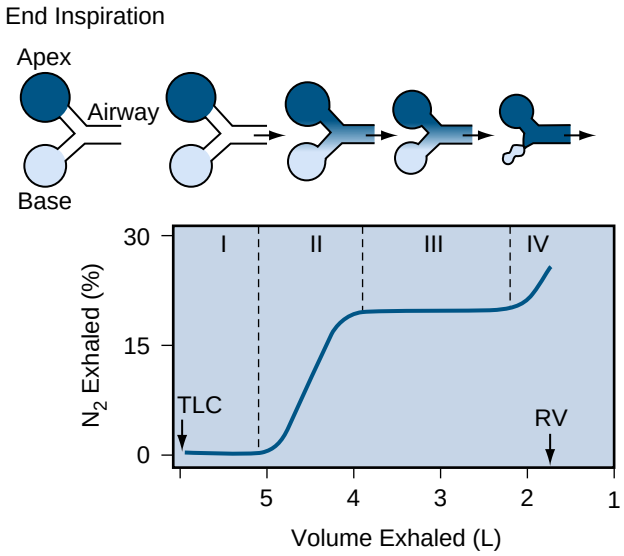
eFigure 31.7 Schematic drawing illustrating the position of an esophageal balloon in relation to adjacent structures. The balloon is made of latex (wall thickness, 0.06 mm; length, 10 cm; circumference, 3.5 cm). The tubing is polyethylene (inner diameter, 0.14 cm; outer diameter, 0.19 cm) with holes placed in a spiral arrangement in the portion inside the balloon. The balloon is filled with 0.2 to 0.4 mL of air and positioned in the lower third of the esophagus. Intraesophageal pressure recorded from the catheter within the balloon is affected by the following factors in addition to static transpulmonary pressure: retractile pressure of balloon wall (*1*), pressure caused by resting esophageal tension (*2*), and pressure caused by mediastinal structures (*3*), including pulsations of the heart (*4*).



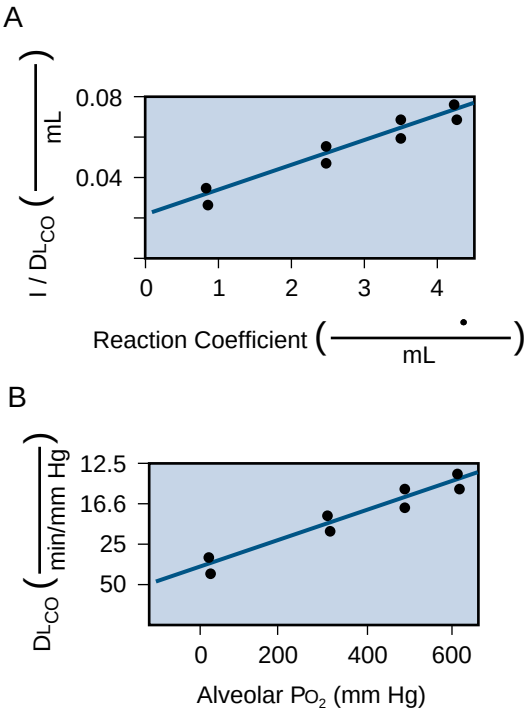
eFigure 31.8 Static pressure-volume curve of the lungs during deflation in a normal subject. Measurements were obtained during five different maneuvers. FRC, functional residual capacity; TLC, total lung capacity.



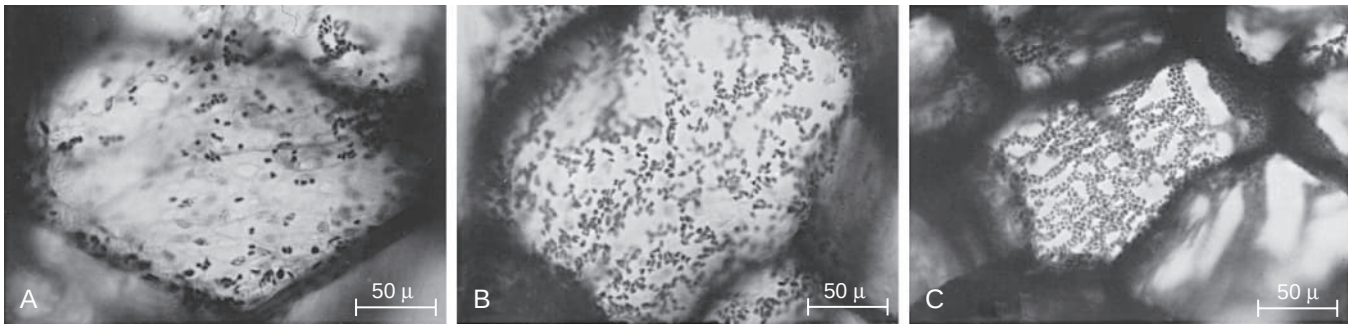
eFigure 31.9 Measurement of expiratory flow limitation by negative expiratory pressure (NEP) method. *Left:* The experimental setup. The subject breathes tidally through a pneumotachygraph that records flow ($\dot{V}$), which is integrated to yield tidal volume (V_T). After recording baseline V_T, a negative expiratory pressure of −5 cm H_2O is applied to the subsequent V_T, in which the pressure at the airway opening (P_{AO}) is reduced by 5 cm H_2O. *Middle and right:* Examples of tidal flow-volume curves. Both results were obtained during exercise. In the normal subject (*middle*), expiratory flow increases, but except for a transient spike of flow, there is no change in flow in a patient with COPD (*right*). Note that the flow and volume scales are different in the two panels, as are the shapes of the curve in the normal individual (rectangular) and in the COPD patient (*right*). The change in volume during exercise is referred to as the functional residual capacity (FRC) at rest. Note the decrease in volume in the normal lung and the increase in volume in the COPD lung during exercise. The *dashed lines* indicate the full maximal flow-volume curves in both subjects. There is a large reserve of expiratory flow in the normal subject, whereas tidal expiratory flow exceeds the full flow-volume envelope at the same volume in the COPD patient. MEFV, maximal expiratory flow-volume. (Modified from Koulouris NG, Dimopoulou I, Volta P, et al. Detection of expiratory flow limitation during exercise in COPD patients. *J Appl Physiol.* 1997;82:723–731.)



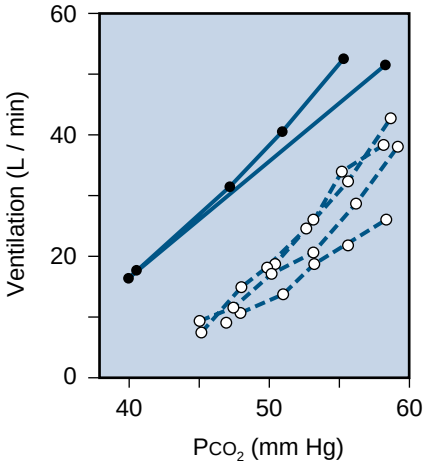
eFigure 31.10 Relationship between nitrogen (N_2) concentrations in different regions of lung (*top*) and the single-breath N_2 washout test of distribution of ventilation (*bottom*). *Top:* Schematic illustration of a ventilatory unit near the lung apex (*dark blue*) and a ventilatory unit near the base (*light blue*) subtended by a common airway. The intensity of color reflects the end-inspiratory concentration of the resident gas (N_2) at the end of a single maximal inspiration of pure oxygen (O_2) (at total lung capacity [TLC]). The differences in N_2 concentration in each unit result from the effect of differences in regional residual volume (RV) and the distribution of inspired gas (see text). *Bottom:* At the start of exhalation, the gas (pure oxygen) in the conducting airway empties first, and 0% N_2 is recorded (phase I). As exhalation continues, gas from both ventilatory units mixes in the airway, and the N_2 concentration increases rapidly (phase II). With continued exhalation, mixed alveolar gas is recorded by the N_2 analyzer (phase III). Finally, dependent airways at the base of the lungs close near RV (closing volume), and exhalation continues from the apical ventilatory unit of the lung only, which contains a higher N_2 concentration than the basal unit (phase IV).



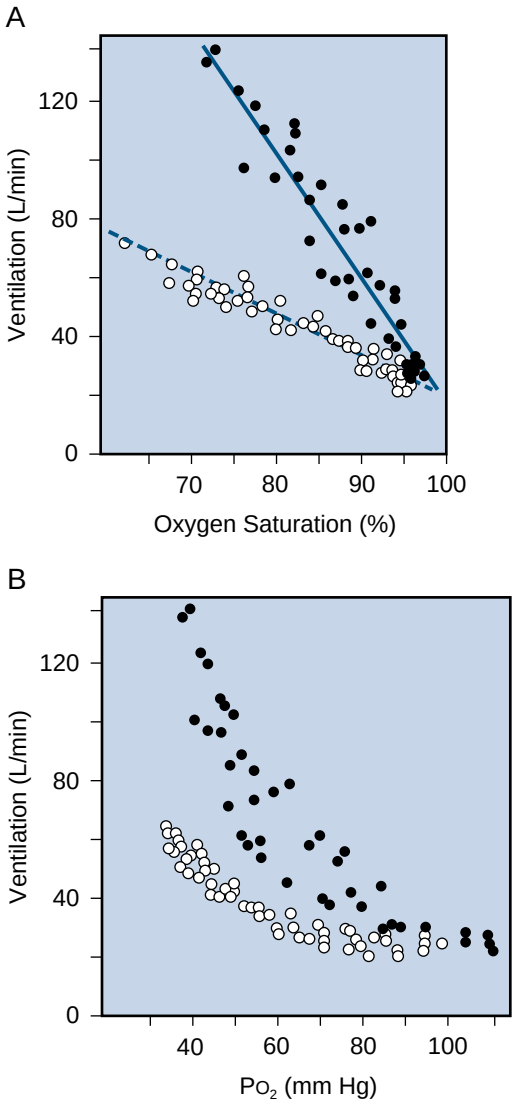
eFigure 31.11 Subdivisions of the diffusing capacity of carbon monoxide. Experimental values of the diffusing capacity of carbon monoxide ($D_{L_{CO}}$) obtained at different alveolar partial pressure of oxygen (P_{O_2}) values (*x*-axis in B) can be analyzed mathematically to obtain the subdivisions of total $D_{L_{CO}}$: the diffusing capacity of the membrane (D_M) and pulmonary capillary blood volume (V_C). As the alveolar P_{O_2} was increased from 40 to 600 mm Hg, the duplicate measurements of $D_{L_{CO}}$ decreased from approximately 45 to 15 mL/min/mm Hg. Changing alveolar P_{O_2} changes the reaction coefficient (θ), reflecting the change in hemoglobin affinity for carbon monoxide. The reaction coefficient is plotted against $1/D_{L_{CO}}$ in part A. There is a linear relationship between $1/D_{L_{CO}}$ and $1/\theta$ such that $1/D_{L_{CO}} = 1/\theta V_C + 1/D_M$. Under these conditions, D_M is derived from the value of the *y*-intercept and V_C from the slope of the line.



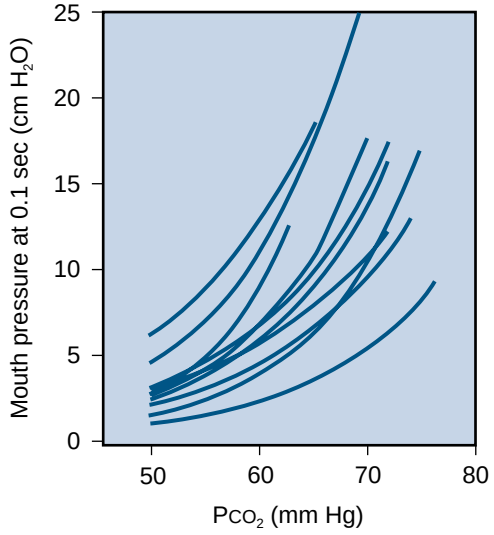
eFigure 31.12 Face-on views of freeze-dried, stained alveolar walls (200 μm thick section) showing the distribution of the pulmonary capillary bed in anesthetized cats. (A) Zone I lobe. (B) Zone II lobe. (C) Zone III lobe. Morphometric analysis showed that 21% of the alveolar walls were occupied by red blood cells in zone I lobes, 43% in zone II lobes, and 61% in zone III lobes. Independent changes in pulmonary arterial or venous pressure were associated with changes in the pulmonary capillary blood volume over a threefold range. (From Vriem CE, Staub NC. Pulmonary vascular pressures and capillary blood volume changes in anesthetized cats. *J Appl Physiol.* 1974;36:275–279.)



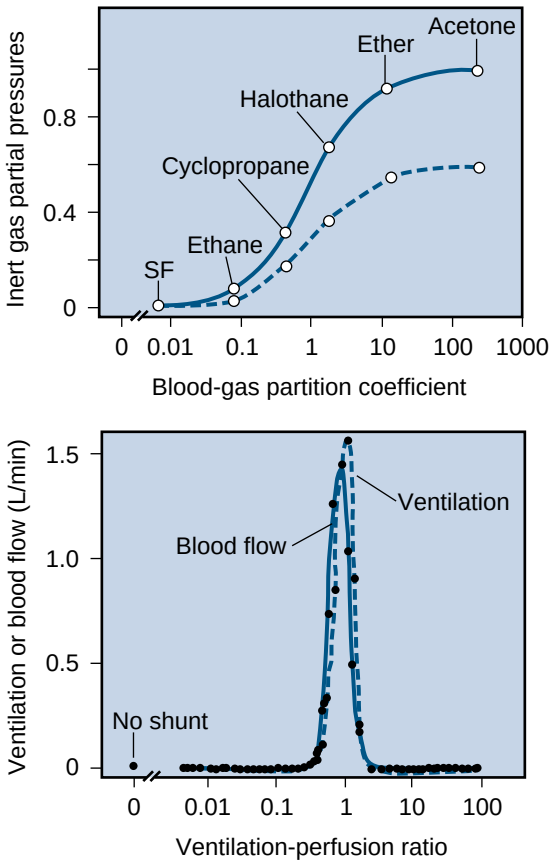
eFigure 31.13 Comparison of rebreathing and steady-state hypercapnic response curves. Response lines defined by the steady-state method (*solid circles*) and by the rebreathing method (*open circles*) are shown for two experiments on the same subject. In one experiment, the steady-state points were defined by inhalation of each of four carbon dioxide mixtures for 20 minutes without intervening periods of air breathing. In the other experiment, the steady-state points were defined by inhalation of each carbon dioxide mixture for 30 minutes, with an intervening rest period of 30 minutes. The figure illustrates a difference in position of the response lines due to a smaller partial pressure of carbon dioxide (P_{CO_2}) gradient between arterial blood and chemoreceptor tissue during the rebreathing method. The close agreement in slope implies that the ratio of change in end-tidal P_{CO_2} to change in chemoreceptor P_{CO_2} is the same in the two methods. (Modified from Read DJ. A clinical method for assessing the ventilatory response to carbon dioxide. *Australas Ann Med.* 1967;16:20–32.)



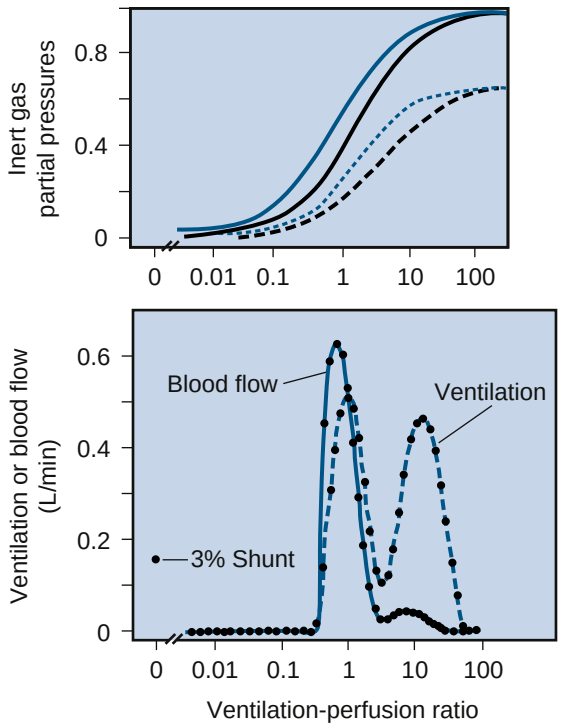
eFigure 31.14 Hypoxic response curves, representing pooled results of four studies in two subjects. (A) Ventilation is plotted against oxygen saturation, producing linear responses. (B) The more traditional hyperbolic relationship is obtained by plotting ventilation against alveolar partial pressure of oxygen (P_{O_2}). (Modified from Rebuck AS, Campbell EJM. A clinical method for assessing the ventilatory response to hypoxia. *Am Rev Respir Dis.* 1974;109:345–350.)



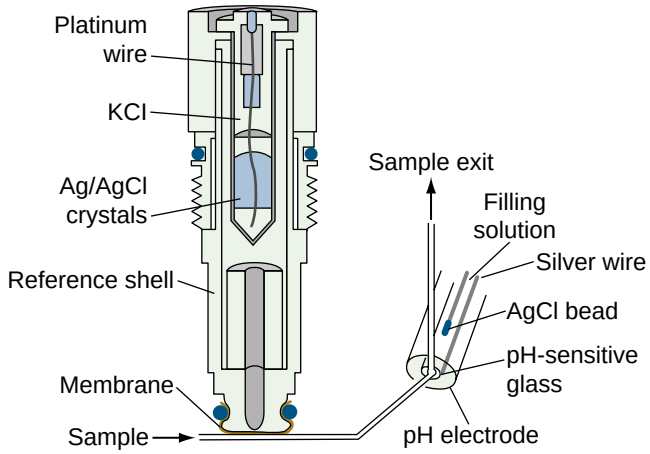
eFigure 31.15 Inspiratory occlusion pressure at 100 msec (0.1 second) in response to hypercapnia. Each curve is the mean regression of mouth pressure at 0.1 second against partial pressure of carbon dioxide (P_{CO_2}) for one subject. Inspiratory occlusion pressure may be used to measure the output of the respiratory center in response not only to hypercapnia but also to hypoxia, exercise, and other factors. (Modified from Whitelaw WA, Dernne J, Milic-Emili J. Occlusion pressure as a measure of respiratory center output in conscious man. *Respir Physiol.* 1975;23:181–199.)



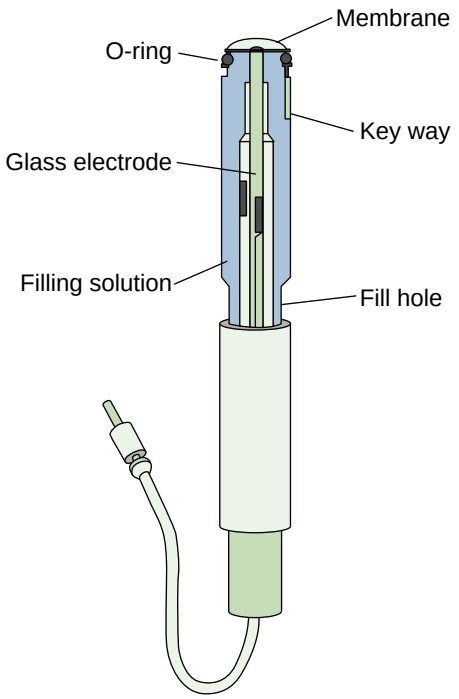
eFigure 31.16 Distribution of ventilation-perfusion ratios in a normal person. *Top:* The retention (arterial/venous, *solid line*) and excretion (expired/venous, *dashed line*) data points together with the curves for a homogeneous lung. *Bottom:* Continuous distribution of ventilation-perfusion ratios as found in a semirecumbent young (22-year-old) normal subject by means of the inert gas elimination method. Note the narrow dispersion and the absence of shunt. The *dashed line* indicates ventilation, and the *solid line* indicates blood flow. SF, sulfur hexafluoride. (Modified from West JB. *Ventilation/Blood Flow and Gas Exchange.* 3rd ed. Oxford: Blackwell Scientific; 1977.)



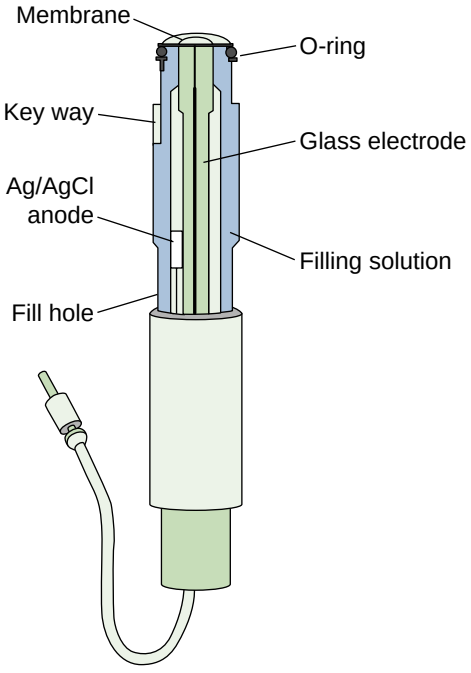
eFigure 31.17 Distribution of ventilation-perfusion ratios in a COPD patient. *Top:* Retention and excretion-solubility curves. *Black lines* indicate data from the patient; *blue lines* indicate data from the normal subject depicted in eFig. 31.16. *Bottom:* Continuous distribution of ventilation-perfusion ratios in a 60-year-old patient with chronic airway obstruction, predominantly emphysema. The *dashed line* indicates ventilation and the *solid line* indicates blood flow. Note the broad bimodal distribution with the large amount of ventilation going to lung units with very high ventilation-perfusion ratios. (Modified from West JB. *Ventilation/Blood Flow and Gas Exchange*. 3rd ed. Oxford: Blackwell Scientific; 1977.)



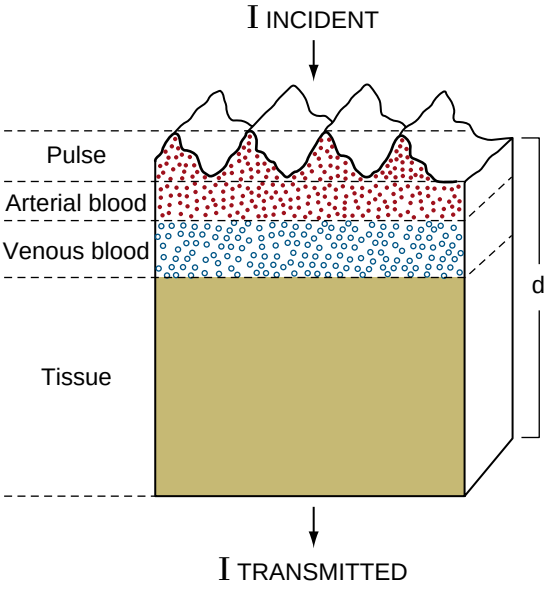
eFigure 31.18 The structure of a pH electrode, which comprises two cells. The measurement half-cell consists of a fine capillary tube of pH-sensitive glass separating the introduced sample of 25 μL from the buffered solution and a silver/silver chloride (Ag/AgCl) electrode to conduct the generated potential difference to the electronic circuitry. The reference half-cell usually contains a calomel (mercury/mercurous chloride) electrode in an electrolyte solution to provide a constant reference voltage and is connected to the measurement half-cell by a contact bridge to complete the circuit. Both cells are enclosed in a sealed jacket and maintained at a constant temperature. KCl, potassium chloride.



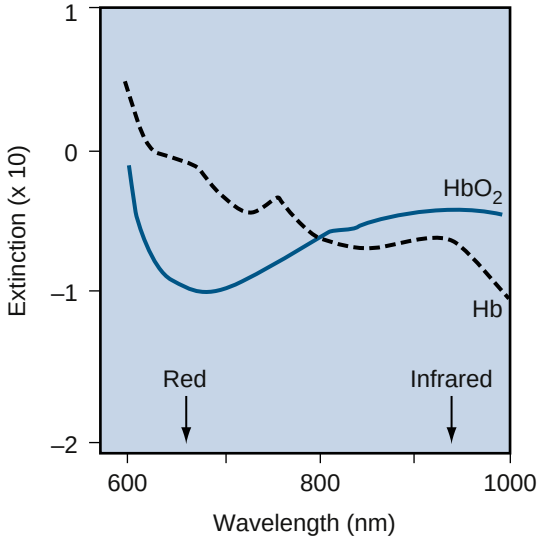
eFigure 31.19 The structure of a carbon dioxide electrode. This electrode uses the combination of the relationship between partial pressure of carbon dioxide (P_{CO_2}) and pH in a buffered solution and the design of a pH electrode. The sample is separated from a buffer solution by a membrane permeable to carbon dioxide. The carbon dioxide molecules diffuse through the membrane, altering the concentration of carbonic acid, and therefore the hydrogen ion concentration in the buffered solution. The change in pH is read by a pH meter with output scaled in terms of P_{CO_2}.



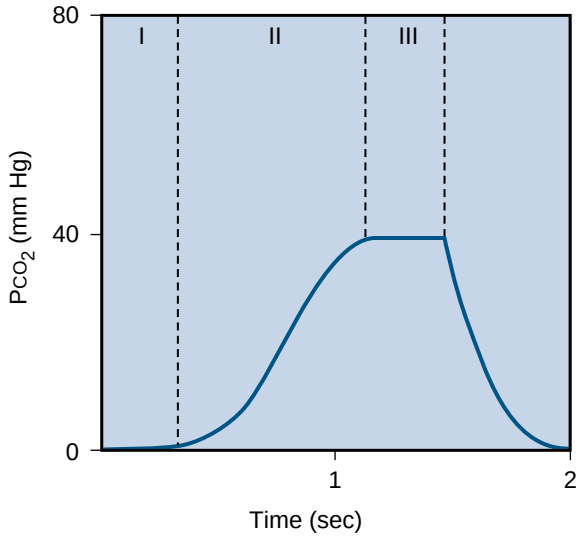
eFigure 31.20 The structure of an oxygen electrode. This electrode consists of platinum and silver electrodes placed in potassium chloride solutions, a polarizing voltage of 0.5 to 0.6 volts, and an electrolyte bridge to complete the circuit. Oxidation at the silver (Ag) electrode secondary to silver reacting with chloride ions to form silver chloride (AgCl) produces electrons that are consumed at the platinum electrode by reduction of oxygen. The flow of electrons (the current) is thus proportional to the concentration of oxygen at the platinum electrode.



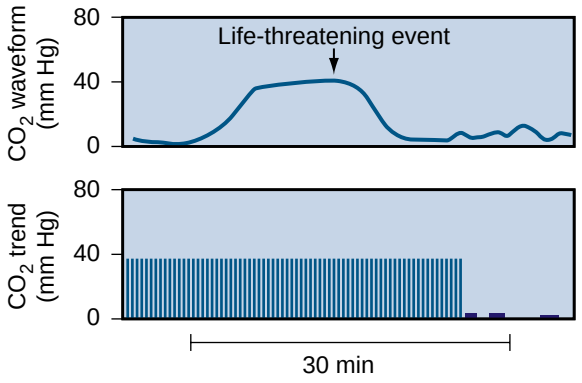
eFigure 31.21 Factors influencing detection by pulse oximetry of light absorption through a pulsatile vascular bed. *Solid red circles* represent light absorption by hemoglobin in arterial blood and by the pulse of arterial blood; *open blue circles* represent light absorption by hemoglobin in venous blood; *shaded zone* represents absorption by tissue that absorbs incident light. d, distance through tissue that absorbs incident light.



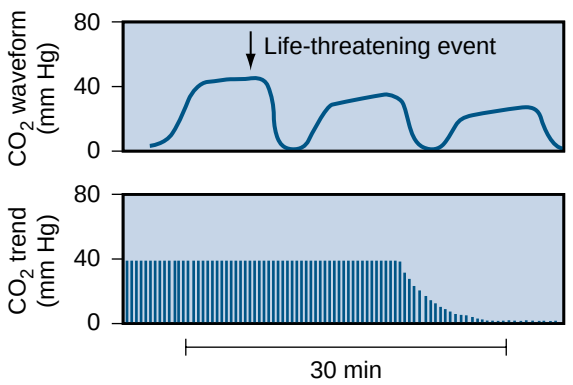
eFigure 31.22 Absorption spectrum of reduced hemoglobin (Hb) and oxyhemoglobin (HbO_2). Readings are made at 660 nm (red) and 940 nm (infrared) wavelengths.



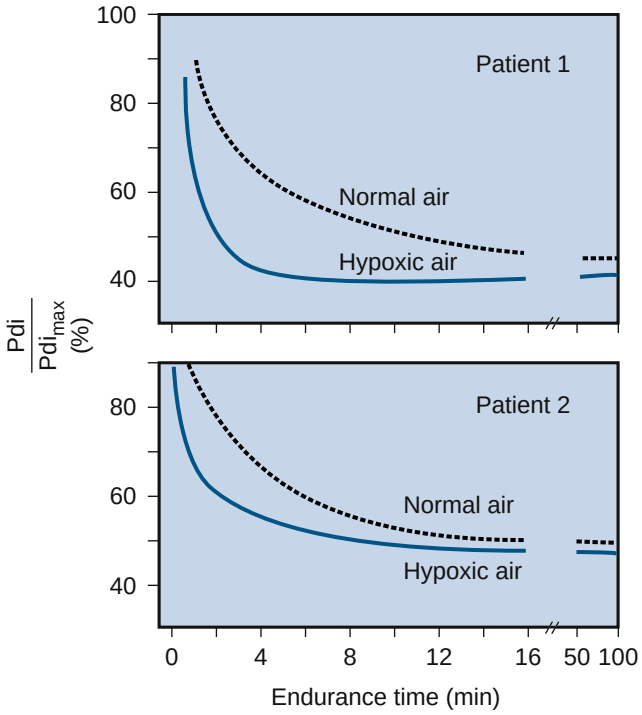
eFigure 31.23 Normal capnogram. During inspiration, partial pressure of carbon dioxide (P_{CO_2}) is zero. At the start of exhalation, P_{CO_2} remains zero as gas from the anatomic dead space leaves the airway (comparable to phase I in the single-breath nitrogen washout test). Next, P_{CO_2} rises rapidly as alveolar gas mixes with gas from the dead space (comparable to phase II in the single-breath nitrogen washout test), and then the P_{CO_2} level stabilizes as gas from the dead space decreases, and all the gas comes from alveoli containing CO_2. The P_{CO_2} at the end of the "alveolar plateau" is called the end-tidal P_{CO_2} (comparable to phase III in the single-breath nitrogen washout test).



eFigure 31.24 Abnormal capnogram. The sudden decrease in end-tidal partial pressure of carbon dioxide (P_{CO_2}) suggests a life-threatening situation in which the capnograph no longer detects carbon dioxide in the exhaled gas. This capnogram suggests the possibility of esophageal intubation, obstructed endotracheal tube, disconnected airway, or ventilator malfunction; these possibilities must be excluded before it can be assumed that the capnograph is malfunctioning.



eFigure 31.25 Abnormal capnogram with an exponential decrease in end-tidal partial pressure of carbon dioxide (P_{CO_2}). Note the progressively more sloping alveolar plateau, reflecting not only abnormal distribution of ventilation but also uneven perfusion relative to ventilation. This pattern suggests a potential life-threatening situation such as cardiac arrest, severe pulmonary hypoperfusion, or pulmonary embolism, as discussed in the text.



eFigure 31.26 Diaphragmatic endurance in two patients in normal and hypoxic conditions. The relationship between endurance and transdiaphragmatic pressure (Pdi) is expressed as a percentage of maximal transdiaphragmatic pressure (Pdi_{max}). Data from two patients breathing normal and hypoxic air are shown. Added resistance leads to an increased Pdi/Pdi_{max} ratio and increases the work of breathing. As the Pdi/Pdi_{max} ratio increases, endurance rapidly decreases. This effect is more pronounced when the respiratory muscles are hypoxic. (Modified from Roussos CS, Macklem PT. Diaphragmatic fatigue in man. *J Appl Physiol.* 1977;43:189–197.)

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32 PULMONARY FUNCTION TESTING: INTERPRETATION AND APPLICATIONS

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INTRODUCTION

Pulmonary function tests are a core tool in the diagnostic approach to common signs and symptoms that bring patients to the pulmonary consultant (Table 32.1). These reasons include cough, shortness of breath, wheezing, hypoxemia, and imaging abnormalities. The results of pulmonary function tests sometimes are a core part of disease definitions, as in the case of asthma and COPD and, in many other cases, narrow the differential diagnosis and suggest further specific testing. Pulmonary function tests also provide objective data for physicians to monitor disease activity and response to treatment. This chapter addresses the applications of pulmonary function tests; the underlying principles are covered in Chapter 31.

MAJOR PATTERNS ON PULMONARY FUNCTION TESTS

Pulmonary function test results can be classified into the following major patterns: normal, obstructive ventilatory defect, restrictive ventilatory defect, mixed pattern (when lung volumes are available) or a pattern that is not clearly obstructive or restrictive (when lung volumes are not available), and a nonspecific pattern (Fig. 32.1). Patient effort and cooperation are essential for acquiring valid spirometry; hence spirometry efforts should be assessed for quality before interpretation. The *American Thoracic Society* (ATS) and *European Respiratory Society* (ERS) guidelines recommend that at least three acceptable spirograms should be obtained.[1,2] Testing should be repeated until the two largest *forced vital capacity* (FVC) measurements and the two largest *forced expiratory volume in 1 second* (FEV_1) measurements from acceptable spirograms are within 150 mL of each other, or, if this is not achieved, until a practical upper limit of eight efforts have been made.[1,2] Failure to meet acceptability criteria should be noted in the report and considered when interpreting results.

OBSTRUCTIVE VENTILATORY DEFECT

Obstruction to airflow is characterized by a decrease in FEV_1/FVC, reduced FEV_1, normal (or reduced) FVC, normal (or reduced) *vital capacity* (VC), and a decrease in measures that may reflect small airway disease (Table 32.2). It is also characterized by an upward concavity in the expiratory flow-volume curve (also described as curvilinear) (Fig. 32.2). Supplementary data supporting airflow obstruction include increased *residual volume* (RV), RV/*total lung capacity* (TLC) ratio and *airway resistance* (RAW), uneven distribution of ventilation, and significant reversibility of airflow obstruction, with or without decreased diffusing capacity. Examples of diseases that manifest with airflow obstruction are shown in eTable 32.1.

eTable 32.1 Examples of Diseases Resulting in the Major Pulmonary Function Test Patterns

Obstructive	Restrictive	Mixed

■ COPD
■ Bronchial asthma
■ Acute bronchitis
■ Bronchiolitis
■ Bronchiectasis
■ Cystic fibrosis
■ Alpha$_1$-antitrypsin deficiency
■ Bronchiolitis obliterans
  ■ Associated with connective tissue disease
  ■ After allogeneic hematopoietic stem-cell transplantation
  ■ After lung transplantation
  ■ Drug toxicity
  ■ Idiopathic
	PARENCHYMAL
	■ Interstitial lung disease
	  ■ Idiopathic pulmonary fibrosis
	  ■ Nonspecific interstitial pneumonitis
	■ Asbestosis
	■ Berylliosis
	■ Eosinophilic pneumonia
	■ Silicosis
	■ Sarcoidosis
	■ Congestive heart failure
	■ Drugs (amiodarone, methotrexate, nitrofurantoin)
	EXTRAPARENCHYMAL
	■ Obesity
	■ Pregnancy
	■ Kyphosis
	■ Scoliosis
	■ Ankylosing spondylitis
	■ Respiratory muscle weakness
	  ■ Guillain-Barré syndrome
	  ■ Amyotrophic lateral sclerosis
	  ■ Muscular dystrophy
	  ■ Myasthenia gravis
	  ■ Diaphragmatic paralysis
	  ■ Botulism
	■ Pleural disease (rheumatoid arthritis, asbestosis, fibrothorax)
	■ Lung resection
		■ Bronchiectasis
		■ Cystic fibrosis
		■ Sarcoidosis
		■ Pulmonary Langerhans cell histiocytosis
		■ Lymphangioleiomyomatosis
		■ Hypersensitivity pneumonitis
		■ Congestive heart failure

Table 32.1 Indications for Pulmonary Function Tests

SPIROMETRY
Diagnose obstruction
Quantify severity
Assess effects of occupation/environment
Assess effects of therapy
Assess preoperative eligibility
Assess disability/impairment
LUNG VOLUMES
Diagnose restriction
Assess hyperinflation and air trapping
DIFFUSING CAPACITY
Diagnose early or mild parenchymal lung disease
Assess progression of parenchymal lung disease
Assess pulmonary involvement in systemic diseases
Differentiate obstructive diseases
Assess pulmonary vascular disease
Assess cardiovascular disease
Assess drug toxicity

Although lung function varies along a continuum, categorization of lung function using thresholds aids in clinical decision making and in recognizing major disease patterns, with the caveat that caution should be exercised in the interpretation of borderline results.

The first step in the interpretation of spirometry is to evaluate the ratio of the FEV_1 to the FVC (see Fig. 32.1). FEV_1/FVC should be interpreted as an absolute ratio and not its percentage of predicted. If this ratio is less than 0.70, it indicates that less than 70% of the VC was exhaled in the first 1 second during a forced exhalation maneuver. FEV_1/FVC less than the fifth percentile is a statistical definition of abnormality recommended by the ATS/ERS document that can reduce bias (e.g., a change associated with age but not disease),[3] although recent data suggest a fixed threshold of less than 0.70 may be more suitable for diagnosing COPD and the associated clinically relevant outcomes, such as hospitalizations and mortality.[4–7] The Global Initiative for Chronic Obstructive Lung Disease document and other respiratory society statements suggest a threshold of less than 0.70 for the postbronchodilator FEV_1/FVC ratio to diagnose COPD.[8–10] A fixed approach posits a uniform threshold below which normal physiologic reserves are overcome. The diagnosis of airflow obstruction should be made using postbronchodilator values because a substantial number of individuals have reversibility of airflow obstruction, and prevalence estimates can vary by as much as 33% depending on whether prebronchodilator or postbronchodilator values are used.[11]

Because the end of a test is sometimes hard to detect or achieve, FVC can be substituted by FEV_6, the forced expiratory volume in the first 6 seconds, thus setting time as the end-of-test criterion rather than plateaued low flow. FEV_6 is generally lower than FVC, especially in those with obstructive lung diseases[12,13]; hence, a ratio of FEV_1/FEV_6 less than 0.73 is equivalent to FEV_1/FVC less than 0.70 for the diagnosis of airflow obstruction.[13,14] Reference equations are also available for FEV_1/FEV_6.[15,16]

When FEV_1/FVC is low, the next step is to evaluate FEV_1 and FVC. A reduced FEV_1 further supports the presence of airflow obstruction, especially when the FVC is normal. The degree of impairment of FEV_1 can be used to grade the severity of airflow obstruction (Table 32.3). An isolated decrease in FEV_1/FVC without abnormalities in FEV_1 or FVC suggests early or mild airflow obstruction.[17] This may also represent *dysanaptic* lung growth leading to a high FVC with a normal FEV_1.[18] Dysanapsis, a mismatch of airway tree caliber to lung size, was historically thought to be a physiologic variant but has now been shown to be associated with symptoms and outcomes.[19,20] Demonstration of bronchodilator responsiveness also supports a diagnosis of airflow obstruction (see section "Bronchodilator Responsiveness").

VC measurements can be obtained while performing a *slow* (SIVC) or a *fast* (FIVC) *inspiratory vital capacity* maneuver or a *slow* (SVC) or *fast* (FVC) *expiratory vital capacity* maneuver. Given that airflow resistance is greater during forced exhalation than during slow inhalation, FIVC > SIVC > SVC > FVC in individuals with obstructive lung disease.[21] FVC is the most commonly reported measure of VC because inspiratory maneuvers are not always performed in pulmonary function testing laboratories, and reference values are most reliably available for FVC. Although either SVC or FIVC can be substituted for FVC in the FEV_1/FVC ratio, there are no normative data available to interpret these ratios adequately.

A number of additional tests may be needed to confirm airflow obstruction in cases in which spirometry results are borderline, or when clinical features suggest an obstructive airway disease but FEV_1 and FEV_1/FVC are normal. A commonly used metric is the *forced expiratory flow at 25% to 75% of the FVC* ($FEF_{25\%–75\%}$), also called the maximum midexpiratory flow.[22] The physiologic basis for this metric is that the lung elastic recoil is lower and airway dimensions are smaller at lower lung volumes; hence, this metric has been postulated to reflect abnormalities in small airways and to be sensitive to early changes in lung elastic recoil. $FEF_{25\%–75\%}$ has high variability, however, due to its dependence on the FVC, and normal values range from 60–140% of predicted. Although a value of less than 60% predicted has often been used to diagnose mild airflow obstruction, its utility in the presence of a normal FEV_1/FVC is questionable. The $FEF_{25\%–75\%}$ is highly correlated with FEV_1 and FEV_1/FVC, and there is minimal discordance between these metrics in population studies.[23] Prediction equations are hard to interpret for this metric because $FEF_{25\%–75\%}$ is measured at a different lung volume in patients with disease (in whom FVC is abnormal) than in healthy subjects (in whom FVC is normal). Mild airflow obstruction can also be detected by the low flow at end expiration. Lung segments with longer time constants, and therefore slower to empty, are represented in the latter part of the spirometry curves. By including a larger component of the distal segment of the expiratory curve, the FEV_3 appears to be more sensitive to mild airflow obstruction than FEV_1/FVC. Compared with FEV_1/FVC, FEV_3/FVC is more sensitive in identifying reductions in terminal expiratory flow.[24,25]

Visual inspection of the flow-volume curve can also aid detection of an obstructive pattern in a few ways. Both

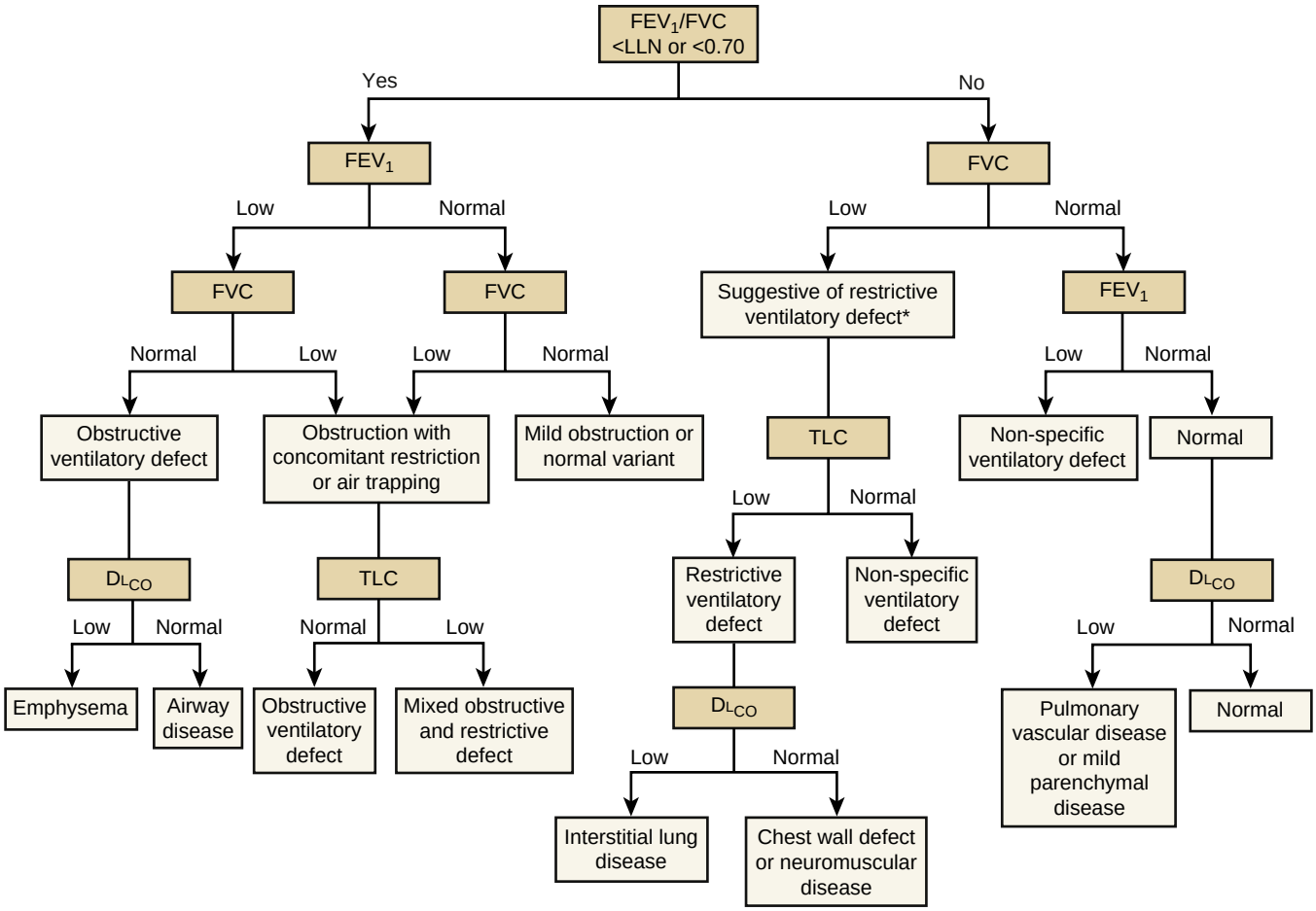

Figure 32.1 Algorithm for interpretation of pulmonary function tests. The major pulmonary function tests include spirometry, lung volumes, and diffusing capacity. The figure provides a simplified schema for interpretation of common lung function patterns. Before interpreting lung function tests, evaluate the flow-volume and volume-time curves to ensure quality of the maneuver(s) and to identify patterns suggestive of obstructive ventilatory defect, restriction, or large airway obstruction. The first step in the interpretation is consideration of the *forced expiratory volume in 1 second* (FEV_1) to the *forced vital capacity* (FVC) ratio. Low FEV_1 and low FVC will lead to a consideration of an obstructive ventilatory defect. *Total lung capacity* (TLC) is necessary for confirmation of a restrictive ventilatory defect. *Diffusing capacity of carbon monoxide* (D_{LCO}) helps assess presence of parenchymal disease in the setting of both obstructive and restrictive patterns; however, as noted in the text, the sensitivity and specificity of the D_{LCO} for detection of emphysema, interstitial lung disease, or pulmonary vascular disease is not high near the LLN. Not infrequently, individuals have features of a mixed obstructive and restrictive pattern. A nonspecific pattern results when the FEV_1/FVC is normal and either the FEV_1 is low or the FVC is low and the TLC is normal. All patterns other than an obstructive ventilatory defect should be either confirmed or further evaluated with sequential testing as suggested in the schema. The schema gives a sequential approach that does not capture all combinations of test results. For combinations not represented (e.g., TLC < LLN and normal FVC, or D_{LCO} and FEV_1 < LLN with normal FEV_1/FVC), the individual abnormalities may require further evaluation. *Low* indicates a value below the LLN; *normal* means at or above the LLN. *When FEV_1/FVC is above LLN and FVC is low but the FEV_1/FVC ratio is lower than expected—for example, considerably lower than the predicted value for the ratio—this can be interpreted as not clearly obstructive or restrictive. This pattern on spirometry alone should be investigated with further lung volume testing or imaging and followed closely.

small airway obstruction and poor elastic recoil due to emphysema can result in reduced flow at lower lung volumes with relatively preserved flows at higher lung volumes, and a resultant concave upwards pattern on the distal part of the flow-volume curve (see Fig. 32.2).[26] Also, when expiratory airflow rates during quiet breathing exceed those during maximal effort, it is attributed to abnormal compressibility or collapse of the airway walls; in this situation, tidal breathing involves less expiratory force, less collapse of highly collapsible airways, and slightly greater flow than seen with a maximal forced expiratory maneuver (see Fig. 32.2). This pattern has been termed *negative effort dependence* and may be seen in diseases associated with airflow obstruction, including emphysema, cystic fibrosis, and bronchiolitis obliterans; small amounts of negative effort dependence may be an artifact of gas compression.[27] Finally, a number of metrics have been derived by mathematically quantifying the shape of the flow-volume and volume-time curves; these include the estimation of the angle between the first and second slopes in the descending part of the flow-volume curve or the "spirographic kink,"[28–31] quantification of the curvature of the expiratory curve,[32,33] the slope-ratio of the middle 20–80% of the expiratory curve to quantify its concavity,[34] flow ratio expressed as a percentage of the instantaneous flow at 75% of the expired vital capacity

Table 32.2 Obstructive Ventilatory Defect

CHARACTERISTICS OF OBSTRUCTIVE VENTILATORY DEFECT
Decreased FEV_1/FVC
Decreased FEV_1
Normal or decreased FVC or VC
OTHER DATA SUPPORTING OBSTRUCTION
Concave upward flow-volume curve (i.e., curvilinear)
Increased forced expiratory time
Decreased $FEF_{25\%–75\%}$
Decreased FEV_3/FVC
Increased RV
Increased TLC
Increased RV/TLC
Increased airway resistance (plethysmography, oscillometry)
Significant response to bronchodilator
Ventilation inhomogeneity on gas dilution (lung clearance index)
Decreased D_{LCO}
Decreased MVV

D_{LCO}, diffusing capacity of carbon monoxide; $FEF_{25\%–75\%}$, forced expiratory flow at 25–75% of FVC; FEV_1, forced expiratory volume in 1 second; FEV_3, forced expiratory volume in the first 3 seconds; FVC, forced vital capacity; MVV, maximal voluntary ventilation; RV, residual volume; TLC, total lung capacity; VC, vital capacity.

Modified from Welch MH. Ventilatory function of the lungs. In: Guenter CA, Welch MH, eds. *Pulmonary Medicine*. Philadelphia: JB Lippincott; 1977: 72–123.

(i.e., FR75),[35] and parameter D, a measure of the rate of rise of volume on the volume-time curve.[36] These measures are sensitive to mild disease and detect additional subjects with normal FEV_1/FVC who have an obstructive ventilatory defect; however, these metrics have not been adapted into clinical practice, in part due to a lack of reference values.

There is growing interest in using *inspiratory capacity* (IC) as an indirect measure of air trapping. With progressive airflow obstruction, FRC increases and results in a reduction in IC, whereas TLC does not change significantly until later stages of the disease.[37] In individuals with COPD, the ratio of IC/TLC (the inspiratory fraction) is associated with survival independently of the BODE (*body mass index, airflow obstruction, dyspnea, and exercise capacity*) index,[38,39] with exacerbations[40] and with exercise capacity.[41,42] An inspiratory fraction less than 0.25 is considered low.[39] Change in IC after bronchodilator therapy is also more closely associated with improvement in symptoms than is change in FEV_1.[37,43] However, when determining eligibility for interventions aimed at reducing air trapping, such as surgical and endoscopic lung volume reduction procedures, the actual measurement of RV should be performed.

R_{AW} and *airway conductance* (G_{AW}), measured using body plethysmography, are rarely used for diagnosis in clinical practice but can be used to support a diagnosis of airflow obstruction in borderline cases and in situations where individuals are unable to perform a forced expiratory maneuver.[44] Assessment of airway resistance can also be made through a forced oscillometry technique and impulse oscillometry.[45] The respiratory resistance at 5 Hz (R5) represents the total airway resistance, and the resistance at 20 Hz (R20) represents the resistance of the large airways. The difference between these two resistances (R5 − R20) is the resistance in the small airways.[45]

Lung volumes can provide supportive evidence for the presence of obstructive lung disease. Lung hyperinflation (TLC > *upper limit of normal* [ULN]) and air trapping (RV or RV/TLC ratio > ULN) may be seen in individuals with more advanced obstructive disease. In individuals at risk for COPD but with normal spirometry, an increased RV/TLC is associated with higher health care use, mortality, and risk for progression to COPD.[46] It should be noted that lung volumes estimated using gas dilution or washout techniques are usually lower than those estimated using body plethysmography, either due to noncommunicating airways, alveolar units with very slow time constants, or overestimation of volumes on plethysmography.[47] A ratio of single-breath alveolar volume measured during a diffusing capacity test (V_A, which is an estimate of TLC minus anatomic dead space) to the TLC measured by multibreath gas dilution less than 0.85 suggests heterogeneous distribution of ventilation.[48] In addition, MVV can be low in obstructive disease, but poor patient effort or a neuromuscular disorder should be considered when MVV is low in the setting of a normal FEV_1 and FVC.

The single-breath *diffusing capacity of the lung for carbon monoxide* (D_{LCO}) can be used to differentiate airflow obstruction associated with intrinsic airway disorders from airflow limitation related to emphysema. A normal single-breath D_{LCO} in the setting of an obstructive pattern argues against the presence of a large amount of emphysema but does not rule out a small amount.[49–51] Several studies have demonstrated a correlation of D_{LCO}, not only with the presence of emphysema, but also with the amount of emphysema.[50,52–54] In fact, a normal or increased single-breath D_{LCO} associated with airflow obstruction is often associated with asthma.[55] The single-breath D_{LCO} may be abnormal in patients with emphysema when there is no evidence of airflow obstruction, and it may decrease more rapidly than tests of airway function.[56–58] Individuals with normal spirometry but an isolated reduction in D_{LCO} are at higher risk of developing airflow obstruction over time than those with a normal D_{LCO}.[59]

RESTRICTIVE VENTILATORY DEFECT

A restrictive ventilatory defect is suggested by a parallel decrease in FEV_1 and FVC with a normal or increased FEV_1/FVC ratio, but this diagnosis requires confirmation with a decreased TLC using plethysmography or using the multiple-breath gas dilution method (Table 32.4). Examples of diseases that may manifest with a restrictive ventilatory defect are shown in eTable 32.1.

In many restrictive disorders, the increased elastic recoil at higher lung volumes leads to a convex upward pattern in the descending limb of the maximal expiratory flow-volume curve (also described as steep and vertically oriented) (see Fig. 32.2). Because spirometry does not estimate RV, a restrictive ventilatory defect on spirometry alone has a low sensitivity for correctly diagnosing restrictive lung disease; only up to 50% of those with this pattern have true restriction on lung volume assessment.[60–62] However, when the VC is normal, spirometry has a 96–97% negative predictive value in ruling out true restriction.[60,63] A TLC less than the *lower limit of normal* (LLN) defines a restrictive ventilatory defect. A reduced RV is also seen in the restrictive diseases

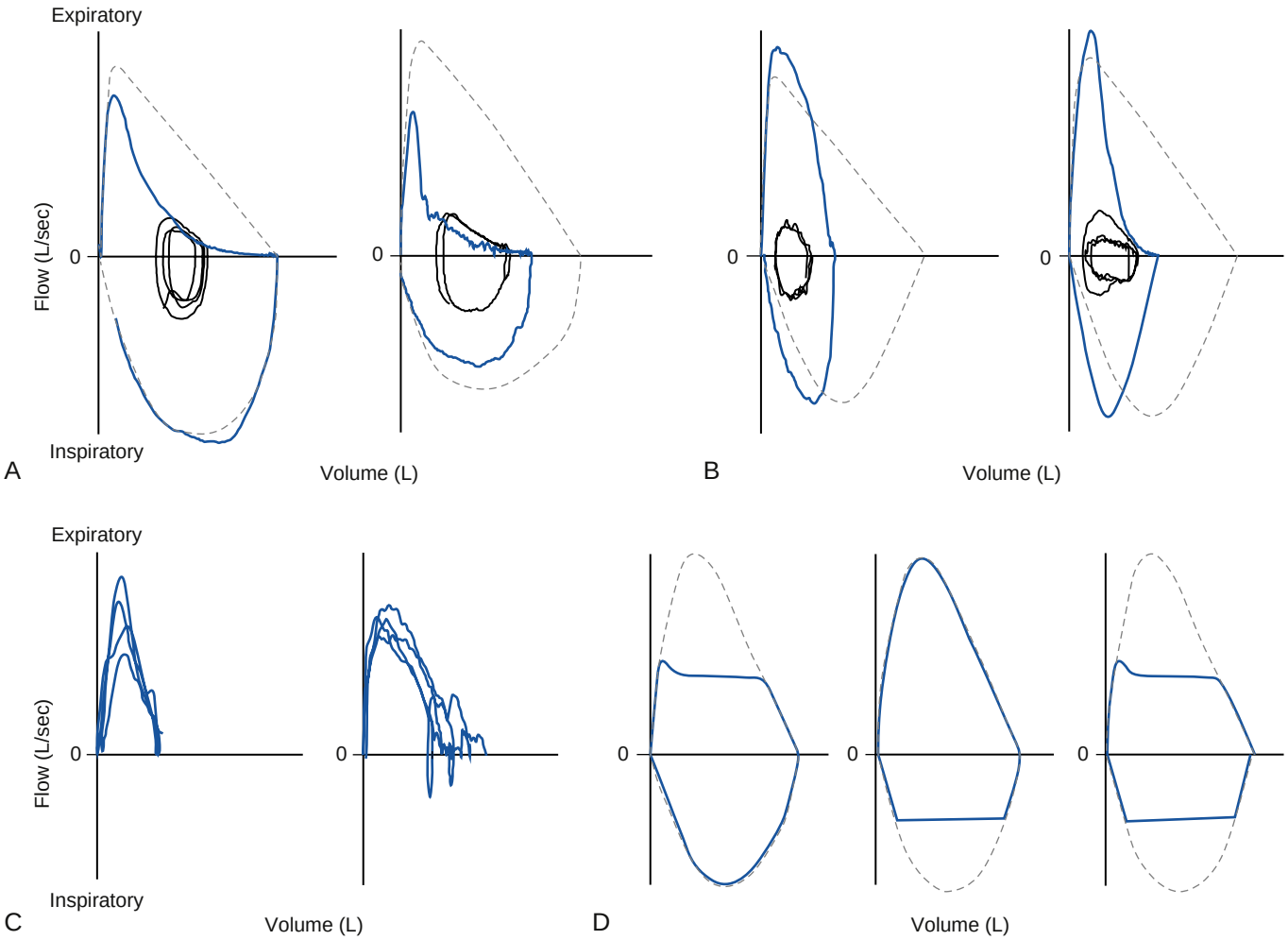

Figure 32.2 Typical flow-volume curves of major pulmonary function test patterns. *Solid lines* indicate curves obtained from patients. *Dashed lines* represent curves derived from the predicted flows and volumes for the corresponding patients. Tidal breathing appears in *gray*. The aspect ratio between the flow and volume axes is 2:1, consistent with standard practice and guidelines.[1] (A) COPD. With an obstructive ventilatory defect, maximal expiratory flow is concave upward, also called curvilinear; this shape reflects a greater reduction in flow at low compared to high lung volumes and can be understood in terms of the inverse relationship between lung elastic recoil and lung volume. Compared to predicted values, expiratory flow is usually reduced more significantly than inspiratory flow. In the example on the right, vital capacity is reduced due to air trapping; flow during tidal breathing (*gray tracing*) exceeds that observed with maximal effort—at low and midlung volumes in this example—a pattern called negative effort dependence. (B) Interstitial lung disease. In restrictive ventilatory defects associated with increased lung elastic recoil, maximal expiratory flow appears steep and vertically oriented (also described as convex upward) with increased flow at high lung volumes. Vital capacity is reduced. In the example on the right, the curve becomes concave upward at low lung volumes, a finding likely due to concomitant airway disease or loss of lung elastic recoil associated with aging. (C) Suboptimal effort manifests as uneven, slurred, or notched curves without repeatability across maneuvers. (D) Large airway obstruction: variable intrathoracic obstruction (*left*), variable extrathoracic obstruction (*middle*), and fixed obstruction (*right*).

associated with increased lung elastic recoil or in situations in which lung units are either collapsed or filled (e.g., pneumonia or hemorrhage). However, an isolated decrease in RV can be due to true restriction (i.e., TLC is read as normal due to small technical or biologic variations, or inaccuracy of predicted values) or obesity, or it could be a normal variant. Unlike in obstructive disease, lung volumes assessed using either dilution methods or plethysmography should be similar in those with a restrictive ventilatory defect.[64] A normal lung volume using either single-breath or multibreath dilution methods rules out restriction.[65] Although lung volume testing is required for the confirmation of spirometric restriction, once a diagnosis of restriction has been made, spirometry alone can be used for follow-up of lung volumes and is preferred due to better repeatability compared to TLC.

In true parenchymal restriction, the high FEV_1/FVC ratio arises from the reduction in FVC and the disproportionately lower decrease in FEV_1 due to a high lung elastic recoil. In these cases, D_{LCO} is usually decreased. In extraparenchymal restriction, however, the high FEV_1/FVC ratio results from the decreased VC. D_{LCO} may be normal in neuromuscular weakness and structural extraparenchymal restriction, such as scoliosis and kyphosis, but can be low when associated with markedly reduced lung volumes and/or basal atelectasis. A pattern of a normal or elevated RV, low TLC, and high RV/TLC ratio suggests a possible neuromuscular or chest wall etiology.[66,67] The flow-volume curve in neuromuscular weakness is not expected to have a convex upward pattern. Rather, it often maintains a nearly normal shape but with reduced flow rates and can feature a sudden drop in forced expiratory flow near RV.[68]

Table 32.3 Severity of Pulmonary Function Impairment*

Impairment	FEV_1†	TLC‡	VC‡	D_{LCO}
Abnormal	<LLN	<LLN	<LLN	<LLN
SEVERITY GRADING				
Mild	≥70%	≥70%	≥70%	≥60%
Moderate	60–69%	60–69%	60–69%	40–60%
Moderately severe	50–59%		50–59%	
Severe	35–49%	<60%	35–49%	<40%
Very severe	<35%		<35%	

*Grading scheme for FEV_1 follows the American Thoracic Society guidelines from 2005[3]; VC limits mirror those for FEV_1.
†Airflow obstruction is based on a decreased FEV_1/VC ratio. If the ratio is decreased below fifth percentile, the severity of airflow is graded on the percentage of predicted FEV_1. The FEV_1/VC ratio itself is not graded.
‡Pulmonary restriction is based on decreased TLC. If TLC is not available, a reduction in VC without a reduction in the FEV_1/VC ratio is considered a restriction of the volume excursion of the lung.
D_{LCO}, diffusion capacity of carbon monoxide; FEV_1, forced expiratory volume in 1 second; LLN, lower limit of the 95% confidence interval; TLC, total lung capacity; VC, vital capacity.

Table 32.4 Restrictive Ventilatory Defect

CHARACTERISTICS OF RESTRICTIVE VENTILATORY DEFECT
Normal or high FEV_1/FVC
Decreased VC
Decreased TLC
OTHER DATA SUPPORTING RESTRICTION
Convex upward flow-volume curve*
Decreased RV†
Decreased D_{LCO}‡
Increased $(A–a)P_{O_2}$

*A convex upward flow-volume curve is not expected with a restrictive ventilatory defect due to extraparenchymal causes such as neuromuscular weakness, chest wall or spine diseases.
†RV may be normal or increased with extraparenchymal causes of a restrictive ventilatory defect, leading to an elevated ratio of RV to TLC.
‡D_{LCO} can be normal or decreased in extraparenchymal diseases.
$(A–a)P_{O_2}$, alveolar-arterial P_{O_2} difference; D_{LCO}, diffusing capacity of carbon monoxide; FEV_1, forced expiratory volume in 1 second; FVC, forced vital capacity; P_{O_2}, partial pressure of oxygen; RV, residual volume; TLC, total lung capacity; VC, vital capacity.
Modified from Welch MH. Ventilatory function of the lungs. In: Guenter CA, Welch MH, eds. *Pulmonary Medicine*. Philadelphia: JB Lippincott; 1977: 72–123.

As mentioned, in approximately 50% of cases where spirometry is suggestive of a restrictive ventilatory defect, lung volumes do not show restriction.[60–62] In this situation, the forced expiratory time and the end-of-test criteria should be evaluated to ensure that the restrictive pattern is not due to inadequate exhalation. In cases of significant air trapping, the FVC may be artificially low and the FEV_1/FVC ratio may be artificially normal or elevated, resulting in a pseudorestrictive pattern. This pseudorestrictive pattern is often interpreted as a mixed obstructive/restrictive process. Pseudorestriction should be suspected when the clinical indication for spirometry is an obstructive airway disease or when the expiratory flow-volume curves show a concave upward obstructive pattern and can be confirmed by demonstrating a normal TLC on lung volume measurement. RV and RV/TLC ratio will also be elevated in this condition. There is, however, no linear relation between the degree of air trapping and the magnitude of decrease in FVC.

A special type of restriction termed *complex restriction* has been described, wherein the reduction in FVC is out of proportion to the reduction in TLC (a >10% difference between the percentage of predicted TLC and percentage of predicted FVC). In one study, approximately 4% of all pulmonary function tests and 33% of restrictive pulmonary function tests showed complex restriction.[69] This pattern was associated with diseases classically associated with restriction and also with a significant number of obstructive diseases, such as COPD, likely due to impaired emptying of the lung during a forced exhalation maneuver. Care should be taken to ensure the disproportionately low FVC is not due to incomplete exhalation. Recognition of this pattern should prompt evaluation for an additional process, such as chest wall limitation, neuromuscular weakness, poor performance, or occult obstruction.

A brief discussion on diffusion capacity in interstitial lung disease is available at ExpertConsult.com.

MIXED VENTILATORY DEFECTS

A mixed obstructive and restrictive ventilatory defect is present when both the FEV_1/FVC and TLC are less than the LLN (see eTable 32.1 for examples). In these cases, both the obstructive and restrictive processes are expected to reduce the FEV_1. In accordance with guidelines, it is reasonable to quantify the total ventilatory impairment by the FEV_1 percentage of predicted.[3] It is logical to assume that using the FEV_1 percentage of predicted to grade the severity of obstruction in a mixed disorder will overestimate the severity due to the concomitant loss of volume contributed by restriction. To address this issue, an FEV_1 percentage of predicted adjusted for the degree of restriction was defined as the FEV_1 percentage of predicted divided by the TLC percentage of predicted.[75] In a cohort of 199 subjects with a mixed ventilatory defect, with use of this *adjusted* FEV_1 percentage of predicted, 33% were classified as having severe or very severe obstruction, whereas, with the *unadjusted* FEV_1 percentage of predicted, 76% were classified in this category.[75] The correlation between the adjusted FEV_1 percentage and RV/TLC was better than with the unadjusted FEV_1 percentage. Because this work has not been validated, there is no consensus on

DIFFUSING CAPACITY IN INTERSTITIAL LUNG DISEASE

In patients with interstitial fibrosis, D_{LCO} (expressed as percentage of predicted normal) correlates modestly with arterial oxygen desaturation during exercise[70,71]; however, the mechanism of this relationship is only partly due to diffusion limitation (eFig. 32.1).[72,73] With advancing severity of interstitial fibrosis, less pulmonary capillary bed is recruited compared to the healthy state during exercise, which leads to reduced red cell transit time and an inability to oxygenate hemoglobin fully. Nonetheless, it is estimated that less than half of the hypoxemia during exercise in interstitial fibrosis is due to this diffusion limitation, with the majority from *ventilation-perfusion* (V/Q) mismatch.[74] In one study the positive predictive value of a reduced D_{LCO} to predict exercise-induced desaturation, at cutoffs ranging from 50–70% of predicted, was only 50–70%.[71]

When the diffusing capacity is reduced in patients with *interstitial lung diseases* (ILDs), it is usually decreased out of proportion to the lung volumes; thus, the *carbon monoxide transfer coefficient* (K_{CO}) is also decreased. However, this may not be the case in all patients with a restrictive defect. A patient with sarcoidosis, for example, may present with a TLC 50% of predicted normal, associated with a D_{LCO} that is also 50% of predicted normal, in which case the D_{LCO}/V_A ratio is normal. After treatment with systemic corticosteroids, the lung volume may return to normal, but diffusion may not, in which case the D_{LCO} and D_{LCO}/V_A ratio may both be 50% of the predicted normal. In such cases it is thought that the granulomas and fibrosis have caused lasting damage to the alveolar membranes and capillaries, even though the lung volumes have returned to normal levels. Therefore, clinical interpretation of the K_{CO} with ILDs is limited. It should not be assumed that a normal K_{CO} indicates that the capillary beds are functioning normally.

A common misconception is that the diffusing capacity is reduced in interstitial fibrosis due to membrane thickening. In the rare circumstances in which a reduction in D_{LCO} is due to membrane thickening, a reduced D_M/V_C is expected (eTable 32.2; see also Chapter 31, Eq. 17).

eTable 32.2 Interpretation of the Total Diffusing Capacity and the Modeled Components of Membrane (D_M) and Capillary Hemoglobin Conductance (θV_C)

Pulmonary Disease	Increased D_{LCO}: Mechanism	Decreased D_{LCO}: Mechanism	D_M/V_C* Relative to Health
Emphysema		Decreased alveolar-capillary surface area (loss of lung units)	No change
IPF		Decreased alveolar-capillary surface area (loss of lung units)	No change
Acute conditions: PNA, ARDS, pulmonary edema		Decreased alveolar-capillary surface area (alveoli filled with fluid)	No change
PAH, CTEPH		Decreased number of capillaries participating in diffusion	No change
Heart failure	Acute: increase in left-sided pressure recruits pulmonary capillary blood volume	Chronic: remodeling of pulmonary vasculature from chronically elevated left-sided filling pressures decreases capillary surface area	Acute: no change. Chronic: studies inconsistent; no change[233] or reduced[234]
HPS, early sarcoidosis,[235,236] PJP[237]		Increased path length (i.e., alveolar-capillary thickness) But only in HPS is the increased path length thought to be related to hypoxemia In PJP pneumonia, hypoxemia still likely, all from V/Q inequality	Reduced
Asthma (D_{LCO} most often normal, although among those with an elevated D_{LCO}, asthma is a common diagnosis[238])	More negative inspiratory pressure resulting in increased pulmonary blood flow to apices during forced inhalation[239]		No change
Obesity (D_{LCO} most often normal[240–242] though among those with an elevated D_{LCO}, obesity is a common diagnosis[238])	More capillary blood volume[243–245]		No change
Left-to-right intracardiac shunt (without pulmonary hypertension)	More capillary blood volume[246]		
Diseases with polycythemia	More Hgb to bind CO	Pulmonary thromboembolic disease	Reduced due to increased V_C (if D_{LCO} elevated)
Pulmonary hemorrhage	More Hgb to bind CO		Reduced due to increased V_C

*As described in Chapter 31, with a number of reasonable assumptions, the D_{LCO} can be modeled as the sum of two conductance elements in series—one for the alveolar epithelial-endothelial cell and plasma barrier (D_M), and one for the noninstantaneous chemical reaction rate of carbon monoxide with hemoglobin (θV_C, where θ is the rate of chemical combination of CO with hemoglobin, and V_C is the volume of capillary blood exposed to alveolar air).[157] The values for these components can be obtained in humans by fitting the model to D_{LCO} acquired at varying inspired oxygen concentrations, which varies the θ. D_M is a function of both total surface area available for diffusion, which itself depends on total alveolar volume, and membrane thickness. V_C is the accessible blood volume and therefore, like D_M, is also a function of total alveolar surface area and volume. Because both D_M and V_C depend on alveolar volume, in most diseases, the two are coupled, and the ratio of D_M/V_C is not different than in health. If there is a reduction in D_{LCO} due to membrane thickening, D_M/V_C is reduced.

ARDS, acute respiratory distress syndrome; CO, carbon monoxide; CTEPH, chronic thromboembolic pulmonary hypertension; D_M, membrane diffusing capacity; HPS, hepatopulmonary syndrome; Hgb, hemoglobin; IPF, idiopathic pulmonary fibrosis; PAH, pulmonary arterial hypertension; PE, pulmonary embolism; PJP, *Pneumocystis jirovecii* pneumonia; PNA, pneumonia; V_C, pulmonary capillary blood volume; V/Q, ventilation-perfusion ratio.

its use in clinical practice; however, it is important for the clinician to be cognizant of the possibility of overestimating the severity of obstruction in a patient when restriction is also present.

In the presence of a restrictive ventilatory defect, the sensitivity of the FEV_1/FVC ratio to detect an obstructive ventilatory defect may be reduced; findings other than a reduced FEV_1/FVC ratio can suggest airflow obstruction. Caution must be exercised in diseases with opposing effects on FEV_1/FVC and TLC, such as combined pulmonary fibrosis and emphysema. In this condition both FEV_1/FVC and TLC can appear to be preserved due to the effects of airflow obstruction and air trapping counterbalanced by the increased elastic recoil of fibrosed lung regions. The only pulmonary function defect observed in this situation may be a disproportionately decreased D_{LCO}.[76]

NONSPECIFIC PATTERNS

When the FEV_1/FVC ratio is normal with a low FVC and/or low FEV_1, but with a normal TLC, this is indicative of a nonspecific pulmonary function test pattern. Although the 2005 ATS/ERS document recommends interpreting this pattern as obstructive, a substantial proportion of individuals with this pattern do not have evidence of obstruction, but rather chest wall limitation, including obesity and muscle weakness, or poor test performance.[3] In a study of 80,929 subjects, a nonspecific pattern was identified in 7702 subjects (≈10%).[77] Longitudinal study of 1284 of these subjects who had one or more pulmonary function tests performed 6 months or more after initial testing, with a median follow-up of 3 years, revealed that the nonspecific pattern was stable and persistent in 64%.[78] Roughly equal numbers of subjects (≈15%) developed a restrictive or obstructive pattern, whereas 3% normalized and 2% showed a mixed pattern. Of note, the definition of the nonspecific pattern differed slightly between the initial (low FVC and FEV_1) and follow-up (low FVC and/or FEV_1) reports.

Due to the absence of measurements of TLC in many datasets, the prevalence and associated patient characteristics of nonspecific patterns on spirometry alone have also been investigated.[79] The definitions share the requirement for a normal FEV_1/FVC ratio but differ in whether the FEV_1, FVC, or both are reduced. A number of conditions have been reported to be associated with these patterns. In particular, a low FVC and normal FEV_1/FVC ratio with or without low FEV_1, termed a restrictive spirometric pattern, has been associated with risk for cardiovascular disease[80,81] and diabetes mellitus.[82] Another nonspecific pattern, a normal FEV_1/FVC ratio with an isolated FEV_1 reduction, was found in 2.1% of 15,192 subjects.[83] Compared to normal subjects, this category included a higher proportion of smokers; individuals with radiologic abnormalities, including emphysema and tuberculosis; and those with a history of respiratory disease, including asthma, chronic bronchitis, and tuberculosis. These data highlight the importance of obtaining a measure of TLC if a restrictive ventilatory defect is suspected and of following patients with nonspecific spirometry patterns. In the setting of a normal TLC, patients with these patterns may have worse outcomes than those with normal spirometry and, in the appropriate clinical context, an evaluation for parenchymal, pleural, chest wall, and neuromuscular disease may be indicated. Tests of airway resistance can also help distinguish obstructive from restrictive processes.

PULMONARY VASCULAR DISEASE

In patients presenting with dyspnea during exertion, a decreased D_{LCO} without evidence of obstructive or restrictive ventilatory defects should raise suspicion for disorders of pulmonary circulation. A decreased D_{LCO} is not a sensitive test to detect pulmonary vascular disease. For example, many patients with elevated pulmonary arterial pressure and pulmonary vascular resistance will have a normal D_{LCO}.[84–86] In systemic sclerosis, an autoimmune condition associated with pulmonary hypertension and *interstitial lung disease* (ILD), two screening algorithms incorporate the D_{LCO} percentage predicted and the ratio of D_{LCO} percentage predicted to FVC percentage of predicted to trigger further testing, including echocardiography or right heart catheterization.[87–89] Because most studies have not reported the reference values used, one should be cautious in applying the literature on the performance of the D_{LCO} in detecting disease. The published reference values for D_{LCO} differ significantly, limiting the applicability of studies that report on the performance of D_{LCO} as a percentage of predicted.

In general, when pretest probability is more than minimal, a normal D_{LCO} should not preclude the pursuit of more detailed pulmonary function studies of the pulmonary circulation. These studies include exercise tests, which are especially useful when signs of pulmonary hypertension are absent and radiographic methods fail to demonstrate obstruction of large pulmonary arteries.

See ExpertConsult.com for a discussion of the changes seen in D_{LCO} in the setting of pulmonary vascular obstruction.

RESPIRATORY MUSCLE WEAKNESS

Tests of respiratory muscle weakness should be considered in individuals in whom neuromuscular disease is known or suspected, such as in cases of weak cough, spirometric restriction, unexplained dyspnea or orthopnea, and hypercapnic respiratory failure. Causes of respiratory muscle weakness are listed in eTable 32.1. Routine pulmonary function tests can provide significant information about neuromuscular disease. Upright and supine VC testing can be used to obtain a global assessment of inspiratory and expiratory muscle function.[96] Unilateral diaphragm weakness is associated with a modest decrease in the VC, whereas severe bilateral diaphragmatic weakness can result in a VC of less than 50% predicted. Repeating VC testing in the supine position can unmask diaphragmatic weakness. A postural decrease in VC of 25% or more is suggestive of diaphragmatic weakness, but a normal supine VC does not rule out clinically significant diaphragmatic weakness.[97–99] The VC does not decrease until substantial inspiratory muscle weakness has set in because only very small pressures are required to inflate the lung fully. MVV is also low in neuromuscular disease, and neuromuscular disease should be suspected when the

Changes in D_{LCO} in Pulmonary Vascular Obstruction

The changes in D_{LCO} in the setting of pulmonary vascular obstruction can be complex, which, combined with the large normal range of D_{LCO}, makes it difficult to use the test to make a straightforward diagnosis. If pulmonary *capillaries* are occluded, single-breath D_{LCO} is decreased.[90] In the presence of *precapillary* vascular obstruction, with the obstruction upstream of the capillaries, the single-breath D_{LCO} may be decreased,[91] normal,[92] or even increased, depending on the effect on pulmonary capillary blood volume. The capillary blood volume, in turn, depends on the relationship between pulmonary arterial pressure, pulmonary venous pressure (or left atrial pressure), and bronchial collateral blood flow. For example, bronchial arterial pressure may distend capillaries via collateral channels so that, even if pulmonary arteries are obstructed, a normal D_{LCO} may be maintained.

Finally, capillary distention may vary in different parts of the lung (eFig. 32.2). According to the model of the zones of lung perfusion presented by West and colleagues,[93] at the lower zone at the lung base, capillaries are distended by pulmonary arterial and pulmonary venous pressures. Even if the pulmonary arteries are obstructed, the capillaries are distended by pulmonary venous pressure, and the D_{LCO} is maintained. D_{LCO} is decreased in this zone if the capillaries are occluded or if pulmonary venous pressure is decreased.

In the middle zone of the lung, capillaries are distended by pulmonary arterial pressure only; they are not affected by pulmonary venous pressure. D_{LCO} would be decreased by pulmonary vascular obstruction alone; however, D_{LCO} would be normal if the obstruction led to an increase in pulmonary arterial pressure that then distended apical capillaries that were not perfused previously. In addition, the D_{LCO} would increase if the pulmonary venous pressure increased, as long as the pulmonary capillaries remained patent despite pulmonary artery occlusion in this zone.

In the upper zone at the lung apex, pulmonary capillaries may be collapsed because *alveolar pressure* (Palv) exceeds both pulmonary arterial and venous pressures. In this situation, obstruction of pulmonary arteries would not affect D_{LCO}. Changes in Palv would affect the analysis of the test and thus might affect D_{LCO}.[94] In conclusion, a decreased D_{LCO} may support the diagnosis of pulmonary vascular obstruction, but a normal D_{LCO} does not rule out this diagnosis.[95]

reduction in MVV is disproportionate to the reduction in FEV_1 and FVC.[66,100]

TLC decreases in parallel with VC, but RV frequently stays normal or elevated. This pattern of an isolated decrease in TLC with normal or elevated RV should raise suspicion for neuromuscular disease.

The initial assessment of muscle strength in individuals with suspected neuromuscular disease is by voluntary tests of respiratory muscle strength. These include the *maximum static inspiratory pressure* (MIP, or PI_{max}) and *maximum expiratory pressure* (MEP, or PE_{max}) at the mouth. These tests offer a simple assessment of overall respiratory muscle strength. The MIP reflects the strength of the diaphragm and other inspiratory muscles and is usually measured at RV. Care should be taken to observe the patient performing the test because involvement of the cheeks can help generate a significant negative inspiratory pressure. The MEP reflects the strength of the abdominal and other expiratory muscles and is usually measured at TLC. The ATS guidelines recommend that the highest 1-second average should be recorded for both MIP and MEP.[101] Lower limits of normal have not been clearly defined for MIP and MEP, and the large variations mean that the LLNs are usually approximately 50% predicted. A normal MIP is 80 cm H_2O or more in men and 70 cm H_2O or more in women.[101] Values greater than these will rule out clinically significant inspiratory muscle weakness. Values less than 60% predicted suggest unilateral diaphragmatic weakness, and those less than 30% predicted suggest bilateral diaphragmatic weakness.[102,103] However, reference data for MIP and MEP vary, and the choice can significantly impact the diagnosis of neuromuscular weakness.[104] These normal ranges can be significantly affected by the presence of underlying obstructive disease, such as COPD, because hyperinflation-induced diaphragmatic flattening can decrease the MIP without true weakness of the diaphragm.

The maximal sniff nasal inspiratory pressure is slightly more invasive in that it requires a transducer catheter to be placed in the nostril. The inspiratory effort usually starts at FRC. The ATS recommends that the highest pressure should be recorded.[101] Normal values for men and women are 70 cm H_2O or more and 60 cm H_2O or more, respectively.[101] Testing maximal sniff nasal inspiratory pressure may be easier to perform for many patients with neuromuscular disease because, unlike MIP, this maneuver is not affected by ineffective mouth seal or having to sustain a maximal inspiratory effort.

Peak cough flow (PCF) provides a measure of expiratory muscle strength and the effectiveness of mucus clearance in neuromuscular disorders. PCF can be measured using a spirometer or handheld peak flowmeter. Normal values in healthy subjects range from 290 to 880 L/min.[105] A PCF less than 270 L/min is associated with a higher likelihood of pulmonary complications in neuromuscular disease.[106]

When these noninvasive measures of muscle strength are equivocal, more invasive assessments, including the measurement of esophageal, gastric, and transdiaphragmatic pressures while sniffing and coughing, may be required (see Chapter 31). Advanced testing, including phrenic nerve stimulation and electromyography, may be required in some cases. These measures are discussed in more detail in Chapter 130. Measures obtained in the pulmonary function laboratory can be complemented by radiographic and imaging measures to track diaphragm movement and thickening while sniffing (see Video 20.1).

LARGE AIRWAY OBSTRUCTION: STENOSIS AND COLLAPSIBILITY (See Chapter 39)

Flow-volume curves may be especially helpful in identifying tracheal or other upper airway lesions as a cause of obstruction.[107] Large (also called central) airway obstruction (i.e., proximal to the tracheal carina) located within the thorax produces a repeatable plateau during forced exhalation instead of the usual rise to and descent from peak flow (see Fig. 32.2). Peak flow is also usually blunted. When more than 50% of the VC has been exhaled, the curve then follows the usual flow-volume curve to RV. In patients with stridor, particular attention should be paid to the configuration of the inspiratory portion as well as the expiratory portion of the flow-volume curve. Lesions that cause either stenosis or collapsibility located in the trachea *inside* the thorax decrease airflow, particularly during exhalation; during inhalation, the posterior tracheal membrane is pulled outward by negative intrathoracic pressure, so increased effort increases airflow rates and the inspiratory limb of the flow-volume curve can appear normal. Conversely, tracheal lesions that cause stenosis or collapsibility located *outside* of the thorax decrease airflow during inhalation; during inhalation, the tracheal membrane is sucked in and is usually associated with stridor, whereas during exhalation, the lesion may be stented open by positive airway pressure and the expiratory limb of the flow-volume curve can appear normal (see Fig. 32.2). When the inspiratory and expiratory limbs are differentially affected, the obstruction is referred to as variable. In contrast, if a lesion is fixed and not altered by surrounding pressures, whether intrathoracic or extrathoracic, airflow should be limited equally during inhalation and exhalation (see Fig. 32.2). Similarly, because a flow-limiting orifice located at the thoracic outlet is not affected by pressure above or below the lesion, airflow is limited equally during both inhalation and exhalation.[108] The diameter of a stenotic lesion can be estimated by analysis of the flow-volume curve (eFig. 32.3), but the length of the flow-limiting segment must be confirmed by computed tomography scan to plan surgical correction, if required. A plateau in maximal expiratory flow associated with central airway obstruction that reduces the size of the tracheal lumen significantly below normal is expected to reduce flow to approximately 4 L/sec or less (see eFig. 32.3). In contrast, normal variants sometimes seen in young adults lead to plateaus at high lung volumes with higher flow.[109,110]

Although the finding of a repeatable plateau on forced inspiratory or expiratory flow suggests central or upper airway obstruction, the FEV_1, FVC, and FEV_1/FVC are not sensitive.[111,112] Ratios derived from individual spirometric variables, such as FEV_1/*peak expiratory flow rate* (PEFR) greater than 10, *forced expiratory flow at 50% lung volume* (FEF_{50})/*forced inspiratory flow at 50% lung volume* (FIF_{50})

greater than 1.2, $FIF_{25\%–75\%}/FEF_{25\%–75\%}$ less than 1, and MVV/FEV_1 less than 25 perform better at identifying large airway obstruction than FEV_1, FVC, or FEV_1/FVC.[112–115] The presence of chronic airflow obstruction from diseases that affect the airways diffusely and heterogeneously (e.g., asthma, COPD) decreases the sensitivity of spirometry to detect concomitant large airway obstruction.[116]

REFERENCE VALUES

Reference values derived from a population without lung disease can yield equations for expected values for a given height, sex, and age. Reference values allow comparison of results between individuals and make it possible to follow the trend of values across time within an individual while removing the average effect of aging. Publications describing reference populations should include not only the prediction equations but also a means to define their lower limits. A lower limit can be estimated from a regression model: for spirometry, where a clinical concern arises from abnormally reduced but not elevated values, the fifth percentile is usually considered the LLN.[117] For some tests in which both high and low values are considered abnormal, the 2.5th and 97.5th percentile define the lower and upper limits of normal, respectively. There is no statistical basis for the common practice of using 80% of the predicted normal values for FEV_1 and FVC as the LLN in adults. A study of 11,413 patients found that using fixed cut points to determine whether lung function is abnormal could misdiagnose more than 20% of patients and could be avoided by using the LLN based on the fifth percentile values. The use of cutoffs based on a percentage of the predicted value has the potential for age and height bias because the spread of the distribution often varies with these parameters,[118] whereas the use of percentile cutoffs (or equivalently, *z*-scores, which represent the number of standard deviations above or below the mean) avoids this problem. When the standing height cannot be measured accurately, as in those with an inability to stand or with thoracic spine abnormalities, height should be estimated from arm span with the use of regression equations accounting for the effects of age, sex, and ethnicity.[119]

The clinical application of pulmonary function tests requires the recognition of the limitations of reference values (eTable 32.3). Although the fifth percentile is often chosen to define the LLN, adjustments can be made depending on the prevalence of the disease in the target population and the desired sensitivity and specificity. Furthermore, reference ranges are derived from healthy individuals, whereas in disease, lung function at 70% of predicted but above the LLN may nonetheless have an impact on symptoms, hypoxemia, and exacerbations or mortality risk.[6,120,121] Values in the normal range might reflect the variability of expression of a disease across patients. This last point is used as an argument for the use of percentage of predicted for disease severity classifications rather than *z*-scores, and there is limited evidence that such an approach is valid in COPD.[122] The causes of differences in lung function between ethnic groups are diverse, not completely understood, and include exposures such as pollution, stress including discrimination, and early-life nutritional differences.[123–125] Large variability within traditionally defined ethnic groups limits the perceived advantages of using specific equations within groups. Chest size is only partially associated with differences within or between groups and confounded with exposures and early life events.[124,126–128] Clinicians and investigators are increasingly grappling with the use of population-specific reference equations—both the potential harms (e.g., underdiagnosis, underestimation of severity, denial of access to therapies, disability, and masking of modifiable risks for reduced lung function) and potential benefits (e.g., avoidance of overdiagnosis, and inclusiveness to meet requirements to work or receive therapies such as resection of lung cancer, stem-cell transplantation, and chemotherapy).

Additional information on reference values can be found at ExpertConsult.com.

GENERAL APPROACH TO INTERPRETATION

Figure 32.1 depicts an algorithm for the interpretation of pulmonary function tests. For this algorithm, we suggest that postbronchodilator spirometry values be used. Prebronchodilator spirometry is the most commonly performed pulmonary function test but, in cases where airflow obstruction is suspected, postbronchodilator spirometry should be performed and be used for interpretation.[8] Although reference equations were derived using prebronchodilator values, LLNs can be applied to postbronchodilator spirometry. In cases of borderline significance, close follow-up and repeat testing are recommended.

The first step in the interpretation of spirometry is visual inspection of the flow-volume curves, which may give clues regarding test quality and the presence of large airway obstruction.

The second step is to assess the FEV_1/FVC ratio. If the FEV_1/FVC ratio is low, the next step is to evaluate the FEV_1. If the FEV_1 is also low, this confirms obstruction. At this point, the FVC is useful: if the FVC is normal, this confirms a simple obstructive defect; if the FVC is also low, this indicates an obstructive ventilatory defect associated with either a concomitant restrictive ventilatory defect or with air trapping. If the FEV_1/FVC ratio is low and the FEV_1 is normal, this could indicate early or mild airflow obstruction or be a normal variant due to dysanaptic lung growth. Lung volumes may support the diagnosis of obstruction when TLC and RV are high or a mixed obstructive and restrictive ventilatory defect when TLC is low.

If the FEV_1/FVC ratio is normal, this could indicate normal spirometry or a restrictive ventilatory defect. The next step is to evaluate the FVC. A low FVC can be due to restriction or due to air trapping and should be investigated with lung volume testing. A low TLC confirms restriction, whereas a normal TLC can often be seen with a low FVC and should be interpreted as a nonspecific pulmonary function pattern. A normal TLC and a high RV suggests air trapping as the etiology of the low FVC (pseudorestriction). If the FEV_1/FVC ratio is normal, a normal FVC essentially rules out restriction, and lung volume testing is not recommended unless

eTable 32.3 Limitations of Reference Values in Interpretation of Pulmonary Function Tests

STATISTICAL CONSIDERATIONS
Large ranges of normal lung function make interpretation of one test imperfect without prior tests.
By the conventional definition, 5% of the normal population will be less than the LLN without evidence of pulmonary disease.
Near the lower limit of normal, repeat testing will yield results above and below the LLN due to test variability independent of changes in respiratory system structure or function.
REFERENCE POPULATION FACTORS
Reference values for most lung function parameters were obtained from white populations. Adjustment for ethnicity can prevent overdiagnosis but may also lead to underdiagnosis and underestimation of severity and hide modifiable risks for reduced lung function.
Varying criteria are found for healthy status among individuals contributing to normal lung function distributions. This is less important if the data are viewed as providing a common reference standard for age, sex, height, and ethnicity adjustment, rather than a gold standard for health.
Stringent selection of healthy individuals for some reference sets may not reflect the general population without pulmonary disease.
Reference values in one geographic region may not reflect the genetic mix, exposures, and nutritional status of the populations in which they are used.
Reference values based on cross-sectional analyses may not match longitudinal change, and therefore equations that fit the population at one point in time may not apply decades later.
Reference values can vary significantly between commonly used sets: e.g., D_{LCO} and MIP/MEP. Optimal interpretation of these parameters requires attention to the entire clinical picture, as well as to the reference set used. Given the possible use of different predicted sets between laboratories and across time within a laboratory, trending of values should include examination of both absolute and percentage of predicted values.

D_{LCO}, diffusing capacity of carbon monoxide; LLN, lower limit of normal; MEP, maximal expiratory pressure; MIP, maximal inspiratory pressure.

ADDITIONAL INFORMATION ON REFERENCE VALUES

The ATS has published a formal recommendation on the selection of reference values and interpretative strategies for lung function tests, including for FVC, FEV_1, FEV_1/FVC, FEV_1/VC, and criteria defining a significant response to a bronchodilator.[129] This statement recommends reference values derived from the *National Health and Nutrition Examination Survey* (NHANES) III, which included whites, African Americans, and Mexican Americans (not applicable to Blacks or Mexicans who are not from the United States).[130] In 2010, the Multi-Ethnic Study of Atherosclerosis Lung Study assessed the performance of the NHANES III reference equations in 3893 participants, of whom approximately one-third were Asian Americans. This study found the equations to be valid for the previously mentioned ethnic groups; in addition, the investigators suggested that an adjustment factor of 0.88 be applied to the predicted and LLN values when comparing whites and Asian Americans.[131] However, the authors also noted that a constant adjustment factor across all ages is suboptimal. The largest and most recent set of predicted values for spirometry was published in 2012 by the *Global Lung Initiative* (GLI).[118] For whites, African Americans, and Northeast Asians, the predicted values are close to those from NHANES III; for Southeast Asians, the predicted values are significantly lower. The diagnosis of obstruction by GLI 2012 and NHANES III differs most for the elderly.[132] Beyond more accurate reference equations for Southeast Asians, another advantage of the GLI set is that the modeling of nonlinear curves with the use of splines led to the creation of one set of equations that apply across the entire 3- to 95-year-old age range. GLI also provides *z*-scores as a way of grading severity, which, unlike percentages of predicted values, lower bias from age, height, and sex.

The published reference sets for D_{LCO} differ significantly from one another. Reasons for differences include variation in the genetic and environmental backgrounds of the populations studied, criteria used to define nonsmoking status, degree to which cardiopulmonary disease was ruled out, requirements for normal values on other lung function tests, imperfect or no adjustment for altitude, levels of hemoglobin and carboxyhemoglobin, methods for estimating anatomic dead space, equipment (e.g., virtual sampling via rapid gas analyzers vs. an actual expiratory gas sample), and quality standards for inspiratory VC and single-breath alveolar volume. Older sets commonly used by many laboratories in the United States are from Crapo and Morris,[134] Knudson and colleagues,[117] and Miller and colleagues.[133] Although all of these were derived from a white population, Knudson yields the highest predicted values and Miller the lowest. The GLI group recently published reference values derived from the largest and first global population.[135] Whites comprised 85% of the population. As with the earlier GLI 2012 spirometry reference values, the derived equations span a large age range, from 5 to 85 years, and provide *z*-scores. The GLI reference values for D_{LCO} provide the lowest values of the commonly used predicted sets to date. The differences between prediction sets are not fixed, in particular varying more or less at different heights. For example, as height increases, the Miller set approximates the GLI values across age and sex, and the Crapo and Knudson sets approach each other at values considerably higher than GLI and Miller. Unlike with spirometry, there is less data available on normal values for D_{LCO} in African Americans and Asians. In one small study of 42 African Americans, a factor of 0.88 applied to predicted values from Miller and colleagues was suggested for African Americans.[135a] A number of ethnicity-specific studies outside the United States have been published, for example, in Asians. Some of these may be applicable to Asians living in the United States.[136]

Publications with reference equations for lung volumes were reviewed in the most recent ATS/ERS statement of the interpretation of pulmonary function tests.[3] Since then, a report on static lung volumes in a large number of healthy adults also included limits of normal for airway resistance.[137] Similar to diffusing capacity, there are limited

normative data available for non-white individuals for TLC and RV. The ATS/ERS recommends a factor of 0.88 be used for TLC in African Americans and Asians. In non-whites, more data are available for FVC than for TLC, further supporting a strategy that first uses a normal FVC to rule out concern for a restrictive ventilatory defect.

Sex, size, aging, past and present health, environmental factors, including smoking and pollution, and socioeconomic factors, including stress, discrimination, and early life nutrition, cause variability among subjects. Although there may be genetic influence on lung function beyond sex and risk for disease, such as by contributing to maximal lung size, the assessment of this effect has been made difficult by the lack of genetic homogeneity and confounding between genetics and environmental and socioeconomic factors within ethnic groups. The causes for the differences in lung function between ethnic groups, and the positive and negative consequences of adjustment for ethnicity in specific situations, await further exploration and consensus.

The ATS statement also emphasizes the importance of laboratory control of technical sources of variation, including strict adherence to ATS guidelines for equipment performance and calibration, minimizing temperature-related errors, careful validation of computer calculations when purchasing or changing equipment or software, and proper performance of the tests. Although certain within-individual sources of variation fall within the control of each laboratory, between-individual sources of variation are crucial to the choice of appropriate reference values.[1,2] Furthermore, environmental sources of variation (e.g., smoking and occupational exposures) pertinent to a given patient (in addition to other relevant clinical data) are likely to be known by the referring clinician. This information should be provided to the laboratory director, who should use it to evaluate the clinical relevance in a given lung function report. When short-term variation caused by disease, drugs, environment, smoking, laboratory instruments, or submaximal effort is excluded, body position, head position, effort dependency of maximal flows, and circadian rhythms comprise the primary residual sources of variation.[129]

STATISTICAL CONSIDERATIONS

Distributions of FEV_1 and FVC in population studies are close to Gaussian in the middle age range but not at the extremes. Furthermore, distributions of flow rates and ratios (FEV_1/FVC) are not symmetrical.[117] Therefore, publications describing reference populations should include not only the prediction equations but also a means to define their lower limits. A lower limit can be estimated from a regression model. For spirometry, values below the fifth percentile are taken as below the LLN.[117] If there are sufficient measurements within each category, percentiles can be estimated directly from the data. If the distribution of individual observations is close to gaussian, the value of the fifth percentile can be approximated.

As stated previously, there is no statistical basis for the common practice of using 80% of the predicted normal values for FEV_1 and FVC as the LLN in adults. For $FEF_{25\%–75\%}$ and for instantaneous airflow rates, this practice causes significant errors because the LLN for these values are close to 50% of predicted normal values. However, using a fixed percentage of the predicted value as an LLN may be acceptable in children when the standard deviation is proportional to the predicted mean value. In general, the lowest 5% of the reference populations may be considered as being below the LLN for any spirometric value.

The ATS suggests that individual laboratories use published reference equations that most closely describe the populations tested in their laboratories. It is useful to compare the results observed in 20 to 40 local subjects with those provided by the intended reference equations. These local subjects should be lifetime nonsmokers selected by age, ethnic group, and sex to match the population usually studied in the laboratory.

When interpreting pulmonary function tests by comparing a number of outputs against their respective LLNs, caution should be exercised because multiple testing may result in false positives and negatives. Because there is some degree of correlation between tests based on shared dependence on the underlying lung structure, this effect of performing multiple statistical tests is not as severe as when all the tests are completely independent. Nevertheless, even among highly correlated measures, test noise will cause some parameters to be less than and others above the LLN. Thus, interpretations are strongest when multiple parameters suggest a pattern.

clinical suspicion is very high for a restrictive ventilatory defect.

Spirometry with an isolated reduction in FEV_1 or FVC with normal FEV_1/FVC ratio should be interpreted as not clearly obstructive or restrictive in the absence of a TLC for further clarification. This pattern can also be read as a nonspecific ventilatory defect and investigated further with lung volume and D_{LCO} testing. The FEV_1/FVC ratio is expected to be higher than normal in cases of parenchymal restriction where there is increased elastic recoil. A high FEV_1/FVC should also be followed up with lung volume testing.

A restrictive ventilatory defect should be further evaluated with D_{LCO}. A low D_{LCO} suggests an intraparenchymal process, but a normal D_{LCO} suggests an extraparenchymal process, such as a chest wall defect or neuromuscular disease. D_{LCO} may be low in neuromuscular disease as well as when there is basal atelectasis. A low D_{LCO} in the setting of normal spirometry and normal lung volumes may be indicative of pulmonary vascular disease, or mild emphysema or ILD.

Once the major pulmonary function pattern has been recognized, the severity is graded using FEV_1 percentage predicted, irrespective of pattern. Restriction can also be graded using percentage predicted TLC. Table 32.3 shows the severity grading recommended by the ATS.[3]

FACTORS AFFECTING PULMONARY FUNCTION TESTING AND INTERPRETATION: CAVEATS AND PRECAUTIONS

A number of factors can affect test results, and care should be taken in the performance and interpretation of pulmonary function tests.

TEST PERFORMANCE CHARACTERISTICS

Pulmonary function tests in general depend heavily on the cooperation of the subject. The following factors should be kept in mind when making decisions about response to therapy and for comparisons on follow-up. If a competent technician performs the procedures and if recordings of the test tracings accompany the measurements, it is usually possible to determine the validity of the data. Suboptimal effort can usually be identified on the basis of the features listed in eTable 32.4. Supplemental data confirming invalid test results include uneven, slurred, or notched curves on inspection; poor repeatability of maximal expiratory flow (see Fig. 32.2), FEV_1, and FVC within a test session; poor agreement between measures of VC across spirometry, lung volumes, and diffusing capacity maneuvers; and poor reproducibility on repeated testing. FVC can be underestimated when end-of-test criteria are not met or when inhalation is incomplete before the forced expiratory maneuver. A valid restrictive pattern differs from a test with poor effort in that it is repeatable, shows smooth expiratory curves on direct examination, a steep slope at the start of the volume-time curve, and a normal or nearly normal MVV. FEV_1 can be frequently underestimated in the setting of significant hesitancy or an incomplete full inhalation before the forced expiratory maneuver. The back extrapolated volume on the volume-time curve should be less than 5% of the FVC or 100 mL, whichever is greater, to ensure that the start of test criteria is satisfactory. The inspiratory curve should be evaluated to confirm a full inhalation.

It should be noted that although lung volumes can be reliably measured using body plethysmography or gas dilution techniques (helium dilution or nitrogen washout), significant differences may be observed in estimates of lung volumes in individuals with obstructive lung disease. Plethysmography can overestimate thoracic gas volume at FRC, but this can be mitigated by coaching patients to pant slowly at 0.5 to 1.0 Hz.[138] Nonetheless, plethysmography is likely more accurate because, unlike the gas dilution estimates of lung volumes, it is not affected by noncommunicating airways. Milite and colleagues[139] reported that the difference in measured thoracic gas volume between the commonly used plethysmography and nitrogen washout methods is approximately 0.5 L in patients with emphysema.

The gas dilution methods are sensitive to leaks, which can result in overestimation of FRC and hence TLC and RV. A leak during plethysmography can result in either overestimation or underestimation of FRC. A leak most often happens during the closed-valve panting phase and tends to shift the baseline of the subsequent tidal breathing. Because the slow expiratory VC maneuver is performed after the panting phase, an upward shift will cause an overestimation of TLC, and a downward shift will result in an underestimation of TLC. Air trapping can be overestimated if the effort-dependent ERV measurement is suboptimal. D_{LCO} can be underestimated if the inspiratory capacity maneuver is submaximal.

SUBJECT CHARACTERISTICS

Medications

Caffeine and alcohol are bronchodilators and hence should not be consumed within 4 hours of testing; the effects are unlikely to be clinically significant with moderate consumption.[140] Alcohol also affects patient cooperation and can interfere with the methane sensor and the measurement of diffusing capacity.[141] When postbronchodilator testing is indicated, short-acting β-agonists and antimuscarinic agents should be withheld for at least 4 hours before testing. Long-acting β-agonists should be withheld for at least 12 hours, whereas long-acting anticholinergics and ultra-long-acting β-agonists should be withheld for at least 24 to 48 hours before testing.

Obesity

The prevalence of obesity is increasing, and hence it is important to consider the effects of obesity on lung function. Due to mechanical constraints, the increased mass of the chest wall decreases ERV, subsequently FRC, and then TLC.[142] Despite a decrease in TLC with obesity, TLC is

eTable 32.4 Suboptimal Effort

CHARACTERISTICS OF SUPOPTIMAL EFFORT
Decreased vital capacity
Poor agreement between measures of vital capacity
Relatively normal expiratory airflows (increased FEV_1/FVC ratio)
SUPPLEMENTARY RESULTS CONFIRMING PATTERN
Decreased total lung capacity
Uneven, slurred, irregular recording of spirograms

FEV_1, forced expiratory volume in 1 second; FVC, forced vital capacity.
Modified from Welch MH. Ventilatory function of the lungs. In: Guenter CA, Welch MH, eds. *Pulmonary Medicine*. Philadelphia: JB Lippincott; 1977: 72–123.

still most often within the normal range.[143,144] As the ERV diminishes, tidal volume is shifted toward RV, graphically depicted when the tidal volume loop is superimposed on the flow-volume loop at low lung volumes. Morbid obesity is often associated with basal atelectasis and decreased D_{LCO}. These effects are worsened in the supine posture. Obesity affects the detection of airflow obstruction in two competing directions. On one hand, because of extrathoracic restriction, individuals with obesity breathe at lower lung volumes where airway diameters are narrower, with resulting higher airway resistance. On the other hand, the detection of this airway resistance is complicated due to the decrease in FVC, which can raise the FEV_1/FVC ratio and thus mask airflow obstruction. Reference equations do not take obesity into account. Furthermore, obesity is commonly measured using the body mass index, which does not specifically reflect the mechanical constraints on the chest.

INTERPRETATION OF CHANGES IN FUNCTION OVER TIME

VARIATION BETWEEN TESTS WITHIN A YEAR

Changes in spirometric measurements may represent a true change or merely variability. A real change is more likely when a series of tests shows a consistent trend. A change varies in significance depending on the variable measured, the time period, and whether the individual has normal or abnormal lung function. The variability is greater with increasing intervals between tests and in individuals with established lung disease. When the FEV_1 and FVC are followed in healthy, normal subjects, within-day changes of 5% or more, between-weeks changes of 11–12% or more, and yearly changes of 15% or more are probably clinically significant.[3] Data are limited for lung volume variability over time and also vary with the method of determination of lung volume. Current guidelines suggest that 5–10% and 200 to 400 mL are thresholds that can be used clinically.[145] For D_{LCO}, within-year changes of greater than 10% or 5 units (mL/min/mm Hg) are likely significant; within-day variability is 5–10% or 2 to 2.5 units.[3,146,147] Other than a change in lung function, sources of fluctuation in D_{LCO} include increased depth of inspiration during the test, changes in altitude, and changes in hemoglobin concentration (for which the D_{LCO} can be adjusted).

AGING LUNG

Aging is associated with a decrease in lung elastic recoil pressure at all lung volumes. Morphologic studies have confirmed increased alveolar dimensions. VC decreases with age, whereas RV and closing volume increase with age,[148] suggesting that lung emptying is limited with increasing age because of airway closure.[149] The consequence of increasing airway closure and loss of elastic recoil is a progressive decline in FEV_1 and FVC beginning in the mid 20s to 30s, with a subsequent linear decline in FEV_1/FVC.[117,150] The rate of decline in FEV_1 and FVC varies, ranging from 17.7 to 46.4 mL/year (median, 22.4 mL/year) for FEV_1 in healthy nonsmokers. Higher rates are observed among current and recent smokers, people with asthma or obesity, those with occupational exposures or who live near traffic, people of certain ethnic backgrounds, and the elderly.[151–155] Differences in the relative decline in FEV_1 are not different between men and women.[155] Application of these average rates to the individual, particularly over short time frames and in those with lung disease, is challenging due to episodic loss of lung function associated with respiratory events. MVV decreases approximately 30% between 30 and 70 years of age, probably as a consequence of decreased maximal respiratory pressures, decreased distensibility of the total respiratory system, decreased lung elastic recoil, and impaired coordination of the respiratory muscles. TLC and R_{AW} are independent of age.[137,148,156] D_{LCO} decreases with advancing age. Experiments with the series resistance model of Roughton and Forster[157] suggest possible mechanisms. The decreases in membrane diffusing capacity after 40 years of age more likely reflects loss of alveolar-capillary surface area than a change in membrane thickness; pulmonary capillary blood volume is maintained until the seventh decade and then decreases rapidly.[158]

BRONCHODILATOR RESPONSIVENESS

Another approach to the differential diagnosis of the obstructive pattern is the assessment of responsiveness of impaired expiratory airflow to acute administration of a bronchodilator. The ATS recommends that VC (slow or forced) and FEV_1 be the primary spirometric indices used to determine bronchodilator response.[3] Total expiratory time should be considered when using FVC to assess the bronchodilator response because in obstructed patients FVC increases when expiratory time increases. A 12% increase above the prebronchodilator value *and* a 200-mL increase in either FVC or FEV_1 indicate a positive bronchodilator response in adults.

BRONCHODILATOR RESPONSIVENESS IN ASTHMA

Variable airflow obstruction is a core functional criterion by which to make a clinical diagnosis of asthma. Variable airflow obstruction can be established by variation over time in peak flow, variation over time in FEV_1,[159] or bronchodilator responsiveness. Repeatable peak flow measurements are very dependent on effort and thus are inherently more variable than other measures of airflow. Often, repeated measures of FEV_1 over time are not available. Therefore, the assessment of bronchodilator responsiveness at a single testing session is a useful test by which to make a diagnosis of asthma. Of importance, one must first consider whether other conditions are present that feature a bronchodilator response before making a diagnosis of asthma. For example, bronchodilator responsiveness is common in COPD.[160]

Failure to demonstrate significant responses to acute bronchodilator therapy does not rule out bronchodilator-responsive airflow obstruction. For example, many reports confirm that asthmatic patients with completely reversible airflow obstruction may fail to respond to inhaled

bronchodilators until after corticosteroid treatment.[161] Bronchodilator response is a continuous phenomenon, and therefore there is uncertainty about the significance of the finding near the threshold. Related to this, there are many reasons why a patient may not have a significant response at any one session: recent use of a short or long-acting bronchodilator, not enough abnormal smooth muscle contraction on that particular day, intraluminal mucus and/or airway edema as the predominant cause of obstruction, limitations of FEV_1 in assessing airflow obstruction, and the effect of a deep breath on airway caliber. The presence or lack of a significant bronchodilator response to short-acting albuterol during one testing session is poorly predictive of the long-term response to bronchodilator treatment in terms of change in FEV_1, symptoms, or exacerbations in asthma or COPD.

BRONCHODILATOR RESPONSIVENESS IN COPD

Between 35–60% of individuals with COPD show a bronchodilator response in FEV_1.[162–164] Hence, bronchodilator reversibility does not differentiate asthma from COPD. Patients with COPD are more likely to show a bronchodilator response in FVC than in FEV_1, likely due to a reduction in air trapping, especially in more severe disease; an FVC response is seen in up to 67% of individuals with COPD.[162] Also, compared to the FEV_1 response, an FVC response is more common in individuals with hyperinflation[43,165] and is more strongly associated with gas trapping.[166] Approximately 5% of individuals with COPD display a paradoxical bronchoconstriction in response to administration of a bronchodilator; this is associated with worse respiratory outcomes, including dyspnea, functional capacity, and exacerbations.[167,168]

Bronchodilator reversibility can change with repeated testing in parallel with the day-to-day variation in lung function and hence may not be a stable phenotype. In the *Inhaled Steroids in Obstructive Lung Disease in Europe* (ISOLDE) study, approximately 50% of subjects changed bronchodilator reversibility status between visits.[169] In the *Evaluation of COPD Longitudinally to Identify Predictive Surrogate End-Points* (ECLIPSE) study, only 16% of subjects considered to have reversibility at the first visit met reversibility criteria at all subsequent visits over the next 3 years.[170] The clinical utility of a positive bronchodilator response in COPD is thus unclear. Multiple studies have also shown that a lack of reversibility does not preclude response to long-acting bronchodilators.[160]

Additional information on bronchodilator responsiveness can be found at ExpertConsult.com.

BRONCHIAL CHALLENGE TESTING

Increased smooth muscle responsiveness is a core pathologic and clinical feature of asthma. Therefore, when patients do not have variable airflow obstruction or bronchodilator responsiveness, a bronchial challenge test can fulfill the functional criteria for asthma. This may be important to do because 25–40% of individuals with physician-diagnosed asthma in the community do not have evidence of airway hyperreactivity.[177] They may be taking medications for asthma unnecessarily and may have another diagnosis that is not being managed.

An abnormal/positive provocation test supports an asthma-focused diagnostic and treatment program but, of note, is frequently seen in other airway diseases (e.g., COPD,[178] sarcoidosis[179]), in the setting of allergic rhinitis without lower airway symptoms, or after recent upper respiratory tract infection or smoking. Airflow limitation in response to methacholine can reflect not only increased smooth muscle responsiveness, but also airway wall edema, luminal mucus, and changes in smooth muscle content and geometry.[180]

A normal/negative test argues strongly against asthma as a cause of current symptoms, except when there is exercise-induced asthma, early occupational asthma, or recent systemic corticosteroid treatment. If there are no symptoms currently, then it may have been some time since exposure to the right trigger/allergen, and a methacholine challenge may be negative. In this case, it can be argued that the patient does not currently have asthma, which highlights alternatives to a categorical asthma versus no-asthma interpretation: features of asthma can wax and wane, and there may be uncertainty in the diagnosis of asthma at any one time point.

The most frequently used type of positive bronchial challenge result is an abnormal increase in airflow limitation after exposure to sequential doses (doubling of concentration between doses) of inhaled methacholine, a direct smooth muscle agonist. The result is often reported as the concentration in mg/mL that leads to a 20% decrease in FEV_1 relative to the value after inhaling a saline control (*provocative concentration* [PC20]; usually extrapolated between doses if FEV_1 falls by more than 20%). Recommendations for a categorical interpretation of methacholine challenge results that nonetheless reflect the continuous relationship between dose/concentration and certainty of asthma are reproduced in eTable 32.5.[181] A significant change in PC20 from one test to another is considered 1.5 dose doublings, a figure informed by short-term repeatability of the test in stable asthma. Recently updated ATS/ERS guidelines recommend reporting the cumulative *provocative dose of methacholine delivered* (PD20), rather than PC20, to ensure reproducibility and comparability across delivery devices and protocols.[181]

An alternative or additional measure of response to methacholine is serial measurement of airway resistance after each dose of methacholine. An increase in specific airway resistance (equivalently, a decrease in *specific airway conductance* [sG_{AW}]) is more sensitive than a decrease in FEV_1 because measurement of FEV_1 necessarily involves a deep inspiration. Deep inhalations are known to reduce smooth muscle tone and have a bronchodilatory effect on airways, although this effect is reduced or absent in asthma.[182,183] Although some data suggest FEV_1 is more specific for asthma than airway resistance, another report suggests that among patients referred for testing, those without a significant change in FEV_1 but with a significant change in airway resistance (≈20% of referrals in this study) have a similar symptom burden as those with a significant decrease in FEV_1.[184] A common threshold for a significant change in sG_{AW} after inhalation of methacholine is a greater than or equal to 40% decrease.[175]

ADDITIONAL INFORMATION ON BRONCHODILATOR RESPONSIVENESS

Inhalation of albuterol (180 μg) 10 to 20 minutes before repeat spirometry testing is used in many laboratories to test reversibility, although ATS guidelines note that the choice of bronchodilator, dose, and mode of delivery depends on the clinical context.[1] Tests of bronchodilator responsiveness should ideally be performed after withholding respiratory medications for a duration based on their duration of action: short-acting bronchodilators for at least 4 hours, long-acting β-agonists for at least 12 hours, and long-acting anticholinergics and ultralong-acting β-agonists for at least 24 to 48 hours. Because many patients with asthma or other forms of airway disease do not respond acutely to β-adrenergic agonists, particularly at low doses, it is worth considering evaluation of reversibility after administration of ipratropium bromide aerosol (36 μg).[3,171] However, the maximal effect of ipratropium bromide may take 30 to 45 minutes. Furthermore, many patients with responsive airway obstruction do not respond to a standard clinical dose of either class of dilator, but airway obstruction still reverses completely if they are treated with larger doses. Thus, in some patients with airway obstruction who have never been treated before and who do not respond to a standard clinical dose of inhaled bronchodilator, we use a cumulative dose-response protocol. Spirometry is measured before (baseline) and 15 minutes after administration of repeated doses of albuterol (180 μg) or ipratropium bromide (36 μg) aerosol. The aerosol is administered every 15 minutes until a maximal increase in FEV_1 or FVC is attained or limiting symptoms are reached, or a prespecified maximal cumulative dose is reached. In this time interval, both agents produce at least 80% of their maximal response, and most patients respond maximally after receiving 8 to 10 puffs.

BASIS FOR THE DEFINITION OF A SIGNIFICANT BRONCHODILATOR RESPONSE

Many individuals without airway disease will have some increase or decrease in lung function with bronchodilator. Thus, there is a continuous distribution of change in lung function (e.g., FEV_1) with bronchodilator. In asthma, this response is shifted toward more positive values. Moreover, because bronchodilator response is a continuous phenomenon in disease, any threshold is imperfect.[165,172] Data from healthy controls show an upper boundary on the 95% confidence interval (i.e., an upper limit of normal) as a 12% change in FEV_1 after inhaling a bronchodilator. However, as the prebronchodilator FEV_1 decreases, increasingly smaller volume changes lead to a given set percentage change, and small fluctuations that may be technical rather than biologic will pass the 12% threshold. Therefore, the guidelines also require that the FEV_1 change by at least 200 mL. The 200 mL requirement does, however, make it harder for those with very small lung volumes to achieve a significant response.

Based on the discussion of air trapping with an increased RV earlier, and the observation that some individuals have large changes in FVC after bronchodilator, even when the change in FEV_1 is small, the ATS guidelines also define a significant change as one when the 12% and 200 mL requirements are met by the FVC *or* the FEV_1.

It has been argued that the limitations in percentage change from baseline and the 200 mL volume requirement can be improved by instead requiring a greater than or equal to 9% change relative to the predicted value without any volume requirement.[165,172–174] Airway resistance (RAW, GAW, *specific airway resistance* [sRAW], *specific airway conductance* [sGAW]) measured by body plethysmography is another measure of airflow obstruction. It represents the total resistance from the alveoli to the mouth, which in health is primarily determined by the large airways. Based mostly on data derived from children, a non–guideline-based cutoff for a significant change in sRAW and sGAW after bronchodilator is 25–50% and 40%, respectively.[175,176]

LIMITATIONS OF THE FEV_1 IN ASSESSING RESPONSIVENESS

FEV_1 is highly repeatable within a testing session and reproducible over time (in health or with stable disease) when the effort exceeds a threshold that is submaximal. Therefore, this is currently the single best metric to use in assessing bronchodilator responsiveness. However, we rely on FEV_1 with the understanding that it is not perfect. Because most of the FEV_1 is derived from exhalation at high lung volumes, it best reflects proximal airway caliber and does not reflect small airway narrowing (i.e., at the level of the bronchioles, which are surrounded by smooth muscle) unless the small airways involve a very large area of the lung. If the site of narrowing is predominantly distal, the FEV_1 may not be reduced significantly and may not change significantly with bronchodilator administration.

eTable 32.5 Categorization of Airway Response to Methacholine

PD20 μmol (μg)	PC20 (mg/mL)	Interpretation
>2 (>400)	>16	Normal
0.5–2.0 (100–400)	4–16	Borderline AHR
0.13–0.5 (25–100)	1–4	Mild AHR
0.03–0.13 (6–25)	0.25–1	Moderate AHR
<0.03 (<6)	<0.25	Marked AHR

AHR, airway hyperresponsiveness; PC20, provocative concentration causing a 20% fall in forced expiratory volume in 1 second (FEV_1); PD20, provocative dose causing a 20% fall in forced expiratory volume in FEV_1.

From Coates AL, Wanger J, Cockcroft DW, et al. ERS technical standard on bronchial challenge testing: general considerations and performance of methacholine challenge tests. *Eur Respir J*. 2017;49(5):1601526.

Small airway obstruction can lead to airway closure or difficulty in reaching a normal RV with exhalation, through the combined action of positive pleural pressure and reduced elasticity of the lung at lower compared to higher lung volumes. Reduced elasticity affects small airway caliber through a decrease in intraluminal pressure (diseased alveoli with reduced recoil will not generate as much driving pressure as normal alveoli) and a reduction in the tethering forces around the airways. Parameters beyond FEV_1 that may better reflect small airway obstruction include measures of air trapping (reduced FVC and/or increased RV, RV/TLC). Airflow at low lung volumes is lost early in diseases that start in the small airways, such as COPD, before there is a significant effect on FEV_1. This greater effect on flows at low compared to high lung volumes is why the flow volume curve becomes curvilinear. More data on the ranges, prevalence, and clinical significance of bronchodilator reversibility of these other measures are needed before they can be used clinically.

Vocal cord dysfunction is in the differential diagnosis of asthma and may coexist with asthma. Vocal cord dysfunction can be induced by methacholine challenge and can cause a decrease in sGAW and abnormal flattening of the inspiratory limb on spirometry. Of note, FEV_1 is expected to be normal.[175]

ADDITIONAL APPLICATION OF PULMONARY FUNCTION TESTS IN DECISION MAKING

In addition to enabling the differential diagnosis of lung disease by recognizing major patterns, pulmonary function testing aids clinical decision making in a number of situations.

INHALER SELECTION

In addition to using appropriate inhaler technique for the proper deposition of inhaled medication into the lung, there is growing evidence that the *peak inspiratory flow* (PIF) is an important factor in the ability to actuate inhalers. This is especially true in the case of dry powder inhalers, where a patient-generated PIF of 60 L/min or greater is considered ideal for actuation of the device and deaggregation of the medication formulation,[185] and PIF less than 30 L/min may be insufficient for optimal delivery of medication.[186] PIF measured using a device with resistance modified to match the specific inhaler resistance is likely to result in more accurate identification of inadequate inspiratory force.[187,188] The most important factors associated with low PIF are age, female gender, and lower lung function.[188]

ASTHMA CONTROL

Stabilization of asthma can be estimated by frequent measurement of the *peak expiratory flow* (PEF). PEF variation correlates strongly with symptom burden as assessed using the Asthma Control Test.[189] PEF is predominantly a reflection of large airway patency and hence can underestimate the involvement of small airways in asthma. It can be measured during spirometry or using a peak flowmeter. Spirometry values are approximately 7% lower than PEF measured using peak flowmeters; hence, peak flowmeters should be used for measuring diurnal variation.[190] Diurnal variability greater than 20% suggests suboptimal asthma control and a higher risk of exacerbations.[191] Baseline PEF is affected by demographics and also restrictive processes that affect full inspiration, such as obesity, chest wall disease, and neuromuscular disease. For these reasons, a baseline *personal best* PEF should be estimated individually in each subject after a period of optimal therapy and should be reevaluated at frequent intervals. Peak flowmeters offer advantages of convenience and portability; however, results from peak flowmeters are also less reproducible than those from standard spirometry. Thus, it is essential that physicians recognize the importance of the use of spirometers in the initial assessment of the patient suspected of having asthma and in periodic monitoring.

LUNG VOLUME REDUCTION

Both surgical and endoscopic lung volume reduction procedures are now available for a subset of patients with severe emphysema who have significant air trapping. The evaluation of patients suitable for these therapies starts with spirometry. The National Emphysema Treatment Trial enrolled patients with FEV_1 of 15–45% predicted and with an RV of 150% or greater than predicted.[192] More recent endobronchial valve trials included patients with various thresholds for air trapping, for instance, RV ranging from 150–200% or greater than predicted.[193–195] Individuals with D_{LCO} less than 20% predicted were excluded from these trials. It is recommended that body plethysmography be used for estimation of lung volumes in these individuals with severe COPD due to concerns of underestimation of lung volumes with gas dilution techniques. Although no thresholds have been defined, an elevated RV/TLC ratio correlates with an improvement in FVC and in FEV_1 post–lung volume reduction.[196–198] The improvement in FEV_1 is partially due to a reduction in airflow obstruction as indicated by the FEV_1/FVC ratio, likely resulting from improvement in elastic recoil, improved matching of the lung and rib cage size, and an improvement in the length-tension relationship of the diaphragm and other respiratory muscles.[196,199]

LUNG TRANSPLANTATION (See Chapter 140)

Spirometry after transplantation shows a characteristic increase in FVC and FEV_1 that on average approaches a plateau at 3 to 6 months after transplantation, with additional smaller increases at 6 to 12 months.[200,201] As expected, the increases in FVC and FEV_1 are greater with double-lung transplantation than with single transplantation. Post-transplantation morbidities, such as acute rejection, infection, pleural effusion, diaphragm injury, myopathy, anastomotic complications, and delayed chest wall healing can influence the trajectory of lung function changes. In relation to predicted values based on characteristics of the transplant recipient, FVC and FEV_1 do not always increase to the normal range, a condition termed *baseline lung allograft dysfunction* (BLAD). Many variables, including donor-recipient size mismatch, have been implicated but, in a multivariable model of data from recipients of bilateral lung transplantation, only heavy donor smoking and ILD as an indication for transplantation were predictors of BLAD; BLAD was also associated with impaired survival.[202] A plateau in expiratory flow at high to mid lung volumes on the flow-volume curve is not unusual after transplantation. This plateau in flow after the initial peak may be due to denervation of the lung and alterations of the large airway(s) at the site of anastomosis.[203,204] Transplantation of two lungs results in a normal TLC in patients with pre-existing chronic hyperinflation (e.g., COPD and cystic fibrosis) but with a persistent increase in FRC and RV.[205]

REJECTION OF TRANSPLANTED LUNGS

A major cause of morbidity and mortality after lung transplantation is *bronchiolitis obliterans* (BO), a progressive obstruction and destruction of bronchioles that may in part be due to an alloimmune response.[206] Histopathologic diagnosis from bronchoscopic biopsies is difficult. Therefore, the *International Society for Heart and Lung Transplantation* (ISHLT) recommends a clinical surrogate for BO termed *bronchiolitis obliterans syndrome* (BOS), which is defined as a 20% decrease in FEV_1 from the best baseline post-transplantation

value.[207] The total cross-sectional area of the numerous bronchioles results in a relatively small overall contribution to resistance to airflow. Thus, early in disease, when there is patchy narrowing, standard tests of pulmonary function, such as FEV_1, are not expected to be abnormal.[208,209] The distribution of ventilation assessed via single- and multiple-breath nitrogen washout has been shown to change earlier than FEV_1 in patients who develop BOS, although this awaits larger-scale validation before becoming part of routine monitoring.[210,211]

The obstructive defect in bronchiolitis obliterans is often accompanied by a decline in FVC due to air trapping. A concurrent decline in FEV_1 and FVC has a poorer prognosis than a subsequent decline in FVC, which is consistent with disease progression.[212] A concurrent decline in FVC can alternatively reflect restrictive allograft syndrome, a form of rejection with parenchymal fibrosis, which may have worse prognosis than bronchiolitis obliterans.[213] Given that FEV_1 may fall in the setting of either BO or restrictive allograft syndrome, an umbrella term was developed to refer to any sustained decrease in FEV_1: *chronic lung allograft dysfunction*.[207] Trending of the ratio of FEV_1 to FVC aids in the distinction between obstructive and restrictive changes after transplantation.

A major limitation to the use of simple lung function monitoring in single-lung transplant patients is the bias caused by the contribution of the native lung to measured lung function. Imaging techniques can help localize function to the transplanted lung.[214]

A brief discussion of the assessment of capacity in lung resections, high altitude, and air travel can be found at ExpertConsult.com and in Chapters 105 and 106.

SHUNT

In understanding the measurement of shunt, one starts with a model of the lung with two compartments, in which one has matched ventilation and perfusion and the other has blood flow but no ventilation (i.e., shunt). In this model, the shunt fraction reflects the fraction of otherwise normal lung that would have to be operating as a pure shunt to explain a deficit in the ability of the lung to oxygenate blood. Using this model, the shunt fraction is calculated from an arterial blood gas measurement after breathing 100% oxygen (see Chapter 31 for details of the calculation[227]). Inhalation of 100% oxygen achieves an oxygen tension in areas of low *ventilation-perfusion* (V/Q) that is nearly the same as in areas with normal V/Q ratios, thereby removing the effect of low V/Q on arterial oxygenation and isolating the effect of the shunt on oxygenation. Measurement after breathing 100% oxygen also ensures that arterial hemoglobin oxygen saturation from the perfused alveoli is 100%, a required assumption in the calculation. The classic textbook normal value for the anatomic shunt fraction is 2–5%.[228,229] However, we recommend using a higher cutoff for the 100% inspired oxygen-based calculation of shunt fraction for a number of reasons. First, 100% oxygen may alter the shunt fraction by changing pulmonary microcirculation vasomotor tone or by inducing reabsorption microatelectasis.[230] Second, the calculation assumes a fixed value for the arterial-venous oxygen content difference ($D(A–V)O_2$), which may not apply to every individual, leading to overestimation of shunt if the $D(A–V)O_2$ is underestimated. Finally, technical factors that may overestimate the shunt fraction are air leaks in the blood gas collection device and decreases in accuracy and precision of blood gas analyzers at the higher than normal arterial P_{O_2} values. A reasonable threshold to trigger further workup is a shunt fraction of 10.5%, which is the average of two studies that used the 100% oxygen-based method.[228,231]

A relatively high shunt fraction is required to affect arterial oxygen saturation while breathing ambient air. Assuming a negligible contribution of dissolved non–hemoglobin-bound oxygen to blood oxygen content, the mixed venous oxygen saturation and shunt fraction can be used to calculate estimated arterial oxygen saturation as in the nomogram in Figure 32.3. For example, at an average mixed venous oxygen saturation of 70%, a shunt fraction of 15% is expected to yield an arterial oxygen saturation of 95%; a shunt fraction of 20% would yield an arterial oxygen saturation of 94%; and a shunt fraction of 30% would yield an arterial oxygen saturation of 91%. This exercise highlights a key difference between this quantitative measurement of shunt and qualitative studies, such as the abnormal passage of saline contrast on an echocardiogram or other quantitative studies, such as abnormal passage of radiolabeled albumin macroaggregates from the right-sided to left-sided circulation. The quantitative measurement of shunt from breathing 100% oxygen provides information about

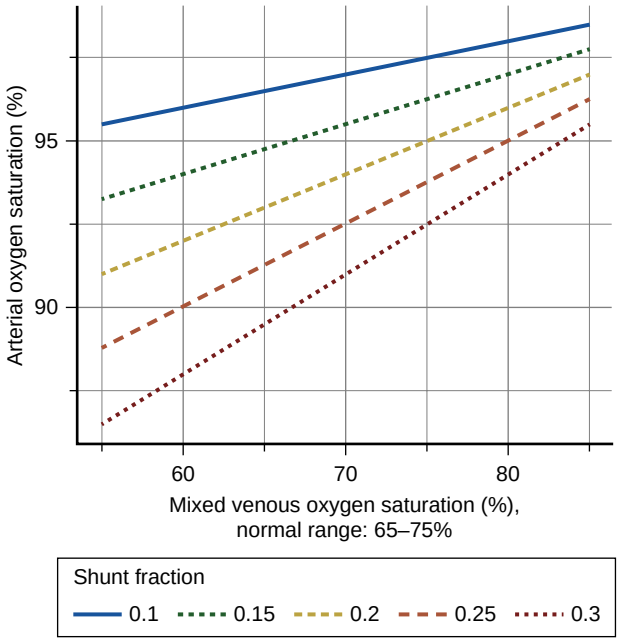

Figure 32.3 A nomogram for estimating the effect of a shunt on arterial oxygen saturation while breathing ambient air. To use the nomogram, first assume a normal mixed venous oxygen saturation of 70%. Then, of the two remaining variables—Sa_{O_2} or shunt fraction—use the measured value of one to locate the curve that allows estimation of the remaining variable. To derive the relationship, an assumption was made that any defect in oxygenation is only due to a fraction of the lung operating as a shunt, and the rest of the lung is normal (see main text and Chapter 31 for the principles of shunt measurement). Dissolved oxygen contributes very little to blood oxygen content, and therefore Sa_{O_2} is simply a weighted sum of blood from the shunt and normal portions of the lung: $Sa_{O_2} = (1 - Qs/Qt) \times 100\% + (Qs/Qt) \times S\bar{v}_{O_2}$. A limitation of this nomogram is that with reduced Sa_{O_2}, mixed venous oxygen saturation may be lower than normal; nonetheless, the nomogram can give a rough estimate as to whether the measured shunt fraction accounts for the observed arterial oxygen saturation. Qs, total shunted blood flow; Qt, total blood flow; Sa_{O_2}, arterial oxygen saturation; $S\bar{v}_{O_2}$, mixed venous saturation of oxygen.

LUNG RESECTION

Chapter 30 covers the utility of preoperative FEV_1 and DL_{CO} in the evaluation of patients before lung resection. This evaluation includes the predicted postoperative lung function. One method is estimation through the segment method[215]:

$$\text{Postoperative \% pred } FEV_1 = \text{preoperative } FEV_1 \times (1 - [\text{Number of segments resected}/19])$$

This method has also been applied to the DL_{CO}. The preoperative and postoperative estimated DL_{CO} are the most important pulmonary function predictors of postoperative morbidity and mortality after lung resection.[216,217] Although estimated postoperative lung function from the segment method is useful for prediction of outcomes after resection, it is not accurate enough for use in interpretation of postoperative pulmonary function tests.[218] In COPD, in which the region of lung removed may be hyperinflated and either contribute little function or negatively impact FEV_1 through hyperinflation, postoperative lung function will be underestimated. Nuclear imaging to assess regional perfusion with or without computed tomography or magnetic resonance imaging is an alternative that provides estimates that agree better with measured postoperative lung function.[218] K_{CO} obtained during the measurement of DL_{CO} has not been shown to adjust for the resected lung and is not recommended for use in interpretation; physiologically, overlap in K_{CO} and DL_{CO} is expected after lung resection as well as with other pulmonary pathology.[219] Trending of lung function can be more useful than measuring at a single time point after lung resection.

HYPOXEMIA AT ALTITUDE (See Chapters 105 and 106)

It is important for family physicians and specialists to be able to advise patients concerning the medical risks with airline travel. Cardiovascular and pulmonary problems are the most common reasons for proscribing air travel. Hypoxia in the aircraft, despite pressurization to the equivalent of 6000 to 8000 feet altitude, may be dangerous for patients with unstable angina, severe congestive heart failure, or severe lung disease.[220] With no change in ventilation, cabin pressure at 7000 feet is expected to yield an alveolar *partial pressure of oxygen* (Po_2) of 63 mm Hg; an arterial Po_2 of 53 mm Hg, assuming an average alveolar-arterial difference of 10 mm Hg (with the difference dependent on alveolar Po_2, with higher values associated with higher alveolar Po_2); and a corresponding hemoglobin oxygen saturation of 85%. Acute hyperventilation stimulated by this hypoxemia yields an increase in alveolar Po_2, with additional gains as ventilation further increases over days to weeks.[221] Alkalosis, especially prominent in the acute phase before there is significant metabolic compensation, shifts the hemoglobin oxygen dissociation curve to the left, increasing oxygen saturation above what is expected from an equivalent arterial Po_2 at sea level. The actual arterial Po_2 and saturations of healthy individuals at cabin pressure has been found to vary from 80% to 94%, likely due to variable hyperventilation in response to hypoxemia and variable activity levels.[222–224]; the steeper relationship between the Po_2 and hemoglobin oxygen saturation in this range, compared to normal, may also influence variability in the measurements.

Patients with chronic lung disease are known to have more desaturation at high altitude than healthy individuals, and this is expected to worsen with activity. If arterial Po_2 at high altitude is 50 mm Hg or greater, the patient should tolerate air travel reasonably well, although this recommendation is based on a general consensus and is not evidence based.[222] Patients with severe lung disease associated with arterial oxygen desaturation should be evaluated at sea level for the risk for hypoxemia during air travel or during travel to high altitude. Measurement of arterial Po_2 or arterial saturation at ground level is inadequate to predict low arterial Po_2 at altitude.[222,225] Instead, a *high-altitude simulation test* (HAST) may be performed. One study in patients with COPD suggests that an algorithm including sea-level pulse oximetry at rest and response in oximetry during a 6-minute walk test can refine the subset of patients who require a HAST to determine the need for supplemental oxygen at altitude.[226]

Using altitude *simulation* (using low-oxygen mixtures [15–16%] or hypobaric chambers), it is possible to assess symptoms, tolerance to exercise, amount of supplemental oxygen required, and effects of controlled hypoxia on associated hematologic, cardiac, and neurologic disorders. Such information cannot be obtained from the prediction of arterial Po_2 at high altitude. Furthermore, the equations for estimation of hypoxemia at altitude are relatively population specific (i.e., limited to COPD patients), do not perform well, and only deal with the effects of altitude on arterial oxygenation.[222]

There are no evidence-based algorithms to guide how much supplemental oxygen a patient needs if a HAST shows arterial Po_2 less than 50 mm Hg. Nor is there evidence-based guidance on how to increase the flow rate for patients who already require supplemental oxygen at sea level. Per the British Thoracic Society 2011 guideline, if a patient does not need supplemental oxygen at sea level but has an arterial Po_2 less than 50 mm Hg or a saturation by pulse oximetry less than 85% during HAST, supplementary oxygen should be given at 2 L/min for adults (1–2 L/min for infants and young children) during flight.[222] For patients on supplemental oxygen at sea level, it is reasonable to increase the flow rate by 2 L/min, which may limit the ability to fly depending on the availability and affordability of equipment to achieve such a flow rate. Initiation of supplemental oxygen at 2 L/min or an increment of 2 L/min if a patient is already on supplemental oxygen are sensible recommendations because the use of typical *fractional concentration of oxygen in inspired gas* (FIo_2) increments per L/min of supplemental oxygen (e.g., 3–4%) in the alveolar gas equation at cabin pressure predicts a return of *pressure of inspired oxygen* (Pio_2) to sea-level conditions. If HAST within a closed box (e.g., body plethysmograph) is available, supplemental oxygen via nasal cannula can be directly titrated to achieve a target oxygen saturation. Alternatively, individuals can use a pulse oximeter in-flight to titrate their O_2 supplementation to keep *oxygen saturation by pulse oximetry* (Spo_2) of 88% or greater.

the effect of the shunt on oxygenation, whereas the other diagnostics do not. The measurement of shunt with the body in different positions has been used to localize areas for embolization that will optimize benefit on oxygenation. In hepatopulmonary syndrome, the 100% oxygen breathing method is expected to give smaller values for the shunt fraction than radiolabeled perfusion scans because the increased alveolar P_{O_2} can overcome the diffusion defect related to diffuse microvascular dilation at the alveolar level (type 1, parenchymal shunts); convergence in the results between the tests is expected when the predominant lesions are discrete precapillary macrovascular (i.e., anatomic) shunts (type 2, vascular lung shunts).[232] (See Chapter 44.)

Key Points

- There are two main ventilatory patterns measured by pulmonary function tests: obstructive and restrictive. Mixed and nonspecific patterns are frequently observed as well, and these need further evaluation and follow-up. The shape of the flow-volume curve can alert the clinician to large airway obstruction.
- Because pulmonary function testing is effort dependent, the clinician must ensure the data meet quality standards for accuracy and repeatability before interpretation.
- Measurements from spirometry alone can be useful in individuals whose main physiologic impairment is airflow obstruction. The findings from spirometry can provide clues that concomitant restriction is present; however, for assessment of restriction, lung volumes must be measured.
- Lung function is different across age, sex, height, and ethnicity. Therefore, interpretation should be based on comparison of test results to reference values that adjust for these effects. The limitations of reference values underscore the importance of correlating pulmonary function test results with other clinical information, as well as testing repeatedly when signs or symptoms of disease persist. Accounting for differences across ethnic groups may have the unintended consequence of hiding causes for these differences, including those due to structural racism, and potentially leads to underdiagnosis and underestimation of severity of disease.
- In individuals with reversible mild airway disease, the results of pulmonary function tests may be normal because the disease is dynamic and individuals with mild airflow obstruction may spontaneously return to normal.
- Methacholine provocation testing is used to identify whether abnormal airway responsiveness is present. Its most important clinical utility is that a negative test makes bronchial asthma highly unlikely.
- In addition to diagnosis, pulmonary function testing is useful for monitoring disease activity and progression, as well as for following the response to or side effects of therapy.
- Pulmonary function testing is also useful for specific applications, such as inhaler selection, candidate selection for lung volume reduction and lung transplantation, and post-transplantation evaluation and monitoring.

Key Readings

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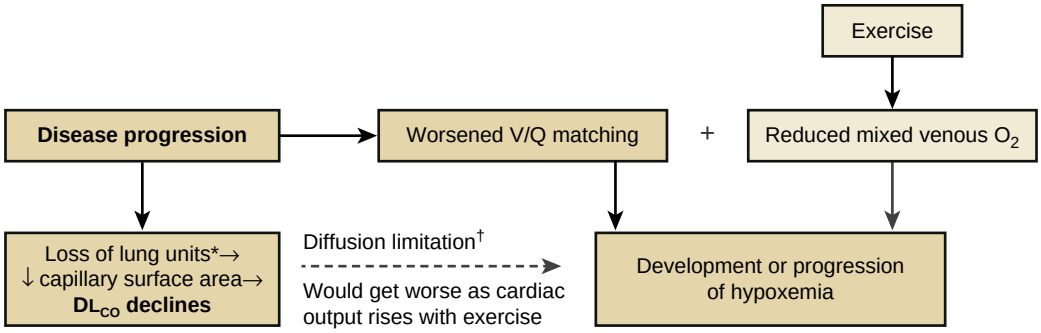
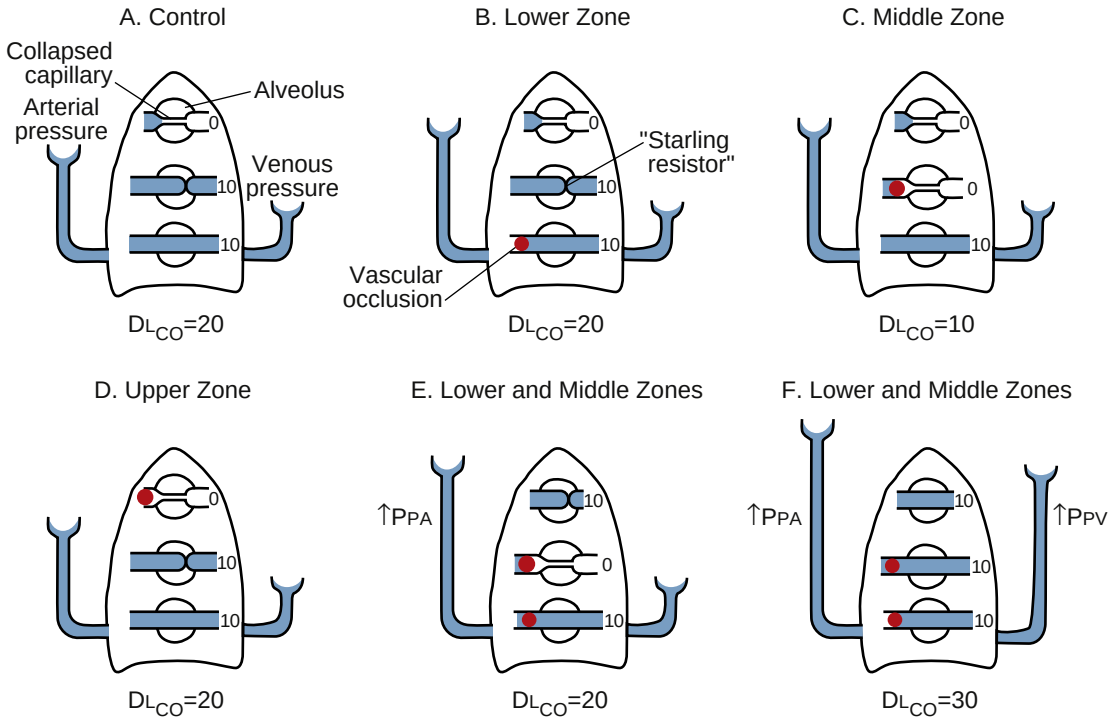
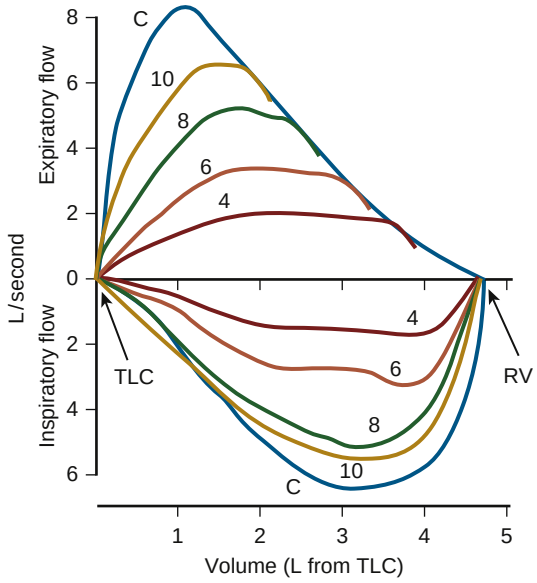
Complete reference list available at ExpertConsult.com.



eFigure 32.1 The path from disease progression to hypoxemia: clearing confusion on the relationship between declining DL_{CO} and hypoxemia. The DL_{CO} is often found to be a predictor of exercise-induced hypoxemia or for the need for supplemental oxygen. Therefore, clinicians often look at the DL_{CO} to determine the need for additional testing. Some take the statistical association a step further and cite the reduced DL_{CO} as a cause of the hypoxemia. However, this is a misconception, as noted in the text. The relationship between a decrease in DL_{CO} and the development or worsening of hypoxemia is largely driven indirectly by worsening *ventilation-perfusion* (V/Q) matching as shown in the figure. We do not have to invoke diffusion limitation during exercise either. During exercise, a fall in mixed venous P_{O_2} will amplify the effect of V/Q mismatching, which itself need not change during exercise and, in fact, often improves with exercise. *There are only a few disease processes in which increased thickness may contribute to a reduction in DL_{CO} (pulmonary arterial hypertension, *Pneumocystis jirovecii* pneumonia, chronic left-sided heart failure, early sarcoidosis), and one case where the increased distance for diffusion contributes to hypoxemia: hepatopulmonary syndrome. †For idiopathic pulmonary fibrosis, there is evidence that increased red blood cell velocity in a reduced pulmonary capillary cross-sectional area (and hence reduced alveolar transit/dwell time) plays a role in some (but not most) of the hypoxemia; the degree depends on how much capillary bed is lost and whether measured at rest or during exercise. In emphysema, diffusion limitation has not been found to contribute to hypoxemia at rest or with exercise. DL_{CO}, diffusing capacity of carbon monoxide; P_{O_2}, partial pressure of oxygen.



eFigure 32.2 Theoretical model showing the effect of *pulmonary arterial pressure* (P_{PA}) and *pulmonary venous pressure* (P_{PV}) on pulmonary capillaries at different levels of the lungs. The magnitude of P_{PA} or P_{PV} is indicated by the height of the fluid columns. For simplicity, the *pressure in alveoli* (Palv) is assumed to be equal to atmospheric pressure. Single-breath *diffusing capacity of carbon monoxide* (DL_{CO}) is given in arbitrary units indicating the relative contribution of various zones of the lung. (A) In the control state, at the bottom of the lung, both P_{PA} and P_{PV} are greater than Palv, and both keep the capillaries open. In the middle zone, P_{PA} is greater than Palv and P_{PV}, so P_{PA} holds capillaries open. (The exact anatomy of capillaries in the zone in which Palv is greater than P_{PV} is unknown; in the diagram, the compressed segment at the end of the capillary is meant to suggest a Starling resistor effect.) In the upper zone, Palv is greater than P_{PA} and P_{PV}, and capillaries are collapsed. (B) When arterial inflow is occluded to the lower zone (*red solid circle*), P_{PV} is greater than Palv, so the capillaries in this zone remain distended, and DL_{CO} is unchanged. (C) When arterial inflow to the middle zone is occluded, Palv is greater than P_{PV}, and capillaries in this area are collapsed, so there is a decrease in DL_{CO}. (D) When arterial inflow to the upper zone is occluded, the capillaries are already collapsed, so there is no change in DL_{CO}. (E) When arterial inflows to the lower and middle zones are occluded simultaneously, capillaries in the middle zone may collapse. However, if P_{PA} increases, capillaries in the upper zone may become distended, and the net result may be no change in DL_{CO}. **Under these circumstances, if P_{PV} also increases (F), DL_{CO} may actually increase.** (Modified from Nadel JA, Gold WM, Burgess JH. Early diagnosis of chronic pulmonary vascular obstruction. Value of pulmonary function tests. *Am J Med.* 1968;44[1]:16–25.)



eFigure 32.3 Volume (as liters [L] from total lung capacity [TLC]) is plotted against inspiratory and expiratory flows. The *blue line* (C) is the control effort; the number on each curve refers to the orifice diameter in millimeters. Lesions must narrow the tracheal lumen to less than 8 mm before abnormalities can be detected by spirometry. RV, residual volume**.** (Modified from Miller RD, Hyatt RE. Obstructing lesions of the larynx and trachea: clinical and physiologic characteristics. *Mayo Clin Proc*. 1969;44:145–161.)

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33 EXERCISE TESTING

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INTRODUCTION

Sustained exercise requires tight integration of the cardiac, neuromuscular, and respiratory systems. Diseases affecting any of these systems can manifest as dyspnea or exercise limitation. In addition to other modalities commonly used to assess patients with these complaints, *cardiopulmonary exercise testing* (CPET) provides a systematic means to evaluate exercise responses, unravel the interacting components, and determine which system contributes the most to the exercise limitation. CPET has other important uses, including quantifying maximal exercise capacity, assessing functional limitation, prescribing rehabilitation and training regimens, and guiding clinical decisions, such as the timing of transplant listing or fitness for surgery.

This chapter describes the clinical application of CPET and assists the reader in understanding the role of CPET in the evaluation of dyspnea and exercise limitation. Because CPET interpretation requires an understanding of the physiologic responses to exercise, the chapter begins with a review of exercise physiology that sets the foundation for the balance of the content. The review includes exercise responses in healthy individuals and those with various forms of cardiopulmonary disease. The chapter then describes the indications and contraindications of CPET, the options for conducting exercise tests, and an approach to test interpretation. It concludes by describing alternative modalities for assessing exercise responses in clinical practice.

PHYSIOLOGIC RESPONSES TO EXERCISE

EXERCISE AS A MULTISYSTEM PROCESS

To support vigorous aerobic exercise, the respiratory system works as a ventilatory pump to move oxygen from the atmosphere into the bloodstream where it binds to hemoglobin, whereas the heart pumps the oxygenated blood to the exercising muscles, which extract oxygen to support *adenosine triphosphate* (ATP) generation and muscle contraction. Muscle activity generates *carbon dioxide* (CO_2), which must be delivered by the circulatory system to the lungs, where it diffuses across the alveolar walls and is eliminated via the ventilatory pump. The nervous system contributes at multiple stages in this process, providing signals to raise ventilation and signals to exercising muscles that drive contractions. All of these systems work in a coordinated manner to support exercise, and problems in one or more of them may manifest as dyspnea or exercise limitation.

HEALTHY INDIVIDUALS

To appreciate changes in exercise tolerance in cardiopulmonary disease, it is helpful to examine the normal physiologic responses to progressive exercise in four major areas: metabolic activity, hemodynamic responses, ventilatory responses, and gas exchange. The major parameters within each area and the expected responses are described later and in other resources.[1]

Metabolic Activity

Oxygen Consumption. *Oxygen consumption,* denoted as $\dot{V}O_2$, (a volume per time, e.g., mL/min) is the most useful parameter for assessing overall exercise capacity. In essence, $\dot{V}O_2$ is the amount of fuel consumed in conducting work; the stronger the motor, the greater the maximal fuel consumption. To understand this concept, consider the determinants of $\dot{V}O_2$ using the Fick equation:

$$\dot{Q} = \dot{V}O_2 \div (CaO_2 - C\bar{v}O_2) \quad [1]$$

where $\dot{Q}$ is cardiac output (mL/min), CaO_2 is arterial oxygen content (mL/dL), and $C\bar{v}O_2$ is mixed venous oxygen content (mL/dL). Rearranging the relationship as follows,

$$\dot{V}O_2 = \dot{Q}\,(CaO_2 - C\bar{v}O_2) \quad [2]$$

demonstrates that oxygen consumption is dependent on cardiac output, oxygen content, which is related to the concentration of hemoglobin and the P_{O_2}, and tissue oxygen utilization. As a result, $\dot{V}O_2$ provides useful information about many of the systems required for sustained high-level exercise.

In addition to providing information on overall exercise capacity, *maximal oxygen consumption* ($\dot{V}O_{2max}$) is useful for assessing cardiac function. Given that the arteriovenous oxygen content difference at maximal exercise is largely the same in healthy individuals and in those with cardiac disease,[2] the wide variation in $\dot{V}O_{2max}$ across individuals is primarily determined by the variation in cardiac output. The greater the $\dot{V}O_{2max}$, the greater the cardiac output and vice versa.

Oxygen consumption can also be used to estimate stroke volume at maximal exercise. To understand this, Eq. 2, where *HR* is heart rate and *SV* is stroke volume, can be rewritten:

$$\dot{V}O_2 = HR \times SV \times (CaO_2 - C\bar{v}O_2) \quad [3]$$

and then rearranged as:

$$\dot{V}O_2/HR = SV \times (CaO_2 - C\bar{v}O_2) \quad [4]$$

Given that the arteriovenous oxygen content difference is largely the same across healthy individuals at maximal exercise, the term $\dot{V}O_2$/HR, referred to as the *oxygen pulse* or *O_2 pulse*, represents a surrogate for stroke volume. The O_2 pulse should increase throughout exercise due to both the increasing stroke volume and the arteriovenous oxygen content difference.

During progressive exercise to a symptom-limited maximum, $\dot{V}O_2$ increases linearly relative to workload from resting values near 250 mL/min for an average-sized person until a plateau is reached at maximum effort ($\dot{V}O_{2max}$). If a plateau is not identified, the term $\dot{V}O_{2peak}$ is applied instead to denote that it may not represent the individual's potential maximum. In average sedentary individuals, $\dot{V}O_{2max}$ is roughly 30 to 40 mL/kg/min at end exercise, whereas very fit athletes can attain values as high as 80 to 90 mL/kg/min. $\dot{V}O_{2max}$ is influenced by many factors, including age and sex, which are discussed further later. With intensive training, unfit subjects can increase their $\dot{V}O_{2max}$ by 15–25%[3,4] but cannot raise their $\dot{V}O_{2max}$ from an average to an elite level. What improves with training is the efficiency of work and the ability to sustain high levels of work. Genetic factors also affect an individual's $\dot{V}O_{2max}$[5] and his or her response to training regimens.[6] In clinical exercise testing, an individual's $\dot{V}O_{2max}$ is typically expressed in reference to that predicted for his or her age and sex based on data from large population studies. Reference values have been published, but methodologic issues limit the wide applicability of many of them.[7] As with all reference values, the normal range is dependent on the population studied.

Carbon Dioxide Output. In early exercise, *CO_2 output* ($\dot{V}CO_2$) increases linearly relative to workload from resting values near 200 mL/min for an average-sized person at about the same rate as oxygen consumption. Above the *ventilatory threshold*, an important time point described later, the rate of CO_2 output steepens as bicarbonate buffering of increasing lactate production leads to CO_2 elimination beyond that generated by aerobic metabolism.[7]

Respiratory Exchange Ratio. Defined as CO_2 elimination divided by oxygen uptake ($\dot{V}CO_2/\dot{V}O_2$), the *respiratory exchange ratio* (R) remains stable between 0.8 and 0.9 in early to mid-exercise, with slight variation between individuals depending on their balance of dietary fats and carbohydrates. It is important to note that R is measured using exhaled gases, in contrast to cellular R, otherwise known as the *respiratory quotient* (RQ), which is measured at the tissue level. Just before and in the early stages of exercise, R may transiently increase due to anticipatory hyperventilation. Above the ventilatory threshold, $\dot{V}CO_2$ increases markedly, and R increases above 1.0. With cessation of exercise, $\dot{V}O_2$ decreases abruptly, whereas $\dot{V}CO_2$ remains high as tissue CO_2 stores continue to be eliminated. R can subsequently increase over 1 to 2 minutes to values as high as 1.3 to 1.5 before finally decreasing.

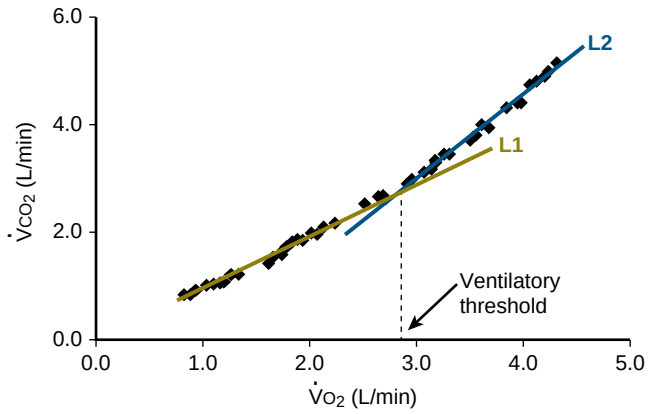

Figure 33.1 The V-slope method for identifying the first ventilatory threshold. Before the threshold, $\dot{V}O_2$ and $\dot{V}CO_2$ rise at the same rate. A best-fit line through these points is labeled L1 and is denoted in *brown*. After the threshold, $\dot{V}CO_2$ rises faster than $\dot{V}O_2$. A best-fit line through these points is labeled L2 and is denoted in *blue*. The point at which the two lines intersect denotes the $\dot{V}O_2$ at which the ventilatory threshold is reached. $\dot{V}CO_2$, carbon dioxide output; $\dot{V}O_2$, oxygen consumption.

Ventilatory Thresholds. Healthy individuals demonstrate a phenomenon termed the *ventilatory threshold* at about 50–60% of the $\dot{V}O_{2max}$, although there is interindividual variability in the timing of this phenomenon.[7,8] This threshold marks a critical point in progressive exercise where blood flow to the exercising muscle is no longer sufficient to meet metabolic demands and the individual transitions from light-moderate to moderate-high intensity exercise.[9] Alternatively referred to as the *lactate threshold, gas exchange threshold,* or *anerobic threshold*, the phenomenon is temporally related to an increase in lactic acid production and a decrease in pH, with considerable debate regarding the mechanisms for the increased lactate production[10,11] and whether it happens suddenly or in a more continuous manner throughout exercise.[12–14] As lactic acid dissociates, hydrogen ions are buffered by intracellular bicarbonate, leading to further CO_2 generation beyond that associated with aerobic metabolism.[9,15] This causes a steep rise in the $\dot{V}CO_2$ versus work relationship as well as the $\dot{V}CO_2$ versus $\dot{V}O_2$ relationship (Fig. 33.1). Identifying the change in slope of the latter relationship is referred to as the *V-slope method* and is a key step in CPET interpretation, as described later.

As work increases beyond the ventilatory threshold, many individuals demonstrate a second ventilatory threshold, sometimes referred to as the *respiratory compensation point*, at which rising lactate concentrations cannot be

buffered by intracellular bicarbonate, and *minute ventilation* ($\dot{V}E$) increases beyond that expected for the increase in $\dot{V}CO_2$, thereby causing a respiratory alkalosis.[9,15] This point, which is not visible in all individuals due to interindividual variation in ventilatory responses to metabolic acidosis, can be identified by finding threshold responses in several ventilatory parameters, as described further later.

Hemodynamic Responses

Cardiac Output. Cardiac output (mL/min) increases linearly with workload before plateauing near peak exercise; it can be estimated from $\dot{V}O_2$ using the Fick principle, measured invasively with a *pulmonary artery* (PA) catheter or estimated noninvasively using inert gas rebreathing techniques.[16,17] The initial increase is due to increasing stroke volume and heart rate, whereas changes near peak exercise result from increases in heart rate.[18]

Heart Rate. Due initially to decreased vagal tone and later to increases in sympathetic activity, heart rate (beats/min) increases linearly with increasing $\dot{V}O_2$. The *heart rate reserve*, defined as the difference between the maximum predicted heart rate and the heart rate achieved at peak exercise, is typically very small in healthy individuals (<20 beats/min), but this parameter is difficult to use in exercise test interpretation due to significant variability in maximum heart rates in healthy age-matched individuals.[7,19] Another measure of heart rate response, also termed the *heart rate reserve*, is the difference between the resting and maximum heart rate. This chapter uses the former definition.

Pulmonary Arterial Pressure. PA pressure rises only modestly with progressive exercise in healthy individuals due to recruitment and distention of the pulmonary vasculature and decreased pulmonary vascular resistance. There is interindividual variability in observed responses,[20] with greater variability in older individuals.[21]

Stroke Volume. Characterized during CPET by the O_2 pulse, stroke volume increases in early exercise before leveling off in late exercise.[18] Initial increases are driven largely by mobilization of blood from lower extremity venous capacitance vessels, whereas later smaller increases result from increased inotropic activity.

Systemic Blood Pressure. Due to increases in cardiac output and vascular resistance in the skin, renal, and splanchnic circulations, systemic blood pressure increases with progressive exercise. Although exercising muscle vasodilation limits the rise in diastolic pressure, systolic pressure rises significantly, particularly after the ventilatory threshold, and may reach values greater than 200 mm Hg at peak exercise.

Ventilatory Responses

Minute Ventilation. Due to an increase in respiratory rate and tidal volume, *minute ventilation* ($\dot{V}E$, mL/min) rises throughout exercise with large increases seen after the ventilatory threshold. The tidal volume plateaus at 50–60% of vital capacity, after which the $\dot{V}E$ increases further due to increases in respiratory rate.[22,23] At peak exercise, $\dot{V}E$ is typically less than 80% of the predicted maximum, as estimated by the *maximum voluntary ventilation* (MVV) or *forced expiratory volume in 1 second* (FEV_1) × 40.[24]

Ventilatory Equivalents for Oxygen and Carbon Dioxide. The ventilatory response can be expressed as a function of the amount of ventilation per liter of oxygen consumed ($\dot{V}E/\dot{V}O_2$, unitless) or per liter of exhaled carbon dioxide ($\dot{V}E/\dot{V}CO_2$, unitless). Both ratios remain relatively steady (~24–30) through early exercise as ventilation rises proportionately with $\dot{V}O_2$ and $\dot{V}CO_2$ and then increases after the ventilatory threshold, peaking around 35 to 40, with slightly greater increases seen in $\dot{V}E/\dot{V}O_2$.[7] Both parameters may be elevated in early exercise in highly fit or anxious individuals but typically return to normal as exercise progresses, reaching a nadir just before the ventilatory threshold. The range of ventilatory equivalents seen across healthy individuals reflects the variability in respiratory drives in the population.

Dead-Space Fraction. Due to increased tidal volume and recruitment of the pulmonary vasculature resulting from increased pulmonary blood flow, the *dead-space fraction* (V_D/V_T, unitless) decreases from 0.3 to 0.4 at rest to less than 0.3 at peak exercise.[7]

Gas Exchange

Arterial and End-Tidal Partial Pressures of Carbon Dioxide. Despite the increasing $\dot{V}CO_2$, the *arterial* P_{CO_2} (mm Hg) and *end-tidal* P_{CO_2} (mm Hg) remain constant and near normal through early exercise due to the fact that alveolar ventilation rises proportionally with $\dot{V}CO_2$. These values may decrease in individuals who hyperventilate at the start of exercise but typically normalize over the first few minutes of work. After the ventilatory threshold is reached, minute and alveolar ventilation rise out of proportion to $\dot{V}CO_2$. As a result, both arterial P_{CO_2} and and end-tidal P_{CO_2} decrease so that both values are nearly always less than 40 mm Hg at $\dot{V}O_{2max}$.[25]

Arterial and End-Tidal Partial Pressures of Oxygen and the Alveolar-Arterial Oxygen Difference. Below the ventilatory threshold, the *end-tidal* P_{O_2} (mm Hg), a surrogate measure of alveolar P_{O_2}, and the arterial P_{O_2} remain constant in the normal range, as do *arterial oxygen saturation* (S_{O_2}, %) and the *alveolar-arterial* P_{O_2} *difference* ($[A-a]P_{O_2}$, mm Hg). Beyond the ventilatory threshold, end-tidal P_{O_2} increases due to alveolar ventilation increasing out of proportion to $\dot{V}O_2$. Although alveolar P_{O_2} increases, arterial P_{O_2} remains unchanged due to a lower $C\bar{v}O_2$ and normal physiologic shunting. As a result, the $(A-a)P_{O_2}$ increases slightly with heavy exercise. In a minority of highly fit individuals with high $\dot{V}O_{2max}$, arterial P_{O_2}, and arterial S_{O_2} can decline in late exercise, a phenomenon referred to as *exercise-induced arterial hypoxemia*.[26–28]

In CPET, the changes in many of the parameters described above can be identified from tabular data or graphically using an approach developed by Wasserman and colleagues[29] in which nine separate graphs are displayed in a standardized format (Fig. 33.2).

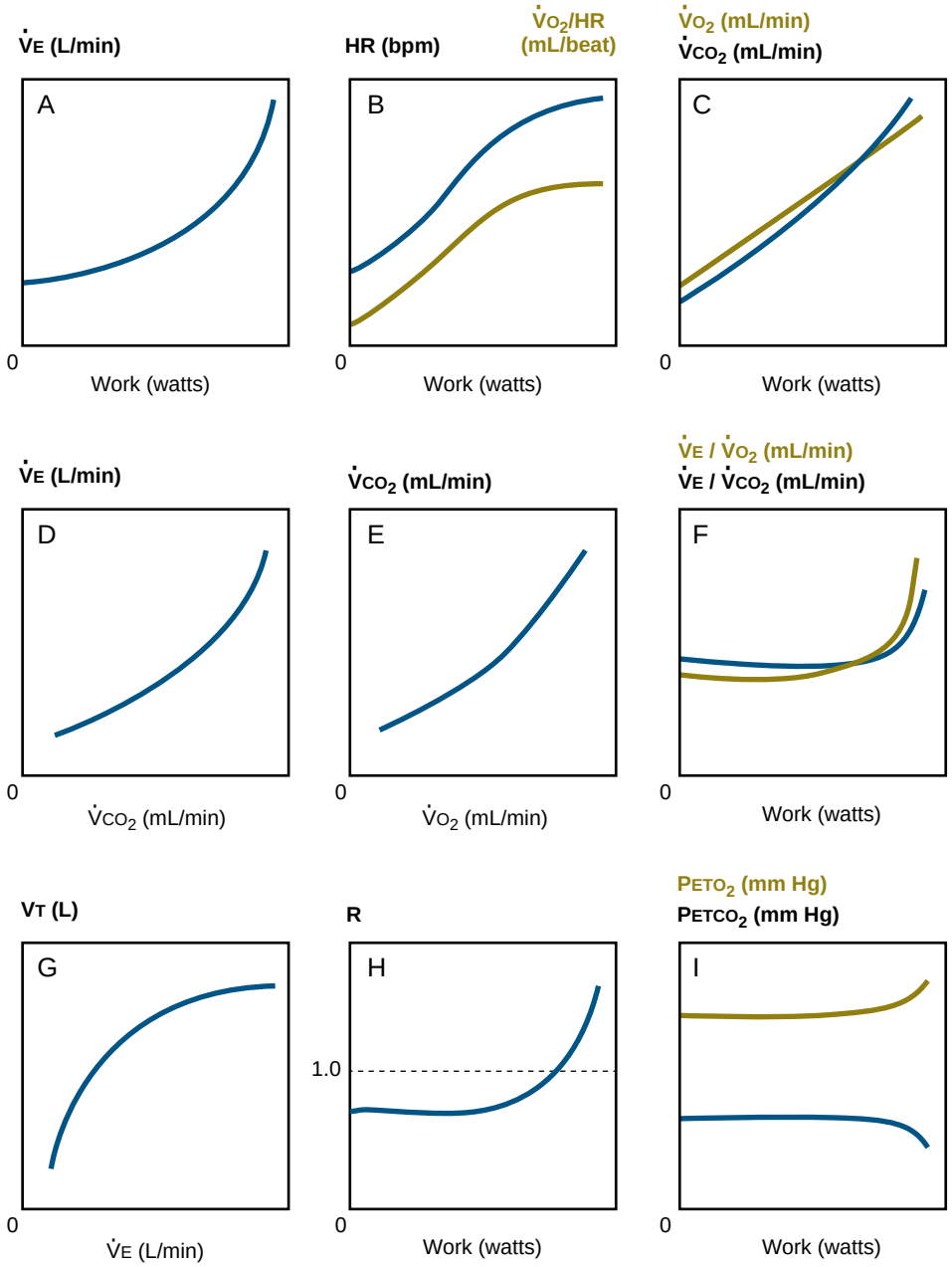

Figure 33.2 Normal pattern of responses to exercise in healthy individuals shown in a nine-box plot. (A) $\dot{V}_E$ vs. watts. (B) Heart rate (HR) and $\dot{V}O_2$/HR vs. watts. (C) $\dot{V}O_2$ and $\dot{V}CO_2$ vs. watts. (D) $\dot{V}_E$ vs. $\dot{V}CO_2$. (E) $\dot{V}CO_2$ vs. $\dot{V}O_2$. (F) $\dot{V}_E/\dot{V}O_2$ and $\dot{V}_E/\dot{V}CO_2$ vs. watts. (G) Tidal volume (V_T) vs. $\dot{V}_E$. (H) Respiratory exchange ratio (R) vs. watts. (I) P_{ETO_2} and P_{ETCO_2} vs. watts. Labels for the *y*-axis variables are presented on the top of each graph. Note that for the variables on the *x*- and *y*-axes the lowest values are in the lower left corner of each plot. P_{ETCO_2}, end-tidal partial pressure of CO_2; P_{ETO_2}, end-tidal partial pressure of O_2; $\dot{V}CO_2$, carbon dioxide output; $\dot{V}_E$, minute ventilation; $\dot{V}O_2$, oxygen consumption.

Changes With Age

A decrease in $\dot{V}O_{2max}$ with increasing age has been consistently reported in cross-sectional[30,31] and longitudinal studies,[32,33] with documented rates of decline in $\dot{V}O_{2max}$ varying from as low as 0.28 mL/kg/min/yr[32] to as high as 1.04 mL/kg/min/yr.[34] Although some studies demonstrate a slower rate of decline in active individuals compared to sedentary individuals,[32] others[35] report no effect of activity level on age-related declines in $\dot{V}O_{2max}$. Training programs in older sedentary individuals may reverse much of the age-related decline,[36] which accelerates in the later stages of life.[37]

Between 20 and 50 years of age, the decline in $\dot{V}O_{2max}$ is attributable to impaired peripheral oxygen extraction,[33] whereas changes later in life relate to impaired peripheral extraction and decrements in maximal cardiac output due to an inability to raise stroke volume at maximal exercise.[38] Observed changes in peripheral extraction may be due to decreased lean body mass, age-related changes in skeletal muscle, or blood flow distribution at peak exercise,[33] whereas the decline in cardiac output may represent increasing incidence of comorbid conditions affecting cardiac performance.[38]

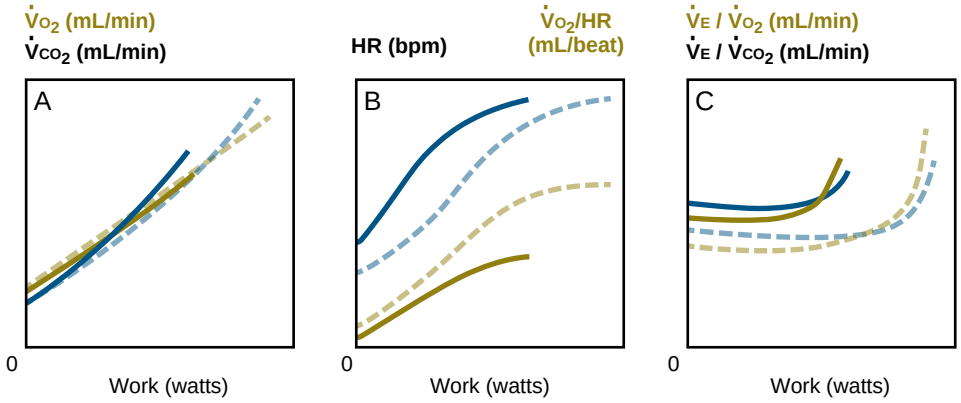

Figure 33.3 Heart failure pattern of responses to exercise compared to normal shown on three key figures from the nine-box plot. The responses for cardiac limitation in heart failure *(solid lines)* are compared to healthy individuals *(dotted lines)*. (A) $\dot{V}O_2$ and $\dot{V}CO_2$ vs. watts. (B) Heart rate (HR) and $\dot{V}O_2$/HR vs. watts. (C) $\dot{V}E/\dot{V}O_2$ and $\dot{V}E/\dot{V}CO_2$ vs. watts. A complete nine-box plot for this pattern of limitation is shown in eFig. 33.1. $\dot{V}CO_2$, carbon dioxide output; $\dot{V}E$, minute ventilation; $\dot{V}O_2$, oxygen consumption.

Sex Differences

Comparisons of exercise responses in men and women are difficult because most studies of physiologic responses to exercise have been performed in men. The available evidence demonstrates that women have the same qualitative responses to exercise as men but have lower $\dot{V}O_{2max}$, even after accounting for differences in lean body mass and training status.[39–41] The mechanism for these differences remains unclear but may relate to differences in blood volume, heart size, hormonal and metabolic status, or autonomic nervous system regulation of the heart and vascular system.[39] Some studies report slower age-related rates of decline in $\dot{V}O_{2max}$ in women compared to men, whereas others have not found such a differences.[37]

Ventilatory responses and gas exchange may also differ by sex, with some studies noting higher $\dot{V}E/\dot{V}O_2$ and $\dot{V}E/\dot{V}CO_2$ in women[37,40,42] and others reporting higher $(A-a)PO_2$ in fit women at very high levels of oxygen consumption.[43] At high exercise intensities, women may also rely more heavily than men on fat oxidation as a fuel source and thus have a lower respiratory exchange ratio.[44,45]

Obesity

Obese individuals with normal underlying cardiac or pulmonary function display a lower $\dot{V}O_{2max}$ than predicted for age and sex when expressed per kilogram of actual body weight but normal values when adjusted for ideal body weight. Because of the increased metabolic requirements resulting from increased weight, however, several important differences are observed relative to nonobese individuals. $\dot{V}O_2$ for any given level of work is higher than in the nonobese, although the *rate of change in oxygen consumption per given change in work rate* ($\Delta\dot{V}O_2/\Delta WR$) remains the same.[46,47] Obese individuals also have increased $\dot{V}O_2$ when pedaling without resistance (unloaded pedaling) due to the energy demands of moving heavier legs against gravity,[48] which is not reflected in the WR on the cycle ergometer.

$\dot{V}E$ is also increased for a given WR compared to the nonobese due to the added CO_2 production from the additional tissues.[46] This is typically achieved by increasing respiratory rate rather than tidal volume, which some data suggest is decreased during exercise relative to nonobese individuals,[49,50] possibly due to the increased inspiratory load associated with extra chest wall soft tissue. Obese individuals also have difficulty decreasing end-expiratory lung volume during exercise, likely due to expiratory flow limitation.[50,51]

The presence and magnitude of differences in these parameters may be a function of the degree of obesity, with greater differences in heavier individuals, as well as the baseline level of fitness[52] and the presence of comorbid conditions, such as obstructive sleep apnea.[53]

INDIVIDUALS WITH UNDERLYING CARDIOPULMONARY DISEASE

Underlying cardiopulmonary disease alters these physiologic responses to exercise with different responses seen depending on the particular disease process.

Heart Failure

As in healthy individuals, maximal exercise in patients with heart failure is limited by the amount of blood that can be delivered to exercising muscle (i.e., a cardiac limitation to exercise). As a result, patients with heart failure demonstrate a similar pattern of physiologic responses during progressive exercise to a symptom-limited maximum, albeit with significant differences in the magnitude of many responses. Selected graphs from a nine-box plot demonstrating key differences relative to healthy individuals are shown in Figure 33.3 (the full nine-box plot can be seen in eFig. 33.1).

The most important difference relative to healthy individuals is the decrease in $\dot{V}O_{2max}$ and peak WR. The decrease in $\dot{V}O_{2max}$, which is similar between patients with systolic or diastolic dysfunction,[54,55] results from an inability to raise cardiac output due to impaired stroke volume responses with progressive exercise, denoted by decreased $\dot{V}O_2$/HR. The ventilatory threshold is still usually reached at 50–60% of $\dot{V}O_{2max}$ but at a lower absolute $\dot{V}O_2$ compared to healthy individuals.

Many patients with heart failure compensate for decreased stroke volume with an increase in heart rate for any given level of work. As a result, the heart rate reserve

at peak exercise is usually small (<20 beats/min). There is considerable variability in these responses, however, with some patients manifesting an inability to raise heart rate with progressive exercise *(chronotropic incompetence)*, which persists even after discontinuation of β-blockers.[56] In addition, heart rate recovery, which happens as a result of reactivation of vagal tone[57] and is defined as the difference between peak heart rate and heart rate 1 minute into recovery, is decreased compared to healthy individuals.

Patients with heart failure also have altered ventilatory responses, including increased airway resistance,[58] expiratory flow limitation at low WRs,[59] and a larger ventilatory reserve due to the fact that they cannot do as much work and therefore do not require a high $\dot{V}E$. Perhaps the most important difference, however, is increased ventilatory inefficiency in patients with moderate to severe systolic or diastolic dysfunction, as indicated by an increased $\dot{V}E/\dot{V}CO_2$ at the ventilatory threshold or an increased slope of the relationship between these parameters ($\Delta\dot{V}E/\Delta\dot{V}CO_2$).[54,55] The most likely cause of this phenomenon, which worsens with aging,[60] is an increase in physiologic dead space due to impaired lung perfusion.[61] Studies have shown, for example, that ventilatory inefficiency is related to abnormal pulmonary vascular tone[62] or right ventricular dysfunction[63] and improves after treatment with phosphodiesterase inhibitors and improvements in right ventricular function even when left ventricular function is unchanged.[64] Abnormal peripheral and central chemoreceptor sensitivity may also augment ventilation above that necessary for a given level of CO_2 production.[65]

Some patients with severe heart failure demonstrate exercise oscillatory ventilation, an abnormal ventilatory response in which exercise ventilation demonstrates periodicity similar to that seen in central sleep apnea (eFig. 33.2).[66,67] The mechanism is not clear but may relate to increases in circulatory times, peripheral chemoreceptor sensitivity, ventilatory responses related to pulmonary congestion, and signaling related to muscle metabolic abnormalities.[67] Exercise oscillatory ventilation may be a marker of reduced cardiac index both at rest and during exercise,[68] is associated with an increased risk of cardiovascular death,[69] and may improve with exercise training,[70,71] administration of acetazolamide,[72] or other therapeutic interventions directed at the underlying heart failure.[73] Despite these altered ventilatory responses, patients with heart failure may have a normal (A−a)P_{O_2} and may not develop hypoxemia during exercise even though PA occlusion pressure is elevated.[74,75]

Pulmonary Vascular Disease

Patients with pulmonary vascular diseases, such as *pulmonary arterial hypertension* (PAH) and *chronic thromboembolic pulmonary hypertension* (CTEPH), demonstrate physiologic responses to progressive exercise that are similar to those seen in patients with heart failure. Relative to healthy individuals, $\dot{V}O_{2max}$, peak WR, and $\dot{V}O_2$/HR are decreased, and the ventilatory threshold is reached at a lower $\dot{V}O_2$. Similar to patients with heart failure, the observed decline in $\dot{V}O_{2max}$, which correlates inversely with mean PA pressure,[76] is due to an inability to raise cardiac output during exercise. The cardiac output is limited because the right ventricle cannot adequately preload the left ventricle due to high pulmonary vascular resistance.[77] The fact that treatment with a pulmonary vasodilator, such as sildenafil, over several months improves both $\dot{V}O_{2max}$ and $\dot{V}O_2$/HR supports this concept.[78]

These patients also demonstrate abnormal ventilatory responses, including increases in $\dot{V}E/\dot{V}O_2$ and $\dot{V}E/\dot{V}CO_2$[79,80] of greater magnitude than those seen in patients with heart failure of similar *New York Heart Association* (NYHA) functional class.[81] This ventilatory inefficiency is due to increased V_D/V_T, as well as increased peripheral chemoreceptor stimulation from exercise-induced hypoxemia, and improves after treatment with sildenafil.[78] Depending on the extent of vascular occlusion and subsequent differences in V_D/V_T, the degree of ventilatory inefficiency, as measured by $\Delta\dot{V}E/\Delta\dot{V}CO_2$, may vary in magnitude between types of pulmonary vascular disease, with higher values seen in CTEPH than PAH.[82]

Aside from these similarities, an important difference between heart failure and pulmonary vascular disease pertains to the PA pressure responses. Unlike in healthy individuals or patients with heart failure, where PA pressure rises only modestly with increasing exercise, patients with pulmonary vascular disease experience large rises in PA pressure with increasing blood flow due to impaired pulmonary vascular recruitment and distention.[83,84]

In addition, whereas V_D/V_T decreases from 0.3 to 0.4 at rest to less than 0.3 at peak exercise in healthy individuals and patients with heart failure, it decreases only mildly and may even increase in pulmonary vascular disease,[82,85] with some variation in observed changes based on the cause of pulmonary hypertension.[86] This response is abnormal because perfusion of many lung units does not increase proportionately with alveolar ventilation due to impaired recruitment and distention. In addition, if patients develop right-to-left shunting by opening a patent foramen ovale during exercise, mean expired CO_2 decreases, leading to a higher calculated V_D/V_T (based on the Enghoff modification of the Bohr dead-space equation).[87] As a result of the abnormal V_D/V_T, end-tidal P_{CO_2} is decreased relative to normal individuals at all stages of exercise in proportion to the patient's functional limitation.[76]

A final difference is the fact that patients with pulmonary vascular disease develop hypoxemia and a widened (A−a)P_{O_2}[25,85] with progressive exercise even in the absence of resting hypoxemia. In some patients hypoxemia develops due to right-to-left shunting through an existing right-to-left communication or through a foramen ovale that opens during exercise due to the rise in PA pressure, a finding predictive of death or need for transplant.[88] In other cases hypoxemia develops due to diffusion limitation; red blood cell capillary transit time decreases with increasing pulmonary blood flow and is no longer sufficient to ensure full equilibration between the capillary and alveolar P_{O_2} when the functional capillary bed is decreased.[89] This latter phenomenon is accentuated by the low $C\bar{v}O_2$ resulting from the low cardiac output in these patients.

Selected graphs from a nine-box plot demonstrating key differences relative to healthy individuals are shown in Figure 33.4 (the full nine-box plot can be seen in eFig. 33.3).

Interstitial Lung Diseases

Patients with *interstitial lung disease* (ILD) manifest physiologic responses during progressive exercise similar to

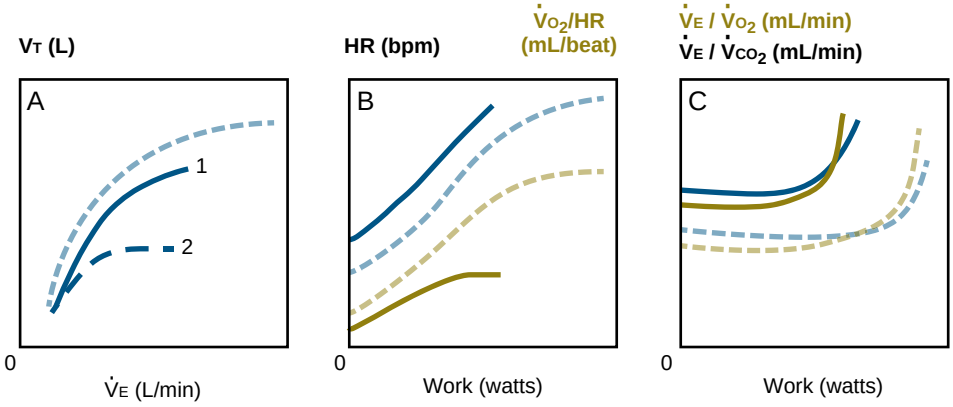

Figure 33.4 Pulmonary vascular or interstitial lung disease patterns of response to exercise compared to normal shown on three key figures from the nine-box plot. Pulmonary vascular or interstitial lung disease patterns of limitation *(solid lines)* are compared to healthy individuals who demonstrate a normal cardiac pattern of limitation *(dotted lines)*. Because the patterns of responses to exercise in each disease are similar, they are represented in parts B and C by a single line. (A) Tidal volume (V_T) vs. $\dot{V}_E$. The *solid blue line* (line 1) represents the expected response for a patient with pulmonary vascular disease, whereas the *dashed blue line* (line 2) represents the expected response for a patient with interstitial lung disease. (B) Heart rate (HR) and $\dot{V}O_2$/HR vs. watts. (C) $\dot{V}E/\dot{V}O_2$ and $\dot{V}E/\dot{V}CO_2$ vs. watts. A complete nine-box plot for this pattern of limitation is shown in eFig. 33.3. $\dot{V}CO_2$, carbon dioxide output; $\dot{V}E$, minute ventilation; $\dot{V}O_2$, oxygen consumption.

those seen in patients with pulmonary vascular disease. In particular, they demonstrate reduced $\dot{V}O_{2max}$ and *maximum WR*, increased $\dot{V}E/\dot{V}O_2$ and $\dot{V}E/\dot{V}CO_2$, reduced tidal volumes and increased respiratory rates, stable or increased V_D/V_T at end exercise as well as reduced arterial P_{O_2}, and increased $(A-a)P_{O_2}$. Although patients with ILD may not have a decreased $\dot{V}O_2$/HR, and the ventilatory threshold may not be decreased relative to their $\dot{V}O_{2max}$, these differences are usually not sufficient to distinguish between ILD and pulmonary vascular disease on the basis of CPET alone, and further studies such as pulmonary function tests (PFTs) and computed tomography imaging are necessary.

Debate exists regarding the underlying mechanism for the reduction in maximal exercise capacity. Hansen and Wasserman,[90] for example, demonstrated that abnormal cardiac function due to pulmonary vascular pathology was more important than respiratory system factors in limiting exercise, whereas Marciniuk and colleagues[91] used dead-space loading during exercise to show that abnormal respiratory mechanics were more important. Ventilatory equivalents are increased due to the increased dead space and the hypoxic ventilatory response, whereas exercise-induced hypoxemia is due to a combination of $\dot{V}A/\dot{Q}$ inequality and diffusion limitation.[92]

Because the term ILD represents a heterogeneous group of disorders, the physiologic responses to exercise vary based on the specific disease. Wells and colleagues,[93] for example, found increased dyspnea and hypoxemia in *idiopathic pulmonary fibrosis* (IPF) compared to systemic sclerosis with ILD, whereas other studies have also shown worse hypoxemia and increased PA pressure responses in patients with IPF compared to sarcoidosis and other forms of ILD.[94,95] The onset of pulmonary hypertension as a complication of ILD or an underlying systemic illness is associated with worse exercise tolerance, hypoxemia, and ventilatory inefficiency compared to otherwise similar patients with normal pulmonary artery pressures.[96,97]

Selected graphs from a nine-box plot demonstrating key differences relative to healthy individuals are shown in Figure 33.4 (full plot can be seen in eFig. 33.3).

Adult Congenital Heart Disease

Similar to patients with heart failure, adults with congenital heart disease demonstrate reductions in $\dot{V}O_{2max}$ that correlate with NYHA functional class,[98] peak WR and maximum heart rate, and increases in $\dot{V}E/\dot{V}CO_2$ compared to healthy individuals.[99] In contrast, however, many congenital heart disease patients develop hypoxemia at end exercise.[100] Given that many patients have coexisting pulmonary hypertension, one might also expect unchanged or increased V_D/V_T at end exercise in many patients, but this variable has not been reported in major series of adult patients.

Owing to the diversity in the type and severity of congenital lesions, there is variability in the magnitude of changes in $\dot{V}O_{2max}$ and $\dot{V}E/\dot{V}CO_2$ with the most serious abnormalities seen in those patients with Eisenmenger syndrome and complex lesions, such as double-outlet ventricle or univentricular physiology.[99,101] Patients with cyanosis and/or pulmonary hypertension also demonstrate greater reductions in these parameters when compared with patients lacking these problems.[101,102] Of importance, functional impairment is not limited to those with significant lesions, as even reportedly asymptomatic patients[103] or those with mild lesions, such as repaired coarctation of the aorta, demonstrate decreased $\dot{V}O_{2max}$ and increased $\dot{V}E/\dot{V}CO_2$ compared to healthy individuals.[99] Surgical repair improves exercise capacity,[104,105] with the degree of improvement related in some cases to whether the abnormality is repaired in childhood or in adulthood.[106]

Although much of the decrement in exercise capacity in these patients is attributable to cardiac and pulmonary vascular dysfunction related to the underlying defect or its repair, some patients are also limited by abnormal respiratory mechanics. Up to 50% of patients who have undergone surgical repairs have findings suggestive of restrictive physiology on spirometry,[107,108] resulting sometimes from

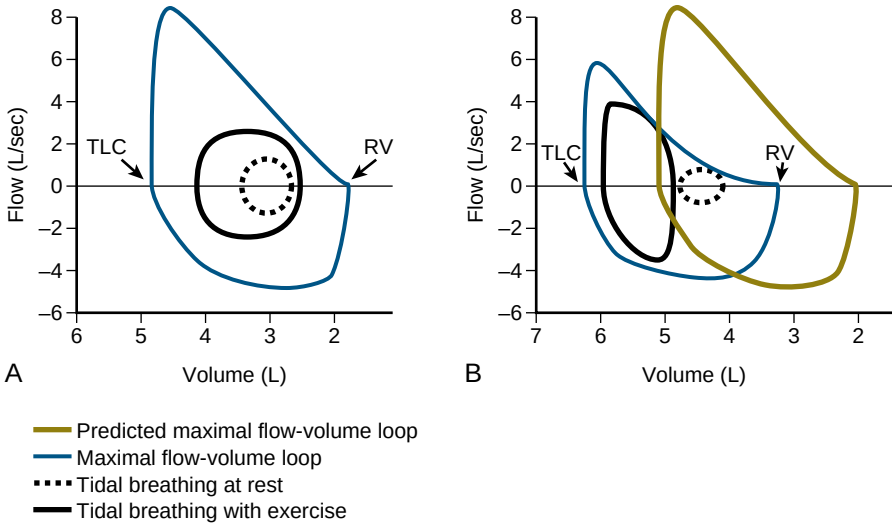

Figure 33.5 Expiratory flow limitation in COPD. (A) The typical pattern in healthy individuals. During exercise, the expiratory flow *(solid black line)* remains below the expiratory flow obtained in a forced vital capacity maneuver *(blue line)*. (B) Similar data are shown for a patient with COPD and expiratory flow limitation. The flow volume loop obtained in a forced vital capacity maneuver *(blue line)* is shifted to the left (higher volumes) relative to the healthy individual *(brown line)*. With exercise, expiratory flow during tidal breathing *(black line)* is equal to maximum expiratory flow over a portion of exhalation. TLC, total lung capacity; RV, residual volume.

multiple thoracotomies and sternotomies and demonstrate worse exercise capacity and NYHA functional class compared to those with normal spirometry.[108]

Chronic Obstructive Pulmonary Disease

Patients with mild COPD may actually have normal exercise capacity, whereas patients with moderate to severe COPD demonstrate decrements in $\dot{V}O_{2max}$ and peak WR proportional to disease severity, as measured by *Global Initiative for Obstructive Lung Disease* (GOLD) stage.[109,110] Of importance, the pattern of physiologic responses to progressive exercise in COPD is very different than it is in patients with heart failure. Whereas exercise is limited in heart disease by an inability to deliver oxygenated blood to exercising muscles, patients with moderate-severe COPD are limited by altered respiratory mechanics; their ventilatory pump fails before the heart does.

The hallmark of this ventilatory limitation is the fact that both arterial P_{CO_2} and end-tidal P_{CO_2} remain stable or increase at end exercise due to an inability to raise alveolar ventilation in response to increasing $\dot{V}_{CO_2}$ and, when present, a metabolic acidosis. This phenomenon, which is present to a greater extent at higher GOLD stages,[110] arises due to mechanical constraints from dynamic hyperinflation during exercise and altered $\dot{V}_A/\dot{Q}$ relationships.[111,112]

In addition, $\dot{V}_E$ at peak exercise will be at or close to the maximum predicted ventilation as measured by the MVV or $FEV_1 \times 40$, a marked contrast from healthy sedentary individuals and those with heart failure in whom $\dot{V}_E$/MVV is normally less than 75–80%. Ventilation is typically higher for any given WR and is usually marked by a high respiratory rate, low tidal volume, higher end-expiratory volume, and lower inspiratory capacity compared to healthy individuals.[113] Although patients with mild disease may still develop a metabolic acidosis[114] and even manifest a ventilatory threshold at lower levels of $\dot{V}_{O_2}$ than normal individuals,[113] most patients with severe disease lack a ventilatory threshold.[115] Along with the fact that peak heart rate is typically well below the maximum predicted heart rate, this finding strongly indicates that the ventilatory pump is failing before the heart.

An important reason for these manifestations of ventilatory limitation is a phenomenon referred to as *dynamic hyperinflation*. Due to expiratory flow limitation that develops even at low-moderate levels of exercise, patients with COPD must increase end-expiratory lung volumes and encroach on their inspiratory reserve volume to raise $\dot{V}_E$ as metabolic activity increases (Fig. 33.5). The resulting hyperinflation causes flattening and decreased contractile strength of the diaphragm, increases respiratory muscle fatigue, and increases dyspnea for any given level of ventilation.[116] One contributor to development of this problem is the increase in minute ventilation as compensation for a higher V_D/V_T than in healthy control subjects.[117] Of interest, patients with dynamic hyperinflation have less locomotor muscle fatigue with exercise[118] because the ventilatory pump fails before the nonrespiratory muscle groups face significant loads.

Dynamic hyperinflation also has hemodynamic effects, including alterations in cardiac preload and afterload that subsequently impair cardiac function and manifest as a decrease[119] in $\dot{V}_{O_2}$/HR. These changes inversely correlate with the increase in end-expiratory lung volumes,[120] and improvement can be seen after interventions that decrease dynamic hyperinflation, such as *lung volume reduction surgery*.[121] Right ventricular function is also impaired by increased pulmonary vascular resistance due to hypoxic pulmonary vasoconstriction and structural changes in the pulmonary circulation.[122] In fact, in patients with COPD and mean pulmonary artery pressure greater than or equal to 40 mm Hg, impaired circulatory function is often the primary factor limiting exercise rather than the ventilatory constraints.[123]

Another important feature of progressive exercise in COPD is the onset of hypoxemia with a widened $(A-a)P_{O_2}$. This problem correlates with reductions in diffusion capacity,[124] is more likely when patients have emphysema rather than chronic bronchitis as the etiology of their COPD, is more severe in patients with pulmonary hypertension,[125] and is more prominent with walking compared to cycling.[126] The predominant mechanism is $\dot{V}_A/\dot{Q}$ inequality, the effects of which are magnified by reductions in $C\bar{v}_{O_2}$ during exercise.[92] Depending on the distribution of blood flow and ventilation, however, $\dot{V}_A/\dot{Q}$ inequality and arterial P_{O_2} may actually improve during exercise.[127,128]

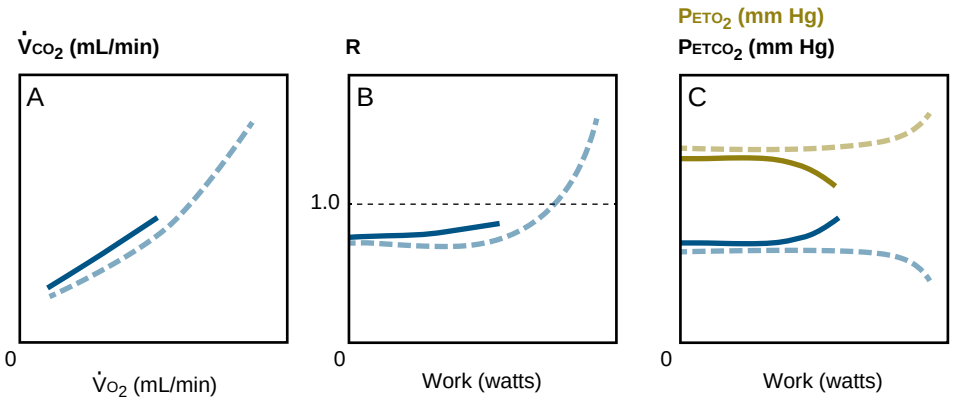

Figure 33.6 Ventilatory limitation pattern of responses to exercise compared to the normal cardiac limitation pattern shown on three key figures from the nine-box plot. The expected physiologic responses to exercise in patients with ventilatory limitation *(solid lines)* are compared to healthy individuals who demonstrate a cardiac pattern of limitation *(dotted lines)*. (A) $\dot{V}_{CO_2}$ vs. $\dot{V}_{O_2}$. (B) Respiratory exchange ratio (R) vs. watts. (C) P_{ETO_2} and P_{ETCO_2} vs. watts. A complete nine-box plot for this pattern of limitation is shown in eFig. 33.4). P_{ETCO_2}, end-tidal partial pressure; P_{ETO_2}, end-tidal partial pressures of O_2; $\dot{V}_{CO_2}$, carbon dioxide output; $\dot{V}_E$, minute ventilation; $\dot{V}_{O_2}$, oxygen consumption.

Selected graphs from a nine-box plot demonstrating key differences relative to healthy individuals are shown in Figure 33.6 (the full nine-box plot can be seen in eFig. 33.4).

CARDIOPULMONARY EXERCISE TESTING

INDICATIONS AND CONTRAINDICATIONS

The indications for CPET sort into five general areas: determining the etiology of exercise limitation, assessing functional status, stratifying risk for surgery, prognosticating outcomes in specific diseases, and creating individualized exercise prescriptions for rehabilitation programs. The list of indications for CPET is largely compiled from expert opinions, and the evidence for the utility of CPET varies by indication, each of which is reviewed later.

Determining the Etiology of Dyspnea and Exercise Limitation

Evaluating Dyspnea. When the cause of dyspnea is not apparent from history, physical examination, laboratory testing (including a hemoglobin and resting arterial blood gas), chest imaging, and PFTs, CPET can be used to (1) quantify a patient's exercise limitation and (2) determine the system limiting exercise. Although CPET can narrow the differential list down to a single limiting system, such as in patients with chronotropic incompetence or myocardial ischemia, it is most useful in identifying the best avenue of investigation in making a definitive diagnosis.

The first step in using CPET to evaluate dyspnea is to determine if the patient's subjective description of his or her limitations are aligned with the ability to do work. It is therefore imperative that the patient gives a maximal effort during the CPET. An arterial blood gas at the end of exercise can be very helpful to determine whether the individual gave a good effort, was limited by ventilation, had excess dead space, or was hyperventilating. It is also important to ask the patient if the CPET reproduced their symptoms. In a group of 50 patients referred for CPET with unexplained dyspnea,[129] for example, broad diagnoses of cardiac limitation, pulmonary limitation, obesity and/or deconditioning, and psychogenic dyspnea were identified.

Evaluating Exercise Limitation. Patients presenting with exercise limitation rather than dyspnea state that they just are not able to perform the amount of work that they could do in the past. CPET is useful in this setting to quantify the amount of work individuals can perform and compare it to what they say they can do during activities of daily living. eTable 33.1 provides a rough estimate of the maximal oxygen consumption that correlates with the level of exercise patients state they are able to perform.[130] It is important to keep in mind that there is a broad spectrum of exercise capabilities across the normal population. Although an individual may have a "normal" exercise study as judged by the maximal oxygen consumption, the observed response for any individual may represent a significant decline in exercise performance from a previous supranormal level and hence evidence of pathology.

Evaluating Combined Cardiovascular and Pulmonary Disorders. When individuals have disease in more than one system, CPET can determine which system is primarily responsible for their exercise limitation. For example, in a patient with both aortic stenosis and COPD, CPET can determine whether or not to proceed with valve repair. Were such a patient to be primarily limited by ventilatory capacity, repairing the aortic valve may not be indicated because after surgery the individual would still be significantly limited. Although it can assist in identifying the primary limiting system, CPET cannot quantitatively partition the degree of limitation due to each of the affected systems.

Diagnosing Exercise-Induced Bronchoconstriction. CPET can be used to diagnose exercise-induced bronchoconstriction, a transient bronchoconstriction that develops during or after strenuous exercise, which is present in greater than 10% of the general population and up to 90% of persons previously diagnosed with asthma.[131] Although administration of inhaled bronchoprovocatory agents,

eTable 33.1 Estimating an Individual's $\dot{V}O_{2max}$ From the History

Activity Limitations	Approximate $\dot{V}O_{2max}$ (mL/kg/min)
Participates in competitive sports with sustained activity like rowing, basketball, and soccer. Engages in regular, endurance training. Tolerates sustained heavy labor well	>40
Tolerates sustained heavy labor well; can play recreational soccer or full-court basketball	35–40
Participates in recreational cross-country skiing or half-court basketball with minimal limitation	30–35
Performs heavy labor with difficulty; downhill skiing somewhat limited by fatigue	25–30
Heavy housework or yard work causes dyspnea; cannot play singles tennis	20–25
Dyspnea with two flights of stairs at own pace; cannot play golf while carrying bag or pulling a cart	17–20
Unable to vacuum average room or change sheets without rest	14–17
Difficulty walking slowly with peers in shopping mall	12–14
Dyspnea while brushing hair, dressing, showering	<12

$\dot{V}O_{2max}$, maximum oxygen consumption.
Modified from Luks A, Glenny R, Robertson H. *Introduction to Cardiopulmonary Exercise Testing*. New York: Springer; 2013.

such as methacholine or mannitol, can be used to make the diagnosis, exercise challenge using free running, treadmill, or cycle ergometry has been used to elicit exercise-induced bronchoconstriction since the 1970s[132] and, along with eucapnic voluntary hyperventilation, is a more sensitive and specific testing modality.[133] Exercise testing for this purpose requires specialized equipment, personnel, and the ability to exercise at 85–95% maximum heart rate with dry medical grade air and high flow rates (>100 L/min)[134] and should be performed according to published guidelines.[135,136]

Due to the logistical issues associated with exercise challenges, the International Olympic Committee Medical Commission recommends eucapnic voluntary hyperventilation[133] as the initial testing modality, followed by CPET if eucapnic voluntary hyperventilation is nondiagnostic.[137]

Assessing Functional Status and Degree of Impairment

Quantitative measures of exercise capacity are also useful in determining eligibility for disability because static tests, such as PFTs and ejection fraction on echocardiography, do not correlate well with exercise capacity.[138–140] Despite these issues, the American Thoracic Society statement on the evaluation of impairment and disability[141] states that impairment can be determined from standard PFTs in most cases and that further testing with CPET may be helpful in selected situations. Of importance, quantifying impairment informs but does not define disability, because disability assessment requires social, economic, environmental, and other input.[142] Largely based on empirical knowledge, rough estimates of the work an individual should be able to perform were proposed (eTable 33.2).

Risk Stratification

Risk Assessment for Thoracic Surgery. Multiple studies have looked at preoperative CPET to determine if patient outcomes can be predicted based on exercise capacity.[143–146] Although the available studies have not used randomized, controlled designs and generally involve small numbers of patients from single centers, they do show an association between exercise capacity and postsurgical outcomes. Drawing on this evidence, an expert panel of the American College of Chest Physicians[147] devised an algorithm that incorporates CPET along with the *Thoracic Revised Cardiac Risk Index* (ThRCRI),[148] spirometry, diffusing capacity for carbon monoxide, and performance on stair climbing or shuttle walk testing to guide selection of the appropriate therapeutic approach in lung cancer patients (eFig. 33.5). The general approach can likely be used as a foundation for any lung resection surgery. Patients who require CPET as part of this algorithm are deemed low risk (expected risk of mortality < 1%) if the $\dot{V}O_{2max}$ is greater than 20 mL/kg/min or greater than 75% of predicted, and considered high risk (expected mortality > 10%) if their $\dot{V}O_{2max}$ is less than 10 mL/kg/min or less than 35% of predicted. The ThRCRI has been shown to be an independent prognostic factor after lung resection for early-stage lung cancer.[149]

Evaluation for Lung Volume Reduction Surgery (LVRS). The landmark National Emphysema Therapy Trial[150] demonstrated that LVRS was of benefit but only to the subset of patients defined by their exercise capacity using a modified but formalized exercise protocol. The study participants underwent a maximal CPET on a cycle ergometer while wearing a face mask delivering a fractional concentration of oxygen in inspired gas of 0.30 and pedaling for 3 minutes without resistance, followed by increasing the wattage by 5 or 10 W/min. Those patients with a low exercise capacity, defined as less than 25 W for women and less than 40 W for men, benefited the most from LVRS.

Risk Assessment for Extrathoracic Surgery. A number of studies have investigated the utility of CPET for risk stratification or identification of other comorbidities that could be addressed in the perioperative period in a variety of major surgeries, including abdominal-aortic repair,[151,152] hepatic transplantation,[153] upper gastrointestinal surgery,[154] and in elderly patients undergoing intra-abdominal surgery.[155] Seven of the nine studies included in a review of this issue[156] found higher mortality in patients with lower $\dot{V}O_{2max}$. In one of the studies[155] $\dot{V}O_2$ at the ventilatory threshold was used to determine the appropriate hospital location for postoperative care with $\dot{V}O_2$ less than 11 mL/kg/min being the cutoff for postoperative intensive care and a marker of increased mortality. Despite this evidence, there are no prospective studies documenting survival benefit or cost-effectiveness for using CPET in this manner.

Prognosticating Clinical Outcomes

In healthy individuals without specific diseases and in general among individuals with disease, improved survival is associated with a higher exercise capacity.[157,158] Interventional studies have not been conducted, however, to demonstrate whether training to improve $\dot{V}O_{2max}$ increases life expectancy. Some of the patient populations for whom $\dot{V}O_{2max}$ and other data derived from CPET provide prognostic information are described later.

Heart Failure. $\dot{V}O_{2max}$ is the most objective data available for assessing exercise capacity in individuals with heart failure. Both the American College of Cardiology and the American Heart Association recommend CPET in patients presenting with heart failure to guide management and determine whether heart failure is the cause of exercise limitation when the contribution of heart failure to exercise limitation is uncertain.[159] A number of early studies[160–162] documented a progressive decline in survival with decreasing $\dot{V}O_{2max}$ and indicated that a $\dot{V}O_{2max}$ greater than 14 mL/kg/min identified a population with a 94% 1-year survival and should be used as a criterion to defer heart transplantation. More recent studies have shown similar relationships between $\dot{V}O_{2max}$ and mortality.[163,164] Of importance, the inclusion of patients on β-blocker therapy in recent series[165–167] suggests a threshold less than 14 mL/kg/min should be considered for heart transplantation. Most studies investigating the utility of $\dot{V}O_2$ for prognostication in heart failure use the traditional weight normalized values (mL/kg/min) but due to the obesity "epidemic," the reported oxygen consumption data may be inappropriately low, and decisions for heart transplantation may be skewed toward the obese. Correcting $\dot{V}O_2$ for lean body mass may improve prognostication.[168,169]

Other CPET variables may augment the predictive value of $\dot{V}O_{2max}$. A series of studies, for example, demonstrate that $\dot{V}E/\dot{V}CO_2$ or the $\dot{V}E/\dot{V}CO_2$ slope[170–175] are

eTable 33.2 Impairment Determined by Cardiopulmonary Exercise Testing

$\dot{V}O_{2max}$ (mL/kg/min)	Description of Work
>25	Capable of all but most physically demanding jobs
15–25	Able to work at the specific job that does not require frequent and extended work above 40% of maximum $\dot{V}O_2$
<15	Unable to perform most jobs

$\dot{V}O_{2max}$, maximum oxygen consumption.
Modified from American Thoracic Society. Evaluation of impairment/disability secondary to respiratory disorders. American Thoracic Society. *Am Rev Respir Dis*. 1986,133:1205–1209.

accurate predictors of mortality and may improve predictive capabilities of models used in heart failure management.[176] Although most of these studies identify a single threshold above which the $\dot{V}E/\dot{V}CO_2$ indicates a higher mortality in patients with heart failure, a more recent analysis by Arena and colleagues[170] created four classes based on the $\dot{V}E/\dot{V}CO_2$ slope and demonstrated that event-free survival was significantly different across the four classes. When combined with the peak $\dot{V}O_2$, the $\dot{V}E/\dot{V}CO_2$ slope further differentiates which patients are at risk for major cardiac events (eFig. 33.6). The available literature suggests individuals with a $\dot{V}O_{2max}$ less than 10 mL/kg/min or a $\dot{V}E/\dot{V}CO_2$ slope greater than 40 have the poorest prognosis.[177]

Other parameters shown to be associated with outcomes such as mortality, need for transplantation, or need for device implantation in patients with heart failure, include heart rate recovery,[178–181] oxygen uptake efficiency,[182–184] exercise oscillatory ventilation,[66,67,185] heart rate variability,[186,187] and blood pressure response.[188,189] A number of different groups have attempted to use multiple CPET parameters[190–192] or combined CPET parameters with other medical information (e.g., renal function, echocardiography, questionnaires)[164,193] to guide prognostication as an alternative to the traditional strategy of using a single parameter.

Adult Congenital Heart Disease. CPET has become a valuable tool in the management of patients with congenital heart disease because it aids in risk stratification and determining the need for and timing of therapeutic interventions.[98,99,194] Whereas NYHA class provides a simple way to assess functional status, CPET provides more specificity regarding the source of exercise limitation in these patients. CPET[195] is thought to be of special importance in this patient population because self-reported exercise capacity is of poor predictive value,[196] and functional limitation can be identified in those who are asymptomatic.[103] Similar to patients with heart failure, $\dot{V}O_{2max}$[103] and $\dot{V}E/\dot{V}CO_2$[197] are strong predictors of mortality. Due to a variety of factors, including the significant heterogeneity of adult congenital heart disease, the decision about when to consider heart transplantation in adult congenital heart disease is particularly complex but can be informed by CPET.[101,198,199]

Pulmonary Arterial Hypertension. Assessment of exercise capacity can also be used to assess prognosis and response to treatment in patients with PAH.[200] Sun and colleagues,[80] for example, found that peak WR, $\dot{V}O_{2max}$, ventilatory threshold, O_2 pulse, and slope of $\dot{V}E/\dot{V}CO_2$ were all correlated with NYHA class, whereas Yasunobu and colleagues[76] demonstrated that end-tidal PCO_2 progressively decreased as the disease severity increased and directly correlated with changes in mean PA pressure. Other studies have demonstrated a relationship between survival and $\dot{V}O_{2max}$ and $\dot{V}E/\dot{V}CO_2$,[77,201,202] and that persistent exercise-induced right-to-left shunting and poor ventilatory efficiency during serial assessments were highly predictive of poor outcomes in patients with PAH.[88]

Although CPET is a safe[80,203] and effective means to grade the severity of exercise limitation, assess prognosis, and measure response to therapy,[204] the use of CPET is limited in most PAH trials due to a number of practical issues. Instead, most trials rely on the simple, less expensive and reproducible *6-minute walking test* (6MWT, described in greater detail later), which, like CPET, provides prognostic information.[205–207] Improvement in the 6MWT after therapeutic intervention may also be associated with decrease in mortality,[208,209] although not all studies have validated this finding.[210]

Exercise Prescriptions for Cardiac and Pulmonary Rehabilitation Programs

Given that the aerobic exercise intensity prescription is directly linked to both the amount of improvement in exercise capacity and the risk of adverse events during exercise, a joint position statement of the European Association for Cardiovascular Prevention and Rehabilitation, the American Association of Cardiovascular and Pulmonary Rehabilitation, and the Canadian Association of Cardiac Rehabilitation stressed the importance of functional evaluation through exercise testing before starting an aerobic training program.[9] Although there are many methods for creating individualized training programs, these guidelines propose that CPET be the gold standard for comprehensive exercise intensity assessment and prescription. The committee's goal is to shift from a "range-based" to a "threshold-based" aerobic exercise intensity prescription to maximize the benefits obtainable by the use of aerobic exercise training in cardiac rehabilitation.[9]

Similarly, the American Thoracic Society and the European Respiratory Society statement on pulmonary rehabilitation[211] states that before initiating rehabilitation for COPD, CPET should be considered as part of a thorough assessment to identify factors contributing to exercise limitation, determine the exercise prescription, and evaluate safety by monitoring electrocardiography and blood pressure for potential risks.[212] Casaburi and colleagues,[213] for example, have shown that high-intensity training programs (80% of *maximum work rate* [W_{max}] in the incremental test) are more effective than less intense programs (50% of W_{max}) in patients with COPD. From a practical standpoint, a formal CPET study may not be necessary to build a tailored exercise program, and others have used variables obtained in the 6MWT, such as peak heart rate,[214] to target exercise levels.

Despite expert opinion that CPET or 6MWT should be used to create individualized training programs, and some evidence that use of CPET to individualize home exercise is safe in certain classes of patients, such as those with heart failure and implanted defibrillators,[215] there are no data demonstrating the exercise prescription derived by these means improves quality of life or survival.

SAFETY CONSIDERATIONS AND CONTRAINDICATIONS TO CARDIOPULMONARY EXERCISE TESTING

CPET is not without risk, and the decision to conduct the test must reflect consideration of those risks relative to the benefits in terms of information gained. Multiple contemporary

surveys indicate that the risks of complications that require hospitalization, including serious arrhythmias, acute myocardial infarction, or sudden cardiac death during or immediately after a CPET, are less than 0.2%, 0.04%, and 0.01%, respectively.[216] These estimates capture the risk for the entire population of individuals performing CPET and likely vary in a given patient based on the underlying disease. Unfortunately, risk estimates are not available for every possible condition, and the clinician must use clinical judgment in assessing risk.

Some diseases carry significantly higher risks and represent absolute or relative contraindications to performing CPET (Table 33.1). Patients with implantable cardiac defibrillators also require special attention. Documentation of the defibrillator settings should be reviewed before exercise to ensure that the peak heart rate during the test does not encroach on the rate at which the defibrillator is set to discharge. The defibrillator should also not be disabled in case the patient has a shockable arrhythmia during the CPET.

CONDUCTING EXERCISE TESTS

Exercise Equipment

There are a number of commercially available exercise monitoring systems that allow breath-by-breath measurements of exhaled gases. The general components of these systems include an airflow transducer to measure the volumes of each inhalation and exhalation and rapid gas analyzers to measure the O_2 and CO_2 during inspiration and expiration. As technologies have improved, these components have become more reliable but still require strict and daily calibration tests to ensure accurate readings. Multiple resources are available with recommendations for calibration procedures and quality control.[7,8,177] Gas exchange measurements during exercise are very reproducible; however, a good practice is to have one or two individuals in the exercise laboratory perform monthly CPET to confirm that their data remain stable over time. Both maximal and submaximal tests can be used for this purpose because reproducible data are generated in either case.

Table 33.1 Contraindications for Cardiopulmonary Exercise Testing

Absolute	Relative
Active myocardial ischemia (unstable angina, myocardial infarction within 30 days)	Severe pulmonary hypertension
Acute heart failure exacerbation	Left main coronary artery stenosis
Exercise-induced syncope	Moderate stenotic valve disease
Uncontrolled arrhythmias	Severe hypertension (SBP > 200 mm Hg, DBP > 120 mm Hg)
Severe aortic stenosis	Hypertrophic cardiomyopathy
Acute endocarditis, myocarditis, pericarditis	High-degree atrioventricular block
Acute aortic dissection or suspected dissecting aortic aneurysm	Severe electrolyte abnormalities
Acute pulmonary embolism or lower extremity deep venous thrombosis	Tachyarrhythmias or bradyarrhythmias
Active COPD exacerbation or uncontrolled asthma	Advanced or complicated pregnancy
Active pulmonary edema	Implanted cardiac defibrillator that cannot be interrogated or temporarily reset due to inaccessibility of an individual qualified to do this (e.g., device manufacturer representative)
Oxygen saturation < 85% breathing air at rest	
Acute respiratory failure	

DBP, diastolic blood pressure; SBP, systolic blood pressure.

EXERCISE MODALITIES AND PROTOCOLS

Cycle Ergometer Versus Treadmill

Functional capacity is usually assessed in CPET by having the individual exercise on a stationary cycle ergometer or motorized treadmill. Progressive work is performed on the cycle ergometer by increasing the resistance to pedaling and quantifying work over time as a rate in *watts* (W). Work rate on the treadmill is primarily determined by the grade and speed of the treadmill. Because arm movement and the uplift of body weight while walking/running on the treadmill add to the work performed, work on a treadmill is more dependent on an individual's weight and, as a result, is harder to quantify than with cycle ergometry, where leg muscles do the vast majority of the work and the individual's weight is supported by the bicycle. Treadmill work is measured relative to each individual's resting energy expenditure and is typically expressed in terms of *metabolic equivalents* (METs). One MET represents the amount of oxygen consumed at rest and each successive stage achieved in a given treadmill protocol corresponds to a higher level of METs that can, in turn, be related to the individual's oxygen consumption (1 MET = 3.5 mL O_2/kg/min in the average adult).[217] As discussed previously, $\dot{V}O_2$ is tightly linked with WR on a cycle ergometer, with $\dot{V}O_2$ increasing 10 mL/min/W above the resting value. Hence watts and METs can be roughly compared through the shared $\dot{V}O_2$ and are dependent on the individual's weight. Table 33.2 provides examples of watts, oxygen consumption, and METs for two individuals of different weights to give the reader a general idea of how these measures of work compare.

Both exercise modalities impose progressively increasing WRs that provide a range of oxygen consumptions to identify exercise patterns described earlier in this chapter. The resistance, and therefore watts, in cycle ergometry can be increased in either a continuous or stepwise manner over time. Treadmill WRs are usually increased according to specific protocols, such as the Bruce,[218] Balke,[219] or Naughton[220] protocols, which define how to change the speed and inclination of the treadmill over time. The WR ramp or steps should be chosen so that the subject can perform 10 to 12 minutes of exercise before reaching $\dot{V}O_{2max}$ because this timeframe usually provides the temporal resolution necessary to identify patterns of exercise responses. $\dot{V}O_{2max}$ estimates tend to be 10–15% higher using a treadmill compared to a cycle ergometer due to the extra work performed by the arms when walking or running. Each modality offers advantages depending on the patient and goals of the test. Whereas cycle ergometry tends to be better for patients who are obese or have gait problems and is more suited for drawing arterial blood gases, treadmill testing may be preferred in patients whose symptoms are elicited with walking and running or in patients with exercise-activated pacemakers that sense arm movement.

Invasive Cardiopulmonary Exercise Testing

When competing comorbidities make it difficult to determine the primary cause of exercise limitation, exercise with a right

Table 33.2 Comparison of Oxygen Consumption and Metabolic Equivalents at Different Levels of Work in Individuals of Two Different Weights

	70-KG PERSON		100-KG PERSON	
Watts	**$\dot{V}O_2$ (mL/min)**	**METs**	**$\dot{V}$ (mL/min)**	**METs**
0 (rest)	250	1.0	350	1.0
25	500	2.0	600	1.7
50	750	3.1	850	2.4
100	1250	5.1	1350	3.9
200	2250	9.2	2350	6.7
300	3250	13.3	3350	9.6
400	4250	17.3	4350	12.4

METs, metabolic equivalents; $\dot{V}$, ventilation flow; $\dot{V}O_2$, oxygen consumption.

heart catheter can provide additional data to help separate out the cardiac and pulmonary systems, further differentiate the broad category of "cardiac limitation" as either right or left heart failure, and identify muscle deconditioning.[221] The data available from the right heart catheter include mixed venous oxygen saturation and content, PA pressure, PA occlusion pressure, and thermodilution cardiac output. With increasing exercise to exhaustion in a normal individual, cardiac output should increase fourfold to fivefold, but the mean PA pressure should remain less than 30 mm Hg.[222] In patients with left heart failure or pulmonary vascular disease, the mean PA pressure may increase above this level and, if associated with symptoms of dyspnea, may give a clue to underlying mechanisms. Pulmonary vascular resistance can be calculated to determine if elevated PA pressures are due to left-sided heart failure or pulmonary vascular disease. Because intrathoracic pressure affects right heart catheterization measurements, the PA occlusion pressure may be difficult to measure accurately. Stroke volume can be calculated from the heart rate and cardiac output rather than assessed through a surrogate measure, the O_2 pulse. Placement of an arterial line with the right heart catheter allows calculation of cardiac output using the Fick equation and determination of the arteriovenous oxygen content difference, with narrow values of the latter providing evidence of deconditioning as a cause of exercise limitation.

Noninvasive Estimates of Cardiac Output During Cardiopulmonary Exercise Tests

A number of noninvasive commercial methods are also available for estimating the cardiac output during exercise, which rely on a variety of technologies, including CO_2 rebreathing,[223] pulse contour analysis,[224] chest bioreactance,[225] echocardiography,[226] and inert gas rebreathing.[227] The technology that has been most rigorously evaluated in exercise[228] is the inert gas rebreathing method using the Innocor Rebreathing System (Innovision A/S). Whereas the available evidence demonstrates these measurements are feasible and that cardiac output and $\dot{V}O_2$ are tightly correlated in both normal subjects and individuals with heart failure,[229] their clinical utility remains unclear.[227]

Indications for Arterial Blood Gases

Arterial blood gases provide additional data that assist in differentiating the causes of exercise limitation and dyspnea. In particular, they allow the determination of the $(A-a)PO_2$ to evaluate gas exchange, the arterial PCO_2 as the gold standard for identifying ventilatory limitation, V_D/V_T as an indicator of pulmonary vascular disease, and base deficit as a surrogate for lactic acidosis. Arterial blood gases can be obtained throughout the CPET to identify the position of the ventilatory threshold or one time at the end of exercise. The former approach requires an arterial line, whereas a single needle puncture can be used for the latter. The operator should be aware that arterial puncture after maximal exertion can cause a vagal reaction and hypotension, especially in younger subjects.

INTERPRETING CARDIOPULMONARY EXERCISE TESTS

Figure 33.7 describes a basic approach to interpreting the results of CPET. Because CPET interpretation is highly dependent on the data quality, before assessing the physiologic responses to exercise, it is important to ensure there are no systematic data collection errors and that the patient gave a full effort. Several key aspects of the interpretation process are considered later.

Reference Values

As is the case in pulmonary function testing, many of the measured parameters and, in particular, the $\dot{V}O_{2max}$, are not assessed by looking at the absolute value of the parameter and, instead, are judged based on comparison of that value to that expected for an individual of that age, sex, body habitus (weight and/or height), and mode of exercise. In conducting and interpreting a CPET, it is essential to use reference values appropriate to the patient undergoing evaluation. A comprehensive list of reference values is available elsewhere.[7]

Identifying the Ventilatory Threshold

One of the important steps in CPET interpretation is identifying whether the patient reached a ventilatory threshold, because it is one of the primary means of distinguishing between cardiac or pulmonary vascular limitation, on the one hand, and ventilatory limitation on the other. The ventilatory threshold can be identified by invasive and noninvasive means. The former involves measurement of arterial lactate or bicarbonate concentrations. A single

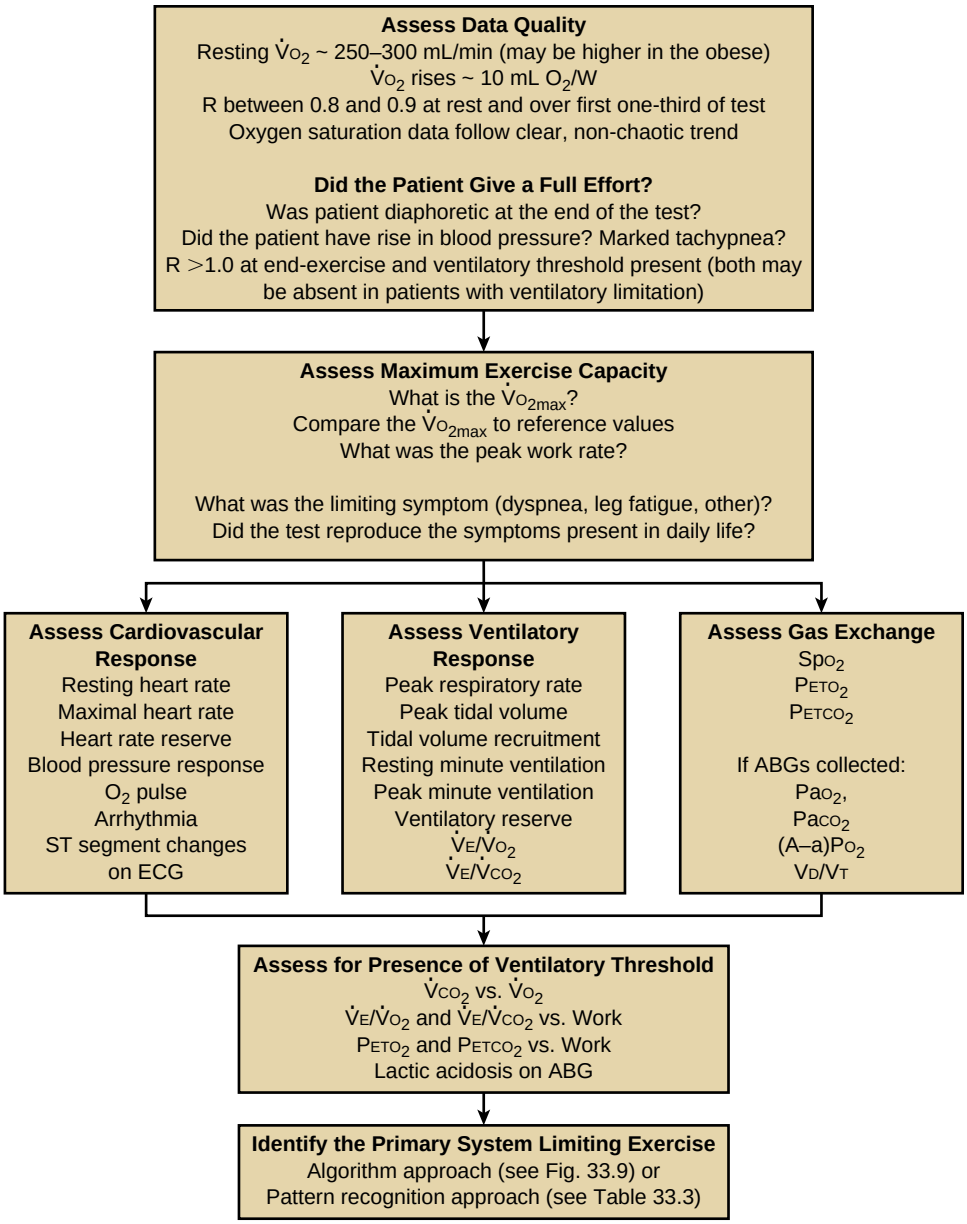

Figure 33.7 A general approach to cardiopulmonary exercise test interpretation. Because data interpretation is highly dependent on the quality of the data, the initial steps involve ensuring there are no systematic data errors and that the patient gave a complete effort. Once this is done, the next tasks are to assess maximal exercise capacity and the cardiovascular, ventilatory, and gas exchange responses and then identify whether a ventilatory threshold is present and determine the primary system limiting exercise.

measurement at end exercise is sufficient for a binary decision as to whether the threshold was reached, whereas serial measurements every other minute during exercise can be used as part of several different techniques to determine the $\dot{V}O_2$ at which the threshold was reached.[12,230] Several noninvasive methods can also be used, including the V-slope method described earlier (see Fig. 33.1), identification of the point at which $\dot{V}E/\dot{V}O_2$ and $\dot{V}E/\dot{V}CO_2$ reach their nadir and begin to increase or the point at which the end-tidal PO_2 starts to rise or and end-tidal PCO_2 starts to decrease (Fig. 33.8). The accuracy of the different methods varies based on operator experience, the testing protocol, and the data collection system,[7] and there is no evidence that any particular noninvasive method is superior to the others.[231,232] This is not a critically important issue in most of CPET interpretation, where the key question is whether or not the threshold was reached rather than the specific time point.

Identifying the Primary System Limiting Exercise: Algorithmic Versus Pattern Recognition Approaches

Perhaps the most important aspect of CPET interpretation is identifying the primary reason for exercise limitation. One approach, first introduced by Wasserman and colleagues,[29] uses a binary tree algorithm and flow charts that direct the interpretation though a series of decision points to specific causes of exercise limitation. A simplified flow chart is shown in Figure 33.9 to demonstrate the concept. The advantages of this approach are that the decision points and values are well defined so that there is no ambiguity in the direction to branch in the flow chart. This strategy is likely easier to follow for the novice interpreter than the pattern recognition approach outlined later. The primary disadvantage is that the interpretation is dependent on a single data point at each bifurcation. Any error in data

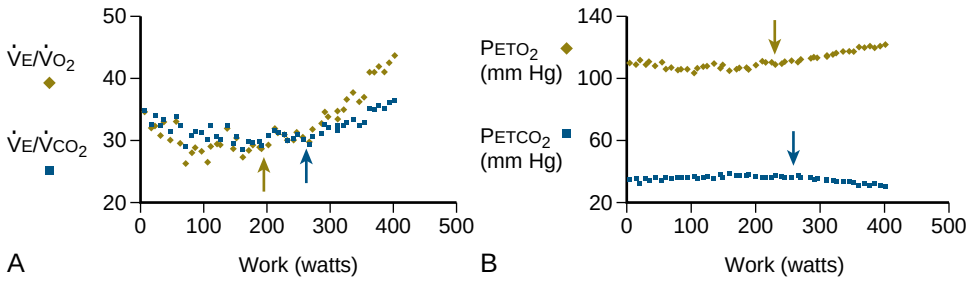

Figure 33.8 Two methods to identify ventilatory threshold during exercise test interpretation. (A) Analysis of ventilatory equivalents to identify whether a ventilatory threshold is present. After the increase in minute ventilation at the ventilatory threshold, $\dot{V}_E/\dot{V}O_2$ (noted in *brown*) and $\dot{V}_E/\dot{V}CO_2$ (noted in *blue*) begin a steady rise. The point at which each variable starts to rise is marked by an *arrow* in the respective colors. The start of the rise in $\dot{V}_E/\dot{V}O_2$ is associated with the first ventilatory threshold, which is expected before the rise in $\dot{V}_E/\dot{V}CO_2$. (B) Using changes in P_{ETO_2} and P_{ETCO_2} to identify whether a ventilatory threshold is present. At the ventilatory threshold, $\dot{V}_E$ increases out of proportion to the changes in $\dot{V}O_2$ and $\dot{V}CO_2$. As a result, P_{ETO_2} (noted in *brown*) begins a steady rise *(brown arrow)*, whereas P_{ETCO_2} (noted in *blue*) begins a steady decrease *(blue arrow)*. P_{ETCO_2}, end-tidal partial pressure; P_{ETO_2}, end-tidal partial pressures of O_2; R, respiratory exchange ratio; $\dot{V}$, ventilation flow; $\dot{V}CO_2$, carbon dioxide output; $\dot{V}_E$, minute ventilation; $\dot{V}O_2$, oxygen consumption; V_T, tidal volume.

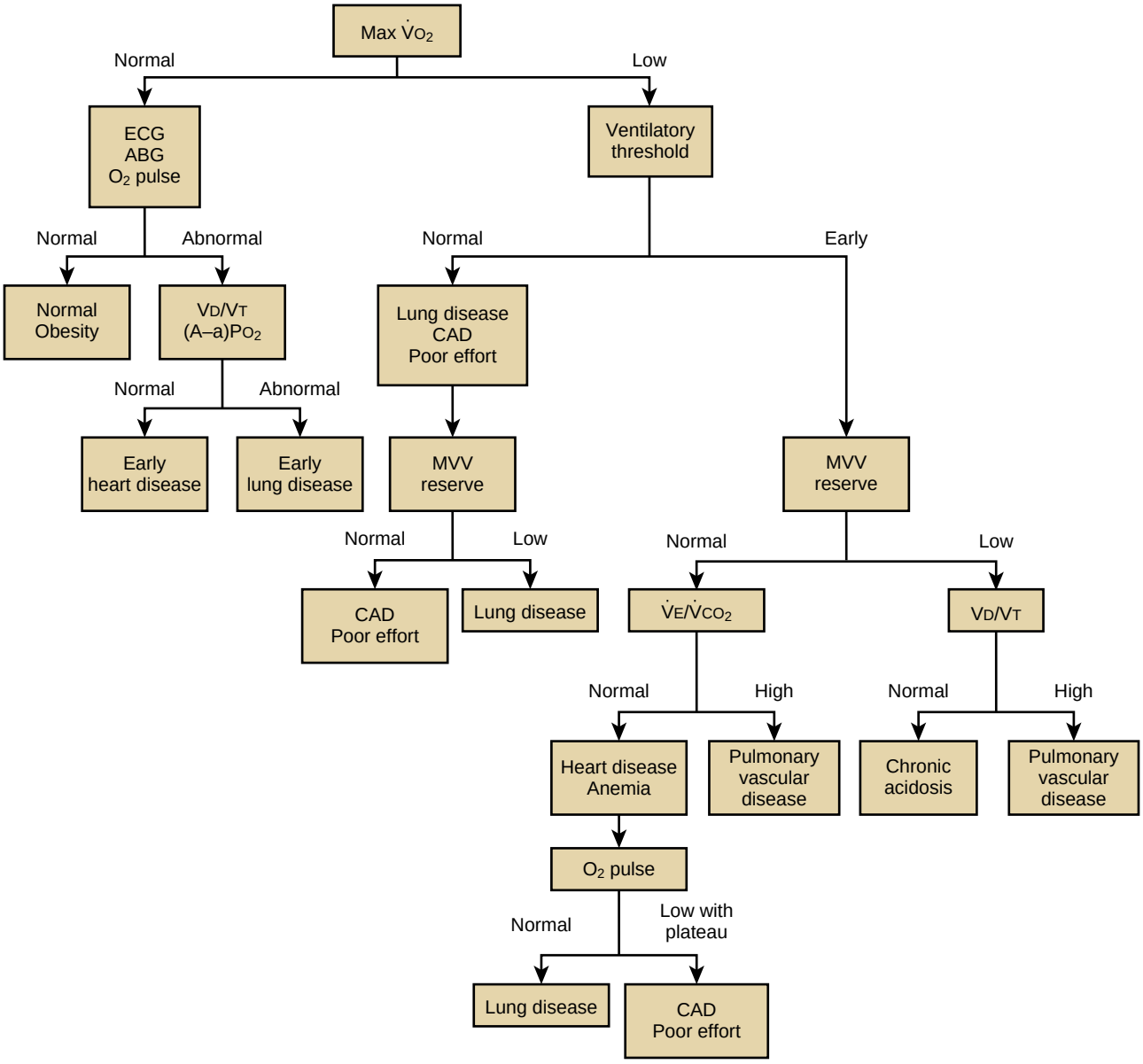

Figure 33.9 Simplified flow chart demonstrating decision making in CPET interpretation. The decision tree begins at the top with the $\dot{V}O_{2max}$ compared to predicted values. ABG, arterial blood gases; CAD, coronary artery disease; ECG, electrocardiogram; $\dot{V}O_{2max}$, maximum oxygen consumption. (Modified from Wasserman K, Hansen JE, Sue DY, et al. *Principles of Exercise Testing and Interpretation.* 5th ed. Philadelphia: Lippincott Williams & Wilkins; 2012.)

collection or misinterpretation at one bifurcation can direct the interpretation down a wrong pathway toward an incorrect diagnosis.

An alternative method is one of pattern recognition that uses the expected trends for multiple variables over the course of progressive exercise to identify the organ system limiting exercise. As discussed earlier, general disease categories, such as heart failure, pulmonary vascular disease, or ventilatory insufficiency, have expected patterns of exercise response (Table 33.3). These patterns can be weighted by their relative specificity for each organ system and then examined in sum to suggest the most likely organ system to be limiting exercise. Patients with cardiac limitation, for example, will demonstrate a ventilatory threshold, decreased end-tidal P_{CO_2} and arterial P_{CO_2}, and increasing ventilatory $\dot{V}_E/\dot{V}_{O_2}$ and $\dot{V}_E/\dot{V}_{CO_2}$ at end exercise. Patients with pulmonary hypertension demonstrate many similar findings but will manifest hypoxemia and a fixed V_D/V_T in late exercise. Other potential findings considered to be specific for an organ system failure, such as exercise oscillatory ventilation in heart failure, can be seen with exercise but not regularly enough to warrant listing in Table 33.3.

Because the various observations listed in Table 33.3 are not necessarily present in every patient, a useful approach in the pattern recognition method is to conceptualize it as a scale on which the different observations are shown as blocks that are placed on the side of the scale representing the potential limiting pattern (Fig. 33.10). Each block may be of different size, representing the relative weight placed

Table 33.3 Identifying the Pattern of Limitation on Cardiopulmonary Exercise Testing

	PATTERN OF LIMITATION		
Observation	**Cardiac**	**Pulmonary Vascular**	**Ventilatory**
Clear ventilatory threshold	◉	◉	
Plateau in O_2 pulse late in exercise	◉	◉	◉*
High $\dot{V}_E/\dot{V}_{CO_2}$	◉	◉	
High $\dot{V}_E/\dot{V}_{O_2}$	◉	◉	
$\dot{V}E_{max}$ far below MVV	◉		
Metabolic acidosis by arterial blood gas late in exercise	◉	◉	
Decreasing P_{ETCO_2} late in exercise	◉	◉	
R clearly rises above 1.0	◉	◉	
Stop exercising due to leg fatigue	◉	◉	
Heart rate near predicted maximum late in exercise	◉		
ST changes on electrocardiography	◉		
Inappropriate blood pressure response	◉		
Increasing or unchanged V_D/V_T by arterial blood gas late in exercise		◉	
Absent ventilatory threshold			◉
Decrease in oxygen saturation		◉	◉
Heart rate far below predicted maximum late in exercise			◉
Increasing or unchanged P_{ETCO_2} late in exercise			◉
Pa_{CO_2} > 40 mm Hg by arterial blood gas (end-exercise)			◉
$\dot{V}E_{max}$ near MVV			◉
Decreasing tidal volume			◉
R does not increase above 1.0			◉
Stop exercising due to dyspnea			◉

The size of the marker indicates the relative importance of the observation.
*Can be seen if air-trapping affects cardiac function.
Modified from Luks A, Glenny R, Robertson H. *Introduction to Cardiopulmonary Exercise Testing*. New York: Springer; 2013.
MVV, maximum voluntary ventilation; P_{ETCO_2}, end-tidal partial pressure of carbon dioxide; Pa_{CO_2}, arterial partial pressure of carbon dioxide; R, exchange ratio; V_D/V_T, dead-space fraction; $\dot{V}E_{max}$, maximum minute ventilation.

on that particular factor. With this method, the presence or absence of a ventilatory threshold would be the biggest block. The side of the scale with the greatest weight (number of blocks) is most likely to be the limiting organ system. By being less dependent on single parameters to make a decision throughout a binary tree, pattern recognition may be less prone to misclassifications of the limiting organ system.

ALTERNATIVE METHODS OF ASSESSING EXERCISE TOLERANCE

THE SIX-MINUTE WALK AND SHUTTLE WALK TESTS

The 6MWT is a widely available, inexpensive, and reproducible submaximal exercise test during which subjects walk back and forth along a flat indoor course varying in length between 30 and 100 m for a period of 6 minutes under the supervision of a trained technician using a specified testing protocol.[233] Individuals move at their own pace, can use supplemental oxygen, and, unlike in CPET, may stop to rest if needed. The primary measurements obtained during the test include the distance walked, heart rate, oxygen saturation, blood pressure, and subjective ratings of dyspnea and leg fatigue.

A primary purpose of the 6MWT is to monitor response to interventions or follow disease activity over time as demonstrated by the extensive use of the distance walked as an outcome in PAH[234] and IPF trials.[235] Studies done in patients with COPD,[236] PAH,[237] IPF,[238] and silicosis[239] have also shown associations between the distance walked or development of hypoxemia and outcomes such as mortality risk. Whether the distance walked is an adequate surrogate for $\dot{V}O_{2max}$ remains unclear, however, because studies have reported varying degrees of correlation between these two variables.[240] Of importance, the 6MWT cannot be used to determine the etiology of exercise limitation and is only useful to assess individuals who are unable to maintain a normal or brisk walking pace, rather than fit individuals.

Use of the test for the purposes noted earlier requires recognition of several important issues. First, the utility of published reference values[241,242] is limited by the fact that test results vary based on differences in testing methodology and in the population under consideration. Second, subject performance is affected by learning, verbal encouragement, and course layout, necessitating strict adherence to published testing protocols.[233] Finally, when using the 6MWT as part of patient assessment, clinicians must understand the minimal clinically important difference, the threshold at which a change in 6MWT is recognized as either important by the patient or associated with other outcomes. Minimal clinically important difference values have been published but vary across studies.[238,243,244]

The incremental shuttle walk test is a less widely used alternative to the 6MWT and requires the patient to walk at a specified pace that increases over time until the individual can no longer maintain the pace or stops due to symptoms.

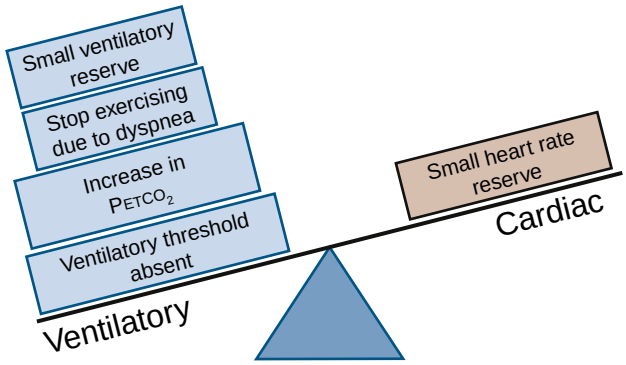

Figure 33.10 The "balance" approach to identifying the pattern of exercise limitation. In this example, the patient has many features consistent with ventilatory limitation due to COPD and only one aspect of the data consistent with a cardiac limitation. Because the preponderance of data favors the left side of the balance, this patient would be best labeled as having a ventilatory limitation pattern.

Designed as a less invasive assessment of maximal exercise capacity, the test correlates reasonably well with $\dot{V}O_{2max}$[245] and can be used to monitor responses to therapeutic interventions[246] and predict mortality in certain patient groups.[247] Only a few sets of reference values have been published,[248] and its use is largely limited to following changes over time in a given patient.

EXERCISE TREADMILL TESTING

In addition to its role in cardiopulmonary testing described earlier, *exercise treadmill testing* (ETT) is also commonly performed without exhaled gas collection. Because data collection is limited in such cases to assessment of symptoms, blood pressure, heart rate, oxygen saturation electrocardiography, and exercise duration, ETT cannot identify the system limiting exercise but can serve other important purposes.

The primary use is to identify coronary artery disease in low- to intermediate-risk individuals capable of exercise who have normal baseline electrocardiograms. The test can be performed in the outpatient setting, and it can be a part of diagnostic protocols for low-risk patients admitted to chest pain units from the emergency department.[249] Myocardial perfusion imaging is combined with ETT for patients with abnormal baseline electrocardiograms and is often necessary when evaluating female patients because the predictive capability of routine ETT is limited by the lower pretest probability of coronary artery disease in these patients.[250]

Using the concept of METs rather than direct measurement of $\dot{V}O_{2max}$, ETT can also be used to assess exercise capacity. Although this approach is less precise than measurements using exhaled gas collection, various studies demonstrate its utility in patient assessment and prognostication.[157,158,251,252] Other variables measured during ETT, such as impaired heart rate recovery,[253] and heart rate or blood pressure responses to increasing work rates,[254,255] have also been linked to various outcomes.

Key Points

- Performance of sustained exercise requires tight integration of multiple systems. Disease within any of these systems can manifest as dyspnea on exertion or exercise limitation.
- Assessment of maximal oxygen consumption provides insight into maximal exercise capacity and important aspects of cardiac function.
- Normal individuals demonstrate a characteristic pattern of responses to progressive exercise to a symptom-limited maximum. Characteristic patterns of deviation from these normal responses are seen in various diseases, including heart failure, pulmonary vascular disease, interstitial lung disease, and COPD.
- Cardiopulmonary exercise testing can be used to characterize the pattern of responses to progressive exercise and identify the primary organ system limiting exercise capacity.
- Cardiopulmonary exercise testing can be used to prognosticate and guide clinical decisions in certain patient groups, guide perioperative management in thoracic and other major surgical procedures, assess disability, and develop exercise prescriptions in rehabilitation programs.

Key Readings

American Thoracic Society, American College of Chest Physicians. ATS/ACCP statement on cardiopulmonary exercise testing. *Am J Respir Critic Care Med*. 2003;167(2):211–277.

Balady GJ, Arena R, Sietsema K, et al. Clinician's guide to cardiopulmonary exercise testing in adults: a scientific statement from the american heart association. *Circulation*. 2010;122(2):191–225.

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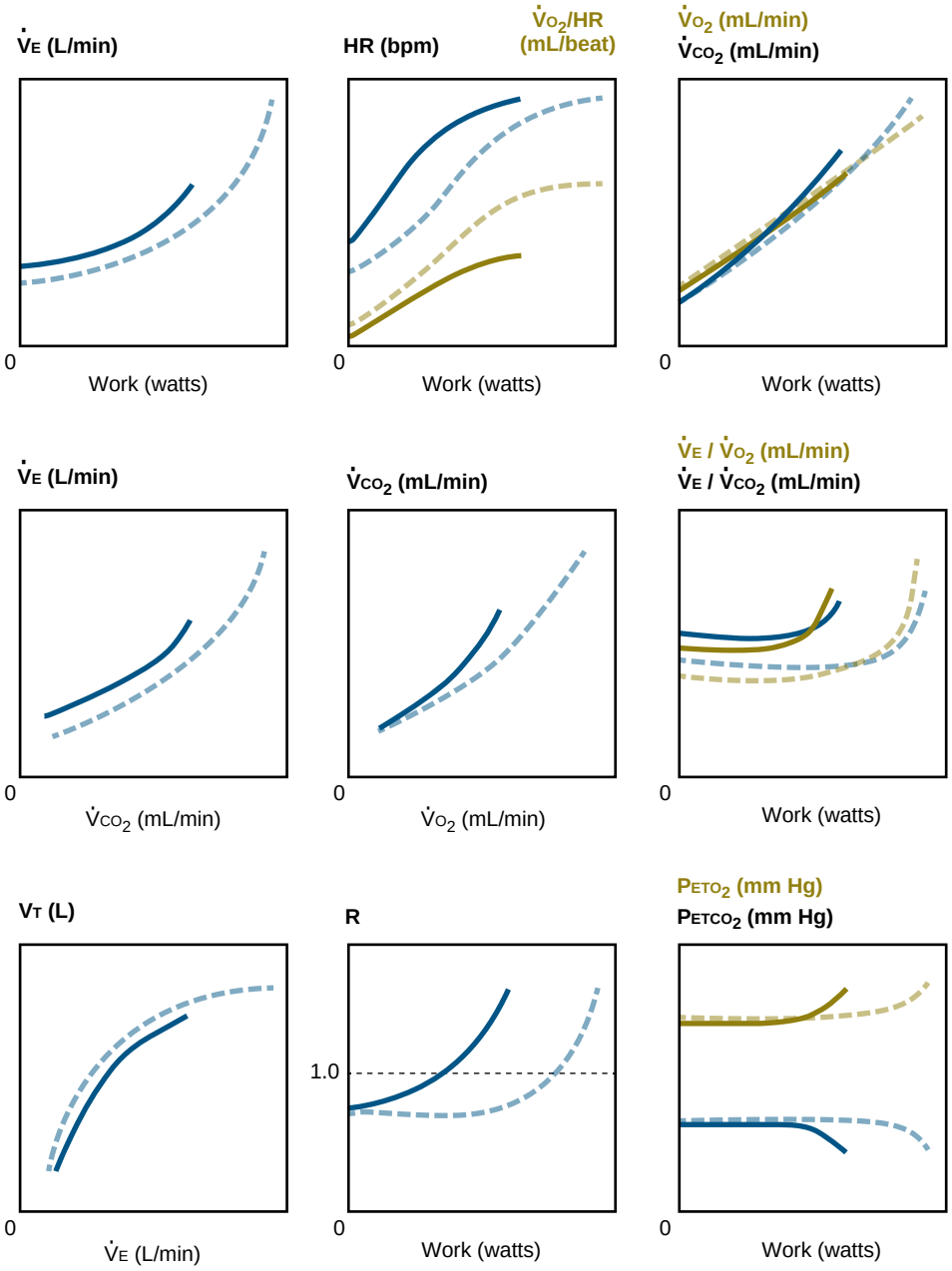
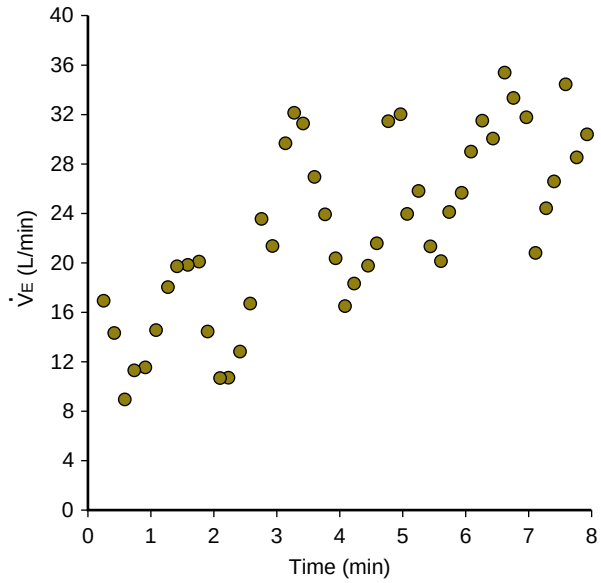
Wasserman K, Hansen JE, Sue DY, et al. *Principles of Exercise Testing and Interpretation*. 5th ed. Philadephia, PA: Lippincott Williams & Wilkins; 2012.

Complete reference list available at ExpertConsult.com.

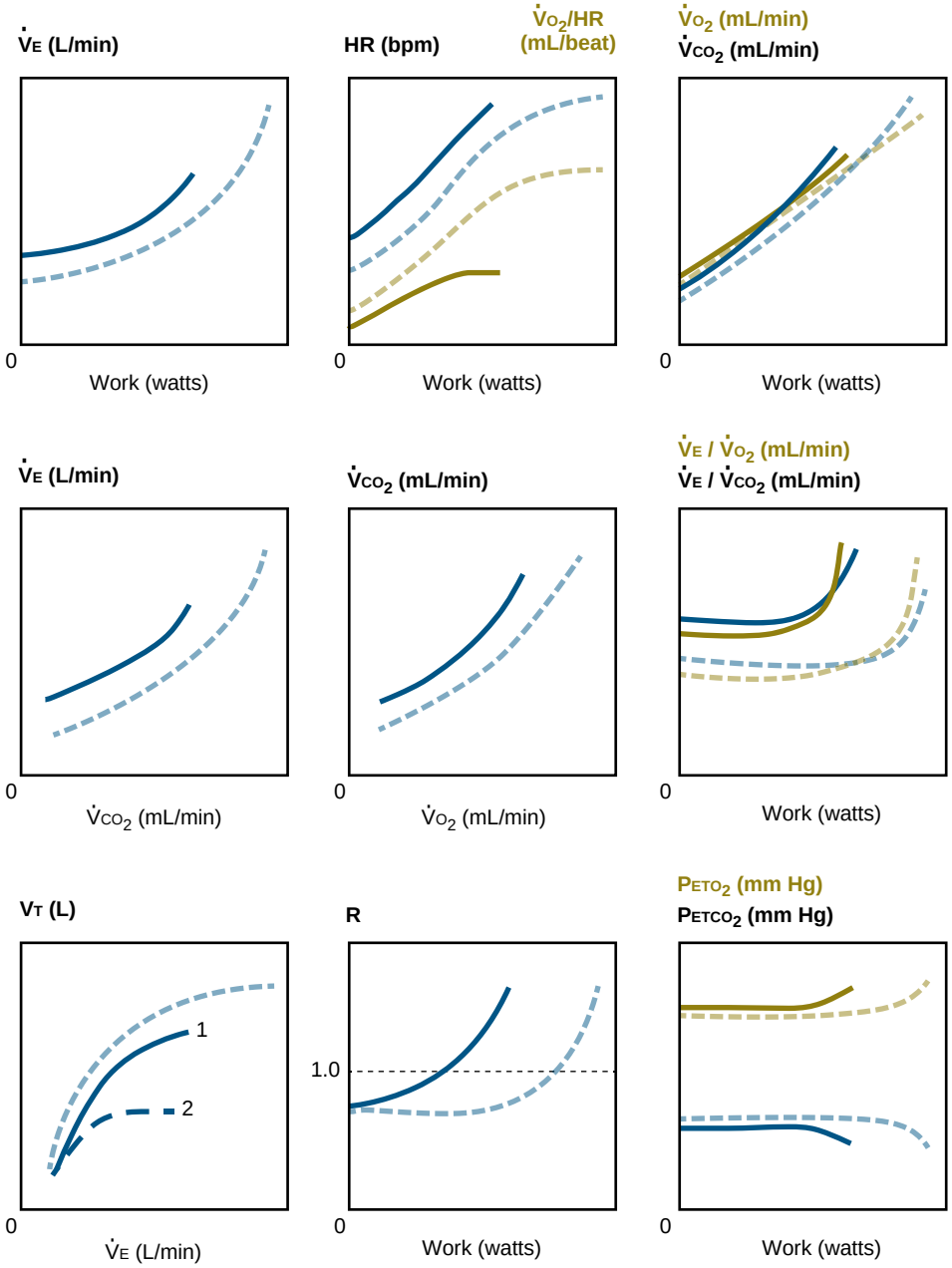
eFIGURE IMAGE GALLERY



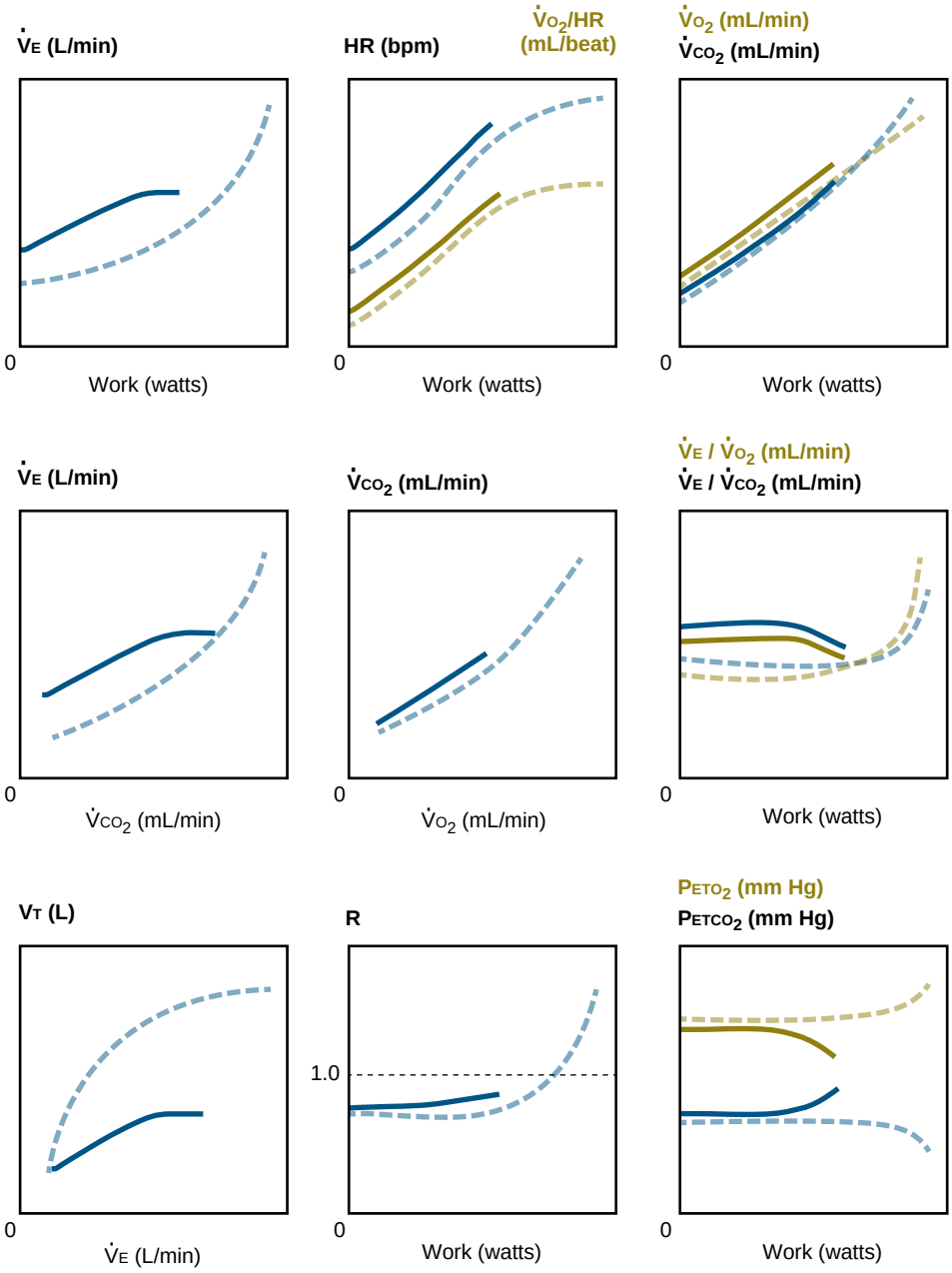
eFigure 33.1 Exercise in heart failure. Nine-box plot demonstrating expected physiologic responses to exercise in patients with cardiac limitation due to underlying heart failure *(solid lines)* compared to healthy individuals *(dotted lines)*. The layout of the graphs is the same as in Figure 33.2.



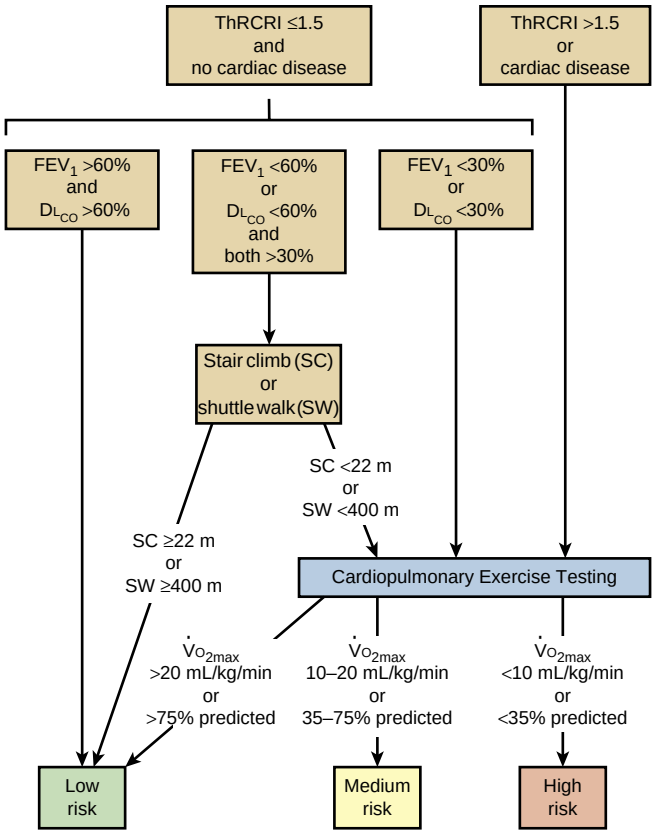
eFigure 33.2 Exercise oscillatory ventilation during a cardiopulmonary exercise test in a patient with severe cardiomyopathy. There are significant fluctuations in minute ventilation ($\dot{V}_E$) with progressive exercise.



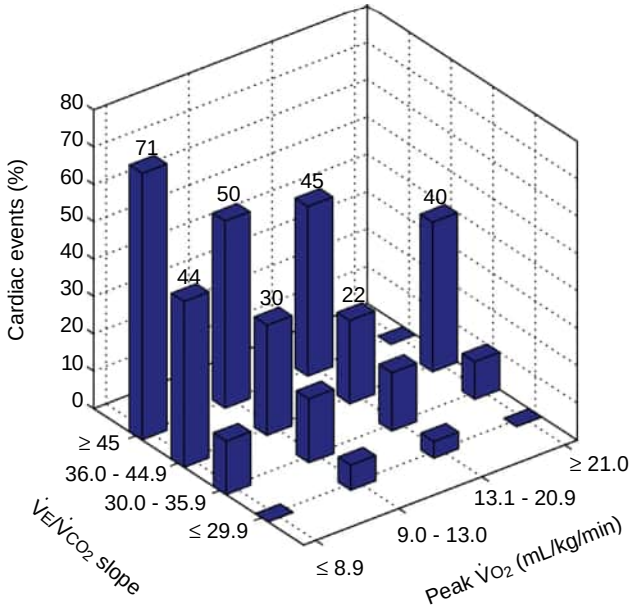
eFigure 33.3 Exercise in pulmonary vascular or interstitial lung disease. Nine-box plot demonstrating expected physiologic responses to exercise in patients with pulmonary vascular or interstitial lung disease patterns of limitation *(solid lines)* compared to healthy individuals who demonstrate a cardiac pattern of limitation *(dotted lines)*. Because the patterns of responses to exercise in each disease are similar, they are represented together above. In the graph in the lower left corner, *tidal volume* (V_T) vs. minute ventilation ($\dot{V}_E$), the *solid blue line* (line 1) represents the expected response for a patient with pulmonary vascular disease, whereas the *dashed blue line* (line 2) represents the expected response for a patient with interstitial lung disease. V_T, tidal volume.



eFigure 33.4 Exercise in ventilatory vs cardiac limitation. Nine-box plot demonstrating expected physiologic responses to exercise in patients with ventilatory limitation *(solid lines)* compared to healthy individuals who demonstrate a cardiac pattern of limitation *(dotted lines)*.



eFigure 33.5 Algorithm for risk stratification for thoracic surgery in patients with lung cancer. The *Thoracic Revised Cardiac Risk Index* (ThRCRI) uses a point system where a pneumonectomy, previous heart disease, and prior stroke or transient ischemic attack receive 1.5 points each and a creatinine greater than 2 mg/dL is given 1 point. The FEV_1 and D_{LCO} cutoffs are based on the predicted post operative values that are calculated by multiplying the preoperative measured values by the fraction of lung remaining after resection. D_{LCO}, diffusing capacity for carbon monoxide; FEV_1, forced expiratory volume in 1 second.



eFigure 33.6 Percentage of patients who had a major cardiac event as a function of their peak $\dot{V}O_2$ and $\dot{V}E/\dot{V}CO_2$ slope from CPET. Patients with a peak $\dot{V}O_2$ of less than 8.9 mL/kg/min and a $\dot{V}E/\dot{V}CO_2$ slope greater than 45 had a greater than 70% chance of having a cardiac event over a 2-year period. CPET, cardiopulmonary exercise testing; $\dot{V}CO_2$, carbon dioxide output; $\dot{V}E$, minute ventilation; $\dot{V}O_2$, oxygen consumption. (Modified from Arena R, Myers J, Abella J, et al. Development of a ventilatory classification system in patients with heart failure. *Circulation.* 2007;115:2410–2417.)

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34 PREOPERATIVE EVALUATION

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INTRODUCTION

A common activity for both general internists and pulmonologists is to provide a medical consultation before surgery. This evaluation may be challenging and seem foreign to many consultants because aspects of the care provided differ from those in the nonsurgical setting. The most important elements to include in all preoperative consultations are estimation of pulmonary risk, cardiac risk, and risk of perioperative venous thromboembolism. In each instance, the consultant estimates risk based on patient-related and procedure-related risk factors, determines the need (if any) for diagnostic testing, and proposes interventions to minimize risk and improve perioperative outcomes. In this chapter we focus on preoperative pulmonary evaluation. This chapter defines *postoperative pulmonary complications* (PPCs), estimates risk for different types of surgery, enumerates risk factors, discusses risk prediction scores, and establishes the value of pulmonary function testing to refine the risk estimate. We also discuss strategies to reduce the risk of PPCs in the preoperative, intraoperative, and postoperative settings. Finally, separate sections are devoted to the impact of sleep-disordered breathing (*obstructive sleep apnea* [OSA]) and considerations specific to airway management. The primary focus is on patients undergoing noncardiothoracic surgery, because the approach to preoperative pulmonary evaluation for patients undergoing lung resection differs (see Chapter 30).

DEFINITION AND MORBIDITY OF POSTOPERATIVE PULMONARY COMPLICATIONS

Although a definition for postoperative cardiac complications (major adverse cardiovascular events, perioperative myocardial infarction, heart failure, cardiac death, etc.) is straightforward, the definition of PPCs is less intuitive. Most authors consider only those events that are morbid, prolong hospital stay, require an intervention to treat, or increase the risk for perioperative mortality. In most research, PPCs are grouped together, and risk factor analysis does not address the risk of specific events separately. Studies of interventions more commonly address strategies that focus on one or several specific outcomes, rather than all types of PPCs. For purposes of our discussion, we consider the following to be the most important PPCs:

- Pneumonia
- Respiratory failure
- Atelectasis
- COPD exacerbation
- Bronchospasm
- Respiratory arrest due to sleep-disordered breathing
- Perioperative pulmonary mortality

Respiratory failure is commonly defined as mechanical ventilation for more than 48 hours after surgery or unplanned reintubation. Unless specifically stated otherwise, the discussion of risk factors and preoperative testing considers all PPC outcomes together, rather than a single outcome.

PPCs are morbid, increase length of stay, often require unplanned intensive care unit stays, and increase perioperative mortality. For example, a recent study evaluated the incidence and morbidity of PPCs among *American Society of Anesthesiologists* (ASA) physical status class III patients,[1] who have severe systemic disease.[2] Excluding the minor outcome of need for postoperative oxygen by nasal canula, 14% of patients had at least one PPC. The length of stay for patients with no PPCs compared to those with three PPCs increased from 3 to 8 days. The need for intensive care unit stay increased by more than threefold. Seven-day mortality increased from 0% to 7%. In a large database study of unselected patients undergoing abdominal surgery, 6% of patients had at least one PPC.[3]

TABLE 34.1 Patient-Related Risk Factors for Postoperative Pulmonary Complications

	ADJUSTED ODDS RATIOS FOR PPCS	
Risk Factor*	**Smetana et al, 2006[5]**	**Yang et al, 2015[3]**
Age		
60–69	2.3	
70–79	3.9	
≥80	5.6	2.4
ASA class ≥3	3.1	2.8
Abnormal chest radiograph	4.8	
Heart failure	2.9	
Arrhythmia	2.9	
Total functional dependence	2.5	2.8
COPD	2.4	

*Risk factors listed are for those with odds ratios ≥2.
ASA, American Society of Anesthesiologists; PPCs, postoperative pulmonary complications.

TABLE 34.2 Procedure-Related Risk Factors for Postoperative Pulmonary Complications

	ADJUSTED ODDS RATIO FOR PPCS	
Risk Factor*	**Smetana et al, 2006[5]**	**Yang et al, 2015[3]**
Surgical site		
Aortic	6.9	
Nonresective thoracic (mainly esophageal)	4.2	5.1
Any abdominal	3.1	
Upper abdominal	3.0	2.0
Neurosurgery	2.5	
Head and neck	2.2	
Vascular	2.1	
Emergency surgery	2.5	
Prolonged surgery (>3–4 h)	2.3	2.1
General anesthesia	2.4	

*Risk factors listed are for those with odds ratio ≥2.
PPCs, postoperative pulmonary complications.

In a study of costs associated with postoperative complications, PPCs were the most costly and were more expensive than infectious, cardiovascular, and thromboembolic complications.[4] Mean costs were $54,430 (PPC), $8209 (infectious), $13,256 (cardiovascular), and $28,355 (thromboembolic).

PATIENT-RELATED RISK FACTORS

It is customary to divide risk factors for PPCs into those that are specific to the patient and those that are intrinsic to the type of surgery and anesthesia. Many patient-related risk factors are not modifiable; hence the approach to risk reduction will be a general one rather than a specific effort to eliminate or reduce a particular risk factor. This subject has been researched extensively, so confident estimates of the relative importance of individual patient-related risk factors are available.

When evaluating a patient before major noncardiac surgery, the first step is to establish the presence of patient-related risk factors for PPCs (Table 34.1). ASA classification and age dominate the patient-related risk factors. Even after adjusting for conditions more common among older patients, age remains a powerful risk factor. With each decade older than 50 years, the risk increases. Therefore even a healthy older patient who is free of other patient-related risk factors is at increased risk for PPCs. This contrasts with postoperative cardiac complications where age drops out of the analysis after multivariable adjustment for confounders.

ASA physical status classification is an important factor. This classification is broadly written to allow a general classification of risk groups based on the presence and severity of major illness.[2] For example, class 2 describes a patient with mild systemic disease, whereas class 4 is a patient with severe systemic disease that is a constant threat to life. The classification allows for clinical judgment in assigning risk class and estimating major disease severity. Several studies have shown that ASA class is an important risk factor for PPCs even after multivariable adjustment for conditions that would be more common among patients with higher ASA class scores.[3,5]

Total functional dependence is the need for assistance with activities of daily living, typically with needs for home care services, such as a visiting nurse or caregiver. This important predictor most likely results from decreased functional capacity and physiologic reserve in such patients. Surprisingly, although COPD is a patient-related risk factor, it is less important than age or ASA class. Other risk factors include an abnormal chest radiograph (discussed later), congestive heart failure, and arrhythmia.

PROCEDURE-RELATED RISK FACTORS

Procedure-related risk factors are those that are specific to the procedure, regardless of the patient's intrinsic risk (Table 34.2). In general, procedure-related risk factors are more important than patient-related factors. Among procedure-related factors, the single most important factor is surgical site. The old adage that the risk increases as the incision becomes closer to the diaphragm is generally true. Aortic and nonresective thoracic (primarily esophageal) surgeries carry the greatest risk, with *odds ratios* (ORs) for PPCs in the range of 4 to 7. Abdominal surgery is the next most important surgical site risk factor. Many studies have shown that upper abdominal surgery, such as cholecystectomy, carries more risk than lower abdominal surgery, such as gynecologic or urologic surgery. Neurosurgery, head and neck, and nonaortic vascular surgeries are additional high-risk surgical sites, although less so than aortic, thoracic, or abdominal. Orthopedic surgery, although a risk

factor for perioperative thromboembolism, is not a risk factor for PPCs.

All other procedure-related risk factors are less powerful than surgical site. Emergency surgery increases PPC rates as does prolonged surgery. Prolonged surgery is generally defined as more than 3 to 4 hours.

The impact of general anesthesia on PPC rates has been the subject of substantial debate. The relevant comparison is to neuraxial anesthesia, which includes spinal and epidural anesthesia. In an early review, general anesthesia was a modest PPC risk factor, with an OR of 2.4.[5] In a recent review of patients with COPD undergoing a variety of surgical procedures, general anesthesia was likewise a modest risk factor for PPCs.[6] Rates of pneumonia (3.3% vs. 2.3%), prolonged mechanical ventilation (2.1% vs. 0.9%), and unplanned reintubation (2.6% vs. 1.8%) were all higher for patients undergoing general anesthesia. There was, however, no difference in mortality between the general anesthesia and the neuraxial anesthesia groups.

A recent systematic review of 20 studies of general anesthesia versus neuraxial anesthesia also found neuraxial blockade to be associated with reductions in several adverse outcomes. Rates of pneumonia (*relative risk* [RR], 0.56) and mortality (RR, 0.71) were lower for neuraxial anesthesia.[7] A query of the National Surgical Quality Improvement Program database revealed similar findings.[8] Although regional anesthesia had no impact on mortality, the RR for respiratory complications was 0.76. It is now possible to state confidently that epidural anesthesia confers fewer PPCs than general anesthesia.

PULMONARY RISK PREDICTION TOOLS

Multifactorial risk indices to predict postoperative cardiac complications have been used for decades.[9] More recently, several investigators have developed risk scoring systems using multivariable analysis to determine the independent contribution of patient-related, procedure-related, and diagnostic test results. In one of the first such studies, Arozullah and colleagues published multivariate risk scores separately for pneumonia[10] and respiratory failure.[11] Both tools effectively stratified patients into five risk classes that accurately discriminated high- versus low-risk scores. The pneumonia risk index was complex and not easily adapted to clinical use. The respiratory failure index was the simpler of the two and provided a useful tool for clinicians.

Building on this methodologic approach, other authors have developed multivariable risk indices for the prediction of PPC rates. Gupta and colleagues developed separate multivariable indices for postoperative pneumonia and respiratory failure. To calculate risk, a spreadsheet can be downloaded at http://www.surgicalriskcalculator.com/home. For patients and physicians who are particularly concerned about one or the other specific outcomes, these are useful tools.

We recommend the *Assess Respiratory Risk in Surgical Patients in Catalonia* (ARISCAT) tool first derived by Canet and colleagues.[12] This index was derived from a study of 2464 patients undergoing a broad variety of surgery types. PPC outcomes included respiratory infection, respiratory failure, pleural effusion, atelectasis, pneumothorax, bronchospasm, and aspiration pneumonitis. The PPC rate was 5.0% and similar to other published estimates. Median length of stay was four times higher for those with a PPC than those without (12 vs. 3 days, respectively). Mortality at 90 days was 24.4% among patients with a PPC and 1.2% without. This study reconfirmed the morbidity associated with PPCs. After multivariable analysis, seven groupings of risk factors appear in the final risk index (Table 34.3). Risk can be stratified into three categories that effectively discriminate between risk groups. The PPC rates in the validation cohort were low risk (1.6%), intermediate risk (13.3%), and high risk (42.1%). This tool has the potential to become the gold standard multivariable risk index to predict PPCs.

ROLE OF PULMONARY DIAGNOSTIC TESTING

Although the utility of functional and anatomic pulmonary diagnostic testing before lung resection is clear, the value of such testing before nonthoracic surgery is limited. In the vast majority of nonthoracic surgery, preoperative diagnostic testing has the same indications as in the nonsurgical setting.

CHEST RADIOGRAPHY

Essentially all thoracic surgery patients undergo chest radiography due to the nature of their surgical disease. Yet, even in cardiac surgery patients, the value of chest radiographs has been debated. Although half of such studies will be abnormal, the results very rarely change management.[13] For nonthoracic surgery, this dilemma is even more pronounced, with routine preoperative chest radiographs being abnormal in 3–20% of patients and changing management in less than 3%.[14] Based on these data, the American College of Physicians, American College of Surgeons, and American College of Radiology all provided American Board of Internal Medicine Choosing Wisely recommendations to limit the use of preoperative chest radiography in noncardiothoracic surgery.[15] Specifically, the American College of Surgeons and American College of Radiology recommend chest radiography only for patients with evidence of acute cardiopulmonary disease or those older than 70 years with a history of chronic stable cardiopulmonary disease who have not had imaging within 6 months.

PULMONARY FUNCTION TESTING

Spirometry and diffusing capacity measurement are standard for preoperative evaluation of patients scheduled for lung resection. For other procedures, the benefit of these tests is questionable. Although spirometry has long been considered standard before cardiac surgery, it rarely alters management in patients without acute symptoms or changes in known pulmonary disease. Most often, the results of spirometry confirm the risk established by a careful history and physical examination. The Society of Thoracic Surgeons provided American Board of Internal

TABLE 34.3 ARISCAT Multivariable Risk Index for Prediction of Postoperative Pulmonary Complications

	Multivariate Analysis OR (95% CI) (n = 1624*)	β Coefficient	Risk Score†
Age (yr)			
≤50	1		
51–80	1.4 (0.6–3.3)	0.331	3
>80	5.1 (1.9–13.3)	1.619	16
Preoperative Spo_2 (%)			
≥96	1		
91–95	2.2 (1.2–4.2)	0.802	8
≤90	10.7 (4.1–28.1)	2.375	24
Respiratory infection in the last month	5.5 (2.6–11.5)	1.698	17
Preoperative anemia (≤10 g/dL)	3.0 (1.4–6.5)	1.105	11
Surgical incision			
Peripheral	1		
Upper abdominal	4.4 (2.3–8.5)	1.480	15
Intrathoracic	11.4 (4.9–26.0)	2.431	24
Duration of surgery (h)			
≤2	1		
>2–3	4.9 (2.4–10.1)	1.593	16
>3	9.7 (4.7–19.9)	2.268	23
Emergency procedure	2.2 (1.0–4.5)	0.768	8

Risk score: low risk, <26 points; intermediate risk, 26–44 points; high risk, ≥45 points.
*Because of a missing value for some variables, three patients were excluded.
†The simplified risk score was the sum of each logistic regression coefficient β multiplied by 10, after rounding off its value.
ARISCAT, Assess Respiratory Risk in Surgical Patients in Catalonia; CI, confidence interval; OR, odds ratio; Spo_2, oxyhemoglobin saturation by pulse oximetry breathing air in supine position.
From Canet J, Gallart L, Gomar C, et al. Prediction of postoperative pulmonary complications in a population-based surgical cohort. *Anesthesiology*. 2010;113(6):1338–1350.

Medicine Choosing Wisely recommendations to avoid obtaining routine spirometry on patients scheduled for cardiac surgery without signs or symptoms of new or worsened cardiopulmonary symptoms. In the setting of nonthoracic surgery, abnormal spirometry results have been shown to correlate with PPCs. However, when added to clinical assessment, they do not provide clear additional risk prediction benefit.[5] Thus preoperative pulmonary function testing should be reserved for patients undergoing lung resection or with evidence of acute or worsened cardiopulmonary disease.

For patients undergoing lung resection, please refer to Chapter 30 for details on preoperative diagnostic testing.

OTHER LABORATORY TESTING

Arterial blood gas analysis provides limited value for perioperative management, even before lung resections.[16] Identification of hypercapnia during preoperative evaluation does not substantially alter clinical risk stratification or perioperative management in most patients with chronic lung disease. Patients with hypercapnia at baseline would rarely escape clinical detection. As in the nonoperative setting, obtaining an arterial blood gas to evaluate new or worsened respiratory symptoms is reasonable. For patients with suspected or known untreated sleep apnea, serum bicarbonate may provide useful risk stratification information. Elevated serum bicarbonate in these patients suggests chronic *carbon dioxide* (CO_2) retention and the presence of obesity hypoventilation syndrome or overlapping obstructive lung disease. The risk of perioperative complications is substantially higher in such patients, and the *Society of Anesthesia and Sleep Medicine* (SASM) recommends delaying nonurgent surgery for further evaluation of suspected sleep apnea with evidence of hypoxemia or CO_2 retention.[17–19]

Some studies have identified an association between PPCs and elevated blood urea nitrogen and low serum albumin.[5] However, the additive prognostic value of these tests in addition to clinical assessment is uncertain.

PREOPERATIVE RISK REDUCTION STRATEGIES

As much as the necessary surgical timeline will allow, clinicians should fully optimize pulmonary function before surgery and delay elective procedures if acute or worsening respiratory problems are present. Furthermore, all medications (except theophylline) used for chronic pulmonary disease are safe to continue through the perioperative period. Providing education to patients and their families about expectations after surgery can improve compliance with postoperative therapies, including lung expansion

TABLE 34.4 Preoperative Interventions for Reduction of Postoperative Pulmonary Complications

Optimization of chronic lung disease
Education about postoperative care
Smoking cessation
Inspiratory muscle training or cardiopulmonary rehabilitation (e.g., prehabilitation)
Oral hygiene

methods. In addition to these basic care methods, other preoperative interventions may also be beneficial in reduction of perioperative pulmonary risk (Table 34.4).

SMOKING CESSATION

Current or recent history of smoking is a risk factor for multiple postoperative complications, including wound infection and respiratory infections (see Chapter 65). Although the risks related to wound infection may be abated with as few as 3 weeks of cessation, available literature suggests that an optimal reduction of PPCs requires cessation for at least 4 to 8 weeks.[20] This is often beyond the timeframe for preoperative planning, but interventions for smoking cessation are still valuable even shortly before surgery. As previously described, these interventions can reduce other perioperative risks. Furthermore, studies have shown that perioperative smoking cessation counseling can increase the chances of long-term abstinence from cigarettes.[21,22] Contrary to older data, recent meta-analyses have found no increased pulmonary risk from quitting smoking less than 4 weeks before surgery, so smoking cessation should be pursued at any stage of the perioperative setting.[20,23]

Similar to the nonsurgical population, strategies for preoperative smoking cessation include behavioral and pharmacologic interventions (see Chapter 66). All perioperative providers should begin with obtaining a complete tobacco use history and then use the "5A's" model for smoking cessation: ask, advise, assess, assist, and arrange.[24] Intensive behavioral counseling, including motivational interviewing, is superior to more moderate methods, but even brief interventions are beneficial.[25,26] Paired with behavioral counseling, nicotine replacement therapy may provide additional benefit in reducing smoking and postoperative complications and does not increase perioperative risks.[25] Varenicline in the perioperative setting has also been associated with increased long-term abstinence and does not increase perioperative risk.[25] The role of electronic cigarettes/vaporized nicotine in perioperative risk remains unknown.

PREHABILITATION

Prehabilitation, the process of improving the patient's physical function *before* surgery, has shown great promise for reducing PPCs. Pulmonary prehabilitation incorporates methods designed to increase inspiratory muscle strength, lung capacity, and mucociliary clearance. In particular, inspiratory muscle training and cardiopulmonary rehabilitation before major abdominal and cardiac surgery have been associated with significant reductions in PPCs.[27,28] The majority of studies have used inspiratory muscle training for at least 1 to 2 weeks before surgery with use of an inspiratory threshold device, most often with initial instruction from or under the direction of respiratory therapists. Such interventions require significant resources and time, but the potential benefit is substantial: PPCs are reduced by up to 50%, with an absolute risk reduction of 15% and the number needed to treat of 7.[29]

ORAL HYGIENE

Substantial reduction in PPCs can also be achieved by promoting good oral hygiene perioperatively. Several studies of daily oral care (toothbrushing and antigingivitis rinse use) for up to 2 weeks preoperatively found decreased rates of pneumonia in patients undergoing cardiac surgery, lung resection, esophagectomy, and other abdominal procedures.[30–32] Given the minimal cost and lack of adverse effects, good oral hygiene should be encouraged in all surgical patients.

INTRAOPERATIVE RISK REDUCTION STRATEGIES

ANESTHESIA

Although decisions regarding type of anesthesia are fully under the discretion of the anesthetist/anesthesiologist, other care providers should be aware of the impact of different anesthetic approaches on pulmonary physiology. Current literature suggests that general anesthesia contributes to the risk of PPCs.[5,8,33] Conversely, neuraxial (spinal or epidural) anesthesia reduces the risk of postoperative PPCs, even when used in combination with general anesthesia.[8,33,34] As noted above, a recent meta-analysis found an OR of 0.38 (99% confidence interval [CI], 0.36–0.40) for PPCs with neuraxial/regional anesthesia compared to general anesthesia.[33]

NEUROMUSCULAR BLOCKADE

When general anesthesia is used, neuromuscular blockade is an intraoperative management element that impacts the risk of PPCs. Use of *neuromuscular blockade* (NMB) is associated with increased risk of postoperative respiratory failure and pneumonia and should be used only when necessary.[35] When NMB is necessary, we recommend avoidance of long-acting neuromuscular blocking agents (e.g., pancuronium) due to the greater risk for residual NMB and PPCs.[36] Controversy remains over the best methods of prevention of residual NMB, including monitoring neuromuscular recovery and using routine pharmacologic reversal of NMB. Routine reversal of NMB with neostigmine and sugammadex, which act by binding blocking agents, is associated with increased risk. Neostigmine given to patients who have near-complete recovery of neuromuscular function can result in impaired upper airway muscle activity and lead to airway collapse.[37] Sugammadex requires proper

dosing based on the determination of the depth of NMB; if underestimated, recurrent NMB may result in respiratory compromise.[37] These issues highlight the importance of effective NMB monitoring. Unfortunately, studies of quantitative NMB monitoring have provided mixed results, and the lack of reliable, easy-to-use technology has impeded its development. Suffice it to say, for patients at increased risk for PPCs, NMB monitoring and reversal are worthy of additional attention by anesthetists/anesthesiologists, and postoperative care providers should be aware of residual NMB as a cause of respiratory failure in the immediate postoperative setting.

MECHANICAL VENTILATION

Intraoperative mechanical ventilation management is also an opportunity for reducing perioperative risk, but much debate on best methods remains. Some studies have suggested that use of lung-protective ventilation reduces the risk of PPCs, whereas others have found no benefit or increased mortality and cardiovascular complications. Significant variability in the methods used in individual studies, including *tidal volume* (Vt), *positive end-expiratory pressure* (PEEP), alveolar recruitment maneuvers, and combinations of these elements, has contributed to these conflicting results.

Available data suggest that use of supraphysiologic Vt (i.e., ≥10 mL/kg) without other methods, such as "open lung" approaches, including PEEP and alveolar recruitment, to prevent atelectasis, is inferior to provision of near-physiologic Vt (i.e., 6–8 mL/kg) with these open lung interventions.[38–40] The two primary concerns for the ventilated patient are barotrauma from excess airway pressure and atelectasis, and achieving the best balance of these opposing negative consequences may be guided by monitoring of airway pressures. One study identified a direct correlation between high airway driving pressure and risk for PPCs, and a large registry study that examined plateau pressures and ventilation strategies found that plateau pressures less than 16 cm H_2O were associated with the lowest risk of PPCs.[41,42] However, a recent interventional trial failed to find an improvement in PPCs with lower driving pressures and higher levels of PEEP.[43] It is reasonable to avoid extremes of Vt (<6 or >10 mL/kg), PEEP, and airway pressures, and emphasize open lung techniques, such as PEEP and alveolar recruitment maneuvers, to balance the risks of alveolar collapse, barotrauma, and impaired hemodynamics.

POSTOPERATIVE RISK REDUCTION STRATEGIES

In the postoperative period, the primary focus of pulmonary risk reduction efforts is on prevention and treatment of atelectasis (Table 34.5). Unless required by surgical restrictions, early and frequent patient ambulation decreases PPCs and increases lung expansion.[44] Adequate pain control is important to allow deep breathing to avoid atelectasis. However, opioid and other sedative use should be minimized; use of epidural-based or *patient-controlled analgesia* (PCA)-administered opioids can limit systemic opioid exposure and reduce PPCs.[36,45] Nonopioid analgesia should also be maximized with acetaminophen, nonsteroidal anti-inflammatory drugs, and application of ice.

TABLE 34.5 Postoperative Interventions for Prevention of Postoperative Pulmonary Complications

Early and frequent ambulation/mobilization
Lung expansion maneuvers (cough/deep breathing exercises, IS, IPPB, CPAP)
Adequate pain control
Minimization of systemic opioids (including by the use of nerve blocks, epidural analgesia, and PCA)
Maximization of nonopioid analgesia (acetaminophen, nonsteroidal anti-inflammatory drugs, and application of ice)

CPAP, continuous positive airway pressure ventilation; IPPB, intermittent positive-pressure breathing; IS, incentive spirometry; PCA, patient-controlled analgesia.

The evidence to support the benefit of other lung expansion methods is mixed. The simplest way to expand the lungs is by cough and deep breathing exercises, but data on effectiveness are limited. Available meta-analyses of incentive spirometry suggest it provides no benefit in preventing PPCs.[46] However, these studies have had a majority of low-risk patients and used mixed methodologies. Incentive spirometry has been incorporated into risk reduction protocols that utilize preoperative education on its use, and these protocols have demonstrated reductions in PPC rates. Intermittent positive-pressure breathing is another option for lung expansion, but it entails additional costs and side effects (abdominal distention) and has not demonstrated better efficacy than incentive spirometry. Intermittent positive-pressure breathing is likely best reserved for patients at high risk for PPCs who are unable or unwilling to comply with incentive spirometry or deep breathing exercises. Stronger efficacy data come from studies of the use of continuous positive airway pressure after abdominal procedures. Application of continuous positive airway pressure immediately after extubation and continued for as little as an hour significantly reduces the incidence of PPCs after major abdominal surgery (OR, 0.37; 95% CI, 0.24–0.56).[47,48]

PERIOPERATIVE RISK REDUCTION PROTOCOLS

Implementation of the above risk reduction measures into perioperative protocols (i.e., bundles) has become increasingly common, and studies of these combined interventions have demonstrated improvement in multiple outcomes, including decreased PPCs. Enhanced recovery programs incorporate several perioperative risk reduction interventions, including smoking cessation, use of regional anesthesia, minimally invasive surgical approaches, goal-directed fluid therapy, opioid-sparing analgesia, and early ambulation, and have demonstrated efficacy in reducing pneumonia and other respiratory complications after multiple types of surgery.[49–54] Other protocols focused on pulmonary risk, including the I COUGH (*i*ncentive spirometry, *c*ough and deep breathing exercises, *o*ral care [brushing teeth and

TABLE 34.6 I COUGH Pulmonary Risk Reduction Protocol

I	Incentive spirometry
C	Cough and deep breathing exercises
O	Oral care (brushing teeth and using mouthwash twice daily)
U	Understanding (patient and family education)
G	Getting out of bed frequently (at least three times daily)
H	Head of bed elevation

Modified from Cassidy MR, Rosenkranz P, McCabe K, Rosen JE, McAneny D. I COUGH: reducing postoperative pulmonary complications with a multidisciplinary patient care program. *JAMA Surg.* 2013;148(8):740–745.

using mouthwash twice daily], *u*nderstanding [patient and family education], *g*etting out of bed frequently [at least three times daily], *h*ead of bed elevation) perioperative pulmonary care program, have shown similar benefits (Table 34.6).[55]

SLEEP-DISORDERED BREATHING CONSIDERATIONS

Sleep-disordered breathing is an increasingly prevalent condition in the general population. The incidence of moderate or severe OSA has been found to be as high as 40% of surgical patients and is undiagnosed in the majority of patients.[56,57] Patients with OSA have increased risk of multiple complications, including infections, respiratory failure, cardiac events, and mortality.[17,57]

The ASA and SASM have both produced guidelines for the perioperative management of patients with known or suspected sleep apnea.[17,58,59] Both societies recommend using a high-sensitivity tool to screen all surgical patients for the presence of sleep apnea. Several tools are available, including the Flemons, Berlin, and STOP-BANG (*s*noring loudly; *t*ired, fatigued, or sleepy during the daytime; *o*bserved episodes [by others] of stopped breathing during sleep; high blood *p*ressure history or treatment; *b*ody mass index > 35 kg/m^2, *a*ge > 50 years; *n*eck circumference > 17 inches for a man or > 16 inches for a woman; male *g*ender) questionnaires, but the majority of recent literature has focused on STOP-BANG (Table 34.7). Patients with known OSA or an elevated STOP-BANG score are at increased risk for perioperative complications and should receive risk reduction interventions.[17,58] When one counts the number of questions that apply to the patient, the STOP-BANG cutoff score to use for determining high risk with a reasonable balance of sensitivity and specificity is 5 or greater (out of a total of 8).[60,61]

Before surgery in patients with known OSA, clinicians should obtain their previous sleep study reports and document the severity and recommended *positive airway pressure* (PAP) settings.[17] Patients using home PAP therapy should be encouraged to maintain compliance and instructed to bring their device to the hospital for perioperative use.[17] For patients without diagnosed sleep apnea who have high

TABLE 34.7 STOP-BANG Questionnaire for Sleep Apnea Risk Assessment

S	Snoring loudly
T	Tired, fatigued, or sleepy during the daytime
O	Observed episodes (by others) of stopped breathing during sleep
P	High blood pressure history or treatment
B	Body mass index > 35 kg/m^2
A	Age > 50 years
N	Neck circumference > 17 inches for a man or > 16 inches for a woman
G	Male gender

Low risk for sleep apnea: yes to 0–2 questions. *Intermediate* risk: yes to 3–4 questions. *High* risk: yes to 5–8 questions.
Modified from University Health Network, www.stopbang.ca.

STOP-BANG scores, SASM does not recommend delaying all surgical procedures for further sleep evaluation.[17] Clinicians should advise patients and the perioperative team of the elevated risks related to potential undiagnosed and untreated sleep apnea and only delay surgery for patients with elevated STOP-BANG scores plus one of the following: uncontrolled or severe systemic disease (e.g., pulmonary hypertension), hypoxemia, or evidence of CO_2 retention (elevated arterial blood CO_2 or serum bicarbonate).[17]

For all patients with known or suspected OSA, a number of intraoperative and postoperative care strategies are recommended to reduce risks related to sleep apnea. The anesthesia team should consider use of regional anesthesia methods and be prepared for a difficult airway.[59] Both intraoperatively and postoperatively, clinicians should use benzodiazepines and opioids with caution and be prepared for variable responses to each.[17,59] After surgery, nonopioid analgesia should be fully utilized, and patients should be kept in a nonsupine position (i.e., head of bed elevated) unless contraindicated by postoperative requirements.[58] Continuous pulse oximetry or capnography during hospitalization is also recommended for all patients with known or suspected sleep apnea for early detection of respiratory insufficiency.[58] Note that continuous pulse oximetry is not sensitive for hypoventilation when the patient is on supplemental oxygen (see Chapter 44).

In ambulatory surgery, special attention to perioperative planning is required for patients with known or suspected OSA. The severity of sleep-disordered breathing is increased perioperatively, and this worsening reaches a peak at 3 days after surgery and persists for up to several days.[62] Thus clinicians need to consider the severity of sleep apnea, intensity of the procedure (depth of anesthesia and duration), and postoperative opioid requirements to determine if alterations in operative and postoperative triage are required. For instance, patients with severe, untreated sleep apnea undergoing a surgery under general anesthesia that will require postoperative opioid treatment may not be good candidates for surgery at an ambulatory surgical center. Surgery at a hospital with appropriate backup mechanisms may be a better choice. Furthermore, some patients with severe sleep apnea undergoing major operations or who will not be able to use PAP after surgery (e.g., some

TABLE 34.8 Predictors of Difficult Endotracheal Intubation

Finding	Sensitivity	Specificity
Inability to bite lower teeth over upper lip (upper lip bite test)	60%	95–96%
Hyomental distance <3 to <5.5 cm	20%	97%
Retrognathia (mandible length < 9 cm)	19%	98%
Decreased neck range of motion	28%	93%
Interincisor gap <2 to 5 cm	36%	90%
Mallampati class III or IV airway	55%	87%
Thyromental distance <4 to <7 cm	45%	86%

Data from Detsky ME, Jivraj N, Adhikari NK, et al. Will this patient be difficult to intubate? The rational clinical examination systematic review. *JAMA*. 2019;321(5):493–503.

ear, nose, and throat and ophthalmologic procedures) may benefit from hospital admission rather than discharge on the same day as surgery.

AIRWAY MANAGEMENT CONSIDERATIONS

Like anesthesia selection and administration, intraoperative airway management is the primary responsibility of the anesthetist/anesthesiologist, but recognition of airway abnormalities and challenges by other perioperative care providers is still essential to provide the anesthesiology team with advance warning. For endotracheal intubation, several different tools have been studied for the prediction of difficulty (Table 34.8). No single tool is sufficiently sensitive and specific to rule in or rule out a challenging intubation; most experts recommend using a combination of these anatomic markers and tests.

For mask ventilation, several factors have been found to be predictors of difficulty, including age 45 years or older, male gender, elevated body mass index, previous difficult intubation, decreased thyromental distance, Mallampati class III or IV, full beard, snoring, sleep apnea, and neck radiation skin changes.[63] Similarly, detection of a combination of more than one of these is most suggestive of increased risk.

Key Points

- Postoperative pulmonary complications are morbid and increase length of stay, the potential for intensive care unit transfer, and mortality.
- Patient-related factors are known to increase risk of postoperative pulmonary complications. The most important patient-related risk factors are age older than 50 years, American Society of Anesthesiologists class greater than 2, and functional dependence.
- Procedure-related risk factors are more important than patient-related risk factors. Surgical site is the single most important predictor, and the highest risk surgeries include aortic, thoracic/esophageal, and upper abdominal.
- Multifactorial risk indices exist to predict postoperative pulmonary complications. Among these, we recommend the Assess Respiratory Risk in Surgical Patients in Catalonia (ARISCAT) tool.
- Preoperative pulmonary diagnostic testing, including chest radiography, spirometry, and blood gas analysis, rarely adds to risk stratification and management.
- Preoperative pulmonary risk reduction methods include optimization of chronic lung disease, patient education, smoking cessation, inspiratory muscle training, and oral hygiene promotion.
- Intraoperative risk reduction methods include use of neuraxial (spinal or epidural) anesthesia, lung-protective mechanical ventilation, and judicious use of neuromuscular blockade.
- Postoperative pulmonary risk reduction methods include early mobilization, lung expansion modalities (e.g., cough/deep breathing exercises, incentive spirometry, intermittent positive-pressure breathing, and continuous positive airway pressure), and adequate pain control with minimization of systemic opioids and sedatives and maximization of nonopioid analgesia.
- Obstructive sleep apnea is a significant risk factor for postoperative complications. Patients with high risk on screening for obstructive sleep apnea should be counseled on their risks and, if they have evidence of uncontrolled or severe systemic disease, hypoxemia, or carbon dioxide retention, delay of nonurgent surgery for further sleep medicine evaluation should be considered.

Key Readings

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35 EVALUATION OF RESPIRATORY IMPAIRMENT AND DISABILITY

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INTRODUCTION

Respiratory impairment refers to an alteration in lung structure and/or lung function that results in decreased or limited functional ability and is usually manifested by dyspnea on exertion. Many respiratory diseases may cause impairment, from airway disease such as asthma and COPD to interstitial lung diseases. A pulmonary physician may be asked to evaluate impairment and/or disability, either for his or her own patients or for others in the context of an independent medical examination through a benefits or compensation program and/or to provide a statement about ability to work.

This chapter reviews the elements of an impairment evaluation. An overview of the major programs in the United States is presented. Impairment ratings are described using the framework for the assessment of respiratory impairment set forth by the *American Thoracic Society* (ATS)[1,2] along with an overview of the most commonly used impairment rating methodology contained in the *American Medical Association* [AMA] *Guides to the Evaluation of Permanent Impairment,* hereafter referred to as the *AMA Guides.* However, the *AMA Guides* are not used by every benefit and compensation system. The evaluating physician must understand and follow the rules and specific requirements of the program under which the patient is being evaluated. The final determination on the award is usually made by personnel in the program or a judge, but the thoroughness of the medical report and its consistency with the program requirements will increase the weight given to the physician's medical opinion. Finally, an overview of workplace protections for workers with lung disease is covered.

Program details, including how impairment and/or disability is determined under specific programs, are available at ExpertConsult.com.

Additional relevant information about specific diseases can be obtained in other chapters, including Chapters 91, 100, 101, 102, and 103.

DEFINITIONS

There is a critical distinction between the terms *impairment* and *disability.* The terms *impairment* and *disability* are often used interchangeably, perhaps made more confusing by the fact that different benefits and compensation programs may use both terms but focus on one more than the other. *Impairment* takes place at the organ or organ system level. *Whole-person impairment* refers to the loss relative to the functioning of the body as a whole. *Disability*, in contrast, refers to the person in terms of limitation in the ability to perform normal activities, including personal, social, and work activities.

Physicians should understand that such determinations are medicolegal decisions that can have additional

ramifications for the patient beyond that of providing a diagnosis. The physician may be asked to address causation (i.e., opine on whether the respiratory condition was caused or at least aggravated by a certain factor, most commonly work, on a more-likely-than-not basis).

Although the terms "impairment" and "disability" are related, it is important that each term be applied in accordance with its precise definition. The definitions used in most existing benefits and compensation programs in the United States are based on the *World Health Organization's* [WHO] *International Classification of Impairment, Disability, and Handicap* (ICIDH) model from 1980.[3] This model was replaced by the *International Classification of Functioning, Disability, and Health* (ICF)[4] in 2001, which uses different definitions of these words. Because these programs have not been updated to incorporate the ICF definitions, the definitions from the ICIDH are presented here to avoid confusion. The ICF model is presented in the "Future Directions" section.

IMPAIRMENT

Impairment refers to the degree of loss of normal use or function of a body part or organ. It is defined by the WHO as "any loss or abnormality of psychological, physiologic, or anatomic structure or function."[3] It is defined by the AMA as "a loss, loss of use, or derangement of any body part, organ system or organ function."[5]

The essential elements that make up an impairment evaluation will vary to some degree according to the program or system through which the evaluation is being performed. Standard components typically include history, with occupational and environmental history and description of limitations in *activities of daily living* (ADLs), physical examination, and review of medical records and diagnostic test results that establish the respiratory condition.

Although *pulmonary function test* (PFT) results are the primary factor that determines the presence and degree of pulmonary impairment, some systems will specify that particular tests should be used for assessment of impairment or disability, whereas others allow physician discretion in choosing another test if he or she believes it to be a more accurate reflection of the patient's true respiratory impairment. Some programs only allow physicians with certain qualifications to perform impairment ratings. Before a physician can determine that a condition has resulted in permanent impairment or disability, the diagnosis should be well defined, the condition stable, and medical treatment either optimized or reasonable options exhausted. When these criteria are met, this point is termed *maximum medical improvement* (MMI).

DISABILITY

Disability refers to any resulting alteration in the individual's capacity to perform customary activities. It was defined by the WHO as "any restriction or lack of ability to perform any activity within the range considered normal for a human being."[3] The AMA defined *disability* as an "alteration of an individual's capacity to meet or perform personal, social, or occupational demands or statutory or regulatory requirements because of an impairment."[5]

Although the degree of impairment frequently correlates with the degree of disability, this is not always the case. The classic example of this is the loss of the fifth finger of the nondominant hand. Under the typical impairment rating system, the loss of this finger would be associated with a small impairment of the whole person. For the average person, this small impairment would result in a correspondingly small disability. For a concert pianist, this small impairment would be associated with significant disability, particularly in the context of work activities.

ADDITIONAL TERMS

Temporary impairment refers to impairment that exists only for a limited period of time after an injury or illness.

Temporary disability insurance covers partial compensation for loss of wages due to a *non–work-related* injury or illness. For *work-related* injuries and illness, partial compensation for lost wages, as well as medical benefits, are covered by workers' compensation.

Permanent impairment can be assessed only once the patient has reached MMI. MMI is defined in the *AMA Guides,* Sixth Edition,[6] as the "point in time in the recovery process…when further formal medical or surgical intervention cannot be expected to improve the underlying impairment" and "symptoms can be expected to remain stable with the passage of time, or can be managed with palliative measures that do not alter the underlying impairment substantially." This is termed "permanent and stationary" in some systems.

Whole-person impairment refers to the alteration in the functioning of the body as a whole and therefore can range from 0% (no impairment) to 100% (essential cessation of all body functions).

Permanent partial impairment is the numeric percentage of the loss of body functioning due to the loss or limited functioning of the affected organ system(s). For most respiratory conditions, the primary organ involved is the lung, but it can include the pulmonary arteries or nose and throat.

Permanent total disability is the medicolegal determination that a person's impairment precludes future gainful employment.

Handicap refers to the societal disadvantage caused by an impairment or disability. It was defined by the WHO in the ICIDH model as "a disadvantage for a given individual that limits or prevents fulfillment of that person's normal role depending on sex, age, social and cultural factors."[3]

CLINICAL APPROACH TO IMPAIRMENT EVALUATIONS

Although the term *impairment rating* is sometimes used interchangeably with the term *impairment evaluation,* the impairment rating itself is but a small part of what should be a comprehensive medical evaluation[7] (Table 35.1). The physician must first fully understand the purpose and requirements of the program for which the evaluation is being conducted. The initial goal of the impairment evaluation should be to confirm the medical diagnosis,[2] through a thorough, detailed patient history, physical examination, and review of diagnostic testing results that established

Table 35.1 Components of a Respiratory Impairment Evaluation

1. Clear understanding of the rules and specific requirements of the program under which the individual is being evaluated.
2. Complete medical history
   a. Complete occupational and environmental exposure history
   b. Limitations in activities of daily living
3. Physical examination
4. Diagnostic testing
   a. Tests that establish the diagnosis
   b. Tests that identify extrapulmonary conditions contributing to impairment
   c. Results used in the assessment of impairment
      i. Pulmonary function tests
         A. Spirometry
         B. Single-breath diffusing capacity (DL_{CO})
      ii. Cardiopulmonary exercise test (when indicated)
      iii. Arterial blood gas measurement (when indicated)
5. Diagnosis
   a. Assessment of causation, usually relationship to work (when indicated)
6. Impairment assessment
   a. Statement of maximum medical improvement
   b. Impairment rating
   c. Ability to work/work restrictions (when indicated)
   d. Apportionment (if requested)
   e. Future medical treatment

the diagnosis. The diagnosis or diagnoses should be clearly stated, along with extrapulmonary conditions that may be contributory to symptoms, limitations in ADLs, and/or impairment. There should also be a review of the treatment and an opinion on MMI. Factors important to the impairment rating itself include items from history, physical examination, and diagnostic testing results that reflect disease severity, including impact on normal ADLs,[5] and current treatment requirements. The physician may be asked to make a statement on causation or apportionment. An outline of reasonably anticipated future medical course and treatment requirements should be given. The following sections describe the various aspects of an impairment evaluation, including the history to be taken, the examination to be conducted, and the testing to be obtained depending on the diagnosis considered and the type of evaluation being performed.

HISTORY

The *history of present illness* (HPI) is the standard, detailed respiratory history used by most pulmonologists, including symptoms of cough, cough with phlegm, wheeze, chest tightness, and shortness of breath. If present, details should be provided that include when the symptom started, exacerbating and alleviating factors along with temporal relationship, progression over time, and current status including frequency, severity, and response to any medication. A scale for the rating of dyspnea is suggested in the *AMA Guides,* based on the Epidemiology Standardization Project,[8] which also provides standardized questions for the assessment of other symptoms. Questions about conditions such as chronic rhinitis, postnasal drip, gastroesophageal reflux disease, cardiac disease, and other lung diseases, including smoking- and vaping-related lung disease, may help the physician understand other possible contributors to respiratory symptoms. Although dyspnea is the primary limiting symptom of respiratory impairment, dyspnea can also result from extrapulmonary causes including cardiovascular disease, obesity, and deconditioning. Frequency, severity, treatment requirements, and duration of periodic exacerbations of diseases such as asthma and bronchiectasis should be well documented. Medications used or tried in the past for the treatment of the respiratory conditions should be described, along with a description of the relief afforded.

Constitutional symptoms are relevant in the HPI in patients with certain diseases, such as fever, sweats, chills, and fatigue in patients with hypersensitivity pneumonitis; chest pain, weight loss, and malaise in patients with asbestos-related lung disease; and night sweats and fatigue in patients with chronic beryllium disease.

A standard detailed past medical and surgical history, list of medications and allergies, family history, and review of systems will provide a good understanding of the patient as a whole. It will also allow the physician to identify other possible diseases that may be contributory to the patient's current status, as well as to assess potential treatment-related side effects. The standard social history should include smoking history, including amount, duration, and current smoking status, as well as a history of vaping or drug use.

An element that may be new to most pulmonologists is the need to obtain a detailed occupational and environmental history. This is necessary to help the physician address whether there is a relationship between a respiratory condition and past or ongoing workplace exposures. The occupational history is most easily performed in chronological order starting from childhood. Details about the period of time spent at each job, the job title, description of the work performed, and details about jobs or processes that may have produced dust, fumes, gas, or smoke should be described, including estimation of intensity, frequency, and duration of exposure. Questions about ventilation and use of respiratory protection can provide helpful clues, as well as whether any immediate symptoms were noted. Chemical exposures, particularly any heavy exposures or exposures that resulted in symptoms, should be detailed. If available, the *Safety Data Sheet* (SDS), formerly called the Material Safety Data Sheet, may be reviewed because it can provide helpful information on the components of the chemicals used in the workplace and potential associated health effects. Unfortunately, SDSs are not required to provide complete information, and thus some are more reliable than others.

An environmental history including questions about heating, cooling, and humidification sources; pets, including birds; hot tubs; water-damaged areas; and exposures from hobbies should also be obtained to determine whether there is a relationship between the disease and any environmental exposures.

In addition, the history should also include a description of how the condition affects the person's ability to perform normal ADLs. Questions most relevant to patients with pulmonary disease include ability to perform basic self-care such as showering; ability to walk, including estimated distance at own pace and at a fast pace or up a hill, estimated pace compared with others one's own age, and number of flights of stairs that can be climbed; and ability to perform

indoor and outdoor home maintenance chores, as well as customary hobby, exercise, and job-related activities. A number of standardized methods can assess ability to perform ADLs, some of which are disease specific. A list of ADLs suitable for all conditions is outlined in the *AMA Guides.*[5,9] Symptoms and limitations in ADLs consistent with the lung disease and objective testing data provide useful supporting information for the impairment rating. Dyspnea scales are often used and can be a helpful way to summarize the relative degree of symptomatology or activity limitation.[8] However, the degree to which dyspnea correlates with objective measures of pulmonary function and exercise performance is variable.[10–13]

PHYSICAL EXAMINATION

A complete physical examination should be performed, with focus on the respiratory and cardiovascular systems.[2,7] A detailed description of the chest should be made, including any deformities or scars, abnormal motion, respiratory rate and effort, breath sounds, and percussion, which can help support the diagnosis. Vital signs should be documented including blood pressure and heart rate, which may affect ability to perform pulmonary function and exercise tests, as well as height and weight, because obesity can cause PFT and exercise test abnormalities and contribute to pulmonary symptoms. Signs of hypoxemia, such as cyanosis and clubbing, should be documented. Signs of right heart failure, such as jugular venous distention, right ventricular heave, and liver engorgement, and peripheral edema provide evidence of severe respiratory impairment in patients with respiratory disease.[2]

DIAGNOSIS, CAUSATION, AND MAXIMUM MEDICAL IMPROVEMENT

Any available or provided medical records should be summarized, with focus on the results of the diagnostic testing that help establish the diagnosis and/or severity of the condition. Medicolegal cases may often involve the review and summarization of large volumes of records. Some independent medical examinations require that only the records provided through the program be reviewed.

The list of medical diagnoses should start with the diagnosis of the condition for which the patient is being evaluated, including disease severity. The diagnosis of asthma associated with workplace exposures may fall under one of three different diagnoses: occupational asthma (new-onset asthma caused by a workplace exposure), work-aggravated asthma (existing asthma aggravated by a workplace exposure), and *reactive airways dysfunction syndrome* (RADS), which can result from a single high-level irritant exposure (see Chapter 100). Other diagnoses that may be contributory to symptoms, limitations in ADLs, or testing abnormalities should be clearly delineated.

If relevant, the diagnosis should also include a statement on *causation,* the physician's opinion as to whether or not a given workplace exposure has caused or aggravated an illness. This is a medicolegal determination, also known as *attribution,* made on a medically probable basis (i.e., "more-likely-than-not"). That is, the physician can opine with greater than 50% certainty that the exposure(s) in the workplace caused the respiratory condition or worsened an underlying condition on the basis of objective criteria, such as change in treatment requirements. This criterion is less rigorous than that required for scientific proof of a hypothesis (i.e., 95% certainty). This is important because, in cases of respiratory illness, there may be multifactorial causation, frequently a long latency between initial exposure and clinical onset of disease, nonspecific clinical manifestations, incomplete understanding of dose-response relationships from epidemiologic studies, and lack of individual exposure data. Although recognition of these limitations is necessary, causation can be attributed in most cases on a more-probable-than-not basis by applying reasonable judgment. This process is easier when the exposure is known, the dose-response relationship is well characterized, and competing diagnoses are unlikely. The physician should clearly describe the specific substances at the workplace; their known health effects according to the medical literature; the relative dose, based on estimated intensity, frequency, and/or duration of exposure; and finally, why it is medically probable that the exposure(s) caused or resulted in permanent aggravation of the diagnosed medical condition in this worker. When one or more of these conditions are not met, attribution should be based on the answers to the following questions.

- Is the diagnosis clearly established, and is it biologically plausible (or consistent with the available epidemiologic data) that the disease could have been caused or aggravated by the exposure in question?
- Have competing diagnoses been adequately considered?
- Is the exposure of sufficient intensity and duration to have caused or aggravated the disease?
- Has there been an adequately long latent period, or is there a temporal relationship between onset of exposure and clinical manifestation of disease?

When the examining physician believes the diagnosis is in question, or the condition is not stable, or the condition may improve with additional treatment, this should be stated, along with recommendations for what is needed to address these issues. If the conditions for MMI are met, a statement of MMI is indicated, and it is appropriate to consider whether there is permanent impairment. What happens logistically following determination of the MMI will depend on the specific program. The examining physician should be aware of the ramifications of making these medicolegal determinations. For example, in workers' compensation systems, determination of MMI allows the worker to be awarded permanent impairment but will also result in the cessation of temporary benefits such as compensation for lost wages, as the case is closed by the workers' compensation insurance company.

GUIDES TO RESPIRATORY IMPAIRMENT RATINGS

AMERICAN THORACIC SOCIETY GUIDELINES FOR EVALUATION OF IMPAIRMENT OR DISABILITY

Many systems have been used to determine respiratory impairment. Most base impairment primarily on lung function. In their "Guidelines for the Evaluation of Impairment/

Table 35.2 American Thoracic Society Impairment Categories, With Corresponding Description of Ability to Perform Job Demands

Category	Criteria	Ability to Perform Job Demands
Normal	FVC ≥ 80% of predicted *and* FEV_1 ≥ 80% of predicted *and* $FEV_1/FVC \times 100$ ≥ 75% *and* DL_{CO} ≥ 80% of predicted	
Mildly impaired	FVC 60–79% of predicted *or* FEV_1 60–79% of predicted *or* $FEV_1/FVC \times 100$ 60–74% *or* DL_{CO} 60–79% of predicted	Usually not correlated with diminished ability to perform most jobs
Moderately impaired	FVC 51–59% of predicted *or* FEV_1 41–59% of predicted *or* $FEV_1/FVC \times 100$ 41–59% *or* DL_{CO} 41–59% of predicted	Progressively lower levels of lung function correlated with diminishing ability to meet the physical demands of many jobs
Severely impaired	FVC ≤ 50% of predicted *or* FEV_1 ≤ 40% of predicted *or* $FEV_1/FVC \times 100$ ≤ 40% *or* DL_{CO} ≤ 40% of predicted	Unable to meet the physical demands of most jobs, including travel to work

DL_{CO}, single-breath carbon monoxide diffusing capacity; FEV_1, forced expiratory volume in 1 second; FVC, forced vital capacity.
From American Thoracic Society (ATS). Evaluation of impairment/disability secondary to respiratory disorders. *Am Rev Respir Dis*. 1986;133:1205-1209.

Disability Secondary to Respiratory Disorders," the ATS recommends that impairment due to most lung diseases be rated on the basis of PFT results.[2] PFT is described in detail in Chapters 31 and 32. The results of the ATS impairment system, based on PFTs, place individuals into four impairment categories. Each of these categories provides a corresponding description of the associated ability to perform job demands (Table 35.2). The ATS did not include a system by which to assign an associated numerically derived percentage of whole-person impairment, on which monetary awards are typically based. Therefore, the ATS guidelines did not lend themselves to use in most compensation systems.

AMERICAN MEDICAL ASSOCIATION GUIDES TO THE EVALUATION OF PERMANENT IMPAIRMENT

The *AMA Guides,* Fifth Edition, adapted the ATS Guidelines into a formula by adding a system through which to assign a numerically derived percentage of whole-person impairment within each of the four impairment classes.[14] Although the *AMA Guides,* Fifth Edition, is no longer the most current edition, the methodology is presented here because it is directly based on ATS Guidelines and because not all compensation systems have adopted the Sixth Edition. The *AMA Guides,* Fifth Edition, assigned the following associated ranges of whole-person respiratory impairment to each of the four ATS classes: class 1 impairment, 0%; class 2 (mild), 10–25%; class 3 (moderate), 26–50%; and class 4 (severe), 51–100% whole-person impairment. After determining the class of impairment based on *forced vital capacity* (FVC), *forced expiratory volume in 1 second* (FEV_1), FEV_1/FVC, *single-breath diffusing capacity* (DL_{CO}), or *maximal oxygen consumption* ($\dot{V}O_{2max}$), the physician determines the final numeric percentage of whole-person impairment on the basis of where the test results fall within that range of impairment as well as other factors, including impact of the respiratory condition on the ability to perform ADLs.

The *AMA Guides,* Sixth Edition, adopts a different methodology, defining four classes of impairment: class 0, 0%; class 1 (minimal), 2–10%; class 2 (mild), 11–23%; class 3 (moderate), 24–40%; and class 4 (severe), 45–65% whole-person impairment.[15] The key factor is the objective test data, FVC, FEV_1, FEV_1/FVC, and DL_{CO}, using the measurement most relevant to the disease process.[15] $\dot{V}O_{2max}$ may be considered as the key factor if one of the other pulmonary function test results is abnormal. The specific value within the impairment class is determined by the physical examination findings, dyspnea, and treatment requirements. The maximum whole-person impairment in the *AMA Guides,* Sixth Edition, for most respiratory disorders is 65% whole-person impairment, rather than 100% whole-person impairment in previous editions, although this rating may still be combined with impairment in other organ systems.

Because a person can never have more than 100% impairment of the body, impairment in any additional organ system needs to be combined rather than added to the respiratory impairment. Each edition of the *AMA Guides* contains a special combining table for this purpose.

CLASSIFICATION OF IMPAIRMENT RESULTING FROM SPECIFIC PULMONARY DISEASES

Regardless of the rating system used, the greatest weight should be placed on objective data.

Asthma

For diagnosis and management of asthma, see Chapter 62. Rating asthma according to the standard respiratory disorder methodology can both underestimate and overestimate impairment, given the episodic and variable nature of airflow limitation and bronchial hyperresponsiveness.[16] The ATS developed "Guidelines for the Evaluation of Impairment/Disability in Patients with Asthma" in 1993 to reflect the true impairment due to this condition.[1] First, a worker with objectively confirmed asthma must be determined to be at MMI and to have achieved optimal therapeutic goals (i.e., minimum medication required and optimal time to allow medication effect).[15] To rate asthma impairment according to ATS methodology (Table 35.3), the postbronchodilator FEV_1, reversibility (% change with bronchodilator), or methacholine challenge results (provocative concentration of methacholine inducing a 20% drop in FEV_1 [PC_{20} in mg/mL]), and minimum medications required to maintain this status are assigned scores using Table 35.3 parts A–C. The class of impairment is defined by the sum of the asthma scores based on Table 35.3 part D. The *AMA Guides,* Fifth Edition, adopted this ATS methodology and assigned a numeric range of whole-person impairment for each impairment class, which is equivalent to the

Table 35.3 American Thoracic Society Impairment Rating Guidelines for Asthma

A. POSTBRONCHODILATOR FEV_1

Score	FEV_1 (% Predicted)
0	> lower limit of normal
1	70–lower limit of normal
2	60–69
3	50–59
4	<50

B. REVERSIBILITY OF FEV_1 OR DEGREE OF AIRWAY HYPERRESPONSIVENESS*

Score	% FEV_1 Change	PC_{20} (mg/mL or Equivalent)
0	<10	>8
1	10–19	8– >0.5
2	20–29	0.5– >0.125
3	≥30	≤0.125
4	—	—

C. MINIMUM MEDICATION NEED†

Score	Medication
0	No medication
1	Occasional bronchodilator, not daily, and/or occasional cromolyn,‡ not daily
2	Daily bronchodilator and/or daily cromolyn‡ and/or daily low-dose inhaled steroid (<800 μg beclomethasone or equivalent)
3	Bronchodilator on demand and daily high-dose inhaled steroid (>800 μg beclomethasone or equivalent) or occasional course (1–3/year) systemic steroid
4	Bronchodilator on demand and daily high-dose inhaled steroid (>1000 μg beclomethasone or equivalent) and daily systemic steroid

D. SUMMARY OF IMPAIRMENT RATING CLASSES§

Impairment Class	Total Score
0	0
I	1–3
II	4–6
III	7–9
IV	10–11
V	Asthma not controlled despite maximal treatment (i.e., FEV_1 remaining < 50% despite use of ≥20 mg prednisone/day)

*When FEV_1 is above the lower limit of normal, the PC_{20} value should be determined and used for rating of impairment; when FEV_1 is < 70% predicted, the degree of reversibility should be used; when FEV_1 is between 70% predicted and the lower limit of normal, either reversibility or the PC_{20} can be used. Reversibility with bronchodilator is calculated as:

$$\frac{FEV_1\,\text{postbronchodilator} - FEV_1\,\text{prebronchodilator}}{FEV_1\,\text{prebronchodilator}} \times 100\%$$

Airway responsiveness is expressed as that concentration of bronchoconstrictor agents that will provoke a fall in FEV_1 of 20% from the lowest postsaline value. Plot the concentration of methacholine or histamine against the fall in FEV_1 using a logarithm scale for the doubling concentrations. The PC_{20} is obtained by interpolation between the last two points. The formula for linear interpolation of the PC_{20} from the log dose response curve is as follows:

$$PC_{20} = \text{antilog}\,C1 + \frac{(\log C2 - \log C1)(20 - R1)}{(R2 - R1)}$$

where *C1* is the second last concentration (<20% FEV_1 fall), *C2* is the last concentration (>20% FEV_1 fall), *R1* is the percentage fall FEV_1 after C1, and *R2* is the percentage fall FEV_1 after C2.

†The need for minimum medication should be demonstrated by the treating physician, e.g., previous records of exacerbation when medications have been reduced.

‡Very limited current use.

§The impairment rating is calculated as the sum of the patient's scores from parts A, B, and C.

From the American Thoracic Society, Medical Section of the American Lung Association. Guidelines for the evaluation of impairment/disability in patients with asthma. *Am Rev Respir Dis*. 1993;147:1056-1061.

impairment assigned for general respiratory conditions.[14] Additionally, the ATS added a fifth class of impairment, defined as asthma not controlled despite maximal treatment (i.e., FEV_1 remaining <50% despite use of ≥20 mg of prednisone daily). The *AMA Guides,* Sixth Edition, additionally recommends that an impairment rating be performed after the patient has achieved optimal therapeutic goals, and that it is prudent to wait at least 2 years after diagnosis and removal from exposure in cases of occupational asthma.[15] If a physician determines that the MMI has been achieved for a patient before then, the report should clearly detail the rationale behind the departure from the 2-year time period. PC_{20} is used as the primary "key factor" by which the class of asthma impairment is determined. Although postbronchodilator FEV_1 may be used as an alternative, there is impairment only if the maximum postbronchodilator FEV_1 is 80% or greater than predicted, which will afford no impairment for the patient with complete reversibility. Minimum medication requirements and frequency of attacks are used to determine the specific numeric rating within the class.[15]

Bronchiectasis (See Chapter 69)

Rating conditions such as bronchiectasis by standard pulmonary function testing methods can underestimate impairment because recurrent episodes of infection and inflammation cause intermittent respiratory symptoms, respiratory dysfunction, and limitations in ADLs, often with normal lung function in between episodes. The *AMA Guides,* Fifth Edition, acknowledge that this method will be applicable only in "limited cases," but they allow the physician to assign a rating on the basis of the extent and severity of these episodes and their impact on ADLs, with objective supporting evidence documented.[14] The *AMA Guides,* Sixth Edition, does not delineate a specific methodology for this condition.[15]

Sleep Disorders (See Chapters 117–122)

Sleep disorders are recognized in the *AMA Guides,* Sixth Edition, as a condition that may cause impairment not well estimated by standard pulmonary function testing or exercise testing.[15] Both the *AMA Guides,* Fifth and Sixth Editions, describe the importance of obtaining sleep testing in an accredited laboratory, and grading severity based on the number of apnea and hypopnea episodes observed during polysomnography and the severity of hypoxemia.[14,15] However, there are no standardized, well-documented criteria for determining level of impairment. Treatment, weight loss, and repeat polysomnography is recommended prior to impairment rating, which should be performed by a sleep specialist. The *AMA Guides,* Sixth Edition, specifies that the rating should not exceed 3% whole-person impairment; however, additional impairment may be assigned for secondary conditions, such as right heart failure and polycythemia.

Lung Cancer (See Chapters 76 and 77)

The *AMA Guides,* Fifth and Sixth Editions, recommend one of two methods be used for rating permanent impairment due to lung cancer.[14,15] All individuals with lung cancer are considered severely impaired at the time of diagnosis. At 1 year after diagnosis, if there is still evidence of tumor or tumor recurrence, the person is considered to be severely impaired. If there is no residual tumor or recurrence, the impairment rating is performed according to the standard rating methodology for respiratory diseases.

Diseases of the Pulmonary Arteries

For discussion of disorders of the pulmonary vascular bed, see Chapters 81 through 88. Diseases rated by this methodology include pulmonary artery hypertension, right heart failure, and pulmonary emboli. In the *AMA Guides,* Fifth Edition,[17] the rating is determined by the presence or absence of physical examination signs (right ventricular heave, increased pulmonic component [P_2] of the second heart sound [S_2], peripheral edema) and symptoms of right heart failure (dyspnea), as well as the observed elevated *pulmonary artery pressure* (PAP). In the *AMA Guides,* Sixth Edition,[9] the objective findings, including PAP, B-type natriuretic peptide, and $\dot{V}O_{2max}$, are the key factors that determine the class of impairment. The specific percentage assigned within the class is determined by history (dyspnea and activity limitations) and physical examination findings (signs of right heart failure).

Conditions of the Upper and Lower Airways (See Chapters 70 and 71)

The *AMA Guides,* Fifth Edition,[18] contain methodology by which to assign impairment due to physical obstruction or scarring of the upper airway, larynx, trachea, and/or bronchi, based on degree and location(s) of the obstruction, nature of the activities that trigger dyspnea, as well as need for ventilation. The *AMA Guides,* Sixth Edition, uses the nature of the activities that trigger dyspnea as the key factor in determining impairment class, and physical examination findings and objective test results, such as sinus computed tomography or findings on laryngoscopy, in determining the final numeric rating.[19] There are also methods for the rating of voice/speech impairment based on audibility, intelligibility, and functional efficiency in the *AMA Guides*, Fifth Edition. These factors are also used to define the key factor for impairment class in the *AMA Guides*, Sixth Edition, as well as consideration of strobovideolaryngoscopy, objective voice and speech measures, and Voice Handicap Index. It is important to note that there are differences in what defines impairment within a given class in the two editions. Impairment related to bronchiectasis is described above.

ROLE OF DIAGNOSTIC TEST RESULTS IN IMPAIRMENT RATINGS

RADIOGRAPHIC DATA

Documentation of chest radiograph or *computed tomography* (CT) scan abnormalities consistent with the lung disorder is frequently required to establish evidence of disease, particularly for diseases such as pneumoconiosis. The chest imaging findings may correlate poorly with the physiologic findings, especially in patients with obstructive lung disease.

Some programs require that chest radiographs be read by a *National Institute of Occupational Safety and Health*

(NIOSH)-certified B Reader and classified according to the *International Labour Organization* (ILO) classification system.[20] This radiographic interpretation system was devised in an attempt to report the presence, appearance, and extent of radiographic changes consistent with pleural and parenchymal evidence of pneumoconiosis in an objective and consistent manner. Chest radiographic findings of opacities with an ILO profusion score of at least 1/0 are "consistent with" asbestosis and are accepted for compensation purposes by programs such as the Department of Labor for that condition. If the opacities are small and irregular (classified as "s" and "t") and are found predominantly in the middle and lower lobes or are found in conjunction with pleural plaques, these findings are highly consistent with a diagnosis of asbestosis.

Whereas the ILO interpretation may help raise suspicion of pneumoconiosis or provide sufficient evidence of disease in the correct clinical situation/compensation program, the physician must determine on a clinical basis whether additional testing is necessary to establish a medical diagnosis and determine whether treatment is necessary. The physician should note that additional testing may or may not be covered by the benefits or compensation program. Because of the variability in the extent of radiographic findings and the degree of physiologic impairment, none of the major programs or rating systems uses radiographic findings in the assessment of impairment due to lung disease. The NIOSH website provides a search tool by which to find certified B Readers by state and country.[21]

A standardized CT classification system similar to the ILO system called the International Classification of High-Resolution Computed Tomography for Occupational and Environmental Disease has been proposed.[22] Although this CT classification system was found to have satisfactory inter-reader reliability by an international panel of experts,[23] the assessment mainly focused on one lung disease, asbestos-related lung disease, so the generalizability of this system is not clear. Neither this nor any other standardized system for reporting CT findings of pneumoconiosis is currently in widespread use.

PULMONARY FUNCTION TESTING (See Chapters 31 and 32)

PFTs are the most important tests, both from a diagnostic standpoint and in their use to determine impairment for most respiratory conditions. Both the ATS[2] and the *AMA Guides* specify the use of FVC, FEV_1, FEV_1/FVC, and D_{LCO}. Some programs mandate that pulmonary function testing be performed pre- and post-bronchodilator and should be done in patients with low FEV_1 or diagnoses of reversible airflow limitation. The ATS specifies that individuals should be evaluated only after they have received an accurate diagnosis and while they are receiving optimal therapy.[2] This is consistent with the *AMA Guides* requirement that the patient be at MMI, as described previously. Measurement of height without shoes is recommended, as is measurement of arm span (distance between the tips of the middle fingers with arms outstretched) in cases of spinal deformity.[2,24]

Both ATS and the *AMA Guides* emphasize the importance of only using test results that meet the quality standards defined in the latest ATS statement "Standardization of Lung Function Testing."[25] This document governs the equipment, quality assurance, and techniques that should be used to perform lung function testing, in addition to the assessment of the quality of the test and the method of interpretation. If a physician has concern that the PFTs were not performed in a manner consistent with the ATS Guidelines, including acceptability and reproducibility, then the physician should request repeating the test. An exception happens when the patient has consistently demonstrated less than optimal technique on past tests despite language-appropriate education and encouragement. The physician may decide not to repeat testing if consistent, unacceptable test performance appears to be due to overall debilitation, pain, or language barrier or when it is unlikely that repeating the test will yield better results. Test results markedly worse than those of prior tests raise concern regarding an exacerbation of the underlying condition and that the patient is not at MMI, or it may be that the patient gave less than full effort; regardless, such results would not be considered to reflect the patient's permanent impairment status. Options include informing the subject of the discrepancy and repeating the test or using the results "as a subsidiary and not the main criterion."[26]

When evaluating PFTs for impairment, the normal values of the laboratory performing the test should not be used, but rather the normal values of the impairment rating system. For example, the ATS and *AMA Guides,* Fifth Edition, use the normal values derived from Crapo and colleagues,[27] while the *AMA Guides,* Sixth Edition, use National Health and Nutrition Examination Survey III–derived prediction equations.[28]

D_{LCO}, measured by the single-breath method of Ogilvie and colleagues[29] and interpreted according to Crapo and Morris,[30] is suggested by both ATS and the *AMA Guides.* Both recommend correction by the methodology of others for factors including hemoglobin, carboxyhemoglobin,[2,14] and altitude and alveolar volume,[2] but correction methodology and interpretive strategies are not explicitly described in the rating criteria. The most recent ATS statement on D_{LCO} describes explicit criteria for evaluating acceptability and repeatability, as well as adjustment for hemoglobin, supplemental oxygen, altitude, and carboxyhemoglobin, while noting that further study is necessary before specific recommendations for lung volume adjustment can be made.[31] In a separate statement, the ATS has noted that low D_{LCO} along with low D_{LCO} *corrected for alveolar volume* (D_{LCO}/VA) suggest parenchymal abnormalities as the cause of the impairment but recommends examining the two separately.[25] Neither the ATS nor the *AMA Guides* utilize D_{LCO}/VA in assessing impairment.

Maximal voluntary ventilation and $FEV_{25\%–75\%}$ are not recommended for use by ATS or the *AMA Guides* in impairment evaluation. ATS defines a restrictive ventilatory defect as a reduction in total lung capacity below the lower limit of normal (i.e., below the fifth percentile of the predicted value), with a normal FEV_1/FVC ratio.[25] Total lung capacity is not included in the standard rating criteria in either the ATS or the *AMA Guides.* Although the *AMA Guides,* Sixth Edition, cautions that a true restrictive defect may not be present even with a reduced FVC in the setting of a normal

Table 35.4 American Thoracic Society Interpretation of Exercise Test Results Using $\dot{V}O_{2max}$

$\dot{V}O_{2max}$	METS	Estimated Work Ability
≥25 mL/kg/min	≥7.1	Continuous heavy exertion throughout an 8-hour day in all but the most physically demanding jobs
15–25 mL/kg/min *and* Metabolic demands of the work ≤ $\dot{V}O_{2max}$		Able to perform that job comfortably, assuming there are no frequent or extended periods (5 min) requiring exertion substantially >40% $\dot{V}O_{2max}$
≤15 mL/kg/min	≤4.3	Unable to perform most jobs because they would be uncomfortable traveling back and forth

METS, the energy demand in liters of oxygen consumption per minute/basal oxygen consumption (3.5 mL/kg/min); $\dot{V}O_{2max}$, maximal oxygen consumption.
From American Thoracic Society. Evaluation of impairment/disability secondary to respiratory disorders. *Am Rev Respir Dis*. 1986;133:1205-1209.

or increased FEV_1/FVC, FVC alone continues to be the test used in the rating of impairment of restrictive lung disease.

CARDIOPULMONARY EXERCISE TESTING (See Chapter 33)

Neither the ATS nor the *AMA Guides* recommend the routine use of exercise test results in the determination of permanent impairment; however, maximal exercise test results, specifically $\dot{V}O_{2max}$, should be considered in specific circumstances. ATS recommended that exercise test results be used in cases where the resting PFTs do not reflect the true impairment present.[2] For example, studies have demonstrated that *alveolar-arterial oxygen pressure difference* [(A–a)P_{O_2}] during exercise is a better reflection of impairment due to gas exchange abnormality than $D_{L_{CO}}$ in many patients with interstitial lung disease.[32] Although exercise limitation does not necessarily correlate with resting lung function testing,[33,34] exercise testing can be helpful in cases where there is a large discrepancy between symptoms and resting physiology,[32] providing a more precise measurement of work capacity.[35]

Airflow limitation and gas exchange abnormality help define the relative degree to which respiratory disease contributes to exercise limitation. When exercise limitation is present, nonrespiratory causes of exercise limitation should be considered as well, including cardiovascular disease, deconditioning, and neuromuscular disease.[36] The ATS guidelines for respiratory impairment note that exercise testing can be used as a valid measure of respiratory impairment when the following criteria are met: (1) exercise testing is not terminated for another extrapulmonary reason, (2) there is low breathing reserve at termination, and (3) there is absence of erratic overventilation at submaximal levels with failure to achieve anaerobic threshold (i.e., there is an absence of evidence of psychogenic dyspnea). However, no details are provided on how these criteria should be met, and the *AMA Guides* do not delineate a specific methodology. The reason for test termination should be noted because tests terminated early due to nonrespiratory causes such as excessive blood pressure, cardiac abnormality, or leg pain do not reflect maximum exercise tolerance.

To determine work capacity, and thus impairment, ATS requires use of $\dot{V}O_{2max}$ to place workers into one of three categories of work tolerance, assuming that workers can comfortably perform sustained work at 40% of $\dot{V}O_{2max}$ and that O_2 requirements of the workers' jobs are known (Table 35.4). The *AMA Guides,* Fifth and Sixth Editions, both consider a $\dot{V}O_{2max}$ greater than 25 mL/kg/min to place one into the lowest (least) category of impairment (class 1 and class 0, respectively) and a $\dot{V}O_{2max}$ less than 15 mL/kg/min to place one into the highest (greatest) category of impairment (class 4). This approach has major limitations, which are detailed below.

BLOOD GAS ANALYSIS

Arterial blood gas analysis is not used for impairment rating purposes on a routine basis. Resting arterial P_{O_2} does not necessarily correlate with exercise capacity. Arterial hypoxemia at rest by itself is not evidence of severe impairment in exercise tolerance. ATS recommends it only be used in "selected patients" under "rigidly controlled laboratory conditions" and should be documented on at least two occasions separated by at least 4 weeks.[2] They consider hypoxemia to be evidence of severe impairment only when accompanied by evidence of right heart failure. Arterial blood gas analysis was considered to be a test infrequently indicated in the evaluation of impairment in the *AMA Guides,* Fifth Edition.[14] It is not included in the Sixth Edition.[15]

ADDRESSING DISCREPANCIES BETWEEN OBJECTIVE AND SUBJECTIVE DATA

A description of the severity of the disease or condition should be given. This can be difficult when there is a discrepancy between the severity reported by the patient and the severity of the disease based on the results of the diagnostic testing. It is important that the physician distinguish between *objective* data (findings evident to the examiner in a reproducible manner and not dependent on only the patient's perceptions), including physical signs and diagnostic testing results, and *subjective* data, which are reported by the patient, such as symptoms perceived by the patient only and not evident to the examiner. Normally, the two are similar, making the history, physical examination, and diagnostic testing findings all helpful in the assessment of true functional impairment. If the subjective complaints are not consistent with the objective findings, the physician should first be sure there is no coexisting disease process responsible for the

symptoms. For example, dyspnea may also be caused by nonrespiratory disorders such as cardiac disease and anemia. *Organic impairment* refers to the presence of objective findings of respiratory dysfunction or disease. *Functional impairment* refers to dyspnea for which an objectively measured abnormality of organ function cannot be identified. Recognizing that tests for organic impairment are not perfectly sensitive, the contribution of functional impairment can range from "negligible" to "perhaps accounting for the entire extent of a patient's dyspnea." When there is a discrepancy between the subjective and the objective data, and other medical conditions have been excluded as possible contributors to the subjective complaints, several steps should be taken. The first and foremost is to review the purpose of the evaluation with the patient to ensure comprehension of questions and performance of PFTs. Second, an evaluation of test performance, including cooperation and the results of effort-independent tests such as functional residual capacity, may be of some use. Examination of test results for comparability over time may show evidence of consistency or the lack thereof. Finally, exercise testing may shed considerable light on a patient's level of effort by demonstrating the relationships of heart rate and ventilatory rate at workloads actually achieved to the predicted maximal values.

Dyspnea due to functional impairment may result from subconscious effects on the perception of symptoms or from outright malingering. Because of the inability of PFTs and other tests to be perfectly sensitive in diagnosing organic causes of impairment, the diagnosis of malingering should be made with caution. The *Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition* (DSM-5), classifies malingering as a condition "that may be a focus of clinical attention."[37] Furthermore, malingering is described as "the intentional production of false or grossly exaggerated physical or psychological symptoms, motivated by external incentives." Specific listed examples of these external incentives include avoiding work and obtaining financial compensation. The DSM-5 recommends that malingering should be strongly suspected if any combination of the following is noted: (1) there is a medicolegal context of presentation, (2) a marked discrepancy between the person's claimed stress or disability and the objective findings is noted, (3) a lack of cooperation during the diagnostic evaluation and a lack of compliance with the prescribed treatment regimen are observed, and (4) there is the presence of antisocial personality disorder. Malingering is differentiated from a factitious disorder in that the motivation for the symptom production is external, rather than an intrinsic need to maintain the sick role. Malingering may also be differentiated from conversion disorder and other somatoform disorders by the intentional production of symptoms and the obvious external incentives associated with it.

Although it is important to identify frank malingering, which represents fraud, it must be emphasized that malingering is relatively rare and should remain a diagnosis made through exclusion and with extreme caution.

APPORTIONMENT AND FUTURE MEDICAL TREATMENT

APPORTIONMENT

When multiple disease processes are present that may contribute to respiratory impairment, the physician may be asked to apportion or make a statement of the relative contribution of each disease process to the total impairment. This is usually performed in the context of workers' compensation in an effort to limit the amount of the monetary award to that specifically attributed to the workplace exposure or event. It does not typically reduce medical treatment benefits or wage compensation. Unfortunately, the scientific basis for this level of precision is rarely present and thus must be acknowledged as arbitrary even if required by the entitlement system.

Cigarette smoking and its sequelae is the most common condition taken into account when considering apportionment of respiratory impairment. For example, much has been written about the difference in symptoms and physical limitations in smoking compared with nonsmoking asbestos workers,[38] and the observation that the most common cause of exercise limitation in one group studied was the cardiovascular system rather than the respiratory system.[39] Specific methods for apportionment have been proposed,[40] but none has been validated scientifically or considered generally accepted. If objective evidence of prior impairment exists, such as diagnostic testing results performed before the work-related exposure or development of disease, some states will allow apportionment to be performed by subtracting the preexisting impairment from the current total impairment.

EXPECTED FUTURE MEDICAL TREATMENT

A description of the expected natural history of the condition, that is, if the condition is expected to remain stable or potentially to deteriorate over time, should be provided. In addition, the recommended medical follow-up and anticipated treatment requirements can provide a helpful measure of reasonably anticipated future medical expenses. This is of value to the worker as well as insurance adjusters and attorneys.

MAJOR STATE AND FEDERAL BENEFIT AND COMPENSATION PROGRAMS

Most impairment and disability evaluations will be performed under the context of a particular state or federal program. A number of different programs exist for individuals and workers in specific employment settings. Some of the larger programs include the Federal Black Lung Program for coal mine workers, Social Security Disability for disabled workers, Workers' Compensation for ill and injured workers through their employers, and the Veterans Administration for veterans with service-related conditions. There are several related programs for workers at Department of Energy sites and uranium workers under the Energy Employees

Occupational Illness Compensation Program. Most of these programs refer to both impairment and disability. In some programs, the primary determination to be made by the physician is disability, usually in the context of making the dichotomous determination of "disabled" or "not disabled" and, in others, the primary determination is impairment. Each system has its own rules by which to establish patient eligibility and rules for assignment of disability and/or impairment. Most major compensation systems require physicians to undergo special training and/or approval before they are permitted to perform these evaluations for benefits programs.

Detailed descriptions of these programs are available at ExpertConsult.com.

WORKPLACE PROTECTIONS

RESPIRATORY PROTECTION

In considering whether respiratory protection may be required in the workplace, it is important to consider NIOSH's recommended hierarchical approach to reducing workplace exposures including (1) elimination, (2) substitution, (3) engineering controls, such as improving ventilation or enclosing exposures, (4) administrative controls, and, as a last resort, (5) personal protective equipment such as respirators.[49] Medical clearance for the use of respirators is mandated by the Occupational Safety and Health Administration, either through use of their standard questionnaire or through a comparable medical examination.[50] Before using a respirator, the worker should undergo tests with the specific make and model of the respirator to be used to ensure proper fit and protection. Fit testing is also regulated by the Occupational Safety and Health Administration.

WORK RESTRICTIONS

Some compensation systems, such as workers' compensation, require a statement on ability to work and whether there are any physical activities or exposures the worker should avoid. Treating physicians may recommend temporary work restrictions for their patients during exacerbations of illness; these restrictions may or may not be accommodated by the workplace because there is no requirement for them to do so. Physicians may also assign permanent work restrictions, which employers are obligated to consider for reasonable accommodation under the *Americans with Disabilities Act Amendments Act* (ADAAA).[51] Restrictions may include limitations in the ability to perform a specific physical activity, perform it safely on a sustained or repeated basis, and/or to be able to work in the presence of certain dust, fume, gas, chemical, and/or antigen exposures, as in the case of occupational allergic asthma and hypersensitivity pneumonitis.

In order for the physician to determine whether the worker can perform job tasks and if restrictions are needed, both the physical requirements of the job and the worker's capabilities need to be ascertained. Exercise testing, with its limitations noted previously, is a standard approach used in this assessment. Although submaximal testing has been used and does have some advantages in terms of administration and merits in terms of demonstrating a worker's ability to sustain activity at a predetermined level of exertion, maximal exercise testing is normally used. Accuracy of exercise testing to predict functional performance can be increased by combining exercise testing with measures of pulmonary function[33] and with heart rate monitoring during the performance of work activities.[52] Actual simulation of work may be performed by a physical or occupational therapist, called a functional capacity evaluation. Interpretation of results and formulation of formal work restrictions should be performed in a manner consistent with the ADAAA considerations, including suggesting possible methods of reasonable accommodation in the workplace.

AMERICANS WITH DISABILITIES ACT AMENDMENTS ACT

The *Americans with Disabilities Act* (ADA) of 1990 and the ADAAA of 2008 prohibit discrimination against a qualified individual with a *disability*, defined as "a physical or mental impairment that substantially limits a major life activity."[51,53]

A brief discussion of the definitions of impairment and accommodation as it relates to this Act and the Family and Medical Leave Act is available at ExpertConsult.com.

A preemployment physical is not permitted under the ADA; an employer may not ask questions about disability or require a medical examination until after a conditional job offer has been made. A postoffer, preplacement medical evaluation is permitted, as long as the employer does this for all employees entering the same job category; if doing so is job related and consistent with business necessity on the basis of objective evidence that a worker will be unable to perform essential job functions or will pose a direct threat because of a medical condition; or when an employer receives a request for reasonable accommodation and the disability or the need for the accommodation is not obvious.

FUTURE DIRECTIONS

AN UPDATED FRAMEWORK OF DISABILITY

As noted above, the WHO replaced the ICIDH model with the ICF in 2001. The ICIDH model had been recognized as problematic in a number of respects, including an implied unidirectional relationship from impairment to handicap, limited definition of the role of the environment, and focus on the disability, rather than the factors that may enable functional ability. The ICF is an international consensus framework constructed in two parts,[4] designed to be used in conjunction with the International Classification of Diseases 10 codes as a uniform description of health and well-being. The first part of the ICF is most familiar to physicians, combining consideration of *body functions and structure*, *activity*, and *participation* in a cohesive manner. The term *functioning* according to the ICF combines the positive aspects of body functions, activities, and participation, whereas the term *disability* is used to describe the combination of the negative aspects of structural/functional loss (impairment), activity limitation, and participation restriction. Part 2 of the ICF encompasses an additional dimension called *contextual factors*, which are divided into *personal factors*, such

PROGRAMS IN WHICH PHYSICIANS PRIMARILY DETERMINE DISABILITY

Some programs provide benefits to individuals who are determined to be unable to work due to a medical condition. The role of the physician is to determine if there is evidence of an illness and, if so, to provide medical evidence that supports the determination that the worker cannot engage either in a particular occupation or in any type of gainful employment. These are typically all or none systems; either the worker is totally disabled due to the condition or not. No benefits are awarded unless the worker is determined to be totally disabled.

Federal Black Lung Program

The Federal Black Lung Program is a medical treatment program for miners administered through the *Department of Labor* (DOL).[41] It arose out of the Federal Coal Mine and Safety Act of 1969, with amendments made in 1977, 1981, and 2000. The Act established mandatory safety and health standards in mines and included provisions for research and training. Title IV of the Act established black lung benefits, recognizing that there are many coal miners who are disabled or deceased because of mining-related lung disease, primarily pneumoconiosis. The amendments that followed the initial act broadened the scope of workers covered and the breadth of lung diseases covered. A *miner* is now defined as "any person who works or has worked in or around a coal mine or coal preparation facility in the extraction, preparation or transportation of coal, and any person who works or has worked in coal mine construction or maintenance in or around a coal mine or coal preparation facility." In addition, the amendments also broadened the disease covered, so *pneumoconiosis* is now defined as any "chronic dust disease of the lung and its sequelae including respiratory and pulmonary impairments, arising out of coal mine employment." Thus, the Federal Black Lung program covers not only coal miners with silicosis or coal workers' pneumoconiosis but also airway disease due to coal mining, such as chronic airway obstruction.

Benefits are awarded to the miners or to their *surviving dependents,* defined as the wife or dependent child, parents, or siblings of the miner. Each miner who applies for benefits is afforded the opportunity to undergo a medical evaluation paid for by the DOL to ascertain if she or he is eligible for benefits. The testing must be performed in the manner outlined in the federal regulations. Only physicians who have been approved by the DOL may perform the examination; they cannot be related to the miner or have examined or treated the miner within the preceding 12 months. Miners may apply for benefits under state workers' compensation as well.

There are strict eligibility requirements. This normally requires the miner to have been employed for a minimum of 10 years in underground mine work. Once determined to be eligible to perform the examination, the physician must then determine if the miner has lung disease due to mining, as defined by the statute. This is most commonly determined on the basis of chest radiograph findings of pneumoconiosis, specifically large or small opacities of profusion 1/0 or greater, read by a NIOSH-certified B Reader, and classified according to the ILO's classification system.[20] A determination may also be made by biopsy or autopsy evidence of pneumoconiosis, or through a reasoned medical opinion that there was a condition that would be reasonably expected to yield the previously discussed chest radiograph or pathology findings. The regulations also specify criteria for posthumous determinations.

The physician then determines if the miner meets the definition of *totally disabled*, defined as being unable to work as a miner or perform comparable work due to respiratory impairment. The medical criteria that establish total disability are PFT results with FVC, FEV_1, or maximal voluntary ventilation below values listed in the tables contained in the regulations (60% of predicted), FEV_1/FVC ratio 55% or less, or arterial blood gas analysis based on a Po_2 at or below a value specified for concurrently measured Pco_2, listed in one of three tables provided for different ranges of altitude. If these criteria are met, the physician must also establish that the miner is unable to perform his or her usual job in the coal mine or is unable to be employed near home with the skills used in the mines. The specific tables noted previously may be accessed at the U.S. DOL's Division of Coal Mine Workers' Compensation page[42] through the Pulmonary Functions Standards and Tables link. This website also contains a link to the specific standards that must be used for the administration and interpretation of PFTs contained in the legislation.

If not covered under state workers' compensation, medical treatment expenses for black lung–related conditions, including medication, will be covered. Home oxygen, pulmonary rehabilitation, and home health care may be covered after special approval.

Social Security Disability

Amendments to the Social Security Act in 1950 established the first legislation for financial assistance "to aid the permanently and totally disabled." Numerous changes in this system have been implemented since that time. The *Social Security Administration* (SSA) oversees two programs: the *Social Security Disability Insurance* (SSDI) program, which pays monthly cash benefits to former workers now unable to work for at least a year due to disability; and the *Supplemental Security Income* (SSI) program, which provides benefits to disabled persons who meet financial need criteria. Former workers are eligible for SSDI if they have earned a sufficient number of work credits while working in the past, based on past contributions made to Social Security. What constitutes a credit is variable, as is number of credits required, with workers aged 62 years or older requiring the greatest number of credits to qualify.

In this program, the physician must first determine whether an applicant is disabled. *Disability* is defined as not being able to do any substantial gainful work activity because of a medically determined physical or mental impairment expected to last at least 12 months or to result in death. The determination may be made on the basis of information submitted by treating physicians and/or through an evaluation by an approved physician. There are strict eligibility criteria. The categories of impairments of the respiratory system and an overview of the impairment criteria are listed in eTable 35.1. The SSA outlines the specific tests and testing criteria, including quality considerations,

eTable 35.1 Social Security Administration Respiratory System Impairment Categories and Criteria by Which to Establish Sufficient Impairment to Result in Disability

Category		Impairment Rating Criteria to Establish Disability
Chronic pulmonary insufficiency	Obstructive disease, any cause	Based on FEV_1 in liters (BTPS) and height without shoes (Table I)*
	Restrictive disease, any cause	Based on FVC in liters (BTPS) and height without shoes (Table II)†
	Pulmonary disease causing gas exchange abnormality	DL_{CO} < 10.5 mL/min/mm Hg, or DL_{CO} < 40% predicted, or ABG result based on Po_2 for a specified Pco_2, at rest or steady state exercise ≤ 5 METS‡
Asthma		Based on Table I criteria or based on frequency of attacks§
Cystic fibrosis		As per COPD or based on frequency of infections or exacerbations‖ or based on infection treatment requirements‖
Pneumoconiosis		Based on Table II criteria
Bronchiectasis		Based on Table II criteria or based on frequency of infections or exacerbations¶
Mycobacterial, mycotic, or other chronic infection		Based on Table II criteria
Right heart failure	Secondary to pulmonary vascular hypertension	Mean pulmonary artery pressure > 40 mm Hg Arterial hypoxemia‡ or based on Section 4.02 (chronic heart failure)
Sleep disorders		As per right heart failure
Lung transplant		As per right heart failure

*SSA Blue Book Section 3.02 Table I.
†SSA Blue Book Section 3.02 Table II.
‡SSA Blue Book Section 3.02 Table III-A, III-B, or III-C, depending on altitude.
§Frequency of attacks, defined as happening every 2 months or at least 6 times a year despite treatment. Attacks requiring inpatient hospitalizations are counted as 2 attacks.
‖Infection treatment requirements, defined as persistent infection accompanied by bacterial infections happening at least once every 6 months requiring intravenous or nebulization antimicrobial therapy.
¶Frequency of infections or exacerbations, defined as number of episodes of bronchitis, pneumonia, hemoptysis, or respiratory failure requiring treatment happening at least every 2 months or 6 times per year. Inpatient hospitalizations are counted as two episodes.
ABG, arterial blood gas; BTPS, body temperature, ambient pressure, saturated with water vapor; DL_{CO}, diffusing capacity for carbon monoxide; FEV_1, forced expiratory volume in 1 second; FVC, forced vital capacity; Pco_2, pressure of carbon dioxide; Po_2, pressure of oxygen.
Modified from the Social Security Administration. Disability Evaluation Under Social Security. http://www.ssa.gov/disability/professionals/bluebook/. Updated Blue Book information can be obtained under the links to the Adult Listings and the link to Section 3.00 Respiratory system.

which form the basis for the determination as to whether the degree of impairment would be expected to prevent an individual from working. Up-to-date Blue Book information can be accessed freely at the SSA website (http://www.ssa.gov/disability/professionals/bluebook/).

PROGRAMS IN WHICH PHYSICIANS PRIMARILY DETERMINE IMPAIRMENT

In addition to the programs outlined previously, some programs compensate workers for permanent impairment remaining after treatment of a medical condition that developed as a direct result of a workplace exposure or activity. A description of a few of these programs follows.

Workers' Compensation

State workers' compensation systems are state specific because they are governed by the rules and laws of each individual state. States began to adopt this European "no-fault" model in the early 1900s in a piecemeal manner.[43] This system affords employees the right to guaranteed treatment and benefits for an injury or illness that happens "in the course and scope" of their work, regardless of fault, but in exchange for the ability to sue their employers for negligence.[44] The determination that a worker has a work-related condition is usually made by a physician on a medically probable basis (i.e., it is at least 51% likely that a work event caused or substantially worsened the condition or illness). Whereas the state workers' compensation systems remain highly variable from state to state, commonalities include employer funding of the system; coverage of medical treatment expenses; temporary wage replacement compensation, usually about two-thirds of salary; vocational rehabilitation training (some states only); and compensation for permanent impairment that remains after the worker has completed medical treatment (i.e., is at MMI). There is usually a statute of limitation, or a time period in which a claim must be made after the worker has received a diagnosis of a work-related disease. In many states, the statute of limitations is 2 years.

The monies a worker may be paid in compensation for persistent permanent impairment of the respiratory system are usually based on the impairment rating provided by the physician. Most states designate the specific system by which permanent impairment is to be determined. Forty-four states and two commonwealths use the *AMA Guides*.[6] Some states mandate the use of the "most recent" or "most current" edition, whereas others specifically mandate that a specific edition of the *AMA Guides* be used. Some states, such as Minnesota, have developed their own guidelines for the rating of permanent impairment. Some states, such as Colorado, require that a physician has undergone training

eTable 35.2 Veterans Administration: Specific Lower Respiratory Diseases for Which Veterans May Be Eligible for Service-Related Disability and General Criteria Used

Disease	Rating Based on the Following Criteria
Bronchitis, chronic	FEV_1, FEV_1/FVC, D_{LCO}
Bronchiectasis	Cough frequency, number and frequency of infections requiring antibiotics, and incapacitating episodes per year
Bronchial asthma	Frequency and type of treatment, physician visits, severity of attacks, FEV_1, FEV_1/FVC
COPD, emphysema	FEV_1, FEV_1/FVC, D_{LCO}, $\dot{V}O_{2max}$ (with cardiorespiratory limit), use of oxygen, evidence of secondary cardiovascular dysfunction*
Tuberculosis	Active vs. inactive disease, respiratory status, x-ray findings, residual lung disease, thoracoplasty
Pulmonary vascular disease	Pulmonary embolism with residual symptoms, ongoing treatment needs, IVC surgery, evidence of secondary cardiovascular dysfunction*
Neoplasm	If in remission 6 months after ending treatment, rating will be reassessed and may decrease from 100% on the basis of residuals
Interstitial lung disease†	FVC, D_{LCO}, $\dot{V}O_{2max}$ (with cardiorespiratory limit), evidence of secondary cardiovascular dysfunction,* use of oxygen
Mycotic lung disease‡	Active vs. inactive disease, respiratory symptoms, constitutional symptoms
Restrictive lung diseases§	FEV_1, FEV_1/FVC, D_{LCO}, $\dot{V}O_{2max}$ (with cardiorespiratory limit), use of oxygen, evidence of secondary cardiovascular dysfunction*
Sarcoidosis	Radiographic involvement, frequency and type of treatment, cardiac involvement, respiratory and systemic symptoms
Sleep apnea	Sleep study results, symptoms, CPAP treatment, respiratory failure

*Evidence of secondary cardiovascular dysfunction: evidence of right heart failure, RVH, or pulmonary hypertension.
†Includes diffuse interstitial fibrosis, DIP, pulmonary alveolar proteinosis, drug-induced pulmonary pneumonitis and fibrosis, radiation-induced pulmonary pneumonitis and fibrosis, HP, pneumoconiosis (silicosis, anthracosis), asbestosis.
‡Mycotic lung disease: histoplasmosis, coccidioidomycosis, blastomycosis, cryptococcosis, aspergillosis, mucormycosis.
§Restrictive lung diseases: diaphragm paralysis/paresis, spinal cord injury with respiratory insufficiency, chest wall deformities, postsurgical residua, chronic pleural fibrosis or effusions.
CPAP, continuous positive airway pressure; DIP, desquamative interstitial pneumonia; D_{LCO}, diffusing capacity for carbon monoxide; FEV_1, forced expiratory volume in 1 second; FVC, forced vital capacity; HP, hypersensitivity pneumonitis; ILD, interstitial lung disease; IVC, inferior vena cava; RVH, right ventricular hypertrophy; $\dot{V}O_{2max}$, maximal oxygen consumption.
From U.S. Department of Veterans Affairs. Web Automated Reference Materials Systems (WARMS). https://www.benefits.va.gov/WARMS/bookc.asp#i.

and become "accredited" before performing impairment evaluations. Because of the variability of the systems used, as well as concerns for validity and internal consistency within some editions of the *Guides* themselves,[45] significant variability exists in impairment ratings performed across the country.[46] Physicians should consult their state regulations or workers' compensation agencies to learn about the system and statutes used in their state.

There are other workers' compensation programs that cover specific groups of workers. For example, the Office of Workers' Compensation administers medical treatment and benefits to current federal workers through the Federal Employees' Compensation Program, *Department of Energy* (DOE) workers through the *Energy Employees Occupational Illness Compensation Program* (EEOICP, described in the next section), and through the Longshore and Harbor Workers' Compensation Program for workers in these industries. Under the Federal Employers' Liability Act, enacted in the beginning of the 20th century, federal railroad workers must establish that negligence of the railroad or other railroad personnel contributed to the injury or illness through a legal claim before full treatment and other benefits are awarded. If there is "contributory negligence" on the part of the worker, partial benefits are awarded. The Merchant Marine Act (Jones Act) describes a similar system.

Veterans Administration

The Department of Veterans Affairs provides medical care for military personnel who have a service-connected condition. Veterans who meet the service requirements and were discharged under other than dishonorable conditions may apply for compensation for disability due to service-connected conditions, defined as injury or illness incurred or aggravated during active military service. Veterans with disabilities can qualify for severance with disability pay or monthly disability compensation. Those veterans who are permanently and totally disabled or 65 years of age and older, had wartime service, and meet the financial eligibility requirement may receive a monthly pension.

Disability ratings are performed according to the Rating Schedule, which contains more than 700 diagnostic codes under 14 different body systems.[47] Although it is called a disability rating, the listed criteria reflect symptoms, impairment, and treatment requirements by which the rater determines the rating, given in 10% increments ranging from 0–100%, rather than a determination of ability or inability to work.

The respiratory system is divided into diseases of the nose and throat, diseases of the trachea and bronchi, and diseases of the lung and pleura. Veterans Affairs–affiliated and Veterans Affairs–designated physicians review medical records and are asked to provide medical history, including current treatment requirements, physical examination findings, and results of diagnostic and clinical tests that support the diagnosis along with any associated conditions, and PFT results. The major criteria that the raters use in the determination of the disability rating for the specified respiratory diseases are shown in eTable 35.2, adapted from

eTable 35.3 EEOICPA Part B Requirements for Eligibility and Diagnosis Under the Act for Beryllium-Related Illness and Silicosis*

Condition	Eligible Workers	Requirements for Diagnosis Under Part B
Beryllium sensitization	See chronic beryllium disease	Abnormal Beryllium Lymphocyte Proliferation Test (BeLPT) performed on blood or BAL cells
Chronic beryllium disease	Employees of the DOE, its predecessor agencies, contractors, and subcontractors; designated atomic weapons workers; and beryllium vendors	For diagnoses made on or after January 1, 1993† An abnormal BeLPT and at least one of the following: 1. Lung biopsy showing a process consistent with CBD 2. A CT scan showing changes consistent with CBD 3. A pulmonary function or exercise tolerance test showing pulmonary deficits consistent with CBD
Chronic silicosis	DOE employee or contractor who worked at least 250 days in underground tunnel operations at the Nevada or Alaska nuclear test sites	One of the following: 1. A chest radiograph B reading confirming pneumoconiosis with a profusion score of 1/0 or greater 2. Results from a CT or other imaging study consistent with silicosis 3. A lung biopsy consistent with silicosis

*The final decision as to whether or not the patient meets the requirements is made by the Department of Labor.

†If the diagnosis was made before January 1, 1993, at least three of the following must be documented: characteristic chest radiograph or CT scan denoting abnormalities; a test showing restrictive, obstructive, or diffusion abnormality; lung pathology consistent with CBD; a clinical course consistent with a chronic respiratory disorder; an immunologic test showing beryllium sensitivity (skin patch test or beryllium test preferred).

BAL, bronchoalveolar lavage; CBD, chronic beryllium disease; CT, computed tomography; DOE, U.S. Department of Energy; EEOICPA, Energy Employees Occupational Illness Compensation Program Act.

From U.S. Department of Labor Medical Requirements under the Energy Employees Occupational Illness Compensation Program Act OMB No. 1215-0197. Form EE-7 April 2005.

the U.S. Department of Veterans Affairs Web Automated Reference Materials website, which contains the up-to-date Book C Schedule for Rating Disabilities.[47] Specific illnesses and medical conditions are presumed to be service connected for select groups of veterans, including prisoners of war, veterans exposed to radiation, Vietnam veterans exposed to agent orange or other herbicides, and Gulf War veterans. These veterans are eligible for disability compensation for those conditions without burden of proof.

ENERGY EMPLOYEES OCCUPATIONAL ILLNESS COMPENSATION PROGRAM

This is a federal program available as an adjunct or alternative to state workers' compensation for workers who were or are employed by or were subcontractors at DOE sites or who worked for businesses that functioned as vendors providing services or goods for the DOE. The compensation program is outlined in the EEOICP Act of 2000, as amended (EEOICPA or Act), which also established the DOL's responsibility for the administration of this program.[48] Part B of the Act provides compensation to current and former workers who meet DOL criteria for beryllium sensitization, *chronic beryllium disease* (CBD) and silicosis (eTable 35.3). Individuals with beryllium sensitization are awarded medical monitoring for possible progression to CBD, whereas those with CBD and silicosis are awarded medical evaluation to follow up and monitor disease, as well as coverage of medications and consequential illness evaluation and treatment as needed, along with a one-time lump-sum payment of $150,000.

DOE employees, contractors, and subcontractors and atomic weapons employees diagnosed with cancer are compensated in a manner similar to that of CBD and silicosis, if that cancer is determined to have developed as a result of working at a covered facility, based on DOL criteria. Members of special cohorts, composed of workers at specific sites during certain time periods, are afforded compensation for specific cancers without further burden of proof. The Radiation Exposure Commission Act provides compensation to individuals who develop these specific cancers and other serious diseases as a result of exposure to radiation during above-ground nuclear weapons testing or during work as uranium miners, millers, and ore transporters. Eligibility is largely determined on the basis of having worked in certain locations during specified periods of time, a minimum duration of exposure, and having a specific type of cancer. A lump-sum payment and medical expenses will be awarded to individuals who have been awarded compensation by the Department of Justice. Because the DOL makes the final determination as to whether the worker meets the requirements for the diagnosis, the evaluating physician should clearly document the history of the claimed illness(es), physical examination findings, the clinical testing data supporting the diagnosis, and the date the illness was first documented. Consequential illness or injury may be accepted if sufficient medical documentation of its relationship to the covered illness is submitted. There are provisions for survivor eligibility provided as part of this compensation program.

The EEOICP Act established Part E and replaced Part D, a program that had been administered by the DOE in which panels of physicians made medical determinations as to whether or not a particular illness was related to DOE work. Under Part E, DOE employees, contractors, and subcontractors, as well as eligible RECA claimants, are awarded payment of medical expenses, as well as a maximum of $250,000 compensation for permanent impairment and loss of wages, if they are determined to have developed an illness as a result of occupational exposure to a toxic substance at a covered DOE facility. Workers with conditions accepted under Part B will be automatically accepted under Part E for compensation for impairment. Unfortunately, DOE vendors are eligible under Part B but are not eligible for compensation under Part E. There is survivor eligibility provided under Part E. Impairment ratings may be performed by physicians who are certified by the American Board of

eTable 35.4 Energy Requirements Expressed as Oxygen Uptake ($\dot{V}O_{2max}$) of Various Types of Work

	$\dot{V}O_{2MAX}$ (APPROXIMATE)		
Level of Work	**mL/kg/min**	**L/min**	**METS**
LIGHT TO MODERATE WORK (SITTING)			
Clerical	5.6	0.42	1.6
Using repair tools	6.3	0.47	1.8
Operating heavy equipment	8.8	0.66	2.5
Heavy truck driving	12.6	0.95	3.0
MODERATE WORK (STANDING)			
Light work, own pace	8.8	0.66	2.5
Janitorial work	10.5	0.79	3.0
Assembly line (lifts > 45 lb)	12.3	0.92	3.5
Paper hanging	14.0	1.05	4.0
STANDING AND/OR WALKING (ARM WORK)			
General heavy labor	15.8	1.19	4.5
Using heavy tools	21.0	1.58	6.0
Lift and carry 60–80 lb	26.2	1.97	7.5

METS, the energy demand in liters of oxygen consumption per minute/basal oxygen consumption (3.5 mL/kg/min).
From Becklake M. Organic or functional impairment. *Am Rev Respir Dis*. 1984;129:S96-S100.

Independent Medical Examiners or American Academy of Disability Evaluating Physicians or who are otherwise considered by the DOL to have the requisite experience or knowledge. Not all physicians approved to provide care for workers under Part B of the program are eligible to provide impairment ratings under Part E. Physicians will be asked to submit such credentials for approval by the DOL to confirm their ability to provide impairment ratings. Alternatively, medical consultants to the DOL may perform the ratings. Currently, the ratings are still performed under the *AMA Guides,* Fifth Edition, which had been the most recent edition at the time the legislation was passed. Each percent whole-person impairment determined through an impairment rating is compensated $2500. Compensation for lost wages is based on the number of years that the employee was unable to work or sustained a reduction in wages because of the illness up to age 65.

The Act applies to individuals who have, have a record of, or are regarded as having a physical or mental impairment. Initially, determination of whether cases met the ADA criteria focused on whether or not the individual met the definition of disabled. More recently, by retaining the original definitions of disability, the ADAAA expanded the definition of "major life activities" to include activities such as sleeping, standing, lifting, bending, concentrating, communicating, thinking, and working and effectively expanded the number of workers who qualify for coverage under the Act.[51] A list of "major bodily functions" is also now covered by the ADAAA, such as functions of the immune system, normal cell growth, and respiratory system. A disease that causes intermittent impairment or that is in remission is considered a disability if it would substantially limit a major life activity when active. The goal of these changes was to focus workplace accommodation for "qualified individuals." A qualified individual is a person who has the requisite skills and experience to do the job and "can perform the essential job tasks with or without reasonable accommodation" without risk of direct threat to self or others. Knowing what the essential job tasks are and what is required to do them physically is essential for the physician to be able to make this determination. This information is often contained in the workers' position description. The worker's job title typically provides insufficient information.

Essential job tasks are defined as the specific functions that an individual in that position must be able to perform without aid or with the assistance of reasonable accommodation. Factors involved in determining whether or not a job activity is an "essential function" include whether all employees in the position are required to perform the task, the position exists to perform the function, the frequency and duration of the job function, and whether other employees are available and qualified to perform the function.

Reasonable accommodation is defined as a modification or adjustment to the job, work environment, or way things are usually done that enables a person with a disability to perform the essential job function. Physicians may suggest means by which reasonable accommodation may be made, but the employer decides whether or not the accommodation is reasonable on a case-by-case basis. Examples of reasonable accommodation for individuals with respiratory impairment can include modification of the workstation to allow use of a wheelchair, scooter, or oxygen equipment; decreasing the need to travel distances, lift or push objects; and/or allowing written rather than lengthy verbal communication. A direct threat exists when an individual poses a significant risk of substantial harm to the health or safety of herself, himself, or others and the risk cannot be reduced to an acceptable level with reasonable accommodation. The risk needs to be defined in terms of the specific behavior or physical limitation that would pose the direct threat, the

duration of the risk, the nature and severity of the potential harm, and the likelihood and imminence of the potential harm. An example of direct threat would be use of oxygen in an area with open flames or sparking materials.

FAMILY AND MEDICAL LEAVE ACT

The Family and Medical Leave Act entitles eligible employees up to 12 weeks of unpaid leave with benefits per year due to a serious health condition of their own or to care for a spouse, child, or parent with a serious health condition.[54] There are additional provisions for child care and service members and their families. Eligibility is based on the number of hours the patient has worked for the employer and the size of the employer. Physicians must complete a standardized form indicating the condition and the expected frequency and duration of the work absences.

as age, education, and attitudes, and *environmental factors*. *Facilitators* are contextual factors that enhance functioning and *barriers* are contextual factors that restrict or limit functioning. This model is a framework by which to describe health status, functioning, and disability in a uniform manner across a wide range of medical disorders on an international level, in the context of a given patient's health condition(s).

Implementation and, in particular, clinical use of the ICF framework has been very limited; the development of tools by which to apply it are complex and there are no tools for many medical conditions. Considerations for use include the ICF domains to be documented (activities and participation, body functions, and/or environmental factors), the perspectives to take (patient, clinician, etc.), the data collection tools to use (when they exist), and how to report the assessment.[55] Several different classification systems have been developed called *sets*, which include generic sets and core sets, which are condition- and/or population-specific lists of ICF codes that limit the categories of the ICF to those considered to be directly relevant. The development of sets is done through a multistage, multidisciplinary consensus and validation process.[56,57] The WHO Disability Schedule 2.0 is a generic set that measures six domains (cognition, mobility, self-care, getting along, life activities, and participation) to assess health status and disability generically among patients with different medical conditions.[58] The data are subjective and many of the questions relate to basic ADLs. Its use as a stand-alone tool in the description of respiratory conditions has been limited to a population of patients with pulmonary hypertension.[59] *ICF core sets* for respiratory diseases are also limited. A core set was developed for patients with cardiopulmonary conditions in rehabilitation facilities.[60] The only disease-specific core set is for obstructive pulmonary diseases. This was developed through a consensus process in 2004, including both a *comprehensive ICF core set*, which encompassed all relevant categories, and a *brief ICF core set*, which encompassed the minimum categories that need to be considered.[61] During validation in 2013 and 2014, most of the categories in the comprehensive ICF core set were confirmed from the patient's perspective, although additional categories were also identified by them.[62] Similar results were found in a validation study of the brief ICF obstructive pulmonary disease core set.[63] The core set was recently revised and applied in a pilot study of patients with respiratory diseases in the rehabilitation setting.[64] Thus, there remains no consensus set that has been validated from multiple perspectives. Core sets for other respiratory diseases need to be developed. Subsequently, consideration of how this schema would be applied within benefits and compensation systems would need to be determined. Use of the ICF has been endorsed in the occupational setting, specifically review of personal and environmental contextual factors to identify facilitators and barriers to recovery, which can help identify additional treatment that is needed or help determine when there is no additional treatment likely to improve the condition (i.e., the patient is considered to be at MMI).[65] We would recommend that the latter be applied with caution, and only under the rubric of specific consensus guidelines developed from a multidisciplinary perspective.

The Institute of Medicine had developed alternative models to update the ICIDH that included pathology, impairment, functional limitation, and disability.[66,67] While their most recent report *Future of Disability in America* (2007) ultimately endorsed the ICF as the basic framework, it called for further refinement of the model to address its shortcomings.[68] One of its authors and others in the United States continue to call for refinement and updating of the ICF model; concerns include the limited distinction between activity and participation in the model, lack of quality of life measures, need for a dynamic model to include factors that affect change of an individual into different levels of functioning and disability, and an updated model to reflect current understanding of both the determinants and consequences of health conditions, not only for patients generically, but also within the context of activity and participation important to the individual patient.[69–71]

Consideration of limitations in the current assessment of respiratory impairment include the following:

1. Use of FVC as the basis for impairment in restrictive lung disease instead of total lung capacity. Low FVC can be caused by submaximal inspiratory or expiratory effort and/or peripheral airflow obstruction.[25] One study showed the predictive value of reduced FVC to be less than 60% for the presence of a true restrictive deficit.[72] Others report concern about reduced lung function test results, including FVC, in obesity,[73,74] but there are no established criteria by which to account for obesity in testing.
2. Use of $\dot{V}O_{2max}$ in isolation without consideration of the criteria listed in the ATS guidelines for respiratory impairment based on exercise physiology, including reason for test termination. The average energy requirements of a number of jobs are listed in eTable 35.4. Major limitations to this approach include the following: (1) little published data that substantiate its use; (2) heterogeneous methods of assessing maximal oxygen uptake[75]; (3) the actual work performed by workers with the same job title can vary markedly from employer to employer or among employees with differing seniority working for the same employer; (4) the questionable relationship between exercise tolerance on the treadmill or bicycle and performance on the job[76]; and (5) the lack of consideration of modifying factors such as the need to talk or use personal protective equipment while performing the work.[77] Additionally, these existing tables are decades old and often no longer reflect the work environment. Other than specifying $\dot{V}O_{2max}$, the *AMA Guides* do not provide any details for how it should be interpreted, including the predicted normal values of the specific test performed (i.e., cycle ergometry versus treadmill, or delineation of the reason for test termination), because nonrespiratory causes such as excessive blood pressure, cardiac abnormality, leg pain, or suspicion of inadequate effort should clearly not form the basis for assignment of impaired ability due to respiratory impairment. The use of exercise testing and $\dot{V}O_{2max}$ overestimates impairment in older workers. As an alternative, it has been proposed that $\dot{V}O_{2max}$ be expressed as percentage of predicted,[78] although this is not in standard use at this time. Although advances have been

made, the recent ATS Statement on Cardiopulmonary Exercise Testing[36] noted that a comprehensive updated framework for impairment/disability is needed urgently.

3. Mandating the use of outdated reference equations that apply to fewer ethnic groups. Neither the Fifth Edition or Sixth Edition of the *AMA Guides* uses the most recent recommended reference values. The ATS/ERS now recommends the use of the *Global Lung Function Initiative* (GLI) 2012 predicted normal values for spirometry that are applicable globally to different ethnic groups. This includes reference equations for whites, Blacks, and North and Southeast Asians up to 95 years of age. A composite equation is used for those of mixed ethnic origin or not represented by one of those four groups.[79] Reference values for DL_{CO} up to age 85 years were also developed.[80]
4. Use of bronchodilator response based on change in FEV_1 from baseline. The assessment of bronchodilator response is based on percent change in FEV_1 from baseline. The ATS guidelines recommend a postbronchodilator change of 12% and 0.2 L increase in FEV_1 or FVC.[25] Change in FVC may be a better measure in some patients, such as those with more severe airflow obstruction.[81,82] Expressing bronchodilator response in terms of percent of baseline can bias impairment toward those with lower baseline values.[82,83] Expressing change in terms of difference in percent of predicted avoids this bias, as well as bias towards taller men when absolute change in volume is used; however, there is not agreement on the value that establishes a bronchodilator response.[82–84]
5. There may be better methods of relating impairment to disability. Consideration of multiple facets of this complex topic has been outlined.[85]

Key Points

- *Impairment* refers to the degree of loss of normal use or function of a body part or organ.
- *Disability* refers to any resulting alteration in the individual's capacity to perform customary activities. That definition has been expanded by the Institute of Medicine to include the "gap between a person's capacities and the demands of relevant, socially defined roles and tasks in a particular physical and social environment," emphasizing the bidirectional nature of the model and the importance of factors in the environment that facilitate or present obstacles to functioning and participation.
- *Maximum medical improvement* (MMI) is the point at which permanent impairment can be assessed. MMI is achieved when the diagnosis has been well defined, the condition is stable, and medical treatment has either been optimized or reasonable options have been exhausted.
- The Americans with Disabilities Act Amendments Act of 2008 greatly expanded the definition of disability to focus on workplace accommodation of "qualified individuals." A qualified individual is a person who has the requisite skills and experience to do the job and "can perform the essential job tasks with or without reasonable accommodation" without risk of direct threat to self or others.
- *Reasonable accommodation* is defined as a modification or adjustment to the job, work environment, or the way things are usually done that enables a person with a disability to perform an essential job function.
- An *impairment evaluation* is a medical evaluation that typically includes history, including a detailed occupational and environmental history and description of limitations in activities of daily living; physical examination; and review of medical records and diagnostic test results that establish the respiratory condition. If the worker is at MMI, a permanent impairment rating can be performed. The physician may be asked to address causation, which is usually the relationship of the disease to workplace exposures, the need for work restrictions, future medical needs, and possibly apportionment of impairment.
- An *impairment rating* is a numeric value from 0–100% that represents the percent loss of total body function due to the respiratory system. This numeric value helps form the basis for the monetary award given to workers with permanent impairment that remains after reaching MMI.
- In addition to state and federal workers' compensation programs, other special benefit and compensation programs exist for certain groups of workers, including miners, Department of Energy workers, veterans, and radiation-exposed workers.

Key Readings

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SECTION F

EVALUATION OF COMMON PRESENTATIONS OF RESPIRATORY DISEASE

36 DYSPNEA

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INTRODUCTION

Each minute of every day, we initiate approximately 10 to 16 breaths. Most of the time, we give little thought to this process, but when there are alterations in the respiratory system, from central control to the ventilatory pump to gas exchange, severe physical discomfort and emotional distress may result. The uncomfortable or unpleasant sensations associated with breathing are termed dyspnea, and as many as one-quarter of middle-aged and older adults may suffer from this experience.[1] The prevalence of dyspnea in noncritically ill hospitalized patients is reported in 16% of admissions in the first 24 hours, with higher numbers (23%) for patients admitted via the emergency department[2] and 49% in critically ill patients.[3]

The impact of breathing discomfort on one's functional status can be significant, and dyspnea is routinely used as a component of quality-of-life measures. In addition, there are increasing data demonstrating that dyspnea is an independent predictor of mortality in patients, with particular emphasis on those at risk for and/or suffering from cardiorespiratory diseases.[4–6] Consequently, identification of patients with breathing discomfort becomes important. Efforts to elicit this symptom, however, may be impaired by the tendency of patients to avoid activities that provoke breathing discomfort by altering their lifestyle or avoiding physical exertion.[7] These reductions in physical activity may lead to ever-worsening cardiovascular and muscular deconditioning, which intensifies dyspnea, leading to additional limitations and a vicious cycle in which

TABLE 36.1 Relationship Among Qualities of Dyspnea, Physiology, and Disease States

Quality of Dyspnea	Physiology	Disease States
Air hunger, urge to breathe, need more air	Stimulation of respiratory controller via chemoreceptors, pulmonary receptors, vascular receptors	Pneumonia, pulmonary edema, pulmonary embolism, COPD with acute gas exchange abnormalities, asthma, pleural effusion, toxic inhalations
Chest tightness	Stimulation of pulmonary receptors	Asthma, pulmonary edema with bronchospasm, toxic inhalations with bronchospasm
Cannot get a deep breath	Stimulation of respiratory controller; dynamic hyperinflation	COPD, asthma
Increased work or effort to breathe	Mechanical load on the respiratory system; neuromuscular weakness	COPD, asthma, obesity, kyphoscoliosis, Guillain-Barré, myasthenia gravis
Breathing more	Increased ventilation; stimulation of metaboreceptors in muscles	Exercise, cardiovascular deconditioning

breathlessness leads to diminished exercise, which leads to greater deconditioning and finally to more breathlessness.[8]

In the *intensive care unit* (ICU), as our understanding of ventilator-induced lung injury has led to strategies of mechanical ventilation that emphasize low tidal volume, we must be cognizant of the impact of these strategies on dyspnea. In the face of a high drive to breathe, constrained tidal volume is a powerful provocation for dyspnea[9] and may contribute to some of the patient ventilatory dyssynchrony seen in these individuals. In addition, breathing discomfort during mechanical ventilation may be a factor in the emotional and behavioral complications seen in survivors of acute respiratory failure.[10]

The physiologic stimuli that provoke dyspnea are varied but have a common effect of increasing the output from the central controller and increasing the drive to breathe. Although inputs from a range of receptors throughout the body may contribute to the perception of dyspnea and the verbal phrases or descriptors used by patients to characterize their sensations, the increased neural output from the controller is most closely associated with the sensation of "air hunger" or a need or urge to breathe. The various descriptors used by patients may provide insights into the pathophysiologic conditions contributing to breathing discomfort. Furthermore, various psychological factors may have an impact on the perception and interpretation of sensations (e.g., "Is this 'normal'?" or "Is this a 'symptom' of a disease?"), and the sensations of breathing discomfort may evoke fear and anxiety.[11–13] This interplay of sensation and emotional or affective state of the individual may explain, in part, the variability between physiologic measures of the severity of cardiorespiratory disease and the intensity of the associated breathing discomfort.

DEFINITION OF DYSPNEA

Many words have been used by patients and doctors to describe breathing discomfort, from shortness of breath to breathlessness to dyspnea. Although the medical term *dyspnea* derives from the Greek word for "difficulty breathing," the most widely used definition was promulgated in a consensus statement of the American Thoracic Society,[14] which states: "Dyspnea is a term used to characterize a subjective experience of breathing discomfort that is comprised of qualitatively distinct sensations that vary in intensity. The experience derives from interactions among multiple physiological, psychological, social, and environmental factors, and it may induce secondary physiological and behavioral responses." The emphasis on a "subjective experience" makes clear that dyspnea is a symptom that can only be described by the patient; it is distinct from physical findings or signs observed and interpreted by doctors or families as evidence of "respiratory distress." The definition further reinforces the complex interplay of physiologic changes, the psychological state of the patient, and the social and environmental conditions leading to the symptom.

LANGUAGE OF DYSPNEA

Doctors have been trained for years to inquire about the quality of pain when caring for a patient with complaints such as headache, abdominal, or chest pain; the characteristics of the pain provide clues to the etiology of the problem.[15] Less well known is a growing body of literature showing a similar range of verbal descriptors used to characterize breathing discomfort. As with pain, the descriptors may provide clues to the underlying physiologic derangements and diagnoses contributing to dyspnea, as well as the emotional and behavioral responses to the discomfort.

QUALITATIVE PHRASES—THE DESCRIPTIVE DIMENSION OF DYSPNEA

For the healthy individual, breathing is taken for granted; we are generally unaware of it. With exercise, we are cognizant of "breathing more" or that our breathing becomes "heavy." But what does it feel like to have dyspnea due to airway resistance or a stiff lung or chest wall, or due to muscle weakness? The only way to answer that question is to inquire systematically about the qualities of the sensation in individuals experiencing dyspnea.

Early investigations proceeded in two directions: (1) systematic questioning of patients with a variety of cardiorespiratory diseases who were experiencing dyspnea and (2) laboratory studies in which investigators induced dyspnea in healthy individuals using interventions to increase respiratory drive or by imposing mechanical loads on the respiratory system and inquired about the resulting sensations.[16–18] From these and subsequent studies, relationships between disease states (e.g., asthma, COPD), physiology (e.g., increased respiratory drive, dynamic hyperinflation), and descriptors began to emerge (Table 36.1). "Air hunger" or "not getting enough air" was associated with stimulation

of the respiratory controller, that is, an increased drive to breathe. "Chest tightness" was quite specific for bronchoconstriction, and an "unsatisfied inspiration" or "inability to get a deep breath" was associated with dynamic hyperinflation. A sense of "increased effort or work of breathing" is characteristic of mechanical loads on the respiratory system or of inspiratory muscle weakness or fatigue. None of these is absolutely sensitive or specific for a particular condition, of course, and multiple physiologic derangements may be present in a single patient. Nevertheless, awareness of these aspects of a patient's dyspnea may be quite helpful in a physician's analysis of the patient's problem.[19]

The few cross-cultural studies performed to investigate the qualitative sensations of dyspnea have found similar associations. Many of the dyspnea questionnaires that have been developed have been translated into different languages and are being used and tested around the world.[11,13] Children also appear to be capable of making qualitative distinctions among different types of dyspnea.[20]

EMOTIONAL PHRASES—THE AFFECTIVE DIMENSION OF DYSPNEA

As noted in the discussion of the definition of dyspnea, breathing discomfort may be affected by one's psychological state, and the experience of dyspnea may provoke strong emotional responses. As we assess the quality and severity of dyspnea, we note that both of these components of breathing discomfort can have implications for the emotional response of the patient. For example, air hunger evokes a stronger affective response than does an increase in the work of breathing.[12] As the intensity of air hunger becomes very high, patients may describe a suffocating feeling; this word is rarely invoked for mild dyspnea. The Multidimensional Dyspnea Profile and the Dyspnea-12 instruments have attempted to quantify and characterize the affective dimension of dyspnea.[11,13]

Because dyspnea can invoke such strong emotional reactions, patients often avoid activities that can provoke the sensations. Individuals with COPD, for example, may limit their activity at home to avoid dyspnea ratings greater than 3 (on a 0–10 scale).[7] Pulmonary rehabilitation programs have been shown to increase exercise capability in patients with COPD without altering lung function; this benefit is likely multifactorial and may include a degree of desensitization to dyspnea by providing patients with a sense of control or mastery over their symptom,[21] that is, by reducing the affective component of the dyspnea. As we increasingly take a patient-centered approach and make greater efforts to relieve discomfort, particularly for individuals with refractory cardiopulmonary disease, we must incorporate considerations of the emotional domain of dyspnea.[22]

MECHANISMS OF DYSPNEA

Perception of breathing discomfort (dyspnea) is an interoceptive process resulting from complex neurophysiologic processing that is incompletely understood.[23] Figure 36.1 is a schema of experimentally established components of this perception; variation in both the number and relative contribution of these elements likely accounts for the differing qualities of dyspnea and the widely observed established disjunction between symptom severity and objective clinical impairment.[24]

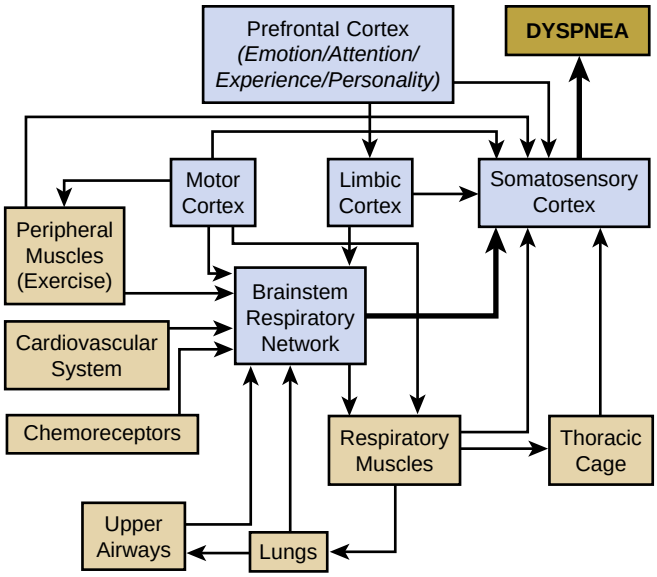

Figure 36.1 Neural basis of dyspnea perception. This schematic summarizes the key elements of the neural substrate for dyspnea perception derived from experimental and clinical studies. Dyspnea perception in the somatosensory cortex primarily reflects the degree of centrally generated drive to respiratory muscles from brainstem respiratory neurons. Respiratory drive emanating from the motor cortex and/or limbic cortex may modulate dyspnea either by direct innervation of the somatosensory cortex or via the brainstem. The primary inputs increasing reflex respiratory output are the central and peripheral chemoreceptors, pulmonary irritant and C fibers, peripheral muscle mechanoreceptors and metaboreceptors, and cardiac receptors. Slowly adapting pulmonary stretch receptors, thoracic cage mechanoreceptors, and upper airway flow receptors may ameliorate dyspnea by direct or indirect (via brainstem) innervation of the somatosensory cortex. Higher central neural activity from the prefrontal cortex can modulate dyspnea in either direction. Peripheral and central neural components of dyspnea are identified in orange and blue, respectively.

Although dyspnea can be experienced at rest, it typically presents clinically as a problem when it first appears at uncharacteristically low levels of exertion. With exertion, sensations of air hunger (also identified as "uncomfortable need to breathe" or "unsatisfied inspiration") and of the work of breathing increase together.[25] They can be separated experimentally, with the former being reported as more unpleasant than the latter in healthy subjects.[12] Similarly, patient populations identify greater morbidity associated with the air hunger component along with increasing disease severity.[25,26] Studies evaluating respiratory discomfort during exertion usually measure unimodal ratings of its intensity as exercise progresses. Such ratings, typically reported as dyspnea intensity, capture an individual's common experience of shortness of breath but not its qualitative components.

When studying dyspnea, investigators may use nonexercise stimuli to induce the sensation, notably constrained ventilation or the addition of an external respiratory load. Although the former produces marked air hunger, the latter is likely perceived as predominantly increased work of breathing at lower loads, with air hunger appearing with more severe loading. Again, these estimates of perceived respiratory discomfort are usually reported as dyspnea intensity. In reviewing the mechanism of dyspnea, this chapter will summarize findings from both healthy and dyspnea-prone populations in whom respiratory discomfort has been induced in a variety of ways.

Like all symptoms, dyspnea results from changes in neural activity within the cortical and subcortical structures of the brain involved in perception (see Fig. 36.1). Respiratory-related afferent information from the upper airway, lungs, chest wall, and chemoreceptors, as well as other signals from the cardiovascular and skeletal muscle systems, provide peripheral inputs that can contribute to the perception of dyspnea. A consistent finding is that, during ventilatory stimulation (e.g., exercise), the intensity of dyspnea correlates with the level of ventilation and that this relationship becomes steeper in the presence of respiratory mechanical impairment.[25] However, when examined relative to central respiratory drive (assessed from measures of esophageal pressure or diaphragmatic electromyography), dyspnea shows a strong correlation to central respiratory drive, independent of mechanical constraints.[27] This supports the view that the central motor command to breathe (respiratory drive) constitutes a key component of the experience of dyspnea.[28] This concept is able to explain the dyspnea noted in nonrespiratory conditions associated with increased respiratory stimulation; these include cardiac arrhythmias, deconditioning, anemia, and anxiety.

The importance of activation of respiratory-related neurons in the brainstem for the genesis of dyspnea is apparent from observations that, in healthy persons, experimental hypoxia, hypercapnia, metabolic acidosis, and exercise all result in an equivalent level of dyspnea relative to the level of ventilatory stimulation.[29] However, the relevance of increased ventilatory drive in the genesis of dyspnea is less clear. On the one hand, volitional isocapnic hyperpnea in patients with COPD causes little dyspnea compared with the same ventilation induced by hypercapnia.[30] On the other hand, in amyotrophic lateral sclerosis, dyspnea is exacerbated in the presence of cortically induced accessory muscle activation.[31] The multifactorial nature of dyspnea perception could accommodate these different observations.

The role of afferent information from respiratory-related receptors in the genesis of dyspnea is variable. As noted earlier, ventilatory activation via central and/or peripheral chemoreceptors or ill-defined ergoreceptors is associated with a level of dyspnea closely linked to the stimulus-independent degree of reflex (brainstem) respiratory drive. Moreover, in the absence of a ventilatory response to a given level of reflex stimulation, the intensity of dyspnea is potentiated.[32,33] This mismatching of ventilatory response to the ventilatory stimulus has been termed *efferent-afferent dissociation,* or neuromechanical dissociation.[25] Indeed, increasing afferent feedback can lessen the sensation of dyspnea. This concept is exemplified by volume-related feedback, with breath-holding as an extreme example. This inflation-related attenuation of dyspnea has been observed in the absence of mechanoreceptor feedback from the chest wall,[9] implicating pulmonary vagal receptors. Support for this comes from the observation that inhalation of furosemide, which potentiates slowly adapting stretch receptor activity in an animal model, has been shown to ameliorate the sensation of experimental dyspnea in healthy subjects.[34] On the other hand, volume-related relief of dyspnea has been documented in the presumed absence of pulmonary vagal afferent feedback,[35] implicating chest wall receptors. A role for afferent feedback from the respiratory system in the relief of dyspnea is consistent with clinical reports of the benefits of using a facial fan[36] (albeit via stimulation of trigeminal [not vagal] receptors) or chest wall vibration.[37] By contrast, conditions thought to activate lung irritant receptors and/or pulmonary C fibers (e.g., pulmonary edema, atelectasis, congestive heart failure) may contribute to dyspnea via vagal nerve afferents either directly or by modulating other sensory inputs that give rise to dyspnea.[38]

In light of the above, dyspnea accompanying respiratory impairment can be accounted for as the perception of the increased respiratory drive necessary to achieve adequate ventilation by a mechanically constrained respiratory apparatus. This would encompass both obstructive and restrictive disorders, including extrinsic restriction, for instance, or amyotrophic lateral sclerosis or myasthenia gravis. This concept fits with the observation that, in COPD patients, progressive hyperinflation is associated with increasing dyspnea because ventilatory demands require greater respiratory muscle activity to overcome increased elastic work at high lung volumes and to offset the foreshortening of inspiratory muscles that places them at a mechanical disadvantage.[25] Moreover, an increased end-expiratory lung volume is likely to exacerbate dyspnea via increased efferent-afferent dissociation.

The idea that dyspnea is the perception of centrally generated respiratory neural activity extends to conditions in which lung disease is not the primary problem. Thus the dyspnea of heart failure might be accounted for in terms of a heightened respiratory drive secondary to expiratory flow limitation[39] or poor peripheral muscle function.[40] Poor peripheral muscle function might also explain the dyspnea seen with anemia and deconditioning.

The sensation of dyspnea, like pain, has a psychological dimension. Dyspnea is worse when it is unexpected, when it happens in inappropriate situations, and when it is perceived by the patient to be dangerous.[41] Studies in healthy subjects and in patients with underlying disease have suggested that the perception of the intensity of breathlessness may be influenced by their prior experience of the sensation.[42] Moreover, experimentally induced changes in mood[43] have been shown to modulate exertional dyspnea independent of respiratory drive. Anxiety is an established cause of dyspnea and can affect pulmonary rehabilitation outcomes.[44] In patients with the hyperventilation syndrome, both dyspnea and ventilation can increase dramatically in the absence of any known physiologic stimulus to breathe[45] and, in patients with panic attacks, most report troublesome dyspnea.[46]

Neuroimaging technologies, principally positron emission tomography and functional magnetic resonance imaging, have been applied to study the neural basis of experimentally induced dyspnea. Despite methodologic differences in dyspnea genesis, a consistent pattern of activation of limbic and paralimbic structures, especially the anterior insular cortex, anterior cingulate gyrus, amygdala, and cerebellum, has been observed.[47] Activation of these phylogenetically ancient regions of the brain has been seen in brain imaging studies of pain, thirst, and hunger and is consistent with the idea that dyspnea is a primal experience associated with behaviors intended to counteract a threat to survival.[48] Whether these areas constitute the primary neural substrate for dyspnea or are more reflective of a generalized morbid experience is unclear. Recent

commentary suggests that a more sophisticated approach to the analysis of functional brain mapping data is needed to gain improved insights into the neural basis of the complex perceptual experience of dyspnea.[49]

In summary, dyspnea may develop when there is an (1) increased central respiratory drive secondary to exercise, hypoxia, hypercapnia, or other afferent input; (2) increased requirement for the respiratory drive to overcome mechanical constraints or weakness; and (3) altered central perception in the presence of efferent-afferent dissociation.

ASSESSMENT OF DYSPNEA

PSYCHOMETRIC MEASUREMENT OF DYSPNEA INTENSITY

Like many clinical symptoms, dyspnea severity can be quickly assessed using a simple unidimensional scale. Numerical rating scales (0–10) and visual analog scales (a horizontal or vertical line usually 10 cm in length) have been widely used in clinical practice and adapted for quantifying dyspnea. The Borg Scale (modified from a preexisting scale for perceived exertion) is a variant of the numerical rating scales with verbal descriptors placed at appropriate points along the scale. All scales request a rating of dyspnea intensity between the extremes of "none" and "maximal." All scales have been validated and compared with one another and, in practice, any one of them should provide a reliable "single point in time" estimate of an individual's dyspnea intensity.[50] Variations on numerical-based assessment of dyspnea have been developed using pictorial representations for use in children[51] and scaling of observed distress in individuals unable to provide a report of their dyspnea (e.g., in the ICU).[52]

MULTIDIMENSIONAL ASSESSMENT OF DYSPNEA

There has been a growing focus on extending the assessment of dyspnea beyond the intensity domain to include the qualitative and affective components of this complex symptom. Using a multidimensional approach, modeled on those used in pain research, investigators have developed a number of validated instruments that are being used in research and clinical studies. A number of these are referenced in the earlier "Language of Dyspnea" section and have been reviewed in the overall context of dyspnea assessment.[11]

EXERCISE PERFORMANCE AS AN INDICATION OF DYSPNEA

Exercise testing is frequently used to assess the causes and functional impact of an individual's dyspnea. Cardiopulmonary exercise testing requires specialized facilities but offers the most definitive approach in evaluating the functional pathophysiologic basis of unexplained dyspnea.[53] Two widely used field tests are the 6-minute walk test and shuttle walking test,[54] which are easy to perform and require minimal equipment. When an exercise test is limited by symptoms, it is important to ask the patient the exact reason for stopping. Although the patient may appear to be in respiratory distress, often joint pain, leg fatigue or discomfort, or generalized weakness is the actual limiting factor.

REPORTED EXERCISE LIMITATION DUE TO DYSPNEA

Early attempts to evaluate the severity of dyspnea involved patient assessments of their own exercise tolerance (e.g., the five-point Medical Research Council scale[55] and its modified version, the American Thoracic Society scale); it is important to remember that such measures assess the impact of dyspnea rather than dyspnea directly. More recently, this simple assessment of *dyspnea* (D) has been supplemented with measures of *body mass index* (B), FEV_1 (O = *obstruction*), and 6-minute walk distance (E = *exercise capacity*) to yield a BODE index, a validated prognostic indicator in COPD.[56] The Baseline Dyspnea Index, a rater-administered test, was developed to rate patients with regard not only to the "magnitude of the task" that elicits dyspnea (e.g., hills compared with level ground) but also to the impact of dyspnea on activities of daily living and the effort required to produce dyspnea.[57] Measurements can be repeated over time or in response to interventions. Several easy-to-use self-administered questionnaires have been developed to assess functional limitation due to dyspnea but in general have not found widespread use.[58]

QUALITY OF LIFE AND DYSPNEA

The negative impact of dyspnea on an individual's quality of life has been increasingly recognized since the mid-1980s and now is an important outcome measure in studies of therapeutic intervention for COPD/dyspnea. Two questionnaires, the Chronic Respiratory Disease Questionnaire and the St. George's Respiratory Questionnaire, are used most often. The Chronic Respiratory Disease Questionnaire is a rater-administered questionnaire with 20 items that focus on four aspects of illness: dyspnea, fatigue, emotional function, and the patient's feeling of control over the disease.[59] Dyspnea is evaluated on a seven-point scale in relation to the five most important activities provoking dyspnea during the previous 2 weeks. In effect, the Chronic Respiratory Disease Questionnaire assesses how breathing sensations alter the quality of the patient's life. The St. George's Respiratory Questionnaire is a self-administered questionnaire with 76 items addressing symptoms, activity, and the impact of disease on daily life. Dyspnea is not evaluated specifically but is included with other respiratory symptoms, such as cough, sputum production, and wheezing.[60]

DIAGNOSTIC APPROACH TO THE PATIENT WITH DYSPNEA

PHYSIOLOGIC CATEGORIES OF DYSPNEA IN THE CONTEXT OF THE RESPIRATORY SYSTEM

Because dyspnea is an integrated sensation that reflects a range of sensory inputs (e.g., from lungs, chest wall, airways, vascular structures, chemoreceptors) and motor outputs to the ventilatory muscles, it is best to consider dyspnea

TABLE 36.2 Relationships Among Physical Examination, Physiology, and Disease States

Physical Examination	Physiology	Disease States
Tachypnea, use of accessory muscles of inhalation	Stimulation of respiratory controller via chemoreceptors, pulmonary receptors, vascular receptors	Pneumonia, pulmonary edema, pulmonary embolism, COPD with acute gas exchange abnormalities, asthma, pleural effusion, toxic inhalations
Pulsus paradoxus, tripod position, wheezes	Stimulation of pulmonary receptors and increased airway resistance	Asthma, pulmonary edema with bronchospasm, toxic inhalations with bronchospasm
Pulsus paradoxus, accessory muscles of inhalation	Increased airway resistance, decreased respiratory system compliance, neuromuscular weakness	COPD, asthma, kyphoscoliosis, Guillain-Barré, myasthenia gravis, diaphragmatic paralysis
Expiratory abdominal rounding	Creation of intrinsic positive end-expiratory pressure	Pulmonary edema
Paradoxical motion of abdomen or rib cage	Movement of abdomen and chest due to changes in intrathoracic pressure and weakness of either the diaphragm (inward movement of abdomen on inspiration) or the intercostal muscles (inward movement of rib cage on inspiration)	Diaphragm paralysis (paradoxical abdominal motion); spinal cord injury (paradoxical rib cage motion)
Kussmaul breathing	Increased alveolar ventilation (with a lower V_D/V_T ratio) to compensate for metabolic acidosis.	Diabetic ketoacidosis, severe lactic acidosis, ingestions leading to anion gap acidosis
Dullness on percussion	Absence of air in thorax	Pleural effusion; dense consolidation/ pneumonia
Hyperresonance on percussion	Diminished lung parenchyma	Pneumothorax, bullous emphysema
Crackles/rales	Reduced compliance of the lung	Interstitial lung disease, pneumonia, pulmonary edema
Rhonchi	Turbulent flow secondary to airway inflammation	Pneumonia, bronchitis

V_D/V_T, ratio of dead space to tidal volume.

initially in terms of the respiratory system and of the ways in which a multitude of diseases can manifest via derangements in the components of that system. This will help us make sense of what is otherwise a long list of possible diagnostic considerations, particularly for the evaluation of the patient with chronic dyspnea.

In concert with the cardiovascular system, the ultimate goal of the respiratory system is to get oxygen from the atmosphere to alveoli to the blood to the organs and cells of the body and then to eliminate carbon dioxide, the product of metabolism. Clinically, dyspnea can be thought to arise in one of four major ways:

1. When the elements of the respiratory system (the respiratory controller, the ventilatory pump, and the gas exchanger) are altered in a way that leads to the development of hypoxemia and/or hypercapnia, with consequent stimulation of chemoreceptors and the respiratory controller;
2. When there is stimulation of discrete sensory receptors throughout the airways, lungs, chest wall, and vasculature;
3. When a mechanical load is imposed on the respiratory system (e.g., increased airway resistance, decreased lung or chest wall compliance); or
4. When neuromuscular weakness arises and inhibits the ability of the body to handle even normal mechanical loads.

Thus, rather than approach the patient by asking which organ system is causing the problem, consider these physiologic categories and the underlying pathology that might contribute to them (Table 36.2).

The first major cause of dyspnea is disease of the respiratory system, leading to abnormal blood gases. Hypoxemia and hypercapnia can be the result of derangements of the gas exchanger (the alveoli and pulmonary vasculature) or due to hypoventilation consequent to suppression of the respiratory control system and/or neuromuscular weakness. The last two can be easily distinguished by the respiratory rate (reduced rate when there is suppression of the controller; rapid rate when there is neuromuscular weakness). The *alveolar to arterial oxygen tension difference* [$(A–a)P_{O_2}$] is also a key indicator of whether the gas exchanger itself is abnormal; when the $(A–a)P_{O_2}$ is greater than normal (i.e., larger than 0.3 × age of the patient), a gas exchanger abnormality is contributing to the problem. One should remember, however, that hypoxemia alone is a relatively weak stimulus for the controller and leads to relatively low intensity dyspnea, and acute hypoxemia secondary to suppression of the controller will not typically lead to breathing discomfort. Acute hypercapnia (or metabolic acidemia), in contrast, can lead to more significant change in ventilation and dyspnea. As noted earlier, the dyspnea associated with stimulation of the controller is generally characterized as a sensation of air hunger, urge to breathe, or "I cannot get enough air."

The second cause of dyspnea comes from stimulation of various sensory receptors. There are multiple receptors throughout the cardiorespiratory system that can stimulate or reduce the drive to breathe from the respiratory controller and contribute to or lessen the intensity of dyspnea. Some of the best studied are unmyelinated nerve endings, stretch receptors, pressure receptors, flow receptors, and metaboreceptors. Pulmonary C fibers (also known as juxtacapillary receptors) are *unmyelinated nerve endings* that may be triggered by inflammation and inhaled chemicals or toxins, as well as by increased pulmonary capillary pressures associated with left heart failure. Airway rapidly adapting

stretch receptors (also known as irritant receptors), in addition to responding to inhaled irritants, are triggered by deflation of the lung (e.g., atelectasis), which can cause an intense sensation of a need to take a deep breath. The dyspnea associated with large pleural effusions, for example, is likely due in part to atelectasis of underlying lung tissue, as well as displacement outward of the chest wall, which increase the mechanical load on the respiratory system. In contrast, lung inflation with large tidal volumes activates slowly adapting stretch receptors in the airways and may diminish the sensation of air hunger (see discussion of efferent-afferent dissociation in the section "Mechanisms of Dyspnea"). The sense of "tightness" associated with bronchospasm most likely originates with receptors stimulated by bronchospasm, most likely irritant receptors. *Pressure receptors* throughout the pulmonary vasculature and right heart may lead to dyspnea associated with primary pulmonary vascular disease (e.g., pulmonary emboli) and left ventricular failure. *Flow receptors* are essentially temperature receptors in the airways (higher flow on inspiration leads to cooling of the receptors); they provide information on inspiratory flow, which assists the brain in monitoring the response of the ventilatory pump to efferent messages from the controller (central drive) and the degree of efferent-afferent matching. There is one additional set of receptors, the *metaboreceptors* or ergoreceptors, located in skeletal muscle, which are apparently stimulated in the setting of low oxygen delivery and play a particular role in the dyspnea arising when we reach the limits of our cardiovascular fitness during exercise and in heart failure.[61]

The third cause, increased mechanical loading on the respiratory system, comprises some of the most common diseases we encounter clinically, that is, COPD and asthma, as well as chest wall problems, such as obesity and kyphoscoliosis. Increased airway resistance and/or decreased respiratory system compliance may lead to a need to exert greater effort to maintain normal alveolar ventilation.

Finally, the fourth cause of dyspnea arises from abnormalities of the neuromuscular system. Diseases that impair neuromuscular function, for instance, Guillain-Barré and myasthenia gravis, lead to dyspnea when the controller attempts to maintain normal alveolar ventilation.

HISTORY

As with all of medicine, a careful history, guided by one's understanding of the pathophysiology of the underlying symptom, is key to creating a differential diagnosis that leads to an efficient yet complete evaluation (see also Chapter 18). When evaluating a patient complaining of breathing discomfort, the history should be focused on five types of information: (1) the language used by the patient to describe his or her dyspnea, (2) the timing of the dyspnea, (3) the positional nature of the symptom, (4) the associated symptoms, and (5) the intensity.

Language

As described earlier, the qualitative descriptors used by patients to characterize their breathing discomfort can provide clues to the underlying problem (see Table 36.1). It is best first to ask the patient to tell you, "What does the breathing discomfort actually feel like?" Some patients are bemused by this question, and it can be helpful to use the analogy to the different types of pain they may have experienced in the past, for instance, sharp, dull, burning, aching. Alternatively, one may ask the patient to choose the terms from a list of phrases[18,19]; if the patient chooses multiple phrases, then ask them to identify the three best descriptors of their breathing discomfort.

Timing

The timing of the dyspnea (acute, intermittent, chronic) adds important information to the story. *Acute* dyspnea is associated with diseases such as asthma; pulmonary edema; mucous plugs leading to hypoxemia in bronchitis or pneumonia, which are conditions also associated with increased airway resistance and/or reduced pulmonary compliance; and pulmonary embolism.

Intermittent dyspnea most commonly reflects dyspnea in association with exercise, that is, the patient has a chronic problem that is not of sufficient severity at rest to lead to breathing discomfort but experiences dyspnea with exercise, with its associated increased demands on the cardiorespiratory system. Patients with asthma, COPD, interstitial lung disease, chest wall abnormalities, pulmonary vascular disease, chronic heart failure, and supply-demand ischemic heart disease may all present with intermittent dyspnea. When confronted with a patient with intermittent dyspnea, one should also inquire about factors or conditions other than exercise that precipitate the symptom, for instance, environmental exposures at work or at home.

Chronic dyspnea at rest typically signifies severe, end-stage cardiopulmonary disease, such as severe COPD or heart failure. Progressive neuromuscular diseases, for instance, amyotrophic lateral sclerosis, can also present in this way.

Position

Positional dyspnea is a subset of intermittent dyspnea. Orthopnea is the consequence of increasing pulmonary vascular pressures (and stimulation of associated lung and vascular receptors) when the patient is in the recumbent position. Bendopnea, breathing discomfort when bending over, is associated most commonly with central obesity; the positional change reduces the compliance of the abdominal compartment and compromises the ability of the diaphragm to descend during inhalation. Platypnea, which is dyspnea associated with moving from the lying to sitting position, is usually associated with orthodeoxia and may be seen with arteriovenous malformations at the base of the lung, interatrial shunts, and dilated pulmonary vasculature, as seen in some patients with severe liver disease.

Associated Symptoms

Because dyspnea may arise from multiple disease states, it is important to inquire about other symptoms associated with these conditions. A patient with peripheral edema and awakening at night with shortness of breath is likely to have heart failure. Alternating chills and sweats, along with cough, may provide clues about a respiratory infection. Complaints of diffuse muscle weakness may be associated with respiratory muscle dysfunction. Symptoms of heartburn and gastroesophageal reflux could be a clue to the presence of recurrent aspiration. Skin changes may be associated

with interstitial lung diseases; lower extremity lesions (erythema nodosum) or pain and blanching of the fingers in cold weather (Raynaud syndrome) can be a sign of sarcoidosis or scleroderma in a patient with exertional dyspnea.

Intensity

Finally, it is important to ask the patient to rate the intensity of dyspnea. We should not confuse the presence or absence of physical signs of "respiratory distress" (see later) with dyspnea, which can only be quantified by the patient. Studies have shown that both doctors and nurses are frequently inaccurate in estimating a patient's dyspnea, most commonly by underestimating the intensity of breathing discomfort.[62] In addition, beware of changes that patients make in their lifestyle to avoid dyspnea; these changes may mask worsening of their underlying physiologic problem. For example, if walking up a flight of stairs provokes breathing discomfort, the patient may move from a house to a one-floor apartment; if walking to the grocery store is a burden because of dyspnea, the patient may have a friend or family member do the shopping for them. Consequently, they may deny worsening dyspnea, even while they have had a marked decrease in functional status.

PHYSICAL EXAMINATION

As with the medical history, we should make attempts to link our observations with the underlying pathophysiology (Table 36.2). Vital signs can provide evidence of the state of the respiratory controller and the ventilatory pump. Tachypnea is indicative of an increased drive to breathe, although it is not necessarily evidence of alveolar hyperventilation, which is determined by rate and alveolar volume. In the absence of cardiac tamponade, pulsus paradoxus above 10 mm Hg is indicative of a derangement of the ventilatory pump; the individual must increase ventilatory muscle exertion to compensate either for increased airway resistance or decreased respiratory system compliance. Use of accessory muscles of inhalation (e.g., sternocleidomastoid, scalene) is also seen with increased respiratory drive and abnormalities of the ventilatory pump. Kussmaul breathing (very deep breathing with mild increase in rate) is typical of severe metabolic acidosis (the large tidal volume decreases the dead space to tidal volume ratio, thereby increasing the efficiency of breathing). Measurement of oxygen saturation by pulse oximetry, which is now considered a vital sign by most providers, is important to determine if oxygenation at rest and with activity is normal.

Next, look at the patient's breathing pattern from the bedside. Use of accessory muscles of ventilation in the upper chest and neck can be indicative of increased ventilation (increased drive to breathe) and/or a problem with the mechanical pump (e.g., increased airway resistance, decreased respiratory system compliance, diaphragmatic weakness). Paradoxical motion of the abdomen or rib cage during the respiratory cycle is another indicator of respiratory muscle weakness. Abdominal rounding (inward movement of the lateral abdomen with outward movement of the periumbilical region on exhalation) is characteristic of acute pulmonary edema; the maneuver is hypothesized to be an attempt by the patient to generate intrinsic positive end-expiratory pressure, thereby reducing afterload for the left ventricle.[63]

Inspection of the chest may reveal the Hoover sign (inward motion of the lower lateral rib cage on inspiration), indicative of hyperinflation and underlying emphysema with a flattened diaphragm pulling the lateral rib cage inward with each inspiration. Percussion can be used to identify pleural effusions and motion of the diaphragm. Auscultation may reveal diminished or absent breath sounds (pleural effusion, pneumothorax, bullous emphysema), wheezes (increased airway resistance), crackles (diminished lung compliance), and rhonchi (turbulence from airway secretions). Cardiovascular examination is focused on assessment of intravascular and total body volume (e.g., jugular venous pulse, S3, peripheral edema) and pulmonary artery pressure (e.g., loud P2).

The assessment of dyspnea in patients with respiratory failure treated with mechanical ventilation in the ICU is particularly challenging when they are not able to communicate with the team. In these cases, recognition of vital sign abnormalities, observation of facial expressions, and examination of ventilator tracings for evidence of patient-ventilator dyssynchrony may provide insights into the causes of patient respiratory discomfort.[63]

LABORATORY ASSESSMENT

The assessment of all the diseases that can contribute to dyspnea is beyond the scope of this chapter. Instead, this chapter concentrates on the initial tests that will help the physician focus the subsequent evaluation.

Assessment of the hematocrit and hemoglobin is important to exclude anemia; the mechanism by which anemia leads to dyspnea is not fully established; low oxygen delivery to the tissue may stimulate metaboreceptors in muscle tissue. Polycythemia can be an indicator of chronic hypoxia. Blood chemistries can detect metabolic acidosis or the elevated bicarbonate seen with compensation for a chronic respiratory acidosis, and B-naturetic peptide can be a clue to underlying heart failure. An arterial blood gas is necessary to detect hypercapnia and to calculate the $(A–a)P_{O_2}$, which assists in the evaluation of the causes of hypoxemia and the status of the patient's gas exchanger.

A chest radiograph is an important screening tool for both respiratory and cardiovascular causes of dyspnea. One may see evidence for COPD, interstitial lung disease, pleural effusions, pneumothorax, pneumonia, and heart failure. Enlarged pulmonary arteries can be a clue for thromboembolic and other pulmonary vascular diseases. Computed tomography scan of the chest with contrast, including computed tomography angiography, is more sensitive for many of these diseases and should be pursued when the evaluation has not excluded these diagnostic considerations. Echocardiography is indicated when there is concern for more subtle abnormalities of valvular and ventricular function and to estimate the pulmonary artery pressure.

PULMONARY FUNCTION TESTING

Spirometry is a useful screening test for both airway and parenchymal lung disease. Because airway obstruction in asthma may be intermittent and absent at the time the patient is in your office, monitoring the patient's peak flow

TABLE 36.3 Relationships Among Qualities of Dyspnea, Physiology, and Symptomatic Treatment

Quality of Dyspnea	Physiology	Symptomatic Treatment
Air hunger, urge to breathe, need more air	Stimulation of respiratory controller via chemoreceptors, pulmonary receptors, vascular receptors	Supplemental oxygen; nasal flow of gas; cool air on the face; chest wall vibration; inhaled furosemide; opiates
Chest tightness	Stimulation of airway receptors	Inhaled bronchodilators (beta agonists, anticholinergics, steroids)
Cannot get a deep breath	Stimulation of respiratory controller; dynamic hyperinflation	Breathing retraining (slower breathing); pursed lips breathing
Increased work or effort to breathe	Mechanical load on the respiratory system; neuromuscular weakness	Inspiratory muscle training; noninvasive ventilation/ BPAP
Breathing more	Increased ventilation; stimulation of metaboreceptors in muscles	Exercise training
All qualities	Altered perception/processing of information centrally	Desensitization treatment in pulmonary rehabilitation; morphine

BPAP, bilevel positive airway pressure.

at home and at work may detect occult asthma. In those cases where there is still a high suspicion despite normal spirometry/peak flow measurements, methacholine inhalation challenge is indicated.

Lung volume measurements are critical for determination of restrictive pulmonary problems and to assess flow limitation and hyperinflation in patients with obstructive lung disease. For those patients in whom ventilatory muscle weakness is being considered, measurement of maximal inspiratory and expiratory pressures can be useful. Diffusing capacity of the lung should be assessed whenever hypoxemia is present at rest or with exercise.

SPECIAL STUDIES

For patients with new or worsening dyspnea in the setting of chronic respiratory and cardiovascular disease, determining which organ system is responsible for the onset of the symptom can be challenging. Cardiopulmonary exercise tests, during which data are collected on both pulmonary and cardiac function, can be particularly helpful in determining the specific defect at the time dyspnea begins.[64] These tests can involve progressively invasive data gathering, culminating in a level 3 test, which is performed with an arterial and pulmonary artery catheter in place. These advanced studies are particularly useful if there is a concern for diastolic heart failure and/or pulmonary vascular disease as the cause of dyspnea (see Chapter 33).

TREATMENT OF DYSPNEA

Having determined the cause of a patient's dyspnea, the first and most effective approach to treatment is to alleviate the underlying cause of the symptom. Unfortunately, many of the chronic cardiorespiratory conditions that lead to dyspnea are not curable and are often refractory to pharmacologic therapy. In the case of severe emphysema, lung volume reduction surgery has been shown to alleviate dyspnea in a subset of patients, but recurrence of symptoms within several years is common. Increasingly, nonsurgical approaches using endobronchial valves are substituting for lung volume reduction surgery with promising results.[65]

When dyspnea persists despite optimal treatment of the underlying disease, treatment should focus on the symptom rather than the disease. In part, this leads back to the underlying physiologic mechanisms of dyspnea (Table 36.3) and our ability to manipulate them (e.g., activity of the controller, oxygenation, and respiratory muscle function).[66]

DECREASING RESPIRATORY DRIVE

An increase in the drive to breathe is a key feature of the physiology of many diseases that lead to a sense of air hunger. Reducing stimulation of the chemoreceptors with supplemental oxygen in hypoxemic patients may reduce dyspnea. A secondary effect is obtained with use of nasal cannula because activation of flow receptors in the nose may further relieve the drive to breathe. Blowing cool air on the face with a fan may have similar effects, via activation of facial sensors innervated by the trigeminal nerve.[67] Further efforts to stimulate receptors that will alleviate the drive to breathe have included chest wall vibration,[68] although the means to provide this clinically await development, and activation of slowly adapting stretch receptors in the lung with inhaled furosemide[34]; the latter has had mixed results in a number of studies and may be effective in only a subgroup of patients.[34,69,70]

REDUCING RESPIRATORY EFFORT AND IMPROVING RESPIRATORY MUSCLE FUNCTION

Patients with COPD have significant mechanical loads on the respiratory system. Abnormal airways lead to a resistive load; hyperinflation, which worsens with activity in the face of flow limitation, results in an elastic load. Both of these increased loads burden the inspiratory muscles and contribute to the increased work and effort of breathing. To address this physiology, breathing retraining, including pursed-lips breathing, can mitigate these problems by slowing and prolonging exhalation, which may reduce dynamic hyperinflation.

By providing inspiratory muscle support with noninvasive mechanical ventilation, such as bilevel positive airway pressure, one can also relieve some of the burden on the inspiratory muscles and reduce the work of breathing and muscle fatigue. This intervention has been used extensively for acute dyspnea in the emergency department and in the ICU and is being attempted increasingly in the outpatient setting. In COPD patients with muscle weakness, nutritional supplementation and inspiratory muscle training may be tried, although evidence for the efficacy of this strategy remains scarce. Although theophylline has been shown experimentally to enhance muscle function, clinical studies in COPD have not demonstrated significant benefit. Data supporting a role for systemic inflammation in COPD are growing; this may be an explanation for some of the muscle dysfunction noted in this disease. To date, however, there are no data supporting the chronic use of systemic steroids or other anti-inflammatory agents in this population.

ROLE OF EXERCISE TRAINING IN RELIEVING DYSPNEA

Exertional dyspnea is a common feature of chronic cardiorespiratory disease, and patients may consciously or unconsciously reduce their activities to avoid breathing discomfort. Not only may this contribute to depression and social isolation, patients are likely to become deconditioned, develop early onset of lactic acidosis during exercise, and demonstrate worsening symptoms when they are active. Pulmonary rehabilitation programs that include exercise, patient education, and breathing retraining have been shown to reduce dyspnea, increase exercise capacity, and improve quality of life.[71] In addition to the physiologic benefits described earlier, reassuring support during exercise training can lead to desensitization to the breathing discomfort; patients may still experience dyspnea, but they no longer have as much anxiety or fear of the sensation and can persist in their activity longer.

ALTERING CENTRAL PERCEPTION

If we can do nothing to change physiology, perhaps we change the perception of dyspnea as sensations are processed in the brain. Desensitization to dyspnea, which has been postulated as part of the effect of pulmonary rehabilitation programs as noted, is one way to alter perception. Viewing the discomfort of breathing as analogous to pain, can we provide a pharmacologic intervention to alter the perception of the dyspnea?

It is interesting that analgesics (a drug to relieve pain) have been with us for centuries, but there is no word for a medication that relieves breathing discomfort. Physicians have used opiates for relief of dyspnea for some time,[72,73] although there is concern about the side effects associated with these drugs, including respiratory depression[74] and, more recently, the fear of developing drug dependence. Although opiates can certainly cause a decrease in ventilation, the doses needed to relieve dyspnea may be associated with relatively minor changes in breathing.[75] When opioids have been used in interstitial lung disease, there was no association with increased admission to the hospital or mortality.[76]

Opiates may have particular benefit in the management of a patient with flow limitation due to asthma or COPD in the acute setting, when one is trying to buy time for standard direct treatment of the disease to take effect. The tachypnea associated with the acute onset of airway obstruction may lead to dynamic hyperinflation, more dyspnea, increased anxiety, and worsening tachypnea; this cycle can lead to intubation and mechanical ventilation. A small dose of opiates in these circumstances may slow breathing, reverse hyperinflation, reduce dyspnea and anxiety, and allow bronchodilators to take effect without the need for intubation.[77] However, there are no large-scale studies of opiates for the management of acute or chronic symptoms in COPD patients.

Although anxiety may lead to tachypnea, increased ventilation, and dyspnea, and dyspnea may lead to anxiety, formal studies of the use of anxiolytics in the treatment of dyspnea have failed to show benefit. In patients with hyperventilation or sighing syndrome—a possible subset of hyperventilation in which patients take intermittent, very large breaths similar to "sighs" and complain of dyspnea—psychological counseling, cognitive behavioral therapy, and anxiolytics may be helpful.

RELIEF OF DYSPNEA IN END-STAGE LUNG DISEASE

Unfortunately, many patients with end-stage lung disease move from intermittent, exercise-induced dyspnea to chronic debilitating dyspnea at rest as their disease progresses. Patients develop a fear of suffocating.[78–80] National respiratory societies have called for more attention to relieving suffering for these patients[37,81,82] as goals of care shift away from extending life to maximizing comfort. Pulmonologists have begun working more closely with palliative care experts to devise the best approach for these patients, particularly with respect to use of pharmacologic and nonpharmacologic interventions (see Table 36.3).

Barriers to effective symptom relief have included lack of provider skill in having conversations about goals of care with patients and families, the fear of using opioids in patients with chronic lung disease, and the fear of taking hope away from patients and families.[83] Nevertheless, coordination of pulmonary and palliative care services has been demonstrated to enhance the patient's sense of breathlessness mastery and to prolong survival,[84] and we all must do better to alleviate suffering in our patients.

Key Points

- Dyspnea is a complex symptom arising from the central processing of information relayed from the central ventilatory control centers with modifying information from numerous afferent sources.
- Breathing discomfort can be affected by behavioral factors and can lead to strong emotional responses.
- The words and phrases used by patients to describe the quality of dyspnea can provide clues to the underlying pathophysiology.
- Most dyspnea is the consequence of problems arising in the respiratory and cardiovascular systems and frequently persists despite acceptable levels of arterial oxygen and carbon dioxide. Conditions that stimulate the drive to breathe, activate receptors in the lungs and pulmonary vasculature, or impair the mechanical response of the ventilatory pump to a given level of central drive should be considered.
- Diagnosis of the underlying cause(s) of dyspnea depends on a careful history, a physical examination that links findings to underlying physiologic derangements, and targeted laboratory studies; cardiopulmonary exercise testing may be particularly helpful in determining the reason why a patient's functional status is limited when both cardiovascular and respiratory problems are present.
- It is important to consider that a patient may gradually limit activities to avoid dyspnea, thereby becoming deconditioned, depressed, and isolated, with progressively worse symptoms when active. Physical rehabilitation can help desensitize a patient to the sensation of dyspnea.
- Treatment of dyspnea begins with interventions directed at correcting the underlying disease state. When this is inadequate, one should consider interventions that reduce the intensity and/or unpleasantness of the symptom.

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37 COUGH

KIAN FAN CHUNG, MD, DSC, FRCP • STUART B. MAZZONE, PHD

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INTRODUCTION

Cough is a protective mechanism, often present for transient (acute) periods of time to facilitate the removal of mucus, noxious substances, or pathogens from the airways and lungs. Impairment of coughing can be harmful or even fatal. Epidemiologic surveys have shown that 11–18% of the general population report a chronic cough,[1] which may be due to cigarette smoking, increased exposure to environmental irritants and pollution, or chronic diseases associated with cough. Chronic cough and cough hypersensitivity syndrome are therefore commonly presented to the clinician. In the United States, cough is the most common complaint for which patients seek medical attention and the second most common reason for a general medical consultation. Many people self-medicate to try to relieve their cough, and over-the-counter cough and cold medicines sold in the United States alone amounted to $2.3 billion between 2007 and 2012. Cough may also be a sign of chronic disease in which patients typically present with chronic cough, defined as a cough lasting for more than 8 weeks. Typically, chronic cough is accompanied by increased sensitivity to cough triggers, a clinical phenomenon known as cough hypersensitivity syndrome.[2–4] Patients with cough hypersensitivity syndrome often complain of a persistent tickling, irritating, or choking sensation in the throat, which often leads to paroxysms of uncontrollable coughing. Of note, chronic cough can be harmful and does not always respond to disease-modifying therapies, needing to be suppressed directly as part of disease management. New therapies to suppress cough have been recently introduced (termed *neuromodulators*), with the prospect of more effective therapies to be introduced in the coming decade.[5]

DEFINITION OF COUGH

Cough usually starts as a deep inspiration, followed by a strong expiration against a closed glottis (compression phase), which then opens with an expulsive flow of air, producing a characteristic cough sound (Fig. 37.1). (Audios 37.1 and 37.2). An initial cough may be followed by a series of expiratory efforts, with closures of the glottis but no intervening inspirations—a "cough bout" or an "epoch." There can be variations of the respiratory pattern, including an expiration-only pattern, or "huff," associated with throat clearing. Cough sounds may have clear harmonic patterns, but their significance has not been established (eFig. 37.1). Cough is usually accompanied by an awareness of airway irritation and the feeling of an "urge to cough," indicating that cough sensations are processed in the higher brain.[6,7] Cough can either be reflexively or voluntarily initiated, and habit or behavioral cough is not uncommon, especially in children.[8]

DEFINITION OF COUGH HYPERSENSITIVITY SYNDROME

The concept of cough hypersensitivity encompasses the abnormal state of chronic coughing, which is often accompanied by other sensations. Thus, many describe a persistent or intermittent tickling, irritating sensation, rawness or itch, or a choking sensation in the throat, with repeated throat clearing, chest tightness, hoarse voice and dysphonia, vocal cord dysfunction, a globus feeling in the throat, and dysphagia. In addition, innocuous triggers of cough include changes in ambient temperature, taking a deep breath, laughing, talking, cigarette smoke, aerosol sprays, and perfumes. Therefore, the cough hypersensitivity syndrome has been defined as a disorder characterized by troublesome coughing, often triggered by low levels of thermal, mechanical, or chemical exposure. There is increasing evidence that this is caused by a disordered sensory neural function, both at the peripheral and *central nervous system* (CNS), with an underlying neuropathy.

PHYSIOLOGY AND NEUROBIOLOGY

MECHANICS OF COUGHING

The inspiratory phase of cough consists of a deep inspiration through a widely opened glottis. The inhaled volume varies greatly, from a low to a nearly complete vital capacity. The inspiration may draw material into the lungs; however, the large lung volume provides a better mechanical efficiency for the expiratory muscles of cough because they are stretched, their stretch reflex is activated, and there is a stronger elastic recoil of the lung to aid expiration. Furthermore, the deep inspiration opens the airways in preparation for their clearance during the expiratory phase.[9]

In the compressive phase of cough, lasting about 200 ms, the glottis closes while the expiratory muscles contract, and the intrapleural and intra-alveolar pressures rise rapidly to a range of values that can vary from 40 to 400 cm H_2O. The expulsive phase follows when the glottis opens. The expiratory flow rate depends on the driving pressure established during the compressive phase and on resistance to airflow, largely reflective of the diameter of the central airways, which are dynamically collapsed as a result of high intrathoracic pressure. The expulsive phase of coughing may be long lasting, with a large expiratory tidal volume, or it may be interrupted by glottic closures into a series of short expiratory efforts, each having a compressive and an expulsive phase.

Maximum expiratory flow is independent of effort because it is limited by dynamic compression of the airways.[9] This compression starts immediately downstream from the equal pressure point, at which intraluminal and extraluminal pressures around the bronchial wall are equal. The effectiveness of cough depends on peak airflow and will therefore be greater with a larger elastic recoil of the lung, *which creates the driving pressure*, and a greater stiffness of the central airways, *which prevents dynamic collapse*. Dynamic compression of the airways downstream from the equal pressure point increases velocity, kinetic energy, and turbulence of the air passing through the proximal airways. Thus, the clearing capacity of the cough is improved. If cough consists of a series of expiratory efforts, with lung volume decreasing with each effort, dynamic compression is predicted to move into the more peripheral

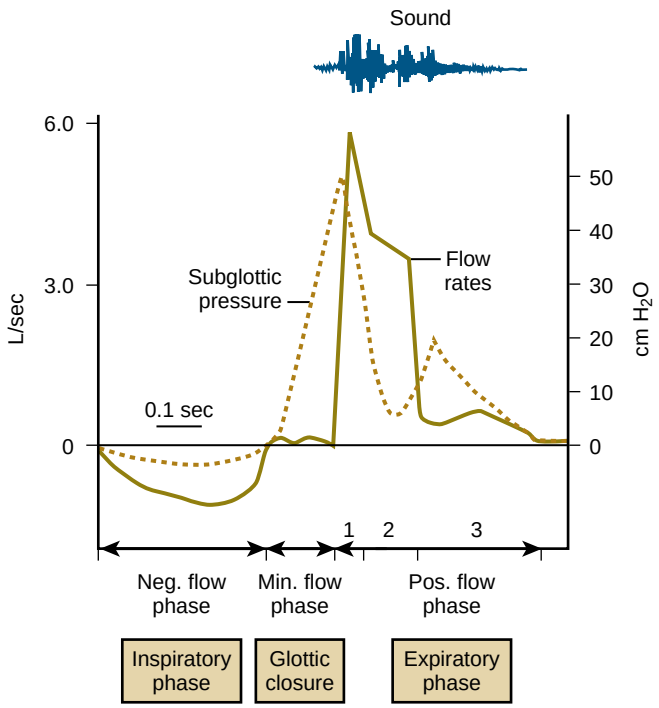

Figure 37.1 Diagrammatic representation of the changes of the following variables during a representative cough: sound, flow rate, and subglottic pressure. During inspiration, the flow rate is negative; at the glottic closure, the flow rate is zero; and during the expiratory phase, the flow rate is positive. The expiratory phase can be divided into three parts: during the first expulsive phase *(1)*, there is an explosive cough sound, the first cough sound; during the second phase *(2)*, as the expulsive airflow diminishes, the sound amplitude diminishes; and during the third phase *(3)*, the vibration of a partly closed glottis produces a regular periodic sound, the second sound. Refer to eFig. 37.1 for a representation of the cough waveform. Min., minimal; Neg., negative; Pos., positive. (From Bonica JJ. *Obstetric Analgesia and Anesthesia.* Amsterdam: World Federation of Societies of Anaesthesiologists; 1980.)

bronchi, which will be progressively cleared of intraluminal material.

Whereas mucociliary transport is the major method of clearing the airway lumen in healthy subjects, cough is an important reserve mechanism. However, in those with lung disease, cough plays a larger role in airway clearance. In many lung diseases, mucociliary clearance is impeded and cough is necessary to remove the increased amount of secretions and debris. Healthy subjects have twice the mucociliary clearance rate of that in patients with chronic bronchitis; with cough, whereas healthy subjects will increase their clearance by only 2.5%, patients with chronic bronchitis can increase their clearance by 22%.[10] As would be expected, all studies point to the fact that cough is effective in causing clearance if there is hypersecretion of mucus; by definition, a dry cough is an unproductive one.

COUGH MOTOR CONTROLS

The inspiratory and expiratory phases of cough rely on coordinated activity of the multiple respiratory muscle groups that ordinarily control breathing. Although glottic closure is usually regarded as definitive of cough, in both human and experimental animals the closure may be incomplete or absent, and this does not seem to impair the effectiveness of the cough in clearing the airway. Coughing is associated with respiratory actions other than those of the respiratory skeletal muscles.[11] There is usually bronchoconstriction, although this may be masked or reversed by the dramatic changes in lung volume. Bronchoconstriction increases the linear velocity of airflow and lessens the inflow of irritant material to deeper parts of the airways. Cough is also accompanied by reflex secretion of mucus from airway submucosal glands. Mucus entraps inhaled particles and irritant chemicals, and the material is thus cleared from the airways by mucociliary transport and by the cough itself. Mucus also can act as a physicochemical barrier between the luminal irritants and the airway wall.

SENSORY RECEPTORS FOR THE COUGH REFLEX

Involuntary coughing can be initiated only from those structures innervated by the vagus nerve.[12] These include the larynx and tracheobronchial tree, the lower part of the oropharynx, tympanic membrane, and the external auditory meatus. The one clear exception to vagally-mediated coughing is voluntary coughing. The most sensitive sites for initiating cough are the larynx and tracheobronchial tree, especially the carina and points of bronchial branching, areas richly innervated by cough-inducing receptors associated with vagal sensory nerve fibers.[12] It is worth noting that it is difficult or impossible to induce coughing from the smaller airways and alveoli. This is teleologically understandable because even a vigorous cough would not produce sufficient airflow to clear substances from the most distal airways. Different types of stimuli induce coughing by acting on at least two types of cough-evoking sensory nerve fiber types, broadly categorized as either vagal *nociceptors*, which detect a range of noxious chemical irritants, including inflammatory mediators, or vagal *mechanoreceptors*, which are highly sensitive to mechanical stimuli, such as particulate matter entering the airways or accumulated intraluminal mucus (Fig. 37.2 and eFig. 37.2).

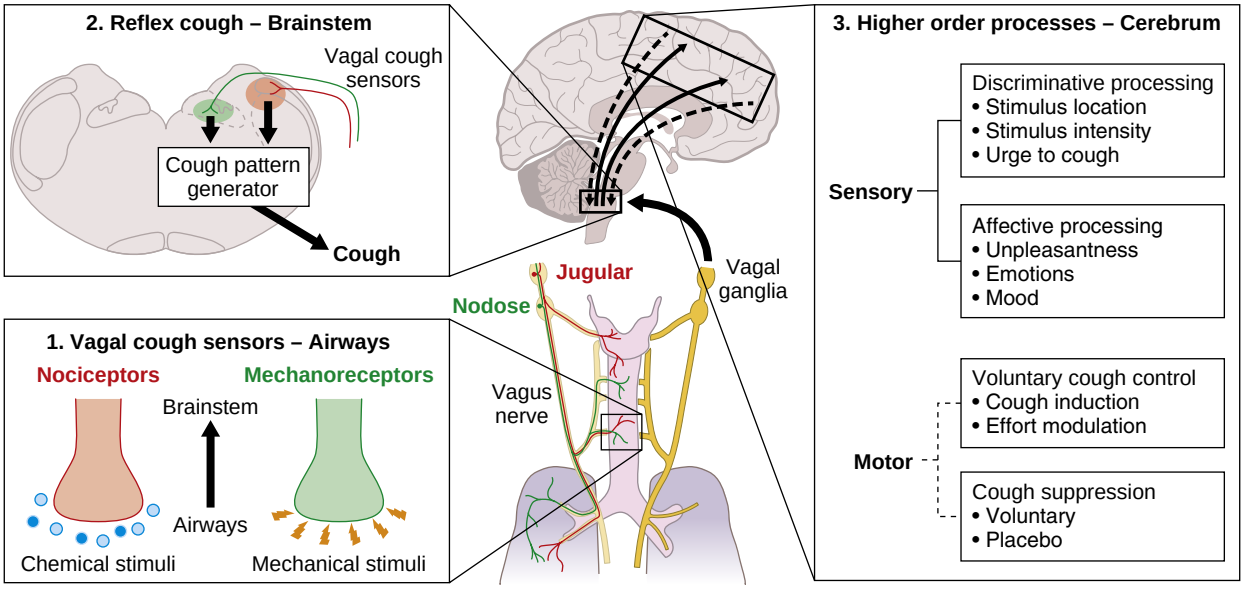

Figure 37.2 Two types of vagal sensory neurons in the airways and lungs can mediate cough. Those sensitive to chemical stimuli are termed nociceptors; those sensitive to physical stimuli are termed mechanoreceptors. Both sensory neuron types connect to the brainstem and send information that can be processed by local circuits to initiate a reflex cough. Sensory information can also ascend into the higher brain, where it encodes more complex aspects of cough, including the accompanying experience of an urge to cough. Higher brain circuits also descend upon the brainstem sites that regulate reflex coughing and can be enlisted to induce a voluntary cough, to modulate cough intensity, or to suppress a cough altogether. Inflammation can alter the sensitivity of these cough-evoking pathways because the vagal sensory neurons express a wide variety of receptors for cytokines and other chemical mediators. (Modified from Mazzone SB, Undem BJ. Vagal afferent innervation of the airways in health and disease. *Physiol Rev.* 2016;96:975–1024; and Mazzone SB, Farrell MJ. Heterogeneity of cough neurobiology: clinical implications. *Pulm Pharmacol Therap.* 2019;55:s62–s66.)

Vagal *nociceptors* are unmyelinated slow-conducting C fibers characterized by their responsiveness to the chemical capsaicin, the active ingredient in hot chili peppers. Nociceptors are also responsive to a wide range of proinflammatory molecules, which notably include bradykinin, prostaglandins, leukotrienes, proteases, and cytokines, as well as noxious irritants, such as capsaicin, acid, nicotine, and acrolein.[12] When inhaled, many such chemicals are a powerful stimulus for coughing.

Vagal *mechanosensors* are myelinated fast-conducting Aδ-fibers that are normally silent, unlike other myelinated vagal mechanosensors in the lung that monitor lung volume. Their stimuli include acid solutions, such as that aspirated from the stomach, hypotonic solutions including inhaled fog, and mechanical stimulation by catheter, mucus, or dust (but not stretch or bronchospasm). All these stimuli can provoke cough.

MEMBRANE RECEPTORS/CHANNELS FOR COUGH TRANSDUCTION

Extensive studies exist on the sensory nerve membrane channels and receptors involved in coughing.[12–14] The details are complex, so they are summarized only briefly. However, the results are of considerable importance as they indicate how chronic coughing manifests and provide a rationale for the antitussive therapeutics available or in development.

Vagal *nociceptors* express several *transient receptor potential* (TRP) channels. Capsaicin and temperature-sensitive *transient receptor potential vanilloid-1* (TRPV1) receptors are directly activated by capsaicin, used commonly as a tussive agent in clinical studies of cough; these receptors are additionally sensitized or indirectly activated by heat, protons, bradykinin, arachidonic acid derivatives, *adenosine triphosphate* (ATP), and phosphokinase C. TRPV4 is osmotically sensitive and mostly found on epithelial cells but also on a subset of vagal sensory nerve fibers, whereas TRP ankyrin 1 is often coexpressed with TRPV1 on many vagal nociceptors in the airways and is activated by allyl isothiocyanate (mustard oil), cinnamaldehyde (from cinnamon), and acrolein (from cigarette smoke). C fibers also express tetrodotoxin-insensitive voltage-gated sodium channels, many G protein–coupled receptors for inflammatory mediators, and receptors for neurotrophins, such as nerve growth factor.

Vagal *mechanosensors* are thought to express mechanically gated membrane ion channels that are unique to this class of airway sensory fibers but have yet to be identified. In addition, they have other channels that can be activated by acids and belong to the *acid-sensing ion channel* (ASIC) family. They possess different types of voltage-sensitive ion channels needed for action potential formation and conduction, including the NaV1.7 subtype of voltage-gated sodium channels, characterized by sensitivity to the neurotoxin tetrodotoxin. However, the vagal mechanosensors lack several TRP channels found in vagal nociceptors, although these TRP channels may be induced during inflammation.

Both nociceptors and mechanosensors often also express receptors for ATP and other purines. Of note, P2X2 and P2X3 purinergic receptors can be expressed alone or in combination, and it is thought that local release of ATP from the injured or inflamed airways is a major contributor to cough hypersensitivity syndrome acting via these receptors.[3]

CENTRAL NERVOUS SYSTEM CONTROL

Reflex coughing is integrated in the brainstem, where the vagal sensory fibers for coughing first terminate (see Fig. 37.2).[15–17] Recipient neurons within these sensory integration sites connect with a collection of respiratory control neurons in the brainstem, loosely defined as the cough pattern generator. Outputs from the cough pattern generator are sent to motoneurons of the respiratory muscles, larynx, and bronchial tree to actuate the cough respiratory pattern.

Vagal sensory inputs to the brainstem are also relayed to higher brain regions where inputs are integrated in pontine, subcortical, and cortical nuclei.[6,7,16] These anatomic pathways have been reasonably well defined in animals, demonstrating several different circuits important for encoding cough sensations. Studies with functional magnetic resonance imaging of the human brain during airway irritation with capsaicin and induced cough have delineated those areas involved in the different sensory discriminative and motor aspects of noxious airway stimulation (see Fig. 37.2 and eFig. 37.3). For example, the anterior insula cortex is thought to play a role in monitoring the amount of sensory input arising from the airways, whereas the primary sensory cortex is involved in assimilating sensory inputs and coding them for the urge-to-cough sensation. The posterior parietal and prefrontal cortices may provide spatial awareness (i.e., where the stimulus is coming from), and the orbitofrontal cortex in the limbic brain helps shape the affective dimensions of cough (i.e., how does it make you feel).[16]

Cough can also be behaviorally induced or modified via higher brain circuits. For example, cough can be initiated voluntarily, a process that originates in motor and premotor cortical brain regions (see Fig. 37.2).[15,18,19] These voluntary descending pathways may bypass brainstem integrative centers because some patients with brainstem damage lack a cough reflex but can voluntarily induce coughing to clear the airways.[20] The motor cortex and inferior frontal gyrus can generate voluntary cough suppression to inhibit reflex coughing temporarily.[19] The placebo effect is prominent in cough, and this involves the dorsolateral prefrontal cortex and an inhibitory pathway that reduces vagal sensory processing in the brainstem, much like the endogenous analgesia system that is proposed to mediate the placebo effect for pain.[15,18] This endogenous inhibitory system relies on endogenous opioids to induce suppression, explaining how opiates can be effective at suppressing cough. Of importance, chronic cough in disease is not simply a matter of too much sensory input from the airways and lungs but also involves a reduction in central cough suppressive mechanisms that ordinarily help to reduce unwanted coughing.[7,19]

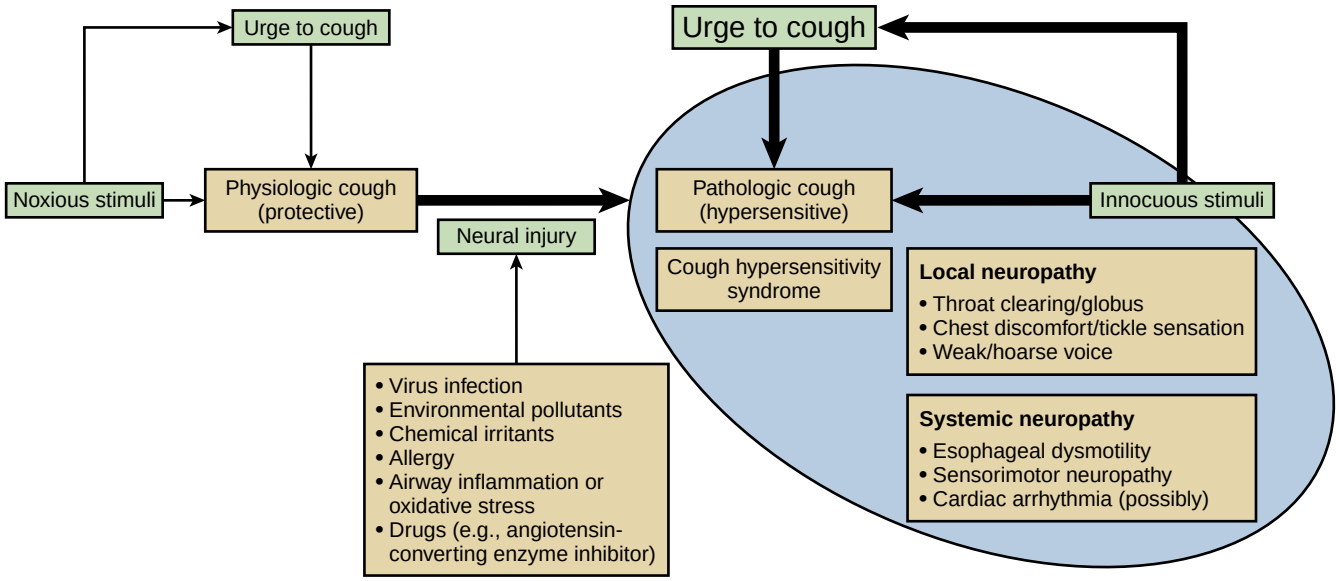

Figure 37.3 Cough hypersensitivity syndrome. On the left is a normal cough response. The proposed effect of vagal nerve injury arises from inflammation caused by airway exposure to infective, physical, chemical, and allergic insults. With neural injury (*arrow to right*), the cough progresses to a pathologic cough. The *blue oval* emphasizes the pathology (neuropathy) of the cough hypersensitivity syndrome. (From Chung KF, McGarvey L, Mazzone S. Chronic cough as a neuropathic disorder. *Lancet Respir Med.* 2013;1:414–422.)

MECHANISMS OF COUGH HYPERSENSITIVITY

In the cough hypersensitivity syndrome, the sensory receptors for cough can show an exaggerated response to stimuli that would normally be harmless or mildly irritating. This increase in sensitivity, termed *peripheral sensitization*, can be caused by allergens, viral infections, ozone, cigarette smoke, and a variety of inflammatory mediators.[12] Vagal mechanosensors can also be sensitized by mucus in the airways, smooth muscle contraction, and mucosal edema. Increases in sensitivity have been related to *neuroplasticity* in the vagal sensory fibers. Thus, terminals of vagal sensory fibers in the airways and lungs can sprout and increase their area of innervation, as well as change their expression of neurotransmitters, ion channels, and receptors, leading to alterations in their normal physiologic properties. This *peripheral sensitization* can be accompanied by *central sensitization*, a neuroinflammatory process in the CNS that amplifies incoming sensory inputs and produces hyperreflexic states.[4,16] The alterations in the structure and function of vagal sensory neurons and central processing pathways in cough hypersensitivity syndrome lead to the clinical symptoms *hypertussia* (increased cough sensitivity to known stimuli) and *allotussia* (cough in response stimuli that do not normally cause cough). This clinical presentation is analogous to a neuropathy, for example, similar to that seen in many patients with chronic pain (Fig. 37.3).[4]

APPROACH TO THE PATIENT WITH COUGH

As emphasized in national cough guidelines,[21–23] the approach to the management of a patient with cough is first to identify the cause(s) of the cough and then to treat the cause(s) (Fig. 37.4). Cough may be indicative of trivial or serious airway or lung diseases, including infections, inflammatory and neoplastic conditions, and many pulmonary and extrapulmonary conditions (Table 37.1). The foremost consideration for the clinician at the first visit is to (1) determine the severity, (2) assess the possible cause(s) of the cough, and (3) plan investigations and treatment. Various indicators in the history and examination of the patient may provide clues to the diagnosis, although these may not be entirely reliable or specific and may be absent in many cases.

The timing and selection of various investigations may vary according to presentation (Table 37.2). Initial investigations may be limited to a chest radiograph, particularly in a cigarette smoker, where abnormalities can be found in 10–30% of chest radiographs. Further investigations (e.g., *computed tomography* [CT] or fiberoptic bronchoscopy) may be pursued despite a "normal" chest radiograph. Often, the cause may not be found, the treatment of the putative cause may not suppress or improve the cough, or the cause may have no effective treatment. In those cases, therapy that suppresses cough by inhibiting the cough pathway without treating the cause is necessary.

The protocol for investigating a chronic cough takes into account several factors pertaining to the pathophysiology of cough and to the most common causes of cough. Postnasal drip ("nasal catarrh" or "upper airway cough syndrome"), asthma, and *gastroesophageal reflux disease* (GERD) are the three most common conditions associated with a chronic cough. Therefore, an initial diagnostic approach to exclude these conditions is sensible. Bearing in mind that there are also myriad other less common causes of a cough, further investigations may be indicated. Lung function tests, including lung volumes and diffusing capacity, as well as CT imaging of the lungs, should be considered to check for bronchiolar or parenchymal disease or unsuspected bronchiectasis. Fiberoptic bronchoscopy should be considered and,

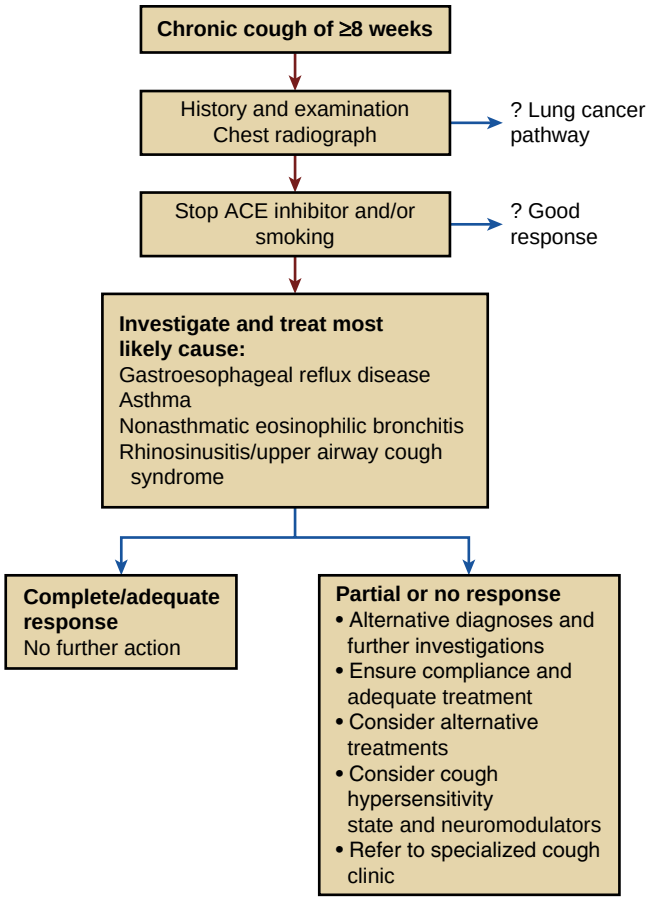

Figure 37.4 Algorithm for the management of chronic cough in adult patients. For a chronic cough lasting for >8 weeks, the evaluation and management should be methodical. After a thorough history and physical examination and chest imaging to exclude lung cancer or other intrathoracic pathology, and after stopping *angiotensin-converting enzyme* (ACE) inhibitor and/or smoking, the workup proceeds through the most common likely entities. These are listed as gastroesophageal reflux disease, asthma, nonasthmatic eosinophilic bronchitis and rhinosinusitis, or upper airway cough syndrome. Exclusion can be determined either by investigations or trial of therapy or both. Ultimately, patients with persistent chronic cough can be referred to specialized cough clinics for alternative diagnosis and treatment.

Table 37.1 Common Causes of Cough

ACUTE INFECTIONS
Tracheobronchitis
Bronchopneumonia
Viral pneumonia
Acute-on-chronic bronchitis
Pertussis
CHRONIC INFECTIONS
Bronchiectasis
Tuberculosis
Cystic fibrosis
AIRWAY DISEASES
Asthma
Eosinophilic bronchitis
Cough-variant asthma
Chronic bronchitis
COPD
Chronic postnasal drip
PARENCHYMAL DISEASES
Interstitial pulmonary fibrosis
Emphysema
Sarcoidosis
TUMORS
Lung cancer
Benign airway tumors
Mediastinal tumors
ASPIRATED FOREIGN BODIES
MIDDLE EAR PATHOLOGY
CARDIOVASCULAR DISEASES
Left ventricular failure
Pulmonary infarction
Aortic aneurysm
OTHER DISEASES
Gastroesophageal reflux disease
Laryngopharyngeal reflux
Recurrent microaspiration
Endobronchial sutures
Obstructive sleep apnea
Laryngeal dysfunction
DRUGS
Angiotensin-converting enzyme inhibitors

apart from excluding small central tumors, mucosal biopsies may be taken for histologic diagnosis (e.g., to diagnose eosinophilic infiltration or sarcoidosis). Lower airway samples can also be obtained for culture for infectious agents. As a result, a protocol based on systematic evaluation using history, physical examination, and laboratory investigations focusing on the anatomic sites of cough receptors that constitute the afferent limb of the cough reflex is the most widely advocated approach to diagnosis and treatment.[21]

Cough with usually clear sputum production often points toward conditions such as chronic bronchitis and bronchiectasis or other causes of bronchorrhea. However, the diagnostic value of knowing that the cough is productive is probably limited because similar causes are often found for both productive and dry cough.[24] For example, an enhanced cough reflex may be present in both productive and nonproductive cough. Features associated with an enhanced cough reflex include cough triggered by taking a deep breath, laughing, inhaling cold air, and prolonged talking. Although the diagnostic approach may be similar whether or not the cough is productive, any change in the color of the sputum that indicates purulence must be considered as potential evidence of a bacterial infection, such as bronchiectasis or bronchitis.

MEASURING COUGH SEVERITY AND FREQUENCY

Cough can be measured by assessing its severity, frequency, intensity, and impact on quality of life. First, assessment of cough severity can be obtained from the history; complications such as vomiting, rib fractures, fatigue, urinary incontinence, and syncope (Table 37.3) can indicate chronicity

Table 37.2 Diagnostic Evaluation of Chronic Cough

1. History and physical examination.
2. Chest radiograph, particularly in smokers.
3. Initial evaluation may lead to diagnosis of chronic bronchitis in cigarette smokers and of angiotensin-converting enzyme inhibitor cough. Discontinue cigarette smoking and offending drug.
4. Further diagnostic evaluation on basis of initial evaluation:
   a. If suggestive of postnasal drip, order a computed tomography (CT) scan of sinuses, and allergy tests.
   b. If suggestive of asthma, request a record of peak expiratory flow measurements at home for 2 weeks and a bronchoprovocation test with histamine or methacholine, and/or a trial of antiasthma treatment.
   c. If suggestive of gastroesophageal reflux disease, request 24-hour pH monitoring and, if necessary, an endoscopic examination of the esophagus or a barium swallow series.
   d. If the chest radiograph is abnormal, consider examination of sputum and a fiberoptic bronchoscopy. A high-resolution CT scan of the thorax and further lung function evaluation may be necessary.
5. Treat specifically for associated conditions. The cause(s) of cough is (are) determined when specific therapies eliminate or improve the cough. There may be more than one associated cause for the cough.

Table 37.3 Potential Complications From Excessive Cough

RESPIRATORY
Pneumothorax
Subcutaneous emphysema
Pneumomediastinum
Pneumoperitoneum
Laryngeal damage
CARDIOVASCULAR
Cardiac dysrhythmias
Loss of consciousness
CENTRAL NERVOUS SYSTEM
Syncope
Headaches
Cerebral air embolism
MUSCULOSKELETAL
Intercostal muscle pain
Rupture of rectus abdominis muscle
Increase in serum creatine phosphokinase
Cervical disc prolapse
GASTROINTESTINAL
Esophageal perforation
OTHER
Social embarrassment
Depression
Sleep disruption
Urinary incontinence
Disruption of surgical wounds
Subconjunctival hemorrhage
Petechiae
Purpura

and intensity. Another indication of severity is the effect on lifestyle and psychological well-being, such as the development of anxiety and depression.

Cough severity can be measured by a *visual analogue scale*, on which the patient records his or her perception ranging from mild to severe or on a nominal line of 10 cm. Severity of cough can also be evaluated using quality-of-life questionnaires specific for the evaluation of the impact of chronic cough. The Leicester Cough Questionnaire uses a seven-point Likert response scale for 19 items from three domains (physical, psychological, and social) and has been shown to be repeatable and sensitive in patients with chronic cough.[25] The Cough-Specific Quality of Life Questionnaire with 28 items in six domains is validated for both acute and chronic cough.[26]

Cough frequency can be measured using a recording device of the cough sound using a microphone.[27] The coughs can either be counted by listening or by using cough detection software. There is a weak correlation between cough frequency and subjective scoring systems measured by the cough visual analogue scale or the Leicester Cough Questionnaire.[28,29]

MEASURING COUGH REFLEX

The *cough reflex* is measured by counting the number of coughs after inhalation of tussive agents, such as capsaicin, the pungent extract of peppers, or citric acid– or low-chloride-content solutions. Chronic cough may result from an increase in the sensitivity of the cough sensors. Due to a variety of causes, most patients with a chronic cough have an enhanced cough reflex when compared with healthy non-coughing subjects, but there is a significant degree of overlap between these groups.[30–33] There is also a heterogeneity of cough responses to different agents that work through different receptors. Thus, cough reflex results may reflect the underlying hypersensitive state to a particular stimulus. A combination of both subjective and objective measurements should ideally be used to assess a patient's cough. These measurements have proven to be useful in assessing the response of patients to antitussive therapies both in the clinic and in randomized controlled studies of antitussives.

ACUTE, SUBACUTE, AND CHRONIC COUGH

Cough may be divided according to its duration. An *acute* cough is defined as lasting less than 3 weeks, a *subacute* cough as lasting between 3 and 8 weeks, and a *chronic* cough as lasting more than 8 weeks.[21]

Acute cough is usually due to a viral or bacterial upper respiratory tract infection. The cough of the common cold is usually self-limiting and usually starts within the first 48 hours with accompanying symptoms of postnasal drip, throat-clearing, sore throat, nasal obstruction, and nasal discharge, which usually resolve within 2 weeks. Acute cough could also be caused by an exacerbation of underlying diseases, such as an upper airway cough syndrome secondary to rhinosinusitis, asthma, COPD, or pneumonia. Patients with the common cold usually self-medicate with over-the-counter antitussive preparations, despite a lack of good evidence for their effectiveness in acute cough.[34] Codeine is ineffective, although dextromethorphan had some variable but small effect. Honey can provide symptomatic relief.[35] The efficacy of antitussive preparations

in children is lacking and, because these medications may be potentially harmful,[36] cough due to acute viral airway infections should be treated only with fluids and humidity, although honey may be tried.[34]

Subacute cough is most commonly due to a prior infection or exacerbations of underlying diseases, such as asthma, COPD, and upper airway cough syndrome. Pertussis should be considered in the differential diagnosis, particularly if the cough has a whooping quality (Audios 37.3 and 37.4) and is associated with vomiting. In adults, the presence of whooping or posttussive vomiting increases the likelihood of the diagnosis of pertussis, whereas a lack of paroxysmal cough or the presence of fever should rule it out.[37] In children, posttussive vomiting is less helpful as a diagnostic test.[37]

Chronic cough can be caused by many diseases, but it is most commonly due to postnasal drip, asthma, GERD, chronic bronchitis, and bronchiectasis.[21] Each of these will be considered along with their specific therapies (Table 37.4).

POSTNASAL DRIP (RHINOSINUSITIS, UPPER AIRWAY COUGH SYNDROME)

Postnasal drip or the upper airway cough syndrome is a common cause of chronic cough.[21,38] Postnasal drip (nasal catarrh) is characterized by a sensation of nasal secretions or of a "drip" at the back of the throat, accompanied by a frequent need to clear the throat. There may also be a nasal quality to the voice due to concomitant rhinonasal blockage and congestion, together with hoarseness. Physical examination of the pharynx is often unremarkable, although a "cobblestoning" appearance of the mucosa and draining secretions may be observed. CT of the nasal passages and sinuses may reveal rhinosinusitis with mucosal thickening or sinus opacification and air-fluid levels. Extrathoracic variable upper airway obstruction is sometimes present.[39]

The best treatment is topical administration of corticosteroid drops in the head-down position, often with the concomitant use of antihistamines.[38] Topical steroids offer a local effect with a minimum of side effects. On occasion, severe symptoms may be controlled initially by a short course of oral steroids, followed by topical therapy. A topical anticholinergic spray to the nose, such as ipratropium bromide, to dry excessive nasal secretions may provide additional benefit. A combination of topical corticosteroid, antihistamine, and anticholinergic treatments has been shown to benefit the chronic cough accompanying postnasal drip, along with an improvement in nasal discharge and endoscopic appearances.[40] Topical decongestant vasoconstrictor sprays may be useful adjunct therapy for a few days, but rebound nasal obstruction may develop after prolonged use. Antibiotic therapy is necessary in the presence of acute sinusitis involving bacterial infection with mucopurulent secretions that have persisted for at least 10 days.

ASTHMA AND ASSOCIATED EOSINOPHILIC CONDITIONS

Asthma may present with chronic cough under different clinical settings. Asthma may present predominantly with cough, often nocturnal, and the diagnosis is supported by the presence of reversible airflow limitation, bronchial hyperresponsiveness, and often elevated fractional levels of nitric oxide in the exhaled breath. This condition of "cough-variant" asthma is a common type of asthma in children.[41] Elderly asthmatics may also give a history of chronic cough before a diagnosis of asthma is made. Cough as the only presenting symptom of asthma has been reported in up to 57% of patients and is often its most prominent symptom.[42] Cough may also be present as a first sign of worsening asthma; the cough usually presents first at night, associated with other symptoms, such as wheeze and shortness of breath with reduction in early morning peak flows. Some patients with asthma may also develop a chronic dry cough despite good control of their asthma, which may be the sign of a cough hypersensitivity syndrome.

Atopic cough is recognized in Japan as an isolated chronic cough characterized by an atopic background, sputum eosinophilia, cough hypersensitivity, normal pulmonary function, and airway hyperresponsiveness.[43] A related entity, eosinophilic bronchitis, is characterized by cough without asthma symptoms or bronchial hyperresponsiveness but with eosinophilia in sputum.[44]

An enhanced cough reflex may be seen in a subgroup of asthmatics with chronic cough.[45] In these patients, cough sensors may be sensitized by inflammatory mediators, such as bradykinin, tachykinins, and prostaglandins. Cough in asthma may also be due to bronchial smooth muscle contraction, which may activate cough receptors through physical deformation. Another potential mechanism for the enhanced cough reflex observed in asthma is the presence of eosinophils. It is of interest to note that, in two conditions presenting with chronic cough, cough-variant asthma and eosinophilic bronchitis, eosinophils predominate in the airways, and inhaled corticosteroids, which inhibit the eosinophilia, are effective in controlling the cough.[46] Recent evidence indicates that eosinophils may be responsible for increasing the airway sensory nerve density that may account for an increase of cough sensitivity in airway conditions associated with cough.[47]

Cough associated with asthma should be treated with a combination of inhaled corticosteroid therapy and long-acting β_2-adrenergic agonists, treatments that should be maintained over a prolonged period (3–6 months). In some patients with cough-variant asthma, β-adrenergic bronchodilators are effective antitussives.[48] Often, a trial of oral corticosteroids (e.g., prednisolone 40 mg/day for 2 weeks) may be recommended, particularly in those asthmatic patients who have had a cough despite being on adequate inhaled antiasthma medication. Cough-variant asthma may respond to leukotriene receptor antagonists.[49] Eosinophilic bronchitis responds well to inhaled or oral corticosteroid therapy.[50]

GASTROESOPHAGEAL REFLUX DISEASE

GERD, the movement of gastric contents from the stomach into the esophagus, usually causes heartburn, chest pain, a sour taste, regurgitation, and often a chronic cough. The mechanisms that link cough with reflux remain unclear. An esophageal-tracheobronchial cough reflex mechanism triggered by acid is based on the observation that cough can

be induced by perfusion of the distal esophagus with acid solutions and can be suppressed by perfusion of the distal esophagus with lidocaine and by inhalation of an anticholinergic agent, ipratropium bromide.[51] In addition, the majority of cough episodes are temporally related to reflux episodes. A heightened cough reflex to capsaicin in GERD patients provides evidence for sensitization of this pathway. Not only the acid but the non–acid reflux components, such as the liquid, gas, and pepsin, have been proposed as stimulating cough.

Patients with GERD may have laryngopharyngeal reflux with evidence of inflammation in the upper airway[52] and, in these patients, cough may result from a direct effect of refluxate reaching the cough receptors in the larynx and trachea. In symptomatic GERD, increases in tracheal acidity with a fall in pH to less than 4 are reported during episodes of reflux.[53] In the presence of reflux and microaspiration, laryngeal symptoms may be present, with dysphonia, hoarseness, frequent throat clearing, a globus sensation (e.g., a feeling of a lump in the throat), and sore throat. Often, posterior vocal cord laryngeal inflammation with edema, erythema, contact ulceration, pachydermia (a thickened mucosa), and/or granuloma is visible. Ineffective esophageal peristalsis has been reported in chronic cough, and this may increase the exposure time of the larynx and pharynx to any refluxate.

Monitoring acid reflux by 24-hour ambulatory pH, together with monitoring non–acid reflux by intraluminal impedance in the proximal and distal esophagus, with analysis of the temporal relationship between the reflux episodes and cough, may be useful. A positive association between acid reflux, non–acid reflux, and cough sounds on an ambulatory cough counter has been reported, together with a heightened cough reflex sensitivity.[54] Other tests include esophageal manometry to measure dysmotility, particularly associated with reflux episodes; upper *gastrointestinal* (GI) contrast series; or an upper GI endoscopy.

Conservative measures, such as weight reduction; a high-protein, low-fat diet; elevation of the head of the bed; and avoidance of coffee and smoking, may be useful. Reduction of acid production from the stomach can be achieved with either H_2-histamine blockers or proton pump inhibitors but, of interest, these agents have not been shown to benefit the chronic cough.[55] It is recommended that those with objective evidence of heightened esophageal acid exposure on pH monitoring or with complaints of heartburn should benefit from acid-suppressive therapy provided for 2 months. There is no good evidence for the use of prokinetics, such as domperidone or metoclopramide, which are associated with potential side effects. The effectiveness of antireflux surgery, such as laparoscopic fundoplication in patients with chronic cough associated with GERD disease whose cough has failed to respond to medical therapy, is unclear.

CHRONIC BRONCHITIS/COPD

Chronic bronchitis is diagnosed in patients who produce sputum on most days over at least 3 consecutive months, particularly during the winter months, over at least 2 consecutive years. Although up to 30% of the community smokes tobacco, chronic bronchitis is only reported in 5% of the patients seeking medical attention for cough. In a smoker, the presence of chronic bronchitis may be predictive of progressive irreversible airflow obstruction, leading to COPD. The cough of chronic bronchitis may result from excessive sputum production associated with mucus cell hyperplasia and bronchiolar inflammation. In addition, there is evidence of an increase in capsaicin cough hypersensitivity in patients with COPD.[33]

The productive cough in chronic bronchitis is exacerbated by upper respiratory infections with common viruses or respiratory bacteria or by exposure to irritating dusts or environmental pollutants. Cessation of cigarette smoking is usually accompanied by a reduction in cough, most often within 4 to 5 weeks. Treatment of chronic airflow obstruction with short-acting and/or long-acting β_2-adrenoceptor agonists and anticholinergic agents should be considered, particularly in the presence of dyspnea. Suppression of the inflammatory process in the small airways may be tried with the combination of inhaled corticosteroids and long-acting β-agonists. Mucolytic therapy may reduce the incidence of exacerbations.

In smokers, a change in the pattern or characteristics of their cough, such as an increase in intensity or an accompanying hemoptysis, should lead to an evaluation to exclude the presence of lung cancer. A chest radiograph is mandatory in this situation, with consideration of CT imaging of the chest.

BRONCHIECTASIS

The cough of bronchiectasis is associated with overproduction of airway secretions together with a reduced clearance, often within a vicious circle of recurrent bacterial infections.[56] Usually, the patient produces 30 mL or more of mucoid or mucopurulent sputum per day, sometimes accompanied by fever, hemoptysis, and weight loss. Early- onset bronchiectasis may present solely as a chronic productive cough. Bronchiectasis may be associated with postnasal drip and rhinosinusitis, asthma, GERD, and chronic bronchitis. Common pathogens cultured from sputum include *Haemophilus influenzae, Staphylococcus aureus,* and *Pseudomonas aeruginosa.* The chest radiograph may show increased bronchial wall thickening, particularly in the lower lobes in advanced cases, but thin-section CT of the chest can reveal early changes of airway wall thickening, dilation, and distortion, with mucus plugging, and evidence of bronchiolitis. There is an increased capsaicin cough response in bronchiectasis.[57]

Cough in bronchiectasis is the most effective mechanism for clearing airway secretions. Chest physiotherapy to improve airway clearance remains essential. Cough during infective exacerbations of bronchiectasis may become a tiring symptom. Long-term macrolide therapy may lead to an improvement in exacerbations and lung function. The cough due to bronchiectasis may be controlled by the use of inhaled β_2-agonists to improve mucociliary clearance and reverse any associated bronchoconstriction, by postural drainage of airway secretions, and by the use of intermittent antibiotic therapy. Use of antitussives is not recommended but, in the context of severe cough, some suppressive effect may be clinically beneficial.

ANGIOTENSIN-CONVERTING ENZYME INHIBITORS

Angiotensin-converting enzyme (ACE) inhibitors, often prescribed for the treatment of hypertension and heart failure, produce cough in 2–33% of patients. The cough is typically described as "dry" and associated with a tickly irritating sensation in the throat. It may appear within a few hours of taking the drug or only after taking the drug for weeks or even months. After withdrawal of the drug, the cough disappears within days or weeks. Patients with ACE inhibitor cough demonstrate an enhanced response to the capsaicin inhalation challenge. Accumulation of bradykinin and prostaglandins, which sensitize cough receptors directly, has been implicated. The best course of action for ACE inhibitor cough is to discontinue the treatment and replace it with alternative therapies, such as angiotensin II receptor antagonists. In any patient with cough who is taking an ACE inhibitor, the first step in the workup is to stop the drug and reevaluate if the cough persists.

POSTINFECTIOUS

Postinfectious cough has been reported in up to a quarter of patients with chronic cough, with up to half of patients after *Mycoplasma* or *Bordetella pertussis* infection.[58] *B. pertussis* infection is now increasingly recognized as a cause of a cough that can last for 4 to 6 weeks, particularly in older children and adults. In children, other respiratory infections associated with chronic cough include viruses (respiratory syncytial virus and parainfluenzae), *Mycoplasma,* and *Chlamydiae.* In most patients with a postinfectious cough, the initial trigger is usually an upper respiratory tract infection; the accompanying cough that would have been expected to last for only a week persists for many months. Such patients are often referred to a cough clinic and are usually investigated for the more commonly associated causes of cough. Inhaled corticosteroids are often prescribed but with variable success. Oral steroids may be successful. Macrolide antibiotics or trimethoprim-sulfamethoxazole are effective in eliminating *B. pertussis* but do not alter the subsequent clinical course.[59]

IDIOPATHIC PULMONARY FIBROSIS

Idiopathic pulmonary fibrosis (IPF) is a progressive lung disease characterized by scarring of the lungs. The main symptoms are dyspnea on exertion and a chronic dry or mildly productive cough.[60] The cough is refractory to antitussive therapy and harms the quality of life. Often cough is the first symptom and is more common during the day than at night. Compared to other conditions of chronic cough, IPF patients usually experience higher rates of cough. The cough is often associated with other comorbidities, such as postnasal drip, GERD, or cough-variant asthma. Cough reflex sensitivity to capsaicin is increased in IPF, which could result from fibrotic distortion of the lungs or by the increased levels of neurotrophins.[61] Of note, perhaps because of the added mechanical stress on the lungs, cough has been found to be an independent predictor of progression in IPF.[62]

The cough of IPF can be debilitating and difficult to treat. Comorbid conditions need to be treated. Conventional antitussive therapies, such as opiates, are often not effective. Corticosteroid therapy may sometimes work. The new antifibrotic treatment for IPF, pirfenidone, has been shown in an observational study to reduce cough frequency and subjective cough measures.[63] A trial of thalidomide has indicated some beneficial effect on the cough of IPF.

OTHER CONDITIONS

Other conditions causing cough include bronchogenic carcinoma, metastatic carcinoma, sarcoidosis, chronic aspiration, interstitial lung disease, or left ventricular failure, conditions that can usually be excluded with a normal chest radiograph. Chronic cough may also be associated with obstructive sleep apnea and chronic tonsillar enlargement. Nocturnal cough associated with obstructive sleep apnea usually presents in patients with snoring, nocturnal heart burn, and symptoms of rhinitis.[64] Continuous positive airway pressure therapy with humidification is usually effective. Psychogenic or habit cough is common, particularly in children, and is usually a diagnosis arrived at after exclusion of other causes. Habit cough is a throat-clearing noise made by a person who is nervous and self-conscious. Cough may be associated with a depressive illness, and long-standing cough may in turn cause depression. In the pediatric population other cough etiologies specific for this age group need to be considered: congenital abnormalities, including vascular rings and tracheobronchomalacia (eFig. 37.4); pulmonary sequestration or mediastinal tumors; foreign bodies in the airway (eFig. 37.5) or esophagus; aspiration due to poor coordination of swallowing or esophageal dysmotility; and heart disease.

CHRONIC COUGH OF UNKNOWN CAUSE (IDIOPATHIC COUGH)

Up to 46% of patients with chronic cough have been identified as having idiopathic cough. Patients should be diagnosed with idiopathic cough or unexplained cough only after an intensive diagnostic evaluation and empirical trial of therapies. Also within this group is the chronic refractory cough when the patient does not respond to treatments for an associated cause, such as postnasal drip or GERD. Idiopathic cough is more commonly found in women aged between 50 and 70 years with a cough onset at menopause and associated with autoimmune disorders.[65] They present with an enhanced cough reflex to capsaicin or citric acid and present with features associated with the cough hypersensitivity syndrome,[4] with a persistent tickling sensation in the throat that leads to paroxysms of coughing triggered by changes in ambient temperature, taking a deep breath, laughing, talking, and exposure to cigarette smoke or aerosol sprays or perfumes or to certain odors. Mucosal biopsies from nonasthmatic patients with idiopathic cough showed increased mast cell numbers and airway wall remodeling with sub-basement membrane thickening, increased airway smooth muscle mass, goblet cell hyperplasia, and

increased number of blood vessels.[66] There is an increase in the expression of the neuropeptide, calcitonin gene-related peptide, and the calcium channel, TRPV1, in the airway epithelium that could contribute to the increased cough reflex.[67,68]

Idiopathic cough may also be caused by an increased sensitivity of the larynx to innocuous stimuli that causes the symptoms of laryngeal paraesthesia with cough associated with dyspnea, dysphonia, and laryngeal spasms.[69] Related disease associated with chronic cough may act as triggers to laryngeal hypersensitivity, such as GERD, rhinosinusitis, and asthma. Assessment of laryngeal dysfunction is becoming an important aspect of the management of chronic idiopathic cough.[70] The treatment of chronic idiopathic or refractory cough is dealt with in the next section.

COUGH SUPPRESSION THERAPIES

When the treatment of the cause of cough is not effective or not available, therapies directed at eliminating the symptom of cough irrespective of the cause of the cough should be tried[71] (Table 37.4).

Table 37.4 Treatments for Chronic Cough

TREATING THE SPECIFIC UNDERLYING CAUSE(S)	
Asthma, cough-variant asthma	Bronchodilators and inhaled corticosteroids
Eosinophilic bronchitis	Inhaled corticosteroids; leukotriene inhibitors
Allergic rhinitis and postnasal drip	Topical nasal steroids and antihistamines Topical nasal anticholinergics (with antibiotics, if indicated)
Gastroesophageal reflux	Conservative measures Histamine H_2-antagonist or proton pump inhibitor
Angiotensin-converting enzyme inhibitor	Discontinue and replace with alternative drug such as angiotensin II receptor antagonist
Chronic bronchitis/COPD	Smoking cessation Treat for COPD
Bronchiectasis	Postural drainage Treat infective exacerbation and airflow obstruction
Infective tracheobronchitis	Appropriate antibiotic therapy Treat any postnasal drip
SYMPTOMATIC ANTITUSSIVE TREATMENT: NEUROMODULATORS (ONLY AFTER CONSIDERATION OF CAUSE OF COUGH)	
Chronic cough (all)	Speech and language therapy
Chronic cough affecting quality of life	Amitryptiline Gabapentin
Chronic refractory cough	Slow-release morphine

NONPHARMACOLOGIC APPROACH: SPEECH PATHOLOGY MANAGEMENT

Speech pathology management or cough suppression therapy consisting of breathing exercises, cough suppression therapy, vocal and laryngeal hygiene training, and psychoeducational counseling has been shown to be effective in improving cough symptom scores and cough counts, as well as breathing, voice, and upper airway symptoms.[72] Some studies also report a reduction in capsaicin cough sensitivity and in cough severity. This treatment administered by a speech therapist or respiratory physiotherapist is now offered for patients with refractory chronic cough in specialized cough clinics. Patients with chronic cough who also present with concomitant muscle tension dysphonia and/or vocal cord dysfunction appear to be those who do particularly well with this approach.

PHARMACOLOGIC APPROACH: ANTITUSSIVE THERAPIES

Antitussives may work by inhibition of central mechanisms within the brainstem or of mechanisms involving the peripheral cough sensors in the airways. An ideal antitussive would be one that suppresses the hypertussive component of cough in disease yet allowing the protective cough to be active.

NARCOTIC AND NON-NARCOTIC ANTITUSSIVES

Opiates including morphine, diamorphine, and codeine are often used as antitussive agents.[73–75] (Diamorphine is not prescribed in the United States). At their effective doses, they cause physical dependence, sedation, respiratory depression, and GI constipation. Morphine and diamorphine are usually reserved for the palliative control of cough and pain of terminal cancer patients. Slow-release morphine can be partially effective in controlling severe chronic idiopathic cough without altering the cough reflex response. These opioids also relieve anxiety and pain. Opioids can exacerbate wheezing through the release of histamine, but this is rare.

Codeine, the methylether of morphine, has long been the standard centrally acting antitussive drug against which the pharmacologic and clinical effects of newer drugs have been measured. However, it has mixed antitussive efficacy activity. Although codeine has activity against pathologic cough and cough in normal volunteers, it has little activity on cough in COPD patients or against acute cough of the common cold.[73]

Dextromethorphan is a non-narcotic antitussive, a synthetic derivative of morphine with no analgesic or sedative properties and is usually included as a constituent of many compound cough preparations sold over the counter. It is as effective as codeine in suppressing acute and chronic cough when given orally[73] and has antitussive efficacy against cough associated with upper respiratory tract infections in adults but not in children. Because of the potential adverse effects and of overdosage associated with antitussive preparations containing dextromethorphan in children, it should be avoided in that group. Side effects are few at the usual dose but, at higher doses, dizziness, nausea, vomiting, and headaches may be reported. Dextromethorphan should be used with caution in patients on monoamine oxidase inhibitors in whom central nervous depression and

death has been reported. Levodropropizine, a nonopioid antitussive with peripheral inhibition of sensory cough receptors, has a favorable benefit/risk profile compared with dextromethorphan.[76]

NEUROMODULATORS

Neuromodulatory agents act on the enhanced neural sensitization that underlies idiopathic or refractory cough. Centrally acting neuromodulators, such as amitriptyline, gabapentin, and morphine, have positive effects on cough-specific quality of life. A prospective, randomized, controlled open trial comparing the effectiveness of amitriptyline versus codeine/guaifenesin for chronic cough after an upper respiratory tract infection showed that amitriptyline led to a complete response of the cough in most subjects, whereas none in the codeine/guaifenesin group had a complete response.[77] In a randomized controlled double-blind trial in patients with refractory cough, gabapentin was effective in reducing cough frequency and visual analogue scores while improving Leicester Cough quality-of-life scores, without affecting the capsaicin cough response.[78] In another randomized, controlled trial of patients with refractory cough, a combination of speech pathology therapy and pregabalin, which is related to gabapentin, reduced cough severity and cough frequency and improved quality of life when compared to speech pathology therapy alone.[79] Both amitriptyline and gabapentin have central antinociceptive actions and may modulate presynaptic *N*-methyl-D-aspartate receptors, leading to reduced transmitter release and postsynaptic excitability. In addition, gabapentin may have an action on gamma-aminobutyric acid neurotransmission or voltage-gated ion channels in the spinal cord and brain. The effectiveness of neuromodulators suggests that chronic cough can be a neuropathic condition in some patients.[4]

EXPECTORANTS AND MUCOLYTICS

Expectorants and mucolytics may alter the volume of secretions or their composition. Despite a lack of good evidence, mucolytic agents such as acetylcysteine, carbocysteine, bromhexine, and methylcysteine are often used to facilitate expectoration by reducing sputum viscosity in patients with chronic bronchitis. A small reduction in the number of exacerbations of bronchitis has been reported with oral acetylcysteine, accompanied by small improvement in cough, a decrease in volume of sputum, and some ease of expectoration.[80] Aromatic agents such as eucalyptus and menthol have decongestant effects in the nose and may be useful in short-term relief of cough.[73] Menthol inhibits capsaicin-induced cough in normal volunteers and acts through a cold-sensitive TRP receptor, TRPM8. Demulcents also form an important component of many proprietary cough preparations and may be useful because the thick sugary preparation may act as a protective layer at the mucosal surface.

POTENTIAL NEUROMODULATORS

New cough suppressants in development include blockers of ion channels on vagal afferent endings and centrally acting agents.[5,14,74] Preclinical studies have identified TRP channels as an exciting target for cough suppression. However, TRPV1, TRPA1, and TRPV4 antagonists all failed in clinical trials for chronic refractory cough. The most promising target currently is the ATP P2X2/3 receptor. A P2X2/3 antagonist, gefapixant, has shown efficacy in suppressing chronic cough in phase II clinical trials with a reduction in cough frequency of 75%[81] and it is currently undergoing phase III testing. The most notable side effect of gefapixant is a reduction in taste because P2X2 receptors are not only expressed by airway sensory nerves but also by gustatory nerves involved in taste processing. More selective P2X3 antagonists are in early phases of development and may reduce the off-target effects further.[5,82] Voltage-gated sodium channels, channels that initiate and conduct action potentials, are also a promising target. Lidocaine is a nonselective blocker of this family of sodium channels and displays some efficacy for cough reduction. The NaV1.7 subunit has been found to be involved in the control of cough responses to citric acid in guinea pigs,[83] but as yet there are no specific blockers of NaV1.7. Centrally acting agonists of the alpha-7 nicotinic acetylcholine receptor are also undergoing development for cough. This target arose from studies demonstrating that nicotine exposure acutely reduced cough sensitivity in humans[84] through an action believed to reside within the CNS. Alpha-7 cholinergic receptors may be expressed on central pathways that mediate cough inhibition.[85] Finally, centrally acting neurokinin 1 receptor antagonists are also currently in trial for chronic refractory cough, showing improvements in cough frequency and patient quality of life in early phase II trials.[86]

Key Points

- Cough may be a sign of disease inside or outside the airways and lungs and a useful indicator for both patient and physician for initiating a diagnostic evaluation and treatment of disease processes.
- Impairment or absence of coughing can be harmful or even fatal in disease. On the other hand, when cough is chronic and excessive, it can itself be harmful and deleterious and may need to be suppressed directly.
- The most sensitive sites for initiating cough are the larynx and tracheobronchial tree.
- In the management of a patient with cough, the first step is to identify the cause(s) of the cough and then treat the cause(s).
- Postnasal drip, asthma, and gastroesophageal reflux are the three most common conditions associated with a chronic cough, and a diagnostic approach to exclude these conditions early on is sensible.
- Many cigarette smokers have a chronic cough, but a change in the pattern or characteristics of their

cough, such as an increase in intensity or an accompanying hemoptysis, should lead a smoker to seek medical attention. A chest radiograph is mandatory in this situation.

- Patients with chronic cough while on angiotensin-converting enzyme inhibitor therapy should discontinue such therapy, with replacement by other appropriate treatments.
- The cough hypersensitive syndrome is defined as a disorder characterized by troublesome coughing triggered by low levels of thermal, mechanical, or chemical exposure, with a persistent tickling sensation in the throat that leads to paroxysms of coughing triggered by changes in ambient temperature; taking a deep breath; laughing; talking; and exposure to cigarette smoke, aerosol sprays, perfumes, or certain odors.
- When the treatment of the cause of cough is not effective, neuromodulatory therapies directed at controlling the hypersensitive cough, irrespective of the cause of the cough, should be tried.

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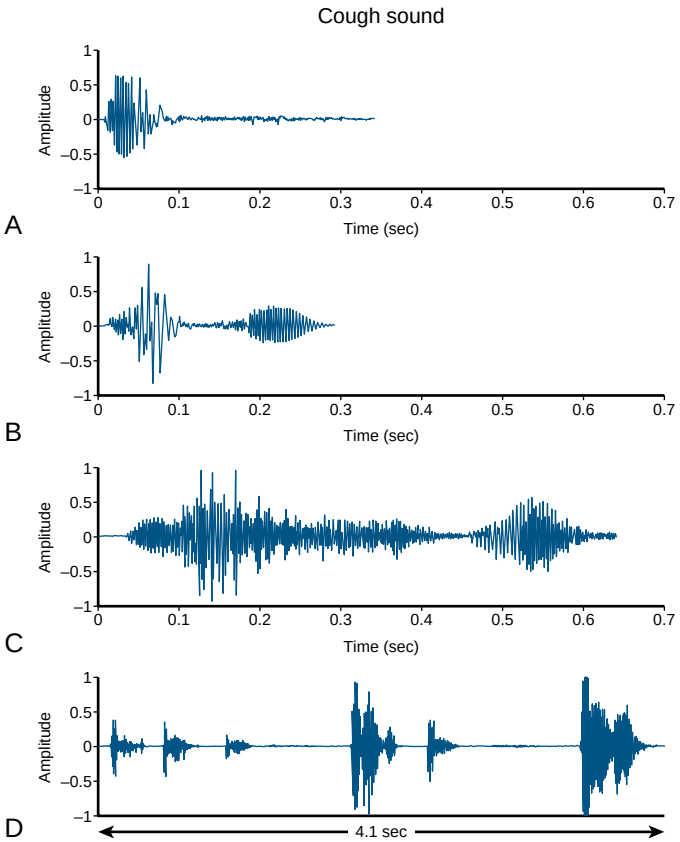
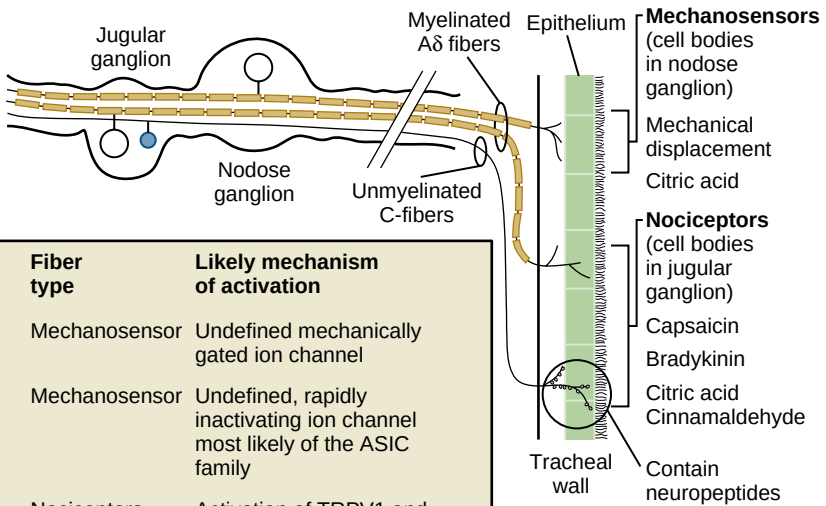
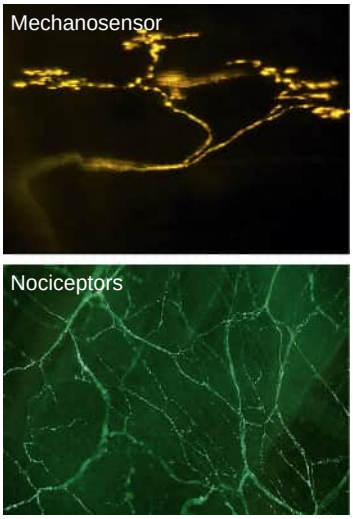
Complete reference list available at ExpertConsult.com.



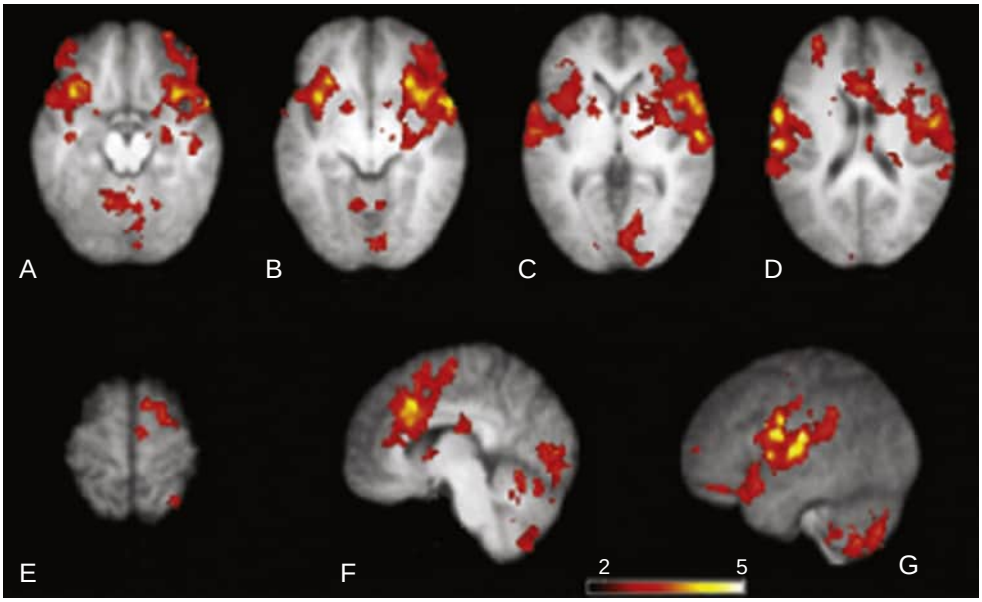
eFigure 37.1 Cough sound waveforms from patients with a chronic cough. (A) Two phases with an initial expulsive phase that is the first cough sound, followed by an intermediate phase with decreasing sound from an idiopathic chronic cough (B) and from a patient with pulmonary tuberculosis (C). These show an additional third phase called *voiced* or *glottal phase,* which gives rise to a second cough sound (refer to Audio 37.1). (D) An epoch of six coughs in succession in a female subject with chronic idiopathic cough (refer to Audio 37.2). (Courtesy Sergio Matos and Surinder Birring, Kings College Hospital, London, and Richard Turner, Charing Cross Hospital, London.)



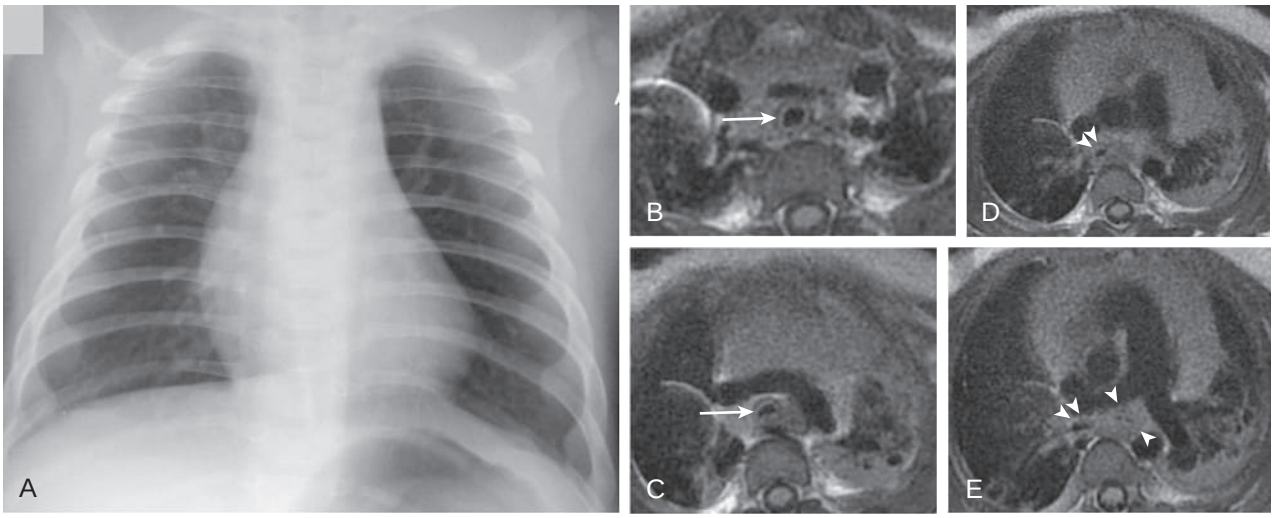
Tussive stimulus	Fiber type	Likely mechanism of activation
Mechanical displacement	Mechanosensor	Undefined mechanically gated ion channel
Citric acid	Mechanosensor	Undefined, rapidly inactivating ion channel most likely of the ASIC family
	Nociceptors	Activation of TRPV1 and activation of undefined ASIC
Capsaicin	Nociceptors	Activation of TRPV1 channels
Bradykinin	Nociceptors	B2 receptor-mediated activation of TRPV1 channels. This may involve protein kinase C and lipoxygenase enzymes
Cinnamaldehyde	Nociceptors	Activation of TRPA1 channels



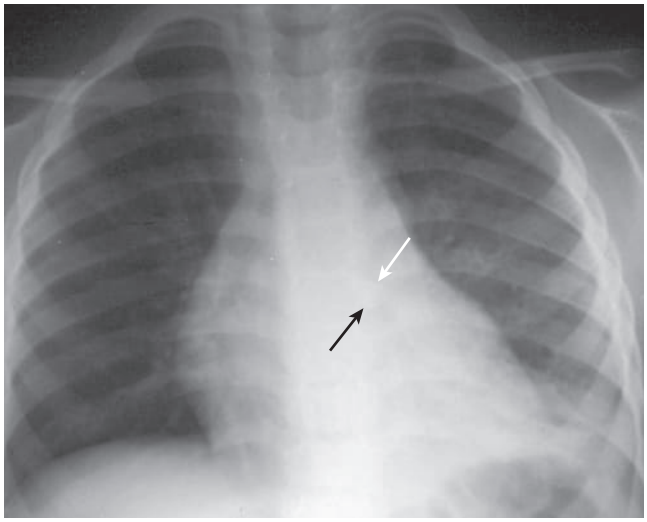
eFigure 37.2 Vagal afferent innervation of guinea pig trachea. Mechanism of sensory nerve stimulation by various cough-inducing stimuli *(table inset)*. The micrographs show the structure of airway mechanosensors *(upper)* and nociceptors *(lower)*. ASIC, acid-sensing ion channel; TRPA1, transient receptor potential ankyrin 1; TRPV1, transient receptor potential vanilloid-1 receptor. (Modified from Undem BJ, Carr MJ, Kollarik M. Physiology and plasticity of putative cough fibers in the guinea pig. *Pulm Pharmacol Ther.* 2002;15:193–198.)



eFigure 37.3 Activation of brain pathways associated with inhalation of capsaicin to cause an urge to cough shown by functional magnetic resonance imaging in normal subjects. The images show activity combined from the different subjects at different levels of the brain. The majority of regional activations were distributed in both hemispheres, including the orbitofrontal cortex (A), inferior frontal gyrus (A and B), anterior insula (B and C), superior temporal gyrus (C), and primary motor and somatosensory cortices (D and G). Midline capsaicin activations include the supplementary motor area (E) and the anterior midcingulate cortex (F). The locations of capsaicin activations in the primary motor and somatosensory cortices were at the caudal end of the central sulci in both hemispheres (D) and are clearly discernible on the three-dimensional rendering of the left hemisphere. (From Mazzone SB, McLennan L, McGovern AE, et al. Representation of capsaicin-evoked urge-to-cough in the human brain using functional magnetic resonance imaging. *Am J Respir Crit Care Med.* 2007;176:327–332.)



eFigure 37.4 Chest radiograph and computed tomography of a child with cough due to tracheobronchial malacia. (A) Frontal chest radiograph in a pediatric patient with tracheobronchial malacia and cough shows diffusely decreased left lung attenuation compared with the right lung, suggesting diffuse air trapping. (B–E) Axial thoracic double inversion recovery T1-weighted magnetic resonance images show a circumferentially thickened tracheal wall (*arrows,* B–C) with a thickened and narrowed right mainstem bronchus (*double arrowheads,* D–E). The left mainstem bronchus (between *single arrowheads,* E) is severely thickened and narrowed, which resulted in the diffuse left lung air trapping seen in A. (Courtesy Michael B. Gotway, MD.)



eFigure 37.5 Chest radiograph of a child with cough due to an aspirated tooth. Frontal chest radiograph in a pediatric patient with unexplained cough shows an aspirated tooth *(arrows)* in the left mainstem bronchus. (Courtesy Michael B. Gotway, MD.)

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38 CHEST PAIN

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INTRODUCTION
EPIDEMIOLOGY
NEUROBIOLOGY OF PAIN
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Visceral Pain
HYPERALGESIA
MEASURING PAIN
CHEST PAIN SYNDROMES
Pleuropulmonary Disorders
Tracheobronchitis
Inflammation or Trauma of the Chest Wall
Cardiovascular Disorders
NONCARDIAC CHEST PAIN
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Psychological Factors
EVALUATION OF CHEST PAIN
Cardiac Ischemia
Pulmonary Embolism
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Cardiac Tamponade
Pulmonary Hypertension
Thoracic Aortic Dissection
Pneumothorax
Thoracic Outlet Syndrome
Chest Trauma
Gastroesophageal Reflux
Pancreatitis
KEY POINTS

INTRODUCTION

Pain is a complex, subjective experience that varies from person to person in its quality, intensity, duration, location, frequency, and associated features. Its perception is influenced by a subject's culture, emotional and cognitive states, socioeconomic status, familial background, psychological factors, anticipation and previous experience, and the clinical context.

Chest pain is characterized by an unpleasant sensation either localized to the thorax or believed to originate from structures located there. It may announce the presence of severe, occasionally life-threatening disease. Diagnosis of chest pain is often complicated by the vague presentations and indistinct anatomic localization of many of its causes.

Given the wide variety of causes and seriousness of chest pain, considerable clinical judgment is required to decide which patients should be thoroughly evaluated and which tests should be used in the workup. In many instances, empirical therapy may need to be initiated even as evaluation proceeds, with subsequent readjustments in treatment protocols as more information is obtained that clarifies the clinical picture.

The most definitive treatment of chest pain, whatever its origin, is to find its cause and to cure it. The general principles of evaluation for respiratory, cardiac, musculoskeletal, esophageal, and panic disorders are available, and the clinician is encouraged to refer to them. Chronic noncardiac chest pain is more difficult to manage, especially when its trigger cannot be found. Because of the complexities and difficulties in dealing with patients who have chronic, severe, and often refractory pain, referral to special pain centers staffed by a multidisciplinary team of specialists is recommended. At times, psychiatric consultation for specific therapies may be helpful.

EPIDEMIOLOGY

Chest pain is often an important factor in studies of acute pain that warrants medical attention. In a study of randomly selected Canadian households, 16% of respondents reported experiencing pain within the 2 weeks preceding the survey.[1] Chest pain was the fifth most common type of temporary pain. Another survey involving selected enrollees of a health care plan revealed a high incidence of pain lasting a whole day or more, several times during the previous 6 months.[2]

Chest pain accounted for 12% of the reported cases but was the most common site of pain that prompted respondents (35%) to seek medical attention. Pain is also a common reason for visits to hospital emergency departments. In one study, stomach pain, other abdominal pain, and chest pain were the most often cited reasons and together accounted for 10.7% of all emergency department visits.[3]

NEUROBIOLOGY OF PAIN

Pain is not a simple sensation. The neurobiologic and functional components of the sensory channels for pain are neither fixed nor immutable. The nervous system, from the level of the nociceptor (the receptor that responds to noxious stimuli) to the supraspinal sites of integration, is characterized by a dynamic response (plasticity) to tissue insult.

Pain arising from *visceral* organs, such as the heart or *gastrointestinal* (GI) tract, differs in many ways from pain originating from *somatic* structures, such as the skin. Visceral pain is difficult to localize, is diffuse in character, and is typically *referred to* somatic structures. Pain is referred when pain is perceived to be arising from a different location from the original source of the pain (Fig. 38.1).

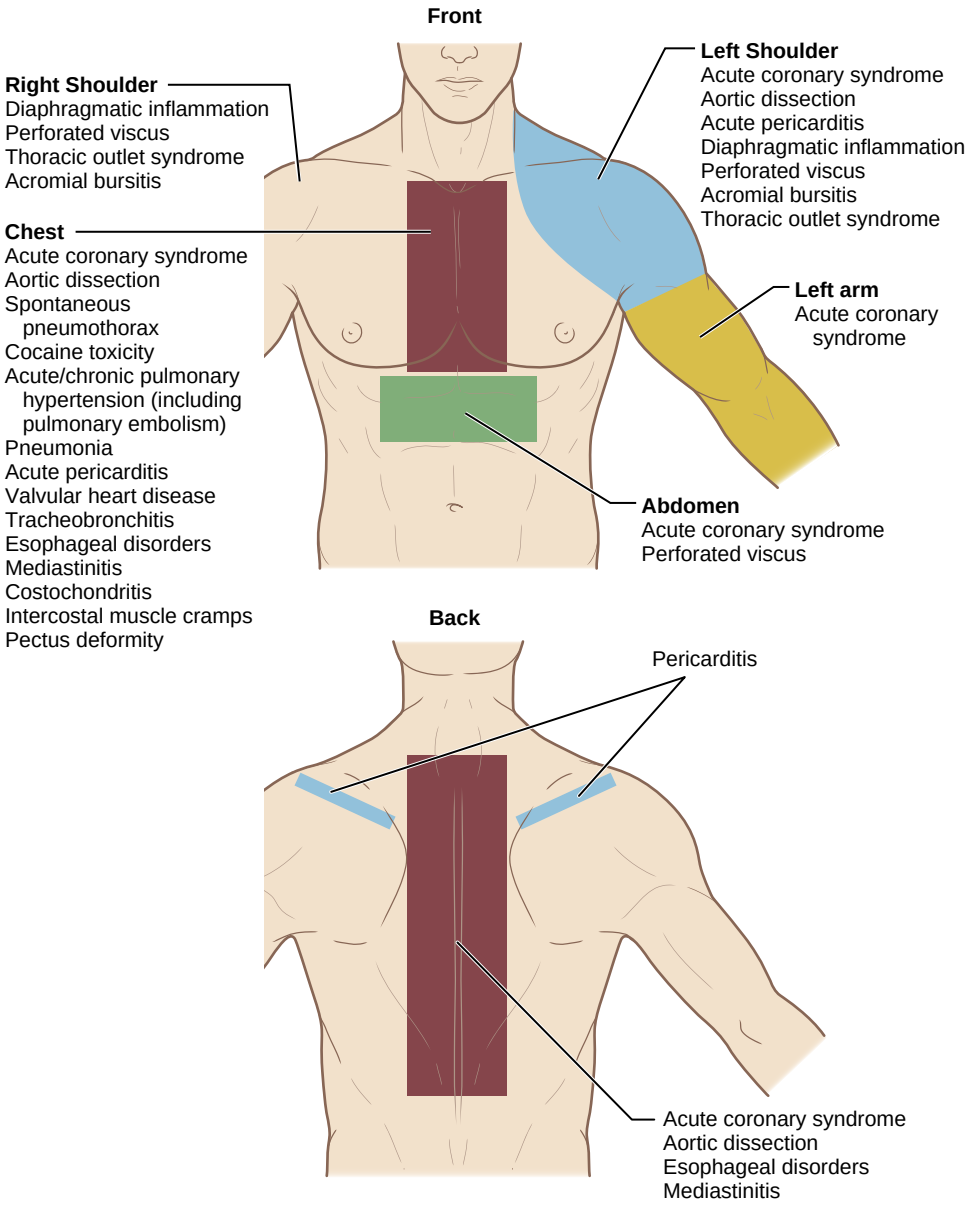

Figure 38.1 Sites of referred pain in the chest. Some conditions are shown that should be considered as sources of referred pain in certain locations of the chest. Referred pain is generally due to viscerosomatic convergence, in which spinal cord neurons receive input from both visceral and somatic sources so that visceral pain can be interpreted as coming from a somatic source. Not shown are psychological causes of pain, which may constitute one of the most common entities, although it should remain a diagnosis only after considering and excluding these sources of pain.

In addition, visceral pain is often associated with greater autonomic and motor responses than is somatic pain. These differences between visceral and somatic pain are related to the characteristic features of sensory innervations that are unique to the viscera.

SOMATIC PAIN

Somatic structures, such as the skin, are invested with a wide variety of nociceptors, each with selective sensitivities to mechanical, thermal, or chemical stimuli, in addition to the polymodal nociceptor that responds to multiple modalities of noxious stimuli.[4,5] Cutaneous nociceptors are characterized by very infrequent or no spontaneous discharges, an ability to encode stimulus intensities in the noxious (but not innocuous) range, and most important, sensitization.

Sensitization refers to an increase in the magnitude of response after tissue insult, sometimes associated with an increase in spontaneous activity and a decrease in response threshold. This attribute of nociceptors contributes to development of hyperalgesia, or an increased response to a painful stimulus.[6] When a tissue is injured, a host of sensitizing chemicals are synthesized at the site of injury or released from circulating cells attracted to the site of injury. These include amines (e.g., histamine and serotonin), peptides (e.g., substance P and calcitonin gene-related peptide), kinins (e.g., bradykinin), neurotrophins, cytokines, prostaglandins, leukotrienes, excitatory amino acids (e.g., glutamate), and free radicals. It is unlikely that any one putative chemical mediator is responsible for nociceptor sensitization.

VISCERAL PAIN

Normal input to the *central nervous system* (CNS) from aortic baroreceptors, gastric chemoreceptors, and pulmonary stretch receptors is rarely perceived. Nevertheless, visceral afferents possess many of the characteristics of nociceptors and may be perceived when abnormal.

All viscera possess a dual innervation. Organs of the thoracic cavity are innervated by vagal afferent fibers with cell bodies in the nodose and jugular ganglia and by spinal afferent fibers with cell bodies in the thoracic dorsal root ganglia. Unlike their somatic counterpart, spinal visceral afferent fibers typically traverse either or both prevertebral and paravertebral ganglia en route to the spinal cord. Thus, in contrast to somatic input to the CNS, which has a single, usually spinal, destination, input to the CNS from organs in the thoracic cavity arrives at two locations, namely the brainstem nucleus tractus solitarii (vagal afferent input) and the thoracic spinal cord (spinal afferent fibers). In accordance, the potential exists for interaction in the CNS from inputs arising from the same thoracic organ. The esophagus and heart also possess an intrinsic nervous system with cell bodies in the organ wall or in ganglia in the epicardial fat.[7]

Somatic and visceral afferents also have a different density of innervation and spinal pattern of termination. In general, the number of visceral afferent fibers is much less than the number of somatic afferent fibers. Although this means that there are fewer central visceral terminals in the spinal cord, visceral afferent fiber terminals have many more terminal swellings (suggestive of synapses) than somatic nociceptor terminals, and they spread their afferent impulses over several spinal cord segments.[8] The obvious consequence of the low number of visceral afferents and greater intraspinal spread is loss of spatial discrimination, consistent with the diffuse, difficult to localize nature of visceral pain.

The axons of visceral sensory neurons are, with rare exception, either thin myelinated Aδ fibers or unmyelinated C fibers. In general, Aδ fibers, having some myelin, carry moderately fast impulses, usually of acute or sharp pain but also of temperature. C fibers, without myelin, carry slow impulses, usually of burning pain. In general, the proportion of Aδ fibers in visceral sensory nerves is less than the proportion of C fibers. In addition, Aδ fibers are fibers with a low threshold for response to mechanical stimulation, whereas C fibers have high thresholds; however, this is not universal.

Unlike tissue-damaging stimuli that produce pain in somatic structures, tissue injury is not required for production of pain in the viscera. For the lower airways, irritants contained in smoke, ammonia, and other inhaled substances are capable of producing discomfort and pain. For the heart and mesentery, ischemia can be an adequate stimulus.[9] For hollow organs of the GI tract, distention of the lumen of the organ, which activates stretch and tension receptors in the smooth muscles, is typically sufficient.

Hollow viscera, including the esophagus, are innervated by two populations of mechanosensitive afferent fibers, namely a larger group (70–80%) of fibers that have low thresholds for response (i.e., within the physiologic range) and a smaller group (20–30%) of fibers that have thresholds for response that fall in the noxious range.[10] All mechanosensitive visceral afferent fibers may function in some circumstances as nociceptors, and low- and high-threshold mechanosensitive fibers contribute to discomfort and pain that arise from the viscera.

Silent nociceptors, a relatively new category of receptor/afferent fibers, may also contribute to altered sensations from visceral structures.[11] Silent nociceptors, more appropriately termed *mechanically insensitive afferents,* have no spontaneous activity and do not respond to acute, high-intensity mechanical stimulation in normal circumstances. After tissue insult, mechanically insensitive afferents typically begin to discharge spontaneously and acquire sensitivity to mechanical stimulation. The contribution of such "silent" or "sleeping" afferent fibers to altered sensations that arise from the viscera continues to be studied.[12,13]

HYPERALGESIA

Some individuals are uniformly more sensitive (i.e., have lowered thresholds for stimulus-produced pain) than others. *Hyperalgesia,* the enhanced response to a stimulus that is normally noxious, consists of primary and secondary components. *Primary hyperalgesia* is the enhanced sensitivity to stimuli applied at the site of tissue injury (e.g., an incision). *Secondary hyperalgesia,* conversely, is the enhanced sensitivity to stimuli applied to uninjured tissue adjacent to, and occasionally distant from, the site of injury. Peripheral mechanisms (sensitization of nociceptors and afferent fibers innervating the insulted tissue) contribute to primary hyperalgesia and central mechanisms (changes in the excitability of spinal and supraspinal neurons) contribute to secondary hyperalgesia.[14] In the spinal cord, glutamate and substance P are co-contained in many small-diameter dorsal root ganglion cells and presumably are concurrently released in the spinal dorsal horn, where *N*-methyl-D-aspartate receptors on nociceptor terminals may act as autoreceptors to facilitate the further release of both glutamate and substance P.[15] In addition, substance P can act synergistically with glutamate to enhance the responses of spinal neurons.[16]

Virtually all spinal cord neurons that receive a visceral input also receive input from somatic structures, including the skin, muscle, and joints. This convergence of inputs in the spinal dorsal horn is believed to be the basis of the referred sensation that characterizes visceral pain. Such convergence suggests that injury to somatic tissue could lead to visceral hyperalgesia and, conversely, that injury to a viscus could lead to somatic hyperalgesia.

Spinal nociceptive transmission can be modulated by electrical or chemical stimulation in the midbrain or medulla.[17] Both facilitatory and inhibitory influences on spinal nociceptive transmission are present and likely play important roles in the maintenance of secondary hyperalgesia.[18] Electrical activation of vagal afferent fibers similarly engages descending facilitatory and inhibitory modulation of spinal nociceptive transmission. In studies of rats, responses of neurons in the thoracic dorsal horn to either esophageal distention[19] or lower airway irritation caused by ammonia or smoke[20] are altered when the cervical spinal cord is blocked or transected or when the vagi are cut. Responses to esophageal or respiratory stimulation would be expected to increase when the cervical spinal cord is blocked because tonic descending inhibitory influences usually present would be removed. Unexpectedly, responses were found to be more commonly reduced, suggesting the presence of a descending facilitatory influence associated with vagal input to the brainstem. Both vagal afferent input and spinal cardiac nerve afferent inputs contribute to the sensation of cardiac pain, particularly referral of such pain to the neck and jaw.[21]

MEASURING PAIN

Pain has proved to be both hard to define and difficult to measure. Because pain can be quantified only indirectly, it has been difficult to determine the optimal measuring tool for all types of pain sensations. Two widely used techniques, namely rating scales and questionnaires, are often used in clinical and epidemiologic studies of chest pain.

Rating scales constitute the simplest measurement of pain. One of the easiest to use is the quantification of pain intensity by a graded rating scale, such as the popular visual analogue scale.[22] However, the sensation of pain has many more components than just its intensity. Thus a single-dimensional rating scale leaves many aspects of the sensation undocumented.

To address the multidimensional qualities of pain, questionnaires have been developed.[23,24] Although questionnaires are a powerful way of obtaining data on both the qualitative and the quantitative aspects of pain, it is not always possible to compare the results of studies using the same questionnaire because of differences in the way they have been used.

CHEST PAIN SYNDROMES

Given the proximity of the various organs and the vagaries of perception of pain of visceral origin, pain arising from the various viscera in the thoracic cavity and from the chest wall is often qualitatively similar and exhibits overlapping patterns of referral, localization, and quality. This leads to difficulty in the differential diagnosis of chest pain (Table 38.1). Nevertheless, many chest pain syndromes are so distinctive that diagnostic efforts often rely on accurate description of the characteristic pattern of pain. The importance of the medical history in unraveling the various causes of chest pain cannot be overemphasized. The locations to which various pain syndromes are referred in the chest are illustrated in Fig. 38.1 (see also Chapter 18).

Table 38.1 Common Causes of Chest Pain

PLEUROPULMONARY DISORDERS
Collagen vascular disease
Familial Mediterranean fever
Malignancy (e.g., mesothelioma)
Pleurisy
Pneumothorax
Pulmonary embolism
Pulmonary hypertension
Sickle cell disease
TRACHEOBRONCHITIS
Infection
Inhalation of irritants
Malignancy
INFLAMMATION OR TRAUMA OF THE CHEST WALL
Herpes zoster infection
Infection
Malignancy
Muscle injury (myalgia)
Neuritis-radiculitis
Rib fracture
Sickle cell disease
CARDIOVASCULAR DISORDERS
Angina pectoris
Angina (variant)
Aortic valve disease
Cocaine toxicity
Eisenmenger syndrome
Hypertrophic cardiomyopathy
Mitral valve prolapse
Myocardial infarction
Pericarditis
DISORDERS OF THE AORTA
Aortic dissection
GASTROINTESTINAL DISORDERS
Cholecystitis
Disorders of intestinal motility
Esophageal motility disorders
Pancreatitis
Peptic ulcer disease
Reflux esophagitis
MISCELLANEOUS
Iatrogenic
Mediastinitis
Thoracic outlet obstruction

PLEUROPULMONARY DISORDERS

Although the lung parenchyma and visceral pleura are considered to be insensitive to ordinary noxious stimuli, immunohistochemical studies from vagal denervation and talc-pleurodesis animal models indicate the presence of nerve fibers in the visceral pleura that may be capable of conducting pain stimuli.[25,26] Pain does arise from stimulation of the mucosa of the trachea and main bronchi.[25] The lungs and bronchi are innervated with mechanoreceptors that respond to stretch (inflation or deflation of the lungs) and chemoreceptors called J receptors that respond to a variety of pain-inducing chemicals, including bradykinin, prostaglandins, serotonin, and capsaicin.[27,28] Inhalation of irritant substances, such as ammonia, can trigger a cough reflex and can produce a sensation of rawness, tightness in the chest, and pain. In addition, rapidly adapting mechanoreceptors that respond to lung deflation are also "irritant receptors" and signal respiratory pain. The J receptors have been proposed to contribute to discomfort and pain that accompanies breathlessness.[27–29]

These receptors are, in turn, innervated by vagal and spinal splanchnic afferent fibers. Most important are the nerve fibers that travel in the vagus nerves, including myelinated axons that carry impulses from slowly adapting stretch receptors in the conducting airways, myelinated axons that lead from rapidly adapting irritant cough receptors in the trachea and bronchi, and unmyelinated axons that subserve the extensive network of C fiber receptors (e.g., "pulmonary" J receptors and "bronchial" C fibers).[30]

The pulmonary causes of chest pain may be related to the pleural tissue, pulmonary vessels, or lung parenchyma. Causes of chest pain related to the lung parenchyma include infection, cancer, or chronic diseases, such as sarcoidosis.

Pleurisy

Pleurisy is a pain typically worse with breathing, which results from inflammation of the parietal pleura.

Inflammatory processes in the periphery of the lung that involve the overlying visceral pleura (e.g., pneumonia) frequently cause inflammation of the adjacent parietal pleura that, in turn, provokes pleuritic pain conveyed by somatic nerves. The portion of the parietal pleura that lines the interior of the rib cage and covers the outer portion of each hemidiaphragm is innervated by the neighboring intercostal nerves. When pain fibers in these regions are stimulated, pleuritic pain is localized to the cutaneous distributions of the involved neurons over the chest wall. In contrast, the parietal pleura that lines the central region of each hemidiaphragm is innervated by fibers that travel with the phrenic nerves. When this portion of the diaphragm is stimulated (e.g., by contiguous inflammation), the resulting pain is referred to the ipsilateral shoulder or neck. This pain referral likely arises because visceral afferent input carried by the phrenic nerve converges with somatic input carried by the supraclavicular nerves that innervate the skin of the shoulder onto C3–C5 spinal dorsal horn neurons (i.e., viscerosomatic convergence, a common feature of visceral pain leading to referred sensations). Thus, when this portion of the diaphragm is stimulated, the resulting pain is referred to the ipsilateral shoulder or neck.

Because of the somatic innervation of the parietal pleura and the localization of most diseases of the lungs or chest wall to one hemithorax or the other, pleuritic pain tends to be limited to the affected region rather than be diffuse, with the exception of referral to the ipsilateral neck or shoulder. Pain may be variously described as "sharp," "dull," "achy," "burning," or simply a "catch." There is a distinctive and unmistakable relationship to breathing movements, and taking a deep breath typically aggravates pleuritic pain.[31] Coughing and sneezing can cause intense distress. Movements of the trunk, such as bending, stooping, or turning in bed, worsen pleuritic pain, so much so that patients often prefer the body position that minimizes the motion of the affected region.

An immediate onset of pleuritic pain suggests traumatic injuries or spontaneous pneumothorax. A sudden onset, often associated with dyspnea and tachypnea, also characterizes the clinical presentation of *pulmonary embolism* (PE).[32] A slower, but still acute, onset over minutes to a few hours often heralds the development of community-acquired bacterial (typically pneumococcal) pneumonia, especially when accompanied by fever and chills. Recurrent acute pleuritic pain is a feature of familial Mediterranean fever.[33] Finally, a gradual onset over days or weeks, often associated with features of chronic illness, such as low-grade fever, weakness, and weight loss, suggests tuberculosis or malignancy.

Pulmonary Hypertension

Persons with pulmonary hypertension may experience crushing or constricting substernal pain that, at times, radiates to the neck or arms, resembling the pain of myocardial ischemia.[34] Pain from pulmonary hypertension has been reported in patients with conditions that are acute (e.g., multiple or massive pulmonary emboli) and chronic (e.g., Eisenmenger syndrome, pulmonary vasculitis, or mitral stenosis). In addition, approximately half of the patients with primary pulmonary hypertension may experience substernal chest pain.[35]

In acute pulmonary hypertension resulting from massive PE, the pain may be caused by sudden distention of the main pulmonary artery and stimulation of mechanoreceptors. In pulmonary arterial hypertension, chest pain may be related to either (1) right ventricular ischemia because coronary blood flow is unable to meet the metabolic needs of the overloaded right ventricular muscle mass as the latter strives to maintain sufficient systolic and diastolic pulmonary arterial pressures[36] or (2) compression of the left main coronary artery by the dilated pulmonary artery trunk.[37]

Although substernal pain related to the sudden onset of pulmonary hypertension can develop in cases of acute PE, embolism-associated pain is much more likely to be pleuritic in character, whether or not there is pulmonary infarction.[38] Pulmonary artery stenosis may also cause substernal pain, presumably by the same pressure-overload mechanism through which pulmonary hypertension with right ventricular hypertrophy provokes pain.[39]

TRACHEOBRONCHITIS

Pain of tracheal origin is generally felt in the midline, anteriorly, from the larynx to the xyphoid. Conversely, pain from either main bronchus is felt in the ipsilateral anterior chest near the sternum or in the anterior neck near the midline.[40] Whatever its origin, pain related to tracheobronchitis is typically described as "raw" or "burning" but may be "dull" or "achy" and is exaggerated by deep breathing. This type of discomfort usually denotes the presence of viral or bacterial tracheobronchitis or, less often, a malignancy but can also be experienced during exposure to noxious gases. Tracheobronchial pain is thought to be mediated by bronchial C fibers, and experimentally induced tracheal pain can be abolished by vagal blockade[41] or by vagotomy.[42]

INFLAMMATION OR TRAUMA OF THE CHEST WALL

Inflammation of, or trauma to, the joints, muscles, cartilages, bones, and fasciae that constitute the thoracic cage can cause chest pain.[43–45] Fibromyalgia, fibrositis, and other rheumatologic disorders of the thoracic cage, such as ankylosing spondylitis, are known to cause pain and discomfort in the chest.[46] Acute or chronic inflammation of the xiphoid process (xiphodynia)[47] and superficial thrombophlebitis of the chest wall (Mondor syndrome)[48] may also be uncommon sources of chest pain. On occasion, pain related to breathing may be experienced along the costal margins after vigorous exercise.[49] In addition, metastatic malignancy may present as painful lesions of the chest wall or with pain from a related rib fracture. Another source of chest pain is infectious arthritis of the sternoclavicular joint or costochondral junctions, which is a known problem among injection drug users.[50]

With *costochondritis,* chest wall pain arises from the costochondral cartilaginous junctions. It is usually described as "dull with a gnawing, aching quality." There is little, if any, relationship to breathing or other body movements. Tenderness to palpation is clearly localized to one or more of the costal cartilages.[51] There may be redness, swelling, and enlargement of the costal cartilages (Tietze syndrome). The most common sites of costosternal perichondritis are

the second, third, and fourth cartilages, but any part of the sternum along the central and lower portions of the anterior thoracic cage may be involved.

The pain of *intercostal neuritis* or *radiculitis,* which often originates from disorders of the cervicodorsal spine or nerve roots, is usually perceived in the rib cage. The superficial, spontaneous lancinating or electric shock-like pain of intercostal neuritis is typically felt over the cutaneous distribution of the involved nerves and may be worsened by taking deep breaths, coughing, and sneezing. Unlike pleurisy, neuritic pain is usually not aggravated by ordinary breathing, and the diagnosis is supported by the presence of hyperalgesia or anesthesia on examination of the skin. In some patients with neuritis/radiculitis, the diagnosis becomes evident 2 or 3 days later with the development of the characteristic vesicular rash of herpes zoster over the involved dermatome. Painful radiculitis is also recognized as an important early manifestation of Lyme disease.[52]

Injuries to the ribs (fracture) and thoracic cage muscles (strain, tears, or hematoma) are common causes of localized chest pain. The relationship of the pain to trauma is obvious in most instances, but diagnosis may be elusive, particularly if the inciting event is relatively minor (e.g., unnoticed episode of coughing) or when the onset of pain is delayed.

CARDIOVASCULAR DISORDERS

Mechanosensitive and chemosensitive afferent fibers are present in the myocardium.[27,53] Chemical stimuli are believed to be the most important causes of cardiac pain, but mechanical distention or distortion may also play a role.[54] Sensory fibers travel from the heart to the spinal cord through the several cardiac nerves, the upper five thoracic sympathetic ganglia, and finally, the upper five thoracic dorsal roots. Afferent fibers also reach the brain through the vagus nerves.[55] Activity in these afferent fibers contained in the spinal afferent innervation of the heart contributes to location of perceived and referred chest pain symptoms.

Acute Coronary Syndrome

Acute coronary syndrome includes all conditions with myocardial ischemia caused by obstruction to coronary blood flow. *Angina pectoris* due to myocardial ischemia is typically described as severe "pressure," "squeezing," or "constriction" with maximal intensity retrosternally or over the left parasternal border. Radiation to the neck, jaw, shoulder, or down the inner aspect of one or both arms may be present. It is usually induced by exercise but may be provoked by heavy meals, excitement, or extreme emotion. Pain tends to recur with repeated provocation, although its severity may vary. Pain usually subsides within 2 to 10 minutes with rest, and relief is accelerated by treatment with sublingual nitroglycerin.[56,57]

Prinzmetal or variant angina is similar in quality and location to typical angina pectoris but appears at rest rather than during exercise or during times of increased myocardial oxygen needs.[58] In this syndrome, the imbalance between myocardial oxygen supply and demand is postulated to arise from epicardial coronary artery vasospasm, usually superimposed on noncritical atheromatous vessel narrowing.

Stress cardiomyopathy, also known as takotsubo cardiomyopathy, apical ballooning syndrome, or broken heart syndrome, can present with similar clinical features to an acute coronary syndrome, including anginal-like chest pain, ischemic *electrocardiogram* (ECG) changes, and elevated cardiac biomarkers. However, a hallmark of stress cardiomyopathy is the absence of a culprit obstructive coronary lesion at the time of coronary angiography. Moreover, the distal left ventricle becomes akinetic with compensatory hypercontractility of the base of the heart (also known as apical ballooning) in a manner atypical for acute myocardial ischemia. Stress cardiomyopathy is often associated with an inciting emotional or physical stress. It is treated with supportive care (including β-blockers and angiotensin-converting enzyme inhibitors) and typically resolves in the weeks to months that follow.

Pain does not always accompany myocardial ischemia, and many electrocardiographically detectable episodes of ischemia in patients with stable angina pectoris are asymptomatic ("silent" ischemia).[59] Conversely, many individuals with angina-like chest pain have normal or nearly normal coronary arteries when studied by arteriography,[60] with the development of chest pain attributed to either coronary microvascular spasm or heightened pain perception.[60,61]

The pain of *acute myocardial infarction* is similar in location to that of angina pectoris but is typically much more severe in intensity, is not relieved by rest or nitroglycerin, often requires large doses of opiates for control, and is frequently associated with profuse sweating, nausea, dyspnea, and profound weakness.[56] Acute myocardial infarction may also be silent,[62] especially in patients with diabetes mellitus.[63]

Valvular Heart Disease

Chest pain can also arise from other *non–coronary artery disorders,* including mitral valve prolapse, myocarditis,[56] pericarditis, and hypertrophic cardiomyopathy.[64] It can also be related to cocaine use.

Patients with aortic stenosis may complain of angina-like pain on exertion. The frequency of chest pain is higher with aortic stenosis than with any other valvular heart disease and is found in two-thirds of patients with severe disease.[56] Aortic stenosis should be considered whenever a patient presents with progressive angina, dyspnea, or syncope. In contrast, patients with mitral stenosis or pulmonic stenosis infrequently experience chest pain.

Pericarditis

The pain of *pericarditis* is most commonly pleuritic and arises from spread of the inflammatory process across the pericardium to the adjacent parietal pleura. Typically, pain is worse in the recumbent position and while lying on the left side, and is partially or completely relieved by sitting up, leaning forward, or lying on the right side. Radiation to the arms is uncommon. Although there are few nociceptors in the pericardium, there appear to be nociceptors in the diaphragmatic portion of its parietal layer, which is innervated by sensory axons that travel in the phrenic nerves.[65] Stimulation of these fibers causes pain that may be sharp, steady, and referred to the margins (ridge) of the trapezius muscles. Pain in this location is claimed to be specific for pericarditis because other diseases seldom cause discomfort in that area[56] (see Fig. 38.1).

Pericardial friction rubs, presumably indicating underlying pericarditis, are more common than pericardial pain during the first few days after acute myocardial infarction or with worsening uremia.[56,66] Other causes of pericarditis, usually associated with pericardial pain, are infections[67] and connective tissue diseases (e.g., lupus erythematosus). Pericarditis, usually with fever, can also develop after open-heart surgery (post-pericardiotomy syndrome) and after myocardial infarction (Dressler syndrome).[68] Often, no diagnosis can be made, and pericarditis in these cases is considered idiopathic.

Cocaine Toxicity

Chief among the presenting complaints of *cocaine toxicity* is chest pain.[69] Cocaine-associated chest pain typically begins approximately 60 minutes after injection or inhalation of the substance and lasts for about 120 minutes.[70] Pain is most frequently substernal in location and pressure-like in character. It may be accompanied by shortness of breath and diaphoresis.

Cocaine-induced chest pain is likely due to the combined effects of an increase in myocardial oxygen demand owing to an increase in heart rate and in systolic and mean arterial pressures and a decrease in myocardial oxygen supply due to vasoconstriction of the epicardial coronary arteries.

Disorders of the Aorta

Dissection of the aorta is usually associated with pain that is nearly always sudden and extremely severe at onset. Pain may be described, aptly, as "tearing" or "ripping" and often spreads widely to the neck, throat, jaw, back, or abdomen, as the dissection extends distally from its point of origin.[71] Frequent associated features are drenching sweats, nausea, vomiting, and lightheadedness. Angina-like chest pain can also arise secondary to aortic dissection or any aortic condition that reduces coronary artery blood flow, such as syphilitic aortitis or Takayasu's vasculitis.

NONCARDIAC CHEST PAIN

The term *noncardiac chest pain* is used to describe entities with pain resembling angina. There are three main categories of extracardiac disease that cause angina-like chest pain, namely (1) musculoskeletal disorders of the chest wall, which may account for 10–20% of cases; (2) a variety of esophageal disorders, particularly gastroesophageal reflux, which may cause 30–40%; and (3) psychological factors, which may explain up to 50% of the total.

MUSCULOSKELETAL DISORDERS

Of the musculoskeletal causes of chest pain, the ones most commonly confused with angina are cervical neck disease, costochondritis, subacromial bursitis, intercostal muscle cramps, or congenital malformations, such as pectus excavatum or carinatum. The best way to distinguish musculoskeletal pain from true angina is by reproduction of the pain with palpation or manipulation of the affected area. A history of recent trauma, chest infection, or coughing can also support this diagnosis.

GASTROINTESTINAL DISORDERS

Receptors are present in the esophagus and may cause pain when activated by mechanical (spasm), chemical (acid reflux), or thermal (hot liquids) stimuli. Afferent nerves travel in both vagal and spinal (T3–T12) pathways.[72] Pain originating from the esophagus is usually referred to midline structures, such as the throat, neck, and sternal regions, but may involve the arms as well. Stimulation of the distal end of the esophagus can cause pain directly over the heart.

Chest pain may arise either from esophageal reflux (the most common identifiable esophageal cause of chest pain) or from disorders of esophageal motility, such as diffuse esophageal spasm, achalasia, hyperactive lower esophageal sphincter, or nutcracker esophagus (a dysmotility disorder with high peristaltic pressures).[73–75] Esophageal pain may mimic angina pectoris by its radiation to the neck and arms and relief by nitroglycerin.[56] Chest discomfort that lasts an hour or more, that leaves a residual dull achy discomfort, or that is associated with heartburn, odynophagia, or dysphagia should suggest pain of esophageal origin.

Last, other GI disorders, such as cholecystitis, peptic ulcer disease, and acute pancreatitis, may present with pain that is perceived in the lower thorax.[65]

PSYCHOLOGICAL FACTORS

Psychological factors clearly affect each person's interpretation of bodily sensations, and a psychiatric cause should be excluded in undiagnosed cases of chest pain.

An association between noncardiac chest pain and anxiety disorders, particularly panic disorder, has been reported. This is particularly well described in patients with mitral valve prolapse.[76] Patients with demonstrable heart disease may also have panic attacks. Alternatively, persons with chest pain may have psychological distress related to the panic syndrome and not to a cardiac condition.

Mediastinitis

Mediastinitis can produce pain that mimics several other serious chest conditions, such as myocardial infarction, aortic dissection, or PE. The chest pain from mediastinitis can be severe, interscapular back or anterior pain, which is sometimes pleuritic. The association with fever or odynophagia can point to mediastinal inflammation or infection. Associated physical signs may include crepitus from subcutaneous emphysema or a crackling sound with the heartbeat on auscultation. Mediastinitis can be the clinical presentation of a silent esophageal perforation, a descending neck infection, or an iatrogenic complication of esophagoscopy or paraesophageal surgery. Other causes of acute mediastinitis include cardiac surgery and tracheal intubation (see Chapter 116).[77]

Thoracic Outlet Syndrome

Thoracic outlet syndrome is usually caused by compression of the neurovascular bundle by a cervical rib or a structural abnormality of the first rib or clavicle.[78,79] The pain can be caused by diverse entities that compress or invade structures in the thoracic outlet, structures including the brachial plexus, subclavian artery, and subclavian vein. Causes can

Table 38.2 Differential Diagnosis of Chest Pain

Diagnosis	Pain	Characteristics	ECG	CXR	Associated Features
Angina pectoris	Substernal, constricting	Transient, effort-related	Local ST depression; occasional elevation	Normal	Relief with NTG
MI	Substernal, crushing	Persistent, severe	Local ST elevation or depression	Possible vascular congestion or cardiomegaly	Relief with opiates; possible hypotension; ↑ troponin
Pulmonary embolism	Pleuritic	Sudden onset with dyspnea	Nonspecific; occasional RV strain	Normal or opacities ± small pleural effusion	Risk factor(s) for venous thrombosis
Pulmonary hypertension	Gradual onset	Associated with dyspnea, fatigue, and edema	Tall right precordial R waves, right axis deviation, RV strain	Prominent pulmonary arteries	Exclude pulmonary thromboembolism and interstitial lung disease
Bacterial pneumonia	Pleuritic	Onset in minutes to hours	Normal	Consolidation	Fever, productive cough
Pneumothorax	Sharp, unilateral	Sudden onset with dyspnea	Normal	Collapsed lung	Asthenic habitus, recurrence
Pericarditis	Pleuritic	Either side; gradual onset; pain referred to trapezius	Generalized ST elevation	Possible enlarged silhouette	Friction rub
Aortic dissection	Substernal, severe	Radiation to the back	Nonspecific; LVH or inferior MI	Widened mediastinum	Prostration, loss of pulse, aortic insufficiency
Esophageal spasm/ reflux	Substernal	May mimic angina; burning	Normal or ST-T changes	Normal	Relief with NTG or antacids
Costochondritis	Dull-achy, localized	↑ by cough or deep breath	Normal	Normal	Localized tenderness
Mediastinitis	Interscapular, upper back, can be pleuritic.	Severe	Normal	Widened mediastinum, mediastinal emphysema	Associated with fever, odynophagia
Herpes zoster	Sharp, unilateral	Dysesthesia	Normal	Normal	Vesicular rash

CXR, chest radiograph; ECG, electrocardiography; LVH, left ventricular hypertrophy; MI, myocardial infarction; NTG, nitroglycerin; RV, right ventricular.

include trauma, repetitive injury, anatomic variations, and tumors, such as the Pancoast tumor or superior pulmonary sulcus tumor. Most commonly, symptoms arise from nerve compression, with pain often reproducible when performing certain activities and associated with paresthesias and weakness.

Miscellaneous Causes

Chest pain may also arise from iatrogenic causes, such as pneumothorax after bronchoscopy or central venous catheter malposition.[80]

EVALUATION OF CHEST PAIN

The evaluation of chest pain begins with a complete medical interview.[81] The history may reveal nuances in the quality, location, duration, provoking events, and relieving measures, which serve to focus the subsequent evaluation. However, with few exceptions, such as evident injury to the chest wall, a specific diagnosis cannot be made with complete confidence from the clinical history alone. Physical examination may reveal evidence of pleural, lung parenchymal, or airway disease; localized chest wall involvement; or signs of mitral valve prolapse, aortic valve stenosis, or other cardiac abnormalities.[82–87]

For adults who present to the emergency department with new-onset chest pain, the immediate concern is to identify and characterize potentially life-threatening conditions, such as myocardial infarction, acute pulmonary embolism, or tension pneumothorax, which require urgent management. Some diagnostic features are listed in Table 38.2.

A standard 12-lead ECG, appropriate chest imaging, measurement of oxygen saturation and arterial blood gas levels, and blood chemistry profiles (e.g., troponin, D-dimer) often provide important data. In the appropriate clinical setting, some patients may require echocardiography or pulmonary function testing. Many other noninvasive or invasive tests are available for the evaluation of pain believed to be of respiratory, cardiac, or GI origin. If the diagnosis remains uncertain, admission to chest pain observation units may be considered.

CARDIAC ISCHEMIA

Initial evaluation of patients with suspected acute coronary syndrome, such as unstable angina or myocardial infarction, should always include a 12-lead ECG. Serial ECGs may be considered if the initial ECG is not diagnostic or if the patient is thought to have evolving myocardial ischemia or injury. Biomarker assessment for myocardial

injury should include cardiac-specific troponin; creatine kinase–MB may be measured if troponin is not available. Patients who are chest pain–free and have no ischemic ECG changes or cardiac biomarker elevation should be considered for risk stratification with a cardiac functional study, including exercise stress electrocardiography, stress echocardiography, or myocardial single-photon emission *computed tomography* (CT) imaging. The indications for stress echocardiography include the evaluation of acute chest pain and other chest pain syndromes, such as anginal equivalent, with or without heart failure, and risk assessment in symptomatic patients after revascularization procedures.

Acute ECG changes, such as ST segment deviations or deep T wave inversions, positive cardiac biomarkers or stress test results, or hemodynamic instability, should prompt admission to an intensive care unit. Hospital admission may also be considered if the diagnosis remains uncertain despite initial limited evaluations. Available risk stratification models may aid in the evaluation of patients presenting with undifferentiated chest pain. The North American Chest Pain Rule score; History, ECG, Age, Risk factors, and Troponin (HEART) score; and Thrombolysis in Myocardial Infarction score have been demonstrated to be useful in detecting low-risk patients. The HEART score may assist in differentiating persons with ischemic chest pain from those with noncardiac chest pain.[88,89]

Evaluation and management of variant or Prinzmetal angina consists of coronary angiography in patients with chest pain accompanied by transient ST segment elevation. Provocative testing may be considered in cases of diagnostic uncertainty if no contraindications exist.

For cardiac ischemic chest pain related to the use of cocaine or methamphetamine, immediate coronary angiography could be considered if electrocardiographic ST elevation (or new ST segment depression or T wave changes) persists despite pharmacologic intervention.

Intracoronary ultrasonography, coronary angiography, 24-hour ambulatory ECG, provocative testing, or coronary flow reserve measurement may be considered to aid with difficult diagnoses.

Risk stratification with exercise ECG (using the Bruce protocol or Duke treadmill score), exercise perfusion imaging, or exercise echocardiography should be considered for patients with symptomatic chronic stable angina who are able to exercise and have no contraindications to such testing. For those who are unable to exercise, pharmacologic stress testing with dipyridamole, adenosine, dobutamine or regadenoson nuclear myocardial perfusion imaging, or dobutamine echocardiography is recommended unless contraindications to such testing exist.[90]

PULMONARY EMBOLISM

PE is a life-threatening feature of venous thromboembolism and most frequently originates from deep venous thrombosis in the lower extremities.

Patients with acute PE who have elevated levels of troponin are at high risk for short-term mortality and adverse outcome events (see Chapter 81).[91,92]

PERICARDIAL DISEASE

Acute pericarditis is often associated with a pericardial effusion, diffuse concave ST segment elevation, and/or PR segment depression. It is essential to search for any underlying cause of the condition (e.g., infection or malignancy). In constrictive pericarditis, echocardiography can demonstrate the presence of pericardial thickening and calcification that limits diastolic filling of the ventricles and causes a characteristic biphasic pattern of venous return with a diastolic component equal to or greater than the systolic component.[93]

CARDIAC TAMPONADE

Cardiac (or pericardial) tamponade is the presence of fluid within the pericardial sac, leading to cardiac compression. This, in turn, impairs ventricular diastolic filling and gives rise to the sensation of chest pain and dyspnea, and signs of tachycardia, falling systemic blood pressure, elevated venous pressure (characteristic loss of the atrial y-descent with maintenance of both the systolic atrial filling wave and the x-descent), and pulsus paradoxus (an exaggerated inspiratory decrease in arterial systolic pressure >10 mm Hg).[94]

Cardiac tamponade should be suspected whenever a patient presents with unexplained hypotension and/or pulsus paradoxus after myocardial infarction, chest trauma, percutaneous coronary intervention, or cardiac surgery. Other risk factors include anticoagulation therapy, malignancy, or an underlying connective tissue disease. A pericardial rub may be appreciated during physical examination.[95] ECG changes compatible with acute pericarditis may be present along with an enlarged cardiac silhouette on chest films.

Diagnosis is generally determined by two-dimensional echocardiography that demonstrates a large pericardial effusion with an inspiratory increase of right ventricular dimensions and decrease of left ventricular dimensions, compression of the right atrium, right ventricular diastolic collapse, and a heart that swings with cardiac contractions. Left atrial collapse is less common than right atrial collapse but is very specific for cardiac tamponade. There is commonly also an abnormal inspiratory increase of blood flow velocity through the tricuspid valve accompanied by a decrease in mitral valve flow velocity and dilation of the inferior vena cava with lack of inspiratory collapse.[96]

PULMONARY HYPERTENSION

Initial evaluation of suspected pulmonary hypertension generally consists of ECG, determination of arterial blood gas levels, a chest radiograph, pulmonary function testing, exercise capacity (6-minute walk test), brain natriuretic peptide or N-terminal brain natriuretic peptide, and noninvasive Doppler echocardiography with and without saline contrast. Chronic thromboembolic disease is evaluated with ventilation-perfusion scanning and chest CT pulmonary angiography. Ultimately, right heart catheterization is required both to confirm the diagnosis and to assess the severity of the pulmonary hypertension.

Testing for connective tissue disease or human immunodeficiency virus infection may be considered in patients with suggestive clinical histories for these disorders. Acute vasoreactivity testing using inhaled nitric oxide (or other pulmonary vasodilators, including epoprostenol, adenosine, or sodium nitroprusside) can be performed for patients with pulmonary arterial hypertension to guide therapy.[97] Polysomnography is indicated for patients with a clinical history suggestive of obstructive sleep apnea (see Chapters 83 and 120).

THORACIC AORTIC DISSECTION

Rapid diagnosis and management are critically important for patients with thoracic aortic dissection. Invasive aortography for the diagnosis of thoracic aortic dissection has been replaced by less invasive imaging techniques, including transesophageal echocardiography, contrast-enhanced chest CT scan, and *magnetic resonance imaging* (MRI). All of these modalities yield clinically reliable data for both confirming and ruling out this condition.[98] The major advantage of CT is its ready availability in most emergency departments, its speed of acquisition, and its ability to assess alternative causes of pain.[99]

PNEUMOTHORAX

Spontaneous pneumothorax can be either primary or secondary, and, if sufficiently large, can be visualized with imaging tests. A tension pneumothorax is a life-threatening condition that requires urgent management. High intrathoracic pressures develop because of ingress of air into the pleural space via a one-way valve process, which, in turn, prevents egress of air. This gives rise to vena caval compression, reduction in venous return, and diminished cardiac output. Radiographically, a tension pneumothorax presents as a complete collapse of the ipsilateral lung, depression/flattening of the ipsilateral hemidiaphragm, and shift of the mediastinum to the contralateral hemithorax (see Chapter 110).[100]

THORACIC OUTLET SYNDROME

Determining the cause of a thoracic outlet syndrome can be challenging and may involve a careful physical examination, electrophysiology, ultrasonography, and imaging via CT or MRI.[79] Superior sulcus tumors (Pancoast tumors) require a definitive tissue diagnosis before initiation of therapy. MRI, with imaging of both mediastinal and extrathoracic structures, is frequently performed to rule out involvement of adjacent neurovascular structures (brachial plexus, vertebral column, or subclavian vessels) that will influence surgical approaches.[101]

CHEST TRAUMA

Blunt and penetrating chest trauma can give rise to chest pain related to hemothorax (bleeding into the pleural space), pneumothorax, rib, sternal or clavicular fractures, or injury to the chest wall musculature.

As little as 5 mL of hemothorax can be appreciated on a decubitus chest radiograph, but a size of approximately 200 mL is required for it to be readily identified on an upright chest radiograph, where it will appear as blunting or, with a greater volume of bleeding, a concave upward sloping of the fluid in the ipsilateral costophrenic angle. In the setting of hemothorax, the presence of an air-fluid level indicates a hemopneumothorax. Chest CT is more sensitive than chest radiographs in detecting a small hemothorax and can offer clues to the origin of the bleeding (see Chapter 113).

Rib fractures may be associated with injuries to the brachial plexus and subclavian veins (upper rib fractures) or spleen and liver (lower rib fractures). A flail chest resulting from at least two fracture sites on at least three consecutive ribs can create regional chest wall instability and respiratory distress. The sternum tends to fracture most commonly at the body or manubrium, generally after direct trauma to the anterior chest or from deceleration. Significant posterior displacement of the sternum may be associated with trauma to the underlying cardiovascular structures. Chest CT is more sensitive than plain chest radiographs for detecting rib and sternal fractures (see Chapter 131).[100]

GASTROESOPHAGEAL REFLUX

Dyspepsia secondary to gastroesophageal reflux can be managed with pharmacologic agents. An empirical trial with these medications may be considered if the clinical history strongly supports the diagnosis of gastroesophageal reflux and if the patient is not at high risk for a GI malignancy. Risk factors, such as use of nonsteroidal anti-inflammatory agents, should be investigated. Endoscopy may be necessary in some patients with unexplained dyspepsia and persistent symptoms. Impedance-pH monitoring may also be indicated in persons with negative endoscopy who fail to respond to antireflux therapy.[102] High-resolution manometry is particularly useful for excluding spastic motor disorders and achalasia, whereas pH monitoring can help identify esophageal acid exposure (see Chapter 126).[103]

PANCREATITIS

Common causes of acute pancreatitis include gallstone disease (≈50% of cases) and alcohol abuse (20–25%). Patients typically complain of abdominal pain and vomiting, but chest pain may develop as well. Elevation of lipase has a higher sensitivity and specificity for pancreatitis than elevation of amylase, perhaps because, compared to amylase, lipase is produced only by the pancreas. In addition, the half-life of lipase is longer than that of amylase. Other helpful laboratory tests include liver chemistry determinations, triglyceride level, and calcium level. When diagnostic doubt exists, abdominal imaging by contrast-enhanced CT may be beneficial (see Chapter 126).

Key Points

- Chest pain is characterized by an unpleasant sensation that is either localized to the thorax or believed to originate from structures located there. It may announce the presence of severe, occasionally life-threatening disease.
- Pain arising from *visceral* organs (e.g., heart or gastrointestinal tract) differs in many ways from that arising from *somatic* structures, such as the skin. Visceral pain is difficult to localize, is diffuse in character, and is typically referred to somatic structures. Visceral pain is also often associated with greater autonomic and motor responses than is somatic pain.
- Visceral and somatic innervations differ in relation to the density of innervations and spinal pattern of termination. In general, the number of visceral afferent fibers is less than the number of somatic afferent fibers, and the rostrocaudal spread of visceral afferent fiber terminals in the spinal cord is considerably greater than the spread of central terminals from somatic afferent fibers. The low number of visceral afferents and greater intraspinal spread is responsible for loss of spatial discrimination, consistent with the diffuse, difficult to localize nature of visceral pain.
- Pain is both hard to define and difficult to measure. Two widely used techniques, namely rating scales and questionnaires, are often used in clinical and epidemiologic studies of chest pain. Although rating scales constitute the simplest measurement of pain, the sensation of pain has many more components than just its intensity. Thus a single-dimensional rating scale leaves many aspects of the sensation undocumented.
- Because of the proximity of the various organs and the vagaries of perception of pain of visceral origin, pain arising from the various viscera in the thoracic cavity and from the chest wall is often qualitatively similar and exhibits overlapping patterns of referral, localization, and quality. This leads to difficulty in the differential diagnosis of chest pain.

Key Readings

Dezman ZD, Mattu A, Body R. Utility of the history and physical examination in the detection of acute coronary syndromes in emergency department patients. *West J Emerg Med*. 2017;18(4):752–760.

Fanaroff AC, Rymer JA, Goldstein SA, et al. Does this patient with chest pain have acute coronary syndrome? The rational clinical examination systematic review. *JAMA*. 2015;314(18):1955–1965.

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39 WHEEZING AND STRIDOR

JESSICA B. BADLAM, MD • DAVID A. KAMINSKY, MD

LUNG SOUNDS
WHEEZING
Definition
Evaluation
Approach
STRIDOR
Definition
Evaluation
Approach
THE FUTURE OF LUNG SOUND ANALYSIS
KEY POINTS

LUNG SOUNDS

Auscultation of the chest has long been useful in diagnosing pulmonary illness and remains an essential part of the physical examination (see also Chapter 18). The usefulness of this component of the physical examination depends on understanding the physiologic basis of respiratory function and proper correlation with the available clinical data. Lung auscultation is low cost, noninvasive, safe, and relatively easy to perform. However, lung auscultation is limited by interobserver variability, inadequate understanding of the physiologic basis of respiratory function, and imprecise nomenclature. These discrepancies in nomenclature should not overshadow the clinical importance and pathogenesis of these valuable diagnostic tools.[1]

Lung sounds heard on chest auscultation can be classified as normal or adventitious. These sounds are characterized by their frequency, intensity, and quality, which help the listener differentiate them and determine the clinical correlation.[2] Abnormal or adventitious respiratory sounds are those heard superimposed on normal breath sounds and are further classified as continuous and discontinuous. Discontinuous sounds (duration < 15 msec) are typically described as "fine or coarse crackles," whereas continuous musical sounds (duration > 80 msec) are known as "wheezes," "rhonchi," or "stridor."[3,4] This chapter focuses on these continuous adventitious sounds and addresses the evaluation and approach to a patient with this problem.

Although there is no one correct way to listen to lung sounds, certain basic principles are important. Ideally, the patient should be in a quiet environment so that the breath sounds can be heard over any ambient noise. The patient should be upright if possible, and the stethoscope should be placed directly on the skin. Overlying clothing will mask or interfere with many breath sounds, particularly crackles. One can begin on the front or back, but it is good to try to be consistent with technique so that a thorough and complete examination is performed every time. Listen to at least one complete breath, including inspiration and expiration, at each level of the lung (apex to base, or vice versa), and compare each side. Examine both the anterior and posterior chest, where the upper and lower lobes, respectively, are best heard. Also examine just under the axilla on both sides, where the lingula on the left and the right middle lobe on the right can be appreciated. Focus on both the quality and intensity of the breath sounds—whether heard better on inspiration or expiration—and try to distinguish normal breath sounds from adventitial sounds. One should listen over the neck and trachea as well, which may help in determining the origin of the adventitial sound; this is a particularly good location to appreciate stridor, but wheezes can be heard well there also. Remember to try to categorize any adventitial sounds as to their persistence within the breath cycle (continuous or interrupted/discontinuous) and their timing (inspiratory, expiratory or both), as well as their intensity (soft or loud) and frequency (low or high pitch).

WHEEZING

DEFINITION

Wheeze is an easily recognized adventitious sound due to its musical quality and long duration (see Audio 18.6).[5] Wheezes are typically louder than underlying breath sounds, expiratory in nature, and largely signify airflow limitation. Wheezes are thought to be produced by the fluttering or resonant vibration of the airway walls at the site of airflow limitation, a result of the driving pressure exceeding the pressure required to produce maximal flow.[6] They are likely generated in the branches of the larger airways, second through seventh generation.[7] The pitch of the wheeze depends on the mass and elasticity of the airway walls and the flow velocity, not on the length or size of the airway. In addition, the volume (intensity) of the sound is not an indicator of degree of airway obstruction, because severe obstruction may limit flow to such a degree that wheezes may be absent. Very high frequency (>1000 Hz) wheezes are usually best heard over the trachea rather than the lung parenchyma and chest wall due to better transmission through the airway tree.[7] Wheezes may be monophonic or polyphonic, which are distinguished by having a single musical note or multiple musical notes, respectively.[5] Classically, monophonic wheezing, which may be inspiratory or expiratory, is associated with asthma. Polyphonic wheezes are thought to arise mainly within the larger, more central airways. A rhonchus is considered a variant of the wheeze, differentiated by a lower pitch similar to snoring (see Audio 18.7). It appears

to share a similar mechanism of generation to wheezing but frequently clears with coughing, suggesting a significant role of secretions in the mechanism.[6] Wheezing, by causing mechanical perturbations of the airways, has been speculated to produce airway injury[8] based on studies of vibration of cultured human bronchial epithelial cells[9] and of the upper airway soft palate in a rat snoring model.[10] In both settings the vibration led to increases in inflammatory cytokine production.

EVALUATION

The clinical significance of wheezing depends on the mechanism of the airflow limitation. The broad differential for wheezing in adults can be seen in Table 39.1. Certain characteristics of the wheeze can give clues as to the underlying etiology. Most commonly, airflow limitation from obstructive lung disease, such as asthma or COPD, results in diffuse expiratory and also inspiratory wheezing. On the basis of auscultation alone, it is frequently difficult to distinguish obstructive airway disease from other causes of diffuse wheezing, such as pulmonary edema or aspiration. Localized or focal wheeze may help identify the etiology and tends to indicate an abnormality, such as an aspirated foreign body, endobronchial tumor, or congenital anomaly. A short, late inspiratory wheeze may also be recognized and is called a "squawk" or "squeak"; these may be found in patients with pulmonary fibrosis, hypersensitivity pneumonitis, pneumonia, or bronchiolitis obliterans.[4]

Table 39.1 Common Causes of Wheezing in Adults

Lower Airway	Intrathoracic Upper Airway
Asthma	Tracheal stenosis
COPD	Angioedema
Pulmonary edema	Foreign body aspiration
Aspiration	Benign or malignant tumors
Bronchiolitis	Tracheobronchomalacia
Cystic fibrosis	
Carcinoid	
Bronchiectasis	
Lymphangitic carcinomatosis	
Parasitic infection	
Vascular malformations	
Anaphylaxis	

Because wheezing may be heard during forced exhalation in healthy people,[11] wheezing during forced exhalation is neither sensitive nor specific for asthma.[12] However, more wheezes are generated during forced exhalation in patients with COPD and asthma than in healthy people,[13] and in patients with unstable asthma compared to stable asthma and healthy persons.[14] Cough is a frequent accompaniment to wheezing in asthma patients. In a study of 1701 patients with asthma, cough and wheezing in asthma were closely correlated; some patients had mostly cough, generally the older overweight women, and some had mostly wheeze, generally the older men.[14a] Monitoring lung sounds may be useful in determining the effect of therapy in asthma[15] or assessing bronchodilator response.[16] It is important to remember that wheezes may be absent in severe airway obstruction due to absolute reduction in airflow; reappearance usually indicates improvement in the underlying obstruction.

Various causes of wheezing not due to asthma or COPD include bronchial carcinoid[17,18] or compression of airways by mediastinal tumor,[19] uncommon causes such as pulmonary embolism,[20] or compression of airways by large vessel vascular malformations[21] (Fig. 39.1) or atrial myxoma.[22] Other mimics of asthma are well described and include anaphylaxis, angioedema, foreign body aspiration, and vocal

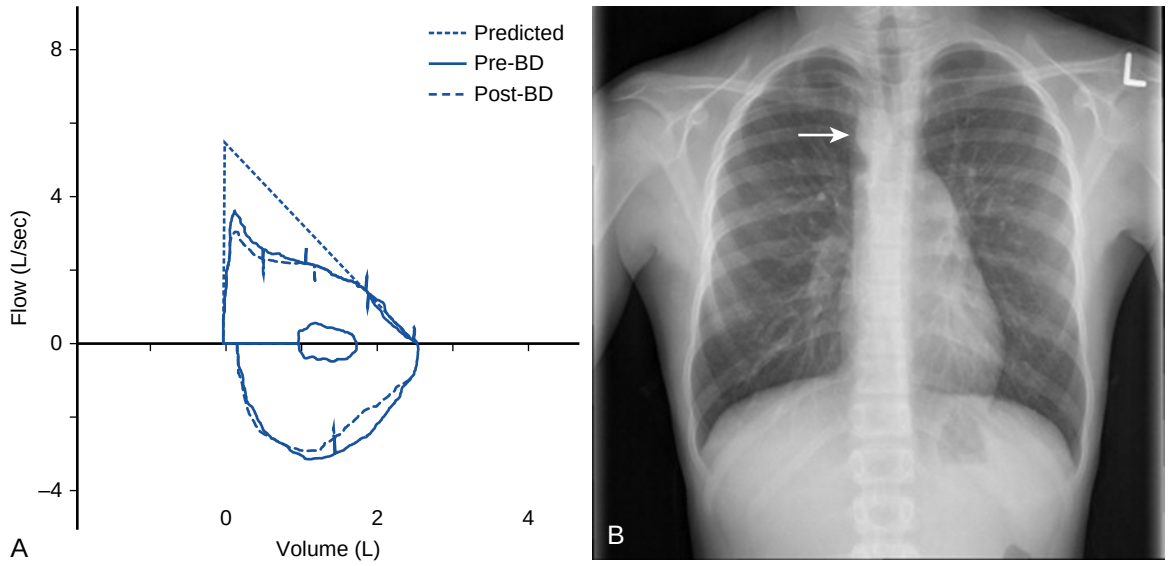

Figure 39.1 Variable intrathoracic obstruction due to right-sided aortic arch and its effect on the flow-volume loop. This patient presented with wheezing but did not respond to bronchodilators and inhaled steroids. (A) Spirometry showed limitation of expiratory flow suggestive of a variable intrathoracic obstruction, with the greatest impact at high flow rates. (B) Frontal chest radiograph showed a mass-like abnormality *(arrow)* found to be a right-sided aortic arch. BD, bronchodilator. (From Nataraj RT, Cockcroft DW, Fladeland DA. An uncommon cause of wheeze. *J Allergy Clin Immunol Pract.* 2014;2:616–617.)

cord dysfunction.[23] In addition, more than one disease may be present causing wheezing, such as tracheal stenosis in a patient with asthma.[24] As Chevalier Jackson reportedly said in 1865, "all that wheezes is not asthma."[25]

It is important to know that wheezing is very common in young children, present in up to 30% of children until age 3 years.[26] Wheezing in children may not indicate disease because the young child's respiratory system is more prone to wheezing due to more compliant and narrower airways.[27] Thus it can be difficult to recognize disease in the very young. Multiple phenotypes of childhood wheezing have been described, which differ in their clinical expression of traits such as atopy, time course, and persistence.[28] Biopsy data indicate that children with persistent, or in some cases even transient, wheezing may develop early pathologic changes of airway inflammation and remodeling, which may be associated with later development of asthma.[28] Acoustical analysis has indicated that high-pitched wheezing in asymptomatic children with asthma may indicate small airways obstruction.[29] However, such analysis was not able to distinguish wheezing from exercise-induced bronchospasm versus histamine-induced bronchospasm.[30] Wheezing in children may be used to determine response to methacholine during bronchoprovocation challenge.[31] A recent review has highlighted the features of six lung function tests that may be used in the clinical evaluation and monitoring of infants and children younger than 6 years with recurrent wheezing, in addition to bronchopulmonary dysplasia and cystic fibrosis; only some of these tests are able to distinguish children with recurrent wheeze from healthy control children.[32] Ongoing research is exploring the use of noninvasive biomarkers from blood, exhaled breath, or urine to help diagnose asthma in preschool children with recurrent wheezing.[33]

Most pathologic wheezing in children is due to acute viral illness, and among children presenting clinically with community-acquired pneumonia, wheezing independently predicted viral infection.[34] Rhinovirus-associated wheezing in the first 3 years of life has been associated with the subsequent development of asthma.[35] Other causes of childhood wheezing include asthma, allergies, gastroesophageal reflux disease, cystic fibrosis, congenital airway abnormalities, obliterative bronchiolitis, and chronic lung disease of immaturity.[36] Sudden onset of wheezing should raise concern for foreign body aspiration.[37]

Evaluating a patient, either a child or an adult, with wheezing involves multiple modalities in addition to the specific findings on lung auscultation. Indeed, one study in young children revealed poor interobserver reliability of clinical assessment of children with acute wheezing and dyspnea, emphasizing the importance of objective testing.[38] However, auscultation for wheezes in adults was rated as the most useful and frequent physical examination finding by more than 2600 internal medicine physicians.[39] Pulmonary function testing, imaging, and direct visualization with laryngoscopy or bronchoscopy are frequently used to evaluate stable patients with wheezing to make the correct diagnosis. Spirometry, including bronchodilator challenge, can be useful in the diagnosis of expiratory airflow limitation but may not be able to distinguish among the various causes. Reversible obstruction is frequently seen in asthma, whereas expiratory airflow limitation that persists despite bronchodilators is more indicative of COPD or other entities such as bronchiectasis (Fig. 39.2). Investigating the flow-volume loop in those that do not meet criteria for asthma or COPD is important in identifying other etiologies of airflow limitation. A variable intrathoracic obstruction, such as tracheobronchomalacia, can produce variable blunting, notching, or oscillations of the expiratory flow loop (Fig. 39.3). An increase in airway obstruction when supine compared to sitting may also be a clue to tracheobronchomalacia.[40] Conventional chest imaging with chest radiograph can be particularly helpful in those patients with acute respiratory distress or focal persistent wheeze. *Computed tomography* (CT) is helpful in evaluating central airway pathology, such as tracheal stenosis or entities that may be extrinsically compressing the airways and may provide valuable information about small airway or parenchymal abnormalities, such as bronchiectasis or bronchiolitis. Dynamic CT with inspiratory and expiratory imaging may be diagnostic for tracheobronchomalacia.[41] Flexible or rigid

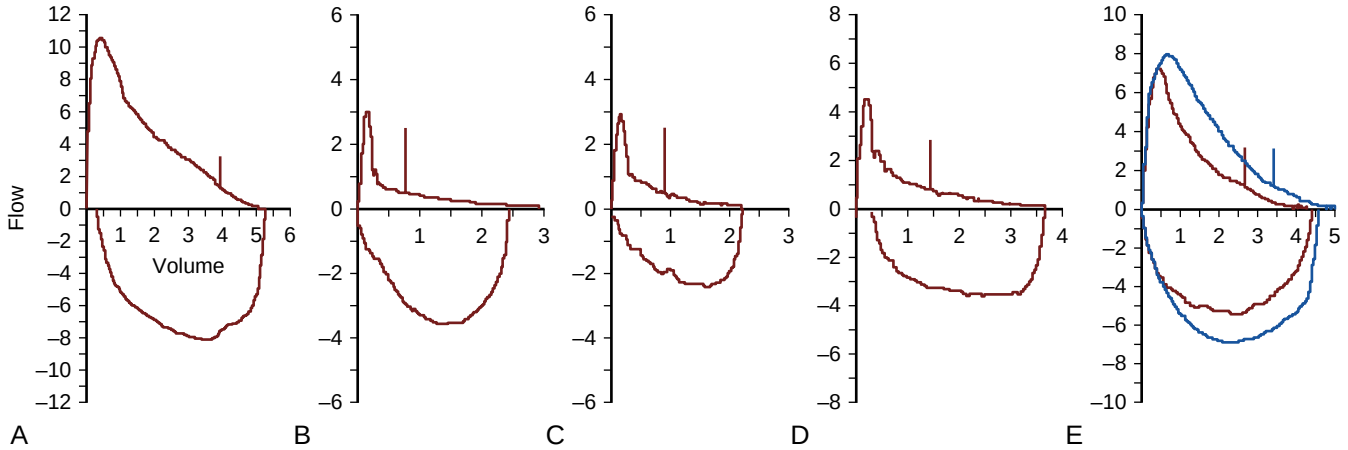

Figure 39.2 Flow-volume loops showing expiratory flow limitation from various causes. Normal (A) and flow-volume loops demonstrating classic expiratory airflow limitation in COPD/severe emphysema (B), bronchiectasis (C), and cystic fibrosis (D), as well as improvement in expiratory airflow limitation after bronchodilator *(blue)* in asthma (E). Note that short vertical lines indicate forced expiratory volume in 1 second. (Courtesy David Kaminsky, MD.)

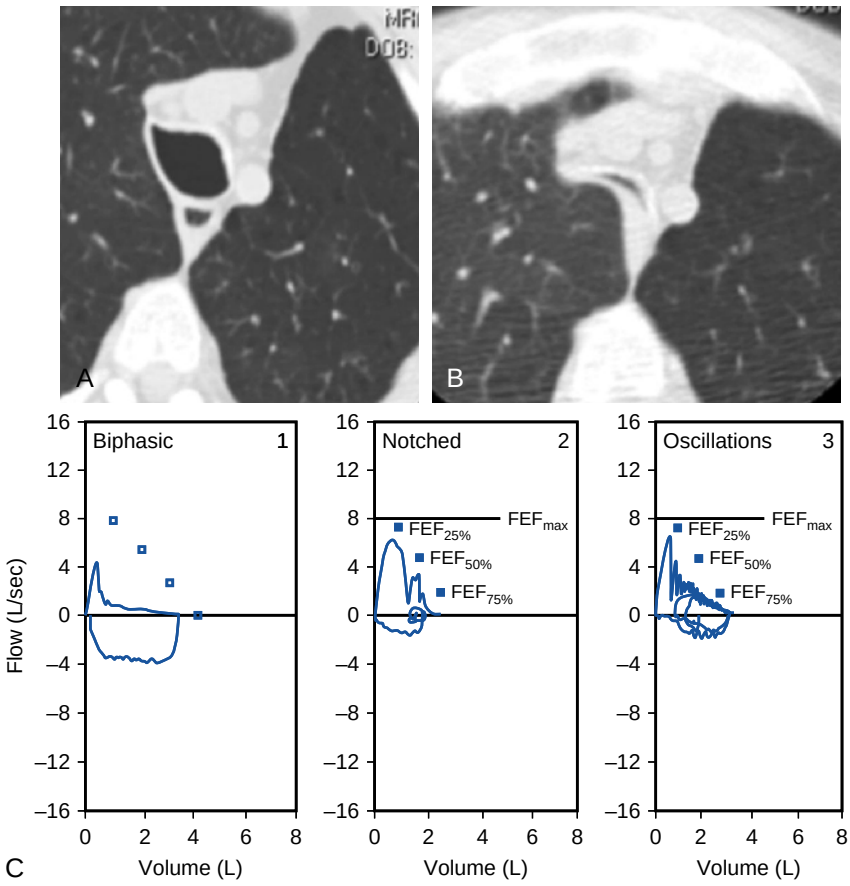

Figure 39.3 Tracheobronchomalacia shown with inspiratory (A), postexpiratory dynamic computed tomography (B), and examples of flow-volume loop patterns (C). The variable intrathoracic airway obstruction can produce findings on the flow volume loop (C) including biphasic (inspiratory and expiratory) blunting (*left*), notching of the expiratory flow (*middle*), or oscillations of the expiratory flow loop (*right*). FEF, forced expiratory flow. (From Majid A, Sosa AF, Ernst A, et al. Pulmonary function and flow-volume loop patterns in patients with tracheobronchomalacia. *Respir Care.* 2013;58:1521–1526.)

bronchoscopy may then be necessary to confirm a diagnostic suspicion of a tracheal or bronchial mass, foreign body, or tracheobronchomalacia.

APPROACH

The approach to wheezing is dictated by the patient's presentation and the breadth of possible diagnoses being considered. Although asthma and COPD remain the most common causes of wheezing, other conditions should be kept in mind, especially if the wheezing is of new onset or has not responded as expected to bronchodilator therapy. As described earlier, history, physical examination, functional studies such as spirometry, and imaging all play an initial role in determining the cause of wheezing. Because wheezing is principally caused by airway narrowing, empirical treatment of wheezing with inhaled bronchodilators to relax airway smooth muscle makes sense. However, due to airway narrowing being contributed to by airway inflammation and smooth muscle constriction, treatment of wheezing with anti-inflammatory therapy is also indicated. The mainstay of treatment of wheezing due to chronic asthma is inhaled corticosteroids with or without inhaled long-acting bronchodilators, depending on asthma severity and control (*Global Initiative for Asthma* [GINA] 2019; www.ginasthma.org). In wheezing due to COPD, the recommended treatment starts with one or two long-acting bronchodilators, before adding inhaled corticosteroids or other drugs (*Global Initiative for Chronic Obstructive Lung Disease* [GOLD] 2019; www.goldcopd.org).

In the patient with acute wheezing without previous history of obstructive lung disease, it is essential to maintain an open mind about the underlying cause. Certain causes require immediate treatment.[23] For example, wheezing may be associated with anaphylaxis, which will be recognized by multiple organ involvement in the presence of hypotension or shock. Congestive heart failure may present with wheezing (so-called "cardiac asthma"), but additional clues related to heart failure, such as orthopnea and pulmonary edema, should reveal the diagnosis. Uncommonly, pulmonary embolus may present with wheezing[20] and may require pulmonary vessel imaging to confirm a diagnosis. Focal wheezing should raise suspicion for foreign body aspiration as a cause of acute wheeze. When wheezing appears to be due to asthma or COPD, the use of *continuous positive airway pressure* (CPAP) or bilevel positive airway pressure may be beneficial to offset dynamic hyperinflation and reduce the work of breathing.[42,43] There is some evidence that CPAP may also reduce airway reactivity by causing sustained stretch of airway smooth muscle,[44] although the effect may be due, at least in part, to the application of the mask to the face and not specifically to the positive airway pressure.[45]

As with adults, the approach to diagnosis and treatment of preschool wheezing should be guided by appropriate clinical circumstances and testing, such as spirometry[46] or exhaled nitric oxide.[47] In children with recurrent wheezing and asthma and evidence of atopy, inhaled corticosteroids are indicated to reduce the risk of exacerbation.[48,49] For the treatment of acute exacerbation of wheezing and shortness of breath, the addition of high-dose inhaled

budesonide has been shown to reduce hospitalization rates compared to standard therapy (short-acting β-agonist plus intravenous steroid).[50] The mechanism is postulated to be an acute anti-inflammatory and vasoconstrictive response. Another acute therapy for wheezing is the use of heliox, a helium-oxygen gas mixture. Although typically advocated for stridor, it may also be useful in pediatric patients with bronchiolitis (see later).[51]

STRIDOR

DEFINITION

Stridor is a type of adventitious sound with a very characteristic high-pitched musical sound predominantly heard during inspiration, frequently without a stethoscope (see Audio 18.12). The term *stridor* originates from the Latin verb *stridere,* meaning "to creak," and indicates a harsh or grating sound. The intensity, location over the anterior neck, and inspiratory predominance helps distinguish it from lower airway wheezing. It is produced as turbulent flow passes through a narrowed segment of the upper respiratory tract.[52] Similar to wheezing, it indicates flow limitation but with a distinct clinical presentation. It is also clinically necessary to distinguish stridor from stertor (patient awake) or snoring (patient asleep), which is a much more low-pitched noise generated from upper airway narrowing in the nasopharyngeal or oropharyngeal areas and is frequently associated with sleep-disordered breathing.[53]

The upper airway is a complex structure comprising muscles and soft tissue involved in a variety of functions, such as the passage of air, swallowing, and phonation. The lack of a rigid cartilaginous or bony structure predisposes the structure to collapse on inspiration.[54] If the obstruction is "variable" and can respond to the pressures generated during inspiration, the obstruction to airflow is also variable. During inspiration, airway pressure becomes negative relative to the surrounding atmospheric pressure, creating a gradient tending to pull the tissues inward and narrowing the lumen of the extrathoracic airways. On expiration intratracheal pressure becomes positive, lessening the obstruction and improving flow. This leads to the classic stridor typically heard only or mainly on inspiration. If the obstruction is caused by a "fixed" or rigid lesion, which does not respond to these changes in airway pressure, then the obstruction remains fixed as well. The stridor may then be heard almost equally on inspiration and expiration. Typically, lesions that reduce the upper airway diameter to about 8 mm cause symptoms with exercise.[55] Once the airway is narrowed to 5 mm, symptoms and signs of obstruction may develop at rest.[56]

EVALUATION

Stridor requires rapid evaluation and may require immediate intervention.[57] The history, including the age of the patient and acuity of onset, can help narrow the differential diagnosis. Stridor is more commonly encountered in the pediatric population due to the smaller diameter and less cartilaginous support of the upper airway. In children one must consider both congenital and acquired etiologies of stridor. Acute causes include foreign body aspiration,[58] anaphylaxis,[59] bacterial tracheitis,[60] or epiglottitis.[61] If the presentation of stridor is more subacute, the most common causes are infectious, with croup (a respiratory illness of the upper airway, e.g., viral laryngotracheitis) accounting for 90% of all cases of stridor in children.[62] Croup is characterized by a gradual onset of symptoms, including fever, hoarseness, barking cough, and progression to inspiratory and sometimes expiratory stridor. Croup and epiglottitis are often confused because they both present with infectious symptoms and stridor. In a prospective study of children presenting to a pediatric hospital with stridor, croup was associated with coughing and absence of drooling and epiglottitis with an absence of coughing but with drooling.[63] Retropharyngeal and peritonsillar abscesses are also subacute infectious etiologies that tend to present with fever, "hot potato" voice, drooling, and inspiratory stridor. Chronic causes of stridor in children tend to be more congenital or structural in nature, such as laryngomalacia or tracheomalacia, subglottic stenosis, vascular ring, or bronchogenic cyst.[64]

Table 39.2 Common Causes of Stridor in Adults

Benign or malignant upper airway tumors
Vocal cord dysfunction/paralysis
Goiter
Epiglottitis
Laryngeal edema
Laryngostenosis or subglottic stenosis
Postextubation edema/granuloma
Deep neck infections (e.g., Ludwig angina)
Anaphylaxis
Obesity

In adults extrathoracic upper airway obstruction and stridor can result from a variety of etiologies (Table 39.2). Some of the most common acute causes in adults are infections (epiglottitis[65] and deep neck infection with Ludwig's angina[66]), laryngeal edema (especially postextubation[67] or due to anaphylaxis [68]), *vocal cord dysfunction* (VCD),[69] and subglottic tracheal stenosis after tracheostomy or prolonged intubation. More chronic causes include tumors/goiters and vocal cord paralysis. Less commonly seen chronic causes may include relapsing polychondritis, cricoarytenoid arthritis, fibromas, granulomatous inflammation, or amyloid involvement. Similar to children, the history and acuity/timing of presentation can be especially helpful in determining the etiology.

Additional diagnostic testing, including radiography, pulmonary function testing, or direct airway visualization, can be useful to identify the cause of stridor. Assessment of a stable patient with stridor involves similar diagnostic modalities as used in patients with wheezing. Pulmonary function testing, specifically the flow-volume loops, can be particularly helpful in diagnosis. Variable extrathoracic obstruction, such as VCD, can manifest as intermittent blunting of the inspiratory loop.[69] Similarly, a large thyroid goiter can flatten the inspiratory loop (Fig. 39.4). Alternatively, a fixed extrathoracic obstruction can flatten both the inspiratory and expiratory loops. Imaging with neck radiographs or CT

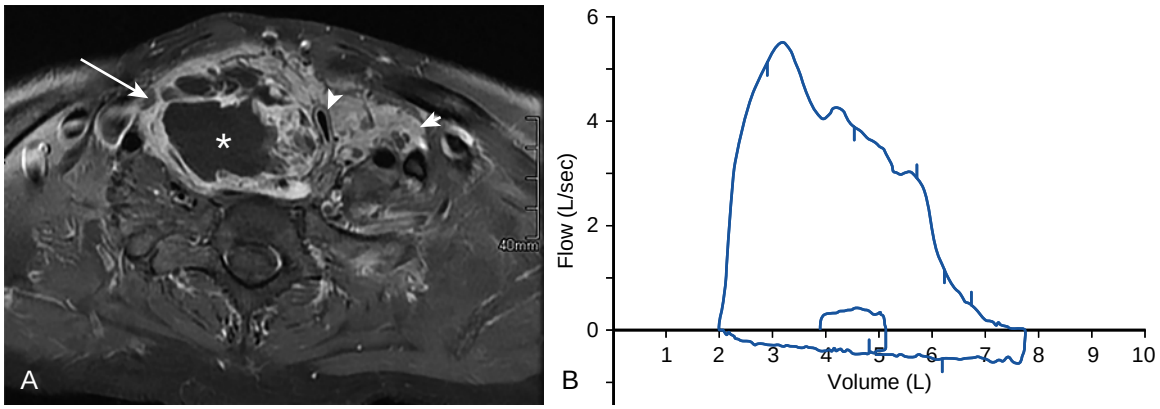

Figure 39.4 Extrathoracic obstruction causing inspiratory flow limitation due to goiter as seen on axial magnetic resonance imaging. (A) A large thyroid goiter *(asterisk)* had produced gradually increasing symptoms of dyspnea and stridor over years, associated with compression of the trachea *(arrowhead)*. (B) The thyroid gland extends from the long arrow to the short arrow. The flow-volume loop demonstrated significant reduction of inspiratory flow with fairly normal expiratory flow, characteristic of a variable extrathoracic obstruction. (Courtesy V. Courtney Broaddus, MD, Khai Vu, MD, and Michael B. Gotway, MD.)

(depending on the clinic stability of the patient) can help to characterize the obstruction further. Frequently, flexible or rigid laryngoscopy is used to visualize the upper airway to determine the specific diagnosis and provide opportunity for biopsy if necessary.

APPROACH

Patients with stridor need to be evaluated rapidly for impending airway closure, especially if the stridor has arisen acutely. Key observational findings include degree of respiratory effort and any evidence of hypoxemia or fatigue, which may suggest the need for close monitoring in the intensive care unit or immediate maintenance of the airway with endotracheal intubation or tracheostomy.

Flexible or rigid laryngoscopy and/or bronchoscopy are appropriate for the patient with an unstable airway or suspected foreign body aspiration. These procedures should ideally be performed in the intensive care unit or operating room with clinicians adept at intubation, anesthesia, and continuous monitoring. A Swiss study investigated chin lift and jaw thrust maneuvers combined with CPAP in anesthetized spontaneously breathing children to perform flexible laryngoscopy. Combining these techniques improved the view of the glottic opening and decreased stridor.[70]

Postextubation laryngeal edema (PLE) with stridor and/or respiratory difficulty is a frequent complication encountered in the critically ill adult patient.[67] This situation also requires rapid evaluation and efforts to prevent further respiratory failure because reintubation is associated with increased morbidity and mortality.[71] Many studies have identified risk factors for postextubation laryngeal edema or stridor that include female gender, longer duration of intubation, use of large tube size/high cuff pressure, and difficult intubation, but unfortunately the data are insufficient to identify high-risk patients for targeted preventative therapies.[72] The current treatment algorithm for postextubation stridor includes reintubation, if necessary, and/or using intravenous methylprednisolone, nebulized budesonide, or epinephrine to reduce inflammation and induce vasoconstriction to reduce the PLE.[72] The optimal dosages of these medications is currently unknown. The use of these strategies has also been extrapolated to other common causes of laryngeal edema, such as anaphylaxis, and may be used as temporizing measures when necessary.

For those patients with stridor without impending airway closure or in whom endotracheal intubation is not advisable or immediately available, there are two approaches to improve airflow past the obstruction: CPAP and heliox. CPAP can quickly pressurize and, in effect, splint open the upper airway to reduce stridor and dyspnea. CPAP in this setting can maintain a higher level of alveolar partial pressure of oxygen, improve ventilation by decreasing work of breathing, and increase airway compliance and positive distending pressure.[54] The resultant increase in lung volume can also reduce the collapsibility of the upper airway.[73] For these reasons, the use of CPAP in the patient presenting with stridor and without the need for an emergent airway may be beneficial as a temporizing measure to allow time to investigate the etiology further and determine an appropriate treatment strategy.

Heliox is a mixture of helium and oxygen that lowers the density of the gas and improves flow without any change in the airway diameter. Heliox, especially if the helium content is as high as 70–80%, can enable airflow to become laminar or, even if turbulence continues, can decrease the pressure required to move the gas through a small orifice. It was first described for therapeutic use in the 1930s[74] and has been used for decades in the treatment of acute upper airway obstruction,[75] but there is a paucity of randomized trials of its use in adults. The inhalation of a heliox mixture decreases airway resistance and work of breathing, but there is currently no evidence on the efficacy of administration in adults, and it has not been shown to change outcomes in children.[76] However, heliox may be of immediate benefit in the setting of upper airway obstruction by facilitating ventilation in patients until further medical or surgical intervention is available or necessary.[77]

THE FUTURE OF LUNG SOUND ANALYSIS

Although the human ear can remarkably distinguish the many types of lung sounds described in the medical

literature, including wheezing and stridor, there are inherent limitations to detection sensitivity and accuracy of classification. Confusion of these two sounds can lead to serious consequences, especially if there is a failure to recognize stridor as a sign of impending airway closure. Recordings of lung sounds by electronic stethoscopes and other devices can now be made and analyzed for specific sound features, including intensity, frequency, and amplitude. Such properties may be depicted visually to allow further understanding of the difference between lung sounds. Machine learning may also be applied to lung sound data, in which different analysis methods, such as support vector machine and artificial neural network, are used to learn to distinguish lung sounds from large data sets of examples. A recent comprehensive review of this field found accuracy of wheeze detection ranging from 71–98%.[78] Such methods may prove useful not only in diagnosis but also in training and education. In particular, this technology might be useful for continuous, ambulatory monitoring for earlier detection of disease.

Key Points

- Wheezes and stridor are types of continuous adventitial lung sounds caused by fluttering of airway walls at sites of airflow limitation.
- The differential diagnosis of wheezes and stridor is broad, and making a diagnosis typically requires confirmation by other functional or imaging studies.
- Common causes of wheezing include asthma, COPD, and focal airway obstruction by mucus, tumor, or foreign body.
- Although asthma and COPD remain the most common causes of wheezing, other conditions should be considered, especially if the wheezing is of new onset, does not follow the typical pattern expected with asthma or COPD, or does not respond as expected to bronchodilator therapy.
- Common causes of stridor include vocal cord pathology, epiglottitis, goiter, laryngeal edema, and subglottic stenosis.
- Stridor may represent a medical emergency and needs to be evaluated rapidly for impending airway closure. Immediate measures to secure the airway with endotracheal intubation or tracheostomy may be necessary. Alternatives to improve airflow include continuous positive airway pressure to stabilize airway diameter during inspiration and heliox to improve airflow.

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40 HEMOPTYSIS

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INTRODUCTION

Hemoptysis is a potentially life-threatening condition that can often prove to be clinically challenging. It is defined as expectoration of blood originating from the tracheobronchial tree or pulmonary parenchyma with varied quantitative definitions of severity. However, any concern for cardiac or respiratory compromise should receive immediate attention. The diagnostic and therapeutic workup of mild hemoptysis should be geared toward identifying and correcting underlying causes, whereas massive hemoptysis should be approached in a multidisciplinary fashion involving pulmonologists, radiologists, thoracic surgeons, and intensive care providers, with the primary aim to stabilize the patient and control the airway.

DEFINITION OF SEVERITY OF BLEEDING

There is no consensus on how to stratify the severity of hemoptysis. Classically, hemoptysis has been defined according to the volume of blood expectorated over 24 hours.[1–3] However, this approach does not account for the patient's susceptibility to the harm of hemoptysis, which may stem from underlying lung and/or cardiac disease (see "Prognostic Indicators" later). In addition, the difficulty of quantifying the volume of expectorated blood further limits the utility of using volumes alone. A more practical approach to grading the degree of hemoptysis is by taking into consideration the clinical relevance of the hemoptysis, whereby severe or massive hemoptysis is any potentially life-threatening bleeding, compared to mild nonmassive hemoptysis. This accounts for additional features, such as the bleeding rate and other medical comorbidities. Any respiratory or hemodynamic instability must be used to prioritize immediate interventions (e.g., endoscopic or arterial embolization, airway, and hemodynamic stabilization).[4,5]

Mild (or nonmassive) hemoptysis is typically the manifestation of an underlying disease process and might not require admission if appropriate diagnostic and therapeutic interventions can be conducted in a reasonable time on an outpatient basis. Furthermore, in contrast to massive hemoptysis, mild hemoptysis is typically self-limited and holds a good prognosis with conservative treatment alone. Therapeutic interventions, such as bronchial artery embolization or surgery, are reserved for those who fail conservative medical management (see "Treatment" later).

EPIDEMIOLOGY AND OUTCOME

A large European epidemiologic study showed that hemoptysis accounted for 0.2% of all hospitalizations.[6] The most common etiologies for hemoptysis in high-income countries are respiratory infections (16–22%), followed by lung cancer (4–19%) and bronchiectasis (6–15%).[6–9] However, in regions with higher *tuberculosis* (TB) prevalence, TB remains a leading cause of hemoptysis (15–25%).[10–12]

In addition to the volume of expectorated blood, morbidity and mortality from hemoptysis depends on the acuity of bleeding, the ability of the patient to protect the airway by coughing blood from the airways, and the extent and severity of additional medical comorbidities. Hemoptysis, especially severe hemoptysis, carries a substantial overall mortality rate ranging from 9–38%.[1,13–16] Risk of death persists beyond the initial episode, with large epidemiologic studies reporting a 10% in-hospital mortality from non–lung cancer–related hemoptysis that increased to 16% and 20% at 1 and 3 years, respectively.[6] Idiopathic or cryptogenic hemoptysis also carries a significant risk of death (9–52%).[6–8,17] The underlying causes of hemoptysis may involve the airway (most common), the pulmonary parenchyma, or the pulmonary vessels (Table 40.1).

VASCULAR ORIGIN OF HEMOPTYSIS

The lung is supplied by both the pulmonary arterial system (a low-pressure circuit) and the bronchial artery system (a high-pressure circuit). Most hemoptysis arises from the bronchial circulation (90%),[18] whereas less common causes of hemoptysis (10%) stem from the pulmonary circulation

Table 40.1 Etiology of Hemoptysis

Airway disease	Cancer (endobronchial metastases, primary tumors)
	Inflammatory (bronchiectasis, cystic fibrosis, chronic bronchitis)
	Bronchovascular fistula
	Airway trauma
	Foreign body
Pulmonary parenchymal disease	Infections (pneumonia, tuberculosis, fungal, lung abscess, septic emboli)
	Inflammatory (vasculitis or collagen vascular disease)
	Lung contusion
	Drugs (cocaine inhalation, anticoagulation, antiplatelet, bevacizumab)
	Idiopathic pulmonary hemosiderosis
	Iatrogenic (lung biopsy)
	Clotting disorders
	Diffuse alveolar hemorrhage or damage
	Catamenial hemoptysis
Vascular disease	Pulmonary embolism/infarct
	Arteriovenous malformation
	Pulmonary artery pseudoaneurysm
	Dieulafoy lesion
	Pulmonary veno-occlusive disease
	Hereditary hemorrhagic telangiectasia
	Cardiac (mitral stenosis, heart failure)
	Iatrogenic (pulmonary artery catheter perforation)

and from nonbronchial systemic vessels, such as the aorta (aortobronchial fistula and ruptured aortic aneurysm), intercostal arteries, coronary arteries, axillary and subclavian arteries, and the upper and inferior phrenic arteries. It should be noted that bleeding from bronchial vessels is typically due to the neovascularization resulting from inflammation (e.g., bronchiectasis, abscess, and tuberculosis). Pulmonary arterial bleeding is usually due to ulceration of vessels caused by parenchymal destruction (cancers, necrotizing bacterial pneumonias, and mycetomas).

PROGNOSTIC INDICATORS

Prognostic scores have been developed to facilitate triage in the *emergency department* (ED) and to predict mortality in the *intensive care unit* (ICU).

Patients presenting to the ED with a score greater than 0 warrant additional in-hospital diagnostic tests, such as a chest CT scan, bronchoscopy, or bronchial artery angiography.[8] This score counts any of the following as warranting hospitalization:

- Systolic blood pressure less than 100 mm Hg
- History of malignancy
- Expectoration of pure blood
- Two or more episodes of hemoptysis in the prior 24 hours

For an ICU patient with hemoptysis, a mortality risk score consists of[19]:

- Need for mechanical ventilation (2 points)
- Malignancy (2 points)
- *Aspergillus* infection (2 points)
- Opacities involving greater than or equal to two quadrants on admitting radiograph (1 point)
- Involvement of pulmonary blood vessels (1 point)
- Chronic alcoholism (1 point)

The predicted probability of death upon ICU admission was as follows: score 0 = 1%; score 1 = 2%; score 2 = 6%; score 3 = 16%; score 4 = 34%; score 5 = 58%; score 6 = 79%; and score 7 = 91%.

DIAGNOSIS

INITIAL EVALUATION

Suspected hemoptysis must be confirmed and distinguished from pseudohemoptysis that may arise from epistaxis or hematemesis. Both severe epistaxis and upper gastrointestinal bleeds can have a similar presentation to hemoptysis and are potentially life threatening as well. In a large retrospective case series, pseudohemoptysis from upper airway or gastrointestinal bleeding was identified in 10% of patients presenting with presumed hemoptysis.[20] Careful history, physical examination, and laboratory tests are required to determine whether the bleeding originates from the upper airway—associated with bleeding gums, epistaxis, history of prodromal cough, sputum, sore throat, or pharyngitis—or the gastrointestinal tract—associated with coffee-ground vomitus, black tarry stools, epigastric pain, signs of chronic liver disease, abdominal pain, or nausea. Early consultation with otolaryngologists and gastroenterologists should be sought when the bleeding source is unclear.

Once pseudohemoptysis is excluded, targeted clinical history and physical examination can provide important clues concerning the etiology of hemoptysis, detail the bleeding severity, and guide diagnostic and therapeutic interventions. The general approach to mild and to massive hemoptysis is shown in Figure 40.1.

The directed history for patients presenting with hemoptysis should include questions about the duration of symptoms, frequency of hemoptysis, associated dyspnea, quantity coughed by patient during 24 hours, and any recent injury to the airway, such as diagnostic procedures, chest injury, or foreign body aspiration. A history of immobilization might be important because pulmonary embolism can present initially as hemoptysis. Also, history of tobacco, antiplatelet, or anticlotting agents, as well as recent toxic inhalants exposure, such as organic chemicals, are important to discern during initial evaluation. Furthermore, concomitant diseases, such as respiratory illness (chronic bronchitis, bronchiectasis, cystic fibrosis, pneumonia, cancer) or other diseases, such as heart disease (e.g., mitral stenosis), venous thromboembolic disease, immunosuppression, renal, hematologic, autoimmune, or systemic

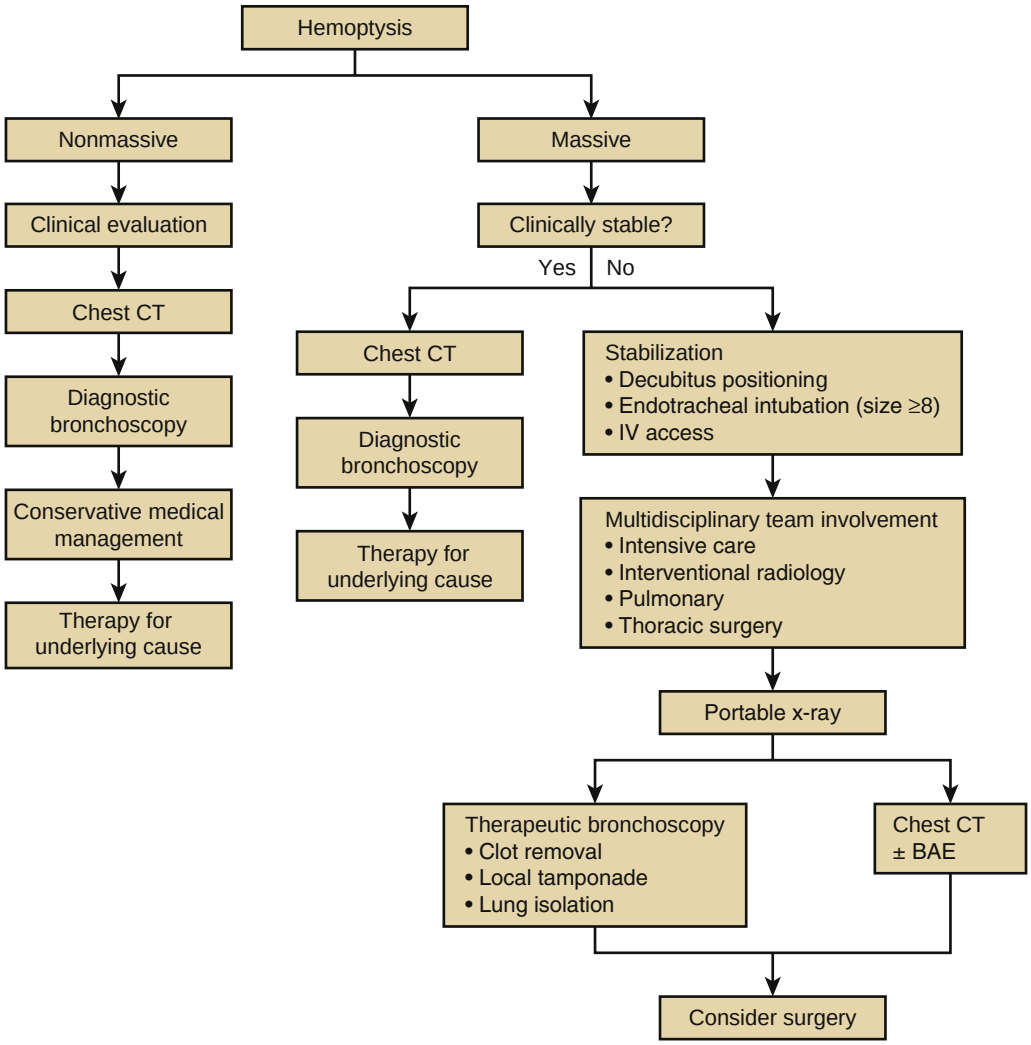

Figure 40.1 Proposed algorithm for the management of the patient with hemoptysis. BAE, bronchial arterial embolization; CT, computed tomography; IV, intravenous.

disease can help differentiate multiple causes of hemoptysis and appropriately guide laboratory work and management.

The physical examination can sometimes be useful for the assessment of the cause and the severity of bleeding but can be normal with most causes of hemoptysis. Careful inspection of the thorax can be very helpful in the setting of trauma because the signs of blunt or penetrating injury are likely to provide information regarding the site of bleeding. Stridor, crackles, wheezing, or diminished breath sounds can suggest the presence of a focal obstruction due to a foreign body, bronchiectasis, or pneumonia. Auscultation of the heart can detect the presence of murmurs for mitral stenosis or mitral regurgitation. Skin inspection for bruising can potentially suggest coagulopathy, telangiectasia of hereditary hemorrhagic telangiectasia or purpura caused by possible cutaneous vasculitis.

A comprehensive laboratory panel including chemistries, blood counts, and coagulation tests should be reviewed to identify potential reversible systemic bleeding dyscrasias. However, it is important to note that coagulation disorders alone are rarely primarily responsible for hemoptysis and, even in the setting of a coagulation disorder, an underlying disease should be thoroughly investigated. Specific studies such as N-terminal pro-B-type natriuretic peptide or D-dimer may direct attention toward specific underlying etiologies, such as congestive heart failure or pulmonary embolism, respectively, as an etiology for hemoptysis. Serologic studies, such as antinuclear antibody and anti-neutrophil cytoplasmic antibody, might uncover an underlying systemic process manifesting with hemoptysis. When a pulmonary infection is suspected, sputum cultures, including for acid-fast bacilli, are warranted. Despite diagnostic evaluations, an underlying etiology of bleeding will not be found in 5–10% of evaluations for hemoptysis.[21]

RADIOLOGY

The initial radiographic investigation of choice to diagnose and localize the source of hemoptysis should be guided by a focused medical history and physical examination. Chest radiographs perform poorly in lateralizing and identifying the cause of bleeding,[1] especially in non–life-threatening hemoptysis. *Computed tomography* (CT) of the chest plays a crucial role in localizing the site and can identify the cause of bleeding in up to 70–88% of the cases.[22,23]

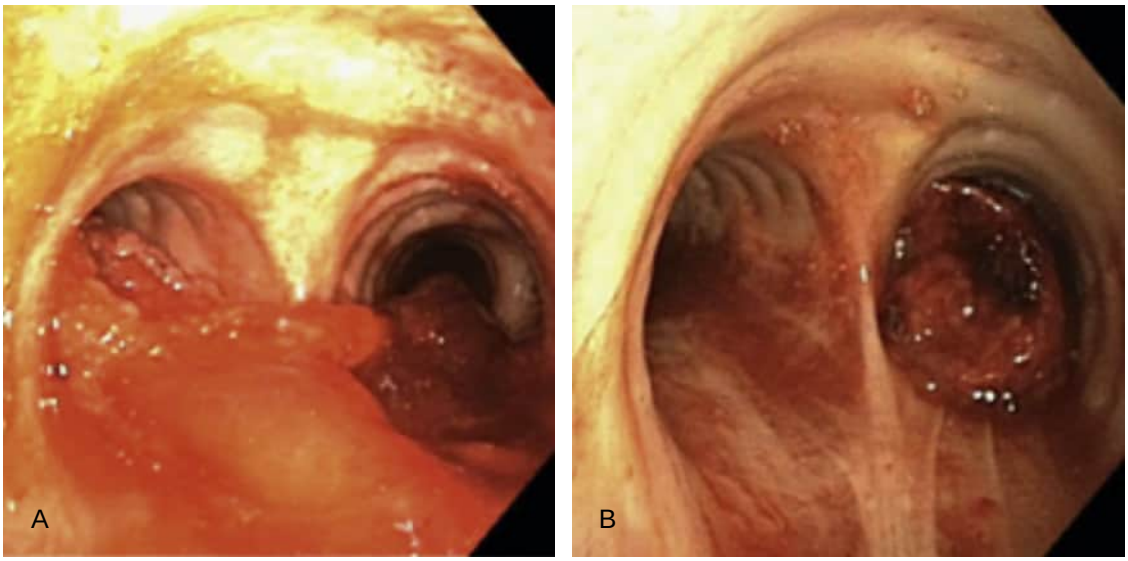

Figure 40.2 Bronchoscopic images of occlusive clots. A patient with massive hemoptysis due to severe bronchiectasis and a large obstructing clot overlying the main carina before (A) and after (B) bronchoscopic clearance of the left mainstem airway.

Chest CTs should be obtained in each of the following clinical situations in patients with hemoptysis:

- Patients suspected of having an underlying lung cancer or other thoracic malignancy, or those with pathologic findings on chest radiographs
- Patients with suspected bronchiectasis or cavitary lung disease
- Patients with life-threatening hemoptysis and active bleeding (after airway stabilization) who are candidates for embolization

CT scans acquired during the arterial phase with multiplanar reconstruction can help visualize the bronchial, nonbronchial arteries, and pulmonary circulation.[24] This detailed visualization of the thoracic vasculature can guide the optimal angiographic approach by identifying the origin and course of the bleeding arterial vessel. Intravenous contrast-enhanced CT chest angiography increases the sensitivity and specificity of hemoptysis localization relative to a non-contrast CT and should be done when feasible. Relevant findings that can be revealed by CT with contrast include bronchial arterial hypertrophy; aneurysm formation and/or tortuosity with artery diameter of 2 to 3 mm or greater; presence of pleural thickening measuring 3 mm or more adjacent to a parenchymal abnormality due to underlying chronic pulmonary inflammatory disease, for instance; and tortuosity along with enhancing vessels within extrapleural fat.[25]

Angiography of either the pulmonary or bronchial arteries has several limitations. It cannot be readily done in unstable patients or in patients with active bleeding who may require immediate endobronchial management. In patients with bilateral lung abnormalities without localizing signs, finding the site of bleeding may be time consuming and challenging.

DIAGNOSTIC BRONCHOSCOPY

The role of diagnostic bronchoscopy for hemoptysis evaluation is controversial. In patients without life-threatening hemoptysis, bronchoscopy has not been shown to increase the diagnostic yield of either benign or malignant causes of hemoptysis in comparison with CT[9,26] and has been shown to have limited ability in visualizing the bleeding source.[27] In patients with massive hemoptysis, it has been argued that early bronchoscopy, either during the active bleeding phase or within 48 hours of hemoptysis termination, can help localize the bleeding source in the airways and guide angiographic embolization.[26,28,29] However, early endoscopic examination does not seem to influence the clinical management and outcome even when it identifies the site of bleeding. Compared to bronchoscopy, CT scans have shown a higher accuracy in detecting the source of hemoptysis when bronchiectasis, pulmonary infections, or lung cancer are the underlying cause of bleeding.[9] Chest CT also has the advantage of characterizing airways that are distal to the level of bronchoscopic inspection, although CT scans are limited in their ability to differentiate between blood clots or an endobronchial tumor. Therapeutic bronchoscopy may have a role in airway management and stabilization, as well as ablative interventions as discussed later.

TREATMENT

GENERAL CONSIDERATIONS

The unpredictable clinical course for patients with hemoptysis mandates a timely evaluation with prioritization of the patient's hemodynamic and respiratory stability. A patient can asphyxiate quickly from bleeding and clotting in the airways even before there is enough blood loss to lead to hemodynamic compromise (Fig. 40.2). Thus the major goal is to protect the airway. Resuscitation should be anticipated with establishment of intravenous access and planning for close patient monitoring, usually in the ICU. Early involvement of different specialties, such as pulmonary, interventional radiology, thoracic surgery, and intensive care, for a multidisciplinary approach is important.

Beyond reversal agents for anticoagulants, no systemic therapies have been shown to be beneficial for hemoptysis

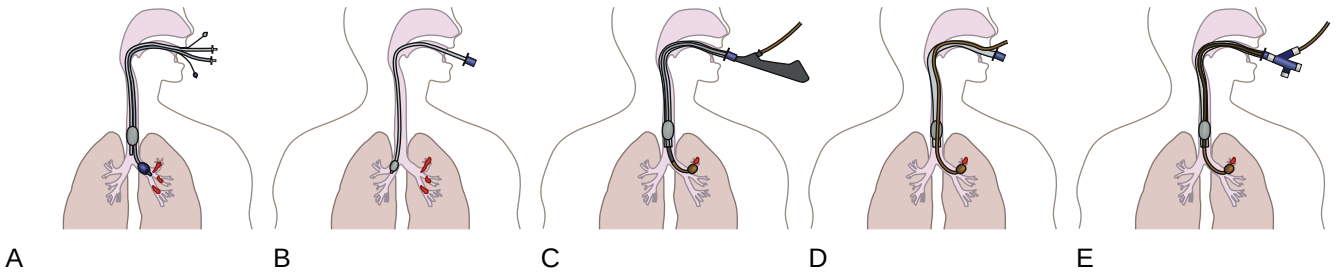

Figure 40.3 Isolation of bleeding using endotracheal tubes and airway blockers. The first two panels demonstrate the isolation of a bleeding left lung using a (A) double-lumen endotracheal tube and (B) right mainstem intubation of a single-lumen endotracheal tube to the nonbleeding lung. The last three panels demonstrate peripheral airway blockage using a balloon. A balloon catheter can be used for temporary tamponade by occluding the bleeding airway through the working channel of a bronchoscope or can be fixed in place after bronchoscopic guidance (C–D). The blocking balloon catheter can be fixed to the proximal end of the endotracheal tube (E). (Courtesy Arnon Brand, PhD.)

in general, and targeting specific underlying causes of hemoptysis should be prioritized. Therapies may include replacement of blood products (e.g., fresh frozen plasma or platelets), desmopressin to improve platelet function in the setting of renal dysfunction, or immunosuppressive therapy in the setting of vasculitis. Use of antitussive agents has been proposed as a means to minimize local irritation of friable blood vessels.[30]

Systemic therapies have been tested. Inhibiting systemic fibrinolytic activity with agents such as tranexamic acid to arrest pulmonary bleeding has been of interest based on data from other fields, such as cardiac or obstetric surgery, where antifibrinolytic use has been shown to decrease blood loss. However, a Cochrane meta-analysis demonstrated insufficient evidence for use of antifibrinolytic agents in hemoptysis, although some decrease in the duration of hemoptysis was suggested.[31] Nebulized tranexamic acid versus inhaled placebo was compared in a randomized controlled trial,[32] where nebulized tranexamic acid therapy was associated with a lower volume of blood loss, a higher rate of resolution of hemoptysis, and fewer procedures and fewer hospitalization days. Systemic use of factor VII has also been proposed, given its hemostatic properties for patients with hemophiliac disease. Experience with its use has been anecdotally reported in cases of life-threatening hemoptysis related to blunt and penetrating thoracic trauma, refractory thrombocytopenia, necrotizing infections, and cystic fibrosis.[33–37] However, concerns for adverse thromboembolic events have focused attention on local administration, although data are limited to small studies or case series.[38] Systemic use of vasopressin has also been suggested as a means to vasoconstrict hemorrhaging vessels, although concerns for the systemic side effects of vasoconstriction have been raised.[39,40]

AIRWAY MANAGEMENT

The potential compromise of the patient's respiratory status requires early consideration of airway protection. If the bleeding side is known, placing the patient in a lateral decubitus position with the affected side down can minimize spillage of blood to the unaffected lung. When the rate of bleeding overwhelms the ability of the patient to clear the airway by coughing, endotracheal intubation is indicated. Although intubation may be beneficial before blood spills to other parts of the lung, the complexity of such intubations may require some delay until the patient can be moved to a controlled environment, such as the operating room, where experienced

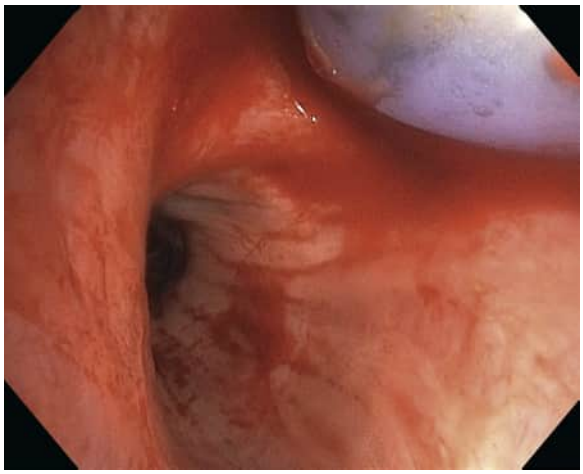

Figure 40.4 Endobronchial blocker in place. Endobronchial blocker inflated in the right upper lobe to occlude it after a lung biopsy, with protection of the bronchus intermedius from bloody spillage. (Courtesy Michael B. Gotway, MD.)

team members can manage a potentially compromised airway despite impaired visualization. Sedating a patient for intubation should be done cautiously because inhibiting the cough reflex may worsen the respiratory status by disabling the patient's own airway clearance mechanisms.

Although the airway can be secured in different ways, the unifying goal is to isolate the bleeding airway segment and ventilate as much of the uninvolved lung as possible (Figs. 40.3 and 40.4). Lung isolation can be achieved with either single- or double-lumen endotracheal tubes. *Double-lumen endotracheal tubes* (DLTs) have two parallel lumens, each cuffed with a tracheal and a bronchial side (either left or right). When the tube is correctly positioned and both balloons are inflated, the DLT effectively isolates each hemithorax (see Fig. 40.3A), allowing parallel and independent ventilation of each side and providing a conduit through which each lung can be suctioned separately. However, DLT placement requires a high level of expertise, and incorrect placement can lead to obstruction and spillage, and airway trauma.[41] In addition, their lumens are relatively narrow, thus limiting suction capacity and potential bronchoscopic interventions.

Single-lumen endotracheal tubes (SLTs) are readily available and easily placed, making them an appropriate choice for intubation for massive hemoptysis, especially if larger tube sizes (≥8) are used, which can facilitate possible bronchoscopic interventions and airway clearance. Different lung

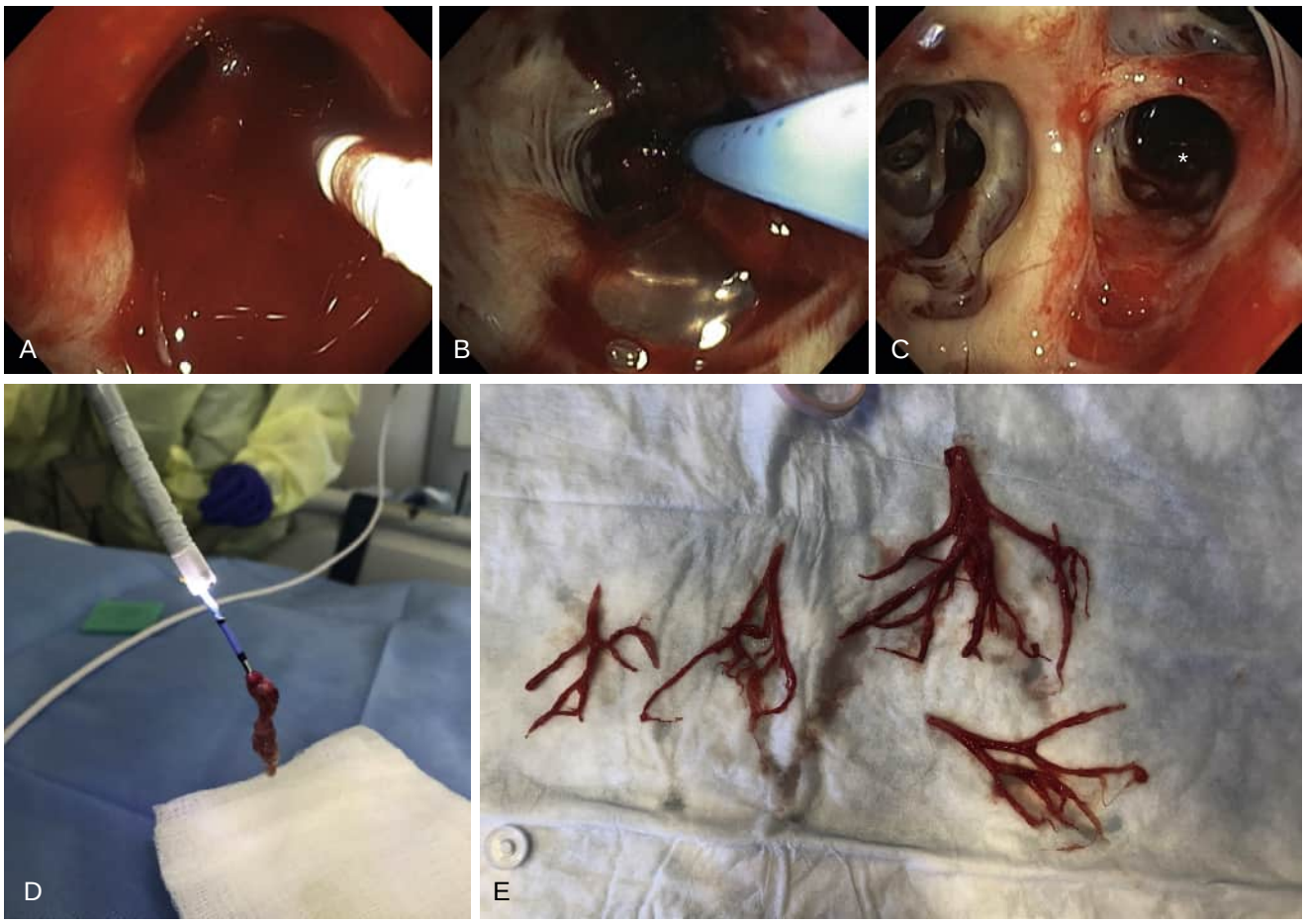

Figure 40.5 Therapeutic bronchoscopic management. Active bleeding originating from the right upper lobe (A) was controlled with a Fogarty balloon through the working channel of a bronchoscope (B). The bleeding was localized to the posterior subsegment of the right upper lobe denoted by the *asterisk* (C). Blood clots were removed from airway segments using a cryoprobe (D–E).

isolation strategies can be used via SLT to minimize lung contamination with blood. Lung isolation with SLT can be achieved through selective intubation of the uninvolved mainstem (see Fig. 40.3B), which will isolate the intubated lung from bleeding from the opposite lung. Alternatively, the SLT can be positioned as usual in the trachea, and the bronchoscope can be used to attempt selective airway tamponade with soft balloons, such as Fogarty balloons, or with blockers (see Fig. 40.3C–E; see "Endoscopic Approach" later).

ENDOVASCULAR APPROACH

Bronchial artery embolization (BAE) can both localize and embolize bleeding vessels (see also Chapter 21). The frequent involvement of the bronchial arteries in hemoptysis and the ability to perform minimally invasive bronchial arteriography in critically ill patients makes BAE an appealing approach. Radiologists can identify suspicious hypertrophic vessels and contrast extravasation, which requires a minimal rate of active bleeding to visualize. Occlusive materials, such as gelfoam, tris-acryl microspheres, coils, or alcohol particles, are then injected to block the bleeding vessel. Arteriography is considered highly effective for a wide variety of underlying causes of bleeding, including tuberculosis, bronchiectasis, and tumors.[42] Initial success rates have been reported to be as high as 85%; however, bleeding recurs in as many as 42% of cases.[43] Radiographic features cannot predict rebleeding, although the underlying etiologies may be more predictive: BAE for hemoptysis due to active tuberculosis and amenable to therapy may be associated with higher success rates, whereas BAE for hemoptysis due to aspergillomas may have a higher chance of recurrence.[44] Recurrence of bleeding after BAE has been associated with coexistent diabetes, with the need for blood transfusion after BAE, and with angiographic evidence of a bronchial artery–pulmonary artery shunt.[44,45] Adverse effects of arterial embolization are rare but include subintimal vascular dissection and neurologic defects due to inadvertent embolism of the anterior spinal artery.[42,46]

ENDOSCOPIC APPROACH

Beyond localization, bronchoscopy can provide therapeutic benefit by controlling the source of bleeding and by preventing asphyxiation by removal of clots and minimizing spillage of blood into uninvolved portions of the lung (Fig.

40.5).[47] Flexible bronchoscopes can be limited in their field of view and have inadequate suctioning capacity, making rigid bronchoscopy advantageous when available. Rigid bronchoscopy has the added advantage of securing the airway and allowing simultaneous ventilation and oxygenation while providing a conduit for ablative tools. Blood and clots can be removed using larger-caliber suctioning catheters that can range up to 4 mm in diameter and various tools, such as cryoprobes, which can extract larger clots en bloc (see Fig. 40.5D–E). However, rigid bronchoscopy requires additional training and typically requires the setting of an operating room.

Local instillation of topical medications can provide a respite in bleeding through clot stabilization until a definitive approach can be decided upon. In their review of cases of massive hemoptysis, Conlan and colleagues[48] reported that bleeding could be stopped in 23 patients by endobronchial instillation of 50 mL aliquots of iced saline, with sustained effect in all but two patients who rebled within days of bronchoscopy. Use of topical vasoconstrictors, such as epinephrine, has been described as a means to minimize bleeding after transbronchial biopsy and is often used for hemoptysis control in other settings.[49] Agents with chronotropic effect should be used with caution because ventricular arrhythmias have been reported.[50]

Local clot stabilization has been attempted using topical application of fibrinogen and thrombin mixtures.[51,52] Clinical experience with this method is limited to small retrospective case series, which report an overall high success rate of immediate bleeding cessation. Tsukamoto and colleagues[52] reported their 5-year experience with instillation of either thrombin or a fibrinogen-thrombin combination with 5-minute bronchoscopic wedging. In a small series of 33 patients with some degree of hemoptysis, of whom 19 had massive bleeding, this approach was deemed effective in all but two patients who ultimately required surgery. Similarly, de Gracia and colleagues[51] reported that all 11 patients treated with a fibrinogen-thrombin mixture had immediate control of bleeding; three of the 11 experienced an early or late recurrence of massive hemoptysis.[51] Anecdotal experience of two patients with biopsy-related bleeding controlled with local instillation of tranexamic acid has also been reported.[53]

Tamponade of the bleeding segments has been achieved by creating an airway plug in situ. Thrombin mixed with gelatin to achieve a viscous sealant has been delivered to the bleeding airway through endobronchial blockers.[54] Airway packing with polymers such as *n*-butyl cyanoacrylate has also been described, with immediate and sustained effect in as many as 90% of patients.[55,56] Valipour and colleagues[57] reported successful tamponade using oxidized regenerated cellulose (Surgicel; Ethicon) in 56 of 57 patients who had persistent massive bleeding despite local treatment with iced saline and vasoconstrictors. However, they also noted mild to moderate recurrence of bleeding in six and obstructive pneumonias in five of those treated.

Local tamponade can also be achieved using endobronchial balloons or prosthetic devices.[58,59] Cheap and readily available balloons, such as Fogarty balloons or pulmonary angiography balloons, have been used.[60] These soft and conforming balloons can occlude distal and segmental airways to prevent bloody spillage from bleeding segments and minimize the loss of healthy lung function while awaiting definitive therapy. They can be deployed through the bronchoscope's working channel as a short-term solution or directed alongside the bronchoscope, either inside or outside of the endotracheal tube, and bronchoscopically guided to the desired airways using forceps to provide longer-term blockade (see Fig. 40.3C–D).

Dedicated commercial bronchial blockers with inflatable cuffs of varying diameter sizes are available and can be inserted into the airway and fixed in place by attaching to an endotracheal tube (Figs. 40.3E and 40.4). Although highly effective at isolating bleeding segments, these are used as temporizing measures until a definitive intervention can be undertaken. Given the potential risk of mucosal injury from prolonged balloon inflation, the airways should be inspected intermittently (every 24–36 hours) to survey the airways and confirm cessation of bleeding. Longer-term prosthetic occlusive devices can be used when other interventions, such as BAE or surgery, have either failed or are contraindicated. Airway blockade can be achieved using prosthetic occlusive devices, such as small caliber silicone spigots. Spigots are pluglike devices that can be delivered to subsegmental airways using flexible bronchoscopy, but unfortunately these are unavailable in the United States.[61] One-way endobronchial valves were originally developed for lung volume reduction and persistent air leaks; however, these have also been used to produce selective atelectasis of the bleeding segments in patients with recurrent hemoptysis.[62] With the one-way valves, there has been success in cases of hemoptysis refractory to BAE in patients who are not surgical candidates.[63,64] As a result of these promising findings, a randomized controlled trial aimed at determining the effectiveness of endobronchial valves in refractory hemoptysis patients, when surgery is not possible and embolization has either failed or is deemed not feasible, is planned.[65] "Jailing" with endobronchial stents, which refers to placing a stent across the orifice of a bleeding airway and thereby blocking it, has also been used successfully to control bleeding when bronchial artery embolization and surgery were not an option.[66,67]

Thermal ablative modalities have been reported as highly effective for the local and immediate control of bleeding (Fig. 40.6). Thermal modalities can be categorized as contact versus noncontact, referring to whether there is a need for physical interaction with tissue to exert an ablative effect. Lasers are an example of a noncontact modality for which there is now a wealth of experience in palliating hemoptysis caused by endobronchial tumors.[68] The *neodymium:yttrium-aluminum-garnet* (Nd:YAG) laser is commonly used in the airway and has been effective in the management of life-threatening hemoptysis.[69] Efficacy in controlling hemoptysis can vary, with success rates from 60–77% in patients with bleeding due to cancer.[70,71] *Argon plasma coagulation* (APC) is another noncontact thermal tool that can be deployed through a flexible scope in the peripheral airways. APC delivers

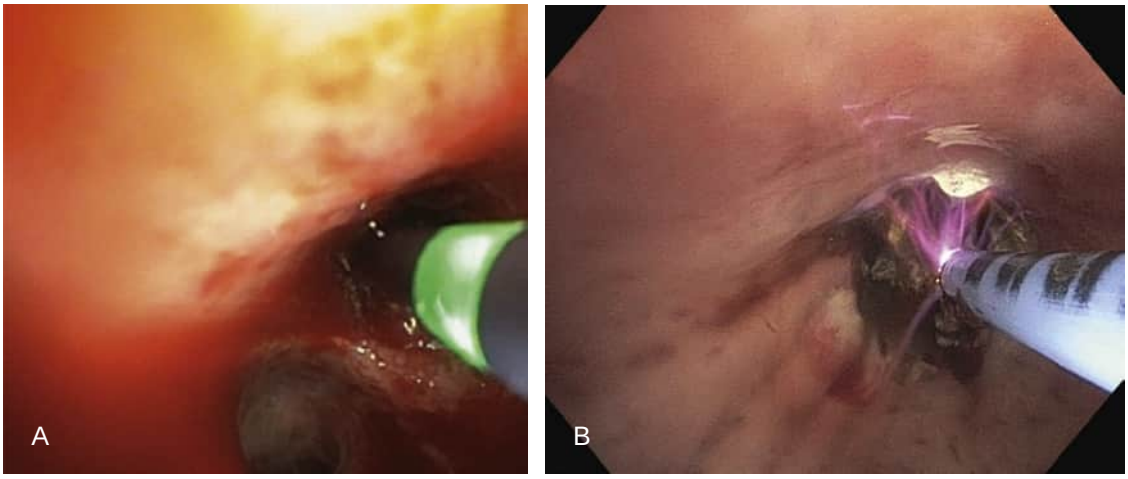

Figure 40.6 Bronchoscopic images of ablation used to stop bleeding. Ablation of a bleeding airway with a bronchoscopic-guided contact electrocautery blunt probe (A) and a noncontact argon plasma coagulation catheter (B). (A, Courtesy Yaron Gesthalter, MD. B, Courtesy Michael B. Gotway, MD.)

an electrical current along a plasma stream that conducts electricity to nearby areas of low resistance, which can superficially cauterize relatively large sections of the airway. Morice and colleagues[72] described their experience using APC in 56 hemoptysis patients in whom all had immediate and sustained effect at the site of treatment. Case reports of the effectiveness of APCs in benign vascular Dieulafoy lesions has also been described.[73,74] Contact electrocautery tools, such as blunt probes, can easily be used through a flexible bronchoscope; however, they require precise application and clear visualization of the bleeding target, given their limited surface area of application (see also Chapter 28).

Ablative modalities with delayed effect have also been used for the management of nonacute hemoptysis. Photodynamic therapy, which requires infusion with a photosensitizer 24 to 48 hours before the procedure, has been reported as having a sustained beneficial effect in patients with pulmonary hereditary hemorrhagic telangiectasia and small vessel bleeding.[75] Brachytherapy has been described in patients with hemoptysis due to endobronchial malignancy.[76,77] However, in a Cochrane review, there was no benefit to brachytherapy over external beam radiation, chemotherapy, or Nd:YAG in hemoptysis control.[78]

SURGICAL APPROACH

Surgical resection may be definitive in the prevention of bleeding recurrence; however, this is typically reserved for cases refractory to all nonsurgical approaches. Postsurgical complications can be seen in a quarter of patients, with mortality ranging from 6–15%.[16,79] Emergent surgical resection for hemoptysis is associated with poorer outcomes than nonemergent resections. Andréjak and colleagues[80] described their experience with surgical treatment of hemoptysis in which 111 of 813 patients admitted for massive hemoptysis underwent surgical lung resection. Emergent resections were associated with higher mortality rates (35%) compared to scheduled procedures (after initial bleeding control, 4%) and planned procedures (after discharge, 0%). Although these data are observational only, they highlight the benefit of preoperative stabilization and early consultation with a thoracic surgeon.

PREVENTIVE STRATEGIES FOR BLEEDING DURING LUNG BIOPSY

Bleeding during bronchoscopy is uncommon, reported in 0.26–5% of cases.[81] *Transbronchial biopsy* (TBB) increases bleeding risk through inadvertent damage to pulmonary or bronchial vessels. New techniques such as larger cryobiopsies for interstitial lung disease, may increase the need to be aware of how to prevent and manage iatrogenic bleeding.[82] Prophylactic instillation of vasoconstrictors, such as epinephrine in the airways, is not well studied and can be associated with adverse cardiac events.[49,50,83] A randomized trial assessing the utility of prophylactic topical vasoconstrictors is subject to an ongoing clinical trial.[84] In cases where TBB is being performed, most experts recommend wedging the bronchoscope into the airway of the biopsied area immediately before biopsy and leaving the bronchoscope wedged for several minutes after the biopsies until hemostasis is achieved. An additional preventive strategy includes the introduction of a deflated bronchial blocker proximal to the airway where the TBB is planned, with balloon inflation in the event of bleeding. Perhaps the most important measure for bleeding prevention is patient selection and preparation, with appropriate discontinuation of antiplatelet medicines and anticoagulants before the procedure, which should be coordinated with the patient's primary providers.[85,86] The risks and benefits of TBB in patients with pulmonary hypertension should be considered carefully and TBB avoided if possible.

Key Points

- Hemoptysis is commonly encountered and can present with a wide range of severity.
- The most common causes for hemoptysis globally include tuberculosis, bronchiectasis, and carcinoma involving the airways.
- Severity of bleeding should be assessed both by the quantity of blood expectorated and its effect on the patient's cardiopulmonary function.
- Mild hemoptysis could suggest an underlying process, such as an endobronchial tumor, and should prompt further investigation. Chest computed tomography has been shown to be more useful than bronchoscopy for identifying the underlying etiology.
- Severe or massive hemoptysis is life-threatening and warrants immediate multidisciplinary attention involving interventional radiologists, pulmonologists, thoracic surgeons, and intensive care doctors.
- Initial workup includes exclusion of pseudohemoptysis, a focused history and physical examination, and basic laboratory studies, especially for causes of coagulopathy. Although it is valuable to determine the underlying etiology, the primary focus in the setting of massive hemoptysis should be airway stabilization and cardiopulmonary support.
- Temporizing measures to spare uninvolved regions of the lung from spillage may involve decubitus positioning of the patient, with the bleeding side down, selective endotracheal intubation, or isolation of bleeding segments with balloons or other airway prosthetics.
- More definitive management can include bronchial artery embolization or endoscopic interventions.
- Surgical resection has an increased morbidity and mortality when used emergently. However, it has a role in the nonurgent setting to prevent bleeding recurrence.

Key Readings

Abdulmalak C, et al. Haemoptysis in adults: a 5-year study using the French nationwide hospital administrative database. *Eur Respir J*. 2015;46:503–511.

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41 PULMONARY NODULE

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INTRODUCTION

A pulmonary nodule is a discrete radiographic density measuring less than 3 cm, surrounded by aerated lung without associated lymphadenopathy or pleural effusion. Pulmonary nodules are often incidentally detected due to increased use of *computed tomography* (CT) scanning for a variety of clinical presentations. With the advent of *low-dose CT* (LDCT) screening for lung cancer, the incidence of pulmonary nodules will continue to rise. The majority of nodules are not malignant; however, they often pose a diagnostic dilemma for clinicians and have the potential to cause distress for patients. This chapter reviews the epidemiology, evaluation, and management of a pulmonary nodule.

EPIDEMIOLOGY

Historically, interest in the "coin lesion" first blossomed in the fifth and sixth decades of the 20th century with the publication of multiple case series that described a high prevalence of cancers among resected pulmonary nodules.[1] Most of these cases were probably identified sporadically, although at least one paper described the incidental detection of pulmonary nodules in a mass screening program for tuberculosis.[2] The subsequent accumulation of evidence linking cigarette smoking and lung cancer in the mid-1960s stimulated early studies of lung cancer screening with chest radiography. In this era, most nodules identified by radiography were relatively large (>10 mm in diameter) and presumed to be cancer until proven otherwise, often leading to unnecessary surgical resection of a benign nodule. In the 1980s, chest CT became widely used and, by virtue of its exquisite sensitivity, unintentionally launched an epidemic of incidental findings, including small, previously unrecognized pulmonary nodules.[3,4]

Chest CT is a ubiquitous presence in clinical chest medicine. In one population-based study of diagnostic imaging in six different health systems, the use of diagnostic CT increased at a rate of approximately 8% per year between 1996 and 2010, with an average rate of 23 chest CT scans per 1000 enrollees in 2008.[5] In another study from a different health system, the rate of chest CT scanning was remarkably similar (24.5 per 1000) in the 7-year period between 2006 and 2012.[6] As might be expected, greater use of imaging begets more incidental findings. In the latter study, at least one nodule measuring between 4 and 30 mm was identified in greater than 28% of diagnostic chest CT scans. Among almost 69,000 persons with an incidentally detected nodule, 3557 (5.2%) had a new diagnosis of lung cancer within 2 years of the index chest CT scan.[6] Even before the advent of lung cancer screening, the incidence of pulmonary nodules was increasing exponentially with wide availability and use of chest CT.

As demonstrated in the *National Lung Screening Trial* (NLST),[7] the introduction of lung cancer screening with LDCT has the potential to reduce lung cancer mortality, but it will simultaneously exacerbate the epidemic of nodules requiring evaluation. Randomized trials and nonrandomized cohort studies of lung cancer screening performed over the last 20 years have used slightly varying inclusion criteria to enroll high-risk current and former smokers who subsequently underwent two or more rounds of LDCT. In a systematic review from 2012,[8] the average prevalence of one or more nodules on the baseline round of screening was 20%. However, the prevalence varied from 3–30% in eight randomized controlled trials and from 5–51% in 13 cohort studies. In general, fewer nodules were identified on subsequent rounds of screening, especially in studies that only reported new (incident) nodules. In most studies, less than 5–10% of nodules were malignant; thus approximately 90–95% of all screening-detected nodules represent a false-positive finding.

Comparing and contrasting the results of studies of screening-detected nodules with more limited evidence from studies of incidentally detected nodules, it appears that nodules are found with similar frequency on both screening and diagnostic CT scans. The main source of variation in detection appears to be the individual radiologist, at least among the mostly expert radiologists who participated in the NLST, who on average identified false-positive nodules in 29% of all screening LDCT scans, with a range of 4–69%.[9] Other, less important, sources of variability in this analysis included patient characteristics, such as female sex, older age, body mass index less than 30 kg/m^2, current smoking,

and greater than 50 pack-years smoking history, all of which were associated with a greater frequency of nodule detection. Nodule detection was similar for academic compared with nonacademic centers, and (surprisingly) for centers inside compared with outside the histoplasmosis belt.

Another potential source of variation in nodule detection arises from differing definitions of a positive screening test result. In the NLST, a positive finding was defined as any noncalcified nodule measuring at least 4 mm in any dimension. One goal of the *Lung Imaging Data and Reporting System* (Lung-RADS) classification scheme is to reduce the percentage of false positives by adjusting the nodule size threshold that defines a positive test result.[10] Thus, instead of using the NLST definition of a positive test result, a positive (category 3) Lung-RADS finding is defined as a solid nodule of undetermined age measuring 6 mm or greater or a nodule known to be new (e.g., not seen on a prior scan) measuring 4 mm or greater. In a secondary analysis of data from the NLST, using Lung-RADS criteria instead of the initial NLST criteria for nodules detected on the initial (baseline) round of screening, the specificity for identifying cancer improved from 73.4% to 87.2%, resulting in an improvement in the positive predictive value from 3.8% to 6.9%, with little change in the negative predictive value.[11] In other words, post hoc classification by Lung-RADS criteria reduced the rate of false-positive findings at baseline scan in the NLST from 27% to 13%, with a slight reduction in test sensitivity (93% to 85%).[11] Lung-RADS is the most widely adopted structured reporting system used for lung cancer screening and will require continued evaluation and updates as large registry data become available.

Most screening-detected nodules are solid in their attenuation characteristics. However, a certain number are nonsolid or part solid. Among 57,496 participants with baseline LDCT scans in the International Early Lung Cancer Action Program, nonsolid (pure ground glass) and part-solid nodules were found in 4.2% and 5.0%, respectively.[12,13] Among 64,677 annual repeat screening examinations, new nonsolid and part-solid nodules were identified in 0.7% and 0.8% of examinations, respectively. The clinical importance of distinguishing between nodules of different types of attenuation is discussed later in this chapter.

EVALUATION AND MANAGEMENT

Most nodules, whether detected incidentally or from lung cancer screening, are benign. However, the most worrisome potential cause is primary lung cancer.[7,14–16] For an individual patient with a nodule, the clinician's overarching management goal is to balance the benefits and harms of immediate versus delayed detection and treatment. Clinical decision-making needs to incorporate multiple factors, such as the likelihood of malignancy: the patient's ability and desire to undergo treatment (surgical resection or curative radiotherapy, usually *stereotactic body radiotherapy* [SBRT]); the risks of diagnostic procedures, including pneumothorax, hemorrhage, and obtaining a nondiagnostic sample; and the patient's distress induced by uncertainty and waiting for a diagnosis. Several management options usually are considered when a patient is first diagnosed with a pulmonary nodule: (1) no further workup; (2) active surveillance by waiting a period of time to obtain repeat radiographic imaging, usually a CT scan; (3) performing a *positron emission tomography* (PET) scan; (4) obtaining a biopsy specimen through a bronchoscopic or percutaneous route; or (5) proceeding directly to curative therapy, with surgical resection or SBRT. The benefits of having a quicker and more definitive diagnosis, with the earliest possible treatment, increases across this spectrum. Unfortunately, the likelihood and magnitude of harms also increase along this spectrum, most important, the unnecessary harm if the nodule is benign.

In general, clinicians and patients do not need to know if a nodule is cancer *at the moment* of detection. On the one hand, the clinician and patient want to detect a cancerous nodule before it increases in size or metastasizes to lymph nodes or other organs, and then treat it at the earliest stage possible, when patients have the highest chance for survival.[17,18] On the other hand, clinicians do not want to harm a patient from the complications of additional radiation, invasive biopsies, and surgical resection or radiation therapy for a benign nodule. Thus, the clinical question hinges on whether it safe to perform further noninvasive testing to establish the malignant potential of a cancerous nodule by showing growth on serial CT scans or by finding metabolic evidence of growth based on a PET scan. The clinician must determine whether the benefit of detecting a cancer at the earliest possible stage is worth the risks of proceeding directly to invasive biopsies or curative therapies.

Certain radiographic findings of a pulmonary nodule definitively indicate that the lesion is benign. The presence of calcification within a pulmonary nodule that takes on one of five appearances is highly suggestive that the nodule is benign. These include diffuse, central, laminar, concentric, and popcorn calcification.[19] These patterns of calcification can indicate postinfectious granuloma and hamartoma. Patterns of calcification that appear stippled or eccentric are more concerning for malignancy and should be followed. Pulmonary hamartoma is a benign lesion that can be composed of various tissues, including fat, epithelial tissue, fibrous tissue, and cartilage. Although not all densities are always present, fat and calcification seen within a nodule is diagnostic for pulmonary hamartoma (see Figs. 20.10 and 20.11).[20] In addition, nodules located within the perifissural area are commonly identified as intrapulmonary lymph nodes. Figure 41.1 demonstrates radiographic features of benign nodules.

Even for those few nodules that are cancer, most are relatively slow growing, so there is usually time to "watch and wait" with a low likelihood that a cancer starting as a nodule will increase in stage.[18] Pulmonologists now widely recognize that it is safe to follow cancerous nodules (e.g., adenocarcinoma in situ) radiographically than proceed directly to a potentially harmful diagnostic procedure.[21] In addition, there is evidence to suggest that not all "early" lung cancers are the same because patients with squamous cell and small cell lung cancers may have less benefit from early detection with formal lung cancer screening than patients with adenocarcinoma.[22,23]

Several organizations have created expert-based follow-up and surveillance guidelines for incidental and screen-detected nodules, which are based on the pretest probability that a nodule is cancerous. As will be discussed further, these guidelines attempt to balance the chance of benefit, treating lung cancer at a stage that is most curable versus the chance of harm, subjecting patients to needlessly harmful tests for benign lesions.

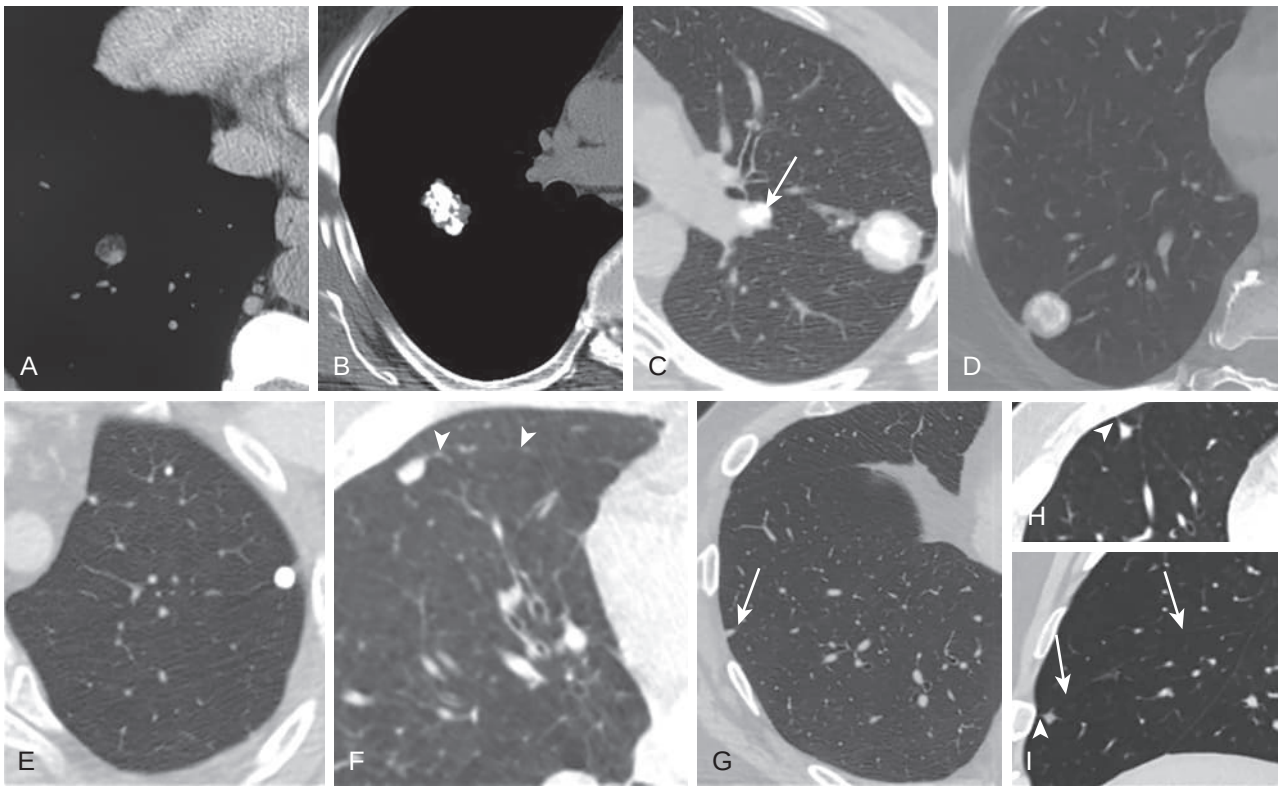

Figure 41.1 Nodules showing benign *computed tomography* (CT) features. (A) Fat within the lesion: hamartoma. (B) Chondroid ("popcorn") pattern of calcification: hamartoma. (C) Benign pattern of calcification (also see eFig. 20.30): central calcification in a postinfectious granuloma. Also note calcified left peribronchial lymph node *(arrow).* (D) Laminar ("target") calcification: one or more concentric rings of calcium. (E) Diffuse calcification (histoplasmosis). (F–I) Perifissural nodules (also see eFig. 20.48). Note nodule in (F) abuts the right minor fissure *(arrowheads).* Nodule in (G) *(arrow)* displays the common triangular shape, with broad-based contract with the visceral pleural surface. Axial (H) and sagittal (I) CT show a 6-mm peripheral nodular opacity with a thin septum *(arrowhead)* connecting the nodule to the visceral pleural surface. The nodule contacts, but does not distort, the adjacent minor fissure *(arrows).* (Courtesy Michael B. Gotway, MD.)

The Fleischner guidelines offer an example of this tradeoff when they suggest that nodules with less than 1% pretest probability of being malignant do not need to be surveilled.[24]

Multiple studies have been conducted to assess the pretest probability that a patient with a pulmonary nodule will be diagnosed with cancer.[15,25–28] Many models include known risk factors for cancer, such as age, smoking history, and other exposures such as asbestos exposure and a personal history of cancer. In general, the size of the nodule at the time of detection contributes the most information to the model. No trials have been performed to evaluate the clinical usefulness of one model over the other. However, in two analyses, the Brock model, developed from data from patients undergoing screening in the Pan-Canadian Early Detection of Lung Cancer Study, was most accurate.[29,30] This model includes an online calculator that can be downloaded from https://brocku.ca/lung-cancer-screening-and-risk-prediction/risk-calculators/, which may be helpful in communicating the risk of cancer to a patient.

GUIDELINES FOR NODULE MANAGEMENT

The first set of recommendations for lung nodule evaluation was published by the Fleischner Society in 2005.[31] Before this time, there was little or no consensus about the frequency or timing of surveillance CT scans in patients with small nodules measuring less than 8 mm in diameter, which typically are not reliably characterized by PET and too small to biopsy or resect. Fortunately, these recommendations defined a reasonable standard of care and probably reduced the frequency of unnecessary surveillance imaging among patients with small nodules. In the absence of moderate- or high-quality direct evidence from randomized trials or even large observational studies that compared different practices for follow-up, the recommendations were predicated on two reasonable assumptions; (1) nodules more suspicious for cancer should be followed earlier and more frequently; and (2) owing to imprecision in measurement, it is difficult to identify growth over short time intervals in smaller nodules. Thus, the original Fleischner Society recommendations were stratified by nodule size and the presence or absence of (unspecified) risk factors for lung cancer. In 2013, additional recommendations were made for nonsolid and part-solid nodules.[32] Because cancers presenting as nonsolid nodules tend to grow slowly, they were felt to require less intensive but perhaps longer follow-up. As for the part-solid nodules, sometimes they resolve, but the nonresolving ones are likely to be cancer; hence short-interval (3-month) follow-up was recommended.

Subsequently, the existing Fleischner Society recommendations were combined, clarified, and updated in 2017, with the goal to "reduce the number of unnecessary follow-up examinations while providing greater discretion to the radiologist, clinicians and patient to make management decisions."[24] New recommendations for patients with multiple nodules were also included, and it was clarified that the guidelines applied only to incidental nodules found in adults who were at least 35 years of age and not for patients who

Table 41.1 Fleischner Society 2017 Guidelines for Management of Incidentally Detected Pulmonary Nodules in Adults

Nodule Type	SIZE <6 mm (<100 mm³)	6–8 mm (100–250 mm³)	>8 mm (>250 mm³)	Comments
SOLID NODULES				
Single				
Low risk*	No routine follow-up	CT at 6–12 mo, then consider CT at 18–24 mo	Consider CT at 3 mo, PET/CT, or tissue sampling	Nodules <6 mm do not require routine follow-up in low-risk patients (recommendation 1A).
High risk*	Optional CT at 12 mo	CT at 6–12 mo, then CT at 18–24 mo	Consider CT at 3 mo, PET/CT, or tissue sampling	Certain patients at high risk with suspicious nodule morphology, upper lobe location, or both may warrant 12-mo follow-up (recommendation 1A).
Multiple				
Low risk*	No routine follow-up	CT at 3–6 mo, then consider CT at 18–24 mo	CT at 3–6 mo, then consider CT at 18–24 mo	Use most suspicious nodule as guide to management. Follow-up intervals may vary according to size and risk (recommendation 2A).
High risk*	Optional CT at 12 mo	CT at 3–6 mo, then at 18–24 mo	CT at 3–6 mo, then at 18–24 mo	Use most suspicious nodule as guide to management. Follow-up intervals may vary according to size and risk (recommendation 2A).

Nodule Type	SIZE <6 mm (<100 mm³)	≥6 mm (>100 mm³)	Comments
SUBSOLID NODULES†			
Single			
Ground-glass	No routine follow-up	CT at 6–12 mo to confirm persistence, then CT every 2 yr until 5 yr	In certain suspicious nodules <6 mm, consider follow-up at 2 and 4 yr. If solid component(s) or growth develops, consider resection (recommendations 3A and 4A).
Part-solid	No routine follow-up	CT at 3–6 mo to confirm persistence. If unchanged and solid component remains <6 mm, annual CT should be performed for 5 yr	In practice, part-solid nodules cannot be defined as such until ≥6 mm, and nodules <6 mm do not usually require follow-up. Persistent part-solid nodules with solid components ≥6 mm should be considered highly suspicious (recommendations 4A–4C).
Multiple	CT at 3–6 mo. If stable, consider CT at 2 and 4 yr	CT at 3–6 mo. Subsequent management based on the most suspicious nodule(s)	Multiple <6 mm pure ground-glass nodules are usually benign, but consider follow-up in selected patients at high risk at 2 and 4 yr (recommendation 5A).

These recommendations do not apply to lung cancer screening, patients with immunosuppression, or patients with known primary cancer. For specific recommendations (1A-5A), see table source.
*Consider all relevant risk factors, as outlined in table source.
†Dimensions are average of long and short axes, rounded to the nearest millimeter.
CT, computed tomography; PET, positron emission tomography.
From MacMahon H, Naidich DP, Goo JM, et al. Guidelines for management of incidental pulmonary nodules detected on CT images: from the Fleischner Society 2017. *Radiology*. 2017;284:228–243.

were immunocompromised or with a known extrathoracic cancer. Perhaps the most important changes were the new recommendations for following nodules less than 6 mm in diameter: If there were no risk factors for lung cancer, no follow-up was needed; if there were risk factors, follow-up was optional. The 2017 recommendations for patients with incidentally detected nodules are summarized in Table 41.1.

For patients with nodules measuring greater than 8 mm, the Fleischner Society recommends consideration of three options: surveillance chest CT at 3 months, PET/CT, or tissue sampling. Additional guidance regarding these three options is provided by evidence-based guidelines from the American College of Chest Physicians[33] (Fig. 41.2). These guidelines suggest using clinical intuition or a validated risk assessment model to make an initial assessment of the pretest probability of cancer. Based on the results of decision analytic models and related studies,[34–36] the guidelines suggest two approaches: When the probability of cancer is low (<5%), plan for CT surveillance at 3 to 6, 9 to 12, and 18 to 24 months; and when the probability of cancer is high (>65%), consider surgical diagnosis of approachable nodules in medically fit patients. For nodules with an intermediate probability of cancer (5–65%), the guidelines suggest either nonsurgical biopsy or PET/CT to characterize the nodule better. Nonsurgical biopsy is also suggested when a risk-averse patient wants confirmation of malignancy before surgery. Elicitation of patient preferences is critically important, in part because these are weak recommendations or suggestions based on low- or very low-quality evidence but also because patient preferences for either aggressive or conservative evaluation are likely to be strong.

Both the *American College of Radiology* (ACR) and the *National Comprehensive Cancer Network* (NCCN) have produced recommendations for the evaluation of screening-detected nodules. The ACR recommendations, newly updated in 2019, are embedded in the Lung-RADS classification system,

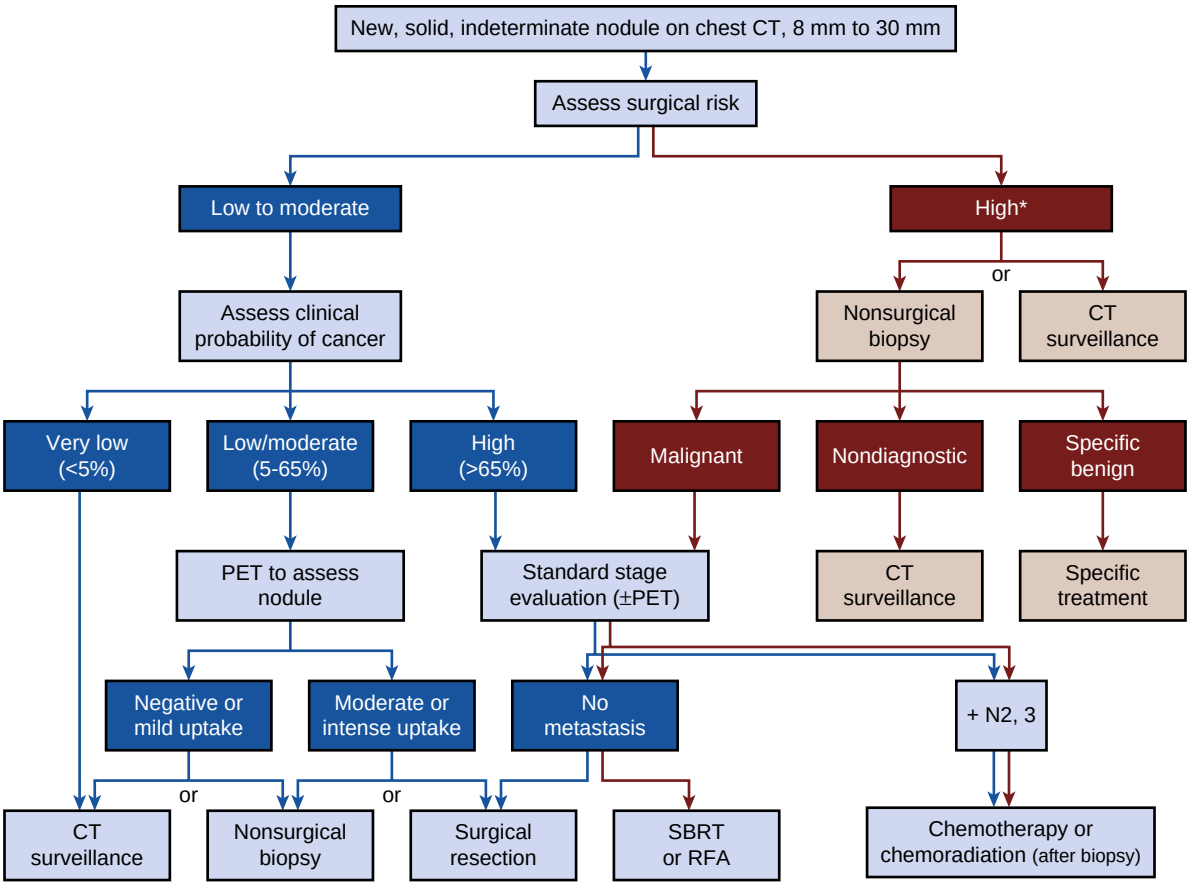

Figure 41.2 Management algorithm for individuals with solid nodules measuring 8 to 30 mm in diameter. *Among individuals at high risk for surgical complications, we recommend either nonsurgical biopsy, when the clinical probability of malignancy is moderate to high, or CT scan surveillance, when the clinical probability of malignancy is low to moderate. CT, computed tomography; PET, positron emission tomography; RFA, radiofrequency ablation; SBRT, stereotactic body radiotherapy. (From Gould MK, Donington J, Lynch WR, et al. Evaluation of individuals with pulmonary nodules: when is it lung cancer? Diagnosis and management of lung cancer, 3rd ed. American College of Chest Physicians Evidence-Based Clinical Practice Guidelines. *Chest.* 2013;143[suppl 5]:e93S–e120S.)

which categorizes nodules according to size, attenuation, and whether they are known to be new or growing.[10] A Lung-RADS category 1 finding of no nodules or a nodule with a benign pattern of calcification is considered to be negative. A category 2 finding of a small solid nodule (<6 mm), new solid nodule (<4 mm), part-solid nodule (<6 mm), nonsolid nodule (<30 mm), or a perifissural nodule (<10 mm) is considered to be a benign finding with a risk of cancer less than 1%. Patients with Lung-RADS category 1 or 2 findings should therefore return for annual screening. As nodule size increases, the risk of cancer increases from 1–2% in Lung-RADS category 3 nodules, to 5–15% in Lung-RADS category 4A nodules, to greater than 15% in Lung-RADS category 4B nodules. Thus, Lung-RADS recommends CT surveillance at 6 months or 3 months for category 3 or 4A findings, respectively, and short-interval chest CT, PET/CT, and/or tissue diagnosis for patients with category 4B findings, depending on the probability of cancer and whether the patient is fit to undergo surgery or nonsurgical biopsy. Additional details about the Lung-RADS classification system can be found in Figure 41.3. NCCN guidelines for lung cancer screening have been updated since their initial publication in 2011 and are largely consistent with Lung-RADS.[37]

Although not well known in North America, the *British Thoracic Society* (BTS) published guidelines for pulmonary nodule evaluation in 2015.[38] These guidelines were developed using rigorous methodology and an exhaustive series of systematic literature reviews. Distinctively, the BTS guidelines endorse CT surveillance for nodules with a risk of cancer less than 10% and the use of CT volumetric analysis at 3 months to check for growth of nodules measuring at least 6 mm in diameter (or 80 mm^3 in volume). Assessing the change in nodule size has traditionally been done by measuring the largest transverse cross-sectional diameter (Fig. 41.4). The volume doubling time of the nodule can then be estimated based on the change in size from baseline to follow-up CT scan. Volume doubling times can vary across histologic subtype of tumor and have been shown to be shorter in solid nodules compared to semisolid nodules or pure ground-glass nodules.[38] For solid nodules, the majority of nodules later determined to be malignant have a volume doubling time of less than 400 days.[39] This can be calculated manually using an exponential growth model that assumes uniform *three-dimensional* (3D) tumor growth. Alternatively, volumetric analysis can be conducted using semiautomated/automated software platforms. Studies comparing standard *two-dimensional* (2D) caliper measurements to semiautomated and automated 3D volumetric analysis have shown a better sensitivity for volumetric-calculated doubling time for malignancy.[40,41] Although these platforms are increasingly available, they are not always routinely used by all radiologists.

Lung-RADS® Version 1.1

Assessment Categories Release date: 2019

Category Descriptor	Lung-RADS Score	Findings	Management	Risk of Malignancy	Est. Population Prevalence
Incomplete	**0**	Prior chest CT examination(s) being located for comparison Part or all of lungs cannot be evaluated	Additional lung cancer screening CT images and/or comparison to prior chest CT examinations is needed	n/a	1%
Negative No nodules and definitely benign nodules	**1**	No lung nodules Nodule(s) with specific calcifications: complete, central, popcorn, concentric rings and fat containing nodules			
Benign Appearance or Behavior Nodules with a very low likelihood of becoming a clinically active cancer due to size or lack of growth	**2**	**Perifissural nodule(s)** *(See Footnote 11)* < 10 mm (524 mm^3) **Solid nodule(s):** < 6 mm (< 113 mm^3) new < 4 mm (< 34 mm^3) **Part solid nodule(s):** < 6 mm total diameter (< 113 mm^3) on baseline screening **Non solid nodule(s) (GGN):** < 30 mm (<14137 mm^3) **OR** ≥ 30 mm (≥ 14137 mm^3) and unchanged or slowly growing **Category 3 or 4 nodules unchanged for ≥ 3 months**	Continue annual screening with LDCT in 12 months	< 1%	90%
Probably Benign Probably benign finding(s) - short term follow up suggested; includes nodules with a low likelihood of becoming a clinically active cancer	**3**	**Solid nodule(s):** ≥ 6 to < 8 mm (≥ 113 to < 268 mm^3) at baseline **OR** new 4 mm to < 6 mm (34 to < 113 mm^3) **Part solid nodule(s)** ≥ 6 mm total diameter (≥ 113 mm^3) with solid component < 6 mm (< 113 mm^3) **OR** new < 6 mm total diameter (< 113 mm^3) **Non solid nodule(s)** (GGN) ≥ 30 mm (≥ 14137 mm^3) on baseline CT or new	6 month LDCT	1-2%	5%
Suspicious Findings for which additional diagnostic testing is recommended	**4A**	**Solid nodule(s):** ≥ 8 to < 15 mm (≥ 268 to < 1767 mm^3) at baseline **OR** growing < 8 mm (< 268 mm^3) **OR** new 6 to < 8 mm (113 to < 268 mm^3) **Part solid nodule(s):** ≥ 6 mm (≥ 113 mm^3) with solid component ≥ 6 mm to < 8 mm (≥ 113 to < 268 mm^3) **OR** with a new or growing < 4 mm (< 34 mm^3) solid component **Endobronchial nodule**	3 month LDCT; PET/CT may be used when there is a ≥ 8 mm (≥ 268 mm^3) solid component	5-15%	2%
Very Suspicious Findings for which additional diagnostic testing and/or tissue sampling is recommended	**4B**	**Solid nodule(s)** ≥ 15 mm (≥ 1767 mm^3) **OR** new or growing, and ≥ 8 mm (≥ 268 mm^3) **Part solid nodule(s) with:** a solid component ≥ 8 mm (≥ 268 mm^3) **OR** a new or growing ≥ 4 mm (≥ 34 mm^3) solid component	Chest CT with or without contrast, PET/CT and/or tissue sampling depending on the *probability of malignancy and comorbidities. PET/CT may be used when there is a ≥ 8 mm (≥ 268 mm^3) solid component. *For new large nodules that develop on an annual repeat screening CT, a 1 month LDCT may be recommended to address potentially infectious or inflammatory conditions*	> 15%	2%
	4X	Category 3 or 4 nodules with additional features or imaging findings that increases the suspicion of malignancy			
Other Clinically Significant or Potentially Clinically Significant Findings (non lung cancer)	**S**	**Modifier - may add on to category 0-4 coding**	As appropriate to the specific finding	n/a	10%

IMPORTANT NOTES FOR USE:

1) Negative screen: does not mean that an individual does not have lung cancer
2) Size: To calculate nodule mean diameter, measure both the long and short axis to one decimal point, and report mean nodule diameter to one decimal point
3) Size Thresholds: apply to nodules at first detection, and that grow and reach a higher size category
4) Growth: an increase in size of > 1.5 mm (> $2mm^3$)
5) Exam Category: each exam should be coded 0-4 based on the nodule(s) with the highest degree of suspicion
6) Exam Modifiers: S modifier may be added to the 0-4 category
7) Lung Cancer Diagnosis: Once a patient is diagnosed with lung cancer, further management (including additional imaging such as PET/CT) may be performed for purposes of lung cancer staging; this is no longer screening
8) Practice audit definitions: a negative screen is defined as categories 1 and 2; a positive screen is defined as categories 3 and 4
9) Category 4B Management: this is predicated on the probability of malignancy based on patient evaluation, patient preference and risk of malignancy; radiologists are encouraged to use the McWilliams et al assessment tool when making recommendations
10) Category 4X: nodules with additional imaging findings that increase the suspicion of lung cancer, such as spiculation, GGN that doubles in size in 1 year, enlarged lymph nodes etc
11) Solid nodules with smooth margins, an oval, lentiform or triangular shape, and maximum diameter less than 10 mm or 524 mm^3 (perifissural nodules) should be classified as category 2
12) Category 3 and 4A nodules that are unchanged on interval CT should be coded as category 2, and individuals returned to screening in 12 months
13) LDCT: low dose chest CT

Additional resources available at - https://www.acr.org/Clinical-Resources/Reporting-and-Data-Systems/Lung-Rads

Link to Lung-RADS calculator - https://brocku.ca/lung-cancer-screening-and-risk-prediction/risk-calculators/

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Figure 41.3 Lung Imaging Reporting and Data System (Lung-RADS) by the American College of Radiology. Version 1.1 Assessment Categories (2019 release): https://www.acr.org/Clinical-Resources/Reporting-and-Data-Systems/Lung-Rads.

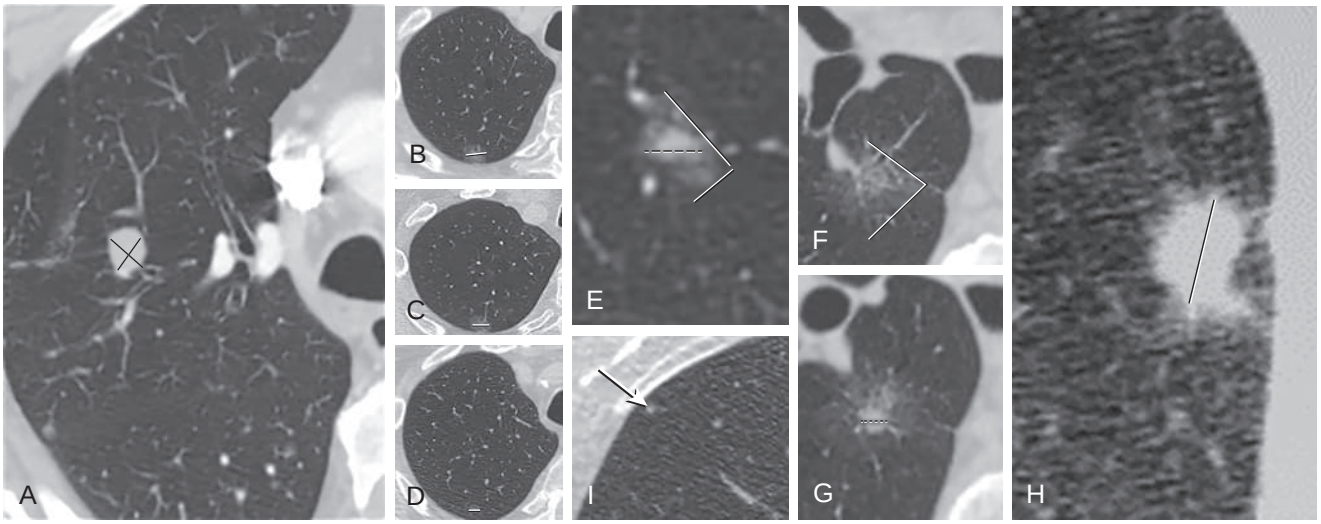

Figure 41.4 Appropriate measurement of lung nodules at chest *computed tomography* (CT). Measurements should be performed on thin-section CT images (reconstruction thickness ≤ 1.5 mm), displayed in lung windows, performed at full inspiration, and reconstructed with a high spatial frequency algorithm. Measurements are typically performed in the axial plane unless other planes, such as coronal or sagittal planes, better demonstrate the maximum nodule dimension. (A) Average of long-axis measurement and perpendicular maximal short-axis measurement *(lines)* of a nodule in the same plane. (B–D) For serial examinations, the current examination should be compared not only with the most recent examination but also with earlier examinations to determine more confidently if there has been nodule growth. In this example growth in the nodule *(line)* between the current (B) and most recent prior CT (C) is difficult to determine but is more clearly shown when the current examination (B) is compared to a more remote prior study (D). (E) For part-solid nodules, perform bidirectional measurements *(solid white lines)* through the largest dimension of nodule, including ground-glass and cystic components, if any, in whatever plane shows the longest dimension of the nodule, and then measure solid component of the nodule *(dashed white lines)* on the image in which the longest dimension is visualized. (F–G) In this example of another part-solid nodule, the solid core of the part-solid nodule (*dashed lines,* G) is at a different level than the longest dimension of the nodule (*solid white lines,* F). Note that it has been suggested by some that the size of the solid component of a part-solid nodule should be measured on soft tissue windows, but the Fleischner Society recommendations advise using thin-section lung windows reconstructed with a high spatial frequency algorithm for such measurements. (H) For spiculated nodules, measure only the solid core of the nodule *(line),* not the spiculations. (I) For nodules <3 mm *(arrow),* do not attempt to measure the nodule. Mark the nodule for reference, and refer to the nodule as a "micronodule." (Courtesy Michael B. Gotway, MD.)

Existing guidelines for pulmonary nodule evaluation provide a solid foundation for current clinical practice. However, there are several limitations, chiefly that they are not based on high-quality evidence from randomized, controlled trials or even from well-designed observational comparative effectiveness studies. In addition, whereas the use of longer-interval follow-up in nodules with a lower risk of cancer has the advantage of reducing unnecessary imaging for the large majority of individuals with benign nodules, a nodule with a low risk of cancer still has the potential to grow and spread if it is malignant. Thus there is a case to be made for short-interval (3-month) follow-up of all nodules. Last, existing guidelines are complicated, and this complexity may limit adherence by radiologists, providers, and patients. Further revision and refinement of existing guidelines should prioritize simplicity to maximize adherence.

COMMUNICATION

As with all diseases and conditions, it is important that clinicians communicate effectively and compassionately with patients with incidental and screen-detected nodules. The harms from procedural complications involved with nodule workup are important to consider,[42,43] but there are additional harms associated with inadequate communication. The harms that result from a "near cancer" diagnosis after a nodule is detected include physical harms plus psychological harms, such as distress, financial strain, and opportunity costs, which can further lead to nonadherence to suggested follow-up imaging and procedures.[44] In addition to harms, there are also benefits. Clinicians often consider diagnosis of a nodule as an opportune time to discuss smoking cessation and try to communicate about it as a teachable moment. Communication strategies include many components and commonly focus on information exchange, patient-as-person by implicit or explicit consideration of the patients' values and preferences, and shared decision making where patients make decisions about their health care with as much or as little autonomy as desired. All these components are important, but they likely have differential effects on subsequent patient-centered outcomes.

There have been no randomized trials of different communication strategies for patients with nodules, but several observational studies can provide insights into high-quality communication techniques.[45] First, many patients suffer from distress as a result of pulmonary nodule detection, sometimes severely and for a prolonged period of time.[47–50] Although patients consistently report low levels of knowledge about their nodule,[48,50] communication strategies that emphasize consideration of the patents' values and preferences seems likely to assuage that distress.[47,51] Second, nonadherence to follow-up imaging surveillance is common.[52,53] Similar to communication strategies for reducing distress, techniques that consider the patients' values and preferences are associated with better adherence.[52] Third, most patients prefer to share decisions regarding nodule management with their clinicians,[54] a notion reflected in nodule evaluation guidelines.[33] Decision-making role concordance, when patients make decisions concordant with their preferences, is associated with medical care satisfaction.[54] Finally, as mentioned, nodule detection might be a teachable moment to facilitate positive smoking behavior

changes. In the context of lung cancer screening, finding a pulmonary nodule is associated with smoking cessation, although the communication strategies that underlie this association are unknown, and this result was not confirmed in a small study among patients with incidentally detected nodules.[55,56]

Thus, it is important to share information with patients with nodules about the benefits and harms of different management strategies in a way that is respectful of their values and preferences and incorporates how they want to make decisions. Several organizations have developed educational materials to help patients with nodules understand the ramifications and likely follow-up procedures (e.g., http://thoracic.org/patients/patient-resources/resources/lung-nodules-online.pdf). Patients and clinicians have also made suggestions for how to communicate effectively, which are included in Table 41.2.[45]

SOLID VERSUS SUBSOLID NODULES

Radiographically, nodules are often divided into solid versus subsolid, the latter further divided into nonsolid versus part-solid. With completely *nonsolid* nodules, the underlying lung parenchyma can still be visualized; these are often referred to as ground-glass opacities or nodules. *Part-solid* nodules have both solid and nonsolid components. These terms are sometimes used interchangeably and often ambiguously in both clinical and research settings. Thus, it is important for clinicians and researchers to exercise proper diligence when interpreting and reading individual images and when applying research findings in practice (see Chapter 20 and eFig. 20.47).

Compared to solid nodules, nonsolid nodules are more likely to have an indolent growth pattern. As a representative example, the investigators from the Multicenter Italian Lung Detection study of lung cancer screening using LDCT reported long-term findings of visually aided and *computer-aided diagnosis* (CAD)-detected nonsolid nodules.[57] Among 66 of 2303 subjects with visually detected nonsolid nodules, 9 subjects (14%) were ultimately diagnosed with lung cancer. Of importance, 30 of 389 (8%) subjects with a nonsolid nodule detected during screening were ultimately diagnosed as having lung cancer over 9.3 ± 1.2 years of follow-up. However, only 27% of these subjects' cancer arose from the original nonsolid nodule (e.g., the majority had cancer in a different nodule). In those who underwent surgical resection of a nonsolid nodule, the median surveillance period before surgery was 77 months, and pathology was adenocarcinoma in all cases. None of the subjects died of lung cancer originating in a nonsolid nodule. Overall, nonsolid nodules determined to be cancer have a very high rate of cure. In a systematic review of 712 lung cancers manifesting as ground-glass opacities, all were found to be stage I adenocarcinoma with a 5-year lung cancer–specific survival of 100%.[58]

Nonsolid nodules can have or can develop solid components. In the International Early Lung Cancer Action Program of lung cancer screening, 4% of subjects had at least one nonsolid nodule, of which only 3% were ultimately diagnosed with lung cancer.[59] Of the cancers, 26% developed a solid component. In general, the larger the solid component, the more likely the nodule is malignant. Table 41.3 shows the outcome of nonsolid nodules detected on a baseline lung cancer screening CT scan by size at detection.

Based on these and other similar findings, surveillance guidelines for nonsolid nodules usually recommend less frequent but longer duration of follow-up. The decision if and when to proceed to more invasive diagnostic procedures is often based on many factors, including the patient's comorbidities; preferences regarding diagnostic certainty; harms of diagnostic procedures, including inability to obtain a definitive diagnosis; and change in overall size or change in the solid component of a nodule.

FUTURE OF PULMONARY NODULE MANAGEMENT

MOLECULAR BIOMARKERS

Molecular biomarkers have the potential to add to nodule diagnostics, either alone or in combination with nodule prediction calculators and functional imaging. They can be tested in serum, blood, sputum, and airway epithelium. Currently, nodule biomarkers using proteomics, autoantibodies, circulating tumor DNA, circulating free DNA, mRNA, DNA methylation, and genomic signatures are in various stages of discovery, development, and validation. The goal is to expedite evaluation and treatment in malignant nodules while minimizing harms in those that are benign. Performance characteristics of the biomarker will depend on its design as a rule-in or rule-out test. A *rule-in test* would allow earlier diagnosis of malignancy without a significant increase in the number of invasive procedures done in patients with benign nodules. Alternatively, a *rule-out test* would result in a reduction of procedures performed on patients with benign nodules without delaying a cancer diagnosis in those with malignant nodules. The biomarker performance must allow clinicians to direct and/or alter management. The result must alter pretest probability of malignancy enough to shift management between categories of low risk and surveillance, intermediate risk and biopsy, and high risk and surgical intervention. Several phases are involved before testing for clinical utility, including biomarker discovery, analytic validation, and clinical validation.[60] There are a number of diagnostic biomarkers in various stages of development and validation with few entering into trials to determine clinical utility.

IMAGING BIOMARKERS AND DEEP MACHINE LEARNING

Radiographic features, including nodule size, contour, and growth, have traditionally been the main differentiators between benign and malignant nodules and are inputs into risk prediction calculators.[15,25,28] Nodule size, one of the strongest predictors of malignancy,[61] was traditionally assessed via measurement of the largest transverse diameter using a manual 2D caliper. More recently, however, screening trials and nodule management guidelines have recommended measurement of volume rather than diameter because it is more representative of a nodule's true size, has less interobserver and intraobserver variability, and is more sensitive to changes compared

Table 41.2 Suggestions to Improve Patient-Clinician Communication Regarding Pulmonary Nodules

PATIENT-AS-PERSON

1. Recognize that identifying a pulmonary nodule is often distressful although frequently underreported.
2. Discuss the nodule directly with the patient and provide a written summary. Examples:
   - Schedule an office or phone visit to discuss the nodule.
   - A written summary should:
     - Provide information about the nodule and address common concerns.
     - Avoid medical jargon or sending the CT report without further explanation.
3. Actively elicit patient feelings.
   - "It's common to be distressed after learning you have a pulmonary nodule. How are you feeling?"
   - "What's on your mind?"
   - "Some people with a nodule worry they have lung cancer… What have you been thinking?"
4. Provide reassurance and resources to decrease distress.
5. Make it easy for patients with persistent concerns to contact a knowledgeable clinician.
   - Provide phone number for nurse coordinator/manager.
   - Clarify ability to message clinician through the electronic health record.
6. Recognize that the nodule may be an important concern for patients and allow time for discussion of the patient's questions. Avoid minimizing or dismissive language.

INFORMATION EXCHANGE

Patient-Level Suggestions

1. Provide information about the causes of nodules, rationale for active surveillance rather than immediate biopsy, and follow-up plan details, including benefits and harms.
2. Report the semiquantitative risk of lung cancer and relevant nodule information that relates to risk prediction (e.g., lack of growth decreases malignancy risk).
3. Describe the follow-up plan in detail, including possible steps if the nodules change (e.g., biopsy or surgery for growing nodule).
4. Use pictures, summary tables, and plain, simple language.
5. Provide list of signs and symptoms that should prompt contact.
6. Outline key imaging dates and subsequent office visits or telephone calls, and provide a copy.
7. Provide written and/or online educational resources for obtaining further information. Examples:
   - Nodule risk calculator: http://reference.medscape.com/calculator/solitary-pulmonary-nodule-risk
   - Nodule patient education: http://www.thoracic.org/patients/patient-resources/resources/lung-nodules-online.pdf
8. Provide smoking cessation guidance if applicable, framed as a "teachable moment."

System-Level Suggestions

1. Health care systems can develop system-wide tools to increase patients' knowledge and understanding of the lung cancer evaluation process.
2. Health care systems should develop tools to monitor and ensure adherence to follow-up recommendations.

SHARED DECISION MAKING

1. Clarify that active surveillance is a decision that the patient can discuss and question.
   - "Let's talk together about what to do about your nodule."
2. Ask what role the patient prefers in the decision-making process.
   - "When we make this decision about what to do about your nodule, some patients want to make the decision on their own, some just want me to decide, and many want something in the middle. How about you?"
3. If the patient is comfortable with a shared approach, actively engage patients in decisions regarding the follow-up evaluation.
4. Take the patient's values and preferences into account before making a final decision.
   - "Some people are worried about getting lung cancer when thinking about nodule follow-up. What do you think?"
   - "I know you have worried about radiation exposure in the past, so let's talk about that before we decide on a plan."
   - "Most of the time the right decision is to watch the nodule over time, when we get another CT scan. But some people want to have an answer right away. How do you feel about waiting?"
   - "How would you like to get the results of your next CT scan?"

THERAPEUTIC ALLIANCE

1. Ask patients what they expect at the outset of the encounter to help define roles and prevent assumptions.
2. Evaluate patients' understanding of the concepts presented.
   - "To make sure I didn't forgot to tell you anything, can you repeat back to me when you're going to get your next CT scan? And what are you going to do if you have more questions or start to feel distressed?"

CT, computed tomography.

From Slatore CG, Wiener RS. Pulmonary nodules: a small problem for many, severe distress for some, and how to communicate about it. *Chest*. 2018;153:1004–1015.

Table 41.3 Frequency of Nonsolid Nodules and Diagnoses of Lung Cancer Identified in 2392 of 57,496 Participants at Baseline CT Screening According to Size of Largest Nonsolid Nodule

	DIAMETER OF LARGEST NODULE					
Parameter	**<6 mm**	**6–9 mm**	**10–14 mm**	**15–30 mm**	**≥31 mm**	**Total**
RESOLVED OR DECREASED	341	177	70	39	1	628
Lung cancer	0	0	0	0	0	0
STABLE OR GROWTH	1063	439	164	92	6	1764
Lung cancer	9	20	27	15	2	73
AAH, ABP	2	3	0	0	0	5
Nonmalignant diagnosis	1	1	1	1	0	4
Total	1404	616	234	131	7	2392

Data are numbers of nodules.
AAH, atypical adenomatous hyperplasia, a diagnosis made on histologic specimens; ABP, atypical bronchioloalveolar proliferation, a diagnosis made on cytologic specimens; CT, computed tomography.
From Yankelevitz DF, Yip R, Smith JP, et al. CT screening for lung cancer: nonsolid nodules in baseline and annual repeat rounds. *Radiology*. 2015;277:555–564.

to 2D measurements.[62] For volumetric measurements to be reliable, nodule segmentation (i.e., the delineation of a nodule boundary) must be accurate.[63] There are software packages that provide manual, semiautomated, and automated volumetrics. Although these provide repeat measurements that are reliable, there is variation between software packages that can make comparisons between images done at differing institutions difficult.[38] Volumetric measurements, while gaining traction, have not been widely adopted in the United States as standard practice for nodule evaluation.

There have previously been attempts to develop CAD algorithms to help radiologists distinguish benign from malignant nodules and improve diagnostic accuracy; however, these did not achieve widespread acceptance.[64] A new paradigm shift in computer-based diagnosis was seen after the introduction of *convolutional neural networks* (CNNs). This set of techniques allows computers to detect patterns beyond human perception, to classify imaging findings further. Research using CNNs to classify pulmonary nodules has demonstrated superiority to standard CAD techniques by reducing the number of false positives.[65–68] This form of deep machine learning has the ability to learn previously unknown features but requires large amounts of validated data. Unfortunately, there are few large validated imaging datasets with pathology-confirmed cancer available to allow training, tuning, and testing.[69] Efforts are underway to advance this technology for analysis of both incidental and screen-detected nodules. Ideally, much like clinician intuition or risk prediction calculators, deep machine learning would incorporate all available imaging, clinical, and biochemical data into determining likelihood for malignancy.

BRONCHOSCOPY

As discussed previously, guidelines recommend consideration of biopsy when pretest probability for malignancy is intermediate, after shared decision making with the patient. Biopsy can be performed using CT guidance with transthoracic needle aspiration with a diagnostic yield of approximately 90%.[70] The decision to pursue biopsy with flexible bronchoscopy hinges on the location of the lesion. Peripheral lesions are not visible beyond the segmental bronchi, whereas central lesions are visible and may have an endobronchial component. The sensitivity for bronchoscopy in central lesions is 88%.[70] The sensitivity for bronchoscopy in peripheral lesions varies depending on the number of transbronchial biopsies performed (six samples at 74% vs. 45% with one sample),[71] CT scan evidence of a bronchus extending to the lesion (60% vs. 25%),[72,73] and the size of the lesion (<2 cm [34%] vs. >2 cm [63%]).[70] Bronchoscopy guided beyond the camera image has seen a variety of advancements over the past 2 decades. These include radial *endobronchial ultrasound* (EBUS), guide sheaths to extend the bronchoscopy working channel, software platforms to assist with locating and planning a pathway to reach the lesion, electromagnetic navigation systems that link the CT plan and location of the tip of the bronchoscope and instruments at the time of bronchoscopy, and, most recently, robotic bronchoscopy.

There are data supporting the use of guided bronchoscopy. A meta-analysis of 39 studies, including studies of a combination of guided bronchoscopy (excluding robotic technology), showed a pooled diagnostic yield of 70%.[74] This study and others supported the guideline recommendations for the use of radial EBUS and/or electromagnetic navigational bronchoscopy in centers with technology and expertise for patients with peripheral lesions suspected to be lung cancer.[70] Results later published from the American College of Chest Physicians Quality Improvement Registry, Evaluation, and Education registry of bronchoscopy, however, demonstrated a lower yield for guided bronchoscopy than for standard bronchoscopy, suggesting that diagnostic outcomes in clinical practice may be different from that seen in large-volume single centers.[75] As new bronchoscopy technologies are evaluated, there is a need for well-designed large trials with clear definitions of what constitutes a diagnostic bronchoscopy to quantify diagnostic accuracy.

EXHALED BREATH ANALYSIS

Analysis of human breath has been described since the 1970s and has applications in other disease states. In

patients with pulmonary nodules, analyzing breath to determine malignancy is desirable because of the noninvasive nature of the testing. Exhaled breath contains thousands of organic compounds; some are exogenous (from the environment) and others are endogenous (by-products from the body's biochemical processes). Although collection of breath is relatively easy, the optimal container for collection and modality for analysis vary. Analysis of breath has been performed by trained canines with sensitivities as high as 99% reported in various cancer types; however, recent studies have suggested outcomes may vary based on extent of training and the material used to carry the breath sample.[76] Volatile organic compounds are analyzed using a variety of techniques. Gas chromatography mass spectroscopy requires a level of skill to use, and careful calibration makes it both expensive and less practical in the clinical setting.[77] Smaller, more portable devices, such as the electronic nose, rely on sensors to detect volatile organic compound profiles. Research in exhaled breath analysis for characterization of pulmonary nodules is underway and has potential for assisting in management in the future.

Key Points

- The incidence of pulmonary nodules is increasing due to wide use of computed tomography imaging. The number of nodules detected will continue to rise with the implementation of lung cancer screening.
- Evaluation and management of pulmonary nodules starts with an assessment of pretest probability of malignancy.
- Pretest probability of malignancy incorporates radiographic features of the nodule (e.g., size, density, contour, and location) and patient level factors (e.g., age, smoking history, history of cancer). Assessment of pretest probability of malignancy can be determined by validated risk calculators or by clinician intuition.
- In solid nodules, those with a low pretest probability of malignancy should be monitored for growth with repeat imaging. Alternatively, those determined to be high risk should be considered for surgical resection if patient health status and nodule location are amenable to surgery. In an intermediate risk nodule, management options can include further evaluation with positron emission and/or computed tomography and/or biopsy, and decisions should include patient preferences.
- Nonsolid nodules, also known as pure ground-glass opacities, are less likely to be malignant and can be followed with less frequent but longer-duration surveillance imaging.
- Good-quality communication that incorporates patient values and beliefs is essential when making decisions surrounding nodule management.
- Biomarker testing to aid in nodule management must be clinically validated and demonstrate clinical utility before widespread implementation.
- The future of nodule management is likely to incorporate biomarkers, advanced bronchoscopic techniques, exhaled breath analysis, and deep machine learning.

Key Readings

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42 POSITIVE SCREENING TEST FOR TUBERCULOSIS

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INTRODUCTION

Approximately 1.7 billion people (22% of the world's population) are estimated to have *latent tuberculosis infection* (LTBI).[1] This population represents a large reservoir of potential future disease because 5–10% of latently infected individuals will develop active disease if untreated.

Although treatment of individuals with active disease is the first priority of *tuberculosis* (TB) control, controlling and eventually eliminating TB also require identifying and treating individuals with LTBI. However, because there are no direct tests to diagnose LTBI definitively, latent TB remains a clinical diagnosis based on evidence of prior TB infection *and* exclusion of active disease. Currently, there are only two approaches available to identify individuals with asymptomatic TB infection: *tuberculosis skin testing* (TST) and *interferon-gamma* (IFN-γ) *release assays* (IGRAs).

INDICATIONS FOR TUBERCULIN SKIN TEST AND/OR INTERFERON GAMMA RELEASE ASSAYS

There are two indications for TST and/or IGRA testing: (1) to screen asymptomatic individuals for LTBI and (2) to guide decisions about empirical treatment for active TB among symptomatic individuals with negative microbiologic results. This chapter outlines the approach to screening individuals for LTBI. TST or/IGRA testing to guide decisions related to empirical treatment for active TB is discussed in Chapter 53.

SCREENING FOR LATENT TUBERCULOSIS INFECTION

In the United States and other low-burden countries, 80% or more of all TB cases are the result of reactivated latent infection,[2] and nearly all reactivated cases can be prevented by treatment of LTBI.[3] Therefore the goal of screening for LTBI is to identify *Mycobacterium tuberculosis (Mtb)*-infected individuals at increased risk of developing active TB. As such, only individuals who would benefit from treatment of LTBI should undergo screening.

Target Populations for Screening

Screening for LTBI should target individuals in two high-risk groups: (1) individuals with increased risk of *Mtb* infection (e.g., recent close contact with individuals with untreated pulmonary TB) and (2) individuals with certain clinical conditions (e.g., immunosuppression) associated with a high risk of reactivation (Table 42.1). Untargeted screening for LTBI (testing individuals without risk factors for infection or reactivation) should not be performed. Although untargeted screening and treatment of all individuals with LTBI would prevent most new cases of active disease, this approach is not cost-effective for settings with low TB incidence and would result in overtreatment because the specificity of current screening tests would yield more false-positive results than true-positive results.

Screening Individuals With Increased Risk of *Mycobacterium tuberculosis* Infection

Although most individuals exposed to *Mtb* lack evidence of sustained infection, approximately 30–50% will develop LTBI contained by host immune responses.[4] Although LTBI has the potential to progress to active TB at any time, risk

Table 42.1 Target Groups for Latent Tuberculosis Infection Screening

INDIVIDUALS WITH INCREASED RISK OF INFECTION
Contacts of individuals with untreated infectious active tuberculosis
Individuals who have immigrated to the United States within the past 5 years from tuberculosis endemic areas
Individuals who work and/or reside in high-risk congregate settings (e.g., hospitals, homeless shelters, prisons, nursing homes)
INDIVIDUALS WITH CONDITIONS ASSOCIATED WITH INCREASED RISK FOR REACTIVATION
High Risk for Reactivation (Risk of Reactivation Is at Least Six Times Higher Than for Healthy Individuals)
Human immunodeficiency virus infection
Severe immunosuppression (e.g., individuals receiving medication for solid-organ transplantation, chemotherapy, tumor necrosis factor-α inhibitors)
Certain malignancies (e.g., hematologic malignancies, head and neck cancers)
Silicosis
End-stage renal disease
Radiographic evidence of prior granulomatous disease (e.g., fibrotic lesions on chest imaging)
Children <5 years with a positive tuberculin skin test reaction
Moderate Risk for Reactivation (Risk of Reactivation Is Less Than Six Times Higher Than for Healthy Individuals)
Corticosteroid use (≥15 mg daily for ≥1 mo)
Diabetes mellitus
Underweight or malnourished individuals (includes malabsorptive conditions, such as gastrectomy, jejunoileal bypass surgeries)
Substance abuse (e.g., smoking, alcohol abuse, injection drug use)
Radiographic evidence of solitary or small granulomas

of developing active disease is greatest within 2 years of infection.[5–9] In a randomized controlled trial of TB vaccines given to children, 2550 unvaccinated children experienced TST conversion (≥10 mm increase in TST induration), of whom 121 (5%) developed active disease during 15-year follow-up.[10] Among those who developed active TB, 82% developed disease within 2 years of TST conversion. Thus individuals at risk for LTBI represent a high-priority group for screening.

Individuals with risk for *Mtb* infection include (1) recent close contacts of untreated individuals with infectious TB, (2) individuals who have recently immigrated from areas with high TB incidence, and (3) individuals who work and/or reside in congregate settings (e.g., hospitals, homeless shelters, prisons, nursing homes) with higher rates of active TB.

Close contacts are considered those sharing an enclosed space more than 4 hours per week.[11] These typically include individuals living in the same household, frequent visitors to the house, and individuals who work or attend school with the index case. *Mtb* transmission has also been documented among casual contacts of a highly infectious index case.[12] Casual contacts—individuals who spend fewer than 4 hours of contact per week with the index case—may include individuals who attend school, work, and/or reside in congregate settings with the index case. TB programs conducting contact investigations prioritize evaluation of close contacts and expand investigation to casual contacts if the index case is deemed to be highly infectious (e.g., high acid-fast bacilli smear grade), evidence of transmission is found among close contacts, and/or the casual contact has risk factors for developing active disease (i.e., immunocompromise). All close and at-risk casual contacts should undergo TST or IGRA testing for LTBI screening, in addition to screening for active disease. If initial TST or IGRA testing is negative and initial testing was performed within 8 weeks of last exposure, testing should be repeated 8 to 10 weeks after last exposure because TB infection may have been so recent (within 3–8 weeks of initial testing) that delayed hypersensitivity has not yet developed (see later, "Approach to Individuals with Possible False-Negative TST or IGRA Results").

Individuals who have recently immigrated from areas with high TB incidence represent a high-priority population for latent TB screening and treatment. Although overall TB incidence among foreign-born persons is 13 times higher than among U.S.-born individuals,[13] the risk of developing active TB (reactivation of infection acquired in their country of origin) is highest within the first 5 years after immigration, with incidence decreasing over time to approach that of the U.S. population.[14] As such, all foreign-born individuals who immigrated to the United States from a high-burden country within the past 5 years should undergo LTBI screening in addition to screening for active disease. Although either TSTs or IGRAs may be used to screen individuals for LTBI, IGRA may be preferred as a more specific screening test for individuals with prior *bacillus Calmette-Guérin* (BCG) vaccination (see later, "Approach to TST-Positive Individuals With Prior Bacillus Calmette-Guérin").

Individuals who work and/or reside in congregate settings with higher rates of active TB are at increased risk of infection due to crowded conditions, which increases the likelihood of *Mtb* transmission. Although risk of infection varies greatly in such settings, serial LTBI screening is recommended for individuals with ongoing *Mtb* exposure risk, including selected groups of health care workers. In the United States, health care workers with high ongoing risk for occupational exposure to *Mtb* include emergency department staff, pulmonologists, and respiratory therapists. Although prior guidelines recommended annual screening for all U.S. health care workers,[15] recent data suggest that this is no longer necessary.[16] However, in the setting of a recognized exposure to *Mtb*, all exposed health care personnel with negative baseline TST or IGRA results should undergo screening for infection and, if TST or IGRA results are negative, testing should be repeated 8 to 10 weeks after last exposure.

Screening Individuals With Increased Risk of Reactivation

Risk of reactivation (i.e., progression of LTBI to active disease) is increased by certain clinical conditions, including immunodeficiency or immunosuppression, malignancy, and radiographic evidence of fibrotic lesions from prior TB (see Table 42.1). Among individuals with LTBI, *human immunodeficiency virus* (HIV) infection is the strongest known risk factor for progression to active disease. As such, all individuals newly diagnosed with HIV should be screened for LTBI. HIV-infected individuals who test negative for LTBI in the setting of advanced immunosuppression (i.e., CD4 cell counts less than 200 cells/μL) should undergo repeat testing after initiation of antiretroviral therapy,

Table 42.2 TST Cut-Point Used to Define a Positive TST Reaction

≥5 mm	≥10 mm	≥15 mm
People living with HIV Recent contacts of individuals with untreated infectious TB Individuals with fibrotic lesions on chest imaging Organ-transplant recipients Individuals with other immunosuppressive conditions (e.g., individuals receiving chemotherapy, TNF-α inhibitors, corticosteroids ≥15 mg/daily for ≥1 month; individuals with certain malignancies)	Recent immigrants (<5 years) from TB-endemic countries Residents and employees of high-risk congregate settings (correctional facilities, homeless shelters, nursing homes, hospitals, other health care facilities) Mycobacteriology laboratory personnel Children <5 years	Individuals with no known TB risk factors

HIV, human immunodeficiency virus; TB, tuberculosis; TNF, tumor necrosis factor; TST, tuberculin skin test.

when CD4 cell counts increase to 200 cells/μL or greater, because of the higher rates of false-negative results associated with immunosuppression. TST- or IGRA-negative HIV-infected individuals with ongoing risk factors for *Mtb* exposure (e.g., work or reside in congregate settings) should undergo annual screening for LTBI.

Other populations at high risk for reactivation (at least six times higher than healthy individuals) for whom testing is recommended include individuals about to receive immunosuppressive therapy (e.g., chemotherapy, tumor necrosis factor-α antagonists); individuals with hematologic malignancies, head and neck cancers, and silicosis; and individuals with radiographic evidence of prior granulomatous disease (e.g., fibronodular changes). Populations with moderate risk for reactivation (less than six times higher than healthy individuals) include individuals receiving corticosteroids and individuals with malnutrition, diabetes mellitus, and/or radiographic evidence of small granulomas. Current U.S. guidelines recommend LTBI screening for populations with moderate or high risk for reactivation.[17]

SCREENING TESTS FOR LATENT TUBERCULOSIS INFECTION

Infection with *Mtb* produces a delayed-type hypersensitivity reaction to mycobacterial antigens; the cell-mediated immune response to such antigens can be measured by TST and IGRA, which serve as measurements of immunologic memory and as indirect evidence for the presence of mycobacteria.

TUBERCULIN SKIN TEST

Tuberculin Skin Test Placement and Interpretation

The TST consists of an intracutaneous injection on the inner surface of the forearm of tuberculin, a purified protein derivative from heat-killed cultures of *Mtb*.[18] Among individuals infected with *Mtb*, TST causes induration due to inflammatory cell infiltration at the injection site, beginning 5 to 6 hours after placement, peaking at 48 to 72 hours, then subsiding over several days. To read the test, the area of induration (not erythema) is measured along its transverse diameter (in millimeters) 48 to 72 hours after TST placement. If the TST cannot be read within 48 to 72 hours, repeat testing should be performed.

Based on the sensitivity and specificity of TST among populations with varying risk for active TB, three cut-points for induration are used to define a positive TST (≥5, ≥10, and ≥15 mm); the TST cut-point used to define a positive result is determined by the presence of certain TB risk factors.[17] Because sensitivity increases (and specificity decreases) as the cut-off for TST positivity decreases, the lowest cut-off (≥5 mm) is used for individuals with highest TB risk (e.g., HIV infection) to minimize the proportion of false negatives (i.e., *Mtb*-infected individuals missed by testing). Conversely, the highest TST cut-off (≥15 mm) is used for individuals with no TB risk factors to minimize the proportion of false positives (i.e., *Mtb*-uninfected individuals for whom latent TB treatment would be associated with unnecessary risk). Table 42.2 summarizes TST cut-points for populations undergoing testing for LTBI.

INTERFERON-GAMMA RELEASE ASSAYS

IGRAs are in vitro blood tests that measure IFN-γ released from memory T cells stimulated by previously encountered *Mtb* antigens: *early secreted antigenic target 6* (ESAT-6) and *culture filtrate protein 10* (CFP-10). ESAT-6 and CFP-10 are absent from all strains of BCG,[19,20] so IGRAs are more specific for *Mtb* than is TST, which uses a mixed purified protein derivative that contains more than 200 mycobacterial antigens, most of which are shared with BCG.[21–23]

Current Interferon-Gamma Release Assay Platforms

Two IGRA platforms using the ESAT-6 and CFP-10 antigens are currently available for commercial use: QuantiFERON-TB (QFT-TB) and T-SPOT.TB (Oxford Immunotec). Because IGRA testing requires more laboratory infrastructure than tuberculin skin testing, its use is generally limited to resource-rich settings.

The QFT-TB Gold In-tube and QFT-TB Plus assays use blood collection tubes coated with *Mtb* antigens ESAT-6 and CFP-10 and include a positive and negative control tube; the positive control contains a nonspecific T-cell stimulator, and

the negative control tube contains no antigenic additives and no stimulator. Blood collected in the tubes is incubated overnight, and an enzyme-linked immunosorbent assay is used to measure the concentration of IFN-γ released by stimulated T cells, which is compared to the control tubes. Unlike TST, which requires two patient visits (one visit for placement and a second visit for interpretation), IGRAs require only one patient visit, and results may be available in 24 hours. Individuals are regarded as QFT positive if the IFN-γ concentration is above the test cut-point after subtracting the background IFN-γ response in the negative control.

Three IGRA assays using the QFT-TB platform have received U.S. Food and Drug Administration approval: QFT-TB Gold (QFT-Gold, Cellestis), Gold In-tube (QFT-GIT), and Gold Plus (QFT-Plus, Qiagen); however, only QFT-Gold and QFT-GIT have received endorsement by the *Centers for Disease Control and Prevention* (CDC) (validation studies for QFT-Plus are ongoing). The QFT-GIT assay includes a third *Mtb*-specific antigen (TB7.7), in addition to ESAT-6 and CFP-10, intended to improve test sensitivity beyond QFT-Gold. The QFT-Plus assay uses two antigen tubes: TB1 and TB2. Both TB1 and TB2 tubes are coated with ESAT-6 and CFP-10; however, TB2 tubes include shorter *Mtb* antigen peptides to stimulate a response from $CD8^+$ T cells, in addition to $CD4^+$ T cells. An individual is considered QFT-Plus positive if either tube is positive.

The T-SPOT.TB platform incubates isolated peripheral blood mononuclear cells with ESAT-6 and CFP-10 in microplate wells and uses an enzyme-linked immunospot (ELISPOT) assay to measure the number of IFN-γ–producing T cells (spots). Individuals are considered T-SPOT.TB positive if the spot counts in the antigen-containing wells exceed a certain threshold relative to negative control wells.

Interferon-Gamma Release Assay Interpretation

IGRA results are reported as both quantitative and qualitative (positive, negative, or uninterpretable) measurements. For QFT-based assays, a result is considered positive if the IFN-γ concentration is 0.35 *international units* (IU)/mL or more above the negative control. For the T-SPOT.TB assay, an individual is considered IGRA positive if there are eight or more spots above the negative control. Individuals are considered IGRA negative if IFN-γ concentrations are less than 0.35 IU/mL (after subtracting the background IFN-γ response in the negative control) for QFT-based assays and four spots or fewer are detected by T-SPOT.TB above the negative control. Uninterpretable results are possible with both QFT-based and T-SPOT.TB assays. For QFT-based assays, uninterpretable results are reported as "indeterminate" when there is an inappropriate response in the positive or negative control: insufficient response in the positive control or excessive response in the negative control (indicating a high level of spontaneous IFN-γ secretion despite the absence of antigen), respectively. For the T-SPOT.TB assay, uninterpretable results include "invalid" and "borderline" results. Invalid T-SPOT.TB results are equivalent to QFT indeterminates, seen when there is an inappropriate response in the positive or negative control. Borderline T-SPOT.TB results are reported when five to seven spots above the negative control are observed. Causes of uninterpretable IGRA results are discussed later.

Table 42.3 Current CDC Guidelines For TST, IGRA, or Dual Testing

SITUATIONS IN WHICH EITHER IGRA OR TST MAY BE USED WITHOUT PREFERENCE
All situations where TST is recommended
SITUATIONS IN WHICH TST IS PREFERRED BUT IGRA IS ACCEPTABLE
Children <5 years
SITUATIONS IN WHICH IGRA IS PREFERRED BUT TST IS ACCEPTABLE
Individuals who have received BCG (as a vaccine or for cancer treatment)
Individuals belonging to groups with low rates of returning to have TSTs read (e.g., homeless individuals, active drug users)
SITUATIONS IN WHICH DUAL IGRA AND TST TESTING MAY BE CONSIDERED
Situations Where the Initial Test Is Negative and Diagnostic Sensitivity Is Prioritized Over Specificity
Individuals with high risk for *Mtb* infection, disease progression, and poor outcomes (e.g., children younger than 5 years who were exposed to an individual with untreated active TB)
Individuals with suspected active TB for whom confirmation of *Mtb* infection is desired
Situations Where the Initial Test Is Positive, and
Additional evidence of *Mtb* infection is needed to encourage treatment acceptance and adherence (e.g., BCG-vaccinated individuals who believe their positive TST is due to prior BCG)
The individual has low risk of both infection and disease progression and additional evidence is desired to support the decision not to initiate treatment

BCG, bacillus Calmette-Guérin; CDC, Centers for Disease Control and Prevention; IGRA, interferon-gamma release assay; *Mtb, Mycobacterium tuberculosis;* TB, tuberculosis; TST, tuberculin skin test.

SELECTION OF TUBERCULOSIS SKIN TEST OR INTERFERON-GAMMA RELEASE ASSAYS FOR LATENT TUBERCULOSIS INFECTION SCREENING

Current CDC guidelines state that "IGRAs can be used in place of (but not in addition to) TST in all situations in which CDC recommends TST as an aid in diagnosing *Mtb* infection."[24] The following sections describe situations in which TST or IGRA is preferred and situations in which dual testing may be considered (Table 42.3).

SITUATIONS IN WHICH TUBERCULOSIS SKIN TEST IS PREFERRED

Children Younger Than 5 Years

TST is preferred but IGRA remains acceptable for testing children younger than 5 years. Although available data from high-quality studies of IGRAs suggest that sensitivity and specificity in children are comparable to estimates in adults, uninterpretable IGRA results appear to be more frequent in children (range, 0–17%). The rate of uninterpretable IGRA results also appears to be significantly higher (up to 40%) among children younger than 5 years,[25–27] the age group at highest risk for severe forms of active TB. Although the causes of uninterpretable IGRA results in children are not fully understood, children younger than 5 years have been shown to have lower IFN-γ response to *Mtb* antigens and mitogen

(used in the positive control) than children 4 years or older,[26,28] suggesting that higher rates of uninterpretable IGRA results in this age group may be due to immunologic immaturity. Based on these results, current U.S. guidelines state that TST is preferred over IGRAs for children younger than 4 years.[24] In addition, some experts have recommended dual TST and IGRA testing for children younger than 4 years to maximize detection of *Mtb* infection, due to potential reduced sensitivity of both tests relative to adults.

SITUATIONS IN WHICH INTERFERON-GAMMA RELEASE ASSAY IS PREFERRED

Individuals With Prior Bacillus Calmette-Guérin

Situations in which IGRA is preferred but TST is acceptable include testing of individuals who have received BCG as a vaccine or as cancer treatment. For individuals who have received prior BCG, IGRAs can be expected to detect *Mtb* infection with greater specificity than can TST (see "Approach to Tuberculosis Skin Test–Positive Individuals With Prior Bacillus Calmette-Guérin"), limiting treatment to individuals most likely to have true *Mtb* infection.

Individuals at Risk of Being Lost to Follow-up

IGRA testing is also preferred for individuals belonging to groups with low rates of returning to have TSTs read (e.g., homeless persons, active drug users). For individuals belonging to groups with low rates of follow-up, IGRAs increase test completion rates, allowing health care providers to focus control efforts on those individuals most likely to benefit from treatment.

SITUATIONS IN WHICH DUAL TESTING MAY BE CONSIDERED

Although dual IGRA and TST testing is not routinely recommended, the CDC recognizes certain situations in which dual testing may be considered. For situations in which sensitivity is strongly prioritized over specificity, dual testing may be considered for individuals with a negative initial test result when (1) the risks for *Mtb* infection, for progression to active disease, and for poor outcomes are increased (e.g., immunosuppressed individuals, children <5 years) and (2) suspicion for active TB persists (based on clinical and/or radiographic assessment) despite negative microbiologic test results. Dual testing may also be considered for individuals with a positive initial test result when (1) additional evidence to support *Mtb* infection may facilitate treatment acceptance and adherence (e.g., BCG-vaccinated individuals who attribute their positive TST result to BCG) or (2) the initial test result is thought to be a false positive (e.g., individuals with low risk for *Mtb* infection) and additional evidence is desired to support the decision not to treat the individual for LTBI in the absence of other treatment indications (e.g., individuals with low risk for disease progression). Dual testing may also be considered for individuals with an uninterpretable IGRA result (on initial and/or repeat testing) and a reason for testing persists.

CLINICAL EVALUATION

Fig. 42.1 summarizes the approach to LTBI screening.

APPROACH TO TUBERCULOSIS SKIN TEST– OR INTERFERON-GAMMA RELEASE ASSAY–POSITIVE INDIVIDUALS

Before initiating treatment for LTBI, clinicians caring for TST- or IGRA-positive individuals should first assess the individual's risk for *Mtb* infection and risk for progression to active disease by obtaining a focused history that includes the following: country of origin and years since immigration, history of diagnosis and treatment for active disease or LTBI, contact with untreated individuals with known or suspected active TB, work and residential environment, and medical history and concomitant medications. If both risk of infection and of progression to active disease are determined to be low, the possibility of a false-positive TST or IGRA result should be considered and the benefits of latent TB treatment weighed against the risk of treatment-related adverse events.

Next, because individuals with *Mtb* infection are also at high risk for active disease, it is imperative to rule out active TB before initiating treatment for LTBI. The goal is to reduce the risk of acquired drug resistance that may develop when individuals with active TB are inadvertently treated for LTBI. Individuals should be screened for active TB by (1) assessing for the presence of symptoms (cough, fever, night sweats, and weight loss), (2) physical examination (abnormal lung examination findings, peripheral lymphadenopathy), and (3) chest radiographic imaging (see Chapter 53). Presence of any symptom, physical examination, and/or radiographic abnormality suggestive of active TB should be viewed as an indication for confirmatory TB testing. Furthermore, for immunosuppressed individuals with positive TST or IGRA results, thresholds for ordering confirmatory TB testing should be lowered because atypical presentation of active disease is more frequent in this population. For individuals with possible active TB, confirmatory TB testing should be performed. Confirmatory TB testing includes collection of at least two sputum specimens for acid-fast bacilli smear microscopy and mycobacterial culture and at least one sputum specimen collected for nucleic acid amplification testing (see Chapter 53). Only after excluding active TB by screening with or without confirmatory TB testing can treatment for LTBI be safely initiated.

APPROACH TO TUBERCULOSIS SKIN TEST–POSITIVE INDIVIDUALS WITH PRIOR BACILLUS CALMETTE-GUÉRIN

Although IGRAs are preferred for screening BCG-vaccinated individuals for LTBI, TST is also acceptable. If TST is performed, current U.S. guidelines state that BCG-vaccinated individuals with positive TST reactions should be regarded as true positives, without modification of the criteria used to define TST positivity.[17] Nonetheless, clinicians should be aware that cross reaction from BCG is a common cause of reduced TST specificity (i.e., false-positive TST reactions). In a meta-analysis of 11 studies of TST performance, pooled specificity of TST was lower among BCG-vaccinated individuals

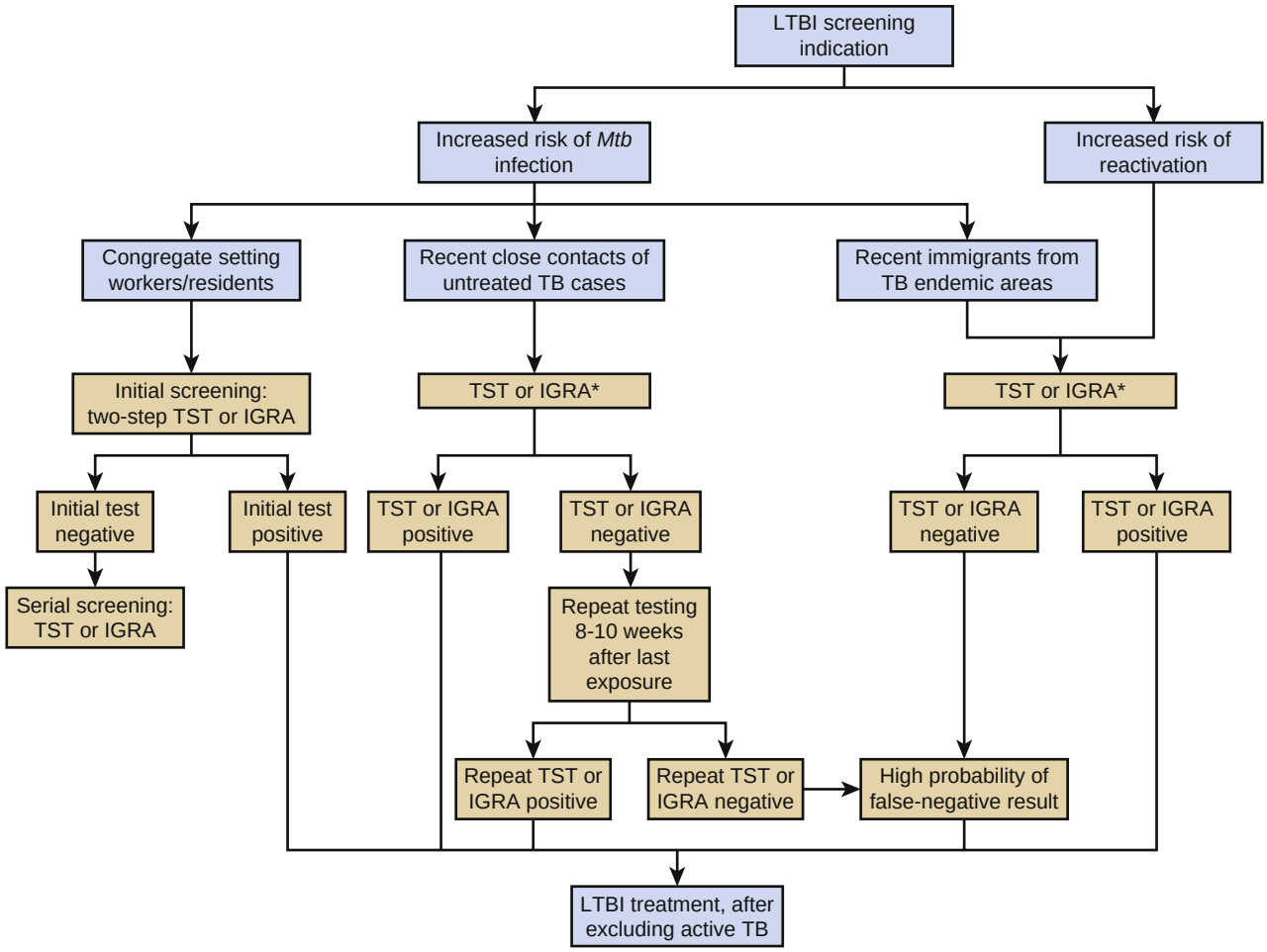

Figure 42.1 Latent tuberculosis infection screening algorithm. Individuals at high likelihood of having LTBI, due to demographic or specific exposure history or an untreated previously positive TST or IGRA, and a high probability of a presently false-negative result, due to immunodeficiency or immunosuppression, should be considered for treatment. *IGRA preferred for individuals with prior bacillus Calmette-Guérin and individuals at high risk for becoming lost to follow-up. TST preferred for children younger than 5 years. Dual testing (not shown) may be considered for certain situations. IGRA, interferon-gamma release assay; LTBI, latent tuberculosis infection; *Mtb, Mycobacterium tuberculosis;* TB, tuberculosis; TST, tuberculin skin test.

compared to unvaccinated individuals (59% vs. 97%).[29] In contrast, IGRA assays measure the T-cell response to antigens specific to *Mtb* and are thus not affected by prior BCG vaccination. A meta-analysis of 16 studies of IGRA performance among BCG-vaccinated and -unvaccinated patients found pooled specificity of QFT-based assays (QFT-Gold and QFT-GIT) and T-SPOT.TB to be similarly high (≥93% for all), regardless of BCG vaccination status.[29]

Among BCG-vaccinated individuals, an individual's age at vaccination and the time between vaccination and TST placement have also been shown to affect reactions to TST. If administered in the first year of life, BCG has been shown to have limited effect on TST specificity because the immune response to BCG given during infancy is less vigorous than the immune response to BCG given after 1 year of age.[30] As such, positive TST reactions among individuals vaccinated in infancy should not be attributed to BCG, whereas positive TST reactions among individuals vaccinated after infancy may be due to BCG or *Mtb* infection. Regardless of age at vaccination, tuberculin reactivity to BCG wanes over time so that positive TST reactions 10 or more years after vaccination should not be attributed to prior BCG.[31]

Although BCG-vaccinated individuals with positive TST reactions may be subsequently evaluated by IGRA, dual testing is not routinely recommended outside of certain situations (see "Situations in Which Dual Testing May Be Considered").

OTHER CAUSES OF FALSE-POSITIVE TUBERCULOSIS SKIN TESTING REACTIONS

Nontuberculous Mycobacterial Infection

Although nontuberculous mycobacterial infections are an uncommon cause of false-positive reactions to TST (responsible for 1–5% of all positive TST results), it is important to consider in areas with very low TB and high nontuberculous mycobacterial infection prevalence, such as in the southern United States. Clinical suspicion for nontuberculous mycobacterial infection as a cause of false-positive TST reactions may be prompted by the absence of *Mtb* infection risk factors (e.g., U.S. born, no known or possible contact with an untreated individual with active TB), presence of certain clinical conditions (e.g., chronic lung disease), and/or certain radiographic findings. However, nontuberculous mycobacterial infection and other potential causes of false-positive TST reactions should not influence treatment decisions for

LTBI for individuals with high risk for *Mtb* infection and/or progression to active TB.

For TST-positive individuals with suspected nontuberculous mycobacterial infection and both low risk for *Mtb* infection and disease progression, subsequent testing with IGRAs (i.e., dual testing) may be considered to support the decision not to initiate treatment for latent infection (see "Situations in Which Dual Testing May Be Considered"). Unlike TST, IGRA specificity is not affected by most nontuberculous mycobacteria, although specificity may be reduced among individuals infected with nontuberculous mycobacteria expressing ESAT-6 and/or CFP-10 (*Mycobacterium kansasii, M. szulgai, M. marinum,* and *M. flavescens*).[32]

Allergic Reaction to Tuberculin

Allergic (immediate hypersensitivity) reactions to tuberculin are also an uncommon cause of false-positive TST, seen in 2–3% of all individuals, more commonly among individuals with atopy.[33] Allergic reactions to tuberculin typically present as localized wheal-and-flare reactions within 6 to 12 hours of injection, but most reactions are immediate (within 20 minutes). Life-threatening systemic hypersensitivity reactions (anaphylaxis, angioedema, urticaria, and dyspnea) to tuberculin have also been reported but are rare; in the United States, 24 cases of life-threatening hypersensitivity reactions were reported over an 11-year period, during which time approximately 300 million tuberculin doses were administered (0.08 reported reactions per million doses of tuberculin).[34] Repeat TST is contraindicated for individuals with a prior allergic reaction to TST. If repeat *Mtb* infection testing is required for individuals with tuberculin allergy, IGRAs should be performed instead.

Tuberculin Skin Test Boosting

Although TST conversion (a positive TST result in a previously TST-negative individual) is considered to indicate new *Mtb* infection, some individuals with remote *Mtb* infection and negative reaction to initial TST (due to waned T-cell–mediated immunity) may have a positive TST reaction on repeat testing that may be misinterpreted as TST conversion. This phenomenon is referred to as "boosting" and is believed to result when tuberculin from the initial test stimulates T-cell memory, causing a positive or boosted reaction to tuberculin on repeat testing.[35] Other populations at risk for boosting include individuals with prior BCG[36,37] and nontuberculous mycobacterial infections[38,39] where cross reactions to tuberculin may be boosted with repeat testing.

The size of the boosted TST reaction is maximal if the interval between the initial and second TST is between 1 and 5 weeks.[6,35,40] However, the boosted reaction may persist 1 or more years after the initial negative TST. For this reason, two-step TST is recommended as the initial test for individuals for whom serial screening is recommended (e.g., health care workers). For such individuals, two-step TST is used to establish baseline LTBI status, thus reducing the risk that a future boosted reaction will be misinterpreted as recent *Mtb* infection. In two-step TST, if the first TST is negative, a second test is performed 1 to 3 weeks later. If the second TST is positive, the positive reaction is attributed to boosting, and the individual is classified as having LTBI after active disease has been ruled out. Of note, repeated administration of tuberculin with TST to *Mtb*-uninfected individuals is not associated with boosting.

CAUSES OF FALSE-POSITIVE INTERFERON-GAMMA RELEASE ASSAYS TESTING RESULTS

Interferon-Gamma Release Assay Boosting

Individuals undergoing a dual testing strategy inclusive of initial TST testing, followed by IGRA testing between 3 days to 3 months of initial TST, may experience IGRA boosting.[41–44] IGRA boosting refers to a phenomenon in which a positive IGRA result is seen in an *Mtb*-uninfected individual due to an increased T-cell response to *Mtb* antigens contained in tuberculin. To minimize the risk of false-positive IGRA results from IGRA boosting, blood for IGRA testing should be collected within 3 days of TST or 3 months after TST.

False Interferon-Gamma Release Assay Conversions

IGRAs have been shown to have poor reproducibility when repeat testing is performed. Poor reproducibility may be due to limitations inherent to IGRA testing (independent of the individual's risk of infection) or to fluctuations in an individual's IFN-γ response. The magnitude of change in quantitative IFN-γ response may be sufficient to cause qualitative changes from negative to positive (conversion) or from positive to negative (reversion). Relative to TST, IGRAs have substantially higher rates of both conversion and reversion.[45] In a study of 9153 U.S. health care workers undergoing serial IGRA screening, 4.4% of health care workers with a negative initial test result experienced conversion at 2 years (using the manufacturer's cut-point of ≤0.35 IU/mL), an 11-fold increase relative to that institution's historic TST conversion rate of 0.4% and expected incidence of LTBI.[46] Of interest, 65% of all converters in this study experienced reversion when IGRA was repeated within 60 days of the second test, suggesting that most IGRA conversions were false conversions.

Biologic causes of IGRA conversions and reversions remain unclear but are thought to represent clearance of *Mtb* infection or transitions within the spectrum of LTBI caused by changes in host immunity, resulting in periodic cycling between mycobacterial persistence, replication, and killing.[47] The clinical significance of conversions and reversions are also poorly understood. Data from longitudinal studies have shown higher TB incidence rates among IGRA converters and reverters, relative to individuals with persistently negative results and similar TB incidence rates among IGRA converters as among reverters.[48,49] However, substantial uncertainty remains regarding the use of IGRAs for serial screening and the use of current cut-points to define IGRA positivity, which are associated with higher conversion and reversion rates than TST.[49] More nuanced approaches to serial IGRA test interpretation have been proposed, including increasing the diagnostic threshold of the initial test (which reduces conversions but may also increase reversions), using more stringent criteria for defining IGRA conversion (e.g., change in IFN-γ values from <0.2 to >0.7 IU/mL), and using quantitative IGRA results to measure the absolute or percentage increase in IFN-γ values (or spot counts) over the initial test. Although such alternative approaches may reduce IGRA discordance and thus reduce the proportion of individuals referred for

unnecessary preventive therapy, the optimal approach to serial IGRA interpretation has yet to be identified. Current U.S. guidelines define IGRA conversion as a qualitative change from negative to positive (using the manufacturer's cut-point) within 2 years, without any consideration of the magnitude of change in quantitative IFN-γ response.[24]

Technical Causes of False-Positive Interferon-Gamma Release Assay Results

Technical issues related to IGRA testing are more frequent causes of false-positive, false-negative, and uninterpretable results than are clinical causes. Potential technical causes of reduced IGRA specificity from false-positive or uninterpretable results include improper specimen collection (e.g., underfilling of tubes, filling positive control tubes before antigen tubes), improper specimen handling (e.g., overshaking of tubes), improper specimen processing (e.g., prolonged incubation time), test run errors, and manufacturing defects.[50] Technical causes of reduced IGRA specificity (and reduced IGRA sensitivity) are minimized by ensuring persons collecting and processing specimens are adequately trained and procedures for IGRA testing are standardized.

APPROACH TO INDIVIDUALS WITH POSSIBLE FALSE-NEGATIVE TUBERCULOSIS SKIN TEST OR INTERFERON-GAMMA RELEASE ASSAYS RESULTS

For individuals with a negative TST reaction or IGRA result, the possibility of a false-negative test should be considered by assessing for the presence of clinical conditions associated with diminished delayed-type hypersensitivity reactions to tuberculin and IGRA, including immunosuppression, very recent *Mtb* infection, recent live virus vaccination, natural waning of immunity, and overwhelming active TB.

False-negative results among immunosuppressed individuals (i.e., patients with HIV infection, patients receiving the equivalent of ≥15 mg/day of prednisone or tumor necrosis factor-α antagonists) are caused by decreased immunocompetence (TST and IGRA) or skin test anergy (TST). Relative to immunocompetent individuals, immunosuppressed individuals demonstrate a 20–30% lower sensitivity of both TST and IGRA.[51] Although current guidelines recommend the use of lower TST cut-points for immunosuppressed individuals to improve TST sensitivity, this strategy is less effective in severely immunosuppressed populations, in which anergy is prevalent. Because studies of HIV-infected individuals have demonstrated that the frequency of skin test anergy increases as risk for active TB increases (i.e., decreasing CD4 cell count),[52,53] severely immunosuppressed individuals should be considered for latent TB treatment despite negative TST reactions, after active TB has been effectively ruled out.

Although prior meta-analyses have found TST and IGRAs to have comparable sensitivity among immunosuppressed individuals,[51] sensitivity estimates of IGRA may be overestimated due to the higher proportion of uninterpretable results in this population. Furthermore, the frequency of uninterpretable IGRA results increases with increasing immunosuppression. A meta-analysis of IGRA performance among HIV-positive individuals found that the pooled proportion of uninterpretable IGRA results to be four times higher among individuals with CD4 counts less than 200 cells/μL (12% vs. 3%).[54] These results suggest that *Mtb*-infected immunosuppressed individuals most in need of and most likely to benefit from treatment are also those individuals most likely to have an uninterpretable IGRA result.

Recent close contacts to untreated individuals with known or suspected TB have high risk of *Mtb* infection and of disease progression. As such, recent close contacts should be considered for empirical treatment for LTBI (after active disease has been excluded), despite negative TST or IGRA results. Individuals initiating empirical latent TB treatment should have TST or IGRA repeated 8 to 10 weeks after last exposure because delayed hypersensitivity reaction to *Mtb* antigens may take up to 10 weeks to develop.[12,35,55] If the second test is positive (i.e., conversion), latent TB treatment should be continued. If the second test is negative, treatment may be continued or discontinued, depending on the individual's risk for progression to active disease. Repeat testing to guide treatment continuation decisions is not warranted for individuals with negative TST or IGRA results caused by immunosuppression.

Technical Causes of False-Negative Tuberculosis Skin Test or Interferon-Gamma Release Assays

Technical problems associated with TST and IGRA testing may reduce test sensitivity. Technical causes of false-negative TST reactions include improper tuberculin storage and injection and improper TST interpretation, which are infrequent when TST is performed by experienced operators and settings. However, because IGRA testing is inherently more complex than tuberculin skin testing, the potential for reduced IGRA sensitivity (false-negative or uninterpretable results) from technical issues is higher than for TST. Reported technical causes of false-negative or uninterpretable IGRA results among individuals with true *Mtb* infection include improper specimen collection (e.g., overfilling of tubes; tubes filled out of standard order: negative control, antigen tube, positive control), improper specimen handling (e.g., insufficient shaking or differential shaking of tubes, delayed incubation), improper specimen processing (e.g., insufficient incubation time, inappropriate incubation temperature), test run errors, and manufacturing defects.[50] Technical causes of reduced IGRA sensitivity are minimized by ensuring persons collecting and processing specimens are adequately trained and procedures for IGRA testing are standardized. For individuals with uninterpretable IGRA results, repeat IGRA testing should be performed. Individuals with a positive or negative IGRA result on repeat testing should be managed in accordance with the repeat test result. Individuals with an uninterpretable IGRA result on repeat testing should undergo TST, and TST results should be used to inform subsequent management, including treatment decisions.

TREATMENT FOR LATENT TUBERCULOSIS INFECTION

Treatment for LTBI should be initiated for *Mtb*-infected individuals (based on TST/IGRA results or clinical suspicion) after active TB has been excluded by clinical history, physical examination, chest radiography, and confirmatory TB testing of respiratory specimens if indicated. Treatment regimens currently supported by the CDC include isoniazid

Table 42.4 Approved Treatment Regimens For Latent Tuberculosis Infection

Treatment Regimens	Duration	Frequency	Dose
INH-BASED REGIMENS			
INH	9 months*	Daily	Adult: 5 mg/kg Children: 10–20 mg/kg Maximum dose: 300 mg
		Twice weekly†	Adult: 15 mg/kg Children: 20–40 mg/kg Maximum dose: 900 mg
	6 months‡	Daily	Adult: 5 mg/kg Children: Not recommended Maximum dose: 300 mg
		Twice weekly†	Adult: 15 mg/kg Children: not recommended Maximum dose: 900 mg
RIFAMYCIN-BASED REGIMENS			
Rifampin	4 months	Daily	Adult: 10 mg/kg Children: 15–20 mg/kg Maximum dose: 600 mg
INH and RPT	3 months§	Weekly	Age >12 years: INH: 15 mg/kg rounding up to nearest 50 or 100 mg Maximum INH dose: 900 mg RPT: 300–900 mg, depending on weight
			Age 2–11 years: INH: 25 mg/kg Maximum INH dose: 900 mg RPT: 300–900 mg, depending on weight
			Age <2 years: not recommended
	1 month¶	Daily	HIV-infected individuals age ≥13 years: INH: 300 mg RPT: 300–600 mg, depending on weight

Shorter course regimens are preferred to facilitate treatment adherence and completion.
*Nine months of daily INH (daily or twice weekly) is the preferred regimen for pregnant women with high risk for progression to active disease (e.g., recent close contact).
†Twice weekly INH regimens must be administered via DOT.
‡Six months of daily INH is not recommended for immunosuppressed individuals (e.g., people living with HIV) or people with fibrotic lesions on chest imaging suggestive of untreated prior tuberculosis and children.
§Three months of daily INH and RPT can be administered via DOT or self-administered therapy.
¶1HP not yet approved by U.S. Centers for Disease Control and Prevention; data limited to HIV-infected individuals.
DOT, directly observed therapy; HIV, human immunodeficiency virus; INH, isoniazid; RPT, rifapentine.

monotherapy and rifamycin-based regimens (Table 42.4). All regimens have been shown to be effective, and no single treatment regimen has been shown to be superior to any other regimen. Therefore, regimen selection is based largely on the risk of adverse events by considering coexisting medical conditions and concomitant medications and the likelihood of treatment adherence and completion. To facilitate treatment adherence and completion, clinicians should consider shorter course regimens whenever possible.[56] Recently, the World Health Organization approved an ultrashort course treatment regimen for LTBI (*1 month of daily isoniazid and rifapentine* [1HP]) for both individuals with and without HIV,[57] although evidence to date has been limited to HIV-infected individuals. In a randomized trial among people living with HIV, 1HP was shown to have similar effectiveness and similar adverse event incidence as 9 months of daily isoniazid. However, the proportion of individuals completing treatment was significantly higher among those receiving 1HP (97% vs. 90%).[58] Based on these results, 1HP is anticipated to receive future CDC endorsement for HIV-infected individuals.

Although treatment regimens for LTBI are associated with hepatotoxicity, baseline liver function testing is not routinely indicated for all individuals before treatment initiation. Baseline liver function testing (serum aspartate aminotransferase, alanine aminotransferase, total bilirubin) is indicated for the following individuals belonging to groups with higher risk for adverse events: liver disease from any cause, risk factors for chronic liver disease, regular alcohol use, HIV infection, and pregnancy or less than 3 months postpartum.[56] Treatment for LTBI is contraindicated for asymptomatic individuals with aminotransferases greater than five times the upper limit of normal and symptomatic individuals with aminotransferases greater than three times the upper limit of normal. Those eligible for treatment who have abnormal baseline liver function tests should undergo repeat testing during LTBI treatment even if symptoms suggestive of acute hepatitis are absent. Similarly, individuals reporting symptoms suggestive of acute hepatitis during the course of treatment should have liver function testing performed, irrespective of their baseline risk for hepatotoxicity. Indications for withholding treatment include

aminotransferases five or more times the upper limit of normal regardless of symptoms or three or more times the upper limit of normal with associated symptoms.

Key Points

- Targeted screening for *latent tuberculosis infection* (LTBI) is indicated for individuals with increased risk of infection and/or reactivation; individuals who test positive by *tuberculin skin testing* (TST) or *interferon-gamma release assays* (IGRAs) should be considered for treatment for LTBI after excluding active tuberculosis disease.
- Current U.S. guidelines support the use of IGRAs in all situations in which TST is recommended. However, TST or IGRAs may be preferred in certain situations, based on test performance and/or operational characteristics: TST is preferred for children younger than 5 years, IGRAs are preferred for individuals with prior *bacillus Calmette-Guérin* (BCG) vaccination and for individuals belonging to groups with low rates of returning to have TSTs read. Dual testing may be considered in certain situations.
- TST and IGRAs have comparable specificity for detecting *Mycobacterium tuberculosis* infection among non–BCG-vaccinated individuals. However, compared to TST, IGRAs have higher specificity among individuals with prior BCG and in settings with high prevalence of nontuberculosis mycobacterial infection.
- TST and IGRAs have comparable sensitivity for detecting *Mtb* infection, and sensitivity of both tests are reduced among individuals with compromised immune systems. Empirical treatment for LTBI should be considered for immunosuppressed individuals with negative TST or IGRA results.
- Before initiating treatment for LTBI, all individuals must be assessed for active disease because neither TST nor IGRAs are able to distinguish LTBI from active tuberculosis.

Key Readings

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43 ASPIRATION

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INTRODUCTION

Aspiration is defined as the inhalation of fluid or solid material beyond the vocal cords and into the lower airways.[1] Aspiration is not always pathologic, and studies have shown that aspiration happens regularly in healthy adults. In one study nearly half of healthy adult male subjects had evidence of microaspiration during sleep.[2] However, aspiration is also associated with a wide range of pathology, ranging from bronchospasm to pneumonia. Aspiration leading to disease states is now thought to be a result of complex interactions between the host and the aspirated material.[3]

Aspiration happens as a result of impaired swallowing, leading to passage of oral or gastric contents into the respiratory tract. It is important to note that *gastroesophageal reflux disease* (GERD) can also contribute to aspiration syndromes. GERD has been associated with many pulmonary diseases, including asthma, chronic obstructive pulmonary disease, *interstitial lung disease* (ILD), and allograft health after lung transplant. The relationship between GERD and lung disease is thought to be related to aspiration or microaspiration of gastric contents as a result of reflux.

As our understanding of the pulmonary microbiome deepens, new hypotheses regarding how aspiration becomes pathologic have evolved. Historically, the lung was considered a sterile environment; however, it is now known there is a diverse range of microbiota throughout the respiratory tract (see also Chapter 17). The current understanding is that the lung microbiome is maintained by a complex relationship between migration of bacteria from the oropharynx and the upper respiratory tract, partly from microaspiration, and elimination of bacteria from host mucosal defense and mucociliary clearance.[4] Studies of healthy controls have found similar microbiota in the upper and lower airways; however, in subjects with respiratory diseases, there is a significant difference between the upper and lower airway microbiota.[5–7] This difference in microbiome may predispose certain subjects to pathology as a result of aspiration. Other possible contributing factors include ineffective host defense and large-volume aspiration that overwhelms clearance mechanisms. Noninfectious injury from aspiration is related to aspiration of acid, pepsin, and bile acids, which cause inflammation, but there is also evidence to support the role of small nonacidified gastric particles in causing airway inflammation. Both acidic and nonacidic substances have been shown to trigger the inflammatory cascade with recruitment of neutrophils in the airways, leading to injury.[8]

Although the mechanisms of pathologic aspiration are still being elucidated, this chapter will cover the presentation, diagnosis, evaluation, and treatment of aspiration in adults, with a focus on manifestations in the pulmonary parenchyma.

EPIDEMIOLOGY AND PATHOGENESIS

The prevalence of aspiration is difficult to estimate because it can often be asymptomatic and requires a high degree of suspicion with appropriate testing for accurate detection. Prior studies have estimated that 5% to 15% of community-acquired pneumonias are related to aspiration.[9] A large Japanese study, in which they evaluated for aspiration in all patients hospitalized for community- or hospital-acquired pneumonia, found that 306 of 382 (80%) of patients 70 years of age and older had aspiration. The overall incidence of aspiration was 60% in community-acquired and 86.7% in hospital-acquired pneumonia.[10] In studies in which aspiration was studied outside of the presence of pneumonia, 70% of patients with depressed consciousness were found to aspirate, compared to 45% of healthy adults.[11] In addition, there have been associations between reflux and microaspiration with progression in ILD[12–14] and chronic rejection after lung transplant,[15,16] indicating that aspiration is relevant in many conditions outside of acute events.

Although aspiration is quite common, there is evidence that aspiration is underappreciated as an important clinical syndrome. For example, in a series of 59 patients who had evidence of aspiration on lung biopsy specimens, only 9% were suspected to have aspiration before biopsy.[17] As discussed later in this chapter, keeping aspiration at the

forefront of the clinician's mind is essential in ensuring this potential contributing factor to the patient's presentation is not missed.

RISK FACTORS

Interruption of the normal function of many organ systems can increase the risk of aspiration (Fig. 43.1). Disease states that cause alteration of consciousness (such as stroke, dementia, or seizure), disorders of the spine, laryngeal abnormalities (including recent intubation or vocal fold paralysis), prior surgery or radiation, any esophageal disorder that causes difficulty with passage of food or saliva, and gastric motility disorders may lead to increased risk of aspiration.

PRESENTING CONDITIONS

The clinical presentation of aspiration is variable, and the clinician may encounter acute, subacute, and chronic forms of aspiration. It is also important to bear in mind that, although aspiration is often associated with cough, cough is not necessarily always present (so-called "silent aspiration"). In fact, patients may be completely asymptomatic. The presentation can include chronic cough, bronchospasm or worsening of asthma symptoms, foreign body aspiration, aspiration pneumonia, pneumonitis, lung abscess, bronchiectasis, bronchiolitis, lipoid pneumonia, ILD, and nontuberculous mycobacterial infection.[18,19]

VOCAL CORD DYSFUNCTION/PARADOXICAL VOCAL FOLD MOTION DISORDER

In *vocal cord dysfunction* (VCD), also known as *paradoxical vocal fold motion disorder* (PVFMD), the vocal folds intermittently adduct (close) with inhalation rather than the expected opening (abduction), which results in dyspnea and in severe cases, even stridor.[20–23] Many factors have been associated with VCD/PVFMD, including environmental irritants, stress, GERD, and *laryngopharyngeal reflux* (LPR), which refers to reflux of gastric contents up to the larynx/pharynx.[21–25] One hypothesis for the link between LPR/GERD and VCD/PVFMD is that repeated injury to the larynx results in an accentuation of the glottic closure reflex.[26] Although VCD/PVFMD often causes shortness of breath, its association with dysphagia (e.g., swallowing dysfunction) and aspiration risk remains unknown (see also Chapter 70).

FOREIGN BODY ASPIRATION

Foreign bodies are most commonly aspirated by children. It is unusual in adults, but its presentation can include wheezing, dyspnea, and chronic cough with or without hemoptysis. Radiographs may reveal radiopaque material with atelectasis, postobstructive or nonresolving pneumonia, or focal bronchiectasis. However, radiographs may also be unrevealing; therefore a high index of suspicion is important to ensure this diagnosis is not missed. Bronchoscopic extraction of a foreign body may be performed, with one large review demonstrating a 90% success rate for foreign body extraction via flexible bronchoscopy.[27] In rare cases, rigid bronchoscopy or surgical removal of a foreign body is necessary.

AIRWAYS DISEASE

Aspiration can cause myriad airway diseases, including cough, bronchospasm, and an asthma-like syndrome. It can also exacerbate asthma. In addition, aspiration can also

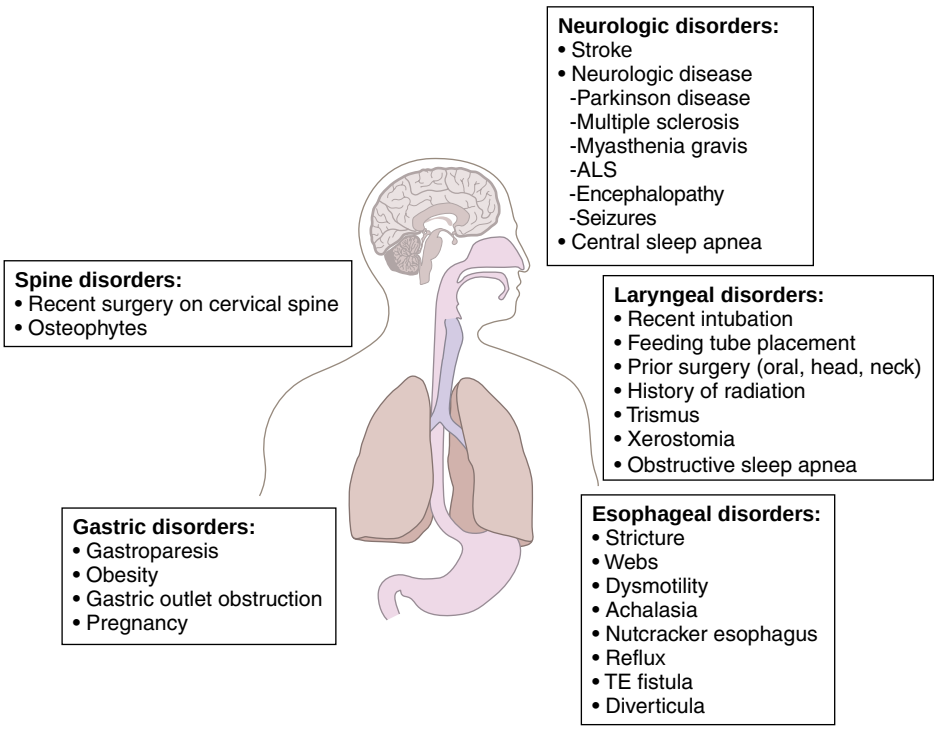

Figure 43.1 Risk factors for aspiration. ALS, amyotrophic lateral sclerosis; TE, tracheoesophageal.

affect the lower airways, with manifestations ranging from bronchiolitis to bronchiectasis.

ASTHMA

There are conflicting reports on the role of aspiration, primarily related to uncontrolled GERD, in asthma exacerbations. There are several studies that report an association between GERD and decreased asthma control.[28,29] However, there are also data showing the relationship between GERD and asthma control may be overstated. In one study of 78 patients who underwent bronchoalveolar lavage, 59% had pepsin detected on bronchoalveolar lavage, but the presence of pepsin was not associated with disease severity, exacerbations, or lung function.[30] The most recent asthma management guidelines recommend evaluation for GERD in poorly controlled asthma, especially when there are nighttime symptoms, even in patients who do not present with typical symptoms of GERD.[31] The benefit of treating or evaluating for GERD in patients with mild-moderate asthma is not clear.

BRONCHIOLITIS AND BRONCHIECTASIS

Aspiration can manifest as bronchiolitis or inflammation in the small airways (bronchioles) of the lungs and bronchiectasis, which causes irreversible thickening and dilation of the airways. The term "diffuse aspiration bronchiolitis" was first coined by Matsuse and colleagues[32] based on autopsy results of patients at high risk for aspiration due to neurologic disorders. A larger series from the Mayo Clinic described 20 patients with diffuse aspiration bronchiolitis, where the majority were diagnosed by lung biopsy (either surgical or transbronchial).[33] The striking finding between these two series is that most of these patients were middle aged (between ages 40 and 50 years), which may be why biopsy was required, because aspiration, which is often thought of as a disease of the elderly, was not considered in this younger population. Typical high-resolution *computed tomography* (CT) findings of aspiration-induced bronchiolitis include micronodules with tree-in-bud changes, consistent with small airway inflammation (Fig. 43.2A). Pathology demonstrates bronchiolar inflammation and thickening with foreign matter. Pathology may also demonstrate foreign matter that displays birefringence under polarized light, although the absence of this finding does not exclude aspiration. Diagnosis can be made by documenting aspiration with typical CT features or by lung biopsy.

Aspiration-induced bronchiectasis is common in children and has been reported to account for about 10% of non–cystic fibrosis bronchiectasis in children.[34] In two large series identifying the etiology of bronchiectasis in adult patients, only 1% to 4% were thought to be related to aspiration, making this is a less common cause of bronchiectasis in adults.[35,36] Typical CT findings of aspiration-related bronchiectasis include lower lobe predominant bronchiectasis, dilated esophagus, or hiatal hernia.

PNEUMONITIS: ASPIRATION VERSUS CHEMICAL

There are two major manifestations of aspiration in the lung parenchyma: aspiration pneumonia, which is related to infection by specific microbes, and chemical pneumonitis, which is an inflammatory reaction in response to aspiration.[9] Aspiration pneumonia is indistinguishable in clinical presentation from non–aspiration pneumonia, which makes it challenging to diagnose. Risk factors for aspiration pneumonia include older age, lower body mass index, increased comorbidities, and decreased functional status. Aspiration pneumonia has a higher mortality, longer hospital length of stay, and higher risk of recurrence than community-acquired pneumonia, which makes it important to identify as an etiology for pneumonia.[37–39] CT findings that may raise suspicion for aspiration include posterior opacities and a pattern of focal, peripheral, or peribronchiolar consolidation involving one or more segments (compared to lobar pneumonia)[40] (see Fig. 43.2B). Aspiration can also result in lung abscess (see Fig. 43.2C) and empyema, as well as interlobular septal thickening and ground-glass opacities (see Fig. 43.2D). There is no evidence to suggest that patients with aspiration pneumonia should be treated with longer duration of antibiotics except in the case of lung abscess.[41] Pleural collections should be drained immediately and sent for routine studies, including culture. The pathology of aspiration pneumonia is illustrated in Fig. 43.3, with pulmonary alveolar septal thickening from type 2 pneumocyte hyperplasia, with increased numbers of macrophages and organizing pneumonia within airspaces. Vegetable matter may also be seen.

Oral hygiene may reduce the risk of aspiration pneumonia.[42,43] In one randomized controlled trial of nursing home residents, subjects with routine oral care and weekly care from dentists had a reduced risk of pneumonia compared to those without oral care. This was true regardless of presence of teeth, indicating oral care is important in edentulous patients as well.[44] However, a multicenter, cluster, randomized controlled trial of oral hygiene care (tooth brushing, chlorhexidine oral rinse twice a day, and upright positioning during meals) did not reduce the incidence of pneumonia in nursing home residents, a high-risk population for aspiration.[45] This is in line with data showing routine oral care in patients receiving mechanical ventilation may not prevent nosocomial pneumonia in certain patient populations.[46] Thus, oral care can be considered as one possible method to reduce risk of pneumonia but must be used in conjunction with other techniques, as discussed later in this chapter.

The classic teaching that aspiration is often associated with anaerobic infections is based on studies from the early 1900s linking bacteria found in lung abscess with gingival flora, and finding that those pathogens were anaerobic bacteria.[47] More recent data have been limited, given the challenges of culturing anaerobic bacteria in the laboratory. In one study using protected specimen brush sampling and minibronchoalveolar lavage in patients with aspiration pneumonia on a ventilator, only one anaerobic organism was isolated, with the rest being enteric gram-negative organisms, *Streptococcus pneumoniae,* and *Haemophilus influenzae,*[48] which calls into question the classic teaching of using anaerobic coverage for patients with suspected aspiration pneumonia. However, given the challenges of isolating anaerobes and the potential for significant pulmonary pathology with anaerobic infection, it is still recommended that anaerobic bacteria be covered empirically in the initial therapy for aspiration pneumonia.[49]

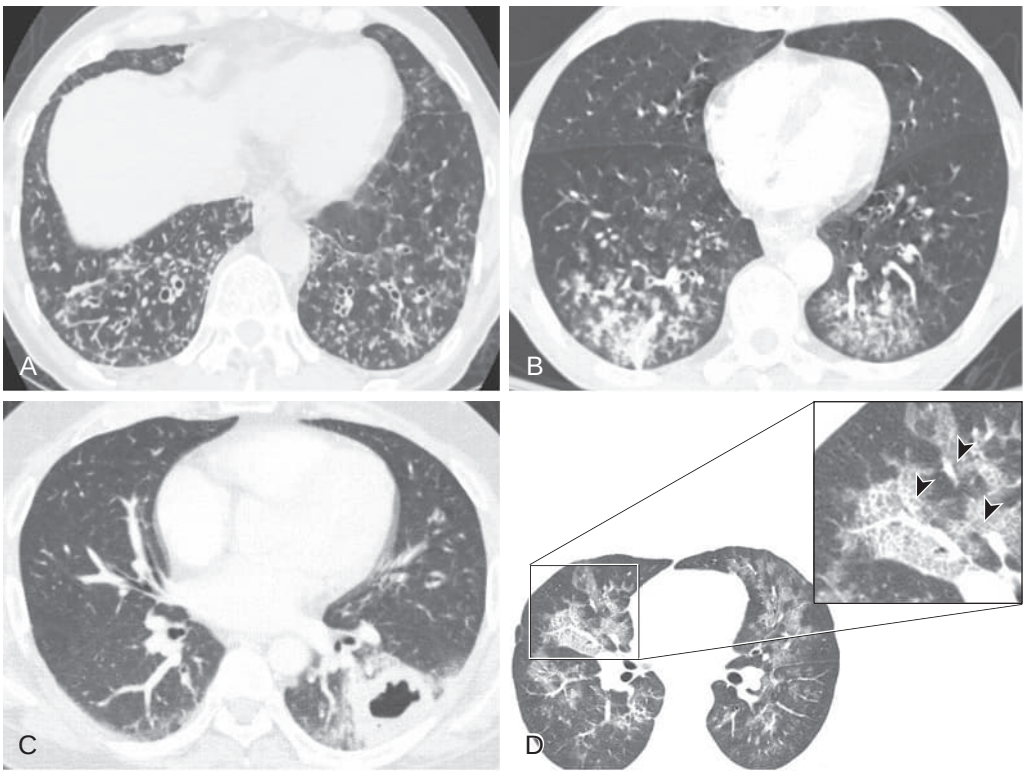

Figure 43.2 Computed tomography findings of aspiration. (A) Basilar predominant, patchy tree-in-bud opacities with mild bronchiectasis typical of recurrent aspiration. (B) Basilar predominant consolidation with tree-in-bud opacities consistent with aspiration-related bronchiolitis. (C) Cavitary lesion. (D) "Crazy paving" appearance in a patient with oil aspiration and lipoid pneumonia. Axial high-resolution computed tomographic image shows patchy, multifocal, geographically distributed ground-glass opacity associated with intralobular interstitial thickening and interlobular septal thickening, causing the reticular appearance in the regions of ground-glass opacity. The smooth interlobular septal thickening *(arrowheads)* is better appreciated in the magnified detail image. (Courtesy Michael B. Gotway, MD.)

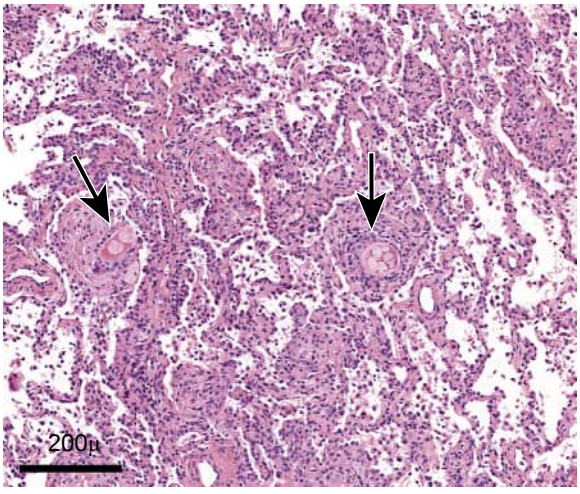

Figure 43.3 Histopathologic findings of aspiration pneumonia. The pulmonary alveolar septa are mildly thickened by type 2 pneumocyte hyperplasia, and there are increased numbers of macrophages and organizing pneumonia within airspaces. Two fragments of vegetable material are noted within the airspace organization *(arrows)*.

Chemical pneumonitis is related to macroaspiration of large-volume acidic fluid, also termed "massive aspiration." This entity is not typically seen after aspiration of tube feeds or blood, which has a higher pH than gastric acid. This is a noninfectious phenomenon whereby the acid recruits inflammatory cells to the lung.[50] This most commonly happens during anesthesia but has also been reported in drug overdose and in nursing home populations.[51] The incidence is low (<1%).[9] Emergency surgery increases the risk more than elective procedures. The clinical presentation can include shortness of breath, hypoxemia, tachycardia, and diffuse crackles or wheezes. Imaging is abnormal and can progress into an acute lung injury pattern. Lower respiratory tract cultures are typically sterile, and this has been used to differentiate pneumonitis from pneumonia.[41] The data do not support the routine use of antibiotics to prevent development of aspiration pneumonia,[41,52] although this may be considered in severely ill patients. Otherwise, management of chemical pneumonitis includes supportive care, including treatment of bronchospasm and edema, and reduction of the amount of acid exposure by aggressive suctioning or bronchoscopy. There is insufficient evidence to support the use of corticosteroids in this condition.

EXOGENOUS LIPOID PNEUMONIA

Aspiration of lipid-laden substances can result in accumulation of lipids in the lung parenchyma, which is known as lipoid pneumonia. Common inhalants include oil-based medications (such as laxatives or nasal instillation of oily substances to treat congestion), radiographic contrast material, or oil in foods.[53] Gagging during administration of oil-based medications, gastroesophageal reflux, or neurologic or psychiatric illness are predisposing factors for development of lipoid pneumonia.[54] Radiographic presentations

can vary, and consolidation, ground-glass opacities, crazy paving (a pattern on CT defined by the combination of ground-glass attenuation, interlobular septal thickening, and intralobular lines, demonstrated in Fig. 43.2D), septal thickening, and mass-like lesions can all be presenting signs. Consolidations are often multilobar and bilateral. The hallmark of lipoid pneumonia is the presence of consolidations with areas of fat attenuation (typical range of −17 to −114 Hounsfield units).[55] Treatment of lipoid pneumonia is avoidance of the inhalant. Lipoid pneumonia can be asymptomatic but, in severe cases, can cause fibrosis. In addition, there can be secondary infections, such as with nontuberculous mycobacteria (described in detail later).

INTERSTITIAL LUNG DISEASE

Various forms of pulmonary fibrosis have been associated with aspiration. Organizing pneumonia, which is a pathologic pattern where plugs of granulation tissue are seen in the air spaces, has been associated with aspiration.[56–58] A careful history focused on dysphagia, swallowing, and reflux should be undertaken in any patient who presents with organizing pneumonia.

Microaspiration and GERD have been associated with *idiopathic pulmonary fibrosis* (IPF), a chronic, progressive fibrotic lung disease. In a study using ambulatory esophageal pH monitoring, 94% of patients with IPF had abnormal acid exposure compared to 50% of control subjects. Of note, only 4 of the 17 patients with IPF and abnormal acid exposure had symptoms.[59] Another large study of patients with IPF found that the use of GER medications was an independent predictor of longer survival time.[12] These data support the link between microaspiration and GER in pulmonary fibrosis, although the exact role is still being elucidated.

A study of laparoscopic fundoplication, an antireflux surgery, in patients with IPF and evidence of acidic GERD on pH monitoring showed that this procedure is safe and well tolerated. There was a nonstatistically significant reduction in exacerbation and death in the fundoplication arm.[60] More data are necessary to understand the utility of surgery in this population.

Esophageal dysmotility and reflux are common manifestations of connective tissue disorders. One study of patients with scleroderma with and without ILD found that reflux was more common in patients with ILD.[61] Whether the ILD makes the reflux worse or vice versa is still being evaluated. Fundoplication and other antireflux procedures are of unclear benefit, given the other gastrointestinal motility issues in this population.

NONTUBERCULOUS MYCOBACTERIAL INFECTION

There have been several case reports in the literature documenting a relationship between lipoid pneumonia and rapid growing mycobacterial infections (*Mycobacterium abscessus* and *M. fortuitum*).[19,62] In addition, patients with achalasia, an uncommon esophageal motility disorder characterized by the absence of esophageal peristalsis and impaired relaxation of the lower esophageal sphincter, are at higher risk for developing *nontuberculous mycobacterial* (NTM) infections.[18,63,64] Aspiration of lipid-laden contents may create an environment for mycobacteria to grow. Patients are often misdiagnosed and have frequent courses of antibiotics, so it is important to consider NTM as an etiology in patients who do not respond to usual treatment with antibacterial therapy.

Aspiration has been implicated in a variety of pulmonary pathology. The exact mechanism between aspiration and disease is unclear but is likely a combination of both acid and non–acid-mediated injury accompanied by changes in the lung microbiome. Aspiration can be silent and is not limited to the elderly, so a high index of suspicion is required to ensure it is not missed. The following section will describe the evaluation and management of dysphagia and aspiration.

CLINICAL PRESENTATION

Swallowing difficulties (dysphagia) are an important risk factor for aspiration and should be evaluated and addressed, although it is important to note that rarely is dysphagia the *only* risk factor present.[65] Taking a comprehensive swallowing history is of critical importance in the identification of potential swallowing dysfunction and risk of aspiration. A simple open-ended question such as "How is your swallowing?" or "What are you eating these days?" can provide an opening for further discussion of this topic. A sample list of questions to be included in a comprehensive swallowing history is included in Table 43.1.[66] A screening questionnaire, such as the Eating Assessment Tool-10 (EAT-10), may help identify patients at risk for swallowing difficulties and aspiration.[67]

Clarification of the nature and type of swallowing difficulty is vital. Different consistencies (e.g., solids, liquids, or pills) may cause variable levels of difficulty; patients may have challenges with one type of oral intake but not others. Some patients may consciously or unconsciously use compensatory mechanisms (e.g., cutting pills in two or

Table 43.1 Pertinent Questions in Comprehensive Swallowing History

How is your swallowing?
What are you eating these days?
■ For instance, regular diet, soft foods only, liquids only
Are you avoiding any particular types of foods?
■ For instance, bread, meat, crackers, nuts
Have you had to change how you eat/drink?
■ For instance, adding more sauces/gravy, cutting food into smaller pieces, taking pills one (instead of a handful) at a time, taking pills with applesauce instead of water, sipping liquids instead of gulping/chugging
How long does it take you to eat a meal?
Are you coughing or choking with liquids?
Does it take effort to swallow?
Does it hurt to swallow?
Do you feel as if food/liquids/pills get "stuck"? If so, can you point to where you feel this?
Has your weight changed lately? How do your clothes fit?
Have you had pneumonia recently?
Have you ever needed the Heimlich maneuver?
Do you regurgitate? If so, is the material digested or undigested?
Do you experience heartburn, reflux, or indigestion?
What makes your swallowing worse?
What makes your swallowing better?

crushing them, adding more sauces/gravy, or cutting food into smaller pieces), which can mask the presence of underlying swallowing difficulties. A thorough history should elucidate these details; often family members or caregivers can provide additional insight. Although changes to swallowing function can be seen as a normal function of age,[68–73] the impact on a patient's ability to function and on his or her nutritional status and weight determines the degree to which any changes become a problem.

When obtaining a comprehensive swallowing history, it is important to note the duration of the symptoms and any precipitating events (e.g., stroke, intubation, acute illness, surgery, etc.). Identification of both aggravating and alleviating factors is also helpful. Many risk factors may contribute to swallowing difficulty and should be identified and addressed, when possible. These are summarized in Fig. 43.1.

Other symptoms, such as dysphonia (hoarseness), dyspnea, otalgia (ear pain), neck mass, dysarthria (slurred speech), globus (sensation of something in the throat), or reflux symptoms, may provide additional clues to identify the presence and/or etiology of concurrent dysphagia. In particular, reflux (either GERD or LPR) may result in swallowing difficulties. As noted earlier, there are multiple studies that suggest a link between LPR/GERD and microaspiration related to reflux, which can cause pulmonary disease. Reflux symptoms may include the traditional heartburn, indigestion, substernal pain, or burning sensation, but other symptoms that are potentially suggestive of reflux can include hoarseness, globus sensation, throat clearing, increased mucus, postnasal drip, chronic cough, bad or metallic taste in the mouth, or burning sensation in the mouth, throat, or chest.[74] The patient's tobacco, drug, and alcohol use history can also be potential risk factors for underlying disorders that can impact swallowing.

Among the many questions in a thorough history, it is particularly important to inquire about coughing or choking with liquids. These events raise a strong clinical suspicion of the potential for aspiration. However, it is vital to remember that aspiration may be taking place even in the absence of coughing (e.g., in the setting of changes in laryngotracheal sensation). This so-called "silent aspiration" can be even harder to identify; thus careful history taking, heightened awareness, and early identification are essential. Moreover, aspiration may not happen with every single swallow, but intermittent aspiration is not necessarily less harmful. In addition, worsening frequency or severity of coughing, choking, or dysphagic episodes can be worrisome signs.

It must be emphasized that choking or even coughing does not necessarily indicate aspiration. Furthermore, aspiration does not always result in pneumonia, and thus even the presence of frank aspiration should not automatically cause patients to be put on NPO status (nothing by mouth). Rather, the presence of choking, coughing, or any other symptoms or signs suggestive of aspiration should trigger a more comprehensive investigation of swallowing function.

EVALUATION AND TESTING

Evaluation of swallowing function is optimally performed in a multidisciplinary fashion with both an otolaryngologist and a speech-language pathologist. This multidisciplinary team should assess the patient's history, symptoms, and physical examination to determine the appropriate next step(s) for assessment. Simply watching patients swallow, even when performed by trained speech-language pathologists in what is commonly termed a "bedside swallow," is *inadequate* to identify the presence or absence of aspiration.[75]

A detailed physical examination of the head and neck should assess the status of all anatomic components that can impact swallowing function (Table 43.2). For example, the lips should be evaluated for masses, weakness, and oral competence (the ability to form a seal); the presence of drooling should be noted. The oral cavity and its mucous membranes should be examined for masses or dry mouth (xerostomia). Dental issues (e.g., presence or absence of teeth; condition of teeth; missing, broken, ill-fitting or unused dentures) can impair the patient's ability to masticate and form a bolus for swallowing. Gingival disease and dental caries provide a source of bacteria that, if aspirated, can provide a nidus of infection in the lung. The tongue should be examined for weakness, deviation to one side, presence of fasciculation, or postsurgical defects. Palatal asymmetry or velopharyngeal insufficiency (leading to nasal regurgitation) can also interfere with swallowing.

A thorough laryngoscopic examination is essential to identify abnormalities in the oropharynx, hypopharynx, larynx, and upper esophageal inlet. Endoscopic laryngeal examination can be performed using either a flexible or rigid laryngoscope. Because of its superior ability to assess neurologic function of the larynx (i.e., vocal fold motion and laryngeal sensation), flexible laryngoscopy is preferred for evaluation in patients with dysphagia complaints. Mirror laryngeal examination is of historical note and rarely used currently due to the advances in laryngoscopy (e.g., ease of use, enhanced quality of images obtained, and high tolerability). On flexible laryngoscopy, structural or anatomic changes (e.g., mass, tumor, surgical defect), vocal fold motion status, pooling of secretions, decreased or absent sensation, or presence of retained food particles are all noteworthy findings.

The flexible laryngoscope can also be used to observe some aspects of the swallowing function directly. This test, a *flexible endoscopic evaluation of swallowing* (FEES), allows direct observation of the nasopharynx and oropharynx before the swallow[76–78] (Videos 43.1 and 43.2). In addition, residual food materials that remain after the swallow

Table 43.2 Important Physical Examination Findings Potentially Related to Dysphagia

Lips: mass, weakness, oral competence (ability to form seal), presence of drooling
Teeth: presence or absence of teeth; condition of teeth; missing, broken, ill-fitting or unused dentures
Oral cavity: masses, xerostomia
Tongue: weakness, deviation, fasciculation, defect (postsurgical changes)
Palate: asymmetry, velopharyngeal insufficiency (leads to nasal regurgitation)
Larynx: unilateral or bilateral vocal fold paralysis, decreased sensation

can be identified, and compensatory strategies may be tested at this time. However, because of the closure of the pharyngeal walls at the moment of swallowing (the so-called "whiteout" phase), direct visualization of vocal fold closure is obscured, and activity at this level during the actual swallow must be inferred. Frank aspiration may be readily visualized but can also be missed due to the whiteout phase. This disadvantage is offset by the advantages of FEES, including lack of radiation exposure and the high tolerance of this examination. During a FEES, the patient often tries to swallow materials of different consistencies. The exact protocol may differ between centers and is often guided by the patient's specific complaints and examination findings. A typical protocol may include thin liquids, thickened liquids (e.g., honey or nectar consistencies), pureed (e.g., applesauce), mixed consistency (solid and liquid together, e.g., fruit cocktail), and/or dry solid (e.g., cracker).

To evaluate swallowing function further, a *modified barium swallow* (MBS) is often pursued.[78] The MBS (also termed *video fluoroscopic swallow study* or *cookie test*) is performed in the fluoroscopy radiology suite in conjunction with a speech-language pathologist (Videos 43.3 and 43.4). This examination provides more detailed information about the oral, pharyngeal, and esophageal phases of swallowing and what can be observed at the level of the vocal folds in the midst of the swallow. Although an MBS does require a small degree of radiation exposure, this test also allows assessment of various consistencies and testing of concurrent compensatory strategies.[79] This test is distinguished from a *barium swallow* or esophagram, which only evaluates the propulsion of thin liquid barium through the esophagus to the stomach, focusing more on the evaluation of the esophageal anatomy. Although a barium swallow may identify gross aspiration, this test does not specifically assess swallowing function and thus is not typically considered sufficient as the sole method of evaluation of swallowing function.

Both FEES and MBS provide different types of information regarding a patient's swallowing function. These tests each have advantages and disadvantages and often provide complementary information about the patient's swallowing status. Thus it is not uncommon for patients to benefit from undergoing both types of evaluations, although both tests are not always required.[78] The comprehensive swallowing history and physical examination should guide decision making about the optimal test to identify the patient's underlying swallowing abnormality, the presence or absence of aspiration, and any potential compensatory strategies.

In situations of aspiration and dysphagia, the presence of reflux is important to note. However, the diagnosis of reflux can be quite challenging.[80] Often the diagnosis of GERD can be straightforward, particularly in patients with classic symptoms of heartburn and abdominal pain. GERD may be identified on esophagram (barium swallow) or endoscopy. By contrast, no gold standard has yet been established to make the diagnosis of LPR, wherein the stomach contents are thought to ascend the length of the esophagus and cause irritation or inflammation of the pharynx and potentially the larynx.[25] Frequently, a *clinical* diagnosis of LPR may be made based on the patient's symptoms and/or a clinical response to an empirical trial of antireflux treatment (often pharmacologic).[81]

A 24-hour dual-channel pH/impedance test, often performed with high-resolution manometry, may provide strong evidence for or even a definitive diagnosis of LPR, but there can be false-negative results as well.[81–83] In this test, a probe is inserted through the nose and left in place for a 24-hour period. During this time, patients note their symptoms (e.g., heartburn, indigestion, cough, regurgitation, throat clearing, globus) using a recording device. The test records the presence and number of reflux events, the pH of these events, how far proximally the events extend, and the correlation of these events with the patient's symptoms. Use of a dual-channel probe allows identification of proximal esophageal or pharyngeal events and is considered superior to a single-channel probe that would only assess distal esophageal events. Concurrent high-resolution manometry testing can provide additional information about the presence of esophageal dysmotility, which may also aggravate reflux symptoms.[84] Although pH/impedance testing with or without manometry may provide useful information about the presence or absence of LPR, it is important to understand that there may be false-negative results, and thus the gold standard for diagnosis of LPR remains elusive at present.[81–83]

TREATMENT

Management of dysphagia can be variable based on the underlying nature of the swallowing dysfunction. Treatment of penetration and aspiration, in particular, is based on the nature and timing of these events. All patients with swallowing difficulties should be monitored routinely for unintentional weight loss, development of lung infection (e.g., pneumonia), or progressive worsening of symptoms. In patients with known aspiration, meticulous oral care is of paramount importance. Patients at risk for aspiration should be counseled to brush their teeth every time after eating, to minimize the microbial load that may be aspirated into the lungs. Regular monitoring by their dentist to optimize dental care is imperative in these patients.

For any patient with swallowing symptoms, especially in the presence of weight loss, diet change, history of pneumonia, or reported coughing/choking when drinking liquids, formal multidisciplinary evaluation of swallowing dysfunction should be pursued, and treatment should be guided by the results of these assessments.

NIL PER OS STATUS

In circumstances of a sudden change in swallowing function, particularly if deemed likely to be temporary in nature (e.g., postsurgery), restricting a patient's oral intake may be indicated. If patients are NPO, then they should be given intravenous fluid hydration, enteral feeds (e.g., via nasogastric tube), or total parenteral nutrition. In cases of prolonged dysphagia and/or aspiration, a gastric (G-) or jejunal (J-) tube may need to be placed surgically. It is imperative to recall that enteral feeding via such tubes may not necessarily improve outcomes or quality of life, nor does it prevent aspiration.[85–87]

NPO status is not automatically required in cases of aspiration, and indeed, sometimes patients may choose to

continue oral intake despite the presence of known aspiration. In this latter situation, patients and their families should be counseled about the risks of continued oral intake and the necessity of strict oral care so that they may make an informed decision about continuing oral intake in these circumstances.

COMPENSATORY STRATEGIES

Patients with dysphagia may be able to swallow safely with the use of various compensatory strategies. The specific strategy to use should be guided by the findings of the swallowing examination(s). Examples of helpful techniques can include changing the consistency of the diet, restricting bolus size to small sips and bites (e.g., cutting food into small pieces), and alternating solid and liquid consistencies. Other beneficial maneuvers can include hard (or consciously effortful) swallow, which improves posterior bolus propulsion and pharyngeal pressures to clear the bolus from the oropharynx; breath-hold during the swallow; or planned cough after swallowing, as well as certain positions, such as chin tuck, head turn, head tilt, or chin up. However, the utility of each of these strategies should be carefully assessed on a swallowing evaluation before clinical implementation.

SWALLOWING THERAPY

Swallowing therapy with a skilled speech-language pathologist may improve swallowing function, decrease dysphagia, and thus decrease the risk of aspiration. Again, the type and nature of swallowing therapy exercises should be determined by the specific findings of the swallowing evaluation, but overall these tend to focus on enhancing strength and coordination of the swallowing mechanism. Details regarding swallowing therapy are beyond the scope of this chapter but are briefly summarized as follows. Commonly used swallowing therapy exercises include the Masako (focused on holding the tongue to strengthen the propulsive ability of the base of tongue),[88,89] Shaker (lifting the head),[90,91] lingual resistance exercises,[92] and laryngeal elevation exercises. Examples of swallowing maneuvers that may improve dysphagia include effortful swallow,[88,93–95] Mendolsohn maneuver (targeting hyolaryngeal elevation, which helps to prolong cricopharyngeal opening during the swallow),[88,93] supraglottic swallow (breath-hold during swallow, followed by voluntary cough),[93] and super–supraglottic swallow (increased effort with supraglottic swallow).[93,96]

MEDICAL TREATMENT

Medical treatment of dysphagia should be directed at the underlying pathology. Addressing esophageal dysmotility (e.g., with prokinetic agents) can improve esophageal flow and decrease dysphagia. Salivary dysfunction (e.g., from postradiation xerostomia or rheumatologic disease) can also impair swallowing and should be addressed with aggressive hydration, sialogogues, artificial saliva, or other measures. Control of underlying rheumatologic disease (when applicable) is crucial.

Treatment of reflux may also be helpful in improving dysphagia and aspiration risk.[80,81] Management of reflux often relies on a combination of dietary and behavioral modifications with or without pharmacologic intervention. Patients should avoid, or at least minimize, specific foods known to trigger reflux, including, but not limited to, fried foods, high-fat content foods, spicy foods, tomato-based foods, dairy products, mint, citrus, caffeine, chocolate, and alcohol. Stress reduction, weight loss, and avoidance of late-night eating may also be beneficial. Use of a MediWedge or elevation of the head of the bed to 30 degrees is also recommended to reduce reflux. It is vital to note that the use of additional pillows to elevate the head alone is *not equivalent* to elevation of the entire head of the bed. The addition of pillows under the head results in increased bending at the stomach, which can increase intra-abdominal pressure and thus worsen reflux. In addition to these strategies, pharmacologic intervention, including proton pump inhibitors with or without histamine blockers may be pursued. For patients who are unwilling or unable to take or who remain symptomatic despite these medication(s), over-the-counter barrier medications (e.g., Gaviscon Advance [from outside the United States], Life Extension Esophageal Guardian, or Reflux Gourmet) may be an adjunctive or alternative option. Antacids may also be helpful in providing temporary symptom relief.

SURGERY

Surgery for dysphagia and aspiration should be targeted at addressing any anatomic changes or deficiencies that interfere with swallowing. A full description of the various surgical options for treatment of dysphagia is beyond the scope of this chapter; however, a brief overview of some common surgical treatments is included for initial reference. Surgery aimed at addressing dysphagia may decrease the risk for aspiration, *although it is important to note that the risk of aspiration cannot be eliminated entirely.*

In cases of incomplete vocal fold closure—often related to unilateral vocal fold paralysis, such as may be caused by thyroid or cervical spine surgery or after a stroke—a vocal fold augmentation procedure to restore vocal fold closure, particularly during the swallow, may be highly successful at improving dysphagia and eliminating aspiration. Vocal fold augmentation may be performed in a temporary or permanent fashion, via injection or open surgical placement of augmentation material, and potentially under local or general anesthesia, depending on the type of augmentation material.[97–100] Evaluation by an otolaryngologist, ideally in conjunction with a speech-language pathologist, will determine the optimal choice for such a procedure.

Cricopharyngeal dysfunction may improve with procedures targeted at the upper esophageal sphincter (e.g., dilation, botulinum toxin injection, or myotomy).[101–103] Velopharyngeal insufficiency may be addressed with a nasopharyngeal injection, if a palatal prosthesis was unsuccessful.[104] More aggressive surgical procedures are rarely performed except in cases of a completely nonfunctional larynx, typically with intractable aspiration and recurrent episodes of lung infection. Although laryngotracheal separation and total laryngectomy are options in these rare cases, they are complex procedures with a high degree of morbidity and should only be undertaken in highly selected cases, often as a last resort.[105–107]

Nissen fundoplication, or antireflux surgery, is a consideration for patients who have severe GERD that cannot be controlled by medical therapy or who have side effects or complications from medication. In this procedure, performed either laparoscopically or via open thoracotomy, a portion of the fundus of the stomach is wrapped around the lower esophageal sphincter. By "tightening" this sphincter function, the ability for gastric contents to come up (i.e., "reflux") into the esophagus is decreased.[108] There are some data to support its use in IPF and chronic lung allograft dysfunction after transplant.[60,109] Fundoplication is generally well tolerated and effective in preventing GERD, with common side effects, including dysphagia, bloating, and nausea.[110] The decision to pursue surgery should be made in careful collaboration with a gastroenterologist and surgeon on a case-by-case basis.

Key Points

- Aspiration can cause a wide variety of pulmonary manifestations, ranging from bronchospasm to lower respiratory tract infection.
- Knowledge of typical clinical, radiographic, and pathologic presentations, along with a high index of suspicion, is critically important because aspiration can be silent and is often missed.
- Detailed evaluation of dysphagia can identify patients at risk for aspiration.
- Taking a comprehensive history is fundamental, with the presence of coughing or choking with liquids raising concern for the potential for aspiration.
- The presence of aspiration does not mean that a patient must be made nil per os.
- Evaluation of swallowing function is optimally performed in a multidisciplinary fashion, including both an otolaryngologist and a speech-language pathologist.
- A flexible endoscopic evaluation of swallowing and a modified barium swallow provide complementary information regarding swallowing function; aspiration may be identified on either or both tests.
- Treatment for dysphagia and aspiration should be guided by the underlying pathology and the findings of the swallowing evaluation.
- Patients with dysphagia and risk of aspiration should be monitored regularly for unintentional weight loss, development of pneumonia, and progressive worsening of symptoms.

Key Readings

Brady S, Donzelli J. The modified barium swallow and the functional endoscopic evaluation of swallowing. *Otolaryngol Clin North Am*. 2013;46(6):1009–1022.

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44 HYPOXEMIA

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INTRODUCTION

Understanding hypoxemia is an important goal for every pulmonologist. Both in its acute and chronic presentations, hypoxemia reflects the functioning of the lung in its major role as a gas exchange organ. The physiologic mechanisms of hypoxemia are explained in Chapter 10. Aspects of hypoxemia are also discussed in several other chapters in this textbook. This new chapter has been introduced to amplify the understanding of the mechanisms of hypoxemia in the clinical context and to explore the practical aspects of this understanding and the approach to hypoxemia.

DEFINITION

It must first be clarified what hypoxemia is and what it is not. Hypoxemia is a low level of oxygen in the blood (-emia), defined as a low oxygen saturation or low *partial pressure of oxygen* (Po_2). The actual level used is somewhat arbitrary.[1] An arterial oxygen saturation less than 90% is a reasonable definition of hypoxemia; at this saturation, the arterial Po_2 is approximately 60 mm Hg (depending on the actual dissociation curve) (Figs. 44.1 and 10.12). At this level, the arterial Po_2 values approach the steep portion of the oxygen-hemoglobin dissociation curve, where small changes in arterial Po_2 have a large effect on saturation. However, investigators have defined hypoxemia at different points anywhere from 88–95% saturation,[1–3] thus emphasizing that the actual level has not been defined, either at rest or during exercise. One reason for the reluctance to set a single value for hypoxemia may be that arterial Po_2 varies significantly with age.[4] It has been pointed out that an arterial Po_2 of 66 mm Hg can be normal in an 80-year-old person.[5]

A key point is that hypoxemia is not the same as hypoxia, although these terms are often used interchangeably. Hypoxia is defined as an insufficient level of oxygen in the tissues (not the blood), and it is recognized by signs of ischemia, such as lactic acidosis, cardiac ischemia, or neurologic dysfunction. Hypoxemia, on the other hand, may not cause symptoms and may instead be detected incidentally, usually with pulse oximetry (see the later section on response).

MEASUREMENTS

Various measures are used to describe hypoxemia, including Po_2, oxygen saturation, *alveolar-arterial Po_2 difference* [(A–a)Po_2], and the *ratio of arterial Po_2 to the fractional concentration of oxygen in inspired gas* (Fio_2) (the P/F ratio).

Arterial Po_2: This is the partial pressure, or tension, of the oxygen in equilibrium with the arterial blood. The difference between the average alveolar partial pressure of oxygen and the arterial Po_2 is a measure of the efficiency of oxygenation, the (A–a)Po_2. Of note, it is the partial pressure that is detected by the carotid bodies. However, it is the saturation that indicates how much oxygen is carried in the blood.

Oxygen saturation: The relationship between the Po_2 (arterial Po_2) and the saturation of the blood is one of the most important relationships in medicine, as described by the oxygen-hemoglobin dissociation curve (also called the oxyhemoglobin dissociation curve) (see Figs. 44.1 and 10.12). This sigmoid relationship explains how oxygen loads and unloads rapidly onto the hemoglobin in the steep portion of the curve with small changes in arterial Po_2 and how, once fully loaded, the partial pressure can fall over a large range without much of a drop in the

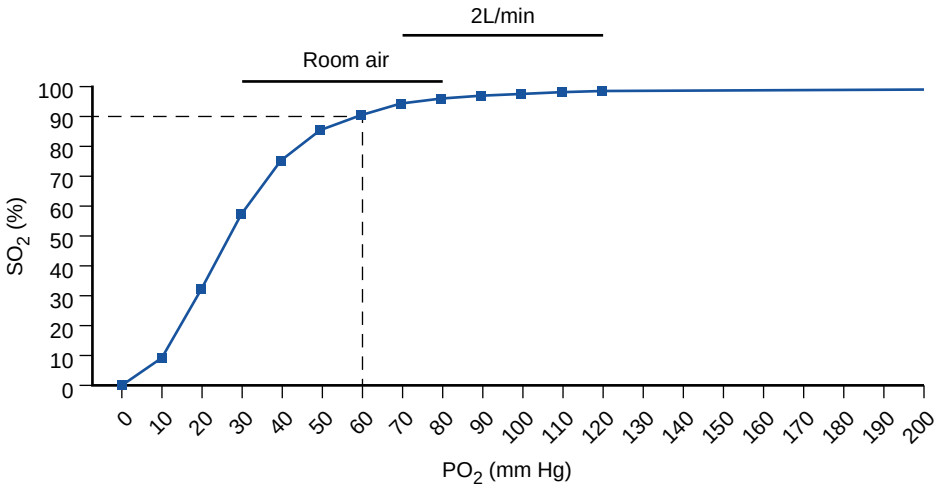

Figure 44.1 The oxyhemoglobin dissociation curve. The two bars show the range of arterial partial pressure of oxygen (P_{O_2}) in a subject breathing room air and breathing supplemental oxygen at 2 L/min. With hypoventilation, the subject's arterial P_{O_2} decreases along the bar, moving to the left. On room air, the fall in partial pressure of oxygen due to hypoventilation will trigger a drop in saturation (S_{O_2}) that can be detected by the pulse oximeter. On 2 L/min, the same fall in partial pressure of oxygen will remain on the flat portion of the curve and will not generate a low saturation and thus not be detected by the pulse oximeter (see also Table 44.1). The *dashed line* represents the defined level of hypoxemia (see text).

oxygen saturation. One can also appreciate that the arterial P_{O_2} can *increase* over a large range, as when high F_{IO_2} is given to patients, with almost no increase in oxygen saturation. The actual position of the curve is sensitive to systemic input; with fever or low pH, for example, the curve moves to the right, allowing more oxygen unloading at the same arterial P_{O_2} (see Fig. 10.12). It is the oxygen saturation that is measured by the pulse oximeter (see later).

(A–a)P_{O_2}: It is important to state up front that this is a difference, not a gradient. Why? Because a gradient implies a difference between two points, from an alveolus to a pulmonary capillary, whereas the "*A*" indicates an average value for the alveoli in the lung and the "*a*" is not capillary blood, but arterial, and also represents something of an average value. The divergence of these two values comes from differences across the lung as a result of the heterogeneity of oxygenation; thus, the term "difference" is more apt than "gradient." At room air, the (A–a)P_{O_2} turns out to be an excellent measure of the efficiency of oxygen transfer. At a higher F_{IO_2}, however, the difference increases and thus is affected by the F_{IO_2}.[6] The P/F ratio was developed in part to address this problem (see below). The (A–a)P_{O_2} also widens with age[7,8]; a standard equation to correct the (A–a)P_{O_2} for the effect of age is (age/4) + 4. Finally, an abnormal (A–a)P_{O_2} is not specific for any single cause of hypoxemia; however, a normal value in the setting of hypoxemia is most compatible with hypoventilation.

P/F ratio: Compared with the (A–a)P_{O_2}, the P/F ratio is more resistant to changes in F_{IO_2} but, even here, it has been shown to vary with the F_{IO_2}.[9,10] Therefore, when monitoring changes over time, it is important to determine the P/F ratio when the F_{IO_2} has been set to the same level and after the lung has been maximally recruited.[11]

CONSEQUENCES

When is hypoxemia harmful? In healthy individuals, profound hypoxemia can be tolerated for short periods.[12] Most hypoxemia studies have been performed in the process of testing the function of pulse oximeters[12] or of measuring the ventilatory responses to hypoxemia.[13] No particular harm has been noted.[5] Clearly, if the hypoxemia is low enough and prolonged enough, the heart and brain will fail. However, the pleasant surprise is how well the average person can tolerate hypoxemia for periods up to 30 minutes without noticeable injury. In the chronic ambulatory setting as well, hypoxemia may be tolerated. We know, however, that providing continuous oxygen to patients with COPD and an oxygen saturation of 88% or less (or arterial P_{O_2} ≤55 mm Hg) increases survival,[14] a finding implying that the low oxygen saturation or the consequence of it is harmful. The reasons for this increased survival are not clear but may involve various consequences of low oxygen saturation: (1) polycythemia, (2) hypoxic pulmonary vasoconstriction and increased pulmonary vascular resistance, (3) a reduced oxygen reserve for any interruption in breathing, especially during sleep, and (4) arrhythmias.

Acutely, if low enough, hypoxemia can cause hypoxic end-organ dysfunction and death. The rapidity of the drop may be important, as well as whether someone has developed physiologic adaptations to decreased oxygen, as shown by persons who can exercise at extremely high altitude.[15]

RESPONSE

Oxygen is sensed as the arterial P_{O_2} by the peripheral chemoreceptors, mainly the carotid bodies (and, to a lesser extent, the aortic chemoreceptors) (see Chapter 12). The ventilatory response to hypoxemia is hyperbolic and is activated at very low P_{O_2} levels; it has been likened to an emergency mechanism[16] (Fig. 44.2). In an early study,[16] healthy participants breathing low oxygen concentrations did not hyperventilate until the inspired oxygen concentration dropped to less than 8%. In a more recent study, similar patterns were found.[13] The other feature of the response to hypoxemia is the wide variability among healthy individuals. The response to hypoxemia is blunted in long-term residents at high altitude (see Fig. 44.2). The ventilatory response is also reduced with age and with coincident disease such as diabetes.[17] The ventilatory response is also dependent on the arterial *partial pressure of carbon dioxide* (P_{CO_2}); if the arterial P_{CO_2} is low, the response to hypoxemia is lessened.[18] The sensation of

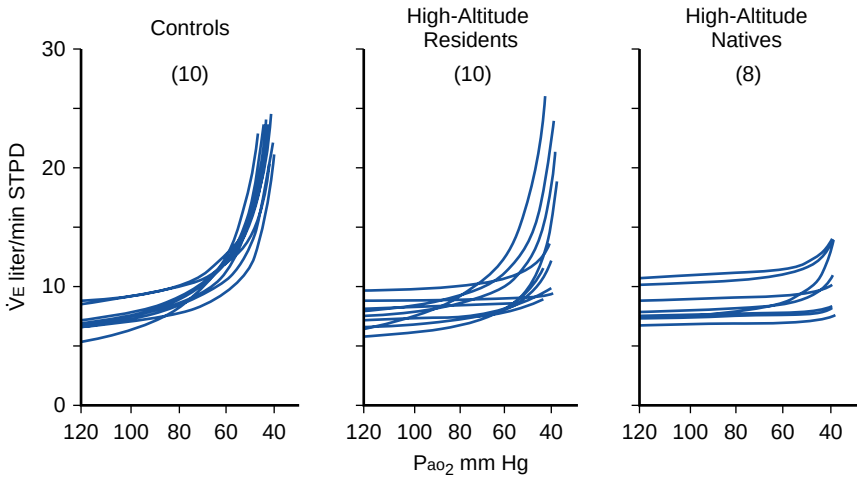

Figure 44.2 Response to hypoxemia in 10 control subjects, 10 who live in high altitude and 8 who are natives of high altitude. The normal response to hypoxemia is activated at low arterial partial pressure of oxygen (Pa_{O_2}) and serves as something of an emergency response to low oxygen tension. The more blunted responses after living at high altitude show that the response can be altered. Interestingly, persons who have lived all their lives at high altitude (Leadville, CO; elevation 3100 m) had almost no response at all. STPD, Standard temperature, standard pressure, and dry; $\dot{V}E$, expired total ventilation. (From Weil JV, Byrne-Quinn E, Sodal IE, Filley GF, Grover RF. Acquired attenuation of chemoreceptor function in chronically hypoxic man at high altitude. *J Clin Invest.* 1971;50:186–195.)

Table 44.1 Hypoventilation Can Cause a Fall in Oxygen Saturation When a Patient Is Breathing Room Air But Not When Receiving Supplemental Oxygen*

	At Room Air		On 2 L/min	
$Paco_2$	Pa_{O_2}	Sa_{O_2}	Pa_{O_2}	Sa_{O_2}
40	80	96	120	100
50	67.5	94	107.5	100
60	55	**88**	95	100
70	42.5	**84**	82.5	96
80	30	**60**	70	95

All values in mm Hg.

*According to the alveolar gas equation, if all else stays constant and the R = 0.8, for every rise in arterial P_{CO_2} of 10 mm Hg, the arterial P_{O_2} will fall by 12.5 mm Hg (see text under Hypoventilation). When the patient is breathing room air, the drop in arterial P_{O_2} will be at the steep portion of the oxyhemoglobin dissociation curve and can be detected as a drop in oxygen saturation (see abnormal saturations in the box); however, when the patient is receiving supplemental oxygen, the same relative fall in oxygen will be on the flat portion of the curve and will not trigger a noticeable fall in oxygen saturation. Thus, the pulse oximeter, by measuring oxygen saturation, cannot detect hypoventilation in a patient receiving supplemental oxygen (see also Fig. 44.1).

Pa_{O_2}, arterial partial pressure of oxygen; Pa_{CO_2}, arterial partial pressure of carbon dioxide; Sa_{O_2}, arterial oxygen saturation.

dyspnea appears to coincide with the initiation of the hypoxemic ventilatory response.[19]

In the recent era, many patients with coronavirus disease 2019 (COVID-19) have been noted to have strikingly low oxygen levels without any sensation of dyspnea. Although this phenomenon has not fully been explained, it is likely that this is a function of the insensitivity and variability described earlier. Older, diabetic patients can be expected to have a depressed ventilatory and dyspneic response to hypoxemia and, even without these factors, certain individuals have a lower sensitivity to hypoxemia as a result of normal variation.[5]

DETECTION

ARTERIAL BLOOD GAS

Obtaining a value for arterial P_{O_2} by analysis of an arterial blood gas is the gold standard for determining oxygenation. With the measures of arterial P_{O_2} and P_{CO_2}, one can calculate the (A–a)P_{O_2}, as a useful assessment of the ability of the lung to oxygenate, and can exclude hypercarbia as a cause of the hypoxemia (see Chapter 10). One can also exclude interference by abnormal hemoglobins (e.g., carboxyhemoglobin, methemoglobin). For the assessment of acid-base and hypercarbia, see Chapters 12 and 45.

NONINVASIVE PULSE OXIMETER

The pulse oximeter enables detection of oxygen saturation. The reader is referred to excellent reviews of the technical aspects and applications of pulse oximetry.[20,21] In general, the technique depends on the detection of absorbance of two wavelengths selected to maximize the ability to distinguish oxyhemoglobin from deoxyhemoglobin and on the ability to separate pulsating (presumably arterial) blood from the background. Thus, without knowing any more, one can see that introduction in the blood of additional materials absorbing at either of these two wavelengths (e.g., carboxyhemoglobin, methemoglobin, methylene blue), interference with absorption (e.g., extraneous light, dark nail polish), or interference with detection of the arterial pulse (e.g., presence of venous pulsations, low cardiac output, an inflated blood pressure cuff) will interfere with the ability of the pulse oximeter to read the arterial saturation. (Pulse oximetry may also be affected by dark skin pigmentation; in a recent report, pulse oximetry was found to be more likely to overestimate oxygen saturation in Black individuals than in white individuals.[21a]) These technical points are important, but additional important errors in interpretation can arise even when the pulse oximeter is reading correctly.

What can go wrong even when the reading is correct? The main clinical problems come from the confounding of saturation with partial pressure. The sigmoid relationship of these two values means that the P_{O_2} can vary significantly without much change in the saturation. This behavior at the upper flat part of the dissociation curve is an advantage biologically because the hemoglobin can stay nearly fully saturated over a range of arterial P_{O_2}, but it means that the pulse oximeter is insensitive to changes in P_{O_2} until a drop in saturation is detectable, often at a P_{O_2} below 60 mm Hg (see Fig. 44.1, room air). Because the rise in P_{CO_2} with hypoventilation is detected *indirectly* by a drop in P_{O_2}, the insensitivity of the

pulse oximeter to changes in P_{O_2} in this range can mean significant delays in detecting hypoventilation.

Importantly, the situation is worse in any patient receiving supplemental oxygen; in this situation, the pulse oximeter loses any ability to detect hypoventilation[22] (Table 44.1). Of all the messages to trainees in this chapter, this may be the most important. Supplemental oxygen moves the arterial P_{O_2} farther up onto the flat portion of the oxyhemoglobin dissociation curve (see Fig. 44.1, at 2 L/min), so that a similar rise in P_{CO_2} and fall in P_{O_2} cannot be detected by a drop in saturation. The inability of pulse oximetry to detect hypoventilation in a patient on supplemental oxygen has mandated the use of other methods to detect arterial P_{CO_2} *directly*, such as by capnography. In addition to pulse oximetry, capnography is now considered standard of care for monitoring during moderate sedation.[23]

A corollary point is worth emphasizing. If the patient does develop hypercarbia during supplemental oxygen administration, the removal of the oxygen, by a well-meaning clinician or by a confused patient, can lead to precipitous and profound hypoxemia (Table 44.2) (see later, under Hypoventilation). Thus, it is wise for the clinician to be aware that hypercarbia can develop silently in the background and, once hypercarbia is present, removal of the supplemental oxygen can be life-threatening. In this setting, prompt efforts to increase ventilation—by reversal of opioids, noninvasive ventilation, or invasive ventilation—are needed.

Table 44.2 The Danger of Undetected Hypoventilation When a Patient Is Receiving Supplemental Oxygen*

	Pao_2	$Paco_2$
Room air	55	50
2 L/min	110	50
2 L/min	97.5	60
2 L/min	85	70
Room air	**30**	70

All values in mm Hg.

*In this patient receiving supplemental oxygen, the arterial P_{CO_2} starts to rise. With each 10 mm Hg rise, the arterial P_{O_2} falls 12.5 mm Hg (see text), although the arterial P_{O_2} (and oxygen saturation, not shown) never falls into a range to trigger the pulse oximeter. At the higher arterial P_{CO_2}, supplemental oxygen becomes a lifeline. The supplemental oxygen in effect allows the arterial P_{CO_2} to rise without detection of a drop in oxygen saturation by the pulse oximeter. Removing the oxygen when the Pa_{CO_2} has risen can lead to a precipitous fall in arterial P_{O_2} (the calculated value of 30).

Pa_{CO_2}, arterial partial pressure of carbon dioxide; *Pa_{O_2}*, arterial partial pressure of oxygen.

At very low oxygen saturations, pulse oximeter readings are not validated, basically because the readings have been determined by calibrating with human volunteers. Understandably, there has not been much calibration of saturations lower than 70% or so. The oximeter has been shown to underestimate the saturation at these low values,[24] a point raised recently in regard to some patients with COVID-19 who have extremely low saturations.

MECHANISMS OF HYPOXEMIA

Mechanisms of hypoxemia can be divided into those resulting from abnormalities of lung function (i.e., low ventilation-perfusion, shunting, and diffusion limitation) and those that do not depend on lung disease (i.e., pure hypoventilation and decreased inspired P_{O_2}) (Table 44.3). (Hypoventilation can, of course, be caused by lung disorders but, in this discussion, we consider hypoventilation as separate from lung disease.) The pathophysiology of these mechanisms is covered in Chapter 10 and in an excellent review.[25] Here we would like to explore their clinical relevance, keeping in mind that the mechanisms rarely exist in isolation. The major mechanisms generating hypoxemia clinically are low ventilation-perfusion, shunt, and hypoventilation. An approach to distinguishing these mechanisms clinically is proposed in Figure 44.3.

MECHANISMS WITH INCREASED ALVEOLAR-ARTERIAL PARTIAL PRESSURE OF OXYGEN DIFFERENCE

As mentioned, the first three mechanisms involve abnormality of the lung, as evidenced by an elevated $(A–a)P_{O_2}$ and venous admixture. Venous admixture is a measure of the amount of mixed venous blood that avoids oxygenation, whether because of low ventilation-perfusion, shunt, or diffusion limitation. With abnormal venous admixture, the mixed venous oxygen saturation contributes to hypoxemia and plays an increasing role as the venous admixture increases (see later).

Low Ventilation-Perfusion

Perfusion to areas with low *ventilation in relation to perfusion* (V/Q) is the most common cause of hypoxemia in clinical practice. Almost all lung diseases can worsen the matching of ventilation to perfusion. In fact, it is important to recall that even the normal lung has V/Q mismatching, leading

Table 44.3 The Five Mechanisms of Hypoxemia and Their Effect on the Alveolar-Arterial Oxygen Tension Difference and Their Response to Moderate Increases in Fractional Concentration of Oxygen in Inspired Gas

Mechanism of Hypoxemia	$(A–a)P_{O_2}$	Response of Arterial P_{O_2} to Increase in F_{IO_2}
Low ventilation-perfusion	Increased	Improves
Shunt	Increased	Minimal improvement
Diffusion limitation	Increased	Improves
Hypercarbia	Normal	Improves
Decreased P_{IO_2}	Normal	Improves

$(A–a)P_{O_2}$, alveolar-arterial partial pressure of oxygen difference; F_{IO_2}, fractional concentration of oxygen in inspired gas; P_{IO_2}, partial pressure of inspired oxygen; P_{O_2}, partial pressure of oxygen.

Modified from Petersson J, Glenny RW. Gas exchange and ventilation-perfusion relationships in the lung. *Eur Respir J.* 2014;44:1023-1041.

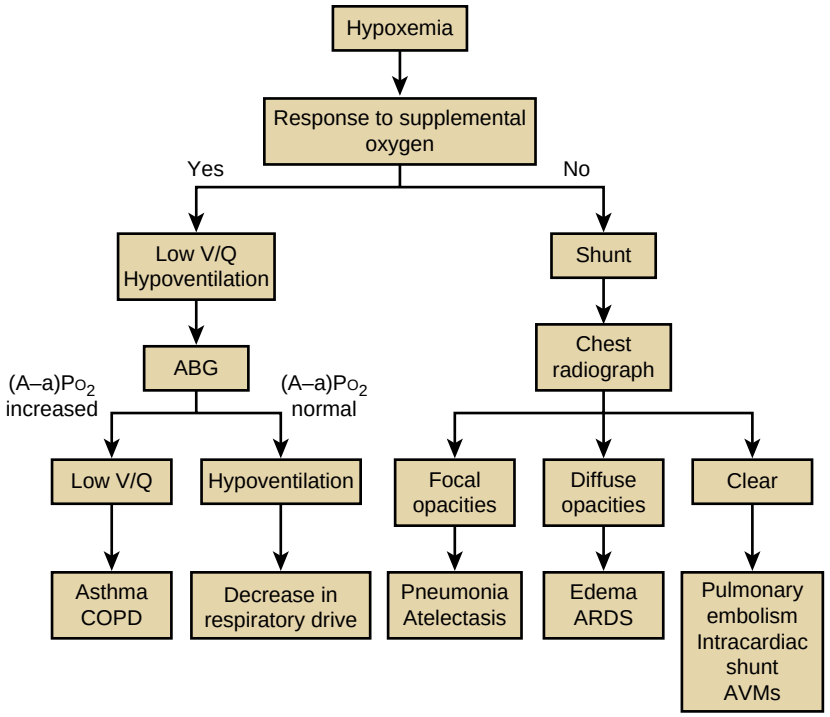

Figure 44.3 A simplified algorithm for distinguishing the major clinical causes of hypoxemia. Clinically, the most important first step is in knowing whether the patient responds well to supplemental oxygen. If the response is good, the likely mechanisms are low ventilation-perfusion (V/Q) or hypoventilation; if so, an arterial blood gas (ABG) determination will be the next step. If the response to oxygen is poor, one is likely dealing with a shunt. Imaging with chest radiography will help determine the likely cause and next steps, recognizing that the chest radiograph is not as sensitive as chest computed tomography. ARDS, acute respiratory distress syndrome; AVMs, arteriovenous malformations.

to variation from top to bottom mainly as a result of the effects of gravity on perfusion (which varies five- to sixfold) and ventilation (which varies three- to fourfold) (see Fig. 10.19). Lower V/Q exists at the base of the normal lung and may be clinically relevant with further decreases in lung volume and poor ventilation of the bases, as in obesity. It is the low V/Q areas that lead to hypoxemia, whereas high V/Q areas have no impact on hypoxemia but impair carbon dioxide elimination. Whenever there are areas in which ventilation is decreased relative to perfusion, as by airway disorders, the alveolar P_{O_2} and the capillary P_{O_2} in that area decrease. A similar low V/Q situation may be created when perfusion is *increased* relative to ventilation, as may happen in conditions such as pulmonary embolism that redirect the pulmonary circulation to other capillary beds.

The best clinical approach to hypoxemia due to the presence of low V/Q areas is to increase inspired oxygen. In those alveoli with at least some ventilation, the increase in P_{IO_2} will raise alveolar P_{O_2} and capillary P_{O_2}, leading to an overall improvement in arterial P_{O_2}. Most of these poorly ventilated alveoli are functioning on the steep portion of the oxyhemoglobin dissociation curve, and small increases in P_{O_2} can cause a large increase in oxygen saturation. Thus, this type of hypoxemia responds to small to moderate amounts of supplemental inspired oxygen. In fact, this response to small amounts of oxygen can be used clinically to identify low V/Q as the likely cause of hypoxemia (see Fig. 44.3).

Shunt

With shunt, mixed venous blood completely bypasses alveoli and is not exposed to alveolar P_{O_2}. The consequences can be profound because no amount of inspired oxygen can reach this shunted blood. A certain degree of shunting is normal; the physiologic shunt from post–pulmonary capillary entry of venous blood into the arterial system from bronchial veins and thebesian veins is estimated at less than 7% of cardiac output. (Measurements of normal physiologic shunt vary by the technique used: 100% oxygen rebreathing detects these shunts, whereas the multiple inert gas technique does not [see later]).

Pathologic shunts can arise from intrapulmonary causes (e.g., complete consolidation resulting from lobar pneumonia or edema, pulmonary arteriovenous malformations) or intracardiac causes (e.g., right-to-left shunts through a patent ductus arteriosus or atrial septal defect). The intrapulmonary shunts can be divided further into two types: (1) those that arise from abnormal lung regions in which alveoli are collapsed or filled with fluid, called *parenchymal shunts;* and (2) those arising from vascular shunts within the lung, as from arteriovenous malformations or dilated pulmonary capillaries, called *vascular lung shunts*.[26] The value in dividing the intrapulmonary shunts into these two categories is that they act differently with regard to contrast echocardiography: the parenchymal shunt does not have the dilated abnormal vessels that allow bubbles to pass, whereas the vascular shunt does. Other differences have been described.[26] However, all types of shunt have a similar oxygenation defect in that the mixed venous blood flowing through the shunt fails to be oxygenated and dilutes and depresses the overall arterial oxygen saturation.

As shunt increases, the arterial P_{O_2} becomes less responsive to increases of F_{IO_2} (Fig. 44.4). In a patient with a large shunt, the main viable strategy for increasing arterial P_{O_2} is to decrease the shunt. In Figure 44.4, this would mean moving from one shunt line to one above it, which would increase the P_{O_2} at the same F_{IO_2}. Means of decreasing shunt include *positive end-expiratory pressure* (PEEP) and moving the patient to a prone position, called proning. Once the shunt has been reduced as much as possible, the other major strategy for improving arterial oxygenation is to elevate the oxygen saturation of mixed venous blood (see later).

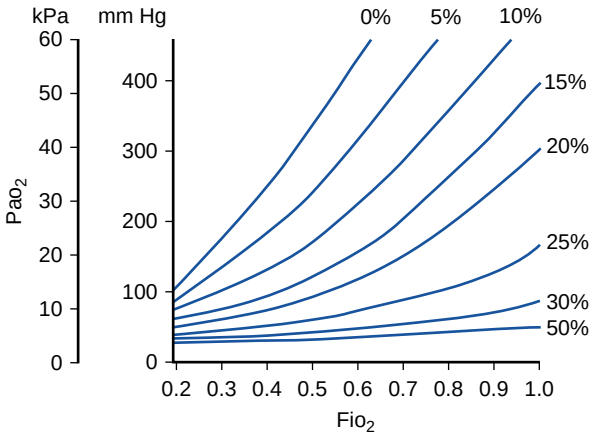

Figure 44.4 The iso-shunt diagram showing the relationship between fractional concentration of oxygen in inspired gas and arterial partial pressure of oxygen at different levels of shunt. With increasing shunt, the slope of the change in arterial partial pressure of oxygen (Pa_{O_2}) becomes increasingly flat so that a high fractional concentration of oxygen in inspired gas (F_{IO_2}) has little effect on arterial P_{O_2}. For shunts greater than 25% of cardiac output, even a fractional concentration of oxygen in inspired gas of 1.0 fails to raise the arterial P_{O_2} higher than 100 mm Hg. (From Petersson J, Glenny RW. Gas exchange and ventilation-perfusion relationships in the lung. *Eur Respir J.* 2014;44:1023-1041.)

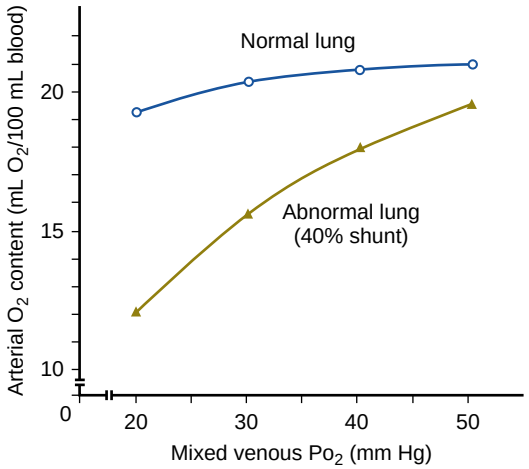

Figure 44.5 Effect of changes in mixed venous partial pressure of oxygen on arterial oxygen content in a normal lung and a lung with a 40% shunt. In this model, the mixed venous partial pressure of oxygen (P_{O_2}) was allowed to vary while the cardiac output and minute ventilation were held constant. In the normal lung, the arterial oxygen (O_2) content changes little over the range of mixed venous P_{O_2}. With a 40% shunt, the arterial oxygen content becomes more sensitive to mixed venous P_{O_2} levels. (From Dantzker DR. Gas exchange in acute lung injury. In: Wiedemann HP, Matthay MA, Matthay RA, eds. *Critical Care Clinics: Acute Lung Injury.* Philadelphia: Saunders;1986:527-536.)

Diffusion Limitation

Diffusion limitation manifests when pulmonary capillary blood does not fully equilibrate with alveolar oxygen. This lack of equilibration means that there is some venous admixture, with some portion of the mixed venous blood reaching the arterial side. In the normal setting (see Fig. 10.16), capillary blood equilibrates fully and with a large reserve capacity. In certain circumstances, there is insufficient time for equilibration, generally when the capillary transit time is reduced, as with loss of capillaries in disease or with extreme exercise; when the alveolar P_{O_2} is low, as in high altitude; or when the mixed venous P_{O_2} is low, thereby increasing the gradient for diffusion.[27] Often, more than one mechanism is involved.

Mixed Venous Oxygen

Although not included as a direct mechanism of hypoxemia, a low mixed venous P_{O_2} is an important contributing mechanism when there is venous admixture. With venous admixture, in which some mixed venous blood reaches the arterial blood, a low mixed venous P_{O_2} can have a large effect on decreasing the arterial P_{O_2}. (Venous admixture is calculated as the amount of mixed venous blood that would have to be added to the postcapillary blood to achieve the observed arterial P_{O_2}). In the three mechanisms described earlier, the mixed venous blood that is not oxygenated drags down the P_{O_2} and oxygen saturation of the arterial blood. The mixed venous oxygen can significantly affect the arterial P_{O_2} even if the V/Q relationships are unchanged or improve (as often seen with exercise). The degree of its effect depends on the P_{O_2} of the mixed venous blood and the amount of venous admixture (Fig. 44.5). The role of mixed venous P_{O_2} in determining the arterial P_{O_2} is a reminder that decreases in arterial P_{O_2} may reflect systemic changes, such as increased muscle activity or dips in cardiac output, instead of decreases in lung function.[29]

MECHANISMS WITH NORMAL ALVEOLAR-ARTERIAL PARTIAL PRESSURE OF OXYGEN DIFFERENCE

The last two mechanisms of hypoxemia do not depend on an abnormality in the lung itself. Neither mechanism requires an increase in the $(A–a)P_{O_2}$ or an increase in venous admixture.

Hypoventilation (see Chapters 45 and 132)

With a decrease in ventilation, there is a reduction in alveolar P_{O_2}. Using the alveolar gas equation, one can calculate the change in P_{O_2} from the change in P_{CO_2} during pure hypoventilation or hyperventilation (i.e., without a change in venous admixture). In general, if the other factors of the alveolar gas equation remain constant (e.g., barometric pressure, F_{IO_2}, the $(A–a)P_{O_2}$), the change in P_{O_2} is reflected by a change (Δ) in P_{CO_2}, as follows: $\Delta P_{O_2} = -\Delta P_{CO_2}/R$. If the R is assumed to be 0.8, the equation can be written so that a change in P_{O_2} is equal but opposite to the change in $P_{CO_2} \times 1.25$. Thus, when all factors mentioned are constant, if the P_{CO_2} goes up by 10 mm Hg, the P_{O_2} goes down by 12.5 mm Hg (see also Fig. 132.2). This shortcut is used in Tables 44.1 and 44.2 to model the effect of changes in arterial P_{CO_2} on arterial P_{O_2}.

As mentioned, supplemental oxygen can be given but, if the carbon dioxide should rise further, the patient will become increasingly dependent on the added inspired oxygen. As described in Chapters 45 and 132, an increase in inspired oxygen may lead to a rise in carbon dioxide because of a blunting of hypoxic pulmonary vasoconstriction that increases the inefficiency of ventilation, an overall decrease in ventilation, or the Haldane effect (in which oxygen decreases the affinity of hemoglobin for carbon dioxide).[30] If, by whatever mechanism, the P_{CO_2} does rise, removal of

the supplemental oxygen can lead to a sudden and profound drop in P_{O_2} (see Table 44.2). Thus, once the P_{CO_2} starts to rise, the patient increasingly needs the higher F_{IO_2} to maintain arterial P_{O_2}. The clinical response to this problem is not to remove the oxygen, but to increase ventilation.

Low Inspired Partial Pressure of Oxygen

A low inspired P_{O_2} and thus a low alveolar P_{O_2} will lead to a decrease in diffusion of oxygen and a lower arterial P_{O_2}. This situation is usually an issue at high altitude, where the inspired P_{O_2} decreases significantly (see Table 105.1). However, at sea level, this situation can be created by the displacement of oxygen by other gases, such as nitrogen[31] or helium, accidentally or by intention. In addition, inspired P_{O_2} can drop and hypoxemia can develop when an increase in ventilation by a spontaneously breathing patient receiving supplemental oxygen leads to increased entrainment of room air.

MECHANISMS ACCOUNTING OF HYPOXEMIA IN RESPIRATORY DISEASES AND CONDITIONS

For most of the studies described in this section, the *multiple inert gas elimination technique* (MIGET) was essential in unraveling the various mechanisms of hypoxemia. Until the development of the MIGET, gas exchange abnormalities were of necessity lumped into three compartments of shunt, ideal, and dead space. This three-compartment model, as initially described by Riley, was a useful construct of gas exchange abnormalities,[32] but it was not possible to separate the presence of low V/Q units from shunt in determining the causes of hypoxemia. The MIGET, developed by Peter Wagner and colleagues in 1974,[33] enabled an almost continuous measurement of the V/Q ratios of the lung, thereby expanding the three compartments to almost 50. In effect, the black box of the lung could be illuminated by measuring how six inert gases with different solubilities were eliminated from the blood and then using computers to model those findings over the range of possible V/Q. The MIGET could also show whether shunt and V/Q abnormalities could fully explain the arterial P_{O_2} and, if not, could identify the residual contribution as due to diffusion limitation, the third possible cause of hypoxemia in an abnormal lung. The major limitation of MIGET is that it cannot localize the abnormalities in the lung. Newer techniques have been developed to visualize the heterogeneity of the diseased lung.[34] In the meantime, V/Q scanning has added some insights into the location of the abnormalities, as described later.

Of note, in the MIGET, healthy individuals have no calculated shunt.[33] Thus, this technique does not measure physiologic shunting from the bronchial and thebesian vessels, and any shunt measured by the MIGET is considered abnormal. The V/Q ratio considered to be low is usually less than 0.1.

PNEUMONIA

The mechanisms of hypoxemia in pneumonia involve an increase in perfusion both to shunt and to low V/Q units. In one study, the MIGET was used in patients with pneumonia of different severity.[35] In the 13 patients with mild to moderate hypoxemia who were spontaneously breathing (arterial P_{O_2} 74 ± 6 mm Hg), there was an increase in the percentage of blood flow to shunt (7.5 ± 1.8%) and to low V/Q regions (4.2 ± 1.0%). These were shown to be sufficient to explain mild hypoxemia. In the same study, in 10 patients with severe pneumonia requiring mechanical ventilation and an elevated F_{IO_2} (0.46 ± 0.04), the percentage of blood going to shunt and to low V/Q regions was more than twice as high as in those patients with milder pneumonia (shunt, 21.9 ± 4.5%; low V/Q, 10.9 ± 4.6%). The likelihood is that, with increasing severity of pneumonia and increasing consolidation, both the shunt fraction and low V/Q areas increase. The response to supplemental oxygen depends on the degree of shunt.

PLEURAL EFFUSION

Pleural effusion can be associated with hypoxemia, generally mild. The effect of thoracentesis on the arterial P_{O_2} is inconsistent; sometimes arterial P_{O_2} increases, does not change, or actually decreases.[36] In one study,[37] MIGET was used in nine patients with effusions, with an arterial P_{O_2} of 82 ± 10 mm Hg, and with an elevated $(A–a)P_{O_2}$ of 29 ± 10 mm Hg. The patients were shown to have a mildly elevated shunt (6.9 ± 6.7%). The increase in shunt with pleural effusions agrees with experimental data.[38] Interestingly, 30 minutes after removal of approximately 700 mL, the arterial P_{O_2}, $(A–a)P_{O_2}$, and shunt did not change significantly; the percentage of blood perfusing low V/Q regions actually increased slightly.[37] Another significant effect of pleural effusion, and one that is not often appreciated, is the effect on cardiac function, mainly on right ventricular filling. Echocardiographic studies have shown that large, mainly right-sided, effusions can have hemodynamic effects similar to that of tamponade[39,40] (see Chapter 14). Hypoxemia in this setting may be explained in part by low cardiac output and low mixed venous P_{O_2} in the setting of venous admixture. The proper approach consists of early recognition and thoracentesis.

PULMONARY EMBOLISM

Although hypoxemia is common in patients with *pulmonary embolism* (PE), it is not universal. In the Urokinase PE Trial, 12% of patients with PE had an arterial P_{O_2} greater than 80 mm Hg, and 5% had arterial P_{O_2} greater than 90 mm Hg. Even massive PE has been described without hypoxemia.[41] In addition, the $(A–a)P_{O_2}$ can be normal in PE. One study reported that, in 3 of 64 patients with PE, the $(A–a)P_{O_2}$ was normal for age.[42] Nonetheless, most patients exhibit hypoxemia.

The mechanism of the hypoxemia of PE has been something of a puzzle. After all, the direct effect of an embolus is to block perfusion to a segment of lung, thereby creating dead space, which would be expected to cause an increase in arterial P_{CO_2}. However, most patients with PE respond to the elevation of P_{CO_2} and to other physical or chemical stimuli produced by the PE with a robust increase in ventilation, and they often present with hypocarbia, not hypercarbia. Nonetheless, it is important to keep in mind that, in patients who are unable to respond to the ventilatory stimulus, as

in those paralyzed on a ventilator, with respiratory depression, or with underlying lung disease, or in those who have extensive pulmonary vascular obstruction, hypercarbia may be seen and should be recognized as a possible clue to a large PE.[43]

The finding of hypoxemia therefore has been somewhat mysterious and was attributed to many causes until the advent of the MIGET, which was able to untangle the contribution of low V/Q, shunt, and diffusion limitation. In one of the most comprehensive MIGET studies,[44] seven patients with large PEs were studied, with a pulmonary artery catheter to measure cardiac output and collect mixed venous blood. The patients were studied from 1 to 9 days after the PEs, which were large enough to occlude 35–65% of the pulmonary circulation. The mean arterial P_{O_2} was 67 ± 11 mm Hg (with all patients on room air except for two on F_{IO_2} 0.3), and the P_{CO_2} was 30 ± 4 mm Hg. In the patients studied soon after the PE, the major oxygenation defect was an increase in perfusion to low V/Q units, without shunt. In the patients studied later, who at that time had opacities or atelectasis on chest radiographs, shunt had developed (from 3–17%). Nonetheless, the abnormalities identified were not large and, by themselves, were not thought sufficient to account for all the hypoxemia. The additional contribution was attributed to a low mixed venous P_{O_2} of 27 ± 5 mm Hg, associated with a depressed cardiac index (2.8 ± 0.9 L/min/m^2). These investigators proposed that the low V/Q was created by redirection of perfusion to nonobstructed units, creating low V/Q areas by an increase in perfusion, although a decrease in ventilation from bronchoconstriction could also have participated. The shunt was seen when opacities or atelectasis appeared, likely reflecting the loss of surfactant. In addition, in the setting of the venous admixture caused by perfusion to low V/Q and shunt, mixed venous P_{O_2} became an important determinant of the arterial P_{O_2}, as also emphasized in other studies.[45] Diffusion limitation was not found. As expected, dead space ventilation had doubled (from the calculated normal in these patients of 27% to an elevated 52%), but the ventilation had increased significantly (to 18 ± 7 L/min), thus accounting for the hypocarbia seen. Other studies, using MIGET in dogs with experimental emboli[46,47] and using quantitative V/Q scans in patients with PE,[48] have provided supporting evidence of the role of overperfusion of nonoccluded areas in generating low V/Q areas and hypoxemia in PE.

All the studies mentioned were in humans or animals with no known lung disease. In those with preexisting lung disease, the impact of PE is less well studied but likely to be more harmful. A presentation with severe hypoxemia also raises the possibility of an intracardiac shunt. Elevated pulmonary resistance and right-sided pressures can open a *patent foramen ovale* (PFO), leading to right-to-left shunting. A PFO can be identified in 9–24% of individuals.[49–51] Case reports have emphasized how a patient with PE can present with or develop profound hypoxemia resistant to increases in F_{IO_2}, thereby leading to consideration of a PFO.[52–54] In these reports, efforts were directed to decrease pulmonary artery pressures by using inhaled nitric oxide, lytic agents, or surgical embolectomy. It is possible that, given the high prevalence of PFO, contribution by intracardiac shunting may also be a factor in less dramatic cases.

PNEUMOTHORAX

Hypoxemia is a common finding in pneumothorax, but the mechanism is still not well understood. In a study reported before the era of MIGET,[55] 12 patients were investigated. Nine of these patients had a P_{O_2} less than 80 mm Hg. In this study, the investigators estimated that the main mechanism of hypoxemia was shunt, which ranged from 2–27% and appeared to increase with the size of the pneumothorax.

ASTHMA OR COPD

Hypoxemia in these common airway diseases is mainly the result of low V/Q units. In asthma, hypoxemia is common,[56] and it can persist for up to 1 week or more after an acute attack.[57] As expected, the mild to moderate hypoxemia is usually responsive to small amounts of supplemental oxygen. In asthma, interestingly, the V/Q abnormalities do not correlate well with abnormalities in *forced expiratory volume in 1 second* (FEV_1), thus raising the suggestion that the low V/Q units are caused by abnormalities in small airways (e.g., resulting from mucus plugging), whereas the low FEV_1 reflects abnormalities in the medium to large airways (e.g., resulting from bronchoconstriction).[58,59] As support for this idea, bronchodilator therapy can improve the FEV_1 without improving the V/Q, which can stay the same or even worsen.[58,60]

In COPD, three different patterns of V/Q disturbance have been described[61] (see Chapter 10 and Fig. 10.21). Type A had predominantly high V/Q units, consistent with an emphysematous pattern and little if any hypoxemia. Type B, however, had increased perfusion to low V/Q units, most consistent with a chronic bronchitis pattern, and with significant hypoxemia. The third pattern had features of both types A and B. No shunt or diffusion abnormality was found, thus addressing controversies long held about the gas exchange abnormalities in COPD, especially because of the decreased single-breath diffusing capacity for carbon monoxide. As in asthma, the low V/Q did not correlate closely with the degree of airway obstruction.[62]

Even at rest, mixed venous P_{O_2} can have a large role on the arterial P_{O_2} in patients with COPD,[63] an effect that can be exacerbated with exercise[64] (see later). With exacerbations, gas exchange worsens, with increasing hypoxemia resulting from an increase in perfusion to low V/Q units in addition to a reduction in the mixed venous P_{O_2}, primarily because of the increased work of the respiratory muscles.[65] Hypoventilation also depresses arterial P_{O_2} and should be considered as a possible mechanism for hypoxemia in patients with COPD. Again, no diffusion limitation has been identified.

INTERSTITIAL LUNG DISEASE OR IDIOPATHIC PULMONARY FIBROSIS

Hypoxemia in interstitial lung disease appears to be primarily the result of perfusion to low V/Q units, at least at rest. Although the restriction in the vascular bed reduces the transit time of erythrocytes through the capillaries, there is minimal to no diffusion limitation at rest. With exercise, the V/Q abnormalities do not change significantly, and the drop

in arterial P_{O_2} is caused by both a drop in mixed venous P_{O_2} and a diffusion limitation created by the rapid transit and inability to recruit additional vessels.[28,66,67] This is one of the few lung diseases in which a diffusion limitation can be demonstrated at sea level.[68] The decrease in oxygenation with exercise is a reasonable marker of severity of disease.

ACUTE RESPIRATORY DISTRESS SYNDROME

In contrast to the conditions already discussed, *acute respiratory distress syndrome* (ARDS) is characterized by a large shunt. In an early MIGET study of ARDS,[69] 16 patients were shown to have shunt along with very low V/Q areas as a cause of the profound hypoxemia; only 52% of the cardiac output flowed to areas with normal V/Q. No diffusion limitation was present. The well-known consequence of this is that increases in inspired oxygen have little effect on the hypoxemia. Instead, the goal must be to decrease the shunt (see Fig. 44.4). In this same study, the effect of PEEP was studied, and PEEP was found to improve oxygenation by decreasing shunt. Later studies have confirmed these early findings.[70]

PEEP decreases shunt by opening and maintaining alveoli open, thereby transforming areas of shunt into areas with access to at least some ventilation (see Chapter 135). Other maneuvers, such as improving perfusion of ventilated areas by using inhaled vasodilators or decreasing perfusion to unventilated regions by using pulmonary vasoconstrictors, have been attempted to decrease shunting. Prone positioning often improves oxygenation (see later).

OBESITY

Hypoxemia is common in morbidly obese patients, and it is thought to result from the lower lung volumes and increased closing volume interfering with ventilation of the lung bases (see Chapters 10 and 131). One review[71] reported that the arterial P_{O_2} of 768 patients with an average body mass index of 48 kg/m^2 was 81 mm Hg (range, 50 to 95 mm Hg). With every 5 to 6 kg of weight loss, the arterial P_{O_2} rose by 1 mm Hg. In a study of 19 morbidly obese women (body mass index 45 kg/m^2), the average arterial P_{O_2} was 76 ± 2 mm Hg; when these women were studied again after bariatric surgery, with a drop in body mass index to 31 kg/m^2, the arterial P_{O_2} rose to 89 ± 2 mm Hg.[72] The MIGET identified a small shunt (4.3 ± 1.1%) and low V/Q areas as the major abnormalities, with improvement in both with weight loss. Interestingly, an earlier study using radioactive tracers for perfusion and ventilation showed that, in upright obese individuals with a low expiratory reserve volume, the ventilation tracer was reduced to the lower lobes, whereas the perfusion tracer was distributed predominantly to the lower lobes. Thus, it could be seen that the base of the lung of the upright obese person was an area of low V/Q or shunt.[73]

HEPATOPULMONARY SYNDROME

Hepatopulmonary syndrome is defined by an increased (A–a)P_{O_2} in the setting of advanced liver disease or portal hypertension, and its severity is based on the level of arterial P_{O_2} (see Chapter 126).[74] Pulse oximetry has been shown to be insensitive, so arterial blood gas analysis is needed to assess oxygenation.[75] The syndrome appears to involve primarily a loss of vasoregulation of pulmonary and systemic vasculature, with pulmonary capillary and precapillary dilation (see Fig. 126.1 and eFigs. 126.1 and 126.2). The role of vasoactivity is supported by the reversibility of abnormalities in V/Q and shunt with liver transplantation.[76]

The causes of the hypoxemia have been difficult to pin down, and all three mechanisms of the abnormal lung—low V/Q, shunt, and diffusion limitation—may participate and may vary with severity of disease. One source of confusion is that patients often have evidence of vascular shunting because of the transit of bubbles in contrast echocardiography, and yet they can respond to supplemental oxygen, which is not consistent with true shunt.

Low V/Q, most investigators agree, is the major mechanism of hypoxemia. This would explain the frequent response to supplemental oxygen. In patients with orthodeoxia, V/Q abnormalities have been shown to worsen with the upright position, because of increased perfusion at the bases.[77,78] In one MIGET study of patients with cirrhosis and a normal arterial P_{O_2}, increased perfusion of low V/Q units was confirmed.[79]

Diffusion limitation may contribute to hypoxemia. Due to both the vasodilation in certain areas and the high cardiac output seen with cirrhosis, the transit time of erythrocytes is reduced, and the distance from the alveolar gas to the erythrocytes, which tend to localize in the center of the flow in the dilated capillaries, is increased. MIGET studies have neither confirmed nor excluded this possibility.[78] A diffusion limitation would also be consistent with the response to oxygen in many patients.

Shunt may also be a feature, especially in patients with more severe hypoxemia. In a MIGET study of cirrhotic patients with severe hypoxemia (arterial P_{O_2} between 35 and 67 mm Hg upright), the major abnormality described was shunt.[78] Shunt is certainly suggested by the passage of bubbles or macroaggregated albumin through the lung but, even in these patients, there may be a response to 100% oxygen. This finding suggests that, at high inspired oxygen, the shunt can behave more like an area of low V/Q or diffusion limitation. Support for this concept has come from studies in which shunt measured by two methods was found to give different results. In one study of eight patients with hepatopulmonary syndrome and hypoxemia (arterial P_{O_2} 61.5 ± 4.5 mm Hg), the average shunt fraction measured by the transit of macroaggregates of technetium-99m–labeled albumin was 32%; however, the shunt fraction measured by the standard 100% oxygen technique was only 19%.[80] This finding indicated that there was some response to the 100% oxygen, thus reducing the calculation of shunt. There was heterogeneity, however; in some patients with cirrhosis, the shunt measurements were similar whereas, in others, they were quite different. Such variation suggests that the dilated vessels may differ either in size or location and may create either a pure shunt unresponsive to high F_{IO_2} or more of a low V/Q or diffusion limitation that can be overcome by high F_{IO_2}. This response to oxygen in areas thought to have shunt was also described in a patient with pulmonary telangiectasias; in this patient, the response to 100% oxygen led to an underestimation of shunt, when compared with the shunt measured by radionuclide

studies.[81] Thus, in patients with either hepatopulmonary syndrome or telangiectasias, there may be a shunt-like mechanism of hypoxemia, in which vascular shunts can be detected by the transit of large particles through the lung, but they can also act as an area of low V/Q or diffusion limitation when they respond to high F_{IO_2}.[81]

CORONAVIRUS DISEASE 2019

The novel coronavirus, severe acute respiratory syndrome coronavirus type 2, which causes COVID-19, can induce significant hypoxemia, sometimes without dyspnea or other respiratory symptoms. This can be a striking presentation, and it has been addressed recently by Tobin and colleagues.[5] The possible reasons for the lack of dyspnea in at least some patients include the following: (1) an insensitivity of the hypoxemic ventilatory response until arterial P_{O_2} drops to quite low values (see Fig. 44.2), (2) the large variability in response seen, even among healthy individuals, (3) the decrease of this ventilatory or dyspnea response with age and with diabetes, and (4) the blunting of the ventilatory response if the arterial P_{CO_2} is also low.

So, what is the cause of the hypoxemia? The reasons for the hypoxemia are currently unknown, and no MIGET study has yet been carried out. Clearly, shunt is a large component. It has been estimated at 50%, although the average fraction of consolidated lung is much less, at only 17%. This ratio of the degree of shunt to the apparent lung consolidation (approximately 3) is greater than that of ARDS (approximately 1.25).[82] The virus may cause pulmonary vasodilation in the nonaerated lung, either by a direct effect on the vessels or by an indirect interference with hypoxic pulmonary vasoconstriction. PEs may also develop[83] and redirect blood to poorly aerated regions. Suggestions have been put forward that there is pulmonary vasodilation seen on dual-energy computed tomography scanning[84] and that there is increased transit of bubbles through the lung[85] although, in a larger study of 60 critically ill patients, transpulmonary shunt was found in only 20% of patients.[86] The response to prone positioning suggests that the shunt behaves similarly to that of ARDS.

APPROACHES TO HYPOXEMIA

INCREASED INSPIRED OXYGEN

The first response of the clinician to hypoxemia is likely to provide supplemental oxygen. The response to that supplemental oxygen will guide the next steps (see Fig. 44.3). Noninvasive oxygen support can be provided from low-flow nasal prongs up to high-flow nasal cannulae (discussed in detail in Chapter 137). When shunts are large, intubation and mechanical ventilation may be necessary to decrease shunt, thus allowing F_{IO_2} to be given at safer levels (e.g., $F_{IO_2} \leq 0.6$) (discussed in Chapters 134 and 135).

LATERAL POSITIONING

Lateral positioning can improve oxygenation in several types of unilateral lung abnormalities, including pneumonia,[87] postthoracotomy status,[88] and pleural effusion.[89] In a study of nine patients with atelectasis or opacities in one lung, the lateral "good lung down" position led to increases of arterial P_{O_2} from an average of 67 mm Hg in the supine position to 106 mm Hg.[87] The positional effect resolved when the underlying unilateral abnormality resolved. In nine patients with unilateral pleural effusions, the arterial P_{O_2} rose from 66.7 to 71.9 mm Hg when the patient was moved from the effusion side down to the normal side down.[89] The general conclusion of these studies is that having the normal lung down can increase arterial P_{O_2}, presumably because of an increase in perfusion to better-ventilated areas. Few studies using MIGET have been applied to study this question: in one MIGET study of four patients undergoing mechanical ventilation with respiratory failure and unilateral opacities (three postoperative), improvements with the good lung down were the result of improved V/Q matching or decreased shunt, or both.[90]

PRONING

For patients with ARDS, the prone position increases the arterial P_{O_2}, which remains elevated while the patient is prone (see also Chapters 133 to 135 and Fig. 134.7). Given that hypoxemia in patients with ARDS is predominantly the result of shunting, it has long been assumed that the prone position reduces shunt. Indeed, in one study using MIGET, patients with ARDS who responded to proning demonstrated a decrease in shunt of 11 ± 5%, whereas patients who did not respond had no change in shunt.[90a] How is this accomplished? Most studies of patients and of animal models point to the following key benefits of the prone position: (1) a more even ventilation of the lung, with the sternum fixed and stiffened against the bed, with less compression by the heart on the left lower lobe, and with less effect of abdominal pressure; in combination with (2) a more even perfusion of the lung,[91] with continued perfusion of the dorsal region even in the prone position as a result of inherent geometric or other structural reasons[92] (Fig. 44.6). Novel imaging studies have confirmed that ventilation and perfusion are more evenly distributed, with less heterogeneity in the prone position (Fig. 44.6). The reasons for this are complicated but many studies concur that, in the prone position, there is a reduction in low V/Q areas and in shunt.[93] Although the reasons for the mortality benefit in patients with ARDS are not known, improved survival may not be related to the improved arterial P_{O_2} or lower F_{IO_2} but rather to the improved pulmonary mechanics.[93]

IMPROVING MIXED VENOUS PARTIAL PRESSURE OF OXYGEN

When efforts to improve V/Q matching and decrease shunt have been maximized, there is still another strategy to improve hypoxemia, that is, by improving mixed venous P_{O_2}.[95] The greater the venous admixture, the more benefit any improvement of mixed venous P_{O_2} will have on the arterial P_{O_2}. Options to improve mixed venous P_{O_2} are either to increase oxygen delivery (e.g., improve cardiac output, increase hematocrit) or to decrease oxygen utilization (e.g., sedate, paralyze, or cool the patient). As was pointed out, in settings of a large venous admixture,

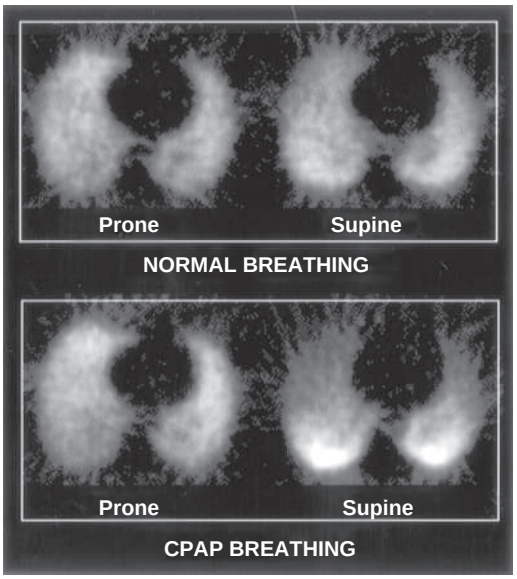

Figure 44.6 Images of single-photon emission computed tomography showing perfusion in prone and supine positions. This volunteer with healthy lungs lay supine or prone during infusion of macroaggregates of technetium-99m designed to lodge in the pulmonary capillaries. Then the subject was imaged in the supine position to detect where the macroaggregates had distributed. The image shows the heterogeneous perfusion of the lung in the supine position (normal breathing) that became more obvious during continuous positive airway pressure (CPAP) breathing. The perfusion was more homogeneous when the subject was in the prone position. (From Nyren S, Mure M, Jacobsson H, Larsson SA, Lindahl SG. Pulmonary perfusion is more uniform in the prone than in the supine position: scintigraphy in healthy humans. *J Applied Physiol.* 1999;86:1135-1141.)

sudden drops in arterial P_{O_2} may most likely be caused by sudden drops in mixed venous P_{O_2}.[29,95]

In patients with anemia, transfusion could be expected to improve oxygen delivery, mixed venous P_{O_2} and, in patients with venous admixture, arterial P_{O_2}. However, this has not been a consistent finding. In a study evaluating 29 patients with sepsis who were in the intensive care unit, transfusion of a mean of 1.4 units of packed red blood cells increased the hemoglobin from 8.1 to 9.4 g/dL; however, this increase in hemoglobin was not found to change the mixed venous oxygen saturation, thus indicating that the transfusion was not effective in improving arterial oxygenation.[96] The role of transfusion is still controversial, and may be limited by the high oxygen affinity of stored blood[96a] or may be better targeted, as for example to patients with lower central venous oxygen.[96b] Finally, the ultimate approach to raise the mixed venous P_{O_2} is with extracorporeal membrane oxygenation (see Chapter 138).

POSITIVE END-EXPIRATORY PRESSURE

As described earlier, PEEP has been shown by many studies to decrease shunt. PEEP is extensively discussed in Chapter 135.

Increases in PEEP can paradoxically act to decrease oxygenation.[97] A decrease in oxygenation may be caused by impairment in cardiac output and lowering of mixed venous P_{O_2}, by the redirecting of perfusion from more compliant areas to consolidated areas, by the advent of pneumothorax or other complication, or by the opening of a PFO.[98] Shunting through a PFO has been found in 19.2% of patients with ARDS.[98] The opening of a large PFO would make lowering the pulmonary artery pressures a priority.

CLINICAL TESTS

EXERCISE

Exercise assesses the entire cardiovascular-pulmonary system and reveals abnormalities that may not be evident at rest. In patients with abnormal lungs, exercise may lead to hypoxemia, which is often used as a guide for oxygen therapy. The causes of this hypoxemia have been found to differ by the underlying disease.

In COPD, V/Q matching and shunt do not show consistent changes with exercise, at least in the patients with severe COPD who have been studied. No problems have been identified with diffusion limitation. Instead, two factors appear most important. The mixed venous P_{O_2}, which may be low in these patients even at rest,[63] falls further and is a large contributor to the ultimate fall in arterial oxygen.[64] This reduction, which can be seen in healthy individuals at the onset of exercise,[99] may account for a rapid drop in arterial P_{O_2} with exercise. In addition, hypoventilation may decrease alveolar and arterial P_{O_2}.

In fibrotic lung diseases, there are some similar findings in that the abnormalities in V/Q and shunt have not been shown to change with exercise. Unlike in COPD, hypoventilation is not a factor (at least until the fibrotic or restrictive disease is at the end stage). However, the fall in mixed venous P_{O_2} is an important factor. As mentioned, there is also evidence that a diffusion limitation contributes in that the diffusion of oxygen is not complete across the blood-gas barrier during exercise.[100]

CONTRAST ECHOCARDIOGRAPHY

Contrast echocardiography is used to evaluate for the presence of vascular shunts, either intracardiac or intrapulmonary (see Chapter 88). The use of a reflective particle, usually an air bubble (~30 μm diameter), allows detection of flow that bypasses the pulmonary capillaries (~7 μm diameter) and reaches the left ventricle.[101] The timing of the appearance may help to distinguish an intracardiac shunt (appearance with fewer than 3 beats) compared with an intrapulmonary vascular shunt (3 to 6 beats), although the accuracy of this distinction has been questioned.[101] This technique would detect the intrapulmonary vascular shunts coming from arteriovenous malformation, hepatopulmonary syndrome and, perhaps, COVID-19. However, it will not detect shunting in many conditions, such as ARDS and pneumonia, in which a normal pulmonary vasculature is supplying collapsed or fluid-filled alveoli, the so-called parenchymal shunting.[26]

BREATHING 100% OXYGEN

Breathing 100% oxygen until the nitrogen has been flushed from the alveoli creates a known alveolar P_{O_2} and enables the shunt to be calculated. With this technique, healthy individuals can be shown to have some

amount of shunt, from less than 8.3%[102] to 9.5%.[103] This may be a slight overestimation because the oxygen may itself create microatelectasis by flushing out the nitrogen or may blunt hypoxic pulmonary vasoconstriction, or because of technical issues, such as tiny leaks. This test should be carried out in a controlled environment such as a pulmonary function laboratory, where any leaks can be scrupulously avoided and the procedure standardized.

As described earlier, the test may underestimate shunt in the setting of arteriovenous malformation, when compared with contrast echocardiography. In a study of patients with hereditary hemorrhagic telangiectasia, 210 patients underwent both contrast echocardiography and 100% oxygen breathing; the 100% oxygen shunt test detected only 51% of patients with arteriovenous malformation.[104] This finding may reflect the ability of oxygen to reach the blood in some of these abnormal vessels, as in the case of hepatopulmonary syndrome, and thus reduce the calculated shunt. Breathing 100% oxygen therefore has limitations when used for calculating intraparenchymal vascular shunts.

SLEEP

Hypoxemia is common during sleep. In healthy individuals, the decrease in ventilation with sleep rarely causes hypoxemia because the oxygen saturation is on the flat portion of the oxyhemoglobin dissociation curve (see Fig. 44.1). However, in persons who have an arterial P_{O_2} close to the steep portion of the curve, sleep, especially rapid eye movement sleep, can lead to a precipitous fall in oxygen saturation (see Chapters 117 and 119). Therefore, the changes during sleep may be of clinical significance for any patient with a lowered arterial P_{O_2}, no matter the underlying cause. Indeed, there may be value in screening patients for hypoxemia during sleep instead of during exercise, as, for example, in patients with COPD who do not meet criteria during wakefulness for supplemental oxygen.

Key Points

- Hypoxemia is generally considered a reduced level of oxygen saturation. It is not the same as hypoxia, which is an inadequate amount of oxygen at the tissues and recognized by elevations in lactate and end-organ ischemia.
- The ventilatory response to hypoxemia is hyperbolic, with a large response only at low arterial partial pressure of oxygen. This is also variable among individuals and reduced with age, thus making the response to hypoxemia insensitive and unpredictable.
- When a patient is receiving supplemental oxygen, the pulse oximeter becomes insensitive to hypoventilation.
- With a patient receiving supplemental oxygen, hypoventilation renders the patient increasingly dependent on the supplied oxygen; its removal can precipitate profound hypoxemia.
- Hypoxemia can be caused by five mechanisms: three are associated with abnormal lungs (low ventilation-perfusion, shunt, diffusion limitation), and two are associated with a low alveolar partial pressure of oxygen (hypoventilation, low inspired fractional concentration of oxygen in inspired gas).
- Hypoxemia in most lung diseases is due to perfusion of low ventilation-perfusion units, either because of decreases in ventilation to perfused units, as in asthma or COPD, or because of increases in perfusion to ventilated areas, as from redistribution of blood due to pulmonary embolism.
- In the initial approach to a patient with hypoxemia, the first step is to give added inspired oxygen; if the patient fails to respond, this likely indicates a major contribution of shunt.
- A large shunt has two clinical consequences: (1) hypoxemia will be resistant to inspired oxygen, and (2) arterial P_{O_2} will become increasingly dependent on the level of mixed venous P_{O_2}.
- Prone positioning acts to decrease shunt by reducing low ventilation-perfusion areas and shunt, by making both ventilation and perfusion more even from top to bottom.

Acknowledgment

We thank Dr. Nirav Bhakta for his careful review and suggestions.

Key Readings

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45 HYPERCAPNIA

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INTRODUCTION

Hypercapnia is defined as a *partial pressure of carbon dioxide in arterial blood* (arterial P_{CO_2}) greater than 45 mm Hg (6.0 kPa) at sea level. The lungs function to move oxygen from the air into the mixed venous blood and eliminate CO_2 from mixed venous blood back into the air. Hypercapnia results when there is a failure of this gas exchange function. Hypercapnia can appear acutely or develop gradually, typically first manifesting during sleep. This chapter discusses the causes of hypercapnia mechanistically, highlighting the complex interplay of the central respiratory controller, effectors, ventilation-perfusion relationship, and sensors in maintaining carbon dioxide homeostasis. Hypercapnia can affect multiple organ systems and timely recognition is important. The clinical manifestations of hypercapnia are discussed, focusing on a diagnostic approach to a patient with suspected hypercapnia. Finally, the chapter outlines an approach to the management of hypercapnia.

NORMAL CARBON DIOXIDE HOMEOSTASIS

Carbon dioxide is a by-product of aerobic cellular metabolism. It is estimated the human body contains 120 L of CO_2 and it is present in all fluids and tissues.[1,2] The partial pressure of carbon dioxide in arterial blood is proportional to the rate of CO_2 production and inversely proportional to the rate of CO_2 elimination as determined by alveolar ventilation. Alveolar ventilation is the component of expired minute ventilation that reaches perfused alveoli to participate in effective gas exchange and is equal to the minute ventilation minus dead space ventilation.

The alveolar ventilation equation:

$$Pa_{CO_2} = \frac{k \bullet \dot{V}_{CO_2}}{\dot{V}_A} = \frac{k \bullet \dot{V}_{CO_2}}{\dot{V}_E \times (1 - V_D/V_T)} = \frac{k \bullet \dot{V}_{CO_2}}{(f)(V_T) \times (1 - V_D/V_T)}$$

where Pa_{CO_2} is arterial P_{CO_2}, K is the proportionality constant, $\dot{V}_{CO_2}$ is CO_2 production (in L/min), $\dot{V}_A$ is alveolar ventilation (in L/min), $\dot{V}_E$ is minute ventilation (in L/min), f is breathing frequency (in breaths/min), V_T is tidal volume (in L), and V_D/V_T is dead space ratio. Normally, under steady-state conditions, the rate of CO_2 production equals CO_2 elimination via the respiratory system to maintain an arterial P_{CO_2} between 35 and 45 mm Hg.

MECHANISMS AND ETIOLOGIES

Mechanistically, hypercapnia results from loss of arterial P_{CO_2} homeostasis caused by:

1. Increased CO_2 production
2. Decreased minute ventilation from disorders of the central respiratory controller or respiratory system effectors
3. Increased dead space ventilation from increased anatomic dead space or ventilation-perfusion mismatch (increased physiologic dead space)

Often multiple mechanisms are involved, especially as hypercapnia progresses.

INCREASED CO_2 PRODUCTION

CO_2 is a product of cellular metabolism and, in adults, approximately 3 to 4 mL/kg/min of CO_2 is produced at rest. CO_2 production can rise with increased levels of activity, hypermetabolic states such as fever (13% increase in arterial P_{CO_2} for every 1°C increase in temperature above normal), thyrotoxicosis, increased catabolism such as sepsis and corticosteroids, metabolic acidosis, and carbohydrate loads or overfeeding.[3-5] Normally, however, ventilation can be increased to offset the increase in CO_2 production and maintain a normal arterial P_{CO_2}. Consequently, increased CO_2 production alone does not typically result in significant hypercapnia unless the individual has impaired ventilatory capacity that limits the ability to augment ventilation. Increased CO_2 production, however, can be a contributing factor to the development of hypercapnia.

DECREASED MINUTE VENTILATION

The respiratory system is a feedback system that consists of a central respiratory controller that processes afferent inputs from various sensors to generate signals to

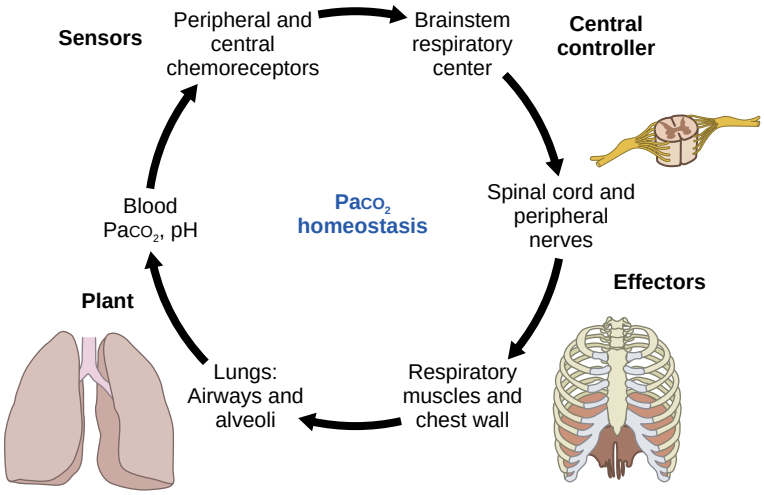

Figure 45.1 Homeostatic regulation of arterial Pco_2. The respiratory feedback system consists of a central respiratory controller that processes afferent inputs from various sensors to generate signals to the effectors of the respiratory system, to maintain tight homeostatic regulation of arterial Pco_2 ($Paco_2$). In a closed-loop system, the plant produces the signal (blood gases) sent to the sensors.

the effectors of the respiratory system, to maintain tight homeostatic regulation of arterial Pco_2 (Fig. 45.1). The central respiratory control center in the medulla and pons of the brainstem generates a respiratory rhythm. In particular, the pre-Botzinger complex in the ventrolateral region of the medulla appears to be crucial for the generation of this intrinsic rhythm. It is influenced by behavioral and cognitive inputs from the cortex. The central respiratory control center receives afferent signals from peripheral chemoreceptors at the carotid artery bifurcation and central chemoreceptors in the brain, close to the ventral surface of the medulla in the caudal region of the retrotrapezoid nucleus, to respond to changes in pH, arterial Pco_2, and arterial Po_2. The central respiratory center also receives input from the lungs and other receptors but, under normal conditions, the arterial Pco_2 is the most important factor in the control of ventilation. Hypercapnia stimulates neural output from the central respiratory control center within the brainstem to the effectors of the respiratory system: motor neurons in the spinal cord, motor nerves, neuromuscular junction, respiratory muscles, and chest wall. The diaphragm is the main muscle of inspiration and is innervated by the phrenic nerve supplied by cervical nerve roots C3 to C5. Contraction of the diaphragm expands the rib cage, causing the pleural and airway pressures to become more negative. Inspiratory airflow is generated resulting in the movement of gas into the lungs where gases can exchange at the alveolar-capillary membrane to eliminate CO_2.

Minute ventilation ($\dot{V}E$) is the product of respiratory rate (f) and tidal volume (VT) and it can be reduced by perturbation anywhere along this axis from the central respiratory control center in the brainstem to the respiratory muscles and chest wall. A reduction in total $\dot{V}E$ with constant CO_2 production and dead space will lead to hypercapnia. Hypercapnia due to reduced minute ventilation can be associated with normal lungs and can mechanistically be divided into disorders of the central respiratory controller or disorders of the respiratory system effectors.

Disorders of the central respiratory controller are characterized by a reduced drive to breathe (i.e., "won't breathe"). Common causes of hypercapnia due to disorders of central respiratory control are outlined in Table 45.1.

Because the brainstem generates respiratory drive, pathologies involving the medulla and pons, such as stroke, encephalitis, neoplasm, and multiple sclerosis, can impair automatic respiratory rhythm and produce specific abnormal patterns of respiration. Medullary lesions have been associated with irregular breathing variable in rate and tidal volume or ataxic breathing, while lesions in the pons can cause sustained deep inspiration followed by brief expiration or apneustic breathing.[6] Similarly, pathologies involving the cerebral cortex can disrupt behavioral input to the control of respiration, thereby leading to hypercapnia.

The pre-Botzinger complex in the brainstem has also been identified as a major site of action mediating the respiratory depressive effects of opioids.[7,8] Opioids have been associated with central depression of the respiratory rate, amplitude, and reflex responses and reduced brain arousability.[8] Various abnormal breathing patterns, including ataxic breathing, Biot's breathing (high-frequency and regular tidal volume breathing interspersed with periods of apnea), Cheyne-Stokes respiration, and both central and obstructive sleep apnea have been described.[8] With the epidemic of opioid use, recognition of opioids and sedatives such as benzodiazepines as a cause for impaired central ventilatory drive and hypercapnia is important.

Congenital central hypoventilation syndrome (CCHS) is a rare disorder characterized by disordered respiratory control and diffuse *autonomic nervous system dysregulation* (ANSD). It is caused by a mutation in the paired-like homeobox 2B (*PHOX2B*) gene, which encodes for a transcription factor that plays a role in the development of the autonomic nervous system and regulation of neural crest cell migration.[9,10] A well-described relationship between *PHOX2B* genotype and CCHS phenotype exists. CCHS is a clinically heterogeneous disorder that can present with a spectrum of severity of hypoventilation and autonomic nervous system dysregulation. Hypoventilation is seen during non-REM sleep but, when more severe, can be present both during wakefulness and sleep. While typically diagnosed in newborns with episodes of cyanosis and apnea, patients can present as old as 35 years with late-onset CCHS, a variable presentation thought to reflect the variable penetrance of *PHOX2B* mutations.[11] Moreover, with advancements in knowledge and treatment, CCHS patients are now

Table 45.1 Causes of Hypercapnia Due to Decreased Minute Ventilation

Mechanism	Etiologies	
Decreased central respiratory drive (won't breathe)	Opioids and sedatives, brainstem and cerebral pathology (e.g., stroke, encephalitis, neoplasm, multiple sclerosis), congenital (e.g., congenital central alveolar hypoventilation), myxedema, metabolic alkalosis, hypothermia, obesity hypoventilation syndrome	
Disorders of the respiratory system effectors (can't breathe)	Spinal cord	Trauma, compressive (e.g., cervical spondylosis, herniated disc), vascular (e.g., infarction or hemorrhage), developmental (e.g., syringomyelia), inflammatory (e.g., transverse myelitis, multiple sclerosis), infectious, neoplasm
	Motor neurons/anterior horn cells	Motor neuron disease, spinal muscular atrophy, poliomyelitis, primary lateral sclerosis, hereditary biochemical, metabolic, toxins (e.g., lead)
	Peripheral nerves	Iatrogenic phrenic nerve injury (e.g., cardiothoracic or neck surgery), hereditary (e.g., Charcot-Marie-Tooth disease), inflammatory (e.g., Guillain-Barré syndrome, neuralgic amyotrophy or Parsonage-Turner syndrome, vasculitides), metabolic (e.g., porphyria, diabetes mellitus), critical-illness polyneuropathy, drugs, and toxins (e.g., organophosphates)
	NM junction	Myasthenia gravis, Lambert-Eaton myasthenic syndrome, botulism, drugs (e.g., paralytics)
	Respiratory muscles	Muscular dystrophies, inflammatory (e.g., polymyositis, dermatomyositis), congenital (e.g., nemaline myopathy), glycogen storage diseases (e.g., Pompe disease, McArdle disease, Tarui disease), mitochondrial myopathies, metabolic, drugs, and toxins (e.g., corticosteroids)
	Chest wall	Kyphoscoliosis, pectus excavatum, thoracoplasty, flail chest, ankylosing spondylitis, fibrothorax, obesity hypoventilation syndrome

surviving into adulthood. *Rapid-onset obesity with hypothalamic dysfunction, hypoventilation, and autonomic dysregulation* (ROHHAD) is another rare disorder that shares clinical similarities with CCHS but is a distinct entity. ROHHAD is characterized by dramatic weight gain, typically between ages 1.5 and 10 years, followed by hypothalamic dysfunction, central alveolar hypoventilation, and ANSD.[12]

Disorders of the respiratory system effectors are characterized by reduced ventilatory supply (i.e., "can't breathe"). Disruption at any level of the efferent arm, from the spinal cord to the muscles of respiration and the chest wall, can diminish minute ventilation causing hypercapnia. Causes of hypercapnia due to failure of the respiratory system effectors can be divided anatomically as shown in Table 45.1. See Chapters 130 and 131 for a more detailed discussion on the respiratory system and neuromuscular disease and chest wall diseases, respectively.

INCREASED DEAD SPACE

Following the movement of gas into the lungs, the arterial P_{CO_2} is ultimately determined by the diffusion of CO_2 from mixed venous blood at the alveolar-capillary membrane into alveolar gas, so-called gas exchange. Not all gas entering and leaving the lungs takes part in gas exchange. Minute ventilation participating in gas exchange is referred to as alveolar ventilation. Dead space ventilation reflects the amount of total ventilation that does not contribute to gas exchange and consists of anatomic and physiologic (or alveolar) dead space. Chapter 10 provides details regarding ventilation, blood flow, and gas exchange.

The anatomic dead space is the volume of gas that fills the conducting airways between the upper airways and terminal bronchioles and does not reach the alveolar-capillary membrane to partake in gas exchange. It is commonly expressed as a ratio of the tidal volume. In normal adults, the anatomic dead space is approximately 150 mL; with a tidal volume of approximately 500 mL, the dead space ratio would be approximately 0.3. An increase in the anatomic dead space can result in hypercapnia even when minute ventilation is maintained. It is commonly seen with any cause of rapid shallow breathing in which the anatomic dead space in the central conducting airways comprises a larger proportion of the smaller tidal volume, increasing the dead space to tidal volume ratio.

Even if gas does reach the alveolar-capillary membrane, effective gas exchange and CO_2 elimination requires the coordinated matching of perfusion with ventilation. CO_2 delivered by perfusion to the alveolar-capillary membrane diffuses into the alveolar gas and is removed from the lungs by ventilation. The partial pressure of oxygen and carbon dioxide in each alveolus is determined by its *ratio of ventilation to perfusion* (V/Q). When considering the simple lung model and one gas exchanging unit, ideally V/Q allows CO_2 and O_2 to be exchanged in a ratio equal to that of total lung CO_2 excretion to O_2 intake (respiratory quotient).[2] If an alveolus receives blood flow but no ventilation, V/Q is zero, O_2 cannot enter and CO_2 cannot leave the alveolus by ventilation, and the alveolar P_{O_2} and alveolar P_{CO_2} will be the same as the mixed venous blood, so-called intrapulmonary, right-to-left shunt. If ventilation is intact but perfusion is absent, V/Q is infinity, O_2 cannot leave and CO_2 cannot enter the alveolus from the blood, and the alveolar P_{O_2} and alveolar P_{CO_2} will be the same as in the conducting airways. Any V/Q ratio between zero and infinity can exist in the lung and will produce a unique alveolar P_{O_2} and alveolar P_{CO_2}. As V/Q increases, alveolar P_{CO_2} falls as ventilation removes more of the delivered CO_2; as V/Q decreases, alveolar P_{CO_2} rises and alveolar P_{O_2} falls.[2] Of note, lungs contain about 500 million alveoli with regional

variations in ventilation and perfusion, leading to a distribution of V/Q ratios even in normal healthy lungs.[13]

Ventilation-perfusion inequality reduces the efficiency of gas exchange of the lungs. Those lung units with high ventilation-perfusion ratios, which are thus inefficient at eliminating CO_2, constitute a physiologic dead space. Increased physiologic dead space or V/Q mismatch is a common cause of hypercapnia. It is typically associated with abnormal lungs and concomitant hypoxemia. Etiologies include disorders of the pulmonary parenchyma, airways, and vasculature.

Ventilatory Supply and Demand

Typically, an increase in dead space stimulates minute ventilation in an attempt to normalize arterial P_{CO_2}. Normally, the available ventilatory supply significantly exceeds ventilatory demand. As a general rule, the maximum spontaneous ventilation that can be maintained without muscle fatigue (the maximum sustainable ventilation)[14] is approximately one-half the maximum voluntary ventilation.[15,16] Consequently, as ventilatory demand increases, the normally large ventilatory reserve means that hypercapnia does not develop unless fatigue of the respiratory muscles develops or there is reduced ventilatory drive to respond to the increased work of breathing.

Specific Diseases

While the causes of hypercapnia can be divided mechanistically as outlined above, more often than not, the hypercapnia observed in a given patient is multifactorial in etiology. This is highlighted in the following discussion of the more common disorders associated with hypercapnia.

COPD is a common, preventable, and treatable disease characterized by persistent respiratory symptoms and airflow limitation (postbronchodilator $FEV_1/FVC < 0.70$) that is due to airway and/or alveolar abnormalities usually caused by significant exposure to noxious particles or gases. Hypercapnia is associated with a poor prognosis in COPD and can be seen both during acute exacerbations and chronically. Multiple mechanisms have been implicated in the development of hypercapnia in COPD, including ventilation-perfusion inequality and abnormalities in ventilatory control, respiratory muscle function, and pattern of breathing, but ventilation-perfusion mismatch predominates.[3] Airflow obstruction, destruction of the alveoli in emphysema, and reduced lung compliance at high lung volumes all contribute to ventilation-perfusion inequality. Hypercapnic COPD patients have been shown to have lower tidal volumes with unchanged or increased respiratory rate, resulting in normal or decreased total ventilation, increased dead space to tidal volume ratio, and ultimately reduced alveolar ventilation.[3] Whereas the work of breathing is increased, hyperinflation and the associated flattening of the diaphragm place this main muscle of inspiration at a mechanical disadvantage. This predisposes patients to fatigue and the development of hypercapnia.

Obesity hypoventilation syndrome (OHS) is characterized by the development of awake daytime hypercapnia in obese individuals (body mass index >30 kg/m^2) in the absence of other known causes of hypoventilation. The risk of developing OHS increases as body mass index increases. Additionally, the degree of hypercapnia seen in OHS appears to increase with weight. All OHS patients are obese but not all obese patients develop daytime hypercapnia. How and why only a subset of patients with obesity develops persistent daytime hypercapnia has been the subject of ongoing research. The mechanism is also thought to be multifactorial and a complex interplay between obesity-related changes in respiratory mechanics, sleep-disordered breathing, changes in central ventilatory drive, neurohormonal changes, and excessive CO_2 production.

Obesity imposes a mechanical load on the respiratory system resulting in reductions in lung volumes. There is a decrease in the functional residual capacity and expiratory reserve volume.[17-19] This is exacerbated in the supine body position where cephalic displacement of the diaphragm further reduces its mechanical efficiency. In addition, obese patients breathe at low lung volumes closer to the residual volume than do other patients. At these low lung volumes, both pulmonary and chest wall compliance are reduced and there is small airway closure, expiratory flow limitation, and air trapping, leading to an additional increase in the work of breathing and pulmonary ventilation-perfusion inequality. The chronic hypercapnia and hypoxemia seen in OHS has also been implicated in contributing to respiratory muscle impairment. With obesity, there is an approximate threefold increase in the work of breathing.[20-23] Normally the increased workload is offset by an increase in respiratory drive, but in OHS this drive is blunted. OHS has been associated with an acquired reduction in ventilatory responsiveness to hypoxia and hypercapnia.[24-26] Leptin resistance may be one mechanism for this reduced central respiratory drive. Leptin is an adipokine that acts on the hypothalamus both to produce satiety and to stimulate ventilation. In humans, a higher level of leptin is seen in obesity and, compared to weight-matched obese controls, even higher levels of leptin have been reported in OHS. As such, leptin resistance, possibly due to decreased CSF penetration, has been implicated in the development of daytime hypoventilation.[27-30]

Obesity is also a key risk factor for sleep-disordered breathing. Approximately 90% of OHS patients will have *obstructive sleep apnea* (OSA), with 70% having severe OSA defined by an apnea-hypopnea index greater than 30 events per hour of sleep. Studies have repeatedly identified severity of OSA as a risk factor for the development of daytime hypercapnia. A failure of compensation for nocturnal hypercapnia by either the lung or kidney has been proposed in OSA patients who go on to develop chronic daytime hypercapnia. Typically, obstructive apneas and hypopneas result in a transient increase in CO_2, but the obstructive respiratory events are usually followed by arousals and augmented ventilation to eliminate the accumulated CO_2 in order to maintain a steady-state arterial P_{CO_2}. Any imbalance between the duration of obstructive respiratory events and compensatory inter-apnea periods may lead to net CO_2 accumulation and daytime hypercapnia.[31-33] Kidney compensation also plays a role. CO_2 retention is partially offset by renal bicarbonate retention; however, if the excretion of bicarbonate is slow, the net retention of bicarbonate can result in further depression of ventilatory responsiveness to CO_2 during wakefulness. Thus, any compromise in the renal compensatory mechanisms may also contribute to the development of daytime hypercapnia.[23,34,35]

Table 45.2 Consequences of Hypercapnia

System	Effect
Cardiovascular	▪ Decreased cardiac contractility ▪ Decreased systemic vascular resistance ▪ Secondary effects due to sympathoadrenal activation ▪ Coronary vasodilation
Respiratory	▪ Rightward shift of oxyhemoglobin dissociation curve ▪ Pulmonary vasoconstriction (mild) ▪ Direct dilation of small airways ▪ Indirect constriction of large airways ▪ Increased lung compliance ▪ Impaired alveolar fluid reabsorption and alveolar epithelial repair[73]
Central nervous system	▪ Cerebral vasodilation and increased cerebral blood flow ▪ Increased intracranial pressure ▪ Increased cerebral oxygenation ▪ Biochemical changes (e.g., increased glutamine) ▪ Stimulation[39]
Metabolic	▪ Intracellular acidosis causing inhibition of glycolysis ▪ Increased renal bicarbonate resorption
Inflammation and Immunity	▪ Inhibition of neutrophil and macrophage migration and adhesion ▪ Decreased secretion of proinflammatory cytokines ▪ Decreased free radical generation

Data from Weinberger SE, Schwartzstein RM, Weiss JW. Hypercapnia. *N Engl J Med*. 321(18):1223–1231, 1989; and Curley GF KB, Laffey JG. Hypocapnia and hypercapnia. In Broaddus VC, Mason RJ, Ernst JD, et al, editors. *Murray & Nadel's Textbook of Respiratory Medicine*, 6 ed. Philadelphia: Elsevier; 2016.

CONSEQUENCES

The effects of hypercapnia vary depending on rate of development, severity, and duration. Hypercapnia leads to acidosis that suppresses most cellular functions affecting multiple organ systems, as summarized in Table 45.2.[35a]

CLINICAL MANIFESTATIONS AND EVALUATION

Given the consequences of hypercapnia, timely recognition of the symptoms and signs of hypercapnia is essential. History and physical examination should be directed at not only the clinical manifestations of hypercapnia but also its underlying cause.

At its most extreme, hypercapnia can present as respiratory failure, coma, and death. Hypercapnia reduces myocardial contractility, which can lead to progressive cardiovascular instability, arrhythmia, and cardiac arrest. At the other end of the spectrum, hypercapnia may be evident only during sleep.

Sleep is associated with changes in ventilation specific to the sleep stage, additionally described in Chapter 117. In healthy individuals, blunting of the drive to breathe, altered ventilatory response to hypoxia and hypercapnia, and increased upper airway resistance result in a decrease in ventilation in both non–rapid eye movement and rapid eye movement sleep when compared to wakefulness.[36] Consequently, there is a small normal physiologic increase in the arterial P_{CO_2} of 4 to 6 mm Hg during sleep. This small increase in arterial P_{CO_2} during sleep is usually of little clinical consequence in healthy individuals; however, in patients with respiratory muscle weakness, altered respiratory mechanics, impaired gas exchange, and/or abnormal ventilatory drive, the patient may be especially likely to develop significant hypercapnia. Nocturnal hypoventilation usually precedes chronic daytime hypercapnia, but the extent to which sleep can elicit and exacerbate hypercapnia is often underappreciated. A detailed sleep history including symptoms of sleep-disordered breathing such as snoring, witnessed apneas, nocturnal gasping and choking, frequent awakenings, morning headaches, and excessive daytime sleepiness should be elicited in any clinical evaluation of hypercapnia.

Hypercapnia can lead to dyspnea and tachypnea, not only due to the underlying cause but also as a result of the initial compensatory increase in respiratory drive induced by the increased levels of arterial P_{CO_2} and associated acidemia. With progressive respiratory muscle fatigue or secondary to an underlying neuromuscular etiology, decreased diaphragmatic excursion and paradoxical thoracoabdominal movements may be seen, best observed supine. In the supine position, most breathing movements are abdominal, whereas in the upright position rib cage motion is greater.[37] Normally, as the diaphragm contracts, the abdominal wall is displaced outward but, as the diaphragm weakens, the fall in pleural pressure produced by contraction of the accessory muscles of inspiration is transmitted across the diaphragm to the abdomen to cause a fall in abdominal pressure and a paradoxical inward displacement of the abdomen.[38] Diaphragmatic fatigue may also cause alternate recruitment and derecruitment of the diaphragm and accessory inspiratory muscles, so that for a few breaths most of the inspiratory motion is abdominal, alternating with inspiratory movements that take place predominantly in the rib cage, so-called *respiratory alternans*.[37] Other symptoms and signs pointing to a neuromuscular disorder may be evident that vary depending on the level, laterality, degree of dysfunction, and associated comorbidities, including obesity. These include but are not limited to orthopnea, dyspnea when immersed in water, positional dyspnea, and difficulties with speech, swallowing, cough, and recurrent lower respiratory tract infections. Hypoventilation is also associated with hypoxemia. Normally, arterial P_{O_2} drops approximately in proportion to the rise in arterial P_{CO_2} as determined by the alveolar gas equation (see Chapter 44). Eventually ventilatory failure will lead to pulmonary hypertension and right heart dysfunction.

Hypercapnia is associated with cerebral vasodilation and increased cerebral blood flow, increased intracranial pressure, and biochemical changes in cerebrospinal fluid that can manifest as confusion, restlessness, asterixis, drowsiness, and loss of consciousness. An acute increase in arterial P_{CO_2}, however, has been shown in healthy volunteers to have *central nervous system* (CNS) stimulating effects, and the progressive CNS depression seen in hypercapnia is thought to be secondary to fatigue, aggravated by acidosis, rather than due to hypercapnia itself.[39] That is, the CNS depression seen in hypercapnia is likely a reflection of the

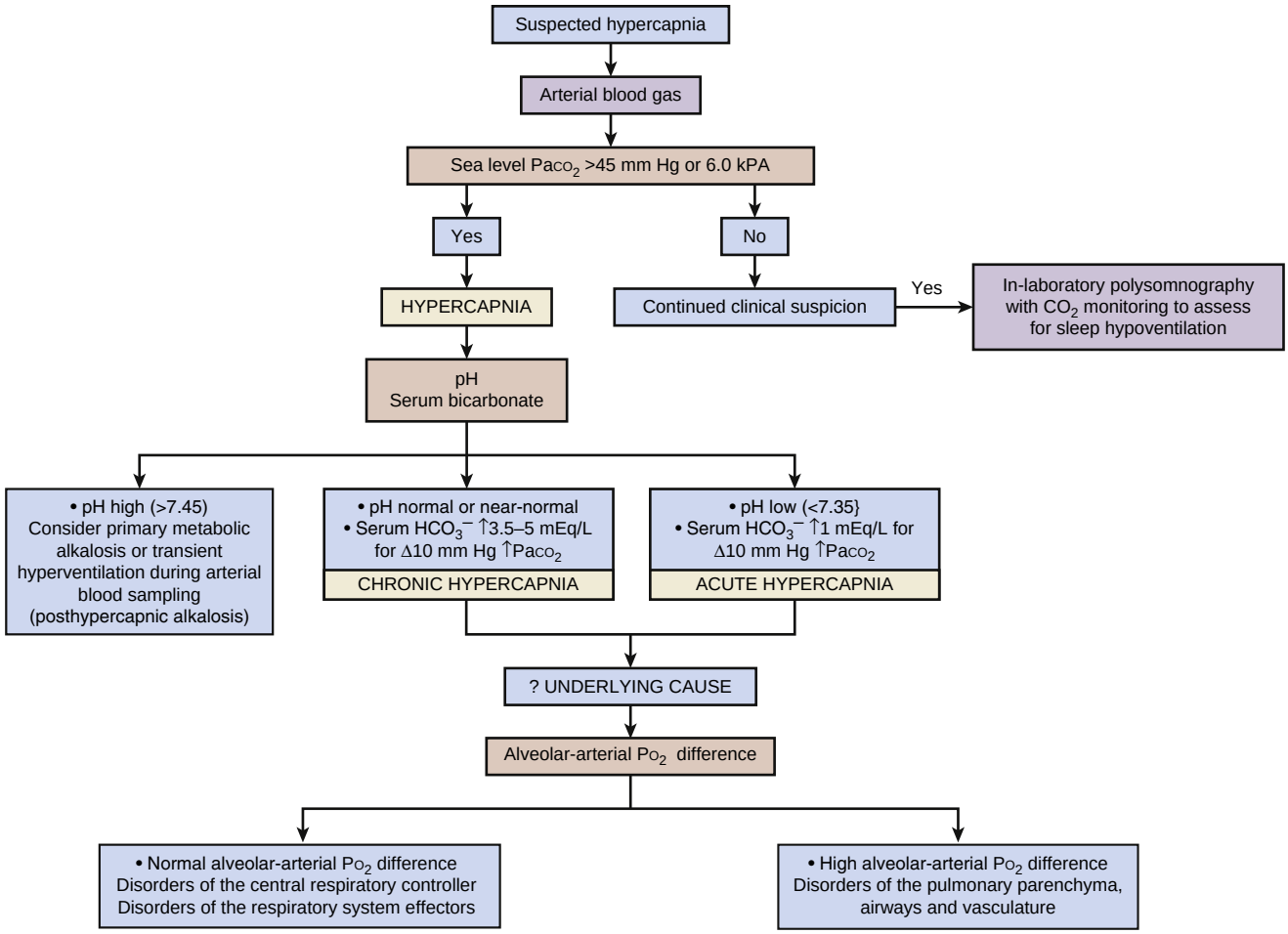

Figure 45.2 Algorithm demonstrating a diagnostic approach to a patient with suspected hypercapnia. PAO_2, alveolar Po_2; PaO_2, arterial Po_2; $PACO_2$, alveolar Pco_2; $Paco_2$, arterial Pco_2.

severity of respiratory failure and exhaustion. Normally, in acute hypercapnia, a depressed level of consciousness is not seen until the arterial Pco_2 is greater than 75 to 80 mm Hg, whereas, in chronic hypercapnia, symptoms and signs may not be evident until the arterial Pco_2 rises acutely to greater than 90 to 100 mm Hg.[5]

DIAGNOSTIC EVALUATION

When hypercapnia is suspected clinically, confirmation with arterial blood gas is required. Subsequent diagnostic testing is directed at finding the underlying etiology and assessing for potential complications and is influenced by the acuity and setting of clinical presentation (Fig. 45.2).

ARTERIAL BLOOD GAS

Arterial blood gas (ABG) allows for direct measurement of pH, arterial Pco_2, and arterial Po_2 and is the gold standard for assessing hypercapnia. The pH electrode measures the potential difference between a known solution within the measuring electrode and the sample solution at 37°C. The arterial Pco_2 electrode measures carbon dioxide tensions by allowing carbon dioxide to undergo a chemical reaction, producing hydrogen ions. The hydrogen ion production causes a potential difference that is measured.[40] The serum bicarbonate HCO_3^- concentration is then calculated by using the Henderson-Hasselbalch equation. The normal pH is 7.35 to 7.45, arterial Pco_2 is 35 to 45 mm Hg (4.7-6.0 kPa), and HCO_3^- is 21 to 27 mEq/L. A common concern is whether the pain or anxiety induced by an arterial puncture leads to transient increase in respiratory rate and tidal volumes, which in turn normalizes arterial Pco_2 with a slightly alkalemic pH. However, one study demonstrated that, in the majority of patients, if local anesthesia with lidocaine was used, the degree of hyperventilation during arterial puncture was not significant.[41]

An arterial Pco_2 measurement greater than 45 mm Hg at sea level confirms hypercapnia. Hypercapnia is associated with predictable physiologic or secondary changes in pH and plasma bicarbonate, which help to differentiate acute from chronic and acute on chronic hypercapnia.[42,43] Acute hypercapnia is characterized by an elevated arterial Pco_2 greater than 45 mm Hg and a low pH less than 7.35. For every acute increase in arterial Pco_2 of 10 mm Hg above normal the pH falls by 0.08.[40] Initially, nonbicarbonate pH buffers present in all fluid compartments of the body give rise to a small increase in serum bicarbonate within 5 to 10 minutes.[44] This secondary response to acute respiratory

acidosis increases the serum bicarbonate concentration by approximately 1 mEq/L for every 10 mm Hg (1.3 kPa) increase in the arterial P_{CO_2}.[43,44] As hypercapnia persists, renal compensation takes place. Over approximately 3 to 5 days, the kidneys increase reabsorption of proximal tubular bicarbonate, increase secretion of hydrogen ions, and increase ammonia production, and a new steady state emerges. Serum bicarbonate concentration increases and there is a rise in the systemic pH towards normal. Consequently, assuming normal renal function, chronic hypercapnia is characterized by an elevated arterial P_{CO_2} greater than 45 mm Hg and normal or near normal pH. Derived mainly from experiments on dogs and studies in hospitalized patients, when hypercapnia is chronic, every 10 mm Hg increase in arterial P_{CO_2} is accompanied by an increase in serum bicarbonate of 3.5 to 5 mEq/L.[42,44,45] A high arterial P_{CO_2} may also be caused by respiratory compensation for a primary metabolic alkalosis, but in this setting the pH will be abnormally high.

In addition to confirming the presence of hypercapnia and determining the rate of development, the arterial blood gas can also provide valuable information as to the possible cause. The *alveolar-arterial P_{O_2} difference* [(A–a)P_{O_2}] is defined as the alveolar P_{O_2} minus arterial P_{O_2}, where alveolar P_{O_2} is the alveolar pressure of oxygen and arterial P_{O_2} is the arterial pressure of oxygen. The normal (A–a)P_{O_2} difference is approximately 10 mm Hg but varies with age.[46] The alveolar-arterial P_{O_2} difference helps to distinguish causes of hypercapnia with normal lungs from causes of hypercapnia due to lung disease, as discussed above. Hypercapnia with an alveolar-arterial P_{O_2} difference within the normal range suggests a reduced minute ventilation due to depressed central ventilatory drive or disorders of the respiratory system effectors, while hypercapnia in the setting of an abnormal alveolar-arterial P_{O_2} difference greater than 20 suggests underlying pulmonary disease may be contributing. (A–a)P_{O_2}, however, can be difficult to calculate in acute respiratory failure when supplemental oxygen is typically required.

SURROGATE ARTERIAL P_{CO_2} ESTIMATES

Arterial blood gas measurements require direct arterial puncture and, accordingly, there is interest in noninvasive measures to estimate the arterial P_{CO_2}, especially when frequent or continuous monitoring is desired.

The peripheral venous P_{CO_2} is a poor predictor of arterial P_{CO_2} and should not be relied on for assessing hypercapnia. A meta-analysis of 16 studies with a total of 1768 subjects that compared P_{CO_2} obtained from peripheral venous blood to arterial blood found poor agreement with sufficiently large differences to be of clinical significance.[47,48] However, a normal peripheral venous P_{CO_2} may have a role in excluding hypercapnia.[49,50] For pH, in contrast to P_{CO_2}, better agreement between peripheral venous and arterial values has been demonstrated. While the serum bicarbonate can increase with sustained hypercapnia, an elevated serum bicarbonate is not specific for hypercapnia and, despite being readily available, a serum bicarbonate alone should not be used as a surrogate for hypercapnia. In OHS, a serum bicarbonate level less than 27 mmol/L has been shown to have a high negative predictive value and has been recommended to exclude the diagnosis of OHS in obese patients with sleep-disordered breathing when suspicion for OHS is not very high.[51] Even so, measurement of arterial blood gas is recommended in patients strongly suspected of having OHS. When compared to peripheral venous P_{CO_2}, the central venous P_{CO_2} allows more accurate estimation of arterial P_{CO_2}, differing from arterial P_{CO_2} by an amount described by the Fick principle.[52] As long as cardiac output is relatively normal, the central venous P_{CO_2} exceeds the arterial P_{CO_2} by approximately 4 mm Hg.[52]

SLEEP STUDIES

As discussed above, the sleep period is particularly vulnerable to the development of hypercapnia, and nocturnal hypoventilation usually precedes chronic daytime hypoventilation. Sleep studies utilizing appropriate signals can often detect hypercapnia before the development of more severe daytime hypercapnia and should be considered in any evaluation of hypercapnia.

In-laboratory *polysomnography* records multiple physiologic parameters including but not limited to airflow, chest and abdominal movements, and oxygen and is the gold standard diagnostic testing for sleep-disordered breathing. Measures of carbon dioxide can be added and are standard of care in pediatric sleep studies. Given the practical limitations of arterial blood gas monitoring during sleep, noninvasive methods for assessing arterial P_{CO_2} using end-tidal P_{CO_2} and *transcutaneous CO_2* ($tcCO_2$) monitoring have been used. These measures are also being increasingly explored in critically ill mechanically ventilated patients.

End-Tidal CO_2 Monitoring

End-tidal CO_2 devices sample exhaled air through a nasal cannula from the spontaneously breathing patient and provide continuous breath-to-breath analysis of CO_2 based on infrared absorption. In intubated and mechanically ventilated patients, the capnograph is placed between the endotracheal tube and the Y-connector of the ventilator circuit. The graphical display of end-tidal P_{CO_2} plotted against either time or exhaled volume is referred to as *time* or *volume capnography,* respectively. While end-tidal P_{CO_2} allows for continuous, breath-by-breath monitoring, its correlation with arterial P_{CO_2} depends on alveolar ventilation, cardiac output, ventilation-perfusion matching, and airflow obstruction.[2] Consequently, in critically ill patients, end-tidal P_{CO_2} can differ significantly from arterial P_{CO_2} and thus is not recommended to estimate arterial P_{CO_2} in this setting.[52] Similar inaccuracies with end-tidal CO_2 monitoring can be seen in the ambulatory setting, especially in specific disorders like COPD where rapid shallow breathing causes increased dead space and an inability to reach an end-tidal CO_2 plateau. In general, end-tidal CO_2 values tend to underestimate the arterial P_{CO_2} slightly.[52,53] End-tidal CO_2 monitoring can also have technical limitations including problems introduced by mouth breathing, which can entrain air and lower the end-tidal CO_2, and by obstruction of the sampling line. Thus, in general, end-tidal CO_2 monitoring should not be used as the sole mechanism in assessing arterial P_{CO_2}.

Transcutaneous CO_2 Monitoring

Compared to end-tidal CO_2 monitoring, $tcCO_2$ monitoring is more reliable and practical. $tcCO_2$ sensors heat the skin locally to increase blood flow and carbon dioxide diffusion. As CO_2 diffuses across the skin, it reacts with an electrolyte-containing solution to produce a measurable change in the pH that is then analyzed to measure $tcCO_2$.[52,53] There are a few considerations in using $tcCO_2$. For one, $tcCO_2$ values are approximately 4 to 5 mm Hg higher than arterial P_{CO_2} because the heat applied to the skin induces a local hypermetabolic state. For another, there is a lag in response to changes in arterial P_{CO_2} due to the time for CO_2 to diffuse across the skin. Nonetheless, $tcCO_2$ can provide an overall trend with respect to arterial P_{CO_2} changes. Practically, $tcCO_2$ is easy to apply and can be used in intubated patients as long as skin perfusion is not impaired. Calibration is required and $tcCO_2$ monitoring is currently expensive.

Because some hypoventilation during sleep is normal, pathologic hypoventilation during sleep has been difficult to define. The *American Academy of Sleep Medicine* (AASM) Sleep Apnea Definitions Task Force revised its scoring of hypoventilation during sleep in adults in 2012 to include two criteria: (1) an increase in arterial P_{CO_2} greater than 55 mm Hg for greater than 10 minutes or (2) an increase in arterial P_{CO_2} greater than 10 mm Hg during sleep in comparison to awake supine values to a value exceeding 50 mm Hg for greater than 10 minutes.[54] Although based on data that normal individuals rarely have an arterial P_{CO_2} greater than 55 mm Hg during sleep, the precise arterial P_{CO_2} level demarcating the transition from physiologic hypercapnia to pathologic hypoventilation remains unclear. Additionally, the duration of 10 minutes selected by the AASM Task Force was arbitrary and based on consensus with a lack of normative data on the amount of total sleep time at different arterial P_{CO_2} values in sleeping adults.

In addition to diagnosing sleep hypoventilation, polysomnography may also reveal a cause for the hypercapnia. OSA is characterized by repetitive reduction of airflow due to upper airway obstruction. It is seen in the majority of patients with OHS where it is typically severe and associated with significant hypoxemia. In contrast to OSA, in central sleep apnea, repetitive absent airflow is associated with absent respiratory effort. Central sleep apnea can be caused by a high or irregular drive to breathe, in which case the CO_2 is typically low or normal, or by a diminished drive to breathe, in which case the CO_2 is typically elevated.

Currently, home sleep apnea testing or portable unattended sleep apnea testing is not recommended for the evaluation of hypercapnia or sleep hypoventilation.[55] Portable monitoring devices differ in the numbers and types of signals recorded but record fewer physiologic variables when compared to polysomnography. Scoring of respiratory events, including obstructive and central apneas, is more challenging with fewer signals, especially in patients with underlying cardiopulmonary and neuromuscular disease prone to baseline hypoxemia or hypoventilation. For this reason, studies comparing an ambulatory management pathway using portable home sleep apnea testing and autotitrating continuous positive airway pressure to the traditional in-laboratory diagnostic and titration polysomnography have largely excluded patients with significant cardiac, pulmonary, and neuromuscular disorders where interpretation of limited channel recordings can be limited.[56] Similarly, continuous recording of oxygen saturation alone can have limitations in the evaluation of hypercapnia. Oxygen desaturation may be associated with hypoventilation but, because oxygen desaturation can also be seen with obstructive and central respiratory events, it cannot be relied on alone in diagnosing sleep hypoventilation.

DIAGNOSTIC TESTING FOR CAUSES OF HYPERCAPNIA

Additional diagnostic testing to try to find the underlying cause(s) is guided by the clinical history and physical examination.

If there is clinical suspicion for a disorder of central respiratory control, testing should be considered for the following: urine toxicology, thyroid function, basic metabolic function, liver function, and genetic associations, as well as CNS imaging including magnetic resonance imaging of the brainstem. If there is clinical suspicion for a disorder of the respiratory systems effectors, additional diagnostic testing is directed by the suspected level of efferent pathway involvement.

Physiologic measures of respiratory muscle function can help confirm respiratory muscle weakness and assess for severity (see also Chapter 130). Various measures of respiratory muscle function exist and combinations of measures may improve diagnostic precision.[57] Inspiratory muscle weakness is characterized by a reduction in *vital capacity* (VC) and *total lung capacity* (TLC). A *forced vital capacity* (FVC) less than 1 L is the best negative predictor of survival in patients with Duchenne muscular dystrophy and, in *amyotrophic lateral sclerosis*, the FVC has been linearly correlated with disease progression and survival.[58-60] In Guillain-Barré syndrome, progression to mechanical ventilation has been associated with a VC less than 20 mL/kg, a reduction of more than 30% in VC, *maximal inspiratory pressure* (MIP) less than 30 cm H_2O, and a *maximal expiratory pressure* (MEP) less than 40 cm H_2O. For these patients, placement in the intensive care unit is recommended when the VC declines rapidly or when it falls below approximately 18 mL/kg of body weight.[61,62] The supine FVC may be a better predictor of diaphragmatic weakness than the upright FVC.[63,64] Normally the VC declines less than 10% when going from upright to supine.[65] When the VC falls to this extent or less, clinically significant diaphragmatic weakness is unlikely, whereas a decrease in VC of 30–50% when supine supports a diagnosis of bilateral diaphragmatic paralysis.[38]

Respiratory muscle weakness can also be associated with reductions in the maximum voluntary ventilation and static MIP and MEP measured at the mouth. The MIP and MEP, when performed appropriately and with good patient effort, are sensitive and easily obtained measures of the strength of inspiratory and expiratory muscles of respiration, respectively; however, their utility is limited by the significant variation in normal reference values reported. MIP and MEP measurements are influenced by

age, gender, posture, lung volume, and the type of mouthpiece used. A normal MIP is useful in excluding clinically important inspiratory respiratory muscle weakness, but an abnormal MIP can be difficult to interpret.[66] In patients with neuromuscular disorders involving the orofacial muscles, obtaining a tight seal around the mouthpiece for MIP and MEP measurements can be difficult. When a patient cannot use a mouthpiece, the *sniff nasal inspiratory pressure* (SNIP), which measures the nasal pressure in an occluded nostril as the patient sniffs through the contralateral unobstructed nostril, may provide a reasonable estimate of inspiratory muscle strength.[66] In amyotrophic lateral sclerosis, the SNIP has been shown to have greater predictive power for hypercapnia than either FVC or MIP.[67] The American Academy of Neurology has recommended consideration of noninvasive ventilation in amyotrophic lateral sclerosis if orthopnea is present, SNIP is less than 40 cm H_2O, FVC is less than 50% predicted, MIP is less than 60 cm H_2O, or when abnormal nocturnal oximetry is present.[67]

Again, depending on the suspected level of effector system involvement, imaging may be helpful. Hemidiaphragm paralysis can cause an elevated hemidiaphragm on chest radiograph. The chest radiograph has reasonable sensitivity in detecting unilateral diaphragmatic paralysis but low specificity (44%).[38,68] When suspected, fluoroscopy of the diaphragm with a sniff test can be used to evaluate diaphragmatic function. In the sniff test, the patient is asked to sniff forcefully while diaphragmatic movement is observed fluoroscopically. In unilateral diaphragmatic paralysis, there is a paradoxical cephalad movement of the paralyzed hemidiaphragm when compared to the descent of the normal contralateral hemidiaphragm (see Video 20.1). The test is not helpful in diagnosing bilateral diaphragmatic paralysis, leading to false-positive and false-negative results.[38] Ultrasonography may be considered in diagnosing both unilateral and bilateral diaphragmatic paralysis. Thickening of the diaphragm by ultrasound reflects diaphragmatic shortening, so that with diaphragmatic paralysis, there is a lack of thickening seen with inspiration. Once diaphragmatic paralysis is identified, computed tomography of the chest is required to evaluate the course of the ipsilateral phrenic nerve and exclude thoracic malignancies. Computed tomography of the chest can also be helpful in evaluating for chest wall deformities and parenchymal lung diseases.

Hypercapnia caused by increased dead space ventilation and disorders of alveolar ventilation is associated with abnormal pulmonary function testing. A decreased diffusion capacity can be seen with pathologies involving the alveolar-capillary membrane. Parenchymal lung diseases involving alveolar filling can also exhibit a decrease in diffusion capacity and restriction. Thus, chest imaging including chest radiographs and often computed tomography are indicated in the assessment of hypercapnia.

MANAGEMENT

Treatment priorities will vary depending on the acuity and severity of hypercapnia at presentation. In patients presenting with acute or acute on chronic hypercapnic respiratory failure, assessment and stabilization of the *airway, breathing, and circulation* (ABCs) take priority. Ventilatory support can be provided either noninvasively using a mask interface or invasively following endotracheal intubation, typically in the intensive care unit. Most ventilators now are positive-pressure devices that deliver pressurized gas to increase transpulmonary pressures and inflate the lungs, thereby augmenting ventilation. *Noninvasive ventilation* (NIV) should be considered in all patients in acute hypercapnic respiratory failure where mechanical ventilation is considered; however, success relies on both appropriate patient selection and proper application. Strong evidence now supports the use of NIV for acute exacerbations of COPD and cardiogenic pulmonary edema, to facilitate extubation in COPD patients, and in immunocompromised patients. An increasing number of studies are suggesting an ever-expanding role for NIV in hypercapnic respiratory failure. However, NIV should be avoided in hemodynamically unstable patients, patients at high risk of aspiration, and patients unlikely to tolerate a mask interface. Decreased mental status is not a contraindication to NIV, but inability to protect the airway (regardless of the mental status) is. NIV is not a substitute for endotracheal intubation when needed. See Chapters 135 and 136 for details on providing ventilatory support.

At the same time that ventilatory support is being provided, there should be efforts to identify the underlying cause(s) to target specific therapies directed at reversing the underlying cause. In chronic hypercapnia, because the patient is generally stable, identification and treatment of the underlying cause typically takes precedence, and the potential risks and benefits of chronic ventilatory support are weighed. Initiation of ventilatory support in the stable ambulatory patient typically starts noninvasively during sleep.

Hypercapnia often coexists with hypoxemia. The administration of supplemental oxygen in this setting has the potential to worsen hypercapnia by various mechanisms.[69] By increasing arterial P_{O_2}, supplemental oxygen can inhibit hypoxic pulmonary vasoconstriction, an important mechanism that normally diverts pulmonary artery blood away from poorly ventilated regions; in this way, the supplemental oxygen can worsen ventilation-perfusion mismatch and reduce the efficiency of CO_2 elimination.[70] This appears to be the predominant mechanism for oxygen-induced hypercapnia. Supplemental oxygen can also worsen hypercapnia by the Haldane effect,[70-72] the phenomenon whereby increasing arterial P_{O_2} reduces the ability of the blood to store CO_2, thereby increasing arterial P_{CO_2}. Additionally, supplemental oxygen may decrease stimuli from peripheral chemoreceptors to the central respiratory center and thereby decrease minute ventilation. Normally, an increase in the arterial P_{CO_2} can be offset by an increase in minute ventilation, but this may not be possible in significant lung disease. Knowing this, the application of supplemental oxygen in hypercapnia should be carefully titrated for a target Sp_{O_2} of 90–93% with close monitoring.

Key Points

- Hypercapnia is defined as a partial pressure of carbon dioxide in arterial blood greater than 45 mm Hg at sea level. It is associated with predictable physiologic changes in pH and plasma bicarbonate, which help to differentiate acute from chronic hypercapnia.
- Hypercapnia results when alveolar ventilation is insufficient to meet the rate of CO_2 production due to a decrease in minute ventilation, an increase in dead space ventilation, or rarely an increase in CO_2 production. (A–a)Po_2 helps to distinguish causes of hypercapnia in the setting of normal lungs from those causes of hypercapnia due to lung disease.
- Hypercapnia caused by reduced total minute ventilation can mechanistically be divided into (1) disorders of the central respiratory controller characterized by a reduced drive to breathe (i.e., won't breathe) or (2) disorders of the respiratory system effectors due to disruption at any level of the efferent arm, from the spinal cord to the muscles of respiration and the chest wall, characterized by reduced ventilatory supply (i.e., can't breathe).
- Hypercapnia affects multiple organ systems and thus timely recognition is essential. Clinical assessment should be directed not only to the clinical manifestations of hypercapnia but also to its underlying cause.
- Sleep is associated with changes in ventilation specific to the stage of sleep and a normal physiologic 4 to 6 mm Hg increase in arterial Pco_2. Nocturnal hypoventilation usually precedes chronic daytime hypercapnia, and a sleep history should be elicited in the clinical evaluation of any patient with hypercapnia.
- Administration of supplemental oxygen has the potential to worsen hypercapnia by inhibiting hypoxic pulmonary vasoconstriction (and thereby worsening ventilation-perfusion inequality), by the Haldane effect, in which O_2 can displace CO_2 from hemoglobin, and by decreasing minute ventilation.

Key Readings

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SECTION G

INFECTIOUS DISEASES OF THE LUNGS

46 COMMUNITY-ACQUIRED PNEUMONIA

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An expanded version of this chapter is available at ExpertConsult.com.

INTRODUCTION

Community-acquired pneumonia (CAP) caused an estimated 2.4 million deaths worldwide in 2016.[1] In the United States, pneumonia accounted for approximately 900,000 hospitalizations in 2014 and one-third of episodes of sepsis.[2,3] Although many episodes are mild, CAP mortality in hospitalized patients is 5–10% and 20–50% for those admitted to the *intensive care unit* (ICU).

CAP implies the presence of lung inflammation of sufficient extent to lead to signs, symptoms, or radiologic features of an opacity with acute onset and community acquisition. An infectious etiology is inferred but is frequently not proven microbiologically,[4] and the condition must be distinguished from other conditions that present with similar features. CAP is distinguished from *hospital-acquired pneumonia* (HAP) by onset in the community or within 48 hours of hospitalization.[5] Its acute onset helps distinguish it in most cases from chronic infectious pneumonias caused by tuberculosis or fungi.

Diagnosis and management of pneumonia are challenging, especially in the growing number of individuals with multiple morbidities, immunocompromise or epidemiologic factors favoring antimicrobial resistance, or geographically restricted infections. Treatment is initially empirical, covering common bacterial or viral causes in the appropriate epidemiological setting but should be tailored by microbiological results and antimicrobial stewardship priorities.

PATHOPHYSIOLOGY AND PATHOGENESIS

As detailed in Chapter 17, the *lower respiratory tract* (LRT) was formerly thought to be sterile but more sensitive molecular techniques now demonstrate that a LRT low-density microbiome exists, with approximately $10^{2\text{-}3}$ bacteria per milliliter of *bronchoalveolar lavage* (BAL) fluid, as opposed to 10^6 bacteria/mL in the oropharynx.[6] The LRT microbiome in adults, although distinct from the upper airway, contains many of the same species. It is dominated by Firmicutes and Bacteroidetes, while the virome is dominated by *Anelloviridae* and bacteriophages.[6] The lung microbiome regulates local immune responses. For

example, *Prevotella* species enhance *T helper 17 cells* (Th17) responses and reduce alveolar macrophage *toll-like receptor* (TLR) 4 responses.[7] Aspiration of oropharyngeal secretions is the main mechanism of microorganism translocation to the LRT in adults, while nasopharyngeal secretions also contribute in children. While a person is awake, glottal reflexes prevent aspiration; during sleep, 50% of normal persons aspirate small volumes of oropharyngeal secretions. Dysphagia and aspiration are more frequent in the elderly and in elderly patients with CAP compared to age-matched controls.[8,9] Dispersion along mucosal surfaces also contributes to colonization.

As an alternative to aspiration of bacteria colonizing the upper airways, *Mycoplasma pneumoniae, Chlamydophila* species, *Coxiella burnetii, Legionella* species, and viruses enter the LRT by direct inhalation. Inhalation pneumonia is most often due to microorganisms that survive suspended in the air for prolonged periods, are present in droplet nuclei smaller than 5 μm, and are able to evade innate immune responses.

The airway of healthy individuals is colonized by multiple microorganisms. These can promote health through limiting surface binding and nutrients, expressing antimicrobial bacteriocins, and promoting beneficial immune responses.[6,10,11] However, dynamic shifts in the population structure, such as by viral infection or exposure to pollutants, favor acquisition of *pathobionts*, that is, normally harmless organisms (i.e., symbionts) that can become pathologic.[6] Colonization is promoted by specific microbial adhesins interacting with cellular receptors. The *Streptococcus pneumoniae* capsule allows it to penetrate mucus so adhesins interact with receptors such as platelet-activating factor receptor on epithelial cells, an interaction enhanced by cigarette smoke, infection with respiratory viruses, and particulate air pollutants.[11–13] Likewise, *Staphylococcus aureus* express multiple adhesins that bind host extracellular matrix proteins.[14,15] Gram-negative bacteria such as *Klebsiella pneumoniae* utilize macromolecular structures, termed pili, to interact with extracellular matrix proteins.[16] Bacterial products or inflammatory responses including generation of reactive oxygen species also impair mucociliary function.[17]

The incidence of CAP is rare in comparison to the frequency of colonization with pathobionts such as *S. pneumoniae*, indicating that effective host defenses prevent CAP. Mucus and the bronchociliary escalator limit pathogen penetration to the distal airway and viral infections subvert bronchociliary function.[18] Respiratory epithelial cells and phagocytes synthesize antimicrobial peptides, termed defensins.[19] In the distal airways and alveoli, pulmonary surfactant proteins A and C can inhibit bacterial binding to host cells and also promote phagocytosis of selected bacteria.[20,21] The presence of complement and immunoglobulins (particularly *immunoglobulin A* [IgA]), also prevents colonization of the airway. Opsonic antibodies are crucial for phagocytosis of encapsulated bacteria, as illustrated for internalization of *S. pneumoniae* by alveolar macrophages.[22]

Inflammatory responses to bacteria and viruses are regulated by pattern recognition receptors (Chapter 15). These regulate production of cytokines and chemokines to activate resident cells and promote recruitment of other immune cells to control respiratory tract infection. In murine models, resident alveolar macrophages clear finite numbers from the alveolus, but their microbicidal responses are limited, and ultimately they undergo apoptosis to kill residual bacteria such as *S. pneumoniae.*[23] When their capacity for clearance is overwhelmed, neutrophils and $CCR2^+$ monocytes enhance pathogen clearance.[23,24] T cells are also key to responses during the escalation of inflammatory responses after alveolar macrophage responses are overwhelmed, but T cells must be regulated to prevent tissue injury.[25] Th17 responses, which are a key effector of mucosal immunity, facilitate macrophage and neutrophil recruitment to clear bacteria. In the upper airway, recruited macrophages control initial exposure to *S. pneumoniae,* while prior exposure promotes neutrophil-dependent clearance of *S. pneumoniae* in murine models.[26] Th17 cells are also increased in the BAL of patients with CAP.[27] The gut microbiota dampens $CCR2^+$ macrophage recruitment to the upper airway in infant mice; this has been suggested as a reason for prolonged colonization with pathobionts like *S. pneumoniae* in infants.[28] Type 1 interferon responses mediated by innate lymphoid cells are critical to promoting viral clearance from epithelial cells. Viral infection frequently modulates innate responses to bacteria by, for example, inhibiting macrophage phagocytosis via *interferon* (IFN)-γ–dependent mechanisms or by induction of apoptosis in key immune cells such as T cells.[29] Influenza virus enhances susceptibility to *S. pneumoniae* by neuraminidase release of sialic acid, which serves as a nutrient for *S. pneumoniae*,[30] or through increasing bacterial adherence to respiratory epithelial cells by exposing glycoconjugates previously capped by sialic acid[31] and/or through direct binding of influenza virus to *S. pneumoniae*.[32]

CAP results when the innate responses, including those of alveolar macrophages, are overwhelmed. Neutrophilic inflammation and activated T cells promote pathogen clearance, but at greater inflammatory cost than processes such as apoptosis-associated killing, and increase tissue injury. Immune responses designed to clear pathogens, such as production of reactive oxygen or nitrogen species and proteases, can promote tissue injury, and dysregulation of these responses impacts the outcome of CAP and can lead to excessive inflammatory responses such as *acute respiratory distress syndrome* (ARDS), a complication of 2% of cases of hospitalized CAP.[33] Viral infections such as influenza A virus can lead to excessive activation of immune cells, such as recruited $CCR2^+$ macrophages.[34] In many cases, CAP presents as a dysregulated acute inflammatory response rather than one of a failure of pathogen clearance. This may explain the inability to identify the causal pathogen in many cases. In other cases, the virulence of the pathogen or the kinetics of replication drive diffuse alveolar damage and extensive epithelial apoptosis; this is the case with many viral pneumonias, especially avian influenza and *Middle East respiratory syndrome coronavirus* (MERS-CoV).[35]

EPIDEMIOLOGY

The burden of CAP varies substantially across the world; the highest risks are associated with extremes of age; poverty; inadequate access to nutrition, sanitation, or vaccines; and immunocompromised status or medical comorbidities. The true incidence of CAP is uncertain because the illness is not reportable and only 20–50% of patients require hospitalization. Incidence estimates of CAP range from 6 to 34 cases per 1000 persons per year, with substantially higher rates in older adults.[36] In a study using active population-based

Table 46.1 Common Causes of Community-Acquired Pneumonia by Patient Location

Outpatient	Hospitalized	ICU
MOST FREQUENT		
Streptococcus pneumoniae *Mycoplasma pneumoniae* Respiratory viruses	*Streptococcus pneumoniae* *Mycoplasma pneumoniae* Respiratory viruses	*Streptococcus pneumoniae* Viruses (e.g., influenza A virus)
OTHER ORGANISMS OFTEN ISOLATED		
Chlamydophila pneumoniae *Coxiella burnetii* *Legionella* species *Haemophilus influenzae*	*Haemophilus influenzae* *Pseudomonas aeruginosa* (and enteric gram-negative bacilli) *Staphylococcus aureus* *Legionella* species Aspiration pneumonia	*Legionella* species *Staphylococcus aureus* *Pseudomonas aeruginosa* (and enteric gram-negative bacilli)

ICU, intensive care unit.
Modified from references 4, 40, 42–45.

surveillance, the incidence rate for CAP requiring hospitalization in adults was reported to be 2.5 per 1000 person-years.[4]

Although the severity of disease is influenced by the patient's age and the presence and type of coexisting conditions,[38–41] disease severity is also related to the pathogen. *S. pneumoniae* and respiratory viruses are common in all settings (Table 46.1).[4,40,42–45] The relative importance of different viruses as causes of pneumonia depends on season and patient age. During outbreaks, influenza virus accounts for more than 50% of viral pneumonia in adults. Additionally, rhinovirus, human metapneumovirus, *respiratory syncytial virus* (RSV), adenovirus, parainfluenza viruses, coronaviruses, and varicella virus cause pneumonia in healthy adults.[4] Other viruses continue to emerge in epidemics of severe acute pneumonitis, including hantavirus, coronaviruses (*severe acute respiratory syndrome* [SARS-1], MERS, and SARS-CoV-2), and avian influenza A viruses.

M. pneumoniae, C. pneumoniae, C. burnetii, and *Haemophilus influenzae* can cause pneumonia sufficiently severe to require hospitalization, though most cases are less severe. The most frequently identified pathogens causing severe CAP (i.e., CAP requiring ICU care) are *S. pneumoniae*, *Pseudomonas aeruginosa*, enteric gram-negative bacilli, *S. aureus, Legionella pneumophila,* and influenza viruses (Table 46.1).[40,42,44,46,47] Up to 20% of severe CAP episodes are caused by polymicrobial infection. The microbial etiology pathogen is not identified in up to 60% of patients with CAP, even with *polymerase chain reaction* (PCR)-based diagnostics.[4]

Pneumonia due to *Legionella* species is often associated with other cases in outbreaks from a common environmental source.[48] Gram-negative bacilli are more common causes in Asia and Southern Africa than in other regions, with *K. pneumoniae* most frequent, particularly in cases admitted to the ICU.[50,51] *P. aeruginosa* infection is uncommon in the absence of specific risk factors (recent antibiotic treatment, immunocompromise, and severe pulmonary comorbidity, especially bronchiectasis, cystic fibrosis, and severe COPD).[40,42,46] *Methicillin-resistant S. aureus* (MRSA), originally a nosocomial pathogen, has appeared in the community, where it is referred to as *community-acquired MRSA* [CA-MRSA]). CA-MRSA can lead to severe pulmonary infections, including necrotizing and hemorrhagic pneumonia.[49,52]

The contribution of *M. pneumoniae* and viral infections to CAP varies with the season. Influenza viruses, *S. pneumoniae,* and *H. influenzae* are more common in winter, while *Legionella* species causes infection predominantly in the summer and autumn.[53] Vaccination can also modify the prevalence of certain pathogens as causes of CAP. Pneumococcal conjugate vaccination in children is reducing the incidence of *S. pneumoniae* CAP, even in adults. In the Netherlands, use of the conjugate vaccine reduced *S. pneumoniae* CAP by 30% from 2004 to 2016,[54] although replacement with non-vaccine serotypes may modify this trend.

The etiology of severe CAP varies with age and medical comorbidities.[42,55-58]

AGE-RELATED FACTORS

Pneumonia is one of the major causes of morbidity in children. In children younger than 2 years, *S. pneumoniae* and RSV are the most frequent causes, whereas *S. pneumoniae,* viruses, and *M. pneumoniae* are common in older children and young adults.

In adults, increased age is associated with a change in the distribution of microbial causes and an increase in the frequency and severity of pneumonia.[59] The annual incidence of CAP in noninstitutionalized older adults is estimated to be between 18 and 44 per 1000 compared with 4.7 to 11.6 per 1000 in the general population.[36,59,60] Although older adults are particularly at risk for pneumococcal pneumonia, they also have increased rates of pneumonia due to *H. influenzae,* group B streptococci, *Moraxella catarrhalis, L. pneumophila,* gram-negative bacilli, *C. pneumoniae,* and polymicrobial infections.[36,46,61] The absolute rate of infection by *M. pneumoniae* does not decrease with age. However, this pathogen accounts for a smaller proportion of pneumonia in older adults than in younger populations. In patients older than 80 years, there is a higher incidence of aspiration pneumonia and lower incidence of infection with *Legionella* species than in younger patients.[62]

PERSONAL HABITS

Alcohol consumption is an important risk factor for CAP because of its potential to increase aspiration of oropharyngeal contents and to impair immune function. Alcoholism increases the rate and severity of pneumonia, especially pneumococcal CAP.[63,64] This predisposition persists several months after cessation of alcohol consumption.[63]

Smoking is one of the most important risk factors for CAP and is associated with an increased frequency of CAP due to *S. pneumoniae, L. pneumophila,* and influenza.[65,66] Smoking not only doubles the risk of CAP and is associated with approximately one-third of cases of CAP, but passive smoking in adults older

than 65 years also increases CAP, making it potentially the most significant modifiable risk factor for CAP.[65,67] Cigarette smoke alters mucociliary transport and humoral and cellular defenses, affects epithelial cells, and increases adhesion of *S. pneumoniae* and *H. influenzae* to the oropharyngeal epithelium.[12]

COMORBIDITIES

The most frequent comorbidity associated with CAP is COPD (see Chapters 63 and 64). Patients with COPD have an increased risk for CAP due to alterations in mechanical and cellular defenses, including alveolar macrophage dysfunction, that increase bacterial colonization of the lower airways.[68,69] Patients with severe COPD (forced expiratory volume in 1 second <30% of predicted) and bronchiectasis have an increased risk for pneumonia caused by nontypeable *H. influenzae, P. aeruginosa,* and *S. aureus.*[66] However, a broad range of pathogens may cause CAP in this group, and many rarer etiologies of CAP have a predilection for patients with COPD. Despite this, *S. pneumoniae* remains a leading cause of CAP in COPD. In patients with COPD treated with oral corticosteroids for long periods, the risk for infection with *Aspergillus* species is increased.[70]

Pneumonia remains the major cause of morbidity and mortality in patients with cystic fibrosis. During the first decade of life, *S. aureus* and nontypeable *H. influenzae* are the most common pathogens, although *P. aeruginosa* is occasionally isolated in infants. By 18 years of age, 80% of patients with cystic fibrosis harbor *P. aeruginosa* and 3.5% harbor *Burkholderia cepacia.*[71] *Stenotrophomonas maltophilia, Achromobacter xylosoxidans,* and nontuberculous mycobacteria are emerging pathogens in this population.[72]

Other comorbidities associated with increased rates of CAP and consequent mortality include congestive heart failure, chronic kidney or liver disease, cancer, diabetes, dementia, cerebrovascular diseases, and immunodeficiencies (e.g., neutropenia, lymphoproliferative diseases, immunoglobulin deficiencies, and *human immunodeficiency virus* [HIV] infection).[73–75] Globally, HIV infection is a major risk factor for CAP and, whereas the widespread availability of antiretroviral therapy has decreased the risk of opportunistic infections, it has had a more modest impact on pneumococcal pneumonia, which remains the leading cause of CAP in this group.[76] High smoking rates and the increased incidence of COPD in people living with HIV compound the risk of CAP.[73,77]

While pneumococcal pneumonia remains the most common cause of CAP in most of these groups, other associations can increase the relative contribution of a particular etiologic agent in a specific comorbidity: liver disease with gram-negative bacteria and diabetes with *S. aureus.*[66] The contribution of proton pump inhibitor use as a CAP risk factor has been controversial; commencement of proton pump inhibitor in the previous 30 days increased CAP risk in a recent case control study, although some other studies including a meta-analysis have not shown an association.[78,78a] There have also been contradictory findings on the association between statin use and CAP; several observational studies have shown lower mortality with prior statin use[79,80] while others have not.[81]

VIRAL CAP IN IMMUNOCOMPROMISED HOSTS

Viral CAP can be an important problem for people with deficiencies in immunity as the result of cytotoxic chemotherapy, immunosuppressive or biologic therapies for autoimmune diseases, organ transplantation, and HIV infection. The major respiratory viruses affecting persons with an intact immune system may also cause pneumonia in immunocompromised hosts; severe and prolonged pneumonias due to adenovirus, RSV, influenza, measles, or parainfluenza virus can develop in such patients. Immunocompromised patients can also shed respiratory viruses for prolonged periods and thus be responsible for extensive transmission of infection to others. Additionally, individuals with severe T cell immunodeficiency may develop pneumonia due to viruses, such as *cytomegalovirus* (CMV), that do not cause LRT infections in normal hosts. CMV causes severe primary viral pneumonia and predisposes patients to bacterial and fungal superinfections due to its immunosuppressive effects.[82] Varicella-zoster and herpes simplex virus pneumonias are relatively uncommon but cause serious infections in those with severe T cell or natural killer cell immunodeficiency.

GEOGRAPHIC AND OCCUPATIONAL CONSIDERATIONS

Geographic factors, seasonal timing, travel history, and occupational or unusual exposures modify the risk of various microbial etiologies of CAP. For example, an increased frequency of *S. pneumoniae* was found in barracked soldiers and South African gold miners, while painters and welders are at risk of developing a fulminant form of pneumococcal pneumonia with high mortality.[83] *Burkholderia pseudomallei* (melioidosis) is endemic in rural Asia.[84] Exposure to pet birds or work on a poultry (especially turkey) farm or processing plant increases the risk of psittacosis (*Chlamydia psittaci*),[85] while contact with horses or other large mammals including cattle, swine, sheep, goats, or deer increases exposure to *Rhodococcus equi.*[86] Rodent contact suggests the possibility of infection with *Yersinia pestis* (plague)[87,88] or hantavirus[89] in the rural southwestern United States, and *Francisella tularensis* (tularemia) in rural Arkansas or Nantucket, Massachusetts.[90,91] Exposure to sheep, dogs, and cats should prompt evaluation for *C. burnetii* (Q fever).[92] Pneumonia causing SARS due to a coronavirus emerged in epidemic form in Southeast Asia,[93,94] and another coronavirus causes MERS.[95] In late 2019 and 2020, the *coronavirus 2019* (COVID-19) pandemic was caused by another coronavirus, SARS-CoV-2. Finally, the infectious agents that cause anthrax, tularemia, and plague may be used for bioterrorism or biowarfare purposes and cause LRT infections.[96–98] Further information may be obtained from organizations such as the *U.S. Centers for Disease Control and Prevention* (CDC; www.cdc.gov), *Infectious Diseases Society of America* (IDSA; www.idsociety.org), and the *World Health Organization* (WHO; www.who.org) (see Chapter 59).

CLINICAL PRESENTATION

Pneumonia is characterized by the presence of fever, malaise, and respiratory symptoms, such as cough, sputum production, dyspnea, pleuritic pain, and hemoptysis. In older and immunocompromised patients, the signs and symptoms of pulmonary infection may be muted due to blunting of the signature inflammatory response and overshadowed by nonspecific complaints. Therefore, chest radiographs

should be examined in these patients despite lack of classic signs and symptoms.

In older patients, especially those with multiple comorbidities, pneumonia may present with general weakness, decreased appetite, altered mental status, incontinence, or decompensation due to underlying disease. The presence of tachypnea may precede other signs of pneumonia by 1 to 2 days. Tachycardia is another common initial sign but is less frequent and specific than tachypnea. Fever is absent in 30–40% of older patients. Owing to the lack of specific symptoms, the diagnosis of CAP is frequently delayed in older adults.[36,61] Older patients with pneumonia who present with altered mental status without fever can have a delay in receiving antibiotics by more than 4 hours after arrival, a delay that increases mortality.[99]

Occasionally, there is a "classic" history, such as that of the patient with pneumococcal infection who presents with sudden onset of rigor followed by pleuritic chest pain, dyspnea, and cough with rusty sputum. Similarly, a patient with *Legionella* pneumonia may complain predominantly of diarrhea, fever, headache, confusion, and myalgia. For *M. pneumoniae* infection, extrapulmonary manifestations such as myringitis, encephalitis, uveitis, iritis, and myocarditis may be present. However, only rarely does the clinical history clearly suggest a specific etiology.

The clinical and radiographic features of sporadic cases of viral pneumonia are usually not sufficiently characteristic to permit specific viral diagnosis or differentiation from bacterial pneumonias on clinical grounds alone. Exceptions include measles (eFig. 46.1) and varicella pneumonia, in which the associated rash establishes the diagnosis. Some cases of viral pneumonia present as severe CAP and have a rapid and relentless fatal course, with generalized alveolar and interstitial opacities, development of ARDS, and progressive respiratory failure.

Information obtained from the clinical history and physical examination is insufficient to confirm the diagnosis of pneumonia. A definitive diagnosis requires the finding of a new opacity on the chest radiograph or *computed tomography* (CT) scan.

TYPICAL VERSUS ATYPICAL PNEUMONIA

CAP has been separated into typical and atypical pneumonia to help define pathogen etiology and empirical therapy.[38–41] Typical CAP was associated with *S. pneumoniae, H. influenzae,* and *K. pneumoniae.* The clinical features included an acute onset, with chill or rigors, cough productive of purulent or bloody sputum, pleuritic chest pain (especially with *S. pneumoniae*), and physical signs of pulmonary consolidation. Neutrophilia was common and chest radiography showed lobar consolidation with air bronchograms (Fig. 46.1A).

In contrast, atypical CAP was associated with *Legionella* sp, *M. pneumoniae, Chlamydia* sp, *C. burnetii,* and viruses. The clinical features included gradual onset of fever, nonproductive cough, and a relatively normal white blood cell count in the absence of culture of a pathogen. Frequently, systemic features predominated over pulmonary ones. However, several studies, including one that included patients with mild CAP treated on an outpatient basis, have found that neither the clinical symptoms nor the radiographic appearance are sensitive or specific enough to classify the etiology or to guide therapy.[100]

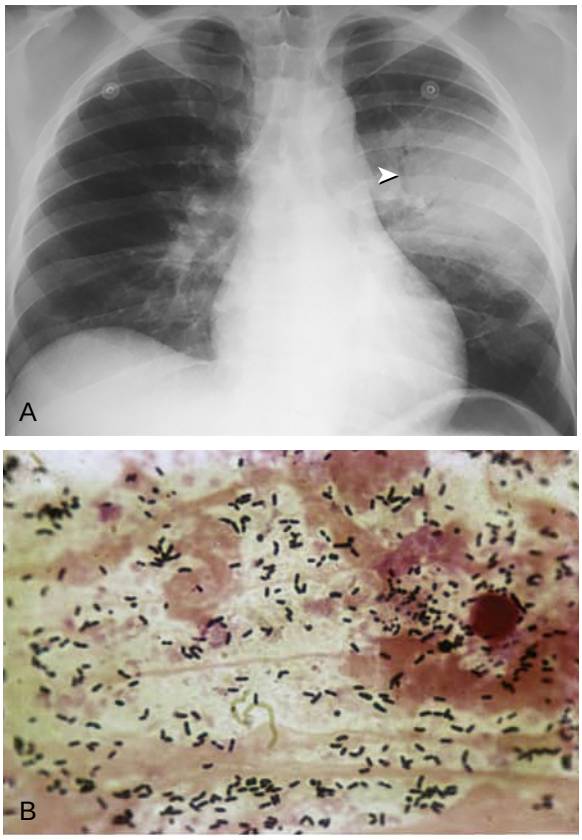

Figure 46.1 Pneumococcal pneumonia. (A) Frontal chest radiograph in a patient with pneumococcal pneumonia shows homogenous consolidation in the left upper lobe extending to the pleural surface. Note presence of air bronchograms (*arrowhead*). (B) Gram stain of sputum from a patient with pneumococcal pneumonia. The predominant organisms are gram-positive lancet-shaped diplococci. (A, Courtesy Michael B. Gotway, MD.)

PATIENT EVALUATION

Clinical Evaluation

The clinical findings that best differentiate CAP from other acute respiratory tract infections are cough, fever, tachycardia, and pulmonary crackles; CAP is present in 20–60% of persons who have all four factors, depending on the baseline prevalence of CAP.[101] Specific signs of pulmonary consolidation, including bronchial breath sounds, are present in only one-third of hospitalized patients and are less frequent in cases treated in the community. Early in disease, cough and physical abnormalities may be absent, and fever may be the only finding. In debilitated older patients, vague clinical presentations are common and undifferentiated fever with no apparent source, especially when accompanied by confusion or tachypnea, mandates a chest radiograph.

Clues to the etiologic diagnosis may lie outside the respiratory tract. Relative bradycardia (pulse should increase by 10 beats/min/°C of temperature elevation) has been associated with pneumonia due to *Legionella, C. psittaci, Mycoplasma,* or *F. tularensis. M. pneumoniae* infection may present with extrapulmonary manifestations, including arthralgia, cervical lymphadenopathy, bullous myringitis, diarrhea, myalgia, myocarditis, hepatitis, nausea, pericarditis, and vomiting.[102] Erythema multiforme or erythema

nodosum may suggest *Mycoplasma* infection (as well as tuberculosis and endemic fungal infection or, for erythema multiforme, other pathogens associated with atypical pneumonia), whereas lesions of ecthyma gangrenosum are most often seen with *P. aeruginosa* infection. Complications such as pleural effusion, pericarditis, endocarditis, arthritis, and *central nervous system* (CNS) involvement may necessitate additional diagnostic procedures, drainage procedures for source control, or modification of antimicrobial selection and duration.[103]

In community settings or in *low- and middle-income countries*, clinical prediction rules are sometimes applied when radiology is not available or deemed nonessential. One example found that patients without alterations in specific vital or physical signs were unlikely to have CAP, and use of these criteria would miss only 5% cases of CAP and so could be applied to low-risk patients if patients could be readily followed up.[104]

Laboratory Evaluation

Patients being investigated for CAP should have pulse oximetry performed and, in those in whom hospital admission is being considered, blood cell counts, serum glucose and electrolyte measurements, and arterial blood gas assays should be performed to assess severity.[38–41] All patients with CAP should have an HIV test in view of the increased incidence of CAP in people living with HIV.

Marked leukocytosis is more often encountered with infections caused by *S. pneumoniae, S. aureus, H. influenzae,* and gram-negative bacilli than with atypical pneumonia or nonbacterial causes of pneumonia. Leukopenia may be seen with overwhelming Panton-Valentine leucocidin-producing *S. aureus* or gram-negative bacillary pneumonia. The serum level of *C-reactive protein* (CRP) and the erythrocyte sedimentation rate are increased to higher values with bacterial than with viral pneumonias. Thrombocytopenia and thrombocytosis are associated with a greater severity of pneumonia and higher mortality.[105]

Blood levels of *procalcitonin* (PCT), a precursor of calcitonin, are increased with bacterial infections, and PCT assays have been used to evaluate the severity, prognosis, and evolution of pneumonia.[106] Results of PCT assays have been used to deescalate antibiotics or to stop antibiotics in patients with severe bacterial infection, when the levels decrease to a certain cutoff point.[107] A randomized trial of a PCT-guided strategy compared with a guideline-based algorithm revealed equivalent primary outcomes of treatment of LRT infections, but the PCT-guided strategy resulted in reduced antibiotic exposure and duration, fewer adverse effects of antibiotic treatment, and shorter length of stay.[108] Despite this, the most recent ATS/IDSA CAP guidelines do not recommend basing initial decisions on whether to treat suspected CAP with antimicrobials on PCT values due to its variable sensitivity (38–91%) in the detection of bacterial infection.[109]

Radiologic Evaluation

Radiologic evaluation is usually required to establish the presence of pneumonia, because there is no combination of historical data, physical findings, or laboratory results that reliably confirms the diagnosis.[40,101,109,110] Limitations of chest radiography include interobserver variability and suboptimal specificity, particularly in patients with ARDS.[40] Reported sensitivity ranges from 44–78%.[111,112] The sensitivity of the chest radiograph is decreased in (1) patients with emphysema, bullae, or structural abnormalities of the lung, who may present with delayed or subtle radiographic changes; (2) obese patients; and (3) patients with very early infection, severe dehydration, or profound granulocytopenia. CT of the chest provides a more sensitive means of detecting minor radiographic abnormalities.[101] It is, however, associated with higher cost and greater radiation exposure. Although high-resolution chest CT may be more sensitive at detecting opacities, it is not routinely recommended when the chest radiograph is negative.[38]

Although several radiographic patterns have been associated with pneumonia caused by specific microorganisms, the presence of a certain pattern is unreliable for diagnosing a specific pathogen.[113,114] Nonetheless, the presence of air bronchograms and a lobar (see Fig. 46.1A and eFig. 46.2) or segmental pattern is more characteristic of pneumococcal than other causes of pneumonia. In contrast, a mixed pattern (alveolar and interstitial disease) (eFig. 46.3) is more frequently observed with other pathogens. Pneumonia complicating aspiration (frequently from anaerobes) (eFig. 46.4) often involves the superior segment of the right lower lobe or posterior segment of the right upper lobe, or both, as well as the corresponding segments on the left. Infections developing from hematogenous seeding often appear as multiple rounded, small opacities, sometimes with cavities, with a basal predominance, where the distribution of blood flow is greatest. Necrotizing pneumonia, which can result in cavitation or a lung abscess (eFig. 46.5), suggests infection by anaerobes, *S. aureus, Streptococcus pyogenes,* gram-negative bacilli, or *Mycobacterium tuberculosis.* Pleural effusion frequently accompanies pneumonia; the size of the pleural effusion on the chest radiograph helps determine whether thoracentesis should be performed. Bedside ultrasound is a cheap and portable diagnostic aid that shows improved sensitivity over chest radiograph. It may be a useful adjunct to diagnosis of CAP in lower- and middle-income countries with sensitivity of 91–95% when compared to chest CT.[111,115]

Microbiologic Evaluation

Identification of the infecting microorganism facilitates the use of pathogen-directed therapy, limiting use of unnecessarily broad-spectrum antimicrobial agents and the collateral damage to the microbiome. Investigations that can establish the etiology of CAP are outlined in Table 46.2. Tests are indicated by clinical severity (eTable 46.1) or epidemiologic risk factors. PCR-based tests, particularly multiplex high-throughput systems, are increasingly available and are rapidly being adopted as the preferred diagnostic approach for pneumonia caused by viruses, by agents associated with atypical pneumonia, and increasingly by other bacteria[116] (see Chapter 19).

Sputum Examination

The current ATS/IDSA guidelines[109] recommend obtaining a sputum sample for Gram stain and culture in patients with CAP sufficiently severe to warrant hospitalization or in those who are believed to be at risk of MRSA or *P. aeruginosa* infection (eTable 46.2). Optimal culture results require that

eTable 46.1 Criteria for Defining Severe Community-Acquired Pneumonia

Validated definition requires one major or at least three minor criteria:
MAJOR CRITERIA
Septic shock requiring administration of vasopressors
Respiratory failure requiring mechanical ventilation
MINOR CRITERIA
Respiratory rate ≥30 breaths/min*†‡§
Pa_{O_2}/F_{IO_2} ratio ≤250* or arterial saturation ≤90% on room air†‡§
Multilobar or bilateral radiographic involvement* or pleural effusion†‡§
Confusion or disorientation*†‡
Uremia (BUN level >20 mg/dL)*†‡
Leukopenia (WBC count <4000 cells/μL)* or extreme leukocytosis (>20,000 cells/μL)§
Thrombocytopenia (platelet count <100,000 cells/μL)*
Hypothermia (core temperature <36°C)*
Hypotension requiring aggressive fluid resuscitation*
Acidosis (pH <7.30)†‡§
Hypoalbuminemia (albumin <3.5 g/μL)†
Hyponatremia (sodium <130 mEq/L)§
Tachycardia (>125/min)†§

BUN, blood urea nitrogen; F_{IO_2}, fractional concentration of oxygen in inspired gas; Pa_{O_2}, arterial oxygen pressure; WBC, white blood cell.
*American Thoracic Society/Infectious Diseases Society of America requires 1 major or ≥3 minor criteria from those on their list.[109]
†SMART-COP.[148]
‡CURXO.[149]
§REA-ICU.[150]

eTable 46.2 Indications for Sputum and Blood Culture in Hospitalized Patients

Patients with markers of severity
Receiving empiric therapy for MRSA or *Pseudomonas aeruginosa*
Prior MRSA or *P. aeruginosa* infection, especially if pneumonia
Hospitalized and received parenteral antimicrobials within 90 days

MRSA, methicillin-resistant *Staphylococcus aureus*.
From Metlay JP, Waterer GW, Long AC, et al. Diagnosis and treatment of adults with community-acquired pneumonia. An Official Clinical Practice Guideline of the American Thoracic Society and Infectious Diseases Society of America. *Am J Respir Crit Care Med*. 2019;200(7):e45-e67.

Table 46.2 Recommended Microbiologic Evaluation in Patients With Community-Acquired Pneumonia

PATIENTS WHO DO NOT REQUIRE HOSPITALIZATION
None*
PATIENTS WHO REQUIRE HOSPITALIZATION
Two sets of blood cultures (obtained prior to antibiotics) in selected patients
Gram stain and culture of a valid sputum sample in selected patients
Urinary antigen test for detection of *Legionella pneumophila* (in endemic areas or during outbreaks)
Stain for acid-fast bacilli and culture of sputum (if tuberculosis is suggested by clinical history or radiologic findings)
Fungal stain and culture of sputum, and fungal serologies (if infection by an endemic fungus is suggested by the clinical history or radiologic findings)
Sputum examination for *Pneumocystis jirovecii* (if suggested by clinical history, HIV infection, or radiologic findings)
Nucleic acid amplification tests for *Mycoplasma pneumoniae, Chlamydophila pneumoniae, Chlamydophila psittaci, Coxiella burnetii, Legionella* species, respiratory viruses (in endemic areas or during outbreaks) and other agents (e.g., *Streptococcus pneumoniae*) if available
Culture and microscopic evaluation of pleural fluid (if significant fluid is present)
ADDITIONAL TESTS FOR PATIENTS WHO REQUIRE TREATMENT IN AN ICU
Gram stain and culture of endotracheal aspirate or bronchoscopically obtained specimens using a protected specimen brush or BAL

*Gram stain and culture should be strongly considered in patients with risk factors for infection by an antimicrobial-resistant organism or unusual pathogen.

BAL, bronchoalveolar lavage; ICU, intensive care unit.

specimens be obtained before initiation of antimicrobial therapy. Sputum samples must be carefully collected, transported, and processed to optimize the recovery of common bacterial pathogens. In many centers, however, sputum analysis, particularly Gram stain, is less often employed.

A valid expectorated sputum specimen can be obtained in about 40% of patients hospitalized with CAP. When interpreting sputum cultures, one must ensure that oropharyngeal contents do not unduly contaminate the specimens. The presence of greater than 10 squamous epithelial cells per low-power field (×100 magnification) indicates excessive oropharyngeal contamination and the specimen should be discarded.[38] A specimen with few or no squamous cells and abundant *polymorphonuclear leukocytes* (PMNs) (>25 cells/low-power field in a sample from a patient who is not granulocytopenic) is ideal. Gram-stained expectorated sputum specimens of acceptable quality should be carefully examined using ×1000 magnification (oil immersion objective). Specific fluorescent antibodies can be used to evaluate sputum or other respiratory tract specimens for the presence of *Legionella* and selected other pathogens (see Chapter 19).

When acceptable sputum is obtained, the specificity of the Gram stain for pneumococcal pneumonia is estimated to be greater than 80%.[117] Because the fastidious nature of *S. pneumoniae* and *H. influenzae* leads to the death of these organisms, the sensitivity of sputum culture may be lower than that of sputum Gram stain. In contrast, *S. aureus* and gram-negative bacilli may dominate cultures even if they are not the cause of the patient's illness, because these bacteria are hardier and may proliferate during sample transport and processing. True pneumonia due to *S. aureus* or gram-negative bacilli is doubtful if the Gram stain of a valid sputum specimen does not corroborate the presence of these bacteria. In a good-quality Gram-stained sputum, the presence of a single or a preponderant morphotype of bacteria (≥90%) is considered diagnostic. In the absence of an informative Gram stain, the predictive value of sputum culture is very low.

Some bacterial agents of pneumonia cannot be cultivated on conventional laboratory media. For example, *Legionella* requires buffered charcoal yeast extract agar for isolation, whereas recovery of *Chlamydophila* species and *C. burnetii* requires culture in mammalian cell lines. When necessary, specimens can be sent to specialized or reference laboratories for appropriate procedures, including nucleic acid amplification assays (Chapter 19). Culture of certain agents of bacterial pneumonia poses major health risks to laboratory workers (e.g., *F. tularensis, Bacillus anthracis, C. burnetii*). Specimens suspected to harbor one of these agents should be dealt with carefully in a biologic safety hood, and isolation of the pathogens should be reserved for specialized laboratories.

Blood and Pleural Fluid Cultures

The latest IDSA/ATS guidelines[109] recommend obtaining blood cultures for hospitalized patients with the same clinical indications as are used to justify sputum collection (see eTable 46.2).

Although the overall yield of blood cultures is less than 20% in patients hospitalized for CAP, a positive culture of blood or pleural fluid can establish the etiologic diagnosis of pneumonia.[118] Unsurprisingly, the detected rate of bacteremia is lower in patients with mild CAP than in patients with severe CAP, especially those warranting ICU care. Prior antibiotic treatment decreases the yield of blood cultures.

A pleural effusion may be present in up to 40% of CAP cases. Although the specificity of pleural exudate cultures is very high, the sensitivity is very low because of the low incidence of pleural invasion. Diagnostic thoracentesis should be performed when a significant pleural effusion is present. Gram stain of pleural fluid may produce an indication of the infecting organisms within 1 hour, while culture identification may require 24 to 48 hours.

Antigen Detection

Commercial assays can be used to detect capsular polysaccharide antigens of *S. pneumoniae* or *L. pneumophila* serogroup 1 in urine, with results available in under an hour. The sensitivity of these tests is little affected by prior antibiotic treatment; indeed, results may remain positive several weeks after successful treatment. For *L. pneumophila* serogroup 1, the sensitivity is approximately 80% and the specificity is 99%.[119] Currently available tests detect *L. pneumophila* serogroup 1 antigen only. Nevertheless, this serogroup accounts for 80% of community-acquired *Legionella* disease.[120]

A meta-analysis estimated the sensitivity and specificity of *S. pneumoniae* urinary antigen for the diagnosis of S. *pneumoniae* infection in adult CAP to be 74% and 97%,

respectively.[121] The degree of positivity for the *S. pneumoniae* urinary antigen test correlates with the Pneumonia Severity Index.[122] The *S. pneumoniae* antigen test may also be applied on pleural fluid with a sensitivity and specificity of almost 100%, but should be interpreted with caution in children due to low specificity caused by nasopharyngeal carriage.[123] Current IDSA/ATS guidelines[109] recommend *S. pneumoniae* and *L. pneumophila* urinary antigen detection with recent travel or exposure to *Legionella* outbreaks, or with severe CAP.

Antigens for many common respiratory viruses, including influenza virus, RSV, adenovirus, and parainfluenza viruses, can be detected by direct immunofluorescence or by enzyme-linked immunoassay. A rapid antigen detection test for influenza can provide an etiologic diagnosis within 15 to 30 minutes. Test performance varies according to the test used, viral strain, sample type, duration of illness, and patient age. Most show a sensitivity ranging from 50–70% and a specificity approaching 100% in adults. However, with the exception of RSV, rapid antigen tests have largely been superseded by nucleic acid amplification tests owing to their superior sensitivity (see Chapter 19).

Nucleic Acid Amplification Tests

Nucleic acid amplification tests are rapid and have much greater sensitivity than conventional methods in the diagnosis of respiratory viruses and atypical bacteria; some are now considered the gold standard.[124,125] The development of real-time multiplex PCR assays allowing detection of multiple respiratory viruses and atypical bacteria simultaneously can facilitate the rapid diagnosis of pneumonia, and has the potential to reduce the unnecessary use of antimicrobial treatment. Multiplex panels are expanding to include other bacterial causes of CAP such as *S. pneumoniae* and MRSA. Moreover, a number of rapid molecular tests primarily for the detection of influenza A and B viruses, RSV, and SARS-CoV-2 have been approved by the U.S. Food and Drug Administration. A result is available within 15 to 30 minutes and greater than 99% sensitivity and greater than 97% specificity are reported.[126]

Caution is necessary in the interpretation of viral PCR results because one or more respiratory viruses can be detected in up to 15% of healthy persons.[127] Detection of virus on nasopharyngeal or oropharyngeal samples may indicate upper respiratory tract infection or convalescent shedding rather than the causative pathogen of CAP. Furthermore, PCR-based methods can only detect targeted pathogens. (See Chapter 19 for detailed information on nucleic acid amplification tests for respiratory pathogens.)

Metagenomic Sequencing

Metagenomic *next-generation sequencing* is an emerging DNA technology that sequences multiple small DNA fragments in parallel. It allows unbiased detection of all microorganisms present, does not require preexisting knowledge of expected pathogens in the sample, and can provide detailed characterization of pathogen species and genomic sequences. Until recently, metagenomic next-generation sequencing of respiratory samples has been limited by poor sensitivity due to the relatively low abundance of pathogen nucleic acids compared to host and commensal nucleic acids (e.g., pathogen/host nucleic acid ratio $1/10^5$ in sputum). Recent studies using hybridization-based sequence capture to enrich for respiratory viral detection,[128] as well as host DNA depletion and nanopore sequencing to detect bacteria and antibiotic resistance genes,[129] report improved sensitivity of greater than 95%. Nevertheless, high cost and the need for sequencing and computational expertise currently limits the use of metagenomic next-generation sequencing to research settings. (See Chapter 19 for detailed information on next-generation sequencing of respiratory pathogens.)

Serologic Evaluation

Before the development of nucleic acid amplification tests, serologic techniques were used to establish a microbiologic diagnosis for pneumonia caused by pathogens that cannot be readily cultured. Examples include common pathogens such as *M. pneumoniae, C. pneumoniae,* and *L. pneumophila* and less common causes of pneumonia such as those caused by the agents of tularemia, brucellosis, and psittacosis, and certain viruses. Diagnosis usually required that a convalescent specimen demonstrate a fourfold increase in IgG titer above that present in an acute specimen. These tests are unhelpful in initial patient management but are of utility in defining the epidemiology of the pertinent infectious agents. Because IgM antibodies appear earlier than IgG antibodies, the detection of pathogen-specific IgM in serum has been used for the early serologic diagnosis of certain acute infections.

Invasive Diagnostic Techniques

Invasive procedures may be necessary to obtain suitable material for microscopy and cultures in certain instances, such as in the management of patients with life-threatening CAP in whom diagnostic materials cannot otherwise be obtained, for patients with progressive pneumonia despite seemingly appropriate antimicrobial therapy, or for immunocompromised patients.[103]

Lower Airway Samples

Samples can also be obtained from the lower airway by bronchial wash obtained via an endotracheal tube or by BAL obtained by bronchoscopy. The reliability of bronchial sampling to determine the microbial etiology of pneumonia depends on the technique used and the organism sought. When compared with sputum cultures, optimally processed bronchial specimens demonstrate improved sensitivity and equal specificity for the culture of pathogenic fungi and mycobacteria but poor specificity for culture of bacteria that commonly cause CAP due to oropharyngeal contamination. Semiquantitative or quantitative cultures of materials obtained bronchoscopically with a protected sheath brush or through BAL and by direct lung aspiration have been successfully used for aerobic and anaerobic bacterial cultures.[130] For protected specimen brush cultures, a threshold of 10^3 cfu/mL has been recommended to distinguish colonization from infection. However, 14–40% of duplicate samples yield disparate quantitative results.

BAL fluid can be quantitatively cultured for bacteria and qualitatively cultured for fungi, mycobacteria, and viruses. A concentrate can be stained for cytochemical and fluorescence evaluation.[131] In one study, the threshold of 10^3 cfu/mL for diagnosing bacterial pneumonia correlated well

with diagnoses based on protected sheath brush results and histologic examination of the lung.[132] BAL permits the immediate diagnosis of infection (i.e., intracellular bacteria in >2–5% of examined PMNs) and the exclusion of infection (i.e., the absence of bacterial pathogens in culture of BAL fluid, although sensitivity is reduced by prior antibiotic administration).[133]

In one ICU study, the use of quantitative cultures obtained by protected sheath brush and BAL, compared with qualitative cultures of endotracheal aspirates and clinical evaluation, was associated with lower 14-day mortality, earlier reversal of organ dysfunction, and less antibiotic use.[134] However, other randomized trials have not replicated these findings.[135,136]

Transthoracic Lung Aspiration

Transthoracic lung aspiration obtains specimens suitable for microbiologic and cytologic examination directly from lung parenchyma (eFig. 46.6). It is more widely used for diagnosing malignant pulmonary lesions than infections. In immunocompetent hosts, the diagnostic yield by transthoracic lung aspiration is approximately 50%. Its main utility has been in children, and it is less useful in adults. Serious complications of transthoracic lung aspiration include pneumothorax and hemoptysis, even when small-gauge needles are used.

Differential Diagnosis

Several diseases may present with fever and chest radiographic opacities and mimic CAP (eTable 46.3);[101] such diseases should be suspected when the radiographic resolution is unusually quick or when there is a lack of response to initial or subsequent antibiotic treatments.

THERAPEUTIC APPROACH TO PNEUMONIA

Once the diagnosis of pneumonia is made, the clinician must decide the appropriate treatment setting: outpatient, general hospital bed, or ICU. Applying prediction rules can facilitate this decision. The second key decision is the selection of initial antimicrobial therapy.

ASSESSMENT OF SEVERITY

The *Pneumonia Severity Index* (PSI) (Table 46.3) is a scoring system derived from a retrospective analysis of a cohort of 14,199 patients with CAP and prospectively validated in a separate cohort of 38,039 patients with CAP.[137] The PSI is heavily weighted by age, which means it is less useful at extremes of age and is not valid in children. Outpatient treatment is recommended for patients with a PSI score of 70 or less (class I or II). Patients with a PSI score of 71 to 90 (class III) may benefit from brief hospitalization, while inpatient care is appropriate for patients with a score greater than 90 (class IV and V). Prospective studies in both community and teaching hospitals demonstrate that hospital admission decisions based on PSI may be safely and effectively applied in clinical practice.[138–140] Additional studies have shown the use of the PSI increases the proportion of patients safely treated as outpatients.[141,142,143]

The British Thoracic Society validated the simpler CURB-65 score for admission triage decisions.[47] Their algorithm assigns 1 point for each of the following findings at presentation: (1) confusion; (2) urea greater than 7 mmol/L (equivalent to blood urea nitrogen >20 mg/dL); (3) respiratory rate of 30 breaths/min or greater; (4) low systolic (<90 mm Hg) or diastolic (≤60 mm Hg) blood pressure; and (5) age 65 years or greater. Outpatient treatment is recommended for 0 to 1 points, brief inpatient or supervised outpatient care is recommended for 2 points, and hospitalization is recommended for 3 or more points, with consideration of ICU care for patients with scores of 4 or 5.

Risk stratification for both PSI and CURB-65 was based on associated mortality. They are therefore not sensitive to logistic and social issues such as reliability of oral intake, including antibiotics, and home support. When compared to CURB-65, the PSI was a better predictor of short-term mortality and classified a larger number of patients as low risk.[144] Furthermore, recent studies in lower- and middle-income countries have demonstrated variable performance of CURB-65 in predicting mortality in adults with CAP, likely reflecting differences in demographics, comorbidities, and microbial etiology in these settings.[76,145] It has not proved particularly useful, for example, in sub-Saharan Africa.

Patients initially admitted to a general floor with subsequent transfer to the ICU have higher mortality than patients with equivalent severity of illness admitted directly to the ICU.[146] Neither PSI nor CURB-65 is accurate for determining need for ICU care in patients without an obvious indication, such as the need for mechanical ventilation or vasopressor support while still in the emergency department. Several scores have been developed for this critical decision.[147–150] These scores share many common risk factors and appear to be similarly effective.[151] Management of severe CAP using these guidelines has been associated with decreased mortality.[152–154] The optimal use of these scores is to identify at-risk patients who need additional evaluation or monitoring, even if not initially admitted to the ICU.

CORRECTION OF HOST ABNORMALITIES

Defects related to the host's immune system may impede recovery from pneumonia. Immunodeficiency may arise as a complication of age, cancer chemotherapy, immunosuppressive agents, or corticosteroid use; or it may result from a congenital (e.g., hypogammaglobulinemia) or acquired (e.g., HIV infection) immune defect. Many of these immune deficiencies are not remediable; however, drug-related immunosuppression may be improved by discontinuing the offending agent or reducing the dose when possible. Although reduction of immunosuppression may promote recovery from the active infection, it can also be complicated by enhanced inflammation due to immune reconstitution.[155]

Granulocytopenia (absolute granulocyte count <500 cells/mm^3) has been associated with fulminant, antibiotic-unresponsive pneumonia, and administration of *granulocyte colony-stimulating factor* (G-CSF) or *granulocyte-macrophage colony-stimulating factor* (GM-CSF) is effective in increasing the number of circulating neutrophils. Despite this effect on neutrophils, routine administration of G-CSF or GM-CSF has not been found

eTable 46.3 Noninfectious Causes of Fever and Radiographic Changes That May Mimic Community-Acquired Pneumonia

Pulmonary edema
Pulmonary infarction
Acute respiratory distress syndrome
Pulmonary hemorrhage
Lung cancer or metastatic cancer
Atelectasis
Radiation pneumonitis
Drug reactions involving the lung
Hypersensitivity pneumonitis
Pulmonary vasculitis
Pulmonary eosinophilia
Organizing pneumonia

Table 46.3 Pneumonia Severity Index Scoring System for Determining Risk of Complications in Patients with Community-Acquired Pneumonia

Patient Characteristic	Points Assigned
DEMOGRAPHIC FACTORS	
Men	Age (yr)
Women	Age (yr) −10
Nursing home residents	Age (yr) +10
COMORBID ILLNESSES	
Neoplastic disease	+30
Liver disease	+20
Congestive heart failure	+10
Cerebrovascular disease	+10
Renal disease	+10
PHYSICAL EXAMINATION FINDINGS	
Altered mental status	+20
Respiratory rate ≥30 breaths/min	+20
Systolic blood pressure <90 mm Hg	+20
Temperature <35°C or ≥40°C	+15
Pulse ≥125 beats/min	+10
LABORATORY FINDINGS	
pH <7.35	+30
BUN ≥30 mg/dL (≥10.7 mmol/L)	+20
Sodium <130 mEq/L	+20
Glucose ≥250 mg/dL (≥13.9 mmol/L)	+10
Hematocrit <30%	+10
Pa_{O_2} <60 mm Hg or O_2 saturation <90%	+10
Pleural effusion	+10

A risk score is obtained by summing the patient's age in years (age −10 for women) and the points for each applicable patient characteristic. Patients with a score <70 are candidates for outpatient treatment, whereas those with scores >90 warrant hospitalization. Proper management of patients with scores of 70 to 90 requires careful application of clinical judgment.

BUN, blood urea nitrogen; Pa_{O_2}, arterial oxygen pressure.

Modified from Fine MJ, Auble TE, Yealy DM, et al. A prediction rule to identify low-risk patients with community-acquired pneumonia. *N Engl J Med*. 1997;336:243–250.

to improve survival from infections.[156] Because pneumonia is the infection most frequently associated with a poor clinical outcome in profoundly neutropenic patients, the use of G-CSF or GM-CSF in these patients may be justified even though a benefit has not been demonstrated.[157] GM-CSF has also been studied as an approach to correct the neutrophil phagocytosis defect in critically ill patients. In a small, multicenter randomized controlled trial, GM-CSF was safe and, although mean neutrophil phagocytosis was not increased, the proportion of patients with neutrophil phagocytosis was 50% or greater, suggesting GM-CSF could increase the proportion of patients with adequate phagocytosis.[158] Corticosteroid treatment has been investigated because of its suppressant effect on inflammatory responses; studies have yielded discordant findings without consistent benefits. Recent guidelines do not recommend corticosteroid therapy for CAP or influenza pneumonia, other than when indicated for refractory shock.[109]

SELECTION OF ANTIMICROBIAL AGENTS

Antimicrobial stewardship principles aim to select the most appropriate antimicrobial agent and optimize the dose and duration while minimizing the potential toxicity and emergence of antimicrobial resistance. Increasing rates of hospital-acquired infections such as MRSA and *Clostridioides* (formerly *Clostridium*) *difficile* infection also influence empiric antimicrobial prescribing. Whenever possible, treatment for pneumonia should use the antibiotic with the narrowest spectrum possible, selected on the basis of the underlying pathogen. However, pathogens are rarely identified at the time of presentation, especially when pneumonia is managed in the outpatient setting. Because optimal outcomes are associated with a rapid initiation of antibiotics, initial treatment for patients with pneumonia must be empirical. In selecting initial empirical antimicrobial therapy, physicians should consider the illness severity, presence of comorbidities and immunosuppression, recent antimicrobial therapy, and geographic and facility-specific epidemiology, such as the local and temporal prevalence of specific microorganisms (e.g., *C. burnetii, L. pneumophila,* endemic mycoses, and *multidrug-resistant* pathogens).

In patients being admitted to the hospital, specimens for culture should be obtained before treatment. A brief delay in starting therapy while performing diagnostic procedures is reasonable in patients who are not hypotensive. However, delays of more than 4 to 8 hours may increase the length of hospitalization and have been associated with increased mortality.[154,159]

It is important to recognize that all CAP treatment guidelines are based on broad epidemiologic considerations that may vary by location with respect to geographically restricted pathogens and antimicrobial resistance. Local incidence and susceptibility patterns guide empiric regimens to cover MRSA, gram-negative Enterobacteriaceae, or *P. aeruginosa*.[46,160]

Recent guidelines suggest use of amoxicillin, doxycycline, or macrolides for outpatient treatment of CAP (Table 46.4) in the absence of medical comorbidity; the guidelines no longer require routine coverage of atypical pneumonia.[109,161–163] Macrolides should not be used if local *S. pneumoniae* resistance exceeds 25%.[109] North American guidelines consider amoxicillin–clavulanic acid or oral cephalosporins combined with a macrolide or doxycycline, or a respiratory fluoroquinolone, for outpatient therapy in patients with medical comorbidity. This is to ensure coverage of additional pathogens, such as *H. influenzae*, that may produce a β-lactamase.[109] For inpatient therapy, a β-lactam is usually combined with an extended-spectrum macrolide (Table 46.5). The British Thoracic Society guidelines exclude the macrolide in mild disease and the European Respiratory Society/European Society of Clinical Microbiology and Infectious Diseases guidelines make it optional outside the ICU. North American guidelines recommend use of β-lactam/β-lactam inhibitors or cephalosporins for all hospitalized patients, while the British Thoracic Society guidelines only recommend these for more severe CAP, preferring amoxicillin or benzylpenicillin. The European Respiratory Society guidelines allow use of any of these β-lactams for mild to moderate CAP.

Table 46.4 Guidelines for Empirical Oral Outpatient Treatment of Immunocompetent Adults With Community-Acquired Pneumonia

ATS/IDSA[109]
No modifying factors[a]: amoxicillin,[b] doxycycline or advanced macrolide if *S. pneumoniae* macrolide resistance <25%[c,d] Comorbidities[a]: β-lactam,[e] macrolide[f] or doxycycline,[d] or fluoroquinolone[g] alone
BTS[161,162]
Primary: amoxicillin Alternatives: clarithromycin or doxycycline
ERS/ESCMID[163]
Amoxicillin or doxycycline with macrolide as alternative if low levels of resistance
DRSPTWG
Primary: amoxicillin, amoxicillin-clavulanate, cefuroxime, doxycycline, macrolide (if low rate of resistance) Alternative: fluoroquinolone[h]

[a]American Thoracic Society/Infectious Disease Society of America comorbidities (modifying factors) include chronic heart, lung, liver or kidney disease, diabetes, asplenia, alcoholism, and malignancy.
[b]Amoxicillin 1 g q8h, doxycycline 100 mg q12h, azithromycin 500 mg on first day then 250 mg/day, clarithromycin 500 mg q8h, or clarithromycin extended release 1000 mg/day.
[c]Advanced macrolides are azithromycin and clarithromycin.
[d]Second-choice agent.
[e]Amoxicillin-clavulanate (500 mg amoxicillin plus 125 mg clavulanate q8h, 875 mg amoxicillin plus 125 mg clavulanate q12h or 2 g amoxicillin plus 125 mg clavulanic acid q12h), cefpodoxime, cefprozil, or cefuroxime.
[f]Because of increasing macrolide resistance, erythromycin cannot be relied upon to ensure coverage of β-lactamase–producing *Haemophilus influenzae*. A combination of a β-lactam/β-lactamase inhibitor is preferred.
[g]Antipneumococcal fluoroquinolones include levofloxacin, and moxifloxacin.
[h]Levofloxacin or moxifloxacin.
ATS/IDSA, American Thoracic Society/Infectious Diseases Society of America; BTS, British Thoracic Society; DRSPTWG, Drug-Resistant *Streptococcus pneumoniae* Therapeutic Working Group; ERS/ESCMID, European Respiratory Society and European Society for Clinical Microbiology and Infectious Diseases.

There is a differing emphasis on fluoroquinolones, with the North American guidelines considering them valid alternatives to the β-lactams plus macrolide combinations; however, European guidelines suggest they are less-preferred alternatives. This follows the European Medicines Evaluation Agency guidance that suggests they should be reserved for settings where other agents cannot be used or have failed. This reflects concerns about levels of hepatotoxicity, QT prolongation, fluoroquinolone-related musculoskeletal and neurologic adverse events, and propensity to contribute to *C. difficile* or MRSA infections.[163,164] Widespread fluoroquinolone use, especially in subtherapeutic doses, and use of ciprofloxacin have been associated with fluoroquinolone resistance in up to 13% of *S. pneumoniae* isolates in Hong Kong. Fluoroquinolone resistance and subsequent treatment failures are reported in pneumococcal CAP,[165–167] but this is less common with use of fluoroquinolones that have improved activity against respiratory pathogens. When tuberculosis is a possibility, fluoroquinolones should be avoided because as few as 10 days of fluoroquinolone administration is sufficient to select for fluoroquinolone-resistant *M. tuberculosis*.[168]

Retrospective studies suggest combination therapy for severe pneumococcal pneumonia and severe CAP in general is associated with lower mortality. A meta-analysis of observational data demonstrated reduced mortality with macrolide use in severe CAP.[169] In a large cohort of older patients with CAP needing hospitalization, antibiotic treatment including azithromycin was associated with a lower 90-day risk mortality compared with other antibiotics.[170] However, this has not been a uniform finding, as other studies have found no such benefit.[171]

In recent North American HAP/*ventilator-associated pneumonia* (VAP) guidelines, the former category of health care–associated pneumonia has been removed because patients previously fitting this category are generally infected with pathogens associated with CAP, which are not multidrug resistant.[172] Empiric coverage of MRSA or *P. aeruginosa* is reserved for hospitalized patients with prior evidence of the pathogens in the respiratory tract or for severe CAP in people who have been recently hospitalized and received parenteral antimicrobials, in addition to having locally validated risk factors for these pathogens.[109]

In most patients with normal immunity, supportive therapy of viral pneumonia is successful with early antimicrobial therapy of secondary bacterial infections, if present. Specific antiviral therapy may be beneficial and is discussed with the individual pathogens. Viral pneumonia with extensive involvement of lung tissue may require prolonged ventilatory assistance and pulmonary rehabilitation. Bacterial superinfections are common in influenza and RSV infections and should be sought and treated when a patient with one of these viral infections worsens clinically.

ADJUSTMENTS IN ANTIMICROBIAL THERAPY IN PATIENTS WHO ARE STABLE OR IMPROVING

If the etiologic agent of a patient's pneumonia has been identified, the initial antimicrobial regimen should be adjusted based on the results of in vitro susceptibility testing. The ideal drug for a known pathogen has the narrowest spectrum of activity and is the most efficacious, least toxic, and least costly. Recommendations for specific drug choices for specific microorganisms are discussed under the sections devoted to individual pathogens and are summarized in eTable 46.4. If a pathogen is not identified, reevaluation of the initial therapeutic regimen must take into account the patient's response to therapy. Change from parenteral to oral antimicrobial therapy can safely be made in hospitalized CAP patients when clinically stable and able to absorb oral antimicrobials[173,174]; this is often achieved within 2 to 3 days. In-hospital observation after switching from intravenous to oral antibiotics for CAP patients is not needed. Treatment duration is usually for as long as required to ensure clinical stabilization, as evidenced by normalization of clinical features such as vital signs and physiologic parameters such as pulse oximetry.[109] Treatment should be for a minimum of 5 days.[109]

eTable 46.4 Agents for Specific Therapy of Selected Respiratory Pathogens

Type of Infection	Preferred Agent(s)	Alternative Agent(s)
COMMUNITY-ACQUIRED PNEUMONIA		
Streptococcus pneumoniae		
Penicillin-susceptible	Penicillin G, amoxicillin, doxycycline	Cephalosporin, macrolide* (MIC <2 g/mL), fluoroquinolone†
Penicillin-resistant	Agents identified using in vitro susceptibility tests, including cefotaxime, ceftriaxone, ceftaroline, vancomycin	Fluoroquinolone,† linezolid, clindamycin
Mycoplasma pneumoniae	Doxycycline, macrolide	Fluoroquinolone†
Chlamydophila pneumoniae	Doxycycline, macrolide	Fluoroquinolone†
Legionella	Azithromycin, fluoroquinolone (levofloxacin or moxifloxacin)	Doxycycline
Haemophilus influenzae	β-lactam/β-lactamase inhibitor, cephalosporin	Trimethoprim-sulfamethoxazole, azithromycin, doxycycline, fluoroquinolone†
Moraxella catarrhalis	β-lactam/β-lactamase inhibitor, third-generation cephalosporin	Trimethoprim-sulfamethoxazole, azithromycin, doxycycline, fluoroquinolone†
Neisseria meningitidis	Third-generation cephalosporin, penicillin G	Chloramphenicol, fluoroquinolone†
Streptococci (other than *S. pneumoniae*)	Penicillin G, cephalosporins	Clindamycin (susceptibility should be confirmed), vancomycin
Anaerobes	β-lactam plus metronidazole, β-lactam/β-lactamase inhibitor	Clindamycin, carbapenem
Staphylococcus aureus		
Methicillin-susceptible‡	Oxacillin, nafcillin	Cephalosporins, vancomycin, clindamycin, fluoroquinolones†
Methicillin-resistant‡	Vancomycin,‡ linezolid	Clindamycin, trimethoprim-sulfamethoxazole, fluoroquinolones,† and tetracyclines may also show activity (in vitro testing required)
Klebsiella pneumoniae and other Enterobacteriaceae (excluding *Enterobacter* sp)	Sensitive organism: third-generation cephalosporin, β-lactam/β-lactamase inhibitor, carbapenem (all ± aminoglycoside) Extended-spectrum β-lactamase producing: carbapenems, fosfomycin (intravenous), tigecycline, colistin Carbapenemase-producing *Klebsiella*: ceftazidime-avibactam	
Influenza	Oseltamivir, zanamivir, peramivir, baloxivir	
Respiratory syncytial virus	Ribavirin	
LESS COMMON PATHOGENS		
Nocardia	Third-generation cephalosporin plus amikacin ± trimethoprim-sulfamethoxazole	Imipenem ± amikacin, third-generation cephalosporin, minocycline, tigecycline, linezolid, fluoroquinolones†
Coxiella burnetii (Q fever)	Doxycycline	Macrolides (clarithromycin or azithromycin), trimethoprim-sulfamethoxazole, fluoroquinolones
Chlamydophila psittaci (psittacosis)	Doxycycline	Macrolide, chloramphenicol

*Azithromycin (IV or PO) is the preferred macrolide; clarithromycin (PO) or erythromycin (IV or PO) may also be used.
†Levofloxacin (IV or PO), gatifloxacin (IV or PO), moxifloxacin (IV or PO), or gemifloxacin (PO only) are preferred for *Streptococcus pneumoniae*. Ciprofloxacin has the best in vitro activity against *Pseudomonas aeruginosa*.
‡Rifampin and gentamicin should be reserved for cases of bacteremic *Staphylococcus aureus* pneumonia, empyema formation, or lung abscesses. Activity of rifampin and gentamicin requires laboratory confirmation for methicillin-resistant *S. aureus*.
§ Antipseudomonal β-lactams include ceftazidime, cefepime, imipenem, meropenem and piperacillin-tazobactam.
IV, intravenous; MIC, minimum inhibitory concentration; PO, by mouth.
Updated from Bartlett JG, Dowell SF, Mandell LA, et al. Practice guidelines for the management of community-acquired pneumonia in adults: Infectious Diseases Society of America. *Clin Infect Dis*. 2000;31:347–382.

Table 46.5 Guidelines for Empirical Parenteral Inpatient Treatment of Immunocompetent Adults With Community-Acquired Pneumonia

MILD TO MODERATE DISEASE

ATS/IDSA[109]

- Primary[c]: ampicillin and sulbactam, cefotaxime, ceftriaxone, or ceftaroline with azithromycin or clarithromycin
- Alternative: fluoroquinolone[a] alone or, if history of prior respiratory isolation of MRSA[d] or *Pseudomonas aeruginosa*,[e] treatment to cover these agents

BTS[161,162]

- Mild: oral amoxicillin. Alternatives parenteral amoxicillin or benzylpenicillin or clarithromycin
- Moderate: oral amoxicillin and clarithromycin (can consider clarithromycin monotherapy if prior therapy with amoxicillin)
- Alternative if unable to take oral medication: parenteral amoxicillin or benzylpenicillin plus clarithromycin (if intolerant of penicillin but able to take a cephalosporin parenteral second- or third-generation cephalosporin plus clarithromycin)
- Alternative: if unable to take penicillin or macrolide, oral doxycycline, or if not able to take any of these, a respiratory fluoroquinolone[a]

ERS/ESCMID[163]

- Aminopenicillin, aminopenicillin with β-lactamase inhibitor, penicillin, cefotaxime, ceftriaxone with or without macrolide
- Respiratory fluoroquinolone alone[a]

DRSPTWG

- Primary: cefuroxime, cefotaxime, ceftriaxone, or ampicillin-sulbactam; macrolide
- Alternative: fluoroquinolone[a]

SEVERE DISEASE

ATS/IDSA[109]

- Primary[c]: Ampicillin and sulbactam, cefotaxime, ceftriaxone, or ceftaroline with azithromycin or clarithromycin
- Alternative: broad-spectrum β-lactam as for primary with fluoroquinolone[a] or, if history of prior respiratory isolation or prior hospitalization with parenteral antimicrobials within 90 days in setting of locally validated risk factors for MRSA[d] or *P. aeruginosa*,[e] treatment to cover these agents

BTS[161,162]

- Primary: amoxicillin/clavulanate (or if penicillin intolerant cefuroxime, cefotaxime, or ceftriaxone) plus macrolide

ERS/ESCMID[163]

- Cefotaxime or ceftriaxone plus macrolide or respiratory fluoroquinolone
- Alternative: respiratory fluoroquinolone alone if no sepsis
- Alternative if risk factors for *P. aeruginosa*: piperacillin/tazobactam, anti-pseudomonal cephalosporin (ceftazidime[f] or cefepime) plus ciprofloxacin or plus macrolide and aminoglycoside[g]

DRSPTWG

- Primary: ceftriaxone or cefotaxime, macrolide; or ceftriaxone or cefotaxime, fluoroquinolone[a]
- Alternative (with caution): fluoroquinolone.[a]

[a]Antipneumococcal fluoroquinolones include levofloxacin 750 mg/day and moxifloxacin 400 mg/day.
[b]Advanced macrolides are azithromycin and clarithromycin.
[c]Ampicillin and sulbactam 1.5-3 g q6h, cefotaxime 1-2 g q8h, ceftriaxone 1-2 g/day, or ceftaroline 600 mg q12h and azithromycin 500 mg/day or 500 mg on day 1 and 250 mg once a day thereafter for mild disease) or clarithromycin 500 mg bid.
[d]Anti-staphylococcal treatments include vancomycin (15 mg/kg q12h, adjust based on levels) or linezolid (600 mg q12h).
[e]Antipseudomonal β-lactams include piperacillin-tazobactam (4.5 g q6h), cefepime (2 g q8h), ceftazidime (2 g q8h), imipenem (500 mg q6h), meropenem (1 g q8h), or aztreonam (2 g q8h).
[f]If ceftazidime used should be combined with penicillin to ensure coverage of pneumococci per ERS/ESCMID guideline.
[g]Recommendation to double cover *P. aeruginosa* with both a β-lactam and either ciprofloxacin or an aminoglycoside per ERS/ESCMID guideline.
ATS/IDSA, American Thoracic Society/Infectious Diseases Society of America; BTS, British Thoracic Society; DRSPTWG, Drug-Resistant *Streptococcus pneumoniae* Therapeutic Working Group; ERS/ESCMID, European Respiratory Society and European Society for Clinical Microbiology and Infectious Diseases.

ADJUSTMENTS IN ANTIMICROBIAL THERAPY IN PATIENTS WHO ARE DETERIORATING OR NOT IMPROVING

The optimal therapeutic approach to nonresolving pneumonia involves close monitoring, often transfer to a higher level of care, and optimization of the antibiotic regimen, including dosing.[175] The optimal time to make these changes is not defined, although it has been suggested to wait until at least 48 hours after treatment initiation except in the presence of severe clinical deterioration or dramatic radiologic progression.

In nonresponding CAP, new cultures should be obtained and empirical coverage for resistant *S. pneumoniae*, *P. aeruginosa*, MRSA, and anaerobes should be considered. Alternative diagnoses must also be considered, including fungal pneumonias in areas where endemic fungi are prevalent and tuberculosis in patients with a plausible history of exposure. The specific antimicrobial regimen chosen depends on patient risk factors, disease severity, and the local epidemiology of antimicrobial resistance. In CA-MRSA, antimicrobial regimens may include linezolid or clindamycin plus vancomycin, depending on results of susceptibility testing.[176] The increasing spread of virulent carbapenemase-producing *K. pneumoniae* also necessitates vigilance for these organisms that are especially challenging to treat.[177]

COMMON CAUSES OF PNEUMONIA

Individual pneumonia pathogens have unique epidemiology, diagnostic tests, and/or treatment. The sections that follow emphasize these unique aspects for selected pathogens (or groups).

MAJOR CAUSES OF PNEUMONIA

Streptococcus pneumoniae (Pneumococcal Pneumonia)

Epidemiology. *S. pneumoniae* is the most frequent cause of CAP among patients who require hospitalization.[40,41] The overall incidence of pneumococcal pneumonia is approximately 200 cases per 100,000 persons per year in the United States and other developed countries. This infection accounts for 40,000 deaths annually in the United States, with most deaths in the very young and the elderly. Risk factors, particularly in adults, include cigarette smoking, HIV infection (even with antiretroviral therapy and normal CD4 counts), heavy alcohol use, chronic liver disease, asthma and chronic lung disease, defects in host immunity, asplenia, and malnutrition.[178,179] Pneumococcal infections present predominantly in the winter and early spring and are often associated with prior infection by influenza or RSV.[180]

Use of the *pneumococcal conjugate vaccine* (PCV) has markedly decreased invasive pneumococcal infections in children, with a secondary reduction in adults in the United States.[181,182] This latter effect probably represents interruption of transmission because the conjugate vaccine reduces colonization.[183] However, widespread use of PCV in the United States has resulted in an increase in the number and proportion of cases of invasive pneumococcal disease due to non-vaccine serotypes.[184] Data from U.S. adults hospitalized with CAP in 2013 to 2016 show that, since a conjugate vaccine containing 13 capsular polysaccharide antigens was approved by the *U.S. Food and Drug Administration* (FDA) in 2012, approximately half of pneumococcal CAP is currently due to non-vaccine serotypes.[185]

Pathogenesis of *S. pneumoniae*. *S. pneumoniae* contains a core genome and a large number of noncore genes, promoting diversity.[186] The polysaccharide capsule exists in at least 92 antigenic types; because the polysaccharide capsule is the target of antibodies that provide protective immunity by promoting phagocytosis and intracellular killing, antigenic variation allows for repeated infections and promotes circulation of multiple antigenic types in a community.[187] Antigenic variation of the capsular polysaccharide also necessitates inclusion of multiple antigenic types in the currently available pneumococcal vaccines. The polysaccharide capsule also helps the pathogen avoid binding to mucus and inhibits recognition by phagocytes in the absence of specific antibodies. An additional virulence factor of *S. pneumoniae* is pneumolysin, a secreted toxin that inhibits ciliary function, limits complement opsonization, modulates reactive oxygen species generation, and promotes inflammation through cytokine production and T cell activation.[188] Pneumococcal surface proteins A and C inhibit opsonization with complement while an IgA protease inhibits IgA function, enabling colonization.[188] *S. pneumoniae* is an obligate extracellular pathogen because it is killed rapidly after being phagocytosed by neutrophils or macrophages. Therefore, its virulence strategies have principally evolved to evade phagocytosis.

Pneumococcal infection is preceded by colonization of the upper respiratory mucosa; bacteria that reach the distal airway are thought to be cleared by alveolar macrophages, especially if they are opsonized by anticapsular antibodies.[22,23] When alveolar macrophages are unable to clear the bacteria, neutrophils are recruited and become essential for bacterial clearance, although neutrophils depend on antibody opsonization of *S. pneumoniae* for optimal phagocytosis and killing.[23] Effective immune responses require a range of pattern recognition receptors, including TLR2, which recognizes lipopeptides, and *nucleotide oligomerization domain (NOD)-like receptor* (NLR) P3 inflammasomes activated by pneumolysin.[186,188] *S. pneumoniae* can also be cleared by apoptosis of bacteria-containing alveolar macrophages without triggering inflammation.[189]

Clinical Manifestations. The classic presentation of pneumococcal pneumonia consists of a rigor followed by sustained fever, cough, dyspnea, and production of rusty or mucoid sputum; gross hemoptysis is unusual. Pleuritic chest pain is common and may be severe. The typical radiographic appearance of pneumococcal pneumonia is lobar consolidation (see Fig. 46.1A and eFig. 46.2) or patchy bronchopneumonia (eFig. 46.7). Although pneumococci can cause necrotizing pneumonia, cavitation rarely develops.[178] Small, parapneumonic effusions are frequently present and can progress to frank empyema. Neutropenia may develop in patients with overwhelming infection and is associated with higher mortality.[190]

Microbiologic Diagnosis. A Gram stain of purulent sputum revealing numerous characteristic lancet-shaped diplococci with blunted ends (commonly seen in pairs and short chains) in the absence of other predominant flora is strongly suggestive of pneumococcal pneumonia (see Fig. 46.1B). However, a good-quality sputum specimen cannot always be obtained.[191] The organism is recovered from sputum culture in fewer than half of cases, and even a single dose of antibiotics can affect the yield of sputum cultures, which contributes to the discrepancy between sputum Gram stain and culture results. The frequency of positive blood cultures in hospitalized patients has decreased in the last few decades.[41] This decrease may reflect a greater percentage of blood cultures drawn after antibiotics due to the emphasis on prompt antibiotic dosing in the emergency department, de-emphasis on blood cultures in CAP in general, and/or a benefit of vaccination on invasive pneumococcal disease.[109]

The rapid urinary antigen *S. pneumoniae* test offers an alternative approach to the diagnosis of pneumococcal CAP and is becoming more widely used in diagnosis and in narrowing antibiotic therapy.[192–195] Despite satisfactory sensitivity and specificity, the urinary antigen test cannot provide information on antimicrobial susceptibility of the infecting organism.

Clinical Course. With an appropriate antibiotic, a clinical response is expected within 24 to 48 hours. The onset of suppurative complications, such as purulent pericarditis, meningitis, endocarditis, arthritis, and cellulitis after initiation of therapy is uncommon in the modern era. The exception is empyema, which appears to be increased due to serotype replacement in the vaccinated populations by serotypes more often associated with empyema.[196] Pneumococcal pneumonia remains a cause of septic shock and ARDS.[197]

Treatment. Antimicrobial resistance complicates treatment for *S. pneumoniae* in much of the world, including in the United States, with increasing rates of penicillin resistance, particularly in children in southern states.[198] For nonmeningeal isolates of *S. pneumoniae,* the redefinition of full susceptibility in 2002 as a *minimum inhibitory concentration* (MIC) of penicillin of 2 μg/mL or less and high-level resistance as MIC of 8 μg/mL or greater markedly changed the reported incidence of penicillin resistance.[199] This redefinition was driven by discordance between previous lower MIC breakpoints and clinical success rates. The rate of increase in the frequency of penicillin resistance may have stabilized, possibly as a consequence of the PCV and a shift in outpatient antibiotic prescription patterns away from β-lactams.[200]

Penicillin resistance in *S. pneumoniae* is due to alterations in penicillin-binding proteins rather than to β-lactamase production, and the anti-pneumococcal third- and fourth-generation cephalosporins (i.e., cefotaxime, ceftriaxone, and cefepime) retain activity against 75–95% of nonmeningeal isolates of *S. pneumoniae.*[201] By 2000, *S. pneumoniae* resistance rates to other antimicrobials in the United States had reached 30% for *trimethoprim-sulfamethoxazole* (TMP-SMX), 16% for tetracyclines, 26% for macrolides, and 9% for clindamycin.[198,200] High-level macrolide resistance (MIC >64 μg/mL) associated with the MLSB (macrolide, lincosamide, streptogramin B) phenotype is more common in Europe[202] and has been associated with in vitro resistance to clindamycin.[203] In the United States, PCV7 and PCV13 vaccination has been associated with reductions in macrolide resistance.[204] In contrast, 67% of pneumococcal isolates in adults with CAP or invasive pneumococcal disease in Asia between 2012 and 2017 had macrolide resistance with emergence of multidrug-resistant non-vaccine serotypes.[205] *S. pneumoniae* resistance to fluoroquinolones has also emerged with associated clinical treatment failures.[200,206] A contemporary study of global patterns of resistance in pneumococcal strains causing CAP in adults found overall resistance was low but most common for macrolides and penicillins and more common in Africa than other regions.[207] In keeping with this observation, African countries report high rates of antimicrobial resistance in pneumococci colonizing the nasopharynx in children; 22% penicillin, 77% TMP-SMX, and 50% doxycycline resistance was reported in Niger in 2014 to 2018.[208]

Recent exposure to an antibiotic increases the likelihood of the patient having a pneumococcal isolate resistant to that antibiotic (or class of antibiotics). Thus, it is important to avoid antibiotics that have been used in the prior 90 days when selecting a regimen for empirical treatment of a pneumococcal infection.[206] Some, but not all, retrospective and prospective observational studies have suggested a benefit to treating severely ill patients with CAP or bacteremic pneumococcal infections with both a β-lactam and a macrolide.[209–211] Possible explanations for these results include nonbactericidal effects, such as inhibiting biofilm production, or an anti-inflammatory effect of the macrolide.

Legionella

Epidemiology. *L. pneumophila* causes outbreaks and sporadic infections; both patterns may be seen either in the community or in hospitals, and the incidence in the United States is increasing.[212] Outbreaks have been linked to contaminated potable water systems, ultrasonic mist devices, whirlpool baths, air-conditioning condensates, and water evaporation systems.[213] Recent stay in a hotel or travel on a cruise ship is also linked to infections,[214] and approximately 25% of cases are related to travel.[215] In 2015, approximately 20% of U.S.-reported cases were health care associated.[213] Person-to-person transmission has also been described.[216]

Unlike other pneumonia pathogens that colonize the upper respiratory mucosa prior to initiating pneumonia, *Legionella* is acquired through direct inhalation of contaminated aerosols. Sporadic cases of *L. pneumophila* pneumonia account for 2–6% of CAPs in immunocompetent hosts,[40] and *L. pneumophila* is one of the most common causes of severe CAP. Risk factors include exposure to contaminated water, immunosuppression, cigarette use, diabetes, chronic cardiac or respiratory conditions, cancer, end-stage renal disease, and alcohol use. In data from Germany, associations with heavy smoking, male sex, and diabetes only held for inpatients.[217] Infection with *L. pneumophila* is more common in specific geographic regions, such as the Mediterranean or the northeastern United States; warm and humid weather conditions increase the risk of pneumonia due to *Legionella,* also called Legionnaires' disease.[218] Effective water system management is a critical step in limiting the incidence of *Legionella* infections.[219]

In addition to *L. pneumophila,* 40 other *Legionella* species have been identified and account for less than 10% of sporadic cases.[217] Many, such as *Legionella micdadei* and *Legionella longbeachae,* produce a pneumonic illness indistinguishable from that of *L. pneumophila.* Much less is known about the epidemiology of non-pneumophila *Legionella* infections, but they also appear to be from water or soil-related sources; *L. longbeachae* has been associated with gardening and compost exposure.[220] Immunosuppression appears to be the major host risk for these species. Patients are less likely to be smokers and may present with severe disease.[221]

Pathogenesis of *Legionella* Infections. Unlike *S. pneumoniae*, legionellae are facultative intracellular pathogens and have evolved strategies to survive and replicate in host cells. In the environment, *Legionella pneumophila* is an intravacuolar resident of protozoa and it uses similar strategies for surviving in protozoa and in host macrophages.[222] Following inhalation of a *Legionella*-containing aerosol, the bacteria infect alveolar macrophages where they form *Legionella*-containing vacuoles that evade fusion with lysosomes and recruit endoplasmic reticulum; the latter supports replication of *Legionella*. Intracellular replication of *Legionella* requires a bacterial type IV

secretion system that translocates over 300 proteins into the host cytosol to modulate host cell signaling.[223] The translocated bacterial proteins provide multiple functions that promote bacterial survival and replication. For example, bacterial replication is facilitated by MitF-mediated mitochondrial fission and a shift to glycolysis[224]; iron acquisition is facilitated by MavN, which inserts into the *Legionella*-containing vacuole to promote iron transport[225]; and the SidE family of effectors enables noncanonical ubiquitination of endoplasmic reticulum–associated Rab guanosine triphosphatases, modifying function and promoting formation of the *Legionella*-containing vacuole.[226] Replication also requires inhibition of host cell progression to S phase by depletion of the cyclin D1 cell-cycle regulator.[227] The secreted protein, RomA, is a methyltransferase that modifies histone H3 to suppress multiple genes, including innate immune responses.[228] By secreting these bacterial proteins into the host cell, *Legionella* optimize their intracellular replication and avoid elimination by innate immune mechanisms.

Legionella innate immune recognition involves TLR2, 5, and 9; the NLR Naip5; and the *cyclic guanosine monophosphate–adenosine monophosphate synthase–stimulator of interferon genes* (cGAS-STING) pathway.[229] An allele encoding reduced cGAS-STING function is associated with increased human susceptibility to *Legionella* species.[230] Flagellin is sensed by TLR5 and also by NLR Naip5, which activates the NLRC4 inflammasome and induces caspase-1–dependent pyroptosis to restrict pathogen replication in macrophages.[231] Neutrophils, recruited monocytes producing tumor necrosis factor-α and *interleukin* (IL)-12, and IFN-γ producing cells, including natural killer T cells and γδ T cells, all aid pathogen clearance.[229] As noted above, to survive and cause infection, *Legionella* utilizes multiple approaches to evade innate immunity. In addition, DNA from *Legionella* can be packaged into extracellular vesicles. These extracellular vesicles can stimulate the cGAS-STING pathway in bystander cells and inhibit T cell proliferation.[232]

Clinical Manifestations. The usual incubation period for *Legionella* pneumonia is 2 to 10 days but can be longer.[214] Lethargy, headache, fever, recurring rigors, anorexia, and myalgias are frequent early symptoms. After several days, cough becomes more pronounced, with thin watery sputum or purulent sputum in up to half of cases. Dyspnea is prominent in half of cases, and pleuritic chest pain may be present.[215] Extrapulmonary manifestations may overshadow respiratory complaints; gastrointestinal (watery diarrhea, nausea, vomiting, abdominal pain) and neurologic symptoms and signs (headache, confusion, obtundation, seizures, hallucinations) are particularly noteworthy. Patients may appear acutely ill and can develop rhabdomyolysis and acute kidney injury. Temperatures reach 40.5°C in one-third of patients, are typically sustained, and may be accompanied by relative bradycardia, a feature that distinguishes *Legionella* pneumonia and some other atypical pneumonias from pneumococcal CAP.[233] Physical findings are usually limited to the chest, including pleural friction rubs, but generalized abdominal tenderness, hepatomegaly, splenomegaly, cutaneous rash, nuchal rigidity, and focal neurologic deficits have all been described.

Hyponatremia and hypophosphatemia are present in more than half of severe cases. Mild elevations of serum creatinine, creatine phosphokinase, and liver enzymes are also common, as are hematuria and proteinuria, occasionally with rhabdomyolysis. There may be leukopenia and thrombocytopenia, especially in severely ill patients. Cold agglutinins may be present, as in infection due to *M. pneumoniae*. The presence of three or more clinical predictors (fever >102°F, erythrocyte sedimentation rate >90 mm/hr or CRP >180 ng/mL, ferritin >2 times normal, creatine phosphokinase >2 times normal, hypophosphatemia, and microscopic hematuria) and the absence of three or more eliminators (sore throat, severe myalgia, leukopenia, thrombocytopenia, negative chest radiograph) have been proposed as a scoring system to identify legionnaires disease as a cause of CAP.[234]

Chest radiographic findings typically lag behind the early clinical illness. Unilobar opacities are most common (Fig. 46.2).[215] Small pleural effusions may develop in up to 50% and may precede the parenchymal process. Multilobar opacities are also commonly seen (eFig. 46.8), particularly on chest CT. Frank cavitation is rare but can develop in immunocompromised hosts.[113] Lung abscesses are rare but can be associated with immunocompromised hosts with lymphopenia or with neutrophil recovery following neutropenia.[235]

Microbiologic Diagnosis. *Legionella* are obligatory aerobic, fastidious, gram-negative bacilli that stain poorly with Gram stain (see Chapter 19, Fig. 19.3). *L. micdadei* and

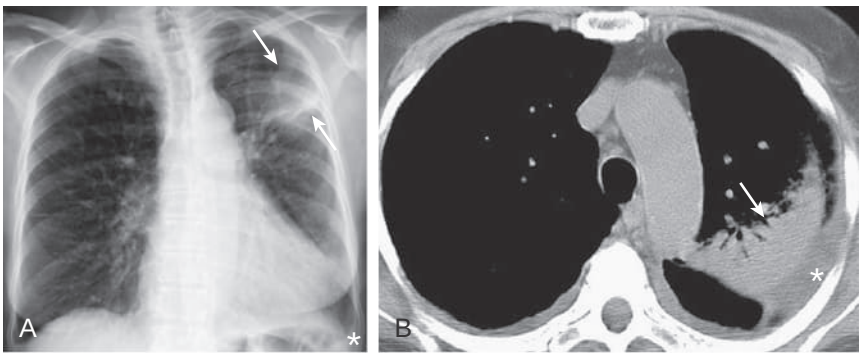

Figure 46.2 *Legionella pneumophila* pneumonia: unilateral disease. (A) Frontal chest radiograph shows subpleural left upper lobe consolidation (*arrows*). (B) Axial chest computed tomography displayed in soft tissue window confirms left upper lobe consolidation (*arrow*). A small left pleural effusion (*asterisk*) is present. (Courtesy Michael B. Gotway, MD.)

some other *Legionella* species may stain weakly acid-fast. Patients may not produce sputum and, early in the infection, even when sputum is available, it may contain few PMNs. Culture-based diagnosis is challenging, requires use of selective media, and has variable sensitivity (20–80%), in part reflecting difficulties in obtaining good-quality respiratory samples.[215]

The *Legionella* urinary antigen test is commonly used and has an overall sensitivity of 60–80%. It only reliably detects certain strains (mAb3/1) of the predominant serogroup 1.[214] However, it may detect other strains when antigen load is high, but with much lower sensitivity.[214] *Legionella* urinary antigen testing is recommended for all CAP that is severe, unresponsive to outpatient therapy, and associated with immunocompromised hosts or epidemiologic risk factors.[147] Direct fluorescent antibody staining of sputum is specific but has low sensitivity.[215] PCR-based assays for sputum are increasingly used and are becoming the preferred diagnostic test, allowing detection of a range of *Legionella* species.[214] Real-time PCR combined with urinary antigen had a 93% sensitivity and 98% specificity during a *L. pneumophila* outbreak, and *Legionella* species PCR can be combined with specific antibody detection to detect *L. longbeacheae.*[236] Adoption of PCR-based testing of respiratory samples enhances diagnosis of *Legionella* pneumonia.[237] Serologic testing with commercial kits has low positive predictive value of approximately 50%, limiting diagnostic utility outside specialist reference laboratories.[214] However, a significant rise in antibodies against serogroup 1 in the appropriate clinical setting can still support a diagnosis.

Clinical Course. A clinical response to appropriate antibiotic therapy is usually observed within 48 hours. In contrast, radiographic findings may continue to progress despite clinical improvement and may take months to resolve.[113] Acute renal failure and oliguria, often independent of shock and myoglobinuria, may develop in approximately 10% of patients, and dialysis may be required. Many patients note lingering fatigue and weakness for months following *Legionella* pneumonia.[215]

The mortality rate of community-acquired *Legionella* pneumonia is approximately 10%.[214] Poor clinical outcomes are associated with immunodeficiencies, comorbidities, delayed initiation of appropriate therapy, and the need for ventilatory support or dialysis.

Treatment. Azithromycin and fluoroquinolones are both superior to erythromycin or clarithromycin for treatment of *Legionella* infections and are associated with similar outcomes.[238] Doxycycline is recommended as an alternative therapy, but combinations with rifampicin are no longer recommended.[147] Durations are often recommended as 5 days for azithromycin and up to 10 days with levofloxacin.[215] Longer durations are recommended for severe or extra-pulmonary disease and immunocompromised hosts.[215] Prevention steps are key during outbreaks, and health care workers should always consider the possibility that one case is related to others. Biofilm formation in pipes and on surfaces limits the effectiveness of standard chlorination-based disinfection used in infection control measures.[239]

COMMON VIRAL CAUSES OF PNEUMONIA

The advent of molecular diagnostic tests has greatly improved the ability to detect and characterize the contribution of respiratory viruses to pneumonia. In contemporary pneumonia cohorts, viruses are the most frequently identified pathogens in CAP, detected in 27% of radiographically proven pneumonias in hospitalized adults[4] and 61–66% in hospitalized children.[240,241] These figures may overestimate the etiologic contribution of viruses to CAP because the diagnosis of viral pneumonia is usually performed on upper respiratory tract specimens (e.g., nasopharyngeal aspirate or swab). Detection of viruses from nasopharyngeal/oropharyngeal samples may represent coincidental upper respiratory tract infection or convalescent-phase shedding. Moreover, studies that have enrolled healthy controls have shown that the asymptomatic carriage of certain viruses (e.g., rhinovirus and adenovirus) is common.[127]

Influenza Virus

See Chapter 47 for a comprehensive review of influenza. This section solely focuses on selected aspects of influenza as a cause of CAP.

Clinical Manifestations. The most common of influenza-associated complications, influenza pneumonia can be categorized into primary viral pneumonia, secondary bacterial pneumonia, or mixed viral and bacterial pneumonia. Primary influenza viral pneumonia was first well documented in the 1957–58 pandemic.[242] The illness begins with typical influenza symptoms, followed by a rapid progression of fever, cough, dyspnea, and cyanosis. Typical radiographic changes include bilateral reticular or reticulonodular opacities (Fig. 46.3, eFigs. 46.9 and 46.10), sometimes suggestive of an acute lung injury pattern or ARDS (eFig. 46.11). Chest CT often shows multifocal areas of ground-glass opacities and peribronchovascular or subpleural consolidation (eFig. 46.12B–E).[243] Sputum cultures are negative for bacteria. Such patients do not respond to antibacterial drugs, and the mortality rate is high.[244]



Figure 46.3 Seasonal influenza. Frontal chest radiograph shows multifocal, bilateral, perihilar, and lower lobe predominant bronchovascular thickening and somewhat nodular consolidation. (Courtesy Michael B. Gotway, MD.)

Secondary bacterial pneumonia is an important complication of influenza (eFig. 46.13). The classic description is of an influenza illness followed by a period of improvement, usually lasting 4 to 14 days. Recrudescence of fever is associated with symptoms and signs of bacterial pneumonia such as cough, sputum production, and an area of consolidation detected on physical examination and chest radiography. The most common bacteria implicated are *S. pneumoniae* and *S. aureus* (including MRSA), followed by *H. influenzae, S. pyogenes,* and gram-negative organisms including *K. pneumoniae* and *Escherichia coli*.[245] Mixed viral and bacterial pneumonia can also happen. Bacterial superinfections of influenza have been postulated as a major cause of death during the pandemic of 1918.[246]

Patients with a wide range of preexisting conditions are well recognized to be at higher risk for the development of pneumonia. During the 2009 pandemic, obese persons[247] and pregnant women[248,249] were noted to have increased risk of hospitalization or death due to influenza A H1N1pdm09, risks that had not been previously described.

Treatment. The CDC and IDSA recommend antiviral treatment for individuals at risk for more severe influenza or in individuals requiring hospitalization.[250,251] Treatment should be started as early as possible, but even delayed therapy can be of benefit in hospitalized patients. The antiviral agents of choice are neuraminidase inhibitors (oseltamivir, zanamivir, or peramivir) or a cap-dependent endonuclease inhibitor (baloxavir), with a recommended treatment duration of 5 days for oseltamivir and zanamivir and a single dose for peramivir and baloxavir.[251,252]

Combinations of antiviral agents have been evaluated in clinical trials,[253,254] but additional clinical benefit has not been demonstrated. Immunomodulatory agents have also been evaluated as adjuncts to antivirals, with variable results. Corticosteroid use in patients with severe influenza was associated with increased mortality in observational studies.[255] A randomized trial of clarithromycin, naproxen, and oseltamivir versus oseltamivir alone was associated with reduced mortality and length of hospital stay in the combination group.[256] Statins were associated with lower mortality in a U.S. surveillance study.[257] However, uncontrolled confounding is likely in this study.

Several antiviral agents are licensed for influenza treatment outside the United States and Europe (eTable 46.5). Additionally, a number of antiviral drugs with novel anti-influenza mechanisms have shown promise in animal models and/or early clinical studies, including sialidase,[258] polymerase inhibitors,[259,260] hemagglutinin inhibitor,[261] monoclonal antibodies,[262,263] and small interfering RNA.[264] Administration of convalescent plasma can also be valuable for treatment of influenza pneumonia, though it is only likely to be available in the later stages of an outbreak or pandemic because it must contain antibodies to the infecting strain of influenza virus.[265,266]

OTHER COMMON CAUSES OF PNEUMONIA

Haemophilus influenzae

Epidemiology. *H. influenzae* is a gram-negative coccobacillus and an obligate human pathogen. With the routine vaccination of children against *H. influenzae* type b, non-typeable *H. influenzae* has emerged as the leading cause of invasive disease and accounts for approximately 70% of cases of *H. influenzae* infections. Eighty percent of cases are seen in adults, and the overall incidence is 1 case per 100,000 adults annually in the United States.[267] Pneumonia and bacteremia are the most common presentations.[268] Advanced age, smoking, and medical comorbidity including structural lung disease are common associations.[269] In a Swedish study including real-time quantitative PCR for *H. influenzae,* and in which a microbiological diagnosis was established in approximately two-thirds of subjects, *H. influenzae* was detected in 5% of adult CAP cases[270] and, in a German study, accounted for 6% of CAP but 26% in patients with COPD.[269,271]

H. influenzae type f is now the leading capsulated cause of disease followed by type e, but these account for less than 10% of infections.[268] *H. influenzae* type b still causes a small amount of pneumonia in the elderly with medical comorbidity.[272] Type a has emerged as a cause of invasive *H. influenzae* in indigenous populations.[273]

Pathogenesis. *Haemophilus* species are a part of the respiratory microbiome, and *H. influenzae* quantity increases in patients with chronic lung disease, predominantly those with COPD.[274] Non-typeable strains may be able to persist inside epithelial cells and macrophages.[275,276] The pathogen can express a capsule to evade phagocytosis while IgA proteases and complement inhibitors prevent opsonization. Alveolar macrophages, neutrophils, and Th17 immune responses play key roles in host defense. Non-typeable strains demonstrate antigenic variation and lipo-oligosaccharides on the surface mimic host glycans to evade antibody generation. Recurrence of disease in children or in exacerbations of COPD can be associated with acquisition of new non-typeable strains, but Th17 responses can recognize conserved epitopes.[277] *H. influenzae* are potent activators of TLR and NODs and induce potent pro-inflammatory cytokine responses via nuclear factor κβ signaling pathways, which may contribute to the prominent neutrophilic inflammation, tissue damage, and pathogenic role in acute exacerbations of COPD.[276] Despite inducing neutrophilic inflammation, they may be able to withstand killing by *neutrophil extracellular traps* (NETs). Protein D and surface-expressed lipo-oligosaccharides promote ciliary disfunction, further contributing to lung dysfunction.

Clinical Manifestations. *Haemophilus* pneumonia is clinically indistinguishable from other bacterial pneumonias.[269] Leukocytosis and CRP greater than 100 mg/L are common. On radiographs, *Haemophilus* pneumonia may appear as a patchy bronchopneumonia or have areas of frank consolidation. Areas of fine nodular shadows on chest radiograph or tree-in-bud appearance on CT may suggest infectious bronchiolitis (eFig. 46.14). Multilobar opacities are seen in less than 15% and pleural effusions in less than 10%. Spherical radiographic opacities (so-called round pneumonia) have been described. Cavitation is uncommon.

Microbiologic Diagnosis. Diagnosing *H. influenzae* pneumonia by a Gram stain of sputum is difficult because the small, pleomorphic coccobacilli are easily overlooked. Culture of expectorated sputum reveals *H. influenzae* in

eTable 46.5 Antiviral Agents Licensed for Treatment Outside the United States and Europe and Investigational Agents

	Mechanism of Action	Route of Administration	License or Investigational Status
LICENSED ANTIVIRAL AGENTS			
Laninamivir	Neuraminidase inhibitor	Inhaled	Licensed in Japan for seasonal influenza
Arbidol	Membrane fusion inhibitor	Oral	Licensed in Russia and China for seasonal influenza
Favipiravir (T-705)	Inhibition of viral RNA-dependent RNA polymerase	Oral	Licensed in Japan for novel or reemerging influenza
INVESTIGATIONAL ANTIVIRAL AGENTS			
Monoclonal antibodies (anti-HA head, anti-HA stem and anti-m2e)	Viral neutralization	Intravenous	Preclinical; clinical trials
Nitazoxanide[261]	Interferon induction; inhibition of hemagglutinin maturation	Oral	Approved for treatment of parasitic infections; preclinical; clinical trials
Pimidovir,[260] VX-787	Inhibition of polymerase basic protein 2	Oral	Preclinical; clinical trials
AL-794[259]	Inhibition of endonuclease domain of influenza virus polymerase	Inhaled	Preclinical
DAS181[258]	Sialidase	Inhaled	Preclinical; clinical trials
AVI-7100[264]	Small interfering RNA construct	Intravenous	Preclinical; clinical trials

Modified from Paules C, Subbarao K. Influenza. *Lancet.* 2017;390(10095):697–708.

only half of well-documented cases of *H. influenzae* pneumonia.[270] Asymptomatic colonization with non-typeable strains in patients with COPD complicates analysis of Gram stain and sputum cultures (eFig. 46.15). Bacteremia is infrequent.[267,271] Multiplex PCR-based diagnostics are increasingly used to diagnose *H. influenzae*.[236]

Clinical Course. The overall mortality rate of *H. influenzae* pneumonia is 2–7%, lower than for CAP in general, and ICU admission is also less frequent.[267,271] Bacteremia, medical comorbidity, and advanced age are associated with worse outcome.[267] Mortality of up to 20% is reported in bacteremic pneumonia, predominantly in elderly patients with comorbidity.[278]

Treatment. *H. influenzae* isolates produce β-lactamase in 20–50% of cases and are therefore often resistant to ampicillin. β-lactamase–negative ampicillin-resistant strains have emerged in Japan and some European countries that are also resistant to some cephalosporins, but these strains are still rare in the United States.[279] Increasing macrolide resistance also compromises empirical therapy with these agents, and azithromycin is the most active macrolide against these infections. Consequently, serious *H. influenzae* respiratory tract infections should be treated with a β-lactam/β-lactamase inhibitor while awaiting results of susceptibility testing. Due to antimicrobial stewardship considerations, second- or third-generation cephalosporin or fluoroquinolones are reserved as alternatives when other factors preclude a β-lactam/β-lactamase inhibitor. Serious infection in areas where β-lactamase–negative ampicillin-resistant strains are prevalent can be treated with ceftriaxone. Milder infections can commence treatment with amoxicillin/clavulanate if risk factors such as COPD make *H. influenzae* a potential pathogen and deescalate to amoxicillin if sensitivity is confirmed, with a macrolide as an alternative agent.

Other infectious causes of CAP are detailed at ExpertConsult.com.

NONRESPONDING PNEUMONIA/ TREATMENT FAILURE

Two different clinical patterns of treatment failure in pneumonia have been described[175]: *progressive* pneumonia, in which there is clinical deterioration, even to the point of respiratory failure or septic shock, and *nonresponding* pneumonia, in which clinical improvement is not achieved (persistence of fever and clinical symptoms). Evaluation for response should be undertaken after 72 hours of antibiotic treatment.[175] In addition to clinical evaluation, reduction of PCT levels after 3 to 4 days of treatment correlates with clinical response.[106] Levels of certain biomarkers, in particular PCT, CRP, and IL-6, have also been found useful for predicting inadequate response. Elevated initial levels of PCT or CRP are independent predictors for inadequate response.[106]

The causes of nonresponding pneumonia are classified as infectious, noninfectious, and of unknown origin.[175] eTable 46.6 lists common infectious and noninfectious causes. Reevaluation of the history and examination, chest CT, and consideration of bronchoscopy to obtain biopsy specimens and BAL for additional microbiological investigations guide diagnosis.

INFECTIOUS CAUSES

In patients hospitalized for CAP, specific infections are responsible for 40% of nonresponding cases. The most frequent microorganisms found are *S. pneumoniae, Legionella, P. aeruginosa,* and *S. aureus.*

Patients with CAP may fail to respond because of resistance to the empirical antibiotic regimen selected. *P. aeruginosa*, which is not covered by empirical therapy for CAP unless a fluoroquinolone is used, causes about 10% of cases of nonresponding CAP.[175] More unusual microorganisms include *Mycobacteria, Nocardia* species, anaerobes, fungi, *Pneumocystis jirovecii,* protozoa, and other organisms requiring antibiotics other than those recommended for CAP (see eFig. 46.61). Investigation of the etiology of nonresponding CAP to identify some of these microorganisms requires intensified microbiologic diagnostic testing as well as an exhaustive search for risk factors, including epidemiology (travel, occupational or animal exposures), personal habits, and environmental factors.

Local or metastatic infectious complications also contribute to treatment failure, as can bronchial obstruction by a tumor, foreign body, or teeth. Empyema (see eFig. 46.39) is one of the most frequent complications in pneumonia and is thus a cause of nonresponse that must be evaluated with thoracentesis when pleural effusion is present. Other causes of treatment failure are abscess formation (see eFig. 46.5) and necrotizing pneumonia (see eFigs. 46.36 and 46.37). Metastatic infections such as endocarditis, arthritis, pericarditis, meningitis, or peritonitis can contribute to treatment failure and are more common in bacteremic pneumonia. In approximately 30% of the cases, no specific cause for lack of response can be identified despite adequate antibiotic treatment. This may be due to the presence of comorbidities or to an exaggerated or diminished inflammatory response.[792]

NONINFECTIOUS CAUSES

Noninfectious diseases with acute involvement of the pulmonary parenchyma may simulate pneumonia. These include pulmonary infarction, pulmonary hemorrhage, organizing pneumonia, eosinophilic pneumonia, hypersensitivity pneumonitis, drug-induced lung disease, and neoplasms. Alveolar cell lung cancer (eFig. 46.62 and Video 46.2) may be particularly difficult to distinguish radiographically from pyogenic pneumonia. The frequency of noninfectious etiologies has been reported to be 22% in CAP.[175]

DIAGNOSTIC EVALUATION

The diagnostic approach to treatment failure requires a complete reevaluation of the history, physical examination,

eTable 46.6 Causes of Nonresponding Pneumonia

INFECTIOUS
Resistant Microorganisms
Community-acquired pneumonia (e.g., *Streptococcus pneumoniae, Staphylococcus aureus*)
Nosocomial pneumonia (e.g., *Acinetobacter*, methicillin-resistant *Staphylococcus aureus, Pseudomonas aeruginosa*)
Uncommon microorganisms (e.g., *Mycobacterium tuberculosis*, *Nocardia* sp, fungi, *Pneumocystis jirovecii*)
Complications of Pneumonia
Empyema
Abscess or necrotizing pneumonia
Metastatic infection
NONINFECTIOUS
Neoplasms
Bronchial obstruction
Pulmonary hemorrhage
Pulmonary embolism
Sarcoidosis
Eosinophilic pneumonia
Pulmonary edema
Acute respiratory distress syndrome
Organizing pneumonia
Drug-induced pulmonary disease
Pulmonary vasculitis

Mycoplasma pneumoniae

Epidemiology. *Mycoplasma pneumoniae* is a tiny gram-negative pleomorphic bacterium that grows by parasitizing mammalian cells. Older studies reported up to 37% of CAP cases involved *M. pneumoniae* on the basis of serologic studies, which may have been confounded by cross-reactivity.[41] It has been argued that, because many infections are mild, the incidence has been underestimated. However, in the CDC *Etiology of Pneumonia in the Community* (EPIC) study with PCR-based testing, *M. pneumoniae* accounted for 2% of adult CAP cases requiring hospitalization, with an annual incidence of 0.5 cases per 10,000 population.[4] The relative contribution to CAP is greater in outpatient CAP, where it causes 5–17% of infections and, in adults younger than 65 years, where it contributed 8.4% of CAP cases.[42,43,280] *Mycoplasma* infections peak in the United States in the fall. Although the infection is endemic, epidemics of reducing amplitude have taken place approximately every 4 years.[281] *Mycoplasma* is transmitted from person to person via aerosolized respiratory droplets, and domestic transmission and outbreaks in closed populations are well described.[282]

Pathogenesis. *M. pneumoniae* lacks a rigid peptidoglycan-containing cell wall. It contains a polar attachment organelle responsible for adherence via the P1 adhesin and internal multiprotein core, which mediates the characteristic gliding motility over the epithelial surface and facilitates its role as a mucosal pathogen.[283,284] A key virulence factor is the community-acquired *respiratory distress syndrome* (RDS) toxin, which exhibits adenosine diphosphate ribosylation activity (similar to pertussis toxin) and induces cell vacuolation.[285] The community-acquired RDS toxin binds surfactant protein A and annexin A2.[284,286] Inflammatory responses are mediated via TLR2/4 and NLRP3, which recognizes the community-acquired RDS toxin.[284] Reactive oxygen species generation can result in ciliary damage and epithelial cell dysfunction. Macrophages are key to pathogen clearance.[287] Th1/Th17 responses contribute to neutrophil inflammation, clinical symptoms, and histopathologic changes in the lung.[288] *M. pneumoniae* produces a nuclease to degrade NETs, which may compromise neutrophil contributions to clearing mycoplasma.[289] Th2 responses promote allergic complications and wheezing.[284]

Clinical Manifestations. The incubation period may be as long as 3 weeks. The prodrome can involve fever, myalgia, and dry cough.[284] Many infections are asymptomatic, and only 5–10% of infections result in LRT infection. Pharyngitis, cervical adenopathy, and bullous myringitis may be encountered, although the latter is not more common with *Mycoplasma* pneumonia than with pneumococcal pneumonia/otitis. A wide variety of exanthems, including maculopapular eruptions, urticaria, erythema multiforme, and erythema nodosum, develop in 10–25% of patients. Chest auscultation may reveal scattered wheezing, but signs of consolidation are less frequent and may suggest coinfection.[284] Chest radiographs usually show an interstitial (eFig. 46.16) or a mixed pattern with consolidation that may be multilobar and more striking than expected based on chest physical findings (eFig. 46.17). Pleural effusions are less common than with pneumococcal pneumonia. Focal consolidation may also be apparent (eFig. 46.18). Leukocytosis is usually mild.

Microbiologic Diagnosis. When obtained, sputum generally displays moderate numbers of PMNs without a predominant organism. Gram staining does not detect *Mycoplasma* species, and culture is not useful in identification. Production of cold agglutinins is not specific to *M. pneumoniae,* and serologic tests that frequently cross-react with other microorganisms are of limited use in diagnosis of CAP, although they can have a role in population-level studies. Nucleic acid tests for *M. pneumoniae* are the preferred testing modality (see Chapter 19), especially those utilizing real-time PCR methodologies.[290] Multiplex PCR assays are also available with other respiratory pathogens.[291]

Clinical Course. *Mycoplasma* pneumonia is usually a benign, often self-limited infection with an excellent prognosis for complete recovery. ARDS and death have been reported but are rare. However, mortality rates of 8% are reported for hospitalized adults, particularly among the elderly.[292] Markers of severe *M. pneumoniae* CAP include bilateral opacities, elevated transaminases or lactate dehydrogenase, and renal impairment.[292] There are a range of extrapulmonary effects due to direct consequences of infection or the indirect result of autoimmune or thromboembolic phenomena.[293] In addition to dermatologic features, extrapulmonary complications can include myopericarditis, cardiac thrombus, meningitis, encephalitis, Guillain-Barré syndrome, optic neuritis, acute disseminated encephalomyelitis, autoimmune hemolytic anemia, thrombocytopenic purpura, IgA nephropathy, glomerulonephritis, renal artery embolism, arthritis, hepatitis, and pancreatitis.[293]

Treatment. Antimicrobial therapy with a tetracycline, macrolide, or fluoroquinolone shortens the course of clinical symptoms and hastens resolution of radiographic abnormalities. Although the optimal duration of therapy for *M. pneumoniae* CAP is undefined and former recommendations were to treat for 14 days, guidelines now emphasize shorter durations of therapy for CAP in general.[147,161] A 5-day duration of azithromycin, which has a long half-life in the lungs, is one option. More prolonged durations are now reserved for non-responders. Tetracycline or quinolone therapy is preferred for non-responders to initial macrolide therapy. Respiratory isolation can limit transmission, and azithromycin prophylaxis can prevent infection in close contacts of patients.[294] Macrolide resistance has emerged globally, with rates of over 90% reported in pediatric populations in China and Japan, but much lower rates in Europe.[295] One study in the United States reported resistance rates of 13%.[296] Recently, rates of macrolide resistance have declined in Japan; it is suggested that this may reflect altered macrolide prescribing, emphasizing the importance of antimicrobial stewardship in controlling this problem.[297]

Staphylococcus aureus

Epidemiology. *S. aureus,* a large gram-positive bacterium with a coccal shape and a tendency to cluster, has emerged as an important cause of CAP, in particular through the emergence of necrotizing pneumonia due to community-acquired USA300 MRSA strains. *S. aureus* also ranks as the second or third leading cause of CAP requiring ICU admission and increases the risk of multiorgan failure.[298] Hospitalization rates for *S. aureus* CAP increased in the United States in the period 2002 to 2011, in contrast to CAP due to *S. pneumoniae*.[299] Approximately 80% of adult *S. aureus* pneumonia cases resulting in hospitalization in the United States were due to MRSA in 2009 to 2012.[300] However, there is wide variation; in the EPIC study, *methicillin-sensitive S. aureus* (MSSA) accounted for just 1.0% and MRSA for 0.7% of CAP in adults.[301] In the GLIMP international study of 54 countries in 2015, CA-MRSA accounted for 3% of CAP.[302] Nasal colonization is the major source for pneumonia and other invasive *S. aureus* infections: 30–50% of healthy adults carry the organism transiently in the anterior nares. Health care workers may have even higher carriage rates.

In general, patients with CAP due to *S. aureus* have similar age and comorbidity profiles to patients with pneumococcal CAP. A Canadian study showed that patients with MRSA-CAP are likely to be younger and less likely to have comorbidities compared to patients with MRSA-HAP.[303] COPD and other chronic heart or lung conditions are common in patients with *S. aureus* CAP but not necessarily more so than in other causes of CAP. However, COPD did increase the risk of CA-MRSA as opposed to CA-MSSA in some but not other studies.[301,304] Diabetes and hemodialysis more consistently increase the risk of MRSA-associated CAP.[301] Nursing home residents and those who have been recently exposed to hospitals are also at increased risk of CA-MRSA. Furthermore, CA-MRSA is second in frequency to *S. pneumoniae* as a cause of post-influenza bacterial pneumonia. Measles and HIV are other viruses associated with *S. aureus* pneumonia. Men who have sex with men and people engaged in contact sports may also be at increased risk of CA-MRSA–associated CAP. Pneumonia due to hematogenous spread of *S. aureus* is a unique type of pneumonia, usually a consequence of intravenous drug use or septic embolization from endocarditis or an infected vascular site.

Pathogenesis. *S. aureus* contains a range of genes encoding virulence factors regulated by the *accessory gene regulator*, which links quorum sensing to gene transcription and *S. aureus* exoproteins. The pathogen can form biofilms, and most strains contain a microcapsule. Microbial surface components reacting with adherence matrix molecules assist adherence. Teichoic acids, lipoteichoic acids, and peptidoglycan fragments are recognized by pattern recognition receptors. Exotoxins and superantigens are key virulence factors regulated by the accessory gene regulator; these include *Panton-Valentine leukocidin* (PVL), suggested to be a key factor in necrotizing pneumonia.[305] Methicillin resistance is mediated by a low-affinity penicillin-binding protein and is carried on the genomic resistance island, termed staphylococcal chromosome cassette mec. Adaptation to the respiratory niche involves production of proteins promoting resistance to oxidative stress, increased fumarate production, and biofilm formation.[306,307]

Approximately 20% of the unique genetic elements in CA-MRSA strains arise from mobile genetic elements including pathogenicity islands and prophages.[308] These strains have enhanced transmissibility and encode a range of toxins. Many but not all express PVL, which may or may not have a role in pneumonia.[309] Associated point mutations in the accessory gene regulator have also been suggested as contributing to pathogenesis rather than the presence of PVL.[310] Other toxins can include potent superantigens (e.g., enterotoxin H expressed by the midwestern clone USA400). In addition, toxins widely expressed by *S. aureus* strains may be differentially up-regulated in CA-MRSA strains, such as the leukocidal and proinflammatory α-phenol soluble modulins. USA300 also expresses the arginine catabolic mobile element that may reduce nitric oxide and promote resistance to low pH.

S. aureus can resist several phagocyte microbicidal responses, inhibit complement activation and induction of chemotaxis via C5a, as well as cause lysis of a range of immune cells using a range of toxins.[311–319] Neutrophils are key effectors of pathogen clearance but also contribute to lung injury, such as in necrotizing pneumonia.[320] In addition to inhibiting neutrophil chemotaxis and causing cell lysis, *S. aureus* can inhibit phagocytosis; staphylococcal enterotoxin-like toxin X modulates neutrophil phagocytosis as well as contributes to T cell activation.[321,322] Excessive T cell activation and excess cytokine responses also contribute to pathology in animal models of MRSA pneumonia.[323] Host responses include IL-17–driven neutrophil recruitment; IL-17A–deficient mice have reduced survival despite equivalent bacterial clearance, likely related to increased dysregulated neutrophil inflammation.[324] γδ T cells are an important source of IL-17 in murine models of *S. aureus* pneumonia, and NLRC4 inflammasome activation dampens IL-17 production and promotes necroptosis and IL-18 generation.[325] A prominent role for necroptosis of lung tissue and immune cells, such as alveolar macrophages, in response to pore-forming exotoxins including α-toxin, α-phenol soluble modulins, and leucocidin AB is described and is mediated via the receptor-interacting serine-threonine kinases 1 and 3.[326] *S. aureus* may also promote macrophage pyroptosis.[327] In contrast, there is resistance to macrophage apoptosis, preventing bacterial killing and perturbation of phagolysosomal maturation in some circumstances by MSSA and MRSA.[189,328] α-Toxin also inhibits efferocytosis.[329] Furthermore, α-toxin can disrupt epithelial cell barrier function by activation of the metalloproteinase ADAM10, resulting in degradation of e-cadherin, a protein that maintains tight junctions.[330] Collectively this illustrates how *S. aureus* strains can modulate immune responses to subvert host defense and promote cell toxicity and loss of barrier function. Autophagy plays a role in helping limit α-toxin–associated damage, especially in endothelial cells, by promoting tolerance.[331]

Clinical Manifestations. *S. aureus* CAP presents with similar signs and symptoms to pneumococcal CAP.[301] At the time of presentation, MRSA-CAP is associated with an increased pneumonia severity index compared to

pneumococcal CAP.[301] It is also associated with higher mortality and length of hospital stay than overall CAP. Laboratory features are also similar and, in the EPIC study, multilobar disease and cavitation were not more frequent than in pneumococcal CAP.

CA-MRSA pneumonia can be seen in young patients without underlying illnesses.[332–335] A syndrome of necrotizing CAP in young adults and children has been described; in the United States, this is typically associated with MRSA but, in Europe, most often with MSSA but, in both settings, is associated with PVL-positive strains.[336,337] After a short prodrome, frequently with a flulike illness (or with skin and soft tissue infection in approximately 20%), patients present with a fulminant respiratory syndrome and shock, requiring mechanical ventilation in approximately 60% and associated with airway bleeding in 40%. Leukopenia (<3,000 cells/μL) is common and associated with mortality in up to 75%.[337] The imaging features of CA-MRSA pneumonia include multilobar opacities and/or cavitary lesions[49] (eFig. 46.19).

In cases acquired hematogenously, such as in endocarditis or other endovascular infection, signs and symptoms related to the underlying endovascular infection predominate; if pulmonary infarction results from a septic embolism, pleuritic chest pain and hemoptysis are often noted. Otherwise, respiratory tract symptoms are mild or absent. The chest radiograph in patients with hematogenous staphylococcal pneumonia often reveals multiple, discrete, and often cavitary shadows with a predilection for the lower lobes (eFig. 46.20).

Microbiologic Diagnosis. Purulent sputum with multiple clusters of large gram-positive cocci, particularly if intracellular, is strong evidence of *S. aureus* pneumonia (eFig. 46.21). The organism is easily recovered from sputum cultures, even after several doses of antibiotics. Blood cultures are frequently positive, especially in hematogenous staphylococcal pneumonia. CA-MRSA pleural effusions are often exudative rather than grossly purulent but are still high yield on culture. An important clue to CA-MRSA is the presence of skin lesions,[338] which are often also positive on Gram stain.

PCR may enable rapid diagnosis of MRSA; PCR on BAL showed a sensitivity of 96% and negative likelihood ratio of 0.04 in one small study, enabling changes to empirical CAP therapy.[339] PCR also enables detection of the *PVL* gene.[340] At least half of patients with MRSA-CAP are previously known to be colonized with MRSA,[303] and PCR-based nasal screening has a high negative predictive value (98%) for MRSA-CAP even though the positive predictive value is only 57%.[341]

Clinical Course. Even with appropriate antibiotics, the duration of fever and need for ICU care are often prolonged for *S. aureus* pneumonia, particularly CA-MRSA. Local complications of staphylococcal pneumonia include empyema and abscess formation. Infection can spread hematogenously to the CNS, bones, joints, skin, and kidneys. Cavities and necrotic tissue may prevent adequate local antibiotic penetration, whereas unrecognized or incompletely drained empyema may prolong fever. Pleuroscopy or decortication is required in a large percentage of cases with empyema. The mortality of *S. aureus* CAP in the EPIC study was 4% for MSSA and 13% for MRSA.[301] *S. aureus* CAP following influenza may have increased mortality, and necrotizing pneumonia, particularly with leukopenia, can have mortality up to 75%.[337]

Treatment. The treatment of choice for MSSA CAP is a penicillinase-resistant penicillin (e.g., oxacillin 8 to 12 g/day) or a first-generation cephalosporin.[147] Therapy for 7 to 10 days is adequate in uncomplicated cases, extended to 2 weeks with uncomplicated bacteremia or at least 4 weeks if associated with endocarditis, lung abscesses, or disseminated abscesses. In the penicillin-allergic patient, clindamycin or linezolid can be used.

Empirical therapy for MRSA-CAP is recommended for all patients being admitted to the ICU or those with lung cavities or empyema.[342] IDSA guidelines recommend MRSA-CAP treatment with vancomycin 15 mg/kg actual body weight, usually intravenously twice a day (aiming for trough levels of 15-20 μg/mL) or linezolid 600 mg twice a day orally or parenterally, for 7 to 21 days, depending on severity of disease and the presence of extrapulmonary involvement. Clindamycin 600 mg 3 times a day orally or parenterally is an alternative if the strain is sensitive and disease is less severe. Although resistance to vancomycin is still rare, the MIC has been shifting upward over the last 2 decades in North America, Europe, and Asia, and MICs greater than 1 μg/mL have been associated with clinical failure. In high-risk patients, such as those with VAP or with underlying renal insufficiency, linezolid has been found to have better clinical response rates than vancomycin, although differences in patient survival have been variable.[343–345] For CA-MRSA, vancomycin therapy alone has been associated with a significant failure rate.[176] Addition of clindamycin or linezolid has been associated with improved outcomes in small case series[176,334] and is also supported by in vitro studies with human neutrophils showing clindamycin reduces production of the nuclease that degrades NETs or animal studies that show treatment with linezolid reduces toxin production and is associated with improved outcomes.[346,347] The optimal treatment of necrotizing CAP due to PVL-positive *S. aureus* is uncertain, but many local guidelines in Europe recommend high-dose linezolid and clindamycin with addition of rifampicin and intravenous immunoglobulin in especially severe cases.[348] Unlike in MRSA skin infections, clindamycin, fluoroquinolones, and TMP-SMX are unreliable in severe CA-MRSA cases. Daptomycin is ineffective for treatment of pulmonary infections because it binds to and is inactivated by pulmonary surfactant.[349] Newer cephalosporins may have a role in therapy for MRSA-CAP; ceftaroline and ceftobiprole are currently awaiting further approvals in CAP, and their exact place in treatment guidelines remains to be established.[350,351] Ceftobiprole has, however, received European approval for HAP and CAP and has been found to be noninferior to ceftriaxone with or without linezolid in CAP.[352]

Various scoring systems have been proposed to guide empirical therapy for MRSA but have only modest performance. One based on admissions to 62 U.S. hospitals, assigned points for prior hospitalization/ICU admission within the last 90 days, parenteral antimicrobials within

30 days, residency in nursing home/long-term care facility, age (<30 or >70 years), cerebrovascular disease, dementia, and diabetes.[353] These seek to identify CAP in patients with ongoing exposure to the health care system but with emphasis on exposures associated with MRSA. Whereas sensitivity and specificity of this model was only modest (approximately 60%) and the positive predictive value was low, the negative predictive value approximated 90% and the authors suggested this could help guide decisions on withholding empiric therapy for MRSA.

Gram-Negative Bacillary Pneumonia

The term gram-negative bacillary pneumonia refers to infections caused by members of two groups, the Enterobacteriaceae and Pseudomonadaceae, and other aerobic gram-negative bacilli. Gram-negative bacilli are more commonly associated with HAP but cause 2–11% of CAP, with even higher rates in Asia.[46,160,354] *P. aeruginosa* accounts for approximately 1–2% of CAP.[354,355] It is observed in two major settings; patients with structural lung disease, such as cystic fibrosis, bronchiectasis, severe COPD, or prior tracheostomy, and patients with neutropenia or low $CD4^+$ T cell counts, including patients with AIDS.

Enterobacteriaceae

Epidemiology. Enterobacteriaceae normally colonize the digestive tract; oropharyngeal colonization is associated with hospitalization and antimicrobial exposure. Risk factors leading to CAP with these microorganisms include factors leading to aspiration, such as alcoholism, diabetes and causes of immunocompromise, and chronic lung disease, particularly COPD.[46,354] Occasionally, contaminated respiratory therapy equipment or hematogenous seeding causes gram-negative bacillary CAP.

Among the Enterobacteriaceae, *K. pneumoniae* and *E. coli* cause the majority of CAP.[46] The classic cause of community-acquired gram-negative bacillary pneumonia, *K. pneumoniae* (Friedlander pneumonia), causes 3–5% of CAP overall but approximately 15% of CAP in Asia.[356] Excessive alcohol use, diabetes, and COPD are the major risk factors for community-acquired *K. pneumoniae* infection. In Asia and South Africa, hypervirulent strains of *K. pneumoniae* have emerged and can present as CAP, occasionally secondary to hematogenous spread from abscesses in other tissues.[357] Approximately 50% of *K. pneumoniae* infections due to hypervirulent strains in Asia are diagnosed in healthy individuals without risk factors, although diabetes is also associated. These infections are increasingly encountered in America and Europe, particularly in Asian patients.

Pathogenesis. A major virulence factor for *K. pneumoniae* infection is the capsule, and hypervirulent strains have higher capsule content due to alterations in regulators of capsule biosynthesis.[357] The capsule inhibits opsonization and phagocytosis and can shield pathogen-associated molecular patterns required to activate TLRs. K1 and K2 capsular types are the most common causes of infection. Lipopolysaccharide is also an important virulence factor. Siderophores sequester iron that the pathogen needs to survive, and *K. pneumoniae* expresses several siderophores. In the face of limitations to phagocytosis and complement activation, host defense requires several other elements, including IL-17 and IL-22 responses; γδ T cells and natural killer cells are important sources of IL-17 and IL-22, respectively. Human β-defensins also play an important role in host defense, and strains vary in their susceptibility to these factors. Lipocalin-2 expressed by neutrophils can counteract siderophores, although one siderophore, yersiniabactin, is expressed in the lung and evades this host response.[358] Other Enterobacteriaceae are more reliant on defects in lung structure or immune defects to establish infection, but the capsule and toxins such as hemolysin and cytotoxic necrotizing factor, the S fimbrial adhesin, and the siderophore iroN, may aid virulence.[359]

Clinical Manifestations. In *Klebsiella* CAP, a syndrome of pleuritic chest pain, hemoptysis, and bloody sputum (occasionally with a "currant jelly" appearance) is classic but rarely seen.[46,357] The clinical manifestations of Enterobacteriaceae pneumonias are not sufficiently unique to distinguish these infections from pneumonias due to other causes.

Most laboratory abnormalities are nonspecific, but neutropenia is associated with a poor prognosis. Chest radiographs often demonstrate lower lobe bronchopneumonia (eFig. 46.22), which is often bilateral. A classic radiographic appearance of *Klebsiella* pneumonia is upper lobe consolidation (especially on the right; eFig. 46.23) with a bulging or bowed fissure, but this manifestation is now uncommon. *Klebsiella* can also cause lung abscess (eFig. 46.24), particularly in patients with hypervirulent strains.[360]

Microbiologic Diagnosis. Enterobacteriaceae pneumonia should be suspected when sputum Gram stain reveals large numbers of uniform-appearing gram-negative rods (eFig. 46.25). Sputum culture alone is nonspecific for Enterobacteriaceae because of oropharyngeal colonization. Bacteremia, if detected, confirms the diagnosis. For mechanically ventilated patients, quantitative cultures can aid diagnosis.[354] PCR can allow rapid diagnosis and detection of resistance.[354]

Clinical Course. Enterobacteriaceae pneumonia fatality rates are 25–50%.[46] Bacteremia, neutropenia, and advanced age contribute to a poor prognosis. Destruction of pulmonary alveolar septae may lead to cavitation. *K. pneumoniae* is a risk factor for mortality in severe CAP.[361] Hypervirulent *K. pneumoniae* CAP presenting with bacteremia is more fulminant than bacteremic pneumococcal CAP, and sepsis or respiratory failure increases mortality.[361] The overall mortality rate was approximately 55% in one study from Taiwan.[362] Mortality rates of up to 75% are reported.[357]

Treatment. Treatment of serious infections due to Enterobacteriaceae is complicated by widespread antimicrobial resistance. Increasing rates of infection with strains expressing extended-spectrum β-lactamases and carbapenemases are reported, and fluoroquinolone and aminoglycoside resistance is also encountered.[363,364] While multidrug resistant strains are more common in individuals with recent health care exposure, community-acquired resistance is increasingly encountered, including to carbapenems. Due to regional and institutional variations in the frequency of resistance to specific drugs and classes of drugs, initial therapy of possible Enterobacteriaceae pneumonia must be

selected using knowledge of local antibiotic resistance patterns. Therapy for gram-negative bacillary pneumonia is usually initiated after there is some supportive diagnostic test, such as initial microbiologic identification. In certain settings with severe CAP, chronic lung disease, or potential exposure to hypervirulent *Klebsiella,* however, it may be commenced empirically. In patients with serious infection, a two-drug regimen of a β-lactam/β-lactamase inhibitor or carbapenem with an aminoglycoside or a fluoroquinolone is recommended for treatment until susceptibility results are known. Where extended-spectrum β-lactamase production is suspected or documented, a carbapenem-based therapy is required. Options for carbapenemase-producing Enterobacteriaceae include colistin, tigecycline, intravenous (not oral) fosfomycin, aminoglycosides, or even carbapenems (as guided by MIC levels) usually in combination, subject to the results of known susceptibility patterns.[365] Ceftazidime-avibactam is a further alternative. Other β-lactam/β-lactamase inhibitor combinations are in development, including those with carbapenems, and some have demonstrated efficacy in extrapulmonary infections.[366] These are challenging infections and require infectious disease input as well as appropriate antimicrobial stewardship of newer agents.

Pseudomonas aeruginosa and Related Organisms

Epidemiology. *P. aeruginosa* is an uncommon cause of CAP and accounts for approximately 1–2% of CAP cases.[354,355] Higher rates are found in patients with structural lung disease, such as cystic fibrosis, bronchiectasis, and severe COPD (forced expiratory volume in 1 second <30%), or in patients with prior tracheostomy. Structural lung disease increases the risk of colonization, and prior documentation of colonization or infection increases the probability of *P. aeruginosa* being the etiologic agent of CAP in these groups.[355] *P. aeruginosa* CAP, frequently with radiologic cavitation, also affects people living with HIV with CD4 T cell counts less than 50 cell/μL, although the widespread availability of antiretroviral therapy has dramatically reduced the incidence of this and has limited this form of CAP to late presenters, people living with HIV not retained in care, or those with other risk factors.[367,368] Patients with neutropenia following chemotherapy are also at risk of *P. aeruginosa* pneumonia, and transplant recipients are also at risk, although this more often presents as health care–associated infection.[369] Elderly nursing home residents occasionally also develop *P. aeruginosa* pneumonia. The incidence of *Pseudomonas* pneumonia is rare in normal hosts, but necrotizing pneumonia can develop after exposure to aerosols of contaminated water, such as in hot tubs.[370,371]

Other nonfermenters, such as *S. maltophilia* and *B. cepacia,* cause HAP in patients after prolonged broad-spectrum antibiotic therapy but are rare causes of CAP. *B. cepacia* occasionally causes pneumonia in outpatients with cystic fibrosis and occasional case reports exist of pneumonia in otherwise healthy adults.[372]

Pathogenesis. *P. aeruginosa* has a large genome containing several pathogenicity islands.[369] Type 4 pili and flagella aid attachment to the respiratory epithelium and stimulate host responses via TLR2 and TLR5 or the NLRC4 inflammasome.[373] Like many other gram-negative bacteria, there is a type 3 secretion system but there are only four effector proteins; ExoY, ExoS, ExoT, and ExoU.[373] Expression of ExoU and ExoS varies between strains; ExoU is a phospholipase and potent cytotoxin causing tissue injury. Components of the rod structure of the type 3 secretion system also activate the NLRC4 inflammasome.[373] Several proteases degrade opsonins; alkaline protease and protease IV degrade complement; and protease IV also degrades immunoglobulin. The LasB elastase degrades surfactant proteins A and D. The lipid A of lipopolysaccharide can vary, altering susceptibility to cationic antimicrobial peptides. Siderophores such as pyoverdine allow iron acquisition. The pigment pyocyanin induces oxidative stress in host cells and impairs catalase-based detoxification; it has been associated with both neutrophil apoptosis and inhibition of efferocytosis by macrophages promoting inflammation. Exotoxin A inhibits host cell protein synthesis and also can promote host cell death, particularly by necroptosis. During acute infection, proteins that elicit proinflammatory responses and factors that promote adherence and mobility are more highly expressed, whereas, during chronic infections, there is a shift from planktonic to sessile growth, which favors biofilm formation and down-regulation of many of these features. In keeping with this, bacteria isolated from patients with cystic fibrosis induce blunted inflammasome responses.[374]

Alveolar macrophages phagocytose *P. aeruginosa* using both opsonic and non-opsonic receptors. They coordinate the inflammatory response, but depletion experiments in mice have failed to demonstrate a consistent role.[369] Epithelial cells also help coordinate the host response and release human β-defensins and other antimicrobial factors against *P. aeruginosa.*[375,376] Human β-defensin 2 is degraded during chronic inflammatory responses and is dependent on acute inflammatory responses, illustrating its important role in host defense against *P. aeruginosa.*[375] Fas-dependent epithelial cell apoptosis has been found to aid pathogen clearance in mice.[377] Neutrophils play key roles in controlling acute infections, although *P. aeruginosa* has developed strategies to evade NET-dependent killing.[378] T cell responses contribute to host defense through production of IFN-γ and IL-17 against *P. aeruginosa.*[376,379]

Clinical Manifestations. The clinical and radiologic picture of pneumonia due to *P. aeruginosa* (eFig. 46.26) is indistinguishable from that of the Enterobacteriaceae. Cough, shortness of breath, and chest pain are common, and hemoptysis may be observed.[371] Bacteremia is slightly more common than for other gram-negative pathogens; physical examination may reveal ecthyma gangrenosum, and leukopenia is common. Its propensity to invade vascular tissue makes *Pseudomonas* the most common cause of cavitary pneumonia (eFigs. 46.27 and 46.28), particularly in immunocompromised patients such as those with HIV infection and low CD4 T cell counts.[368] Empyema can develop. A number of reports, including in otherwise healthy patients, describe bilateral involvement and upper lobe disease, particularly in the right upper lobe.[371,380]

Microbiologic Diagnosis. Gram-stained sputum from patients with *Pseudomonas* pneumonia typically shows many slender, gram-negative bacilli (eFig. 46.29); neutrophils are abundant in the sputum except in neutropenic patients. Because *Pseudomonas* and other gram-negative bacilli colonize the oropharynx in hospitalized or debilitated patients, Gram stain results in these patients can be misleading. Quantitative cultures on tracheal aspirates or BAL can aid the diagnosis.[46]

Clinical Course. Even in otherwise healthy individuals, *P. aeruginosa* CAP mortality is 30%,[46] and median survival of less than 12 hours after admission has been described.[371]

Treatment. The decision to include empirical therapy for *P. aeruginosa* pneumonia in CAP is based on identification of risk factors such as chronic lung disease or history of prior *P. aeruginosa* infection.[147] As discussed above, recent guidelines favor only treating in the presence of prior evidence of respiratory isolation or with recent hospitalization with parenteral antimicrobials in the presence of locally validated risk factors for *P. aeruginosa*.[109] Otherwise, therapy should be guided by initial microbiological identification. The antipseudomonal regimen should initially include two antimicrobial agents expected to be active against isolates in the region, such as an aminoglycoside and an antipseudomonal β-lactam antibiotic; this is especially true for bacteremic or neutropenic patients.[381] Amikacin is the most reliably active aminoglycoside in most regions. A fluoroquinolone can be considered as an alternative but, in many regions, fluoroquinolone resistance is widespread.[382] Rapid emergence of adaptive resistance precludes fluoroquinolone monotherapy. The β-lactam antibiotics, in descending order of probable activity against *P. aeruginosa,* are the carbapenems (imipenem and meropenem), the acyl ureidopenicillins (e.g., piperacillin), cefepime, and ceftazidime.[383] Due to antimicrobial stewardship considerations, a combination such as piperacillin-tazobactam with an aminoglycoside is preferred, with a carbapenem-containing regimen reserved for cases where extended β-lactamase production is encountered. Options for carbapenemase-producing organisms depend on the specific carbapenemase produced by the isolate.[365] Ceftazidime-avibactam and ceftolozane-tazobactam may be useful in treating these infections, although ceftolozane-tazobactam may need higher doses than currently licensed to allow treatment of lung infections; this is an emerging area. Infections resistant to these agents may require colistin and meropenem combination treatment or, if susceptible, aztreonam with or without ceftazidime-avibactam. Other combinations of carbapenems or aztreonam with β-lactamase inhibitors are in development and may also prove to have roles for these infections.[365,366]

S. maltophilia is inherently resistant to most standard antibiotics.[384] TMP-SMX is the most reliable agent, while fluoroquinolones or ticarcillin-clavulanate have activity against some strains.[385,386] Isolates of *S. maltophilia* may become resistant in the face of seemingly effective therapy. *B. cepacia* may be susceptible to acyl ureidopenicillins, ceftazidime, carbapenems, TMP-SMX, fluoroquinolones, and aminoglycosides. Resistance rates are higher in isolates from patients with cystic fibrosis. Therapy usually includes at least two parenteral agents, ideally including a β-lactam and TMP-SMX or a fluoroquinolone.

Other Viral Pneumonias

Respiratory Syncytial Virus. RSV is a pleomorphic (150 to 300 nm), enveloped virus with a single-stranded, nonsegmented RNA genome. Two surface proteins, the *fusion* (F) protein and the *glycoprotein* (G) protein, are major viral antigens that play a key role in the virulence of RSV and are the most frequent targets for vaccine-induced immunity. The G protein mediates RSV attachment to host cell, while the F protein is responsible for fusion of the viral envelope with the host cell membranes and formation of syncytium. RSV is classified into two subgroups (A and B)[387] based on antigenic differences in the G glycoprotein. Subgroups are classified further into genotypes based on genetic analysis. Group A and B viruses tend to co-circulate, though infections by group A strains appear to be more severe.[387,388]

Epidemiology and Transmission. RSV is worldwide in distribution. In temperate climates, annual outbreaks of RSV infection are most common in winter months[389] while, in tropical regions, RSV seasonality is less predictable and more prolonged, often coinciding with the rainy season.[390,391]

RSV is the most frequent cause of bronchiolitis in infants and young children and accounts for more than 80% of LRT infections in infants younger than 1 year. Nearly 50% of children are infected within the first year of life, and almost all have been infected by 2 years of age. Reinfections are quite common even with the same strain,[392] suggesting that immunity is only partial.

RSV is increasingly recognized as a cause of severe disease in older adults[393]; mortality rates are substantially greater among adults 65 years or older than in infants.[394] Other groups at risk of LRT infection include immunocompromised patients[395] and those with chronic respiratory[396] or cardiac[397] disease.

RSV spreads by large-particle droplets during close personal contact and by hand contamination with infectious secretions and subsequent self-inoculation of the eye or nose.[398] The virus can survive on fomites for up to 6 hours.[399] RSV is a major nosocomial pathogen, and high attack rates have been reported during outbreaks in hospitals, transplantation units, and elderly care homes. In the family setting, secondary infection develops in up to one-third of adult contacts.[400,401]

Pathogenesis of RSV LRT Infections. Viral replication generally begins in the nasopharynx, then moves to the bronchiolar epithelium, and gradually progresses (1 to 3 days) to involve the LRT. Pathologic findings of RSV infection include necrosis of bronchiolar epithelium, loss of ciliated epithelial cells, and marked peribronchiolar monocytic and T cell infiltration.[252] Virus-induced cytopathology and associated submucosal edema lead to airway obstruction, air trapping, and increased airway resistance.

Both serum and mucosal antibody responses are observed but are associated with limited protection. The magnitude of the antibody response is related to the age at primary infection, with infants younger than 8 months having approximately 10-fold lower antibody levels than older ones.[402] There may be reinfection within weeks after primary infection.[392] Circulating and mucosal antibody levels increase with each successive infection and appear to be associated with milder illness.[403] Higher titers of serum neutralizing antibody are generally associated with a lower risk of severe RSV disease in children and adults.[404]

Cell-mediated immunity appears to be important in viral clearance and may also be involved in pathogenesis. For example, the greater risk of severe lower respiratory disease from RSV observed in adult bone marrow transplant patients is likely due to prolonged periods of decreased cellular immunity.[405] In contrast, AIDS patients with decreased cellular immunity may suffer only mild disease, but viral shedding may persist for up to 6 months.[406]

Studies that have investigated genetic predisposition to severe RSV disease in children have identified associations with polymorphisms in several innate and adaptive immune genes, including surfactant proteins,[407] TLR4,[408] the CX3CR1 chemokine receptor,[409] IL-4,[410] and the CCR5 chemokine receptor.[411]

Clinical Manifestations. The incubation period is usually 4 to 6 days. The clinical manifestations of infection depend on both the age and immunologic state of the host. The majority of RSV infections in healthy adults are associated with upper respiratory tract illness,[412] typically with coryza, pharyngitis, productive cough, and a low-grade fever. Nevertheless, up to one-quarter of healthy adults with RSV infection develop LRT infection. Pneumonia is more common in the elderly; approximately 177,000 hospitalizations and more than 14,000 deaths in the United States are associated with RSV annually in adults over 65 years.[413] In this age group, the clinical features of RSV infection can mimic those of influenza, although fever is less frequent and wheezing is more frequent.[414] In a large prospective cohort study in the United States, RSV infection developed in 3–7% of healthy elderly and 4–10% of high-risk adults annually.[392] Among hospitalized patients, those with RSV infection had similar lengths of stay, rate of ICU admissions (15% vs. 12%), and mortality (7% vs. 8%) compared to influenza-infected patients. RSV also contributes to 5–10% of COPD exacerbations.[415]

In immunocompromised adults, RSV, often nosocomially acquired, can cause severe pneumonia. Mortality rates of RSV infection in transplant recipients are significantly higher than in the general population; rates of up to 80% have been reported, falling to 6–25% with prompt supportive care and/or treatment.[416] Recent studies that involved the use of ribavirin in hospitalized patients reported 5–16% mortality among hematopoietic stem cell transplant patients and 10–13% in solid organ transplant recipients in the context of ribavirin treatment.[395,417,418]

Chest radiographic findings in RSV LRT infection include bronchial wall thickening, peribronchial shadowing, air trapping (eFig. 46.30A) and, in pneumonia, multilobar patchy shadowing or poorly defined nodularity (eFigs. 46.30B and eFig 46.31). Although no radiographic pattern is specific, air trapping is highly associated with RSV infection in hospitalized children.[419] Chest CT findings (eFig. 46.32) are also nonspecific, often resembling other viral pulmonary infections, including multifocal areas of ground-glass opacity, consolidation, and small nodules, which may show branching configurations (tree-in-bud opacities).

Transient alteration of airway reactivity following RSV infection has been described in otherwise healthy adults.[420] Prolonged pulmonary function abnormalities, including increased airway resistance, peripheral airway obstruction, and decreased arterial oxygen saturation, have also been detected in children years after bouts of bronchiolitis.[421]

Diagnosis. RSV infection can be diagnosed by rapid antigen detection, PCR-based assays, or viral culture. Rapid antigen tests can be performed in less than 30 minutes. The sensitivity of the test is related to the amount of antigen being shed; hence it is generally greater in children than adults (80% vs. 29%).[422] PCR-based assays are therefore preferred in adult patients. In transplant patients with suspected RSV pneumonia, samples of the LRT by BAL are more sensitive than throat swabs for detection of RSV antigens.[423] RSV grows well in several human cell lines, where it causes formation of characteristic syncytia, the basis for the name of the virus.

Treatment and Prevention. Correction of hypoxemia is the most important aspect of managing RSV LRT infection.[424] There are currently two licensed drugs for the management of RSV infection: palivizumab for prophylaxis and aerosolized ribavirin for treatment. Palivizumab, an RSV-specific humanized monoclonal antibody targeting the F protein, has been shown to be a highly effective in preventing RSV morbidity in high-risk pediatric patients.[425] Palivizumab has not been shown to be effective in the treatment of established RSV disease in adults.[426,427]

Ribavirin is highly active against RSV in vitro, and aerosolized ribavirin has been shown to reduce viral shedding and shorten the course of illness in some, but not all, studies. A number of randomized placebo-controlled trials of ribavirin in children with RSV pneumonia have demonstrated decreased illness severity; reduced duration of mechanical ventilation, oxygen therapy, and hospital stay; as well as decreased viral shedding[428–430]; others have shown no clinical benefit, however.[431,432]

Treatment of RSV in adults has not been well studied, and optimal treatment is unclear. Ribavirin (oral and aerosolized) has been used, particularly in hematopoietic stem cell transplant recipients, as preemptive treatment to prevent progression to pneumonia.[433] Combinations of aerosolized ribavirin and immunomodulators, including intravenous immunoglobulins, corticosteroids, and palivizumab, have been reported to improve outcome in immunocompromised patients with RSV pneumonia, though existing evidence is mostly derived from case reports, small trials, and retrospective reviews of RSV-infected patients who have undergone lung or hematopoietic stem cell transplantation.[434,435] A number of experimental RSV therapeutics are under investigation, including monoclonal and polyclonal antibodies, siRNA-interference, fusion inhibitors, and small molecules.[436]

An effective vaccine for prevention of RSV has not yet been developed. A trial of a formalin-inactivated RSV vaccine in infants in the 1960s resulted in enhanced RSV disease and two deaths.[437] The enhanced respiratory disease is thought to be due partly to formalin-mediated destruction of neutralizing epitopes in the vaccine,[438] while an enhanced Th2 response[439] and the development of non-neutralizing antibodies[440] to formalin-inactivated RSV have also been implicated. This adverse experience has prompted extra caution. Nevertheless, current RSV vaccine development efforts are ongoing, with a number of live, attenuated, subunit, particle-based, and vector-based vaccines in clinical trials.[436] One of the candidate vaccines at an advanced stage of development is a recombinant RSV-F protein nanoparticle vaccine developed by Novavax. In a Phase II trial, the RSV-F vaccine administered to healthy women of childbearing age was safe, immunogenic, and reduced RSV infections.[441] However, preliminary results from a multicountry Phase III study suggest that the vaccine had no impact on medically significant RSV LRT infection in infants up to 90 days of age.[442] It was, however, associated with a reduction in RSV-related LRT infection hospitalizations in infants up to 90 days of age. Target populations that may benefit from an RSV vaccine include infants younger than 6 months, children older than 6 months, pregnant women, and the elderly. Identifying the most important target population will be key to future RSV immunization strategies.

LESS COMMON CAUSES OF PNEUMONIA

A variety of pathogens are less common causes of pneumonia. These agents may be suspected in the presence of specific risk factors or presentations or may be diagnosed by results of cultures or other diagnostic tests.

Acinetobacter baumannii

Epidemiology. *A. baumannii*, a gram-negative bacteria, is a rare cause of CAP and more commonly associated with HAP/VAP.[443] *Acinetobacter* causes CAP in hot climates, both dry[444] and humid.[443,445] CAP due to *A. baumannii* has been particularly reported from southeast Asia, where risk factors include alcoholism, smoking, COPD, malignancy, diabetes, and other medical comorbidities.[443,445,446] In the United States, *Acinetobacter* CAP is most commonly seen in male alcoholics.[447] Infections caused by *Acinetobacter* show seasonal variation, peaking in late summer.

Clinical Manifestations. Patients with *Acinetobacter* CAP often present acutely with shock, ARDS, and disseminated intravascular coagulation.[443,445,446] Investigations frequently show leukopenia and thrombocytopenia, while radiologic features of ARDS or pleural effusions are common.

Microbiologic Diagnosis. Examination of expectorated sputum, which is usually purulent, may reveal a predominance of paired gram-negative coccobacilli that resemble *Neisseria, Haemophilus,* and *Moraxella* species. Bacteremia is common.[443]

Clinical Course. The mortality rate of community-acquired *Acinetobacter* pneumonia is often over 50%.[445,446] Patients at greatest risk of death are those with leukopenia, septic shock, or respiratory failure.

Treatment. Community isolates of *A. baumannii* can be susceptible to β-lactam/β-lactam inhibitor combinations, carbapenems, fluoroquinolones, and TMP-SMX.[446] If the patient has had recent contact with health care facilities, the risk of infection with a multidrug-resistant infection increases; these infections frequently require combinations of colistin with meropenem, tigecycline, or aminoglycosides.[365]

Anaerobic Bacteria

Epidemiology. Anaerobic bacteria usually cause pneumonia in association with aspiration. Risk factors for aspiration are reduced cough and impaired clearance of oropharyngeal secretions, which are frequently associated with advanced age.[448] Anaerobic infections are the second most common cause of severe aspiration pneumonia, after aerobic gram-negative bacilli, and are often polymicrobial infections.[449] Although acute complications of macroaspiration are largely due to a chemical injury pneumonitis (Mendelson syndrome) and/or infection by pathogenic aerobes in the oral flora, many of these episodes later result in the emergence of mixed aerobic and anaerobic pneumonia. Rarer causes of anaerobic infection include rupture of the esophagus and extension of intra-abdominal abscesses. Anaerobic lung infection may also complicate malignancy and pulmonary infarction. Molecular testing using 16S ribosomal RNA has detected anaerobic bacteria in a higher percentage of cases of CAP than has been previously detected by standard culture. One small study identified anaerobic bacteria as prominent phylotypes in 15% of cases of CAP, primarily those with polymicrobial infection or in whom no pathogen was identified by routine culture.[450] Because this study included patients with mild CAP and did not primarily study aspiration pneumonia, the authors conclude anaerobic bacteria may contribute more to CAP than previously assumed.

Clinical Manifestations. Anaerobic infections are associated with three different syndromes associated with aspiration pneumonia: chemical pneumonitis, aspiration pneumonia, or anaerobic pleuropneumonia.

Chemical pneumonitis can precede anaerobic pneumonia and is characterized by the acute onset of hypoxemia, fever, cough (often dry), dyspnea, and pleuritic pain. The risk of bacterial infection is dependent on the nature of the inoculum; many cases of aspiration pneumonitis are inflammatory alone, and the aspirated bacteria may play a less-prominent pathogenic role, although they may be detected by molecular techniques. Imaging may demonstrate bronchopneumonic opacities, but usually not lobar consolidation, in the aspiration-prone segments of the lung (e.g., posterior segment of the right upper lobe and superior segment of the right lower lobe; see eFig. 46.4). ARDS is a common complication of aspiration of low-pH gastric fluid.

Aspiration pneumonia is indistinguishable from either CAP or HAP (eFig. 46.33), with the exception that it is seen in patients with risk factors for macroaspiration. Rapid development of pulmonary opacities over a short period of time may suggest the diagnosis of aspiration pneumonia (eFigs. 46.34 and 46.35). High concentrations of amylase or pepsinogen in BAL fluid are very suggestive of this entity.[451] Localization of an opacity in a dependent lung segment has less discriminating value.

Anaerobic pleuropneumonia is characterized by necrosis and suppuration of lung parenchyma and typically presents at least 1 to 2 weeks after aspiration.[452] Patients commonly present with fatigue, low-grade fever, weight loss, and productive cough for several weeks, often after an episode of loss of consciousness. Approximately half describe putrid sputum, and some may have hemoptysis. Patients appear chronically ill and toxic, with temperatures up to 39°C. Early in the course, imaging may demonstrate dense segmental opacification with multiple small areas of necrosis that evolve into cavities (<2 cm in diameter), usually without air-fluid levels (eFig. 46.36). In the absence of appropriate treatment, these lesions may evolve into a primary lung abscess (eFig. 46.37) and empyema. In some patients, a single lung abscess greater than 2 cm in diameter is detected in a dependent lung segment on radiography, but the location can be anywhere in the lung (eFig. 46.38). The abscess may be multilocular; occasionally, multiple abscesses are located in different lung segments. Occasionally in anaerobic bacterial pneumonia, pleural features may dominate over those of pneumonia, particularly in association with esophageal rupture or intra-abdominal abscesses.

More information on lung abscesses is in Chapter 50 and on pleural empyema is in Chapter 109.

Microbiologic Diagnosis. Gram stain of sputum or BAL fluid of a patient with anaerobic pneumonia reveals PMNs with an abundance of intracellular and extracellular bacteria. Typically, a mixture of Gram stain reactions and morphologies are seen, including pale-staining gram-negative rods with tapered ends (suggestive of *Fusobacterium nucleatum*), small, pale-staining gram-negative coccobacilli, and chains of tiny gram-positive cocci.

Because the upper respiratory tract endogenous flora contains a predominance of anaerobic bacteria, cultures of expectorated sputum do not aid diagnosis of anaerobic pneumonia. Anaerobic bacteria may be cultured from BAL or aspiration of abscess or empyema. The most common anaerobes in pleuropulmonary infections include *F. nucleatum, Prevotella, Porphyromonas, Peptostreptococcus,* and microaerophilic *Streptococcus* species. *Veillonella* species are also increasingly detected with molecular techniques.[450] Since many of these microorganisms are part of the normal LRT microbiome, their contribution to disease implies dysbiosis.[6] The major aerobic and facultative organisms recovered in conjunction with anaerobes are *Streptococcus* species potentially facilitated by interactions with anaerobes such as *Veillonella* species that promote biofilm formation.[6] Although *S. aureus,* various enteric gram-negative bacilli, and *Pseudomonas* may also be isolated, their significance is often questionable. Molecular techniques such as sequencing of 16S ribosomal RNA can help identify anaerobes in culture-negative cases.[450]

Clinical Course. Uncomplicated aspiration pneumonia generally responds promptly to appropriate antibiotics. Fatality rates are low in adequately treated patients, except those with necrotizing pneumonia. However, in individuals who present with severe anaerobic aspiration pneumonia, mortality of 36% is reported on the basis of small series.[449] Complications of lung abscess and empyema are described in Chapters 50 and 109, respectively.

Treatment. β-Lactamase–mediated resistance is common among anaerobes. Empirical treatment for serious anaerobic pneumonia requires the use of a β-lactam/β-lactamase inhibitor (e.g., ampicillin-sulbactam, ticarcillin-clavulanate, or piperacillin-tazobactam) or clindamycin. Because of the frequent simultaneous presence of aerobes, metronidazole monotherapy is not adequate for suspected anaerobic pneumonia. Occasional pulmonary isolates are resistant to one or more of these agents and, once anaerobes are cultured, therapy should be tailored to known susceptibility patterns. For example, *Eikenella corrodens* is resistant to clindamycin. Carbapenem monotherapy is also effective but generally provides unnecessarily broad coverage.

Five to 10 days of total treatment is usually adequate for uncomplicated pneumonitis. Necrotizing pneumonia, abscess, and empyema require prolonged parenteral therapy and subsequent oral therapy; drainage procedures may also be appropriate.

Bordetella pertussis

Bordetella pertussis, a small gram-negative coccobacillus, is the etiologic agent of pertussis, also known as whooping cough. Incorporation of pertussis in the childhood vaccination schedule has now made this infection rare, but milder forms may be seen in adolescents and young adults with waning immunity, and infections may still be seen in children who have not received the vaccine.[453] Worldwide, the pathogen still causes many infections. The pathogen produces several toxins, including adenylate cyclase toxin that inhibits chemotaxis, phagocytosis, and oxidative burst by phagocytes; tracheal cytotoxin that inhibits mucociliary function; and pertussis toxin that induces lymphocytosis by blocking lymphocyte trafficking to lymph nodes and other lymphoid tissues.

The incubation period is typically 6 to 10 days. The initial catarrhal phase lasts 1 to 2 weeks and is followed by the paroxysmal stage, which lasts 3 to 6 weeks and is associated with the characteristic whooping cough, apnea, cyanosis, and vomiting after bouts of coughing.[453] These symptoms gradually resolve during the subsequent convalescent phase, which can last months. In immunized individuals, the symptoms may be milder and cough may predominate. Complications include encephalopathy, otitis media, and pneumonia, which may be due to either *B. pertussis* or bacterial superinfection. Pneumonia is present in 6% or less of infections.[454] Rates are likely lower in adolescents and younger adults but may be higher in older adults. Pneumonia may be the result of aspiration during vomiting. Signs and symptoms are similar to other causes

of CAP, but the history of protracted coughing or vomiting may suggest the disease, while lymphocytosis may be a feature on blood examination. Microbiological diagnosis now usually uses PCR, although serologic tests and culture also establish the diagnosis. Treatment is with a macrolide: erythromycin for 14 days or shorter courses with newer macrolides. Close household contacts should receive chemoprophylaxis with macrolides. In the United States, adults receive a booster with acellular pertussis vaccine at the time of routine tetanus and diphtheria boosters (as a combined vaccine) or during pregnancies (at 20 to 32 weeks' gestation), while in the United Kingdom boosters are administered only to pregnant women.

Chlamydophila pneumoniae (Formerly *Chlamydia pneumoniae*)

Epidemiology. *C. pneumoniae* is a gram-negative coccobacillus. Older serologic studies suggested *C. pneumoniae* caused up to 15% of cases of CAP, but they were limited by cross-reactivity of enzyme-linked immunosorbent assay and high background seroprevalence. A recent meta-analysis implicated *C. pneumoniae* in 4% or fewer cases of CAP.[45,455] Seroprevalence studies suggest seropositivity of 40–70%, implying that exposure is common.[456] Outbreaks take place in correctional, long-term care, and military facilities, facilitated by shedding of the pathogen for over 2 months in some cases.[457] Human isolates are genetically similar, suggesting relatively recent zoonotic acquisition of strains that originated from amphibians.[458]

Pathogenesis. The pathogen is an obligate intracellular bacterium. The infective elementary bodies are taken up into cells via the interaction of the adhesin Pmp21 with epidermal growth factor receptor.[459] In the cytoplasm, they develop into the reticulate body that divides in membrane-bound vacuoles and utilizes the chlamydial protease-like activity factor to acquire nutrients via fragmentation of the Golgi apparatus. *C. pneumoniae* actively inhibit mitochondrial apoptosis pathways to ensure intracellular survival.[460] The host response involves activation of various pattern recognition receptors including TLR2/4, NLRP3, NODs, and mitochondrial anti-viral signaling proteins to induce type 1 interferons and Th1/Th17 responses, which contribute to pathogen clearance.[461–465] A mouse genetic locus linked to susceptibility to intracellular pathogens, *supersusceptibility to tuberculosis* (sst1), influences susceptibility to *C. pneumoniae* and susceptible mice have enhanced type 1 interferon responses, which despite enhanced pathogen clearance and apoptosis induction, promote excessive inflammation and tissue injury.[462]

Clinical Manifestations. Primary infection by *C. pneumoniae* is usually asymptomatic: an acute, mild respiratory tract infection is observed in up to 20% of cases.[456] The incubation period is approximately 21 days, with gradual onset of symptoms such as cough, headache, hoarseness, sore throat, and malaise.[466] There may be bronchitis, sinusitis, laryngitis, tonsillitis, or exacerbations of asthma, with or without associated pneumonia. *C. pneumoniae* infection may result in prolonged wheezing and may also be associated with exacerbation of asthma.[467] The erythrocyte sedimentation rate is elevated, but leukocytosis or elevated PCT may be absent.

Microbiologic Diagnosis. *C. pneumoniae* cannot be visualized by Gram stain, and tissue culture is required to grow the pathogen. Although direct fluorescent antibody detection of *C. pneumoniae* is available, nucleic acid testing is emerging as a rapid, sensitive mode of detection that yields results in a timeframe useful for clinical management (see Chapter 19). Real-time PCR is preferable to nested assays.[467] Serologic diagnosis is compromised by high seroprevalence and cross-reactivity of IgM enzyme-linked immunosorbent assay with other atypical pathogens such as *M. pneumoniae*.[468]

Clinical Course and Treatment. Complete recovery following *C. pneumoniae* infection is the rule; fatalities are principally seen in patients with mixed infection or preexisting illness.[467,469] When associated with an exacerbation of asthma, *C. pneumoniae* can require a prolonged time for recovery. Azithromycin 1.5 g over 5 days (500 mg on day 1 and 250 mg daily for days 2–5) is often the first choice of therapy, with a 2-week treatment with doxycycline or a fluoroquinolone used in non-responders or those intolerant to macrolides.[147,469] The role of short duration therapy for CAP is not established in *C. pneumoniae,* but a meta-analysis of short course therapy has included patients with *C. pneumoniae.*[470]

Chlamydia psittaci (Formerly *Chlamydophila psittaci*): Psittacosis

C. psittaci is a gram-negative bacterium that causes psittacosis in humans. Psittacosis causes less than 1% of CAP cases.[471] Exposure to birds is the classic risk factor for psittacosis, and greater than 70% of cases have a clear recreational or occupational exposure.[472] History of exposure is more likely with more severe disease.[473] Infections are classically associated with psittacine birds—parakeets, cockatiels, and parrots—but many other avian species, including canaries, chickens, turkeys, ducks, and pigeons, have been associated with human infection. Some avian-transmitted infections may be related to other *Chlamydia* species; for example, *C. gallinaceae* in chickens is an emerging ornithosis.[474] Infected birds may be ill, but human infections may also result from pathogen shedding by asymptomatic birds. Human acquisition of *C. psittaci* is typically via inhalation of aerosols generated from contaminated bird excreta, respiratory secretions, and bedding or from contact with feathers from infected birds.[472]

Like other *Chlamydophila* species, *C. psittaci* expresses a type III secretion system and uses this to secrete effectors during the intracellular stage of its life cycle, allowing its survival and replication within a membrane-bound vacuole.[85] Several effectors, such as the proteins IncA-C and related proteins, modify the inclusion membrane and interaction of host endosomes with the parasitophorous vacuole. Fusion with lysosomes is inhibited, while proximity to mitochondria allows adenosine triphosphate acquisition and proximity to the Golgi apparatus allows acquisition of lipids. In comparison with other *Chlamydophila* species, *C. psittaci* has a shorter period to complete its life cycle and

forms larger inclusions in cell culture. The pathogen inhibits apoptosis, but complement and Th1 responses appear important to control replication.

Infection is most common in those 40 to 65 years of age. The incubation period is 5 to 14 days.[85] The symptoms of psittacosis typically develop rapidly, with high fever and chills, or they may evolve slowly. Headache, arthralgia, and painful myalgia (especially in the head and neck) are prominent features. A dry, nonproductive cough is most common. Chest pain and dyspnea are present with extensive pulmonary involvement, but auscultation may underestimate the extent of disease. Pulse-fever dissociation is frequently observed, in which there is a normal or slow pulse despite fever. Splenomegaly or occasionally a pale macular rash (Horder spots) can be seen. Myocarditis, pericarditis, endocarditis, encephalitis, arthritis, hepatitis, and keratoconjunctivitis are occasional complications.[85] Hematologic and blood chemistry findings are nonspecific, except occasionally for findings consistent with granulomatous hepatitis. Radiologic features are usually of lobar consolidation or of interstitial changes.

C. psittaci is an obligate intracellular parasite and is not detected by Gram stain. Culture is not routinely available outside reference laboratories. Serologic testing was formerly the main diagnostic approach, and the microimmunofluorescence test was more sensitive and specific than the complement fixation test, which cross-reacted with *C. burnetii* and *Brucella* species. A fourfold rise in IgG supported a diagnosis but required an early acute sample and could be delayed, particularly after antimicrobials. PCR-based diagnosis is now preferred and is available in reference laboratories on respiratory samples and blood but requires discussion to ensure optimal specimen collection.[473]

Treatment with doxycycline is recommended, but clinical response may be slow.[475] Because of the risk of relapse, therapy should be given for a minimum of 2 weeks after fever has resolved. Macrolides represent an alternative when doxycycline cannot be administered, but experience with macrolides is more limited. The case-fatality rate is about 1% with antimicrobial therapy.

Coxiella burnetii: Q Fever

C. burnetii, a gram-negative bacterium, causes Q fever and is a rare cause of CAP. Interestingly, in Cayenne, French Guiana, an area hyper-endemic for *C. burnetti*, it can cause 24% of CAP cases.[476] The pathogen is found worldwide, particularly in cattle, sheep, and goats, but *C. burnetii* asymptomatically infects a wide variety of domestic and wild animals as well as ticks. Transmission to humans is primarily via inhalation of aerosolized bacteria. Birth products contain the highest concentration of bacteria, but they are also found in urine, feces, and unpasteurized milk. The largest outbreak to date resulted in approximately 4000 reported cases in the Netherlands between 2007 to 2010 and was linked to goat farming.[476] Since many infections are asymptomatic, estimates suggest there may have been in excess of 40,000 infections. Outbreaks have also happened in tanneries, dairies, and wool-rendering plants; among laboratory personnel; and in household members exposed to an infected cat or dog during parturition.[477,478]

Following an incubation period of 2 to 3 weeks, an atypical pneumonia syndrome develops in approximately 10% of infected persons.[476,478] Approximately 86% of acute infections in the Netherlands outbreak presented as CAP.[476] Patients are most often middle-aged men without medical comorbidity. Fever, cough, dyspnea, myalgia, arthralgia, abdominal pain, and diarrhea are common. Headache may be severe, and there may be confusion. On physical exam, coarse crackles and pulse-fever dissociation are frequently observed, and conjunctivitis or hepatosplenomegaly may be detected. Myocarditis or pericarditis can be acute complications. A maculopapular or vesicular rash can be detected but is observed in only 1–9% of cases. White cell counts are often normal, but lymphopenia or increased white cell counts may be observed. CRP is markedly elevated, and 30–60% of patients have elevated liver function test results. Radiologic appearances vary from focal consolidation or interstitial opacities to rounded opacities, sometimes with a surrounding halo.[476,478] Pleural effusions are found in approximately 10%.[92]

C. burnetii is a small, obligate intracellular bacterium that utilizes a type 4 secretion syndrome to enhance intracellular persistence and replication. Dot/Icm genes encode the secretion system, which overall shows some similarity to the Dot/Icm system of *Legionella* species.[479] The pathogen subverts the later stages of phagolysosomal fusion, delaying acquisition of cathepsin D, and *C. burnetii* lipopolysaccharide fails to activate p38α mitogen-activated protein kinase.[476] IL-10 also contributes to impaired phagolysosomal fusion. Host responses are characterized by Th1 responses to induce IFN-γ and reactive species generation, but the pathogen inhibits reactive oxygen species generation. The host response involves granuloma formation, but the pathogen inhibits apoptosis and manipulates autophagy to enable intracellular replication and persistence.[479]

C. burnetii cannot be cultured on standard media or visualized on Gram stain. Recent advances in specialized laboratories allow culture on specialized media.[476] Because of the high infectivity of the organism, cultures should be attempted only by experienced personnel in biosafety level 3 laboratories. Indirect immunofluorescent antibody detection has traditionally been used in diagnosis, and detection of IgM 1:50 or greater or of Phase II IgG at titers 1:200 or greater or fourfold rises in IgG suggests acute infection.[476] IgG against phase II antigens is higher than against phase I antigen in acute infections, while the converse is seen with chronic infection. Serologic cross-reactions are possible with other species such as *L. micdadei* and *Bartonella* sp. A quantitative PCR test had a reported sensitivity of 92% and specificity of approximately 99% in the outbreak in the Netherlands.[476] Biopsy specimens may show granulomata, which, in liver or bone marrow, may show a characteristic "doughnut" appearance.

Although patients may be acutely ill on presentation, the disease is rarely fatal and generally runs its course in 1 to 2 weeks.[478] The mortality in patients without comorbid illness in the Netherlands outbreak was approximately 1%.[92] Myocarditis can be a fatal complication. Some patients, particularly older adults, have a very prolonged illness. The most concerning aspect of Q fever is the potential for chronic infections (observed in approximately 1–2% of infection).[479] These manifest as vascular complications, including endocarditis, vascular graft infections, and infected aortic aneurysms, as well as chronic hepatitis or

chronic fatigue syndromes. Acute Q fever pneumonia during pregnancy is often associated with fetal loss.

Doxycycline 200 mg orally for 10 days is the preferred treatment regimen. Fluoroquinolones and macrolides are alternatives, and some authorities have recommended macrolides combined with rifampicin.[92] Clarithromycin is the preferred macrolide because poorer outcomes have been reported with azithromycin. TMP-SMX is a further alternative if options are limited. Quinolones have excellent in vitro activity and may be advantageous in the treatment of meningoencephalitis.[477]

Melioidosis (*Burkholderia pseudomallei*)

B. pseudomallei is a gram-negative bacillus that causes melioidosis, a disease endemic in Southeast Asia, Singapore, Malaysia, and northern Australia. The disease is hyperendemic in northeastern Thailand and northern Australia and, in these areas, melioidosis may be the most common cause of severe CAP.[480] *B. pseudomallei* is a saprophyte found in wet soil, vegetation, and water throughout tropical regions between latitudes 20 degrees N and 20 degrees S.[84,480] There are multiple reports of sporadic human or animal cases in non-tropical locations. Inhalation and inoculation are the commonest routes of infection.[84] Risk factors for disease include diabetes, alcoholism, and renal disease.[481] Heart disease, smoking, and COPD are also associated with *B. pseudomallei* pneumonia.[482] Cystic fibrosis is also a risk factor in those who live or travel to an endemic area. Typhoons or episodic heavy rain may increase the risk of acute fulminant pneumonia; more than 75% of cases happen during the rainy season.[483] There is also an association with near-drowning, including following tsunami.[484]

The pathogen uses a type III secretion system to inhibit autophagy in host cells such as epithelia. Macrophages ingest the pathogen, but it may subvert phagolysosomal maturation and ultimately can cause cell lysis, sometimes via caspase-1–dependent pyroptosis, followed by release of the bacteria to infect other cells. Reactive oxygen and reactive nitrogen species help control infection, and Th1 responses are important.[485]

The incubation period is 1 to 21 days (mean, 9 days). Melioidosis can produce either acute fulminant pneumonia or indolent, cavitary disease. A large series from Northern Australia determined that approximately half of cases of melioidosis presented with pneumonia; of these, 91% had an acute or subacute presentation, with only 9% chronic.[482] In extrapulmonary disease, which is most often manifest as skin or soft tissue abscesses or genitourinary disease, hematogenous spread of bacteria led to pulmonary disease in approximately 19% of cases in that series. Primary pneumonia led to bacteremia in 63% and septic shock in 33%. Some patients present with productive cough, dyspnea, and fever. Hemoptysis and pleuritic chest pain may be prominent. Patients may present with prostration and signs of sepsis rather than with a pneumonic illness. Others may have signs of extrapulmonary infection, including bone or CNS disease. Chronic melioidosis is usually defined as the presence of symptoms for at least 2 months and presents with fever, weight loss, and productive cough with or without hemoptysis. The chest radiograph typically shows diffuse miliary nodules, which may expand and cavitate. Approximately half of patients present with upper lobe changes, and one-third have multilobe involvement.[482] Chronic disease typically presents with upper lobe cavitary disease that can resemble tuberculosis. Subacute or chronic *B. pseudomallei* pneumonia is milder and often manifests after a period of latency. Patients may be entirely asymptomatic (i.e., abnormal radiograph only) or present with an illness clinically and radiographically indistinguishable from tuberculosis. The overall mortality has ranged from 20–40% with higher rates associated with sepsis and CNS disease. Primary pneumonia due to melioidosis has been associated with a 20% fatality in the Northern Territories in Australia.[482]

B. pseudomallei grows readily on routine culture media. It can be cultured from sputum, blood or aspiration of abscesses. PCR-based diagnosis is increasingly used.

B. pseudomallei is not sensitive to the usual CAP antibiotics, and initial therapy most often involves ceftazidime (50 mg/kg up to 2 g 3 times daily intravenously) therapy or meropenem (25 mg/kg up to 1 g 3 times daily intravenously).[486] Meropenem is preferred for severe disease requiring admission to an ICU, persistent bacteremia, and CNS disease. A small series suggests there may be benefits with adjunctive therapy with G-CSF in that it delayed mortality and might buy further time for antimicrobial therapy. However, it did not influence overall mortality, so further studies are required. Imipenem is an alternative carbapenem, and there is also experience with TMP-SMX added for severe infection during the intensive phase, which typically is continued for 10 to 14 days or longer with severe disease. Intravenous amoxicillin/clavulanate is regarded as a second-line choice for initial therapy and is only used when the other agents listed cannot be used. The continuation phase involves TMP-SMX (1600/320 mg orally twice daily) for 20 weeks. Addition of doxycycline has not improved outcomes. Oral amoxicillin/clavulanate is the alternative if there is resistance or intolerance to TMP-SMX. Rates of resistance to TMP-SMX have been suggested to approach 20% in Thailand.[487] However, difficulties with interpretation, particularly for disc-diffusion of sulfamethoxazole, have led other authorities to suggest that resistance is still relatively rare.[488]

Moraxella catarrhalis

M. catarrhalis, a gram-negative diplococcus, is an exclusive human pathogen most often associated with acute exacerbations of COPD, acute otitis media in children, maxillary sinusitis, and pneumonia.[489] Pneumonia typically is seen in the elderly and in patients with underlying COPD,[490] although other cardiopulmonary comorbidities, alcoholism, malnutrition, and malignancy with neutropenia are also risks.[491] Symptoms are typically mild, and high fever or pleuritic chest pain is uncommon. Productive cough and dyspnea are the usual symptoms. On chest radiology, lower lobe opacities predominate.

Because *M. catarrhalis* is part of the normal upper respiratory tract flora, only adequately screened sputum samples provide useful diagnostic information. A purulent specimen that contains many intracellular gram-negative diplococci and yields heavy growth of *M. catarrhalis* is highly suggestive of true pneumonia. Blood cultures are rarely positive.[491]

The mortality with *M. catarrhalis* CAP is approximately 10%, primarily due to exacerbations of severe underlying pulmonary disease.[491] These infections are most often treated with β-lactam/β-lactamase inhibitor combinations. Alternatives include cephalosporins and quinolones, but concerns relating to *Clostridioides difficile* infection in the elderly and other antimicrobial considerations mean these are less often the first choice. Other agents with activity include macrolides, tetracyclines, and TMP-SMX.[489] Virtually all isolates are resistant to penicillin and ampicillin because of β-lactamase production.

Neisseria meningitidis

N. meningitides, a gram-negative diplococcus, is the cause of meningococcal disease, of which *N. meningitidis* pneumonia is the second most common organ-specific form. The pneumonia has a bimodal age distribution, with one peak at less than 30 years of age and a second peak over 60 years of age.[492] The estimated incidence of sporadic primary meningococcal pneumonia is 0.4 cases per 100,000 adults annually; pneumonia also complicates 5–15% of invasive meningococcal infections.[493] Pneumonia is most often due to serogroup Y; serogroup W is also common.[494] Medical comorbidities are sometimes encountered, including diabetes, COPD, and malignancy, but many of those infected are otherwise healthy. Asymptomatic carriage rates are increased under conditions of crowding.[493] Clusters of meningococcal pneumonia have been described in military recruits and college dormitories.[494] Nosocomial transmission has also been reported. Clinical features are indistinguishable from common bacterial causes of CAP; fever, productive cough, and pleuritic chest pain are common. Leukocytosis and high CRP are common. Chest radiology reveals unilateral or bilateral consolidation, and pleural effusions are often observed.

N. meningitidis has a similar appearance in sputum to *Moraxella* and *Acinetobacter.* Because it is a common colonizer in young adults, and occasionally in older individuals, isolation in sputum alone does not establish the diagnosis, whereas growth in blood or pleural fluid does. Bacteremia rates are highly variable, but rates up to 80% are reported in case series.[494] PCR is increasingly used for detection of invasive meningococcal disease, but there is limited experience of its utility for meningococcal pneumonia.

A third-generation cephalosporin such as ceftriaxone is usually administered as therapy for at least 5 to 7 days. Close household or intimate contacts should receive ciprofloxacin chemoprophylaxis, with rifampicin or ceftriaxone as alternatives. Droplet and contact infection control measures are used to limit nosocomial transmission during the first 48 hours of antimicrobial therapy. Health care workers rarely require chemoprophylaxis. Occasionally a health care worker may require chemoprophylaxis when exposed to a patient during resuscitation or intubation during the first 48 hours of therapy, or to a patient not suspected of having meningococcal disease and for whom appropriate infection control measures are not in place.

Pasteurella multocida

P. multocida, a gram-negative coccobacillus, is part of the normal oral flora of many domestic and wild mammals. Although skin and soft tissue infections following a cat or dog bite are the more common manifestations of human infection, sporadic cases of pneumonia following inhalation, lung abscess, and empyema are seen in the elderly and in patients with chronic respiratory diseases, including COPD, carcinoma, and bronchiectasis.[495] Most patients recall prior exposure to animals.

Pasteurella pneumonia is indistinguishable from other etiologies of CAP, although empyema may be more frequent. Fever and productive cough with dyspnea are most frequent, and the duration of symptoms is typically short. Chest radiographs typically show a lobar area of consolidation though multilobar opacities, and empyema are also observed. The organism is a small, gram-negative coccobacillus indistinguishable from other gram-negative rods by Gram stain. Identification of the organism by culture of sputum, blood, and pleural fluid is easily accomplished.

The treatment of choice for *P. multocida* pneumonia is penicillin G, 4 to 12 million units daily for 10 to 14 days. However, some animal strains express β-lactamases and amoxicillin-clavulanate or other β-lactam/β-lactamase combinations may be required. Second- and third-generation cephalosporins, tetracyclines, TMP-SMX, fluoroquinolones, and chloramphenicol are also active. *P. multocida* is resistant to clindamycin and macrolides.

Plague Pneumonia *(Yersinia pestis)*

Y. pestis, a gram-negative coccobacillus, is the cause of plague, a zoonosis typically associated with ground squirrels, rabbits, prairie dogs, rats, and other small ground-dwelling animals.[496] Dogs and cats may also act as reservoirs, although, unlike dogs and many other carnivores, cats usually become ill with infection. Rodent fleas are responsible for transmission of the organism between animal hosts, and the likelihood of human infection is related to the likelihood of being bitten by fleas.[88] Humans become infected when bitten by an infected rodent flea, by handling an infected animal carcass, or by inhaling an aerosol from a human or animal with pulmonary involvement. Veterinarians, hunters, and others at risk of encountering infected animals are at particular risk.[88] In the United States, most cases of plague are in the southwest in rural New Mexico, Arizona, Colorado, Nevada, Oregon, and California, and ground squirrels are most often implicated.[88] Pneumonic plague is rare in the United States. Human infections most often present in the United States in May to September. Due to disease severity and the potential for aerosol transmission and secondary transmission, *Y. pestis* is a potential bioterrorism weapon, and bioterrorism should be suspected when multiple cases of pneumonic plague are identified.[98] Key virulence determinants include a siderophore, yersinabactin, and other iron-scavenging systems and, for the pneumonic form, the aspartic protease Pla, which cleaves plasminogen.[497]

Three clinical forms of infection exist: pneumonic, bubonic, and septicemic. In the United States, bubonic plague is most common; pneumonic plague has only accounted for approximately 2% of cases.[88] Although the pneumonic form presents as a primary pneumonia, the lung may also be involved in approximately 12% of bubonic or septicemic infections. The incubation period for primary pneumonic plague is typically 1 to 3 days, while

for bubonic plague it is 2 to 6 days. The illness starts as a flulike illness but rapidly progresses with high fever, chest pain, productive cough, dyspnea, and hemoptysis. Shock is usually present, and the white blood cell count is usually significantly elevated. Disseminated intravascular coagulation is common in the later stages of disease. The presence of hemoptysis can cause confusion with the hantavirus pulmonary syndrome, whose geographic distribution overlaps with plague in the United States. If pulmonary disease complicates bubonic plague, painful lymphadenopathy is also noted, mostly in the groin. In the septicemic form, the patient may show only signs of septic shock. Chest radiographs in cases of pneumonic plague commonly reveal bilateral lower lobe alveolar opacities, but there may also be nodules, cavities, hilar lymphadenopathy, and pleural effusions. The mortality of pneumonic plague is high and approaches 100% without antimicrobial therapy, but the overall mortality for plague in the United States is now less than 15%.[88]

Most patients with pneumonic plague have positive blood cultures. In addition, the organism can be recovered from sputum and lymph node aspirates by routine bacteriologic techniques. Gram stain reveals bipolar staining and a "safety pin" morphologic appearance.[88] Fluorescent antibody staining for the F1 capsular antigen of sputum and tissues facilitates the rapid diagnosis of plague but is available only in specialized laboratories. Since expression of this antigen is temperature sensitive, refrigeration of samples can reduce the sensitivity of this test.[88] Serology for anti-F1 antibodies involving an acute and convalescent sample and PCR-based diagnostic tests are also available from the CDC and other reference laboratories.

Because of the potential for person-to-person transmission, all patients with plague pneumonia should be isolated and respiratory droplet precautions instituted. Recommended treatment consists of gentamicin or doxycycline.[98,498] Streptomycin is preferred for treatment in many countries but is not readily available in the United States. Alternative treatments include fluoroquinolones or chloramphenicol. For all regimens, the duration of treatment is a minimum of 10 days.

Pulmonary Anthrax *(Bacillus anthracis)*

B. anthracis, a very large gram-positive spore-forming bacillus, is endemic in many regions of the world and in selected parts of the western United States. In endemic areas it is primarily an infection of farm animals, and human infections are linked to exposure to animal products. Spores, the transmissible agent of infection, reside in soil, water, and vegetation and primarily infect large herbivorous animals (e.g., cows, sheep, and horses). Humans are infected by contact with contaminated animal hides, wool, meat, or bones.[499] This usually involves exposure to the spore but can occasionally involve ingestion of the vegetative form in meat. A further route of infection is through injection of spores in contaminated heroin in people who inject drugs.[499] *B. anthracis* is a proven agent of bioterrorism, and clustering of respiratory cases should raise this possibility, as in 2001 in the United States.[500–502]

The manifestations of anthrax are cutaneous, gastrointestinal, inhalational (woolsorter's disease), and injectional; inhalational anthrax is the most severe. Spores are ingested by alveolar macrophages and are subsequently carried to regional lymph nodes where they germinate, resulting in hemorrhagic mediastinitis. The bacteria contain a capsule that helps resist phagocytosis and produces two toxins, lethal toxin and edema toxin, that inhibit mitogen-associated protein kinases and up-regulate intracellular cyclic adenosine monophosphate levels respectively.[499]

The incubation period for inhalational anthrax is 4 days.[503] Clinical illness begins insidiously with a flulike illness. Fever, myalgia, malaise, nonproductive cough, and precordial pain are common, and nausea and vomiting are also noted. Without treatment, the patient experiences a biphasic illness in which the first phase progresses rapidly to a fulminant phase characterized by dyspnea and shock. There is rapid pulmonary deterioration with dyspnea, stridor, chest pain, tachypnea, cyanosis, and drenching night sweats. Diffuse edema of the neck and anterior chest may be evident due to the action of edema toxin. Meningitis is a common complication. Laboratory abnormalities can include a neutrophilia, raised hematocrit, low platelet count, and elevated level of serum transaminases.[503,504]

Radiographically, the lung parenchyma is initially clear. In one series, 73% of cases developed opacities.[504] A widened mediastinum and bilateral pleural effusions are clues to inhalational anthrax. Mediastinal widening, pleural effusions, or both were observed in 100% of a series of 22 inhalational anthrax cases,[504] although a chest CT scan may be required to define these characteristics. The combination of mediastinal widening, confusion, and a raised hematocrit helps distinguish inhalational anthrax from CAP.[504] Later findings include vascular engorgement and lung parenchymal opacities.

B. anthracis grows readily on routine culture media and can be rapidly recovered from cultures of blood, sputum, and pleural fluid. In advanced disease, the organism may be demonstrated by Gram stain of peripheral blood. Cultures may show long "boxcar" chains, but chains are usually much shorter in direct Gram stain of blood or tissue aspirates. Immunohistochemistry and PCR can be used to confirm the diagnosis.[499] *B. anthracis* can be detected in nasal swabs of persons exposed to anthrax spores; the predictive value of this test for diagnosing clinical disease is ill defined. Samples of suspected inhalational anthrax should be sent to a Laboratory Response Network reference laboratory and local and state health departments should be notified.[499]

Treatment recommendations for inhalational anthrax may be affected by resistance and the potential need to treat mass casualties. Agents with potential activity include fluoroquinolones, clindamycin, clarithromycin, tetracycline, imipenem, meropenem, penicillin, ampicillin, chloramphenicol, and rifampin.[96] Recommended initial treatment regimens include intravenous administration of ciprofloxacin 400 mg every 8 hours, doxycycline 100 mg twice a day combined with clindamycin 600 mg every 8 hours, penicillin G 4 million units every 4 to 6 hours, meropenem 1 g every 6 to 8 hours, or rifampin 300 mg twice daily.[499] If the isolate is susceptible, therapy can be changed to high-dose penicillin G or doxycycline. Intravenous therapy may be converted to oral therapy once the patient's condition stabilizes. Because pulmonary anthrax and systemic anthrax are associated with high mortality rates, therapy with an FDA-approved humanized monoclonal antibody

(raxibacumab) to anthrax lethal toxin is recommended as an adjunct to antimicrobial therapy.[499] Anthrax immune globulin, derived from individuals who have received an anthrax vaccine, has also been used in treatment when raxibacumab is not available. It has also been used against cases of injectional anthrax. Antimicrobial treatment is continued for 60 days to eliminate spores that could be the source of relapse. This continuation phase most often uses ciprofloxacin 500 mg twice daily orally or doxycycline 100 mg orally twice daily. Although the reported mortality rate with inhalational anthrax has been as high as 90% historically, it was 46% (5 of 11 patients) with inhalational anthrax during the 2001 anthrax attacks in the United States.[505] Improved outcomes have been linked to earlier diagnosis, optimization of supportive care, and combination antimicrobial therapy plus adjunctive therapy. Post-exposure prophylaxis can also be used following aerosolized release of anthrax spores.

Streptococci Other Than Pneumococci

S. pyogenes (group A β-hemolytic streptococcus) can be found in the oropharynx of more than 20% of children and a smaller percentage of adults. Carriage rates increase greatly during epidemics and in crowded conditions.[506] In the United States, the incidence of invasive group A streptococcus disease was 3.5 per 100,000 persons per year in 2000 to 2004 with regional variations.[507] Pneumonia accounts for 10% of these infections but, in adults, 17% of invasive infections were due to pneumonia.[508] In northern Spain, a small series reported an annual incidence of group A streptococcal pneumonia of 1.1 per 100,000 persons annually.[509] The organism is easily transferred between contacts, leading to outbreaks of group A streptococcal pneumonia in military recruits as well as nursing homes and other crowded settings.[506] Classically, pneumonia due to *S. pyogenes* has been associated with influenza, but recent series emphasize that as many as half of cases arise outside peak influenza season and, in many of those diagnosed during influenza season, there is no evidence of influenza infection.[507] Other risk factors include infection with HIV, measles, or varicella, increased age, and history of alcohol abuse, diabetes, COPD, or cancer.[508-510] *S. pyogenes* can cause necrotizing pneumonia[511] and is often associated with pleural empyema.[512]

Group B (i.e., *Streptococcus agalactiae*) streptococci are a major cause of neonatal sepsis and pneumonia. In adults, pneumonia accounts for approximately 15% of adult infections by group B streptococci.[513] Most adults with group B streptococcal pneumonia are debilitated and develop pneumonia as a consequence of aspiration.[513] Age, diabetes, cirrhosis, and neurologic disease are the main risk factors.

The *Streptococcus anginosus* group of streptococci (formerly known as the *S. milleri* group) are viridans streptococci. Bacteria in this group, including *Streptococcus intermedius, S. anginosus,* and *S. constellatus*, have emerged as significant respiratory pathogens, predominantly causing empyema (eFig. 46.39 and Video 46.1) and lung abscesses as well as superinfection pneumonia in severe viral pneumonia.[514,515] Infections with bacteria in this group share many of the features of anaerobic infections, including increased risk with periodontal disease, cerebrovascular disease, and alcoholism. Diabetes and malignancy are other common associations.[516] Other viridans and microaerophilic streptococci (α-hemolytic, nonpneumococcal) are rarely the sole pathogens in patients with pneumonia; they are more commonly found mixed with other facultative and anaerobic organisms in aspiration pneumonia.

CAP due to these pathogens is clinically indistinguishable from pneumococcal pneumonia. Exudative pharyngitis may be evident and unilobar involvement is common with group A streptococcal pneumonia. Bacteremia and sepsis are frequent with group A streptococcal infection and, in the Spanish series, 25% of cases in adults were complicated by streptococcal toxic shock.[509] In this series, mortality was 20% overall and 30% in the elderly. Other series report mortality of 47% and emphasize that the majority of those who die do so in the first 24 hours of hospitalization.[512] Group A streptococcal pneumonia may cause necrotizing pneumonia and cavities.[511] Pleural effusions in group A streptococcal pneumonia are frequent, may be large, accumulate rapidly, and appear early in the course of the disease, particularly in children. Other complications include pericarditis, pneumothorax, mediastinitis, and bronchopleural fistula formation. The only classic nonsuppurative complication that follows *S. pyogenes* pneumonia is glomerulonephritis. Pneumonia caused by other β-hemolytic streptococci is usually less abrupt and milder; pleural effusions are uncommon, and lung tissue necrosis is rare despite frequent bacteremia.[513] Although *S. anginosus* group infections are relatively rare causes of CAP, they are over-represented as causes of lung abscess and of empyema. In one series of respiratory infections due to the *S. anginosus* group, one-third resulted in empyema.[516] *S. anginosus* group bacteria can be cultured from the pleura in approximately half of cases of CAP-associated empyema.[514] Mortality rates of 10–30% are described, reflecting the debilitated state of many individuals with these infections. However, one more recent series reported in-hospital mortality of less than 10% with these infections.[516] Pneumothorax at initial presentation appears to be more common with *S. anginosus* than with empyema caused by other streptococci. *S. anginosus* infections may spread to the mediastinum or extrapulmonary abscesses following bacteremia.

Since streptococci are common in the oropharynx, documentation of infection from these organisms requires isolation from a culture of blood, pleural fluid, or respiratory specimen obtained by means of an invasive procedure (eFig. 46.40). PCR technology holds promise for aiding diagnosis, especially of group A streptococcal infections[517] and *S. anginosus* group empyema.[515] Most of these streptococci are susceptible to penicillin G, ampicillin, and many cephalosporins, although α-hemolytic streptococci may require a high dosage due to the phenomenon of tolerance (growth inhibition without killing at low and intermediate drug concentrations). Because resistance to clindamycin and erythromycin is found in up to 15–20% of isolates, susceptibility testing is advisable before monotherapy is begun with a macrolide or clindamycin.[518] As is the case for empyema caused by other pathogens, drainage of empyema fluid is an important component of therapy. (See Chapter 109.)

Tularemia *(Francisella tularensis)*

F. tularensis, a pleomorphic, gram-negative bacillus, causes a zoonotic infection found mainly between latitude 30 degrees N and 71 degrees N in the United States. Missouri, Arkansas, Oklahoma, and South Dakota have reported the greatest number of cases, and Martha's Vineyard in Massachusetts has had outbreaks.[90] Cases peak in spring to summer. Ticks, mosquitoes, and biting flies can transmit the infection, as can exposure to infected animals such as rabbits, hares, and rodents, particularly when skinning carcasses, or exposure to carnivorous animals such as domestic cats, which may transiently carry bacteria acquired from their prey on their claws or mouths.[91] Aerosolization of bacteria in water or mud may transmit infection; in the Martha's Vineyard outbreak in 2000, lawn mowing and brush cutting were identified as risk factors.[90] Persons engaged in landscaping or agricultural activities that generate aerosols in endemic areas are at particular risk for development of pneumonic tularemia. In the United States, tick or deerfly bites are the most common vectors of infection, and direct contact with tissues of an infected animal (as when skinning or eating an infected animal) or inhalation of contaminated aerosols are alternative routes. Because of the efficiency of aerosol transmission, *F. tularensis* is regarded as a potential agent of bioterrorism.

Between 10–20% of cases of tularemia are associated with pneumonia. Pneumonia may be the primary clinical syndrome that arises from inhalation of contaminated aerosols or as a complication of bacteremia, most often associated with the more common ulceroglandular form or from typhoidal tularemia. The incubation period may range from 1 to 21 days but is most often 3 to 5 days.[519] Clinical manifestations typically begin abruptly with fever, chills, malaise, and headache. Shortly thereafter dyspnea, cough, and chest pain may develop.[519] Laboratory findings vary, but there may be an increase in lymphocytes and in liver function test results, while elevations in CRP may be less than in bacterial CAP. Chest radiographs may be normal at the onset (3 to 5 days following aerosol exposure) but ultimately show diffuse bronchopneumonia or nodules. Hilar adenopathy may be more common with the less-severe type B disease than with the more virulent type A disease predominating in states such as Arkansas. Pleural effusion is common, reported in one-third of cases in some series, and may be seen without parenchymal involvement.[519]

F. tularensis is rarely visualized on Gram stain of sputum and requires specially enriched media for optimal recovery by culture. Because of the hazardous nature of the organism, culture is best undertaken by reference laboratories. The organism can also be identified rapidly in tissues, secretions, and exudates by use of immunohistochemical techniques. Retrospective diagnosis can be accomplished by demonstrating a fourfold rise in agglutinating titers, and the microagglutination assay is most sensitive. A single titer of 1:128 or greater is suggestive of past or current infection, but cross-reactivity with other infections such as Brucellosis or *Yersinia* species may confound the interpretation. PCR assays are increasingly being used to diagnose tularemia.[519]

Mortality can be as high as 60% if pneumonic tularemia is not suspected and treated appropriately, but the overall mortality for tularemia has decreased to less than 5%.[519] Although gentamicin has been used successfully, streptomycin remains the preferred therapy.[519] Ciprofloxacin is an acceptable alternative agent; doxycycline and chloramphenicol are associated with higher relapse rates and require a longer duration of therapy.[519] Ceftriaxone is unsatisfactory despite in vitro activity. After a known aerosol exposure to *F. tularensis,* prophylaxis with doxycycline or ciprofloxacin for 14 days is recommended.[97]

Chronic Pneumonias

Chronic pneumonias are distinguished from CAP due to the persistence of symptoms for at least 6 weeks.[520] They are typically caused by slow-growing microorganisms such as mycobacteria and dimorphic fungi (see Chapters 53, 55, 56, and 57). However, they can present with radiologic appearances typical of CAP, such as consolidation, and therefore may be erroneous classified as CAP if the chronic nature of symptoms is not recognized.

Actinomycosis. *Actinomyces,* which are gram-positive non–spore-forming, branching filamentous bacilli, cause human disease, of which *A. israelii* is the commonest cause.[521] *Actinomyces* are commensals in the oropharynx, gastrointestinal, and genital tracts. Pulmonary actinomycosis follows aspiration of oropharyngeal material, and risk factors include poor dental hygiene, smoking, alcohol abuse, and chronic lung disease.[522]

Clinical features of pulmonary disease include a chronic history with a productive cough and chest pain.[522] Hemoptysis has been reported in 30% of patients. Weight loss and malaise are common, but fever and night sweats are observed in only 20–30%. Chest wall lesions and draining sinuses are now uncommon, and presentation with a radiologic abnormality with some of the above features is now more usual. Physical signs are nonspecific. The differential diagnosis includes lung abscess, malignancy, tuberculosis, and other causes of chronic pneumonia. It is now rare for pulmonary actinomycosis to present as the result of contiguous or metastatic spread from another location.

The imaging finding classic for actinomycosis is direct extension of a cavity or mass through an interlobar fissure. The propensity to cross tissue planes raises the concern of malignancy. More commonly, changes are confined to a single lobe with consolidation, nodules, or one or more small cavitary lesions (eFig. 46.41). Pleural thickening or effusions are also encountered. In advanced cases, the findings may be more distinctive, with penetration through the chest wall and/or destruction of adjacent bone tissue (eFig. 46.42). CT imaging may reveal bone erosion.

Actinomyces are branching filamentous bacilli, with the exception of *A. meyeri* which is non-branching.[521] *P. propionicum* is a gram-positive anaerobic bacillus that can cause a clinical syndrome similar to actinomycosis. The requirement for strict anaerobic processing and prolonged culture combined with the fact that *Actinomyces* are usually isolated as part of a polymicrobial flora, including oral anaerobes and streptococci, limit the diagnostic yield. Culture of swabs is unhelpful because the organisms are part of the commensal flora. Appropriately cultured specimens (e.g., anaerobic cultures on chocolate blood agar) of pus or tissue

samples from a sterile site can aid diagnosis and should be incubated for 10 days or longer. This requires clear communication of the suspicion of actinomycosis with the microbiology laboratory. 16S ribosomal RNA or PCR on tissue can also enable diagnosis. Histopathologic analysis of tissue samples is more sensitive than culture. Transbronchial biopsies are usually not helpful, and CT-guided needle biopsies are more often diagnostic.[522] Supportive histopathologic features include identification of filamentous forms on Gomori methenamine silver stain or modified Gram stain, identification of basophilic "sulfur granules" containing a mass of mycelial elements in a protein and polysaccharide matrix, and granulomatous-like reactions, although classic granulomata are rare. In patients with a cutaneous chest wall sinus, the best means of establishing a diagnosis of actinomycosis is by detection of sulfur granules that, when crushed and stained, form a characteristic pattern of gram-positive branching filaments (eFig. 46.43). Definitive diagnosis depends on demonstrating the characteristic histopathology and culture from a sterile site or tissue biopsy. Cultures are frequently negative or contain other organisms.

Complications include empyema, cutaneous thoracic sinuses, mediastinitis, pericarditis, and vertebral or rib osteomyelitis. Metastatic infection, including brain, skin, and bone, is now rare. With adequate therapy, death from actinomycosis is rare. *Actinomyces* may be found in association with lung cancer but, because *Actinomyces* may colonize devitalized tissue, clear evidence of clinical disease should be sought before embarking on prolonged therapy.

Actinomyces are universally susceptible to penicillin G, which should be given in intravenous doses of 18 to 24 million units daily for 2 to 6 weeks, followed by at least 6 to 12 months of oral penicillin V or ampicillin. More recently, shorter durations of therapy have been reported in selected patients without abscesses or chest wall involvement. These patients had at least 3 months of total therapy, including 1 to 2 months after clinical and radiologic resolution.[523] Poorer outcomes have been reported with cephalosporins. Multiple other drugs have been used successfully; prolonged therapy is essential, and doxycycline is the most often prescribed alternative as oral therapy. With polymicrobial infection, the presence of the other organisms may require modification of therapy, although the exact role and need to treat these other bacteria is debated.[522] Rarely, surgical resection is required for cure and may be indicated to manage hemoptysis, fistulae, abscesses or empyema, or, in cases where the diagnosis remains in doubt, to obtain surgical specimens.

Nocardiosis. *Nocardia* species, gram-positive bacilli that appear as beaded, branching filaments, can cause pulmonary nocardiosis. *N. asteroides* cause approximately 90% of pulmonary nocardiosis, while a range of other *Nocardia* sp occasionally cause pulmonary disease.[524] In some reports, the more resistant *N. farcinica* has predominated.[525] The organisms are saprophytes found widely in nature, primarily in soil and water. Inhalation is the main route of infection, but skin inoculation and oral ingestion are alternative routes. Impaired cell-mediated immunity is the major risk factor, although approximately one-third of individuals may not have known immunocompromise or a recognized risk factor such as alcoholism or diabetes.[526] Among transplant patients, lung transplant recipients are at particular risk. Persons with pulmonary alveolar proteinosis are also at increased risk. There are reports of nocardiosis in association with bronchiectasis and COPD, the latter linked to oral or inhaled corticosteroid use.[527] Chronic granulomatous disease is also a risk factor.[528]

Clinical presentation of pulmonary nocardiosis is usually with subacute or chronic respiratory symptoms. Some immunocompromised hosts present with a shorter duration of symptoms mimicking CAP, with cough, with or without sputum, dyspnea, chest pain or hemoptysis, fever, fatigue, and weight loss.[526] Although nocardiosis and actinomycosis are clinically similar infections of the LRT, nocardiosis can be distinguished by less proclivity for sinus tract formation and a greater tendency for hematogenous dissemination. Dissemination may involve almost every organ system, but the CNS and skin are most common.[529] Physical examination is nonspecific unless sites of dissemination are present. Neurologic signs of a mass lesion may be prominent. Cutaneous dissemination appears as multiple subcutaneous abscesses with or without sinus tracts. Imaging commonly demonstrates localized bronchopneumonia or lobar consolidation (eFig. 46.44), but there may also be solitary, multiple (eFig. 46.45), or miliary nodules, and abscesses (eFig. 46.46). Cavities are frequently observed. Pleural effusion develops in up to one-third of cases. Because brain abscesses can develop in up to 40% of patients, CNS imaging should be considered in all patients with pulmonary nocardia.

Unlike the anaerobic Actinomycetaceae, *Nocardia* requires aerobic growth conditions and is usually weakly acid-fast when stained by the modified Kinyoun acid-fast stain (eFig. 46.47). The beaded appearance helps distinguish the microorganism from mycobacteria.[526] *Nocardia* can be cultivated on conventional blood agar or Sabouraud medium grown under aerobic conditions. The organisms are typically identified after 3 to 5 days but growth may be delayed, so cultures should be held for up to 21 days. Although an occasional colonizer of the upper respiratory tract in association with lung disease, this is infrequent, and recovery of *Nocardia* from a culture of sputum or invasively obtained material strongly suggests a clinical diagnosis of nocardiosis. PCR is increasingly used in diagnosis, and 16S ribosomal RNA aids speciation.[527] Tissue biopsy may reveal granulomata.[525]

Mortality approaches 50% in those with CNS lesions but is less than 20% in those with isolated pulmonary disease.[524] Susceptibility testing should be performed on all isolates.[526] Because of in vitro synergy, TMP-SMX (dosed at 5–10 mg/kg of TMP per day) is frequently included in the regimen. Other agents that often show activity against *Nocardia* sp include minocycline, amikacin, ceftriaxone, cefotaxime, imipenem, tigecycline, fluoroquinolones, and linezolid, but choices should always be guided by the results of susceptibility testing. *N. farcinica* in particular is associated with increased resistance and is encountered in transplant recipients who may have been exposed to a range of antimicrobials used against *Nocardia* species. Initial regimens include two agents or three agents if there is severe disease. Combinations usually include a β-lactam with amikacin and/or TMP-SMX.[526] Combination parenteral therapy is

continued for several weeks until there is clinical improvement and a continuation phase of oral therapy is used for a prolonged period to prevent relapse. Pulmonary disease in an immunocompetent patient is often treated with approximately 6 months of therapy, while severe disease, infections in immunocompromised hosts, or CNS disease often receive 12 months of therapy or longer. Adequate drainage or excision of abscesses and empyema is a crucial adjunct to antimicrobial therapy. Pulmonary nocardiosis can be prevented in at-risk immunocompromised hosts by TMP-SMX prophylaxis.

Rhodococcus equi. *R. equi,* an intracellular gram-positive bacillus, is a veterinary pathogen that may cause lung abscess and pneumonia.[86] Infection is caused by inhalation. Most cases are seen in patients with impaired cell-mediated immunity (e.g., high doses of corticosteroids, HIV infection with CD4 counts <100 cells/μL, solid organ transplantation), in persons with an occupational history of animal exposure, particularly farm animals, and in persons exposed to dry soil. Occasional cases are reported in immunocompetent hosts. Illness develops subacutely, mimicking mycobacterial or fungal infection. Fever, cough, which may be productive, chest pain, and sometimes hemoptysis are reported. Chest radiographs show opacities, nodules, or cavities. Cavities are seen in approximately 50% of cases, are often multiple, and frequently involve the upper lobes. Pleural effusions, empyema, and mediastinitis may develop. Extrapulmonary complications may be observed, including abscesses in subcutaneous tissue, bone, or brain.

The organism may stain weakly acid-fast but is much smaller than mycobacteria. It is cultured from sputum, bronchial washings, and blood. In malakoplakia, a chronic granulomatous condition, *R. equi* is the most commonly isolated pathogen. *R. equi* survives in macrophages by inhibiting phagolysosomal fusion and resisting reactive oxygen species. Therapeutic agents with activity include vancomycin, imipenem, meropenem, rifampicin, linezolid, fluoroquinolones, macrolides, and aminoglycosides. Milder disease in immunocompetent patients can be treated with two oral agents, but most pulmonary cases are in immunocompromised hosts and require regimens with vancomycin or a carbapenem combined with one or two other agents. Intravenous therapy is continued until initial response and usually for least 2 to 3 weeks. An oral combination regimen is then prescribed to complete a total of 2 to 6 months of therapy.

LESS-COMMON VIRAL PATHOGENS

Adenovirus

Adenoviruses (AdV) are nonenveloped viruses with a linear double-stranded DNA genome (eFig. 46.48). There are 52 identified human AdV types based on serology, which are further classified into seven species (A to G). However, additional AdV genotypes (AdV-53 to AdV-90) have been identified based on bioinformatic and genomic analysis of the complete genome sequences.[429a]

Epidemiology and Transmission. Human AdV respiratory infections are predominantly caused by species B (including types 3, 7, 11, 14, 21, and 55), C (types 1, 2, 5, and 6), and E (type 4). AdVs account for 1–7% of adult respiratory tract infections, which are mostly mild and self-limiting.[530] However, in immunocompromised persons, such as organ transplant recipients or patients with HIV infection, severe pneumonia and disseminated disease (colitis, hepatitis, hemorrhagic cystitis, nephritis, and encephalitis) can develop and have significant mortality.[531] Outbreaks of AdV pneumonia have been reported in closed or crowded settings, particularly among military recruits,[532,533] as well as in adults in long-term care facilities and hospital wards.[534] Community-acquired AdV pneumonia is rare in immunocompetent adults.[535,536] Virus is transmitted through inhalation of aerosolized droplets or direct conjunctival inoculation but may also spread via the fecal-oral route or by contact with environmental surfaces.

New variants of AdV have occasionally emerged and have been associated with outbreaks worldwide. Since 1996, a specific variant of AdV type 7 has been responsible for several civilian outbreaks and a large military outbreak.[537] More recently, AdV type 14, a previously rare serotype, has been responsible for outbreaks of pneumonia in both military and civilian populations.[538–540]

Pathogenesis. Most adenoviruses, as well as coxsackie B viruses, bind to the coxsackie virus and AdV receptor, whose usual function is to mediate cell interactions with extracellular matrix proteins. Group B AdVs use the complement regulatory protein CD46 as a cellular receptor. Virus entry into the cell is also promoted by interaction of the penton base of the virus with alpha-v integrins. Viral type–specific antigens, which give rise to neutralizing antibody, are present on the hexons and fibers of the capsid. The hexons also contain a complement-fixation antigen with cross-reactivity among the mammalian adenoviruses.

Adenoviruses have been isolated from the upper airway, eye, urine, stool and, rarely, blood. Cytopathologic changes have also been observed in bronchial epithelial cells,[541] and crystalline arrays of virus particles have been found in alveolar lining cells of infected persons with severe illness.[542] The extent of damage to the respiratory tract in nonfatal AdV respiratory disease is not well defined but may result from a combination of direct viral mechanisms and inflammatory responses to infection. In cases of fatal AdV pneumonia, bronchial epithelial necrosis, bronchial obstruction, and interstitial pneumonia have been seen.[543] Cells containing large basophilic, intranuclear inclusions, so-called smudge cells, appear to be characteristic (eFig. 46.49). In lung transplant recipients, necrotizing bronchitis, bronchiolitis, and pneumonia with diffuse alveolar damage has been reported.[544,545]

Clinical Manifestations. The incubation period for AdV infection ranges from 2 to 14 days. Typical presentations include pharyngitis, rhinitis, conjunctivitis, laryngotracheitis, bronchitis, or pneumonia. Conjunctivitis is not a feature of infection with the other major respiratory viruses; therefore, when present, it is a useful diagnostic finding in AdV respiratory disease.

The clinical characteristics of AdV pneumonia are similar to those of other pneumonias, so it is difficult to make an accurate etiologic diagnosis on the basis of clinical features. Chest radiography in adenoviral pneumonia usually shows

diffuse bilateral pulmonary opacities, similar to other viral pneumonias. In fatal cases, there has been extensive pulmonary damage, with death intervening 2 to 3 weeks into the illness. Intravascular coagulopathy has also been a late feature of some cases, and septic shock has been described.[534] Long-term sequelae of AdV infection may include persistent radiographic abnormalities, abnormal pulmonary function tests, bronchiectasis, and bronchiolitis obliterans.

Diagnosis. Diagnosis of AdV infections was previously achieved by virus culture or antigen detection by immunofluorescence staining. However, limited sensitivity and the time required for the test limit their utility in guiding clinical management. PCR of adenoviral DNA has become the standard tool for diagnosis due to superior sensitivity and specificity. A positive result from the upper respiratory tract is more difficult to interpret because it may represent viral shedding rather than symptomatic infection; therefore it needs to be interpreted in the context of clinical findings. Quantitative measurement of AdV DNA levels in plasma may be useful for diagnosis and response to therapy.[546]

In biopsy specimens, the appearance of characteristic intranuclear basophilic inclusion bodies seen by light microscopy or of crystalline arrays of virus seen by electron microscopy is useful in histopathologic diagnosis.

Treatment and Prevention. Antiviral treatment of AdV infection is controversial because no randomized trials have been conducted. Cidofovir, a cytosine nucleotide analogue that inhibits DNA polymerase, has the greatest in vitro activity against AdV and is the first-line presumptive therapy of AdV infection in high-risk immunocompromised patients.[547] Adverse effects include nephrotoxicity, myelosuppression, and uveitis. The standard treatment dose is 5 mg/kg per week for 2 weeks and at 2-week intervals thereafter. An alternative schedule of 1 mg/kg 3 times a week has been suggested to limit nephrotoxicity.[548] Concomitant hydration and probenecid are recommended. Brincidovir, an orally available lipid conjugate of cidofovir, is currently an investigational agent for the treatment of AdV infection. It has demonstrated greater in vitro activity against adenoviruses and lower potential for nephrotoxicity compared to cidofovir.[549,550] In a randomized placebo-controlled trial evaluating the use of brincidofovir as preemptive treatment in asymptomatic AdV viremia in pediatric allogeneic hematopoietic stem cell transplant recipients, brincidofovir did not prevent progression to probable or definitive AdV disease or increasing AdV viremia, though in patients with initial low viral loads, more patients in the brincidofovir arm had undetectable viremia than in the placebo arm.[551] Both ganciclovir and ribavirin have limited activity against adenoviruses in vitro, and evidence of in vivo efficacy is limited to several anecdotal reports.[552,553]

Effective and safe live oral vaccines for AdV types 4 and 7 were developed for military use and, when delivered in enteric-coated capsules, have controlled acute respiratory disease outbreaks in recruit populations.[554] Use of these vaccines was not associated with replacement by nonvaccine serotypes. When manufacturing of these vaccines was discontinued in the 1990s, adenoviruses reemerged as important causes of acute respiratory disease in this population. A new live, oral vaccine for AdV types 4 and 7 was introduced in 2011,[555] with a dramatic decline in AdV disease.[556]

Coronaviruses

SARS-CoV-2, the causative agent of COVID-19, is covered in Chapter 46a.

Coronaviruses are enveloped single-stranded, positive-sense RNA viruses with large genomes of 27 to 33 kb. Distinctive club-shaped projections are present on the virus surface, giving the appearance of having a crown or corona, the source of its name. Coronaviruses are classified into four genera: alpha, beta, gamma, and delta. The beta genus is further subdivided into four lineages, A through D. Until late 2019, six *human coronaviruses* (HCoV) had been identified, including alpha coronaviruses 229E and NL63, and beta coronaviruses, OC43, HKU1, SARS-CoV, and MERS-CoV. In late 2019, a novel human coronavirus termed SARS-CoV-2 emerged and caused an ongoing worldwide pandemic (see Chapter 46a).

Coronaviruses contain five structural proteins: *spike* (S protein), *hemagglutinin-esterase* (HE), M (*matrix*), E (*envelope*), and N (*nucleocapsid*). The spike protein is the major envelope glycoprotein and mediates both attachment to cells and fusion with the cell membrane; antibodies to the spike protein are thought to be associated with protection and thus are candidates for therapeutic and vaccine targets. The second envelope protein, HE, is only found in some coronavirus strains. Nonstructural proteins such as the viral replicases and proteinases, particularly the 3C-like proteinase, are antiviral drug targets.

Epidemiology and Transmission. Human coronaviruses OC43 and 229E, first discovered in the 1960s, have been recognized as causes of the common cold. HCoV-NL63 and HCoV-HKU1 were subsequently discovered in 2004 and 2005, respectively, and were found to have worldwide distribution.[557,558] In adults, HCoVs account for 5–10% of upper respiratory tract infections in adults and up to one-third during outbreaks.[559] Community-acquired HCoVs are an infrequent cause of adult CAP, detected in 2–13% of cases.[37,45,560,561] Their etiologic role is unclear because several studies that concurrently enrolled healthy controls demonstrated a high prevalence of coronaviruses (3.8–7.4%).[45,561] In temperate climates, coronaviruses usually circulate during winter and early spring but can be detected year-round. The incubation period for SARS is estimated from 2 to 10 days,[562] and for conventional HCoVs, 3 to 4 days.

Novel coronaviruses have recently been associated with severe respiratory disease in outbreaks around the world. SARS emerged in southern China in 2003 and quickly spread globally.[563] The causative virus was subsequently named SARS-CoV. Cases of SARS were detected in 29 countries, with the majority of cases in China and Hong Kong. Health care workers and their contacts were disproportionately affected. Ultimately, at least 8098 probable cases of severe respiratory disease and 774 deaths in all ages were attributable to SARS worldwide before the outbreak terminated in 2004. The virus has not been detected in the human population since. More recently, a second outbreak of coronavirus severe respiratory illness was recognized, with cases primarily found in Middle Eastern countries.[564]

In June 2012, the first case of MERS-CoV was observed in a man admitted to hospital with acute pneumonia and acute kidney injury in Saudi Arabia.[565] Subsequently, over 2400 laboratory-confirmed cases were reported globally. The majority of patients have been male; over 80% of the cases were in Saudi Arabia, but cases have also been reported from 26 other countries. Case-fatality rate is in excess of 30%. The latest information on MERS-CoV can be found at http://www.cdc.gov/coronavirus/mers/.

Both SARS and MERS are zoonoses; virologic and genetic data suggest that bats are the reservoir hosts for both SARS and MERS coronaviruses,[566,567] and civets and dromedary camels, respectively, act as intermediary hosts before transmission to humans. Direct contact with intermediary hosts or consumption of milk, urine, or uncooked meat is hypothesized to be the routes of transmission of SARS and MERS coronaviruses from animal to humans, though the precise mechanisms remain unclear.

Human-to-human transmission of coronaviruses likely involves close contact and inoculation of the respiratory tract with infectious secretions via large droplets. For SARS-CoV, virus shedding peaked at day 10 of symptom onset, which was at the height of disease severity.[562] This phenomenon accounted for the preponderance for nosocomial transmission, a feature that allowed the outbreak to be controlled with infection control procedures.

Secondary human-to-human transmission of MERS is also limited, mostly reported within health care settings and close household contacts. The first cluster was retrospectively identified in a public hospital in Jordan in 2012.[568] Multiple nosocomial outbreaks have since been identified; the largest outbreak outside the Middle East was in Korea in June 2015, which resulted in 186 cases and 38 deaths across multiple health care facilities.[569]

Pathogenesis. Knowledge of the pathogenesis of conventional human coronaviruses, as well as SARS-CoV and MERS-CoV, is limited. HCoV-NL63 and SARS-CoV use the *angiotensin converting enzyme* (ACE2) as a receptor for cell entry.[570,571] ACE2 is expressed on alveolar endothelial cells, trachea, bronchi, and alveolar monocytes and macrophages. Down-regulation of ACE2, as happens during SARS-CoV infection, is believed to contribute to pathologic changes in the lung.[572] HCoV-NL63 also uses ACE2 for cell entry but tends to cause only a mild respiratory illness. The difference in pathogenicity is thought to be due to lower-affinity interaction by the S protein of HCoV-NL63 with ACE2 compared to that by the S protein of SARS-CoV.[573]

MERS-CoV utilizes human dipeptidyl peptidase 4 (also known as CD26) receptors on the surface of human nonciliated bronchial epithelial cells in the LRT, rather than in the upper respiratory tract. MERS-CoV also has a broader tissue tropism than the other human coronaviruses.[574] Dipeptidyl peptidase 4 expression is significantly higher in the alveolar cells of both smokers and adults with COPD.[575] Human aminopeptidase N (CD13), a cell-surface metalloprotease on intestinal, lung, and kidney epithelial cells, has been identified as the receptor for HCoV-229E,[576] while 9-O-acetylated sialic acid is the receptor for HCoV-OC43. The receptor for HCoV-HKU1 has yet to be identified.

The hallmark of pulmonary pathology in fatal cases of both SARS and MERS is diffuse alveolar damage.[577,578] Furthermore, abundant viral antigen was detected within bronchial epithelial cells.[577,579] Of note, no evidence of extrapulmonary MERS-CoV antigens was detected. From these findings, it is postulated that disease pathogenesis involves both direct damage to pulmonary epithelia by the virus in combination with an excessive or dysregulated host inflammatory response.

Clinical Illness. Conventional human coronaviruses produce a typical coryzal illness indistinguishable from colds due to other viruses, and are occasionally associated with more severe respiratory diseases, including pneumonia. Outbreaks of HCoV-OC43 respiratory infections in older adults residing in long-term care facilities have been described, with a case-fatality rate of 8%.[580,581]

SARS has a nonspecific prodrome of fever, malaise, headache, and myalgia. Cough and dyspnea are the dominant respiratory symptoms but may not be present initially. Respiratory disease becomes more severe over 4 to 7 days, and about 25% of patients require respiratory support. SARS fatality rates were 9.6% for all ages but higher in older adults.[582] SARS-associated laboratory abnormalities include elevations in lactate dehydrogenase, transaminases, and creatine kinase, as well as hematologic abnormalities, particularly lymphopenia (depletion of CD4 and CD8 T cells) and thrombocytopenia.

In contrast, most cases of MERS-CoV infection have been in adults with severe pneumonia, occasionally with acute kidney injury.[583] A high proportion of patients require mechanical ventilation and some require extracorporeal membrane oxygenation.[584] Extrapulmonary manifestations include gastrointestinal symptoms, pericarditis, and disseminated intravascular coagulation. High mortality is related to the development of ARDS and is also associated with individuals with comorbidities and high viral load.[583]

For SARS and MERS, common findings on chest CT include unilateral or bilateral areas of ground-glass opacifications and interlobular septal and intralobular interstitial thickening. In most patients, peripheral involvement in the lower lung zones has been observed. Other imaging findings include air space, patchy, or nodular or reticular opacities; lobar consolidation; and pleural effusions.

Diagnosis. Diagnosis of SARS-CoV and MERS-CoV is based on a comprehensive contact and travel history and confirmed by laboratory tests. *Real-time PCR* (RT-PCR) of RNA extracted from respiratory samples is the most common diagnostic method. For both SARS and MERS, LRT samples usually yield significantly higher viral loads than URT samples[585]; hence LRT specimens should be prioritized. MERS-CoV RNA has also been detected in blood or serum samples from up to one-third of patients presenting with MERS.[586] Collection of LRT, upper respiratory tract, and serum samples for testing is recommended to confirm MERS-CoV infection.[587]

Antigen detection assay is another diagnostic tool for SARS-CoV and MERS-CoV; serum antibodies typically develop after 2 to 3 weeks of illness; therefore they are of little diagnostic use in the acute phase of illness.

Treatment and Prevention. At present, there are no CoV-specific antiviral treatments available. A number

of agents have shown activity against coronaviruses in animal or in vitro experiments, including HIV protease inhibitors, ribavirin, type I interferons, niclosamide, and anti-inflammatory agents such as indomethacin, but none has undergone randomized trials.[588,589] No antiviral agent has demonstrated benefit in treating SARS. Most patients were treated with high-dose steroids and ribavirin during the epidemic, but neither provided clear benefit and toxicities were common.[590] An exploratory meta-analysis found that convalescent plasma was associated with reduced mortality in SARS-CoV patients if administered within 14 days of illness.[591] Combination therapy of ribavirin and IFN-alfa-2a in patients with severe MERS-CoV infection was associated with improved survival at 14 days, but not at 28 days.[592] Glucocorticoids and macrolides were not associated with reduction in mortality in MERS.[593,594] A randomized trial of oral lopinavir-ritonavir, an HIV protease inhibitor, and IFN-beta is ongoing in Saudi Arabia.[595] Other experimental therapies under investigation include convalescent plasma, monoclonal antibodies,[596] a polyclonal IgG antibody produced from transchromosomic cattle (which are engineered to have a human artificial chromosome for the human antibody heavy and kappa chains, and produce mostly human IgG) immunized with a MERS-CoV vaccine,[597] and fusion inhibitors targeting the MERS-CoV spike protein.[598] The WHO has issued recommendations for the management of SARS infections due to suspected MERS-CoV infection.[599]

Immunity against coronaviruses appears to be short lived. Epidemiologic studies of coronavirus infection have demonstrated high reinfection rates.[600] In human volunteer experiments, infection with a 229E-like coronavirus only induced short-term immunity; rechallenge with homotypic virus, the 229E serotype, resulted in infection and illness.[601] In addition, under certain circumstances, vaccines against animal coronaviruses have led to enhanced disease.[602] This is being taken into consideration but is not deterring efforts to develop an efficacious vaccines against SARS and MERS.[603] A large number of vaccine candidates have been developed for SARS,[604] most of which are focused on developing antibody to the surface S glycoprotein, because neutralizing antibody is directed against the receptor-binding portion of this molecule. Several vaccine candidates against MERS-CoV are currently under evaluation in Phase I human clinical trials, using adenovirus (ChAdOx1 MERS) and modified vaccinia virus Ankara vectors, both of which encode the full-length MERS-CoV spike glycoprotein.[605]

Cytomegalovirus

CMV is the largest of the herpes viruses (200 nm), and it contains a linear double-stranded DNA in its nucleocapsid and an envelope derived from the host-cell nuclear membrane. (For a discussion of CMV disease in HIV-infected persons and transplant recipients, see Chapters 123 and 125, respectively.)

Epidemiology and Transmission. The major reservoir for CMV is asymptomatic infected persons because CMV infection in healthy individuals is followed by prolonged excretion of virus in bodily fluids. Virus shedding persists for years in children with congenital and perinatal CMV infections. The virus is believed to be transmitted by direct contact, especially under conditions of intimacy such as found in child care centers and the family setting.[606] Thus, the rate of acquisition of infection is greater in populations with high density, leading to infection at an early age. In addition to transmission by sexual intercourse, passage through the birth canal, and ingestion of breast milk, CMV infection can be acquired from transfused blood products and transplanted organs. No seasonal patterns of CMV infection have been observed.

Pathogenesis. In human fibroblast cell cultures, CMV produces a slowly progressive lytic infection. Infected cells contain large irregular basophilic intranuclear inclusions and also eosinophilic inclusions in paranuclear areas. The intranuclear inclusions are a hallmark of CMV infection and have been found in cells of a number of organs, including the kidney, liver, and the gastrointestinal tract, as well as the lung. In the lung, fibroblasts, epithelial cells, endothelial cells, and smooth muscle cells are all targets for CMV.[607]

The pathogenesis of CMV pneumonia is partly related to viral replication but also thought to have an immunopathologic basis.[608] The development of CMV pneumonitis reflects a complex interaction between viral infection and graft-versus-host disease, particularly in marrow transplant recipients (see Chapter 125).[609,610] Two distinct histopathologic patterns have been described in the lungs of bone marrow transplant patients with CMV pneumonia[611]: (1) a miliary pattern, with multiple focal lesions showing extensive cytomegaly with localized necrosis, alveolar hemorrhage, fibrin deposition, and neutrophilic response (see eFig. 46.50), or (2) an interstitial pattern, with alveolar cell hyperplasia, interstitial edema, lymphoid infiltration, and diffusely distributed cytomegalic cells.

Clinical Manifestations. In immunocompetent persons, most CMV infections are asymptomatic or may present as an acute pharyngitis, with features similar to mononucleosis. The main impact of CMV as a respiratory pathogen is in immunocompromised patients, including transplant recipients, patients on immunosuppressive treatment, and those with severe immunodeficiency, such as untreated HIV infection. CMV is the most common infectious cause of interstitial pneumonia among allogeneic bone marrow transplants as well as solid organ transplant recipients. The risk of CMV pneumonia is greatest between 30 and 90 days posttransplant. However, late-onset CMV syndromes at more than 180 days posttransplantation have been increasingly recognized with effective control of earlier-onset disease.

Risk factors for the disease include advanced age, the presence of acute graft-versus-host disease, intensive conditioning regimens, and allografts. CMV infection and pneumonitis also develops more frequently in transplant recipients, particularly lung transplant recipients, who are seronegative and receive a graft from a seropositive donor. When infection develops in a single-lung recipient, disease is especially marked in the transplanted lung.[612] In these patients, CMV pneumonitis may be a factor in the development of bronchiolitis obliterans. CMV can also be a primary pathogen in HIV-infected persons, although it is more often encountered in conjunction with other pulmonary

pathogens, and whether it causes lung disease as the sole cause in the context of HIV remains controversial (see Chapter 123).[613] Characteristically, patients with CMV pneumonitis have sustained fever, nonproductive cough, and dyspnea. Crackles and tachypnea are often present, and marked hypoxemia is an indicator of life-threatening infection. Pneumonitis may be accompanied by mild neutropenia, thrombocytopenia, and elevated liver enzymes, which may be helpful in differential diagnosis.

Chest radiographic changes (eFig. 46.51A) are bilateral, with diffuse or patchy ground-glass shadowing involving the mid and lower lung fields, patchy consolidation, or small nodules. Both miliary and interstitial radiographic patterns have been described. Patients with a miliary pattern may have a sudden onset of tachypnea, severe respiratory distress, and hypoxemia resulting in a rapidly fatal course, whereas patients with an interstitial pattern of disease often have an insidious onset of pneumonia with slowly progressive hypoxemia. In these patients, pulmonary opacities may be initially localized, with bilateral spread over days or weeks. Common chest CT scan findings include small nodules (see eFigs. 46.51B–C, 46.52B, and 46.53), consolidation (see eFig. 46.54), and ground-glass attenuation (eFigs. 46.51B–C and 46.52A).[614]

Diagnosis. CMV pneumonia should be in the differential diagnosis for any immunocompromised patient with unexplained lower respiratory symptoms or pulmonary opacities. However, the clinical assessment of patients with suspected CMV pneumonia is complicated due to the broad differential diagnosis of potential pathogens and the fact that concurrent infections with other pathogens are common (such as *Pneumocystis jirovecii*), and the clinical features and radiographic appearance of CMV pneumonia are insufficiently distinct to permit an accurate etiologic diagnosis. Additionally, noninfectious etiologies are common in the population at risk for CMV pneumonitis, including pulmonary malignancy or hemorrhage and posttransplant lymphoproliferative disorder (see eFigs. 46.55 and 46.56).

In patients with possible CMV pneumonia, the preferred approach to diagnosis is quantitative PCR in serum or BAL fluid.[615] Detection of CMV in respiratory secretions, urine, or blood does not necessarily implicate CMV as the causative organism for a particular clinical syndrome. This is particularly true in patients with HIV infection, in whom detection of CMV in BAL is often not associated with pulmonary pathology.[616] In this group, histologic evidence of viral inclusions on biopsy establishes the diagnosis. In contrast, the presence of CMV viremia in transplant recipients does increase the risk of subsequent development of CMV pneumonia, and CMV viral load is used in guiding preemptive therapy. Serologic testing has no role in diagnosis of acute infection and is used only to determine the serologic status of donors and recipients before transplantation.

Treatment and Prevention. The treatment of choice for CMV pneumonitis is ganciclovir, a nucleoside analogue that competitively inhibits CMV DNA synthesis, given intravenously at 5 mg/kg every 12 hours (with dose adjustment for renal impairment). IV ganciclovir can be switched to oral valganciclovir once the patient has shown clinical improvement and can tolerate oral medications. CMV viral load should be monitored weekly to assess treatment response and guide duration of therapy. CMV immune globulin was previously recommended as an adjunctive therapy to ganciclovir in stem cell transplant recipients. However, recent studies have demonstrated no clinical benefit.[617,618] Foscarnet and cidofovir are alternative antiviral drugs with activity against CMV.[619,620] Both have been used successfully to treat CMV retinitis, but their effectiveness for treating CMV pneumonia has not been established. All of the available CMV antivirals have the potential for serious side effects that require close monitoring. Maribavir and brincidofovir are newer oral agents that may have a role for refractory disease or against resistant viruses, but their role in CMV pneumonitis needs to be established.[621,622]

No vaccines are available for the prevention of CMV infection or disease, although several strategies are being actively pursued, including live attenuated and inactivated subunit vaccines. Letermovir is a CMV terminase complex inhibitor that, in a randomized clinical trial, reduced CMV infection in CMV-seropositive allogeneic hematopoietic stem cell transplant recipients and has been approved for prophylaxis in this group.[622a]

Hantaviruses

Hantaviruses are enveloped RNA viruses causing two major forms of hantavirus disease: hantavirus pulmonary disease and hemorrhagic fever with renal syndrome. The virions contain a dense envelope surrounded by fine surface projections. Filamentous nucleocapsids are present within the virions. The genome consists of negative-sense single-stranded RNA arranged in three physically discrete gene segments. The *small* (S) segment encodes the nucleoprotein, the *middle* (M) segment, the two envelope glycoproteins, G1 and G2, and the *large* (L) segment, the RNA-dependent RNA polymerase and endonuclease. The genome is segmented, and genetic reassortment in dually infected cells is common. It is believed that new pathogenic strains arise by this mechanism.

Epidemiology and Transmission. The *hantavirus pulmonary syndrome* (HPS) is a rodent-born zoonosis in which humans experience severe, often fatal disease. Each of the individual hantavirus strains appears to be associated with a specific rodent host. The rodent hosts experience prolonged asymptomatic infection, but the features associated with maintenance of these viruses in rodent populations and with rodent-to-rodent transmission are unclear. Serologic studies suggest that hantaviral infection of feral rodents is widespread throughout North America.[623] Hantavirus was first discovered in North America in 1993 after an outbreak of unexplained fever and ARDS in previously healthy young adults in the Four Corners region of the United States. Sera from affected patients cross-reacted to hantaviruses from Europe and Asia, associated with hemorrhagic fever with renal syndrome. The virus was subsequently identified as Sin Nombre virus,[624] which is one of the most severe forms of HPS, along with Andes virus.

Transmission to humans is presumed to result from inhalation of aerosols of infected rodent excreta. Hantaviruses

are stable and can persist in the environment for 10 to 15 days without loss of infectiousness.[625] Risk factors for acquisition of HPS include high densities of rodents in the household, cleaning of contaminated environments, agricultural activities, and other forms of occupational exposure to rodent droppings.

Person-to-person transmission has not been observed in the North American outbreaks[626] but has been documented in several outbreaks of Andes virus in Argentina and Chile.[627,628] Currently, approximately 11 to 48 cases of HPS per year are reported in the United States, with a case fatality rate of 35%.[629]

Pathogenesis. Hantaviruses use cell surface beta-3 integrins to enter endothelial cells, resulting in aberrant endothelial cell adhesion and interaction with extracellular matrix.[630] Beta-3 integrins regulate the maintenance of vascular integrity and vascular permeability, which may explain the disease processes observed in HPS.[631]

Hantavirus infections are predominantly contracted via the airborne route. Once in the lung parenchyma, the virus is taken up in phagocytes and transported to draining lymph nodes and then disseminated to distant organs. Antibody and cellular responses in humans are usually detectable at the time of presentation.[632] Neutralizing antibody is directed against the surface glycoproteins G1 and G2, and lower titers on presentation correlate with greater disease severity.[633] Viremia is detectable at presentation and declines promptly after resolution of fever.

Pathologic findings in fatal cases include pleural effusions, alveolar edema and fibrin, and interstitial mononuclear cell infiltrates, with little necrosis or neutrophil infiltration.[634] These findings are consistent with a capillary leak syndrome with subsequent noncardiogenic pulmonary edema. Immunopathologic responses play a major role in HPS.[635] Human infection with Sin Nombre virus and other hantaviruses results in widespread expression of viral antigens in endothelial cells of pulmonary and cardiac tissues.[636] CD8 T cell responses to a European hantavirus, Puumala virus, peak at the time of maximal clinical symptoms, implicating these responses in the pathogenesis of disease.[637] Myocardial depression has also been ascribed to induction of nitric oxide and locally secreted cytokines in response to infection.[638] Another pathogenic mechanism may be antagonism of the host innate immune response by the hantavirus G1 tail.[639]

Clinical Features. The typical incubation period of HPS is 2 to 3 weeks (range, 1 to 51 days). Presentation of HPS begins with a prodrome of fever, chills, and myalgias, occasionally accompanied by abdominal discomfort and gastrointestinal symptoms, and generalized malaise. Myalgias can be severe. Upper respiratory symptoms are usually absent. After a variable period of several days, the cardiopulmonary phase follows, with a nonproductive cough and dyspnea rapidly progressing to pulmonary edema, arrhythmias, coagulopathy, and cardiogenic shock.[640] Case-fatality rates of HPS range from 30–50% for severe forms and 10–30% for milder forms.

Laboratory studies generally reveal hemoconcentration, mild thrombocytopenia, and mildly elevated liver function tests. The triad of thrombocytopenia, left shift with circulating myeloblasts, and circulating immunoblasts is highly suggestive of HPS.[641] Multivariate analysis has identified dizziness, nausea or vomiting, and the absence of cough as well as thrombocytopenia, elevated hematocrit, and decreased serum bicarbonate as features to distinguish HPS from other causes of ARDS, such as pneumococcal pneumonia and influenza.[642] Mild acute kidney injury may be detected. However, unlike hantavirus hemorrhagic fever with renal syndrome, HPS does not progress to renal failure. Renal dysfunction may be more common in HPS associated with the Bayou hantavirus.[643]

Chest radiographs are typical of pulmonary edema without consolidation. Pleural effusions are present in most cases. Early in the course of HPS, these effusions are transudative, while later they develop higher fluid protein content and, in severe cases, have the protein characteristics of plasma.[640] In patients who survive, exertional dyspnea and reduced expiratory flow are common in early convalescence and resolve in most patients.[644] However, some patients have manifested long-term pulmonary and cognitive dysfunction.[645]

Diagnosis. Serology is the mainstay of diagnosis. In the absence of immunodeficiency, patients universally have detectable serum IgM and IgG antibody at the time of symptom onset. In low-prevalence areas, a positive IgM is diagnostic.[646] Virus can also be detected in blood by RT-PCR during the first 10 days of illness.[647] In contrast, hantaviruses are difficult to isolate from clinical material in cell culture and grow slowly. Isolation of virus from tissue is laborious and time consuming and must be undertaken in suitable containment facilities, so it is not useful for diagnosis.

Treatment and Prevention. Treatment is supportive and requires careful management of fluid status to maintain perfusion without exacerbating pulmonary edema. It has been suggested that high-dose steroid therapy may be useful because of the pathogenesis of the disease and potential utility of steroids in systemic capillary leak syndrome. However, a randomized trial of high-dose methylprednisolone in HPS demonstrated no clinical benefit.[648] In severe cases, extracorporeal membrane oxygenation may be beneficial.[649,650] The broad-spectrum antiviral agent ribavirin is active against hantavirus in vitro and was effective in reducing mortality in hantavirus-induced hemorrhagic fever with renal syndrome in China.[651] However, trials of ribavirin in HPS have shown no survival benefit.[652]

Herpes Simplex Virus

Herpes simplex viruses (HSV) are double-stranded DNA enveloped viruses consisting of a central core and containing viral DNA encased within an icosahedral capsid, which is surrounded by an envelope that contains viral glycoproteins. HSV is classified into two types, HSV-1 and HSV-2, based on antigenicity profile. HSV-1 is most commonly associated with oral or peri-oral lesions (cold sores) but is also frequently involved in respiratory infection, whereas HSV-2 is more commonly associated with genital infection. (See also Chapters 123 and 125 for HSV disease in HIV-infected persons and transplant recipients, respectively.)

Epidemiology and Transmission. Humans are the reservoir for HSV-1 and HSV-2 viruses. With primary infection, infectious virus is produced in the skin and mucous membranes, and is present in vesicle fluid and cellular debris from herpetic ulcers. After establishing latency in the regional nerve ganglia, the virus is intermittently shed in respiratory, vaginal, or urethral secretions in the absence of clinical disease. Asymptomatic respiratory tract shedding can be detected in about 1–2% of seropositive children and adults. HSV-1 spreads by transfer of virus-containing respiratory secretions, vesicle fluid, and cellular debris under conditions of close personal contact.[653] HSV-1 typically transmits through oral-to-oral, oral-to-genital, or occasionally genital-to-genital contact as well as by contamination of skin breaks with infected oral secretions. Cases of HSV-1 arise sporadically throughout the year, occasionally in small clusters. HSV-1 infection is usually acquired in childhood or adolescence.

Seroprevalence of HSV-1 is estimated to be approximately 67% in those younger than 50 years globally, with highest prevalence in sub-Saharan Africa, Southeast Asia, and the Western Pacific.[654]

Pathogenesis. Primary HSV infection begins at a local site, with rapid viral replication in parabasal and intermediate epithelial cells and resultant cell destruction and initiation of host inflammatory responses. In immunocompetent individuals, regional lymph nodes may be involved during primary infection, but the disease is usually contained at the primary site by innate antiviral responses. In immunocompromised individuals, local infection may be followed by contiguous mucosal spread, resulting in esophageal, tracheal, or pulmonary involvement or visceral dissemination to skin, liver, brain, adrenals, and lungs.[655] Disease may also disseminate in such individuals following reactivation of latent infection. Visceral infection is characterized by a highly destructive coagulation necrosis of involved sites.[656] In a series of fatal cases of HSV pneumonia, inflammatory infiltrates, parenchymal necrosis, and hemorrhage were found at autopsy.[657]

Latent infection is established in sensory nerve ganglia and is followed by lifelong recurrences of virus shedding and often lesions on skin and mucous membranes of the involved dermatomes. Cellular immunity is key in controlling HSV infection; studies in HIV-infected patients with severe mucocutaneous HSV indicate that both $CD4^+$ and $CD8^+$ T cells contribute to control of viral replication and spread.[658]

Clinical Manifestations. HSV-1 pneumonia is very uncommon and is predominantly seen in immunocompromised patients, such as those with malignancy,[659] burns,[660] organ transplantation,[661] and advanced HIV infection (CD4 count <200 cells/μL).[55] HSV-1 may have reached the LRT through aspiration of infected oropharyngeal secretions, contiguous mucosal spread from tracheobronchial tree to the lungs, viral reactivation in vagal nerve ganglia, or through hematogenous dissemination of the virus from mucocutaneous lesions of the upper airway or genitourinary tract. HSV pneumonia has very rarely been observed in immunocompetent persons.[662,663]

Clinical symptoms of HSV pneumonia are indistinguishable from other types of pneumonia, though gingivostomatitis or orolabial ulceration are frequently present. Other associated findings include thrombocytopenia, disseminated intravascular coagulation, abnormalities in liver function, and deterioration during antimicrobial treatment.

High-resolution CT findings commonly include bilateral, symmetric ground-glass opacities and air space consolidation but are nonspecific.[664] In one study, over half of the patients had concomitant pulmonary infection with another organism, including bacteria, *Candida* species, *Aspergillus* species, and CMV.[657] Histologic evidence of herpetic esophagitis was present in 10 of 16 patients with HSV pneumonia in whom esophageal examination was performed. Some cases may be nosocomially acquired.[665]

HSV is commonly isolated from LRT secretions from mechanically ventilated patients (16–27%) and is associated with worse outcome.[666,667] However, it is unclear whether this represents oropharyngeal contamination, viral reactivation as a consequence of severe illness, or active HSV bronchopneumonitis.[668,669]

Diagnosis. The diagnosis of HSV pneumonia should be suspected in any immunocompromised patient with unexplained pulmonary opacities, especially in the presence of herpetic laryngotracheitis or herpetic lesions of other mucocutaneous sites, including the genital area. HSV pneumonia is often diagnosed by detecting HSV DNA by PCR from LRT specimens (e.g., BAL) or lung biopsy. Identification of HSV-specific intranuclear inclusions from cells from BAL (eFig. 46.57) or bronchial biopsy may help to confirm diagnosis when it is unclear if HSV PCR positivity reflects true infection or contamination from oral secretions.

Treatment and Prevention. Antiviral susceptibility testing should be considered in patients with severe HSV infection who do not respond to initial treatment with oral valacyclovir or intravenous acyclovir. Foscarnet is probably the best available alternative therapy.

No vaccine against HSV is currently available. Intravenous acyclovir is the most commonly used treatment for HSV pneumonia, but its use in this condition has not been evaluated in controlled trials.

Measles Virus

Measles virus is a nonsegmented, negative-sense RNA virus. Its surface glycoproteins include a hemagglutinin responsible for attachment to cells, a fusion protein responsible for cell membrane fusion and virus penetration of cells, but no neuraminidase. The cell surface molecule signaling lymphocyte activation molecule, or CD150, serves as a receptor for viral entry into susceptible cells.[670] Additionally, the complement regulatory protein CD46 can also serve as a receptor, particularly for the vaccine strain.[671] Twenty-four genotypes are recognized by the WHO.[672] However, only five have been detected since 2016, suggesting that many genotypes are no longer circulating.[673] Despite its genotypic diversity, there is only one serotype of wild measles virus. Hence attenuated measles vaccines derived from a single measles virus genotype isolated in the 1950s,[674] including the Schwarz and

Moraten vaccine viruses, are still protective and widely used worldwide. Humans are the sole natural host for measles virus.

Epidemiology and Transmission. Measles is found worldwide, but epidemic patterns vary depending on population density and levels of acquired immunity. Before the introduction of a live, attenuated measles vaccine in 1963, major epidemics happened every 2 to 3 years and caused an estimated 2.6 million deaths annually.[675] From 2000 to 2016, measles incidence decreased by 87%.[673] Despite this, more than 100,000 measles-related deaths still happen each year, mostly in children under 5 years. Unfortunately, measles has reemerged over the past few years due to a fall in public confidence in the MMR vaccine, with reported outbreaks in multiple countries in Europe and the United States.[676]

Measles virus infection is highly contagious and can spread despite high levels of acquired immunity in the population. Airborne transmission via small-particle aerosols and possible spread by fomites appear to account for its high communicability. The virus remains infectious in small-particle aerosols for several hours at low relative humidity and has caused secondary infections in the absence of face-to-face contact with an index case.[677] Infected persons are infectious from 4 days before the onset of rash to 4 days after. They are most infectious during the late prodrome, when respiratory involvement contributes to creation of infectious aerosols.

Severe measles is more common in young children, pregnant women, and immunocompromised and undernourished persons (particularly children with vitamin A deficiency).[678] Measles-associated mortality in developed countries is usually 0.1% or less but approaches 2% of cases in the developing world. Case fatality rates have been as high as 25% in some areas. Most deaths result from respiratory tract and/or neurologic complications and are related to various combinations of malnutrition, young age, and complications of the immunosuppression induced by measles virus infection itself. Natural measles infection confers lifelong protection against reinfection.

Pathogenesis. Measles virus is acquired through respiratory droplets or aerosolized particles, initially infecting lymphocytes, dendritic cells, and alveolar macrophages in the respiratory tract.[679] The virus replicates and spreads to the local lymphoid tissue, then disseminates through the bloodstream via infected lymphocytes to the epithelial cells of the skin, respiratory tract, gut, bile duct, bladder, and lymphoid organs.

Measles infection induces transient suppression of T cell responses, resulting in suppression of delayed-type hypersensitivity, as well as restriction of cellular and humoral responses to new antigens.[680,681] Measles-induced immunosuppression can predispose to secondary bacterial and viral infections, including pneumonia and gastroenteritis.[682]

The pathologic changes in involved organs include lymphoid hyperplasia, mononuclear cell infiltration, and the presence of multinucleated giant cells. LRT involvement may be associated with the destruction of ciliated respiratory epithelium, interstitial pneumonia, epithelial cell hyperplasia, and syncytial cell formation.

Clinical Manifestations. The median incubation period is around 10 to 12 days but may be longer in adults. Measles typically presents with a prodrome of high fever, malaise, anorexia, cough, coryza, conjunctivitis, and Koplik spots (small white papules on buccal mucosa). A characteristic erythematous maculopapular rash appears 3 to 4 days after the onset of fever, beginning on the face and neck and spreading to the trunk and extremities. The rash typically resolves after 5 to 6 days. Leukopenia is common during the prodromal and early exanthematous stages of measles. Pronounced leukopenia (<2000 cells/μL) is associated with a poor prognosis. The development of neutrophilic leukocytosis suggests the possibility of bacterial superinfection or other complications.

Pneumonia accounts for most measles-related morbidity and mortality[683] and is most frequent in children under 5 years or adults older than 20 years. In young adults, multilobar reticulonodular opacity is the most common radiographic abnormality (see eFig. 46.1).[684] In patients with deficient cell-mediated immune function[685] and rarely in immunocompetent persons, infection by wild measles virus can cause a lethal giant cell pneumonia with or without rash.[674,686] Severe measles-induced pneumonia has been recognized in pregnant women[687] and in those infected with HIV.[687a] In hospitalized patients, mortality rates are approximately 70% in oncology patients and 17% in HIV-infected patients.[687a]

Secondary bacterial infection has been found in 30–50% of young adults with measles-related pneumonia. Symptoms and signs indicative of bacterial infection usually begin 5 to 10 days after onset of the rash. One study utilizing transtracheal aspiration found a range of bacterial pathogens in adults, most commonly *H. influenzae, N. meningitidis,* and *S. pneumoniae.*[684]

An atypical form of measles infection was recognized among adolescents and young adults who received inactivated measles vaccine in the United States between 1963 and 1967.[688] The vaccine sensitized recipients to measles antigens without providing full protection. Now rare, atypical measles is characterized by a high fever, headache, myalgia, vomiting, abdominal pain, and nonproductive cough. A polymorphous eruption, which may include vesicles, petechiae, purpura, and urticarial lesions, typically begins on the distal extremities and spreads proximally. Koplik spots are usually absent. Pulmonary abnormalities are found in most cases; respiratory symptoms including dry cough and pleuritic chest pain are common, and acute respiratory failure has been described. Chest radiographic changes include patchy, diffuse, or dense lobar opacities, pleural effusions, and hilar lymphadenopathy.[689] Residual nodular pulmonary opacities may persist for years. The fever and other symptoms usually resolve in 1 to 3 weeks.

Diagnosis. The most common laboratory method for confirming measles virus infection is by detecting measles virus–specific IgM from sera or oral fluid. Anti-measles IgM is usually detectable from 3 days after rash onset, peaks within 1 to 3 weeks of rash onset, and falls to undetectable levels within 4 to 8 weeks.[690] Acute infection can also be confirmed by a fourfold or greater rise in measles virus–specific IgG between acute and convalescent titers, or by detecting measles virus RNA by RT-PCR in throat,

nasal, nasopharyngeal or urine samples; samples can be sent to the CDC (http://www.cdc.gov/measles/lab-tools/rt-pcr.html). Measles virus may also be cultured from the blood, conjunctival swabs, urine, or respiratory secretions during the prodromal phase,[691] but culture is slow and inefficient. Respiratory and conjunctival secretions or urine sediment stained by various techniques reveals multinucleated giant cells in most cases.

Treatment and Prevention. The treatment of measles involves supportive care and prompt recognition and treatment of secondary bacterial infections. No specific antiviral agents exist for measles virus, though ribavirin, interferon alpha, and immunoglobulin have been used in treating measles pneumonia.[687,692] Vitamin A therapy reduces morbidity and mortality in severe measles in children.[693] Patients suspected of having measles should be placed in respiratory isolation.

Measles can be prevented through vaccination. Currently, licensed measles vaccines are live attenuated, given in combination with mumps and rubella vaccines (MMR). Two doses of MMR vaccine are recommended: first dose at 12 to 15 months (6 to 9 months during outbreaks or in endemic settings) and the second dose at 4 to 6 years. Two doses of MMR vaccine are 97% effective, while one dose is 93% effective. A 92–95% vaccination coverage is necessary to achieve herd immunity to protect unvaccinated, susceptible individuals. The vaccine is safe, and it has been conclusively shown to have no association with autism.[694,695]

Metapneumoviruses

Human metapneumovirus (hMPV) is a large enveloped negative-sense single-stranded RNA virus. It is closely related to RSV, though hMPV possesses a different gene order and lacks nonstructural proteins NS1 and NS2. Phylogenetic analysis has identified two major genetic lineages, A and B, and two clades within each lineage—A1, A2, B1, and B2. Concurrent circulation of all four clades is common, though the predominant clade varies by year.[696]

Epidemiology and Transmission. hMPV was first identified by Dutch researchers in 2001 from archived pediatric respiratory specimens in which no pathogen had been isolated.[697] Since then, it has been found to be distributed worldwide. Seroepidemiology studies suggest that most children are infected by the age of 5 years.[697] There may be reinfection throughout life due to incomplete protective immunity and/or infection by different hMPV strains.[698] Prolonged presentation and/or severe disease have been observed in immunocompromised subjects such as hematopoietic stem cell transplant recipients,[699,700] lung transplant recipients,[701] and HIV-infected persons.[702] Outbreaks of severe disease have been documented in residential care facilities in older adults.[703] hMPV is thought to be transmitted through direct or close contact with contaminated secretions, including saliva, droplets, large particle aerosol, or fomites.[704] Seasonality is similar to that of influenza and RSV, with peak activity in late winter and early spring.[705]

Clinical Features. Incubation period is thought to be 5 to 9 days.[706] hMPV predominantly causes mild self-limited respiratory infections. In children, severe respiratory presentations are similar to that of RSV with bronchiolitis and pneumonitis.[707,708] LRT presents less frequently in adults than in children. In a population-based surveillance study in the United States, hMPV was detected in 3.8% of hospitalized adults with CAP.[4] Frail elderly patients and those with underlying lung disease or immunocompromise are at greater risk of severe disease.[709,710] hMPV infection has also been identified as a trigger for asthma[711] and COPD[712] exacerbations. Unlike RSV and influenza, asymptomatic hMPV infection is common in adults.[709]

Pathogenesis. Relatively little is known regarding the pathogenesis of this disease. Alpha-v beta-1 integrin has been identified as a functional receptor for hMPV facilitating epithelial cell infection.[713] In hospitalized children with hMPV, levels of nasal secretion of the chemokine *regulated upon activation, normal T cell expressed and secreted* (RANTES) have been reported to be suppressed, while levels of nasal IL-8 were increased.[714] The immune responses elicited by hMPV are similar to those of RSV but often are not as vigorous.[715]

Diagnosis. Most hMPV infections are detected by nucleic acid amplification techniques such as RT-PCR. Numerous commercial molecular panels to detect respiratory viruses including hMPV are available (see Chapter 19).[716] Viral culture and serology testing are insensitive.

Treatment and Prevention. Treatment is supportive. No antiviral agents or vaccines are currently licensed for treatment or prevention of hMPV infections. Ribavirin is active in vitro against hMPV,[717] but there are no data to support the therapeutic efficacy of this drug. There are no specific monoclonal antibodies available for clinical use, although intravenous immunoglobulin has been suggested as a possible therapeutic agent in immunocompromised hosts.[718]

Parainfluenza Viruses

Parainfluenza viruses (PIV) are medium-sized (150 to 200 nm), pleomorphic, enveloped viruses with a nonsegmented, single-stranded RNA genome contained in a helical nucleocapsid. There are two virus surface proteins: *hemagglutinin-neuraminidase* (HN), which mediates adsorption of virus to host cell receptors for entry into host cells and the subsequent release of new virions from infected cells after viral replication, and the *fusion* (F) protein, which mediates the fusion of the viral envelope with the host cell membrane.[719] Neutralizing antibodies that target HN and F proteins are important determinants of long-term protection from PIV infections.[720] There are four types of human parainfluenza viruses (PIV 1 through 4), which are subdivided into two genera: Respirovirus (PIV1 and PIV3) and Rubulavirus (PIV2 and PIV4).[721]

Epidemiology and Transmission. Parainfluenza viruses have a worldwide distribution, and almost all persons are infected during childhood. By adulthood, over 90% of individuals have antibodies to PIVs.[722] However, the antibodies only confer partial protection, thus reinfections are possible, though they are usually limited to mild disease.[723]

PIVs were detected in 3% of CAP requiring hospitalization in a study of approximately 2500 U.S. adults.[4] Similar prevalence has been reported in smaller studies.[560,724,725] Adults with advanced age and immunocompromise are at increased risk for severe PIV infection.[726,727] PIV3 is the most prevalent serotype, followed by PIV1, PIV2, and PIV4.[728] The four serogroups exhibit differing seasonalities: PIV1 has biennial epidemics which peak in the fall; PIV3 has outbreaks annually in early spring or summer; PIV2 has less frequent outbreaks, which tend to peak in autumn; and PIV4 has no notable seasonality.[728]

Parainfluenza viruses are transmitted through direct person-to-person contact with infectious respiratory secretions or via respiratory droplets and fomites. The incubation period ranges from 2 to 6 days. Virus is transmitted readily in families. Outbreaks of infection have been seen in closed populations, such as nurseries, day care centers, and hospitals, in which susceptible populations have high infection rates (40–80%).

Pathogenesis. Replication of parainfluenza viruses is generally restricted to the respiratory tract epithelium, initially infecting nasal and oropharyngeal airways, and spreads distally to large and small airways. This selective tropism correlates with the absence of viremia in healthy persons and may reduce exposure of viral antigen to antigen-presenting cells, resulting in attenuated immune response that predisposes to reinfections.[729] The viral load in respiratory secretions tends to correlate with illness severity.[730] Virus shedding commonly continues for 8 to 10 days in initial infections but may last for 3 weeks or longer. Prolonged shedding (months) of PIV1 and PIV3 has been reported in healthy[731] and immunocompromised adults.[732] PIV induces innate immune responses, CD8 and CD4 T cell responses, type I interferon production, and local IgA and IgG responses, which contribute to viral clearance.[733] However, inflammatory cytokine production and subsequent cellular infiltration may also contribute to PIV pathogenesis, while IgE production contributes to croup and wheezing in infants and children.[734] Pathologic findings in fatal cases of PIV are typical of other viral pneumonias and include peribronchiolar and alveolar lymphocytic infiltration.[735]

Clinical Manifestations. PIV infection in adults predominantly manifests as a common cold, including cough, rhinorrhea, and sore throat.[736] PIV-associated exacerbations of asthma and COPD have been described.[737,738] Although less common, PIV pneumonia can evolve from upper respiratory infections and may be the presenting manifestation. In a retrospective cohort of U.S. adults hospitalized with PIV infection, over half required supplementary oxygen, and nearly one-fourth required admission to the ICU.[739] In immunodeficient patients, presentations can be particularly severe, such as fatal giant cell pneumonia.[740]

Diagnosis. Rapid diagnosis of parainfluenza infection can be made by detection of viral antigen or RNA in respiratory secretions obtained using throat or nasopharyngeal swabs. Detection of parainfluenza RNA is performed in multiplex PCR panels for respiratory viruses[716] (see Chapter 19). Respiratory secretions contain the virus at the time of symptom onset. PIVs can also be detected by viral culture, but with lower sensitivity and speed than by PCR. Virus replication in cell culture is usually detected by hemadsorption of guinea pig erythrocytes or immunofluorescence.

Treatment and Prevention. There are currently no available antiviral agents of proven effectiveness against PIV. Ribavirin, intravenous immunoglobulin, and corticosteroids have been used to treat severe PIV pneumonia in immunocompromised patients, with variable benefit.[741–743] DAS181, a sialidase fusion protein, is a promising investigational nebulized antiviral that inhibits attachment of PIV to respiratory cells. It has shown efficacy in small clinical studies,[744,745] and a Phase II clinical trial in hematopoietic stem cell transplant recipients demonstrated that a higher proportion of patients who received DAS181 discontinued supplemental oxygen and were discharged from hospital by day 45.[746] Additionally, there was also a trend towards lower mortality in the DAS181 group. A Phase III trial is underway.

There is no licensed vaccine against PIV. Initial attempts to develop vaccines for the prevention of PIV involved use of formalin-inactivated virus. However, these vaccines were not sufficiently immunogenic to provide protection in field trials carried out in children in the 1960s.[747] In contrast to RSV and measles vaccines, the use of formalin-inactivated parainfluenza vaccine was not associated with disease potentiation on subsequent infection. Subunit vaccines containing purified HN and F glycoproteins were shown to induce functional antibodies in animal models,[748] while a modified vaccinia Ankara recombinant vaccine expressing H or F proteins of PIV3 tested in rhesus monkeys showed significant protection of the LRT against PIV3 challenge but not of the upper respiratory tract.[749] Several live attenuated vaccine candidates have been developed using cell culture passage or chemical mutagenesis for virus attenuation and reverse genetics technology; most are focused on PIV3, but there are also several PIV1 and PIV2 candidates.[750-752] Clinical trials of these are ongoing, but no FDA-approved vaccine is currently available.

Rhinovirus

Rhinoviruses (RVs) are small (30 nm), nonenveloped, positive-sense, single-stranded RNA viruses. The viral capsid comprises four viral proteins, VP1 to VP4. The exposed surface of VP1, VP2, and VP3 proteins accounts for the virus' antigenic variation, while VP4 anchors the RNA core to the capsid.[753] There are three known species of rhinovirus—A, B, and C[754]—with more than 150 types defined by sequencing and serologic methods. The phylogenetic diversity of RV types presents a major challenge to the development of an RV vaccine. Infection with one type of RV is unlikely to provide immunity to other types. Thus, individuals are likely to have infections to different RV types throughout life. RV-A and RV-C are associated with more severe disease and asthma exacerbations than RV-B.[755]

Epidemiology and Transmission. RVs are worldwide in distribution. RV infections happen year-round, with peak circulation in early fall and a smaller peak in spring in temperate climates.[756] The different RV types circulate in a given population in an apparently random manner.

RV is transmitted between individuals primarily by direct contact, contact with fomites, or inhalation of aerosols (small or large particle).[757] RV is present in nasal secretions for 5 to 7 days but may persist for up to 3 weeks in the nasopharynx.[758] Studies of experimental RV infections have shown that RV is efficiently spread by contaminated fingers accidentally depositing virus into the nose or eye.[759] Experimental RV transmission has also been achieved by the airborne route.[760]

Pathogenesis. Previously, the majority of RV types were known to bind the intercellular adhesion molecule-1, while a minority utilized the low-density lipoprotein receptor for binding.[761] However, a specific variant of cadherin-related family member 3 has been identified as the primary receptor for RV-C.[762] Manipulation of these receptor proteins has been explored as a potential control measure for rhinovirus infection. Approximately two-thirds of both natural and experimental RV infections result in overt illness. Small doses of RV instilled into the nose or eye of susceptible volunteers regularly lead to infection, indicating that mucociliary clearance is not effective against the virus. In general, the number of RV-infected cells in the nasopharynx appears to be limited, and infection seldom results in damage to the nasal epithelium.[763] These results suggest that symptoms are cause by inflammatory rather than virus-induced cellular injury.[764]

In the few reports of RV LRT infection with histopathology, findings have included bronchiolitis obliterans with organizing pneumonia,[765] interstitial pneumonitis and/or ARDS,[766] acute and chronic inflammation with fibrinopurulent alveolar debris,[767] and hyperplasia and desquamation of alveolar cells.[768]

Clinical Manifestations. RVs are the commonest cause of upper respiratory tract infections in adults and children. The incubation period of RV is usually 2 days but may be up to 1 week. Symptoms begin within 1 day following experimental infection. Although the optimal temperature for RV replication is 33°C, thus accounting for its predilection for the nasal passages, there is increasing evidence for an important role of rhinoviruses in LRT disease,[769] particularly among individuals with preexisting lung disease or immunosuppression. RV was the most common pathogen identified (9%) in a study of 2259 adults with radiographic evidence of pneumonia in the United States.[4] RV also commonly causes exacerbations of asthma[770] and COPD.[771] Prolonged RV shedding has been reported in immunocompromised persons.[772] Furthermore, progression to LRT infection is associated with substantial morbidity and mortality,[766] and coinfection with one or more bacterial, viral, and/or fungal pathogens is commonly identified.

Diagnosis. Detection of RV nucleic acid in multiplexed PCR-based assays (see Chapter 19) is now commonly used to diagnose RV infection, though these assays generally do not distinguish rhinoviruses from enteroviruses within the *Picornaviridae* family. RV-A and RV-Bs can be isolated in cell culture, but isolation rates are generally low due to their fastidiousness in vitro. Virus is present in nasopharyngeal secretions in highest concentrations during the first and second days of illness but may be shed for as long as 3 weeks. When indicated, identification of the specific serotype of an RV isolate is made by neutralization test.

Treatment and Prevention. There are currently no approved antiviral therapies for RV. Treatment is largely supportive, including analgesics, antihistamines, and decongestants. Although handwashing is undoubtedly important in preventing transmission, a randomized study showed no benefit to routine hand disinfection in the prevention of RV infections.[773] As mentioned above, the plethora of rhinovirus serotypes suggests that an effective vaccine will not be forthcoming in the foreseeable future. Several antiviral agents, including capsid-binding agents (e.g., pleconaril[774] and pirodavir[775]) and protease inhibitors (ruprintrivir[776]) have been evaluated in randomized trials. However, due to lack of efficacy, drug toxicities, and interactions, none of these agents has reached approval for clinical use.

Varicella-Zoster Virus

Varicella-zoster virus (VZV) is an enveloped double-stranded DNA virus with a large genome (≈125,000 bp). Primary VZV infection causes varicella, more commonly known as chickenpox. VZV can be reactivated endogenously many years after the initial infection. This secondary infection is known as herpes zoster (or shingles).

Epidemiology and Transmission. Primary VZV infection is predominantly a childhood disease in unvaccinated populations. In temperate settings, greater than 90% of people are infected before adolescence, whereas, in semitropical and tropical areas, disease is acquired later in life and adults often remain susceptible to primary infection.[777] Outbreaks are more frequent in late winter and early spring months in temperate regions. Herpes zoster is nonseasonal and is seen in persons of all ages, although its incidence increases almost linearly after 30 years of age. About 10–20% of adults experience zoster, typically as a single episode after the fifth decade of life. Though uncommon, clinically apparent reinfections can be seen with VZV.

VZV is highly contagious, with a secondary household attack rate of 90%. It is predominantly spread from person to person through airborne transmission. The virus can also be spread through direct contact with conjunctival fluid, saliva, or fluid from a vesicle of an infected individual. Herpes zoster is less infectious because the only source of infection is the vesicular fluid.

The introduction of the varicella vaccine into routine childhood immunization in 1995 has led to significantly reduced disease incidence, complications, hospitalizations, and deaths in all ages, with a further decline in incidence after a second dose of vaccine was introduced in 2006.[778]

Pathogenesis. The incubation period of varicella averages 2 weeks, and almost all cases of varicella develop within 10 to 21 days after exposure.[779] The initial portal of infection is the respiratory tract, with viremic dissemination leading to the extensive cutaneous and mucous membrane lesions. Following infection, VZV establishes latency in the posterior dorsal root ganglia. Reactivation of virus replication and centrifugal spread along sensory nerves lead to the unique dermatomal distribution of shingles (herpes zoster).

In immunocompromised hosts with zoster, virus may disseminate to other sites.

Clinical Manifestations

Varicella Zoster. Varicella usually begins with a fever and a self-limited, pruritic vesicular rash that affects most of the body and occasionally mucosal sites. Systemic symptoms are common. In adults, varicella is associated with a greater number of complications, of which pneumonia is the most common and severe. Other complications include secondary bacterial infection, meningoencephalitis, and hepatitis. Pneumonia complicates 5–15% of adult chickenpox.[780] Risk factors for VZV pneumonia include pregnancy, older age, history of pulmonary disease, smoking, and immune suppression.[780] Pulmonary involvement usually manifests within a week of the onset of rash. Symptoms include cough, dyspnea, pleuritic chest pain, and hemoptysis. Physical findings other than fever and tachypnea are often modest. Varicella pneumonia is associated with a high rate of respiratory failure. Mortality rate of varicella pneumonia ranges from 11% in healthy adults to approximately 50% in pregnant women and immunocompromised persons.[781]

The characteristic chest radiographic pattern is that of diffuse nodular (1 to 10 mm) opacities (eFigs. 46.58), which may resolve with miliary calcified nodules (eFig. 46.59).[782] Hilar lymphadenopathy, pleural effusions, and peribronchial opacities are frequently present. Chest CT in patients with varicella pneumonia typically shows multifocal or diffuse, variably sized nodules (1 to 10 mm), which may be circumscribed or poorly defined (eFig. 46.60). Ground-glass opacity halos may be seen around some of the nodules. Pulmonary function studies have found normal expiratory flow values but decreased carbon monoxide diffusing capacity, which may persist for months. However, many individuals with radiographic changes are relatively asymptomatic.

Herpes Zoster. Herpes zoster represents reactivation of latent VZV along one to three dermatomes and, in adults, is usually associated with pain. The thoracic dermatomes are involved in about one-half of cases. Prolonged severe pain, termed postherpetic neuralgia, can be a serious complication, with increased frequency in those older than 50 years.[783] In patients with impaired cell-mediated immunity, disseminated disease with widespread cutaneous and visceral involvement can develop. Pneumonia is a rare complication in patients with herpes zoster.[784]

Diagnosis. Real-time PCR assays are now commonly used to confirm VZV infection from skin lesions as well as from BAL or cerebrospinal fluid. A rapid diagnosis of VZV infection can also be made using direct fluorescent antibody testing on scrapings from vesicular skin lesions. VZV can be isolated by culture, but culture is insensitive and has a longer turnaround time than PCR. Serology is less useful for diagnosis of acute infection; VZV IgM antibodies appear 1 to 2 days after appearance of VZV or herpes zoster rash, but the absence of antibodies does not exclude the diagnosis. The presence of VZV IgG antibodies correlates with a history of varicella and protection against subsequent infections.

Treatment and Prevention. First-line treatment for varicella pneumonia or other VZV complication is intravenous acyclovir (10 mg/kg every 8 hours) for 7 days. Patients showing clinical improvement can be switched to oral valacyclovir or famciclovir, which have superior bioavailability to oral acyclovir. The role of adjunctive corticosteroids in varicella pneumonia is unclear. A retrospective cohort study from Saudi Arabia reported better oxygenation parameters in patients who received steroids than those who did not,[785] while a French study reported no impact in mortality, but patients treated with steroids had more bacterial superinfection as well as longer duration of mechanical ventilation and hospital stay, compared to patients who did not receive steroids.[786]

Two live attenuated vaccines are available for the prevention of varicella: a single-antigen varicella vaccine, and a combination vaccine (MMRV). A single dose is 80% effective in preventing varicella disease of any severity and more than 99% effective in preventing severe disease.[787] Two doses of varicella vaccine are recommended for children 12 months or older, adolescents, and adults without evidence of prior immunity.[788] Second-dose catch-up vaccination is recommended for those who previously received only a single dose of vaccine. Previously, a single, higher-dose live attenuated vaccine was recommended for all healthy individuals 60 years or older, which has been shown to reduce the frequency of reactivation and the clinical severity of herpes zoster.[789] In 2017, a two-dose recombinant, adjuvant vaccine was approved by the FDA in immunocompetent adults aged 50 years or older after demonstrating vaccine efficacy of 97–98% in a Phase III trial.[790] Due to greater and longer-lasting efficacy, the Advisory Committee on Immunization Practices currently recommends its use preferentially over the live attenuated vaccine.[791]

and laboratory studies, including factors that may be related to delayed response.[175,793] Reconsideration of the initial diagnosis is also an important component of the diagnostic approach. Important epidemiologic clues may suggest unusual microorganisms along with unexpected resistance to antimicrobials, or underlying immunodeficiency such as HIV infection.

MICROBIOLOGIC STUDIES

The microbiologic investigation of treatment failures requires comprehensive reexamination of initial microbiologic results, together with obtaining new samples for culture and other assays. A bronchoscopy to evaluate the airways for potential obstruction and obtain microbiologic samples from the LRT is recommended if not otherwise contraindicated. Both protected specimen brush and BAL sampling should be done during the same procedure for bacterial cultures, direct fluorescent antibody staining, and nucleic acid testing. Although culture results may be altered by the prior administration of antibiotics, the sensitivity of brush or BAL cultures approaches 40% in nonresponding CAP. In patients undergoing mechanical ventilation, the tracheal aspirate can provide diagnostic information. Gram stain of cytocentrifuged BAL fluid can rapidly identify intracellular microorganisms[794] and may guide decisions regarding changes in antimicrobial therapy. Comprehensive microbiologic studies should also be performed on samples from nonrespiratory sites (see Table 46.2). When present, pleural fluid should be obtained for culture, direct fluorescent antibody, and nucleic acid testing for likely pathogens. The role of transbronchial biopsy is not established, and its indication depends on the possible alternative diagnosis suspected.

IMAGING STUDIES

Chest radiographs may demonstrate complications such as pleural effusion, cavitation, or new opacities. Chest CT scans provide a more detailed study of the parenchyma, interstitium, pleura, and mediastinum, potentially suggesting specific microorganisms or alternative diagnoses. In a patient with applicable risk factors, the appearance of nodular opacities with the halo sign (i.e., a nodule surrounded by a halo of ground-glass attenuation, especially near the pleura) on CT scan is suggestive of pulmonary aspergillosis (eFigs. 46.63A and 46.64) or mucormycosis (eFig. 46.65).[795] Nodules of similar appearance have also been described in CMV infection (see eFig. 46.54), granulomatosis with polyangiitis, Kaposi sarcoma, and metastases with necrosis and/or hemorrhage. Ground-glass opacities consistent with interstitial pneumonia suggest *P. jirovecii* pneumonia. Nodules or multiple masses with or without cavitation are compatible with *Nocardia* species, *M. tuberculosis,* or Q fever. Diffuse or mixed interstitial and alveolar opacities may be due to viral infections or *M. pneumoniae.* Other imaging studies, such as chest CT pulmonary angiography, should be considered to evaluate the possibility of pulmonary emboli and to exclude endobronchial lesions causing obstruction.

PREVENTION OF PNEUMONIA

VACCINES

The risk of pneumonia can be reduced by administering influenza and pneumococcal vaccines. Recommendations for administration of influenza[796] are included in Chapter 47. Recommendations for pneumococcal[797] vaccines are presented in eTable 46.7.

Inactivated influenza vaccination is recommended annually for all persons aged 6 months and older, including pregnant women. For those averse to injections, a live attenuated influenza vaccine can be given by intranasal administration to healthy persons 6 months to 49 years old. The live, attenuated vaccine must be avoided in pregnancy, in high-risk persons with chronic underlying diseases or immunodeficiencies, and in health care staff caring for immunosuppressed patients; it is not approved for use in those over 49 years. The standard-dose inactivated vaccine is less immunogenic and efficacious in individuals over 65 years[798]; thus high-dose (containing 60 μg hemagglutinin antigens compared to 15 μg in standard-dose vaccine) or adjuvanted preparations are recommended for this age group.[796] See Chapter 47 for further details on influenza vaccines.

Two pneumococcal vaccines are currently available. The purified polysaccharide vaccine (PPSV23) contains capsular antigens isolated from 23 of the most prevalent capsule types and is immunogenic in adults, although antibody levels decrease to prevaccination levels after 4 to 7 years. The pneumococcal conjugate vaccine (PCV13) contains polysaccharide antigens from 13 of the most prevalent capsule types, conjugated to a nontoxic mutant of diphtheria toxin protein, which generates T cell help and long-lived memory B cells specific for pneumococcal antigens. PPSV23 should be administered to all individuals 65 years of age and older as well as those aged 19 to 64 years with chronic conditions that increase the risk of invasive pneumococcal infection (e.g., diabetes; chronic lung, heart, or liver disease; cigarette smoking; or alcoholism). Patients aged 19 years and older with immunodeficiencies or other conditions that impose an especially high risk of invasive pneumococcal infection (asplenia, HIV or other congenital or acquired immunodeficiencies, myeloma, lymphoma, leukemia, chronic renal failure) should receive an initial dose of PCV13 followed at least 8 weeks later by PPSV23. eTable 46.7 lists the conditions and indications for which administration of each of the pneumococcal vaccines is currently recommended.[797] In 2014, the updated ACIP recommendations are that both PCV13 and PPSV23 should be administered in series to all adults 65 years and older. A dose of PCV13 should be received first followed by a dose of PPSV23 6 to 12 months later. Individuals previously vaccinated with PPSV23 should be given a dose of PCV13 after approximately 1 year.[797,799]

eTable 46.7 Recommendations for PCV13 and PPSV23 by Risk Group for Adults 19 Years and Older*

Risk Group	PCV13 Recommended	PPSV23 Recommended¶	PPSV23 Revaccination 5 Years After First Dose
Immunocompetent	Cerebrospinal fluid leak Cochlear implant	Chronic heart diseases† Chronic lung diseases‡ Diabetes Chronic liver diseases Cerebrospinal fluid leak Cochlear implant Alcohol Smoking	
Asplenia	Sickle cell disease/ hemoglobinopathy Congenital or acquired asplenia	Sickle cell disease/ hemoglobinopathy Congenital or acquired asplenia	Sickle cell disease/ hemoglobinopathy Congenital or acquired asplenia
Immunocompromised	HIV Congenital or acquired immunodeficiency Chronic renal failure Leukemia/lymphoma Generalized malignancy Solid organ transplant Multiple myeloma Iatrogenic immunosuppression§	HIV Congenital or acquired immunodeficiency Chronic renal failure Leukemia/lymphoma Generalized malignancy Solid organ transplant Multiple myeloma Iatrogenic immunosuppression	HIV Congenital or acquired immunodeficiency Chronic renal failure Leukemia/lymphoma Generalized malignancy Solid organ transplant Multiple myeloma Iatrogenic immunosuppression

*All adults aged 65 years and older should receive PVC13 and PPSV23, with the sequence and interval depending on previous history of vaccination with pneumococcal vaccine.
†Including congestive heart failure and cardiomyopathies.
‡COPD, emphysema, and asthma.
§Including long-term systemic corticosteroids and radiation therapy.
¶Where both PCV13 and PPSV23 are recommended, the PCV13 should be administered first and the PPSV23 at the indicated interval, as outlined in the text.
Modified from Tomczyk S, Bennett NM, Stoecker C, et al. Use of 13-valent pneumococcal conjugate vaccine and 23-valent pneumococcal polysaccharide vaccine among adults aged ≥ 65 years: recommendations of the Advisory Committee on Immunization Practices (ACIP). *MMWR Morb Mortal Wkly Rep*. 2014;63(37):822–825.

SMOKING CESSATION

Not only is smoking a risk factor for pneumococcal disease, quitting smoking reduces the risk.[179] IDSA/ATS recommend smoking cessation counseling and pneumococcal vaccination for smokers who are hospitalized with pneumonia.[39]

Key Points

- All patients with suspected pneumonia should have a chest radiograph. Gram stains of sputum and blood cultures should be obtained before treatment in all patients considered for hospitalization and in those with certain risk factors for methicillin-resistant *S. aureus* or *P. aeruginosa. S. pneumoniae* and *L. pneumophila* urinary antigens can make an etiologic diagnosis with reasonable sensitivity and specificity.
- Aspiration is the cause of infection with *S. pneumoniae, H. influenzae,* gram-negative bacilli, and other organisms, whereas aerosolization is the route of infection with intracellular bacteria: *Legionella* sp, *M. pneumoniae, Chlamydophila* sp, *C. burnetii,* and viruses such as influenza viruses.
- Nucleic acid amplification tests are increasingly used to diagnose viruses and fastidious bacteria, *M. pneumoniae, C. pneumoniae, L. pneumophila,* and *B. pertussis*, because culture procedures are too insensitive and too slow to guide treatment.
- In older and immunocompromised patients, the signs and symptoms of pneumonia may be muted and overshadowed by nonspecific complaints. Temperature greater than 38.5°C or accompanied by chills should never be attributed to bronchitis without examining a chest radiograph. Older patients with pneumonia who present with altered mental status without fever often have a delay in receiving antibiotics; this delay can increase mortality. Immunocompromised hosts may have a normal chest radiograph because signs of inflammation may be blunted. Computed tomography scans may be required to identify pneumonia.
- Treatment for pneumonia should be directed at a specific pathogen, but definitive identification of the patient's causal pathogen may be difficult. Therefore, disease severity, patient age, the presence of comorbidities and immunosuppression, previous antimicrobial therapy, and specific clinical and radiologic manifestations of the illness are used to select initial empirical antimicrobial therapy.
- If the etiologic agent has been identified, the antimicrobial regimen should be adjusted based on the results of in vitro susceptibility testing. The ideal drug for a known pathogen has the narrowest spectrum of activity and is the most efficacious, least toxic, and least costly.

Key Readings

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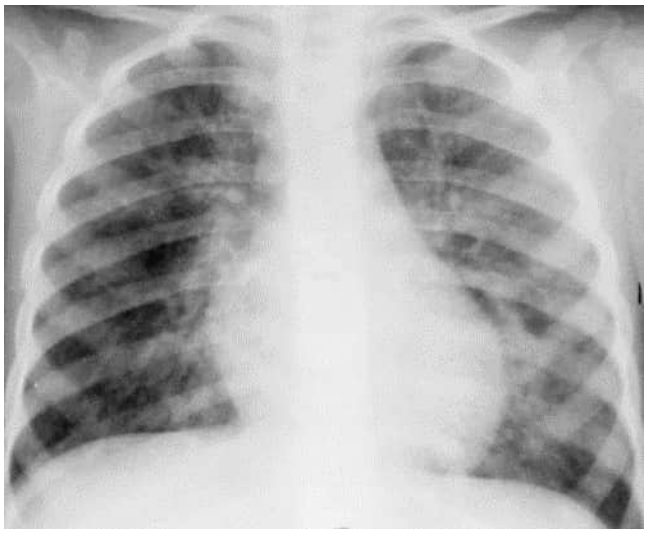
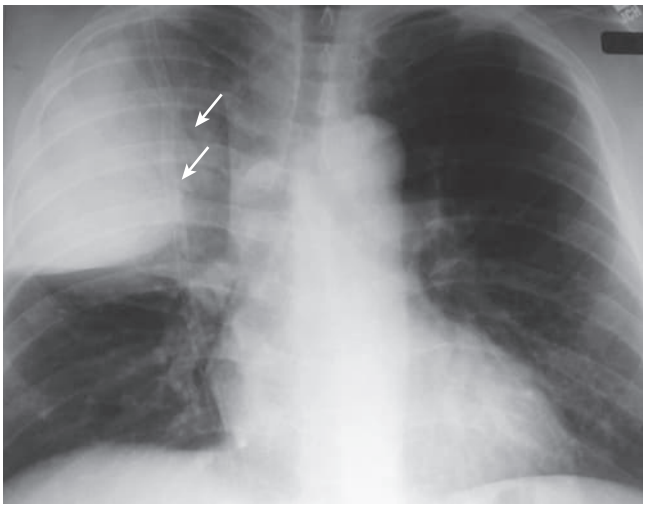
Complete reference list available at ExpertConsult.com.

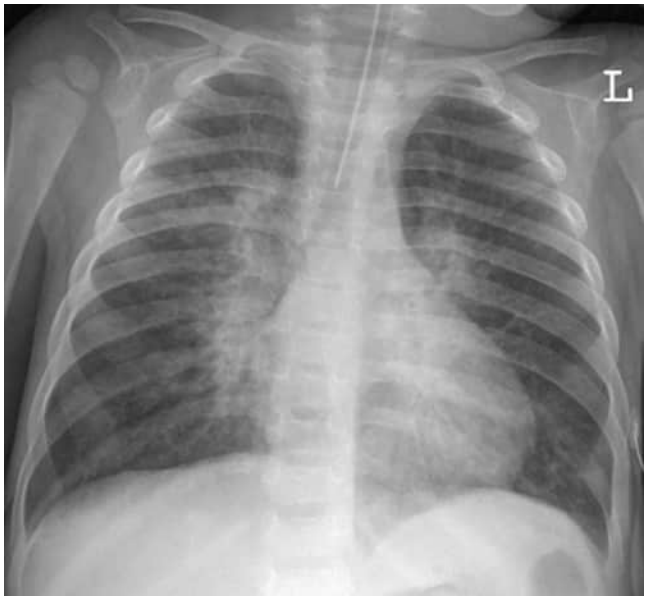
eFIGURE IMAGE GALLERY



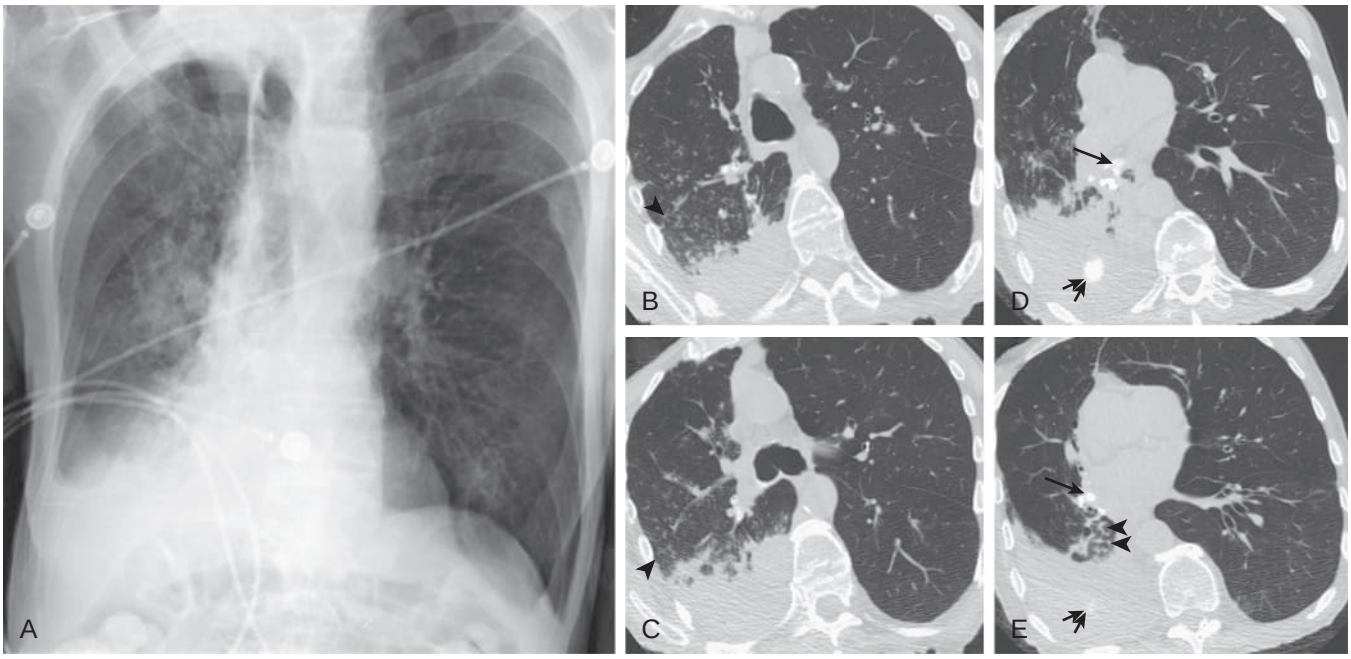
eFigure 46.1 Chest radiography: measles pneumonia. Frontal chest radiograph in a child with a typical measles rash shows patchy, bilateral faintly nodular bronchovascular thickening with a predominantly perihilar distribution. The imaging features are consistent with viral infection but nonspecific regarding potential etiologic agents. (Courtesy Michael B. Gotway, MD.)



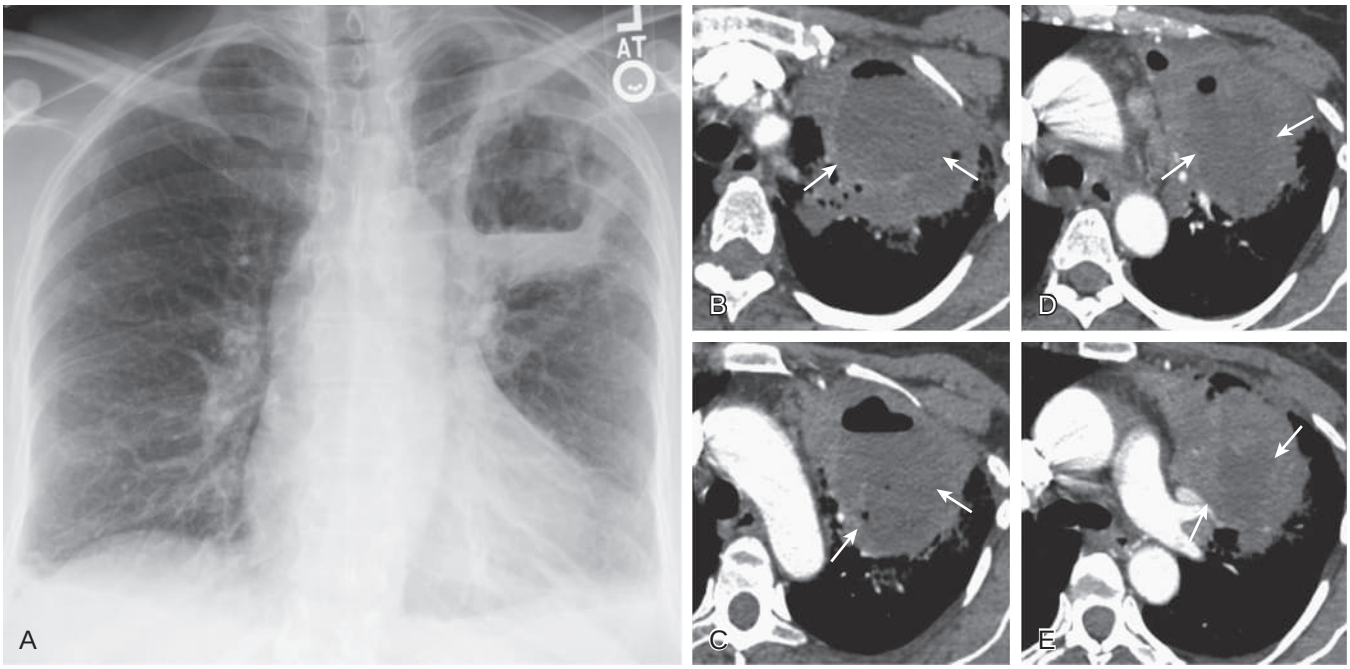
eFigure 46.2 Lobar pneumonia due to pneumococcus. Frontal chest radiograph shows homogeneous increased opacity conforming to the shape of the right upper lobe, extending to the pleural surfaces, associated with air bronchograms (*arrows*). These findings are typical of air space consolidation, and the pattern is consistent with lobar pneumonia, commonly seen with pneumococcal or *Klebsiella* pulmonary infections. (Courtesy Michael B. Gotway, MD.)



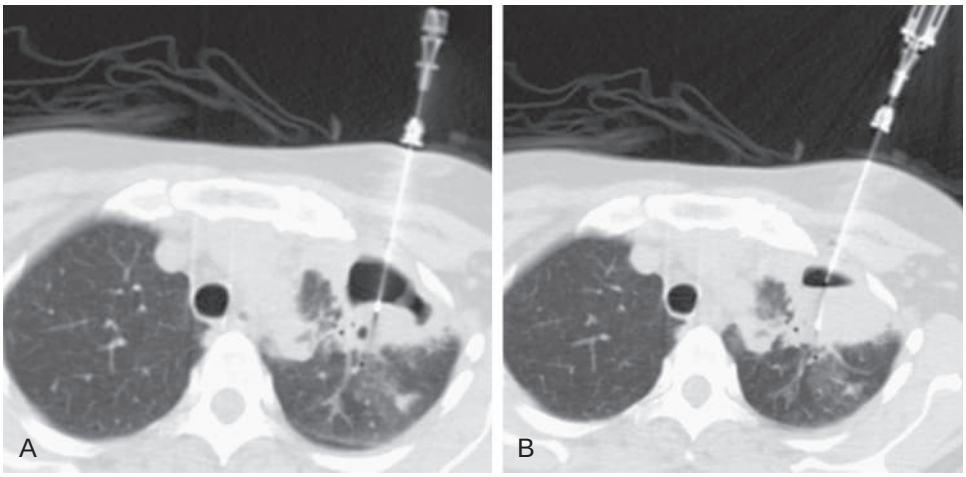
eFigure 46.3 Atypical pneumonia due to adenovirus. Frontal chest radiograph in a pediatric patient shows multifocal, bilateral central peribronchial thickening, typical of an infiltrative process involving the pulmonary interstitium, such as viral infection. (Courtesy Michael B. Gotway, MD.)



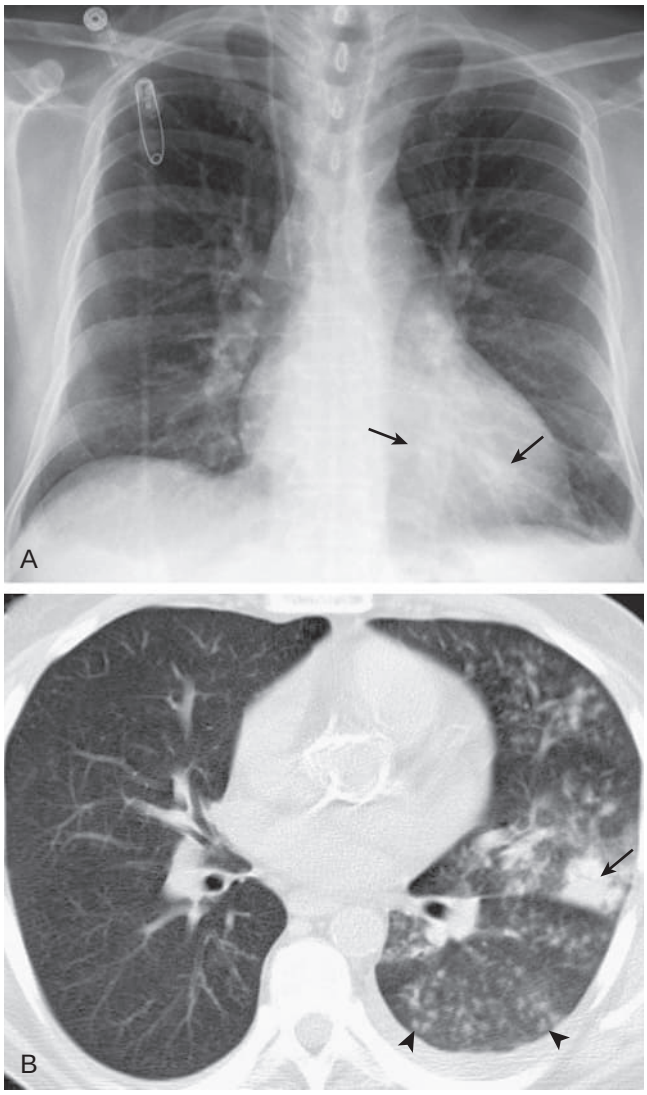
eFigure 46.4 Aspiration pneumonia. (A) Frontal chest radiograph shows right lower lobe consolidation and volume loss; note shift of trachea and cardiomediastinal structures toward the right. Trace right pleural effusion is present. (B–E) Axial chest computed tomography displayed in lung windows shows right lower lobe consolidation associated with small centrilobular nodules (*arrowheads*) consistent with bronchopneumonia and bronchiolitis. This pattern is consistent with aspiration pneumonia, particularly when seen in dependent lung regions, but is not specific for aspiration; community-acquired or health care–acquired bronchopneumonia may have a similar appearance. However, what is specific for aspiration in this circumstance is the frank aspiration of orally administered contrast (E, *single arrow,* oral contrast in right lower lobe bronchus; D–E, *double arrows,* oral contrast extending into right lower lobe pulmonary parenchyma), which flows directly into the affected regions of lung. (Courtesy Michael B. Gotway, MD.)



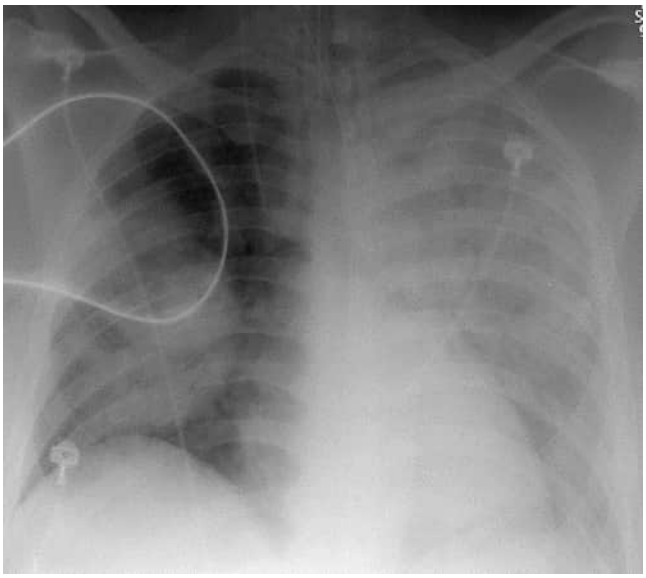
eFigure 46.5 Lung abscess. (A) Frontal chest radiograph in a patient with cough and purulent sputum shows a thick-walled cavity with an irregular internal lining and air-fluid level in the left apex. (B–E) Axial chest computed tomography displayed in soft tissue windows shows a rounded area of low attenuation (*arrows*) in the left upper lobe, surrounded by consolidation consistent with a pulmonary abscess. The internal low attenuation is fluid density, and an air-fluid level is present, typical of pulmonary abscess. Reactive prevascular lymph node enlargement is also evident. (Courtesy Michael B. Gotway, MD.)



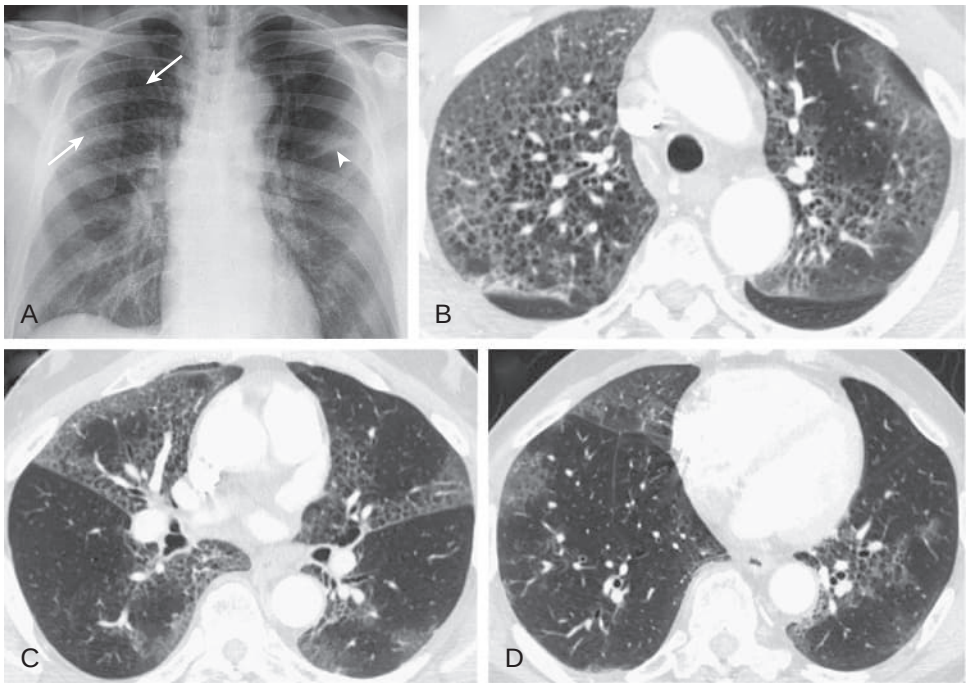
eFigure 46.6 Percutaneous transthoracic sampling of a pulmonary abscess. (A–B) Axial chest computed tomography shows placement of a needle into a left apical cavity (same patient as in eFig. 46.5). Purulent fluid was recovered, with microbiologic analysis disclosing polymicrobial infection. The lesion resolved with antibiotic therapy. (Courtesy Michael B. Gotway, MD.)



eFigure 46.7 Pneumococcal bronchopneumonia. (A) Frontal chest radiograph shows patchy bronchovascular thickening (*arrows*) in the left lower lobe; trace blunting of the left costophrenic angle is present. (B) Axial chest computed tomography 2 days following A shows nodular lingular consolidation (*arrow*) and numerous small centrilobular nodules (*arrowheads*) consistent with bronchopneumonia. This bronchopneumonia pattern contrasts with the lobar pneumonia pattern (see Fig. 46.1). Both imaging patterns may be seen with pneumococcal pneumonia. (Courtesy Michael B. Gotway, MD.)



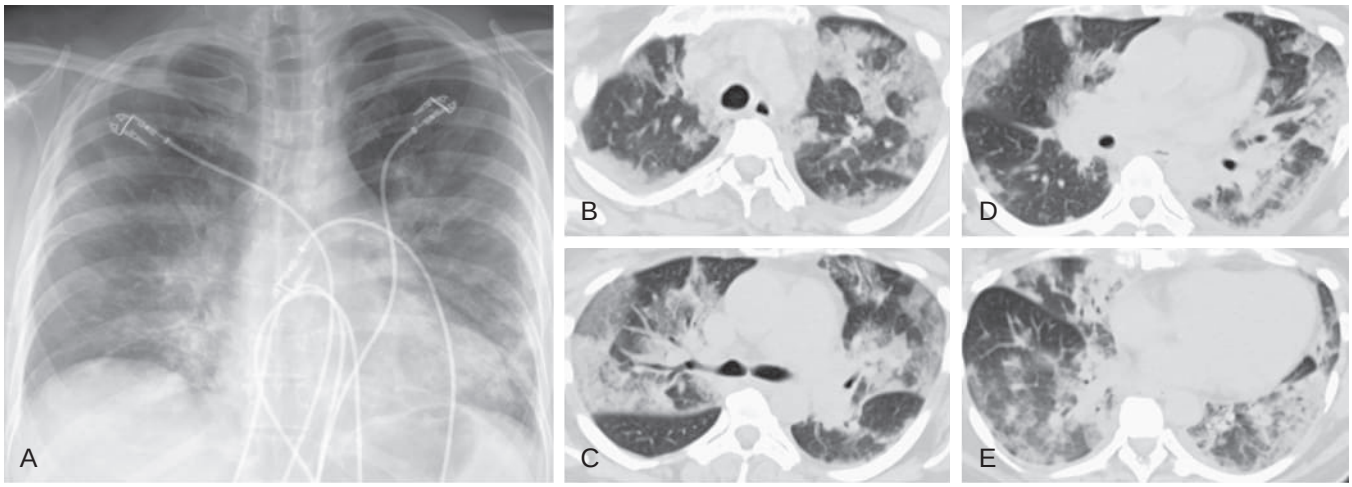
eFigure 46.8 *Legionella pneumophila* pneumonia: multilobar pneumonia. Frontal chest radiograph in a patient with *Legionella* pneumonia and respiratory failure shows left-greater-than-right multilobar consolidation. (Courtesy Michael B. Gotway, MD.)



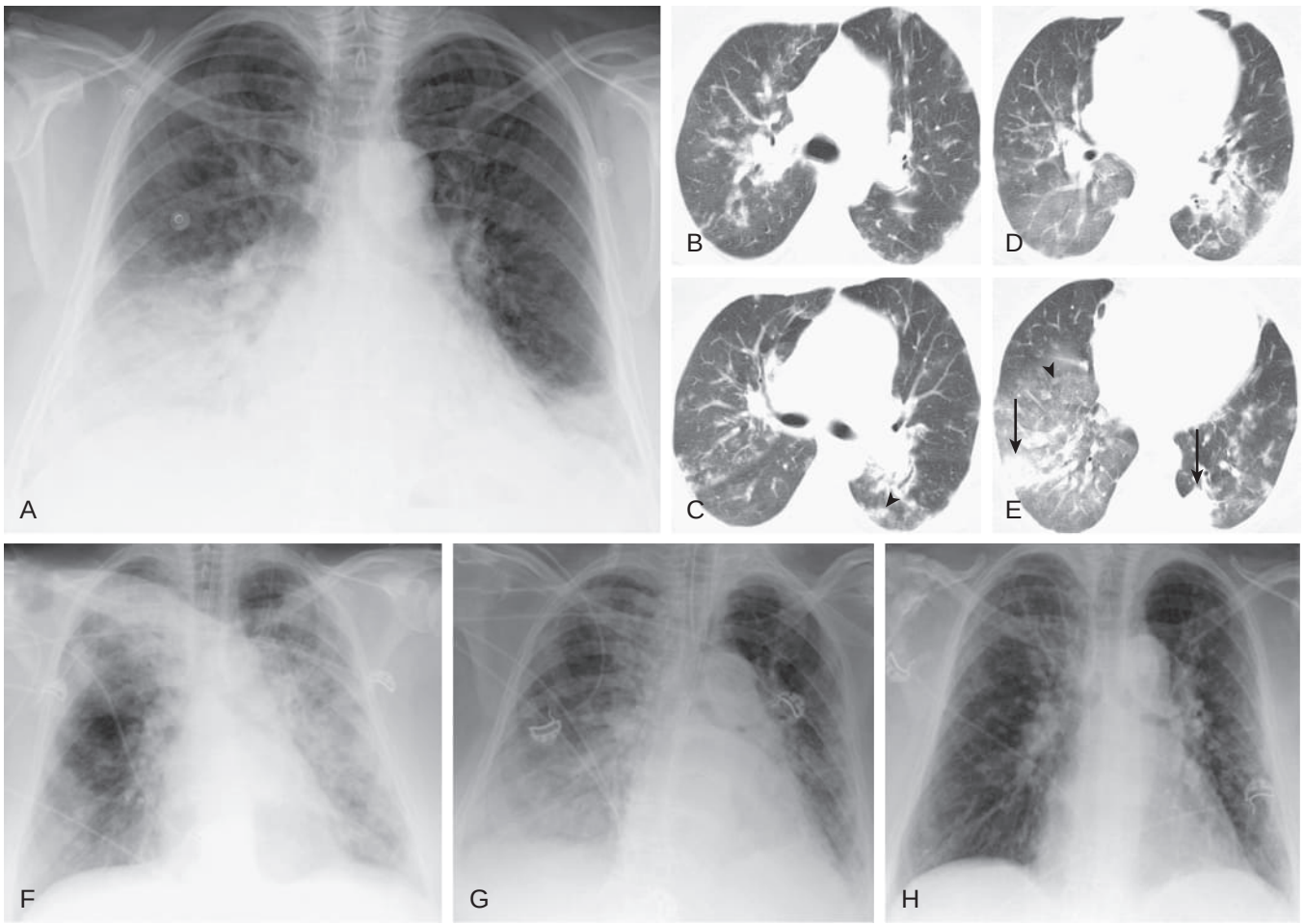
eFigure 46.9 Seasonal influenza A infection: imaging findings. (A) Frontal chest radiograph shows patchy, bilateral linear interstitial thickening in a perihilar distribution, some of which represents bronchial thickening. Abnormalities are slightly more nodular appearing in the right upper lobe (*arrows*), and consolidation is developing in the left upper lobe (*arrowhead*). (B–D) Axial chest computed tomography displayed in lung windows shows multifocal, bilateral, upper lobe predominant ground-glass opacity associated with linear abnormalities consistent with mild, smooth interlobular septal thickening and intralobular interstitial thickening. The cystic appearance is due to centrilobular emphysema outlined and contrasted with the surrounding infiltrative lung abnormalities. (Courtesy Michael B. Gotway, MD.)



eFigure 46.10 Seasonal influenza A infection: variable chest radiographic findings. Frontal chest radiograph shows predominantly left perihilar peribronchovascular thickening and nodularity. The imaging findings are nonspecific and could be the result of a number of causes of bronchopneumonia. (Courtesy Michael B. Gotway, MD.)



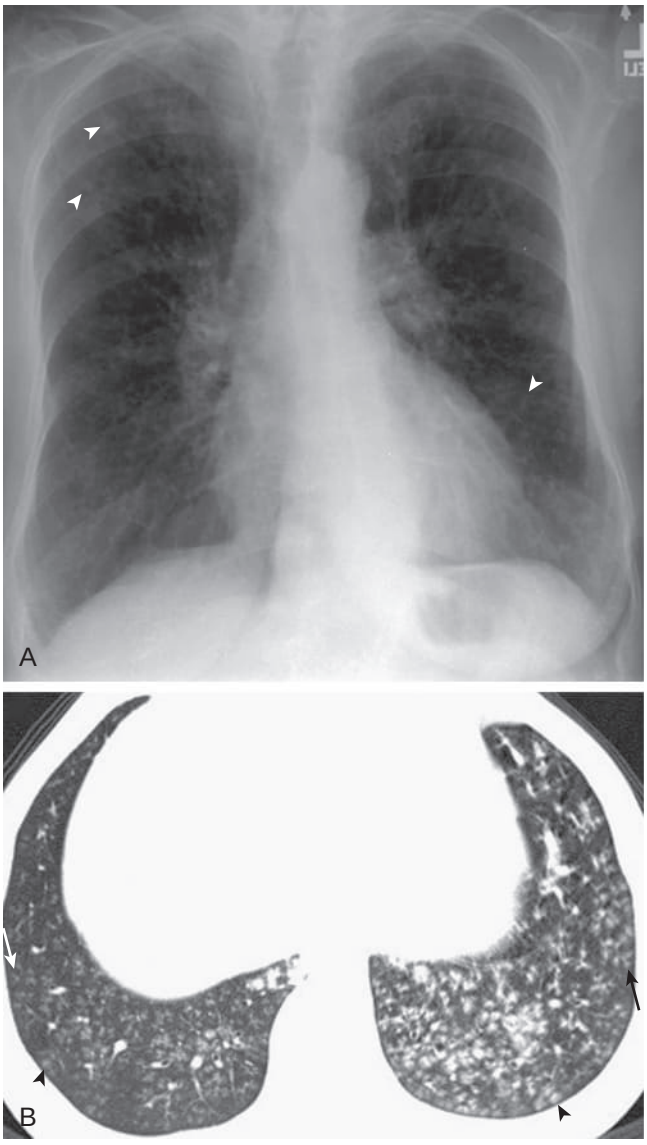
eFigure 46.11 Seasonal influenza A infection progressing to respiratory failure with diffuse alveolar damage. (A) Frontal chest radiograph in a previously healthy 51-year-old woman with no significant previous medical history presenting to the emergency department with fever, cough, and nasal congestion shows multifocal, perihilar predominantly linear opacity and bronchovascular thickening and hazy opacities. The patient had been seen as an outpatient and treated with several broad-spectrum antibiotics with no improvement. At the time the chest radiograph was performed, the patient was mildly leukopenic with an oxygen saturation of 82% on room air. (B–E) Axial chest computed tomography displayed in lung windows shows multifocal, bilateral, nonsegmental areas of ground-glass opacity, in some areas peripherally and peribronchially distributed, associated with intralobular interstitial thickening, mild interlobular septal thickening, and a few areas of consolidation. The imaging findings are nonspecific and can be seen with numerous causes of noninfectious acute lung injury and other pulmonary infections including severe acute respiratory syndrome. Surgical lung biopsy showed diffuse alveolar damage with some intrabronchiolar and alveolar inflammatory cells suggesting the possibility of an infectious insult, and bronchoscopy before the surgical biopsy recovered influenza A. The patient suffered hypoxic respiratory failure requiring mechanical ventilation but subsequently recovered. (Courtesy Michael B. Gotway, MD.)



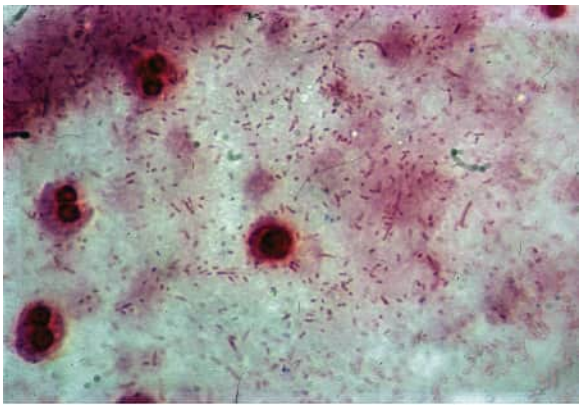
eFigure 46.12 H1N1 influenza A infection: imaging findings. (A) Frontal chest radiograph in a patient subsequently diagnosed with H1N1 influenza during the 2009 pandemic shows multifocal basal predominant consolidation, consistent with bronchopneumonia, but nonspecific. (B–E) Axial chest computed tomography displayed in lung windows shows nonspecific bilateral areas of ground-glass opacity, nodular subpleural consolidation (*arrows*), and other foci of patchy, peripheral, increased lung attenuation, and small nodules (*arrowheads*), some of which appear centrilobular. (F–H) Serial frontal chest radiograph obtained during the course of the disease shows worsening of bilateral opacities associated with hypoxemic respiratory failure (F–G) but subsequent clearing of bilateral lung opacity following recovery (H). (Courtesy Michael B. Gotway, MD.)



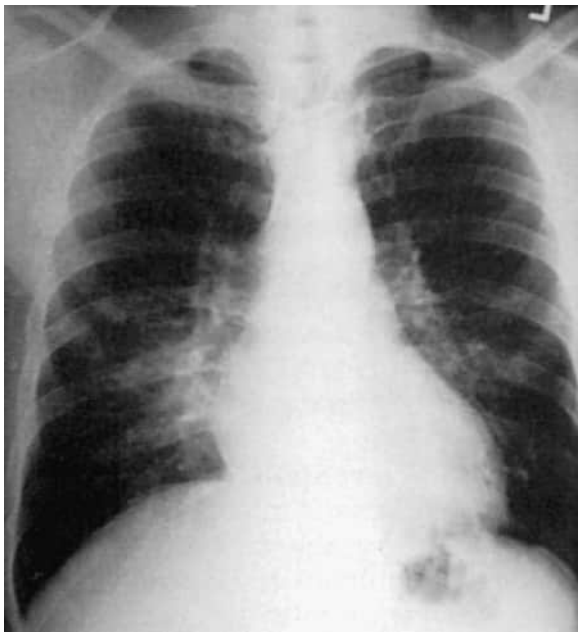
eFigure 46.13 Seasonal influenza A infection complicated by bacterial pneumonia. Frontal chest radiograph in a pediatric patient shows multifocal bilateral consolidation. The patient had been diagnosed with seasonal influenza A infection 2 weeks earlier and was recovering but then developed a high fever and new productive cough, which resolved following broad-spectrum antibiotic therapy. (Courtesy Michael B. Gotway, MD.)



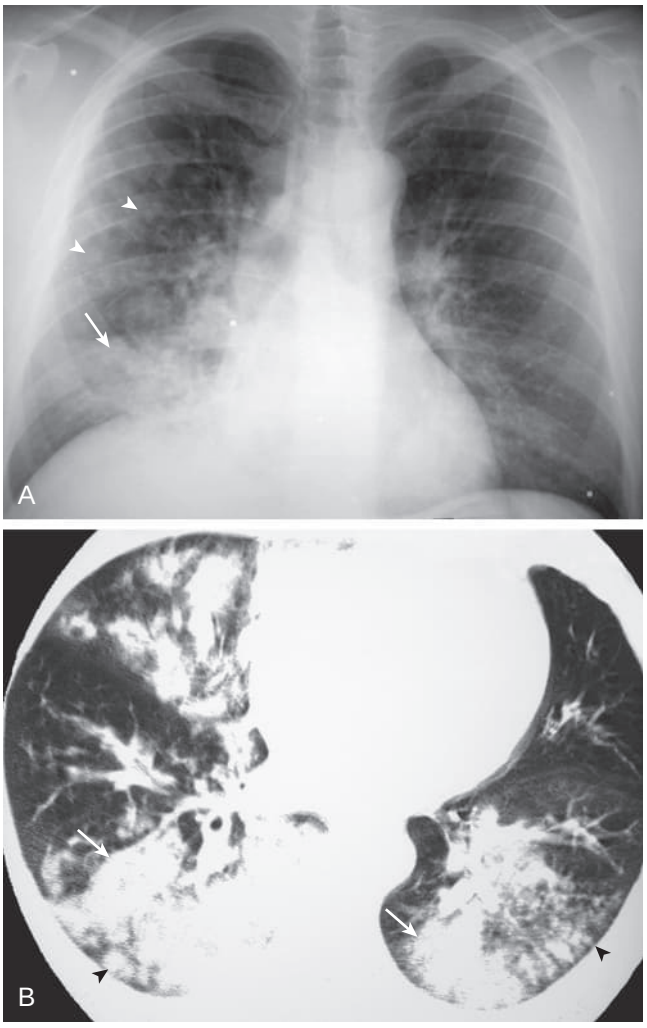
eFigure 46.14 *Haemophilus influenzae* pneumonia: bronchiolitis. (A) Frontal chest radiograph shows several nonspecific small nodular opacities bilaterally (*arrowheads*). (B) Axial chest computed tomography through the lung bases shows numerous small centrilobular nodules (*arrowheads*), some with branching configurations (*arrows*), the latter consistent with tree-in-bud opacity, representing infectious bronchiolitis. The appearance of small centrilobular nodules with branching configurations is not specific for *Haemophilus influenzae* pneumonia and can be seen with other bacteria and occasionally with fungi or even viruses. (Courtesy Michael B. Gotway, MD.)



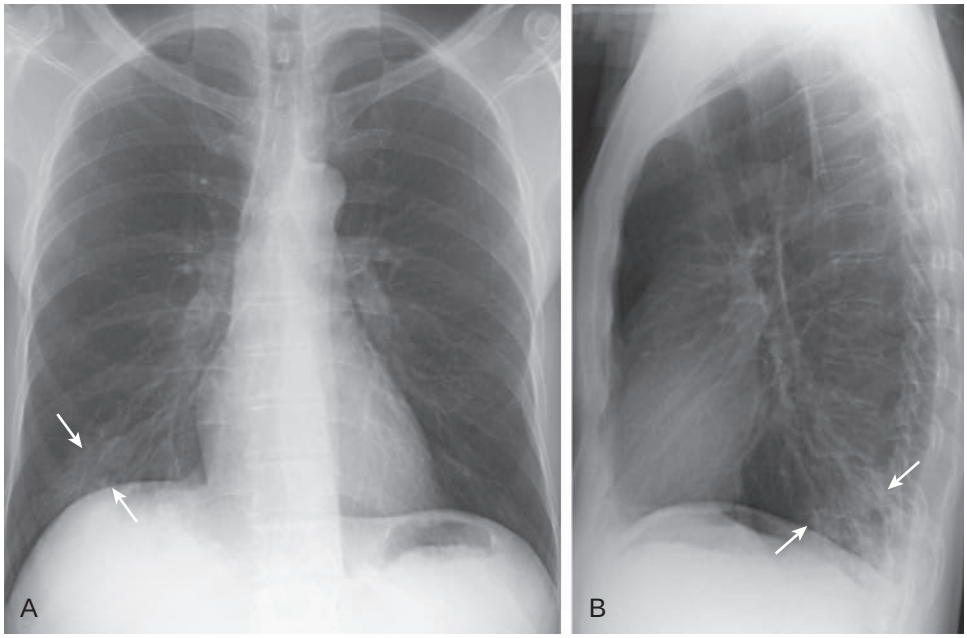
eFigure 46.15 *Haemophilus influenzae*. Gram stain shows small pleomorphic coccobacilli diffusely across the field that, because of their size, can be missed on sputum examination.



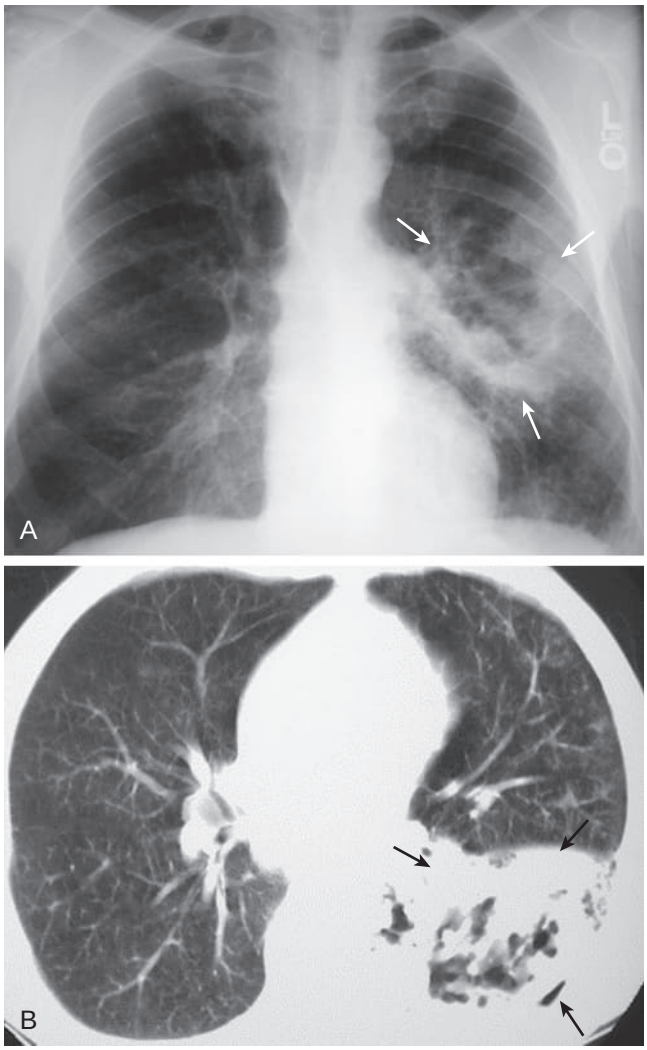
eFigure 46.16 Radiographic findings in *Mycoplasma pneumoniae* pneumonia are nonspecific. Bilateral bronchopneumonia is seen in this patient.



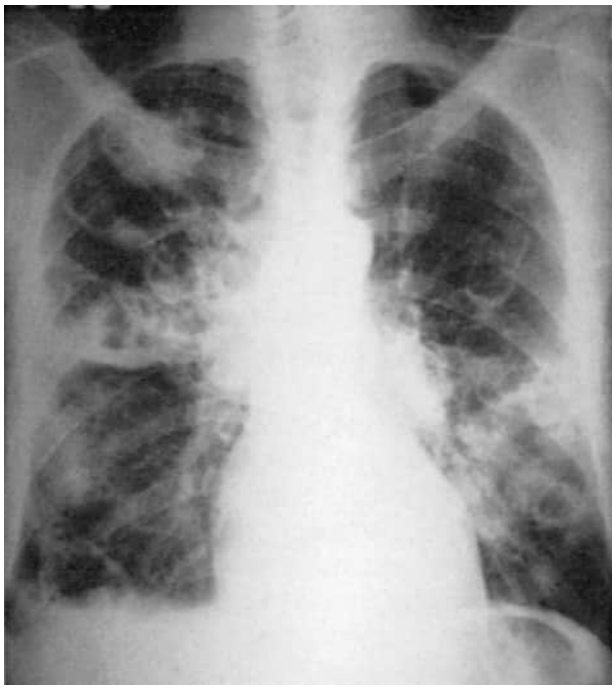
eFigure 46.17 ***Mycoplasma pneumoniae*** **pneumonia: multilobar pneumonia.** (A) Frontal chest radiograph shows right lower lobe consolidation (*arrow*) associated with several small nodular opacities (*arrowheads*), the latter consistent with acinar or air space nodules. (B) Axial chest computed tomography through the lower lungs displayed in lung windows shows extensive bilateral consolidation (*arrows*) associated with small nodules (*arrowheads*) varying from 3 to 4 mm to 1 cm in size. (Courtesy Michael B. Gotway, MD.)



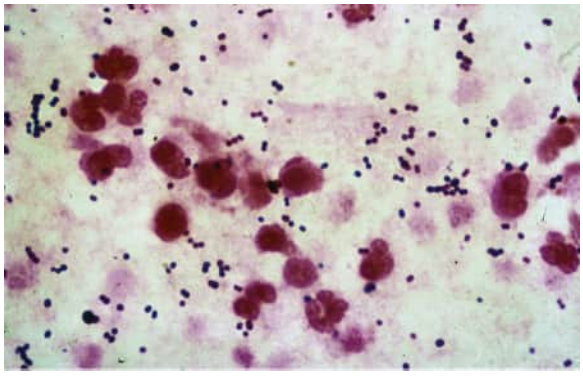
eFigure 46.18 *Mycoplasma pneumoniae* pneumonia: unilateral bronchopneumonia. Frontal (A) and lateral (B) chest radiographs in a patient with *Mycoplasma pneumoniae* pneumonia show patchy right lower lobe consolidation (*arrows*) consistent with bronchopneumonia but nonspecific with regard to the specific microbiologic etiology. (Courtesy Michael B. Gotway, MD.)



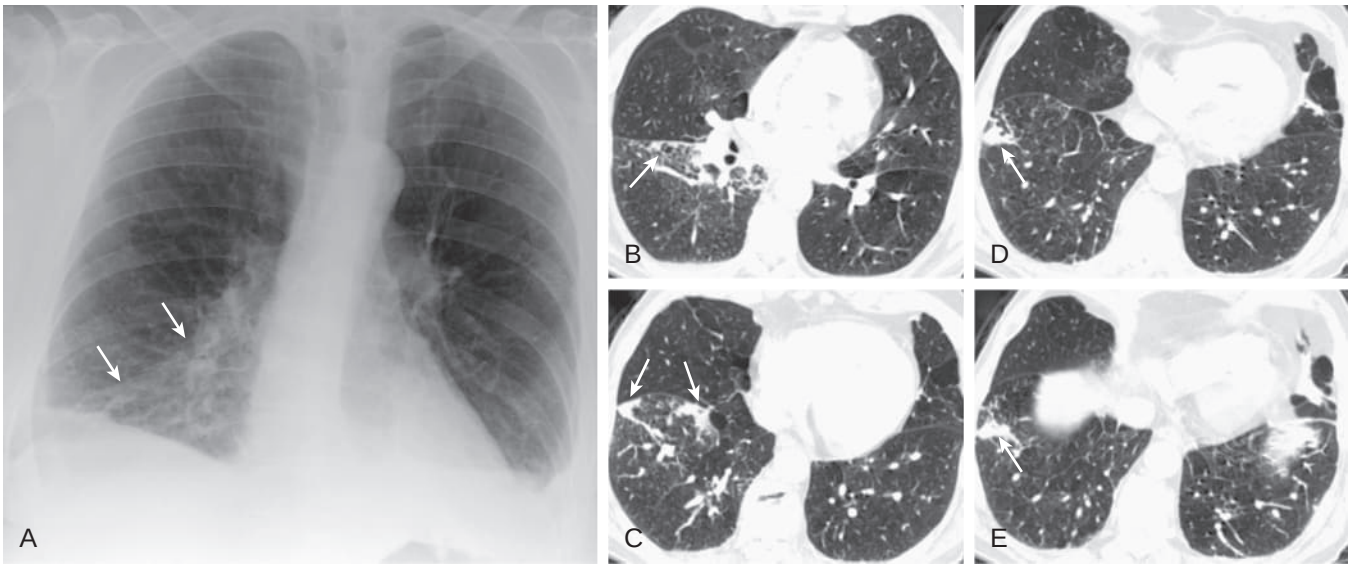
eFigure 46.19 Methicillin-resistant *Staphylococcus aureus* pneumonia. (A) Frontal chest radiograph in a patient subsequently proven to have methicillin-resistant *Staphylococcus aureus* pneumonia shows left lung consolidation (*arrows*) with internal lucency consistent with necrosis and cavitation. (B) Axial chest computed tomography displayed in lung windows shows left lower lobe consolidation with internal lucency (*arrows*) consistent with a necrotic pneumonia. The patient recovered following antibiotic therapy. (Courtesy Michael B. Gotway, MD.)



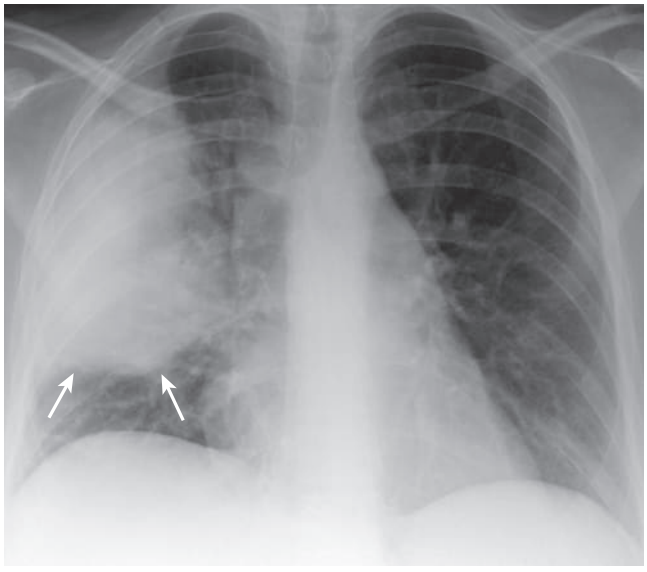
eFigure 46.20 Chest radiograph shows hematogenous staphylococcal pneumonia associated with bacterial endocarditis. The pneumonia is characterized by many cavities.



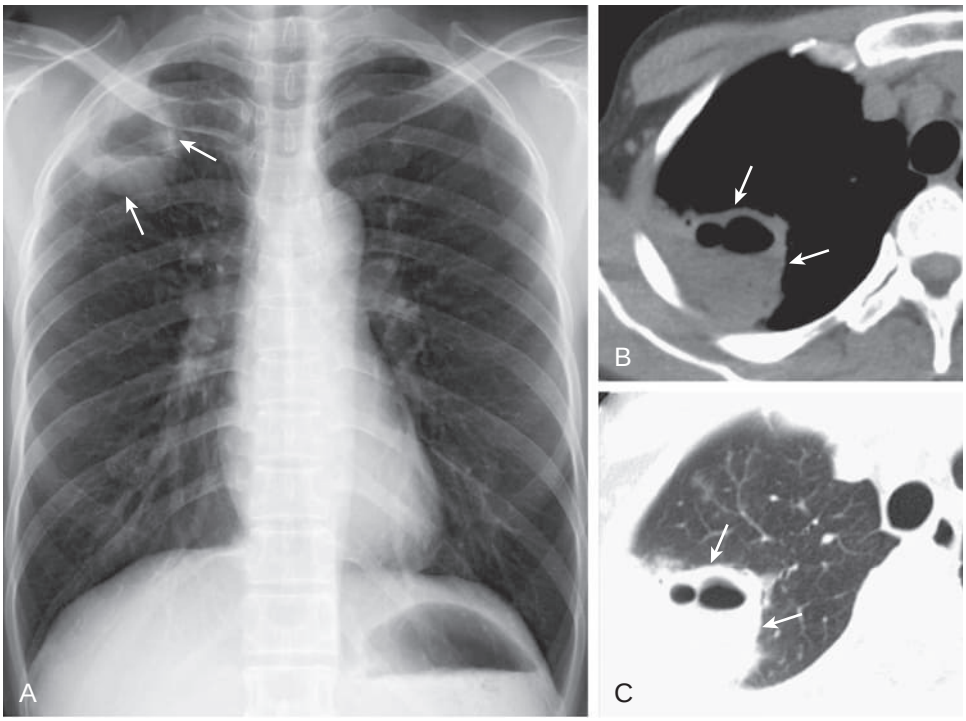
eFigure 46.21 *Staphylococcus*. Gram stain of sputum from a patient with staphylococcal pneumonia shows abundant large, round gram-positive cocci in clusters.



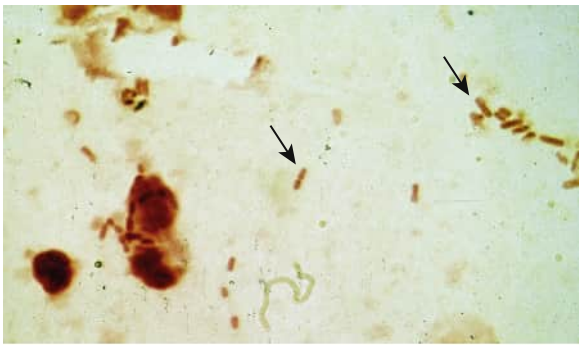
eFigure 46.22 *Klebsiella pneumoniae* bronchopneumonia. (A) Frontal chest radiograph shows patchy right lower lobe opacity (*arrows*). (B–E) Axial chest computed tomography through the lower lobes displayed in lung windows shows patchy nodular opacities (*arrows*) consistent with bronchopneumonia but not specific for a microbial etiology. (Courtesy Michael B. Gotway, MD.)



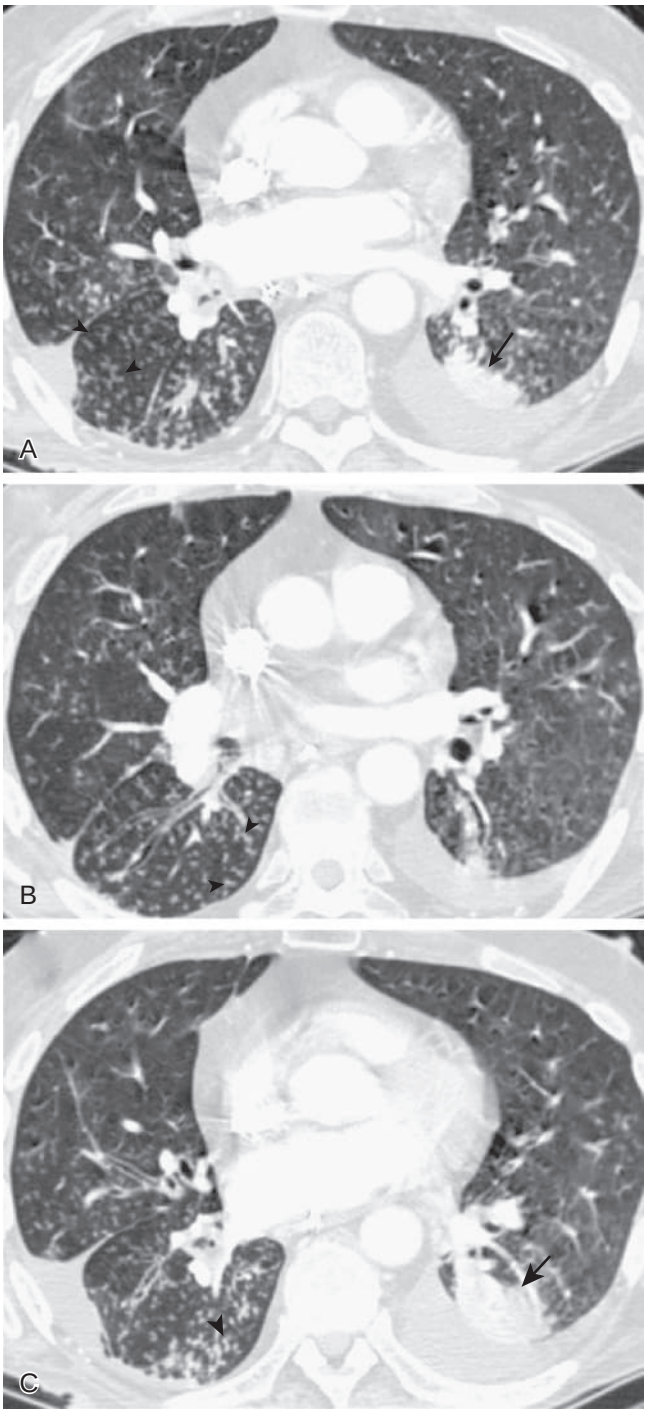
eFigure 46.23 *Klebsiella pneumoniae* lobar pneumonia with bulging fissure. Frontal chest radiograph shows dense right upper lobe air space opacity, which bows the right minor fissure inferiorly (*arrows*). The bulging fissure sign at chest radiography is traditionally associated with *K. pneumoniae* infection but is actually nonspecific and can be seen with other pulmonary infectious and noninfectious pulmonary processes as well. (Courtesy Michael B. Gotway, MD.)



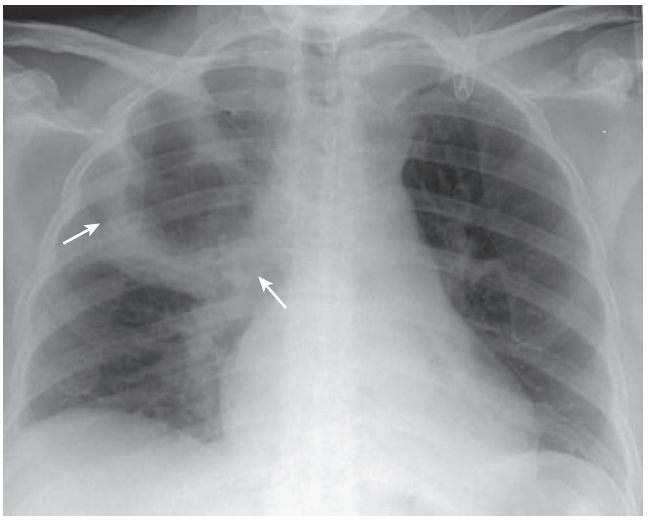
eFigure 46.24 *Klebsiella pneumoniae* lung abscess. (A) Frontal chest radiograph shows a subpleural right apical cavity (*arrows*) with an air-fluid level consistent with a pulmonary abscess. Axial chest computed tomography displayed in soft tissue (B) and lung (C) windows shows a nonspecific cavity (*arrows*) consistent with a pulmonary abscess but not specific for a specific microbiologic etiology. (Courtesy Michael B. Gotway, MD.)



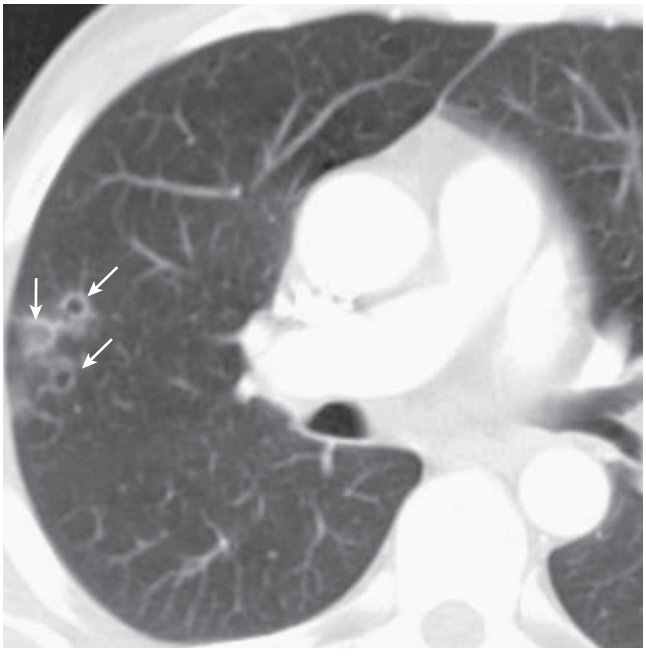
eFigure 46.25 *Klebsiella pneumoniae.* Large gram-negative rods in the sputum of a patient with *K. pneumoniae* pneumonia (*arrows*).



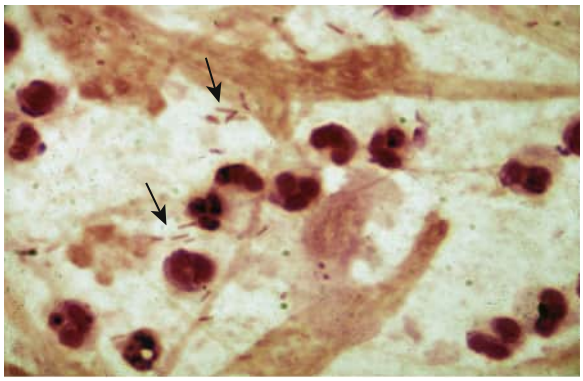
eFigure 46.26 *Pseudomonas aeruginosa* bronchopneumonia. (A–C) Axial chest computed tomography through the lower lobes displayed in lung windows shows nodular consolidation (A and C, *arrows*) and numerous small centrilobular nodules with branching morphologies consistent with tree-in-bud opacities (*arrowheads*). (Courtesy Michael B. Gotway, MD.)



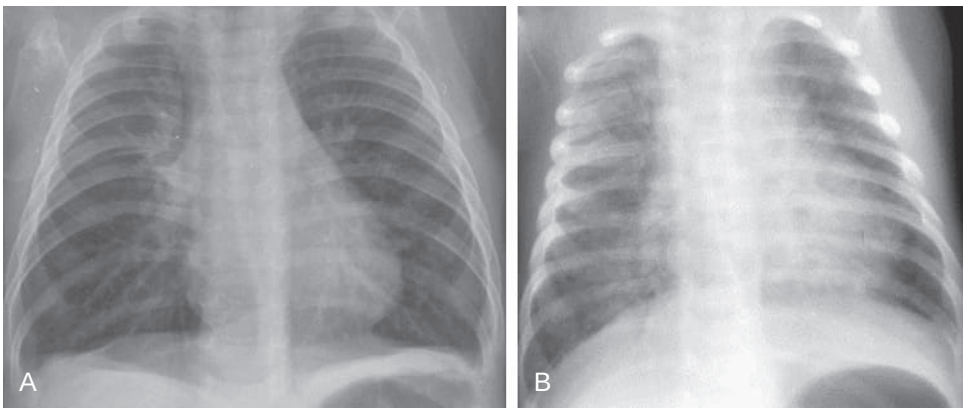
eFigure 46.27 *Pseudomonas aeruginosa* cavitary pneumonia. Frontal chest radiograph in a patient with *P. aeruginosa* pneumonia shows a large right upper lobe thick-walled cavity (*arrows*). (Courtesy Michael B. Gotway, MD.)



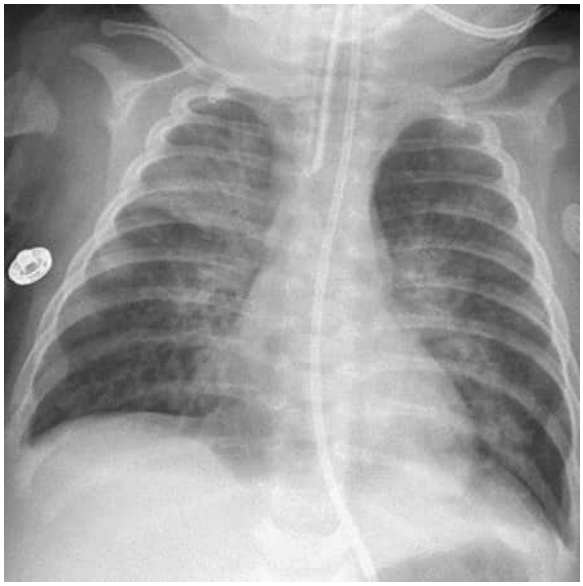
eFigure 46.28 *Pseudomonas aeruginosa* cavitary pneumonia. Axial chest computed tomography displayed in lung windows of a patient with *P. aeruginosa* pneumonia shows several small, relatively thin-walled peripheral right upper lobe cavities (*arrows*). (Courtesy Michael B. Gotway, MD.)



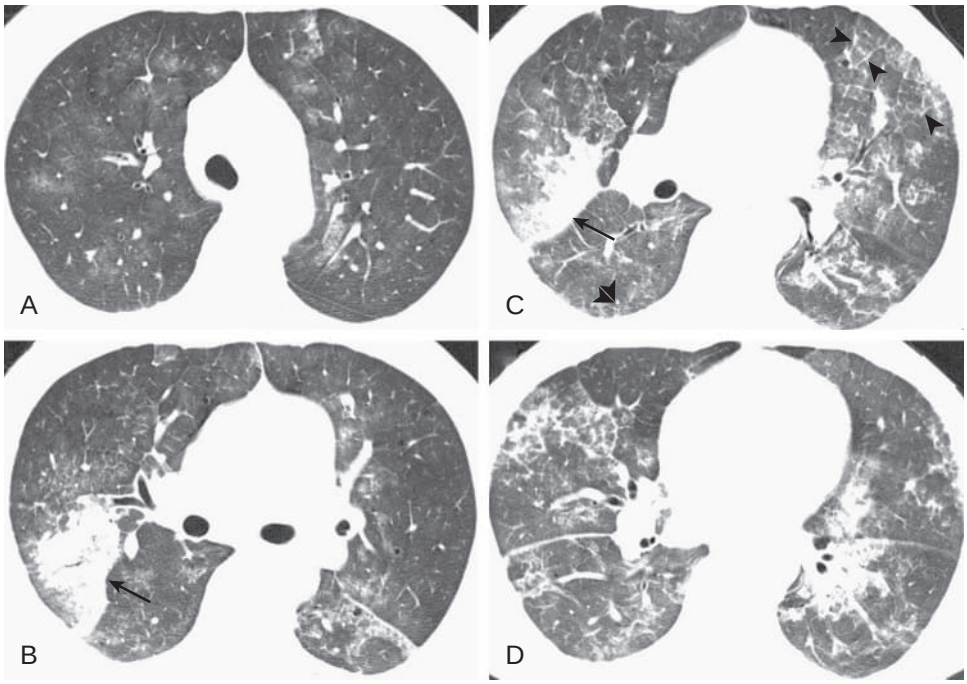
eFigure 46.29 *Pseudomonas*. Gram stain of sputum showing slender gram-negative bacilli (*arrows*).



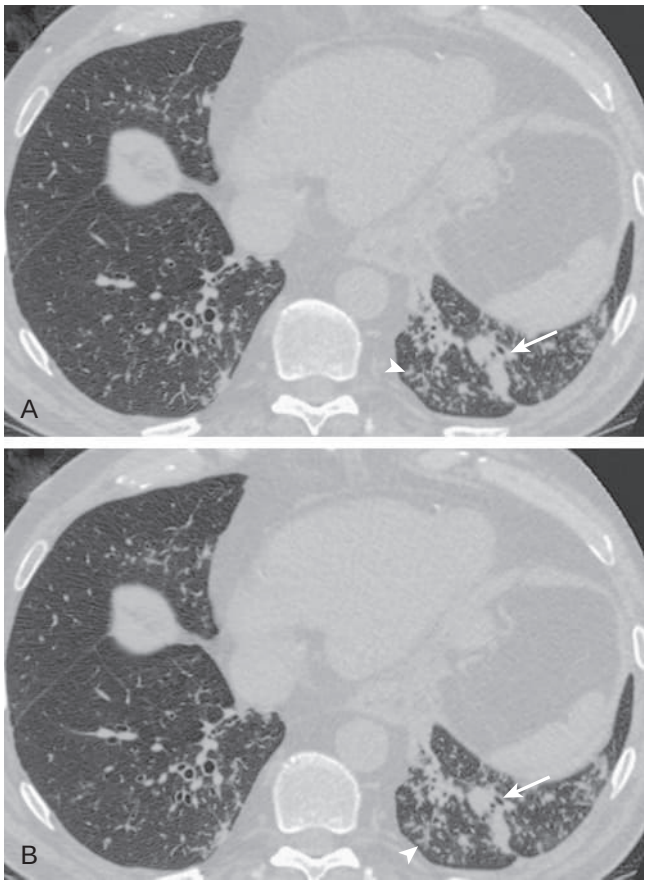
eFigure 46.30 *Respiratory syncytial virus* (RSV) bronchiolitis and pneumonia: chest radiographic findings. (A) Frontal chest radiograph in a young child with RSV bronchiolitis shows bilateral basal streaky opacities associated with significant diaphragmatic flattening bilaterally, consistent with air trapping due to small airway inflammation and obstruction. (B) Frontal chest radiograph in an infant with RSV pneumonia shows patchy, somewhat perihilar-predominant bronchovascular thickening. The right diaphragm is somewhat flattened, suggesting basal air trapping. (Courtesy Michael B. Gotway, MD.)



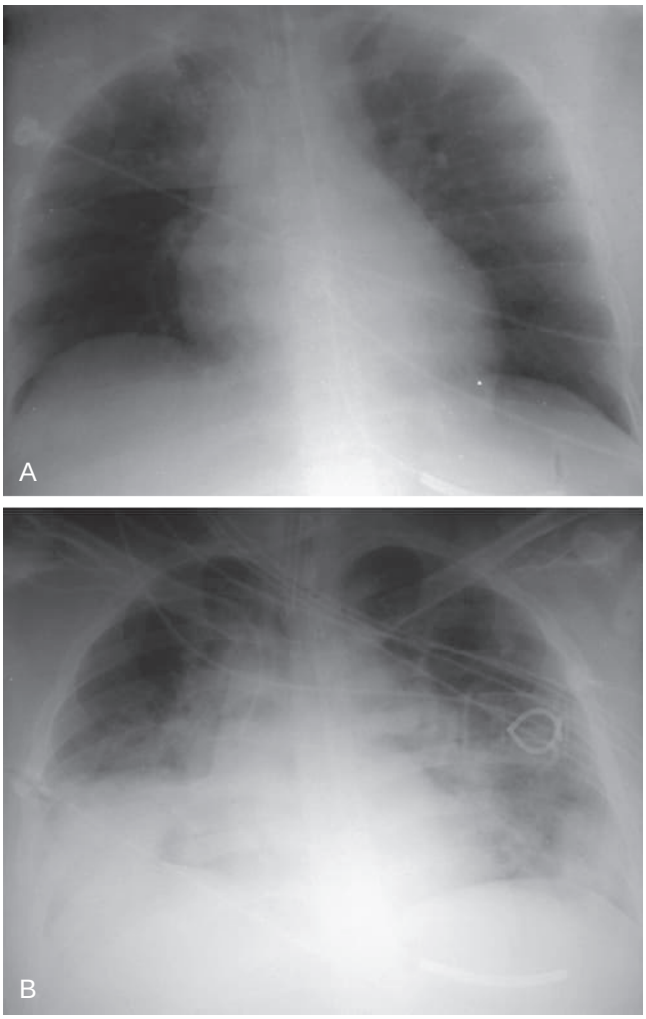
eFigure 46.31 Respiratory syncytial virus pneumonia. Frontal chest radiograph in an intubated infant shows bilateral peribronchial interstitial thickening and right upper and left lower lobe consolidation; the right upper lobe opacity is associated with mild volume loss. (Courtesy Michael B. Gotway, MD.)



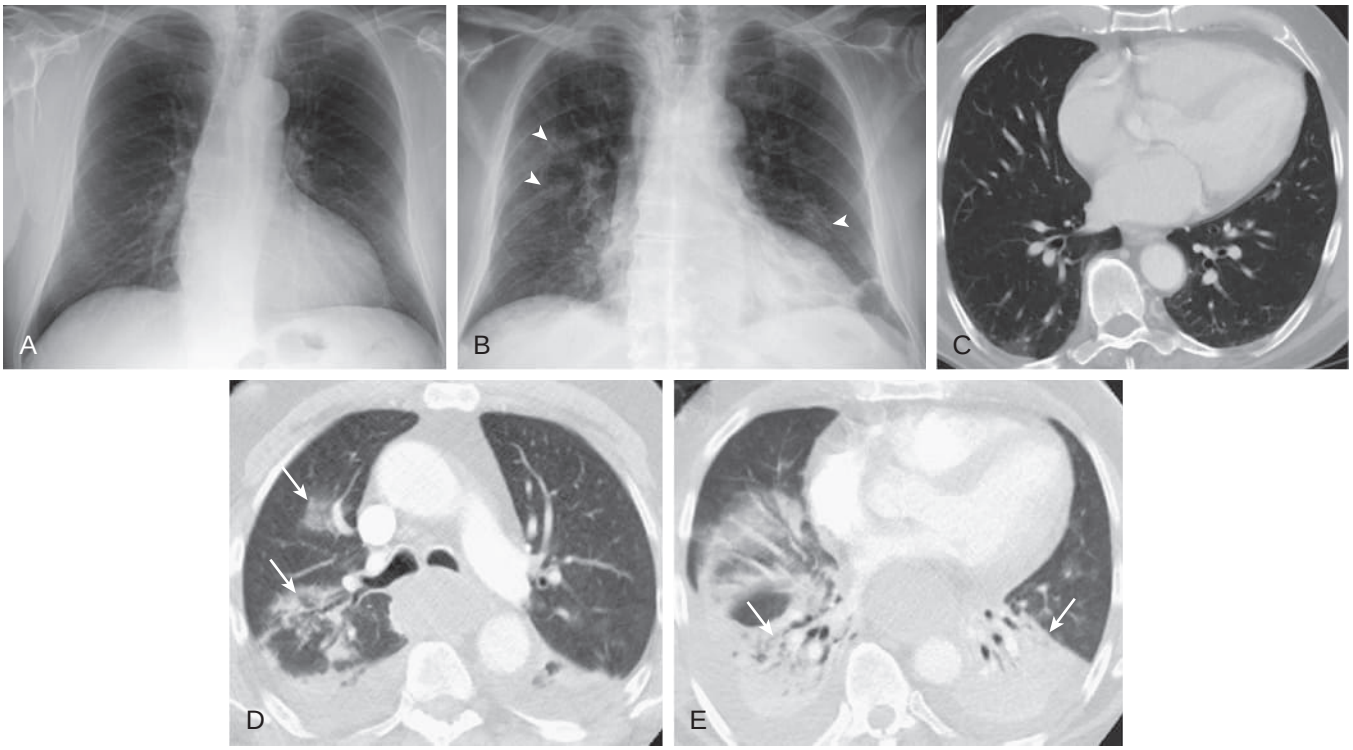
eFigure 46.32 Respiratory syncytial virus pneumonia. (A–D) Axial chest computed tomography displayed in lung windows shows multifocal, bilateral patchy areas of ground-glass opacity associated with more focal right upper lobe posterior segmental consolidation (*arrows*). In some areas the ground-glass opacity is associated with intralobular interstitial thickening and interlobular septal thickening (*arrowheads*). Small solid nodules (C, *double arrowheads*) are also present. (Courtesy Michael B. Gotway, MD.)



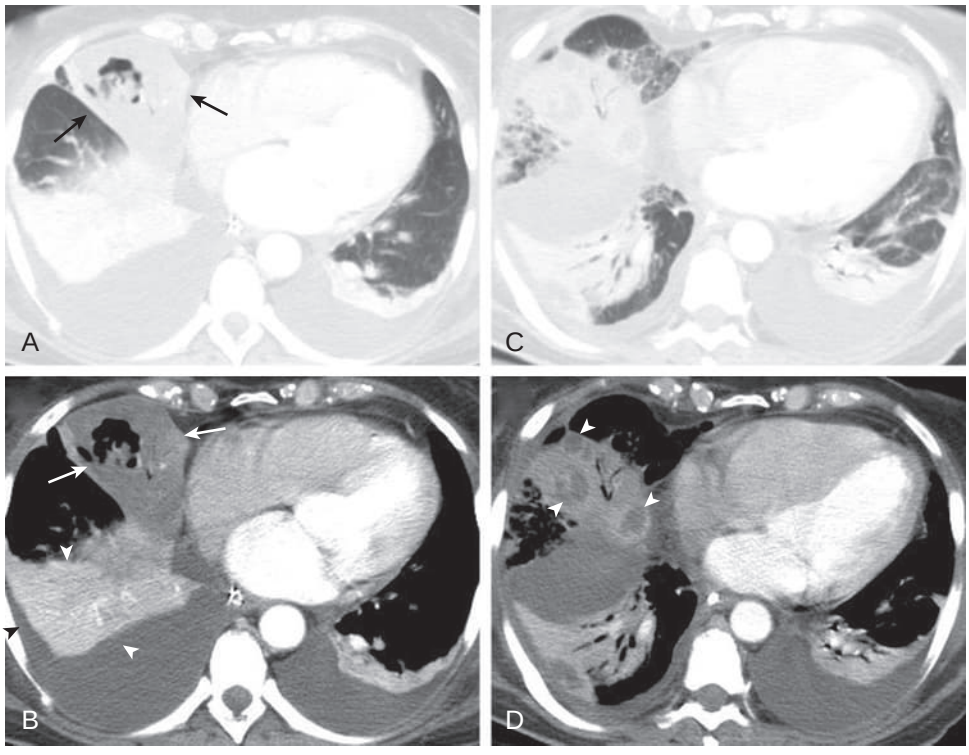
eFigure 46.33 Aspiration pneumonia: bronchopneumonia/bronchiolitis appearance at chest *computed tomography* (CT). (A–B) Axial chest CT through the lower lobes displayed in lung windows in a patient with swallowing dysfunction shows numerous small centrilobular nodules, some with branching morphologies (*arrowheads*), and peribronchial consolidation (*arrows*). The imaging appearance is consistent with bronchopneumonia but not specific for aspiration. Note resemblance of this CT appearance with *Pseudomonas aeruginosa* pneumonia (see eFig. 46.26), *Haemophilus influenzae* pneumonia (see eFig. 46.14B), and pneumococcal bronchopneumonia (see eFig. 46.7). (Courtesy Michael B. Gotway, MD.)



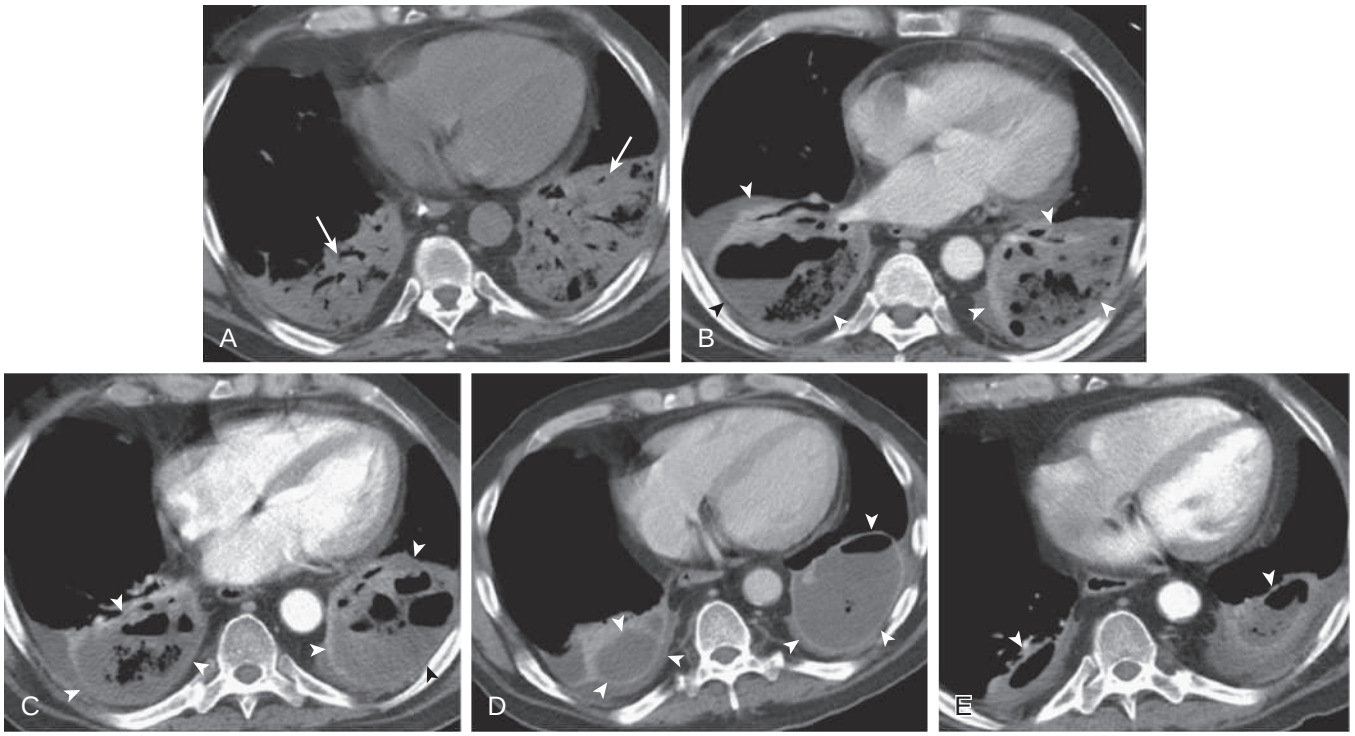
eFigure 46.34 Aspiration pneumonitis: rapid interval development of pulmonary opacities. (A) Frontal chest radiograph performed for central venous catheter placement shows a right subclavian central venous catheter without pneumothorax; the lungs are clear. (B) Repeat frontal chest radiograph obtained following an episode of altered level of consciousness and vomiting only a few hours after A shows interval development of extensive mid and lower lung consolidation. Such rapid development of extensive pulmonary opacities in the context of mental status changes accompanied by vomiting is characteristic of aspiration. The differential diagnosis of rapid interval appearance of extensive pulmonary opacities also includes increased pressure edema, noncardiac edema injury, and hemorrhage. (Courtesy Michael B. Gotway, MD.)



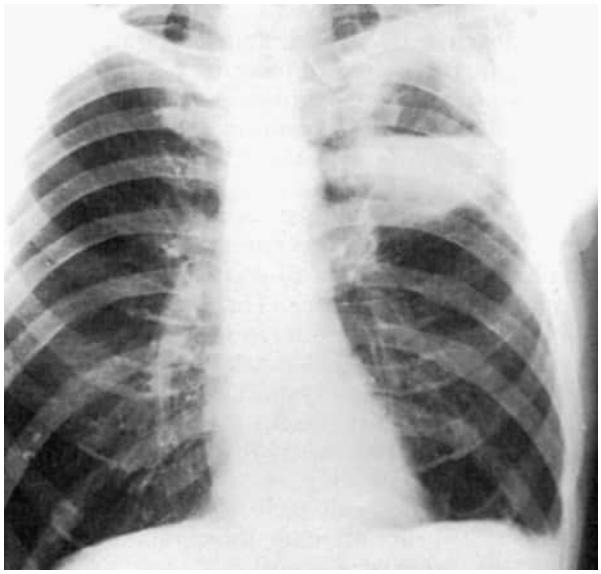
eFigure 46.35 Aspiration bronchopneumonia: rapid appearance of new lung opacity at imaging and dependent lung involvement. (A) Frontal chest radiograph performed at admission shows clear lung. (B) Several days later, following a witnessed aspiration event, the radiograph shows development of multifocal peribronchial nodular foci (*arrowheads*). (C) Lower thoracic images from an abdominal computed tomography scan several weeks before A and B shows only minimal basal atelectasis. (D–E) Axial chest computed tomography through the lower lobes performed immediately following B shows peribronchial consolidation (D, *arrows*) and extensive lower lobe, dependent consolidation (E, *arrows*). Note volume loss, evidenced by posterior displacement of the major fissures. (Courtesy Michael B. Gotway, MD.)



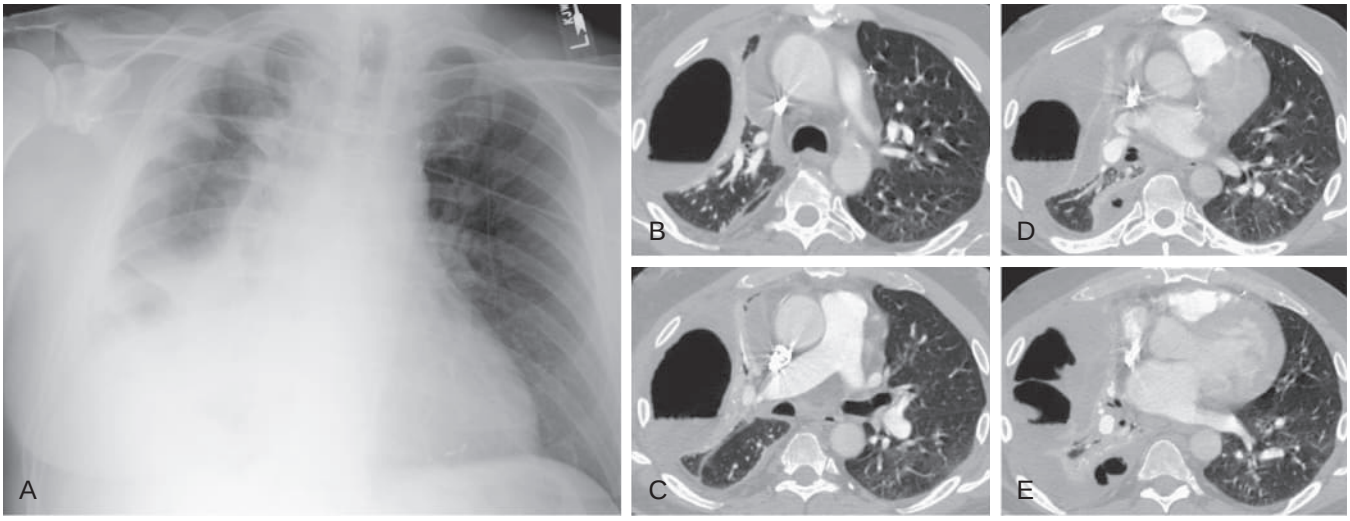
eFigure 46.36 Anaerobic pneumonia. (A–D) Axial chest computed tomography in a patient with polymicrobial anaerobic pneumonia shows multifocal consolidation in the right middle lobe (A–B, *arrows*) and bilateral lower lobes. The soft tissue window images show the right middle lobe consolidation to be hypovascular; compare attenuation characteristics of the right middle lobe opacity (*arrows*, B) with the appearance of the lower lobe consolidation (*arrowheads,* B). After several days, the poorly defined hypovascular right middle lobe consolidation (B, *arrows*) evolved into discrete abscesses (D, *arrowheads*). (Courtesy Michael B. Gotway, MD.)



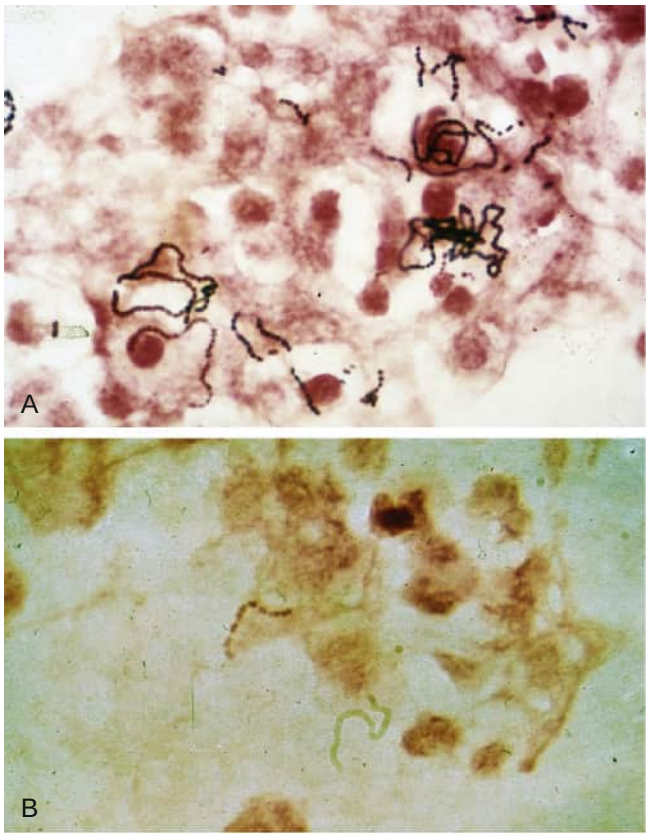
eFigure 46.37 Evolution of pulmonary aspiration into lung abscess. (A) Axial chest *computed tomography* (CT) displayed in soft tissue windows performed shortly following a witnessed aspiration event shows extensive bilateral lower lobe consolidation (*arrows*). (B) Contrast-enhanced chest CT performed several days following A shows developing necrosis and cavitation (*arrowheads*) within the lower lobe consolidation. (C–D) Repeat contrast-enhanced chest CT performed over the ensuing week following A and B shows maturation of frank bilateral lower lobe pulmonary abscesses (*arrowheads*); note well-defined, enhancing walls surrounding these gas and fluid collections. (E) Axial enhanced chest CT following 3 weeks of antibiotic therapy shows partial resolution of the bilateral lower lobe pulmonary abscesses (*arrowheads*). (Courtesy Michael B. Gotway, MD.)



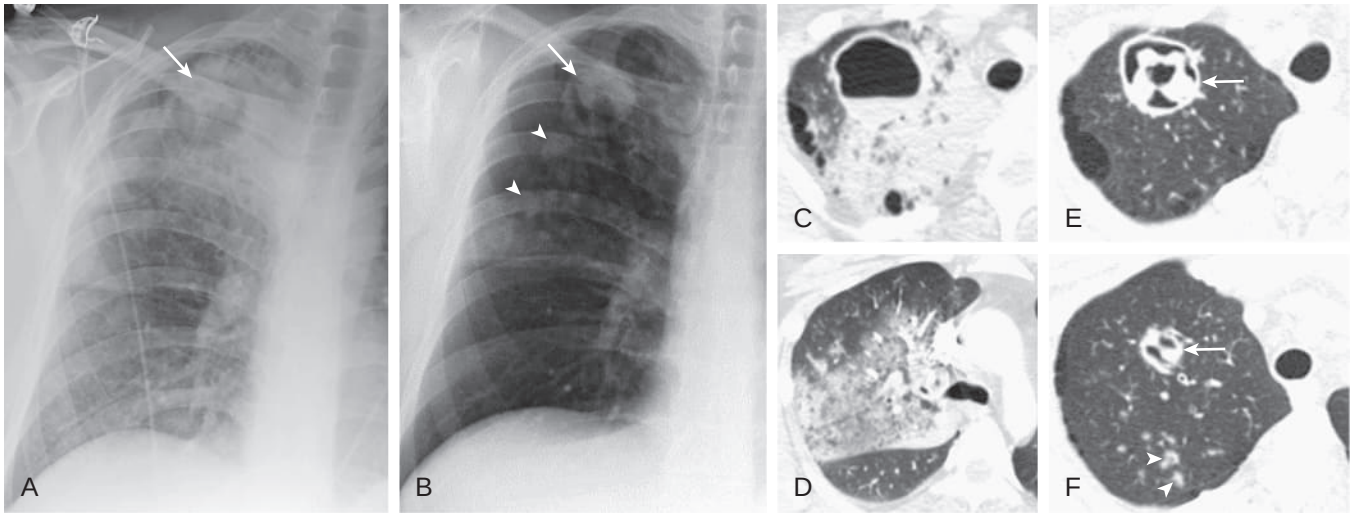
eFigure 46.38 A single parenchymal cavity with an air-fluid level typifies an anaerobic lung abscess. Most often, these lesions are located in the dependent, aspiration-prone lung segments (superior segment of the right lower lobe and left lower lobe and posterior segments of the upper lobes). This patient also has a small left empyema.



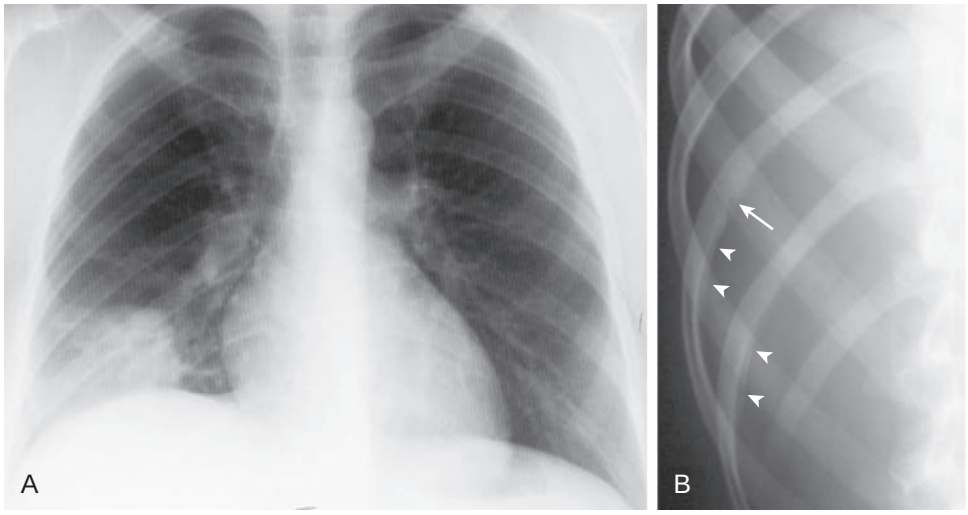
eFigure 46.39 *Streptococcus intermedius* pneumonia and empyema. (A) Frontal chest radiograph shows right lung consolidation and volume loss. Some increased opacity adjacent to the chest wall suggests pleural disease but the findings are nonspecific. (B–E) Axial chest computed tomography displayed in an intermediate window to highlight the lung parenchyma and soft tissue features simultaneously, obtained shortly after A, shows a rounded gas collection containing fluid along the right chest wall consistent with empyema and bronchopleural fistula. *S. intermedius* was recovered following right thoracostomy tube placement. (Courtesy Michael B. Gotway, MD.)



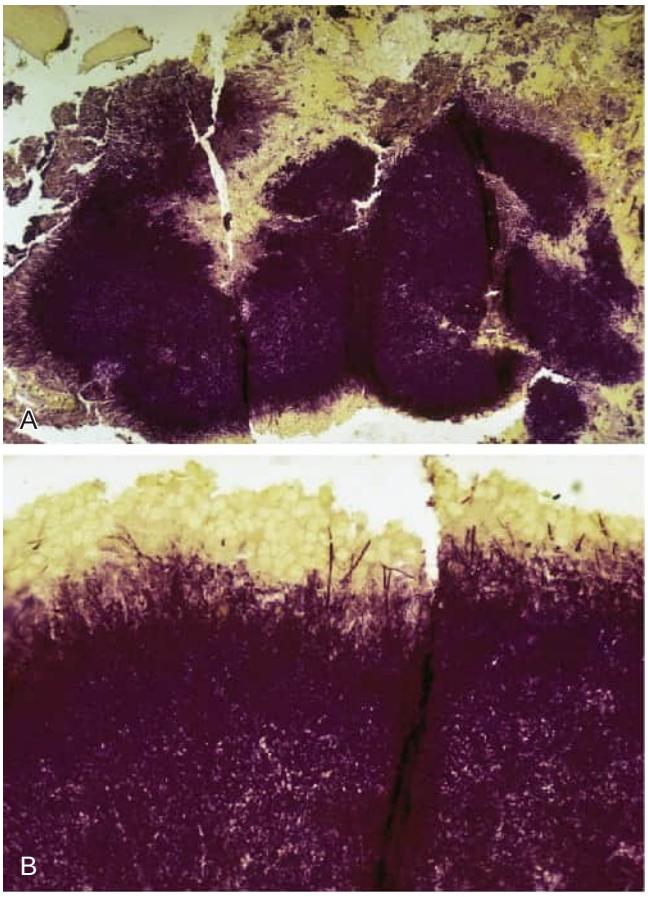
eFigure 46.40 Streptococcus. (A) Group A streptococcus (*Streptococcus pyogenes,* β-hemolytic streptococcus). (B) Group B streptococcus *(S. agalactiae)* are indistinguishable from *S. pneumoniae* on Gram stain. Both form long chains containing multiple bacteria.



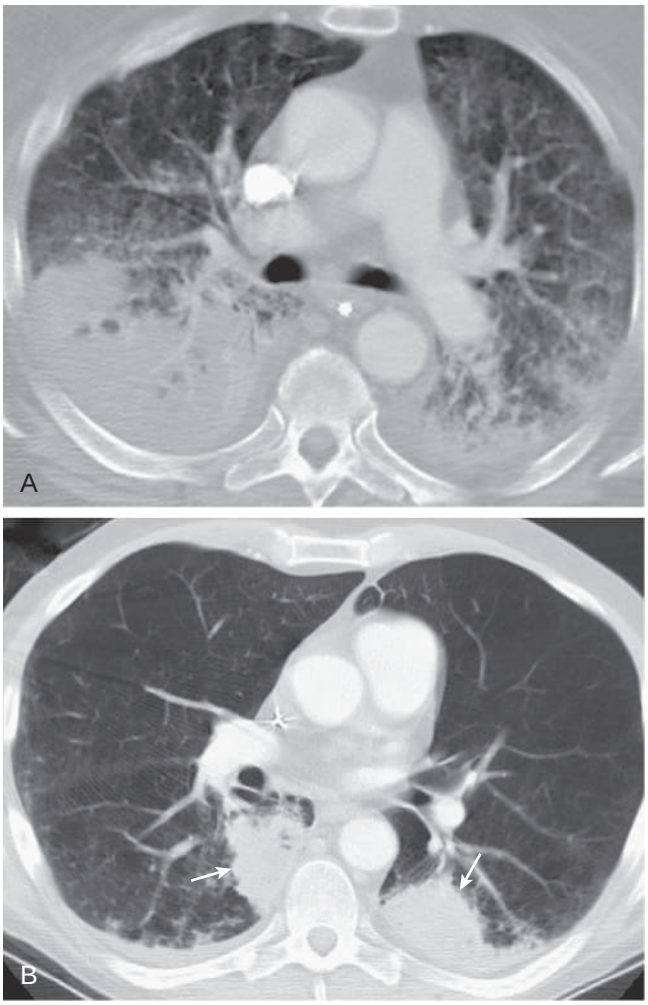
eFigure 46.41 Actinomycosis: cavitary nodule. (A) Frontal chest radiograph shows right upper lobe consolidation and a poorly defined nodular opacity (*arrow*). (B) Frontal chest radiograph 2 weeks following A shows resolution of the right upper lobe consolidation, now exposing a dominant cavitary right apical nodule with internal opacity (*arrow*), and small surrounding nodules (*arrowheads*). (C–D) Axial chest computed tomography displayed in lung windows performed within 1 day of the presenting chest radiograph (A) shows the right apical opacity as a cavitary nodule with an internal air-fluid level; surrounding ground-glass opacity and consolidation are present, as seen on the chest radiograph (A). (E–F) Chest computed tomography displayed in lung windows performed the same day as B shows the dominant right apical opacity with complex internal architecture (*arrows*) and confirms small surrounding nodules (*arrowheads*). Biopsy of this lesion recovered *Actinomyces israelii*. (Courtesy Michael B. Gotway, MD.)



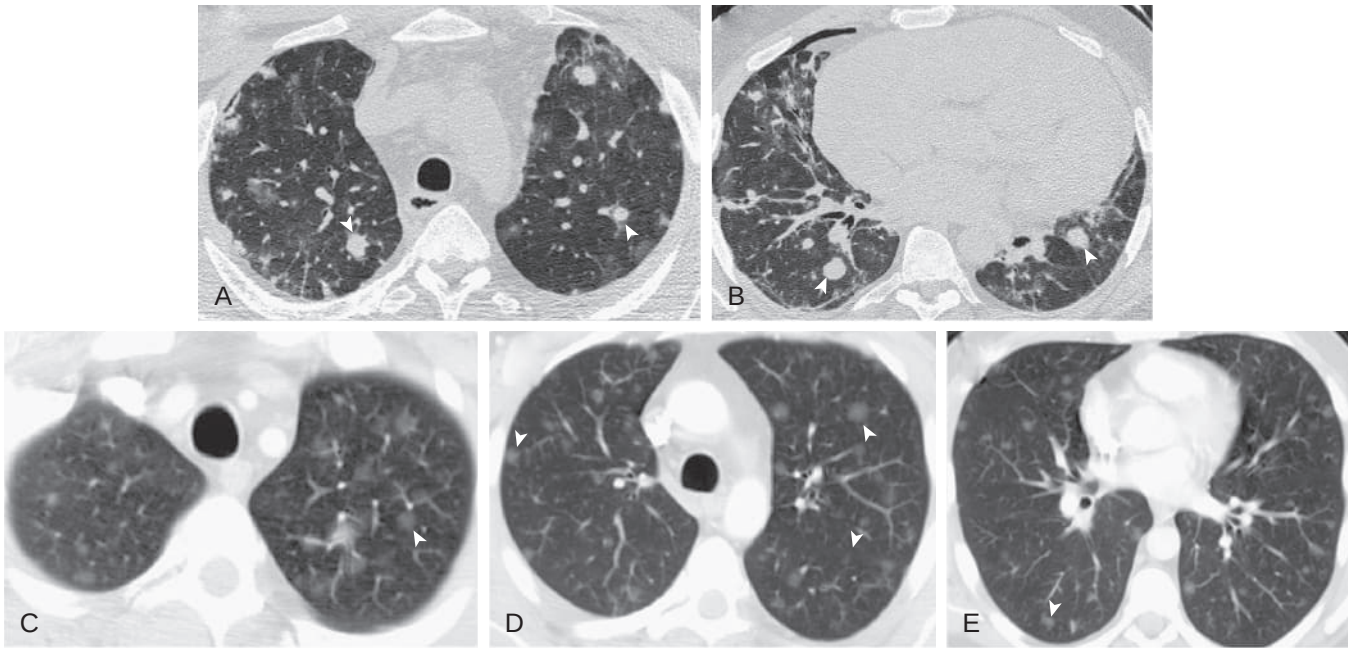
eFigure 46.42 Actinomycosis: chest wall involvement. (A) Frontal chest radiograph shows a right lower lung mass. This finding is nonspecific. (B) Rib detail radiograph shows subtle periosteal reaction (*arrowheads*) with erosion of the inferior rib cortex (*arrow*) consistent with chest wall invasion. Biopsy of the right lung mass recovered *Actinomyces israelii*. (Courtesy Michael B. Gotway, MD.)



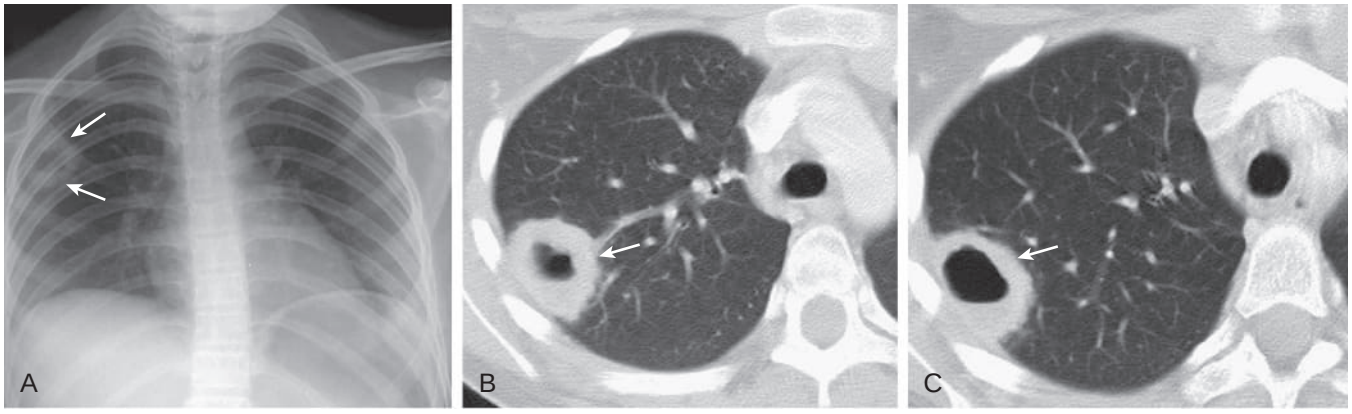
eFigure 46.43 Gram stain of an actinomycotic sulfur granule. (A) Original magnification ×100. (B) Original magnification ×400.



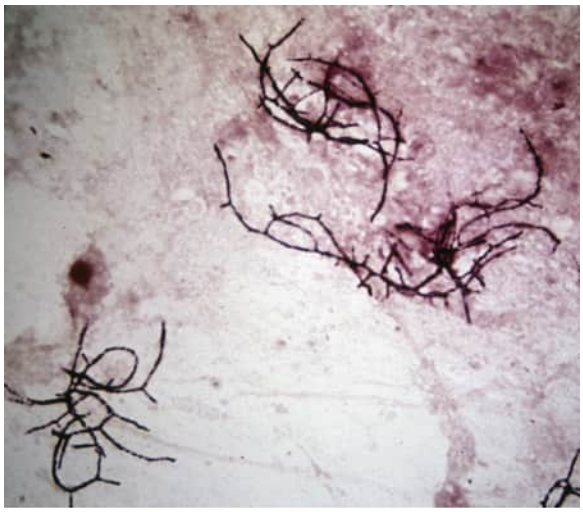
eFigure 46.44 *Nocardia asteroides* pulmonary infection: consolidation. (A) Axial chest computed tomography shows extensive bilateral lower lobe consolidation and more anteriorly located interstitial thickening and ground-glass opacity. The right lower lobe consolidation was cavitary at a more inferior level. (B) Axial chest computed tomography in a different patient shows bilateral lower lobe masslike opacities (*arrows*); biopsy of the left lower lobe lesion recovered *Nocardia asteroides*. (Courtesy Michael B. Gotway, MD.)



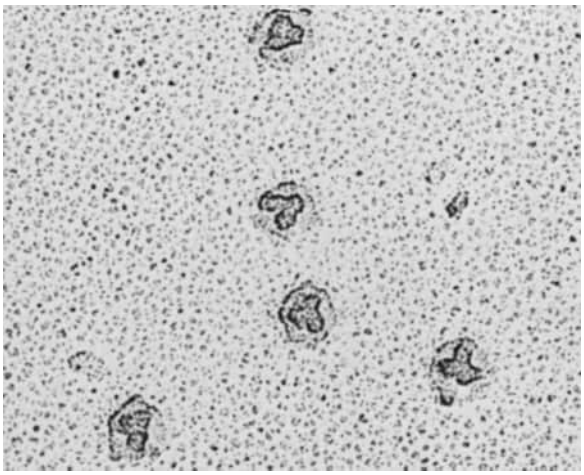
eFigure 46.45 *Nocardia asteroides* pulmonary infection: multiple nodules. (A–B) Axial chest *computed tomography* (CT) in an immunosuppressed renal transplant recipient shows multiple bilateral nodules, many of which are solid-appearing (*arrowheads*), due to *N. asteroides.* (C–E) Axial chest CT in another immunosuppressed renal transplant recipient shows ground-glass opacity nodules (*arrowheads*), also shown to be due to *N. asteroides.* (Courtesy Michael B. Gotway, MD.)



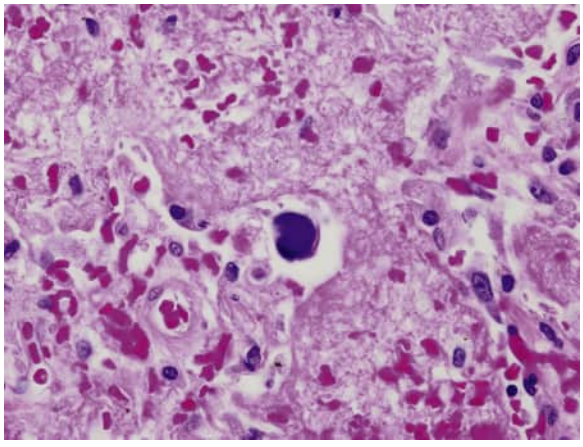
eFigure 46.46 *Nocardia asteroides* pulmonary infection: abscess. (A) Frontal chest radiograph shows a poorly defined opacity (*arrows*) in the subpleural right upper lobe. (B–C) Axial chest computed tomography displayed in lung windows shows a subpleural right upper lobe cavity (*arrows*) containing an air-fluid level. This lesion is nonspecific in appearance and could be the result of a number of infections, but *N. asteroides* was recovered at biopsy. (Courtesy Michael B. Gotway, MD.)



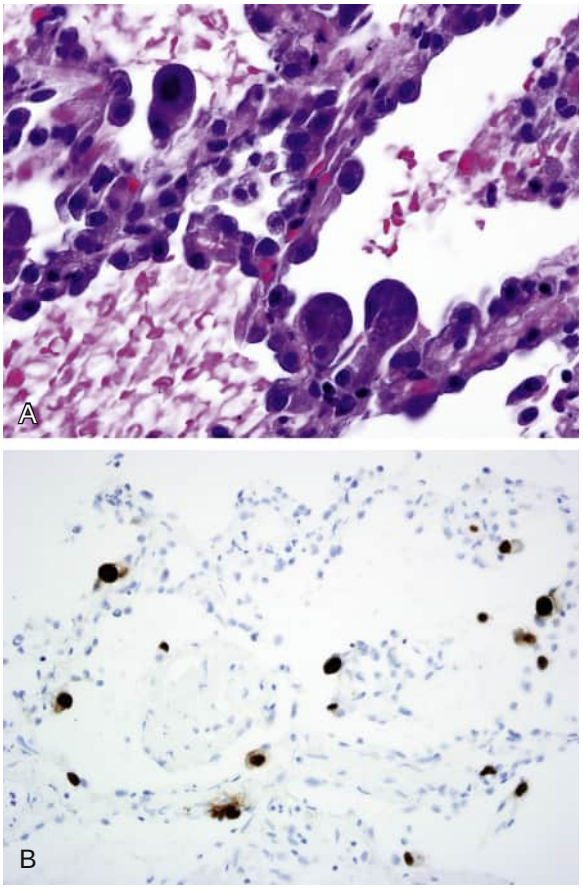
eFigure 46.47 Modified acid-fast stain of sputum containing *Nocardia asteroides* shows filamentous branching organisms.



eFigure 46.48 Photoelectron micrograph showing human adenovirus type 2. Each virion contains a lobulated group of three adenosomes, which are composed of DNA and protein. Full virion particles contain a total of 12 adenosomes, each of which is found below one vertex of the icosahedral capsid. (Courtesy J. Brown and W. Newcomb, University of Virginia.)



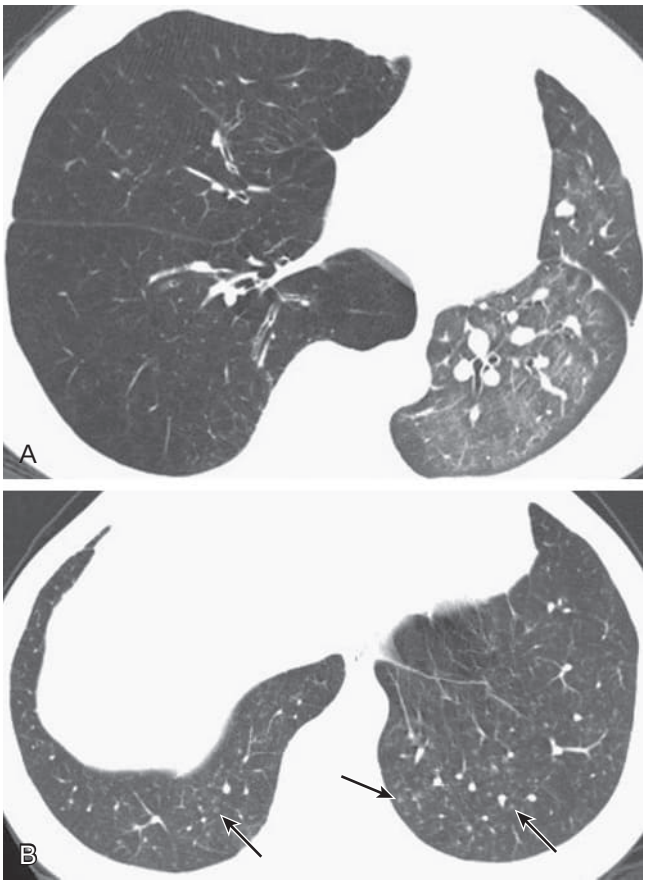
eFigure 46.49 Adenovirus causing necrotizing pneumonia. Focal necrosis is apparent; the prominent cell in the center of the field is an adenovirus-infected smudge cell, with an enlarged nucleus with basophilic inclusions surrounded by a thin rim of cytoplasm (Hematoxylin and eosin, ×80 original magnification.) (Courtesy William D. Travis, MD, Memorial Sloan Kettering Cancer Center, New York, NY.)



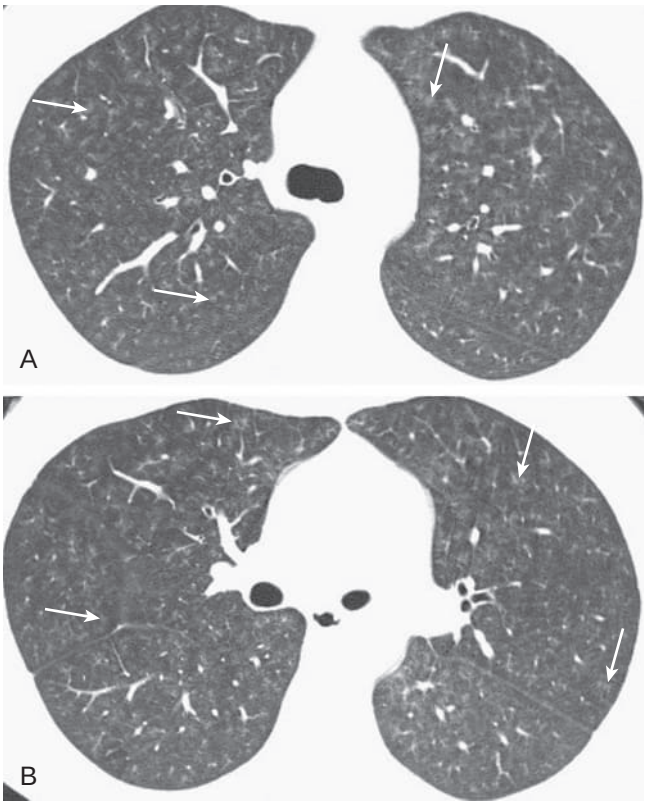
eFigure 46.50 *Cytomegalovirus* (CMV) infection. (A) CMV pneumonitis with mild alveolar wall thickening and hyperplastic type II pneumocytes, some of which are infected, showing cytomegaly, nucleomegaly, thickened basophilic nuclear membranes and nuclear inclusion, and small basophilic cytoplasmic inclusions (hematoxylin and eosin, ×80 original magnification). (B) CMV pneumonitis with infected cells highlighted by immunohistochemistry with a brown color (CMV immunohistochemistry, ×40 original magnification.) (Courtesy William D. Travis, MD, Memorial Sloan Kettering Cancer Center, New York, NY.)



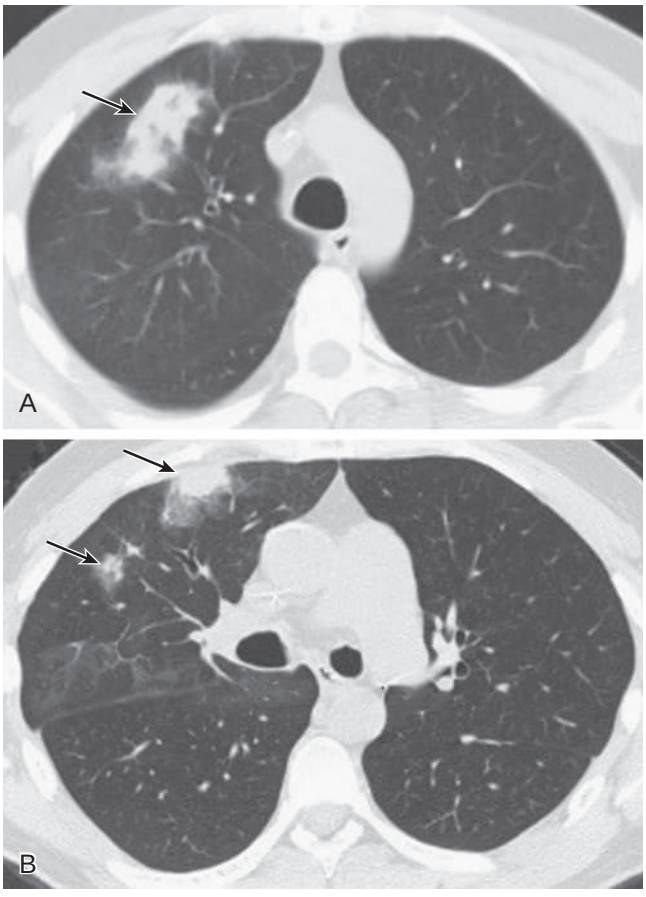
eFigure 46.51 Cytomegalovirus infection in a stem cell transplant recipient. (A) Frontal chest radiograph shows extensive, bilateral poorly defined nodular consolidation without pleural effusion. Axial chest computed tomography through the mid (B) and lower (C) lungs shows extensive ground-glass opacity and consolidation with small, solid, centrilobular nodules (*arrows*). (Courtesy Michael B. Gotway, MD.)



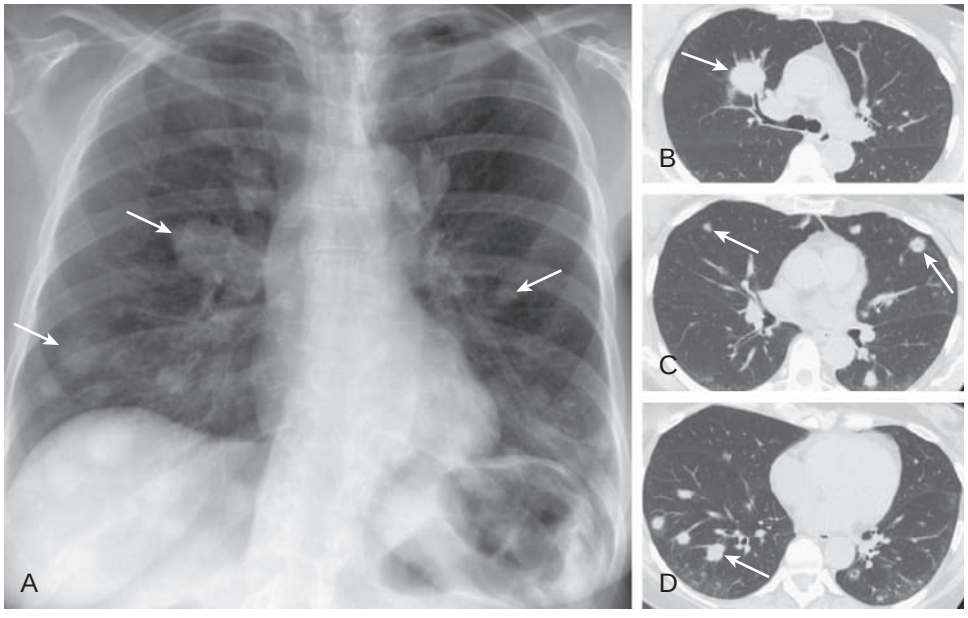
eFigure 46.52 Cytomegalovirus infection in a lung transplant recipient: variable chest computed tomography appearances. (A–B) Axial chest computed tomography through the lower lungs in two lung transplant recipients shows patchy left lower lobe ground-glass opacity in one patient with proven cytomegalovirus infection (A) and small nodules (*arrows*), also proven to represent cytomegalovirus infection, in a different patient (B). (Courtesy Michael B. Gotway, MD.)



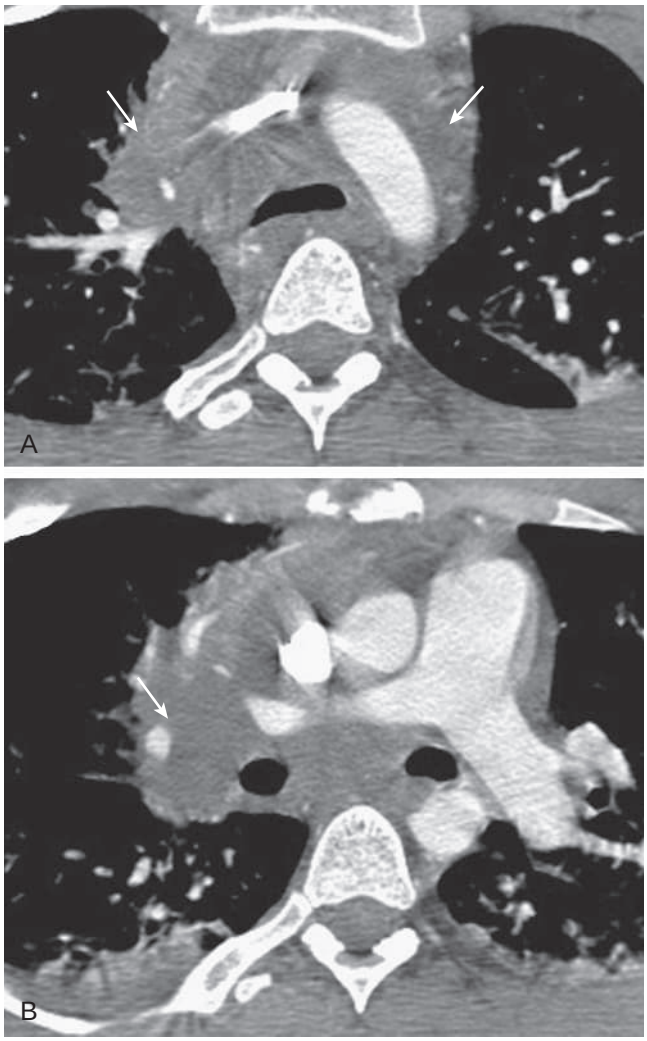
eFigure 46.53 Cytomegalovirus infection in a renal transplant recipient. Axial chest computed tomography through the upper (A) and mid (B) lungs shows diffuse, bilateral, poorly defined centrilobular nodules (*arrows*) shown to represent cytomegalovirus infection. The appearance resembles hypersensitivity pneumonitis. (Courtesy Michael B. Gotway, MD.)



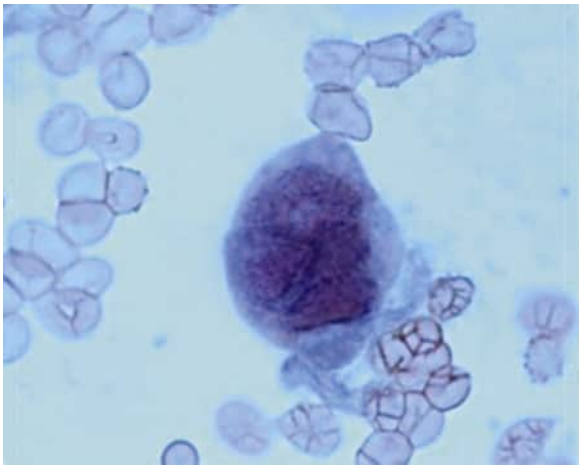
eFigure 46.54 Cytomegalovirus infection in a lung transplant recipient. (A–B) Axial chest computed tomography through the upper (A) and mid (B) lungs shows nodular opacities (*arrows*) with peripheral ground-glass opacity halos, suggesting the possibility of invasive fungal infection. Tissue sampling, however, established the presence of cytomegalovirus infection. (Courtesy Michael B. Gotway, MD.)



eFigure 46.55 Posttransplant lymphoproliferative disease in a renal transplant recipient. (A) Frontal chest radiograph shows multiple, bilateral pulmonary nodules (*arrows*). (B–D) Axial chest CT performed through the upper (B), mid (C), and lower (D) lungs, displayed in lung windows, shows multiple nodules (*arrows*), many associated with bronchi. Tissue sampling established the diagnosis of posttransplant lymphoproliferative disorder. (Courtesy Michael B. Gotway, MD.)



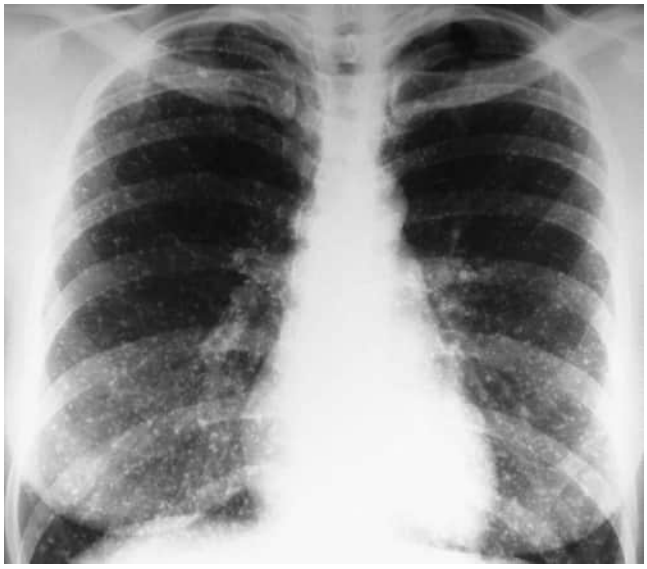
eFigure 46.56 Posttransplant lymphoproliferative disease in an allogenic stem cell recipient. (A–B) Axial enhanced chest computed tomography through the upper (A) and mid (B) lungs shows extensive mediastinal and hilar lymphadenopathy (*arrows*), proved to represent posttransplant lymphoproliferative disorder. (Courtesy Michael B. Gotway, MD.)



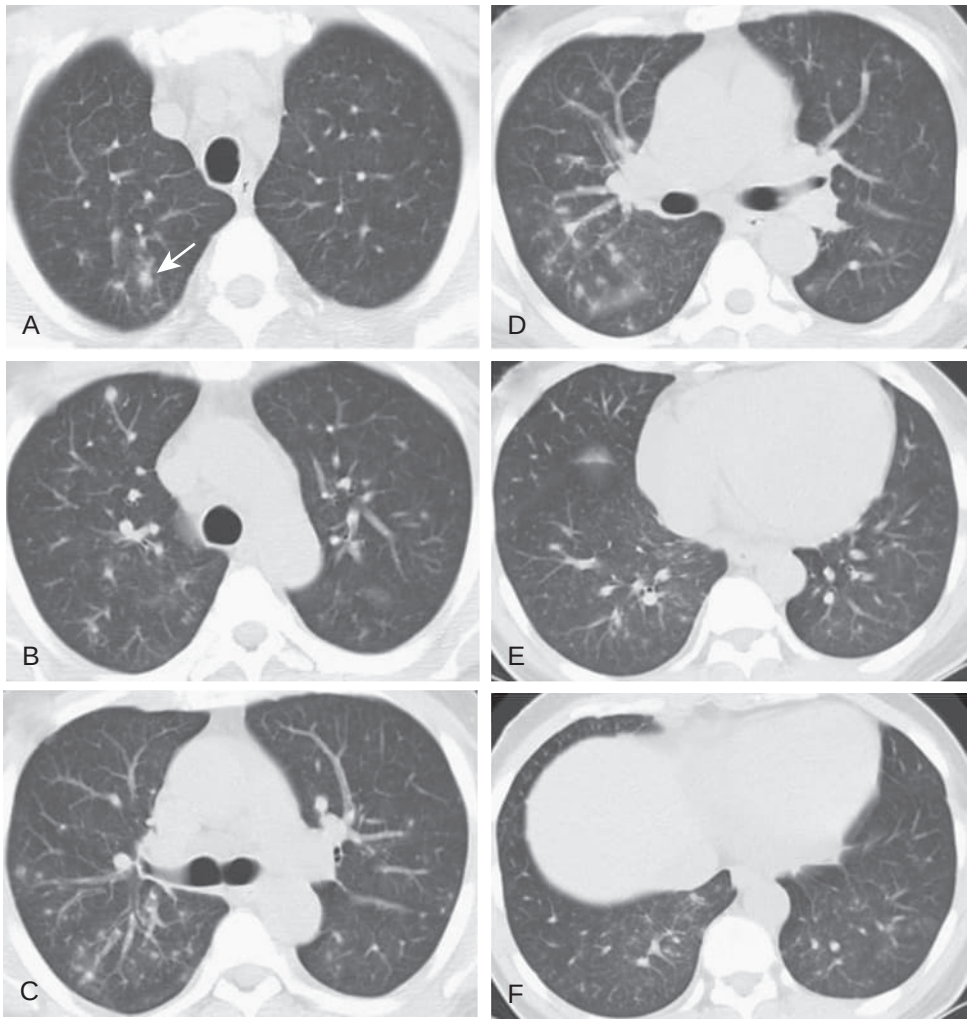
eFigure 46.57 Herpes simplex virus-specific nuclear inclusion in cell recovered from bronchoalveolar lavage fluid. (From Luyt CE, Combes A, Trouillet JL, Nieszkowska A, Chastre J. Virus-induced acute respiratory distress syndrome: epidemiology, management and outcome. *Presse Med*. 2001;40[12 Pt 2]:e561-568.)



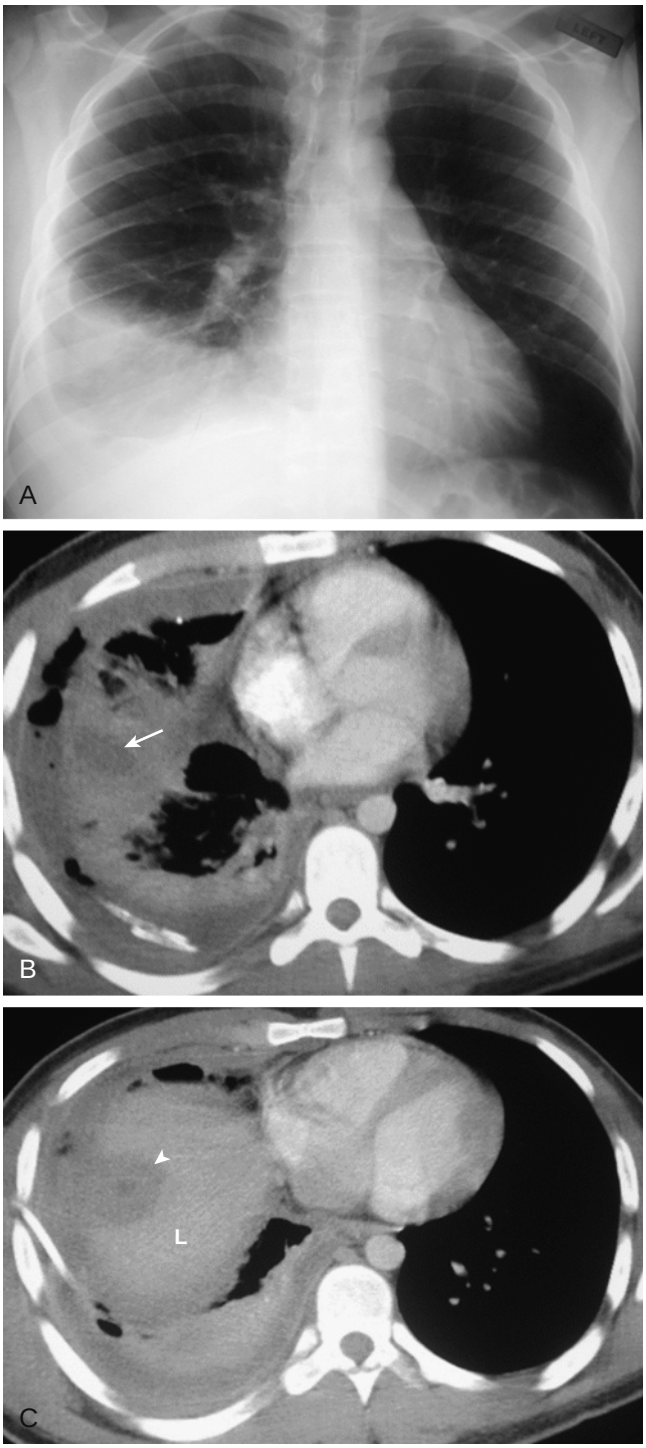
eFigure 46.58 Acute varicella pneumonia. Frontal chest radiograph shows multifocal, bilateral, poorly defined nodular opacities in a predominantly perihilar and lower lobe distribution. No pleural effusion is present. (Courtesy Michael B. Gotway, MD.)



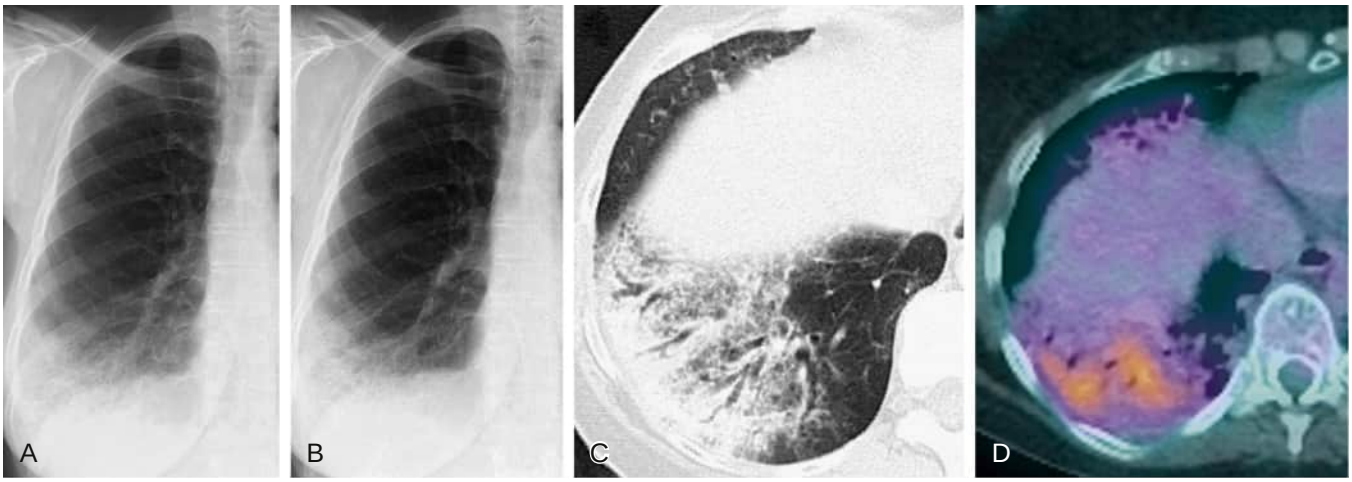
eFigure 46.59 Varicella-zoster virus pneumonia: chest radiographic findings of remote infection. Frontal chest radiograph shows numerous, small, circumscribed bilateral calcified nodules. (Courtesy Michael B. Gotway, MD.)



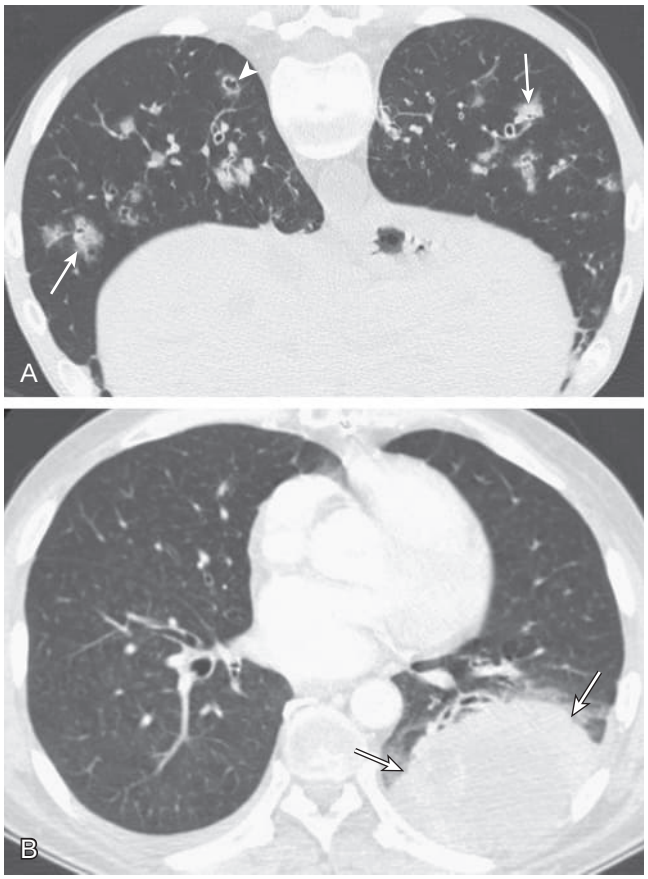
eFigure 46.60 Varicella-zoster virus pneumonia: chest computed tomography findings of acute infection. (A–F) Axial chest computed tomography displayed in lung windows shows multiple, bilateral small nodules, most of which are poorly defined. A faint ground-glass opacity halo is present around one of the nodules (*arrow*). The imaging findings are consistent with pulmonary infection but nonspecific as regards the etiologic agent. (Courtesy Michael B. Gotway, MD.)



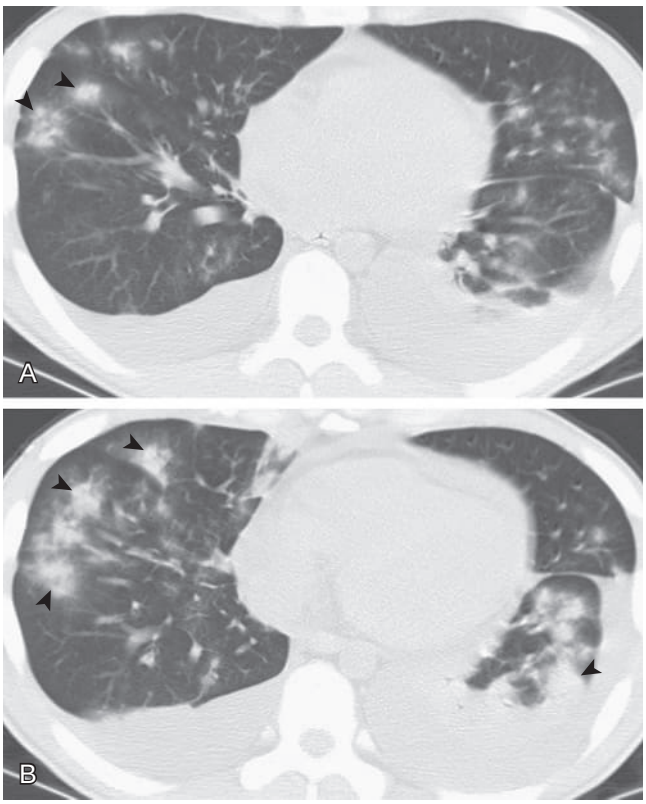
eFigure 46.61 An infectious cause of "nonresponding" pneumonia: amebic pleuropulmonary infection. (A) Frontal chest radiograph in a 23-year-old man with fever and chest pain shows right lower lobe consolidation and a small-to-moderate right pleural effusion, presumed to represent pneumonia and parapneumonic effusion. (B–C) Axial chest *computed tomography* (CT) after the patient did not respond to therapy for community-acquired pneumonia was performed to assess right pleural fluid drainage following thoracostomy tube placement (the thoracostomy tube is visible posteriorly in B). (B) Chest CT performed through the right lower lung shows consolidation with central low attenuation (*arrow*), the latter consistent with a pulmonary abscess or area of necrosis. (C) Chest CT through the extreme lung base and upper abdomen shows a low-attenuation focus (*arrowhead*) in the cranial liver (*L*), also consistent with an abscess. The liver and lung lesions are in close proximity to one another, suggesting that the liver lesion may have extended through the diaphragm to produce the lung findings; such behavior is typical of an amebic abscess. Further evaluation revealed that the patient recently immigrated to the United States from Mexico, and stool analysis recovered *Entamoeba histolytica* trophozoites. (Courtesy Michael B. Gotway, MD.)



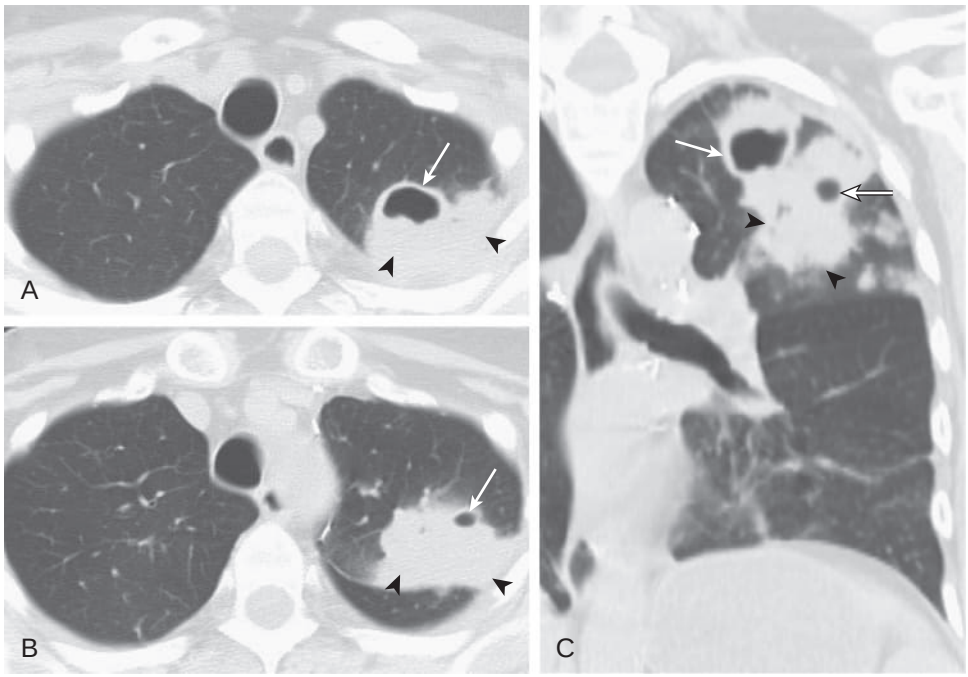
eFigure 46.62 Noninfectious "nonresponding" pneumonia: invasive mucinous adenocarcinoma (formerly referred to as mucinous bronchioloalveolar carcinoma). (A) Frontal chest radiograph in a patient with persistent shortness of breath shows right lower lobe consolidation. The patient was treated with broad-spectrum antibiotics for presumed community-acquired pneumonia. (B) Repeat frontal chest radiograph 3 months following A shows no change in the appearance of the right lower lobe opacity. (C) Axial chest computed tomography through the right lung base shown in lung windows reveals relatively nonspecific subpleural consolidation with air bronchograms and reticulation associated with ground-glass opacity. (D) Fused fluorodeoxyglucose-positron emission tomography image shows the right lower lobe opacity to be hypermetabolic. Bronchoscopic evaluation did not disclose a specific diagnosis for the persistent right lower lobe opacity. Resection of the right lower lobe proved invasive mucinous adenocarcinoma. (Courtesy Michael B. Gotway, MD.)



eFigure 46.63 *Aspergillus fumigatus* infection in a lung transplant recipient: variable chest computed tomography appearances. Prone (A) and axial (B) chest computed tomography in two separate lung transplant recipients shows extensive peribronchial ground-glass opacity and consolidation (*arrows*, A) and a small cavitary nodule (*arrowhead*, A) in one patient and a large mass (*arrows*, B) in another patient; both represent Aspergillus infection. (Courtesy Michael B. Gotway, MD.)



eFigure 46.64 Invasive *Aspergillus fumigatus* infection in a stem cell transplant recipient. (A–B) Axial chest computed tomography through the lower lungs shows basal consolidation and pleural effusions with poorly defined nodules with surrounding ground-glass opacity halos (*arrowheads*); the latter finding is consistent with the ground-glass halo sign typical of angioinvasive aspergillosis when encountered in severely immunocompromised patients. (Courtesy Michael B. Gotway, MD.)



eFigure 46.65 Non-*Aspergillus* mold infection in a lung transplant recipient: mucormycosis. Axial (A–B) and (C) coronal chest computed tomography shows a left upper lobe subpleural mass (*arrowheads*) with areas of cavitation (*arrows*) consistent with invasive fungal infection, proven to represent mucormycosis. (Courtesy Michael B. Gotway, MD.)

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46a COVID-19

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INTRODUCTION

Coronaviruses are important human pathogens, and research into their behavior is nearly a century old.[1] In late 2019, a novel coronavirus emerged in Wuhan, China and spread worldwide. In February 2020, the World Health Organization designated COVID-19 (for coronavirus disease 2019) as the name of the human disease caused by *severe acute respiratory syndrome coronavirus 2* (SARS-CoV-2), which was previously known as 2019-nCoV.[2] Viral pneumonia is the most frequent serious clinical manifestation of COVID-19, prominently featuring fever, cough, dyspnea, hypoxemia, and bilateral opacities on chest radiography.[3–6] Severe hypoxemic respiratory failure consistent with the Berlin definition of *acute respiratory distress syndrome* (ARDS) develops in a significant proportion of patients with COVID-19 pneumonia.[7,8] Patients who require mechanical ventilation may have a high risk for death.[9] Since the outbreak, more than 22 million persons have been infected and more than 1 million have died. In the United States, as tracked by the Johns Hopkins Coronavirus Resource Center (https://coronavirus.jhu.edu/map.html), more than 28 million cases and more than 500,000 deaths were reported by March 2021.[10]

VIROLOGY

SARS-CoV-2 is a member of the Coronaviridae family of enveloped, single-stranded RNA viruses. Coronaviruses are so named because of the corona (crown) seen on electron micrographs that represents its densely packed membrane proteins.[11] SARS-CoV-2 is a novel virus related to, but distinct from, SARS-CoV and Middle East Respiratory Syndrome coronavirus.[12] SARS-CoV-2 is closely related to bat and pangolin coronaviruses, and it has been theorized that bats are the natural reservoir of the virus, whereas the pangolin, an endangered and commonly trafficked mammal, may have served as an intermediate host.[12,13] Although a market in Wuhan, China was initially thought to be the source of the outbreak, this has not been definitively proven.[13]

The life cycle of SARS-CoV-2 is believed to be similar to that of SARS-CoV and other coronaviruses (Fig. 46a.1). The spike protein on the virion surface binds to the *angiotensin-converting enzyme 2* (ACE2) protein, which acts as a receptor on host cells.[14] The virus is then internalized by endocytosis, which is mediated by spike protein cleavage by the transmembrane serine protease 2.[15] The viral genome is then translated by host machinery into a polyprotein that is cleaved by both host and viral proteases; a viral RNA-dependent RNA polymerase then amplifies the genome, and virions are assembled and then released by exocytosis.[11] It is notable that the ACE2 receptor has broad tissue distribution, including in the lungs (alveolar epithelial cells), upper airway, myocardium, gastrointestinal tract, kidneys, and vascular endothelial cells in most tissues.[16,17] This likely in part explains the broad clinical manifestations of COVID-19 (see later).

TRANSMISSION

Person-to-person spread by respiratory droplets is considered the predominant mode of transmission. Specifically, such transmission is thought to take place through respiratory droplets larger than 5 μm in diameter in close range (less than 6 feet, or 2 m). For example, when persons with SARS-CoV-2 infection cough, sneeze, or talk, their respiratory secretions may make direct contact with the mucous membranes of an uninfected individual. This is consistent with laboratory

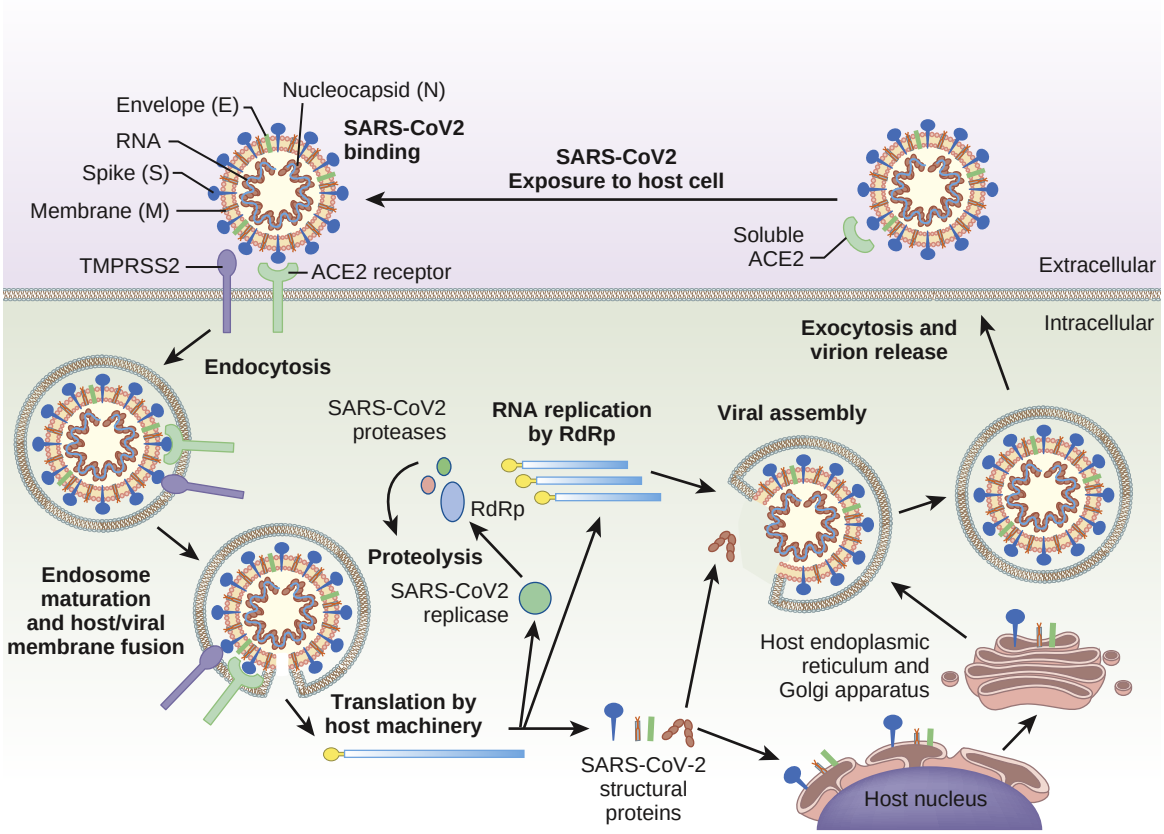

Figure 46a.1 Life cycle of *severe acute respiratory syndrome coronavirus 2* (SARS-CoV-2). SARS-CoV-2 binds to the *angiotensin-converting enzyme 2* (ACE2) receptor on the host cell membrane. After endocytosis, the membrane fuses between the mature endosome and virion with help from the *transmembrane serine protease 2* (TMPRSS2), followed by release of the SARS-CoV-2 RNA into the intracellular space. The RNA is translated by host machinery to produce the replicase and structural proteins. Host and SARS-CoV-2 proteases cleave the replicase into nonstructural proteins, including the RNA-dependent RNA polymerase (RdRp). RdRp mediates RNA replication and amplification. SARS-CoV-2 transmembrane proteins (spike [S], envelope [E], and membrane [M]) are shuttled through the endoplasmic reticulum and Golgi apparatus to the forming viral capsids. The virus is assembled with addition of the viral RNA and nucleocapsid (N) protein through association with the transmembrane viral proteins. Exocytosis results in release of the newly synthesized viral particles. (Modified from Atri D, Siddiqi HK, Lang JP, Nauffal V, Morrow DA, Bohula EA. COVID-19 for the cardiologist: basic virology, epidemiology, cardiac manifestations, and potential therapeutic strategies. *JACC Basic Transl Sci.* 2020;5:518–536.)

evidence of high levels of viral shedding in the upper respiratory tract of infected individuals (Fig. 46a.2).[18,19] For this reason, wearing masks in the community is considered a mainstay of SARS-CoV-2 prevention, with indirect evidence indicating efficacy.[20] For example, there was a 79% reduction among families in China who wore masks versus those that did not.[21]

Aerosol transmission plays a role, although its prominence is uncertain.[22] The importance of aerosolized virus (particles smaller than 5 μm in diameter that may remain suspended in the air) as a mode of transmission over distances greater than 2 m is controversial, but it likely contributes to some cases.[23] Evidence that supports aerosol transmission includes the following: (1) SARS-CoV-2 grown in tissue culture remained viable in aerosol for up to 3 hours; (2) SARS-CoV-2 RNA has been identified in ventilation systems of hospitals caring for patients with COVID-19; and (3) respiratory droplets generated by speaking have been shown to dehydrate into aerosols remaining airborne for extended periods.[24–27] More study is needed to clarify the relative contribution of aerosol transmission. Superspreading events, such as a choir practice where 88% of attendees were found to be infected, highlight the potential of airborne transmission.[28–30]

Fomite transmission, in which persons touch an infected surface and then touch their faces or mucous membranes, has been documented as a source of infection with SARS-CoV-2. SARS-CoV-2 can persist on cardboard, steel, and plastic surfaces for days and can be detected in patients' rooms and on shoes of hospital staff.[25,31,32] Reassuringly, many types of disinfectants inactivate coronaviruses similar to SARS-CoV-2.[33]

Blood-borne or non–mucous membrane transmission is less likely to spread the virus. Although SARS-CoV-2 has been detected in nonrespiratory specimens, including stool, blood, semen, and even ocular fluid, extrapolating from experience with other respiratory viruses and with SARS-CoV and Middle East Respiratory Syndrome coronavirus, the likelihood of blood-borne or non–mucous membrane transmission appears to be low.[34–36] There is also no current conclusive evidence of vertical transmission.[37]

The precise duration of infectivity of a person with SARS-CoV-2 virus is not clear, but current evidence suggests that infected individuals may be infectious 2 to 3 days before the onset of symptoms, and that asymptomatic or presymptomatic infection plays a large role in disease transmission.[38] Viral RNA shedding is variable and potentially depends on the severity of illness; however, it is unclear whether RNA shedding correlates with the presence of infectious virus.[39,40] In a small study of nine patients with mild

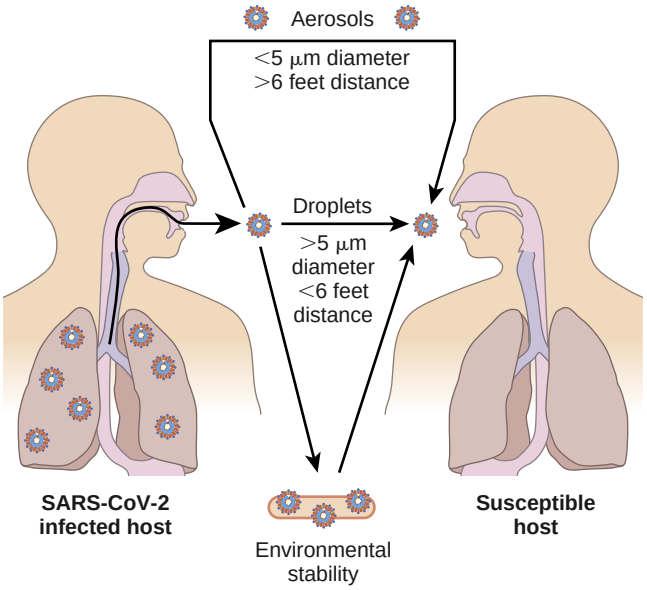

Figure 46a.2 Transmission of *severe acute respiratory syndrome coronavirus 2* (SARS-CoV-2) from person to person. The major mode of transmission is by droplets (>5 μm diameter), generated by coughing, sneezing, or talking, consistent with the known presence of virus in the upper respiratory tract. Aerosol transmission has been strongly suggested by certain spreading events, in which small particles (<5 μm) can spread more than 6 feet and remain suspended. Fomite transmission, by touching surfaces and spreading virus to the face, happens but appears to be a minor mode of transmission.

COVID-19, culturable virus was isolated from respiratory tract specimens only during the first 8 days of illness despite ongoing SARS-CoV-2 RNA detection beyond this period.[18]

With regard to presymptomatic transmission, a prospective study of patients with laboratory-confirmed COVID-19 cases and their close contacts found that the primary case transmitted the virus to secondary cases just before or within the first 6 days of symptom onset.[41] Another modeling study of transmission pairs in China suggested that individuals became more infective 2 to 3 days before symptom onset, with peak infectiveness 0.7 days before.[38] In a serial point-prevalence survey at a skilled nursing facility, 56% of 48 residents who tested positive for SARS-CoV-2 were asymptomatic at the time of testing, and the majority of these residents went on to develop symptoms as long as 6 days later.[42]

Transmission is also related to the type and duration of exposure, with prolonged close contact in closed indoor, crowded, or poorly ventilated settings conveying the highest risk.[43]

EPIDEMIOLOGY

Since the first reports of COVID-19 cases in Wuhan, China in late 2019, the SARS-CoV-2 virus has spread worldwide.[44,45] Within each country and community, the incidence of COVID-19 depends on population density, degree of testing, and timing of mitigation strategies such as social distancing. Multivariate models factoring in these variables have provided varying predictions of pandemic dynamics, although all predict at least 18 to 24 months of COVID-19 activity with periodic spikes or surges.[46,47]

Older patients and patients with comorbidities are at increased risk for severe illness and COVID-19 mortality.[4,6,48] Specifically, data from China,[49] Italy,[50] and the United States[51] have demonstrated incrementally higher rates of hospitalization and mortality from COVID-19 with increasing age. For instance, the Chinese Centers for Disease Control reported case-fatality rates of 8% and 15% among COVID-19 patients 70 to 79 years old and more than 80 years old, respectively, compared with the overall case-fatality rate of 2.3%.[8]

Other established epidemiologic risk factors for severe COVID-19 include chronic illness such as diabetes, hypertension, cardiovascular disease, chronic lung disease, and obesity.[4,6,48,52] Among 5700 patients hospitalized for COVID-19 in New York State, the median number of total comorbidities at admission was four.[53] In a prospective observational cohort of patients from 208 hospitals in the United Kingdom, there was significantly increased mortality among patients with chronic comorbidities, including cardiovascular disease (hazard ratio, 1.16), liver disease (hazard ratio, 1.51), obesity (hazard ratio, 1.33), and chronic kidney disease (hazard ratio, 1.33).[52] Immunosuppression has been a presumed risk factor for severe COVID-19, but data vary depending on the population studied. Specifically, patients with malignant disease and solid organ transplant recipients appear to be at increased risk of severe COVID-19 disease and death, whereas for persons with other types of immunocompromise, the evidence is less clear.[54]

Emerging evidence has also illustrated racial disparities in COVID-19 disease and death, with Black Americans accounting for a much larger proportion of COVID-19 deaths compared with the rest of the local population. For example, Black patients accounted for 81% of COVID-19 deaths in a 69% Black county in Georgia[55] and 73% of COVID-19 deaths in a 26% Black county in Wisconsin.[56] A subsequent analysis of the impact of COVID-19 on Black communities demonstrated that social conditions, structural racism, and other factors elevated risk for COVID-19 diagnoses and deaths in Black communities.[57,58] The burden of COVID-19 also appears to be higher in Hispanic, Native American, and Alaskan Native populations.[58]

CLINICAL PRESENTATION

It is currently estimated that approximately 40–45% of SARS-CoV-2 infections are asymptomatic.[59] The implications of this finding on the dynamics of SARS-CoV-2 transmission are significant, as previously discussed. For the remaining patients with symptomatic infection, data from China, Italy, and the United States indicate that approximately 80% of infections are mild (not requiring hospitalization), 15% are moderate to severe (requiring hospitalization), and 5% are critical (requiring intensive care unit care).[8,60–62] COVID-19 can involve almost every system in the body (Fig. 46a.3). For issues related to COVID-19 and pregnancy, see Chapter 129.

SYSTEMIC MANIFESTATIONS

The main systemic manifestations of COVID-19 are fever (>75%), myalgias (10–50%), and fatigue (20–40%).[4,48,53,62–64] Fever is present in the majority of

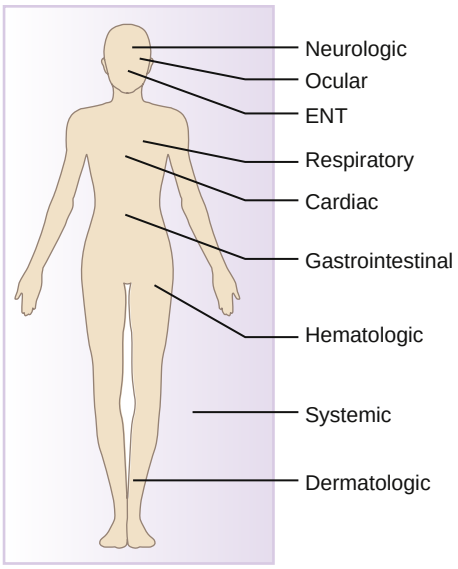

Figure 46a.3 Clinical manifestations of COVID-19. Neurologic manifestations are present in 36–57% of patients, with the most common findings of dizziness, headache, and impaired consciousness. The most common ocular manifestation is conjunctivitis. Disorders of taste and smell are very common *ear, nose, and throat* (ENT) manifestations, affecting as many as 89% of patients. Cough (45–80%) and dyspnea (20–55%) are common respiratory manifestations. Arrhythmias affect 7–17% of patients, and myocarditis is a cardiac manifestation described in several case reports. Gastrointestinal manifestations are less common (7–9% in meta-analyses), but they may be the only symptoms in some patients. Elevated D-dimer levels are a common hematologic disorder and likely confer an increased risk for thromboembolism. Rash may present as a dermatologic feature in up to 20% of patients with COVID-19, and these rashes may appear as erythema, urticaria, or vesicles. Fever, myalgias, and fatigue are common systematic symptoms in the influenza-like illness characteristic of COVID-19.

hospitalized patients, but it is present at the time of admission in only 25–50%. Therefore, the absence of fever does not exclude a diagnosis of COVID-19.

RESPIRATORY MANIFESTATIONS

Cough is a sign in 45–80% of patients (dry cough is more common than a productive cough); 20–55% of patients are dyspneic.[4,48,53,62–64] Headache and symptoms of upper respiratory tract infection (sore throat and rhinorrhea) are present in less than 20% of patients. In severely ill patients, hypoxemia is common (see Chapter 44). Among critically ill patients who require invasive mechanical ventilation, an increased ventilatory ratio (a surrogate for increased physiologic dead space) has been observed.[65–67] Abnormalities in ventilation-perfusion relationships attributed to vascular and endothelial damage have been revealed using dual-energy computed tomography.[68]

GASTROINTESTINAL MANIFESTATIONS

Nausea, vomiting, or diarrhea is present in up to 34% of patients with COVID-19 across different clinical studies.[4,48–53,62–64,69] However, two meta-analyses indicated that the pooled prevalence of nausea, vomiting, or diarrhea is lower, at 7–9%.[70,71] Gastrointestinal symptoms can be the only symptoms at presentation in up to 14% of patients.[72–74]

CARDIAC MANIFESTATIONS

There are multiple case reports of acute myocarditis associated with COVID-19.[75,76] Arrhythmias have been described in 7–17% of hospitalized patients.[5,63] One early small study of critically ill patients showed that one-third of patients (7 of 21) developed acute cardiomyopathy; however, this has not been observed in other studies of critically ill patients with COVID-19.[77,78] Finally, cardiac injury has been reported in 7–28% of patients and is associated with an increased risk of complications and death; a limitation of this finding, however, is that cardiac injury is defined largely by elevation of blood biomarker levels, which may be an unreliable method of diagnosing cardiac injury in acutely or critically ill patients.[5,79–81]

Because SARS-CoV-2 uses the ACE2 protein as its cell entry receptor (see the earlier section on virology), the effects of ACE inhibitors and angiotensin receptor blockers have been examined. These medications increase expression of ACE2, which raised the hypothetical possibility that their use could make patients more susceptible to SARS-CoV-2 infection or at risk for more severe COVID-19.[82] However, multiple studies have determined that there is no association between the use of these medications and the risk of SARS-CoV-2 infection or severe disease.[83–86]

EAR, NOSE, AND THROAT MANIFESTATIONS

Disorders of taste (dysgeusia, ageusia) and smell (hyposmia, anosmia) in COVID-19 are common, ranging from 34–89%.[87–89] These symptoms can manifest before other respiratory symptoms and can be present without nasal congestion. This latter finding raises the possibility that disorders of taste and smell may be in part direct effects of the virus rather than solely the results of nasal inflammation and obstruction.[88]

Symptoms related to taste and smell were rarely reported in early clinical studies from China; it is not clear whether this discrepancy is related to differences in symptom reporting or whether there is a true difference that may be mediated by variations in viral strain or ACE2 receptor density in the nasopharynx.[4,90]

OCULAR MANIFESTATIONS

Ocular symptoms have been described in 1–32% of patients.[91–95] The most common ocular finding is conjunctivitis, which appears to be more common in patients with severe disease.

NEUROLOGIC MANIFESTATIONS

Neurologic findings have been described in 36–57% of hospitalized patients.[96–98] The most common symptoms are dizziness, headache, and impaired consciousness; stroke has been observed in 2–3% of patients. A small but high-profile case series reported stroke in young patients with COVID-19, some of whom did not have clear vascular risk factors.[99] However, larger prospective studies are needed to clarify the risk of stroke in COVID-19, in particular among younger patients. It is unclear whether neurologic effects are related to a direct effect of the virus, to hypercoagulability or inflammation caused by the virus, or to the concurrent incidence of severe medical illness in patients with preexisting

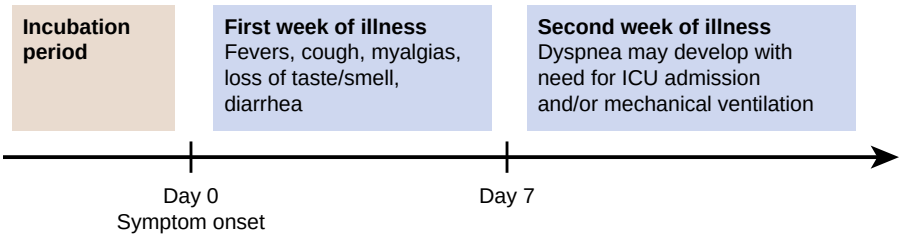

Figure 46a.4 Clinical course of COVID-19. The presymptomatic incubation period may last a median of 5 days. During the first week of illness, symptoms tend to be flulike, with the added symptoms of losses of taste and smell. Severe disease may develop in the second week, with dyspnea and the need for *intensive care unit* (ICU) treatment. Many patients remain asymptomatic during their illness.

vascular risk factors.[96,100] Several reports have also described Guillain–Barré syndrome in patients with COVID-19.[101–103]

HEMATOLOGIC MANIFESTATIONS

The incidence of venous thromboembolism (deep venous thrombosis or pulmonary embolism) in patients hospitalized with COVID-19 ranges from approximately 25–50%, and the risk appears to be higher in patients with elevated D-dimer levels.[104–109] The role of therapeutic anticoagulation in severe COVID-19 is controversial and, at present, limited data support anticoagulation in the absence of overt evidence of thromboembolism; the risks and benefits remain unclear, and prospective trials are needed.[110]

DERMATOLOGIC MANIFESTATIONS

Rash has been reported in less than 1% to 20% of patients.[4,111,112] The most common morphologic forms reported are erythematous, urticarial, and vesicular rashes. Chilblain-like lesions (known colloquially as "COVID toes") have been described commonly in patients during the COVID-19 pandemic, although a causal link to the virus has not yet been made.[113,114]

INFLAMMATORY SYNDROMES

The increased levels of inflammatory markers in patients with severe COVID-19 (discussed in detail later) have raised the possibility that critical illness in COVID-19 is a manifestation of an uncontrolled release of inflammatory mediators called a cytokine storm.[115] This concept underlies the rationale for trying to treat COVID-19 with anti-inflammatory medications (e.g., immunosuppression and steroids). Whether circulating inflammatory cytokines are higher in COVID-19 compared with other critical illnesses is uncertain at this time.[116] Another multisystemic inflammatory syndrome has been described in children; it has similarities to Kawasaki disease but is thought to be a distinct entity and is postulated to be immune system mediated.[117,118]

IMMUNOCOMPROMISED PATIENTS

Two questions with respect to immunocompromised patients are as follows: (1) Do they have atypical clinical manifestations? and (2) Are they at risk for more severe disease, or could immunosuppression actually be protective against deleterious inflammatory effects of COVID-19? Existing data indicate that immunocompromised patients have typical clinical manifestations of COVID-19.[54] Regarding risk for more severe disease, patients with cancer and solid organ transplant recipients appear to be at higher risk for more severe disease and increased mortality, whereas patients taking biologic agents for inflammatory disorders do not appear to have increased risk.[54] Data on COVID-19 in persons with human immunodeficiency virus infection are conflicting, and the risk in this patient population is not yet clear.

CLINICAL COURSE

The median incubation period between infection and symptom onset is 5 days. Patients often do not manifest signs and symptoms of severe disease until the second week of illness (Fig. 46a.4).[48,119]

LABORATORY FINDINGS

Clinical studies have reported the results of both routine laboratory testing and biomarkers in hospitalized patients with COVID-19.[4,48,53,62–64] Patients with COVID-19 usually have a normal or low white blood cell count, with leukopenia in 15–45% of patients and leukocytosis seen in less than 25%. Lymphopenia is reported in 33–90% of patients. Platelet levels are usually normal, although they can be slightly low in up to one-third of patients. Transaminase levels are elevated in approximately 5–45% of patients, with two meta-analyses showing the pooled prevalence of transaminase elevation at 15–20%.[70,71]

Biomarkers of inflammation are commonly elevated in COVID-19, with C-reactive protein elevated in approximately 40–85% and lactate dehydrogenase in 30–75% of patients. Procalcitonin is elevated (using a cutoff of 0.5 ng/mL) in 5–17% of patients, although it is more commonly elevated in patients with severe disease or critical illness. High levels of inflammatory markers (including C-reactive protein, D-dimer, interleukin-6, ferritin) are associated with more severe disease and risk of death.[48]

Bacterial and viral coinfections are uncommon in patients presenting with COVID-19, with most studies indicating a coinfection rate less than 7%.[53,63,64,78] However, coinfections are clearly documented, and several studies show high rates of coinfections.[120] Therefore, the presence of another virus or bacterial infection does not exclude the possibility of COVID-19.

IMAGING

Chest radiographic findings are abnormal in 60% of patients hospitalized with COVID-19, whereas chest *computed tomography* (CT) scans are abnormal in 86%.[4] Two meta-analyses showed that the most common chest CT findings are ground-glass opacities (83–87%), which were usually bilateral (78–80%) and in a peripheral distribution

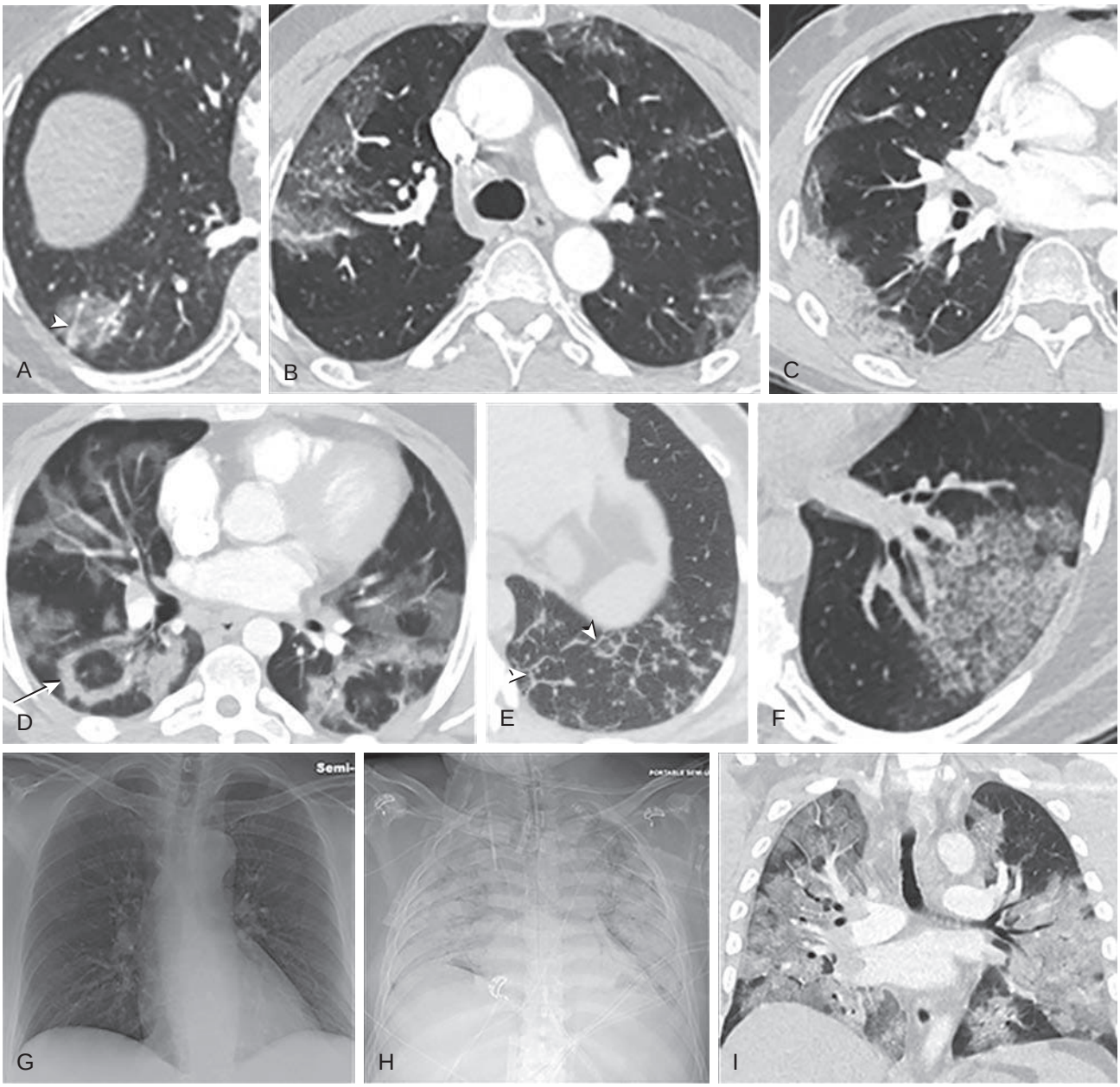

Figure 46a.5 COVID-19 pneumonia: chest radiographic spectrum and suggestive *computed tomography* (CT) findings. (A) Peripheral rounded ground-glass opacity. Note that the vessels (*arrowhead*) in the area of ground-glass opacity appear slightly larger than vessels in the unaffected lung, a feature that has been variously referred to as the "microvascular dilation" or "vascular dilation" signs. (B) Subpleural multifocal, bilateral ground-glass opacity. (C) Subpleural consolidation. Often, consolidation develops in areas previously affected by ground-glass opacity later in the disease course. (D–E) CT imaging features suggesting organizing pneumonia. (D) The "reverse [ground-glass opacity] halo" or "atoll sign": peripheral consolidation surrounding areas of central clearing (*arrow*). (E) Perilobular opacity: linear opacities outlining the secondary lobules (*arrowheads*), resembling interlobular septal thickening. (F) Crazy paving: ground-glass opacity associated with smooth interlobular septal thickening and intralobular interstitial thickening. (G) Essentially normal chest radiograph at presentation. Same patient as in the CT image in A, which was obtained 4 days after this chest radiograph. (H) Diffuse bilateral homogeneous opacities in a patient with respiratory failure who was undergoing extracorporeal membrane oxygenation. (I) CT in the same patient as in H, obtained at presentation and 6 days before the chest radiograph in H, shows multifocal bilateral ground-glass opacity–associated smooth interlobular septal thickening and intralobular interstitial thickening. (Courtesy Michael B. Gotway, MD.)

(75–77%).[121,122] Consolidations, septal thickening, and a crazy paving pattern are also considered typical in COVID-19 cases. Ground-glass opacities may evolve into a more consolidated appearance (eFig. 46a.1). Atypical findings have included pleural effusions, nodules, lymphadenopathy, tree-in-bud opacities, and pneumothorax. Abnormalities on plain chest radiographs or chest CT scans are similar to those found in other viral pneumonias. Typical CT findings are shown in Figure 46a.5.

DIAGNOSIS

The two major categories of SARS-CoV-2 diagnostic studies are tests for viral nucleic acid and tests for antibodies. The likelihood of detection of SARS-CoV-2 and the immune response to it depends on when the assay is performed relative to the time of exposure or infection (Fig. 46a.6).

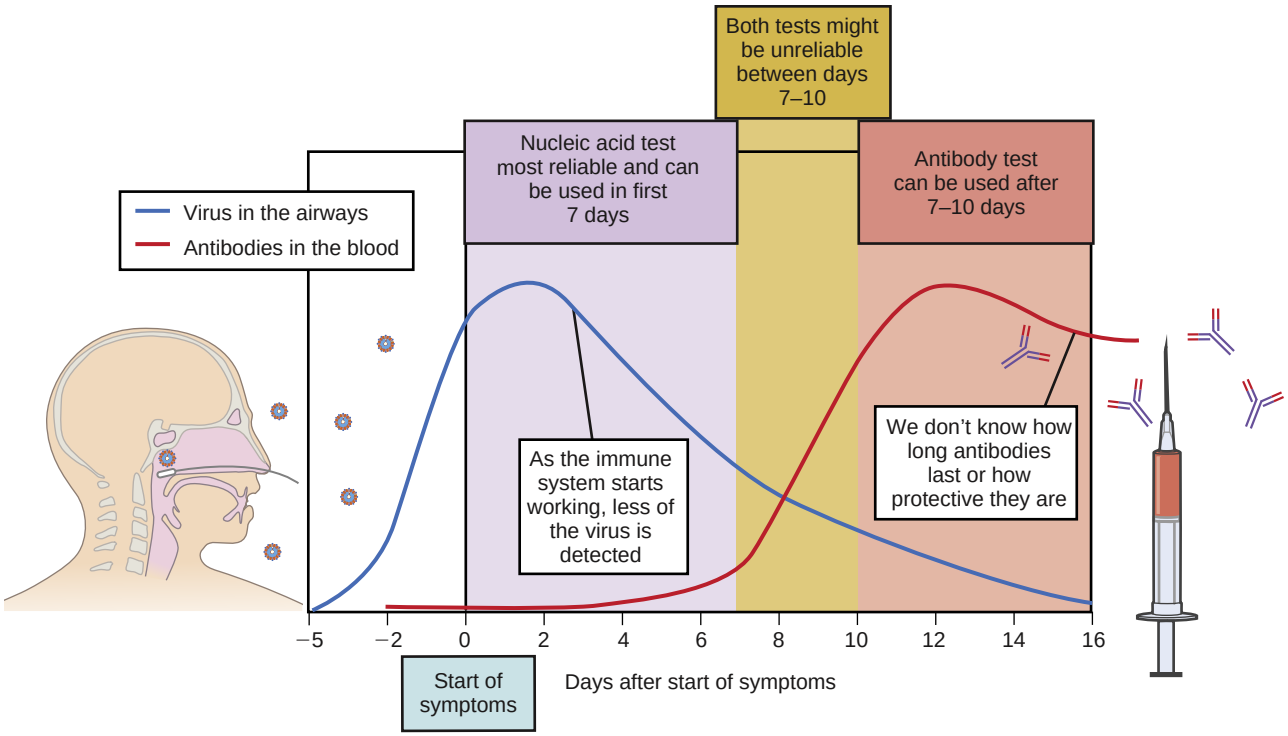

Figure 46a.6 Time course of viral exposure, clinical infection, and the results of clinical assays for severe acute respiratory syndrome coronavirus 2 and the immune response to it. Given the high virus counts, the patient may be most contagious in the few days before and after symptoms begin (see virus in airways, *blue line*). During the first week of symptoms, when virus is abundant, the nucleic acid tests are most reliable. With the onset of an immune response, virus numbers start to decline. By the second week, the immune system has been activated and, from 7 to 10 days after symptoms, the antibody test may be useful in detecting infection. Interestingly, both tests may be unreliable between the first and second weeks. (From UK Research and Innovation. What is the purpose of testing for COVID-19? 2020. https://coronavirusexplained.ukri.org/en/article/vdt0006/.)

SARS-COV-2 NUCLEIC ACID TESTING

Viral nucleic acid detection is the mainstay of testing for active infection. These *nucleic acid amplification tests* (NAATs) most commonly use reverse-transcriptase polymerase chain reaction technology, of which there are multiple kits that amplify and detect different regions of the SARS-CoV-2 genome (e.g., nucleocapsid gene, envelope gene, spike gene, open reading frame, RNA-dependent RNA polymerase gene).

The available NAATs are highly specific for SARS-CoV-2, but sensitivity can vary depending on the clinical scenario (Table 46a.1). Specifically, SARS-CoV-2 viral load in the upper respiratory tract is highest during the presymptomatic period or in the first week after symptom onset, whereas, later in the illness, the upper respiratory tract NAAT result may be negative even if lower respiratory tract involvement has developed.[36,123] In a retrospective study of patients in China with clinically diagnosed COVID-19 pneumonia, 12.5% of patients with an initial negative NAAT result were confirmed positive on a second test, a finding suggesting that the initial upper airway viral load was low.[124]

Beyond the issue of a low viral load, false-negative results may also arise because of improper sampling, sampling the wrong site, or viral mutations in the region targeted by the polymerase chain reaction. For this reason, among symptomatic patients who are either hospitalized or in high-risk settings such as congregate living, one or more negative NAAT results may not be sufficient to rule out COVID-19. Among patients with evidence of lower respiratory tract infection, polymerase chain reaction testing should be performed on a sample obtained from the lower respiratory tract while acknowledging that this approach may be limited by the transmission risk of the procedures.

SARS-COV-2 SEROLOGY TESTING

Serologic tests detect antibodies to SARS-CoV-2 in the blood. Multiple assays have been developed using different viral epitopes, and the available tests vary widely in their diagnostic performance (Table 46a.2).

In a study of 173 patients with COVID-19, the median time to antibody detection using an assay against the receptor-binding domain of the SARS-CoV-2 spike protein was 12 days for immunoglobulin M and 14 days for immunoglobulin G.[125] Because of this timeframe, current U.S. Centers for Disease Control and Prevention and World Health Organization guidelines recommend not using antibody tests to diagnose active SARS-CoV-2 infection where a false result may be caused by testing too early in the course of infection. Additionally, because there are limited data on whether certain antibodies confer immunity and on the duration of protection of neutralizing antibodies, SARS-CoV-2 serologic testing results should not be used to determine whether it is safe to return to work or to enter group living situations. Serologic testing has demonstrated value as a public health surveillance tool.

OTHER TESTS

Tests that identify SARS-CoV-2 antigen are under development and hold potential as rapid point-of-care assays. However, these assays are typically less sensitive than

Table 46a.1 The Sensitivity and Specificity of Nucleic Acid Amplification Tests for Severe Acute Respiratory Syndrome Coronavirus 2 Based on the Clinical Scenario

Test	Sensitivity, % (95% CI)	Specificity, % (95% CI)
SAMPLE LOCATION (3 STUDIES)		
Upper respiratory tract	76 (51–100)	100 (99–100)
Lower respiratory tract	89 (84–94)	100 (99–100)
UPPER RESPIRATORY TRACT SAMPLES (11 STUDIES)		
Oral	56 (35–77)	99 (99–100)
Nasal	76 (59–94)	100 (99–100)
Nasopharyngeal	97 (92–100)	100 (99–100)
Saliva	85 (69–94)	100 (99–100)
Midturbinate	100 (93–100)	100 (99–100)
REPEAT TESTING (WITH NP SWABS; 3 STUDIES)		
Single test	71 (65–77)	100 (99–100)
Repeat test	88 (80–96)	100 (99–100)

CI, confidence interval; NP, nasopharyngeal.
Modified from Hanson KE, Caliendo AM, Arias CA, et al. Infectious Diseases Society of America guidelines on the diagnosis of COVID-19: molecular diagnostic testing. *Infect Dis Soc Am.* 2020;Jan 22:ciab048.

Table 46a.2 Serologic Testing for Severe Acute Respiratory Syndrome Coronavirus 2

Type of Test	Time to Results	What It Tells Us	What It *Cannot* Tell Us
Rapid diagnostic test (RDT)	10–30 min	The presence or absence (qualitative) of antibodies against the virus present in patient serum	The amount of antibodies in the patient serum, or whether these antibodies are able to inhibit viral growth
Enzyme-linked immunosorbent assay (ELISA)	2–5 hr	The presence or absence (quantitative) of antibodies against the virus present in patient serum	Whether the antibodies are able to inhibit viral growth
Neutralization assay (plaque reduction neutralization test [PRNT])	3–5 days	The presence of active antibodies in patient serum able to inhibit viral growth ex vivo, in a cell culture system	May miss antibodies to viral proteins not involved in replication
Chemiluminescent immunoassay (CLIA)	1–2 hr	The presence or absence (quantitative) of antibodies against the virus present in the patient serum	Whether the antibodies are able to inhibit viral growth

Modified from Johns Hopkins University Center for Health Security. Serology-based tests for COVID-19. https://www.centerforhealthsecurity.org/resources/COVID-19/serology/Serology-based-tests-for-COVID-19.html.

NAATs. SARS-CoV-2 viral culture is performed only for research purposes.

PATHOLOGY AND PATHOMECHANISMS

PATHOLOGY OF COVID-19 PNEUMONIA

The main pathologic finding in SARS-CoV-2 lung infection is diffuse alveolar damage in the exudative or proliferative phase[126–132] (Fig. 46a.7). As in other forms of diffuse alveolar damage, there is alveolar epithelial cell desquamation, alveolar type 2 cell hyperplasia, and septal edema. Hyaline membranes contain viral antigen. Epithelium-derived syncytial cells, which form in response to the action of viral fusion proteins, are sometimes found in alveoli. Inflammatory infiltrates are either neutrophilic (particularly in the acute phase) or lymphocytic. A distinctive finding is the large burden of platelet-rich thrombi in the microvasculature.[132] Medium and large vessels can also contain embolic thrombus. Megakaryocytes, normal cellular constituents of the lung, are present within alveolar capillaries in increased numbers.[133] SARS-CoV-2 virions or proteins can be detected in the epithelium of the airways, in the alveoli, and in alveolar macrophages. Some studies have detected SARS-CoV-2 virions within lung endothelial cells; however, other studies have not, and identification of virions is challenging as a result of virus-mimicking cellular structures.[129,132,134–138] In summary, the pathology of COVID-19 pneumonia falls within the spectrum of diffuse alveolar damage seen in other disorders; endothelial injury (endotheliitis) and microvascular thrombosis are distinctive, but not diagnostic, features.

IMMUNOPATHOLOGIC OBSERVATIONS IN COVID-19 PNEUMONIA

The immune response to SARS-CoV-2 pneumonia has been characterized by detailed analyses of cytokines and leukocytes in peripheral blood and in bronchoalveolar lavage

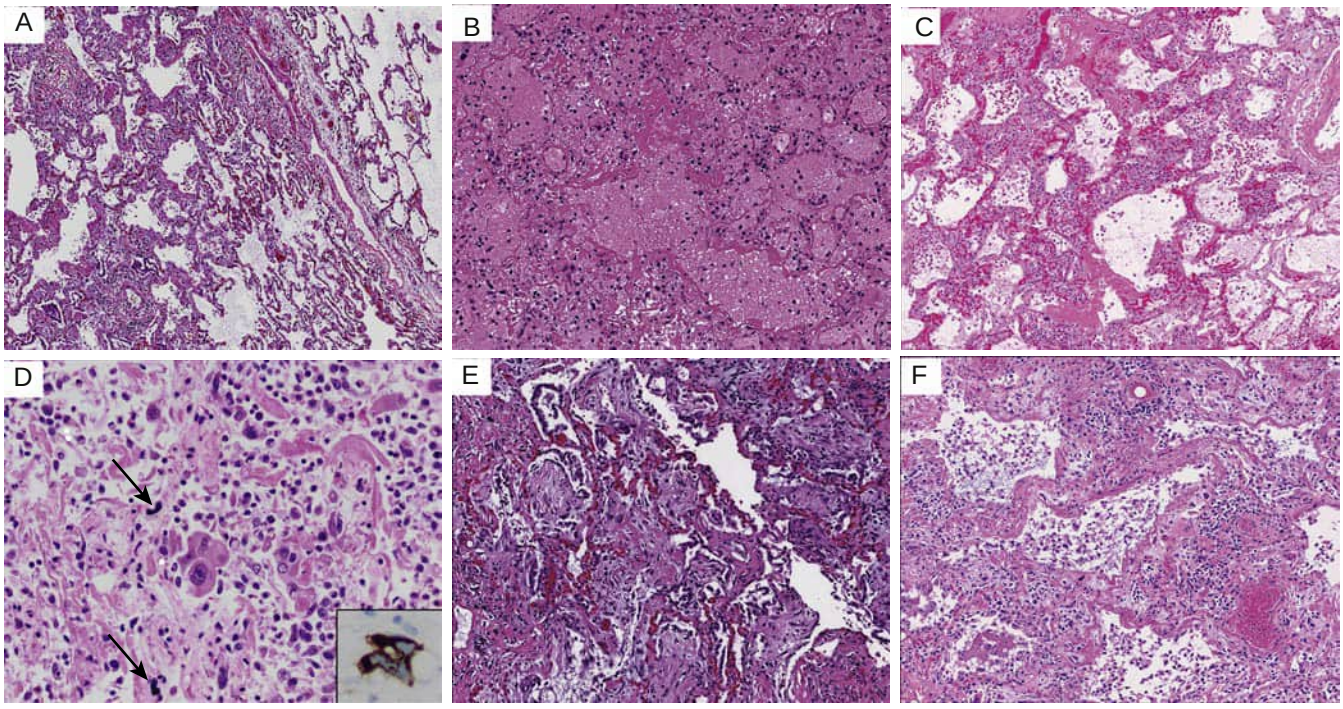

Figure 46a.7 Spectrum of diffuse alveolar damage seen in COVID-19 pneumonia. (A) All cases demonstrated diffuse alveolar damage, and seven of eight cases showed a component of acute phase diffuse alveolar damage. Note the demarcation between affected lung parenchyma with thickened alveolar septa and hyaline membranes (*lower left*) and the relatively preserved lung parenchyma (*upper right*) separated by a thickened edematous interlobular septum. (B) Edema of variable severity was seen in all cases and is marked in this example. Note also the conspicuous hyaline membranes. (C) The presence of interstitial neutrophilic infiltrates was seen in focal areas with acute diffuse alveolar damage. (D) Reactive alveolar type 2 epithelial cells within alveolar spaces showed abundant eosinophilic cytoplasm, irregular nuclear contours, occasional binucleation, vesicular condensed chromatin, and prominent macronucleoli. Intracapillary megakaryocytes (*arrows*) were also present within alveolar capillaries and were highlighted by CD61 immunohistochemistry (*inset*). (E) Lungs from six patients showed organizing phase diffuse alveolar damage alone or in combination with acute phase diffuse alveolar damage, with characteristic alveolar type 2 cell and fibroblastic proliferation within alveolar walls with focal intraluminal plugs of loose connective tissue. (F) Some areas within organizing diffuse alveolar damage showed interstitial chronic inflammation. (Modified from Sauter JL, Baine MK, Butnor KJ, et al. Insights into pathogenesis of fatal COVID-19 pneumonia from histopathology with immunohistochemical and viral RNA studies. *Histopathology*. 2020;77:915-925.)

fluid.[139–149] Lymphopenia is common, and its severity at an early stage correlates with the risk of severe disease and death.[150] $CD4^+$, $CD8^+$, and γδ T cells, T regulatory cells, and natural killer cells are decreased in peripheral blood, probably because of a combination of recruitment from the vasculature to lymphoid organs and to sites of infection and of cell death by mechanisms involving *interleukin-6* (IL-6) and Fas-Fas ligand signaling.[139] Numerous cytokines are elevated in blood; IL-6, IL-2, *interferon* (IFN)-γ, IL-8, IL-10, IP-10, macrophage chemotactic protein 3, and IL-1 receptor antagonist levels have been correlated with disease severity. Production of type I and III IFN, an antiviral response downstream of activation of pattern recognition receptors, can be impaired by viral mechanisms that block detection of viral RNA or inhibit downstream signaling responses.[139,151] The importance of an effective type I IFN response in controlling SARS-CoV-2 is provided by the findings that approximately 15% of patients with severe COVID-19 lack effective type I IFN responses because of genetic defects[152] or because of autoantibodies that neutralize type I IFNs.[153] Whether serum cytokine levels in COVID-19 represent a cytokine storm that is different from or more severe than in non-COVID ARDS is controversial.[116]

The phenotypes of mononuclear cells in blood and lung are altered.[139] Severely ill patients with COVID-19 have increased numbers of granulocyte-macrophage colony-stimulating factor–expressing $CD4^+$ T cells, which can secrete proinflammatory cytokines and may recruit inflammatory monocytes and macrophages.[139] Peripheral T cells, especially $CD8^+$ T cells, are activated in higher numbers than in control subjects, and they express markers suggestive of exhaustion (programmed cell death 1 and T cell immunoglobulin and mucin domain 3). Natural killer cells are functionally impaired, both in their ability to secrete chemokines and cytokines and in their expression of cytotoxic molecules. Natural killer cells from COVID-19 patients also express higher levels of immune checkpoint inhibitors. There are higher numbers of inflammatory monocytes in the peripheral blood of COVID-19 patients and, in the lung, there appears to be recruitment of inflammatory monocytes and monocyte-derived macrophages.[146]

Within 2 weeks of infection, $CD4^+$ and $CD8^+$ T cells with antigen receptors specific for SARS-CoV-2 antigens are detectable and, within 1 to 2 weeks, COVID-19 patients seroconvert.[139] Antibodies to the viral nucleocapsid and spike proteins are common. The receptor binding domain of the S protein is particularly immunogenic, and anti–receptor binding domain antibodies can be neutralizing. The relationship of circulating antibody levels to clinical disease is complex. Although increasing levels of anti-SARS-CoV-2 antibodies correlate with decreasing viral load, increasing titers of specific antibody can also correlate with increasing disease severity.[139] This finding suggests that viral clearance alone may not prevent severe disease or that differences in antibody targets or specific antibody functions influence the outcome of infection. Antibody-dependent

enhancement, a process by which virus opsonized by antibody is able to access and activate macrophages in an Fc-receptor–dependent manner and thereby worsen disease, has been described in experimental models of SARS-CoV-1 infection, but there is no evidence yet of antibody-dependent enhancement in humans with SARS-CoV-2.[154,155] An antibody response may not be essential for recovery, however, because patients with X-linked agammaglobulinemia have recovered from COVID-19 after relatively mild illness.[156,157]

PATHOMECHANISMS OF COVID-19

The portals of entry for SARS-CoV-2 are ACE2-expressing epithelial cells in the upper and lower respiratory tract (eFig. 46a.2).[158] Viral loads in the upper airway peak sooner in SARS-CoV-2 infection than in SARS-CoV-1 infection.[19] The virus is also taken up by macrophages, which are probably unable to support SARS-CoV-2 replication.[134] Although macrophages likely contribute to viral clearance, virus-containing macrophages also amplify the inflammatory response and may act to spread viral infection within and outside the lung.[159] In an animal model of SARS-CoV-1 pneumonia, depletion of inflammatory monocyte-macrophages improved survival.[160]

Engagement of pattern recognition receptors during the initial stages of a viral infection triggers two general antiviral responses: release of types I and III IFNs, which induce expression of IFN-stimulated genes, and release of cytokines and leukocyte-recruiting chemokines, resulting in activation and recruitment of virus-clearing cells such as natural killer cells, inflammatory monocyte-macrophages, and neutrophils. In SARS-CoV-2 pneumonia, there may be a distinctive imbalance in these responses: the IFN-I or III response is blunted, at least in the early phase of infection, whereas release of other proinflammatory molecules is prominent.[161] The complexity of the response and the importance of timing are suggested by a SARS-CoV-1 animal model in which early IFN-I signaling is protective, whereas late signaling increases lethality,[162] as well as by observations that IFN-stimulated genes are up-regulated in bronchoalveolar lavage cells of COVID-19 patients in comparison with patients with SARS.[147] The type I IFN response may be more suppressed with a higher initial viral load and in older patients.[151] Recruited inflammatory monocyte-macrophages and activated resident macrophages likely become drivers of the hyperinflammatory response through release, in particular, of tumor necrosis factor-α and IL-6. The resulting response has similarities to a final common pathway of severe and systemic inflammation (in which macrophages, cytotoxic T cells, and natural killer cells drive tissue injury) also seen in disorders such as secondary hemophagocytic lymphohistiocytosis and the cytokine release syndrome seen with chimeric antibody receptor–T cell infusions.[163,164]

The endothelium is also a key contributor to COVID-19 lung pathology (eFig. 46a.3). In viral pneumonia, the endothelium regulates aspects of the inflammatory response, such as leukocyte egress, vascular leak, and the innate immune response.[165] In COVID-19 pneumonia, additional factors target the endothelium. ACE2 is down-regulated as a consequence of viral infection, and the resulting ACE-ACE2 imbalance may lead to an excess of angiotensin II signaling.[166,167] Angiotensin II induces endothelial injury, vasoconstriction, and thrombosis. *Ace2* knockout mice develop more severe disease in lung injury models, and ACE2 has protective effects on lung beyond the epithelium, findings that support the idea that ACE-ACE2 imbalance is relevant to COVID-19.[166] In addition, endothelial cells may be directly infected by SARS-CoV-2, thus adding to endothelial cell injury and loss. Loss of endothelial cells and the resultant exposure of the basement membrane promote clot formation. The prominent microvascular thrombosis, as well as macroscopic thrombosis and thromboembolism, in COVID-19 is likely caused by a severe "immunothrombosis" state[168] resulting from endothelium dysfunction and loss, along with other prothrombotic phenomena (high levels of von Willebrand factor, factor VIII, fibrinogen, and possibly activation of complement[169] and formation of neutrophil extracellular traps).[170]

TREATMENT

At this time, treatment for COVID-19 is principally supportive. As of March 2021, the *U.S. Food and Drug Administration* (FDA) has issued emergency use authorizations for medical treatment (including remdesivir and convalescent plasma) and for medical devices in the care of COVID-19 patients. The best evidence for efficacy at the time of this publication is for remdesivir and dexamethasone (see later). We will discuss the evidence for the use of these treatments and refer the reader to updates here and elsewhere for the latest therapies.

Patients whose severity of illness does not warrant hospitalization should remain at home and as isolated as much as possible from uninfected close contacts. The duration of isolation depends on several factors. The U.S. Centers for Disease Control and Prevention make recommendations based on symptomatic versus asymptomatic infection.[171] Isolation should persist for 10 days after the resolution of symptoms *and* 24 hours after the resolution of fever (without the use of antipyretic agents). Hospitalized patients should wear surgical masks to limit droplet transmission whenever feasible, and they should be housed in negative-pressure isolation areas to limit nosocomial spread of SARS-CoV-2. Clinical care providers should wear personal protective equipment consisting of an impermeable clear face shield, an N-95 (or higher) respirator mask or a contained air-purifying respirator or powered air-purifying respirator, impermeable gloves, and an impermeable gown, as appropriate based on patient care activity.

For practical purposes, COVID-19 can be classified as mild, severe, or critical. In mild disease, patients have either no pneumonia or mild pneumonia, and they do not meet criteria for severe or critical illness.[8] Severe COVID-19 is defined as dyspnea, persistent tachypnea (respiratory rate ≥30/min), hypoxemia (oxyhemoglobin saturation <93%), a Pao_2/Fio_2 ratio less than 300, or an increase in lung opacities greater than 50% over 24 to 48 hours. Critical COVID-19 is characterized by respiratory failure, shock, or multiorgan dysfunction or failure.

Mild COVID-19 should be treated symptomatically, with measures taken to prevent contagion and monitor for clinical deterioration. The goals of treatment in severe or critical COVID-19 are supportive. Clinicians should provide measures required to reverse or prevent further clinical deterioration while avoiding overtreatment and the harms associated with it.[172–174]

RESPIRATORY CARE

Patients may be hypoxemic without other symptoms or signs of respiratory failure, such as dyspnea or use of accessory breathing muscles.[175,176] Despite their lack of dyspnea, patients with hypoxemia should receive supplemental oxygen. Clinicians often prescribe supplemental oxygen to achieve oxyhemoglobin saturations higher than a given threshold, often more than 90%. This goal may be difficult to achieve in some patients with severe COVID-19, for unknown reasons. Because the goal of supportive critical care is to provide sufficient arterial oxygen delivery to preserve or restore normal cellular metabolism, the therapeutic target for oxyhemoglobin saturation should focus on the value required to avoid or reverse anaerobic cellular metabolism, which may vary depending on individual patient characteristics.[176,177] Close monitoring for evidence of anaerobic metabolism (e.g., lactic acidosis) or incipient organ failure (e.g., altered mentation, myocardial injury) is advisable. Standard nasal cannulas, Venturi masks, and non-rebreather masks may supply enough oxygen to reverse critical hypoxemia in many patients, but severely ill patients may require additional therapy. High-flow or high-velocity nasal cannulas provide higher flows of oxygen and consequently a higher effective fractional concentration of oxygen in inspired gas. Furthermore, these devices may lower the work of breathing, rest the respiratory muscles, and limit oxygen consumption.[178] Noninvasive positive-pressure ventilation may be helpful in selected cases (when there is an imminently reversible cause of respiratory distress or when guided by advance directives), but because respiratory failure is often prolonged in patients with critical COVID-19 (median duration of mechanical ventilation in survivors >2 weeks), noninvasive ventilation should be used cautiously.[179] The use of high-flow nasal oxygen or noninvasive ventilation may increase the dissemination of SARS-CoV-2 and the risk of infecting health care personnel, so these treatments should take place in areas where appropriate isolation and environmental precautions and use of personal protective equipment by medical personnel are maintained. For patients with hypoxemia despite supplemental oxygen, prone positioning may improve oxygenation, but the results of limited preliminary reports involving small observational cohorts show mixed results. Many patients do not tolerate a prone position but, among those who do, improvements in oxygenation and respiratory rate are frequently, although not universally, observed. These improvements may not be durable.[180,181] More recommendations on the use of this intervention will require the results of ongoing clinical studies: at least 60 trials of prone positioning in COVID-19 were registered as of August 2020.[182] The use of inhaled selective pulmonary vasodilators is also an area of intense interest, and clinical trials of inhaled nitric oxide or inhaled prostacyclin are currently registered.[183,184]

The decision to proceed to endotracheal intubation and invasive positive-pressure ventilation for patients with severe COVID-19 is complicated. Some experts advocate early intubation and controlled ventilation to limit excessive patient breathing efforts that may damage already injured lungs.[185] Other experts advise caution and reserve intubation for frank respiratory failure only, by recognizing that a solid set of criteria for defining the need for intubation and ventilation remains elusive.[186,187] Without the results of clinical trials describing clinical benefit associated with a standardized set of criteria for progressing from supplemental oxygen and other noninvasive methods of respiratory support (see earlier) to intubation and mechanical ventilation, the decision will remain in the realm of clinical judgment. A small, retrospective, single-center study suggested that early intubation is not associated with a lower risk of death.[188] Because mechanical ventilation is often prolonged in patients with severe COVID-19, and because invasive mechanical ventilation is often accompanied by complications, clinicians should proceed carefully and use a broad evaluation to formulate a decision about whether to intubate and provide positive-pressure ventilation by assessing several parameters to determine whether an individual patient's work of breathing is too high to sustain.[189] Serial careful and consistent physical examinations are crucial, and patients who may require mechanical ventilation should undergo close monitoring with the highest level of care possible depending on the availability of resources. The most experienced and skilled clinician available should perform endotracheal intubation, and rapid sequence intubation with induction of anesthesia and neuromuscular blockade has been associated with increased intubation success.[190] The breathing circuit should contain a filter capable of trapping viral particles at all times to limit dispersion of SARS-CoV-2. Clinicians involved in intubation may have a high risk of exposure to SARS-CoV-2, even when they are wearing recommended personal protective equipment.[191]

Lung-protective ventilation to prevent alveolar overdistention and ventilator-associated lung injury is essential.[192] The targeted tidal volume should be based on the patient's predicted body weight, and tidal volumes between 6 and 8 mL/kg are advised, as long as the plateau airway pressure, driving pressure, or mechanical power (a summary variable including pressures, volumes, flows, and respiratory rate[193]) remains low. Either volume-controlled or pressure-controlled ventilation is acceptable, but clinicians should be aware that excessive patient efforts during pressure-controlled ventilation may result in excessive tidal volumes and in transalveolar pressures higher than the set inspiratory pressure target.[194] Patients who require mechanical ventilation for COVID-19 ARDS show heterogeneity of respiratory mechanics similar to the heterogeneity present in patients with ARDS from all other causes.[195] Clinicians should individualize ventilator settings, sedation, analgesia, and neuromuscular blockade to minimize the work of breathing when required, improve patient comfort and patient-ventilator coordination, and facilitate the earliest possible return to independent breathing, as long as airway pressures and gas exchange remain within safe ranges. The use of rescue therapies (lung recruitment, high positive end-expiratory pressure settings, inhaled selective pulmonary vasodilators, and extracorporeal gas exchange) remains undefined at present, although the results of large studies should guide practice in the near future.

Because the duration of mechanical ventilation may be prolonged, and because patients who undergo mechanical ventilation appear to be at high risk for death, clinicians should carefully discuss advance directives, goals of care, and surrogate decision making with their patients who

have progressive respiratory failure. The need for timely and thorough conversations that elucidate patients' values and preferences regarding advanced medical interventions and end-of-life care is heightened by hospital infection-control policies that may severely limit visiting by families and loved ones. Clinicians and hospitals may choose to use technologies such as video conferencing to alleviate the isolation of hospitalized patients with COVID-19.

ANTIVIRAL AND ANTI-INFLAMMATORY THERAPIES

Remdesivir is an intravenous nucleotide prodrug that binds to the viral RNA-dependent RNA polymerase. inducing a premature termination of RNA transcription. On May 1, 2020, the FDA issued an emergency use authorization for the use of remdesivir for the treatment of COVID-19.[196] However, the evidence in support of remdesivir is still evolving. One single-center, prospective, double-blind, randomized controlled trial performed in Wuhan, China assessed the efficacy of remdesivir for COVID-19. The study enrolled 237 patients, and 158 of these patients received remdesivir. The primary end point of the study was time to clinical improvement, and no difference was observed between the placebo and remdesivir groups.[197] A larger multicenter, prospective, placebo-controlled, double-blind trial that enrolled 1062 patients, who were assigned 1:1 to receive remdesivir or placebo, with more than 98% adherence to remdesivir in the assigned group, found more favorable results. Time to recovery (as defined by an 8-point ordinal scale and assessed by log-rank analysis) was shorter, with a reduction of approximately 5 days in the duration of illness. This effect was more pronounced in the subgroup of patients with more severe disease, in whom the duration of illness was shortened by a median of 7 days. The remdesivir group had a lower number of deaths, and the effect on the risk of death was more pronounced in the group with severe respiratory illness. Remdesivir also appeared to reduce the risk of respiratory deterioration, such as a new requirement for supplemental oxygen or a new need for assisted ventilation, as well as a shorter duration of mechanical ventilation or extracorporeal membrane oxygenation, when used.[197] A single-center, open-label, prospective trial of combination lopinavir-ritonavir did not observe clinical benefit compared with placebo.[198]

Dexamethasone has been shown to have value in severely ill COVID-19 patients, supporting a pathogenic role for inflammation. An open-label randomized controlled trial of dexamethasone, 6 mg daily given either orally or intravenously, enrolled patients across 176 centers in the United Kingdom, with 2014 patients receiving dexamethasone and 4321 patients receiving usual care (RECOVERY). In the study, investigators observed an absolute reduction of 2.8% in the risk of 28-day mortality among all patients who received dexamethasone.[200] Among patients receiving supplemental oxygen at the time of randomization, the absolute risk reduction was 2.9% and, in patients undergoing mechanical ventilation at the time of randomization, the absolute risk reduction was 11.8%. Among patients neither receiving oxygen nor undergoing mechanical ventilation, mortality was 3.8% higher, although the 95% confidence interval for the risk ratio crossed 1.0. Dexamethasone was associated with a greater likelihood of reducing the risk for 28-day mortality among patients who had symptoms for 7 days or more before randomization. Dexamethasone was also associated with a lower risk of progressing to mechanical ventilation as well as a shorter duration of intensive care unit and hospital stay. The magnitude of mortality benefit among ventilated patients is similar to that found in a recently published trial of dexamethasone for patients with non–COVID-19 ARDS.[201]

The publication of the results of the RECOVERY trial resulted in a loss of equipoise and the cessation of several other studies of the effects of glucocorticoids in severe COVID-19.[202] The results of the CoDEX, CAPE COVID, and REMAP CAP trials were subsequently published despite early termination.[203–205] The World Health Organization, with the cooperation of several prospective trialists, carried out a prospective meta-analysis of seven ongoing randomized controlled trials that included RECOVERY, CoDEX, CAPE COVID, REMAP CAP, as well as three others that have not yet been published.[206] The meta-analysis included a total of 1703 patients, with 678 randomized to receive glucocorticoids and 1025 randomized to receive placebo. A total of 222 of 678 (33%) patients who received steroids died, whereas 425 of 1025 (42%) placebo-assigned patients died, thus resulting in a lower odds ratio for death among the glucocorticoid-treated group (odds ratio, 0.66; 95% confidence interval, 0.53 to 0.82). Glucocorticoids were associated with lower mortality among severely ill patients who were undergoing invasive mechanical ventilation at the time of randomization, as well as among severely ill patients who were not undergoing invasive ventilation. Glucocorticoids also appeared to be associated with more ventilator-free days. The meta-analysis found little heterogeneity among the seven studies, with little variation between the effects of hydrocortisone and dexamethasone; insufficient evidence was available about other formulations of glucocorticoids. Uncertainty persists about the dose, the duration of administration, and the timing of administration with respect to the onset of COVID-19 symptoms. Although the benefit of steroids appears to apply to severely ill patients who are not undergoing invasive mechanical ventilation, the exact level of severity at which an individual patient should receive steroids remains undefined.[202] A common approach is that severely ill COVID-19 patients with hypoxemic respiratory failure receive a minimum of hydrocortisone, 150 mg/day in divided doses, or dexamethasone, at a minimum dose of 6 mg daily, for at least 7 days, with a tapering schedule determined by the treating clinicians. Clinicians should weigh the risk-benefit balance carefully for patients with less severe disease.

Multiple investigations of additional anti-inflammatory or immunomodulating drugs are in progress at this time. Drugs under investigation include multiple formulations of glucocorticosteroids, immunotherapy with convalescent plasma or anti–SARS-CoV-2 monoclonal antibodies, intravenous immunoglobulin, and drugs that interrupt pathways involving various inflammatory molecules. A device that adsorbs circulating inflammatory mediators (CytoSorb, CytoSorbents Corp), which is approved in the European Union, received FDA emergency use authorization on April 10, 2020, for use in patients with established or imminent respiratory failure from COVID-19; data regarding the efficacy of this device remain preliminary.[199]

ANTICOAGULANT AND ANTITHROMBOTIC THERAPY

Multiple groups of investigators have observed an increased risk for arterial and venous thromboembolism and abnormal coagulation biomarkers in patients with COVID-19.[105,207–210] Abnormal coagulation may be associated with worse prognosis.[211] Although some reports associate therapeutic anticoagulation with improved outcomes, decisions about whom and when to treat remain uncertain.[212] Without more data to guide prescribing decisions, a common approach is to limit therapeutic anticoagulation with unfractionated heparin, low-molecular-weight heparin, or direct thrombin inhibitors to patients with overt evidence of venous or arterial thromboembolism. All hospitalized patients should receive thromboprophylaxis (in the absence of contraindications) according to current guidelines. Whether to commence therapeutic anticoagulation in response to suspected microthrombosis or severe abnormalities in coagulation biomarkers such as D-dimer levels remains uncertain.

FUTURE DEVELOPMENTS

Important advances are eagerly awaited in vaccine development, (with 3 vaccines now approved for emergency use by the FDA), as well as in other preventive approaches such as inhaled antibodies[213] or repurposed drugs to block the viral infection.[214] Further studies are in progress for rapid diagnostic tests and effective treatments. There is much to learn about the effects of SARS-CoV-2 on the lung, and studies are underway to ascertain the short-term and long-term effects of COVID-19.

This chapter will be updated frequently at ExpertConsult.com.

Key Points

- *Severe acute respiratory syndrome coronavirus 2* (SARS-2-CoV) is a member of the Coronaviridae family of enveloped, single-stranded, RNA viruses. It uses the angiotensin-converting enzyme 2 protein as its principal receptor to enter host cells.
- Person-to-person transmission through small respiratory droplets is probably the main means of spread, although aerosol transmission is also likely. Transmission by fomites may also happen. Asymptomatic carriage likely plays an important role in propagating viral spread.
- Approximately 40–45% of SARS-CoV-2 infections are asymptomatic. In the remainder, fever, fatigue, myalgias, and dry cough are common. Absence of fever does not preclude the diagnosis of COVID-19 because many infected patients do not manifest fever. Gastrointestinal symptoms are present in approximately one-third of patients. Neurologic or sensory manifestations are also common.
- Older patients with comorbidities such as diabetes mellitus, arterial hypertension, cardiovascular disease, chronic lung disease, and obesity have a higher risk for developing severe disease from SARS-COV-2 infection. Racial and ethnic disparities in risk for death exist in the United States, with members of Black, Hispanic, and Native American communities experiencing a high risk for death; the causes are likely related to disparities in social determinants of health.
- Hypoxemia is the most common severe manifestation of COVID-19, but evidence of renal, hepatic, and myocardial injury, as well as abnormal coagulation parameters, is also common. Chest radiography is abnormal in the majority of patients hospitalized with SARS-CoV-2 infection.
- The diagnosis of SARS-CoV-2 infection relies on nucleic acid amplification tests to detect the presence of virus in a suspected patient. These tests are highly specific, but sensitivity depends on factors including timing from symptom onset and sample type.
- The main pathologic finding in COVID-19 pneumonia is diffuse alveolar damage. Although no pathologic features of COVID-19 are diagnostic, COVID-19 pneumonia is characterized by an unusual degree of endothelial injury and microvascular thrombosis.
- Lung damage caused by SARS-CoV-2 results from direct viral injury and from the host immune response, with the latter likely more important in severe cases. The injurious immune response appears to consist of a markedly imbalanced immune response characterized by profound lymphopenia and lymphocyte exhaustion, hyperactivation of the innate immune response in monocyte-macrophages, and an aberrant interferon-I/III response.
- Hospital treatment is mainly focused on supportive care with supplemental oxygen and, if needed, mechanical ventilation. Patients with respiratory failure often meet criteria for acute respiratory distress syndrome, and mechanical ventilation for patients with respiratory failure caused by COVID-19 should be similar to that provided to patients with acute respiratory distress syndrome from other causes, with a focus on lung-protective ventilation.
- Thromboembolic complications are common in COVID-19, and therapeutic anticoagulation with unfractionated heparin or other drugs is advised when pathologic clots are detected. The utility of anticoagulation for patients with markedly abnormal coagulation parameters (but without clinical evidence of thromboembolism) is unknown.
- The antiviral agent remdesivir may be associated with earlier clinical improvement, but its effects on other important clinical end points remains unknown. Glucocorticoid administration is associated with a reduced risk for death among patients who require oxygen supplementation or mechanical ventilation.

Key Readings

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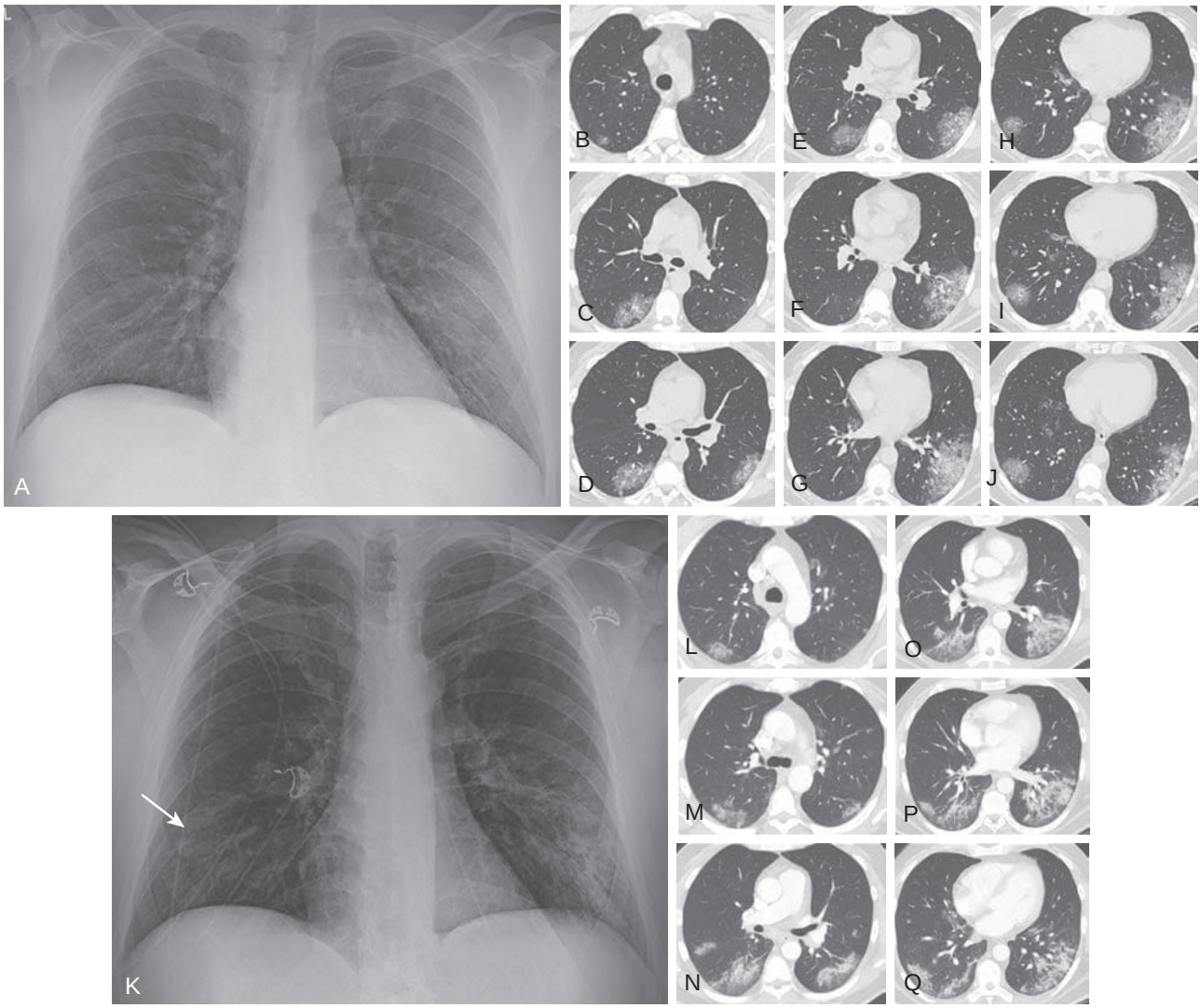
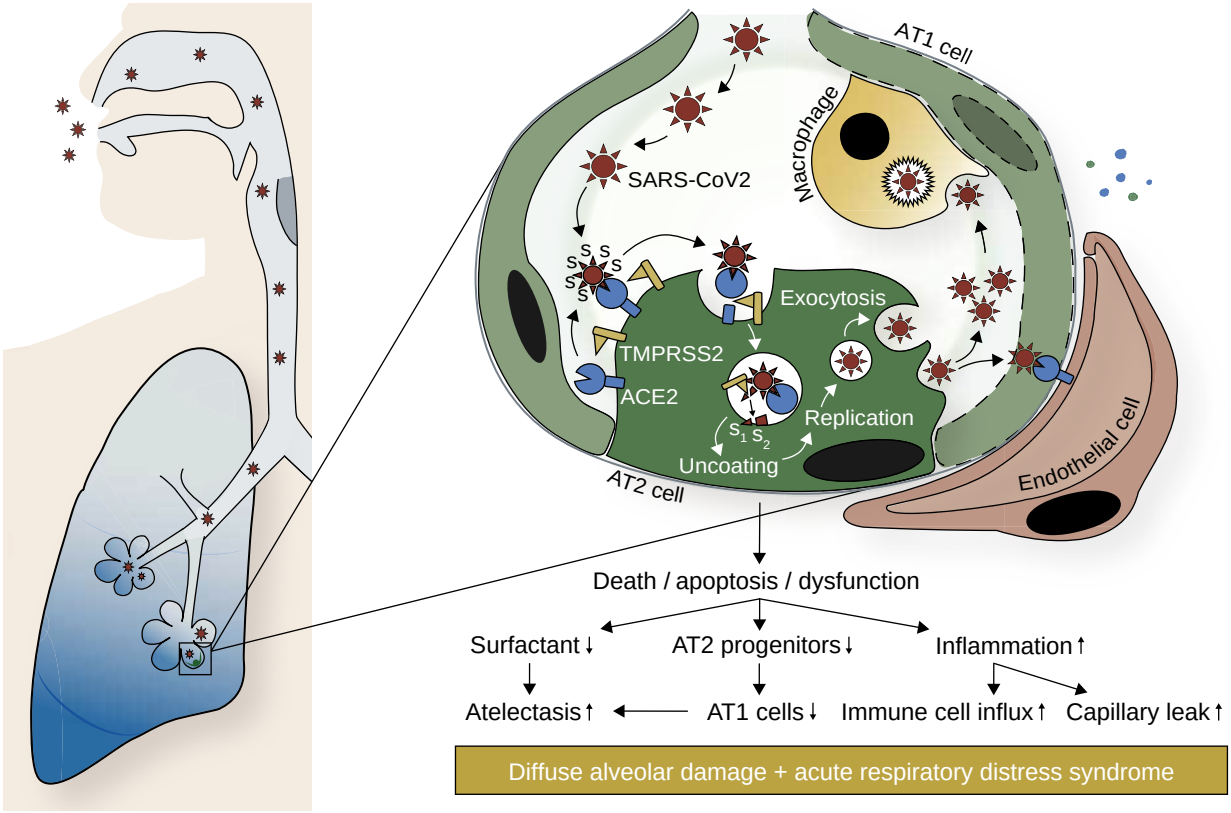
Complete reference list available at ExpertConsult.com.

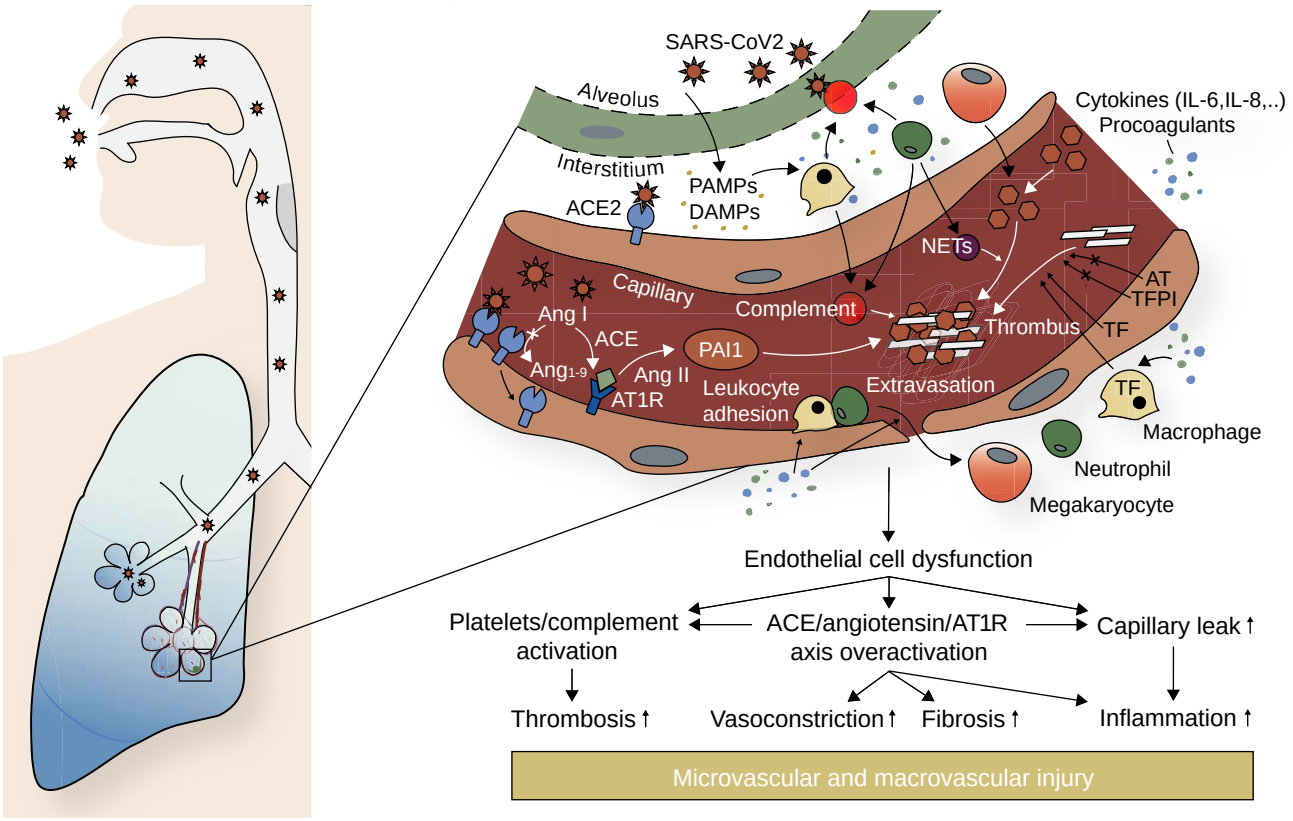
eFIGURE IMAGE GALLERY



eFigure 46a.1 COVID-19 pneumonia: chest radiographic and *computed tomography* (CT) findings and evolution. (A) Frontal chest radiograph at presentation, several days after symptom development, shows focal, somewhat rounded opacity at the left base. (B–J) Axial unenhanced chest CT displayed in lung windows shows patchy, multifocal, somewhat rounded or oblong areas of ground-glass opacity preferentially distributed in the subpleural lower lungs bilaterally. The areas of ground-glass opacity show internal mild interlobular septal thickening and intralobular interstitial thickening. (K) Frontal chest radiograph 12 days after symptom development shows patchy peribronchovascular thickening in the left lower lobe at the site of the previously noted, somewhat rounded opacity on the presentation chest radiograph in part A. Very faint abnormalities are now visible in the right lower lobe (*arrow*). (L–Q) CT pulmonary angiography shows that opacities have worsened, with an overall greater extent and transitioning from a more "pure" ground-glass opacity appearance to a more consolidative appearance. No pulmonary embolism was noted. The patient subsequently recovered. (Courtesy Michael B. Gotway, MD.)



eFigure 46a.2 Potential mechanisms of alveolar damage caused by *severe acute respiratory syndrome coronavirus 2* (SARS-CoV-2) infection. SARS-CoV-2 host entry through alveolar epithelium critically depends on expression of *angiotensin-converting enzyme 2* (ACE2) and *transmembrane serine protease 2* (TMPRSS2). First, coronavirus binds through one of its four structural proteins, glycoprotein S (spike) to ACE2 on *alveolar type 2* (AT2) cells, initiating fusion of virus and host cell membranes. Second, TMPRSS2 simultaneously cleaves ACE2, thereby promoting cell surface clearance of ACE2, and the viral glycoprotein S into subunits S_1 and S_2, resulting in viral uncoating and release of the viral genome into the cytoplasm. The virus is then replicated using both viral and host cell machinery, translation of the viral core proteins S, M, N, and E in the endoplasmic reticulum, assembly of virus particles in the endoplasmic reticulum–Golgi-intermediate compartment, and packaging into small vesicles routed to the plasma membrane for exocytosis. SARS-CoV-2 infection–induced AT2 cell dysfunction or loss is deleterious to the injured lung for several reasons: (1) decrease in surfactant increases the risk for alveolar collapse and atelectasis; (2) decrease in AT2 progenitor cells causes impaired *alveolar type 1* (AT1) cell replacement, thus affecting alveolar repair and likely promoting fibrosis; (3) ACE2 down-regulation drives geographically restricted overactivity of the ACE-angiotensin II–AT1 cell receptor axis, worsening the tissue destructive effect of the inflammatory response; and (4) virus-induced cytokine release by AT1 and AT2 cells results in capillary leak and alveolar interstitial immune cell infiltration. (From Brosnahan SB, Jonkman AH, Kugler MC, Munger JS, Kaufman DA. COVID-19 and respiratory system disorders: current knowledge, future clinical, and translational research questions. *Arterioscler Thromb Vasc Biol.* 2020;40:2586–2597.)



eFigure 46a.3 Potential mechanisms of pulmonary vascular injury in *severe acute respiratory syndrome coronavirus 2* (SARS-COV-2) infection. SARS-CoV-2 infection of endothelial cells, from either the luminal or alveolar interstitial side, triggers endothelial release of cytokines, which cause increased capillary permeability, thereby allowing adhesion and extravasation of neutrophils and monocytes into the alveolar interstitial space. Stimulated by *pathogen-associated and damage-associated molecular patterns* (PAMPs and DAMPs, respectively), neutrophils and macrophages secrete a multitude of cytokines, procoagulants, and complement, which promote viral attack and clearance but induce further vascular injury, thus enhancing the risk for thrombosis. Several factors may contribute to the prothrombotic environment, thereby promoting intravascular thrombus formation: (1) neutrophil-mediated secretion of *neutrophil extracellular traps* (NETs) and complement enhances platelet aggregation; (2) cytokine-triggered secretion of *tissue factor* (TF) by endothelial cells and macrophages stimulates the coagulation cascade and increases fibrin clot formation; (3) endothelial damage decreases secretion of anti-cothrombotic mediators, such as *antithrombin* (AT) and *tissue factor pathway inhibitor* (TFPI); (4) lung residential megakaryocytes produce locally available platelets for aggregation; and (5) overactivation of the *angiotensin-converting enzyme* (ACE)–*angiotension II* (Ang II)–*angiotensin type 1 receptor* (AT1R) axis as a result of virus-induced ACE2 down-regulation increases production of *plasminogen activator inhibitor 1* (PAI1), thus reducing plasmin activation and fibrinolysis. **IL, interleukin.** (From Brosnahan SB, Jonkman AH, Kugler MC, Munger JS, Kaufman DA. COVID-19 and respiratory system disorders: current knowledge, future clinical, and translational research questions. *Arterioscler Thromb Vasc Biol.* 2020;40:2586–2597.)

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47 INFLUENZA

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INTRODUCTION

Influenza viruses are respiratory pathogens transmitted mainly by droplets of respiratory secretions of infected persons.[1] Although most people with influenza illness experience mild, self-limited disease of the upper respiratory tract manifested by fever, cough, sore throat, myalgias, and/or malaise, complications are common and include primary influenza pneumonia, secondary bacterial pneumonia, exacerbations of underlying chronic diseases, and death. Influenza viruses circulate globally and cause seasonal epidemics in temperate regions and prolonged epidemics or year-round illness in tropical and subtropical regions.[2] The annual influenza attack rate is estimated to be 5–10% in adults and 20–30% in children.[1] Worldwide, seasonal influenza is responsible for an estimated 291,243 to 645,832 influenza-associated respiratory deaths each year,[3] with an increased risk of severe disease in children, older adults, and persons with chronic illness.[1,4]

CHARACTERISTICS OF INFLUENZA VIRUSES

Influenza viruses are members of the Orthomyxoviridae family of viruses. Three genera cause human disease: influenza A, influenza B, and influenza C.[5] Of these, influenza A and B are clinically most important. Although influenza A viruses infect many species of birds and mammals,[5] nonhuman influenza A virus strains occasionally infect humans and cause disease.[6] Influenza B viruses nearly exclusively infect humans.[7] Influenza A and B viruses continuously undergo mutations selected by immunologic pressure (called *antigenic drift*) that allow them to evade immune protection and to cause subsequent infections over the course of a lifetime.[8,9] Antigenic drift also accounts for the need to reformulate influenza vaccines up to twice annually to match the viral strains circulating globally.[10] Influenza A virus strains can also undergo genetic reassortment within a common host, resulting in novel viruses to which a population may have little or no immunity (termed *antigenic shift*).[5]

An influenza pandemic can happen if novel influenza viruses emerge to which a population has little or no preexisting immunity, the virus can spread efficiently from person to person, and the virus causes disease. The 1918 influenza pandemic killed 50 to 100 million people worldwide within 1 year, resulting in the deadliest single event in recorded human history.[11]

Formally, the full names of influenza virus strains follow a convention, for example, A/Brisbane/59/2007 (H1N1), describing the antigenic type (e.g., A, B, C); the host of origin (e.g., swine), although for human-origin viruses, no host of origin is given; the city or country of the initial isolate; and the strain number and year of isolation. Such nomenclature is typically not necessary for scientific communications unless a specific strain is being described; this chapter uses simplified nomenclature referencing virus type/subtype without further specification. For the virus that caused the 2009 influenza pandemic, the letters "pdm" follow the name (i.e., influenza A/H1N1pdm). For naming influenza A viruses, the *hemagglutinin* (H) and *neuraminidase* (N) antigens are further denoted, such as A/H1N1 or A/H3N2. The name is often shortened to refer only to the hemagglutinin and neuraminidase types.

The 1918 influenza pandemic was caused by an influenza A/H1N1 virus that spread directly from an avian reservoir to humans, without passage through another mammalian species, such as pigs.[12] The 1957 influenza A/H2N2 pandemic virus and the 1968 influenza A/H3N2 pandemic virus resulted from genetic reassortment between avian influenza viruses and seasonal influenza viruses.[12] The 2009 influenza A/H1N1pdm virus resulted from genetic reassortment between triple-reassortant North American swine influenza A/H1N1 (i.e., a virus containing genes from three different host sources: birds, humans, and swine) and a Eurasian swine influenza A virus.[12,13]

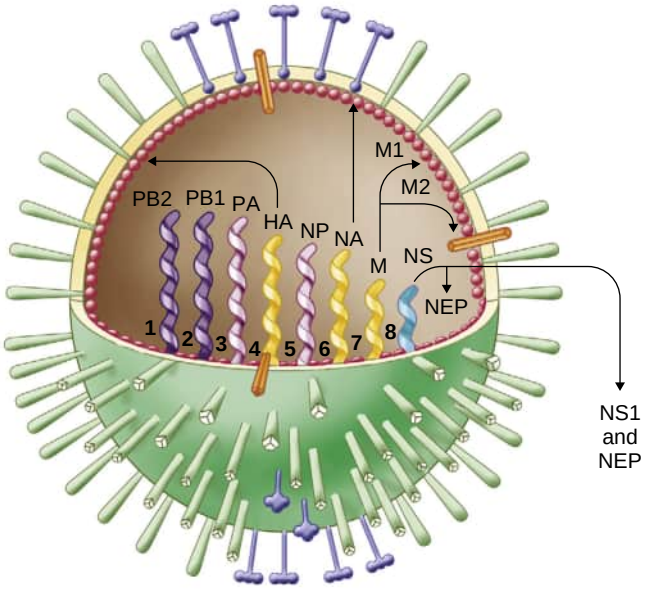

Figure 47.1 Influenza virus structure. Eight segments of viral RNA are contained within the lipid envelope and matrix (M1) shell. Each codes for one or more proteins that form the virus or regulate its intracellular replication. HA, hemagglutinin; M1, matrix; M2, proton channel; NA, neuraminidase; NP, nucleoprotein; NS1, nonstructural interferon antagonist; PB1, PB2, PA, polymerase proteins (1, 2, A); NEP, nuclear export protein. (Courtesy Dr. Robert G. Webster, St. Jude's Children's Research Hospital.)

Influenza viruses are enveloped, segmented, negative-strand RNA viruses.[5] The influenza A envelope consists of a lipid bilayer and three transmembrane proteins: *hemagglutinin* (HA), *neuraminidase* (NA), and a *proton channel* (M2). The eight RNA segments encode 11 proteins, including three RNA polymerase subunits, which have poor proofreading ability, leading to high mutation rates and antigenic drift; structural proteins (M1, a matrix protein, and M2, a proton channel protein needed for nuclear export and other functions), HA, and NA (Fig. 47.1).[14]

HA is responsible for binding to sialic acid, also known as neuraminic acid, the receptor on target cells.[5] HA comprises a globular head and stem (or stalk) regions. The receptor binding site lies in the globular head, the most variable region of the protein.[5] NA is less abundantly expressed than HA; it is responsible for release of new virus particles from infected cells by cleaving sialic acid moieties on cell membrane glycolipids and glycoproteins.[8,15] The NA is the target of the *NA inhibitor* (NAI) class of influenza antivirals.[16]

As of 2019, 18 different influenza HA glycoproteins and 11 different NA glycoproteins have been described.[17] The currently circulating influenza A virus subtypes in humans emerged from pandemics in 1968 (A/H3N1) and 2009 (A/H1N1pdm).[12] Two antigenically distinct influenza B virus lineages are cocirculating (B/Victoria and B/Yamagata).[5]

The titer of neutralizing antibodies to the HA glycoprotein correlates with protection against influenza after infection or vaccination.[18] From human challenge studies, an *HA inhibition* (HAI) titer of 40 or greater was associated with 50% protection of subjects from influenza illness, and higher HAI titers were associated with higher rates of protection.[19,20] A larger inoculum of influenza virus is required to cause infection in persons with higher HAI titers, and persons with higher HAI titers are less likely to develop clinical illness after influenza exposure.[21–23] *Inactivated influenza vaccines* (IIVs) are designed to induce immunity to HA, and induction of HAI greater than or equal to 1:40 serves as the standard for IIV licensure.[9,18] More recent studies have shown the importance of other immune parameters, including antibodies to NA and the HA stalk, IgA, and T cell immunity, in protection from influenza.[24–29]

EPIDEMIOLOGY

In temperate regions, influenza viruses circulate in seasonal epidemics during the winter,[2] although summertime influenza illness may also happen.[30] In subtropical and tropical regions, influenza virus circulation may be prolonged or year round, with peak circulation typically during the cold or rainy season.[2] Influenza attack rates and severity differ from year to year, depending on circulating viruses and population immunity. Globally, seasonal influenza is estimated to cause more than 400,000 deaths annually from *lower respiratory tract infection* (LRTI).[3] This may be an underestimate of the total mortality due to influenza because approximately one-third of all influenza hospitalizations do not present as LRTI.[30] The economic costs of influenza, including work absenteeism and decreased productivity, associated costs of care, and disruptions in health care delivery during influenza epidemics, make seasonal influenza a major economic burden.[1] Influenza pandemics have an even greater health and economic impact.[1]

The highest influenza attack rates typically are seen in school-age children (from 5–20% annually) due to their limited preexisting immunity and extensive social mixing.[31] Although the risk of severe influenza is lower in this age group than in others, school-age children are thought to be the major drivers of influenza transmission within communities. As a result, rates of severe influenza illness in older persons typically increase 1 to 2 weeks after influenza is detected in children in a community. Influenza morbidity is greatest at the extremes of age and in persons with certain underlying morbidities. The *Centers for Disease Control and Prevention* (CDC) estimates that from 54,523 to 430,960 people in the United States have influenza-associated hospitalizations annually, with 9% of these in children younger than 5 years and 63% in persons older than 65 years.[32] The CDC also estimates that from 3349 to 48,614 people in the United States die from influenza each year.[33]

Persons with certain underlying medical conditions have a greater risk of severe influenza disease.[34] Among adults age 65 years and older, the risk of death is increased with an underlying lung disease (16-fold), heart disease (8-fold), and both lung and heart disease (21-fold) compared to persons without such conditions. A list of health factors and host factors associated with serious complications of influenza virus infection is in Table 47.1.[35]

INFECTION CONTROL

Influenza is primarily transmitted from person to person by large-particle respiratory droplets, generated by coughing and sneezing. Large-particle droplets generally travel only short distances through the air, requiring close contact for transmission. Indirect contact by touching virus-contaminated objects and then touching one's mucous

Table 47.1 Risk Factors for Serious Complications From Influenza Virus Infection

HEALTH RISK FACTORS
Asthma
Neurologic and neurodevelopment conditions
Blood disorders, such as sickle cell disease
Chronic lung disease, such as COPD and cystic fibrosis
Endocrine disorders, such as diabetes mellitus
Heart disease, such as congenital heart disease, congestive heart failure, and coronary artery disease
Kidney disorders
Liver disorders
Metabolic disorders, such as inherited metabolic disorders and mitochondrial disorders
Obesity with a body mass index of ≥40
Age <19 years on long-term aspirin- or salicylate-containing medications
A weakened immune system due to disease, such as people with HIV or AIDS, or some cancers, such as leukemia; taking medications, such as those receiving chemotherapy or radiation treatment for cancer; or persons with chronic conditions requiring chronic corticosteroids or other drugs that suppress the immune system
OTHER HIGH-RISK GROUPS
Adults ≥65 years
Children <2 years
Pregnant women and women up to 2 weeks after the end of pregnancy
Native Americans, including Alaska Natives
People who live in nursing homes and other long-term care facilities

AIDS, acquired immunodeficiency syndrome; HIV, human immunodeficiency virus.

Courtesy Centers for Disease Control and Prevention. People at high risk for flu complications; 2018. https://www.cdc.gov/flu/highrisk/index.htm.

membranes can also transmit influenza. The contribution of transmission by aerosol, a suspension of fine particles, to the overall influenza burden is uncertain, although it is likely low.[36] However, airborne precautions should be used during aerosol-generating procedures.

Influenza is moderately transmissible from person to person. The number of secondary cases produced by a single infection in a susceptible person has been estimated from contact tracing in outbreak investigations. On average, each person with seasonal influenza transmits the virus to one to two persons causing influenza illness,[37] although transmission depends on multiple viral, host, and environmental factors.[38]

Preventing transmission of influenza virus in health care settings requires multipronged strategies. The CDC core prevention strategies include (1) administration of annual seasonal influenza vaccine to all health care workers exposed to patients, (2) implementation of appropriate respiratory hygiene and cough etiquette to minimize potential exposures, (3) monitoring and management of ill health care workers to prevent or control nosocomial transmission, (4) adherence to standard and droplet precautions for all patient-care activities and respiratory precautions for aerosol- and droplet-generating procedures, and (5) environmental and engineering infection control measures.[39]

PATHOGENESIS

The incubation period from exposure to clinical illness is typically 2 to 3 days.[40] Virus shedding is maximal at the onset of illness and may continue for 5 to 7 days or longer in children.[41,42] Viral shedding precedes symptoms by 12 to 24 hours, although the viral load is typically low during this presymptomatic period.[41] In immunocompromised patients, especially recipients of solid-organ or hematopoietic stem-cell transplants, viral shedding can be prolonged for weeks to months.[24]

Influenza A viruses primarily infect epithelial cells of the airways.[43,44] The viral HA recognizes host cell glycoprotein and glycolipid sialic acid (also termed *neuraminic acid*) residues coupled to galactose by either α-2,3 or α-2,6 linkages. Human influenza virus strains preferentially bind α-2,6–linked sialic acid, which predominates in the upper respiratory tract but can also be found in the lower respiratory tract at lower abundance.[43] The human lower respiratory tract epithelium predominantly expresses α-2,3–linked sialic acid, in common with epithelial cells of birds, the natural reservoirs for most influenza viruses.[43] Animal influenza viruses that gain the ability to bind α-2,6–linked sialic acid can more efficiently be transmitted from human to human.[43] Viral attachment induces endocytosis, followed by acidification of the endosomes and a pH-dependent conformational change of the HA that enables fusion of the viral envelope with the endosome membrane and release of viral RNA into the cell cytoplasm for viral replication. The infection cycle is completed by NA-dependent release of new viral particles from the infected cells, allowing spread to neighboring cells for additional cycles of viral replication and amplification.[43] The influenza viral load in respiratory tract specimens generally correlates with levels of inflammatory mediators and with the severity of clinical illness. Mild influenza illness predominantly involves the upper respiratory tract and trachea, whereas severe influenza illness often involves the lower respiratory tract.[44]

Histologic changes due to influenza are nonspecific. Multifocal destruction and desquamation of the pseudostratified columnar epithelium of the upper respiratory tract and large airways are characteristic and can be found early in influenza illness.[44] Submucosal edema and congestion may be pronounced.[44,45] Influenza virus infection induces production of proinflammatory cytokines, including interleukin (IL)-1β, tumor necrosis factor, and IL-6, which activate epithelial and endothelial cells and increase their adhesion properties and permeability. Influenza virus also leads to production of CC motif chemokine ligand-2 and IL-8, which recruit monocytes and neutrophils, respectively.[45] Severe influenza pneumonia exhibits diffuse alveolar damage with hyaline membranes lining the alveoli; the alveolar air spaces contain edema fluid, strands of fibrin, desquamated epithelial cells, and inflammatory cells. The inflammatory state of influenza virus infection can activate inflammatory cells in atherosclerotic plaques and induce expression of genes linked to platelet activation, increasing the risk of influenza-associated myocardial infarction.[46] The pathophysiologic consequences of the respiratory tract damage and endothelial inflammation can persist after viral clearance and clinical resolution of the infection.[47,48]

Bronchoscopy of individuals with influenza may reveal diffuse inflammation of the larynx, trachea, and bronchi, as well as a range of histologic findings in biopsy samples, from vacuolization of columnar cells with cell loss to extensive desquamation of the ciliated columnar epithelium

down to the basal layer of cells.[49–51] In influenza pneumonia, the tissue response becomes more prominent as one moves distally in the airway. Recovery is associated with rapid regeneration of the epithelial cell layer and pseudometaplasia.

Abnormal pulmonary function can be found in otherwise healthy, nonasthmatic young adults with uncomplicated influenza. Defects include diminished forced expiratory flow rates, increased total pulmonary resistance, and decreased forced expiratory flow rates consistent with generalized increased resistance in airways less than 2 mm in diameter[52,53] and increased responses to bronchoprovocation.[53] Abnormalities have also been found in the carbon monoxide diffusing capacity and the alveolar-arterial oxygen tension difference. Pulmonary function defects can persist for weeks after clinical recovery. Influenza in patients with asthma or COPD may result in acute declines in forced vital capacity and/or forced expiratory volume in 1 second. Individuals with acute influenza may be more susceptible to bronchoconstriction from air pollutants, such as nitrates,[52–54] or to bronchoprovocation.[53,55,56]

COPATHOGENESIS OF INFLUENZA WITH BACTERIA

The association between influenza and bacterial pneumonia is a well-established phenomenon, with recognition dating back to the 1918 pandemic, when most of the deaths likely resulted from secondary bacterial pneumonia.[57–59] Bacterial pneumonia is associated with contemporary pandemics and with seasonal influenza but is thought to cause less excess mortality than in the 1918 pandemic. Nonetheless, one-quarter to one-half of severely ill patients with 2009 A/H1N1pdm influenza had bacterial infections.[60–64] There is evidence that the incidence of secondary bacterial infection in critically ill patients with influenza is increasing, and that there is greater morbidity associated with secondary bacterial infection.[65,66]

The most common etiology of secondary infection is *Streptococcus pneumoniae,* but *Staphylococcus aureus* (including *methicillin-resistant S. aureus* [MRSA]) has become increasingly common, and *Streptococcus pyogenes* has also been reported.[61,67–74] Increasing age and immunosuppression may be risk factors for influenza-associated bacterial pneumonia.[65]

Animal models have shown that influenza virus infection enhances susceptibility to bacterial pneumonia.[69] The peak window of susceptibility is 1 to 2 weeks after influenza virus infection, although viral effects increasing susceptibility may persist for weeks to months.[75–78] The mechanisms leading to secondary bacterial pneumonia are complex. Influenza virus infection results in the compromise of natural physiologic barriers, such as the respiratory epithelium, with resulting exposure of attachment sites for invading bacteria; decreased mechanical clearance of bacteria due to impaired ciliary function; impairment in phagocyte, lymphocyte, and antimicrobial peptide function; depletion of alveolar macrophages; and reduced pathogen pattern recognition receptor sensing.[68,69,75] Interferons induced by influenza virus appear to be particularly important in suppressing the host response to invading bacteria.[68,75] Influenza NA also releases free sialic acid, which can serve as a carbon source to promote growth of *S. pneumoniae,*[79] and there is evidence that influenza viruses can bind directly to *S. pneumoniae* or to *S. aureus* to promote bacterial binding to host epithelial cells.[80]

Susceptibility to pathogens after influenza virus infection may not be limited to bacteria because there have been several reports of influenza-associated pulmonary aspergillosis in severely ill patients.[81–86] Influenza-associated pulmonary aspergillosis has been found in both immunocompetent and immunocompromised patients, but at higher rates in the latter. One retrospective, multicenter cohort study found that 19% of adult influenza patients with acute respiratory failure admitted to the *intensive care unit* (ICU) had invasive pulmonary aspergillosis; the mortality rate exceeded 50%.[83] These studies suggest that influenza may be an independent risk factor for invasive pulmonary aspergillosis.

VACCINES

Two classes of influenza vaccines are currently available: IIVs and *live-attenuated influenza vaccines* (LAIVs). IIVs induce antibodies to the influenza virus HA glycoprotein as their primary mechanism of action.[5,18] They differ by production system (chicken eggs, cultured mammalian cells, or recombinant protein synthesized in cultured insect cells), manufacturing process, presence of adjuvants, dose and valence (number of strains), and age groups for which their use is approved (Table 47.2).[4,17] Recombinant vaccines, typically categorized with IIVs but more accurately called *nonreplicating influenza vaccines*, contain influenza antigens produced in noninfluenza virus systems but protect by the same mechanism of action as IIVs. Recombinant vaccines may be produced more rapidly than those produced in chicken eggs after identification of a new circulating virus type.

The major LAIV in use globally, FluMist (Fluenz in Europe), is licensed in the United States for use in persons 2 to 49 years of age. LAIVs were developed to mimic natural infection more closely by stimulating a broader immune response, resulting in more durable immunity than IIVs.[5] LAIVs are cold adapted so that they replicate optimally in nasal mucosa and are less able to replicate in the (warmer) lower respiratory tract. Early clinical trials found greater efficacy of LAIVs compared to IIVs in children, but subsequent observational vaccine effectiveness studies have not shown this benefit.[87] The presence of an underlying medical condition that can put people at higher risk of severe influenza complications (see Table 47.1) is considered a precaution to vaccination with LAIVs.[88]

In the United States, all persons age 6 months and older are recommended to receive annual influenza vaccination; no one vaccine product is currently prioritized for use.[4] However influenza vaccine policies differ among countries. Those with national influenza vaccine programs typically prioritize specific risk groups and may even prioritize certain vaccine products.[89] For example, the United Kingdom prioritizes LAIVs for children and adjuvanted or high-dose IIVs for older adults.[89,90]

Table 47.2 Influenza Vaccines: United States, 2019–20 Influenza Season

Trade Name	Age Indication	Antigen Amount per Vaccine Dose (HA Concentration in IIVs and RIV4) or Virus Count (LAIV4) (Each Vaccine Virus)	Production System	Adjuvant	Route
QUADRIVALENT* IIV (IIV4): STANDARD DOSE, CONTAINS INACTIVATED VIRUS					
Afluria Quadrivalent	≥6 mo	7.5 μg/0.25 mL (for <3 years) 15 μg/0.5 mL (for ≥3 years)	Egg	No	IM
Fluarix Quadrivalent	≥6 mo	15 μg/0.5 mL	Egg	No	IM
Flulaval Quadrivalent	≥6 mo	15 μg/0.5 mL	Egg	No	IM
Fluzone Quadrivalent	≥6 mo	7.5 μg/0.25 mL (for <3 yr) 15 μg/0.5 mL (for any age)	Egg	No	IM
Flucelvax Quadrivalent	≥4 yr	15 μg/0.5 mL	Cell culture	No	IM
TRIVALENT† IIV3: HIGH DOSE, CONTAINS INACTIVATED VIRUS					
Fluzone High Dose‡	≥65 yr	60 μg/0.5 mL	Egg	No	IM
TRIVALENT† IIV3: ADJUVANTED, CONTAINS INACTIVATED VIRUS					
Fluad‡	≥65 yr	15 μg/0.5 mL	Egg	Yes (MF59)	IM
QUADRIVALENT* RIV (RIV4): CONTAINS RECOMBINANT HA					
Flublok Quadrivalent	≥18 yr	45 μg/0.5 mL	Recombinant	No	IM
QUADRIVALENT* LAIV (LAIV4): CONTAINS LIVE, ATTENUATED, COLD-ADAPTED VIRUS					
FluMist Quadrivalent	2–49 yr	$10^{6.5–7.5}$ fluorescent focus units/0.2 mL	Egg	No	NAS

*Contain antigens from four viral strains, two to three from influenza A and one to two from influenza B.
†Contain antigens from three viral strains, usually two influenza A and one influenza B.
‡Licensed for those ≥65 years.
HA, hemagglutinin; IIV, inactivated influenza vaccine; IM, intramuscular; LAIV, live-attenuated influenza vaccine; NAS, intranasal; RIV, recombinant influenza vaccine.
From Grohskopf LA, Alyanak E, Broder KR, et al. Prevention and control of seasonal influenza with vaccines: recommendations of the Advisory Committee on Immunization Practices—United States, 2019–20 influenza season. *MMWR Recomm Rep.* 2019;68:1–21.

Although there is evidence that effectiveness of IIVs decreases over the course of the influenza season, potentially due to waning humoral immunity and/or drifting circulating virus strains, public health officials generally do not recommend delaying influenza vaccination once vaccines become available. The poor ability of the available IIVs to induce long-lived immunologic memory has led to efforts to develop new formulations of influenza vaccines that generate more durable protection.[91] Efforts to develop so-called "universal" influenza vaccines based on generation of broadly-neutralizing antibodies that recognize influenza antigens that do not mutate at high frequencies have shown promising results in preclinical studies.[92]

The effectiveness of influenza vaccines depends on many different factors, including the degree of antigenic match between the vaccine and circulating viruses, product differences, the age of the individual being vaccinated, and the outcome being measured. The CDC reports all-age vaccine effectiveness against medically attended, laboratory-confirmed influenza illness has ranged from 10–60% in recent years.[93] Observational studies have shown influenza vaccine effectiveness among persons with high-risk conditions,[94–101] and influenza vaccines are effective at preventing clinically important outcomes, such as hospitalizations,[95–98] critical illness,[94–98,102] and death.[103,104] A 2015 systematic review and meta-analysis found that in *randomized controlled trials* (RCTs) of influenza vaccine among persons with cardiovascular disease, vaccination significantly decreased the risk of all-cause cardiovascular deaths by 55%.[105] Influenza vaccination also reduces the severity of *breakthrough* disease (infections that develop despite vaccination with the appropriate strain), including decreased in-hospital death, ICU length of stay, and hospital length of stay.[103,104]

Even with suboptimal vaccine effectiveness, the number of severe illnesses averted by vaccination programs is substantial. During the unusually severe 2017–18 influenza season, there were an estimated 953,000 hospitalizations and 79,400 deaths associated with influenza in the United States.[106] Although the seasonal influenza vaccine was only 38% effective that year, an estimated 109,000 hospitalizations and 8000 deaths were still averted by vaccination, mostly among persons age 50 years and older.[106]

Despite public health recommendations that all persons receive annual influenza vaccination, vaccine coverage remains suboptimal, particularly among groups at the highest risk of severe influenza complications (see Table 47.1). In the United States during 2012, only 45% of adults aged 18 to 64 years with at least one high-risk condition received the influenza vaccine, and coverage ranged from 44–53% among those with pulmonary diseases, diabetes, heart disease, and cancer.[107,108] White adults have about 10% greater influenza vaccine coverage than African Americans or Hispanics.[109] Behavioral studies have found that more adults would accept the influenza vaccine if it were recommended by a health care provider, if there were more opportunities for vaccination, and if systems were in place that bypassed the health care provider to determine patient vaccination status and to offer vaccination routinely.[110,111]

PATIENT MANAGEMENT

CLINICAL PRESENTATION

Influenza often presents with the sudden onset of symptoms, commonly fever, cough, and sore throat. Other symptoms associated with acute influenza illness include arthralgia, chest tightness, chills, conjunctivitis, nasal congestion, sinus congestion, coryza, decreased appetite, diarrhea, dry cough, dyspnea, fatigue/tiredness, headache, myalgia, nausea, rhinorrhea, and sweats.[112] No combination of clinical signs and symptoms is sufficiently predictive of influenza illness, necessitating laboratory testing to confirm influenza virus infection. Furthermore, research using highly sensitive and specific diagnostic tests has demonstrated great variability in presenting signs and symptoms among persons with influenza virus infection. In particular, very young, older, and immunocompromised patients may present with atypical symptoms, and hospital surveillance studies have shown that about 40% of hospitalized adults with confirmed influenza do not have a fever.[113] Contact testing in influenza outbreaks and controlled human infections with influenza have demonstrated that subclinical influenza virus infection can be common.[114]

The clinical practice guidelines prepared by the *Infectious Diseases Society of America* (IDSA) recommend that decisions to test patients for influenza should rely on consideration of the broader clinical and epidemiologic context, including the risk of patient exposure to circulating influenza, the presence of high-risk conditions, the likelihood that antiviral treatment would be provided if there were a positive result, and whether a positive result would reduce the use of unnecessary antibacterial medicines.[34] An influenza testing algorithm adapted from the IDSA Clinical Practice Guidelines is shown in Fig. 47.2. This algorithm applies during periods of known influenza circulation. Although the risk of influenza illness substantially decreases outside of the traditional influenza season, summertime outbreaks and travel-related infections are observed.[115–117] The presence of sick contacts and travel-related exposures should be assessed when patients with influenza-like illness present outside of the usual influenza season. The differential diagnosis for influenza-like illness is broad, including other respiratory viruses, such as adenovirus, respiratory syncytial virus, metapneumovirus, coronavirus, rhinovirus, and parainfluenza virus; bacterial upper and lower respiratory tract infections; and systemic infections such as malaria. Therefore clinicians should also consider host factors, such as presence of high-risk conditions (see Table 47.1) or recent exposure to health care facilities and travel history or place of residence that may affect susceptibility or exposure to different pathogens, and should be prepared to treat sick patients presumptively for infection broadly and early as the diagnostic evaluation proceeds. The influenza vaccination status of the patient should not be considered when making testing decisions because vaccine failures are common.[93]

Not all hospitalized patients with influenza present with primary respiratory processes. Modeling studies

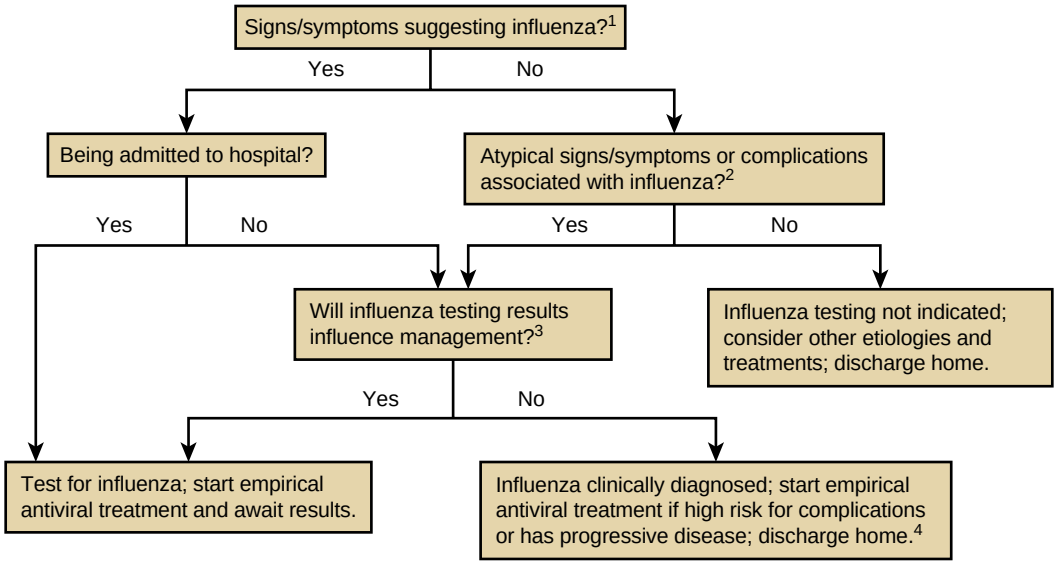

Figure 47.2 Algorithm for considering influenza testing during periods of known influenza circulation. *1,* Signs and symptoms may include fever with cough or other suggestive respiratory symptoms, often with myalgias or headache. Note that some individuals, especially older adults, infants, and immunocompromised, may have atypical presentations, including a lack of fever. *2,* Atypical signs and symptoms may include unexplained fever only or lack of fever with any respiratory symptoms, especially in immunocompromised or high-risk patients. Complications associated with influenza include pneumonia or exacerbation of chronic conditions, such as asthma, COPD, or heart failure. *3,* Influenza testing may be used to guide decisions on use of antibiotics or continuation of antiviral medication, on need for further diagnostic tests, on consideration for home care, or on recommendations for ill persons living with others who are at high risk for influenza complications. Influenza testing may be required to guide decisions on infection control practices. *4,* Antiviral treatment is recommended for outpatients with suspected influenza who are at high risk for complications from influenza or those with progressive disease not requiring hospital admission. Antiviral treatment of outpatients who are not at high risk for influenza complications can be considered based upon clinical judgment if presenting within 2 days of illness onset. (Modified from Uyeki TM, Bernstein HH, Bradley JS, et al. Clinical practice guidelines by the Infectious Diseases Society of America: 2018 update on diagnosis, treatment, chemoprophylaxis, and institutional outbreak management of seasonal influenza. *Clin Infect Dis.* 2019;68:895–902.)

suggest that one-third of hospitalized influenza cases may not have pneumonia but rather primary circulatory diagnoses, such as septic shock.[29] Influenza can exacerbate underlying conditions such as chronic lung disease or diabetes, or cause extrapulmonary complications, including encephalitis or myocarditis.[47,48] Influenza-triggered cardiovascular events, including myocardial infarction, heart failure, arrhythmias, and strokes, are increasingly recognized.[46,118,119] Patients presenting with symptoms suggestive of influenza should be evaluated to ensure identification of physiologic derangements such as hypoxemia, respiratory compromise, or hemodynamic instability.

DIAGNOSTIC TESTING

The definitive diagnosis of influenza requires laboratory testing. When influenza virus is circulating in the community, patients with influenza-like illness, pneumonia, or other nonspecific respiratory illness should be tested because these data will affect treatment, postexposure prophylaxis of close contacts, and infection control measures.

Specimens

Respiratory tract sampling is the optimal approach to influenza detection. For most patients, upper respiratory tract sampling is appropriate, preferably a nasopharyngeal swab. If nasopharyngeal specimens cannot be obtained, midturbinate nasal or combined nasal-throat swabs are acceptable. For patients with influenza-like illness undergoing mechanical ventilation, endotracheal aspirates should be obtained in parallel.[66,120–123] Invasive collection of respiratory specimens, such as by bronchoalveolar lavage, solely for the purpose of influenza testing is not recommended; however, such testing can be performed on these samples collected for other reasons.[124,125] Although viremia and detection of virus in other organs have been observed in severe influenza, there is no role for sampling of sites other than the respiratory tract in clinical practice.[126–128]

Rapid Antigen Detection Tests

Rapid antigen detection tests can be performed within 15 minutes and have low to moderate sensitivity but high specificity.[129–131] Use of these tests is not recommended if more sensitive, rapid molecular tests are available.

Immunofluorescence Assay

Immunofluorescence assay tests may be direct or indirect. They take 1 to 4 hours and have moderate sensitivity but high specificity.[132] Use of these tests is not recommended if more sensitive, rapid molecular tests are available.

Molecular Diagnostics

Molecular tests for influenza include *reverse-transcription polymerase chain reaction* (RT-PCR) and other nucleic acid amplification tests (see Chapter 19). Some rapid molecular tests can be performed within 30 minutes. All molecular tests are highly sensitive and specific.[130] Molecular tests may also indicate the subtype of influenza virus and can be combined in multiplex assays to detect other viruses. RT-PCR-based tests are the preferred diagnostic method for clinical decision making.[34]

Culture

Culture of virus takes several days but is sensitive and specific.[133] Unlike molecular diagnostics, only infectious (live) virus will be detected. Although culture is not recommended for routine use, this method has the advantage of furnishing virus for additional testing such as subtyping, antigenic identification, and antiviral drug susceptibility analyses.

Serology

Serologic diagnosis of influenza virus infection by HAI requires paired—acute and convalescent—sera tested at least 2 weeks apart demonstrating a fourfold or greater increase in antibody titer.[134] Serology cannot, therefore, be used for the timely diagnosis of influenza but may have a role for retrospective diagnosis or serologic epidemiology studies.

Summary

The IDSA Clinical Practice Guidelines recommend molecular influenza assays for testing outpatient and hospitalized patient specimens due to the high sensitivity and specificity, as well as the speed of these tests.[34] In hospitalized patients, the use of multiplex RT-PCR assays that identify a variety of respiratory pathogens should be considered; these multiplex assays are recommended in immunocompromised patients.[34]

RADIOGRAPHIC FINDINGS

The clinical manifestations of influenza virus infection may vary greatly and include severe influenza pneumonia and secondary bacterial pneumonia. Patients with clinical features suggesting pneumonia, such as dyspnea, hypoxemia, or hemodynamic instability, should undergo chest imaging. Radiographic findings in influenza pneumonia tend to be nonspecific in both immunocompetent and immunocompromised patients.[135,136] Chest radiographs may show bilateral abnormalities suggestive of pulmonary edema or multifocal pneumonia (Fig. 47.3 and eFig. 47.1), although unilateral consolidation is also reported.[135,137] Chest computed tomography scans in influenza pneumonia commonly demonstrate multifocal areas of ground-glass opacity and consolidation[138] (Fig. 47.4 and eFig. 47.2), although widely different patterns can be present (Fig. 47.5). Pleural effusions are uncommon. Point-of-care lung ultrasound may reveal evidence of interstitial syndrome, that is, the presence of B lines or lung consolidation.[139,140] Differentiating primary influenza pneumonia from influenza-associated bacterial pneumonia using chest imaging is difficult, although the presence of necrotizing pneumonia with cavitation or evidence of empyema suggest a bacterial etiology (eFig. 47.3).

ANTIVIRAL THERAPIES

Three classes of antiviral agents are currently approved in the United States for treatment and/or prevention of influenza: adamantanes (e.g., amantadine and rimantadine), which target the M2 ion channel protein of influenza A viruses; NAIs (e.g., oseltamivir, zanamivir, and



Figure 47.3 Influenza A virus infection. Frontal chest radiograph shows multifocal, bilateral, perihilar, and lower lobe predominant bronchovascular thickening and somewhat nodular consolidation. (Courtesy Michael B. Gotway, MD.)

peramivir), which block the viral NA enzyme of influenza A and B viruses; and the cap-dependent endonuclease inhibitor (baloxavir), which interferes with viral RNA transcription and viral replication in both influenza A and B viruses. Outside the United States three additional antiviral agents are available: laninamivir, an inhaled NAI; arbidol, an oral drug that interacts with HA to prevent membrane fusion; and favipiravir, an oral inhibitor of viral RNA-dependent RNA polymerase.[8]

Adamantanes

The M2 protein, the target of adamantanes, is located in the viral envelope, where it functions as a proton channel and is essential for viral entry into the host cell cytoplasm, where viral replication takes place. The M2-inhibiting adamantanes specifically block the ion channel function of the influenza A M2 protein and are not active against influenza B viruses. Resistance to these drugs emerges readily in treated individuals, particularly children, and there may be prolonged shedding of resistant viruses in immunocompromised patients.[141,142] For reasons that remain unclear, the first decade of this century has seen the emergence and spread of adamantane-resistant influenza A/H3N2 viruses;

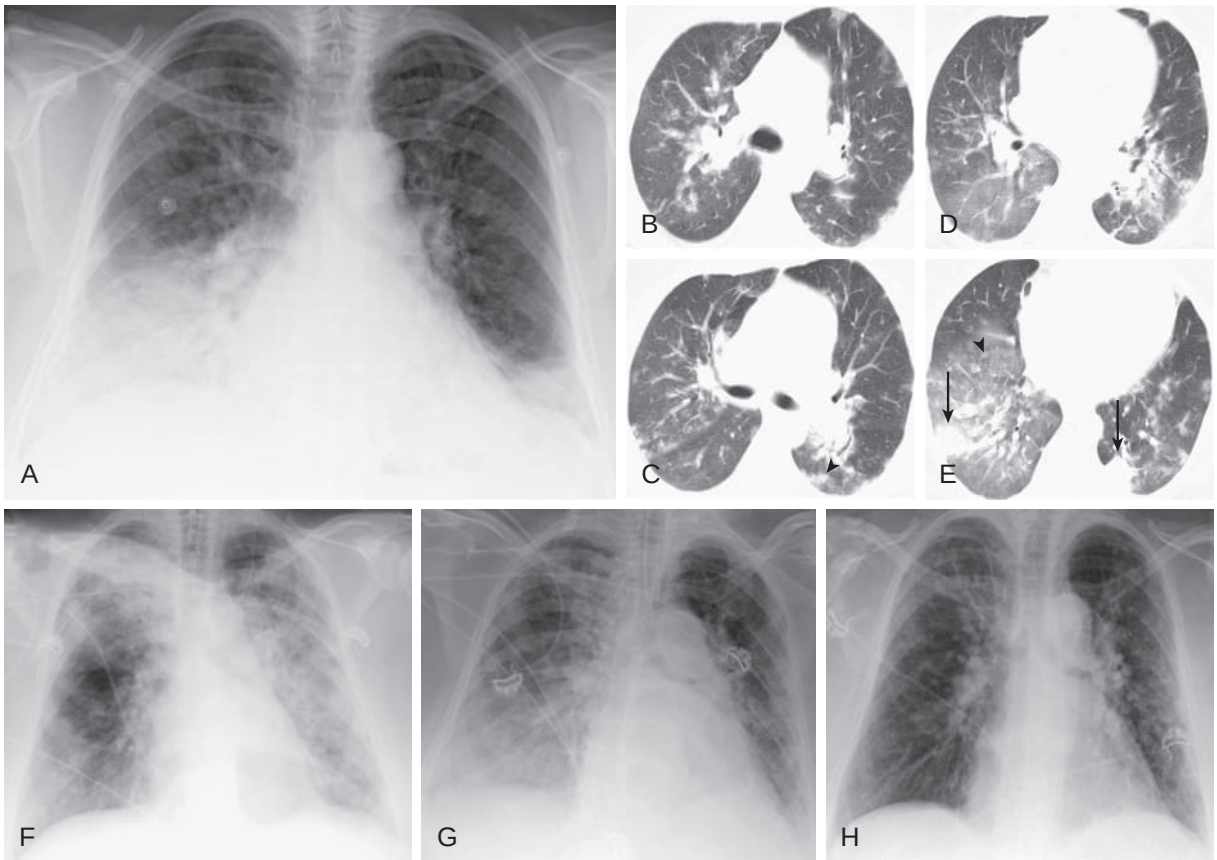

Figure 47.4 Influenza A/H1N1pdm virus infection: imaging findings. (A) Frontal chest radiograph in a patient subsequently diagnosed with A/H1N1pdm influenza during the 2009 pandemic shows multifocal basal predominant consolidation, consistent with bronchopneumonia but nonspecific. (B–E) Axial chest computed tomography displayed in lung windows shows nonspecific bilateral areas of ground-glass opacity, nodular subpleural consolidation *(arrows),* and other foci of patchy, peripheral, increased lung attenuation, and small nodules *(arrowheads),* some of which appear centrilobular. (F–H) Serial frontal chest radiographs obtained during the course of the disease show worsening of bilateral opacities associated with hypoxemic respiratory failure (F and G) but subsequent clearing of bilateral lung opacity after recovery (H). (Courtesy Michael B. Gotway, MD.)

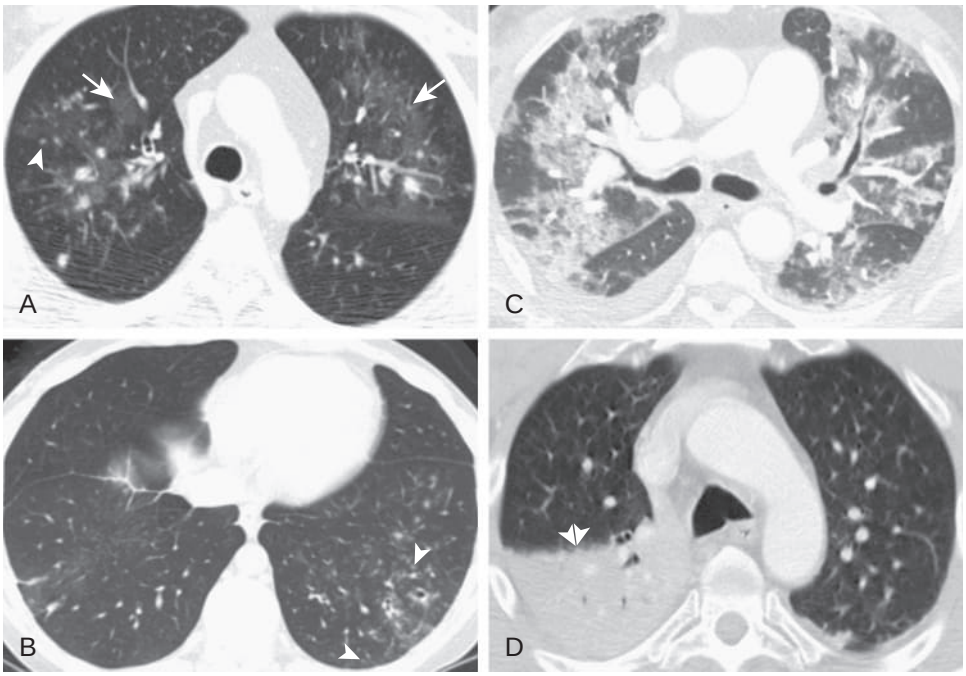

Figure 47.5 Influenza A/H1N1pdm virus infection in four different patients: strikingly different imaging findings at chest *computed tomography* (CT). (A–B) Axial chest CT displayed in lung windows shows patchy areas of upper lobe predominant ground-glass opacity *(arrows)* and small, solid, centrilobular nodules *(arrowheads)*. The opacity in the left lower lobe (B) appears somewhat segmental, suggestive of bronchopneumonia. (C) Axial chest CT shows multifocal, bilateral areas of ground-glass opacity associated with interlobular septal thickening and intralobular interstitial thickening but no clear zonal distribution; these findings are nonspecific and can be observed with numerous infections and noninfectious inflammatory pulmonary insults. (D) Axial chest CT shows right lower lobe superior segmental dense consolidation *(double arrowhead),* suggestive of a lobar pneumonia pattern. (Courtesy Michael B. Gotway, MD.)

A/H1N1pdm viruses are also uniformly resistant.[143] Therefore the adamantane M2 inhibitor drugs do not have utility against current influenza viruses and are not presently recommended for use. They may have a role if susceptible strains emerge in the future.

Neuraminidase Inhibitors

NAIs are potent inhibitors of influenza virus in vitro and in vivo because NA activity is essential for viral release from infected cells, a necessary step for viral spread to other cells. Influenza B viruses are less sensitive to NAIs than influenza A viruses but are susceptible at clinically achievable concentrations. Oseltamivir phosphate is an orally bioavailable ethyl ester prodrug rapidly absorbed from the gastrointestinal tract and metabolized by hepatic esterases to the active metabolite, oseltamivir carboxylate. The metabolite is excreted unchanged in the urine by tubular secretion, with a serum half-life of 6 to 10 hours. The major adverse effects of oseltamivir are nausea and vomiting.[144,145] Oseltamivir is approved for treatment of adults and children and for prophylaxis in adults and children at least 3 months of age. Zanamivir is not orally bioavailable and is administered as a dry powder for inhalation. After inhalation, zanamivir concentrates in the respiratory tract, and systemic absorption is low.[146] Inhaled zanamivir may be associated with bronchospasm, particularly in those with underlying airways disease; this acute bronchospasm has sometimes been severe and has resulted in a recommendation that inhaled zanamivir not be given to patients with respiratory disease, such as asthma or COPD.[147] Zanamivir is approved for treatment of adults and children at least 7 years of age and for prophylaxis in adults and children at least 5 years of age. Peramivir is the most recent NAI to become available in the United States, having been approved in 2014 for single-dose *intravenous* (IV) administration. Peramivir binds with greater affinity than oseltamivir to NA and has a half-life of 20 hours with renal clearance.[148] Peramivir is approved for the treatment of influenza in adults and children age at least 2 years of age but is not recommended for prophylaxis. All three NAIs are associated with risks of serious skin reactions and sporadic, transient neuropsychiatric events, mostly in children.

Cap-Dependent Endonuclease Inhibitor

Baloxavir marboxil is the newest antiviral agent available for use in the United States. Baloxavir marboxil is an oral prodrug of baloxavir acid that is a selective inhibitor of influenza cap-dependent endonuclease, thus preventing initiation of viral messenger RNA synthesis.[149] A phase III RCT found a significant reduction in time to alleviation of symptoms from 80.2 hours for individuals treated with placebo versus 53.7 hours for individuals treated with a single dose of baloxavir.[150] This was similar to oseltamivir. In addition, viral loads at 1 day were lower in patients treated with baloxavir compared to either placebo or oseltamivir.[150] To date, few adverse events have been associated with baloxivir.[151]

ANTIVIRAL RESISTANCE

The high mutation rate of influenza RNA polymerase can alter susceptibility to antiviral agents.[152,153] Although

resistance to adamantanes is widespread, as of 2019, resistance to NAIs in circulating influenza viruses is uncommon.[143,154] For example, surveillance data through 2018 indicated that among seasonal influenza viruses, the frequency of oseltamivir resistance was less than 3.5%, and zanamivir resistance was less than 1%.[154] However, the emergence of resistance among seasonal influenza viruses has been observed, as for an H1N1 A/Brisbane/59/2007–like virus with a single amino-acid substitution that impaired oseltamivir binding. This strain rapidly became the predominant circulating strain globally, although it was subsequently replaced by the oseltamivir-sensitive A/H1N1pdm virus.[152] Therefore reemergence of influenza NAI resistance remains of great concern. Testing for resistance may be considered in patients who develop influenza while receiving prophylaxis with an NAI, in those who are immunocompromised, in those who have severe illness and continue to have evidence of viral replication or lack of improvement, and in those who received subtherapeutic treatment with NAIs with severe disease and evidence of viral replication.[34] In phase II and III trials of baloxavir, the emergence of viruses with mutations of the polymerase acidic protein (PA/I38X) was noted in 2.2–9.7% of baloxavir-treated patients.[150,153] These variant viruses were associated with increased infectious virus titers, prolonged shedding, delay in symptom alleviation, and symptom rebound.[153]

ANTIVIRAL TREATMENT DECISIONS

The efficacy of antiviral treatment depends on several factors, including the host's age, immune status and medical comorbidities, the virus type or subtype, and the timing of treatment initiation relative to the course of infection.[144,155–166] Several RCTs conducted primarily in outpatients indicate that NAIs, administered within 36 to 48 hours of illness onset, reduce the duration of fever and symptoms by 1 to 2 days.[157–159,167–170] Starting treatment within 6 hours of illness reduced symptoms by about 4 days.[164,171,172] Moreover, NAI treatment may decrease other complications, such as otitis media in children or need for antibiotic treatment for lower respiratory infection and hospitalization in adults.[144,145,173] A large individual patient-level meta-analysis of high-risk outpatients showed that NAI treatment reduced the likelihood of hospital admission.[174] There are limited RCT data of antiviral therapy in hospitalized patients to guide management of severe influenza. However, observational studies, individual patient-level meta-analyses, and meta-analyses suggest a clinical benefit of NAIs in hospitalized patients, even when therapy is delayed, although this may not include improvement in survival.[144,155–157,160,165,166,175–180] The CDC notes that prompt treatment with antivirals reduces the duration of symptoms and risk of some complications and may decrease mortality in high-risk groups,[181] and therefore clinical practice guidelines recommend the treatment of high-risk outpatients (see Table 47.1) and severely ill or hospitalized patients.[34] Treatment should be considered for symptomatic individuals who do not meet these criteria but who have been ill for less than 2 days or who are close contacts, including health care providers, of individuals at risk of complications from influenza, to prevent transmission to the latter. In these circumstances the CDC recommends initiating treatment for suspected influenza without awaiting laboratory confirmation.[151]

For nonhospitalized patients with uncomplicated influenza, any of the three NAIs (oral oseltamivir, inhaled zanamivir for 5 days, or a single dose of IV peramivir) or baloxavir is suggested. However, the CDC recommends prescribing oseltamivir for patients with severe, complicated, or progressive illness who are not hospitalized. For hospitalized patients, oseltamivir is the recommended NAI because there are limited or no data about the efficacy of inhaled zanamivir, IV peramivir, or oral baloxavir in patients with severe influenza. Oseltamivir is also preferred for pregnant women, and NAIs are generally considered safe in pregnancy.[151]

Clinicians should refer to clinical practice guidelines for further advice regarding influenza chemoprophylaxis and for further information regarding influenza diagnosis and treatment, particularly in special circumstances.[34,39,151]

PATIENTS WITH PNEUMONIA

Patients with influenza and radiographic evidence of pneumonia may have primary influenza pneumonia or bacterial pneumonia. Bacterial cultures of respiratory tract specimens and blood, and urinary antigen testing, should therefore be performed according to American Thoracic Society/ISDA guidelines.[182,183] Until the etiology of pneumonia is confirmed, empirical therapy for community-acquired or hospital-acquired pathogens should be administered as dictated by the patient's recent history of potential exposure to resistant pathogens.[182,183] In particular, antibiotics to cover common influenza-associated bacterial pathogens, especially *S. pneumoniae* and *S. aureus*, should be administered promptly. Due to the association of community-acquired MRSA pneumonia with influenza, severely ill patients should be given antibiotics active against MRSA.[34] Antibacterial treatment should be continued until bacterial infection is ruled out or adequately treated. Although several studies have evaluated the use of serum procalcitonin measurements to discriminate bacterial infection associated with influenza, a clear role for procalcitonin measurements in management of influenza patients has yet to be defined.[184,185]

CRITICALLY ILL PATIENTS

Seasonal influenza causes a substantial burden of disease worldwide.[3] As evidenced by the 2009 pandemic, influenza pandemics also place tremendous demands on critical care resources.[186–189] A 2019 review reported that among patients with influenza admitted to the ICU, A/H1N1pdm was the most common strain identified. Influenza pneumonia was present in 70%, secondary bacterial infection in 20%, and mortality associated with acute respiratory failure was 20%.[190] To reduce the risk of death, critically ill patients with suspected or diagnosed influenza illness should be given NAI therapy, preferably oseltamivir, without delay, even if symptoms have been present longer than 48 hours.[156] Appropriate concurrent antimicrobial coverage for bacterial respiratory pathogens is imperative. Oseltamivir administered via the enteral route yields adequate serum levels.[191] There does not appear to be a benefit of higher-dose oseltamivir.[192] The dose of oseltamivir should be reduced in patients receiving continuous renal replacement therapy but does not need adjustment during extracorporeal life support.[193–195] Zanamivir has a limited

role in treatment of critically ill patients because the inhaler device is difficult to use effectively in individuals not breathing spontaneously and because the lactose powder formulation of zanamivir may cause ventilator filter obstruction in patients receiving mechanical ventilation.[196,197] Few studies guide the appropriate use of IV peramivir and, despite one study showing no benefit from peramivir in hospitalized patients, it remains an option if enteral administration of oseltamivir is not possible.[198] The optimal duration of antiviral therapy in critically ill patients with influenza is not known. Due to concern for prolonged viral replication and shedding in critically ill patients, longer courses of antiviral therapy may be considered.[121,199] In these cases repeat virologic testing may help guide therapy. Baloxavir has not been studied in severe illness, and combined antiviral therapy is not recommended.[34]

Clinicians should also be aware of the increased risk of myocardial infarction in the setting of influenza virus infection, and abnormal troponin levels should prompt further investigation of this possibility.[46] Among patients with influenza who have clinical indications for statins and aspirin, the medications should be continued or may be initiated if no contraindications are present.[46]

The inflammatory response induced by influenza, with or without secondary bacterial infection, can result in sepsis and multiorgan failure. Influenza-associated respiratory failure and *acute respiratory distress syndrome* (ARDS) are predominantly caused by influenza A viruses and are associated with high mortality.[60,200–204] Management of influenza-associated ARDS is similar to treatment of other etiologies of ARDS and should include lung protective ventilation and consideration of appropriate positive end-expiratory pressure, conservative fluid management, prone positioning, neuromuscular blockade, inhaled pulmonary vasodilators, and use of extracorporeal membrane oxygenation.[205,206]

OTHER THERAPIES

Corticosteroids are sometimes considered as adjunctive therapies of influenza because of studies suggesting possible benefit in sepsis and community-acquired pneumonia.[207,208] However, based on data from observational studies, corticosteroids may be associated with increased mortality.[166,209–217] This was confirmed by a recent Cochrane systematic review and meta-analysis, but the certainty of the evidence was very low due to concern about confounding by indication.[218] Corticosteroids are also associated with prolonged shedding, secondary infections, and development of antiviral resistance.[166,219–225] For these reasons, corticosteroids are not recommended for patients with severe influenza. However, corticosteroids should not be withheld if given for other indications, such as treatment of COPD exacerbation, refractory septic shock, or adrenal insufficiency.

Other therapies have been proposed to treat influenza, including passive immunotherapy with plasma or IV immunoglobulin, 3-hydroxy-3-methylglutaryl coenzyme A reductase inhibitors, and macrolide antibiotics.[179,226–229] There are insufficient data to recommend these therapies at present. Several additional therapeutics are currently being evaluated in preclinical or clinical studies, including monoclonal antibodies to influenza proteins, and nitazoxanide, a thiazolide anti-infective that inhibits replication of influenza viruses by blocking maturation of HA.[230–234]

HUMAN INFECTION WITH NOVEL INFLUENZA VIRUSES

Numerous avian influenza A viruses have infected humans, including H5N1, H6N1, H7N2, H7N3, H7N7, H7N9, H9N2, H10N7, and H10N8 virus subtypes.[235] Avian influenza viruses are classified as *low pathogenic avian influenza* (LPAI) or *highly pathogenic avian influenza* (HPAI) on the basis of molecular and pathogenicity criteria in birds. The LPAI and HPAI classifications have no bearing on pathogenicity in humans. Clinical illness from human infection with avian influenza A viruses has ranged from asymptomatic infection to severe disease and death.[235] To date, none of these avian viruses has been able to sustain human-to-human transmission, but there is a risk that mutation or reassortment could allow the acquisition of this ability.[236] The CDC and the World Health Organization conduct routine risk assessments for the emergence of pandemic viruses, and two avian influenza viruses currently circulating in avian populations (A/H5N1 and A/H7N9) have caused human illness and are considered to have the greatest pandemic potential.[236]

A/H5N1

HPAI influenza A/H5N1 first emerged in wild birds in 1996 and was subsequently identified as the cause of a high-mortality outbreak in humans in Hong Kong in 1997. Since then, more than 800 human infections have been identified with Asian HPAI A/H5N1 viruses,[237] mostly in Southeast and East Asia, the Middle East, and Egypt. One case of human infection with A/H5N1 has been identified in the Americas in a traveler recently returned from China. As of 2019, A/H5N1 is enzootic in wild birds in six countries: Bangladesh, China, Egypt, India, Indonesia, and Vietnam.[238] Greater than 50% of human cases have been fatal. Transmission is thought to take place by inoculation of virus-contaminated poultry meat, blood, or feces on human mucous membranes. Risk factors for A/H5N1 infection in humans include close or direct contact with infected birds or infected sick contacts, visiting a live poultry market in endemic areas, or living in an area where A/H5N1 viruses are circulating among poultry.[238] Most patients with A/H5N1 virus infection present to the hospital with fever and features of lower respiratory tract infection. RT-PCR is the recommended diagnostic test; however, most clinical laboratories do not have the capacity to test specifically for A/H5N1, but they may identify influenza A virus that is unsubtypable, raising concerns of a novel influenza A virus infection and requiring confirmatory testing by a public health reference laboratory.[239] Oseltamivir, administered as early as possible, is the recommended antiviral treatment for suspected or confirmed A/H5N1 patients. Supportive care and specialized intensive care management are indicated for severe illness. Rapid implementation of infection control measures is recommended.[240]

A/H7N9

Asian lineage A/H7N9 is an avian influenza A virus that has caused five annual waves of high-mortality human epidemics focused in China since 2013.[241] Human infection is associated with exposure to infected poultry.[241] Until 2017, A/H7N9 from human and environmental samples was categorized as LPAI, with infections in birds causing only asymptomatic or mild illness.[242] Beginning in February 2017, a genetically similar HPAI A/H7N9 emerged in the same region, was found in environmental and bird samples, and has caused human illness.[242] Only sporadic cases were reported in 2018 and in early 2019.[240,241] The cumulative case-fatality of the detected cases is approximately 39%, with similar mortality seen with LPAI and HPAI infections in humans. Although limited cases of human-to-human transmission have been reported, there is no evidence of sustained transmission among persons.[240,241] As with A/H5N1, RT-PCR is the recommended diagnostic test for A/H7N9 cases, although, as with A/H5N1, most clinical laboratories may only detect it as influenza A virus that is unsubtypable, requiring confirmatory testing by specialty reference laboratories.[239] Oseltamivir therapy as early as possible, appropriate supportive therapies, and rapid implementation of infection control measures are recommended.[240]

Clinicians who suspect A/H5N1, A/H7N9, or other novel influenza viral illness should refer to public health recommendations for clinical guidance[240,243–246] and are encouraged to contact their local or state health department for further assistance.

Key Points

- Influenza is a high-burden disease. Persons at high risk of complications of influenza virus infection include children younger than 2 years; adults older than 65 years; pregnant women up to 2 weeks after the end of the pregnancy; people with certain underlying medical conditions, including obesity, kidney disease, heart disease, lung disease, and weakened immune systems; Native Americans, including Alaska Natives; and nursing home and other long-term care facility residents. Complications may include secondary infections, especially bacterial pneumonias,[247] and increased incidence of myocardial infarction.
- Influenza virus infection can cause a broad spectrum of nonspecific signs and symptoms of disease, including asymptomatic or subclinical illness, febrile acute respiratory infection, exacerbation of an underlying chronic disease, acute lower respiratory tract infection, and death. Infants, older adults, and the immunocompromised are more likely to have afebrile and atypical manifestations of influenza illness.
- Even with only moderate vaccine effectiveness, vaccines have a substantial public health impact, given the massive burden of influenza experienced annually.
- Patients are more likely to receive influenza vaccines if recommended by their health care providers. Even specialist physicians who do not provide immunization services have an important role in increasing coverage in their vulnerable patients by inquiring about vaccination status, recommending vaccination, referring for vaccination, and documenting vaccine receipt.
- Clinicians should use rapid molecular assays to diagnose influenza, with reverse-transcription polymerase chain reaction–based assays for hospitalized patients to improve detection of influenza virus infection.
- Prompt treatment with antivirals reduces the duration of symptoms and risk of some complications and may decrease mortality in high-risk groups. Treatment decisions, particularly in high-acuity settings, should take into account the likelihood of influenza illness and the risk of severe outcomes.
- In institutional and inpatient settings, infection control measures (standard and droplet precautions) should be implemented as soon as possible when outbreaks are suspected, without waiting for results of influenza testing. Airborne precautions should be used during aerosol-generating procedures.
- Health care workers are at risk for infection by and transmission of influenza virus; therefore they should receive annual influenza vaccination and take additional precautions in the event of acute respiratory illness, such as influenza testing, not going to work, respiratory hygiene, face mask use, and/or potential reassignment when exposed to high-risk patients.

Key Readings

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Complete reference list available at ExpertConsult.com.

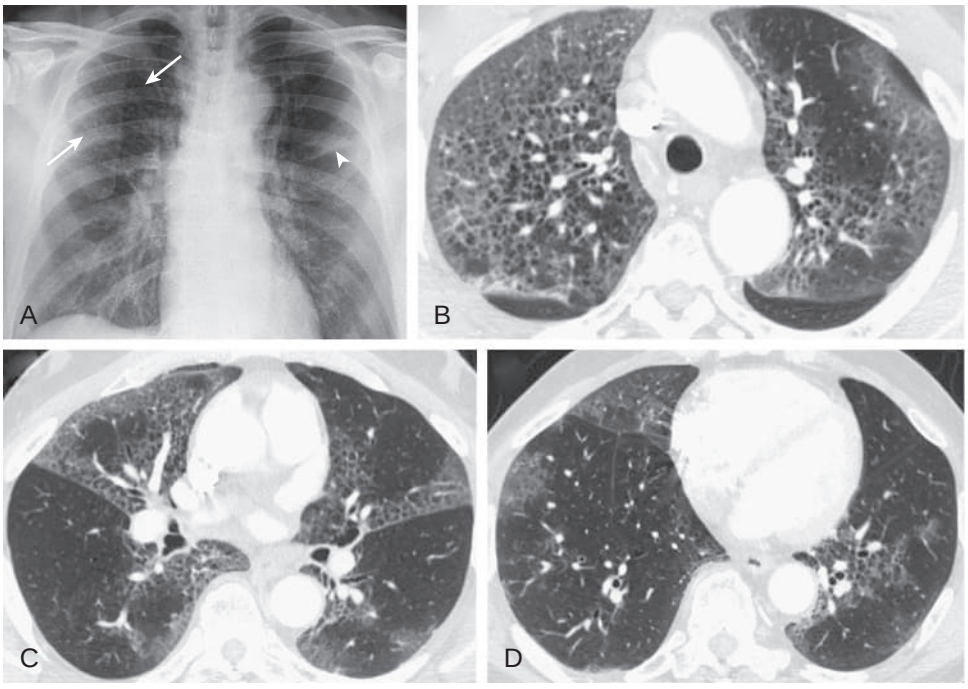
Acknowledgments

We thank the authors of the Viral Infections chapter of *Murray and Nadel's Textbook of Respiratory Medicine,* 6th edition, Drs. Frances Eun-Hyung Lee and John J. Treanor. We retained some of their original work in the Pathogenesis and Antiviral Therapies sections, as well as some radiographic descriptions. We thank Dr. Joel Ernst for advice and editing the chapter and Dr. Mike Gotway for providing radiographic images and for editing the figure legends. We thank Ms. Hanna LeBuhn for her help with the chapter references and Dr. Leslie Cramblet Alvarez for editorial assistance.

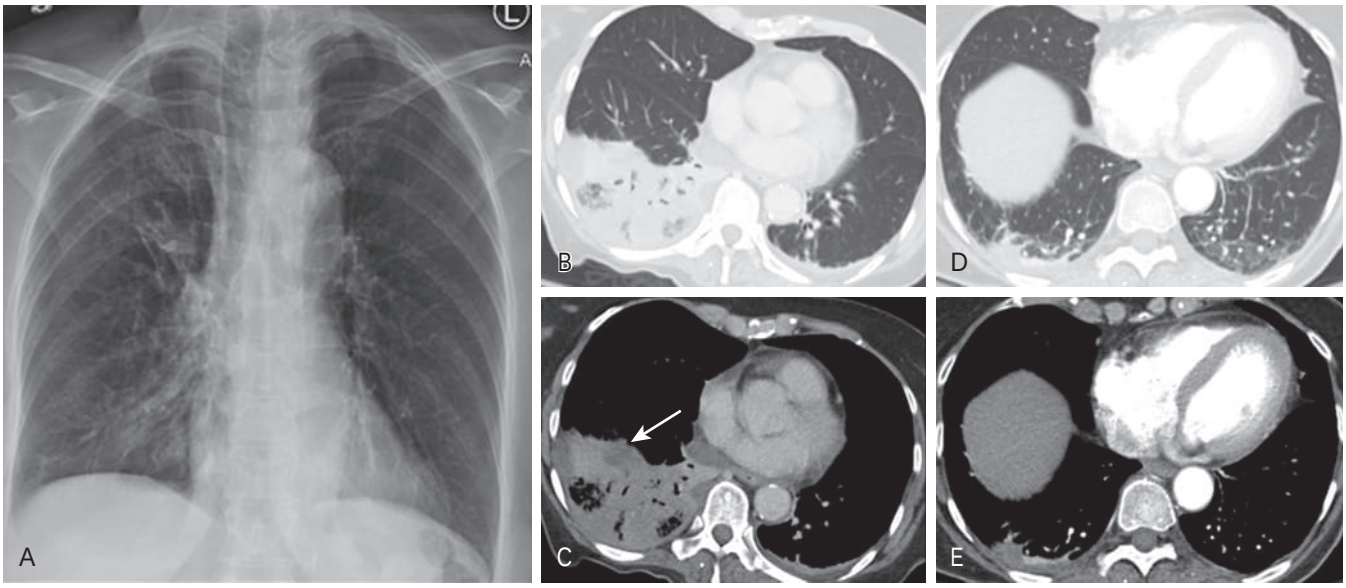
eFIGURE IMAGE GALLERY



eFigure 47.1 Seasonal influenza A virus infection: nonspecific chest radiographic findings. Frontal chest radiograph shows predominantly left perihilar peribronchovascular thickening and nodularity. The imaging findings are nonspecific and could be the result of a number of causes of bronchopneumonia, or potentially other pulmonary diseases. (Courtesy Michael B. Gotway, MD.)



eFigure 47.2 Seasonal influenza A virus infection: imaging findings. (A) Frontal chest radiograph shows patchy, bilateral linear interstitial thickening in a perihilar distribution, some of which represents bronchial thickening. Abnormalities are slightly more nodular appearing in the right upper lobe *(arrows),* and consolidation is developing in the left upper lobe *(arrowhead).* (B–D) Axial chest computed tomography displayed in lung windows shows multifocal, bilateral, upper lobe predominant ground-glass opacity associated with linear abnormalities consistent with mild, smooth interlobular septal thickening and intralobular interstitial thickening. The cystic appearance is due to centrilobular emphysema outlined and contrasted with the surrounding infiltrative lung abnormalities. (Courtesy Michael B. Gotway, MD.)



eFigure 47.3 Influenza virus infection complicated by bacterial pneumonia. (A) Frontal chest radiography performed at presentation in a patient with cough and low-grade fever shows mild perihilar and infrahilar, bilateral bronchovascular thickening, more pronounced on the right side; patient tested positive for influenza B. The patient was treated conservatively and improved over the next few weeks. (B–C) Axial enhanced chest *computed tomography* (CT) displayed in lung (B) and soft tissue (C) windows performed because the patient subsequently worsened, with development of cough and fever about 25 days after initial presentation, shows right lower lobe foci of ground-glass opacity and consolidation with a focus of low attenuation *(arrow),* suggesting necrosis; findings are suggestive of new bacterial superinfection. (D–E) Axial enhanced chest CT displayed in lung (B) and soft tissue (E) windows performed 43 days after presentation after the patient underwent broad-spectrum antibiotic therapy shows near-complete resolution of the right lower lobe consolidation. (Courtesy Clinton E. Jokerst, MD, Assistant Professor of Radiology, College of Medicine, Mayo Clinic, AZ.)

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48 HOSPITAL-ACQUIRED PNEUMONIA

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INTRODUCTION

Hospital-acquired pneumonia (HAP) is one of the most common hospital-acquired infections.[1] Substantial evidence links HAP to poorer patient outcomes due to increased mortality, morbidity, including admission to the ICU, need for mechanical ventilation, hospital length of stay, and cost.[2,3]

Despite its high prevalence, HAP is likely overdiagnosed because other respiratory complications in hospitalized patients can mimic it. Unlike patients with *ventilator-associated pneumonia* (VAP) in whom lower respiratory secretions can easily be sampled, obtaining samples in nonintubated patients is more difficult. Consequently, in most patients with HAP, adequate cultures of respiratory tract secretions are not obtained. In addition to necessitating the use of empirical antibiotic therapy without the benefit of confirmatory cultures, this factor adds to the difficulty in diagnosing HAP and limits our understanding of its epidemiology and microbiology.

To standardize the terminology surrounding this condition, the 2016 Infectious Diseases Society of America/American Thoracic Society (IDSA/ATS) HAP/VAP guidelines defined HAP and VAP as mutually exclusive entities.[4] HAP was defined as pneumonia in a nonventilated patient becoming apparent more than 48 hours after admission to the hospital. Postoperative pneumonia, therefore, is a subcategory of HAP. Pneumonias in patients living in non–acute care facilities such as nursing homes and rehabilitation centers were not considered to be HAP. VAP was defined as pneumonia in a patient receiving mechanical ventilation for more than 48 hours and is addressed in Chapter 49.

PATHOGENESIS

HAP, like most other pneumonias, develops when oropharyngeal secretions contaminated with pathogenic bacteria are aspirated into the lung in sufficient amounts to evade local host defenses and replicate. Less common mechanisms that can lead to HAP include large volume gastric aspiration or hematogenous spread of infection. An additional cause of HAP is inhalation of contaminated aerosols; this is the most common cause of HAP due to *Legionella*.[5]

Normal individuals have multiple mechanisms to protect the lungs from infection. The larynx protects against aspiration and coughing expels aspirated material. When these mechanisms fail, mucociliary clearance and the immune system come into play. In addition to the physical action of the cilia moving bacteria trapped in the mucus, numerous substances in the mucus layer assist in preventing infection. These include secretory immunoglobulin A and proteins such as lysozyme and lactoferrin. The airways and alveolar spaces possess numerous other immune mechanisms, including both cellular and humoral immune function, phagocytosis by resident macrophages and recruited neutrophils, and antimicrobial activity of surfactant proteins.[6]

Hospitalized patients are at greater risk than normal individuals of aspirating secretions contaminated with pathogenic bacteria due to two major factors. The first factor is that hospitalized patients develop oropharyngeal colonization with pathogenic bacteria, most commonly with gram-negative bacilli.[7,8] While the mechanisms resulting in this colonization are not known, alterations in mucosal cell surface carbohydrates may facilitate bacterial adherence.[9] A second factor is that hospitalized patients are at increased risk of aspiration of oropharyngeal secretions. This is due to impairment of consciousness related to anesthesia, opioids, and other sedating medications, as well as underlying acute and chronic neurologic comorbidities that impair level of consciousness and swallowing function. Other patient-level risk factors for HAP common in hospitalized patients include impairment of cough due to pain or sedation, and immune defects due to malnutrition, iatrogenic causes and, in the elderly, immune senescence.

EPIDEMIOLOGY

INCIDENCE

A point prevalence survey performed in U.S. hospitals in 2011 found that HAP was the third most prevalent hospital-acquired infection after surgical-site infection and gastrointestinal infection.[1] The authors' extrapolations suggested that approximately 96,000 patients develop HAP each year in the United States; a follow-up study using similar methods estimated approximately 110,000 per year.[10] Notably, HAP is two- to threefold more frequent than VAP in these and other studies.[11] These point prevalence studies demonstrated that approximately 0.6% of hospitalized nonventilated patients have HAP at any time. Other studies report that approximately 0.5–2% of hospitalized patients will develop HAP.[12–14] The risk for HAP varies greatly depending upon the underlying acute illness and comorbidities, with certain conditions resulting in markedly increased risk. Approximately 13% of non–*intensive care unit* (ICU) stroke patients develop HAP.[15] Among surgical patients overall, approximately 1% develop postoperative pneumonia,[16] with large variation depending on the type of surgery. Among patients undergoing lobar pulmonary resection, the postoperative pneumonia rate has been reported as high as 5.8%[17] but is decreased by at least one-third in patients who undergo video-assisted thoracic resection as compared to open resection.[18] Approximately 3% of patients undergoing major abdominal surgery develop postoperative pneumonia.[19] Overall, cardiothoracic and abdominal surgeries (especially upper abdominal) increase the risk of postoperative pneumonia more than surgeries involving other parts of the body,[20] likely due to impairment of deep breathing and cough related to direct and indirect effects of the surgical manipulation, including pain.

Numerous other risk factors for HAP have been identified. Predictive tools have been developed for patients hospitalized for common conditions, including various types of surgery.[20–22] COPD predisposes to HAP in both medical and surgical patients,[23,24] as does the presence of a higher comorbidity index[25] and of measures of acute severity of illness.[14] Other than COPD, comorbidities that appear to increase the risk of postoperative pneumonia include advanced age, diabetes, malnutrition, cerebrovascular disease, and dysphagia.[2,19,26,27] Preoperative oropharyngeal colonization or bronchial colonization/infection with pathogenic organisms has been reported to increase the risk of postoperative pneumonia in patients undergoing surgery.[28,29] Gastric acid suppression with proton-pump inhibitors is also a risk for HAP in non-ICU patients,[30] although this was not found in patients undergoing elective surgery.[31]

IMPACT ON OUTCOMES

Patients who develop HAP have significantly worse outcomes compared to similar patients who do not. They are at increased risk of mortality, ICU admission, subsequent need for mechanical ventilation, and prolonged hospital length of stay. No study has rigorously quantified the attributable mortality associated with HAP, but case-control studies have found excess mortality rates of between 2% and 14%.[2,12] Excess hospital length of stay has been estimated as 2.5 days to 15.9 days and excess cost approximately $30,000 to $40,000 per case.[12]

ETIOLOGIC AGENTS

Studies of the microbiology of HAP are hindered by several factors that make the relevant data less robust and less reliable compared to the extensive data available for VAP. First, it is often difficult to obtain adequate samples of respiratory secretions in patients with HAP because these patients frequently have impaired cough due to mental status changes, debility, and pain from surgical incisions. This is in contrast to VAP, in which an endotracheal tube provides direct access to the lower airways. In as many as 50–90% of patients with HAP, no pathogens are isolated,[2,32] either because respiratory samples are not obtained[33] or because they are inadequate or obtained after antibiotics are started. Second, because of the difficulty in obtaining respiratory secretions, the studies reporting microbiology are likely biased by more rigorous attempts to obtain respiratory secretions in higher risk or more severely ill patients, with these patients more likely to be infected with high-risk, antibiotic-resistant pathogens. Indeed, a retrospective study of HAP limited to ICU patients found that 84% of patients had a respiratory sample cultured, much higher than studies not limited to the ICU. In that study, there was a higher prevalence of *Pseudomonas aeruginosa* and *methicillin-resistant Staphylococcus aureus* (MRSA) than in studies of HAP not limited to the ICU.[34] Finally, respiratory secretions may be contaminated with oral flora, which in hospitalized patients often contain potentially pathogenic bacteria but may not represent the etiology of the pneumonia.

These factors notwithstanding, those bacteria causing HAP are more similar to those causing VAP than to *community-acquired pneumonia* (CAP). Gram-negative bacilli account for approximately 35% of isolates. These include nonfermenting organisms (approximately 20%) such as *P. aeruginosa*, *Stenotrophomonas maltophilia*, and *Acinetobacter* sp, and enteric gram-negative bacilli (approximately 15%) such as *Escherichia coli*, *Klebsiella* sp, *Proteus* sp, and *Enterobacter* sp. *S. aureus* causes about 15% of HAP. In the meta-analysis reported in the 2016 IDSA/ATS HAP-VAP guidelines,[4] *P. aeruginosa* accounted for 13% of HAP, *Acinetobacter* sp 4%, enteric gram-negative bacilli 16%, methicillin-sensitive *S. aureus* 10%, and MRSA 6%. These rates are similar to the rates seen in VAP but are generally slightly lower. *Acinetobacter* has been increasing in frequency as a cause of HAP but is less common in the United States than the 4% figure obtained in the meta-analysis. Most cases of bacterial HAP not caused by the above organisms are caused by *Streptococcus* sp. and *Hemophilus influenzae* or by organisms that could not be identified. *Legionella pneumophila* may cause clusters of HAP because of contamination of the hospital water supply,[35] but overall it is a rare cause of HAP. HAP can also be caused by nonbacterial pathogens. Respiratory viruses can be identified in over 20% of patients with HAP, often with bacterial coinfection, especially in immunocompromised patients.[2,36] The most common viruses detected in the largest study were rhinovirus, influenza, and parainfluenza. In severely immunocompromised patients, HAP may be caused by fungi, most commonly *Aspergillus* sp. Although *Candida* sp may rarely

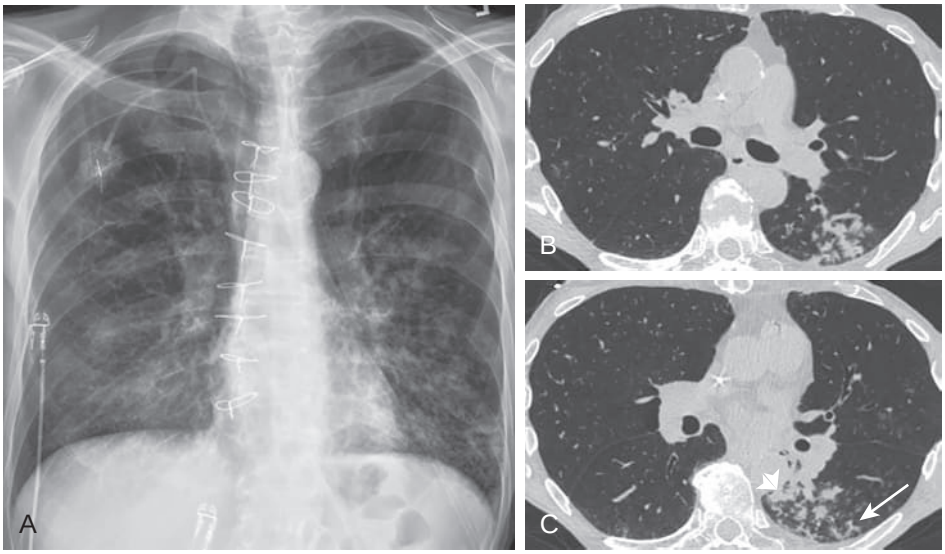

Figure 48.1 Hospital-acquired bronchopneumonia. (A) Frontal chest radiograph shows patchy, faintly nodular opacity with a segmental distribution in the left lower lobe. (B–C) Axial chest computed tomography displayed in lung windows shows left lower lobe small, branching nodules *(arrow)* and small foci of consolidation *(arrowheads)* consistent with bronchopneumonia.

cause pneumonia in critically ill ventilated patients, there is no evidence to suggest that it causes pneumonia in nonventilated patients. The etiologic agents of HAP in patients with specific underlying conditions such as stroke[37] or postoperative pneumonia do not differ greatly from those of HAP patients overall.

Risk factors for developing HAP caused by antibiotic-resistant organisms have not been studied as extensively in HAP as in CAP and VAP; however, similar to these other entities, recent exposure to intravenous antibiotics within 90 days is a significant risk factor for HAP.[38–40]

DIAGNOSIS

ESTABLISHING A CLINICAL DIAGNOSIS

The 2016 IDSA/ATS guidelines[4] defined HAP as pneumonia appearing more than 48 hours after admission in a nonventilated hospitalized patient. These same guidelines adopted the definition of pneumonia stated in the 2005 guidelines, the presence of a "new lung infiltrate plus clinical evidence that the infiltrate is of an infectious origin, which include the new onset of fever, purulent sputum, leukocytosis, and decline in oxygenation."[41] At the bedside, clinical manifestations are those commonly associated with bacterial pneumonia, including cough, sputum, dyspnea, fever, and a decline in mental status, such as lethargy or delirium. Common signs include worsening oxygenation, manifesting as a decreased oxygen saturation or requirement for higher levels of oxygen supplementation, tachypnea, and abnormal lung exam. Laboratory findings of sputum purulence and an elevated white blood cell or band form count also support the diagnosis. The presence of some of these signs and symptoms, in combination with a new or worsening pulmonary opacity seen on chest radiograph (Fig. 48.1A) or chest *computed tomography* (CT) scanning (Fig. 48.1B–C) leads to a clinical diagnosis of HAP.

Most published studies use a similar definition that requires the presence of a new or progressive pulmonary opacity and at least two of the following: fever or hypothermia, leukocytosis or leukopenia, dyspnea, signs of consolidation on respiratory exam, and purulent respiratory secretions.[2,14,34] However, there is no consensus about which or how many of these signs and symptoms must be present to confirm a diagnosis of HAP, nor have any studies tested the accuracy of these criteria for the diagnosis of HAP. A recent review of HAP diagnosis demonstrated that each of 10 cohort studies of HAP used different criteria for inclusion in the HAP cohort.[42]

The clinical diagnosis of HAP may be inaccurate. Many patients will manifest some of the common clinical findings associated with HAP for reasons other than pneumonia; they may demonstrate fever due to noninfectious causes or to other hospital-acquired infections, abnormal lung sounds due to impaired secretion clearance or heart failure, or abnormal chest imaging due to atelectasis, heart failure, or pleural effusions. In one study, 35% of patients diagnosed with HAP did not have radiographic findings consistent with pneumonia, and these patients had lesser elevations of inflammatory markers than in patients with chest imaging suggestive of pneumonia.[33] In another study of ICU patients with pneumonia, mostly HAP and VAP, chest radiography showed poor sensitivity and specificity compared to CT (Fig. 48.2) and ultrasound.[43] Due to the inaccuracy of chest radiography and the nonspecific nature of many of the signs and symptoms associated with HAP, there is a common belief among experts that HAP is overdiagnosed. To maximize the accuracy of a clinical diagnosis of HAP, clinicians should carefully consider other explanations for the clinical findings that prompt the evaluation for HAP. Furthermore, a good quality frontal and lateral chest radiograph provides more accurate information than a portable film alone (Fig. 48.3), so if the patient is stable enough to be sent to the radiology suite, doing so is preferable. If doubt persists, a chest CT is the most sensitive for detecting opacities.

In addition to the usual clinical criteria, other modalities have been explored for their use in the diagnosis of HAP. Biomarkers such as procalcitonin and C-reactive protein, which have been extensively investigated as aids to the diagnosis of CAP and VAP, have also been investigated in HAP, although there are much less data available[44-46] so

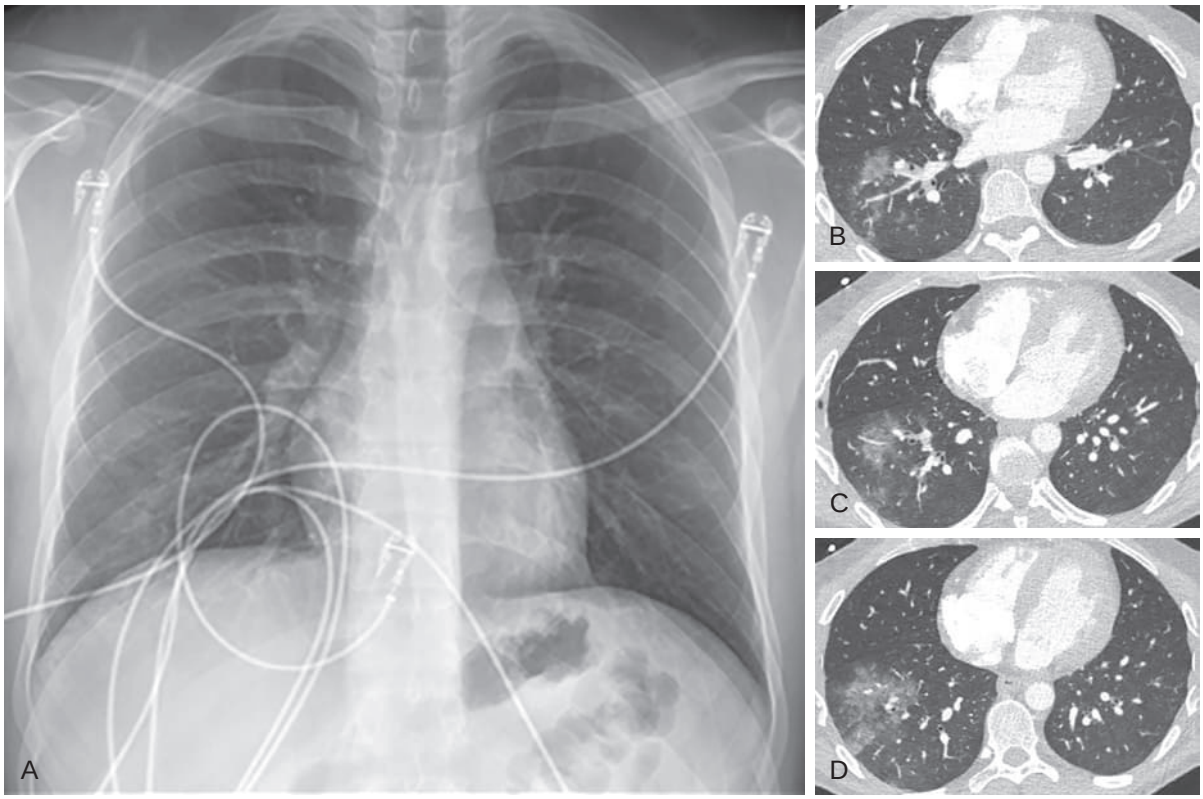

Figure 48.2 Detection of subradiographic pneumonia using computed tomography. (A) Frontal chest radiograph in a recently hospitalized patient re-presenting with fever and cough shows no clear findings to suggest pneumonia. (B–D) Axial chest computed tomography displayed in lung windows shows poorly defined lobular ground-glass opacity in the right lower lobe consistent with bronchopneumonia. The abnormalities are difficult to visualize at chest radiography and were overlooked prospectively.

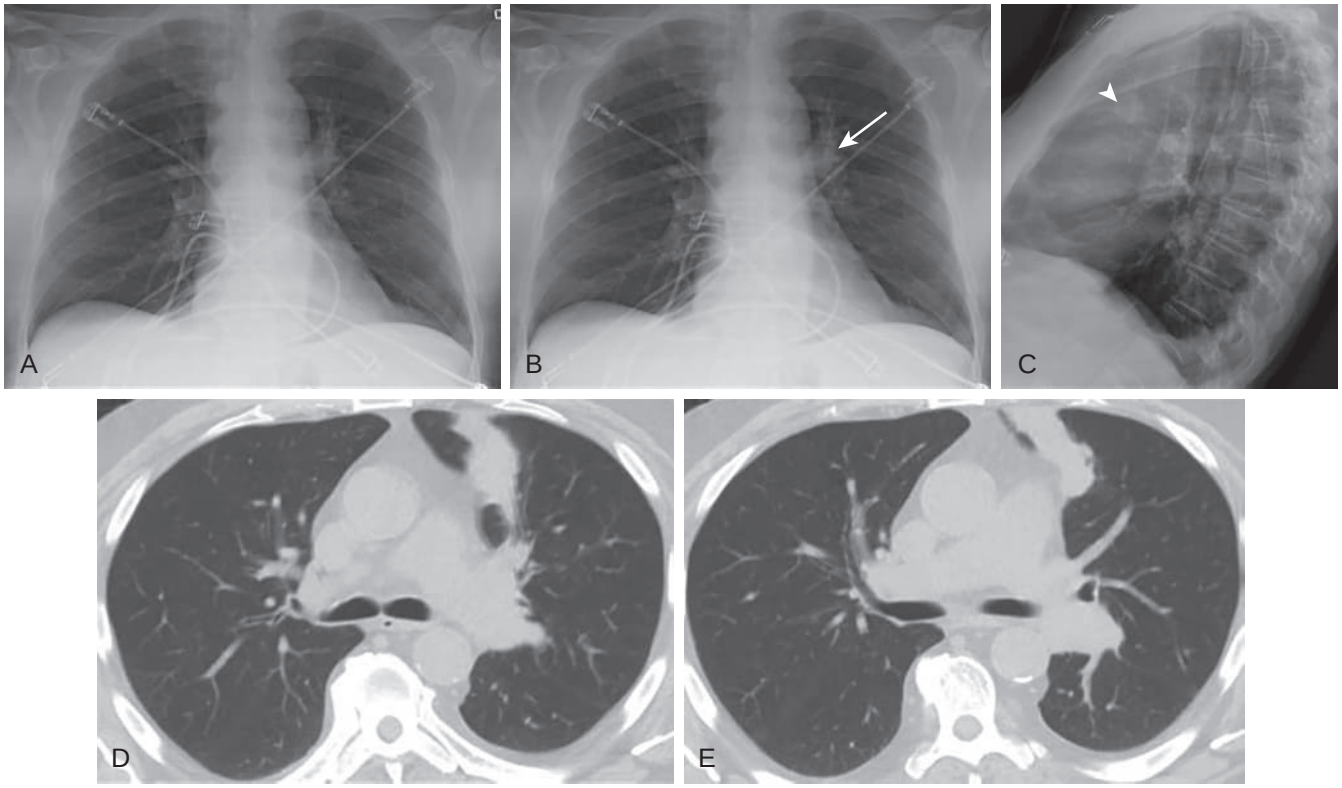

Figure 48.3 Value of frontal and lateral chest radiography over portable radiography for pneumonia detection. (A) Frontal portable chest radiography in a patient with new fever and cough shows no specific abnormalities. (B–C) Frontal and lateral chest radiography performed shortly following the portable chest radiograph shows increased opacity overlying the left hilum *(arrow)* corresponding to a nodular focus on the lateral projection *(arrowhead).* (D–E) Axial chest computed tomography displayed in lung windows confirmed left upper lobe consolidation, representing pneumonia, as the cause of the frontal and lateral chest radiographic findings.

neither of these is currently recommended for identifying HAP.

The *clinical pulmonary infection score* (CPIS) is a set of six criteria (temperature, white blood cell count, volume and purulence of respiratory secretions, oxygenation, chest radiograph findings, and semiquantitative culture of respiratory secretions) used by some clinicians to determine the need for antibiotic treatment in ventilated patients with suspected VAP.[47] However, the 2016 IDSA/ATS HAP/VAP guidelines did not recommend utilization of the CPIS for patients with VAP.[40] The CPIS has not been studied with respect to its performance characteristics for the diagnosis of HAP.

Pulmonary ultrasound has been shown to be highly sensitive and specific for the diagnosis of CAP in expert hands[48] and has also been used for VAP.[49] Although there are limited data for HAP, ultrasound may have similar value in diagnosing HAP (see Chapter 23).

DETERMINING THE ETIOLOGIC AGENT

Because of the high prevalence of potentially *multidrug-resistant* (MDR) pathogens as the causative agents of HAP, guidelines recommend an attempt to identify the pathogen by culturing respiratory secretions.[50,51] Doing so provides three potential advantages. First, the Gram stain of an adequate quality respiratory sample may allow more accurate targeting of empirical antibiotic therapy. Second, accurate culture results with accompanying antimicrobial susceptibility data could ensure accurate, narrower-spectrum antibiotic therapy. Finally, a negative culture of an adequate quality respiratory sample could allow discontinuation of broad-spectrum antibiotics targeting MDR pathogens (especially if obtained prior to antibiotic treatment). Despite these potential advantages, there is little evidence specific to HAP to support the recommendation to obtain a culture of respiratory secretions or to support the three rationales above. Instead, the recommendation is based on the inherent logic that it is helpful to know the pathogen causing a serious infection when there is likelihood that MDR could result in inadequate empirical therapy or need for prolonged broad-spectrum empirical therapy. Inadequate initial empirical therapy has been associated with increased mortality in HAP.[52] Early studies found high rates of inadequate initial empirical therapy in HAP,[53,54] but it is unknown if this continues in the era of widely disseminated guidelines for broad-spectrum initial empirical therapy for HAP.

Some of the reasoning in favor of obtaining culture data is extrapolated from the experience with CAP and VAP. In CAP, the Gram stain of a good quality sputum is considered reliable in identifying the class of pathogen (gram-positive vs. gram-negative) when a predominant morphotype is found. In VAP patients, cultures of tracheal aspirates accurately predict the pathogen obtained from invasive modalities. However, these cultures may prompt overtreatment because pathogens present in low numbers may represent colonization and may not need to be treated with antibiotics or might need only a very short course of antibiotics. There are data in HAP patients that the culture of expectorated sputum usually correlates with the results of invasive sampling using bronchoscopy, supporting the use of expectorated sputum results to guide antibiotic therapy.[55] Despite low sensitivity, blood cultures are also suggested in patients with suspected HAP, since a positive blood culture can identify the etiologic source of HAP and direct antibiotic therapy.[50] In sum, samples for cultures of sputum and blood should be obtained and the results should be used to guide antibiotic therapy in HAP.

The published guidelines on HAP have considered whether noninvasive or invasive modalities should be employed to obtain a sample of respiratory secretions.[4] The noninvasive modality most commonly used is spontaneously expectorated sputum, occasionally nasotracheally suctioned sputum in patients unable to cough effectively, or endotracheal aspirate culture in a patient with HAP who subsequently requires invasive mechanical ventilation. Bronchoscopy with bronchoalveolar lavage is the most frequently used invasive modality to obtain respiratory samples. The potential advantages of using bronchoscopy include the ability to obtain samples in the 50% or more of patients with suspected HAP who cannot produce an adequate sample and to obtain a sample less likely to be contaminated with oropharyngeal flora. The potential risks of bronchoscopy are adverse events related to sedation and worsening gas exchange due to instillation of lavage fluid into the lungs, increasing the risk of respiratory deterioration and requirement for respiratory support.

There are few studies specifically designed to investigate the optimal approach to identifying the etiologic agent of HAP. This is in contrast to VAP, in which an invasive approach, usually with bronchoalveolar lavage and quantitative cultures, has been promulgated as a method to decrease inappropriate antibiotic use. In patients with suspected VAP who have a negative culture or a positive culture but with low numbers of organisms, antibiotics can be safely withheld. Given the likely frequent overdiagnosis of HAP, the same logic might apply. However, bronchoscopy is more difficult and carries greater risk in a patient suffering from respiratory distress who is not already intubated. For these reasons, few studies have investigated invasive diagnosis of HAP. One randomized controlled trial investigated an invasive strategy for HAP and found that patients randomized to bronchoscopy with protected specimen brushing had no improvement in outcomes relative to patients receiving empirical treatment.[56] However, this study was underpowered to detect a difference in most important outcomes. In a larger retrospective observational study of ICU-acquired HAP, the diagnostic yield and patient outcomes were compared among those who had noninvasive and invasive sampling. Approximately 60% of patients had bronchoscopic sampling, often after intubation. Among patients who were never intubated, about 50% produced a sputum sample, of which about 30% were positive, a yield similar to bronchoscopy (34%) in patients who were not intubated. While patient outcomes stratified by sampling methodology were not reported, there was a higher rate of antibiotic de-escalation in patients who had invasive sampling.[55] Other studies have reported diagnosing the etiologic agent of HAP with sputum culture in 13–50% of patients,[32,33] although, in the study reporting the lowest yield, sputum samples were obtained as late as 7 days after diagnosis, by which time antibiotic therapy would be expected to decrease the yield of sputum culture significantly.[32]

The use of nasal MRSA screening for pneumonia has been assessed in several studies and two meta-analyses.[57,58] These studies included patients with CAP/*health care–associated pneumonia* (HCAP)/HAP and VAP. Specificity was low because many patients have nasal colonization with MRSA but have other etiologies of pneumonia. Sensitivity for all types of MRSA pneumonia was 70–80%, while the sensitivity for HAP was not provided. Despite this low sensitivity, the negative predictive value is over 90% due to the low prevalence of MRSA as a cause of HAP. As expected, the accuracy in predicting MRSA pneumonia diminishes the longer the time between the performance of the MRSA screening test and the clinical suspicion of pneumonia. This is important in the case of HAP because in many hospitals MRSA screening is performed routinely at the time of admission, but not subsequently. Because *polymerase chain reaction* (PCR)-based MRSA screening has a rapid turnaround time, a negative screen, especially if performed at the time that pneumonia is suspected, may allow safe withholding or rapid discontinuation of anti-MRSA antibiotic therapy.[57]

Culture-independent methods are available for diagnosis of infectious diseases and detection of resistance genes (see Chapter 19). Multiplex PCR platforms for rapid detection of respiratory viruses, bacteria, and antimicrobial resistance genes are widely implemented by hospitals for use in patients with community-acquired respiratory tract infections, although evidence of improved outcomes or decreased antibiotic utilization (if a virus is detected) are limited. Other methods include mass spectrometry, exhaled breath biomarkers, and fluorescence microscopy. In many of these, differentiating colonization from infection can be difficult due to the ability of these techniques to detect low numbers of organisms. Data using these platforms in the setting of HAP are limited,[59] so none of these techniques can be recommended for routine use. However, it is likely that these platforms will find a role for more rapid pathogen and antibiotic susceptibility identification. Given the prevalence of viruses as a cause of HAP, detection of a virus, perhaps in the setting of a normal serum inflammatory biomarker, may allow the avoidance of unnecessary antibiotic therapy.

In summary, because of the prevalence of MDR pathogens in HAP and the potential usefulness of positive cultures to allow targeted therapy and antibiotic de-escalation, guidelines recommend an attempt to obtain and culture a noninvasive sample of respiratory secretions from patients with suspected HAP.[4] Invasive sampling is not generally recommended given the potential risks and the lack of evidence that doing so improves patient outcomes. In certain patients, invasive sampling should be considered, such as in a patient who is not improving despite antibiotic therapy or in a patient at risk for unusual or opportunistic infections. Although not recommended by any guidelines, because of the prevalence of influenza in HAP,[2,36] consideration should be given to testing for influenza in patients with suspected HAP who have a suggestive clinical presentation at a time when influenza is circulating in the community. The use of PCR-based MRSA screening may allow anti-MRSA therapy to be withheld safely, although definitive data are lacking. There is limited experience with multiplex PCR platforms in the setting of HAP, but there is a potential for these modalities to establish a rapid identification of specific bacteria, respiratory viruses, and genes conferring antibiotic resistance.

TREATMENT

The optimal treatment of HAP requires consideration of all evidence available, including epidemiologic, clinical, laboratory, radiologic, and microbiologic data.[4,40,50,51] At the patient's initial evaluation, it is rare to have definitive microbiologic information to guide antibiotic therapy; thus the choice of initial antibiotic therapy is mostly based on empirical evidence, while completion of treatment should be with targeted therapy selected according to results of cultures and antibiotic susceptibilities.

EMPIRICAL TREATMENT APPROACH

The choice of the empirical antibiotic regimen requires balancing the competing goals of ensuring the most effective coverage while avoiding the use of unnecessary antibiotics. The time to HAP onset (i.e., early onset versus late onset) cannot reliably determine the risk of MDR infection[60-64]; thus, information on the time to onset should not be used alone to guide empirical antibiotics. To maximize the efficacy of the empirical regimen, a combination of three factors must be evaluated for the risk of MDR HAP[4]:

1. *History of intravenous antibiotic use*: the use of intravenous antibiotics within 90 days prior to current hospitalization puts patients at higher risk for MDR infections.
2. *Local antibiogram*: an antibiogram is a summary of the percentage of individual bacterial pathogens cultured at that location, with their antimicrobial susceptibility information. The antibiogram should be based on data collected in the hospital unit where the patient is currently located but, if this is not available for specific units due to the small size of the hospital, an institutional antibiogram could also guide the empirical therapy. There are concrete benefits to be gained from the antibiogram; the knowledge of the prevalence of respiratory microorganisms can provide the relevant information as to whether specific antibiotic coverage is necessary (or not) for the empirical treatment of patients with HAP. For example, if only 2% of all HAPs are due to *P. aeruginosa* based on the hospital antibiogram, then 98% of all patients with HAP would not benefit from the empirical use of antibiotics against *P. aeruginosa*. The frequency of specific MDR patterns in the hospital antibiogram can help to direct the empirical coverage for MDR HAP. For example, in a hospital where 40% of all gram-negative isolates are resistant to multiple broad-spectrum antibiotics, the use of empirical antibiotics to cover MDR organisms should be part of the routine standard of care.
3. *Disease severity*: if the patient with HAP requires intubation due to the infection, or develops septic shock, it is more likely that the HAP could be secondary to MDR microorganisms, so the empirical coverage should be broader.[50,51]

In clinical practice, the empirical approach for HAP falls within three treatment categories: (1) low disease severity and no risk factors for MRSA (antibiotic monotherapy with anti-pseudomonal activity), (2) low disease severity and presence of risk factors for MRSA (one anti-pseudomonal plus one anti-MRSA antibiotic), and (3) high disease severity (either septic shock or need for intubation due to HAP dual anti-pseudomonal plus anti-MRSA antibiotics). Once the antibiotic susceptibility is known, then the combination

Table 48.1 Recommended Initial Empirical Antibiotic Therapy for Hospital-Acquired Pneumonia (Non–Ventilator-Associated Pneumonia)

Not At High Risk of Mortality* and no Factors Increasing the Likelihood of MRSA†‡	Not At High Risk of Mortality* but with Factors Increasing the Likelihood of MRSA†‡	High Risk of Mortality or Receipt of Intravenous Antibiotics During the Prior 90 Days*‡
One of the following:	**One of the following:**	**Two of the following (avoid 2 β-lactams):**
Piperacillin-tazobactam§ 4.5 g IV q6h *or* Cefepime§ 2 g IV q8h *or* Ceftazidime/avibactam 2.5 g IV q8h *or* Ceftolozane/tazobactam 3 g IV q8h	Piperacillin-tazobactam§ 4.5 g IV q6h *or* Cefepime§ or ceftazidime§ 2 g IV q8h *or* Ceftazidime/avibactam 2.5 g IV q8h *or* Ceftolozane/tazobactam 3 g IV q8h	Piperacillin-tazobactam§ 4.5 g q6h *or* Cefepime§ or ceftazidime§ 2 g q8h *or* Ceftazidime/avibactam 2.5 g q8h *or* Ceftolozane/tazobactam 3 g q8h
Levofloxacin 750 mg IV daily	Levofloxacin 750 mg IV daily *or* Ciprofloxacin or 400 mg IV q8h	Levofloxacin 750 mg IV daily *or* Ciprofloxacin 400 mg IV q8h
Imipenem 500 mg IV q6h *or* Meropenem§ 1 g IV q8h	Imipenem§ 500 mg IV q6h *or* Meropenem§ 1 g IV q8h	Imipenem§ 500 mg IV q6h *or* Meropenem§ 1 g IV q8h
	Aztreonam 2g IV q8h	Aztreonam¶ 2 g IV q8h
		Amikacin 15–20 mg/kg IV daily *or* Gentamicin 5–7 mg/kg IV daily *or* Tobramycin 5–7 mg/kg IV daily *or*
	Plus: Vancomycin 15 mg/kg IV q8 –12h with goal to target 15–20 mg/mL (trough level) (consider a loading dose of 25–30 mg/kg × 1 for severe illness), *or* Linezolid 600 mg IV q12h	**Plus:** Vancomycin 15 mg/kg IV q8 –12h with goal to target 15 to 20 mg/mL (trough level) (consider a loading dose of 25–30 mg/kg × 1 for severe illness), *or* Linezolid 600 mg IV q12h
If patient has severe penicillin allergy and aztreonam is going to be used instead of any β-lactam-based antibiotic, include coverage for MSSA. Options include levofloxacin, clindamycin.		If MRSA coverage is not going to be used, include coverage for MSSA. Options include piperacillin-tazobactam, cefepime, levofloxacin, imipenem, and meropenem Oxacillin, nafcillin, and cefazolin are preferred for the definitive treatment of MSSA, but would ordinarily not be used in an empirical regimen for HAP.

*Risk factors for mortality include intensive care unit admission, need for ventilatory support due to pneumonia, septic shock, and markedly elevated procalcitonin.

†Indications for MRSA coverage include prior detection of MRSA culture or nonculture screening, antibiotic treatment during the prior 90 days, and treatment in a unit where the prevalence of MRSA among *S. aureus* isolates is not known or is >20%. The 20% threshold was chosen to balance the need for effective initial antibiotic therapy against the risks of excessive antibiotic use; hence individual units can elect to adjust the threshold in accordance with local values and preferences. If MRSA coverage is omitted, the antibiotic regimen should include coverage for MSSA.

‡If patient has factors increasing the likelihood of gram-negative infection, two anti-pseudomonal agents are recommended. If patient has structural lung disease increasing the risk of gram-negative infection (i.e. bronchiectasis or cystic fibrosis), two anti-pseudomonal agents are recommended. A high-quality Gram stain from a respiratory specimen with numerous and predominant gram-negative bacilli provides further support for the diagnosis of a gram-negative pneumonia, including fermenting and non–glucose fermenting microorganisms.

§Extended infusions may be appropriate.

¶In the absence of other options, it is acceptable to use aztreonam as an adjunctive agent with another β-lactam based agent because it has different targets within the bacterial cell wall.

HAP, hospital-acquired pneumonia; MRSA, methicillin-resistant *Staphylococcus aureus*; MSSA, methicillin-sensitive *Staphylococcus aureus*.

Modified from Kalil AC, Metersky ML, Klompas M, et al. Management of adults with hospital-acquired and ventilator-associated pneumonia: 2016 clinical practice guidelines by the Infectious Diseases Society of America and the American Thoracic Society. *Clin Infect Dis*. 2016;63(5):e61-e111.

therapy can be safely changed to monotherapy. The specific selection of initial empirical antibiotics according to the patient's risk profile can be seen in Table 48.1. These antibiotic recommendations are based on the 2016 IDSA/ATS HAP/VAP guidelines, with some additional antibiotics that became available after these guidelines were written.[65,66] These recommendations will not apply to all situations. For example, in a hospital with very low rates of gram-negative resistance to a certain antibiotic, single gram-negative coverage with this agent may be appropriate, even in critically ill patients at risk for gram-negative infection.

There is accumulating evidence that a negative nasal MRSA screen by PCR performed at the time of diagnosis of respiratory infection is associated with a very high negative predictive value for MRSA pneumonia, with some of the evidence in patients with HAP but most in CAP.[57] While not supported by prospective controlled studies, many clinicians will withhold or discontinue MRSA coverage in HAP and CAP patients with a negative MRSA screen, a practice supported by expert opinion and small retrospective studies in which outcomes in patients in whom anti-MRSA therapy was withheld or discontinued had similar outcomes as those treated for MRSA.[67]

TARGETED TREATMENT APPROACH

Once the etiology of HAP becomes known through culture results of respiratory or, less commonly, blood specimens, the empirical therapy can be safely changed to targeted therapy, with the goal to focus the treatment on the causal microorganism as well as to avoid the continuation of unnecessary antibiotics. The selection of targeted antibiotics is based on the susceptibility results from the final culture of respiratory or blood specimens. Antibiotics that

can be used for the treatment of HAP are provided in Table 48.1. As a general rule, vancomycin and linezolid can be used to treat HAP due to MRSA. (Telavancin can be used as a backup option but generally only if the patient does not respond to vancomycin and cannot receive linezolid, because there were safety concerns in a telavancin clinical trial.[68]) Daptomycin should never be used for a pulmonary infection because it is inactivated due to binding to pulmonary surfactant.[69] For HAP due to *methicillin-sensitive S. aureus* (MSSA), cefazolin, oxacillin, and nafcillin are the preferred choices but, if the patient also needs gram-negative coverage, cefepime, piperacillin-tazobactam, levofloxacin, imipenem, or meropenem can also cover MSSA. For HAP due to *P. aeruginosa*, piperacillin-tazobactam, levofloxacin, cefepime, ceftazidime, ceftazidime-avibactam, ceftolozane-tazobactam, imipenem, meropenem, and aztreonam are options. For HAP due to lactose-fermenting organisms (e.g., enterics), piperacillin-tazobactam, levofloxacin, ciprofloxacin, ceftriaxone, cefepime, ceftazidime-avibactam, and ceftolozane-tazobactam are appropriate choices. Ceftaroline is not FDA approved for the treatment of HAP, while ceftobiprole is approved for the treatment of HAP caused by a small number of specific organisms, but not for empiric therapy.

PHARMACOKINETIC/PHARMACODYNAMIC ANTIBIOTIC DOSING

One of the important goals for the treatment of severe respiratory infections such as HAP is to maximize the antibiotic delivery to the source of infection (i.e., lungs) while minimizing the toxicity risk of antibiotic overexposure. One way to achieve these goals is through use of *pharmacokinetic/pharmacodynamic* (PK/PD) principles to optimize the dosing of antibiotics. The PK/PD optimization methods include measurement and targeting of serum antibiotic concentrations, extended and continuous infusion, and weight-based dosing of specific antibiotics. While the use of PK/PD has been controversial in the past, there is growing and consistent evidence that the use of PK/PD for the antibiotic treatment of HAP is associated with survival benefits. The 2016 IDSA/ATS guideline performed several meta-analyses on PK/PD studies and found improvements in mortality, clinical cure, and ICU length of stay.[4] In addition, other studies published after the guideline provided further support for these PK/PD benefits.[70-72]

INHALED ANTIBIOTICS

There is an intuitive biologic rationale for inhaled antibiotics to be among the therapeutic choices for treatment of HAP due to their high peak concentration and low systemic exposure, which in turn could lead to less selective pressure and less frequent development of bacterial resistance than intravenous antibiotics.[73] However, there is no strong evidence supporting the use of inhaled antibiotics as either monotherapy or adjunctive therapy of HAP. If there will be a role for inhaled antibiotics in the future, the optimal antibiotic chemical properties and the best device delivery method still need to be determined. Hence, intravenous antibiotics remain the mainstream approach to treat HAP. However, there is one exception: patients who develop HAP due to MDR gram-negative microorganisms sensitive only to aminoglycosides or polymyxins. In this situation, there is evidence supporting the use of inhaled antibiotics in conjunction with intravenous antibiotics.[4]

ANTIBIOTIC DE-ESCALATION AND DURATION OF TREATMENT

When culture and susceptibility results are available, antibiotic de-escalation from empirical to targeted therapy should be performed by selecting the antibiotics to which the isolated bacteria are susceptible, and then making the final antibiotic choice based on its PK/PD properties to achieve optimal lung parenchyma penetration. De-escalation is more complex when there is no identified bacterial etiology for HAP, which is common. In this case, a thorough evaluation of the clinical, laboratory, and radiologic picture at regular intervals will determine the direction of patients' progression while receiving the empirical treatment. If patients' clinical symptoms are resolving; fever, white blood count, and inflammatory markers are decreasing; and imaging is improving, consideration for narrowing antibiotic coverage can be made in an individual basis. If anti-MRSA coverage is still being provided, a negative MRSA screen supports the discontinuation of such coverage.

Another tool that can guide antibiotic de-escalation is the assay of inflammatory biomarkers. One of these biomarkers, procalcitonin, has been evaluated in randomized trials and meta-analyses of patients with HAP and has been shown to be an effective adjunct tool to de-escalate antibiotics safely.[74-78] Antibiotic de-escalation has been shown to be safe[79] and may have potential beneficial survival outcomes in patients with sepsis and VAP.[80,81] There are no systematic data assessing the safety of antibiotic de-escalation in HAP patients in whom there are no culture data. In HAP patients with a negative culture of an adequate quality respiratory sample obtained before the start of antibiotics, some experts believe de-escalation to a single broad-spectrum antibiotic is safe, especially if a nasal MRSA screen is negative, but data supporting this practice are limited.

The recommended duration of antibiotic therapy for pneumonia has varied substantially in the past. However, more recent studies (observational and randomized) and meta-analyses have demonstrated that short courses (7 days) are as effective as longer courses (8–15 days) of antibiotics.[82-87] One of the previous concerns with short courses was the potential for recurrence of HAP, especially due to *P. aeruginosa.* However, a new analysis with updated evidence performed by the IDSA/ATS guideline panel demonstrated that, even in HAP caused by nonfermenting gram-negative bacteria, there were no significant differences between short course and longer course therapy regarding mortality, clinical cure, recurrent pneumonia, or mechanical ventilation duration.[4] Thus, based on current evidence, 7 days of antibiotic therapy is recommended for most patients with HAP. In some patients, treatment can be shorter or longer, depending on the individual patient progression with respect to clinical, radiologic, and laboratory parameters.[50,51]

PREVENTION

Since bacterial HAP is commonly caused by aspiration of pathogens from the oropharynx into the lower airways, HAP prevention strategies are comprised of two fundamental approaches: minimizing colonization of the oropharynx with pathogenic bacteria and minimizing the opportunity for resident pathogens to reach the lower airways.

MINIMIZING OROPHARYNGEAL COLONIZATION

Several modalities of oral care interventions have been studied for their efficacy in preventing HAP, presumably by decreasing the intensity of oropharyngeal colonization with pathogenic bacteria. These include mechanical interventions such as professional dental care, toothbrushing, and the use of antimicrobial agents such as chlorhexidine and povidine-iodine.[88,89] Meta-analyses of these studies have found statistically significant reductions in HAP rates associated with these interventions; however, when only high-quality studies were considered, the benefit was less apparent. Furthermore, chlorhexidine can cause oral irritation, allergic reactions and, if aspirated into the lungs, acute lung injury. Increasing the concern regarding potential toxicity of chlorhexidine, accumulating evidence, including a recent meta-analysis and observational study, have demonstrated increased risk of mortality associated with the use of chlorhexidine oral hygiene.[90,91]

While mechanical oral care such as toothbrushing would seem to have little risk of harm, the evidence of benefit of this modality in isolation is limited and, even in combination with other modalities, the results have been mixed with respect to prevention of pneumonia. A multicomponent intervention including toothbrushing twice daily and chlorhexidine rinse failed to prevent pneumonia in a large-cluster randomized study of at-risk nursing home patients.[92]

Gastric acid suppression increases the reservoir of potentially pathogenic bacteria residing in the stomach and is associated with increased risk of HAP in a general non-ICU hospitalized population[93] and in specific patient populations such as stroke[30] and hematology/oncology.[94] To the extent that gastric acid–suppressing medications predispose to HAP, avoiding their use in patients who do not need them may reduce the risk of HAP and of other complications such as *Clostridioides difficile* colitis.

Vaccines targeting common pathogens in HAP, including *P. aeruginosa* and *S. aureus*, are under investigation for VAP but have not yet been studied in patients at risk for HAP. The pneumococcal vaccines prevent morbidity from *S. pneumoniae* and should be provided to individuals for whom they are indicated, but they have not been studied specifically in the context of HAP. Similarly, because viruses, including influenza, cause a substantial percentage of HAP episodes, influenza vaccination should be provided to all individuals in whom there is no contraindication and to all health care workers who have direct patient contact. A large matched cohort study demonstrated lower rates of postoperative pneumonia and mortality in elderly patients who had preoperative influenza vaccine than in those who did not.[95]

PREVENTING ASPIRATION

Dysphagia is common among hospitalized patients and increases the risk for aspiration and pneumonia. Its causes are numerous, including neurologic conditions, frailty, sedating medications, prolonged intubation, and oropharyngeal and laryngeal anatomic abnormalities. Patients at risk should be promptly evaluated for dysphagia. In patients with dysphagia, interventions including diet modification, swallowing training and nonoral feeding may reduce the frequency of HAP, although the evidence is derived mostly from observational studies, predominantly in stroke patients. While a meta-analysis of RCTs failed to find decreased rates of HAP associated with dysphagia screening and treatment, a subsequent pre-post study did.[96,97] In patients with dysphagia, it is not clear whether nasogastric or percutaneous gastric tube feedings decrease the risk of pneumonia compared to oral feedings, although there is evidence supporting this practice.

Sedating medications such as opioids and benzodiazepines increase the risk of aspiration and, in adults living in the community, both opioid and benzodiazepine use have been associated with an increased risk of pneumonia. The contribution of opioid-induced immunosuppression to this increased risk is unclear. There is much more limited evidence regarding this issue in hospitalized patients, but one study found an increased risk of postoperative respiratory complications, including an increased risk of pneumonia, in patients who received higher doses of fentanyl intraoperatively.[98] Other studies have found decreased risk for postoperative respiratory complications overall (pneumonia rates not specified) with the use of multimodality postoperative pain control versus opioid-only pain control.[99] Taken together, these data suggest that minimizing the use of sedating medications, especially opioids, may reduce the risk of HAP.

AIRWAY CLEARANCE, EARLY MOBILIZATION, PAIN CONTROL

In hospitalized patients, factors including sedation, physical inactivity and, in postoperative patients, pain, decrease the clearance of respiratory secretions. This has led to the use of various modalities designed to improve respiratory secretion clearance. One frequently used device is the incentive spirometer, which is provided to postoperative patients in many hospitals. Meta-analyses and systematic reviews have concluded that there is low-quality evidence demonstrating lack of benefit in preventing postoperative pulmonary complications, including pneumonia.[100] Pain control is a challenge with respect to postoperative pulmonary complications, including pneumonia. Inadequate pain control can increase the risk of pulmonary complications by preventing mobilization, cough, and deep breathing, while excessive sedation can increase the same complications. Epidural pain control may decrease the risk of these complications, including pneumonia, after cardiac surgery, high-risk abdominal surgery, and vascular surgery, but meta-analysis results were mixed.[101-103] Intercostal nerve blocks for postoperative pain after upper

abdominal surgery reduced pulmonary complications in patients undergoing biliary surgery via a subcostal incision but increased the risk in patients who had an upper abdominal incision.[104]

PROPHYLACTIC ANTIBIOTICS

Some studies have demonstrated an increased risk of postoperative pneumonia in patients who have respiratory tract colonization with potentially pathogenic bacteria at the time of surgery.[105,106] Based in part on this knowledge, prophylactic antibiotic treatment beyond the 24 hours typically given for surgical site infection prevention has been studied to prevent postoperative pneumonia. Most studies demonstrated no improvement,[105,107] while one observational study found lower rates of postoperative pneumonia in lung cancer resection patients who received antibiotics for 3 days after the surgery. However, the control group in this study had a very high rate of pneumonia (16%), limiting the interpretation of the results.[108]

MULTIPRONGED INTERVENTIONS

There have been several reports of multipronged interventions to reduce postoperative pulmonary complications, including postoperative pneumonia. All had a quasi-experimental/pre-post intervention design without a concurrent control or randomization. Interventions included incentive spirometry, coughing and deep breathing, oral care, patient and family education, early mobilization, and head-of-bed elevation.[109-111] These reports described successful reductions in postoperative pulmonary complication rates, including pneumonia. But, given the imprecise nature of HAP diagnosis, the lack of high-quality evidence supporting any of the individual interventions, and the lack of a concurrent control group, higher-quality evidence is needed before recommending widespread adoption of these multipronged interventions.

In summary, numerous strategies have been recommended to prevent HAP, but high-quality evidence regarding the effectiveness of these strategies is lacking. Therefore, no major guidelines provide specific recommendations for HAP prevention. There is some evidence in support of oral care to minimize bacterial colonization as well as evaluation and intervention for dysphagia, particularly in stroke patients. There is reason to believe that employing best practices with regard to several processes of care, including minimization of sedating medications, optimizing pain control, avoidance of proton pump inhibitors in patients for whom they are not indicated, and early mobilization might improve patient outcomes through mechanisms that include a reduction in HAP rates. Standard infection prevention practices, including hand hygiene and isolation of patients with communicable infectious diseases should be adhered to, although evidence of benefit for HAP prevention is lacking.

Key Points

- *Hospital-acquired pneumonia* (HAP) is the third most common hospital-acquired infection after surgical site infection and gastrointestinal infections. Approximately 100,000 people develop HAP in the United States each year, representing over 0.5% of hospitalized patients.
- HAP is associated with excess mortality, hospital length of stay, and cost.
- HAP is most commonly caused by aspiration of oropharyngeal secretions contaminated with pathogenic bacteria. Risk factors include numerous comorbidities, impairment of swallowing, and altered mental status.
- The pathogens responsible for HAP include *P. aeruginosa*, *Staphylococcus aureus*, enteric gram-negative bacilli, *Streptococcus* sp, and less frequently *S. pneumoniae* and *H. influenzae*. Respiratory viruses, including influenza, may cause up to 20% of hospital-acquired pneumonia episodes.
- Attempts to diagnose the etiologic agent should be made to allow accurate antibiotic therapy; use of expectorated sputum is recommended in most cases.
- Initial treatment is usually empirical and should target potentially resistant organisms such as methicillin-resistant *S. aureus* and *P. aeruginosa* unless there is evidence that the patient has low risk for these organisms, or the hospital antibiogram shows low prevalence of multidrug-resistant organisms. When a definitive culture returns, antibiotics should be de-escalated to a narrow-spectrum agent targeting the pathogen identified.
- For most patients, a 7-day course of antibiotics is recommended.
- There are no preventive measures supported by high-quality evidence, but there may be a benefit of optimal oral hygiene and assessment and intervention for risk of aspiration.

Key Readings

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49 VENTILATOR-ASSOCIATED PNEUMONIA

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INTRODUCTION

Ventilator-associated pneumonia (VAP) is the most frequent *intensive care unit* (ICU)–acquired infection among patients who are treated with mechanical ventilation.[1,2] In contrast to infections of other organs (e.g., urinary tract and skin), for which mortality ranges from 1–4%, the mortality rate for VAP, defined as pneumonia developing more than 48 hours after the onset of mechanical ventilation, ranges from 20–50%, and can even be higher when lung infection is caused by high-risk pathogens.[3] Although the attributable mortality rate for VAP is still debated, good evidence indicates that VAP prolongs the duration of mechanical ventilation and of the ICU stay.[2,3] Approximately 50% of all antibiotics prescribed in an ICU are administered for true or supposed respiratory tract infections.[4] Because several studies have shown that appropriate antimicrobial treatment of patients with VAP significantly improves outcome, rapid identification of infected patients and accurate selection of antimicrobial agents are important clinical goals.[3] Agreement is lacking, however, about the appropriate diagnostic, therapeutic, and preventive strategies for VAP.

PATHOGENESIS

Multiple defense mechanisms protect the normal human respiratory tract from infection. Examples include anatomic barriers, such as the glottis and larynx; cough reflexes; constituents of tracheobronchial secretions; mucociliary clearance; epithelial lining fluid and surfactant components; cell-mediated and humoral immunity; a phagocytic system that involves alveolar macrophages and recruited neutrophils; and both humoral and cell-mediated adaptive immunity. When these coordinated components function properly, invading microbes are eliminated and clinical disease is avoided. When these defenses are impaired, or if they are overcome by a high inoculum of organisms or organisms of unusual virulence, pneumonitis results.[5,6]

As suggested by the infrequent association of VAP with bacteremia, most of these infections appear to result from aspiration of potential pathogens that have colonized the mucosal surfaces of the oropharyngeal airways, the dental plaque, and/or the paranasal sinuses. Endotracheal intubation not only compromises the natural barrier between the oropharynx and trachea, it also facilitates the entry of bacteria into the lungs by pooling and leakage of contaminated secretions around the endotracheal tube cuff from the subglottic area to below the true vocal cords. Contaminated secretions leak into the lungs of most intubated patients and may be facilitated by the supine position. Moreover, biofilm formation on the inner and outer surfaces of the endotracheal tube provides a protected environment for pathogens. Bacterial aggregates in biofilm dislodged during suctioning are dangerous for the lung because they are difficult to clear by host immune defenses and difficult to eradicate with antibiotics.[3,6]

Tracheobronchial colonization with *gram-negative bacilli* (GNB) usually precedes the onset of VAP. Risk factors for tracheobronchial colonization appear to be the same as those that favor pneumonia, and include advanced age, more severe illness, longer hospitalization, prior or concomitant use of antibiotics, malnutrition, endotracheal intubation, depressed level of consciousness, immune suppression from disease or medication, azotemia, underlying pulmonary disease, and longer duration of mechanical ventilation.[7,8] Experimental studies have linked some of these risk factors with changes in adherence of GNB to respiratory epithelial cells. Although formerly attributed to protease-induced changes in epithelial cell surface proteins, these changes in adherence also reflect alterations of cell surface carbohydrates. Bacterial adhesins and prior antimicrobial therapy appear to facilitate the process. Interestingly, Enterobacteriaceae usually appear first in the oropharynx, whereas *Pseudomonas aeruginosa* more often appear first in the trachea.[9]

Although the stomach can be a reservoir for potential pneumonia pathogens, the gastropulmonary route

of infection is not the primary route of infection in most critically ill patients.[10] Progression of colonization from the stomach to the upper respiratory tract with subsequent episodes of VAP could not be demonstrated in several studies, and efforts to eliminate the gastric reservoir with antimicrobial therapy without decontaminating the oropharyngeal cavity have generally failed to prevent VAP.[10] In fact, there is more than one potential pathway for colonization of the oropharynx and trachea in such a setting, including cross infection from the hands of health care personnel and contaminated respiratory therapy equipment. Patient care activities, such as bathing, oral care, tracheal suctioning, enteral feeding, and tube manipulations, provide many opportunities for transmission of pathogens when meticulous infection control practices are not followed.

EPIDEMIOLOGY

INCIDENCE

The exact incidence of VAP varies widely depending on the case definition of pneumonia and the population being evaluated. For example, the incidence of VAP may be up to two times greater in patients when the diagnosis is made by qualitative or semiquantitative sputum cultures rather than by quantitative cultures of lower respiratory tract secretions. However, studies have confirmed that nosocomial pneumonia is considerably more frequent in ventilated patients than in other ICU patients, with the incidence being as much as 6-fold to 20-fold higher in ventilated patients than in nonventilated patients.[3,11] VAP manifests in 9–27% of all intubated patients, and its incidence increases with duration of intubation. The risk of VAP is highest early in the course of the hospital stay—estimated to be 3% per day during the first 5 days of intubation, 2% per day during days 5 to 10 of intubation, and 1% per day after day 10.[7] Because most mechanical ventilation is short term, approximately half of all episodes of VAP develop within the first 4 days of mechanical ventilation. In a large epidemiologic study, independent predictors of VAP determined by multivariate analysis were: primary admitting diagnosis of burns, trauma, central nervous system disease, respiratory disease, or cardiac disease; mechanical ventilation during the preceding 24 hours; witnessed aspiration; and use of paralytic agents.[7] Exposure to antibiotics conferred protection, but this effect was attenuated over time. According to four studies, the VAP rate was higher in patients with *acute respiratory distress syndrome* (ARDS) than in other ventilated patients, affecting between 34% and more than 70% of patients with ARDS and often leading to the development of sepsis, multiple organ failure, and death.[12,13]

Attributable Mortality, Morbidity, and Costs

In mechanically ventilated patients in the ICU, those with VAP appear to have a 2-fold to 10-fold higher risk of death than those without pneumonia. Although these statistics indicate that VAP can be lethal, previous studies have not clearly demonstrated that pneumonia is responsible for the higher mortality rate of these patients. It is often difficult to determine whether ICU patients with severe underlying illness would have survived if they had not developed VAP. VAP, however, has been recognized in several case-control studies or studies using multivariate analysis as an important prognostic factor for different groups of critically ill patients.[14-18] Based on a multistate progressive disability model that appropriately handled VAP as a time-dependent event in a high-quality database of 2873 mechanically ventilated patients, VAP-attributable mortality was found to be 8.1% overall.[19] These results are consistent with those obtained in other observational studies using also multistate models and causal analysis, detecting a relatively limited mortality attributable to VAP.[20]

Other factors beyond the simple development of VAP, such as the severity of the disease, the adequacy of antimicrobial therapy, or the responsible pathogens, may be more important determinants of outcome for patients in whom pneumonia develops. Indeed, it may be that VAP increases mortality only in the subset of patients with intermediate severity of illness,[21] in those for whom initial treatment is inappropriate,[22] and/or in patients with VAP caused by high-risk pathogens, such as *P. aeruginosa*.[23] Patients with very low severity and early-onset pneumonia caused by organisms such as *Haemophilus influenzae* or *Streptococcus pneumoniae* have excellent prognoses with or without VAP, whereas very ill patients with late-onset VAP would be unlikely to survive.

Studies have clearly shown that patients with VAP have prolonged duration of mechanical ventilation and lengthened ICU and hospital stay than do patients who do not have VAP.[1,3] Summarizing available data, VAP appears to extend the ICU stay by at least 4 days, with the attributable ICU length of stay being longer for medical than surgical patients and for patients infected with high-risk rather than low-risk organisms.[24] The prolonged hospitalization of patients with VAP underscores the considerable financial burden imposed on the health care system by the development of VAP.[24,25]

Etiologic Agents

Microorganisms responsible for VAP differ according to geographic areas, characteristics of the ICU patients, durations of hospital and ICU stays before onset of the disease, and risk factors for *multidrug-resistant* (MDR) pathogens.[26,27] However, multiple studies have shown that GNB—particularly *P. aeruginosa* and Enterobacteriaceae—cause many of the respiratory infections in this setting, with relatively minor changes in the distribution of the pathogens during the last decade.[28,29] Although VAP typically involves infection with a single pathogen, polymicrobial infections are also common.[30]

Until recently, MDR pathogens were isolated more frequently in late-onset VAP cases than in early-onset (within 4 days of hospital admission) cases, mostly reflecting prior use of broad-spectrum antibiotics in these patients.[31] However, several later studies found similar rates of etiologies in patients with early- and late-onset VAP, emphasizing that the local ICU ecology is the most important risk factor for acquiring MDR pathogens, irrespective of the length of intubation.[32,33]

Extended-spectrum β-lactamase–producing Enterobacteriaceae (ESBL-PE) are increasingly encountered in patients with hospital-acquired infections, including VAP, with additional mortality and cost.[34] They now represent 19–61% of the episodes caused by Enterobacteriaceae, varying according

to species and to countries. Systematic screening of ESBL-PE fecal carriage may help to guide initial therapy in patients with VAP when cultures are negative because they have a very good negative predictive value for subsequent ESBL-PE infections. Conversely, a positive specimen only has a predictive value from 35–40% and thus does not imply that initial antimicrobial therapy should systematically cover this pathogen.

Tracheal colonization *with P. aeruginosa* increases with increased length of hospitalization, prior antibiotic use, and severity of illness and is an important risk factor for VAP caused by this microorganism. In one study, the odds of developing *P. aeruginosa* VAP were eight times higher in patients with prior *P. aeruginosa* colonization than in noncolonized patients, confirming that screening for *P. aeruginosa* tracheal colonization by biweekly active surveillance cultures could reliably exclude the need for targeting this microorganism when cultures are negative for this microorganism.[35] *Acinetobacter baumannii* is also a common cause of ICU-acquired infection, accounting for 8–14% of VAP in the United States and Europe, but much higher rates (19% to >50%) in Asia, Latin America, and some Middle Eastern countries.[36,37] Importantly, many isolates are now resistant to all antimicrobials except colistin (polymyxin E) and tigecycline, and some infections are resistant to these antimicrobial agents as well.[38]

The emergence of infections caused by *carbapenem-resistant Enterobacteriaceae* (CRE) worldwide represents another alarming problem, although the prevalence of such infections is highly variable across different countries.[39] Prior use of carbapenems and prior hospitalization in a country where CRE is highly prevalent have been reported as independent risk factors for the acquisition of carbapenemase-producing Enterobacteriaceae and other CRE.

Legionella sp, anaerobes, fungi, viruses, and even *Pneumocystis jirovecii* are also potential causative agents, but these microbes are not commonly found when pneumonia is acquired during mechanical ventilation. Several of these causative agents, including viruses, might be more common than reported because they are difficult to identify.[40,41] Isolation of fungi, most frequently *Candida* sp, poses interpretative problems. Invasive disease has been reported in VAP, but yeasts are isolated frequently from respiratory tract specimens in the absence of apparent disease. The use of the commonly available respiratory sampling methods (bronchoscopic or nonbronchoscopic) in ventilated patients is not sufficient to make the diagnosis of *Candida* pneumonia, and evidence of lung tissue invasion is also needed.[42-45]

DIAGNOSIS

VAP is typically identified at the bedside by combining three criteria: (1) clinical observations suggesting infection, such as the new onset of fever, purulent sputum, leukocytosis, increased minute ventilation, arterial oxygenation decline, and/or the need for increased vasopressor infusion to maintain blood pressure; (2) new or progressive persistent radiographic opacities; and (3) "positive" microbiologic culture results for a potentially pathogenic microorganism isolated from tracheal aspirates, *bronchoalveolar lavage* (BAL) fluid, pleural fluid, and/or blood.[1,3] However, this definition of VAP is frequently inaccurate and leaves room for subjective interpretation.[46–48] Because a new pulmonary opacity is the only criterion confirming involvement of the intra-alveolar pulmonary spaces by the infectious process, it is considered a prerequisite for the diagnosis of VAP. However, most of the time it is not present, with the infection remaining confined to an already abnormal region of the lung. Thus, it is mandatory to consider the diagnosis of VAP in patients who deteriorate clinically, and/or in whom vasopressors need to be increased in order to maintain blood pressure, even in the absence of a clear-cut progression of radiographic abnormalities.

The presence of a pathogen at the level of the proximal airways does not suffice for making the diagnosis of VAP because most ventilated patients are colonized with pathogens very early after the initiation of mechanical ventilation. Even deciding which threshold should be applied to define a "positive" culture when using semiquantitative or quantitative tracheal aspirate or BAL fluid cultures can be challenging, especially for specimens obtained after starting new antibiotics.[3] Thus, the absence of indisputable reference standards continues to fuel controversy about the adequacy and relevance of many studies in this field and has led investigators to describe other types of lower respiratory tract infection, such as ventilator-associated tracheobronchitis, or even to abandon the concept of VAP and replace it by a new construct that comprises different levels of ventilator-associated events, including infection-related ventilator-associated condition.[49-52]

In practice, either of two conceptually different diagnostic strategies can be used when VAP is suspected.[3] Current evidence is insufficient to favor either approach to diagnosis of VAP regarding clinical outcomes, although evidence indicates that the second (invasive) approach can reduce use of antibiotics.

The first strategy is to treat every patient clinically suspected of having a pulmonary infection with new antibiotics, even when the likelihood of infection is low, arguing that several studies showed that immediate initiation of appropriate antibiotics is associated with reduced mortality.

The second strategy is to use an invasive diagnostic approach based on quantitative cultures of distal *lower respiratory tract* (LRT) specimens obtained using bronchoscopic or nonbronchoscopic techniques, such as BAL or a protected specimen brush, to improve the identification of patients with true VAP and facilitate decisions about whether or not to treat with antibiotics.[53] Although no consensus exists on the best diagnostic strategy for patients clinically suspected of having VAP, the goal of each strategy is to institute early appropriate antibiotic therapy in patients with true VAP and to withhold it in others.[54]

THE CLINICAL DIAGNOSTIC STRATEGY

With the clinical strategy, all patients suspected of having VAP are treated with antibiotics that they have not received recently. The selection of appropriate empirical therapy is based on risk factors and local microbiologic and resistance patterns and involves qualitative testing to identify possible pathogens. The initial antimicrobial therapy is adjusted

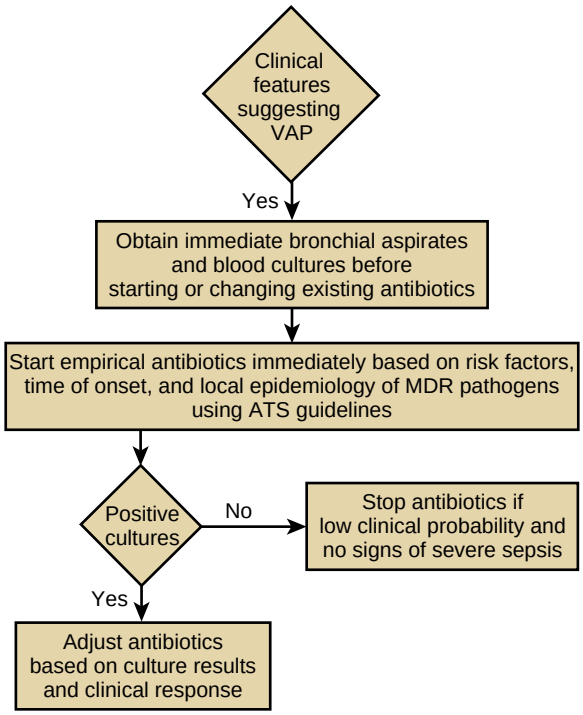

Figure 49.1 The clinical diagnostic strategy. Diagnostic and therapeutic algorithms applied to patients with a clinical suspicion of *ventilator-associated pneumonia* (VAP) managed with the clinical strategy. ATS, American Thoracic Society; MDR, multidrug resistant.

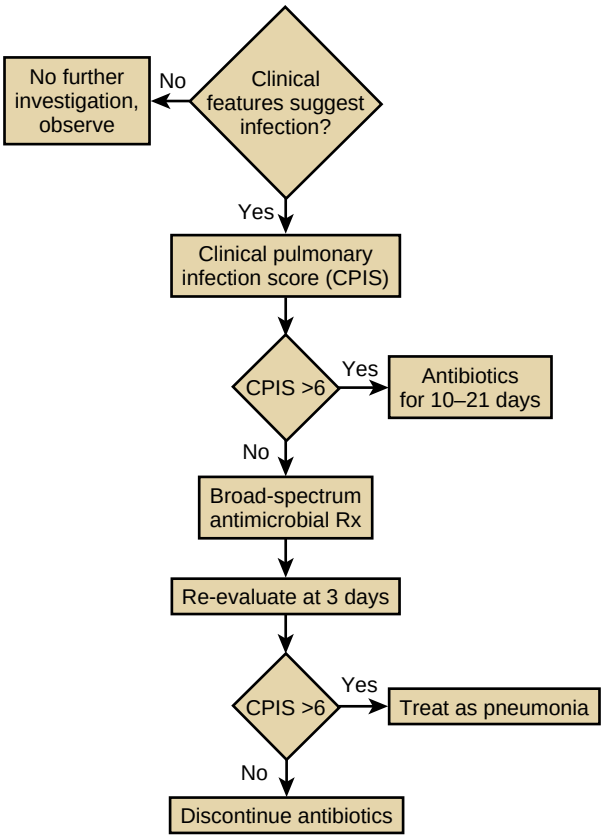

Figure 49.2 The clinical diagnostic strategy guided by a clinical score. Diagnostic and therapeutic strategy applied to patients managed with a clinical strategy guided by the *Clinical Pulmonary Infection Score* (CPIS).[57]

according to culture results or clinical response (Fig. 49.1). Antimicrobial treatment is discontinued only if the following three criteria are fulfilled on day 3: (1) clinical diagnosis of VAP is unlikely (there are no definite opacities found on chest radiography at follow-up and no more than one of the three following findings is present [temperature greater than 38.3°C, leukocytosis or leukopenia, and purulent tracheobronchial secretions]) or an alternative noninfectious diagnosis is confirmed, (2) tracheobronchial aspirate culture results are nonsignificant, and (3) severe sepsis or shock is not present.[55]

This clinical approach has two undisputable advantages: first, no invasive and/or specialized diagnostic procedures, such as fiberoptic bronchoscopy, BAL, and quantitative microbiologic techniques are required and, second, the risk of missing a patient who needs antibiotic treatment is minimal when all suspected patients are treated with new antibiotics. The disadvantages include the potential sampling errors inherent in specimens obtained from the proximal airways and lower specificity) for distinguishing airway colonization from true pneumonia.

Slightly different variants of the clinical approach including the use of quantitative or semiquantitative cultures of endotracheal aspirates for defining a positive result have been described to increase specificity and avoid undue prolongation of antibiotic therapy. While the simple qualitative culture of tracheal aspirates is a technique with a high percentage of false-positive results, several studies suggest that the diagnostic accuracy of quantitative cultures is similar to the accuracy of more invasive techniques, limiting the risk of overusing antibiotics in patients with colonized proximal airways and/or a mild form of tracheobronchitis but no true pneumonia.[56] Another option when using the clinical approach is to follow the strategy described by Singh and colleagues, in which decisions regarding initial antibiotic therapy are based on a clinical score constructed from seven variables, the *Clinical Pulmonary Infection Score* (CPIS).[57] Patients with a CPIS greater than 6 are considered to have VAP and are treated with antibiotics for 10 to 21 days; if the CPIS score is 6 or less, antibiotics are discontinued after 3 days (Fig. 49.2). Such an approach avoids prolonged treatment of patients who have a low likelihood of infection while allowing immediate treatment of patients who are more likely to have VAP. Antibiotics can also be stopped very early in patients with suspected VAP but minimal and stable ventilator settings. These patients may not have pneumonia at all or they may have comparatively mild pneumonias that can be adequately treated with very short courses of antibiotics (1 to 3 days).[58]

THE INVASIVE DIAGNOSTIC STRATEGY

With the invasive strategy, direct microscopic examination and quantitative cultures of LRT secretions obtained using BAL (performed with or without a bronchoscope) are used to define both the presence of pneumonia and the etiologic pathogen.[3,59] Growth above a threshold concentration is required to make a diagnosis of VAP and determine the causative microorganisms. Growth below the threshold is assumed to be due to colonization or contamination. Using this strategy, therapeutic decisions are made according to

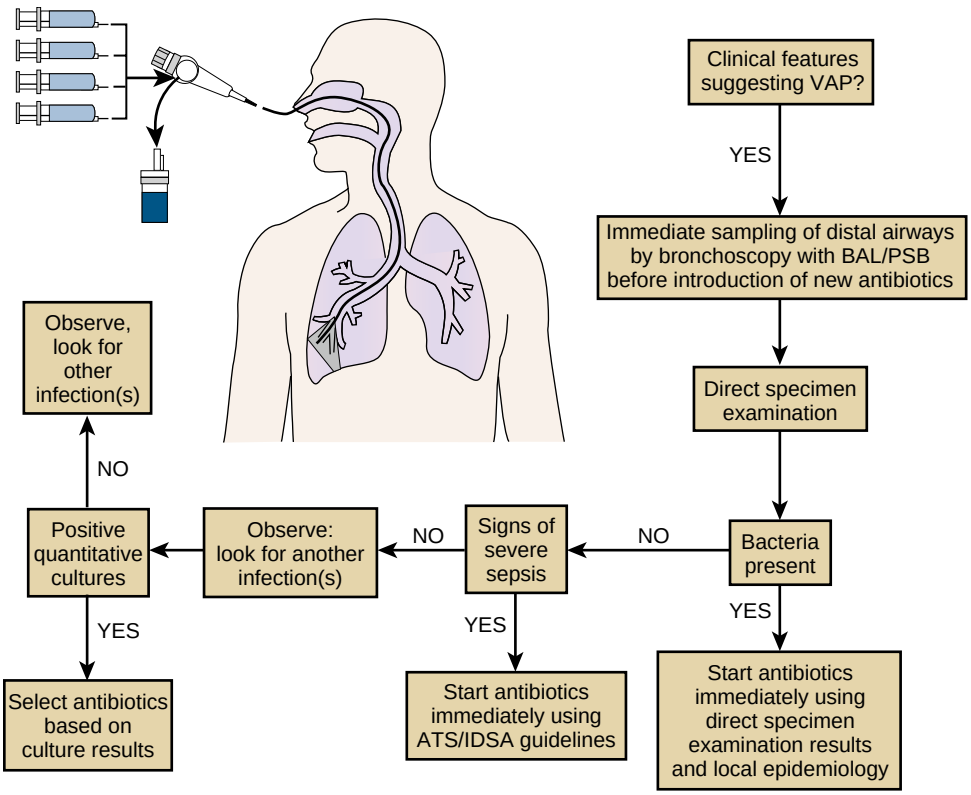

Figure 49.3 The invasive diagnostic strategy. Diagnostic and therapeutic strategy applied to patients with a clinical suspicion of *ventilator-associated pneumonia* (VAP) managed according to the invasive strategy. ATS, American Thoracic Society; BAL, bronchoalveolar lavage; IDSA, Infectious Diseases Society of America; PSB, protected specimen brush.

a strict protocol, using the results of direct examination of distal pulmonary samples and results of quantitative cultures in deciding whether to start antibiotic therapy, which pathogens are responsible for infection, which antimicrobial agents to use, and whether to continue therapy (Fig. 49.3).

Quantitative cultures of BAL specimens consistently yield a lower frequency of positive results (based on a quantity of microorganisms above the diagnostic threshold) than are obtained when only qualitative cultures of tracheal aspirates are used. Thus, when therapeutic decisions are based on these data, fewer patients are treated with antibiotics and a potentially narrower spectrum of therapy is used than when using the clinical approach, thereby limiting the emergence and dissemination of drug-resistant strains and antibiotic toxicity.

Another compelling argument in favor of the invasive strategy is that this approach directs attention away from the lungs as the source of fever when BAL quantitative culture results are negative. Many ICU patients with negative bronchoscopic cultures have other sites of infection, such as wounds, the urinary tract, or intravascular catheters that need to be identified to avoid delays in initiating appropriate treatment.

The accuracy of quantitative cultures of LRT secretions obtained using BAL is questionable in patients who have received prior antibiotics, particularly when new antibiotics are introduced after the onset of the symptoms suggestive of nosocomial pneumonia and before pulmonary secretions are collected. In that case, the newly initiated antibiotics can increase the number of false-negative results, regardless of the way in which the secretions are obtained.[60]

One major technical problem with all bronchoscopic techniques is proper selection of the sampling area in the tracheobronchial tree. The sampling area is usually selected based on the location of the radiographic opacity or on the bronchoscopic identification of a pulmonary segment that has purulent secretions. In patients with diffuse pulmonary opacities or minimal new changes in a previously abnormal chest radiograph, determining the correct segment to sample can be difficult. In such cases, sampling should be directed to the area where endobronchial abnormalities are maximal. Because autopsy studies indicate that VAP frequently involves the posterior portion of the right lower lobe, this area should probably be given priority for sampling.

SUMMARY OF THE EVIDENCE

Aside from decision-analysis studies and a single retrospective study, five trials to date have used a randomized scheme to assess the effect of a diagnostic strategy on antibiotic use and outcome in patients suspected of having VAP.[53,61-64] No differences in mortality and duration of mechanical ventilation were apparent by analysis of pooled data.[65] However, in a randomized study of 413 patients, those managed with an invasive strategy that combined quantitative cultures of BAL specimens with an algorithm for treatment de-escalation had a significant increase in antibiotic-free days at day 14 (5.0 vs. 2.2) and day 28 (11.5 vs. 7.5) compared with noninvasive methods using qualitative cultures, clearly indicating a decrease in antibiotic exposure.[53] Several prospective studies have also concluded that antibiotics can be stopped in patients with negative quantitative cultures, without adversely affecting the recurrence of pneumonia and mortality.[66-69]

Although no consensus has yet been reached on appropriate diagnostic strategies for VAP, the authors of the recent European guidelines on HAP/VAP suggest obtaining

Table 49.1 Proposed Strategy for Managing Antimicrobial Therapy in Patients with Ventilator-Associated Pneumonia

Proposed Strategy	Rationale
Step 1: Start therapy using broad-spectrum antibiotics	Due to the emergence of multiresistant GNB, such as *P. aeruginosa* and ESBL-producing GNB, and the increasing role of MRSA, empirical treatment with broad-spectrum antibiotics is justified in most patients with a clinical suspicion of VAP (see Fig. 49.4).
Step 2: Stop therapy if the diagnosis of infection becomes unlikely	The goal is to ensure that ICU patients with true bacterial infection receive immediate appropriate treatment. However, this can result in more patients receiving antimicrobial therapy than necessary because clinical signs of infection are nonspecific.
Step 3: Use narrower spectrum antibiotics once the etiologic agent is identified	For many patients with VAP, including those with late-onset infection, therapy can be narrowed once the results of respiratory tract and blood cultures are available, either because an anticipated organism (e.g., *P. aeruginosa* and *Acinetobacter* sp or MRSA) was not recovered, or because the organism isolated is sensitive to a more narrow-spectrum antibiotic than used in the initial regimen.[118,119]
Step 4: Use pharmacokinetic-pharmacodynamic data to optimize treatment	Clinical and bacteriologic outcomes can be improved by optimizing the therapeutic regimen according to pharmacokinetic and pharmacodynamic properties of the agents selected for treatment.
Step 5: Switch to monotherapy on days 3 to 5	There are no clinical benefits to using a regimen combining two antibiotics for more than days 3 to 5, provided that initial therapy was appropriate, the clinical course appears favorable, and microbiologic data do not point to a very difficult-to-treat microorganism.
Step 6: Shorten the duration of therapy	Reducing duration of therapy in patients with VAP has led to good outcomes with less antibiotic use. Prolonged therapy leads to colonization with antibiotic-resistant bacteria, which may precede a recurrent episode of VAP.

ESBL, extended-spectrum β-lactamase; GNB, gram-negative bacteria; ICU, intensive care unit; MRSA, methicillin-resistant *Staphylococcus aureus;* VAP, ventilator-associated pneumonia.

LRT quantitative samples (prior to any antibiotic treatment) to reduce antibiotic exposure in stable patients with suspected VAP and to improve the accuracy of the results (weak recommendation, low quality of evidence).[1] Because BAL removes cells (approximately 1 million) and secretions from a large lung area and samples can be examined microscopically immediately after the procedure to verify the presence or absence of intracellular or extracellular bacteria in the lower respiratory tract, this examination is particularly useful and well adapted to allow rapid identification of an infection having reached the distal bronchioles and the intra-alveolar spaces. As such, our own position is to recommend the use of a strategy based on systematically performing BAL in all patients clinically suspected of having VAP.[46] If BAL performed with or without a bronchoscope is not available, results of tracheal aspirate quantitative cultures can be used as an acceptable substitute, provided that a sufficiently high threshold (i.e., $\geq 10^5$ CFU/mL) is applied, to avoid overusing antibiotics in patients with only proximal airway colonization.

Whether the diagnosis of VAP can be improved by lung ultrasonography and/or new methods for identifying and quantifying the bacterial burden present in the lower respiratory tract warrant investigation. A growing number of rapid diagnostic techniques using biomolecular approaches, including quantitative and multiplex polymerase chain reaction, *matrix-assisted laser desorption ionization time-of-flight mass spectrometry* (MALDI-TOF MS), peptide nucleic acid fluorescence in-situ hybridization, and morphokinetic cellular analysis using advanced optics microscopy, are available that allow early pathogen identification and determination of antimicrobial susceptibility.[70,71] These new technologies, when coupled with strong antibiotic stewardship programs, are expected to reduce the time to appropriate antimicrobial therapy in patients infected with MDR pathogens, as well as avoiding broad-spectrum regimens when the infection can be treated by a narrow-spectrum antibiotic, but these assays remain susceptible to the problems of contamination and colonization.

TREATMENT

Antimicrobial therapy of patients with VAP is a two-stage process. The *first* stage involves administering broad-spectrum antibiotics to avoid inadequate treatment of patients with true bacterial pneumonia. The second stage focuses on achieving this objective without overusing or abusing antibiotics. In general, the first stage can be accomplished by rapidly identifying patients with pneumonia and starting therapy with an empirical regimen likely to treat the most common etiologic agents in a particular institution. This requires that the initial antibiotic choice be driven by knowledge of the likely etiologic pathogens and the local patterns of antimicrobial resistance. The *second* stage involves stopping therapy in patients with a low probability of VAP, focusing and narrowing treatment once the etiologic agent is known, switching to monotherapy after day 3 whenever possible, and shortening the duration of therapy to 7 to 8 days in most patients, as determined by the patient's clinical response and information about the bacteriology (Table 49.1).[1,3,72]

INITIAL TREATMENT

Optimal treatment of VAP implies that the initial antimicrobial agents could be selected based on an accurate prediction of the responsible pathogens and of their susceptibility patterns, to avoid both ineffective therapy when

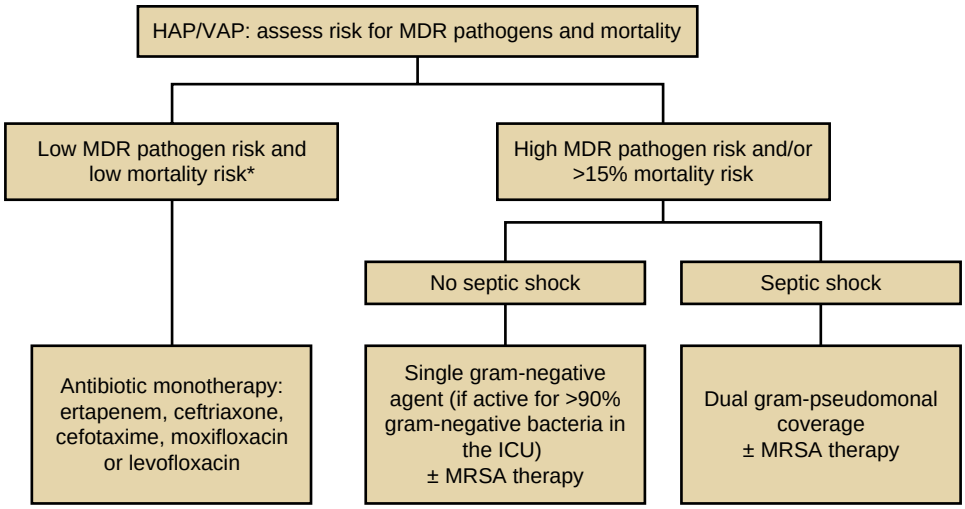

Figure 49.4 Empirical antibiotic treatment algorithm. The algorithm follows the European Guidelines for hospital-acquired pneumonia/ventilator-associated pneumonia (HAP/VAP) in selecting initial empiric use of antibiotics.*Low risk for mortality is defined as a ≤15% chance of dying, a mortality rate that has been associated with better outcomes using monotherapy than combination therapy when treating serious infection. ICU, intensive care unit; MDR, multidrug-resistant; MRSA, methicillin-resistant *Staphylococcus aureus*. (From Torres A, Niederman MS, Chastre J, et al. International ERS/ESICM/ESCMID/ALAT guidelines for the management of hospital-acquired pneumonia and ventilator-associated pneumonia. *Eur Respir J* 50[3]:2017.)

the pathogen is highly resistant to antibiotics and excessive antibiotic use when it can be covered by a narrow-spectrum agent. Failure to initiate prompt appropriate therapy (i.e., using an agent to which the etiologic organism is sensitive, with the optimal dose and route of administration) has been consistently linked with increased mortality in patients with VAP.[73] Due to the emergence of multiresistant GNB, such as *P. aeruginosa*, ESBL Enterobacteriaceae, and carbapenemase-producing *Klebsiella pneumoniae,* and the still-important role of gram-positive bacteria, such as *methicillin-resistant Staphylococcus aureus* (MRSA), empirical treatment with broad-spectrum antibiotics is justified in most patients with a clinical suspicion of VAP.[1,2] The choice of agents should be based on local patterns of antimicrobial susceptibility and anticipated side effects, and should take into account the antibiotics that the patients have received within the prior 2 weeks, striving not to use the same antimicrobial classes, if possible. Having current knowledge about local bacteriologic patterns can increase the likelihood that appropriate initial antibiotic treatment will be prescribed. A suggested approach for the selection of the initial treatment, as proposed in the European Guidelines for HAP/VAP, is summarized in Figure 49.4. Only patients with a low mortality risk and low MDR pathogen risk, such as those without prolonged duration of hospitalization, admission from a health care–related facility, or recent prolonged antibiotic therapy, can be treated with a relatively narrow-spectrum drug, such as a nonpseudomonal third-generation cephalosporin.[1]

Several published reports have demonstrated the need to adjust the target dose of antimicrobial agents used in treating severe VAP to the individual patient's pharmacokinetics and the putative bacterial pathogens' susceptibilities.[74,75] Most investigators distinguish between antimicrobial agents that kill by a concentration-dependent mechanism (e.g., aminoglycosides and fluoroquinolones) and those that kill by a time-dependent mechanism (e.g., β-lactams and vancomycin). Altered pharmacokinetics secondary to an increase in the volume of distribution in critically ill patients can result in insufficient serum β-lactam concentrations when standard doses are administered, emphasizing the need to monitor peak and trough levels of antibiotics carefully when treating resistant pathogens.[74] Regimens with higher doses than those usually recommended and/or a prolonged duration of infusion are frequently needed in such circumstances. Development of dosing algorithms based on minimal inhibitory concentrations, patient creatinine clearance and weight, and a clinician-specified area under the inhibitory curve target, as well as therapeutic drug monitoring, might be a valid way to improve treatment of these patients, leading to a more precise approach than provided by current antimicrobial guidelines.

AVOIDING OVERUSE OF ANTIBIOTICS

The need to ensure that ICU patients with true bacterial infections promptly receive an appropriate antibiotic regimen can lead to many more patients receiving antimicrobial therapy than is actually necessary, because clinical signs of infection are nonspecific. Thus, when a clinical approach to VAP is used, it is important to perform serial clinical and microbiologic evaluations, and to reevaluate therapy after 48 to 72 hours so that it can be stopped if infection is unlikely. To accomplish this, all diagnostic strategies designed for managing patients with a clinical suspicion of VAP should make explicit the decision tree used to identify patients with a low probability of infection, in whom therapy can be stopped when infection appears improbable.

For many patients with VAP, including those with late-onset infection, therapy can be narrowed once the results of respiratory tract and blood cultures are available, if no resistant organism (e.g., *P. aeruginosa*, *Acinetobacter* sp, or MRSA) is recovered or if the isolated organism is sensitive

to a narrower spectrum antibiotic. For example, vancomycin and linezolid should be stopped if MRSA is not identified, unless the patient is allergic to β-lactams and has an infection caused by a gram-positive microorganism. Very-broad-spectrum agents, such as carbapenems, piperacillin-tazobactam, and/or cefepime, should be restricted to patients with infection caused by pathogens only susceptible to these agents. Clinicians must be aware that the emergence of resistant variants may lead to treatment failure when third-generation cephalosporins are chosen to treat infections caused by *Enterobacter, Citrobacter, Morganella morganii*, indole-positive *Proteus*, and *Serratia* sp due to the presence of inducible β-lactamases, even if the isolate is initially characterized as susceptible.

The most common reason to use combination therapy in initial management of patients with VAP is to achieve synergy in treating *P. aeruginosa* or other difficult-to-treat GNB. However, antibiotic synergy has been shown to be valuable only in vitro and in patients with neutropenia or bacteremic infection, which is uncommon in VAP. A meta-analysis evaluated all prospective randomized trials of β-lactam monotherapy compared with β-lactam/aminoglycoside combination regimens in 7586 patients with sepsis, of whom at least 1200 patients had VAP.[76] The clinical success rates were similar with monotherapy versus combination therapy, and combination therapy had no advantage in the treatment of *P. aeruginosa* infections. Importantly, combination therapy did not prevent the emergence of antimicrobial resistance during treatment, but it was associated with a significantly higher rate of nephrotoxicity. Based on these data, therapy can be switched to monotherapy in most patients after 3 or 5 days, as long as initial therapy is appropriate, the clinical course is favorable, and microbiologic data do not identify a difficult-to-treat microorganism with a high in vitro minimal inhibitory concentration, as is found with some lactose-nonfermenting GNB.

Efforts to reduce the duration of therapy for VAP are justified by studies of the natural history of the response to therapy. Most patients with VAP who receive appropriate antimicrobial therapy have a good clinical response within the first 6 days.[77] Prolonged therapy promotes colonization with antibiotic-resistant bacteria, which may lead to a recurrent episode of VAP. A multicenter randomized controlled trial of 401 patients with microbiologically proven VAP showed that the clinical outcomes of patients who received appropriate empirical therapy for 8 days were similar to those of patients who received therapy for 15 days.[78] A trend to greater rates of relapse for short-duration therapy was seen when the etiologic agent was *P. aeruginosa* or *Acinetobacter* sp, but the clinical outcomes were indistinguishable. These results were confirmed in two later studies, including a prospective randomized trial of 290 patients evaluating an antibiotic discontinuation policy.[79,80] Patients for whom a shorter duration of therapy may not be appropriate include immunosuppressed patients, those whose pneumonia was complicated by empyema and/or pulmonary abscess, those whose initial antimicrobial treatment was not appropriate for the causative microorganisms, and those whose infection was caused by nonfermenting GNB and who had no improvement in clinical signs of infection.

Many clinicians remain hesitant about prescribing antibiotics for fewer days for patients with VAP, and they prefer to customize antibiotic duration based on the clinical course of the disease and/or using serial determinations of a biomarker such as procalcitonin. The rationale for using a biomarker to tailor antibiotic treatment duration relies on evidence that the inflammatory response is often proportional to infection severity. When that response is absent or low, it might be logical to discontinue antibiotics earlier. Thus, adapting antimicrobial treatment duration to procalcitonin kinetics seems reasonable and has been demonstrated as useful in several randomized trials targeting patients with acute respiratory infection, including five trials conducted in the ICU.[81,82]

AEROSOLIZED THERAPY

The recent development of vibrating-mesh nebulizers has renewed interest in antibiotic aerosolization in patients with VAP. Their use allows very high concentrations of antimicrobial agents to be achieved in respiratory secretions, including the fluid lining the alveolar compartment, far above those achievable using the intravenous route.[83] However, data in critically ill patients with pneumonia are limited; most reported experiences are case reports, descriptive studies, or literature review. Moreover, aerosols are likely to reach only ventilated regions of the lungs, and not consolidated areas involved with pneumonia. According to systematic reviews and meta-analyses results, administration of aerosolized antibiotics might increase the likelihood of clinical resolution, particularly in VAP caused by MDR pathogens.[84] However, no significant improvements in important outcomes such as mortality or duration of mechanical ventilation have been consistently documented, and results of a double-blinded, placebo-controlled, randomized trial failed to demonstrate superiority of adjunctive aerosolized antibiotics versus standard of care in any clinically relevant end point.[85] Thus, although promising, the widespread use of aerosolized antibiotics to treat pneumonia in the ICU setting cannot be recommended.[84] It should be restricted to the treatment of extensively resistant gram-negative pneumonia susceptible only to antibiotics with limited efficacy and high toxicity when given by the IV route (i.e., aminoglycosides and colistin), or in patients who are not responding to IV antibiotics alone, as a last resort therapy, whether the infecting organism is or is not MDR.[2] In these cases, the use of a vibrating-mesh nebulizer seems to be more efficient, but specific settings and conditions are required to improve lung delivery.[86]

PREVENTION

Because VAP is associated with increased morbidity, longer hospital stay, increased health care costs, and higher mortality rates, prevention is an important goal.

CONVENTIONAL INFECTION CONTROL APPROACHES

The design of the ICU has a direct effect on the potential for nosocomial infections. Adequate space and lighting, properly functioning ventilation systems, and appropriate

handwashing facilities all lead to lower infection rates.[87] It is important to note, however, that upgrading the physical environment does not reduce the infection rate unless the attitudes and practices of health care personnel are also optimized. In any ICU, one of the most important factors is the health care staff, including the number, quality, and motivation of medical, nursing, and ancillary members. The team should include a sufficient number of nurses to minimize their movement from one patient to another and to avoid having them work under constant pressure.[88] The importance of personal cleanliness and attention to aseptic procedures must be emphasized at every opportunity. It is clear that careful monitoring, decontamination, and compliance with guidelines for the use of respiratory equipment all reduce the incidence of nosocomial pneumonia.[89] Handwashing and hand rubbing with alcohol-based solutions remain the most important components of effective infection control practices in the ICU.[90]

Environmental and patient-oriented microbiologic monitoring facilitates the early recognition of colonization and infection and has been associated with significant reductions in nosocomial infection rates. The focal point for infection control activities in the ICU is a surveillance system designed to establish and maintain a database that identifies endemic rates of nosocomial infections. This information facilitates the recognition of outbreaks, when infection rates rise above the endemic threshold for a specific type of nosocomial infection.

An antibiotic policy that restricts the prescription of broad-spectrum agents and inappropriate antibiotics is of major importance. Better use of antibiotics in the ICU can be achieved by implementing strict guidelines, avoiding the treatment of patients who do not have bacterial infections, using narrow-spectrum antibiotics whenever possible, and reducing the duration of treatment.[91,92] Similarly, transfusion of red blood cells and other allogenic blood products should follow a strict policy because several studies have identified exposure to allogenic blood products as a risk factor for postoperative infection and pneumonia.[93]

SPECIFIC PROPHYLAXIS AGAINST VENTILATOR-ASSOCIATED PNEUMONIA

Specific strategies aimed at reducing the duration of mechanical ventilation (a major risk factor for VAP), such as improved methods of sedation, use of protocols to facilitate and accelerate weaning, mobilizing patients as soon as possible, and using low tidal volume with adequate levels of positive end-expiratory pressure, are integral parts of any VAP prevention program.[94-97] All are based on the application of strict protocols. Similarly, noninvasive positive-pressure ventilation using a face mask should be used whenever possible.[98]

Some very simple, safe, inexpensive, and logical measures may have beneficial effects on the frequency of VAP in mechanically ventilated patients. These include avoiding nasal insertion of endotracheal and gastric tubes, maintaining the endotracheal tube cuff pressure above 20 cm H_2O to prevent leakage of bacteria around the cuff into the lower respiratory tract, promptly reintubating patients who are likely to fail extubation, keeping patients in the semirecumbent position when enteral nutrition is used, removing tubing condensate, and providing adequate oral hygiene with sterile water alone, even though the level of evidence for the efficacy of these measures is low.[89,99,100]

Continuous or intermittent suctioning of oropharyngeal secretions has been proposed as a means to avoid chronic aspiration of secretions through the tracheal cuff of intubated patients. However, an updated meta-analysis of subglottic secretion drainage reported no impact on duration of mechanical ventilation, ICU length of stay, or mortality, casting some doubt on the efficacy of such a measure.[101] Investigators have also proposed a number of innovations in endotracheal tube cuff materials, shape, and design, as well as more consistent and frequent cuff pressure monitoring, in order to prevent microaspirations of microbe-laden secretions along the vertical microfolds that develop along the endotracheal tube cuff. Unfortunately, none of these innovations have thus far been proven to prevent VAP or improve objective patient outcomes.[102-104]

Gastric colonization by potentially pathogenic organisms increases with decreasing gastric acidity. Thus, medications that decrease gastric acidity (antacids, histamine 2 blockers) can increase the gastric bacterial burden and increase the risk of VAP. However, whether stress ulcer prophylaxis increases VAP incidence is still debated. Krag and colleagues randomized 3298 patients in 33 European ICUs to daily intravenous pantoprazole versus placebo.[105] Patients randomized to pantoprazole had a lower rate of clinically notable gastrointestinal bleeding (2.5% vs. 4.2%) but no difference in the rates of red blood cell transfusions, pneumonia, *Clostridioides difficile* infections, or 90-day mortality. While this trial somewhat tempers the concern that stress ulcer prophylaxis may increase the risk of pneumonia in critically ill patients, it simultaneously fails to provide clear evidence that stress ulcer prophylaxis improves objective patient outcomes.

Oral care with chlorhexidine was considered until recently as an important measure for preventing VAP; however, new data have questioned its true efficacy and safety. While meta-analyses of randomized trials have reported that oral care with chlorhexidine lowers VAP rates by about 30%, this signal is only evident in open-label studies. If one restricts the meta-analysis to double-blind studies, the signal is diminished and no longer significant. Furthermore, no benefit in duration of mechanical ventilation or mortality has ever been demonstrated.[106] There are also some concerns regarding a possible increased risk of mortality and ventilator-associated events, as noted on meta-analyses of randomized trials and several observational studies.[106,107]

Selective decontamination of the digestive tract (SDD) includes a short course of systemic antibiotic therapy, such as cefotaxime, trimethoprim, or a fluoroquinolone, and topical administration of nonabsorbable antibiotics (usually an aminoglycoside, polymyxin E, and amphotericin) to the mouth and stomach, to eradicate potentially pathogenic bacteria and yeast that may cause infections. Since the original study published by Stoutenbeek and coworkers in 1984, which demonstrated a decrease of the overall infection rate in patients receiving the SDD regimen, more than 40 randomized controlled trials and eight meta-analyses have been published.[108,109] All eight meta-analyses reported a significant reduction in the risk

of VAP, and four reported a significant reduction in mortality. Several prospective, randomized, controlled trials, all performed in ICUs with low rates of antibiotic resistance, that were large enough to show a significant survival benefit in SDD-treated patients have been published.[110-113] All were in favor of treatment with SDD, the largest and most recent one demonstrating a relative decrease in 28-day mortality rate (odds ratio, 0.83; 95% confidence interval, 0.72 to 0.97) and an absolute survival benefit of 3.5%.[112] Even so, widespread use of SDD in ICU patients remains controversial. The major concern with use of SDD is that it can promote the emergence of resistant bacteria, particularly gram-positive bacteria such as MRSA. This is likely to be an even greater problem in ICUs with a high baseline rate of resistance. In contrast to what was expected, most studies that have evaluated this issue showed a lower incidence of colonization with resistant bacteria in SDD-treated patients than in control patients, even after many years of utilization, possibly because decontamination prevents some infections and thus saves some patients from needing treatment with intravenous antibiotics.[109,114] Nonetheless, active surveillance for resistant pathogens among all ICU patients (not just those receiving digestive or oral decontamination) suggests that SDD is associated with small but significant and sustained increases in the unit-wide prevalence of antibiotic-resistant organisms.[110,113] The most recent European guidelines on the management of HAP and VAP issued a weak recommendation in favor of selective oral decontamination alone, not SDD, and only for settings with low rates of antibiotic-resistant bacteria and low rates of antibiotic consumption.[1] The recent publication of a trial that assessed the value of oral care with 2% chlorhexidine versus selective oral decontamination versus SDD, each compared with standard of care, in a cluster randomized crossover trial among 13 European ICUs with moderate to high rates of antibiotic resistance at baseline supports this recommendation, having found no differences between arms in either ICU-acquired bloodstream infections with resistant organisms or 28-day mortality.[111]

IMPLEMENTING A STRUCTURED PREVENTION POLICY

The application of consistent evidence-based interventions to prevent VAP has been highly variable from one ICU to another and is often suboptimal. Furthermore, no single preventive measure can succeed alone, emphasizing the need to use multifaceted and multidisciplinary programs to prevent VAP. Such programs are frequently referred to as *care bundles*. A care bundle is a set of readily implementable interventions required to be undertaken for each patient on a regular basis. The goal is for every intervention to be implemented for every patient on every day of his or her stay in the ICU. Compliance is assessed for the bundle as a whole, so failure to complete even a single intervention means failure of the whole bundle. The interventions need to be packaged in such a way that compliance is readily assessed, which usually means that no more than five interventions are included in each care bundle. The performance goal is to achieve over 95% compliance routinely. Care bundles make it possible to introduce evidence-based preventive measures, including achieving appropriate nurse staffing levels, avoiding intubation, and initiating specific strategies aimed at reducing the duration of mechanical ventilation, as described above. Several studies using quasi-experimental design have confirmed the usefulness of this strategy for preventing VAP in the ICU.[115,116]

The lack of methodologic rigor of the reported studies, however, precludes any conclusive statements about "care bundle" effectiveness or cost-effectiveness. The exact set of key interventions that should be part of the VAP-prevention bundle is also not currently known, nor are factors contributing to its success. Successful VAP prevention requires an interdisciplinary team, educational interventions, system innovations, process indicator evaluation, and feedback to health care workers. As shown in a recent study, simply having a checklist available for reference without consideration of a robust implementation and adherence strategy is unlikely to maximize patient outcomes.[117]

In the United States, the Centers for Medicare and Medicaid Services has proposed ending hospital reimbursements for care made necessary by preventable complications, including nosocomial infections, aiming for a zero VAP rate. Although this plan may have the desirable consequences of improving the quality of care, it also may penalize hospitals that admit high-risk patients and inadvertently encourage institutions to underreport VAP or to overuse antibiotics, thereby favoring dissemination of MDR microorganisms. This possibility further underscores the need to evaluate all new strategies potentially aimed at preventing VAP by comparing them to current best clinical practices.

Key Points

- *Ventilator-associated pneumonia* (VAP) is associated with mortality in excess of that caused by the underlying disease alone, particularly in the case of infection due to high-risk pathogens, such as *P. aeruginosa* and methicillin-resistant *S. aureus*, and/or when the initial therapy is inappropriate.
- The predominant organisms responsible for infection are *P. aeruginosa, S. aureus,* and Enterobacteriaceae, but etiologic agents differ widely according to the population of hospital patients, the duration of hospital stay, and prior antimicrobial therapy.
- Because even a few doses of an antimicrobial agent can negate results of microbiologic cultures, pulmonary secretions in patients suspected of having developed VAP should always be obtained before new antibiotics are administered.
- The initial approach to antimicrobial therapy involves administering broad-spectrum antibiotics to avoid inadequate treatment in patients with true bacterial pneumonia.
- The management of antibiotic therapy for VAP should optimize care without overusing and abusing antibiotics by stopping therapy in patients with a low probability of VAP, streamlining treatment once the etiologic agent is known, switching to monotherapy after days 3 to 5, and shortening duration of therapy

to 7 to 8 days, as dictated by the patient's clinical response to therapy and information about the bacteriology of the infection.

- Evidence-based preventive measures include staffing nurses at appropriate levels, avoiding intubation by using noninvasive ventilation whenever possible in suitable populations, and reducing the duration of ventilation by maintaining low tidal volume ventilation and sedating at minimal levels coupled with paired daily spontaneous awakening and breathing trials.
- Current evidence is insufficient to favor either a clinical or invasive approach to diagnosis of VAP regarding clinical outcomes, although evidence indicates that the invasive approach can reduce use of antibiotics.

Key Readings

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50 LUNG ABSCESS

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INTRODUCTION

A lung abscess forms as a result of lung tissue necrosis, most commonly due to a polymicrobial infection creating a cavity. Organisms originating in the oral cavity are usually responsible for causing lung abscesses; however, other organisms may be involved in certain contexts, such as in patients with immunodeficiency. This chapter discusses the clinical manifestations, differential diagnosis, diagnostic studies, and therapeutic options for lung abscesses.

DEFINITION

A lung abscess can be defined by chronicity or by the isolation of a specific organism. For example, if symptoms have been present for more than 1 month prior to seeking medical attention, the abscess is considered chronic. If an organism is isolated on culture, the lung abscess can be defined by the organism (e.g., a *Pseudomonas* lung abscess). As detailed later, isolation of anaerobic organisms requires specialized culture conditions and, if a sample is not handled rapidly and properly, cultures may be negative even if organisms are apparent on Gram-stained specimens. If no pathogen is identified, it is termed a nonspecific lung abscess.

A lung abscess can also be described as primary or secondary. Primary lung abscesses develop in immunocompetent individuals most commonly due to large-volume or frequent, small-volume aspiration. Secondary lung abscesses are associated with an underlying pulmonary parenchymal condition or immunodeficiency.

PATHOPHYSIOLOGY

Most lung abscesses are thought to be caused by aspiration of anaerobic bacteria from the oral cavity, primarily from the gingival crevices. Periodontal disease is a major risk factor for the development of anaerobic pleuropulmonary infections.[1] Individuals with teeth or dentures have an increased incidence of oropharyngeal colonization by respiratory pathogens compared to edentulous patients. Aspiration may be secondary to dysphagia or a reduced level of consciousness from alcohol, sedating drugs, head trauma, seizures, or general anesthesia. With a decreased level of consciousness and a defective cough reflex, patients cannot clear the bacteria from their lungs. Pneumonitis can develop over 7 to 14 days and, in certain circumstances, necrosis may follow. Apart from primary lung infection, pulmonary cavities may develop due to many noninfectious causes (see later), which may mimic infectious lung abscesses. A small subset of lung abscesses are due to complications from bronchoscopic procedures, including from transbronchial forceps biopsy, endobronchial ultrasound-guided mediastinal biopsy, and transbronchial lung cryobiopsy.[3,4]

CLINICAL MANIFESTATIONS

In lung abscesses caused by anaerobic bacteria, symptoms are usually indolent. Fever, cough, and sputum production can develop over weeks to months. Symptoms can also include night sweats and weight loss, especially when an underlying systemic process exists. Occasionally, patients report pleuritic chest pain, hemoptysis, and foul-smelling sputum. The physical examination is often nonspecific. Findings may include fever, a decreased level of consciousness, and poor dentition. Lung exam may reveal crackles, egophony, and/or dullness to percussion if a pleural effusion is present.

DIFFERENTIAL DIAGNOSIS

Bacterial organisms are the leading cause of tissue necrosis and lung abscess formation; however, fungi and parasites must also be kept in the differential diagnosis. The cavity appearance on imaging is not specific for the type of organism (Figs. 50.1 and 50.2). Noninfectious causes of pulmonary cavities include septic emboli, vasculitis (e.g., granulomatosis with polyangiitis), malignancy, bronchiectasis, and bronchostenosis caused by a foreign body or an obstructing mass (Figs. 50.3 and 50.4).

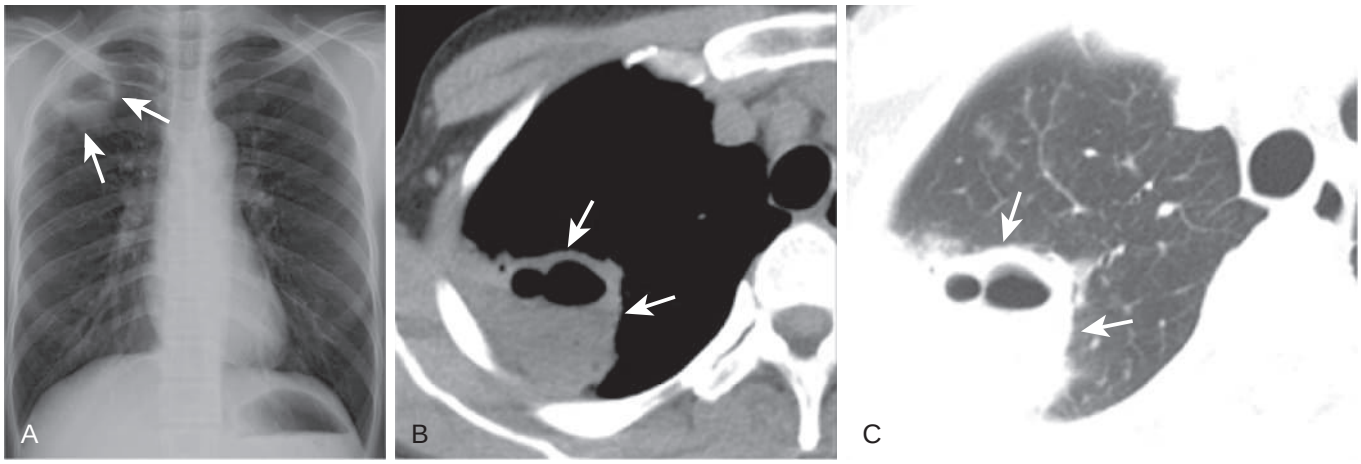

Figure 50.1 ***Klebsiella pneumoniae*** **lung abscess.** (A) Frontal chest radiograph shows a subpleural right apical cavity (*arrows*) with an air-fluid level consistent with a pulmonary abscess. Axial thoracic computed tomography displayed in soft tissue (B) and lung (C) windows shows a nonspecific cavity (*arrows*) consistent with a pulmonary abscess. (Courtesy Michael B. Gotway, MD.)

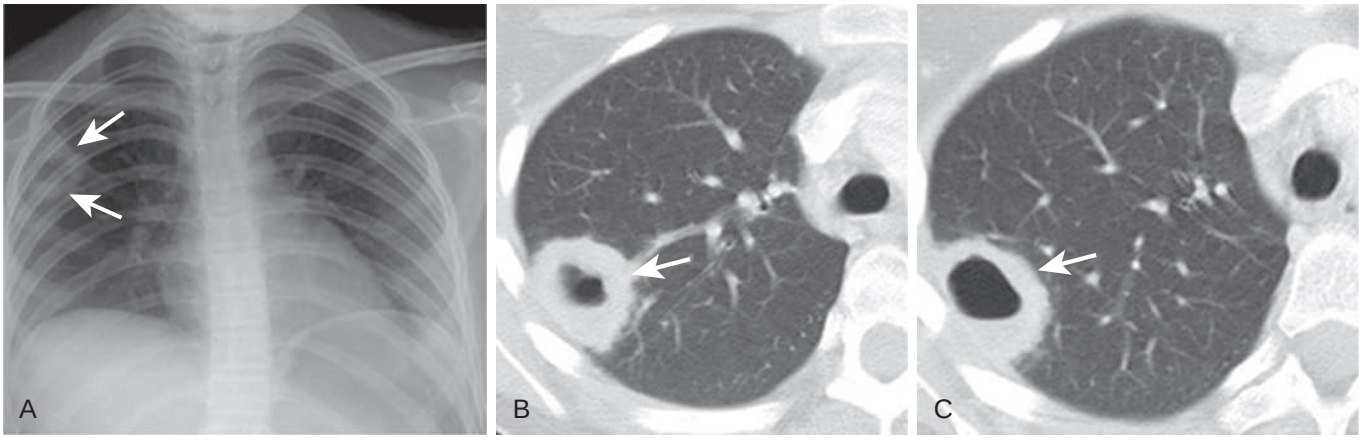

Figure 50.2 ***Nocardia asteroides*** **lung abscess.** (A) Frontal chest radiograph shows a poorly defined opacity (*arrows*) in the subpleural right upper lobe. (B–C) Axial thoracic computed tomography displayed in lung windows shows a subpleural right upper lobe cavity (*arrows*) containing an air-fluid level. This lesion is nonspecific in appearance and could be the result of a number of infections, but *Nocardia asteroides* was recovered at biopsy. (Courtesy Michael B. Gotway, MD.)

RADIOGRAPHIC FEATURES

Chest imaging allows the practitioner to confirm a diagnosis of lung abscess. Chest radiographs may demonstrate a cavity with an air-fluid level and a surrounding infiltrate (Fig. 50.5). The abnormality is commonly noted in the posterior segment of the upper lobes or the superior segment of the lower lobes, areas most dependent in a supine person and thus most susceptible to aspiration. Because the right main bronchus is shorter, larger in diameter, and more vertical than the left bronchus, aspiration tends to favor the right lung.[5] If there is uncertainty in the diagnosis based on chest radiographs, *computed tomography* (CT) of the chest can be obtained. Chest CT can also be helpful in evaluating secondary causes of lung abscess.

Features on CT imaging may help to distinguish a pulmonary abscess from a benign cavity, a malignant lesion, septic emboli, or an empyema. Benign cavities tend to have a thin wall without surrounding abnormalities such as ground-glass opacities or a consolidation. Although data are limited, features that favor a lung abscess include an air-fluid level, a surrounding parenchymal opacity such as ground-glass opacity or consolidation, and an irregular ("shaggy") inner wall. Characteristics that suggest a malignant lesion include a more nodular inner wall and a wall thickness of 16 mm or greater, although this can vary depending on the type of malignancy (see Fig. 50.3).[6] Lymphadenopathy and a pleural effusion may also favor a malignant process. In contrast, septic emboli in the lung usually manifest as multiple, distinct nodules (1 to 3 cm in diameter) with cavities in different stages. They also cause subpleural wedge-shaped infiltrates.[7] A pleural empyema is often oblong in appearance, has a smooth lining, and compresses the surrounding lung, whereas a pulmonary abscess is typically round (a similar dimension in different views), has a ragged inner lining, and does not compress the adjacent lung because it primarily causes necrosis of the lung parenchyma (see Fig. 108.2). Additional nodules and cavities in the lung strongly suggest embolization or a noninfectious inflammatory disorder, such as vasculitis (see Fig. 50.4).

DIAGNOSTIC STUDIES

When a pulmonary abscess is suspected, expectorated sputum should be sent for Gram stain and aerobic culture. Because many anaerobic bacteria are rapidly killed by exposure to atmospheric oxygen, accurate results from anaerobic cultures require rapid transport and handling by the microbiology

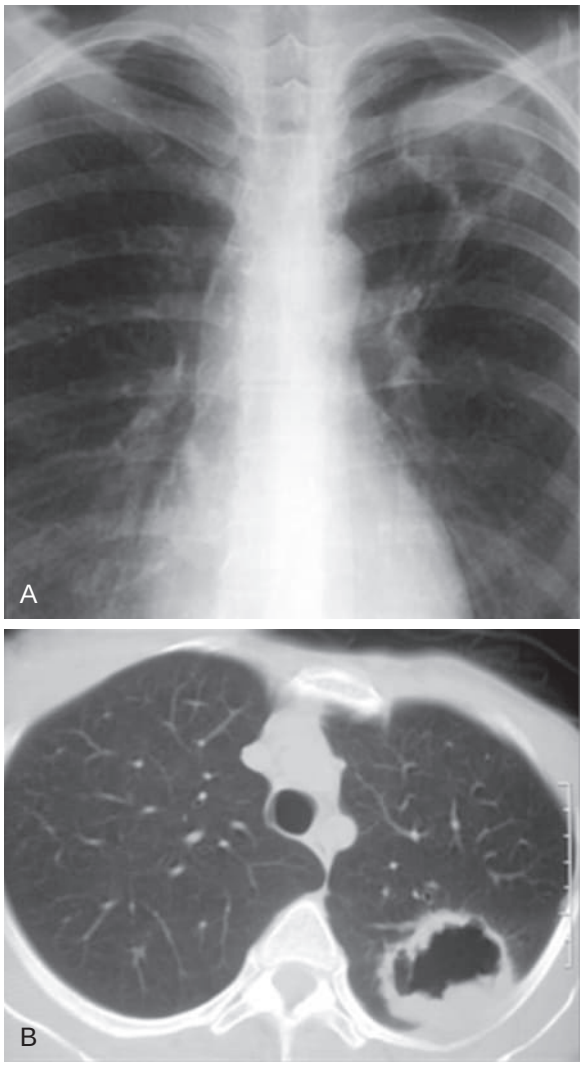

Figure 50.3 Lung abscess mimics: squamous cell carcinoma of the lung. (A) Frontal chest radiography shows a left apical cavitary lesion. The patient had poor dentition with a history of alcoholism and presented with fever; aspiration pneumonia and abscess were considered. Follow-up chest radiography 2 weeks later following broad-spectrum antibiotic therapy showed no change in the lesion, which prompted *computed tomography* (CT). (B) Axial CT displayed in lung windows shows that the cavitary left apical lesion has an irregularly thick posterior wall (>15 mm) with a grossly nodular appearance. The asymmetric wall thickening and nodularity suggest a malignant etiology for the cavity. (Courtesy Michael B. Gotway, MD.)

laboratory. Even with appropriate handling, samples may be contaminated by bacteria from the oral cavity. Whether metagenomic sequencing can be useful in diagnosis and treatment decisions remains to be determined.[8] For optimal results, samples should be obtained and submitted to the microbiology laboratory prior to initiation of antibiotic therapy.

Procedures such as thoracentesis, bronchoscopy, and transthoracic needle aspiration may be warranted, especially if an individual is not improving with antibiotic therapy. A thoracentesis should be performed if a pleural effusion exists because it provides an uncontaminated specimen that may represent the etiologic agent of an adjacent abscess. If the abscess is anerobic, bronchoscopy with bronchoalveolar lavage or quantitative brush catheter cultures may not recover the causative organism, because there are only a limited number of cases in which anaerobic organisms have been isolated.[9] Nonetheless, efforts should be made to recover a causative organism, and bronchoalveolar lavage samples should be sent for bacterial, mycobacterial, and fungal cultures. Outside of obtaining cultures, bronchoscopy can be used to evaluate the airways, biopsy a mass, or remove a foreign body if present. Bronchoscopy with bronchoalveolar lavage is often considered early in immunocompromised patients, for whom evaluating opportunistic infections is a high priority.

Transthoracic needle aspiration can provide a clean specimen for culture. It can also be helpful for drainage of abscesses that do not openly communicate with a bronchus. The procedure should be considered early in those with an abscess greater than 4 cm because they have a higher risk of not responding to antibiotic therapy.[10]

If a vasculitis is suspected (see Fig. 50.4), serum markers (e.g., *antineutrophil cytoplasmic antibodies* [ANCAs]) should be obtained. Blood cultures are not routinely recommended in those who do not have sepsis or septic shock. However, when septic emboli are a possibility, especially in the setting of multiple abscesses, blood cultures and a transthoracic echocardiogram to evaluate for vegetations should be obtained.

MICROBIOLOGY[5,11–13]

Most infectious causes of a lung abscess are due to anaerobes and facultative anaerobes that colonize the oral cavity. Lung abscesses are usually polymicrobial, with the most common organisms being *Peptostreptococcus*,



Figure 50.4 Lung abscess mimics granulomatosis with polyangiitis. (A) Frontal chest radiography shows a large left upper lobe cavity with a gas-fluid level resembling a pulmonary abscess. (B–C) Axial computed tomography through the mid and lower lungs demonstrates additional nodules and cavities in the right lung. This strongly favors either systemic embolization or a noninfectious inflammatory disorder, such as vasculitis, over a pulmonary abscess. (Courtesy Michael B. Gotway, MD.)

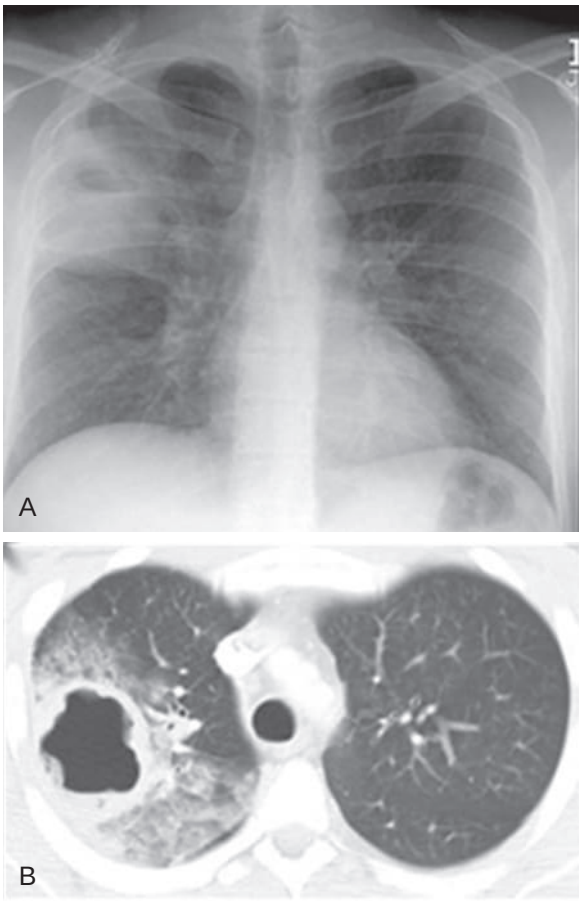

Figure 50.5 Pyogenic lung abscess. (A) Frontal chest radiography shows a subpleural right upper lobe cavitary lesion with a gas-fluid level. (B) Axial computed tomography displayed in lung windows shows a mildly thick-walled cavitary lesion with a lobulated internal border and surrounding ground-glass opacity located within the subpleural right apex. (Courtesy Michael B. Gotway, MD.)

Fusobacterium, *Prevotella*, and *Bacteroides* species (usually not *B. fragilis*).[14–16] Monomicrobial abscesses can be caused by *Staphylococcus aureus*, *Streptococcus pyogenes*, *Klebsiella pneumoniae*, *Pseudomonas aeruginosa*, and other gram-negative bacilli. Multidrug-resistant *K. pneumoniae* has been isolated from lung abscesses of patients in Taiwan, suggesting a possible shift in the bacteriology of abscesses or a different prevalence based on region.[17] Fungi, parasites, and mycobacteria may also cause pulmonary abscesses. These organisms must be considered, especially if a patient is not responding to antimicrobial therapy or is immunocompromised.

Some organisms have unique characteristics. *S. aureus* is known to cause a secondary infection with cavity formation in patients with underlying influenza virus. *Pneumocystis jirovecii* can cause cysts in the lung mimicking cavities.

COMPLICATIONS

Complications of a lung abscess can include hemoptysis, bronchopleural fistula, empyema, and mediastinitis. The latter three complications can be seen after surgical intervention in attempts to drain a lung abscess. With bronchoscopic drainage, pus can also spill from the abscess to other areas of the lung.[18,19]

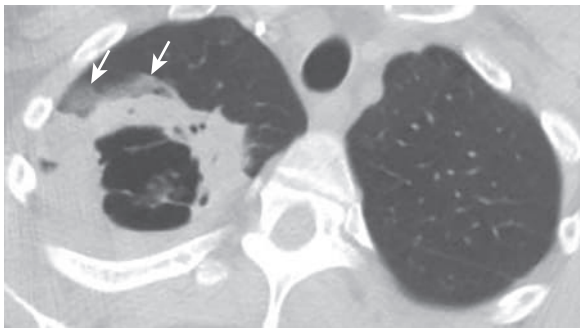

Figure 50.6 Lung abscess with hemoptysis. Axial chest computed tomography displayed in lung windows shows a complex, thick-walled right apical cavity consistent with a pyogenic abscess. Ground-glass opacity (*arrows*) surrounds the anterior margin of the cavity, consistent with hemorrhage given the history of hemoptysis, although the imaging appearance is nonspecific. (Courtesy Michael B. Gotway, MD.)

The bronchial arteries are responsible for supplying blood to a lung abscess and are the major source of hemoptysis.[22] Minor hemoptysis may be seen with a lung abscess (Fig. 50.6). Although rare, life-threatening hemoptysis can also be a complication of abscess[20,21] and may require emergent pulmonary resection of the lesion to allow for hemostasis.[23]

Central nervous system complications, such as stroke[24] and brain abscess, are recognized consequences of lung abscess. These may arise because clots and bacteria can bypass the filtering action of the lung to reach the systemic circulation. In a population-based, nested case-control study of more than 1300 patients with brain abscess, lung abscess or bronchiectasis was associated with brain abscess by an adjusted odds ratio of 8.2 (95% confidence interval, 3.6 to 18.5).[25]

TREATMENT

In a landmark paper in 1936 (pre-antibiotic era), 2114 cases of pyogenic lung abscesses were divided between conservative management, drainage by bronchoscopy or posturing, and surgery. For all three therapies, the mortality rate was between 32% and 34%.[26,27] With the advent of antibiotics, the mortality from lung abscess has decreased to 15–20%. In immunocompromised patients, those with bronchial obstruction, or large abscesses (>6 cm), mortality may be as high as 75% despite appropriate therapy.[28,29]

ANTIMICROBIAL THERAPY

Empirical therapy must include antibiotics to cover strict anaerobes and facultative anaerobic streptococci. Recommended therapy is a combination of a β-lactam plus β-lactamase inhibitor or clindamycin.[30] Clindamycin is a good option if a patient has a β-lactam allergy; however, it is generally avoided due to the concern for developing *Clostridium difficile* infection. A carbapenem with good bioavailability in the lung parenchyma is another option;

however, monotherapy with meropenem does not have activity against streptococci and hence should be avoided.

Monomicrobial *S. aureus* abscesses are a known complication of influenza.[31] For methicillin-susceptible *S. aureus*, choice of antibiotic includes cefazolin, nafcillin, or oxacillin. For methicillin-resistant *S. aureus* infection, the drug of choice is linezolid with the alternative being vancomycin. Of note, daptomycin has poor bioavailability in the lungs and should not be used.

With empirical antibiotic therapy, clinical improvement should be apparent within 3 to 4 days, with defervescence in 7 to 10 days. If clinical improvement is not apparent, one must consider reasons for a delayed response, such as an obstruction (foreign body vs. neoplasm), resistant bacteria, mycobacteria or fungus, large cavity size (>6 cm in diameter), or empyema. Vasculitis and septic emboli should also be reconsidered and evaluated based on clinical suspicion.

Duration of antibiotic therapy averages between 4 and 6 weeks. This largely depends on radiographic improvement. If the patient is worsening clinically or new symptoms develop, imaging should be obtained sooner. On chest radiographs or CT, the abscess should completely resolve or reduce in size to a stable lesion prior to the discontinuation of antibiotics. This can usually be achieved with an oral antibiotic regimen.

SURGICAL INTERVENTION

Surgical resection of an abscess is needed in approximately 10% of cases.[32] Indications for surgical intervention include hemoptysis, bronchopleural fistula, empyema, large cavity size (>6 cm), an obstructed bronchus, or lack of response to 12 weeks of antibiotic therapy. Lobectomy is preferred to segmentectomy due to concern for incomplete removal of the abscess and necrotic tissue with risk of reinfection.[33] Video-assisted thoracoscopy is preferred if the lung abscess is peripherally located and there are no pleural adhesions. A double-lumen endotracheal tube is often used to avoid spillage of contents into the unaffected lung. Other less invasive alternatives to surgery include percutaneous and endoscopic drainage of the lung abscess.

PERCUTANEOUS TUBE DRAINAGE

Percutaneous tube drainage is largely considered in those who cannot tolerate surgery; however, it is becoming more commonly used when available.[34,35] First described in 1938, it was initially used to drain cavities caused by tuberculosis. It grew to be used for the management of all lung abscesses prior to the antibiotic era (see eFig. 21.9). Indications for this intervention include abscess size of greater than 4 cm, peripherally located lesions, and lack of adequate spontaneous drainage.[36,37] Evaluation with bronchoscopy is important in ruling out a bronchial obstruction because this would be an indication for surgery instead. Percutaneous tube drainage can be used for palliation in septic patients with lung abscess and underlying lung cancer.[38]

The procedure is usually performed under CT guidance but can be performed at the bedside with ultrasound guidance.[39] The affected lung is placed down to minimize spillage into the unaffected lung. Once the catheter is in place, the fluid is aspirated. Gentle irrigation with normal saline is performed daily. The value of placing fibrinolytic agents into the abscess is unknown but is not recommended due to concern for complications.[40] A reduction in the size of the abscess with clinical improvement and no evidence of purulent drainage for 3 days is one measure used to determine the appropriate time to remove the catheter.

Complications of percutaneous tube drainage include hemoptysis, pneumothorax, hemothorax, and obstruction of the catheter. A bronchopleural fistula may also develop and cause contamination of the pleural space resulting in an empyema.

ENDOSCOPIC DRAINAGE

Endoscopic drainage is considered when medical therapy has failed and percutaneous tube drainage is not an option. An endoscopic approach typically is used when the location of the abscess is central, if there is concern for an endobronchial obstruction, or in patients with coagulopathies.[41]

Bronchoscopy is performed by the nasal approach with a flexible bronchoscope, after which a guidewire is placed into the cavity under fluoroscopic guidance. The bronchoscope is then removed and a pigtail catheter is placed over the guidewire. With the use of contrast through the pigtail catheter, the appropriate positioning is confirmed. The guidewire is then removed and the catheter secured to the nose. In one study, the catheter was kept open to gravity and flushed with a mixture of gentamycin and normal saline twice a day. The primary concern of doing this procedure is spillage of abscess contents to unaffected portions of the lung.[18]

Endoscopic drainage using laser to access the cavity has also been reported. The pigtail catheter is introduced via bronchoscopy and the laser is used to puncture the abscess to create a path to insert the catheter. Catheters were kept in for 4 to 6 days with both clinical and radiographic improvement.[19]

Key Points

- Most lung abscesses are caused by aspiration of anaerobic bacteria from the oral cavity.
- Patients typically present with indolent symptoms such as fever, cough, and sputum production over weeks to months.
- Symptoms, duration of symptoms, and chest imaging (chest radiography or computed tomography) with findings of a cavity and often an air-fluid level lead to the diagnosis.
- Routine Gram stain and culture (including mycobacterial and fungal) should be sent, although false-negative cultures are common due to the prevalence of anaerobic bacteria. Coverage of anaerobic bacteria is crucial when choosing antibiotic therapy.
- If a pleural effusion exists, a thoracentesis should be performed to obtain an uncontaminated specimen and evaluate for an empyema.

- If a patient is not improving clinically, it is important to consider other conditions such as bronchial obstruction, cancer, vasculitis, resistant organisms, or other organisms such as mycobacterium and fungi not adequately covered by the current antibiotic regimen.
- Duration of antibiotic therapy ranges from weeks to months, depending on clinical and radiographic improvement. Close clinical monitoring with a low threshold for repeat radiographic imaging is imperative.
- If a patient is not responding to antibiotic therapy, surgery, percutaneous transthoracic tube drainage, or endoscopic drainage may be warranted.

Key Readings

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51 TUBERCULOSIS: EPIDEMIOLOGY AND PREVENTION

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INTRODUCTION

Tuberculosis (TB) has been recognized as a scourge of humanity since antiquity. TB was considered the "captain of all these men of death," according to John Bunyan—a plague that seemingly carried away the young and talented members of society. TB continues to ravage much of the developing world and is still the single most common infection causing death.[1]

TB is caused by any one of three mycobacterial pathogens that are part of the *Mycobacterium tuberculosis* complex: *Mycobacterium tuberculosis, Mycobacterium bovis,* and *Mycobacterium africanum. M. bovis* and *M. africanum* produce relatively few cases of human TB and *M. africanum* is restricted to specific regions of Africa or people from those regions. *Mycobacterium canettii* is not part of the *M. tuberculosis* complex, but has been identified as a cause of TB in a small number of patients from or with connection to East Africa.[2]

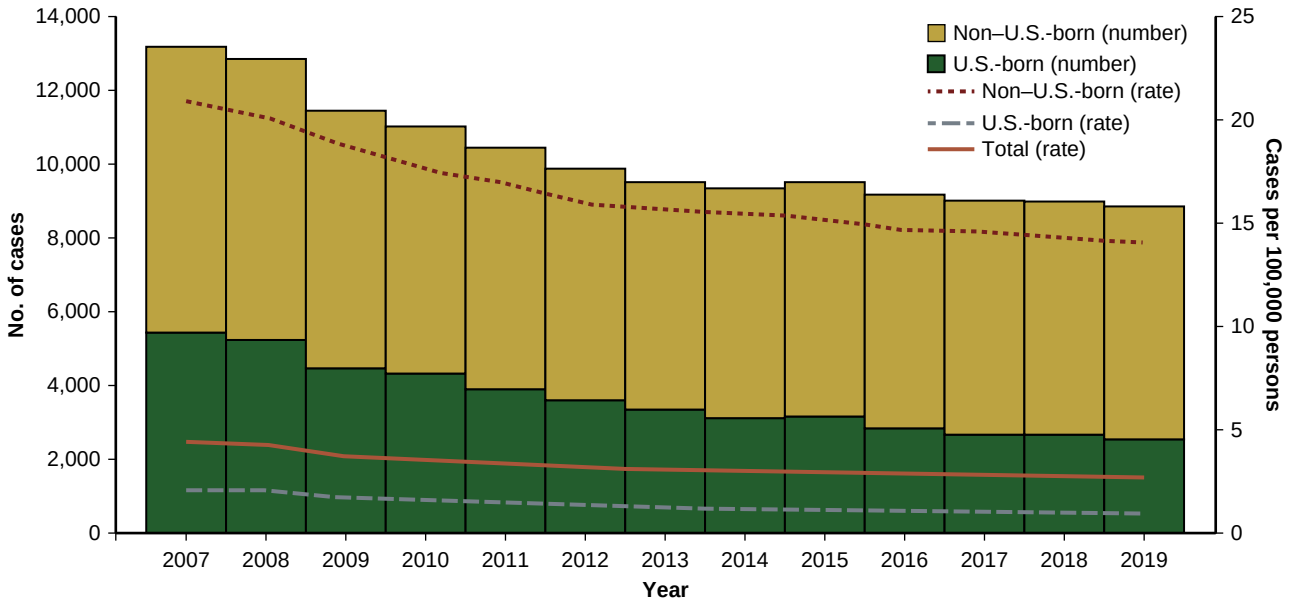
The *M. tuberculosis* phylogenetic tree has a geographic structure from which the initial *M. tuberculosis* major lineage names were derived: Indo-Oceanic (lineage 1), East-Asian (lineage 2), Indian and East-African (lineage 3), Euro-American (lineage 4), West-African 1 (lineage 5), West-African 2 (lineage 6), and Ethiopian (lineage 7).[3] The two West-African lineages together comprise *M. africanum*.[4] Studies have suggested that different lineages of *M. tuberculosis* may be associated with different degrees of pathogenicity, as reflected in differing rates of *tuberculin skin test* (TST) conversion, rates of TB following exposure, genotypic clustering, and virulence in guinea pigs.[5-13]

EPIDEMIOLOGY OF TUBERCULOSIS

Infection with *M. tuberculosis* is prevalent throughout the world. It is estimated that one-fourth of the world population (1.7 billion people in 2014) is infected with *M. tuberculosis*, although the distribution is heterogeneous.[14,15] TB infection and disease are found in all countries regardless of their state of development, and the movements of people from and to areas of high prevalence influences the incidence of TB everywhere. For this reason, TB has been declared by the *World Health Organization* (WHO) as a global public health emergency to be addressed by global strategies and initiatives, the most recent being a United Nations high-level meeting on TB in 2018, in which heads of state endorsed a commitment to end TB by 2030.[16]

For most of recorded history, TB has been a problem of enormous dimensions worldwide—and it still is. Although both the number of new cases of TB and the number of deaths has been decreasing in the last 15 years, the annual reduction trend will not be sufficient to reach the goal of 90% reduction in TB incidence (relative to 2015) by 2035.[17,18] In 2018, there were an estimated 10 million new TB cases, of which only 7.0 million were reported to national public health authorities, leaving an estimated 3 million unaccounted for.[17] In the same year, there were 1.2 million deaths due to TB[17] with a case fatality rate of 15%.[18] Relative to 2017, in 2018 there was no decline in the number of new cases, but there was a decline of 9% in the number of deaths.[18] The epidemiology of TB varies widely around the world. In 2018, 86% of the cases were identified in the WHO regions of Southeast Asia (44%) (incidence 220 per 100,000 persons), Africa (24%) (incidence 231 per 100,000 persons), and the Western Pacific (18%) (incidence 96 per 100,000).[17] Most of the high-income countries have an incidence of less than 10 new cases per 100,000 population,[17] and TB elimination is an achievable goal.

The prevalence of the *human immunodeficiency virus* (HIV) infection is an important determinant of TB epidemiology.[18] *People living with HIV* (PLHIV) are 20 to 30 times more likely to develop TB than those without HIV.[19]



* Number of cases with unknown national origin not shown (range = 2–60 per year; median = 7). Total rate includes cases with unknown national origin.

†Rates for non–U.S.-born and U.S.-born persons were calculated using Current Population Survey estimates. Total rate was calculated using U.S. Census Bureau population estimates.

Figure 51.1 Tuberculosis case counts and rates by national origin, United States: 2007–19. The number of cases with unknown national origin is not shown (range, 2–60 per year; median = 7). Total rate includes cases with unknown national origin. Rates for non-U.S.-born and U.S.-born persons were calculated using Current Population Survey estimates. Total rate was calculated using U.S. Census Bureau population estimates. (From Schwartz NG, Price SF, Pratt RH, Langer AJ. Tuberculosis—United States, 2019. *MMWR Morb Mortal Wkly Rep*. 2020;69:286–289.)

In 2018, 8.6% of all TB cases were among persons with HIV infection. TB causes one in three HIV deaths.[20] Most of the cases of HIV-TB and deaths were in Africa, where 70% of the 37 million people living with HIV live.[20]

Diabetes mellitus triples the risk for TB and increases the likelihood of poor treatment outcomes. In 2017, there were an estimated 425 million people living with diabetes and it is predicted that it will increase by 48% to 629 million in 2045, which will likely make achievement of the global TB targets even more difficult. The biggest increases will be in Africa and Asia, where most of the TB burden is located.[21,22] In patients with TB worldwide, the prevalence of diabetes was 15.3% and varied from 0.1% in Latvia to 45.2% in Marshall Islands.[21]

Poverty is a powerful determinant of TB. Although it is not possible to quantify the number of TB cases directly associated with poverty, crowded and poorly ventilated living spaces, malnutrition, and lack of empowerment to act on health issues, all of which are associated with poverty, are important risk factors for TB and TB transmission.[23]

Drug-resistant TB is challenging global control efforts and is an important component of the TB epidemic. Despite the reduction in the number of cases of TB worldwide, progress is threatened by *multidrug-resistant* (MDR) TB (caused by organisms resistant to at least isoniazid and rifampin) and *extensively drug-resistant* (XDR) TB (MDR organisms also resistant to at least one fluoroquinolone and to at least one injectable second-line agent).[24] It is estimated that in 2018, 500,000 people developed TB resistant to rifampicin, the most effective first-line anti-TB drug, 78% of whom had MDR-TB.[17] Almost half of the rifampin-resistant/MDR-TB cases were seen in people from three countries: India (24%), China (13%), and Russia (10%).[17] In 2006, XDR TB was reported for the first time[25,26] and, by the end of 2018, XDR-TB had been reported by 131 WHO member states.[17] In 2017, 6.2% of MDR TB cases had XDR-TB.[17] In 2018, only 32% of patients with MDR TB received second-line treatment and cure rates were far lower than those with drug-susceptible TB (56% vs. 85%, respectively).[17] Since 2000, WHO has implemented programs to increase access to drugs and to increase quality care for persons with drug-resistant TB. In spite of these efforts, a mathematical model forecasted that drug-resistant TB will increase in the four countries studied, reaching 12.4% among incident cases in India, 8.9% in the Philippines, 32.5% in Russia, and 4.7% in South Africa.[24] This increase will be driven by transmission of resistant strains rather than acquisition of resistance during treatment.[24]

In the United States following the introduction of effective chemotherapy, rates of TB decreased at an average annual rate of approximately 5%. However, from 1984 to 1992, the number of TB cases increased by 20%, because of the epidemic of infection with HIV and the deterioration of public health systems.[27] This resurgence clearly made the point that, no matter how successful the fight against TB seems to be, the guard cannot be let down. Interacting with and amplifying these two major factors were socioeconomic conditions, particularly homelessness that led to crowding, and immigration of persons from countries with high prevalence of TB.[27,28] With renewed effort and increased funding, case rates began to decline in 1993 (Fig. 51.1).[29] However, since 2012,

the rate of decline has slowed to −1.5% per year, which is not sufficient to achieve TB elimination in the United States.[29]

In 2019 in the United States, 8920 cases (2.7 cases per 100,000 persons) were reported, the lowest number since systematic national reporting began in 1953; 71% of the cases were reported in non-U.S.-born persons. While the incidence of TB decreased overall by 71% from 1993 to 2019, the reduction was seen disproportionately among the U.S.-born population (86% reduction vs. 57% among non-U.S.-born persons).[29a]

TRANSMISSION OF *M. TUBERCULOSIS*

The key to elimination of TB is halting transmission of *M. tuberculosis*. Knowledge of the factors that govern transmission from a potentially infectious source and of the sequence by which the disease develops in a new host is vital for devising strategies for TB control and for evaluating the risk of a person becoming infected after exposure.[30]

The determinants of TB epidemiology differ in high-burden and low-burden settings.[31] In high-burden settings, ongoing transmission with rapid (within 1–2 years) progression to disease is the driving force.[32] In low-burden settings, TB more commonly results from reactivation of latent infection acquired earlier. However, both pathogenic sequences are seen in high- and low-burden settings.

The infectiousness of patients with TB is very heterogeneous. Transmission of *M. tuberculosis* is influenced by features of the source case, particularly the bacillary load, by the closeness of the potential recipient of the organism to the source, and by the circumstances of the exposure. A possible additional factor is the infectivity of the organism—the degree to which *M. tuberculosis* is able to establish itself within the lung or other sites in the new host. However, even taking these factors into account, there is substantial unexplained variability in the degree to which persons with untreated TB transmit the infection to persons to whom they are exposed.[33]

SOURCE CASE

TB is an airborne infection.[34] In nearly all instances infection is acquired by inhalation of *M. tuberculosis* contained in airborne particles (1 to 5 μm) that reach the alveoli. For a person with TB to be infectious, the organisms must access the environmental air and be aerosolized. *M. tuberculosis* expelled from the lungs in small droplets may remain suspended in the air for several hours.[35,36] Generally, only patients with pulmonary TB are infectious. Rarely, however, aerosols may be generated from other sources (e.g., irrigation of a tuberculous abscess).[37] There are at least four key factors determining infectiousness of a source case (Table 51.1).

Table 51.1 Factors Influencing Infectiousness of the Source Case

Severity of coughing
Bacillary population
Antituberculosis therapy
Strain of *M. tuberculosis*

The first factor determining infectiousness is the ability of the source case to generate aerosols containing droplets. Coughing is the most effective mechanism for generating aerosols that include droplet nuclei, but it is not the only way. Forced expiratory maneuvers, such as sneezing, yelling, singing, and loud talking can also generate infectious droplets. In general, the greater the volume of respiratory secretions, the greater the number of potentially infectious droplets will be present. Studies have demonstrated marked variability in the infectious potential of TB patients that, in part, could be related to the severity of coughing.[38,39] Simple maneuvers, such as covering the mouth while coughing, can reduce formation of droplet nuclei by deflecting droplets from the air stream. Similarly, a mask worn by the patient is effective because particles are trapped while they are still large, before the water content has evaporated. For exposed persons, especially health care personnel, properly fitting N95 masks (disposable particulate respirators) are very efficient in removing respirable particles that may contain *M. tuberculosis*.[40]

The infectiousness of HIV-infected patients with TB is very heterogeneous. In an HIV-TB hospital ward, 90% of the infections in guinea pigs exposed to air exhausted from the ward were caused by 10 of 97 hospitalized patients.[41] Likewise, in a study of household contacts of TB patients, the likelihood of transmission was lower if the source case was HIV-infected and had a CD4 T cell count lower than 250/μL.[42]

A second factor determining infectiousness of the source case is the bacillary population in the lungs. This can be inferred from the extent and morphology of the disease, as determined by the chest radiograph and more directly estimated by microscopic examination of sputum. The bacillary population of tuberculous lesions depends on the morphology of the lesion.[43] The number of bacilli in solid nodular lesions ranges from 10^2 to 10^4 organisms, whereas in cavitary lesions, populations are on the order of 10^7 to 10^9 bacilli.[43] The prevalence of tuberculin reactors among contacts of patients with TB increases as the radiographic extent of involvement increases.[39] Thus, in TB control, the contacts of persons with more-extensive TB should be accorded a higher priority for evaluation than the contacts of persons with less-severe disease.

Another means of estimating bacillary population is microscopic examination of stained sputum smears. An average viable bacillary population of 5000 to 10,000 organisms per milliliter of sputum is required for the organisms to be seen in an acid-fast-stained sputum smear.[44] The contacts of patients who have organisms detected in sputum smears have a much higher prevalence of infection than do contacts of patients with negative smears and either positive or negative cultures.[45-48] However, the contacts of sputum smear-negative patients may still acquire tuberculous infection and develop TB.[49] Surprisingly, in a study of contact investigation conducted in the United States, neither smear positivity nor

cavitation on the chest radiograph of the index case was a risk factor for incident TB among contacts.[50] However, the investigators did not examine incident infections (TST or *interferon-γ release assay* [IGRA] conversion from negative to positive). Other studies have shown that infectiousness was associated with the presence of cultivable organisms in coughed aerosols, which did not correlate with sputum smear results.[51]

A third important factor in determining the infectiousness of a source case is the use of antituberculous chemotherapy. Patients who had positive sputum smears but who were receiving antituberculosis drugs were much less infectious for guinea pigs than were untreated patients.[38,52] The relative infectiousness of untreated patients in comparison with treated patients was estimated at 50:1.[38,41,52] Consistent with these observations, clinical data indicate that, once treatment is begun to which the organisms are susceptible, transmission of *M. tuberculosis* decreases quickly and the major factor associated with persistent culture-positive aerosols is lack of effective treatment.[51] The most important mechanism by which anti-TB chemotherapy reduces infectiousness is the direct effect of the drug on the bacillary population in the lungs. There is a reduction in colony counts of nearly 2 $\log_{10}$ per milliliter of sputum in the first 2 days of treatment[53]; overall, in the initial 2 weeks of treatment there is a reduction of 99.9% in colony counts.[44] In addition to reducing the number of viable bacilli, anti-TB chemotherapy also promptly decreases coughing by 40% after 1 week of treatment and by 65% after 2 weeks.[39] The sum of these effects is that, once a patient with TB is placed on effective therapy, transmission of tubercle bacilli ceases to be a concern.

A final factor in the infectiousness of the source case is the particular strain of *M. tuberculosis*. Different strains of *M. tuberculosis* have different degrees of infectiousness. Estimates for the relative fitness of drug-resistant *M. tuberculosis* are heterogeneous, but overall showed a decrease in the ability to cause secondary cases, lower growth rate in vitro,[54] less progression to disease in guinea pigs,[55] or less transmissible and less able to progress to disease in modelling studies.[56] For example, strains of *M. tuberculosis* resistant to isoniazid caused fewer secondary cases than fully susceptible organisms.[57,58] However, even if there is lesser pathogenicity, this effect can easily be offset by a prolonged period of infectiousness, as might be expected with ineffective treatment or with exposure of an immunocompromised host.[41] In fact, outbreaks of TB caused by MDR and XDR strains of tubercle bacilli have taken place in hospitals or correctional facilities and disproportionately involve HIV-infected persons, although immunocompetent persons have also been involved.[25]

ENVIRONMENTAL FACTORS

The physical laws that apply to aerosolized particles dictate that droplet nuclei essentially become part of the environmental air; thus, environmental factors are of extreme importance in influencing transmission. In a study, under standard conditions of temperature and humidity indoors, 60% to 71% of aerosolized *M. tuberculosis* organisms survived for 3 hours, 48% to 56% for 6 hours, and 28% to 32% for 9 hours.[59] The influence of the concentration of organisms in the environmental air in transmission of *M. tuberculosis* is exemplified by the outbreak that took place aboard a U.S. Navy vessel with a closed, recirculating ventilation system.[60] The index case had a positive sputum smear and a brisk cough, and infected 53 of 60 persons (88%) in his berth compartment, of whom six developed TB. In a second compartment connected to the same ventilation system, 43 of 81 persons (53%) became infected and one developed TB. Environmental factors may be manipulated to decrease the concentration of tubercle bacilli, mainly removing them by effective filtration, killing them with ultraviolet light, or both.[61] Since early in the twentieth century, it has been known that exposure to ultraviolet radiation kills tubercle bacilli.[38] The major usefulness of ultraviolet lights is for providing ultraviolet irradiation of room air, for example, by using appropriately shielded lamps on the upper walls in hospital areas or clinics where patients with untreated TB are likely to be encountered, such as waiting rooms.[62]

CIRCUMSTANCES OF EXPOSURE

The circumstances of exposure have a major influence on the number of infectious particles inhaled. If the exposure is of long duration and takes place under conditions that would be associated with a high concentration of droplet nuclei in the air inhaled by the contact, there is a greater likelihood of transmission.[63] This is reflected in data from the United States showing that rates of both clinical TB and tuberculin reactivity are much higher among close (generally household) than among nonclose (generally out-of-household) contacts. In general, the rate of TB is in the range of 15 per 1000 close contacts and 3 per 1000 nonclose contacts. Of close contacts, approximately 50% are infected, in comparison with approximately 15% of nonclose contacts.[64] Because the risk of TB is higher among close contacts, they should be screened and considered for preventive therapy. In the United States, treatment of *latent TB infection* (LTBI) among infected contacts reduced the rate of TB from 9.8% to 0.2% among contacts who completed a full course of treatment.[50] However, studies using molecular epidemiology to track transmission dynamics have shown that substantial transmission may take place outside the household, especially in areas with a high burden of TB.[65-68]

HOST FACTORS

There is substantial evidence that susceptibility to acquisition of infection with *M. tuberculosis* is highly variable. Not all individuals exposed to *M. tuberculosis* will become infected. In San Francisco, only 11% of household contacts and 3.8% of nonhousehold contacts developed new infection as reflected by conversion from negative to positive of the TST or IGRA.[68] Although variations in the intensity of exposure contribute to the likelihood of becoming infected, variations in host susceptibility are also likely to contribute. Strong evidence for variable susceptibility to acquisition of infection with *M. tuberculosis* was provided by a prospective study of student nurses in a TB hospital in Philadelphia in the era before anti-TB chemotherapy.[69] In that study, in which student nurses were assigned to

rotations on the same TB wards, 30% remained uninfected (TST unreactive) after 2 years of nursing school, indicating that despite repeated exposure, some of the student nurses were less susceptible to infection. However, by the end of the third year of nursing school, 100% of the students had become infected, indicating that resistance to infection is quantitative, not absolute, and can be overcome by sufficient exposure.

Studies suggest that human genetic variability contributes to susceptibility or resistance to *M. tuberculosis* infection and in regulating both the establishment and the progression of the infection.[70,71] Both twins are more likely to develop TB if they are monozygotic than dizygotic (66.7% vs. 23%).[72] More recently, a review of host genetic studies concluded that, "the involvement of a human genetic component in susceptibility to infection with *M. tuberculosis* and progression to active disease is incontestable."[73] Several studies have demonstrated mutations associated with resistance or susceptibility to TB. However, there is little overlap in the loci identified in the individual studies.

LESSONS FROM GENOTYPING *M. TUBERCULOSIS*

Since the early 1990s, genotyping of *M. tuberculosis* has been used to determine if TB develops from exogenous or endogenous infection. *M. tuberculosis* DNA fingerprinting derived from different genotyping markers and methods has been used to track specific isolates of *M. tuberculosis* in a community.[74] Patients with TB with similar or identical genotypes are considered to be part of the same transmission chain.[75] In such situations, TB can be assumed to be due to a recent exogenous infection with rapid progression to TB. In contrast, patients with a unique DNA fingerprint are considered to have TB due to reactivation of latent infection acquired previously.

Genotyping can similarly be used to differentiate relapse from reinfection in a patient with recurrent TB: a patient with relapse will have a similar *M. tuberculosis* DNA fingerprint in both episodes while a patient with reinfection will have different strains.[76] Since the early 1990s, these markers have also enabled TB control programs, mainly in high-income settings, to track specific isolates of *M. tuberculosis* in a community to determine population-level risk factors for transmission, establish tailored public health strategies, and gauge the success of control measures.[77,78]

The genetic markers used to track strains in the community are sufficiently polymorphic to distinguish among unrelated isolates yet stable enough to recognize isolates that are part of the chain of transmission.[79] Genotyping using CRISPR (also known as spoligotypes)[80] and MIRU-VNTR (MIRU-type)[81] are currently widely used to track a strain in the community. More recently, the availability of high-throughput sequencing technology and the dramatic decrease in costs have enabled the use of whole genome sequencing to study transmission of *M. tuberculosis.*[82] Whole genome sequencing resolves transmission clusters with greater precision.[83] It also allows the identification of microevolutionary events (i.e., at the level of single nucleotide polymorphisms) within a chain of transmission, which can be used to determine the directionality of the transmission events.[84,85]

RISK FACTORS FOR DISEASE

After acquiring an infection, not all persons are at equal risk of developing TB.[86] Many conditions increase the likelihood of TB and serve as markers of increased risk. In healthy populations, the risk of developing TB is highest during the first year after infection; from 3–10% of newly infected persons develop TB during this period. The three factors presumably involved are the pathogenicity of the bacterial strain, the dose of bacilli implanted in the lungs, and the adequacy of the host response in countering the invasion. The "inoculum effect" (in which the likelihood of infection is directly related to the dose of bacteria) has not been clearly demonstrated in humans but is strongly suggested by results of animal experiments.[38] It is currently assumed that beyond the first year after infection has taken place, the immune response has fully developed, the number of organisms has been substantially reduced, and the remaining bacterial population has shifted to a state of persistence and slow replication. Understanding how this latent infection can shift to disease is critical in controlling TB.

Age is another risk factor. Among persons with TB infection, case rates vary markedly with age. Rates are considerably increased in infants and relatively increased in adolescents and young adults.[87] The reasons for the variations are not fully understood but are likely to relate to age-dependent influences on the effectiveness of the immune response.[88]

HIV infection is by far the most potent risk factor for TB worldwide. In the era before effective antiviral therapy, the TB case rate for persons who were infected with both HIV and *M. tuberculosis* was 7.9 per 100 person-years, which exceeds the rate in a population with LTBI without HIV infection.[89] It also appears that the risk of rapid progression to TB among persons who are infected with HIV and who then become infected with *M. tuberculosis* is tremendously increased, as has been demonstrated in descriptions of two such outbreaks.[90,91] The reported rates of TB in cohorts of persons with HIV infection vary widely and depend on the prevalence of TB in the environment, particularly the presence of infectious cases; the frequency with which treatment for LTBI is used; the severity of immune compromise within the HIV-infected group; and whether dually infected persons are receiving antiretroviral therapy, which substantially reduces the risk.[92,93]

Antiretroviral treatment of HIV markedly reduces the incidence of TB, although the effect is not complete. A meta-analysis revealed that antiretroviral treatment and reconstitution of $CD4^+$ T cell counts reduces the incidence of TB as much as sixfold.[93] However, despite immune reconstitution to CD4 T cell counts greater than 700 cells/μL, the incidence of TB in antiretroviral-treated HIV-infected people remains 4.4-fold higher than in HIV-uninfected people in the same community.[94]

In persons with both HIV and LTBI, antiretroviral therapy and preventive treatment with isoniazid substantially decrease the incidence of TB. In Ivory Coast, a randomized trial demonstrated that a 6-month regimen of isoniazid preventive therapy in patients with HIV (median $CD4^+$ T cell count of 463) receiving early or delayed antiretroviral therapy resulted in significantly fewer TB events than those assigned to no isoniazid preventive therapy.

Results showed a significant adjusted hazard ratio (aHR) of 0.43 in individuals with positive IGRA and a non-significant aHR among those with a negative IGRA. In this trial, isoniazid lowered the incidence of TB by 56% (31–72%) during the first 2.5 years of follow-up and lowered mortality by 37% (3–59%) after 4.9 years (median) of follow-up.[95,96] In South Africa, another randomized study demonstrated that 12 months of isoniazid resulted in 37% (6–59%) reduction in the hazard of TB over a median follow-up time of 2.5 years.[97] A mathematical model, using the data from South Africa, estimated that the use of antiretroviral therapy and isoniazid preventive therapy for 12 months will lower the incidence of TB by 23% among people receiving antiretroviral therapy and by 5.2% in the total population because of the impact on transmission.[98]

Inhibition of *tumor necrosis factor* (TNF) is another well-characterized risk factor for TB. TNF can be antagonized by treatment with a biologic agent, either with a monoclonal antibody to TNF itself or soluble receptor analogues that block the interaction of TNF with its receptor.[99] TNF plays a major role in the initial and long-term control of TB. The mechanisms by which this cytokine contributes to the control of *M. tuberculosis* infection are multiple (see Chapter 52). Patients treated with TNF antagonists have up to a 25-fold higher risk of TB.[100] Screening patients by TST or IGRA, followed by treatment of LTBI before initiating TNF antagonists, reduces the risk of TB in this setting.[101,102]

Other conditions or therapies that interfere with cell-mediated immunity also increase the risk of TB. These relationships, although well described and generally accepted, are poorly quantified. Examples of these disorders include hematologic malignancies and cancer chemotherapy. In addition, conditions such as diabetes mellitus and uremia are thought to fit into this general category of risk-enhancing diseases, although the basis for this effect is not established.[103] The risk of TB is also increased considerably in persons with silicosis, presumably owing to the effect of silica on both the innate and adaptive immunity.[104,105]

As mentioned earlier, genetic factors have been associated with both infection and disease. Genetic differences are also suggested by the pattern of TB noted among Filipinos in the U.S. Navy, whose rate of disease increased with duration of enlistment, in contrast to the decrease observed in African Americans and whites.[106]

Undernutrition is known to interfere with cell-mediated responses and thus is thought to account for the increased frequency of TB in malnourished persons.[107,108] Vitamin D deficiency has also been linked to TB. Studies on several continents have documented a higher frequency of vitamin D deficiency in patients with active TB than in control subjects. Moreover, a study in South Africa revealed reciprocal seasonal variations in serum vitamin D levels and TB notification rates: During the winter, vitamin D levels were lowest and TB notifications were highest, whereas the converse was true in the summer.[109] Because in vitro studies have revealed a role for vitamin D in regulating macrophage expression of antimicrobial peptides that restrict intracellular growth of *M. tuberculosis,* it is likely that vitamin D deficiency increases the risk of TB, rather than that vitamin D deficiency is a consequence of TB.

Despite the number of risk factors for TB that have been identified, the majority of cases have no identified immunologic or physiologic abnormality.

Table 51.2 Approaches for Prevention

Prompt diagnosis and effective treatment
Infection control
Treatment of latent TB infection
▪ Persons with HIV
▪ Close contacts
▪ Persons with recent infection
▪ Persons with stable radiographic findings consistent with prior TB
▪ Persons with other conditions
Vaccination with BCG in children

BCG, bacille Calmette-Guérin; HIV, human immunodeficiency virus; TB, tuberculosis.

PREVENTION OF TUBERCULOSIS

There are four approaches to the prevention of TB: Prompt diagnosis and effective treatment (see Chapters 53 and 54) to reduce the bacillary population rapidly in persons with the disease, infection control measures to prevent transmission of *M. tuberculosis* in health care and congregate living settings, treatment of LTBI to prevent progression from infection to active TB, and administration of *bacille Calmette-Guérin* (BCG) vaccine that decreases severity of TB in infants and children, although it has inconsistent protective effects in adults (see Table 51.2).

PROMPT DIAGNOSIS AND EFFECTIVE TREATMENT

In regions with a low TB burden and adequate resources, a pillar of TB control consists of evaluating contacts of active cases of pulmonary TB, and treating the contacts with the highest risk of infection and progression to disease.[110] This approach has not been widely applied in high-burden regions because of a lack of evidence of effectiveness. However, a recent cluster-randomized trial in a high-burden country (Vietnam) demonstrated that active surveillance of household contacts (with symptom screen, physical examination, and chest radiograph at baseline, 6, 12, and 24 months after diagnosis of the index case) was effective, because it identified 2.5-fold more cases of TB than did passive case finding.[111] Moreover, a cluster-randomized study of community-wide screening using Xpert TB/RIF to assay sputum in community members, regardless of symptoms, compared the prevalence of TB in the screened versus the control communities after 3 years of community screening.[112] This revealed that, in the screened communities, TB prevalence was reduced by 44% compared with that in the control communities (126 vs. 226 per 100,000). In addition, the rate of TB infection (IGRA positivity) in children 3 to 10 years of age was 50% lower in the screened compared with the control communities, consistent with a reduction in TB transmission due to sputum screening of adults irrespective of symptoms.

Together, these studies provide evidence of feasibility and effectiveness of enhanced TB screening in preventing TB transmission.

INFECTION CONTROL MEASURES TO REDUCE TRANSMISSION OF *M. TUBERCULOSIS*

Measures to reduce transmission of *M. tuberculosis* fall into four main categories: clinician awareness and prompt, appropriate responses; administrative controls; environmental controls; and personal protective equipment.[113] Together, these measures protect health care workers and patients.

Clinician Awareness

Clinical suspicion of TB generally varies inversely with the frequency of the disease in the population served by the facility or provider. However, TB may appear in almost anyone at any time. Given the frequency of comorbidities in persons with TB, clinical presentations are commonly confusing, thus, maintaining a heightened index of suspicion and obtaining appropriate diagnostic tests is critical to early diagnosis and treatment. Ideally a rapid molecular test should be available as per current guidelines.[114] A rapid and specific diagnosis will minimize unnecessary time in isolation for the patient,[115] and an effective treatment will rapidly reduce the infectious potential; thus, this is an effective preventive measure.

Administrative Controls (Policies)

Prompt respiratory isolation of persons with or suspected of having TB which, in some facilities, may be triggered automatically by the act of ordering a sputum examination for mycobacteria, serves to reduce exposure of health care workers and other patients to a person with potentially infectious TB. Patients should wear disposable surgical masks when being transported within the facility.

Environmental Controls

Engineering features such as a specified number of air exchanges per hour and ventilation features that create pressure gradients that exhaust the air to the outside augment other preventive measures.[116] Upper room germicidal irradiation may also be used as a highly effective disinfectant.[117]

Personal Respiratory Protection

N95 respirators (defined as a mask that, properly fitted, blocks out 95% of particles as small as 0.3 microns) should be worn by staff and visitors entering a respiratory isolation room.[118] In some circumstances, such as bronchoscopy on a highly infectious patient, personal air-purifying respirators should be used.

TREATMENT OF LATENT TUBERCULOSIS INFECTION

LTBI is defined by WHO as a state of persistent immune response to stimulation by *M. tuberculosis* antigens with no evidence of clinically manifest active TB.[119] Several large U.S. Public Health Service studies involving approximately 70,000 participants demonstrated the effectiveness of isoniazid in preventing TB. The findings were remarkably similar in all groups who had a variety of risk factors for TB. Participants given isoniazid had a reduction of approximately 80% in the incidence of TB during the year the medication was given, in comparison with those given placebo. The protective effect decreased during subsequent years, but the treated groups still showed approximately 50% less TB than did the control groups each year after the medication year through 10 to 12 years of observation. Overall, isoniazid reduced the incidence of TB by approximately 60%.[120]

The effectiveness of antituberculosis drugs in preventing TB is presumably a result of the reduction of the viable bacilli population in inactive or radiographically invisible lesions in the lungs and elsewhere. However, on occasion, treatment may be given to persons who have been exposed to TB but do not have a positive tuberculin reaction or IGRA. In this situation, treatment is assumed to prevent the establishment of infection with *M. tuberculosis*, an example of "primary prophylaxis."

Indications for Treating Latent TB Infection

The recommendations for testing for and treatment of LTBI reflect the concept that only persons who are at increased risk of TB should be tested for latent infection: persons who are either known or presumed to have been recently infected with *M. tuberculosis* and persons who have clinical conditions that increase the risk of progressing from latent infection to active TB. Any person who is tested and is found to have a positive test should be considered for treatment.[121,122] The specific groups in which treatment is indicated are as follows (in order of decreasing degree of risk for developing TB).

Persons with HIV Infection. The rates of TB among persons who are infected with both *M. tuberculosis* and HIV are extremely high, ranging from 3–16% per year.[123,124] It is estimated that people living with HIV are 21 times more likely to develop active TB than those without HIV infection.[125] Moreover, TB is the leading cause of death in PLHIV.[17] In a Cochrane review, preventive therapy (any anti-TB drug) versus placebo was associated with a lower incidence of active TB with a relative risk (RR) of 0.68. The benefit was greater in individuals with a positive tuberculin skin test (RR, 0.38) than in those who had a negative test (RR, 0.89). The efficacy was similar for all regimens, regardless of drug type, frequency, or duration of treatment.[126] More recent studies have shown that the benefit persists in persons receiving antiretroviral therapy.[119]

Currently, WHO recommends that all PLHIV who do not have evidence of active TB should receive preventive therapy, regardless of the tuberculin skin test or IGRA result.[119] (See screening approaches to exclude TB in Chapter 53.) Some data suggest that a 36-month treatment duration further reduces the risk of TB in persons with HIV infection in a high TB incidence country, perhaps by reducing reinfection with *M. tuberculosis*.[127] This duration of treatment is conditionally recommended by WHO.[119]

Close Contacts of New TB Cases. Two percent to 4% of persons in close contact with a person with infectious TB develop TB in the year after exposure.[128-130] In young

children and adolescents, the risk is perhaps twice that in adults. Because the tuberculin reaction or IGRA result may be negative if infection is recent, all close contacts should be treated. Those with a reaction of 5 mm or more should be considered to be infected and should receive a full course of preventive therapy. Close contacts who have negative tuberculin reactions should be retested 2 to 3 months after the index case is no longer infectious or after contact has been broken. If the tuberculin reaction at that time is less than 5 mm or the IGRA has not converted, treatment can be discontinued and, if the reaction is 5 mm or more or an IGRA has converted from negative or indeterminate to positive, treatment should be continued for a full course. Contacts who are known to be HIV-infected should be treated even if the tuberculin test result is negative.[119]

Persons With Recent Infection. Because the risk of developing TB is greatest during the initial 1 to 2 years after acquisition of the infection, any person who is documented to have had a conversion of the skin test reaction or an IGRA from negative to positive should be considered newly infected and receive treatment. A skin test conversion is defined as an increase in reaction size of 10 mm or more within a 2-year period for persons younger than 35 years and a 15 mm or more increase for persons older than 35 years. Tuberculin skin test reactors younger than 5 years should be accorded a high priority for preventive therapy; because they obviously have been infected relatively recently, the risk of infections is high[131] and there is a potential for severe disease in this age group. There is no consensus on the change in the IGRA result that defines a conversion.

Persons with Stable Radiographic Findings Consistent with Previous Tuberculosis. This group includes persons with a history of TB who never received anti-TB chemotherapy or who were not treated adequately, and persons with no known history of the disease. The rate at which new episodes of TB develop in these groups ranges from approximately 0.4–3.5% per year.[132-134] The risk is lowest in persons with small lesions that have been stable for a long period. In persons with radiographic abnormalities, it is essential that current TB be excluded by a careful clinical and bacteriologic evaluation. Because exclusion of active TB might not be feasible or possible at the initiation of therapy, an alternative approach is to begin therapy with multiple drugs: isoniazid, rifampin, and pyrazinamide, sometimes with ethambutol. If active disease is present as determined by a positive culture or by radiographic improvement, therapy should be continued for 6 months. If there is no suggestion of active disease, therapy can be stopped after 4 months, and the course of treatment will be sufficient for preventive purposes.

Persons with Other Conditions That Increase the Risk of Tuberculosis. Although the risk of TB is not always quantifiable, there is sufficient evidence to warrant preventive therapy in certain situations: silicosis or coal worker's pneumoconiosis; prolonged therapy with corticosteroids (usually 15–20 mg or more of prednisone daily, or its equivalent, for more than 2 to 3 weeks); immunosuppressive therapy; hematologic or reticuloendothelial malignancies, and perhaps certain solid tumors; end-stage renal disease; clinical conditions associated with rapid weight loss (including intestinal bypass for obesity and inadequate nutritional intake); after gastrectomy; and before treatment with TNF antagonists.[135] In addition, even in the absence of any of these risk factors, persons in the following circumstances who have tuberculin skin test readings of 10 mm or more should be considered for preventive therapy: foreign-born persons from areas of high TB prevalence; medically underserved, low-income populations, including high-risk racial and ethnic groups; residents of long-term care facilities (e.g., correctional institutions and nursing homes); and other groups that, on the basis of local epidemiologic patterns, have been shown to have a high incidence of TB (e.g., migrant workers, homeless persons).[121]

Current Treatment Regimens

For many years the only regimen available for treating latent infection was isoniazid given for 6, 9, or 12 months; but as a result of several clinical trials, three preferred regimens and two alternative regimens were released in February 2020.[136] These regimens apply to persons infected with *M. tuberculosis* that is presumed to be susceptible to isoniazid or rifampin.

Preferred Regimens

1. Three months of once-weekly isoniazid and rifapentine for a total of 12 doses. In a controlled clinical trial, the 12-dose regimen was demonstrated to be non-inferior to isoniazid alone given for 9 months.[137] A subsequent systematic review and meta-analysis concluded that this regimen achieved substantially higher treatment completion rates.[138] This regimen is recommended for adults and children older than 2 years of age with or without HIV infection. Disadvantages include the cost, the possibility of an influenza-like syndrome that can include syncope and hypotension, and potential drug interactions. The recommended doses for individuals 12 years of age and older are isoniazid 15 mg/kg rounded up to the nearest 50 or 100 mg (900 mg maximum) and rifapentine 300 mg (weight 10–14 kg), 450 mg (14.1–25 kg), 600 mg (25.1–32 kg), 750 mg (32.1–49.9), or 900 mg (>50 kg). For children aged 2 to 11 years, the recommended doses are isoniazid 25 mg/kg (900 mg maximum) and rifapentine as described for older children.[136]
2. Four months of daily rifampin. Rifampin alone given in a daily single dose of 10 mg/kg for adults and 15 to 20 mg/kg for children with a maximum dose of 600 mg is the preferred treatment for individuals not infected with HIV.[139] Caution should be taken due to the many drug interactions.
3. Three months of daily isoniazid plus rifampin. This regimen is conditionally recommended for adults and children with or without HIV infection. The recommended doses for adults are isoniazid 5 mg/kg (300 mg maximum) and rifampin 10 mg/kg (600 mg maximum). For children, the doses are isoniazid 10 to 20 mg/kg (300 mg maximum) and rifampin 15 to 20 mg/kg (600 mg maximum).[136]

Alternative Regimens. The alternative regimen is 6 or 9 months of daily isoniazid. The 6-month regimen is strongly recommended for HIV-negative adults and children of all ages and conditionally recommended for HIV-positive adults and children of all ages. The 9-month regimen is conditionally recommended for adults and children of all ages, both HIV negative and HIV positive. Isoniazid is given in a single daily dose of 5 mg/kg for adults and 10 to 20 mg/kg for children up to 300 mg/day. It may also be given at 15 mg/kg for adults and 20 to 40 mg/kg for children up to 900 mg twice weekly to facilitate direct observation of treatment.

Treatment of latent tuberculous infection with isoniazid or a rifamycin should not be undertaken in persons who have active, unstable liver disease. Stable chronic liver disease is not a contraindication, but such patients deserve careful consideration regarding the indications and need close attention during the course of treatment. Other persons who should be monitored especially closely during the administration of preventive therapy include persons older than 35 years; those taking other medications with which there may be interactions (such as phenytoin, disulfuram, or antiretroviral drugs); and persons with other disorders such as alcoholism, diabetes mellitus, or renal insufficiency that may increase the risk of adverse reactions, mainly hepatitis and peripheral neuropathy.

Pregnancy is not a contraindication to isoniazid; however, in view of the concern with elective administration of any drug during the course of pregnancy, it is generally prudent to wait until after delivery to give isoniazid. The exceptions to this are women who have a documented tuberculin conversion during pregnancy or who are HIV-infected and have a positive tuberculin reaction. However, a recent randomized trial in HIV-infected pregnant women revealed a higher rate of adverse pregnancy outcomes in those that received daily isoniazid in the immediate period (during pregnancy) compared to the deferred period (initiated 12 weeks postdelivery).[140] In both groups, a high rate (~6 per 100 person-years) of postpartum hepatotoxicity was observed, indicating that especially close monitoring is necessary in this patient population.

Management of Exposure to Drug-Resistant Organisms

The treatment of contacts exposed to MDR-TB or LTBI with *M. tuberculosis* that is presumed to be resistant to isoniazid and rifampin is based on limited data, and expert consultation should be obtained. The guidelines published in 2019 suggest offering treatment for LTBI versus following with observation. For treatment of MDR LTBI (conditional recommendation, very low certainty in the evidence), the regimens include 6 to 12 months of a later-generation fluoroquinolone alone or with a second drug on the basis of drug susceptibility of the source case *M. tuberculosis* isolate. Because of the toxicity, pyrazinamide should not be used as the second drug. If fluoroquinolone resistance is suspected, pyrazinamide/ethambutol (if source case isolate drug susceptibility testing shows susceptibility to these drugs) can be used.

Monitoring for Adverse Reactions

Adverse reactions have been associated with all drugs used in preventive therapy regimens, although most reactions are minor (see Chapter 54). Patients receiving treatment for LTBI should be seen by a provider at regular intervals (depending on the regimen) and questioned regarding possible symptoms of adverse reactions.[119] Patients receiving treatment should be advised to contact a provider promptly should symptoms develop that are suggestive of hepatotoxicity such as anorexia, nausea, vomiting, abdominal discomfort, persistent fatigue or weakness, dark urine, pale stools, or jaundice. If a health care provider is not available, the patient should be instructed to stop treatment immediately. There is insufficient evidence to support baseline testing of liver function. Baseline testing is, however, strongly encouraged for patients with a history of liver disease, regular use of alcohol, chronic liver disease, HIV infection, age older than 35 years, and pregnancy or in the immediate postpartum period (within 3 months of delivery). For individuals with abnormal baseline test results, clinical judgment is required to ensure that the benefit of treatment outweighs the risks, and liver function should be tested at subsequent visits. Liver function testing should also be performed for patients who develop symptoms while on treatment. Persons at risk for peripheral neuropathy, such as those with malnutrition, alcohol use disorder, HIV infection, renal failure or diabetes, or who are pregnant or breastfeeding, should receive vitamin B_6 supplements when taking isoniazid-containing regimens.

IMMUNIZATION WITH BACILLE CALMETTE-GUÉRIN

BCG is an attenuated *M. bovis* that was found to protect a variety of animal species against TB. It was first used in humans in 1921 and has since become the most widely used vaccine in the world: up to 80% of infants in developing countries receive BCG immunizations, yet no vaccine has been the subject of greater controversy.[141] In children, BCG has been demonstrated to reduce both the frequency and severity of disseminated TB and TB meningitis.[142,143] In addition to the ameliorating effects on severe forms of TB, a meta-analysis of studies using IGRAs to detect new infection in children given BCG compared with control cohorts found that BCG provided protection against tuberculous infection.[144,145]

In adults, the results of BCG vaccination are less clear; in controlled clinical trials of BCG vaccination against pulmonary TB in adults, protection has ranged from 0–77%.[141,146] No protection was seen in the South Indian Trial of more than 200,000 people monitored for 15 years, although all patients who developed TB had developed TST positivity following administration of the vaccine.[147] In contrast, BCG was effective in studies performed in the United Kingdom.[146] It is unclear why BCG appears to be effective in some parts of the world and not in others (a finding that is also evident in protection against leprosy).[143]

There are many variables that potentially could account for the discordant results.[148] These include host genetic factors, variations in pathogenicity of tubercle bacilli, variations in potency of the strains of BCG used, technique of administration, handling of the vaccine, and prevalence of infection with nontuberculous mycobacteria, which may

confer some degree of protection.[143,149] Partly because of these factors, it is now generally accepted that BCG is not a tool that can be used to decrease the overall incidence of TB in a population. However, it appears that BCG reduces the likelihood of the more severe forms of the disease in children, and it is with this goal in mind that it continues to be a component of WHO immunization recommendations for developing countries. Due to the widespread acceptance and use of BCG and its benefits to young children, it is not likely that new vaccines for TB will immediately replace BCG. Instead, they will likely be used initially to boost responses after an initial dose of BCG, in an effort to induce responses that reliably protect adults against pulmonary TB.

In the United States, BCG has limited applicability. It is recommended only for TST-negative persons who are repeatedly exposed to potentially infectious patients who are being ineffectively treated. In general, the recommendation is limited to children. As a live vaccine, BCG should not be given to immunocompromised persons, including those with HIV infection, or to pregnant women.

NEW TUBERCULOSIS VACCINES

New approaches to vaccination are being shown to protect against TB. A prevention of infection trial in HIV-infected, IGRA-negative adolescents at high risk of infection compared placebo, revaccination with BCG, and an adjuvanted protein vaccine called H4:IC31.[150] Although neither vaccine regimen reduced the rate of IGRA conversion from negative to positive (interpreted as initial infection), revaccination with BCG significantly increased the frequency of IGRA reversion to negative after initial conversion (interpreted as prevention of sustained infection); the effect of H4:IC31 was not statistically significant. Another prevention of disease trial in HIV-uninfected, IGRA-positive adults compared M72/AS01E, an adjuvanted protein vaccine, to placebo and revealed an overall efficacy of 54% for the vaccine in preventing bacteriologically confirmed active pulmonary TB.[151] Initial analyses of this trial revealed substantial variation in efficacy depending on age and gender; subsequent analyses after longer follow-up determined that the vaccine efficacy of approximately 50% was maintained for 3 years, and there was no difference in efficacy dependent on age or gender.[152] Moreover, antibody and CD4 T cell responses were maintained through the third year of follow-up. These results provide evidence for proof of principle that an adjuvanted subunit vaccine can be efficacious in preventing TB disease and indicate that studies in additional populations are warranted. More recently, when delivery by the intravenous route was compared to intradermal or aerosol routes, the intravenous administration of BCG showed better protection against *M. tuberculosis* infection in a highly susceptible rhesus macaque model. The intravenous immunization induced systemic and CD4 and CD8 T cell responses, especially in the peripheral blood mononuclear cells and lung, which may facilitate the elimination of *M. tuberculosis*.[153]

Key Points

- Although tuberculosis cases and case rates are consistently declining in high- and most middle-income countries, the disease continues to be highly prevalent in low- and some middle-income countries.
- The epidemic of HIV infection, especially in sub-Saharan Africa, is leading to extremely high tuberculosis case rates.
- Both HIV infection and resistance to antituberculosis drugs, especially multidrug resistance and extensive drug resistance, present major problems in worldwide tuberculosis control.
- Adequate treatment for tuberculosis, both drug susceptible and drug resistant, is the major intervention for decreasing transmission of *M. tuberculosis.*
- Newer, shorter regimens are available for treatment of latent TB infection and wide implementation of latent TB infection treatment will be necessary to reach the goals of a 90% reduction in new cases and 95% reduction in deaths by 2035.
- New TB vaccines are in development and in clinical trials and have the potential to make a large impact on the global TB epidemic.

Key Readings

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52 TUBERCULOSIS: PATHOGENESIS AND IMMUNITY

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INTRODUCTION
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INTRODUCTION

Despite its discovery in 1882 as the cause of tuberculosis, the mechanisms of *Mycobacterium tuberculosis* pathogenesis and protective host immunity were not elucidated until the twenty-first century. Although the understanding of *tuberculosis* (TB) pathogenesis is far from complete, it is now known that complex biologically active lipids and certain secreted proteins account for several of the mechanisms that allow *M. tuberculosis* to evade macrophage microbicidal mechanisms and use host cells as survival and replication niches. Likewise, while multiple mechanisms of innate and adaptive immunity have been discovered to contribute to protection against TB disease, it remains unclear what immune mechanisms can be targeted by vaccines to prevent infection, disease, and transmission.

M. TUBERCULOSIS AND THE *M. TUBERCULOSIS* COMPLEX

Tuberculosis is caused by several species of the *Mycobacterium tuberculosis complex* (MTBC), including *M. tuberculosis*, *M. africanum*, *M. bovis*, and rarely by other animal-adapted species. The rod-shaped bacteria grow slowly, and are characterized by their acid-fastness (they retain chemical dyes after washing with solutions of strong acid in alcohol), which in turn is attributable to a bacterial envelope composed of mycolic acids with acyl chains up to 90 carbons in length, with diverse structural characteristics including cyclopropane rings, methyl branches, ketones, and methoxy groups.[1] Although *M. tuberculosis* can infect and cause disease in many mammalian species, humans are the only significant reservoir and, with rare exceptions, infected humans are the source of transmission.

The genome of the MTBC consists of approximately 4.4 × 10^6 nucleotides in a single circular chromosome and is guanine-cytosine rich (overall 65.6%). The genome of the reference strain H37Rv (isolated from a patient in 1905) encodes 4006 proteins and 50 RNA species[2]; there is also experimental evidence for noncoding RNAs with regulatory functions.[3]

Much of the MTBC genome contains genes in common with other bacteria, including those whose products function in metabolism, cell wall synthesis, membrane transport, cell division, RNA synthesis, and adaptation to environmental conditions. The MTBC genome encodes at least three distinct protein secretion systems. Of these, the type VII secretion system, which is also present in certain gram-positive bacteria, consists of five loci, termed Esx loci due to the initial discovery of the locus that secretes *early secreted antigenic target of 6* kD (ESAT-6). Of these, ESX-1 is responsible for secreting proteins (ESAT-6 and CFP-10), which are important for virulence and are also targets of recognition by host immune responses (see later and Fig. 52.1). ESX-3 secretes the substrate EsxH, implicated in impeding phagosome maturation and MHC class II antigen presentation,[4,5] and essential for bacterial iron acquisition.[6,7] ESX-5 is required for secretion of PE and PPE proteins (described later) that contribute to regulation of virulence and immunity. The functions of ESX-2 and ESX-4 are not yet defined.

The genome of the MTBC includes several multigene families, including the *proline-glutamate (pe)* and *proline-proline-glutamate (ppe)* genes, named for proline-glutamic acid or proline-proline-glutamic acid motifs, near the amino termini of their protein products. These gene families are unique to mycobacteria and are markedly expanded in pathogenic mycobacteria (e.g., 99 *pe* and 69 *ppe* genes in *M. tuberculosis* H37Rv).[8] Although the functions of the *pe* and *ppe* genes are poorly understood, the individual members of these gene families are under markedly different evolutionary selection pressures, indicating that they do not serve redundant functions,[9] despite their sequence and structural similarities.

Comparative genomic studies have established that the MTBC comprises a phylogenetic structure with seven major branches, with each branch having a geographic

association, indicating that the MTBC coevolved with humans after major human population migrations transported ancestral MTBC strains from their origin in East Africa,[10] followed by differentiation and expansion coincident with the human populations in the respective regions (Fig. 52.2). The significance of the phylogenetic diversity of the MTBC remains a topic of investigation, although there is evidence that strains in a given lineage may be especially well adapted to humans in the ethnic groups in which the corresponding lineages coevolved.[11,12]

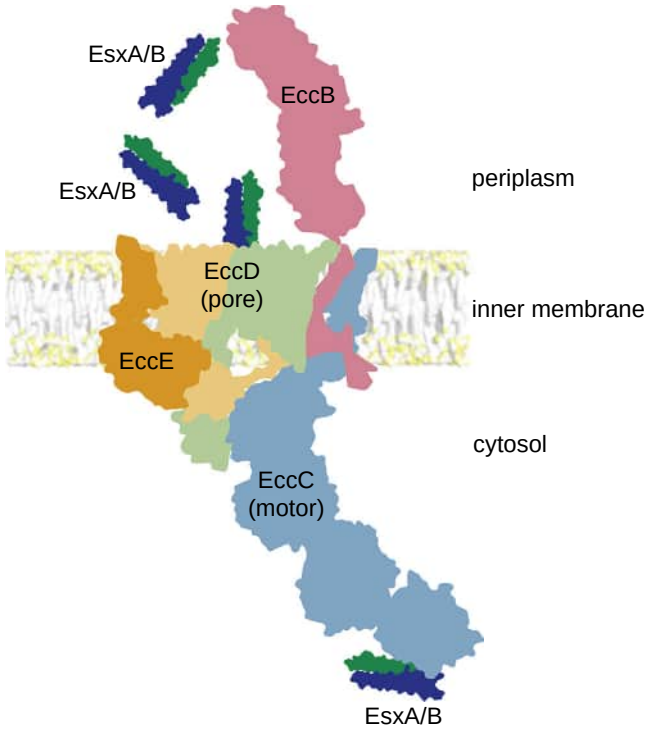

Figure 52.1 Structural model of the ESX-1 type VII secretion system based on cryo-EM analysis of the purified intact ESX-3 complex of *M. smegmatis*. Substrates shown here, dimers of *EsxA/B* (also termed ESAT-6 and CFP-10, respectively) are selected by interaction with ATPase 3 of *EccC* in the bacterial cytoplasm and transported via the upper cytoplasmic gate to the *EccD* translocon pore for secretion to the bacterial periplasm and extrabacterial space, using the energy generated by hydrolysis of ATP. The other ESX type VII secretion systems are thought to function similarly, to export distinct substrates (such as EsxG/EsxH, by ESX-3). (Courtesy Oren Rosenberg, MD, PhD, University of California San Francisco.)

INNATE IMMUNITY

Innate immunity serves as a front-line defense against microbes (see Chapter 15). Although innate immune responses undoubtedly play an important role in tuberculosis, studies in individuals with *human immunodeficiency virus* (HIV) and in animal models demonstrate that innate immunity is insufficient to control *M. tuberculosis* infection. Normally, during an effective immune response, macrophages and neutrophils kill and clear bacteria, and dendritic cells promote development of adaptive immune responses. An important aspect of *M. tuberculosis* pathogenesis is its ability to undermine the function of these innate immune cells. Indeed, instead of killing *M. tuberculosis*, these cells serve as niches for bacterial replication.

CELLULAR NICHES AND GRANULOMAS

M. tuberculosis is transmitted by aerosolized respiratory secretions and infects numerous innate immune cell types in the lung, including macrophages, neutrophils, and dendritic cells.[13] After inhalation, *M. tuberculosis* first infects alveolar macrophages,[14] a macrophage population adapted to minimize lung injury,[15] which makes it poorly equipped to control *M. tuberculosis*.[15,16] Over time, monocyte-derived and interstitial macrophages also become infected by *M. tuberculosis*; however, prior to the onset of adaptive immunity, they confer only modest control over bacterial replication. Numerous phagocytic receptors can mediate uptake of *M. tuberculosis* into macrophages.[17,18] The particular phagocytic receptors that *M. tuberculosis* engages may influence the subsequent ability of macrophages to control infection,[19] and mycobacteria may selectively parasitize more permissive macrophages.[20] Neutrophils are recruited to the lung in the first two weeks of infection and, rather

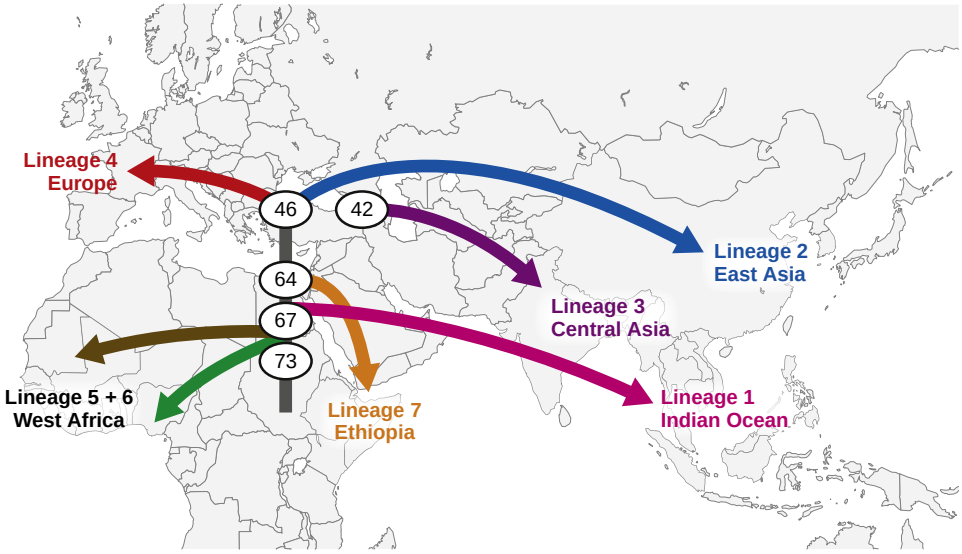

Figure 52.2 Global phylogeography of the *M. tuberculosis* complex emphasizing the lineages causing human disease. Evidence supports evolution of the common ancestor of the *M. tuberculosis* complex in East Africa, with subsequent evolution in isolated human populations after major early population migration events out of East Africa.[170] Major lineages are indicated on the map by the predominant geographic associations of contemporary isolates and are labeled with the time (in thousands of years) of divergence of the lineage. (Modified from Comas I, Coscolla M, Luo T, et al: Out-of-Africa migration and Neolithic coexpansion of *Mycobacterium tuberculosis* with modern humans. *Nat Genet.* 2013;45[10]:1176–1182.)

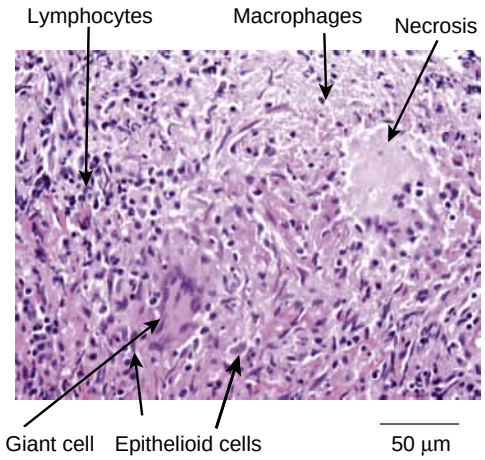

Figure 52.3 Representative granuloma from a human patient with tuberculosis. The granuloma consists of dense aggregates of macrophages, accompanied by variable numbers of lymphocytes. Some macrophages fuse to form multinucleated giant cells, while others undergo transitions to epithelioid cells, and some die by necrosis. While most lymphocytes in granulomas are T cells (predominantly CD4 T cells), B cells can also be found in and adjacent to granulomas. Dendritic cells and variable numbers of neutrophils can also be detected in tuberculous granulomas. The hematoxylin and eosin staining procedure does not visualize the bacteria. (Courtesy Stephen Nishimura, MD, University of California San Francisco.)

than restricting infection, overly exuberant neutrophil recruitment can create a nutrient-rich environment that supports *M. tuberculosis* replication.[21,22]

As the infection progresses, the cellular response is characterized by an organized collection of cells termed a granuloma, including macrophages, neutrophils, and lymphocytes. Macrophages aggregate, and some undergo an epithelioid transformation or form multinucleated giant cells (Fig. 52.3). Granulomas can undergo necrosis and cavitation, where *M. tuberculosis* can replicate to high numbers extracellularly. A characteristic feature of these granulomas is *caseating* necrosis, in which there is loss of tissue structure until the texture resembles soft cheese. (The term *caseating* derives from the Latin word *caseum*, meaning cheese.) The granuloma was long thought to serve a host-protective function in restricting dissemination of *M. tuberculosis*. This is supported by the observation that patients with immune defects imposed by HIV or *tumor necrosis factor* (TNF)-α inhibitors fail to form well-organized granulomas and, in such patients, there is also an increased risk of dissemination of infection outside of the lungs. However, granulomas can also facilitate cell-to-cell bacterial spread within macrophage aggregates. In addition, the granuloma architecture may stimulate the bacilli to enter a nonreplicating, drug-tolerant state and may also block access of adaptive immune cells and antibiotics to the bacteria.[23–25] Indeed, progressive disease is characterized by an increase in granuloma size and number; the increased infiltration in immune cells leads to increasing tissue damage rather than to effective microbial killing. Even within a given person, there are differences in the rate of progression of individual granulomas, and the mechanisms that account for this heterogeneity are not well understood. In conclusion, the initial innate immune cells that encounter *M. tuberculosis* are unable to control bacterial replication and, whereas the organized collection of cells in granulomas may benefit the host in certain stages of infection, it also appears that the pathogen is adapted to use the granulomatous response to its advantage. The bacilli are able to respond to and adapt to distinct host environments through two component systems, such as DosS/DosT, and PhoP/PhoR, as well as sigma factors. These enable the bacteria to detect and respond to altered levels of oxygen, nitric oxide, and carbon monoxide.

MACROPHAGE SUBCELLULAR NICHES

Once *M. tuberculosis* is ingested by host phagocytes, it resides in distinct subcellular environments and perturbs the normal function of these cells.[26,27] Considerable work has explored how *M. tuberculosis* impacts macrophage biology. Seminal studies by Armstrong and Hart and colleagues revealed that pathogenic mycobacteria survive and replicate in macrophages by perturbing the maturation of the *phagosome*. Normally, after microbial ingestion, the phagosome acidifies, acquires lysosomal hydrolases and antimicrobial peptides, and restricts essential nutrients such as iron.[28–30] The NADPH oxidase is also recruited to the phagosome where it generates *reactive oxygen species* (ROS) that can kill invading microbes and also promote a phagosome maturation pathway called microtubule-associated protein *light chain 3* (LC3)-associated phagocytosis.[31,32] *M. tuberculosis* and related species such as *M. marinum* prevent these normal maturation events. Instead of maturing to a phagolysosome, the mycobacterial vacuole retains early endosomal markers normally cleared from the maturing phagosomal surface, while the NADPH oxidase, LC3, and numerous late endosomal and lysosomal markers are diminished or absent.[33] There are numerous protein and lipid effectors that have been identified that enable *M. tuberculosis* to impair phagosome maturation,[34] thereby avoiding the degradative environment of the lysosome. However, this is not the only intracellular niche inhabited by *M. tuberculosis*. Some bacilli are delivered to lysosomes, where they are able to survive by resisting mechanisms of lysosomal killing, using enzymes that protect against redox stress, including catalase, *superoxide dismutase* (SOD), and alkyl hydroperoxidase, while the membrane protein Rv3671c maintains a neutral bacterial pH in the face of a low pH environment.[35,36]

Central to the pathogenesis of *M. tuberculosis* is its ability to perforate the phagosome membrane.[37] Perforating the phagosome allows *M. tuberculosis* to deliver effectors to the cytosol and access host nutrients and, over time, with increasing membrane damage, bacteria can translocate to the host cell cytosol.[38–40] When the phagosomal contents are exposed to the cytosol, they also provoke a host response, as discussed in more detail later. Phagosomal damage depends upon the ESX-1 type VII secretion system. ESX-1 is essential for virulence of *M. tuberculosis* and it is missing in BCG, the nonvirulent strain of *M. bovis* used as a tuberculosis vaccine.[41–43] ESX-1–deficient bacteria do not perforate efficiently or escape the phagosome into the cytosol,[38,40,44] and they do not stimulate the host signaling pathways, which have sensing mechanisms in the cytoplasm.[45,46] Recent work shows that the mycobacterial lipid *phthiocerol dimycocerosate* (PDIM) works in concert with ESX-1 in mediating phagosomal damage.[47–49] Like mutants defective in ESX-1, PDIM mutants are attenuated, and they fail to promote

host cell death or induce type I interferon responses that are correlated with phagosomal damage. The host detects and repairs minor damage to membranes with a multiprotein system called the *endosomal sorting complex required for transport* (ESCRT).[50,51] ESCRT responds to mycobacterial-induced phagosomal damage.[52,53] However, the *M. tuberculosis* EsxH protein, which is secreted by the ESX-3 type VII secretion system, interferes with ESCRT.[4,52] Thus two important virulence systems of *M. tuberculosis* are involved in modulating the integrity of the phagosomal membrane: ESX-1 causes damage, and ESX-3 interferes with host repair of the damage.

Disruption of phagosome membrane integrity also activates host signaling pathways (type I interferon signaling and the inflammasome, discussed later) and a lysosomal trafficking pathway called macroautophagy (hereafter, autophagy). The autophagy system, originally characterized for its role in degradation of endogenous cellular proteins and organelles, recognizes damaged phagosomes and bacilli that have escaped into the cytosol. *Autophagy-related proteins* (ATG) coordinate the formation of a double-membrane compartment, the autophagosome, which can sequester the microbe, and fuse with lysosomes.[54] *Interferon-gamma* (IFN-γ) and small molecules that augment autophagy promote *M. tuberculosis* clearance, while under basal conditions, autophagy makes a limited contribution to controlling *M. tuberculosis*.[21,44,55,56] The limited efficacy of autophagy in clearing *M. tuberculosis* points to evasion mechanisms on the part of the bacilli.[57,58] *M. tuberculosis* inhibits expression of *ATG* genes and secretes protein effectors such as PE_PGRS47, a member of the *pe* family described earlier, to interfere with autophagy.[59–61]

In addition to altering intracellular trafficking pathways of macrophages, *M. tuberculosis* induces profound changes in the metabolic state of the cells it infects. *M. tuberculosis* alters macrophage metabolism by inducing the Warburg effect,[62–64] a shift from oxidative phosphorylation to glycolysis, initially described in cancer cells. *M. tuberculosis* also modulates host lipid metabolism and induces the formation of lipid-droplet-filled or "foamy" macrophages.[65–67] Foamy macrophages are found within the inner layers of granulomas, and the bacilli themselves can be found in close approximation to intracellular lipid droplets. It is thought that lipid bodies serve as a source of nutrients for the bacilli in the form of cholesterol esters and fatty acids.[67–73] The relationship between these host metabolic changes and *M. tuberculosis* pathogenesis is an active area of investigation, and a number of host-directed therapies under investigation for TB, such as statins and metformin, modulate host metabolism.[74,75]

CYTOKINE RESPONSES

In addition to phagocytosing *M. tuberculosis*, innate immune cells respond to microbial challenge by initiating signaling pathways that result in secretion of proinflammatory and anti-inflammatory cytokines. These signaling pathways are initiated when cells detect bacterial components that activate *pathogen-recognition receptors* (PRRs). *M. tuberculosis* has numerous pathogen-associated molecular patterns that activate *toll-like receptors* (TLR2, 4, and 9) and C-type lectin receptors (DC-SIGN, Dectin-1, Mincle, and MCL).[76] Because *M. tuberculosis* bacilli perforate the phagosome, they also activate cytosolic sensors, including *nucleotide-binding and oligomerization domain* (NOD) 2, cGAS-STING, and the inflammasome (discussed later).

In response to activation of these PRRs, macrophages and dendritic cells secrete cytokines that contribute to control of infection and regulate specific aspects of immunity. Of the cytokines induced by *M. tuberculosis*, TNF is especially well characterized as essential for immunity to tuberculosis in humans. Patients with rheumatoid arthritis and other conditions treated with agents that block TNF activity have up to a 25-fold higher risk of tuberculosis than control populations[77] and are more likely to have disseminated infection.[78] TNF contributes to immunity to tuberculosis by activating microbicidal activities of macrophages and by enhancing the death of infected cells.[79–81] In addition, infliximab, one of the antibodies used to block TNF, increases the risk of tuberculosis by depleting a specific subset of CD8 T cells containing membrane-bound TNF that may contribute to killing intracellular *M. tuberculosis*.[82]

IFN-γ plays an essential role in immune control of tuberculosis. IFN-γ–deficient[83,84] or IFN-γ receptor–deficient [85] mice succumb to rapidly progressive *M. tuberculosis* infection and, in patients with IFN-γ receptor mutations, tuberculosis is especially severe, with a greater likelihood of disseminated and/or recurrent disease.[86] IFN-γ is believed to contribute to immune control of tuberculosis through activating the microbicidal activities of macrophages, including the production of nitric oxide and enhancement of autophagy,[55,56,87,88] and by modulating inflammation at the site of infection.[85,89] Although multiple cell types can be sources of IFN-γ, the principal cellular sources are lymphocytes, including innate lymphoid cells, as well as adaptive CD4 and CD8 T cells.

Interleukin (IL)-12 is another innate cytokine essential for immunity to tuberculosis. The best-characterized role of IL-12 is in directing differentiation of CD4 T cells into type 1 T helper cells that secrete IFN-γ and other cytokines and contribute to control of tuberculosis (see later). Evidence that IL-12 is essential for control of tuberculosis is provided by experiments in IL-12-deficient mice[90,91] and by observations that children with mutations in the IL-12 receptor beta-1 chain are susceptible to tuberculosis and other mycobacterial infections.[92]

Other cytokines can enhance *M. tuberculosis* pathogenesis. One important aspect of tuberculosis pathogenesis is the induction of type I IFN (IFN-α and/or IFN-β) secretion. Production of type I IFN depends upon ESX-1 secretion, the lipid PDIM, and phagosome permeabilization, as discussed earlier. Mycobacterial DNA and mitochondrial DNA that enter the cytosol trigger the cGAS-STING pathway, leading to IFN production.[44,93–96] The importance of type I IFN in human infection was revealed by whole blood transcriptome analysis of human genes that are differentially expressed in tuberculosis, which revealed a transcriptional signature dominated by IFN-responsive genes[97–100] that correlated with the extent of disease.[101] Whether type I IFN plays a pathogenic role or is a secondary effect of active tuberculosis in humans remains to be defined, although humans with a hypofunctional mutant type I INF receptor have a lower frequency of tuberculosis.[102] In mice, type I IFNs play a pathogenic role,[103] at least partially by enhancing

recruitment of mononuclear cells that support intracellular bacterial replication.[104,105] In addition, type I IFNs limit expression of IL-1β, a cytokine that is essential for control of *M. tuberculosis* (see later).[106,107] There are strain-dependent differences, including those related to drug resistance, that result in differences in the production of type I IFN and IL-1-β production and their importance during infection.[96,108] Despite the growing evidence for a detrimental role of type I IFNs in tuberculosis, therapeutic administration of type I IFN for multiple sclerosis or hepatitis C has not been accompanied by a noticeable increase in the frequency of active tuberculosis.

M. tuberculosis activates another cytosolic immune sensor called the inflammasome, leading to IL-1β and IL-18 secretion. The inflammasome is composed of *NOD-like receptors* (NLRs), apoptosis-associated speck-like protein containing a caspase recruiting domain, and the caspase-1 protease. There are many NLRs that can activate the inflammasome in response to distinct stimuli. During *M. tuberculosis* infection of macrophages, the NLRP3-inflammasome is activated in response to phagosomal damage,[109,110] and there is evidence that *M. tuberculosis* blocks activation of the AIM2-inflammasome.[111,112] The inflammasome processes IL-1β and IL-18 to their mature forms and triggers a distinct cell death pathway termed pyroptosis. IL-1β and IL-18 are important cytokines for host immune defense against *M. tuberculosis*.[106,113,114] In addition, they can contribute to exuberant inflammation and tissue damage.[115-117] Thus the activation of the inflammasome can be beneficial or detrimental.

VITAMIN D

Vitamin D (whose active form is 1,25-dihydroxyvitamin D) has extensive associations with tuberculosis (reviewed by Martineau[118]). Vitamin D deficiency is commonly found in humans at the time of TB diagnosis, and exposure to sunlight (which activates synthesis of vitamin D in the skin) was thought to be valuable as a component of TB treatment in sanatoria in the prechemotherapy era. Moreover, in some populations, but not all, polymorphisms in the genes encoding the vitamin D receptor and vitamin D binding protein have been associated with the risk of active TB.

Vitamin D acts through a nuclear receptor to regulate specific genes, including genes whose products relate to TB immunity. Treatment of cultured human macrophages with 1,25-dihydroxyvitamin D induces expression of the antimicrobial peptide cathelicidin LL37, which has direct antimycobacterial activity and also enhances autophagy; production of reactive oxygen and nitrogen intermediates is also increased.

Considering the evidence for a role of vitamin D in immune control of TB, multiple clinical trials have been performed to determine whether vitamin D supplementation is a useful adjunct to drug treatment of TB. A recent meta-analysis concluded that addition of vitamin D does not accelerate sputum clearance in cases of drug-susceptible TB, although a beneficial effect has been more consistently observed in cases of multidrug-resistant TB.[119] Despite the modest impact on bacterial clearance, vitamin D supplementation has been found to accelerate resolution of inflammation during treatment of TB.[120]

CELL DEATH PATHWAYS

Infection can cause host phagocytes to undergo a variety of different types of cell death, which influences the infection outcome.[121] *M. tuberculosis* promotes necrotic cell death while limiting apoptosis (programmed cell death). This is a strategy that appears to favor the bacilli, because apoptosis minimizes inflammation, and *M. tuberculosis*–infected macrophages that undergo apoptosis can be rapidly ingested by neighboring uninfected macrophages and the bacilli killed, through a process called efferocytosis.[122] In addition, by inhibiting uptake of apoptotic cells, *M. tuberculosis* limits cross-presentation to CD8 T cells that would otherwise result from bacterial antigens associated with apoptotic cell fragments.[123] The ability of *M. tuberculosis* to cause necrosis depends upon the ESX-1 secretion system and the NAD^+ glycohydrolase, tuberculosis necrotizing toxin, which induces necrotic cell death by depleting NAD^+.[124] *M. tuberculosis* also potentiates necrosis by causing mitochondrial inner membrane disruption[125] and inhibiting plasma membrane repair.[126] Many bacterial factors have been shown to limit apoptosis,[34] some of which appear to work by limiting host ROS, including mycobacterial proteins NuoG, a subunit of the type I NADH dehydrogenase, and SodA, superoxide dismutase.[127–130] Evidence that inhibition of apoptosis is a virulence mechanism is provided by the findings that proapoptotic mutants of *M. tuberculosis* are less pathogenic in vivo in animal models.[131]

ADAPTIVE IMMUNITY

CLASSICAL T CELLS

The term *classical T cells* refers to CD4 and CD8 T cells that express *T cell antigen receptors* (TCRs) consisting of an α- and β-chain, and that recognize peptides bound to HLA class II or class I molecules, respectively.

Considerable evidence supports an essential role for CD4 T cells in control of *M. tuberculosis*. In mice, developmental absence or antibody depletion of CD4 T cells leads to rapid progression and accelerated mortality with high burdens of *M. tuberculosis*.[132] In humans, HIV infection with CD4 T cell depletion markedly increases susceptibility to active tuberculosis.[133] CD4 T cells recognize a vast range of peptide epitopes derived from several hundred *M. tuberculosis* proteins, though it is currently unknown whether CD4 T cell responses to certain antigens are better able to provide protective immunity than are responses to other antigens. In mice, CD8 T cells also contribute to control of *M. tuberculosis*, although the impact of their absence is less striking than the absence of CD4 T cells.[132] The contributions of CD8 T cells to protective immunity to *M. tuberculosis* in humans are less clear, principally due to a lack of evidence.

T cells can provide protective immunity through secretion of cytokines, expression of membrane effector molecules, and cytolytic activity targeting *M. tuberculosis*–infected cells. Of the cytokines produced by T cells, IFN-γ, TNF, IL-17, and granulocyte-macrophage colony-stimulating factor have each been implicated in contributing to immune control of *M. tuberculosis* in mice; genetic unresponsiveness to IFN-γ[134,135] and therapeutic blockade of TNF[136] have established the importance of these cytokines for immunity

to *M. tuberculosis* in humans (as discussed earlier). Recent evidence in mice, nonhuman primates, and humans indicates that a CD4 T cell membrane effector molecule in the TNF superfamily (TNFSF8, also known as CD153) contributes to control of *M. tuberculosis* infection.[137] Although each of these effector mechanisms is implicated in immune protection, it is currently unclear which ones should be prioritized as goals of TB vaccine development (see later).

The importance of T cell recognition of specific *M. tuberculosis* antigens is the topic of active investigation, to identify those antigens whose recognition by T cells (or antibodies) makes the greatest contributions to protective immunity. *M. tuberculosis* differs from other pathogens in that its antigens do not vary at high frequency as a mechanism of immune escape.[138,139] Current efforts focus on antigens expressed by actively replicating bacteria, by "dormant" bacteria, or during resuscitation from dormancy, with the goal of providing protective immunity during all stages of *M. tuberculosis* infection.

NONCLASSICAL T CELLS

T cells that express antigen receptors consisting of γ and δ (instead of α and β) chains do not recognize peptide fragments and do not depend on HLA class I or II molecules as the basis for their target recognition. A specific subset of γδ T cells characterized by TCRs containing the Vγ9 and Vδ2 chains respond to isoprenyl pyrophosphates and other phosphorylated small molecules,[140] and are activated by *M. tuberculosis*–infected macrophages.[141]

Mucosal-associated innate-like T cells (MAITs) share certain properties with γδ T cells, but their TCRs recognize low-molecular-weight microbial metabolites, including intermediates in vitamin biosynthesis, bound to the HLA class I–like molecule, MR-1.[142] Although γδ T cells and MAITs are enriched at mucosal surfaces and can be activated by *M. tuberculosis*–infected cells, their contributions to immune control of *M. tuberculosis* remain unclear.[143,144]

Another subset of T cells expresses TCR αβ chains that recognize specific complex mycobacterial lipids (for example, glucose monomycolate, dideoxymycobactin, and phosphomycoketide) bound to the HLA class I–like molecules CD1a, CD1b, or CD1c.[145] Although the contributions of CD1-restricted lipid antigen-specific T cells to protective immunity remains to be determined, there is evidence that these cells are expanded in persons with active TB,[146] and a polyporphism in the *CD1a* gene is associated with increased susceptibility to TB.[147]

OTHER MECHANISMS OF IMMUNITY

Although antibodies were thought unlikely to contribute to protective immunity to TB, recent investigations have provided evidence that some individuals exposed to *M. tuberculosis* who remain well produce antibodies with protective activity in vitro and upon passive transfer to mice.[148] Moreover, *M. tuberculosis*–reactive antibodies isolated from human subjects with active TB exhibit distinct properties compared with those from humans that remain healthy, including differential glycosylation of the Fc domains and isotype prevalence.[149] These and other studies (reviewed in [150]) have intensified investigation of the value of developing TB vaccines that induce protective antibodies.

Aside from the contributions of adaptive (T and B) lymphocytes, functionally similar *innate lymphoid cells* (ILCs) can contribute to early responses to pathogens, including *M. tuberculosis*. Analogous to subsets of T cells, there are three major subsets of ILCs, categorized by their lineage-defining transcription factors and functional responses. ILC1s express T-bet and produce IFN-γ; ILC2s express GATA-3 and produce IL-4, IL-5, and IL-13; and ILC3s express Rorγt and secrete IL-17 and/or IL-22. Unlike B or T cells, ILCs lack antigen receptors, and are activated by cytokines and other stimuli produced by mucosal epithelial and mononuclear cells. ILC3s have been found to contribute to immunity to *M. tuberculosis* by expanding, accumulating in the lungs of humans with active TB, and controlling bacterial growth in the lungs of infected mice.[151]

EVASION OF ADAPTIVE IMMUNITY

A characteristic of immunity to *M. tuberculosis* is that it is often incomplete and unable to eliminate the bacteria reliably. As a consequence, a proportion (5–10%) of individuals can develop progressive or reactivation disease. Incomplete immunity may also underlie the necessity for prolonged antimicrobial therapy for active TB. Multiple mechanisms have been discovered that contribute to *M. tuberculosis* manipulating, evading, or exploiting immune responses to survive and to be transmitted. As discussed earlier, numerous bacterial proteins and lipids are implicated in evading the innate immune response. Similarly, to limit the efficacy of CD4 T cells in immunity to *M. tuberculosis*, the bacteria employ multiple mechanisms for evading CD4 T cell recognition of infected cells. Since the bacteria reside prominently in antigen-presenting cells (macrophages and dendritic cells), they are well-positioned to limit the activities of CD4 T cells by modulating antigen presentation. At least three mechanisms contribute to *M. tuberculosis* manipulation of antigen presentation. The ESX-3 effector protein, EsxH, directly interacts with the host protein hepatocyte growth factor–regulated tyrosine kinase substrate, and interferes with MHC/HLA class II antigen presentation to CD4 T cells by limiting antigen processing.[5] An additional *M. tuberculosis* protein, PE_PGRS47, inhibits autophagy and antigen presentation to CD4 T cells,[152] and *M. tuberculosis*–infected cells divert bacterial antigens from the class II antigen presentation pathway and export them to the extracellular space.[153] As another mechanism for evasion of T cells, *M. tuberculosis* dynamically regulates expression of the genes encoding certain immunodominant antigens such as Ag85B. Ag85B is expressed early after infection, allowing priming and expansion of Ag85B-specific CD4 T cells, but markedly downregulates Ag85B expression later in infection, thereby avoiding the effects of Ag85B-specific T cells.[154] Together, these results indicate that *M. tuberculosis* employs multiple mechanisms to manipulate antigen presentation and recognition of infected cells by CD4 T cells. Evidence for the functional importance of limiting antigen presentation is the finding that *M. bovis* BCG-infected cells present the same antigen more effectively than do *M. tuberculosis*–infected cells, and yet *M. bovis* BCG can be eliminated from mouse lungs in a T cell–dependent manner.[155]

In addition to manipulating CD4 T cell activation and recognition of infected cells, *M. tuberculosis* possesses mechanisms to counter T cell effector mechanisms such as the effects of the cytokine IFNγ. One antimicrobial IFNγ-induced gene encodes the enzyme indoleamine-2,3-dioxygenase, which catalyzes the essential amino acid tryptophan to kynurenine; tryptophan depletion is lethal to many pathogens, but *M. tuberculosis* responds by synthesizing tryptophan, allowing the bacteria to survive and replicate despite the effects of IFNγ.[156]

LATENCY/DORMANCY AND REACTIVATION

Although for clinical and public health purposes, latent TB infection is considered to represent persistent infection contained in most individuals by effective immune responses, the biologic state of latent TB infection is likely to be more complex, and has been suggested to comprise a spectrum of bacterial and immune states.[157,158] Because existing assays of TB infection depend on T cell responses to selected *M. tuberculosis* antigens and thereby reflect immunologic memory rather than persistent infection, the spectrum may include at one extreme, elimination of the bacteria, and at the other extreme, a state of subclinical active infection with bacterial replication uncontained by host immunity. The importance of latent TB infection is that, in 5–10% of individuals, it progresses to active, transmissible TB, so it can contribute to sustaining the TB epidemic,[159] although an alternative perspective recently has been provided.[160]

Diverse risk factors, such as age, nutritional state, diabetes, malignancy, and smoking, are associated with higher rates of progression from latent to active TB, but only two, HIV and TNF blockade, have clear immunologic mechanisms.[161] While the contributions from the other risk factors may be related to waning or fluctuating immunity, bacterial factors may also contribute to progression from latent to active TB, as exemplified by specific mechanisms used by *M. tuberculosis* to adapt to and manipulate the host environment. Among these are regulatory mechanisms that promote adaptation of *M. tuberculosis* to hypoxic environments and allow the bacteria to recover from hypoxia and to resume growth.[162,163] *M. tuberculosis* also expresses "resuscitation promoting factors" that act on bacterial cell wall peptidoglycan to promote growth during recovery from dormancy.[164,165] Together, these findings suggest that, under some circumstances, *M. tuberculosis* may itself drive reactivation of latent TB infection, in the absence of identifiable host immune deficits.

An additional topic of current investigation is identification of the tissue and cellular sites of *M. tuberculosis* during latent infection. Although early studies identified viable bacteria in lung and lymphoid tissues of individuals with latent TB infection, recent studies have reported evidence for residence of dormant bacteria in adipose tissue, lymphatic endothelial cells, and mesenchymal and hematopoietic stem cells (reviewed in Mayito et al.[166]).

NEW TUBERCULOSIS VACCINES

Two recent clinical trials provide optimism for the development of TB vaccines that are more efficacious than the widely used intradermal BCG vaccine.

A novel prevention of infection trial compared BCG revaccination or an adjuvanted protein subunit vaccine (termed H4:IC31) to placebo in adolescents at high risk but no evidence of prior *M. tuberculosis* infection (as reflected by a negative result on an *interferon gamma release assay* [IGRA]). While neither BCG revaccination nor H4:IC31 prevented initial infection as indicated by conversion from IGRA-negative to positive, BCG revaccination but not H4:IC31 prevented "sustained" infection (IGRA conversion from negative to positive, without reversion to negative) with approximately 45% efficacy.[167] Although the significance of IGRA reversion is uncertain, it may reflect clearance of infection.

A prevention of disease trial at multiple sites in Africa compared another adjuvanted protein subunit vaccine termed M72:AS01$_E$ and placebo, given to IGRA-positive, HIV-negative adults who had previously been vaccinated with BCG. When participants were followed for 2 years, the M72:AS01$_E$ vaccine exhibited overall efficacy of 54% in preventing progression to definite pulmonary TB compared with the control.[168] The efficacy was age dependent and may have been more efficacious in men than in women.

In addition to these human trials, a study in nonhuman primates using a vaccine consisting of recombinant rhesus cytomegalovirus expressing *M. tuberculosis* antigens exhibited dramatic protection with sterile immunity following *M. tuberculosis* challenge.[169] Additional studies in nonhuman primates revealed that intrapulmonary mucosal[171] or intravenous administration of BCG provided a high level of protection, including sterile immunity, after inhalational challenge with virulent M tuberculosis.[172]

Together, the results of these studies provide substantial evidence for the feasibility of developing efficacious TB vaccines, though more studies are needed to determine the optimal target populations and strategies for vaccine implementation.

Key Points

- *M. tuberculosis* is evolutionarily ancient and has coevolved with humans.
- *M. tuberculosis* employs multiple mechanisms of pathogenesis, using specific lipid and protein virulence factors to survive intracellularly, predominantly in mononuclear phagocytes.
- Human immunity protects most individuals from active tuberculosis disease. Immunity requires CD4 T cells; other mechanisms of immunity, including antibodies, may also contribute to protection against progression of tuberculosis.
- *M. tuberculosis* employs multiple mechanisms to evade CD4 T cell recognition, resulting in partial immunity and, in some people, lifelong infection.
- Novel tuberculosis vaccines are in development, and initial results of clinical trials provide optimism for the development of effective tuberculosis vaccines.

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53 TUBERCULOSIS: CLINICAL MANIFESTATIONS AND DIAGNOSIS

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INTRODUCTION

Tuberculosis (TB) continues to be a global public health threat, with more than 10 million people developing the disease and an estimated 1.2 million deaths each year.[1] Early diagnosis followed by linkage to appropriate treatment remains essential for improving patient outcomes and reducing transmission. This chapter reviews the general approach to evaluating persons who may have TB and the available diagnostic tests.

DIAGNOSIS OF PULMONARY TUBERCULOSIS

DIAGNOSTIC EVALUATION

Clinicians must recognize that, in evaluating persons who may have TB, they are both providing care to an individual patient and assuming an essential public health function. Early and accurate diagnosis is critically important to TB care and control.[2] Despite dramatically improved access to high-quality TB services worldwide during the past 2 decades, there is substantial evidence that failure to identify and treat cases early is a major weakness in efforts to ensure optimal outcomes for the patient and to control the disease. Diagnostic delays result in ongoing transmission in the community and more severe, progressive disease in the affected person.

Globally, there are three main reasons for delays in diagnosing TB: the affected person not seeking or not having access to care; the provider not suspecting the disease; and the lack of sensitivity of the most commonly available diagnostic test, smear microscopy of sputum (or other specimen).[3,4] Approaches to reducing these delays are, obviously, quite different. Reducing delays on the part of the affected person entails providing accessible health care facilities, enhancing community and individual awareness, and pursuing active case finding in high-risk populations. Reducing delay by the provider is best approached by increasing provider awareness of the risks for and symptoms of TB and by enhancing the availability and use of appropriate diagnostic tests. Rapid molecular tests that increase both the speed and the sensitivity for identifying *Mycobacterium tuberculosis* are increasingly available and now recommended by the *World Health Organization* (WHO) as the initial diagnostic test for *M. tuberculosis* where available.[5,6]

PATIENT HISTORY

There must be a clinical suspicion of TB before proper diagnostic tests are ordered. Clinical suspicion is prompted largely by the presence of symptoms and by awareness of comorbidities and epidemiologic circumstances that increase the risk of TB in an individual patient. These risks are summarized in the WHO guidelines for screening for TB.[7] The most commonly reported symptom of pulmonary TB is persistent cough that generally, but not always, is productive of mucus and sometimes blood. In persons with TB, cough is often accompanied by systemic symptoms, such as fever, night sweats, and weight loss. In addition, findings such as lymphadenopathy, consistent with concurrent extrapulmonary TB, may be noted, especially in patients with *human immunodeficiency virus* (HIV) infection. However, chronic cough with sputum production is not always present, even among persons with sputum smears showing acid-fast bacilli. Data from several TB prevalence surveys in countries with a high incidence of the disease show that many persons with active TB do not have cough of 2 or more weeks' duration, a criterion

that, conventionally, has been used to define suspected TB.[8,9] In these studies, 10–25% of patients with bacteriologically confirmed TB do not report cough.[10,11] These data suggest that evaluation for TB using a symptom review that includes *cough of any duration, fever, night sweats, or weight loss* may be indicated in selected risk groups, especially in areas where there is a high prevalence of the disease and in high-risk populations and individuals with increased susceptibility, such as persons with HIV infection. Use of this broadened set of questions in a population of persons with HIV infection was found to have a negative predictive value of 97.7% for TB.[12] The presence of any one of the symptoms should be viewed as an indication for an evaluation for TB in high-risk groups or in high-incidence areas.

Hemoptysis is usually seen with more extensive involvement but does not necessarily indicate an active tuberculous process. Hemoptysis may also result from inactive TB, as from bronchiectasis left as a residual of healed TB; from rupture of a dilated vessel in the wall of an old cavity (*Rasmussen aneurysm*); from bacterial or fungal infection (especially in the form of a fungus ball [*aspergilloma* or mycetoma]) in an old residual cavity (eFig. 53.1); or from erosion of calcified lesions into the lumen of an airway (*broncholithiasis*).

The systemic features of TB include fever in approximately 35–80%, malaise, and weight loss; there may be a variety of hematologic abnormalities, especially leukocytosis and anemia.[13–15]

PHYSICAL EXAMINATION

In most cases, physical findings are not specific for pulmonary TB. Crackles may be heard in the area of involvement, along with bronchial breath sounds, when lung consolidation is close to the chest wall. Amphoric breath sounds (like the low sound produced by blowing across the top of an open bottle), if present, may be indicative of a cavity. Findings such as lymph node enlargement, suggestive of extrapulmonary TB, may also indicate concurrent pulmonary involvement.

RADIOGRAPHIC FEATURES

Radiographic examination of the chest is commonly the first diagnostic study undertaken, after the history and physical examination.[16,17] However, in resource-limited settings, a chest radiograph is not necessarily included as part of the routine evaluation because of cost, complexity, and nonspecificity of the findings.[18]

Pulmonary TB nearly always causes detectable abnormalities on the chest radiograph, although, in patients with HIV infection, a chest radiograph may be normal in up to 11% of patients with positive sputum cultures, and the chest radiograph may be normal in laryngeal TB.

In *primary* TB, resulting from recent infection, the process is generally seen as a middle or lower lung zone opacity, often associated with ipsilateral hilar adenopathy (Fig. 53.1). Atelectasis may result from compression of airways by enlarged lymph nodes. If the primary process persists beyond the time when specific cell-mediated immunity develops, cavities may form (so-called progressive primary TB).

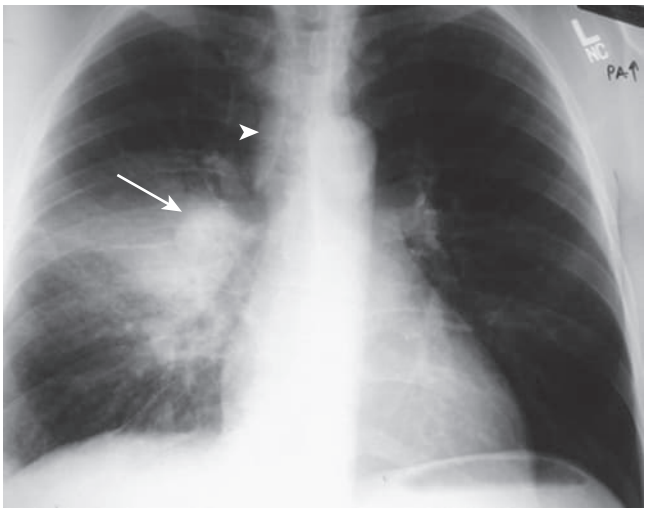

Figure 53.1 Primary tuberculosis. Frontal chest radiograph in a young adult shows superior segment right lower lobe consolidation associated with right hilar lymphadenopathy (*arrow*) due to primary *Mycobacterium tuberculosis* infection. Mild right paratracheal lymph node enlargement (*arrowhead*) is also visible. (Courtesy Michael B. Gotway, MD.)

In *reactivation* TB, developing at a time remote from the original infection, one sees involvement of the upper lobes of one or both lungs. Cavitation is common in this form of TB. The most frequent sites are the apical and posterior segments of the right upper lobe (Fig. 53.2) and the apical-posterior segment of the left upper lobe. Healing of the tuberculous lesions usually results in development of a fibrotic scar with shrinkage of the lung parenchyma and, often, calcification. Involvement of the anterior segments alone is unusual. In the immunocompetent adult with TB, intrathoracic adenopathy is uncommon. When the disease progresses, infected material may be spread via the airways (i.e., "bronchogenic" spread) into the lower portions of the involved lung or to the other lung. Erosion of a parenchymal focus of TB into a blood or lymph vessel may result in dissemination of the organism and a miliary pattern on chest imaging (Fig. 53.3; see Fig. 20.21). Radiographic findings in HIV-infected patients are affected by the degree of immunosuppression. As further explained and illustrated in Chapter 123, TB early in the course of HIV infection—before profound depletion of CD4 T cells—tends to produce typical radiographic findings with predominantly upper lobe infiltration and cavitation.[20] With more advanced HIV disease and CD4 T-cell deficiency, the radiographic findings become more "atypical": cavitation is uncommon, and lower lung zone or diffuse opacities and intrathoracic adenopathy are frequent (Fig. 53.4). Surprisingly, a substantial number of HIV-infected patients with pulmonary TB have normal radiographs at the end of their course of treatment.[21]

The activity of a presumed tuberculous process cannot be determined simply from a single chest radiograph, although new imaging modalities may assist with making this distinction (see below). A cavity might be a sterile residual of an old infection, whereas a fibrotic-appearing lesion may be active. Conversely, not all radiographic worsening of the residua of prior tuberculous lesions can be ascribed to reactivation of the disease, although such worsening



Figure 53.2 Cavitary tuberculosis. Frontal chest radiograph in a patient with tuberculosis shows extensive right upper lobe cavitation. (Courtesy Michael B. Gotway, MD.)



Figure 53.3 Disseminated tuberculosis. Frontal chest radiograph in a patient with disseminated tuberculosis shows numerous small, randomly distributed nodules bilaterally, representing the miliary pattern. (Courtesy Michael B. Gotway, MD.)

should always be of concern. Superimposed infections with other organisms or bleeding from bronchiectasis or from residual cavities may cause new infiltrations to appear. In addition, carcinomas may arise from within the area of scarring (so-called scar carcinomas) and can be the cause of radiographic changes.[22]

Chest radiography in most settings remains a central component of radiographic evaluation of pulmonary TB, particularly of primary pulmonary TB. However, emerging evidence describes the potential role of other imaging modalities such as *computed tomography* (CT), *magnetic resonance imaging* (MRI), and *positron emission tomography* (PET) scan, especially for nonparenchymal changes and to characterize post–primary TB. Chest CT, for example, is more sensitive at detecting lymphadenopathy than is chest radiography and is better at demonstrating bronchogenic spread characteristic of TB caused by reactivation.[23] In addition, CT has higher sensitivity of predicting active TB compared to chest radiography, with a sensitivity of 96% compared to 48%.[24] This is primarily because CT scans can demonstrate radiographic findings more associated with highly infectious progressive primary TB disease, including consolidation involving the lung apices, consolidation involving the superior segments of the lower lobes, cavitary lesions, and characteristics of nodules, including clusters.[25]

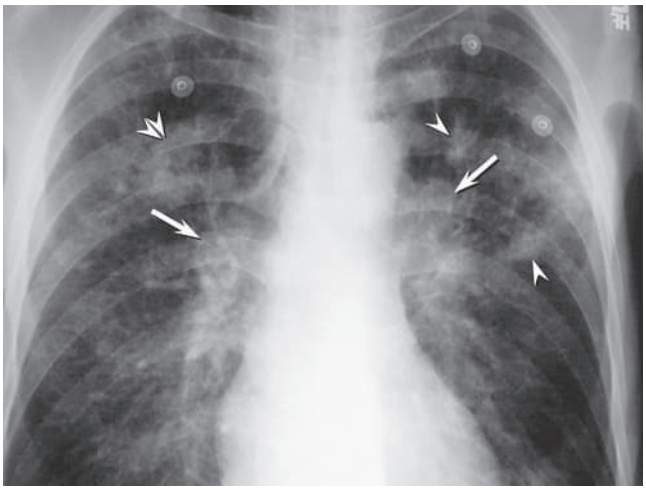

Figure 53.4 Tuberculosis in an patient with human immunodeficiency virus. Frontal chest radiograph in a patient with tuberculosis shows bilateral hilar lymph node enlargement (*arrows*) associated with poorly defined parenchymal nodular opacities (*arrowheads*) and nodular areas of consolidation (*double arrowheads*). (Courtesy Michael B. Gotway, MD.)

Although CT increasingly is being used for the diagnosis and characterization of progressive primary pulmonary TB, alternative imaging methods without ionizing radiation are also being adapted, including MRI. Traditionally, MRI has not been used to evaluate for pulmonary diseases due to the concern of poor image quality caused by low proton density in the lung, rapid signal decay due to high magnetic susceptibility at the air-tissue interface, and intrinsic motion artifacts from respiratory motion.[26] With new motion-correcting protocols, MRI may be better than CT for evaluation of pleural involvement including pleural effusion and to characterize the presence of caseous necrosis and liquefaction. MRI has been shown to be comparable to CT in describing lymphadenopathy and consolidations, although sensitivity for pulmonary nodules is lower.[27] Thus, radiographic surveillance with MRI as opposed to CT should be considered in vulnerable populations in whom the use of ionizing radiation is of concern, such as pregnant women and children.[28] Finally, there is growing evidence for the additional role that fluorodeoxyglucose-PET/CT may have in monitoring treatment response and differentiating active pulmonary TB from old or inactive disease,[29] with sensitivity and specificity reported to be 100% when using a maximal standardized uptake value threshold of at least 1.05. Additional research is needed to establish standardized uptake value thresholds that predict disease activity in specific populations.

Consideration should be given to the extensive resources that CT, MRI, and PET/CT may require in most settings.

Because primary TB infection can result in parenchymal disease, lymphadenopathy, pleural effusion, or miliary disease, the differential diagnosis of radiographic abnormalities that may be consistent with TB is still broad. Parenchymal disease with or without associated cavitation can mimic a variety of bacterial or fungal pneumonias. Nodules with or without concomitant ground glass may be consistent with other infections or with malignancy, and bronchiectasis may be consistent with *nontuberculous mycobacterial* (NTM) disease. Therefore, a nondiagnostic microbiologic evaluation should prompt a careful assessment for other causes of the radiographic abnormality. From this discussion, it should be obvious that the radiologic findings, although extremely valuable, cannot provide a definitive diagnosis of TB. Because of the radiographic similarities among the other disorders in the differential diagnosis, and because of the uncertainties in assessing disease activity and in determining the reasons for progressive radiographic changes, careful microbiologic evaluation is always indicated.

LABORATORY DIAGNOSTIC EVALUATION

Testing for Suspected Pulmonary Tuberculosis

All adults and children who are suspected of having active pulmonary TB should have at least two sputum specimens collected for *acid-fast bacilli* (AFB) smear microscopy and mycobacterial culture and at least one sputum specimen collected for *nucleic acid amplification testing* (NAAT). Although collecting more than two sputum specimens increases the yield only slightly, in the United States, collection of three sputum specimens for AFB smear microscopy and culture is considered routine practice and is strongly recommended to improve sensitivity by the Centers for Disease Control and Prevention, American Thoracic Society, and Infectious Disease Society of America.[30] NAAT is recommended for the initial sputum specimen in the United States and other low-incidence countries; however, NAAT results should be interpreted in conjunction with AFB smear microscopy results. For AFB smear–positive persons, a positive NAAT result offers rapid confirmation of TB diagnosis. A negative result may suggest another etiology, such as NTM, because NAATs are able to distinguish *M. tuberculosis* from nontuberculous mycobacteria. For AFB smear–negative persons with intermediate to high probability of disease, a positive NAAT result is used as presumptive evidence of TB. For AFB smear–negative persons with low probability of disease, a positive NAAT result should be interpreted with caution because of the higher probability of false positives in this population. For AFB smear–negative persons with suspected pulmonary TB, a negative NAAT result does not exclude active disease; current NAATs do not possess sufficient sensitivity to replace mycobacterial culture.

In most countries with a high incidence of TB, culture is not routinely performed in the evaluation of persons with suspected pulmonary TB because culturing mycobacteria from clinical specimens requires costly laboratory infrastructure and biosafety conditions not available in many low-resource settings. As such, TB diagnosis in high-incidence settings relies primarily on AFB smear microscopy and increasingly, Xpert MTB/RIF (Cepheid), an automated, self-contained real-time NAAT that detects *M. tuberculosis* complex and rifampin resistance in 90 minutes. Although U.S. policymakers recommend using NAATs including Xpert MTB/RIF as an adjunct test to AFB smear microscopy, the WHO recommends Xpert MTB/RIF as the preferred initial test for suspected pulmonary TB cases with HIV infection, risk factors for multidrug-resistance, and serious illness.[31] In addition, the WHO recommends that, where feasible, Xpert MTB/RIF testing can be used as the initial test in place of two specimens submitted for smear microscopy for all adults and children with suspected TB. However, individuals diagnosed with active TB by Xpert MTB/RIF testing should submit additional sputum for AFB smear microscopy and culture (if rifampin resistance is detected) because conventional microscopy remains essential for monitoring treatment response and culture is required for phenotypic drug susceptibility testing.

Specimen Collection

As noted previously, a definitive diagnosis of TB can be established only by isolation of tubercle bacilli in culture or by identification of specific nucleic acid sequences. When the lung is involved, sputum is the initial specimen of choice. Two sputum specimens should be collected, which can be obtained on the same day because the sensitivity of tests using same-day specimens is similar to tests using specimens collected on different days.[32] The collection of the sputum on one day allows results to be available the same day, thereby increasing the efficiency of sputum smear microscopy.[32] The strategies for same-day microscopy include the preparation of two or three slides from sputum samples obtained the first day the patient is assessed. Collecting more than two sputum specimens increases the yield only slightly.[33]

There are several options for obtaining specimens from patients who are not producing sputum. The first and most useful in terms of yield and avoidance of patient discomfort is *sputum induction,* in which sputum production is enhanced by the inhalation of a hypertonic (3–5%) saline mist generated by an ultrasonic nebulizer. Sputum induced by this technique is clear and resembles saliva; thus, it must be properly labeled or it may be discarded by the laboratory. This is a benign and well-tolerated procedure, although bronchospasm may be precipitated in asthmatic patients.

Sampling of gastric contents via a nasogastric tube has a lower yield than sputum induction and is more complicated and uncomfortable for the patient. However, in children and some adults, gastric contents may be the only specimen that can be obtained. Gastric lavage should be performed early in the morning before the patient has gotten out of bed, eaten, or performed dental hygiene. Once the specimen is obtained, the specimen should be sent to the laboratory and processed the same day. To prolong the viability of the bacteria, neutralization of gastric acid with an equal volume of sterile 1% sodium bicarbonate is recommended when the specimen is not processed inmediately.[34,35]

Depending on the clinical circumstances, if the sputum is negative or cannot be obtained, the next diagnostic step is usually fiberoptic bronchoscopy with bronchoalveolar lavage and, in some instances, transbronchial lung biopsy. The yield of bronchoscopy is high in miliary TB and in focal disease as well. Bronchoscopic procedures

have been especially helpful in the diagnostic evaluations of patients with HIV infection with negative sputum smear microscopy.[36] Needle aspiration-biopsy may also provide specimens from which mycobacteria are isolated, but the technique is especially suited to the evaluation of peripheral nodular lesions for which there is a suspicion of malignancy.

A diagnosis of TB can also be made by an appropriate response to antituberculosis therapy. For example, in some situations, a trial of antituberculosis chemotherapy may be indicated before more invasive studies are undertaken. For example, when there is a radiographic abnormality consistent with TB in a person younger than 40 years, a nonsmoker, and from a country with a high prevalence of TB, either current or past TB is much more likely than a neoplasm, even in the presence of negative smears and cultures of sputum. In such a patient, improvement in the chest radiograph concomitant with antituberculosis treatment would be sufficient reason for making a diagnosis of TB and continuing with a full course of therapy. A response should be seen within 2 months of starting treatment. If no improvement is noted, the abnormality must be the result of either old TB or another process. An algorithm illustrating this approach is shown in Figure 53.5. However, for individuals with risk factors for drug-resistant TB (e.g., prior TB, high prevalence of drug-resistant TB in the country of origin), empiric trials of antituberculosis chemotherapy should be avoided and microbiologic confirmation should be aggressively pursued for drug susceptibility testing whenever possible.

Because of the potentially disastrous consequences of delays in diagnosis of TB, it is essential that tests for *M. tuberculosis* be performed rapidly and the results be reported promptly. Waiting days for the results of AFB smear microscopy and NAAT, weeks for culture results, and months for speciation and susceptibility studies is not acceptable.

Acid-Fast Staining

Historically, the first step in the diagnostic sequence consisted of staining and examining readily available specimens for AFB. Current recommendations now support both AFB smear microscopy and NAAT on the initial respiratory specimen (see below for recommendations for use of rapid molecular tests in the initial evaluation). Finding AFB is generally specific for mycobacteria but provides no information about species. However, the sensitivity of microscopic examination is relatively low; the level of detection is approximately 10,000 bacilli/mL of secretions if 100 oil immersion microscopic fields are examined. The sensitivity of sputum smear microscopy can be increased by concentrating the sample either by centrifugation or sedimentation after chemical processing.[37] Sensitivity can also be increased by about 10% using a fluorochrome staining procedure with auramine O, a fluorescent stain.[38] This procedure requires use of a fluorescent microscope, which requires an excitation light source. There are two types of light sources. The first one is the short-arc mercury vapor lamp, which has a limited lifespan (200 to 300 hours), is costly, requires high maintenance, and is potentially toxic due to its mercury content. The second is the light-emitting diode, which has a life span of more than 50,000 hours, is less expensive, and has a performance similar to the MVP-based microscopy.[39] Fluorochrome-based procedures are faster than acid-fast staining because the intensity and contrast of the fluorescent signal on a dark background enables slides to be scanned at lower magnification.

Smears are generally interpreted as negative or, if positive, are reported as rare (3 to 9 organisms per slide), few (10 or more per slide), or numerous (1 or more per high-power oil immersion field). In most situations in which acid-fast organisms are detected by microscopy, they should be assumed to be *M. tuberculosis* until proven otherwise. Assuming the patient has TB will trigger the appropriate prompt responses from the physicians responsible for treatment and from public health agencies. In practice, the sensitivity of sputum smears varies widely: 20–80% of patients with *M. tuberculosis* isolated in culture have positive smears.[37]

Mycobacterial Culture

Culture in liquid media is considered the current diagnostic gold standard and can detect as few as 10 to 1000 viable mycobacteria/mL of sputum. Culture is a necessary step for diagnosis and is essential for phenotypic drug susceptibility testing. Culture of sputum usually involves digestion, decontamination, and concentration of the specimen before inoculation of media. This process decreases bacterial overgrowth and, when solid media are used, enables more uniform plating of the specimen. For specimens other than sputum, digestion and decontamination are not required. At a minimum, laboratories performing culture should be able to identify *M. tuberculosis* by phenotypic or molecular methods (see below). Isolates that are not *M. tuberculosis* or are of questionable identity should then be sent to a more specialized laboratory for definitive speciation.

Culture can be performed in solid or liquid media. Solid media are usually less expensive and allow the morphologic examination of the colonies to be used for presumptive species identification. However, results on solid media are delayed due to the slow growth of mycobacteria and, in some settings, the delayed culture results may have limited or no impact on patient management.[40] The solid media can be based on egg such as Lowenstein-Jensen media or on agar such as Middlebrook 7H10 or 7H11 media. *M. tuberculosis* colonies appear in 2 to 8 weeks, and cultures without growth at 8 weeks are reported as negative, although they are generally kept for another 2 to 4 weeks before being discarded because some strains grow more slowly than the average.

Liquid media are more sensitive and increase the yield by 10%. They enable *M. tuberculosis* growth to be detected in 10 to 14 days. However, liquid media also have a higher rate of contamination with other bacteria or fungi.[41] The growth of *M. tuberculosis* in liquid media produces fluorimetric or colorimetric reactions, detected using manual or automated systems. The automated systems permit a higher throughput and should be used in settings with high workloads, especially for drug susceptibility testing. The manual systems are less expensive and are used in areas with limited resources.

***M. tuberculosis* Identification.** The methods to identify *M. tuberculosis* can be classified as (1) phenotypic methods including biochemical tests and specific cell and colony characteristics and (2) molecular methods targeting *M. tuberculosis complex*–specific nucleic acids or proteins.

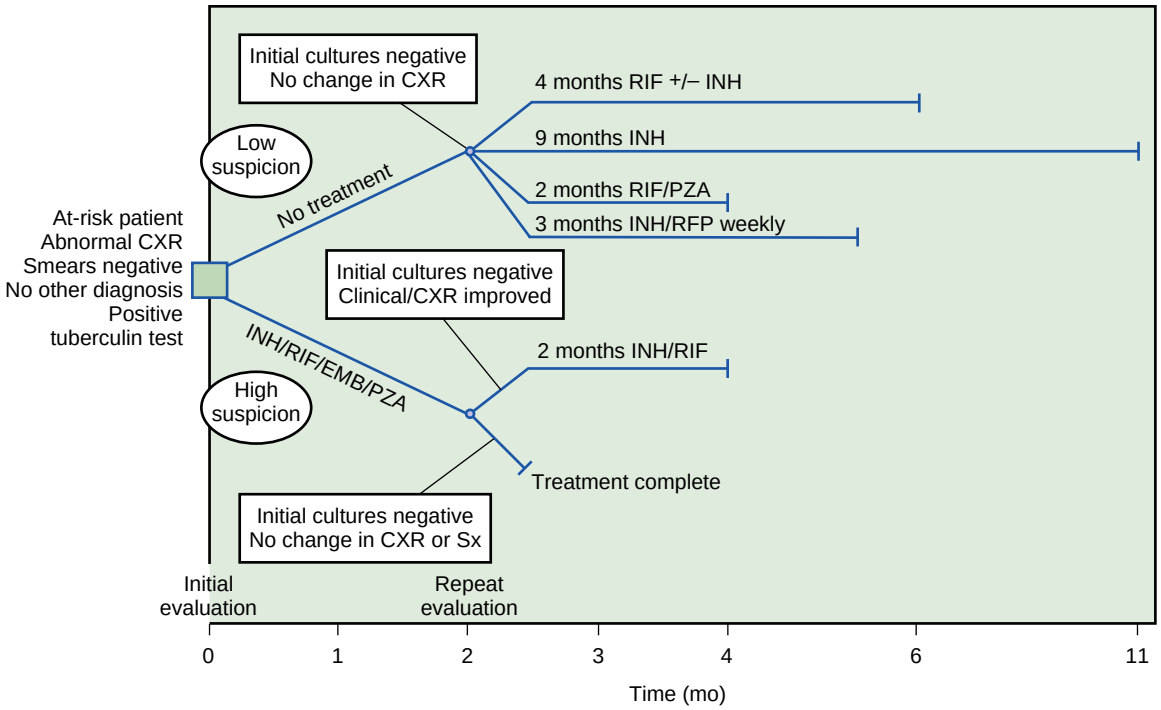

Figure 53.5 Approach to diagnosis and treatment for active, culture-negative pulmonary tuberculosis and inactive tuberculosis. The decision to begin treatment for a patient with sputum smears that are negative depends on the degree of suspicion that the patient has tuberculosis. If the clinical suspicion is high (lower portion of figure), then multidrug therapy should be initiated before acid-fast smear/culture results are known. If the diagnosis is confirmed by a positive culture, treatment can be continued to complete a standard course of therapy. If initial cultures remain negative and treatment has been with multiple drugs for 2 months, then there are two options depending on repeat evaluation at 2 months (lower portion of figure). In option 1, if the patient demonstrates symptomatic or radiographic improvement without another apparent diagnosis, then a diagnosis of culture-negative tuberculosis can be inferred. Treatment should be continued with isoniazid and rifampin for an additional 2 months. In option 2, if the patient demonstrates neither symptomatic nor radiographic improvement, then tuberculosis is unlikely and treatment can be stopped. In low-suspicion patients not initially on treatment (upper portion of figure), if cultures remain negative, the patient has no symptoms, and the chest radiograph is unchanged at 2 to 3 months, there are four treatment options: (1) isoniazid for 9 months; (2) rifampin with or without isoniazid for 4 months; (3) rifampin and pyrazinamide for 2 months; or (4) isoniazide and rifapentine weekly for 3 months. (See discussion of latent tuberculous infection.) CXR, chest radiograph; EMB, ethambutol; INH, isoniazid; PZA, pyrazinamide; RIF, rifampin; RFP, rifapentine; Sx, symptoms. (From Blumberg HM, Burman WJ, Chaisson RE, et al, for the American Thoracic Society/Centers for Disease Control and Prevention/Infectious Diseases Society of America. Treatment of tuberculosis. *Am J Respir Crit Care Med.* 2003;167:603–662.)

Phenotype-Based Identification Methods. The classical phenotype-based methods to identify *M. tuberculosis* complex require a positive culture for mycobacteria. These tests include niacin production, nitrate reduction, and inactivation of catalase at 68°C. The tests also use the time to growth, usually 12 to 42 days in solid media; the presence of rough, cauliflower-like, and colorless colonies; and the presence of organisms that are tangled and form corded masses when observed by microscopy.

The *microscopic observation of drug susceptibility* (MODS) assay is a culture-based method that discriminates between *M. tuberculosis* complex and NTM and determines the drug susceptibility to rifampin and isoniazid at the same time. MODS incorporates the antituberculosis drugs in the culture media at the beginning of the assay. The method uses a sealed 24-well tissue-culture plate with liquid culture media containing different antibiotics and controls that are examined periodically under an inverted light microscope. *M. tuberculosis* can be identified by the observation of a tangled or corded mass of organisms and by a time to detection (including susceptibility test), typically less than 2 weeks. The overall sensitivity of MODS to detect *M. tuberculosis* growth was 92% and the specificity was 96% compared with conventional culture. The mean time from receipt of specimen to results was 9.2 days, and contamination was present in 7%.[42] There is currently a MODS kit commercially available, and its use is recommended by the WHO in laboratories where genotypic or automated liquid culture and drug-susceptibility testing capacity are being developed.[43]

Molecular Identification Methods. Several molecular methods are available to identify *M. tuberculosis* directly on the specimen or in mycobacterial culture. They are based on nucleic acid amplification technologies in which as few as 1 to 10 copies of DNA or ribonucleic acid specific to *M. tuberculosis* complex are amplified to detectable levels. Other targets include proteins specific to *M. tuberculosis.* All these tests identify the presence of *M. tuberculosis* complex and can rule out the presence of NTM. Importantly, some NAATs are able to identify the presence of *M. tuberculosis* complex and drug resistance–associated mutations in the same test. There are several commercial technologies, although only two, Xpert MTB/RIF and GenProbe Amplified *M. tuberculosis* Direct test, are available in the United States. The current recommendation by the Centers for Disease Control and Prevention is to use a NAAT on at least one specimen, preferably the first diagnostic specimen from each patient in whom a TB diagnosis is being considered.[44] The recommended interpretation algorithm includes the use of clinical judgment when the NAAT is negative. This

limitation has been applied because it has been found that the sensitivity of the tests is not sufficiently high to exclude *M. tuberculosis*.[44,45]

A major breakthrough in NAAT has been the development of Xpert MTB/RIF. As noted previously, Xpert MTB/RIF is an automated, self-contained, real-time *polymerase chain reaction* (PCR) assay capable of detecting *M. tuberculosis* complex and rifampin resistance–associated mutations directly in clinical specimens with results in 90 minutes.[46] This system is based on the amplification of a sequence of the *rpoB* gene specific to members of the *M. tuberculosis* complex and the rifampin resistance–determining region. It can be used directly on clinical specimens or specimens that have been digested and decontaminated.[47] It requires minimal biosafety measures[48] and minimal hands-on technical time.[49] It consists of two main components: (1) a disposable cartridge that contains sample processing and the *M. tuberculosis*–specific real-time PCR reagents and (2) an instrument that controls the fluidics in the cartridge and performs the PCR analysis.[46] The operational challenges are related to the specific needs of the components: cartridges require a temperature below 28°C and have a 12-month shelf-life, and the instrument requires a stable electrical power supply and an ambient temperature below 30°C.[49] A meta-analysis showed that, as an initial test replacing smear microscopy, Xpert MTB/RIF pooled sensitivity was 89% and pooled specificity 99%.[50] As an add-on test following a negative smear microscopy result, Xpert MTB/RIF pooled sensitivity was 67% and specificity 99%. For smear-positive, culture-positive TB, Xpert MTB/RIF pooled sensitivity was 98%. For people with HIV infection, Xpert MTB/RIF pooled sensitivity was 79% and, for people without HIV infection, it was 86%. The pooled sensitivity to detect rifampin resistance was 95%, and the pooled specificity was 98%.[50] This assay has a median time to detection of *M. tuberculosis* of hours compared with 1 day for microscopy, 16 days for culture in liquid media, and 30 days for culture on solid media. The median time to detection of rifampin resistance with the automated and self-contained real-time PCR assay was 1 day compared with 106 days for phenotypic tests.[51] More importantly, Xpert MTB/RIF reduced the median time to treatment of patients with sputum smear-negative TB from 56 days to 5 days.[51] On the basis of its diagnostic accuracy, WHO endorsed the Xpert MTB/RIF for the diagnosis of TB in 2010.[52,53] WHO recommends that, for all patients (including children) who are suspected of having pulmonary TB and are capable of producing sputum, a single specimen submitted for Xpert MTB/RIF testing can be used as the initial test in place of two specimens submitted for smear microscopy. In addition, WHO recommends that Xpert MTB/RIF should be used as the preferred initial test for patients who are at risk for drug resistance, who have HIV risks, or who are seriously ill; because of the speed of diagnosis, the test is also preferred for use with *cerebrospinal fluid* (CSF) in patients suspected of having tuberculous meningitis.

WHO recommendations for the use of Xpert MTB/RIF now also apply to the use of Xpert MTB/RIF Ultra,[54] Cepheid's next-generation assay developed to improve sensitivity of TB diagnosis, as the initial test for all adults and children with suspected pulmonary TB and in the testing of selected extrapulmonary specimens (e.g., CSF, lymph nodes, and tissue specimens). Key modifications to improve assay sensitivity for the detection of *M. tuberculosis* include a larger DNA reaction chamber that doubles the amount of purified DNA delivered to the PCR reaction (50 μL PCR reaction in Ultra vs. 25 μL in Xpert MTB/RIF) and detection of two different multicopy *M. tuberculosis* DNA targets (IS6110 and IS1081) instead of a single-copy *M. tuberculosis* DNA target (*rpoB*). These modifications have resulted in the Ultra assay having a lower limit of detection (16 bacterial colony forming units/mL) compared to Xpert MTB/RIF (114 colony forming units/mL). A multicenter noninferiority diagnostic accuracy study comparing the Ultra assay to Xpert MTB/RIF in reference to culture found that overall sensitivity of the Ultra assay was higher than the standard assay (88% vs. 83%), higher among smear-negative culture-positive TB cases (63% vs. 46%), and higher among people with HIV coinfection (90% vs. 77%).[55] However, overall specificity of the Ultra assay was lower compared to the Xpert MTB/RIF (96% vs. 98%) and lower among individuals with a history of TB (93% vs. 98%) because the increased sensitivity of the Ultra assay enables detection of nonreplicating or nonviable bacilli present in individuals with a recent history of TB, reducing the overall specificity of Ultra in high-incidence settings. The Xpert MTB/RIF Ultra assay is not yet available in the United States for clinical use.

Other commercially available molecular methods can be used directly on clinical samples (smear-positive specimens) or mycobacterial cultures for identification of the *M. tuberculosis* complex and drug resistance–associated mutations on the same day the specimen is received.[56] However, because of the higher risk of exposure to TB, these technologies require more technical expertise and a more complex laboratory infrastructure (separate rooms for DNA extraction, preamplification procedures, and amplification/postamplification procedures; unidirectional workflow, stringent cleaning protocols, and restricted access to avoid contamination; and biosafety level 3 laboratories if performed using culture specimens).

The line probe assay uses a DNA strip-based test that allows the simultaneous identification of *M. tuberculosis* and common genetic mutations causing resistance to isoniazid and rifampin from smear-positive sputum samples or from positive cultures. Line probe assays determine the drug resistance profile of a strain by the pattern of binding of amplified DNA to probes on the strip. When one of the known mutation resistance genes is amplified in the TB strain, a line or band appears on the strip. Currently, four line probe assays exist: the INNO-LiPARif.TB assay (Fujirubio),[57] which is available for research use only for the detection of *M. tuberculosis* and rifampin resistance, GenoscholarNTM+MDRTBII(Nipro)andtwoversionsofthe GenoTypeMTBDR assay (Hain LifeScience). Genoscholar NTM+MDRTB II and the GenoTypeMTBDRplus detect *M. tuberculosis* and rifampin and isoniazid resistance,[58] and the GenoTypeMTBDR*sl* detects the most common mutations in the *gyrA* gene for fluoroquinolone resistance; in the *rrs* gene for amikacin, capreomycin, and kanamycin resistance; and in the *embB* gene for ethambutol resistance.[59] Of these, the GenoTypeMTBDR assays have been the most widely studied and used at reference laboratories in low- and middle-income countries following WHO endorsement initially in 2008[60] and updated in 2016.[58]

The gene targets and sensitivity and specificity data for the commercial line probe assays approved for clinical use are summarized in eTable 53.1.

Non–Sputum-Based Tests

Urine Tests. Recently, tests based on the detection of *lipoarabinomannan* (LAM) antigen in urine have emerged as novel tests for TB diagnosis. LAM is a lipopolysaccharide present in mycobacterial cell walls released from metabolically active or degenerating bacterial cells from people with active TB disease. Detecting LAM in urine for TB diagnosis has several advantages relative to conventional sputum-based diagnostics: urine is easily accessible, thus facilitating TB testing for adults and children unable to produce sputum; collection and processing of urine specimens for TB testing requires minimal biosafety measures; and detection of LAM is amenable to inexpensive point-of-care platforms. However, the only commercially available urine LAM assay (Determine TB LAM Ag; Alere) has been shown to have suboptimal sensitivity for active TB. However, unlike traditional tests, sensitivity was higher among people living with HIV and further increased as CD4 cell count decreased.[61] The higher sensitivity of urine LAM in those settings may be explained by a higher mycobacterial burden, increased likelihood of extrapulmonary TB (i.e., genitourinary TB), and increased glomerular permeability associated with HIV-related immunosuppression.[62]

A meta-analysis evaluating the diagnostic accuracy of Determine TB LAM Ag among people living with HIV showed a pooled sensitivity of 42% and a pooled specificity of 91%.[63] Pooled sensitivity and specificity significantly varied by testing indication (e.g., whether by targeted testing of patients presenting with TB symptoms vs. screening of unselected patients irrespective of symptoms), health care setting (e.g., hospitalized patients vs. outpatients), and degree of HIV-associated immunosuppression (i.e., CD4 cell counts). Pooled sensitivity was higher (and pooled specificity generally lower) for (1) symptomatic patients than unselected patients (pooled sensitivity 42% vs. 35%), (2) symptomatic inpatients than symptomatic outpatients (pooled sensitivity 62% vs. 31%), and (3) symptomatic patients with CD4 cell counts less than 200 cells/μL than symptomatic patients with CD4 cell counts 200 cells/μL or greater (pooled sensitivity 45% vs. 16%). A meta-analysis evaluating the incremental change in sensitivity and specificity when combined with smear or Xpert MTB/RIF found that when Determine TB LAM Ag was combined with sputum smear microscopy (i.e., using any positive test), pooled sensitivity was 59% (a 19% increase relative to smear microscopy alone) and pooled specificity was 92% (a 6% decrease relative to smear microscopy alone).[64] When Determine TB LAM Ag was combined with sputum Xpert MTB/RIF, pooled sensitivity was 75% (a 13% increase relative to Xpert MTB/RIF alone) and pooled specificity was 93% (a 4% decrease relative to Xpert MTB/RIF alone). Based on these results, the Determine TB LAM Ag test is recommended by the WHO as the initial test for all HIV-infected inpatients and outpatients with TB symptoms, irrespective of CD4 cell count and irrespective of symptoms if CD4 cell count less than 200 cells/μL (inpatients) or CD4 cell count less than 100 cells/μL (outpatients),[65] although this test is not currently available in the United States.

Because urine LAM has a high potential for use as a point-of-care assay for TB diagnosis, development of next-generation highly sensitive and specific urine LAM assays is a current area of active research. Possible methods for improving urine LAM sensitivity include novel approaches to concentrating LAM antigen in urine,[66] removal of inhibitors in urine,[67] and pairing high-affinity monoclonal antibodies to target LAM epitopes.[68] The FujiLAM assay (FujiFilm), which combines pairing high-affinity monoclonal antibodies to target LAM epitopes and a silver-based amplification step that increases the visibility of test and control lines of a lateral flow assay, has been shown in studies using stored specimens to increase sensitivity substantially among HIV-infected inpatients (70% vs. 42%) and outpatients (68% vs. 45%), relative to Determine TB LAM.[63,69] FujiLAM is currently available for research use only; prospective evaluations are currently ongoing.

Serologic Tests. Several antigens, including highly purified and recombinant antigens specific for *M. tuberculosis* complex, have been used in serologic antibody tests with variable results. A systematic review found that the results of serologic tests are highly variable and not better than sputum smear microscopy.[70,71] On the basis of these results, WHO has strongly recommended against the use of serologic tests for the diagnosis of pulmonary and extrapulmonary TB.[72]

Tuberculin Skin Test or Interferon-γ Release Assays to Guide Empiric Treatment Decisions for Active Tuberculosis. Clinicians caring for suspected TB cases with negative smear and NAAT results are often faced with the dilemma of whether to initiate empiric treatment for individuals for active disease or to wait up to 8 weeks for final culture results. Although smear- and NAAT-negative patients are less infectious than smear and/or NAAT-positive patients, patients with paucibacillary TB are still capable of transmitting infection, with a relative transmission rate of smear-negative cases compared to smear-positive cases estimated to be 24%.[73] Furthermore, because half of all TB cases are smear negative, the population-level contribution of paucibacillary TB cases to overall disease transmission is substantial, with molecular studies estimating smear-negative cases to be responsible for 13–17% of all TB transmission.[73–75] While early initiation of antituberculosis chemotherapy for all patients with active disease is necessary to reduce disease transmission and individual morbidity and mortality risk, careful selection of patients for empiric treatment is required to minimize medication toxicity for individuals without active disease.

Decisions regarding initiation of empiric treatment are based on clinical presentation, radiographic findings, presence of TB risk factors, and exclusion of other non-TB diseases. Assessing for the presence of TB risk factors should include *tuberculin skin testing* (TST) or *interferon-γ release assay* (IGRA) testing to identify individuals with *Mtb* infection. If TST or IGRA results are positive, suspicion for active disease is increased because a positive TST or IGRA result has been shown consistently to be a strong predictor of a positive culture result among smear-negative individuals with suspected TB.[76,77] However, the suboptimal sensitivity of both TST and IGRAs for *Mtb* infection precludes decisions to withhold empiric therapy based on negative test results

eTable 53.1 Accuracy of Line Probe Assays for Detecting *M. tuberculosis* Drug Resistance

		SENSITIVITY*		SPECIFICITY*	
Assay	**Targets**	**Direct**	**Indirect**	**Direct**	**Indirect**
GENOSCHOLAR NTM+MDRTB II					
Rifampin	*rpoB*	96.5%	92.4%	97.5%	97.5%
Isoniazid	*katG, inhA*	94.9%	89.4%	97.6%	98.9%
GENOTYPEMTBDR*plus*					
Rifampin	*rpoB*	98.2%	91.3%	97.8%	97.1%
Isoniazid	*katG, inhA*	96.4%	89.9%	98.8%	99.4%
GENOTYPEMTBDR*sl* V.2.0					
Fluoroquinolone	*gyrA, gyrB*	86%		98.5%	
Second-line injectables	*rrs, eis*	87.3%		99.5%	

*Direct = testing of smear-positive sputum specimens; indirect = testing of culture; insufficient data to compare indirect vs. direct testing for GenoTypeMTBDR*s*/v.2.0.

alone; empiric therapy may still be warranted despite negative TST and IGRA results if suspicion for active disease is sufficiently high.

Drug Susceptibility Testing

Determination of susceptibility to antimicrobial agents is of considerable clinical importance. Because of concerns regarding TB caused by drug-resistant organisms, drug susceptibility testing is recommended for all initial *M. tuberculosis* isolates. Unfortunately, due to lack of resources, drug susceptibility testing is not done in most high-burden areas or is limited to *M. tuberculosis* strains isolated from patients at high risk of having drug-resistant TB. There are two general methods for determining resistance: phenotypic and genotypic.[78] Some of the methods are designed to identify *M. tuberculosis* and determine the drug susceptibility in the same test, such as MODS, Xpert MTB/RIF, and line probe assays, all of which are described in the preceding section on *M. tuberculosis* identification.

The *phenotypic methods* are based on culture of *M. tuberculosis.* There are two methods: absolute and proportional. These can be done in liquid or solid media. The reference standard is the proportional method, and it is recommended in liquid media. The proportional methods involve inoculating one or more dilutions of cultured mycobacteria on drug-free media and on media containing appropriate concentrations of antituberculosis drugs. Resistance is generally considered to be present when the growth on the drug-containing medium is 1% or more of the control growth on the drug-free media.

There are several approaches to detect mycobacterial growth.[79] The colorimetric method is based on the reduction of an oxidation-reduction indicator (i.e., alamarBlue, resazurin, or tetrazolium) added to the culture media after the cells of *M. tuberculosis* are exposed to the antibiotic. Resistance to antibiotics is identified by the presence of a change in color in the media due to the oxidation/reduction process by viable mycobacteria. This method is highly sensitive and specific for the detection of rifampin and isoniazid resistance (98% and 97% sensitive, respectively; 99% and 98% specific, respectively) when compared with conventional culture-based drug susceptibility methods.[78,80] The nitrate reductase assay is based on the ability of *M. tuberculosis* to reduce nitrate to nitrite, also detected by a color reaction. The sensitivity of the test was 97%, and the specificity was 100% for the detection of rifampin resistance and 97% and 99%, respectively, for detection of isoniazid resistance.[78,80]

Testing for susceptibility to isoniazid and rifampin is accurate,[80] and resistance to rifampin has been used as an indicator for multidrug-resistant TB.[81] Testing for susceptibility to streptomycin, ethambutol, and pyrazinamide is less reliable and reproducible.[80] Testing for second-line drugs is generally performed in reference laboratories and is recommended mainly for *multidrug-resistant* strains. Critical drug concentrations have been established and resistance testing is recommended preferably using automated liquid culture systems for all WHO group A drugs (moxifloxacin, levofloxacin, bedaquiline, and linezolid), the WHO group B drug clofazimine, and the group C drugs (amikacin, delamanid, and pyrazinamide[82]). However, pyrazinamide resistance testing can lead to high rates of false-positive results without appropriate quality assurance. Testing for resistance to the other recommended second-line drugs (group B: cycloserine, terizidone; group C: ethambutol, ethionamide, prothionamide, para-aminosalicylic acid, imipenem-cilastatin, meropenem) is not standardized and not currently recommended.[82]

The *genotypic methods* to identify drug resistance are integrated with the *M. tuberculosis* identification methods; therefore, these methods are faster than culture-based tests. The genotypic methods are based on the detection of drug resistance–associated mutations: mutations in the *rpoB* rifampin resistance–determining region are present in 96% of rifampin-resistant strains,[83] mutations in *katG* or *inhA* in 65–75% of isoniazid-resistant strains,[83] and mutations in *gyrA* and *gyrB* in 42–85% of quinolone-resistant strains.[83,84]

In addition to PCR-based genotypic methods, *next-generation sequencing* is increasingly being used to provide comprehensive drug resistance profiles. Next-generation sequencing can provide rapid and comprehensive sequence information for whole genomes or all gene regions of interest, overcoming the limitations of PCR-based genotypic methods. There are at least two commercial targeted next-generation sequencing assays. The Deeplex Myc-TB assay (GenoScreen) identifies mutations in 18 main MTB drug resistance–associated gene targets to detect resistance to 13 anti-TB drugs/drug classes including all first- and most second-line drugs (i.e., injectables, fluoroquinolones, bedaquiline, clofazimine, linezolid, and ethionamide). DeepChek-TB (Advanced Biological Laboratories) identifies the established high- and medium-confidence drug resistance targets for the same 13 anti-TB drugs/drug classes as the Deeplex Myc-TB assay. Both assays can be performed directly on clinical specimens and provide results within 48 hours. Both also include applications for rapid and automated analysis of raw sequence data, user-friendly interpretation, and reporting.[85–90]

A common limitation of all genotypic methods is the inability to detect drug-resistant strains that do not harbor the common mutations. Therefore, it is essential to use conventional phenotypic methods to exclude drug-resistant TB.

EXTRAPULMONARY TUBERCULOSIS

Extrapulmonary TB presents more of a diagnostic problem than does pulmonary TB. In part this relates to its being less common and therefore less familiar to most clinicians.[91,92] In addition, extrapulmonary TB involves relatively inaccessible sites and often, because of the vulnerability of the areas involved, much greater damage can be caused by fewer bacilli. The combination of small numbers of bacilli in inaccessible sites makes bacteriologic confirmation of a diagnosis more difficult, and invasive procedures are frequently necessary to establish a diagnosis. In addition to the need for invasive diagnostic procedures, surgery may be an important component of management.

PLEURAL TUBERCULOSIS

Although the pleural space is within the thorax, for reporting purposes, it is considered an extrapulmonary site of TB. The difference in pathogenesis of pleural TB results in different clinical presentations, approaches to diagnosis, treatment, and sequelae. TB pleuritis may present as either acute or subacute syndromes, likely due to early pathogenesis and host response to infection. The first mechanism manifests early in the course of a tuberculous infection—a few tubercle bacilli may gain access to the pleural space and, in the presence of cell-mediated immunity, can cause an inflammatory response.[93,94] This form of tuberculous pleuritis commonly goes unnoticed, and the process may resolve spontaneously; those with resolved tuberculous pleuritis, however, have a high likelihood of developing active TB in the next 2 years,[95] so tuberculous pleuritis should be considered and treated if found. In some patients, the tuberculous involvement of the pleura is manifested as an acute illness with fever, cough, pleuritic pain, and occasionally dyspnea and weight loss.[96,97] If the effusion is large, it may cause dyspnea, although the effusions are generally small and rarely bilateral.

The diagnosis of pleural TB is generally established by analysis of pleural fluid and by a pleural biopsy with concomitant sputum evaluation. In a patient with a pleural effusion that might be tuberculous, a diagnostic thoracentesis should be performed. Sufficient fluid should be obtained for cell count, cytologic examination, biochemical analysis, and microbiologic evaluation, but enough fluid should be left to allow a needle biopsy to be performed if the original specimen proves to be exudative and no diagnosis is evident. Diagnosis of TB pleuritis requires identification of the bacilli in either fluid or pleural tissue using microscopy, GeneXpert, or culture; or by visualization of caseating granulomas in pleural tissue biopsy. The fluid is nearly always straw colored, although it may be slightly bloody. Leukocyte counts are usually in the range of 100 to 5000 cells/μL.[98] Early in the course of the process, polymorphonuclear leukocytes may predominate, but subsequent influx of lymphocytes causes them to predominate later. The fluid is exudative, with a protein concentration greater than 50% of the serum protein concentration, and the glucose level may be normal to low. Therefore lymphocyte to neutrophil ratio for exudative effusions is typically greater than 0.75, which reflects a later stage in the course of an effusion, when lymphocytes predominate.[99]

The second variety of tuberculous involvement of the pleura, which is much less common than tuberculous pleurisy with effusion, is a true empyema that follows the spilling into the pleural space of a large number of organisms, usually from rupture of a cavity or an adjacent parenchymal focus via a bronchopleural fistula.[100] Tuberculous empyema is usually associated with evident pulmonary parenchymal disease on chest films. In this situation, the fluid generally is thick and cloudy and may contain cholesterol, which causes the fluid to look like chyle. The fluid is exudative and usually has a relatively high white blood cell count, nearly all of which are lymphocytes. In TB empyema, acid-fast smears and mycobacterial cultures are usually positive, making pleural biopsy unnecessary.

Diagnosis of non-empyematous pleural TB, a paucibacillary disease, remains challenging. Because few organisms are present in the pleural space, acid-fast smears of pleural fluid are rarely positive, and *M. tuberculosis* is isolated by culture in only 20–40% of patients with proven tuberculous pleuritis.[96,101] A single closed-needle biopsy of the pleura with a Cope or an Abrams needle, with collection of three or four specimens for histologic examination, acid-fast staining, and culture of the tissue, confirms the diagnosis in approximately 65–75% of patients in whom tuberculous pleuritis is ultimately diagnosed. NAATs such as Xpert MTB/RIF have variable sensitivity in pleural fluid, likely due to the paucibacillary nature of the disease. But in pleural tissue, Xpert MTB/RIF, for example, has a sensitivity of 90% and a specificity of 90–100%.[102] A second set of specimens in patients whose initial biopsy is negative increases the yield to 80–90%.[101] The results of thoracoscopy are nearly always diagnostic, but the procedure is invasive, costly, and not always available. In a patient with an exudative lymphocytic pleural effusion that remains undiagnosed after a full evaluation, including pleural biopsy, and who has a positive tuberculin reaction or IGRA result, antituberculosis treatment should be initiated.

Challenges with diagnosis have led to increased interest in biomarkers to assist in clinical decision making and diagnosis of pleural TB. *Adenosine deaminase* (ADA) is a T-lymphocyte enzyme that has been shown to have high sensitivity (93%) and specificity (92%) for diagnosing pleural TB[103] when present at greater than 35 U/L in pleural fluid. The effect of variability in laboratory techniques for measuring ADA has not been shown to affect diagnostic accuracy.[104] A significant exception to the utility of ADA has been in diagnosing TB pleuritis in HIV-infected patients and others with acquired or induced immunosuppression, including the elderly who have fewer functional lymphocytes.[105] Individuals with parapneumonic effusions and empyemas as well as lymphomas may test as false positives for pleural TB based on their high ADA levels. Two additional biomarkers, *interferon* (IFN)-γ and *interleukin* (IL)-27, have been considered for the diagnosis of pleural TB and have been reported to have both high specificity in HIV-infected and HIV-uninfected patients. However, sensitivity is considerably lower than for ADA (sensitivity of 89% and 94%, in IFN-γ and IL-27, respectively).[106,107] In addition, unlike with ADA, there are no established guidelines for IFN-γ and IL-27 thresholds most predictive of pleural TB, and testing is too costly for routine health care settings.[108] The evidence concerning ADA test characteristics for the general population (not HIV-infected or immunosuppressed individuals) suggests that, even in settings with low to medium incidence of TB, pleural fluid ADA should be used to rule out suspected TB and should be performed before considering more invasive and potentially morbid procedures such as closed pleural biopsies.[108]

DISSEMINATED TUBERCULOSIS

Miliary TB, although it nearly always involves the lungs, is considered extrapulmonary because of the multiplicity of

organs affected. The term *miliary* is derived from the similarity of the lesions to millet seeds. Grossly, these lesions are 1- to 2-mm yellowish nodules that are granulomas on histologic examination.

Because of the multisystem involvement in disseminated TB, the clinical manifestations are protean. Initial screening laboratory studies are not particularly helpful. The chest radiograph, however, is abnormal in most but not all patients with disseminated TB: the frequency of a classic miliary pattern has ranged from 50–90% (See Fig. 53.3). Overall, it appears that, at the time of diagnosis, approximately 85% of patients have the diffuse tiny nodules characteristic of miliary TB.[109] Other abnormalities may be present as well. These include upper lobe opacities with or without cavitation, pleural effusion, and pericardial effusion. As noted previously, HIV-infected patients may not be able to form granulomas; thus, they may have a diffuse uniform pattern of opacification instead of discrete individual lesions.

Autopsy series have shown the liver, lungs, bone marrow, kidneys, adrenal glands, and spleen to be the organs most frequently involved in miliary TB, although any organ can be the site of disease.[110] Because of the multiplicity of sites involved, there are many potential sources of material to provide a diagnosis. Acid-fast smears of sputum are positive in 20–25% of patients (even when the patient is not spontaneously coughing), and cultures of sputum are positive in 30–65%.[111–113] In a patient with an abnormal chest radiograph and negative sputum examinations, bronchoscopy should be the next step, with appropriate biosafety protections for the medical staff. Combinations of bronchoalveolar lavage culture and PCR in combination with transbronchial biopsy can increase the diagnostic rate of culture-positive, smear-negative, and PCR-negative TB to 92%.[114,115] Other potential sites for biopsy include liver and bone marrow, each of which has a high likelihood of showing granulomas (70–80%), but only a 25–40% chance of providing bacteriologic confirmation; urine cultures may be positive in up to 25% of patients.[112,113] Selection of other potential sources of diagnostic material should be guided by specific findings.

The role of rapid NAATs for identification of *M. tuberculosis* in patients with miliary TB has not been defined, and neither of the two tests licensed by the U.S. Food and Drug Administration is approved for nonrespiratory specimens, although the WHO recommends Xpert MTB/RIF for use with specimens from extrapulmonary sites.[116] The reported data are difficult to interpret because, often, the results of specimens from different sites are combined, patients are selected by a variety of criteria, and test performance varies.[117–119] In contrast, several studies have shown that Xpert MTB/RIF can provide rapid molecular diagnostic assessment when extrapulmonary TB is suspected. The growing body of literature, including two large studies, demonstrated a sensitivity of 81% and specificity of 99%.[120–122]

Before the era of chemotherapy, disseminated TB was uniformly fatal. With recognition and treatment, however, the reported case-fatality rates range from 29–64%.[113] Meningeal involvement increases mortality and, when it is present, the duration of standard chemotherapy should be extended from 6 to 9 or 12 months, and corticosteroids may be useful to reduce mortality.[123]

LYMPHATIC TUBERCULOSIS

Tuberculous lymphadenitis usually presents as painless swelling of one or more lymph nodes. The nodes most commonly involved are those of the cervical chain or supraclavicular fossa. Frequently the process is bilateral, and other noncontiguous groups of nodes can be involved. At least initially, the nodes are discrete and the overlying skin is normal. With ongoing disease, the nodes may become matted and the overlying skin inflamed. Rupture of the node can result in formation of a sinus tract, which may persist for years. Although cervical lymphadenopathy (i.e., scrofula) is one of the most common forms of extrapulmonary TB, there may also be axillary and inguinal TB lymphadenopathy. Intrathoracic adenopathy, with or without concomitant pulmonary TB, can cause compression of bronchi and atelectasis, thereby leading to lung infection and perhaps bronchiectasis. Although rare, upper airway obstruction may result from cervical node enlargement. Chylothorax and chylous ascites have resulted from intrathoracic or abdominal node involvement with obstruction of the thoracic duct or retroperitoneal lymphatics. Epidemiologically, TB lymphadenitis is rarely associated with pulmonary TB but is associated with HIV infection and is slightly more likely to affect women than men.[124] TB lymphadenitis may also appear or worsen as a manifestation of immune reconstitution inflammatory syndrome among HIV-infected individuals (Fig. 53.6). Finally, TB lymphadenitis has historically been more prevalent in children than adults; however, increasing evidence suggests that the prevalence is actually higher in adolescents and young adults than in children.[125]

The diagnosis of tuberculous lymphadenopathy is established by lymph node biopsy or aspiration with histologic examination, including stains for acid-fast organisms, and culture of the material. Smears show acid-fast organisms in approximately 25–50% of biopsy specimens, and *M. tuberculosis* is isolated in approximately 70% of instances in which the final diagnosis is considered to be TB.[126] Caseating granulomas are seen in nearly all biopsy specimens from immunocompetent patients. In immunodeficiency states, granulomas may be poorly formed or absent.[127]

GENITOURINARY TUBERCULOSIS

Genitourinary TB is a common form of extrapulmonary TB, accounting for 15–40% of all extrapulmonary TB cases.[128] In patients with genitourinary TB, local symptoms predominate and systemic symptoms are less common.[129,130] Delayed diagnosis and care can lead to serious sequelae, including renal failure and death. Delays in diagnosis typically happen because of subtle initial symptoms such as dysuria and increased urinary frequency that later can progress to hematuria, flank pain, and ultimately renal failure.[131] However, in general the symptoms are subtle, and often there is advanced destruction of the kidneys by the time a diagnosis is established.[132] Whereas it is suspected that genitourinary TB predominantly affects females, the



Figure 53.6 Tuberculous lymphadenitis in a patient with immune reconstitution inflammatory syndrome after initiation of antiretroviral therapy. With development of immune reconstitution inflammatory syndrome, there was swelling of an anterior cervical node and onset of purulent drainage from the node. (Courtesy Dr. Henry M. Blumberg, Emory University.)

true burden of disease in women is likely underreported. In women, genital involvement is more common than in men and may cause pelvic pain, menstrual irregularities, and infertility as presenting complaints; however, these symptoms are likely indolent, underreported, and receive TB evaluation only after infertility is noted.[130,133] In men, a painless or only slightly painful scrotal mass is probably the most common presenting symptom of genital involvement, but symptoms of prostatitis, orchitis, or epididymitis may also exist.[129] A substantial number of patients with any form of genitourinary TB are asymptomatic, and the disease is detected because of an evaluation for an abnormal urinalysis. In patients with renal or genital TB, urinalyses are abnormal in more than 90%; the main findings are pyuria, hematuria, or mixed pyuria and hematuria. Pyuria in an acidic urine with no organisms isolated from a routine urine culture should prompt an evaluation for TB. Occasionally, when there is an isolated genital focus of disease or when a tuberculous kidney is blocked by a ureteral stricture, the urinalysis may be normal and cultures may be sterile.

The suspicion of genitourinary TB should be heightened by the presence of abnormalities on the chest film. In most series, 50–75% of patients have chest radiographic abnormalities, although many of these may be the result of previous, not current, pulmonary TB.[129,130] When genitourinary TB is suspected, at least three first-voided early morning urine specimens should be collected and stained for AFB and cultured for mycobacteria. In settings with heightened risk of drug-resistant TB, drug susceptibility testing should be conducted. In men, saprophytic *Mycobacterium smegmatis* may cause a positive smear. However, in the presence of abnormalities suggesting TB, the finding of a positive smear should be interpreted as confirming the diagnosis of genitourinary TB until the results of cultures are known. *M. tuberculosis* is isolated from the urine in 80–95% of cases of genitourinary TB.[129,130] Diagnosis of isolated genital lesions usually requires biopsy because the differential diagnosis often includes neoplasia as well as other infectious processes. There are advances being made in the diagnosis of genitourinary TB. For example, one multicenter evaluation of Xpert MTB/RIF for detecting urinary tract TB from urine samples demonstrated a sensitivity of 94% and specificity of 89% in comparison to the gold standard of liquid culture.[134] Additional studies are required to evaluate the utility of Xpert testing for rapid diagnosis of genitourinary TB.

Positive urine cultures may manifest in the absence of any clinical, laboratory, or radiographic findings, which suggests concomitant genitourinary TB in patients with other forms of TB. Bentz and colleagues[135] found unanticipated positive urine cultures in 21% of patients with other extrapulmonary forms of TB and in 5% of those with pulmonary TB alone.

Renal TB, at least as indicated by a positive urine culture, may develop in patients with HIV infection. In one series, positive urine cultures were found in 12 (71%) of 17 cultures submitted in patients with TB and advanced HIV infection, although this was not a systematic sampling.[136]

BONE AND JOINT TUBERCULOSIS

It is presumed that most osteoarticular TB results from endogenous reactivation of foci of infection seeded during the initial bacillemia, although spread from paravertebral lymph nodes has been postulated to account for the common localization of spinal TB to the lower thoracic and upper lumbar vertebrae. It is also postulated that the predilection for TB to localize in the metaphyses of long bones is due to the relatively rich blood supply and scarcity of phagocytic cells in this portion of the bone.[137] After beginning in the subchondral region of the bone, the infection spreads to involve the cartilage, synovium, and joint space. This produces the typical findings of metaphyseal erosion and cysts and loss of cartilage with narrowing of the joint space. Typically, in the spine, these changes involve two adjacent vertebrae and the intervertebral disc (Fig. 53.7). An "atypical" form of spondylitis without evidence of disc involvement may be seen and may account for more than half of the patients.[138–140] Paravertebral or other para-articular abscesses may develop with occasional formation of sinus tracts. Although weight-bearing joints are the most common sites for skeletal TB, any bone or joint may be involved.[137] In most series of osteoarticular TB, TB of the spine (Pott disease) makes up 50–70% of the cases reported.[141,142] In adults, the lower thoracic and upper lumbar vertebrae are most commonly involved, whereas in children the upper thoracic spine is the most frequent site. The hip or knee is involved in 15–20% of cases, and shoulders, elbows, ankles, wrists, and other bones or joints also make up 15–20%. Usually only one bone or joint is involved, but occasionally the process may be multifocal. Evidence of either previous or current pulmonary TB is found in approximately half the reported patients, and other extrapulmonary sites may be involved as well.

The first diagnostic test undertaken is usually a radiograph of the involved area. Early in the process, the only abnormality noted may be soft tissue swelling. MRI of the spine is considerably more sensitive than routine radiographs and should be obtained when there is a high index of suspicion of an infectious process. MRI can diagnose a tuberculous bone lesion with 100% sensitivity and 88% specificity, allowing for diagnosis before deformity develops.[143] Findings on MRI consistent with osteoarticular TB include disease of the vertebral bodies, disk destruction,

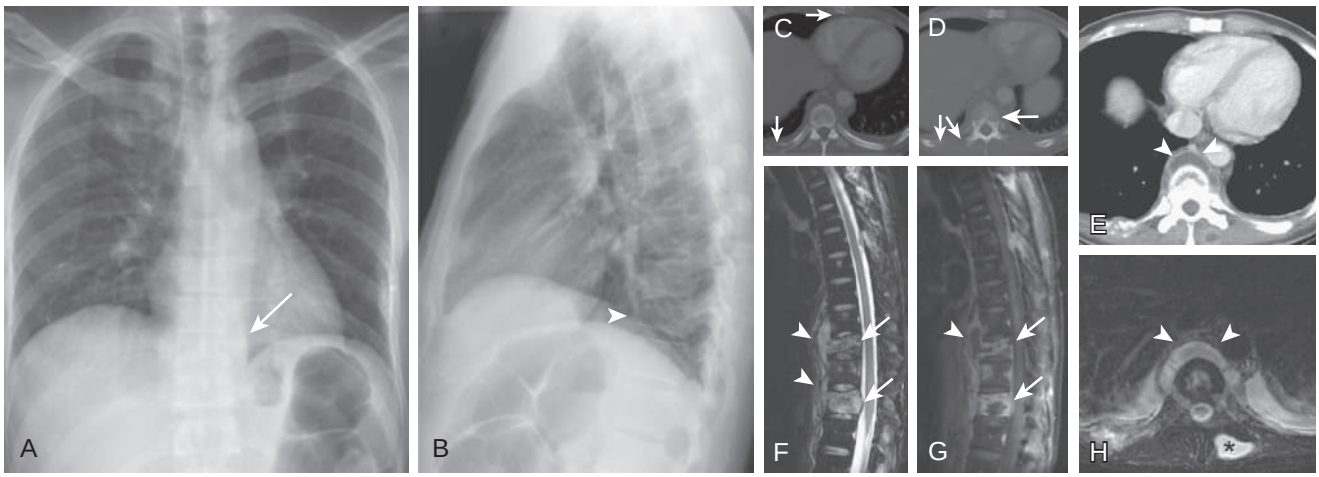

Figure 53.7 Tuberculosis involving the spine. (A) Frontal and (B) lateral chest radiographs show left inferior paraspinous line displacement (*arrow,* A) consistent with a posterior mediastinal mass. The lateral chest radiograph shows loss of height of a thoracic vertebral body (*arrowhead*) at this level, but the adjacent intervertebral disc spaces are maintained. Contrast-enhanced axial chest computed tomography displayed in bone (C–D) and soft tissue (E) windows shows lytic vertebral body destruction (*long arrows,* D) at the level of vertebral body loss of height seen on the lateral chest radiograph (B). Osseous lytic foci are also present in the sternum (*short arrows,* C) and posterior ribs (*short arrows,* C–D). A paraspinous fluid collection with peripheral enhancement, consistent with an abscess (*arrowhead,* E) is seen anterior to the involved thoracic vertebral body. Sagittal T2-weighted (F) and contrast-enhanced T1-weighted (G) and axial T2-weighted (H) magnetic resonance images show the anterior paraspinous abscesses (*arrowhead*), typical of subligamentous spread. Note the extensive high signal within the vertebral bodies (*arrows,* F) representing bone marrow edema. The clear vertebral body enhancement (*arrows,* G) indicates the presence of osteomyelitis. Note the relative sparing of the intervertebral disc spaces, typical of granulomatous infections and distinct from the common appearance of other causes of bacterial osteomyelitis. Extensive fluid collections are seen in the left erector spinae muscle (*asterisk*) and involve the adjacent right posterior rib as well. These findings were all the result of tuberculosis. (Courtesy Michael B. Gotway, MD.)

cold abscess, vertebral collapse, and presence of vertebral column deformities.[144]

The differential diagnosis of vertebral TB includes brucellar spondylitis, pyogenic spondylitis, sarcoidosis, osteoporosis, and metastatic disease, including lymphoma and multiple myeloma.[145] Confirmation of the diagnosis is obtained by aspiration of joint fluid or periarticular abscesses or by biopsy of bone or synovium with histologic and microbiologic evaluation of the material obtained. Acid-fast stains are positive in 20–25% of samples of joint fluid, and *M. tuberculosis* is isolated in approximately 60–80% of them.[137] Biopsy specimens of synovium or bone have a higher yield and enable histologic examination as well. More recently, the use of Xpert MTB/RIF for diagnosis of bone and joint TB demonstrates good diagnostic accuracy irrespective of the type of specimen sampled.[146] The pooled sensitivity and specificity of Xpert MTB/RIF were 81% and 99% compared to a composite reference standard, respectively, and 96% and 85% compared to culture, respectively. Evidence of granulomatous inflammation even in the absence of bacteriologic proof of the diagnosis is sufficient evidence of TB to begin therapy unless another cause is found.

CENTRAL NERVOUS SYSTEM TUBERCULOSIS

Central nervous system (CNS) manifestations of TB and their sequelae can be challenging to diagnose because the symptoms and imaging studies of CNS TB are often indistinguishable from those of other diseases. The most common CNS manifestations of TB include TB meningitis and intracranial tuberculomas.

TB meningitis is the most lethal form of TB. If left untreated, TB meningitis is fatal, with a median time to death from symptom onset of 19 days.[147] Among adults, HIV is the single most important epidemiologic driver of disease, likely due to impaired host response to the pathogen, particularly in the CSF.[148] Despite this, evidence is equivocal on whether HIV-infected individuals have different symptomatology from TB meningitis than HIV-noninfected persons; however, it is more lethal, with a mortality rate approaching 50% for treated patients with HIV.[149] While TB meningitis represents approximately 1% of TB cases among adults, incidence rates are as high as 10% in children.[148] Meningitis is thought to result from direct meningeal seeding and proliferation during a tuberculous bacillemia either at the time of initial infection or reactivation of an old pulmonary focus, or it can also result from reactivation of an old parameningeal focus with rupture into the subarachnoid space.[150] The consequences of subarachnoid space contamination include diffuse meningitis, a localized arteritis, encephalitis, and myelitis. The symptoms depend primarily on which of these processes predominates. With meningitis, the process is primarily located at the base of the brain.[151] Symptoms therefore include those related to cranial nerve involvement in addition to headache, decreased level of consciousness, and neck stiffness.[148] The duration of illness before diagnosis is variable. In a large series of patients, the average duration of illness was 12 days, although the range between symptom onset and presentation is between 5 and 30 days and does not vary based on comorbid conditions including HIV coinfection.[152] Although symptom duration less than 5 days has been used to distinguish between bacterial meningitis and TB meningitis in children and immunosuppressed individuals, it is important to note that subacute symptoms (>5 days) can also be consistent with cryptococcal meningitis.[153] In most series, more than 50% of patients with meningitis have abnormalities on chest radiograph consistent with an old or current tuberculous process, often miliary TB. At autopsy, disseminated disease is found in a high percentage of patients with meningitis.

In patients with tuberculous meningitis, sputum cultures have been positive in 40–50%; thus, a substantial number of patients have pulmonary and systemic symptoms in addition to those referable to the CNS. Patients in whom arteritis is the predominant manifestation of meningitis can present with a variety of focal CNS ischemic syndromes in addition to the symptoms already described.

In tuberculous meningitis, the lumbar puncture usually shows increased opening pressure, and the CSF usually contains between 10 and 1000 cells/μL.[91,152] In approximately 65–75% of patients, lymphocytes predominate, whereas polymorphonuclear leukocytes predominate in the remainder, generally early in the course of the illness.[154] More recently, specific genotypes for *leukotriene A4 hydrolase* have been identified that are linked to either inadequate inflammatory response or hyperinflammation in response to mycobacterial infection.[155] While routine genotyping of individuals with TB meningitis is not currently clinically feasible in most contexts, it is important to note that different outcomes to adjuvant use of corticosteroids in the treatment of TB meningitis may be linked to these leukotriene A4 hydrolase genotypes. A recent systematic review and meta-analysis, however, showed that use of corticosteroids as adjuvant therapy for TB meningitis drastically reduced mortality by 25%.[156] The CSF protein concentration is elevated in nearly all patients. Very high protein concentrations have been associated with a poor prognosis; the glucose concentration in CSF is usually low, but not as low as that often found in pyogenic bacterial meningitis.[152,157] Acid-fast organisms are seen on smears of CSF in only 10–20% of patients, and the rate of culture positivity varies from 25–80% but is generally in the lower end of the range.[152] In a substantial number of patients, *M. tuberculosis* is isolated from other sources, which, in the presence of compatible CSF findings, is sufficient to diagnose tuberculous meningitis. Additional potential CSF biomarkers include CSF ADA, which may be considered as a rule-in test for levels greater than 8 U/L or a rule-out test for levels less than 4 U/L.[158] However, CSF ADA cannot distinguish between bacterial meningitis and TB meningitis. CSF tryptophan may be a useful metabolite for diagnosing TB meningitis. In one observational study, it was differentially detected in patients with TB meningitis as compared to those without disease, and had a substantially higher level in patients who died from TB meningitis than in those who survived.[157] In view of the severity of TB meningitis, a presumptive diagnosis justifies empirical treatment if no other diagnosis can be established promptly. Because of the difficulty in establishing a diagnosis of TB meningitis by bacteriologic methods, a consensus case definition has been proposed by Marais and colleagues[159] that supports a scoring system based on clinical manifestations, CSF studies, CNS radiographic findings, and findings of TB elsewhere as well as the exclusion of other explanatory diagnoses (Table 53.1).

A meta-analysis of 14 studies of NAATs for the diagnosis of tuberculous meningitis found a combined sensitivity of 56% and a specificity of 98%.[117] Thus, when a NAAT is positive, one can assume that the etiology is TB, but a negative result does not exclude the diagnosis and should be treated with caution.

The other major CNS form of TB, the tuberculoma, presents a more subtle clinical picture than does TB meningitis.[160] The usual presentation is that of a slowly growing focal lesion, although a few patients have increased intracranial pressure and no focal findings. The CSF is usually normal, and the diagnosis is established by CT or MRI and subsequent resection, biopsy, or aspiration of any ring-enhancing lesion.

Table 53.1 Diagnostic Criteria for Classification of Definite, Probable, Possible, and Nontuberculous Meningitis[159]

	Diagnostic Score
CLINICAL CRITERIA (MAXIMUM 6 POINTS)	
Symptom duration >5 days	4
Systemic symptoms suggestive of tuberculosis (one or more of the following): weight loss (or poor weight gain in children), night sweats, or persistent cough for >2 weeks	2
History of recent (within past year) close contact with an individual with pulmonary tuberculosis or a positive TST or IGRA (only in children <10 years)	2
Focal neurologic deficit	1
Cranial nerve palsy	1
Altered consciousness	1
IMAGING CRITERIA (MAXIMUM 6 POINTS)	
Hydrocephalus	1
Basal meningeal enhancement	2
Tuberculoma	2
Infarct	1
Precontrast basal hyperdensity	2
CSF CRITERIA (MAXIMUM 4 POINTS)	
Clear appearance	1
Cells: 10–500 per μL	1
Lymphocytic predominance (>50%)	1
Protein concentration greater than 1 g/L	1
CSF to plasma glucose ratio of <50% or an absolute CSF glucose concentration <2.2 mmol/L	1
EVIDENCE OF TUBERCULOSIS ELSEWHERE (MAXIMUM 4 POINTS)	
Chest radiograph suggestive of active tuberculosis: signs of tuberculosis = 2; miliary tuberculosis = 4	2/4
CT/MRI/ultrasound evidence for tuberculosis outside the CNS	2
AFB identified or *Mycobacterium tuberculosis* cultured from another source (i.e., sputum, lymph node, gastric washing, urine, blood culture)	4
Positive commercial *M. tuberculosis* NAAT from extraneural specimen	4

A definite diagnosis is considered *M. tuberculosis* culture and/or NAAT positivity. When imaging is not available, a probable diagnosis is considered with a score ≥10 (out of 20); possible, 6–9; and other than TB, <6.

AFB, acid-fast bacilli; CNS, central nervous system; CSF, cerebrospinal fluid; CT, computed tomography; IGRA, interferon-γ release assay; MRI, magnetic resonance imaging; NAAT, nucleic acid amplification testing; TST, tuberculin skin test.

From Marais M, Thwaites G, Schoerman J, et al. Tuberculous meningitis: a uniform case definition for use in clinical research. *Lancet Infect Dis.* 2010;10:803–812.

INTESTINAL TUBERCULOSIS

The clinical manifestations of intestinal TB depend on the areas of involvement. In the gut itself, TB may be in any location from the mouth to the anus, although lesions proximal to the terminal ileum are unusual. The most common sites of involvement are the terminal ileum and cecum; other portions of the colon and the rectum are involved less frequently.[161] In the terminal ileum or cecum, the most common manifestations are pain (which may lead to a misdiagnosis of appendicitis) and intestinal obstruction. A palpable mass may be noted that, together with its radiographic appearance, can easily be mistaken as a carcinoma. Rectal lesions usually present as anal fissures or fistulas or perirectal abscesses. In addition to carcinoma, the differential diagnosis of these findings includes inflammatory bowel disease. Because of the concern regarding carcinoma, the diagnosis often is made surgically.[162] The similarities in symptoms between intestinal TB and inflammatory bowel disease are likely responsible for delays in starting antituberculosis treatment for patients with intestinal TB.[163] Symptoms include abdominal pain, weight loss, nausea, change in bowel habits, and fever. Imaging with abdominal CT scan may be helpful at raising suspicion for intestinal TB. While some findings, such as bowel wall thickening, are relatively nonspecific, other findings, such as lymphadenopathy with central necrosis, are likely to distinguish intestinal TB from inflammatory bowel disease.[164] In addition, colonoscopic evaluation may be particularly helpful both for visualizing intestinal lesions and for obtaining biopsies for histopathologic evaluation. Colonoscopic findings that point towards a diagnosis of intestinal TB include terminal ileitis with ulceration, pseudodiverticulae, and atrophic mucosa.[165] In case series, histopathology provided a diagnosis of intestinal TB in 40–55% of specimens, whereas yield from culture alone was 20–50%.[164,166,167] Finally, histopathology and culture are important in distinguishing intestinal TB from infections caused by *M. bovis* or *M. fortuitum*, which are both linked to consumption of unpasteurized dairy products and can also present with abdominal pain, appendicitis, and peritonitis.[168]

PERITONEAL TUBERCULOSIS

Tuberculous peritonitis commonly causes pain as its presenting manifestation, often accompanied by abdominal swelling. Fever, weight loss, and anorexia are also common. Active pulmonary TB is uncommon in patients with tuberculous peritonitis. Because the process frequently coexists with other disorders, especially cirrhosis with ascites, the symptoms of TB may be obscured. The combination of fever and abdominal tenderness in a person with ascites should always prompt an evaluation for intra-abdominal infection, and paracentesis should be performed. Ascitic fluid in tuberculous peritonitis is exudative and contains between 50 and 10,000 leukocytes/μL, the majority of which are lymphocytes, although polymorphonuclear leukocytes occasionally predominate.[169] Acid-fast organisms are rarely seen on smears of the fluid, and cultures are positive in only approximately 50%, although the yield increases if a large volume of fluid is submitted for culture. Ascitic fluid ADA has a high sensitivity and specificity for tuberculous peritonitis (93% and 96%, respectively).[170] Because of the generally low yield from culture of the ascitic fluid, laparoscopic biopsy is often necessary to confirm the diagnosis using histopathology.

PERICARDIAL TUBERCULOSIS

The most common form or stage of tuberculous pericarditis is characterized by pericardial effusion with little pericardial thickening or epicardial involvement. Because in most instances the fluid accumulates slowly, the pericardium can expand to accommodate large volumes (2 to 4 L) with little apparent hemodynamic compromise. Symptoms of cardiopulmonary origin tend to manifest later and include cough, dyspnea, orthopnea, ankle swelling, and chest pain.[171] The chest pain may occasionally mimic angina but usually is described as being dull, aching, and often affected by position and inspiration.

The pericardial fluid itself is usually serosanguineous or occasionally grossly bloody, is exudative, and has a white blood cell count ranging from 500 to 50,000 cells/μL, with an average of 5000 to 7000 cells/μL.[172] The cells are predominantly mononuclear, although polymorphonuclear leukocytes occasionally predominate. Tubercle bacilli have been identified in pericardial fluid in approximately 40–60% of cases (with higher yield when combined with culture).[172] Biopsy of the pericardium with both histologic and bacteriologic evaluation is much more likely to provide a diagnosis, although a nonspecific histologic pattern and failure to recover the organisms do not exclude a tuberculous cause. Because TB pericarditis represents a disseminated form of TB, chest radiography as well as evaluation of sputum for AFB, TB PCR, and culture should be performed because 30–80% of patients with pericardial TB also have pulmonary TB.[173] Finally, elevated ADA levels in the context of a lymphocytic pericardial exudate are sufficient for a clinical diagnosis, where ADA has a sensitivity of 87% and specificity of 89%. A composite scoring system including pericardial ADA, lymphocyte/neutrophil ratio, peripheral leukocyte count, and HIV status reported a sensitivity of 96% and specificity of 97% for diagnosing tuberculous pericarditis even in the absence of biopsy.[172] Like other forms of extrapulmonary TB, the utility of PCR such as GeneXpert for diagnosis of pericardial TB is equivocal, especially in nonendemic settings. Sensitivity of the test on pericardial fluid has been reported as low as 52% and thus should be included as part of a complete workup but not as a stand-alone diagnostic test.[174]

Chronic fibrotic pericarditis may develop in 30–60% of patients with or without antituberculosis therapy or steroids.[175] Before the advent of antituberculosis therapy, 88% of one series of patients who had tuberculous pericarditis showed evidence of chronic constriction.[176] Constriction has also been observed to develop during the course of antituberculosis chemotherapy, although this appears to be uncommon in patients who have had symptoms for less than 3 months; it is frequent in patients who have had symptoms for more than 6 months. The fibrotic reaction progresses to complete fusion of visceral and parietal pericardium and encasement of the heart in a rigid scar that often becomes calcified. Impairment of coronary circulation is common. At this point the histologic pattern is usually nonspecific; thus, confirmation of a tuberculous etiology is infrequent.

The HIV epidemic has increased the burden of tuberculous pericarditis in endemic settings and is a major consideration in understanding the natural history, clinical manifestations, and treatment of this disease. In contrast to the slowly developing effusion in immunocompetent patients with TB pericarditis, TB pericarditis develops quickly in HIV-infected individuals in whom TB represents the cause of pericarditis 85% of the time.[177] In addition, myocardial damage, or myopericarditis as measured by ST segment changes on electrocardiogram, presents more frequently in HIV-infected patients, and correlates with lower CD4 counts.[178] HIV-infected patients are less likely to develop constrictive pericarditis.[179] Finally, mortality from TB pericarditis is higher in HIV-infected patients than in immunocompetent patients.

The definitive diagnosis of tuberculous pericarditis requires identification of tubercle bacilli in pericardial fluid or tissue. Although not conclusive, demonstration of caseating granulomata in the pericardium and consistent clinical circumstances provide convincing evidence of a tuberculous etiology. Less conclusive but still persuasive evidence is the finding of another form of TB in a patient with pericarditis of undetermined cause. Approximately 25–50% of patients with tuberculous pericarditis have evidence of other organ involvement, particularly pleuritis, at the time pericarditis is diagnosed.[180] Still less direct and more circumstantial evidence of a tuberculous etiology is the combination of a positive intermediate-strength TST or IGRA reaction and pericarditis of unproved cause.

Key Points

- Clinical suspicion for *tuberculosis* (TB) should remain high in endemic settings, or in settings in which patient risk factors and local epidemiology suggest a high risk of infection.
- All patients suspected of having pulmonary TB should have at least two sputum samples collected for acid-fast bacilli smear microscopy and mycobacterial culture and at least one sputum specimen collected for nucleic acid amplification testing.
- Tuberculin skin tests and interferon-γ release assays have no role in the diagnosis of active pulmonary TB but can increase suspicion for active disease among smear-negative individuals with suspected TB.
- Therapeutic trials of antituberculosis chemotherapy may be indicated even if testing of sputum or other specimens is negative, especially when high clinical suspicion remains. However, empirically treated patients require close follow-up to assess for clinical and radiographic improvement.
- Phenotypic drug susceptibility testing is recommended for all initial *M. tuberculosis* isolates; drug resistance is increasingly detected by molecular genotyping assays.
- Extrapulmonary TB should be diagnosed using tissue or fluid sampling from the suspected site of disease, although yield is variable depending on the specimen type, and recommended tests in addition to smear and culture are evolving.

Key Readings

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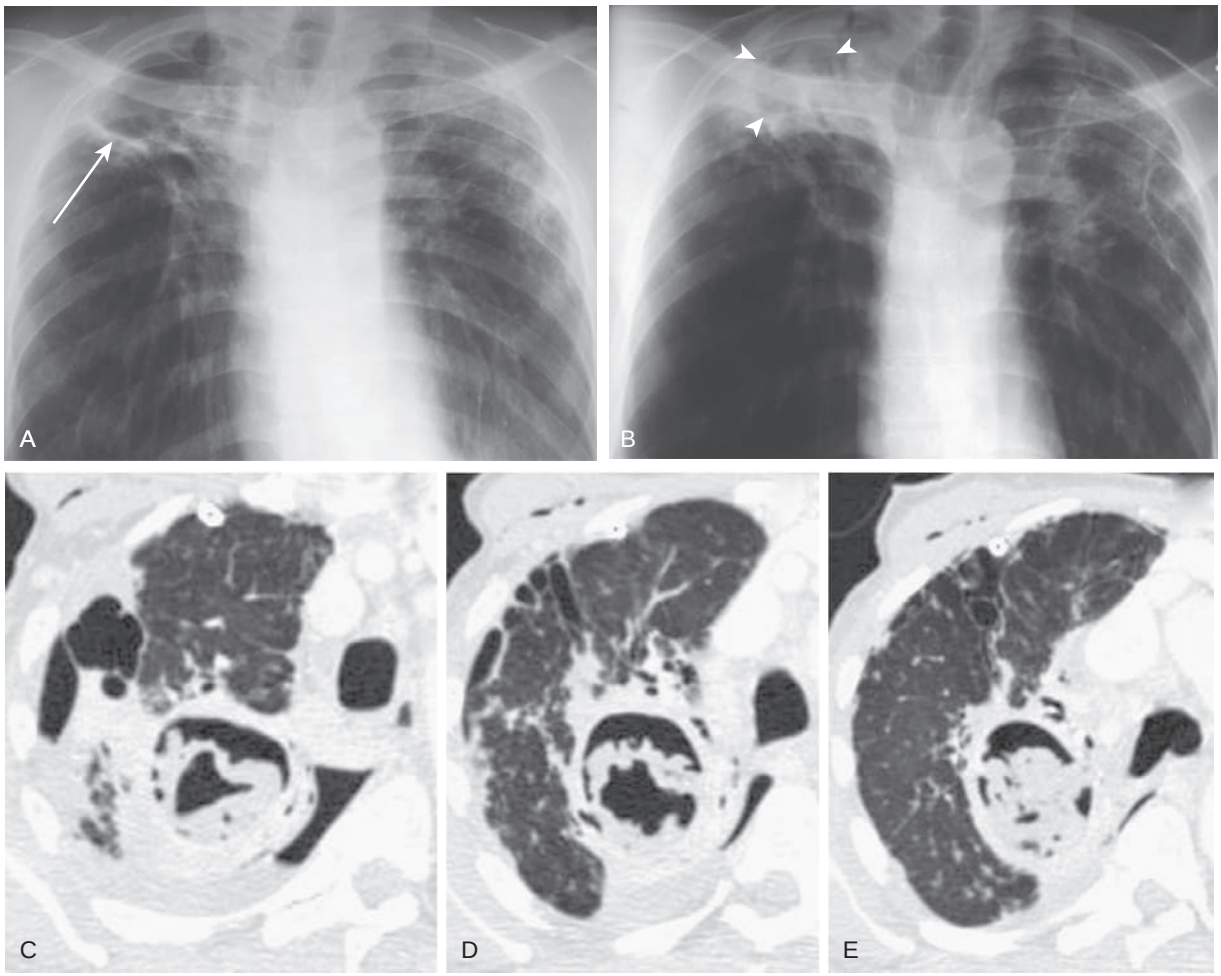
eFIGURE IMAGE GALLERY



eFigure 53.1 Aspergilloma developing in an old tuberculosis cavity. (A) Frontal chest radiograph in a patient with tuberculosis shows bilateral upper lobe fibronodular changes with a right apical cavity (*arrow*). (B) Frontal chest radiograph several years later when the patient complained of hemoptysis shows development of an opacity within the right apical cavity (*arrowheads*) representing aspergilloma. (C–E) Focused axial chest computed tomography confirms the presence of aspergilloma. (Courtesy Michael B. Gotway, MD.)

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54 TUBERCULOSIS: TREATMENT OF DRUG-SUSCEPTIBLE AND DRUG-RESISTANT

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INTRODUCTION

BACKGROUND

Before the availability of effective chemotherapy, tuberculosis was often fatal. Among individuals with smear-positive pulmonary *tuberculosis* (TB), the case-fatality rate was approximately 70%.[1] The era of effective antituberculosis chemotherapy was launched in 1946 with the introduction of streptomycin.[2] In a landmark study considered the first randomized trial in medicine,[3] streptomycin resulted in clinical responses and improved short-term mortality but showed little benefit over 5 years of follow-up due to the emergence of streptomycin-resistant *Mycobacterium tuberculosis*. The use of a two-drug regimen that included *p*-aminosalicylic acid resulted in a significantly decreased risk of streptomycin resistance.[4] This lesson resonates today. Treatment of TB disease requires a combination of drugs because treatment with a single drug fails by selecting for resistant bacteria. TB treatment was greatly enhanced by the introduction of *isoniazid* (INH) in 1952, a drug that is bactericidal and less toxic than the other antituberculous medications of that era. Further studies in the 1960s identified the importance of *rifampin* (RIF) as a sterilizing agent and the advantage of *pyrazinamide* (PZA) for the first 2 months in allowing shorter courses of curative therapy.[4] Studies in multiple international settings led to the regimen that remains the cornerstone of therapy for drug-susceptible TB. Subsequent efforts have sought shorter treatment regimens and new medications for treatment of drug-resistant TB. Governmental and nongovernmental organizations have been essential to the support of research and development of new drugs and regimens.[5] These include not-for-profit product development partnerships such as the Global Alliance for TB Drug Development and the TB Drug Accelerator. The U.S. *Centers for Disease Control and Prevention* (CDC) and National Institutes of Health–supported consortia, including the TB Trials Consortium and *Acquired Immunodeficiency Syndrome* (AIDS) Clinical Trials Group, have performed critical multicenter international trials of novel treatment regimens. Information on drugs in development is available at the Stop TB Partnership's Working Group for New TB drugs site (https://www.newtbdrugs.org/pipeline/clinical).

PRINCIPLES OF TREATMENT

The treatment of TB benefits the individual by limiting organ damage and preventing death and benefits the community by interrupting transmission. Treatment regimens are chosen based on their success in curing the patient of TB

disease while minimizing relapse rates, drug toxicity, selection of resistant bacteria, and medication nonadherence.[2,4] The success of drug treatment depends upon many factors, and studies have found an increased risk of relapse among patients with signs of more extensive disease (e.g., cavitation, more diseased lung on chest radiograph, or higher bacterial burdens),[6–10] and/or slower response to treatment (e.g., delayed culture conversion at 2 or 3 months).[2,7,11,12] More recently, an analysis of data from several contemporary *randomized controlled trials* (RCTs) demonstrated additional risk factors for poor treatment outcomes, including submaximal treatment adherence, *human immunodeficiency virus* (HIV) infection, and low body mass index.[13]

RCTs have supported the use of an initial intensive phase of treatment followed by a continuation phase. Effective, uninterrupted treatment is more important in the *intensive phase* of therapy when the bacillary population is highest and the chance of selecting drug-resistant mutants greatest. During the *continuation phase*, the number of bacilli is much lower, and the goal of therapy is to kill persisting organisms. The preferred regimen for treating adults with TB caused by organisms not known or suspected to be drug resistant consists of an intensive phase of 2 months of INH, RIF, PZA, and *ethambutol* (EMB), followed by a continuation phase of 4 months of INH and RIF (Tables 54.1 and 54.2).[4,14,15] INH and RIF are currently the most important drugs for the treatment of drug-susceptible TB because they are key to effective short-course treatment.

The "three-populations" model of chemotherapy hypothesizes the presence of different populations of *M. tuberculosis* (MTB) bacilli with differing levels of metabolic activity.[16,17] These bacillary populations consist of (1) an actively multiplying extracellular population, (2) a slowly multiplying population present in acidic compartments, and (3) a sporadically multiplying population. The composition of the standard regimen for drug-susceptible TB can be explained by referencing this model.[2,17] INH exhibits the greatest early bactericidal effect (i.e., bacillary death within the first 48 hours of drug action), which greatly reduces the population of extracellular actively multiplying bacilli.[18,19] PZA has high sterilization capacity, and its unique effectiveness against bacilli in acidic environments allows the overall treatment length to be shortened from 9 to 6 months. RIF has excellent sterilizing activity resulting in greater killing of both slowly and sporadically multiplying bacilli.[20] Due to the proportion of new TB cases worldwide caused by organisms resistant to INH, EMB is included in the intensive phase of treatment to protect against the emergence of RIF-resistant bacteria because PZA is not considered protective against the emergence of resistance to other antituberculosis drugs.[16]

See the Appendix on ExpertConsult.com for a detailed description of antituberculous chemotherapeutic drugs.

MECHANISMS AND PHARMACOLOGY OF DRUGS USED TO TREAT DRUG-SUSCEPTIBLE TUBERCULOSIS

INH is a prodrug activated by the mycobacterial enzyme KatG, which exerts its concentration-dependent bactericidal activity by inhibiting mycolic acid synthesis. INH is metabolized by *N-acetyltransferase 2* (NAT2), a hepatic phase II drug-metabolizing enzyme with a trimodal phenotypic distribution,[21] which varies in frequency by ethnicity.[22]

- *Rifampin* (also termed *rifampicin*, [RIF]) is a semisynthetic rifamycin derivative that inhibits bacterial DNA-dependent RNA polymerase and suppresses the early elongation of the nucleotide chain in RNA synthesis. RIF's bactericidal activity is concentration dependent.[20]
- *Pyrazinamide* (PZA) is a prodrug activated by mycobacterial pyrazinamidase to *pyrazinoic acid* (POA). The mechanism of action of POA is incompletely understood and likely relies on multiple targets for effect, including inhibition of fatty acid synthesis.[23] PZA is generally considered bacteriostatic against MTB.
- *Ethambutol* (EMB) inhibits synthesis of arabinogalactan of the mycobacterial cell wall and is bacteriostatic at usual doses.[24]

The *pharmacokinetics* (PKs) of antituberculosis drugs vary in different individuals (see Table 54.3).[18] This is a concern for clinicians because cure of TB is predicated on achieving adequate drug exposure. The use of *pharmacokinetic/pharmacodynamic* (PK/PD) data allows for the most effective use of antimicrobials by achieving maximal pathogen killing in the shortest time.[18] PK thresholds associated with treatment failure in the first-line treatment of drug-susceptible TB have been reported[25] and underscore the wide variability seen in drug exposures, especially in those with HIV, renal, and hepatic disease (see "Therapeutic Drug Monitoring" later).

TB treatment is often straightforward, but it can be complicated. Drug-resistant TB, adverse drug effects, HIV and other comorbidities, and complex drug-drug interactions are some of the situations in which expert consultation should be obtained. Consultation support for TB diagnosis and management is available through local health department TB control programs and/or regional CDC-supported TB Centers of Excellence for Training, Education, and Medical Consultation (http://www.cdc.gov/tb/education/rtmc/default.htm) (Fig. 54.1).

TREATMENT

TREATMENT INITIATION

The decision to initiate antituberculous chemotherapy is based on clinical, radiographic, laboratory, patient, and public health factors. The decision is clear in patients with a positive culture for *M. tuberculosis* or a positive rapid molecular test, but the decision to initiate treatment often must be made before microbiologic confirmation is available. In the presence of clinical evidence of TB, a positive *acid-fast bacillus* (AFB) smear provides strong support for treatment initiation. If the diagnosis is confirmed by isolation of *M. tuberculosis* or a positive rapid molecular test, or is inferred from clinical or radiographic improvement consistent with a response to TB treatment, the regimen is continued to complete a standard course of therapy.

In patients with a positive AFB smear but a negative rapid molecular test,[26,27] it is unlikely that the positive smear is due to *M. tuberculosis*, particularly if molecular testing of a second smear-positive specimen fails to detect *M. tuberculosis*.[28] In these situations, which are suggestive of infection

Table 54.1 Drug Regimens for Microbiologically Confirmed Pulmonary Tuberculosis Caused by Drug-Susceptible Organisms

	INTENSIVE PHASE		CONTINUATION PHASE				
Regimen	**Drugs***	**Interval and Doses† (Minimum Duration)**	**Drugs**	**Interval and Doses†‡ (Minimum Duration)**	**Total Doses**	**Comments‡§**	**Regimen Effectiveness**
1	INH RIF PZA EMB	7 days/wk for 56 doses (8 wk) *or* 5 days/wk for 40 doses (8 wk)	INH RIF	7 days/wk for 126 doses (18 wk) *or* 5 days/wk for 90 doses (18 wk)	130–182	This is the preferred regimen for patients with newly diagnosed pulmonary tuberculosis.	Greater
2	INH RIF PZA EMB	7 days/wk for 56 doses (8 wk) *or* 5 days/wk for 40 doses (8 wk)	INH RIF	Three times weekly for 54 doses (18 wk)	94–110	Preferred alternative regimen in situations in which more frequent DOT during continuation phase is difficult to achieve.	
3	INH RIF PZA EMB	Three times weekly for 24 doses (8 wk)	INH RIF	Three times weekly for 54 doses (18 wk)	78	Use regimen with caution in patients with HIV and/or cavitary disease. Missed doses can lead to treatment failure, relapse, and acquired drug resistance.	
4	INH RIF PZA EMB	7 days/wk for 14 doses then twice weekly for 12 doses‖	INH RIF	Twice weekly for 36 doses (18 wk)	62	Do not use twice-weekly regimens in HIV-infected patients or patients with smear positive and/or cavitary disease. If doses are missed then therapy is equivalent to once weekly, which is inferior.	Lesser

*Other combinations may be appropriate in certain circumstances; additional details are provided in section "Recommended Treatment Regimens for Drug-Susceptible Tuberculosis."
†When DOT is used, drugs may be given 5 days/wk and the necessary number of doses adjusted accordingly. Although there are no studies that compare five with seven daily doses, extensive experience indicates this would be an effective practice. DOT should be used when drugs are administered for fewer than 7 days/wk.
‡Based on expert opinion, patients with cavitation on initial chest radiograph and positive cultures at completion of 2 months of therapy should receive a 7-month (31 wk) continuation phase.
§Pyridoxine (vitamin B_6), 25–50 mg/day, is given with INH to all persons at risk of neuropathy (e.g., pregnant women; breastfeeding infants; persons with HIV; patients with diabetes, alcoholism, malnutrition, chronic renal failure, or with advanced age). For patients with peripheral neuropathy, experts recommend increasing pyridoxine dose to 100 mg/day.
‖See reference 206. Alternatively, some U.S. tuberculosis control programs have administered intensive-phase regimens 5 days/wk for 15 doses (3 wk) then twice weekly for 12 doses.
DOT, directly observed therapy; EMB, ethambutol; HIV, human immunodeficiency virus; INH, isoniazid; PZA, pyrazinamide; RIF, rifampin.
From Nahid P, Dorman SE, et al. Official American Thoracic Society/Centers for Disease Control and Prevention/Infectious Diseases Society of America clinical practice guidelines: treatment of drug-susceptible tuberculosis. *Clin Infect Dis*. 2016;63:e147–e195.

Table 54.2 Doses of Drugs for Treatment of Adults and Children with Drug-Susceptible Tuberculosis

Medication	Administration	Dose*	Notes
INH	Oral: tablets (50/100/300 mg), elixir Intravenous Intramuscular	Daily: 5 mg/kg (max 300 mg), tiw: 15 mg/kg (max 900 mg), biw: 15 mg/kg (max 900 mg)	Avoid taking with fatty foods because absorption is decreased up to 50% No dosing adjustments for renal impairment
RIF	Oral: capsules (150/300 mg) Intravenous	Adults: daily/biw/tiw: 10 mg/kg (max 600 mg) Children†: daily/biw/tiw: 10–20 mg/kg (max 600 mg)	Avoid taking with fatty foods because absorption is decreased No dosing adjustments for renal impairment
PZA	Oral: tablets (500 mg)	40–55 kg: 1000 mg (daily), 1500 mg (tiw), 2000 mg (biw) 56–75 kg: 1500 mg (daily), 2500 mg (tiw), 3000 mg (biw) 76–90 kg: 2000 mg (daily), 3000 mg (tiw), 4000 mg (biw) <40 kg: 30–40 mg/kg (daily), 50 mg/kg (tiw/biw)	If CrCl < 30 mL/min, reduce dose to 25–35 mg/kg tiw Consider not using if patient has gout
EMB	Oral: tablets (100/400 mg)	40–55 kg: 800 mg (daily), 1200 mg (tiw), 2000 mg (biw) 56–75 kg: 1200 mg (daily), 2000 mg (tiw), 2800 mg (biw) 76–90 kg: 1600 mg (daily), 2400 mg (tiw), 4000 mg (biw) <40 kg: 20 mg/kg (daily), 50 mg/kg (tiw/biw)	If CrCl < 30 mL/min, reduce dose to 20–25 mg/kg tiw Avoid antacids within 2 hours of EMB administration

*Dosing based on actual weight is acceptable in patients who are not obese. For obese patients (>20% above ideal body weight), dosing based on ideal body weight may be preferred for initial doses.
†Adult dosing begins at 15 years of age or weight >40 kg in younger children.
biw; twice weekly; CrCl, creatinine clearance; EMB, ethambutol; INH, isoniazid; max, maximum; PZA, pyrazinamide; RIF, rifampin; tiw, three times weekly.
From Nahid P, Dorman SE, et al. Official American Thoracic Society/Centers for Disease Control and Prevention/Infectious Diseases Society of America clinical practice guidelines: treatment of drug-susceptible tuberculosis. *Clin Infect Dis*. 2016;63:e147–e195.

Table 54.3 Pharmacology and Adverse Effects of Antituberculosis Medications

Drug	Pharmacology	Adverse Effects
INH	Prodrug, activated by bacterial catalase/peroxidase, KatG Peak plasma concentration: 1–2 hr after ingestion C_{max}: 3–5 μg/mL Half-life: 2–5 hr (slow acetylators), 0.5–2 hr (fast acetylators) Metabolism: hepatic acetylation (NAT2 enzyme) and excreted in urine	Liver injury Peripheral neuropathy due to pyridoxine deficiency; give pyridoxine (25–50 mg) with each INH dose if at risk (patients with diabetes, HIV, renal disease, alcohol abuse, malnutrition, pregnancy) or if neuropathy develops CNS toxicity: headache, poor concentration, depression, seizures, optic neuritis Rash Hematologic abnormalities INH inhibition of cytochrome P-450 causes increases in serum concentrations of certain medications including phenytoin, carbamazepine, valproic acid, clopidogrel, warfarin, theophylline, ketoconazole
RIF	Peak plasma concentration: 1–4 hr after ingestion C_{max}: 8–24 μg/mL Half-life: 2–3 hr; prolonged with liver disease Metabolism: hepatic deacetylation to enterohepatically recirculated active metabolite	Liver injury: usually cholestatic pattern of injury GI upset Hypersensitivity (flulike syndrome); symptoms include fever, headache, malaise, myalgias that start 1–2 hr postadministration; may resolve with change from intermittent to daily RIF therapy Rash Hematologic abnormalities Discoloration of body fluids (e.g., urine, feces, tears) Cytochrome P-450 induction causes decrease in serum concentrations of many medications, including antiretrovirals, anticonvulsants, anticoagulation, immunosuppressants, chemotherapy, methadone, oral contraceptives, levothyroxine, and antihypertensives
PZA	Prodrug, activated by bacterial pyrazinamidase enzymes Peak plasma concentration: 1–4 hr after ingestion C_{max}: 20–40 μg/mL Half-life: 10 hr Metabolism: hydrolyzed by liver, excreted in urine	Liver injury Arthralgias, gout: consider avoiding in patients with gout GI upset Rash Photosensitivity
EMB	Peak plasma concentration: 2–4 hr after ingestion C_{max}: 2–6 μg/mL Half-life: 3–4 hr Primarily excreted through kidneys in unchanged form Reduce dose in patients with impaired renal function	Optic neuritis: perform patient education, baseline and monthly assessment of visual acuity, and color discrimination while receiving EMB Rash GI upset
Levofloxacin	Peak plasma concentration: 1–2 hr postingestion C_{max}: 8–12 μg/mL Half-life: 6–8 hr Primarily excreted through kidneys in unchanged form; if CrCl < 30 mL/min, administer tiw (not daily)	GI: nausea, vomiting, diarrhea, abdominal pain CNS toxicity: headache, insomnia, dizziness, tremulousness QT prolongation Tendon effects: tendonitis, tendon rupture (more common in elderly) Arthralgias Peripheral neuropathy Rash
Moxifloxacin	Peak plasma concentration: 1–3 hr postingestion C_{max}: 3–5 μg/mL Half-life: 11–13 hr Hepatic metabolism via glucuronide and sulfate conjugation; approximately 45% excreted unchanged in urine and feces	GI: nausea, vomiting, diarrhea, abdominal pain CNS toxicity: dizziness, headache, insomnia, tremulousness, confusion QT prolongation Tendon effects: tendonitis, tendon rupture (more common in elderly) Arthralgias Peripheral neuropathy Rash Liver injury (rare)
Bedaquiline	Peak plasma concentration: 5 hr after ingestion (should be taken with food which increases bioavailability) C_{max}: 2.7 μg/mL (200 mg dose) Half-life: ~5.5 mo Hepatic metabolism via CYP3A4, excreted in feces	Nausea QT prolongation Headache Rash Arthralgia Transaminitis
Linezolid	Peak plasma concentration: 1–2 hr after ingestion C_{max}: 12–24 μg/mL Half-life: 5 hr Hepatic metabolism, urinary excretion	Peripheral neuropathy Hematologic: thrombocytopenia, leukopenia, anemia GI: diarrhea, nausea Optic neuropathy Serotonin syndrome: risk increased in presence of other serotonergic medications

Table 54.3 Pharmacology and Adverse Effects of Antituberculosis Medications—cont'd

Drug	Pharmacology	Adverse Effects
Clofazimine	Peak plasma concentration: 4–8 hr if taken with food (take with food to improve absorption and tolerability) C_{max}: 0.5–2.0 μg/mL Half-life: 70 days Hepatic metabolism, excretion unknown	Skin discoloration (reversible) in 75–100% of patients Photosensitivity GI: abdominal pain, nausea, splenic infarction Dry skin QT prolongation
Cycloserine	Peak plasma concentration: 2–4 hr after ingestion, C_{max}: 20–35 μg/mL Half-life: 12 hr Hepatic metabolism; approximately 65% excreted unchanged in urine	CNS toxicity: lethargy, difficulty with concentration, depression, confusion, psychosis, seizures; pyridoxine may prevent/treat symptoms Peripheral neuropathy Rash
Delamanid	Prodrug, activated by bacterial nitroreductase Peak plasma concentration: 4 hr after ingestion (take with food, which increases bioavailability threefold) C_{max}: 0.37 μg/mL Half-life: 30–38 hr Metabolized by plasma albumin, excreted in feces	GI: nausea, vomiting, abdominal pain Headache, insomnia, dizziness, tinnitus QT prolongation Palpitations
Pretomanid	Prodrug, activated by bacterial nitroreductase Peak plasma concentration: 4–5 hr after ingestion (take with food, which increases bioavailability 75%) C_{max}: 2 μg/mL Half-life: 16–20 hr No single major metabolic pathway identified, although CYP3A4 contributes ~20% to metabolism; excreted in urine and feces	Adverse effects reported based on combination treatment with bedaquiline and linezolid: peripheral and optic neuropathy, QT prolongation Myelosuppression: hematologic: thrombocytopenia, leukopenia, anemia Transaminitis, hepatic toxicity Lactic acidosis GI: diarrhea, nausea Rash Headache

C_{max}, maximum concentration; CNS, central nervous system; CrCl, creatinine clearance; CYP3A4, cytochrome P-450 enzyme; EMB, ethambutol; GI, gastrointestinal; HIV, human immunodeficiency virus; INH, isoniazid; NAT2, *N*-acetyltransferase 2; RIF, rifampin; PZA, pyrazinamide; tiw, three times weekly.

with nontuberculous mycobacteria, it is reasonable to withhold TB treatment pending culture results.

A failure to isolate *M. tuberculosis* from specimens in persons suspected of having pulmonary TB on the basis of clinical and/or radiographic findings does not exclude a diagnosis of active TB. Low bacillary populations, inadequate sputum specimens, temporal variations in the number of expelled bacilli, overgrowth of cultures with other microorganisms, and errors in specimen processing can lead to false-negative results.[28a] Whereas in resource-limited settings empirical initiation of TB treatment is uncommon, U.S. guidelines recommend that empirical treatment with a standard regimen be initiated promptly in patients with a high likelihood of having TB or in those seriously ill with a disorder suspicious for TB, even before AFB smear microscopy, molecular tests, and mycobacterial culture results are known.[29] Use of molecular tests directly on clinical samples has been shown to shorten time to diagnosis,[28,30] and some tests (GeneXpert MTB/RIF, Xpert MTB/RIF Ultra [Cepheid])[31] provide information on drug susceptibility. The decision to treat empirically is based on the risk versus benefits of TB regimens. Severely ill individuals, especially those suspected to have *central nervous system* (CNS) and/or disseminated TB, or those at risk of becoming severely ill, particularly young children (<5 years) and immunocompromised individuals, will benefit from initiation of empirical antituberculosis treatment. The initiation of empirical treatment may enable earlier release from contact isolation, allowing patients to return sooner to work, school, and other social settings while the diagnosis of TB is being further evaluated. Given the low risk of serious adverse effects related to TB medications early in the course of treatment, especially in patients younger than 60 years,[32] the benefits of empirical treatment outweigh treatment-related risks in patients considered to have moderate to high risk for TB.

If empirical treatment is started and adhered to, and serial cultures throughout are negative, patients who show clinical and radiographic improvements at 2 months may be diagnosed with culture-negative TB (discussed later). In patients without a clinical and radiographic response to treatment despite full adherence, treatment for TB may be discontinued and alternative diagnoses should be pursued. If the patient has evidence of latent TB infection (i.e., positive interferon gamma release assay or tuberculin skin test), then consideration of TB preventive therapy is warranted (see Chapters 42 and 51).

RECOMMENDED TREATMENT REGIMENS FOR DRUG-SUSCEPTIBLE TUBERCULOSIS

Recommended treatment regimens for drug-susceptible TB are listed in Tables 54.1 and 54.2. If therapy is being initiated after drug susceptibility test results are known and the patient's isolate is susceptible to both INH and RIF, EMB is not necessary and the intensive phase can consist of INH, RIF, and PZA only. EMB can be discontinued as soon as the results of drug susceptibility studies demonstrate that the isolate is susceptible to INH and RIF.

DOSING FREQUENCY AND TREATMENT ADHERENCE

The most recent *American Thoracic Society/CDC/Infectious Diseases Society of America* (ATS/CDC/IDSA) guidelines recommend that, resources permitting, daily therapy in both

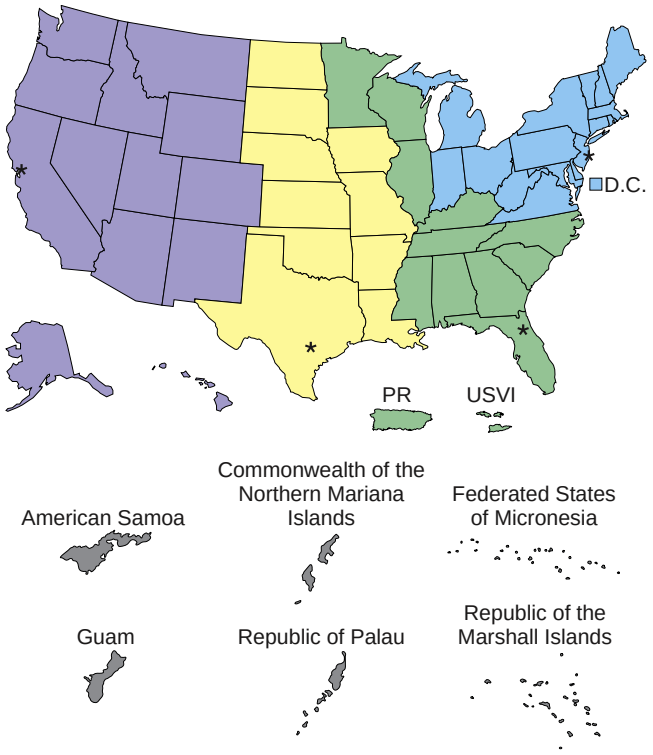

Figure 54.1 Centers for Disease Control and Prevention–funded TB Centers of Excellence for Training, Education, and Medical Consultation. These centers support domestic *tuberculosis* (TB) control and prevention efforts with a focus on increasing knowledge, skills, and abilities for TB prevention and control through communication, education, and training activities (https://sntc.medicine.ufl.edu/rtmccproducts.aspx) and on improving sustainable evidence-based TB clinical practices and patient care through the provision of expert medical consultation. PR, Puerto Rico; USVI, U.S. Virgin Islands. (Courtesy the Centers for Disease Control and Prevention, Atlanta, GA.)

the intensive and continuation phases be used.[29] Since the guidelines were published, a patient-level analysis of several RCTs that evaluated TB treatment regimens has provided new information on adherence, dosing frequency, and outcomes that adds evidence to this recommendation.[13] In that analysis, even minimal nonadherence to a standard treatment regimen was associated with an increased risk of poor treatment outcomes. Greater than 90% (but less than perfect) adherence was associated with a *hazard ratio* (HR) of 2.4 (95% *confidence interval* [CI], 1.6 to 3.6), and 90% or less adherence was associated with an HR of 5.9 (95% CI, 3.3 to 10.5) for poor treatment outcomes. Similarly, a dosing schedule of 5 or 6 out of 7 days was associated with poor treatment outcomes compared to 7 days per week administration.[13] These results support a strict dosing of TB treatment of 7 days per week through the intensive and continuation phases.[13]

PATIENT-CENTERED CARE

It is crucial that the patient be involved in making decisions concerning treatment supervision and overall care for TB. In most public health settings, a patient with TB is assigned a case manager who assesses patient needs and barriers that may interfere with treatment adherence.[33] Together, the case manager and the patient develop an individualized case management plan with interventions to address the identified needs and barriers.[34–36] The plan is reviewed periodically and revised as needed.

DIRECTLY OBSERVED THERAPY

Given the critical importance of chemotherapy for the patient and for public health, ensuring adherence to the treatment regimen is a major focus of the management plan. Management strategies should use a broad range of approaches to maximize treatment completion.[29] Among these, *directly observed therapy* (DOT), the practice of observing the patient swallow the antituberculosis medications, has been widely used as the standard of practice in many programs and deserves special emphasis. DOT, compared to *self-administered therapy*, is associated with improved treatment success (the sum of patients cured and patients completing treatment) and with decreased time-to-sputum smear conversion, but not with significant differences in mortality, treatment completion, and relapse.[29,37] Because DOT is a multifaceted public health intervention that may not be amenable to conventional clinical trial approaches, and because participation in DOT can be advantageous for early recognition of adverse drug reactions and treatment irregularities and for allowing providers to establish rapport with the patient, DOT remains the standard of practice in the majority of TB programs in the United States[38–40] and Europe.[41] DOT decisions about protecting privacy and other concerns must be made in concert with the patient,[41–43] including the location for medication administration. Many TB programs use Internet-based video and mobile phones as less resource-intensive forms of DOT, especially in patients who have demonstrated good adherence with traditional DOT.

PATIENT EVALUATION

Recommended baseline and follow-up evaluations for patients suspected of having TB and treated with first-line medications are summarized in eFig. 54.1. At a minimum, a sputum specimen for AFB smear and culture is obtained at monthly intervals until two consecutive specimens are negative on culture. For patients who had positive AFB smears at the time of diagnosis, follow-up smears may be obtained at more frequent intervals (e.g., every 1–2 weeks until two consecutive specimens are negative) to provide an early assessment of the response to treatment, especially for patients who are awaiting release from isolation.

Susceptibility testing for INH, RIF, EMB, and PZA is performed on an initial positive culture. A rapid molecular test for drug resistance, which identifies mutations associated with resistance to first- and/or second-line antituberculosis medications, is performed in patients at risk for drug-resistant TB.[41,44] Second-line drug susceptibility testing should be done only in reference laboratories and is limited to specimens from patients who have had prior therapy,

have been in contact with a patient with known drug-resistant TB, have suspected or demonstrated resistance to RIF and/or other first-line drugs, are unable to tolerate RIF, have positive cultures after more than 3 months of treatment, or are from a region or population with high rates of *multidrug-resistant* (MDR)-TB.[41,44]

Additional indicated testing includes the following:

- Chest radiograph at baseline for all patients. An end-of-treatment chest radiograph is optional, but it serves as a new baseline reference if the patient develops future respiratory symptoms, including those suggesting TB recurrence. For patients treated for culture-negative TB, a chest radiograph should be obtained at 2 months to assess treatment response.
- Liver function tests at baseline for all patients. Further monitoring of liver function is indicated if there are baseline abnormalities or as clinically indicated. In the presence of baseline abnormalities and/or ongoing risk factors (e.g., alcohol use disorder), liver function may be tested more frequently than monthly.
- Creatinine at baseline for all patients, with further monitoring if there are baseline abnormalities or as clinically indicated.
- HIV testing in all patients.
- Monitor weight monthly to assess response to treatment; adjust medication doses if there are changes in weight.
- While receiving EMB, baseline visual acuity (Snellen test) and color discrimination tests, followed by monthly testing.[45]
- Patients with hepatitis B or C risk factors, such as injection drug use, birth in Asia or Africa, or HIV infection, should have screening tests for these infections.
- Fasting glucose or hemoglobin A1c for patients with risk factors for diabetes, according to the American Diabetes Association, including age older than 45 years, body mass index greater than 25, first-degree relative with diabetes, and race/ethnicity of African American, Asian, Hispanic, Native American/Alaskan Native, or Hawaiian Native/Pacific Islander.

PATIENT RESPONSE TO TREATMENT

BACKGROUND

The overall rate of failure or relapse in patients with drug-susceptible TB receiving DOT with a standard rifamycin-based regimen is low.[46–48] In patients receiving 6-month regimens who have drug-susceptible organisms, the estimated failure rate is less than 1% and the relapse rate is 4%.[14] Studies from low-burden settings, where reinfection with *M. tuberculosis* is uncommon, have identified relapse and recurrence rates that are even lower.[49–51] Although current TB regimens are highly effective, their generalized use means that some patients are overtreated, whereas other patients may be undertreated and at greater risk for poor outcomes.[13] The most effective means of decreasing the likelihood of relapse for patients at risk has not yet been determined by clinical trials; however, indirect evidence from a controlled clinical trial and an observational study among patients with pulmonary TB in Hong Kong showed that prolonging treatment decreased the rate of relapse.[52,53] It has also been reported that for patients at high risk of relapse, prolongation of the once-weekly INH/rifapentine continuation phase from 4 to 7 months resulted in a decreased relapse rate.[54]

IDENTIFYING PATIENTS AT RISK FOR POOR OUTCOMES

Certain baseline and on-treatment characteristics may identify patients who might benefit from treatment prolongation. The result of a sputum culture obtained at completion of the intensive phase of treatment (2 months) correlates with the likelihood of relapse, albeit with low sensitivity.[10,55–57] Cavitation has also been shown to be a risk factor for relapse.[10,53] Having both cavitation and a positive culture at completion of 2 months of therapy is associated with relapse rates of approximately 20%, compared with 2% among patients with neither factor, after a 6-month treatment regimen.[10,57] Therefore, for patients who have cavitation on the initial chest radiograph and a positive culture at completion of 2 months of therapy, the continuation phase with INH and RIF is extended an additional 3 months (i.e., a continuation phase of 7 months, corresponding to a total of 9 months of therapy).[29]

Because patients who had either cavitation or a positive culture at 2 months have increased relapse rates,[10,57] patients with one of these risk factors are followed more closely, and consideration is given to extending treatment duration (i.e., 9 months of total treatment) if there is evidence of a poor response. Additional factors to be considered in prolonging treatment in patients with either cavitation or a positive culture at 2 months include being more than 10% underweight (especially with poor weight gain during the intensive phase of treatment); being a smoker; having diabetes, HIV infection, or other immunocompromising condition; or having extensive disease on chest radiograph.[13,56,58–62] Poor adherence, particularly if less than 90% of the intended doses are ingested, is also associated with poor treatment outcomes.[13]

POOR TREATMENT RESPONSE AND TREATMENT FAILURE

Treatment failure is defined as continuously or recurrently positive cultures after four (United States) or five (European and *World Health Organization* [WHO])[63] months of treatment in a patient receiving appropriate chemotherapy. Among patients with drug-susceptible pulmonary TB, even with extensive lung cavitation, 90–95% will be culture negative after 3 months of treatment with a regimen that contains INH and RIF. During this time, most patients show clinical improvement. Patients with persistently positive cultures after 3 months of chemotherapy should be evaluated to determine the cause of delayed response.

Multiple reasons for poor treatment response and treatment failure exist. For patients not receiving DOT, nonadherence should be considered as an explanation. Other potential reasons include unrecognized drug resistance (drug susceptibility testing not done, misreported, or misinterpreted; reinfection with a drug-resistant strain),

malabsorption (diarrhea, prior *gastrointestinal* [GI] resection, or taking TB medications with antacids or other drugs/substances that interfere with drug absorption), or diabetes mellitus.[64–72] Some experts use therapeutic drug monitoring (see later) to evaluate poor drug exposure as a contributing factor to treatment failure.[73] Laboratory error (e.g., cross contamination or mislabeling of specimens) is a possible reason for a positive culture in a patient who is doing well clinically.[74]

On occasion, patients have smear-positive sputum samples with no growth on culture. Culture conversion before smear conversion is thought to represent the presence of nonviable or dead bacilli.[75] The reappearance of smear-positive sputum samples in a patient with multiple negative prior smears and cultures may also be due to this phenomenon. These findings are more common in patients with high-burden (e.g., initial 4+ smear positivity) pulmonary TB.[76]

Patients treated for TB may experience transient clinical or radiographic worsening (paradoxical reactions) despite appropriate therapy. Examples of this include ongoing inflammation at sites of lymphadenitis, worsening symptoms in CNS TB, or the new appearance of pleural effusions. Such paradoxical worsening can be seen in patients with or without HIV infection. The diagnosis of a paradoxical reaction is made only after a thorough evaluation for other etiologies, including the emergence of drug resistance.[77–79]

For patients who meet criteria for treatment failure, the possible reasons listed earlier should be addressed promptly. The patient's recent mycobacterial isolates should be sent to a reference laboratory for susceptibility testing with first- and second-line drugs. Clinicians not familiar with the management of drug-resistant TB should consult with a specialty center immediately. If treatment failure is suspected to be due to drug resistance and the patient is seriously ill or has a positive sputum AFB smear, an empirical regimen for drug-resistant TB is started immediately and continued until susceptibility tests are available to guide therapy. However, if the patient's clinical presentation is not severe, one may either initiate an empirical treatment regimen or wait for drug susceptibility results from a recent isolate. Of note, patients who are not on the correct regimen remain infectious.[80,81] A single new drug should *never* be added to a failing regimen because it can lead to amplification of drug resistance, including acquired resistance to the newly added drug.[82] To lessen the likelihood of increasing resistance, it is prudent to add two to three new drugs to which susceptibility could be inferred (e.g., using regional drug-resistance surveillance data and the patient's history of medication use). When drug susceptibility results are available, the regimen is adjusted accordingly.

CASE MANAGEMENT

ADVERSE EFFECTS

In a single-center study, approximately 9% of patients treated for TB experienced major adverse effects requiring permanent discontinuation of the offending drug, with higher risk in patients older than 60 years, women, people living with HIV, and Asian-born patients.[32] PZA was responsible for most of the major adverse effects. Patients should be advised in advance about the possible adverse effects of the medications in their regimen (listed in Table 54.3) and that they must stop taking their medications and inform their health care team immediately if problems arise. Informing patients in advance will also increase their investment in finding a well-tolerated regimen.

Mild adverse effects usually can be managed with treatment directed at controlling the symptoms. For more severe adverse effects known to be attributable to a single drug in the regimen, that medication may be stopped, and a replacement drug, typically from a different drug class, may be included in the regimen.

The following suggested practices for handling common adverse effects during treatment are based on expert opinion.

Hepatotoxicity

Drug-induced hepatitis is the most frequent serious adverse reaction to first-line drugs; INH, RIF, and PZA can all cause liver injury.[83] Given its greater specificity, *alanine aminotransferase* (ALT) is preferred over *aspartate aminotransferase* (AST) for diagnosing drug-induced liver injury. An asymptomatic increase in ALT concentration may be observed in nearly 20% of patients treated with the standard four-drug regimen and is frequently due to INH through a process called hepatic adaptation, which resolves despite continuation of treatment.[84,85] Therapy should not be altered because of modest asymptomatic elevations of ALT, but the frequency of clinical and laboratory monitoring should be increased. However, if ALT levels are more than five times the *upper limit of normal* ([ULN], with or without symptoms) or more than three times normal in the presence of symptoms, hepatotoxic drugs must be stopped and the patient evaluated. Other causes of abnormal liver tests (e.g., viral hepatitis, biliary tract disease, alcohol use, other hepatotoxic drugs) must be excluded before diagnosing drug-induced hepatotoxicity. Serum ALT and prothrombin time or international normalized ratio levels should be followed until they return to baseline. The clinician should consult a liver specialist if the patient's clinical or laboratory status continues to worsen. Liver injury that produces transaminitis only is more likely to be due to INH or PZA. Similarly, a significant increase in bilirubin and/or alkaline phosphatase is cause for a prompt evaluation; disproportionate increases in bilirubin and alkaline phosphatase (compared to increases in serum ALT) may be seen with RIF hepatotoxicity.[83]

Whether to initiate a "liver-sparing regimen" while awaiting normalization of aminotransferases depends on the patient's infectiousness, severity of disease, and treatment phase. A liver-sparing regimen typically includes EMB, a fluoroquinolone such as *levofloxacin* (LFX), and an aminoglycoside. If a patient is advanced in treatment and/or has a low bacillary burden, it is reasonable to hold all TB treatment while awaiting normalization of liver function.

Once the ALT returns to less than two times the ULN, antituberculosis medications are restarted individually.[83] In patients with elevated baseline ALT from preexisting liver disease, drugs are restarted when the ALT returns to near baseline levels. The optimal approach to reintroducing TB treatment after hepatotoxicity

is not known.[86,87] However, most TB programs use sequential reintroduction of drugs. If symptoms recur or ALT increases, the last drug added should be stopped. Because RIF is much less likely to cause hepatotoxicity than INH or PZA, it is restarted first (with or without EMB, depending on the treatment phase). If there is no increase in ALT after 3 to 7 days, INH may be restarted. The decision to restart PZA (3–7 days after INH) depends on the treatment phase and the severity of liver injury. A prolonged (several weeks) time course to normalization of aminotransferases supports PZA as the responsible medication.[83] If RIF and INH are tolerated and hepatitis was severe, PZA can be assumed to be responsible and is discontinued. In this last circumstance, depending on the number of doses of PZA taken, severity of disease, and bacteriologic status, the total duration of therapy may be extended to 9 months.

Gastrointestinal Symptoms

GI reactions, including nausea, vomiting, poor appetite, and abdominal pain, are the most common adverse effects seen early in treatment.[88] Aminotransferases and bilirubin should be checked to ensure that GI symptoms are not due to hepatotoxicity. If applicable, pregnancy should be considered as an etiology of the patient's symptoms.

- To minimize symptoms, patients receiving self-administered or video-observed therapy may take the medication that is causing symptoms at bedtime.
- GI intolerance can be treated with antacids, including proton pump inhibitors.[89]
- A light snack (low-fat food) before taking medications may decrease symptoms.
- Nausea may be treated by giving antiemetics 30 minutes before TB medications. Options include ondansetron, promethazine, and metoclopramide.

Rash

All first-line antituberculosis drugs can cause rashes, the severity of which determines management.[90] If a rash is mainly itchy without mucous membrane involvement or systemic signs, such as fever or mucosal involvement, treatment is symptomatic with antihistamines with or without corticosteroid creams. Specific types of dermatologic adverse effects require different responses:

- Photosensitivity may be due to PZA and may persist for weeks after stopping PZA. Patients should avoid sun exposure and use sunscreen.
- A petechial rash is concerning for thrombocytopenia, which may be caused by RIF.[91] If the platelet count is low, RIF should be stopped. When the platelet counts have recovered, *rifabutin* (RFB) may be considered as a replacement for RIF.[92]
- Involvement of mucous membranes and/or fever suggests Stevens-Johnson syndrome or toxic epidermal necrosis. Rash with eosinophilia, lymphadenitis, fever, and/or other organ system involvement is consistent with *drug rash with eosinophilia and systemic symptoms* (DRESS) syndrome. A dermatologist should be consulted in addition to a TB expert for these syndromes.

When the rash has improved, medications can be reintroduced serially at intervals of 2 to 3 days. If the rash recurs, the last drug added is stopped.

Neurotoxicity

Neurotoxic effects of antituberculosis medications include peripheral neuropathy, headaches, drowsiness, and problems with concentration and irritability. INH causes a functional deficiency of pyridoxine (vitamin B_6) that is usually clinically significant only in high-risk patients. Pyridoxine (25–50 mg) is given with each INH dose to all persons at risk of neuropathy, including patients with diabetes, HIV, renal disease, alcohol abuse, or malnutrition; pregnant or breastfeeding mothers, or those with chronic renal failure or of advanced age.[93,94] Some experts routinely provide pyridoxine supplementation to all patients receiving INH. For patients who develop neuropathy while on pyridoxine, doses may be increased to 100 mg daily; pyridoxine supplementation above this dose is unlikely to be helpful. The other listed neurotoxic adverse effects typically resolve with continuation of TB medications and are best addressed with supportive methods. Seizures, including status epilepticus, may develop as a result of INH toxicity, including overdoses; patients should be immediately hospitalized and treated with intravenous pyridoxine and antiepileptic drugs.[95,96]

Optic Neuritis

EMB-related visual impairment during treatment of active TB has been estimated to happen in 19 of 1000 persons receiving EMB at 27.5 mg/kg/day or less for 2 to 9 months' duration.[97] The onset of optic neuritis is usually more than 1 month after treatment initiation but can happen within days.[98,99] To avoid permanent deficits, EMB is promptly discontinued if visual abnormalities are found, and ophthalmologic consultation should be obtained. Recovery of vision takes 3 months on average.[97]

THERAPEUTIC DRUG MONITORING

Therapeutic drug monitoring (TDM) consists of measurements of drug concentrations in serum specimens, usually collected 2 and 6 hours after a dose of a drug. No prospective randomized trials clearly define the role of TDM for antituberculosis drugs, and opinions vary regarding its utility. TDM should be reserved for specific indications because the majority of patients will not require it. TDM may be helpful in situations in which drug malabsorption, drug underdosing, or clinically important drug-drug interactions are suspected. Situations in which TDM may be indicated include (1) patients with delayed sputum conversion or treatment failure not explained by nonadherence or drug resistance, (2) patients with medical conditions (e.g., malabsorption or reduced renal function) suspected of leading to subtherapeutic or toxic drug concentrations, and (3) patients undergoing treatment for drug-resistant TB. Practical considerations in obtaining TDM include the following:

- Blood should be obtained after the patient has been on a stable dose of the medication for approximately 1 week to ensure a steady state.

- For INH, RIF, EMB, and PZA levels, blood should be collected 2 and 6 hours after ingestion of the medication. The 2-hour blood draw captures peak concentration and is usually higher than the 6-hour sample.
- If the 6-hour level is higher than the 2-hour level, this is consistent with delayed absorption.
- If both the 2-hour and 6-hour levels are low, then malabsorption may be present.
- Laboratories with extensive experience in analyzing TB drug levels may be found at the University of Florida, Gainesville (http://idpl.pharmacy.ufl.edu) and National Jewish Health, Denver (http://njlabs.org). Results from these laboratories include target serum drug levels.
- If drug concentrations are lower than the targeted range, then the dose of that medication should be increased.

INTERRUPTIONS IN THERAPY

Interruptions in therapy are common in the treatment of TB. When therapy is interrupted, the person responsible for supervision must decide whether to restart a complete course of treatment or to continue as originally intended. In general, the earlier the break in therapy and the longer its duration, the greater the need to restart treatment from the beginning. Continuous treatment is more important in the intensive phase of therapy, when the bacillary population is highest and the chance of developing drug resistance is greatest. During the continuation phase, the number of bacilli is much lower, and the goal of therapy is to kill persisting organisms. The duration of the interruption and the bacteriologic status of the patient before and after the interruption are also important considerations. The approach summarized in Table 54.4 is presented as an example.[100]

CULTURE-NEGATIVE TUBERCULOSIS

Patients who have negative cultures but are presumed to have pulmonary TB should have thorough clinical and radiographic follow-up after 2 months of therapy. The most recent CDC guidelines recommend that a 4-month treatment regimen is adequate for HIV-uninfected adults with culture-negative pulmonary TB.[29] Treatment is initiated with the intensive phase of daily INH, RIF, PZA, and EMB. If all cultures on adequate samples are negative and there is clinical or radiographic response after 2 months of intensive phase therapy, the continuation phase with INH and RIF can be shortened to 2 months. Clinical and radiographic response, assessed at the end of treatment, is used to determine whether an extension in treatment to a full standard 6-month regimen is needed. The local health department should be notified of individuals with culture-negative TB.

EXTRAPULMONARY TUBERCULOSIS

With the exceptions of CNS and bone and joint TB, treatment of patients with extrapulmonary TB is similar to that of patients with pulmonary TB.[29] The preferred frequency of dosing for extrapulmonary TB is once daily for both the intensive and continuation phases. In extrapulmonary TB, response to treatment is often judged on the basis of clinical and radiographic findings because of the difficulty in obtaining samples for follow-up cultures.[29]

Table 54.4 Management of Treatment Interruptions*

Time Point of Interruption	Details of Interruption	Approach
During intensive phase	Lapse is <14 days in duration	Continue treatment to complete planned total number of doses (as long as all doses are completed within 3 mo)
	Lapse is ≥14 days in duration	Restart treatment from the beginning
During continuation phase	Received ≥80% of doses and sputum was AFB smear negative on initial testing	Further therapy may not be necessary
	Received ≥80% of doses and sputum was AFB smear positive on initial testing	Continue therapy until all doses are completed
	Received <80% of doses and accumulative lapse is <3 mo in duration	Continue therapy until all doses are completed (full course), unless consecutive lapse is >2 mo If treatment cannot be completed within recommended time frame for regimen, restart therapy from the beginning (i.e., restart intensive phase, to be followed by continuation phase)†
	Received <80% of doses and lapse is ≥3 mo in duration	Restart therapy from the beginning, new intensive and continuation phases (i.e., restart intensive phase, to be followed by continuation phase)

*According to expert opinion, patients who are lost to follow-up (on treatment) and brought back to therapy, with interim treatment interruption, should have sputum resent for AFB smear, culture and drug susceptibility testing.

†The recommended time frame for regimen, in tuberculosis control programs in the United States and in several European countries, is to administer all of the specified number of doses for the intensive phase within 3 mo and those for the 4-mo continuation phase within 6 mo so that the 6-mo regimen is completed within 9 mo.

Modified from Bureau of Tuberculosis Control. *Clinical Policies and Protocols*, 4th ed. New York City Department of Health and Mental Hygiene; 2008.

AFB, acid-fast bacillus.

CENTRAL NERVOUS SYSTEM

CNS TB may present with meningitis or intracranial tuberculomas. Tuberculous meningitis remains a potentially devastating disease associated with death rates of 18–40%[101] and disabling neurologic deficits in 10–30% of survivors[101,102] despite prompt initiation of appropriate chemotherapy.[103] Current U.S. guidelines recommend an intensive phase that includes INH, RIF, PZA, and EMB, with a continuation phase of INH and RIF.[29] However, the continuation phase should be extended to 7 to 10 months for 9 to 12 months of total treatment.

In children with tuberculous meningitis, the *American Academy of Pediatrics* (AAP) lists an initial four-drug regimen of INH, RIF, PZA, and ethionamide or an aminoglycoside for 2 months (in place of EMB), followed by 7 to 10 months of INH and RIF,[104] although there are no data from controlled trials to guide selection of EMB versus an injectable or ethionamide as the fourth drug for TB meningitis.[105] A trial of TB meningitis treatment regimens that evaluated LFX and higher-dose RIF did not detect a difference in outcomes compared to standard treatment.[102] There are several studies of alternative regimens (e.g., high-dose RIF, adding linezolid; http://clinicaltrials.gov) or host-directed therapeutics[106] to improve outcomes in patients with TB meningitis.

Based on expert opinion, repeated lumbar punctures should be considered to monitor changes in cerebrospinal fluid cell count, glucose, and protein, especially early in the course of therapy. As a closed-space infection, an overly robust inflammatory response may worsen patient outcomes, and TB meningitis is one of the few infections where high-quality evidence supports the clinical use of corticosteroids,[101] although the benefit may be limited to subsets of patients with greater inflammatory responses.[107] An updated systematic review that informed the current CDC guidelines found a mortality benefit from the use of adjuvant corticosteroids, which may be administered as dexamethasone. Whereas the CDC guidelines do not make dexamethasone dosage recommendations, based on contemporary trials, the following dosages of corticosteroids can be considered: adults (>14 years) should receive dexamethasone 0.4 mg/kg/24 hr with a reducing course over 6 weeks (some experts extend to 8 weeks). Children (<14 years) should receive prednisolone 4 mg/kg/24 hr (or equivalent dose of dexamethasone: 0.6 mg/kg/24 hr) for 4 weeks, followed by a reducing course over 2 to 4 weeks.[29,105]

Cerebral tuberculomas may be present in patients with and without TB meningitis, and antituberculosis treatment may lead to a paradoxical worsening in tuberculoma size and symptoms. Adjunctive corticosteroids may decrease tuberculoma size and improve symptom control.[105] Selected complications of tuberculous meningitis warranting neurosurgical intervention include hydrocephalus, tuberculous cerebral abscess, and paraparesis.[105]

BONE AND JOINT

Guidelines recommend 6 to 9 months of treatment for bone and joint TB (i.e., extending the continuation phase by an additional 3 months).[108] In the setting of extensive orthopedic hardware involvement, some experts extend treatment to 12 months. Several trials found no additional benefit of surgical débridement in combination with chemotherapy compared with chemotherapy alone for spinal TB.[109–113] Uncomplicated cases of spinal TB are managed with medical rather than surgical treatment. Surgery should be considered when (1) there is poor response to chemotherapy with evidence of ongoing infection or clinical deterioration, (2) relief of cord compression is needed, or (3) there is instability of the spine.[114]

PERICARDIAL

Previously, corticosteroids were recommended as adjunctive therapy for tuberculous pericarditis.[115–117] However, a large RCT did not find a difference in outcomes between study arms, although subgroup analysis suggested a benefit in preventing constrictive pericarditis.[118] The current U.S. guidelines recommend that adjunctive corticosteroids should not be used routinely in the treatment of patients with pericardial TB.[108] There may be a role for the selective use of corticosteroids in patients at the highest risk for inflammatory complications, such as those with large pericardial effusions, high levels of inflammatory cells or markers in pericardial fluid, or signs of constriction.[119]

LYMPH NODE

A 6-month regimen is adequate for treatment of drug-susceptible tuberculous lymphadenitis,[120–125] although responses may be slower than in pulmonary TB. Paradoxical upgrading reactions, defined as enlarging or new nodes or a new draining sinus in patients who have received at least 10 days of treatment, develop in more than 20% of patients with lymph node TB regardless of HIV status.[126] These paradoxical reactions are not indicative of treatment failure, although drainage or fine-needle aspirate may be obtained for culture and to ensure drug susceptibility. Some experts use corticosteroids to decrease inflammation.[127] Incision and drainage techniques applied to cervical lymphadenitis, however, have been reported to be associated with prolonged wound discharge and scarring.[128]

SPECIAL POPULATIONS

PEOPLE LIVING WITH HUMAN IMMUNODEFICIENCY VIRUS

The principles of treatment of TB in patients living with HIV and receiving antiretroviral therapy are similar to those in patients who are HIV negative. However, there are important differences in people living with HIV, including interactions between antiretroviral drugs and rifamycins, which are potent inducers of *cytochrome P-450* (CYP) enzymes and thus accelerate metabolism of many drugs. *Cytochrome P-450 3A4* (CYP3A4) is especially relevant because it is involved in metabolism of multiple classes of antiretroviral drugs.

Other considerations are the *immune reconstitution inflammatory syndrome* (IRIS) and increased risk for poor treatment outcomes. HIV infection in the presence of TB increases the risk of TB relapse[129–131] and death.[132] In addition, intermittent TB treatment regimens in people living with HIV are associated with the emergence of drug resistance.[10,133,134] Use of a thrice-weekly RIF-based regimen during the intensive and continuation phases of treatment

was associated with higher relapse rates and rifamycin resistance in people living with HIV not receiving antiretrovirals, compared with antiretroviral-treated people living with HIV or patients without HIV infection.[135]

U.S. guidelines make the following recommendations[29]:

- For antiretroviral-treated people living with HIV, the standard 6-month daily regimen consisting of an intensive phase of 2 months of INH, RIF, PZA, and EMB, followed by a continuation phase of 4 months of INH and RIF, for the treatment of drug-susceptible pulmonary TB is appropriate.
- For people living with HIV who are *not* receiving antiretrovirals, the continuation phase should be extended for an additional 3 months (i.e., a continuation phase of 7 months in duration for a total of 9 months of therapy).
- Treatment should be given daily in both the intensive and continuation phases to avoid recurrent disease and the emergence of rifamycin resistance.

IRIS in association with TB treatment is the worsening of symptoms in a patient receiving appropriate treatment and may include high fevers, worsening respiratory symptoms, increase in size and inflammation of involved lymph nodes, new lymphadenopathy, expanding CNS lesions, worsening of pulmonary parenchymal infiltrations, new or increasing pleural effusions, and development of intra-abdominal or retroperitoneal abscesses.[136] IRIS is more common in patients with severe immunosuppression at baseline (CD4-cell counts < 50 cells/mm^3) and antiretroviral-naive individuals who initiate antiretrovirals earlier in the TB treatment course.[137] The diagnosis of IRIS is made only after excluding other possible causes. Management of IRIS is symptomatic. For most patients with mild IRIS, TB and antiretroviral therapies can be continued with the addition of nonsteroidal anti-inflammatory drugs.[29] For patients with worsening pleural effusions or abscesses, drainage may be necessary. In severe cases of IRIS, treatment with corticosteroids may be required.[138] Prednisone may be given at a dose of 1.25 mg/kg/day (50–80 mg/day) for 2 to 4 weeks, with tapering over a period of 6 to 12 weeks or longer. In an RCT, prednisone (40 mg/day for 14 days, followed by 20 mg/day for 14 days), given to TB/HIV coinfected individuals (CD4 cell counts < 100 cells/mm^3) who were initiating antiretroviral therapy within 30 days of starting antituberculosis therapy resulted in a lower incidence of IRIS compared to placebo.[139]

Through induction of CYP3A4 and other P-450 cytochromes, rifamycins accelerate the metabolism of many antiretroviral agents, potentially leading to subtherapeutic levels. *Integrase strand transfer inhibitor* (INSTI)-based regimens are the first-line regimens for treatment of HIV infection in the United States and Europe and were endorsed by the WHO as the preferred regimen.[140] Trough concentrations of the INSTIs raltegravir and dolutegravir are significantly reduced by concomitant use of RIF.[141,142] The REFLATE TB trial showed that RIF-based antituberculosis treatment and raltegravir at 400 mg or 800 mg twice daily was associated with similar antiviral effectiveness; both raltegravir doses were more effective than efavirenz 600 mg daily.[141] However, PK data favor increasing the raltegravir dose to 800 mg twice daily, and expert opinion in the United States favors this strategy.[143] PK studies demonstrate that coadministration of RIF and dolutegravir at a dosage of 50 mg twice daily results in adequate trough concentrations of dolutegravir.[142] RIF is contraindicated in patients receiving tenofovir alafenamide–containing formulations, protease inhibitors, PK boosters (e.g., cobicistat, ritonavir), and most non-nucleoside reverse transcriptase inhibitors other than efavirenz.

RFB is a less potent inducer of CYP3A4 and may be used in patients receiving non-nucleoside reverse transcriptase inhibitors and boosted protease inhibitors, as well as dolutegravir or raltegravir (400 mg twice daily). RFB itself is metabolized by CYP3A enzymes, and the antiretroviral agent ritonavir (used to boost protease inhibitor levels) inhibits CYP3A enzymes, resulting in increased concentrations of RFB. High concentrations of RFB are associated with an increased risk of uveitis and other toxicities, so dose adjustment of the standard RFB dosage of 300 mg daily is necessary.[144] Expert opinion is to use RFB at a dose of 150 mg/day or 300 mg every other day as part of a combination antituberculosis regimen for patients receiving ritonavir-boosted protease inhibitors.[145] In patients receiving dose-adjusted RFB because of concomitant protease inhibitor use, frequent assessment of adherence to both medicines is prudent because discontinuation of the protease inhibitor while continuing dose-adjusted RFB (i.e., in the context of DOT TB therapy but self-administered antiretrovirals) may result in subtherapeutic concentrations of rifamycin. These complicated interactions underscore the importance of expert consultation in treating individuals with concurrent HIV and TB. For situations involving complex drug-drug interactions, some clinicians prefer to measure the concentrations of the interacting drugs and to dose these drugs based upon individualized data.[73]

For people living with HIV who are receiving antiretroviral therapy and are diagnosed with TB, the antiretroviral regimen may need modifications to allow use of a rifamycin (RIF or RFB). Useful sources regarding drug interactions (TB/HIV and other) are available through the following organizations: AIDSinfo, CDC, University of California San Francisco, University of Liverpool, and Indiana University. For individuals with TB who are not receiving antiretrovirals, there are guidelines on when to initiate antiretroviral therapy[146]:

- Individuals with CD4 count less than 50 cells/mm^3: Start antiretrovirals within the first 2 weeks of TB treatment; this has been shown to reduce morbidity and mortality.[147–149]
- Individuals with CD4 counts greater than or equal to 50 cells/mm^3: Start antiretrovirals within the first 8 weeks of TB treatment.
- People living with HIV with TB meningitis: Use caution with early initiation of antiretroviral therapy because a study from Vietnam demonstrated a higher rate of severe IRIS events in participants randomized to immediate antiretrovirals compared to those started on antiretroviral therapy at month 2 of TB treatment.[150]

HEPATIC DISEASE

TB treatment in patients with liver disease poses challenges because the likelihood of drug-induced hepatitis is increased

with advanced liver disease,[151] liver transplant,[152] or viral hepatitis.[83,153,154] Abnormal baseline aminotransferases alone are an independent risk factor for drug-induced liver injury.[151,155] Hepatic TB may also cause elevated aminotransferases, which improve with effective TB treatment.[156]

PZA, INH, and RIF may all cause hepatic injury. Regimens with fewer potentially hepatotoxic agents are selected in patients with advanced liver disease or whose serum ALT is more than three times the ULN at baseline (and thought not to be caused by TB). The importance of INH and RIF warrant their use, if at all possible, even in the face of preexisting liver disease. Expert consultation is advisable, and adjustments during treatment may be necessary. Alternative regimens for use in patients with hepatic disease (i.e., ALT > 3 × ULN) include the following[83]:

- Treatment without PZA: PZA has often been implicated in drug-induced liver injury. A potential regimen could be INH and RIF for 9 months with EMB given for the first 2 months, or until susceptibility to INH and RIF is determined.[157,158]
- Treatment without INH and PZA: For advanced liver disease patients, RIF and EMB with a fluoroquinolone (injectable), or cycloserine for 12 to 18 months, depending on the extent of the disease and response.[159]
- Regimens with little or no potential hepatotoxicity: For severe, unstable liver disease patients, EMB combined with a fluoroquinolone, cycloserine, and second-line injectable for 18 to 24 months (similar to an MDR-TB regimen) can be considered.[160] Some experts avoid aminoglycosides in patients with severe, unstable liver disease due to concerns about renal insufficiency or bleeding from the site of injected medication due to thrombocytopenia and/or coagulopathy.

Clinical monitoring and patient education for manifestations of liver injury are warranted for all patients.[83] In patients with known hepatic disease, serum aminotransferases and total bilirubin concentrations should be assessed at baseline and every 1 to 4 weeks for at least the first 2 to 3 months of treatment. The international normalized ratio may also be periodically followed for patients with severe hepatic impairment.[83,161,162] Reintroduction of antituberculosis treatment may entail rechallenge and/or substitution of agents, and strategies have been published.[83] Whenever feasible, management of TB in the setting of severe hepatic disease should include expert consultation.

KIDNEY DISEASE

TB patients with chronic renal failure have worse clinical outcomes than those without renal failure, and experts recommend close monitoring during TB treatment.[163] The PKs of antituberculosis drugs are altered because some are cleared by the kidneys and/or removed via hemodialysis.[164,165] RIF and INH are metabolized by the liver, and conventional dosing can be used in the setting of renal insufficiency. PZA is also metabolized by the liver, but its metabolites may accumulate in patients with renal insufficiency. Approximately 80% of EMB clearance is by the kidneys and may accumulate in patients with renal insufficiency. For patients with a creatinine clearance of less than 30 mL/min and those receiving hemodialysis, guidelines recommend maintaining the dosage of PZA and EMB but decreasing the frequency of administration (i.e., changing from daily to three times weekly).[29,73,166] Postdialysis administration of all antituberculosis medications is preferred to facilitate DOT and to avoid premature clearance of drugs. Monitoring serum drug concentrations, along with careful clinical and pharmacologic assessment, in patients with end-stage renal disease may be necessary. For patients receiving peritoneal dialysis, there is a paucity of PK and dosing data, and the appropriate dosages are not known. Such patients may require close monitoring for toxicity, and measurements of the serum concentrations of antituberculosis drugs before and after peritoneal dialysis should be considered.

OLDER PATIENTS

By age, the highest TB rates in the United States are among individuals 65 years and older.[167] The treatment of TB in older populations may be complicated by comorbidities, polypharmacy, and frailty, which can result in undesirable treatment outcomes, including increased rates of medication-related adverse reactions.[168] Because PZA is the most common cause of severe adverse effects,[32,169,170] the benefits of including PZA in the initial regimen for elderly patients with modest disease and low risk of drug resistance have been questioned, and some experts avoid the use of PZA during the intensive phase among patients older than 75 years.[29] However, recent studies have not demonstrated higher rates of PZA-related adverse effects in the elderly compared to younger patients,[170] or among elderly patients, based on the inclusion of PZA in TB treatment regimens.[171] If PZA is not used during the intensive phase, the total duration of TB treatment should be extended to at least 9 months. When elderly patients have TB with high bacillary burden, the benefits and risks of keeping PZA or adding a fluoroquinolone versus no fourth drug should be carefully considered. The frequency of drug interactions is increased in the elderly, and dose adjustments or use of alternative regimens may be necessary.

CHILDREN

The diagnosis of TB in children is challenging due to the paucibacillary nature of the disease, and sputum specimens for bacteriologic evaluations cannot usually be obtained in younger children,[172] so drug susceptibility or resistance often must be inferred from results from the presumed source case. When drug resistance is suspected or no source case isolate is available, attempts to isolate organisms are critical; approaches including obtaining three early morning *gastric* aspirations (optimally during hospitalization), sputum induction,[173] bronchoalveolar lavage,[174] or tissue biopsy must be considered.[29]

Because TB in infants and children younger than 4 years is more likely to disseminate, empirical treatment must be started as soon as the diagnosis is suspected, and particular care is given to drug dosage selection as an important component of achieving adequate concentrations of bactericidal drugs in body fluids, including cerebrospinal fluid.[175]

Several controlled and multiple observational trials of 6-month therapy in children with known or presumed drug-susceptible pulmonary TB have been published.[176] The AAP[177] and WHO[178,179] list a four-drug regimen (INH, RIF, PZA, and EMB) for 2 months, followed by a two-drug (INH and RIF) regimen for 4 months, as the preferred regimen for children with suspected or confirmed pulmonary TB. When feasible, daily dosing is preferred[177,179,180]; however, twice- or thrice-weekly dosing has also been endorsed during the continuation phase of treatment for HIV-uninfected children in settings where DOT is well established.[177] The AAP recommends that children receiving EMB should be monitored monthly for visual acuity and color discrimination if they are old enough to cooperate. The decision to use EMB in young children whose visual acuity cannot be monitored requires consideration of risks and benefits, but it can be used to treat TB disease in infants and children unless otherwise contraindicated.[177] Some clinicians use a three-drug regimen (INH, RIF, and PZA) in the initial 2 months of treatment for children who are HIV uninfected, have no prior TB treatment history, are living in an area of low prevalence of drug-resistant TB, and have no exposure to an individual from an area of high prevalence of drug-resistant TB. However, because the prevalence of and risk for drug-resistant TB can be difficult to determine, the AAP and most experts include EMB as part of the intensive phase regimen for children with TB.

Most forms of extrapulmonary TB in children can be treated with the same regimens as are used in adults.[29] For tuberculous meningitis, the AAP lists an initial four-drug regimen of INH, RIF, PZA, and an aminoglycoside or ethionamide for 2 months, followed by 7 to 10 months of INH and RIF. For patients who may have acquired TB in regions where resistance to streptomycin is common, amikacin is used instead of streptomycin.[177] In the United States, DOT is the default programmatic approach to treating children with TB.[181] Parents should not supervise DOT for their children.[29]

PREGNANCY AND BREASTFEEDING

Untreated active TB poses a far greater hazard to a pregnant woman and her fetus than does treatment for the disease.[182] Although antituberculosis drugs cross the placenta, they do not appear to have teratogenic effects in humans.[183–186] Due to limited data, the inclusion of PZA in the treatment regimen for pregnant women is controversial in the United States, and the CDC has recommended against its use during pregnancy. However, PZA has been used extensively in high-burden countries for many years and is recommended by the WHO for TB in pregnancy as part of the standard treatment regimen.[63] Expert opinion is that in pregnant women with TB and HIV, extrapulmonary or severe TB, it is more beneficial to include PZA in the treatment regimen than to not include PZA. Discussions regarding the risks and benefits of the different treatment regimens will support the patient in making an informed decision, recognizing that for all first-line drugs, risk cannot be ruled out as there are no adequate and well-controlled studies in humans. If a decision is made to exclude PZA from the regimen, a minimum of 9 months of INH, RIF, and EMB is required.

Breastfeeding is encouraged for women who are noninfectious and are being treated with first-line agents. The low concentrations of antituberculosis drugs measured in breast milk neither present a risk to the infant[177] nor reach adequate concentrations to be considered effective treatment for active TB in a nursing infant. Whenever INH is given to a pregnant or nursing woman, supplementary pyridoxine, 25 to 50 mg/day, is prescribed.[93,94,187,188] According to the AAP, supplementary pyridoxine (1–2 mg/kg/day) is also prescribed to exclusively breastfed infants, even those not receiving INH,[177,189] although liquid formulations may be difficult to obtain.

DRUG-RESISTANT TUBERCULOSIS

Drug-resistant TB is due to *M. tuberculosis* isolates resistant to any of the first-line drugs. Due to the importance of INH and RIF in the treatment of drug-susceptible TB, disease caused by isolates resistant to both these drugs defines MDR-TB. MDR-TB that is resistant to a fluoroquinolone or a second-line injectable drug (amikacin, kanamycin, or capreomycin) is termed *pre-extensively drug-resistant TB* (pre–XDR-TB) and if resistant to both classes of drugs is termed *extensively drug-resistant TB* (XDR-TB). For an in-depth discussion of this complicated and evolving topic, guidelines should be consulted.[45,190,191]

INITIATING EMPIRICAL TREATMENT FOR DRUG-RESISTANT TUBERCULOSIS

In patients who are being treated for TB and had drug susceptibility results at the start of treatment that demonstrated susceptibility to the standard first-line regimen, drug-resistant TB should be suspected when there is lack of culture conversion by months 3 to 4 (especially if the initial AFB smear results were less than 4+)[76] and/or when there is lack of improvement or worsening of TB symptoms or imaging.[45] Suspicion for the emergence of drug resistance should be heightened when the patient has been receiving treatment without DOT.

In patients with a history of treated TB who present with a strong suspicion or new diagnosis of TB, the following are situations in which drug-resistant TB should be suspected:

- Patients with a history of treatment for drug-resistant TB
- Patients who did not receive DOT throughout the course of their TB treatment
- Patients who were treated with a nonstandard or inappropriate regimen
- Patients who did not complete the entire recommended duration of treatment (e.g., 6 months of treatment for uncomplicated drug-susceptible pulmonary TB)
- People living with HIV who received an intermittent regimen[133,134]

Efforts should be made to obtain past treatment records whether the patient was treated within or outside the United States.

For patients without a history of treated TB who present with a new diagnosis of TB or are strongly suspected of having TB, the following are situations in which drug-resistant TB should be suspected:

- Close contact with an individual with drug-resistant pulmonary TB
- Origin in a country with high rates of drug-resistant TB, such as countries formerly part of the Soviet Union

In all the above situations, rapid testing for drug resistance should be performed. GeneXpert MTB/RIF can simultaneously detect *M. tuberculosis* and RIF resistance, and results are available 2 hours after processing (see Chapters 19 and 53). The CDC provides a Molecular Detection of Drug Resistance Service to identify mutations that are most frequently associated with INH and RIF resistance; testing is also available for mutations associated with resistance to second-line drugs (https://www.cdc.gov/tb/topic/laboratory/default.htm). Results of rapid testing should be confirmed with culture-based drug-susceptibility testing. When resistance to RIF or more than one first-line drug is identified, drug susceptibility testing should be requested for the second-line drugs.[45] Resistance to fluoroquinolones should be evaluated whenever INH resistance is found.

KEY PRINCIPLES OF TREATING DRUG-RESISTANT TUBERCULOSIS

For patients being evaluated and treated for any form of drug-resistant TB, the following principles apply[191]:

- Consultation should be requested with a TB expert. In the United States, TB experts can be found through CDC-supported TB Centers of Excellence for Training, Education, and Medical Consultation (http://www.cdc.gov/tb/education/rtmc/default.htm).
- Regimens should include only drugs to which the patient's *M. tuberculosis* isolate has documented or high likelihood of susceptibility. Drugs known to be ineffective based on in vitro growth-based or molecular resistance should *not* be used.
- Never add a single new drug to a "failing" regimen; this will likely select for resistance to the new drug. Rather, multiple new drugs must be initiated.
- Treatment response should be monitored clinically, radiographically, and bacteriologically, with cultures obtained at least monthly for pulmonary TB. When cultures remain positive after 3 months of treatment, susceptibility tests for drugs should be repeated.

MECHANISMS AND PHARMACOLOGY OF DRUGS USED TO TREAT DRUG-RESISTANT TUBERCULOSIS

- Fluoroquinolones: Fluoroquinolones, which exhibit concentration dependent killing, are bactericidal through inhibition of bacterial DNA gyrases, preventing DNA synthesis. LFX and moxifloxacin are the preferred fluoroquinolones for treatment of TB because they have greater activity against MTB than ciprofloxacin or ofloxacin.[192] Fluoroquinolones should not be given within 2 hours of ingestion of milk-based products or antacids because absorption is impaired. LFX is primarily excreted through urine in an unchanged form; for this reason, dosing is thrice weekly (not daily) in patients with creatinine clearance less than 30 mL/min.
- Bedaquiline is a diarylquinolone with strong bactericidal activity against MTB through inhibition of mycobacterial ATP synthase and is active against both replicating and nonreplicating bacilli.
- Linezolid is an oxazolidinone that blocks bacterial ribosomal protein synthesis through binding to the 50S bacterial ribosomal subunit. Linezolid has modest early bactericidal activity against rapidly growing bacilli[193] and sterilizing activity.[194] Linezolid exhibits time-dependent killing, in which the 24-hour area under the curve to minimum inhibitory concentration ratio is predictive of bacillary eradication. Because discontinuation of linezolid due to adverse effects is common, some experts recommend monitoring trough levels after 2 weeks of therapy and minimizing toxicity by maintaining levels less than 2 μg/mL.
- Clofazimine is an *r*-iminophenazone pigment used to treat leprosy. The mechanism of clofazimine's bactericidal activity against MTB is incompletely understood, although it likely involves respiratory inhibition and production of reactive oxidant species.[195] Obtaining clofazimine requires the submission of an Investigational New Drug application to the *U.S. Food and Drug Administration* (FDA) and accessing the medication through the manufacturer (Novartis).
- Cycloserine is an analog of an amino acid, D-alanine, that impairs bacterial cell wall synthesis through competitive inhibition of two enzymes. Depending on tissue concentrations, cycloserine may be bacteriostatic or bactericidal. Cycloserine may cause adverse psychiatric effects including depression, psychosis, and suicidal ideation and should be avoided in patients with a history of psychiatric illness. Concomitant provision of pyridoxine may ameliorate these effects and should be given at 50 mg per 250 mg of cycloserine.[45] Adverse effects may be reduced by monitoring cycloserine levels to maintain peak concentration less than 35 μg/mL.
- Delamanid, a nitrodihydroimidazooxazole, is a prodrug bioactivated by mycobacterial nitroreductase.[196] Delamanid has bactericidal activity through inhibition of mycolic acid synthesis and is effective against actively and sporadically multiplying bacilli. Although approved for use in Europe, it has not yet been approved by the FDA.
- Pretomanid, like delamanid, is a nitroimidazole that inhibits mycolic acid synthesis and is bactericidal against actively and sporadically multiplying bacilli.[197] Pretomanid was approved by the FDA in 2019 for inclusion in a regimen for treatment of XDR-TB and resistant/intolerant MDR-TB (see later).

EMPIRICAL EXPANDED REGIMENS

There are situations in which an expanded empirical regimen is initiated for suspected drug-resistant TB, even before having results from rapid or phenotypic drug susceptibility testing. This decision is based on the probability that the patient has drug-resistant TB and on the severity of the patient's illness. An expanded regimen includes first-line drugs (INH, RIF, PZA, EMB) because the patient may have drug-susceptible TB and two or more new drugs for possible

drug-resistant TB. An expanded regimen may include a fluoroquinolone, linezolid, and/or amikacin, in addition to the first-line drugs (Table 54.5).

EMPIRICAL REGIMENS FOR MULTIDRUG-RESISTANT TUBERCULOSIS

If drug susceptibility testing reveals RIF (±INH) resistance, an empirical MDR-TB treatment regimen should be prescribed. Guidelines on the treatment of drug-resistant TB encourage the use of all oral regimens whenever possible.[190,191] A recent patient-level meta-analysis investigated associations between treatment outcomes in MDR-TB and the specific drugs in a regimen, the number of drugs in the regimen, and the duration of the different phases of treatment.[198] Treatment success was most likely when five or more effective drugs were included in the intensive phase. For the continuation phase, four drugs were associated with the greatest success.[198] Table 54.5 shows the recommended algorithm for building an empirical MDR-TB treatment regimen. The hierarchy of drug selection is based on treatment success associated with the different second-line agents and the adverse effect profiles of these medications.[198] If drug-susceptibility testing subsequently identifies resistance to any of the medications in the treatment regimen, the drug to which the isolate is resistant should be replaced with an effective medication. The final choice of drugs depends on patient preferences, harms and benefits associated with the agents, the capacity to monitor for significant adverse effects, consideration of drug-drug interactions, comorbidities, and drug availability. The doses of the drugs for treating adults and children with MDR-TB are provided in eTable 54.1.

TREATMENT DURATION

Similar to drug-susceptible TB, treatment of drug-resistant TB is composed of an initial intensive phase that uses more medications when the bacillary burden is highest and a continuation phase with fewer medications. Unlike the treatment of drug-susceptible TB, the duration of the intensive phase in MDR-TB is based on the timing of culture conversion. Based on findings from a patient-level meta-analysis,[198] guidelines recommend an intensive-phase treatment of between 5 and 7 months *after* culture conversion in patients

Table 54.5 Clinical Strategy to Build an Individualized Treatment Regimen for MDR-TB

Build a regimen *using five or more drugs to which the isolate is susceptible* (or has low likelihood of resistance), preferably with drugs that have not been used to treat the patient previously.
Choice of drugs is contingent upon capacity to monitor appropriately for significant adverse effects, patient comorbidities, and preferences/values (choices therefore subject to program and patient safety limitations).
In children with TB who are contacts of infectious MDR-TB source cases, the isolate from the source case can be used for drug susceptibility testing if an isolate is not obtained from the child. TB expert medical consultation is recommended (ungraded good practice statement).

Step	Action	Drug
1	Choose one later-generation fluoroquinolone	Levofloxacin Moxifloxacin
2	Choose both of these drugs	Bedaquiline Linezolid
3	Choose both of these drugs	Clofazimine Cycloserine
4	If a regimen cannot be assembled with five effective oral drugs, *and the isolate is susceptible*, use one of these injectable agents*	Amikacin Streptomycin
5	If needed or if oral agents are preferred over injectable agents in Step 4, use the following drugs†	Delamanid‡ Pyrazinamide Ethambutol
6	If limited options and cannot assemble a regimen of five effective drugs, consider use of the following drugs	Ethionamide or prothionamide§ Imipenem-cilastin/clavulanate *or* meropenam/clavulanate¶ *p*-Aminosalicylic acid‖ High-dose isoniazid**

*Amikacin and streptomycin should be used only when the patient's isolate is susceptible to these drugs. Because of their toxicity, these drugs should be used only when more effective or less toxic therapies cannot be assembled to achieve a total of five effective drugs.
†Patient preferences in terms of the harms and benefits associated with injectables (the use of which is no longer obligatory), the capacity to appropriately monitor for significant adverse effects, consideration of drug-drug interactions, and patient comorbidities should be considered in selecting step 5 agents over injectables. Ethambutol and pyrazinamide had mixed/marginal performance on outcomes assessed in the IPDMA; however, some experts may prefer these drugs over injectable agents to build a regimen of at least 5 effective oral drugs. Use pyrazinamide and ethambutol only when the isolate is documented to be susceptible.
‡Data on dosing and safety of delamanid are available in children down to 3 years of age.
§Mutations in the *inhA* region of *Mycobacterium tuberculosis* can confer resistance to ethionamide/prothionamide as well as to INH. In this situation, ethionamide/prothionamide may not be a good choice unless the isolate is shown to be susceptible with in vitro testing.
¶Divided daily intravenous dosing limits feasibility. Optimal duration of use not defined.
‖Fair/poor tolerability and low performance. Adverse effects reported to be less common in children.
**Data not reviewed in the IPDMA, but high-dose isoniazid can be considered despite low-level isoniazid resistance, but not with high-level INH resistance.
The following drugs are no longer recommended for inclusion in MDR-TB regimens: capreomycin and kanamycin, amoxicillin/clavulanate (when used without a carbapenem), azithromycin and clarithromycin.
INH; isoniazid; IPDMA, individual participant data meta-analysis; MDR-TB, multidrug-resistant tuberculosis.
Data from Nahid P, Mase SR, Migliori GB, et al. Treatment of drug-resistant tuberculosis. An official ATS/CDC/ERS/IDSA clinical practice guideline. *Am J Respir Crit Care Med*. 2019;200:e93–e142.

eTable 54.1 Doses of Drugs for Treatment of Adults and Children With MDR-TB

Step	Drug	Route of Administration	Adults	Children	Renal Insufficiency (Creatinine Clearance < 30 mL/min)
1	Levofloxacin	PO/IV	750–1000 mg/day*	15–20 mg/kg/day once daily*	tiw
	Moxifloxacin	PO/IV	400–(600–800 mg) daily†	10–15 mg/kg/day once daily	No change needed
2	Bedaquiline	PO	400 mg/day × 14 days, then 200 mg tiw	≥12 years and ≥30 kg: adult dose Studies ongoing in lower age groups and weights; based on expert opinion, for children >6 yr and weight 15–30 kg, half the adult dose can be used (200/day biw then 100 mg MWF for 22–24 wk	No change needed
	Linezolid	PO/IV	600 mg/day	≥12 years: 10 mg/kg once daily (300 or 600 mg) <12 yr: based on modeled pharmacokinetic data for lower weight bands[190,207,208]: 5–9 kg: 15 mg/kg once daily 10–23 kg: 12 mg/kg once daily >23 kg: 10 mg/kg once daily	No change needed
3	Clofazimine	PO	100 mg/day	2–5 mg/kg/day	No change needed
	Cycloserine/terizidone	PO	250–750 mg/day‡ Ensure within therapeutic range 20–35 mg/L in plasma to limit toxicity§	15–20 mg/kg/day	Start with 250 mg daily and verify with TDM in setting of renal disease
4	Amikacin	IV/IM	15 mg/kg/day	15–20 mg/kg/day	Patients with decreased renal function may require the 15 mg/kg dose to be given only 2–3 times weekly to allow for drug clearance
	Streptomycin	IV/IM	15 mg/kg/day; some clinicians prefer 25 mg/kg tiw	15–20 mg/kg daily *or* 25–30 mg/kg biw¶	Patients with decreased renal function may require the 15 mg/kg dose to be given only 2–3 times weekly to allow for drug clearance
5	Delamanid	PO	100 mg bid	≥35 kg: adult dose ≥6 yr and 20–34 kg: 50 mg bid >3–5 yr and 10–20 kg: 25 mg bid Lower age/weight: studies ongoing	Mild-moderate renal insufficiency: no change Severe insufficiency: limited data, use with caution
	Ethambutol	PO/IV	Low dose (companion drug): 15 mg/kg/day High dose (bacteriostatic drug): 25–30 mg/kg/day	20–25 mg/kg/day	tiw
	Pyrazinamide	PO	25–40 mg/kg/day	30–40 mg/kg/day	tiw

eTable 54.1 Doses of Drugs for Treatment of Adults and Children With MDR-TB—cont'd

Step	Drug	Route of Administration	Adults	Children	Renal Insufficiency (Creatinine Clearance < 30 mL/min)
6	Ethionamide	PO	15–20 mg/kg total (usually 250–500 mg/day or bid)‖	15–20 mg/kg total (divided 1–2 times daily)	No change needed
	Prothionamide	PO	15–20 mg/kg total (usually 250–500 mg/day or bid)‖	15–20 mg/kg total (divided 1–2 times daily)	No change needed
	Imipenem-cilastatin	IV	1000 mg tid–qid	Imipenem component, 15–25 mg/kg/dose qid	May reduce frequency
	Meropenem	IV	1000 mg tid	20–40 mg/kg/dose tid	May reduce frequency
	Clavulanate (component of amoxicillin-clavulanate) for co-administration with carbapenems	PO/IV	250 mg tid	25 mg/kg/dose of amoxicillin component tid	May reduce frequency to match carbapenem
	p-Aminosalicylic acid	PO/IV	4 g, bid–tid**	200–300 mg/kg/day in two divided doses	No change needed
	High-dose isoniazid††	PO/IV	15 mg/kg/day	15–20 mg/kg/day	No change needed

bid, 2 times/day; biw, 2 times/week; CNS, central nervous system; IM, intramuscular; IV, intravenous; MIC, minimum inhibitory concentration; PO, oral; qid, 4 times/day; TDM, therapeutic drug monitoring; tid, 3 times/day; tiw, 3 times/week.

*Levofloxacin doses of up to 1250 mg have been used safely when needed to achieve therapeutic concentrations. A population pharmacokinetic study in South African children found that higher levofloxacin doses from 18 mg/kg/day for younger children, up to 40 mg/kg/day for older children, may be required to achieve adult-equivalent exposures.[210]

†Higher moxifloxacin doses have been used safely when the isolate is resistant to ofloxacin and the MIC for levofloxacin or moxifloxacin suggests higher doses may overcome resistance. Higher doses also are used in cases of malabsorption.

‡Cycloserine doses can be divided if needed (typically twice daily). Doses >750 mg are difficult for many patients to tolerate.

§Cycloserine dose may be lowered if serum concentrations exceed 35 μg/mL, even if the patient is not experiencing toxicity, to prevent CNS toxicity.

‖Ethionamide can be given at bedtime or with a meal to reduce nausea. Experienced clinicians suggest starting with 250 mg once daily and gradually increasing the dose over 1 week. Serum concentrations may be useful in determining the appropriate dose. Few patients tolerate 500 mg bid.

¶Modified from adult intermittent dose of 25 mg/kg, and accounting for larger total body water content and faster clearance of injectable drugs in most children. Dosing can be guided by serum concentrations.

**Some experts prescribe *p*-aminosalicylic acid at 6 g, and up to 12 g, administered once daily.[45,211]

††Isoniazid is tested at two concentrations. Some experts use these results (or resistance conferred through mutations in *inhA*) to select a higher dose when it tests resistant at the lower concentration and susceptible at the higher concentration. The higher dose may achieve in vivo concentrations sufficiently high to overcome low-level resistance.[45]

Data from references 29, 45, 73, 209; and Nahid P, Mase SR, Migliori GB, et al. Treatment of drug-resistant tuberculosis. An official ATS/CDC/ERS/IDSA clinical practice guideline. *Am J Respir Crit Care Med.* 2019;200:e93–e142.

with MDR-TB.[191] The optimal duration for the continuation phase was 15 to 18 months.[198] The ATS/CDC/IDSA guidelines recommend that MDR-TB treatment be continued for 15 to 21 months after culture conversion (5–7 months of which include the intensive phase).[191]

NEW REGIMEN FOR EXTENSIVELY DRUG-RESISTANT TUBERCULOSIS OR TREATMENT-INTOLERANT OR NONRESPONSIVE MULTIDRUG-RESISTANT TUBERCULOSIS

The efficacy, safety, and tolerability of an all-oral 6-month regimen comprising bedaquiline, pretomanid (a nitroimidazooxazine), and linezolid (BPaL [bedaquiline + pretomanid + linezolid] regimen) was recently evaluated in a single-arm trial enrolling patients with highly-resistant TB (Nix-TB Trial, ClinicalTrials.gov identifier: NCT02333799). The three-drug, all-oral, 6-month regimen stably converted sputum cultures to negative with a median time of less than 6 weeks, with 90% of the 109 patients enrolled in the study achieving relapse-free cure. In August 2019, the FDA approved the BPaL regimen for the treatment of a specific limited population of adults with pulmonary XDR-TB or treatment-intolerant or nonresponsive MDR-TB.[2,141] Additional trials that include diverse patient populations will be essential to understand optimal use of the regimen, including the best approaches to minimizing toxicities. Neuropathy and other linezolid-associated adverse events caused more than 60% patients to interrupt treatment at least once in the trial.

ISONIAZID MONORESISTANCE

Monoresistance to INH is frequent, with an estimated global prevalence of 8% of TB cases.[199] INH monoresistance has been reported in up to 20% of non–U.S.-born residents from high-risk Asian countries.[200,201]

A meta-analysis found that the treatment of INH-monoresistant TB with first-line drugs, including the previously recommended regimen of RIF, EMB, and PZA for 6 months,[202] was associated with poorer treatment outcomes compared to drug-susceptible TB.[203] For this reason, current guidelines make the following recommendations for the treatment of INH-resistant TB[191]:

- A later-generation fluoroquinolone (i.e., moxifloxacin or LFX) should be added to a regimen of RIF, EMB, and PZA, all given daily for 6 months.
- PZA may be included for only the first 2 months of treatment in situations when the initial disease burden is low (e.g., noncavitary pulmonary TB) and/or when there are PZA-related adverse events.

Recommendations are available on treatment regimens for other drug-resistance patterns and special situations.[45]

SURGERY

Surgery was one of the first therapeutic approaches for TB, but since effective chemotherapy became available, surgery has been relegated to specific situations. For the management of MDR-TB, there appears to be a benefit from an elective partial lung resection (e.g., lobectomy or wedge resection) when offered together with a recommended MDR/XDR-TB regimen compared to medical therapy alone.[191] Specifically, surgery may be indicated when clinical judgment, supported by bacteriologic and radiographic data, suggest a strong risk of treatment failure or relapse with medical therapy alone.[204,205]

Key Points

- *Tuberculosis* (TB) treatment should be administered through directly observed therapy, and this is particularly important when treating patients living with HIV infection, on intermittent therapy, or with drug-resistant TB.
- Adequate treatment for TB is the major intervention needed for decreasing transmission of *M. tuberculosis*, both for drug-susceptible and drug-resistant strains. Treatment consists of an initial *intensive* phase to eliminate actively replicating bacteria, followed by a *continuation* phase to eliminate the persisting organisms.
- Assuming an adequate regimen, patient adherence is the critical factor that determines the success of treatment.
- When drug resistance is suspected or identified during treatment, two or more new drugs active against the patient's isolate must be added. A single drug should *never* be added to a failing regimen.
- The treatment of extrapulmonary TB is largely the same as the treatment of pulmonary TB. The exceptions are central nervous system TB and TB involving bones and joints, in which treatment of longer duration is recommended.
- Expert consultation should be obtained when treating patients with drug-resistant TB, those who develop medication-related adverse effects, and patients with TB/HIV coinfection or underlying liver disease. In the United States, TB experts can be found through local health department TB control programs and/or regional Centers for Disease Control and Prevention-supported TB Centers of Excellence for Training, Education, and Medical Consultation (http://www.cdc.gov/tb/education/rtmc/default.htm).

Key Readings

Ahmad N, Ahuja SD, Akkerman OW, et al. Treatment correlates of successful outcomes in pulmonary multidrug-resistant tuberculosis: an individual patient data meta-analysis. *Lancet*. 2018;392(10150):821–834.

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Complete reference list available at ExpertConsult.com.

eFIGURE IMAGE GALLERY

Activity	Baseline	Month of Treatment Completed 1	2	3	4	5	6	7	8	End of Treatment Visit
MICROBIOLOGY										
Sputum smears and culture[1]	☐	☐	☐	☐	☐					☐
Drug susceptibility testing[2]	☐			☐						
IMAGING										
Chest radiograph or other imaging[3]	☐		☐							☐
CLINICAL ASSESSMENT										
Weight[4]	☐	☐	☐	☐	☐	☐	☐	☐	☐	
Symptom and adherence review[5]	☐	☐	☐	☐	☐	☐	☐	☐	☐	
Vision assessment[6]	☐	☐	☐	☐	☐	☐	☐	☐	☐	
LABORATORY TESTING										
AST, ALT, bilirubin, alkaline phosphate[7]	☐	☐	☐	☐	☐	☐	☐	☐	☐	
Platelet count[8]	☐	☐	☐	☐	☐	☐	☐	☐	☐	
Creatinine[8]	☐	☐	☐	☐	☐	☐	☐	☐	☐	
HIV[9]	☐									
Hepatitis B and C screen[10]	☐									
Diabetes screen[11]	☐									

eFigure 54.1 Baseline and follow-up evaluations for patients treated with first-line *tuberculosis* (TB) medications. Shading around boxes indicates activities that are optional or contingent on other information. *1,* Obtain sputa for smear and culture at baseline, then monthly until two consecutive specimens are negative. Collecting sputa more often early in treatment for assessment of treatment response and at end of treatment is optional. At least one baseline specimen should be tested using a rapid molecular test. *2,* Obtain drug susceptibility for INH, RIF, EMB, and PZA. Repeat drug susceptibility testing if patient remains culture positive after completing 3 months of treatment. Molecular resistance testing should be performed for patients with risk for drug resistance. *3,* Obtain chest radiograph at baseline for all patients and also at month 2 if baseline cultures are negative. End-of-treatment chest radiograph is optional. Other imaging for monitoring of extrapulmonary disease. *4,* Monitor weight monthly to assess response to treatment; adjust medication dose if needed. *5,* Assess adherence and monitor improvement in TB symptoms (e.g., cough, weight), as well as development of medication adverse effects (e.g., jaundice, nausea, vomiting, fever, rash, malaise, neuropathy, arthralgias). *6,* Patients on EMB: Test baseline visual acuity (Snellen test) and color discrimination tests, followed by monthly inquiry about visual disturbance and monthly color discrimination tests. *7,* Obtain liver function tests only at baseline unless there were abnormalities at baseline, symptoms consistent with hepatotoxicity develop, or patient chronically consumes alcohol, takes other potentially hepatotoxic medications, has viral hepatitis or history of liver disease, HIV infection, or prior drug-induced liver injury. *8,* Obtain at baseline for all patients. Further monitoring if there are baseline abnormalities or as clinically indicated. *9,* Test for HIV in all patients. CD4 lymphocyte count and HIV viral load if positive. *10,* Screen for hepatitis B or C in all patients with risk factors, such as injection drug use, birth in Asia or Africa, or HIV infection. *11,* Obtain fasting glucose or hemoglobin A1c for patients with risk factors for diabetes, according to the American Diabetes Association, including age older than 45 years, BMI greater than 25, first-degree relative with diabetes, and race/ethnicity of African American, Asian, Hispanic, American Indian/Alaskan Native, or Hawaiian Native/Pacific Islander. ALT, alanine aminotransferase; AST, aspartate aminotransferase; BMI, body mass index; EMB, ethambutol; HIV, human immunodeficiency virus; INH, isoniazid; PZA, pyrazinamide; RIF, rifampin.

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APPENDIX: ESSENTIALS OF CHEMOTHERAPY

INTRODUCTION

The development of successful chemotherapy for *tuberculosis* (TB) must rank as one of the greatest achievements of medical science. Beginning in the late 1940s, chemotherapy began to slow—little by little—the centuries' long and ever-growing toll from the incurable "captain of all these men of death," John Bunyan's name for the plague that has killed an estimated 2 billion human beings—more, by far, than any other disease. Notable victims included kings and princes, cardinals, famous poets, writers, musicians, and artists, and, of course, countless anonymous poor people. Finding a cure for this scourge did not happen easily, quickly, or by serendipity. It was the cumulative work over decades by many men and women dedicated to that single purpose, and—keep this in mind—these efforts are ongoing.

Even though effective treatment has been available for more than 60 years, TB continues to plague vulnerable regions of the world. More and more strains of disease-producing *Mycobacterium tuberculosis* are resistant to standard antituberculosis regimens. The most recent statistics report an estimated 10.0 million new cases and 1.2 million deaths.[1] Globally, 3.4% of new cases and 18% of previously treated cases are estimated to have *rifampin* (RIF)-resistant or *multidrug-resistant* (MDR)-TB (i.e., resistant at least to *isoniazid* [INH] and RIF). It is estimated that 6.2% of MDR cases are *extensively drug-resistant TB* (XDR-TB) (MDR-TB with resistance to at least one fluoroquinolone and one second-line injectable drug [amikacin, kanamycin, or capreomycin]), with 131 countries having reported at least one case of XDR.

BEGINNINGS

To understand where we currently stand and to appreciate the enormity of the task ahead, this appendix provides a brief chronology of the use of chemotherapy for treating TB, starting with streptomycin, the original breakthrough agent, which was first injected into a desperately ill young woman in November 1944. To everyone's astonishment and relief, she did not die but slowly began to recover. Then, seemingly miraculously, so did others.[2]

But within a few years, after many more patients with TB had been treated with streptomycin, it became apparent that the striking clinical and radiographic improvement observed initially did not always last; after several months of treatment, patients began to worsen, and the reason was immediately obvious: their tubercle bacilli had become resistant to streptomycin.[3] The findings of clinical failure and emergence of drug resistance served to define the major bacteriologic principle on which successful chemotherapy for TB depends: bacillary populations are not uniform in their susceptibility to antituberculosis agents. Hence it is always necessary to treat active disease with more than one drug to which the organisms are susceptible.

The concept of multiple-drug chemotherapy was first validated in 1950 by a British Medical Research Council study in which streptomycin was partnered with *p-aminosalicylic acid* (PAS). Long-lasting success was achieved because PAS prevented organisms from becoming resistant to streptomycin and vice versa, and two drugs have more bacteriologic and clinical effect than only one.[4] Since that time, treatment with more than one drug has been standard in the management of patients with TB. Although the combination of streptomycin and PAS was effective, neither agent was well tolerated, and clinical improvement was slow and hampered by side effects. The long-sought solution to antituberculosis chemotherapy arrived in 1952 with the introduction of INH, a powerful drug that was not only highly effective but well tolerated and inexpensive.[5] However, once again it was learned that single-drug treatment with INH was inadequate because resistance to the agent developed quickly. The solution was clear: combine INH with both streptomycin and PAS. This triple therapy became the standard treatment for TB until 1967, when a new antituberculosis agent, *ethambutol* (EMB), an easily tolerated and minimally toxic drug, was welcomed as a substitute for PAS.[6]

Subsequent experiments have shown that, in any wild-type strain of *M. tuberculosis,* there are subpopulations with spontaneous mutations in genes that confer drug resistance. The frequency of drug-resistant mutants is 1 in 3.5×10^6 for INH, 1 in 3.8×10^6 for streptomycin, 1 in 3.1×10^8 for RIF, and 1 in 0.5×10^4 for EMB.[7] Thus a bacillary population of more than 10^{12} organisms would be required before one would expect to find (statistically) a single bacillus resistant to both INH and streptomycin.

Once optimum doses of each component were established, wide use of triple therapy revolutionized the care of patients with TB. Springett[8] reviewed death rates from TB for cohorts of patients in Birmingham, England, for the years 1947, 1950, 1953, 1956, and 1959. With increasing use of antituberculosis chemotherapy, deaths decreased dramatically during the 10 years after diagnosis, and nearly all of the reduction was accounted for by improvements in survival during the first year after diagnosis. In addition, not only were survivors more numerous, but among survivors, far fewer than in the prechemotherapy era continued to be potential sources of new infections. In the Springett study,[8] both the decrease in mortality rate and the reduction in the prevalence of chronically infectious patients reached their maximum in 1956, with no further improvement in 1959.

The next major advance in chemotherapy for pulmonary TB resulted from the discovery of rifampin (or rifampicin, as it is known in many parts of the world) and the demonstration that the combination of INH and RIF, generally with EMB or streptomycin, could dramatically shorten the necessary duration of treatment.[9] In a series of important studies from East Africa during the 1970s, the British Medical Research Council established that a 6-month regimen consisting of INH, streptomycin, and RIF was as effective as the standard regimen used at the time in developing countries (18 months of INH and thiacetazone, plus streptomycin given during the first 2 months).[10]

A critical factor influencing the effectiveness of chemotherapy was, and continues to be, the adherence (or lack thereof) of patients to the prescribed regimen, a fact well documented both in the United States and in developing countries.[11–13] In spite of initial high rates of success elsewhere, the results of a U.S. Public Health Service multicenter cooperative trial indicated that a 6-month regimen of INH and RIF did not have an acceptable rate of favorable outcome.[14] Positive cultures were found in 6.1% of the patients between 3 and 6 months after treatment began. Of greater importance was that 9.2% experienced relapse after completion of treatment. Strikingly, 16.8% of the patients were withdrawn from the study because they had been delinquent about clinic visits during the 6 months of treatment. This outcome was a setback for efforts to shorten the duration of treatment to 6 months, which—assuming equal effectiveness and tolerance—would have considerable clinical and logistical advantages over 18- to 24-month regimens.

Studies of chemotherapy then began to focus on the possible benefits of *pyrazinamide* (PZA).[15] Dickinson and coworkers[16] demonstrated that streptomycin, RIF, and INH are quickly bactericidal for rapidly growing *M. tuberculosis* in vitro. The in vitro conditions could be likened to the conditions under which the extracellular organisms in tuberculous lesions are living. Although both RIF and INH are rapidly bactericidal, Mitchison and Dickinson[17] demonstrated that RIF is more effective in killing organisms that grow in spurts rather than continuously. Although both INH and RIF are effective in killing intracellular organisms, PZA is especially effective for this purpose, suggesting that the addition of PZA would strengthen the INH-RIF combination. Subsequently, two studies substantiated the fact that the addition of PZA for 2 months to a regimen of INH and RIF does indeed improve the effectiveness of a 6-month regimen.[18,19] Thus a 6-month regimen of INH and RIF supplemented by PZA and EMB for the initial 2 months is now recommended as standard treatment for most patients with newly diagnosed pulmonary TB.[20]

DRUGS IN CURRENT USE

The preferred drugs for treating drug-susceptible and drug-resistant TB are shown in Table 54.2 and eTable 54.1, respectively. Together with Table 54.3, the tables list first- and second-line drugs, their pharmacology, the available preparations, and the doses used to treat TB.

FIRST-LINE DRUGS

Isoniazide (INH), used for the treatment of TB since the 1950s, is very effective, specific for certain mycobacteria, relatively nontoxic, easily administered, and inexpensive. INH is a prodrug and is activated by bacterial KatG, a catalase/peroxidase enzyme.[21] Once it is activated, INH inhibits reduced nicotinamide adenine dinucleotide–dependent enoyl–acyl carrier protein reductase encoded by *inhA*. This process ultimately results in the inhibition of synthesis of essential mycolic acids.[22] The most common cause of resistance to INH is deletion of, or mutations in, KatG that result in loss of catalase/peroxidase activity. A mutation in *katG* that results in substitution of threonine for serine in codon 315 (S315T) is the most common mutation found in INH-resistant clinical isolates.[23] Mutations in the promoter of *inhA* cause resistance to INH and the second-line drug ethionamide.[24] These mutations are less frequent than those in *katG*. In a study of global clinical isolates, 78.6% of the *M. tuberculosis* isolates resistant to INH had a mutation in *katG* only, 6.8% had mutations in *inhA* only, and 14.6% had mutations in both.[23] Other mutations reported to be associated with INH resistance are mutations in the *furA-katG* intergenic region and in the *oxyR-ahpC* region.[25] When INH is used alone, a population of organisms resistant to the drug emerges rapidly. This was demonstrated in an early clinical trial in which 11%, 52%, and 71% of patients to whom INH alone was given developed resistant strains after 1, 2, and 3 months of treatment, respectively.[26]

INH is highly active against *M. tuberculosis:* most strains are inhibited by concentrations of 0.05 to 0.20 μg/mL, and it has profound early bactericidal activity.[27] The drug is 90% absorbed from the *gastrointestinal* (GI) tract, although food (especially high fat) and antacids decrease absorption. Blood concentrations of 3 to 5 μg/mL peak 1 to 2 hours after administration of 3 to 5 mg/kg of body weight. The drug penetrates well into all body fluids and cavities, producing concentrations similar to those found in serum.

The hepatic elimination rate and differences in serum INH concentrations between individuals taking daily INH are primarily due to acetylation rates determined by polymorphic variation in the N-acetyltransferase 2 enzyme gene *(NAT2)*, which has a trimodal phenotypic distribution.[28] After a 10 mg/kg dose of INH, mean values of the area under the concentration curve were 7.7, 16.5, and 31.1 mg/hr/L for fast, intermediate, and slow acetylators, respectively.[28] Differences in acetylation status are seen between ethnicities; approximately 50% of whites and Blacks are rapid acetylators, whereas 80–90% of Asian individuals are rapid acetylators.[29,30] Of importance, a meta-analysis of associations between INH pharmacokinetic variability among individuals treated for active TB and clinical outcomes showed that rapid acetylators were significantly more likely than slow acetylators to experience microbiologic failure, acquired drug resistance, and TB relapse.[31] Individuals who are slow acetylators undergoing treatment for active TB have been shown to be at higher risk for hepatic injury from INH compared to intermediate or rapid acetylators.[32] The serum half-life varies, depending on whether a person is a rapid or slow acetylator; half-lives are 2 to 5 hours in slow acetylators and 0.5 to 2 hours in rapid acetylators.[33] Despite these differences, INH dosing is not changed based on acetylation status.

Hepatitis is the major toxic effect of INH.[34,35] Asymptomatic elevations of aminotransferase—up to five times the upper limit of normal—are seen in 10–20% of persons receiving INH alone for the treatment of latent tuberculous infection.[34] The enzyme levels usually return to normal even with continued administration of the drug. A meta-analysis estimated the rate of clinical hepatitis to be 0.6% with INH alone and 2.6% when INH was administered with RIF.[36] In a recent randomized, controlled trial of INH compared to RIF for the treatment of latent TB infection,[35] 2.0% of INH-treated participants experienced grade 3 or 4 hepatotoxic events compared to 0.3% in the

RIF arm.[37] Among INH-treated participants with hepatotoxicity, 75% of these events developed within the first 4 months of treatment. For INH alone, the risk was greater with increasing age, starting at age 35 years.[37] The incidence of INH-related hepatotoxicity increases with older age, the coadministration of other potentially hepatotoxic drugs, increased doses of INH, liver disease, heavy alcohol use, and in the peripartum period, particularly among Hispanic women.[37–39] A study of INH treatment for latent TB infection during pregnancy in *human immunodeficiency virus* (HIV)-infected pregnant women found a higher incidence of adverse pregnancy outcomes in participants who received INH while pregnant compared to initiation of INH 12 or more weeks postpartum.[40]

INH interferes with pyridoxine (vitamin B_6) functions and may lead to dose-related neurologic side effects, including peripheral neuropathy and paresthesias. In otherwise healthy persons, this adverse effect is uncommon (<0.2%) at conventional doses.[41,42] The risk is increased in individuals with nutritional deficiency, diabetes, renal failure, and alcoholism; people living with HIV; and pregnant and breastfeeding women.[20] Individuals at risk for neurologic side effects and those who develop neuropathy should receive pyridoxine supplementation (25–50 mg/day) to minimize the risk of neuropathy.

Less common adverse effects related to INH include drug-induced lupus syndrome (<1%) and central nervous system effects, such as headaches, difficulties with concentration, seizures, optic neuritis, and depression. INH also inhibits the *cytochrome P-450* (CYP) system and may cause increases in serum concentrations of concomitant medication, such as phenytoin, carbamazepine, clopidogrel, and warfarin. Rare hematologic reactions include agranulocytosis; thrombocytopenia; eosinophilia; and hemolytic, sideroblastic, or aplastic anemia. Hypersensitivity reactions include fever, skin eruptions, lymphadenopathy, and vasculitis. Metabolic and endocrine reactions include pellagra, hyperglycemia, metabolic acidosis, and gynecomastia.

Rifampin (RIF) is a semisynthetic rifamycin derivative that is highly active against mycobacteria, most gram-positive bacteria, and some gram-negative bacteria. It is rapidly bactericidal for both intracellular and extracellular microorganisms; susceptible strains are inhibited by concentrations of 1.0 μg/mL or less.[43] By inhibiting prokaryotic DNA-dependent RNA polymerase, RIF suppresses the early elongation of the nucleotide chain in RNA synthesis.[44]

Resistance to RIF results from mutations in the *rpoB* gene, the product of which is the β-subunit of RNA polymerase. Although many different mutations may be involved, alterations in *rpoB,* specifically in a "hot spot" of 81 base pairs (the rifamycin resistance–determining region), account for approximately 96% of the RIF-resistant strains isolated from patients in many different parts of the world.[25,45] The mechanism for resistance in the remaining 4% is not known. Among susceptible strains of *M. tuberculosis,* the rate of mutation seems to be less for RIF than for INH. David[7] reported the rate of mutation to RIF resistance to be approximately 10×10^{10} per generation. In spite of this rather low rate of in vitro mutation, resistance rapidly develops when RIF is used alone in vivo.[46] Resistance to RIF unaccompanied by resistance to other antituberculosis drugs has been reported to be much more common among patients with HIV infection, particularly among patients being treated with once- or twice-weekly intermittent regimens containing rifamycins.[47–49]

RIF is easily administered and is relatively nontoxic. The drug is normally absorbed completely when taken orally, but food delays absorption. After 1 to 4 hours, a 600-mg dose yields a peak blood level of 8 to 24 μg/mL.[50] The half-life of RIF varies from 2 to 3 hours, and it is shortened by approximately 20–40% after the first week of daily treatment because of the induction of hepatic microsomal enzymes. The half-life is unaffected by renal impairment but is increased by liver disease or biliary obstruction. RIF is deacetylated to an enterohepatically recirculated active metabolite, and 50–60% is excreted in the feces. Up to 30% of a dose is excreted in the urine. Approximately 85% of circulating RIF is bound to plasma proteins and is widely distributed throughout the body. Although RIF penetrates well into tissues and cells, penetration through noninflamed meninges is poor; however, therapeutic concentrations are achieved in cerebrospinal fluid when the meninges are inflamed.[51]

In the usual daily doses of 10 mg/kg (maximum, 600 mg), RIF is well tolerated. It often causes harmless red-orange discoloration of tears, sweat, saliva, feces, and urine. Less than 4% of TB patients experience significant adverse reactions to RIF. GI adverse effects are the most common and include epigastric distress, anorexia, nausea, vomiting, cramps, and diarrhea. Hepatitis rarely happens in persons who have normal baseline hepatic function and is substantially lower than that for INH or PZA. In a recent randomized, controlled trial of INH compared to RIF for the treatment of latent TB infection,[35] grade 3 or 4 hepatotoxic events were observed in 0.3% of RIF-treated participants, and none of the investigated risk factors, including age, was associated with RIF-induced hepatic injury.[37]

Rifamycins have been associated with several types of immune-mediated allergic reactions termed hypersensitivity.[52] A common presentation for rifamycin hypersensitivity reactions is a flulike syndrome with nonspecific symptoms, including fever, chills, malaise, headaches, dizziness, and/or bone pain. The syndrome has been associated in some studies with the development of anti-RIF antibodies or with complement activation.[53] Hypersensitivity reactions are more common with intermittent RIF administration, particularly at doses higher than 600 mg. Such reactions are uncommon using the 600 mg RIF dose given daily. In a very small proportion of patients, the flulike syndrome is associated with interstitial nephritis, acute tubular necrosis, thrombocytopenia, hemolytic anemia, dyspnea, and shock.[54]

RIF can occasionally cause thrombocytopenia and thrombocytopenic purpura, with or without other symptoms of abnormal bleeding. Thrombocytopenia is usually associated with intermittent RIF therapy but has also been reported with daily treatment. No permanent abnormality of platelet production or function has been observed, and fatalities attributed to cerebral hemorrhage have resulted only when RIF administration was continued or resumed after the appearance of purpura. If purpura arises during RIF administration, the drug should be stopped and not readministered.

Drug-drug interactions due to RIF induction of CYP enzymes, especially CYPs 1A2, 2C9, 2C19, and 3A4, are common and apply to a broad range of drugs. In the case of TB, these interactions are especially relevant in people living with HIV infection. RIF is contraindicated in patients receiving tenofovir alafenamide–containing formulations, protease inhibitors, pharmacokinetic boosters (e.g., cobicistat, ritonavir), and most non-nucleoside reverse transcriptase inhibitors aside from efavirenz. *Integrase strand transfer inhibitor* (INSTI)-based regimens are the first-line regimens for the treatment of HIV infection in the United States and Europe and are endorsed by the World Health Organization as the preferred regimen.[55] Trough concentrations of the INSTIs raltegravir and dolutegravir are significantly reduced by concomitant use of RIF.[56,57] Pharmacokinetic data support increasing the raltegravir dose to 800 mg twice daily, and expert opinion in the United States favors this strategy.[58] Pharmacokinetic studies demonstrate that coadministration of RIF and dolutegravir at a dosage of 50 mg twice daily results in adequate trough concentrations of dolutegravir.[57] Of the rifamycins, rifabutin is the least potent inducer of cytochrome isoenzymes and may be used in patients receiving non-nucleoside reverse transcriptase inhibitors and boosted protease inhibitors, as well as dolutegravir or raltegravir. As dose adjustments of antiretroviral and rifamycins may be required, expert consultation in treating individuals with concurrent HIV-infection and TB is strongly recommended.

RIF induces the metabolism of a number of other drugs, including methadone, warfarin, oral contraceptives, cyclosporine, tacrolimus, antiepileptics, and others.[50] Doses of these drugs need to be adjusted when RIF is given.

Rifabutin, although not approved by the *U.S. Food and Drug Administration* (FDA) for the treatment of TB, may be used as a substitute for RIF in most treatment regimens.[20] Because of its lesser propensity to induce CYP enzymes, rifabutin is generally reserved for patients who are taking any medication for which there are unacceptable interactions with RIF. It may also be used for patients who are intolerant of RIF.[59] There is extensive cross-resistance among the rifamycins for *M. tuberculosis.*

Ethambutol (EMB) acts by inhibiting the synthesis of arabinogalactan of the mycobacterial cell wall and is bacteriostatic against *M. tuberculosis* at usually administered doses.[60] Minimum inhibitory concentrations of the drug for *M. tuberculosis* range from 1 to 5 μg/mL.[43] Mutations in the *embB* gene, which codes for arabinosyltransferases, are found in approximately 70% of EMB-resistant strains.[25,44,45]

The primary purpose of EMB in the treatment of drug-susceptible TB is to reduce the risk of selection for RIF resistance in patients with TB caused by strains that have resistance to INH, because PZA is not thought to protect other drugs from selection for drug resistance. EMB is easily administered and has a low frequency of adverse reactions. Peak plasma concentrations are recorded 2 to 4 hours after ingestion. With doses of 15 mg/kg, the peak concentration is 2 to 6 μg/mL.[50] In persons with normal renal function, the half-time in blood is 3 to 4 hours. As EMB is primarily excreted unchanged in urine, dosing is adjusted in patients with impaired renal function. Protein binding is minimal, but penetration into cells is thought to be poor. Cerebrospinal fluid concentrations of EMB, even in the presence of meningeal inflammation, are low, averaging 1 to 2 μg/mL after a dose of 25 mg/kg.

Optic neuritis is the main adverse effect of EMB. Symptoms include blurred vision, central scotomata, and red-green color blindness. EMB-related visual impairment during treatment of active TB has been estimated to happen in 19 of 1000 persons receiving EMB at 27.5 mg/kg/day or less for 2 to 9 months duration.[61] The onset of optic neuritis is usually more than 1 month after treatment initiation but can happen within days.[62,63] To avoid permanent deficits, EMB is promptly discontinued if visual abnormalities are found, and ophthalmologic consultation should be obtained. Recovery of vision takes 3 months on average.[61] The frequency of ocular effects is increased in patients with renal failure, presumably owing to increased serum concentrations of the drug.

PZA is a prodrug that is bioactivated by *Mycobacterium tuberculosis* (MTB) pyrazinamidase enzymes to *pyrazinoic acid* (POA). It is rapidly bacteriostatic but only slowly bactericidal. The mechanism of action of POA is incompletely understood and likely relies on multiple targets for effect, including inhibition of fatty acid synthesis.[64] PZA is active against *M. tuberculosis* in acidic environments, which suggests that the drug is activated under these conditions.[65] The inclusion of PZA in the first 2 months of treatment of drug-susceptible TB allows total treatment length to be shortened to 6 months from 9 months.[20] The genetic mechanism of mycobacterial resistance to PZA is predominantly due to any of a large number of mutations in the *pncA* gene, which encodes the enzyme pyrazinamidase, necessary for the intracellular conversion of PZA to POA. Mutations in the *pncA* gene are found in approximately 70–85% of PZA-resistant strains.[44,45,66]

Absorption from the GI tract is nearly complete; serum concentrations peak 1 to 4 hours after ingestion. Concentrations generally range from 20 to 40 μg/mL with doses of 20 to 25 mg/kg.[50] The serum half-life is 9 to 10 hours. At a pH of 5.5, the minimal inhibitory concentration of PZA for *M. tuberculosis* is 20 μg/mL. Penetration of the drug into cells and tissues seems to be fairly good, although data with regard to tissue concentrations are limited.

Among the four first-line drugs for TB treatment, PZA is the drug most commonly responsible for adverse effects.[67] The most important adverse reaction to PZA is liver injury. Hepatotoxicity was significantly higher among participants treated with PZA, INH, and RIF (2.6%) compared to treatment with INH and RIF alone (0.8%).[68] Because PZA impairs renal urate clearance, hyperuricemia is reported in nearly all patients taking the drug. Clinical gout is not common, but diffuse arthralgias, apparently unrelated to the hyperuricemia, are common. The drug may also cause nausea and vomiting and skin rashes, especially photosensitive dermatitis.

SECOND-LINE DRUGS

The second-line drugs are usually reserved for patients with drug-resistant TB, although they may be used in patients with contraindications to, or intolerance of, the first-line drugs. All second-line drugs have important limitations—effectiveness, toxicity, and/or cost—that interfere with their general applicability in treating TB.[69]

Of the second-line drugs, the fluoroquinolones *levofloxacin* and *moxifloxacin*, are the most widely used because both agents possess good bactericidal activity against *M. tuberculosis* and are widely available, familiar to clinicians, and relatively well tolerated. The fluoroquinolones are currently not considered as first-line agents but should be reserved either for patients with drug-resistant organisms or those who cannot tolerate first-line drugs. The target of the fluoroquinolones is DNA gyrase, an enzyme that operates to increase coiling of DNA. Resistance to these agents is mediated by mutations in the *gyrA* and *gyrB* genes that encode for DNA gyrase.[25,44] In a systematic review of 46 studies, 87% of moxifloxacin-resistant *M. tuberculosis* isolates had mutations in *gyrA* and 1–2% had *gyrB* mutations; alternative mechanisms for fluoroquinolone resistance may be due to low cell wall permeability, efflux-related mechanisms, and drug sequestration.[70]

Levofloxacin and moxifloxacin are generally well tolerated.[71] The most frequent adverse effects include nausea, vomiting, dizziness, anxiety, tremulousness, and other central nervous system effects. Additional adverse effects include QT prolongation, tendonitis and tendon rupture, arthralgias, and peripheral neuropathy.

Bedaquiline was approved by the FDA in 2012 as part of combination therapy (minimum four drugs) administered by direct observation to adults 18 years or older with MDR-TB, when an effective treatment regimen cannot otherwise be provided (i.e., no other drug to which *M. tuberculosis* is susceptible or drug intolerance). Bedaquiline is a diarylquinoline that has strong bactericidal activity against MTB through inhibition of the proton pump of mycobacterial *adenosine 5′-triphosphate* (ATP) synthase.[72] It has in vitro activity against both replicating and nonreplicating bacilli and has bactericidal and sterilizing activity in the murine model of TB infection. Mutations in the *atpE* gene, which encodes the mycobacterial F1F0 proton ATP synthase, a key enzyme in ATP synthesis and membrane potential generation, has been associated with bedaquiline resistance. Off-target mutations in *rv0678,* leading to efflux-based resistance, are associated with cross-resistance to bedaquiline and clofazimine.[73]

Bedaquiline serum concentrations peak approximately 5 to 6 hours after ingestion at a level of 2 to 3 μg/mL.[50] Administration with food increases bedaquiline bioavailability twofold. The half-life of bedaquiline is long, approximately 5.5 months. It is metabolized by the liver, although dose adjustment in hepatic disease is not required. Although relatively well tolerated,[71] bedaquiline may cause QT prolongation, especially when administered with other QT-prolonging medications (e.g., fluoroquinolones, clofazimine). Other adverse effects include nausea, headache, rash, arthralgia, and transaminitis. Monitoring during treatment with bedaquiline includes obtaining electrocardiographs at baseline, 2, 12, and 24 weeks of treatment and monthly liver function testing.[50] Of note, bedaquiline has also been reported to enhance macrophage bactericidal activities independently of its direct antimycobacterial action, which may increase its effectiveness.

Linezolid is an oxazolidinone that blocks bacterial ribosomal protein synthesis through binding to the 50S bacterial ribosomal subunit. Linezolid has modest early bactericidal activity against rapidly growing bacilli[74] and sterilizing activity.[75] *M. tuberculosis* resistance to linezolid is most commonly (≈90% of resistance) due to mutations in the *rplC* gene.[73] Linezolid serum concentrations peak approximately 1 to 2 hours after ingestion at a level of 12 to 24 μg/mL.[50] The half-life of linezolid is approximately 5 hours. It is metabolized by the liver and excreted in urine.

Linezolid may be poorly tolerated when given over months.[71,76] Common adverse effects are neuropathy (including unusual manifestations, such as loss of taste or hearing), myelosuppression, optic neuropathy, and serotonin syndrome when taken with other serotonergic agents. All patients should receive pyridoxine while taking linezolid. Routine monitoring includes complete blood counts (weekly during initial period and monthly thereafter) and monthly evaluations of visual acuity and color discrimination. Because discontinuation of linezolid due to adverse effects is common, some experts recommend monitoring trough levels 2 weeks after initiating therapy and minimizing toxicity by maintaining levels less than 2 μg/mL.

Pretomanid is a nitroimidazole that inhibits mycolic acid synthesis and is bactericidal against actively and sporadically multiplying bacilli.[77] Pretomanid was approved by the FDA in 2019 as part of a combination regimen, including bedaquiline and linezolid (i.e., BPaL), for the treatment of XDR-TB and resistant and intolerant MDR-TB based on a trial, Nix-TB.[76] Nix-TB, an open-label, single-arm trial of BPaL administered to patients with XDR-TB or complicated MDR-TB, resulted in 90% of patients having favorable outcomes after 6 months of treatment (compared to 50% in historical series).[76,78]

Pretomanid resistance has been associated with mutations in five *M. tuberculosis* genes involved in bioreductive activation of pretomanid: *ddn, fgd1, fbiA, fbiB,* and *fbiC*.[79] Pretomanid serum concentrations peak at a median of 5 hours after ingestion. Ingestion of pretomanid with a meal increases serum levels, and BPaL should be taken with food. Pretomanid is metabolized by multiple pathways with no single pathway dominating.[79] CYP3A4 accounts for approximately 20% of pretomanid metabolism; for this reason coadministration with efavirenz or RIF should be avoided. Pretomanid is excreted as metabolites in urine and feces. Because pretomanid is used as part of a regimen (BPaL), monitoring is described under the bedaquiline and linezolid sections. No significant prolongation of the QT interval has been observed in healthy adults taking pretomanid.[79]

Clofazimine is an *r*-iminophenazone pigment long used to treat leprosy. The mechanism of its bactericidal activity against *M. tuberculosis* is incompletely understood, although it likely involves respiratory inhibition and production of reactive oxidant species.[80] A reversible skin discoloration is observed in nearly all patients taking clofazimine. Obtaining clofazimine requires the submission of an Investigational New Drug application to the FDA and accessing the medication through the manufacturer (Novartis).

Cycloserine is an analog of an amino acid, D-alanine, that impairs bacterial cell wall synthesis through competitive inhibition of two enzymes. Depending on tissue concentrations, cycloserine may be bacteriostatic or bactericidal.

Cycloserine may cause many psychiatric adverse effects including depression, psychosis, and suicidal ideation and should be avoided in patients with a history of psychiatric illness. Concomitant provision of pyridoxine may ameliorate these effects and should be given at 50 mg per 250 mg of cycloserine.[50] Adverse effects may be reduced by monitoring cycloserine levels to maintain peak concentration less than 35 μg/mL.

Delamanid, a nitrodihydroimidazooxazole, is a prodrug bioactivated by mycobacterial nitroreductase.[81] Delamanid has bactericidal activity through inhibition of mycolic acid synthesis and is effective against actively and sporadically multiplying bacilli. Although approved for use in Europe, it has not yet been approved by the FDA.

All of the other oral agents are difficult to administer because of adverse effects. It is strongly recommended that consultation with an expert be obtained before treatment with these drugs is undertaken.[69] Administration of PAS causes a high frequency of GI upset plus hypersensitivity reactions in 5–10% of patients. In addition, the usual dose of 10 to 12 g/day requires ingestion of 20 to 24 tablets, although administration has been made somewhat easier by the availability of a granular formulation. Ethionamide likewise causes a high frequency of GI side effects, often necessitating discontinuation of the drug. In addition to the adverse effects of PAS and ethionamide, neither of these drugs is particularly potent against *M. tuberculosis*.

The term "injectable drugs" generally refers to streptomycin, amikacin, kanamycin, and capreomycin. Injectable drugs are challenging to administer because of the route of administration; patient preference; significant adverse effects, such as hearing loss or vertigo; and costs of administration and monitoring.[69] Both international[82] and U.S. guidelines[69] de-emphasize the use of injectables for the treatment of drug-resistant TB and recommend that fully oral regimens should be prioritized and become the preferred option for most patients. Kanamycin and capreomycin are no longer recommended for the treatment of TB due to lack of evidence of benefit.[69,83] Amikacin or streptomycin may be included in a regimen for treatment of patients with MDR-TB when susceptibility to these drugs is confirmed. Both drugs may cause hearing loss related to both peak concentrations and cumulative doses and, in addition, may impair renal function.

Another unapproved intravenous antituberculosis agent is the β-lactam imipenem with clavulanate (in the United States administered as the oral antibiotic amoxicillin-clavulanate).[83,84] The currently available compounds of the macrolide class of agents, which are useful against *Mycobacterium avium* complex, do not have antituberculosis effects.

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55 NONTUBERCULOUS MYCOBACTERIAL INFECTIONS

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INTRODUCTION

Soon after the discovery of *Mycobacterium tuberculosis* in 1882 by Robert Koch, several other species of mycobacteria were described. It was not until half a century later, however, that these mycobacteria were recognized to cause disease in humans and, by the 1980s, they were known to cause a broad spectrum of disease.[1] Over the years, these organisms have gone by many names, including mycobacteria other than tuberculosis, environmental mycobacteria, anonymous or atypical mycobacteria, and *nontuberculous mycobacteria* (NTM), which is the preferred term.[2–4] The epidemic of the *human immunodeficiency virus* (HIV) heralded a new awareness of NTM infections because of the high rates of disseminated infections due to *Mycobacterium avium complex* (MAC)[5] and other species.[6] On the one hand, disseminated NTM infections have declined significantly in HIV-infected populations after the advent of antiretroviral drugs; on the other hand, rates of NTM disease in those without HIV are increasing.

NTM represent a broad array of organisms ubiquitous in the environment. They have been isolated from natural and municipal (tap) waters and from soil, and exposure to these reservoirs is thought to be the primary source of human infection. Approximately 200 species and subspecies of NTM have been identified (http://www.bacterio.net/mycobacterium.html), and many of these have been reported to cause disease in both immunocompetent and immunocompromised patients. Unlike *M. tuberculosis,* NTM do not appear to be transmitted from human to human in the absence of extraordinary circumstances; they vary greatly in their ability to cause disease; and they do not show evidence for latency. Unfortunately, NTM are difficult to treat because of high levels of resistance to antimicrobial drugs, which require long courses of therapy with relatively poor outcomes when compared to *tuberculosis* (TB). Not surprisingly, these factors result in a treatment cost comparable to other chronic infectious diseases, such as HIV/*acquired immunodeficiency syndrome* (AIDS).[7] To date, our lack of understanding of the transmission and pathogenesis of these increasingly important infections has limited our ability to develop public health measures aimed at preventing infection.

MICROBIOLOGY AND TAXONOMY

The genus *Mycobacterium* has traditionally consisted of organisms within the *M. tuberculosis* complex, *Mycobacterium leprae*, and NTM. The latter were classified in 1959 by Runyon into groups based on pigmentation in the presence or absence of light (photochromogens, scotochromogens, nonchromogenic) and growth characteristics (slow vs. rapid).[8] Recently, investigators proposed that the genus *Mycobacterium* be divided into five genera, including four new genera: *Mycobacteroides*, *Mycolicibacter*, *Mycolicibacterium*, and *Mycolicibacillus*.[9] The proposed new genera are based on genomic analysis, but the taxonomy is controversial and has not been widely adopted.[10] The proposed genera do not replace the traditional taxonomy used by microbiologists, scientists, and clinicians for the past century. This chapter uses the traditional genus and species designations.

All mycobacteria are characterized by their relatively slow growth rate when compared with other bacterial species. NTM can be divided into rapidly growing and slowly growing organisms: Rapid growers can be distinguished by growth in subculture in less than 7 days. NTM, like all

mycobacteria, are also characterized by a thin peptidoglycan layer surrounded by a thick lipid-rich outer membrane.[11] The lipid-rich outer membrane results in a number of properties that allow the organisms to survive in diverse and ostensibly hostile environments. For example, the hydrophobic cell surface allows surface attachment, resistance to disinfectants and antibiotics, slow growth, and tolerance to heat.[12] Additional important properties that allow survival in the environment are the ability to grow in low carbon concentrations (i.e., oligotrophic) and low oxygen concentrations.

The availability of molecular methods for NTM species identification has rendered the Runyon classification obsolete for clinical purposes and resulted in a marked increase in the identification of new NTM species. In 1997, approximately 50 species of NTM had been identified, with only 13 described as respiratory pathogens. Currently, there are approximately 200 identified NTM species and subspecies with at least 80 associated with lung disease, although for most, only rarely (http://www.bacterio.net/mycobacterium.html) (Table 55.1).

The primary explanation for the increase in NTM species can be found in the mycobacteriology laboratory. Before the era of DNA sequencing for organism identification, NTM were identified based on their morphologic and biochemical characteristics and in vitro susceptibility patterns. The inadequacy or insensitivity of these techniques was reflected in the number of organisms grouped as complexes, such as the *Mycobacterium fortuitum* complex, which previously included multiple rapidly growing species, such as *M. fortuitum, Mycobacterium chelonae,* and *Mycobacterium abscessus.* Although, it was apparent that multiple species were present with similar growth and morphologic properties, standard laboratory techniques were not adequate to distinguish them at the species level.

The revolutionary change in NTM identification was due to the advent of readily available DNA sequencing, especially the sequencing of the 16S ribosomal RNA gene, which is highly conserved so that 1% or greater differences in this gene sequence can define an NTM species. Publicly available databases of 16S ribosomal RNA gene sequences allow relatively easy comparison of mycobacterial isolates to identify the species or to determine whether a new NTM species is present. Alternatively, sequences of the heat shock protein 65 (*hsp65*), *rpoB*, and *secA* genes, or the entire genomic DNA sequence of an NTM species, can be compared to other publicly available gene sequence databases. Although the molecular methods are quite appealing, no method is flawless and applicable in all circumstances. For instance, even with *whole-genome sequencing* (WGS), controversy exists about criteria to define species and subspecies designations. It is also increasingly clear that organisms can appropriate genetic material from other organisms, further blurring the lines between species.

The expansion of new NTM species in the past 20 years is therefore primarily a consequence of more sensitive identification techniques capable of separating closely

Table 55.1 Nontuberculous Mycobacteria Reported to Cause Pulmonary Disease

SLOWLY GROWING MYCOBACTERIA		RAPIDLY GROWING MYCOBACTERIA	
M. alsense	*M. malmoense*	*M. abscessus**	*M. immunogenum*
M. arosiense	*M. marseillense*	*M. alvei*	*M. iranicum*
M. arupense	*M. nebraskense*	*M. aubagnense*	*M. goodii*
M. asiaticum	*M. nonchromogenicum*	*M. boenickei*	*M. holsaticum*
M. avium	*M. palustre*	*M. brisbanense*	*M. houstonense*
M. bouchedurhonense	*M. paraense*	*M. brumae*	*M. llatzerense*
M. branderi	*M. paraffinicum*	*M. canariasense*	*M. mageritense*
M. chimaera	*M. parascrofulaceum*	*M. celeriflavum*	*M. monacense*
M. celatum	*M. persicum*	*M. chelonae*	*M. moriokaense*
M. colombiense	*M. phlei*	*M. chubuense*	*M. mucogenicum*
M. conspicuum	*M. riyadhense*	*M. conceptionense*	*M. novocastrense*
M. europaeum	*M. saskatchewanse*	*M. confluentis*	*M. peregrinum*
M. florentinum	*M. scrofulaceum*	*M. cosmeticum*	*M. phocaicum*
M. fragae	*M. seoulense*	*M. elephantis*	*M. porcinum*
M. gastri	*M. senuense*	*M. fortuitum*	*M. rhodesiae*
M. gordonae	*M. sherrisii*	*M. houstonense*	*M. septicum*
M. haemophilum	*M. shimodei*		*M. thermoresistible*
M. heckeshornense	*M. shinjukuense*		
M. heidelbergense	*M. simiae*		
M. genavense	*M. szulgai*		
M. interjectum	*M. talmoniae*		
M. intermedium	*M. timonense*		
M. intracellulare	*M. triviale*		
M. kansasii	*M. triplex*		
M. kubicae	*M. tusciae*		
M. kyorinense	*M. xenopi*		
M. lentiflavum	*M. yongonense*		

*Including *Mycobacterium abscessus* subsp. *abscessus, massiliense,* and *bolletii.*
From *List of Prokaryotic Names With Standing in Nomenclature.* http://www.bacterio.net/mycobacterium.html.

related NTM species. Predictably, many of these newly identified species have microbiologic properties very similar to other closely related NTM so that identification of the new NTM species may not be associated with any new or surprising clinical properties. It remains to be seen if this revolution in NTM species identification will have an equally profound impact on clinical NTM disease. What is certain, however, is that clinicians will need to become familiar with many more NTM species names as new NTM species are identified.

EPIDEMIOLOGY

INCIDENCE AND PREVALENCE

The epidemiology of NTM disease has been difficult to determine because reporting of NTM pulmonary disease is not mandatory in most countries, including most of the United States. Our lack of understanding of early disease presentation and the difficulty differentiating between *infection* (i.e., NTM isolation without clinical or radiographic evidence of progression) and *disease* presents even more formidable epidemiologic obstacles, especially for determining disease incidence. The prevalence of NTM infections has varied significantly across studies, partially because the studies have used different methodologies and studied different populations.[13] Data suggest that the prevalence of NTM infections is increasing in many areas.

Delayed-type hypersensitivity reactions to subcutaneously injected mycobacterial antigens (i.e., skin test reactivity to NTM) have been reported in 11–33.5% of the population in the United States.[14–16] One study used data from the *National Health and Nutritional Examination Survey* (NHANES) cohort to describe skin reactivity to *purified protein derivative-B* (PPD-B, or the Battey antigen), believed to be indicative of exposure to *M. avium* complex, during two time periods. For the years 1971–72 and 1999–2000, rates of a positive skin test were 11.2% and 16.6%, respectively.[16] Skin test reactivity was noted to increase between the two time periods in foreign-born but not in U.S.-born individuals, suggesting either a higher rate of exposure and infection in the foreign-born individuals or possibly cross-reactivity to infection with *M. tuberculosis*.

Early laboratory-based studies used consecutive isolates from a well-defined catchment area to estimate the frequency of infection. Survey data from state laboratories in the United States in the early 1980s estimated a prevalence of NTM infection of 1 to 2 cases per 100,000 population.[17] A similar follow-up survey from 1993–96 reported an annual case rate of 7 to 8 per 100,000, documenting an increase in NTM isolation when compared to the previous survey.[18] More recent laboratory-based surveys have demonstrated higher prevalences, including a large laboratory-based study from Japan that reported that, of 26,059 patients who tested positive for NTM at least once, 27.5% of these patients met *American Thoracic Society/Infectious Diseases Society of America* (ATS/IDSA) criteria for disease, giving a 2-year prevalence of 24.0 per 100,000.[19]

Studies using clinical isolates from many countries, including Czechoslovakia,[20] England and Wales,[21–23] Ireland,[24] Australia,[25–27] Korea,[28,29] Taiwan,[30] Canada,[31,32] and the United States,[33] have reported increases in prevalence. In some reports, the increase in the rate of NTM infection was associated with a decline in the rate of TB.[34] For example, in Japan from 1971–84, the incidence of pulmonary TB decreased from 133.1 to 46.3 per 100,000, whereas the incidence of NTM pulmonary disease increased from 0.9 to 2.2.[35] Similarly, in Switzerland, the incidence of pulmonary TB decreased from 16.2 to 13.2 per 100,000 over 6 years, whereas the incidence of pulmonary NTM increased from 0.4 to 0.9 per 100,000.[36] The frequencies of *M. tuberculosis* and NTM isolates also showed a reciprocal trend in Taiwan from 2002–07, with NTM isolates increasing 2.6-fold.[37]

Perhaps the most significant increases in NTM prevalence have been reported from North America. Marras and coworkers[31] reported an increase in the number of pulmonary NTM isolates (isolation prevalence) in Ontario from 9.1 per 100,000 in 1997 to 14.1 per 100,000 in 2003; during this same time period, the rate of TB declined. In a subsequent analysis of these data, Iseman and Marras [38] noted that the prevalence was likely to be in the range of 14 to 35 per 100,000, far exceeding the prevalence of TB in Ontario. A study from the United States reported a significant increase in the annual prevalence of NTM pulmonary disease in patients hospitalized in 11 states between 1998 and 2005.[39] Annual prevalence increased among men and women in Florida (3.2%/yr and 6.5%/yr, respectively) and among women in New York (4.6%/yr), but there was no significant increase in California. The annual prevalence of NTM pulmonary disease in U.S. Medicare beneficiaries (all ≥65 years of age) increased from 20 per 100,000 in 1997 to 47 per 100,000 in 2007.[40] The annual percentage change for women was 9.1%, which was significantly higher than that for men (6.4%). In a study from Oregon, clinical and radiographic data from patients with NTM respiratory isolates were evaluated. This study found an overall prevalence of 8.6 per 100,000 persons and 20.4 per 100,000 in those at least 50 years of age.[41] Although not all studies have documented an increase in NTM prevalence,[42] the preponderance of evidence suggests that pulmonary disease due to NTM is increasing.

The lack of reporting of NTM cases in the United States has made it difficult to determine the incidence of NTM. Investigators in Oregon contacted all laboratories in the state and collected demographic and specimen information for patients with NTM isolated during 2007–12.[33] They were able to determine that the incidence of NTM pulmonary disease increased from 4.8 per 100,000 in 2007 to 5.6 per 100,000 in 2012. Incidence increased with age to more than 25 per 100,000 in those 80 years of age or older. Using a large managed care database in the United States, investigators reported that the annual incidence of NTM pulmonary disease increased from 3.1 per 100,000 person-years in 2008 to 4.7 per 100,000 in

2015, and the prevalence increased from 6.8 to 11.7 per 100,000 person-years[43] (Fig. 55.1). The increases were particularly notable among women and those older than 65 years.

The reasons for the increase in incidence and prevalence have not been explained, although increased clinician awareness of the disease and improved diagnostic techniques, especially the widespread application of high-resolution chest *computed tomography* (CT) scanning, could be factors. Once diagnosed with NTM pulmonary disease, patients are more refractory to treatment than TB patients, which means they accumulate or persist, thereby augmenting prevalence figures. A true increase in incidence could be related to changes in the host, such as an aging population, an increased prevalence of chronic lung disease, or an increase in the number of immunocompromised individuals. The observation of a decreased incidence of pulmonary TB and an increased incidence of pulmonary NTM, as noted previously, could be explained by cross-immunity between mycobacterial species. An increase in the prevalence or virulence of environmental organisms or changes in human behavior leading to increased exposure to organisms could be contributing factors.

NTM pulmonary disease is associated with a high mortality, although most patients die as a result of causes other than NTM infection. A systematic review reported an all-cause 5-year mortality for MAC pulmonary

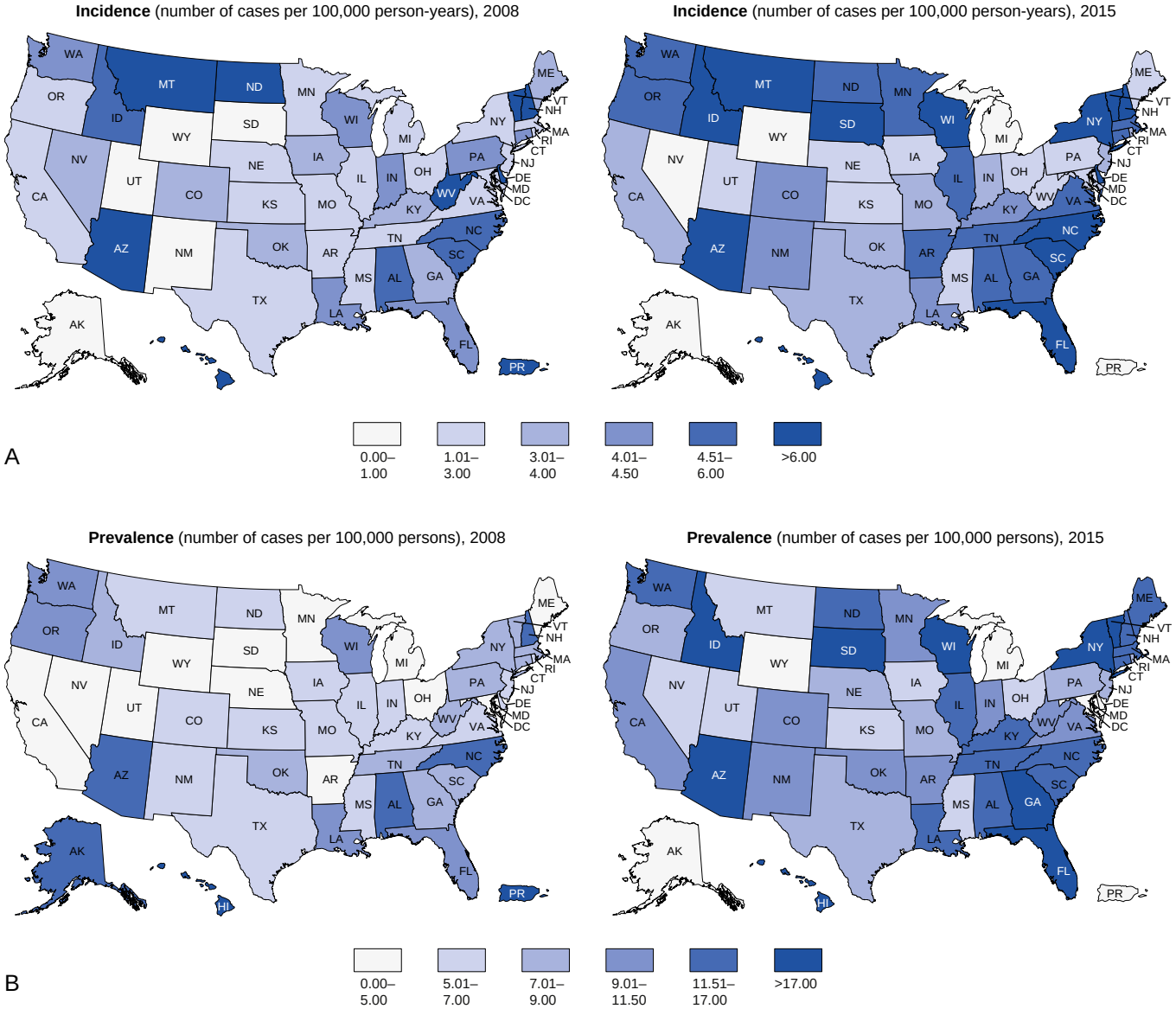

Figure 55.1 Incidence (A) and prevalence (B) of *nontuberculous mycobacteria* (NTM) pulmonary disease in the United States, by state, in 2008 and 2015. (From Winthrop KL, Marras TK, Adjemian J, et al. Incidence and prevalence of nontuberculous mycobacterial lung disease in a large U.S. managed care health plan, 2008–2015. *Ann Am Thorac Soc.* 2020;17:178–185.)

disease of 27%, ranging from 10–48%.[44] In Oregon, 35% of patients with NTM pulmonary disease (84% with MAC) died within 5 years of isolating NTM from a respiratory specimen.[45] Patients with NTM pulmonary disease (per ATS/IDSA criteria) had a slightly higher risk of death compared with those who had infection only. In a population-based study from Ontario, Canada, both NTM pulmonary disease and pulmonary infection had a higher mortality than "unexposed" matched individuals, and those with disease had a higher rate of death than those with only infection.[46] A recent study from Korea described prognostic factors associated with long-term mortality among patients with NTM pulmonary disease.[47] Among 1445 treatment-naive patients, the 5-, 10-, and 15-year cumulative mortality rates were 12.4%, 24.0%, and 36.4%, respectively. In these studies, factors associated with mortality included older age, male gender, low body mass index, chronic pulmonary aspergillosis, malignancy, chronic heart or liver disease, and elevated erythrocyte sedimentation rate.[44,47] Mortality was also associated with the infecting species (e.g., infection with *Mycobacterium intracellulare* and *M. abscessus* was associated with a worse prognosis than with *M. avium*) and radiographic presentation (e.g., cavitary disease had a worse prognosis than noncavitary).[47]

GEOGRAPHIC DISTRIBUTION AND VARIATION

NTM have been reported to cause pulmonary disease around the globe, although there is marked variation in the prevalence of disease and in the species that predominates.[48] In the United States, the southeastern region (southern Atlantic and Gulf coasts) has traditionally been considered to have the highest rates of infection.[13,49,50] NTM have been recovered with higher frequency from water samples in the southeastern than in the northern United States, so exposure is likely higher in these regions.[51] However, a recent study reported that, among Medicare patients, the states with the highest period prevalences of pulmonary NTM were Hawaii (396 per 100,000), followed by California (191 per 100,000).[40] Florida, Louisiana, and Mississippi also had high period prevalences ranging from 151 to 200 per 100,000. Another study that used a large managed care database also documented important geographic variations in both incidence and prevalence of NTM pulmonary disease, including marked increases in both the incidence and prevalence of NTM pulmonary disease in Florida and adjacent states.[52] Among *cystic fibrosis* (CF) patients in the United States, the prevalence of NTM isolation varied geographically; for MAC, the highest prevalences were in Nevada (24%), Kansas (21%), Hawaii (20%), and Arizona (20%) and, for *M. abscessus*, the highest prevalences were in Hawaii (50%), Florida (17%), and Louisiana (16%)[53] (Fig. 55.2).

The reasons for such geographic variation are not well understood. Pulmonary NTM cases were identified from a nationally representative sample of Medicare Part B beneficiaries, and their counties of residence were divided into low- and high-risk counties to identify potential sociodemographic and environmental risk factors.[54] The investigators identified seven clusters of pulmonary NTM cases and compared them to five low-risk areas. Counties in the high-risk areas were larger and had greater population densities, higher education, and income levels than the low-risk counties. In addition, high-risk counties had a higher mean daily potential for evapotranspiration (combination of *evaporation* [transfer of water from land to atmosphere] and *transpiration* [transfer of water from plants to atmosphere]) and greater percentages of their area covered by surface water. Thus, specific environmental factors appear to correlate with the rates of pulmonary NTM infection.

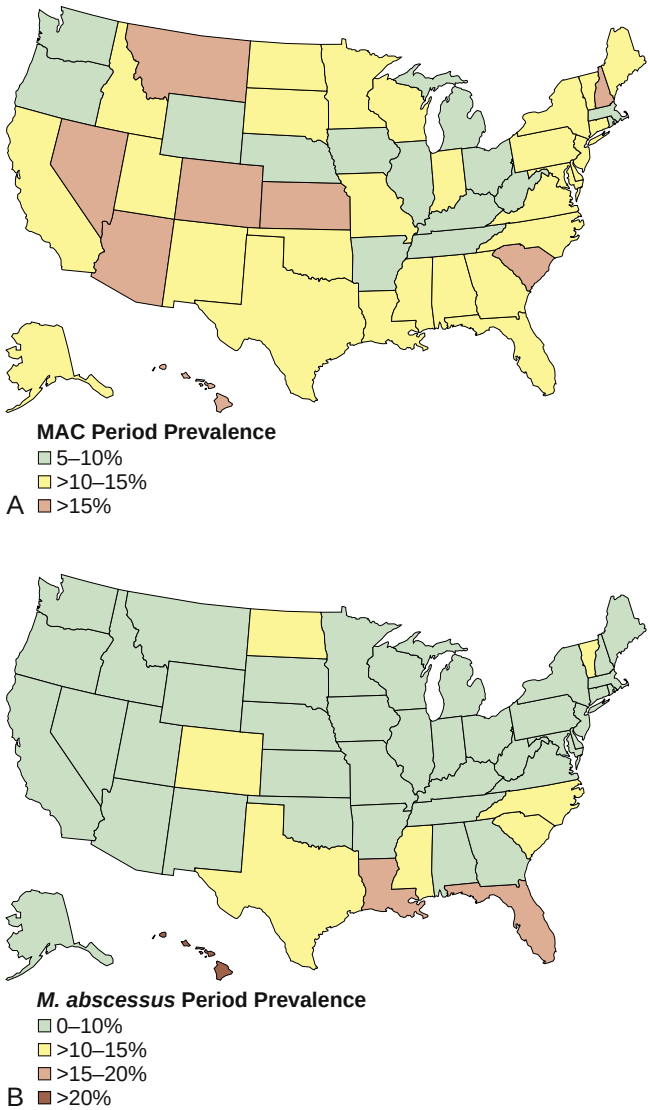

Figure 55.2 Geographic distribution of *nontuberculous mycobacteria* (NTM). The distribution is shown as prevalence of NTM cultured from patients with cystic fibrosis during the period 2010–14 by U.S. state for (A) *Mycobacterium avium* complex (MAC) and (B) *Mycobacterium abscessus*. (From Adjemian J, Olivier KN, Prevots DR. Epidemiology of pulmonary nontuberculous mycobacterial sputum positivity in patients with cystic fibrosis in the United States, 2010–2014. *Ann Am Thorac Soc.* 2018;15:817–825.)

The predominant species causing pulmonary disease in North America is MAC. Data from a national hospitalization database, including more than 5 million patients, demonstrated that MAC was the most common species causing disease, ranging from 61–91%, with the highest frequency in the southern and northeastern regions.[55] *M. abscessus*/*M. chelonae* ranged from 2–18% and was more common in the western region. Other NTM, such as *M. fortuitum* and *Mycobacterium kansasii,* ranged from 7–26% and again were more common in the West. MAC has also been reported as the predominant species in Central and South America, Europe, and Asia.[13] Which species of MAC predominates also varies from region to region. In some areas, such as Europe and South America, *M. avium* is the predominant species whereas, in Australia and South Africa, *M. intracellulare* in the most common MAC isolate. A large laboratory study from Japan reported that *M. avium* pulmonary disease was more common in northeastern Japan, whereas *M. intracellulare* was more common in southwestern Japan.[19] *Mycobacterium xenopi* is common in Europe and Canada, whereas *Mycobacterium malmoense* is more common in Northern than Southern Europe. Populations of miners in Czechoslovakia[20] and South Africa[56,57] have been reported to have high rates of *M. kansasii* infection.

TRANSMISSION AND PATHOGENESIS

TRANSMISSION

NTM are ubiquitous in the environment and have been found in natural and drinking waters, biofilms, soil, and aerosols.[12,58,59] The presumed source of infection is exposure to these environmental reservoirs because human-to-human transmission has only been documented under extraordinary circumstances.[60–62] Studies using genotyping techniques, such as *pulsed field gel electrophoresis* (PFGE), variable number tandem repeat analysis, and WGS have been able to isolate the same strains of NTM from patients and their environments.[63–65] Although the mechanism by which an environmental exposure eventually leads to pulmonary infection is poorly understood,[66] it has been hypothesized that exposure to infected aerosols can lead to infection and possibly disease. To determine whether household plumbing could serve as a source for NTM infection, 394 water samples were obtained from 37 households across the United States.[67] Seventeen (46%) of the households yielded one or more mycobacterial isolate of the same species found in the patient, and in seven patients the isolate had the same genotype. In a study from Philadelphia, Pennsylvania, variable number tandem repeat genotyping and WGS with core genome single-nucleotide polymorphism analysis were used to compare *M. avium* from household plumbing biofilms with *M. avium* isolates from patient respiratory specimens. *M. avium* was recovered from 30 (81.1%) of 37 households, including 19 (90.5%) of 21 *M. avium* patient households. For 11 (52.4%) of 21 patients with *M. avium* disease, isolates recovered from their respiratory and household samples were of the same genotype. Within the same community, 18 (85.7%) of 21 *M. avium* respiratory isolates genotypically matched household plumbing isolates.[68] In a report from Australia, 35% of patients with NTM pulmonary disease had the same species isolated from their home water supply.[69]

A study conducted in Oregon and Washington used interviews to evaluate aerosol-generating activities and water supply features in the homes and gardens of patients with MAC pulmonary disease compared with controls and found that that these activities and factors seemed not to be risk factors for MAC pulmonary disease in HIV-negative adults.[70] Prior lung disease and immunosuppressing drugs were associated with susceptibility. Although it appears that underlying host susceptibility is the major risk for developing NTM pulmonary disease, exposure to NTM is still required for infection. A subsequent case-control study using the same subjects reported that NTM were isolated from shower aerosols more often than in control subjects.[71] Other home environmental samples, such as tap water and soil, were not associated with NTM disease.

Until recently, human-to-human transmission was considered an unlikely mode of transmission.[72] However, several studies have described possible transmission from human to human in CF clinics.[60–62] The first report described a potential outbreak of *M. abscessus* subsp. *massiliense* in a CF clinic in Seattle.[60] It is presumed that a smear-positive patient transmitted infection to four other CF patients at the same clinic because the infecting strain was indistinguishable by PFGE and polymerase chain reaction analysis. In a retrospective study using WGS from Papworth hospital in the United Kingdom, there were genomically highly similar clusters of *M. abscessus* subsp. *massiliense* among 31 adult CF patients, some of whom had opportunities for cross-infection.[61] The authors noted that direct person-to-person transmission was unlikely but that cross-infection (i.e., transfer of infection between patients through physical contact or shared environmental source, such as spirometric or bronchoscopic equipment) in the hospital setting was likely. A study from the Great Ormond Street hospital in the United Kingdom used a similar approach, focusing on *M. abscessus* subsp. *abscessus* isolates in 20 pediatric CF patients.[73] Although high genetic similarity was noted among four patients, no epidemiologic connections were made except for a sibling pair living in the same household.[73] A study from Italy analyzed 162 *M. abscessus* isolates from 48 patients across four geographically diverse CF centers.[74] They identified genetically similar isolates across all three subspecies with seven possible transmission episodes; however, in only three was there epidemiologic evidence of potential cross-infection. Moreover, the authors were unable to identify any significant outbreaks over a 12-year period at the centers, suggesting minimal risk for person-to-person transmission. A study that sequenced 145 isolates of *M. abscessus* from 62 patients at four hospitals in two countries over a 16-year period was able to identify only

one episode of possible transmission in a sibling pair.[75] Further evidence for potential transmission comes from a study that performed WGS on more than a 1000 isolates of *M. abscessus* from 510 CF patients across Europe, the United States, and Australia.[62] The study identified three dominant circulating clones among all CF clinics and countries studied. These same clones were identified in non-CF populations[76] and in a nationwide outbreak of soft tissue infections in Brazil.[77] *M. abscessus* appears to be a highly genomically conserved organism, and the widespread geographic presence of these dominant clones associated with disease makes it difficult to use molecular methods to identify suspected transmission events either between patients or the environment.[78] Whether the widespread geographic presence of these clones in patients with CF is due to person-to-person transmission or to resident genotypes more fit for human infection is not known.

Extrapulmonary NTM infections involving soft tissue or bone and joints are usually the result of a puncture wound or surgery. A recent outbreak of skin and soft tissue infections due to *M. abscessus* subsp. *massiliense* involved more than 2000 patients who had undergone invasive procedures, such as laparoscopic, arthroscopic, plastic, or cosmetic surgery.[79] Since 2013, at least 52 patients from nine states have been diagnosed with skin and soft tissue infections after undergoing cosmetic surgery in the Dominican Republic.[80–82] There is even potential for an NTM, specifically *Mycobacterium chimaera*, to cause disease intraoperatively without direct inoculation but rather after aerosolization and subsequent deposition onto vulnerable tissue.[83–85]

FACTORS ASSOCIATED WITH INFECTION

A prospective study using skin testing data from Palm Beach, Florida, reported that 32.9% of 447 participants in a population-based random household survey had a positive reaction to *M. avium* sensitin.[86] (*Sensitin* is the standardized antigenic material used for delayed-type hypersensitivity skin testing for *M. avium*, analogous to tuberculin for *M. tuberculosis*).[87] Independent predictors of a positive reaction included Black race, birth outside the United States, and more than 6 years' cumulative exposure to soil. Exposure to water, food, or pets was not associated with skin test reactivity. Using NHANES data, investigators reported similar findings with regard to sensitization to *M. intracellulare*[16]: male sex, non-Hispanic Black race, and birth outside the United States were each independently associated with sensitization. The highest rate of skin test reactivity was in persons who were 20 to 39 years of age. These two studies are interesting in that skin test reactivity to either *M. avium* or *M. intracellulare* sensitin was associated with likely soil exposure and was more common in men and foreign-born individuals. However, in contrast to skin reactivity, disease seems to be more common in older women and in U.S.-born individuals. In addition, the source for *M. avium* infection, frequently associated with nodular bronchiectatic MAC pulmonary disease, appears to be primarily municipal (tap) water in the United States, whereas *M. intracellulare* infection is acquired through some other source, likely soil.[88] Pathophysiologically, it is still not clear what positive skin test reactions to mycobacterial sensitin signify. For tuberculin skin test reactors, it is assumed a positive test reflects "latent" infection; however, a latent state has not yet been demonstrated for NTM pathogens. In that context, it is possible that positive skin test responses to NTM sensitins reflect subclinical infection and therefore that the risk factors for infection are different from those associated with disease.

FACTORS ASSOCIATED WITH DISEASE

Most NTM are significantly less pathogenic than *M. tuberculosis* and likely require some degree of host impairment to establish infection. A number of risk factors for disease have been described, which can be subdivided broadly into three groups: (1) factors leading to impaired local (lung) immunity (e.g., lung disease), (2) factors impairing host immunity, and (3) factors relating to the infecting species. These factors can be reduced further into the "susceptible person" model and the "unusual dose" model.[89] In the susceptible person model, it is assumed that some susceptibility is necessary for infection whereas, in the unusual dose model, it is postulated infection happens because of an unusually large exposure to NTM. It is likely that, in most patients, both models of pathogenesis are at play to varying degrees.

Chronic pulmonary disease is perhaps the most important risk factor for the development of NTM pulmonary disease. NTM disease has been described in association with bronchiectasis (with or without CF), COPD (including alpha$_1$-antitrypsin deficiency), cavitary lung disease, pneumoconiosis, prior TB, and pulmonary alveolar proteinosis.[90] Studies have documented a high prevalence of NTM in sputum cultures from patients with CF, with estimates ranging from 6.6–13.7%.[91–93] Among 16,153 persons with CF in the United States from 2010–14, risk factors for NTM isolation included having a diagnosis of CF at an older age, having a lower body mass index, higher *forced expiratory volume in 1 second* (FEV$_1$)% predicted, and fewer years on chronic macrolide therapy.[94]

Gastroesophageal reflux disease (GERD) or other esophageal disorders are often found in patients with NTM pulmonary disease. Historically, it has been reported that patients with *rapidly growing mycobacteria* (RGM) often have associated esophageal disorders[95–97]; recent reports have also described a high frequency of GERD in patients with MAC pulmonary disease.[98,99] In a report from South Korea using pH probes to diagnose GERD, the authors reported that the prevalence of GERD in patients with NTM lung disease was 26%; those with GERD were more likely to have smear-positive sputum and more extensive disease than those without GERD. Of interest, a minority of those with GERD (27%) had symptoms of GERD.[98]

Postmenopausal women make up one of the most interesting patient populations to develop NTM pulmonary disease. These women often have characteristic morphologic features, including pectus excavatum, scoliosis, thin body habitus, and mitral valve prolapse. This constellation was first described by Prince and colleagues[100] in 1989 and

subsequently by Iseman and others.[101] Recently, investigators reported that women with pulmonary NTM disease were taller and thinner and weighed less than matched control subjects[102] (Fig. 55.3); 51% had scoliosis, 11% had pectus excavatum, and 9% had mitral valve prolapse, all significantly more common than in reference populations. Another interesting feature of this syndrome is the predilection for right middle lobe and lingular bronchiectasis. To date, extensive evaluation of the immune system of these patients has shown mixed results, but mutations in the *cystic fibrosis transmembrane regulator* (CFTR) gene are common.[102–104] Among 103 women with pulmonary NTM, the normal relationship between the adipokines and body fat was lost compared with uninfected control subjects.[104] In addition, in one study, interferon-γ (IFN-γ) and *interleukin-10* (IL-10) levels were significantly suppressed in stimulated whole blood of patients with pulmonary NTM.[104] However, it remains uncertain if these findings are clinically significant.

Impairment in host immunity is also a risk factor for NTM disease but, in this setting, it often leads to disseminated disease or skin and soft tissue involvement rather than pulmonary disease. In AIDS, NTM most commonly cause disseminated disease that presents with nonspecific symptoms, such as fever, night sweats, diarrhea, abdominal pain, and lymphadenopathy, with *M. avium* being the most frequently isolated NTM.[105] The incidence of disseminated MAC can be as high as 20– 40% in people with HIV and advanced immunosuppression in the absence of effective *antiretroviral therapy* (ART) or chemoprophylaxis.[105,106] Fortunately, the incidence of disseminated MAC has continued to decline in the modern ART era to fewer than two cases of MAC per 1000 person-years.[107] Factors associated with MAC disease include CD4 cell counts less than 50 cells/mm^3, plasma HIV RNA levels greater than 1000 copies/mL, ongoing viral replication despite ART, previous or concurrent opportunistic infections, and reduced in vitro lymphoproliferative immune response to *M. avium* antigens.[108–110] Despite the fact that MAC is isolated from the sputum in up to 10% of AIDS patients with CD4 T cell counts less than 50 cells/μL, pulmonary disease due to MAC is uncommon.[111] Pulmonary disease has been reported in 2.5–8% of patients with disseminated MAC[112] and, rarely, has also been reported in the absence of dissemination.[113] Patients with pulmonary disease tend to have higher CD4 counts and focal alveolar opacities, which rarely cavitate. *M. kansasii* can also cause disease in patients with HIV and AIDS. In one study, the risk for infection with *M. kansasii* was increased 150-fold in HIV-infected patients and 900-fold in those with AIDS.[114] In contrast to MAC, *M. kansasii* only rarely causes indolent disease and should almost always be treated as a pathogen.[115]

Other immunocompromised populations, including transplant recipients, have been noted to develop pulmonary disease due to NTM. Rates may be as high as 6.5% after heart or lung transplantation[116] and 2.9% after bone marrow transplantation,[117] but are probably much lower in patients after liver or kidney transplantation.[118,119]

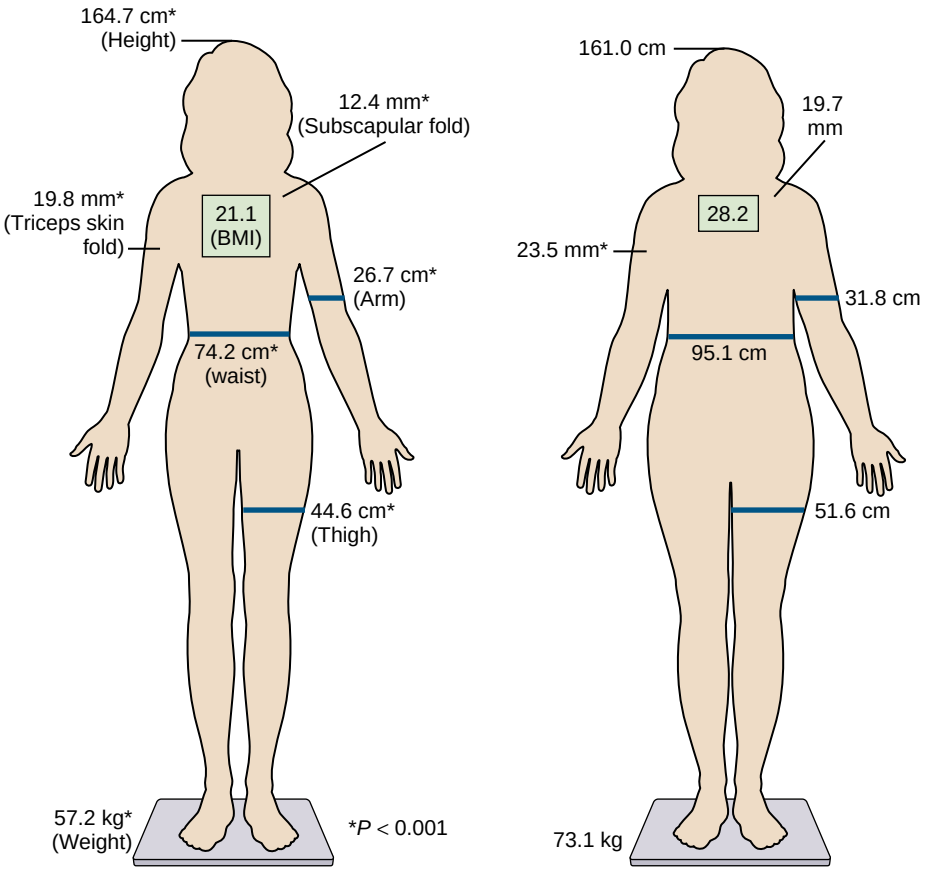

Figure 55.3 Schematic depiction of the anthropometrics of women with pulmonary nontuberculous mycobacterial disease (*n* = 60) (*left*) compared with National Health and Nutrition Examination Survey age-, sex-, and race-matched control subjects (*right*). BMI, body mass index. (From Kim RD, Greenberg DE, Ehrmantraut ME, et al. Pulmonary nontuberculous mycobacterial disease: prospective study of a distinct preexisting syndrome. *Am J Respir Crit Care Med.* 2008;178:1006–1074.)

M. abscessus infection in patients with CF who have undergone lung transplantation has sometimes been associated with severe and sometimes fatal disease.[120–122] Patients with rheumatoid arthritis are more likely to develop NTM disease than individuals without rheumatoid arthritis.[123,124]

Cytokine or certain cellular defects may predispose to NTM infection, including pulmonary disease. Multiple cytokines are necessary for granuloma formation and eventual containment of mycobacterial infections. The most important among these are interferon-γ, IL-12, and tumor necrosis factor-α. Patients with defects in each cytokine are susceptible to infection with NTM. Mutations in the *IFN-γ receptor 1* (IFN-γR1), IFN-γR2, IL-12 p40, and the IL-12 receptor are all associated with human disease.[125] The dominant and recessive IFN-γR1 deficiencies have distinct clinical presentations. Adult-onset immunodeficiency can result from the development of autoantibodies against IFN-γ; this condition is associated with severe disseminated opportunistic infections, including NTM.[126] Mutations in a transcription factor involved in stem cell maintenance, GATA2, are associated with autosomal dominant and sporadic monocytopenia and disseminated mycobacterial infections called the monoMAC syndrome.[127]

Inhibitors of tumor necrosis factor-α and of other cytokines are now routinely given therapeutically to large numbers of patients with inflammatory bowel disease, rheumatoid arthritis, or psoriatic arthritis. Although initially demonstrated to predispose to TB,[128] recent reports have linked these therapies to NTM infections as well.[129–131] Patients with suspected or known mycobacterial infections should not receive these medications without proper antimycobacterial therapy. Corticosteroids, including inhaled corticosteroids, have been associated with an increased risk of developing NTM disease,[70,132,133] with a strong dose-response relationship between incident NTM pulmonary disease and cumulative inhaled corticosteroid dose over 1 year.[132]

Microbial factors are also likely to be important in explaining NTM disease. A population-based assessment of the clinical significance of NTM in a region of The Netherlands demonstrated a wide range of pathogenicity among different NTM species.[134] Studies have identified isolates and phenotypes associated with increased virulence with in vitro models.[135–137] For example, *M. abscessus* is known to exist in a smooth (colonizing) and rough (invasive) phenotype. The presence of glycopeptidolipids on the smooth strains appears to mask the underlying antigenic cell wall lipids, allowing the smooth organisms to evade the immune response, colonize, and form biofilms in the lung airways.[135] When the organism switches to a rough phenotype, the glycopeptidolipids are lost, and the rough strain now elicits an innate immune response. Limited clinical data suggest that the rough phenotype may be more virulent than the smooth variety.[138,139]

DIAGNOSIS AND MANAGEMENT OF SPECIFIC PATHOGENS

Approximately 80% of patients with NTM infection present with pulmonary disease, which can have diverse manifestations (Table 55.2).[33,140] This chapter focuses on the most common clinical presentations in the immunocompetent host—chiefly, TB-like (cavitary) disease and disease associated with nodules and bronchiectasis (nodular bronchiectatic disease). However, it is important to recognize that there is a great deal of overlap between these two phenotypes. The diagnostic evaluation usually consists of (1) assessment for the presence of one or more compatible symptoms, which are usually insidious in onset (cough, sputum production, fatigue, weight loss, fever, hemoptysis); (2) radiographic evaluation, which frequently includes CT scans of the chest; and (3) microbiologic evaluation, which consists of three or more sputum specimens for microscopy and mycobacterial culture and/or bronchoscopic specimens. The most important diagnosis to exclude is TB. Additional laboratory evaluation aimed at identifying potential reasons for underlying lung disease, specifically bronchiectasis, that might predispose to NTM infection may include testing for CF, alpha$_1$-antitrypsin deficiency, primary ciliary dyskinesia, or esophageal disorders in patients with pulmonary disease.

Making the diagnosis of NTM pulmonary disease can be challenging. Unlike pulmonary TB, in which a single positive culture of a sputum or bronchoscopic specimen establishes the diagnosis (barring laboratory contamination), confirmation of the diagnosis of NTM pulmonary disease usually requires repeated isolation of a particular NTM species. Diagnostic criteria have been developed to aid the clinician in the evaluation of persons suspected of having pulmonary NTM disease.[2,4] The NTM diagnostic criteria outlined in Table 55.3 are based on experience with common and well-described respiratory pathogens, such as MAC, *M. kansasii,* and *M. abscessus.* However, it is important to note that, because of the varying pathogenicity among the many NTM species, no single diagnostic approach will work for all cases. Diagnostic criteria that are too sensitive promote overdiagnosis and the unnecessary exposure of patients to potentially toxic antimicrobial medications. By contrast, diagnostic criteria that are overly rigid put patients at risk for undertreatment and progressive NTM disease. Fortunately, NTM lung disease is usually sufficiently indolent that there is enough time for a careful patient assessment to determine with confidence the presence or absence of significant disease.

Table 55.2 Diversity of Nontuberculous Mycobacteria Pulmonary Disease

Tuberculosis-like (cavitary) disease
Disease associated with nodules/bronchiectasis
Disease associated with genetic airway abnormalities and abnormal airway clearance (cystic fibrosis, primary ciliary dyskinesia, alpha$_1$-antitrypsin deficiency)
Hypersensitivity-like lung disease
Disease associated with esophageal motility disorders
Disease associated with disseminated disease and immune suppression ▪ HIV/AIDS ▪ Defects in interferon-γ and interleukin-12 pathways ▪ Tumor necrosis factor-α antagonists

AIDS, acquired immunodeficiency syndrome; HIV, human immunodeficiency disease.

Table 55.3 Microbiologic Criteria for Diagnosis of Nontuberculous Mycobacteria Lung Disease

Specimen	Results
At least three sputum results available *or*	Two positive cultures* regardless of the results of AFB smear
Single available bronchial wash or lavage *or*	One positive culture regardless of the results of AFB smear
Tissue biopsy	Compatible histopathology (granulomatous inflammation) and a positive biopsy culture for NTM Compatible histopathology (granulomatous inflammation) and a positive sputum or bronchial wash or lavage culture for NTM

*Two positive cultures isolating the same species or subspecies in the case of *Mycobacterium abscessus*.
AFB, acid-fast bacilli; NTM, nontuberculous mycobacteria.
Data from Daley CL, Iaccarino JM, Lange C, et al. Treatment of nontuberculous mycobacterial pulmonary disease: an official ATS/ERS/ESCMID/IDSA clinical practice guideline. *Clin Infect Dis*. 2020;71(4):905–913.

The difficulty in determining the clinical significance of an NTM respiratory isolate results from several factors. NTM isolates can contaminate clinical specimens, usually from environmental sources. Many NTM species, such as *Mycobacterium gordonae,* are generally nonpathogenic and almost invariably represent specimen contamination rather than true infection. NTM can be found in potable (municipal or tap) water, such as *M. kansasii,* MAC, *Mycobacterium simiae, M. abscessus,* and *M. xenopi,* so that their presence in a clinical specimen can be due to waterborne contamination of the specimen, even though the isolated species is sometimes associated with significant clinical disease. Sometimes, the recovery of even potentially virulent and pathogenic NTM may not be associated with active or progressive disease for reasons that are not understood. Unfortunately, no easily applied algorithm addresses all NTM species in all clinical circumstances. The clinician must have not only some knowledge of the disease-producing potential of NTM species but also an awareness of the circumstances associated with the isolation of the NTM species.

A single positive sputum culture for NTM is usually regarded as indeterminate for the diagnosis of NTM pulmonary disease. In contrast, when two or more sputum cultures are positive, the diagnosis of disease is more likely. For example, in a study from Japan, 98% of patients with two or more positive sputum cultures for MAC had evidence of progressive disease during follow-up.[141] Unlike sputum, a single positive NTM culture from bronchoscopy can be diagnostic for disease (see Table 55.3). However, the clinician must keep in mind NTM species that are usually respiratory contaminants (especially *M. gordonae*) and NTM species that can be found in tap water (discussed earlier), which may result in pseudo-outbreaks of NTM disease if the bronchoscopic equipment has been inappropriately rinsed with tap water.[142] The criterion that a single positive culture from bronchoscopy is diagnostic does not mean that bronchoscopy has a better yield for detection of NTM than expectorated (induced) sputum, but rather that it would be inappropriate to subject a patient to multiple bronchoscopic procedures simply to obtain multiple respiratory specimens. In fact, in the largest study comparing bronchial washing cultures with sputum cultures, the yields were equivalent.[143] Patients who are suspected of having NTM lung disease but do not meet the diagnostic criteria should be followed clinically until the diagnosis is either firmly established or excluded, a process that can take months to years.

Even among those who meet ATS/IDSA diagnostic criteria, progressive disease does not inevitably follow, at least in short-term follow-up. In two studies from Korea that included almost 1000 patients who met ATS/IDSA diagnostic criteria for MAC pulmonary disease, 24–41% were stable without antimicrobial treatment over a period of at least 3 years.[144,145] In both studies, approximately 50% of the stable patients spontaneously converted cultures to negative with airway clearance measures alone. In another study from Korea, 45% of 1012 patients with noncavitary NTM pulmonary disease did not initiate treatment over a median follow-up period of 3.6 years; 34% spontaneously converted, but 17% redeveloped NTM pulmonary disease with a species different from the original species.[146]

Diagnosis of NTM pulmonary disease does not necessitate the institution of therapy, which is a decision based on potential risks and benefits of therapy for individual patients. Factors that might influence the decision to treat NTM pulmonary disease include the virulence of the NTM pathogen and the potential for disease progression, the severity (or lack of severity) of symptoms and radiographic findings, the presence of known indolent disease, and the presence of advanced age and/or severe comorbid conditions (with limited life expectancy). Another factor is the inability to tolerate the prolonged and sometimes toxic antimicrobial regimens for NTM disease. Again, there is no substitute for physician familiarity with NTM pathogens and the individual patient for optimal management of NTM pulmonary disease.

Other clinical manifestations of NTM infection include lymphadenitis; disseminated disease; and skin, soft tissue, and bone disease. Lymphadenitis is the most common NTM disease manifestation in children and is usually due to MAC or, less commonly, *Mycobacterium haemophilum* or *Mycobacterium scrofulaceum.*[147] The most important differential diagnosis is TB lymphadenitis, although NTM account for approximately 90% of mycobacterial lymphadenitis in American children (but only 10% in adults).[148] Symptoms are usually minimal, with frequent unilateral involvement of submandibular, submaxillary, preauricular, or cervical lymph nodes. Skin and soft tissue infections are usually due to the RGM—*M. abscessus, M. fortuitum, M. chelonae,* or *Mycobacterium marinum*—and are the result of direct inoculation after either trauma or surgery.[2,149] Dissemination of NTM pathogens is most often associated with the severe immunosuppression of advanced AIDS and is caused by MAC.[105,150–152] NTM infections can disseminate in other immunocompromised states, such as organ transplantation, or in association with indwelling foreign bodies, such as venous catheters, dialysis catheters, or other prosthetic devices.[153–156]

LABORATORY DIAGNOSIS

Diagnosis of NTM disease is based on isolation of these organisms from clinical specimens. Cultures should include

both solid and broth media for detection of mycobacteria, with a semiquantitative reporting of colony counts.[2] A meta-analysis of nine studies showed a 15% increase in the sensitivity of culture for NTM if a solid medium was incubated along with a liquid culture system.[157] Despite the increased yield with inoculation of both solid and liquid media, most referral laboratories in the United States use liquid media only.

The optimal temperature for growth of most NTM species is between 28°C and 37°C, although some species require either higher or lower temperatures for optimal growth, and some species require special supplementation for recovery from culture. The Clinical and Laboratory Standards Initiative has suggested incubation temperatures of 36 ± 1°C for slow growers and 28 ± 2°C for rapid growers.[158] Most NTM grow within 2 to 3 weeks of subculture, but the group of rapidly growing NTM appear within 7 days of subculture.

Speciation can be based on phenotypic characteristics, analysis of biochemical and lipid profiles, *mass-assisted laser desorption/ionization–time of flight mass spectrometry* (MALDI-TOF MS), and molecular methods. NTM can be categorized phenotypically by their growth rate and pigmentation, although these characteristics are not specific enough for final speciation. Biochemical testing, such as niacin production and nitrate reduction tests, often is not sufficient to differentiate all NTM, particularly some of the newly identified species. High-pressure liquid chromatography, which analyzes the chromatographic profile of the mycolic acids extracted from the bacterial cell wall, can be used to speciate a large number of NTM.[159] However, high-pressure liquid chromatography is unable to differentiate all species, and of importance, it cannot differentiate the subspecies of *M. abscessus*. MALDI-TOF MS is based on disruption of bacterial cells by laser and ionization of proteins and can provide a cheaper alternative to sequencing but remains less discriminatory for subspeciation of *M. abscessus.* Although MALDI-TOF MS works well on pure cultures, its performance on newly positive respiratory specimens is less robust.[160,161] In a small study from The Netherlands, only 12 (22%) of 54 respiratory isolates were identified directly from liquid culture.[160] A recent study evaluated two commercially available systems and reported that 92–95% of the NTM strains tested were able to identify to the complex/group level.[162] However, both systems had difficulty differentiating between members of *M. abscessus*, *M. fortuitum*, *Mycobacterium mucogenicum*, *M. avium*, and *Mycobacterium terrae* complexes/groups.

Molecular methods for speciation include nucleic acid probes, polymerase chain reaction and other amplification methods, and nucleic acid sequencing.[163–168] Identification of mycobacteria by 16S ribosomal DNA sequencing[163,164] provides more accurate determination of the species, although 16S ribosomal DNA sequencing cannot differentiate all species of NTM. The commercially available AccuProbe technology (Gen-Probe) is currently recommended for identification of *M. tuberculosis* complex, *M. avium* complex (as well as *M. avium* and *M. intracellulare* separately), *M. kansasii,* and *M. gordonae.* Given the varying pathogenicity of the many NTM species and variation in treatment outcomes by species and, in the case of *M. abscessus* subsp., additional methods of speciation are needed. Partial gene sequencing targeting *rpoB*, *hsp65*, and *secA* can provide high degrees of discrimination but are costly and are only feasible in laboratories with sequencing capabilities.[169,170] Multilocus sequencing can increase the discriminatory power to the level of subspecies for *M. abscessus*.[171,172] Line probe assays can identify more common species and provide rapid detection of resistance mutations for macrolides and amikacin.[173] In addition, line probe assays can identify the normal or truncated *erythromycin resistance methylase* (*erm*) gene, *erm(41)*, and the presence of C28T mutations that can render the *erm(41)* gene nonfunctional.

Antimicrobial susceptibility testing has unclear value for the management of patients with NTM disease because in vitro results do not correlate well with clinical outcomes for some drugs.[4] For MAC, the Clinical and Laboratory Standards Initiative recommends broth microdilution for antimicrobial testing against clarithromycin and amikacin only.[174] Seeking guidance from in vitro susceptibility results for other antibiotics is unreliable and often misleading. Initial isolates should be tested for response to clarithromycin and amikacin, as should isolates from patients with treatment failures and relapses, patients who have taken macrolides previously, and AIDS patients who develop bacteremia on macrolide prophylaxis. For clarithromycin, a *minimal inhibitory concentration* (MIC) of 32 or greater is considered resistant.[174] For amikacin, an MIC of 64 or greater and an MIC of 128 or greater are considered resistant for parenteral and liposomal inhaled, respectively. For *M. kansasii,* isolates should be tested for response to rifampin (rifampicin) because resistance to rifampin is associated with treatment failure or relapse.[175] For rifampin, the cutoff for resistance is an MIC of 2 or greater.[174] If rifampin resistance is documented, additional drugs, including clarithromycin and moxifloxacin, should be tested. For RGM, broth microdilution MIC determination for susceptibility testing is recommended.[175] In general, for most species, antimicrobial susceptibility testing should be used to guide selection of antibiotics to be used in the treatment regimen recognizing the limitations of such testing.

SLOWLY GROWING MYCOBACTERIA

Although there are slightly fewer species of slowly growing NTM than rapidly growing species, the slow growers are more common causes of pulmonary disease (see Table 55.1). The slow growers include approximately 90 species (http://www.bacterio.net/mycobacterium.html), with a wide range of pathogenicity, from organisms such as *M. kansasii,* which are probably second only to *M. tuberculosis* in terms of disease-producing capability, to *M. gordonae,* which rarely causes disease.[4]

Mycobacterium avium Complex

MAC includes 12 species, of which *M. avium, M. intracellulare,* and *M. chimaera* are the most common to cause pulmonary disease.[176] Differentiation of the separate MAC species is not possible with routine laboratory techniques, although DNA probes can identify *M. avium* and *M. intracellulare.* In most circumstances, the differentiation of *M. avium* and *M. intracellulare* does not likely make a significant

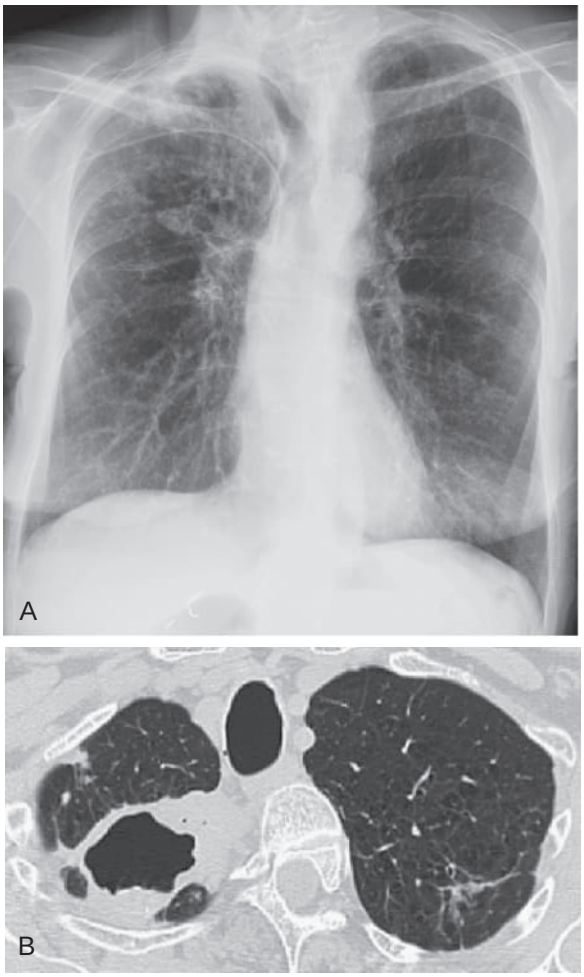

Figure 55.4 Cavitary *Mycobacterium avium* complex (MAC) pulmonary disease. A 63-year-old woman with smoking history with cavitary MAC lung disease. The patient, who presented with cough, fatigue, weight loss, and intermittent hemoptysis, was diagnosed with MAC in 2004. She did not respond to two courses of multidrug therapy, and her sputum remained strongly culture positive for MAC. (A) Chest radiograph showing cavitary consolidation in the right apex and scattered nodular and reticulonodular opacities in both lungs. (B) Computed tomography scan showing large cavity in right apex.

difference clinically or therapeutically, although recent data from South Korea suggest that *M. intracellulare* may be more virulent than *M. avium;* patients with *M. intracellulare* presented with more severe disease and had a worse prognosis.[177,178]

The traditionally recognized presentation of MAC pulmonary disease has been as apical fibrocavitary disease similar to TB, sometimes with large cavities, usually in men but also in women; patients generally are in their fifth or sixth decade of life and have a history of cigarette smoking and alcohol abuse (Fig. 55.4). If left untreated, this form of disease is generally progressive, can result in extensive cavitary lung destruction, and is associated with increased mortality compared with noncavitary MAC lung disease.[179–181] The necessity for initiation of therapy with cavitary MAC pulmonary disease is clearly much more pressing than with noncavitary MAC disease.

MAC pulmonary disease also presents with nodular opacities associated with bronchiectasis, which frequently involve the right middle lobe or lingula, predominantly in postmenopausal nonsmoking white women (Fig. 55.5). This form of disease, termed nodular bronchiectatic disease, tends to have a much slower progression than cavitary disease so that long-term follow-up may be necessary to demonstrate clinical or radiographic changes. Even with this more indolent form of disease, however, death may result from progressive disease.[100] Nodular bronchiectatic MAC pulmonary disease is radiographically characterized by CT findings that include multiple small peripheral pulmonary nodules and cylindrical bronchiectasis (see Fig. 55.5). The CT pattern of these predominantly peripheral small nodular densities has been described as tree-in-bud and reflects inflammatory changes including bronchiolitis (eFig. 55.1).

Patients with nodular bronchiectatic MAC pulmonary disease often have additional coinfections associated with bronchiectasis, including respiratory cultures positive for *Pseudomonas aeruginosa; Nocardia* sp; fungal species, such as *Aspergillus*; and occasionally other NTM, such as *M. abscessus.* Nonmycobacterial exacerbations of bronchiectasis often complicate the assessment and management of MAC disease and strategies aimed at treatment of the bronchiectasis may improve patients' symptoms.

Therapy of *Mycobacterium avium* Complex Pulmonary Disease. Several aspects of treatment for MAC pulmonary disease are difficult to explain and are even counterintuitive. The greatest misunderstanding about treatment regimens for NTM pathogens is the expectation that all NTM infections should respond in a predictable manner to antimicrobial therapy, as does *M. tuberculosis* infection. In reality, when treatment regimens are based on in vitro susceptibility testing, the NTM pathogen very often does not respond to antimicrobial agents as predicted. A frustrating aspect of NTM therapy for many clinicians is the lack of a clear association between the in vitro susceptibility results and the clinical (in vivo) response. For many NTM, including MAC, laboratory cutoffs for "susceptible" and "resistant" do not have a demonstrable clinical correlate and have not been confirmed to be clinically meaningful. For disease caused by MAC, response to treatment correlates primarily with in vitro susceptibility to macrolides (clarithromycin and azithromycin) and amikacin but not to other antimicrobial agents.[182–190] Several other NTM species (*M. abscessus, M. simiae, M. malmoense, M. xenopi,* etc.) lack established correlation between in vitro susceptibilities and in vivo responsiveness to any antimicrobial agent. The explanations for the dichotomy between laboratory susceptibility testing results and clinical benefit for many NTM are currently not known. In accordance, clinicians must use in vitro susceptibility data for many NTM with the awareness that, unlike for TB, the results are an imperfect guide to treatment outcome. Three comprehensive reviews summarize the multiple and complicated factors that likely account for this troubling aspect of NTM disease therapy.[191–193]

There is another difficult-to-explain phenomenon associated with MAC drug therapy. Patients who have not responded to prior MAC therapy, with or without a macrolide, have lower sputum conversion rates with macrolide-containing treatment regimens, even with macrolide-susceptible MAC isolates, than do patients with no prior therapy.[183,186,194,195]

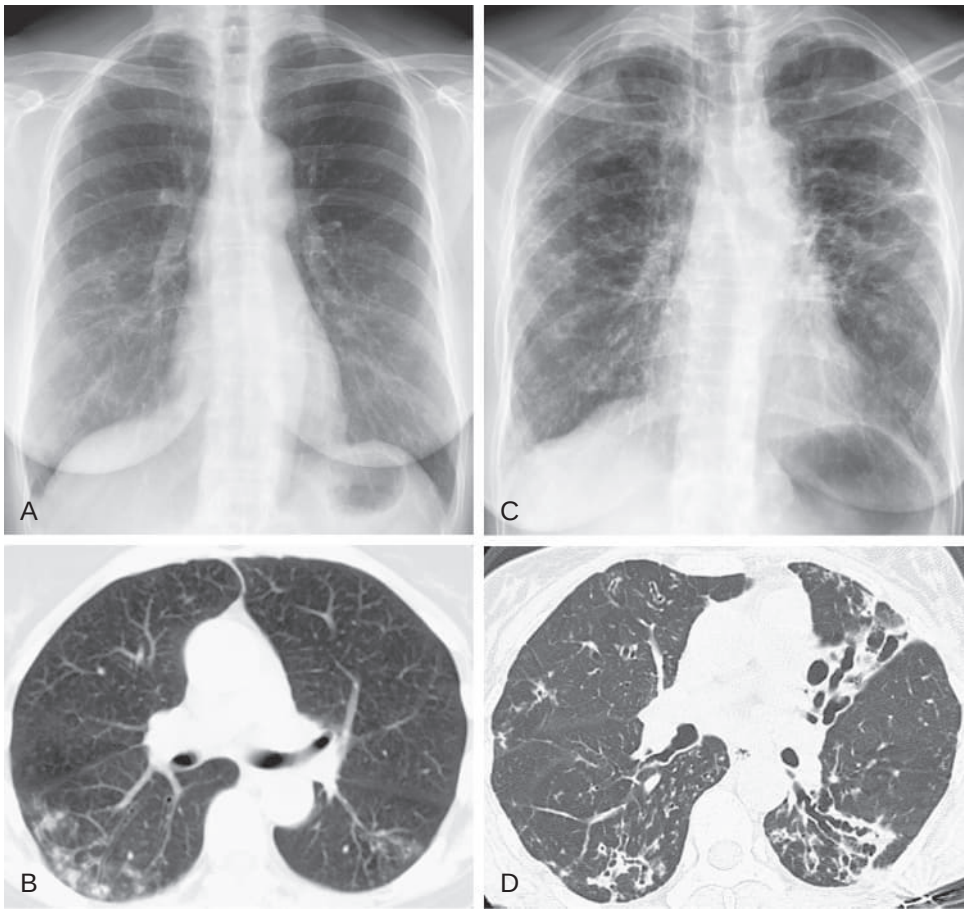

Figure 55.5 Nodular bronchiectatic *Mycobacterium avium* complex (MAC) pulmonary disease in two patients. (A) Posteroanterior chest radiograph from a 60-year-old nonsmoking woman with several years of chronic cough and recurrent "pneumonia." Sputum was acid-fast bacilli smear positive and culture positive for MAC at the time of the radiograph and on multiple subsequent collections. Chest radiograph shows primarily middle and lower lung nodular and reticulonodular abnormalities. (B) High-resolution chest computed tomography from this patient showing bilateral bronchiectasis with variable-sized nodular and reticulonodular opacities in a tree-in-bud pattern. (C) Posteroanterior chest radiograph from a 74-year-old woman with more than 20 years of cough with sputum production, recurrent "pneumonia," severe fatigue, and weight loss. Sputum was strongly acid-fast bacilli smear positive and culture-positive for MAC on multiple collections. (D) High-resolution chest computed tomography from this patient showing extensive, severe, multilobar bronchiectasis.

Although the explanation for this observation is not clear, it is evident that the best chance for treatment success in MAC pulmonary disease is the first treatment effort. Finally, patients who are successfully treated for nodular bronchiectatic MAC disease can be reinfected by new MAC strains, sometimes with renewal of progressive disease.[196–198]

The recommended regimen for the treatment of MAC pulmonary disease includes a macrolide (azithromycin or clarithromycin), ethambutol, and a rifamycin (rifampin or rifabutin).[4] The regimen can be administered three times weekly in patients with nodular bronchiectatic disease but should be administered daily in those with cavitary disease. For those with cavitary or otherwise extensive radiographic disease or with macrolide-resistant disease (see later), a parenteral aminoglycoside (amikacin or streptomycin) should be considered.[4]

Because the macrolides azithromycin and clarithromycin are the principal and most important antimicrobial agents for which there is a demonstrated correlation between in vitro susceptibility and in vivo response for MAC pulmonary disease, these agents, partnered with ethambutol, serve as the cornerstones of MAC therapy (Table 55.4). Azithromycin is preferred over clarithromycin because it is associated with fewer drug interactions and has improved tolerance, lower pill burden, and once-daily dosing. Addition of a third drug, such as a rifamycin, may

Table 55.4 Treatment of *Mycobacterium avium* Complex Pulmonary Disease

Type of Disease	Regimen
Nodular/bronchiectatic disease	1. Clarithromycin 1000 mg tiw or azithromycin 500–600 mg tiw *and* 2. Ethambutol 25 mg/kg tiw *and* 3. Rifampin 600 mg tiw
Cavitary disease	1. Clarithromycin 500–1000 mg/day or azithromycin 250–300 mg/day *and* 2. Ethambutol 15 mg/kg daily *and* 3. Rifampin 450–600 mg daily *and* 4. Include streptomycin or amikacin 15 mg/kg tiw for first 2–3 months
Advanced or previously treated disease	1. Clarithromycin 500–1000 mg/day or azithromycin 250–300 mg/day *and* 2. Ethambutol 15 mg/kg daily *and* 3. Rifabutin 150–300 mg daily or rifampin 450–600 mg daily *and* 4. Include streptomycin or amikacin 15 mg/kg tiw for first 2–3 months
Treatment-refractory disease	1. Add amikacin liposome inhalation suspension 590 mg once daily

tiw, three times per week.

From Daley CL, Iaccarino JM, Lange C, et al. Treatment of nontuberculous mycobacterial pulmonary disease: an official ATS/ERS/ESCMID/IDSA clinical practice guideline. *Clin Infect Dis*. 2020;71(4):905–913.

reinforce the regimen and possibly prevent the emergence of macrolide-resistant MAC isolates. Macrolides should *never* be used as monotherapy for treatment of MAC disease, either pulmonary or disseminated.[199]

For some patients who are taking clarithromycin, the doses may need to be split (e.g., 500 mg twice daily) because of gastrointestinal intolerance. For patients of low body weight (<50 kg) or older age, the clarithromycin dose for daily regimens may need to be reduced to 500 mg/day because of gastrointestinal intolerance. However, it should be noted that in a small (n = 34) three-arm retrospective study from Japan, a dose of 400 mg daily was associated with a lower sputum conversion rate at 18 months than a daily dose of 800 mg.[200] Patients receiving clarithromycin and rifabutin should be carefully monitored for rifabutin-related toxicity, especially hematologic (leukopenia) and ocular (uveitis). For some patients, especially those with nodular bronchiectatic MAC disease, intermittent or thrice-weekly therapy may facilitate tolerance of the multidrug treatment regimen.

MAC pulmonary disease should be treated until there are 12 months of sputum culture negativity,[2] a goal that requires patients to have sputum collected for mycobacterial culture on a regular basis throughout the course of treatment. The optimum duration of a parenteral aminoglycoside is unknown, but a retrospective study from Korea reported that patients with cavitary MAC pulmonary disease who received 3 or more months of an aminoglycoside showed higher treatment success rates than those treated for less than 3 months.[201]

Treatment outcomes for MAC pulmonary disease have varied significantly across studies but are better when macrolide-based regimens are used. A systematic review reported sustained sputum culture conversion in 54% (191 of 356) of patients on macrolide-containing regimens versus 32% (38 of 120) for macrolide-free regimens.[202] Another systematic review reported overall treatment success using macrolide-containing regimens was 52.3% (95% confidence interval [CI], 44.7–59.9%), and success increased to 61.4% if treated with an ATS/IDSA three-drug regimen, and to 65.7% if further treated for at least 12 months.[203]

Some patients do not respond to therapy despite administration of an appropriate regimen. A definition for treatment failure was proposed to be the reemergence of multiple positive cultures or the persistence of positive cultures with the causative species from respiratory samples after 12 or more months of antimycobacterial treatment while the patient is on treatment.[204] However, detection of treatment failure at an earlier time point is likely to be beneficial to the patient. In a study reporting the treatment outcomes of patients with MAC pulmonary disease, 83% of patients had their first negative culture within 6 months of starting therapy, and the change in semiquantitative culture scores as early as 2 to 3 months was predictive of culture status at 12 months.[205] In a study from Korea, culture conversion by 6 months was predictive of culture status at 12 months.[206] In a randomized clinical trial evaluating the efficacy and safety of *amikacin liposome inhalation suspension* (ALIS) in patients with treatment-refractory MAC pulmonary disease, cultures converted by 6 months in only 9% of patients who continued to receive *guideline-based therapy* (GBT) alone (the control arm).[189] Based on these studies, lack of culture conversion after 6 months of therapy may be a better time point at which to determine treatment failure.

For patients with treatment-refractory MAC pulmonary disease, ALIS should be added to GBT.[4] ALIS was introduced as a way to increase amikacin uptake into alveolar macrophages, allow biofilm penetration, and limit systemic exposure.[189] In a phase II controlled trial, treatment-refractory patients (e.g., with culture positivity after at least 6 months of GBT that included a macrolide) with MAC (n = 57) or *M. abscessus* (n = 32) pulmonary disease were kept on their multidrug regimen and randomized to investigational ALIS (n = 44) versus placebo (empty liposomes, n = 45).[190] Although the primary end point of reduction in semiquantitative mycobacterial culture growth from baseline was not achieved, significantly more patients who received ALIS achieved culture conversion by day 84 and had greater improvement in distance achieved on the 6-minute walk test. In a recent randomized controlled phase III trial, ALIS, when added to GBT for treatment-refractory MAC pulmonary disease, was associated with a higher proportion of patients with negative cultures at 6 months compared to those who continued to take the standard regimen only.[189] Culture conversion was achieved by 29.0% (65 of 224) of patients treated with ALIS plus GBT compared with 8.9% (10 of 112) with GBT alone. Adverse reactions were reported in 10% or more of patients in the ALIS plus GBT arm, including dysphonia, cough, hemoptysis, dyspnea, fatigue, diarrhea, nausea, and oropharyngeal pain. These events infrequently led to early discontinuation of ALIS or withdrawal from the study. Based on the phase II and III trial results, ALIS was approved by the U.S. Food and Drug Administration for treatment of MAC pulmonary disease in patients who have not responded to therapy after at least 6 months of GBT.

Other treatment options include addition of parenteral amikacin (or streptomycin), oral clofazimine, bedaquiline, or moxifloxacin. Parenteral amikacin has been associated with improved culture conversion in patients with treatment-naive disease[207] and improved treatment outcomes in patients with macrolide-resistant disease (see later).[199,208] Clofazimine has been reported to be associated with culture conversion in patients with MAC pulmonary disease also receiving a macrolide and ethambutol,[209] with relatively good tolerance.[209,210] Bedaquiline was used in treatment-refractory disease, and again the drug was well tolerated; although some patients demonstrated microbiologic improvement, few converted over the 6 months of therapy.[211] In Korea, addition of moxifloxacin to treatment-refractory patients with MAC pulmonary disease was associated with culture conversion in approximately 30% of patients, although that has not been our experience.

Disease recurrence is common and often due to reinfection. Studies have reported recurrence rates of 25–50%, of which 50–75% have been reinfected as determined by either PFGE or repetitive element palindromic polymerase chain reaction.[197,198,212] Microbiologic recurrence was twice as common among patients with nodular bronchiectatic disease compared with cavitary disease, so lifelong follow-up is particularly important is this patient population.[198]

Macrolide-resistant MAC pulmonary disease is associated with a poor prognosis.[199,208,213] The two major risk

factors for macrolide-resistant MAC disease are macrolide monotherapy or macrolide therapy with inadequate companion medications.[199,208] The treatment strategy associated with the most success for macrolide-resistant MAC pulmonary disease includes both the use of a multidrug regimen, including a parenteral aminoglycoside (amikacin or streptomycin), and surgical resection (debulking) of diseased lung.[199,208] The optimal drug regimen for treating macrolide-resistant strains is unknown, but some experts recommend ethambutol, rifabutin, a parenteral aminoglycoside, and possibly another oral drug, such as clofazimine or bedaquiline. The role for ALIS in this setting has yet to be determined. The continuation of a macrolide or addition of moxifloxacin has not been shown to improve outcomes.[208,214]

Therapy of Disseminated *Mycobacterium avium* Complex Disease. Successful treatment of disseminated MAC in persons with AIDS is based on treatment of both the mycobacterial and HIV infections. ART should be started as soon as possible after the diagnosis of MAC disease.[107] Clinicians must therefore be aware of the drug-drug interactions between the antimycobacterial and antiretroviral medications. Current guidelines for the use of antimycobacterial drugs together with HIV therapies can be found at https://clinicalinfo.hiv.gov/en/guidelines/adult-and-adolescent-arv/whats-new-guidelines.

Patients with disseminated MAC disease should be treated with clarithromycin, 1000 mg/day or 500 mg twice daily (or, as an alternative, azithromycin at a dose of 500 mg daily), and ethambutol at a dose of 15 mg/kg daily.[215–217] A third drug, such as rifabutin, may be added because one clinical trial reported that the addition of rifabutin to a regimen of clarithromycin and ethambutol was associated with improved survival and, in two randomized trials, this approach reduced the emergence of resistance.[215,218] It should be noted that the combination of clarithromycin and rifabutin may lead to increased risk of drug toxicity to rifabutin, so azithromycin may be a better companion macrolide. As with macrolide-resistant MAC pulmonary disease, patients with disseminated disease from macrolide-resistant strains are far less likely to be treated successfully.[219] Treatment of MAC in patients with AIDS should be considered lifelong, unless immune restoration is achieved by ART. MAC treatment may be stopped for patients who are asymptomatic, have completed 12 months or more of therapy, and have maintained a $CD4^+$ T cell count greater than 100 cells/mm^3 for at least 6 months after initiation of ART.[107]

Primary prophylaxis (e.g., prevention of the first infection) against disseminated MAC disease is not recommended for adults and adolescents who immediately initiate ART.[107] However, patients who are not receiving ART or who remain viremic should receive prophylaxis if they have CD4 counts less than 50 $CD4^+$ cells/mm^3. Several operational cohorts have demonstrated that the overall incidence of MAC disease is very low and not different between those who did and did not take MAC prophylaxis while on ART.[109,220,221] Plasma HIV RNA level greater than 1000 copies/mL was the main risk factor for developing MAC disease regardless of MAC prophylaxis.[109,221] If primary prophylaxis was previously initiated, it should be discontinued in those who are continuing on a fully suppressive ART regimen.[107] Two randomized, placebo-controlled trials and observational data have demonstrated that patients can discontinue primary prophylaxis safely.[222–226]

Based on efficacy and ease of use, azithromycin—given as 1200 mg once weekly—is the preferred agent for primary prophylaxis.[227] Clarithromycin is also effective; however, it is considered an alternative agent because it must be given twice daily, and the risk of breakthrough with macrolide-resistant strains is higher with daily clarithromycin than with weekly azithromycin. Rifabutin is also effective but should only be used when a macrolide cannot be tolerated. Primary MAC prophylaxis should be discontinued among adult and adolescent patients who are continuing on a fully suppressive ART regimen.[107] Primary prophylaxis should be reintroduced if the $CD4^+$ T lymphocyte count decreases to less than 50 to 100 cells/mm^3.

Secondary prophylaxis (i.e., prevention of reinfection) should be provided to those patients in whom a fully suppressive ART regimen is not possible and who have a decline in their CD4 count to levels to below 100 cells/mm^3.

Therapy of *Mycobacterium avium* Complex Lymphadenopathy. The treatment of choice for MAC lymphadenopathy and localized lymphadenopathy due to most NTM pathogens is complete surgical resection of the involved lymph nodes.[147,148,228,229] When complete surgical resection is not possible due to, for instance, nerve impingement or encasement by infected nodes, then chemotherapy with MAC treatment regimens similar to those for lung and disseminated disease is effective.[230] Some studies have also suggested that a conservative, "wait and see" approach is also as effective as either surgery or antibiotic therapy for the majority of children with this process.[231–233] Clearly, expert evaluation is advisable for optimal management of these children.

Mycobacterium kansasii

M. kansasii is the second most common cause of pulmonary disease caused by a slow grower in the United States but has also been reported in Europe, Asia, and Africa. So far, municipal tap water is the only known reservoir for *M. kansasii*.[234–236] *M. kansasii* lung disease most closely parallels the clinical course of *M. tuberculosis*, including radiographic abnormalities (Fig. 55.6, eFig. 55.2). Although most patients with *M. kansasii* pulmonary disease have upper lobe fibrocavitary findings, some patients have been reported with nodular bronchiectatic radiographic abnormalities. In HIV-infected patients, *M. kansasii* can present with essentially any pattern of radiographic abnormality.[237]

Therapy of *Mycobacterium kansasii* Pulmonary Disease. *M. kansasii* is susceptible to a broad array of antimicrobial agents, including rifamycins, macrolides, fluoroquinolones, clofazimine, ethambutol, isoniazid, trimethoprim-sulfamethoxazole, and aminoglycosides. Newer agents, such as bedaquiline and delamanid, have in vitro activity also.[238] Initially, a regimen including isoniazid was used, but treatment success was unsatisfactory[239] until the introduction of rifampin.[240,241] The recommended regimen for treating pulmonary *M. kansasii* disease has traditionally included daily rifampin (600 mg/day), isoniazid

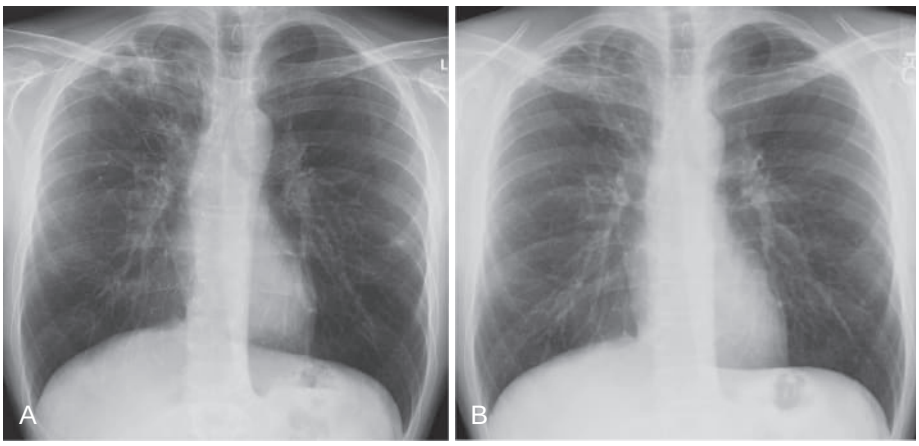

Figure 55.6 *Mycobacterium kansasii.* A 46-year-old man with smoking history with *M. kansasii* lung disease. The patient presented with cough and weight loss. He was treated as a tuberculosis suspect initially, but his sputum specimen was strongly culture positive for *M. kansasii.* (A) Chest radiograph showing right upper lobe cavitary consolidation. (B) Chest radiograph with improvement in abnormalities after completing therapy.

(300 mg/day), and ethambutol (15 mg/kg/day) for at least 12 months.[2,3] Sputum cultures convert in approximately 90% of patients with this regimen[242] and in nearly 100% in patients who complete therapy.[241,243–246] Limited data suggest that therapy with rifampin, ethambutol, and clarithromycin for *M. kansasii* disease can also be successful,[247,248] including when taken as intermittent therapy.[249] Based on the in vitro activity of macrolides against *M. kansasii*, and the two studies that demonstrated good treatment outcomes when clarithromycin was substituted for isoniazid, either isoniazid or a macrolide can be used in combination with rifampicin and ethambutol.[4] Expert opinion favors inclusion of a macrolide over isoniazid. Parenteral aminoglycosides are seldom needed in the treatment of *M. kansasii*.

In patients treated with rifampin, ethambutol, and a macrolide, treatment can be administered either daily or three times a week.[4] However, for those with cavitary disease, daily treatment is recommended instead of intermittent administration. For patients treated with an isoniazid, ethambutol, and rifampicin regimen, daily therapy is also recommended because data regarding intermittent administration of this regimen are lacking. Treatment should continue for at least 12 months.[4] A study that evaluated a two-drug (rifampin, ethambutol) regimen given for 9 months was associated with a culture conversion of 89%, but the recurrence rate was high at 10%.[243]

When *M. kansasii* isolates have become resistant to rifampin as a result of previous therapy, patients have been treated successfully with a regimen that consists of high-dose daily isoniazid (900 mg), high-dose ethambutol (25 mg/kg/day), and sulfamethoxazole (1.0 g three times/day) combined with several months of streptomycin or amikacin.[250] The excellent in vitro activity of clarithromycin and moxifloxacin against *M. kansasii* suggests that multidrug regimens containing these agents and at least one other agent, such as ethambutol or sulfamethoxazole, based on in vitro susceptibilities, are likely to be even more effective for treatment of a patient with rifampin-resistant *M. kansasii* disease.

Therapy of Disseminated *Mycobacterium kansasii* Disease. The treatment regimen for disseminated disease, as usually observed in patients with AIDS, should be the same as for pulmonary disease.[2] Because of the critically important role of rifamycins in the treatment of *M. kansasii* disease, it is important to construct *M. kansasii* and antiretroviral treatment regimens that are compatible (see https://clinicalinfo.hiv.gov/en/guidelines/adult-and-adolescent-arv/whats-new-guidelines). An option for treating HIV-infected patients who receive an antiretroviral regimen not compatible with rifamycins is to substitute a macrolide or moxifloxacin for the rifamycin. There is no recommended prophylaxis regimen for disseminated *M. kansasii* disease.

Mycobacterium xenopi

M. xenopi is a thermophile that survives in hot water systems and natural hot water reservoirs. Its survival in flowing water systems and resistance to common disinfectants enable *M. xenopi* to contaminate laboratory samples and medical devices, such as bronchoscopes, thus causing health care–acquired disease (pseudoinfections) and laboratory contamination of specimens. Clusters of isolates related to pseudoinfections from contamination of bronchoscopes have been reported from the United States and Europe.[251] Because of its environmental presence, the differentiation of true clinical infection from pseudoinfection may be difficult but is of paramount importance. Among 40 patients in The Netherlands who met NTM pulmonary disease criteria, at least half were thought to have disease related to the isolate.[252]

M. xenopi is rarely isolated in the United States; however, it is the second most common cause of NTM lung disease in Canada, the United Kingdom, and some parts of Europe.[252] Pulmonary *M. xenopi* infections are most common, but extrapulmonary and disseminated infections have been reported. Impaired immunity, either local (i.e., preexisting pulmonary disease) or systemic (i.e., HIV, immunosuppressive medications) appear to predispose *to M. xenopi* infections. Radiographic findings with *M. xenopi* pulmonary disease are variable but most often include upper lobe cavitary abnormalities compatible with TB.

Treatment outcomes have been reported as variable. A systematic review that examined 48 studies, including 1255 subjects, described that, among 188 subjects who received at least 6 months of therapy, 65% had a sustained disease-free outcome, with better long-term success in those

who received fluoroquinolones.[253] However, another systematic review reported sputum culture conversion, after subtracting recurrence, in only 32% of patients.[242]

Mortality is high. In one report describing treatment outcomes for *M. xenopi* infections, overall mortality was 68% and mostly unrelated to *M. xenopi* disease; the response to chemotherapy was not correlated with in vitro susceptibility results.[254] *M. xenopi* isolates demonstrated favorable in vitro sensitivities to isoniazid, rifampin, and ethambutol.[252] In this study, even with variable treatment regimens, antimicrobial treatment cured 58% of patients who met ATS/IDSA criteria for *M. xenopi* pulmonary disease. There was no correlation between failure or treatment relapse and in vitro susceptibility results. In a randomized controlled trial, a regimen of clarithromycin, rifampin, and ethambutol was compared to ciprofloxacin, rifampin, and ethambutol; treatment success, failure, or relapse did not differ between the two groups.[255] All-cause mortality was again relatively high and higher in the ciprofloxacin, rifampin, and ethambutol arm (47%) than the clarithromycin-containing arm (29%). A combination of ethambutol and rifampin with either clarithromycin or moxifloxacin was shown to be bactericidal in vitro and ex vivo.[256] In a mouse model, amikacin-containing regimens were the most effective.[256] Although the optimal pharmacologic management has yet to be determined, a regimen is recommended consisting of a macrolide (or moxifloxacin), rifampin, and ethambutol, administered for a duration of therapy that includes 12 months of sputum culture negativity.[4] In patients with cavitary or advanced/severe bronchiectatic *M. xenopi* pulmonary disease, parenteral amikacin should be added to the regimen. The unusually high overall mortality is likely a reflection of the comorbidities of the patients with *M. xenopi* disease.

Mycobacterium malmoense

M. malmoense is considered the second most serious pathogen after MAC in Northern Europe.[257] The clinical relevance (i.e., met ATS/IDSA diagnostic criteria for disease) of *M. malmoense* isolates has been described as 70–80% in Europe, although isolates in the United States are infrequently deemed clinically significant.[258] Patients with *M. malmoense* pulmonary disease frequently have preexisting obstructive lung disease. Not surprisingly, *M. malmoense* pulmonary disease often presents in a manner similar to that of other cavitary NTM disease pathogens. Overall, treatment response does not correlate with in vitro susceptibility to antimicrobial agents. A recent systematic review[242] reported a weighted average proportion of treatment success of 54.4% (95% CI, 34.7–73.4%); however, this estimate is limited by the high all-cause mortality in the studies. In a randomized controlled trial, clarithromycin, rifampin, and ethambutol were compared to a regimen consisting of ciprofloxacin, rifampin, and ethambutol.[259] Although a more favorable response to therapy was attained with the macrolide-containing regimen, overall mortality did not differ between the two regimens. The optimal antimicrobial management of *M. malmoense* has yet to be determined, although treatment should probably include at least three agents guided by in vitro susceptibility: azithromycin 250 to 500 mg/day, rifampin 600 mg/day, and ethambutol 15 mg/kg/day. Amikacin 10 to 15 mg/kg/day *intravenous* (IV) or 15 to 25 mg/kg three times a week should be considered for cavitary/severe disease. Moxifloxacin 400 mg/day or clofazimine 100 mg/day may be used as alternative drugs. Although the optimal treatment duration is not known, experts have recommended that treatment continue for 12 months beyond the date of culture conversion.[2]

Mycobacterium simiae

M. simiae has been recovered from clinical specimens in several geographic regions, including Israel, Cuba, Réunion Island, and the southwestern United States.[2,260] The organism is most often isolated as a single positive culture from a patient who is smear negative and without clinical disease. Several pseudo-outbreaks have been reported in which the organisms were recovered from the local tap water.[261–263] In most published series, the majority of *M. simiae* isolates have been judged not to be clinically significant.[264,265] When *M. simiae* is a significant pathogen, it is most often associated with pulmonary disease or, in immunocompromised hosts, with disseminated disease.

As with other NTM, there is no established correlation between in vitro susceptibility of the organism and clinical response to antimicrobial agents, nor is there an established, predictably reliable treatment regimen for *M. simiae* disease. In a study from Israel,[265] there were no recurrences reported in 102 patients with *M. simiae* pulmonary disease after treatment with rifampin, ethambutol, and clarithromycin given daily for at least 12 months of negative sputum cultures. These results are in sharp contrast to the experience of many expert consultants in the United States who find *M. simiae* to be among the most difficult to treat of the pulmonary NTM pathogens. Some experts suggest using macrolide-based regimens with other agents, such as amikacin, fluoroquinolones, sulfamethoxazole, and linezolid.[2] A reasonable regimen would include at least three of the following drugs: azithromycin 250 to 500 mg/day, moxifloxacin 400 mg/day, trimethoprim-sulfamethoxazole 800 or 160 mg twice a day, linezolid 600 mg/day, and amikacin 10 to 15 mg/kg/day IV or 15 to 25 mg/kg three times a week. Optimal treatment duration is unknown, and experts consider treating at least 12 months after culture conversion.[2]

Mycobacterium szulgai

M. szulgai is characterized primarily by cavitary disease in patients with underlying chronic pulmonary disease that resembles disease due to *M. tuberculosis.* As with other NTM pathogens, it can also be associated with nodular bronchiectatic disease. The organism is often susceptible in vitro to most anti-TB drugs and to the fluoroquinolones and macrolides.[266–270] Most respiratory isolates of *M. szulgai* are associated with significant lung disease: 73% (11 of 15) of patients in The Netherlands who grew *M. szulgai* from their sputum met current ATS/IDSA criteria for disease.[271] In vitro susceptibilities demonstrate susceptibility to rifampin, isoniazid, ethambutol, and clarithromycin. Regimens containing rifamycin, ethambutol, and clarithromycin, with or without a fluoroquinolone administered for approximately 12 months, have almost 100% treatment success.[271] Unlike many other NTM pathogens,

susceptibility on in vitro testing for *M. szulgai* appears to predict favorable treatment response.

RAPIDLY GROWING MYCOBACTERIA

RGM are distinguished by growth in subculture in less than 7 days and comprise approximately 100 distinct species (http://www.bacterio.net/mycobacterium.html), at least 30 of which have been associated with lung disease, although rarely (see Table 35.1). Because many RGM are not pathogenic in humans, it is important to subclassify organisms within this group to the species, and even subspecies level in the case of *M. abscessus,* because this affects both treatment and prognosis. Although RGM can produce pulmonary disease, they have a propensity to produce skin and soft tissue infections.

Mycobacterium abscessus

M. abscessus causes at least 80% of pulmonary infections due to RGM in the United States.[95] Genomic sequencing has determined that *M. abscessus* can be divided into three subspecies: *M. abscessus abscessus, M. abscessus bolletii,* and *M. abscessus massiliense*.[272] Most patients with pulmonary disease due to *M. abscessus* are nonsmoking white women older than 60 years who have no predisposing conditions, a similar patient population as seen with nodular bronchiectatic MAC pulmonary disease.[95] The usual clinical presentation is similar to that of other NTM pulmonary infections and includes cough and easy fatigability. For most patients with no predisposing conditions, the disease is slowly progressive; however, more fulminant, rapidly progressive disease has been seen in patients with gastroesophageal disorders and CF. The chest radiograph usually shows multilobar, patchy, reticulonodular, or mixed reticulonodular-alveolar opacities (Fig. 55.7). High-resolution CT findings include the presence of cylindrical bronchiectasis with multiple small nodules, similar to the findings in MAC pulmonary disease.[95,273,274] Cavitation has been reported in 10–20% of patients.

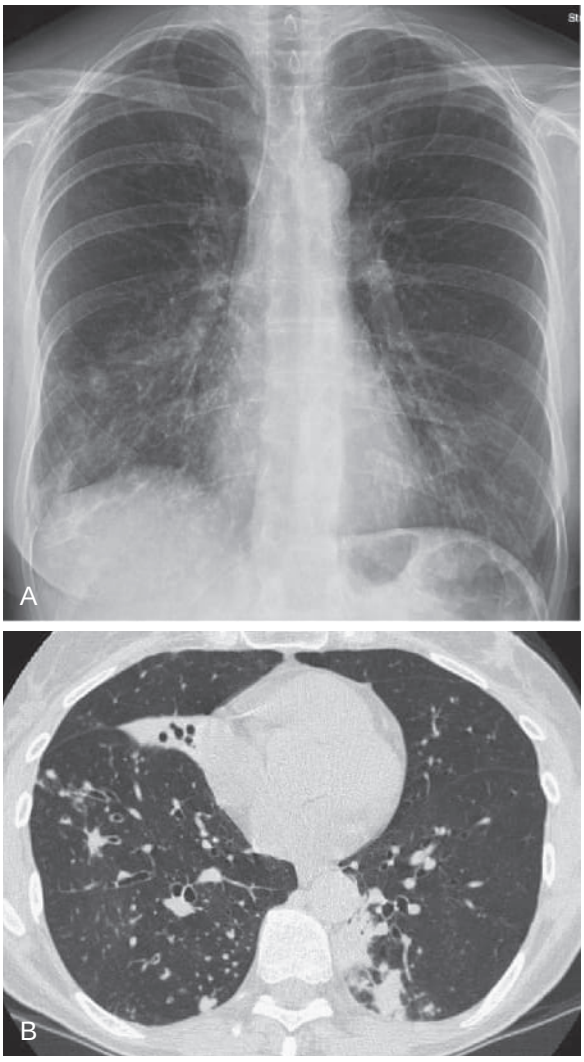

Figure 55.7 *Mycobacterium abscessus.* A 68-year-old nonsmoking woman with several-year history of cough, fatigue, and weight loss. Her sputum cultures were consistently positive for *M. abscessus.* (A) Chest radiograph showing middle and lower lung zone nodular opacities and bronchiectasis. (B) Chest computed tomography scan showing right middle lobe atelectasis and bronchiectasis with bilateral lower lobe bronchiectasis and nodular opacities. Note the left lower lobe air space opacity in this patient with severe reflux and probable chronic aspiration.

Therapy of *Mycobacterium abscessus* Pulmonary Disease. *M. abscessus* is typically resistant in vitro to most of the medications used to treat TB and has demonstrated in vitro activity to only a few antimicrobial agents. Cure can be elusive for many patients with *M. abscessus* disease. Among 65 patients from South Korea with *M. abscessus* pulmonary disease treated with a standardized regimen, including 4 weeks of IV amikacin and cefoxitin, along with oral ciprofloxacin, clarithromycin, and doxycycline for a total duration of 24 months, 58% of patients had sputum conversion with maintenance of negative sputum cultures for more than 12 months.[275] In a study from the United States, 107 patients were treated with individualized therapy that included IV imipenem (or cefoxitin) and amikacin along with various oral and inhaled combinations of therapy.[276] Results showed that 48% converted and maintained negative cultures for at least 12 months.

Current guidelines recommend that therapy usually consists of 2 to 4 months of IV agents, such as imipenem, cefoxitin, tigecycline plus amikacin given daily or three times weekly.[4] Oral agents demonstrating in vitro activity should be included in the treatment regimen. Although macrolides have traditionally been used in this role, recent studies have questioned the importance of macrolides in the treatment of *M. abscessus* subsp. *abscessus* because approximately 80–90% of strains contain a functional *erm(41)* gene[277–279]; when the organism is incubated in the presence of clarithromycin, the gene is induced and the organism rapidly acquires macrolide resistance. (Approximately 15% of strains of *M. abscessus* subsp. *abscessus* have a T to C mutation at position 28 that renders the *erm(41)* gene nonfunctional.) In contrast, *M. massiliense* has a truncated, nonfunctional copy of the gene, so macrolide resistance is not induced in the presence of clarithromycin.[279] In a study from South Korea, patients infected with *M. massiliense* were more likely to improve clinically, radiographically, and bacteriologically than those with *M. abscessus*: Eighty-eight percent of those with *M. massiliense* converted sputum cultures to negative, compared to 25% with *M. abscessus*.[279]

In a recent systematic review and meta-analysis, sustained culture conversion was reported in 54% of those with subsp. *massiliense* compared to only 34% of patients with subsp. *abscessus*.[280] Similarly, an individual patient data meta-analysis noted treatment success in 57% of patients with subsp. *massiliense*, compared to only 33% of patients with subsp. *abscessus*.[281] Limited data suggest that azithromycin may be more effective against *M. abscessus* than is clarithromycin.[281–283]

Species identification discriminating between subsp. *abscessus* and subsp. *massiliense* would inform clinicians about the likely presence of an active *erm(41)* gene and the best presumptive antibiotic choices but is frequently not available from hospital or reference laboratories. However, the presence of an active *erm(41)* gene can be ascertained in most specialized mycobacteriology laboratories in a relatively short time frame and is the critical information needed by the clinician to guide antibiotic therapy for isolates initially identified as *M. abscessus*.

Linezolid, an oxazolidinone, is active against some strains of *M. abscessus* but is frequently associated with significant hematologic toxicity and peripheral neuropathy, particularly at higher doses.[284–286] Tedizolid, another oxazolidinone, has greater in vitro activity than linezolid, but clinical data are lacking.[287,288] Tigecycline has significant in vitro activity against *M. abscessus* but is available only as an IV preparation and is associated with significant nausea and vomiting.[289,290] Eravacycline and omadacycline are two recently released cyclines with similar activity to that of tigecycline and may be better tolerated.[288] Clofazimine has in vitro activity against *M. abscessus* and synergistic activity with amikacin,[291] but its role in the management of these patients remains to be defined. Studies that included clofazimine in treatment regimens in patients with *M. avium* complex and also *M. abscessus* have demonstrated modest improvement in patients with refractory disease.[210,292]

Once the patient has demonstrated a clinical response to therapy, there are several possible choices for continued treatment: (1) stop therapy after 2 to 4 months and follow the patient for signs of progression of disease and, if present, periodically reinstitute treatment; (2) stop the aminoglycoside and continue the cefoxitin or imipenem for a longer period along with oral agent(s); or (3) continue the oral agent(s) and institute inhaled amikacin. The studies published to date reported experiences with options 2 and 3. However, the optimum choice is not known; ultimately, treatment decisions therefore will need to be individualized, and often some form of therapy will be given periodically on a lifelong basis. Expert consultation is strongly recommended.

A combination of surgical resection and chemotherapy may increase the chance of cure in patients who have focal lung disease and who can tolerate resection.[275,276] If resection is planned, patients should be treated with an initial period of antimicrobial drug therapy before surgery to lessen the bacillary load. In three studies, patients who underwent surgical resection in addition to antimicrobial chemotherapy had improved microbiologic outcomes compared with those who received chemotherapy alone.[95,275,276] As with MAC pulmonary disease, surgery should be performed by thoracic surgeons experienced in performing this type of surgery.[293]

Therapy of *Mycobacterium abscessus* Skin, Soft tissue, and Bone Infections. Serious infections should be treated with a regimen similar to that used for pulmonary disease. Skin and soft tissue infections should be treated for a minimum of 4 months and bone infections for a minimum of 6 months.[2] Surgery is generally indicated for extensive disease, abscess formation, or when drug therapy is difficult. Foreign bodies, such as prosthetic joints, percutaneous catheters, and breast implants, should be removed and the patient treated with a prolonged antimicrobial treatment regimen.

Mycobacterium chelonae

M. chelonae is more likely to produce skin, soft tissue, and bone infections than pulmonary disease.[149] Keratitis due to *M. chelonae* has been associated with wearing contact lenses and with ocular surgery, such as *laser-assisted in situ keratomileusis* (LASIK).[294,295] Disseminated disease has been reported in immunocompromised patients and usually presents with characteristic cutaneous lesions.[296] The clinical and radiographic presentation of *M. chelonae* pulmonary disease is similar to that of other RGM.

Isolates of *M. chelonae* are usually susceptible to tobramycin, macrolides, linezolid, and imipenem.[155,297,298] The *M. chelonae* genome does not include an active *erm* gene, so macrolides should be considered active.[277] Other active drugs may include amikacin, clofazimine, doxycycline, and the fluoroquinolones. *M. chelonae* isolates are uniformly resistant to cefoxitin. Treatment of *M. chelonae* infections should be based on in vitro susceptibility results. Administration of clarithromycin 500 mg twice daily for 6 months was reported to have a high cure rate in patients with cutaneous lesions associated with disseminated disease.[299] However, one patient who relapsed did so with a macrolide-resistant strain, so multidrug regimens are recommended. Patients have also responded to linezolid with or without clarithromycin.[300,301] Patients with serious skin, soft tissue, and bone infections should be treated with two or more drugs similar to those used in *M. abscessus* disease. For corneal infections, both topical and oral agents are often used, and many patients may require corneal transplants for recovery of vision or cure.

Mycobacterium fortuitum Complex

Mycobacterium fortuitum complex consists of 12 species,[302–304] of which *M. fortuitum* is the most common in respiratory specimens.[305] *M. fortuitum* is responsible for at most 15% of RGM infections in the United States but is a relatively uncommon cause of pulmonary disease except in patients with disorders associated with chronic aspiration.[95] Among 26 patients in the Republic of Korea with two or more positive cultures for *M. fortuitum*, only one was treated, and none of the 25 untreated patients showed progression over a median of 12.5 months of follow-up.[306] The clinical and radiographic presentation of patients with pulmonary disease is similar to that of other RGM. Application of current diagnostic guidelines must be used with caution and even some skepticism when evaluating patients with *M. fortuitum* respiratory isolates. Skin, soft tissue, and bone infections are more common than pulmonary disease. Both sporadic and clustered outbreaks of furunculosis due to *M. fortuitum* (and other RGM) have

been reported after exposure to contaminated water during pedicures.[307–309]

In contrast to *M. abscessus, M. fortuitum* demonstrates broader in vitro susceptibility to both oral and IV antimicrobial drugs, including the newer macrolides, the fluoroquinolones, doxycycline, minocycline, the sulfonamides, and two IV drugs—imipenem and cefoxitin.[2] Although most isolates of *M. fortuitum* are susceptible in vitro to the macrolides, these drugs should be used with caution because of the presence of an inducible erythromycin methylase (*erm*) gene, *erm(39)*.[310] Greater than 80% of *M. fortuitum*, *Mycobacterium porcinum*, and *Mycobacterium septicum* are inducibly resistant to clarithromycin, in contrast to *Mycobacterium peregrinum,* which is inducibly resistant in about one-third of isolates.[305]

M. fortuitum lung disease should be treated with at least two drugs to which in vitro susceptibility has been demonstrated.[2] As with other NTM pulmonary infections, treatment should be continued for at least 12 months of negative sputum cultures. Skin, soft tissue, and bone infections should be treated similarly to *M. abscessus* infections, although more effective oral agents are usually available.

CYSTIC FIBROSIS AND NONTUBERCULOUS MYCOBACTERIA

Individuals with CF have particularly high rates of NTM pulmonary disease, which appear to be increasing. The true rate of NTM infection is difficult to determine due to variability in screening practices, culture techniques, and data collection.[78] Estimates of the prevalence of NTM isolation in people with CF have ranged from a low of 1.3% in the earliest study from 1984[311] to as high as 50% in individuals older than 40 years seen at an adult CF clinic in Colorado.[312] Some of the largest studies, including more than 1000 patients each, reported isolation prevalences ranging from 6.6–13.7%.[91–93] More recent longitudinal data from the U.S. CF Patient Care Registry reported that, of 16,153 persons with CF, 20% had a least one pathogenic NTM species isolated over a 5-year period, although this varied geographically (see Fig. 55.2).[94]

As with NTM disease in non-CF patients, the prevalence appears to be increasing in persons with CF. Among individuals younger than 16 years, the prevalence of an NTM-positive respiratory culture increased from 1.3% in 2010 to 3.8% in 2015. In a study from Israel the NTM prevalence increased threefold from 5% in 2003 to 14.5% in 2011.[313] Using data from the U.S. CF Patient Care Registry, NTM disease prevalence showed a significant relative increase of 5% per year from 11.0% in 2010 to 13.4% in 2014.[94]

The most common NTM to cause pulmonary disease in people with CF are MAC and *M. abscessus*. Their relative importance varies by geographic area and age. For example, in Europe, *M. abscessus* is isolated in 40–60% of cases compared with 15–25% in the United States.[314] And, in the United States, MAC, on the other hand, has been isolated in up to 70% of people with CF who have NTM isolated. Of importance, approximately 25% of patients have another NTM isolated in 5 years and 36% at 10 years, so reinfection is common.[315] *M. abscessus* affects patients at a younger age than MAC, with one study from France reporting that 90% of people with CF acquired *M. abscessus* by 10 years of age.[316]

A number of risk factors have been associated with acquisition of NTM infection. Studies from both the United States and Europe have described increasing NTM prevalence with increasing age.[91,317] For example, data from the European CF Registry showed that for every decade increase in life, the risk of acquiring NTM increased by 17.5%.[317] In Denver, Colorado, among adults with CF who were older than 40 years, 32.7% had positive NTM cultures.[312] Other risk factors for NTM infection have included concurrent allergic bronchopulmonary aspergillosis, chronic *Pseudomonas* infection, and use of inhaled steroids.[314] Proximity to water and high amounts of atmospheric water content have been associated with an increased risk of NTM infection. In one study in the United States, for every one-unit increase in saturated water vapor pressure, the risk of NTM infection increased by 6%.[53]

Chronic azithromycin has been shown to decrease pulmonary exacerbations and improve lung function in people with CF and chronic *Pseudomonas* infection.[318] Concern has been raised about the potential of azithromycin monotherapy leading to development of macrolide-resistant NTM infections. A nested-case control study using data from the U.S. Cystic Fibrosis Foundation Patient Registry found that long-term azithromycin use was associated with a decreased risk of acquiring NTM (MAC or *M. abscessus*) in adolescents and adults with CF.[319] A study of adults with CF in France reported similar findings, but one *M. avium* isolate acquired macrolide resistance.[320] The development of macrolide-resistant NTM remains a concern, so individuals with CF should be screened for evidence of NTM pulmonary infection before initiation of macrolide monotherapy and periodically while on therapy.

As noted previously (see "Transmission and Pathogenesis"), several studies have described possible transmission of *M. abscessus* from human to human in CF clinics,[60–62] whereas other studies have been unable to confirm transmission despite high degrees of genomic similarity between strains of *M. abscessus*.[73–75] Although WGS has provided a powerful tool to improve our understanding of transmission of NTM, the sequencing information will need to be paired with rigorous environmental assessments and epidemiology to explain the transmission dynamics of NTM in CF populations.

The U.S. CF Foundation and European Cystic Fibrosis Society have published guidelines for the diagnosis and treatment of NTM infections in people with CF.[321] Cultures for NTM are recommended annually in spontaneously expectorating individuals even when stable. ATS/IDSA diagnostic criteria (see Table 55.3) are recommended, but, because of the high rate of concurrent bacterial and fungal infections and universally abnormal radiographs, application of the criteria is often more challenging than in a non-CF bronchiectasis population. Approximately 50–60% of those with CF who have an NTM isolated from respiratory specimens will convert cultures to negative without antimicrobial therapy.[315,322] In retrospective studies of children and adults with CF, approximately 60–70% of patients had evidence of transient or stable NTM disease.[315,323] As in non-CF bronchiectasis, isolation of NTM from a respiratory

specimen does not necessarily mean that progressive disease will follow. Ultimately, the decision to treat will be based on whether the patient is responding to treatment of other copathogens (e.g., *Pseudomonas*), the virulence of the infecting species, evidence of radiographic progression, loss of lung function over time, and bacterial load (e.g., acid-fast bacilli smear status).

Treatment of NTM pulmonary disease uses the same general approach as is used in non-CF patients. A three-drug macrolide-containing regimen is administered for macrolide-susceptible MAC pulmonary disease; however, unlike with non-CF bronchiectatic disease, intermittent therapy is not recommended because of the concern for inadequate drug absorption and lung penetration.[321] As in non-CF patients, azithromycin is the preferred macrolide. With the widespread use of CFTR-modulating drugs, rifamycins have become difficult to use because of drug interactions through the CYP3A4/5 system. Rifamycins are strong inducers of this enzyme system, and ivacaftor is metabolized through this system, resulting in low serum concentrations when coadministered with a rifamycin.[324] Currently, rifamycins are not recommended to be used with CFTR modulators.

Treatment outcome data are very limited but tend to mirror those in non-CF patients with NTM pulmonary disease. In a retrospective review of CF patients from Colorado, the rate of culture conversion in response to treatment for MAC was 60%.[315] Eradication of *M. abscessus* in children and adults with CF has been reported in 20–50% of patients using GBT.[325–328] In a retrospective study, including 37 CF patients with *M. abscessus* pulmonary disease, of whom most were treated with a multidrug GBT regimen, only 10 patients experienced sustained culture conversion.[325] In a retrospective review of CF patients from Colorado, the rate of culture conversion in response to treatment for *M. abscessus* (not subspeciated) was 45%.[315] However, lung function improved, demonstrating a treatment benefit. In another study reporting treatment outcomes in patients with NTM pulmonary disease, treatment was associated with a reversal of the pretreatment decline in FEV_1% predicted.[315] As in non-CF patients with *M. abscessus* pulmonary disease, treatment outcomes for *M. abscessus* subsp. *massiliense* are much better than for subsp. *abscessus*, with cultures converting in greater than 80% of patients with subsp. *abscessus* compared with 25% of those with subsp. *abscessus*.[93]

CF is the most common indication for lung transplantation in children and the third most common condition leading to lung transplantation in adults.[329,330] The U.S. CF Foundation and European Cystic Fibrosis Society recommend that all individuals with CF being considered for lung transplantation should be evaluated for NTM pulmonary disease and that the presence of NTM should not preclude individuals from being evaluated for transplant.[321] In the largest CF-specific cases series from the University of North Carolina, approximately 20% of people with CF referred for lung transplantation had NTM isolated from respiratory specimens.[331] In a study of CF and non-CF transplants, NTM was isolated after transplantation in 22.4% (53 of 237 individuals), of whom two fulfilled ATS/IDSA diagnostic criteria for disease.[332] Although morbidity after transplant can be significant, mortality has varied between studies.

M. abscessus pulmonary disease has been considered by some to be a relative contraindication for lung transplantation in CF patients[122,333]; however, recent reports suggest that lung transplantation for CF patients with *M. abscessus* infection can be accomplished with success rates comparable to CF patients without infection.[334–337] For patients with isolation of *M. abscessus* before transplantation, treatment with a multidrug regimen before and after transplantation has been successful even when the organism could not be eradicated pretransplantation.[336,337] In one report, patients infected with *M. abscessus* subsp. *massiliense* did better than those with subsp. *abscessus*.[338] Nevertheless, *M. abscessus* infection in patients with CF who have undergone lung transplantation can have significant posttransplant infections that can be severe and sometimes fatal.[120–122] Current guidelines do not recognize infection with NTM, including *M. abscessus,* as a contraindication for lung transplant.[321]

SURGICAL RESECTION

Patients with NTM pulmonary disease whose disease is predominantly localized to one lung and who can tolerate resectional surgery should be considered for surgery under the following conditions: (1) poor response to drug therapy, (2) development of macrolide-resistant MAC disease, or (3) presence of significant disease-related complications, such as hemoptysis. Outcomes of surgery have generally been good, with greater than 80% culture conversion documented postoperatively.[4,293,339,340] Operative mortality has been low, and complications (e.g., bronchopleural fistula, prolonged air leak, and pneumonia) have been reported in 7–35% of cases.[4] In a study reporting the outcomes of 134 patients undergoing video-assisted thoracoscopic surgery, there were no deaths, the complication rate was 7%, and cultures converted in 84% of the patients.[340] Whenever possible, surgery should be performed by thoracic surgeons who have had considerable experience with resectional lung surgery for mycobacterial disease.[293] Surgery for NTM pulmonary disease can be technically difficult due to pleural adhesions, fibrotic lung tissue, fused fissures, and hypertrophied bronchial circulation.[341]

THERAPEUTIC DRUG MONITORING

The role of therapeutic drug monitoring remains unclear. Low serum concentrations of clarithromycin have been reported when the drug is given in combination with rifampin.[342,343] A study that examined the pharmacokinetic and pharmacodynamic relationships in 481 patients with MAC pulmonary disease reported that peak serum concentrations were below the target range for ethambutol (48%), clarithromycin (56%), and azithromycin (35%).[343] Concurrent administration of rifampin reduced the serum concentration of clarithromycin by 68% and that of azithromycin by 23%. Pharmacodynamic indices were seldom met for rifampicin, clarithromycin, amikacin, and moxifloxacin. This study did not examine a possible correlation between clinical outcome and the poor pharmacodynamics indices. A study from South Korea reported that peak plasma concentrations of clarithromycin were lower in MAC patients who received daily or intermittent

therapy when in conjunction with rifampicin compared with *M. abscessus* patients who received clarithromycin without rifampicin.[344] In this study, treatment outcomes were not associated with plasma drug concentrations; however, no attempt was made to increase the dosage in patients with low concentrations to see if outcomes would have improved. In a subsequent study, a higher maximum azithromycin serum concentration was associated with favorable microbiologic responses in patients who received daily therapy but not in those who received intermittent therapy.[345] Therapeutic drug monitoring should be considered in patients who are not responding to therapy, have end-stage renal disease, are receiving aminoglycosides, or are taking medications known to cause drug interactions.[2]

HYPERSENSITIVITY PNEUMONITIS–LIKE NONTUBERCULOUS MYCOBACTERIA PULMONARY DISEASE

Most reports describing the development of a typical pattern of hypersensitivity pneumonitis-like pulmonary disease have been in patients associated with hot tub exposure, although similar clinical presentations have been associated with other indoor standing water sources and exposures.[64,346,347] In the cases of exposure to hot tubs, MAC has been isolated from sputum, bronchoalveolar lavage, tissue, and hot tub water. Furthermore, when assessed by genotyping methods, MAC isolates from both the hot tub water and the lung specimens have demonstrated identical patterns. Controversy still exists, however, as to whether hot tub lung is an infectious process, inflammatory process, or a combination.

Patients with hypersensitivity pneumonitis-like lung disease tend to be young and without preexisting lung disease. The clinical presentation varies from mild respiratory symptoms to respiratory failure requiring mechanical ventilatory support.[348] Key elements to the diagnosis of MAC hypersensitivity-like lung disease include a compatible clinical history (subacute onset of respiratory symptoms, hot tub exposure); characteristic radiographic findings (diffuse centrilobular nodules and ground-glass opacities) (eFig. 55.3); and MAC isolates in sputum, bronchoalveolar lavage, tissue, and hot tub water (and compatible histopathology when available).

Patient prognosis is generally excellent independent of severity on presentation.[346] The most benefit is gained by simply removing the patient from further antigen exposure. In the case of hot tub lung, removal from antigen exposure generally involves drainage of hot tub water and complete avoidance of hot tub use. Whether continued exposure to ambient environmental MAC organisms can propagate the hypersensitivity pulmonary reaction is uncertain. For selected patients with hypersensitivity pneumonitis-like lung disease, use of systemic corticosteroids may be of benefit and hasten recovery of pulmonary symptoms, gas-exchange abnormalities, and radiographic abnormalities. Likewise, antimycobacterial therapy, with the same medications as for standard pulmonary MAC lung disease, may be required in some patients but for shorter durations of therapy, usually 3 to 6 months. Most patients can be expected to have nearly complete resolution of respiratory symptoms and of pulmonary function and radiographic abnormalities.

PREVENTION OF NONTUBERCULOUS MYCOBACTERIA INFECTIONS

NTM are ubiquitous in the environment, so complete avoidance is difficult, if not impossible. The organisms generally have very low virulence for humans compared with *M. tuberculosis,* so NTM disease may be more of a problem with host susceptibility than with organism virulence. With some notable exceptions previously discussed, the specific susceptibility of an individual patient to NTM infection may be impossible to determine at this point; in accordance, disease prevention remains problematic. The question remains, however, should patients with known vulnerabilities to NTM infection be advised to avoid known environmental sources of NTM? For instance, should vulnerable patients be advised not to take showers, which are known to be colonized with NTM?[63,64,349,350] Currently the answer is unknown, and prevention of most environmentally acquired NTM infection remains a challenge.

HEALTH CARE–ASSOCIATED NONTUBERCULOUS MYCOBACTERIA DISEASE

Transmission of NTM disease in the health care setting has most frequently been linked to tap (municipal) water exposure.[142] Since 2013, there has been a global outbreak of disseminated disease due to *M. chimaera* related to exposure to heater-cooler units during various cardiac surgeries.[83–85] The infections were eventually tracked to water contamination at the factory.[351,352] Although various NTM species, including MAC, *M. kansasii, M. xenopi,* and *M. simiae*, have been isolated from municipal water supplies, *M. fortuitum* and *M. abscessus* have been most often implicated in health care–associated NTM disease. Even with use of potent disinfectants, including organomercurials, chlorine, bromine, 2% formaldehyde, and glutaraldehyde, NTM organisms may persist on equipment or devices after tap water exposure. The large outbreak of *M. massiliense* in Brazil involved a single clone tolerant to 2% glutaraldehyde.[79] The inability to eliminate these organisms underscores the importance of avoidance of tap water for preventing health care–associated NTM diseases, such as those after median sternotomy; cosmetic surgery procedures; liposuction; LASIK; dialysis; and the implantation of long-term central IV catheters, tympanostomy tubes and prosthetic devices, such as heart valves, knee and hip joints, lens implants, and metal rod bone stabilizers.[2] Pseudo-outbreaks have involved bronchoscopes contaminated with *M. abscessus, M. simiae,* and *M. immunogenum.* Documented outbreaks of *M. fortuitum* and *M. mageritense* furunculosis in association with use of contaminated whirlpool footbaths have been described in nail salons.[307–309,353]

As a result of the increased understanding of environmental NTM reservoirs and reports linking the use of tap water to health care–associated NTM infections (and pseudoinfections), it is recommended that tap water never be used in preparation of surgical procedures, prosthetics, intravascular catheters, in cleaning fiberoptic endoscopes, or in rinsing the mouth out before collecting expectorated sputum samples. Moreover, recognition that alternative medicines or unapproved substances for injection may also be at risk of contamination by NTM warrants caution against use of these products as well.

Key Points

- *Nontuberculous mycobacteria* (NTM) comprise approximately 200 different species and subspecies that are ubiquitous in our environment. Members of the *Mycobacterium avium* complex (MAC) are the most common causes of NTM pulmonary disease.
- Infection follows exposure to NTM in the environment: Human-to-human transmission is exceptionally uncommon, except perhaps in the setting of cystic fibrosis.
- Epidemiologic studies suggest that the prevalence of NTM infections is increasing in some areas of the world, including the United States.
- Risk factors for pulmonary NTM disease include underlying chronic lung diseases, such as bronchiectasis, chronic obstructive pulmonary diseases, cystic fibrosis, alpha$_1$-antitrypsin deficiency, and prior tuberculosis.
- Diagnosis of NTM pulmonary infections is often challenging and requires that the patient meet certain clinical, radiographic, and microbiologic criteria.
- The recommended treatment for MAC pulmonary disease is a macrolide, plus ethambutol and a rifamycin, with or without an aminoglycoside administered for at least 12 months of culture negativity. Macrolides should *never* be used as monotherapy for treatment of MAC disease, either pulmonary or disseminated.
- For treatment-refractory MAC, amikacin liposome inhalational suspension should be added to guideline-based therapy.
- The recommended treatment for *Mycobacterium kansasii* pulmonary disease is a macrolide (or isoniazid), a rifamycin, and ethambutol administered for at least 12 months.
- Resectional surgery should be considered for patients with focal disease and (1) poor response to drug therapy, (2) development of macrolide-resistant MAC disease, or (3) presence of significant disease-related complications, such as hemoptysis.
- Treatment of rapidly growing mycobacterial infections should be based on the results of in vitro drug susceptibility testing, but the clinical outcome varies significantly depending on the causative species and presence of a functional erythromycin resistance methylase (41) gene.
- Health care–associated infections have been linked to the use of tap water, a reservoir for certain NTM. Tap water should never be used to wash surgical instruments, clean fiberoptic endoscopes, or rinse out the mouth before collecting sputum samples.

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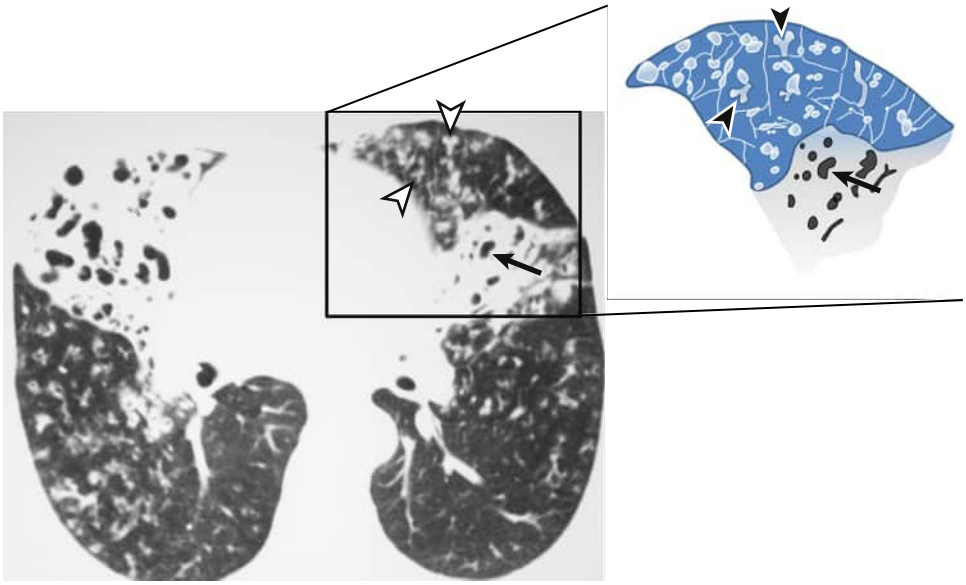
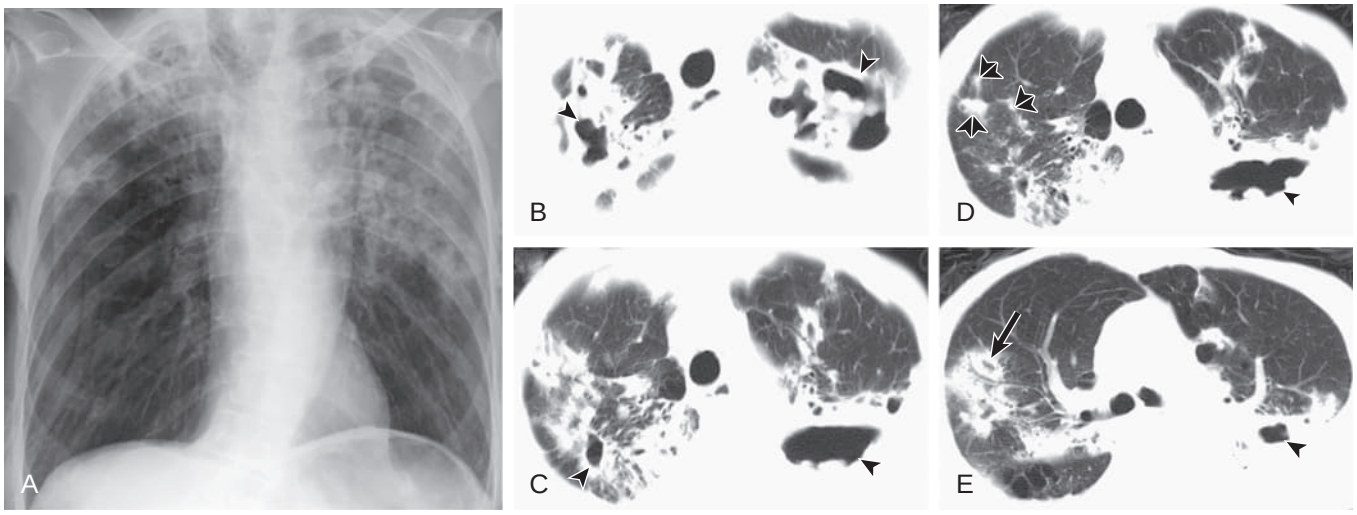
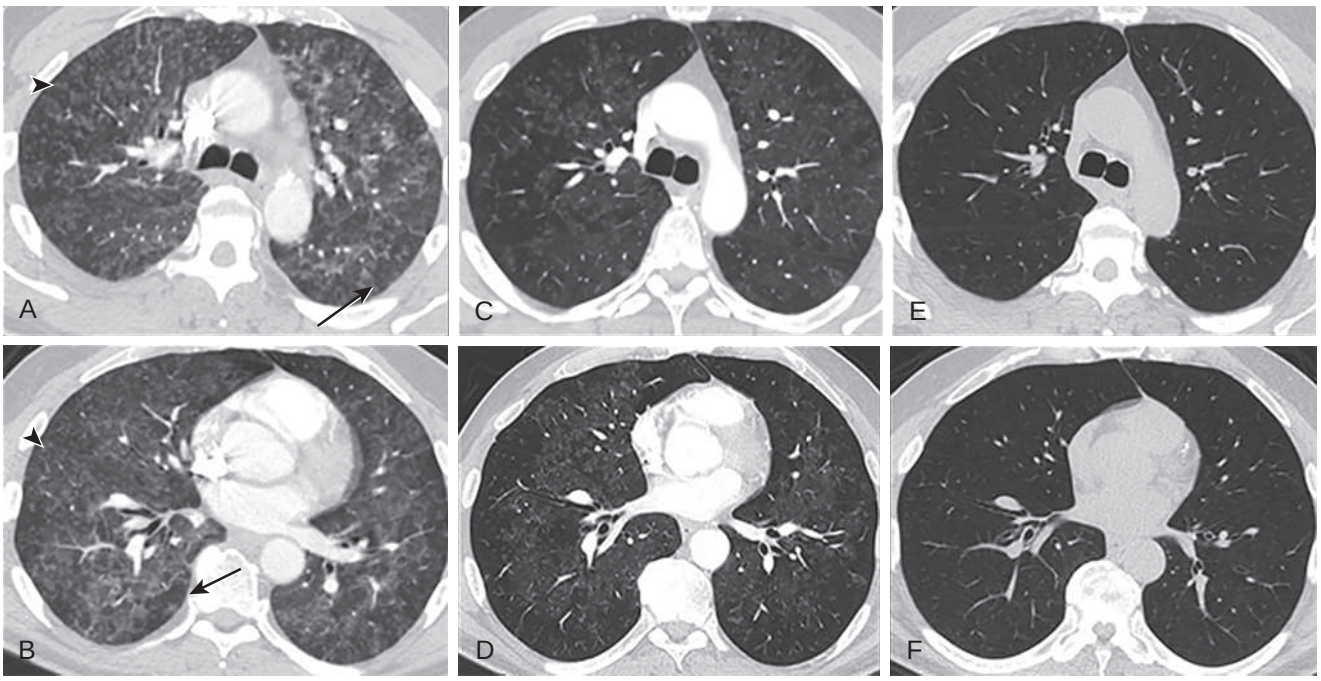
eFIGURE IMAGE GALLERY



eFigure 55.1 Nodular/bronchiectatic *Mycobacterium avium* complex: high-resolution thoracic computed tomography (CT) appearance. Axial high-resolution CT shows extensive bronchiectasis in the right middle lobe and lingula (*arrow*). Numerous small centrilobular nodules with branching configurations, representing tree-in-bud opacity *(arrowheads*), are present. The inset diagram illustrates the lingular CT findings. (Modified from Gotway MB, Reddy GP, Webb WR, Elicker BM, Leung JW. High-resolution CT of the lung: patterns of disease and differential diagnoses. *Radiol Clin North Am.* 2005;43[3]:513–542.)



eFigure 55.2 *Mycobacterium kansasii* pulmonary infection. (A) Frontal chest radiography shows multifocal areas of nodular consolidation and cavitation bilaterally. (B–E) Axial thoracic computed tomography displayed in lung windows shows extensive complex cavitation (*arrowheads*), variably-sized nodules (*double arrowheads*), and areas of consolidation (*arrow*).



eFigure 55.3 "Hot tub lung." (A–B) Axial chest computed tomography in the upper (A) and lower (B) lungs shows widespread multifocal, bilateral, diffuse ground-glass opacity with a faintly centrilobular nodular appearance (*arrowheads*) with areas of lobular low attenuation (*arrows*), the latter suggesting gas trapping due to small airway obstruction. (C–D) Axial chest computed tomography in the upper (C) and lower (D) lungs 1 year after hot tub exposure cessation and corticosteroid therapy shows improvement in the pulmonary parenchymal findings. (E–F) Axial chest computed tomography in the upper (E) and lower (F) lungs 5 years after presentation shows complete clearing of the infiltrative lung abnormalities. (Courtesy Michael B. Gotway, MD.)

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56 FUNGAL INFECTIONS: ENDEMIC

JOSHUA D. NOSANCHUK, MD • GEORGE R. THOMPSON III, MD

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Note: Antifungal drugs and their use are included in Chapter 57.

INTRODUCTION

Geographically restricted (or endemic) mycoses include histoplasmosis, coccidioidomycosis, blastomycosis, paracoccidioidomycosis, sporotrichosis, talaromycosis (formerly penicilliosis), and emergomycosis (Fig. 56.1). These are *dimorphic* pathogens because they grow as two forms: as mycelium in nature and as yeasts (or spherules) upon acquisition by humans. *Mycelium*, the vegetative part of a fungus, consists of branching structures called hyphae and represents the mold form of the fungus. *Yeasts* are single-celled forms of the fungus and represent the major pathogenic form. These phases can be achieved in the laboratory by cultivation of the fungi at lower (≈25°C, mycelial) or higher (37°C, yeast) temperatures. Hence these fungi are termed thermally dimorphic. Acquisition is typically via inhalation of spores or mycelial fragments, although sporotrichosis is most commonly acquired by direct inoculation through the skin. The severity of clinical illness is linked to the quantity of the inoculum as well as to the immunologic status of the individual. Defects in cellular immunity are especially associated with more severe disease. Latent infections can reactivate in individuals whose immune responses have been compromised, such as by corticosteroid therapy, receipt of *tumor necrosis factor* (TNF) inhibitors or other immune-modulating agents, chemotherapy, or *human immunodeficiency virus* (HIV). The geographically restricted mycoses are often overlooked as etiologies of infectious syndromes, including as causes of community-acquired pneumonia.[1] In part this happens when clinical disease manifests in individuals outside of the geographic territories historically linked to endemicity of the pathogens. Diagnosis is frequently delayed, and treatment of these diseases requires several months to more than 1 year. Because the forms that exist in tissues differ from the forms transmitted in the environment, these pathogens are not transmitted between humans.

HISTOPLASMA

HISTORY AND EPIDEMIOLOGY

Histoplasma is a dimorphic fungus primarily acquired via respiratory exposure that is responsible for approximately 500,000 infections annually in the United States, which makes it the most prevalent cause of fungal pulmonary disease.[2] Similarly, these calculations also indicate that nearly 50 million Americans are latently infected with the fungus. The fungus can be found worldwide, although there are areas with a high incidence of disease. The Ohio and Mississippi River valleys are highly endemic regions, and skin testing has shown that up to 90% of adults in these regions have been exposed to the fungus.[3,4] High endemicity areas are also present in Latin America, particularly in Brazil, Venezuela, Ecuador, Paraguay, Uruguay, and Argentina.[5]

The most recent data on rates of clinically significant disease in the United States are from an analysis conducted by the Centers for Disease Control and Prevention between 2011 and 2014.[6] This report relied on surveillance data available from state health departments and did not include two states with a high incidence of histoplasmosis (Missouri and Tennessee). Even with this limitation, 3409 symptomatic cases were reported. The median age of patients was 49 years and 61% of patients ($n = 1273$) were male; 57% were hospitalized and 7% died. The incidence rates variedly markedly between and within states, and the majority of cases were observed in counties abutting the Mississippi

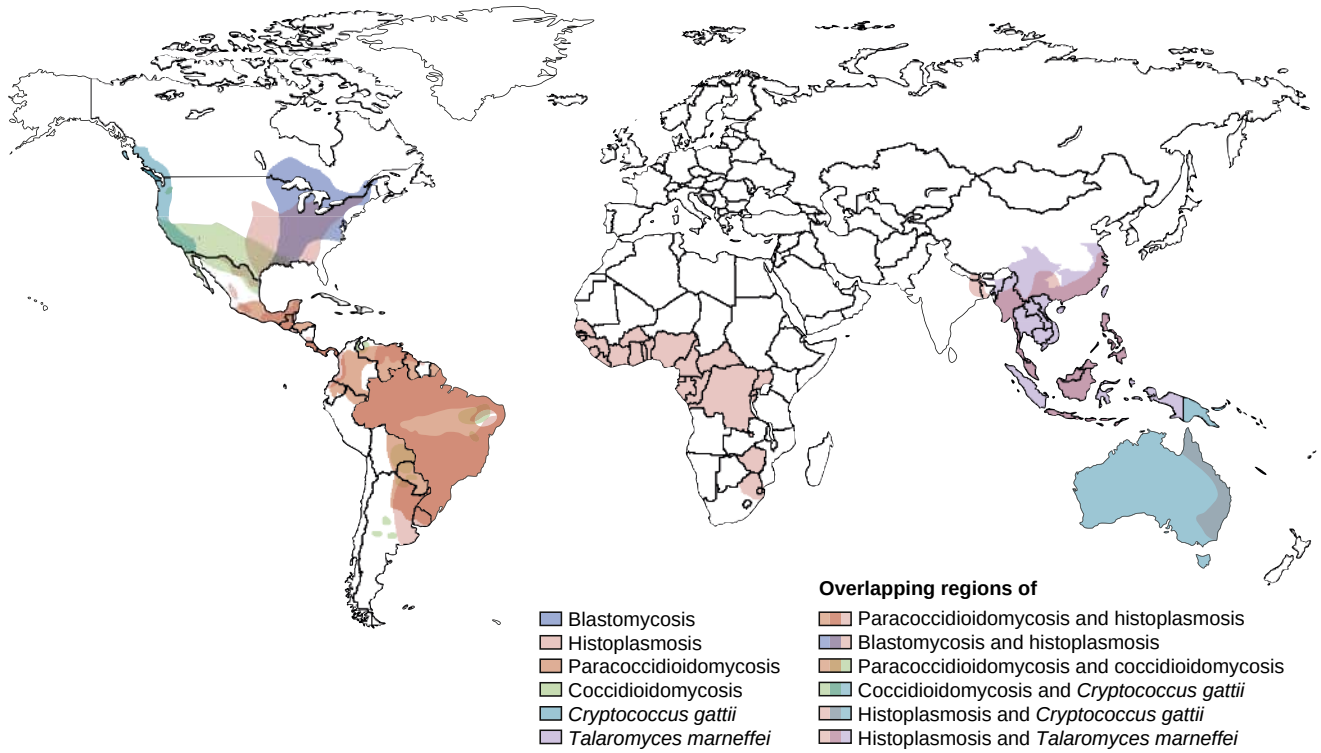


Figure 56.1 Global distribution of the endemic fungi. Although there is geographic restriction of the specific fungi, there is also overlap in the geographic ranges, and the differential diagnosis in those overlapping regions is more challenging. (From Schwartz S, Kontoyiannis DP, Harrison T, Ruhnke M: Advances in the diagnosis and treatment of fungal infections of the CNS. *Lancet Neurol* 2018;17[4]:362–372.)

River. The high hospitalization rate suggests that histoplasmosis surveillance underestimates the true number of cases. A similar male predominance has been observed in other studies of histoplasmosis and for patients with other fungal infections, including coccidioidomycosis and blastomycosis.[7–9] The reasons for this gender disparity are not clear, although differences in recreational or occupational exposure have been proposed.[10]

The genus *Histoplasma* was designated in 1906 by Samuel Darling, who described the fungus in the lungs, liver, spleen, and lymph nodes of a carpenter from Martinique working on the Panama Canal.[11] Darling incorrectly characterized the 1- to 4-μm intracellular ovoid yeast as protozoa, similar to *Leishmania* sp. A genome-wide population genetic study suggested that the genus *Histoplasma* contains at least four species that are genetically isolated, although these taxonomic changes have not been uniformly accepted.[12]

PATHOGENESIS

Histoplasma exists in either a mycelial or yeast form, depending mainly on temperature and nutritional conditions.[13] In the environment and at ambient temperatures, *Histoplasma* is mycelial. This saprophytic mold grows particularly well in soils enriched with organic nitrogen sources, such as soil contaminated with bird or bat droppings. Hyphal elements are 1.25 to 2.0 μm in diameter, and they produce two types of conidia: thick-walled macroconidia (8–15 μm diameter) and microconidia (2–5 μm). Both conidial forms are produced singly at the tips of narrow, short conidiophores that branch at right angles to vegetative hyphae. The microconidia are believed to be the infectious form because their size is most effective for aerosolization and inhalation and deposition into distal lung structures. Environmental disturbances, especially construction or tree removal, are associated with aerosolization of *Histoplasma* and have been associated with outbreaks.[7] At 37°C or in humans, the yeast form predominates. Yeast cells have thin walls and are oval with diameters of 2 to 5 μm. The cells reproduce by polar budding with a narrow bridge between the mother and daughter cells. Rarely it is possible to find both yeast and mycelial forms in lung tissues[14] as well as on endovascular devices,[15] so the presence of mycelial forms should not rule out histoplasmosis.

Histoplasmosis is initiated by inhalation and deposition of microconidia within alveoli. This event is followed by conversion of microconidia to the yeast form,[16] which begins within several hours to days.[17] Morphogenesis is initiated by the shift in temperature and availability of nutrients. Notably, despite Darling including "capsulatum" in the fungi's name based on a mistaken observation of encapsulation, the cells lack a capsule. During primary infection, the yeast cells are phagocytosed into the endosomal compartment of phagocytes, and these infected host cells then migrate to hilar and mediastinal lymph nodes and subsequently disseminate hematogenously, distributing the fungus into diverse tissues. In fact, autopsy studies have found that approximately 70% of individuals with history of histoplasmosis have splenic granulomas.[18] The incubation period for disease manifestations is typically 8 to 17 days, though heavy exposure may result in disease in as few as three days.[19]

Effective immune control of histoplasmosis requires activation of cellular immunity in concert with innate responses

because, when cellular immunity is compromised, the infection can disseminate.[20] Additionally, impairment of cellular immunity in latently infected individuals can result in reactivation of previously controlled foci of infection. Although less common in the current era of effective antiretroviral therapy, individuals with *acquired immunodeficiency syndrome* (AIDS) are at high risk for reactivation disease. Reactivation histoplasmosis has increasingly been seen in patients receiving anticytokine therapies.[21] Reactivation disease has also been documented in liver transplant recipients with disease originating from latent infections in the transplanted organs,[22] and disease is associated with a high incidence of graft loss and mortality.

Neutrophils are considered the primary responders to *Histoplasma* in the lung[23]; however, in a murine model, the majority of yeast are found within immature dendritic cells on the first day after experimental pulmonary infection. In the same murine model, neutrophils predominate for several days thereafter. Human neutrophils effectively inhibit the fungus, and azurophilic granules are responsible for this fungistatic effect.[24] After experimental infection, resident and inflammatory macrophages contain yeast cells by 3 days, and inflammatory macrophages contain most of the yeast cells by the end of the first week. Although experimental systems have shown that murine dendritic cells and macrophages fail to control replication and facilitate dissemination, human dendritic cells and macrophages, especially activated macrophages, can kill *Histoplasma* yeast cells.[25] Moreover, human dendritic cells can inhibit conidial germination,[26] which can modify subsequent disease progression by presenting fungal antigens to $CD8^+$ T cells. Several experimental studies have suggested that $CD8^+$ T cells are instrumental in initial clearance of *Histoplasma* yeast cells, whereas $CD4^+$ T cells are required for survival.[20] The role of antibodies in histoplasmosis is controversial, although administration of monoclonal antibodies can modify the course of disease.[27,28] Consistent with an immunoregulatory role for B cells in histoplasmosis is the finding that depletion of B cells significantly enhances the severity of disease.[29]

Among the many innate elements engaged in protective immunity to *Histoplasma* are several cytokines, including interleukin-12 and -17, TNF-α, granulocyte-macrophage colony-stimulating factor, and interferon-γ.[20] The ability of lymphocytes and phagocytes to produce these cytokines constitutes a major effector mechanism of host resistance. The critical role of TNF is underscored by the association of inhibition of this cytokine and the development of severe histoplasmosis. In the setting of intact immunity, granuloma formation can be caseating and indistinguishable from that caused by *Mycobacterium tuberculosis*. Also similar to tuberculosis, healing of granulomas can result in calcification, especially in lymph nodes and the liver and spleen.[18]

CLINICAL MANIFESTATIONS

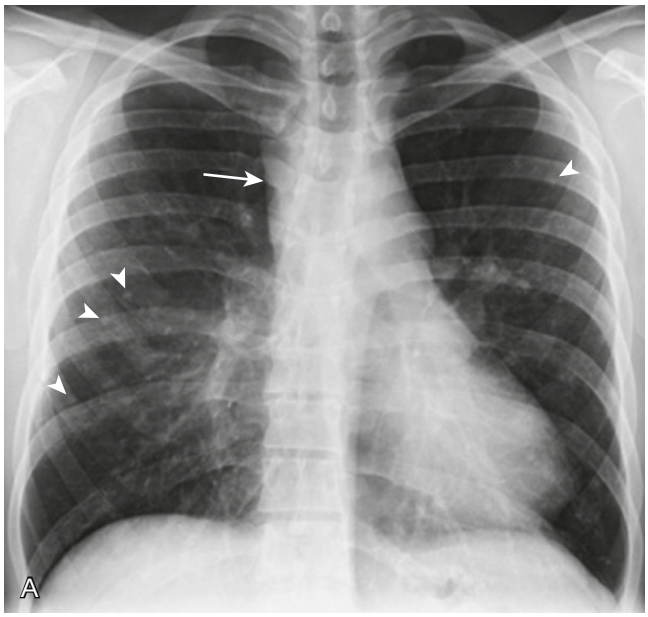
The severity of histoplasmosis is closely linked to the number of spores inhaled, the virulence of the infecting strain, and the immunologic status of the exposed individual.[30] The most common presentation is pneumonia, though the disease can also manifest as a fulminant life-threatening disseminated sepsis that may involve virtually any tissue. Low inoculum infection leads to asymptomatic disease in 99%, with 1% of individuals developing self-limiting disease.[31] In contrast, high inoculum infection leads to symptomatic disease in 50–100% of exposures.[32] In general, infection usually results in a mild, often asymptomatic respiratory illness, but may progress to life-threatening systemic disease, particularly in immunocompromised individuals. In the setting of HIV infection, disseminated histoplasmosis has been considered an AIDS-defining illness, although the prevalence of histoplasmosis in individuals with HIV has been markedly reduced with the widespread use of antiretroviral drugs.

Acute Histoplasmosis

The most common outcome after exposure to *Histoplasma* is asymptomatic infection. However, in some individuals, symptomatic acute disease manifests 1 to 3 weeks after exposure.[33] Symptomatic histoplasmosis typically presents as a flulike illness with the rapid onset of fever, chills, headache, myalgia, nonproductive cough, and chest pain. Chest radiographs are generally unrevealing, although mediastinal lymphadenopathy with or without opacities may be seen (Fig. 56.2A). Approximately 1 in 2000 exposed adults will develop acute progressive pneumonia,[34] often associated with a heavy exposure to *Histoplasma.*[35] In acute disease, approximately 10% of patients have rheumatologic symptoms, such as arthritis or severe arthralgia accompanied by erythema nodosum.[36] Pericarditis can develop in approximately 10% of patients with acute disease,[37] although pericarditis is typically a late manifestation or can manifest after the resolution of pulmonary symptoms.

Histoplasmosis has a propensity to involve the mediastinal lymph nodes (see Chapter 116). Clinical disease may include mediastinal adenitis (eFig. 116.7), an acute presentation that may respond to antifungal agents, and two late presentations, mediastinal granuloma and fibrosing mediastinitis, which appear to be inflammatory and fibrotic reactions to fungal components. Mediastinal granuloma is thought to arise from a conglomeration of lymph nodes that expand and compress mediastinal structures (Figs. 116.6 and 116.7, eFigs. 116.8 and 116.9). Surgery may be warranted to drain the inflammatory semiliquid material to relieve pressure; of note, antifungal agents or anti-inflammatory agents may not be particularly effective (see Chapter 116). Fibrosing mediastinitis, a rare but serious postinfectious complication, is a fibrosing process in the mediastinum that may compress and occlude vital mediastinal structures, including airways and vessels[38] (Fig. 116.5, eFig. 56.1). Fibrosing mediastinitis is thought to be due to an abnormal inflammatory response to residual *Histoplasma* proinflammatory components.[39] Steroids or antifungal agents are not useful in combating fibrosing mediastinitis, and surgery has not proven to be effective, although endovascular stenting has been reported to alleviate vascular complications[40] (see Chapter 116).

The majority of patients with acute pulmonary histoplasmosis recover over several weeks without sequelae, though occasional patients complain of fatigue persisting for months. Subsequent radiographs may appear normal or demonstrate a single calcified (eFig. 56.2) or noncalcified nodule or "coin" lesion or a miliary pattern of calcified granulomas indistinguishable from that found in certain tuberculosis patients[19] (Fig. 56.3). The miliary appearance



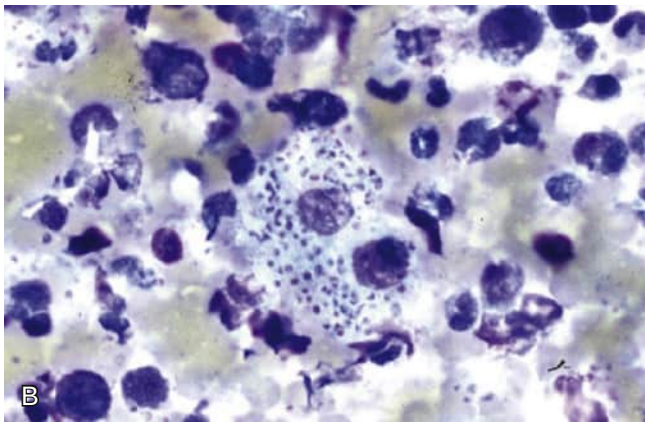


Figure 56.2 Acute histoplasmosis. (A) Frontal chest radiograph in a patient with acute histoplasmosis shows numerous bilateral small nodules *(arrowheads)* and right paratracheal lymphadenopathy *(arrow)*. (B) Photomicrograph of bone marrow biopsy specimen shows abundant small yeast in macrophages. There were no well-formed granulomas. (Wright stain; ×450 original magnification.) (A, Courtesy Michael B. Gotway, MD.)

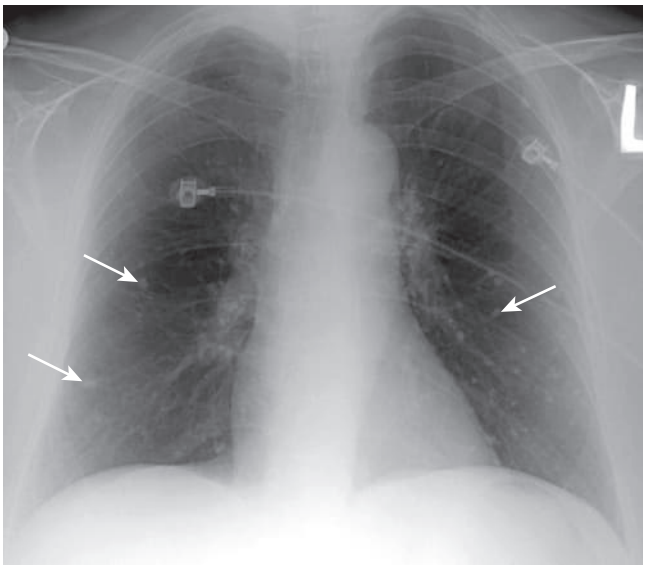


Figure 56.3 Multiple calcified pulmonary granulomas due to histoplasmosis. Frontal chest radiograph shows numerous small calcified nodules *(arrows)* bilaterally due to previous disseminated histoplasmosis. (Courtesy Michael B. Gotway, MD.)

is more common after a high inoculum exposure or in immunocompromised patients. Although it is well recognized that pulmonary coin lesions can be sequelae of histoplasmosis, surgical resections continue to be performed due to suspicion of neoplasm.[41] Positron emission tomography scans are not helpful in distinguishing infection from tumor because they can display enhanced uptake in histoplasmosis nodules.[42]

Disseminated Histoplasmosis

H. capsulatum can rapidly spread throughout an infected host as the fungus is transported intracellularly by phagocytes from the lungs via the hilar lymphatics into the systemic circulation.[23] Although the majority of infected patients control this process, systemic histoplasmosis develops in approximately 0.05% of individuals after exposure.[34] Disease most commonly disseminates in individuals with preexisting immunosuppression, largely due to malignancy, corticosteroid use, or HIV (eFig. 56.3). Clinical manifestations of disseminated histoplasmosis can vary from indolent to fulminant disease. Patients typically present with fever, weight loss, and respiratory symptoms with hepatomegaly and/or splenomegaly. Cutaneous and mucous membrane lesions are not uncommon, and patients should be considered to have disseminated disease if *Histoplasma* is isolated from these sites. Patients with acute disease often have anemia, thrombocytopenia, leukopenia, and abnormal liver function tests as well as coagulopathies.[43] The majority of patients have diffuse pulmonary opacities, but chest radiographs can be unrevealing in approximately 30% of patients.[44] The central nervous system can be involved in 10–20% of cases.[45] Endovascular disease is not common; interestingly, in patients with endovascular prostheses, mycelial and yeast forms have both been found in the vegetations.[15] Adrenal dysfunction, including bilateral adrenal masses, may develop in approximately 50% of patients with disseminated histoplasmosis, although adrenal insufficiency is uncommon.[46] Mucocutaneous involvement is uncommon in immunologically normal individuals, but typically presents as one or more ulcers of the skin, oral mucosa, and gastrointestinal tract. Acute progressive disease is lethal without treatment.

Chronic Pulmonary Histoplasmosis

Individuals with long-standing lung diseases, particularly emphysema or COPD, can develop a chronic respiratory illness after acquiring *Histoplasma*. The disease can manifest after acute infection or after reactivation of previously latent infection. Chronic histoplasmosis is characterized by indolent, progressive lung opacities, fibrosis, and cavitation[47] (Fig. 56.4). Bullae are most frequently located in the apices. The majority of patients present with fever, weight loss, increasingly severe cough, and dyspnea. This disease manifestation is clinically and radiologically similar to that of cavitary tuberculosis.[48] Without therapy, progression of disease develops in approximately 50% of affected individuals.[47] It is not uncommon for these patients to receive several

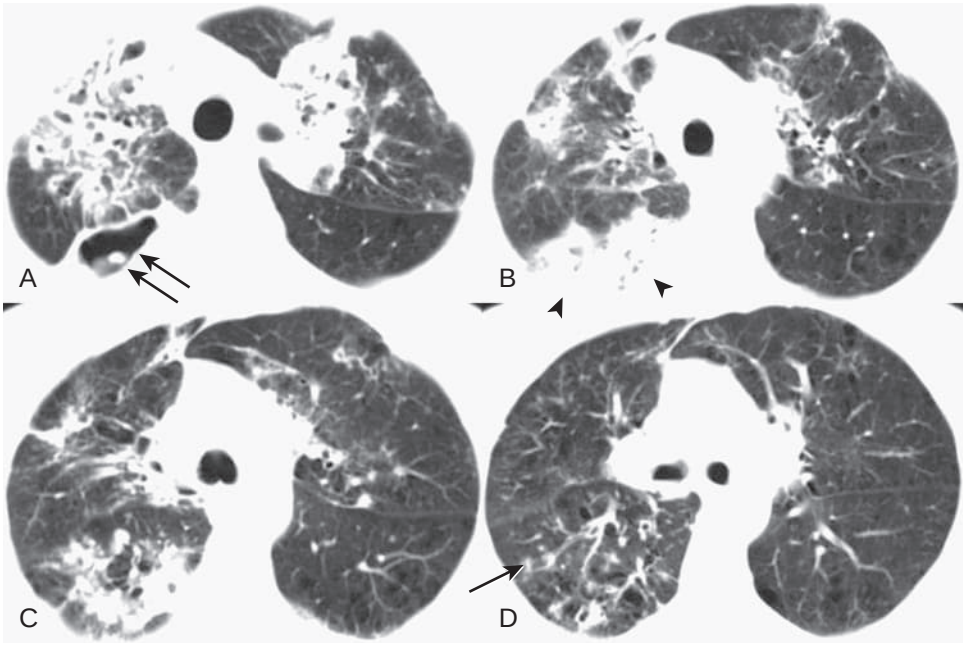


Figure 56.4 Chronic histoplasmosis. (A–D) Axial chest computed tomography shows upper lobe bronchovascular thickening with architectural distortion and areas of consolidation (*arrowheads*, B). Small nodules (*single arrow*, D) are also present. A cavity (*double arrows*, A) is present within the right upper lobe. The appearance closely resembles postprimary tuberculosis. (Courtesy Michael B. Gotway, MD.)

courses of antibacterial antibiotics for suspected anaerobic infections prior to consideration of histoplasmosis.[49]

Transmissibility

In general, *Histoplasma* is not contagious via the person-to-person route.[50] However, transmission has been reported in the setting of organ transplant with reactivation of *H. capsulatum* in the implanted organ.[51] The risk of reactivation of endogenous infection during immunosuppression is very low (<0.5%), even in high-risk groups such as renal or bone marrow transplant patients.[52] The mycelial phase of *H. capsulatum* is extremely hazardous to laboratory workers, and the ability to disperse large numbers of spores makes this organism a potential biological weapon. Biosafety level 3 precautions are indicated when processing *H. capsulatum* mold cultures, soil, or other material potentially contaminated with conidia. In the laboratory, biosafety 2 precautions are appropriate for the yeastlike form.

DIAGNOSIS

The gold standard for diagnosis is culture of *Histoplasma*; however, this process takes a minimum of 1 week and growth may not be detected for approximately 1 month. Moreover, respiratory cultures are positive in less than 50% of patients with acute pulmonary histoplasmosis.[53] In contrast, cultures are positive in 65–85% of patients with chronic pulmonary histoplasmosis. These data are complicated by the fact that studies have not critically examined the relative worth of different respiratory samples, although bronchoscopy with biopsy may provide the most effective testing mechanism because it can allow rapid visualization of the fungus in tissue. Direct observation of the fungus in respiratory secretions has a high specificity, but low sensitivity. In disseminated disease, the fungus is usually detectable in bone marrow aspirates[54] (Fig. 56.2B), and can even be identified in peripheral blood, especially in a buffy coat.[55] (see Chapter 19).

In the absence of positive cultures, serologic techniques such as immunodiffusion,[56] complement fixation,[57] enzyme immunoassay,[58] and radioimmunoassay[59] have been used to provide immunologic evidence of *Histoplasma* infection. These serologic tests for the detection of either antibodies and/or antigen in clinical specimens (such as serum or urine) offer a rapid alternative methodology for the diagnosis of histoplasmosis. Notably, there are issues with each of these methodologies and cross reactivity with other geographic fungi. Although promising, polymerase chain reaction or mass spectroscopy methodologies for detecting *Histoplasma* are not yet well-developed enough for routine use.

In the United States, antigen detection is commonly used in diagnosis of histoplasmosis. Polysaccharide *H. capsulatum* antigen can be detected in the urine of 92% of patients with disseminated histoplasmosis, 83% with acute disease, and 88% with chronic pulmonary histoplasmosis.[53] Additionally, antigen can frequently be detected in the serum of patients with disseminated disease, suggesting that testing of both urine and blood will increase the sensitivity of testing. Antigen testing of bronchoalveolar lavage fluid or cerebrospinal fluid can lead to the diagnosis of pulmonary or meningeal histoplasmosis, respectively. The assay is useful for following response to therapy and evaluating for disease relapse. The current *Infectious Diseases Society of America* (IDSA) guidelines recommend following antigen levels during and after treatment of histoplasmosis.[60] However, this and other antigen assays have significant cross reactivity with other endemic fungi.[61]

At present, the aforementioned tests are costly and frequently impractical for use in less economically developed countries. A mainstay of diagnosis in many regions is an immunodiffusion test for detection of H and M precipitin bands utilizing *histoplasmin* (HMIN) as the antigen; HMIN is a well-characterized antigen obtained from *Histoplasma* mycelia.[62] The H antigen is a β-glucosidase[63] and the M antigen is a catalase.[64] These antigens can be detected

by approximately 1 month after infection. The M band is detectable in approximately 75% of patients and can persist for years, whereas the H antigen can be identified in less than 25% of patients and is absent within 6 months.[65] Complement fixation tests utilize both HMIN and intact yeast cells; this reaction is positive by approximately 3 weeks of disease and can persist for months to years.[66] A titer of 1:32 or greater is strongly suggestive of acute disease, though a titer of 1:8 in a patient with a high suspicion of histoplasmosis is consistent with disease. Titers are negative in approximately 30% of patients with acute histoplasmosis and in 50% with disseminated disease. Most laboratories perform both the immunodiffusion and complement fixation tests concurrently for increased sensitivity. Immunocompromised patients with histoplasmosis frequently fail to mount an effective antibody response and specific antibodies to the disease cannot be routinely detected, which complicates and delays diagnosis.[67]

Enzyme-linked immunsorbent assay (ELISA) has been reported for the detection of antibodies in sera using HMIN, and deglycosylated or metaperiodate-treated HMIN to improve sensitivity and reduce cross reactivity. ELISAs using HMIN compared to deglycosylated HMIN have sensitivities and specificities of 57% and 93% versus 92% and 96%, respectively.[58,68] Treatment of purified HMIN with metaperiodate further improved the ELISA resulting in an overall specificity of 96% with sensitivities of 100%, 90%, 89%, 86%, and 100% in acute disease, chronic disease, disseminated infection in individuals without HIV infection, disseminated disease in the setting of HIV infection, and mediastinal histoplasmosis, respectively.[69]

TREATMENT

Comprehensive treatment recommendations for histoplasmosis have been made by the *American Thoracic Society* (ATS) in 2011[70] and the IDSA in 2007.[60] The majority of individuals who acquire histoplasmosis are either asymptomatic or have a mild, self-limited flulike illness. Unless the patient is immunocompromised, there is no need to administer antifungal agents under these conditions.[71]

Mild to Moderate Acute Pulmonary Histoplasmosis

If a patient has been symptomatic for more than 3 weeks or if a patient has moderate disease, itraconazole is appropriate. Itraconazole should be given as a loading dose of 200 mg three times daily for 3 days followed by 200 mg twice daily for 6 to 12 weeks. Ketoconazole should not be used as a systemic antifungal and fluconazole is less effective than itraconazole. Voriconazole and posaconazole can be considered for use in patients not responding to itraconazole.[72–74] Echinocandins should not be used to treat *Histoplasma* because of intrinsic resistance of *Histoplasma* to this class of drugs.[75]

Moderately Severe to Severe Acute Pulmonary Histoplasmosis

Liposomal amphotericin is more effective than itraconazole in clearance of *Histoplasma* in experimental histoplasmosis.[76] Liposomal amphotericin is favored over the conventional deoxycholate formulations because the liposomal amphotericin has an improved toxicity profile and may provide a survival benefit.[77] Liposomal amphotericin should be administered at 3 to 5 mg/kg daily for 1 to 2 weeks, followed by itraconazole 200 mg three times daily for 3 days and then 200 mg twice daily for 12 weeks. If liposomal amphotericin is not available or if the patient is at low risk for nephrotoxicity, 0.7 to 1 mg/kg deoxycholate amphotericin should be used. In patients with hypoxemia or significant respiratory distress, corticosteroids should be considered, particularly in HIV-infected individuals receiving antiretroviral therapy at risk for immune reconstitution syndromes.[78] Methylprednisolone 0.5 to 1 mg/kg can be intravenously administered for the first 1 to 2 weeks adjunctively with antifungals. Alternatively, oral prednisone 40 to 60 mg/day can be used.

Chronic Cavitary Histoplasmosis

Itraconazole should be given as a loading dose of 200 mg three times daily for 3 days, followed by 200 mg twice daily for a minimum of 1 year. Extending treatment to 18 to 24 months may reduce the likelihood of relapse, which otherwise can be expected in approximately 15% of patients. Critically ill patients may benefit from initial treatment with amphotericin.[79]

Disseminated Histoplasmosis

Treatment should be initiated with liposomal amphotericin, if available, for 1 to 2 weeks, followed by itraconazole. Treatment should be continued for a minimum of 1 year.[62] Occasionally, disseminated disease can be diagnosed in patients who have only mild to moderate symptoms. In immunocompetent individuals, itraconazole can be considered for initial therapy.

Immunocompromised Patients

Therapy with itraconazole 200 mg once or twice daily should be continued indefinitely in immunocompromised patients whose immunosuppression cannot be discontinued.[62] In patients with HIV, therapy should be continued lifelong unless CD4 counts can be restored to levels greater than 200/μL. Patients on maintenance itraconazole should have *Histoplasma* antigen testing performed each year.

Drug Monitoring

Serum levels of itraconazole should be measured at 2 weeks of therapy and then every 3 to 6 months while on therapy.[80] Similarly, if voriconazole or posaconazole are being used as salvage, serum drug levels should be monitored.[81]

Management of Complications

Pericarditis is generally managed with administration of nonsteroidal medications. Pericardiocentesis should be performed if hemodynamic compromise is present. In patients with hemodynamic compromise or persistent symptoms despite nonsteroidal therapy, prednisone should be administered with a taper performed over approximately 2 weeks. Patients treated with steroids should receive itraconazole treatment for 6 to 12 weeks. Broncholithiasis (eFig. 56.4) is an uncommon condition in which patients experience wheezing, dyspnea, or hemoptysis after erosion of a calcified lymph node into the airway. If the patient fails to expectorate the broncholith, bronchoscopic removal may be

required[82]; rarely, surgery is necessary for severe obstruction, fistualization, or massive hemoptysis.[83] No antifungal treatment should be administered for patients with broncholithiasis in the absence of other findings.

Of the different types of mediastinal involvement, mediastinal adenitis usually does not require treatment, but severe disease with compression complications should receive steroids and itraconazole. Mediastinal granuloma may warrant surgery to drain the caseous material pressing on structures. As noted above, there is no effective medical treatment for fibrosing mediastinitis. However, if it is unclear whether a patient has fibrosing mediastinitis, mediastinal granuloma, or mediastinal adenitis due to *Histoplasma*, then itraconazole should be administered at 200 mg/kg orally once or twice a day for 12 weeks (see Chapter 116).

Rheumatologic syndromes are also generally managed with nonsteroidal therapy. However, if symptoms do not remit, prednisone and itraconazole should be given. No antimicrobial therapy should be administered when biopsy of a nodule incidentally shows *Histoplasma* in an asymptomatic individual, especially when the fungus cannot be cultured.

COCCIDIOIDES

HISTORY AND EPIDEMIOLOGY

Coccidioidomycosis is a primary pulmonary infection caused by two species of *Coccidioides*, *C. posadasii*, and *C. immitis*, endemic to Arizona, New Mexico, western Texas, the Central Valley of California, central Washington state, and in sections of Central and South America where there are arid to semiarid life zones. Coccidioidomycosis is also known as San Joaquin Valley Fever or simply Valley Fever since the San Joaquin Valley of California is a historic hot spot for the microbe. In the United States, it is estimated that there are approximately 150,000 infections annually and that approximately 50,000 of these develop symptomatic disease.[84] California and Arizona actively track cases of coccidioidomycosis, and both states have reported increases in disease rates over the past decade,[84] with California now having more cases yearly than Arizona. In 1995, the annual incidence was 1.9 per 100,000; in 2009, it increased to 8.4 per 100,000; in 2016, it further increased to 13.7 per 100,000.[85] A nationwide analysis found an estimated 3000 hospitalizations per year, with a mortality rate of 1–5%.[86]

Disturbances of the soil are highly associated with acquisition of the fungus. Hyphae grow in moist soil and, during dry periods, viable arthroconidia can survive for protracted periods. The organism is thought to grow in soil to a depth of approximately 8 inches and is frequently isolated from rodent burrows. Arthroconidia are frequently aerosolized due to agricultural activity, excavation, or construction, and individuals participating in these activities are at high risk for coccidioidomycosis in endemic regions. Additionally, soldiers marching behind tanks or other vehicles are at risk for inhalation of arthroconidia. Individuals with advanced HIV infection or patients on corticosteroids or other immunosuppressants are at increased risk for severe disease, as are women in their third trimester of pregnancy and individuals of African or Filipino descent.[87]

Disease is indistinguishable between the two species of *Coccidioides*. The separation into the species was possible due to phylogenic studies demonstrating divergence between the historically well-described species, *C. immitis*, and the newer named species, *C. posadasii*.[88] There are phenotypic differences, such as differential growth rates under stress conditions, but they are morphologically indistinguishable and routine laboratory testing does not separate the species. Initially, *C. immitis* was thought to be limited to the San Joaquin Valley in California and in Washington state, whereas *C. posadasii* was thought to be present throughout the endemic regions detailed for the fungus, but more recent data suggest that there is significant overlap in the distribution of the two species.[89,90]

Coccidioidomycosis was first described in 1892 by Alejandro Posadas in an Argentinian soldier.[91] The organism was initially thought to be a protozoan of the order Coccidia, leading to its name. *Coccidioides* was not confirmed to be a fungus until 1900.[92]

PATHOGENESIS

The specialized environmental structures, arthroconidia, arise from hyphae and form chains of cells. The arthroconidia are 2 to 4 μm × 5 to 6 μm ovoid cells, and the chain usually consists of an intact multinucleate arthroconidium alternating with a degenerated cell (disjunctor cells). The thinner wall of the degenerated cell is readily disrupted when the chain is disturbed, such as during a wind storm or construction, and individual or small collections of arthroconidia can then be aerosolized and subsequently inhaled.[93] The arthroconidia undergo morphogenesis in humans or under specialized laboratory conditions at 37°C into a unique structure, a spherule. Arthroconidia convert to a spherule over approximately 2 to 4 days. The arthroconidia first develops into a round cell and then the spherule forms by successive growth and segmentation into an oval structure of 20 to 150 μm in diameter that contains dozens to hundreds of 2 to 4 μm endospores (Fig. 56.5A). Rupture of mature spherules leads to the release of endospores that, in the absence of effective host immunity, can develop locally into spherules or disseminate through hematogenous or lymphatic routes to other tissues. Notably, arthroconidia and septate hyphae can be identified in some patients with chronic disease, especially diabetes, in which there is low oxygen tension and tissue necrosis.

Coccidioides causes disease in immunocompetent or immunocompromised individuals, with disease severity typically being worse in immunocompromised patients.[94] Initial host responses to arthroconidia include influx of macrophages and neutrophils. Interestingly, neutrophils may stimulate arthroconidia to convert into spherules,[95] yet they can impede morphogenesis after the induction of antibody and with activated complement.[96] Phagocytosis is augmented in the presence of antibody to *Coccidioides* antigens. The oxidative burst is effective against arthroconidia and immature, but not mature, spherules. Additionally, after conversion to a spherule, the sheer size of this form precludes its phagocytosis by neutrophils or macrophages.[97] In tissues, organized necrotizing granulomatous inflammation predominates, with significant numbers of T and B cells present at the margins of the lesions.

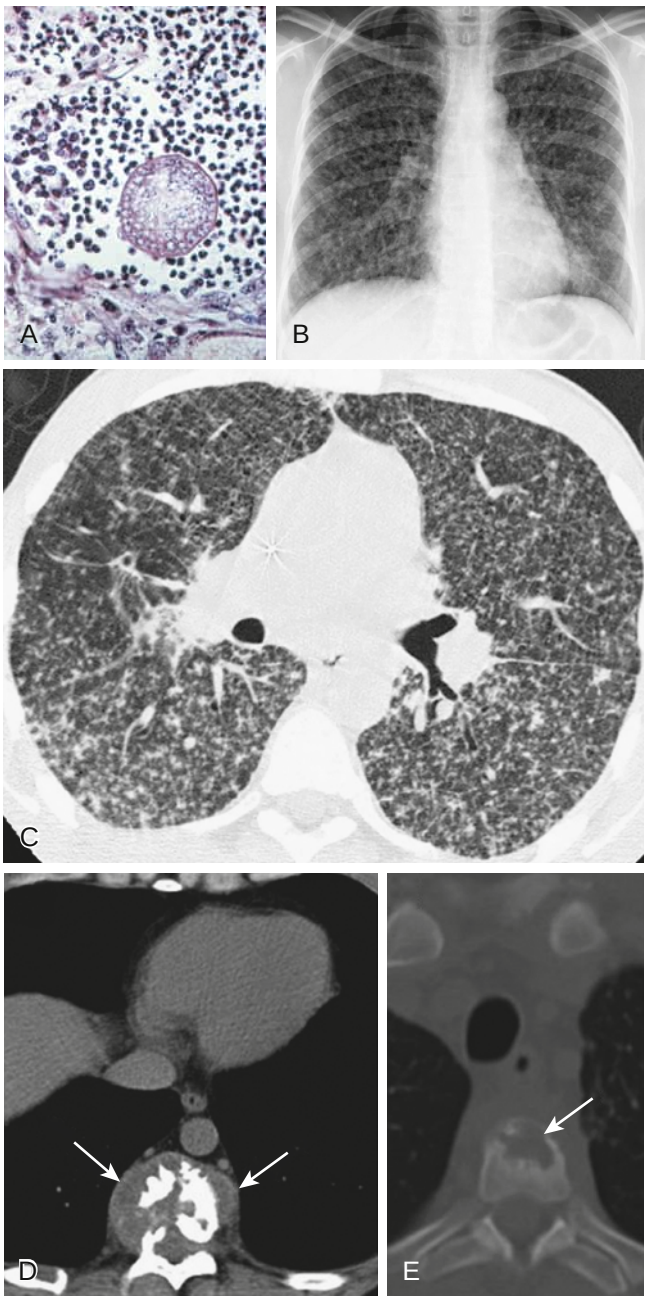


Figure 56.5 Disseminated coccidioidomycosis in an immunosuppressed patient. (A) Photomicrograph shows a characteristic giant spherule of coccidioidomycosis in a lung biopsy. (Hematoxylin and eosin stain; ×450 original magnification.) (B) Frontal chest radiograph shows numerous, randomly disseminated nodules bilaterally consistent with a miliary pattern. (C) Chest computed tomography (CT) shown in lung windows confirms the miliary pattern. Axial chest CT shown in soft tissue (D) and bone (E) windows demonstrates bilateral paraspinous masses *(arrows)* associated with vertebral body destruction. The CT image shown in bone windows (E) reveals the vertebral body destruction *(arrow)* to advantage. (Courtesy Michael B. Gotway, MD.)

T lymphocyte responses are critical for protection against *Coccidioides*. Moreover, Th1 responses are protective, whereas Th2 responses are less effective. Consistent with this, cytokines such as interferon-γ are associated with resistance whereas interleukin-4 is linked to susceptibility.[98] Consistent with the importance of $CD4^+$ T lymphocytes, disease is often more severe in patients with advanced HIV infection. Additionally, individuals with delayed-type hypersensitivity responses to *Coccidioides* antigens generally have improved outcomes relative to those who do not react.

Individuals with prior symptomatic infection are generally protected against reinfection with either species of *Coccidioides*. However, waning immunity, such as in advanced HIV, or treatment with immunosuppressants can lead to reactivation of latent lesions or abolish protection against reinfection.

CLINICAL MANIFESTATIONS

Disease manifestations can range from asymptomatic infection to pneumonia, cavitary pulmonary disease, and disseminated infection that can involve skin, bone, central nervous system, and visceral organs.[99] Approximately 60% of individuals infected with *Coccidioides* are either asymptomatic or have only mild respiratory symptoms.[100] However, 1 to 4 weeks after inhalation of the arthroconidia, approximately 40% develop moderate to severe respiratory symptoms. Although the majority of these patients resolve without sequelae, approximately 5% have persistent or progressive pulmonary disease (eFig. 56.5). Furthermore, approximately 1% will have disseminated disease, which is more common in immunocompromised patients[94] (Fig. 56.5B–E).

Pulmonary Coccidioidomycosis (Valley Fever or Primary Coccidioidal Infection)

Primary symptomatic infection is typically a subacute pulmonary disease. The initial symptoms are flulike, with patients commonly presenting with fever, cough, dyspnea, fatigue, headaches, myalgias, and arthralgias. Patients who progress to pneumonia typically have segmental or lobar disease, and mediastinal and/or hilar lymphadenopathy is characteristic (eFig. 56.6). In areas with high endemicity, up to 15–30% of cases of community-acquired pneumonia are due to *Coccidioides*.[101] Dermatologic immunologic manifestations such as erythema nodosum or erythema multiforme may develop, and are associated with a favorable host response to the fungus. Pleural effusions complicate 5–15% of patients, though the presence of an effusion does not correspond to increased severity of disease. The pleural fluid can be either transudative or exudative, and lymphocytes and eosinophils predominate.[102] In approximately 20% of those with effusions, coccidioidal empyema can develop, requiring aggressive intervention (Fig. 56.6A).

Acute Respiratory Failure and Acute Respiratory Distress Syndrome

Fortunately, the presentations of acute respiratory failure or *acute respiratory distress syndrome* (ARDS) are uncommon; they can accompany advanced immunosuppression. However, massive exposures to arthroconidia during construction or archeological excavation can lead to rapidly progressive respiratory failure. Mortality rates for ARDS due to disseminated coccidioidomycosis approach 100% (eFig. 56.7).

Disseminated Coccidioidomycosis

The presentation of disseminated disease may be acute or chronic. Disease may be multifocal or restricted to a

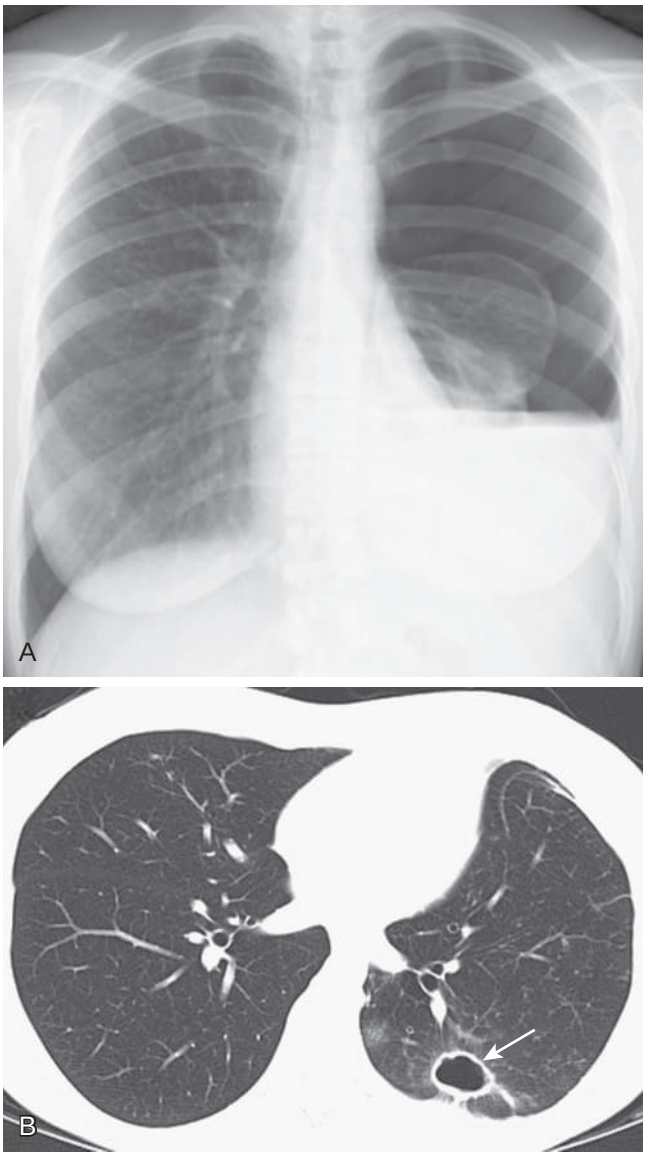


Figure 56.6 Coccidioidomycosis peripheral cavity with rupture into pleural space and empyema and bronchopleural fistula. (A) Frontal chest radiograph shows a large left hydropneumothorax; note air-fluid level. The patient was treated with extended tube thoracostomy, antifungal therapy, and eventually video-assisted thoracoscopic pleural space débridement. *Coccidioides* spherules were recovered from the left pleural space. (B) One year later, the chest computed tomography shows a uniformly thin-walled, peripheral cavity *(arrow)* characteristic of prior *Coccidioides immitis* pulmonary infection. (Courtesy Michael B. Gotway, MD.)

single extrapulmonary site. Prognosis of the single extrapulmonary lesion is typically better than multifocal disease, except in the case of meningitis (eFig. 56.8). Multifocal disease has a mortality rate of approximately 50%. Meningitis is frequently progressive, and shunts are often required to manage increased intracranial pressures. As mentioned, immunosuppression is a risk factor for disseminated disease as are advanced age, male gender, pregnancy, and being of Filipino and African descent.[103]

Miliary coccidioidomycosis is an unusual presentation in which numerous small granulomas develop throughout the lungs and other organs. Radiographs depict 3 to 4 mm nodules (eFig. 56.9) throughout the lung fields, indistinguishable in appearance from miliary tuberculosis. Notably, this presentation is a risk factor for the development of ARDS.

Pulmonary Nodule (Coccidioidoma)

A coccidioidoma typically is a single nodule (eFigs. 56.10 and 56.11A) in the peripheral lung tissue. Coccidioidomas are frequently misdiagnosed as a possible malignancy, leading to invasive procedures being performed. It is difficult to distinguish a coccidioidoma from other lesions without histopathologic or culture evidence.[104]

Cavitary Coccidioides

Although uncommon, thick- or thin-walled cavities (Fig. 56.6B, eFig. 56.11B–D) may develop during resolution of coccidioidomycosis. Cavities likely form as a consequence of infarction or necrosis. If the cavities are peripheral, there are risks for fistula formation and/or pneumothorax. Surgical resection may be considered for large cavities to prevent cavity rupture. Smaller cavities can be monitored radiographically (see eFig. 56.11B–D) and do not always close. Another cavitary disease process is a chronic fibrocavitary pneumonia (eFig. 56.12) characterized by multilobar opacities and cavities. This disease is more common in people with diabetes, and fever, chills, night sweats, and weight loss are typical symptoms.

Transmissibility

Person-to-person transmission is rare and almost exclusively seen in donor-derived organ transplant infections.[105,106] The infectivity of *Coccidioides* from the environment or culture is quite high, making this organism a potential biological weapon. There is significant risk of *Coccidioides* for laboratory workers, and these fungi have been associated with severe infections due to exposures.[107] In fact, Valley Fever was first associated with *Coccidioides* in 1929 when a medical student at Stanford, Harold Chope, opened a petri dish with mycelial *Coccidioides* and subsequently developed classic symptoms of Valley Fever. *Coccidioides* should only be handled under biosafety level 3 conditions.

DIAGNOSIS

The gold standard for diagnosis remains isolation of *Coccidioides* from infected tissues; however, patients frequently do not produce sputum, and cultures may take a minimum of a week to several weeks to grow. Direct examination of sputum is not sensitive. The majority of testing utilizes serologic methodologies. However, antibody responses may lag behind clinical symptoms, especially in immunocompromised individuals, and provide only a presumptive diagnosis. Hence, negative antibody testing in such patients does not exclude infection with *Coccidioides*. Immunodiffusion assays for *immunoglobulin* (Ig) M and IgG antibodies have been commonly used because they are considered to be highly specific. Commercial enzyme-linked immunoassays can detect IgM and IgG antibodies to *Coccidioides*, and are more sensitive but less specific than immunodiffusion assays.[108] A complement-fixing antibody method in which the major antigen is a chitinase detects IgG antibodies to *Coccidioides* and is useful to follow response to therapy.[109] Notably, both immunodiffusion and

complement fixation can be used to monitor responses to treatment. An antigen test has become available and can be used in selected circumstances and may be of use in the highly immunocompromised population.[110] Molecular methodologies have only recently been validated for coccidioidomycosis but are not in wide use.[102,111]

TREATMENT

Comprehensive treatment recommendations for coccidioidomycosis have been made by the ATS in 2011[70] and the IDSA in 2016.[84] An update in recommendations is currently in progress by the IDSA.

Uncomplicated Acute Pneumonia

Mild to moderate pulmonary disease in an immunocompetent individual is not an indication for treatment.[112] However, patients with HIV, pregnant women, or otherwise immunosuppressed patients are typically treated. In immunocompetent individuals, treatment is recommended if symptoms persist for more than 8 weeks or if the patient has lost more than 10% total body weight, has night sweats for more than 3 weeks, or if disease is present in more than half of a single lung, is multilobar, or is associated with persistent hilar lymphadenopathy. Additionally, complement fixation titers of greater than 1:16 often prompt treatment. If antifungal therapy is initiated for mild to moderate disease, it is generally administered for 3 to 6 months. If disease progresses to chronic fibrocavitary pneumonia, a minimum of one year of antifungal therapy is recommended. Long-term azole therapy should be considered for severely immunocompromised individuals.

Treatment is usually with either oral fluconazole (400 to 800 mg/day) or itraconazole (200 mg two or three times daily), with the higher doses used in more severe cases of *Coccidioides*.[113] Drug levels for itraconazole should be obtained after 2 weeks of therapy.[80] In more severe disease, liposomal amphotericin B (2.0 to 5.0 mg/kg/day) or deoxycholate amphotericin B (0.5 to 1.5 mg/kg/day) can be administered. Although promising, there are insufficient data to evaluate the efficacy of voriconazole and posaconazole for coccidioidomycosis, although utility in refractory cases has been demonstrated.[114,115] Echinocandins are not recommended because of intrinsic resistance in dimorphic fungi such as *Coccidioides*. Even in the absence of treatment, patients should be monitored every 3 to 6 months to document resolution of radiologic evidence of disease and confirm the absence of pulmonary or other complications.

Complicated Pneumonia With or Without Dissemination

Diffuse disease, particularly reticulonodular pneumonia or miliary opacities, is treated initially with an amphotericin formulation (followed with fluconazole) or high-dose fluconazole. If dissemination is present, especially if the patient has meningitis, treatment with fluconazole is preferred. Steroid therapy may be useful in patients with severe pulmonary coccidioidomycosis with ARDS using approaches validated for *Pneumocystis jirovecii*: prednisone 40 mg two times daily for 5 days, then 40 mg/day, and then 20 mg/day for 11 days. For complicated pneumonia, recovery is frequently slow, with symptoms resolving over weeks. Treatment is for a minimum of 1 year.

Pulmonary Nodule

If a solitary nodule is identified as being due to *Coccidioides* after a biopsy, there is no need to administer antifungal therapy or to resect the lesion. If the nodule was excised, no additional treatment is necessary. Treatment with an azole should be considered in a patient with a nodule if the patient becomes immunocompromised.

Pulmonary Cavity

Asymptomatic cavities should be followed clinically and radiographically (see eFig. 56.11). If a patient is symptomatic or has an elevated antibody titer, treatment with an azole for 3 to 6 months should be considered, although 12 to 18 months may be necessary for immunocompromised individuals. Larger cavities are often resected after 2 or more years if they have not resolved. Bacterial superinfection is a complication that requires aggressive antimicrobial treatment, and subsequent resection of the cavity is prudent. Cavity rupture is rare, but can lead to pyopneumothorax (see Fig. 56.6A–B) requiring antifungal therapy and decortication.

BLASTOMYCES

HISTORY AND EPIDEMIOLOGY

Blastomyces sp, dimorphic fungi endemic to North America, are the causative agents of blastomycosis. Genomic evaluation has identified numerous novel species of *Blastomyces* including *B. gilchristii, B. helicus, B. parvus,* and *B. silverae*. Most *Blastomyces* are soil-based fungi associated with riverbanks along the Mississippi, Ohio, and St. Lawrence rivers as well as in regions adjacent to the Great Lakes.[116] *B. helices,* however, has been found primarily in the Rocky Mountain region of North America.[117] Risk factors for acquisition of the fungus include exposures to waterways, soils, or woods. Interestingly, approximately 30% of forestry workers in endemic areas of Minnesota and Wisconsin have serologic evidence of prior infection.[118] Infection with *Blastomyces* is thought to follow inhalation of aerosolized conidia, and the common clinical manifestations include pneumonia, skin and bone lesions, and involvement of the genitourinary tract.

The rates of disease significantly vary with regions, even within the same state. For example, a 1992 study of 11 years of laboratory-confirmed blastomycosis showed that the rate of disease in Wisconsin was approximately 1.4 cases per 100,000, but there were regions with approximately 40 cases per 100,000.[119] Most cases are sporadic, but outbreaks have been observed. In 2003, there were 771 patients hospitalized with a diagnosis of blastomycosis, with a 6% mortality rate in adults.[120] A later analysis has shown an increasing rate of hospitalizations for blastomycosis, with 64% of hospitalizations among men.[121]

Thomas Gilchrist described blastomycosis in 1894,[122] and blastomycosis is also referred to as Gilchrist disease. Gilchrist misidentified the fungus as a protozoan but later corrected this error. Early descriptions emphasized the cutaneous manifestations, so blastomycosis was initially

considered primarily as a localized dermatologic condition rather than a systemic infection.

PATHOGENESIS

Blastomyces exists as a mycelial form in the environment or under laboratory conditions at approximately 25°C. Inhalation of conidia or cultivation at 37°C results in their transformation into yeast cells (8 to 12 μm in diameter) that bud with a broad-based connection between the mother and daughter cells (Fig. 56.7A and Fig. 19.4B–C). In tissue, yeast forms of 25 to 40 μm in diameter can also be found. After inhalation, conidia are engaged by neutrophils and macrophages, which can kill the cells and/or inhibit conidial morphogenesis.[123] The yeast form is more resistant to killing, especially by neutrophils,[124] and conidia have been reported to inhibit the enzymatic activity of macrophage-inducible nitric oxide synthase.[125] The yeast cells can disseminate from the lungs via the bloodstream or lymphatics to any tissue. In tissues, neutrophilic infiltrates appear early in disease followed by a granulomatous response characterized by multinucleated giant cells and noncaseating granulomas. Activation of effective cell-mediated responses is required to halt disease.[126] *Blastomyces* adhesin-1, an essential virulence factor of *B. dermatitidis,* suppresses host inflammatory response by inhibiting TNF-α.[127] The outcome of this dynamic between host and pathogen responses dictates disease manifestations.

CLINICAL MANIFESTATIONS

Pulmonary infection with *Blastomyces* leads to asymptomatic infection, acute or chronic pneumonia, or disseminated disease. Patients are asymptomatic in approximately 50% of infections[118,128]; when disease develops, it is usually after an incubation period of 4 to 8 weeks. Some studies suggest a seasonality to blastomycosis, which corresponds to outdoor activities in the endemic regions, resulting in mild, self-limited pulmonary infections at the end of summer into early fall, with these individuals subsequently presenting with extrapulmonary disease in the next year.[129] The initial mild presentations manifest with influenza-like symptoms, including fever, cough, myalgias, and arthralgias.[130]

Acute Pulmonary Blastomycosis

The diagnosis of pulmonary blastomycosis is often delayed because the manifestations are nonspecific and not different from those of community-acquired pneumonia. In addition to fever and cough, mild hemoptysis may be present.[131] Radiologic findings can vary in acute disease and similar manifestations can be present in chronic disease. The most common presentation is focal (Fig. 56.7B) or diffuse airspace consolidations,[44,132] and the upper lobes are most frequently involved. However, even asymptomatic patients can have masslike lesions, cavities (eFig. 56.13), or single or multiple (eFig. 56.14) nodules. Acute progressive blastomycosis is infrequent, but pulmonary disease can progress to ARDS, which is associated with mortality rates of approximately 75%.[133] Progressive disease can manifest as diffuse multilobar opacities, endobronchial infection, or miliary blastomycosis. Approximately half of the patients with severe disease are immunosuppressed,[134] including cancer patients, transplant recipients (eFig. 56.15), patients on TNF-inhibitors, or individuals with advanced HIV infection.[135]

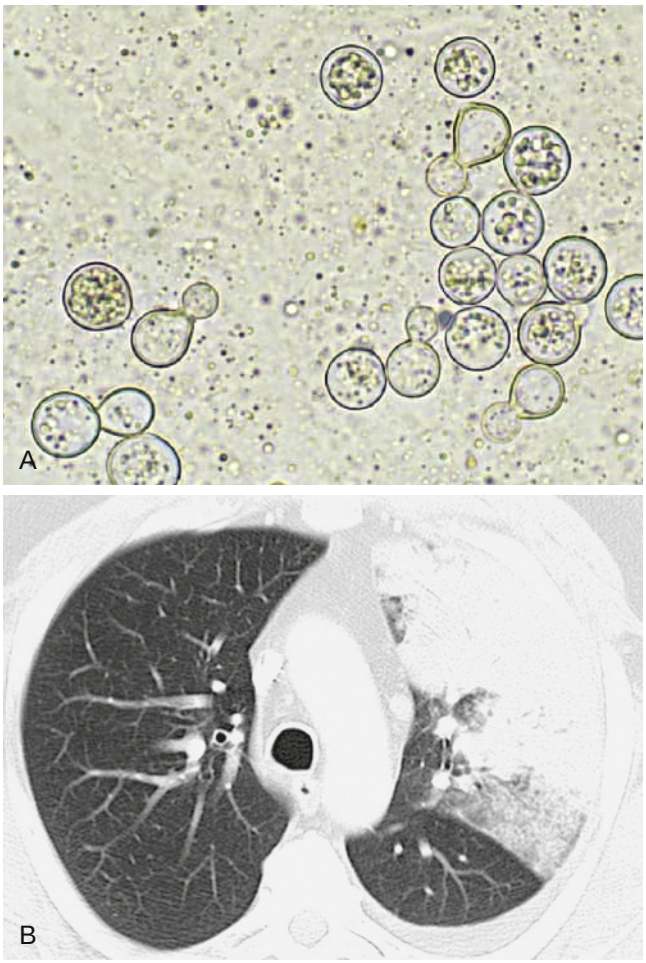


Figure 56.7 Focal pulmonary blastomycosis. (A) Micrograph shows *Blastomyces dermatitidis* in fresh sputum after 10% potassium hydroxide digestion. Note the broad neck of attachment, the double refractile cell wall, and the multiple nuclei. (×1000 original magnification.) (B) Axial chest computed tomography shows a lobar left upper lobe consolidation pattern. (B, Courtesy Jeff Kanne, MD, Associate Professor, Thoracic Imaging, Department of Radiology University of Wisconsin School of Medicine and Public Health.)

Chronic Pulmonary Blastomycosis

Similar to histoplasmosis and coccidioidomycosis, blastomycosis can present as a chronic pneumonia clinically indistinguishable from tuberculosis or as a pulmonary malignancy. Patients with chronic blastomycosis frequently report being ill for more than 2 months, with fever, weight loss, night sweats, cough, and chest pains.[128,136] The most frequent radiographic findings include consolidations, mass lesions, and interstitial fibronodular opacities.[132] Cavitation is uncommon, though small pulmonary effusions may be present.

Extrapulmonary Disease

The reported incidence of extrapulmonary disease has been approximately 20–75% of cases, with the upper range being present in patients with chronic blastomycosis.[119,128] More recently, overall rates of disseminated disease are

closer to 25–40%.[137] The most frequent site to manifest disseminated lesions is the skin, seen in 40–80% of cases of extrapulmonary disease. The typical presentation is a crusting verrucous lesion with a central draining microabscess (or microabscesses) (Fig. 56.8), although nodular, pustular or ulcerative lesions can be present.[138] Multiple lesions are typical, and mucous membranes can also be involved. Cutaneous lesions can overlay osteomyelitis with sinus tracts to the skin. *Blastomyces* can infect the bone in approximately 5–50% of patients with extrapulmonary disease, although approximately 75% of patients with osseous disease have concomitant active pulmonary involvement.[9] Bone radiographs typically reveal focal osteolytic lesions without periosteal reactivity, though lesions can be highly destructive. The third most frequent site of extrapulmonary disease is the genitourinary tract, seen in 10–30% of cases. The incidence is higher in men in whom disease frequently manifests in the prostate, testicle, or epididymis. Although *Blastomyces* can affect any tissue, the most formidable disease is that of the central nervous system, which is found in up to 10% of extrapulmonary blastomycosis, generally in immunosuppressed patients. Prior to the availability of effective combination antiretroviral therapy, 40% of individuals with AIDS developed central nervous system disease resulting in approximately 40% mortality.[139] Risk factors for severe or extrapulmonary disease and increased mortality include cellular immunodeficiencies, older age, and Aboriginal or Hmong ethnicity.[136]

Transmissibility

B. dermatitidis is generally not transmissible from person to person. However, there have been rare cases of presumed conjugal transmission as well as acquisition in utero. Dogs are at high risk for blastomycosis in endemic areas; a vaccine utilizing the *Blastomyces* adhesin-1 protein has recently been shown to be protective in canines[140] and may be a candidate for use as a human vaccine. Bites from infected dogs have led to cutaneous blastomycosis in humans.



Figure 56.8 Cutaneous lesion of blastomycosis. (Courtesy Bruce Klein, MD, University of Wisconsin Departments of Pediatrics and Medical Microbiology and Immunology.)

DIAGNOSIS

The gold standard for diagnosing blastomycosis is culture.[9] Growth can be detected after several days to weeks on mycologic medium. However, cultures are not a perfect test because, even with specimens obtained by bronchoscopy, the rate of positivity is less than 70%. Direct observation is the most rapid method for diagnosis. Sputum, other fluids, or skin scrapings treated with potassium hydroxide should be examined by microscopy; similar assessment of respiratory specimens can reveal *Blastomyces* yeast forms (see Fig. 56.7A and Fig. 19.4B–C) in up to 46% of patients. Cytologic evaluation with Papanicolaou or other stains can detect *Blastomyces* in up to 71% of patients with pulmonary disease. Histologic examination can also be helpful, with identification of the yeast as described above.

A commercial enzyme immunoassay for *Blastomyces* antigen, similar to the *Histoplasma* antigen assay, has an overall sensitivity of approximately 93%.[141] Antigenuria can be detected in patients with pulmonary or extrapulmonary disease, and testing can also be performed on serum, plasma, cerebrospinal fluid, bronchoalveolar lavage fluid, or other sterile fluids. The test is also reportedly useful to follow response to treatment or assess for relapse. However, there is substantial cross reactivity with *H. capsulatum* and other dimorphic fungi. Although commercial antibody tests are available, they lack clinical utility given the cross reactivity with other endemic mycoses. Molecular testing of patient samples for *Blastomyces* is promising, although its utility has not been confirmed.

TREATMENT

Comprehensive treatment recommendations for *Blastomyces* were made by the ATS in 2011[70] and the IDSA in 2008.[142] It is important to note that, in immunocompetent individuals, acute disease is often mild and resolves without antifungal therapy. Nevertheless, expert opinion is that treatment should be administered because it is not currently possible to identify individuals with a negligible risk of dissemination, and triazole therapies are effective and well tolerated.

Mild to Moderate Blastomycosis

Current consensus is that mild to moderately ill patients with pulmonary blastomycosis should receive itraconazole (200 mg twice daily) for 6 months. Levels of itraconazole should be verified after 2 weeks of administration and periodically during treatment.[80] Therapy for mild to moderate pulmonary blastomycosis is not altered if there is nonmeningeal dissemination, except in the setting of bone disease, for which therapy is extended to 1 year.

Moderately Severe to Severe Blastomycosis

Patients with moderately severe to life-threatening pulmonary blastomycosis, including those with ARDS, are initially treated with liposomal amphotericin B (5 mg/kg/day) or amphotericin deoxycholate (0.7 to 1.0 mg/kg/day) until clinical improvement is evident (usually 1 to 2 weeks) and then switched to itraconazole (200 mg twice daily for 6 to 12 months). Though there are limited data to support the use of corticosteroids, administration of steroids in the setting of extensive disease with hypoxemia may be efficacious. In patients with meningitis, amphotericin with or without fluconazole (800 mg daily) or

itraconazole (200 mg twice daily) is used initially (typically for 4 to 6 weeks) followed by 6 to 12 months of treatment with an azole, with many experts favoring a minimum of 12 months. Voriconazole may be considered for use in refractory disease. Echinocandins should not be used because *Blastomyces* and other dimorphic fungi are intrinsically resistant. If the patient is immunocompromised, treatment should be a minimum of 12 months or continued indefinitely.

PARACOCCIDIOIDES

EPIDEMIOLOGY

Paracoccidioides sp, the causative agent of paracoccidioidomycosis, is a dimorphic, soil-based fungus that is endemic in southern Mexico, Central America, and South America. *Paracoccidioides* has recently been split into two closely related species (*P. brasiliensis* and *P. lutzii*).[143] However, to date, the diseases caused by these species are indistinguishable. *Paracoccidioides* is the major causative agent of systemic mycosis in Latin America,[144] and it is a leading cause of disability and death among young adult rural workers.[145] A 2001 analysis estimated that approximately 10 million people were infected with *Paracoccidioides* sp.[146] However, only approximately 1–2% develop symptomatic disease, with pulmonary disease the most common form. An epidemiologic study in Brazil reported a mean incidence of 2.7 cases per 100,000 inhabitants per year, a stable incidence from 1960 to 1999.[147]

PATHOGENESIS

In the environment or under laboratory conditions at less than 28°C, *Paracoccidioides* grows as a mycelium that produces chlamydoconidia, terminal conidia, and arthroconidia, the purported infectious form. In tissues or at greater than 37°C, yeast forms predominate, which typically are a 5- to 30-μm diameter ovoid mother cell displaying several blastoconidia (forming a "pilot's wheel") (Fig. 56.9) or with two larger buds (reminiscent of Mickey Mouse's head).

Interestingly, the ratios of clinical disease in men to women average approximately 13:1, but can be as high as 150:1. Perhaps women have less clinical disease because *Paracoccidioides* expresses β-estradiol receptors on the conidial cell membrane; binding to these receptors inhibits morphogenesis to the yeast form, blocking disease progression.[148] Women are not protected against infection, but clinical disease is less likely.

Disease is more severe in the setting of immunosuppression. The initial host response to *Paracoccidioides* predominantly consists of neutrophils followed by recruitment of macrophages and granuloma formation. This process is highly regulated by cellular responses; Th1 responses are protective, whereas Th2 responses are common in patients unable to control their disease.[149,150] The impact of cellular immunity is further underscored by the increased incidence of disseminated disease in patients with AIDS. A review of mortality due to systemic mycoses in 3583 AIDS patients in Brazil from 1996 to 2006 revealed that paracoccidioidomycosis was responsible for approximately 50% of deaths.[151] Individuals on steroids, receiving chemotherapy, or status post–organ transplant are also at increased risk for severe disease.

CLINICAL MANIFESTATIONS

The majority of infections are asymptomatic, and individuals are believed to acquire the infection in childhood. There are two patterns of disease manifestation: the acute or subacute form (also called juvenile type) and the chronic form (or adult type). The juvenile type, which accounts for less than 10% of cases, most frequently develops in prepubescent teenagers to adults younger than 30 years. Patients are acutely ill, often presenting with fever, weight loss, and lymphadenopathy. Additionally, patients can have hepatosplenomegaly, intestinal lesions, and bone disease with or without bone marrow dysfunction. In contrast, the chronic form involves the lungs in approximately 90% of patients; this is believed to be due to reactivation of latent disease. However, new acquisition of the fungus is possible. Disease is localized to the lung in approximately 25% of patients, with the remainder presenting with multifocal disease, including dissemination to mucous membranes, lymph nodes, skin, adrenals, and other organs. Importantly, disease manifestations can mimic tuberculosis, which can also coinfect approximately 10% of these patients.[152]

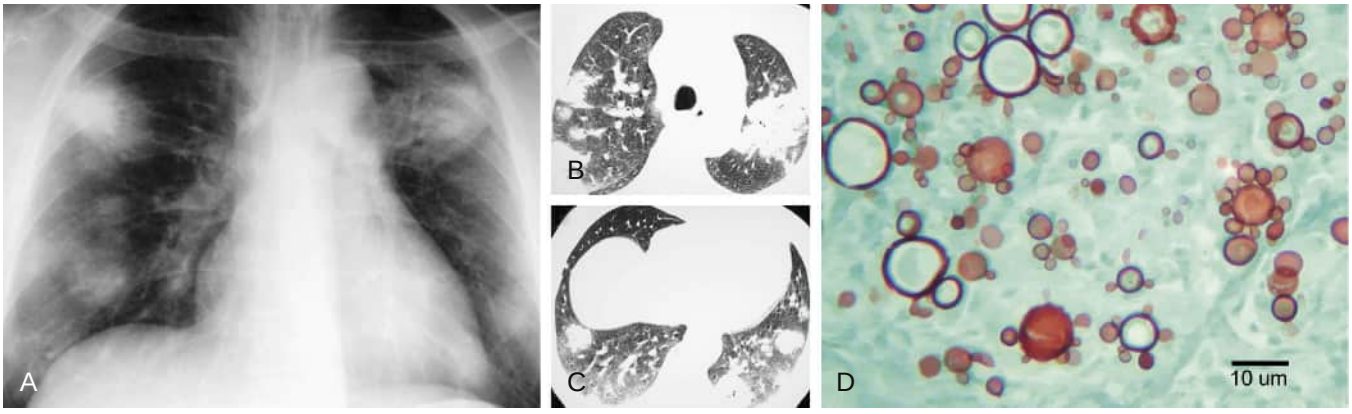


Figure 56.9 Pulmonary paracoccidioidomycosis. (A) Frontal chest radiograph shows bilateral poorly defined masses. (B–C) Axial chest computed tomography images confirm the presence of bilateral nodules, masses, and masslike areas of consolidation. Percutaneous transthoracic needle biopsy subsequently proved paracoccidioidomycosis. (D) *Paracoccidioides braziliensis* yeast forms. Several large mother cells with associated blastoconidia (forming a "pilot's wheel") are present. (Gomori methenamine silver stain.) (A–C, Courtesy Michael B. Gotway, MD; D, courtesy Dr. Carlos Taborda, PhD, University of São Paulo, Brazil.)

Radiologic findings are nonspecific and range from diffuse opacities to masses (see Fig. 56.9) and cavities (eFig. 56.16). Lymphadenopathy is often prominent. More than 50% of patients with significant chronic pulmonary disease develop long-term complications, most often impaired respiratory function due to fibrosis (eFig. 56.17). The development of right heart dysfunction is common in these patients. Additionally, compression of structures, such as the trachea, can develop. Single residual nodules without calcification are common.

DIAGNOSIS

Culture and microscopy are generally used for diagnosis. As noted, the yeast form has distinct shapes that can be identified in approximately 60–70% of sputum samples from patients with chronic paracoccidioidomycosis (see Fig. 56.9D). Culture remains a problem because the fungus routinely takes approximately 30 days to grow on mycologic agar. Diagnosis can also be supported by results of serologic testing. The major diagnostic antigen is a 43 kDa glycoprotein of *P. brasiliensis* (gp 43, a laminin-binding molecule), identified in approximately 90% of patients in the plasma, urine, or saliva.[153,154] An immunodiffusion test with antigen from the culture filtrate of yeast is highly specific and is positive in 65–100% of cases of acute or chronic pulmonary infection or disseminated paracoccidioidomycosis. A complement fixation test using the antigen from yeast culture filtrate is less specific than the immunodiffusion test, and cross reactions are observed with histoplasmosis. However, complement fixation titers of 1:8 or more are considered presumptive evidence of paracoccidioidomycosis[155] and, where the complement fixation test is available, it can be useful in following responses to treatment, which are accompanied by decreases in the titer.

TREATMENT

Optimal treatment regimens for paracoccidioides have not been formally validated.[70,152] In severely ill patients with dissemination, amphotericin therapy is usually initiated, often with deoxycholate formulations due to cost constraints in the endemic countries. Amphotericin is either continued until approximately a 2-g total dose or until the patient improves and is switched to an oral drug. Ketoconazole (200 to 400 mg/day) or itraconazole (200 to 400 mg/day) are the most commonly utilized azoles for paracoccidioidomycosis. Voriconazole and posaconazole may also have utility but have not been extensively studied. In patients with less severe disease, primary azole therapy is administered. Interestingly, in addition to amphotericin and azole drugs, sulfonamide derivatives have potent activity against the fungus.[156,157] Typical regimens for mild to moderate paracoccidioides with sulfonamide derivatives include sulfadiazine (4 to 6 g/day) or trimethoprim/sulfamethoxazole (160 mg/800 mg two or three times daily). Azole regimens usually range in duration from 6 to 18 months, whereas sulfa-based regimens range from 18 to 24 more months.

SPOROTHRIX

Sporotrichosis is principally caused by the dimorphic fungus *Sporothrix schenckii,* which is globally ubiquitous and grows in decaying vegetation, sphagnum moss, soil, and other environmental niches. The vast majority of infections follow cutaneous inoculation of the fungus, though pulmonary disease is increasingly recognized.[158] Such cases of pulmonary disease are primarily seen in men of middle age; risk factors include COPD and alcoholism. Radiographically, pulmonary sporotrichosis appears as cavitary and fibronodular disease.[159] Disseminated disease is rare and is primarily in severely immunocompromised individuals, especially in individuals with advanced HIV infection. Hence diagnosis of sporotrichosis in a patient with AIDS should lead to an assessment for dissemination.

The standard for diagnosis of invasive sporotrichosis is culture. However, culture results generally take 1 to 4 weeks. Biopsy material is often unrevealing of the organism, largely due to the small number of organisms that are needed to cause disease. The ovoid yeast cells are 3 to 5 μm in diameter, and eosinophilic projections from the yeast may be present, representing the "asteroid body" associated with *S. schenckii*. Severe to life-threatening pulmonary sporotrichosis should be initially treated with amphotericin B (liposomal amphotericin 3 to 5 mg/kg/day or deoxycholate amphotericin 0.7–1.0 mg/kg).[160] Once the patient's condition has stabilized, typically within 2 weeks, itraconazole (200 mg twice daily) can be administered for at least 1 year of total antifungal therapy. Adjunctive surgery may be especially useful in the setting of severe focal disease. If the disease is less severe at the outset, itraconazole can be used as initial therapy.[159] Serum levels of itraconazole should be verified after 2 weeks of administration and periodically thereafter. Treatment is generally from 3 to 6 months. Importantly, antifungals used for other manifestations of sporotrichosis, such as terbinafine, saturated solution of potassium iodide, or fluconazole, are not effective for pulmonary disease. Voriconazole is not effective and experience with posaconazole is limited.

TALAROMYCES

Talaromyces marneffei (formerly *Penicillium marneffei*), is a dimorphic fungus responsible for a systemic mycosis geographically restricted to southeast Asia, India, and southern China, especially in individuals with HIV.[161] In the environment, *T. marneffei* exists as a mycelial form whereas, in tissues, it is in a yeastlike form (arthroconidium) that is notable for replicating by fission. Talaromycosis is the third most common opportunistic infection in individuals with HIV in parts of tropical Asia, after tuberculosis and cryptococcosis. Although the majority of cases take place in the setting of advanced HIV infection, disease also presents in patients with immunosuppression due to malignancy or medical therapies as well as in patients with underlying lung disease. Patients with disseminated disease develop fever, weight loss, generalized lymphadenopathy, skin lesions (frequently papules with central necrosis), and hepatomegaly. The pathobiology of *T. marneffei* is comparable to that of histoplasmosis because *T. marneffei* survives in macrophages and manifests a similar spectrum of disease. Diagnosis is typically by culture and microscopy. The simplest approach is biopsy of skin lesions or lymph nodes with histologic assessment for fission arthroconidium. *T. marneffei* can also be visualized in peripheral blood smears

in patients with fulminant disease. Initial therapy with amphotericin B has been proven superior to itraconazole.[162]

EMERGOMYCES

Emergomyces (formerly *Emmonsia*) is a newly described genus first identified as a cause of disseminated disease in AIDS patients within South Africa (*Es. africanus*).[163] This dimorphic fungus is the most common endemic mycosis in South Africa. Presenting symptoms are most frequently fever, weight loss, elevated liver enzymes, and radiographic findings of the chest are similar to those of tuberculosis. Skin disease is also common and presents concurrently with other clinical findings. Subsequent investigation has identified other *Emergomyces* sp, including *Es. orientalis, Es. canadensis, Es. europaeus, and Es. pasteurianus*.[164,165] Isolates are frequently misidentified as *Blastomyces* and sequencing is often necessary to differentiate these organisms. Treatment of this infection has yet to be refined; however, initial therapy with amphotericin B is recommended until clinical improvement is observed, followed by itraconazole, voriconazole, or posaconazole.[166]

Key Points

- Endemic mycoses are able to infect and cause disease in previously healthy immunocompetent hosts.
- Exposure may be unavoidable with travel or residence within the endemic region because of the high density of the fungi in certain environments.
- Clinical manifestations may be nonspecific, but respiratory symptoms are common at early and late stages of infection.
- The fungi that cause endemic mycoses have specific morphologic features in tissue samples and when cultured in the laboratory.
- Noninvasive testing (antigen testing and serology) are available for the majority of these infections.
- Many infected individuals resolve endemic fungal infections without treatment but, in some individuals, severe pulmonary and disseminated infections develop and can be life-threatening.

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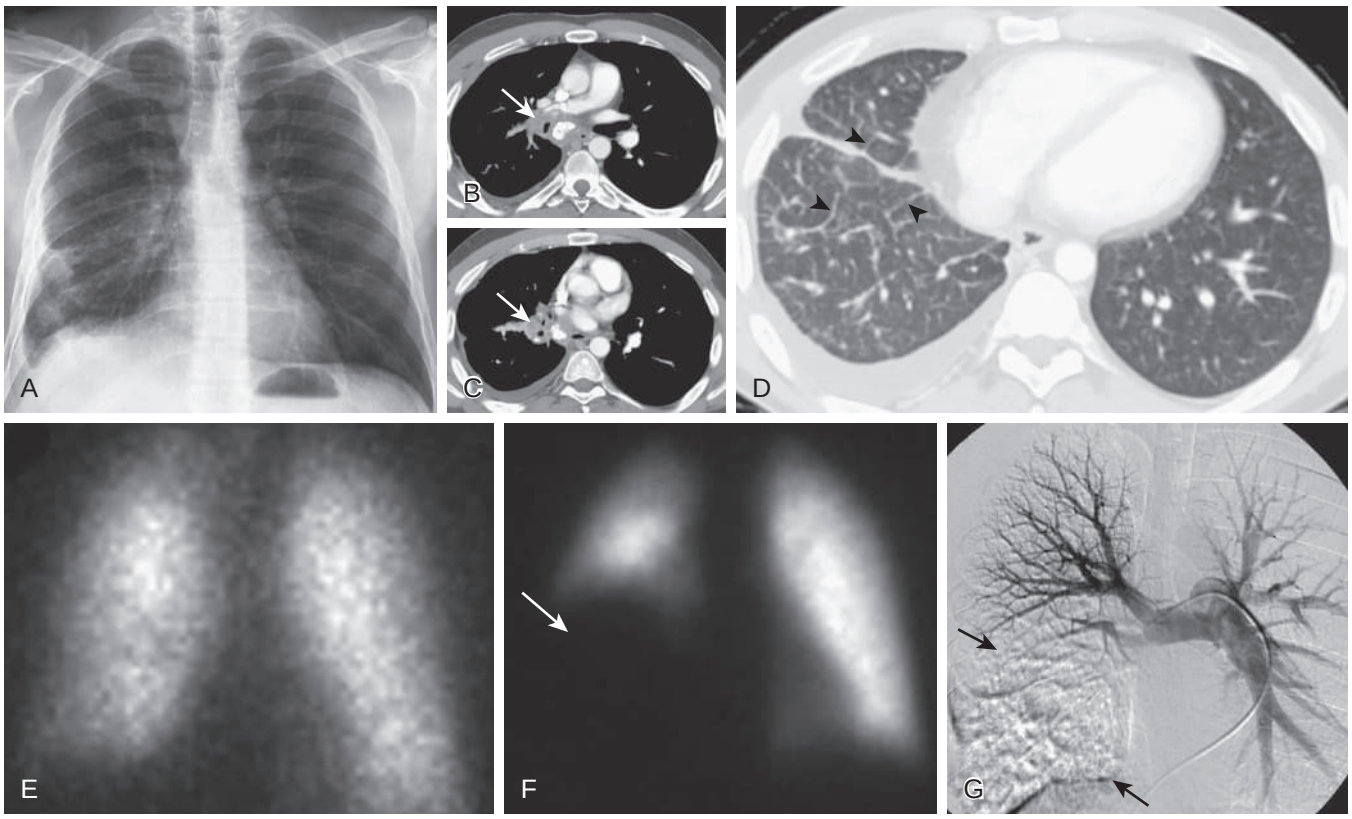
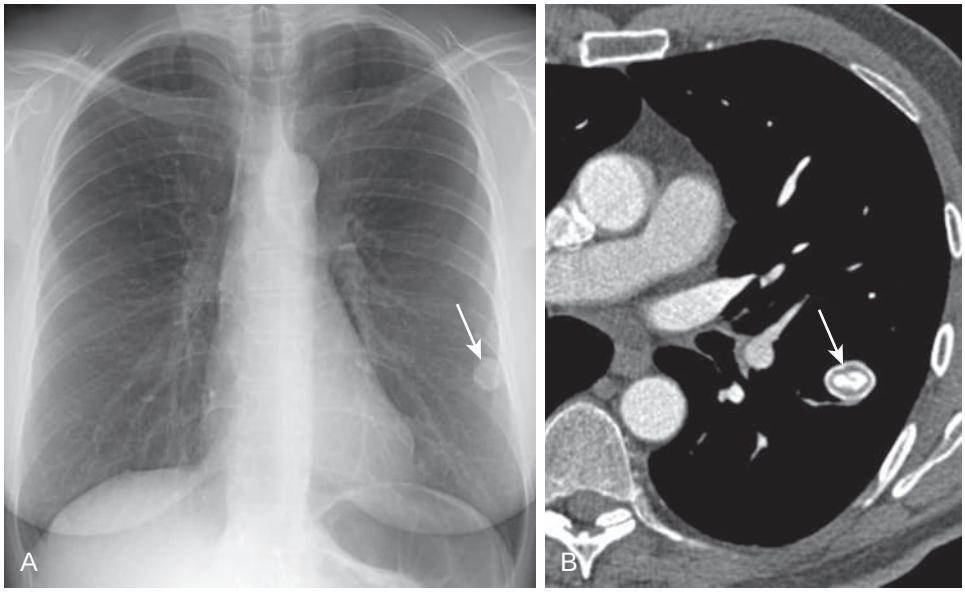
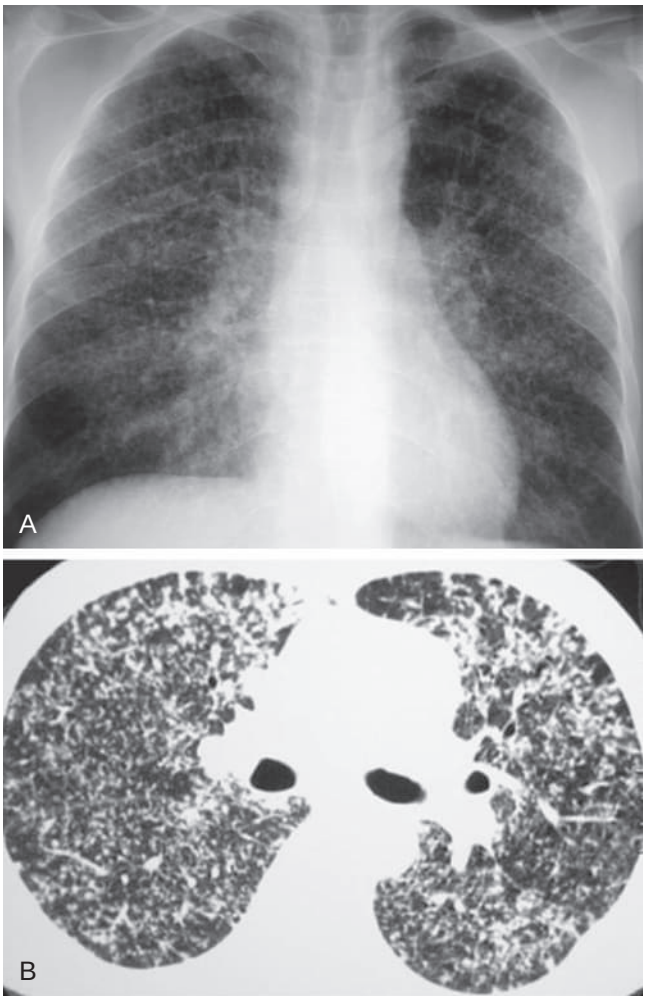
eFIGURE IMAGE GALLERY



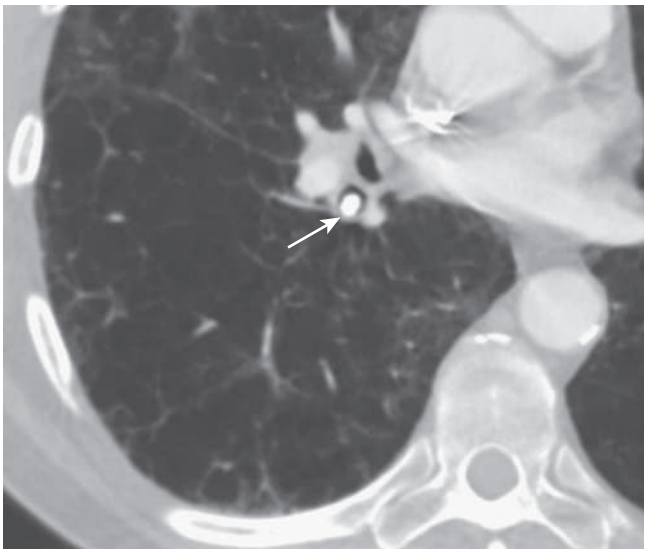
eFigure 56.1 Fibrosing mediastinitis due to histoplasmosis. Frontal chest radiograph (A) in a patient with fibrosing mediastinitis shows linear and reticular abnormalities in the right perihilar region and right lower lobe and a small right pleural effusion. Chest computed tomography (CT) shown in soft tissue windows (B–C) demonstrates calcified mediastinal lymphadenopathy and noncalcified right peribronchial tissue *(arrows)*. Note that the peribronchial tissue compresses and narrows adjacent vascular structures. A small right pleural effusion is present. Chest CT shown in lung tissue windows (D) reveals right lung smooth interlobular septal thickening *(arrowheads)*, which accounts for much of the linear abnormality apparent on chest radiography. Ventilation (E) and perfusion (F) scintigraphy in the anterior projection shows mildly decreased ventilation in the right lower lung (E), but absent perfusion in the same region on the perfusion images (F). Left lung perfusion is normal. Catheter pulmonary angiography (G) confirms absent perfusion in the right lower lung (area between arrows is right lower lobe lung parenchyma without demonstrable pulmonary blood flow) due to arterial compression, confirming the findings seen on CT (B–C). (Courtesy Stacy M. Rissing, MD, Assistant Professor of Clinical Radiology and Imaging Sciences, Indiana University.)



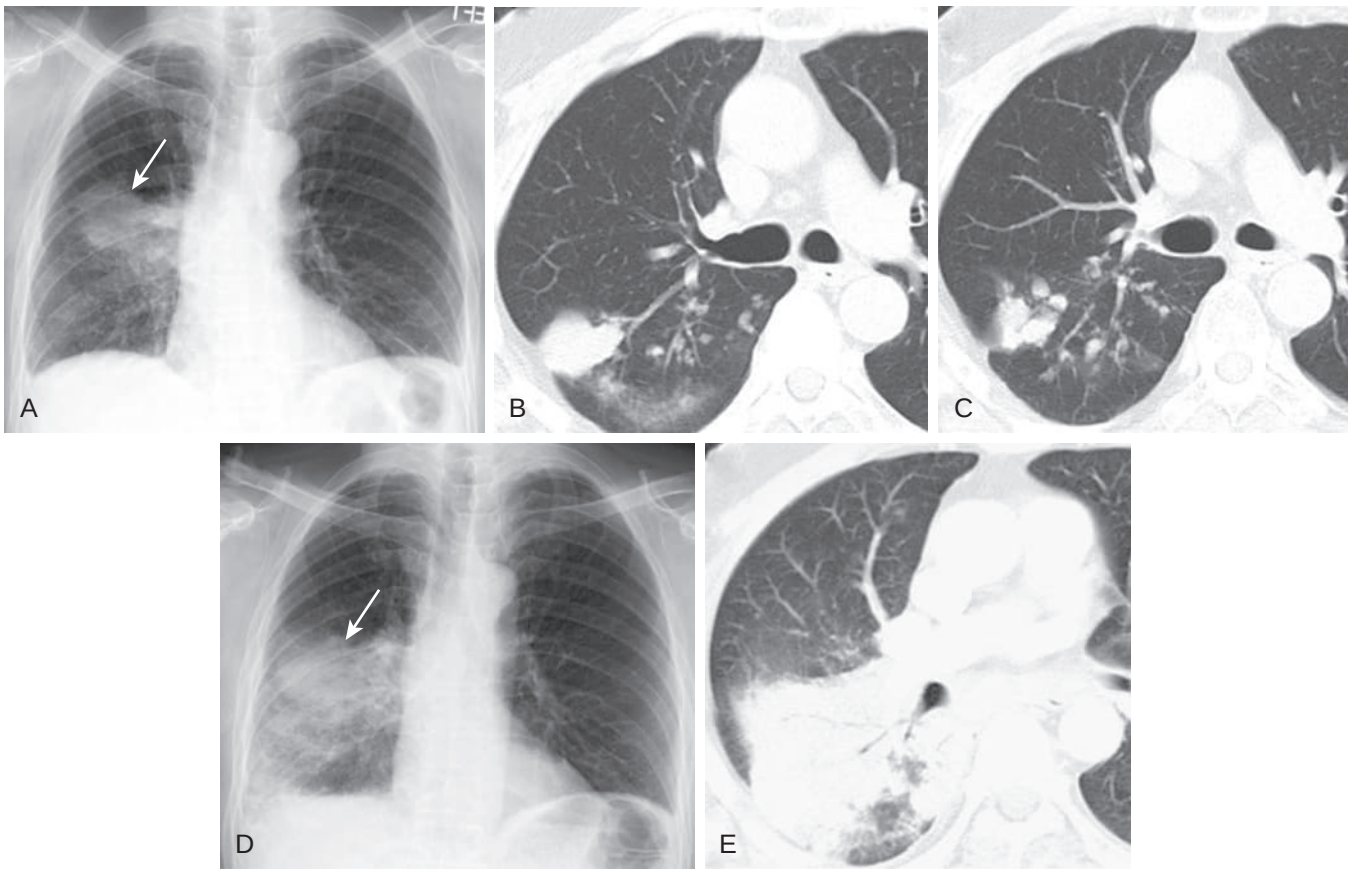
eFigure 56.2 Single calcified pulmonary granuloma due to histoplasmosis. (A) Frontal chest radiograph shows a left lower lobe circumscribed nodule *(arrow)* with peripheral increased attenuation consistent with calcification. (B) Axial chest computed tomography confirms both peripheral and central calcification within the nodule *(arrow)*. (Courtesy Michael B. Gotway, MD.)



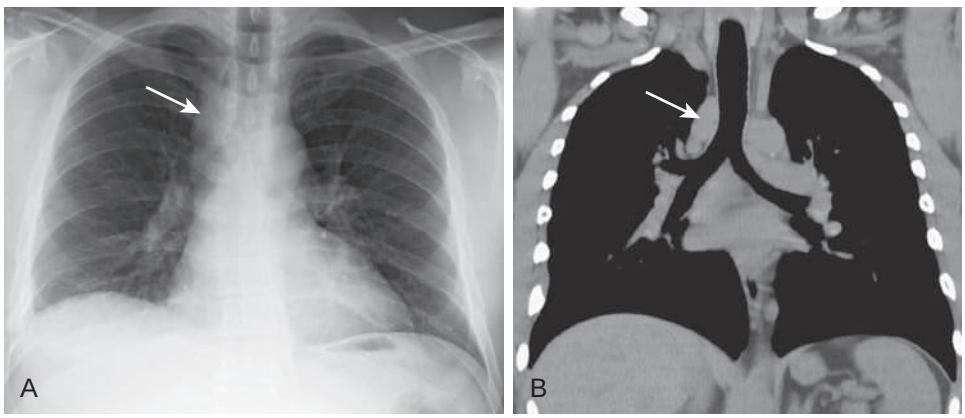
eFigure 56.3 Disseminated histoplasmosis in a patient with acquired immunodeficiency syndrome. (A) Frontal chest radiograph shows numerous, randomly distributed nodules bilaterally associated with thickening of the right paratracheal region, consistent with mediastinal lymph node enlargement. (B) Chest computed tomography confirms numerous, randomly disseminated small nodules consistent with a miliary pattern, due to histoplasmosis. The organism was recovered from mucocutaneous lesions. (Courtesy Michael B. Gotway, MD.)



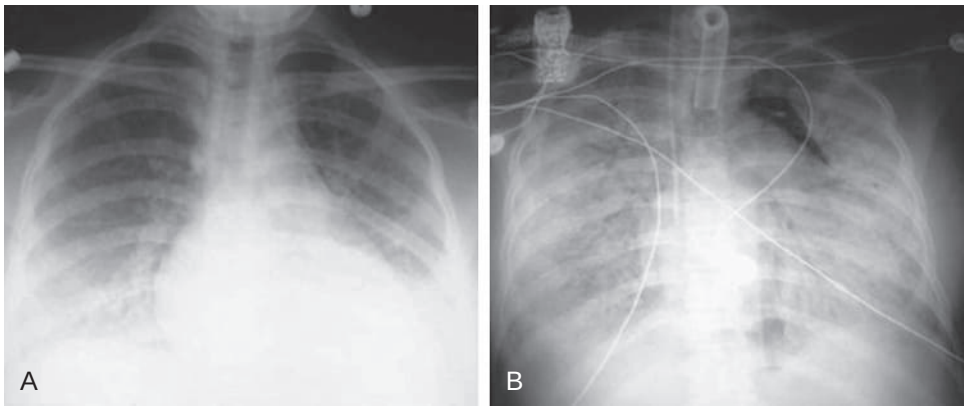
eFigure 56.4 Broncholithiasis due to histoplasmosis. Axial chest computed tomography focused on the right lower lobe shows a high attenuation broncholith *(arrow)* within the right lower lobe bronchus. (Courtesy Stacy M. Rissing, MD, Assistant Professor of Clinical Radiology and Imaging Sciences, Indiana University.)



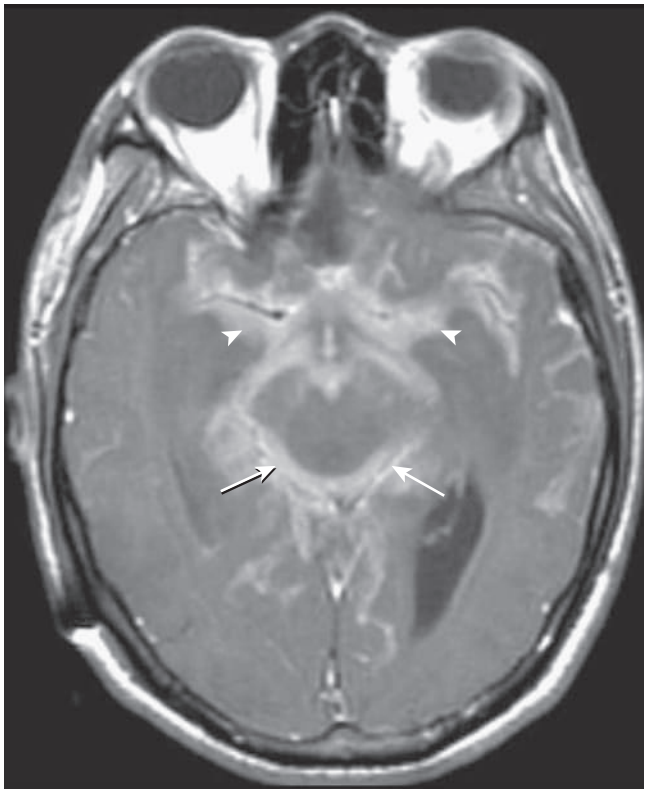
eFigure 56.5 Progressive pulmonary coccidioidomycosis. (A) Frontal chest radiograph shows a right perihilar mass *(arrow)* with surrounding reticulation. Chest computed tomography (CT) shown in lung windows (B–C) reveals a right upper lobe mass adjacent to the right major fissure as well as numerous surrounding centrilobular nodules. Biopsy of the mass proved coccidioidomycosis. Antifungal therapy was begun. Follow-up chest radiograph (D) shows increased size of the right perihilar masslike area of consolidation *(arrow)*, and chest CT (E) confirms increasing consolidation in the area affected on the previous CT. (Courtesy Michael B. Gotway, MD.)



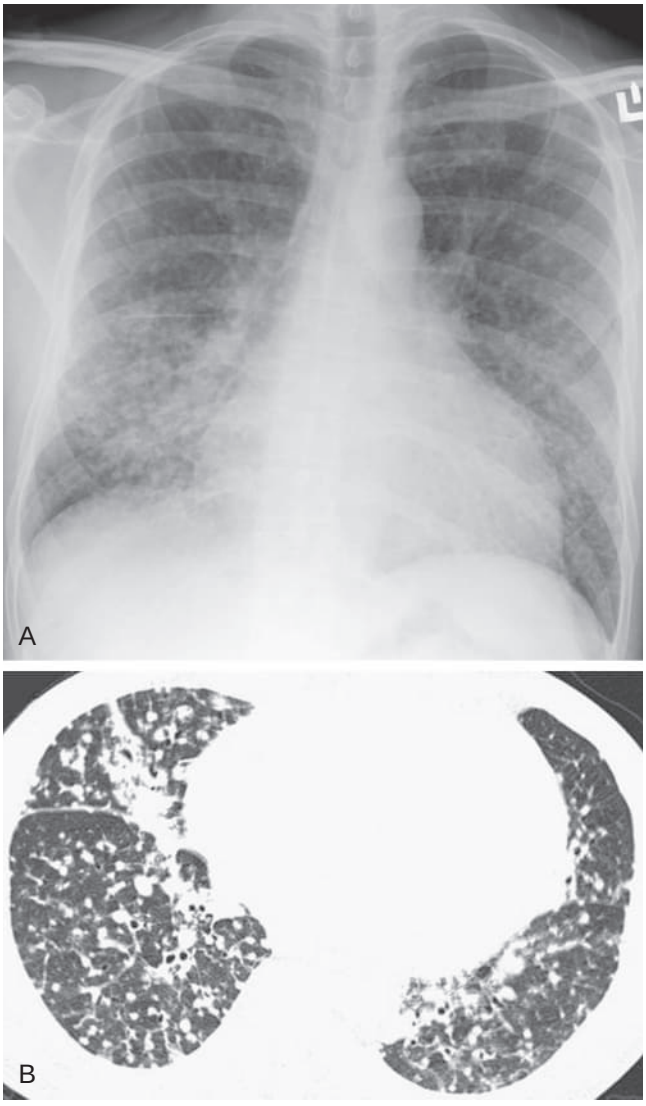
eFigure 56.6 Lymphadenopathy due to coccidioidomycosis. (A) Frontal chest radiograph shows right paratracheal lymphadenopathy *(arrow)* due to acute coccidioidomycosis. (B) Unenhanced coronal chest computed tomography shown in soft tissue windows confirms right paratracheal lymphadenopathy *(arrow)*. (Courtesy Michael B. Gotway, MD.)



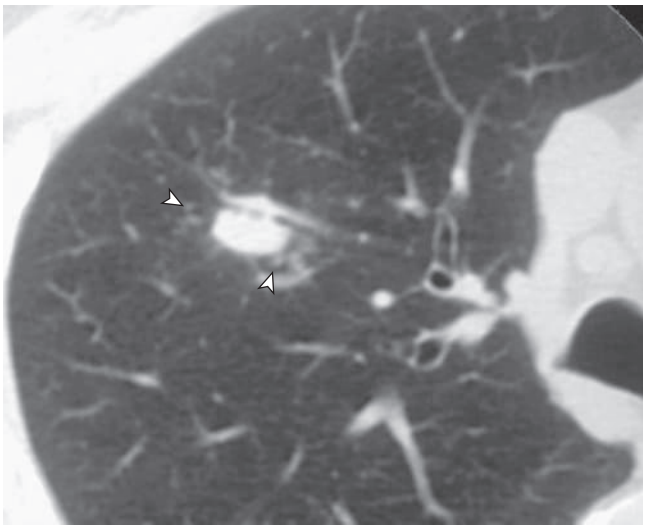
eFigure 56.7 Coccidioidomycosis causing acute respiratory distress syndrome. (A) Frontal chest radiograph in a pregnant woman shows diffuse, fine, bilateral small nodules consistent with a miliary pattern of infection. (B) Frontal chest radiograph obtained 2 weeks later when respiratory failure developed shows bilateral consolidation with air bronchograms consistent with acute respiratory distress syndrome. A tracheostomy has been placed in the interim and pneumomediastinum (the lucent area occupying the upper left mediastinal border) developed while the patient was on mechanical ventilation. The patient died 2 weeks after admission. (Courtesy Michael B. Gotway, MD.)



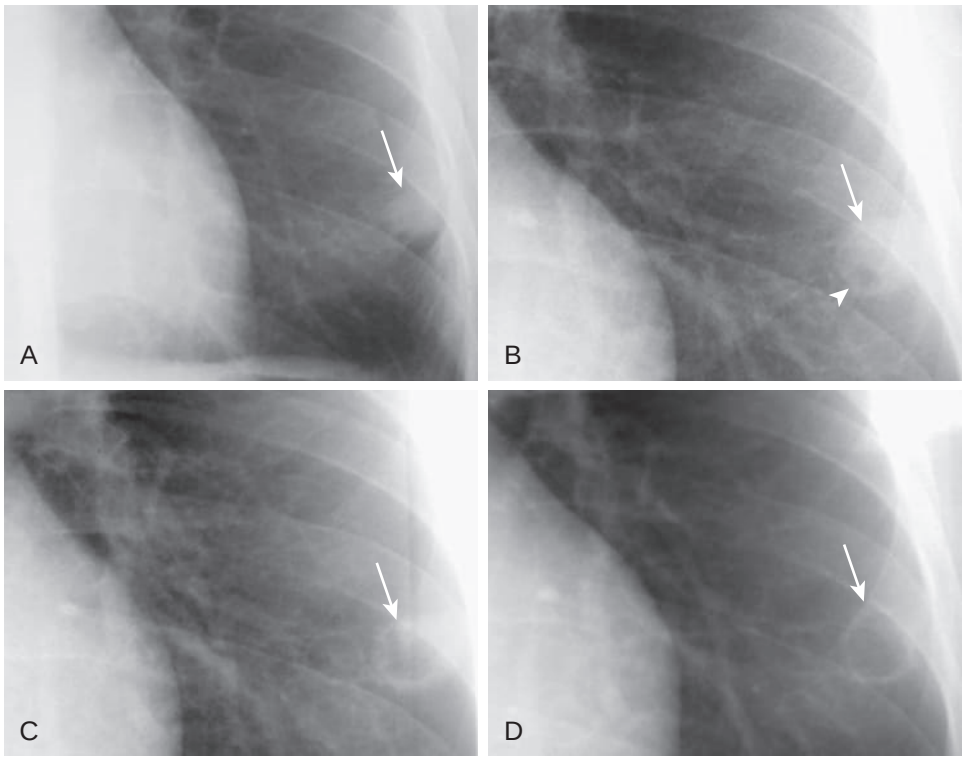
eFigure 56.8 Coccidioidomycosis meningitis. Axial contrast-enhanced magnetic resonance image of the brain shows extensive basal meningeal enhancement, particularly involving the middle cerebral artery cisterns *(arrowheads)* and quadrigeminal plate cistern (*arrows*). (Courtesy Michael B. Gotway, MD.)



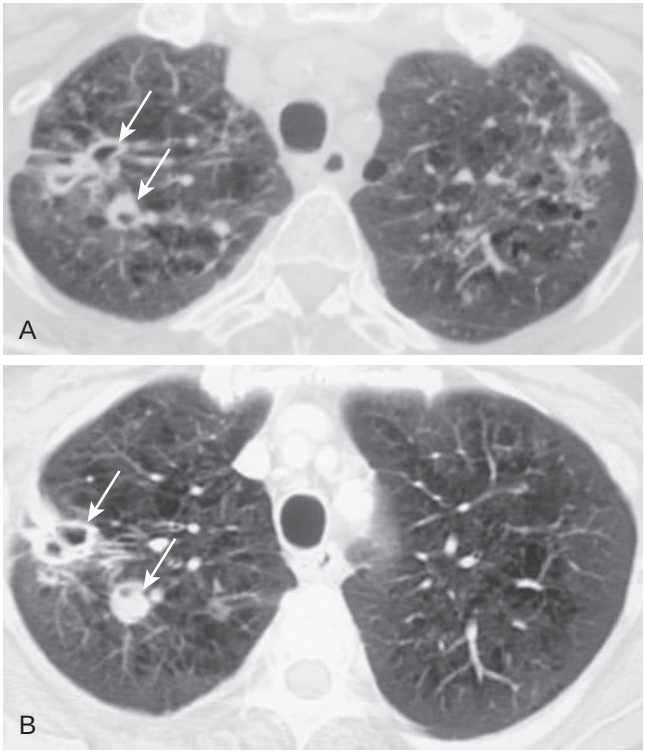
eFigure 56.9 Miliary coccidioidomycosis. (A) Frontal chest radiograph shows multiple bilateral, small, randomly disseminated nodules consistent with a miliary pattern. (B) Chest computed tomography shown in lung windows confirms these findings. (Courtesy Michael B. Gotway, MD.)



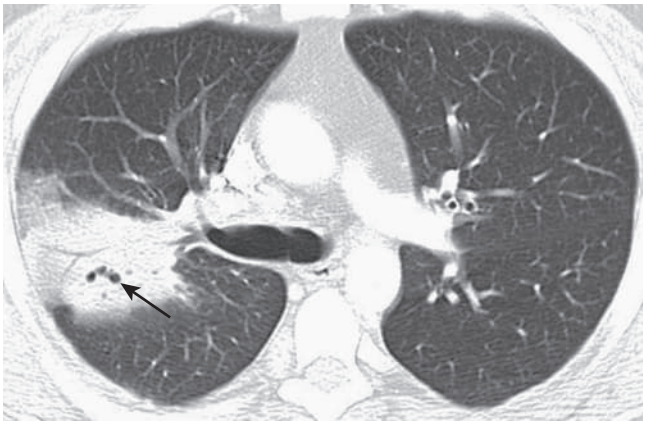
eFigure 56.10 Solitary pulmonary nodule due to *Coccidioides immitis*. Focused axial chest computed tomography image shown in lung windows demonstrates a right upper lobe nodule with an air bronchogram. Although the appearance closely resembles bronchogenic malignancy, the very small nodules surrounding the dominant opacity, often referred to as satellite nodules *(arrowheads)*, are common with granulomatous infection, particularly coccidioidomycosis. Percutaneous transthoracic needle biopsy confirmed *Coccidioides immitis* infection, and the nodule resolved following treatment. (Courtesy Michael B. Gotway, MD.)



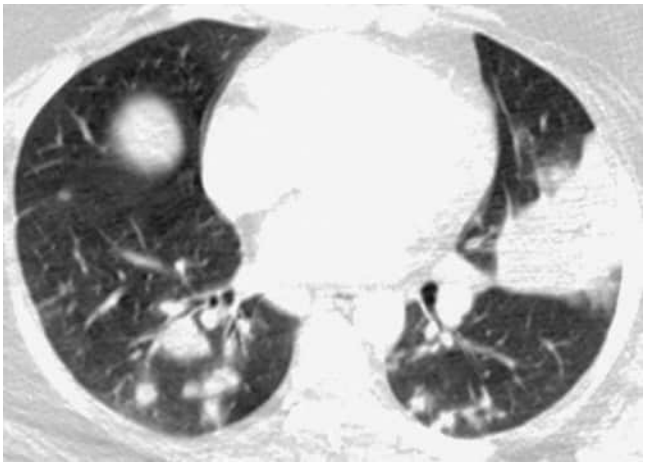
eFigure 56.11 Cavitary coccidioidomycosis. Focused frontal chest radiograph shows a nonspecific left lower lobe nodule (*arrow*, A); percutaneous transthoracic needle biopsy confirmed *Coccidioides immitis* infection. Focused serial chest radiographs obtained over the subsequent year (B–D) show progressive cavitation (*arrowhead*, B) within the nodule (*arrow*, A–D). Note that the nodule subsequently evolved into a thin-walled "grape-skin" cyst (*arrow*, D). This evolution happened without treatment and the patient was asymptomatic throughout this time. The lesion subsequently resolved completely. (Courtesy Michael B. Gotway, MD.)



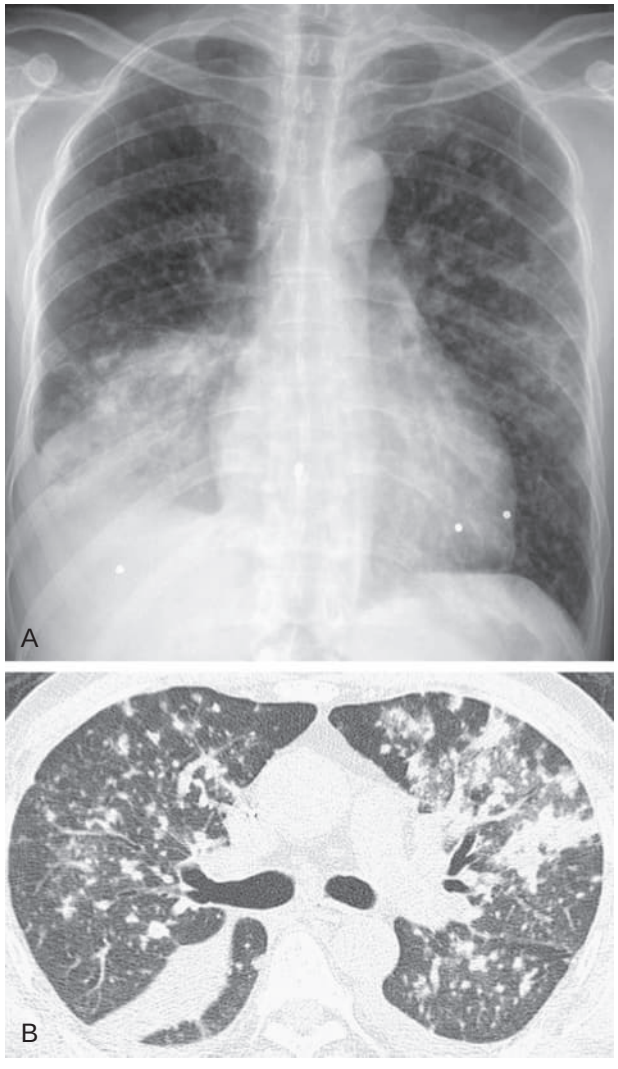
eFigure 56.12 Chronic fibrocavitary coccidioidomycosis. (A–B) Axial chest computed tomography through the upper lobes shows cavitary nodules *(arrows)* associated with architectural distortion and peribronchovascular thickening and nodularity superimposed on emphysema. (Courtesy Michael B. Gotway, MD.)



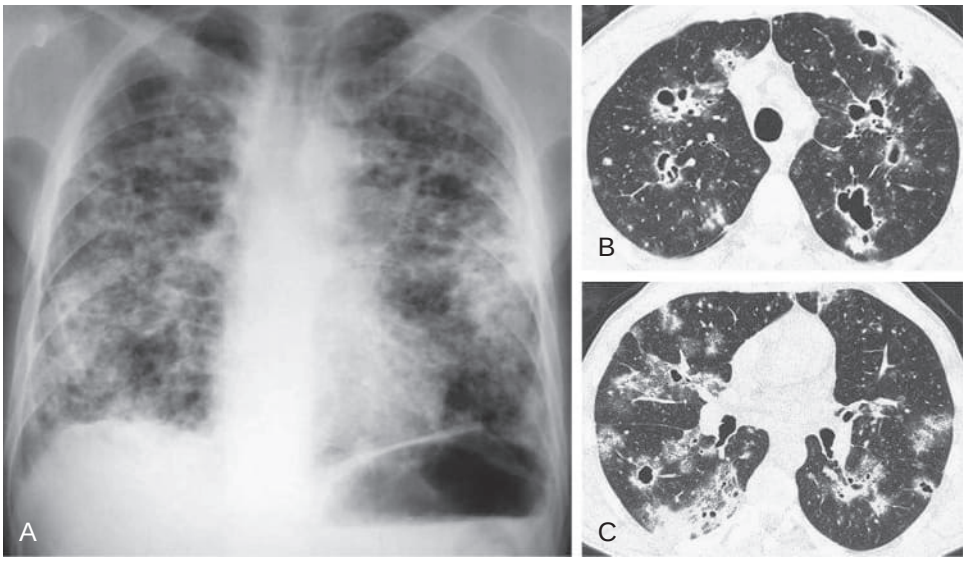
eFigure 56.13 Cavitary pulmonary blastomycosis. Axial chest computed tomography shows cavitary *(arrow)* right upper lobe consolidation. (Courtesy Jeff Kanne, MD, Associate Professor, Thoracic Imaging, Department of Radiology University of Wisconsin School of Medicine and Public Health.)



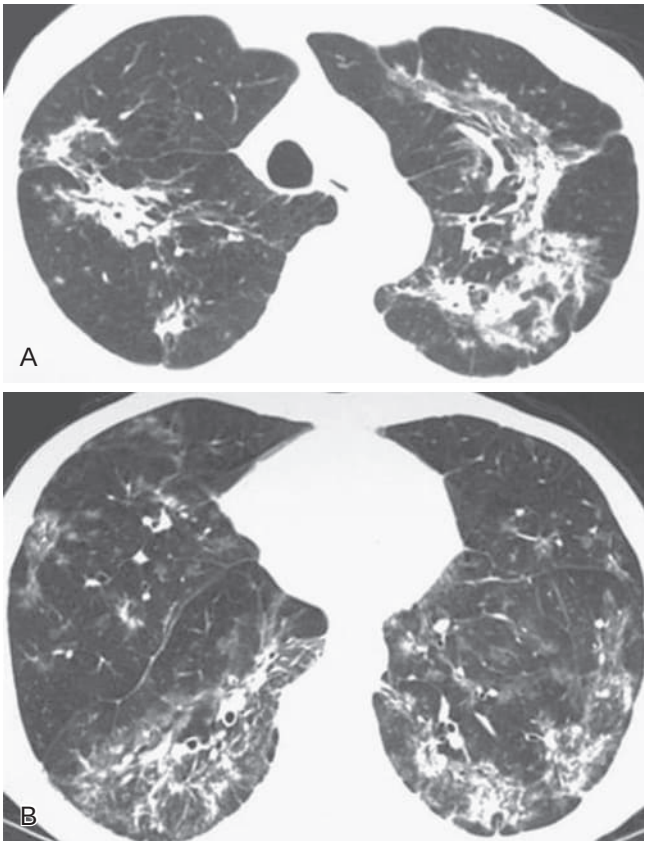
eFigure 56.14 Pulmonary blastomycosis presenting with multiple nodules. Axial chest computed tomography shows masslike left upper lobe opacity with multiple, bilateral pulmonary nodules. (Courtesy Jeff Kanne, MD, Associate Professor, Thoracic Imaging, Department of Radiology University of Wisconsin School of Medicine and Public Health.)



eFigure 56.15 Pulmonary blastomycosis in an immunosuppressed patient. (A) Frontal chest radiograph in an immunosuppressed renal transplant patient shows extensive right lower lobe consolidation and multiple, bilateral, poorly defined nodules. (B) Axial chest computed tomography shows numerous, bilateral, poorly defined nodules and peribronchial consolidation in the left upper lobe. (Courtesy Jeff Kanne, MD, Associate Professor, Thoracic Imaging, Department of Radiology University of Wisconsin School of Medicine and Public Health.)



eFigure 56.16 Pulmonary paracoccidioidomycosis. (A) Frontal chest radiograph shows bilateral poorly defined masses. (B–C) Axial chest computed tomography images confirm the presence of bilateral nodules, masses, and masslike areas of consolidation. Percutaneous transthoracic needle biopsy subsequently proved paracoccidioidomycosis. (Courtesy Michael B. Gotway, MD.)



eFigure 56.17 Fibrosis in chronic pulmonary paracoccidioidomycosis. Axial chest computed tomography performed through the upper (A) and lower (B) lungs shows peribronchial consolidation associated with bronchial dilation and architectural distortion. (Courtesy Edson Marchiori, MD, Associate Professor, Radiology, Federal University of Rio de Janeiro.)

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57 FUNGAL INFECTIONS: OPPORTUNISTIC

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INTRODUCTION

The epidemiology of opportunistic mycoses is evolving. In certain populations, the frequency of opportunistic mycoses is increasing due to expanding use of immunomodulating therapies, a higher frequency of invasive procedures and devices, and changes in climate and regional environments. In other populations, the frequency of opportunistic mycoses is decreasing due to antifungal prophylaxis in high-risk patients and reconstitution of immunity with antiretroviral therapy for *human immunodeficiency virus* (HIV) infection. Heightened clinical awareness of fungal infections and the availability of improved diagnostics contribute to their increased recognition, and the availability of newer antifungal drugs provides broader therapeutic options.

Fungi are eukaryotic microorganisms that grow as yeasts or molds. Yeasts are unicellular fungi and exist as single rounded or elongated cells and reproduce primarily by budding. The primary opportunistic yeasts reviewed here are *Candida* and *Cryptococcus*. In contrast, molds are multicellular filamentous fungi composed of hyphae that grow by branching with extension at the hyphal apices. Clinically relevant opportunistic molds are often categorized on the basis of their hyphae. Aseptate (or sparsely septate) hyphae infrequently demonstrate cross walls that divide the hyphae into compartments, whereas septate do contain these cross walls. This distinction can be used in identifying molds in respiratory samples and tissue histopathology. Aseptate (or sparsely septate) hyphae are seen in mucormycosis, caused by molds such as *Mucor* and *Rhizopus* (historically referred to as *Zygomycetes*). Septate hyphae are found in opportunistic molds that are further subdivided as hyaline or dematiaceous molds. Hyaline molds produce colorless or lightly pigmented hyphae in tissue and infections are referred to as *hyalohyphomycoses*. Dematiaceous or black molds are septate molds that contain melanin in their cell walls, resulting in brown pigmentation, which can be seen in histopathology specimens and under direct microscopic examination. Infections with the dematiaceous molds are referred to as *phaeohyphomycoses*. Endemic fungi such as *Blastomyces dermatitidis* and *Histoplasma capsulatum*, reviewed in Chapter 56, are considered dimorphic fungi, growing as molds at room temperature and yeast or yeastlike forms at body temperature.

This chapter discusses the most common opportunistic mycoses of the respiratory tract and their epidemiology, clinical characteristics, diagnosis, and treatment. Although *Pneumocystis jirovecii* (previously *P. carinii*) is an opportunistic yeastlike fungus, it is discussed in Chapters 123 and 125 because of its distinctive biology and approaches to therapy.

ANTIFUNGAL THERAPY

Rapid initiation of antifungal therapy is essential in the management of *invasive fungal infections* (IFIs). The primary classes of antifungal agents target either the plasma membrane or the cell wall. *Amphotericin B* (AmB) was previously the primary antifungal agent for IFIs; however, newer antifungals, including the extended-spectrum azoles and echinocandins, have broadened the therapeutic options, and lipid formulations of AmB have less toxicity. In addition, combination therapy should be considered in certain IFIs. The following section is a broad overview of the major antifungal agents. eTables 57.1 and 57.2 summarize details of the available agents, including their spectrum of activity, primary toxicities, interactions, recommendations for therapeutic drug monitoring, and the *U.S. Food and Drug Administration* (FDA)–approved indications.

eTable 57.1 Comparison of Antifungal Agents

Antifungal Therapy	Fungal Spectrum of Activity[1,7,18,370,404–416]	Therapeutic Drug Monitoring[7,16,405–423]	Major Adverse Effects[1,7,370,405–416,423*]	Major Drug Interactions*[,1,7,370,405–416]
POLYENES				
Amphotericin B deoxycholate (AmBd, Fungizone) Lipid formulations: Lipsomal AmB (LAmB, AmBisome) AmB Lipid Complex (ABLC, Abelcet) *Dosage form: IV only*	*Aspergillus* (resistance in *A. terreus*, reduced susceptibility in *A. nidulans*, *A. ustus*) *Candida* (resistance in *C. lusitaniae*, possible in *C. auris*) *Cryptococcus* Dematiaceous molds Endemic fungi Mucormycosis Non-*Aspergillus* hyaline molds (resistance in some species including *Fusarium*, *Scedosporium*, *Lomentospora*, and *Purpureocillium lilacinum*)	Not recommended	Anemia (typically normocytic, normochromic) Electrolyte imbalance (e.g., hypokalemia, hypomagnesemia) Infusion-related reactions (e.g., chills/rigors, fever, nausea, vomiting; can be reduced with preinfusion acetaminophen and diphenhydramine; meperidine may be used for rigors) Nephrotoxicity (can be reduced with hydration, often 500 mL normal saline given pre- and postinfusion) *Note: nephrotoxicity is reduced with the lipid formulations of AmB*	Close monitoring when used with other nephrotoxic therapies
AZOLES				
Fluconazole (FLUC, Diflucan) *Dosage form: IV, PO suspension, PO tablet*	*Candida* (intrinsic resistance with *C. krusei*; high levels of resistance with *C. auris*, variable susceptibility with *C. glabrata*) *Cryptococcus* Some activity against endemic mycoses (e.g., coccidioidomycosis)	Not recommended Renal dose adjustment is required	Alopecia (with prolonged therapy) Exfoliative skin disorders GI effects (nausea, vomiting, diarrhea) Hepatotoxicity Headaches QT prolongation	FLUC is a moderate CYP2C9 and CYP3A4 inhibitor Critical to assess for drug interactions with concomitant medications that either share this metabolic pathway or modify CYP450 activity See package insert and drug interactions screening database for important drug interactions Potentiation of QT prolongation when used with other QT-prolonging drugs
Itraconazole (ITRA, Sporanox) *Dosage form: PO only: capsule, tablet, and solution*	*Aspergillus* *Candida* (including *C. krusei*, *C. glabrata*, and *C. tropicalis*) *Cryptococcus* Dematiaceous molds Endemic mycoses (including paracoccidioidomycosis) *Talaromyces* (formerly *Penicillium*) *marneffei* *Sporothrix schenckii* *Trichophyton* ITRA is not typically active against mucormycosis or many *Fusarium* and *Scedosporium* sp	Recommended for systemic infection Random concentration measured after ≥2 weeks of therapy with goal ≥1.0 μg/mL (when tested via HPLC) For HPLC, the goal concentration is sum of ITRA and active metabolite, hydroxy-ITRA Capsules: take with food and acidic beverage (e.g., cola); avoid proton-pump inhibitors and H_2 blockers due to decreased absorption Solution: take on empty stomach Blood concentrations ≈30% higher with ITRA solution vs. ITRA capsule formulation	Adrenal insufficiency (long-term use, rare) CHF (avoid use in patients with ventricular dysfunction or history of CHF) GI effects (nausea, vomiting, diarrhea) Headache Hearing loss Hepatotoxicity Neuropathy Peripheral edema QT prolongation Rash	ITRA is a potent CYP3A4 inhibitor and substrate of CYP3A4 Critical to assess for drug interactions with concomitant medications that either share this metabolic pathway or modify CYP450 activity See package insert and drug interactions screening database for important drug interactions Potentiation of QT prolongation when used with other QT-prolonging drugs

eTable 57.1 Comparison of Antifungal Agents—Cont'd

Antifungal Therapy	Fungal Spectrum of Activity[1,7,18,370,404–416]	Therapeutic Drug Monitoring[7,16,405–423]	Major Adverse Effects[1,7,370,405–416,423*]	Major Drug Interactions*[,1,7,370,405–416]
Isavuconazole (ISA, Cresemba) *Dosage form: IV, PO capsule*	*Aspergillus* *Candida* *Cryptococcus* Endemic fungi, limited data Non-*Aspergillus* hyaline molds (species-dependent, limited data) Mucormycosis Dematiaceous mold, limited data	TDM not currently routinely recommended Renal dose adjustment is not required with PO or IV formulation	GI effects (nausea, vomiting, diarrhea) Headache Hypokalemia Peripheral edema Hepatotoxicity Cardiac effects: can cause shortening of the QT interval and is contraindicated in patients with familial short QT syndrome	ISA is a substrate and moderate inhibitor of CYP3A4 and mild inhibitor of P-glycoprotein and organic cation transporter 2 Critical to assess for drug interactions with concomitant medications that either share or modify the activity of these metabolic pathways See package insert and drug interactions screening database for important drug interactions
Posaconazole (POSA, Noxafil) *Dosage form: IV, PO suspension, PO delayed-release tablet*	*Aspergillus* *Candida* *Cryptococcus* Endemic fungi, limited data Non-*Aspergillus* hyaline molds (species-dependent, limited data) Mucormycosis Dematiaceous molds	Recommended for prophylaxis and treatment of infection Goal trough >0.7 μg/mL for prophylaxis and >1.0 μg/mL for treatment, measured after 7 days of therapy Posaconazole suspension given with high-fat meal, acidic beverage (e.g., cola, ginger-ale); avoid proton-pump inhibitors Posaconazole delayed-release tablet administered with food IV formulation typically avoided if CrCl < 50 mL/min because cyclodextrin (solubilizing vehicle) may accumulate	GI effects (diarrhea, nausea, vomiting) Headache Hepatotoxicity QT prolongation	POSA is a strong inhibitor of CYP3A4 and substrate of P-glycoprotein Critical to assess for drug interactions with concomitant medications that either share or modify the activity of these metabolic pathways See package insert and drug interactions screening database for important drug interactions Potentiation of QT prolongation when used with other QT-prolonging drugs
Voriconazole (VORI, VFEND) *Dosage form: IV, PO suspension, PO tablet*	*Aspergillus* *Candida* sp *Cryptococcus* Dematiaceous molds Endemic fungi, limited data Non-*Aspergillus* hyaline molds including *Acremonium, Fusarium, Paecilomyces, Scedosporium,* and *Trichoderma* VORI is not active against mucormycosis	Recommended for prophylaxis and treatment of systemic infections Trough concentration measured ≥day 5 of therapy with goal trough ≥1.0 μg/mL to 5.5 μg/mL; some argue for target of ≥2.0 μg/mL for treatment Administer 1 hour before or after a meal IV formulation typically avoided if CrCl < 50 mL/min because cyclodextrin (solubilizing vehicle) may accumulate	Fluorosis and periostitis GI effects (diarrhea, nausea, vomiting) Headache Hepatotoxicity QT prolongation Skin rash, photosensitivity Visual disturbances (e.g., photopsia, color-vision change, photophobia, other visual hallucinations), rare optic neuritis and papilledema Long-term use and association with skin cancer	VORI is substrate of CYP2C9, CYP2C19, and CYP3A4 and is a moderate inhibitor of CYP2C9 and CYP2C19 and a strong inhibitor of CYP3A4 Critical to assess for drug interactions with concomitant medications that either share this metabolic pathway or modify CYP450 activity See package insert and drug interactions screening database for important drug interactions Potentiation of QT prolongation when used with other QT-prolonging drugs

eTable 57.1 Comparison of Antifungal Agents—Cont'd

Antifungal Therapy	Fungal Spectrum of Activity[1,7,18,370,404–416]	Therapeutic Drug Monitoring[7,16,405–423]	Major Adverse Effects[1,7,370,405–416,423*]	Major Drug Interactions*[,1,7,370,405–416]
ECHINOCANDINS				
Caspofungin (CAS, Cancidas) Micafungin (MICA, Mycamine) Anidulafungin (ANI, Eraxis) *Dosage form: IV only*	*Aspergillus* (fungistatic) *Candida* sp (fungicidal, elevated MICs reported with *C. parapsilosis* and *C. guilliermondii*) Echinocandins have moderate activity against the mycelial phase of dimorphic fungi but lack activity against the yeast phase and are not utilized in treatment Echinocandins lack significant activity against mucormycosis, dematiaceous molds, and non-*Aspergillus* hyaline molds (although some use in combination therapy, see text)	Not recommended No dosage adjustment required for renal dysfunction	GI effects (diarrhea, nausea, vomiting) Hepatotoxicity (uncommon) Infusion reactions (histamine-induced, greatest with CAS) Injection site thrombophlebitis	Minimal drug interactions overall with echinocandins In general, poor CYP substrates (CAS/MICA) and/or weak inhibitors of CYP3A4 (MICA) and not affected by P-glycoprotein Assess for drug interactions with concomitant medications that either share this metabolic pathway or modify CYP activity See package insert and drug interactions screening database for important drug interactions ANI undergoes no hepatic metabolism, only chemical degradation
OTHER				
Flucytosine (5-FC, Ancobon) *Dosage form: PO only (capsule)*	*Aspergillus* *Candida* *Cryptococcus* Dematiaceous fungi (species-dependent, limited data) Note that 5-FC is used in combination therapy, typically with AmB	Cryptococcal infection: concentration measured on day 3–5 of therapy, 2 hours after dose, target: 30 to 80 μg/mL When TDM not available both renal function and cell counts must be closely monitored Renal dose adjustment is required	Bone marrow suppression GI effects (abdominal pain, diarrhea, nausea, vomiting) Hepatotoxicity Nephrotoxicity	Aluminum hydroxide or magnesium hydroxide suspension (delayed 5-FC absorption) Cytarabine (cytosine arabinoside, competitive inhibitor of 5-FC) Close monitoring when used with other nephrotoxic and myelosuppressive therapies
Terbinafine (TBF, Lamisil) *Dosage form: PO tablet, PO packet, topical (not for use in systemic infection)*	*Aspergillus* *Sporotrichosis* Combination therapy for non-*Aspergillus* hyaline molds (species dependent, limited data) and dematiaceous molds (species dependent, limited data)	Not recommended Clearance is decreased by 50% when CrCl ≤ 50 mL/min	Depressive symptoms Hepatotoxicity Neutropenia Rash Smell and taste disturbances	TBF is an inhibitor of CYP2D6 Critical to assess for drug interactions with concomitant medications that either share this metabolic pathway or modify CYP450 activity See package insert and drug interactions screening database for important drug interactions

*This is not an all-inclusive list of adverse effects and/or drug interactions.

ABLC, amphotericin B lipid complex; AmB, amphotericin B; AmBd, amphotericin B deoxycholate; ANI, anidulafungin; CAS, caspofungin; CHF, congestive heart failure; CrCl, creatinine clearance; CYP, cytochrome P450 enzyme system; FLUC, fluconazole; GI, gastrointestinal; HPLC, high-performance liquid chromatography; ISA, isavuconazole; ITRA, itraconazole; IV, intravenous; MIC, minimal inhibitory concentration; MICA, micafungin; LAmB, liposomal amphotericin B; PO, oral; POSA, posaconazole; TBF, terbinafine; TDM, therapeutic drug monitoring; VORI, voriconazole; 5-FC, flucytosine.

eTable 57.2 FDA-Approved Indications for Antifungal Therapies

Antifungal Agent	FDA-Approved Treatment Indications[370,405–416]
POLYENES	
Amphotericin B deoxycholate (Fungizone) U.S. generic available: yes	Potentially life-threatening fungal infections including: Aspergillosis Blastomycosis Candidiasis, systemic Coccidioidomycosis Cryptococcosis Histoplasmosis Mucormycosis Sporotrichosis
Amphotericin B lipid complex, ABLC (Abelcet) U.S. generic available: no	Invasive fungal infections in patients who are refractory to or intolerant of conventional amphotericin B therapy
Liposomal amphotericin B (AmBisome) U.S. generic available: no	Aspergillosis and candidiasis (in patients with renal impairment or who are refractory to or intolerant of conventional amphotericin B therapy) Cryptococcosis (in HIV patients with cryptococcal meningitis and for cryptococcal infections in patients with renal impairment or who are refractory to or intolerant of conventional amphotericin B) Empirical therapy for presumed fungal infection in febrile neutropenic patients
AZOLES	
Fluconazole (Diflucan) U.S. generic available: yes	Candidiasis (including chronic mucocutaneous candidiasis, esophageal and oropharyngeal candidiasis, *Candida* urinary tract infection and peritonitis, other systemic *Candida* infections including candidemia, disseminated candidiasis and pneumonia, vaginal candidiasis) Cryptococcal meningitis Prophylaxis for patients undergoing HCT who receive cytotoxic chemotherapy and/or radiation therapy
Itraconazole (Sporanox) U.S. generic available: yes	Aspergillosis (pulmonary and extrapulmonary in patients who are refractory to or intolerant of amphotericin B) Blastomycosis (pulmonary and extrapulmonary infection) Histoplasmosis (including chronic pulmonary disease and disseminated non-meningeal infection) Onychomycosis of the fingernails and toenails due to dermatophytes (non-immunocompromised patients)
Isavuconazole (Cresemba) U.S. generic available: no	Invasive aspergillosis and mucormycosis
Posaconazole (Noxafil) U.S. generic available: no	Oropharyngeal candidiasis including that which is refractory to itraconazole and/or fluconazole Prophylaxis of invasive aspergillosis and invasive candidiasis (in severely immunocompromised patients such as HCT recipients with GVHD or those with hematologic malignancies with prolonged neutropenia from chemotherapy)
Voriconazole (VFEND) U.S. generic available: yes	Aspergillosis (invasive) Candidiasis (esophageal candidiasis, candidemia in non-neutropenic patients and the following *Candida* infections: disseminated infections in skin and infections in abdomen, kidney, bladder wall, and wounds) Serious infections caused by *Scedosporium apiospermum* and *Fusarium* species including *Fusarium solani*, in patients refractory to or intolerant of other therapy
ECHINOCANDINS	
Caspofungin (Cancidas) U.S. generic available: yes	Aspergillosis (invasive disease in patients who are refractory to or intolerant of other therapies) Candidiasis (esophageal candidiasis, candidemia, and the following *Candida* infections: intra-abdominal abscesses, peritonitis, and pleural space infections) Empirical therapy for presumed fungal infections in febrile neutropenic patients
Micafungin (Mycamine) U.S. generic available: no	Candidiasis (esophageal candidiasis, candidemia, acute disseminated candidiasis, peritonitis, and abscesses) Prophylaxis of *Candida* infections in patients undergoing HCT
Anidulafungin (Eraxis) U.S. generic available: no	Candidiasis (esophageal candidiasis, candidemia and other forms of *Candida* infections including intra-abdominal abscess and peritonitis)
OTHER	
Flucytosine (Ancobon) U.S. generic available: yes	Candidiasis (susceptible strains causing septicemia, endocarditis, urinary tract infections, and pneumonia) Cryptococcosis (susceptible strains causing meningitis, pulmonary infections, septicemia, and urinary tract infections) Note that flucytosine should be used in combination with amphotericin B for the treatment of systemic candidiasis and cryptococcosis because of the emergence of resistance to flucytosine monotherapy.
Terbinafine (Lamisil) U.S. generic available: yes, product dependent	Onychomycosis of the toenail or fingernail due to dermatophytes

FDA, Food and Drug Administration; GVHD, graft-versus-host disease; HCT, hematopoietic cell transplant; HIV, human immunodeficiency virus.

POLYENES

The polyenes include nystatin and AmB. AmB binds to ergosterol, an essential component of the fungal cell membrane. AmB binding increases membrane permeability and causes fungal cell death.[1] AmB also induces proinflammatory cytokines by activating toll-like receptor 2, which contributes to the acute side effects of fever and myalgias, and may augment host responses to fungal infection.[2] AmB has activity against multiple fungal pathogens including *Aspergillus, Candida,* the endemic mycoses (e.g., blastomycosis, coccidioidomycosis, cryptococcosis, histoplasmosis), and mucormycosis.[3] However, certain fungi, including *Aspergillus terreus, Candida lusitaniae, Lomentospora* (previously *Scedosporium*) *prolificans,* and *Trichosporon beigelii,* may be intrinsically resistant to AmB, and other pathogens, such as *Fusarium* species and select dematiaceous molds, may have high *minimal inhibitory concentrations* (MICs) to AmB.[4]

The lipid formulations of AmB were introduced to reduce nephrotoxicity seen with conventional amphotericin, called *amphotericin B deoxycholate* (AmB-d). The lipid formulations of AmB are now often used as first-line therapy, particularly in patients with renal dysfunction or on concurrent nephrotoxic medications. Lipid formulations include *liposomal AmB* (LAmB) and *AmB lipid complex* (ABLC). Encochleated AmB, MAT2033, the first orally administered polyene formulation, is a suspension of AmB carried in cochleates (stable multilayered phospholipid-cation precipitates) to facilitate oral absorption. It has demonstrated activity in animal models of candidiasis and aspergillosis with multiple phase I and II clinical trials either planned or ongoing.[5]

AZOLES

Triazoles (i.e., "azoles") have emerged as a primary class of antifungals for treatment and prevention of IFIs. The most widely used azoles are fluconazole, itraconazole, isavuconazole, posaconazole, and voriconazole. These agents act on the fungal cell membrane by inhibiting the cytochrome P-450–dependent 14-α-demethylase, a critical enzyme in the conversion of lanosterol to ergosterol. This is encoded in yeasts and molds by *ERG11* and *cyp51*, respectively.[6] The azoles are fungistatic or fungicidal, depending on the specific azole and fungal species.[7] Immunomodulating effects have been described with azoles and may contribute to their efficacy.[2] While earlier azoles, such as fluconazole, are only active against yeasts, the extended-spectrum azoles, including itraconazole, voriconazole, isavuconazole, and posaconazole, are active against yeasts and molds. Fluconazole is active against *Cryptococcus* and *Candida* and has variable activity against endemic fungi, including *Coccidioides. Candida krusei* is intrinsically resistant to fluconazole and high-level resistance has emerged among some non-*albicans Candida* species, including *Candida glabrata*. Itraconazole has little role in treatment of most opportunistic fungal infections; its principal indications are treatment of indolent, non–*central nervous system* (CNS) blastomycosis or histoplasmosis and as an alternative to fluconazole for treatment of indolent non-CNS coccidioidomycosis. Itraconazole is also indicated in treatment of allergic bronchopulmonary aspergillosis and some forms of chronic pulmonary aspergillosis. Itraconazole exhibits highly variable absorption and pharmacokinetics; therapeutic drug monitoring is essential to guide optimal dosing for an individual patient.

The extended-spectrum azoles have activity against many molds, including *Aspergillus,* non-*Aspergillus* hyaline hyphomycetes such as *Fusarium, Scedosporium, Lomentospora*, and *Paecilomyces,* and some dematiaceous molds. Voriconazole is the drug of choice for the treatment of invasive *Aspergillus* infections. Isavuconazole, the newest of the extended-spectrum azoles, is also FDA approved for the treatment of *invasive aspergillosis* (IA) as well as mucormycosis.[8] Isavuconazole is a water-soluble prodrug and, unlike other extended-spectrum azoles such as voriconazole and posaconazole, the intravenous formulation is devoid of the solubilizing moiety cyclodextrin, which can accumulate in patients with renal dysfunction. In contrast to other azoles that can prolong the QT interval, isavuconazole has been shown to shorten the QT interval, though the full clinical significance of this remains unclear.[8] Among the azoles, only posaconazole and isavuconazole have significant activity against the agents of mucormycosis.

ECHINOCANDINS

The echinocandins, including caspofungin, micafungin, and anidulafungin, are increasingly used given their efficacy, tolerability, lack of drug interactions, and the prevalence of azole-resistant *Candida* species. Unlike AmB and the azoles, the echinocandins act on the fungal cell wall via noncompetitive binding to the catalytic subunits of (1→3)-β-D-glucan synthase, thereby inhibiting production of (1→3)-β-D-glucan (β-D-glucan), an essential component of the fungal cell wall. Echinocandins are fungicidal against multiple *Candida* species, including *C. albicans, C. dubliniensis, C. glabrata,* and *C. krusei;* however, certain *Candida* species, such as *C. guilliermondii* and *C. parapsilosis,* typically have higher MICs. The echinocandins are fungistatic, rather than fungicidal, against filamentous fungi such as *Aspergillus* species because their activity is restricted to sites where the fungal cell wall is actively growing (i.e., hyphal tips and branching junctional cells) but not on subapical hyphal cells.[9] Echinocandins lack significant activity against other fungal pathogens such as *Cryptococcus, Mucorales,* and *Trichosporon* species and the endemic fungi.[10] Immunostimulatory effects of echinocandins on monocytes and monocyte-derived macrophages may be of particular importance against *Aspergillus.*[11,12]

A novel, next-generation echinocandin, rezafungin (CD101), is a structural analog of anidulafungin with a long half-life allowing for once-weekly intravenous dosing. Rezafungin is currently under investigation in phase III clinical trials for treatment of candidemia and/or invasive candidiasis as well as for prophylaxis of *Aspergillus*, *Candida*, and *Pneumocystis* in high-risk allogeneic *hematopoietic cell transplant* (HCT) recipients. Ibrexafungerp (SCY-078), the first member of a new glucan synthase inhibitor subclass that also targets (1→3)-β-D-glucan, is available as an oral formulation. Ibrexafungerp has activity similar to echinocandins but also offers promise for use with some echinocandin-resistant fungal pathogens

including *Candida auris*.[13] In vitro activity against some non-*Aspergillus* molds such as *Paecilomyces variotti* and the often multidrug-resistant *Lomentospora prolificans* has also been demonstrated, although the clinical applicability against such non-*Aspergillus* molds remains to be determined.[5,14]

FLUCYTOSINE

Flucytosine (5-FC) is an antimetabolite that inhibits fungal DNA and protein synthesis. It is used in combination with other antifungal agents given the high frequency of emergence of resistance with monotherapy.[15] It is fungistatic or fungicidal, depending upon the organism, and is most often used in combination with AmB against *Cryptococcus*[16] and in severe *Candida* infections such as endocarditis and CNS infections.[17]

TERBINAFINE

Terbinafine is a synthetic allylamine that exerts its antifungal effects via inhibition of fungal squalene epoxidase, an enzyme involved in ergosterol formation. Terbinafine is fungicidal and is used most commonly for dermatophyte infections and the treatment of chromoblastomycosis.[18] In vitro synergy data have led to its use in combination, most often with extended-spectrum azoles and AmB, for the management of severe or refractory mold infections such as *Lomentospora,*[19] *Fusarium,*[20] and other hyaline and dematiaceous molds.[18]

CRYPTOCOCCOSIS

EPIDEMIOLOGY

Cryptococcosis is an invasive fungal infection caused primarily by *Cryptococcus neoformans* and *C. gattii. C. neoformans* is most common and has a global distribution and can be isolated from the soil and excreta of birds such as pigeons. *C. neoformans* var. *grubii* is the predominant pathogen worldwide; however, infections with *C. neoformans* var. *neoformans* are prevalent in Northern Europe.[21] *C. gattii* was originally found in tropical and subtropical regions including Australia, Southeast Asia, and Central Africa. However, serious infections with *C. gattii* have also been recognized in Vancouver, British Columbia, and in the Pacific Northwest United States.[22,23] With advances in molecular diagnostics, the genetic diversity of cryptococcosis is increasingly recognized. New taxonomy has been proposed to divide *C. neoformans* further into *C. neoformans* and *C. deneoformans,* and *C. gattii* into five distinct species.[24] While infections with *C. gattii* can develop in immunocompetent hosts, most cryptococcal infections are seen in immunocompromised hosts, including patients with advanced HIV infection,[25] malignancies,[26] *solid organ transplants* (SOTs),[27] and other conditions.[28] Cryptococcosis is one of the most common life-threatening fungal infections in HIV-infected patients,[29] and it is the third most common invasive fungal pathogen (after *Candida* and *Aspergillus*) in SOT recipients in whom it causes 8% of IFIs.[30] *Cryptococcus* affects HCT patients less often, causing 0.6% of IFIs.[31]

PATHOGENESIS

Infections with *Cryptococcus* are typically initiated by inhalation of small yeast or spores. Once in the alveoli, the outcome is determined by the virulence of the infecting strain, host genetic polymorphisms, innate and adaptive immune responses, and the presence of comorbidities. The virulence of *Cryptococcus* is related to its polysaccharide capsule as well as the presence of specific enzymes, including laccase, phospholipase B, and inositol phosphosphingolipid-phospholipase.[32] In the lungs, the *Cryptococcus* capsule protects against phagocytosis and impairs host immune response by interfering with macrophage antigen presentation to T cells, reducing cytokine production, depleting complement components, and reducing leukocyte migration.[33] Successfully phagocytosed cryptococci reside and replicate in mature phagolysosomes and subsequently spread to other cells using multiple mechanisms.[34]

The innate immune response to *Cryptococcus* results in cytokine production and a Th1 $CD4^+$ T cell response.[35] $CD4^+$ cells are necessary to prevent dissemination from the lungs; both $CD4^+$ and $CD8^+$ cells are required for clearance of infection in mice.[36] Although antibody-mediated immunity contributes to control of cryptococci in mice,[35,37] defects in humoral immunity are less commonly associated with cryptococcal infections in humans than are defects in cellular immunity.[38] The presence of autoantibodies to granulocyte-macrophage colony-stimulating factors may predispose otherwise immunocompetent individuals to infection with *C. gattii*.[39]

CLINICAL MANIFESTATIONS

The clinical presentation of cryptococcal infection is determined by the immune status of the host, the *Cryptococcus* species, and the site of infection. The lungs are the most commonly involved primary site; the CNS is the most common site of dissemination. *Cryptococcus* is also believed to cause latent infection in the lung and reactivate in the setting of depressed immunity. In fact, most infections may represent reactivation, and transfer of infection with donor organs may contribute to infection in SOT recipients.[40] Dissemination may develop during primary infection or reactivation. Most pulmonary infections are asymptomatic or mildly symptomatic in immunocompetent hosts and may be discovered incidentally on radiographic imaging. Acute infection in the immunocompetent host may manifest with fever, fatigue, cough, and sputum production. In immunocompromised patients, severe symptoms, including fever, cough, and shortness of breath, can rapidly progress to respiratory failure and acute respiratory distress syndrome. In a prospective multicenter international study of 111 SOT recipients, cryptococcal infections were diagnosed a median of 21 months after transplant, and pulmonary (60%) and CNS (58%) involvement predominated.[41] In patients with advanced HIV infection, meningoencephalitis is the predominant presentation.[42]

The radiographic findings in cryptococcal pulmonary infections commonly include focal or diffuse pulmonary nodules or patchy airspace consolidation (eFig. 57.1). However, other findings include cavitation (see Fig. 57.1A, eFig. 123.21), mass lesions (i.e., cryptococcomas

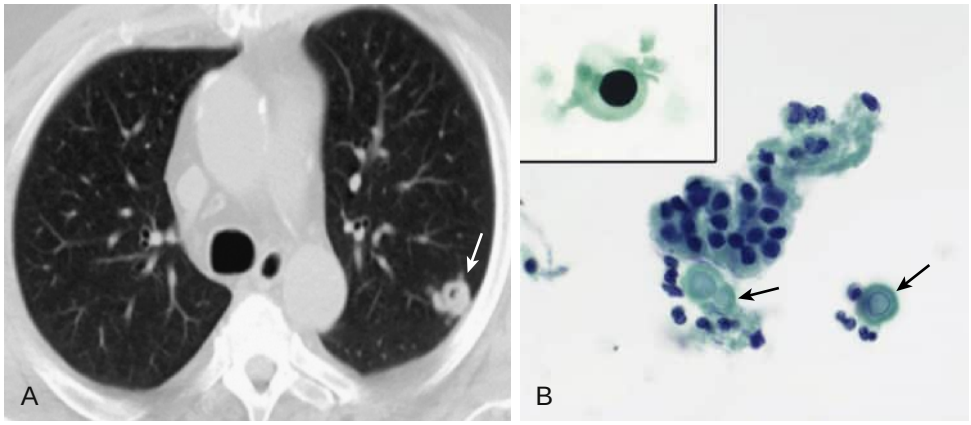

Figure 57.1 Cryptococcosis. Pulmonary infection with *Cryptococcus* in an asymptomatic cardiac transplant patient on chronic immunosuppression with new, bilateral pulmonary nodules. (A) Axial chest computed tomography (CT) demonstrates a cavitary nodule (*arrow*) with small surrounding satellite nodules. (B) CT-guided fine-needle aspiration of the pulmonary nodule shows encapsulated yeast (*arrows*), with the typical morphology of *Cryptococcus neoformans.* (Papanicolaou stain; ×400 original magnification.) *Inset*, Yeast showing mucin capsule with organism staining positive. (Methenamine silver stain; ×400 original magnification.) (B, Courtesy Dr. Thomas Sporn, Duke University Medical Center, NC.)

[see eFig. 123.23]), reticulonodular patterns, ground-glass attenuation (see eFig. 123.21), and associated effusions or lymphadenopathy (see eFig. 123.24A–B).[43,44] In a study of *computed tomography* (CT) radiographic findings of cryptococcosis, immunocompromised patients had more extensive pulmonary involvement with cavitation and parenchymal consolidation than did immunocompetent hosts—a finding that contrasts with that in tuberculosis.[43] Cryptococcomas in both the CNS and in the lungs are seen more commonly with *C. gattii* than with *C. neoformans* infection, and they are more common in immunocompetent hosts.[45]

DIAGNOSIS

The diagnosis of pulmonary cryptococcosis is based on symptoms, chest radiography, culture, histopathologic findings (Fig. 57.1B), and *cryptococcal antigen* (CrAg) testing. *Cryptococcus* can be cultured from respiratory specimens, including sputum and *bronchoalveolar lavage* (BAL), lung biopsy tissue specimens, and from pleural cultures in cases associated with pleural involvement. Blood cultures are typically only positive in disseminated infections. *Cryptococcus* is easily identified under the microscope as 5- to 10-μm, spherical to oval yeast cells with a surrounding capsule, although capsule-deficient variants do exist. Biochemical testing can be used to confirm the identification.[46] In tissue samples, specialized stains such as Mayer's mucicarmine, which stains mucin within the polysaccharide capsule, are also helpful in establishing a diagnosis.[46] *Matrix-assisted laser desorption ionization–time of flight mass spectrometry* (MALDI-TOF MS) and molecular methods such as the *polymerase chain reaction* (PCR) are increasingly utilized by clinical laboratories as a less labor-intensive means of rapid identification of cryptococci.[47,48]

Commercial assays available for detection of the CrAg in clinical specimens (e.g., serum, *cerebrospinal fluid* [CSF]) include the latex agglutination test, enzyme-linked immunosorbent assay, and the *lateral flow assay* (LFA). The latter was more recently introduced as a rapid, inexpensive point-of-care diagnostic and is ideally suited for resource-limited settings. While the serum CrAg assays have high sensitivity and specificity in disseminated infection and cryptococcal meningoencephalitis, they can be negative in patients with isolated pulmonary infection. In a study of patients undergoing SOT, serum CrAg was detectable in 73% of patients (22 of 30) with isolated pulmonary involvement and was more likely to be negative with solitary pulmonary nodules than with multiple nodules and more extensive pulmonary disease. Titers of serum CrAg were higher in those patients with concurrent extrapulmonary infection.[49] False-negative results related to a prozone phenomenon[50] in samples containing a large burden of antigen as well as false-positive results due to cross reaction with other pathogens (e.g., *Trichosporon,*[51] *Ustilago maydis*,[52] and *Stomatococcus*[53]) and disinfectants[54] have also been reported.

Determining the presence of disseminated infection and extent of organ involvement is crucial to the selection of appropriate therapy. Thus, CSF evaluation (e.g., cell count, fungal culture, CrAg) should be performed in all immunosuppressed patients with pulmonary cryptococcosis. Multiplex PCR testing platforms have also been applied to CSF specimens but may not reliably rule out cryptococcal CNS infection.[55] Whether CSF analysis is essential in immunocompetent patients with pulmonary cryptococcosis is less clear. Factors associated with higher likelihood of disseminated disease and the need for CSF analysis include neurologic findings, signs of systemic infection, such as fever and weight loss, and serum CrAg titer of at least 1:64.[56]

TREATMENT

The choice of therapy depends on the immune status of the host and the presence of extrapulmonary infection; current treatment recommendations are available from both the *American Thoracic Society* (ATS)[57] and *Infectious Diseases Society of America* (IDSA).[16] For cryptococcosis in patients with evidence of disseminated infection, CNS involvement, or severe pneumonia, treatment is separated into induction, consolidation, and maintenance regimens (Fig. 57.2). The choices of antifungals, doses, and duration are dependent on the patient's underlying risk group (e.g., organ transplant recipient, HIV infected, or non–HIV infected,

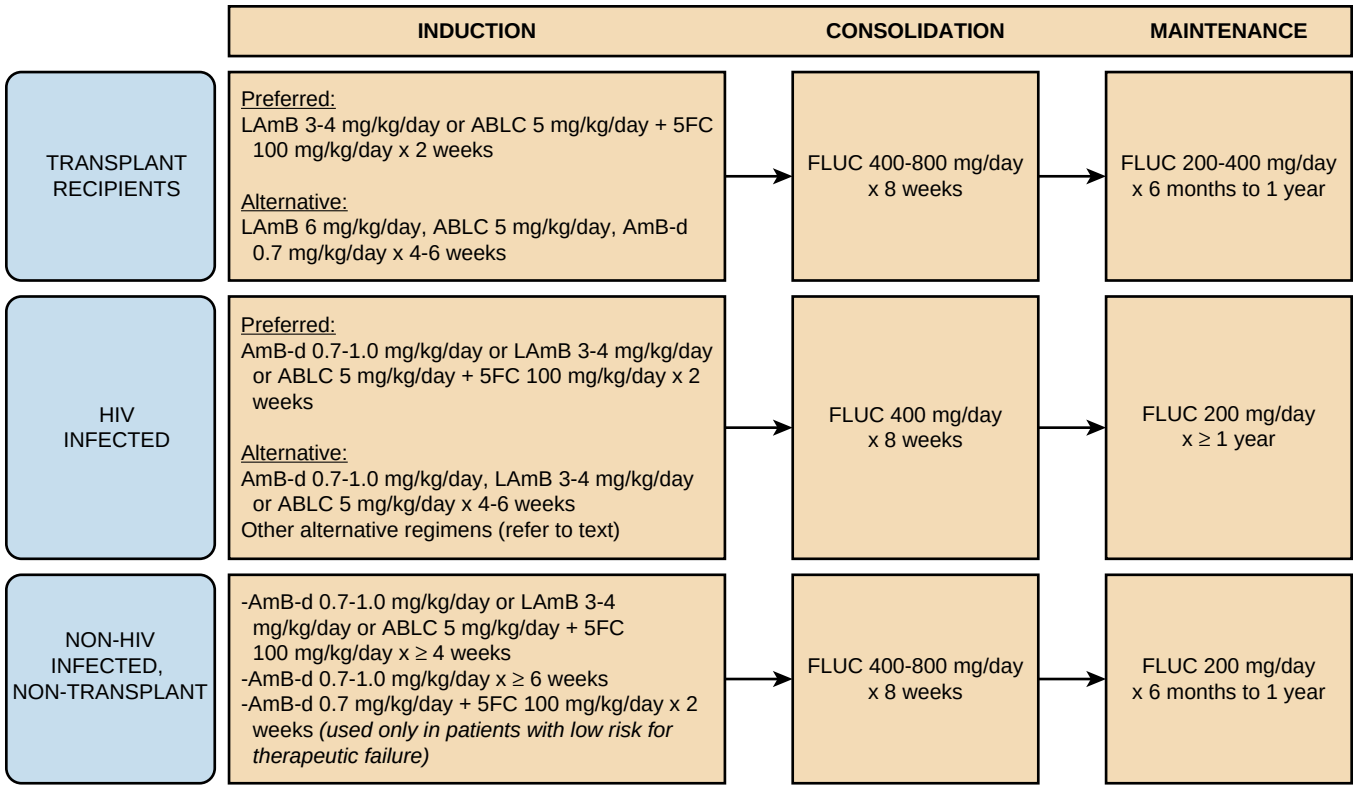

Figure 57.2 Treatment of cryptococcosis in patients with evidence of disseminated infection, central nervous system involvement, or severe pneumonia. ABLC, amphotericin B lipid complex; AmB-d, amphotericin B deoxycholate; FLUC, fluconazole; HIV, human immunodeficiency virus; LAmB, liposomal amphotericin B; 5FC, flucytosine. (Data from Perfect JR, Dismukes WE, Dromer F, et al: Clinical practice guidelines for the management of cryptococcal disease: 2010 update by the Infectious Diseases Society of America. *Clin Infect Dis* 2010;50[3]:291–322.)

non-transplant recipient).[16] In HIV-infected patients with cryptococcal meningoencephalitis in resource-limited settings, data have emerged demonstrating comparable efficacy with induction courses consisting of one week of AmB or 2 weeks of high-dose fluconazole (1200 mg/day), each in combination with 5-FC.[58] Mild-to-moderate infection isolated to the lungs is treated with fluconazole 400 mg/day for a minimum of 6 to 12 months. Some experts maintain that asymptomatic patients with resected solitary nodules, undetectable serum CrAg, and no evidence of extrapulmonary infection may be observed closely without specific antifungal therapy.[16] Infections with *C. gattii* have been associated with delayed clinical response to antifungal therapy; potential explanations include high in vitro antifungal MICs, particularly with fluconazole, and a higher incidence of pulmonary and cerebral cryptococcomas with decreased drug penetration to these lesions.[16,59,60]

Immune reconstitution inflammatory syndrome (IRIS) may complicate treatment of any opportunistic mycosis but is most common in cryptococcosis. IRIS is usually characterized by worsening of clinical signs and symptoms of the original infection, which can be misinterpreted as progressive infection.[16,61] IRIS arises most commonly with initiation of antiretroviral therapy in HIV infection and with abrupt reduction of immunosuppression in SOT recipients. IRIS can also manifest in patients with hematologic malignancies during neutrophil and monocyte recovery following myeloablative chemotherapy[62] and with lymphocyte recovery after receipt of monoclonal antibodies such as alemtuzumab.[63] Manifestations of IRIS in pulmonary disease may be severe and include acute respiratory distress syndrome. Transplant recipients developing IRIS also have increased potential for allograft loss.[64] While nonsteroidal anti-inflammatory drugs may be sufficient to ameliorate the symptoms of IRIS, high-dose corticosteroids may also be required, and treatment of IRIS in transplant recipients includes careful adjustment of immunosuppressive drugs.[16] (See also Chapter 123.)

CANDIDIASIS

The epidemiology of invasive *Candida* infections has evolved substantially in recent decades and depends on a multitude of factors including patient-specific risks and geography.[65–71] Non-*albicans Candida* species including *C. glabrata*, *C. parapsilosis*, *C. tropicalis*, and *C. krusei* account for an increasing proportion of infections.[17,67,71,72] *C. auris*, which can be multidrug-resistant and associated with poor clinical outcomes, was first identified clinically in 2009[73] and subsequently emerged as a global threat, associated with horizontal transmission seen in large outbreaks in health care facilities.[74–77]

Candida infections of the thorax include empyema, tracheobronchial and mediastinal infection, and pneumonia. *Candida* pneumonia is rare and is most often found in the setting of candidemia with dissemination to the lung in immunocompromised patients.[78,79] Rarely, primary pneumonia develops due to aspiration of oropharyngeal contents.[78,80,81] Mediastinitis may complicate thoracic surgical

procedures,[82] and pleural space infection, as well as tracheobronchial infection, can follow lung transplantation.[83,84]

Candida species have multiple virulence determinants; virulent strains consistently exhibit adherence to devices and tissues and form biofilms.[66] Multiple human genetic polymorphisms have been identified that contribute heightened susceptibility to mucosal and invasive *Candida* infections. These include common and rare sequence variants in toll-like receptors 1, 2, and 4, cytokine signaling (*interleukin* [IL]-10, and the shared subunit of IL-12 and IL-23 receptors), and multiple genes whose products contribute to generating or responding to IL-17.[85,86]

Manifestations of *Candida* pneumonia include cough, dyspnea, and fever. Radiographic findings are variable and can include lobar (eFig. 57.2) and multilobar consolidation as well as cavitation.[79] The diagnosis of *Candida* pneumonia is complicated by the generally low specificity and low *positive predictive value* (PPV) of isolating *Candida* in respiratory specimens, which is often interpreted as colonization.[78,79,87,88] Consequently, histopathologic evidence of tissue invasion is required to prove *Candida* pneumonia. Detection of the fungal cell wall component β-D-glucan in serum may assist in distinguishing colonization from invasive *Candida* infection. In patients with hematologic malignancy and in critically ill patients, detection of β-D-glucan has been shown to result in earlier diagnosis of candidemia and invasive candidiasis,[89,90] although the specificity of this test is limited by multiple sources for false-positive tests and cross reactivity due to synthesis of β-D-glucan by other fungi, and low PPV. Blood cultures have an overall low sensitivity for detection of invasive candidiasis along with slow turnaround times due to the extended period required for organism growth and identification.[91] MALDI-TOF MS[92] and molecular techniques including peptide nucleic acid fluorescence in situ hybridization[93,94] and multiplex PCR[95] are currently used to expedite the identification of *Candida* species but still require growth in culture. *C. auris* is often misidentified using commercial identification platforms including MALDI-TOF MS; a national effort to improve recognition/identification of this particular pathogen by clinical laboratories is being led by the Centers for Disease Control and Prevention.[96] Culture-independent methods to expedite the diagnosis of invasive candidiasis include T2Candida (T2 Biosystems), which utilizes PCR and T2 magnetic resonance to detect nanoparticle-labeled probes for five *Candida* species, namely *C. albicans*, *C. glabrata*, *C. parapsilosis*, *C. tropicalis*, and *C. krusei*, directly in whole blood.[97,98] While other molecular methods for invasive candidiasis have been developed, to date none are FDA approved for clinical use.[99,100]

Given the increasing number of infections with non-*albicans Candida* species and the potential for infection with azole cross-resistant strains,[101–104] echinocandins are typically preferred for initial therapy while awaiting species identification and susceptibility testing. Lipid formulations of AmB should be considered in patients with extensive prior echinocandin exposure; *C. glabrata* in particular has demonstrated resistance to echinocandins with associated poor outcomes, most often in the context of prior echinocandin exposure and *FKS1* and *FKS2* gene alterations.[105–108] *C. lusitaniae* is often resistant to AmB, and *C. tropicalis* has shown increasing acquired resistance to azoles and to echinocandins.[105,106,109,110] *C. parapsilosis* and *C. guilliermondii* tend to have higher MICs for the echinocandins than do other species, but the clinical significance is unclear.[111–113] *C. auris* can harbor or develop resistance to antifungal therapy, particularly fluconazole, but multidrug resistance has also been reported inclusive of extended-spectrum azoles, AmB, and echinocandins.[114] These observations underscore the importance of knowing the local epidemiology and resistance patterns for *Candida* within an institution and the patient's prior antifungal exposure, infecting species, and susceptibility pattern to guide therapeutic decision making. Adequate drainage of infected fluid collections, including those in the mediastinum or pleural space, is essential for cure.

ASPERGILLOSIS

INTRODUCTION AND EPIDEMIOLOGY

Aspergillus is a ubiquitous saprophytic fungus found indoors and outdoors in association with soil, organic debris, food, and water. *Aspergillus* produces large numbers of 2 to 3 μm conidia, which easily enter the lungs via inhalation. Outbreaks often follow renovation and construction, activities that place a large number of *Aspergillus* conidia in the air. While the lung is the most common site of entry, *Aspergillus* may gain access to the host via other routes, including direct cutaneous inoculation. Among *Aspergillus* species, *A. fumigatus* is the most common pathogen, in part due to specific virulence factors,[115] but non-*fumigatus* species, including *A. flavus, A. niger,* and *A. terreus,* also cause human disease.[30,31,116] *A. terreus* is notable for intrinsic AmB resistance.[117,118] Application of azole prophylaxis has also led to the emergence of breakthrough infections with *A. ustus* complex, which tends to have high MICs to the mold-active azoles.[119] In addition, *A. nidulans,* an otherwise rare pathogen, is uniquely associated with chronic granulomatous disease, second only to *A. fumigatus* as the most common mold infections in this population.[120]

Aspergillus is a hyaline hyphomycete characterized by septate, narrow (3 to 6 μm) hyphae with acute angle (45 degrees) branching (Fig. 57.3) in respiratory secretions and tissue specimens. The non-*Aspergillus* hyaline hyphomycetes, discussed later, have a similar appearance in clinical specimens and are differentiated from *Aspergillus* in culture based on the morphologic characteristics of their reproductive structures. Aspergillosis most commonly presents as infection limited to the lung but may also present as a skin/soft tissue, ocular, gastrointestinal, cardiac, sinus, CNS, or disseminated infection.[121]

Two major forms of pulmonary aspergillosis are addressed in this chapter: *invasive pulmonary aspergillosis* (IPA), and *chronic pulmonary aspergillosis* (CPA). *Allergic bronchopulmonary aspergillosis* (ABPA), a saprophytic, noninvasive form of aspergillosis, caused by hypersensitivity to *Aspergillus* antigens is covered in detail in Chapter 96.

PATHOGENESIS

Although *Aspergillus* species are not obligate pathogens, their evolution to survive in decomposing organic matter has provided them with mechanisms that contribute

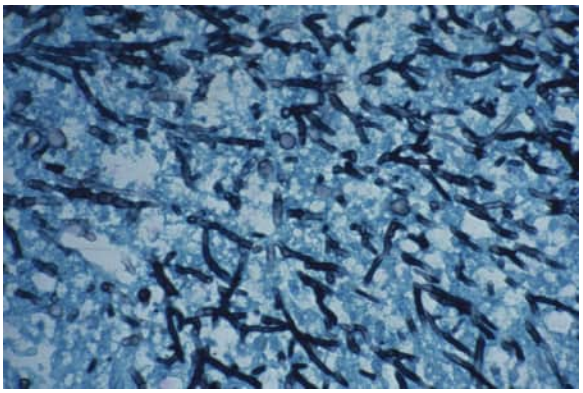

Figure 57.3 Invasive aspergillosis. Micrograph shows findings of invasive *Aspergillus* infection represented by septate hyphae with finger-like branching at acute angles. (Methenamine silver stain; ×450 original magnification.)

to virulence in humans and other mammals. *Aspergillus* possesses multiple defenses against reactive oxygen intermediates; some of these defenses include melanin,[122] catalases,[123] superoxide dismutases,[124] and glutathione transferases.[125] *Aspergillus* is also able to survive in hypoxic environments, which may confer a survival advantage when it renders tissues hypoxic by invading blood vessel walls. Other mechanisms that may contribute to pathogenesis include production of diverse toxins, including gliotoxin and fumagillin, and secretion of elastase, which may promote tissue invasion.[126]

Work in humans and in murine models has provided considerable insight into the elements and mechanisms of innate and adaptive immune responses that provide protection against invasive *Aspergillus* infections (see Chapters 15 and 16).[127–130] *Aspergillus* spores possess a hydrophobic protein coat made up of rod-shaped structures (rodlets), which mask the cell wall and prevent recognition by innate immune receptors.[131] This allows individuals to inhale millions of fungal spores every day without induction of an inflammatory response. Spores that swell and germinate before being killed expose the fungal cell wall that contains multiple pathogen-associated molecular patterns recognized by innate immune cells. In particular, β-D-glucan is recognized by host dectin-1, which initiates production of proinflammatory cytokines and chemokines, and modulates differentiation of $CD4^+$ T cells. The importance of specific pathways of innate immune recognition has been demonstrated by finding that HCT recipients who receive donor cells that possess sequence variants of toll-like receptor 4 or dectin-1 are at increased risk for invasive *Aspergillus* infections.[132–134] Other important elements of innate immunity have been identified by finding that polymorphisms of mannose-binding lectin,[135,136] chemokine (C-X-C motif) ligand 10 (CXCL-10),[137] tumor necrosis factor,[138,139] plasminogen,[140] and others[141,142] are associated with increased susceptibility to ABPA or IA in certain populations. In humans and mice, $CD4^+$ T cells also contribute to defense against IA; both Th1 and Th17 cells contribute to optimal immunity. In contrast, excessive Th2 responses contribute to the pathogenesis of ABPA.

INFECTION TYPES

Invasive Pulmonary Aspergillosis

Epidemiology and Pathogenesis. IPA is the most severe form of pulmonary aspergillosis and is a major cause of fungal morbidity and mortality. It is seen most commonly in immunocompromised hosts, including transplant recipients and those with advanced HIV infection, primary immunodeficiency diseases including chronic granulomatous disease, and hematologic malignancies. In a retrospective Italian cohort of nearly 12,000 patients with hematologic malignancies, more than half of the 538 proven or probable IFIs were due to molds, primarily *Aspergillus,* and patients with acute myelogenous leukemia were most commonly affected.[143] The elevated risk in this population is primarily driven by prolonged neutropenia induced by cytotoxic chemotherapy.[144] The application of targeted immunomodulating therapies is changing the epidemiologic landscape of IFIs, including IPA, in hematologic malignancy as well as other patient populations. For example, historically lower risk groups for IFIs, such as patients with chronic lymphoproliferative disorders, are increasingly diagnosed with IFIs with pathogens such as *Aspergillus*, including disseminated infections to the CNS, when treated with ibrutinib, an irreversible inhibitor of Bruton tyrosine kinase.[145] Multicenter, prospectively obtained epidemiologic data confirm *Aspergillus* as the most common cause of invasive mold infection in both HCT and SOT recipients.[30,31] In HCT recipients, *Aspergillus* is the most common IFI overall, predominantly seen during two periods: (1) early after transplantation during neutropenia, and (2) after engraftment, in the setting of graft-versus-host disease. Of the SOT patients, lung transplant recipients are at highest risk for IPA. IPA has also been described in critically ill patients in the intensive care unit lacking "traditional" risks but with underlying comorbidities including renal failure, diabetes, COPD, and cirrhosis[146–148] and in association with severe influenza infections.[149,150]

IPA is characterized by tissue invasion, frequently involving blood vessels. Hyphae within the alveoli penetrate the respiratory mucosa and alveolar capillaries into endothelial cells and pulmonary arterioles. Cell injury and inflammation contribute to intravascular thrombosis, local hypoxia, and necrosis. Angioinvasive disease is accompanied by tissue infarction and coagulative necrosis, whereas nonangioinvasive disease is more commonly associated with pyogranulomatous inflammation and inflammatory necrosis.[151]

Clinical Presentation and Diagnosis. The clinical presentation of IPA typically involves fever, cough, hemoptysis, and pleuritic chest pain. Angioinvasive IPA is seen predominantly in the setting of neutropenia during which progression can be rapid, with clinical deterioration over hours to days. Patients with disseminated disease may have additional symptoms related to other sites of infection. *Aspergillus* can extend directly to surrounding areas, including the chest wall (see eFig. 123.27),[152] mediastinum, and great vessels.[153]

Early diagnosis of IPA is essential for prompt initiation of therapy, which has been associated with improved survival.[154] However, multiple factors make the diagnosis

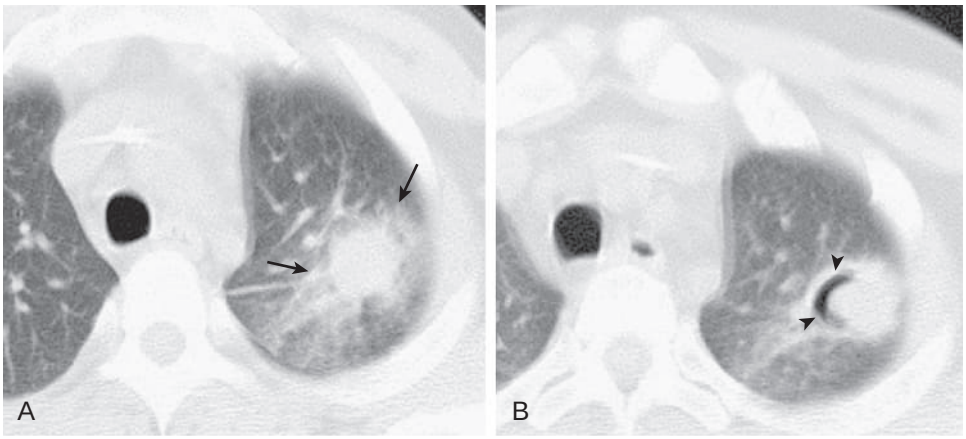

Figure 57.4 Invasive pulmonary aspergillosis. (A) Axial chest computed tomography displayed in lung windows performed in a hematopoietic cell transplant recipient during profound neutropenia demonstrates a poorly defined nodule with surrounding ground-glass opacity (*arrows*) representing the halo sign. (B) The nodule has become cavitary (*arrowheads*), representing the air crescent sign. (Courtesy Michael B. Gotway, MD.)

difficult, including the lack of symptoms early in the course of illness, challenges in obtaining appropriate tissue for histopathology and culture in critically ill or cytopenic hosts, and the variable sensitivity and specificity of many of the available diagnostic tests. Imaging findings associated with IPA are often nonspecific, including nodules (see eFig. 123.27B), consolidation (see eFig. 125.3), cavitation (see eFigs. 123.26A–B and 123.27), and effusions (see eFig. 125.3). The halo sign, demonstrated by ground-glass opacities surrounding a pulmonary nodule, is the result of alveolar hemorrhage around an infarcted area of the lung (Fig. 57.4A, see eFig. 125.3) and is typically seen early in the course of infection.[155] The halo sign has a high specificity for IPA in neutropenic patients.[156] The air crescent sign tends to be seen later in the course of infection (typically with recovery of neutrophils in the neutropenic host) and represents air that has filled the space between necrotic and healthy lung tissue (see Fig. 57.4B).[157]

Direct microscopy of sputum or BAL lacks both sensitivity and specificity.[158] Histopathologic evaluation of tissue specimens using standard hematoxylin and eosin, periodic acid–Schiff, and/or Gomori's methenamine silver staining with demonstration of characteristic hyphae supports the diagnosis of IPA (see Fig. 57.3), but culture is required to confirm the identity of the pathogen. Furthermore, in up to 70% of tissues with evidence of invasive septate hyphae, *Aspergillus* fails to grow in culture.[159] When positive, cultures for most *Aspergillus* species typically grow within 48 to 72 hours.[160] The application of molecular assays directly to fresh or formalin-fixed paraffin-embedded tissue specimens has also been employed in the diagnosis of *Aspergillus*, though this testing lacks standardization and is not currently approved by the FDA for clinical use.

Other primary diagnostic modalities for *Aspergillus* include assays for fungal *galactomannan* (GM) and β-D-glucan. GM is a heteropolysaccharide component of the cell wall of *Aspergillus* and other fungi released during hyphal growth. Platelia *Aspergillus* EIA (Bio-Rad Laboratories) is an FDA-approved, commercially available test for detecting GM in serum and in BAL specimens from patients with hematologic malignancies and recipients of HCT. The positive cutoff value is an *optical density index* (ODI) of 0.5. A meta-analysis of 27 studies using surveillance serum GM in immunocompromised hosts with invasive *Aspergillus* reported an overall sensitivity and specificity of 71% and 89%, respectively.[161] Subgroup analysis showed that test performance was higher in patients with hematologic malignancy (sensitivity, 70%; specificity, 92%) and in HCT recipients (sensitivity, 82%; specificity, 86%) compared to SOT recipients (sensitivity, 22%; specificity, 84%). The poor performance of serum GM testing in the SOT population resulted in the recommendation that it not be used in cardiothoracic organ transplant recipients in guidelines from the *International Society for Heart and Lung Transplantation* (ISHLT).[162] Better performance in patients with hematologic malignancies and in those undergoing HCT may be related to the higher likelihood of neutropenia and angioinvasion in these populations, which, in turn, is associated with increased GM release into the circulation.[163] Other factors that influence the utility of the GM assay include cross reactivity with other fungi (e.g., *Alternaria, Fusarium, Geotrichum, Histoplasma, Paecilomyces,* and *Penicillium*), false-positive results secondary to the presence of GM in antimicrobials[164] and nutritional supplements,[165] and lower sensitivity with the concomitant administration of antifungal therapy.[166,167] The magnitude of GM and/or trend with serial testing may predict clinical outcomes.[168,169]

Assaying BAL specimens for GM complements testing of serum, particularly in a non-neutropenic host with IPA who may lack a positive serum GM. A meta-analysis of 30 studies evaluating BAL GM using a cutoff ODI of 0.5 for proven and probable IA found an overall sensitivity of 87% and specificity of 89%. Compared to serum GM, BAL GM had a higher sensitivity but a lower specificity.[170] Increasing the positive ODI cutoff value from 0.5 to 1.0 improved specificity, albeit with some compromise to sensitivity (from 88–78% based on a more contemporary meta-analysis of 17 studies).[171] The ideal ODI cutoff in BAL specimens remains uncertain. In the lung transplant population, high rates of colonization with molds such as *Aspergillus* and *Penicillium* can result in false-positive tests for BAL GM, thereby limiting application in this population.[172] However, the BAL GM is considered an acceptable diagnostic modality for cardiothoracic organ recipients in the current ISHLT guidelines.[162] Standardization of the process of GM testing in BAL

is also imperative because certain factors, such as the volume of BAL collected, have been shown to impact results significantly.[167]

Assays of β-D-glucan, another fungal cell wall component, may detect many medically relevant fungal pathogens, including *Aspergillus*, *Candida*, and *Pneumocystis*, based on the abundance of β-D-glucan in their cell wall. Noted exceptions include *Cryptococcus* and the agents of mucormycosis.[173] The FDA-approved assay, the Fungitell test, has a positive cutoff value of 80 pg/mL or more (sensitivity, 64%; specificity, 92%) for patients with proven or probable IA.[174] Compared to GM, β-D-glucan may be detectable earlier in the course of IA.[175] False-positive β-D-glucan results happen, associated with cellulose membranes used in hemodialysis,[176] intravenous immunoglobulin and other blood products,[177,178] and bacterial bloodstream infections.[173,179] In a study to assess the utility of serial monitoring in lung transplant recipients with the β-D-glucan assay, 90% of subjects without an IFI had at least one positive β-D-glucan result (≥80 pg/mL), leading to a low PPV (9%).[175] Similar issues were encountered when β-D-glucan assays were used to monitor for invasive candidiasis in an intensive care unit setting; 45% of subjects had false-positive results ultimately attributed to receipt of intravenous immunoglobulin and hemodialysis.[90] These issues resulted in ISHLT guidelines not recommending β-D-glucan testing in the cardiothoracic populations.[162]

Nucleic acid-based tests (NATs), including real-time PCR, have the potential for specificity to the genus and species level and, while many laboratory-developed and commercial *Aspergillus* NAT tests exist, there is currently no FDA-approved *Aspergillus* NAT for testing clinical specimens. The European *Aspergillus* PCR initiative was established to standardize PCR testing for clinical use and has defined methods for specimen processing and nucleic acid extraction so that PCR testing will be included in the new *Mycoses Study Group/European Organization for Research and Treatment of Cancer* (MSG/EORTC) definitions for IA.[180] However, the kinetics of *Aspergillus* nucleic acid circulation in the systemic circulation are incompletely understood and may be intermittent and/or influenced by angioinvasion and receipt of prophylactic antifungals, as is also seen with GM. Accordingly, performance of a NAT test will likely have different performance characteristics in different patient populations and with different specimen types. White et al[181] found the sensitivity of PCR was higher while the specificity was lower than that of GM and β-D-glucan, with an overall high negative predictive value. A meta-analysis evaluating PCR testing in blood, primarily in high-risk patients with hematologic malignancy and/or undergoing HCT, found lower sensitivity (58%) but improved specificity (96.2%) by requiring two consecutive positive test results.[182] A combined monitoring strategy in high-risk hematologic malignancy and HCT patients utilizing serum GM and *Aspergillus* PCR was associated with an earlier diagnosis of IA, suggesting these blood tests may be used to complement, rather than replace, one another.[183] Regarding BAL testing, studies of a commercially available *Aspergillus* PCR assay in BAL collected from lung transplant recipients suggested the assay performs more as a detection test for the presence of *Aspergillus* rather than as a diagnostic test for invasive disease. Accordingly, BAL PCR results should be used as a diagnostic test only in combination with other tests (e.g., radiology, culture).[184] Avni and associates[185] found improved sensitivity with stable specificity when BAL PCR and BAL GM were used together, suggesting an advantage to combination testing.

Newer diagnostic tests, including LFAs to detect antigens secreted during the growth of *Aspergillus* species, may provide rapid and inexpensive point-of-care testing.[186] Data evaluating the application of LFAs to urine,[187] serum,[188] and BAL[189] in comparison to and in combination with other diagnostic tests, including GM and PCR, are promising.

Diagnostic criteria for IPA have been proposed by the MSG/EORTC and include proven, probable, and possible IA.[190] A diagnosis of proven IPA requires microscopic evidence of *Aspergillus* tissue invasion or a positive culture from a normally sterile site. A diagnosis of probable IPA requires an at-risk host, corroborating radiographic findings, and direct or indirect mycologic evidence. An updated revision of these definitions is forthcoming.[191] Other clinical algorithms continue to be introduced to assist in differentiating *Aspergillus* colonization from true IPA in critically ill intensive care unit patients without clear predisposing host factors (as identified by MSG/EORTC) but with positive respiratory specimens and/or clinical concern for IPA.[192]

Treatment. As with other IFIs, management of IPA may involve a combination of surgical, pharmacologic, and other adjunctive interventions. Attempts to restore host immunity should be made wherever feasible, being mindful of the risk for IRIS.[193] Indications for surgical intervention include life-threatening hemoptysis, presence of lesions contiguous to the great vessels and/or pericardium, and invasion of the chest wall, as well as presence of isolated lesions in patients with impending intensive chemotherapy or HCT.[121] Based on recommendations from both IDSA[121] and ATS[57] and data from a large prospective randomized trial of IA that demonstrated significantly better response and overall survival in those treated with voriconazole than those treated with AmB-d, the drug of choice for IPA is voriconazole.[194] Therapy is typically administered intravenously in critically ill patients and in patients otherwise not tolerating oral therapy, with transition to the oral route once patients stabilize and can tolerate oral medications. While most patients are treated for a minimum of 6 to 12 weeks, the total duration of therapy for IPA is not clearly defined and is dependent upon the immune status of the host and clinical response to treatment (eFig. 57.3).

Isavuconazole, the newest extended-spectrum azole, is also FDA approved for first-line treatment of IA. This approval was based on a randomized controlled trial in 527 patients with suspected IFI wherein isavuconazole demonstrated noninferiority to voriconazole on the basis of the primary end point of 42-day all-cause mortality in the intent-to-treat population (19% with isavuconazole, 20% with voriconazole).[195] Significantly fewer patients in the isavuconazole treatment arm reported drug-related adverse events (109 [42%] vs. 155 [60%]; $P < 0.001$), including fewer hepatobiliary, eye, and skin disorders. In subgroup analysis, voriconazole had greater success among patients with unresolved neutropenia.[196] This latter finding may prove significant given reports of breakthrough IA and other IFIs when applying isavuconazole as

prophylaxis in high-risk hematologic malignancy and HCT patients.[197] However, clinical trials demonstrating isavuconazole efficacy in the prophylactic setting are lacking and breakthrough reports remain limited to retrospective, single-center experiences.[197–199]

Posaconazole may be an effective alternative to voriconazole or isavuconazole, although it has not been studied as primary treatment. In patients with IA who are refractory to or intolerant of other antifungal therapies, response to posaconazole was superior (45 of 107; 42%) compared with the external control group (22 of 86; 26%), the latter primarily treated with AmB or itraconazole.[200] Other researchers have also shown success with posaconazole as salvage therapy in patients receiving prior voriconazole.[201,202]

The emergence of azole resistance among fungal pathogens, including *Aspergillus*, is an important clinical concern. Resistance acquisition is typically dependent on scenarios of prolonged azole exposure, such as in treatment for CPA.[203] However, it is more commonly described in association with environmental exposure and broad application of azoles as fungicides in agricultural settings[204] for which the mechanism of resistance involves mutations (TR34/L98H or TR46/Y121F/T289A) in *cyp51A*, which encodes the azole target, 14-α-demethylase.[205] Importantly, the TR34/L89H mutation confers resistance to all mold-active azoles, and clinical infections with isolates carrying these mutations have been associated with poor outcomes.[206] A prospective international surveillance study reported this acquired azole resistance in *A. fumigatus* to be widespread in Europe, detected in 3.2% of *A. fumigatus* clinical isolates recovered in 11 of 17 European centers in nine countries,[207] but with a prevalence as high as 30% in one HCT center in Germany.[208] Based on passive surveillance data accrued since 2011 in the United States, seven such isolates have been recovered from clinical specimens in three states in the United States, and notably, four of the seven patients had no known previous exposure to antifungal medications.[209] The emergence of such resistant isolates emphasizes the importance of susceptibility testing as a tool for informing clinical care. The Clinical Laboratory Standards Institute[210] has standardized methods for performing antifungal susceptibility testing on fungi. Although Clinical Laboratory Standards Institute interpretive breakpoints defining clinical resistance are limited to those for *A. fumigatus* to voriconazole, epidemiologic cutoff values (the upper limit of the wild-type MIC distribution range) are useful for detecting isolates with potential resistance mutations (i.e., if the isolate's MIC is greater than the epidemiologic cutoff value, then the isolate may harbor a resistance mutation).[211] IDSA clinical practice guidelines[121] currently recommend antifungal susceptibility testing for *Aspergillus* species only in cases of suspected azole resistance, including for patients who are unresponsive to therapy; however, other international experts advocate screening in all patients requiring antifungal therapy in regions where the prevalence of azole resistance is high.[212]

Polyenes are used for the treatment of IPA in patients refractory to or intolerant of azoles. The lipid formulations of AmB are currently preferred because of their reduced nephrotoxicity compared with that of AmB-d. Currently, the IDSA recommends ABLC 5 mg/kg/day or LAmB 3 to 5 mg/kg/day for the treatment of IPA.[121] LAmB 3 mg/kg/day was compared with LAmB 10 mg/kg/day in a double-blind trial of patients with proven or probable IA to assess whether higher doses would improve response; there was no clinical advantage with the higher dose, but there was significantly more hypokalemia and nephrotoxicity.[213]

Echinocandins are an appealing option for IA given their favorable toxicity profile and lack of significant drug interactions. However, echinocandins are static against *Aspergillus,* and use is typically limited to patients who are refractory to or intolerant of other first-line therapies or in combination regimens. Randomized controlled trials evaluating echinocandins as primary therapy for IA are lacking. Maertens et al[214] evaluated 83 adults with proven or probable IA refractory to or intolerant of standard anti-*Aspergillus* therapy, including 64 with IPA, who were treated with caspofungin; 45% (50% of those with IPA) obtained a complete or partial response. Based on these data, caspofungin was cleared by the FDA as salvage therapy for IA. For micafungin, a large report from Japan indicated a 71% (90 of 130) clinical response rate in patients with IA treated with micafungin monotherapy (doses ranged from 50 to 300 mg/day)[215] but, in other reports, response rates ranged from 38–44%.[216,217] To date, minimal data exist for anidulafungin as monotherapy in the treatment of IA.

Given the high mortality associated with IPA and emerging concerns for azole-resistant *Aspergillus* isolates, combination therapy is often considered. While in vitro and in vivo data support a role for combination therapy,[218,219] it is not recommended first line in all patients with IA due to the lack of significant supporting data from randomized controlled trials. When combination therapy is used, echinocandins are most often paired with polyenes or azoles based on their activity at a different site: the echinocandins act on the fungal cell wall while the azoles and polyenes act on the fungal membrane. A large randomized controlled trial comparing voriconazole monotherapy with combination voriconazole plus anidulafungin for IA in high-risk patients with hematologic malignancy or HCT failed to show significant benefit with the combination in 6-week mortality.[220] However, subgroup analysis showed a significant reduction in 6-week mortality in patients diagnosed with probable IA based on the combination of radiographic imaging and serum or BAL GM testing, possibly reflecting earlier disease. On the basis of available data, current IDSA guidelines suggest use of combination therapy with echinocandins and voriconazole in severe disease, particularly in patients with hematologic malignancy and/or prolonged neutropenia.[121] Other expert consensus supports combination therapy in regions with high prevalence of azole resistance (defined as >10%) until susceptibility can be confirmed.[212] Additional adjunctive measures used to optimize outcomes of IPA include granulocyte or granulocyte-macrophage colony-stimulating factor, interferon-gamma, and granulocyte infusions.[121]

Invasive Tracheobronchial Aspergillosis

Epidemiology and Pathogenesis. While there can be saprophytic, allergic, and invasive forms of *tracheobronchial aspergillosis* (TBA), this section focuses on invasive TBA. TBA can be seen alone or with IPA and should be considered as a spectrum, including mild tracheobronchitis and obstructive, ulcerative, and pseudomembranous TBA, often with

more than one form present concurrently.[221] Mild tracheobronchitis demonstrates only superficial mucosal inflammation; obstructive, ulcerative, and pseudomembranous forms may be superficial or progress to involve the entire bronchial wall with necrotizing tracheobronchitis and invasion of the surrounding tissue.[222] A rare form of IPA, TBA is most commonly encountered in lung and heart-lung transplant recipients,[223,224] although it has been reported in other patient populations including those with advanced HIV,[225] diabetes,[226] COPD,[227,228] and hematologic malignancies, and those undergoing HCT.[229,230]

Clinical Manifestations, Diagnosis, and Treatment. In lung and heart-lung transplant recipients, TBA is often discovered early in the posttransplant period when patients may have asymptomatic ulceration and/or pseudomembrane formation at the bronchial anastomotic site visible by bronchoscopy (Fig. 57.5).[231] In contrast, patients with hematologic malignancies are typically symptomatic at the time of discovery, with productive cough, dyspnea, fever, wheezing, stridor, hemoptysis, and respiratory failure.[221,228] Early diagnosis is crucial given the potential for progressive symptoms and disseminated infection and complications, including bronchial obstruction, anastomotic rupture, and bronchopleural or bronchoarterial fistulas.[223,232] While chest imaging may demonstrate bronchial wall thickening, luminal narrowing, and/or endobronchial lesions (eFig. 57.4),[228,233] the findings are not diagnostic. Serum GM is often of limited value for isolated tracheobronchial aspergillosis.[234] Diagnosis is made via bronchoscopy with visualization of plaques, ulceration, pseudomembranes, and obstructive mucous plugs and/or masses (Fig. 57.6) together with pathologic and microbiologic findings.

Treatment of TBA is similar to that for other forms of IPA.[121] Voriconazole is the preferred first-line therapy; other antifungals, including isavuconazole, posaconazole, AmB, and echinocandins, may be used. Systemic therapy has also been combined with aerosolized and topical endobronchial application of AmB in severe TBA in lung transplant recipients.[235] In addition to pharmacologic therapy, bronchoscopic débridement with removal of obstructive lesions may be necessary but can be associated with significant bleeding.[236,237] Other adjunctive approaches, including serial dilation and airway stenting in cases of pseudomembranous TBA with airway obstruction, have been described.[238]

Chronic Pulmonary Aspergillosis

Epidemiology and Definitions. CPA, based on consensus definitions,[239] is an overlapping spectrum of clinical entities differentiated by the affected host, clinical presentation, and radiographic findings. It includes *Aspergillus* nodule(s), aspergilloma, *chronic cavitary pulmonary aspergillosis* (CCPA), *chronic fibrosing pulmonary aspergillosis* (CFPA), and *subacute invasive pulmonary aspergillosis* (SIPA), the latter formerly called chronic necrotizing pulmonary

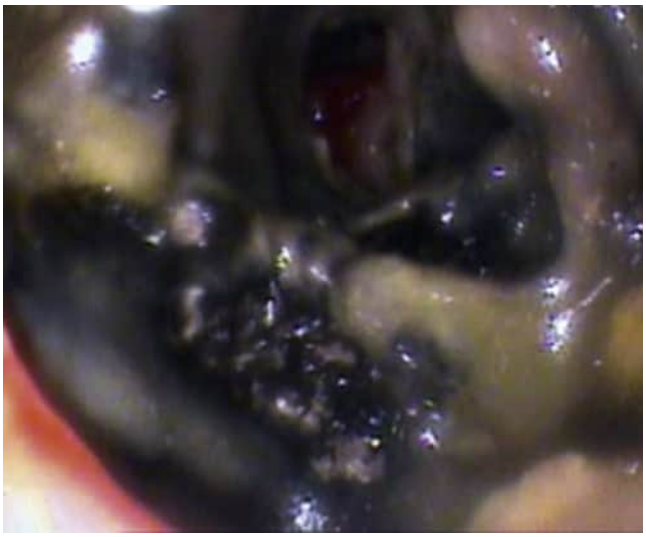

Figure 57.5 Tracheobronchial aspergillosis. Bronchoscopic visualization of the right mainstem bronchus in a lung transplant recipient demonstrates tracheobronchial aspergillosis with *Aspergillus fumigatus*. Stenosis and extensive necrotic pseudomembranes and debris are seen at the anastomotic site. (Courtesy Dr. Scott Shofer, Duke University Medical Center, NC.)

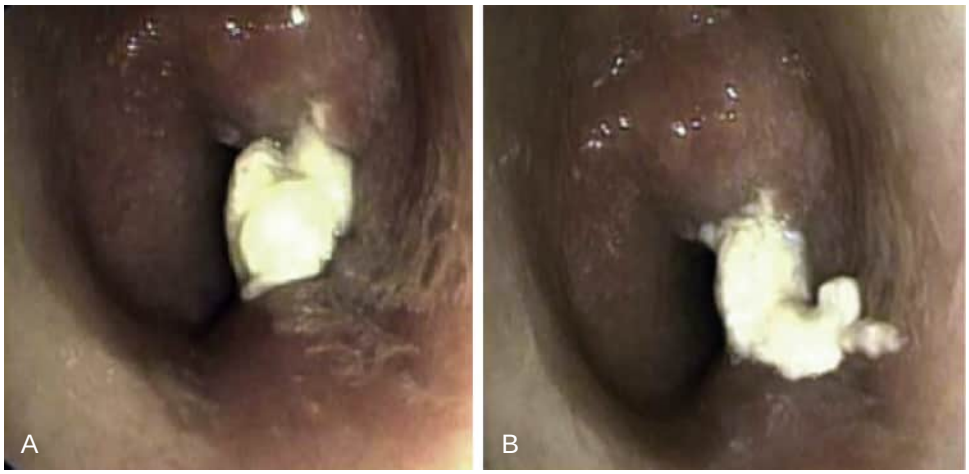

Figure 57.6 Tracheobronchial aspergillosis. Subglottic mass in a patient with a hematologic malignancy and prolonged neutropenia with histopathologic and culture data consistent with *Aspergillus fumigatus* tracheobronchial aspergillosis. (A) Bronchoscopic visualization beyond the vocal cords revealing a friable subglottic tracheal mass with surrounding mucosal edema resulting in approximately 50% obstruction. (B) Movement of the mass with breathing creating a ball-valve, extrathoracic obstruction. (A, closing partially with inspiration; B, opening partially with expiration.) (Courtesy Kamran Mahmood, MD, MPH, Duke University Medical Center, NC.)

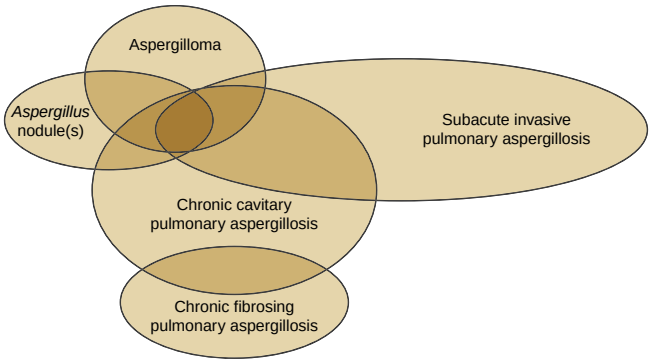

Figure 57.7 The overlapping spectrum of chronic pulmonary aspergillosis. (From Denning DW, Cadranel J, Beigelman-Aubry C, et al: European Society for Clinical Microbiology and Infectious Diseases and European Respiratory Society. Chronic pulmonary aspergillosis: rationale and clinical guidelines for diagnosis and management. *Eur Respir J.* 2016;47[1]:45–68.)

aspergillosis (Fig. 57.7). It affects at least three million individuals worldwide.[240] Aspergillus nodule(s), a rare form of CPA, is characterized by one or more nodules, with or without cavitation, and without an invasive component.[241] This generally benign entity is often diagnosed when a nodule is removed due to concerns for malignancy. An aspergilloma (or fungus ball) develops within a preexisting pulmonary cavity; it is a tangled mass of fungal hyphae, cellular debris, mucus, and fibrin that may or may not adhere to the cavity wall. It can be seen in all forms of CPA except *Aspergillus* nodules. CCPA, the most common form of CPA, is characterized by multiple cavities, with or without intracavitary aspergillomas, alongside pulmonary and systemic symptoms demonstrated over at least a 3-month period.[242] Progression of untreated CCPA can result in expanding cavitation, pericavitary opacities, and even pleural involvement. Further, CCPA can progress to CFPA, defined by marked fibrosis and irreversible fibrotic destruction of at least two lobes of the lung.

Most subtypes of CPA are found in apparently immunocompetent individuals with structural lung disease due to prior or concomitant etiologies such as infections with mycobacteria[243] and other fungi,[244,245] sarcoidosis, lung cancer, cystic fibrosis, COPD, or asthma.[242] In contrast, SIPA is a subtype of CPA that is invasive and spans the boundaries of both IPA and CPA in patients with variable degrees of immunosuppression and/or comorbidities including diabetes, alcoholism, and advanced HIV.[246,247] SIPA is associated with more rapid progression than CCPA. Further, this notion of a reasonably "immunocompetent" host in most subtypes of CPA is continually challenged as underlying immune defects and genetic polymorphisms associated with CPA are increasingly understood.[135,136,248]

CPA is most commonly caused by *A. fumigatus* but can be seen with non-*fumigatus Aspergillus* molds. It can be confused with other infectious processes, including chronic lung infections due to mycobacteria or other fungal pathogens such as endemic fungi and non-*Aspergillus* molds,[249–252] as well as lung cancer.

Clinical Presentation and Diagnosis. Patients with *Aspergillus* nodules and aspergillomas are often asymptomatic, with lesions discovered incidentally on chest imaging. Aspergillomas may remain stable and asymptomatic

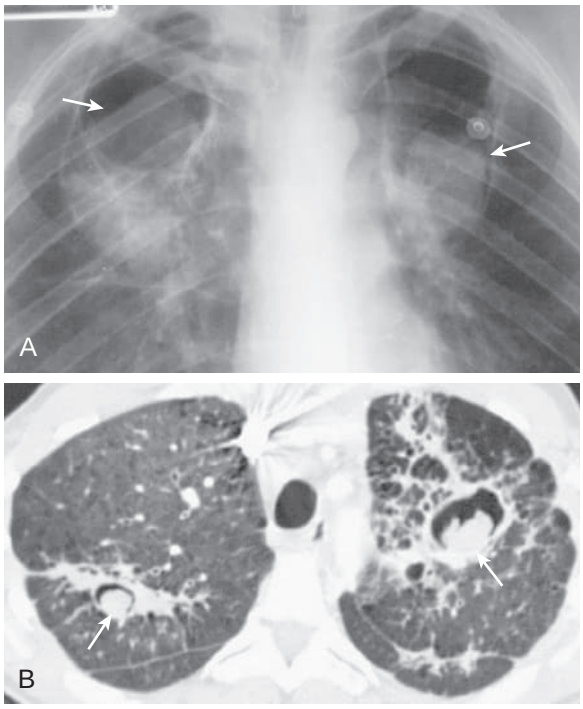

Figure 57.8 Aspergillomas in sarcoidosis cavities. (A) Frontal chest radiograph in a patient with sarcoidosis demonstrates biapical thin-walled cavities containing rounded intracavitary opacities (*arrows*) that represent aspergillomas. (B) Axial chest computed tomography displayed in lung windows performed in another patient with sarcoidosis demonstrates biapical aspergillomas (*arrows*). The background bronchovascular thickening and subpleural nodularity reflects sarcoidosis. (Modified from Gotway MB, Dawn SK, Caoili EM, et al: The radiologic spectrum of pulmonary *Aspergillus* infections. *J Comput Assist Tomogr.* 2002;26:159–173.)

over long periods, regress, spontaneously resolve, or progressively enlarge.[253] Symptoms, when present, are most commonly cough, shortness of breath, and hemoptysis; hemoptysis may develop in up to of 85% of cases and ranges from mild to life-threatening.[253,254] Systemic symptoms, including fever, fatigue, weight loss, and night sweats, are more commonly seen in CCPA, CFPA, and SIPA.

Radiographically, *Aspergillus* nodules may be single or multiple cavitary or noncavitary nodules (eFig. 57.5). Aspergillomas are typically found in the upper lung fields and classically appear as a solid rounded mass within a cavity (Fig. 57.8). The mass may be mobile (eFig. 57.6) or adherent to the cavity wall; peripheral lesions may be associated with pleural thickening. Imaging findings with CCPA and SIPA show cavities of variable wall thickness (eFig. 57.7), consolidation, and pericavitary opacities often with varying degrees of associated pleural thickening.[239,242] Overlap between these two entities exists, and differentiation is often made based on the clinical presentation and radiographic progression, which are both typically more indolent in CCPA compared with SIPA.[255] CFPA is demonstrated by the development of extensive concomitant pulmonary fibrosis.

Diagnostic criteria for CPA have been proposed by the *European Society of Clinical Microbiology and Infectious Disease and European Respiratory Society* (ESCMID/ERS)[242] and the IDSA[121]; however, differences exist in these criteria, particularly in the types of direct or indirect evidence for *Aspergillus* accepted for definitive diagnosis.[256] In general,

diagnosis requires incorporation of patient history and clinical presentation, characteristic radiographic imaging findings across time, and evidence of *Aspergillus* infection or an immunologic response to *Aspergillus* antigens. Further, to be classified as CPA, disease must be present for a minimum of 3 months. *Aspergillus* IgG or precipitins are detectable in serum of nearly all patients (>90%) with an aspergilloma[239,242] though *Aspergillus* IgG testing is preferred because it is a more sensitive and overall superior test compared to *Aspergillus* precipitins in diagnosing CPA.[240] Respiratory cultures and biopsy specimens may be positive for *Aspergillus,* and other diagnostic tests such as a positive serum and/or BAL GM or PCR as well as elevated erythrocyte sedimentation rate or C-reactive protein further support the diagnosis. Histopathologic findings of resected pulmonary lesions demonstrate chronic inflammation with hyphae within the cavities, with or without granulomas. The presence of invasion into surrounding tissues or vasculature signals the presence of either SIPA or IPA and should not be seen with the other forms of CPA.

Treatment. The goals in treatment of CPA include symptom reduction and prevention of disease progression. Due to the overall rarity of disease, optimal treatment has not been defined and is based in large part on expert opinion and data derived from cohort studies and case reports.[121,242] For aspergillomas in asymptomatic patients with stable lesions, monitoring alone is sufficient. In symptomatic patients, particularly with hemoptysis or progressing lesions, the primary curative approach is surgical resection. However, surgical resection remains a high-risk intervention in individuals with lung disease and poor pulmonary reserve. Potential complications include contamination of the pleural space and *Aspergillus* empyema, persistent hemorrhage, and death.[257] Application of pre-, peri-, and postoperative antifungal therapy is recommended in cases wherein spillage and pleural contamination are possible.[121,257] Bronchial artery embolization may be used as a temporizing measure in the setting of acute bleeding. Nonsurgical interventions in symptomatic patients include direct intracavitary instillation of antifungal agents such as AmB, nystatin, natamycin, and itraconazole via endobronchial and percutaneous CT-guided approaches; they may further reduce fungal burden and the risk of recurrent bleeding but are not curative.[258–260]

The primary treatment of selected cases of aspergilloma and the remaining types of CPA is systemic antifungal therapy. Indications for surgical intervention in CPA outside of aspergilloma include persistent hemoptysis or other evidence of refractory disease, including azole-resistant *Aspergillus*.[121,242] Azoles are most commonly used, and the preponderance of data are with oral itraconazole, which is considered first-line therapy.[261–265] The only randomized controlled trial of itraconazole in CPA compared itraconazole ($n = 17$) to supportive care ($n = 14$) and demonstrated higher overall response rates (defined as a composite of clinical and radiographic response) in the itraconazole group compared with the control group (76.5% vs 35.7%, respectively; $P = 0.02$). Voriconazole[266–271] is now considered a first-line therapy, and posaconazole[271–274] is also utilized in this setting. Major concerns with long-term azole administration are the emergence of resistance and toxicities. Toxicities of particular concern with extended use of voriconazole include the development of skin cancers.[203,271,275,276] Isavuconazole demonstrated improved overall tolerability in patients treated for CPA compared with voriconazole.[277] Intravenous agents such as LAmB and echinocandins are typically reserved for patients refractory to or intolerant of azoles, including those with azole-resistant *Aspergillus* infections and/or severe disease.[242] Duration of therapy is a minimum of 4 to 6 months; however, in responders, therapy is often continued indefinitely.

MUCORMYCOSIS

EPIDEMIOLOGY

Mucormycosis is caused by molds in the order Mucorales in the subphylum Mucormycotina.[278] *Rhizopus* and *Mucor* are the genera most commonly associated with infections although *Lichtheimia, Apophysomyces, Cunninghamella, Rhizomucor, Saksenaea* complex, *Syncephalastrum,* and others also cause disease.[279–286] These are ubiquitous molds found in soil and decaying plant material that gain access to the host via inhalation, skin penetration, or, less commonly, ingestion. Infection sites include skin and soft tissue, rhino-orbital-cerebral, gastrointestinal, and lower respiratory tract, as well as disseminated infection with multiorgan involvement.[279,283,286,287] Mortality rates are as high as 96% in patients with disseminated disease.[286] In a comprehensive review and meta-analysis of 851 cases of mucormycosis from 2000 to 2017, the most commonly affected patients had diabetes (340 of 851; 40%), and the most frequent presentation was sinus involvement, including rhino-orbital-cerebral infections.[279] Hematologic malignancy was the second most common underlying condition (275 of 851; 32%), most often acute myeloid leukemia (116 of 275; 42%), and pulmonary infection predominated. Based on a prospectively maintained database across multiple centers, mucormycosis is the third most common IFI in the HCT population, representing 8% of IFIs[31] compared with 2% of IFIs in SOT recipients.[30] Surveillance data suggest an increasing incidence of mucormycosis.[31,286,288,289] Further, there are multiple reports of "breakthrough" mucormycosis in patients receiving azole therapy, most notably voriconazole, which lacks activity for Mucorales species,[290–293] although reports are also emerging with isavuconazole,[197,198] which has activity against some species. These reports raise the question of whether the antifungal therapies pose a unique risk, perhaps by increasing pathogen virulence as suggested in fly and murine models.[294,295] However, this association is likely multifactorial, including changes in immunosuppression and improved patient survival across time, and not solely attributable to the antifungal therapies.

PATHOGENESIS

After fungal spores gain access to the host, mononuclear and polymorphonuclear phagocytes normally serve as a primary host defense against invasion.[296] However, hyperglycemia and acidosis in people with poorly controlled diabetes impair phagocyte function.[297] Moreover, growth of pathogenic Mucorales is enhanced by free iron; thus iron

overload and treatment with deferoxamine, which behaves as a siderophore that increases iron availability to the fungus, are associated with mucormycosis. Likewise, systemic acidosis increases free iron by decreasing iron binding to transferrin.[287] Similar to *Aspergillus* and certain other pathogenic molds, mucormycosis is angioinvasive, resulting in thrombosis, infarction, and tissue necrosis, with risk for dissemination to other sites. One mechanism that may promote angioinvasion by *Rhizopus arrhizus* (also called *R. oryzae*) is glucose- and iron-induced expression of glucose-regulated protein 78 by vascular endothelial cells, which promotes binding of *Rhizopus* to endothelial cells in vitro and in vivo.[298]

CLINICAL MANIFESTATIONS

Pulmonary mucormycosis is often acute and severe, particularly in neutropenic patients, with fever, cough, dyspnea, pleuritic chest pain, and hemoptysis.[299,300] In patients with diabetes, the course may be more subacute.[301] Pulmonary involvement may also be associated with life-threatening hemoptysis due to vascular invasion by the fungus, and the infection may disseminate or expand locally to involve contiguous structures, including the mediastinum and chest wall.[299] Although uncommon, bronchopleural, bronchocutaneous, and bronchoarterial fistulas have been reported.[299,302] Tracheobronchial infections present rarely in diabetics and in patients with chronic lung disease as well as those with underlying hematologic malignancies and transplant recipients. Endoscopic findings include luminal narrowing or obstruction with pseudomembranes and necrosis.

Pulmonary mucormycosis may present radiographically similar to IPA, including with nodular (eFig. 57.8) and mass (eFigs. 57.9 and 57.10) lesions, ground-glass opacities, and consolidative and cavitary (see eFig. 125.5) lesions. The presence of multiple (10 or more) pulmonary nodules and pleural effusions favors the diagnosis of mucormycosis over IPA, although this is not absolute.[300] Both the halo sign and the reversed halo sign (i.e., a ground-glass opacity surrounded by either a ring or a crescent of consolidation; Fig. 57.9) may be seen,[156] but the reversed halo appears to be more common in mucormycosis.[303,304] However, this CT finding has been noted less frequently in non-neutropenic than neutropenic patients, an important distinction to keep in mind when considering this diagnosis.[305]

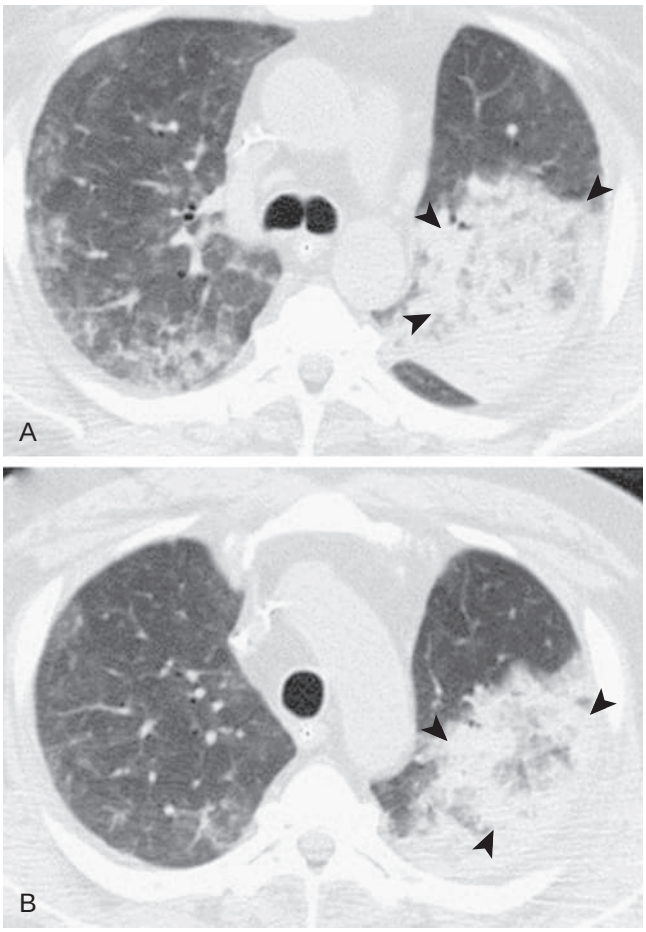

Figure 57.9 Mucormycosis. (A–B) Axial chest computed tomography displayed in lung windows performed in a hematopoietic stem cell transplant patient demonstrates left upper lobe consolidation (*arrowheads*) with surrounding ground-glass opacity consistent with the reversed halo sign. (Courtesy Michael B. Gotway, MD.)

DIAGNOSIS

Timely diagnosis is essential to optimizing outcomes in mucormycosis because mortality increases with delays in diagnosis and in initiation of therapy.[306,307] The diagnosis is typically made based on a combination of clinical, imaging, culture, and histopathologic findings. Currently available noninvasive tests (i.e., serum β-D-glucan and serum GM) are not helpful in the diagnosis of mucormycosis because Mucorales species lack significant quantities of these components in their cell walls. Direct examination of sputum and BAL specimens may show the characteristic broad 10- to 20-μm, ribbon-like, irregularly branching hyphae. Potassium hydroxide wet mounts enhanced with calcofluor (which stains chitin) may assist in detecting the fungus in fresh specimens; periodic acid–Schiff and/or Gomori's methenamine silver staining are used to visualize the fungi in tissue samples.[308] Prior receipt of mold-active therapy may alter the characteristic morphology in fresh specimens. In addition, although organisms may be visualized in tissue or respiratory specimens, cultures can be negative in up to one-third of cases.[309] Mucorales species may also be identified directly from culture and tissue specimens via molecular methods such as sequencing.

TREATMENT

Treatment of invasive mucormycosis includes pharmacologic therapy, nonpharmacologic intervention (e.g., reducing immunosuppression, correcting metabolic acidosis, and optimizing control of diabetes; eFigs. 57.11 and 57.12), and often surgery. Surgery, when feasible, is useful for debulking infection and preventing spread to contiguous structures, and is associated with decreased mortality compared to medical treatment alone.[310–313] Controlled trials to guide antifungal selection for mucormycosis are lacking given the rarity of infection, so recommendations are based on information gained through in vitro testing, animal models, and clinical observations. Guidelines for management of mucormycosis have been proposed based on consensus recommendations.[314,315] The use of susceptibility testing to guide antifungal therapy is

controversial given the lack of established clinical breakpoints (i.e., the selected levels of the antifungal concentrations used to define susceptibility). Thus therapy is currently recommended by consensus guidelines, particularly because the activity of antifungal therapy varies depending on the drug and species of the infecting pathogen.[316,317]

Polyenes appear to be the most active agents and remain the agents of choice in the empiric management of mucormycosis. AmB-d has largely been replaced by lipid formulations; LAmB is considered by many to be the preferred agent, due to reduced nephrotoxicity, superior activity in murine models of infection,[318] retrospective clinical data,[319] and rabbit models showing improved CNS penetration compared to both AMB-d and ABLC.[320] LAmB is typically initiated at a dosage of 5 mg/kg/day but has been increased to 10 to 15 mg/kg/day in severe infections that fail to respond.[321] Despite the lack of approved clinical breakpoints, in a limited dataset wherein AmB was used as first-line therapy for proven and probable IFIs with non-*Aspergillus* molds, including mucormycosis (representing 8 of 10 cases), the 6-week response was significantly better when the pathogen MIC was 0.5 μg/mL or less versus more than 0.5 μg/mL (83% vs 0%, $P = 0.05$).[322]

Azoles are typically utilized for step-down therapy or as a component of salvage regimens in patients refractory to or intolerant of AmB. Among the azoles active against molds, posaconazole, and isavuconazole have in vitro activity against mucormycosis. Among 91 cases of mucormycosis in which posaconazole was used for salvage therapy (either alone or in combination), 60% showed complete or partial response at 12 weeks.[323] Similar responses were reported in another retrospective review of 96 cases of mucormycosis.[324] Posaconazole delayed-release tablets were approved by the FDA in late 2013, and the intravenous formulation was approved in 2014. Available data suggest improved overall bioavailability with the delayed-release tablets compared with the original posaconazole suspension.[325–328] Therapeutic drug monitoring is recommended with therapy to maintain trough concentrations of at least 1.0 mg/L. Isavuconazole was evaluated for treatment of mucormycosis in a single-arm open-label trial of 37 patients with proven or probable mucormycosis who received primary isavuconazole therapy and were compared to external controls receiving AmB.[329] Day 42 crude all-cause mortality was 33% (7 of 21) in the isavuconazole primary treatment group compared to 39% (13/33) in the AmB-treated controls ($P = 0.595$). Whereas isavuconazole was FDA approved for the treatment of mucormycosis, because of the overall small sample size in this open-label trial and the lack of abundant clinical experience, isavuconazole cannot be recommended as first-line therapy.

Echinocandins do not have significant in vitro activity against agents of mucormycosis and should not be used as monotherapy in the treatment of these infections. However, there may be a role for polyene-echinocandin combination therapy. Animal studies have shown improved survival with caspofungin compared with no treatment in mice[330] and with polyene-echinocandin combination therapy.[331,332] Combination azole (isavuconazole) and echinocandin (micafungin) did not demonstrate synergy in a mouse model.[333] Clinical data for combination therapy including any combination of a polyene, echinocandin, or azole are limited and mixed. A small retrospective study from two centers evaluated 41 patients, most of whom had diabetes (83%) with rhino-orbital and rhino-orbital-cerebral mucormycosis, and found that polyene-caspofungin combination therapy improved outcomes compared to polyene monotherapy.[334] However, the benefit of combination therapy was not demonstrated in a 20-year retrospective evaluation of mucormycosis in 106 high-risk patients with hematologic malignancy including HCT recipients. In that population, there was no benefit in propensity score–adjusted probability of 6-week survival—60% versus 56% ($P = 0.71$) for patients receiving combination therapy.[335]

The duration of therapy for invasive mucormycosis is not well defined and is determined on a case-by-case basis and is dependent on multiple factors including extent of infection, clinical response, and immune reconstitution. In patients receiving up-front AmB therapy, transition to azole step-down therapy is typically done after patients have demonstrated clear-cut improvement and clinical stability. Although adjunctive therapy with the iron chelator deferasirox showed promise in both murine models and a small clinical trial,[336,337] a multicenter clinical trial comparing LAmB-deferasirox to LAmB-placebo found a significantly higher 90-day mortality in those receiving deferasirox.[338] The increased mortality may have been related to an unbalanced enrollment, because more patients in the deferasirox treatment group had hematologic malignancies and neutropenia, which are associated with poorer outcomes. Nonetheless, its use is not currently recommended. Other adjunctive agents that have been used include hyperbaric oxygen, granulocyte colony-stimulating factors, and interferon-γ.[314,339]

NON-*ASPERGILLUS* HYALINE HYPHOMYCETES

EPIDEMIOLOGY AND PATHOGENESIS

Hyalohyphomycosis refers to infections caused by septate molds with colorless or lightly pigmented hyphae. *Aspergillus* is the most common of the hyaline molds; however, non-*Aspergillus* hyphomycetes, including *Acremonium,*[340,341] *Fusarium,*[342] *Paecilomyces/Purpureocilium,*[343,344] *Rasamsonia* (previously *Geosmithia*),[345,346] *Scedosporium/Lomentospora,*[347] and *Trichoderma,*[348] among others, are increasingly reported.[119,288,349,350] These pathogens can cause infection in immunocompetent or immunocompromised hosts. *Fusarium* and *Scedosporium/Lomentospora* are the most common causes of infection from this group in SOT and HCT recipients.[288]

The majority of these molds are ubiquitous in nature and can be recovered from clinical specimens as nonpathogens/colonizers. Invasive infections can be associated with local inoculation of nails, eyes, skin, and soft tissues. Inhalation of airborne conidia can lead to sinopulmonary infections ranging from mild allergic sinusitis and *allergic bronchopulmonary mycosis* (ABPM) to severe and invasive sinopulmonary infections. Many of these pathogens are uniquely capable of sporulating in infected tissue, a process called *adventitious sporulation,* which, when coupled with endovascular invasion, results in fungemia. Although fungemia is uncommon in *Aspergillus* infections, it has been reported in more than 50% of patients with disseminated *Fusarium* infections.[351] Adventitious sporulation has also been described with *Acremonium,*[352] *Paecilomyces/Purpureocilium,*[352] *Scedo-*

sporium/Lomentospora,[353] and *Trichoderma.*[348] Mycotoxin production and adherence factors that promote colonization and infection may contribute to the pathogenicity of these molds.[354]

Localized skin, soft tissue, ocular, and sinopulmonary infections are seen in immunocompetent hosts, and chronic colonization can be present in patients with chronic lung diseases (e.g., cystic fibrosis, pulmonary fibrosis). Fungemia and invasive infections develop predominantly in patients with impaired cellular and/or humoral immunity. In these patients, dissemination from the lungs or local spread from the sinuses can lead to extension to the CNS and brain abscess formation. Severe invasive infection is typically limited to immunodeficient patients with one notable exception: in immunocompetent near-drowning victims, CNS and sinopulmonary infections have been described with pathogens including *Scedosporium*, presumably because the submersion in water resulted in alveolar damage with fungal penetration and severe fungal pneumonia.[355–357]



Figure 57.10 Disseminated *Fusarium* infection. Skin lesions in a patient with disseminated *Fusarium* infection demonstrating central necrosis with surrounding erythema.

CLINICAL PRESENTATION AND DIAGNOSIS

The respiratory presentation of non-*Aspergillus* hyalohyphomycosis resembles that of IA and includes sinusitis, ABPM, tracheobronchial disease, pneumonia, and pleuropulmonary infections. Patients may present with fever, sinus congestion and pain, cough, purulent sputum, and hemoptysis (eFig. 57.13). In patients with disseminated infection, depending on the pathogen, skin manifestations may be an early clue. Skin lesions are typically painful, erythematous, nodular eruptions that rapidly develop central pallor and necrosis (Fig. 57.10).

The diagnosis of infection with one of these pathogens is challenging due to difficulties in differentiating between fungal colonization and true infection, and in obtaining appropriate tissue specimens for evaluation. Furthermore, while histopathologic, cytopathologic, or direct microscopic examination from affected tissue is critical in making the diagnosis, these findings do not discriminate among the hyaline molds; culture data are required for definitive identification and diagnosis. Radiographic findings (e.g., pulmonary nodules, cavitation, and halo, reversed halo, and air-crescent signs) provide further support for infection but are not specific.[358] Noninvasive diagnostic testing such as serum or BAL GM, used primarily for the diagnosis of IA, may cross-react with the non-*Aspergillus* hyaline molds including *Fusarium,*[359] *Paecilomyces/Purpureocilium,* and *Penicillium,*[360] but lack both sensitivity and specificity in diagnosing these infections; the same applies to β-D-glucan.[361] The role of other molecular diagnostic tests such as sequence-based identification[362,363] and MALDI-TOF MS[364] continues to be defined.

TREATMENT

Treatment of these infections is multimodal. Immunosuppression should be reduced whenever feasible, and augmentation of host responses with growth factors and granulocyte transfusions should be considered. Removal of foreign devices and surgical intervention/débridement, particularly in localized disease, are also critical in management. Many of these pathogens are intrinsically resistant to conventional antifungal therapies and/or have species-dependent variability in MICs to antifungal drugs; identification to the species level is imperative. While clinical breakpoints need to be defined, in many cases susceptibility testing can provide additional guidance in drug selection.

Exemplifying the complexity of managing infections with non-*Aspergillus* mold infections, *Fusarium*[365,366] and *Scedosporium/Lomentospora*[367,368] species exhibit variable levels of resistance to most antifungals. *F. solani*, the most common of the clinical isolates, is also often azole-resistant, with high MICs to voriconazole and posaconazole.[342,365] Therefore, the optimal antifungal regimen for fusariosis is not clear; single-agent lipid formulations of AmB or voriconazole may be applied up front, though initial combination therapy may be employed, particularly in severe infections while awaiting MIC data.[366] ABLC treatment of invasive *Fusarium* infections in patients with hematologic malignancy or undergoing HCT resulted in improvement or cure of infection in 46% of patients evaluated.[369] Pooled analysis of 21 patients with invasive *Fusarium* infections treated with voriconazole showed similar success in 43%, resulting in FDA approval of voriconazole for refractory infections or intolerance to other therapies.[370] While it is not FDA approved for this indication, posaconazole has been used as salvage therapy in patients with hematologic malignancies and invasive fusariosis.[371] *Fusarium* species are intrinsically resistant to echinocandins; however, in combination therapy with AmB, synergy has been demonstrated in vitro and in vivo.[372–374] Other combinations including lipid formulations of AmB and voriconazole[375] have been used with clinical success, as have combinations that include terbinafine.[376]

Lomentospora (formerly *Scedosporium*) *prolificans* often demonstrates high-level resistance to all antifungals and is associated with poor clinical outcomes.[377] In contrast, *S. apiospermum* tends to be more susceptible to antifungals, particularly extended-spectrum azoles such as voriconazole.[378] Successful responses to voriconazole were demonstrated in 63% (15 of 24) of patients with *S. apiospermum* infections resulting in FDA approval for this specific *Scedosporium* species. A compilation of 107 cases of scedosporiosis managed

with voriconazole derived from the voriconazole global clinical trials database (maintained by Pfizer) reported a successful therapeutic response in 57% (61 of 107) of patients with overall higher success in *S. apiospermum* (45 of 70; 64%) compared with *S. prolificans* (16 of 36; 44%) infections ($P = 0.052$).[378] Combination therapies of voriconazole with terbinafine[379,380] or with an echinocandin with or without AmB,[381] particularly in multidrug-resistant infections, may be effective.

Finally, there are important considerations when managing infections due to *P. variotti* and *P. lilacinum* given differing antifungal susceptibility patterns. AmB has poor activity against *P. lilacinum* but is highly active against *P. variotti.*[382] In addition, while voriconazole demonstrates low MICs with *P. lilacinum,* MIC ranges are notably higher for the *P. variotti* species complex so that posaconazole is the preferred extended-spectrum azole for this group.[383,384]

DEMATIACEOUS (MELANIZED) HYPHOMYCETES

The dematiaceous fungi, the agents of phaeohyphomycoses, represent an assorted group of molds with more than 70 genera and 150 species.[385] The overall burden of infection is underrepresented because their presence in culture is often dismissed as contamination; however, invasive infection can be seen in immunodeficient and immunocompetent hosts. Dematiaceous fungi contain melanin in their cell walls, which contributes to their pathogenicity and accounts for the dark brown color seen in culture and/or histopathology.[386] These fungi are found in soil and vegetation worldwide and can enter the host via inhalation or the cutaneous route. They are responsible for an array of infections, including skin and soft tissue infections, allergic and invasive sinopulmonary disease, ocular, CNS, and disseminated infections. Isolated skin and soft tissue infections are more common in immunocompetent hosts, whereas pulmonary and disseminated infections are predominantly seen in immunosuppressed patients. Among a prospective transplant cohort inclusive of SOT and HCT recipients, of 2191 invasive fungal infections, 2.6% represented phaeohyphomycoses.[387]

Alternaria, *Bipolaris*, *Cladophialophora*, *Curvularia, Exophiala*, *Exserohilum*, *Ochroconis* (previously *Dactylaria*), *Phialemonium*, and *Phialophora* are some of the more common black molds associated with infection. Intrathecal injection of corticosteroids contaminated with *Exserohilum* led to a large outbreak of fungal meningitis in immunocompetent patients in the United States.[388,389] Accurate identification is important because molds within this group may have a particular tropism that is important to consider when determining the sites of infection. *Bipolaris* and *Curvularia* are often associated with allergic and chronic inflammatory diseases, including allergic fungal sinusitis and ABPM.[390] *Cladophialophora bantiana*,[391,392] *Rhinocladiella mackenziei*,[393,394] *Exophiala (Wangiella) dermatitidis*,[395] and *Ochroconis gallopava*[396] have a predilection for dissemination to the brain and can cause severe disease in immunocompetent and immunosuppressed patients.[397] Disseminated infections with dematiaceous molds have been associated with mortality rates of up to 80%.[398]

Sinopulmonary manifestations with the dematiaceous molds include allergic fungal sinusitis, ABPM, and asymptomatic pulmonary nodules, as well as invasive sinus and pulmonary infections. The latter two entities more commonly affect immunocompromised hosts and those with preexisting lung disease. CT findings are nonspecific (eFig. 57.14) and consistent with findings described with the other invasive pulmonary mycoses. Fungal elements seen on direct microscopy from clinical specimens can be associated with either colonization or contamination; documentation of tissue invasion is essential for diagnosis. Pigmented hyphae can be seen on standard hematoxylin and eosin stains. However, the Fontana-Masson stain is often preferred to ensure that those with decreased amounts of pigmentation are not misidentified as hyaline molds.[399] Other diagnostic methods including sequence-based identification and MALDI-TOF MS continue to evolve.[400]

As with other invasive molds, treatment includes reduction of immunosuppression and surgical debulking (when feasible) to augment antifungal therapies. Clinical breakpoints for antifungal susceptibility are not defined for the dematiaceous molds. Although resistance to AmB has been seen,[401] AmB demonstrates good in vitro activity against most of the dematiaceous molds. However, the extended-spectrum azoles, including voriconazole and posaconazole, have demonstrated in vitro activity against the majority of dematiaceous molds[385,401,402] and are used more frequently given their improved toxicity profile. Data with isavuconazole are sparse, with variable MICs dependent on the pathogen; however, clinical success with isavuconazole therapy has been demonstrated, suggesting this may represent a viable treatment option.[403] Combination therapies including azoles, AmB, terbinafine, and echinocandins have been employed for severe disease; however, an optimal regimen has not been defined.[399]

Key Points

- Invasive pulmonary aspergillosis may have a clinical presentation similar to that of other angioinvasive molds such as mucormycosis and the non-*Aspergillus* hyphomycetes such as *Fusarium* and *Scedosporium* and dematiaceous molds, such as *Exophiala.*
- Galactomannan is a component of the cell wall of some but not all fungi and can be a useful noninvasive diagnostic aid in serum or bronchoalveolar lavage.
- Voriconazole is the treatment of choice for invasive pulmonary aspergillosis. The total duration of therapy depends on the immune status of the host and clinical and radiographic response to infection. However, patients are treated for a minimum of 6 to 12 weeks.
- Although mucormycosis can be associated with a multitude of clinical manifestations with multiorgan involvement, the most common presentations include rhino-orbital-cerebral and pulmonary infections, particularly in those with poorly controlled diabetes and in immunodeficient patients, especially those with hematologic malignancies.
- *Candida* pneumonia is rare and develops most often following candidemia and dissemination to the lung in immunocompromised populations.
- Combination antifungal therapy may offer benefit in infections due to drug-resistant fungi.

Key Readings

de Heer K, Gerritsen MG, Visser CE, Leeflang MM. Galactomannan detection in broncho-alveolar lavage fluid for invasive aspergillosis in immunocompromised patients. *Cochrane Database Syst Rev*. 2019;5:Cd012399.

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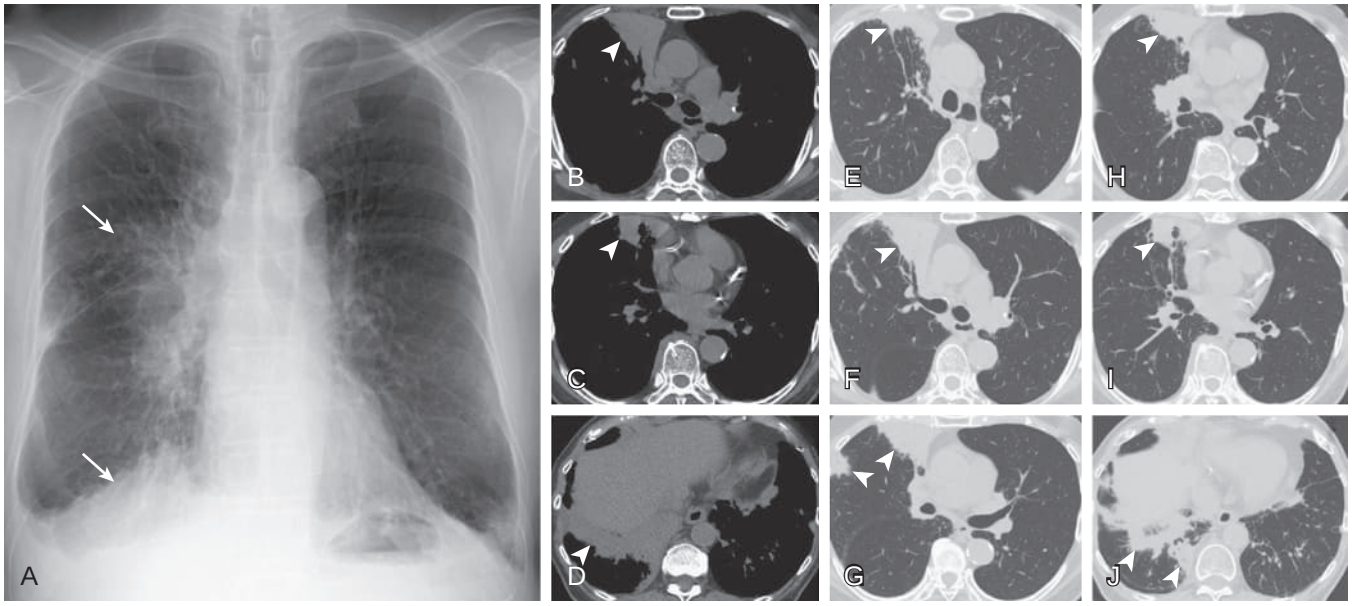
Complete reference list available at ExpertConsult.com.



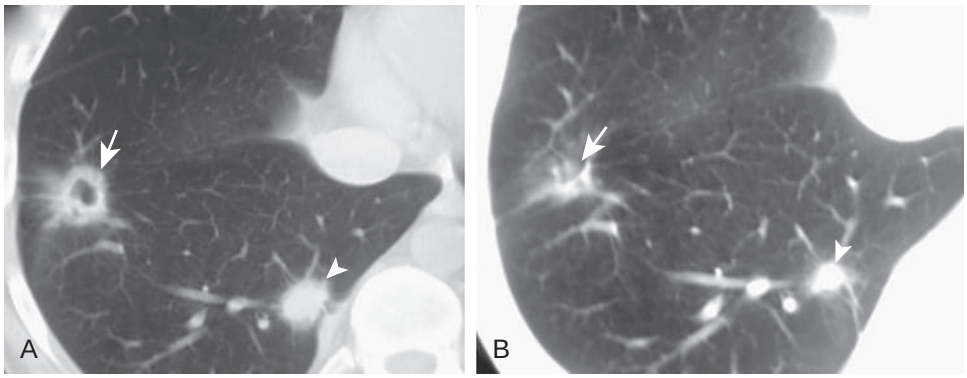
eFIGURE IMAGE GALLERY



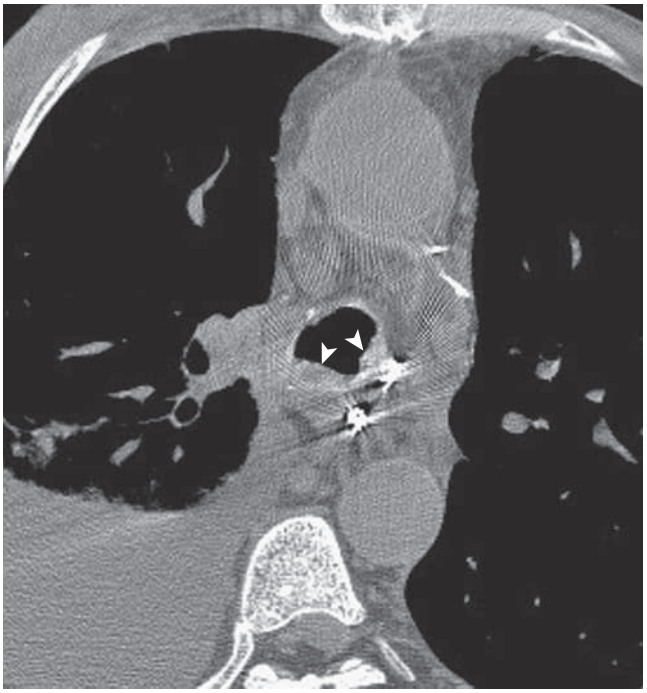
eFigure 57.1 Cryptococcal pneumonia. (A) Frontal chest radiograph in an 80-year-old man with idiopathic CD4 lymphocytopenia shows patchy consolidation and bronchovascular thickening projected over the right hilum and in the right lower lobe (*arrows*). (B–D) Axial unenhanced chest computed tomography displayed in soft tissue windows shows consolidation (*arrowheads*). (E–J) Lung windows show consolidation *(arrowheads)* with air bronchograms in the anterior segment of the right upper lobe with more nodular and lobular consolidation in the right middle and right lower lobes (*arrowheads* in J). *Cryptococcus neoformans* was diagnosed at bronchoscopy. (Courtesy Michael B. Gotway, MD.)



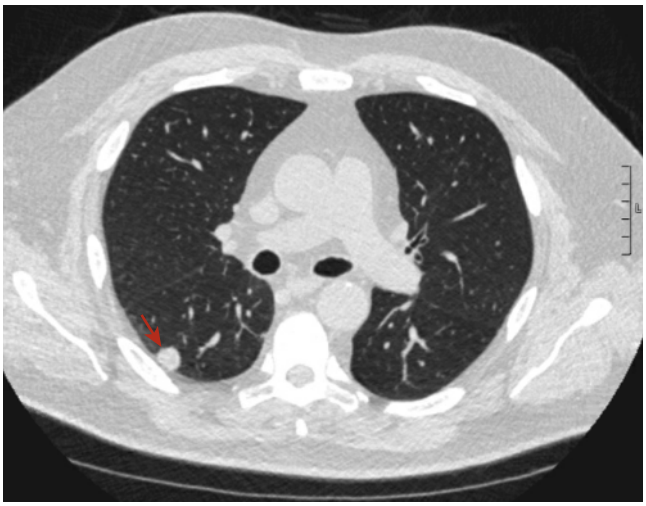
eFigure 57.2 *Candida albicans* pneumonia. Frontal chest radiograph in a severely immunosuppressed patient following treatment for hematologic malignancy shows a subpleural masslike opacity proven on tissue sampling to reflect candidiasis. (Courtesy Michael B. Gotway, MD.)



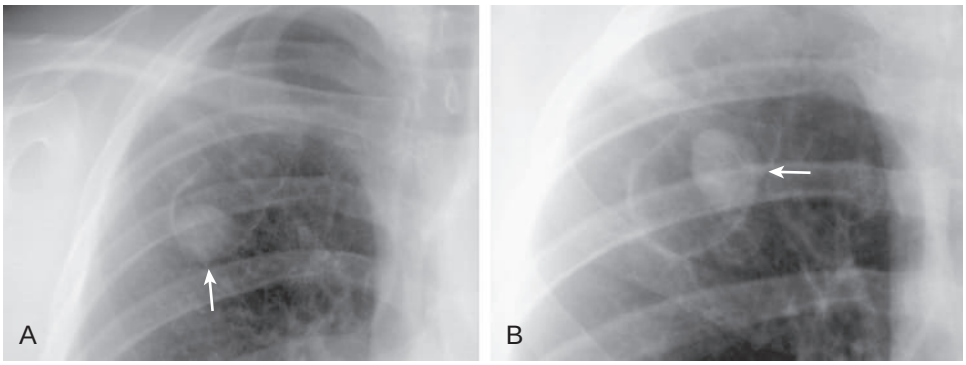
eFigure 57.3 Invasive *Aspergillus* infection: treatment response. (A) Axial chest *computed tomography* (CT) performed for a severely immunosuppressed patient following stem cell transplantation shows a right lower lobe cavity *(arrow)* and poorly defined nodule (*arrowhead*), consistent with invasive pulmonary aspergillosis. (B) Axial chest CT performed following 6 weeks of antifungal therapy shows involution of the right lower lobe cavity (*arrow*) with reduction in size of the right lower lobe nodule (*arrowhead*). (From Gotway MB, Dawn SK, Caoili EM, et al: The radiologic spectrum of pulmonary *Aspergillus* infections. *J Comput Assist Tomgr.* 2002;26:159–173.)



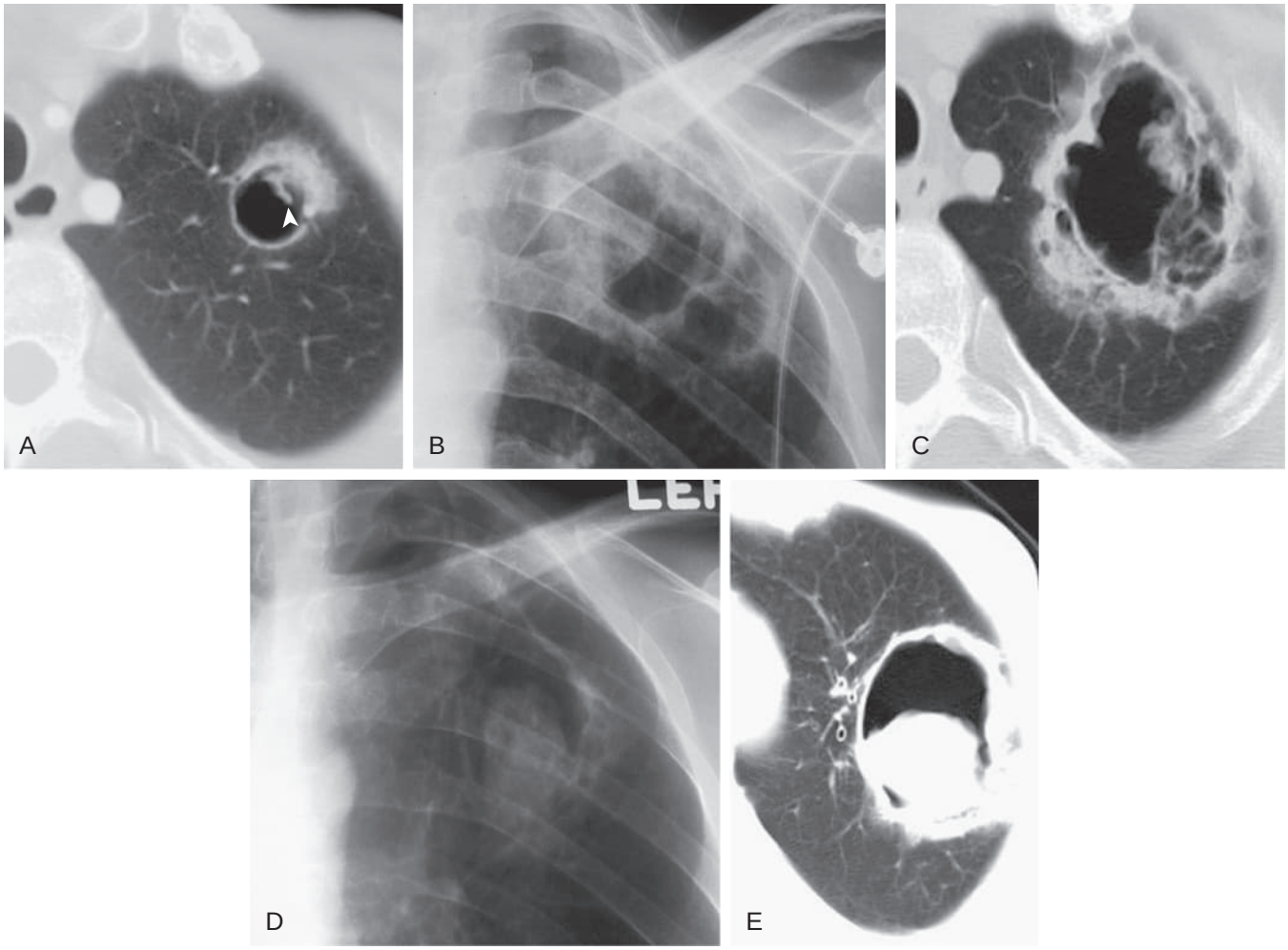
eFigure 57.4 *Aspergillus* tracheobronchitis. Axial chest computed tomography performed in a 62-year-old woman immunosuppressed following heart-lung transplantation shows high-attenuation plaques (*arrowheads*) within the trachea, confirmed on bronchoscopy to represent *Aspergillus* infection. (Modified from Gotway MB, Dawn SK, Caoili EM, et al: The radiologic spectrum of pulmonary *Aspergillus* infections. *J Comput Assist Tomgr.* 2002;26:159–173.)



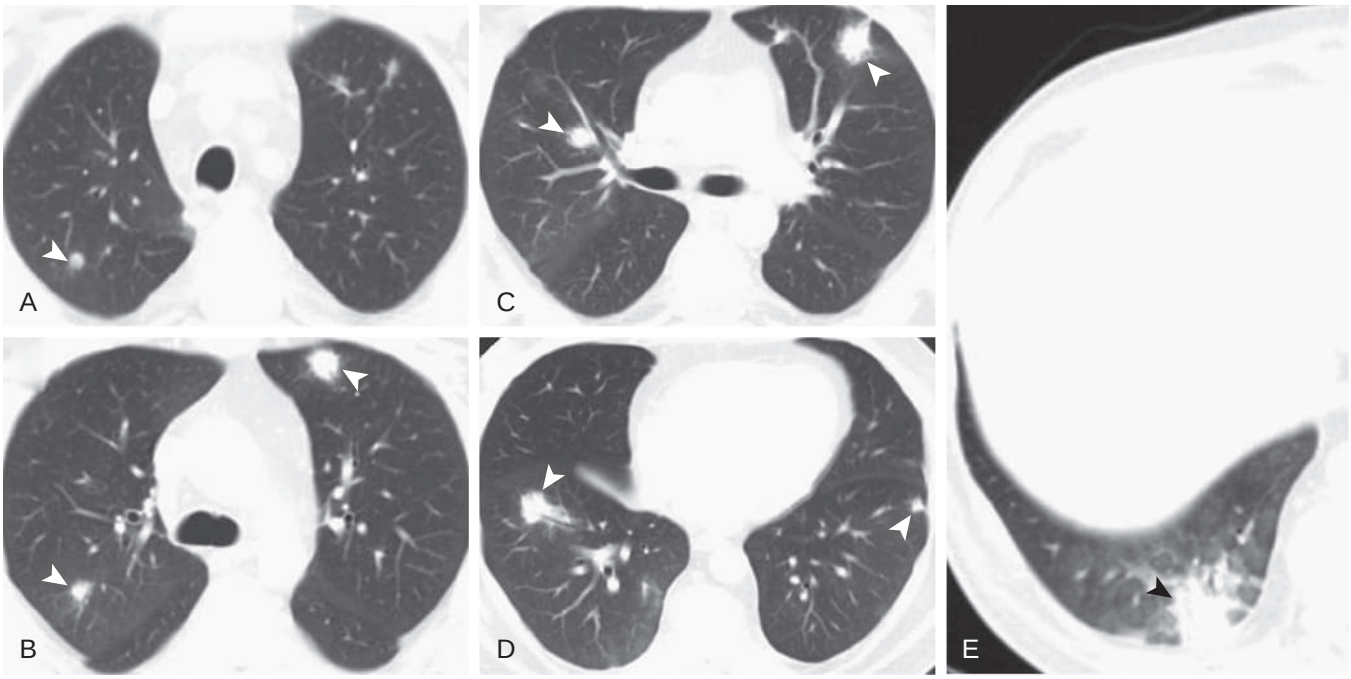
eFigure 57.5 Aspergillus nodule. Axial chest computed tomography performed in a 58-year-old immunocompetent man shows a right lower lobe 1.5 cm subpleural nodule (*arrow*) confirmed on wedge resection to represent *Aspergillus* pulmonary nodule.



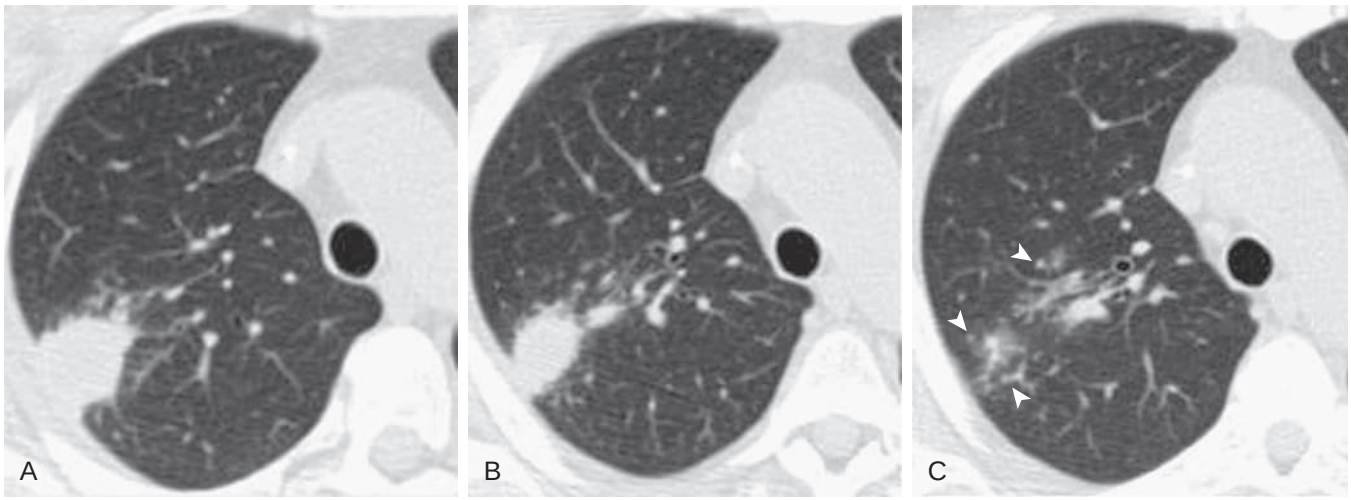
eFigure 57.6 Mycetoma: mobility demonstrated at imaging. Upright (A) and left lateral decubitus (B) focused chest radiographs show a mobile intracavitary mass (*arrow*) characteristic of mycetoma. (Modified from Gotway MB, Dawn SK, Caoili EM, et al.: The radiologic spectrum of pulmonary *Aspergillus* infections. *J Comput Assist Tomgr.* 2002;26:159–173.)



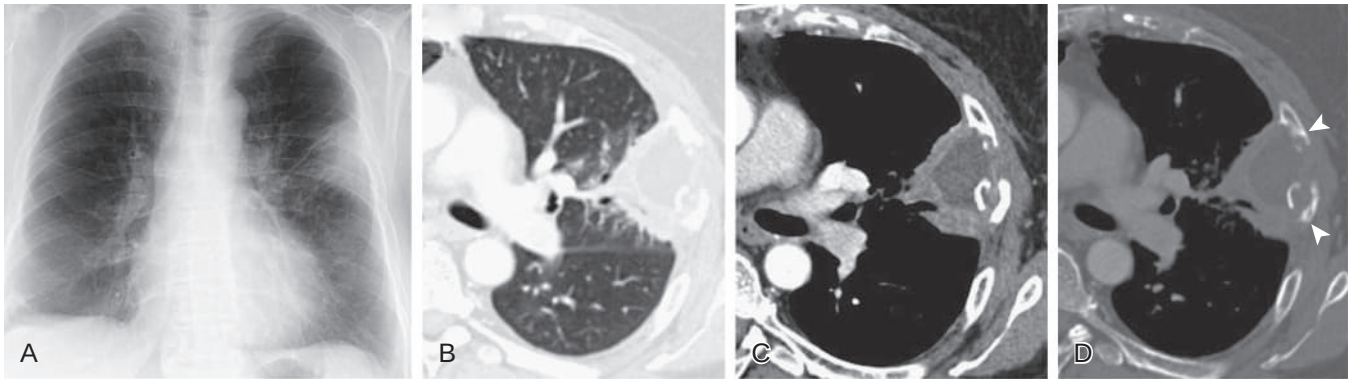
eFigure 57.7 Subacute invasive pulmonary aspergillosis (previously chronic necrotizing aspergillosis): progressive cavitation. (A) Axial chest computed tomography (CT) in a patient with acquired immunodeficiency virus and diabetes shows a small cavity with an eccentrically thickened wall and early internal opacity (*arrowhead*). (B) Focused frontal chest radiograph (B) and axial chest CT (C) performed 9 months after the first image shows increased size of the cavity with increasing wall thickness and irregularity as well as progression of the intracavitary opacity. Focused frontal chest radiograph (D) and axial chest CT (E) performed 15 months after the first image now shows an eccentrically thickened left upper lobe cavity with an internal fungus ball. (Modified from Gotway MB, Dawn SK, Caoili EM, et al.: The radiologic spectrum of pulmonary *Aspergillus* infections. *J Comput Assist Tomgr.* 2002;26:159–173.)



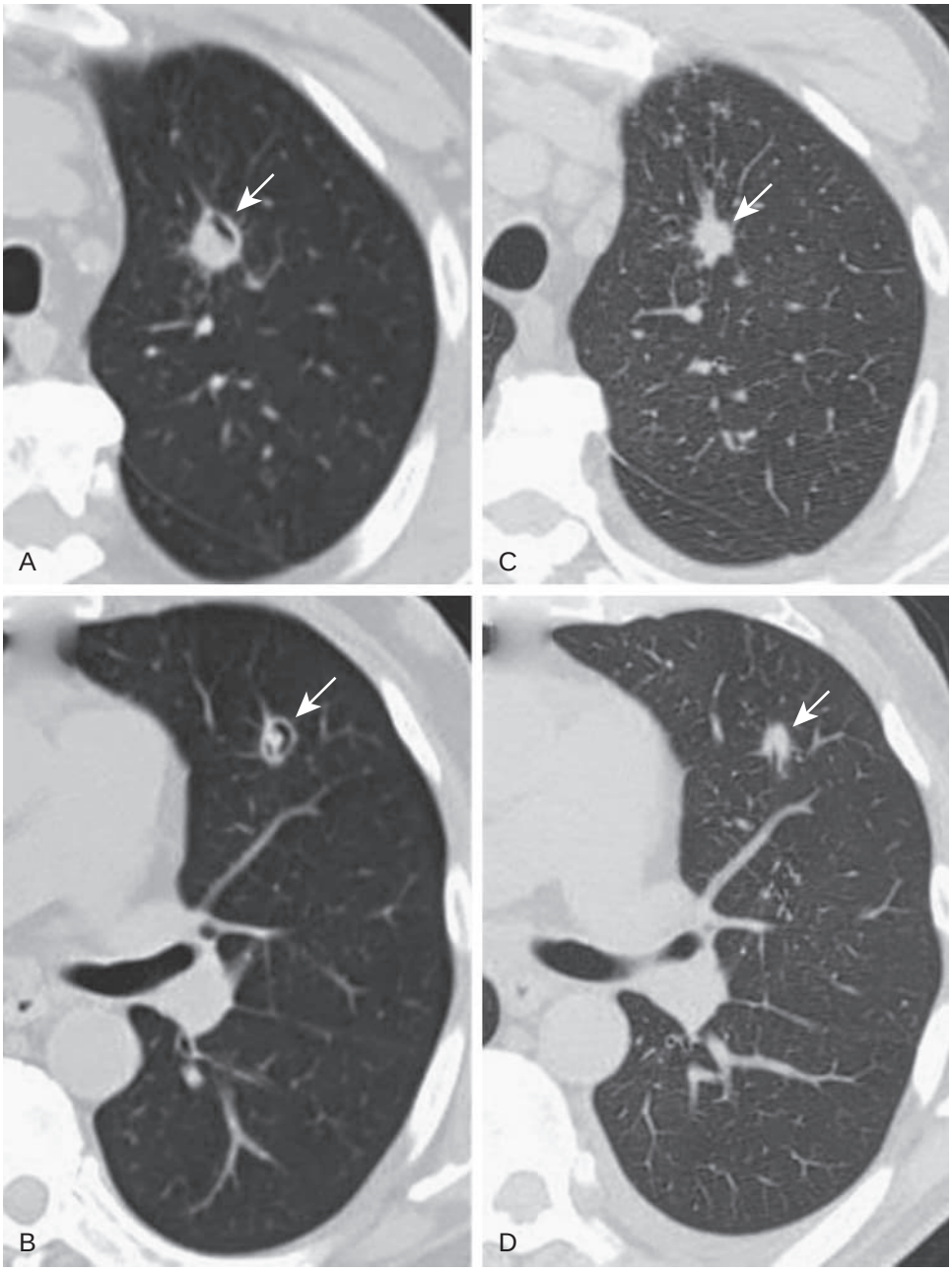
eFigure 57.8 Mucormycosis: multiple nodules. (A–E) Axial chest computed tomography displayed in lung windows performed in a severely immunosuppressed patient shows multiple, bilateral nodules (*arrowheads*), some associated with bronchi (right lower lobe in D, and left upper lobe in B), and some with ground-glass opacity halos (left upper lobe in C). (Courtesy Michael B. Gotway, MD.)



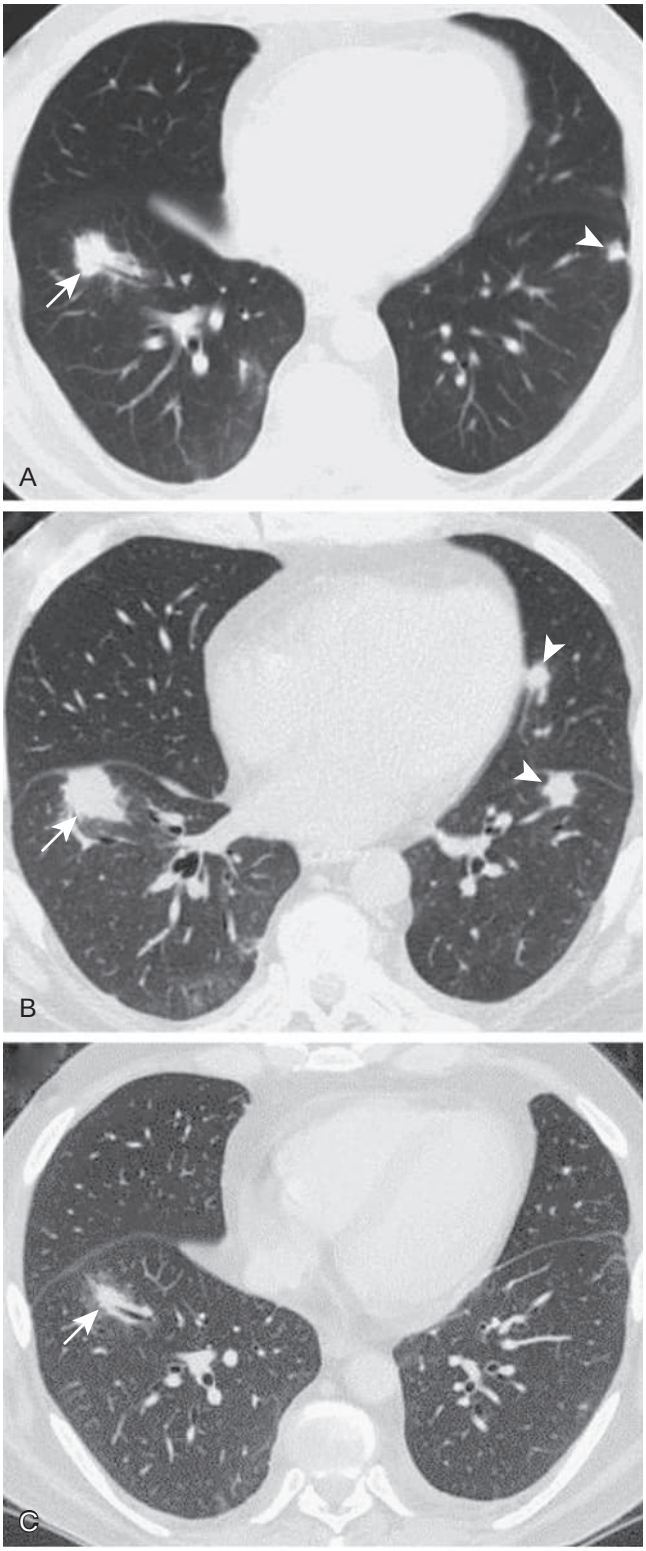
eFigure 57.9 Mucormycosis: large nodule/mass. Axial chest computed tomography displayed in lung windows performed in a severely immunosuppressed patient shows an irregular opacity just exceeding 3 cm in size in the subpleural right upper lobe (A–B), proven to reflect *Mucor* on biopsy. Small satellite nodules (*arrowheads*) are seen along the inferior margin of the lesion in C. (Courtesy Michael B. Gotway, MD.)



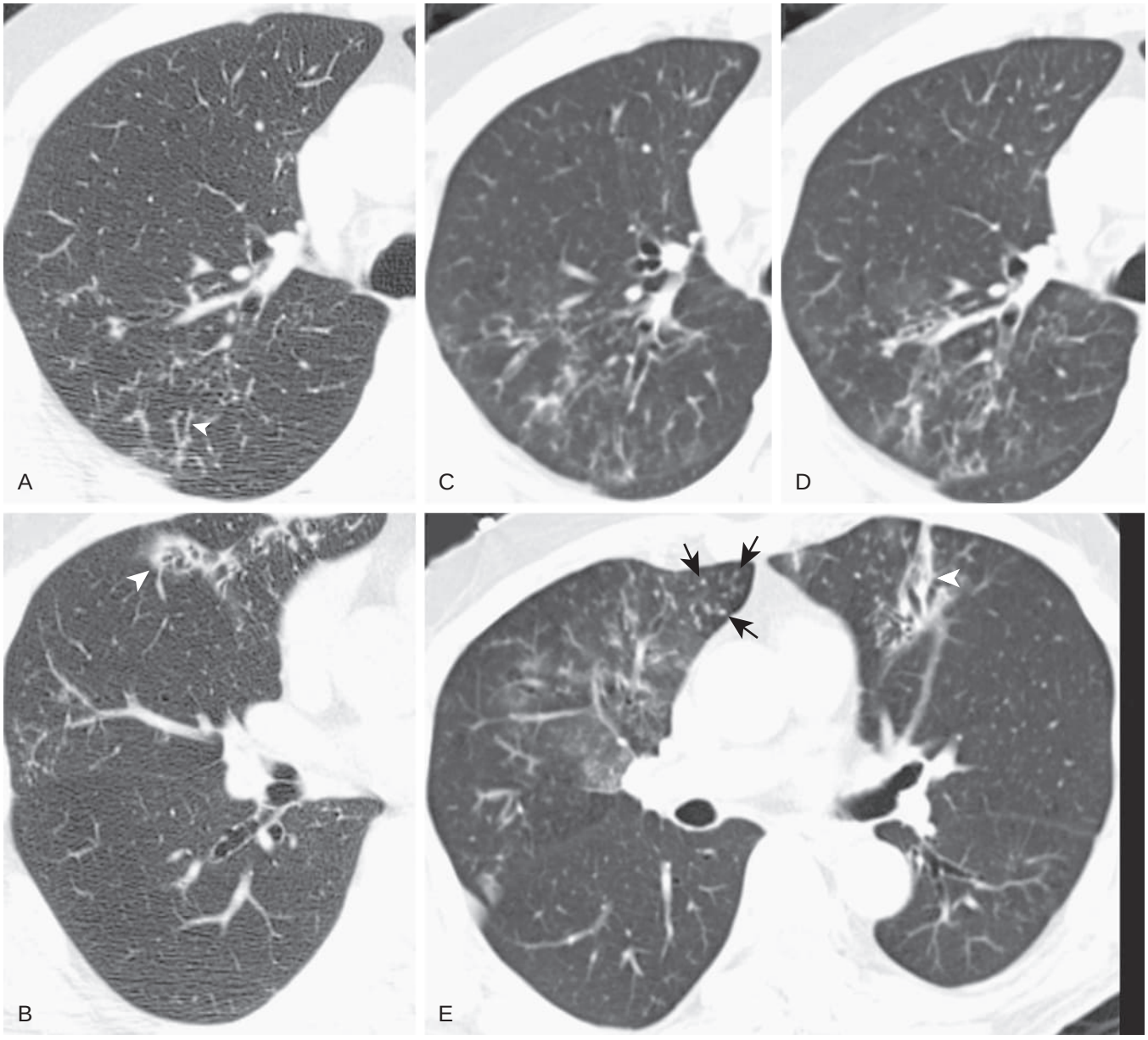
eFigure 57.10 Mucormycosis: mass with chest wall invasion. (A) Frontal chest radiograph performed in a severely immunosuppressed patient shows a masslike subpleural opacity in the left upper lobe. Focused axial chest computed tomography displayed in lung (B), soft tissue (C), and bone (D) windows show the subpleural mass is necrotic (note low attenuation centrally in C) associated with chest wall invasion, evidenced by rib destruction (D, *arrowheads*). (Courtesy Michael B. Gotway, MD.)



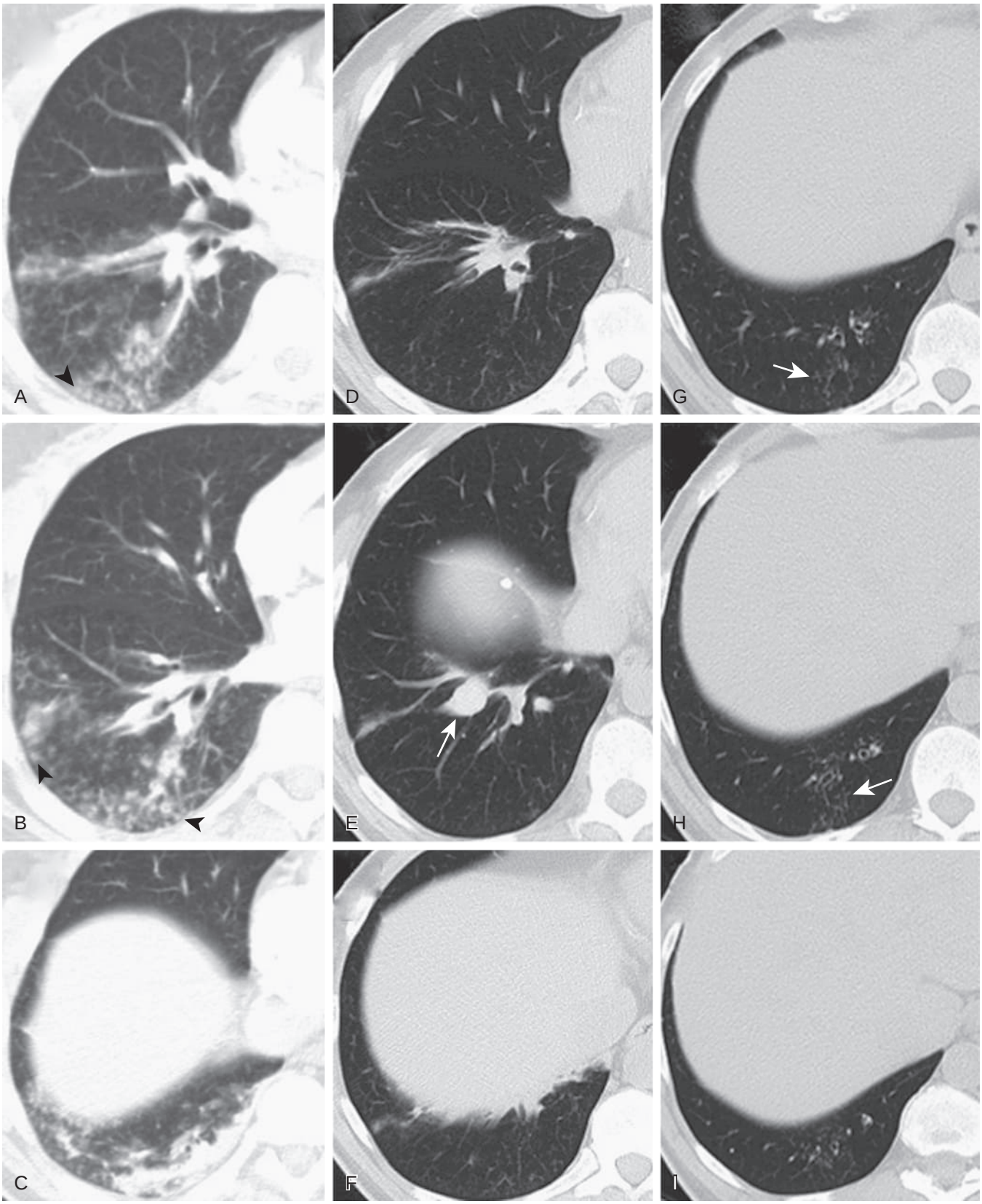
eFigure 57.11 Mucormycosis: treatment response. (A–B) Axial chest computed tomography (CT) displayed in lung windows performed in a severely immunosuppressed patient shows cavitary left upper lobe nodules with internal opacity (*arrows*), proven to reflect Mucor. (C–D) Following antifungal therapy and restoration of immune function, the left upper lobe nodules are no longer cavitary and have decreased in size. Follow-up chest CT (not shown) showed complete resolution of the nodules. (Courtesy Michael B. Gotway, MD; case by Robert Viggiano, MD, Pulmonary and Critical Care Medicine, Mayo Clinic, Scottsdale, AZ.)



eFigure 57.12 Mucormycosis: treatment response. (A) Axial chest computed tomography (CT) displayed in lung windows performed in a severely immunosuppressed patient shows a dominant right lower lobe nodule associated with an air bronchogram (*arrow*) and small subpleural left lower lobe nodule (*arrowhead*) due to *Mucor*. (B) Follow-up chest CT shows enlargement of the right lower lobe nodule (*arrow*) and new left base nodules (*arrowheads*). (C) Following antifungal treatment and resolution of immunosuppression, the dominant right lower lobe nodule (*arrow*) has decreased significantly in size. Other smaller nodules (*arrowheads*, A–B) also resolved. (Courtesy Michael B. Gotway, MD.)



eFigure 57.13 *Scedosporium apiospermum* infection. (A–E) Axial chest computed tomography displayed in lung windows in an 80-year-old man with cough and hemoptysis shows right upper lobe and anterior segment left upper lobe bronchiectasis and bronchovascular thickening (*arrowheads*), associated with small nodules (*arrows*, E). Bronchoscopy with bronchoalveolar lavage found old blood and recovered *S. apiospermum* organisms. (Courtesy Michael B. Gotway, MD.)



eFigure 57.14 *Bipolaris* infection. (A–C) Axial chest *computed tomography* (CT) displayed in lung windows shows right lower lobe peripheral consolidation and numerous small centrilobular nodules (*arrowheads,* A–B). Bronchoscopy recovered *Bipolaris* organisms. (D–F) Axial chest CT displayed in lung windows 2 months after A–C and following antifungal therapy shows improvement in basal consolidation and nodules, but appearance of large airway impaction (*arrow,* E). (G–I) Axial chest CT displayed in lung windows 6 months after A–C shows near-complete clearing of the right lower lobe process, with mild residual bronchiolitis *(arrows).* (Courtesy Michael B. Gotway, MD; case by Paul J. Conomos, MD, Arizona Pulmonary Specialists, Phoenix, AZ.)

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58 PARASITIC INFECTIONS

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INTRODUCTION
INITIAL EVALUATION OF A PATIENT WITH POSSIBLE PARASITIC INFECTION OF THE LUNGS
HELMINTHS
Nematodes
Trematodes
Cestodes
PROTOZOA
Amebiasis
Malaria
Toxoplasmosis
Other Protozoa
KEY POINTS

INTRODUCTION

Parasitic infections that involve the lungs include both multicellular helminths and unicellular protozoa. *Paragonimus,* the lung fluke, specifically targets the lung, but several other parasitic infections that primarily target other organs commonly present with pulmonary manifestations. Helminths, for example, migrate through the lungs en route to the gastrointestinal tract and, during migration, cause pulmonary disease (e.g., eosinophilic pneumonia). Many parasites that affect the lungs more commonly infect the gastrointestinal tract (e.g., *Entamoeba*, *Echinococcus*); others involve the lungs as part of a generalized systemic infection (e.g., *Toxoplasma, Plasmodium*) (Table 58.1).

Although these infections classically have been associated with tropical and subtropical regions, they also have been seen in temperate and arctic regions. Furthermore, travel and immigration have led to the globalization of many of these formerly geographically restricted infectious diseases. The increased population of immunosuppressed patients living with *human immunodeficiency virus* (HIV) and *acquired immunodeficiency syndrome* (AIDS) or being treated with immunemodulating therapy used in organ transplantation, rheumatologic diseases, and cancer has resulted in the expansion of populations vulnerable to opportunistic parasitic diseases. Moreover, climate change and ecologic perturbations have affected the transmission and geographic range of certain human parasites. These factors necessitate greater familiarity of all physicians with parasitic infections previously seen only by specialists in tropical medicine.

This chapter reviews the pulmonary complications of parasitic infections that exhibit four major patterns: (1) parasites that primarily involve the lungs, (2) parasites that involve the lungs as a transient event in their life cycles, (3) parasites that involve the lungs less often than they involve other organs such as those of the gastrointestinal tract, and (4) parasites that involve the lungs during widespread, systemic infections (see Table 58.1). Specific aspects of certain parasitic infections are also discussed in Chapter 123 on the pulmonary complications of HIV and Chapter 96 on eosinophilic lung diseases.

INITIAL EVALUATION OF A PATIENT WITH POSSIBLE PARASITIC INFECTION OF THE LUNGS

Because parasitic infections differ in their geographic distribution, to arrive at a differential diagnosis, clinicians must consider the diseases found in areas where a patient has traveled or resided. Parasites can have complex life cycles with numerous hosts; many are vector borne and others are acquired by exposures to contaminated soil or water. Many emerging parasitic infections are zoonoses, in which the disease is spread from nonhuman animals to humans. It is therefore important to obtain a detailed travel and contact history with information on foods and liquids consumed, swimming or wading, insect bites, animal exposures, and medications taken.

In developing a differential diagnosis for respiratory complaints that may have a parasitic etiology, knowledge of the geographic distribution of various parasites, potential vectors, and potential sources of environmental contamination is essential. The interval between the time of travel or emigration and the onset of symptoms may provide clues: enteric protozoa or helminthic infections typically present more than 2 weeks after exposure and some parasites such as *Strongyloides, Plasmodium vivax* or *ovale,* and *Entamoeba histolytica* can present years after exposure.

Laboratory tests that may be helpful in initial evaluations include a complete blood count with differential, liver function tests, and a basic metabolic panel; in some contexts, examination of the sputum and/or stool samples is essential. Peripheral eosinophilia suggests a potential parasitic cause of pulmonary disease, but most protozoan infections are not associated with eosinophilia, and a lack of eosinophilia does not exclude parasitic infection. Diagnosis of intestinal parasites often depends on microscopic exams that require adequate specimens and experienced lab personnel. Depending on the parasite suspected, stool antigen tests (*E. histolytica)*, microscopic examination of blood smears (malaria and babesiosis), or collection of respiratory samples including sputum or *bronchoalveolar lavage* (BAL), or serologic tests (*Strongyloides enzyme-linked immunosorbent assay* [ELISA]) may be warranted.[1,2] Specialized laboratories are able to

Table 58.1 Characteristics of the Most Common Parasites Causing Pulmonary Pathology

Parasite	Distribution	Pulmonary Manifestation	Extent of Lung involvement*	Diagnosis	Treatment
HELMINTHS					
Nematodes (Roundworms)					
Ascariasis: *Ascaris lumbricoides*	Worldwide, but widely in tropics	Loeffler syndrome, usually 9–12 days after exposure to eggs; cough, substernal discomfort, rales and wheezing, transient opacities	Transient	Examination of sputum; eosinophilia during larval migration; stool ova and parasite, usually positive after pulmonary symptoms resolved; serology	Albendazole Mebendazole
Dirofilariasis (dog heartworm): *Dirofilaria immitis* and *D. repens*	Worldwide (associated with dogs)	Pulmonary nodule	Primary	Usually requires biopsy to rule out other causes	None (benign, so no treatment necessary)
Hookworm: *Ancylostoma duodenale* and *A. ceylanicum*; *Necator americanis* and *N. brasiliense*	Worldwide, especially tropics	Loeffler syndrome; transient opacities	Transient	Eosinophilia during larval migration	Albendazole Mebendazole
Strongyloidiasis (also a hookworm, but unique due to autoinfection cycles): *Strongyloides stercolasis* (and sometimes other *Strongyloides* sp)	Worldwide but particularly in tropic or subtropical regions	Loeffler syndrome; chronic cough; pneumonia or sepsis in hyperinfection	Systemic (rarely primary)	Sputum examination; eosinophilia during larval migration; stool ova and parasite; serology (cannot discriminate acute vs. past)	Ivermectin (may need longer doses for immuno-compromised hosts); due to risk of hyperinfection, consider treating all seropositives, screening all patients receiving immune modulating agents
Trichinosis (also a hookworm but encysts): *Trichinella spirallis*	Worldwide zoonosis	Respiratory distress, radiographic appearance variable	Transient	Muscle biopsy	Albendazole
Tropical pulmonary eosinophilia (lymphatic filariasis): *Wucharia bancrofti* and *Brugia malayi*	Tropics, particularly South Asia	Tropical eosinophilic pneumonia with interstitial opacities, chronic cough	Systemic	Circulating antigen, serology, BAL, eosinophilia	Diethylcarbamazine Doxycyline (treats endosymbiont)
Visceral larval migrans (nonhuman ascarid): *Toxocara canis* and *T. cati*	Worldwide	Interstitial opacities with eosinophilic pneumonia	Transient	Serology, eosinophils in blood and sputum	May not be needed; Albendazole (or ivermectin) in severe cases
Trematodes (Flukes)					
Paragonimiasis (lung flukes): *Paragonimus westermani, P. africanus, P. caliensis, P. kellicotti* (U.S.)	Southeast Asia, Central and South America, Africa; United States	Pulmonary parenchymal invasion (larvae mature in lung) with cavitary lesions; hemoptysis	Primary	Eosinophilia; eggs in sputum or stool; serology	Praziquantel
Schistosomiasis: *Schistosoma mansoni, S. haematobium, S. japonicum, S. intercalatum*	Asia, South America, Africa	Hematogenous seeding with heavy infection; pulmonary hypertension	Systemic	Eosinophilia; serology; stool ova and parasite	Praziquantel
Cestodes (Tapeworms)					
Hydatid cyst: *Echinococcus granulosus* and *E. multilocularis*	Worldwide (especially in sheep-rearing locales)	Pulmonary cyst; second most common site after liver; hemoptysis	Other organs (usually liver)	Serology, eosinophilia rare	Surgical, albendazole

Table 58.1 Characteristics of the Most Common Parasites Causing Pulmonary Pathology—cont'd

Parasite	Distribution	Pulmonary Manifestation	Extent of Lung involvement*	Diagnosis	Treatment
PROTOZOA					
Amebiasis: *Entamoeba histolytica*	Worldwide; mostly tropical	Abscess; lungs second most common extraintestinal site after the liver, hemoptysis	Systemic or secondary extension	Percutaneous aspiration, serology, antigen, PCR	Metronidazole Tinidazole
Malaria: *Plasmodium* sp (*falciparum, vivax, ovale, malariae, knowlesi*)	Africa, Asia, Central and South America	Interstitial opacities; ARDS	Systemic	Blood smear, RDT; PCR	Antimalarial treatment, specifics depend on species and geographic distribution of drug resistance
Toxoplasmosis: *Toxoplasma gondii*	Worldwide; most common in immunocompromised especially, HIV-infected with CD4 < 100	Interstitial pneumonia usually associated with disseminated disease	Systemic	Smear of BAL, PCR; serology (cannot discriminate acute from past)	Pyrimethamine/sulfadiazine Pyrimethamine/clindamycin
Rarer Protozoan Pulmonary Parasite Syndromes					
Free-living ameba: *Acanthamoeba castellani* or *A. polyphagia*, *Balamuthia mandrillaris*, *Naeglaria fowleri*	Worldwide	Rare, usually immunocompromised; more frequently seen as CNS disease	Systemic	Smear/tissue section	No highly effective treatment Treatment varies according to species involved in the infection
Babesiosis: *Babesia microti, B. divergens*	U.S., Europe	Interstitial opacities: ARDS	Systemic	Blood smear; PCR	Quinine/clindamycin Atovaquone/azithromycin
Cryptosporidiosis: *Cryptosporidium parvum* and *C. hominus*	Worldwide	Primarily gastrointestinal; respiratory syndrome and transmission proposed	Primary (rare)	Smear of BAL or sputum; stool ova and parasite; PCR	No highly effective treatment (nitizoxinide approved for children with diarrhea)
Leishmaniasis: *Leishmania donovani*	Africa, Central and South America	Interstitial pneumonia usually associated with disseminated disease	Systemic	Smear or histopathology of tissue, PCR	Pentavalent antimonials, amphotericin B, miltefosine
Microsporidiosis (related to fungi): Many species	Worldwide; especially in immunocompromised	Interstial pneumonia, tracheobronchitis	Primary or systemic	Stains of sputum, smears or tissue, PCR	Albendazole, fumagillin
American trypanosomiasis: *Trypanosoma cruzi*	Central and South America	Interstitial pneumonia usually associated with disseminated disease	Systemic	Serology, blood smear, PCR	Nifurtimox, benznidazole

Serologic testing can be performed by enzyme-linked immunosorbent assay (ELISA also often abbreviated EIA), immunofluorescence (IFA), or Western blot. In general ELISA is most common because there are standardized cutoff points and less operator variability. Antigen tests can be performed by Western blot or ELISA designed to detect the antigen of choice. For gastrointestinal pathogens and blood pathogens, PCR is increasingly available or being incorporated into multipathogen panels. These tests may be available at the CDC or state public health laboratories.

*Extent of lung involvement: (1) *primary:* parasites that primarily involve the lungs, (2) *transient:* parasites that involve the lungs as a transient event in their life cycles, (3) *systemic:* parasites that involve the lungs during widespread systemic infection as part of dissemination of the infection, and (4) *secondary extension:* parasites that form an abscess or other collection that can rupture through the diaphragm infecting the lung.

ARDS, acute respiratory distress syndrome; BAL, bronchoalveolar lavage; CNS, central nervous system; HIV, human immunodeficiency virus; PCR, polymerase chain reaction; RDT, rapid diagnostic test.

perform polymerase chain reaction tests or other nucleic acid–based tests for specific parasites. Several recently available molecular gastrointestinal panels (e.g., BioFire Film array) include pathogenic protozoa (e.g., *E. histolytica*, *Cyclospora*, *Cryptosporidia*, and *Giardia*),[3] but they do not include pathogenic metazoa (e.g., helminths, cestodes). Rapid antigen tests for the diagnosis of malaria are approved and widely available. In some cases, specialized testing is available at the *US Centers for Disease Control and Prevention* (CDC); the CDC website provides useful resources for diagnostic testing (http://dpd.cdc.gov/dpdx/Default.htm), and the CDC provides access for certain antiparasitic medications not routinely available in the United States.

HELMINTHS

Helminths are common parasites divided into two major phyla: (1) nematodes (roundworms), which include the major intestinal worms and the filarial worms that cause lymphatic filariasis and onchocerciasis, and (2) platyhelminths (flatworms), which include flukes (or trematodes), such as *Schistosoma*, and tapeworms (or cestodes).[4] These parasites are most common in areas of poverty, particularly in rural environments. Disease is proportional to worm burden, as assessed by the number of eggs per gram of feces. With the exception of *Strongyloides*, these infections do not have significant autoinfective cycles in the host.

NEMATODES

Infection with helminths is an important etiology of eosinophilic pneumonia, which can be caused by several infectious and noninfectious syndromes (see Chapter 96).[5] The parasitic nematodes (roundworms) of humans that cause ascariasis, hookworm disease, trichinosis, and strongyloidiasis have a respiratory phase as part of their life cycles.[6] In each, larvae migrate through the lungs in transit to the gastrointestinal tract. In most cases, this migratory phase is asymptomatic, but cough, substernal discomfort, and wheezing may be accompanied by transient opacities and eosinophilia (Loeffler syndrome). This is often accompanied by peripheral eosinophilia, bronchospasm, and elevated serum IgE levels. If the burden of infection is high, the eosinophilic pneumonia may result in an asthma-like syndrome or in pulmonary damage due to release of cytotoxic, cationic proteins from eosinophil granules.[7] After larvae migrate through the lungs, they move up the respiratory tree and are swallowed, thereby reaching the gastrointestinal tract where they mature into adult worms. During acute infection and migration, stool ova and parasite examinations are often negative because adult worms often are not yet present in the gastrointestinal tract.

Ascariasis

Ascariasis, caused by the nematode *Ascaris lumbricoides,* is the most common human helminth infection and is estimated to infect almost 1 billion people.[4,6] Although highly prevalent, ascariasis is associated with chronic disability rather than death. It has a worldwide distribution, being most common in tropical and semitropical regions. An estimated 4 million people in the United States are infected,[8] primarily children in rural areas of the southern United States. Humans are the only known host of *Ascaris lumbricoides*, although the pig species *A. suum* is very similar biochemically and morphologically. Eggs (ova) shed in the stool mature in moist environments; humans are infected by swallowing eggs that contaminate water, food, or soil. The eggs bear noninfective, first-stage rhabditiform larvae that hatch in the intestine. The resulting larvae burrow through the intestinal wall, enter the hepatic circulation via capillaries and lymphatics, and migrate via the right side of the heart into the lungs. The worms migrate up the bronchial tree, are swallowed, and make their way to the duodenum, where they mature into adults after several months. They can live as adults in the intestine for 1 to 2 years. Once the worms reach the intestines, patients may have nausea, vomiting, abdominal pain, and anorexia, reflecting high worm burdens that can lead to obstruction or chronic malnutrition.[8]

Clinical Features. Infected individuals are typically asymptomatic. The most common symptoms are nonspecific abdominal complaints. Some patients experience malaise and fever with or without respiratory symptoms such as cough, chest pain, dyspnea, bronchospasm, and hemoptysis. Pulmonary symptoms can develop 9 to 12 days after ingestion of eggs and can persist 2 to 3 weeks. This stage of the infection can be associated with leukocytosis and eosinophilia. Rarely, acute eosinophilic pneumonia can cause respiratory distress requiring intubation.[9,10] Pneumonitis can be seen seasonally in geographic regions where climate conditions favor seasonal transmission of ascariasis.[11]

Diagnosis. Thoracic imaging during the initial stage of infection may reveal transient unilateral or bilateral opacities (eFig. 58.1). The diagnosis is difficult to confirm during acute infection because ova do not appear in the stool until 2 to 3 months following initial infection. Peripheral eosinophilia may be detected, and larvae, eosinophils, or Charcot-Leyden crystals may be found in sputum or gastric contents.

Treatment. The treatment of choice for ascariasis is albendazole, although mebendazole and ivermectin are also efficacious against adult worms. Although the pulmonary phase is self-limiting, the persistent gastrointestinal phase warrants treatment to relieve symptoms and reduce transmission.

Hookworm Disease

Hookworm disease is caused by *Ancylostoma duodenale*, *A. ceylanicum*, or *Necator americanus*. These helminths infect at least 500 million people worldwide,[4,6] primarily in tropical and subtropical regions. They reside in the small intestine where they attach to the mucosa and feed on blood and host tissue, causing iron deficiency anemia as their major morbidity. Unlike the case with other helminths, hookworm prevalence increases with age, and there is no protective immunity.

Clinical Features. Hookworm ova are passed in the stools of an infected person, which then hatch into rhabditiform larvae that molt and become filariform larvae in contaminated soil. Filariform larvae then penetrate the skin, classically on the feet. This is often associated with a pruritic rash. The larvae then enter lymphatics or venules and ultimately reach the pulmonary circulation where they break through capillaries and enter the alveolar spaces. This stage can be associated with cough, bronchospasm, and transient pulmonary opacities with or without fever.[12,13] Peripheral and pulmonary eosinophilia are common during this stage of infection. The larvae then migrate up the tracheobronchial tree and are swallowed. Once the worms reach the intestine, an individual may have nonspecific gastrointestinal symptoms, including nausea and abdominal pain. Iron-deficiency anemia is the most important consequence of hookworm infection and can lead to cognitive problems. Malnutrition and hypoproteinemia can also complicate hookworm infection.

Diagnosis and Treatment. Stool examination will reveal hookworm ova 2 to 3 months after pulmonary symptoms but, in cases of light infection, concentration of stool may be necessary to detect the ova. Diagnosis during the pulmonary phase is difficult and relies upon identification of larvae in respiratory secretions, BAL fluid, or gastric secretions. The treatment of choice is albendazole (single dose) or mebendazole (twice daily for 3 days). These drugs kill the adult worms but are not effective against the pulmonary larval stages. Patients should be screened for ova in stools 1 month after treatment; if ova are still present, retreatment is indicated to eliminate adults that developed after the initial treatment.

Strongyloidiasis

Although there are more than 50 species of *Strongyloides*, *Strongyloides stercoralis* is the species seen in most human infections. *S. stercoralis* is present in most geographic environments. It is endemic in Latin America, South Asia,

sub-Saharan Africa, the United States (especially the southern states and Appalachia), Europe, and Australia.[14] At least 100 million people are estimated to be infected,[15] and many experts believe that the prevalence of infection is significantly higher.[16] Due to lack of awareness among clinicians and its prevalence in people in resource-poor settings, *Strongyloides* infection is often undiagnosed.

Strongyloides has a complex life cycle consisting of free-living and parasitic forms. Humans are the primary reservoir and acquire infection from soil or vegetation contaminated with human feces. Similar to hookworm infection, strongyloidiasis is initiated by penetration of the skin by infective filariform larvae, frequently through the soles of the feet. Unlike hookworm, *Strongyloides* sp are capable of an autoinfective life cycle, in which rhabditiform larvae may molt into filariform larvae while still in the small bowel and then invade the mucosa of the colon or the perianal area, recapitulating the early migratory phase.[17,18] After penetration of the infective filariform larvae through the skin or gut mucosa, they are carried via the circulation to the lungs and penetrate into alveoli and then ascend the tracheobronchial tree. The larvae are swallowed and reside in the small intestine where they ultimately develop into adult worms. Ova are released and hatch into rhabditiform larvae, which are passed in feces. These larvae can transform into filariform larvae, some of which can cause autoinfection. The larvae can also molt and transform into free-living adults in soil, where they may transform into infective filariform larvae.

Infection with *Strongyloides* results in a variety of clinical syndromes ranging from a mild disease to the hyperinfection syndrome seen in immunocompromised hosts.[19,20] Cell-mediated immunity that develops after primary infection limits the extent of autoinfection, so larvae and adult worms largely remain confined to the intestine, where they can survive for decades in immunocompetent individuals. With immunosuppression, especially caused by steroids, and other immunodeficient states, especially infection with *human T-lymphotropic virus-1* (HTLV-1),[21] autoinfection can become pronounced and lead to hyperinfection.

Clinical Features. The clinical manifestations of strongyloidiasis depend on the intensity of infection and immunologic status of the individual. Acute infection is rarely symptomatic, but pneumonitis can develop during the larval migration phase. More than 50% of patients with chronic infections are asymptomatic. Up to 75% of symptomatic patients have peripheral eosinophilia and elevated serum IgE levels; strongyloidiasis should be in the differential diagnosis of any person who presents with persistent eosinophilia. Patients can present with abdominal pain, diarrhea, and weight loss.[15] Dermatologic symptoms include pruritis, urticaria, and skin eruptions, including larva currens, manifest as linear streaks that can be seen on the trunk, thighs, and buttocks due to migrating larvae (Fig. 58.1). Reactive arthritis, nephrotic syndrome, chronic malabsorption, duodenal obstruction, and hepatic lesions have also been associated with chronic strongyloidiasis.

The common pulmonary manifestations in immunocompetent individuals are transient pulmonary opacities with productive cough, dyspnea, and bronchospasm. Chest radiographs range from being normal to showing bilateral nonspecific opacities. Strongyloidiasis may cause asthma, and improvement may follow eradication of the infection. Patients from highly endemic areas who have asthma or COPD with eosinophilia should always be screened for *Strongyloides* infection before instituting steroid therapy in order to avoid hyperinfection.

The *Strongyloides* hyperinfection syndrome develops due to accelerated autoinfection. Hyperinfection is usually observed in the setting of immunosuppression, especially when caused by high-dose corticosteroids,[19,21–24] although other immunosuppressive drugs and radiation therapy have also been implicated. Infection with HTLV-1 markedly predisposes to hyperinfection; this is thought to be secondary to deficiency of Th2 cells that normally contribute to control of helminths.[19,25] In addition, immunosuppression associated with lymphoma, leukemia, malnutrition, organ transplantation, and HIV/AIDS predisposes to *Strongyloides* hyperinfection (see eFig. 123.29), although some studies indicate the risk is not increased by HIV.[19,26] Hyperinfection is characterized by prominent gastrointestinal symptoms, including abdominal pain, nausea, vomiting, diarrhea, and ileus.

The lung is also an important target in hyperinfection. One study found that 15 of 16 cases with severe infection had pulmonary symptoms, with 13 cases having detectable organisms in respiratory secretions.[27] As filariform larvae migrate through the lungs, they cause pneumonitis with cough, hemoptysis, and respiratory failure. As the larvae leave the lumen of the gastrointestinal tract and invade the intestinal mucosa, they may carry bacteria from the gastrointestinal

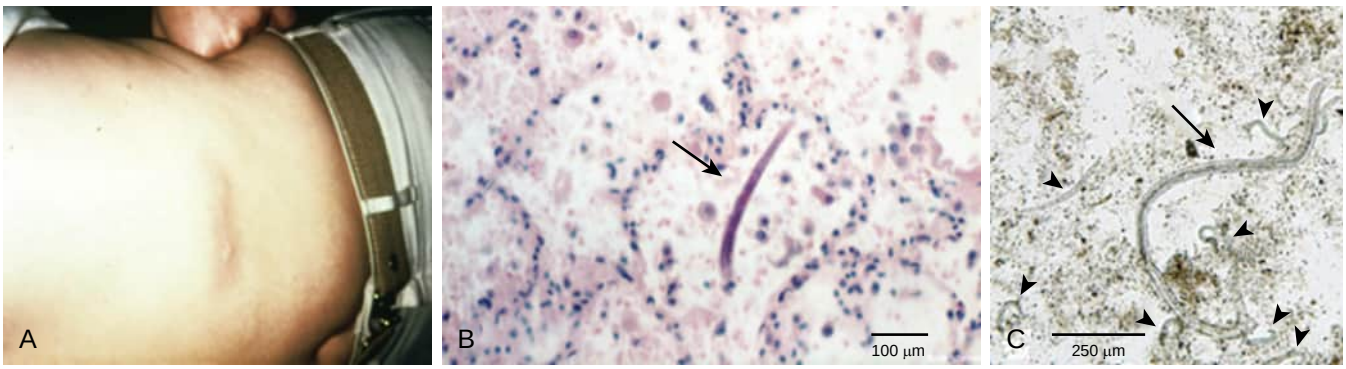

Figure 58.1 Strongyloidiasis. (A) Larva currens in a patient with chronic strongyloidiasis. (B) Filariform larva (*arrow*) in a pulmonary biopsy specimen. (C) Filariform (*arrow*) and rhabditiform (*arrowheads*) larval stages of *Strongyloides stercoralis* in the stool from a patient with hyperinfection syndrome. These were also found in the sputum. (A–B, From Zaiman H. A Pictorial Presentation of Parasites. https://www.astmh.org/education-resources/zaiman-slide-library. Courtesy American Society of Tropical Medicine and Hygiene.)

tract resulting in polymicrobial bacteremia, bacterial pneumonia, ARDS, and gram-negative bacillary meningitis.[27,28] *Strongyloides* hyperinfection has also been reported to mimic accelerated idiopathic pulmonary fibrosis.[29] Mortality of disseminated strongyloidiasis can be as high as 90%.

Diagnosis. In *Strongyloides* hyperinfection, larvae, ova, and adult worms may be observed in sputum, urine, BAL fluid, and other body fluids (see Fig. 58.1 and eFig. 123.29C). Diagnosis of *Strongyloides* infection may be difficult if the parasite load is low because the most common diagnostic test is based on detection of *Strongyloides* ova in stool samples (see Fig. 58.1). Serology assays use ELISA or immunofluorescence to detect serum antibodies to *Strongyloides*. Although ELISA is more sensitive than detecting ova in stool, the specificity of this test is suboptimal in regions where other nematodes such are filariae are endemic, because cross-reactive antibodies are common.[30] *Polymerase chain reaction* (PCR) tests exist for diagnosis but are not commercially available. It is not known how long DNA persists in the stool after successful treatment. Eosinophilia is common during hyperinfection; lack of eosinophilia is associated with a poor prognosis.[19,25]

Treatment. Ivermectin is the treatment of choice, eliminates the worm in over 90% of subjects,[16] and is more effective than albendazole.[32] All patients with *S. stercoralis* infection should be treated because of the risk of autoinfection and dissemination. For routine infection, a 2-day course of ivermectin is sufficient; however, treatment for hyperinfection is usually extended and individualized to ensure eradication.[19] Elimination or reduction of immunosuppression is important in achieving cure in the hyperinfection syndrome. HTLV-1 coinfection is associated with a higher rate of treatment failure,[33] and some patients may require additional therapy to prevent recurrence. Combination treatment with ivermectin and albendazole has also been proposed in severe cases or in chronic infections with HTLV-1 coinfection when ivermectin alone has failed. In hyperinfection cases where oral treatment cannot be absorbed or tolerated, the veterinary preparation of ivermectin has been administered subcutaneously.[34–36] There is no reliable test to monitor for cure, but many individuals have reversion or decline of IgG serologies with successful treatment.[30]

Most experts recommend that patients from highly endemic areas have a screening serology for strongyloidiasis before (or at the time of) starting steroids or organ transplantation; if they are seropositive, treatment is indicated to prevent the hyperinfection syndrome.

Tropical Pulmonary Eosinophilia

Tropical pulmonary eosinophilia (TPE) is a distinct clinical syndrome in patients from tropical areas endemic for lymphatic filariasis such as *Wuchereria bancrofti* or *Brugia malayi*.[37] Most cases have been described in India, Pakistan, Sri Lanka, Southeast Asia, parts of the African continent, and South America, especially Brazil and Guyana. TPE is now recognized in nonendemic areas, predominantly in immigrants; TPE is not thought to be a significant risk during a brief visit to an endemic area.

Clinical Features. Filariae have five morphologic stages. Humans are infected with third-stage larvae transmitted by mosquitoes. Infective larvae molt twice and develop into adults that survive in a human host for up to 20 years. The first-stage larvae, or microfilariae, are released into the circulation by female adult worms. *Wucheria* and *Brugia* microfilariae circulate in the blood in a temporal pattern that coincides with the feeding habits of their mosquito vectors. TPE is seen predominantly (80%) in men, usually in middle age. The major clinical features of TPE include nocturnal paroxysmal cough and bronchospasm, low-grade fever, weight loss, and lymphadenopathy; some patients also have hepatosplenomegaly. Leukocytosis, marked peripheral eosinophilia, and elevated serum IgE levels are common, and sputum or BAL specimens often contain eosinophils. Pulmonary function tests reveal both restrictive and obstructive defects. Although TPE is caused by filaria, patients with TPE do not have detectable microfilaremia. The pathogenesis of TPE is poorly understood but is believed to represent a response to microfilariae trapped in the lungs.[38,39]

Diagnosis. The diagnosis of TPE is based on the combination of clinical, radiologic, epidemiologic, and laboratory data, without the need for lung biopsy. Patients have nocturnal dyspnea with eosinophilia, elevated serum IgE, and a positive serologic test (ELISA) for antibodies to filarial antigens. Because the specificity of filarial serology tests is compromised by cross-reactivity with other helminths, other data are important for an accurate diagnosis.[1,40] Chest radiographs usually reveal increased bilateral bronchovascular markings and reticulonodular opacities or diffuse miliary lesions, or opacities in the middle and lower lung fields

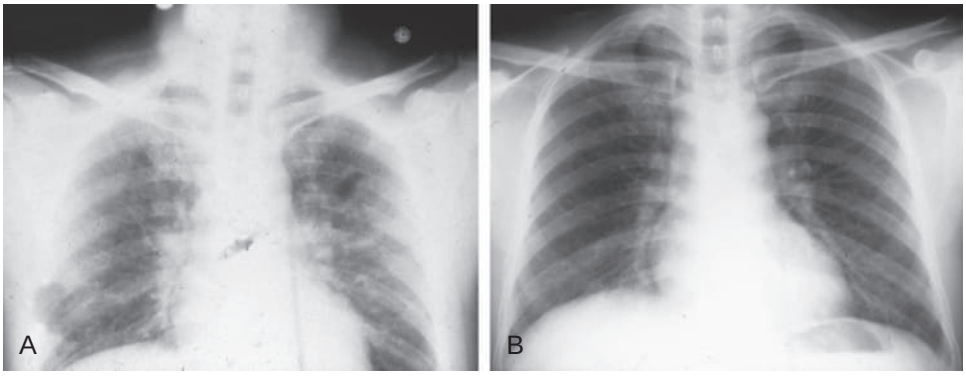

Figure 58.2 Tropical pulmonary eosinophilia. (A) Chest radiograph of a patient from Sri Lanka with confirmed tropical pulmonary eosinophilia shows subpleural right lung consolidation, subpleural left midlung opacity, and bilateral perihilar interstitial thickening. (B) Chest radiograph of the same patient after treatment with diethylcarbamazine. Note the improved opacities.

(Fig. 58.2, eFig. 58.2). Cavitation, bronchiectasis, and pleural effusion have been reported but are uncommon; chest radiographs may also be normal. When pathologic specimens have been obtained, eosinophilic infiltration of the interstitial and perivascular areas, eosinophilic abscess formation, and eosinophilic granulomas can be observed, and worm fragments are occasionally found.[41] Electron microscopic examination of the lung has demonstrated degranulation of the eosinophils, implying that tissue destruction may be mediated by cytotoxic granule proteins released by these cells. Fibrosis may be present if the course of the disease has been prolonged.

Treatment. All patients should be treated because TPE can progress to chronic restrictive lung disease. Administration of diethylcarbamazine, an antifilarial drug, results in improvement in the signs and symptoms of TPE, with reduced eosinophilia and serum IgE levels. The optimal duration of therapy is not established, but most guidelines recommend 3 weeks of diethylcarbamazine, although response may be incomplete or some patients may relapse.[42] Some experts have suggested ivermectin therapy either alone or in combination with diethylcarbamazine, although ivermectin has little effect on adult filariae and some patients require retreatment, regardless of the regimen. Steroid therapy should be administered with caution because TPE and pulmonary strongyloidiasis have similar presentations and steroids may enhance the morbidity and mortality of strongyloidiasis.

Wolbachia, a bacterial endosymbiont of *W. bancrofti*, is thought to play an importat role in the survival and the pathogenesis of *Wuchereria*. Doxycycline, which eliminates *Wolbachia*, has been shown to be effective in the treatment of filariasis.[43] *Wolbachia* is proving a valuable target for many of the filarial diseases, especially because it can be targeted with doxycycline, which is better tolerated than diethylcarbamazine, but no trials have compared the efficacy of short versus long courses of diethylcarbamazine with diethylcarbamazine with doxycycline.

Visceral Larva Migrans

Visceral larva migrans (VLM) is a clinical syndrome caused by human zoonotic infection with *Toxocara canis* (from dogs) or *Toxocara cati* (from cats).[44] Infection is acquired by ingesting eggs in contaminated soil or sandbox contents; a history of pica is common in infected children.[45] Although VLM usually afflicts children, adults have also been described with VLM. A VLM-like syndrome has also been reported as a result of infection with *A. suum*, the parasite of pigs,[46] and *Baylisascaris procyonis*, the raccoon ascarid.[47,48] The hatched larvae cannot mature into adults in humans (which are dead-end hosts), and the larvae migrate throughout the visceral organs of humans causing an acute eosinophilic syndrome.

Clinical Features. VLM affects multiple organs.[49] Pulmonary manifestations are found in 80% of cases and include cough, shortness of breath, and wheezing, resembling asthma.[50] Although symptoms are usually mild, severe respiratory symptoms have been reported.[51,52] VLM damages the lung due to immune responses to migrating larvae.[53] Other manifestations that can be seen are urticaria, lymphadenopathy, hepatosplenomegaly, seizures and other CNS involvement,[54–56] ocular disease, and myocardial disease.[57,58]

Diagnosis and Treatment. The radiographic appearance in VLM is variable and includes bilateral or segmental and patchy opacities, which can be migratory; subpleural opacities may be detected by *computed tomography* (CT). Laboratory evaluation may reveal leukocytosis, marked eosinophilia, elevated anti-A or anti-B isohemagglutinin titers, and abnormal liver function tests; IgE levels are frequently elevated. The diagnosis is made by ELISA and immunoblot testing. Because larvae do not mature to adults in humans, there are no ova in the stool. Because VLM is a self-limited syndrome, antiparasitic drugs may not be required. However, if the symptoms are moderate or severe, albendazole is the drug of choice; diethylcarbamazine is an alternative therapy. In severe cases, adjunctive steroids may accelerate symptom resolution. Preventive measures include control of soil contamination, curbing pica, and regular deworming of dogs and cats.

Dirofilariasis

Dirofilaria immitis, the dog heartworm, is an important cause of morbidity and mortality in dogs.[59] It is transmitted by mosquitoes, but humans are dead-end hosts. In the United States, most cases have been described in the Southeast. The worms migrate via the venous circulation and right heart where they reach the pulmonary arteries. In humans, the filariae are vascular parasites in the pulmonary artery, inducing vasculitis and formation of a pulmonary nodule upon death of the parasite (Fig. 58.3).[59] The majority of cases are asymptomatic, although some individuals may have cough and pneumonitis.[60] Eosinophilia

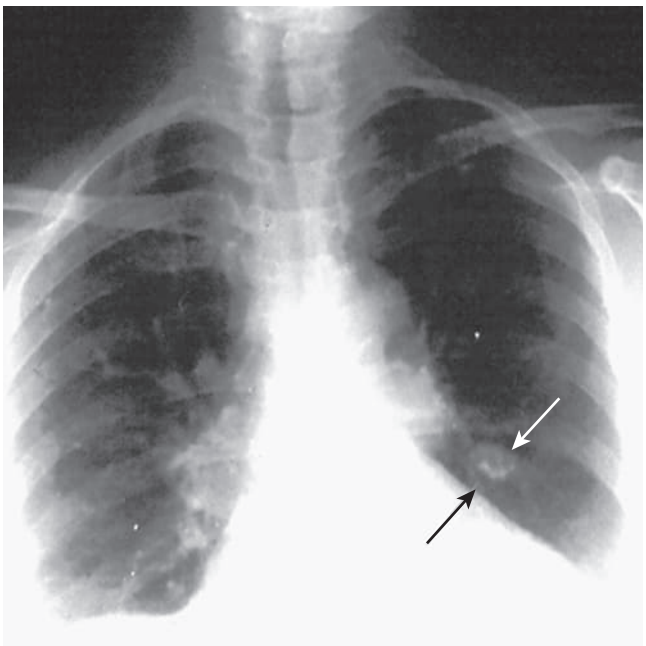

Figure 58.3 *Dirofilaria immitis*. Chest radiograph showing a solitary nodule (*arrows*) in the lung from a patient with confirmed *Dirofilaria immitis*. (From McCall GW, Genchi C, Kramer LH, et al. Heartworm disease in animals and humans. *Adv Parasitol.* 2008;66:193–285.)

is absent. Chest radiographs usually reveal a well-defined homogeneous spherical or oval coin lesion with smooth edges. Because there is no reliable noninvasive test for *Dirofilaria* infection, nearly all cases require biopsy to establish the diagnosis. Surgery is both diagnostic and curative.

Trichinosis

Trichinosis is caused by the parasites of the genus *Trichinella,* especially *T. spiralis.* These nematodes are found intracellularly in striated muscle. Humans usually acquire the infection by ingesting cysts containing the coiled larvae in raw or partially cooked pork, pork products, or game such as wild boar.

Clinical Features. Larvae emerge in the gastrointestinal tract from contaminated meat and invade the small intestine and disseminate throughout the body. This enteral stage may be either asymptomatic or may be accompanied by signs and symptoms of gastroenteritis. During dissemination, the larvae enter the bloodstream and circulate to various organs. Larvae encyst in peripheral skeletal muscle, forming the "nurse cell," consisting of an infected myocyte fed by vessels formed by neoangiogenesis. Most symptoms are due to inflammation associated with the invasion of larvae through the intestine and with influx of eosinophils and mast cells in the region of nurse cells. During the acute stage of infection, common symptoms include malaise, abdominal pain, fever, nausea, vomiting, myalgias, and muscle weakness with facial and generalized edema. Respiratory tract involvement is uncommon but, in severe cases, there may be dyspnea and transient pulmonary opacities. Dyspnea may result from larval invasion of the diaphragm and the accessory muscles of respiration[61]; however, lung inflammation may also play a role.[62]

Diagnosis and Treatment. Trichinosis is diagnosed based on its clinical presentation, epidemiology, eosinophilia, and a positive ELISA.[1] Muscle biopsy is definitive but has a low sensitivity. Treatment is with albendazole; corticosteroids may be added in severe cases, especially those with pneumonitis, myocarditis, or meningoencephalitis. It is unclear whether treatment alters the course of infection, particularly because it does not appear to affect worms after they have already encysted. Trichinosis is prevented by consuming meats fully cooked to a temperature of 140°F.

Gnathostomiasis

Gnathostomiasis is caused by helminths of the genus *Gnathostoma* and is endemic in South Asia and Southeast Asia, China, and Latin America, especially in cultures in which uncooked fish is consumed.[63,64] *Gnathostoma spinigerum* is the most common agent of human infection with this zoonotic pathogen. *G. spinigerum* has a complex life cycle involving two intermediate hosts; its definitive hosts are cats and dogs.[65] Humans usually become infected with third-stage larvae by ingesting raw or inadequately cooked freshwater fish or other intermediate hosts such as snakes, frogs, and chickens. Alternative routes of infection are ingestion of water containing infected copepods and penetration of the skin of food handlers by third-stage larvae from infected meat.[64] Larvae migrate from the gastrointestinal tract to the liver and abdominal cavity and then return to the stomach, where they embed in the wall, resembling a tumor with an aperture communicating with the lumen to release eggs.[66] The mechanical damage of migrating larvae has been cited as the primary cause of symptoms. Migration of larvae through tissues results in characteristic hemorrhagic tracts, surrounded by eosinophilic infiltration. When the lungs are involved, patients present with cough, pleuritic chest pain, hemoptysis, lobar consolidation, lobar collapse, pleural effusion, pneumothorax, or hydrothorax. Subcutaneous swellings, unexplained eosinophilic pleural effusion, and peripheral eosinophilia are considered a clinical triad and should prompt consideration of gnathostomiasis.

Diagnosis and Treatment. Diagnosis is based on the presence of eosinophilia, migratory inflammation, and history of exposure risk. The diagnosis can be confirmed by identification of the worm in tissue or by serology. The treatment of choice is albendazole or ivermectin.

TREMATODES

Paragonimiasis

The lung flukes of the genus *Paragonimus* encompass several species important in human disease.[67] *Paragonimus westermani* is found in humans and animals in Asia, Africa, and South America. More than 90% of cases are seen in Asia and *P. westermani* is rarely contracted in the United States.[68] Most cases of paragonimiasis acquired in the United States are due to *Paragonimus kellicotti*[65,69] from the ingestion of crayfish. This parasite has a complex life cycle involving freshwater snails, crustaceans, and mammals. Humans become infected by ingesting raw, partially cooked, or pickled crustaceans such as crab or crayfish containing an encysted larval form called a *metacercaria*, which excyst in the duodenum and penetrate the intestinal wall to enter the peritoneal cavity. Larval forms penetrate the diaphragm and enter the pleural cavity and lung parenchyma where they mature to adult worms. Pairs of adult worms live in cystic cavities near bronchial passages (Fig. 58.4) and produce eggs. Cystic cavities eventually rupture into a bronchiole, allowing eggs to be expectorated or swallowed and passed in feces.

Clinical Features. Although most acute infections are asymptomatic, some individuals present with abdominal pain, diarrhea, fever, chest pain, cough, urticaria, peripheral eosinophilia, and elevated levels of IgE.[70] These symptoms and signs usually manifest 2 weeks after ingestion of the metacercaria. Following acute infection, clinical disease has an insidious onset with clinical manifestations 5 to 10 years following exposure. These late clinical symptoms include cough productive of thick, rusty-colored or bloody sputum with Charcot-Leyden crystals, with or without pleuritic chest pain.[71] There may be frank hemoptysis resembling that in tuberculosis[72] (see Fig. 58.4). Fever and eosinophilia are often absent. A common finding is an abnormal chest radiograph in an asymptomatic patient. Pneumonia, bronchiectasis, and vasculitis may be present.

Diagnosis. Chest radiographs demonstrate a variety of lesions including focal involvement or consolidation.

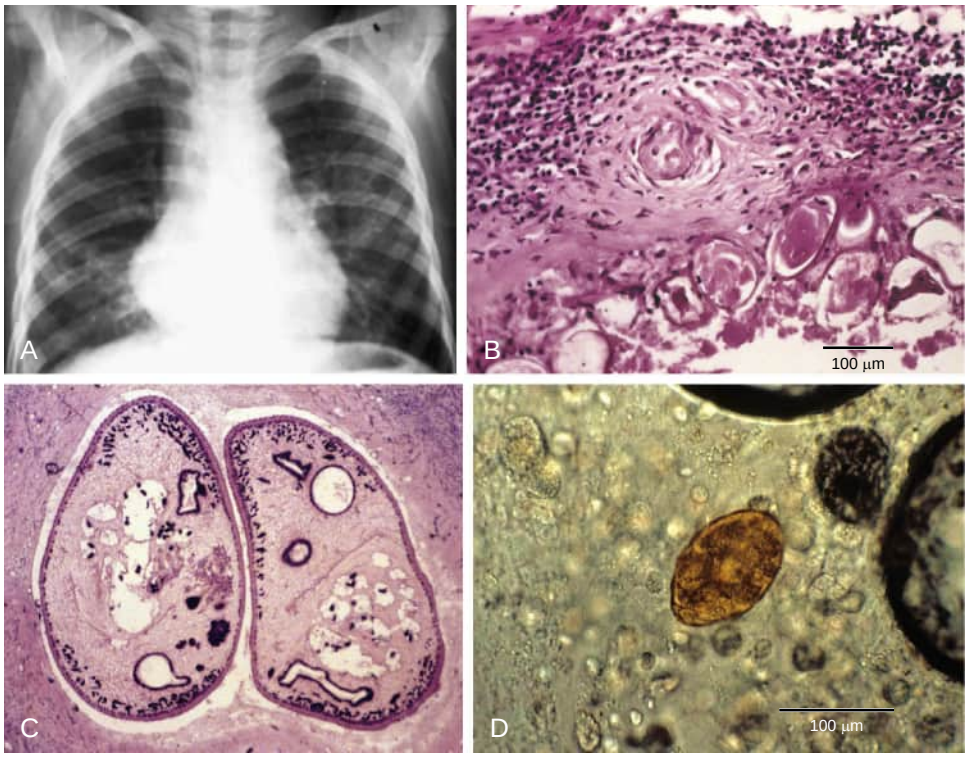

Figure 58.4 *Paragonimus westermani*. (A) Chest radiograph of a patient who presented with hemoptysis shows minimal perihilar left and right infrahilar linear and reticular opacities. (B) Granuloma surrounding ova. (C) Cross section of a pair of adults in the lung. (D) Ovum in the sputum.

Cavitary lesions may measure up to 4 cm in diameter; small cysts and calcified or noncalcified nodules (eFig. 58.3) may be present. Pleural effusion, pneumothorax, and pleural thickening may develop in a minority of patients.[71–73] The pleural fluid characteristically contains leukocytes, many eosinophils, elevated concentrations of protein and lactate dehydrogenase, and low concentrations of glucose. Histopathologic examination of the lung reveals adult worms within fibrous cysts communicating with bronchi or bronchioles; granulomas may contain eggs at the center (see Fig. 58.4B). Acute and chronic pathologic changes may coexist within the same pulmonary lesions.

When the diagnosis of paragonimiasis is suspected, it can be confirmed by finding morphologically characteristic eggs in sputum, stool, gastric aspirates, or tissue (see Fig. 58.4D). Bloody sputum is the most likely to yield positive results. ELISA and immunoblot assays that detect antibodies to *Paragonimus* antigens are useful for diagnosis.

Treatment. Praziquantel is the drug of choice. Untreated pulmonary paragonimiasis may resolve within 5 to 10 years (the life span of the adult worms), but chronic infection may be accompanied by extensive fibrosis. Paragonimiasis can be prevented by avoiding eating uncooked crabs and crayfish.

Schistosomiasis

Schistosomiasis is found in tropical and subtropical areas of the world including South America, Africa, the Middle East, and East Asia, including the Philippines.[74] The World Health Organization estimates that more than 200 million people are infected worldwide.[75] Five species of schistosomes cause human disease: *Schistosoma hematobium, S. mansoni, S. japonicum, S. mekongi,* and *S. intercalatum*. Infection is acquired when the free-swimming larval forms called *cercariae* penetrate the skin during contact with fresh water while the person is bathing, wading, or doing laundry. After penetrating the skin, the cercariae lose their tails and quickly transform into juvenile forms (schistosomula) that migrate to the lung and liver. These transform into adults that mate and then travel to their tissue destination. *S. hematobium* are found in the venous plexus of the urinary bladder while *S. mansoni* and *S. japonicum* reside in mesenteric veins. Female worms lay eggs that are excreted either in the urine (*S. hematobium*) or feces (*S. mansoni, S. japonicum*). Adult schistosomes may live and produce eggs for as long as 30 years.

Clinical Features. A rash consisting of erythematous raised 1- to 3-cm lesions may develop within hours (and as late as 1 week) after cercarial penetration of skin (especially in those infected for the first time). Symptoms usually develop between 4 and 8 weeks after exposure, which coincides with maturation of adults and the beginning of egg laying. In acute infection, in naive hosts, "Katayama fever" can develop after heavy exposure to *S. japonicum* or *S. mansoni*.[76,77] Katayama fever is characterized by urticaria, fever, chills, cough, wheezing, headaches, lymphadenopathy, hepatosplenomegaly, peripheral eosinophilia, and elevated serum IgE levels. The symptoms usually resolve within several weeks but can lead to death in rare instances. The major pathologic finding in schistosomiasis is that of granulomas surrounding eggs.[78] Chronic pulmonary schistosomiasis is the result of deposition of eggs in pulmonary vessels followed by granuloma formation and obstruction of blood flow.[79] Vasospasm and inflammation also contribute to the pulmonary findings in chronic pulmonary schistosomiasis.[80] Pulmonary hypertension develops in approximately 5% of patients with hepatosplenic schistosomiasis, usually after many years of untreated infection.[81,82]

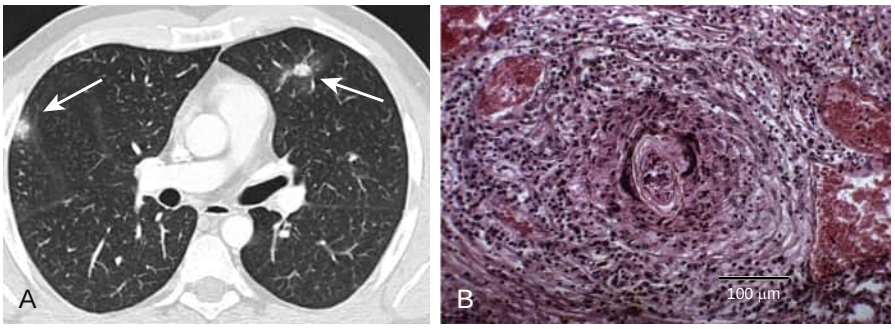

Figure 58.5 Schistosomiasis. (A) Computed tomography scan of the lung showing macronodules with ground-glass halo *(arrow)*. (B) Granuloma in the lung surrounding a *Schistosoma* ovum. (A, From Weber-Donat G, Donat N, Margery J. Acute pulmonary schistosomiasis: computed tomography (CT) findings. *Am J Trop Med Hyg.* 82:364, 2010. B, From Zaiman H. A Pictorial Presentation of Parasites. https://www.astmh.org/education-resources/zaiman-slide-library. Courtesy American Society of Tropical Medicine and Hygiene.)

Diagnosis and Treatment. Chest radiographs of patients with Katayama fever often demonstrate diffuse pulmonary opacities or nodules with indistinct borders, which may have a ground-glass "halo" appearance on CT (Fig. 58.5A).[83] Pleural effusions and thoracic lymphadenopathy may also be present. In chronic pulmonary schistosomiasis, imaging demonstrates nodules, miliary lesions, and cavitary lesions as well as signs of pulmonary hypertension.

Diagnosis is made by stool or urine examination or rectal biopsy, although shedding of eggs usually does not commence until 6 weeks after exposure.[84] Nearly all patients with Katayama fever have eosinophilia and elevated serum IgE levels. ELISA and immunoblot assays that detect antibodies to schistosomal antigens are available, but these tests may be negative in acute infection and may remain positive years after treatment. Lung biopsies may reveal the granulomas surrounding eggs (Fig. 58.5B).

The treatment of choice for schistosomiasis is praziquantel. Praziquantel kills adult worms but may not kill immature parasites. In some cases, symptoms can transiently worsen after treatment; this is presumed to be due to release of proinflammatory components of dead parasites. Pulmonary hypertension due to schistosomiasis can also worsen with antiparasitic treatment.

CESTODES

Echinococcosis

Echinococcus granulosus, the dog tapeworm, has a scattered worldwide distribution.[85] It remains an important public health problem in the Mediterranean basin where it is especially common in Italy, Spain, Albania, and the countries of the former Yugoslavia. It is also found throughout Central America and South America and in scattered areas of sub-Saharan Africa, China, Russia, and the countries of the former Soviet Union. *Echinococcus multilocularis,* the fox tapeworm, is endemic in Canada, parts of the United States, central Europe, the countries of the former Soviet Union, China, and northern parts of Japan.[85–88]

E. granulosus (Fig. 58.6) usually infects canines and sheds millions of eggs in feces. Intermediate hosts, including sheep and humans, become infected when they ingest the ova in contaminated food or water. Larvae are released from ova after ingestion and migrate via the bloodstream or lymphatics to various organs, usually the liver and lung, but kidney, bone, and brain may also be involved. The larvae mature into cysts, called echinococcal or hydatid cysts. The *E. granulosus* cyst is fluid filled and unilocular, consisting of an inner germinal layer and an outer acellular laminated layer. Daughter cysts may arise from the inner layer, the endocyst. There is also an outer layer, the pericyst, composed of fibrous tissue, which is host derived.

Clinical Features. The lungs are involved in 20–40% and the liver in 50–70% of cases of cystic echinococcosis.[85,89] Infection usually presents as a solitary cyst involving one organ; 10–15% of individuals have more than one organ involved. In children, the lungs are involved more often than the liver.[90] Pulmonary echinococcosis is commonly discovered as an incidental finding on chest imaging (eFig. 58.4). In symptomatic patients, the clinical manifestations of pulmonary echinococcosis are most often the consequence of cyst rupture; less frequently, symptoms are due to compression by an enlarging cyst. Rupture of a hydatid cyst into a bronchus results in fever and cough, which can have an abrupt onset. In some patients, the sputum can contain macroscopic fragments of the parasite. Ruptured cysts that communicate with an airway can become secondarily infected by bacteria and/or fungi. Rupture of a hydatid cyst into the pleural space can be associated with hypersensitivity responses, including fever, urticaria, and wheezing; frank anaphylaxis can also develop, but is rarely fatal. Rupture into the pleural space can also cause empyema, with or without bacterial superinfection. Cysts that enlarge without rupturing may erode into adjacent structures and cause bone pain, hemorrhage, or airway compression.[91]

Diagnosis and Treatment. Diagnosis depends on the combination of imaging, serology, and microscopy. On chest radiographs, uncomplicated (unruptured) hydatid cysts appear as homogeneous oval or round masses 1 to 20 cm in diameter with smooth borders and normal adjacent lung tissue (see Fig. 58.6C and eFig. 58.4). If a cyst ruptures into a large airway, partial discharge of the cyst contents results in an air-fluid level. If the cyst ruptures, cyst fragments, especially the rigid mouthparts (scolices) of the parasite, may be detected by microscopic examination of sputum or pleural fluid. A hydatid cyst completely emptied of liquid contents and collapsed can exhibit a "water lily" sign (see Fig. 58.6D), which is pathognomonic of a collapsed cyst but is rare. The water lily sign is created when air enters the cyst, allowing detachment of the inner endocyst from the outer pericyst, so that the endocyst collapses to float on the fluid in the partially filled pericyst, creating the appearance of a water lily floating on a pond. CT scans may allow distinction of hydatid cysts from other pulmonary cysts by revealing the presence of daughter cysts within a larger cyst. Other complications, such as cardiac echinococcosis and pulmonary embolization of organisms are rare (eFig. 58.5).

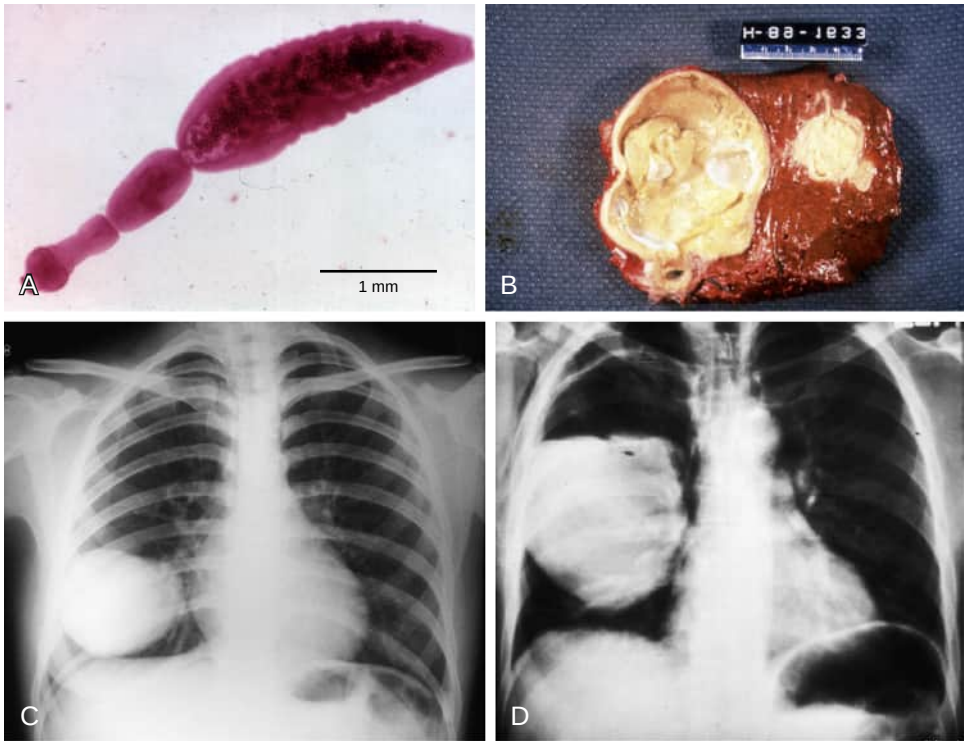

Figure 58.6 Echinococcal cysts. (A) Adult *Echinococcus granulosis*. (B) *Echinococcus* cyst of the liver near the diaphragm. (C) *Echinococcus* cyst of the lung. (D) Ruptured *Echinococcus* cyst of the lung with the "water lily" sign. (A and D, From Zaiman H. A Pictorial Presentation of Parasites. https://www.astmh.org/education-resources/zaiman-slide-library. Courtesy American Society of Tropical Medicine and Hygiene. C, Courtesy Dr. Saul Santivanez, Lima, Peru.)

Serologic testing consists of an ELISA that detects antibodies to a cyst antigen. Although the assay is quite sensitive in patients with hepatic involvement, the sensitivity in patients with pulmonary echinococcosis is only about 50%, so serology is confirmatory rather than diagnostic. The current ELISA also has cross-reactivity to cysticercosis.

Treatment. Surgical removal is the principal therapeutic approach in patients who can tolerate the procedure.[85] Surgery must be planned to minimize the likelihood of intraoperative cyst rupture, because rupture can result in anaphylaxis and parasite dissemination with subsequent relapse. Preoperative administration of albendazole can reduce the consequences of dissemination.[91] Praziquantel is added to albendazole, particularly if the cyst has ruptured, because it has a scolicidal effect. Intraoperative administration of a helminthicide agent such as hypertonic saline or 1% formaldehyde, left in place in the cyst lumen for 15 minutes or more before further manipulation, is also thought to minimize the consequences of spillage of cyst contents.[91–93] In patients with symptomatic or complicated echinococcal cysts who cannot tolerate a thoracic surgical procedure, prolonged treatment with albendazole may improve symptoms, but is curative in only a minority of cases. Praziquantel also has activity, and a combination of albendazole and praziquantel may have greater efficacy than either drug alone. Monitoring responses to drug treatment must be based on clinical findings and imaging procedures; serial serologic assays have been found to be without value.

Echinococcus multilocularis

Alveolar echinococcosis caused by *E. multilocularis* is a rare but potentially fatal disease. Wild canines are the definitive hosts and small animals are the intermediate hosts. The liver is the initial target of this parasite and the incubation period can be exceedingly long. It can spread to the lung as a result of metastatic dissemination or by direct extension through the diaphragm of a liver cyst with rupture into the thorax. *E. multilocularis* can involve the bronchial tree, pleural cavity, and mediastinal structures. The diagnosis is made by serology and biopsy. The only cure is radical resection followed by long-term therapy with albendazole. If not amenable to surgery, life-long treatment with albendazole may be beneficial.

PROTOZOA

Protozoa are unicellular eukaryotic organisms. They are usually acquired either by ingestion or by the bite of a vector. Gastrointestinal or systemic symptoms generally predominate in protozoal infections, although pulmonary symptoms can develop.

AMEBIASIS

Amebiasis, caused by *E. histolytica*, predominantly affects individuals who live in Mexico, Central and South America, Africa, and the Indian subcontinent; however, travel and immigration have globalized this infection. *Entamoeba* are estimated to cause 40,000 to 100,000 deaths yearly[94] and infect 500 million people,[94] although more recent data suggest many of these are infected with the nonpathogenic *Entamoeba dispar* rather than pathogenic *E. histolytica*.[95] *E. histolytica* does not involve intermediate hosts and has a simple life cycle, alternating between environmentally hardy cysts and invasive trophozoites. Cysts have a chitinous cell wall that enables them to persist in the environment for weeks to months and to infect subsequent hosts

that ingest contaminated food or water. In 4–10% of individuals infected with *E. histolytica,* trophozoites invade the intestinal mucosa to cause intestinal disease. In others, the trophozoites enter the bloodstream and can establish infection in the liver, brain, or lungs.[96,97]

Clinical Features. Intestinal amebiasis is associated with abdominal pain, tenesmus (constant urge to defecate), and diarrhea, which may be bloody, mucoid, or watery. Fever may be present. Symptoms can last several weeks. Fulminant infection with ileus and intestinal perforation can also develop. The most common site for extraintestinal amebiasis is the liver (eFig. 58.6); a smaller proportion of cases affect the lungs, and amebic brain abscesses are uncommon. The typical patient with an amebic liver abscess is an adult man who has acquired the infection in an endemic area and presents with fever and right upper quadrant pain without intestinal symptoms. Amebic liver abscesses are approximately 10-fold more common in men than women; the reason for this sex difference is unknown but it is not due to differences in rates of infection.[98] Mouse models of amebiasis also demonstrate differences in host immune response between male and female mice.[99] Many patients presenting with extraintestinal amebiasis do not have cysts or trophozoites in the stool. A prior amebic abscess or amebiasis does not confer immunity to recurrence. Extraintestinal manifestations of amebiasis can present years after leaving an endemic area.[94]

The lung is the second most common extraintestinal site of *E. histolytica* infection and usually results from the extension of a right lobe hepatic abscess, so patients may have right upper quadrant abdominal pain as well as pulmonary symptoms. Pleuropulmonary amebiasis complicates amebic liver abscess in 7–20% of cases,[4] although the chest radiograph is abnormal in nearly 50% of cases. Although any lobe of the lungs can be affected, the right lower lobe is most commonly involved,[100] and pulmonary amebiasis can be confused with bacterial pneumonia (see eFig. 46.61).[94] Findings include an elevated right hemidiaphragm, right pleural effusion, right lobe atelectasis, pulmonary consolidation with abscess formation, and hepatic-bronchial fistulas. An empyema may develop from rupture of a liver abscess into the pleural space.[101] Patients can present with shortness of breath[102] or rarely with respiratory failure[103] or the expectoration of "anchovy-paste" sputum, which represents the contents of an amebic abscess.[104] Rarely, pulmonary amebiasis results from hematogenous spread without liver abscess. Hepatic abscesses can also rupture into the pericardium and cause cardiac tamponade.[101,105,106]

Diagnosis. *Entamoeba* infections can result from either *E. histolytica* or the nonpathogenic *E. dispar. E. histolytica* and *E. dispar* trophozoites are indistinguishable; however, antigen and PCR assays can differentiate these species.[107] Serology tests are highly sensitive for the diagnosis of extraintestinal amebiasis, but can remain positive for years after an infection. Therefore, serology cannot distinguish current and past infection. In cases of suspected pulmonary involvement in amebiasis, CT scanning of the lung and adjacent liver should be used to define the extent of involvement and presence of fistulae (see eFig. 46.61).[108]

Treatment. Because of the potential for asymptomatic infection to develop into dysentery or extraintestinal disease, or to be transmitted, all *E. histolytica* infections should be treated.

Patients with liver abscesses can usually be managed medically without percutaneous aspiration, but pleural or pericardial effusions[101] should be drained and larger lesions (>300 mL) may improve more quickly if drained.[109] Metronidazole is highly effective and can be used orally or systemically. Monitoring responses with repeated imaging procedures is not useful, because it is not unusual for the radiographic appearance to worsen before improvement.[108] Another nitroimidazole, tinidazole, is an alternative and has efficacy and toxicity similar to that of metronidazole. Agents such as paromomycin and diloxanide furoate that kill cysts in the intestine are not effective against extraintestinal amebiasis. After tissue-invasive amebiasis has been treated with metronidazole or tinidazole, a cysticidal agent is usually used (e.g., paromomycin or diloxanide) to decrease the possibility of relapse or transmission of infection.[94]

MALARIA

Human malaria is caused by *P. falciparum, P. vivax, P. malariae, P. ovale,* or *P. knowlesi. P. knowlesi*, a simian malaria seen in Southeast Asia, has been associated with zoonotic malaria infections in humans.[110] Because this species resembles *P. malariae* morphologically, the parasite was mistaken for *P. malariae,* but *P. knowlesi* malaria has a more virulent course that can result in death. The World Health Organization estimates in 2017 there were 219 million malaria cases and approximately 435,000 deaths due to malaria, primarily in children infected with *P. falciparum* in sub-Saharan Africa. Severe malaria, including cerebral malaria, is seen in many areas of the tropical and subtropical world and among travelers and immigrants in nonendemic areas. Severe malaria can include anemia, coma, and respiratory failure; these are most frequent with *P. falciparum* infection. Most fatalities in the developed world are due to delayed diagnosis because patients and clinicians are unaware of the risk of severe malaria.

Plasmodium species are transmitted by the bite of the female *Anopheles* mosquito. Sporozoites injected into the bloodstream traffic to the liver and initiate the clinically silent hepatic phase, which results in the release of thousands of merozoites that infect erythrocytes. The erythrocytic stages are responsible for clinical disease. The pathogenesis of severe malaria is not completely understood, but is thought to be caused by inflammatory mediators such as cytokines and chemokines and by vascular leukocyte adhesion molecules. *P. falciparum* elaborates a family of variant antigens that enables infected erythrocytes to adhere to microvascular endothelium.[111] Sequestration of infected erythrocytes in tissue microvessels is thought to be critical for pathogenesis of the most severe manifestations of malaria including cerebral malaria.[112] There is no sterile immunity (i.e., resulting in the elimination of all organisms) to malaria, and malaria has exerted a profound selective pressure upon human evolution. Nearly all genetic erythrocyte defects, including sickle cell anemia, thalassemia, and pyruvate kinase deficiency, are most prevalent in regions of the world with high malaria prevalence and some, including heterozygous HbS, protect from severe malaria.[113]

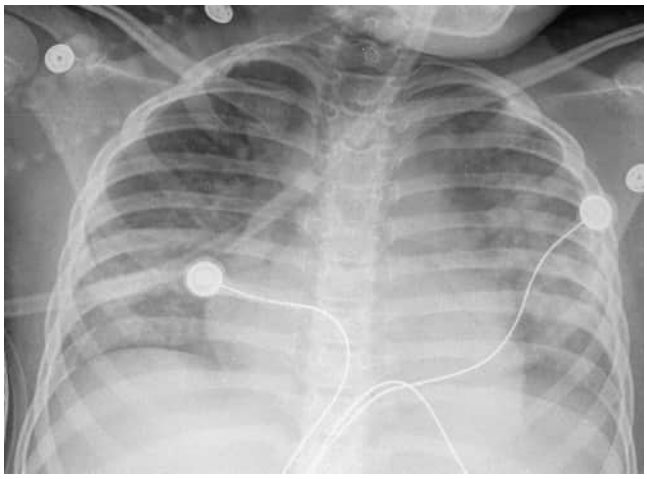

Figure 58.7 Malaria. Diffuse bilateral symmetric lung opacities resembling pulmonary edema in a child with malaria.

Clinical Features. Severe malaria is associated with fever, chills, anemia, thrombocytopenia, jaundice, and renal failure. *P. falciparum* malaria can progress within days to cause multiorgan failure, especially in nonimmune patients. Fever is associated with the lysis of infected erythrocytes, and is classically periodic (every day for *P. knowlesi*, every 2 days for *P. falciparum, P. vivax,* and *P. ovale;* every 3 days for *P. malariae*) and nocturnal. However, this is not a reliable clinical sign, particularly for *P. falciparum*.

Patients with malaria may present with cough and minimal involvement of the lung or with severe symptoms and signs of acute lung injury and acute respiratory distress syndrome.[114] Children, pregnant women, and nonimmune travelers to endemic areas are most susceptible to pulmonary complications (Fig. 58.7). Chest radiographs may reveal bilateral opacities and lobar consolidation and pleural effusions, and alveolar macrophages may contain hemozoin, a brown degradation product of hemoglobin produced by the parasite. Bronchiolitis and pneumonia have been reported in the setting of *P. vivax* infection.[115] Patients in coma as a result of cerebral malaria may be susceptible to aspiration pneumonia, and may require antibiotic therapy.

Noncardiogenic pulmonary edema may develop in patients with severe malaria with any species of *Plasmodium,* even after several days of antimalarial therapy. The pathogenesis of the noncardiogenic pulmonary edema is unclear. Increased permeability of the alveolar capillaries appears to be an important mechanism by which the liquid fills the alveolar space, and pulmonary edema may be aggravated by fluid overload. The mortality rate of severe falciparum malaria is high.

Diagnosis. Diagnosis is made by rapid diagnostic test or examination of a blood smear, although PCR may be available from some reference labs. Thick blood smears are used to determine whether parasites are present, while thin blood smears are used by experienced technicians to identify the *Plasmodium* species by morphology. For *P. falciparum*, only the immature ring forms are detectable in the peripheral blood, so initial malaria smears may be negative. Mature intraerythrocytic forms of *P. falciparum* cause infected cells to adhere to the microvasculature and are thus rarely evident in peripheral blood. The presence of mature *P. falciparum* forms in the blood and high parasitemia (>10% of erythrocytes containing parasites) are signs of severe disease. *P. vivax* infects only reticulocytes, so parasitemias are lower than with *P. falciparum.* Because initial malaria smears may be negative, a smear should be repeated after 8 hours, and empirical treatment begun if the patient is seriously ill.

Rapid diagnostic tests for *P. falciparum* and *P. vivax* malaria antigens are available as point-of-care diagnostic tests and are often the only test used in malaria endemic settings. Because antigen can persist, these tests do not reliably discriminate current from very recent infection. PCR tests are not currently commercially available.

Treatment. All travelers to malaria endemic regions are advised to take antimalarial prophylaxis and use insecticide-treated bed nets to prevent malaria, but a history of malarial prophylaxis does not rule out malaria and some travelers who have taken prophylaxis either had subtherapeutic levels of drug or acquired resistant organisms.

Supportive care, in addition to specific antimalarial therapy, is extremely important, especially in the case of noncardiogenic pulmonary edema. The treatment of malaria is dependent on the species and the geographic area of the world where it was contracted. Although *P. vivax, P. ovale, P. malariae,* and *P. knowlesi* can be treated with chloroquine, *P. falciparum* is nearly universally resistant to chloroquine. *Intravenous* (IV) artesunate is the treatment of choice for patients with pulmonary manifestations of malaria, which usually signifies severe malaria.[116] IV quinidine or quinine is no longer available in the United States; as of March 2019, severe malaria must be treated with IV artesunate, available by contacting the toll-free CDC Malaria Hotline (855-856-4713). Outside business hours, providers should call 770-488-7100 and ask to speak with a CDC malaria expert. IV quinidine is still approved and available outside the United States.

Artesunate resistance has been detected in *P. falciparum* with increasing frequency, especially in Southeast Asia, and is manifested by slower clearance of parasitemia, thus requiring a longer duration of treatment to achieve cure.[117] Careful attention to fluid balance is required to maintain adequate end-organ perfusion and prevent respiratory insufficiency due to fluid overload. Correction of hypoglycemia and attention to oxygenation are critical. The CDC no longer recommends exchange transfusion in patients with high parasitemias (>10%) because the clinical benefit of exchange transfusion has not been established. Severe malaria may also be complicated by concurrent pneumonia or bacterial sepsis that must be managed with appropriate antibiotics.

Clinicians seeking help for diagnosis or treatment of malaria should consult www.cdc.gov/malaria/, or call the phone numbers given previously. Once the patient improves, there are a variety of choices for oral treatment. *P. vivax* and *P. ovale* treatment regimens should include primaquine to eliminate hypnozoite forms within the liver after determining the patient's glucose-6-phosphate dehydrogenase status.

TOXOPLASMOSIS

Toxoplasma gondii is a ubiquitous Apicomplexa protozoan parasite of mammals and birds. *T. gondii* can propagate clonally in its intermediate hosts via tissue cysts, which can initiate infection in hosts that ingest these cysts in raw or

undercooked meat. Cats are the definitive hosts and oocysts shed in cat feces are highly infectious, providing a source for contamination of food and water. In humans, infection can transmit vertically to the fetus in a serologically naive mother, leading to congenital toxoplasmosis.[118] The prevalence of infection, as assayed by seropositivity, varies with geography and ranges from 10–90%. *T. gondii* can cause opportunistic infections in immunocompromised hosts, including individuals with AIDS (see Chapter 123).[119] *T. gondii* has a predilection for the central nervous system, where it causes necrotizing encephalitis, and for the eye, where it causes retinochoroiditis. The development of clinically apparent toxoplasmosis is usually a consequence of reactivation of slowly replicating bradyzoites found within tissue cysts into actively replicating, morphologically distinct tachyzoites.[120–122]

Clinical Features. In most cases of pulmonary toxoplasmosis, pulmonary disease is part of multisystem disease in an immunocompromised host such as in persons with HIV/AIDS (CD4 T cells < 50/μL[123–126]), in patients with hematologic malignancies, and in organ transplant recipients.[127–130] Pulmonary toxoplasmosis may rarely develop in immunocompetent persons where it may resemble atypical pneumonia.[131] Clinical symptoms include fever, cough, and shortness of breath.[123–125] A more fulminant pneumonia associated with acute toxoplasmosis has been seen in South America where highly virulent strains of *T. gondii* have caused "Amazonian toxoplasmosis," presenting as severe disseminated systemic disease.[132]

Diagnosis. Chest radiographs reveal bilateral diffuse opacities and/or nodular bilateral opacities that may be confused with *Pneumocystis* pneumonia.[123–125] Examination of the sputum or fluid from BAL may reveal organisms that stain with Giemsa.[133] Pleural fluid, if present, may contain tachyzoites.[134] PCR-based molecular techniques are also available if the parasite is suspected but cannot be found by staining. At autopsy, the lungs are congested and hemorrhagic with areas of consolidation. Histopathologic examination reveals an interstitial pneumonitis and alveolar damage. A frank necrotizing pneumonia may also be observed, with many extracellular and intracellular tachyzoites. Nearly all patients with toxoplasmosis are seropositive, and a negative serologic test suggests another diagnosis. Rarely, primary infection can present as disseminated disease, and serologies may be negative.

Treatment. The treatment of choice for toxoplasmosis is pyrimethamine and sulfadiazine with leucovorin to prevent bone marrow toxicity, but there are several alternatives, including pyrimethamine and clindamycin with leucovorin. Although pyrimethamine and sulfadiazine are considered the treatment of choice, trimethoprim-sulfamethoxazole is active against *T. gondii* and has been suggested as primary therapy in resource-poor areas due to its low cost.[135]

OTHER PROTOZOA

Several other protozoa have been reported to be associated with pulmonary manifestations. Some of the more common parasites that can occasionally present with pulmonary disease are discussed here. Many of these have been increasingly reported, presenting as disseminated disease involving multiple organs, including the lungs, in association with HIV infection or other immunocompromised states.[136] In addition, *Cyclospora cayetanensis, Trichomonas vaginalis, Trichomonas tenax, Trichomonas hominis,* and *Balantidium coli* have been reported to present with pulmonary disease.[136]

Babesiosis

Babesia are intraerythrocytic protozoan parasites.[137–139] *Babesia microti* is transmitted by the tick *Ixodes scapularis*, the Lyme disease tick vector, and has been described in infections in Massachusetts, New York, Rhode Island, Connecticut, New Jersey, and the upper Midwest. Other *Babesia* species have been described in California, Oregon, and Washington. In Europe, babesiosis is rarer but more frequently lethal, and is associated with *Babesia divergens*. Blood transfusion is another mode of transmission. The onset is usually gradual with malaise, fever, chills, sweats, and myalgias. Nausea, vomiting, headache, and psychiatric problems are also reported. There may be splenomegaly, anemia, thrombocytopenia, a normal or low white blood cell count, mild elevation of hepatic enzymes, and evidence of hemolysis. Asplenic and immunocompromised patients often have more severe disease, including jaundice, renal failure, pancytopenia, high-level parasitemia, shock, and disseminated intravascular coagulation. The major pulmonary complication is noncardiogenic pulmonary edema.[140,141] As in malaria, the etiology of noncardiogenic pulmonary edema is not well understood.

Diagnosis. The diagnosis of babesiosis is made by identification of the parasitized erythrocytes on blood smears or by PCR. Immunofluorescence antibody-based serologic tests for *Babesia* have also been developed, but the high rate of seroprevalence in endemic regions limits the usefulness of these tests. Blood can be injected into a hamster for verification of active infection, and PCR-based diagnostic tests may be deployed for blood screening.[142] *B. microti* is treated with quinine and clindamycin or azithromycin and atovaquone.[143] There have been reports of immunocompromised persons developing possible resistance to azithromycin and atovaquone after multiple treatments.[144]

Cryptosporidiosis

The genus *Cryptosporidium* contains several species widely distributed in animals including birds, cattle, and sheep. *C. parvum, C. hominis,* and *C. meleagridis* most commonly infect humans and are acquired by the ingestion of oocysts via water or food. The most common clinical manifestation of cryptosporidiosis is watery diarrhea, which is self-limiting in immunocompetent hosts but chronic in immunocompromised hosts. In patients with HIV/AIDS, diarrhea may be persistent, and may be massive and fatal.[145] Extraintestinal manifestations of cryptosporidiosis have been observed. *Cryptosporidium* involvement of the lower respiratory tract is most common in patients with HIV/AIDS but can also develop in patients with other

conditions.[146–148] Common symptoms include cough, fever, and shortness of breath; there may also be respiratory insufficiency.

Although the mechanism by which *Cryptosporidium* colonizes the respiratory tract is not clear, aspiration and hematogenous spread from the intestinal tract have both been suggested.[149] Chest radiographs are consistent with interstitial pneumonitis. Alveolar damage and interstitial fibrosis and hyperplasia of alveolar epithelial type 2 cells have been found at autopsy of patients with pulmonary cryptosporidia.[149]A study of HIV-negative Ugandan children with *Cryptosporidium* diarrhea and cough or other respiratory symptoms revealed that 17 of 48 (35.4%) had *Cryptosporidium* in their sputum,[150] suggesting that *Cryptosporidium* may cause more pulmonary disease than previously suspected and that respiratory transmission is possible.

Diagnosis. *Cryptosporidia* can be detected in stool or respiratory samples by a modified acid-fast stain or by immunofluorescence, although PCR is now emerging as the test of choice as part of multipathogen panels.

Treatment. Treatment in immunocompromised individuals has been suboptimal. Nitazoxanide is approved for treatment of cryptosporidiosis in immunocompetent children and adults.[151–153] Nitazoxanide is not efficacious in immunodeficient individuals. Although azithromycin and paromomycin have been associated with improvement in some patients, clinical trials have not confirmed their efficacy in immunodeficient adults.

Free-Living Ameba

Four genera of free-living ameba infect humans: *Naegleria, Acanthamoeba, Balamuthia,* and *Sappinia.*[154] Infections with these species are rare but worldwide. *Naegleria* and *Acanthamoeba* are commonly found in lakes, swimming pools, tap water, and air conditioning units. *Acanthamoeba* sp are usually associated with granulomatous skin lesions and corneal ulcers. In immunocompromised patients, *Acanthamoeba* sp and *Balamuthia mandrillaris* may cause subacute or chronic granulomatous encephalitis accompanied by respiratory symptoms, nodular opacities, consolidation, and respiratory failure. In those patients, parasites have been recovered from BAL; organisms can also be detected in lung tissue (Fig. 58.8). *Naegleria fowleri* is associated with primary amebic meningoencephalitis that is acute and usually lethal. A PCR-based assay to identify ameba species in clinical samples is available from the CDC.[155] The mortality of these infections is high. Based on case reports, miltefosine is currently used for therapy.

Leishmaniasis

Leishmania sp are found in Asia, Africa, Central and South America, and regions of Europe that border the Mediterranean.[156] Transmission of *Leishmania* sp is through the bites of sand flies, and three clinical syndromes are recognized: cutaneous, mucocutaneous, and visceral. Cutaneous and mucocutaneous forms may also be observed in the viscera in immunocompromised individuals. Visceral leishmaniasis caused by *Leishmania donovani, L. infantum,* and *L. chagasi* is characterized by fever, abdominal pain, and hepatosplenomegaly, often accompanied by anemia, thrombocytopenia, leukopenia, and generalized bone marrow suppression. In immunocompromised patients such as those with HIV/AIDS,[157] intracellular forms (amastigotes) may be observed in macrophages of many organs. In the respiratory tract, amastigotes have been observed in the mucosa of the larynx and in the lung and pleura.[158–163] Interstitial pneumonitis, granulomatous inflammation of the bronchial mucosa, and mediastinal lymphadenopathy have all been described in patients with visceral leishmaniasis.[164]

Diagnosis and Treatment. Identification of the parasite by microscopy is the most commonly used method of diagnosis. Culture and molecular techniques such as PCR with *Leishmania* species-specific primers are also available. *Leishmania* amastigotes can be found in samples obtained by BAL, thoracentesis, or transbronchial biopsy.[165] Therapy of leishmaniasis includes pentavalent antimony compounds and amphotericin B formulations.[157] Miltefosine, an oral agent, has also been approved for the treatment of leishmaniasis.[166]

Microsporidiosis

Microsporidia are ubiquitous intracellular parasites found in invertebrate and vertebrate hosts and are related to the Cryptomycota (i.e., fungi). The phylum contains more than 200 genera and over 1500 species. Microsporidia infect nearly all animal phyla. They predominantly infect the digestive tract, but infections of almost all organ systems are documented. The microsporidia that cause human

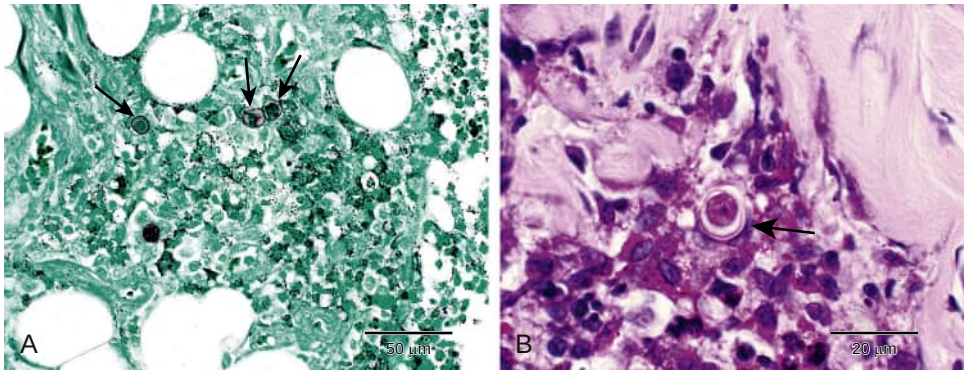

Figure 58.8 *Acanthamoeba*. (A) Silver stain showing *Acanthamoeba (arrow)*. (B) Periodic acid–Schiff stain showing the organism (*arrow*). (A, From Zaiman H. A Pictorial Presentation of Parasites. https://www.astmh.org/education-resources/zaiman-slide-library. Courtesy American Society of Tropical Medicine and Hygiene. B, Courtesy Dr. Govinda S. Visvesvara.)

disease are zoonotic and/or water borne. *Enterocytozoon bieneusi* and *Encephalitozoon intestinalis* are the most common human pathogens, followed by *Encephalitozoon cuniculi* and *Encephalitozoon hellem.* In immunocompromised hosts, particularly in patients with advanced AIDS, these organisms have been associated with a diarrheal and chronic wasting syndrome. Other risk factors for infection include treatment with anti–tumor necrosis factor-α antibodies, chemotherapy, other immune-modulating drugs, and organ transplantation. Immune restoration by antiretroviral therapy has markedly reduced the incidence of microsporidiosis in HIV infection.[135]

Clinical Features. Involvement of the respiratory tract and the sinuses by microsporidia can cause rhinitis, sinusitis, and nasal polyposis.[167–173] Involvement of the lower respiratory tract has been observed in the setting of disseminated disease and presents as an interstitial pneumonitis. *E. hellem* infection has been reported to involve the entire length of the respiratory tract, with manifestations including erosive tracheitis and bronchiolitis. There are case reports of *E. cuniculi*, *E. hellem,* and *E. intestinalis* causing bronchiolitis with and without pneumonia. Respiratory tract infection due to *E. bieneusi* has also been reported.[174] *Tubulonosema acridophagus* infection with respiratory failure and pulmonary opacities has been described in which spores of the organism were recovered by BAL.[175]

Diagnosis and Treatment. Diagnosis of this infection can be made by finding microsporidian spores in clinical samples by microscopy; PCR-based molecular techniques are also available. Treatment depends on the species identified. In general, albendazole combined with immune reconstitution is the treatment of choice, although albendazole is not recommended for *E. bieneusi* or *Vittaforma corneae* infection due to intrinsic resistance.[135] Fumagillin, an agent with a broader anti-microsporidian activity, is another option.[176]

Trypanosomiasis

Trypanosoma cruzi is the cause of Chagas disease, which is found in areas of Mexico and in Central and South America.[177] It is transmitted by Triatominae bugs (e.g., bloodsucking insects also called kissing bugs) or by blood transfusion, organ transplantation, ingestion of contaminated food and fluids, or vertical transmission (mother to child). Babies born with congenital Chagas disease have a variety of manifestations including pneumonia and, in these cases, amastigotes have been reported in the lung.[178] Pneumonitis and acute pulmonary edema may be seen in acute Chagas disease. Congenital and acute disease are treated with either nifurtimox or benznidazole.[179]

Patients with chronic Chagasic cardiomyopathy may have congestive heart failure and thromboembolic events. Chronic Chagasic patients with megaesophagus may have a variety of pulmonary complications including aspiration pneumonia, bronchiectasis, and lung abscess.

Key Points

- Helminthic parasites often migrate through the lungs en route to another organ, particularly the gastrointestinal tract. Migration is often associated with eosinophilia or eosinophilic pneumonia.
- Tropical pulmonary eosinophilia is in the differential diagnosis of eosinophilic pneumonias, and should be considered in any patient from an endemic area of filarial infections and who presents with eosinophilia and pulmonary opacities.
- Paragonimiasis, echinococcosis, and dirofilariasis can be symptomatic or asymptomatic, and present as pulmonary nodules or mass lesions.
- Pulmonary paragonimiasis is commonly associated with hemoptysis. Because tuberculosis and paragonimiasis often coexist in the same geographic areas of the world, it is important to consider the diagnosis of paragonimiasis in a TB suspect and, if indicated, to examine the sputum and stools for ova and to perform a serologic test for this parasite.
- Schistosomiasis can cause pulmonary hypertension, usually after many years of untreated infection, which is thought to be due to deposition of eggs in pulmonary vessels, granuloma formation, and obstruction to blood flow.
- Strongyloidiasis is unique in that there is chronic infection with autoinfection that can result in a potentially lethal hyperinfection syndrome, particularly in patients given glucocorticoids.
- Protozoan parasites usually do not preferentially infect the lungs but, because many are highly prevalent in human populations, pulmonary disease may be seen, particularly as part of a disseminated infection.

IN MEMORIAM

This chapter is dedicated to Dr. Herbert B. Tanowitz, an exceptional physician and scientist, whose contributions significantly enhanced our understanding of parasitic infections and the pathophysiology of these important diseases.

Key Readings

Jourdan PM, Lamberton PHL, Fenwick A, Addiss DG. Soil-transmitted helminth infections. *Lancet*. 2018;391:252–265.

Krolewiecki A, Nutman TB. Strongyloidiasis: a neglected tropical disease. *Infect Dis Clin North Am*. 2019;33:135–151.

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Nabeya D, Haranaga S, Parrott GL, et al. Pulmonary strongyloidiasis: assessment between manifestation and radiological findings in 16 severe strongyloidiasis cases. *BMC Infect Dis*. 2017;17:320.

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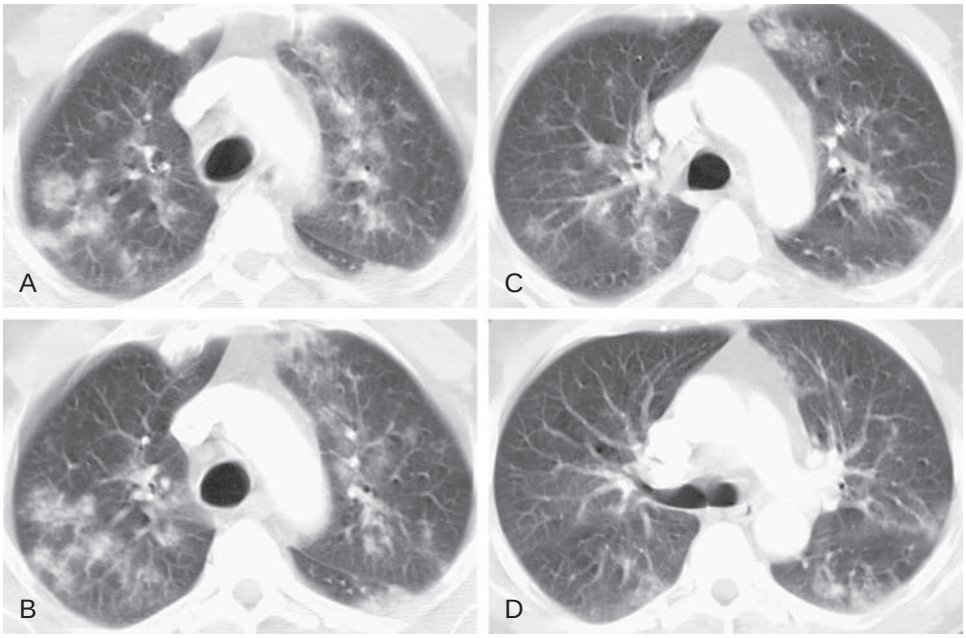
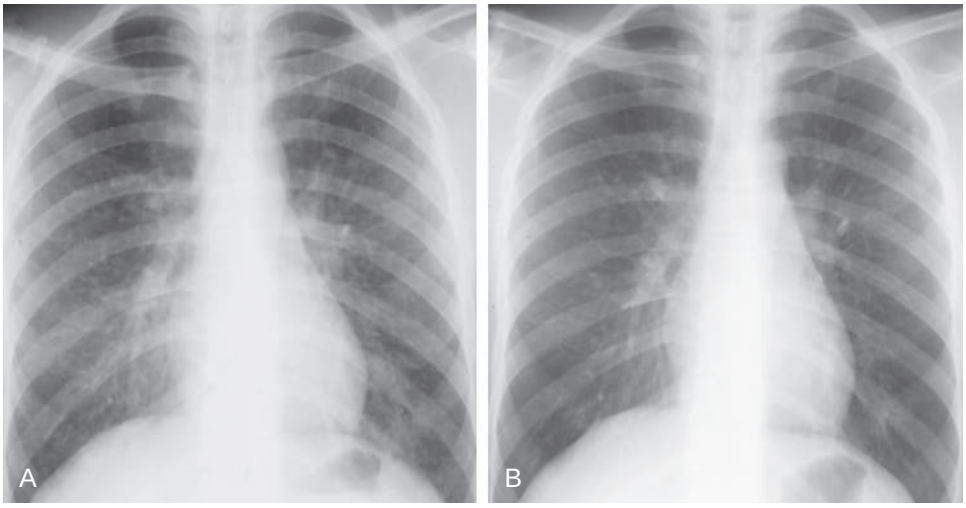
Complete reference list available at ExpertConsult.com.

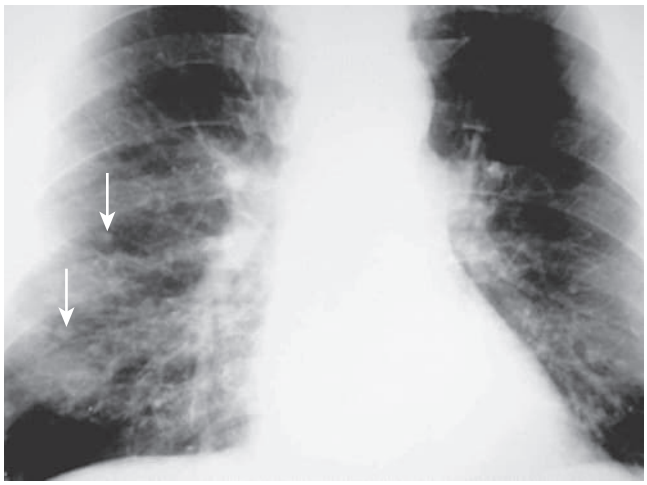
eFIGURE IMAGE GALLERY



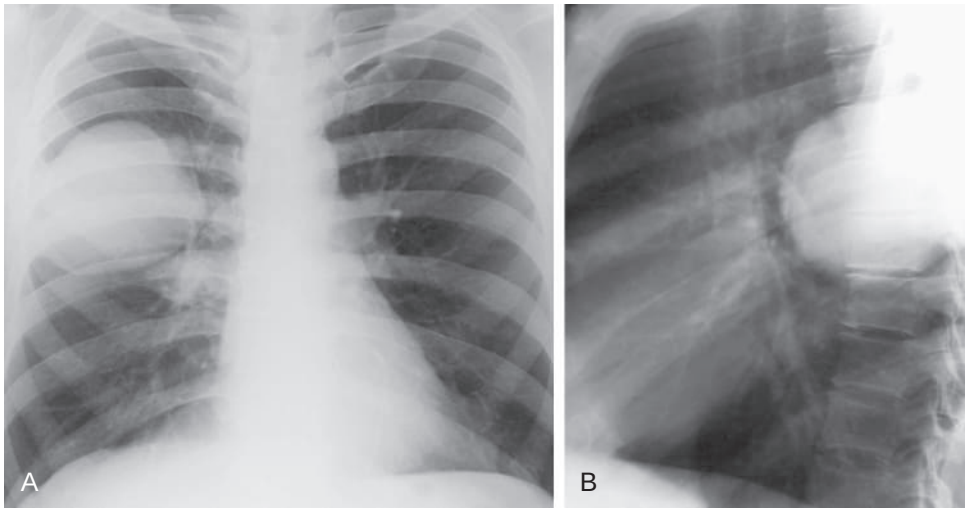
eFigure 58.1 Loeffler syndrome caused by ascariasis. (A–D) Axial chest computed tomography displayed in lung windows shows patchy bilateral nodular areas of ground-glass opacity. The patient complained of cough, hemoptysis, and chest pain, and was found to have peripheral eosinophilia. *Ascaris lumbricoides* infection was later diagnosed. (Courtesy Michael B. Gotway, MD.)



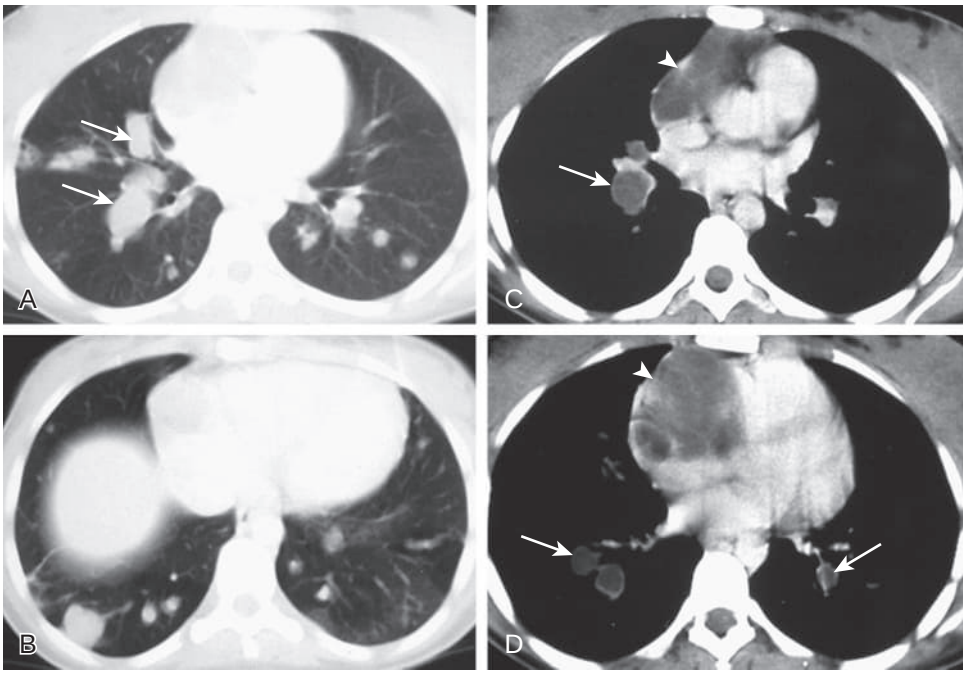
eFigure 58.2 Tropical eosinophilia. (A) Frontal chest radiograph shows bilateral perihilar small nodules. The appearance is nonspecific and could be seen in a number of infections. *Wuchereria bancrofti* infection was confirmed. (B) The patient was subsequently treated with diethylcarbamazine and doxycycline, leading to resolution of the small nodules. (Courtesy Michael B. Gotway, MD.)



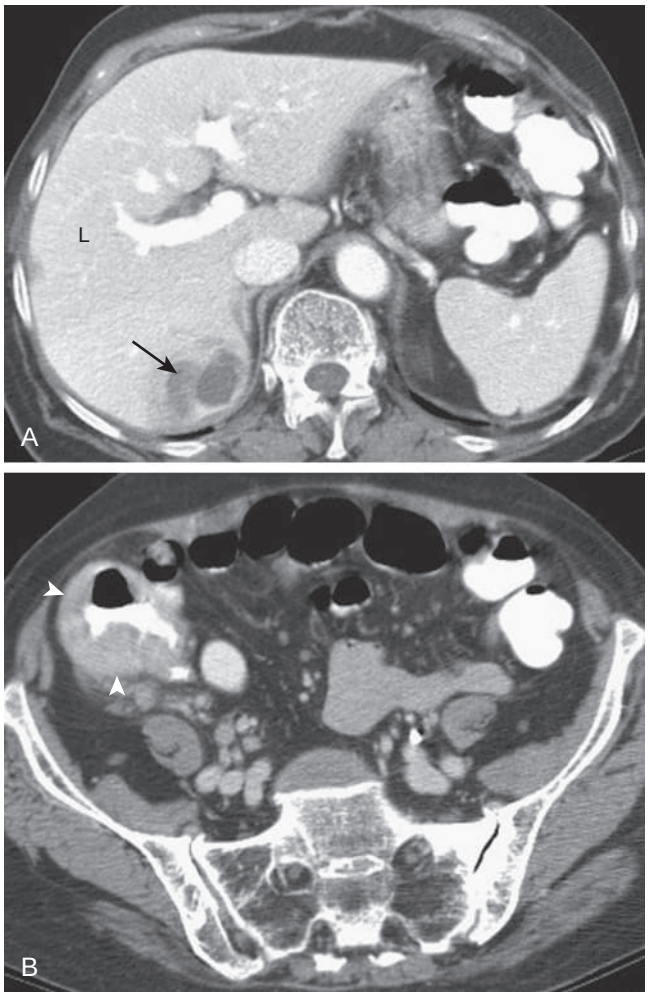
eFigure 58.3 Paragonimiasis. Frontal chest radiograph in a patient with paragonimiasis shows patchy bilateral linear opacities and interstitial thickening associated with small nodules (*arrows*). (Courtesy Michael B. Gotway, MD.)



eFigure 58.4 Hydatid disease: *Echinococcus granulosus* infection. Frontal (A) and lateral (B) chest radiographs show a large homogeneous mass in the posterior right upper lobe. (Courtesy Michael B. Gotway, MD.)



eFigure 58.5 Hydatid disease: cystic echinococcal embolization. (A–D) Axial enhanced chest computed tomography performed in a 23-year-old woman shows multiple bilateral circumscribed nodules, some with a somewhat tubular shape (*arrows*, A). The soft tissue window images (C–D) show low attenuation embolic material, representing *Echinococcus* organisms, filling and expanding the pulmonary arteries (*arrows*, C–D). The source of the embolic material is the right atrium (*arrows*, C–D); note the faint internal septation within this mass. (Courtesy Michael B. Gotway, MD; case by Elaine M. Caoili, MD, University of Michigan, Ann Arbor.)



eFigure 58.6 Amebiasis: colitis and liver abscess. (A) Axial contrast-enhanced computed tomography image through the liver (L) shows a low attenuation posterior right lobe liver abscess (*arrow*). (B) Axial image through the pelvis shows thickening of the cecum (*arrowheads*), consistent with colitis. (Courtesy Michael B. Gotway, MD.)

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59 OUTBREAKS, PANDEMICS, AND BIOTERRORISM

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INTRODUCTION

The U.S. *Centers for Disease Control and Prevention* (CDC) lists 27 bacteria, natural toxins, and viral families that are potential agents of bioterror; seven are listed as high priorities given their lethality, relative ease of production, hardiness, and suitability for airborne dissemination.[1] Intentional release of such agents is not hypothetical. In 2001, spores of anthrax were mailed to U.S. lawmakers and journalists. In total, 22 people contracted anthrax, five of whom died. Ricin, a toxin found in castor beans, was mailed in a similar attack on U.S. officials. In addition, naturally occurring outbreaks of known and novel pathogens have long been a feature of human existence but are now almost routine. Examples include the global influenza pandemic of the early twentieth century and the spread of human immunodeficiency virus from a small region of West Africa to all inhabited parts of the world. More recently, there have been recurrent outbreaks of viral hemorrhagic fevers, particularly Ebola; the resurgence of arthropod-borne infections such as Dengue, Chikungunya, and Zika; and ongoing outbreaks of measles, including in the United States. The ongoing pandemic of COVID-19, caused by *severe acute respiratory syndrome–associated coronavirus 2* (SARS-CoV-2), demonstrates the dramatic worldwide impact of a serious viral disease readily transmitted by the respiratory route. Whether naturally occurring or the result of a laboratory accident or deliberate attack, additional future outbreaks are increasingly likely given geopolitical and climate-related upheavals and the emergence of synthetic biology. Although the circumstances of an outbreak will vary, in any such event many of those affected will likely require intensive care, highlighting the unique and important roles for the pulmonary critical care clinician.

This chapter first reviews the major roles that the critical care clinician can expect to play during a consequential bioterrorism event or outbreak. Foremost, it is the clinician who may be among the first to notice unusual signs and symptoms or atypical manifestations of a disease process in the severely ill that signal suspicion of an outbreak. As the course of the public health emergency unfolds, the critical care physician may be called upon to play roles beyond that of the bedside clinician, such as adapting frameworks and triggers for patient triage when intensive care capacity is overwhelmed and when population-based critical care is needed; advising on allocation of scarce resources (e.g., ventilators, dialysis machines); supporting optimal infection prevention and control measures; and setting hospital policies and procedures. They may also be expected to participate in data collection efforts aimed at tracking and controlling the event, understanding the natural history of a disease, or developing and testing treatments. Finally, the involved intensivist is often a trusted source of information in crises and can be called upon to explain the situation to hospital staff or, through media, to the broader community. Responding to such events therefore requires not only clinical acumen, but also a readiness to act in a variety of ways that may be unfamiliar to the critical care clinician.

Next, major clinical syndromes that may signal a consequential event and their treatment are outlined. Although pandemic influenza is the infectious agent most likely to cause a worldwide crisis (see Chapter 47 for a full discussion of influenza), and the ongoing pandemic of COVID-19 (see Chapter 46a), which demonstrates the large impact of other respiratory viruses, this chapter focuses on the recognition of other dangerous pathogens that may be less familiar to most clinicians and the countermeasures available to prevent or treat them. Attacks involving chemicals, trauma, or nuclear weapons/radiation (see Chapters 103 and 104) are beyond the scope of this review, although there are commonalities in the critical care clinician's roles in response to biologic and nonbiologic catastrophic events.

CLINICAL PRESENTATIONS

AWARENESS AND RECOGNITION

Like a mass shooting, chemical attack, earthquake, or severe weather event, a novel virulent infection incident may first present without warning. More likely, however, an outbreak of a consequential pathogen, such as a novel influenza virus or the coronaviruses responsible for the SARS

Table 59.1 Clues of an Emerging Outbreak or Bioterror Attack

EPIDEMIOLOGIC CLUES

- A rapidly increasing disease incidence
- Unusual clustering of disease for the geographic area
- Disease outside of the normal transmission season
- Simultaneous outbreaks of different infectious diseases
- Disease outbreak in humans after recognition of disease in animals
- Unexplained number of dead animals or birds
- Disease requiring a transmission vector previously not seen in the area
- Rapid emergence of genetically identical pathogens from different geographic areas

MEDICAL CLUES

- Unusual route of infection
- Unusual age distribution or clinical presentation of common disease
- More severe disease and higher fatality rate than expected
- Unusual variants of organisms
- Unusual antimicrobial susceptibility patterns
- Uncommon disease with bioterrorism potential

and COVID-19, will emerge and spread more slowly, quietly smoldering before it is recognized. The clinical manifestations of some public health emergencies are pathognomonic, but particularly when an unexpected, highly communicable disease presents with syndromic symptoms only, the clinical diagnosis will not be immediately recognized.

While public health agencies continually monitor patterns of illness or health care utilization (especially emergency department visits and hospitalizations) for signals that could portend significant outbreaks, the astute clinician is often the first to recognize and report an unusual case or illness cluster (Table 59.1). The storied recognition of *Legionella pneumophilia* in 1976 is attributed to a Bloomsburg, Pennsylvania, physician who noted that three men under his care died unexpectedly in rapid succession shortly after attending a convention in Philadelphia.[2] One of the first men to die was presumed to have suffered a myocardial infarction and, even when scores became ill, swine flu was initially believed to be the culprit. The physician's report to state health authorities helped to trigger an investigation that ultimately resulted in the identification of the pathogen and its transmission via a hotel air conditioning system. Likewise, the 2001 anthrax attack was first suspected by a clinician who noted box-car shaped bacilli on a Gram stain from the cerebrospinal fluid of a patient who presented to the emergency department and rapidly deteriorated.[3] The 2015 Zika outbreak was initially recognized when a practicing obstetrician noted an unusual cluster of cases of neonatal microcephaly in northeastern Brazil.[4]

In each of these examples, observant clinicians noted suspicious patterns that led to the recognition of an emerging event. However, an awareness of emerging events can also help the clinician to recognize suspected cases. Growth in global travel coupled with decreases in flight times mean that within a day, a contagious traveler can be almost anywhere on the planet. Given this relatively recent connectivity of humanity, the critical care clinician needs to maintain a general awareness of major outbreaks developing around the world.

The necessity of such a perspective was dramatically highlighted during the 2014 to 2015 West Africa Ebola outbreak, when an asymptomatic man boarded a flight to the United States four days after helping transport a symptomatic pregnant woman to an Ebola treatment unit in Liberia.[5] He became ill after arriving in Texas, presenting to a health care facility with fever, abdominal pain, nausea, and headache. A travel history was not noted and, diagnosed with sinusitis, he was sent home with antibiotics. Only when his condition deteriorated and he returned to the emergency department was a travel history obtained, revealing his recent travel to Liberia during its raging Ebola outbreak. A diagnosis of Ebola virus disease was ultimately made late in the clinical course; the patient died, and two nurses involved in his care were infected. Alerts about emerging infections and outbreaks from trusted sources are readily available and can be subscribed to for automated email delivery. Electronic health records can be programmed to incorporate such alerts. Epidemiologic reports issued by state public health authorities should be reviewed regularly by all potential health care first responders, including intensivists, and relevant threats shared with staff.

Classical Syndromes and High-Consequence Pathogens

Central to the detection of any emerging outbreak or biologic threat is making a diagnosis. Illness caused by natural or human-produced threats can range in severity from mild to severe and present with subtle signs and symptoms that could be mistaken for routine illnesses. They can also present with highly unusual, often pathognomonic manifestations. Clusters of three common symptom complexes—typically accompanied by fever—should raise the suspicion of a potentially serious outbreak: rash, respiratory distress, and hemorrhage.

Dermatologic Syndromes

Rash accompanied by fever can be caused by a number of common infectious and noninfectious etiologies but, when the skin manifestations are atypical or when observed in a cluster of patients, they should raise concern about novel infections. Anthrax, tularemia, smallpox, measles, and a host of other potentially epidemic diseases can present foremost with skin lesions, but the pathognomonic presentation of each of these pathogens is different[1,6-9] (Fig. 59.1).

Skin lesions following exposure to anthrax are typically small and blister-like, often located in groups on the face, neck, or upper extremities. They are painless, with a central black eschar. Tularemia, caused by infection with the bacterium *Francisella tularensis*, can also cause an ulcerative skin lesion but one that is painful, with associated swelling of regional lymph nodes and high fever.

Although smallpox was eradicated in 1980, stocks of the virus exist in U.S. and Russian government laboratories, and there are concerns about its release as a bioterror agent or during a laboratory accident.[10] The viral exanthem associated with smallpox is a centrifugally spread vesicular rash with all lesions at the same stage of development appearing first in the mouth, then spreading to the face and the extremities followed by the trunk, palms, and soles. Over time the vesicles fill with fluid and grow before forming a



Figure 59.1 Anthrax, tularemia, smallpox, and plague. (A) The anthrax lesion on the skin of the forearm is caused by the bacterium *Bacillus anthracis*. The cutaneous ulceration has begun to turn black, hence the origin of the name "anthrax," after the Greek word for coal. (B) A tularemia lesion is shown on the dorsal skin of the right hand caused by the bacterium *Francisella tularensis*. (C) The maculopapular lesions on this patient's arm were caused by the smallpox virus, variola major. These lesions were in their pustular phase of development. (D) An axillary bubo and edema exhibited by a patient with plague. (Courtesy Centers for Disease Control and Prevention, Public Health Image Library. A, #2033, James H. Steele. B, #2032, Dr. Brachman. C, #10495, Dr. John Noble Jr. D, #2061, Margaret Parsons and Dr. Karl F. Meyer.)

crust and then a scab that eventually falls off. Again, fever accompanies the rash.

Measles (rubeola), noted here because of its preventable worldwide reemergence in 2019,[11] is associated with a morbilliform rash that initially appears on the face at the hairline and spreads downward to the neck, trunk, arms, legs, and feet, often described as centripetal spread. The presence of Koplik spots (small mouth lesions that appear like white grains of sand surrounded by a red ring, often on the buccal mucosa) and patchy erythema with central pallor on buccal mucosa should arouse a high level of clinical suspicion for measles, especially in the unvaccinated or under-vaccinated.

Pulmonary Syndromes

The pneumonic form of many high-consequence infections, including anthrax, plague, avian influenza, tularemia, and coronavirus-associated infections (e.g., SARS, Middle East respiratory syndrome, COVID-19), is clinically indistinguishable from the clinical presentation of pneumonia due to other bacterial and viral etiologies; thus clinical suspicion is driven by clustering or by exposure and travel history.[1]

Anthrax spores, considered by the CDC to be the most likely bioterror agent to be used in an attack,[12] can be inhaled and then germinate in the mediastinal lymph nodes, where released toxins cause hemorrhagic necrosis. Mediastinitis ensues, producing the classic widened mediastinum on chest imaging, sometimes with necrotizing pneumonia (Fig. 59.2). The course is biphasic; prodromal symptoms are nonspecific and can easily be mistaken for influenza. Nausea, odynophagia, chest pain, and hemoptysis are distinguishing features of the presentation that should raise suspicion for a diagnosis other than influenza. Unrecognized and untreated, the respiratory status deteriorates to a fulminant phase that is typically fatal even if antibacterial therapy is initiated. Monoclonal antibodies to the anthrax lethal toxin have been approved by the *U.S. Food and Drug Administration* (FDA) for treatment of inhalational anthrax (see later).

Pneumonic plague, caused by *Yersinia pestis,* can arise naturally but, like anthrax, is rare in the United States.[13] It is a rapidly progressive illness that begins acutely and is often fatal if antibacterial therapy is not instituted on the first day. The tempo of the illness and often the presence of hemoptysis may be clues, along with any that are epidemiologic, such as travel to an endemic area, such as the southwest United States, or clustering of similar cases.

Hemorrhagic Fevers

Viral hemorrhagic fevers (VHFs), including Ebola virus disease, Marburg virus disease, and Lassa fever, often present with nonspecific symptoms that evolve into a sepsis phenotype that is difficult to distinguish from other sepsis etiologies.[14-17] Despite their being labeled hemorrhagic, most patients infected with these viruses do not have evidence of significant bleeding. However, the recent outbreaks of Ebola in West Africa and the Democratic Republic

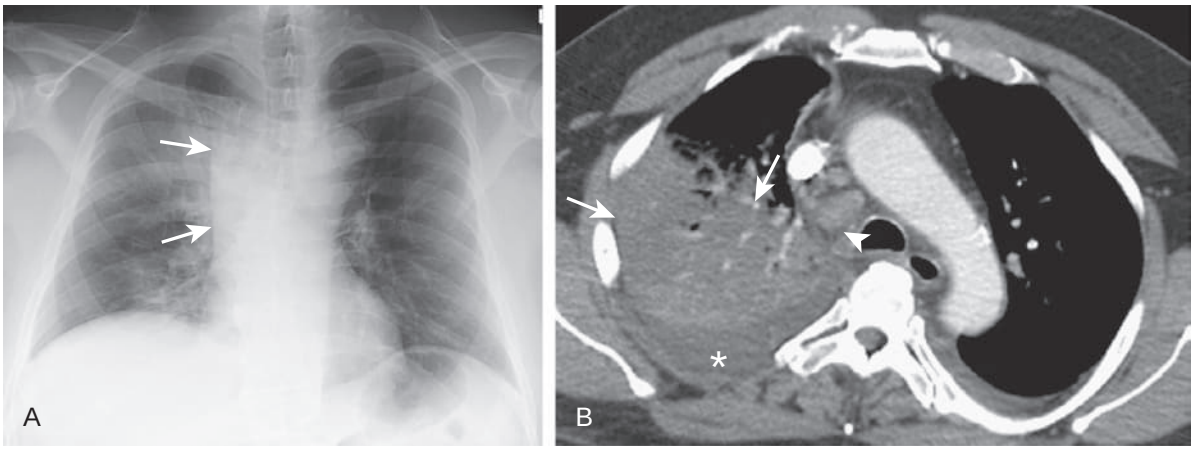

Figure 59.2 Imaging findings in inhalation anthrax: chest radiography. (A) Frontal chest radiograph in a 61-year-old man with a 3-day history of productive cough, fever, and exertional dyspnea shows poorly defined medial right upper lobe ground-glass opacity associated with a markedly widened right mediastinum (*arrows*). During recent travel through parks in the western United States, he had been exposed to animal antlers and hides, wild bison, and donkeys. (B) Axial enhanced chest computed tomography scan displayed in soft tissue windows shows right upper lobe consolidation (*arrows*) and a small right pleural effusion (*asterisk*) and trace left pleural liquid associated with right paratracheal lymphadenopathy (*arrowhead*). *Bacillus anthracis* was isolated from blood culture. (Courtesy Mark D. Sprenkle, MD, Pulmonary and Critical Care Medicine, Hennepin County Medical Center, Minneapolis, MN. From Sprenkle MD, Griffith J, Marinelli W, et. Al. Lethal factor and anti-protective antigen IgG levels associated with inhalation anthrax, Minnesota, USA. *Emerg Infect Dis.* 2014;20:310–314.)

of the Congo have sensitized many clinicians to the hemorrhagic manifestations of VHFs and, in endemic areas, gastrointestinal bleeding or continued ooze from venipuncture sites can trigger concern for a VHF. In those with advanced VHFs, petechiae, ecchymosis, and gastrointestinal and vaginal bleeding can accompany late stages of the disease.

Other Syndromes

Outbreak pathogens can present in myriad ways in addition to the most common syndromes noted earlier.[1] Botulism, for instance, produced by the toxin of *Clostridium botulinum* bacteria, produces profound neurologic symptoms starting with bilateral cranial neuropathies and symmetrical descending weakness in the absence of fever. Patients are responsive with slow to normal heart rates, are normotensive, and have no sensory deficits other than blurred vision. Ricin toxin, in contrast, can produce less-specific symptomatology that can be predominantly pulmonary or gastrointestinal depending on the route of exposure.

MANAGEMENT

INFECTION PREVENTION AND CONTROL

When a suspected outbreak or exposure is identified, immediately implementing infection prevention and control procedures (including isolation of the patient, use of appropriate personal protective equipment) and informing local health authorities are paramount.

The critical care clinician, along with the hospital infection prevention team, has an obligation to ensure that staff and unaffected patients are protected from exposure. Therefore, appropriate infection prevention measures should be implemented as soon as a potentially transmissible disease is suspected, even before a diagnosis is confirmed. Such procedures are routine in hospital settings, such as in the case of suspected tuberculosis, *Clostridioides difficile* colitis, or varicella. The type of isolation followed (e.g., respiratory, droplet, contact) and protective equipment used depends on the nature of the transmission of the suspected or confirmed pathogen. Hospital infection prevention staff should be involved immediately so that protective approaches can be coordinated in all areas and for all staff of potential relevance (i.e., laboratories, radiology). While the critical care clinician will likely not be responsible for implementing infection and control procedures, all clinicians should recognize that infection prevention involves much more than use of personal protective equipment, be familiar with the tiered nature of infection control practices, and advocate for their full implementation in their institutions.

For pathogens for which there are preventive vaccines, it is also important to incorporate immunization into response plans. Vaccination for routine infections like influenza may need to be augmented to include pathogens with a potential to become epidemic or be used as biologic weapons. First responders and health care personnel are priority groups for vaccination during influenza and coronavirus pandemics to reduce the likelihood that they themselves would become ill and to reduce transmission to other patients and staff. Licensed vaccines are available to prevent anthrax and smallpox, and health care personnel would likely be prioritized to receive vaccination in the setting of an emergency involving one of these pathogens. Vaccines for other consequential pathogens such as Q fever, agents of viral encephalitis, and Ebola Zaire may be available from the CDC.

REPORTING

Each state has requirements for the reporting of certain pathogens, and these policies need to be followed to ensure centralized data collection and epidemiologic surveillance. Clearly, not all biologic threats are included on lists of reportable pathogens; therefore, critical care clinicians should work with hospital infection control staff to communicate suspicions regarding a pathogen of consequence to health authorities, who in turn may alert federal public health entities. In the United States, state health departments as well as the CDC are available every hour of every

day of the year. For many infectious and noninfectious public health threats, specialized testing of biospecimens and/or environmental samples may be available only at state or national public health laboratories.

SUPPORTIVE CARE

Because the precise etiology of disease may not be immediately apparent, supportive care represents the foundation of patient management. Effective supportive care involves close patient monitoring with frequent clinical assessments and intervention as needed; intravenous and oral fluid resuscitation accompanied by monitoring and correction of metabolic, glycemic, and electrolyte abnormalities; identification and treatment of coinfections and comorbidities; management of advanced organ-supportive care such as renal replacement therapy and mechanical ventilation; and the support for essential organ function until either the body's endogenous immune response or pathogen-specific therapy can control the infection.

Data from the West African Ebola outbreak highlight the value of supportive care even in the setting of this progressive and highly lethal VHF.[15,18] Among the 27 expatriate patients transported back to the United States or Europe, the case fatality rate was 19% compared to over 60% for those managed in West Africa. Investigational therapeutics were administered to most of the repatriated patients, but it was the advanced supportive care, including laboratory monitoring, fluid resuscitation, and mechanical organ function support, that is considered to have been most consequential.[18]

Important considerations during the management of any serious systemic illness are sepsis, septic shock, and *acute respiratory distress syndrome* (ARDS); often these are the final common pathways for infections with high-consequence pathogens. For example, sepsis has been recognized as a cause of rapid deterioration in patients with Ebola virus disease, and bacterial pneumonia with methicillin-resistant *Staphylococcus aureus* is a common complication of ARDS, including from pandemic influenza.[19,20] Patients with these diseases experience better rates of survival when cared for in centers with more resources, lower provider-to-patient ratios, and greater clinical experience.[21] For diseases of outbreak potential, the rapid recognition of both the source of infection and the severity of illness will also help to reduce community and nosocomial transmission through the transfer of that patient to a designated area prepared for high-consequence or highly transmissible pathogens.

The Surviving Sepsis campaign has prioritized the use of *Quick Sepsis-Related Organ Failure Assessment* (qSOFA) scoring using altered mental status (Glasgow Coma Scale score of <15), respiratory rate (≥22 breaths/min), and hypotension (systolic blood pressure ≤100 mm Hg) to identify patients with sepsis rapidly in order to institute lifesaving supportive care.[22,22a] The Surviving Sepsis Hour-1 bundle targets the measurement of serum lactate and the collection of blood cultures prior to initiation of antibiotics. The administration of broad-spectrum antibiotics, initiation of intravenous crystalloid resuscitation for mean arterial pressures less than 65 mm Hg or a lactate level greater than 4 mmol/L, and infusion of vasopressors in the presence of hypotension during or after fluid resuscitation are considered key interventions to reduce sepsis and septic shock–associated morbidity and mortality.

Anthrax, tularemia, plague, avian or pandemic influenza, Middle East respiratory syndrome, SARS, and COVID-19 can all present with pneumonia-associated respiratory failure.[1] In the absence of controlled studies demonstrating the efficacy of one supportive intervention over another, the management of these illnesses follows recommendations created for ARDS. Data from the ARDS literature suggest improved mortality with the use of low tidal volume ventilation; conservative fluid management once there is no evidence of shock for 12 hours; avoidance of high-dose systemic corticosteroids in the context of most viral pneumonias unless needed for adrenal insufficiency, refractory hypotension, or obstructive lung disease; prone ventilation for severe ARDS; and the consideration of extracorporeal membrane oxygenation in the setting of refractory hypoxia.[23,24] A notable exception to the avoidance of corticosteroids is in the management of COVID-19, because administration of dexamethasone has been shown to provide a survival advantage to patients who require oxygen, with or without mechanical ventilation.[24a] Current guidelines recommend targeting lower tidal volumes of 4 to 8 mL/kg per breath calculated using predicted body weight to reduce volutrauma, targeting a lower plateau pressure of less than 30 cm H_2O to limit barotrauma, and the use of prone positioning for at least 12 hours a day in patients with severe ARDS (Pa_{O_2}/F_{IO_2} ratio <100 mm Hg).[25]

DIAGNOSTICS

Appropriate diagnostic tests should be directed by clinical presentations, physical exam findings, and epidemiologic links. Appropriate specimens (e.g., plasma, serum, upper and lower respiratory secretions, cerebrospinal fluid, skin lesion swabs) should be collected early and empiric treatment begun, pending laboratory analyses. Stains and cultures of blood or involved tissues or fluids can confirm the diagnosis of some bacterial pathogens of outbreak potential, including anthrax, botulism, pneumonic plague, and tularemia. Molecular techniques are increasingly able to detect consequential viruses rapidly, including SARS-CoV-2, many VHFs, and smallpox. Fluorescent antibody testing can also play a role, such as for the diagnosis of tularemia.

Coordination with state health officials and the CDC can facilitate the transfer of appropriate samples to state or regional reference labs for relevant diagnostic testing. At present, each U.S. state public health laboratory has the ability to respond to a biologic terrorism emergency, either individually or through a regional reference lab.[26] Laboratories (state or local) should be made aware when highly communicable pathogens are being considered in the differential diagnosis so that protective measures can be implemented to safeguard laboratory staff.

THERAPEUTICS

Direct treatment of an outbreak pathogen, when available, is often administered empirically given the severity of the disease on presentation and potential delays in confirmation of the diagnosis. For bacterial pathogens such as anthrax, tularemia, and plague, antibacterials with activity against these infections exist (Table 59.2).[1,26] Antitoxins can be used to neutralize toxins associated with anthrax, botulism, and ricin.[27] Immune globulin directed against botulinum

Table 59.2 Clinical Features and Management of Biothreat Agents

Disease	Signs and Symptoms	Incubation Time (Range)	Person-to-Person Transmission	Isolation	Diagnosis*	Postexposure Prophylaxis	Treatment†
Anthrax *(Bacillus anthracis)*							
Inhalation	Flu-like symptoms including fever and chills, shortness of breath, cough, sweats, fatigue, and myalgias May also have confusion, headache, nausea, vomiting or stomach pain	1–43 days (range, up to 60 days)	None	Standard	CXR with widened mediastinum; cultures of sputum and blood	Antibiotics, vaccine	Antibiotics, antitoxin
Cutaneous	Initially a group of small blisters or bumps that may itch Swelling may develop around the sore; blisters develop into a painless skin sore (ulcer) with a necrotic (black) center; lesions most commonly on face, neck, arms, or hands	5–7 days (range, 1–12 days)	Rarely	Contact	Cultures of blood and lesion (swab)		
Gastrointestinal	Fever and chills, lymphadenopathy (neck), pharyngitis, dysphagia, nausea and vomiting (may be bloody), diarrhea, headache, abdominal pain, and flushing and conjunctivitis	1–6 days	None	Standard	Cultures of blood and stool		
Botulism (*Clostridium botulinum* toxin) via inhalation	Double or blurred vision, ptosis, dysarthria, dysphagia, dysphonia, shortness of breath, dry mouth, muscle weakness; ascending flaccid paralysis Suggested by absence of fever, symmetrical neurologic deficits, patient responsive, normal or slow heart rate with normal blood pressure, and no sensory deficits with exception of blurred vision	12–72 hours (2 hours to 8 days)	None	Standard	Presumptive based on clinical findings Identification of toxin in serum, stool, or vomitus Culture of stool, wound, or food source	None	Antitoxin, botulinum immune globulin
Pneumonic plague (*Yersinia pestis*)	Fever, headache, weakness, and a rapidly developing pneumonia with shortness of breath, chest pain, cough, and sometimes bloody or watery mucus Septicemic plague may develop	1–4 days	Via respiratory droplets	Droplet	Cultures of blood (usually positive), sputum, bronchial washings	Antibiotics	Antibiotics

Table 59.2 Clinical Features and Management of Biothreat Agents—cont'd

Disease	Signs and Symptoms	Incubation Time (Range)	Person-to-Person Transmission	Isolation	Diagnosis*	Postexposure Prophylaxis	Treatment†
Smallpox (Variola)	Initial stage (2-4 days): high fever, prostration, myalgias, vomiting Rash: starts as small red spots on tongue and in mouth, changes to sores that rupture, then rash on face that spreads to arms and legs, and then to hands and feet	10–14 days (range, 7–19 days)	Via airborne spread	Contact, airborne (special precautions required)†	PCR of clinical specimens (i.e., skin lesions, NP swab, blood), isolation of small virus, serology**	Vaccine	Vaccine, tecovirimat
Pneumonic tularemia (*Francisella tularensis*)	Cough, chest pain, shortness of breath	3–5 days (range, 1–14 days)	None	Standard	Culture of skin lesions (swab or scrapings), lymph node (aspirate or biopsy), pharynx (swab), or sputum	Antibiotics	Antibiotics
VHF§: Ebola virus	Fever, severe headache, myalgias, weakness, fatigue, diarrhea, vomiting, abdominal pain, unexplained hemorrhage (bleeding or bruising)	8–10 days (range, 2–21 days)	Via direct or indirect contact	Contact (special precautions required)†	PCR of clinical specimens (blood)**	Vaccine‡	Supportive, monoclonal antibodies for Ebola Zaire
VHF§: Marburg	Sudden onset of fever, chills, headache, myalgias Around fifth day after onset of symptoms, maculopapular rash on trunk; then nausea, vomiting, chest pain, pharyngitis, abdominal pain, diarrhea May progress with jaundice, delirium, shock, liver failure, massive hemorrhage, and multiorgan dysfunction	5–10 days	Via direct or indirect contact	Contact (special precautions required)†	PCR of blood or tissue, ELISA and IgM-capture ELISA**	None	Supportive
VHF§: Lassa	Mild disease: slight fever, malaise, weakness and headache Serious disease: hemorrhage (gums, eyes, nose), respiratory distress, vomiting, pain in chest and abdomen, and shock	6–21 days	Via direct or indirect contact	Contact (special precautions required)†	ELISA (IgM, IgG), RT-PCR of clinical specimens, viral culture**	Antivirals	Ribavirin

*Always alert lab before sending specimens for diagnosis.
†Consult infectious disease physician, infection prevention personnel, health department, review current guidelines (e.g., CDC, WHO).
‡Investigational (contact state health department, Food and Drug Administration).
§Other viral hemorrhagic fevers could be used as a biothreat agent and present with similar findings such as Junin (Argentine hemorrhagic fever) and Machupo virus (Bolivian hemorrhagic fever).
¶Alert lab if patient has meningeal symptoms; obtain spinal fluid culture.
**Alert lab, Public Health Department, and CDC as soon as diagnosis suspected.
CXR, chest radiograph; CDC, Centers for Disease Control and Prevention; ELISA, enzyme-linked immunosorbent assay; NP, nasopharyngeal; PCR, polymerase chain reaction; VHF, viral hemorrhagic fever; WHO, World Health Organization.
Modified from Centers for Disease Control and Prevention. Control of Communicable Diseases Manual, 20th edition, 2015.

toxin is also available, and two monoclonal antibodies that neutralize *Bacillus anthracis* toxin, raxibacumab and obiltoxaximab, are approved by the FDA for the prevention and treatment of inhalational anthrax.[28] Viral infections present a greater therapeutic challenge because there are fewer antivirals available and most have not been tested against these rarer pathogens. For smallpox, tecovirimat is FDA approved based on studies in nonhuman primates but is available only via the U.S. Government's Strategic National Stockpile.[29] Ribavirin is routinely used to treat Lassa fever, although its efficacy is questionable. Two monoclonal antibody products have recently shown promise for treating Ebola Zaire,[30] and monoclonal antibodies are in clinical trials for SARS-CoV-2.

Chemoprophylaxis may also play a role in an outbreak. Antimicrobials can be administered to prevent disease in those potentially exposed to anthrax, plague, tularemia, brucellosis, and Q fever.[26] Oseltamivir prophylaxis is a part of almost every pandemic influenza plan, although it will be important to establish that the virus is susceptible to the drug.

COORDINATION

LEADERSHIP

Critical care clinicians may be looked to not only for the medical management of individual patients but also for leadership of the response within a facility or health care network. As the steward of the units where intensive care is delivered, the critical care clinician will almost always need to supervise the coordination of the intensive care unit response, including triage, staffing, resource management and supplies, and care plans. Although many critical care clinicians have worked in hospitals that have experienced shortages of intravenous fluids or essential medicines, an outbreak can present a much graver situation. While most will be involved in bedside care, their duty to care for an individual patient may conflict with the need to provide population-based care, including allocation of scarce resources. The National Academy of Medicine has promoted guidelines for avoiding such situations and recommends that triage and allocation decisions be made by experts not directly involved in bedside care.[31]

Working with infection prevention experts, the critical care clinician will also implement policies to reduce intrafacility transmission of infection or contamination. Depending on the scale of an event, the clinician may also work to coordinate with counterparts at other medical centers such as those nearby or where special expertise or resources are located. In the United States, almost all hospitals have an incident command system and participate in local or regional health care coalitions, and the critical care clinician must be prepared to be part of such a system, because it will be responsible for handling the crisis.

COMMUNICATION

Epidemics of infectious diseases are often accompanied by secondary epidemics of fear. Communication among health care providers and patients, patients' family members, and affected communities ensures that sound scientific advice is shared and disseminated and that rumors do not interfere with the rapid identification, isolation, and initiation of care for suspect and confirmed patients. Delays in identification, isolation, and care of severe progressive infections can have profound effects on outcomes and may also perpetuate community transmission. Community engagement and communication strategies, when effective, can crowdsource surveillance efforts that will ultimately accelerate the identification, isolation, and initiation of care for suspect patients.

By being directly involved in the care of affected patients, the critical care clinician may also be asked to serve as a public face for communications with other patients in the hospital as well as with the media and the public. Updates on the status of affected patients, on system responses to meet treatment and infection control needs, and on the event itself may fall to the critical care clinician. Coordination of messaging with other stakeholders inside and outside of the facility, such as emergency department providers and other clinicians (including those in neighboring facilities), infection prevention staff, public health authorities, community leaders, elected officials, and security (police, military), will be critical, albeit often difficult in the dynamic situation of such events. Clarity regarding communications with the public should be established early through the local public information officer, followed closely, and revised as necessary by those leading the response.

PREPAREDNESS

The best response is built on strong day-to-day systems and begins prior to an outbreak with preparedness. Because the critical care clinician is often at the front line of care in a public health emergency, he or she will want to ensure that the hospital, as well as other facilities in the community, is fully prepared for such an event. Although outbreaks and other consequential public health events typically appear with little or no warning, measures can be taken to prepare for such emergencies by developing relevant procedures and policies, conducting training and drills, and stocking supplies, equipment, and medications. Crucial aspects of preparedness include rostering of essential staff, establishing a safe and effective health care structure, optimizing systems such as predeveloped care protocols and checklists, ensuring adequate infection prevention and control and biosecurity, and knowing other facility plans, as outlined in Table 59.3.

The critical care clinician has a stake in the development of hospital policy for determining who will and will not be expected to care for infected patients. In the setting of an outbreak, there may be a need for surge capacity to attend to a growing number of suspected and confirmed cases, all the while maintaining routine medical care to others to the extent possible. At the same time, health care providers and/or their family members may become ill and therefore may be unavailable. In addition, restrictions regarding who is eligible to be part of the care team

Table 59.3 Preparedness for Managing a Highly Communicable Emerging Infectious Disease

GENERAL

- Ensure the facility has a comprehensive plan for managing a highly communicable emerging infectious disease. This should be contained within the general disaster plan.
- Base the plan on the route(s) of transmission for the infectious agent.
- Learn the basics of the hospital incident command structure and ensure it is part of the plan.
- Periodically train key personnel on the plan.
- Ensure plan includes care of single patients (e.g., Ebola) as well as management of a large number of patients in an epidemic (e.g., novel influenza).
- Incorporate communications with local and state health department officials.
- Develop a plan for prophylaxis of health care workers and facility staff.
- Develop a plan with neighboring health care facilities, ideally through a regional health care coalition, to coordinate patient distribution for highly pathogenic respiratory viruses and other highly transmissible infections when tertiary care facilities or designated facilities are not available.

SCREENING AND SIGNAGE (WHEN APPROPRIATE BASED ON THE THREAT OF A HIGHLY COMMUNICABLE DISEASE)

- Place signs at every entrance to the hospital and clinics that include the following: epidemiologic clues to possible disease exposure (i.e., travel locations), signs and symptoms of infection, and whom to notify if the patient or visitor has both exposure and appropriate signs and/or symptoms.
- Include messaging about the signs and symptoms of the concerning disease in all telephone contacts with the patient (e.g., reminders about appointments) and who to contact prior to arrival at the health care facility.
- Screen all patients immediately at the time of all health care visits.
- Include screening in the electronic medical record (also have alerts in the medical record that require screening).
- Place an appropriate isolation sign on the door of all patients being isolated due to the possibility of a highly communicable disease.
- Emphasize respiratory hygiene for diseases transmitted via the droplet or airborne routes (i.e., immediate use of a mask and proper disposal of tissues) as well as proper hand hygiene.
- Ensure all messaging is in appropriate languages for the region.

TRIAGE

- Train front-line personnel in all clinics and the emergency department in appropriate use of personal protective equipment.
- Identify and make appropriate personal protective equipment available. Use dedicated equipment during the patient evaluation.
- Have a designated location in the emergency department and all clinics in which to place the patient (a private room; ideally with access to a sink and toilet and, if possible, one that meets standards for a disease transmitted by the airborne route [i.e., negative pressure, out exhausted air, >12 air exchanges per hour]) if applicable. For diseases transmitted by the airborne route and when an airborne isolation room is not available, ideally place a portable high-efficiency particulate air machine in the room.
- Have a well-defined process for alerting key health care facility officials about the presence of a patient with a possible highly communicable disease (e.g., disaster manager, infection control preventionist).
- Avoid blood tests or other procedures that may place the laboratory staff or other health care personnel at risk.
- Have a well-defined and safe method for transporting a patient either to a properly equipped emergency department or to a hospital facility able to care for a patient safely.

INPATIENT CARE

- Have a well-defined plan for the inpatient location that will provide care to a patient with a highly communicable disease (or a plan for transporting such a patient to facility that can provide such care).
- Designate areas that are "hot" (i.e., potentially contaminated) and "cold" (i.e., areas that are not contaminated), and monitor compliance with that designation as appropriate.
- Develop appropriate staffing models based on the infectious agent and anticipated patient acuity.
- Have a preidentified, multidisciplinary, and well-trained medical care team. For highly communicable diseases (e.g., Lassa, Ebola), ideally provide three-step training: (1) Individual training, including demonstration of competencies, on personal protective equipment donning and doffing (including how to manage contamination of the environment from a spill and a breach of the personal protective equipment). Such training should be individualized to the specialty of the health care providers (i.e., physician, nurse, respiratory therapist, etc.). (2) Team training using mannequins. (3) Team training in the designated containment unit.
- Train team personnel on donning and doffing using an explicit written list of all donning and doffing steps.
- Screen and exclude health care personnel unable to wear the proper personal protective equipment. Consider excluding from the care team personnel at high risk for disease acquisition and/or more severe illness such as persons with nonintact skin, pregnancy, and immunocompromise. Consider excluding trainees from providing care.
- Store an adequate supply of personal protective equipment.
- Have dedicated point of care laboratory equipment.
- Develop a method to dispose of solid and liquid wastes safely.
- Restrict visitors (if indicated) and maintain a log for all visitors.
- Maintain a log of all health care personnel providing care.
- Develop a plan for monitoring symptoms among health care workers providing care.
- Develop a plan for managing health care personnel with unprotected exposure to the infectious agent (e.g., needlestick).
- Develop a plan for decedent management.
- Ensure that care team members receive proper rest and psychological first aid as needed.
- Develop specific protocols for special populations, such as pediatric and obstetric patients.

should be considered, such as exclusion of pregnant care providers or less-experienced staff (e.g., medical and nursing students, physicians in training such as residents). Critical care clinicians supervising intensive care units may be expected to care for patients with highly communicable diseases; arguably there is a duty to care for such patients. However, for other staff, participation in the care of patients with serious communicable infections may be considered voluntary. Steps to ensure a safe care environment and to address fear among staff and their families are essential. In some centers, clinical staff, including physicians, nurses, respiratory therapists, and others, may

volunteer as first-line providers; a roster of those willing to care for such patients can facilitate adequate staffing. The critical care clinician will also want to ensure that staffing is available to provide laboratory and radiologic and other services, including environmental services and security. Being involved in the establishment of plans and criteria before an outbreak situation is preferable to developing these during an evolving crisis.

Key Points

- A novel infectious agent, whether related to an emerging infectious disease or to bioterrorism, can present without warning.
- Early recognition of an emerging infection or a bioterrorism agent almost always relies on the astute clinician.
- High-consequence pathogens may present with signs and symptoms that may be mistaken for other illnesses. Clusters of common symptom complexes should raise the suspicion of a potentially serious outbreak: fever, rash, respiratory distress, and hemorrhage.
- In addition to providing clinical care, the critical care clinician may be expected, and should thus be prepared, to play other roles in the hospital or community, including provision of population-based critical care.
- Hospital infection prevention and control staff and public health authorities should be alerted immediately if a novel infectious disease or bioterror agent is suspected, in order to protect other patients, health care workers, and the community.
- Aggressive supportive care, including frequent monitoring, fluid management, and early recognition and treatment of sepsis and acute respiratory distress syndrome, are the mainstays of critical care.
- Licensed vaccines and/or therapeutics are now available to prevent and treat key bioterror agents, including smallpox, anthrax, botulism, plague, and tularemia. Approved vaccines and therapeutics for Ebola Zaire are available, and clinical trials are ongoing for COVID-19 vaccines and therapeutics, many of which have received Emergency Use Authorization by the U.S. Federal Drug Administration at the time of this printing.

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SECTION H

OBSTRUCTIVE DISEASES

60 ASTHMA: PATHOGENESIS AND PHENOTYPES

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INTRODUCTION

Asthma is a common disease with a prevalence that has increased throughout the world for several decades. Studies of the epidemiology, natural history, and pathogenesis have clearly demonstrated that asthma is a heterogeneous disease, with multiple etiologies and contributing cofactors, complex pathobiologic mechanisms, and diverse molecular phenotypes. Understanding these differences is critically important for developing therapeutic strategies that will be effective for the various phenotypes of asthma.

EPIDEMIOLOGY

PREVALENCE

In the United States, the overall prevalence of asthma has risen since 1980, even after accounting for changes in the definition of current asthma in National Health Interview Survey questionnaires (Fig. 60.1). In 2017 (the most recent data), the overall current prevalence of asthma in the United States was 7.9%. There are marked and persistent differences in asthma prevalence across specific subgroups of the U.S. population, making asthma extremely common in certain vulnerable populations (Fig. 60.2). In 2017, current asthma prevalence was very high in Black non-Hispanics (10.6%), those of Puerto Rican heritage (12.8%), and among those living below the poverty threshold (11.7%). Current asthma prevalence was higher in children (age <18 years; 8.4%) than adults (age 18+ years; 7.7%) and was higher among females (9.3%) than males (6.4%) overall, although the female/male balance changes with age so that asthma is less common in females than males during childhood (<18 years, 7.3% vs. 9.5%, respectively) but more common in females than males during adulthood (≥18+ years, 9.8% vs. 5.4%, respectively). These imbalances in prevalence between women and men, adults and children, ethnic groups, and across poverty levels have not changed since 2001.

The global burden of asthma in 2017–18 was assessed by the Global Asthma Network in 135 countries using standardized methods (similar to the International Study of Asthma and Allergies in Childhood study). They found that asthma affects approximately 339 million people, causes approximately 1000 deaths per day, and is in the top 20 causes of years of life with disability.[1] As in the United States, the international prevalence has increased over time,[2] although this increase

may have plateaued in some high-income countries.[3] Two large multinational studies have systematically assessed the worldwide prevalence of asthma: the European Community Respiratory Health Survey in adults[4] and the *International Study of Asthma and Allergies in Childhood in Children* [ISAAC].[5] ISAAC phase I studied 156 centers in 56 countries cross-sectionally during the period 1992–96[6,7] and confirmed the great geographic variability in asthma prevalence inferred from prior smaller studies. However, it also found that some low- and middle-income countries had a prevalence of asthma symptoms similar to those in western, developed countries. Thus, the geographic trends are not absolute.

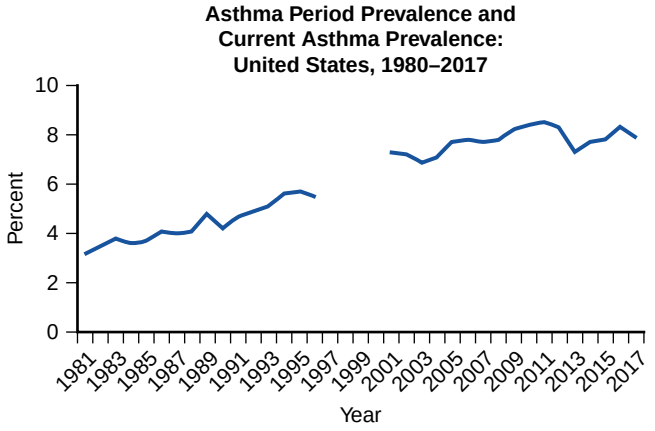

Figure 60.1 Prevalence of current asthma in the United States. Data are based on the National Health Interview Survey over two periods that used different case definitions (1980–96 and 2001–17). (Data from the U.S. Centers for Disease Control and Prevention, https://www.cdc.gov/asthma/asthma_stats/default.htm, compiled Aug 26, 2019.)

ISAAC confirmed the overall increase in asthma prevalence from phase I (1992–96) to phase III (2000–03). However, these time trends in asthma symptom prevalence showed different regional patterns.[8] With the exception of India, all of the countries with very low symptom prevalence rates at first evaluation reported increases in prevalence. However, in English-speaking, developed countries, in which asthma prevalence was already high, there was little further increase. The *European Community Respiratory Health Survey* (ECRHS) studied representative samples of 20- to 44-year-old men and women in 48 centers, predominantly in Western Europe.[9] Although ECRHS included data from fewer countries than ISAAC, there was relatively good agreement between ISAAC and ECHRS with respect to the prevalence of asthma symptoms across the 17 countries that both studies sampled.[10]

MORTALITY

Although death from asthma was once thought to be uncommon,[11] data from the World Health Organization in 2007 suggested that there are 250,000 asthma-related deaths each year worldwide.[12] The countries with the highest death rates in the World Health Association report were not necessarily those with the highest prevalence, suggesting that poor access to care and medications are contributing factors to mortality. In specific instances, asthma medications may have contributed to increased mortality. For example, there was an abrupt increase in asthma deaths in the 1960s in the British Isles, Australia, New Zealand, and Norway.[13] This increase was attributed to a high-dose preparation of a potent, nonselective inhaled β-agonist, isoproterenol, and mortality fell following the preparation's withdrawal. A second, even more dramatic increase in

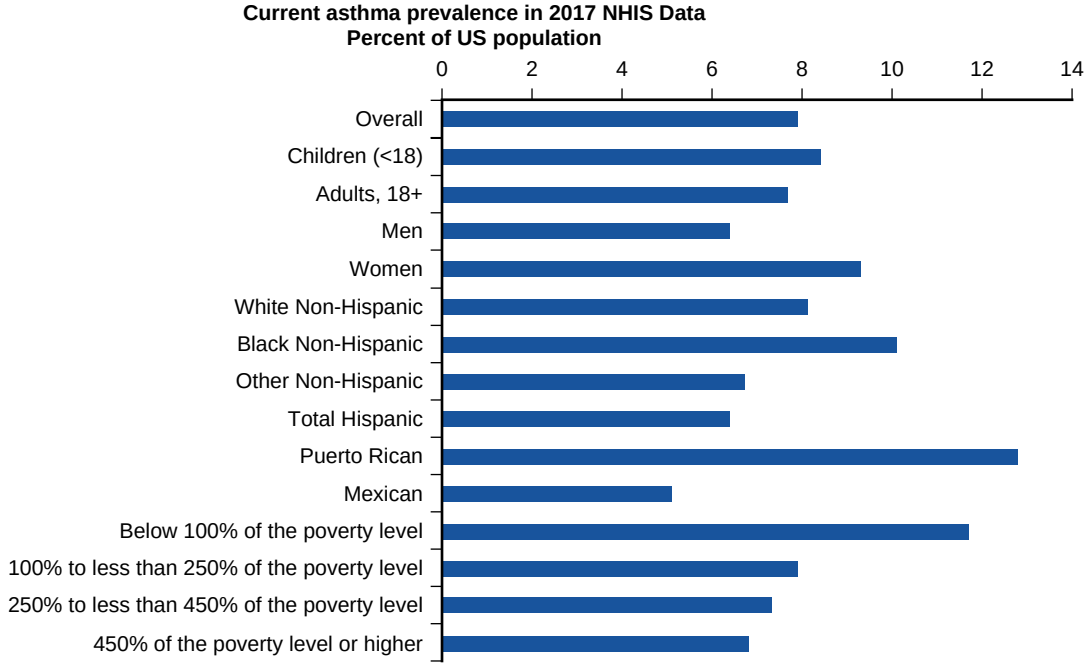

Figure 60.2 Current asthma prevalence in the United States by age, gender, ethnic group, and income. Asthma prevalence is highest in certain vulnerable populations, including children, Puerto Ricans, non-Hispanic Blacks, and those living below the poverty level. NHIS, National Health Interview Survey. (Data from the U.S. Centers for Disease Control and Prevention, https://www.cdc.gov/asthma/most_recent_national_asthma_data.htm, compiled Aug 26, 2019.)

asthma mortality in New Zealand in the 1970s was again attributed to sales of a particular β-agonist, fenoterol.[14] The increased asthma mortality observed with inhaled isoproterenol and fenoterol may relate to their increased potential for extrapulmonary effects (inotropy and hypokalemia).[15]

In 2017, the U.S. death rate attributable to asthma was 9.9 per 1 million population. As is true for asthma prevalence, asthma mortality disproportionately affects certain segments of American society such as Black non-Hispanics (22.7 per 1 million persons).[16] This excess mortality in Black Americans may be due to both biologic factors and societal factors such as access to health care, insurance coverage, access to medication or asthma education, environmental exposures, and racism.

RISK FACTORS

Allergy

The strongest risk factor for asthma is a family history of atopic disease,[17,18] which increases the risk of developing asthma by threefold to fourfold.[19] In children 3 to 14 years old, both positive skin tests and higher total serum *immunoglobulin* (Ig) E are strongly associated with asthma.[20,21] Serum IgE also correlates strongly with bronchial hyperresponsiveness.[22] In adults, the odds of having asthma increases with the number of positive skin tests to common allergens.[23]

Because much allergic asthma is associated with sensitivity to indoor allergens, and because western styles of housing favor greater exposure to indoor allergens, attention initially focused on increased exposure to these allergens in infancy and early childhood as a primary cause of the rise in asthma. Specific allergens of interest include house dust mites,[24,25] dog and cat dander,[26] and cockroach allergen,[27] especially in the inner city. These and other observations support the hypothesis that allergen controls should be valuable in the treatment or prevention of asthma.[28,29] However, even after more than 50 individual studies of allergen control have been completed, the conclusions drawn from those studies via meta-analyses and expert review have been at odds and hotly debated.[30,31] One alternative hypothesis is that appropriate exposure to allergens early in life could induce tolerance and decrease both sensitization to these allergens and the development of allergic disease. Recent experience in the prevention of peanut-related food allergy through controlled exposure to peanut allergens early in life support this alternative hypothesis.[32]

The Hygiene Hypothesis

The *hygiene hypothesis* holds that the rise in allergies in children is an unintended consequence of the success of domestic hygiene in reducing the rate of infections or exposure to bacterial products in early childhood. This hypothesis was proposed to explain the inverse relationship between hay fever and family size[33] and was cited later when children raised in West Germany were found to have significantly higher rates of asthma and hay fever than those raised in East Germany[34] despite the more severe air pollution in East Germany.[35] In these studies, children living on farms had a lower prevalence of hay fever and asthma than their nonagrarian peers. The risk reduction was greater for children living on a full-time farm, and risk was even lower if the farm housed livestock.[36,37] Long-term exposure to stables until age 5 years was associated with very low rates of asthma (0.8%), hay fever (0.8%), and atopic sensitization (8.2%).[38] Follow-up studies of the protective effects of farm life have shown that endotoxin levels in the home were inversely related to the development of hay fever, atopic asthma, and atopic sensitization.[39] Another study employing two cohorts found that farm children had lower prevalences of asthma and atopy, were exposed to a greater variety of environmental microorganisms than the children in the reference groups, and that the diversity of microbial exposure was inversely related to the risk of asthma.[40]

The Human Microbiome

One potential link between changes in hygiene and allergic disease is the effect that "improved" hygiene may have on our indigenous microbiota and the role this microbiota may play in shaping our immune system.[41–45] The biologic model most commonly cited to explain this association is that early life exposure to factors that promote *type 1* (T1) immunity are necessary to blunt exuberant *type 2* (T2) immunity. Animal studies provide some support for this model[46–54] (see also Chapter 17).

Respiratory Viral Infections

Viral respiratory tract infections appear to play an important role in the development of asthma.[55,56] Children who have lower respiratory tract infections caused by respiratory syncytial virus (are at a three- to fourfold risk of subsequent wheezing during early school-years.[57–60] The presence of *rhinovirus* during wheezing episodes is an even stronger predictor of subsequent asthma.[61,62] Some studies suggest that viral lower respiratory tract infections interact with concurrent atopic disease in conferring subsequent asthma risk.[61]

Longitudinal studies of the natural history of wheezing illnesses have identified complex and, at times, inconsistent relationships between early wheezing phenotypes and the ultimate development of asthma. Briefly, some children who have wheezing illnesses at younger than 3 years of age continue to wheeze at age 6 years. However, not all children fit this "persistent wheezer" pattern. Similarly, there are children who wheeze at age 6 who never had wheezing illnesses before age 3 years. Thus, a propensity for wheezing can be transient and the causes may be different at different ages. Factors associated with wheezing before age 3 years include small airway caliber and maternal smoking, whereas factors associated with wheezing after age 3 include elevated serum IgE and a maternal history of asthma.[63] Furthermore, viral lower respiratory tract infections may unmask a predisposition to predominant T2-like responses already present at the time of the infection[64] and that manifest later as asthma.

Atypical Bacterial Infections

Although typical bacterial infections are not thought to cause asthma, at least two bacterial causes of "atypical" pneumonia have been implicated in the development of chronic wheezing illnesses, *Chlamydia pneumoniae* and *Mycoplasma pneumoniae*.[65] These atypical infections may be associated with asthma exacerbations.[66] Despite this evidence, a randomized trial of clarithromycin for the treatment of suboptimally controlled asthma showed no improvement in asthma control, whether or not *M. pneumoniae* or *C. pneumoniae* was detected by PCR in endobronchial biopsies.[67]

Air Pollution

Air pollution is associated with both the development of asthma and exacerbation of preexisting asthma.[68,69] In principle, exposure of the lung to air pollution could increase local oxidative stress, induce or modify local inflammation, enhance sensitization to allergens, impair lung development, or injure small airways. Several studies have focused specifically on asthma incidence and prevalence by proximity to heavy automobile traffic and suggest that exposure to respirable particulate matter and nitrogen dioxide in this setting are both associated with the future development of asthma[69–75] (see also Chapter 102).

Other Early Life Factors

Intrauterine risk factors include growth rates (both high and low),[76,77] dietary vitamin D and E,[78,79] exposure to microbial products,[80] parental smoking,[81] and parental stress.[82] Perinatal risk factors associated with asthma include prematurity[83] and chorioamnionitis.[84] Finally, early childhood risk factors associated with asthma include a shorter period of breastfeeding,[85,86] obesity,[76] absence of older siblings or daycare attendance,[87] bacterial colonization of the airways in early childhood,[88] antibiotic use,[89] and acetaminophen use.[90]

Occupational Exposures

Finally, occupational exposures constitute an important risk factor for a specific subset of patients. Asthma induced by occupational exposure accounts for as much as 17% of all adult-onset asthma.[91] A full description of the occupational exposures that can cause asthma is beyond the scope of this chapter because the known exposures number in the hundreds. However, in general, occupational asthma can either result from immunologically mediated sensitization to occupational agents (i.e., *sensitizer-induced asthma*) or from exposure to high concentrations of irritant compounds (i.e., *irritant-induced asthma*) (see Chapter 100).

NATURAL HISTORY

Neonatal Period

A predisposition to asthma may begin as early as the neonatal period. The immunologic milieu at the fetal-maternal interface is skewed towards a T2 phenotype, and this immune bias is carried into neonatal life.[92] Unless the pattern of immune response in the airways is "reprogrammed" towards a T1 pattern, the infant may have a prolonged high-risk window for allergic sensitization to aeroallergens.[93]

Childhood

Although asthma is the most prevalent chronic disease in children, it is difficult to diagnose in infants and preschoolers. Recurrent wheezing is the most common early symptom associated with asthma; however, only a minority of preschoolers with recurrent wheezing still have "asthma" at the age of 6 years. Patterns of wheezing in early childhood have been intensively studied in longitudinal cohorts such as the Tucson Children's Respiratory Health Study[63] and the British Avon Longitudinal Study of Parents and Children.[94] The Tucson Children's Respiratory Health Study found that 48% of children had at least one wheezing illness at some point in the first 6 years of life, 34% had at least one wheezing illness before age 3 years (defined as early wheezing), and approximately half of these children continued to have wheezing at age 6 years. In the remainder of children with wheezing episodes before age 3 years, these episodes were transient and resolved before the age of 6 years. Finally, approximately 15% of children presented with late-onset wheezing, defined as wheezing illnesses after age 6 years. Most of the early wheezing illnesses (before age 3 years) can be ascribed to viral respiratory infections such as respiratory syncytial virus or rhinovirus and do not necessarily reflect atopy.[95] In addition, transient early wheeze is associated with maternal smoking. However, wheezing at and after age 6 years (persistent and late-onset wheeze, respectively) is more strongly associated with atopy. Furthermore, children who had either persistent or late-onset wheeze were more likely to go on to wheeze later in life and be diagnosed with asthma. The risk for continued wheeze after age 6 years appears to be associated with severity of airflow obstruction and the degree of allergen sensitization.[96] The British Avon Longitudinal Study of Parents and Children provided some additional granularity to the categories of childhood wheezing illnesses by defining intermediate-onset wheeze (onset of symptoms after 18 months of age) and early prolonged wheeze (onset in the first year of life but with remission at 69 months of age).[94]

Atopic or Allergic March

The terms *atopic march* and *allergic march* are synonyms referring to a characteristic pattern of atopic disease development during infancy and childhood.[97,98] The most common pattern begins with atopic dermatitis or eczema in the first year of life, sometimes associated with food intolerance or food allergy, followed by rhinoconjunctivitis and/or wheezing illnesses that are ultimately diagnosed as asthma. Thus, the natural history of atopic disease may more generally follow a specific pattern of organ-specific development, which suggests a stereotyped set of underlying cellular and molecular mechanisms.[99]

Teenage Years

After puberty, the demographics of patients with prevalent asthma switches from a male predominance to a female predominance, which suggests a change in the nature of incident cases of asthma. One straightforward inference would be that some incident cases of asthma in girls during teenage years relate specifically to hormonal factors. This is a compelling hypothesis and some data provide clues to potential mechanisms, including possible protective effects of androgens and deleterious effects of estrogens and progesterone.[100,101]

Remission

In long-term follow-up of a population-based birth cohort evaluated annually to age 26 years,[102] just over half (51%) reported wheezing at more than one assessment. In this cohort, wheezing persisted until adulthood in 15%, whereas wheezing remitted in 27%. This remission was often temporary, however, because wheezing recurred by age 26 years in nearly half of those in whom it had remitted. This finding echoes those of 15 earlier studies of the natural history of asthma, showing that about 50% of adults who recall having childhood asthma continue to have symptoms.[103] Risk factors associated with persistence into adulthood include house dust mite sensitization, lower forced expiratory

volume in 1 second, airway hyperresponsiveness, female gender, and smoking.[102] Whether "spontaneous remission" truly reflects the disappearance of airway T2 inflammation in asthma is unknown. Even in patients with complete absence of symptoms and medications, exhaled *nitric oxide* (NO) is elevated, airway responsiveness is increased, and bronchial biopsies show increases in eosinophils, T cells and mast cells, and subepithelial fibrosis.[104,105]

Progressive Airflow Obstruction

Some people with asthma have accelerated rates of decline in pulmonary function, and asthmatic smokers have greater rates of decline than healthy smokers.[106,107] Furthermore, many nonsmoking asthmatics develop severe, irreversible airflow obstruction.[108,109] One possibility is that progressive narrowing of the airways in chronic asthma results from airway remodeling, which is a summary term for the deposition of collagen and accumulation of blood vessels, smooth muscle, secretory cells, and glands in the asthmatic airway.[110,111] Nonetheless, it is not possible to prove that airway remodeling is the cause of progressive airflow obstruction in asthma.

Adulthood

Even though many adults with asthma had asthma during childhood, adult asthma is particularly heterogeneous. The female predominance that first appears in teenage years continues in adult asthma. Alternatively, asthma symptoms can begin de novo in an adult, and not all patients have atopic features. In some instances, the onset of wheezing is attributed to a specific acute respiratory illness that became persistent. In others, it is possible that atopy and wheezing illness as a child were modest and subclinical.

Asthma in the Elderly

If asthma is present in an adult, it will often remain as the adult ages. Surprisingly, new-onset asthma can also present in the elderly.[112] In this age group, misdiagnosis of asthma (often as COPD) and under-treatment appear to be common.[113,114] Furthermore, elderly patients with asthma are more likely to have fixed airway obstruction.[115] The term *intrinsic asthma*, often used to describe nonatopic reversible bronchoconstriction, has traditionally been associated with asthma in the elderly,[116] and more than 60% of elderly patients in one study reported the first onset of asthma symptoms following an upper respiratory infection.[112] However, at least one study has shown positive skin reactivity to one or more common allergens in almost two-thirds of elderly asthmatic patients.[117] In addition, a subset of adult-onset asthmatics have high blood eosinophils, poor asthma control, and high exacerbation rates despite the use of inhaled corticosteroids, a distinct clinical entity now termed *adult-onset eosinophilic asthma*.[118]

GENETICS OF ASTHMA

EARLY EVIDENCE THAT ASTHMA IS HERITABLE

The genetic basis for asthma was described in 1860 by Henry Salter, who reported that asthma showed "distinct traces of inheritance" among related individuals.[119] Genetic variation influences asthma susceptibility through the cumulative effects of many different genes that are polymorphic (contain gene variants or polymorphisms) or interact with multiple potential environmental exposures to cause asthma. The first genetic studies for asthma susceptibility were early family-based genome-wide linkage studies that used genetic variants equally spaced throughout the genome to identify chromosomal susceptibility regions for asthma and associated phenotypes (bronchial hyperresponsiveness, serum IgE levels, etc.).[120–130] These studies identified evidence for linkage with asthma and related phenotypes in multiple different chromosomal regions (chromosomes 5q, 6p, 7q, 11q, 12q, 14q, and 16q), which have subsequently been studied to identify specific genes.[121,128,130–143] These studies also demonstrated gene-gene interactions in asthma susceptibility between chromosomes 5q31, 8p23, 12q22, and 15q13 and evidence for gene-by-environment interactions with passive cigarette smoking at chromosomes 1p, 5q, and 9q, and 17q21.[122,127,144–146]

The first novel gene for asthma susceptibility identified using family-based linkage approaches was the *a disintegrin and metalloprotease-33* (*ADAM33*) gene on chromosome 20p13.[125] *ADAM33* is among the most replicated genes from linkage analysis for asthma and affects lung growth, morphogenesis, and airway remodeling while also being implicated in longitudinal progression of airflow obstruction.[147–155] Several other asthma susceptibility genes have been identified using fine mapping or positional cloning techniques and include the genes encoding *protocadherin-1* (*PCDH1*), HLA-G, *neuropeptide S receptor-1* (*GPRA*), *PHD finger protein-11* (*PHF11*), and *peptidase-10* (*DPP10*), a locus identified in a subsequent genome-wide association study of African Americans and African Caribbeans.[121,141,156–161]

CANDIDATE GENE ASSOCIATION STUDIES

Case-control association studies compare the frequency of the alleles of a gene variant between unrelated cases and controls, typically leveraging *single nucleotide polymorphisms* (SNP, denoted by a reference sequence number). Over 100 biologic candidate genes have been examined in candidate gene studies based on plausible biologic mechanisms and chromosomal regions linked to asthma. Before genome-wide association studies, the most replicated candidate genes were in the broad categories of lung development (*ADAM33*), T2 inflammation (*IL4, IL13, IL4R, FCER1B*), innate immunity (*HLA-DRB1, HLA-DQB1, CD14*), and cellular inflammation (*TNF, DPP10*).[121,125,156,157,161–171]

GENOME-WIDE ASSOCIATION STUDIES

In 2007, the first asthma *genome-wide association study* (GWAS) was performed by the *Multidisciplinary Study to Identify the Genetic and Environmental Causes of Asthma in the European Community* (GABRIEL) consortium in a European cohort. This study found asthma-associated SNPs in the *orosomucoid 1-like 3* gene (*ORMDL3*) region on chromosome 17q12; a second larger GWAS by the GABRIEL consortium found additional susceptibility loci in the neighboring *gasdermin-like* genes (*GSDMB* and *GSDMA*).[120,172] The 17q12 locus is the most frequently replicated asthma risk locus with the highest statistical significance across studies in individuals of European descent, including Puerto Ricans (eTable 60.1).[173–182] Variation in this locus regulates the mRNA expression of both *ORMDL3* and *GSDMB*, but the

eTable 60.1 Highly Replicated Asthma Susceptibility Loci Identified Through Genome-Wide Association Studies

Gene Names	Chr Pos	Gene ID	Racial or Ethnic Populations	Initial Reported Locus	References
CD247	1q24	*CD247*	European Ancestry, European American	rs1723018	200, 202
Interleukin-1 Receptor	2q12	*IL1RL1*	European Ancestry, European American, African American, African Caribbean, Hispanic	rs1420101	172, 175, 178, 200, 202, 215, 356
Interleukin-18 Receptor	2q12	*IL18R1*	European	rs3771166	172, 356
Dipeptidyl Peptidase-10	2q14	*DPP10*	African American	rs1435879	156
D-2-Hydroxyglutarate Dehydrogenase	2q37	*D2HGDH*	European Ancestry, European American	rs34290285	200, 202
Thymic Stromal Lymphopoietin	5q22	*TSLP*	European Ancestry, European American, African American, African Caribbean, Hispanic, Japanese	rs1837253	172, 178, 200, 202, 357
WD Repeat Domain 36	5q22	*WDR36*	European Ancestry, East Asian	rs2416257	175, 202, 358
RAD50 Homolog	5q31	*RAD50*	European Ancestry, European American, African American, African Caribbean, Hispanic	rs2244012	170, 175, 200, 202
Interleukin-13	5q31	*IL13*	European Ancestry, European American, African American, Hispanic	rs1295686	170, 215, 359
Nedd4 Family Interacting Protein 1	5q31	*NDFIP1*	European Ancestry, European American, African American, Hispanic	rs200634877	200, 215
Human Leukocyte Antigen Complex DRA	6p21	*HLA-DRA*	European Ancestry, European American	rs2395185	356, 359
Human Leukocyte Antigen Complex DQB1	6p21	*HLA-DQB1*	European Ancestry, Japanese	rs9273349	170, 172, 202
Human Leukocyte Antigen Complex DQA1	6p21	*HLA-DQA1*	European Ancestry, European American	rs9272346	200, 202, 360
Human Leukocyte Antigen Complex C	6p21	*HLA-C*	European Ancestry, European American	rs2428494	200
BTB Domain and CNC Homolog 2	6q15	*BACH2*	European Ancestry, European American, African American, Hispanic	rs58521088	200, 202, 215
Cadherin-Related Family Member 3	7q22	*CDHR3*	European Ancestry, European American	rs6959584	199, 200
Interleukin-33	9p24	*IL33*	European Ancestry, European American, African American, African Caribbean, Hispanic	rs1342326	172, 175, 178, 200, 202
GATA Binding Protein 3	10p14	*GATA3*	European Ancestry, European American, African American, Hispanic, Japanese	rs10508372	202, 215, 357
BRCA2 Interacting Transcriptional Repressor	11q13	*EMSY*	European Ancestry, European American, African American, Hispanic	rs7936323	200, 215
Signal Transducer and Activator of Transcription 6	12q13	*STAT6*	European Ancestry, European American, African American, African Caribbean, Hispanic	rs3001426	173, 200, 202, 215
SMAD Family Member 3	15q22	*SMAD3*	European Ancestry, European American, African American, Japanese, Hispanic	rs744910	172, 175, 200, 202, 215
RAR-Related Orphan Receptor A	15q22	*RORA*	European Ancestry, European American, African American, African Caribbean, Hispanic	rs11071559	172, 173, 175, 202, 215
C-Type Lectin Domain Containing 16A	16p13	*CLEC16A*	European Ancestry, European American, African American, Hispanic	rs7203459	200, 202, 215
ORM1-Like 3	17q12	*ORMDL3*	European Ancestry, European American, African American, African Caribbean, Hispanic, Chinese	rs7216389	120, 172–182
Gasderminlike B	17q12	*GSDMB*	European Ancestry, European American, African American, African Caribbean, Chinese	rs2305480	172, 177, 178, 181, 359
Ikaros Family Zinc Finger 3	17q21	*IKZF3*	European Ancestry, Hispanics	rs907092	
Zinc Finger Protein 652	17q21	*ZNF652*	European Ancestry, European American, African American, Hispanic	rs17637472	202, 215
Interleukin-2 Receptor, β-Subunit	22q12	*IL2RB*	European Ancestry	rs2284033	172, 175

precise mechanisms through which these genes contribute to asthma pathogenesis remains unclear.[183–185] The second GABRIEL GWAS was among the first of many to identify additional novel risk loci, including the genes coding for *thymic stromal lymphopoietin* (*TSLP*), *IL1RL1/IL18RL1* (between the IL-1 and IL-18 receptor genes), *HLA-DQ*, *IL33*, and *SMAD3* (see eTable 60.1).[172,178] These associations are both highly significant and reproducible associations across independent cohorts.

Asthma in Diverse Ethnic Groups

Only a few GWASs have been performed in multiethnic populations including Hispanic and African American subjects. This is of particular importance because African Americans and Puerto Ricans have a greater asthma incidence, morbidity, and mortality compared to whites and other Hispanic groups (i.e., Mexican Americans).[186,187] GWASs in these groups have been substantially less frequent with smaller sample sizes compared to whites, but have identified both overlapping and unique asthma risk loci (see eTable 60.1). A GWAS from the EVE consortium was the first large-scale, multiethnic study representing Americans of European descent, African Americans, African Caribbeans, and Hispanics (Mexican Americans and Puerto Ricans) and identified significant associations in the 17q12 locus, *IL1RL1*, *TSLP*, and *IL33*, confirming their importance as asthma risk loci in ethnically diverse populations.[120,172,178] The 17q21 locus has been replicated in African descent multiethnic cohorts that included Puerto Ricans, and in Puerto Ricans alone, but has not been replicated in African Americans alone who have, on average, higher African and lower European ancestry compared to Puerto Ricans.[156,173,180,188] Another large multiracial GWAS identified SNPs in the *pyrin and HIN domain family member 1* (*PYHIN1*) gene that were only associated with asthma in African Americans and African Caribbeans.[178] Additional GWASs of populations from a primarily African ancestry have identified additional novel, race-specific susceptibility loci including the *DPP10* locus and the gene encoding *patched domain-containing protein-3* (*PTCHD3*), which is related to the hedgehog signaling pathway implicated as a genetic determinant of lung function.[121,156,157,188–194] These ancestry-specific differences in asthma risk loci have been recapitulated in larger multiethnic GWASs of asthma, but the number of GWASs consisting of African Americans and Hispanics remains relatively small.[189,195]

Severe Asthma and Disease Severity

GWASs of cohorts enriched for severe asthma have confirmed prior asthma genes and identified novel risk loci including multiple SNPs in *RAD50* adjacent to *IL13*, *HLA-DQB1*, and between *HLA-DQB1* and *HLA-DQA2*.[128,143,170,196–198] A GWAS of children with severe asthma identified four previously identified susceptibility loci in *GSDMB*, *IL33*, *RAD50*, and *ILRL1* and a novel SNP in the gene encoding *cadherin-related family member-3* (*CDHR3*), which was subsequently confirmed in an independent asthma GWAS and found to function as a receptor for rhinovirus C.[199–201] A recent large GWAS for moderate-to-severe asthma based on the U.K. Biobank population confirmed 21 risk loci including novel variants in genes encoding a GATA binding protein (*GATA3*) and *MUC5AC*, a gene that encodes for an asthma-relevant secreted mucin glycoprotein.[202]

GWASs in asthma cohorts have identified loci associated with lung function, a fundamental determinant of asthma severity. A GWAS of lung function in a U.S. non-Hispanic white cohort enriched for severe asthma identified novel variants associated with lung function and asthma severity in T1 immunity pathway genes that regulate the inflammatory response associated with viral and bacterial infections (*IL12A*, *IL12RB1*, *STAT4*, *IRF2*).[203] In addition, GWASs of lung function in a general population have found SNPs in *HHIP* (hedgehog-interacting protein) and *PTCH1*, which are cumulatively associated with lower lung function across different ethnic groups with asthma.[193,194,204] These findings suggest that gene variants that determine asthma severity can be different from those that determine risk. As one exception, variants in the IL-6 receptor gene (*IL6R*) were associated both with asthma risk and with lung function in two, independent GWASs.[175,205] Another strongly linked coding variant in *IL6R*, Asp^{358}Ala, is also associated with lung function and with bronchial responsiveness in individuals with asthma.[206]

Lessons Learned

To date, GWASs have discovered more than 73 loci associated with asthma susceptibility, most of which are in regulatory or noncoding regions due either to the fact that most of the human genome is noncoding or the fact that identified GWAS SNPs potentially tag for variation that could be within coding exons. Highly replicated asthma susceptibility loci identified through GWASs are presented in eTable 60.1. These GWASs have revealed several lessons about the genetic factors that underlie asthma risk. First, asthma risk loci span multiple genes from biologic pathways related to (1) epithelial responses triggered by allergens or infection (*IL1RL1, IL33, CDHR3*); (2) airway inflammation, remodeling, and hyperresponsiveness in response to tobacco smoke, lipopolysaccharides, allergens, or alterations in sphingolipid biosynthesis (*ORMDL3, GSDMB*); (3) T2 inflammation (*TSLP, IL13, GATA3, DENND1B*); (4) innate immunity (*TLR1, MICB, IL2RB*, HLA locus); and (5) cellular inflammation (*TNFSF4, TNIP1, IL6R*). Second, the genetic determinants of asthma risk vary across ethnic groups from different ancestral backgrounds, and GWASs in diverse multiethnic cohorts have identified ethnic-specific loci (*PTCHD3, PYHIN1, ADRAB1, PTGES*) not found in whites of European descent.[156,178,188,189] Finally, identified variants have weak effects and cumulatively account for a small proportion of the observed heritability of asthma.[189,200] This "missing heritability" of asthma is related, at least in part, to the challenges of objectively diagnosing asthma in large cohorts and to gene-gene and gene-by-environment interactions.[207]

EPIGENETIC STUDIES FOR ASTHMA SUSCEPTIBILITY AND SEVERITY

Environmental exposures may trigger epigenetic modifications and therefore contribute to asthma pathogenesis in ways not detectable using traditional genetic approaches. The epigenome can be regulated through DNA methylation, altered histone binding, and chromatin condensation

at gene promoters, which alter gene transcription without changes in the DNA code. Some asthma susceptibility genes from early linkage studies and GWASs have been evaluated with epigenetic approaches. For example, a small epigenetic study of the 17q21 locus in peripheral blood leukocytes from European pediatric asthma cases and controls identified differences in methylation across CpG sites at *ORMDL3* that associated with *ORMDL3* mRNA expression and asthma, independent of adjacent risk SNP loci.[208] *Epigenome-wide association studies* have been relatively small and limited by the availability of whole-blood DNA or asthma-relevant tissues but have provided some insight into how environmental exposures interact with genes to influence asthma risk.[209–211] Epigenome-wide association studies of whole blood inflammatory cell and nasal epithelial cell tissue DNA from an inner city cohort have identified multiple sites of differential CpG methylation near genes within biologic pathways relevant to nitric oxide synthesis (*CAT, KLF6*), immunity (*HLA-DPA1, TNFSF13, IFNGR2, EXOC2*), T2 inflammation (*IL4, IL13, POSTN, ALOX15, CAPN14*), collagen, and the extracellular matrix (*COL16A, COL5A2, COL5A3, HAS3, MMP14*).[212,213] An epigenome-wide association study of cord blood mononuclear cell DNA from infants identified *SMAD3*, a gene from prior GWASs, as a gene with increased methylation associated with childhood asthma risk.[172,200,214,215] The genes and biologic pathways associated with asthma through GWASs and epigenome-wide association studies seem to overlap, but larger studies in cohorts with available tissue will be needed to characterize the epigenetic mechanisms that contribute to the missing heritability of asthma.

MOLECULAR AND CELLULAR BASIS OF ASTHMA

HISTOPATHOLOGY OF ASTHMA

Asthma is a disease of the airways characterized by pathologic changes in both the epithelium and the submucosa (Fig. 60.3). These changes, often summarized by the term airway remodeling, include abnormal deposition of collagen in the subepithelium and changes in structural cells such as goblet cells, submucosal gland cells, smooth muscle cells, and blood vessel cells. Goblet cell metaplasia and hyperplasia increase the amount of stored gel-forming mucins in the airway epithelium.[216] Desquamation of epithelial cells can be seen in acute severe asthma exacerbations but not in chronic stable asthma.[217] Deposition of collagen types I, III, and IV and of fibronectin and tenascin in the subepithelium immediately under the true basement membrane is most prominently seen in T2 asthma,[218–220] even in early-onset disease. Myofibroblasts are increased in number in asthma and are an important cellular source of matrix protein deposition in the subepithelium. Hyperplasia of airway smooth muscle is easy to demonstrate by morphometric measurements, even in mild forms of asthma, whereas true airway smooth muscle hypertrophy is found in more severe subtypes of asthma.[221,222] By contrast, inherent smooth muscle dysfunction and hypercontractility, which are modeled in vitro, are more difficult to demonstrate in vivo in asthmatics.[221] Measurements of isometric tension in airway smooth muscle tissue from asthmatic subjects have not shown consistent evidence for enhanced force generation but have shown increased shortening.[223] Such increases in isotonic shortening in airway smooth muscle could result not only from alterations in the contractile apparatus,[224] but also from alterations in the biophysical properties of the extracellular matrix.[225] Bronchial blood vessel number and size are increased in asthma, and these vessels may have an important role in regulating airway caliber because an increase in vascular volume may swell the mucosa and narrow the airway lumen.[226–228] Many inflammatory mediators cause vasodilation, which may be accompanied by increased permeability at the postcapillary venule, plasma extravasation, and airway mucosal edema. Histologic analyses of lungs from patients who die from acute severe asthma show extensive mucus plugging of airways, airway wall thickening, smooth muscle hypertrophy, and submucosal gland hypertrophy.[229] Silicone rubber casts of autopsy lungs from patients with asthma show marked airway truncation from mucus plugs and also reveal longitudinal ridges and horizontal corrugations corresponding to elastic bundles and smooth muscle hypertrophy.[229]

NERVES AND NERVE RECEPTORS IN ASTHMA

The neurologic "wiring" of the airway includes innervation of airway smooth muscle by sympathetic and parasympathetic nerves. When activated, airway nerves can markedly constrict airways or dilate contracted airways. The nervous system is therefore an important regulator of airway caliber. A key detail is that the predominant contractile innervation of airway smooth muscle is parasympathetic and cholinergic in nature, while the primary relaxant innervation of the airways is comprised of noncholinergic (nitric oxide synthase– and vasoactive intestinal peptide–containing) parasympathetic nerves.[230,231] These anatomically and physiologically distinct parasympathetic nerves are differentially regulated by reflexes. Perhaps surprisingly, given the clinical utility of adrenergic agonists as bronchodilators, sympathetic-adrenergic nerves have only minor physiologic roles in regulation of airway smooth muscle tone.[232]

The term neurogenic inflammation refers to the inflammatory responses caused by tachykinins, which are peptidergic neurotransmitters that activate specific receptors as part of the *nonadrenergic noncholinergic* system.[233] Excitatory nonadrenergic noncholinergic effects are mediated by release of tachykinins such as neurokinin A and substance P acting on *neurokinin-1 and -2 receptors*. In general, neurokinin-1 receptor mediates gland secretion, plasma extravasation, vasodilation, and leukocyte adhesion, whereas neurokinin-2 receptor mediates contraction of airway smooth muscle. Inhibitory nonadrenergic noncholinergic effects are thought to be mediated principally by vasoactive intestinal peptide and nitric oxide. Evidence for an operative nonadrenergic noncholinergic system in asthma comes from studies showing that asthmatic subjects develop bronchoconstriction after inhaling neurokinin A or substance P.[234] Although a neurokinin-1 and -2 receptor antagonist protected against

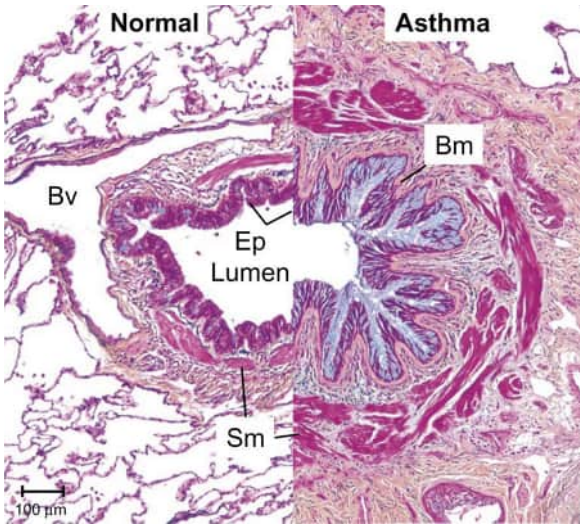

Figure 60.3 Airway pathology in asthma. Photomicrograph illustrating pathologic differences in a medium-sized airway from a nonasthmatic patient (*left*) and a patient with asthma (*right*). The stain is a Movat pentachrome stain. The airways in asthma show significant structural remodeling. The epithelium in asthma shows goblet cell hyperplasia, subepithelial fibrosis, and increased smooth muscle (Sm) volume. Scale bar 100 µm. Bm, basement membrane; Bv, blood vessel; Ep, epithelium. (From Wadsworth S, Sin D, Dorscheid D. Clinical update on the use of biomarkers of airway inflammation in the management of asthma. *J Asthma Allergy.* 2011;4:7786.)

bradykinin-induced bronchoconstriction in asthmatic subjects, a selective neurokinin-1 receptor antagonist did not protect against hypertonic saline-induced cough or bronchoconstriction.[235]

Cholinergic nerves innervate airway smooth muscle, and hyperresponsiveness of airway smooth muscle is a central pathophysiologic feature of asthma. The mechanism of this hyperresponsiveness is complex and not fully understood. Past concepts that the hyperresponsiveness reflects an imbalance in neural signals that constrict or dilate airways have been difficult to prove in human studies and are likely to underestimate the role of non-neural mechanisms. Parasympathetic nerves also innervate submucosal glands and regulate mucin secretion from submucosal gland cells. Notably, inflammatory cells in the airway all express parasympathetic receptors, so that these cells may be under parasympathetic nerve control. These nerves produce and release inflammatory mediators and can contribute to the recruitment and activation of leukocytes. These leukocytes can then alter production and release of neurotransmitters from nerves. In this way, crosstalk between airway nerves and leukocytes may help maintain chronic inflammation in asthma. Consequently, anticholinergic treatment should benefit patients with asthma not just because of bronchodilator effects. Indeed, it is known that vagotomy decreases inflammation in the lungs of asthmatic patients and that treating patients with uncontrolled asthma with a long-acting anticholinergic drug (tiotropium bromide) improves asthma control.[238]

Transient receptor potential vanilloid 4 (TRPV4) is a broadly expressed, polymodally gated ion channel highly expressed in airways.[239] It is an osmosensor and thermosensor activated by temperature or by endogenous or exogenous chemical stimuli. TRPV4-mediated activation of airway afferents is a putative mechanism of cough and bronchoconstriction, and pharmacologic inhibitors of TRPV4 are being considered as novel asthma treatments.[240]

OVERVIEW OF MOLECULAR IMMUNOLOGY OF ASTHMA

Asthma is a clinical diagnosis that results from heterogeneous immune disorders of the airways. These disorders include aberrant T2 (allergic) immune responses that underlie the dominant T2-high subtype of asthma and non-allergic immune responses that underlie disease in smaller subsets of patients (T2-low forms of asthma).

T2-high asthma is characterized by T2 immune responses. T2 immune responses include prominent eosinophil infiltration of tissues, driven by T2 cytokines (IL-4, IL-5, and IL-13) secreted by multiple immune cell types, including the Th2 subset of $CD4^+$ T cells, group 2 *innate lymphoid cells* (ILCs), mast cells, and basophils. To perform key functions in T2 immunity, mast cells and basophils are armed with IgE derived from B cells under the influence of IL-4. T2 immune responses usually arise in response to helminth and parasite infections, where eosinophils undergo cytolysis and release toxic granules to kill the parasite, and epithelial cells overproduce mucus to encapsulate the helminths and facilitate expulsion from the gastrointestinal tract. In response to insect and snake bites, mast cell and basophil proteases usually function to neutralize extracellular toxins. If all of this fails, a fibrosis program is initiated as a barrier against the parasite or toxins. T2 immune responses can also be inappropriately mounted against innocuous environmental antigens (allergens) resulting in allergy and asthma. Specifically, an excess of T2 cytokines in the lower airway in patients with T2-high asthma will promote IgE-mediated hypersensitivity, activate epithelial cell mucus production, mediate inflammatory eosinophil-rich cell influx to the airway, cause remodeling responses in the epithelium and subepithelial matrix, and promote alterations in smooth muscle reactivity leading to bronchial hyperreactivity. The sensitivity of T2 inflammation to corticosteroids explains why T2-high asthma is usually responsive to corticosteroid treatment.[220]

T2-low forms of asthma represent a more heterogeneous and less well-understood group, yet the prevalence is high. In patients with less severe asthma, the prevalence of patients who lack airway eosinophilia or other markers of T2 inflammation is 60–70%; in those with more severe asthma, the lack of T2 inflammation may be seen in 40–50%.[241–244] Although analyses of inflammation in airway specimens collected from patients with asthma have shown a lack of airway inflammation in a subset of patients (paucigranulocytic asthma),[245] other subsets of patients show signals for activation of pathways related to T1 or *type 3* (T3) immunity or for neutrophilic inflammation independent of T3 immunity.[246] T1 immunity consists of interferon-γ–producing cells (group 1 ILCs, $CD8^+$ cytotoxic T cells, and $CD4^+$ Th1 cells), which normally protect against intracellular microbes through activation of mononuclear phagocytes but which can be co-opted to drive chronic inflammatory disease. T3 immunity is mediated by group 3 ILCs and Th17 cells producing IL-17, IL-22, or both, which activate mononuclear phagocytes but also recruit neutrophils and induce epithelial antimicrobial responses, thus protecting against extracellular bacteria and fungi. Although T1 and T3

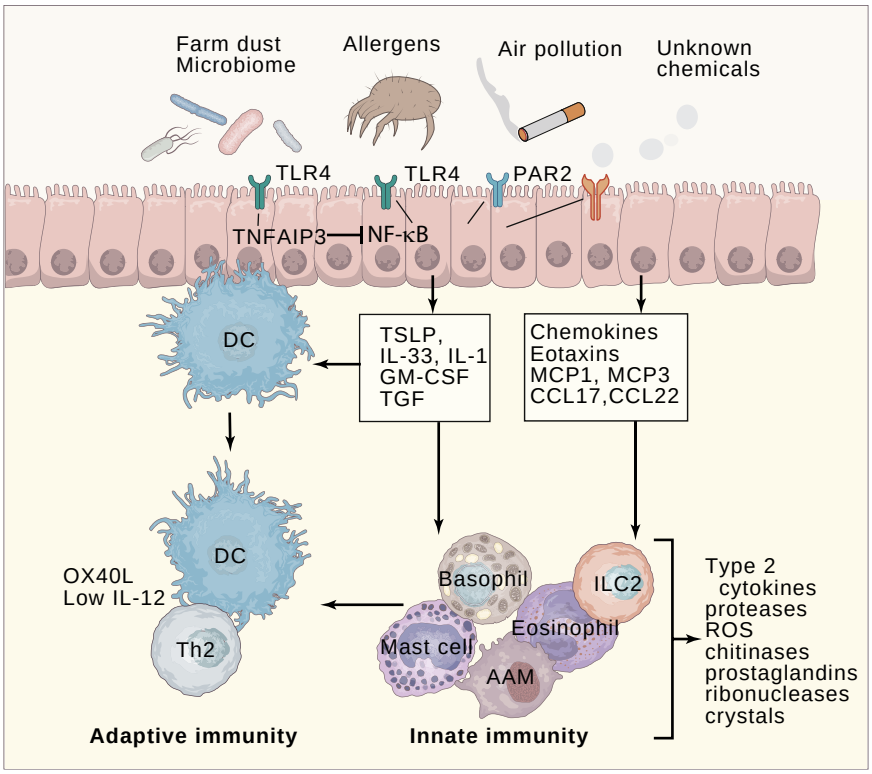

Figure 60.4 Early innate immune response driving asthma. Most allergens and many air pollutants trigger epithelial cell production of cytokines and chemokines through activation of toll-like receptors (TLRs) or protease-activated receptors. This leads to activation of dendritic cells (DCs) that migrate to draining lymph nodes. DCs in lymph nodes will promote Th2 development in the presence of OX40 ligand (OX40L) and when interleukin (IL)-12 levels are relatively low. In addition, epithelial cell production of cytokines leads to activation of innate immune cells that are recruited to the airways and produce mediators that contribute to airway inflammation. Cytokines like thymic stromal lymphopoietin (TSLP), IL-33, and granulocyte-macrophage colony-stimulating factor (GM-CSF) and chemokines such as monocyte chemokine proteins, eotaxins, and C-C chemokines (CCL17- and CCL22) are all potential drug targets for new biologics. Some environmental exposures such as chronic exposure to farm dust can suppress the airway epithelial response to allergens because these induce expression of a negative regulator of nuclear factor-κB (NF-κB) activation called tumor necrosis factor-α induced protein-3 (TNFAIP3). AAM, alternatively activated macrophages; ILC2, innate lymphoid cell 2; MCP, monocyte chemoattractant protein; PAR2, proteinase activated receptor 2; ROS, reactive oxygen species; ILC2, innate lymphoid cell 2; TGF, transforming growth factor.

immunity are usually implicated in autoimmune diseases, there are data to implicate these responses as a disease mechanism in subgroups of asthma patients. In addition, subsets of patients have systemic inflammation and metabolic dysfunction,[241] and asthma in these patients may represent airway dysfunction caused by inflammatory stimuli that arise outside the lung.

MOLECULAR IMMUNOLOGY OF T2-HIGH ASTHMA

Airway epithelial cell crosstalk with immune cells in the underlying submucosa is a fundamental mechanism of T2-high asthma (Fig. 60.4).[247,248] Inhaled insults, including microbes, aeroallergens, and oxidants (cigarette smoke, car exhaust pollutants) activate airway epithelial cells through multiple pattern recognition receptors that detect and respond to danger signals. These receptors include toll-like receptors and receptors for alarmins such as uric acid and adenosine triphosphate. Other exposures such as farm dust can suppress airway epithelial response to allergens via increased expression of *tumor necrosis factor* (TNF)-α induced protein-3, a negative regulator of nuclear factor-κB activation (see Fig 60.4). Activated epithelial cells release TSLP, IL-33, IL-1β, and *granulocyte-macrophage colony-stimulating factor* (GM-CSF). These cytokines and chemokines recruit *dendritic cells* (DCs) from the bone marrow to the airway epithelium where the DCs sample inhaled antigens, process them to linear peptides, and present them on their cell surface as part of the class II major histocompatibility heterodimer complex to naive T cells in the draining lymph nodes, thus initiating allergic T2 sensitization upon first exposure to allergens. Upon repeated encounter with an allergen, DCs can also stimulate effector and memory T cells to orchestrate inflammation locally in the airways. Full-blown effector differentiation of $CD4^+$ T cells initiated in draining lymph nodes is completed following exposure of $CD4^+$ Th2 cells to IL-33 and TSLP in the epithelial and subepithelial space[249] (Fig. 60.5). The epithelial cytokines also activate cells of the innate immune system, including mast cells, basophils, and ILC2s, that work together with $CD4^+$ Th2 effector cells to produce IL-13 and IL-5. IL-5 promotes the development and activation of eosinophils. IL-13 activates airway epithelial cell programs that increase expression of chemokines, mucins, and inducible nitric oxide synthase. Chemokines such as eotaxins and stem cell factor recruit eosinophils and mast cells, and mucins are secreted apically to create an adherent and stiff mucus gel. Nitric oxide, produced from L-arginine by inducible nitric oxide synthase activity, is a potent mediator of vascular permeability, and exhaled nitric oxide is a useful biomarker of IL-13 activation of the airway epithelium. Other less well-understood products of IL-13-activated epithelial cells have roles in promoting smooth muscle pathology in asthma and

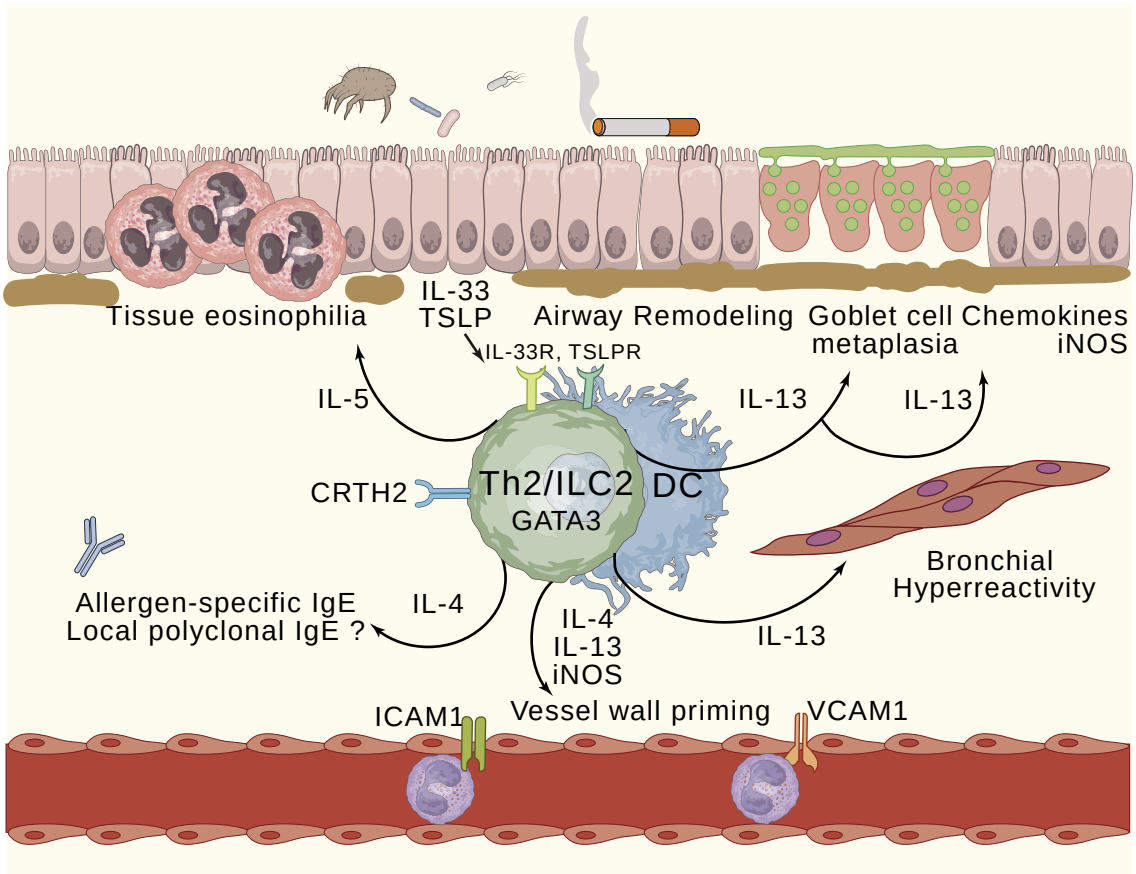

Figure 60.5 Central role of type 2 (T2) and innate lymphocytes in controlling key features of T2-high asthma. T2-high asthma is marked by airway eosinophils and by nitric oxide in exhaled air (iNOS). It is often accompanied by goblet cell metaplasia and high-level production of the airway mucin MUC5AC. T2 memory lymphocytes are restimulated by dendritic cells (DC) upon allergen recognition and produce interleukin (IL)-4, IL-5, and IL-13. In some patients with T2-high asthma, group 2 innate lymphoid cells (ILC2) are activated directly by epithelial cytokines such as thymic stromal lymphopoietin (TSLP) and IL-33 to produce IL-5 and IL-13. Th2 cells and ILC2s share many features such as expression of cytokine receptors, transcription factor GATA-binding protein 3 (GATA3), and chemokine receptor expressed by Th2 cells (CRTH2). IL-5 drives the development and activation of airway eosinophils. IL-13 drives iNOS production in airway epithelial cells, goblet cell metaplasia, and bronchial hyperreactivity. IL-4 promotes immunoglobulin E (IgE) synthesis (allergen specific in the case of allergic asthma) and primes the vessel wall for extravasation of eosinophils through induction of vascular cell adhesion molecule (VCAM-1) and intercellular adhesion molecule (ICAM-1) by acting on IL-4R. The *brown lines* beneath the airway epithelium signify excess subepithelial collagen.

in driving subepithelial cell collagen deposition, a hallmark of T2-high asthma.

T2-high forms of asthma can develop in childhood or in adulthood. In childhood, T2-high asthma typically presents as a lung manifestation of atopy. Adult-onset T2-high asthma is more typically associated with upper airway disease (chronic rhinosinusitis with nasal polyps) and sensitivity to aspirin. The relative roles of $CD4^+$ Th2 cells, ILC2s, mast cells, and basophils as cellular sources of T2 cytokines in childhood versus adult-onset T2 asthma is an area of active research.

Mast cells are considered central effector cells in T2-high forms of asthma (Fig. 60.6). Mast cells constitutively express multiple receptors on their cell surface, including the *high affinity IgE receptor* (FcεRI), the IL-33 receptor (ST2), and Siglec8. Basophils are circulating granulocytes that also express FcεRI, the prostaglandin D2 receptor (*chemokine receptor expressed by Th2 cells* [CRTH2]), ST2, and the *IL-5 receptor* (IL-5R). Antigen-induced cross-linking of IgE leads to aggregation of IgE-FcεRI complexes, which stimulate mast cells and basophils to release autocoids (histamine, serotonin), proteases (tryptase, chymase, carboxypeptidase A3), proteoglycans (heparin and/or chondroitin sulfates), lipid-derived mediators (*prostaglandin D2* [PGD_2], leukotriene B_4, leukotriene C_4, leukotriene D_4, and leukotriene E_4), and T2 cytokines. The aggregate response to mediators released shortly after mast cell and basophil degranulation is called an immediate hypersensitivity (or early phase) reaction and includes airway smooth muscle contraction, heightened bronchovascular permeability, and increases in mucin secretion. The physiologic consequence is a decrease in airflow but, in extreme cases, also includes hypotension and anaphylaxis if the response is systemic. Although the inflammation and functional changes associated with early phase responses resolve within 1 to 3 hours, a second late phase reaction can develop in some asthmatics, typically beginning 2 to 6 hours after exposure and lasting for 24 to 48 hours, accompanied by influx of more DCs, CD4 T cells, eosinophils, and basophils. Late-phase responders are often studied in proof-of-concept studies of novel controller medications for asthma because a drug's ability to inhibit late phase responses to inhaled allergen in these studies is a good predictor of its efficacy in improving asthma control outcomes in clinical trials.[250]

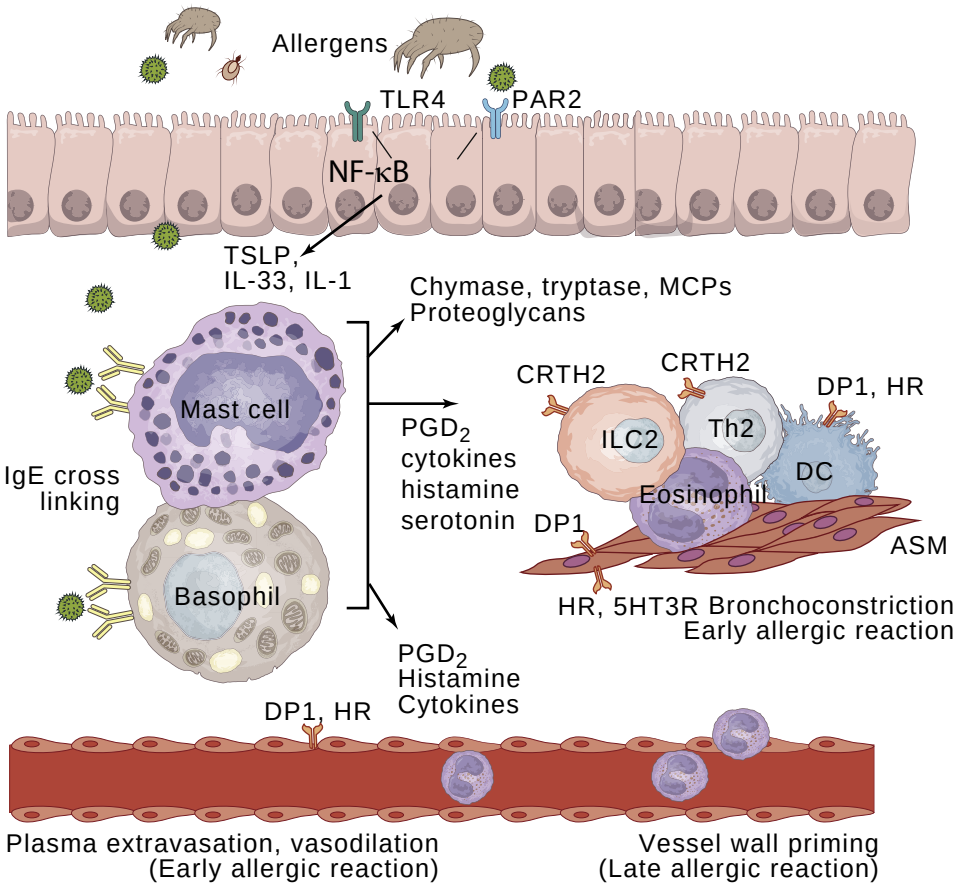

Figure 60.6 Role of mast cells and basophils in asthma. Aeroallergens may be sensed by protease-activated receptors on airway epithelial cells leading to secretion of multiple epithelial cell cytokines, including thymic stromal lymphopoietin (TSLP), interleukin (IL)-33, and IL-1. In addition, aeroallergens (*in green*) cross-link allergen-specific immunoglobulin E (IgE) on mast cells and basophils leading to immediate degranulation and release of many mediators such as prostaglandin D2 (PGD_2), which can act on the type 1 prostaglandin D1 receptor (DP1) or the chemokine receptor expressed by Th2 cells (CRTH2) to cause inflammation and immediate bronchoconstriction (early allergic reaction). Histamine will also cause bronchoconstriction and plasma leakage from nearby vessels. Cytokines released with PGD_2 will prepare the vessel wall for later extravasation of leukocytes (late allergic reaction). ASM, airway smooth muscle; HR, histamine receptor; 5HT3R, human serotonin 3 receptor; MCPs, monocyte chemoattractant proteins; NF-κB, nuclear factor-κB.

Eosinophils are major effectors of T2 asthma and act through release of toxic granules containing eosinophil peroxidase, cationic proteins, and eosinophil-derived neurotoxins.[251] Major basic protein can cause bronchial hyperreactivity by interfering with bronchoconstricting muscarinic receptors.[236] Eosinophil degranulation can alter the characteristics of airway mucus gels in asthma (Fig. 60.7). For example, *eosinophil peroxidase* catalyzes oxidation of thiocyanate (transported from the blood compartment to the airway lumen by SLC26A4 transporter/pendrin, an epithelial cell transporter) by hydrogen peroxide to generate oxidants that cross-link mucin polymers and stiffen mucus gels.[252] In addition, eosinophil-derived Charcot-Leyden crystals can stimulate mucin production, and the presence of these crystals within the mucus plugs could plausibly alter the biophysical properties in ways that decrease mucus clearance.[253] Although eosinophils are very corticosteroid sensitive in vitro by undergoing apoptosis, corticosteroid-induced apoptosis in vivo is less common. When corticosteroids reduce eosinophil numbers, therefore, they may do so via suppression of upstream cytokine networks, such as suppression of the eosinopoietins IL-5 and GM-CSF or prevention of activation of the cells producing these cytokines. Because IL-5 and GM-CSF are produced by corticosteroid-sensitive $CD4^+$ Th2 cells in many asthmatics, corticosteroids reduce eosinophilia in most T2-high asthmatics. In patients with alternative sources of IL-5, such as ILC2s producing IL-5 in severe asthmatics with nasal polyposis, corticosteroids are not as effective, perhaps because ILC2s are more corticosteroid resistant. These patients benefit much more from therapeutic proteins that block the action of IL-5 directly or cytotoxic antibodies that directly deplete eosinophils by targeting IL-5R (and potentially Siglec8).

A consistent feature of T2-high forms of asthma in childhood and adulthood is the persistence of aberrant T2 immunity over long periods of time. Recent advances in understanding the molecular basis of "trained immunity" provide a framework to explain this persistence.[254,255] *Trained immunity* results when innate immune cells, adaptive immune cells, or epithelial stem cells display long-term changes in their functional program through metabolic and epigenetic programming. Although such memory is a mechanism of adaptive host protection, it can also be a mechanism

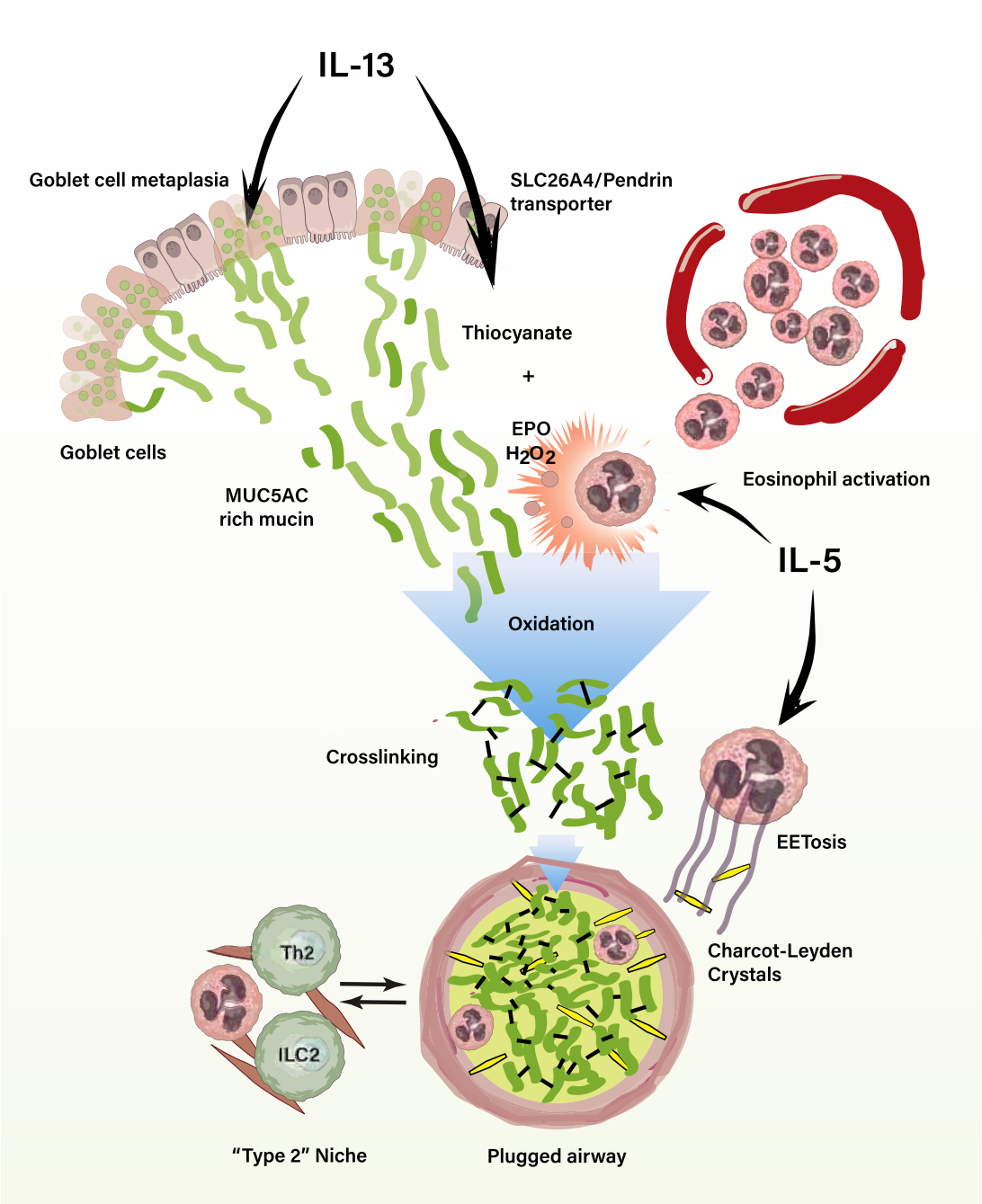

Figure 60.7 Contribution of type 2 immunity and the eosinophil to mucus plugging of the airways. Interleukin (IL)-13 from Th2 cells and from group 2 innate lymphoid cells (ILC2s) drive goblet cell metaplasia and overproduction of MUC5AC-rich mucin. IL-13 also drives expression of pendrin, a transporter protein that carries thiocyanate into the airway lining fluid. IL-5 from Th2 cells and ILC2s drives the activation of eosinophils that release eosinophil peroxidase (EPO). In the presence of H_2O_2 and thiocyanate, airway mucins get cross-linked, stiffening the elastic mucus gel and inhibiting expectoration. Profound eosinophil activation leads to eosinophilic extracellular trap cell death (EETosis), the release of DNA nets and granules coated with galectin-10, which can form Charcot-Leyden crystals (mainly observed in mucus plugs in severe acute asthma and in allergic bronchopulmonary aspergillosis). Regions with mucus plugging have intense type 2 inflammation; the remodeled airway tissue around a chronic mucus plug may form a niche for eosinophils and persistent activation of type 2 lymphocytes. MUC5AC, mucin gene 5AC; SLC26A4, solute carrier family 26, member 24.

of immune dysregulation including chronic T2 inflammation. Trained immunity can be demonstrated in vitro. For example, ex vivo cultured basal cells from the upper airways in patients with chronic rhinosinusitis with nasal polyps are known to retain intrinsic memory of IL-4/IL-13 exposure,[256] and lung epithelial cells can continue to produce GM-CSF even after prolonged culture in vitro. Thus, it is possible that aberrant T2 immune programs in the airway in childhood-onset T2-high asthma become fixed because they are established during critical time windows in early life when the immune system and lung epithelium is plastic and susceptible to epigenetic changes. A second window may open in later life, perhaps the result of immune senescence and other age-related failures in normal immune regulation.

Because epigenetic changes persist in dividing cells, they provide a mechanism for environmental factors to cause stable alterations in phenotype without changes in genotype. The epigenome may not change uniformly in all the airways of an individual patient. For example, airway mucus plugs are a feature of T2-high asthma and have been observed in specific airways within a patient, persisting in the same airways over many years.[252] These mucus plugs mark airways with intense T2 inflammation and represent an inflammatory niche (T2 airway niche). The biology of immune niches is just beginning to be understood, but it is likely that genomic or metabolic reprogramming of airway epithelial cells, immune cells, and neuronal pathways renders T2 airway niches self-sustaining because of feed-forward reinforcing signals between the key cellular players. As understanding of this biology improves, it may be possible to provide treatments that interrupt persistent T2 inflammation in T2-high forms of asthma.

MOLECULAR ASPECTS OF T2-LOW FORMS OF ASTHMA

Many patients with asthma do not have an excess of airway eosinophils or other markers of T2 inflammation.[241–244] Because T2 inflammation is decreased by corticosteroid treatment, the common use of corticosteroids in patients with more severe forms of asthma may lead to underestimation of T2-high disease in these patients. Despite this possibility, there is consensus now that non-T2 mechanisms of disease exist in all forms of asthma and account for poor corticosteroid responsiveness and disease control in many patients. The cellular and molecular drivers of T2-low forms of asthma are uncertain, but research to date has identified a subset of patients with no inflammation signals (paucigranulocytic asthma) and other subsets with signals for T1 immunity, T3 immunity, airway neutrophilia, or systemic inflammation.

Paucigranulocytic Asthma

Granulocytes such as neutrophils and eosinophils are not always present in excess in airway secretions or tissues from patients with asthma.[257] Similarly, transcriptomic analyses of airway biopsies do not always show signals for specific pathology.[258] The lack of airway inflammation in some patients with asthma is puzzling, and it may mean that chronic inflammation is not needed for expression of phenotypic features of asthma, including smooth muscle dysfunction. In general, patients with paucigranulocytic asthma have less severe forms of asthma.

Type 1 Immunity in Asthma

T1 immunity is an important mechanism for host defense against intracellular microorganisms. By secreting *interferon* (IFN)-γ and TNF-α, the $CD4^+$ Th1 cells, $CD8^+$ cytotoxic T cells, and group 1 ILCs activate mononuclear phagocytes to convert them to potent effector cells. T1 immunity also plays pathogenic roles in autoimmune organ-specific disorders and may be a disease mechanism in subgroups of asthma patients as well. For example, pathway analysis of epithelial cell transcripts in mild asthma shows increased expression of IFN-stimulated genes, and there is an inverse association between expression of these genes and reduced lung function.[259] In addition, other studies have shown that airway IFN-γ^+ $CD4^+$ T cells (Th1 cells) are more prevalent in severe asthma than in mild-to-moderate asthma.[260] Despite these findings, the role of T1 immunity as a molecular subtype of asthma and the potential for treatment of any T1 immune dysfunction to improve asthma control in targeted population has not yet been established.

Type 3 Immunity in Asthma

T3 immunity is devoted to protection against extracellular bacteria and fungi and relies on lymphocytes that produce IL-17 and/or IL-22 as signature cytokines. These lymphocytes include $CD4^+$ Th17 cells, $CD8^+$ Tc17 cells, and group 3 ILCs. The cooperative activity of IL-17 and IL-22 leads to upregulation of chemokines and growth factors in epithelial cells and endothelial cells, which recruit and sustain neutrophils. IL-17–mediated upregulation of proteases and growth factors in fibroblasts and other stromal cells also enhances access of neutrophils to tissues and further promotes neutrophilia. Although beneficial in combatting infection, IL-17–mediated recruitment of neutrophils and immune cells is also a mechanism of chronic inflammation and autoimmunity, and it has been implicated in the pathophysiology of diseases such as rheumatoid arthritis, psoriasis, and inflammatory bowel disease. Although data for upregulation of IL-17 in asthma are not as robust, some studies have identified subsets of asthma patients with increases in IL-17 gene signatures in airway specimens.[261] However, a clinical trial of therapeutic antibody targeting IL-17 in patients with asthma was negative,[262] casting doubt on the role of IL-17 as an important mediator of T2-low forms of asthma. It remains possible that improved selection for patients with elevated levels of IL-17 will result in better clinical trial results.

Neutrophils and Asthma

Independent of any putative role for T3 immunity in asthma, neutrophilic inflammation is considered a possible mechanism of T2-low forms of asthma. Neutrophils are an abundant cell type in airway secretions in both healthy subjects and asthmatic subjects, reflecting important roles in host defense.[263,264] The relatively large numbers of airway neutrophils even in health can make it difficult to determine when neutrophils are contributing to disease severity. In large asthma datasets, it is possible to find correlations between airway neutrophils and measures of airflow obstruction,[265,266] but other analyses that rely on neutrophil cutoffs have had less consistent results. One lesson from these studies is that the activation state of neutrophils rather than their number may be a more important indicator of the contribution of neutrophils and their products to disease severity. Possible mechanisms by which activated neutrophils could impair lung function in asthma include neutrophil-mediated oxidative stress, neutrophil protease-mediated activation of airway epithelial cells, or neutrophil protease-mediated goblet cell degranulation. In addition, *neutrophil extracellular traps* mediate inflammasome activation and IL-1β secretion from monocytes and cause airway epithelial cell injury. Indeed, high extracellular DNA concentration in sputum has been found to mark a subset of patients with more severe asthma.[267] Despite a

plausible mechanism by which neutrophils can injure airways, a clinical trial targeting neutrophils did not show clinical benefit in patients with asthma.[268] It is possible that this trial was negative because it relied on neutrophil counts rather than neutrophil activation biomarkers, but it remains the case that definitive evidence linking neutrophilic inflammation to the pathogenesis of chronic asthma is lacking. Relevant here is the consistent finding of a subset of patients who have both airway eosinophilia and airway neutrophilia.[269,270] These patients are notable for having more severe disease. The mechanism for sustained combined eosinophilic and neutrophilic granulocytic inflammation is poorly understood.

Systemic Inflammation and Metabolic Dysfunction

Analyses of clinical traits in asthma cohorts show that the clusters of patients with more severe asthma typically include those who are older and those who are obese.[271] This association with age and obesity raises the possibility that systemic inflammation—common in obesity because of increased production of IL-1, IL-6, or TNF-α by white adipose tissue—could have consequences for airway function in asthma. Evidence for this possibility comes from studies showing that patients with asthma who have high plasma IL-6 levels have more severe asthma than those with normal IL-6 levels,[241] IL-6 is regulated by IL-1β so that increased IL-6 in these studies may be marking increased IL-1β activity as well. Circulating IL-1β could plausibly cause airway epithelial cell dysfunction. Studies in mice and human bronchial epithelial air-liquid interface cultures have shown that IL-1β triggers a cytokine response in epithelial cells leading to production of IL-33, TSLP, and GM-CSF.[272] The importance of systemic inflammation as a driver of organ dysfunction and cancer has recently been highlighted by successful clinical trials of IL-1β inhibition in patients at risk for cardiovascular disease and selected on the basis of high circulating IL-6. In these trials, inhibiting IL-1β using a monoclonal antibody, canakinumab, not only reduced the risk of cardiovascular events,[273] it also reduced rates of lung cancer.[273] Efforts are now underway to initiate clinical trials of IL-1β or IL-6 inhibitors in patients with asthma selected for having biomarkers of systemic inflammation. This effort marks formal acknowledgement that T2 axis cytokines are not the only cytokines that should be considered therapeutic targets in asthma.

LIPID MEDIATORS

The *cysteinyl leukotrienes* (cys-LTs) are peptide-conjugated arachidonic acid-derived inflammatory mediators generated by multiple cells, including eosinophils, basophils, mast cells, macrophages, and type 2 DCs.[274] Cys-LTs are generated in the lipid bilayer of the cell membrane when arachidonic acid is oxidized by 5-lipoxygenase in successive enzymatic conversions to generate leukotriene C_4, LTD_4, and LTE_4.[274] There are two main receptors for Cys-LTs: Cys-LT1R and Cys-LT2R. Cys-LT1R is expressed on airway smooth muscle cells and Cys-LT1R and Cys-LT2R are coexpressed on inflammatory cells, airway epithelial cells, and vascular endothelial cells. Activation of Cys-LT1Rs on smooth muscle cells induces muscle contraction, whereas activation of Cys-LT1R and Cys-LT2R on endothelial cells increases vascular permeability. Medications targeting this pathway, including zileuton (a 5-lipoxygenase inhibitor) and montelukast/zafirlukast (selective antagonists of Cys-LT1R), are effective in asthma, especially in patients with aspirin sensitivity and Samter triad (i.e., aspirin sensitivity, nasal polyps, and asthma).[275] When these patients ingest cyclooxygenase-1 inhibitors, such as aspirin or other nonsteroid anti-inflammatory drugs, arachidonic acid metabolism is diverted away from prostanoid metabolites of arachidonate and towards excessive generation of cys-LTs. Consequently, urinary LTE_4 levels are especially high in aspirin-sensitive patients.[276]

Prostaglandins are generated by metabolism of arachidonic acid by prostaglandin synthase enzymes and cyclooxygenase. PGD_2 is the prostanoid most relevant to asthma pathogenesis. Mast cells are the most important cellular source of PGD_2, but Th2 cells, DCs, and airway epithelial cells also produce PGD_2 at relatively low levels.[277,278] There is good evidence that PGD_2 participates in airway responses to inhaled allergen in asthmatics. Allergen challenge in asthmatic patients leads to rapid and large increases in PGD_2 in bronchoalveolar lavage fluid,[279] and PGD_2 inhalation challenge causes bronchoconstriction and airway eosinophilia.[280] PGD_2 exerts its biologic effects via two receptors—*prostaglandin D1 and D2 receptors* (DP1/DP and DP2/CRTH2)—that collectively are expressed on a wide range of cells, including hematopoietic cells, DCs, epithelial cells, goblet cells, endothelial cells, and platelets.[278] Small molecule inhibitors of CRTH2 are currently in clinical trials as treatments for asthma, atopic dermatitis, and allergic rhinitis and are showing some promise.

Lipoxins are also enzyme-derived products of arachidonic acid metabolism with putative but less well-established roles in asthma. Lipoxins are derived from arachidonic acid and omega-3 fatty acids; they are counter-regulatory lipid mediators that inhibit inflammation and are rapidly inactivated.[281] Their anti-inflammatory actions include inhibition of granulocyte activation and locomotion, promotion of monocyte-derived macrophage phagocytosis of apoptotic granulocytes, blockade of T lymphocyte cytokine release, and epithelial proinflammatory cytokine and chemokine release. Lipoxin A_4 also prevents PGD_2-stimulated release of IL-13 from ILC2s.[282]

ASTHMA EXACERBATIONS AND INTERFERON BIOLOGY IN THE AIRWAY

Asthma exacerbations represent an acute worsening of airflow obstruction in the setting of chronic disease, due to worsening of airway smooth muscle contraction, airway wall edema, and luminal obstruction with mucus.[283] The mucus plug pathology reflects formation of pathologic mucus gels characterized by increases in the elastic behavior of the mucus gels with consequences including poor clearance from the airway. As a result, the airways become occluded with mucus plugs. Autopsy studies indicate that mucus-plugged airways are especially prominent in fatal and near fatal asthma.[284] Common upper respiratory tract viruses, especially rhinoviruses, are the most common and important cause of exacerbations in both children and adults.[285,286] Airway mucosal remodeling increases

susceptibility to this acute reduction in airflow in asthmatics. Changes in the epithelium that increase mucin stores in airway smooth muscle that render it more hyper-reactive and in blood vessels that render them more leaky, predispose many asthmatics to exaggerated airway responses to inhaled environmental insults, such as viruses, allergens, or pollutants.[283] Asthmatic airways are hyperreactive in several ways; concentric smooth muscle contraction from hyperresponsiveness is one element, but mucosal edema from vascular permeability and excess mucus from mucin hypersecretion are others. The efficacy of corticosteroids in preventing exacerbations likely relates to their effects not only in reducing inflammatory cell numbers (especially eosinophils) but also through improvements in pathologic changes to goblet cells, smooth muscle cells, and blood vessels.

Viral infections are among the most important of the environmental stimuli implicated in asthma initiation. Airway epithelial cells are considered active sentinels and master coordinators of antiviral responses in the lung, usually mediated by IFNs. There are three distinct IFN families.[287] The type I IFN family mainly comprises IFN-α subtypes and IFN-β. The type II IFN family consists of just IFN-γ. The type III IFN family comprises IFN-λ subtypes with similar functions to type I IFN cytokines but restricted activity because their receptor is restricted to epithelial cell surfaces. Type I IFNs are important for host defense against viruses, and it has been hypothesized that dysregulation of IFNs in the airway may promote virus-induced exacerbations. Indeed, it has been shown that rhinovirus-induced IFN-λ induction is deficient in epithelial cells and alveolar macrophages from asthmatics.[288,289] However, it is not clear whether these impaired IFN responses represent a feature of asthma or an effect of treatment. For example, corticosteroids—frequently used to treat asthma—impair IFN responses,[290] and suppression of IFNs by corticosteroids during virus-induced exacerbations of airway disease may be a mechanism of infection and exacerbation risk. Also, mice deficient in the type I IFN-α/β receptor have suppressed antimicrobial peptide and enhanced mucin responses to rhinovirus infection.[290] These data have provided rationale for inhaled IFN-β therapy to prevent exacerbations, but preliminary reports of the efficacy of this approach in asthma have not been encouraging. Much more encouraging have been the beneficial effects of therapeutic proteins targeting T2 immunity (IgE, IL-4Rα, and IL-5 pathways) on asthma exacerbation rates. Notably, genetic polymorphisms in *IL4RA* are associated with a history of severe asthma exacerbations.[291] Potential mechanistic explanations include reversal of the inhibitory effect of T2 cytokines on production of type I IFNs, or improvement of inflammatory and remodeling features of asthma that render asthmatics more susceptible to viral infection, or exacerbations in general. Related to this, mice infected with influenza and mild asthmatics experimentally infected with rhinovirus produce IL-33 that subsequently suppresses production of type I IFN and antiviral immunity.[292] Omalizumab reverses the inhibitory effect that IgE has on production of type I IFNs by plasmacytoid DCs, a mechanism that may explain how it reduces exacerbation frequency.[293]

PHENOTYPING

ASTHMA HETEROGENEITY

By definition, all asthmatics manifest either airflow limitation on spirometry with a significant response to bronchodilators or airway hyperresponsiveness to specific or nonspecific challenge, as well as symptoms that include shortness of breath, chest tightness, wheeze, and cough. Nonetheless, patients with asthma can have a great deal of heterogeneity with respect to severity of airflow limitation, symptoms, degree of reversibility, and therapeutic response. In up to 45% of asthmatics, lung function does not improve with high doses of *inhaled corticosteroids* (ICS).[294,295] Furthermore, there is significant heterogeneity in asthma triggers, the frequency and severity of exacerbations, and long-term outcomes such as progressive loss of lung function.

Several approaches have been taken to assign asthmatics to distinct sub-phenotypes. Simple categories based on degree of airway obstruction on spirometry or frequency of symptoms and rescue medication use have been in national guidelines for asthma classification and care,[296] but these categories do not provide insight into molecular or cellular mechanisms. These guidelines have been instrumental in public health efforts to improve asthma education and care through the promotion of ICS use, but a better appreciation of disease heterogeneity at a molecular and cellular level will be important in treating severe asthma and in the clinical application of emerging asthma therapies.

CELLULAR PHENOTYPES

Analyses of sputum, bronchoalveolar lavage, and endobronchial biopsy specimens from living asthmatics and postmortem samples from those who died with asthma have found that the majority of asthmatics have elevated eosinophils.[297] However, not all asthmatics have eosinophils in their sputum and, based on analysis of induced sputum samples, non-eosinophilic asthma may be seen in up to 73% of asthmatics not on treatment and 50% of those on treatment[298] Non-eosinophilic asthma responds poorly to ICS.[244,299–301] Furthermore, non-eosinophilic asthma is seen across a range of asthma severity and, in those with severe asthma, has been associated with fewer mast cells, and less sub-epithelial fibrosis (i.e., airway remodeling).[302] These observations and others have led to a cellular classification of asthma based on induced sputum cytologic analysis with four categories: (1) eosinophilic (often defined as >2–3% in induced sputum), (2) neutrophilic (>60–75%), (3) mixed eosinophilic and neutrophilic, and (4) paucigranulocytic asthma, which lacks observable inflammatory cells.[269,298,303,304] Eosinophilia is most commonly seen in classic atopic asthma with allergen-induced inflammation. Patients with eosinophilia, except for severe cases, generally respond well to ICSs with reduced eosinophils, airway obstruction, and symptoms.[298,305–307] Neutrophilia has been noted in asthmatics with acute and chronic infection, obesity, smoking, and irritant exposure such as pollutants,[298] in subsets of patients with severe asthma,[302] and during acute asthma exacerbations.[263] Neutrophilia is also associated with reduced forced expiratory volume in 1

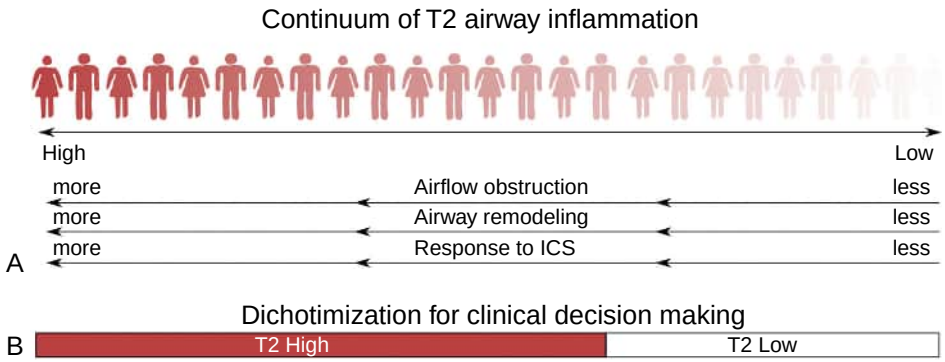

Figure 60.8 Molecular phenotypes (endotypes) in asthma. (A) Type 2 (T2)-driven inflammation is a dominant inflammatory signal in asthma. Nonetheless, across individuals, there is a continuum of T2 inflammation ranging from high levels of T2 inflammation to very low levels, approaching the baseline activity found in healthy controls. Higher T2 inflammation is associated with greater airflow obstruction and airway remodeling, and a greater improvement in lung function with inhaled corticosteroids. The long-term temporal stability of these phenotypes is not yet known. (B) The level of T2 inflammation can guide the use of targeted therapies by dichotomizing individuals to either T2-high or T2-low groups.

second, independent of the presence of eosinophils.[266,308] Mixed neutrophilia and eosinophilia have been reported in refractory asthma. One study found that subjects with mixed neutrophilia and eosinophilia had the lowest lung function, highest frequency of daily wheeze, and highest health care utilization.[269]

MOLECULAR PHENOTYPES (ENDOTYPES)

Subgrouping asthma based on the activity of specific molecular pathways has the advantage of pointing to specific pharmaceutical targets and biomarkers for clinical trials of targeted pharmaceuticals. Subgroups of patients who share an underlying disease biology have been named *endotypes*.

T2-High Endotype

One such endotype emerged from a study that analyzed the expression levels of three epithelial genes that serve as surrogate markers of inflammation associated with T2 cytokines, especially IL-13.[220] These three genes, *periostin*, *CLCA1*, and *serpinB2*, were identified using genome-wide profiling of airway epithelial brushing obtained at bronchoscopy.[309] In this study, nearly half of subjects with mild to moderate asthma were indistinguishable from healthy controls based upon the expression of these three genes in epithelial brushings. This suggested that this population of asthmatics was heterogeneous; some had T2-high inflammation and others T2-low inflammation. In subsequent analyses, T2-high asthma showed exaggerated airway hyperresponsiveness (based on the PC_{20} methacholine test), serum IgE levels, and both blood and especially bronchoalveolar lavage eosinophilia.[220] T2-high subjects also had greater sub-epithelial fibrosis, differences in epithelial mucin gene expression (higher *MUC5AC*/*MUC5B* ratio), and higher numbers of intra-epithelial mast cells.[310] In a randomized placebo-controlled trial of ICS in this same study, those in the T2-high endotype showed improved lung function with ICS, whereas those in the T2-low endotype did not. Although these analyses suggest distinct endotypes of asthma based on degree of T2 inflammation and dichotomous classification of subjects can be clinically useful, the degree of T2 inflammation present in subjects with asthma can alternatively be seen as a continuum (Fig. 60.8).

Across a range of asthma studies and severity, the group of individuals with high levels of T2 cytokines represents 30–70% of asthmatics and is enriched for chronic rhinosinusitis with nasal polyps, atopic dermatitis, more bronchodilator reversibility, and airway mucus plugging as seen on chest computed tomography scans.[252,311,312] Aspirin-exacerbated asthma as well as allergic bronchopulmonary aspergillosis are also associated with high levels of T2 inflammation. Eosinophils are usually present in the blood and sputum of those with elevated levels of T2 inflammation in the airways, a process driven by IL-5. These eosinophils likely contribute to many of the clinical associations, including mucus plugs. An increased level of T2 inflammation can be found across the age spectrum and, when it persists despite high doses of ICS or systemic corticosteroids, it is associated with older age and more airflow obstruction and exacerbations.[312] Thus, although T2 airway inflammation is generally associated with a favorable response to corticosteroids, a number of patients with severe asthma on adequate corticosteroid treatment have persistent, or refractory, T2 inflammation.

The many clinical implications of the T2 endotype have led to the study of potential noninvasive biomarkers. Sputum eosinophils have the best performance, which may be better with repeated determinations.[244,312,313] However, sputum induction and the accurate quantification of eosinophils is limited to specialized centers, and not all patients can produce an acceptable sample for analysis. Fortunately, although blood eosinophil levels are not in perfect correlation with sputum measures, they track well enough with eosinophilic airway inflammation to be a clinically useful biomarker in a number of trials of ICSs and monoclonal antibodies targeting T2 cytokines.[244,314,315] Generally, the number of eosinophils per microliter of blood has been studied. Although blood eosinophil count tracks with airway inflammation and treatment response in a continuous manner, a large range of cutoffs has been proposed to guide clinical management. For example, large treatment trials of monoclonal antibodies targeting the IL-5 pathway used blood eosinophil cutoffs ranging from 150 to 400/μL.[314,316,317] In morbidly obese individuals, blood eosinophils may not accurately reflect airway T2 inflammation.[312] Serum IgE levels poorly reflect airway

T2 inflammation, though they may have value in younger patients.[311,312,318]

Measurement of the *fraction of nitric oxide in exhaled breath* (FeNO) is an alternative noninvasive biomarker of T2 airway inflammation in asthma. FeNO levels are increased in asthma[319,320] and are highly reproducible.[321] In the setting of T2 cytokine-driven airway inflammation, cells such as eosinophils and epithelial cells can increase NO production in part through increased transcription of inducible NO synthase. Although there is a strong rationale for the use of FeNO as an asthma biomarker, the results of clinical trials that apply FeNO to guide treatment have been mixed. Possible reasons for the mixed performance of FeNO in these clinical studies include high sensitivity but poor specificity for eosinophilic inflammation based on the cutoff selected in specific studies,[322] the existence of non-eosinophilic T2-high asthma, the use of fixed rather than age and sex-adjusted cutoffs, and confounding by comorbidities that influence FeNO such as nasal polyps.[323]

T2-Low Asthma

Individuals with asthma but without elevated T2 airway inflammation have poor response to existing therapies and represent a major unmet need. In general, T2-low asthma is associated with less severe airflow obstruction and exacerbation frequency compared to T2-high asthma. However, these patients often have symptoms that are refractory to treatment. Mechanisms for T2-low asthma may be unique to T2-low asthma or may be present across a spectrum of T2 inflammation (see Fig. 60.8). Some of these mechanisms may reflect a consequence of corticosteroid treatment. Therefore, the study of non-T2 mechanisms has the potential to produce novel therapies that also help patients with T2-high asthma, particularly those resistant to existing T2-directed treatments.

Although specific molecular mechanisms of T2-low asthma remain elusive, some clues have emerged from studies of gene transcripts and immune cells in airway biospecimens from patients with T2-low asthma. In T2-low asthma, gene expression studies of cells obtained from induced sputum have revealed gene signatures indicative of mitochondrial oxidative stress, inflammasome-activation (with increased sputum IL-1β), and reduced $CD8^+$ T cell cytotoxicity.[324–326] IL-17 and other cytokines such as IL-6 may also be important. Bronchoalveolar lavage samples from patients with asthma and uncharacterized T2 status have shown increased numbers of IL-17A-producing cells[327–330]; there was evidence of Th17 activity through identification of specific Th17 cells, and IL-17A/F was found in human airway tissue.[331–335] In general, higher levels of IL-17 are associated with more airway neutrophilia. However, transcriptional profiling of epithelial brushings and induced sputum cells has not consistently shown more IL-17–related inflammation in asthma compared to health.[336–338] These findings, the absence of IL-17–driven signatures in other studies, and a negative clinical trial of an anti–IL-17 receptor monoclonal antibody—albeit in a population not selected for high biomarker levels—make the relevance of this pathway in asthma uncertain.[262] Elevated plasma IL-6 is present in both T2-low and -high asthma, probably reflects systemic inflammation, and is associated with obesity.[241] Heightened IL-6-mediated signaling in epithelial cells was associated with more barrier dysfunction, airway inflammation, and more exacerbations.[339] Other studies have suggested a role for Th1 cells and IFN-driven inflammation, dysbiosis, and neutrophil extracellular traps.[260,267,340–342] Impaired resolution of inflammation by natural killer cells may also contribute to airway inflammation across the spectrum of T2 airway inflammation.[343] The transition of these potential non-T2 pathways into asthma endotypes awaits successful coupling to targeted therapies.

Noninflammatory mechanisms may also contribute to T2-low endotypes of asthma (see Fig. 60.8).[327–335,344–354] Airway hyperresponsiveness is in part the result of an abnormal airway smooth muscle response to mediators of contraction such as histamine and acetylcholine. Although a proinflammatory cytokine milieu and infiltration of smooth muscle with inflammatory cells are likely a major influence on abnormal airway smooth muscle contraction, intrinsic abnormalities in the signal transduction or contractile functions of smooth muscle cells in human asthma are relatively less well studied. Because a role for airway smooth muscle hyperplasia or hypertrophy has been demonstrated in patients with asthma,[221,355] abnormal accumulation of smooth muscle and increased airway narrowing on that basis represents another possible noninflammatory mechanism for increased airway hyperresponsiveness in asthma. Epithelial barrier dysfunction, neuronal abnormalities, and underlying disturbances in mucin production and characteristics may also interact with inflammation or smooth muscle pathology to contribute to an asthma phenotype.

Key Points

- Asthma is a common disease, and its prevalence has increased throughout the world for the past several decades.
- Studies of the epidemiology, natural history, and pathogenesis demonstrate that asthma is a heterogeneous disease, with multiple etiologies and contributing cofactors, complex pathobiologic mechanisms, and diverse molecular phenotypes.
- Genetic variation has major effects on asthma susceptibility and represents the effects of many different genes that are polymorphic or undergo epigenetic regulation.
- Family-based studies provided the first clues about the polygenic nature of asthma; however, subsequent biologic candidate gene studies and larger genome-wide association studies have resulted in discoveries of important susceptibility and disease-modifying loci.
- The clinical heterogeneity of asthma may be explained by different underlying mechanisms. For example, *type 2* (T2) inflammation is associated with eosinophils, greater airflow obstruction, and airway remodeling including mucus plugging. However, the degree of T2 inflammation varies across individuals, ranging from high levels (T2-high asthma) to low or absent levels (T2-low asthma).
- The recognition that asthma is heterogeneous and comprises molecular phenotypes, or endotypes, has led to the development of targeted therapies and of biomarkers that can identify those who will respond to these treatments. Nonetheless, T2-low asthma does not respond well to existing therapies and non-T2 mechanisms are an important focus of research.

Key Readings

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61 ASTHMA AND OBESITY

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INTRODUCTION

Obesity is a growing global epidemic. The obesity epidemic has fundamentally shifted the burden of chronic disease in the developed world, and being overweight or obese is now the fifth leading risk factor for death worldwide.[1,2] Obesity, defined as a *body mass index* (BMI) measurement greater than 30 kg/m^2, is particularly common in the United States, where 40% of adults and 21% of adolescents are obese.[3]

Obesity is remarkably common in patients with asthma,[4–6] raising the possibility that obesity plays an important role in the development and pathobiology of asthma. The observation that obesity and asthma are common comorbidities was initially described in a cohort study of nurses in the United States. Camargo et al. found that obese women ages 26 to 46 years had a threefold increased risk of developing asthma over 4 years compared with lean women.[4] These findings were confirmed in a large meta-analysis demonstrating that asthma incidence increased by 50% in overweight/obese individuals compared to normal-weight individuals.[7] Similar data have been reported in children; obese children have an 18–38% increased risk of developing asthma when compared to healthy weight children. These findings suggest that up to 25% of new asthma cases in children are related to obesity.[8]

This increased asthma incidence in obese patients results in an asthma prevalence significantly higher in people with obesity than in those with normal weight. In the United States, the prevalence of asthma in lean, overweight, and obese adults is 7.1%, 7.8%, and 11.1%, respectively.[9] The association between BMI and asthma is remarkably pronounced in patients with severe obesity; the frequency of asthma in patients with a BMI greater than 60 may be greater than 30%.[10]

There is a sex disparity in the prevalence of asthma between obese men and women. Asthma rates are higher in overweight (9.1%) and obese (14.6%) women compared to lean women (7.9%). However, in men, these differences in asthma prevalence across obese subgroups may be less pronounced; obese men suffer from asthma at a frequency (7.1%) only slightly higher than lean men (6.1%).[9] This observation that the interaction between obesity and asthma is more pronounced in female patients has been observed in some, but not all, asthma studies[7,10–12] and has led to the hypothesis that obese female patients exhibit a unique asthma phenotype.[11]

The relationship between obesity and asthma is bidirectional; obesity is a risk factor for the development of asthma, and asthma is also a risk factor for the development of obesity. Studies in children with early-onset allergic asthma show that asthma at the age of 4 years approximately doubles the risk of developing obesity by the age of 8 years.[13] Thus obesity likely causes asthma in some patients and is a complication associated with asthma in others. These epidemiologic links between asthma and obesity are striking; the reasons for the association are multifactorial.

PATHOPHYSIOLOGY

The excessive accumulation of visceral adipose tissue results in two important metabolic derangements collectively called *metabolic dysfunction* (Fig. 61.1). The first is a state of chronic low-grade systemic inflammation (meta-inflammation) characterized by increased blood levels of a variety of pro-inflammatory cytokines, including *interleukin* (IL)-6, IL-1, tumor necrosis factor-α, and leptin.[14] The second is insulin resistance seen when cells in muscle, fat, and liver tissue fail to respond appropriately to insulin.[15] This impaired insulin sensitivity requires the pancreas to secrete additional insulin to enable glucose uptake into cells. This cycle leads to higher levels of insulin and glucose in the systemic circulation, which, if unchecked, progresses to diabetes.[16] These two principal features of metabolic dysfunction are established risk factors for the development of cardiovascular disease, neurovascular disease, renal failure, and certain types of cancer.[14] Until recently, the association between features of metabolic dysfunction and asthma was poorly understood (see Fig. 61.1). Lately, studies measuring systemic IL-6 protein levels in asthma have repeatedly demonstrated that increases in systemic IL-6 are associated with features of more severe asthma, including lower lung function,

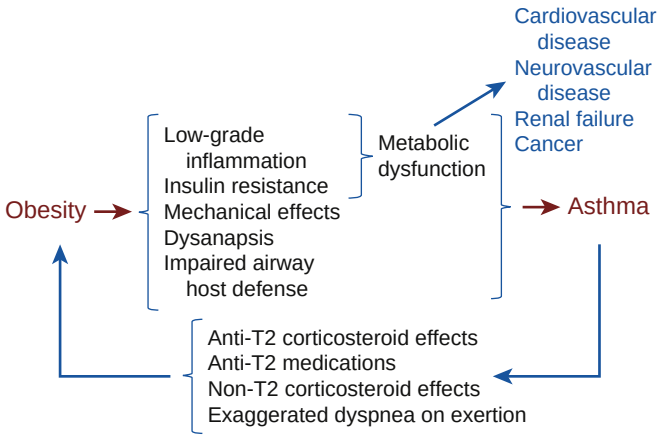

Figure 61.1 The interaction of obesity and asthma. Excessive visceral adipose tissue deposition leads to both chronic low-grade systemic inflammation and insulin resistance, characteristic of metabolic dysfunction. The various effects of obesity lead to multiple disease states and are now appreciated as risk factors for asthma. In turn, asthma and its therapies are recognized to increase the risk for obesity.

worse asthma symptoms, and higher asthma exacerbation rates.[17,18] These patients with high plasma IL-6 levels are also characterized by other features of metabolic dysfunction, including high rates of hypertension, diabetes, and increased BMI, suggesting that asthma and airway disease are made worse by the associated metabolic dysfunction.[17] However, whereas this association between metabolic dysfunction and more severe asthma is now well established, the principal pathologic abnormality linking metabolic dysfunction to asthma severity remains unknown.

OBESITY AND INHIBITION OF TYPE 2 INFLAMMATION

Increases in airway *type 2* (T2) inflammation is the most well-established pathobiologic mechanism in asthma.[19] One of the essential functions of the T2 immune response is to control parasitic infections, but this response is also increasingly recognized as an important regulator of organism homeostasis and metabolism. For example, IL-33 promotes adipose tissue T2 innate lymphoid cells to secrete IL-5, which in turn leads to adipose tissue eosinophilia and activation of alternatively activated macrophages.[20,21] Classically activated macrophages play key roles in the recognition and elimination of microbes.[22] However, in the presence of eosinophils and the canonical T2 cytokines IL-4 and IL-13, macrophages shift to an alternatively activated macrophage phenotype.[20,23] Alternatively activated macrophages are important in eliminating parasitic infections, but they also function to maintain visceral adipose tissue homeostasis via lipolysis, maintenance of insulin sensitivity, and induction of thermogenesis.[20,24,25] Thus, immune cells responsible for orchestrating the T2 immune response are also protective against the development of obesity. Conversely, obesity leads to a shift in adipose tissue macrophages from an alternatively activated macrophage to classically activated macrophage phenotype.[20,26] This transition results in the chronic low-grade systemic inflammation associated with obesity and metabolic dysfunction. Furthermore, the role of the IL-33/innate lymphoid cell-2 axis and metabolism is not limited to the effect of IL-33 in adipose tissue. It is now known that IL-33 impacts whole body metabolism by induction of nonshivering thermogenesis, an increase in metabolic heat production not caused by muscle activity and thought to be a mechanism opposing obesity. Treatment with IL-33 promotes pancreatic insulin production and glucose clearance.[21,24] These findings demonstrate a pivotal role of the T2 immune system in maintaining visceral tissue homeostasis and suggest that medications that inhibit T2 inflammation (such as corticosteroids or new anti-T2 biologic agents) might lead to increases in obesity and metabolic dysfunction. Thus, one potential mechanistic link between obesity and asthma is by treatment with asthma drugs. Principally, medications that reduce airway T2 inflammation might promote obesity and metabolic dysfunction by decreasing the homeostatic role of T2 inflammation in adipose tissue (eFig. 61.1).

OBESITY AND NON–TYPE 2 MECHANISMS OF ASTHMA

In addition to the potential link between the inhibition of T2 inflammation and obesity, it is likely that obesity impacts airway immunity via non-T2 pathways. In fact, human studies investigating the association between biomarkers of T2 inflammation and obesity conclude that T2 biomarkers are either no different or lower in obese asthma subjects compared to nonobese asthma subjects.[11,12,27] These findings suggest that both T2 and non-T2 mechanisms contribute to disease in patients with obese asthma.

Unfortunately, non-T2 mechanisms of asthma remain poorly understood, and thus a thorough understanding of how non-T2 inflammation alters obese asthma remains an area of significant uncertainty. However, one of the more intriguing possibilities is that obesity and metabolic dysfunction lead to impairments of airway host defense. This hypothesis is substantiated by the recent observation that metabolic dysfunction increases the risk of developing severe respiratory viral illnesses such as COVID-19 and influenza.[28,29] Recent work suggests a similar susceptibility in asthma in which obesity and metabolic dysfunction increase the risk of developing exacerbation-prone asthma.[31,32] The molecular underpinning for why obesity leads to more severe or more frequent viral illness is unclear, but multiple immune cells involved in initiating adaptive immune responses are impaired in obesity. Specifically, cytotoxic T lymphocytes (natural killer cells and $CD8^+$ T cells) are essential for identifying and eliminating cells infected by virus or cells that have undergone malignant transformation.[33–35] Obesity can result in cytotoxic T cell dysfunction and an impaired ability of these cells to eliminate infected cells or cells that have undergone malignant transformation.[35] This dysfunction of cytotoxic T lymphocytes increases susceptibility to viral infections and encourages tumor progression.[35,36] This impairment has been demonstrated in asthma and, compared to lean asthmatics, obese asthmatics have alterations in natural killer cell function and decreases in airway gene expression signals for cytotoxic T lymphocytes.[27,37] Further work is needed to confirm the role of cytotoxic T lymphocytes in the obese asthma phenotype, but it is possible that impairments in host immune defense could explain the increase in asthma exacerbation rates in obese asthma patients and their increased susceptibility to viral upper respiratory infections[31,32] (see eFig. 61.1).

IMPACT OF OBESITY ON PULMONARY AND ASTHMA PHYSIOLOGY

Obese patients breathe at decreased lung volumes because mechanical loading of the chest wall and abdomen with adipose tissue decreases *functional residual capacity* (FRC), the point at which elastic outward recoil of the chest wall is in equilibrium with the inward recoil of the lungs[38] (Fig. 61.2; see also Chapter 131 and Fig. 131.12). At low lung volumes, airway diameter is smaller; thus, breathing at low lung volumes means an increased work of breathing. Obese individuals can have the sensation of dyspnea even without increased airway responsiveness. Because of increased airway closure at the bases, obese individuals may direct more of the initial breath to the apices (see Chapter 10). Such differences in air distribution can affect the regional delivery of methacholine for testing and the delivery of inhaled medications.

Studies in normal volunteers suggest that breathing at low lung volumes (without taking deep breaths) may increase airway reactivity,[39] leading to speculation that breathing at low lung volumes instigates airway reactivity in patients with obesity.[40] However, many obese people with a decreased FRC do not have asthma. Also, in studies in mice, increased airway reactivity in obese compared with lean mice is independent of lung volume.[41] Furthermore, while the negative association with FRC and BMI is uniform in obese people, the relationship between BMI and airway reactivity is significantly more heterogeneous.[42] Thus, whereas reduced lung volume may modulate airway reactivity, it does not completely account for the relationship between asthma and obesity.[43,44]

Obese patients with asthma demonstrate unique physiologic characteristics. These unique traits suggest that the physiology of asthma in obesity differs from that in lean individuals. For example, weight loss in obese patients with asthma is associated with improvements in peripheral lung compliance, suggesting that obese asthma patients have predominantly small airway disease.[45] The physiologic characteristics of airway reactivity itself differ in obese compared with lean patients; obese patients develop greater dynamic hyperinflation (air trapping) than lean patients during bronchoconstriction. This air trapping suggests that small airway closure limits exhalation to produce progressive air trapping and increased work of breathing in obese patients.[46] In addition, the closing index—the degree of airway closure relative to airway narrowing during induced bronchoconstriction—increases in patients with obesity[47,48] and, related to this, sensitivity to airway closure (measured by the dose of methacholine required to produce a given amount of closure) improves significantly with weight loss surgery.[49] Asthma in obese adults affects peripheral airway function, increasing the tendency towards airway closure and air trapping during bronchoconstriction.

Superimposed upon altered airway function may be anomalies related to altered growth patterns in those with childhood-onset obesity. Obesity in children is associated with an increase in FVC relative to *forced expiratory volume in 1 second* (FEV_1) (a phenomenon known as *dysanapsis*, or a discrepancy in size due to a greater growth of the lungs than of the airways). This growth pattern produces a decrease in the FEV_1/FVC ratio and contributes to the development of airflow limitation.[50,51] How abnormalities in airway growth related to obesity affect airway function in adults with lifelong obesity is not yet known, but will require longitudinal studies to address this question.

CLINICAL FEATURES

Asthma in obese patients tends to be more severe than asthma in lean patients.[11] Studies in the United States of patients with severe asthma report that nearly 60% of people with severe asthma are obese.[52] One manifestation of this is the increased risk of asthma exacerbations in obese compared with lean patients,[53] and the twofold to fourfold risk of requiring hospitalization.[54,55] Among those hospitalized for asthma, obese patients have a higher risk of requiring mechanical ventilation or noninvasive ventilation for respiratory support, and a longer hospital stay.[56] Obese asthma patients frequently have increased asthma

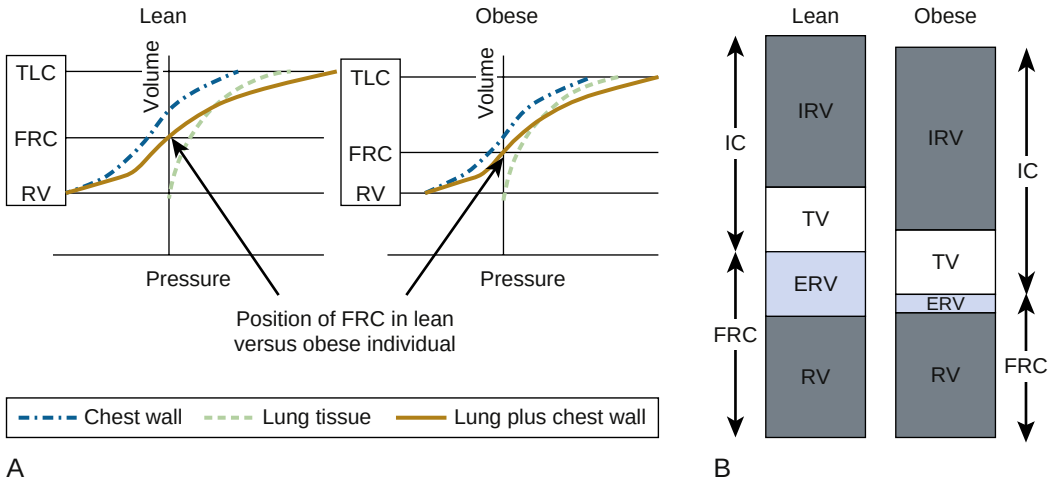

Figure 61.2 Mechanics of the thorax in lean and obese state. (A) Pressure-volume relationship of chest wall and lung in the lean and obese states. The volume of the lung within the chest *(brown line)* is determined by the balance between the recoil pressure of the chest wall *(blue dotted line)* and that of the lung tissue *(green dotted line)*. In the obese state, the chest wall is weighted with adipose tissue, and this reduces the resting volume of the lung (the *functional residual capacity* [FRC], *arrows*). (B) Overall effect of pressure-volume relationship on lung volumes in lean and obese state. In the obese state, *expiratory reserve volume* (ERV) and FRC are particularly decreased. IC, inspiratory capacity; IRV, inspiratory reserve volume; RV, residual volume; TLC, total lung capacity; TV, tidal volume.

Table 61.1 Factors Contributing to Increased Asthma Severity in Obese Patients

Altered physiology (e.g., decreased functional residual capacity, dysanapsis)
Lower baseline lung function
Increased risk of infection
Altered response to infection
Impaired response to medications
Comorbidities

Table 61.2 Comorbidities That May Contribute to Asthma Severity in Obese Patients

Gastroesophageal reflux
Obstructive sleep apnea
Depression
Nasal polyposis

Table 61.3 Treatment of Asthma in Obesity

Standard asthma medications*
Treatment of comorbidities
Dietary intervention
Lifestyle weight loss interventions (including exercise)
Bariatric surgery

*Note that response to bronchodilators and inhaled corticosteroids may be decreased. Systemic steroids should be avoided if at all possible. Also note that anti-T2 therapies may worsen obesity.

symptoms and worse asthma control; obese patients have increased asthma symptoms during both the day and night and increased rescue use of short-acting β-agonists compared to nonobese people with asthma.[57]

Many factors likely contribute to increased severity and worse control (Table 61.1). One factor may be that, at baseline, obese patients have reduced lung function[47] compared to lean patients. This decrease in lung function results in less pulmonary reserve during illness. However, as previously discussed, these spirometric decrements in lung function are unlikely to explain the entire role of obesity as a mechanism for asthma severity.

Another important factor may be the increased risk of—and worse outcomes related to—respiratory infections, as previously mentioned.[58] For example, compared to lean individuals, obese individuals are more likely to develop influenza infection despite vaccination and have worse outcomes following influenza infection.[59,60] This may explain why obese adults with asthma who experience a respiratory tract infection are nearly three times more likely to require systemic corticosteroids than lean patients.[31] Furthermore, obese asthma patients demonstrate labile asthma control and are more likely to self-report viruses as the cause of their asthma exacerbations.[32] Interestingly, obese children do not appear to have the same susceptibility to more severe asthma during respiratory tract infections, suggesting that a factor related to aging as well as obesity may explain the predilection to worse outcomes in adults with asthma and respiratory tract infections.[31]

Other factors possibly contributing to increased severity and worse control are altered responses to medications and the presence of comorbidities, which are discussed in detail below.

DIAGNOSTIC EVALUATION

PHARMACEUTICAL INTERVENTIONS

The general pharmacologic approach to patients with asthma is similar whether they are obese or not, and many obese asthma patients can be managed according to conventional asthma medication algorithms. Some obese patients may not respond as well as lean patients to medications[61,62]; this impaired response likely reflects slightly lower rates of T2 inflammation in patient populations with obesity[11] and perhaps some intrinsic biologic differences in obese patients. However, overall differences in treatment response rates are relatively small and generally should not alter the initial treatment approach.

Comorbidities may be particularly important in obese patients (Table 61.2). Many obese patients have comorbid conditions related to obesity, including gastroesophageal reflux, obstructive sleep apnea, and depression, as well as comorbidities seen in lean severe asthma patients, such as nasal polyposis. Treating underlying comorbid conditions is particularly important in effective management of the obese asthma patient (Table 61.3).

MEDICATION RESPONSE TO CONVENTIONAL ASTHMA MEDICATIONS IN OBESE ASTHMA PATIENTS

Rescue medications are important in asthma management, but obese asthma patients may be less likely to respond appropriately to bronchodilator treatment. Obese Black and Hispanic children with asthma are less likely to respond to bronchodilators than their lean counterparts,[63] and obese adults with asthma have smaller improvements in FEV_1 with short-acting β-agonists than lean adults.[64]

Many studies report impaired responses both to inhaled corticosteroids and to combination therapy with inhaled corticosteroids and long-acting β-agonists in older children and adults who are obese.[62,65–68] Response to long-acting muscarinic antagonists, at least in terms of lung function, appears to be similar in lean and obese patients with asthma.[66] However, effects of long-acting muscarinic antagonists on asthma control and asthma exacerbations in obese individuals with asthma have not been reported. One intriguing finding is that, for unclear reasons, obese patients can have a paradoxical response to theophylline, with increased exacerbations in obese patients on theophylline compared with placebo.[70] Thus, the response rate to conventional controller medications may be slightly altered in the setting of obesity.

These differences in treatment effects are similar to differences observed between individuals with T2-high and

T2-low asthma phenotypes—fewer obese patients may be responsive because fewer obese patients have T2-high disease.[11,12] Other factors that might decrease response rates to traditional asthma medications include differences in deposition of inhaled medication due to altered ventilatory patterns,[71] changes in medication pharmacokinetics,[72] and impaired induction of anti-inflammatory pathways in response to corticosteroids.[67]

MEDICATION RESPONSE TO ASTHMA BIOLOGICS IN OBESE ASTHMA PATIENTS

Treatment of obese patients with anti-T2 biologic agents has not been directly assessed in randomized clinical trials, but some retrospective studies have evaluated the effectiveness of this class of medications in obese asthma patients. One complicating factor in evaluating T2 inflammation and response is that obesity may alter traditional T2 biomarkers, including eosinophils and exhaled nitric oxide. Because eosinophils play key roles in metabolism, circulating blood eosinophils could reflect changes in metabolism or nutritional status[20,21,73,74] and thus change the performance characteristics of blood eosinophils as a biomarker of airway T2 inflammation. Indeed, blood eosinophil cell counts, while a useful biomarker of airway T2 inflammation in normal-weight individuals with asthma, have been shown to perform poorly as a biomarker of airway T2 inflammation in obese patients.[12,75] The fraction of exhaled nitric oxide might also be altered in obese individuals, and some studies have reported alterations in exhaled nitric oxide based upon age of asthma onset in obesity.[76] This alteration in the performance characteristics of T2 biomarkers in obesity complicates the evaluation of T2 biologic inhibitors responses in obese asthma patients because many trials stratify treatment response or enrollment by blood eosinophil cell counts.[77,78] Few publications have compared responses to biologics in lean and obese patients, and the limited available data show conflicting results. One study suggested a similar response to the anti-immunoglobulin E therapeutic, omalizumab,[79] while another study suggested differing responses.[80] Weight-based dosing also precludes the use of omalizumab in severely obese patients. The role of anti-T2 biologic agents, and also the assessment of T2 inflammation in obese individuals with asthma, is not yet clear.

One intriguing and as yet unstudied potential side effect of T2 inhibitors is their potential to worsen obesity and metabolic disease. Clearly, murine models have demonstrated a role for T2 immunity in preventing obesity, and blocking these important cytokines could potentially worsen obesity in some patients.[20,24] Further work is needed to address this possibility, but it is important that clinicians are aware of this potential complication. Similarly, other medications such as intermittent or chronic systemic or inhaled corticosteroids that suppress T2 inflammation could have similar unwanted side effects. Furthermore, corticosteroids worsen obesity and metabolic dysfunction via direct effects on cortisol and the hypothalamic-pituitary-adrenal axis.[81] Thus, it is of paramount importance to limit overall exposure to systemic corticosteroids in asthma patients with obesity. Use of as-needed inhaled corticosteroid regimens in patients with mild to moderate persistent asthma[82] might be a strategy to limit total corticosteroid exposure. Finally, prior to escalating therapy, treatment of comorbidities and lifestyle interventions should be attempted.

COMORBIDITIES

Obese patients with asthma have increased comorbidities related to their obesity compared with lean patients, some of which can significantly impact asthma (see Table 61.2). Pertinent comorbidities include gastroesophageal reflux disease, obstructive sleep apnea, and depression.

Gastroesophageal reflux disease (GERD) may contribute to poorly controlled asthma in some patients, but there are no compelling data that this is the case in obese patients with asthma. In a study of obese adults with asthma without symptomatic GERD requiring active treatment, acid reflux was not associated with worse asthma control or lower lung function, suggesting that treatment of asymptomatic acid reflux is unlikely to be helpful in this patient population.[83] A similar study in children found that GERD symptoms were associated with worse asthma control but better lung function, and the authors speculated that perhaps symptoms of GERD were being misattributed to asthma.[84] The available data do not suggest that acid reflux contributes to poor asthma control in obesity, but perhaps that GERD symptoms may be misattributed to asthma.

Obstructive sleep apnea (OSA) is more prevalent in obesity. In fact, asthma itself may also predispose to the development of OSA.[85] Some studies suggest OSA is associated with poor asthma control and worse asthma outcomes.[83,86] OSA is also associated with altered airway inflammation, in particular with increased sputum neutrophils.[87] There are some small studies suggesting that treatment of OSA might improve some outcomes related to asthma,[88] but there are no definitive studies of the efficacy of treating OSA on asthma outcomes. Because OSA should be treated for its own sake and is associated with poor asthma control and increased neutrophilic airway inflammation, it seems reasonable to screen for OSA in obese patients with poorly controlled asthma and treat when appropriate with some expectation that it might improve asthma control.

Depression is another comorbidity increased in obese people with a possible effect on asthma. Epidemiologic studies show an increased prevalence of depression in obese people.[89] Some studies have also shown that depression in obese patients with asthma is associated with poor asthma control.[90,91] There are no prospective studies addressing whether treatment of depression might affect asthma control in obese patients but, because uncontrolled depression is a serious comorbidity, assessing and treating this condition is reasonable in obese patients with asthma.

Obese patients with asthma commonly also have comorbidities found in lean asthma patients, such as nasal polyposis. We are not aware of any data that obesity worsens nasal polyposis but, as with lean asthma patients, these comorbidities need to be addressed.

DIET, EXERCISE, AND WEIGHT LOSS INTERVENTIONS

Prospective studies suggest that losing at least 5% of body weight is associated with improvement in asthma control,[92]

and that addition of exercise might also be beneficial.[93] Weight loss is also an effective treatment for many comorbidities and is therefore a desirable goal for a patient's overall health. While weight loss is likely to improve asthma control, simply stating a need to lose weight is only modestly effective.[94] A more effective intervention is enrollment into a structured weight loss program.[95]

Losing weight is challenging for anyone and, for those with asthma, the challenge is greater due to the additional anxiety of shortness of breath and bronchoconstriction during exercise. Thus, improving diet quality is an important weight loss intervention in addition to efforts focused on exercise. Obesity is often associated with poor dietary quality—a diet high in processed foods and sugars and low in fiber, fruit, and vegetables. Despite limited data, some studies suggest a beneficial role for dietary interventions in asthma, apart from effects on obesity.[93] Poor dietary quality might affect airway inflammation and decrease bronchodilator responsiveness,[96] and a diet high in fruit and vegetables might decrease asthma exacerbations.[97] Given the beneficial effects of improving dietary quality, and the small studies suggesting dietary quality might affect outcomes relevant to asthma, it seems reasonable to focus on improving dietary quality in obese patients with asthma.[96]

Because weight loss is difficult, diet and exercise may be inadequate interventions in many patients with morbid obesity. Bariatric surgery is a reasonable approach in morbidly obese patients. Bariatric surgery improves other comorbid conditions associated with obesity and has been shown to improve asthma control.[43,98,99] In one retrospective study, there was a significant reduction in asthma exacerbations in the 2 years after bariatric surgery compared with the 2 years before bariatric surgery.[99] While patients with uncontrolled asthma likely are at increased risk related to surgery, laparoscopic approaches are well tolerated and minimize surgical risks. Therefore, bariatric surgery is a reasonable intervention in some obese patients with asthma who have not responded to nonsurgical approaches. This surgery should only be considered after carefully discussing the risks and benefits with the patient.

Key Points

- Obesity is associated with severe, difficult-to-control asthma.
- Obesity is a risk factor for the development of asthma, and asthma is also associated with an increased risk of developing obesity.
- The immune cells responsible for initiating airway *type 2* (T2) inflammation also play key roles in adipose tissue homeostasis. Thus, medications inhibiting T2 inflammation may worsen metabolic dysfunction and contribute to weight gain.
- Patients with obesity and metabolic dysfunction demonstrate deficiencies in immune cells responsible for host defenses against viral and bacterial pathogens. This defect in host defense may predispose obese asthma patients to the development of viral upper respiratory tract infections.
- Both T2-high and T2-low phenotypes of asthma can be seen in obese individuals, though performance characteristics of biomarkers for type 2 disease are altered in obese individuals.
- Airway disease in obesity is related to multiple factors, including altered lung mechanics, poor diet, immune dysfunction, and metabolic dysfunction.
- Obese patients do not respond as well to standard therapies and likely need an approach that includes consideration of treatment of lifestyle factors and comorbidities as well.

Key Readings

Camargo Jr CA, Weiss ST, Zhang S, Willett WC, Speizer FE. Prospective study of body mass index, weight change, and risk of adult-onset asthma in women. *Arch Intern Med*. 1999;159:2582–2588.

Dixon AE, Pratley RE, Forgione PM, et al. Effects of obesity and bariatric surgery on airway hyperresponsiveness, asthma control, and inflammation. *J Allergy Clin Immunol*. 2011;128:508–515. e501–502.

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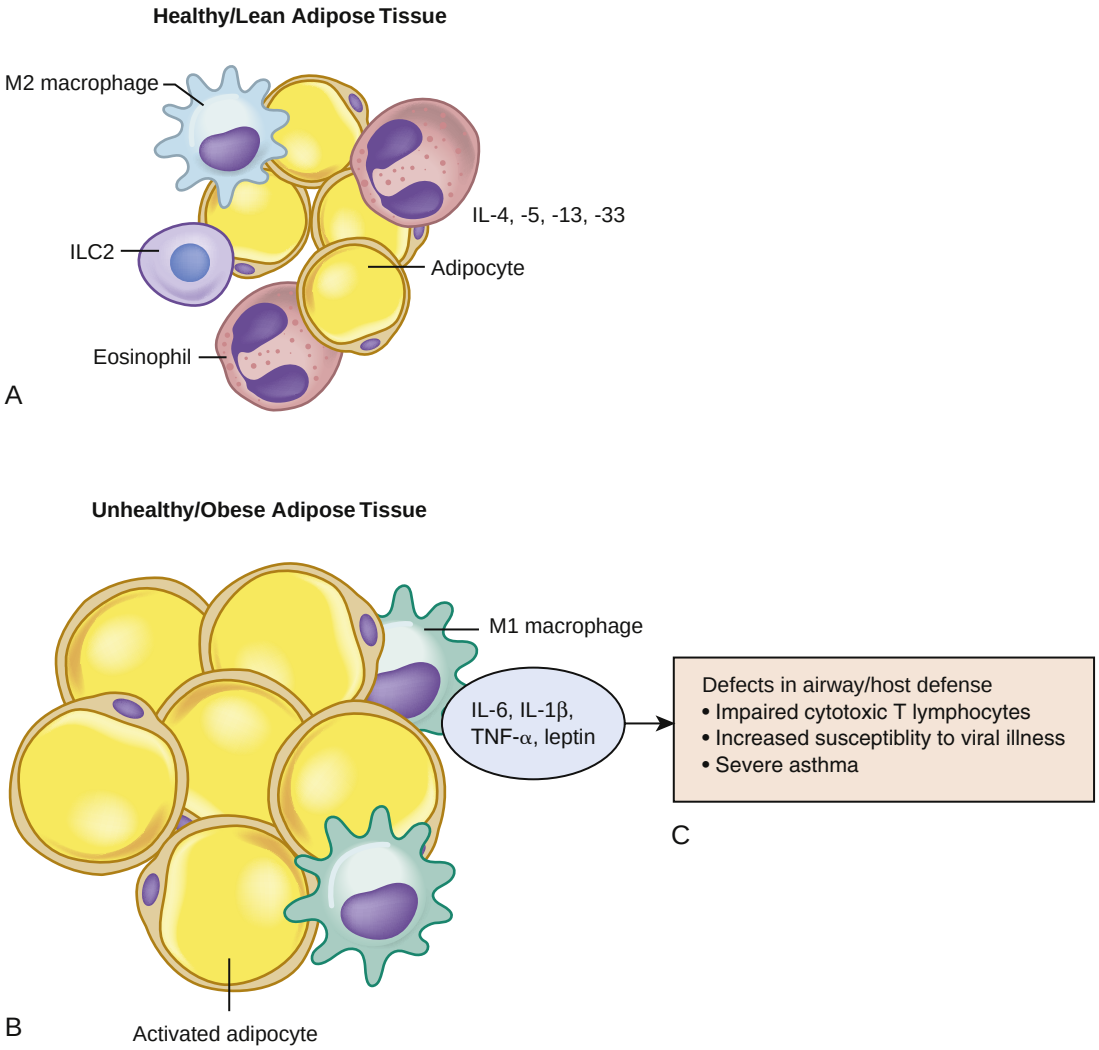
Complete reference list available at ExpertConsult.com.

eFIGURE IMAGE GALLERY



eFigure 61.1 Inhibition of T2 inflammation can promote obesity and unhealthy adipose tissue. (A) Eosinophils, alternatively activated macrophages (M2), and T2 innate lymphoid cells (ILC2) secrete T2 cytokines (IL-4, -5, -13, -33) that, in addition to driving T2 inflammation, play key roles in the maintenance of adipose tissue homeostasis. (B) When T2 inflammation is blocked, adipose tissue homeostasis is disrupted, leading to excessive adipose tissue growth and activation of classically activated macrophages (M1). Activated adipocytes and classically activated macrophages release inflammatory cytokines such as interleukin (IL)-6, IL-1β, tumor necrosis factor-α (TNF-α), and leptin into the systemic circulation. (C) This release of systemic cytokines may cause lung dysfunction including impairments in host defense leading to more frequent asthma exacerbations and worse asthma control.

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62 ASTHMA: DIAGNOSIS AND MANAGEMENT

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INTRODUCTION

Asthma is a common chronic heterogeneous disease of the airways. Asthma affects 8% of the U.S. population, which is more than 26 million Americans, including 7 million children.[1] In 2010, 1.8 million people sought emergency department attention for asthma, and almost 500,000 required hospitalization due to an asthma attack.[1] Between 1980 and 2010, childhood asthma prevalence almost tripled.[1,2] In response to this public health concern, asthma has attracted a tremendous scope of biomedical investigation, from evaluation of endotype-defining inflammatory pathways at the gene transcription level to studies of novel biologic pharmaceuticals for severe asthma. These studies continue to refine the scientific understanding of asthma and promote novel approaches to primary prevention and treatment. This chapter reviews the foundational clinical knowledge of asthma and incorporates some high-impact, transformative scientific achievements informing our approach to diagnosis and treatment. This chapter builds on Chapter 60, which explores the pathogenesis and phenotypes of asthma, and Chapter 61, which focuses on the phenotype of obesity and asthma.

DEFINITION

Asthma has been more often described than defined. The earliest feature described was the labored, rapid breathing typical of asthmatic attacks; the word "asthma" is derived from the ancient Greek word for "panting." As knowledge about asthma has grown, the features described as characteristic of asthma have expanded. Measurement of maximal expiratory flow led to recognition of *reversible airflow obstruction* as a characteristic feature; measurement of changes in airflow after inhalation of chemical or physical irritants led to the definition of *bronchial hyperresponsiveness*. In addition, studies of bronchial biopsies added a description of characteristic pathologic features including *chronic inflammation*. This evolution in the understanding of asthma is summarized in the definition offered in the 2019 *Global Initiative for Asthma* (GINA) guidelines (http://ginasthma.org): "Asthma is a heterogeneous disease, usually characterized by chronic airway inflammation. It is defined by the history of respiratory symptoms such as wheeze, shortness of breath, chest tightness, and cough that vary over time and in intensity, together with variable expiratory airflow limitation."

This consensus conference "definition" of asthma serves well as a description of the major features of asthma but does not hold up as a precise definition. No feature is unique to asthma, and no feature is universal in patients with the condition. Thus, the modern approach to asthma diagnosis, assessment, and treatment has changed in response to the recognition that asthma is a heterogeneous disease that encompasses many phenotypes with variable responses to therapy. For example, focusing a clinical trial on a certain asthma phenotype, characterized by observed characteristics such as the presence of eosinophilic inflammation, allergy, or chronic airflow limitation, has improved our ability to identify targeted therapeutics for individuals with these characteristics. This recognition of asthma as a complex, multifactorial disorder has led to a greater focus on the individual and is advancing the field toward more precise understanding of asthma pathogenesis and treatment.

CLINICAL DIAGNOSIS

The diagnosis of asthma is often made in the ambulatory care setting and is based on a careful personal history, physical examination, and lung function testing (Fig. 62.1). A number of different diseases can mimic asthma and cause some or all of the symptoms of asthma. These include vocal cord dysfunction, COPD, cystic fibrosis, bronchiectasis, congestive heart failure, sleep apnea, pneumonia, sarcoidosis, and psychosomatic diseases and should be considered when making the diagnosis of asthma.

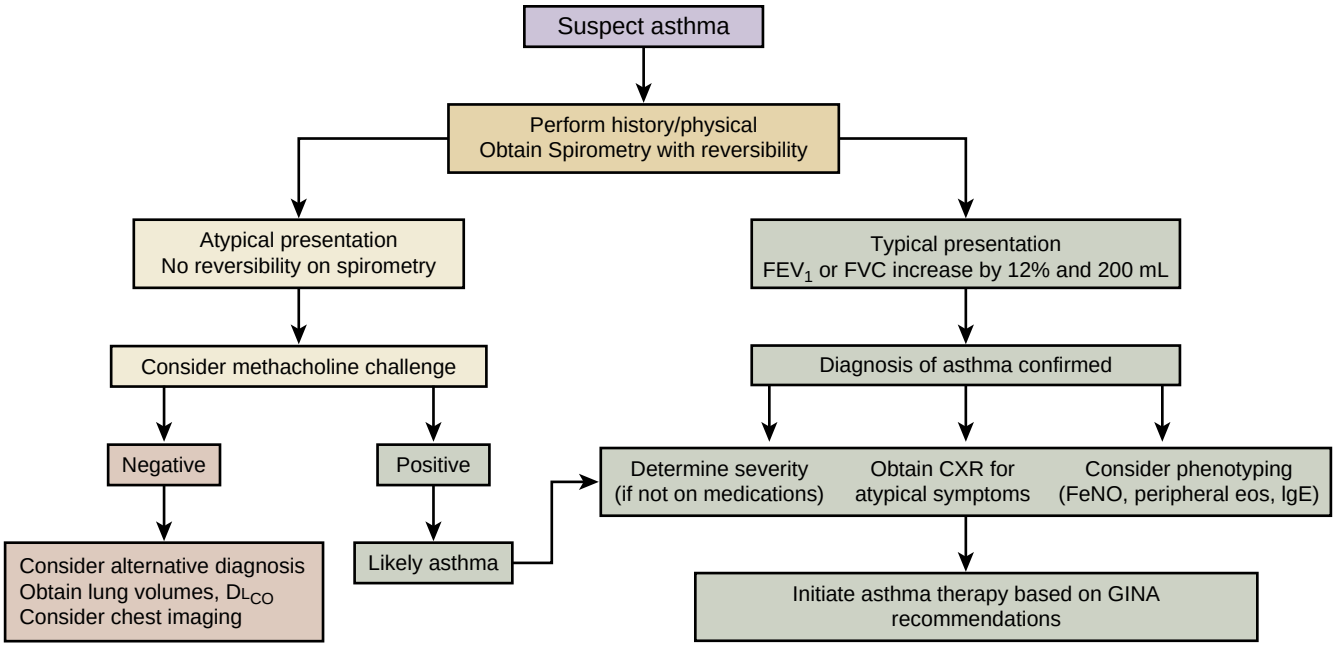

Fig. 62.1 Algorithm for diagnosing asthma in adults. The diagnosis of asthma is based on a careful personal history, physical examination, and lung function testing. Spirometry should be obtained in every patient in whom asthma is suspected. Other tests are useful when clinical features are atypical, and to determine severity and asthma phenotype. CXR, chest radiograph; D_{LCO}, diffusing capacity for carbon monoxide; eos, eosinophils; FeNO, fraction of exhaled nitric oxide; FEV_1, forced expiratory volume in 1 second; FVC, forced vital capacity; IgE, immunoglobulin E; GINA, Global Initiative for Asthma.

PERSONAL HISTORY

Asthma can arise at any age but often presents for the first time in childhood.[2] Risk factors for childhood asthma include a family history of asthma and a personal or family history of atopy (e.g., atopic dermatitis, seasonal allergic rhinitis, conjunctivitis).[3] In addition, asthma can develop in individuals sensitive to aspirin or exposed to chemical toxins.[4]

A comprehensive history for symptoms suggestive of the reversible airflow obstruction and *airway hyperresponsiveness* (AHR) characteristic of asthma is essential for the assessment of the asthmatic patient. Most patients with asthma report intermittent symptoms including cough, shortness of breath, chest tightness or heaviness, and/or wheezing, often described as a high-pitched musical whistling, heard usually at the end of expiration but may also be heard in both inspiratory and expiratory phases. They often experience periods of symptom-free normal breathing interrupted by periods of difficulty breathing. Asthma symptoms can last for a few minutes or days. Cough is a frequent complaint in asthma; the cough may or may not be accompanied by sputum production, may worsen at night or with activity, and may develop after exposure to allergens.[5,6] Shortness of breath and wheezing manifest during an exacerbation and can be triggered by infection, cold air, exercise, exposure to chemical fumes or other airborne irritants, pet dander, molds, house dust mites, or other allergens.[7] In contrast, wheezing heard predominantly during inspiration may be a sign of stridor. Complaints of sharp stabbing or knifelike pain would be unusual in asthma and should direct the clinician to alternative diagnoses (see Chapter 39).

Asthma guidelines support applying characteristics of these asthma symptoms toward determining a patient's asthma severity, as indicated by degree of impairment or risk of exacerbations.[8] For example, the frequency with which an individual experiences asthma symptoms can differentiate between someone with mild or severe disease. Similarly, an individual for whom the asthma symptoms markedly impair daily activities and function would likely indicate requirement for therapy for more severe disease than an individual for whom the same symptoms had little effect on function. Patients may report one or many prior diagnoses of "bronchitis" treated with systemic steroids and short-acting bronchodilators, which could be interpreted as exacerbations of asthma.

WORK HISTORY

Symptoms that improve on weekends and vacations and worsen at work should raise the suspicion of occupational and/or work-exacerbated asthma. Occupational asthma is new-onset asthma due to causes and conditions attributable to a particular occupational environment, whereas work-exacerbated asthma is defined as exacerbation of known asthma by the work environment.[9] Indeed, up to 15% of all adult asthma can be attributed to occupation.[10,11] The work exposure history should focus on identifying agents present at the time of asthma diagnosis or when asthma symptoms worsened. There are two major types of occupational asthma: sensitizer-induced asthma and irritant-induced asthma. Sensitizers are often further classified into low-molecular-weight (small chemicals) and high-molecular-weight (usually protein) agents.[4] *Reactive airway dysfunction syndrome*, the best-defined form of irritant-induced asthma, results from a single high-dose exposure to irritants. (For a more detailed discussion of

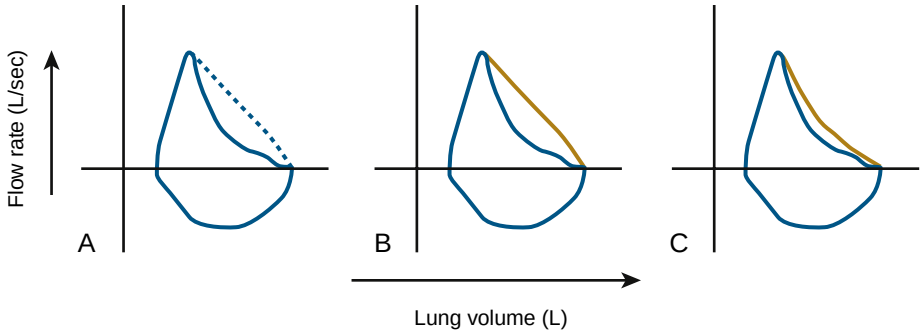

Fig. 62.2 Flow-volume loops in asthma. (A) The typical scooped appearance of the flow-volume loop in asthma is shown as the *solid blue line.* The predicted normal flow-volume loop is shown by the *dashed line.* (B) The scooped appearance of the initial flow-volume loop (*blue line*) may show complete reversal following use of a bronchodilator (*brown line*). (C) In some cases, the reversal of the scooped appearance following use of a bronchodilator is incomplete (*brown line*). (From Sameer KM. Asthma: diagnosis and management. *Med Clin North Am.* 2006;90:39–60.)

reactive airway dysfunction syndrome and occupational asthma, see Chapter 100.)

PHYSICAL EXAMINATION

The physical examination should focus on the head and neck, chest, and skin. The physical examination is often normal, particularly for patients who are asymptomatic at the time of examination; however, findings such as wheezing during normal breathing and/or a prolonged expiratory phase may suggest asthma. Forced exhalation, a maneuver to enhance wheezing, is not specific for asthma and suggests airway obstruction or collapse.[12] In addition to breathing abnormalities, subjects with asthma often have concomitant signs of associated allergic conditions and evidence of upper respiratory tract inflammation and obstruction with inflamed nasal passages and/or nasal polyps or large tonsils. The findings of eczema, hives, or atopic dermatitis on skin examination are supportive of an atopic asthma diagnosis.[8]

Objective measurements of lung function support an asthma diagnosis when the clinical history is suspicious for asthma (Fig. 62.2). Commonly available tests for measurement of airflow obstruction include spirometry and *peak expiratory flow* (PEF) measurement. Comparison of results before and after treatment with a bronchodilator will assess for reversibility of obstruction. Finally, AHR can be determined through inhalational or exercise challenges. Application of these tests is described in the following sections.

PHYSIOLOGY OF AIRFLOW LIMITATION

As understanding of the pathogenesis of asthma improves and strategies for treatment evolve, it is important to recognize that the link between the pathophysiology and the treatment of asthma is functional, involving variable limitation of airflow. These two cardinal manifestations of asthma, limitation of airflow and variability of symptoms in response to environmental factors, are crucial to making the diagnosis of asthma and distinguishing asthma from other obstructive lung diseases.

During asthma exacerbations, diffuse narrowing of the airways results in profound physiologic consequences. This narrowing has been thought to take place disproportionately in the small bronchi,[13] resulting in abnormal lung function tests with an increase in airway resistance and a decline in maximal expiratory flow. Airway narrowing also prevents the lungs from completely emptying (air trapping) due to resistance to expiratory flow and bronchial closure at higher than normal lung volumes. The breath-to-breath variability of asthmatic obstruction and air trapping can lead to dynamic hyperinflation,[14] a situation in which patients breathe at higher total lung volumes (i.e., increased residual volume).[15] Despite elevated total lung volumes, asthmatics typically have reduced tidal ventilation.

At high lung volumes, flow limitation due to bronchial narrowing is offset somewhat by increased circumferential traction on the bronchial airways due to "tethering" of airways to inflated alveoli,[16] thereby reducing airway resistance. However, the diaphragm and intercostal muscles become overloaded due to thoracic hyperinflation and are mechanically disadvantaged due to suboptimal positioning on their length-tension curves.[17] As a result, accessory muscles of respiration, including the abdominal muscles and the sternocleidomastoids, are recruited.[18] Overall, due to the mechanical disadvantage of the respiratory muscles and recruitment of additional muscle groups, the work of breathing at higher lung volumes is increased.

The airway obstruction and closure in asthma is nonuniform, with significant regional variability.[19,20] Ventilation-perfusion mismatching leads to a widened alveolar-arterial oxygen tension difference that tracks with increasing asthma severity.[21,22] Arterial carbon dioxide tension initially falls as alveolar ventilation increases because carbon dioxide elimination is less impaired by ventilation-perfusion mismatching than is oxygen uptake.[23] As respiratory muscles fatigue, carbon dioxide tension increases, so a normal or elevated partial pressure of carbon dioxide during an asthma exacerbation suggests impending respiratory failure.[24]

PULMONARY FUNCTION TESTING

In ambulatory patients, decreased expiratory flow can be easily and reproducibly detected with a peak flowmeter; PEF measurements attempt to correlate physiologic function with the clinical severity of asthma. However, peak flow measurements are not standardized and do not correlate well with other measures of lung function.[25] PEF as a percentage of its predicted value is 10% higher than the percent predicted of the *forced expiratory volume in 1 second* (FEV_1) on average, with a great deal of variability between measurements.[26] Currently, the recommended use of PEF

measurement is for the daily monitoring of ambulatory patients with difficult-to-manage asthma.

Spirometry

The most standardized test of airflow obstruction is FEV_1. FEV_1 may be normal or near-normal between asthma flares. It has the advantage of being an objective, non-patient-reported measurement of lung function. Improvement in FEV_1 of greater than 12% and 200 mL after bronchodilator treatment indicates reversible airflow obstruction and is suggestive, but not diagnostic, of asthma.[27]

Accurate measurement requires stopping *long-acting β_2-agonists* (LABAs) for at least 12 hours and short-acting bronchodilators for at least 6 hours. The absolute value of the FEV_1 is dependent on the *forced vital capacity* (FVC). Interpretation of FEV_1 therefore requires simultaneous FVC measurement. In asthma, the relative reduction in FEV_1 is typically greater than the reduction in the FVC. As a result, the FEV_1/FVC ratio in asthma is usually less than 70%. However, in severe asthma, this ratio may actually increase as air trapping increases residual volume and reduces the FVC. A 20% and 200 mL increase in the FVC after bronchodilator is also suggestive of asthma.[27]

An alternative measure of airflow obstruction is the mid-expiratory flow, measured between 25% and 75% of the FVC (*forced expiratory flow* $[FEF]_{25\%–75\%}$). Measured at lower lung volumes than FEV_1, reductions in the $FEF_{25\%–75\%}$ may be more sensitive for identifying obstruction in small airways.[28] However, the clinical utility of the $FEF_{25\%–75\%}$ is limited by the lack of acceptable standardized values and poor reproducibility.[29] High numbers of false-positive and false-negative results are seen when 80% of predicted $FEF_{25\%–75\%}$ is used to define normal.[30]

Single-breath diffusing capacity is a marker of carbon monoxide gas transfer in the lungs. In asthma, the diffusing capacity is normal or elevated if airflow obstruction is not severe; this finding can be useful in distinguishing asthma from other obstructive lung diseases.[31] Elevated diffusing capacity in asthma has been attributed to increased perfusion of the upper lung zones and is associated with large lung volumes. The unexpected finding of an increase in diffusing capacity should raise the possibility of undiagnosed asthma, whereas decreased diffusing capacity in a suspected asthmatic is suggestive of an alternative diagnosis or coexisting condition.[32]

Provocative Challenges and Airway Hyperresponsiveness

Airway Hyperresponsiveness. AHR to environmental stimuli is a hallmark of asthma. Patients suspected of having asthma despite normal lung function testing usually develop bronchoconstriction in response to a provocative stimulus. Direct stimulation with methacholine inhaled into the airways is the most widely used method of assessing bronchial hyperresponsiveness. Nebulized methacholine is delivered in doubling concentrations until FEV_1 falls by more than 20%, referred to as the PC_{20} (provocative concentration resulting in 20% fall in the FEV_1). The PC_{20} can be used to quantify the degree of AHR. A PC_{20} less than 16 mg/mL is consistent with mild AHR, less than 4 mg/mL is consistent with moderate AHR, and less than 1 mg/mL with severe AHR,[33] with lower PC_{20} levels generally corresponding to more severe asthma[34] (see Chapter 31).

Impulse Oscillometry. Impulse oscillometry is a form of forced oscillometry testing, a noninvasive technique to characterize the airway through the superimposition of sound waves on normal tidal breathing.[35] The disturbances in flow and pressure caused by the sound waves are used to calculate resistance to airflow at frequencies of 5 Hz (R5) and at 20 Hz (R20) and reactance, the energy generated by the lungs' recoil against that pressure wave at 5 Hz (X5). These measurements allow calculation of the force necessary to propagate this pressure wave through the respiratory system, known as impedance. The site of airway disease can also be localized because lower-frequency oscillations tend to travel to the lung periphery and higher-frequency ones reach only the most proximal airways.

Measurements are recorded during normal passive tidal breathing and require little training. Not surprisingly, the majority of impulse oscillometry studies in asthma have been in children. Significant correlations between FEV_1 and FVC by spirometry and impedance and resistance by impulse oscillometry have been described.[36] A decrease in R5 by 30–35% in children is considered to be a positive bronchodilator response.[37,38] In another study of children, a 50% decrease in X5 was found to be roughly equivalent to a 20% decrease in FEV_1.[39] Most impressively, impulse oscillometry has outperformed spirometry in sensitivity and specificity for the diagnosis of asthma in young children when compared to a methacholine challenge and validated clinical questionnaire.[38,40] Despite increasing acceptance in the pediatric population, experience in adult patients remains limited.[41]

EVALUATION AND TREATMENT OF ASTHMA

INTRODUCTION

The *National Heart Lung and Blood Institute* (NHLBI) *Expert Panel Report* (EPR) Guidelines for the Diagnosis and Management of Asthma and GINA documents have provided clinicians with a reliable framework for evidence-based management of patients with asthma.[1,8] These guidelines emphasize maintaining long-term control of symptoms through attention to environmental and social components of asthma and using treatment regimens tailored to the severity of each patient's symptoms. Crucial components of management as recommended by the EPR and GINA guidelines include initial evaluation of control (Table 62.1)[41a]; determination of severity by "step" of treatment required to control symptoms (Table 62.2); appropriate pharmacologic therapy to reverse bronchoconstriction and ameliorate inflammation; identification and control of environmental factors that worsen symptoms or trigger exacerbations; and creation of a partnership between the patient and the health care professional to ensure that therapy is tailored to each patient's needs. Modern approaches to therapy also recognize that heterogeneity of asthma pathobiology will lead to variability in each individual's clinical response to each therapy, and therefore incorporate

Table 62.1 Classification of Asthma Control in Adults and Adolescents >11 Years per GINA Guidelines

Asthma Symptom Control	Yes	No
In the past 4 weeks, has the patient had: ■ Daytime asthma symptoms more than twice per week? ■ Any night waking due to asthma? ■ Reliever needed for symptoms more than twice per week? ■ Any activity limitation due to asthma?		
Total:		
Level of asthma symptom control is based on total number of "yes" responses: ■ If 0, asthma is well controlled ■ If 1–2 of these, asthma is partly controlled ■ If 3–4 of these, asthma is uncontrolled		
Risk factors for poor asthma outcomes: ■ Uncontrolled symptoms ■ Medication challenges (frequent short-acting bronchodilator use, poor adherence, incorrect technique, not on inhaled corticosteroid) ■ Comorbidities (obesity, chronic rhinosinusitis, GERD, pregnancy) ■ Exposures (smoking, allergens, air pollution) ■ Low lung function (FEV_1 <60% predicted) or highly reversible bronchoconstriction ■ Psychological or socioeconomic factors ■ History of severe exacerbation	Any of these risk factors increases the patient's risk of exacerbations even if they have few asthma symptoms	

FEV_1, forced expiratory volume in 1 second; GERD, gastroesophageal reflux disease; GINA, Global Initiative for Asthma.
Courtesy GINA, www.ginasthma.org.

Table 62.2 Classification of Asthma Severity (GINA 2019)

ASSESS SYMPTOM CONTROL WHEN PATIENT HAS BEEN ON REGULAR CONTROLLER TREATMENT FOR SEVERAL MONTHS	
Mild asthma	Well controlled with step 1 or step 2
Moderate asthma	Well controlled with step 3
Severe asthma	Requires step 4 or step 5 to prevent it from being uncontrolled, or is still uncontrolled despite this therapy

Steps are levels of treatment, as defined in Fig. 62.3.
Uncontrolled asthma is defined by the International European Respiratory Society/American Thoracic Society Guidelines for Severe Asthma as described later.
FEV_1, forced expiratory volume in 1 second; GINA, Global Initiative for Asthma.
Courtesy GINA, www.ginasthma.org.

biomarker and phenotype assessments to optimize treatment decisions.

ASSESSMENT

Asthma Impairment and Risk

The assessment of patients with asthma involves two essential steps: determining the current degree of *impairment* from asthma based on symptoms, reliever medication use, recent exacerbations, and lung function; and evaluating the *risk of future adverse outcomes* including exacerbations, lung function decline, and adverse medication outcomes. With this in mind, the NHLBI updated guidelines and GINA offer a parallel scheme for asthma assessment based on expert opinion[1,8] (see Tables 62.1 and 62.2). The NHLBI and GINA classifications represent categorical interval variables with threshold values to determine severity and control. The importance of control indices is underscored by the relationship between poor asthma control and substantial degrees of physical impairment and diminished quality of life, even after taking the baseline severity of asthma into account.[42]

Several different validated instruments exist for assessing asthma within this framework, including the Asthma Control Questionnaire, Asthma Control Test, Asthma Therapy Assessment Questionnaire, and Asthma Control Scoring System.[43–46] All are useful because they direct history taking, provide goals for the management of symptoms, and guide adjustments in treatment.[47]

While the NHLBI guidelines suggest that asthma severity is to be determined initially based on the severity of symptoms—both impairment and risk domains—at the time of diagnosis, the GINA guidelines recommend defining severity by the amount of medication required to control asthma symptoms (see Table 62.2). While guidelines provide recommendations for starting therapy at each severity level (Fig. 62.3), providers must reassess every patient to ensure adequate asthma control. Importantly, in determining severity, guidelines also take into account the amount of treatment necessary to maintain control of asthma.

Lung Function

Lung function testing is an important part of assessing asthma, both for making the initial diagnosis and as a means of evaluating the response to therapy. Although the FEV_1, FEV_1/FVC ratio, and PEF are useful in the diagnosis and monitoring of asthma, the utility of these measurements in improving the outcome of asthma remains incompletely defined. However, a low FEV_1 is a strong predictor of decline in asthma control and of increased risk of needing acute care.[48] In mild asthma, however, FEV_1 is often normal or near-normal and thus may not show significant bronchodilator response. PEF measurement is a standard method to correlate physiologic function with asthma severity and has been used as a marker of asthma control in many clinical trials. However, individual PEF measurements are highly variable and the *variability* in peak flow has a greater predictive value for future exacerbations than individual PEF measurements themselves.[48] The clinical usefulness of

	Step 1	Step 2	Step 3	Step 4	Step 5
Preferred Controller *To prevent exacerbations and control symptoms*	As-needed low-dose ICS-formoterol*	Low-dose ICS, *or* as-needed ICS-formoterol*	Low-dose ICS-LABA	Medium-dose ICS-LABA	High-dose ICS-LABA Refer for phenotypic assessment ± add-on therapy (e.g., tiotropium, anti-IgE, anti-IL5/5R, anti-IL4R)
Other controller options	Low-dose ICS taken whenever SABA is taken†	LTRA or low-dose ICS taken whenever SABA is taken†	Medium-dose ICS, *or* low-dose ICS+LTRA‡	High-dose ICS, add-on tiotropium, *or* add-on LTRA‡	Add low-dose oral corticosteroids, but consider side effects
Preferred Reliever	As-needed low-dose ICS-formoterol*				
Other reliever option	As-needed SABA				

At all levels:	Assess	Adjust	Review Response
	Confirmation of diagnosis *Symptom control & modifiable risk factors (including lung function)* *Comorbidities* *Inhaler technique & adherence* *Patient goals*	*Treatment of modifiable risk factors & comorbidities* *Non-pharmacological strategies* *Education & skills training* *Asthma medications*	*Symptoms* *Exacerbations* *Side effects* *Lung function* *Patient satisfaction*

Fig. 62.3 Medication recommendations for control of asthma in adults and children older than 12 years. Controller medications should be initiated and subsequently adjusted up or down in a stepwise approach with a goal of achieving good control of symptoms and minimizing future risk of exacerbations, airflow obstruction, and adverse effects from medications. At onset of treatment and every 2 to 3 months thereafter, assess clinical factors, adjust medications, and review response. *Off-label; data only available for budesonide-formoterol. †Off-label; separate or combination ICS and SABA inhalers. ‡Consider adding house dust mite sublingual immunotherapy for sensitized patients with allergic rhinitis and FEV_1 >70% predicted. ICS, inhaled corticosteroid; Ig, immunoglobulin; IL, interleukin; LTRA, leukotriene receptor antagonist; LABA, long-acting β_2-agonist; SABA, short-acting β_2-agonist. (Modified from GINA 2019 Guidelines, www.ginasthma.org.)

PEF measurements is also limited by patient resistance to home monitoring and difficulty with consistently maintaining peak flow records.

Imaging

Although traditionally thoracic imaging has been used to rule out alternative pathologies, recent advances in imaging offer additional noninvasive techniques to support the diagnosis of asthma. The chest radiograph is most commonly normal in stable asthmatics, although nonspecific findings such as hyperinflation and bronchial wall thickening can be appreciated.[49] In patients admitted with status asthmaticus, pneumothorax and pneumomediastinum identified on chest radiograph have been reported in 0.5–2.5% of patients, respectively.[50] The primary role of the plain chest radiograph remains to rule out asthma mimics in those with atypical symptoms and to evaluate difficult-to-control symptoms.

Clinically, chest *computed tomography* in asthma is used to evaluate chest radiographic abnormalities, diagnose complications of associated conditions (i.e., pneumothorax and pneumomediastinum), and identify mimics less apparent on plain chest radiographs (i.e., bronchiolitis, bronchiectasis, tracheobronchomalacia, endobronchial lesions, and vascular anomalies).[49,51] Increasingly, high-resolution chest computed tomography techniques offer a useful tool to assess large and small airway pathology. Nonspecific findings such as bronchial wall thickening, airway dilation, bronchiectasis, mucoid impaction, and mosaic lung attenuation consistent with air trapping are described in studies of asthmatic subjects.[52]

Asthma Phenotypes, Endotypes, and Biomarkers

The identification of asthma *phenotypes,* which are collections of clinical characteristics that define a particular type of asthma, and their *endotypes*, which are defined by particular biologic pathways, has now moved into center stage when evaluating the patient with asthma, particularly severe asthma.[53]

The endotypes associated with *type 2* (T2) inflammation characterized by T2 cytokines such as *interleukin* (IL)-4, IL-5, and IL-13 include early-onset allergic asthma with or without obesity, aspirin-sensitive asthma and late-onset eosinophilic asthma, exacerbation prone asthma, and exercise-induced asthma. Clinical phenotypes of asthma not associated with T2 inflammation (T2-low), and for which the pathobiologic pathways are not yet defined, include patients with obesity-related late-onset asthma, asthma with fixed airflow obstruction and very little inflammation (paucigranulocytic), and asthma associated with neutrophilia. Other T2-low clinical phenotypes that are less well defined but that may share similar endotypes include smoking-related

Table 62.3 Asthma Biomarkers and Associated Phenotypes as Predictors of Response to Specific Therapies

Biomarker	Asthma Phenotype	Predicts
Elevated exhaled nitric oxide (>50 ppb in adults, >35 ppb in children)	T2-high	Response to inhaled steroids
Sputum eosinophils >3%	T2-high	Response to inhaled steroids
Peripheral blood eosinophils (>0.3 × 10^9/L or 300/μL)	T2-high	Response to anti-IL-5 therapy
Elevated total IgE >30 IU	Allergic/T2	Response to omalizumab
Allergy skin tests and elevated specific IgE	Allergic/T2	Response to immunotherapy, omalizumab
Lack of elevated peripheral and sputum eosinophils and low FeNO	T2-low	Response to tiotropium and macrolides (likely to be poor responders to steroids)

FeNO, fraction of exhaled nitric oxide; IgE, immunoglobulin E; T2, type 2.

asthma, occupational asthma due to low-molecular-weight agents[54] or environmental pollution,[55] and respiratory infections.[56]

Biomarkers. The emergence of an increased body of literature to support the presence of asthma phenotypes and endotypes has made it imperative that we have tools at our disposal for identification of these patient cohorts. *Biomarkers* are measurable characteristics of an individual that relate to a disease, such as an elevated level of blood eosinophils. Applying biomarkers to identify phenotypes and endotypes of severe asthma may have a variety of purposes. For example, the currently recognized and published phenotypes and endotypes of severe asthma are largely defined by observable and measurable characteristics of the disease or patient and not yet by specific diagnostic biomarkers[53] (Table 62.3). For example, early-onset, allergic asthma is characterized by the presence of allergen-specific *immunoglobulin E* (IgE), and late-onset, hypereosinophilic asthma is characterized by elevated peripheral blood and sputum eosinophils. Eosinophil and IgE levels can be used as diagnostic biomarkers for these phenotypes. However, blood eosinophils are commonly present in patients with early-onset allergic asthma, and allergen-specific IgE may be present in patients with late-onset, hypereosinophilic asthma. Although these commonly used biomarkers may give clues as to the phenotype or endotype of a severe asthmatic patient, they are not pathognomonic or mutually exclusive and do not necessarily address the molecular mechanisms underlying each endotype. Notably, asthma endotypes are not yet well described and mechanisms are not well defined, perhaps contributing to these limitations. Combinations of biomarkers may be more helpful to characterize patients into one of these categories, and novel biomarkers in development may provide improved specificity for one or multiple phenotypes. Furthermore, these biomarkers could be applied as diagnostic of a phenotype, as predictive of a response to therapy, and as useful dynamic markers of a response to therapy. These varied applications of biomarkers may be useful to drive therapy with targeted biologic agents, which is discussed in more detail in the section on treatment of asthma.

Eosinophils and Eosinophil-Related Biomarkers. Eosinophils may be detected in one or multiple compartments, including the peripheral blood, the airway submucosa, and the airway lumen. The presence of eosinophilia is not always consistent in these compartments.[57,58] Eosinophils are primarily tissue-dwelling leukocytes, and therefore blood counts may not necessarily indicate the extent of eosinophil involvement in the affected tissues.[58,59] A systematic review and meta-analysis of blood biomarkers found that peripheral blood eosinophil counts had a sensitivity of 71% and specificity of 77% for detecting sputum eosinophils of greater than 3%.[60] The extremes of blood eosinophil levels may be more sensitive and specific for identifying sputum eosinophils.[61–63] For example, patients with blood eosinophil counts of less than 90 eosinophils/μL are highly unlikely to have airway eosinophilia; alternatively, almost all patients with more than 400 eosinophils/μL of blood can be expected to have significant sputum eosinophilia.[64] Reference values for sputum eosinophil percentages have been determined through epidemiologic studies of healthy patients.[65,66] In general, sputum eosinophil levels of greater than 2–3% and blood eosinophil counts of greater than 300/μL may be used to define eosinophilic disease.[63,67]

Similarly, sputum eosinophilia can identify patients who will likely have a clinical response to systemic and inhaled corticosteroids.[68,69] However, measurement of sputum eosinophils in the clinical arena requires specialized expertise that is not widely available.

A limitation of the eosinophil number as a predictive biomarker for diagnosis or treatment of asthma may include the failure to identify eosinophil functional stimulation and activity related to severe asthma. Markers of eosinophil activation may be more pathophysiologically relevant as diagnostic and predictive biomarkers for response to therapy or other disease characteristics. For example, eosinophil peroxidase is one of the major granule contents released by eosinophils on activation.[70] In sputum, eosinophil peroxidase is highly correlated with sputum eosinophil levels, increases with allergen challenge, and is specific for those with eosinophilic disease.[71] Eosinophil peroxidase is also readily detected in nasal and pharyngeal swabs, and values at both sites are highly correlated with sputum eosinophils in patients with poorly controlled eosinophilic asthma.[72]

Bromotyrosine is an oxidation product of eosinophil peroxidase. Elevated levels of bromotyrosine can be identified in the airway of clinically stable patients with asthma[73] and can be induced by airway allergen challenge.[74] Bromotyrosine is a stable compound excreted

in the urine[75] where it can be measured noninvasively. Elevated urinary levels of bromotyrosine strongly correlate with uncontrolled asthma and risk of asthma exacerbations in children.[76] As might be expected, urinary bromotyrosine also can be used as a predictor of clinical response to *inhaled corticosteroids* (ICSs) in asthma,[77] further emphasizing the distinction between the pathobiologic contribution of total eosinophil counts compared to measures of activated eosinophils.

Fraction of Exhaled Nitric Oxide. *Nitric oxide* (NO) and related compounds are generated by various resident and inflammatory airway cells and have a broad variety of functions as inflammatory mediators, vasodilators, bronchodilators, and neurotransmitters.[78] In the asthmatic airway, NO exhibits a paradoxical response by enhancing airway dilation at low concentrations but propagating inflammatory responses at higher concentrations.

The measurement of the *fraction of exhaled NO* (FeNO) is used clinically as a biomarker of airway inflammation related to IL-4– and IL-13–mediated pathways. This relationship is supported by the observation that FeNO levels decline with IL-4 and IL-13 inhibition.[79–81] Higher levels of FeNO are related to severe, early-onset, allergic, and eosinophilic asthma and therefore can help to identify patients with these phenotypes.[82] More recent studies show that not only is FeNO a strong predictor of sputum eosinophils, it predicts sputum eosinophilia better than serum eosinophils do and also predicts response to ICSs and long-acting muscarinic antagonists.[83]

Noninvasive measurements of FeNO have been standardized for clinical use and may serve as a complementary tool in asthma diagnosis and management. In 2011, guidelines for interpretation of clinical use of FeNO in the diagnosis and management of asthma were published by the *American Thoracic Society* (ATS); however, a *European Respiratory Society* (ERS)/ATS task force later recommended against routine use of FeNO to diagnose asthma and to monitor therapy in patients with severe disease.[84] More recently, Essat et al.[85] and the Agency for Healthcare Research and Quality[86] advocated for additional research to establish a role for FeNO in asthma management.

FeNO has some advantages in detecting eosinophilic asthma and monitoring asthma control compared with counting the number of sputum eosinophils. FeNO can be measured rapidly in a primary care setting, requires less technical expertise, and provides real-time objective physiologic data. Major limitations of using FeNO to confirm the diagnosis of asthma include the relatively high prevalence of noneosinophilic phenotypes characterized by a lack of increased FeNO and the difficulty with clinical interpretation of values obtained in the setting of concomitant steroid use that may lead to false-negative results.[78] However, there is still a role for FeNO in phenotyping patients by identifying those with a Th2 high/eosinophilic phenotype, regardless of asthma severity.

Immunoglobulin E. IgE is an important marker of airway inflammation and may play a key role in allergic asthma. The presence of allergen-specific IgE is required to define the phenotype of early-onset allergic asthma, with panels of clinically relevant aeroallergen skin testing or specific IgE serology functioning as essential biomarkers. In addition, it may be present and relevant in adult-onset asthma. The *National Institutes of Health* (NIH) Asthma Outcomes Workshop suggested that total and specific serum IgE be considered important outcomes for interventional and observational studies of asthma.[59] Independent of specific aeroallergen sensitization, total IgE is a marker of asthma risk.[87] Both specific aeroallergen sensitization and elicitation of symptoms on exposure to that specific aeroallergen should be present in the clinical syndrome of allergic asthma. This requires clinician assessment of exposure-related symptoms in addition to specific IgE testing through percutaneous skin testing or specific IgE serum assays.

IgE levels are informative and diagnostic in the setting of allergic bronchopulmonary aspergillosis or, as more generally called, *allergic bronchopulmonary mycosis*, which is an endotype of severe asthma. Pathognomonic diagnostic and dynamic biomarkers of allergic bronchopulmonary mycosis include markedly elevated serum total IgE and specific IgE to molds (detected by percutaneous skin testing or serum analysis, most commonly to *Aspergillus fumigatus*) in the setting of severe asthma, mucus plugging, and often central bronchiectasis.

Blood Neutrophils. A significant proportion of patients with severe asthma will have airway granulocytes, including neutrophils and eosinophils.[88] Those with significant proportions of airway neutrophils (ranging from 40–76% of total sputum cells) but lacking significant airway eosinophils are considered to have the neutrophilic phenotype of severe asthma. Therefore, sputum granulocyte counts can be used as a diagnostic biomarker for this severe asthma phenotype. However, the use of systemic or ICSs at the time of sputum collection, because these treatments induce neutrophilia, could make interpretation of this finding more challenging. This phenotype is not well understood but may be driven by chronic infection, such as with atypical bacteria or occupational/environmental exposures.[89]

Imaging as a Biomarker. There is increased interest in using quantitative computed tomography to evaluate disease severity in asthma.[90] In 123 subjects enrolled in the NIH Severe Asthma Research Program, airway percentage wall thickness (wall thickness divided by outer airway diameter) was higher in subjects with severe asthma than in those with mild asthma or no disease. Percentage wall thickness also inversely correlated with baseline FEV_1% and positively correlated with change in FEV_1% with bronchodilator challenge. Similar results for the percent airway wall area (airway wall area divided by the total area of the airway) and the percent airway lumen area (airway lumen area divided by the total area of the airway) were also seen.[91] These studies and others support a further relationship between asthma severity and measured airway thickness.[91–93]

Also gaining in acceptance are research tools for investigating regional lung structure and function using high spatial resolution ventilation images with hyperpolarized gas (helium-3 and xenon-129) magnetic resonance imaging.[90,94–96] Moreover, the ability of magnetic resonance imaging to measure regional variation in ventilation may be particularly useful for severe asthmatics for whom bronchial thermoplasty is considered.

ASTHMA TREATMENT APPROACHES

Overview

Current guidelines recommend adjusting therapy in a stepwise fashion to reduce daily symptoms and risk of exacerbations while minimizing the use of medications (see Fig. 62.3).[1,8] The hierarchy of treatment recommendations is based on the available literature about efficacy and safety and provides a prominent role for controller medications at all levels of asthma treatment. In general, the strategy and recommendations in adults and children are similar, with differences attributable to lack of clinical trials in pediatric populations.

Specific Pharmacologic Agents

β_2-Agonists. The bronchodilatory effect and tolerability of selective β_2-agonists have cemented these drugs as the cornerstone of asthma therapy.[97] β_2-agonist activity is primarily mediated by binding to a specific G-coupled transmembrane receptor found in high abundance on airway smooth muscle. Receptor binding leads to increased intracellular cyclic adenosine monophosphate and relaxation of airway smooth muscle.[98] Notably, β_2-receptors are also found on other resident airway cells, including airway epithelial cells and circulating immune cells, and binding to these sites may reduce vascular permeability and inflammatory mediator release.[99] One concern raised about the chronic use of β_2-agonists is that of receptor desensitization.[100] As with most signaling receptors, repeated exposure to β_2-agonists can lead to decreased responsiveness of membrane receptors through receptor down-regulation via receptor endocytosis and uncoupling of receptors from downstream transduction pathways. However, clinical data suggest that "as-needed" versus scheduled *short-acting β_2-agonist* (SABA) treatment is associated with improved physiology[101–103] and fewer, less-severe exacerbations.[104] Therefore, the risk of receptor desensitization may be most pronounced when albuterol is overused for asthma management.

β_2-selective agonists are usually administered by aerosol, which maximizes delivery to target tissue while minimizing the exposure of nontarget tissues. SABAs and LABAs are available, and the onset and duration of action are primarily related to lipophilicity.[105] SABAs are used for rescue or emergent treatment, whereas LABAs are used in combination with ICSs for chronic management of asthma.

A number of highly selective SABA preparations are now available, and all have a rapid onset of action with peak action between 60 and 90 minutes. Because they are inhaled directly into the airways, systemic side effects are minimal, even at high doses. Standard albuterol is racemic, that is, it contains two enantiomers: R- (levalbuterol) and S-. A β_2-agonist preparation containing only levalbuterol was developed in an attempt to minimize side effects due to unwanted activation of β_2-receptors in nonpulmonary tissue. Cardiac stimulation causes tachycardia and arrhythmias, whereas skeletal muscle stimulation causes tremors and hypokalemia. However, clinical trials have not shown significant differences in outcome or tolerability compared with standard (racemic) albuterol.[106]

On the basis of current guidelines, SABAs should be used to treat patients with symptoms despite a regimen of long-acting controller agents. Increased frequency of SABA use is a sign of inadequate control of symptoms or overreliance on rescue medication. Patients requiring more than two SABA doses per week should be considered for a step up in therapy.[1,8] LABAs have minimal utility for treating acute asthmatic symptoms because of their delayed onset of action. However, in patients with inadequately controlled asthma, they can be added to ICSs to improve symptoms and efficacy of the ICS. Multiple LABA preparations are available with differential properties. Of these, formoterol has a shorter onset of action, whereas the ultra-LABA preparations may be administered once daily. Each has been shown to improve lung function, reduce symptoms, and reduce the frequency of exacerbations.[107] Although LABAs are effective at improving symptoms and lung function, a study of salmeterol (LABA) monotherapy versus triamcinolone (ICS) monotherapy demonstrated significantly more treatment failures in the salmeterol group.[108] For this reason, LABA monotherapy for asthma is not recommended. In addition, adverse events with LABAs have been of concern, specifically related to the increased risk of death in African American subjects in the Salmeterol Multicenter Asthma Research Trial,[109] which was attributed in part to overall poorer control of symptoms at baseline (with more exacerbations and hospitalizations) and a lower rate of ICS use than in the white patients.[109] This further supports the recommendation against LABA monotherapy for asthma. Importantly, the use of LABAs with ICSs in the same metered-dose inhaler has since been shown to be safe and effective in adults and children.[110–112] Commonly used inhaled steroid-LABA combination inhalers are summarized in eTable 62.1.

Several studies have explored the relationship between polymorphisms in the β_2-receptor and responses to β-agonist therapy. Specifically, in patients treated with scheduled albuterol, the presence of the Arg/Arg polymorphism at the codon 16 locus (B16) was associated with lower PEF and FEV_1, increased symptoms, and more rescue inhaler use compared with patients who were Arg/Gly or homozygous Gly/Gly. All of these symptoms improved when regular albuterol was withdrawn.[101,103,113] Use of LABAs (with and without ICSs) has been shown to worsen physiologic markers of respiratory function in Arg/Arg patients in some studies, although these findings are not consistent.[114,115] The LARGE study demonstrated beneficial effects of LABAs in combination with ICS irrespective of B16 genotype, and the authors recommended against alterations in the current use of LABAs.[116] Further research is required; however, thus far there are no indications that use of LABAs in the Arg/Arg genotype is associated with undue risk. Additional genetic studies are examining potential mechanisms by which β-adrenergic receptor polymorphisms may contribute to the risk of LABA therapy in some patients with asthma.[117]

Anticholinergics. Anticholinergic agents act as bronchodilators by competing with acetylcholine at neuromuscular junctions, thereby blocking transmission of bronchoconstrictor reflexes.[118] The short-acting anticholinergic ipratropium bromide is effective in patients with COPD but is

eTable 62.1 Inhaled Steroid Preparations and Dosages

			DAILY DOSE		
Inhaler	**Dosage Forms**	**Age (yr)**	**Low**	**Medium**	**High**
Beclomethasone (QVAR)	Redihaler MDI: 40 or 80 μg/puff	5–11	80–160	>160–320	>320
		≥12	80–240	>240–480	>480
Budesonide (Pulmicort, Symbicort [with formoterol])	Respules for nebulization: 0.25, 0.5, 1.0 mg/neb	0–4	0.25–0.5	>0.5–1.0	>1.0
		5–11	0.5	1.0	2.0
	Flexhaler DPI: 90 or 180 μg/inh	5–11	180–400	>400–800	>800
	HFA MDI: 110 or 220 μg/puff	≥12	180–600	>600–1200	>1200
	Symbicort HFA MDI: 80/4.5 or 160/4.5 μg/puff	≥12	320 (80/4.5 2 puffs bid)	640 (160/4.5 2 puffs bid)	
Ciclesonide (Alvesco)	HFA MDI: 80 or 160 μg/puff	5–11*	80–160	>160–320	>320
		≥12	160–320	>320–640	>640 (mfr highest recommended dose)
Fluticasone propionate (Flovent, Advair [with salmeterol])	HFA MDI: 44, 110, or 220 μg/puff	0–11	88–176	>176–352	>352
		≥12	88–264	>264–440	>440
	Flovent Diskus DPI: 50, 100, or 250 μg/inh	5–11	100–200	>200–400	>400
		≥12	100–300	>300–500	>500
	Advair HFA MDI: 45/21, 115/21, or 230/21 μg/puff	4–11	180 (45/21 2 puffs bid)		460–920 (115–230/21 2 puffs bid)
		≥12	180 (45/21 2 puffs bid)	460 (115/21 2 puff bid)	920 (230/21 2 puffs bid)
	Advair Diskus DPI: 100/50, 250/50, or 500/50 μg/inh	4–11	200 (100/50 1 inh bid)		500–1000 (250–500/50 1 inh bid)
		≥12	200 (100/50 1 inh bid)	500 (250/50 1 inh bid)	1000 (500/50 1 inh bid)
Fluticasone furoate (Arnuity, Breo [with vilanterol], Trelegy [with vilanterol and umeclidinium])	Arnuity Ellipta DPI: 50, 100 or 200 μg/inh	5–11		50, 1 inh daily	
		≥12		100, 1 inh daily	200, 1 inh daily
	Breo Ellipta: 100/25 or 200/25 μg/inh	≥12		100/25, 1 inh daily	200/25, 1 inh daily
	Trelegy Ellipta: 100/62.5/25 μg/inh, 200/62.5/25 μg/inh			100/62.5/25, 1 inh daily	200/62.5/25, 1 inh daily
Mometasone (Asmanex, Dulera [with formoterol])	Asmanex Twisthaler DPI: 110 or 220 μg/inh	4–11	110 (mfr highest recommended dose)	220–440	>440
		≥12	220	440	>440 (mfr highest recommended dose 800 μg/day)
	Dulera HFA MDI: 100/5 or 200/5 μg/puff	≥12		400 (100/5 2 puffs bid)	800 (200/5 2 puffs bid)

*Not Food and Drug Administration approved for children <12 years.
DPI, dry powder inhaler; HFA, hydrofluoroalkane, a safe propellant; MDI, metered-dose inhaler; mfr, manufacturer.

considered a second-line agent for treating asthma, most likely because cholinergic tone contributes less to bronchoconstriction in asthma. While short-acting anticholinergics and SABAs both provide bronchodilation,[119,120] randomized trials studying the addition of anticholinergics to β-agonists do not show any additional benefit in patients with chronic asthma.[121] However, specific asthma phenotypes might be more likely to respond to anticholinergic treatment, including patients with fixed airflow obstruction, advanced age,[122] or longer duration of disease.[123] Furthermore, anticholinergics may be an acceptable alternative for certain subgroups of patients who do not tolerate β-agonist treatment or for patients with the Arg/Arg B16 genotype, although this has not been studied directly.

Tiotropium, a long-acting anticholinergic agent, was approved by the U.S. *Food and Drug Administration* (FDA) for treatment of asthma after multiple randomized controlled trials indicated a role for tiotropium as add-on therapy to both ICS and ICS/LABA combination therapy in patients with moderate to severe asthma.[124–126] Bronchodilator responsiveness to albuterol, higher resting cholinergic tone (defined by a lower resting heart rate), and increased airway obstruction (defined by a lower FEV_1/FVC ratio) are predictors of response to tiotropium.[127] The Steroids in Eosinophil Negative Asthma study by the NHLBI AsthmaNet group compared the relative benefit of ICSs and tiotropium in mild asthma with low sputum eosinophils (<2%).[83] In this clinical trial, among those with low eosinophils, there was no significant difference in treatment response in this group, suggesting tiotropium may be a reasonable alternative for mild asthma control in this phenotype.

Inhaled Corticosteroids. With recognition of the central role of inflammation in the pathophysiology of asthma, contemporary treatment strategies emphasize ICSs for long-term control of symptoms. Corticosteroids suppress inflammatory responses by broadly influencing signal transduction and gene expression pathways. Corticosteroids bind to a specific cytoplasmic receptor that translocates to the nucleus, where it modulates expression of inflammatory genes through inhibition of histone acetyltransferases and recruitment of histone deacetylases, two classes of histone modifiers that control DNA unwinding and gene expression epigenetically.[128,129] Corticosteroids thereby reduce airway inflammatory cell influx and markers of airway inflammation in asthma.[130,131]

Systemic corticosteroids have been used in the treatment of asthma since the 1940s and continue to be a cornerstone of the management of acute exacerbations. However, systemically administered corticosteroids are associated with a variety of undesirable side effects. The introduction of ICSs in the 1970s ushered in a new era in the treatment of asthma. As with bronchodilators, delivery of drug directly into the lungs through the use of inhaled preparations minimizes systemic toxicity and improves therapeutic benefit.

The use of ICSs improves all aspects of asthma control. ICSs reduce asthmatic symptoms, improve lung function, decrease airway inflammation, and control AHR.[132,133] A large meta-analysis showed that ICSs reduce asthma exacerbations by 55% when compared with placebo[134] and reduce the risk of hospitalization by 50% when compared with use of as-needed β-agonists alone.[135] Furthermore, ICSs reduce the risk of death from asthma in a dose-response manner.[136] As a result, ICS are considered to be first-line therapy for all patients requiring more than twice-weekly β-agonist use.[1,8] Predictors of response to ICSs include FeNO level greater than 47 ppb,[137] reversibility to albuterol and a decreased FEV_1,[138] and the presence of increased sputum eosinophils (>2–3%).[139] Interestingly, a large proportion of asthma patients are persistently noneosinophilic and unlikely to respond to therapy with ICSs, supporting the need for standard phenotyping of asthma with subsequent personalized therapy.[139–141]

The initial recommendations regarding the use of ICSs in patients with mild to moderate persistent asthma emphasized their use on a daily to twice-daily basis. Recently, there has been increased evidence that ICSs can be efficacious at reducing asthma symptoms and achieving asthma control when used intermittently in both children and adults, and the GINA guidelines now recommend that mild asthma be treated with intermittent budesonide/formoterol or that intermittent ICSs be taken every time rescue therapy is used.[8,142–145]

There are multiple different ICS preparations and delivery devices on the market (see eTable 62.1). The inhalers differ in particle size, ranging from a mass median aerodynamic diameter of about 1 μm to those with large particles 2 to 5 μm in size. The delivery devices include dry powder inhalers and metered-dose inhalers. The choice of ICS is based on the physician's discretion about the patient's needs and often rests on cost, convenience of dosing, and reduction of side effects. Some patients with very severe obstruction may be unable to generate the high inspiratory flows required for dry powder inhalers and may therefore do better with metered-dose inhalers (see also Chapter 13).

One key factor that warrants consideration is the role of small airway inflammation and associated obstruction as a key component of asthma pathophysiology. The presence of preserved FEV_1 with decreased mid expiratory flow and increased distal resistance is indicative of a small airway phenotype.[146] Targeted therapies to help modulate small airway inflammation are important, and there are several small particle size inhalers that have improved deposition into the distal lung.[147] Utilization of these inhalers may result in improvements in lung function measurements and asthma control.[147,148] In spite of the increased evidence that small particle size inhalers are efficacious, superiority comparisons with large particle size inhalers are lacking, and specific recommendations to help guide clinicians on choice of ICS for any particular patient therefore cannot be made at this time.[149]

The risk of systemic toxicity from steroids is diminished with the use of ICSs, particularly at doses less than 400 μg budesonide daily or the equivalent, but the risk is not absent. Data are conflicting about the risk of bone demineralization from ICSs; although a small observational study suggested increased risk,[150,151] a meta-analysis of several randomized controlled trials did not corroborate this finding.[151,152] The risks of cataract formation[152] and glaucoma[153] are slightly increased, whereas hypothalamic-pituitary axis suppression, gastrointestinal bleeding, and other complications of systemic steroids are not associated with inhaled preparations. The Towards a Revolution in COPD Health trial of the use of ICSs for COPD showed an increased risk of

pneumonia, but this has not been demonstrated in patients with asthma.[154] The use of ICSs in the pediatric population has raised concerns about growth suppression. However, available data show only a small and transient decrease in growth trajectory that does not translate into a reduction in adult height.[133,140,155]

Leukotriene Modifiers. *Leukotrienes* (LTs) are derived from cell membrane arachidonic acid metabolism. LT receptors on airway smooth muscle and macrophages mediate bronchoconstriction, mucus hypersecretion, and mucosal edema.[156] As a result, the LT pathway is a primary target for the development of asthma controller medications. Commercially available *leukotriene modifiers* (LTMs) work in one of two places in the LT pathway. Zileuton inhibits the activity of 5-lipoxygenase, the enzyme that converts arachidonic acid to leukotriene A_4, which is the first step in LT synthesis. Montelukast, zafirlukast, and pranlukast are all cysteinyl leukotriene-1–receptor antagonists, blocking the final step in the LT pathway. All are taken orally as either once-daily or twice-daily doses.

LTMs have a modest bronchodilator effect and may improve asthma symptoms and exacerbation rates.[157] Physiologic benefits have also been seen, with improvements in spirometry and measures of airway inflammation.[158] Whereas the subpopulation of patients with aspirin-sensitive asthma may derive great benefit from LTMs,[159] data also suggest that LTMs are adequate as single agents in mild persistent asthma.[160,161] Although LTMs treat multiple asthma symptoms, they are less effective than low-dose ICSs. LTMs can be used as monotherapy in exercise-induced asthma and in patients with relatively mild asthma symptoms that do not require therapy with ICSs, and can be combined with ICSs as a step up in therapy.[161] The addition of LTMs may lead to a reduction in the required corticosteroid dose or an improvement in asthma control.[162,163] In general, LTMs are less effective than LABAs as adjunctive therapy and do not seem to confer added benefits when added to a regimen that includes an ICS and a LABA.[164,165]

Overall, LTMs are well tolerated. Initial reports suggested a link between LTMs and eosinophilic granulomatosis with polyangiitis, but this is now thought more likely to be due to an unmasking of the syndrome by a reduction in corticosteroid dose with the introduction of an LTM.[166] LTMs have been linked to mood changes and suicidal ideation, particularly in children; therefore, monitoring of these symptoms is prudent.[167] Zileuton is metabolized by the cytochrome P-450 system and has been associated with reports of hepatotoxicity. As a result, liver function should be monitored during its use. At present, zileuton is reserved for patients with refractory asthma or who have an asthmatic phenotype suggesting benefit from the use of a leukotriene modifier.[168]

Phosphodiesterase Inhibitors. Theophylline is a well-established phosphodiesterase inhibitor that has mild anti-inflammatory properties. Because of its narrow therapeutic index, theophylline is not widely used in treating asthma. However, the discovery of additional anti-inflammatory properties, likely mediated by histone deacetylation, has led to a resurgence of interest.[169] Although no longer a recommended therapy and not recommended for use in children, theophylline is sometimes used in low doses as adjunctive treatment for moderate to severe asthma difficult to control with steroids alone.[8,170] The addition of theophylline to an existing drug regimen for poorly controlled asthma improves markers of control (e.g., less rescue inhaler use, better lung function) to a greater extent than LTMs.[171] Dose-related side effects, such as anorexia, palpitations, dysrhythmias, and seizures, require careful clinical and laboratory monitoring. Newer specific phosphodiesterase type 4 inhibitor drugs have been developed, and their safety profile is better than that of theophylline. Roflumilast has demonstrated efficacy in improving FEV_1 in asthma.[172,173] Although roflumilast is not approved for asthma, it has bronchodilating and anti-inflammatory properties that may be beneficial in asthma.

Macrolides and Asthma. Macrolides were initially shown to be effective in a subset of asthma patients who had evidence of mycoplasma in their airways by polymerase chain reaction.[174,175] These positive results generated interest in a broader use of macrolides for poorly controlled asthma. Subsequent clinical trials demonstrated variable effects on improving asthma symptoms or exacerbation risk.[176–178] In a recent clinical trial, azithromycin 500 mg 3 times weekly was associated with fewer exacerbations in both eosinophilic and noneosinophilic phenotypes and was well tolerated.[179] Additional studies to identify phenotypic or endotypic markers of response to therapy will help drive the most appropriate use of this intervention.

Targeted Biologic Agents. Over the past 5 years, there has been a significant increase in the number of biologics approved for the treatment of asthma. The era of personalized therapy in asthma is slowly being realized, making it imperative for clinicians to understand each individual patient's asthma phenotype as detailed in the biomarkers section of this chapter. The latter is especially important in those with severe asthma and is essential in identifying those more likely to respond to biologic therapies. At this time, there are five FDA-approved biologics for the treatment of asthma: omalizumab (Xolair), mepolizumab (Nucala), reslizumab (Cinqair), benralizumab (Fasenra), and dupilumab (Dupixent) (Table 62.4).

Immunoglobulin E Targeted Therapies. Omalizumab was the first FDA-approved monoclonal antibody for asthma and is now also indicated for the treatment of idiopathic urticaria. Omalizumab targets the FCεRI receptor–binding portion of IgE, preventing it from interacting with immune cells to cause degranulation.[180] Treatment with omalizumab reduces unbound IgE capable of binding to its receptor by 90–95%.[181] It must be administered subcutaneously, and the dose is based on IgE levels and body surface area. The addition of omalizumab to ICSs in poorly controlled allergic asthmatics is associated with improved asthma control and fewer exacerbations.[182] Omalizumab is generally well tolerated, but rare reports of anaphylaxis have been reported.[183] The importance of utilizing biomarkers to identify potential responders to omalizumab was highlighted by the EXTRA study, which demonstrated significantly decreased numbers of exacerbations in subjects with high FeNO, high serum eosinophils, and elevated serum

Table 62.4 Summary of FDA-Approved Biologics for Treatment of Moderate to Severe Asthma

Biologic Agent	MOA	Patient Selection	Dosing	Notes
Omalizumab (Xolair) FDA approved in 2003	Humanized IgG1 antibody that binds to the Cε3 domain of free IgE and prevents it from binding to FcεR1	▪ Age ≥6 years in the U.S. (≥12 years in the UK) ▪ IgE: 30-700 IU/mL ▪ Allergic sensitization by skin prick or specific IgE testing	75–375 mg SC per IU every 2-4 weeks based on age, weight and IgE levels	▪ Highest efficacy in T2-high patients ▪ Efficacy not based on IgE level or eosinophil count ▪ Data from real-world studies demonstrate efficacy when dosed outside accepted weight and IgE levels ▪ Indicated for *moderate to severe* allergic asthma
Mepolizumab (Nucala) FDA approved in 2015	Humanized IgG1 antibody that inhibits IL-5 from binding to the α-subunit of the IL-5 receptor complex on eosinophils	▪ ≥12 years ▪ Blood AEC of ≥150 cells/μL at the time of testing or ≥300 cells/μL in the previous year ▪ ≥300 cells/μL only in the UK	▪ 100 mg SC every 4 weeks ▪ 300 mg SC every 4 weeks for EGPA	▪ Approved for home administration via the auto injector ▪ In clinic dosing using the lyophilized powder ▪ Only biologic currently approved for EGPA ▪ Demonstrated OCS-sparing effects ▪ Indicated for severe eosinophilic asthma
Reslizumab (Cinqair) FDA approved in 2016	Humanized IgG4 antibody that inhibits IL-5 from binding to the α-subunit of the IL-5 receptor complex expressed on eosinophils	▪ Age ≥18 years ▪ Blood AEC ≥400 cells/μL in the previous year	3 mg/kg IV infusion every 4 weeks	▪ Response is better with higher eosinophil counts ▪ No data on OCS-sparing effects; SC OCS dosing study was negative ▪ Indicated for severe eosinophilic asthma
Benralizumab (Fasenra) FDA approved in 2017	Humanized recombinant IgG1 antibody that binds with high affinity to the α-subunit of the IL-5 receptor	▪ Age ≥12 years ▪ Blood AEC ≥300 cells/μL in the previous year	30 mg SC every 4 weeks for the first 3 doses then every 8 weeks	▪ Available for prefilled auto injector ▪ Results in total depletion of eosinophils ▪ Demonstrated OCS-sparing effects ▪ Indicated for severe eosinophilic asthma
Dupilumab (Dupixent) FDA approved in 2018	Fully human monoclonal antibody to the α-unit of IL-4 receptor; blocks IL-4 and IL-13	▪ Age ≥12 years ▪ Moderate to severe asthma ▪ Blood AEC ≥300 cells/μL in the previous year ▪ FeNO >25 ppb	▪ 200 mg or 300 mg SC every 2 weeks after initial loading dose. No loading dose required for nasal polyps ▪ 200 mg for moderate to severe persistent asthma, 300 mg for atopic dermatitis, nasal polyps and oral steroid-dependent asthma	▪ Home administration only ▪ Antidrug antibody in 2–5% patients ▪ Indicated for nasal polyps, atopic dermatitis, and asthma (*moderate to severe* persistent eosinophilic asthma or oral steroid–dependent asthma regardless of T2 markers) ▪ Demonstrated OCS-sparing effects ▪ Exercise caution in patients with baseline eosinophils >1500 cells/μL due to transient elevation of eosinophils for 4 months post initiation of therapy

AEC, absolute eosinophil count; OCS, oral corticosteroid; EGPA, eosinophilic granulomatosis with polyangiitis; FDA, Food and Drug Administration; FeNO, fraction of exhaled nitric oxide; Ig, immunoglobulin; IL, interleukin; IU, international units; IV, intravenous; SC, subcutaneous.

periostin compared with subjects with low biomarker levels.[184] Interestingly, the recently published PROSPERO real-world study demonstrated that peripheral eosinophils and FeNO levels at baseline had variable impacts on asthma outcomes. For instance, high eosinophils and FeNO had no impact on the response to omalizumab with regard to exacerbations and hospitalizations but were associated with more significant improvements in FEV_1 and mean change in Asthma Control Test scores from baseline.[185] Furthermore, this study demonstrated that patients outside the approved dosing tables on the basis of either IgE level or weight had similar improvements in Asthma Control Test scores to those dosed within the recommended levels, further supporting the assertion that baseline IgE level is a poor

predictor of clinical response to omalizumab and should be interpreted with caution. In addition, it is imperative to note that IgE levels should not be used in isolation. Clinicians must identify evidence of allergic sensitization using specific IgE measurements or skin prick testing to identify individuals most likely to respond to omalizumab therapy. In addition, clinical evidence of allergic disease is necessary, and a history of allergic rhinitis, seasonal variability in exacerbations, allergic conjunctivitis, eczema, and urticaria should be sought to understand the impact of allergic disease on the patient's asthma.

Interleukin-5 Targeted Therapies. There are currently two anti–IL-5 antibodies (mepolizumab and reslizumab) and one anti–IL-5 receptor antibody (benralizumab) approved for use in the United States. Mepolizumab, a humanized monoclonal antibody to IL-5 approved by the FDA in 2015, has demonstrated efficacy in reducing exacerbations in patients with severe asthma and is dosed as a once-monthly subcutaneous injection.[186,187] The anti–IL-5 antibody significantly decreases eosinophil differentiation, maturation, and migration.[188] Mepolizumab significantly decreases exacerbations[189] and oral corticosteroid dose in oral corticosteroid–dependent asthma.[189] Mepolizumab results in modest improvements in FEV_1, asthma control, and quality of life.[189] In long-term safety studies, continued use of mepolizumab persistently reduces exacerbations.[190] No significant safety issues have been identified.[191] The safety profile of the medication led to its approval for home dosing via an auto-injector device by the FDA in 2019. Mepolizumab is indicated as add-on maintenance therapy for patients older than 12 years with severe eosinophilic asthma. In clinical trials, patients were required to demonstrate eosinophils greater than 150 cells/μL at baseline or greater than 300 cells/μL within the past year. Adverse reactions including hypersensitivity may be seen within hours of administration of the medication but are rare overall. There is a warning regarding herpes zoster infection based on the presence of two cases of zoster in the registration trials. It remains unclear if this was associated with the medication. Vaccination for zoster is recommended if possible prior to initiation of therapy.

Reslizumab was approved by the FDA in 2016 for use in asthma. It is a humanized IgG4 antibody that inhibits IL-5 from binding the α-subunit of the IL-5 receptor complex expressed on eosinophils. Reslizumab improves FEV_1, asthma control, quality of life, and exacerbation rates.[192] Patients with high blood eosinophils and frequent exacerbations had the greatest benefit in terms of exacerbation reduction and improvement in FEV_1.[193,194] Reslizumab is indicated as add-on maintenance therapy for patients with severe eosinophilic asthma; the clinical trials required peripheral eosinophils 400 cells/μL or greater. Reslizumab is administered at a dose of 3 mg/kg by intravenous infusion over 20 to 50 minutes every 4 weeks. Hypersensitivity reactions including anaphylaxis are rare and, in general, reslizumab is well tolerated. Long-term efficacy was demonstrated in an open-label study.[195]

Benralizumab was approved by the FDA in 2017 and is a humanized recombinant IgG1 antibody that has high affinity binding to the α-subunit of the IL-5 receptor, resulting in inhibition of proliferation and activation of eosinophils. Benralizumab also mediates apoptosis of eosinophils, leading to peripheral eosinopenia.[196] In Phase III trials, benralizumab demonstrated a significant reduction in exacerbation rates and improvements in FEV_1 similar with every 4-week and every 8-week dosing.[197,198] In addition, benralizumab resulted in a significant reduction in oral steroid dose while maintaining a concomitant reduction in exacerbations in patients with oral steroid–dependent asthma.[199] Benralizumab is indicated as add-on maintenance therapy for patients with severe eosinophilic asthma, and the best results were noted in those with eosinophil counts greater than 300 cells/μL. It is administered subcutaneously at 30 mg once a month for 3 months (loading phase) and then every 2 months thereafter. Adverse reactions include a low rate of hypersensitivity reactions (3%), which is slightly higher than those reported with mepolizumab and reslizumab. Benralizumab results in total depletion of eosinophils in the airway, blood, and bone marrow.[200] Long-term safety concerns of total depletion of eosinophils remain, but thus far no significant issues have been identified.[201] Post hoc analysis identified clinical markers that predict a more robust response to benralizumab including adult-onset asthma, decreased FVC, presence of nasal polyps, and oral steroid–dependent disease.[202]

IL-4 Targeted Therapies. Dupilumab is a fully human monoclonal IgG4 antibody to the α-subunit of the IL-4 receptor. The IL-4 receptor binds both IL-4 and IL-13, two key cytokines produced by T cells and by type 2 innate lymphoid cells, and results in downstream up-regulation of IgE production (mediated by IL-4) and mucus hypersecretion and AHR (mediated by IL-13). Dupilumab was approved by the FDA in 2018 and is indicated for atopic dermatitis, moderate to severe persistent eosinophilic asthma, oral steroid–dependent asthma, and chronic rhinosinusitis with nasal polyposis. Dupilumab resulted in a significant reduction in exacerbations, particularly in patients with an elevated FeNO and/or elevated blood eosinophil count (>300 cells/μL).[203] In oral steroid–dependent asthma, patients responded to dupilumab regardless of eosinophil count or FeNO level with improvements in FEV_1 and a reduction in oral steroid dose.[204] It is approved for home dosing exclusively and is available in two formulations in a prefilled syringe (200 mg and 300 mg) for administration subcutaneously every 2 weeks. The higher doses were studied in atopic dermatitis, nasal polyposis, and oral steroid–dependent asthma. In asthma, dupilumab is approved for patients older than 12 years. Patients with asthma receive a loading dose (2 injections of the formulation prescribed) followed by every-2-week dosing. Dupilumab results in transient elevations in peripheral eosinophils over the initial 4 months of therapy; therefore caution must be exercised in prescribing the drug to patients with peripheral eosinophil counts greater than 1500 cells/μL. Hypersensitivity reactions are rare. Local skin reactions are seen more frequently in those receiving the higher dose of medication, although these are not common.

Biologic Therapy: Patient Selection, Response, and Switching. The increased availability of biologic therapies for asthma has led to the need for a paradigm shift in the manner in which clinicians manage severe asthma. Clinical decision making surrounding which therapy to initiate first, how to monitor patients for response, how to define response, and whether or not to switch therapies has become increasingly

complex and warrants a systematic approach. GINA guidelines now include a pocket guide for the management of severe asthma that aims to address these challenges by providing algorithms that clinicians can follow while managing patients with severe asthma. Biologics should be considered early in the course of therapy for patients with severe asthma who are adherent to conventional inhaled therapies but continue to have poorly controlled disease. Poor control can be recognized by at least one of the following: frequent exacerbations, decreased lung function, poor quality of life and, in the most extreme cases, dependence on oral corticosteroids. A suggested algorithm for when to consider initiating a biologic agent is shown in Figure 62.4.

The selection of initial biologic therapies should be based on the clinical features and baseline biomarkers. For instance, allergic sensitization and the presence of uncontrolled allergic asthma may prompt initiation of anti-IgE targeted therapies. Comorbid conditions such as nasal polyps, atopic dermatitis, and idiopathic urticaria that require concomitant therapy will likely alter the initial therapy selected. Concomitant eosinophilic diseases such as eosinophilic granulomatosis with polyangiitis, hypereosinophilic syndrome, and other eosinophilic disorders should be considered as well. Baseline biomarkers are important for making therapeutic decisions, but the limitations of these biomarkers should always be taken into consideration. Peripheral eosinophils are highly variable and affected by steroid therapy; therefore, caution should be exercised with interpretation of single values, and the clinical context must be taken into consideration. Repeating biomarkers is recommended in the current GINA guidelines.[8] FeNO and eosinophils may be less reliable in obese patients.[205,206] The majority of severe asthma patients will have overlapping T2 biomarkers, making the clinical characteristics and comorbid conditions associated with each individual's asthma more important in selecting a biologic therapy. Shared decision making regarding the biologic to initiate is essential in severe asthma, particularly given the prevalence of many different dosing schedules, drug delivery mechanisms, and the options for home dosing (with two of the available biologics). Patient preference is key because all the biologics appear to have similar safety and efficacy profiles overall. Biologics are costly medications and a commitment to adhere to therapy is essential, particularly when embarking on home-dosing regimens. We propose the algorithm shown in Figure 62.5 for initiating T2 biologic therapy based on biomarkers and clinical characteristics.

It is imperative to determine which markers of response will be monitored in advance of initiation of biologic therapies and to allow a sufficient amount of time to assess response. The responses in the following domains should be measured and recorded consistently to allow for consideration when switching between available therapies. Biologic therapies can improve some or all of these outcomes in patients. The degree to which one responds in each of these areas can be used to identify partial as well as complete response to therapy.

1. Exacerbation reduction by a factor of between 30% and 50% compared to baseline.
2. Oral corticosteroid use reduction. Remember that not all biologics have been shown to reduce oral corticosteroid dose.

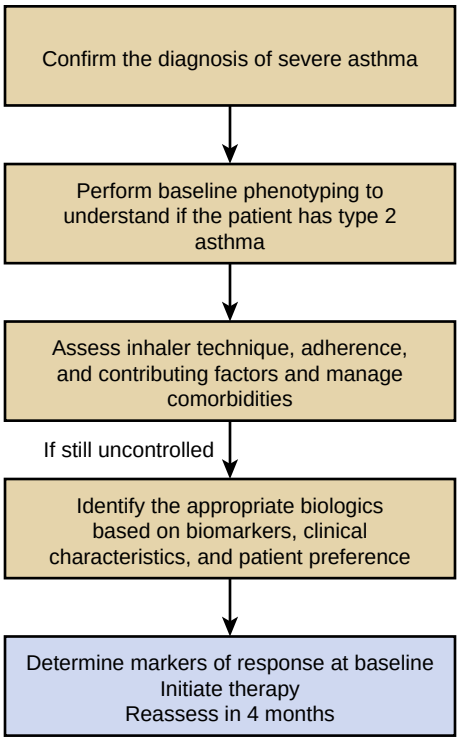

Fig. 62.4 Recommended process toward initiating biologic therapy. A diagnosis of severe asthma should be confirmed using objective measures of lung function, and evidence for type 2 asthma should be assessed. Before initiating biologic therapy, evaluate for comorbid conditions, alternative diagnoses, and poor inhaler technique or adherence. Measurement of type 2 biomarkers will help select initial therapy. Reassess for clinical response in 4 months.

3. Asthma control improvement. The Asthma Control Questionnaire or Asthma Control Test should be measured consistently. Improvements are often modest and usually at the minimally clinically important level.
4. Lung function improvement. Not all patients experience increases in FEV_1 and improvements are often delayed, with a change of between 120 to 300 mL in general.
5. Rescue bronchodilator use reduction.
6. Adequate safety and tolerability.
7. A positive overall impression of the patient regarding response to therapy and satisfaction with the changes. It is important to identify what the patient's expectations are up front and to follow the response with regard to patient expectations.

Response can be identified in three ways. A small proportion of patients, the complete responders, experience a remarkable response to biologics with complete amelioration of all the factors described above. Most patients, the partial responders, experience meaningful improvements in some, but not all, the parameters. About 10–15% of patients, the nonresponders, show no response despite careful patient selection and an expectation that response should be more robust. In these patients, attention should be paid to compliance with background therapy, optimization of comorbid conditions, and adherence to biologics. Alternative diagnoses and contributing factors should also be considered. These patients likely have multiple inflammatory pathways causing asthma symptoms and will benefit from either switching to other biologic therapies or, in

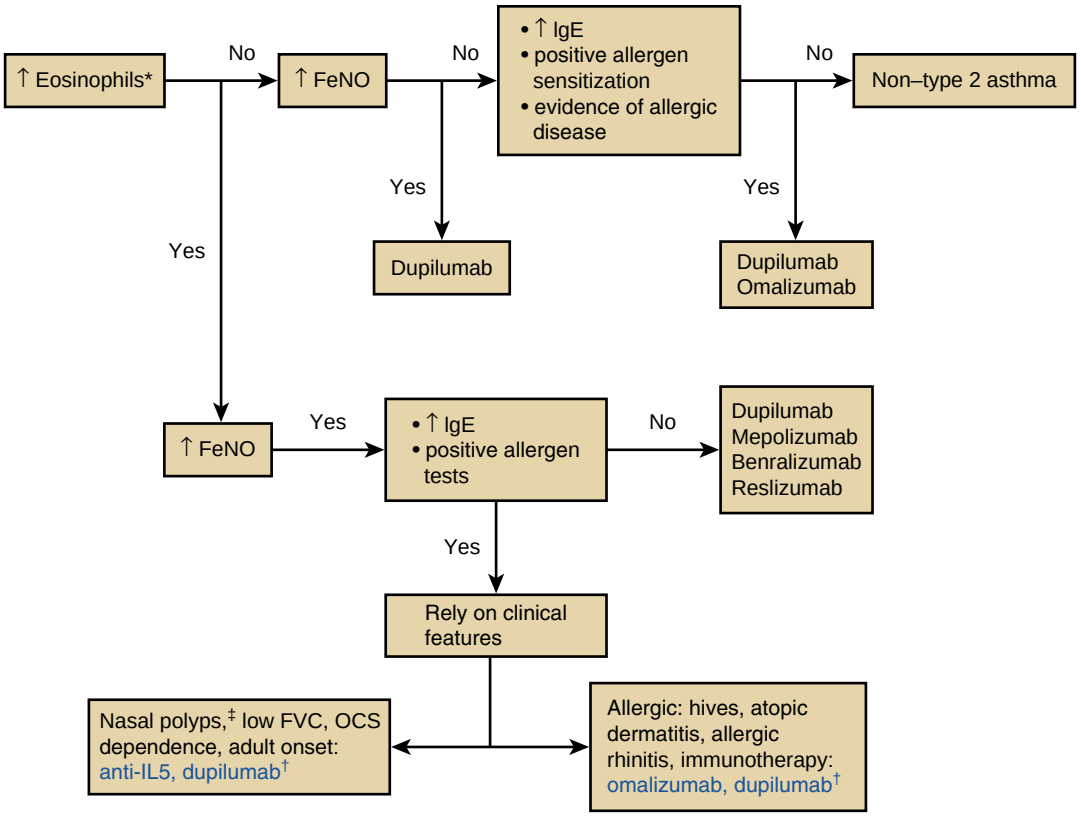

Fig. 62.5 Decision tree for selecting initial biologic therapy for severe asthma in patients with type 2 features. This algorithm is guided by high-quality evidence from clinical trials and supporting data. Medications are listed alphabetically, not in order of preference. Patients should have regular assessment of clinical benefit, and treatment should be adjusted until asthma control is achieved. *Increased eosinophils is defined by blood eosinophil counts >150–300/μL. Dupilumab should not be used for patients with >1500 eosinophils/μL. †At the time of publication, dupilumab is also FDA approved for use in nasal polyps and atopic dermatitis. Omalizumab is also FDA approved for use in chronic urticaria. ‡Nasal polyps predict an enhanced response to these T2 biologics when targeting asthma. The efficacy of each biologic for nasal polyps may differ. FDA, U.S. Food and Drug Administration; FeNO, fraction of exhaled nitric oxide; FVC, forced vital capacity; IgE, immunoglobulin E; OCS, oral corticosteroid.

rare instances, to dual therapies. Recommended management algorithms on the basis of response to biologic therapy are depicted in Figure 62.6.

Bronchial Thermoplasty

One alternative nonpharmacologic treatment goal for asthma is the mechanical reduction of airway smooth muscle mass to improve physiologic function. Bronchial thermoplasty is the application of controlled thermal energy via a radiofrequency catheter to reduce smooth muscle mass. In a clinical trial of thermoplasty or sham thermoplasty in patients with moderately severe asthma, thermoplasty reduced airway responsiveness to an inhaled constrictor, improved lung function, and improved asthma symptoms and quality of life; however, concurrent improvements were also seen in those receiving the sham procedure.[207,208] In addition, treatment requires a series of three bronchoscopies, exposing patients to the concomitant procedural risk, and requires providers have advanced procedural training. Long-term 5-year data demonstrate sustained improvements in asthma control, reduced exacerbations, decreased medication use, and a lack of evidence of long-term adverse effects.[209] Despite this, in 2014, the ERS/ATS severe asthma guidelines recommended against the widespread use of bronchial thermoplasty and suggested that this procedure should be recommended only in the context of a clinical trial or in a large academic center coupled with a registry aimed at identifying predictors of response.[84] As for other expensive asthma therapies, it is imperative to identify responders and target this therapy to those who are most likely to benefit from the procedure.

ADDITIONAL MANAGEMENT STRATEGIES

Medication Adjustment Based on Asthma Control

All patients should be reassessed for control regardless of the therapy. Recent studies support the importance of focusing on asthma control as a means of reducing exacerbations and morbidity.[210] Depending on the extent of control, a more or less aggressive approach to symptom management may be necessary, such as dose adjustment or use of alternative medication class. Published guidelines provide a framework for medication choices when "stepping up" therapy to improve asthma control and "stepping down" therapy when control has been achieved (see Fig. 62.3).

Uncontrolled asthma is defined by the International ERS/ATS Guidelines for Severe Asthma[84] as presence of any of the following four criteria:

1. Poor symptom control, defined as an Asthma Control Questionnaire score consistently 1.5 or greater or Asthma Control Test score of 19 or less (or "not well controlled" by National Asthma Education and Prevention Program or GINA guidelines over the 3 months of evaluation)

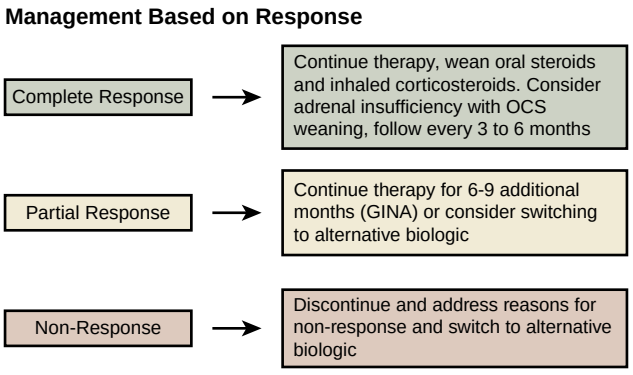

Fig. 62.6 Assessing response to biologic therapy. Before initiating biologic therapy, choose markers of response that will be monitored (e.g., exacerbations, oral corticosteroid use, asthma control, lung function, rescue bronchodilator use, patient comfort, and satisfaction). Most patients will experience at least a partial response to biologic therapy, 10–15% will have no response, and a small proportion will have a complete response. Assess response continuously and adjust asthma medications and/or biologics based on response. GINA, Global Initiative for Asthma; OCS, oral corticosteroids.

2. Frequent severe exacerbations, defined as two or more bursts of systemic corticosteroids (≥3 days each) in the previous year
3. Serious exacerbations, defined as at least one hospitalization, intensive care unit stay, or mechanical ventilation in the previous year
4. Airflow limitation, defined as FEV_1 less than 80% predicted (in the presence of reduced FEV_1/ FVC defined as less than the lower limit of normal) following a withhold of both short- and long-acting bronchodilators

For patients with mild, intermittent asthma, with symptoms that return to baseline between episodes, as-needed use of a short-acting bronchodilator is usually sufficient to achieve relief of symptoms and is recommended per EPR guidelines. In contrast, in the most recent GINA guidelines, SABA-only treatment (without ICSs) is not recommended, even for patients with mild intermittent asthma. Because even patients with mild asthma show chronic airway inflammation, GINA guidelines suggest that all patients with mild asthma should receive a low-dose inhaled steroid, for use either as needed with SABA or in combination with a LABA (as budesonide/formoterol), or daily, to prevent risk of exacerbations. For all patients with persistent asthma (symptoms >2 times/week, nocturnal symptoms, or symptoms that affect activity), the addition of a controller medication is necessary and an ICS is the initial agent of choice.[133,211,212] As mentioned previously, when used properly, ICSs can ameliorate all asthma symptoms, improve airway physiology, and reduce hospitalizations and asthma mortality. Failure to respond to an ICS suggests either nonadherence to medications, uncontrolled trigger exposures and/or comorbidities, or a steroid-nonresponsive phenotype. Approximately 30–50% of asthmatics fall into the latter category and demonstrate noneosinophilic inflammation and associated decreased response to conventional asthma therapy with ICSs,[83,139] unlike patients with eosinophilic inflammation who demonstrate significant response to a low dose of ICS.[213,214] LTMs are an alternative for patients who do not tolerate or respond to ICS and may provide additional symptom relief for patients with concomitant allergic rhinitis.[157,158]

Guidelines offer several different options for stepping up therapy. Some guidelines recommend the addition of a LABA to low-dose ICS (usually in a combination inhaler) based on a large amount of efficacy data.[108,215–217] Increasing the ICS dose is an alternative approach, and the preferred approach for pediatric patients. Recommendations regarding up-titration of inhaled steroids have typically focused on doubling the dose of ICSs in patients not well controlled on a low-dose ICS. However, there is increased recognition that doubling the dose is not consistently efficacious at improving asthma control or lung function measurements.[218] Furthermore, glucocorticoid resistance has been described in obese asthmatics.[219-221]

Once symptoms are controlled for a protracted period of time, therapy can be stepped down. Strategies for de-escalation of therapy are determined by a patient's controller regimen but may also be influenced by patient-specific factors. Patients on an ICS alone can be considered for a decrease in dose or dosing interval. Some data suggest that conversion to as-needed combined ICS/SABA may be effective with a lower total steroid dose.[144,222] However, an as-needed regimen is not yet part of NHLBI-EPR guidelines; it is, however, recommended by GINA. For patients on a combined ICS/LABA or ICS/LTM regimen, clinicians may focus first on reducing the ICS component for patients with steroid phobia or for whom steroid side effects are noted; alternatively, withdrawal of the nonsteroid agent may be appropriate for patients with high exhaled NO levels.[8] During down-titration of medications, care should be taken that patients not transition to LABA monotherapy, which is associated with worse outcomes.[108]

Difficult-to-Treat and Severe Asthma

Patients whose asthma symptoms are not controlled despite use of high-dose ICS and additional controller therapy (LABA or long-acting muscarinic antagonist), or whose symptoms require high-dose ICS to maintain control, are considered to have difficult-to-treat asthma.[8] Chronic use of systemic corticosteroids to control asthma is included in this definition. For many of these patients, modification of factors such as exposure to triggers, comorbid conditions (Table 62.5), incorrect inhaler technique, medication nonadherence, and adverse environmental exposures (tobacco smoke, particulates) may help to gain control of asthma and reduce medication requirements. Alternative diagnoses should also be considered, including bronchiectasis, COPD, vocal cord dysfunction, cardiac conditions, vasculitis, bronchomalacia, and lung masses. Those for whom asthma remains difficult to treat despite adequate control of these modifiable factors are considered to have *severe asthma*.[223]

Control of Triggers

Because treatment of comorbidities often improves the control of asthma, all difficult-to-treat patients with asthma should be evaluated for these underlying conditions.[224–229] Environmental factors and individual comorbid conditions have been shown to contribute to the pathogenesis and manifestations of asthma at all levels of severity

Table 62.5 Factors That Contribute to Worsening Asthma Control and Coexisting Conditions

Contributing Factor	Proposed Intervention
Tobacco use	Encourage tobacco cessation and assist with both nonpharmacologic and pharmacologic methods to help patients quit smoking; discuss avoidance of secondhand smoke
GERD	Consider empiric therapy for symptomatic GERD Barium swallow or pH probe study to diagnose GERD Impedance study if nonacid reflux is suspected Referral to gastroenterology for evaluation and treatment Consider surgical management for refractory cases
Atopy and allergic rhinitis	Consider empiric therapy with nasal steroids, nasal and oral antihistamines, leukotriene antagonists Consider skin prick testing or specific IgE testing to guide allergen identification and avoidance Referral to allergist or otolaryngologist for evaluation Consider allergen immunotherapy
Nasal polyps and chronic sinusitis	Refer to otolaryngologist for evaluation and treatment Possible surgical intervention for refractory cases Consider aspirin desensitization for patients with nasal polyps and aspirin sensitivity
Vocal cord dysfunction*	Laryngoscopy to diagnose vocal cord dysfunction Referral to speech pathologist for evaluation and treatment
Obesity*	Encourage weight loss Consider bariatric surgery
Obstructive sleep apnea*	Referral for sleep study and initiate therapy for sleep apnea Referral to sleep specialist for complex cases
Psychological factors*	Evaluate for anxiety and depression

*May coexist with asthma with overlapping symptoms (see also Chapter 61).
GERD, gastroesophageal reflux disease; Ig, immunoglobulin.

and therefore should be addressed as appropriate for each patient (Table 62.5). Cigarette smoking decreases asthma control and reduces the efficacy of corticosteroids.[230] All patients with asthma who smoke cigarettes should be strongly encouraged to quit.[231] Exposure to secondhand smoke should be avoided. Obesity complicates asthma through multiple mechanisms including reducing steroid efficacy and compounding symptoms and is reviewed thoroughly in Chapter 61.

Reduction of allergen exposure and provision of allergen-specific subcutaneous immunotherapy are common strategies for treating asthma. Allergic asthmatics benefit from allergen avoidance, but environmental control in the home or workplace is often difficult to achieve.[232] The most common allergens triggering asthma include molds, dust mites, and cat dander. Although overall data are mixed, several studies have shown clinical benefits from dust mite control measures (e.g., impermeable mattress covers, frequent vacuuming, cockroach control).[233–235] For patients with an allergic asthma phenotype, allergen-specific subcutaneous immunotherapy may reduce asthma symptoms and improve bronchial hyperreactivity.[236,237] However, subcutaneous immunotherapy must take place under careful conditions owing to the risk of anaphylaxis, and the optimal duration of treatment is not completely clear. As an alternative, sublingual immunotherapy specific for dust mite allergen showed potential for reducing asthma exacerbations, is well tolerated, and is commercially available.[238]

Assessment and Management of Concomitant Diagnoses

Vocal Cord Dysfunction. *Vocal cord dysfunction* (VCD), also referred to as paroxysmal vocal fold motion, was first described as a separate clinical entity in 1983 and is one of the great mimics of asthma (see also Chapter 70). VCD presents more often in women than in men and is more common in persons 20 to 40 years old.[239,240] It is characterized by intermittent abnormal paradoxical adduction of the true vocal cords during breathing. Patients with VCD often experience shortness of breath, neck/chest tightness, stridor, wheezing, hoarseness, frequent throat clearing, and cough. VCD patients can have normal head and neck and lung examinations or abnormal examinations with upper airway noise or stridor. Although many causes of VCD have been identified, most patients experience one of three subtypes: psychogenic VCD, exercise-induced VCD, or irritant-associated VCD.

Psychogenic VCD is most often identified in those previously diagnosed with a psychiatric illness such as depression, anxiety, or factitious or somatoform disorder.[241] For these patients, the vocal cords are their "stress organ" and learning how to manage stress is key to treating their disease. Exercise-induced VCD is often described as episodic dyspnea or shortness of breath that manifests within the first 5 minutes of exercise and resolves abruptly. These patients are frequently misdiagnosed with exercise-induced bronchospasm but fail to respond to bronchodilator therapy or steroids.[242] Irritant-associated VCD is linked to chronic irritation of the throat resulting in vocal cord hypersensitivity. The irritants are categorized as either intrinsic (gastroesophageal reflux, laryngopharyngeal reflux, allergic rhinitis) or extrinsic (chemical or sensory irritants).

The diagnosis of VCD can be challenging because symptoms are frequently intermittent, and patients need to be symptomatic during testing. Difficulty in making the diagnosis is further complicated by the fact that up to 75% of asthmatics have coexistent VCD.[239,243] Pulmonary function studies can reveal normal spirometry (without bronchodilator responsiveness) or an abnormal truncated inspiratory flow volume loop. Methacholine challenge has been used as a provocative measure to recreate symptoms and induce paradoxical closure of the vocal cords. Flow volume loops before and after methacholine challenge in patients with VCD often demonstrate flattening of the inspiratory curve after methacholine challenge.[244] Flexible laryngoscopy and videolaryngostroboscopy are the gold standards for diagnosing VCD. Direct visualization of the cords classically demonstrates abnormal adduction of the anterior two-thirds of the true vocal cords with inspiration and "chinking" of the posterior cords; the chink describes the small triangular opening that remains patent at the

posterior segment of the vocal cords.[245] The vocal cords can be seen in adduction during inspiration or during both inspiration and expiration.

Beyond treating the underlying disorder (gastroesophageal reflux disease, rhinitis, and depression), there is no specific medication that treats VCD. Acute severe VCD, manifesting as laryngospasm, can be managed with heliox to reduce airway resistance rapidly[246] or with anxiolytics. Long term, patients are often referred to speech therapy for initiation of relaxed throat breathing exercises and diaphragmatic breathing exercises. Although these exercises have been reported to be effective in case reports, randomized clinical trials to validate effectiveness are needed.

MANAGEMENT OF ACUTE ASTHMA

Asthma is a common cause of emergency department visits and hospital admissions. The treatment of acute asthma is based on the cornerstones of chronic asthma therapy but typically requires greater attention to patient monitoring and an escalation in the aggressiveness of asthma care.

Asthma exacerbations are characterized by increased shortness of breath, coughing, and/or chest tightness, and airflow limitation (as measured by decreased peak flow or FEV_1). Increased symptoms typically precede a detectable decrease in airflow,[247,248] although a subset of patients is at high risk of exacerbations due to poor perception of airflow limitation. In the outpatient setting, an increased requirement for rescue inhalers, especially in a patient previously on a stable regimen, suggests an asthma exacerbation. There is increased recognition that the pathophysiologic mechanisms underlying asthma exacerbations are as heterogenous as the underlying disease itself. Although we currently treat all exacerbations similarly, some data suggest that targeted therapies for asthma exacerbations and the management of triggers may be warranted and have the potential to reduce the morbidity associated with our current therapies.[249] Exacerbations have a significant impact on asthma morbidity and mortality, and therefore it is imperative to decrease the rate of asthma exacerbations whenever possible.[250] Research studies focused on asthma exacerbations have used a variety of definitions, which makes it particularly challenging to compare studies. Given the recognition that standardization was needed, the NIH convened a task force that defined an exacerbation as "a worsening of asthma requiring the use of systemic corticosteroids (or for patients on a stable maintenance dose, an increase in the use of systemic corticosteroids) to prevent a serious outcome."[251] Exacerbations are caused by a variety of triggers, including infection, environmental exposures, and allergens, as well as nonadherence with prescribed asthma medications.

Patients with asthma exacerbations require prompt evaluation and treatment to limit morbidity and mortality. Goals include relief of airflow obstruction and amelioration of respiratory symptoms. Patients with milder symptoms (with peak flow decrease by <20%) may be evaluated in an outpatient setting but should be referred to an acute care facility if they fail to respond promptly to aggressive treatment with bronchodilators and systemic glucocorticoids.[1] Conversely, certain patients are at high risk of asthma-related death and should be evaluated in the emergency department as soon as possible when their symptoms worsen. This includes patients with a history of recent exacerbation or previous near-fatal asthma, overutilization of SABAs or underutilization of ICS, recent oral glucocorticoid use, poor compliance with asthma action plans, or concomitant psychiatric disease.[247]

In the acute care setting, the severity of an asthma exacerbation should be assessed by physical examination, oximetry, and measurement of PEF. Use of accessory muscles, ability to complete sentences, and arterial oxygen saturation should all be evaluated. Patients require close monitoring during the early stages of treatment because it may take several hours for symptoms to resolve. Chest radiography is useful if pneumothorax is suspected but does not usually provide clues as to the etiology of an exacerbation. Arterial blood gas measurement typically reflects mild hypoxemia and respiratory alkalosis; the normalization of arterial P_{CO_2} in the absence of significant symptomatic improvement suggests impending respiratory failure. pH and P_{CO_2} on venous blood gases can also be used to monitor asthma in the critically ill[252,253]; anion gap metabolic acidosis may also be present, which is usually due to elevated lactate levels. Patients who fail to respond to albuterol administration within 30 to 60 minutes, with persistent dyspnea and peak flow less than 70% of baseline, require hospital admission.[1]

Key pharmacologic components of treatment include repeated or continuous short-acting bronchodilator administration (via nebulizer or metered-dose inhaler with a spacer) and systemic glucocorticoids.[254,255] The combination of SABAs and ipratropium at the initiation of treatment is associated with physiologic improvements and a reduced rate of hospitalization, but the benefits do not persist after hospitalization.[256] Systemic corticosteroids are unequivocally associated with a more rapid return to baseline function and are considered the first-line therapy for acute asthma exacerbations. More importantly, the early administration of steroids is important in reducing the need for hospitalization and improving asthma symptoms.[257,258] The initial dosing range for adult patients is from 1.5 to 2 mg/kg of intravenous methylprednisolone or the equivalent.[259] Oral steroids have been shown to have similar efficacy to intravenous preparations in the treatment of acute asthma exacerbations and therefore are an acceptable alternative in patients without life-threatening asthma.[260] ICSs are typically not used acutely, although data suggest that the addition of inhaled budesonide to systemic corticosteroids following an emergency department visit leads to improved symptoms and a decreased relapse rate.[261–263] Intravenous magnesium sulfate, usually given as a 2-g bolus or 40 mg/kg of body weight for children up to a maximal dose of 2 g, may act as a smooth muscle relaxant and has been shown to reduce hospital admission rates.[264] Supplemental oxygen to keep saturations above 90% helps maintain oxygen delivery to peripheral tissues and minimizes hypoxic pulmonary vasoconstriction.

Severe exacerbations of asthma are characterized by persistent reductions in PEF to less than 40% predicted with a poor response to initial treatment. These patients may demonstrate progressive hypercapnia, fatigue, altered sensorium, and dysrhythmias and are at high risk for respiratory arrest. Low-level noninvasive positive-pressure ventilation without positive end-expiratory pressure has been shown to reduce the rate of hospitalization and may be considered in alert, cooperative patients who are not in immediate need of intubation.[265] Heliox increases flow at the same pressure and may be a useful adjunct in patients with severe

exacerbations that do not respond to initial emergency treatment.[266–268] Inhaled volatile anesthetics, such as halothane and isoflurane, are potent bronchodilators and have also been used for decades to treat refractory asthma.[269]

Intubation and mechanical ventilation are mandatory for patients in respiratory arrest or impending respiratory arrest. Mechanical ventilation in patients with severe asthma exacerbations may be complicated by immediate postintubation worsening of gas exchange and hemodynamic instability due to increased airway and intrathoracic pressures from dynamic lung hyperinflation. Provided that the patient is adequately oxygenated, briefly decreasing the mandatory respiratory rate to allow an extended expiratory phase is often successful in reducing intrathoracic pressure. Initial ventilator settings should be focused on minimizing dynamic hyperinflation by using a relatively low minute ventilation (with respiratory rate between 12 and 14/min and tidal volumes in the 6 to 8 mL/kg range), a high inspiratory flow rate, and minimal to no positive end-expiratory pressure.[270] With these low settings of rate and volume, the arterial P_{CO_2} may rise; this strategy of "permissive hypercapnia" is a sensible approach to avoiding barotrauma in severely obstructed patients (see Chapter 132). Aggressive sedation should be given to improve comfort and patient-ventilator synchrony. Short-term paralysis may be necessary in patients for whom ventilator synchrony cannot be achieved with sedation alone. Bronchodilator administration should be continued until airway resistance decreases.

CLINICIAN-PATIENT PARTNERSHIP

For chronic asthma, treatment should balance the best symptom control with the lowest possible dosage of medication.[1] Effective management requires that patients form a partnership with health care providers to ensure an appropriate flow of information, with the patients assuming a major role in the assessment and treatment of their disease. Through collaborative effort, a guided self-management plan can be developed, allowing patients to titrate their own treatment on the basis of changes in symptoms with some degree of independence. The use of such guided self-management reduces asthma morbidity in different patient populations and patient care settings.[271] Interestingly, patient-guided use of asthma medications based on symptoms was superior to physician and biomarker-based adjustments to asthma therapies as reported by the Asthma Clinical Research Network,[102] further highlighting the importance of actively involving patients in decisions regarding management of their asthma.

Crucial components of self-management plans include education, self-monitoring with symptoms and/or peak flow, regular review, and patient-directed self-management using a written action plan. Effective patient education is central to this approach. Better communication by health care providers translates into measurably better outcomes with no additional physician time commitment. Even for patients unable to engage in guided self-management, regular follow-up and medication review is beneficial because approximately 50% of patients on long-term therapy fail to take medications as directed at least some of the time.[272]

Key Points

- The approach to the diagnosis, assessment, and treatment of asthma has changed with the recognition that asthma is a heterogeneous disease encompassing many phenotypes with variable responses to therapy.
- Currently, the two main phenotypes appear to be *type 2* (T2)-high and T2-low asthma.
- T2-high asthma is characterized by increases in sputum and/or blood eosinophils and/or FeNO; in T2-low asthma, these biomarkers are not increased.
- Inhaled corticosteroids are the mainstay of asthma therapy; however, only 50% of patients have eosinophilic inflammation that predicts response to inhaled corticosteroids.
- Several biomarkers, including blood immunoglobulin E levels, blood eosinophils, and fraction of exhaled nitric oxide, can be used to diagnose mild to moderate asthma in patients and guide therapy toward biologics in patients with severe asthma.
- Multiple biologic therapies targeting T2 inflammatory pathways are available as add-on therapy for moderate to severe asthma.
- Assessment and management of asthma comorbidities, triggers, and medication nonadherence will help achieve asthma control, particularly for patients with moderate to severe asthma.
- Asthma education and collaboration between physicians and patients are essential in improving asthma-related outcomes.
- Future approaches to managing asthma will require better phenotyping of patients and better therapies for asthmatics with noneosinophilic inflammation.

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63 COPD: PATHOGENESIS AND NATURAL HISTORY

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Mechanisms of Oxidant Injury and Antioxidants
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Small Airway Remodeling and Matrix Damage
Proteases/Antiproteases
Innate Cellular Responses
Mediators of Inflammation and of its Resolution
Pulmonary Microvascular Changes Induced by Oxidant Injury
COPD as a Disease of Accelerated Aging
Adaptive Immune Inflammation and Autoimmunity
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Sex as a Factor in COPD Heterogeneity
AAT Deficiency
Preserved Ratio Impaired Spirometry
Progression and Mortality
KEY POINTS

INTRODUCTION

COPD is a heterogeneous and variably progressive spectrum of lung pathologies primarily induced by injury and repair following prolonged oxidative inhalational exposures.[1,2] Most COPD in high-income nations results from direct *cigarette smoke* (*CS*) exposure but, worldwide, indoor and outdoor air pollution may be equally or more common risks.[3] COPD is highly prevalent. In many countries, it is the only leading non-communicable cause of death increasing in frequency.[4,5] COPD develops with a long latency, can progress despite removal of inciting factors,[6] and is greatly underdiagnosed.[7,8] Only some exposed individuals develop COPD, which is not explained solely by their premature death from other smoking-related diseases. The biologic basis for this restricted susceptibility is incompletely understood, but genetic predispositions are increasingly being identified.

The diagnosis of COPD currently requires incompletely reversible airflow obstruction (i.e., reduced expiratory airflow) during forced exhalation, as assessed by postbronchodilator spirometry.[9,10] In individual COPD patients, reduced maximum expiratory flow results from varying degrees of increased resistance in conducting airways and increased lung compliance from loss of lung elastic recoil. Both diagnosing COPD and classifying its severity currently depend on measuring *forced expiratory volume in one second* (FEV_1) and its ratio to *forced vital capacity* (FVC). Whether an abnormal FEV_1/FVC ratio, which defines airflow obstruction, should be based on a fixed ratio of 0.7 versus age-specific lower limits of normal remains controversial.[11] COPD was formerly attributed solely to accelerated loss of lung function relative to normal aging.[12] However, defective lung growth before adulthood, even without subsequent accelerated decline, was recently identified as an alternative pathway to COPD[13,14] (Fig. 63.1).

The validity of defining COPD by spirometry alone has been questioned based in part on results of two ongoing observational cohort studies, the *Genetic Epidemiology of COPD* (COPDGene)[15] and the *Subpopulations and Intermediate Outcomes in COPD Study* (SPIROMICS).[16] Both studies showed that some symptomatic ever smokers not meeting spirometric criteria used to diagnose COPD nevertheless exhibit characteristics of established COPD, including having acute respiratory events.[17,18] The Subpopulations and Intermediate Outcomes in COPD Study found that ever smokers with normal FEV_1 but FEV_1/FVC between 0.70 and the lower limits of normal had radiographic evidence of smoking-induced lung damage.[19] COPD also has significant systemic components that contribute greatly to functional impairment.[20] Collectively, these findings and those of other recent studies[21–23] suggest that spirometric criteria incompletely capture the range of pathologies induced by inhalational oxidative stress. Despite a recent proposal for a new approach,[24] no alternative classification has as yet gained international acceptance.

PATHOLOGIC CHANGES IN ESTABLISHED COPD

Clinical COPD phenotypes are heterogeneous[25,26] because inhalational stressors induce four key pathologic processes: small airway disease, mucus hypersecretion, emphysema,

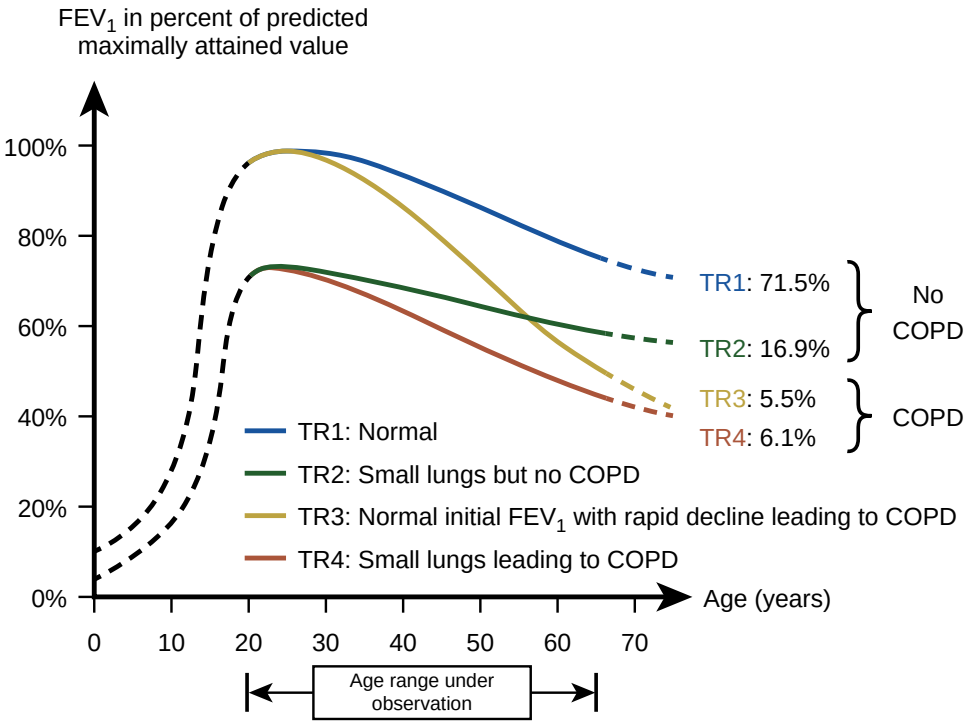

Figure 63.1 Both accelerated loss of lung function and defective lung growth contribute to development of COPD. Distributions (indicated as percentages) of participants of the Framingham Offspring Cohort and the Copenhagen City Heart Study (N = 2864) into the four *trajectories* (TRs) defined according to baseline level of *forced expiratory volume in 1 second* (FEV_1) (below or above 80% of predicted value) and presence or absence of Global Initiative for Obstructive Lung Diseases grade >2 COPD at each study's final examination. The *solid lines* represent the schematic natural history of FEV_1 for the age range of this study; the *dashed lines* represent hypothetical trajectories. TR3 represents the classic pathway to COPD, whereas TR4 represents an alternate pathway to COPD. (From Lange P, Celli B, Agusti A, et al. Lung-function trajectories leading to chronic obstructive pulmonary disease. *N Engl J Med.* 2015;373:111–122.)

and vascular dysfunction. Recent correlations between lung histology and novel imaging modalities have accelerated understanding of the relationships among these processes.

SMALL AIRWAY DISEASE

Small airways are defined as those with an internal diameter less than 2 mm. In health, they contribute minimally to airflow resistance.[27] Because even a 50% loss of small airways only doubles airflow resistance, they have been termed the lung's "quiet zone."[28] However, in COPD, small airways become the principle site of obstruction.[29–31] *Small airway disease* (SAD) results from remodeling, obstruction by mucus, and disappearance of terminal and transitional bronchioles, the last airways before the gas exchanging region of the lung. SAD is an early pathologic lesion in susceptible smokers who develop COPD.[32] By the time that FEV_1/FVC ratios are abnormal, small airway loss is already considerable.[33,34] SAD leads to air trapping and dynamic hyperinflation, which can limit exercise capacity even in spirometrically mild disease.[35]

SAD cannot be visualized directly by conventional *computed tomography* (CT) in living humans, but it can be inferred from air trapping on expiratory CT scans as functional SAD.[36] A refinement, termed *parametric response mapping* (PRM), uses dynamic image registration to quantify changes in voxel density between inspiration and expiration. The PRM technique[37] permits phenotyping of COPD patients by identifying both functional SAD and emphysema. This approach has been validated in severe COPD by comparison to histologic SAD detected by micro-CT analysis of inflated frozen lung sections.[38] Importantly, serial PRM analysis indicates that SAD precedes emphysema[39] (Figs. 63.2 and 63.3). In mild-to-moderate COPD, where one finds the greatest rates of spirometric decline, SAD contributes more than emphysema does to FEV_1 decline; in advanced COPD, each contributes.[40]

CHRONIC BRONCHITIS AND MUCUS HYPERSECRETION

Chronic bronchitis (CB) is a common COPD phenotype, but it can also exist without airflow obstruction. CB is significantly associated with many occupational exposures.[41] CB is most commonly defined clinically as chronic cough with sputum production for 3 months in 1 year for 2 consecutive years.[41] CB is associated histologically and radiographically with airway wall thickening.[42] Findings from three observational cohorts indicate that CB independently contributes to multiple adverse respiratory outcomes in ever smokers.[43,44] Interestingly, the National Heart Lung and Blood Institute Pooled Cohort study recently confirmed increased risk of attributable hospitalizations and death in both smokers and nonsmokers with nonobstructive CB, but only smokers lost lung function over time.[45]

CB is increasingly viewed as a manifestation of hypersecretion and altered physical properties of airway mucus.[46,47] The healthy airway surface liquid consists of an aqueous periciliary layer[48] and an upper mucus layer containing secreted mucins. Mucins are large glycoproteins characterized by repeated threonine-rich domains modified by a range of complex O-linked polysaccharides. Airways express two types of mucins: tethered mucins, including MUC1, MUC4, MUC13, MUC16, which contribute to maintaining hydration of the periciliary layer; and secreted mucins, products of the *MUC5AC* and *MUC5B* genes. Both large and small airways are now known to secrete MUC5B and lesser amounts of MUC5AC in the physiologic state.

Oxidative stress adversely impacts mucus clearance by altering both airway surface liquid components. It induces mucus hyperconcentration,[49] in part due to smoking-induced disruption of the cystic fibrosis transmembrane conductance regulator.[50,51] It also causes hypersecretion of

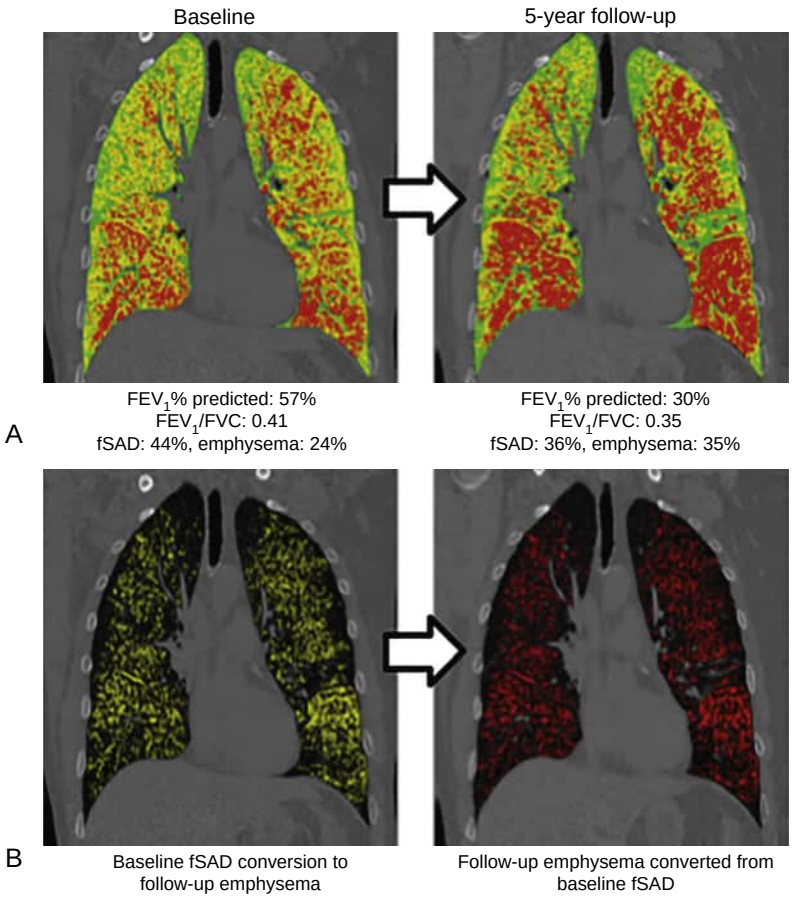

Figure 63.2 ***Small airway disease*** **(SAD) precedes emphysema in** ***parametric response mapping*** **(PRM) metrics in a representative male COPD patient.** Representative coronal computed tomographic sections of the same individual at baseline (*left*) and after 5-year follow-up (*right*). (A) All PRM metric values are depicted as normal lung parenchyma (*green*), functional small airway disease (fSAD; *yellow*) and emphysema (emph; *red*). (B) Only individual voxels classified as fSAD at baseline (*yellow*) that became emphysema 5 years later in this same subject (red) are shown. FEV_1, forced expiratory volume in 1 second; FVC, forced vital capacity. (From Labaki WW, Gu T, Murray S, et al. Voxel-wise longitudinal parametric response mapping analysis of chest computed tomography in smokers. *Acad Radiol.* 2019;26:217–223.)

MUC5AC, which has traditionally been considered to be the central abnormality in mucus clearance in COPD. However, in some patients, markedly decreased MUC5B may be more important.[52] By occluding terminal bronchi, mucus hypersecretion can contribute to SAD. However, not all COPD patients develop the symptomatic CB phenotype. Conversely, CB does not invariably lead to airflow obstruction,[53] although it appears to mark a group at increased risk.[54]

EMPHYSEMA

Emphysema is defined as permanent enlargement of airspaces distal to the terminal bronchioles due to alveolar wall destruction.[1] Three types of emphysema are recognized histologically and by CT: *centrilobular* (CLE), *panlobular* (PLE), and *paraseptal* (PSE) (see Fig. 20.24).[55] CLE (Fig. 63.4A and C) is common; among the three emphysema types, it is most closely associated with smoking history.[56] CLE is a frequent manifestation of spirometrically advanced COPD, but it can also be present with minimal or no airflow obstruction.[22] CLE begins with destruction of respiratory bronchioles within a single acinus and progresses by coalescence of such primary lesions.[57,58] Further progression can lead to confluent CLE, which extends across several secondary pulmonary lobules without generalized architectural distortion, and to advanced destructive emphysema, with distortion from hyperinflation.[55]

By contrast, PLE affects all acini equally (see Fig. 63.4B and D). PLE is characteristic of homozygous *alpha$_1$-antitrypsin* (AAT) deficiency but has also been described in another genetic disease[59] and in users of intravenous methylphenidate.[60]

The third type of emphysema, PSE, forms by rupture of distal acini adjacent to the pleura.[61] PSE can develop along the chest wall, particularly in the upper and middle lobes, but is often prominent along the mediastinum, intralobar fissures, and bronchovascular bundles.[55] PSE is the type of emphysema most closely associated with bulla formation and spontaneous pneumothorax and, when adjacent to the trachea, with central airway expiratory collapse.[62] However, PSE is more commonly asymptomatic, least associated with impairment of lung function,[56] and even found to a minimal degree in healthy never smokers.[63,64] PSE in smokers is a highly inflammatory lesion associated with a greater lung density than is seen in CLE patients.[65]

Since the earliest modern descriptions of emphysema, there have been two major hypotheses about the initial mechanisms and anatomic sites of injury,[57,58,66] termed the Canadian and Denver schools, based on their recent proponents.[67] The Canadian school, which emphasized the role of

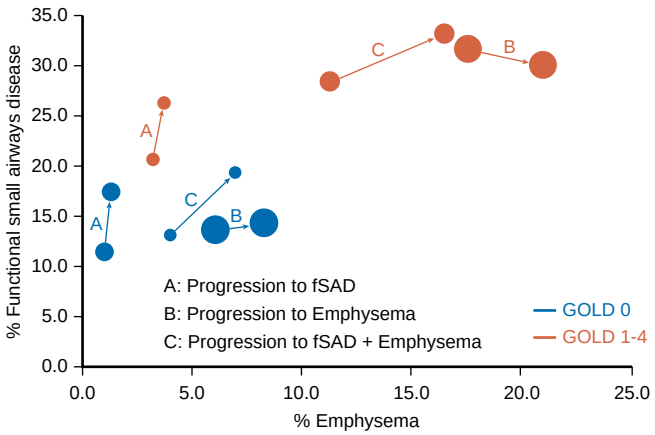

Figure 63.3 Evidence suggesting that emphysema evolves from *small airway disease* (SAD). Representation of the changes over 5 years in *parametric response mapping* (PRM) metrics among COPDGene participants initially without (*Global Initiative for Obstructive Lung Diseases* [GOLD] grade 0) vs. with COPD (GOLD grade 1–4). Data are from 725 high-resolution computed tomographic scans that showed interval progression. The center of each circle represents the mean coordinates (% emphysema and % functional small airways disease on PRM) for each type of progression (to functional SAD [fSAD; *A*], emphysema [*B*], or both [*C*]) at baseline and follow-up visits (identified by the direction of the arrows). The area of each circle is proportional to the number of subjects with a given type of progression (A, B, or C) within their GOLD grade (0 or 1–4). (From Labaki WW, Gu T, Murray S, et al. Voxel-wise longitudinal parametric response mapping analysis of chest computed tomography in smokers. *Acad Radiol.* 2019;26:217–223.)

SAD, has considerable support from analysis of human pathologic tissue[32–34,38,68] and, more recently, from imaging.[69,70] Because advanced stages of both CLE and PLE are associated with loss of terminal bronchioles,[33] SAD might contribute to development of either type of emphysema depending on genetic background. The Denver hypothesis, which focused on vascular endothelial cell apoptosis, originally derived from experimental results.[71–73] Recent support for this mechanism came from the Multi-Ethnic Study of Atherosclerosis COPD Study, which assessed pulmonary microvascular blood flow using dynamic contrast-enhanced MRI. Results showed 30% reductions in pulmonary microvascular blood flow even in mild COPD; correlations were strongest with emphysema and were independent of measures of SAD.[74]

Importantly, these two pathogenic mechanisms need not be mutually exclusive. Instead, varying degrees of epithelial damage, vascular injury, and *extracellular matrix* (ECM) degeneration[75,76] might contribute to emphysema development at specific disease stages or in different individuals. An additional seminal insight is that by transmitting mechanical stress to adjacent areas of normal lung, emphysema can become self-perpetuating.[77]

PULMONARY AND SYSTEMIC VASCULAR DYSFUNCTION

The healthy pulmonary circulation provides low resistance to blood flow, even during exercise (see also Chapter 85). It can do so in part by recruiting blood vessels, particularly in the upper lobes, not perfused at rest. An equally important contributor to low resistance is endothelial-dependent vascular relaxation, which results from the balance between the vasodilators, endothelial-derived nitric oxide and prostacyclin, and vasoconstrictors of the endothelin and serotonin pathways.[78]

In COPD, even in spirometrically mild stages, endothelial-derived nitric oxide production by *pulmonary artery* (PA) tissue is reduced in vitro, relative to PA tissue from never smokers or smokers without airflow obstruction.[79,80] Some pathology in COPD, especially the "vascular COPD phenotype,"[81] might represent pulmonary circulatory aspects of a generalized vascular response to inhaled insults. With worsening spirometric severity, mild to moderate elevations in PA pressures frequently develop, especially during exercise,[82,83] due to an abnormal increase in PA pressure relative to the rise in cardiac output. Mild *pulmonary hypertension* (pHTN) (20 mm Hg < PA pressure ≤35 mm Hg) is detectable in up to 90% of COPD patient with severe airflow obstruction[84] (Fig. 63.5).

Acute exacerbations of COPD (AE-COPD) are also accompanied by PA pressure elevations in groups including but not consisting entirely of those with left heart failure.[85] A ratio of PA to aortic diameters greater than 1.0 on CT scans was a strong independent predictor of AE-COPD in a study from two large cohorts.[86] In severe COPD, PA to aortic diameter ratio was significantly associated with resting pHTN in the absence of left heart failure and outperformed transthoracic echocardiogram as a predictor of pHTN.[87] Elevated PA to aortic diameter ratio detected right heart remodeling in mild-to-moderate COPD with preserved left ventricular function, independently of diastolic dysfunction.[88]

Severe pHTN (PA pressure >35 mm Hg) is uncommon in COPD in the absence of sustained severe hypoxemia or of alternative causes including untreated sleep apnea, occult thromboembolic disease, or left-sided heart failure.[89–92] Although such severe pHTN can be accompanied by right heart failure (classical cor pulmonale), more common findings in COPD are pruning of pulmonary arteries with right ventricular enlargement[93] or even diminished right ventricular size (cor pulmonale parvus), which has been attributed to compression by lung hyperinflation.[94] Criteria have been proposed to distinguish classes of pHTN in COPD patients.[81,95,96]

COPD patients also exhibit systemic circulatory dysfunction. These findings, seen prominently in the renal circulation[97] and associated with microalbuminuria,[98,99] but also present elsewhere,[100] might partially explain some extrapulmonary manifestations of COPD.

EPIDEMIOLOGY

COPD AS A WORLDWIDE DISEASE

COPD is a global health problem and a leading cause of mortality throughout the world. The Global Burden of Disease Study reported a worldwide prevalence of 251 million COPD cases in 2016 and estimated that the disease caused 3.2 million deaths in 2015 (5% of all deaths globally in that year).[101] More than 90% of COPD deaths take place in low- and middle-income countries,[101] highlighting its significant worldwide public health impact. Further, COPD is likely to increase in developing countries due to aging and more widespread smoking.

COPD is also associated with significant economic burden. In the European Union, annual costs of health care and lost productivity due to COPD are estimated as

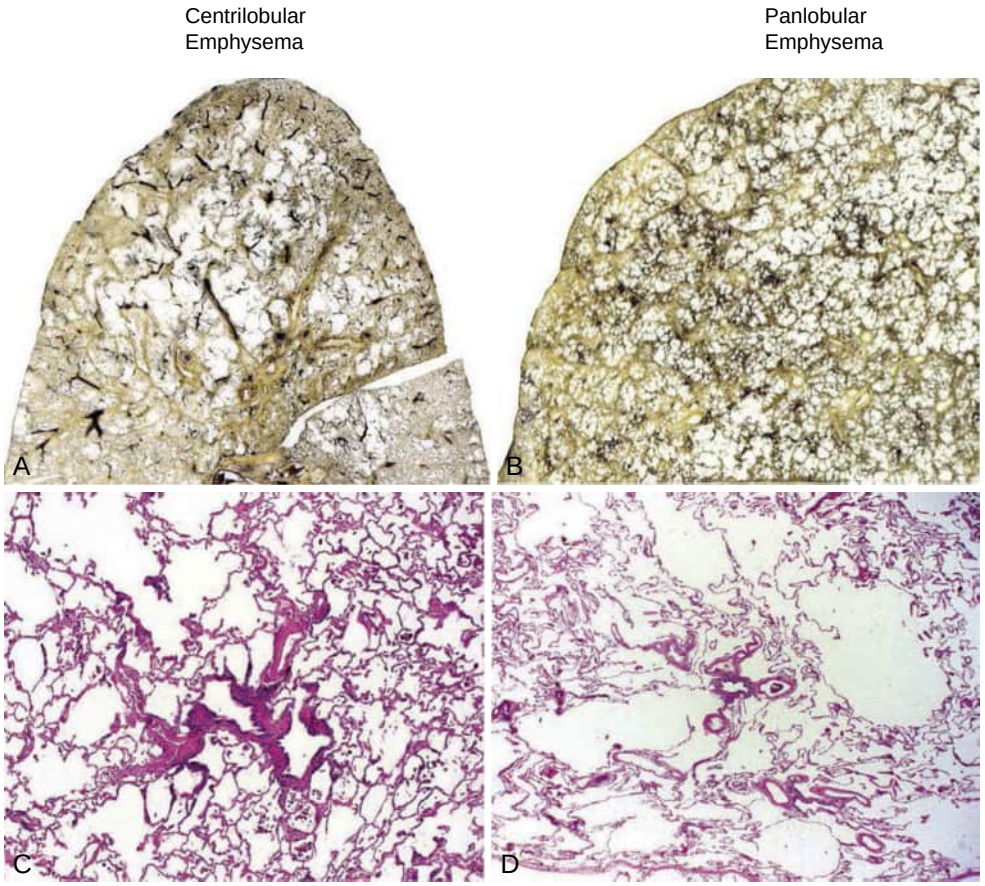

Figure 63.4 Gross and histologic appearance of *centrilobular emphysema* (CLE) and *panlobular emphysema* (PLE). (A–B) Paper-thin Gough-Wentworth sections prepared from whole lungs. (A) CLE in a smoker. (B) PLE in alpha$_1$-antitrypsin deficiency. The type and severity of emphysema may be difficult or impossible to determine on histopathologic grounds. (C–D) Hematoxylin and eosin–stained histologic sections. C, CLE with dilation of the air spaces surrounding the bronchiole. (D) PLE featuring a more diffuse air space dilation. (A–B, Original Gough sections prepared by T.V. Colby and the Charles B. Carrington Memorial Lung Pathology Library. C–D, From Leslie KO, Wick MR. *Practical Pulmonary Pathology: A Diagnostic Approach*, 2nd ed. Philadelphia: Saunders; 2011.)

€48 billion.[102] In the United States, the Centers for Disease Control and Prevention estimated the total medical cost attributable to COPD in 2010 at $32 billion, with the projected rise to $49 billion by 2020.[103] The greatest proportion of these costs comes from AE-COPD, especially from hospitalizations, which increase rapidly as COPD severity increases. Indirect costs are difficult to assess in COPD; however, in the United States an estimated 16.4 million days of work are lost due to COPD annually. The economic impact of COPD on workplace and home productivity, particularly in developing countries, may exceed the direct costs of disease management.

PREVALENCE AND INCIDENCE

The Global Burden of Disease Study reported a prevalence of 251 million cases of COPD globally in 2016, but estimates of COPD prevalence continue to vary by geographic location and also by differences in survey methods and diagnostic criteria.[103] The widespread under-recognition and under-diagnosis of COPD means that self-report surveys may underestimate its true prevalence.[104] In studies using spirometry, prevalence depends on the diagnostic criteria. Using the criteria suggested by the *Global Initiative for Obstructive Lung Diseases* (GOLD) will lead to higher prevalence in older individuals than using the lower limits of normal for the FEV_1/FVC ratio.[105] Partly due to global population growth, smoking prevalence, and aging, worldwide COPD prevalence increased by 44% between 1990 and 2015.[106] However, in the United States, the prevalence of COPD decreased from 7.2% in 2008 to 2009 to 6.4% in 2014 to 2015.[107] COPD prevalence is higher among adults with lower income, public insurance, and a history of smoking and varies by geographic location, ranging from 3.4% in Hawaii to 13.8% in West Virginia.[108] Existing data on COPD prevalence are limited or totally lacking in many regions of Europe; recently, however, by using inverse distance-weighted interpolation mapping, the mean prevalence in Europe was estimated to be as high as 12.4%, with significant variation across different areas.[109] Thus, standardized data on COPD prevalence across the globe remain lacking and incidence data are even fewer.

SMOKING AND OTHER ENVIRONMENTAL FACTORS

The primary cause of COPD in developed countries is exposure to tobacco smoke (either active smoking or secondhand smoke) (see also Chapter 65). Although tobacco smoking is a major risk factor, not all smokers develop COPD for several reasons, including differences in smoking behavior and in susceptibility to smoking. A dose-effect relationship between smoking and COPD risk has long been recognized. Recently, in the COPDGene cohort of current and former smokers, investigators found that, though smoking intensity is important, smoking duration is more strongly associated with estimates of COPD risk than is the number of cigarettes

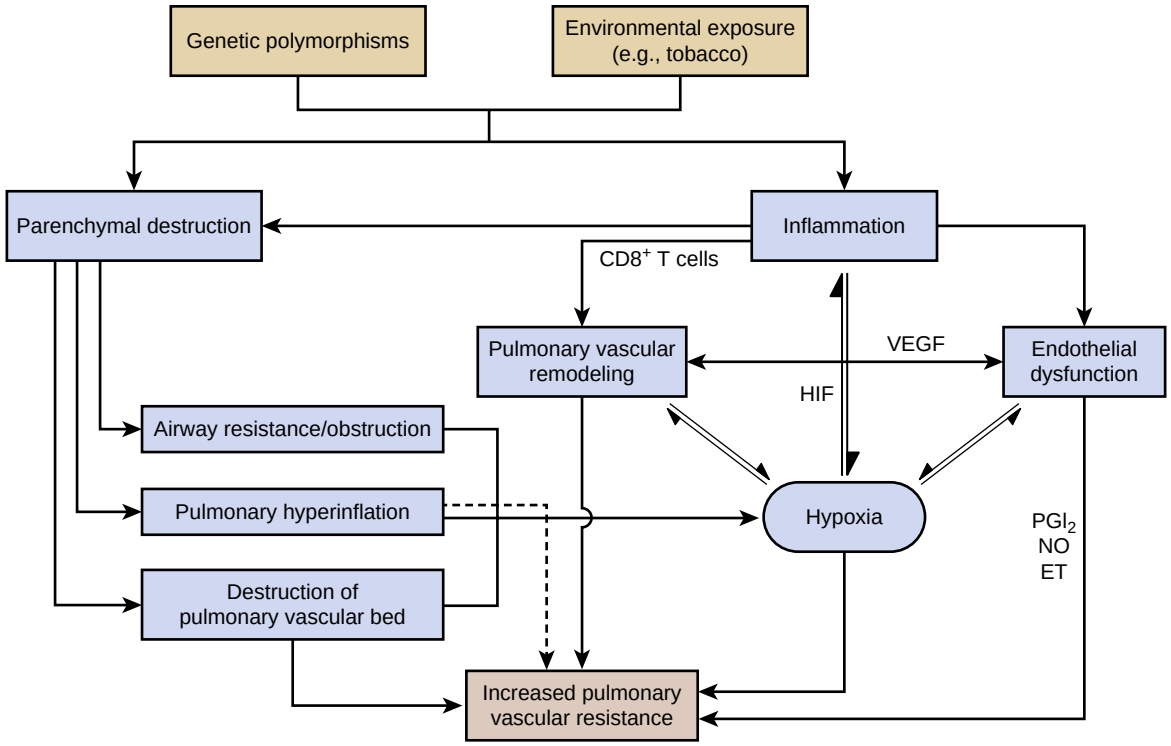

Figure 63.5 Cardiac, lung, and pulmonary vascular factors contributing to the development of pulmonary hypertension in COPD. The complex pathogenic interactions underlying increased *pulmonary vascular resistance* (PVR) in COPD. Genetic and environmental exposures contribute to parenchymal destruction and inflammation. Parenchymal destruction alters respiratory mechanics and causes destruction of the pulmonary vascular bed, which increases PVR and also leads to hypoxia. Inflammation is likely involved in pulmonary vascular remodeling and endothelial dysfunction, which also increases PVR and leads to hypoxia. The schema highlights the central role of hypoxia but also indicates that hypoxia is not essential to the development of an increased PVR in COPD. VEGF, vascular endothelial growth factor; HIF, hypoxia-inducible factors; PGI2, prostacyclin; NO, nitric oxide; ET, endothelin. (From Wrobel JP, Thompson BR, Williams TJ. Mechanisms of pulmonary hypertension in chronic obstructive pulmonary disease: a pathophysiologic review. *J Heart Lung Transplant*. 2012;31[6]:557-564.)

smoked per day or the composite index of pack-years.[110] It was hypothesized that a longer duration of smoking may be associated with accumulation of genetic and epigenetic changes or with sustained alterations in the lung microbiome contributing to disease progression. Further, accelerated decline in lung function persists even among those who smoke less than five cigarettes per day, reinforcing the view that there is no safe level of tobacco smoke exposure and that smoking cessation remains the primary intervention to modify disease risk.[111] Worldwide, however, it is estimated that 2–45% of patients with COPD never smoked,[3] and that non–tobacco-related exposures contribute substantially.

Indoor air pollution from biomass exposure has emerged as an important risk factor worldwide. In a recent meta-analysis including 35 studies with more than 70,000 participants, exposure to solid biomass fuel increased risk of COPD by 2.7 (95% confidence interval, 2.1 to 3.3) times compared to those without biomass fuel exposure.[112] Almost 3 billion people worldwide use biomass and coal as their main source of energy for cooking, heating, and other household needs; thus, in these communities, household air pollution is responsible for a large fraction of COPD risk.[101] Fewer studies have investigated the effect of indoor pollution in high-income countries, where indoor environmental exposure levels may be significantly lower than in low-income countries or in biomass-using homes. Still, research suggests that even low particulate levels may have adverse effects on the respiratory tract and are linked to worse COPD outcomes.[113,114] This low level of indoor particulates may have tobacco and non-tobacco contributions, but there have also been consistent studies linking both cumulative home and workplace *secondhand smoke* exposure to COPD development.[115] Among those with COPD, evidence suggests that secondhand smoke exposure contributes to worse disease morbidity, including worse quality of life, dyspnea, and heightened risk for COPD exacerbation, even among those who are actively smoking.[116–119] (See also Chapter 102.)

Workplace exposures contribute to the burden of COPD, and estimates suggest that they may be the cause of 15–21% of COPD.[120–122] After accounting for smoking, occupational exposures to vapors, dust, and gases are associated not only with COPD risk but also with a higher degree of emphysema and with more disease of small and large airways.[123] For those with established COPD, occupational exposures are associated with greater morbidity, including shorter walk distance, greater breathlessness, worse quality of life, and increased exacerbation risk.[124]

Outdoor air pollution has long-term effects on lung function, with higher pollution exposure leading to more rapid lung function decline,[125–127] which may contribute to COPD development. Results from recent large cohort-based studies further strengthen the evidence supporting a link between ambient pollution exposure and COPD. Analysis of the UK Biobank data on more than 300,000 individuals aged 40 to 69 years associated air pollution with lower lung function and higher COPD prevalence.[128] In a cohort study conducted between

2000 and 2018 in six U.S. metropolitan regions, long-term exposure to ambient air pollutants, especially ozone, was significantly associated with increasing emphysema, assessed quantitatively using CT imaging, and with worsening lung function.[129] A large body of literature supports the contribution of ambient pollution exposure to several measures of COPD morbidity, including increased respiratory symptoms, risk of exacerbations, and higher mortality.[114] For example, exposure to ozone caused an additional 254,000 (95% confidence interval, 97,000 to 422,000) deaths and a loss of 4.1 million (range, 1.6 to 6.8 million) disability-adjusted life years from COPD in 2015.[130] (See also Chapter 102.)

EARLY CHILDHOOD FACTORS, ASTHMA AND BRONCHIAL HYPERREACTIVITY, AND NUTRITIONAL STATUS AS PREDISPOSITIONS TO COPD

There are additional risk factors for COPD, and it is becoming increasingly clear that respiratory health in adult life is influenced by factors affecting lung growth in early life. In particular, frequent childhood lower respiratory infections, asthma, and premature birth have been linked to increased COPD risk. As early as the 1970s, respiratory ailments during childhood were linked to adult respiratory disease and ventilatory limitation.[131] Subsequently, several studies have supported this hypothesis. For instance, recurrent childhood lower respiratory infections have been associated with COPD development.[132] In the COPDGene Study, reported childhood pneumonia was associated with 40% increased odds of COPD as well as increased COPD exacerbations and lower lung function. Having both pneumonia and asthma in childhood further increased the risk of developing COPD.[133]

Asthma is a chronic inflammatory respiratory disease with variable and reversible airway obstruction; however, persistent airway obstruction and an accelerated decline in lung function may develop, particularly in those with severe disease or frequent exacerbations.[134] Results from the European Community Respiratory Health Survey showed that subjects with a history of childhood asthma had a 10-fold increased risk of developing COPD.[135] Further, the combination of asthma and smoking can have a synergistic effect on lung function decline.[136] Increased *airway responsiveness*, a hallmark feature of asthma, has also been associated with lung function decline and COPD.[132,137] Airway responsiveness is also a common feature of COPD; results from the Lung Health Study demonstrated that baseline airway responsiveness is a strong predictor of future lung function decline among those with mild to moderate COPD[138] and that increased airway responsiveness is also associated with a higher risk of mortality from COPD.[139]

In addition to early respiratory conditions, nutritional status has been associated with lung health, and several studies have linked micronutrient and general nutritional status with lung function and COPD severity.[140,141] Hence, poor nutritional status may contribute to disease burden worldwide, particularly in low- and middle-income countries. Among COPD patients, nutritional status has been linked to worse morbidity. Polyunsaturated fatty acids have emerged as a dietary component capable of modifying inflammation; higher omega-3 and omega-6 intake was associated with lower and higher COPD morbidity, respectively.[142]

Prematurity is often associated with low birth weight, recurrent respiratory infections, poor early lung function, and nutritional problems. Given that preterm birth appears to be increasing in most countries, it is becoming a rising concern for its potential contribution to the global COPD burden.[143,144] Thus, it is becoming increasingly important to recognize and reduce both environmental and nonenvironmental risk factors to COPD burden.

GENETICS OF COPD

METHODS OF DETERMINING SUSCEPTIBILITY

Studies in severe early-onset COPD[145] and in twins[146] confirmed that COPD has a genetic component. Notably, evidence for genetics persists even after controlling for CS exposure and excluding the most important known genetic risk factor, deficiency of AAT due to mutations of the *SERPINA1* gene. The clinical syndrome resulting from *AAT deficiency* (AATD) is considered later in this chapter. Heritability, the genetic contribution to disease susceptibility, for COPD has been estimated at 35–60%, depending on the study design and population.[146,147] Identifying the actual genetic sequences responsible for COPD heritability has been challenging. Studies using linkage and candidate gene approaches have proven hard to replicate. The most successful method of identifying susceptibility loci in the past decade has been *genome-wide association studies* (GWASs). Predicated on the existence of common variants (those present in at least 5% of the population) with weak effect sizes, the GWAS design requires very large cohorts.[148] Nonetheless, GWASs have identified dozens of replicated COPD risk loci.[149]

GWASs have several limitations. First, they are not optimal to identify the impact of rare variants. Studies attempting to identify rare variants have had variable results and produced no loci as convincingly replicated as AATD.[150–155] Second, GWASs usually identify a region, not the causal variant. Due to linkage disequilibrium, the "top" association is usually highly correlated with other genetic variants in the region. Third, the causal variant may act indirectly by affecting regulatory circuitry of genes millions of base pairs away. To define the function of a disease-associated locus, fine mapping, high-throughput variant screening,[156] and integrative omics that exploit intermediate phenotypes (such as gene expression or methylation)[157] have all been used.

Another key factor in genetic association is identifying the specific phenotype. To date, most COPD genetic association studies have been based on the GOLD definition, and hence on spirometric evidence of airflow limitation. GWASs of FEV_1 and FEV_1/FVC ratio in the general population have found similar associations to COPD studies, even though the former included those with and without obstructive prebronchodilator spirometry, and both smokers and nonsmokers.[158,159] Intriguingly, sensitivity analyses of population-based studies have not found substantial differences using pre- versus postbronchodilator spirometry or, for most loci, an effect in smokers versus nonsmokers. Gene-by-environment studies in COPD or lung function have largely not identified significant evidence of interaction,[160] which might be an issue of statistical power.[161]

For most GWASs, power is among the most important concerns. Thus, the analysis in large cohorts of lung function as a quantitative trait, rather than the binary trait of COPD versus healthy, has generally been more powerful. Such studies have identified hundreds of associations with FEV_1, FVC, and FEV_1/FVC ratio, most of which also show an association with COPD.[149,162]

COPD is heterogeneous, so analysis of specific phenotypes may yield additional insight into pathogenesis and hence the potential for targeted therapies. One study of severe COPD (GOLD stages 3 to 4) demonstrated associations not found in moderate COPD and also strengthened associations with previously identified loci.[163] Studies of phenotypes defined by imaging, such as emphysema and airway abnormalities, also discovered novel associations.[163–165] Notably, these studies identified significant associations of heterozygous *SERPINA1* Z alleles (e.g., MZ) with severe COPD and emphysema, a result not seen in milder COPD or in lung function studies. Although most studies of COPD-related phenotypes have suffered from smaller sample sizes,[166,167] large studies of cigarette smoking behavior have identified several regions of genetic susceptibility.[168]

However, GWASs have not disclosed associations in many important phenotypes, chief among them accelerated lung function decline. Although this trait is heritable,[169] to date GWASs have found interesting but not well-replicated results.[170,171] This failure for a longitudinal outcome, in contrast to successes using cross-sectional data, may be due to the smaller sample size, inadequate follow-up time, measurement error or random noise, or a lower overall contribution of genetic variants to this phenotype. Similar limitations may apply to studies of COPD exacerbations, for which the heritability has not been well studied. Surprisingly, most loci found in GWASs based on cross-sectional data do not appear to be associated with lung function decline.[172] Thus, while one of the main interests in COPD genetic association is to identify loci impacting ongoing inflammatory and destructive processes, these studies may have mostly identified developmental or early life processes that reduce attainment of maximal lung function by young adulthood,[172] thus increasing susceptibility to COPD via the alternative pathway (see Fig. 63.1).

CONFIRMED GENETIC RISK FACTORS

Despite these limitations, the discovery of dozens to hundreds of associated genetic loci holds great promise for elucidating COPD pathobiology. Only a few loci have been followed up by functional studies, though novel insights have already resulted (Table 63.1). The first GWAS-identified locus for COPD[173] is located at 15q25, which contains the nicotinic receptor genes *CHRNA3* and *CHRNA5*, and the iron-responsive element binding protein 2, which has a key role in iron homeostasis. Although this locus is clearly associated with smoking behavior, effects independent of smoking have been seen in some, but not all, genetic analyses.[162,174,175] Contemporaneous with identification of this locus by GWASs, the region was also linked to COPD via gene expression of iron-responsive element binding protein 2.[176] Iron homeostasis has intriguing connections to COPD; mice with reduced dietary iron intake or lacking the murine analog (iron regulatory protein 2) were less susceptible to CS-induced air space enlargement and lung injury, whereas increased iron loading increased severity of CS-induced airway phenotypes.[177]

This initial GWAS also identified an association with lung function and COPD at the 4q31 locus.[173,178] Functional studies including *expression quantitative trait loci* analysis and chromosomal conformation capture identified *hedgehog interacting protein* (HHIP) as the likely causal gene.[179] HHIP binds ligands of the hedgehog pathway, which regulates both embryonic body segmentation and adult stem cell maintenance. Subsequent studies identified influences of HHIP on noncanonical pathways, including those related to ECM.[179] The haploinsufficient *HHIP* mouse shows increased sensitivity to CS- and age-related emphysema, possibly related to increased oxidative stress.[180] Although *HHIP* variants have to date not been associated with lung function decline in humans, these data suggest that genes identified by GWAS could still have an effect later in life.

The 4q24 region harbors several susceptibility loci. The first is near the *family with sequence similarity, member 13 (FAM13A)* gene,[181] and additional studies support the likelihood that *FAM13A* is the effector gene at this locus.[182] Recent work identified *FAM13A* as a negative regulator of the β-catenin/Wnt pathway; *Fam13a*$^{-/-}$ mice have increased levels of β-catenin and resistance to CS-induced emphysema.[183] A second locus in the 4q24 region is near *GSTCD*, *INTS12*, and *NPNT*. These genes are expressed by several airway cell types and appear to be at least partially coregulated.[184,185]

Though several other regions identified by genetic association have not been subject to functional study, other evidence implicates specific genes or pathways. The most significant signal in the *AGER* region is a nonsynonymous variant associated with lung function, COPD, soluble receptor for advanced glycation end product levels, and emphysema.[186] A nonsynonymous variant in *surfactant protein D (SFTPD)* was also previously identified in a candidate gene study.[187] Rare variant studies have found associations in small COPD cohorts by examining phenotype association and variant function in specific telomerase-related genes (*TERT* and *NAF1*).[152,188] A putative functional variant was identified in the *TGFB2* region, and genetic signals near *TGFBR3, ACVR1B, ITGA2, ITGAV, MFAP2, GDF5,* and *SMAD3*[149,162,189,190] lend strong support for the importance of the *transforming growth factor-β* (TGF-β) pathway in COPD pathogenesis. Associations near *KIAA0753*, *CEP72*, and *LRCC45*, as well as rare variant studies, all support a role for cilia-related genes.[149,162,191,192] Similarly, an association near *PTCH1* lends further support for the role of the hedgehog pathway.[193]

Importantly, the ability to identify a likely causal gene (and variant, and cell type) appears to be locus dependent. For example, an association near *desmoplakin (DSP)* colocalizes (is highly statistically likely to be due to the same variant) with expression of *DSP* in the lung.[158] However, other loci illustrate the complexities of identifying a causal gene. The *HTR4* locus was first identified as associating with lung function, and later with COPD.[158,175,193,194] Gene expression studies and murine knockouts support its role in pulmonary function[195,196]; however, gene expression of *HTR4* in the lung is low relative to other tissues, and newer gene expression and colocalization suggest a role for other genes

Table 63.1 Selected Putative Genes Identified from COPD Genetic Association Studies

Gene	Putative Function	Supportive Evidence (see text)	References
ADAM19	A disintegrin and metallopeptidase domain 19; member of a family of proteins involved in cell-cell and cell-matrix interactions through integrin binding, expressed in airway epithelium, smooth muscle, and inflammatory cells	Gene expression	158, 557
AGER	Receptor for advanced glycan end products; binds to molecules implicated in inflammation; soluble form (sRAGE) is a biomarker for emphysema	Nonsynonymous variant	186
CHRNA5	Neuronal acetylcholine receptor subunit alpha-5; affects cigarette smoking behavior	Coding variants	555
DSP	Desmoplakin, component of desmosomes required for epidermal integrity	Colocalized gene expression	158
FAM13A	Family with sequence similarity 13, member A; induces β-catenin degradation; increases fatty acid oxidation and reactive oxygen species	Reporter assay (variant), murine model	182, 183, 556
FBXO38	F-box protein 38; orphan F-box protein, may act by coactivating *KLF* family genes to affect airway remodeling	Colocalized splicing	197
HHIP	Hedgehog interacting protein; deficiency leads defects in branching morphogenesis, increased lymphoid aggregates, and increased oxidative stress	Chromosomal conformation capture (variant), murine model	179, 180
HTR4	5-hydroxytryptamine receptor 4; expressed in developing lung, murine model with increased airways resistance	Murine models	196, 558
IREB2	Iron responsive element binding protein 2; increases mitochondrial iron loading and mitochondrial dysfunction	Gene expression, murine model	176, 177
NPNT	Nephronectin; extracellular matrix protein located in the basement membrane, known role in kidney development, but also expressed in lung	Gene and protein expression	162
SFTPD	Surfactant protein D; component of pulmonary surfactant, and responsible for immune and inflammatory regulation (see below)	Nonsynonymous variant	187
TGFB2	Transforming growth factor β2; member of the TGFB family, with roles in wound healing, development, and fibrosis	Colocalized expression, functional assay	149, 189

in the region, particularly *FBXO38*.[197] An analysis of coding variation associated a nonsynonymous variant in *IL27* with COPD.[197] However, this variant is correlated with several other regulatory variants and with an inversion polymorphism that affects the expression of multiple genes, including *TUFM*, whose product interacts with *NLRX1*, a gene implicated in cytokine response, virus-induced autophagy, and COPD.[197] Thus, putative genetic association of specific genes and pathways with COPD susceptibility must always be considered in view of all available evidence.

Bioinformatic tools can help support specific gene sets, pathways, and cell types. Such approaches have implicated *IL17RD, CHIA,* genes in the integrin family including *ITGAV,* and genes involved in cell-matrix interactions like *ADAMTSL3*.[149,162] Consistently, tests of overall enrichment identify a strong signal related to lung development, based on (1) gene set enrichment and (2) overlap of associations with regulatory regions in fetal lung.[149,162] These studies also support a role for smooth muscle, and some additional support also exists for endothelial cells, alveolar epithelial type 2 cells, basal-like cells, and fibroblasts.[149,159,162]

PATHOGENESIS

MECHANISMS OF OXIDANT INJURY AND ANTIOXIDANTS

Oxidant stress and injury resulting from *reactive oxygen species* (ROS) is the ultimate trigger for the four major pathologic changes (SAD, mucus abnormalities, emphysema, and pulmonary microvascular changes) culminating in distinct COPD clinical phenotypes. The principal ROS are superoxide anion, hydrogen peroxide, and the hydroxyl radical, the most damaging ROS.[198,199] ROS arise either exogenously, from CS and air pollution, or endogenously. Mainstream CS contains high concentrations of oxidants (1014 molecules/puff) and 3000 ppm nitric oxide/puff, and over 4700 chemical compounds.[200] ROS in CS range from short-lived oxidants, such as the superoxide radical and nitric oxide, to long-lived organic radicals, such as semiquinones.[199]

Aerosols from vaping and heat-not-burn tobacco products have much lower free radical levels than CS[201] but do emit volatile carbonyls, furans, and toxic metals, including chromium, lead, and nickel. Inhalational exposure to e-cigarette vapor causes adverse respiratory outcomes in animal models.[202–206] One study of e-cigarette users showed elevated lung concentrations of *neutrophil elastase* (NE) and the *matrix metalloproteinases* (MMPs)-2 and -9 with no change in antiprotease concentrations.[207] Insights have come from the public use data files for the Population Assessment of Tobacco and Health, which collected nationally representative, population-based, longitudinal data three times from 2013 to 2016. Results imply that use of e-cigarettes is a risk factor for respiratory disease, independent of combustible tobacco smoking, and that dual use, the most common pattern, is riskier than using either alone.[208] These devices were also recently associated with a syndrome of acute lung injury in humans[209] (see also Chapter 65).

Table 63.2 Categories of Lung Damage Due to Reactive Oxygen Species

Mediator	Target	Reaction	Result
Aldehydes	Proteins	Protein adduct formation	Altered protein function, indirect effect on gene expression via HDAC-2
Multiple reactive oxygen species	DNA	Double-strand breaks, ring-opened and rearranged guanine products	Apoptosis; accelerated senescence; DDR activation, leading to proinflammatory cytokine production; mutagenesis
Peroxide	Lipids	Peroxidation	Cell membrane damage, formation of reactive aldehydes
Peroxynitrite	Proteins	Tyrosine nitration	Altered protein function, MMP-9 activation, indirect effect on gene expression via HDAC-2
Reactive carbonyl species	Proteins and carbohydrates	Carbonylation	Potentially antigenic self-proteins

DDR, DNA damage response; HDAC-2, histone deacetylase 2; MMP-9, matrix metalloproteinase 9.

Smoking and other oxidative inhalational stressors induce endogenous ROS production by lung epithelial cells, *alveolar macrophages* (AMø), and other phagocytes. Reduced nicotinamide adenine dinucleotide phosphate oxidase is the principal intracellular ROS source, but mitochondrial respiration and the xanthine/xanthine oxidase system also participate.[199] The impact of oxidant stress is amplified in smokers due to the increased levels of iron in their lungs,[210] which, by redox cycling of Fe^{++} and Fe^{+++} (via the Fenton and Haber-Weiss reactions), can produce the highly toxic hydroxyl radical. Phagocytes also produce two very damaging oxidants, hypochlorous acid and hypobromous acid, via cell-type specific enzymes that include myeloperoxidase and eosinophil peroxidase. During severe AE-COPD, oxidant stress in the lungs increases markedly in parallel with neutrophil recruitment.[211] Oxidative stress can be measured by a host of biomarkers.[212]

Excessive ROS damage cells in multiple ways (Table 63.2).[198] Lipid peroxidation of polyunsaturated fatty acids causes them to reorient out of the membrane plane, making them targets for scavenger receptors.[213] Because the reaction of a radical with a nonradical always produces another free radical, lipid peroxidation can proceed as a chain reaction. One stable product of lipid peroxidation, 8-isoprostane, potently stimulates airway smooth muscle contraction via the thromboxane A_2 receptor.[214] ROS produce diffusible reactive aldehydes, including acrolein, that create protein adducts by targeting cysteine, histidine, and lysine residues. Such adducts impair the function of matrix components and of enzymes crucial to regulating gene expression, such as histone deacetylase 2, which is important for inactivation of proinflammatory genes.[215] The reaction of ROS with nitric oxide forms peroxynitrite, which causes tyrosine nitration, particularly of histone deacetylase 2,[216] perpetuating inflammatory mediator production.[217] Carbonylation describes two distinct kinds of damaging results of oxidants, both the direct non-enzymatic, irreversible oxidation of amino acid side chains, and non-oxidative covalent adduction of reactive carbonyl species generated by the oxidation of lipids or carbohydrates.[218] Multiple pathways lead to reactive carbonyl species, particularly by metal-catalyzed oxidation of lysine, arginine, proline, and threonine residues.[219] Carbonylation may be important in late stages of COPD because it renders proteins potentially antigenic.[220] Finally, ROS can damage DNA directly, particularly at guanine residues.[221]

Besides direct damage, excessive ROS subvert physiologic gene expression, which may be more consequential for COPD development. During homeostasis, controlled intracellular ROS production is a crucial component of signal transduction pathways central to cell proliferation, differentiation, migration, senescence, and apoptosis. ROS targeting of redox-reactive cysteine residues creates disulfide bonds, changing protein structure and hence function.[222] The most important ROS for such intracellular communication functions is hydrogen peroxide, a relatively weak oxidizer.[223] These changes are mostly reversible via thioredoxin and peroxiredoxin, which are themselves targets of redox cysteine regulation. Excessive intracellular ROS activate the *phosphoinositide 3′-kinase* (PI3K) pathway, which is coupled with multiple receptor tyrosine kinases that recognize growth factors, including *epidermal growth factor receptor* (EGFR), platelet-derived growth factor receptor, and *vascular endothelial growth factor* (VEGF) receptor. Thus, inappropriate ROS-induced PI3K activation can drive proliferation of multiple lung cell types.

Excessive ROS can also exaggerate the activation of several of the four major *mitogen-activated protein kinase* (MAPK) signaling cascades: extracellular signal-related kinases, c-Jun N-terminal kinases, p38 kinase, and the big MAP kinase 1. The MAPK cascades comprise triads of linked kinases that sequentially phosphorylate their downstream target. Like PI3K, MAPKs transduce signals from multiple cell-surface growth receptors,[224] so excessive ROS can bypass their physiologic control. One ROS target is apoptosis signal-regulated kinase 1, an upstream MAPK that regulates the c-Jun N-terminal kinases and p38 kinase MAPK pathways, ultimately triggering apoptosis in response to various cellular stressors.[222] ROS can also directly inhibit multiple phosphatases, some irreversibly, via formation of sulfinic and sulfonic acid adducts.[222] The net result is deranged signal transduction leading to dysplasia or cell death.

Finally, excessive ROS can subvert a key physiologic function of ROS, the cotranslational redox regulation of transcription factors such as p53, activator protein 1, cyclic adenosine monophosphate response element binding protein, early growth response protein-1, hypoxia inducible factor 1,

Table 63.3 Antioxidant Defenses of the Lungs[199,226]

NON-ENZYMATIC ANTIOXIDANTS
Glutathione, ascorbic acid (vitamin C)*
Uric acid, alpha-tocopherol (vitamin E), albumin†
ENZYMATIC ANTIOXIDANTS
Cu,Zn-SOD, EC-SOD, Mn-SOD, catalase, thioredoxin, glutathione peroxidase, heme oxygenase-1, glutathione-S-transferase

EC, extracellular; SOD, superoxide dismutase.
*These have higher concentrations in the airway lining fluid relative to plasma.
†These have lower concentrations in airway lining fluid than in plasma.

nuclear factor kappa B (NF-κB), and paired box containing proteins. This action is normally accomplished via the activity of the multifunctional DNA repair enzyme apurinic/apyrimidinic endodeoxyribonuclease 1 (Gene ID 328), better known in this role as redox factor-1.[225] By maintaining cysteine residues in the reduced state, redox factor-1 controls the DNA binding activity of these transcription factors. Unchecked intracellular ROS antagonizes this activity by directly oxidizing crucial cysteine residues, including in redox factor-1 itself. Redox factor-1 also targets the transcription factor commonly known as Nrf2 (nuclear factor, erythroid 2 like; Gene ID 4780). Nrf2 counters oxidative stress by activating genes whose promoters contain antioxidant response elements.[222] Thus, oxidative stress may contribute centrally to COPD development by inducing sustained adverse changes in gene expression, especially if there are changes in self-replicating committed progenitor cell types.

The lungs are defended against ROS by non-enzymatic and enzymatic antioxidants (Table 63.3). Non-enzymatic antioxidants include glutathione, ascorbic acid (vitamin C), and uric acid, and by alpha-tocopherol (vitamin E).[226] Glutathione and ascorbic acid are co-secreted by alveolar epithelial type 2 cells, whose loss in emphysema may thus accelerate deterioration of antioxidant defenses. Even in those without airflow obstruction, active smoking reduces lung concentrations of ascorbate, alpha-tocopherol, and especially glutathione.[198] In COPD, regardless of smoking status, glutathione concentrations are particularly decreased and fall further during severe AE-COPD.[211] There are also multiple enzymatic antioxidants, all altered in COPD.[199] These include three types of superoxide dismutase (Cu,Zn- extracellular [EC], expressed around airways and blood vessels[227]; and Mn), as well as catalase, thioredoxin, glutathione peroxidase, heme oxygenase-1, and glutathione-S-transferase.

SMOKING-INDUCED EPIGENETIC REPROGRAMMING OF THE AIRWAY EPITHELIUM

Epigenetic changes triggered by oxidative inhalational stress lead to SAD and chronic mucus hypersecretion, which collectively form the basis for the multiple clinical phenotypes seen in mild COPD. For small airways, efficient mucus clearance and local self-defense depend on the integrity of a normal pseudostratified epithelium composed of diverse cell types.[228] All these cell types derive from multipotent stem cells within the heterogeneous *basal cell* (BC) population (Fig. 63.6A).[229,230] BCs also give rise to two rare airway cell types, pulmonary neuroendocrine cells[231–233] and pulmonary ionocytes, which are rich in cystic fibrosis transmembrane conductance regulator expression.[234] In human airways, only the respiratory bronchioles lack BCs, making that anatomic locus uniquely susceptible to inhalational damage,[235] and the initial site of CLE development. Unlike the predominance of ciliated cells (60–80%) in proximal airways, the most common small airway cell type is secretory cells, which produce CC-16 (secretoglobin family 1A member 1 [SCGB1A1]; Gene ID 7356) and other innate immune molecules (Table 63.4), including cathelicidin LL37, H-ficolin, lactoferrin, *secretory immunoglobin A* (sIgA), and surfactant proteins A and D. Most of these innate immune molecules have been shown to have altered expression in COPD.[236–247]

Smoking causes BC epigenetic reprogramming, inducing changes that include hyperplasia of BCs and mucus-producing goblet cells, squamous metaplasia, dropout of ciliated cells and secretory cells, and damage to remaining cilia (Fig. 63.6B).[248] These changes arise in all smokers and precede inflammatory cell inflammation,[249] implying that they are necessary but insufficient for progression to COPD. However, it is also possible that BC exhaustion could contribute to SAD and emphysema.[250]

Altered community structure of small airway epithelial cells results in part from an imbalance between signal transduction via Notch family members, which induce physiological secretory cell and neuroendocrine cell differentiation,[251,252] and EGFR, a receptor tyrosine kinase of the ErbB family. Oxidative stress induces EGF production by ciliated cells, and additionally, by increasing epithelial permeability, overcomes the normal sequestration of EGFR from its ligands on opposite sides of the polarized epithelium.[253,254] EGFR activation induces an alternative EGFR ligand, amphiregulin. By promoting its own expression, amphiregulin can drive epithelial hyperplasia even after oxidative stress is removed. Amphiregulin causes hyperplasia of BCs and mucus cells, which along with other smoking-induced alterations, culminates in an airway epithelium susceptible to bacterial invasion.[255]

Such bacterial invasion is facilitated by yet another result of BC epigenetic reprogramming, impairment of defensive systems reliant on small airway secretory cells (see Table 63.4). One defensive system is CC16/SCGB1A1, the most abundant protein in normal distal airway secretions, which blocks production of proinflammatory cytokines and lipid mediators by antagonizing NF-kB activation and by inhibiting phospholipase A_2. Loss of CC16/SCGB1A1 appears to contribute to SAD.[256] However, best characterized and potentially most important of these systems is immune exclusion of microbes by sIgA.[67] In normal small airways, sIgA is translocated into the airway lumen by the polymeric immunoglobulin receptor (see Fig. 63.4C). This requirement does not apply to more proximal airways, where sIgA can gain access to the lumen via submucosal glands. In lung tissue ranging from healthy never smokers to severe COPD, focal loss of the polymeric immunoglobulin receptor and luminal sIgA correlated tightly with small airway damage (see Fig. 63.4D).[257]

Loss of translocation of sIgA into the lumen of small airways permits bacteria to invade epithelial cells, which induces focal NF-κB activation.[257] The identity of these bacteria is so far unreported but plausibly includes *nontypeable*

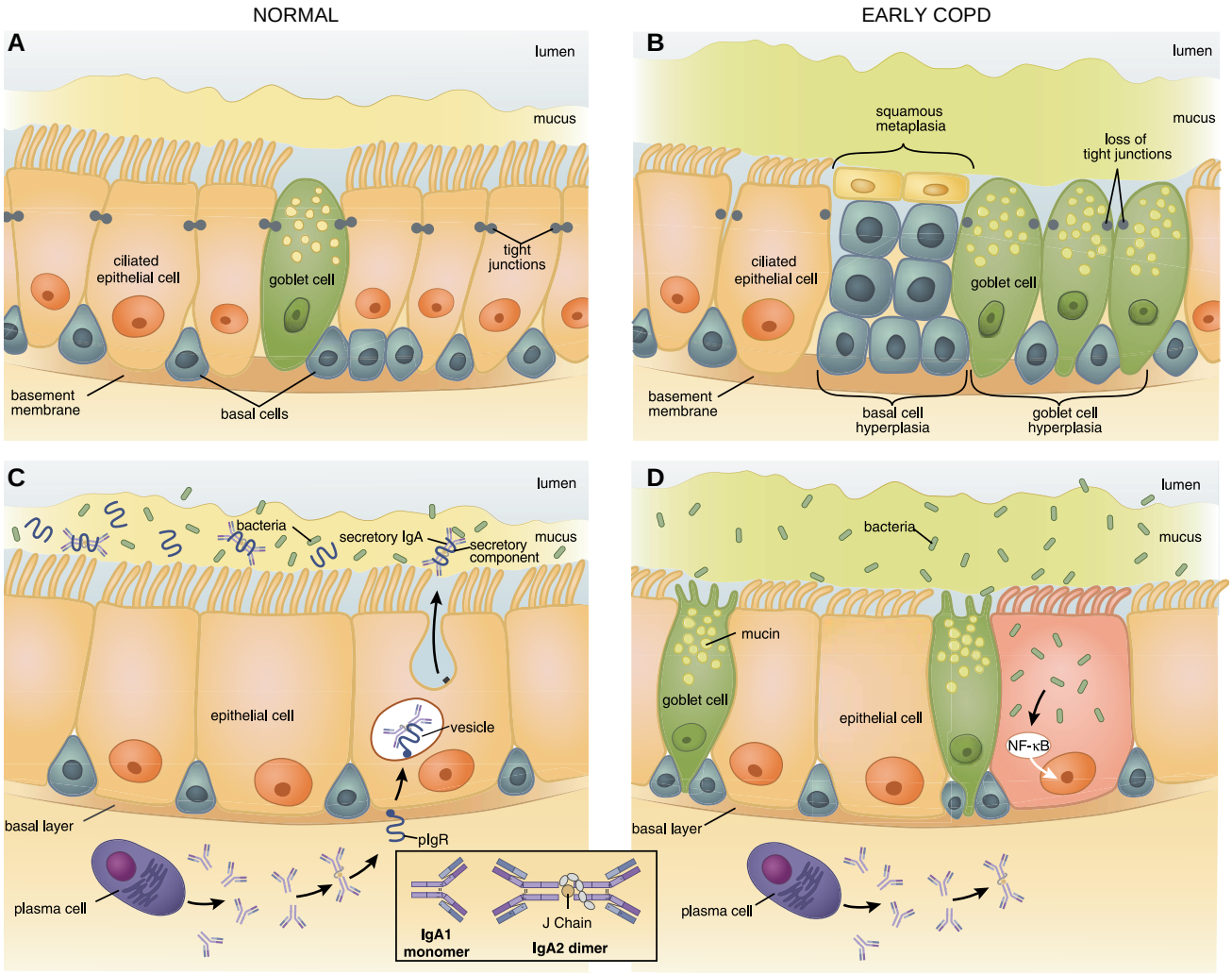

Figure 63.6 Epigenetic changes induced by smoking lead to progressive small airway damage and inflammation in early COPD. (A and C) Normal small airways. (B and D) Small airways in early COPD. (A–B) Cellular constituents. (A) Normal distal epithelium contains self-renewing basal cells, which differentiate into ciliated, mucus-producing goblet, and secretory (club) cells (not depicted), joined by tight junctions that form an impermeable barrier. Mucus is separated from the epithelial surface by a robust aqueous periciliary layer. (B) Smoking induces hyperplasia of basal and goblet cells, squamous metaplasia, loss of ciliated and club cells, a decrease in the periciliary layer and ciliary damage and crowding, and junctional barrier loss. (C–D) Role of secretory immunoglobulin A (IgA) in physiology and early COPD. (C) In normal small airways, dimeric IgA (*inset*) is transcytosed by the polymeric immunoglobulin receptor (pIgR) into the mucosal lumen. pIgR cleavage at the luminal surface liberates secretory IgA, which prevents bacterial invasion. (D) Smoking reduces pIgR expression, leading to localized secretory IgA deficiency in small airways, allowing bacteria to invade and induce sustained airway inflammation. NF-κB, nuclear factor-κB. (From Martinez FJ, Han MK, Allinson JP, et al. At the root: defining and halting progression of early chronic obstructive pulmonary disease. *Am J Respir Crit Care Med*. 2018;197:1540-1551. Illustration by Patricia Ferrer Beals.)

Haemophilus influenzae and *Streptococcus pneumoniae*, which both have this ability. Such invasion is facilitated due to the up-regulation by airway epithelial cells of both smokers and COPD patients of adhesion molecules that pathogens exploit: intercellular adhesion molecule 1, also known as CD54, by nontypeable *H. influenzae* and rhinovirus[258] and platelet activating factor by pneumococcus.[259] In advanced COPD, epithelial barrier integrity appears to be lost.[260]

Thus, the earliest stages of COPD pathology appear to result from impaired innate immune defenses. Active smoking may also prevent appropriate regulation by the adaptive immune system via the immunosuppressive properties of nicotine,[261] which reduces lymphocyte proliferation and impairs T cell polarization both directly[262,263] and indirectly via actions on *dendritic cells* (DCs).[264]

SMALL AIRWAY REMODELING AND MATRIX DAMAGE

The earliest overt lesion of COPD is small airway remodeling, which is the deposition of excess connective tissue in the subepithelial and adventitial compartments of the airway wall.[32,68] Remodeling is one component of SAD (along with obstruction by mucus and disappearance of terminal and transitional bronchioles). In later stages, these changes are accompanied by inflammatory cell infiltration, considered below.

The healthy lung ECM consists of the basement membrane to which cells attach plus the interstitial matrix. ECM is formed by collagen and elastin fibers interwoven by proteoglycans, fibronectin, and laminin.[75] Most abundant of

Table 63.4 Lung Host Defense and Homeostatic Soluble Mediators

Molecule	Function	Effect of Smoking and COPD	Reference
β-Defensins	■ Have direct antimicrobial effects via membrane lysis ■ Block bacterial toxins ■ Are chemotactic for DCs and T cells via CCR6	Increased in sputum in COPD	236, 237
CC-16/SCGB1A1	■ Reduces IL-8 production by epithelial cells ■ Suppresses phospholipase A_2 and NF-κB	Airway levels lower in smokers and in COPD. Reduced serum concentrations independently associated with accelerated decline in FEV_1	238, 239, 256
Cathelicidin LL37	■ Has direct antimicrobial effects ■ Is chemotactic for neutrophils, monocytes, and T cells via FPRL-1 ■ Reduces Mø responses to LPS ■ Can damage epithelial cells at high concentrations	Elevated in sputum in COPD; reduced plasma levels independently associated with longitudinal loss of lung function in ever smokers	236, 240, 241
H-ficolin (ficolin 3)	■ Opsonizes bacteria ■ Triggers lectin pathway of complement activation ■ Binds LPS	Not yet reported to play a role in smoking and COPD	242
Lactoferrin	■ Has direct antibacterial and antiviral effects due to cationic charge ■ Sequesters iron to reduce bacterial growth and biofilm formation	Reduced iron-to-lactoferrin ratios in BAL of smokers	243, 244
sIgA	■ Binds to bacteria and viruses without activating complement	Reduced in BAL in COPD	245–247
Surfactant protein A	■ Opsonizes bacteria and apoptotic cells without activating complement ■ Binds LPS ■ Blocks TLR2, TLR3, TLR4, MD2, and CD14 ■ Enhances multiple negative regulators of AMø proinflammatory function	Reduced in BAL both by smoking and in COPD	242
Surfactant protein D	■ Opsonizes bacteria and apoptotic cells without activating complement ■ Binds LPS ■ Blocks TLR2, TLR3, TLR4, MD2, and CD14	Reduced in BAL both by smoking and in COPD	242

AMø, alveolar macrophages; BAL, bronchoalveolar lavage; DC, dendritic cell; FEV_1, forced expiratory volume in 1 second; FPRL-1, formyl peptide receptor-like 1; IL, interleukin; LPS, lipopolysaccharide; Mø, macrophage; NF-κB, nuclear factor kappa B; SCGB1A1, secretoglobin family 1A member 1; TLR, toll-like receptor.

these are collagens, which can be divided into the interstitial type I and type III fibrillar collagens and the nonfibrillar type IV, which forms basement membranes. Elastin is chiefly responsible for lung elastic recoil and hence airflow velocity during exhalation. Elastin is particularly consequential because it is not typically replaced during adult life.[265] Proteoglycans consist of core proteins decorated by glycosaminoglycan(s) that sequester water and ions and regulate cellular migration. Rather than contributing to lung mechanical strength, fibronectin and laminin are important for promoting cell migration and survival and for storing growth factors that can be released during matrix damage. ECM also contains latent TGF-β, cytokines, proteases, and other enzymes essential for its continuous physiologic remodeling and for the participation of immune effectors in COPD pathogenesis.[266,267]

Smoking and development of COPD alter lung concentrations of these ECM constituents in a complex fashion. Elastin is increased in smokers without airflow obstruction, relative to both never smokers and COPD patients.[75] Despite up-regulation of elastin gene expression, advanced COPD is associated with reduced elastin content, including in small and large airways[75] but not in alveolar walls, where it is increased.[268] Genetic defects in elastin have been identified as a cause of severe emphysema.[269,270] Expression of tenascin C and its binding partner, fibronectin, is also increased in COPD.[75,271,272] Tenascin and fibronectin may enhance COPD pathology by inducing MMP expression and activity and via tenascin's adverse effect on endothelial cell survival,[273] an example of how SAD could contribute to early pulmonary vascular disease. Collagen content of the alveolar walls appears to be increased in emphysema but is considerably disorganized.[274,275]

Remodeling is associated with up-regulation of the zinc finger transcription factor *Krüppel-like factor* 5 (KLF5) in lung fibroblasts. KLF5 drives myofibroblast survival and differentiation; controls release of collagen and MMPs[276]; and regulates expression of platelet derived growth factor-α, fibroblast growth factor, VEGF, and TGF-β.[277] KLF5 is induced by the Ras-MAPK pathway downstream of multiple growth factors, and also by Wnt signaling, angiotensin II, and early growth response protein-1. Hence, KLF5 production may be one result of oxidant-induced aberrant gene regulation. Remodeled small airways also express multiple members of the TGF-β superfamily,[278] which have potentially profibrotic properties. One member, activin-A, is increased in COPD in parallel with decreases in its endogenous inhibitor, follistatin.[279] Activin-A has some potentially beneficial properties in smokers (e.g., stimulating development of *regulatory T cells* [T_{reg}][280]) but its profibrotic properties likely contribute to airway remodeling.

Tissue degradation around small airways in COPD has been shown by global gene analysis to predominate over repair.[281] This finding suggests that small airway narrowing due to remodeling may be only one feature of a process that simultaneously increases lung compliance even before the advent of overt emphysema. Such tissue degradation results from actions of proteases that destroy ECM faster than it can be replaced.

PROTEASES/ANTIPROTEASES

Since the initial recognition of the strong association between AATD and emphysema, an imbalance between proteases and antiproteases has been postulated to drive emphysema development.[282] As originally formulated, the most important contributor to this imbalance was believed to be NE,[283,284] but MMPs, especially macrophage-derived MMP-12,[285] are now considered more crucial for overall emphysema development.[266,286,287] A promoter variant in MMP12 has been associated with COPD onset and severity, though not all studies have replicated this finding.[163,288]

Nevertheless, neutrophil proteases are also crucial for lung destruction in COPD. Neutrophils are a major source of MMP-9, which, through the serial action of another neutrophil serine protease, prolyl endopeptidase, degrades collagen to release *N-acetyl-Pro-Gly-Pro* (Ac-PGP), a tri-peptide that is a potent neutrophil chemoattractant.[289,290] Ac-PGP shares sequence and structural homology with a domain of CXC chemokines containing a glutamic acid-leucine-arginine motif. Such acid-leucine-arginine+ CXC chemokines, particularly *interleukin* (IL)-8, have traditionally been considered the major drivers of neutrophil recruitment in COPD. However, Ac-PGP is a specific agonist for the chemokine receptors CXCR1 and CXCR2, which are required for its neutrophil chemoattractant activity.[291] Hence, in the process of damaging collagen, neutrophils induce a self-perpetuating loop for their own recruitment to the lungs.[292] This loop is normally broken when Ac-PGP is degraded by the aminopeptidase activity of leukotriene A_4 hydrolase, a proinflammatory enzyme that also generates a lipid neutrophil chemoattractant, leukotriene B_4. However, CS inhibits the aminopeptidase activity of leukotriene A_4 hydrolase,[293] thus amplifying neutrophil recruitment via the Ac-PGP loop.

Proteolytic damage initiated by SAD can spread into the surrounding tissues.[294] By eliminating tethering of small airways through destruction of bronchiolar-alveolar attachments,[295–297] proteolysis accelerates airflow obstruction and triggers the earliest damage leading to CLE.[34,298,299] These findings suggest that, although distinct *endotypes* (i.e., subtypes of a clinical disorder defined by a distinct pathophysiological mechanism[300]) likely contribute to the heterogeneity of COPD phenotypes,[25,301,302] there may also be a core pathologic pathway that evolves from airway epithelial epigenetic reprogramming to SAD and finally to CLE adjacent to individual airways. To date, the existence of this pathway is an extrapolation from cross-sectional histologic results, but it is supported by longitudinal imaging data[39] that, in advanced COPD, correlate to histology.[34,38,297] Hence, understanding the cell types contributing to proteolytic damage is key to developing novel therapies to arrest COPD progression.

INNATE CELLULAR RESPONSES

Lung *macrophages* (Mø) serve crucial immunoregulatory functions that minimize lung inflammation[303,304] but are also key sources of proteolytic enzymes that contribute to emphysema development[266,285–287] (see also Chapter 15). Mø are broadly distributed in the lungs, as in every other organ, and they appear to be essential for organogenesis[305] and for resistance to cellular stress.[306] The adult lung contains at least three types of Mø. *Alveolar Mø* (AMø) arise from a distinct progenitor during embryogenesis[307] and are maintained during health by low-level in situ proliferation.[308,309] Relative to DCs, AMø are poor antigen-presenting cells but can generate T_{reg}.[310] AMø from a subset of COPD patients exhibited impaired immune responses to TLR4 stimulation in vitro by respiratory pathogens or by molecules derived from them, which correlated with increased risk of future exacerbations.[311] Interstitial Mø, by contrast, are a minor population that express phenotypic markers suggesting that they derive from bone marrow via maturation of monocytes.[308,312–315] Interstitial lung Mø have been difficult to study but appear to segregate into several subsets with distinct anatomic localizations[315,316] and to be capable of immunoregulatory functions.[313,315,317] Finally, blood monocytes, which, in health, migrate through the lungs without differentiation,[312,318] can differentiate during acute inflammation into mature phagocytes with properties spanning the spectrum from those of Mø to DCs.[319]

Lung Mø numbers increase soon after initiation of smoking[320,321] and further increase during COPD progression.[68] The molecular basis for this expansion is incompletely defined, but evidence favors oxidant-induced resistance to apoptosis as the predominant factor.[322–324] Smoking and, to a greater extent, the progression of COPD itself are associated with defective AMø phagocytosis of bacteria and of apoptotic cells.[325,326] Defects in the latter process, also known as *efferocytosis*, are believed to foster lung inflammation.[327] AMø from COPD patients show a reduced ability to kill bacteria,[328] in part related to deficient Nrf2 activation.[329] Smoking additionally decreases the capacity of AMø to provide anti-inflammatory mediators to lung epithelial cells via extracellular vesicles.[330] Collectively, these changes, plus increased Mø production of proinflammatory cytokines in COPD,[331] likely exacerbate the focal immunocompromise resulting from small airway epithelial reprogramming.

DCs are essential in the regulation of both innate immunity, because they can prime *natural killer* (NK) cells for cytotoxicity, and adaptive immunity, because they are the preeminent antigen-presenting cell that activates and polarizes naive T cells.[332,333] The lungs contain three types of DCs, each with a specialized function[334]: *type 1 and type 2 conventional DCs* (cDC1 and cDC2, respectively) and plasmacytoid DCs. cDC1s reside in airway mucosa and vascular walls, cross-present antigens derived from apoptotic cells, and are essential to generate T_{reg} and thus to maintain self-tolerance at mucosal surfaces. On maturation in response to danger signals, cDC1s can elicit *type 1 T helper* (Th1) cells and cytotoxic T cell responses, which are essential for antiviral defenses but are also linked to COPD pathology. cDC2s, which are more numerous, reside primarily in the airway lamina propria and are the major producers of proinflammatory chemokines. cDC2s are also responsible for polarization of T cells to the

Th2 and Th17 phenotypes. Plasmacytoid DCs are widely distributed throughout the lung, including airways and alveolar septa. Their rapid ability to elaborate large amounts of type 1 interferons is essential for antiviral responses. Progression of COPD has been associated with increased numbers and activation state of all three lung DC subsets within lung parenchyma in some,[335–337] but not all, studies.[338,339]

Neutrophils have traditionally been considered to be crucial to COPD pathogenesis, primarily for their secretions of proteases,[340] but are also increasingly recognized to serve immunoregulatory functions that include mediator elaboration, activation of γδ T cells, and antigen presentation[341] (though the last action has been contested[333]). Constitutive migration of neutrophils through the lungs, following a circadian rhythm, appears important for IL-22–dependent production of antimicrobial peptides.[342] Neutrophils store preformed mediators, including *B-cell activating factor* (BAFF), and *a proliferation-inducing ligand/tumor necrosis factor ligand superfamily member 13* (APRIL) (which are B cell trophic factors), *TNF-related apoptosis-inducing ligand* (TRAIL), CXCL8, CCL20, and IL-1R antagonist. Neutrophil secretion of extracellular vesicles can profoundly influence their surroundings and sustain lung inflammation.[343,344]

Eosinophils are increased in the sputum of a sizeable percentage of patients with stable COPD, relative to healthy never smokers, with the exact frequency depending on the threshold considered abnormal.[345–350] Eosinophils are also elevated in bronchoalveolar lavage and lung tissue of some COPD patients,[347,351] even in the absence of peripheral blood eosinophilia,[352] and are associated with reticular basement membrane thickening.[351] Eosinophils potently produce chemokines and T2 cytokines. They can express class II major histocompatibility antigens and, in murine models, localize to the same areas of mediastinal lymph nodes as the DCs,[353] supporting the ability of eosinophils to polarize T cells to a Th2 phenotype. Eosinophils are also associated with a specific subtype of exacerbation risk, discussed below.

NK cells, by far the most numerous type of *innate lymphoid cell* (ILC), are common in healthy lungs. NK cells mediate rapid lysis of damaged cells, but require initial priming by cDCs,[354,355] which is increased in COPD.[356] Most lung NK cells display the differentiated ($CD56^{dim}$) phenotype associated with cytotoxicity, regardless of smoking status or COPD,[357,358] in contrast to other organs and within tumors, where cytokine-secreting $CD56^{bright}$ NK cells predominate. Evidence supports a contribution of NK cell killing of airway epithelial cells to the development of SAD and the progression to emphysema,[356,358,359] although their role relative to that of $CD3^+$, $CD8^+$ cytotoxic lymphocytes remains to be defined.[360] The involvement of the other, far less common ILC subsets,[361] especially ILC2 and ILC3, in the development of specific COPD endotypes is highly plausible but as yet undefined.

MEDIATORS OF INFLAMMATION AND OF ITS RESOLUTION

In the stable state, COPD is characterized by increased expression of multiple proinflammatory cytokines (notably IL-1α, IL-1β, tumor necrosis factor-α, and IL-6) and chemokines (especially CXCL8).[361–363] However, no single mediator can account for the four key pathologies characterizing lung damage in COPD and, to date, the specific therapeutic blockade of individual mediators has had mixed results in arresting progression or reducing exacerbation frequency.[364] The anti-IL-1β *monoclonal antibody* canakinumab was ineffective (ClinicalTrials.gov NCT00581945). Infliximab, an anti–tumor necrosis factor-α monoclonal antibody, showed no benefit and was associated with increased cancers and other adverse events.[365] A monoclonal antibody against CXCL8 was ineffective,[366] and trials inhibiting its receptor, CXCR2, were equivocal, showing some promise but also potential for toxicity.[367,368]

Nevertheless, recent progress in identifying key roles for several of these soluble mediators suggests the possible existence of COPD endotypes that could be targeted selectively.[302] Mutually exclusive subsets of COPD patients with predominately Th2-high versus Th17-high inflammation appear to exist and to denote steroid-responsive versus unresponsive disease, respectively.[369,370] Hence, the future of targeted cytokine blockade will likely involve more precise selection of COPD patients based on specific types of inflammation. Attractive targets for this approach include more upstream cytokines produced by and near the epithelium, such as thymic stromal lymphopoietin (Gene ID: 85480)[371] and IL-33 (or its receptor, ST2),[372] which define the tissue niche for ILC2 cells.[373]

Rather than resulting passively from dilution of inflammatory mediators, resolution of inflammation is an active process. Resolution depends crucially on specific lipid mediators derived from essential polyunsaturated fatty acids, which fall into four families: lipoxins, resolvins, protectins, and maresins (the last short for *ma*crophage mediators in *re*solving *in*flammation).[374] Collectively, these lipids are termed *specialized pro-resolving mediators* (SPMs); they act via stereospecific G-protein–coupled receptors. SPM biosynthesis is tightly controlled spatially and temporally because individual cell types can both class-switch their lipid mediator production[375] and may lack enzymes needed for the initial or the final steps of production, necessitating transcellular biosynthesis.[376] Specific SPMs reduce leukocyte cytokine production and adhesion, arrest neutrophil migration and favor their apoptosis, enhance efferocytosis, and reduce antigen presentation and IL-12 production by DCs. SPMs appear to be reduced in COPD.[377] Because they favor resolution without being broadly immunosuppressive, SPMs are promising therapeutic agents.[378]

PULMONARY MICROVASCULAR CHANGES INDUCED BY OXIDANT INJURY

Oxidative stress causes endothelial cell death,[379–381] a process linked to atherogenesis in the systemic circulation. Potential contributors to endothelial cell death include apoptosis by p53 due to DNA damage[380] or ROS-induced activation of the MAPK family member apoptosis signal-related kinase,[222] and decreased Notch signaling.[382] The pulmonary microvasculature maintains distal lung architecture, as demonstrated both in human pathologic samples[72,383–385] and in animal models. Death of pulmonary microvascular endothelial cells can lead to irreversible destruction of entire secondary pulmonary lobules, as seen in severe confluent CLE and PLE. The peripheral

blood of COPD patients contains elevated levels of circulating endothelial microparticles, an indicator of endothelial cell damage.[386–388] Microparticle concentrations fall following smoking cessation in those without airflow obstruction but not in those with COPD,[389] suggesting that endothelial cell death might be causally linked to loss of lung function.

Death of pulmonary microvascular endothelial cells could become self-sustaining via *endothelial monocyte activating protein 2* (EMAP-2), which causes endothelial cell apoptosis.[390,391] EMAP-2 (also known as p43; Gene ID 9255) is a noncatalytic component of the multi-aminoacyl-tRNA synthetase complex that also functions as a multifunctional proinflammatory cytokine when released by stressors such as hypoxia, lipopolysaccharide, viral infections, or CS.[392] Neutralizing antibodies against EMAP-2 block emphysema development in a murine CS exposure model.[393]

Additionally, as in other organs, the activation states and responses to injury of pulmonary microvascular endothelial cells is governed by tissue-resident parenchymal and stem cells by production of angiogenic factors such as VEGF-A, fibroblast growth factor-2, CXCL12, thrombospondin-1, and angiopoietins.[394] VEGF concentrations and endothelial expression of VEGF receptor are reduced in COPD.[72] Hence, damage to pericytes or airway mesenchymal cells, which could result from changes in their surrounding ECM, could be another reason for loss of pulmonary microvasculature in COPD.

It is known that prenatal lung development depends on reciprocal, mutually supportive signals between endothelial and epithelial cells. These reciprocal relationships are also likely necessary to sustain adult physiology. In the experimental model of compensatory lung hypertrophy following left pneumonectomy, propagation of alveolar epithelial type 2 cells requires endothelial expression of cell-bound MMP-14. Following activation by platelet-derived CXCL12, endothelial cells up-regulate MMP-14, which activates EGFR on alveolar epithelial progenitor cells.[395] This mechanism also sustains airway BCs,[395] further support that the epithelial and endothelial theories of emphysema origin are not mutually exclusive.

COPD AS A DISEASE OF ACCELERATED AGING

Age is one of the strongest risk factors for COPD development[396]; conversely, COPD is proposed to be a disease of accelerated aging.[397–400] Evidence supporting this hypothesis fits the framework of nine proposed hallmarks of normal aging,[401] which segregate into three categories (Fig. 63.7):

1. *Primary hallmarks*: genomic instability, telomere attrition, epigenetic alterations, and loss of proteostasis, all of which are intrinsically negative;
2. *Antagonistic hallmarks*: deregulated nutrient sensing, mitochondrial dysfunction, and cellular senescence, which are initially beneficial responses to the primary hallmarks but become detrimental when intense and sustained;
3. *Integrative hallmarks*: stem cell exhaustion and altered intercellular communication, including "inflamm-aging."[306]

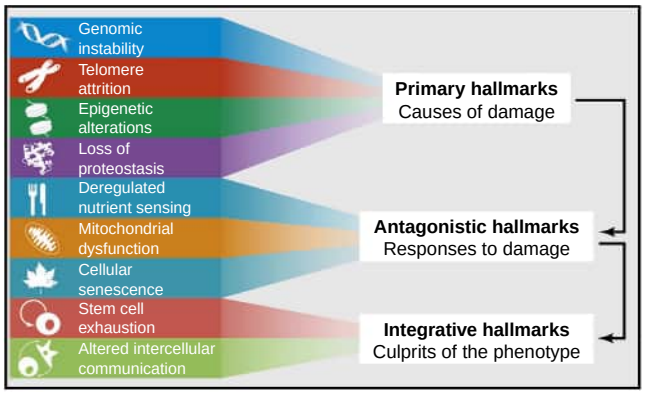

Figure 63.7 Functional interconnections between the hallmarks of aging. The proposed nine hallmarks of aging are grouped into three categories. *Top,* Those considered to be the primary causes of cellular damage. *Middle*, Those considered to be part of compensatory or antagonistic responses to the damage. These responses initially mitigate the damage but eventually, if chronic or exacerbated, become deleterious themselves. *Bottom,* Integrative hallmarks that are the end result of the previous two groups and that are ultimately responsible for the functional decline associated with aging. (From Lopez-Otin C, Blasco MA, Partridge L, Serrano M, Kroemer G. The hallmarks of aging. *Cell*. 2013;153:1194–1217.)

Primary Hallmarks

Genomic instability due to oxidant-induced DNA damage is found in smokers regardless of COPD status, but the oxidant-induced damage is greater in COPD, and increased DNA repair is restricted to those without airflow obstruction.[402,403] Ineffective DNA repair in COPD may result from selective reduction of Ku86, a component of the complex that repairs double-stranded DNA breaks.[402]

Telomeres support chromosome stability, but their maintenance requires telomerase because conventional DNA polymerases cannot completely replicate the ends of linear DNA stands. Telomerase is absent from most somatic cell types so that, with repeated cell division, telomere lengths fall, leading to replicative senescence or apoptosis. Pulmonary endothelial cell telomere length is reduced in COPD.[404] Shorter leukocyte telomere length associates with lower adult lung function and higher COPD prevalence.[405–407] Lower spirometry at a mean age of 50 years was predicted by faster leukocyte telomere length attrition between mean ages of 30 to 40 years (but not by leukocyte telomere length at baseline or follow-up). Because lung function was measured only once in that study, whether leukocyte telomere length reduction is causally related to spirometric decline remains unproven[408]; however, genetic defects in telomere maintenance have been identified in emphysema.[152,188]

Epigenetic alterations could contribute to COPD pathogenesis by perpetuating lung damage even after removal of the initiating stimulus. Epigenetic alteration is a composite term for processes that collectively regulate gene transcription. Types of epigenetic alteration include DNA methylation (which induces transcriptional repression), chromatin remodeling, reversible post-translational modifications of histones (including methylation, acetylation, phosphorylation, ubiquitination, SUMOylation, and adenosine diphosphate ribosylation), and alterations in transcription of noncoding RNAs.[409] Histone modifications either disrupt

chromatin organization or provide new binding surfaces to recruit DNA-binding proteins to specific chromosomal regions, while noncoding RNA alterations can have broad-reaching effects on translation of multiple genes. Besides the changes in histone deacetylase 2 cited above, extensive changes in other enzymes mediating post-translational modifications are induced by smoking, both in epithelial cells in vitro and in CS-exposed mice.[410] The net effect of altered histone post-translational modifications is heterochromatin decay, which has been linked to cellular senescence. Smoking also induces AMø to down-regulate many, but not all, microRNAs (hence increasing expression of their target genes) via dysfunction of the cytosolic RNA endonuclease DICER.[411,412]

Proteostasis refers to the combination of maintenance of correct protein synthesis and folding, and the quality control mechanisms that rely on the ubiquitin-proteasome and autophagy-lysosomal pathways. Defective proteostasis can activate the unfolded protein response, which contributes to cell death in some variants of AATD.[413,414] In smokers, ROS-induced damage, especially carbonylation (see Table 63.3), greatly challenges protein quality control[219] and leads to rapid compensatory up-regulation of the unfolded protein response.[415] Proteasome function is defective in COPD, perhaps because it is overwhelmed. CS activates autophagy, which might initially play a protective role in lung epithelial cells. Indeed, autophagy is globally elevated in the lungs of COPD patients,[416] but multiple aspects of selective autophagy are impaired, contributing to ciliary dysfunction, which may reflect failure to complete autophagy ("incomplete autophagic flux").[417]

Antagonistic Hallmarks

Deregulated nutrient sensing degrades cellular homeostasis. The primary mediator of normal regulation is the intracellular signaling pathway shared by insulin and *insulin-like growth factor-1* (IGF-1), termed insulin and IGF-1 signaling, the most evolutionarily conserved of any aging control mechanism. Levels of IGF-1 decline during normal aging,[418] which has been interpreted to indicate a down-modulation of the insulin and IGF-1 signaling pathway as a defensive strategy to minimize cell growth in the context of cellular damage.[401] Regulation of nutrients also involves (1) the PI3K-AKT–mammalian target of rapamycin pathway, which senses high amino acid levels, is partially controlled by the insulin and IGF-1 signaling pathway, and accelerates aging; (2) *5′-AMP-activated protein kinase* (AMPK), which detects low energy states and inhibits mammalian target of rapamycin; and (3) sirtuins, which reciprocally regulate and are regulated by AMPK and that, by activating peroxisome proliferator activated receptor-γ coactivator 1α, suppress aging via mitochondriogenesis, enhanced antioxidant defenses, and improved fatty acid oxidation. COPD is characterized by abnormalities in all three pathways,[419–429] arguing that they may be therapeutic targets to combat progression both of COPD and of its comorbidities.[400,430]

Mitochondrial dysfunction, affected by multiple pathways that promote aging,[431] is also described in COPD.[432–435] In cultured murine alveolar epithelial cells, CS extract at nontoxic doses induced excessive fusion of mitochondria, an initially adaptive but ultimately potentially harmful response.[436]

Cellular senescence, a stable block on proliferation, results from DNA damage or telomerase attrition.[430] Senescence is of evolutionary benefit by blocking tumorigenesis, albeit at the cost of shortening lifespan. Senescence is triggered either by pathways distal to p53, Arf, and Rb tumor suppressor or by the DNA damage response, which is orchestrated by the ATR (gene ID: 472) and ATM (gene ID: 545) serine/threonine kinases.[437–439] Senescence is maintained by heterochromatin formation.[440] Senescent cells up-regulate NF-κB and CCAAT enhancer binding protein beta. By inducing a positive feedback loop via CXCR2 and its ligands,[441] these transcription factors reinforce growth arrest but also sustain local and systemic inflammation through the *senescence-associated secretory phenotype* (SASP).[442,443] The known secretome of SASP-affected cells, dominated by IL-6 and IL-1α/β, closely matches cytokines recognized to be central to COPD pathogenesis. However, invoking SASP as the sole mediator of COPD progression would be overly simplistic. The SASP secretome is heavily pro-angiogenic and lacks the angiostatic factors[442] believed to contribute to development of emphysema.

Integrative Hallmarks

Stem cell exhaustion leading to loss of regenerative capacity is one of the most obvious features of aging. It likely contributes to COPD progression, especially via reduction of bone marrow–derived endothelial progenitor cells, which are essential to maintain pulmonary microvascular integrity. Endothelial progenitor cell numbers are decreased in COPD in parallel with spirometrically defined disease severity.[388,444–448] Thus, failure of the bone marrow to supply sufficient endothelial progenitor cells might contribute to emphysema in some individuals.

Altered intercellular communication during aging compounds the previously mentioned hallmarks of aging, which are all cell-autonomous defects. Examples of altered intercellular communication include dysregulation of the renin-angiotensin and adrenergic systems, which collectively impair homeostatic responses to stress and fail to restrain inflammation. A key subset of altered intercellular communication is "inflamm-aging," a progressive increase in the proinflammatory state with greater chronological age. Inflamm-aging is the net result of the inflammatory cytokines produced by SASP and exhaustion of specific immune components, especially T cell function, which leads to reduced clearance of pathogens and damaged cells. The damage that incites SAD and the toxic state of the ECM in COPD provide nonresolvable triggers for the classic stimuli for inflamm-aging, namely ongoing inflammation, and for interference with counterinflammatory regulatory mechanisms.[449] Inflamm-aging also accelerates many cardiovascular and metabolic comorbidities of COPD.

ADAPTIVE IMMUNE INFLAMMATION AND AUTOIMMUNITY

Several lines of evidence support involvement of adaptive immune mechanisms in COPD pathogenesis (see also Chapter 16). More severe COPD stages, defined spirometrically, exhibit lymphocytic infiltration of lung parenchyma not seen in milder COPD, with eventual development of organized tertiary lymphoid tissue, known as lung lymphoid

follicles.[68,450] The cytokine B-cell activating factor is a key trigger to this process.[451,452] Lung lymphoid follicles contain germinal centers, indicating class switching of B cells to produce high-affinity antibodies, which might contribute to host defense, but might also accelerate lung pathology. B cells have been strongly associated with emphysema in integrative genomic analyses[453,454] and experimental models.[455–457] Tissue-specific autoantibodies can be detected in advanced COPD,[458–465] potentially driven by smoking-induced modification of self-proteins.[220,466] These findings suggest that early damage triggered by innate immune mechanisms can lead to a break in self-tolerance accelerating lung destruction.

Simultaneously, components of protective physiologic adaptive immunity appear to be reduced in established COPD. $CD8^+$ T cells have a deficient ability to protect against respiratory viruses in COPD, due to up-regulated expression of programmed cell death protein 1.[467] Because viral infections themselves can induce programmed cell death protein 1,[468] there is risk of a positive feedforward loop favoring recurrent virally induced exacerbations. In many COPD patients, lung $CD4^+$ T cells display markedly reduced mRNA transcripts for the transcription factors controlling Th1, Th2, Th17, and *forkhead box P3* $(FOXP3)^+$ T_{reg} subsets and their signature cytokines; these patients' lung $CD4^+$ T cells produce little to no inflammatory cytokines following in vitro stimulation.[469] Therefore, defective T cell function may compound the already deficient immune defense of the distal airways in COPD.

One potential cause of adaptive immune involvement in COPD is loss of the physiologic restraint on inflammation provided by T_{reg}, which are increased in the distal lung parenchyma of smokers without airflow obstruction relative to never smokers, but markedly decreased in COPD.[459,469–472] T_{reg} typically control effector T cell populations such as Th1, Th2, and Th17 cells, and also NK cells,[473–477] all of which could contribute to specific lung damage. The mechanism of lung T_{reg} decrease in COPD is unknown but might involve their local conversion into Th17 cells.[478]

PHENOTYPIC HETEROGENEITY AND NATURAL HISTORY

SEX AS A FACTOR IN COPD HETEROGENEITY

COPD has historically been considered a disease of older men, but its prevalence among women has been increasing. This change is due to the narrowing gap in gender disparities in smoking prevalence in high-income countries and greater likelihood of biomass exposure among women in low-income nations. Thus, COPD now affects men and women almost equally.[479] However, female smokers who visit a physician are less likely than male smokers to be diagnosed with COPD, to receive spirometry testing, or to be referred to a pulmonologist.[480,481] Sex differences in lung size are present throughout childhood and adolescence and persist into adulthood.[482] On CT imaging, female smokers exhibit higher wall area percentage compared with male smokers, but lower luminal area, internal diameter, and airway thickness.[483] This sex difference in airway dimensions may explain differing susceptibility to disease and phenotypic presentation. Women appear to be more susceptible to tobacco because they have more severe disease despite lower cumulative tobacco consumption, earlier onset of COPD, and faster decline in lung function.[480,484] Female sex hormones may increase metabolism of CS to generate oxidative stress and thus may contribute to greater airway injury[485]; however, postmenopausal women may have faster rates of lung function decline.[486] The role of estrogen and progesterone is unclear, and hormone replacement therapy has not been consistently associated with COPD risk.[487] Further, in terms of phenotypic presentation, women with COPD suffer disproportionately from higher levels of anxiety, depression, and worse dyspnea and symptom-related quality of life for the same degree of lung function impairment.[488] Yet, they may report lower prevalence of other symptoms, such as cough and sputum production. There are differences between the sexes in prevalence of related comorbidities that can affect health outcomes, including higher rates of chronic heart failure and osteoporosis in women but lower rates of ischemic heart disease and alcoholism.[488,489] Gender-linked disparities are also seen in patient perceptions, expectations of the health care system, and access to health care.[489] These differences suggest that varying approaches to individual treatment may be necessary to optimize care. Given the growing burden of COPD among women, understanding sex differences in disease diagnosis, presentation, and management is increasingly important.

AAT DEFICIENCY

AAT, a serine protease inhibitor (serpin) derived principally from hepatocytes, is the most prevalent anti-protease in peripheral blood. Normal AAT serum concentrations are 120 to 200 mg/dL. AAT concentrations are higher in children and, as an acute phase reactant, increase during infection and pregnancy. Although originally named for its ability to block trypsin activity in vitro, AAT provides 95% of the inhibition of NE. AAT binds NE in equimolar concentrations and inactivates it. Importantly, CS damages AAT by converting the active site Met[358] to methionine sulfoxide, reducing its association constant for NE 2000-fold.[490] AAT also blocks the neutrophil enzymes cathepsin G, proteinase 3 (as does alpha-2 macroglobulin but not secretory leukoprotease inhibitor), mast cell–derived tryptase and chymase,[491] and possibly other proteases.[491] AAT does not inhibit MMPs, except ADAM-17,[492] although it blocks Mø release of MMP-12 in response to CS.[493] Conversely, MMPs can degrade AAT, leading to a neutrophil chemoattractant moiety.[494]

The most common form of AATD causing lung disease in adults results from homozygous expression of the Z allele (PI*ZZ). The AAT in PI*ZZ individuals forms an insoluble protein whose egress from hepatocytes is reduced by 85%, has slower kinetics of NE inactivation,[490] and tends to polymerize, producing a proinflammatory molecule.[495,496] Serum AAT concentration in PI*ZZ individuals is typically less than 50 mg/dL (11 μM). Prevalence of PI*ZZ AATD is estimated at 1:2500 to 1:5000 individuals in North America and Europe.[497,498] Worldwide, heterozygosity of the S allele, an E264V mutation that also produces a misfolded protein, with the Z allele is even more

common.[499] The overwhelming majority (estimated up to 95%) of those with AATD are undiagnosed. Unexpectedly, some individuals with PI*ZZ AATD can have normal lung function throughout their lives, even despite significant smoking.[500,501]

Multiple groups, including the World Health Organization, recommend testing for AATD in all patients with COPD or unexplained bronchiectasis, regardless of race, ethnicity, or age.[502] Those with confirmed concentrations at or below the low normal range should undergo genotyping for at least the Z and S alleles.[502] Augmentation therapy significantly slows the rate of decline in lung density in PI*ZZ cases as assessed by quantitative CT scanning, a surrogate measure for emphysema progression.[503] Augmentation therapy is not currently recommended for PI*ZZ individuals who continue to smoke.[502]

AATD is classically associated with early development of PLE with lower lobe predominance, but some individuals exhibit upper zone predominance.[504] Other pulmonary manifestations of AATD are chronic productive cough (in 40%), bronchiectasis (in 27%), asthma (in 35%), and partial reversibility of airway obstruction (in 61%).[505–507] AATD is associated with more frequent and more lethal anti–proteinase 3 vasculitis, hypothyroidism, and inflammatory bowel disease, particularly ulcerative colitis.[508] AATD is also associated with liver disease with manifestations that vary from cholestasis presenting in infancy and liver failure requiring transplantation in childhood to late-onset cirrhosis and hepatocellular carcinoma, which are significant causes of death in PI*ZZ never smokers older than 50 years.[509] Surprisingly, cirrhosis develops in only a minority of affected individuals, mostly men.[510]

AATD also provides insights into the pathogenesis of COPD in those without genetic deficiency due to its many immunomodulatory properties.[491,511] During inflammation, AAT is also produced by innate immune cells and has biphasic immunoregulatory properties; AAT initially induces IL-1β but later causes release of IL-1 receptor antagonist.[512,513] AAT regulates neutrophil chemotaxis in response to IL-8[492] and reduces release of neutrophil secondary and tertiary granules, both spontaneously and in response to tumor necrosis factor-α.[514] AAT shifts the balance of cytokine production from pro- to anti-inflammatory, particularly via multifactorial regulation of tumor necrosis factor-α release. AAT also favors development of T_{reg} over polarized T effector cell subsets.[491,511] Finally, AAT has antibacterial and antiviral properties.[491] Hence, immunomodulatory actions of AAT are important to all COPD patients.

PRESERVED RATIO IMPAIRED SPIROMETRY

Although current criteria for a diagnosis of COPD are based on rigid dichotomies between "normal" and "abnormal," as defined by spirometry, the distribution of lung function as plotted by FEV_1% predicted versus FEV_1/FVC ratios among ever smokers, and indeed in the general population, is a continuum that does not separate into distinct populations. A subset of ever smokers was identified in the COPDGene cohort with reduced FEV_1 but normal FEV_1/FVC; this group had greater dyspnea and radiographic abnormalities and worse exercise capacity relative to ever smokers with normal spirometry.[515,516] This subset is termed *preserved ratio impaired spirometry* (PRISm) (Fig. 63.8). Longitudinally, PRISm subjects show increased mortality, particularly due to cardiovascular causes; some develop overt COPD.[517,518]

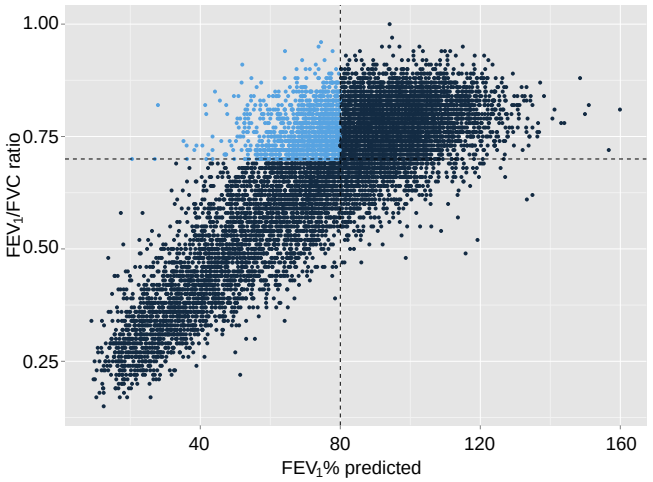

Figure 63.8 Distribution of spirometry in the Genetic Epidemiology of COPD cohort, which led to description of the *preserved ratio impaired spirometry* (PRISm) phenotype. *Forced expiratory volume in 1 second* (FEV_1) % predicted is plotted on the *x*-axis while FEV_1/*forced vital capacity* (FVC) ratio is plotted on the *y*-axis. *Dashed lines* represent fixed threshold criteria used to delineate PRISm subjects (highlighted in blue, upper left quadrant), control (upper right quadrant), and COPD (lower left quadrant) subjects. (From Wan ES, Castaldi PJ, Cho MH, et al. Epidemiology, genetics, and subtyping of preserved ratio impaired spirometry [PRISm] in COPDGene. *Respir Res*. 2014;15:89.)

PROGRESSION AND MORTALITY

Consistent with the observation that abnormal adult spirometry can result from failure to attain predicted lung size, and not simply from subsequent accelerated lung function decline (see Fig. 63.1), progression of COPD is variable among individuals. Both individuals with initially reduced FEV_1% predicted and those with increased lung function decline (mean loss ≥40 mL/yr, normal loss ≈20 mL/yr[486]) have the greatest risk of progression to overt COPD.[13,519] COPD resulting from biomass fuel exposure alone may have slower progression than disease resulting from tobacco smoking.[520,521] Evidence on whether the two exposures cause additive damage is conflicting.[522–524]

AE-COPD accelerates loss of lung function,[525,526] especially in those with spirometrically mild disease, but whether that is the case in ex-smokers has been questioned.[527] Interestingly, similar respiratory events did not increase the rate of spirometric decline in those without airflow obstruction or in PRISm subjects.[526] Recovery from exacerbations is variable and may be incomplete at 3 months in 7% of events.[528]

Eosinophilic COPD[351] has been suggested to be a subset of COPD patients distinct from the asthma-COPD overlap syndrome.[529] This concept arose from demonstration of eosinophilic lung inflammation in nonatopic individuals without history of asthma or marked bronchoreversibility.[347,351,352] It is supported by findings in longitudinal cohorts,[350,530] in randomized controlled trials,[348,531,532] and in the general population[533] that peripheral blood eosinophils identified patients at increased risk of exacerbations, often frequently. Such exacerbations are characterized by increased blood and

sputum eosinophilia and are independent of those related to bacteria or viruses.[534–536] The most recent report of the GOLD Scientific Committee recommended measuring blood eosinophil absolute numbers (with thresholds of <100 and >300 eosinophils/μL) to aid in deciding which COPD patients should receive therapies containing inhaled corticosteroids.[537]

Due to the high burden of comorbidities associated with COPD,[400,538,539] the causes of mortality vary between individuals and are strongly affected by spirometric severity and smoking status.[540,541] Cardiovascular death and lung cancer predominate in less severe COPD stages, whereas the proportion of respiratory deaths rises considerably in advanced COPD.[542] Prognosis can vary greatly even among those with identical lung function. Relative to FEV_1% predicted alone, prediction of mortality is improved by multidimensional indices such as BODE (body mass index, airflow obstruction [FEV_1% predicted], dyspnea, and exercise capacity),[543] ADO (age, dyspnea, and airway obstruction [FEV_1% predicted]),[544] and DOSE (dyspnea, airway obstruction [FEV_1% predicted], smoking status, and exacerbation frequency),[545] although even these tools are limited.[546] pHTN of even moderate severity has a strong adverse impact on survival in COPD.[92,547–549] Prognostic indices incorporating imaging variables will likely improve future mortality predictions.[24,93]

No currently available pharmacologic intervention alters COPD progression or mortality. Lung volume reduction surgery is associated with decreased mortality in those with upper zone–predominant emphysema and low exercise capacity after pulmonary rehabilitation.[550] Supplemental oxygen reduces mortality in COPD patients with severe resting hypoxemia but not in those with only intermittent or moderate desaturation.[551–554]

Key Points

- Airflow obstruction in adults that meets the spirometric definition of COPD can result either from accelerated loss of initially normal lung function or from defective lung growth before adulthood.
- Most COPD in high-income nations results from direct cigarette smoke exposure, but workplace exposures and indoor and outdoor air pollution are also important and may be equal or greater risks worldwide.
- Clinical COPD phenotypes are heterogeneous because inhalational stressors induce four key pathologic processes: small airway disease, mucus hypersecretion, emphysema, and vascular dysfunction.
- Both mucus hypersecretion and the reduced defenses against bacterial invasion that lead to small airway disease are initiated by smoking-induced epigenetic reprogramming of airway basal progenitor cells. The subsequent progression of those two processes into phenotypic manifestations in individuals who develop COPD is highly variable for reasons that remain incompletely understood.
- Three types of emphysema are recognized histologically and are identifiable by computed tomographic scanning: centrilobular, panlobular, and paraseptal.
- COPD can be considered a disease of accelerated aging. Nine hallmarks of aging have been proposed, in the categories of damage, responses to damage, and integrative failure.
- Multiple groups, including the World Health Organization, recommend testing for $alpha_1$-antitrypsin disease in all patients with COPD or unexplained bronchiectasis, regardless of race, ethnicity, or age.[502] Those with confirmed concentrations at or below the low normal range should undergo genotyping.[502]

Key Readings

Agustí A, Hogg JC. Update on the pathogenesis of chronic obstructive pulmonary disease. *N Engl J Med.* 2019;381:1248–1256.

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64 COPD: DIAGNOSIS AND MANAGEMENT

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INTRODUCTION AND HISTORY

Chronic obstructive pulmonary disease (COPD), as it is currently defined, is a spectrum of lung abnormalities characterized physiologically by persistent airflow obstruction. The histologic abnormalities seen most commonly are lung tissue destruction, or emphysema, and airway disease, recognized clinically as chronic bronchitis. From a historical perspective, emphysema was recognized first. Dating back to the 17th and 18th centuries, clinicians recognized what were termed abnormally "voluminous" lungs.[1] In 1789 Baillie published a series of illustrations demonstrating the classic pathologic features of emphysema. A bit later chronic bronchitis was described, best documented by the clinician, pathologist, and inventor of the stethoscope, Laennec. In his 1821 "A Treatise on the Diseases of the Chest," Laennec describes lungs that are hyperinflated and do not empty well.[2] But, upon pathologic inspection, he also noted the "bronchus of the trachea are often…filled with mucous fluid." At that time smoking was not common, and Laennec attributed the principal causes of this disease to environmental and genetic factors. However, it is important to note that Laennec identified both of the characteristic features of COPD: emphysema and chronic bronchitis.

By the 1940s, master clinicians were becoming familiar with an entity characterized by dyspnea on exertion in patients with physical signs of emphysema along with chronic bronchitis and asthma.[3] However, the ability to diagnose this entity reliably was not possible until the invention of spirometry. In 1846, John Hutchinson invented the spirometer, which was capable of measuring vital capacity, but 100 years later, it was Tiffeneau who introduced the concept of a timed vital capacity as a measure of airflow that allowed the spirometer to become a diagnostic instrument for airflow obstruction.[4] By the 1950s, clinicians recognized that specific spirometric and flow volume patterns indicated the presence of emphysema.[5] In fact, the first edition of Hinshaw and Garland's *Diseases of the Chest,* in 1956, depicted spirograms indicating airflow obstruction in emphysema.[6]

Groundwork for the modern definition of COPD was established at two major scientific conferences, the CIBA Guest Symposium[7] in 1959 and the *American Thoracic Society* (ATS) Committee on Diagnostic Standards[8] in 1962. The ATS committee defined chronic bronchitis clinically as chronic productive cough lasting at least 3 months, with bouts recurring over at least 2 years; emphysema was defined histologically as enlarged alveolar spaces; asthma was defined as airway hyperresponsiveness.[9] It was then that Dr. William Briscoe, at the ninth Aspen Emphysema Conference in 1965, first introduced the term COPD. Several years later Drs. Charles Fletcher and Richard Peto provided support for the link between smoking and the development of COPD in their 1976 landmark book documenting that continued smoking accelerates the loss of lung function, a process ameliorated by smoking cessation.[10]

The modern definition of COPD, as put forth by the ATS and *European Respiratory Society* (ERS), describes it as "a preventable and treatable disease state characterized by airflow limitation that is not fully reversible. The airflow

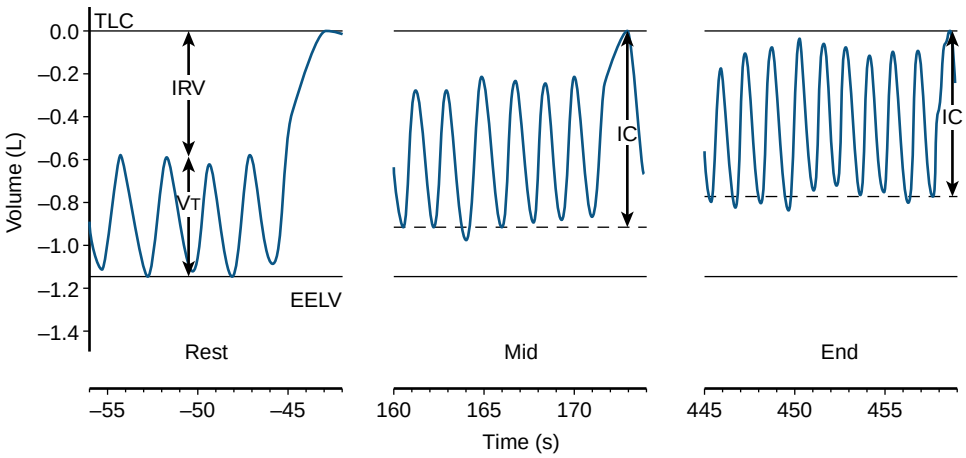

Figure 64.1 Dynamic hyperinflation. Volume tracing from a patient with severe COPD who demonstrated ventilatory-dependent dynamic hyperinflation. Inspiratory capacity (IC) decreases and end-expiratory lung volume (EELV) increases as ventilation increases during exercise. IRV, inspiratory reserve volume; TLC, total lung capacity; VT, tidal volume. (From Dolmage TE, Evans RA, Goldstein RS. Defining hyperinflation as "dynamic": moving toward the slope. *Respir Med*. 2013;107[7]:953–958.)

limitation is usually progressive and is associated with an abnormal inflammatory response of the lungs to noxious particles or gases, primarily caused by cigarette smoking. Although COPD affects the lungs, it also produces significant systemic consequences."[9] Although this definition describes a physiologic abnormality associated with exposure to noxious stimuli, the challenge that remains for both clinician and researcher is understanding the significant heterogeneity in disease presentation and progression that still exists within this umbrella definition.

CLINICAL FEATURES

SYMPTOMS

Individuals with early COPD are often asymptomatic. However, as the disease progresses, dyspnea, cough, and sputum production typically become more prominent. Any of these features should trigger an evaluation including spirometry both for diagnosis, if not already established, and for disease staging. Early in the disease course, dyspnea may be experienced only with exertion, and patients may attribute these symptoms to other factors and not seek treatment. Patients may also modify their activities to avoid dyspnea, and so the progression of pulmonary limitation may therefore be rather insidious. In fact, patients' activity may be severely limited even when they believe their disease process is still mild.[11] Eventually, however, as the disease progresses, dyspnea may ultimately be present with activities of daily living. Whereas the mechanism for dyspnea in COPD is likely multifactorial, exercise-induced air trapping, otherwise known as "dynamic hyperinflation," likely plays a significant role (Fig. 64.1).

As with dyspnea, cough may be attributed to other factors, such as smoking, and therefore patients may not complain about this symptom unless prompted. In general, sputum production is more common in current smokers, although, paradoxically, it may increase transiently after smoking cessation.[12] Although the presence of cough and sputum production in COPD is often more variable than the presence of dyspnea, it can significantly impact quality of life.[11] Sputum, when present, tends to be mucoid, clear to white in appearance, and more purulent with exacerbations. Chronic bronchitis is also clinically significant because it is associated with more frequent exacerbations[13] and has specific therapeutic implications (see "Treatment").[14,15] Excessive sputum production (>2–3 tablespoons daily) may indicate the presence of bronchiectasis, which has been reported to range in prevalence from 29–52% in moderate to severe COPD and has been associated with increased mortality.[16] Hemoptysis may be seen with both chronic bronchitis and bronchiectasis, particularly during COPD exacerbations. However, the presence of hemoptysis in a patient with COPD should raise concern for other possible causes, including lung cancer, given the increased risk for lung cancer in this patient population.[17]

Several instruments have been developed to assess health status in COPD, most notably the *St. George's Respiratory Questionnaire*[18] (SGRQ) and the *COPD Assessment Test*[19] (CAT) (eFig. 64.1). Both are multidimensional instruments encompassing symptoms such as dyspnea, cough, and sputum production, as well as activity limitation. Both the SGRQ and CAT demonstrate rough but imperfect correlations with *forced expiratory volume in 1 second* (FEV_1) but, more important, demonstrate changes after interventions[20,21] and with exacerbations.[22,23] Although the SGRQ is longer and used primarily in the research setting, the CAT consists of only eight questions and is practical for use within the clinical setting. The *Modified Medical Research Council* (mMRC) scale is a 5-point dyspnea scale[24] that, although not developed specifically for COPD, is relevant because the measure is associated with mortality in COPD, either when used alone[25] or when used as part of the BODE (body mass index, obstruction, dyspnea, exercise capacity) composite index[26] (Tables 64.1 and 64.2).

PHYSICAL EXAMINATION

Early in the course of the disease, no specific abnormalities may be noted on physical examination. Wheezing may or may not be present and does not necessarily relate to the severity of airflow obstruction. Prolonged expiratory time

Table 64.1 The BODE Index: Four Variables Predictive of Survival in Patients with COPD

Variable	POINTS ON THE BODE INDEX			
	0	**1**	**2**	**3**
B: Body mass index (kg/m^2)*	>21	≤21	—	—
O: FEV_1 (% of predicted)†	≥65	50–64	36–49	≤35
D: Distance walked in 6 min (m)	≥350	250–349	150–249	≤149
E: mMRC dyspnea scale (score)	0–1	2	3	4

Values (0-3) are assigned to each variable and summed, providing a score from 0 to 10.
*Values for body mass index are 0 or 1 owing to the inflection point in the inverse relationship between survival and body mass index at a value of 21 kg/m^2.
†FEV_1 categories are based upon stages identified by the American Thoracic Society.
FEV_1, forced expiratory volume in 1 second; mMRC, modified Medical Research Council.
From Celli B, Goldstein R, Jardim J, Knobil K. Future perspectives in COPD. *Respir Med*. 2005;99:S41–S48.

is a more consistent finding in COPD, particularly as the disease progresses. A forced expiratory time of more than 6 seconds corresponds to an FEV_1/*forced vital capacity* (FVC) ratio of less than 50–60%.[27,28] In very severe disease, patients develop physical signs indicative of hyperinflation, including a barrel-shaped chest, decreased breath sounds, distant heart sounds, and increased resonance to percussion. Patients may breathe in a "tripod" position in which the individual leans forward and supports his or her upper body with extended arms. This maneuver takes advantage of the accessory muscles of the neck and upper chest to increase air movement. Patients with severe disease may also use pursed-lip breathing, which involves exhaling through tightly pressed, pursed lips. This technique creates back-pressure and is thought to reduce dynamic hyperinflation, although it may also work by reducing bronchoconstriction via neurally mediated mechanisms.[29]

In patients with severe disease, other systemic manifestations may include signs of right-sided heart failure, leading to lower extremity edema. An accentuated pulmonic component of the second heart sound (P2) may also be appreciated. Tar stains on the fingers from cigarette smoking may be present. Clubbing is not a typical feature of COPD, even when hypoxemia is present, and should suggest evaluation for other comorbidities, including lung cancer.

Two commonly recognized COPD subtypes are the "pink puffers" and "blue bloaters." Pink puffers, typically associated with significant emphysema, compensate by hyperventilation and often manifest muscle wasting and weight loss. Compared with blue bloaters, pink puffers are less hypoxemic and therefore appear "pink." Blue bloaters typically have chronic bronchitis and tend to have decreased ventilation and greater ventilation-perfusion mismatch than pink puffers, leading to hypoxemia and hence cyanosis and to right heart dysfunction with edema or "bloating."

PULMONARY FUNCTION TESTING AND DIAGNOSIS

Spirometry

Pulmonary function testing (PFT) (see Chapters 31 and 32) and, in particular, spirometry is essential to establish a diagnosis of COPD. Although symptoms suggest a diagnosis, unfortunately their predictive value for a diagnosis of COPD is poor.[30] Several screening tools have been developed, including questionnaires[31] used in conjunction with peak expiratory flow.[32] Several studies suggest that, among the various risk factors, older age and smoking history are the two most important risk factors for development of COPD.[30,31,33] Spirometry can be performed in the physician's office and should be done for any patient with symptoms (e.g., cough, sputum, dyspnea) and risk factors. When performing spirometry (see Chapter 31), a subject exhales forcefully, and the FEV_1 is compared against the total air exhaled, which is the FVC. COPD is defined by a reduction in the FEV_1/FVC ratio. The degree of FEV_1 reduction defines the severity of airflow obstruction. The flow-volume loop in COPD typically has a concave appearance that may be apparent before the FEV_1 and FEV_1/FVC ratio decrease significantly, and the volume-time curve demonstrates a prolonged expiratory time (Fig. 64.2).

The ATS and the *Global Initiative for Chronic Obstructive Lung Disease* (GOLD) recommend that postbronchodilator values be used to help distinguish COPD from asthma. GOLD recommends an FEV_1/FVC less than 0.70 as the threshold for presence of airflow obstruction.[34] Rather than using the fixed ratio, the ATS/ERS recommends using the fifth percentile for the lower limit of normal.[9] In general, the fixed ratio approach leads to overdiagnosis in older subjects because the FEV_1/FVC ratio declines with age, even in healthy individuals.[35] However, the fixed ratio approach carries the advantage of simplicity.

Although COPD severity has typically been graded based on FEV_1% predicted, which is part of the GOLD (see Fig. 64.7) and ATS/ERS recommendations, updates to the GOLD[34] recommendations now incorporate symptoms and exacerbation history as part of disease staging. Two or more exacerbations in the prior year or one severe (hospitalized) exacerbation are the thresholds used by GOLD to identify individuals at risk for future events. Finally, it should be noted that, although airflow obstruction as quantified by spirometry is the internationally accepted definition for COPD, more recent data demonstrate the prognostic significance both of symptoms and of significant radiographic abnormality among at-risk smokers who do not meet spirometric criteria for airflow obstruction.[36] However, for this population at the moment, there is no evidence to support specific management strategies other than smoking cessation, although at least one *National Heart, Lung, and Blood Institute* (NHLBI)-supported study is currently underway.[37]

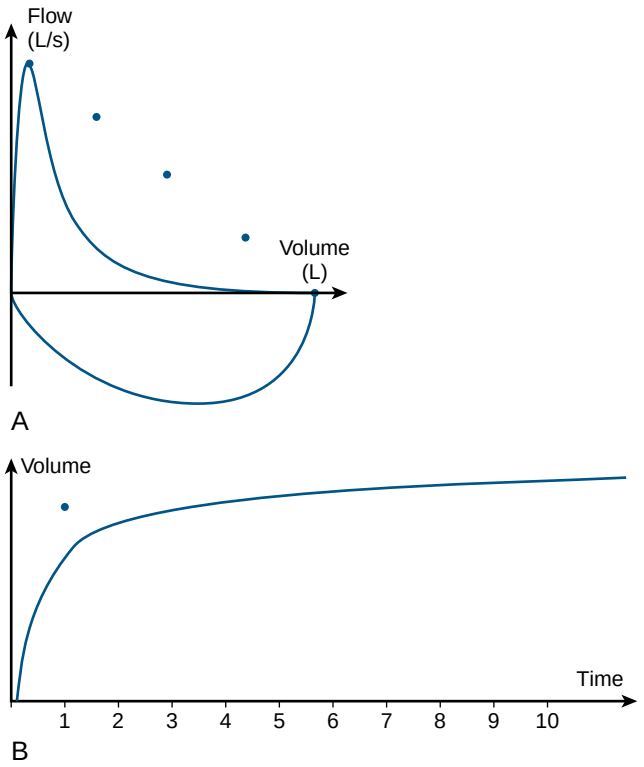

Figure 64.2 Flow volume loop in COPD. (A) The tracing shows a concave flow volume loop with reduction of flow at all lung volumes. The *dots* indicate the expected flow at various lung volumes. (B) The volume-time curve shows a prolonged expiratory time. The *dot* demonstrates the predicted forced expiratory volume in 1 second.

Table 64.2 Estimates of Mortality Based on BODE Index

	MORTALITY RATE (%)		
BODE Index Score	**12 Months**	**24 Months**	**52 Months**
0–2	2	6	19
3–4	2	8	32
5–6	2	14	40
7–10	5	31	80

Index score is used to predict mortality at different times.
Data from Celli BR, Cote CG, Marin JM, et al. The body-mass index, airflow obstruction, dyspnea, and exercise capacity index in chronic obstructive pulmonary disease. *N Engl J Med.* 2004;350(10):1005–1012.

Lung Volumes

Other lung volumes, including *total lung capacity* (TLC) and *residual volume* (RV), must be measured via plethysmography, not by dilution of a test gas, because of the heterogeneity of air flow and underestimation of volumes. Such tests are typically performed in a pulmonary function laboratory. TLC is increased in COPD, particularly in the presence of emphysema, where there is significant loss of elastic recoil resulting in lung hyperinflation. Increases in RV and functional residual capacity may also be seen. RV tends to increase to a greater extent than TLC, leading to an increase in the RV/TLC ratio. Vital capacity in COPD is also typically decreased because of hyperinflation.

Diffusing Capacity

Diffusing capacity for carbon monoxide (D_{LCO}) reflects the alveolar capillary blood volume and consequently is decreased in the presence of emphysema but may also be reduced in the presence of other abnormalities that affect the alveolar capillary bed, including pulmonary fibrosis and pulmonary vascular disease. Near-normal spirometry and lung volumes in the setting of severely reduced diffusing capacity and radiographic evidence of emphysema should suggest a possible diagnosis of combined pulmonary fibrosis and emphysema syndrome.[38]

Exercise Testing

The *6-minute walk test* (6MWT) is probably the most frequently used exercise test in COPD. The distance that a patient can walk in 6 minutes is termed the *6-minute walk distance* (6MWD).[39] Measuring distance walked during a defined time period was first described in the early 1960s.[40] An advantage of the 6MWT is that it requires little training to administer and no specialized equipment. Although a 6MWT is not required to make a diagnosis of COPD, it allows the clinician to measure oxygenation during ambulation and assess the potential need for supplemental oxygen. 6MWD is also frequently used during lung transplant evaluation to gauge functional status and prognosis. 6MWD relates to mortality in COPD and is a component of the BODE mortality index (Tables 64.1 and 64.2).[26] Although there is good correlation between 6MWD and peak oxygen uptake in end-stage lung disease,[41,42] the 6MWT should be considered complementary to cardiopulmonary exercise testing (see later). Most patients do not achieve maximal exercise capacity during the 6MWT, and consequently the 6MWD may better reflect functional exercise capacity.[43] The 6MWD also correlates better with quality-of-life measures; therapeutic interventions resulting in changes in 6MWD also correlate with improvements in dyspnea.[44–46] Some form of exercise testing is typically used before and after pulmonary rehabilitation to assess improvement.

Compared to the 6MWT, *cardiopulmonary exercise testing* (CPET) can provide diagnostic information regarding specific causes for dyspnea and exercise limitation. CPET can be performed with either a treadmill or cycle ergometer.[47] A large number of parameters can be measured or derived during a CPET, including *maximal oxygen uptake* ($\dot{V}O_2$), *carbon dioxide output* ($\dot{V}CO_2$), maximal work rate, and anaerobic threshold. CPET is also a necessary part of evaluation for *lung volume reduction surgery* (LVRS), because a low work rate after pulmonary rehabilitation predicts a survival benefit from LVRS (see Chapter 33).[48]

IMAGING

Chest radiography and *computed tomography* (CT) are the two imaging modalities most commonly used in COPD. Although not required to diagnose COPD, imaging can be helpful to rule out concomitant processes. Chest radiographs are frequently obtained to investigate dyspnea or hemoptysis or to look for pneumonia, heart failure, lung cancer, or pneumothorax. Chest radiography is not particularly sensitive or specific for the diagnosis of COPD. There are certain features, however, that are often seen in COPD. Radiolucency, diaphragmatic flattening, and increased

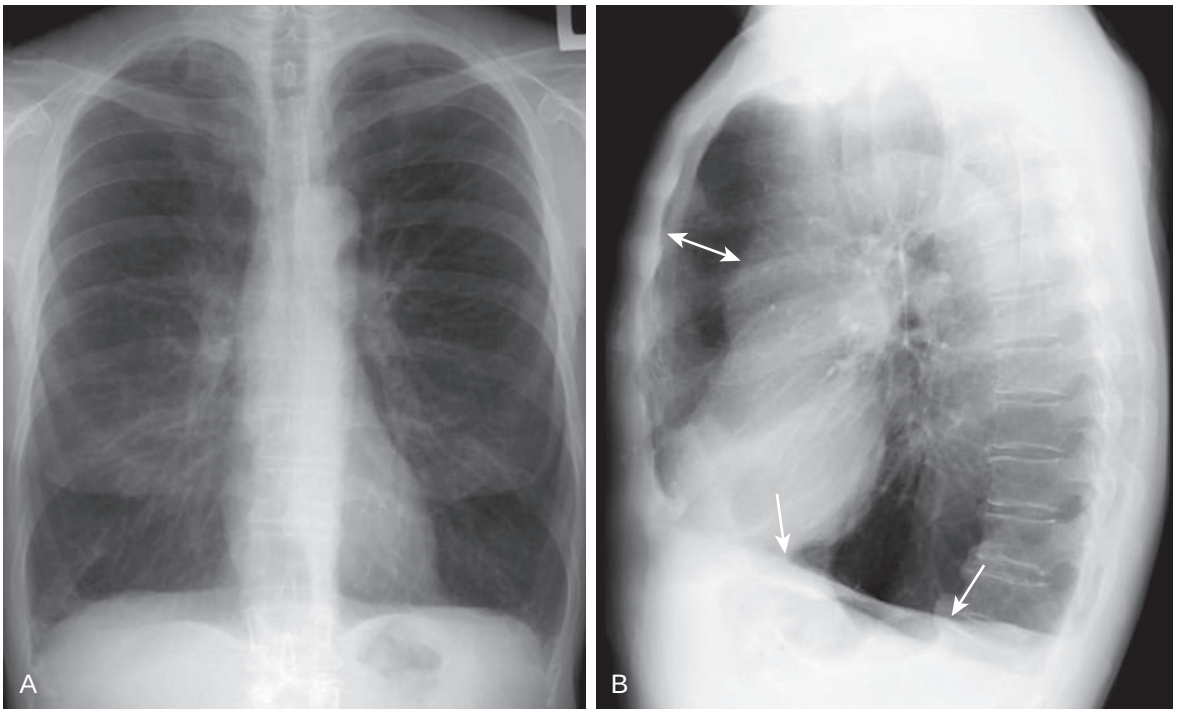

Figure 64.3 Centriacinar emphysema. Frontal (A) and lateral (B) chest radiograph in a 54-year-old female smoker with centriacinar emphysema. Note the very large lung volumes, with hyperlucency primarily seen in the upper lobes, consistent with a centriacinar emphysema pattern. Flattening of the diaphragms *(arrows),* a prominent retrosternal clear space on the lateral radiograph *(double arrow),* and a small-appearing heart on the frontal radiograph are findings consistent with abnormally increased lung volumes and are typical of advanced emphysema. The upper lobe lucency, typical of centriacinar emphysema, contrasts with the lower lobe predominant lucency seen in patients with panacinar emphysema. See Video 64.1 for computed tomography video of this patient.

retrosternal airspace on the lateral radiograph may be seen when hyperinflation is present (Fig. 64.3 and Video 64.1). On occasion, large bullae may manifest as radiolucent areas.

Chest CT allows better detection and quantification of emphysema than does traditional chest radiography. Areas of low attenuation are a marker of emphysema; thickened airways indicative of bronchial thickening may also be seen (Fig. 64.4). If expiratory views are obtained, areas of air trapping indicative of small airway obstruction and emphysema may also be seen. CT is not indicated in the routine diagnosis or evaluation of COPD but can be helpful when evaluating individuals with very severe COPD. CT imaging is required to quantify emphysema extent and distribution for the purposes of LVRS.[48] Individuals with very severe COPD undergoing transplant evaluation typically require a chest CT to rule out lung cancer and aid with surgical planning. CT imaging is also helpful when the clinician is concerned about a concomitant process such as interstitial lung disease, which may be suggested on PFT (see "Pulmonary Function Testing and Diagnosis"), or when hemoptysis or other unexplained changes in symptoms develop. Bronchiectasis, which may be reflected by copious sputum production and cough and has been associated with increased mortality,[16] is also best assessed on CT.

Although CT is not required for routine practice, the potential clinical importance of CT imaging is becoming better appreciated. Several studies demonstrate a strong relationship between emphysema and both lung function decline[49,50] and mortality.[51–53] Advances in CT technology allowing higher resolution at lower radiation dose, have provided valuable information in research studies and offer potential for early diagnosis.[54] CT-defined small airway abnormality has also been associated with lung function decline and exacerbations.[55,56] Bronchial thickening as assessed by CT also appears to have a strong relationship with symptoms as measured by the SGRQ.[57]

The COPD patient population is at increased risk for lung cancer, and the mortality benefit of screening CTs in smokers has now been established in large US and European studies.[58–60] Therefore a low-dose screening CT for lung cancer in individuals age 55 to 74 years with at least a 30 pack-year smoking history, including those who quit in the preceding 15 years, may be appropriate, assuming the patient would be an eligible candidate for lung cancer treatment (see Chapters 20 and 75).

LABORATORY TESTING

Arterial Blood Gases

Arterial blood gases (ABGs) are not indicated as part of the routine evaluation for patients with mild to moderate COPD. For many patients, pulse oximetry will suffice to provide an estimate of oxygen saturation. However, ABGs can be helpful to assess hypoxemia and to provide information regarding hypercapnia, particularly in individuals with more severe disease or during an acute exacerbation. ABG abnormalities also tend to worsen during exercise[61] and sleep.[62] Early in the disease course, mild to moderate hypoxemia without hypercapnia is typically seen. Later in the disease course, hypercapnia may develop, particularly in individuals with FEV_1 less than 1 L.

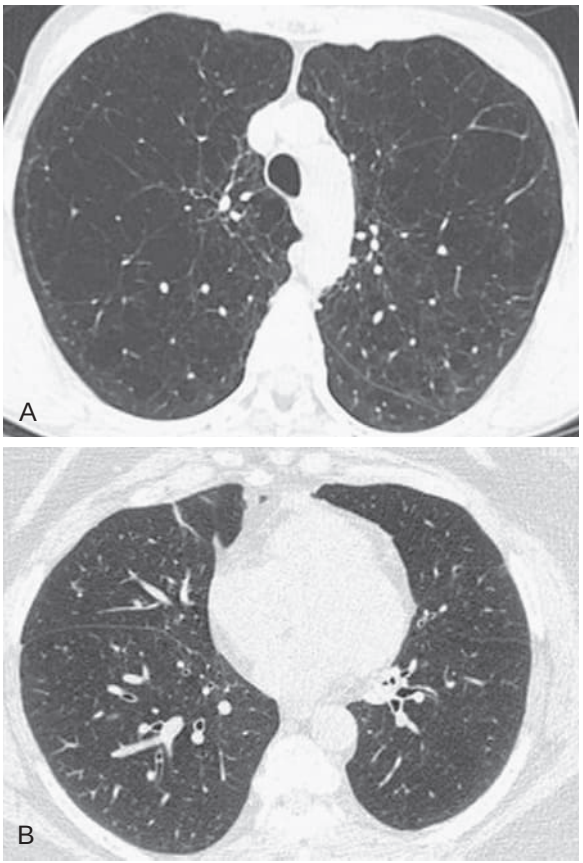

Figure 64.4 Two radiologic phenotypes of COPD. Computed tomography of two patients with COPD demonstrating the significant difference in the type of disease that may be present. Two patients with moderately severe disease are shown. (A) This patient demonstrates predominantly emphysema, whereas the second patient (B) demonstrates predominantly airway thickening. (From Han MK, Kazerooni EA, Lynch DA, et al. Chronic obstructive pulmonary disease exacerbations in the COPDGene study: associated radiologic phenotypes. *Radiology.* 2011;261:274–282.)



Figure 64.5 Panacinar emphysema. Frontal chest radiograph in a 51-year-old woman with alpha$_1$-antitrypsin deficiency presenting for lung transplant evaluation. Note the very large lung volumes with hyperlucency primarily seen in the bases, consistent with panacinar emphysema, as well as flattening of the diaphragms. Contrast the lower lobe lucency in this radiograph with Fig. 64.3, which shows upper lobe hyperlucency in a patient with centriacinar emphysema. See Video 64.2 for computed tomography video of this patient.

Erythrocytosis

Elevated hemoglobin may be seen in COPD, particularly in the presence of chronic hypoxemia. A hemoglobin value is also helpful in the evaluation of dyspnea because anemia is a common cause of dyspnea that should be excluded. In addition, D_{LCO} is most accurate when adjusted for hemoglobin.

Serum Bicarbonate

An elevated serum bicarbonate suggests chronic hypercapnia; in the setting of hypercapnia, serum bicarbonate is increased due to compensatory metabolic alkalosis (see Chapter 45).

Alpha$_1$-Antitrypsin Serum Levels

The ATS guidelines recommend testing for *alpha$_1$-antitrypsin* (A1AT) deficiency for all individuals with persistent airflow obstruction.[63] A1AT is a protease that inactivates neutrophil elastase. Clinical features suggestive of A1AT deficiency include emphysema at a young age, emphysema in an individual with minimal or no smoking history, lower lobe predominant emphysema, and a family history of emphysema. However, A1AT deficiency can also be present in patients with more typical COPD presentations. In individuals with established COPD, diagnostic testing is recommended. Concern for the diagnosis is raised based on A1AT serum levels below 11 micromol/L (≈50 mg/dL using nephelometry [i.e., immunoturbidimetry] and 80 mg/dL by radial immunodiffusion) but should be confirmed with genotyping (high-risk genotypes include S, Z, and null alleles, with null as the most deficient). On occasion, the serum level and genotyping are discordant; in this situation, protein phenotype analysis via electrophoresis can identify alleles with abnormal protein migration patterns. The chest radiograph and CT show the predominantly lower lobe distribution of emphysema, consistent with a panacinar pattern (Fig. 64.5 and Video 64.2) and different from the more common centriacinar pattern (see Fig. 64.3 and Video 64.1).

Blood Eosinophils

Recent studies have demonstrated a relationship between blood eosinophil levels and response to *inhaled corticosteroids* (ICSs).[64,65] When eosinophil counts are less than 100 cells/μL, ICSs are less likely to be of benefit; in patients with blood eosinophils greater than or equal to 300 cells/μL, ICSs are more likely to reduce exacerbations.[66] Although conceptually sputum eosinophils would seem relevant in this regard and are associated with increased frequency of exacerbations,[67] because they are more difficult to collect, we do not have data from large therapeutic trials regarding the utility of sputum eosinophils to identify patients more likely to be responsive to ICSs.

Sputum

Sputum evaluation is not indicated in the routine diagnosis and care of the COPD patient. In patients with stable disease,

sputum examination typically reveals a predominance of macrophages and few bacteria. During exacerbations, the number of organisms on Gram stain typically increases. The most common pathogens identified on sputum culture include *Haemophilus influenzae, Moraxella catarrhalis,* and *Streptococcus pneumoniae.*[68] Less frequently identified organisms include *Staphylococcus aureus, Pseudomonas aeruginosa,* and other gram-negative rods. However, the relationship between identification of organisms in sputum and their pathogenic contribution to acute exacerbations has been questioned because longitudinal studies have suggested that the incidence of bacterial isolation from sputum during an acute exacerbation of COPD was no different from that of the stable state,[69,70] although bacteria identified in sputum during stable COPD have been associated with a greater exacerbation frequency[71] and lung function decline.[72] In general, exacerbations typically respond to empirical treatment.

COMPLICATIONS

PNEUMOTHORAX

Pneumothoraces may develop spontaneously in patients with COPD. Depending on the degree of respiratory impairment, a pneumothorax may result in significant dyspnea and even acute respiratory failure. Pneumothoraces are treated similarly in COPD as in other conditions, although patients with severe emphysema are at increased risk for persistent air leaks, which may be difficult to treat (see also Chapter 110).

GIANT BULLAE

Emphysema may present with large bullae that can occupy a good portion of the hemithorax. Surgical treatment can be considered if compression of adjacent lung tissue is significant and surgical intervention is expected to improve pulmonary mechanics (see "Surgical Treatment of Emphysema").[60] Bullae may also become infected. An increased frequency of lung cancer has been reported in association with large bullae, seen either as a mass within the bulla or a thickening of the wall.[61,62]

PNEUMONIA

Pneumonia is not uncommon in patients with COPD and should be in the differential diagnosis for any patient with COPD presenting with increased dyspnea, cough, sputum production, and/or fever, which can make it difficult to distinguish from an acute exacerbation of COPD without a chest radiograph. Although COPD is believed to increase the risk for pneumonia, epidemiologic data are limited.[76,77] ICS, which are frequently used in the treatment of COPD because they reduce the frequency of COPD exacerbations, have been associated with an increased risk for pneumonia, particularly in older patients with COPD.[78] All patients with COPD should be immunized against *Pneumococcus.*[79]

RIGHT VENTRICULAR DYSFUNCTION

The *right ventricle* (RV) alters its structure and function due to the *pulmonary hypertension* (PH) associated with chronic lung disease (see Chapter 85). The prevalence of RV dysfunction in COPD is not known with certainty, but reported prevalence ranges from 1% to greater than 70%, depending on the patient population examined and the methodology used for defining PH.[79] When PH develops in the setting of COPD, the severity tends to be modest; severe resting PH due to COPD is relatively uncommon (see Fig. 85.2). Signs and symptoms of RV dysfunction include an increase in dyspnea, chest pain, and syncope. RV failure often presents with an increase in lower extremity edema, which should prompt further investigation. Other physical examination findings include RV heave, prominent pulmonic component to the second heart sound, tricuspid regurgitation murmur, and a right-sided S4. Electrocardiographic findings may include right axis deviation, evidence of RV hypertrophy, and right bundle-branch block (see Fig. 85.5), but overall these findings are rather insensitive for the diagnosis of PH. Echocardiography can be diagnostically helpful (see Fig. 83.3), although not infrequently, images are limited in patients with parenchymal lung disease and hyperinflation. In addition, the correlation between echocardiogram and right heart catheterization is imperfect; sensitivity tends to be better than specificity, suggesting that normal results on echocardiogram can help exclude significant RV dysfunction. Right heart catheterization remains the gold standard for diagnosis (see Fig. 83.7). PH in COPD is associated with worse outcomes, including increased risk for hospitalization[80] and worse survival.[81,82] There are few data to support the use of vasodilators for treatment of PH in COPD. Oxygen is the only therapy for PH in COPD and it improves mortality in appropriately selected patients (see Chapter 85).[83]

SLEEP DISORDERS

As many as 40% of COPD patients report sleep difficulties, such as poor sleep quality or difficulties initiating or maintaining sleep.[84] The combination of COPD and *obstructive sleep apnea* (OSA) is commonly referred to as "COPD-OSA overlap syndrome." The frequency of COPD-OSA overlap syndrome in the COPD patient population has been estimated to be approximately 16%,[85] which is roughly similar to that of the general population, although the consequences of OSA in patients with COPD are more significant. Compared to patients with OSA alone or with COPD alone, patients with COPD-OSA overlap syndrome tend to have more severe nocturnal hypercapnia, hypoxemia, and increased risk for PH.[86] OSA in COPD is also associated with poorer quality of life, frequent exacerbations, and increased mortality.[87,88] Diagnosis of OSA in COPD is important because *continuous positive airway pressure* (CPAP) therapy for patients with COPD-OSA overlap syndrome has been associated with both decreased risk of death and decreased incidence of severe exacerbations[88] (see Chapters 119 and 120).

SYSTEMIC MANIFESTATIONS AND COMORBIDITIES

Cardiovascular Disease

Ischemic cardiovascular disease is a leading cause of death in COPD.[89] Tobacco use is a shared risk factor that

contributes to this association, but epidemiologic data suggest impaired lung function is an independent risk factor for increased cardiovascular mortality even when adjusted for smoking status.[90] Among those with COPD, an abnormal FEV_1 also predicts the presence of atherosclerosis[91] and cardiovascular mortality.[92,93] Patients with COPD are also at increased risk for hospitalization due to cardiovascular events.[94] Atherosclerosis is a disease of systemic inflammation,[95] which may help explain the link to COPD. Elevated C-reactive protein levels correlate not only with the presence of COPD but also with the presence of exacerbations, severity of lung function, and risk for hospitalization and death.[80] Although clinicians need to be aware of the increased risk for the presence of both disorders, no therapeutic strategies have yet been demonstrated to benefit this subgroup of patients specifically. Cardioselective β-blocker medications frequently used in patients with cardiovascular disease have traditionally raised safety concerns in patients with COPD. Indeed, a recent prospective randomized trial of 532 patients with moderate-severe exacerbation-prone COPD, but no established indication for β-blocker use, found that the risk of a COPD exacerbation was similar in the metoprolol and placebo groups but that hospitalization for exacerbation was more common in patients treated with metoprolol.[96]

Osteoporosis

A clear association between osteoporosis and COPD has been established, with studies suggesting a twofold to fivefold increase in prevalence of osteoporosis in patients with COPD compared with age-matched control subjects.[97,98] Multiple shared risk factors between COPD and osteoporosis likely influence this association, including oral and ICS use, smoking, and low body mass index. However, these factors do not completely explain the association because lower bone mineral density in patients with COPD has been documented even in the absence of systemic corticosteroids.[99] Clinicians must be mindful of this association in both their male and female patients with COPD. Pulmonary rehabilitation improves the functional status of patients with COPD and may diminish fracture risk by decreasing the risk of falls.[100]

Diabetes

Diabetes is another comorbidity with increased prevalence in COPD. Decreased lung function has been associated with the coexistence of metabolic syndrome and the development of insulin resistance and diabetes.[101–103] The cause for this association is not known with certainty. ICS may be a contributing factor. Some data suggest a dose-dependent association between ICS use and diabetes control or new-onset diabetes,[104] although a retrospective analysis of 8 COPD trials and 26 asthma trials found no association between ICS use and new-onset diabetes or hyperglycemia.[105]

Gastroesophageal Reflux Disease

The prevalence of *gastroesophageal reflux disease* (GERD) in COPD also appears to be increased.[106,107] Possible contributions to the development of GERD in COPD include respiratory medications that may lower esophageal sphincter tone and lung hyperinflation that may also compromise the antireflux barrier. More important, GERD in the setting of COPD has specific clinical implications. GERD in COPD is associated with poorer quality of life[108] and more frequent exacerbations.[107,109] GERD may also be more common in COPD patients with chronic bronchitis.[110] A clear cause for the association between GERD and COPD has not been identified. Unfortunately, only limited data suggest that treatment for GERD may reduce the risk of exacerbations.[111]

Depression and Anxiety

Coexistent depression and anxiety are prevalent in COPD,[112,113] with conservative estimates suggesting that in COPD the prevalence of anxiety ranges from 7–50%, and depression ranges from 10–57%.[114] Patients with severe COPD are among those most impacted by anxiety and depression.[115] Risk factors for depression in COPD also include limited mobility, need for supplemental oxygen therapy, comorbid conditions, and female gender.[116,117] Patients with COPD and comorbid depression and anxiety experience poorer clinical outcomes. Patients with anxiety are at increased risk for COPD exacerbations and higher mortality.[118] Depressive symptoms are also associated with increased risk of death.[119,120] Specific therapies for anxiety and depression have not been demonstrated to improve COPD outcomes, although pulmonary rehabilitation has been shown to improve not only anxiety and depression but also other outcomes in patients with COPD, including quality of life and functional capacity.[121]

DIFFERENTIAL DIAGNOSIS

Several disorders may mimic aspects of COPD, and certainly many conditions may be associated with dyspnea. However, there are a handful of disorders that are particularly challenging because they may be associated with cough, sputum production, airflow obstruction, or emphysema-like radiographic changes. Careful clinical assessment can help differentiate these disorders from COPD, although, in some instances these disorders may be present in addition to COPD.

CHRONIC OBSTRUCTIVE ASTHMA

Chronic asthma may be associated with the development of persistent airflow obstruction that is not completely reversible (i.e., due to "remodeling"). Hence a clear distinction from COPD may not be possible; chronic asthma may also coexist with COPD (asthma-COPD overlap).[122] However, several clinical features tend to be more likely associated with each of the two disorders. In general, the age of onset for asthma tends to be earlier. Asthmatic patients may have a history of atopy and a family history of asthma. Airflow obstruction abnormalities are usually less severe with asthma, with greater prevalence and magnitude of reversibility. Sputum production is less common in asthma. These patients also tend to have less of a smoking history and greater corticosteroid responsiveness than patients with COPD. Chronic asthma is also not associated with emphysema; the D_{LCO} is normal or increased in chronic asthma, whereas it is decreased in emphysema.

CHRONIC BRONCHITIS WITHOUT AIRFLOW OBSTRUCTION

Chronic cough and sputum production may be present in the absence of airflow obstruction. The accepted definition for chronic bronchitis is a productive cough lasting for 3 months, recurring over at least 2 successive years.[123] Diagnostically, this is often mistaken for COPD because chronic bronchitis, even in the absence of airflow obstruction, is often associated with smoking. Chronic exposure to poor air quality or industrial dusts/fumes also increase risk for this disorder. Although no specific therapies have been developed for chronic bronchitis without airflow obstruction, the morbidity and mortality associated with this disorder should not be ignored. Such patients still experience poorer quality of life and increased risk of death as opposed to healthy control subjects.[124–126] On a related note, the *Subpopulations and Intermediate Outcomes in COPD Study* (SPIROMICS) identified at-risk smokers with respiratory symptoms as defined by CAT score greater than or equal to 10 and with normal spirometry, and it demonstrated that these patients had increased frequency of exacerbations and thickened airway walls as measured by CT imaging.[127] Further analyses of sputum demonstrated increased mucin concentrations even among non-obstructed patients with either chronic bronchitis symptoms or elevated CAT scores.[128] It is not known with certainty which of these patients will ultimately develop airflow obstruction, although evidence suggests that the presence of chronic bronchitis is a risk factor for more rapid lung function decline.[129] Whether or not these patients ultimately develop spirometric airflow obstruction, their symptoms and morbidity suggest the need for specific therapies.

BRONCHIECTASIS

Bronchiectasis is characterized by dyspnea and, in particular, copious mucopurulent sputum that tends to be greater than in typical COPD. The diagnosis can be established with the aid of high-resolution CT scan wherein bronchial wall thickening and luminal dilation is seen. Bronchiectasis in COPD is associated with increased mortality.[16] Whereas mild bronchiectasis is commonly seen in both COPD and asthma, moderate to severe bronchiectasis should raise a clinician's concern for immunodeficiency, cystic fibrosis, rheumatic disorders, ciliary motility disorders, alpha$_1$-antitrypsin deficiency, allergic bronchopulmonary aspergillosis, mycobacterial infection, and recurrent aspiration. (See Chapter 69.)

BRONCHIOLITIS OBLITERANS

Bronchiolitis obliterans (BO) is also known as constrictive bronchiolitis. This disorder is characterized by submucosal fibrosis, resulting in narrowing of the bronchiolar lumen. BO is a known complication of lung, heart, and bone marrow transplants but also may be seen in association with connective tissue diseases and inflammatory bowel disease. Inhalation of dusts or toxins, infection, and drug reactions are less frequent causes of BO. In some cases no clear etiology is identified. As opposed to those with COPD, patients with BO may have no significant smoking history and typically do not have significant emphysema on CT, which may show only hyperinflation and air trapping. Mosaic attenuation indicative of localized air trapping is common. Bronchial wall thickening may also be present. PFT demonstrates severe, progressive, and irreversible airflow obstruction but is not typically associated with severe D_{LCO} impairment. Unfortunately, BO responds poorly to therapy. (See Chapter 72.)

DIFFUSE PANBRONCHIOLITIS

Diffuse panbronchiolitis is a rare form of bronchiolitis involving the upper and lower respiratory tracts seen primarily in Japan and only rarely outside the Far East.[130,131] Genetic factors, specifically human leukocyte antigen haplotypes, are thought to contribute to the pathogenesis and geographic distribution of this disease. Such patients typically present with chronic sinusitis, cough productive of copious sputum, dyspnea, wheezing, and weight loss. Airflow obstruction is a common feature, and high resolution CT may show diffusely thickened and dilated bronchi or tree-in-bud opacities corresponding to bronchiolitis. Confirming this diagnosis is important because diffuse panbronchiolitis often improves with macrolide antibiotics.

LYMPHANGIOLEIOMYOMATOSIS

Lymphangioleiomyomatosis is a rare disorder affecting women almost exclusively.[132] It is caused by a mutation in the tuberous sclerosis-1 or sclerosis-2 gene, either sporadically or in the setting of tuberous sclerosis, resulting in the proliferation of interstitial smooth muscle cells and pulmonary cyst formation. Other clinical characteristics include renal angiomyolipomas and chylous effusions. Lymphangioleiomyomatosis is also characterized by airflow obstruction and spontaneous pneumothoraces. Therefore it is not infrequently mistaken for emphysema. However, an expert radiologist should be able to distinguish pulmonary cystic changes from emphysematous holes. The presence of other characteristic clinical features can be helpful in the diagnosis. (See Chapter 97.)

TREATMENT

Until recently, treatment of COPD was focused entirely on relief of symptoms because treatment options were few and were believed to be largely ineffective. In fact, the literature reported that the only interventions that changed the natural history of COPD were smoking cessation[133,134] and oxygen in patients with hypoxemia.[135,136] More recently, however, clinical trials have demonstrated that pharmacologic treatments can prevent or attenuate acute exacerbations of COPD, and the data suggest that some can slow the inexorable loss of lung function over time, which is the hallmark of COPD.[137–139] These observations have appropriately shifted the focus to a more proactive approach, aiming to identify patients earlier in the course of their disease and to implement treatment regimens that would not only relieve symptoms but also prevent exacerbations,

prevent disease progression, improve exercise tolerance, and improve quality of life.

GENERAL PRINCIPLES OF TREATMENT

Goals of treatment of COPD are to *reduce risk* by preventing and treating exacerbations, preventing disease progression, and reducing mortality; to *reduce symptoms*, which include relief of dyspnea, improved exercise tolerance, and improved health status; and, at the same time, to *minimize the adverse effects* of medications.

Reduction of Risk Factors

In the case of COPD, risk reduction refers to interventions that may decrease the likelihood of developing the disease, slow disease progression, decrease exacerbations, and reduce mortality. Although our knowledge of the factors that contribute to each of these is limited, there are substantial data on some factors that contribute to each of these.

Smoking Cessation. Throughout the developed world, cigarette smoking is the most important risk factor for the development of COPD. Public health and educational programs aimed at discouraging people from smoking ("primary prevention") and efforts to help active smokers stop are probably the most important interventions for COPD. In their landmark publication in 1977,[134] Fletcher and Peto showed that, in patients with COPD who stopped smoking, the accelerated loss of lung function slowed until it more closely paralleled the annual decrement seen in nonsmokers (Fig. 64.6). Nearly 2 decades later, the National Institutes of Health–sponsored Lung Health Study demonstrated that, in smokers with COPD, smoking cessation reduced the rate of decline in lung function, whereas inhaled bronchodilator therapy did not.[133] In a 14.5-year follow-up to the Lung Health Study, Anthonisen and colleagues[140,141] reported that the lung-function benefit continued for persistent quitters; there was also a mortality (all-cause) benefit for those who maintained abstinence. Perhaps more important, even those whose smoking cessation was intermittent experienced a benefit compared with continued smokers. Smoking cessation education and support should be offered to every patient with COPD at every visit. (For more details on smoking hazards and cessation, see Chapters 65 and 66).

Biomass Fuel. In the developing world, cigarette smoke is less of an issue than is exposure to smoke from biomass fuel, used for cooking and heating. The exposure is particularly great for women and their young children, who may spend the greater part of each day indoors with an unvented fire, fueled by wood, dung, or kerosene. Such exposure has been associated with chronic bronchitis and COPD.[142–145] Guarnieri and colleagues[146] showed that something as simple as a vented stove can decrease gene expression for markers of inflammation in sputum. (For more information, see Chapter 102.)

Environmental Controls. In addition to active and secondary smoke exposure, allergens and air pollutants may have an impact on COPD. Catastrophic air pollution events in the Meuse Valley, Belgium; Donora, Pennsylvania; and London, England[147–149] speak to the potential for air quality

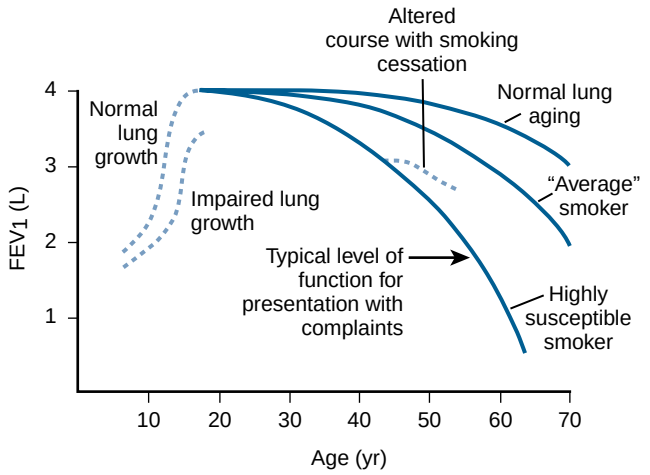

Figure 64.6 Fletcher-Peto curve of the natural history of COPD. Lung function increases with growth in childhood and adolescence. Fetal and childhood events can affect lung growth and development, resulting in reduced maximally attained lung function, for convenience shown here as a forced expiratory volume in 1 second (FEV_1) of 4 L. Actual predicted values depend on height and gender. After growth is completed, lung function remains constant for some time, the "plateau phase," after which lung function declines at an accelerating rate with age. Smoking reduces the duration of the plateau phase and accelerates the rate of lung function loss. Smoking cessation early in the course of the disease can reduce the rate of lung function loss to that of a nonsmoker. Patients typically present with symptoms when lung function declines below 50% of that in young adulthood but may have limitation much earlier.

to impact people with lung disease. In addition, a growing body of evidence suggests that long-term exposure to even low levels of air pollution increases the risk for COPD.[150] Also, people with COPD who also have allergic disease have higher levels of respiratory symptoms and are at higher risk for COPD exacerbations.[151] As a consequence, people with COPD should avoid noxious exposures, heed air quality warnings, and be cautious of ongoing occupational exposures.

Prevention of Respiratory Infections. A significant proportion of COPD exacerbations are triggered by respiratory infections. Although there are data to suggest that patients with COPD are more susceptible to respiratory infections because of impaired mucociliary clearance, a more important issue is that those with COPD are more susceptible to the *consequences* of respiratory tract infections. As a general rule, every patient with COPD should be immunized annually against influenza, which is effective at reducing the incidence of influenza, regardless of the severity of COPD,[152] and has been demonstrated to reduce mortality in older adults.[153,154] In addition, all should be vaccinated against *S. pneumoniae*. Despite a belief that older patients with COPD might not respond well to immunization, pneumococcal vaccines have been shown to be effective in this population.[155,156] Chronic antibiotics for prophylaxis are not a part of standard care for COPD because early trials showed they were not useful.[157–160] However, more recent trials with erythromycin and moxifloxacin have demonstrated a reduction in exacerbations.[161,162] There has been a particular interest in macrolide antibiotics because of their demonstrated value in diffuse panbronchiolitis and in cystic fibrosis and because they may have anti-inflammatory

and antimicrobial properties. In a prospective, randomized, double-blind trial of 1142 patients with exacerbation-prone COPD, the NHLBI's COPD Clinical Research Network found that daily azithromycin for 1 year decreased the frequency of exacerbations by 27% and improved quality of life.[163] Enthusiasm for this approach has been tempered by the small risk of ototoxicity and by the potential for QTc prolongation by macrolides. Data suggest that screening subjects for history of cardiac disease and obtaining electrocardiograms before starting macrolides virtually eliminates the risk of cardiac rhythm disturbance.[164] Thus, in selected patients who neither have cardiac disease nor take concomitant medications that affect the QTc interval, and who experience frequent exacerbations with the attendant morbidity and mortality, the use of azithromycin is probably warranted.

Prevention of Exacerbations. Exacerbations of COPD are sentinel events and are closely associated with disease progression. Increasing severity of COPD is associated with increased exacerbations and need for hospitalization, but, for every stage of severity, severe exacerbations are associated with increases in short-term and long-term all-cause mortality.[165] Exacerbations are independently associated with prognosis, and mortality increases with the frequency of hospitalizations. In one study of 305 men with COPD, only 20–30% of patients who were readmitted for exacerbation after an initial hospitalized exacerbation survived 5 years.[166] Although supporting data are lacking, the hope is that, by preventing exacerbations, lung function may be preserved and deterioration prevented. ICSs, long-acting β-agonists, long-acting muscarinic antagonists, and macrolide antibiotics have all been shown to reduce exacerbations. Unfortunately, even patients taking these medications may still experience as many as 1.4 exacerbations per year.[167]

PHARMACOTHERAPY

The goals of treatment include dyspnea relief and exacerbation prevention with the aim to preserve functional status and quality of life. Most medications for COPD are administered by inhalation. Standard therapy consists of inhaled bronchodilators, either β-agonists or muscarinic antagonists (antimuscarinics or anticholinergics), and inhaled corticosteroids. The latter have been demonstrated to be most effective in patients at increased risk for exacerbations and who demonstrate increased peripheral blood eosinophils. Oral agents include phosphodiesterase-4 inhibitors (e.g., roflumilast) and, less commonly, methylxanthines (e.g., theophylline).

The choice of medications should be based on an assessment of the severity of airflow obstruction, symptoms, frequency and severity of exacerbations, the patient's functional limitation, and the availability and local cost of medications. Formerly, medication decisions were based primarily on severity of airflow obstruction; guidelines now, as exemplified by GOLD,[34] emphasize a metric that includes obstruction (GOLD grade), based on the FEV_1% predicted; symptoms, based on either the mMRC dyspnea scale[168] or the CAT[19]; and risk of exacerbations, based on events documented in the prior year as a marker of future risk. Using this tool, patients can be categorized into class A, B, C, or D (Fig. 64.7), and GOLD provides specific treatment recommendations for each category at initial diagnosis (Table 64.3). Patients' level of symptoms and exacerbations should be further reviewed periodically and medications adjusted as outlined in Figure 64.8.

Bronchodilators

Bronchodilators are recommended for all patients with COPD. Pharmaceutical classes of bronchodilators include β-agonists, muscarinic antagonists (antimuscarinics or anticholinergics), and methylxanthines. Unlike asthma, where bronchodilator reversibility is part of the definition, airflow obstruction in COPD is often thought of as "irreversible." This is not, however, completely true. Although the diagnosis of COPD requires airflow obstruction that persists after bronchodilators, most patients with COPD demonstrate some improvement in spirometry. This response can vary from day to day.[169] In one study of 1552 patients with COPD who were tested with albuterol, ipratropium, or the combination on four occasions over 3 months, only 37–56% had 15% or better improvement in FEV_1 on all four test dates, but 90% or more had greater than or equal to 15% reversal on at least one occasion.[170] Therefore even patients who do not respond to bronchodilator testing in the pulmonary function laboratory should be given a clinical trial of bronchodilators. Although the increase in FEV_1 may be modest, it may be sufficient to improve lung emptying and, by this mechanism, reduce dynamic hyperinflation.[171–173] In multiple studies, bronchodilators have been shown to reduce dyspnea and increase exercise tolerance in patients with chronic stable COPD.[174,175]

β-Adrenergic Agonists

These medications bind directly to β-receptors located on airway smooth muscle and dilate the airway. Less prominent effects include increased ciliary beat frequency that promotes mucus transport along the mucociliary escalator[176] and improved respiratory muscle endurance.[177] β-Agonists are available in both short-acting and long-acting preparations and can be administered by inhalation, orally, subcutaneously, or intravenously. For treatment of COPD, β-agonists should only be given by inhalation because the other routes are associated with an unacceptably high risk of systemic adverse effects.

Short-acting β-agonists (SABAs) include albuterol (salbutamol), levalbuterol, terbutaline, and fenoterol. Albuterol is a racemic mixture of both (R)- and (S)-enantiomers of albuterol; levalbuterol is the (R)-enantiomer alone. The (R)-enantiomer is thought to be responsible for bronchodilation, whereas the (S)-enantiomer is believed to cause tremor, tachycardia, and perhaps airway inflammation. Thus levalbuterol would be expected to be better tolerated than albuterol. In fact, for most patients with stable COPD who use their SABA for symptom management, the added advantage of levalbuterol over albuterol[178] is probably not significant.[179] Albuterol is also available in combination with ipratropium (a muscarinic antagonist). Terbutaline inhalers are no longer sold in the United States; fenoterol is available in many parts of the world but not in the United States.

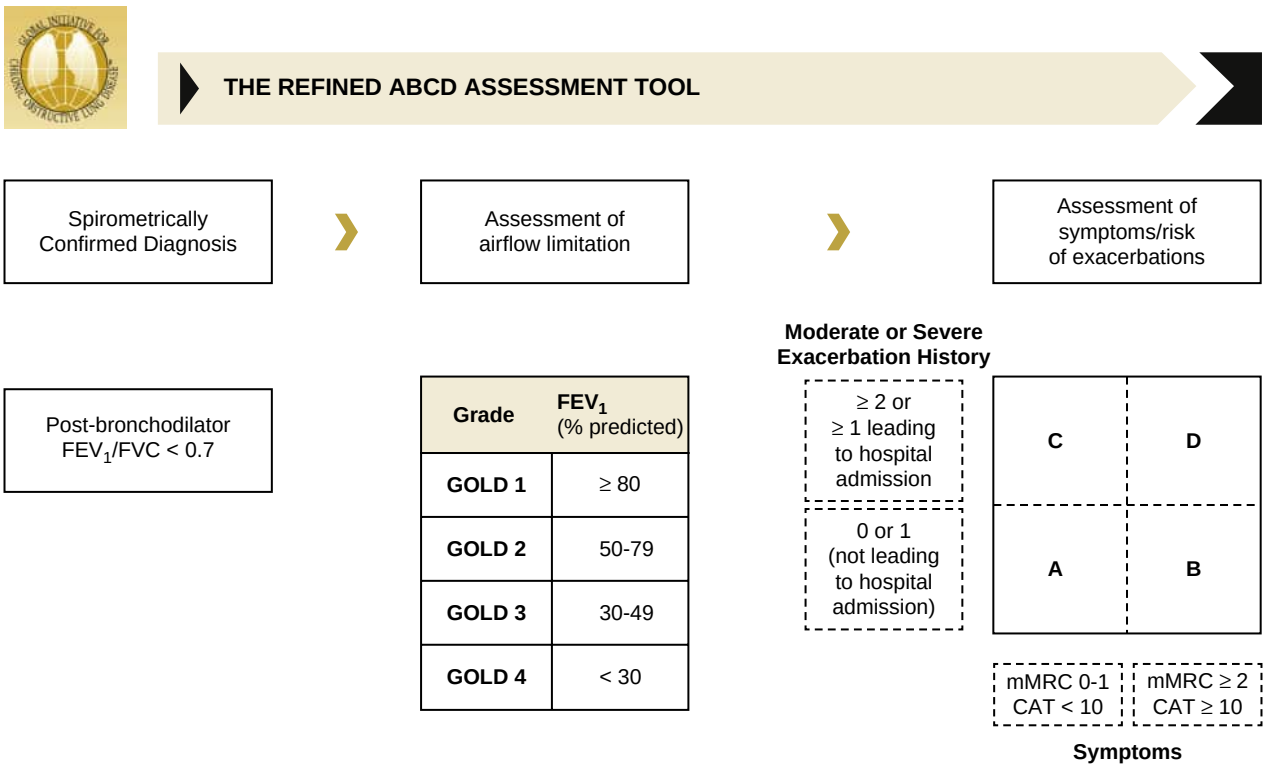

Figure 64.7 ***Global Initiative for Chronic Obstructive Lung Disease*** **(GOLD) classification system.**[34] When assessing risk, two or more moderate exacerbations or one severe (hospitalized) exacerbation history places patients into the high-risk category. When assessing symptoms, Modified Medical Research Council (mMRC) dyspnea scale score of 2 or greater or COPD Assessment Test Score of 10 or greater places patients into the "high symptoms" category. CAT, COPD Assessment Test; FEV_1, forced expiratory volume in 1 second; FVC, forced vital capacity. (From Global Initiative for Chronic Obstructive Lung Disease. Global Strategy for the Diagnosis, Management, and Prevention of Chronic Obstructive Pulmonary Disease, 2019. http://www.goldcopd.org/.)

Table 64.3 Initial Pharmacologic Management of COPD

Patient Group	Initial Pharmacologic Treatment
A	Bronchodilator
B	Long-acting bronchodilator (LAMA *or* LABA)
C	LAMA
D	LAMA *or* LAMA + LABA* *or* ICS + LABA†

*Consider if highly symptomatic (e.g., CAT ≥ 20).
†Consider if eosinophil count is ≥ 300.
LABA, long-acting β-agonist; LAMA, long-acting muscarinic antagonists; ICS, inhaled corticosteroids.
From Global Initiative for Chronic Obstructive Lung Disease. Global Strategy for the Diagnosis, Management, and Prevention of Chronic Obstructive Pulmonary Disease, 2019. http://www.goldcopd.org/.

SABAs for inhalation are available in solution for administration by a nebulizer, metered-dose inhaler, and *dry powder inhaler* (DPI). The combination of albuterol and ipratropium is available in a soft mist inhaler. Many studies have shown that metered-dose inhalers, DPIs, and soft mist inhalers are as effective as nebulizers in patients who are able to use the devices properly. Unfortunately, the proper technique for using different devices is not the same, and patients need detailed instructions and periodic assessment of their technique. In addition, DPIs require a much higher inspiratory flow to inhale the proper dose than do metered-dose inhalers, and some patients with moderate to severe COPD may not be able to generate adequate flows. For these individuals and for those whose medical or mental status makes coordinated breathing efforts difficult, nebulized β-agonists may be preferable.[180]

The major advantage of SABAs is their rapid onset of action, within 5 to 15 minutes after inhalation. Their effects last for 2 to 6 hours. As noted earlier, most patients with COPD demonstrate a modest improvement in FEV_1, and many studies and meta-analyses support their use for COPD.[181] The combination of albuterol and ipratropium results in greater and more sustained improvement in lung function than either drug alone.[182–184] When used at the recommended doses, inhaled SABAs are thought to be safe. The major adverse effects include tremor, anxiety, tachycardia, and hypokalemia. In a retrospective case-control cohort study of more than 70,000 patients with COPD, initiation of short- or long-acting β-agonists was associated with increased risk for arrhythmias,[185] but the study did not account for multiple potential confounders. Adverse effects are dose dependent and are less common with inhaled compared with systemic dosing and with optimized inhaler technique. Fortunately, tachyphylaxis to the systemic side effects of β-agonists is greater than tachyphylaxis to the bronchodilator effect.

Long-acting β-agonists (LABAs) typically produce bronchodilation that lasts for 12 hours or more. Salmeterol was the first LABA to be studied extensively. Its onset of action is much slower than that of albuterol, on the order of 20 to 30 minutes. Formoterol has a similar duration of action to salmeterol but an onset of action nearly identical

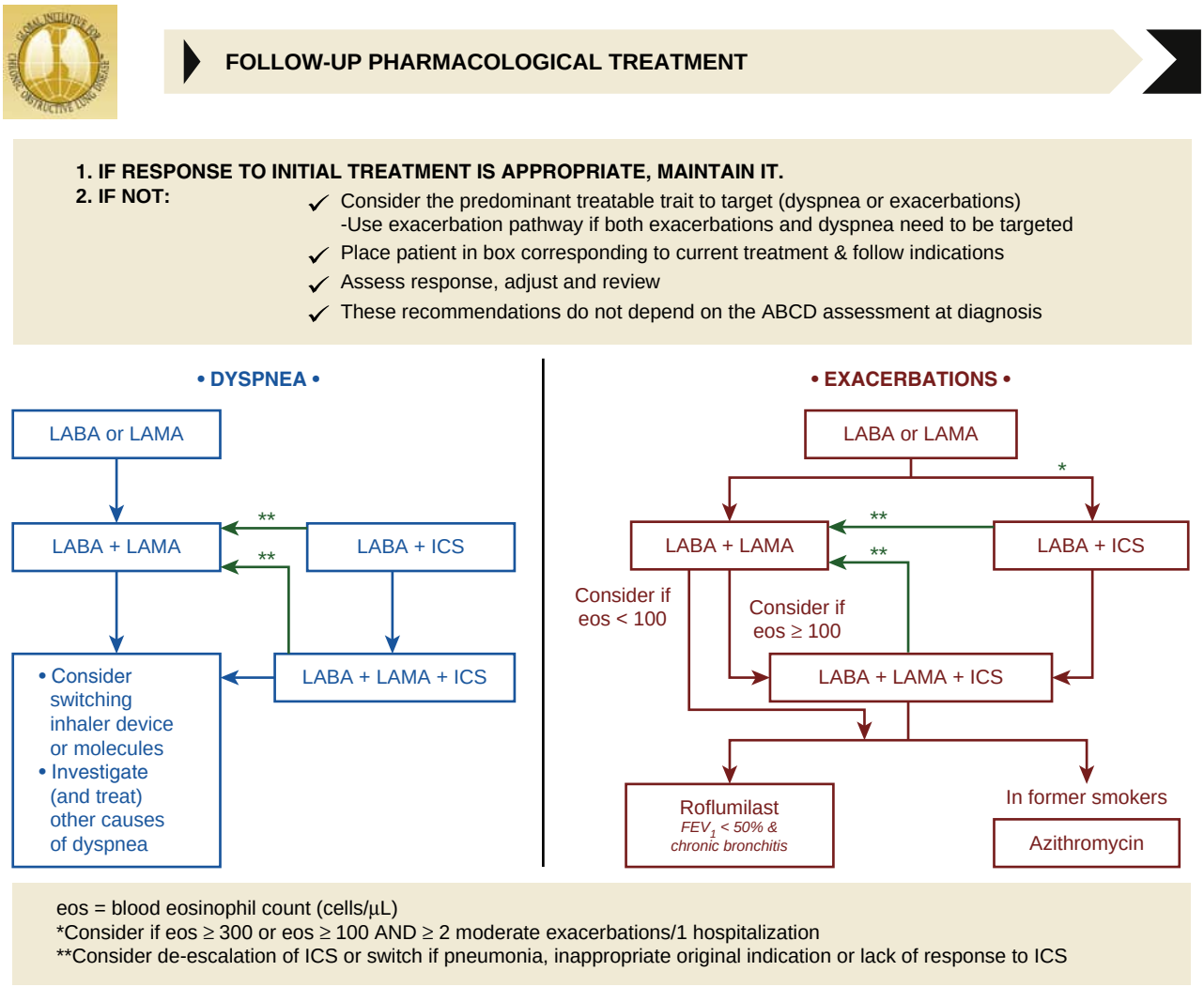

Figure 64.8 Follow-up pharmacologic treatment, *Global Initiative for Chronic Obstructive Lung Disease* (GOLD). If response to initial treatment is appropriate, maintain it. If not, consider the predominant treatable trait to target (dyspnea or exacerbations), use exacerbation pathway if both exacerbations and dyspnea need to be targeted. FEV_1, forced expiratory volume in 1 second; ICS, inhaled corticosteroids; LABA, long-acting β-agonist; *LAMA,* long-acting muscarinic antagonists. (From Global Initiative for Chronic Obstructive Lung Disease. Global Strategy for the Diagnosis, Management, and Prevention of Chronic Obstructive Pulmonary Disease, 2019. http://www.goldcopd.org/.)

to albuterol. Both salmeterol and formoterol must be taken twice daily. Arformoterol is the (R)-enantiomer of formoterol. Indicaterol has a rapid onset and a duration of action of nearly 24 hours and thus requires only once-daily dosing. The bronchodilator effect of indicaterol is greater than that of salmeterol or formoterol. Vilanterol is another LABA with a rapid onset of action and a duration of action of approximately 24 hours. It is not used as monotherapy but has recently been approved in the United States and in Europe for use in combination with the ICS fluticasone or the long-acting muscarinic antagonist, umeclidinium.

Many studies have demonstrated a benefit of LABAs in patients with stable COPD.[78,186–193] Salmeterol and formoterol significantly improve lung function, dyspnea, and quality of life, and decrease the rate of exacerbations.[78,194–198] Salmeterol has been shown to reduce hospitalizations.[78] Indicaterol improves dyspnea and health status and reduces exacerbations.[199–202] The adverse effects reported with LABAs are similar to those described for SABAs. Of note, the association of LABA use with deaths that raised concern in the asthma community (see Chapter 62) has not been seen for COPD, and monotherapy with a LABA appears to be both safe and efficacious for COPD.

LABAs are frequently combined with an ICS in the same inhaler, and currently available preparations include fluticasone-salmeterol, budesonide-formoterol, mometasone-formoterol, and fluticasone-vilanterol. Many studies have shown that combination therapy is often more effective than either agent alone, and various guidelines provide recommendations for how and when to escalate treatment beyond short-acting bronchodilators. In general, ICS are reserved for patients who are prone to exacerbations.

Muscarinic Antagonists

Muscarinic antagonists, also known as anticholinergics or antimuscarinics, block the effects of acetylcholine on the M3 muscarinic receptors on airway smooth muscle. The M3 receptor is the predominant subtype of receptor mediating parasympathetic control of smooth muscle. Anticholinergics were used historically, long before β-agonists, in the form of stramonium and belladonna alkaloids,[203,204] then atropine. The newer quaternary amines,

such as ipratropium and glycopyrrolate, as well as tiotropium and aclidinium, are better tolerated because they do not cross the blood-brain barrier. In addition, tiotropium, aclidinium, glycopyrrolate, and umeclidinium have pharmacokinetic selectivity for the M3 receptor and dissociate more rapidly from M2 receptors, which are found on cholinergic nerve terminals and inhibit acetylcholine release.[205] Thus the relative lack of M2 binding by these muscarinic antagonists may allow acetylcholine to bind to M2 receptors, thereby inhibiting further acetylcholine release and reducing bronchoconstriction.[206]

Short-acting muscarinic antagonists (SAMAs) include ipratropium and oxitropium. They increase FEV_1 with an onset of action of 10 to 15 minutes and a duration of action of 4 to 6 hours. Ipratropium improves lung function, increases exercise capacity, decreases dyspnea, and decreases cough.[207] Ipratropium monotherapy is more effective than SABAs at improving lung function, health status, and need for systemic corticosteroids,[208] but, when used in combination, their effects are additive and the duration is longer.[182–184]

Long-acting muscarinic antagonists (LAMAs) include tiotropium, aclidinium, umeclidinium, glycopyrrolate, and revefenacin. Most are slower in onset than ipratropium but last longer, with bronchodilation lasting at least 12 hours after aclidinium[209] and glycopyrrolate and more than 24 hours after tiotropium, umeclidinium, and revefenacin.[210–212] Tiotropium decreases symptoms, improves health status, and reduces exacerbations by 20–25%[213,214] and reduces hospitalizations.[211] It appears to improve the effectiveness of pulmonary rehabilitation, perhaps by decreasing dynamic hyperinflation.[215] When compared head-to-head with salmeterol, tiotropium increased time to first exacerbation and reduced the annual rate of exacerbations more than did salmeterol.[216] Although less data are available for the newer LAMAs, their effects on lung function and on dyspnea and exacerbations appear to be similar.[209]

In general, both SAMAs and LAMAs have good safety profiles. The most common side effects are dry mouth and urinary retention. Medication that contacts the eye, either by hand contact or by aerosolization, can cause blurred vision and can precipitate glaucoma. A retrospective database review[217] and a meta-analysis of ipratropium and tiotropium in COPD[218] suggested that anticholinergic therapy was associated with an increased risk of cardiovascular death, myocardial infarction, and stroke. However, a prospective study of almost 6000 patients with COPD who were treated with tiotropium or placebo found no increased risk of cardiovascular events or mortality.[219,220] A long-term study of more than 17,000 patients with COPD, designed specifically to examine safety of a soft mist Respimat device, concluded that tiotropium administered by the Respimat device had a safety profile similar to tiotropium delivered by the DPI HandiHaler device in patients with COPD and was not associated with an increased risk of death.[221]

Methylxanthines

Methylxanthines are nonselective inhibitors of phosphodiesterase and, by this mechanism, have a modest bronchodilator effect.[197,222,223] Theophylline is the most commonly used methylxanthine and, in stable COPD, its effect is greater than that of placebo but less than that of LABAs or LAMAs. In addition to its bronchodilator effect, theophylline is reported to improve inspiratory muscle function[224–226] and to have anti-inflammatory effects.[227] Its effect on reducing symptoms is greater than its effect on airway function, suggesting that these alternative mechanisms may be important. However, a recent placebo-controlled, double-blinded study of low-dose theophylline (200 mg once or twice daily) as add-on therapy to inhaled corticosteroids found no difference in the rate of exacerbations[228] Further, because theophylline is a nonselective phosphodiesterase inhibitor, its actions are not all beneficial. The major adverse effects are insomnia, nausea, vomiting, cardiac arrhythmias, and seizures. These toxicities are dose dependent, but the onset of severe adverse events (e.g., ventricular arrhythmias, seizures) may not be heralded by warning symptoms, such as nausea or insomnia. In addition, blood levels are affected by age, liver disease, congestive heart failure, and many drug interactions. To minimize toxicity, current guidelines recommend targeting blood levels of 5 to 10 μg/mL rather than 15 to 20 μg/mL as was done previously. Because of its narrow therapeutic index and modest benefits, theophylline is not recommended as a first-line drug but can serve as an alternative for patients intolerant of LABAs and LAMAs or in settings where these drugs are too expensive.

Phosphodiesterase-4 Inhibitors

Phosphodiesterase-4 (PDE-4) inhibitors act by blocking the breakdown of cyclic adenosine monophosphate. By this mechanism, they decrease airway inflammation; they have no direct bronchodilator activity. Roflumilast is an oral PDE-4 inhibitor that has been approved for patients with chronic bronchitis and a history of exacerbations.[14] In a meta-analysis of 23 randomized trials of two different PDE-4 inhibitors (roflumilast and cilomilast), the PDE-4 inhibitors reduced exacerbations (odds ratio, 0.78; 95% confidence interval, 0.72–0.85) and produced a modest increase in FEV_1 (50 mL; 95% confidence interval, 39–52).[229] When roflumilast was added to salmeterol or tiotropium, the prebronchodilator FEV_1 increased.[14,15] Roflumilast appears to have greatest effect in patients with two or more exacerbations in the prior year or a hospitalized exacerbation[230] and high blood eosinophils.[231] Because its effect on exacerbations is much greater than its effect on airway function, guidelines recommend that roflumilast be used in combination with a long-acting bronchodilator.[34] Use of PDE-4 inhibitors has been limited by side effects. The most common are nausea, anorexia, abdominal pain, diarrhea, weight loss, sleep disturbances, and headache.[14,15,232] Monitoring weight during treatment is warranted.[34]

Corticosteroids

Inhaled Corticosteroids. Airway and systemic inflammation are critical components of the pathogenesis of COPD.[233–235] Therefore corticosteroids, with their anti-inflammatory effects, are an appealing intervention. ICS offer the additional advantage of minimizing systemic exposure. Early studies were not able to show that ICS altered the natural history of COPD. However, ICS have been shown to improve symptoms, lung function, and quality of life and to reduce the frequency of COPD exacerbations, especially in patients with an FEV_1 less than or equal to 60% of predicted. The improvement in FEV_1 achieved with ICS

(50–100 mL) is typically less than that observed with bronchodilators.[137,138] The reduction of exacerbations by ICS is more significant and is comparable to that observed with LABAs or LAMAs (≈20–25%).[236–238] Guidelines recommend that ICS be used in combination with a long-acting bronchodilator in subjects who are prone to exacerbations but that they not be used as monotherapy.[34] Four large trials in which patients with COPD were treated with ICS for 3 to 5 years failed to demonstrate a reduction in loss of lung function over time.[137,138,239,240] However, in a post hoc analysis of the *Towards a Revolution in COPD Health* (TORCH) trial, in which 6112 subjects with moderate to severe COPD were randomly treated for 3 years with placebo, fluticasone, salmeterol, or the fluticasone-salmeterol combination, Celli and colleagues[241] reported that each active treatment arm reduced the rate of decline in FEV_1. Whether this benefit reflects the reduction in exacerbations or a more direct effect on the airway, perhaps by decreasing inflammation, is not known.

Most recently, ICS has been studied as part of "triple" combination therapy along with LABA and LAMA. The IMPACT study recently demonstrated among on-treatment subjects a reduction in all-cause mortality in the two ICS-containing arms (ICS/LABA/LAMA and ICS/LABA) compared to the non–ICS-containing arm (LABA/LAMA) of the study.[242] These are the strongest data to date demonstrating a role for ICS in reducing mortality in COPD. It should be noted, however, that the *InforMing the Pathway of COPD Treatment* (IMPACT) trial patient population had fairly severe COPD. The mean FEV_1% predicted was 45% and mean CAT score approximately 20. Nearly half the patient population experienced a moderate exacerbation in the prior year, and roughly one-quarter had experienced a hospitalized exacerbation in the prior year. Hence the results with respect to mortality reduction should be judged within the context of the patient population studied.

ICS are relatively safe, especially compared to systemic corticosteroids. The most common adverse effects are oral candidiasis (thrush) and dysphonia, both of which can be minimized by careful inhalation technique, followed by rinsing the mouth and gargling.[137,138] Increased skin bruising is probably a manifestation of steroid-induced capillary fragility. Reduced bone density has been reported after long-term treatment with triamcinolone,[243] but studies with budesonide and fluticasone have not found similar results, perhaps because these patients with COPD had a high prevalence of osteoporosis at baseline.[244,245] However, although ICS clearly reduce the frequency of exacerbations in COPD, they have been associated with an increased incidence of pneumonia.[78]

Systemic Corticosteroids. With rare exceptions, the use of systemic corticosteroids should be reserved for the treatment of exacerbations; in patients with stable disease, even when severe, the risk of adverse effects is probably greater than the likelihood of benefit. Chronic use of systemic corticosteroids is associated with increased mortality,[246,247] which may reflect corticosteroid effects or the underlying severity of the COPD. On occasion, in exacerbation-prone patients who require frequent courses of high-dose systemic corticosteroids, a very low daily dose of corticosteroids may protect against exacerbations and thereby reduce the total annual steroid exposure. If this unusual approach is followed, the lowest possible dose of corticosteroids should be used. If patients are reluctant to reduce their dose, they may be reassured by spirometry demonstrating a stability of FEV_1.

Combination Therapy

Patients who remain symptomatic after a period of treatment with a single long-acting bronchodilator (either LAMA or LABA) may benefit from addition of a second drug. Choices include either an ICS or a second long-acting bronchodilator from the other pharmacologic class. Accumulating data suggest that patients with significant dyspnea experience even greater benefit with dual bronchodilator therapy.[248] Increasing evidence also suggests that patients with elevated levels of blood eosinophils experience greater benefit with inhaled corticosteroids.[66,249] Although no threshold perfectly identifies ICS responders, an eosinophil count may be useful. Data suggest that ICS have little effect on exacerbation reduction at a blood eosinophil count less than 100 cells/μL, whereas greater than 300 cells/μL identifies patients with greatest likelihood to respond.

In two large trials, combination therapy improved outcomes significantly compared to each of the other treatment arms alone (placebo, LABA, ICS, LAMA). In the TORCH trial of 6112 patients with moderate to severe COPD, the combination of fluticasone-salmeterol improved lung function, health status, and exacerbations more than either agent alone[78] and was cost-effective.[250] In the *Investigating New Standards for Prophylaxis in Reduction of Exacerbations* (INSPIRE) trial, 1323 patients with severe COPD were randomly treated with fluticasone-salmeterol or tiotropium for 2 years.[251] There was no difference in exacerbations, but mortality was less in the fluticasone-salmeterol group, and health status was better, despite the finding that pneumonia was more frequent in the fluticasone-salmeterol group. Combinations of budesonide-formoterol, mometasone-formoterol, and fluticasone-vilanterol have also been shown to improve some clinical outcomes.

Several more recent studies have compared ICS/LABA to LABA/LAMA. The FLAME study compared fluticasone-salmeterol to indacaterol-glycopyrrolate for exacerbation reduction. The annual rate of moderate or severe exacerbations was higher in the fluticasone-salmeterol group compared to the indacaterol-glycopyrrolate group (1.19 vs. 0.98; rate ratio).[252] However, the IMPACT study also compared ICS/LABA to LABA/LAMA, specifically examining fluticasone-vilanterol versus umeclidinium-vilanterol, and found the annual rate of exacerbations to be *lower* with fluticasone-vilanterol than with umeclidinium-vilanterol (1.25 vs. 1.40).[242] It is not completely clear why these two studies produced different results, although several key study design aspects lend some insights. The IMPACT patient population had to have CAT greater than or equal to 10 and at least one moderate or severe exacerbation in the prior year if FEV_1 was less than 50% predicted and at least two exacerbations or one hospitalized exacerbation in the prior year if FEV_1 was greater than 50% predicted. There was also no medication "run-in" for IMPACT. Patients were transferred directly from maintenance medication to study medication. The FLAME study enrolled patients with at least one exacerbation in the prior year and also required a one-month

run-in on tiotropium. Hence patients in IMPACT may have been sicker than those in FLAME.

Of interest, the IMPACT patient population also demonstrated increased ICS response with higher eosinophils that was not seen in the FLAME population,[253] again suggesting different types of patients. The SUNSET study compared patients on indacaterol-glycopyrrolate to those on fluticasone-tiotropium-salmeterol, where the fluticasone was withdrawn.[254] Here ICS withdrawal was associated with an increase in exacerbations for those with greater than or equal to 300 eosinophils/μL. The totality of the data would suggest that there are patients more likely to respond to ICS than others and that elevated eosinophils may be of assistance in identifying those patients. GOLD now identifies the threshold of 300 eosinophils/μL as those with greater likelihood to benefit from ICS, less than 100 eosinophils/μL as lower likelihood of benefit, and the range of 100 to 300 eosinophils/μL as an intermediate zone where ICS may be tried and response assessed.

Finally, guidelines suggest "triple inhaler therapy" for subjects whose symptoms or exacerbations are not controlled by any of the combinations already described.[34] Several recent studies support this recommendation, demonstrating greater lung function and symptom improvement and exacerbation reduction for ICS/LABA/LAMA compared to either ICS/LABA or LABA/LAMA.[242,255–258] The majority of these studies examined patients with significant symptoms as measured by CAT of 10 or greater and at least one exacerbation in the prior year, supporting triple therapy as a treatment option for patients with either persistent symptoms or exacerbations despite dual therapy.

Stepwise Pharmacologic Management

Enormous progress has been made from the time, not long ago, when few drugs for COPD were available in the therapeutic armamentarium. Now, many pharmaceutical categories have been shown to improve outcomes in COPD. Often there are many choices within each drug class and a variety of ways to progress through a therapeutic algorithm. The GOLD recommendations provide a framework for making these decisions.

In the past, recommendations for pharmacologic treatment were based primarily on spirometry. Recognizing that FEV_1 alone is a poor descriptor of disease status, the GOLD committee revised the approach to focus on symptoms and exacerbation history (see Fig. 64.7). Based on these variables, patients are assigned to groups A, B, C, or D, and recommendations for initial management are provided for each group (see Table 64.3).

After implementation of initial treatment, patients should be reassessed periodically to see if they are achieving goals of treatment. Common barriers to success include failure to adhere to prescribed regimen, poor inhaler technique, inappropriate choice of initial treatment, and comorbid conditions. For patients with good control, de-escalation should be considered. GOLD provides a second algorithm for follow-up management, where escalation and de-escalation or change in medications are based on dyspnea, exacerbations, and the presence or absence of peripheral blood eosinophilia (see Fig. 64.8).

Antioxidants and Mucolytics

Increased mucus production by hypertrophied and hyperplastic airway submucosal glands and goblet cells, together with impaired mucociliary clearance and cough, are frequent in patients with COPD. Although mucolytics have been evaluated in a number of long-term studies in COPD, the results are mixed and, in those studies demonstrating benefit (often those using higher doses), the effect is modest.[259–263] *N-acetylcysteine* (NAC) is a mucolytic and antioxidant that has been tested for its ability to slow the decline in lung function and prevent exacerbations. In the *Bronchitis Randomized on NAC Cost-Utility Study* (BRONCUS) trial, 523 patients at 50 centers were randomly assigned to 600 mg NAC or placebo daily. Patients were followed for 3 years. Neither the yearly rate of decline in FEV_1 nor the number of exacerbations per year differed between the NAC and the placebo group. However, subgroup analysis of those subjects who were not treated with an ICS suggested that NAC reduced exacerbations and hyperinflation.[264] A Cochrane review of 30 trials that included more than 7000 patients treated with NAC or other mucolytics concluded that there was a small effect on exacerbations but no effect on quality of life.[265] In its 2019 revision, the GOLD panel suggested that mucolytics may be useful in selected populations.[34]

Leukotriene Modifiers

Although the 5-lipoxygenase inhibitor zileuton and the cysteinyl leukotriene antagonists montelukast and zafirlukast are sometimes used for COPD, no data support their use, and guidelines do not recommend their use.[34]

NONPHARMACOLOGIC TREATMENT

Mucus Clearance

In patients with mucus hypersecretion and airflow obstruction, it may be very difficult to mobilize secretions. Maneuvers such as controlled cough[266] and the huff cough[267] can be helpful. In the former, patients take a deep breath, hold their breath for a few seconds, then cough two or three times with their mouth open and without taking another breath. The sequence is then repeated several times. Huff coughing involves one or two forced expirations starting at mid–lung volume and performed with the glottis open. Mucus clearance can also be facilitated by having patients breathe or cough through a device that generates high-amplitude oscillations[268] or with an external percussive device. These maneuvers are considered safe, but data supporting their use are limited.[269–272]

Oxygen

Two landmark studies conducted more than 30 years ago demonstrated the value of long-term oxygen therapy in patients with COPD and hypoxemia. The National Institute of Health's *Nocturnal Oxygen Therapy Trial* (NOTT) randomized 203 patients with COPD and hypoxemia to receive oxygen either for 12 hours overnight or for 24 hours/day for at least 12 months.[135] Overall mortality in the nocturnal oxygen group was 1.94 times that in the continuous oxygen group ($P = 0.01$). Almost simultaneously, the British mMRC compared the effect of oxygen administered for 15 hours/day with no oxygen (control) in 87 patients with

COPD, hypoxemia, carbon dioxide retention, and heart failure. Forty-five percent of the oxygen-treated patients died during the 5-year follow-up period compared with 67% of the control group.[136] In addition to this survival benefit, several studies have confirmed that administration of oxygen for at least 15 hours/day improves quality of life and neuropsychiatric metrics, reduces erythrocytosis, and improves pulmonary hemodynamics in patients with COPD and hypoxemia.[135,273,274]

Since then the National Institutes of Health sponsored the *Long-Term Oxygen Treatment Trial* (LOTT), which examined the benefits of supplemental oxygen therapy to patients with moderately low levels of oxygen[275] saturation. Specifically, patients with a blood oxygen saturation (peripheral capillary oxygen saturation, or Spo_2) from 89–93% at rest (moderate resting hypoxemia), or an Spo_2 below 90% during a 6MWT were randomized to 24-hour oxygen if their resting Spo_2 was 89–93% and oxygen only during sleep and exercise, if they had desaturation only during exercise. The primary outcome measure was time to first hospitalization or death. No significant difference in the primary outcome was seen between groups. Further, no differences were seen in quality of life, lung function, or 6MWD at the end of the study. Hence, although the NOTT and mMRC studies suggest mortality benefit of supplemental oxygen treatment with more severe hypoxemia, the LOTT study does not show clear benefit for treatment of individuals with more mild to moderate hypoxemia.

Indications for Oxygen. Based on these data, guidelines recommend long-term administration of oxygen (>15 h/day) to patients with COPD with resting hypoxemia. Criteria include arterial *partial pressure of oxygen* (Po_2) less than 55 mm Hg, or arterial Spo_2 less than 88% while breathing room air at rest. For those whose resting arterial Po_2 is between 56 and 59 mm Hg, long-term oxygen treatment is indicated if they demonstrate erythrocytosis (hematocrit ≥ 55%) or right heart dysfunction. After an exacerbation or another acute respiratory event, patients often have hypoxemia that resolves slowly over 1 to 2 months. For this reason, patients given oxygen as they are recovering should be reevaluated after approximately 1 month to determine if they continue to meet criteria for long-term oxygen treatment.

Oxygen During Exercise. Patients whose arterial Po_2 or Spo_2 are borderline at rest may develop worsening hypoxemia with exercise. This is especially true for patients with emphysema and a low diffusing capacity. Supplementary oxygen improves exercise endurance,[276,277] and even patients without hypoxemia may improve their exercise capacity with supplementary oxygen.[278] Although the LOTT study did not demonstrate benefit of oxygen therapy in this group of patients, it is still possible that supplemental oxygen during exertion is beneficial in some patients with mild hypoxemia at rest or exercise-related desaturation. Hence, although routine oxygen use in this group of patients is not recommended, individual patient factors may warrant a trial of oxygen.

If oxygen is prescribed, one of the goals of oxygen therapy is to permit patients to remain active. Ambulatory oxygen systems are intended to provide a lightweight, portable source of oxygen that can be carried as the patient pursues activities of daily living. Unfortunately, patients are often provided with "portable" systems that are not really conducive to ambulation. The standard E-cylinder, for example, weighs 22 pounds and must be pulled along on a bulky wheeled cart. Various lightweight oxygen reservoirs do exist, weighing as little as 4 pounds; portable oxygen concentrators weighing less than 3 pounds are another lightweight option. Health care providers must specify to oxygen vendors which ambulatory system they want for their patients.

Oxygen During Sleep. Just as they do with exercise, patients with COPD may experience a significant drop in arterial oxygen tension during sleep, due to a combination of increases in ventilation-perfusion mismatch and a change in ventilatory pattern[279] (see also Chapter 117). In patients who are not hypoxemic at rest, the long-term consequences of these episodes of nocturnal hypoxemia are unknown, as are the benefits of long-term oxygen.[280–282] Although many clinicians prescribe nocturnal oxygen for these patients, there is no evidence to support this approach. The International Nocturnal Oxygen Trial, a 4-year, multicenter, randomized, placebo-controlled trial of nocturnal oxygen in COPD patients without resting hypoxemia or OSA, was completed in 2019, and results will be available soon.[283]

Oxygen for Air Travel. When flying at altitudes higher than 12,000 feet, aircraft are pressurized to protect passengers and crew from hypoxemia, barotrauma, and other manifestations of altitude (see Chapter 106). The Federal Aviation Administration mandates that the cabin pressure must not drop below that of an altitude of 8000 feet (equivalent to 564 mm Hg). Although this pressurization is sufficient to prevent most barotrauma and altitude sickness, it does not eliminate the possibility of hypoxemia. Arterial Po_2 will drop and, in patients who are hypoxemic at rest at sea level or those who are borderline, the arterial Po_2 may fall to dangerous levels at altitude. Patients whose resting arterial Po_2 at sea level is greater than 70 mm Hg are likely to be safe to fly without supplementary oxygen.[284,285] When there is uncertainty about a patient's potential oxygen requirement at altitude, an altitude simulation test can be performed, using 16% oxygen to simulate the partial pressure of oxygen at 8000 feet.[286]

For patients who require in-flight oxygen, arrangements must be made with the airline in advance. In general, patients may not bring their own oxygen supply, and airlines usually charge for the oxygen they provide. Lightweight portable oxygen concentrators have become available, and these are approved by the Federal Aviation Administration for commercial air travel. Some airlines allow passengers to travel with their own concentrators (see Chapter 106).

Technical Issues for Oxygen Use. Most patients receive oxygen via a nasal cannula. Flow rates should be adjusted to achieve an Spo_2 greater than 90% (arterial Po_2 > 60 mm Hg). In general, patients who use oxygen 24 hours/day should increase the oxygen flow by 1 L/min during sleep and exercise, to prevent drops in arterial Po_2 during these periods. Oxygen-conserving devices that improve the efficiency of oxygen delivery increase the time that a

given volume of portable oxygen will last, allowing patients greater mobility. These include nasal cannulae with reservoirs that store oxygen during exhalation for delivery during inhalation, as well as breath-activated regulators that deliver an oxygen pulse only during inspiration. For use in the home, electric-powered oxygen concentrators are the most convenient, for they do not require replacement or refilling as is the case with gas cylinders or liquid oxygen. It is important that patients who depend on a concentrator have back-up cylinders on hand, in case of a power failure. Ambulatory systems include E-cylinders on wheeled carts, lightweight aluminum cylinders, liquid oxygen reservoirs, and portable concentrators. Many of these ambulatory systems weigh as little as 3 to 4 pounds and provide oxygen for 4 to 6 hours at a flow of 2 L/min.

Noninvasive Ventilation

For patients with acute exacerbations of COPD with hypercapnia and acidosis, bilevel positive airway pressure decreases mortality, need for intubation, and hospital length of stay.[287] For patients with stable COPD, the use of nocturnal noninvasive ventilation has been proposed to prevent desaturations during sleep and to improve both nocturnal and daytime respiratory function by "resting" respiratory muscles. Unfortunately, studies have provided conflicting results, with several trials each demonstrating prolonged time to readmission or death,[288,289] improved survival that was not sustained beyond 36 months,[290] or no benefit.[291,292] Some experts suggest a trial of high-pressure or high-intensity nocturnal noninvasive ventilation in hypercapneic patients with COPD who desaturate during sleep despite supplementary oxygen, but this recommendation is not included in COPD management guidelines.

PULMONARY REHABILITATION

Pulmonary rehabilitation is a comprehensive program that combines exercise training, smoking cessation, nutrition counseling, and education, in an attempt to improve the functional capacity and quality of life of patients with COPD. Formal rehabilitation programs have been shown to improve exercise capacity and quality of life and to decrease dyspnea and health care utilization.[293–296] In addition, a Cochrane review has suggested that pulmonary rehabilitation decreases mortality.[297] Pulmonary rehabilitation should be offered to all patients with COPD who are symptomatic (see Chapter 139).

SURGICAL TREATMENT OF EMPHYSEMA

More than 50 years ago, anecdotal reports of symptomatic improvement in patients with emphysema who underwent resection of concomitant lung cancers or bullae led physiologists to consider LVRS to improve the mechanical efficiency of respiratory muscles. Because of hyperinflation, respiratory muscles are forced to operate on the disadvantageous part of the length-tension curve; reducing hyperinflation was predicted to improve force generation by respiratory muscles, to improve lung elastic recoil, and to improve expiratory flow rates. Unfortunately, early procedures were associated with an unacceptably high mortality rate. In 1995 Cooper and colleagues[298] reported on their experience with 20 patients who underwent bilateral LVRS. By using a linear stapling device and strips of bovine pericardium to minimize air leak through the staple holes, they were able to eliminate this major cause of early mortality and reported very impressive improvements in FEV_1, arterial Po_2, 6MWD, dyspnea, and quality of life. This was followed by the *National Emphysema Treatment Trial* (NETT), a precedent-setting collaborative effort of the Centers for Medicare and Medicaid Services, the NHLBI, and the Agency for Healthcare Research and Quality. NETT enrolled 1218 patients with severe emphysema and compared LVRS to maximal medical treatment.[48] In patients with upper lobe–predominant emphysema and a low postrehabilitation exercise capacity, LVRS improved survival and quality of life.[299] In those patients with FEV_1 of 20% or less predicted and either homogeneous distribution of emphysema or DL_{CO} of 20% or less predicted, mortality was greater with LVRS compared to medical management.[300] These criteria are currently used to select patients for LVRS.

TREATMENT OF EMPHYSEMA WITH ENDOBRONCHIAL VALVES

Nonsurgical methods for reducing hyperinflation in severe emphysema have also been explored. In particular, endobronchial valves leading to lobar deflation mimic the mechanism of lung volume reduction surgery. The evidence basis for efficacy of this procedure is growing.[301–303] The LIBERATE study randomized 190 subjects to Zephyr endobronchial valve versus standard of care.[302] Patients with hyperinflation, greater than 50% emphysema in the target lobe, and at least 15% greater emphysema in the target versus ipsilateral lobes were enrolled. Patients also had to have no evidence of collateral ventilation between target and adjacent lobes. Endobronchial valve placement was studied in patients with both heterogeneous and homogenous emphysema. Patients receiving the valve demonstrated improvements in FEV_1, 6MWD, and SGRQ score. However, pneumothorax developed in 26.6% of valve-treated subjects. After the 45-day postprocedural period, patients treated with endobronchial valves trended toward lower numbers of exacerbations. This therapy is now clinically available and approved for treatment in many countries, including the United States. A second endobronchial valve, the Spiration valve, was also approved by the U.S. Food and Drug Administration in December 2018[303] (see Chapter 28).

ACUTE EXACERBATIONS

Definition

Perhaps surprisingly, it has not been easy to define an acute exacerbation of COPD. GOLD[34] states, "An exacerbation of COPD is an acute event characterized by a worsening of the patient's respiratory symptoms that is beyond normal day-to-day variations and leads to a change in medication."[304–306] This works sufficiently well that it allows classification of events in various studies and for comparisons across trials.

Triggers

Exacerbations of COPD are precipitated most often by respiratory tract infections. These may be viral or bacterial. A key event, even in individuals whose airways are chronically

colonized by bacteria, may be the acquisition of bacterial strains that are new to that patient.[307] Many patients are sensitive to air pollutants and experience an exacerbation when ambient levels increase.[308–310] In perhaps 30% of patients with COPD, no cause for exacerbations can be identified. Of interest, some patients have an exacerbation whenever one of these events takes place; others rarely do. Those who experience two or more exacerbations per year are often defined as "frequent exacerbators" and pose a unique challenge for management.

Treatment

The goal of treatment is to minimize the impact of the current exacerbation, to minimize loss of lung function, and to prevent the development of subsequent exacerbations. The vast majority of exacerbations can be managed without hospitalization. Indications for hospitalization include severe dyspnea or respiratory insufficiency, severe underlying COPD, serious comorbidities, frequent exacerbator phenotype, older age, and insufficient support at home. Supplemental oxygen should be administered if necessary to achieve an Spo_2 greater than 88%. After 30 to 60 minutes, arterial blood gases should be assessed for evidence of carbon dioxide retention.

Bronchodilators. During an acute exacerbation, SABAs should be used aggressively, alone or in combination with muscarinic antagonists. Although metered-dose inhalers, when used correctly, can be as effective as nebulizers,[311] it can be difficult for severely dyspneic patients to coordinate their efforts to use a metered-dose inhaler or to generate sufficient inspiratory flow required for some devices. Therefore nebulizers are a reasonable approach for delivering bronchodilator therapy in the setting of an acute exacerbation.

Corticosteroids. Substantial data support the use of systemic corticosteroids for treatment of exacerbations of COPD. Their use is associated with a more rapid recovery, improvement in lung function and hypoxemia, and a reduced risk of relapse.[312–315] Guidelines recommend 40 to 60 mg prednisone per day for 2 weeks, but a more recent prospective trial of more than 300 patients found that 5 days of prednisone was not inferior to 14 days for preventing reexacerbation within 6 months and was associated with a significantly lower total corticosteroid exposure.[316] A retrospective study of more than 17,000 patients admitted to intensive care units with acute exacerbations found that those treated with more than 240 mg/day of methylprednisolone equivalents or 300 mg/day prednisone equivalents had greater mortality, length of stay, ventilator days, complications, and costs.[317]

Antibiotics. The use of antibiotics for exacerbations of COPD is somewhat controversial, largely because of the paucity of data documenting bacterial colonization or infection. Studies have suggested that nearly 50% of acute exacerbations are associated with *H. influenzae, S. pneumoniae,* and *M. catarrhalis.*[318] Even when patients are chronically colonized, changes in strain may be associated with exacerbations.[307] Sputum cultures are of limited utility because they do not distinguish between colonization and infection and because of the time required for results. Most guidelines recommend empirical treatment when infection seems likely, based on what are sometimes called the "Anthonisen criteria": increased dyspnea, sputum volume, and sputum purulence,[319] with greater weight given to meeting all three criteria. The recommended length of antibiotic treatment is 5 to 10 days.

DEVELOPMENT OF NEW TREATMENTS

Despite advances in recent years, treatment options for COPD are woefully inadequate. Other than smoking cessation and supplementary oxygen in patients who are hypoxemic, there are no treatments that clearly and consistently reduce mortality. Several factors have contributed to the lack of progress. COPD is highly heterogeneous: In some patients, emphysema predominates; in others, bronchitis predominates; and still others may have both. COPD is a systemic disease and, as a consequence, comorbid extrapulmonary conditions are common. Because treatment effects are small, very large studies are required to test potential new interventions. For all of these reasons, investigators are beginning to explore individual patient subtypes, looking for subpopulations that might benefit from unique therapeutic regimens, and for intermediate outcomes measures that might increase the efficiency of clinical trials. To this end, the NHLBI has funded the SPIROMICS,[320] a prospective observational study of COPD subjects and control subjects. Complementary studies, such as *Evaluation of COPD Longitudinally to Identify Predictive Surrogate Endpoints* (ECLIPSE)[321] and COPDGene,[322] will hopefully add to the explosion of knowledge in the next few years, aiming at improving treatment for patients with COPD.

Key Points

- COPD is a highly prevalent disease and a leading cause of mortality. COPD is significantly underdiagnosed.
- COPD is characterized by airflow obstruction that is not fully reversible. Spirometry is required for diagnosis.
- Older age and a history of smoking are the two most important risk factors for COPD.
- Emphysema at a young age or in an individual with minimal or no smoking history should suggest $alpha_1$-antitrypsin deficiency.
- Smoking cessation is the only intervention demonstrated to alter the course of lung function decline. Smoking cessation also conveys a long-term mortality benefit.
- Pharmacotherapy is no longer for symptom relief only. Short- and long-acting muscarinic antagonists, long-acting β-agonists, and inhaled corticosteroids have been shown to improve exercise capacity, improve quality of life, and reduce exacerbations.
- Choice of medications is based in part on the availability of medication and the patient's response. The Global Initiative for Chronic Obstructive Lung Disease has proposed a stepwise treatment algorithm, based on symptoms, and exacerbation history.
- In patients with persistent hypoxemia, continuous oxygen treatment for at least 15 hours/day improves survival, quality of life, and a number of other measures.

- Patients with arterial Po_2 less than 55 mm Hg or Spo_2 less than 88% while breathing room air at rest or patients with arterial Po_2 56 to 59 mm Hg and erythrocytosis or right heart dysfunction should be offered continuous oxygen treatment.
- Pulmonary rehabilitation improves exercise capacity and quality of life and decreases dyspnea and health care utilization, as well as hospitalizations and mortality. Pulmonary rehabilitation should be offered to any patient who develops shortness of breath while walking.
- Lung volume reduction surgery may be beneficial for the small subgroup of patients with upper lobe–predominant emphysema and a low postrehabilitation exercise capacity. Endobronchial valve therapy may also benefit patients with emphysema.

Key Readings

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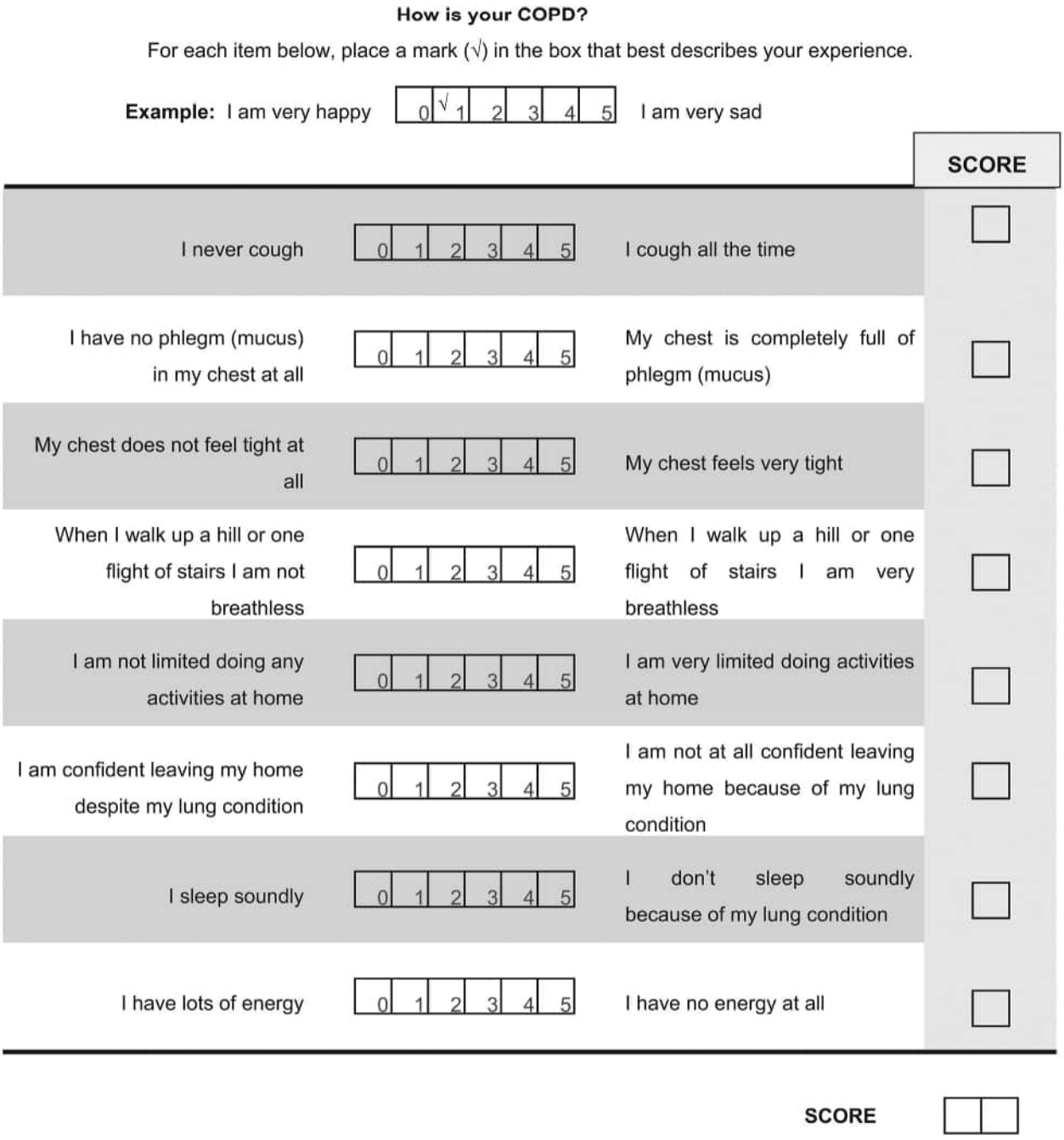
eFIGURE IMAGE GALLERY



How is your COPD?

For each item below, place a mark (√) in the box that best describes your experience.

Example: I am very happy | 0 | √ 1 | 2 | 3 | 4 | 5 | I am very sad

			SCORE
I never cough	0 1 2 3 4 5	I cough all the time	☐
I have no phlegm (mucus) in my chest at all	0 1 2 3 4 5	My chest is completely full of phlegm (mucus)	☐
My chest does not feel tight at all	0 1 2 3 4 5	My chest feels very tight	☐
When I walk up a hill or one flight of stairs I am not breathless	0 1 2 3 4 5	When I walk up a hill or one flight of stairs I am very breathless	☐
I am not limited doing any activities at home	0 1 2 3 4 5	I am very limited doing activities at home	☐
I am confident leaving my home despite my lung condition	0 1 2 3 4 5	I am not at all confident leaving my home because of my lung condition	☐
I sleep soundly	0 1 2 3 4 5	I don't sleep soundly because of my lung condition	☐
I have lots of energy	0 1 2 3 4 5	I have no energy at all	☐

SCORE ☐☐

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eFigure 64.1 COPD assessment test. The *COPD Assessment Test* (CAT) is an eight-item questionnaire used to assess impact of COPD on quality of life. The CAT is also a recommended instrument to grade COPD symptom severity by GOLD. The scoring range is 0–40. CAT scores from 21–30 indicate a high impact of COPD on patient's life; a score of <10 means COPD has little impact on daily activities. The minimal clinically important difference is a change of 2 or more units over 2 to 3 months. (Courtesy GlaxoSmithKline.)

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65 SMOKING HAZARDS: CIGARETTES, VAPING, MARIJUANA

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INTRODUCTION

From cigarette smoking to cocaine, this chapter covers the greatest preventable cause of lung disease and of other preventable smoking hazards. Despite significant public health efforts to control its use, cigarette smoking remains the leading global risk factor for disability-adjusted years of life lost.[1–4] Secondhand smoke causes tens of thousands of cardiovascular deaths and several thousand lung cancer deaths annually. *Electronic cigarettes* (e-cigarettes), which deliver nicotine in an aerosol of propylene glycol, vegetable glycerin, and flavorings, have jumped in prominence over the last 15 years, even as the health risks and the potential benefits for smoking cessation remain controversial. *E-cigarette/vaping–associated lung injury* (EVALI) is a newly described syndrome of acute respiratory distress syndrome of unclear mechanism associated with vaping *delta-9-tetrahydrocannabinol* (THC) obtained from the black market. Cannabis, now legalized in many states in the United States, has not been shown to cause COPD or cancer but is associated with upper airway irritation, wheezing, chronic cough, sputum production, and barotrauma. Finally, cocaine and methamphetamine have acute cardiovascular toxicity and are associated with pulmonary edema, alveolar hemorrhage, emphysema, and pulmonary hypertension. The important related topic of smoking cessation is covered in Chapter 66.

CIGARETTE SMOKING

EPIDEMIOLOGY OF CIGARETTE SMOKING

Currently, about 41 million individuals (19% of the adult population) in the United States are smokers of cigarettes or other combustible tobacco products, including cigars and cigarillos, pipes, and water pipes.[5] Heavy smoking (≥20 cigarettes/day) has declined substantially over the past 30 years, and in the United States, about 25% of smokers do not smoke every day. People who are less well educated and/or have unskilled occupations are more likely to smoke. For example, 37% of people with a high school education are smokers compared to 7.1% of those with a college degree. High rates are seen in those living below the federal poverty level (28%) and in those working in construction and extraction industries (30%).[6]

There are more than 1 billion smokers worldwide, the majority of whom live in low- and middle-income countries.[7] Tobacco use remains the leading global risk factor for disability-adjusted life years lost. The World Health Organization Framework Convention on Tobacco Control aims to reduce both the demand and the supply of tobacco around the world through educational, political, and legislative means.[8]

TOXICOLOGY OF CIGARETTE SMOKE

Tobacco smoke is an aerosol of droplets (particulates) containing water, nicotine and other alkaloids, and tar suspended in a gaseous phase. Tobacco smoke contains several thousand different chemicals, many of which may contribute to human disease.[9] The *particulate* phase contains major toxic chemicals, such as nicotine, benzo(a)pyrene and other polycyclic hydrocarbons, 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanone, *N*′-nitrosonornicotine, β-naphthylamine, polonium-210, nickel, cadmium, arsenic, and lead. The *gaseous* phase contains carbon monoxide, acetaldehyde, acetone, methanol, nitrogen oxides, hydrogen cyanide, acrolein, ammonia, benzene, formaldehyde, nitrosamines, and vinyl chloride. Tobacco smoke contains a high concentration of free radicals and other oxidizing chemicals, as well as fine particulates, which contribute to disease. Tobacco smoke may produce illness by way of systemic absorption of toxins and/or cause local pulmonary injury by oxidants and other chemicals.

SMOKING-RELATED DISEASES

Tobacco use is a major cause of death from cancer, cardiovascular disease, and pulmonary disease (Table 65.1). Smoking is also a major risk factor for osteoporosis, reproductive disorders, and fire- and trauma-related injuries.

TABLE 65.1 Health Hazards of Tobacco Use (Risks Increased by Smoking)

CANCER (SEE TABLE 65.2)
CARDIOVASCULAR DISEASE
Sudden death
Acute myocardial infarction
Unstable angina
Stroke
Peripheral arterial occlusive disease (including thromboangiitis obliterans)
Abdominal aortic aneurysm
PULMONARY DISEASE
Lung cancer
Chronic bronchitis
Emphysema
Asthma
Increased susceptibility to/severity of pneumonia, influenza, and pulmonary tuberculosis
Increased susceptibility to desquamative interstitial pneumonia, respiratory bronchiolitis–interstitial lung disease, pulmonary Langerhans cell histiocytosis
Increased morbidity from viral respiratory infection
GASTROINTESTINAL DISEASE
Peptic ulcer
Esophageal reflux
REPRODUCTIVE DISTURBANCES
Reduced fertility in women
Erectile dysfunction
Premature birth
Lower birth weight
Ectopic pregnancy
Spontaneous abortion
Abruptio placentae
Orofacial clefts
Increased perinatal mortality (including sudden infant death syndrome)
ORAL DISEASE (SMOKELESS TOBACCO)
Oropharyngeal cancer
Leukoplakia
Dental caries
Periodontitis
Tooth staining
OTHER
Non–insulin-dependent diabetes mellitus
Earlier menopause
Osteoporosis
Hip fracture
Cataract
Age-related macular degeneration
Rheumatoid arthritis
Poor wound healing
Premature skin wrinkling
Aggravation of hypothyroidism
Altered drug metabolism or effects

TABLE 65.2 Cigarette Smoking and Cancer Risk

Cancer Site	Average Relative Risk
Lung	15.0–30.0
Urinary tract	3.0
Oral cavity	4.0–5.0
Oropharynx and hypopharynx	4.0–5.0*
Esophagus	1.5–5.0*
Larynx	10.0*
Pancreas	2.0–4.0
Nasal cavity, sinuses, nasopharynx	1.5–2.5
Stomach	1.5–2.0
Liver	1.5–2.5
Kidney	1.5–2.0
Uterine cervix	1.5–2.5
Acute myeloid leukemia	1.5–2.0

*Synergistic interaction with alcohol use.

Modified from Vineis P, Alavanja M, Buffler P, et al. Tobacco and cancer: recent epidemiological evidence. *J Natl Cancer Inst*. 2004;96(2):99–106; International Council for Research on Cancer. Tobacco smoking and involuntary smoking. IARC monographs on the evaluation of carcinogenic risks to humans. *IARC Sci Publ*. 2004;83.

Cancer

Smoking, the largest preventable cause of cancer (Table 65.2), is responsible for about 30% of cancer deaths.[10] Many chemicals in tobacco smoke may contribute to carcinogenesis as tumor initiators, cocarcinogens, tumor promoters, or complete carcinogens.[9] Complexes of tobacco smoke carcinogens with DNA are thought to be a crucial step in cancer induction. Cigarette smoking induces specific patterns of *p53* gene mutations associated with squamous cell carcinomas of the lung, head, and neck.[11] Lung cancer is the leading cause of cancer deaths in the United States and is predominantly attributable to cigarette smoking.[4] The risk of lung and other cancers is proportional to the number of cigarettes smoked per day and, even more strongly, to the duration of smoking.[12]

Workplace exposure to asbestos or α-radiation, the latter in uranium miners, synergistically increases the risk of lung cancer in cigarette smokers.[13] Alcohol use interacts synergistically with tobacco in causing oral, laryngeal, and esophageal cancer[14]; the mechanism of interaction may involve alcohol solubilizing tobacco carcinogens and/or alcohol-related induction of liver or gastrointestinal enzymes that metabolize and activate tobacco carcinogens. Smoking is associated with 15% of leukemia cases in adults and 20% of colorectal cancers.[15,16]

A detailed description of the epidemiology and the pathogenesis of smoking-induced lung cancer is presented in Chapters 73 and 74.

Chronic Lung Disease

Greater than 80% of COPD in the United States is attributable to cigarette smoking. Cigarette smoking also increases the risk for respiratory infection, including pneumonia, and results in greater disability from viral respiratory tract infections.[17,18] Pulmonary disease from smoking includes the overlapping syndromes of chronic bronchitis (cough and mucus secretion), emphysema, and airway obstruction.[19] Whereas the diagnosis of COPD is based on evidence of airflow obstruction on spirometry, smokers with normal spirometry can also have chronic respiratory symptoms, reduced exercise tolerance, and evidence of emphysema or bronchiolitis on imaging.[20]

The pathologic changes in the lung produced by cigarette smoking include loss of cilia, mucous gland hyperplasia, increased number of goblet cells in the central airways, inflammation, goblet cell metaplasia, squamous metaplasia, mucus plugging of small airways, destruction of alveoli, and pruning of the distal small (<5 mm^2) pulmonary arteries[21,22] (see also Chapter 63). The mechanisms of injury are complex and include both innate and adaptive immune inflammatory pathways,[23] as well as direct injury by oxidant chemicals, increased elastase activity (a protein that breaks down elastin and other connective tissue), and decreased antiprotease activity.[24] A genetic deficiency of α_1-antiprotease (α_1-antitrypsin) activity produces a similar imbalance between pulmonary protease and antiprotease activity and is a risk factor for early and severe smoking-induced pulmonary disease.[25] Epigenetic changes related to cigarette smoking are associated with decreased lung function and may contribute to the pathogenesis of COPD.[26]

In addition to cigarette smoke–induced injury, the delivery of carbon monoxide from cigarette smoke serves to worsen the level of functioning in smokers who have significant COPD. Carbon monoxide avidly binds to hemoglobin, reduces the capacity of hemoglobin to carry oxygen, and impairs oxygen release at the tissues. Thus carbon monoxide exposure produces a functional anemia. Carboxyhemoglobin levels are typically 5–10% in smokers compared to 1% or less in nonsmokers. In a normal person, carbon monoxide from cigarette smoke causes few symptoms, but, in patients with pulmonary disease, carbon monoxide has the potential to cause significant impairment. Exposure to carbon monoxide at levels even less than that derived from cigarette smoking has been shown to reduce exercise tolerance in patients with COPD.

Cigarette smoking may contribute to the development of asthma, although this potential link could be confounded by the increased rate of pulmonary infections observed in smokers. A longitudinal study of 5800 individuals taking part in a national British cohort study suggested that regular smoking was associated with asthma in people between 17 and 33 years of age (*odds ratio* [OR], 4.4).[27] More recently, a longitudinal study of more than 46,000 women revealed increased adult-onset asthma in former smokers (*hazard ratio* [HR], 1.4; *95% confidence interval* [CI], 1.1 to 1.7) and active smokers (HR, 1.4; CI, 1.2 to 1.8).[28] Current smokers, compared to never and ex-smokers, demonstrate higher asthma severity scores, more frequent asthma symptoms, and more frequent asthma attacks (OR, 2.4).[29] Silverman and coworkers[30] evaluated 1847 emergency department patients presenting with acute asthma and found that 35% of patients were current smokers. Half of these smoking asthmatic patients reported that cigarette use worsened their asthma symptoms.

The link between secondhand smoke and asthma would support the hypothesis that tobacco exposure worsens bronchial hyperresponsiveness. Several studies have reported increased prevalence of airflow obstruction and asthma in children exposed in utero to maternal smoking.[31,32] In addition, a study evaluating infants exposed to smoking mothers in their first year of life demonstrated they were 2.1 times more likely to develop asthma than were children of nonsmoking mothers.[33] Likewise, the Swiss Study on Air Pollution and Lung Disease in Adults suggested that secondhand smoke was associated with an increased risk for asthma (OR, 1.4) or reactive airway disease in nonsmoking adults.[34]

There are other links between smoking and both acute and chronic inflammatory lung conditions. In a small cohort of healthy nonasthmatic smokers, bronchoalveolar lavage fluid documented altered macrophage cytokine release, increased cellularity, and depressed levels of interleukin-6.[35] The risk of acute respiratory distress syndrome is increased in smokers[36] and, in experimental studies, smokers exposed to nebulized endotoxin had increased markers of lung injury and inflammatory cytokines in bronchoalveolar lavage.[37]

Cigarette smoking has been associated with multiple nonneoplastic pulmonary disorders other than emphysema and chronic bronchitis. These include respiratory bronchiolitis–associated interstitial lung disease, desquamative interstitial pneumonitis, pulmonary Langerhans cell histiocytosis, and cryptogenic interstitial fibrosing alveolitis.[38] Ninety percent of patients with pulmonary Langerhans cell histiocytosis are smokers. Respiratory bronchiolitis–associated interstitial lung disease and desquamative interstitial pneumonitis have similar histopathologic features and are characterized by the accumulation of pigmented macrophages within the alveoli. Respiratory bronchiolitis ("smoker's bronchiolitis") refers to the presence of pigmented macrophages, in the absence of respiratory symptoms or significant fibrosis.[39,40] Desquamative interstitial pneumonitis often affects individuals in their fourth or fifth decade of life, and the symptoms are more frequent in smokers.[41] Smoking may also have an association with idiopathic pulmonary fibrosis.[42] Smoking is over-represented in patients with idiopathic pulmonary fibrosis compared to the general population, and the overall OR for smoking as a risk factor for idiopathic pulmonary fibrosis has been reported to be 1.6.[43]

Infection

Cigarette smoking is a major risk factor for respiratory tract and other systemic infections. Both active and passive cigarette smoke exposure increase the risk for infection.[44,45] The mechanisms by which smoking increases risk are multifactorial and include structural and immunologic alterations. As mentioned previously, cigarette smoking causes structural changes in the respiratory tract. These changes include peribronchiolar inflammation and fibrosis, increased mucosal permeability, impairment of mucociliary clearance, changes in pathogen adherence, and disruption of the respiratory epithelium. A number of components of cigarette smoke, including acrolein, acetaldehyde, formaldehyde, free radicals produced from chemical reactions within the cigarette smoke, and nitric oxide, may contribute to the observed structural alterations in airway epithelial cells.

Immunologic mechanisms include alterations in cellular and humoral immune system function. These include a decreased level of circulating immunoglobulins, a depression of antibody response to certain antigens, a decrease in $CD4^+$ lymphocyte counts, an increase in $CD8^+$ lymphocyte counts, depressed phagocyte activity, and decreased release of proinflammatory cytokines. Many of the immunologic disturbances in smokers resolve within 6 weeks after smoking cessation, supporting the idea that smoking cessation

TABLE 65.3 Cigarette Smoking and Risk of Infection

	Odds Ratio (95% CI)
Tuberculosis	4.5 (4.0–5.0)
Legionnaires' disease	3.5 (2.1–5.8)
HIV infection	3.4 (1.6–7.5)
Periodontal disease	2.8 (1.9–4.1)
Pneumococcal pneumonia	2.6 (1.9–3.5)
Meningococcal disease	2.4 (0.9–6.6)
Influenza	2.4 (1.5–3.8)
Helicobacter pylori	2.2 (1.2–4.0)
Common cold	1.5 (1.1–1.8)

CI, confidence interval; HIV, human immunodeficiency virus.

is highly effective in a relatively short period of time in the prevention of infection.[44]

Cigarette smoking is associated with an increased risk for bacterial and viral infections (Table 65.3). Cigarette smoking is a substantial risk factor for pneumococcal pneumonia, especially in patients with COPD. Smoking is strongly associated with invasive pneumococcal disease in otherwise healthy adults.[18] A population-based case-control study showed smoking was the strongest independent risk factor for invasive pneumococcal disease among immunocompetent adults. The OR was 4.1 (95% CI, 2.4 to 7.3) for active smoking and 2.5 (95% CI, 1.2 to 5.1) for passive smoke exposure in nonsmokers compared to nonexposed nonsmokers. The attributable risk in this population was 51% for cigarette smoking and 17% for passive smoking, with a strong dose response. The risk for pneumococcal disease declined to nonsmoker levels 10 years after cessation. Cigarette smoking has also been shown to be associated with a nearly twofold increased risk for community-acquired pneumonia, with 32% of the risk attributable to cigarette smoking.[46]

Cigarette smoking increases both the incidence and severity of viral infections, including the common cold, influenza, and varicella. Influenza infections are more severe, with more cough, acute and chronic phlegm production, breathlessness, and wheezing in smokers.[17] Influenza infections produce more lost workdays in smokers compared to nonsmokers. Influenza vaccination is effective in preventing the disease in smokers, and smoking should be considered a high-priority indication for influenza vaccination. The development of varicella pneumonitis in adults is reported to be substantially greater in smokers compared to nonsmokers.[47] Of interest are early epidemiology studies of smoking and COVID-19 (SARS-CoV-2) infection. These studies suggest that smokers are less likely to become infected and less likely to be hospitalized but, once hospitalized, are more likely to progress in severity and more likely to die than never or former smokers.[48,49]

Tuberculosis is perhaps the most important smoking-associated infection. Cigarette smoking is a risk factor for tuberculin skin test reactivity, skin test conversion, and the development of active tuberculosis. A large case-control study from India examined smoking and tuberculosis in men between 35 and 69 years of age. The tuberculosis prevalence *relative risk* (RR) was 2.9 (95% CI, 2.6 to 3.3) with ever smokers compared to never smokers, and the prevalence was higher with a higher level of cigarette consumption.[50] The mortality from tuberculosis among men 25 to 69 years old showed an RR of 4.5 (95% CI, 4.0 to 5.0) and 4.2 (95% CI, 3.7 to 4.8) for urban and rural residents, respectively. The authors found that the proportion of deaths from tuberculosis attributable to smoking was 61% greater than the proportion of deaths from vascular disease or cancer attributable to smoking. Thus, it is likely that smoking contributes substantially to the worldwide disease burden of tuberculosis.[51]

Of historical interest is the relationship between tuberculosis and the risk for cigarette smoking in the early 20th century. Before that time, chewing tobacco was the preferred type of tobacco. Public fear that users of chewing tobacco who spit in public places might be spreading tuberculosis is one of the factors that led to the increase in cigarette sales in the United States. This is nicely described by Kluger[52] as follows:

"Chewing tobacco was no longer merely messy but socially disagreeable in more crowded urban America, and its inevitable byproduct, spitting, was now identified as a spreader of tuberculosis and other contagions, and thus an official health menace. The leisurely pipe all at once seemed a remnant of a slower-tempo age, and cigar fumes were newly offensive amid thronged city life. The cigarette by contrast, could be quickly consumed and easily snuffed out on the job as well as to and from work."

Cardiovascular Disease

Although not the focus of this text, cardiovascular disease is common in patients with respiratory disease and often complicates management of respiratory illness. This relates to the fact that both diseases are common and both increase with age, and that smoking is a major risk factor for both respiratory disease and cardiovascular disease.

Cigarette smoking accounts for about 20% of cardiovascular deaths in the United States. Risks are increased for coronary artery disease, sudden death, cerebrovascular disease, and peripheral vascular disease, including abdominal aortic aneurysm.[9,53] Cigarette smoking accelerates atherosclerosis and promotes acute ischemic events. The mechanisms of the effects of cigarette smoking include (1) hemodynamic stress (nicotine increases the heart rate, transiently increases blood pressure, and increases myocardial work), (2) endothelial injury and dysfunction (nitric oxide release and resultant vasodilation are impaired), (3) development of an atherogenic lipid profile (smokers have on average higher low-density lipoprotein, more oxidized low-density lipoprotein, and lower high-density lipoprotein cholesterol than nonsmokers do), (4) enhanced coagulability, (5) arrhythmogenesis, and (6) relative hypoxemia from the effects of carbon monoxide.[54] As a compensation for the reduced oxygen-carrying capacity, polycythemia often develops in smokers, with hematocrit values of 50% or more. The polycythemia and the increased fibrinogen levels found in cigarette smokers also increase blood viscosity, which adds to the risk of thrombotic events. Cigarette

smoking also produces insulin resistance, increases the risk of non–insulin-dependent diabetes, and induces a chronic inflammatory state, as evidenced by increased neutrophil count and increased levels of fibrinogen and C-reactive protein in the blood of smokers. Insulin resistance and chronic inflammation are thought to contribute to accelerated atherogenesis.

Cigarette smoking acts synergistically with other cardiac risk factors to increase the risk of ischemic heart disease. Although the risk of cardiovascular disease is roughly proportional to cigarette consumption, the risk persists even at low levels of smoking, that is, at one to two cigarettes per day.[55] Cigarette smoking reduces exercise tolerance in patients with angina pectoris and intermittent claudication. Vasospastic angina is more common, and the response to vasodilator medication is impaired in patients who smoke. The number of episodes and total duration of ischemic episodes, as assessed by ambulatory electrocardiographic monitoring in patients with coronary heart disease, are substantially increased by cigarette smoking.[56] The increase in relative risk of coronary heart disease because of cigarette smoking is greatest in young adults who, in the absence of cigarette smoking, would have a relatively low risk.[53] Women who use oral contraceptives and smoke cigarettes have a synergistically increased risk of both myocardial infarction and stroke. Data suggest that implementing smoking bans at the community level has an appreciable impact on lowering hospital admission rates for coronary artery disease.[57,58]

After acute myocardial infarction, the risk of recurrent myocardial infarction is higher, and survival is half over the next 12 years in persistent smokers as compared with quitters.[59] Smoking also interferes with revascularization therapy for acute myocardial infarction. After thrombolysis, the reocclusion rate is fourfold higher in smokers who continue than in those who quit.[60] The risk of reocclusion of a coronary artery after angioplasty or of occlusion of a bypass graft is increased in smokers.[61] Cigarette smoking is not a risk factor for hypertension per se but does increase the risk of complications, including the development of nephrosclerosis and progression to malignant hypertension.[62] Cigarette smoking has been shown to be a substantial contributor to morbidity and mortality in patients with left ventricular dysfunction. The mortality benefit of stopping smoking in such patients is equal to or greater than the benefit of therapy with angiotensin-converting enzyme inhibitors, β-blockers, or spironolactone.[63]

Wound Healing/Postoperative Complications

Cigarette smoking is a major cause of adverse postoperative events and delayed wound healing.[64,65] The mechanisms include cutaneous vasoconstriction (reducing skin blood flow), local thrombosis, and reduced oxygen-carrying capacity, all of which can delay tissue repair. Impaired clearance of secretions, altered immune function, altered collagen synthesis, and the influence of underlying tobacco-related diseases (e.g., COPD and altered cardiovascular function) also contribute to postoperative complications.

A meta-analysis of 107 studies found that smoking within 30 days of operation significantly increased complications as follows: general morbidity (RR, 1.5), wound complications (RR, 2.2), infections (RR, 1.5), pulmonary complications (RR, 1.7), neurologic complications (RR, 1.4), and admission to an intensive care unit (RR, 1.6).[64] A study of 489 adult patients undergoing ambulatory surgery demonstrated a significantly higher rate of respiratory complications (32.8% in smokers vs. 25.9% in nonsmokers) and wound infections (3.6% in smokers vs. 0.6% in nonsmokers).[66] Causes of major pulmonary events after pneumonectomy were sought in a retrospective analysis of 261 patients.[67] Patients who continued to smoke within 1 month of operation were determined to be at an increased risk of pulmonary events, which was associated with increased postoperative mortality. Cigarette smoking is associated with an increased risk of hepatic artery thrombosis after liver transplantation, and cessation 2 years before transplantation was associated with a decreased risk.[68] Similar data exist regarding renal transplantation and allograft survival in smokers compared to nonsmokers.[69] Recent studies describe substantially increased risk of postoperative complications in elective plastic surgery procedures, of wound complications after coronary bypass surgery, and of marginal ulcers after Roux-en-Y gastric bypass.[70–72]

Smoking cessation substantially reduces postoperative complications. Moller and colleagues[73] published the results of a randomized, controlled trial of smokers awaiting elective hip or knee surgery at three hospitals in Copenhagen. They compared 56 patients in a smoking cessation intervention arm (83% stopped or reduced smoking) versus 62 patients in a usual care arm. The overall complication rate was 18% in the intervention arm and 52% in the control group, a highly significant difference. The greatest differences were seen in wound complication rates (5% vs. 31%, respectively) and cardiovascular complications (0% vs. 2%, respectively).

The optimal window for smoking cessation intervention may be at 8 weeks before elective surgery, as suggested by data demonstrating that patients who had stopped smoking at least 2 months preoperatively had nearly maximal reduction in postoperative respiratory complications.[74] A meta-analysis of six trials of smoking cessation found that cessation reduced postoperative complications by 41% and that each week of cessation increased the magnitude of benefit by 19%.[75] An important issue related to elective surgery is that patients are often highly motivated to quit smoking just before surgery and can benefit from cessation counseling before surgery, as well as from in-hospital cessation counseling and medication in the postoperative setting. Specific issues related to smoking cessation are discussed in Chapter 66.

Other Complications of Cigarette Smoking

Cigarette smoking increases the risk of duodenal and gastric ulcers, delays the rate of ulcer healing, and increases the risk of relapse after ulcer treatment.[76] Smoking is also associated with esophageal reflux symptoms. Smoking produces ulcer disease by several proposed mechanisms: increasing acid secretion, reducing pancreatic bicarbonate secretion, impairing the gastric mucosal barrier (related to decreased gastric mucosal blood flow and/or inhibition of prostaglandin synthesis), reducing pyloric sphincter tone, and increasing the risk of *Helicobacter pylori* infection.[77]

Cigarette smoking is a risk factor for osteoporosis in that it reduces the peak bone mass attained in early adulthood and increases the rate of bone loss in later adulthood. Smoking antagonizes the protective effect of estrogen replacement therapy on the risk of osteoporosis in postmenopausal women.[78] Hip fractures are more common in women who smoke cigarettes. Cigarette smoking is a major cause of reproductive problems, including fetal growth restriction, preeclampsia, stillbirth, perinatal mortality, and sudden infant death syndrome.[79] Growth retardation from cigarette smoking has been termed *fetal tobacco syndrome.*[80] Cigarette smoking causes reproductive complications by causing placental ischemia mediated by the hypoxic effects of chronic carbon monoxide exposure, endothelial dysfunction, and the general increase in coagulability produced by oxidant chemicals in cigarette smoke.[81]

Other adverse effects of cigarette smoking include premature facial wrinkling, an increased risk of cataracts, age-related macular degeneration, olfactory dysfunction, and fire-related injuries. The last effect contributes significantly to the economic costs of tobacco use. Smoking reduces the secretion of thyroid hormone in women with subclinical hypothyroidism and increases the severity of clinical symptoms of hypothyroidism in women with subclinical or overt hypothyroidism, the latter effect reflecting antagonism of thyroid hormone action.[82] Cigarette smoking also potentially interacts with a variety of drugs by accelerating drug metabolism or by the pharmacologic interactions that nicotine and/or other constituents of tobacco have with other drugs (see Chapter 66).

Health Hazards of Secondhand Smoke

Considerable evidence indicates that exposure to secondhand smoke is harmful to the health of nonsmokers (Table 65.4).[83] The U.S. Environmental Protection Agency classifies secondhand smoke as a class A carcinogen, which means that it has been shown to cause cancer in humans.[84]

Secondhand smoke consists both of *sidestream* smoke generated while the cigarette is smoldering and of *mainstream* smoke exhaled by the smoker. Of the total combustion product from a cigarette, 75% or more enters the air. The constituents of secondhand tobacco smoke are qualitatively similar to those of mainstream smoke. However, some toxins, such as ammonia, formaldehyde, and nitrosamines, are present in much higher concentrations in secondhand tobacco smoke than in mainstream smoke. The Environmental Protection Agency has estimated that secondhand smoke is responsible for approximately 3000 lung cancer deaths annually in nonsmokers in the United States, is causally associated with 150,000 to 300,000 cases of lower respiratory tract infection in infants and young children up to 18 months of age, and is causally associated with the aggravation of asthma in 200,000 to 1 million children.[84] Secondhand smoke exposure promotes atherosclerosis and thrombosis by multiple mechanisms[85] and is estimated to be responsible for 40,000 cardiovascular deaths.[86] An appreciation of the hazards of secondhand tobacco smoke is important to the physician because it provides a basis for advising parents not to smoke when children are in the home,[87] insisting that child care facilities be smoke free, and recommending smoking restrictions in work sites and other public places.

TABLE 65.4 Health Hazards of Secondhand Tobacco Smoke in Nonsmokers

Children	Adults
Hospitalization for respiratory tract infection in first year of life	Lung cancer
Chronic respiratory symptoms	Myocardial infarction
Middle ear disease	Stroke
Asthma	Reduced pulmonary function
Reduced birth weight (maternal exposure)	Irritation of eyes, nasal congestion, headache
Sudden infant death syndrome	Cough

ELECTRONIC CIGARETTES

E-cigarettes, or electronic nicotine delivery devices, heat a nicotine solution to generate an aerosol that is inhaled without the combustion of tobacco and its toxic constituents. *Vaping* refers to the act of using of an e-cigarette. These devices have evolved substantially over the last decade but have in common (1) a reservoir that contains an e-liquid (propylene glycol, vegetable glycerin, nicotine, and flavorings), (2) a resistance metal coil (nickel, chromium, stainless steel, or a related alloy) that heats the e-liquid, (3) a wick (typically made of silica or cotton) that conducts the e-liquid to the coil, and (4) a battery that supplies electric current to the coil in response to airflow or a button push initiated by the user, generating a plume of small droplets (aerosol) (Table 65.5). E-cigarettes have been marketed with claims of health benefit compared with smoking cigarettes; they are marketed for use in reducing and quitting smoking, for use when a person is forbidden to smoke cigarettes, and for avoiding generating smelly and irritating secondhand smoke. The use of e-cigarettes in the United States has increased substantially since they were first marketed in 2006, with 2.8% (6.9 million) current e-cigarette users in 2017.[5] A concerning trend has been the explosive increase in e-cigarette use by young people, with 28% of high school students and 11% of middle school students reporting current e-cigarette use in 2019.[88]

As of 2020, there are thousands of e-cigarette devices on the U.S. market, and they vary with respect to size, power, coil architecture and metal type, and cartridge design. Some look like cigarettes and are disposable; others look like pens or cigars and have refillable tanks. E-cigarette liquids are sold over the Internet or in vape shops, in which the user can select the liquid, including the vehicle (varying proportions of propylene glycol and vegetable glycerin), nicotine concentration, and flavor. Over the last 3 years, pod-based devices with USB-compatible batteries, such as JUUL, have captured the majority of market share, in part because of overwhelming popularity with younger users.[88,89] Nicotine aerosolization depends on coil temperature (power), airflow, and the concentration of nicotine in the e-liquid, which ranges from 3 mg/mL or less for high-power devices to 60 mg/mL or higher for low-power devices, such as JUUL. More recently, vaping devices have been developed to aerosolize more viscous substances, such as *tetrahydrocannabinol* (THC) and cannabidiol-containing oils derived from cannabis. Vaping of THC-containing liquids has recently been implicated in an outbreak of severe acute respiratory disease (see "Cannabis" section).

TABLE 65.5 E-Cigarette Designs, Descriptions, and Brand Names*

Product	Description	Sample Brands†
Disposable e-cigarette 	Cigarette-shaped device consisting of a battery and a cartridge containing an atomizer to heat a solution (with or without nicotine). Not rechargeable or refillable and is intended to be discarded after product stops producing vapor.	NJOY, Blu, Green Smoke
Rechargeable e-cigarette 	Cigarette-shaped device consisting of a battery that connects to an atomizer used to heat a solution typically containing nicotine. Often contains an element that regulates puff duration and/or how many puffs may be taken consecutively.	V2 Cigs, Halo G6, MarkTen
Pen-style, medium-sized rechargeable e-cigarette 	Larger than a cigarette, often with a higher-capacity battery, may contain a prefilled cartridge or a refillable cartridge (often called a clearomizer). These devices often come with a manual switch allowing the smoker to regulate length and frequency of puffs.	eGo, Kanger EVOD, Halo Triton
Tank-style, large-sized rechargeable e-cigarette 	Much larger than a cigarette with a higher-capacity battery and typically contains a large, refillable cartridge. Often contains manual switches and a battery casing for customizing battery capacity. Can be easily modified.	Kanger Aerotank, Innokin iClear, Aspire Nautilus
Pod-style e-cigarette 	Low-power devices, typically USB-rechargeable; e-liquid pods typically contain a high concentration of nicotine. Some pods are refillable.	JUUL, SMOK, Aspire AVP

*E-cigarettes come in various sizes and designs. All contain a cartridge, a heating element, and a battery and provide an aerosol containing nicotine.
†Some brands may have been discontinued.
Modified from Grana R, Benowitz N, Glantz SA. Background paper on e-cigarettes (electronic nicotine delivery systems). Prepared for the 7th Meeting of the WHO Study Group on Tobacco Product Regulation. San Francisco: University of California; 2013.

PULMONARY TOXICITY

Given the relatively recent introduction of e-cigarettes, it is not surprising that their health effects are controversial and poorly characterized. Indeed, it took many decades for the toxicity of combustible cigarettes to be fully appreciated. The simpler chemical nature of e-cigarette aerosol, lacking many of the harmful components of cigarette smoke, would seem to predict less short- and long-term pulmonary toxicity, but few rigorous studies have been performed.

Population-based studies of e-cigarette users have revealed increased reports of chronic cough, sputum production,[90–92] asthma diagnoses,[93,94] and dyspnea,[94] although limitations of all of these studies include a reliance on self-reporting and frequent dual use of e-cigarettes with combustible cigarettes. Chronic smokers who are able to switch from cigarettes to e-cigarettes typically report improvements in respiratory symptoms,[95,96] but most of these studies have not rigorously compared e-cigarette use to quitting smoking without the use of e-cigarettes. A recent study from the United Kingdom randomized 886 smokers interested in cessation, using e-cigarettes or nicotine-replacement therapies as choices. The primary outcome, 1-year abstinence from cigarettes, was more frequent in the e-cigarette group (18.0 % vs. 9.9%, RR, 1.8 [CI, 1.3 to 2.6], respectively). Those randomized to e-cigarettes also had significant reductions in self-reported cough and wheeze, effects not fully accounted for by the increase in abstinence from smoking.[97]

Acutely, e-cigarette aerosol has variably been shown to cause obstructive physiology,[98–100] but whether long-term use results in persistent changes in spirometry is not yet clear. Bronchoscopic studies of healthy e-cigarette users have revealed erythematous mucosa with increased levels of inflammatory mucin proteins and damaging enzymes, including elastase, although many or most of the participants were former smokers.[101,102] Of note, the toxicity of e-cigarette aerosol is likely to be greater under high coil temperature conditions, which increase the production of toxic aldehydes and other oxidizing chemicals. A recent study in healthy young occasional cigarette smokers demonstrated impaired gas exchange after 15 minutes vaping an aerosol from a high-wattage (60-watt) device.[103] Case reports have identified several patterns of e-cigarette–associated respiratory disease, including organizing pneumonia, lipoid pneumonia, barotrauma, and hypersensitivity pneumonitis, although the incidence of these diseases and attributable risk from e-cigarettes at the population level remains unclear.[104] Experiments exposing mice to several months of e-cigarette aerosol have demonstrated major changes in surfactant and lipid metabolism, including oil-filled macrophages that stain with oil red O.[105]

E-CIGARETTES AND SMOKING CESSATION

There is currently considerable debate in the public health community about the safety and benefit of e-cigarettes. Most agree that e-cigarettes could be a health benefit if people would use e-cigarettes and stop smoking cigarettes entirely. A recent clinical trial demonstrated that e-cigarettes enhance smoking cessation with a substantially greater

benefit than nicotine medication, although 80% of those who quit smoking with e-cigarettes continued to vape at 1 year.[97] Epidemiology studies in the United States find that regular use of e-cigarettes is associated with higher rates of quitting smoking, whereas other studies find that dual use of cigarettes and e-cigarettes may be associated with lower quit rates.[106,107] Many e-cigarette users report smoking fewer cigarettes per day while using e-cigarettes, but the health benefits of such reductions are not clear.

OTHER POTENTIAL TOXICITIES OF E-CIGARETTES

In addition to pulmonary toxicity, which was discussed earlier, there are concerns that e-cigarette use may cause cardiovascular toxicity, reproductive toxicity, and possibly impair brain development in adolescents. Whereas products of combustion are thought to be the main mediators of smoking-induced cardiovascular disease, constituents of concern with e-cigarettes include oxidant chemicals, nicotine, particulates, and possibly metals.[108]

The manner in which an e-cigarette is puffed depends on the concentration of nicotine in the e-liquid,[109] the power of the device,[110] and prior cigarette use,[111] among other factors. Similarly, aerosols generated by e-cigarettes vary based on the device, power setting, e-liquid composition, and characteristics of the puff, with longer puffs resulting in higher coil temperatures and greater carbonyl production.[112] Broadly speaking, e-cigarettes produce much lower levels of oxidants than cigarettes while delivering similar levels of nicotine and particulates. The particulates in e-cigarette aerosol are similar in number and size distribution to those in cigarette smoke but are primarily liquid, rather than carbonaceous, and their toxicity is unknown. Nicotine causes sympathetic neural activation, which has some potentially deleterious effects on cardiovascular hemodynamics (increased heart rate, blood pressure, and myocardial contractility) and may impair endothelial function and promote insulin resistance; however, its effects are certainly much less than those of the combustion products in cigarette smoke. Acutely, e-cigarette use produces endothelial dysfunction similar to cigarette smoking, but when smokers switch from cigarettes to e-cigarettes, endothelial function substantially improves.[113] E-cigarette use can enhance platelet aggregation, an effect not related to nicotine, but long-term effects on coagulation are unknown.[114,115] Nicotine has neuroteratogenic effects in the fetus, but e-cigarettes are likely less toxic than smoking, which exposes the fetus not just to nicotine but also to myriad other reproductive toxins.[116] In adolescent rodents, nicotine impairs brain maturation, which has been a concern in light of the large number of young people now using e-cigarettes, but whether nicotine will impair brain maturation in people has been difficult to assess due to many social and environmental confounders.[117]

The *U.S. Food and Drug Administration* (FDA) has the authority to regulate e-cigarettes but has only very recently begun to promulgate regulations.[118] FDA regulation will be particularly useful to ensure the safety of these products, limit marketing and access to youth, and restrict use in situations where smoking is banned—both to minimize environmental pollution with e-cigarette vapor and to mitigate the renormalization of smoking behavior. Some clinicians recommend and/or support e-cigarette use in patients who have been unable to quit smoking using traditional counseling and medications, although the use of e-cigarettes in such a role is not approved by the FDA.

CANNABIS

During the past decade, many U.S. states have legalized cannabis for medical or recreational use and, although federal laws remain on the books, enforcement has declined, with nearly 9.8% of the U.S. population 12 years of age and older reporting use during the past month in 2017–18 compared to 6.4% in 2008–09.[119] Use frequency varies widely, with approximately 4 million U.S. residents estimated to have *cannabis use disorder* in 2016.[120] Furthermore, with the growth of the marketplace for cannabis and its psychoactive constituent, THC, the last several years has seen the extraordinary growth of new methods of consumption. These include the extraction of THC using butane and other solvents into waxes and oils, which are then heated and inhaled, and the development of new vape pens designed to aerosolize viscous liquids, including oils.[121] These novel methods of use have the potential to deliver concentrations of THC that exceed the use of combustible cannabis by an order of magnitude, with unknown consequences for addiction and health.[122]

PULMONARY TOXICITY

In contrast to cigarette smoke, comparatively little is known about cannabis-related pulmonary toxicity, and what is known nearly exclusively concerns traditional combustible cannabis use. Not surprisingly, cannabis smoke contains many of the same carcinogens and toxicants as cigarette smoke; perhaps surprisingly, cannabis smoking has been associated with greater increases in carboxyhemoglobin and inhaled tar per "cigarette" than cigarette smoking.[123] Typically, cannabis smoke is inhaled less frequently, but more deeply, and includes a long breath-holding time.[123] Coughing at near-total lung capacity likely explains the association of cannabis smoking with barotrauma, including pneumothorax and pneumomediastinum.[124] Most studies of chronic cannabis smoking have reported increased symptoms of upper airway irritation, including laryngitis, wheezing, and chronic cough and sputum production.[125,126]

Few high-quality studies of pulmonary function have been performed, with some showing reductions in forced expiratory volume in 1 second/forced vital capacity and reduced diffusing capacity but others showing no differences compared to control subjects.[126] Of note, two studies using high-resolution computed tomography scans have not found evidence that cannabis smoking causes emphysema.[127,128] Bronchoalveolar lavage studies have revealed increased neutrophils and alveolar macrophages,[129] with impaired responses to bacterial challenge.[130] Of importance, pulmonary fungal infections have been reported in cannabis smokers who are immunocompromised by diabetes mellitus, leukemia, and chronic steroid use.[131] Despite containing many of the same carcinogens as tobacco

smoke, cannabis smoke has not been clearly linked to lung cancer.[132] Most likely this is because cannabis smoking is generally much less frequent than cigarette smoking.

In the summer of 2019, a new syndrome of severe acute hypoxemic respiratory failure/acute respiratory distress syndrome was described, notable for the development of diffuse ground-glass opacities on computed tomography scan (frequently with subpleural sparing) in the context of gastrointestinal and constitutional symptoms.[133] Termed EVALI, this syndrome has been linked to the use of mostly illicitly produced THC-containing vape pens. At the time of this writing the etiology remains unclear, but high levels of vitamin E acetate have been found in many of the implicated devices and nearly all of the bronchoalveolar lavage samples of EVALI patients, suggesting that the toxicity may be due to vitamin E acetate.[134] Vitamin E acetate is used as a cutting agent for THC oil for resale or in the THC oil extraction process due to its similar viscosity and aerosol appearance. The Centers for Disease Control and Prevention have published recommendations for evaluating and caring for EVALI patients.[135]

CARDIOVASCULAR TOXICITY

The use of cannabis products containing THC has been associated with acute cardiovascular events, including myocardial infarction, stroke, arrhythmias, and sudden death.[136–138] The cardiovascular toxicity of marijuana smoking can be viewed as a result of one or more of these mechanisms: inhalation of combustion products (with a similar toxicity to cigarette smoking); direct sympathomimetic and other cardiovascular effects of THC; and indirect effects of THC related to extreme anxiety, hallucinations, and/or psychosis.[136] THC use acutely increases heart rate (20–100%), which can be associated with supine hypertension and increased myocardial work. Systemic catecholamine release can constrict coronary arteries and/or activate platelets. The net result can be markedly increased myocardial work and oxygen demand combined with an inadequate compensatory increase in coronary blood flow, resulting in myocardial ischemia or infarction. THC can also produce orthostatic hypotension, which poses a risk in the elderly. The cardiovascular impact of THC depends on the product (marijuana leaf vs. THC oil vs. edibles), dose consumed, route of administration, pattern of use, and degree of tolerance. Cardiovascular toxicity is likely to be greater in people with underlying cardiovascular disease.

COCAINE AND METHAMPHETAMINE

Cocaine and methamphetamine are sympathomimetic drugs that produce vasoconstriction, tachycardia, and hypertension. Cocaine hydrochloride may be inhaled nasally or injected; its free base form ("crack") can be smoked by a pipe or mixed with other substances, such as tobacco or cannabis, and smoked or vaped in an e-cigarette. Co-use of other substances with cocaine has made it challenging to discern its unique pulmonary toxicities. Smoking crack cocaine can result in hemorrhagic alveolitis and diffuse alveolar damage with a prominent eosinophilic inflammatory component.[139] Pulmonary edema may be increased due to elevated left ventricular end-diastolic pressures related to cocaine's acute vasoconstricting and hypertensive effects. Other patterns of disease reported with cocaine include acute eosinophilic pneumonia,[140] barotrauma,[141] emphysema,[142] and pulmonary hypertension.[143] Excipients (i.e., inactive materials used as the vehicle for a drug), including talc and cotton, have been associated with foreign body granulomatosis,[144] and adulterants, including levamisole, have caused systemic illness, including vasculitis[145] (see Chapter 99).

Like cocaine, methamphetamine can be taken intravenously or smoked. Its use has been associated with many of the same pulmonary diseases as cocaine, including cardiogenic pulmonary edema and diffuse alveolar damage.[146] One important difference is that methamphetamine is more frequently associated with a progressive form of pulmonary hypertension that carries a dismal prognosis.[147] Both cocaine and methamphetamine can cause acute cardiovascular injury, including myocardial infarction, stroke, and dissecting aortic aneurysm, as well as aggravate ischemia in users with underlying cardiovascular disease. For patients suffering from pulmonary toxicity from cocaine and methamphetamine, the cornerstones of management are cessation counseling and supportive care. In addition, acute eosinophilic lung disease and organizing pneumonia may respond to corticosteroid therapy.[140]

Key Points

- Tobacco use remains the leading global risk factor for disability-adjusted years of life lost.
- In addition to causing cancer and COPD, smoking increases the risk for other pulmonary diseases, including respiratory infection (including pneumococcal pneumonia and tuberculosis), asthma, interstitial lung disease, and acute respiratory distress syndrome; it also increases the incidence of cardiopulmonary complications after surgery and in critically ill patients.
- Smoking causes 20% of cardiovascular deaths and increases the risk of peptic ulcer disease, diabetes mellitus, and osteoporosis.
- Secondhand smoke causes tens of thousands of cardiovascular deaths and several thousand lung cancer deaths annually.
- Electronic cigarettes deliver nicotine in an aerosol of propylene glycol, vegetable glycerin, and flavorings, and use has increased over the last 15 years, markedly so among young people, with 28% of high school students reporting current use in a 2019 survey.
- The health risks of electronic cigarettes and potential benefits in smokers remain controversial.
- Electronic cigarette/vaping–associated lung injury is a newly described syndrome of acute respiratory distress syndrome of unclear mechanism associated with vaping THC obtained from the black market.
- Cocaine and methamphetamine have acute cardiovascular toxicity and are associated with pulmonary edema, alveolar hemorrhage, emphysema, and pulmonary hypertension.

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66 SMOKING CESSATION

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INTRODUCTION

Pulmonologists have a highly experienced view of the burden of tobacco-related diseases, which are reviewed in Chapter 65. Unfortunately, pulmonary specialists may have little understanding of the neuropsychiatric impact of nicotine addiction and the psychological underpinning of chronic tobacco use. Consequently, many providers may not be comfortable prescribing smoking cessation medications and thus may not provide optimal tobacco cessation support. The U.S. Public Health Service Guidelines recommend that all health care providers practice the "5 A's" as the primary approach for smoking cessation: (1) ask about tobacco use, (2) advise to quit, (3) assess readiness to quit, (4) assist in connecting to tobacco treatment, and (5) arrange follow-up to review progress toward quitting.[1] Despite the clarity of this approach, only 20.9% of smokers in the United States are provided counseling, and only 7.6% receive cessation medications.[2,3] Even in the setting in which a smoker develops cancer, a 2009 survey of National Cancer Institute–designated cancer centers revealed that only 21% of patients were offered cessation treatment services, and only 62% routinely received tobacco-education materials. This core gap is now being addressed by the National Cancer Institute Moonshot program, which has launched a national Cancer Center Cessation Initiative, providing support and grants to 20 centers in the United States.[4] The Department of Health and Human Services devoted the U.S. Surgeon General's 2020 report entirely to smoking cessation, underscoring the importance of preventing tobacco-related disease.[5] With this recent background in mind, this chapter is designed to familiarize health care practitioners with currently available support options, counseling, smoking cessation medications, and trends in their use.

Medications are a key component to increase the chance a smoker will quit successfully. Spontaneous cessation with the "cold turkey" approach (without medications or counseling) yields only a 2–5% cessation rate at 1 year.[2,3] Many smokers try unsuccessfully on multiple occasions to quit with an unsupported approach before a health care provider may start to discuss tobacco use. The combination of medications and counseling/behavioral support will provide patients with the best chance of quitting successfully. The availability of *nicotine replacement therapy* (NRT) *over the counter* (OTC) is important for some patients who may not interact with a health care provider during their quit attempt.[6]

NICOTINE ADDICTION

Tobacco use is motivated primarily by the desire for nicotine. Drug addiction is defined as the compulsive use of a psychoactive substance in which the consequences are detrimental to the individual or society. Understanding addiction is useful in providing effective smoking cessation therapy.[7] Nicotine is absorbed rapidly from tobacco smoke or e-cigarette vapor into the pulmonary circulation. It then moves quickly to the brain, where it acts on nicotinic cholinergic receptors to produce its gratifying effects within 10 to 15 seconds after a puff. Chronic exposure to high levels of nicotine will cause an increased concentration of nicotinic receptors in different regions of the brain, accounting for the development of tolerance and intense withdrawal symptoms. Nicotine has a half-life of approximately 2 hours. Nicotine from smokeless tobacco is absorbed more slowly and results in less intense acute pharmacologic effects. With long-term use of tobacco, physical dependence develops, associated with an increased number of nicotinic cholinergic receptors in the brain[8,9] (Fig. 66.1). When nicotine is unavailable, even for only a few hours, withdrawal symptoms begin, including anxiety, irritability, difficulty concentrating, restlessness, hunger, craving for tobacco, disturbed sleep and, in some people, depression.

Addiction to nicotine is multifactorial, including a desire for the direct pharmacologic actions of nicotine, relief of withdrawal symptoms, and learned associations. Smokers report a variety of reasons for smoking, including pleasure, arousal, enhanced vigilance, improved performance, relief of anxiety or depression, reduced hunger, and control of body weight. Environmental cues, such as after eating a meal, drinking coffee or an alcoholic beverage, talking on the phone, or being around friends who smoke, often trigger an urge to smoke. Compared to the general population

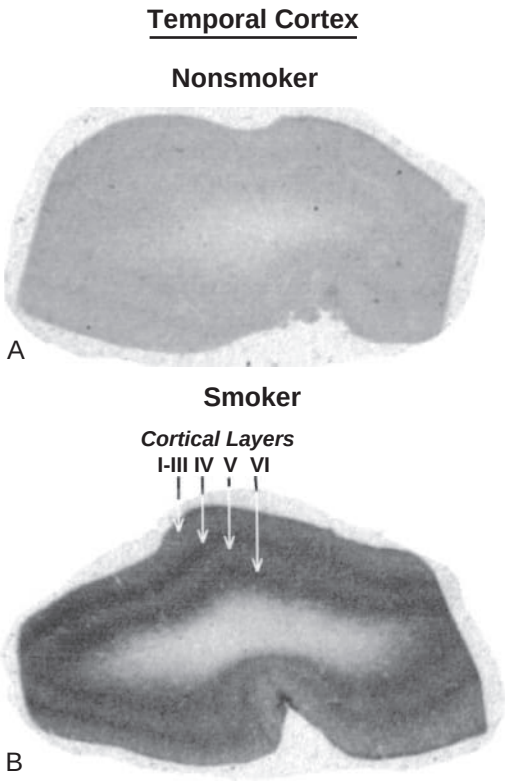

Figure 66.1 Increased nicotinic receptors in the brains of smokers. A representative autoradiographic image of radiolabeled ligand binding to nicotinic receptors in comparable sections of autopsy-derived human temporal cerebral cortex from a nonsmoker (A) and a smoker (B). In the smoker, nicotinic receptors are clearly increased throughout multiple cortical layers. (From Perry DC, Dávila-García MI, Stockmeier CA, Kellar KJ. Increased nicotinic receptors in brains from smokers: membrane binding and autoradiography studies. *J Pharmacol Exp Ther.* 1999;289:1545–1552.)

in the United States, United Kingdom, and Australia, smoking is two to three times more prevalent among people with mental illness. It is particularly high among patients with schizophrenia, bipolar disorder, posttraumatic stress disorder, and alcohol or illicit drug use disorders.[10] Smoking and depression are strongly linked. Smokers are more likely to have a history of major depression than are nonsmokers. Smokers with a history of depression are also likely to be more highly dependent on nicotine and have a lower likelihood of quitting.[11] When they do quit, depression is more apt to be a prominent withdrawal symptom.

Often tobacco use begins in childhood or adolescence.[12] Risk factors for youth smoking include peer and parental influences; behavioral problems (e.g., poor school performance); personality characteristics, such as rebelliousness or risk taking, depression, and anxiety; and genetic influences. The adolescent's desire to appear older and more sophisticated, such as by emulating more mature role models, can be another strong motivator. Environmental influences, such as advertising and smoking in movies, also contribute. Smoking rates among adults have been declining in economically advanced countries. Similarly, initiation rates for youth have gradually declined over the past 3 decades, although this is counterbalanced by the rapid increase of e-cigarette use by youth over the past 5 years. Approaches to preventing tobacco use and addiction in youth include educational activities in schools, aggressive antitobacco media campaigns, taxation of tobacco products, increasing the age for purchase from 18 to 21 years, changing the social and environmental norms (e.g., restricting indoor smoking and educating parents not to smoke around children), and deglamorizing smoking. Unfortunately, the current e-cigarette epidemic has intensified nicotine addiction in youth, and new data validate that e-cigarette use has increased cigarette use.[13]

NEUROBIOLOGIC MECHANISMS OF ADDICTION

(S)-Nicotine binds stereoselectively to *nicotinic cholinergic receptors* (nAChRs) in the brain, as well as in the autonomic ganglia, the adrenal medulla, and neuromuscular junctions. Most relevant to nicotine addiction are the receptors found throughout the brain, with the greatest number in the cortex, thalamus, and interpeduncular nucleus. There is also substantial binding in the amygdala, septum, brainstem motor nuclei, and locus coeruleus. The nAChR is a ligand-gated ion channel composed of five subunits. Most brain nAChRs are composed of α- and β-subunits. Usually, there are two α- and three β-subunits, with the α-subunits responsible for ligand binding and the β-subunits mediating other aspects of receptor function.[14] Nicotinic receptors in the brain have different chemical conductances for sodium and calcium and sensitivity to nicotinic agonists. Brain imaging studies in smokers have confirmed that smoking causes the upregulation of high-affinity nAChRs, which is maintained for up to 4 weeks after cessation of nicotine exposure.[15–17]

The various nicotinic receptors are believed to mediate different pharmacologic actions of nicotine, perhaps corresponding to the multiple effects of nicotine experienced by human smokers.[18] Adolescent nicotine exposure also appears to alter *gamma-aminobutyric acid* (GABA) signaling in the developing brain but not in the adult brain. GABA receptors are now known to alter the nicotine reward effect, which may have an impact on enhancing alcohol self-administration.[19]

Nicotinic receptor activation facilitates the release of neurotransmitters, including acetylcholine, norepinephrine, dopamine, serotonin, β-endorphin, GABA, and others.[20] Pharmacologically, nicotine is a stimulant. It enhances fast excitatory synaptic transmission, which may contribute to learning and memory.[21,22] Nicotine also releases growth hormone, prolactin, vasopressin, and adrenocorticotropic hormone. Behavioral rewards from nicotine and nicotine addiction appear to be linked largely to dopamine release[23] with an impact from GABA receptors as well.

Nicotine metabolism can vary significantly among individuals. *Cytochrome P-450* (CYP) isoenzymes impact the speed of metabolism and are categorized as poor, extensive, or ultrarapid.[24] These differences can have an impact on smoking behavior and the metabolism of nicotine replacement therapies. In addition, exposure to tobacco smoke has a wide-ranging impact on the metabolism of many drugs. Polycyclic aromatic hydrocarbons, products of combustion in cigarette smoke, upregulate certain CYP enzymes, primarily CYP1A2, and accelerate the metabolism of drugs that go through the CYP1A2 pathway. Several drugs have important pharmacokinetic interactions with smoking.

Table 66.1 Interaction Between Cigarette Smoking and Drugs

DRUGS		Interaction (Effects Compared With Nonsmokers)	Significance
Caffeine Chlorpromazine Clozapine Desmethyldiazepam Estradiol Estrone Flecainide Fluvoxamine Haloperidol	Imipramine Lidocaine Olanzapine Oxazepam Pentazocine Phenacetin Phenylbutazone Propranolol Theophylline	Accelerated metabolism	May require higher doses in smokers, reduced doses after quitting
Combined hormonal contraceptives		Enhanced thrombosis, increased risk of stroke and myocardial infarction	Do not prescribe to smokers, especially if ≥35 years old and smoke ≥15 cigarettes daily
Cimetidine and other H_2-blockers		Lower rate of ulcer healing, higher ulcer recurrence rates	Consider using mucosal protective agents
Propranolol		Less antihypertensive effect, less antianginal efficacy; more effective in reducing mortality after myocardial infarction	Consider the use of cardioselective β-blockers
Nifedipine (and probably other calcium blockers)		Less antianginal effect	May require higher doses and/or multiple-drug antianginal therapy
Diazepam, chlordiazepoxide (and possibly other sedative-hypnotics)		Less sedation	Smokers may need higher doses
Chlorpromazine (and possibly other neuroleptics)		Less sedation, possibly reduced efficacy	Smokers may need higher doses
Propoxyphene		Reduced analgesia	Smokers may need higher doses

Caffeine clearance is increased by more than 50% when a person smokes. Therefore, upon smoking cessation, it is advised that patients cut their caffeine intake by half. Nicotine in tobacco smoke also has pharmacodynamic interactions with certain drugs through antagonistic pharmacologic actions. (See Table 66.1 for pharmacokinetic and pharmacodynamic interactions with smoking.)

Nicotine causes an increase in the firing of ventral tegmental area neurons, resulting in release of dopamine in the nucleus accumbens.[23] Dopamine release is potentiated and sustained by nicotine-mediated release of glutamate.[25] Rapid dopamine release in the outer shell of the nucleus accumbens is characteristic of the effects of many addicting drugs (e.g., heroin, cocaine, and alcohol) and is thought to be an important site for drug-mediated reinforcement.[26] The addiction potential for inhaled nicotine is extremely high, in part due to the rapid attainment of the maximal concentration for nicotine achieved from an inhaled cigarette. NRT (e.g., patch, gum, and lozenge) has significantly slower and lower maximal concentration attainment and therefore has minimal addiction potential.

Acute exposure to nicotine produces stimulation of the release of dopamine from neurons in mesolimbic pathways, whereas chronic exposure to nicotine and other drugs of abuse produces other changes in mesolimbic function. Chronic nicotine exposure results in neuroadaptation, or the development of tolerance, and the absence of nicotine results in subnormal release of dopamine and other neurotransmitters. Thus, nicotine withdrawal may result in a state of deficient dopamine responses to novel stimuli in general and to a state of malaise and inability to experience pleasure. This has been termed *hedonic dysregulation* by Koob.[27] Hedonic dysregulation may explain craving, and sensitivity to drug effects may explain why even a single slip might easily result in a return to compulsive drug use.

The release of various neurotransmitters discussed previously results in behavioral arousal, sympathetic neural activation, and a number of other effects believed to be rewarding.[28,29] The release of certain neurotransmitters has been linked to the reported reinforcing effects of nicotine. For example, enhanced release of dopamine and norepinephrine may be associated with pleasure and appetite suppression, the latter of which may contribute to lower body weight. Release of acetylcholine may be associated with improved performance on behavioral tasks and improvement of memory. Release of β-endorphin may be associated with reduction of anxiety and tension. Although smokers give different explanations for their smoking, most agree that smoking produces arousal, particularly with the first cigarettes of the day, and relaxation, particularly in stressful situations, which may in part be due to the relief of nicotine withdrawal throughout the day (Fig. 66.2).

SMOKING CESSATION

Among current cigarette smokers, approximately 70% would like to quit, and about half try to quit each year.[30,31] Spontaneous quit rates (i.e., without support) are about 1% per year. Simple physician advice to quit increases the quit rate to 3%. Minimal intervention programs increase quit rates to 5–10%, whereas more intensive treatments, including smoking cessation clinics, can yield quit rates of 25–30%.[32]

The main strategies for cessation are behavioral counseling, pharmacologic intervention, or a combination of the two, which is strongly recommended. Assessing triggers

such as stress and exposure to family members or roommates who smoke is an important part of history taking before a therapeutic intervention is undertaken.

GUIDELINES

Evidence-based guidelines for the treatment of tobacco addiction emphasize identifying all tobacco users in a clinical practice setting and ascertaining each patient's intent with respect to quitting smoking (Fig. 66.3).[1,5,33,34] Identification of tobacco use is facilitated by the implementation of an office-based system so that patients are queried about tobacco use at every visit. Tobacco use should be treated as a vital sign, with reminders placed in the electronic medical record to screen patients. The practice of routinely recording a patient's tobacco use status increases the *odds ratio* (OR) for quitting by twofold.

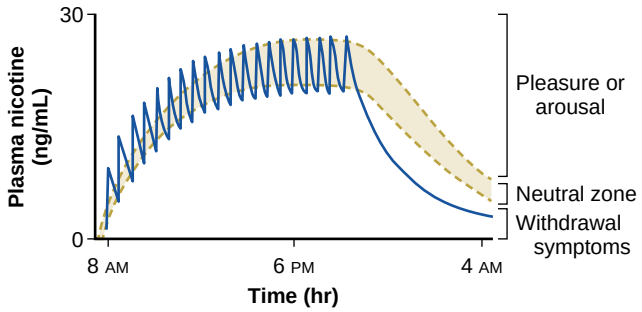

Figure 66.2 Nicotine levels in a person who smokes cigarettes. The peaks and troughs of nicotine concentrations throughout the day in a person smoking 20 cigarettes. Levels are low in the morning and drop rapidly with sleep. Smokers begin to experience withdrawal symptoms as the nicotine concentration drops below the shaded area, prompting another cigarette. The shaded area (neutral zone) represents the zone of nicotine concentrations in which the smoker is comfortable without pleasure/arousal or withdrawal symptoms. Note that the threshold levels for pleasure/arousal and withdrawal symptoms rise progressively during smoking due to development of tolerance. The magnitude of pleasure/arousal is greatest with the first cigarette of the day but becomes less intense with subsequent cigarettes. (From Benowitz NL. Cigarette smoking and nicotine addiction. *Med Clin North Am.* 1992;76:415–437.)

Brief strategies to help a patient quit, which can be implemented in as little as 3 minutes, increase cessation rates significantly. In a meta-analysis of 31 trials, brief physician advice increased quit rates by 70%.[32] Intensive behavioral treatment of tobacco dependence produces higher success rates than does brief advice (the 5 A's) and is cost-effective. However, these intensive programs are less widely available and can be challenging to provide for busy clinicians. Nevertheless, clinicians with training in intensive smoking cessation therapy should be identified as a referral source and champion for smokers who are interested.

The 2008 Public Health Service guidelines and other international guidelines recommend that all smokers trying to quit should be offered pharmacotherapy (Table 66.2).[1,34] Three types of medications have been approved by the *U.S. Food and Drug Administration* (FDA) for smoking cessation: bupropion, which was originally marketed as an antidepressant drug, NRT, and varenicline (Table 66.3). Unfortunately, smoking cessation medications are underutilized by patients and providers. It is estimated that only approximately one-third of patients use medications when

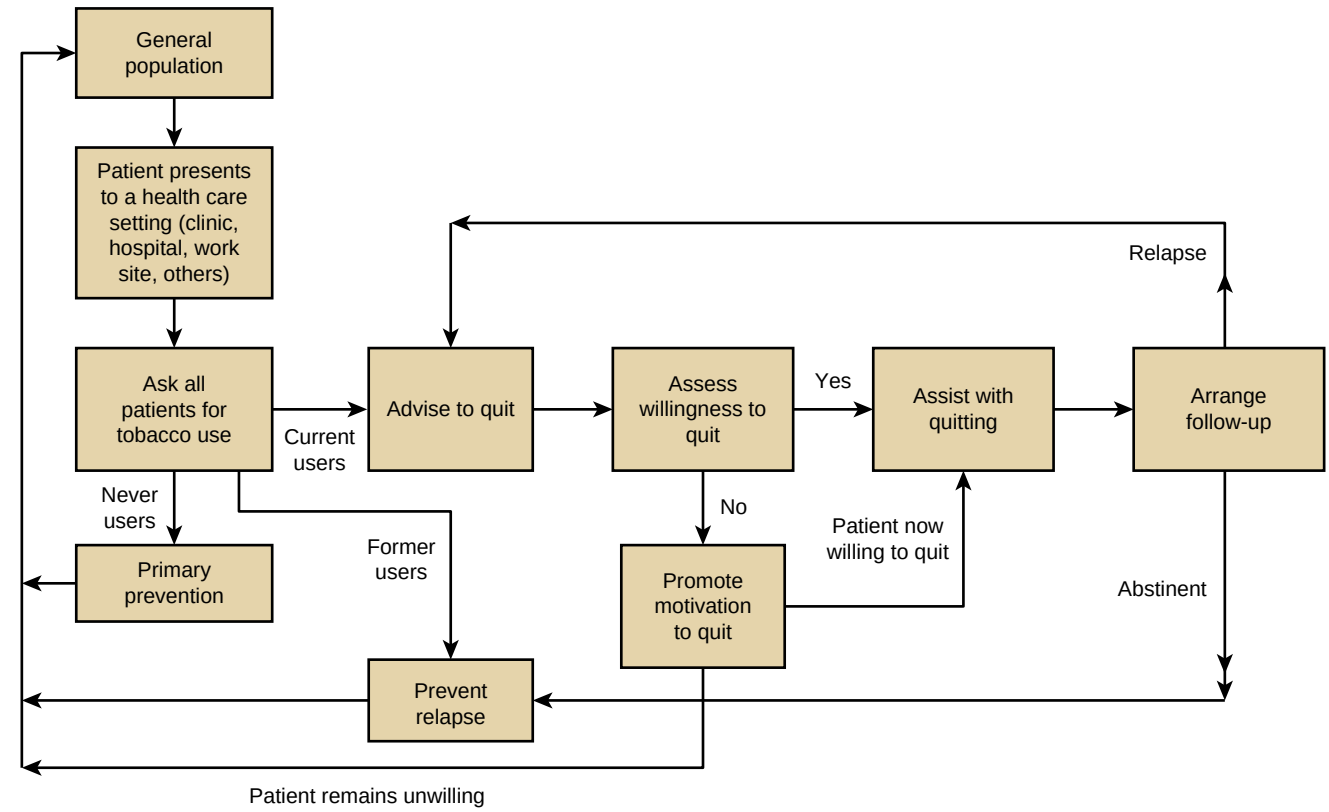

Figure 66.3 An algorithm for treating tobacco use. (From Clinical Practice Guideline Treating Tobacco Use and Dependence 2008 Update Panel, Liaisons, and Staff. A clinical practice guideline for treating tobacco use and dependence: 2008 update. A U.S. Public Health Service report. *Am J Prev Med.* 2008;35[2]:158–176.)

Table 66.2 General Clinical Guidelines for Prescribing Pharmacotherapy for Smoking Cessation

- In general, all smokers trying to quit smoking should be offered pharmacotherapy.
- There are seven first-line smoking cessation medications—five types of *nicotine replacement therapy* (NRT), sustained-release bupropion, and varenicline. Varenicline or the combination of nicotine patch plus ad libitum short-acting nicotine products appear to be most effective. However, the choice of first-line therapy should be governed by patient preference, familiarity of the clinician with the medication, contraindications for specific patients, and prior experience of the patient with specific pharmacotherapies.
- Second-line therapies include clonidine and nortriptyline. These should be reserved for individuals with contraindications to or failure of response to first-line medications.
- Bupropion and NRT may delay but not prevent weight gain after smoking cessation. It is recommended that patients start or increase physical activity, but strict dieting is discouraged because this appears to increase the likelihood of relapse to smoking. Patients should be reassured that weight gain after quitting is self-limited and poses much less of a risk to health than smoking.
- All first-line therapies appear to be safe for patients with chronic cardiovascular disease. The over-the-counter NRT therapies (gum, lozenge, and patch) contain precautions for use if the following exist: recent (≤2 weeks) myocardial infarction, serious or underlying arrhythmias, or serious or worsening angina pectoris. This labeling is for over-the-counter use only. Bupropion and varenicline are likely to be safer than smoking in the presence of cardiovascular disease.
- In individuals with prolonged withdrawal symptoms or those who are unable to abstain in the absence of medication, extended use or long-term therapy with NRT, bupropion, or varenicline appears to be safe and effective therapy.

Modified from 2008 PHS Guideline Update Panel, Liaisons, and Staff. Treating tobacco use and dependence: 2008 update U.S. Public Health Service Clinical Practice Guideline executive summary. *Respir Care.* 2008;53:1217–1222.

trying to quit.[31] Other drugs such as nortriptyline and clonidine have been shown in clinical trials to be effective in smoking cessation but have not yet been approved by the FDA for this purpose.

SMOKING CESSATION COUNSELING

Counseling smokers about the benefits of quitting and the health consequences of tobacco should be incorporated into routine medical practice and has been shown to be an effective method to improve cessation rates. Motivational interviewing, a patient-centered values-based form of counseling, has demonstrated a clear benefit in smoking cessation.[35,36] Based on a review of 188 randomized trials, personal advice and encouragement to stop smoking provided by a physician during a routine office visit resulted in an estimated 2% of all smokers stopping and not relapsing over 1 year.[37] Although this percentage seems low, it is both cost-effective and important when considering the large population and the risk for disease. Specific patient populations may have better results: 8% of pregnant smokers, 21% of healthy men at risk for cardiovascular disease, and 36% of survivors of *myocardial infarction* (MI) will stop smoking when receiving advice and encouragement. This high success rate likely reflects the patient's inherent motivation once challenged by a condition that has been caused by or may be aggravated by cigarette smoking.

Group counseling is less cost-effective than brief advice but is a highly effective option for smokers who are not successful with less intensive therapy. A review of 16 studies comparing group counseling found increased rates of cessation compared to self-help programs (16 studies; OR, 2.0) or no intervention (six studies; OR, 2.2).[32] There is no evidence that group counseling is more effective than a similar intensity of one-on-one counseling with a clinician.[38]

Telephone counseling is also effective in promoting cessation. In a large *randomized controlled trial* (RCT) of 1973 intensively counseled callers versus 1309 control subjects, telephone counseling through a quitline nearly doubled abstinence rates.[39] The 12-month self-reported cessation rates for those who made one or more cessation attempts was 23.3% in the treatment group and 18.4% in the control group. Telephone quitlines are available at no cost in most of the United States. Thus, when clinicians are unable to provide counseling due to lack of time, they can easily refer patients to a quitline, such as 800-QUIT-NOW in the United States, for cessation counseling and support.

Counseling for smokers during hospitalization has been found to be effective for patients admitted with cardiovascular disease; this is not well studied in other populations. Molyneux[40] evaluated 274 patients in an RCT and found that NRT given with brief counseling is more effective than counseling alone or usual care. Counseling alone was not more effective than usual care, and differences between all groups disappeared at 12 months. Counseling for hospitalized patients appears to be most effective when it includes at least 1 month of supportive contact after discharge.[41]

MOTIVATING SMOKERS TO QUIT

The well-known association between cigarette use and morbidities, such as lung cancer, MI, stroke, and COPD, is often insufficient to motivate many cigarette smokers to quit. This is likely due to the significant addiction to nicotine. A telephone-based survey conducted in 1999 found that only 29% of smokers felt that they were at greater risk of MI, and only 40% felt they were at greater risk for development of cancer compared to nonsmokers.[42] This clearly indicates denial of risk and may explain why many smokers only become motivated to quit when they develop a medical condition later in life.

As described previously, many smokers depend on nicotine to cope with stressors encountered in daily life because they perceive smoking as having a stress-reducing effect. Becoming a nonsmoker requires a profound change of self-image and a discovery of personal coping skills that may have not been used previously.

Health care providers' role in the motivation process can be substantial. The message to the smoker must be consistent and inspirational (Table 66.4). Patients respect advice from their provider, and hopelessness can be allayed by describing the many options available for cessation medications and counseling. Smoking cessation is the most important health initiative many patients will ever undertake and is highly cost-effective for the health care system. It is difficult to address smoking with patients when three or four medical issues are being managed in addition to smoking cessation. For this reason, a separate planned visit focused solely on smoking cessation is recommended.

Table 66.3 First- and Second-Line Smoking Cessation Medications

Pharmacotherapy	Precautions/ Contraindications	Adverse Effects	Dosage	Duration	Availability
FIRST-LINE					
Bupropion sustained release (SR)	Current or history of seizure Current or history of eating disorders	Insomnia, dry mouth, neuropsychiatric symptoms (rare)	150 mg every morning for 3 days then 150 mg twice daily (begin treatment 1–2 wk before quit date) Allow at least 8 hr between doses Avoid bedtime dosing	7–12 wk maintenance, up to 6 mo	Prescription
Varenicline	Renal impairment	Severe nausea, trouble sleeping, abnormal or vivid/strange dreams, neuropsychiatric symptoms (rare)	0.5 mg/day for 3 days 0.5 mg twice/day for next 4 days, then 1 mg twice/day Begin treatment 1 wk before quit date	3–6 mo	Prescription
Nicotine gum	Temporomandibular joint disorder	Mouth and throat irritation, dyspepsia, hiccups	First cigarette ≥30 min after waking: 2 mg First cigarette ≤30 min after waking: 4 mg Up to 24 pieces/day	3 mo	OTC
Nicotine lozenge		Mouth and throat irritation, dyspepsia, hiccups	First cigarette ≥30 min after waking: 2 mg First cigarette ≤30 min after waking: 4 mg Up to 20 pieces/day	3 mo	OTC
Nicotine inhaler	Bronchospastic disease	Mouth and/or throat irritation	6–16 cartridges/day	3–6 mo	Prescription
Nicotine nasal spray	Chronic nasal disorders, including rhinitis, polyps, and sinusitis Severe reactive airway disease	Nasal and/or throat irritation, ocular irritation/tearing, sneezing	1 dose = 1 spray in each nostril 8–40 doses/day Maximum of 5 doses/hr or 40 doses/day	3 mo	Prescription
Nicotine patch	Skin diseases, such as atopic or eczematous dermatitis	Local skin reactions, insomnia	>10 cigarettes daily: 21 mg 14 mg 7 mg ≤10 cigarettes daily: 14 mg 7 mg	 4 wk then 2 wk then 2 wk 6 wk then 2 wk	Prescription and OTC
SECOND-LINE					
Clonidine	Rebound hypertension	Dry mouth, drowsiness, dizziness, sedation	0.15–0.75 mg/day	3–10 wk	Prescription only (oral formulation, patch)
Nortriptyline	Risk of arrhythmias	Sedation, dry mouth	75–100 mg/day	3 mo	Prescription only

Note: Tapering will vary across different medications; information is available in the package insert and the regulatory approval label.
OTC, over the counter.
Modified from 2008 PHS Guideline Update Panel, Liaisons, and Staff. Treating tobacco use and dependence: 2008 update. US Public Health Service Clinical Practice Guideline executive summary. *Respir Care*. 2008;53:1217–1222.

Motivating patients to quit needs to be more than steering them away from the health consequences of tobacco-related disease but also steering them toward greater self-control, self-expression, independence, and positive role modeling. Table 66.4 provides a few simple framing do's and don'ts to keep in mind when talking with cigarette and e-cigarette users.

Exercise during trials of smoking cessation may reduce anxiety, tension, and stress but was not found to be an independent predictor of success in a RCT.[43] Walking on a regular basis is a reasonable initial step and, in many cases, improves self-esteem and investment in health.

Other interventions for smoking cessation, such as acupuncture and hypnotherapy, are available. In many cases the interventions are either incompletely studied or have poor study methodologic quality to render a solid recommendation. Both acupuncture and hypnotherapy have significant variability in the practice of the intervention. A recent systematic review of acupuncture suggested a short-term benefit, with greater benefit when used in

Table 66.4 Key Points When Counseling Smokers

DO'S

- Determine where the person is on the spectrum of smoking cessation (precontemplation, contemplation, action, maintenance, relapse). Your focus is to move them stepwise toward action, and after cessation keep them in maintenance.
- Dose adjust nicotine replacement therapy to the maximally effective dose based on the person's cigarette use, response to medications and frequency of urges.
- Ask "Have you used any tobacco or nicotine products in the past 30 days"?

DON'TS

- Ask "Do you smoke?" People with regular tobacco use may not identify as a regular smoker and answer *no* to this question.
- Call it a habit. Cigarette smoking and nicotine addiction is an acknowledged disease with significant withdrawal symptoms.
- Do not think that talking about a tobacco-related disease like lung cancer or COPD leads to an increased motivational level. Fear can reduce energy level and lead to discouragement. Frame the benefit of cessation in a positive manner (improved breathing, greater freedom, greater control of health).

combination with counseling.[44] Hypnotherapy was systematically reviewed across 14 studies of 1926 participants. The authors concluded there was insufficient evidence to determine if hypnotherapy was more effective than other forms of behavioral support or unassisted quitting.[45] Mobile phone texting and app-based smoking cessation interventions have been studied in multiple settings. A comprehensive review of 26 studies and 33,849 participants updated in 2018 concluded that there is moderate-certainty evidence that text-based interventions result in greater quit rates than minimal support.[45a] The evidence evaluating the benefit of smartphone apps was of low certainty, clearly suggesting the need for RCTs in this area.[45a,46]

PHARMACOTHERAPY FOR SMOKING CESSATION

All types of smoking cessation medications, if used properly, double to triple smoking cessation rates compared with placebo treatments.[33]

NICOTINE REPLACEMENT THERAPY

NRT is typically started on the person's designated quit date and includes nicotine gum, transdermal nicotine patches, nicotine nasal spray, nicotine inhaler, and nicotine lozenges. Patch, gum, and lozenge formulations are available over the counter, and the nicotine nasal spray and oral inhaler are by prescription only. All have comparable efficacy when used as monotherapy. In a randomized study, adherence was greatest for the patch, lower for gum, and very low for the spray and the inhaler.[47] The use of combination therapy (nicotine patch plus a short-acting NRT used as needed for cravings) appears to be more effective.[48]

Both the nicotine gum and lozenge are available in two doses: 2 mg and 4 mg. Their dose is based on when a patient has the first cigarette upon waking. If it is within the first 30 minutes, the 4-mg dose is used; if a person waits more than 30 minutes after waking up, the 2 mg-dose is used. A person will use one piece every 1 to 2 hours while awake for the first 6 weeks, then taper over the next 6 weeks with instructions not to taper too quickly if experiencing significant urges. Optimal use of nicotine gum includes providing instructions on how to chew properly (i.e., use the chew-park-chew-park method) and to park in different areas of the mouth. A piece of gum will last about 30 minutes. Optimal use of nicotine lozenge[49] includes placing in the mouth and allowing to dissolve (it should not be chewed or swallowed) and to rotate to different areas of the mouth. A lozenge will dissolve over 20 to 30 minutes. Nicotine is absorbed across the buccal mucosa for both products. Patients should not eat or drink 15 minutes before or while using the gum or lozenge. Side effects of the gum and lozenge are primarily local and include mouth and throat irritation, upset stomach, and hiccups. The gum can also cause jaw muscle soreness.

Transdermal nicotine patches come in three strengths: 21 mg, 14 mg, and 7 mg; all deliver nicotine over a 24-hour period. A patch is applied in the morning and removed the next morning. If a patient experiences intrusive or disturbing dreams, the patch should be removed at bedtime. If a patient smokes more than 10 cigarettes a day (more than half a pack), then the 21 mg strength should be started; if a patient smokes less, then the 14-mg strength should be started (see Table 66.3 for full dosing information). It is important to rotate the sites where the patch is applied and to not use the same site for at least 1 week. The patch is generally applied to the upper body or upper outer part of the arm and to clean, dry skin (as hairless as possible) to ensure good adhesion. Although the patch provides a steady level of nicotine, the challenge becomes how to manage acute cravings; in this situation, combination NRT can be very effective, in which a short-acting NRT is used per its usual directions but on an as-needed basis.

Nicotine nasal spray is dosed one spray into each nostril and should be dosed one to two doses per hour. A patient should use at least eight doses per day for the first 6 to 8 weeks and then slowly taper over an additional 4 to 6 weeks as tolerated. It has unique side effects from the local irritation of the nasal mucosa (e.g., burning, sneezing, and watery eyes); with regular use, patients develop tolerance to these effects.

The nicotine inhaler delivers nicotine vapor across the mucosa of the mouth to the back of the throat. The nicotine is contained in a cartridge inserted into a plastic mouthpiece. A patient should use one cartridge every 1 to 2 hours, inhaling into the back of the throat or puffing in short breaths. The cartridge is depleted after 20 minutes of active puffing. Patients should not eat or drink 15 minutes before or while using the inhaler. Side effects of the inhaler are primarily local and include mouth and throat irritation, upset stomach, and hiccups. Although the labeling includes bronchospastic disease as a precaution, smoking cigarettes is likely a much greater trigger for irritation than the nicotine vapor from the inhaler.

All nicotine medications appear to be safe in patients with cardiovascular disease and can be offered to cardiovascular patients.[50–52] Although smoking cessation medications are recommended by the manufacturer for relatively short-term

use (generally 3–6 months), the use of these medications for 6 months or longer (i.e., extended use) is safe and may be helpful in smokers who fear relapse without medications.[53]

In pregnancy, the two recommended interventions are counseling and the use of NRT. The safety of other medications, such as bupropion and varenicline, has not yet been adequately studied to support a clear recommendation for use in pregnancy. Potential fetal side effects are of paramount concern, and the opportunity to quit smoking still exists in the postpartum period. Pregnancy and the parent's concerns about immediate fetal health and postpartum secondhand smoke exposure to the infant can create a highly motivated focus to stop smoking and should receive extra support and attention.[54–56] Additional high-quality research is needed to determine optimal and safe non-NRT interventions or optimal combinations of therapies.

BUPROPION

Bupropion sustained release (Wellbutrin SR, formerly available as Zyban) is a dopamine-norepinephrine reuptake inhibitor originally marketed and still widely used as an antidepressant. Bupropion was found to aid smoking cessation independent of whether a smoker was depressed.[57] In this study, Hurt demonstrated that, with a 300 mg SR dose, 44% of patients quit at 7 weeks versus 19% of control subjects. This difference was sustained at 12 months (23% vs. 12%). This study also indicated that, when smokers quit, they gained less weight while taking bupropion compared to placebo.[38] An additional randomized, placebo-controlled trial demonstrated that the combination of bupropion with nicotine patch is safe and that bupropion alone or in combination was as effective or more effective than the patch alone.[58] The combination of bupropion and nicotine patch has been approved by the FDA for smoking cessation. Bupropion used for 1 year for relapse prevention was demonstrated to be safe and effective and significantly better at promoting cessation (55%) than placebo (42%).[59] Given its antidepressant properties, bupropion is a logical choice for smokers with depression but, as mentioned previously, has clear efficacy in smokers without depression as well.

Bupropion SR is by prescription only and is dosed at 150 mg daily for 3 days, then 150 mg twice a day for 12 weeks. Bupropion should be started 1 to 2 weeks before the quit date to ensure that therapeutic levels are attained because it has a long half-life (21 hours). Dose tapering is not needed at the end of 12 weeks. Bupropion in higher doses can cause seizures and should not be used in an individual with (or a history) of seizures or with eating disorders (bulemia or anorexia). Common side effects are dry mouth and insomnia.

VARENICLINE

Varenicline (Chantix), available by prescription only, is a nicotinic receptor partial agonist that selectively binds to $\alpha 4\beta 2$ nicotinic cholinergic receptors in the brain. This receptor mediates dopamine release and is thought to be the major receptor involved in nicotine addiction. A partial agonist means that the drug activates the receptor but at a lower-level agonist activity (about 50% of that of nicotine) and also blocks the effects of other agonists (e.g., nicotine) on the receptor. It primarily works to help alleviate nicotine withdrawal symptoms. In the case of a relapse, if a person smokes, the effects of the nicotine are likely blocked by varenicline.

Varenicline is initiated in a dose of 0.5 mg daily for 3 days, then 0.5 mg twice daily for 4 days, followed by a maintenance dose of 1 mg twice daily. Varenicline generally should be started 1 week before the quit date to ensure therapeutic levels are attained because it has a long half-life (24 hours). A flexible (quit within a month) or gradual (quit within 12 weeks) quit approach can also be used after starting varenicline. Lower doses may be used if nausea is a problem at higher doses. Because varenicline is eliminated by the kidneys, dose reduction is required in the presence of severe renal disease. The treatment duration is 3 months, and an additional 3 months is possible in selected patients who have significant urges and are at high risk of relapse.

In clinical trials, varenicline treatment for 12 weeks has been shown to be more effective than bupropion SR 300 mg or placebo. Continuous abstinence rates after study medication discontinuation out to 52 weeks were 29%, 21%, and 11% for varenicline, bupropion, and placebo, respectively.[60,61] Varenicline has also been shown to be effective in preventing relapse over 6 months. In a network meta-analysis, varenicline was associated with an increased odds of quitting, with an OR of 2.9 (2.4–3.5) compared to placebo, and varenicline monotherapy was comparable to dual NRT use (OR of 2.7 vs. placebo).[48] The common side effects of varenicline are nausea and insomnia; it is important to take it with food and a full glass of water.

Both bupropion and varenicline have been associated with a variety of neuropsychiatric symptoms described in the warnings and precautions sections of their respective FDA labels. A boxed warning for severe neuropsychiatric symptoms from varenicline was removed in December 2019 as a result of the *Evaluating Adverse Events in a Global Smoking Cessation Study* (EAGLES),[62] which demonstrated that varenicline and bupropion were not associated with an increased risk of neuropsychiatric symptoms compared with NRT or placebo. The American Thoracic Society released an official clinical practice guideline on initiating cessation treatment in tobacco-dependent adults in May 2020.[63] Five "strong" recommendations (based on National Academy of Medicine criteria) were developed from an analysis of the most recent published data and included (1) using varenicline rather than a nicotine patch, (2) using varenicline rather than bupropion, (3) using varenicline rather than a nicotine patch in adults with a comorbid psychiatric condition, (4) initiating varenicline in adults even if they are unready to quit, and (5) using controller therapy (varenicline, bupropion or nicotine patch) for an extended treatment duration more than 12 weeks. Patients should be monitored for neuropsychiatric events during treatment and instructed to discontinue bupropion or varenicline and contact a health care provider if they experience adverse events.

COMBINATION THERAPY

An important consideration in smoking cessation medication strategy is the use of combination therapies. Combined

medications for smoking cessation can be more effective than individual therapies, particularly when combining long-acting medications such as nicotine patch or bupropion with short-acting NRT used at times of intense urges or cravings to smoke. Only bupropion and transdermal nicotine in combination have been approved by the FDA. However, a number of studies have looked at various combinations of medications.[63–67] Combination NRT (patch plus quick-acting NRT) is more effective than monotherapy and therefore is generally recommended over monotherapy.[48]

Combination therapies can also give people more flexibility in their plan, particularly if they start with one therapy and feel it is not fully effective and want to add a second therapy. Because there is significant individual variability in the metabolism of nicotine, some patients who rapidly metabolize nicotine may require higher doses of replacement therapy.[66] Experiencing breakthrough urges could suggest that some people are significantly underdosed by one form of NRT and that a second form or higher doses could be more effective. One prospective study found that the combination of bupropion and varenicline was more effective than varenicline alone in a specific subset of patients with a high level of dependency.[67] Published guidelines[1] have not kept pace with emerging combination data in the literature, and multiple publications have demonstrated that combinations of smoking cessation medications can be more effective than monotherapy. The safety of unapproved combination therapies is unclear and must be considered to enable an appropriate benefit versus risk assessment for an individual patient.

ELECTRONIC NICOTINE DELIVERY SYSTEMS AND E-CIGARETTES

The toxicity and side effects associated with e-cigarettes are emerging and are reviewed in Chapter 65. Several studies have begun to evaluate the use of e-cigarettes as a smoking cessation modality. However, the main concern is that this constitutes a switch from one highly addictive form of inhaled nicotine (cigarettes) to another highly addictive form of inhaled nicotine (e-cigarettes) without the intention to end nicotine addiction. The e-cigarette industry is not regulated, and there is no formal FDA-supported safety database providing accurate safety information. For these reasons, the use of e-cigarettes will remain controversial in clinical practice because their safety is unclear in comparison to health authority–approved cessation medications. Some studies have started to evaluate the use of e-cigarettes as a cessation aid. A systematic review in 2015 of the potential efficacy of e-cigarettes versus other cessation therapies revealed six RCTs and nine cohort studies of 7551 participants. Among 1242 smokers in the RCTs, 18% reported smoking cessation after using nicotine-containing e-cigarettes for a minimum duration of 6 months.[68] A separate retrospective study of 25- to 44-year-olds in the National Health Interview Survey database conducted by the Centers for Disease Control and Prevention[69] demonstrated that e-cigarette use was associated with higher quit attempts and greater smoking cessation (adjusted OR, 1.6; $P = 0.001$) in recent years compared to 2006 data. This could suggest that the new technology and media messaging associated with e-cigarettes provides an incentive to attempt quitting compared to other modalities. In contrast, a prospective cohort study from 2015–16[70] performed a random probability sample of 1284 U.S. adult smokers evaluated over 1 year. In this sample, the adjusted odds of quitting smoking were lower for those using e-cigarettes at baseline compared to those who did not use e-cigarettes (adjusted OR, 0.30). In summary, individual studies may suggest evidence for or against the potential benefit of e-cigarettes for smoking cessation but, in aggregate, in a systematic review,[71] there does not appear to be a place for their use, particularly when compared to approved smoking cessation medications.

Perhaps the most important recent trial[72] was an open-label RCT of 886 participants in the United Kingdom randomly assigned NRT (alone or combination) for 3 months versus an e-cigarette and refillable bottle of nicotine e-liquid (18 mg/mL), with all participants receiving 4 weeks of behavioral support. The 1-year abstinence from smoking was 18.0% in the e-cigarette group versus 9.9% in the NRT group (relative risk, 1.8; $P < 0.001$). Eighty percent of the participants in the e-cigarette group were using e-cigarettes at 12 months versus 9% in the NRT group. This important trial warrants significant analysis and context. Although the cessation rate was higher in the e-cigarette group at 1 year, the trial was not blinded, and the e-cigarette cessation rate was similar to rates seen with medications such as bupropion (≈20% at 1 year), varenicline (≈30% at 1 year), and a common combination of bupropion and patch (28% at 1 year[73,74]). The cessation rate of 9.9% with the convenience (multiple option) NRT treatment approach is significantly lower than a recent meta-analysis review of NRT, which yielded a 1-year point estimate of 19.8%. Of importance, as mentioned, 80% of participants in the e-cigarette group continued their use at 1 year, raising the concern about long-term safety and providing a contrast to NRT and other medications that have an intended use of approximately 3 months.

Because the health effects of e-cigarettes are only beginning to be understood, clinicians should recommend medications with a proven benefit and safety profile before considering new options. There may be a role for e-cigarettes in smokers who have a strong desire to quit smoking but refuse other cessation medications or have tried other interventions and found them to be unsuccessful. Even in this case, it is reasonable to recommend that e-cigarettes for smoking cessation should be used short term (3–6 months) because the medical goal is to end nicotine addiction.[75] Clinicians should educate patients about lung disease and other health risks that are emerging from vaping.

A recent cross-sectional analysis in the U.S. Population Assessment evaluated the risk of MI in cigarette users compared to e-cigarette users and to those with dual use. These data demonstrated that e-cigarette use and cigarette use conferred a similar risk of MI and demonstrated that dual use had an OR of 6.6 for an MI compared to never-cigarette or e-cigarette users.[76] The Forum of International Respiratory Societies has actively called for the regulation of e-cigarettes and the American College of Cardiology/American Heart Association Guidelines on the Prevention of Cardiovascular Disease (2019) recommend against the use of e-cigarettes for smoking cessation.[77] In light of the newly recognized epidemic of vaping-associated severe lung disease and associated

deaths, it appears reasonable for all physicians to discourage e-cigarette use until both the short- and long-term dangers associated with their use are understood.[78]

BENEFITS OF QUITTING

The benefits of quitting smoking are substantial for smokers of any age. A person who quits smoking before age 50 years has half the risk of dying in the next 15 years compared with a continuing smoker.[79] Smoking cessation reduces the risks of developing lung cancer, with the risk falling to half that of a continuing smoker by 10 years and one-sixth that of a smoker after 15 years' cessation. Quitting smoking in middle age substantially reduces lung cancer risk, with a 50% reduction in risk if a lifelong smoker quits at age 55 years compared with age 75 years.[80] The risk of acute MI falls rapidly after quitting smoking and approaches nonsmoking levels within 1 year of abstinence. Cigarette smoking produces a progressive loss of airway function over time characterized by an accelerated loss of *forced expiratory volume in 1 second* (FEV_1) with increasing age. Loss of FEV_1 due to cigarette smoking cannot be regained by cessation, but the rate of decline slows after smoking cessation and returns to that of nonsmokers[81] (see Fig. 64.6). Women who stop smoking during the first 3 to 4 months of pregnancy reduce the risk of having a low-birthweight infant to that of a woman who has never smoked.

After quitting, smokers gain an average of 10 pounds, which is often perceived by some smokers as undesirable and may be a barrier to quitting. Smokers tend to be thinner because nicotine increases energy expenditure and suppresses a compensatory increase in food consumption. Upon quitting, ex-smokers tend to reach the weight expected had they never smoked. Of course, the benefits of quitting far outweigh the risks associated with weight gain, and patients should be counseled accordingly.

RESOURCES FOR HEALTH CARE PROVIDERS

Most hospitals have smoking cessation services available that will enable referral of smokers if deemed necessary. Most states have free quitlines that can be accessed through a national network at 800-QUIT-NOW (800-784-8669) that provides smoking cessation information and counseling and has been shown to be effective. The American Lung Association (www.lung.org/quit-smoking) has a wealth of information and an online program called "Seven Steps to a Smoke-free Life" to which patients can be referred. The Centers for Disease Control and Prevention has information that can be downloaded for adults, youth, and Spanish-speaking patients (www.cdc.gov/tobacco/). Other web-based counseling resources include www.smokefree.gov and www.becomeanex.org. If patients do not have their own computer, the public library is a smoke-free environment where they can access computers. Patients suspected of having underlying depression, anxiety, or other substance abuse disorders may benefit from psychiatric referral to evaluate these conditions known to reduce the likelihood of smoking cessation. Finally, the Rx for Change: Clinician-Assisted Tobacco Cessation training program is available; it equips practicing clinicians and health professional students with evidence-based knowledge and skills for how to assist patients with quitting. Lectures (with downloadable PowerPoint slides) and other educational materials have been created by pharmacists and experts in smoking cessation for the medical community as a free educational and clinical resource (http://rxforchange.ucsf.edu).

Acknowledgment

Many thanks to Dr. Neal Benowitz, who as a prior contributing author to this chapter provided much of the nicotine neurobiology information still featured.

Key Points

- Nicotine is an intensely addictive chemical that causes the upregulation of nicotinic cholinergic receptors in the brain.
- Nicotine has a short half-life, and withdrawal symptoms can be severe.
- Cigarette smoking is the most important preventable cause of respiratory disease.
- Most smokers would like to quit smoking but have difficulty doing so because of nicotine addiction.
- Smoking cessation counseling and medications are extremely underutilized in the United States and many countries around the world.
- Smoking cessation medications come in two broad categories: nicotine replacement therapies and the oral medications bupropion and varenicline. Both individual therapies and combinations are effective.
- E-cigarettes represent a new and addictive technology.
- The efficacy of e-cigarettes for smoking cessation continues to be evaluated, but long-term data on safety are unknown. E-cigarettes are not recommended for smoking cessation by major medical societies.

Key Readings

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CYSTIC FIBROSIS: PATHOGENESIS AND EPIDEMIOLOGY

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INTRODUCTION

Cystic fibrosis (CF) is a multisystem genetic disease that affects children and young adults. CF is the most common monogenetic disease in white populations. The disease is caused by mutations in the *CF transmembrane conductance regulator* (CFTR) protein, an anion channel expressed on the epithelial surface. CF is typified by the presence of chronic upper and lower respiratory tract infection leading to bronchiectasis and end-stage lung disease. Manifestations in the pancreas, gastrointestinal tract, skin, and male reproductive tract are also prominent.

Understanding the biology and treatment strategies in CF is important for several reasons. First, CF is the most common cause of both chronic respiratory failure and pancreatic exocrine dysfunction in children and young adults. Second, it is a major cause of bronchiectasis and pansinusitis, among other sinopulmonary conditions in this age group, and therefore represents an essential consideration in the differential diagnosis of numerous clinical syndromes. Third, the pathobiology has substantial commonalities with other mucociliary disorders, thus representing common principles. Finally, advances in CF research have provided a roadmap for understanding the pathophysiology and treatment for other severe airway diseases, including COPD, asthma, and non-CF bronchiectasis. This chapter highlights the current understanding of CF pathobiology, with particular emphasis on the role of CFTR in disease pathogenesis.

HISTORICAL PERSPECTIVE

The first comprehensive description of CF as a distinct clinical entity was published in 1938 by Anderson, who named the disease "cystic fibrosis of the exocrine pancreas."[1] In 1945, Farber described the condition as a generalized *mucoviscidosis* resulting in obstruction of exocrine glands.[2,3] Also in the 1940s, clinical descriptions first linked mucoviscidosis to severe and recurrent lung infections. With the development of effective antimicrobials, new treatments to address severe pulmonary infection were applied to CF for the first time.

An extreme heat wave in the northeastern United States in the summer of 1948 led di Sant'Agnese[4] to describe high salt concentrations in the sweat of infants with CF and introduce the concept of abnormal ion transport as contributing to the disease. End-organ dysfunction in the sweat gland was among the first characteristics recognized for the disorder. Di Sant'Agnese demonstrated elevated levels of sweat sodium and chloride in greater than 98% of subjects with CF, a finding that remains a cornerstone for diagnosis today. A traditional Irish folk saying, "if your baby tastes of salt, he is not long for this world," may have presaged these fundamental scientific discoveries regarding sweat hypersalinity in CF.

Before identification of the *CFTR* gene and protein in 1989,[5–7] early observations led investigators to postulate an ion transport abnormality as a proximate cause of CF. To measure this phenomenon, Gibson and Cooke[8] developed the modern pilocarpine method of sweat chloride testing. Later, Quinton[9,10] demonstrated that sweat gland ducts in CF patients are impermeant to chloride. At the same time, a number of contributions regarding the physiology of ion transport within nasal epithelium by Knowles and colleagues[11,12] and subsequent membrane patch-clamp analysis of airway epithelial cells by Welsh and Liedtke[13] and Frizzell[14] provided conclusive evidence for defective chloride transport within plasma membranes

of epithelial cells in the upper and lower respiratory tract of patients with CF, in addition to associated abnormalities of sodium uptake.[11,12] Transformational chromosome mapping technology applied by Collins, Riordan, and Tsui[6,15,16] identified the causative gene, which they named the *cystic fibrosis transmembrane conductance regulator*. This finding set the stage for molecular cloning of the gene; independent verification that *CFTR* encoded a chloride channel protein; elucidation of the most common mutation, F508del; and definition of myriad other disease-associated variants. These studies comprise the basis for current understanding of CF pathogenesis and new therapeutics directed toward the fundamental molecular defect.[17,18]

EPIDEMIOLOGY

CF is the most common monogenetic lethal disease in white populations, found in 1 in 2500 to 3500 live births in the United States, with lower frequencies among African Americans (1:17,000). There is a varied incidence in particular ethnic groups, ranging from 1:569 in an isolated Ohio Amish population to 1:90,000 in Asian populations.[19]

CFTR mutations are most prevalent among persons descended from central and northern European populations. Non-European white populations demonstrate intermediate rates of *CFTR* mutation, and Native Americans, Asian populations, and Black Africans demonstrate the lowest rates. Proposed reasons for the selectivity of *CFTR* mutations in these populations include a heterozygote advantage in epidemic illnesses, such as cholera, tuberculosis, or plague. Cholera is of particular interest because the absence of CFTR-dependent chloride transport could confer an advantage on *cyclic 3′,5′-adenosine monophosphate* (cAMP) activation by cholera toxin.[20] Conversely, selectively lower rates of *CFTR* mutations in populations living in tropical or semitropical environments could be due to propensity for excess salt loss conferred by heterozygosity. In white populations, approximately 1 in 25 is a carrier for a *CFTR* gene mutation,[21] resulting in a carrier rate of 2–5%. CF carriers do not exhibit manifestations of CF illness, although carrier status has been proposed to increase the propensity for a wide variety of respiratory and non-respiratory disorders.[22]

GENETIC BASIS

CF is an autosomal recessive condition caused by mutations of *CFTR*, a gene located on the long arm of chromosome 7.[6,15,16] *CFTR* encodes a protein in the *adenosine triphosphate* (ATP) *binding cassette* (ABC) transporter family, sharing primary and secondary structural elements with many other proteins in this group. The approximately 190-kB *CFTR* encodes 27 exons and a full-length protein consisting of two *membrane-spanning domains* (MSDs), two *nucleotide binding domains* (NBDs), and a single *regulatory domain* (R domain). A schematic of CFTR is shown in Figure 67.1; the protein crystal structure has been solved using cryoelectron microscopy, opening the door for structural-based drug design.[23,24]

A very large number of *CFTR* mutations have been linked to clinical disease, including a current estimate of more

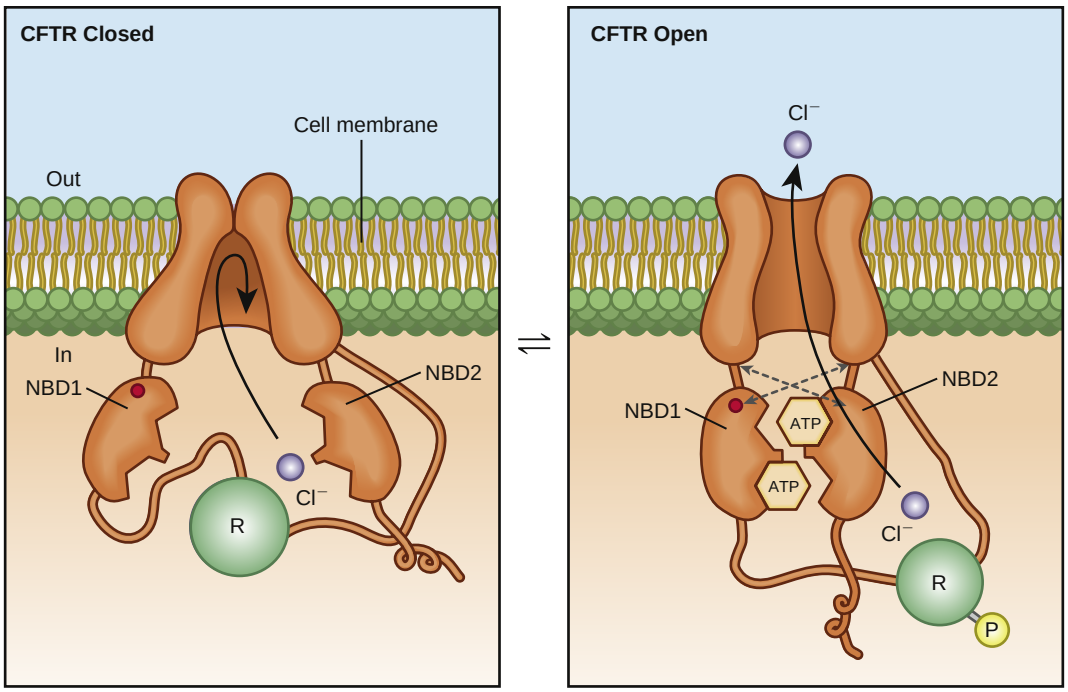

Figure 67.1 CFTR structure and domain assembly. Schematic representing the proposed structure of the *cystic fibrosis transmembrane conductance regulator* (CFTR) in its closed (*left*) and open (*right*) configurations. The two transmembrane spanning domains consist of six α-helices each and together form the channel pore. Gating of the channel is controlled by the two intracytoplasmic nucleotide binding domains (NBD1 and NBD2) as they bind and hydrolyze *adenosine triphosphate* (ATP) (*hexagons*) and a regulatory domain (R), which contains numerous sites of phosphorylation. Normal activation of the protein requires phosphorylation (P) of the regulatory domain. The NBDs bind and hydrolyze ATP, inducing channel gating by conferring opening of the pore through interfaces with the transmembrane domains via their extracellular loops (*dashed lines*), which also function to stabilize the overall protein structure. The location of the F508del mutation (*red dot*) is on the surface of NBD1, compromising its stability and interrupting interactions with the transmembrane domains.

than 1900 disease-associated variants, of which more than 350 are confirmed to cause disease.[19] That being said, a much smaller number of mutations account for the majority of disease in the CF patient population (eTable 67.1). For example, the most frequent 159 mutations account for 96% of defective CF alleles. As already stated, the most prevalent variant is F508del (c.1521_1523delCTT), which causes a three–base-pair nucleotide deletion and omission of phenylalanine at CFTR position 508. This mutation accounts for approximately 75% of CF-causing alleles, although distribution of the abnormality is heterogeneous among particular ethnic populations and as high as 86% in northern European white populations.[19]

F508del CFTR exhibits severe protein misfolding and leads to endoplasmic reticulum–associated retention and destruction of CFTR by the proteasome. The F508del defect represents a severe form of the prototypic class II variant (i.e., abnormalities resulting in premature degradation or incomplete maturation). Other less common CFTR variants fall into various mutation classes on the basis of molecular mechanism (Fig. 67.2). Additional classes include defects that confer incomplete CFTR synthesis due to premature termination codons (class I); disordered regulation and gating, causing diminished ATP binding and hydrolysis (class III), seen with the G551D mutation; defective chloride conductance (class IV); a reduced number of CFTR transcripts, such as due to a promoter or splicing abnormality (class V); and reduced protein stability at the cell surface, first reported as a defect in terminal CFTR variants that lack sequences anchoring the protein to the cell membrane (class VI). Ultimately, molecular classes reduce channel number, inhibit its function, or exhibit a combination of these effects, and the severity of these effects influences clinical outcome. Mutations in class I, II, and III tend to cause severe CFTR functional abnormalities, whereas class IV, V, and VI variants may exhibit residual function, reducing their severity (i.e., mild/variable activity) and CF phenotype. It is notable that many variants exhibit features of more than one molecular category; thus, the system is imperfect but a useful construct that has guided drug discovery efforts. For example, whereas the F508del mutation principally reduces channel number through its class II defect in processing and trafficking, it also exhibits abnormal gating (class III) and class VI (reduced channel stability) properties.[25] Understanding the molecular abnormality in each mutational class is important for addressing the defect with pharmacologic interventions such as CFTR modulators, discussed in Chapter 68.

Despite extensive knowledge concerning various mutations in *CFTR*, only approximately 90% of CF patients have both of their disease-causing alleles identified, although this number is increasing with more frequent use of full-length *CFTR* sequence analysis. Moreover, the pathogenic role of many mutations remains unknown, and knowledge in this area has dramatically improved through the CFTR2 project, which critically evaluates CFTR variants in the context of clinical phenotype on a global scale (www.CFTR2.org).[26] It has been estimated that more than 1000 *CFTR* variants are present, causing disease in fewer than five CF patients each.[18] Common nucleotide transversions, such as M470V, are designated as simple polymorphisms rather than disease-causing alleles, despite a potential (secondary) role of M470V impacting expression and/or function of F508del CFTR.[19] Other polymorphisms, such as the poly-T sequence located within intron 8, can modify CFTR expression, thus acting as important covariates of disease.[27]

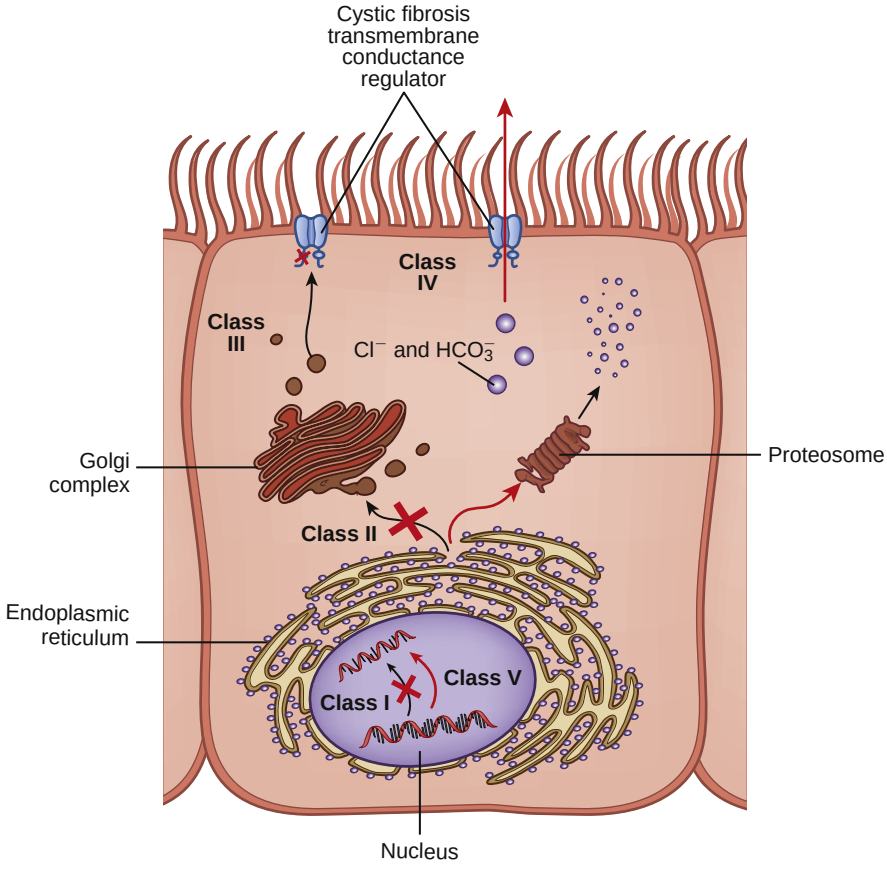

Figure 67.2 *Cystic fibrosis transmembrane conductance regulator* (*CFTR*) gene mutations and molecular consequences. Classes of defects in the CFTR gene product include the absence of synthesis (class I); defective protein maturation and premature degradation (class II); disordered regulation, such as diminished adenosine triphosphate binding and hydrolysis (class III); defective chloride conductance or channel gating (class IV); and a reduced number of CFTR transcripts due to a promoter or splicing abnormality (class V). Another class of defect has reduced protein stability at the cell surface (class VI, not shown).

eTable 67.1 Prevalence of the 25 Most Common CFTR Mutations in People With CF Seen in 2018

CFTR MUTATION				
Legacy Name	**cDNA Name**	**Protein Name**	**No. of Individuals**	**% of Individuals**
F508del	c.1521_1523delCTT	p.Phe508del	26,037	84.7
G542X	c.1624G>T	p.Gly542X	1404	4.6
G551D	c.1652G>A	p.Gly551Asp	1347	4.4
R117H	c.350G>A	p.Arg117His	924	3.0
N1303K	c.3909C>G	p.Asn1303Lys	716	2.3
W1282X	c.3846G>A	p.Trp1282X	691	2.2
3849+10kbC->T	c.3717+12191C>T		558	1.8
R553X	c.1657C>T	p.Arg553X	543	1.8
621+1G->T	c.489+1G>T		483	1.6
1717-1G->A	c.1585-1G>A		481	1.6
2789+5G->A	c.2657+5G>A		433	1.4
3120+1G->A	c.2988+1G>A		350	1.1
D1152H	c.3454G>C	p.Asp1152His	305	1.0
5T	c.1210–12[5]		280	0.9
I507del	c.1519_1521delATC	p.Ile507del	241	0.8
3272-26A->G	c.3140-26A>G		236	0.8
2184insA	c.2052_2053insA	p.Gln685ThrfsX4	231	0.8
R1162X	c.3484C>T	p.Arg1162X	229	0.7
1898+1G->A	c.1766+1G>A		213	0.7
3659delC	c.3528delC	p.Lys1177SerfsX15	208	0.7
G85E	c.254G>A	p.Gly85Glu	201	0.7
L206W	c.617T>G	p.Leu206Trp	188	0.6
R347P	c.1040G>C	p.Arg347Pro	183	0.6
A455E	c.1364C>A	p.Ala455Glu	172	0.6
R334W	c.1000C>T	p.Arg334Trp	172	0.6

The number and percentage of individuals with a given mutation include those with one or two copies of the mutation.
From the Cystic Fibrosis Foundation Patient Registry 2018 Annual Data Report. Bethesda, MD. Copyright 2019, Cystic Fibrosis Foundation.

The functional basis underlying specific *CFTR* mutations allows the correlation of genotype to phenotype, noting that other genetic modifiers and the environment also play prominent roles in disease expression. For example, when two severe (e.g., class I, II, or III) mutations are present, pancreatic insufficiency typically results, especially in patients homozygous for F508del. The finding of two severe mutations also confers risk for clinical manifestations, such as meconium ileus or hepatobiliary disease. On the other hand, presence of one or more mild/variable mutations may allow sufficient residual CFTR activity to diminish disease severity. CF patients with mild mutations often exhibit intermediate sweat chloride values, which correlate with pancreatic sufficiency.[19,28] When two mild/variable mutations are present, atypical forms of CF are more frequently observed, such as congenital absence of the vas deferens, "idiopathic" pancreatitis, or late-onset respiratory disease without other characteristic features of a complete CF phenotype.[27,29–31] Disease severity and expression can also be affected by non-*CFTR* genetic modifiers, which have been extensively studied. *Transforming growth factor* (TGF)-β has been shown to modify lung disease severity, specifically among subjects homozygous for F508del *CFTR*.[32,33] Other modifier loci on chromosome regions 4q35, 8p23, 11q25, and 19q13 confer increased risk of meconium ileus,[34,35] and various additional genes have been associated with acquisition of *Pseudomonas aeruginosa* infection.[36,37] Effect sizes for findings such as these have not been sufficient for routine use in the clinic, and a significant component of missing heritability may contribute to pulmonary decline in CF patients with two copies of F508del.

PATHOPHYSIOLOGY

CFTR AS AN ABC GENE

As described earlier, *CFTR* is a member of the ABC transporter or the traffic ATPase family of genes.[17,38,39] Proteins in this group are ancient and include hundreds of prokaryotic and eukaryotic polypeptides that transport nutrients, metabolites, toxins, and other small molecules across cellular membranes. All ABC proteins are characterized by two NBDs encoding canonical Walker A and B motifs (polypeptide sequences within the protein capable of binding and hydrolyzing ATP). CFTR gating, induced by ATP binding, hydrolysis, and release, confers conformational changes that allow pore opening and closing. Like other ABC proteins, CFTR encodes for two membrane-spanning domains with multiple α-helices that form highly selective passageways across lipid bilayers. Among ABC proteins, CFTR is atypical by virtue of a regulatory domain with numerous sites for *protein kinase A* (PKA)/cAMP-dependent phosphorylation, and a regulatory insertion in NBD1 shown to play an important role during channel gating[17,40,41] (see Fig. 67.1). Lasso helical structures near the CFTR amino-terminal region represent additional distinctive features of CFTR.[23,24]

STRUCTURE/ACTIVITY AND CFTR GATING MECHANISM

The CF gene product is composed of approximately 1500 amino acids and functions as a transporter of chloride ion (Cl^-) and bicarbonate ion (HCO_3^-) in numerous epithelial tissues. Site-directed mutagenesis indicates that gating is enabled by PKA/cAMP-dependent phosphorylation of the R domain. The phosphorylation step has been shown to elicit a conformational change in the regulatory insertion, leading to NBD1/NBD2 heterodimerization and structural realignments of MSD1 and MSD2, which permit opening of the ion conductive pore.[42] Key interactions between intracellular loops of the transmembrane domains and NBDs are integral to CFTR stability and interdomain assembly, as well as to transmission of forces required for channel gating (see Fig. 67.1).[43–45] NBD dimerization is greatly augmented when two ATP binding sites (at the NBD1/2 interface) are occupied; closing of CFTR is attributable to ATP hydrolysis.[46,47] It should be noted that ATP binding is not absolutely required for ion transport by CFTR; so-called ATP-independent channels can also open, for example, based on the tendency of NBDs to realign spontaneously in the open or outward-facing channel conformation.[47] Transepithelial anion flow through CFTR is governed by the electrochemical driving force, and a CFTR bioelectric signature (using membrane patch-clamp analysis or planar lipid bilayer reconstitution) describes PKA/cAMP or PKA-dependent currents through an approximately 8-picosiemen channel with linear current/voltage relationship and characteristic opening bursts. CFTR therefore uses ATP binding to enable passive ion transport, rather than subserving a function more typical of the ABC gene family (i.e., pumping of larger metabolites with stoichiometric dependence on ATP hydrolysis).

BIOGENESIS AND PROCESSING OF NATIVE CFTR

Wild-type CFTR matures and reaches the cell surface by conventional pathways that include cotranslational insertion in the *endoplasmic reticulum* (ER) membrane and post-translational modifications, such as *N*-linked glycosylation (Fig. 67.3). Subdomain folding (e.g., within NBDs) and achievement of final tertiary structure requires complex domain-binding interactions—and represents a topic of intense interest—because CFTR misfolding is a crucial mediator of clinical disease.[43,44,48–51] Wild-type CFTR processing may not be completely efficient and, in most experimental expression systems that express too much CFTR, a portion of wild-type CFTR becomes targeted for hydrolysis by *ER-associated degradation* (ERAD) and can stimulate ER stress. For CFTR advancing from the ER to the Golgi apparatus, complex glycosylation takes place at two asparagine residues. CFTR reaching the Golgi apparatus is transported to the cell surface by vesicular traffic with subsequent recycling through sorting and recycling endosomes and reinsertion in the plasma membrane or routing to the lysosome (or other cellular compartments). The cell surface apparatus governing CFTR peripheral stability (i.e., at the plasma membrane) has been well characterized and includes ubiquitin conjugation to regulate internalization.[52]

CELLULAR DEFECTS ATTRIBUTABLE TO F508del CFTR

The vast majority of F508del CFTR is retained in the ER, heavily ubiquitinated, and routed to the proteasome by ERAD.[53]

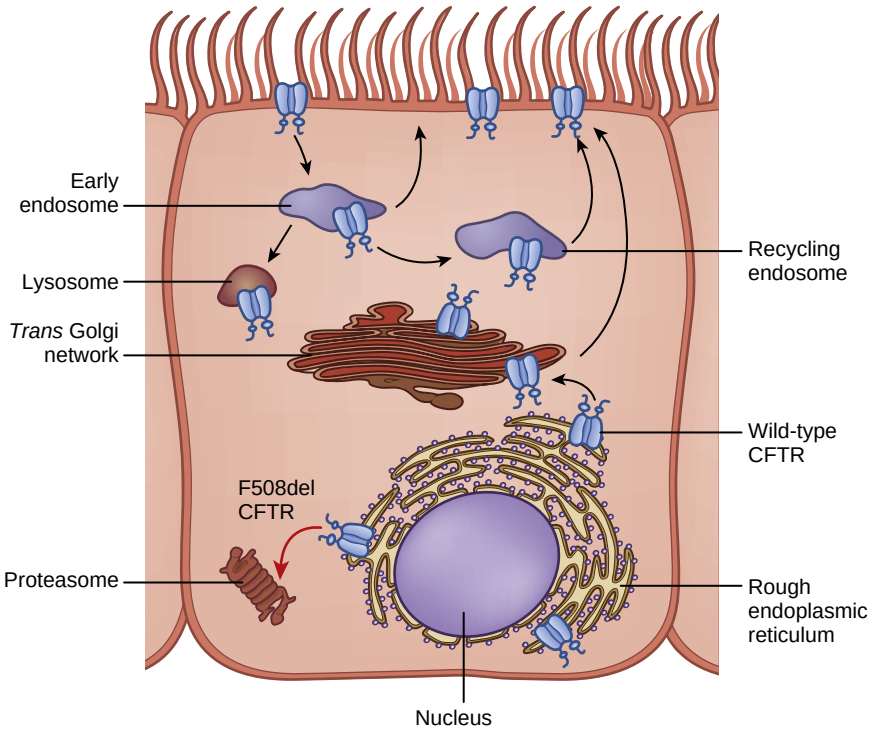

Figure 67.3 Scheme of *cystic fibrosis transmembrane conductance regulator* (CFTR) biogenesis. Biogenesis of CFTR in normal epithelial cell (*black arrows*) and F508del CF-affected epithelial cell (*red arrow*). In the normal epithelial cell, CFTR is synthesized in the rough endoplasmic reticulum, glycosylated and folded in the Golgi apparatus, and chaperoned to the cell surface. In the F508del-affected epithelial cells, the CFTR polypeptide is misfolded and tagged for premature degradation via endoplasmic reticulum–associated degradation (*red arrow*) before reaching the cell surface (class II mutation). (Modified from Ameen N, Silvis M, Bradbury NA. Endocytic trafficking of CFTR in health and disease. *J Cyst Fibros* 2007;6:1–14.)

As a consequence, F508del CFTR visualized by polyacrylamide gel electrophoresis is predominantly an ER-localized, approximately 150-kDa core glycosylated (band B) form. This is in contrast to a substantial portion of the post-ER wild-type protein, which migrates more slowly on polyacrylamide gel electrophoresis due to complex glycosylation (≈180-kDa band C). The F508del trafficking defect is temperature sensitive, and growth of epithelium at 27°C leads to measurable levels of F508del band C CFTR, with partial restoration of cell surface activity. Although likely not relevant in vivo, except perhaps at the nasal surface, this improvement in function at low temperature provided an early indication that pharmacologic intervention could diminish the cellular recognition machinery necessary for protein degradation.

Maturational processing abnormalities attributable to F508del arise from at least two distinct features.[43,44,54] Omission of F508, which is located on an externally exposed peptide loop of the first nucleotide binding domain, leads to pronounced loss of NBD1 stability as judged by thermal and isothermal calorimetry, protein aggregation, and protein yield measurements after recombinant overexpression.[43,44] In addition, F508 facilitates binding of NBD1 to a cytosolic loop from MSD2, and disruption of the NBD1/MSD2 interface (independent of NBD1 stability) leads to further impairment of F508del maturation. F508del CFTR molecules that do reach the cell surface, as shown through in vitro techniques, such as pharmacologic therapy or, alternatively, low temperature correction of cellular processing, display intrinsic channel gating abnormalities, diminished plasma membrane stability, and pronounced thermal unfolding with loss of function.[55,56] The observation of multiple distinct CFTR defects attributable to F508del presents a challenge to identifying single agents capable of restoring mutant CFTR to therapeutically relevant levels. Of note, intramolecular suppressor mutations that specifically ameliorate F508del NBD1 instability or the defective NBD1/MSD1 interface have been well characterized.[43,44] CFTR constructs encoding these suppressors provide a means to improve F508del corrective strategies and have enabled compound library screening tailored to specific CFTR folding defects (see also later).

OVERVIEW OF LUNG PATHOPHYSIOLOGY

An improved understanding of CF pathogenesis has led to better diagnostic strategies, understanding of features leading to the onset and progression of respiratory decline, and therapeutic approaches to target the underlying disease. An overview is provided in Figure 67.4 and described in further detail later. Absent or dysfunctional CFTR results in diminished protein activity, leading to deficient chloride and bicarbonate transport across airway epithelium. Several key aspects of CF pathophysiology include delayed mucociliary clearance resulting from depletion of the periciliary compartment of the *airway surface liquid* (ASL), defects involving the rheologic properties of CF mucus that contribute to mucus stasis and adhesion to the epithelial surface, predisposition to early infection because of abnormal mucosal defense, and pronounced and/or dysregulated inflammation. These processes initiate and perpetuate a cycle of destruction that ultimately results in irreversible lung injury, bronchiectasis, and respiratory failure.[17,57]

In the respiratory tract, CF manifests with infected mucus that compromises the airway lumen and contributes to obstructive pulmonary disease and reduced FEV_1 (Fig. 67.5). Respiratory damage is thought to begin in the small airways, resulting in airflow obstruction detected by spirometry midflows (i.e., $FEF_{25\%–75\%}$). Submucosal gland hyperplasia and inspissated mucus secretions emanating from the glands are also prominent in early CF

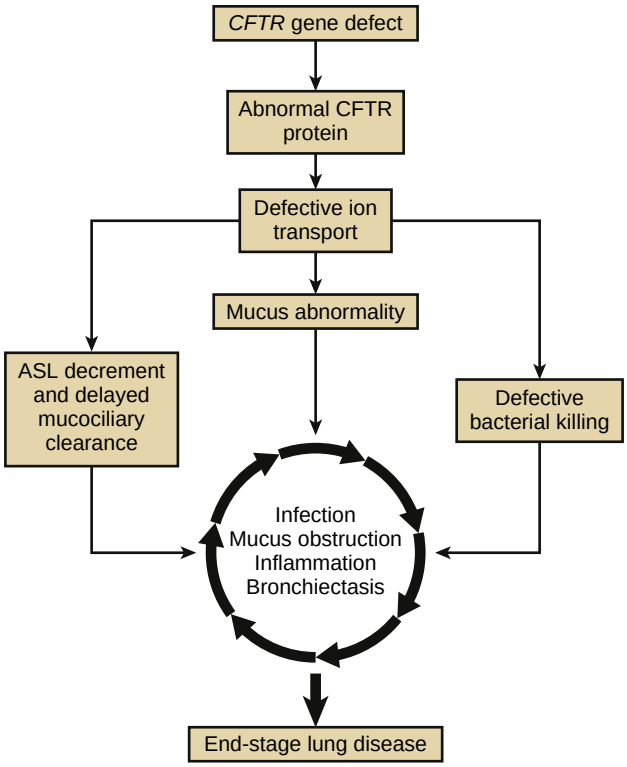

Figure 67.4 *Cystic fibrosis* (CF) pathophysiology. CF lung disease results from consequences of genetic mutations in the cystic fibrosis transmembrane conductance regulator gene (*CFTR*). Major operative pathways include reduced mucociliary clearance due to depleted airway surface liquid (ASL) hydration, abnormal mucus adhesion and viscosity, and defective bacterial killing, which each contribute to the cycle of destruction.

lungs. Radiographic changes consistent with small airway obstruction (e.g., tree-in-bud opacities) followed by bronchiectasis become apparent over time. Development of bronchiectasis leads to irreversible changes that predispose to worsening infection and accelerate disease pathogenesis.

CELLULAR FUNCTIONS OF THE *CFTR* GENE PRODUCT

The *CFTR* gene is hundreds of millions of years old on an evolutionary basis and used by diverse species, including fish, amphibians, fowl, and mammals.[58] Although best described as a chloride and bicarbonate transporter, the protein appears to regulate numerous cellular processes in addition to anion secretion (see also earlier). CFTR is situated within membrane complexes by virtue of its C-terminal anchoring sequence via a PDZ-type binding motif. CFTR is configured in close proximity to a number of integral membrane proteins, including other ion channels. By establishing electrochemical gradients, CFTR also exerts a regulatory influence on other apical ion transporters, including the *epithelial sodium channel* (ENaC), alternative chloride transporters, and bicarbonate/chloride exchangers.[59] Proteomic and transcriptome analyses demonstrate hundreds of cellular gene products that may directly bind or are impacted by CFTR.[60]

With the advent of single-cell sequencing came the surprising observation that CFTR is predominantly expressed in the airways in a minority cell type termed the *ionocyte*. The identification of the ionocyte as a major site of CFTR signaling has important implications for pathogenesis and gene therapy.[61,62] It is unknown whether the ionocyte regulates

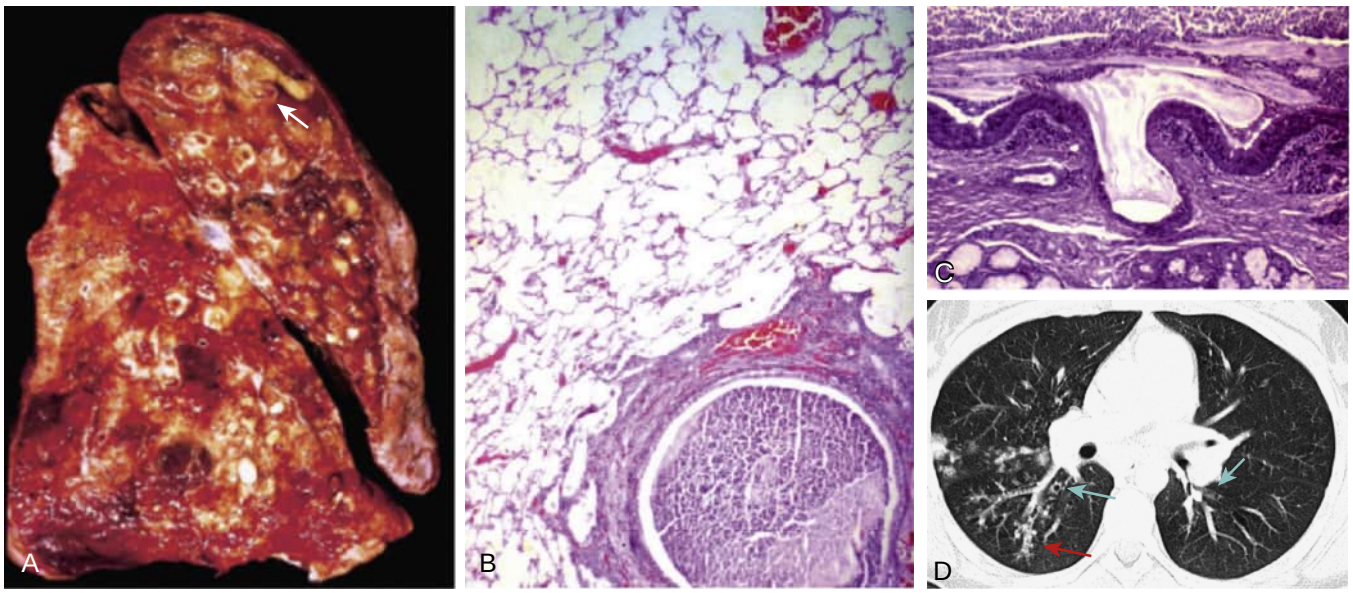

Figure 67.5 *Cystic fibrosis* (CF) pathologic and radiologic correlation. (A) Gross pathologic specimen of explanted CF lung from a patient with advanced CF. This specimen (sagittal section) shows heavy lungs characterized by ectatic bronchi (e.g., *arrow*) and numerous mucopurulent plugs. (B) Large airway pathology of CF. A large mucus plug filled with inflammatory infiltrate is seen, in addition to remodeling of the medium-size airway (hematoxylin-eosin stain). (C) Representative photomicrograph from a CF patient with end-stage lung disease is depicted. Note the thickening of the lamina propria (higher Reid index), the prominent arborized mucus plug extruding from the submucosal gland onto the airway lumen, and the hypertrophic surface epithelium (periodic acid–Schiff stain). (D) Axial high-resolution computed tomography image from a 16-year-old male patient with CF demonstrating mild to moderate multilobar bronchiectasis (*blue arrows*) and tree-in-bud opacities representing small airway mucus plugs (*red arrow*). (A–C, Courtesy Dr. David Kelly, University of Alabama, Birmingham.)

the ion transport environment of the epithelia by establishing electromotive forces or serves other unique functions yet to be discerned. This has notable implications for attempts to repair CFTR through gene therapy because it is not yet known if ionocyte repair will be a prerequisite for efficacy. In the lung, CFTR is also expressed in low numbers in surface epithelial cells and glandular epithelia, where it functions to regulate the formation and maturation of mucus.

REGULATION OF SWEAT CHLORIDE BY CFTR

The concentration of chloride in human sweat is determined by the balance of secretion and reabsorption of sodium and chloride in the sweat gland and duct. Chloride is secreted by two parallel pathways. One involves CFTR; the other uses a CFTR-independent, calcium-activated chloride channel. Because CFTR is not the only pathway by which chloride exits the apical membrane, chloride is secreted into sweat even in the absence of functional CFTR. Normally, sodium is reabsorbed along the sweat gland duct by ENaC in the apical membranes of ductular cells. Chloride follows sodium into the cell through CFTR. In CF, absent or defective CFTR significantly reduces chloride reabsorption, and the chloride content of sweat is therefore abnormally high, providing a convenient indicator of CFTR function. With differences in CFTR function either due to genetic variation or to drug therapy, sweat chloride is a dynamic and sensitive indicator of the modulation of CFTR activity.

REGULATION OF AIRWAY SURFACE LIQUID HOMEOSTASIS

The absence of apical CFTR leads to failure of chloride and bicarbonate secretion.[17,63] Because release of water into the periciliary region is driven in part by a CFTR-dependent osmotic gradient, CFTR deficiency leads to failure of mucus hydration, particularly when combined with excess mucus expression and secretion. Persistent airway fluid absorption through ENaC, which can be augmented by free nucleotides and other inflammatory stimuli, further exacerbates airway desiccation.[64–66] Hyperconcentrated mucus contributes to its elevated viscosity and correlates with disease severity across the spectrum of mucociliary diseases.[67] Osmotic forces induced by entangled mucus in the overlying mucus layer draw fluid from the periciliary layer, which normally provides the environment for appropriate ciliary function and mucus transport (Fig. 67.6). The harm caused by ASL dehydration is underscored by the therapeutic improvement among patients treated with hypertonic saline aerosols and dry powder mannitol to augment mucociliary clearance in CF lung disease by providing airway hydration, although their influence on the electrostatic environment of gel forming mucins has also been postulated.[67]

Through bicarbonate transport, CFTR serves to regulate airway pH. In people with CF and in CF pigs, the absence of the chloride bicarbonate exchanger ATP12a, present in mice, prevents compensation for airway pH abnormalities,[68] leading to an acidic airway surface. The acidic pH environment is postulated to have several effects, including a defect in bacterial killing through pH-sensitive defensins; this may be a crucial early event that initiates CF infections, particularly early in life when aspiration events are common and where fast-acting bacterial killing is highly relevant.[69] The absence of bicarbonate transport and the acidic pH environment also has consequences to the formation of mucus and its rheologic properties, as detailed later.

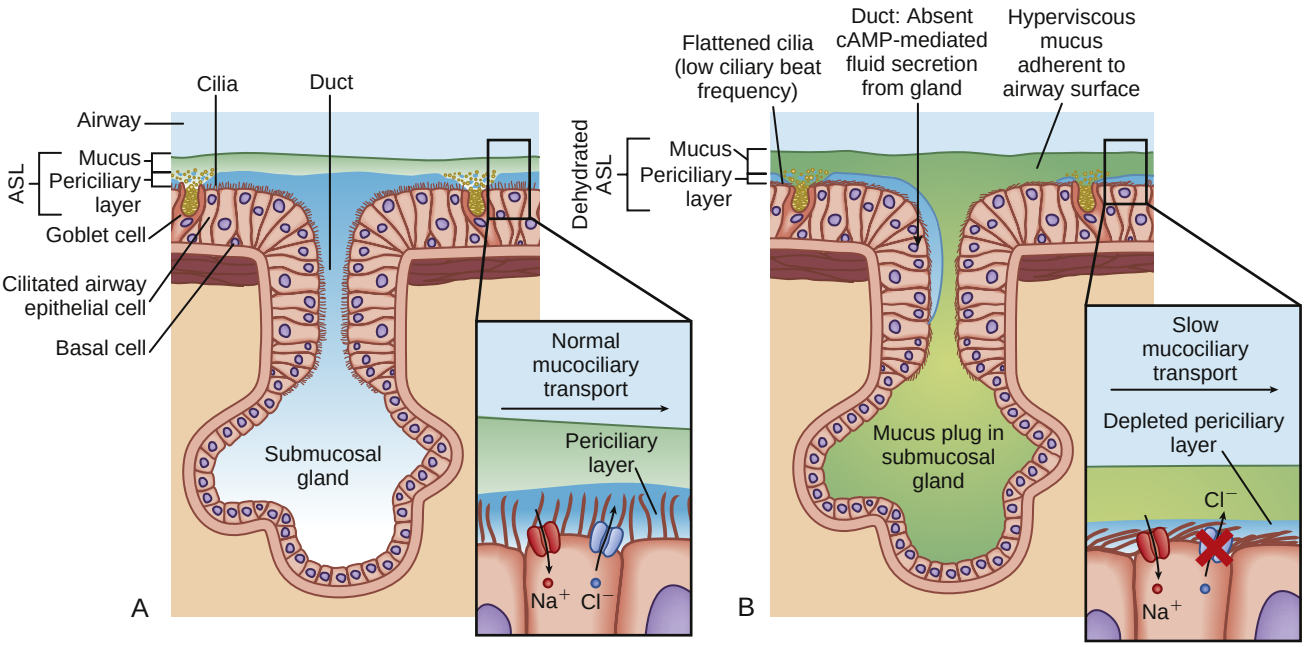

Figure 67.6 Schematic of the mucociliary transport defect in *cystic fibrosis* (CF). (A) In the healthy state, adequate airway surface homeostasis ensures effective transport of mucus extruding from airway surface goblet cells and the submucosal glands. The airway surface liquid (ASL) is maintained by fluid secretion via the cystic fibrosis transmembrane conductance regulator (CFTR) and fluid absorption via the epithelial sodium channel (ENaC) (*inset at right*) (CFTR, surface receptor in *blue*; ENaC, surface receptor in *red*). (B) In CF, the ASL is depleted through the absence of CFTR-mediated fluid secretion, accompanied by tonic fluid absorption via the ENaC. CFTR-dependent liquid dehydration decreases the depth of the ASL, including the periciliary layer, causing abnormal clearance of mucus from the epithelial cell surface in the airways. cAMP, cyclic monophosphate.

MUCUS BIOGENESIS, ADHESION, AND TRANSPORT

Hyperviscous respiratory secretions obstruct small- and medium-size airways in CF, leading to profound failure of mucociliary clearance that can be verified macroscopically by radioligand imaging[70] and direct visualization of the mucociliary transport apparatus in human nasal airways.[71] Quantitative analyses have indicated this is multifactorial, with airway dehydration and hyperviscous acidic mucus each contributing independently.[71,72] Even early in disease, before robust infection, insoluble mucus plaques (also called "flakes") can be observed in the bronchoalveolar lavage fluid of affected infants.[73] As mucus obstruction ensues, proinflammatory cytokines, such as interleukin-1β, are released, perpetuating mucus expression and exacerbating the consequences of CFTR deficiency.[73]

Specific mucins expressed in respiratory secretions include the gel-forming mucins MUC5B and MUC5AC, in addition to a complex array of extracellular proteins that participate in host defense.[74] Evidence for a primary biochemical defect in mucus composition includes the adhesion of large MUC5B strands in CF porcine airways or in those deficient in both bicarbonate and chloride transport[75] and the role of enzymatic release of mucus in the intestine.[76] Defective bicarbonate transport, in part through its effects on airway pH, contributes to mucus hyperviscosity through electrostatic forces.[77] Exocrine mucins (highly negative in charge) are produced intracellularly as compacted forms assisted by bound calcium, which shields the negative repulsive force between sulfates and other anionic groups on constituent mucins.[2] Under normal circumstances, bicarbonate secretion via CFTR, likely coordinated with mucus secretion, chelates the calcium and permits mucin expansion and a viscoelastic state compatible with physiologic clearance.[78] Failure of bicarbonate secretion results in defective mucin expansion, leading to hyperviscous secretion with abnormally adherent properties (i.e., mucus that is tightly bound to the respiratory surface and difficult to mobilize). Therapeutics in development to alter electrostatic interactions can ameliorate abnormal mucus rheology.[79] Excessive mucus adhesion that can be reversed by bicarbonate has been observed in the intestine of CF mice,[80,81] but this bicarbonate-mediated effect on mucus may not be sufficient to reverse airway mucus obstruction because CF mucus also becomes oxidized, a secondary phenomenon that also serves to increase its viscosity and may be less readily reversed. DNA strands released from dying bacteria, injured epithelial and inflammatory cells, and inflammatory secretions, such as *neutrophil extracellular trap* (NET)osis from polymorphonuclear leukocytes, represent important contributors to excess mucus viscosity and provide a rationale for the use of recombinant DNAse as an aerosolized mucolytic.

CYSTIC FIBROSIS EXOCRINE GLANDULAR EPITHELIUM

Submucosal glandular ducts filled with inspissated mucus are observed early in the course of CF pulmonary involvement. CFTR is highly expressed within epithelial cells of submucosal glands, where it functions to activate fluid and electrolyte secretion and promote release of mucus onto the airway surface.[3,82] The relative contributions of submucosal glands to overall CF respiratory pathophysiology are an area of considerable interest. Illustrating this notion, in CF rats, mucus stasis is only apparent with the development of glands as they age, even though both pH and airway dehydration are evident early in life, and is augmented by stimulation of mucus secretion.[83] Adhesive mucus at the outlet of gland ducts may further contribute to airway obstruction and provide a nidus for infection.

HOST DEFENSE AND INFECTION

CF lungs are characterized by intense neutrophilic inflammation with polymorphonuclear cells densely infiltrating airway secretions. Whether robust lung inflammation is mediated directly by CFTR, as opposed to a consequence of polymicrobial infection, is a topic of considerable debate. Sterile mucus obstruction plays an important role in experimental animals,[84] and interleukin-1β can serve as a positive feedback loop that furthers mucus stasis.[85] Neutrophil chemoattractants, such as interleukin-8, tumor necrosis factor-α, and a collagen fragment, proline-glycine-proline, are present at high levels in airway secretions, and abnormalities of CFTR-dependent macrophage function have also been implicated. Although anti-inflammatory therapies can improve lung function and slow the rate of CF respiratory decline, immune blockade also can predispose individuals to worsening lung infection, and the proper clinical balance has been difficult to achieve.[86]

Bacteria typically colonize the CF respiratory tract during infancy or early childhood. Longitudinal analysis of *P. aeruginosa* indicates sentinel infection due to a single genotype of the organism often persisting throughout the life of an individual patient.[87] The factors that lead to early colonization are not well understood. Studies have implicated acidic pH within the ASL, attributable to absent CFTR bicarbonate release, as a likely cause of the increased susceptibility to bacteria.[69] Findings such as these may, in some cases, be most relevant to early colonization events.[3]

Virulent respiratory pathogens such as *P. aeruginosa* evolve in a stereotypic fashion during the lifespan of individuals with CF and are characterized by rapid phenotypic change and hypermutability.[88] After several years of pulmonary infection, *P. aeruginosa* typically develops a mucoid phenotype in which considerable metabolic reserves are expended to synthesize and release the polyanionic protein, alginate. The appearance of mucoid *P. aeruginosa* in CF is a negative prognostic indicator. The selective advantage of alginate release has been attributed to the immunomodulating role of this exoproduct.[89,90] Studies have demonstrated the complexity of the CF microbiome, which can be altered during exacerbations by the presence of a dominant pathogen.[91] Further, co-culture studies provide evidence of synergistic interactions between bacteria that perpetuate and accelerate chronic infections.[92]

Animal Models of Cystic Fibrosis

Mouse models of CF have provided an important base of knowledge regarding the CF ion transport abnormality. A key strength of CF mice has been the ability to perform tissue-specific expression models, allowing the role of CFTR to be

explored in various tissues[93]; humanized versions of mice have also informed therapeutic evaluation. Nevertheless, CF mice have proved more limited in elucidating features of lung disease pathogenesis, unless hyperexpression of ENaC is implemented, which provides a model of airway dehydration but not other characteristic features of CF lung disease.[94] Filling the gap, porcine, ferret, and rat models of CF pulmonary disease have proved highly informative. Mice are likely protected from CF lung disease due to several features, including important differences in cell types that populate the airway, the absence of airway glands that serve as reservoirs for mucus production (see Chapter 1 for background differences between mouse and human lungs), and expression of the aforementioned ATP12a exchanger that protects mice from pH abnormalities, in addition to high expression of alternative chloride channels such as TMEM12a.[68,95] Rats, ferrets, and pigs each provide increasingly more faithful disease modeling of the airway defects and have been crucial to insights regarding lung disease pathogenesis, particularly regarding mechanisms of mucociliary clearance and CF defects in host defense. Each species exhibits elements of airway disease due to mucus obstruction and host defense abnormalities; ferrets and pigs exhibit spontaneous and progressive lung disease, whereas infection must be experimentally initiated in CF rats. These species provide informative models to assess pathophysiology, although cost, experimental complexity, and reagent availability serve as limitations that counterbalance how well they each replicate CF lung disease.

When combined with the evaluation of very young CF patients by newborn screening, animal models have provided particularly important means to clarify relationships existing among initial bacterial colonization, chronic infection, and inflammation in CF lungs. Longitudinal monitoring of CF respiratory infection in humans and transgenic animals will also facilitate a more sophisticated understanding of the complex CF microbiome and could provide new therapeutic opportunities in the future, particularly as robust models of chronic infection evolve. As gene therapy advances, animal models will also be essential to assess issues of gene delivery, tissue and cellular level expression, and correction of physiology.[96]

CFTR AND PULMONARY REMODELING

Measurements in the CF porcine model indicate a change in tracheal diameter and density of submucosal glands before the advent of hyperviscous mucus obstruction. Similar findings have been reported in human CF lungs and in CF rats (i.e., preceding the appearance of other pulmonary manifestations).[97] For tissues such as porcine and human pancreas, fibrotic damage and fatty replacement can be profound, with extensive parenchymal scarring.[98] Myofibroblast proliferation has been implicated as mediating some of these effects, and TGF-β signal transduction, which engenders myofibroblast transformation, is markedly increased throughout the CF lung.[99] TGF-β is also a well-established genetic modifier of F508del homozygous CF lung disease,[32,100] and these findings suggest that changes in TGF-β–dependent profibrotic pathways contribute to lung tissue remodeling, in addition to inflammatory responsiveness elicited by the cytokine.

Key Points

- *Cystic fibrosis* (CF) is the most common monogenic lethal disease in white populations and results from mutations in the *CF transmembrane conductance regulator* (*CFTR*) gene.
- *CFTR* genetic variants can be classified according to their molecular consequences to cell biology, which has implications for disease phenotype and for possible response to pharmacologic intervention.
- The most common *CFTR* mutation is F508del, one of more than 2000 variants, of which 350 have been confirmed to cause disease. Nearly 90% of CF individuals have one or more F508del alleles.
- CFTR is a tightly regulated anion channel of chloride and bicarbonate in the ABC transporter family. CFTR is expressed on epithelial cells and recently found on a novel cell, the ionocyte, and serves to regulate membrane potential and to influence the function of other channels.
- Absent CFTR causes delayed mucociliary clearance, abnormalities in mucus biogenesis and rheology, and host immunologic defects, which lead to chronic, progressive sinopulmonary infections and a cycle of lung destruction, bronchiectasis, and end-organ failure.
- Extrapulmonary manifestations are observed in numerous tissues that express CFTR, including the endocrine and exocrine pancreas, gastrointestinal tract, skin, bone, and male reproductive tract.

Key Readings

Boucher RC. Muco-obstructive lung diseases. *N Engl J Med*. 2019;380(20):1941–1953.

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68 CYSTIC FIBROSIS: DIAGNOSIS AND MANAGEMENT

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INTRODUCTION

Cystic fibrosis (CF) care has benefited from an increased understanding of CF pathobiology and from the partnership of academic and pharmaceutical research enterprises with a multinational team of care centers and the Cystic Fibrosis Foundation and other committed research entities. As a result, CF care constitutes a model for advancing treatment of chronic, life-threatening diseases through evidence-based quality improvement initiatives and comprehensive multidisciplinary care directed at multiple deleterious manifestations. It also provides a seminal example of the potential for translational medicine to deliver scientific discoveries that have transformed a universally fatal condition with targeted therapeutics addressing the underlying defect in the function of the *cystic fibrosis transmembrane conductance regulator* (CFTR). Future advances will capitalize on even more personalized therapies directed at the underlying cause of the condition and will address the potential for a genetic-based cure.

This chapter extends upon the concepts demonstrated by CF molecular pathobiology detailed in Chapter 67 to focus upon its diagnosis, prognosis, and natural history. CF therapeutics are also described, including the development of new therapies that target the basic defect.

DIAGNOSIS

OVERVIEW

The diagnosis of CF is predicated on clinical suspicion for the disease, as indicated by clinical manifestations or family history, or alternatively through newborn screening programs. Early detection through newborn screening is leading to recognition of illness before clinical findings become apparent. The first organized CF newborn screening programs were developed in the 1980s and implemented in Colorado (1987) and Australia and Europe (1980s)[1] after retrospective studies demonstrated improved clinical outcomes and decreased mortality as a result of early disease detection.[2] The number of such programs in the United States and abroad has grown in the past decade, and all states in the United States implemented newborn screening programs after a U.S. Centers for Disease Control and Prevention/Cystic Fibrosis Foundation Consensus Statement in 2004 recommended this practice.[3] The report invoked emerging prospective data that screening and early interventions in CF infants led to improved nutritional, gastrointestinal, respiratory, and cognitive functioning.[4–7]

In North America, newborns are screened using a heel prick blood test for immunoreactive trypsinogen, a byproduct of prenatal pancreatic inflammation. In most U.S. states, this test is paired with a DNA probe panel for common *CFTR* mutations. Immunoreactive trypsinogen is not a highly specific measurement due to elevated levels observed in prematurity, traumatic delivery, and other neonatal gastrointestinal disorders.[8] Because of declining immunoreactive trypsinogen levels in the first few months after birth in CF and non-CF infants,[9] this test is only useful for screening during the first few weeks postnatally. Family history or clinical suspicion based on clinical findings becomes the main impetus for diagnostic evaluation once the neonatal period has passed.

If the immunoreactive trypsinogen is elevated or in situations where CF is suspected for other reasons, a diagnosis should be confirmed by sweat chloride testing per the algorithm at a certified sweat testing lab once the newborn reaches an age where this testing may be performed accurately (usually after 10 days of age). Sweat chloride measurements are available in many clinical laboratories and have been standardized to ensure accuracy. Because of high sensitivity, sweat chloride testing has a central role in establishing the diagnosis in both the Cystic Fibrosis Foundation and European algorithms, once a positive newborn screen or compatible clinical characteristics are established.

Diagnostic Algorithms

The diagnosis of CF is based on a positive newborn screening test in newborns or CF clinical characteristics (Table 68.1). In 2017, the Cystic Fibrosis Foundation published comprehensive diagnostic guidelines for infants and adults with suspected CF[10] (Fig. 68.1) that emphasized a similar algorithmic approach for newborns, children, and adults. Similar European guidelines primarily differed only in the timing of *CFTR* mutation analysis and sweat chloride normative values.[11] There is good concordance when comparing the U.S. and European framework in terms of diagnostic accuracy.[12]

Table 68.1 Diagnostic Criteria for CF by Clinical Phenotypic and CFTR Functional Abnormalities

DIAGNOSIS OF CF CONFIRMED BY THE PRESENCE OF APPROPRIATE PHENOTYPIC CLINICAL FEATURES (ANY OF):
Chronic sinopulmonary disease ■ Chronic cough and sputum production ■ Persistent infection with characteristic pathogens (*Staphylococcus aureus, Pseudomonas aeruginosa,* other gram-negative organisms) ■ Airflow obstruction ■ Chronic chest radiographic abnormalities ■ Sinus disease; nasal polyposis
Gastrointestinal and nutritional abnormalities ■ Exocrine pancreatic insufficiency ■ Recurrent pancreatitis ■ Fat-soluble vitamin deficiency ■ Meconium ileus; DIOS
Obstructive azoospermia in males
***PLUS* LABORATORY EVIDENCE OF CFTR ABNORMALITY (ONE OR MORE OF FOLLOWING):**
Elevated sweat chloride
Disease-causing mutation in *CFTR* gene in both alleles
Characteristic bioelectric abnormalities (potential difference) in nasal epithelium
Abnormal ex vivo intestinal short-circuit current measurement

CF, cystic fibrosis; CFTR, cystic fibrosis transmembrane conductance regulator; DIOS, distal intestinal obstruction syndrome.

In the new approach, a low sweat chloride concentration (≤29 mmol/L) effectively rules out CF, whereas a high sweat chloride concentration (≥60 mmol/L) definitively establishes the diagnosis. In the case of clinical suspicion with an intermediate sweat chloride concentration (30 to 59 mmol/L), guidelines recommend performing *CFTR* sequencing or high-sensitivity DNA probe testing to establish the presence of *CFTR* mutations, usually coordinated through specialized commercial laboratories or via coordination and referral to a CF center for evaluation. Genetic confirmation by commercial *CFTR* sequencing in certified laboratories is recommended to confirm the diagnosis and to guide mutation-specific treatments, independent of the diagnostic yield of sweat chloride testing. Worldwide catalogs of CF phenotypic information by genotype are housed in the CFTR-2 repository (www.cftr2.org) and can help provide guidance about expected severity based on sequence information.

If two *CFTR* mutations are found, the diagnosis of CF is established. If one or zero mutations are present, then repeat sweat chloride testing is recommended. It should be noted that standard genetic panels (i.e., panels that test fewer than 40 mutations) are not sufficient in patients with elevated sweat chloride and atypical manifestations, because rare, partial function mutations are common in these cases and may not be detected by limited panels;

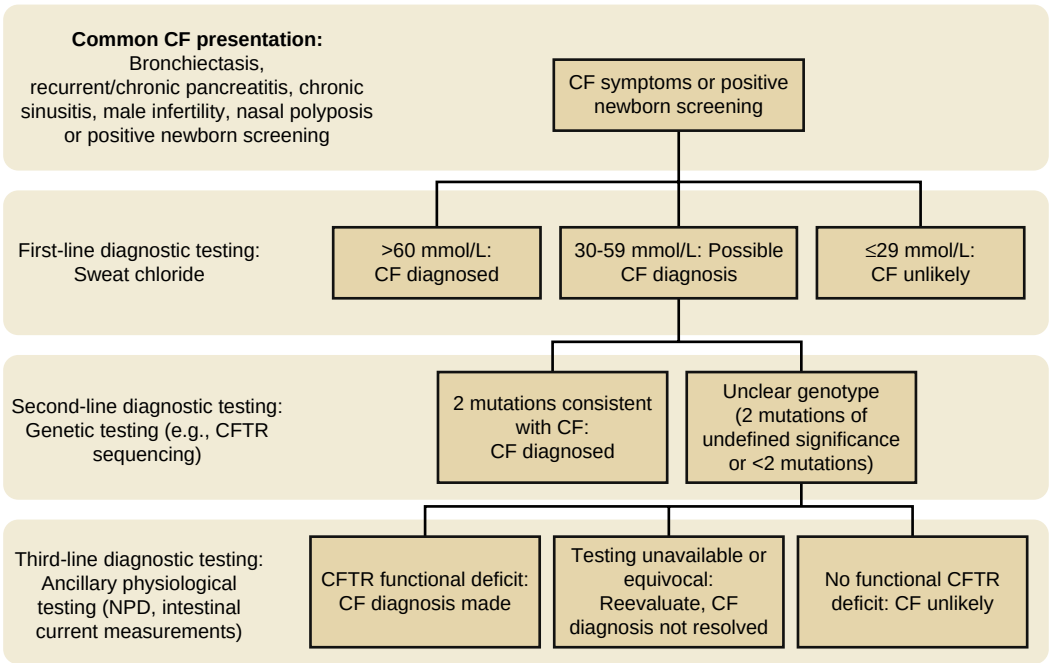


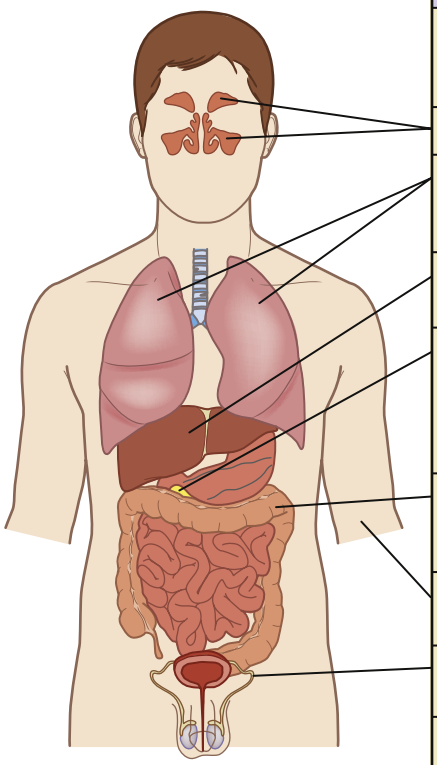
Figure 68.1 Diagnostic algorithm for *cystic fibrosis* (CF). Schematic depiction of algorithm for the diagnosis of CF in newborns through adults emphasizing sweat chloride as the cornerstone for diagnosis. Genetic testing for intermediate probability cases should trigger *cystic fibrosis transmembrane conductance regulator* (CFTR) sequencing because analysis for only a limited number of mutations can result in false-negative evaluations in this disease category. NPD, nasal potential difference. (Modified from Farrell PM, White TB, Ren CL, et al. Diagnosis of cystic fibrosis: Consensus guidelines from the Cystic Fibrosis Foundation. *J Pediatr.* 2017;181S:S4-S15.e1.)

they are also biased towards mutations prevalent in those of Caucasian descent. Some patients exhibit CF-like disease even in the absence of *CFTR* mutations, a finding that might be caused by changes in genes encoding other proteins that can mimic mutations in *CFTR* (i.e., mutations in the epithelial sodium channel) or in other noncoding regions of the *CFTR* gene itself.[13]

If clinical suspicion remains and sweat chloride is in the intermediate range, there are several alternatives to confirm CFTR functional deficits. *Nasal potential difference* (NPD) testing, available at many CF research centers, can be an acceptable alternative in cases of inconclusive sweat chloride or inadequate genetic analysis. Alternatively, intestinal current measurements to estimate CFTR activity require a biopsy of rectal mucosa but the test is only available at a few centers worldwide.[14,15] Other measures of pancreatic function, such as fecal elastase, may also help support a diagnosis in this setting.

It is increasingly recognized that CFTR-related disorders represent a spectrum of disease, with pancreatic-insufficient CF as the most severe form and borderline CF-like syndromes representing the other extreme (Fig. 68.2). It is notable that functional assessments of CFTR reflect this diversity, although the relationship between genotype and CFTR functional decrements can vary on an individual level and on the tissues affected. Functional CFTR assays can help distinguish between mild and severe phenotypes by measuring the decrement in CFTR function along this continuum and can be informative beyond genotype information alone.[16] These tests are done at specialized centers throughout North America and usually are coordinated through CF referral centers. Cell-based assays are increasingly used to help resolve the functional implications of cryptic or ultra-rare mutations.

With widespread acceptance of newborn screening programs in the United States, it is now typical to diagnose CF before the onset of respiratory disease. A high index of suspicion must be maintained to ensure correct diagnosis in the event of screening failure or among individuals born before the initiation of newborn screening programs. Screening programs have led to the detection of CFTR-related dysfunction, as demonstrated by indeterminate range sweat chloride values in subjects without phenotypic CF. These individuals should be designated as having CFTR-related metabolic syndrome or, synonymously, a CF screen–positive inconclusive diagnosis. Current recommendations are that these individuals be followed annually by experienced CF providers because many have been reported to develop phenotypic CF later in life.[17] A significant number of CF patients may therefore present in adulthood because symptoms are unusual, subtle, or even absent early in life,



Organ System	CF-Pancreatic Insufficient	CF-Pancreatic Sufficient	CFTR-Related Disorder*
Typical genotype	Two severe mutations	At least one mild/variable mutation	Two mild mutations or heterozygous
Sinus	Chronic sinusitis	Chronic sinusitis	Chronic sinusitis
Airways	Severe chronic bacterial infection	Chronic bacterial infection, later onset, variable	Chronic bacterial infection, mild, later onset, variable
Liver	Severe hepatobiliary disease (5-10%)	Usually absent	Absent
Pancreas	Exocrine insufficiency	Adequate exocrine function until late in life, pancreatitis (pancreatitis in minority)	Adequate exocrine function, pancreatitis (can be presenting symptom)
Bowel	Risk of meconium ileus, DIOS	Nonspecific bowel complaints, low risk of DIOS	Nonspecific bowel complaints
Sweat chloride	90-110 mmol/L	60-90 mmol/L	40-60 mmol/L
Vas deferens	Obstructive azoospermia	Obstructive azoospermia	Normal, CUAVD, or CBAVD
Endocrine Pancreas	High risk of CF-related diabetes mellitus	Low risk of CF-related diabetes mellitus	Minimal risk of CF-related diabetes mellitus

Figure 68.2 Spectrum of cystic fibrosis disorders. A comparison between findings in severe *cystic fibrosis* (CF) and milder forms of the disease is shown. Although manifestations are variable, severity in each organ system is generally consistent with degree of *cystic fibrosis transmembrane conductance regulator* (CFTR) dysfunction conferred by genotype. CBAVD, congenital bilateral absence of the vas deferens; CUAVD, congenital unilateral absence of the vas deferens; DIOS, distal intestinal obstruction syndrome. *Refers to CFTR-related metabolic syndrome or CFTR-related disorders.

resulting in a delayed presentation. Oftentimes these CFTR-related metabolic syndrome–associated presentations are due to partially active *CFTR* alleles or other ameliorating mutations or factors resulting in milder CFTR functional defects (e.g., sweat chloride in the 30 to 59 mmol/L range or NPD in the intermediate severity range).[18] Recognition of the variable manifestations of CF is required to detect CF after early childhood.

Finally, the diagnosis of CFTR-related syndrome is usually made in older children and adults presenting with single-organ CF involvement (e.g., isolated bronchiectasis, sinusitis, pancreatitis, or congenital absence of the vas deferens) with inconclusive CFTR functional testing and genotype. The complexity of inconclusive diagnostic scenarios is outlined in eTable 68.1.

CLINICAL MANIFESTATIONS

CF has historically presented with protean manifestations and symptoms that may mimic or resemble other diseases. Usual presentations include early onset of respiratory tract findings, particularly persistent cough and recurrent or refractory chest radiographic changes. Gastrointestinal presentations are also prominent and include meconium ileus (in approximately 15% of patients) and failure to thrive with steatorrhea due to pancreatic insufficiency. A list of unusual presentations is compiled in Table 68.2. Clinical severity can vary widely; less severe disease states can be initially misdiagnosed as other more common respiratory conditions.

LOWER RESPIRATORY TRACT DISEASE

Progressive obstructive lung disease leading to bronchiectasis and respiratory failure accounts for the vast majority of mortality among individuals with the disease. Even seemingly healthy infants with CF often have significant subclinical lung findings, including inflammation often disproportionate to the degree of infection.[19,20] The most common manifestation of lung disease is cough in association with bronchitis. Early in life, symptoms are often intermittent and exacerbated by episodes of acute respiratory tract infection that tend to exhibit a protracted course. With time, cough becomes a daily event. It is often more pronounced at night and on rising in the morning. With progression or during exacerbations of lung disease, cough typically becomes productive with tenacious, mucopurulent sputum secondary to chronic bacterial infection and neutrophilic inflammation, especially after the onset of chronic infection.

Hyperinflation of the lungs is common and often observed early in the progression of CF lung disease.[21] Asthmatic or bronchiolitic-type wheezing is often observed during the first 2 years of life but may be encountered at any age. Wheezing is noted in up to one-third of infants and may be present with or without evidence of atopy.[22] Early in life, CF can mimic the clinical manifestations of asthma and/or coexist with asthma, leading to delayed recognition if newborn screening is not definitive for a diagnosis.

Lung sounds are typically unremarkable at presentation; the first detectable abnormalities may be subtle retractions, diminished intensity of breath sounds, or prolongation of the expiratory phase. Once CF lung disease becomes clinically apparent, adventitious lung sounds are usually first noted in the upper lobes. CF patients may have only mild bronchitic findings for long periods during the time lung homeostasis is maintained but still manifest exacerbation of symptoms such as increased cough intensity and sputum production. Respiratory exacerbations often present as tachypnea, shortness of breath, malaise, anorexia, and weight loss. Viral respiratory tract infection is a frequent trigger, as are other infectious agents, cigarette smoke,[23] pollutants,[24] allergens, and respiratory irritants that have been implicated as disturbing lower airway physiology. Initiation of broad-spectrum antibiotic therapy and aggressive maneuvers to facilitate clearance of mucus are usually required to improve symptoms and restore lung function. Pulmonary exacerbations are now recognized as a major driver of overall disease progression, and aggressive attempts to recognize and treat these events before the advent of irreversible injury have become a priority.[25] As CF lung disease progresses, exacerbations characteristically become more frequent and severe, often requiring extended courses of intravenous antibiotics and hospitalization. End-stage lung damage associated with impairment of daily activities heralds a sequence of terminal events in the absence of lung transplantation, including hypoxemia, pulmonary hypertension, right ventricular dysfunction, hypercapnic respiratory failure, and death.

Table 68.2 Atypical Presentations of Cystic Fibrosis*

Respiratory	■ Bronchiolitis/asthma ■ ***Pseudomonas aeruginosa* or *Staphylococcus aureus* colonization of the respiratory tract** ■ Staphylococcal pneumonia ■ **Nasal polyposis** ■ **Nontuberculous mycobacterial infection**
Gastrointestinal	■ Meconium plug syndrome ■ Rectal prolapse ■ **Recurrent abdominal pain and/or right lower quadrant mass** ■ Hypoproteinemic edema ■ Prolonged neonatal jaundice ■ **Biliary cirrhosis with portal hypertension** ■ Vitamin deficiency states (A, D, E, K) ■ *Acrodermatitis enteropathica*–like eruption with fatty acid and zinc deficiency ■ **Recurrent pancreatitis**
Genitourinary	■ **Male infertility** ■ **Female infertility**
Other	■ Hypochloremic, hyponatremic alkalosis ■ **Mother of a child with cystic fibrosis**

*__Bold__ type signifies possible presentation in adolescents or adults with cystic fibrosis.

MICROBIOLOGY

Patients with CF demonstrate bacterial colonization of the airways early in life. Chronic infection of the lower airways, once established, is difficult to eradicate. *Staphylococcus aureus* and *Haemophilus influenzae* are usually the first organisms detected in CF lungs (Fig. 68.3) and often present

eTable 68.1 Summary of Inconclusive Cystic Fibrosis Diagnosis Scenarios

	NBS Status	Sweat Chloride Range (mmol/L)	Ancillary CFTR Testing	Genotype Results
CRMS/CFSPID Scenario 1	+	<30	Inconclusive/NA	<2 mutations with known clinical significance
CRMS/CFSPID Scenario 2	+	30–59	Inconclusive/NA	0-1 mutations of clinical significance
CFTR-related syndrome Scenario 1	No NBS	<30	Inconclusive/NA	<2 mutations with known clinical significance
CFTR-related syndrome Scenario 2	No NBS	30–59	Inconclusive/NA	0-1 mutations of clinical significance

CFSPID, cystic fibrosis screen positive, inconclusive diagnosis; CFTR, cystic fibrosis transmembrane conductance regulator; CRMS, CFTR-related metabolic syndrome (CFSPID and CRMS are equivalent terms); NA, not available; NBS, newborn screening.

Data from the CFTR 2 Database, https://cftr2.org; and Farrell PM, White TB, Ren CL, et al. Diagnosis of cystic fibrosis: consensus guidelines from the Cystic Fibrosis Foundation. *J Pediatr*. 2017;181S:S4-S15.e1. Erratum *J Pediatr*. 2017;184:243.

with a comparatively benign clinical picture.[26] Historically, acquisition of *Pseudomonas aeruginosa* or *Burkholderia cepacia* was regarded as a particularly ominous clinical finding because these infections are associated with accelerated decline in lung function and increased mortality.[27] With the increased prevalence of microbiologic screening and more aggressive antimicrobial treatment regimens, a more broad and diversified group of respiratory pathogens has emerged.[28] These pathogens include *methicillin-resistant S. aureus* (MRSA), multidrug-resistant gram-negative rod bacteria, nontuberculous mycobacteria, and fungal organisms.[29] When present, these new opportunistic infections may be associated[30] with declining lung function. Often the clinical significance and complex factors contributing to the presence of these organisms in sputum culture are multifactorial and thus require careful clinical consideration to determine the appropriate timing and intensity of treatment. This is particularly true because certain organisms, such as nontuberculous mycobacterial and fungal organisms, may represent benign colonizers of CF lower airways.

The prevalence of *P. aeruginosa* increases with age, infecting more than two-thirds of patients by the third decade of life. The frequency of detection earlier in life has increased in the era of newborn screening and may be as high as 20% in children younger than 2 years; detection in infants at the time of diagnosis is common. Acquisition of *P. aeruginosa* increases longitudinally (see Fig. 68.3) and may be associated with genotype severity—individuals homozygous for F508del demonstrate a higher prevalence of chronic infection.[31] The effect of CFTR modulators on the eradication of bacteria appears promising at the population level based on the effect of ivacaftor in patients with gating mutations but continues to emerge for more common CFTR mutations[32,33] and for microbiome analyses.[34,35]

Nosocomial acquisition of new infections and transmission of multidrug-resistant organisms is a substantial concern in CF care.[36] Because eradication of sentinel infection has become an increasing priority, identification and earlier treatment of initial infection (e.g., due to *P. aeruginosa*) based on frequent sputum monitoring is recommended for those not previously colonized.[37–39] Sputum bacteriology correlates reasonably well with specimens obtained directly from the lower respiratory tract, although microbial sequencing is lending new insights into the validity of this conclusion. Oropharyngeal swab cultures that yield *S. aureus* or *P. aeruginosa* are modestly predictive of results from bronchoscopic specimens, but negative pharyngeal cultures do not rule out growth of these organisms in lower airways.[40] Nevertheless, recent studies supporting sputum or oropharyngeal swab culture surveillance and subsequent treatment with intent to eradicate infection have demonstrated similar efficacy to more invasive detection regimens.[41] Other, more sensitive means to detect *P. aeruginosa,* such as polymerase chain reaction or circulating markers, may further improve sensitivity of noninvasive techniques. Quantitative bacteriology may be particularly useful for determining the relative contributions of isolated organisms in this setting.

As lung disease progresses, *P. aeruginosa* often becomes the predominant organism recovered from sputum and may be present in multiple strains with distinct antibiotic sensitivity patterns. The emergence of a mucoid phenotype due to elaboration of large amounts of *alginate*, an exopolysaccharide that protects the bacteria from adversity in its surroundings and also enhances adhesion to solid surfaces, is associated with worsened clinical outcome.[42] Mucoid organisms are found as microcolonies of pseudomonads embedded and growing in biofilms of alginate.[43] Biofilms inhibit phagocytosis and enhance bacterial adherence while limiting exposure to antibiotics and reactive intermediates produced by leukocytes.[44–47] Although the presence of a mucoid phenotype is clearly associated with colonization, new mucoid *Pseudomonas* infection or conversion to a mucoid phenotype may also be amenable to aggressive eradication strategies.[48,49] Isolation of *P. aeruginosa* from the lower respiratory tract of a child or young adult with chronic lung symptoms is highly suggestive of CF but has been reported in patients with primary ciliary dyskinesia, bronchiectasis, or other severe obstructive lung diseases.[50]

Although *P. aeruginosa* has remained the dominant pathogen in adult CF lung disease, MRSA has emerged as a significant contributor to disease progression and mortality.[51] In contrast, methicillin-susceptible strains are associated with improved outcomes.[52] Two studies using the U.S. CF registry have demonstrated an association between MRSA and worsened lung function, and another has shown MRSA infection to be an independent risk factor for mortality.[53,54] Considerable interest has emerged in the epidemiology and biologic significance of the staphylococcal chromosomal

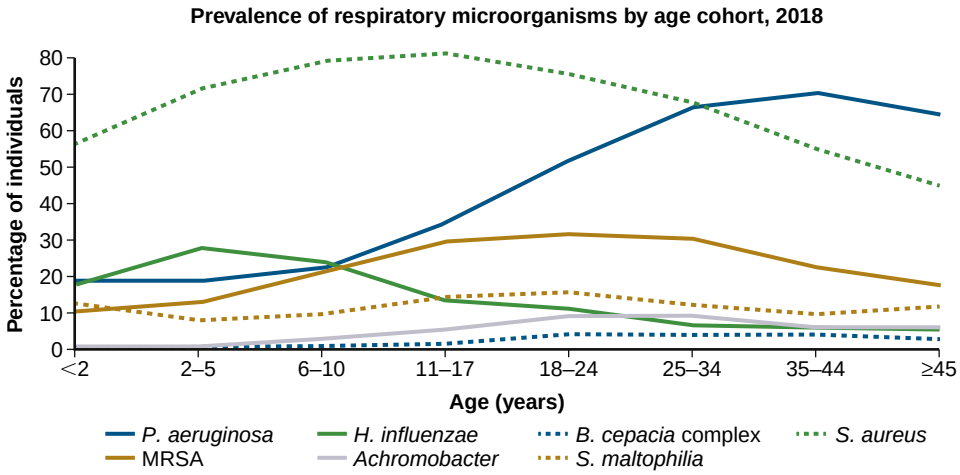


Figure 68.3 Alterations in sputum microbiology with age. Chronic infection with *Pseudomonas aeruginosa* and *methicillin-resistant Staphylococcus aureus* (MRSA) changes as a function of advancing age, based on data from cystic fibrosis care centers in the National CF Patient Registry. This is in contrast to a higher prevalence of *Haemophilus influenzae* and methicillin-sensitive *S. aureus* in childhood and adolescence among patients with cystic fibrosis. (Data from the Cystic Fibrosis Foundation, Patient Registry; Bethesda, MD; 2018.)

cassette containing the methicillin resistance gene and the Panton-Valentine leukocidin expressing strains, both of which have an effect on their virulence and impact disease severity.[29] Although the clinical significance of MRSA infection and colonization must be recognized, evidence is not sufficient to support aggressive eradication strategies in individuals with MRSA who are clinically stable.[55] Small-colony staphylococcus variants may also represent a distinct entity highly resistant to traditional therapy.[56] In addition, there is increasing recognition that MRSA exhibits biofilm-forming behavior in chronic infection.[57]

Numerous gram-negative pathogens in addition to *P. aeruginosa* have demonstrated a significant clinical impact on respiratory health, lending support to the notion that CF lung infection represents a significantly more complex microbiome than previously realized.[58] Of these, *B. cepacia* has remained the most ominous, due to its inherent multidrug antibiotic resistance and association with rapid decline in CF pulmonary reserve.[59] Infection from *B. cepacia* can spread from patient to patient, requiring stringent infection control measures within CF care settings.[60,61] Infection has been linked to the rapid clinical deterioration and death of a small percentage of patients with what has been referred to as *cepacia* syndrome.[62] Molecular analyses have shown that *B. cepacia* complex is composed of at least nine phenotypically indistinguishable but genetically distinct species (genomovars).[38,63,64] Genomovars II (*Burkholderia multivorans*) and III (*Burkholderia cenocepacia*) have been associated with *cepacia* syndrome, and genomovar III includes a highly transmissible strain that may be linked to expression of the cable pilus, which enhances infectivity and virulence.[64–66] Other gram-negative rods present in CF sputum include mucoid *Escherichia coli, Stenotrophomonas maltophilia, Achromobacter xylosoxidans, Klebsiella,* and *Proteus*. Of these, *S. maltophilia* and *A. xylosoxidans* appear to have the strongest association with poor respiratory outcomes, but their clinical significance warrants further evaluation. Additional gram-negative organisms such as *Pandoraea* and *Ralstonia* sp have been isolated from CF sputum samples, but further clinical investigation will be necessary to determine their pathogenic significance. Obligate anaerobes have also been identified from CF lung tissue. These are typically undetected by standard clinical laboratory microbiologic analyses and may be found in large abscess cavities on rare occasions.[67,68]

Infection with *nontuberculous mycobacteria* (NTM) is increasingly observed in the CF population, presumably due to concomitant antibacterial therapy resulting in a favorable ecologic niche, host susceptibility, improved detection, and environmental prevalence.[69–74] Up to 20% of adult patients in some clinics are colonized by NTM, and its incidence has been increasing in recent years. Although culture positivity is sometimes transient, the deleterious clinical impact of these organisms once established is increasingly appreciated.[75] *Mycobacterium avium* complex infection is of variable clinical significance, whereas rapidly growing organisms such as *Mycobacterium abscessus* can exhibit a virulent course, prompting aggressive and prolonged treatment regimens.[72] In contrast, *Mycobacterium tuberculosis* infection has only been seen in sporadic cases. Studies to standardize treatment for these emerging pathogens in CF are underway.[76] (See also Chapter 55 for a detailed discussion of NTM infections in CF patients.)

Nearly 40% of individuals with CF will grow *Aspergillus fumigatus* in the sputum during their lifetime; patients who have severe lung disease appear to have an even higher incidence of sputum positivity.[77] The pathogenic nature of *Aspergillus* in an otherwise immunocompetent CF host is not well established, although it may contribute to the burden of excess mucus production. However, *Aspergillus* is clearly associated with *allergic bronchopulmonary aspergillosis* (ABPA). ABPA is present in approximately 2% of CF patients and adds a considerable burden of care.[78,79] ABPA is described later and in Chapters 69 and 96.

IMAGING

The earliest radiographic finding in CF lung disease is typically hyperinflation of the lungs, reflecting obstruction of small airways. Central airway thickening and linear opacities produce a "tram track" appearance representing bronchiectasis (eFig. 68.1) and often progress with age (Fig. 68.4, eFig. 68.2). Frequently, these findings are most

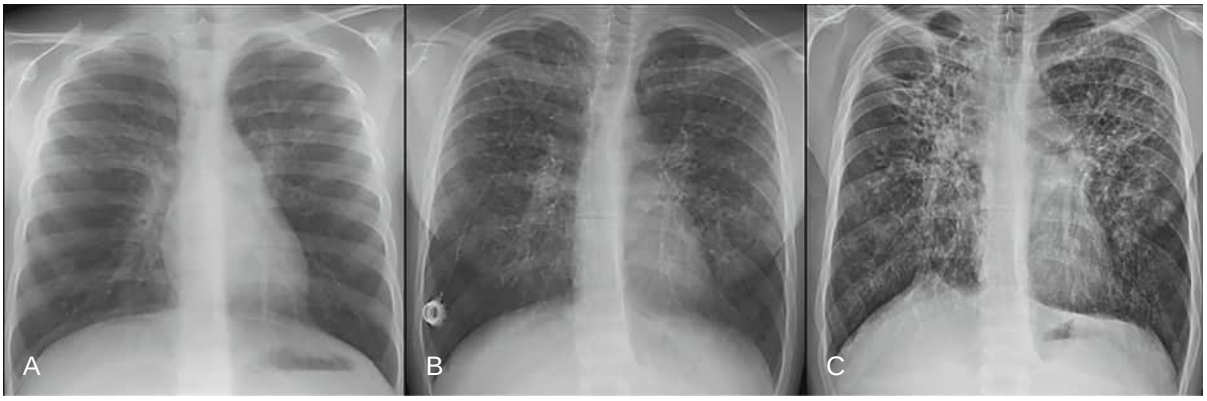


Figure 68.4 Cystic fibrosis: chest radiographic findings over 2 decades. (A) Frontal chest radiograph in a 9-year-old boy shows mid and upper lung predominant bronchovascular thickening, consistent with the bronchial wall thickening and bronchiectasis typical of cystic fibrosis. (B) Frontal chest radiograph performed in the same patient at age 19 years shows progression in the upper lobe predominant vascular thickening, now with a slightly more cystic appearance in the right upper lobe. (C) Frontal chest radiograph performed in the same patient at age 29 years, after the patient had become oxygen dependent, shows further worseninng of bronchial wall thickening and bronchiectasis, particularly in the right suprahilar region, now with hilar retraction suggesting upper lobe scarring. Bullae formation at the right apex is also now apparent. Note that the chest radiographic technique for this image used edge enhancement. (Courtesy Michael B. Gotway, MD.)

readily appreciated in the right upper lobe (eFig. 68.3) because this region is often involved before other areas. The appearance of bronchiectasis by *computed tomography* (CT) of the chest is highly characteristic of CF pulmonary involvement (see eFigs. 68.1B–E and 68.2B–E and Chapter 69). Although chest radiography is appealing due to accessibility and relatively low-dose radiation exposure, sensitivity for detecting acute or subtle chronic changes during a period of acute exacerbation remains limited.[80] Nonetheless, chest radiographs remain a standard first-line imaging test for surveillance and during acute exacerbations, for episodes of hemoptysis (eFig. 68.4), or to identify complications such as pneumothorax[81] (eFig. 68.5). Use of CF monitoring by chest CT is recommended biannually in stable CF patients.[82]

Chest CT, with its high-resolution cross-sectional imaging, is clearly superior for detecting mild disease and quantifying the extent and pattern of bronchiectasis (see eFigs. 68.1B–E and 68.2B–E).[83,84] Mosaic perfusion, manifesting as areas of inhomogeneous lung opacity resulting from air trapping and disordered parenchymal blood flow, is a common CT finding in patients with CF (eFig. 68.6). Small nodules due to bronchial and bronchiolar impaction are commonly observed (eFig. 68.7). CT studies have also demonstrated significant changes in young children, before obvious symptomatic disease, supporting the notion that CF lung disease begins early in life and disease detection is limited by the sensitivity of routine clinical procedures including spirometry.[83] Regardless of the imaging modality used, the degree of hyperinflation generally increases over time. As endobronchial infection and reactive inflammation emerge, peribronchial cuffing becomes increasingly apparent. Manifestations of bronchiectasis, including enlarged ring shadows or airway dilation and cysts, are common even early in life (see eFig. 68.1); upwards of 50% of CF patients demonstrate bronchiectasis by 3 to 5 years of age.[84]

During acute pulmonary exacerbation, a variety of radiographic findings may be noted. These include peripheral round densities and mucoid impaction seen radiographically as branching opacities. Such findings may be transient and resolve during therapy or be replaced by emergence of frank bronchiectatic or cystic changes. Additional findings, including subpleural blebs, often become evident during the second decade of life and are most prominent along the mediastinal border.[85]

The clinical justification for CT scanning in place of routine chest radiography is not well established. Clear indications may include management of a patient with focal disease being considered for lobectomy or of a patient experiencing acute deterioration—as a means to detect complications or evidence of new infection. Magnetic resonance imaging, which avoids radiation associated with CT, can define lung morphology, particularly as techniques have improved, although relative sensitivity and specificity of magnetic resonance techniques in CF have not yet been firmly established.[86] Recent imaging studies using hyperpolarized gas magnetic resonance imaging have begun to uncover early ventilation defects in young pediatric patients before obstruction is detected by spirometry. These findings correlate with the severity of obstruction; they mirror early defects of ventilation measured on more sensitive testing such as multiple breath washout and confirm that early imaging abnormalities are present in patients with preserved lung function.[87]

LUNG FUNCTION

Lung function in CF is believed to be normal at birth, although recent studies have demonstrated that, within weeks to months of delivery, the cycle of inflammation and infection has begun, and reduced cartilage size very early in life may predispose to airway obstruction.[88] Infants with CF can exhibit increased airway resistance, gas trapping, and diminished flow rates.[89–91] A few centers use infant pulmonary function testing to detect early evidence of airway obstruction and guide institution of therapeutic strategies before permanent lung injury has been established. *Lung clearance index*, a test performed by measuring the time for clearance of an inert gas through the multiple breath washout technique and a test not confounded by patient effort, has emerged as an important research tool used to detect early evidence of ventilation abnormality.[92–94] Reliable and consistent spirometry can be obtained routinely at 5 to 6 years of age, when children are able to cooperate.[95,96]

The earliest evidence of airway obstruction is typically limited to the small airways and thus is often first detectable by reduced forced mid-expiratory flow rates, reduced flows at low lung volumes, and gas trapping (i.e., elevated residual volume to total lung capacity ratio). Although infrequently applied during clinical management, abnormalities such as increased alveolar-arterial oxygen tension difference, frequency dependence of dynamic compliance, reduced response of flows to a helium-oxygen mixture, elevated slope of phase 3 of the single-breath nitrogen washout, and an elevated physiologic dead space are often present.[97] Spirometry is the most clinically useful test to follow the course of respiratory disease progression and is typically measured at each clinic visit. Equally important is assessment of the flow volume loop, which may demonstrate obstruction by concavity, with low flows especially in the terminal portion of the curve, earlier than either the *forced expiratory volume in 1 second* (FEV_1) or mean forced expiratory flow from 25–75% of the forced vital capacity. As discussed earlier, early ventilatory defects can be uncovered using imaging techniques in the research setting.

Over time, patients with active CF lung disease typically experience progressive deterioration of lung function. The annualized rate of decline in FEV_1 is approximately 2–3% of predicted FEV_1.[98] Despite recent advances, this progressive loss of pulmonary reserve often accelerates in young adulthood.[99] As respiratory disease progresses, peripheral airway obstruction yields to more generalized blockage and air trapping as increasingly damaged airways cease to contribute to gas exchange, mimicking a restrictive pattern by spirometry.[100]

The chronic cycle of inflammation and infection contributes to CF lung disease, and patients typically exhibit progressive decrements of arterial Po_2. Oxygenation declines slowly throughout life but may not become symptomatically limiting until late in the disease course. Patients who are able to sustain adequate oxygenation usually function well despite the presence of obstructive impairment.

When arterial P_{O_2} values are chronically below 55 mm Hg, patients are at high risk for development of pulmonary hypertension.[101,102] Clinically significant hypoxemia most commonly presents during sleep, particularly during rapid eye movement–associated hypoventilation, and it is a significant factor leading to pulmonary hypertension.[103] Desaturation at rest or with exertion as measured during a 6-minute walk test is a negative prognostic indicator and associated with increased risk of CF mortality.[104] Elevation of arterial P_{CO_2} and FEV_1 less than 30% define end-stage CF lung disease. Patients with FEV_1 less than 30% of predicted, arterial P_{CO_2} greater than 50 mm Hg, or arterial P_{O_2} less than 55 mm Hg have a predicted 2-year mortality of 50% and should be considered for lung transplantation.[105] Other prediction tools can facilitate appropriate patient selection for referral and outperform reliance on any single criterion.[106]

Bronchial hyperresponsiveness is a consistent finding in asthma, but its presence and clinical significance in CF remains controversial.[107,108] Bronchial hyperresponsiveness in CF has been demonstrated during exercise testing, during bronchoprovocation testing, or by the response to bronchodilators, with two-thirds of CF patients demonstrating decreased forced expiratory flows after a bronchoconstrictive challenge. In contrast to cross-sectional studies, repeated tests every 1 to 3 months for a year have demonstrated bronchodilator responsiveness at least once in 95% of subjects.[109] Despite its frequency, the pathogenesis of bronchial hyperresponsiveness in CF is unclear. The finding is unrelated to the severity of pulmonary disease or indices of atopy but appears to be more prevalent during winter months. Hyperresponsiveness diminishes during acute exacerbations of CF lung disease, but often returns as lung function improves following 2 weeks of intensive antibiotic therapy. Patients with CF may also have a lack of response to bronchodilators that may be related to diminished tone in bronchiectatic airways.

Exercise tolerance in CF is related to the severity of airway obstruction.[110] Nearly 50% of patients with moderate to severe airway obstruction may experience oxygen desaturation to below 90% during peak exercise.[111] Persons with CF have higher than expected ventilatory muscle endurance, and this endurance can be further improved with inspiratory muscle training. However, improved inspiratory muscle strength and endurance do not augment exercise performance, suggesting that this is not the limiting factor in exercise.

Exercise therapy in CF has many physiologic and biologic benefits although it does not improve standard spirometry. Nevertheless, standardized aerobic and resistive exercise does improve cardiorespiratory fitness and *quality of life* (QOL) and has been associated with a reduced risk of hospitalization.[112] Maximum oxygen consumption during exercise has been suggested as a better predictor of survival than routine pulmonary function testing, although the test is time-consuming and not available in all clinical settings.[113] Several more clinically efficient measures of physical fitness show strong correlation with maximum oxygen consumption and CF disease prognosis, further reinforcing the notion that improved physical health through exercise may benefit overall clinical status.[114]

UPPER RESPIRATORY TRACT DISEASE

Chronic rhinosinusitis is present in virtually all patients with CF. CF sinus disease manifests as chronic, relapsing symptoms of increased upper airway secretions, moderate airflow obstruction, and widening of the nasal bridge.[115] This can be noted during imaging (eFig. 68.8) as opacification of the paranasal sinuses and has been reported in more than 90% of patients during the first year of life. Nasal polyps are seen in an additional 15–20% of individuals with CF.[116] Nasal polyps usually present towards the end of the first or during the second decade of life and may be the clinical finding that triggers diagnostic evaluation.[117] The presence of acute and chronic nasal obstruction can diminish olfactory function and contribute to diminished dietary intake with subsequent nutritional decline.[118] Despite the presence of pronounced radiographic abnormalities, nasal symptoms can be surprisingly well tolerated. Complaints related to acute or chronic sinusitis manifest in less than 10% of children and approximately 24% of adults.[119,120] Nevertheless, colonization of the upper airway may contribute to lower airway disease (e.g., as a reservoir for CF pathogens), although more recent pediatric literature suggests that there may be discordance between upper and lower airway tract flora.[121] In symptomatic patients, sinus débridement remains a mainstay of therapy for those who have not responded to medical treatments, but there is inconclusive evidence for the role of endoscopic sinus surgical treatment in management of symptoms of lower respiratory tract disease.[122]

COMPLICATIONS OF RESPIRATORY TRACT DISEASE

Atelectasis is present in approximately 5% of CF patients during the first 5 years of life and diminishes in frequency with advanced age.[123] Atelectasis can be lobar or subsegmental, with the right lung most commonly affected, and may develop concurrently with pulmonary exacerbations or in the absence of clinical symptoms. Occasionally, atelectasis results from endobronchial aspergillosis presenting as mucoid impaction and volume loss.[124] In most instances, however, a discrete mucous plug is not evident on bronchoscopy.

Pneumothorax (see eFig. 68.5) is a well-recognized CF complication caused by air trapping and subsequent rupture of subpleural blebs. Although the finding is equal among sexes and fairly rare (about 1% per year), incidence increases sharply with age and disease severity. Up to 20% of adults with CF experience at least one pneumothorax during their lifetime,[125] and recurrence is common. Typical presentations include acute onset of chest pain, dyspnea, respiratory distress, or hemoptysis.[126] Simultaneous bilateral pneumothoraces have been described and may constitute a medical emergency. Tension pneumothorax, which is more common in CF than in other obstructive lung diseases, may be life-threatening. Small asymptomatic pneumothoraces may be discovered in patients on routine surveillance chest radiography.

Hemoptysis is a relatively common event in CF (see eFig. 68.4) and is believed to result from mucosal erosions and bronchial artery hypertrophy, which are a consequence of

chronic inflammation.[127] The presence of hemoptysis correlates with disease severity and is more common in the setting of chronic MRSA infection.[126] Blood streaking in the sputum is a frequent finding and may be intermittent and chronic. Massive hemoptysis (>240 mL blood in 24 hours) presents in approximately 5% of patients during their lifetime.[128] Due to the strong correlation between new-onset hemoptysis and exacerbation of lung infection, initial treatment should include antibiotic therapy, with omission of chest physiotherapy. Typically, aerosol treatments are temporarily held, and measures to promote clot stabilization are considered. There are anecdotal reports describing use of the antifibrinolytic agent tranexamic acid in this setting.[129] Beta-blockade has also been reported to provide benefit during acute and chronic hemoptysis, presumably by reducing blood pressure and blunting the sympathetic response to coughing.[130] Although bronchoscopy can help localize the site of bleeding, emergent bronchoscopy or radiographic imaging are of limited clinical utility and are not currently recommended in the emergent evaluation of hemoptysis. Instead, rapid assessment for emergent bronchial artery embolization (see eFig. 68.4F–G) is preferred. Advances in invasive vascular intervention and improved clinical management strategies have resulted in significantly reduced mortality, which was historically as high as 10% following massive hemoptysis.[131](See also Chapter 40.)

ABPA has a lifetime incidence of 2–8% among CF patients, although a few small cohort studies have reported incidence as high as 20%.[132,133] *Aspergillus* is a common environmental mold and is frequently recovered in sputum culture. Although up to 50% of patients with CF may demonstrate precipitating antibodies to *A. fumigatus* in their serum, an immunoglobulin E (IgE)-mediated allergic hypersensitization must develop to manifest symptoms of ABPA infection.[134] Clinical features include increased cough, dyspnea, wheezing, and expectoration of rusty-brown plugs with eosinophilic infiltrates by microscopy. Radiographic findings can be present, including a characteristic finger-in-glove pattern (see Fig. 96.7). Atelectasis and volume loss may also result from hyphae-laden mucoid impaction in segmental bronchi. A diagnosis of ABPA is made by fulfilling major and minor criteria that include characteristic clinical findings plus skin test hypersensitivity, elevated total IgE, and increased levels of IgG and IgE antibodies against *A. fumigatus* or other fungi.[78] (For full details on diagnosis, see Chapter 96.)

Staphylococcal and pseudomonal empyemas have been described in patients with CF, but respiratory tract infections typically spare the pleural space, making complications such as pleural effusion and empyema uncommon. Nonetheless, pulmonary exacerbations commonly present with pleuritic-type pain.[135]

Digital clubbing, which is caused by hyperplasia and hypertrophy of connective tissue and increased vascularity of the distal phalanges, appears in virtually all patients with advanced CF and is often present early in individuals with active lung disease (see Fig. 18.3). The cause of clubbing is unknown, and the finding may resolve following lung transplantation.[136] Severity generally correlates with extent of lung disease.[137] Hypertrophic pulmonary osteoarthropathy is a common clinical entity presenting with advanced CF lung disease in up to 15% of older adolescents and adults.[102] Radiographic evidence for periostitis may be present in up to 8% of subjects (see eFig. 18.1). Distal aspects of the tibia, fibula, radius, and ulna are most commonly affected. Symptoms can include pain, bone tenderness, swelling, and warmth over the involved areas. Pain with ambulation or following strenuous physical exercise is common.[138] Hypertrophic pulmonary osteoarthropathy is worsened during periods of poorer respiratory health and exacerbation and tends to subside with resolution of pulmonary exacerbation. During end-stage lung disease, persistent joint symptoms may require chronic analgesic therapy. Rare instances of cutaneous vasculitis causing self-limited, painless, palpable purpura, typically involving the lower extremities, have also been reported in CF.[139–141]

Respiratory failure is the greatest contributor to mortality and is the cause of death in more than 90% of CF patients. In early CF, hypoxemia is observed during exertion or sleep and progresses in concert with lung disease.[103,142] Hypercapnia is a late finding reflecting advanced pulmonary decline, which often worsens during clinical exacerbation. Pulmonary hypertension and right ventricular dysfunction may develop late in the disease process, resulting in hepatic congestion and peripheral edema.[143] The role of pulmonary hypertension in CF is an area of considerable interest, particularly with regard to determining optimal treatment regimens.[144] Hypoxemia, if not recognized or adequately treated, contributes to worsening pulmonary hypertension and cardiac failure. Pneumothorax, hemoptysis, and infections such as respiratory syncytial virus or influenza can cause acute respiratory failure that is reversible with aggressive treatment.[145,146]

GASTROINTESTINAL MANIFESTATIONS

Meconium ileus is observed in approximately 15% of newborns with CF and is highly specific for the diagnosis of CF in the neonatal period. Failure to pass thick inspissated meconium during the first 48 hours of life is associated with abdominal distention and rapidly advances to bilious emesis. Affected infants are at risk for intestinal perforation and peritonitis accompanied by shock. Radiographic features are typical of high-grade bowel obstruction and reveal multiple dilated loops of intestine and air-fluid levels (eFig. 68.9). A granular appearance of the lower abdomen may be noted due to accumulated meconium containing small air bubbles. The colon is characteristically small when visualized with contrast imaging (eFig. 68.10). Scrotal and peritoneal calcification may be observed if the ileum has perforated in utero. Meconium obstruction of the colon can also interfere with passage of stool, but it presents a distinct clinical scenario that has been termed the meconium plug syndrome and is much less specific for CF.[147]

Beyond the newborn period, approximately 20% of CF patients develop the distal intestinal obstruction syndrome annually. This relatively common sequela is characterized by obstruction in the cecum, proximal colon, or terminal ileum associated with voluminous, viscous, and incompletely digested intestinal contents and is otherwise similar to meconium ileus (eFig. 68.11). Partial obstruction may manifest as a chronic or recurrent condition with intermittent crampy abdominal pain as the only symptom. Fulminant, complete obstruction is associated

with failure to pass stool, resulting in abdominal distention and vomiting that may be bilious or fecal if allowed to progress. A mobile right lower quadrant mass may be palpable. Risk factors for distal intestinal obstruction syndrome include previous episodes, dehydration, change of diet, immobilization, bacterial overgrowth, hospitalization for pulmonary exacerbations, treatment with antibiotics, and constipating medications. Other causes of acute abdominal pain with obstruction should also be considered, including intussusception, intestinal adhesions from previous abdominal surgery, and appendicitis, which may be clinically less evident due to concurrent antibiotic therapy.[148] Appendicitis is thought to be uncommon in CF, with a 2% lifetime risk compared with 7–8% risk in the general population.[149] Nonfilling of the appendix with contrast enema has been observed in patients with CF. Radiographic and histologic findings of a dilated, mucus-filled appendix are typical features,[150,151] although the uninflamed appendix is also frequently enlarged on CT in the absence of appendicitis (eFig. 68.12). Inadequate pancreatic and bowel secretion of bicarbonate in CF may also contribute to duodenal irritation and recurrent epigastric pain by failing to buffer gastric acid.[152]

Gastroesophageal reflux is prevalent in CF, in part due to increased abdominal pressure associated with obstructive lung disease resulting in decreased lower esophageal sphincter tone. In addition, a direct effect of gastric acidification due to CFTR protein dysfunction resulting in decreased buffering capacity in the stomach may contribute.[153] Consideration of gastroesophageal reflux is important because the condition can impair nutritional status and may contribute to microaspiration, accelerating respiratory decline. The presence of gastroesophageal reflux has been associated with worsened outcome after lung transplantation, and patients with CF considered for transplant should be evaluated thoroughly in this regard. Certain transplant centers recommend surgical therapy for ongoing reflux during the peritransplant period.[154]

Rectal prolapse develops in nearly 20% of children with CF but is an infrequent event for adults.[155] Rectal prolapse in a child should raise suspicion for an underlying CF diagnosis, even if this is the only clinical finding. The clinical diagnosis of prolapse is often precipitated by the presence of bulky, sticky stools that adhere to rectal mucosa, associated poor nutritional status, and loss of perirectal fat that normally supports the rectum, as well as presence of high intra-abdominal pressure due to frequent paroxysmal coughing.

Colorectal carcinoma in adults with CF is up to10 times more frequent than in the general population, probably as a consequence of chronic inflammation. Colorectal carcinoma is up to 30 times more frequent in CF patients after organ transplantation, probably due to the additional risk associated with immunosuppression.[156] Current recommendations include colonoscopy screening at age 40 years with 5-year rescreening and 3-year surveillance intervals (unless a shorter interval is indicated by individual findings) and a CF-specific intensive bowel preparation.[156] Organ transplant recipients with CF should initiate colorectal screening at age 30 years within 2 years of the transplantation because of their additional risk.

PANCREATIC DISEASE

Exocrine pancreatic insufficiency, due to intraductal obstruction by thickened, dehydrated secretions, is present from birth in approximately 85% of patients with CF.[157,158] Adequate exocrine pancreatic secretion is present in up to 15% of patients and has been associated with certain (residual function) *CFTR* genotypes. Insufficient release of pancreatic enzymes into the gut impairs fat and protein digestion and reduces absorption by the small bowel. Pancreatic insufficiency results in frequent bulky, greasy, foul-smelling stools and protuberance of the abdomen due to increased intraluminal bacterial gas production. Assessment of pancreatic function by enzyme-linked immunosorbent assay measurement of stool fecal elastase-1 is diagnostic in the clinical assessment of pancreatic insufficiency.[159] Complete fatty replacement of the pancreas is common, as judged by CT (eFig. 68.13), and pancreatic lipomatosis and fibrosis are characteristic of pediatric CF. Pancreatic ductal dilation and calcifications are also observed in CF patients. Rarely, there may be cystic replacement of the pancreas, referred to as pancreatic cystosis.

Untreated malabsorption due to exocrine pancreatic insufficiency results in nutritional failure and impaired linear growth, which has been linked to worsened clinical outcomes.[160] Patients with CF often grow slowly because of factors other than poor nutritional intake and intestinal malabsorption. For example, increased expenditure of energy to accomplish the work of breathing may be an important contributor, and systemic inflammation may also play a role.[158] Fat-soluble vitamin deficiency due to nutritional failure was historically common in young children with CF but is much less common in the era of early diagnosis via newborn screening with early vitamin and pancreatic enzyme replacement.

Symptomatic pancreatitis with paroxysmal pain develops in less than 1% of adolescent or adult CF patients, usually in those who maintain at least some residual exocrine pancreatic function.[161] Recurrent painful pancreatitis can be the presenting feature of CTFR-related disorders.[162,163]

HEPATOBILIARY DISEASE

Diagnosis of cystic fibrosis liver disease[164] is formally made by the presence of two or more of the following: hepatomegaly and/or splenomegaly, confirmed by ultrasonography; abnormalities of alanine aminotransferase, aspartate aminotransferase, and γ-glutamyltransferase greater than 1.5 to 2 times the upper limits of normal for more than 6 months after excluding other causes of liver disease; ultrasonographic evidence of coarseness, nodularity, increased echogenicity, or portal hypertension; or, liver biopsy showing focal biliary cirrhosis or multilobular cirrhosis. Histologically, CF liver damage manifests as focal biliary cirrhosis and has produced clinically significant liver pathology in greater numbers of CF patients as they live longer. One description of clinically significant disease includes the constellation of an abnormal physical exam, characteristic liver function testing, and radiographic findings.[165] Liver disease may present as hepatosplenomegaly or most commonly as persistent elevation of hepatic enzymes (aspartate aminotransferase/alanine aminotransferase and/or bilirubin and γ-glutamyltransferase). Current guidelines

recommend a comprehensive evaluation for CF liver disease when enzymes are greater than 3 times the upper limit of normal or remain 1.5- to 2-fold increased for a period of 3 months. Patients with CF-associated liver disease rarely develop acute fulminant hepatic failure but may progress to advanced cirrhosis, portal hypertension, and clinically significant esophageal varices.[166] Steatosis is a common clinical finding and has been associated with malnutrition, essential fatty acid deficiency, and/or oxidative stress in the setting of CF hepatobiliary dysfunction.[165] Ultrasound is generally used to monitor severity of CF liver injury, including in longitudinal studies.

Biliary tract disease is common in CF. Cholelithiasis develops in approximately 10% of patients but causes significant clinical symptoms in less than 4% of cases.[167] The risk of stone formation is increased due to abnormal ion transport within the gallbladder, which may result in biliary colic or symptomatic cholelithiasis. A small or microgallbladder, seen in 20–30% of CF patients, is of unknown clinical significance.[168]

GENITOURINARY TRACT ABNORMALITIES

The vas deferens is absent in almost all adult men with CF.[169] Semen analysis can be used to identify the 1% of male CF patients who remain fertile. Volume of ejaculate in men with the disease is usually one-third to one-half of normal and exhibits complete absence of spermatozoa in addition to a number of chemical abnormalities that reflect aberrant secretions from the seminal vesicles.[170] Male infertility is increasingly overcome via sperm harvest paired with in vitro fertilization methods, which have become more widespread and effective. The patient and family may consider prenatal genetic testing of partners or spouses and early preimplantation genetic testing if in vitro fertilization methods are used. An increased incidence of inguinal hernia and hydrocele has also been reported.

Although significantly less common than vas deferens atresia, female infertility in CF may be as high as 20%.[171] Many women with CF and advanced lung disease and/or malnutrition are anovulatory. Another obstacle to conception is the presence of thick tenacious cervical mucus and increased endocervicitis. Dehydrated cervical mucus is characterized by abnormal electrolyte and other compositions, preventing the physiologic ferning of midcycle. As a result, CF abnormal mucus is thought to impede normal sperm migration.[171]

Pregnancy in women with CF appears to be increasing as clinical outcomes have improved. A longitudinal study of 325 pregnant women with CF demonstrated 258 live births (79%).[172] Pregnancy in women in a large observational study did not contribute to pulmonary decline or mortality over 2 years.[173] Successful pregnancy and delivery are possible and can be carried out safely, but it is essential that women with CF consider implications to their health as they embark on family planning.[174] CFTR modulators may increase fertility due to effects on cervical mucus; however, recommendations on their use during pregnancy are still emerging. Successful breastfeeding has also been reported among women with the disease.[175]

Urinary incontinence can be seen beginning in adolescence and does not clearly correlate with CF disease severity; rather, incontinence probably reflects chronic cough and increased abdominal pressure due to airflow obstruction.[176]

SWEAT GLAND DYSFUNCTION

Sweat sodium chloride is elevated in most CF patients due to abnormal reabsorption of chloride from the sweat duct lumen in the absence of CFTR (see also earlier). This may predispose individuals with CF to excessive salt loss in certain settings. Young children are especially susceptible to salt depletion, especially when exposed to warm, arid climates or when there is additional salt loss due to vomiting or diarrhea. Children in this circumstance typically present with lethargy, anorexia, and hypochloremic alkalosis and/or hyponatremia.[177]

TREATMENT

OVERVIEW

A concerted effort to address the pulmonary manifestations in a comprehensive fashion has led to improved CF outcomes.[178] Therapies including mucolytics,[179] hydrators of the airway surface,[180,181] inhaled antimicrobials,[182–184] systemic anti-inflammatory treatments,[185–187] and nutritional support are traditional mainstays of CF treatment (Table 68.3). These supportive therapies, in addition to comprehensive care undertaken at organized CF clinical centers, are partly responsible for a steadily improving life expectancy observed over the past 3 decades

Table 68.3 Supportive Cystic Fibrosis Therapeutics by Category

Agent	Predominant Mechanism of Action
RESTORATION OF AIRWAY SURFACE HYDRATION	
Hypertonic saline*	Osmotic increase of airway hydration; expectorant
Mannitol†	Osmotic increase of airway hydration; expectorant
MUCOLYTICS	
Dornase alfa	Cleavage of DNA polymers
ANTI-INFLAMMATORY	
Ibuprofen	Reduction of airway inflammation
ANTI-INFECTIVES	
Inhaled tobramycin	Chronic treatment of *Pseudomonas aeruginosa*
Inhaled aztreonam	Chronic treatment of *P. aeruginosa*
Dry powder tobramycin	Chronic treatment of *P. aeruginosa*
Azithromycin	Anti-inflammatory/anti-infective for chronic *P. aeruginosa* infection
NUTRITIONAL THERAPIES	
AquADEKs	Restoration of fat-soluble vitamin levels
Pancrelipase	Restoration of pancreatic enzyme levels

*Therapy commonly used but not approved by the U.S. Food and Drug Administration.
†Therapy approved in the United States, Europe, Australia, and New Zealand; other approvals under consideration.

in the United States (Fig. 68.5), resulting in a median life expectancy of 41 years in 2012 increasing to 47 years in 2018.[188] Similar improvements have been observed in other developed countries. More recently, treatments that address the basic defect by restoring CFTR function have emerged, resulting in marked clinical improvement for the majority of individuals with CF, promising to transform the disease.[189] Other therapies that address rare *CFTR* alleles not yet impacted by CFTR modulators, including genetic-based treatments, are in various stages of development (Fig. 68.6).

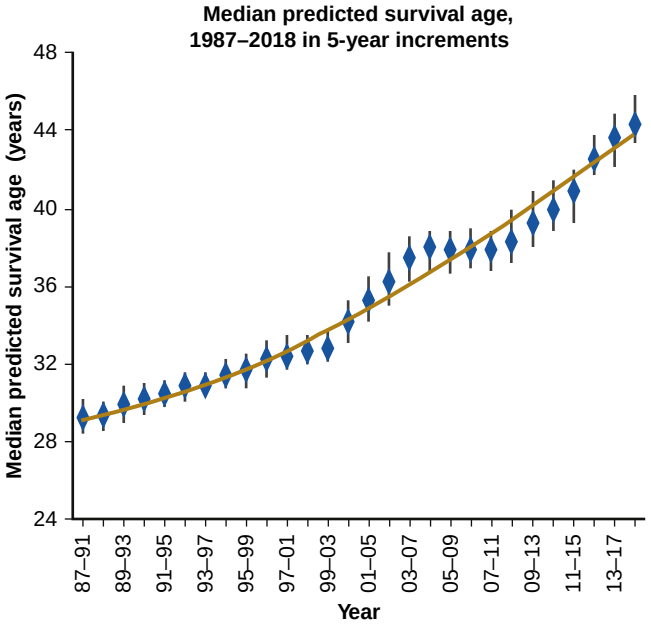


Figure 68.5 Median predicted survival in cystic fibrosis. Median predicted survival for *cystic fibrosis* (CF) patients in U.S. CF centers in the CF registry is depicted as the median for each 5-year time span from 1987 to 2018. Since the mid-1980s, predicted survival has increased from about 27 years of age to older than 40 years for the most recent 5-year time span. (Data from the Cystic Fibrosis Foundation Patient Registry, Bethesda, MD; 2018.)

MONITORING AND AGGRESSIVE APPROACH

Aggressive monitoring and treatment of pulmonary infections and other common CF complications have contributed significantly to improved clinical status in the disease.[99,190,191] Substantial attention has focused on efforts to delay or prevent chronic colonization with *P. aeruginosa,* with a number of studies evaluating various regimens to achieve sustained bacterial clearance. Coincident with this approach is increased attention to infection control as a means to forestall acquisition of virulent organisms, particularly in health care settings where risk from these pathogens is significant. Segregation of clinics by *Pseudomonas* status can reduce spread of highly prevalent organisms (i.e., standard infection control procedures alone may not be sufficient).[192,193] Observations of this type have led to rigorous guidelines for patient isolation and prevention against comingling and consequent infection.[194] Once established, *P. aeruginosa* is challenging to eradicate with antimicrobial therapy alone,[195–199] although this can be accomplished in certain patients,[49] including a subset of individuals initiating CFTR modulator therapy (see later). Chronic colonization with *Pseudomonas* is associated with a more rapid decline in respiratory status.[27,42,200] Virulent organisms such as *B. cepacia*[201,202] confer an even worse prognosis and have been associated with outbreaks due to nosocomial spread. Despite advances in lung function and inhibition of *Pseudomonas* growth, delaying progression of CF disease during adolescence remains a challenge. However, early aggressive care, particularly prior to substantial respiratory decline, is thought to forestall permanent loss of lung function.[203] As with chronic pulmonary infection, early and aggressive nutritional therapy, particularly among young children with CF, has been crucial to achieving improved outcomes.

CF centers have embarked on a rigorous quality improvement program to facilitate best practices in CF care. Outcomes are compared between centers and made publicly available to encourage continuous improvement.[204] A culture of cooperation among centers, patients, families, and the Cystic Fibrosis Foundation has led to evidence-based

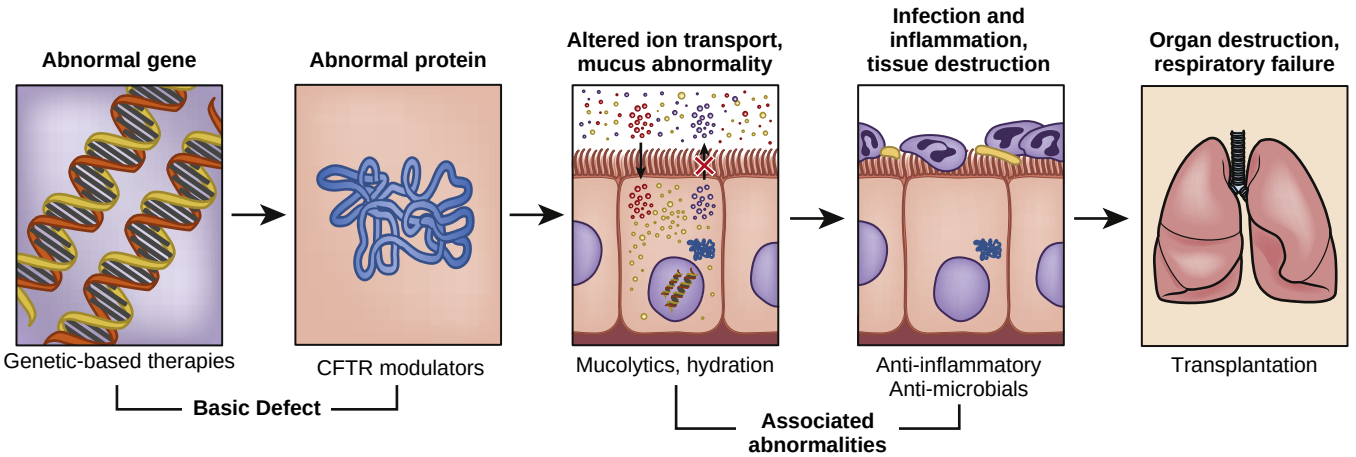


Figure 68.6 *Cystic fibrosis* (CF) therapeutics by category. This figure depicts the mechanisms and possible therapeutics for CF airway pathology. CF therapeutics attempt to address defective *cystic fibrosis transmembrane conductance regulator* (CFTR) function by genetic-based therapy or modulation of CFTR expression or function; to address the diminished airway surface liquid, abnormally viscous mucus, and disrupted mucociliary clearance; and, finally, to treat chronic airway infection and inflammation. When respiratory failure develops, lung transplantation is the remaining option.

guidelines, protocol-driven therapies, and rapid dissemination of results to facilitate advances in health care delivery.[205]

Cystic Fibrosis Transmembrane Conductance Regulator Potentiators, Correctors, and Other Treatments for the Basic Defect

On the basis of functional consequences of various *CFTR* mutations, specific therapeutic strategies to restore deficient or defective protein activity have been developed by altering CFTR expression or function (Fig. 68.7 and Table 68.4). Following ambitious high-throughput drug screening efforts to bolster their discovery,[206–210] benefits of these new CFTR modulators have rapidly come to fruition and expanded beyond initial indications. Rescue of CFTR protein function to sufficient levels, now termed "highly effective," as first established by the archetype CFTR modulator ivacaftor, is associated with marked improvement in the clinical outcome that is dramatically more efficacious than previous therapies.[189,211,212] *CFTR potentiators* activate CFTR channels located at the cell surface by potentiating cyclic adenosine monophosphate–mediated channel gating.[206,213–215] Ivacaftor, a potentiator-type modulator that improves CFTR gating, was the first to be approved and was initially demonstrated in CF patients with the G551D gating mutation, an allele represented in approximately 4% of those with the disease. Subsequently, ivacaftor was also shown to activate 23 additional CFTR alleles as a monotherapy, based on clinical and in vitro data that justified[216,217] expansion of its indications. The highly efficacious treatment benefit observed with ivacaftor therapy led to strong interest in recapitulating the effect among other, more common *CFTR* alleles.[218] This includes correctors of F508del CFTR misfolding, termed CFTR correctors. *CFTR correctors* restore normal CFTR processing of the most common *CFTR* mutation, F508del, and of other alleles with class II properties, and are used in one or two corrector combinations with CFTR potentiators to restore CFTR function. Agents that induce translational readthrough (or suppression) of premature termination codons (class I) to induce expression of full-length CFTR are also under development.[219–222] *CFTR amplifiers* augment translation efficiency and thus increase protein levels, which could augment function for various CFTR genotypes. Approaches beyond these small molecule

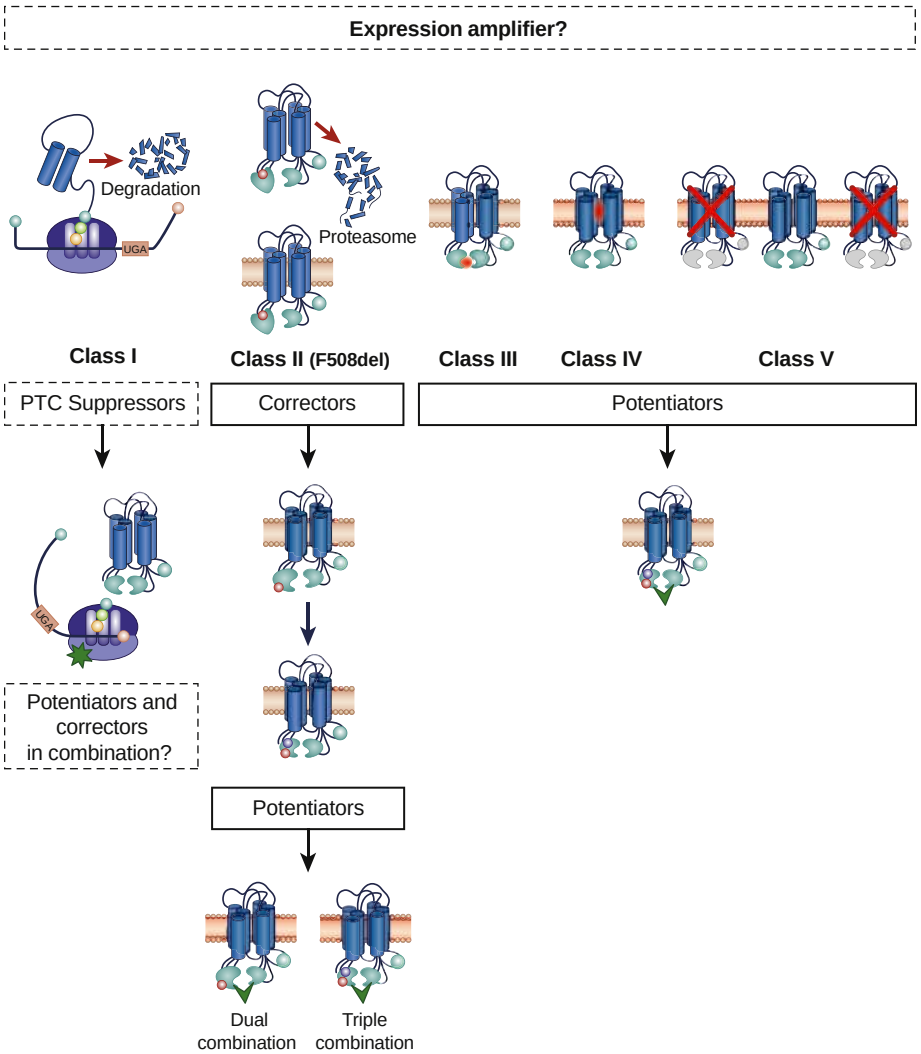


Figure 68.7 Schematic of approach to *cystic fibrosis transmembrane conductance regulator* (CFTR) restoration with small molecules, by mutation class. Therapeutic approaches with definitive studies are shown in solid boxes; those under investigation are noted by dashed boxes. CFTR mutations can be addressed pharmacologically based on their underlying molecular defect (see Chapter 67). CFTR expression amplifiers increase CFTR transcription and/or translation efficiency and would be expected to have broad-ranging effects across mutation classes. Nonsense mutations (a form of class I mutation) have the potential to be restored by *premature termination codon* (PTC)-suppressing drugs that induce full-length functional CFTR protein. Because some protein forms generated by translational readthrough are dysfunctional, the addition of correctors and potentiators may also be needed. Misfolded mutations (class II), including F508del, require multiagent therapy to restore processing and trafficking with a CFTR corrector and then to augment ion channel function with CFTR potentiators. CFTR proteins that are localized to the cell surface but are dysfunctional, or reduced in number, as in class III, IV, and/or V mutations (in addition to class VI, not shown), can be addressed by CFTR potentiators alone. *Green star,* PTC suppressor; *green circles*, correctors; *green chevrons,* potentiators. (Data from Mall MA, Mayer-Hamblett N, Rowe SM. Cystic fibrosis: Emergence of highly effective targeted therapeutics and potential clinical implications. *Am J Respir Crit Care Med*. 2019; and Bell SC, Mall MA, Gutierrez H, et al. The future of cystic fibrosis care: a global perspective. *Lancet Respir Med*. 2020;8[1]:65–124.)

Table 68.4 Approved Therapeutics Targeting Each CFTR Mutational Class

CFTR Modulator Class	Molecule	CFTR Mutations Affected	CFTR Mutation Class Affected
Potentiator	Ivacaftor	G551D/S Non-G551D gating mutations Surface localized CFTR Alleles F508del*	II III IV V
Correctors	Lumacaftor (VX-809) (in combination with ivacaftor)	F508del (homozygous)	II
	Tezacaftor (VX-659) (in combination with ivacaftor)	F508del (homozygous) F508del heterozygous (with residual function mutation)	II
	Elexacaftor (VX-445) (in combination with tezacaftor and ivacaftor)	F508del (homozygous or heterozygous)	II

*Investigational.
CFTR, cystic fibrosis transmembrane conductance regulator.

CFTR modulators are also being advanced. For example, gene replacement by viral and nonviral gene therapy remains an approach under active investigation,[223] as well as newer strategies that attempt to express CFTR through translation of delivered mRNA alone.[224,225] Because many CF patients (≈40%) are complex heterozygotes and encode more than one *CFTR* mutation,[226] combination therapeutics addressing more than one *CFTR* variant or use of multidrug therapy will likely dictate a need for individualized therapeutics optimized for particular patients in the future.[218]

Cystic Fibrosis Transmembrane Conductance Regulator Potentiators. *CFTR potentiators* activate mutant CFTR localized to the cell surface by potentiating channel gating stimulated by physiologic activation of cyclic adenosine monophosphate.[206,210,227–229] The impetus for development included the anticipated need to activate F508del CFTR once localized to the cell surface, in addition to the need to activate other mutant channels residing at the plasma membrane but dysfunctional due to aberrant gating, impaired conductance, or a reduced number of channels due to mild processing mutations or splice variants. Early attempts at potentiation included use of genistein, a natural flavonoid molecule that demonstrates strong activation of CFTR but is poorly absorbed and exhibits other undesirable physiologic properties.[228,230,231] Subsequently, ivacaftor and other investigational CFTR potentiators were discovered via high-throughput screening approaches that identified small-molecule potentiators optimized for druglike qualities through traditional medicinal chemistry approaches.[206,210,228–230] Ivacaftor induced about 50% CFTR activity in G551D/F508del CFTR-expressing primary epithelial cells, a benchmark for preclinical development of CFTR modulators.[206]

In a landmark trial conducted in older children and adults (age 12 years and older) with CF and with at least one copy of the G551D-*CFTR* gating mutation, ivacaftor caused a roughly 10% absolute improvement in FEV_1% predicted at 24 weeks, an effect durable through 48 weeks of testing, providing confirmation of positive prior phase II testing results.[189] In addition, multiple secondary clinical end points showed meaningful and statistically significant improvements, including a 55% reduction in the probability of experiencing a pulmonary exacerbation, improved weight gain, and an improvement in respiratory symptoms. Posttreatment sweat chloride testing also exhibited marked improvements (mean of sweat chloride was about 55 mEq/L, a value below the traditional diagnostic threshold). In a smaller study that enrolled pediatric G551D CF patients 6 to 12 years old,[212] benefit was also documented by lung clearance index measurements in CF patients with minimal detectable lung function abnormality by spirometry, likely reflecting improved function of the small airways.[232] The degree of improvement in spirometry among participants of the phase III trial of ivacaftor compares favorably with that of commonly used therapies for chronic CF care. In clinical studies to date, ivacaftor appeared safe and well tolerated, although monitoring of liver function tests is recommended.[233]

These findings formed the basis of clinical approval for ivacaftor in CF patients with the G551D mutations, and this treatment has rapidly been deployed to children and adults with closely related mutations. Registry-based comparisons demonstrated a reduced rate of decline in FEV_1 in individuals treated with ivacaftor,[234] and multiple studies have demonstrated reduced rates of exacerbation coupled with an approximately 30% reduction in *Pseudomonas* infection rates (depending on the population) that have been durable over time.[32,33,235] Mechanistic evaluations have shown improved airway pH,[236] mucus clearance,[235] mucus plugging,[237,238] and radiographic parameters of mucosal thickening by CT imaging,[239] attributable to the improved CFTR function. More detailed microbiome analyses have shown the potential for rebound of bacterial counts in those that do not eradicate *Pseudomonas*,[35] and measures of airway inflammation have been conflicting. Long-term use has reduced the risk of bacterial acquisition, but initial attempts to augment bacterial eradication with ivacaftor use have not demonstrated efficacy, although further research into this concept is warranted given continued improvements in CFTR modulator efficacy and antimicrobial strategies.[240] The relatively large magnitude of weight gain observed with ivacaftor in CF patients with G551D-*CFTR* has been attributed to its beneficial effect on intestinal pH via bicarbonate secretion that improves enzyme function

and raises the possibility that mucosal integrity might also be improved throughout the gut.[235,241] Other potential avenues for exploration include the effect of CFTR modulation on other manifestations of CF, such as glucose metabolism, innate immunity and leukocyte function, osteopenia, pancreatic insufficiency, and gastrointestinal absorption, many of which may be directly tied to CFTR activity.[242] As ivacaftor approval has extended to younger and younger children with CF, presently age 1 year and older, evidence has emerged that preservation of pancreatic function may be possible[243] and suggests the potential for the rescue of other organs if instituted early in life, as demonstrated in a G551D ferret model.[244]

Ivacaftor also increased CFTR activity in other class III mutations beyond G551D in vitro,[245] and the beneficial effects of ivacaftor were also observed in patients with other non-G551D gating mutations. Patients observed a large increase in FEV_1 and a similar decrease in sweat chloride compared with that seen in patients with G551D, indicating a class effect.[246] Ivacaftor also activates other groups of *CFTR* mutations that allow low levels of partially active CFTR channels to reach the cell surface; such mutations include conductance mutations, mild processing mutations, or noncanonical splice variants (meaning abnormal splicing does not take place with absolute fidelity, as with canonical splice mutations, leaving some channels with the wild-type sequence).[247] The beneficial effect of ivacaftor on partially active missense mutations from these CFTR classes is generally proportionate to basal CFTR function, reflecting the ability of increased gating to compensate in part for reduced surface expression or conductance.[217] In contrast, ivacaftor monotherapy had no meaningful effect in CF patients homozygous for F508del *CFTR*, establishing that CFTR potentiation alone is not effective without concomitant administration of a corrector molecule to bring F508del CFTR to the cell surface.[248] In sum, CFTR potentiator monotherapy can benefit approximately 10–15% of the CF population, noting this is often supplanted by dual corrector-potentiator therapy when a patient also expresses F508del.

Cystic Fibrosis Transmembrane Conductance Regulator Correctors. Significant efforts toward the goal of correcting the folding of F508del CFTR, thus restoring ion channel activity to the misfolded protein, have come to fruition, potentially transforming outcomes and rivaling the benchmark set by ivacaftor in G551D patients. With the use of multiagent corrector potentiator therapy, rescue of F508del CFTR function can be achieved efficiently, making highly effective CFTR corrector therapy applicable to nearly 90% of the population, as defined by genetics.[249] Early attempts included 4-phenyl butyrate to alter protein processing chaperones,[250,251] curcumin, and 8-cyclopentyl-1, 3-dipropylxanthine, which did not successfully translate from in vitro studies to clinical results.[252–254] More recent efforts have resulted from high-throughput library screens for chloride channel function following incubation of test compounds with F508del-expressing cells.[208,210,255] Pharmacologic activity of correctors includes improved processing and trafficking of CFTR and may also affect F508del CFTR half-life in the plasma membrane through altered surface recycling attributed to features of the cellular processing machinery or reduced endocytic trafficking, depending on their underlying mechanism.[256] The correctors now in clinical use, lumacaftor and tezacaftor, have been shown to interact with CFTR directly and may offer greater specificity than agents that alter general aspects of cell folding or cellular quality control.[257,258] Success toward correction of F508del CFTR in patients was first seen during initial phase II testing of lumacaftor (formerly VX-809).[259] Although results established that improved function of F508del CFTR in patients was achievable by a systemically delivered small molecule, the degree of CFTR rescue was insufficient to confer clinical improvement. Because F508del CFTR also exhibits abnormal channel gating, in addition to aberrant cellular processing, an approach to address insufficient activity is to coadminister a CFTR potentiator with a CFTR corrector.[257] Following successful phase II testing,[260] lumacaftor-ivacaftor therapy was shown to be efficacious in individuals homozygous for F508del in two large randomized controlled studies; however, the magnitude of benefit was modest (≈3% improvement in FEV_1 and ≈30% reduction in exacerbations) compared with prior experience with ivacaftor.[261] Long-term studies showed that the improved rates of exacerbation were sustained, and the reduced rate of lung function[262] decline and efficacy has been duplicated in younger patients.[263] Lumacaftor-ivacaftor was also associated with chest tightness upon initiation, a finding more common in individuals with severe pulmonary dysfunction, and lumacaftor induced drug-drug interactions involving CYP metabolism, including the induction of ivacaftor metabolism.[264] An alternative corrector, tezacaftor (formerly VX-661), which has a similar cellular mechanism as lumacaftor but more advantageous pharmacologic properties, resulted in similar efficacy as lumacaftor-ivacaftor (4% FEV_1 improvement), but did not induce chest tightness or induce the drug metabolism of ivacaftor.[265] Further, tezacaftor-ivacaftor was efficacious in people with CF who are complex heterozygotes for F508del CFTR and an array of CFTR mutations that are partially functional and responsive to ivacaftor in vitro; in these individuals, the magnitude of benefit was approximately 7% predicted FEV_1, reflective of both correction of the F508del mutation and potentiation of the residual functional allele.[217] Neither lumacaftor-ivacaftor nor tezacaftor-ivacaftor benefited CF patients heterozygous for F508del *CFTR* and a minimal function allele that does not respond to ivacaftor, providing evidence of a gene-dose effect but also illustrating the need to address this sizable population.[266]

Despite the success of corrector-potentiator therapy, the activity of correctors is inherently less efficient than potentiators for CFTR gating mutations, likely because F508del and trafficking is a multistep process, limiting the potential of any single pharmacologic intervention. Additive or synergistic rescue of F508del CFTR using more than one corrector with distinct mechanisms of action on the cellular level could potentially overcome this limitation, leading to efforts to advance multiagent corrector therapy, to be combined with CFTR potentiators.[267] The next-generation correctors, elexacaftor and other related agents, were discovered via high-throughput screening programs conducted in the presence of tezacaftor.[268,269] When used in combination, elexacaftor-tezacaftor-ivacaftor delivered pronounced efficacy in vitro, meeting or exceeding levels observed with

ivacaftor in gating mutations, including in cells derived from individuals with only a single responsive F508del allele. Initial clinical results matched this pronounced benefit in patients heterozygous for F508del and a minimal function allele in comparison to placebo and in patients homozygous for F508del in comparison to tezacaftor-ivacaftor.[268] In confirmatory testing, results were recapitulated, with patients heterozygous for F508del and a minimal function allele exhibiting an approximately 14% improvement in FEV_1, a 50% reduction in exacerbations, and sweat chloride changes that were greater than 50 mmol/L.[270] Patients homozygous for F508del experienced a 10% additional improvement in FEV_1 over tezacaftor-ivacaftor comparator therapy.[271] Overall, prior experience guided by ivacaftor use in patients with gating mutations suggests highly effective CFTR modulator therapy is likely to be transformative and could substantially alter the progression of disease if initiated prior to substantial lung dysfunction. Longer-term evaluation studies are in progress, as are efforts to examine efficacy in patients younger than 12 years.

Presently, multiple other corrector-potentiator regimens are also in development with potentially unique pharmacologic features that could be advantageous. Successful further development could set the stage for comparator studies in the future or attempts to optimize CFTR modulator therapy at the individual level using cell-based assays or other techniques. There are also pronounced efforts to understand how highly effective CFTR modulator therapy could be brought to bear on rare mutations that may be susceptible to improved activity with various correctors and potentiators. Given that exceedingly rare mutations make up a disproportionately large number of patients in whom CFTR modulator therapy is not yet proven, alternative approaches beyond routine clinical trials will be needed to foster availability of effective modulator therapy to this group of patients.[272]

Translational Readthrough. Readthrough of *premature termination codons* (PTCs) represents a potential approach to address CF caused by nonsense mutations, which could also be applicable to many other genetic diseases. The approach was identified when certain aminoglycoside antibiotics were found to interact with the eukaryotic rRNA within the ribosomal subunits.[273] Through this interaction, the fidelity of eukaryotic translation can be altered by interrupting the normal proofreading function of the ribosome.[274–280] Insertion of a near cognate amino acid at a PTC allows protein translation to continue normally.[275] Specificity is conferred by greater termination codon fidelity at the authentic (3′) end of mRNA and has been established in vitro by demonstrating that there is no detectable elongation beyond native termination codons.[281–284] This has subsequently been investigated as a potential approach to a number of relatively common genetic diseases aside from CF in which premature termination codons are relatively prevalent, including Duchenne muscular dystrophy,[285–287] Hurler syndrome,[1,288,289] ceroid lipofuscinosis,[290] nephropathic cystinosis,[291] and expression of mutated p53.[292]

Proof of concept experiments with aminoglycosides established that PTCs within *CFTR* in human subjects can be suppressed, resulting in the synthesis of full-length, functional CFTR protein.[281–284,293] The approach has also demonstrated success in mouse models of CF.[294,295] Following two small pilot trials indicating restoration of chloride secretion in CF subjects harboring PTCs,[284,284] a double-blind, placebo-controlled trial showed correction of nasal ion transport specifically in subjects with nonsense mutations following topical administration of gentamicin and, as expected, not in CF controls homozygous for F508del.[283] A trial examining systemic gentamicin in seven French subjects with Y122X *CFTR*, a mutation highly susceptible to readthrough therapy, also indicated rescue of CFTR activity in the airway and sweat duct.[181] Not all aminoglycoside trials in CF have demonstrated success, suggesting variable levels of protein correction.[296] Regardless, due to the known toxicity and poor bioavailability of aminoglycosides, more efficacious agents that avoid undesirable properties of aminoglycosides will be needed for the long-term genetic treatment of CF. One promising approach uses medicinal chemistry optimization to identify the antimicrobial, toxic, and readthrough effects of aminoglycoside scaffolds, a strategy demonstrating initial success using in vitro reporters of efficacy and toxicity,[297] and cell- and animal-based models of CFTR rescue.[298] Addition of CFTR correctors and potentiators have the potential to augment function further by activating the processing and function of CFTR readthrough products, which include missense mutations from near-cognate amino acid insertion.[299,300]

Other attempts to address nonsense mutations include novel compounds without the disadvantages of aminoglycosides, and efforts remain ongoing in this regard. One such molecule, ataluren (formerly PTC124), induced translational readthrough in experimental systems.[301,302] Although the agent is available for the treatment of Duchenne muscular dystrophy, clinical development ultimately failed for people with CF[303] after mixed results in preceding clinical trials[220,293,304,305] that raised questions about insufficient efficacy.[306,307] The effects of readthrough agents are likely substantially affected by low levels of steady-state *CFTR* mRNA due to nonsense-mediated decay. The level of nonsense-mediated decay has been associated with readthrough efficacy and may need to be addressed to achieve effective CFTR rescue.[220,308] Given new knowledge regarding the best models to identify and optimize CFTR drug candidates that has emerged since the identification of ataluren, it is possible that identification of new chemicals using alternate readthrough assays that incorporate the influence of nonsense-mediated decay might yield more efficacious compounds. Other strategies such as pseudouridinylation of the mRNA encoding nonsense mutations or gene editing the PTC sequence are in early development.[309]

Gene Therapy

Within years after discovery of the *CFTR* gene, initial enthusiasm for gene therapy was robust, but variable efficiency of vectors coupled with heterogeneous transgene expression and adverse effects from inflammation impeded progress in this area. Using NPD as an outcome, viral vectors demonstrated transgene delivery using adenovirus[310,311] and adeno-associated adenovirus,[312] but positive results have not been observed by all groups conducting studies of this type.[313] Improvements in Cl^- transport using lipid-based gene transfer vectors were initially limited to modest changes,[314–316] improvements in specific subgroups,[315–319]

or inconsistent CFTR expression[320–322] and therefore were not convincing. Depletion of immunogenic CpG motifs for plasmid delivery used during a large, long-term clinical trial by the UK Gene Therapy Consortium demonstrated safety and provided a roadmap for trials of this sort, but efficacy was again not convincing.[323] With the success of gene therapy in immune-privileged organs such as the eye, research into CF gene therapy has experienced renewed vigor, with the goal of a "one-time cure," especially for those not helped by CFTR modulator treatment. Use of the latest adeno-associated and hybrid lentiviral-based gene transfer is a major emphasis, but limitations including cargo size (noting *CFTR* is a large gene), durability of gene integration, and possible off-target effects remain challenging. Alternative approaches such as gene editing with CRISPR-Cas9 are also engendering considerable interest, although the efficiency of homology-directed repair of the target has been challenging thus far. All gene therapy approaches must navigate past the mucociliary barrier and must target specific cell types, such as basal progenitors, to induce sustained expression, unless repeat administration is envisioned.[324,325]

mRNA Replacement and Other Nucleotide Repair Strategies

Splicing mutation represents a relatively common minority of *CFTR* alleles seen in patients with CF. For example, one CF mutation is 3849+10kb C→T, which leads to inclusion of an 84-base pair cryptic exon in the mature mRNA.[326] This cryptic exon contains an in-frame nonsense codon, which leads to production of truncated nonfunctional proteins. Splicing machinery is heterogeneous both among patients and also among tissues within an individual, resulting in relatively heterogeneous expression of the disease. This forms the basis of examining usefulness of a CFTR potentiator in patients with relatively preserved CFTR expression due to alternatively spliced forms of CFTR and partially retained expression, and ivacaftor is now approved in the United States for the treatment of several noncanonical splice variants. The variation in splicing efficiency can also be exploited using antisense oligonucleotides to induce normal splicing by masking mutant splice sites.[309] Although this would require specific antisense oligonucleotides to be developed for each *CFTR* splice mutation, use of such technology has shown therapeutic efficacy in Duchenne muscular dystrophy.[327] Full-length RNA transduction is also being pursued for the treatment of genetic diseases and is being exploited in CF, with sequences optimized for translation efficiency. As with gene therapy, similar challenges with delivery of nucleotides and dependence on cell type will need to be addressed with these therapeutic strategies. To that end, editing the RNA sequence with nasal delivery showed promise using NPD as an outcome,[328] but it did not improve lung function following inhalation.[329]

RESPIRATORY THERAPIES

Physical Airway Clearance

The combination of cough augmented with chest vibration or percussion to loosen mucus represents a cornerstone of the daily care of CF to reduce airway obstruction and prevent CF exacerbations.[330] Daily clearance maneuvers, including chest physiotherapy by vibropercussion, hand-administered therapy, or the chest physiotherapy vest clearance systems, are considered standard of care.[331,332] Alternative airway clearance techniques include positive expiratory pressure, huff coughing, and the use of vibratory flutter valves.[332]

Exercise therapy can provide additional improvement in mucus clearance in concert with physical maneuvers.[333] Standardized, aerobic exercise programs targeting 70–85% of maximal heart rate have demonstrated benefits with regard to exercise tolerance but do not improve lung function. Similar results have been obtained in isometric exercise programs.[334] Supervised pulmonary rehabilitation in severe CF lung disease can be an important supportive modality (see also Chapter 139).

Airway Rehydration Therapy

Rehydration of the airway surface liquid to augment mucociliary clearance can be achieved with nebulized *hypertonic saline* (HTS), which causes a durable increase in mucociliary clearance in CF subjects.[181] A multicenter, randomized, placebo-controlled trial of HTS showed a modest improvement in pulmonary function and a 56% reduction in frequency of CF pulmonary exacerbation despite relatively poor compliance.[180] Evidence suggests that the effects of HTS are additive to rhDNase.[180,335,336] In infants too young for reliable spirometry, HTS improved infant pulmonary function tests ($FEV_{0.5}$) and lung clearance index, an effort-independent measure of pulmonary obstruction through inert gas washout, although it did not alter an already low rate of pulmonary exacerbations.[337] Confirmatory studies have established that lung clearance index improvements are reproducible and associated with other indicators of clinical benefit, such as weight gain.[82,338,339]

Because a minority of subjects develop bronchospasm following administration of HTS, inhaled β_2-agonist is generally recommended before HTS dosing; moreover, HTS should be used cautiously in those with severe pulmonary obstruction. Many patients exhibit excessive cough following HTS administration (a feature that limits use), although this will often decrease with repeated HTS use.[180] Lower concentrations (3%) can sometimes be used when excess cough or bronchospasm is a problem with the standard HTS (7%).

Airway treatments with the nonabsorbable sugar mannitol to hydrate the mucosal surface by generating an osmotic gradient represent an alternative to HTS. Following success in early-phase trials,[340] two large-scale clinical trials demonstrated reduced exacerbations and a small increase in lung function.[341,342] On the basis of this success, inhaled mannitol therapy is approved for use in some countries (including the United States in 2019), though intolerance of dry powder inhalation has been a barrier to substantial uptake. Other strategies to circumvent CFTR by inducing non–CFTR-dependent fluid secretion or inhibiting epithelial sodium channel–mediated fluid resorption remain an active area of research and clinical development.[343]

Dornase Alfa

Use of inhaled recombinant human dornase alfa, a pharmacologic treatment to improve the physical properties of mucus, has been shown beneficial in randomized, placebo-controlled trials among CF subjects and was among the first

CF-specific medicines to be approved for respiratory disease. Dornase alfa causes dissolution of excess DNA debris that accumulates due to bacterial infection, mucus stasis, and the large influx of neutrophils into the CF airway lumen. The drug augments pulmonary function, diminishes frequency of pulmonary exacerbation, and enhances QOL.[179] Trials examining dornase alfa therapy in individuals with severe CF pulmonary disease (forced vital capacity < 40% predicted) also show benefit.[344] With regard to milder lung disease, dornase alfa stabilized inflammatory markers in bronchoalveolar lavage fluid of young children[345] and improved radiographic measures of gas trapping,[346] suggesting the potential to benefit even when mucus production is not clearly evident. The treatment also improved ventilation inhomogeneity as determined by the lung clearance index in pediatric patients with minimal decrements in spirometry.[347] Thus, dornase alfa therapy is recommended for CF patients in all ranges of disease severity.[348]

Inhaled Antibiotics

Refractory infection is a sine qua non of bronchiectasis, and aggressive antimicrobial therapy is a mainstay of chronic CF care. The inhaled route provides higher doses of antibiotics directly to the mucopurulent airways, and several treatment strategies have been shown to improve CF lung function and reduce pulmonary exacerbations. Intermittent use of chronic inhalational antibiotics is intended to target the airways while avoiding systemic toxicity and to limit emergence of bacterial resistance through continuous selection pressure. The first drug to be approved for this purpose was inhaled tobramycin, which has been shown to improve pulmonary function, reduce exacerbation rate, and increase weight gain compared with placebo when administered twice daily during alternate 4-week periods.[82,349] Concerns about daily burden of therapy and patient nonadherence have led to the development of a dry powder formulation, which was shown to be noninferior to conventional nebulized tobramycin and improved patient satisfaction when tolerated.[182]

The inhaled monobactam aztreonam has also been developed for chronic use in CF. Initial studies demonstrated improved QOL and a prolonged gap between exacerbations.[350,351] In a large 6-month trial involving CF patients older than 6 years who previously used inhaled tobramycin, improved FEV_1 and reduced exacerbations were observed with inhaled aztreonam given every other month[352] compared with inhaled tobramycin every other month. A similar study in subjects with milder lung function abnormalities demonstrated more modest improvements in FEV_1 and QOL.[353] Inhaled colistin is often used as an alternative antipseudomonal agent in subjects with resistant strains, although it is not approved by the U.S. Food and Drug Administration for this purpose and is associated with side effects such as bronchospasm.[82,354,355]

It is not yet clear which antimicrobial agent is best for individual patients, and the choice of agent is generally driven by the dominant pathogen, antimicrobial resistance patterns, and patient preference. Nevertheless, antimicrobial resistance profiles do not predict clinical response effectively. The difficulty in predicting response is probably due to intrinsic resistance conferred by biofilms and intermicrobial interactions that alter susceptibility in the lung but are not modeled in routine clinical bacterial culture methods, a limitation that poses substantial clinical challenges in antibiotic selection.[356] Continuous alternating 28-day cycles of inhaled tobramycin and aztreonam for individuals who experience increased infection or symptoms during off-cycle are frequently used and may be beneficial.[357] A number of other inhaled therapies are in development, and treatments that target dissolution of biofilms are of particular interest.

Bacterial Eradication

The primary morbidity and mortality in CF are attributable to obstructive respiratory disease associated with chronic endobronchial infection by opportunistic bacteria. *P. aeruginosa* infection is clearly associated with decline in respiratory function, and early acquisition of *Pseudomonas* is associated with increased morbidity and mortality.[27,358–363] Consequently, infection and eradication via treatment with anti-pseudomonal antibiotics has been sought as a means to sustain lung function and delay mortality.[44,364] Early bacterial isolates from CF lungs are present at lower density, are generally nonmucoid, and display favorable microbial resistance profiles, reflecting a potential window of opportunity for treatment and eradication.[365,366] As noted earlier, *Pseudomonas* infection becomes more prevalent with increasing age; positive respiratory tract cultures are reported in up to 30% of infants, 30–40% of children aged 2 to 10 years, and 60–80% of adolescents and adults.[367] Newborn screening for CF allows earlier identification of *P. aeruginosa* infection in children prior to onset of significant lung disease that limits efficacy of treatment. Following detection of *P. aeruginosa* in asymptomatic children, standard of care includes clinical interventions to eradicate the organism. Antimicrobial regimens differ depending on the clinical setting but, for individuals detected by surveillance, 28-day treatment periods with inhaled antibiotics are sufficient to achieve reasonable eradication rates.[368] More aggressive strategies should be reserved for extenuating circumstances, such as with clinical deterioration or advanced disease. Although several studies have validated efficacy of various treatment regimens, no single approach has demonstrated clear superiority.[369] Suppression and eradication of *Staphylococcus* species, including MRSA, is possible and is possibly associated with clinical benefit.[370,371] Of note, prophylaxis for *S. aureus* has led to increased *Pseudomonas* infection, warranting caution.[372]

Macrolide Therapy. Although macrolide antibiotics do not exhibit significant antipseudomonal properties, the utility of these agents in diffuse panbronchiolitis, a rare disease that resembles CF (including chronic infection with *P. aeruginosa*), led to therapeutic trials in CF patients.[373–376] In a multicenter, randomized, placebo-controlled trial, alternating-day oral azithromycin demonstrated improved pulmonary function accompanied by a large reduction in pulmonary exacerbations.[377] Similar results were seen in a Canadian study using clarithromycin.[378] Beneficial effects of azithromycin have also been observed in CF patients not chronically infected with *Pseudomonas* (presumably due to less well-described anti-inflammatory effects), suggesting a contributory mechanism independent of antimicrobial properties. One large clinical trial demonstrated reduced rates of exacerbation,[379] although

an FEV_1 benefit was not observed. On the basis of current evidence, present guidelines assign a lower priority for chronic azithromycin in noninfected patients.[185] However, the use of azithromycin in young children has become more common because several trials have demonstrated safety and efficacy in decreasing pulmonary exacerbations and improving health metrics such as nutritional health. The rising incidence of NTM infections raises concern about long-term use of azithromycin due to the potential for inducible macrolide resistance. Some data suggested increased risk of promoting infection by NTM mycobacteria,[82] although this has been refuted by epidemiologic studies.[380] Nevertheless, annual screening for NTM is recommended and is particularly important among azithromycin-treated patients. Azithromycin use may inhibit the efficacy of inhaled tobramycin, a finding under evaluation in prospective clinical studies.[381]

Anti-inflammatory Therapy

Intense neutrophilic inflammation is characteristic of CF and remains a therapeutic target that has not been fully exploited.[69,382–384] Early trials utilizing chronic, alternate-day systemic corticosteroids showed a beneficial effect of prednisone (1 mg/kg) on CF lung function, but use remains limited by steroid toxicities, and chronic corticosteroid therapy is not generally recommended.[385–387] Inhaled steroids have frequently been studied in small trials. In some studies, reduced airway reactivity has been observed, but sustained effects on lung function have not been shown.[388,389] Use of oral steroids in CF is generally limited to individuals with an asthmatic phenotype. Concerns include the potential for bone demineralization, adrenal suppression, and growth retardation in pediatric patients.

A number of other anti-inflammatory molecules have been studied in CF, although identifying an appropriate therapeutic window that allows blockade of excessive inflammation without causing increased susceptibility to infection has been difficult. High-dose ibuprofen, a nonsteroidal anti-inflammatory drug, has been shown to diminish the rate of pulmonary function decline, but beneficial effects appear greatest in young children.[390] Other studies have confirmed these findings.[187,391] Despite this evidence, nonsteroidal anti-inflammatory drug therapy is not widely utilized in the United States due to concerns of chronic toxicities, particularly in older individuals, and the need for pharmacokinetic monitoring to achieve adequate serum levels.[392] For example, inadequate levels have been associated with paradoxical proinflammatory effects, leading to increased neutrophil migration.[187,393]

Attempts to extend the observed benefits of anti-inflammatory therapy to other eicosanoid-active agents (e.g., leukotriene inhibitors) have indicated variable results, including studies showing increased pulmonary complications with a nonselective leukotriene B4 antagonist.[394,395] Synthetic cannabinoids and more specific leukotriene modifiers are presently in development to improve efficacy. Along similar lines, initial attempts to block protease activity with inhaled antitrypsin were not effective,[396] although other inhaled neutrophil elastase inhibitors are under consideration. Other agents such as 3-hydroxy-3-methylglutaryl coenzyme reductase inhibitors, hydroxychloroquine, and methotrexate have not demonstrated convincing benefit, illustrating the challenge of successfully targeting this mechanism, which may be suited to young patients with less-established disease and fewer activated inflammatory pathways. Development remains challenging given limitations in anti-inflammatory biomarkers to guide early advancement, and given the large number of subjects needed to demonstrate reductions in exacerbations compared to improvements in lung function.[397]

OTHER SUPPORTIVE CARE

Pulmonary Exacerbations

Exacerbations of CF pulmonary disease are characterized by increased cough and sputum production, respiratory distress, diminished exercise tolerance, weight loss, decreased spirometry, worsened hypoxemia, or development of a major pulmonary complication such as hemoptysis.[398–401] Treatment includes intensified airway clearance measures and systemic antimicrobial therapy generally directed against the most recently acquired pathogens. Both inpatient and outpatient treatment are utilized; factors important to consider during management include severity of disease, baseline lung function, microbial organisms and resistance pattern, presence of additional complications, and the ability to adhere to an outpatient regimen. Acute pulmonary exacerbation is the most common indication for hospitalization in CF and is warranted when episodes are severe, refractory to outpatient care, or not suited to home therapy for psychosocial reasons. Hospitalization facilitates controlled administration of intravenous antibiotics to address exacerbating infections and provides a setting conducive to sustained intensification of chest physiotherapy. Although the historical standard for pulmonary exacerbations is hospital-based treatment, outpatient management that includes use of parenteral antimicrobials and mucus clearance procedures may achieve equivalent outcomes in appropriately selected patients.[402] In general, the primary goal in this setting is to improve clinical symptoms and to return pulmonary function to baseline. In some patients, however, lung function does not return to previous levels despite clinical improvement and can decline further in the days to weeks following intervention.[403–405] A severe decrement in spirometry from baseline at the onset of pulmonary exacerbation is a major risk factor for sustained loss of lung function, suggesting the need for early and aggressive treatment.[404–406]

Antibiotic therapy should be broad based due to the polymicrobial nature of CF lung disease and is typically selected on the basis of respiratory tract culture and susceptibility results. Notwithstanding this recommendation, in vitro sensitivity profiles are poor predictors of clinical response, indicating significant limitations to the general strategy.[406] Treatment of *Pseudomonas* is the first consideration, and two mechanistically distinct antibiotics should be administered to maximize efficacy. In some clinical scenarios where oral therapy is used, fluoroquinolones as single agents are a mainstay but can be associated with the risk of promoting bacterial resistance.[407] Aminoglycosides have optimal antimicrobial activity as intravenous

anti-*Pseudomonas* drugs but require careful monitoring to optimize therapy. Traditional dosing of aminoglycosides two to three times a day has shifted in favor of once-daily dosing.[408,409] Aminoglycoside schedules in the range of 8 to 12 mg/kg once daily achieve higher peak concentrations (20 to 30 μg/mL) that potentiate bactericidal effect and limit toxicity by extending the duration of low, near-trough drug concentrations, which approach undetectable levels in the setting of normal renal function.[100,410] Patients should be monitored during aminoglycoside therapy for emergence of nephrotoxicity and ototoxicity. Aminoglycosides are usually paired with a β-lactam to maximize efficacy. A third antibiotic may also be useful for controlling MRSA or other atypical organisms. Although there is no consensus regarding duration of therapy, a clinical response with respect to symptoms or pulmonary function is usually apparent 4 to 7 days after initiating treatment, depending on severity of the initial decrement and degree of underlying lung disease. Ten to 14 days appear adequate to achieve maximal improvement in lung function and sustained health in most cases.[411,412] With refractory infection, treatment for 3 weeks or more is sometimes warranted but may not be successful. Certain studies have demonstrated that the FEV_1 reaches a plateau following 10 days of inpatient treatment, raising a question concerning the benefit (and risk) of longer hospital and parenteral antibiotic courses.[413] Each treatment schedule therefore requires careful and somewhat individualized assessment by the clinician. Shorter treatments may improve QOL and compliance, limit drug-associated morbidities, and be less costly. However, prolonged regimens may be necessary to clear an infection, achieve sustained benefit, and preclude early recurrence of exacerbation. Prospective comparator studies evaluating treatment duration are currently underway.[414] Extended courses of antibiotic therapy should also include longitudinal respiratory tract cultures for bacterial and fungal organisms because antibiotic sensitivities can shift.[415] For patients requiring frequent or long-term home antibiotic therapy, subcutaneous central intravenous catheters can provide stable intravenous access to facilitate treatment. Chronic port access carries a risk of catheter-associated infections and thrombosis.[416] For this reason, exogenous estrogen should be avoided in female patients with central venous catheters if possible.

TREATMENT OF LUNG COMPLICATIONS

Treatments directed to control airway infection, limit inflammation, and optimize airway clearance represent the cornerstone of therapy in both early and advanced CF lung disease. Hypoxemic respiratory insufficiency should be recognized and treated with supplemental oxygen. Low-flow oxygen is effective at relieving nocturnal, exertional, and resting hypoxemia and does not usually cause significant hypercapnia.[417]

Pulmonary hypertension (PH) and increased mortality are strongly associated with the development of nocturnal or resting hypoxemia.[418] The development of PH is correlated with declining lung function and the development of respiratory failure; however, direct evidence that it increases the risk of mortality is lacking.[419] Treatment for PH, including diuretics, inotropic agents, and theophylline, provides little to no benefit in CF and is rarely used; however, sildenafil is associated with improved exercise capacity.[420,421] Right ventricular dysfunction is an end-stage finding in advanced disease with few viable treatment options beyond those that stabilize lung disease and symptomatically treat pulmonary hypertension.[422] Thus, advancing PH is largely an indication for referral for lung transplantation (see also Chapter 85).

Acute respiratory failure due to reversible insults can be managed by either noninvasive measures or invasive ventilatory support.[145,423,424] Although mortality associated with mechanical ventilation in CF is high, the intervention can be beneficial. It has been reported, for example, that one-third of CF patients with advanced lung disease survive events requiring intubation and ventilatory support.[146] Mechanical ventilation and extracorporeal membrane oxygenation can also be used as a bridge to lung transplant at appropriate centers[146,424–426] (see also Chapter 138).

Atelectasis in CF is managed by escalating the intensity and frequency of airway clearance, together with other therapies directed towards addressing pulmonary exacerbations. Systemic or inhaled corticosteroids may be helpful in the presence of asthma, ABPA, or significant airway inflammation refractory to antimicrobial therapy. There is little evidence that bronchoscopy and lavage are effective in treating atelectasis. However, bronchoscopic evaluation of atelectasis and treatment of mucoid impaction in association with endobronchial aspergillosis and ABPA have been described.[427,428]

ABPA is a common complication of CF, seen in about 10% of the CF population annually. ABPA typically responds to standard doses of systemic corticosteroids (1 mg/kg).[124] Inhaled corticosteroids,[429] paired with suppressive oral antifungal therapy,[430] and more recently, omalizumab[431] (an anti-IgE monoclonal therapy), has been shown to limit the systemic steroid burden in cases of steroid refractoriness or steroid intolerance.

Pneumothorax, when small and minimally symptomatic, may be managed by observation with the expectation of spontaneous resolution. Pneumothoraces of greater volume (e.g., >20%) or that compromise ventilation or physiologic stability require chest tube re-expansion immediately.[432] Recurrent pneumothoraces are common in advanced lung disease and are associated with higher mortality. Patients with nonexpandable lung after pneumothorax who experience significant morbidity may benefit from video-assisted thoracic surgery to take down adhesions followed by chemical and/or mechanical pleurodesis.[433] Prior pleurodesis is not considered a contraindication to lung transplantation, although it increases surgical complexity.[433]

Major hemoptysis is treated with antibiotics, limitation of aggressive physiotherapy, and inhaled respiratory health medications, although reinstitution of postural drainage therapy has become increasingly accepted in this setting. Supplemental vitamin K should be given if the prothrombin time is prolonged due to malabsorption. Clot stabilization with intravenous or inhaled tranexamic acid and systemic blood pressure reduction with beta-blockade may have some clinical utility but are not indicated as first-line therapies.[129,434] Massive hemoptysis may resolve with conservative therapy, but bronchial artery embolization provides

more definitive clinical control and should be considered in recurrent or refractory cases of submassive bleeding.[130] Recurrent submassive or massive hemoptysis episodes should prompt consideration for lung transplant referral.

Treatment of Gastrointestinal Complications

Meconium ileus often can be relieved with enemas refluxing water-soluble radiographic contrast into the terminal ileum under fluoroscopy.[131] If this is not successful, or there is concern for intestinal perforation due to severity of involvement, surgical consultation should be sought. The distal intestinal obstruction syndrome is typically treated with large volume-balanced electrolyte solutions containing osmotic laxatives (polyethylene glycol) and mucolytics (N-acetylcysteine).[435] Contrast enemas that reach the terminal ileum can complement this therapy. In the setting of significant abdominal distension or intractable emesis, bowel obstruction or bilious/fecal emesis may require surgical intervention.[436] Rectal prolapse can be voluntarily reduced in patients experienced with techniques involving the abdominal, perineal, and gluteal muscles. Young children often require manual reduction by gentle pressure in the knee-chest position.[436] Pancreatic enzyme replacement therapy, improved nutritional status, and control of lung disease usually prevent recurrence. Surgical stabilization of the rectum is required if prolapse is chronic and refractory to medical management.

Liver disease is thought to result from abnormal bile secretion due to CFTR dysfunction. Ursodeoxycholic acid (ursodiol) is used to treat primary biliary cirrhosis.[155] Although its impact on CF liver disease is unclear, several studies have demonstrated that ursodiol improves or stabilizes liver function tests. Long-term effect on CF hepatocellular injury, however, remains unknown.[437] Thresholds for initiating therapy and clinical outcomes are under investigation, although current guidelines recommend aggressive nutritional support and consideration of ursodiol treatment.[438] Bleeding esophageal varices that complicate cirrhosis can often be managed with banding or sclerotherapy. Portal hypertension and severe, refractory variceal bleeding have been treated successfully with portosystemic shunt procedures.[439] CF hepatic failure and ascites are treated in standard fashion. Liver transplantation is successful in CF, with survival rates at 1 and 5 years reported at greater than 80%.[440] CFTR modulator therapy may be associated with elevated hepatic enzymes, but this is also seen sporadically in CF, often in association with treatment for pulmonary exacerbations.[264]

Hyperglycemia can complicate CF at any age but is generally first encountered during the second and third decades of life.[441,442] Ketoacidosis is not typically a feature of CF-related diabetes mellitus. Treatment of elevated blood glucose in CF has become more aggressive as patient longevity has improved. This is in part due to appreciation of complications from diabetes among older adults with CF and increased recognition concerning the impact of CF-related diabetes mellitus on pulmonary disease progression and its association with declining lung function.[443] Vascular disease affecting the retina and kidneys has been documented in CF patients who have had prolonged hyperglycemia.[443,444] Intensive screening and management regimens have been recommended for control of blood sugar, including annual oral glucose tolerance testing for previously unaffected patients.[442,445–447] Insulin therapy is the mainstay of treatment, and the anabolic effects of insulin may be beneficial in this setting.[442,446–448] Increasing use of continuous glucose monitoring improves glucose control and clinical outcomes[449] (see also Chapter 128).

Surgical Therapy

Endoscopic sinus surgery and nasal polypectomy to relieve obstruction are the most common surgical procedures conducted in the CF patient population.[448,450,451] Although most individuals with CF experience improvement postoperatively, recurrence is common and often requires repetitive procedures.[452] The incidence of nasal polyposis tends to wane in adulthood.[450] More aggressive sinus surgery to marsupialize the sinus cavity may also be beneficial.[453] Other frequently encountered procedures include cholecystectomy to treat symptomatic gallstones.[452] Pulmonary resection has historically been considered when severe focal lung disease leads to clinical instability and accelerated decline in lung function. Although surgical therapy has been reported to stabilize the clinical course and reduce exacerbation frequency, such treatment has become rare due to improved therapeutic strategies and overall health of individuals with CF.[167,454–457] Patients under consideration for partial pneumonectomy must be carefully selected because short-term loss of lung function postoperatively is expected.[458] Massive hemoptysis refractory to standard interventional therapy may require lobectomy.

Lung Transplantation

Sequential double-lung transplantation is an accepted therapy for respiratory failure secondary to CF.[459] More than 3000 lung transplants have been performed for CF around the world, and the rate is increasing. The 5-year survival is just above 50% and improving, which compares favorably to survival following pulmonary transplantation performed in other lung diseases.[460] Given the limited survival and complexity of treatments required, consideration of lung transplantation requires careful psychological and social evaluation. Patients should be referred when death is expected over the ensuing 2 to 3 years.[106] Recent consensus guidelines emphasize early patient discussion and referral, especially with complicating factors that include patient size and gender, CF medical complications, and psychosocial barriers.[461] Following successful transplantation, CF patients may experience dramatically improved respiratory status and QOL, but significant medical treatment burden remains (see also Chapter 140).

Nutrition

Improved nutritional status in patients with CF is associated with better long-term clinical outcomes.[456] Individuals with the disease have increased caloric requirements attributable to intestinal malabsorption, increased work of breathing, and factors associated with infection and/or inflammation. Dietary recommendations include high caloric intake (20–50% greater than standard), high-protein diet with a moderate amount of dietary fat (35–45% of caloric intake), and limited processed carbohydrates.[462] Patients with a body mass index below the 25th percentile are typically considered to be in nutritional failure and warrant aggressive

dietary counseling and supplementation. If nutritional adjustments are unsuccessful, consideration of appetite stimulants, gastrostomy tube feedings, or other approaches may be warranted. This is in part because supplementation with elemental dietary preparations by mouth is unlikely to be sustained over an extended period of time.

Almost all patients with CF require pancreatic enzyme replacement therapy due to cystic destruction of the exocrine pancreas early in life. The enzymes are supplied as capsules containing acid-resistant enteric-coated granules, with doses of lipase from 3,000 to 40,000 units. The replacement therapy is typically administered based on patient weight and adjusted to ameliorate symptoms of malabsorption such as abdominal cramping, excessive flatulence, and fatty stools. Dose ranges should be limited to current guidelines (2500 lipase units/kg/meal; 10,000 lipase units/kg/day), because more intense drug schedules have been associated with fibrosing colonopathy.[463–466] Recombinant forms are in development, and enzyme replacement cartridges for nocturnal use can improve absorption of nocturnal feeding.[467] With earlier use of highly effective CFTR modulator therapy, pancreatic enzyme replacement may not be needed if pancreatic function can be preserved.[468]

A daily multivitamin is standard in CF care, and additional supplementation is dependent on clinical evaluation. Vitamins A and E are often adequately supplied by a standard (daily) multiple-vitamin preparation. Vitamin A deficiency is readily corrected by dietary supplementation. Symptomatic deficiency is rare and may result in increased intracranial pressure, xerophthalmia, and night blindness. Vitamin D deficiency presenting as rickets is rarely seen. That being said, patients with CF often have inadequate levels of vitamin D (<30 to 60 ng/mL) that can be refractory to high-dose supplementation. Bone demineralization is common, and association of inadequate vitamin D levels with poor health-related outcomes in other clinical scenarios has led to recommendations of aggressive supplementation. Vitamin E is deficient only in non-supplemented patients and rarely causes increased red blood cell destruction or neuroaxonal dystrophy.[469] Insufficient vitamin K may result in bleeding diathesis. Although clinically significant hemorrhagic problems manifest mostly in children, vitamin K deficiency in the setting of hemoptysis may present a significant challenge in older CF patients. Other vitamins and trace minerals, specifically zinc, may be deficient and require supplementation on an individualized patient basis.[470]

Psychosocial Factors

With the advent of newborn screening and with individuals with CF surviving into adulthood, psychosocial aspects of CF have broadened and continue to affect patients, families, and the community. Medical therapies offer significant benefit but can be limited by problems with psychosocial well-being, attitude, and ultimately adherence to treatment. Approaches to delivery of clinical care that promote a positive self-image and support the patient and/or family efforts to manage their own medical therapy while maximizing health-related QOL are likely to have substantial impact on outcomes. Partnering strategies between providers and patients to sustain daily care routines are recognized as a beneficial approach in CF.[471]

Providers with expertise in psychosocial support are invaluable to the CF care team.[463] Major depression and anxiety disorder is a common comorbidity as patients grow older and can interfere with good clinical outcomes. Aggressive monitoring and treatment of these aspects of CF are warranted and recommended annually for all patients with CF.[472] At present, no CF-specific medical treatments for major depression have been investigated.

Key Points

- Effective treatment and monitoring through a network of specialized *cystic fibrosis* (CF) care and research centers has led to improvement in morbidity and mortality among patients with CF.
- The diagnostic paradigms emphasize early detection by newborn screening and a high index of suspicion to recognize atypical cases later in life, which are generally caused by *cystic fibrosis transmembrane conductance regulator (CFTR)* alleles coding for partially active CFTR.
- Aggressive treatment of CF pulmonary exacerbations is required to delay progression and reduce complications of end-stage lung disease.
- Treatment strategies for chronic lung disease generally address downstream manifestations of CF pathophysiology. Such therapies include airway clearance techniques, hydration of airway surface liquid, mucolytics to enhance mucus clearance, antimicrobials, and chronic use of anti-inflammatory agents.
- The successful development and approval of ivacaftor for CF patients with the G551D *CFTR* mutation has provided a roadmap invigorating investigators working to develop novel modulators of CFTR function to correct the underlying defect caused by the most common *CFTR* alleles.
- Combination CFTR modulator therapy has been developed to treat lung disease in all patients with F508del CFTR (≈90% of the U.S. CF population as defined by genotypic prevalence). The most recent of these is a triple combination (elexacaftor/tezacaftor/ivacaftor).
- Ongoing efforts are aimed at various gene-based methods to cure all patients with CF.

Key Readings

Bell SC, Mall MA, Gutierrez H, et al. The future of cystic fibrosis care: a global perspective. *Lancet Respir Med.* 2020;8(1):65–124. Erratum: *Lancet Respir Med.* 2019;7(12):e40.

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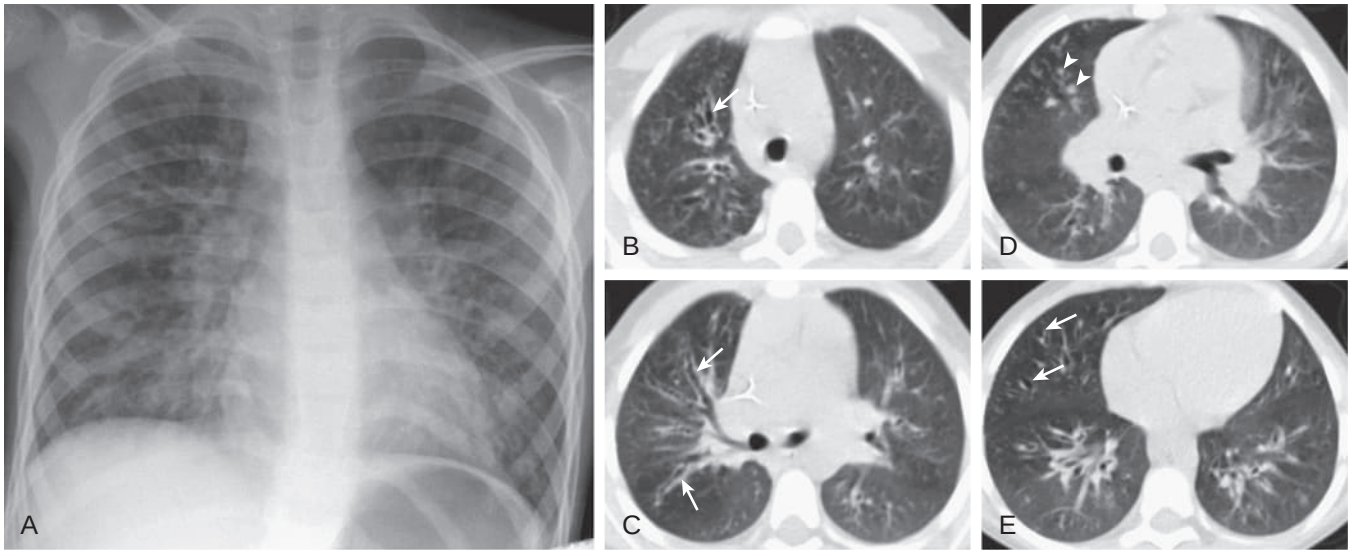
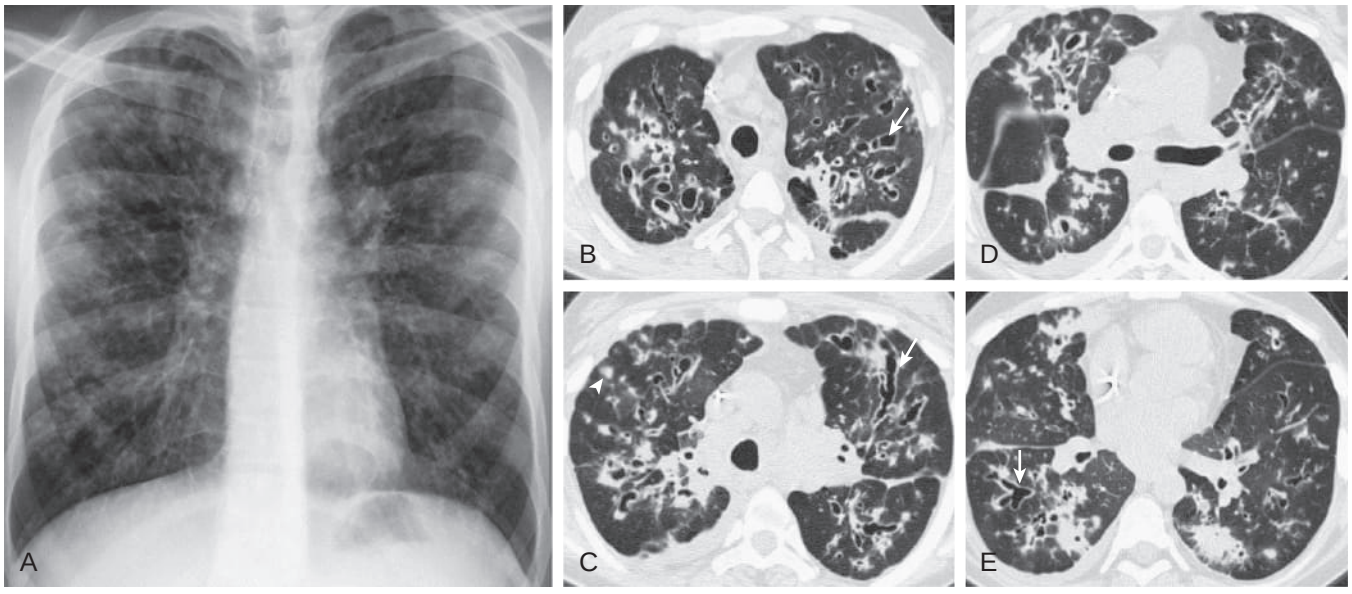
Complete reference list available at ExpertConsult.com.

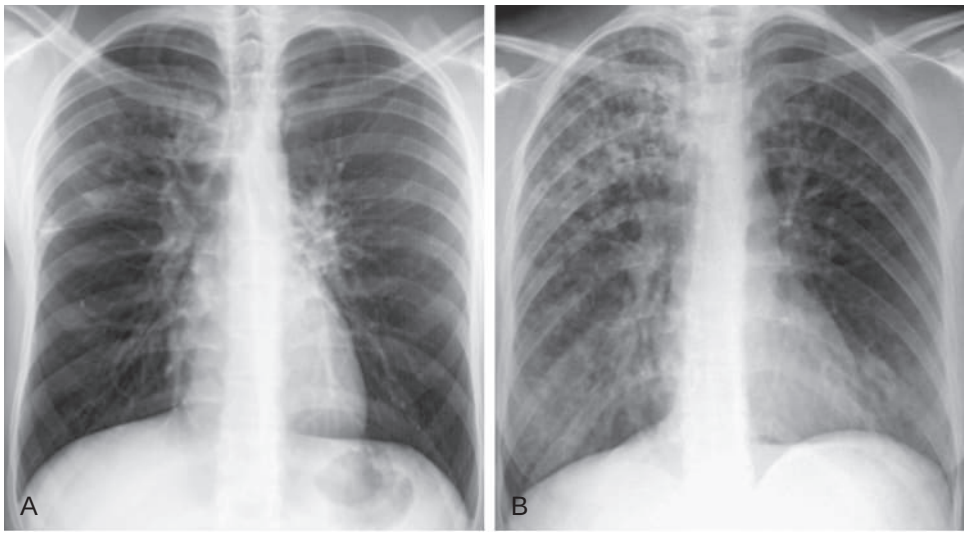
eFIGURE IMAGE GALLERY



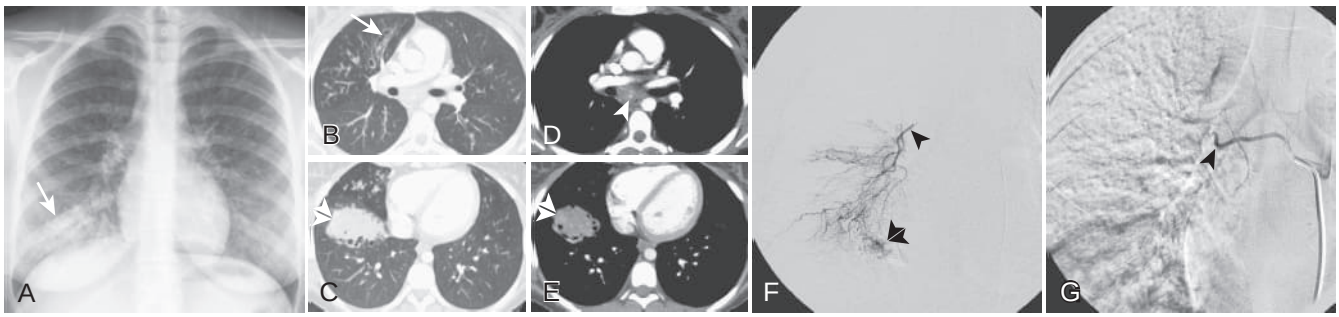
eFigure 68.1 Cystic fibrosis: chest radiographic and chest computed tomography findings. (A) Frontal chest radiograph in a 4-year-old patient with cystic fibrosis shows mildly increased lung volumes associated with central airway thickening and extensive linear opacity representing bronchiectasis and bronchial wall thickening. (B–E) Axial chest computed tomography displayed in lung windows shows extensive cylindrical bronchiectasis (*arrows*), as well as extensive bronchial wall thickening and small nodules (*arrowheads*), the latter reflecting distal bronchial and small airway impaction. (Courtesy Michael B. Gotway, MD.)



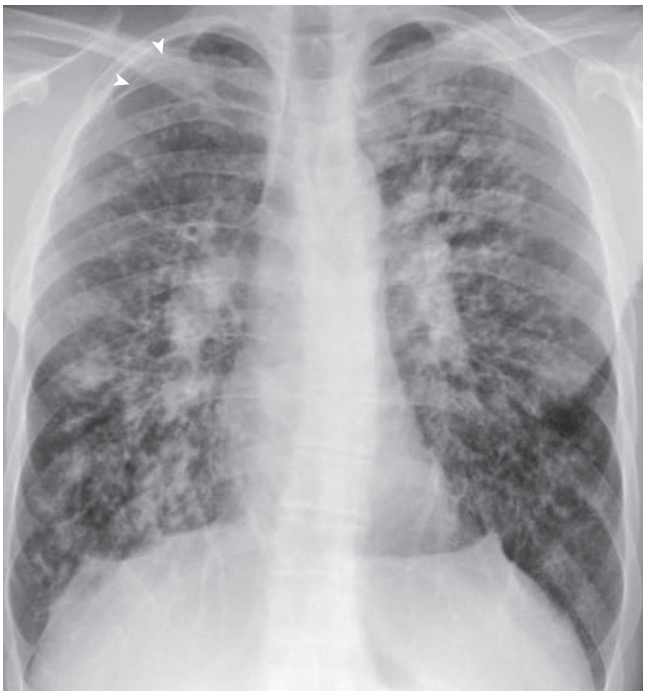
eFigure 68.2 *Cystic fibrosis* (CF): chest radiographic and chest computed tomography findings. (A) Frontal chest radiography in a young adult with CF shows large lung volumes associated with central airway thickening and extensive linear opacity representing bronchiectasis and bronchial wall thickening. (B–E) Axial chest computed tomography displayed in lung windows shows extensive cylindrical bronchiectasis (*arrows*), as well as extensive bronchial wall thickening and small nodules (*arrowhead*), the latter reflecting distal bronchial and small airway impaction. In comparison to eFig. 68.1 of a young child with CF, there is significantly worse disease in this older patient. (Courtesy Michael B. Gotway, MD.)



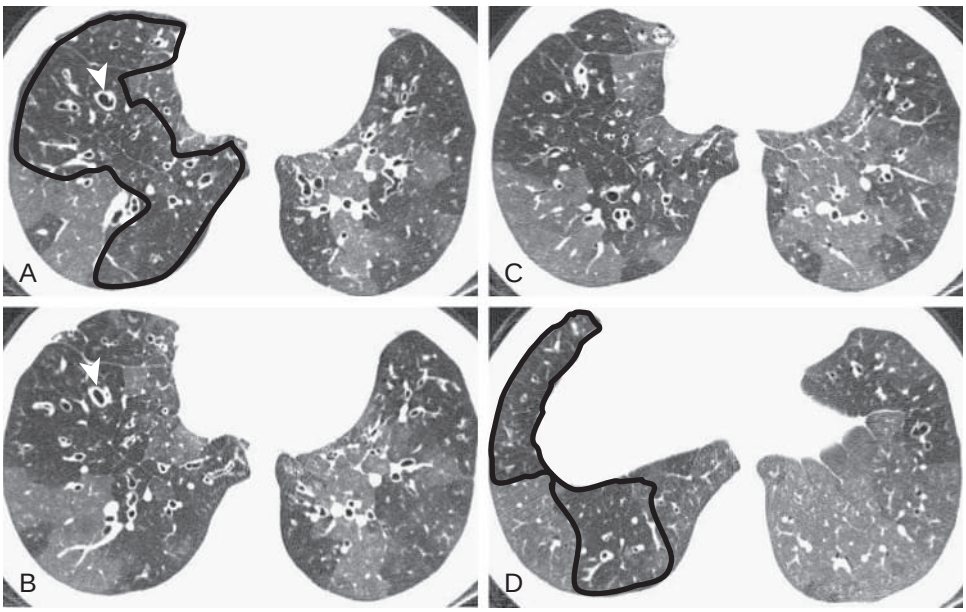
eFigure 68.3 Cystic fibrosis: predominant right upper lobe involvement. (A–B) Frontal chest radiograph in two separate patients with cystic fibrosis shows multifocal bronchial wall thickening and dilation, most pronounced in the right upper lobe. (Courtesy Michael B. Gotway, MD.)



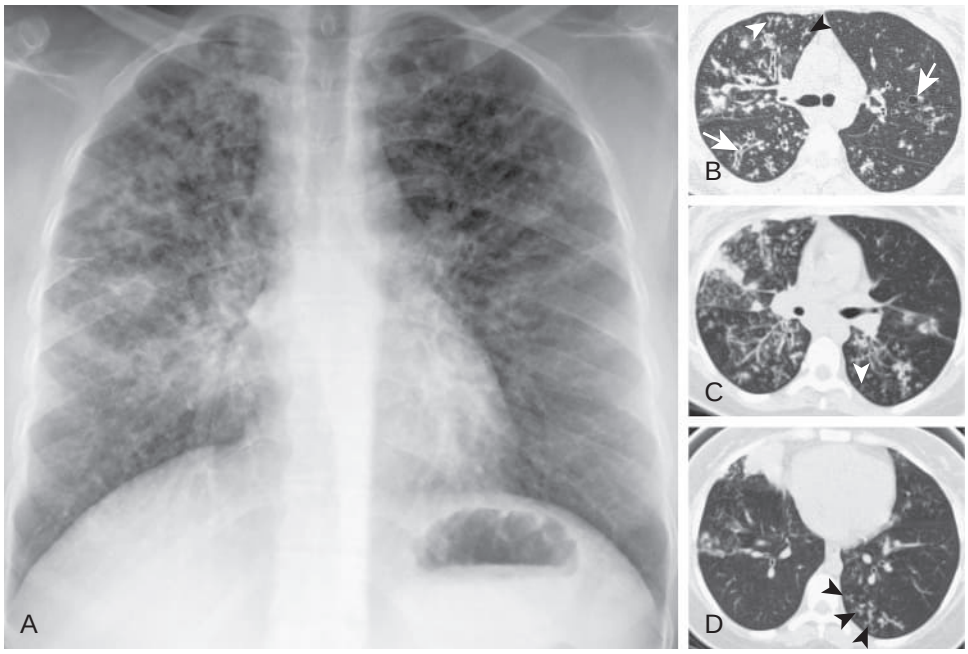
eFigure 68.4 *Cystic fibrosis* (CF) with hemoptysis treated with bronchial arterial embolization. (A) Frontal chest radiograph shows central perihilar predominant bronchial wall thickening and bronchiectasis. Focal consolidation (*arrow*) in the right lower lobe was new compared with prior studies. (B–E) Axial enhanced chest *computed tomography* (CT) displayed in lung (B–C) and soft tissue (D–E) windows shows multifocal bronchiectasis (*arrow*), typical of CF. Bronchial artery hypertrophy (*arrowhead,* D) is present, commonly observed in patients with chronic inflammatory airway diseases. (E) A mildly hyperattenuating mass (*double arrowheads*) is present in the anterior right lower lobe, correlating with the new finding at chest radiography and presumed to reflect hematoma in the setting of a patient with CF and new hemoptysis. (F–G) Precatheter (F) and postcathether (G) bronchial artery embolization images show an enlarged bronchial artery (*arrowhead*) associated with a prominent "vascular blush" (*double arrowhead*) in the region of the anterior right lower lobe mass at chest CT. The postembolization image (G) shows lack of opacification of the region of the vascular blush, and essentially no flow is now seen in the hypertrophied bronchial artery (*arrowhead*). (Courtesy Michael B. Gotway, MD.)



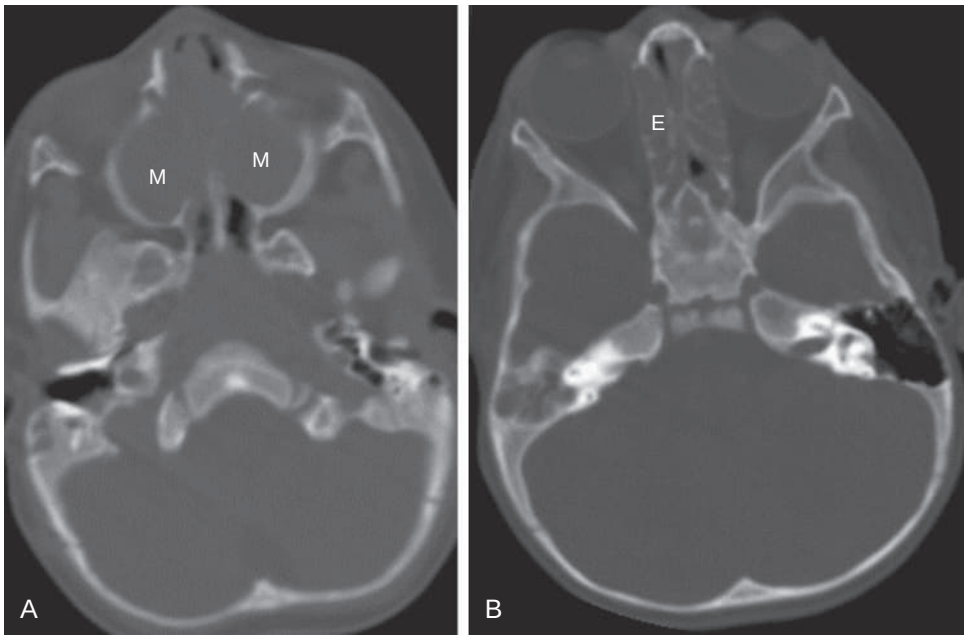
eFigure 68.5 Cystic fibrosis with spontaneous pneumothorax. Frontal chest radiography shows typical changes of cystic fibrosis, including extensive bronchiectasis and peribronchial consolidation with large lung volumes. A small, spontaneous right apical pneumothorax (*arrowheads*) is present. (Courtesy Michael B. Gotway, MD.)



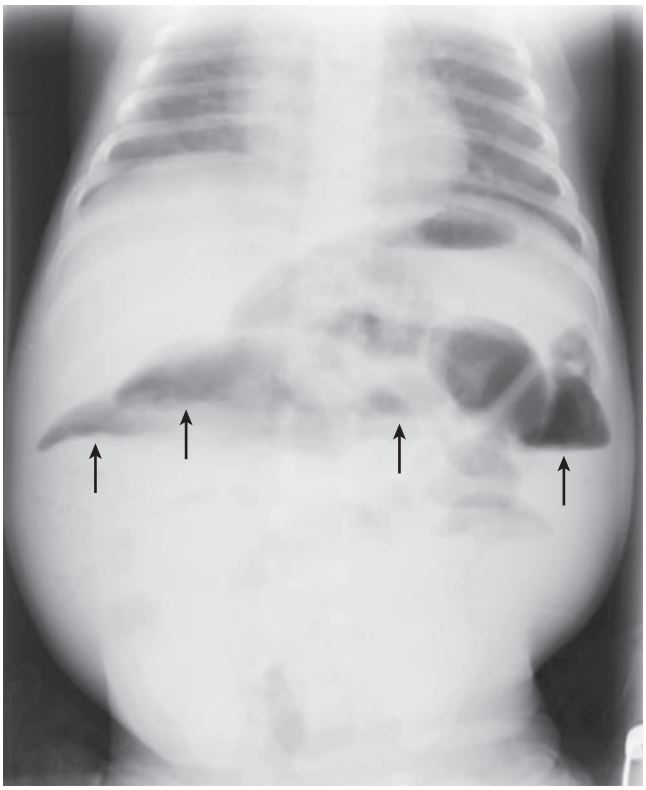
eFigure 68.6 Cystic fibrosis: mosaic perfusion. (A–D) Axial chest computed tomography through the lung bases displayed in lung windows shows cylindrical bronchiectasis (*arrowheads*) and extensive bronchial wall thickening, typical of cystic fibrosis. Extensive, bilateral inhomogeneous lung opacity is present, manifesting as geographic areas of increased and decreased pulmonary parenchymal attenuation. The areas of decreased attenuation (*black outlines* in A and D) show small pulmonary vessels, reflecting vasoconstriction and decreased pulmonary parenchymal perfusion due to air trapping, and are referred to as mosaic perfusion. Although the areas of increased attenuation resemble ground-glass opacity, they actually represent relatively normal but hyperperfused pulmonary parenchyma. Such findings may happen with large or small airway obstructive disorders. (Courtesy Michael B. Gotway, MD.)



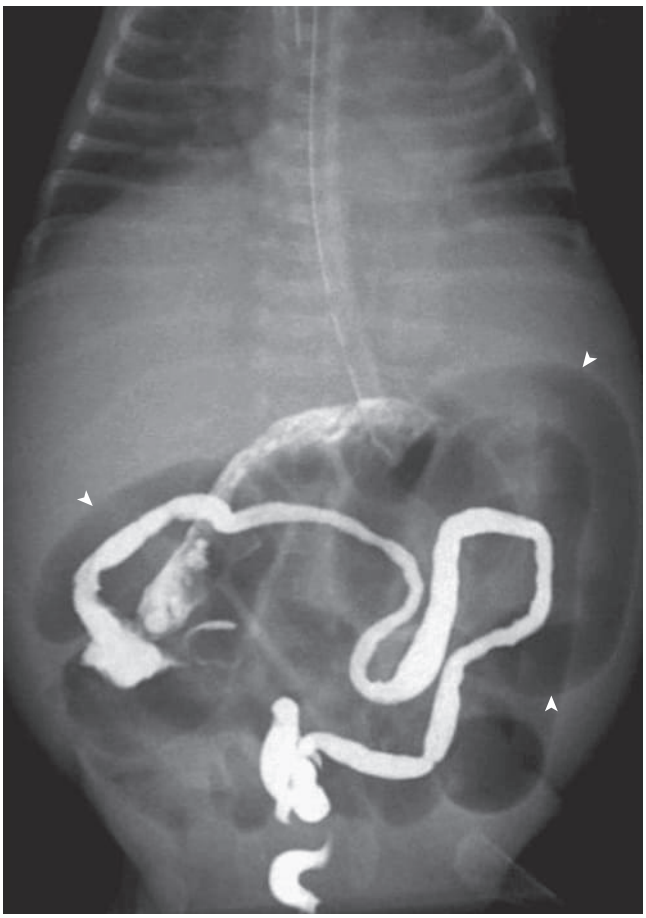
eFigure 68.7 Cystic fibrosis: chest radiographic and chest computed tomography findings of small airway impaction/obstruction. (A) Frontal chest radiography in a patient with cystic fibrosis shows large lung volumes associated with central airway thickening and extensive linear opacity, representing bronchiectasis and bronchial wall thickening. A number of small, poorly defined upper lobe opacities, particularly on the right, are evident. (B–D) Axial chest computed tomography displayed in lung windows shows extensive cylindrical bronchiectasis (*arrows*) and extensive bronchial wall thickening. Numerous small, solid, centrilobular nodules showing branching configurations, consistent with tree-in-bud opacity (*arrowheads*), are evident. (Courtesy Michael B. Gotway, MD.)



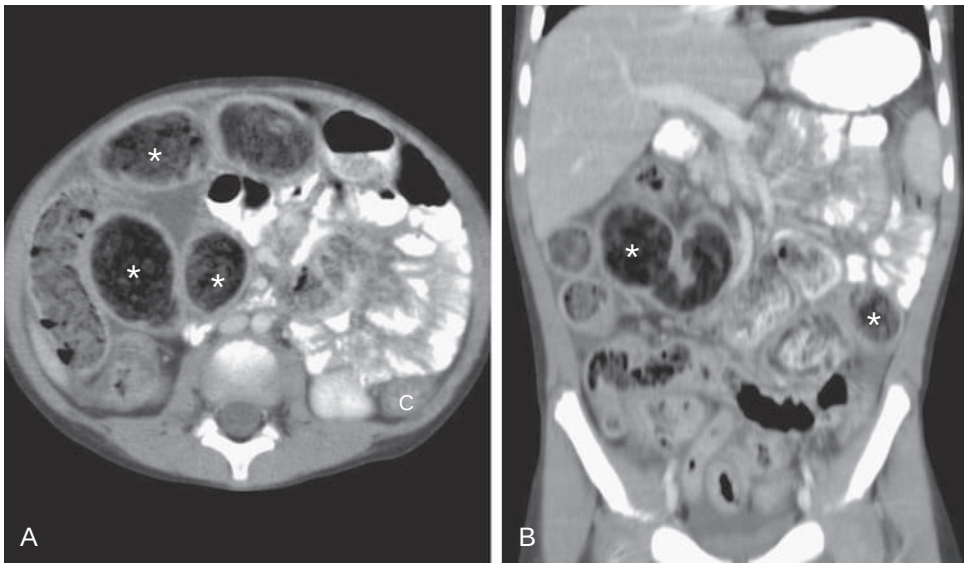
eFigure 68.8 Upper respiratory tract manifestations of cystic fibrosis: sinusitis. (A–B) Axial sinus computed tomography shows complete opacification of the maxillary sinuses *(M)* and ethmoid *(E)* air cells. (Courtesy Michael B. Gotway, MD.)



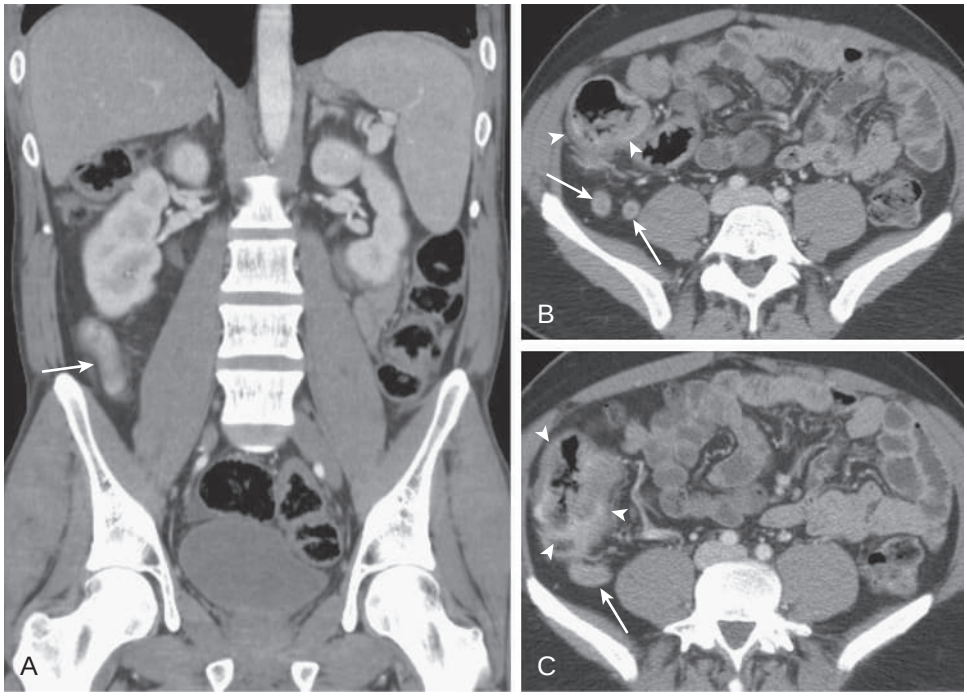
eFigure 68.9 Gastrointestinal complications of cystic fibrosis: meconium ileus with small bowel obstruction. Frontal view of the abdomen shows dilated small bowel with numerous gas-fluid levels (*arrows*) representing small bowel obstruction. The appearance is not specific for meconium ileus, but that diagnosis was proved subsequently. (Courtesy Michael B. Gotway, MD.)



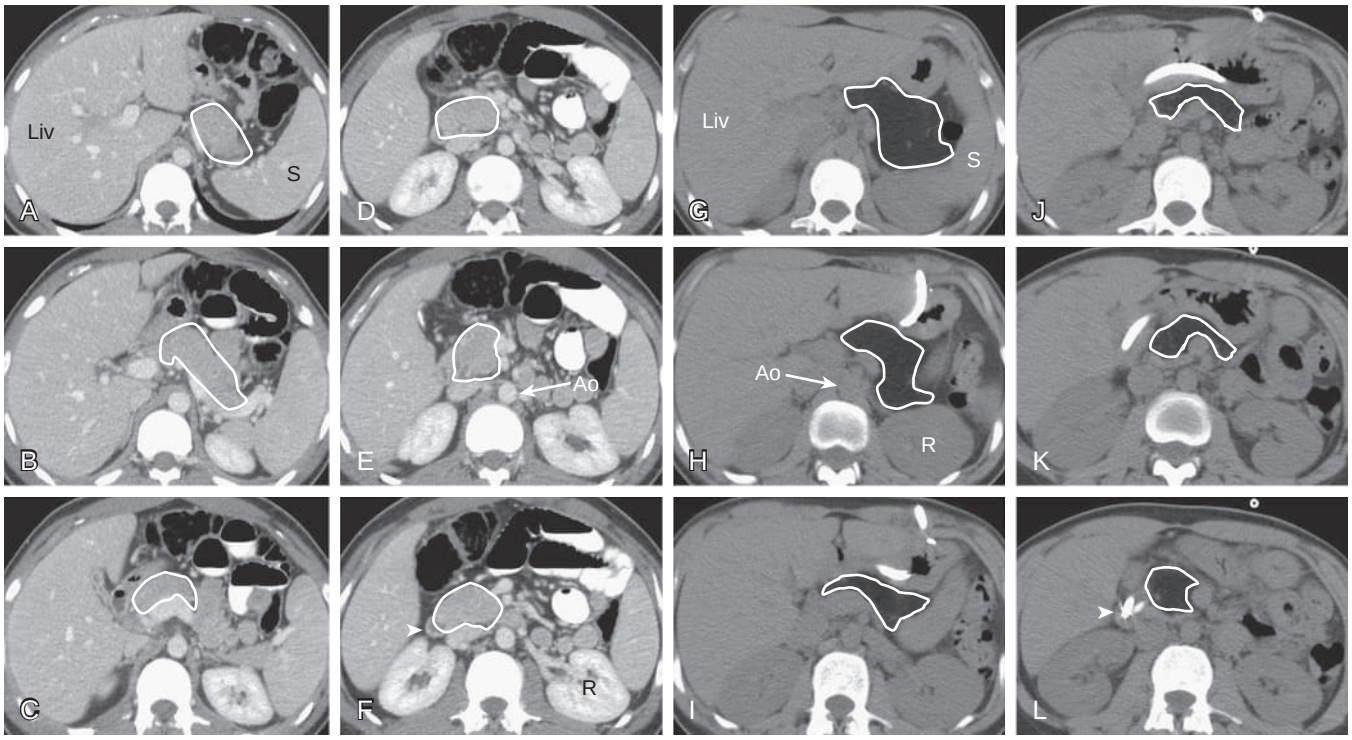
eFigure 68.10 Gastrointestinal complications of cystic fibrosis: meconium ileus. Postevacuation image following contrast enema shows a small, opacified colon, consistent with a microcolon. Distended small bowel (*arrowheads*) consistent with small bowel obstruction is present. (Courtesy Michael B. Gotway, MD.)



eFigure 68.11 Gastrointestinal complications of cystic fibrosis: distal intestinal obstruction syndrome. (A) Axial and (B) coronal contrast-enhanced abdominal-pelvic computed tomography in a child with cystic fibrosis shows opacified normal caliber proximal small bowel but dilated, debris-filled distal small bowel (*asterisks*) consistent with the distal intestinal obstruction syndrome. C, left colon. (Courtesy Michael B. Gotway, MD.)



eFigure 68.12 Gastrointestinal manifestations of cystic fibrosis: enlarged appendix. (A) Coronal and (B–C) axial enhanced abdominal computed tomography shows a dilated appendix (*arrows*); this finding was unchanged from a study several years earlier. The colon (*arrowheads*) is somewhat redundant and thick-walled, with mild infiltration of the pericolonic fat. (Courtesy Michael B. Gotway, MD.)



eFigure 68.13 Gastrointestinal manifestations of cystic fibrosis: fatty replacement of the pancreas. (A–F) Axial enhanced abdominal *computed tomography* (CT) in a patient without *cystic fibrosis* (CF) shows a normal pancreas (*white outline*); note close relationship of the tail of the pancreas to the spleen (*S*). The normal pancreas is obliquely oriented with the tail superiorly and left laterally positioned compared with the more medial and inferiorly located pancreas head (*white outline,* E–F); the head of the pancreas is closely related to the junction of the second and third portions of the duodenum (*arrowheads,* F and L). The enteric tube in L also marks the position of the duodenum). (G–L) Axial unenhanced abdominal CT in a patient with CF shows complete fatty replacement of the pancreas; note the homogeneous low attenuation, consistent with fat and equivalent in attenuation to subcutaneous fat, occupying the position of the pancreas (*white outline,* G–L). *Ao and arrow,* abdominal aorta; *Liv,* liver; *R,* renal/kidney. (Courtesy Michael B. Gotway, MD.)

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69 BRONCHIECTASIS

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INTRODUCTION

Bronchiectasis is defined by dilation, or ectasia, of the large airways or bronchi. The primary clinical manifestations of bronchiectasis are recurrent, chronic, or refractory infections. Other significant sequelae include hemoptysis, chronic airflow obstruction, and progressive impairment of pulmonary function.

There are varied pathways that lead to the development of bronchiectasis (Table 69.1 and Fig. 69.1). Broadly, bronchiectasis may develop because of an incidental event or episode that does not necessarily reflect impairment of the patient's intrinsic host defenses. Such examples include a necrotizing pneumonia after aspiration or chronic infection distal to an obstructing bronchial mass or foreign body. Often, however, bronchiectasis evolves due to underlying genetic risk factors and/or recurrent exposures to environmental mycobacteria. Regardless of the underlying etiology of bronchiectasis, superimposed bacterial infection is common and frequently drives the progression and exacerbation of bronchiectasis.

A central issue in understanding the pathogenesis of bronchiectasis is whether infection is truly the proximate cause of bronchiectasis or whether infections develop because of an underlying predisposing condition. For example, a commonly held adage is that many cases of bronchiectasis in adults are associated with childhood bouts of pertussis, measles, or other infections, including adenovirus.[1,2]

It is important to emphasize that these findings provide, at most, only an associative link and not a causal link.[1] Although childhood infections can undoubtedly cause bronchiectasis, one might be skeptical of this simple construct, asking why formerly common childhood illnesses resulted in bronchiectasis in only a small proportion of patients. Recently emerging is the concept that neutrophils and other inflammatory cells release elastase and reactive oxygen intermediates in response to infection, and that this unresolved inflammatory response to infection may damage airways.[3,4]

CLASSIFICATION SCHEMA

Although there is considerable overlap and coexistence among the various forms of bronchiectasis, the radiographic patterns and distribution may provide clues to diagnosis, management, and prognosis.[5] Thus, characterizing the morphologic features and distribution of bronchiectasis is a useful exercise. Bronchiectasis is most accurately diagnosed by *high-resolution computed tomography* (HRCT). Radiographic correlates to HRCT findings are summarized in eFigs. 69.1 to 69.3.

Cylindrical bronchiectasis is described as failure of the involved airways to taper progressively in their distal course. Usually, in this condition, the bronchial walls are smooth or regular. *Varicoid* bronchiectasis is an allusion to varicose veins and is marked by irregular dilation, narrowing, and outpouching of the airways. *Saccular* bronchiectasis, also known as *cystic* bronchiectasis, includes focal or cystic distortion of the distal airways. These bronchiectatic forms are summarized in Figure 69.2. Cystic distortion may become confluent, producing the appearance of bronchiectatic consolidation and volume loss (eFig. 69.4).

A traditional "wet" versus "dry" bronchiectasis paradigm is now less commonly used because newer paradigms regarding phenotypes have emerged based on underlying diagnosis, type of infectious agent(s) causing or exacerbating the bronchiectasis,[6] and clinical phenotype.[7]

The most well-characterized, clinically relevant example is the *frequent exacerbator* phenotype.[8] Within this group, frequent exacerbations are the strongest predictor of future exacerbation frequency. Patients with frequent

Table 69.1 Conditions Associated With Bronchiectasis

POSTINFECTIOUS CONDITIONS
Childhood lower respiratory tract infections
Granulomatous infections
Necrotizing pneumonias in adults
Other respiratory infections
PRIMARY IMMUNE DISORDERS
Humoral defects
Cellular and/or mixed disorders
Neutrophil dysfunction
Other
CYSTIC FIBROSIS (CF)
Classic CF
Variants of CF
Young syndrome
ALPHA$_1$-ANTITRYPSIN ABNORMALITIES
Deficiencies
Anomalies
HERITABLE STRUCTURAL ABNORMALITIES
Primary ciliary dyskinesia
Williams-Campbell syndrome
Mounier-Kuhn syndrome
Marfan syndrome
Sequestration, agenesis, hypoplasia
IDIOPATHIC INFLAMMATORY DISORDERS
Sarcoidosis
Rheumatoid arthritis
Ankylosing spondylitis
Systemic lupus erythematosus
Sjögren syndrome
Inflammatory bowel disease
Relapsing polychondritis
INHALATION AND OBSTRUCTION
Gastroesophageal reflux/aspiration
Pneumonia
Toxic inhalation/thermal injury
Postobstruction accident
Foreign body
Tumors, benign and malignant
Extrinsic airway compression
Allergic bronchopulmonary aspergillosis/mycosis
MISCELLANEOUS
Human immunodeficiency virus infection
Yellow nail syndrome
Radiation injury

exacerbations have a poorer *quality of life* (QOL), are more likely to be hospitalized and, at up to 5 years of follow-up, have a higher mortality, proportional to the number of exacerbations per year.[8]

EPIDEMIOLOGY

Incidence and prevalence of bronchiectasis is difficult to estimate but likely varies in different regions of the world.[9] The prevalence of *non-cystic fibrosis* (non-CF) bronchiectasis, based on narrow case-finding criteria, is estimated to be 139 cases per 100,000 persons, to be higher among women versus men (180 vs. 95 per 100,000), and to increase substantially with age (from 7 per 100,000 for ages 18–34 years to 812 per 100,000 for ages ≥75 years); annual incidence is estimated to be 29 cases per 100,000 persons. Disease prevalence based on broad case-finding criteria is estimated to be 213 cases per 100,000 persons.[9] This study suggested that, in the United States (in 2013), between 340,000 and 522,000 adults were receiving treatment for bronchiectasis and that 70,000 adults were newly diagnosed with bronchiectasis. More recent data indicate that bronchiectasis is much more common than previously reported, and the incidence has risen with an estimated annual growth rate of 8% since 2001.[10–12] Whether these rising rates reflect a true increase in incidence and/or enhanced detection due to more frequent use of *computed tomography* (CT) scans is not known. The observation that bronchiectasis was the *primary* diagnosis in only a minority (<20%) of all the bronchiectasis-associated hospitalizations supports the concept that greater incidental diagnosis is being made, at least in part, from more frequent use of CT scans.[13]

There are significant economic burdens of increased incidence and prevalence of bronchiectasis. The major drivers of annual health care costs appear related to hospitalizations, but total cost is currently unknown.[14]

In the United States and many parts of the world, there appear to be increasing numbers of bronchiectasis cases associated with *nontuberculous mycobacteria* (NTM) (see Chapter 55).[15–23] NTM appears capable of both initiating[24] and driving the evolution of bronchiectasis[25,26] through a chronic neutrophil-driven process in the airways, resulting in enhanced airway damage and initiation of the vicious cycle of inflammation.

PATHOPHYSIOLOGY

Various mechanisms operate to produce bronchiectasis. In the simplest terms, they may be thought of in terms of *traction, pulsion*, and *weakness* of the airways. In most cases, the pathogenesis becomes inextricably linked with and propelled by the destructive effects of chronic infection, as summarized in Figure 69.1.

Traction bronchiectasis implies that local retractile forces dilate the airways. As the lung undergoes fibrotic changes due to disorders such as sarcoidosis, interstitial lung disorders, or infections such as tuberculosis, those increased forces are transmitted to the airways. In contrast, in normal lungs, airways are held patent by a combination of negative intrapleural pressure, which maintains the lungs in an inflated state, and the cartilaginous rings of the trachea and the large and medium airways. The distending forces of the negative intrapleural pressure are transmitted to the airways by a diffuse system of interstitial tethering.

Pulsion bronchiectasis implies that intense inflammation originating in the lumen leads to permanent airway dilation. The prototype is *allergic bronchopulmonary aspergillosis* (ABPA). In ABPA, there are intense, immunologically mediated reactions to inhaled *Aspergillus* lodged in the airways. The proliferating fungi form large mucoid conglomerates that fill the central airways; a sequela of this airway inflammatory process and mucoid impaction is bronchiectasis (eFig. 69.5).

Weakness of the airways may take many forms. Classic postinfectious bronchiectasis presumably is mediated in part by damage to the walls of the airways, resulting in secondary loss of structural integrity.[27,28] This is

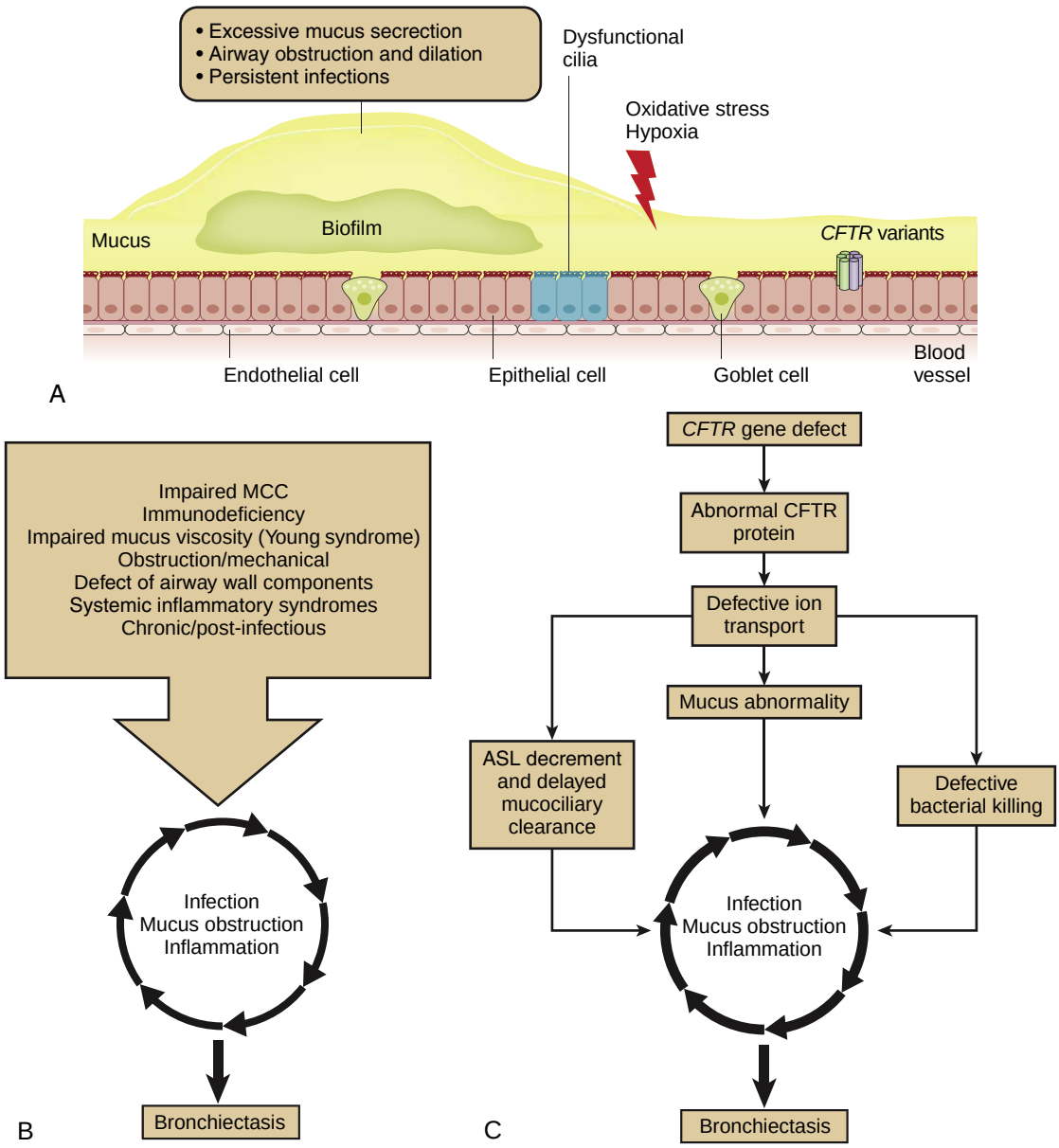

Figure 69.1 General pathophysiologic mechanisms for the development of bronchiectasis. (A) General pathophysiologic mechanisms in the airway epithelium leading to bronchiectasis. (B) Due to the underlying bronchiectatic defect (e.g., impaired *mucociliary clearance* [MCC]) and predisposition to infections (e.g., immunodeficiencies), there is biofilm formation and accumulation of mucus leading to chronic bacterial colonization. A vicious cycle ensues, wherein mucus accumulation predisposes to bacterial colonization and infection, which then incites more inflammation and bronchiectasis, leading back to greater impaired mucus clearance. (C) A prototypical example is cystic fibrosis, wherein a defect in the *cystic fibrosis transmembrane regulator* (*CFTR*) gene leads to a primary ion transport defect. These defects create abnormalities in *airway surface liquid* (ASL) and mucus clearance, inherent changes in airway mucus, and impaired bacterial killing resulting in the vicious cycle of bronchiectasis development in cystic fibrosis.

coupled with scarring and loss of volume of the local lung units, leading to regional increases in retractile forces. Examples of primary weakness of the airways contributing to bronchiectasis include Mounier-Kuhn syndrome (congenital tracheobronchomegaly due to atrophy of airway elastic fibers), Williams-Campbell syndrome (absence of cartilaginous rings in the segmental and subsegmental generations of bronchi), Marfan syndrome, and relapsing polychondritis.

Weakened airways and airway collapsibility impair the effectiveness of the cough mechanism. Coughing is an essential, primary element of lung defense. An effective cough sends columns of air rushing upward through the bronchial tree at peak speeds measured in the range of 600 mph.[29] To support these high flow rates, the cartilaginous rings must have the structural integrity to remain patent while the posterior membranous element invaginates into the lumen of the airway, thereby decreasing the cross-sectional diameter of the airway and accelerating airflow. Bronchoscopy of patients with bronchiectasis commonly reveals extraordinary collapsibility of the airways, virtually completely obstructing the bronchi with each cough. It seems likely that such amplified airway compressibility impedes the air-driven propulsion of secretions out of the

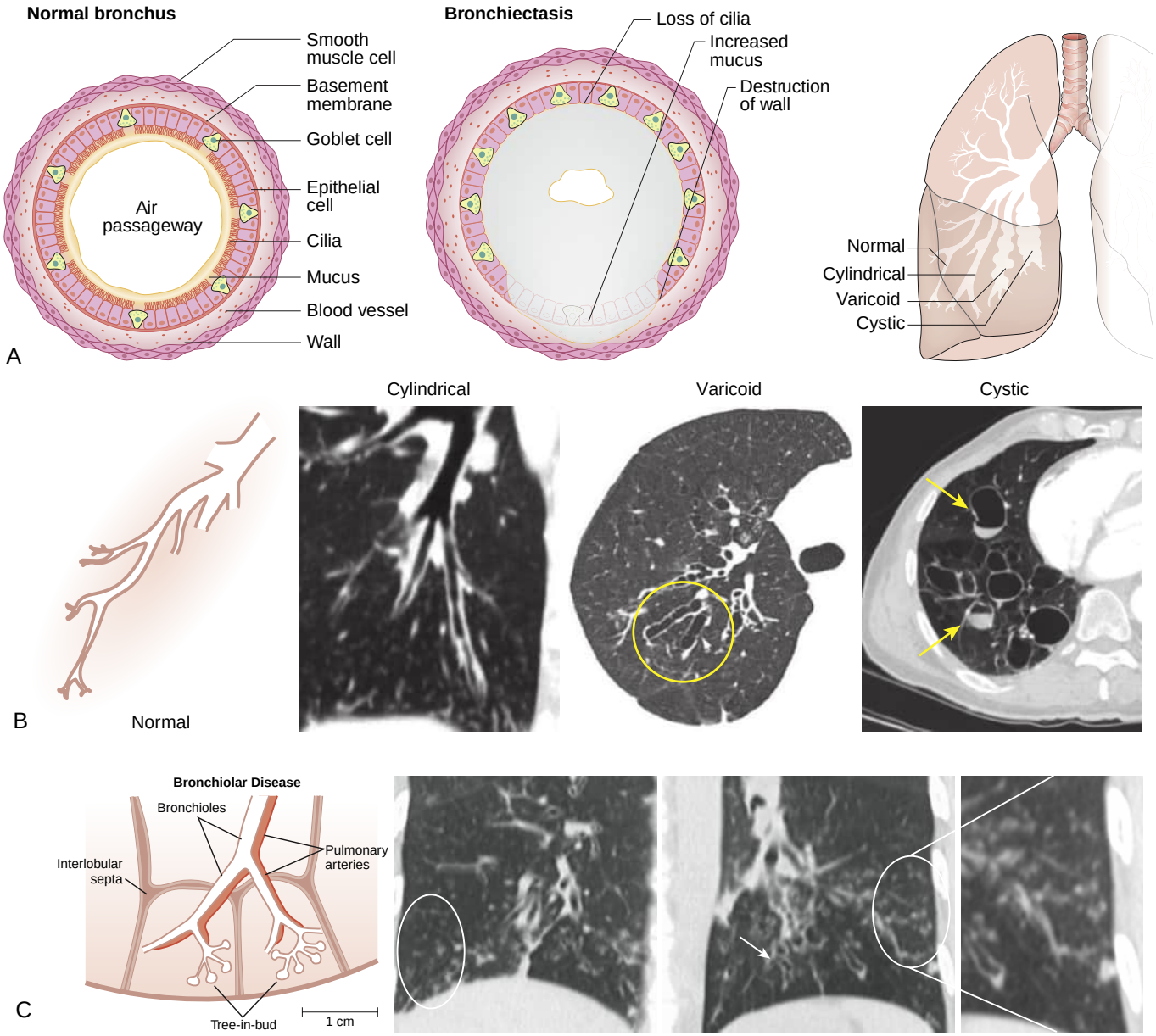

Figure 69.2 Radiographic examples of different forms of bronchiectasis. (A) The three top figures show a cross-section diagram of a normal airway, a bronchiectatic airway, and the three different forms of bronchiectasis on longitudinal view. (B) The middle panel shows a diagram of a normal bronchial tree demonstrating usual tapering as the airway branches distally (*far left*) and axial computed tomography images showing cylindrical bronchiectasis (*middle left*), varicoid bronchiectasis (*middle right, yellow circle*), and cystic bronchiectasis (*arrows, far right*). (C) The bottom panel shows a diagram of bronchiolitis (*left*) and a coronal computed tomography image (*right*) of inflammatory bronchiolitis manifested as tree-in-bud opacification *(white ovals)* (enlarged at *far right*) and bronchiectasis (*arrow*) in a patient with nontuberculous mycobacterial lung disease.

bronchial tree and helps perpetuate the chronic or recurring infections that mark most cases of bronchiectasis.

"VICIOUS CYCLE" AND MICROBIOLOGY

Because the lung is constantly exposed to the environment, resident or recruited lung phagocytes, such as macrophages, dendritic cells, and neutrophils, must play an important host defense role against inhaled or aspirated microbes. In addition, the host uses an array of other mechanisms to defend against microbial organisms that invade the respiratory tract, including the cough reflex, mucociliary escalator, antimicrobial peptides (lysozymes, secretory leukocyte protease inhibitor, defensins, and cathelicidin), secretory *immunoglobulin* (Ig) A, and, with more sustained infection, recruited T-effector lymphocytes. Airway epithelial cells are also able to contribute to the lines of defense by secreting antimicrobial peptides.[30,31] (See Chapter 15.) Thus, in addition to the three aforementioned mechanisms by which physical forces or primary weakness of the airway walls may result in bronchiectasis, the other major element in the pathogenesis of bronchiectasis is the vicious cycle of recurrent or sustained infection and inflammation, as described by Cole.[32,33]

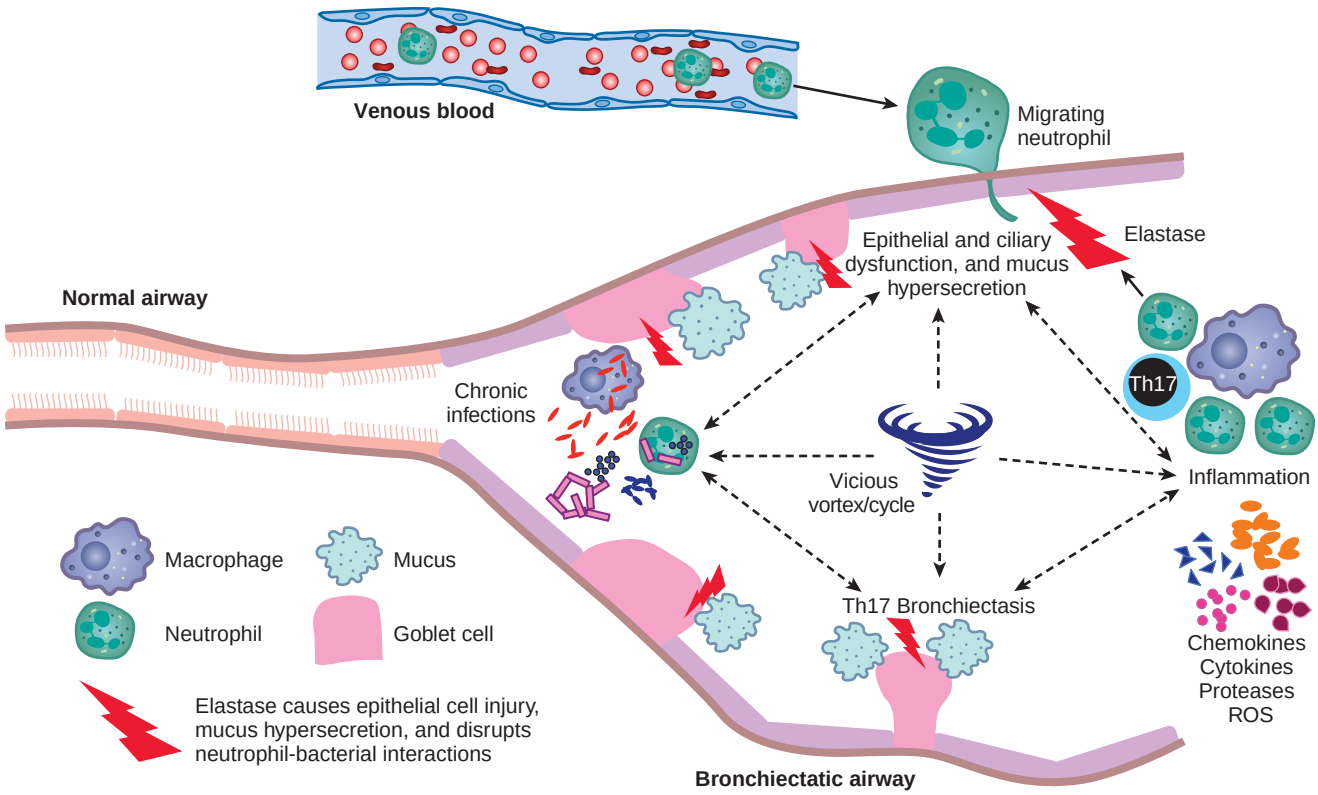

Figure 69.3 Cellular pathophysiologic mechanism of bronchiectasis. Cross-sectional view of the bronchiectatic airway demonstrating the components that play a role in the pathogenesis, including neutrophils, neutrophil elastase, goblet cells that produce mucus, and the chemokines and proinflammatory cytokines produced by macrophages and *T helper type 17 cells* (Th17). The epithelial and ciliary dysfunction, mucus hypersecretion, inflammation with unchecked protease (elastase) activity, chronic infection, and resultant bronchiectasis are intertwined and help perpetuate each other, creating the paradigm of the "vicious vortex/cycle" central to bronchiectasis pathogenesis. ROS, reactive oxygen species.

More recently, it has been proposed that a tetrad of events leads to bronchiectasis, the so-called "vicious vortex," a new term proposed because each of these factors may help perpetuate the other three (Fig. 69.3): (1) airway epithelial and ciliary dysfunction, and mucus hypersecretion; (2) chronic infections that induce further mucus hypersecretion; (3) inflammation, resulting in permanent airway injury and dilation; and (4) resultant bronchiectatic airways that are poor in mucociliary clearance, perpetuating the chronic infection, inflammation, and airway epithelial cell and ciliary dysfunction.[34] Transmural inflammation causes damage to the bronchi and bronchioles, which then become susceptible to chronic colonization by certain microorganisms, such as *Pseudomonas aeruginosa,* NTM, and *Aspergillus,* resulting in further injury and in less resistance to infection. Analysis of cellular and noncellular constituents in the bronchiectatic airways typically demonstrates intense infiltration by neutrophils, as well as by mononuclear cells and lymphocytes.[35] When the initial defenses are unable to contain the infection, an exuberant immune response ensues, orchestrated by airway epithelial cells and phagocytes through the release of inflammatory cytokines and chemokines that include macrophage inflammatory protein-2, *interleukin-8* (IL-8), and tumor necrosis factor-α. In consequence, airway infiltration by predominantly neutrophils, macrophages, and lymphocytes causes damage to the airway epithelium through the release of various proteolytic enzymes, such as neutrophil elastase and metalloproteinases, which results in erosion of mucosal barriers, creating microabscesses that can harbor bacteria. For instance, neutrophil elastase has also been shown to cause ciliary dysfunction, mucous gland hyperplasia, and increased mucus secretion, thus further impairing clearance, summarized in Figure 69.3.[36–38]

Moreover, elastase and other proteases released by neutrophils can cleave Fcγ receptors and complement receptor 1 from neutrophil surfaces, as well as digest Ig and complement components from bacterial surfaces. These activities impair opsonization of bacteria and reduce recognition of bacteria by neutrophils, leading to decreased phagocytosis and bacterial killing (see Fig. 69.3).[39,40] Neutrophils undergo both necrotic and apoptotic forms of cell death. Necrotic neutrophils can incite more inflammation and the release of highly viscous DNA, which contributes to the volume and inspissated quality of bronchiectatic mucus. Although phagocytosis of apoptotic neutrophils—a process known as efferocytosis, which requires engagement of phosphatidylserine on apoptotic cells and phosphatidylserine receptor on macrophages—can limit inflammation, elastase can inhibit efferocytosis by cleavage of phosphatidylserine.[41] In summary, damaged airways are vulnerable to infection, begetting more damage.

Simple colonization and infection of the airways is not sufficient to produce true bronchiectasis. Sputum from patients with smoking-related chronic bronchitis typically yields organisms such as *Haemophilus influenzae, H. parainfluenzae, Streptococcus pneumoniae,* and *Moraxella catarrhalis,* a microbial spectrum similar to that seen with bronchiectasis.[42–45]

In addition, in this setting, there is heavy cellular traffic and the presence of a variety of inflammatory mediators. However, significant bronchiectasis is uncommon among patients with typical chronic bronchitis. Hence it is probable that systemic conditions or additional focal disturbances as described earlier are required for the development of classic bronchiectasis. Of note, however, the appearance in respiratory secretions of *P. aeruginosa* on a chronic or recurring basis does pose the risk for deleterious effects on ciliary function and other host defenses.[46] Pseudomonal infections may be of particular importance due to their role in the formation of biofilms (see later). Indeed, chronic *P. aeruginosa* infection or colonization plays a major role in the pathogenesis of bronchiectasis and poorer health outcomes, including increased exacerbations and hospital admissions and an approximately threefold increased risk of death.[47] In a longitudinal study of the microbiologic characteristics of 89 patients with bronchiectasis over a 5-year period, 47% were colonized with *H. influenzae,* 12% with *P. aeruginosa,* and 21% had no identifiable pathogen. After 5 years, there was a slight increase in the number of those colonized with *P. aeruginosa.* As expected, those with the mildest disease had no identifiable pathogens, whereas those with the worst disease were colonized with *P. aeruginosa.*[48]

Genetic techniques have been used to identify the bacterial flora in patients with bronchiectasis. Using 16S ribosomal RNA gene pyrosequencing of paired induced sputum and bronchoalveolar lavage samples, the bacterial flora of lower airway samples was analyzed in 41 adult patients with non-CF bronchiectasis.[49] A group of core bacterial species, defined as those frequently detected, was found to consist of commonly recognized pathogens (e.g., *P. aeruginosa, H. influenzae,* and *S. pneumoniae*) but also organisms not typically detected by routine cultures (e.g., *Veillonella, Prevotella*).[49] Studies genetically categorizing the lung microbiome in patients with bronchiectasis and determining its significance relative to clinical end points, such as exacerbations, continue to be advanced. Although a study showed that there was no significant difference in the overall microbial community diversity between patients with stable bronchiectasis and those with exacerbations, it was clear that *Acinetobacter* and *Stenotrophomonas* were seen primarily during exacerbations.[50] In an editorial that accompanied this report, the authors raised the critical question of whether analyzing the mountain of 16S ribosomal RNA–derived microbiota data ("the forest") masks the importance of individual microbes detected ("the trees").[51]

BIOFILMS

In 1984, Costerton[52] hypothesized that *P. aeruginosa* in human infections "attaches to solid or tissue surfaces and grows predominantly in biofilms." These natural and pathogenic biofilms are covered by an exopolysaccharide matrix (glycocalyx) that serves as a barrier against hostile factors, such as host immune cells and antibiotics.[52] Since this discovery, there has been clear evidence for the importance of biofilms in promoting chronic bacterial infection in the airways of CF patients,[53] and in promoting infections with NTM and methicillin-resistant *Staphylococcus aureus*.[54] In addition, biofilms have been identified in bronchoalveolar lavage of patients without overt signs of infection.[55] *P. aeruginosa,* among its various attributes, uses cilia-driven motility, which appears critically important in the aggregation phase of early biofilm formation.[56] Once biofilm formation commences, features of growth and gene activation that release virulence factors are influenced by a type of cell-cell communication called *quorum sensing,* in which the individual bacteria share genetic information in a paracrine fashion. Owing to a combination of physicochemical factors that protect the microbes from host defense cells and/or antibiotics, infection may persist despite aggressive treatment. In vitro testing indicates that bacteria embedded in biofilms can survive despite exposure to concentrations of antimicrobials that exceed the minimal inhibitory concentration by 1000-fold.[57] We may anticipate that future understanding and optimal management of patients with bronchiectasis will entail interventions to modify or interfere with biofilms.[56] Among potential treatments, macrolides inhibit quorum sensing,[58] and *N*-acetylcysteine disrupts biofilm formation and enhances bacterial killing in in vitro studies.[59]

ASSOCIATED DISEASE STATES AND ETIOLOGIC CONSIDERATIONS FOR BRONCHIECTASIS

APPROACH TO DIAGNOSIS OF BRONCHIECTASIS ETIOLOGY

A diverse set of medical conditions is strongly associated with or complicated by bronchiectasis. Given the increasing attention to developing treatments for these unique and diverse etiologies, a systematic approach to diagnosis is recommended (Fig. 69.4).[60–62] Of special importance is the recognition of CF because of the highly efficacious and more specific therapies available to these patients (see also Chapter 68).

In addition to this schema, determining the etiologic cause of bronchiectasis may be enhanced by understanding distribution patterns on HRCT imaging. The anatomic distribution of bronchiectasis associated with various etiologies is outlined in Figure 69.5 (also see eFig. 20.52).

LUNG INJURY DUE TO ACUTE INFECTION

In the modern era in industrialized nations, most adequately treated episodes of lower respiratory tract infection resolve without residual damage. However, among the older generations who were not protected by readily available antibiotics and vaccines, some individuals offer a convincing history of recurring, localized infections after a discrete episode of "pneumonia" in their childhood or early adult years that presumably produced irreversible damage leading to bronchiectasis.[1]

Specific pathogens believed to cause bronchiectasis include *Bordetella pertussis,* mucoid strains of *S. pneumoniae, S. aureus, Klebsiella pneumoniae,* adenoviruses, rubeola (measles), and influenza. Chronic granulomatous pathogens commonly related to bronchiectasis include *Mycobacterium tuberculosis, Histoplasma capsulatum,* and NTM such as *Mycobacterium avium* complex (MAC). In

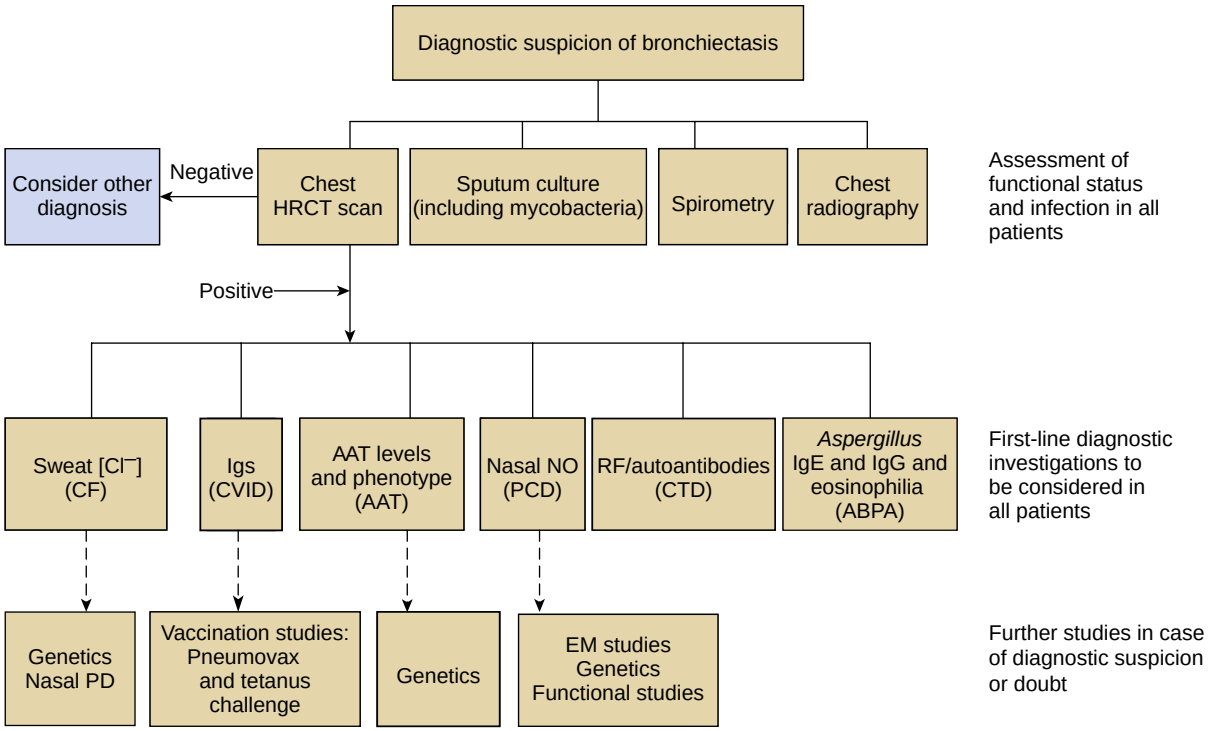

Figure 69.4 Diagnostic algorithm for the evaluation of suspected bronchiectasis. Although chest radiographs may suggest bronchiectasis, the diagnosis is confirmed by *high-resolution computed tomography* (HRCT). Sputum cultures and spirometry define the presence of infection and functional status. Subsequently, first-line laboratory and other ancillary tests are obtained to differentiate the more common causes of the bronchiectasis. Additional testing may be needed to diagnose less common causes if the initial evaluation is unrevealing. ABPA, allergic bronchopulmonary aspergillosis; AAT, alpha$_1$-antitrypsin; CF, cystic fibrosis; [Cl⁻], chloride concentration; CTD, connective tissue disease; CVID, common variable immunodeficiency; EM, electron microscopy; IgE, immunoglobulin E; IgG, immunoglobulin G; NO, nitric oxide; PCD, primary ciliary dyskinesia; PD, potential difference; RF, rheumatoid factor. (Modified from Drain M, Elborn S. Assessment and investigation of adults with bronchiectasis. *Eur Respir Monogr*. 2011;52:32–43.)

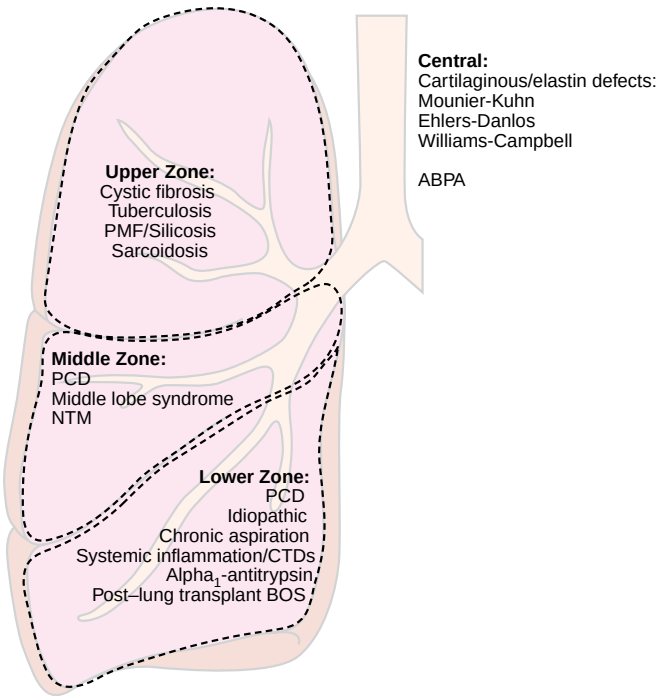

Figure 69.5 Anatomic clues to diagnosis of bronchiectasis. The causes of the bronchiectasis stratified by the predominant anatomic location of the lung abnormality; that is, upper, middle, or lower zone of the lungs and the central airway. ABPA, allergic bronchopulmonary aspergillosis; BOS, bronchiolitis obliterans syndrome; CTDs, connective tissue diseases; NTM, nontuberculous mycobacteria; PCD, primary ciliary dyskinesia; PMF, progressive massive fibrosis.

addition, mixed infection, including anaerobic mouth flora related to aspiration, may result in extensive damage to the parenchyma ("lung abscesses") with subsequent bronchiectasis.

BRONCHIECTASIS ASSOCIATED WITH NONTUBERCULOUS MYCOBACTERIA

NTM-associated bronchiectasis is discussed separately because the NTM may be a primary cause of bronchiectasis or a secondary infection complicating preexisting bronchiectasis. Chronic lung disease due to NTM is manifested by two main radiographic patterns, although both types may be found in a single patient: (1) an upper lobe fibrocavitary pattern seen mostly in persons with underlying lung disease, such as COPD, and (2) a nodular-bronchiectasis pattern with or without cavitary disease that often involves the right middle lobe, lingula, and/or right upper lobe seen in those with neither preexisting lung disease nor known genetic predisposition.[63,64] Although NTM can exacerbate preexisting bronchiectasis, such as that associated with CF,[65] *primary ciliary dyskinesia* (PCD),[66] prior tuberculosis,[67] and COPD,[68] it is also believed to cause bronchiectasis. Furthermore, there is increasing evidence that heterozygosity of the *cystic fibrosis transmembrane regulator* (CFTR) or *alpha$_1$-antitrypsin* (AAT) gene prediposes individuals to NTM infections resulting in secondary bronchiectasis.[69–71] Indeed, in the Bronchiectasis Research Registry for non-CF bronchiectasis, comparison of four different underlying

causes for bronchiectasis—idiopathic, AAT deficiency, *common variable immunodeficiency* (CVID), and PCD—revealed that those with AAT deficiency were significantly more likely to have NTM isolated from their respiratory samples than those with the other three underlying conditions.[72]

In patients with NTM lung disease, a careful family history should be obtained for bronchiectasis. We recommend that patients with NTM lung disease be screened for CFTR abnormalities, AAT anomalies, CVID, and swallowing dysfunction and, in certain groups such as those with sinusitis, infertility, and lower lung zone bronchiectasis, for PCD. Individuals with NTM-associated bronchiectasis who have no known predisposing factors have been observed by clinicians to possess marfanoid physical features, such as constitutively slender body habitus, scoliosis, and pectus excavatum, more commonly than anticipated by chance alone.[71,73–77] Of interest, this phenotype in those with NTM lung disease seems disproportionately to involve predominantly slender white or Asian women,[78,79] although it is also seen in men.[80] We and others have postulated that these skeletal abnormalities may be a marker for an underlying and yet-to-be identified genetic predisposition speculated to be related to a minor variant of Marfan syndrome or ciliary dysfunction.[71,74-76,81–83] In those with the marfanoid body habitus, do the airways dilate because of an intrinsic structural defect? This hypothesis is plausible because fibrillin-1 is a component of the extracellular matrix, and a fibrillin mutation is the cause of Marfan syndrome. Is there an immune defect that increases the risks for infections that set in motion the coughing and inflammation that lead to bronchiectasis? This supposition is supported by the fact that the morphologic anomalies seen with Marfan syndrome have been associated with increased localized production of transforming growth factor-β, a cytokine that increases susceptibility to mycobacteria.[84–87]

More recently, it has been hypothesized, based on gene sequencing, that a combination of variants of ciliary, immune-related, connective tissue, and *CFTR* genes, in addition to other factors such as body weight, age, and environmental exposure, cooperate to increase vulnerability to NTM lung disease.[88,89]

Regardless of the presence or absence of an underlying predisposing condition for NTM lung disease, there is also increasing evidence and experience that aspiration from swallowing dysfunction or *gastroesophageal reflux* (GER) may predispose to NTM infection.[90–92]

CYSTIC FIBROSIS

CF and CF variants are arguably the most common causes of bronchiectasis in the United States and other industrialized nations of the Western Hemisphere today. Being the most common autosomal recessive disorder among whites (1 in 2000–2500 live births),[93] CF is increasingly prevalent as improved therapies allow those who are afflicted to live longer (see Chapter 67 for full details on the incidence and prevalence of CF).

In addition to "typical" cases in which CF is recognized early in life, variants may be present in the population that predispose to bronchiectasis in adults. Among a large series of adult patients with bronchiectasis associated with NTM seen at National Jewish Health in Denver, 117 of 865 (13.5%) were found to have one or more abnormal alleles of the *CFTR* gene,[94] well in excess of the anticipated carrier rate of 6% in the general population. In 19 of these patients (2.2% overall), there were two abnormal alleles and, in the remaining 98 (11.3%), there was only one mutation. Of note, the mean age of these patients was 61 years. The clinical importance of these heterozygous mutations may be disputed; however, patients in this cohort had a high frequency of chronic airflow obstruction, sinusitis, difficulties with conception, and coinfection with pathogens typical of CF, including mucoid strains of *P. aeruginosa*, all features compatible with clinical CF.[94] Among another series of patients with bronchiectasis and/or NTM lung disease, 24 of 50 (48%) had one or more *CFTR* mutations.[95] Similarly, among a cohort of 63 patients with NTM lung disease studied at the National Institutes of Health, 36% had mutations in the *CFTR* gene.[96] Consistent with the assertion that these heterozygous mutations are clinically relevant is a series of 30 patients with clinical features of CF who were reported to have normal *CFTR* alleles on comprehensive gene sequencing.[97] The authors concluded that factors other than mutations in *CFTR* could result in a clinical condition consistent with CF. It is our contention that heterozygous anomalies in the CF gene act as a predisposing factor for NTM infections that lead to bronchiectasis.

Bronchiectasis has been described in a condition identified in the 1970s called Young syndrome. Although Young syndrome is not CF, it has a number of similar clinical features, such as bronchiectasis, sinusitis, and infertility.[98] However, unlike CF, the genetic basis for Young syndrome is not known and, because the definition includes azoospermia, it is seen only in men. Furthermore, whereas the azoospermia related to CF is due to congenital absence of the vas deferens, in Young syndrome it is due to obstruction in the distal epididymis (i.e., obstructive azoospermia).[99,100] In a comprehensive study of 15 patients with a clinical diagnosis of Young syndrome, the mean nasal mucociliary clearance was prolonged nearly threefold compared to nonsmoking control subjects, but the ciliary beat frequency and ultrastructural anatomy of the cilia were considered to be within normal limits.[100] Of interest, in one subject in whom a sample of epididymis was available, microtubular disarrangement, mostly missing or "displaced" microtubules, was seen in approximately 13% of the cilia examined.[100] Because the incidence of Young syndrome appears to be decreasing dramatically since it was originally reported in the 1970s, it has been hypothesized that Young syndrome may be due to poisoning from mercurous chloride (calomel), a compound contained in teething powder and antihelmintics, which has since been banned.[101,102] Furthermore, we posit that, with more comprehensive testing for the *CFTR* mutation, it is quite plausible that some cases diagnosed as Young syndrome were in fact CF.

DISORDERS OF IMMUNITY

The most common immunodeficiency associated with bronchiectasis is CVID. CVID is mostly sporadic but familial inheritance is seen in approximately 10% of cases.[103] CVID is best considered a syndrome comprised of a collection of

diseases with different genetic defects and characterized by reduced or absent serum IgG, IgA, and/or IgM, as well as reduced or absent antibody production to specific antigen challenge after exclusion of defined causes of hypogammaglobulinemia.[104] Specific molecular defects have been described in 2–10% of CVID patients.[105,106] Several cellular defects have been described, with the most prominent one being failure of immature B cells to differentiate into memory B cells and plasma cells. However, an array of defects in other immune cell types are commonly seen in CVID, including impaired dendritic cell function and reduced number and function of $CD4^+$ T-effector cells and T-regulatory cells.[103] Given the heterogenous clinical presentation, ranging from recurrent infections to autoimmune diseases, granulomatous inflammation, and lymphoid malignancies, CVID should not be viewed as a single disease entity.[103,107] It is believed that the recurrent infections with encapsulated bacteria, such as *S. pneumoniae* and *H. influenzae,* and subsequent uncontrolled inflammation underlie the pathogenesis of bronchiectasis in CVID, which aligns with the generally accepted hypothesis set forth by Cole,[34] that a vicious cycle of chronic infection and inflammation is a key driver of bronchiectasis. Thus, recurrent infections and resultant bronchiectasis should raise the suspicion for CVID and should prompt further evaluation for an underlying immune defect.

Deficiency of *natural killer* (NK) cells has also been linked to the development of bronchiectasis and, of interest, a deficiency of circulating NK-cell subsets has been described with CVID.[108] Other less common to rare primary antibody deficiencies that can result in bronchiectasis include IgG subclass deficiency (total IgG is normal, but there is decreased level of one or more IgG subclasses: IgG1, IgG2, IgG3, IgG4), selective IgA deficiency (seen in up to 10% of the population studied), and a specific antibody defect (normal IgG, IgG subclass, IgA, and IgM but impaired antibody response to polysaccharide antigens).[109–111] Although agammaglobulinemia and CVID may be the most common primary immunodeficiencies associated with bronchiectasis, several other genetic primary immunodeficiencies can manifest with bronchiectasis, including those associated with *signal transducer and activator of transcription-3* (STAT-3) gain-of-function, *phosphoinositol-3-kinase* (PI3K) gain-of-function (*activated PI3K delta syndrome* or APDS), hyper-IgE syndrome (STAT-3 loss-of-function, DOCK8 and Tyk2 deficiency), cytotoxic T lymphocyte–associated protein 4 haploinsufficiency, and lipopolysaccharide-responsive beige-like anchor protein deficiency, among others.[112]

CVID in individuals older than 2 years is diagnosed by decreased serum levels of IgG and IgA of at least two standard deviations lower than normal for age and abnormal antibody responses to specific antigen challenge. For a specific diagnosis of CVID, the IgG level should be less than 4.5 g/L (normal: 7–18 g/L for adults), IgA should be absent or markedly reduced (normal: 0.7–3.5 g/L), and IgM should be normal or reduced (normal: 0.4–2.6 g/L). Rarely, IgM may be elevated due to a concomitant hyper-IgM syndrome or a class switch defect. An isolated reduction in IgG should prompt further analysis of IgG subclass deficiency (normal for adults in g/L: IgG1, 4.8–9.5; IgG2, 1.1–6.9; IgG3, 0.3–0.8; IgG4, 0.2–1.1).[103] In addition, it is important to exclude other causes of hypogammaglobulinemia, such as (1) nephrosis and other causes of Ig loss; (2) myriad drugs that can reduce Ig levels, including glucocorticoids, rituximab, alkylating agents, anticonvulsants (carbamazepine, valproic acid, phenytoin), and sulfasalazine; (3) underlying malignancy, such as chronic lymphocytic leukemia, lymphoma, and thymoma; and (4) various genetic abnormalities, such as X-linked agammaglobulinemia, Wiskott-Aldrich syndrome, ataxia telangiectasia, and severe combined immunodeficiency.[103,104,113] Of note, replacement with IgG does not always protect CVID patients from recurrent infections and bronchiectasis.[114] In patients with hypogammaglobulinemia on IgG replacement therapy, those able to secrete IgM (hyper-IgM syndrome) have a significantly lower risk of nontypeable *H. influenzae* carriage compared to those who lack IgM production (panhypogammaglobulinemia) despite equivalent trough levels of IgG.[115] Therefore, IgM probably plays a more prominent role in the protection against recurrent infection in CVID than previously thought, and patients should also be screened for low IgM because they might need prophylactic antibiotics in addition to IgG supplemention.[115]

Determining antibody responses to specific antigens (using commercially available vaccines) is most useful when there is a mild to moderate reduction in IgG.[103] Antibody responses to at least two protein-based vaccines (e.g., tetanus, diphtheria toxoid, or *H. influenzae* type b vaccine) should be assessed. A fourfold or greater increase in IgG level 4 weeks after immunization (or at least the presence of protective titers if less than a threefold increase from baseline) argues against CVID. The 23-valent pneumococcal vaccine (Pneumovax), which contains only polysaccharides, can be used to assess B cell responses independent of T cell help.[103] In contrast, the 13-valent pneumococcal vaccine (Prevnar) is used to assess B cell responses dependent on T cell help. In addition, in patients already receiving intravenous immunoglobulin, a *Salmonella typhi* polysaccharide vaccine may be used to assess the antigen response without discontinuing the therapy.[116] If testing for basal and stimulated immunoglobulins is suggestive of CVID, it is prudent to refer such patients to a clinical immunologist, because assessment of lymphocyte subset, B cell subsets, T cell function, and genetic testing for specific gene mutations are often warranted to prognosticate and formulate an optimal treatment regimen.

Among persons with acquired immunodeficiency syndrome, bronchiectasis has been identified in a significant proportion of those undergoing CT scans, including children.[117,118] Obviously this is skewed by the selection of those with respiratory problems for imaging. Presumably, the pathogenesis of the bronchiectasis involves severe, chronic, and recurrent infections with a variety of opportunistic pathogens.[119,120] An additional element that has not been fully addressed is the potential impact of oxidative damage associated with infection or other stressors on the AAT system.[121,122] Impairment of AAT function may contribute to the accelerated lung damage, including bronchiectasis, in persons with acquired immunodeficiency syndrome.[123,124]

Autosomal dominant hyper-IgE syndrome (AD-HIES) due to heterozygous STAT-3 mutation is a primary

immunodeficiency characterized by eczema, elevated serum IgE, and connective tissue and skeletal findings, and recurrent infections of the skin (abscesses), joints, gums, sinuses, middle ear, airways, and lung parenchyma.[125] These infections include severe recurrent bronchopneumonia, especially due to *S. aureus*, which leads to bronchiectasis and pneumatoceles. In addition, bronchiectasis in AD-HIES can also result from impaired remodeling of lung tissue due to a STAT-3 defect.[126] Bronchiectasis in AD-HIES predisposes to opportunistic NTM infection and invasive fungal infection, which contribute significantly to mortality in AD-HIES.

Chronic granulomatous disease (CGD) is caused by a mutation in one of the components of the *reduced nicotinamide adenine dinucleotide phosphate* (NADPH)-oxidase complex, subsequently resulting in deficient NADPH-dependent reactive oxygen species production. Individuals with CGD are vulnerable to severe recurrent bronchopneumonia, particularly with *S. aureus* and fungal infections, which can result in structural lung damage.[127] Although patients are often identified in early childhood due to the typical and severe infections, mild forms of CGD may present in adulthood, and thus CGD could be a cause of unexplained bronchiectasis.[128]

ALPHA$_1$-ANTITRYPSIN ANOMALIES

AAT deficiency may be associated with bronchiectasis.[129–132] Parr and colleagues[130] examined 74 patients with the protease inhibitor ZZ genotype, the most common genotype that results in AAT deficiency, and found that 70 (95%) had bronchiectatic changes on CT scan involving an average of 3.7 lobes and 20 (27%) had "clinically significant bronchiectasis," defined as bronchiectasis affecting four or more lobes *and* "regular sputum production." In contrast, a study of more than 200 bronchiectasis patients found that the frequency of abnormal AAT genotypes was not significantly different from those without bronchiectasis.[133] Thus, based on these studies, it seems that AAT anomalies are uncommon in unselected patients with bronchiectasis, whereas bronchiectasis is common in patients with known AAT deficiency.[134] Because the "Z" isoform of AAT may polymerize in the lungs and act as a chemoattractant for neutrophils, which can then release inflammatory mediators and elastase that incite airway damage, this is a plausible mechanism by which an abnormal AAT protein may predispose to bronchiectasis.[135] However, caution must be exercised in ascribing bronchiectasis to AAT deficiency because one potential confounder is that COPD itself may be associated with bronchiectasis as discussed later.

COPD

Over the past decade, likely due to increasing use of HRCT scans, a relatively high prevalence of bronchiectasis has been reported in patients with moderate to severe COPD and the presence of bronchiectasis has been associated with increased morbidity and mortality.[136–140] Given the 30–60% prevalence of bronchiectasis found in COPD patients in these studies, it would be important to evaluate AAT phenotypes to determine whether the bronchiectasis is associated more closely with severe COPD itself, with associated AAT anomalies, or with both. In one study, COPD patients with bronchiectasis had higher levels of the neutrophil chemoattractant IL-8 in their sputa, increased bacterial colonization of their lower airways, and more severe exacerbations than those without bronchiectasis.[139] Whether bronchiectasis is a sequela in COPD patients with frequent exacerbations, identifies a subgroup of COPD patients with a different pathogenic mechanism, or both, remains to be determined.[141]

PRIMARY CILIARY DYSKINESIA

PCD is an uncommon inherited condition, with an estimated prevalence of 1:10,000. PCD is caused by mutations of various genes that encode for dynein proteins that are components of cilia or for cytoplasmic proteins responsible for cilia assembly.[142,143] Respiratory manifestations result from defective ciliary structure and function in the middle ear, nose, sinuses, and tracheobronchial tree, and include chronic oto-sinopulmonary disease.[142,144–146] Because ciliary function is critically important for proper organogenesis and laterality of organs during embryonic development, there may also be complex congenital heart disease and inversion of the normal anatomic locations for the organs of the thorax and abdomen, whether *situs inversus universalis* (Kartagener syndrome) or *partialis*[147] (eFig. 69.6). Reduced fertility is another hallmark feature among men and women with PCD due to abnormal ciliary function that results in impaired sperm motility or fallopian tube dysfunction, respectively.

Because of impaired function of ciliated respiratory epithelium, PCD patients typically have a history of recurrent otitis media, sinusitis, chronic rhinitis, bronchitis, and bronchiectasis. Newborns with PCD often experience respiratory distress shortly after birth despite term gestation, which is believed to be a consequence of defective ciliary function causing inefficient clearance of lung fluid. In contrast to CF, the bronchiectasis associated with PCD tends to be lower lung zone predominant and milder in severity.[66,148] Compared to those with other causes of non-CF bronchiectasis, those with PCD are generally younger, have lower lung function, and perhaps have more exacerbations/hospitalizations.[72] Although PCD-associated bronchiectasis may not manifest until the late teens or early adulthood, asymptomatic or symptomatic bronchiectasis may be seen by imaging in PCD-affected children of all ages, including those younger than 5 years.[147] *H. influenzae*, *S. aureus*, and smooth strains of *P. aeruginosa* are commonly found in children with PCD, but infection or colonization with mucoid strains of *P. aeruginosa* typically does not happen until adulthood.[66,149] Other historical and clinical features associated with PCD include parental consanguinity, nasal polyps, pectus excavatum, and scoliosis.[149,150]

In contrast to CF, PCD is a genetically heterogeneous disease with numerous implicated genes leading to various abnormalities in ciliary structure and function. As a consequence, diagnosing PCD is not a trivial process.[62,66,152–154] A complement of functional and genetic tests is of value to diagnose PCD, and multiple tests may be required to confirm the diagnosis.[153]

Behan and coworkers[155] formulated and validated a clinical scoring tool, the *Primary Ciliary Dyskinesia Rule* (PICADAR), to help clinicians diagnose PCD in patients with chronic productive cough, using seven clinical parameters: situs inversus (4 points), full-term gestation (2 points), neonatal chest symptoms (2 points), neonatal intensive care admittance (2 points), congenital cardiac defect (2 points), chronic rhinitis (1 point), and ear symptoms (1 point). This PICADAR tool demonstrated a sensitivity and specificity of 90% and 75% for PCD diagnosis with scores of 5 or more out of a possible 14 points. A modified PICADAR score was subsequently developed for PCD screening in adult bronchiectasis because gestational age is often not known and thus omitted from the scoring criteria; in addition, "neonatal chest symptoms" and "neonatal intensive care admittance" were combined to "neonatal respiratory distress."[156] Using a cutoff score of 2 or more points with the modified PICADAR score, the sensitivity and specificity for PCD were 100% and 89%, respectively.[156]

Nasal nitric oxide (nNO) is a noninvasive test that has emerged as a screening test due to its high sensitivity for PCD.[153] Although nNO testing is still often limited to a few centers, the development of electrochemical portable analyzers that are relatively easy to operate will likely increase the availability of PCD screening.[157] Affected individuals have nNO that is significantly lower (<77 nL/min) than the range seen in unaffected individuals. Hypothesized mechanisms for the low nNO in PCD include reduced NO synthesis by the abnormal airway epithelium, increased NO breakdown by denitrifying bacteria, reduced storage capacity of NO in the paranasal sinuses, and NO trapped in obstructed paranasal sinuses.[158] It should be noted that approximately one-third of patients with CF have nNO below the diagnostic threshold for PCD, which underscores the importance of eliminating CF as a potential cause in anyone suspected of having PCD.[66,153,154] nNO is measured by aspirating nasal air while instituting measures to prevent sampling air from the lower respiratory tract (exhaled NO), which typically has much lower NO levels than nNO. A meta-analysis of 12 studies (514 PCD patients and 830 non-PCD subjects) comparing nNO with either ultrastructural analysis by *transmission electron microscopy* (TEM) alone or TEM plus genetic testing found nNO had a sensitivity of 98% and specificity of 96%.[159] But it is important to emphasize that patients with low nNO may also have negative genetic testing or normal/nondiagnostic TEM analysis for PCD.[160] The specificity of low nNO for PCD may be further compromised if CF and patients with acute viral infections, chronic sinusitis, nasal polyposis, human immunodeficiency infection, cigarette smoking, and diffuse panbronchiolitis are not excluded, because these conditions may be associated with low nNO.[152,153]

Genetic testing for PCD is becoming more available with development of commercial testing panels. Currently, mutations of more than 40 genes have been identified to cause PCD. Because it is likely that not all genes associated with PCD have been identified, the sensitivity of genetic testing for PCD is estimated to be about 50–80% with the 26-gene panel, increasing to 94% with the 32-gene panel.[62,153,154] Biallelic autosomal mutations or hemizygous X-linked mutations in one of the approximately 40 PCD genes are present in greater than 70% of patients with PCD.[161] The majority of these mutations are either deletion or nonsense mutations leading to a loss-of-function of ciliary proteins (e.g., DNAI1, DNAI2, or DNAH5) or cytoplasmic proteins involved in the preassembly of the cilia.[152] Mutation of any of the cytoplasmic proteins involved in cilia assembly results in loss of both outer and inner dynein arms, causing ciliary immotility or severe dysmotility, and mutation of genes that encode for dynein arm components results in partial or complete situs inversus. Complicating genetic diagnosis, several mutations implicated in PCD can be associated with normal ultrastructural findings (≈30% of cases) and may even demonstrate normal ciliary beat frequency and motility.[152,162]

The traditional gold standards for diagnosis of PCD are TEM of ciliated epithelium revealing ultrastructural defects of the cilia ultrastructure (e.g., absence of outer and/or inner dynein arms) and measurements of ciliary beat frequency or coordination via high-speed video microscopy. However, each has its own considerable limitations, as discussed later. Ultrastructural findings of abnormal cilia include complete or partial absence of outer or inner dynein arms, a lack of radial spokes, and transposition of one or more outer doublet microtubules into the central area of the cilia resulting in dyscoordinated and chaotic ciliary movement. These tests are limited by availability and expertise required, as well as the fact that, due to chronic sinopulmonary infection, the biopsied samples often contain inadequate or infection-induced damage to the ciliated epithelium, precluding accurate assessment.[152,163] Furthermore, based on clinical manifestations and genetic testing consistent with PCD, it is estimated that about 30% of PCD patients have normal or near-normal cilia ultrastructure, as exemplified by those with mutation of *DNAH11*.[152,154,164–166] Thus, absence of ultrastructural abnormalities does not rule out PCD.

Measurement of ciliary beat frequency and analysis of dysmotility, by high-speed video microscopy alone (120–500 frames/sec) or combined with ciliary wave form analysis (also known as ciliary beat pattern, which assesses ciliary coordination and the presence of a full sweep motion), require experienced investigators and specialized techniques. Despite optimal conditions, known limitations to assessing ciliary function include the presence of ciliary dysfunction due to infection, inflammation, and/or injury during sample collection, as well as the overlap of ciliary beat frequencies between PCD patients, disease controls, and even normal subjects.[152] Thus, an abnormal ciliary beat frequency or dysmotility does not definitively diagnose PCD and, conversely, a subset of genetically confirmed PCD patients have normal ciliary beat frequency. Hence, there was less enthusiasm for measurement of ciliary beat frequency in the 2018 guideline for diagnosing PCD.[153,154]

Among adult men, semen analysis may be useful to diagnose PCD. Dysmotile or immotile spermatozoa may be demonstrated using traditional light microscopy, using a slide prepared with a drop of nondiluted semen at 200× to 400× magnification. Abnormal motility is diagnosed if greater than 50% of sperm are immotile or nonprogressive, meaning that they move but do not make forward progression.[167] However, visualization of motile sperm does not rule out the possibility of PCD. Sperm tails may appear morphologically normal using light microscopy; therefore, ultrastructural analysis of the sperm flagella using TEM is needed to confirm the diagnosis. Sperm tails often, but not always,

demonstrate the same inner and/or outer dynein arm defects present in the respiratory cilia.[168] Although infertility due to impaired or absent sperm motility is supportive of a diagnosis of PCD, fatherhood (or motherhood) of PCD subjects has been reported, and thus male (or female) fertility does not rule out a diagnosis of PCD.[169]

Given the complexities and uncertainties of the various tests available to confirm the diagnosis of PCD and the order they should be performed, a recently published American Thoracic Society guideline on PCD diagnosis generated an algorithm that aids clinicians in PCD assessment (eFig. 69.7).[153,154]

BRONCHIAL CARTILAGE OR ELASTIC FIBER DEFECTS

Mounier-Kuhn syndrome, or congenital tracheobronchomegaly, is a rare disorder associated with gross enlargement or dilation of the trachea and segmental bronchi[170] (eFig. 69.8). The underlying defect is atrophy and even absence of elastic fibers and smooth muscle tissues of the large airways.[171] Atrophy of the connective tissue between the rings may result in outpouchings (diverticulae) that can serve as reservoirs for recurrent infections. Clinically, Mounier-Kuhn patients may present in early childhood or as late as the fourth decade with recurring lower respiratory infections. The diagnosis is readily made by finding extraordinary dilation of the trachea and central bronchi on CT scans, especially in the presence of tracheal and/or bronchial diverticula (see eFig. 69.8); for men, transverse and sagittal tracheal diameter greater than 25 mm and greater than 27 mm, respectively, is considered abnormally enlarged, whereas in women, the respective values are greater than 21 mm and greater than 23 mm.[172] Special considerations in management include positive end-expiratory pressure support and silicone or metallic stenting. Lung transplantation is an option, although unique issues associated with Mounier-Kuhn syndrome include recurrent infections when tracheal diverticula are present and difficulty with bronchial anastomosis due to discrepancy in the airway diameters between the donor and the recipient lungs.

Williams-Campbell syndrome arises due to absence of cartilaginous rings in the fourth- to sixth-generation subsegmental bronchi in a symmetrical distribution, although more proximal bronchi may also be involved.[173] In addition to the subsegmental and segmental bronchiectasis, bronchomalacia of the more proximal airways may be seen[174] (eFig. 69.9). Familial cases have been reported in this condition, although the precise genetic defect is not known. Patients with Williams-Campbell syndrome are particularly predisposed to proximal bronchomalacia after transplantation due to the combined effects of cartilage deficiency in their mainstem bronchi in addition to the usual decrement of blood supply to the proximal airways due to loss of collateral circulation of the transplanted lung.[175]

CONNECTIVE TISSUE DISORDERS

Among the various formally described heritable disorders of the connective tissues, Marfan syndrome, caused by mutations of the *fibrillin 1 (FBN1)* gene, with more than 600 different mutations of *FBN1* identified, has been reported to be associated with bronchiectasis.[176–178] Other lung disorders associated with Marfan syndrome include distal acinar emphysema, cystic degeneration, spontaneous pneumothorax, bullae, apical fibrosis, and a congenital pulmonary malformation known as middle lobe hypoplasia.[178]

CONGENITAL AND DEVELOPMENTAL ANOMALIES

Conditions such as sequestration, agenesis, hypoplasia, and atresia may primarily cause bronchiectasis or may predispose to infections that secondarily cause bronchiectasis. Sequestrations presumably develop from accessory primordial lung buds, which may be invested within normal lung tissue (intralobar) or external to the normal lungs (extralobar). Sequestrations may or may not connect with the bronchial tree and often derive their blood supply directly from the aorta. Clinically, intralobar sequestration most commonly presents with recurrent and/or chronic lower respiratory tract infections beginning in the second or third decade of life, whereas extralobar sequestration is usually asymptomatic due to lack of communication with the airways. Radiographically, they usually appear as irregular, peculiar densities abutting the diaphragm in the posterior basal regions. Unilateral hyperlucent lung (Swyer-James-MacLeod syndrome) is characterized by unilateral bronchiolitis leading to hyperinflation. In some cases, bronchiectasis is present. The etiology and pathogenesis of this rare disorder are uncertain but may involve developmental or acquired disturbances of the bronchial tree.

IDIOPATHIC INFLAMMATORY DISORDERS

There is a wide array of idiopathic inflammatory conditions associated with bronchiectasis. They are all systemic illnesses that variably involve the lungs and may or may not result in bronchiectasis.

Sarcoidosis is by far the most common of these disorders (see Chapter 93). Broadly, sarcoidosis may involve the airways by several fundamental mechanisms: diffuse parenchymal scarring resulting in traction and airway distortion; endobronchial granulomatous inflammation, including stricture with poststenotic infection; or compression secondary to hypertrophic peribronchial lymphadenopathy.[179]

Rheumatoid arthritis (RA) may entail a variety of pulmonary manifestations. In two early series, bronchiectasis was seen in 3.2%[180] and 5.2%[181] of RA patients. More recently, bronchiectasis has been described in considerably higher percentages of RA patients undergoing HRCT scanning (20–35%)[182]; these studies were likely skewed by the selection of patients with respiratory problems. However, bronchiectasis was seen in 8% of RA patients without respiratory symptoms.[183] Of note, the majority of the patients in the previously discussed series did not have RA-associated interstitial lung disease as a presumed cause of the bronchiectasis. Potential causal mechanisms include increased propensity for infections, either intrinsic to RA or secondary to glucocorticoid or cytotoxic therapy. Clinically, the presence of bronchiectasis in RA patients was associated with an unfavorable prognosis in one series.[184]

Ankylosing spondylitis has been classically associated with upper lung zone fibrocystic degeneration and ankylotic fusion of the junctions of the ribs and vertebrae, resulting in restricted ventilation. However, in a large series from the Mayo Clinic, pulmonary involvement was described in only 1.2% of the patients.[185] Bronchiectasis independent of apical fibrocystic disease has been seen in a small series from the United Kingdom.[186]

Systemic lupus erythematosus may involve an assortment of pulmonary complications, including those intrinsic to the disorder itself, whereas others may be iatrogenic (see Chapter 92). Bronchiectasis was described in 21% of systemic lupus erythematosus patients studied with HRCT.[187] As with RA, the presence of Sjögren syndrome may be a comorbid element that predisposes to bronchiectasis.

Sjögren syndrome, keratoconjunctivitis sicca, and xerostomia (dry eyes and mouth) may exist in the primary form or in association with other collagen vascular diseases, such as RA or systemic lupus erythematosus. Pulmonary complications of Sjögren syndrome include lymphocytic interstitial pneumonia, lymphoma or pseudolymphoma, and/or pulmonary hypertension (see Chapter 92). Bronchiectasis has also been noted.[188–190] It is reasoned that lymphocytic inflammation results in impaired function of mucous glands, in turn resulting in decreased volumes and increased desiccation and viscosity of mucus. This leads to airway obstruction, poor clearance, and chronic infection. There have not been large CT scan surveys in patients with Sjögren syndrome to quantify the incidence of bronchiectasis.

Inflammatory bowel disease–associated bronchiectasis appears to be more common with ulcerative colitis than with Crohn disease.[191,192] In the majority of cases, the bowel disease antedates the lung manifestations, but the conditions may be temporally reversed. One unique observation of ulcerative colitis–associated bronchiectasis is that it may develop after therapeutic colectomy.[193] Proposed pathogenic relationships include a cryptogenic infection that incites both airway and intestinal inflammation, common epithelial targets of autoimmunity, or sensitizing agents that are inhaled and/or ingested, resulting in both lung and bowel disease.

Relapsing polychondritis is identified essentially as progressive inflammation, weakness, and deformity of cartilaginous structures, including the ears, nose, larynx, and tracheobronchial tree, typically associated with nonerosive polyarthritis. In addition, there may be inflammatory and/or functional disturbances of the eyes, auditory/vestibular components of the ears, and aorta (vasculitis with aneurysm). Respiratory involvement is characterized by tracheal and bronchial cartilage inflammation, resulting airway collapse, and airflow limitation (eFig. 69.10). Bronchiectasis in such patients may be due to primary bronchial damage and/or recurrent infection.[194]

ASPIRATION/INHALATION ACCIDENTS (See Also Chapter 43)

Spillage of foreign matter into the airways may result in bronchiectasis. There are two fairly distinct scenarios in which such matter might be aspirated into the lungs and cause sufficient damage to result in chronic deformity of the airways. One is the direct spillage of secretions from the oropharynx—infamous for containing a plethora of microorganisms, including microaerophilic and anaerobic bacteria—producing necrotizing pneumonia. The other is introduction of materials refluxed from the esophagus and/or stomach, which, in addition to the microorganisms noted earlier, contain food particles, hydrochloric acid, biliary or pancreatic secretions that contain various proteases, and microbes indigenous to the gut.[195]

Laryngeal protective functions are imperfect, and "microaspiration" is common. Thus, we might presume that aspiration leading to lower respiratory tract infections involves greater-than-usual volumes and/or more noxious contents. Also, it is reasonable to posit that once the airways have been damaged, a lesser inoculum may be adequate to incite the same damage, a variant of the "vicious cycle" theory.

Many factors influence the likelihood/frequency of aspiration. They include (1) depressed sensorium (trauma, alcohol or drug abuse, postictal confusion state, and general anesthesia), (2) altered brainstem function (cerebrovascular accident, polio, and primary neurologic diseases, such as multiple sclerosis, amyotrophic lateral sclerosis, or syringomyelia), (3) altered laryngeal structure/function (after surgery or irradiation), (4) esophageal disorders (dysmotility, obstruction by tumors or strictures, muscular dystrophy, achalasia, tracheoesophageal fistulas, or lower esophageal sphincter incompetence), and (5) gastric dysfunction (dysmotility or outlet obstruction).

Although all of these elements may contribute to the risk for infection (and bronchiectasis), it seems likely that GER is the most common factor. Among a cohort of bronchiectasis patients noted previously, approximately three-fourths of them had demonstrated abnormalities of esophageal morphologic features (dilation and thickening), function (dysmotility), anatomy (hiatal herniation), or competence (overt reflux).[196] Indeed, the frequency of esophageal disturbances was so high that one might question whether the esophageal findings were the cause of recurring infections/bronchiectasis or, in some cases, an effect. In the latter regard, among a series of patients with asthma and idiopathic pulmonary fibrosis, the incidence of esophageal dysfunction ranged from 80–95%.[197,198] It is plausible that labored breathing with wide disparities between intraabdominal and intrathoracic pressure and/or chronic coughing, which stresses and dilates the diaphragmatic ring, might disrupt the lower esophageal sphincter and subject the esophagus to distending forces.[199] An additional factor that could contribute to GER disease is the medical therapy used for these lung disorders; anticholinergics, β_2-agonists, theophylline, and corticosteroids can impair lower esophageal sphincter function,[200] and broad-spectrum antibiotics alter gastroesophageal flora.

For those suspected of disordered swallowing, tailored hypopharyngography using contrast materials of varying consistency may identify unsuspected aspiration, even in the absence of awareness or coughing. A speech therapist can also instruct patients on safer techniques for eating, drinking, and swallowing.

Impaired esophageal motility may be suggested on CT scans of the lungs, manifesting as grossly dilated esophagus, excessive luminal air in the esophagus, and/or thickened esophageal walls. Impaired motility may often be

demonstrated on a simple barium swallow. The extent of impaired contractility may be measured by esophageal manometry; this is essential if a reconstitution of the lower esophageal sphincter is contemplated. Demonstrating actual reflux may be challenging. If gross reflux is demonstrated on a routine study, it is sufficient for a presumptive diagnosis. However, if symptoms or other clinical features suggest GER disease, and the upper gastrointestinal series has negative results, an 18- to 24-hour pH probe with or without measurement of impedance may both identify and quantify reflux episodes.[197] Non-acid reflux may result in chronic cough and even lung injury.[201] Among the implications of these findings is that acid inhibition measures may not be sufficient to protect the airways. For individuals with evidence of recurrent aspiration, elevation of the head of the bed should be done routinely.

Toxic inhalation or thermal injury may also be associated with bronchiectasis. Acute and chronic inflammation of the tracheobronchial tree, bronchiolitis, bronchiolitis obliterans, and diffuse alveolar damage may be a consequence of exposure to toxic metal fumes (e.g., aluminum, cadmium, chromium, nickel) or toxic gases (e.g., ammonia, chlorine, phosgene, sulfur dioxide) (see Chapter 103). In severe cases, bronchiectasis may ensue because of infectious complications of the exposure, denuding of the ciliated epithelium, or progressive fibrosis. Similarly, chronic airway damage and bronchiectasis may evolve after thermal or smoke injury.

POSTOBSTRUCTIVE DISORDERS

Foreign bodies may be aspirated into the airways, especially in infants and children. Adults may aspirate with eating, trauma, or loss of consciousness. In some cases, the obstructing object may be radiopaque (teeth, bone, or metal objects) but, in most instances, the obstructing material (e.g., peanuts, vegetables) is not discernible by standard chest radiography. Tumors, benign or malignant, may also result in airway obstruction, poor drainage, recurrent/chronic infection, and bronchiectasis. The more common tumor types include bronchogenic carcinomas (particularly the squamous cell variety), carcinoid tumors, and papillomas. Extrinsic airway compression due most often to hypertrophic lymphadenitis from granulomatous diseases, such as sarcoidosis or infections and including tuberculosis or histoplasmosis, may severely narrow or even occlude large airways. In patients with "focal" bronchiectasis, particularly those with disease limited to only one region (eFig. 69.11), bronchoscopic examination to exclude an obstructing lesion should be performed early if other causes are not evident.

ALLERGIC BRONCHOPULMONARY ASPERGILLOSIS (See also Chapter 96)

ABPA is a relatively uncommon condition, estimated in approximately 2.5% of patients with asthma.[202] ABPA is a hypersensitivity reaction, usually to *Aspergillus fumigatus,* but other fungi, including *Candida albicans,* may also be a source of the antigenic stimulus (allergic bronchopulmonary mycoses). The exaggerated type 2 T helper cell response seen in ABPA is likely due to *human leukocyte antigen* (HLA)-DR2/5 polymorphism resulting in greater efficiency in presenting *Aspergillus* allergens to T cells.[203] As a result of type 2 T helper cell expansion and release of IL-4, IL-5, IL-9, IL-10, and IL-13, there is increased expansion and influx of eosinophils and mast cells, as well as isotype switching to IgG and IgE.[203]

ABPA may manifest with fever, wheezing, eosinophilia, and fixed or fleeting pulmonary opacification (often upper lobes). The opacifications range from subsegmental to lobar and are due to eosinophilic infiltration and/or lymphocytic interstitial pneumonia. Other radiographic findings include atelectasis due to mucus plugging, manifesting clinically as expectoration of thick, brown mucous plugs. The inflammation and distention from the plugs typically result in thin-walled bronchiectasis that is often multilobar and central (Fig. 69.6). The mucoid impaction may show high attenuation, reflecting the organism's ability to fix calcium salts, iron, and manganese (see eFig. 69.5D and F).

The diagnosis of ABPA should be considered in patients with asthma or CF who have frequent exacerbations requiring anti-inflammatory drugs to affect symptomatic relief. The diagnostic criteria for ABPA have evolved but include a number of clinical, radiographic, and laboratory features.[203] A more current diagnostic criterion was proposed by the International Society for Human and Animal Mycology, which allows a diagnosis of ABPA to be made in the absence of radiographic changes[202,204,205] (Table 69.2). However, many patients with ABPA do not have all the criteria, especially with early disease or if taking glucocorticoids. If patients fulfill all the criteria for ABPA except for bronchiectasis, they are diagnosed with seropositive ABPA, likely an early stage of disease.

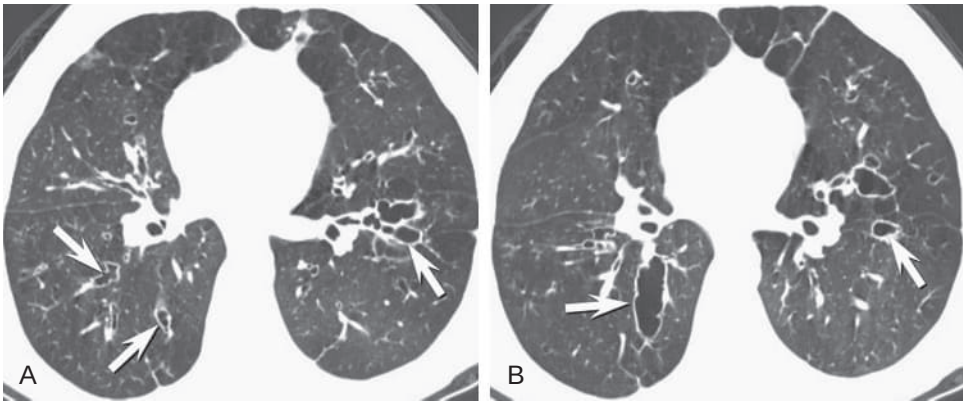

Figure 69.6 Bronchiectasis: allergic bronchopulmonary aspergillosis. (A–B) Axial chest computed tomography shows central bronchiectasis (*arrows*), typical of allergic bronchopulmonary aspergillosis. (Courtesy Michael B. Gotway, MD.)

Table 69.2 Diagnostic Criterial for Allergic Bronchopulmonary Aspergillosis

Predisposing condition: asthma or cystic fibrosis
ESSENTIAL CRITERIA
1. Type I immediate cutaneous hypersensitivity reaction (wheal and flare) to *Aspergillus fumigatus** or elevated serum IgE against *A. fumigatus* and
2. Elevated total IgE (>1000 IU/mL†)
OTHER CRITERIA (≥2 OF 3 NEEDED)
1. Presence of serum precipitating or IgG against *A. fumigatus*
2. Radiographic pulmonary opacities consistent with ABPA (e.g., pulmonary opacification and/or bronchiectasis)
3. Total eosinophil count >500 cells/μL in patients not on recent corticosteroids

*Although cutaneous skin testing is nearly 100% sensitive and is a useful screening test for ABPA, it is not specific for ABPA.
†Total of IgE <1000 IU/mL may be acceptable if patient meets all other criteria.
ABPA, allergic bronchopulmonary aspergillosis; IgE, immunoglobulin E; IgG, immunoglobulin G.
From Agarwal R, Chakrabarti A, Shah A, et al; ABPA Complicating Asthma ISHAM Working Group. Allergic bronchopulmonary aspergillosis: review of literature and proposal of new diagnostic and classification criteria. *Clin Exp Allergy*. 2013;43:850–873.

Distinguishing ABPA from CF can be difficult, given the similarities between the two disorders, including the presence of bronchiectasis and positive serologic tests for *Aspergillus*. The CF Foundation has established diagnostic criteria for ABPA in CF patients: (1) clinical deterioration not attributable to another cause, (2) IgE greater than 1000 IU/mL, (3) skin test positivity to *Aspergillus,* (4) precipitating antibody or specific IgG to *Aspergillus*, and (5) abnormalities on chest imaging unresponsive to antibiotics or standard chest physiotherapy.[203]

IDIOPATHIC BRONCHIECTASIS

Depending on the extent of evaluation and perhaps referral bias, "idiopathic" bronchiectasis, for which no known predisposition is identified, is estimated to account for 25–50% of cases of bronchiectasis.[1,206,207] Although the diagnosis of idiopathic bronchiectasis can only be made after known causes of bronchiectasis are effectively excluded, it often has a characteristic phenotype of bilateral lower lobe bronchiectasis and chronic rhinosinusitis.[1] Genotyping studies of class I and class II major histocompatibility complex molecules indicate that allelic polymorphism for certain HLA subtypes are statistically associated.[208–211] NK cell activation may play a role. NK cells use their killer cell Ig-like receptors to recognize abnormal HLA-C molecules on the surfaces of infected cells, and genotypic analysis of HLA-C–killer cell Ig-like receptor combinations have supported a role for increased NK cell activation in the pathogenesis of idiopathic bronchiectasis.[208] However, to the best of our knowledge, functional studies to confirm excessive NK cell activity in patients with idiopathic bronchiectasis have not been done. Nevertheless, this hypothesis is supported by the presence of bronchiectasis in patients with the transporter-for-antigen-presentation deficiency syndrome, a genetic disorder with impaired HLA class I expression and dysregulated NK, γδ cytotoxic T cell, and $CD8^+$ T cell function. In this disorder, the defective HLA class I expression results in increased NK and γδ T cell activities because HLA class I normally serves as an inhibitory ligand for these cell types.[212]

MISCELLANEOUS

There are numerous other causes of bronchiectasis, including such diverse entities as yellow nail syndrome and radiation therapy injury.

Yellow nail syndrome is an uncommon disorder marked by the triad of yellow, thick, dystrophic nails; chronic lymphedema of the face, hands, and lower extremities; and pleural effusions.[213] Women are more commonly affected than men; the median age of onset is 40 years, with cases ranging from infancy to the seventh decade. The most prominent pulmonary finding is bilateral exudative pleural effusions.[214] Recurrent sinusitis and lower respiratory tract infections are common, the latter resulting in bronchiectasis.[215] Contributing factors for bronchiectasis include abnormal lymphatic structure, increased vascular permeability, deficient immunoglobulin production, and/or ciliary dysfunction.

Radiation therapy, typically delivered for carcinoma of the breast or mediastinal tumors, including lymphomas, may result in profound damage to the central airways. This reaction is marked by focal damage to the cartilage and mucosa of the airways leading to distention and irregularities of the major bronchi in the field of irradiation. Bronchiectasis secondary to radiation therapy for neoplasms has become less common as radiation dosage and field used have become more refined. This condition may be recognized by lung parenchymal scarring in the field of irradiation (eFig. 69.12).

MANAGEMENT

The care of patients with bronchiectasis typically involves many layers, which may be partitioned into five broad components: airway hygiene, antimicrobial treatment, anti-inflammatory therapy, surgery, and miscellaneous. Although most patients with bronchiectasis require various elements of each of these components to enjoy optimal health, there is no standard formula for treating this disorder. The great majority of recurrently or chronically symptomatic patients benefit from a regular mucus-clearing regimen and periodic antibiotic therapy. For most patients, a pragmatic or trial-and-error approach is required to determine individual needs, preferences, and tolerances.

It is important to note that most elements described in this section have not been shown to be efficacious by randomized, controlled clinical trials. Thus, meta-analyses, such as those reported in the Cochrane Database of Systematic Reviews, generally cannot confirm the benefits or disutility of such approaches.[216–223] Perhaps because bronchiectasis is such a complex mix of varying conditions and has been an underappreciated "orphan" disease, a paucity of systematic research has been directed at this very troublesome

disorder, although this is changing. The available evidence and assessment of the value of integrated therapies have been summarized in two guidelines by the British Thoracic Society[60] and the European Respiratory Society.[61]

AIRWAY HYGIENE AND HYPEROSMOTIC AGENTS

Airway hygiene consists of nonantibiotic therapies directed toward mobilizing and eliminating inflammatory secretions from the tracheobronchial tree and from the paranasal sinuses. Modern devices to facilitate airway clearance of secretions include the Flutter valve, Acapella valve, Aerobika valve, and high-frequency chest wall oscillation devices. See eFig. 69.13 for a summary of potential airway clearance therapies. Also included under this rubric are steps to prevent/limit aspiration of oropharyngeal or gastroesophageal contents into the airways.

Hypertonic saline, 3% or 7% two to four times daily, has been shown to accelerate mucus clearance, decrease exacerbations, and improve lung function in CF patients.[224] However, its role in non-CF bronchiectasis remains to be seen because studies show conflicting results. When hypertonic saline was used for mucus clearance as part of an algorithm in combination with protocolized chest physiotherapy, exacerbations were reduced.[225] Inhaled dry-powder mannitol, recently approved for adult CF patients,[226] appears promising in airway clearance in bronchiectatic patients,[227,228] although it may be difficult to tolerate.

The mucolytic drug *N*-acetylcysteine (600 mg twice daily) was found to be effective at reducing exacerbations when taken orally,[229] although studies to confirm this small sample size trial are needed. Other mucoactive drugs, such as recombinant human deoxyribonuclease, failed to reduce exacerbations and had a trend toward more frequent and severe exacerbations in patients with idiopathic bronchiectasis.[230]

ANTIMICROBIAL THERAPY

Antimicrobial therapy historically has been the centerpiece of bronchiectasis care. However, there is no clear consensus on the major questions in this area, including whether treatment should be given on a routine, periodic schedule (rotating) or an as-needed basis for clinical exacerbations. In a meta-analysis of the use of prolonged oral antibiotics for purulent bronchiectasis, sputum volume/purulence was shown to decrease, but there were no significant beneficial effects in regard to rates of exacerbations, lung function, or death.[231] There are also limited data on the empirical selection of an antimicrobial agent or treatment guided by species identification and in vitro susceptibility testing. For patients unresponsive to empirical antibiotics or who experience frequent exacerbations, it appears prudent to obtain comprehensive microbiologic cultures, including for NTM and fungal organisms, and to tailor antibiotics based on the type of organism identified and drug susceptibility profile.

Aerosolized antibiotics also appear promising in treating or preventing exacerbations. Given the role of chronic *P. aeruginosa* in the pathogenesis and prognosis of bronchiectasis, there is ongoing research to develop strategies for acute and chronic treatment of this infection.

The success of inhalational antibiotics targeted toward *P. aeruginosa* in CF lung disease has prompted extensive evaluation of this strategy in non-CF bronchiectasis. In the earliest studies, addition of inhaled tobramycin to oral ciprofloxacin for *Pseudomonas*-associated exacerbation of non-CF bronchiectasis showed improved microbiologic outcome; however, there was no additional clinical benefit over ciprofloxacin alone, perhaps due to approximately threefold greater incidence of bronchospasm in the tobramycin arm.[232] In patients with CF, inhaled tobramycin twice daily given in alternating months decreased the frequency of exacerbations due to *P. aeruginosa.*[233] Even in patients without CF, inhaled tobramycin was found to be efficacious.[234] In a randomized study of nebulized gentamicin (twice daily for 12 months) versus saline for 65 patients with non-CF bronchiectasis, the gentamicin-treated subjects had reduced microbial burden, airway neutrophils, and sputum purulence.[235] Improved exercise capacity, decreased exacerbation frequency, and better health-related QOL measure were also seen in the gentamicin arm, with the caveat that patients were not blinded to the treatment.[236] Compared to nebulized saline, nebulized gentamicin given prophylactically for 12 months also showed significant reduction in markers of inflammation in both the airways and circulation.[237]

Inhaled ciprofloxacin has been studied for its efficacy in preventing exacerbations from *Pseudomonas* and several other chronic infections associated with frequent exacerbations. In companion Phase III studies (RESPIRE 1 and 2), the effect of ciprofloxacin in varied on-off cycles was examined in reducing time to next exacerbation.[238,239] Given the inconsistent results on the primary end point, inhaled ciprofloxacin was not approved. In a separate trial of aerosolized liposomal ciprofloxacin (150 mg liposome encapsulated plus 60 mg of free ciprofloxacin) in 582 subjects, there was no significant difference in the time to first exacerbation between the ciprofloxacin and placebo arms, although the ciprofloxacin arm had a significant reduction in the annualized exacerbation frequency.[240]

Inhaled aztreonam was studied in two companion trials (AIR-BX1 and 2) for effects of improved QOL by the *QOL-Bronchiectasis Questionnaire* (QOL-B) in patients with chronic *Pseudomonas* infection. A total of 540 patients were randomized to receive on-off periods of 38 days of inhalational aztreonam versus placebo. There was no significant difference in the primary end point of improved QOL. Subsets of patients experienced reduced exacerbations and improved QOL, but inhaled aztreonam was not approved for use in this subset of bronchiectasis patients.[241]

Finally, inhaled colistin, at a dose of 1 million international units (aerosolized), was studied in a randomized trial versus saline in 144 subjects with *P. aeruginosa* in their sputum and who were randomized after a course of intravenous antipseudomonal antibiotics for an exacerbation. The median time to first exacerbation was not significantly different in the colistin subjects compared with the placebo subjects. The patients receiving colistin had improved QOL and reduced bacterial sputum density of *Pseudomonas*.[242]

In summary, the role of inhalational antibiotics is not supported by large-scale pivotal studies. However, in many of the studies, subsets of patients had improvements in QOL or bacterial density. Therefore, expert opinion advocates the use of these therapies in individualized therapeutic regimens for patients with chronic *Pseudomonas* or other gram-negative infections.

Due to the role of *Pseudomonas* in propagating pathology and accelerating clinical decline, attention has been paid recently to eradication of initial infections.[61] Several groups have evaluated eradication protocols predicated on a period of systemic antipseudomonal antibiotics followed by suppression with inhalational antibiotic therapies, with varied success at achieving long-term eradication.[243,244] Approaches to *P. aeruginosa* eradication are summarized in eFig. 69.14.

ANTI-INFLAMMATORY THERAPY

The rationale for using the anti-inflammatory agents in bronchiectasis is to dampen the inflammatory cascade, with the goals of reducing symptoms and limiting the progression of disease and decline in lung function. Anti-inflammatory agents that have been examined in bronchiectasis include the *nonsteroidal anti-inflammatory drugs* (NSAIDs) and inhaled corticosteroids. Intermittent macrolides have been studied for their antimicrobial activities as well as their anti-inflammatory and other nonmicrobicidal activities (see next section).[245]

Nonsteroidal Anti-inflammatory Drugs

Because prostaglandins may play a role in augmenting airway secretions, NSAIDs, by blocking the cyclooxygenase pathway, have been studied in bronchiectasis. In a double-blind, placebo-controlled study in patients with bronchorrhea due to chronic bronchitis, diffuse panbronchiolitis, and bronchiectasis, inhaled indomethacin significantly decreased both the amount of sputum and the perceived dyspnea.[246] Another mechanism by which indomethacin may help in bronchiectasis is via inhibition of both neutrophil chemotaxis and neutrophil degradation of fibronectin, thereby decreasing airway inflammation and purulence.[247] In a comprehensive Cochrane Database review of randomized trials of NSAIDs in CF patients, high-dose ibuprofen was shown to slow the progression of lung disease, especially in children.[248] In contrast, there have been no randomized, controlled trials on the use of NSAIDs in non-CF bronchiectatic patients.[249]

The anti-inflammatory properties of statins were studied in a Phase II trial demonstrating reduction in cough and improved QOL.[250] Although larger trials failed to replicate these findings, treatment was associated with improved cough and QOL, indicating that further exploration of statins is warranted.[251]

Inhaled Corticosteroids

Although some studies show improved symptoms and lung function in CF patients treated with *inhaled corticosteroids* (ICS),[252,253] others, including a review of clinical trials, have not found ICS to be beneficial.[254,255] In non-CF bronchiectasis, relatively small studies indicate that ICS provides symptomatic relief (e.g., reduction in dyspnea, cough, and sputum production).[256–259] High doses of ICS are typically tried in bronchiectasis because of the notion that neutrophils, dominant in bronchiectatic airways, are relatively resistant to the (apoptotic) effects of corticosteroids.[260] Although bronchiectatic patients are often treated with β_2-agonists and ICS based on extrapolation by clinicians of treatment for COPD and asthma, there is limited evidence of their efficacy with bronchiectasis. Martinez-Garcia and associates[260] performed a pilot study comparing high-dose budesonide 800 μg every 12 hours to budesonide 640 μg plus formoterol once daily and found that the combined treatment with the lower dose of ICS resulted in a greater improvement of dyspnea score, health-related QOL assessment, and reduced ICS-associated side effects, such as pharyngeal irritation and dysphonia. Because of the potential risk for pneumonia with ICS use, as has been documented with COPD,[261] it seems prudent to limit the duration of ICS whenever possible, while monitoring closely for worsening respiratory symptoms and function. It is clear that larger studies are needed to determine the benefits and risks of ICS, long-acting β_2-agonists, or the combination as maintenance treatment or rescue therapy for exacerbations.[262]

THERAPIES FOR TREATMENT OF FREQUENT EXACERBATIONS

Intermittent Macrolide Therapy

Independent of their antimicrobial properties, macrolide antibiotics hold promise in inhibiting disease activity in bronchiectasis because of their immunomodulatory effects.[263] Intermittent macrolide therapy may help in bronchiectasis by decreasing the chloride diffusion potential gradient across the airway mucosa (resulting in decreased sputum volume), reducing airway levels of the neutrophil chemokine IL-8, inhibiting both neutrophil and *Pseudomonas* migration, suppressing *Pseudomonas* quorum sensing, disrupting the established biofilm layer, and enhancing alveolar macrophage phagocytic ability.[264,265] Thus macrolide therapy is posited to antagonize several of the mechanisms of pulmonary exacerbation and pathogenesis of bronchiectasis.

Clinical trials have explored the benefits of macrolides. In older studies, clarithromycin, but not amoxicillin or cefaclor, was shown to reduce sputum production in patients with chronic bronchitis or bronchiectasis.[266] Beneficial effects plus improvement in lung function have been shown in various trials using intermittent azithromycin therapy in CF patients chronically infected with *P. aeruginosa* and also in younger CF patients before they have been colonized with *P. aeruginosa.*[267] In a double-blind, placebo-controlled trial of approximately 120 patients with non-CF bronchiectasis and a history of frequent pulmonary exacerbations, low-dose erythromycin (400 mg twice daily) for 12 months significantly reduced (1) the number of pulmonary exacerbations overall by roughly one-third, as well as in those with baseline *P. aeruginosa* airway infection, (2) sputum production, and (3) lung function decline as measured by *forced expiratory volume in 1 second* (FEV_1).[268] However, erythromycin prophylaxis was associated with increased frequency of macrolide-resistant oropharyngeal streptococci.[268] Two double-blind, placebo-controlled trials of azithromycin (250 mg daily for 12 months or 500 mg thrice weekly for 6 months) resulted in significantly lower rates of exacerbations compared to placebo.[269,270] In an individual patient data meta-analysis that comprised three studies totaling 341 subjects with bronchiectasis, long-term macrolide antibiotics significantly reduced the frequency of exacerbations, improved the time to first exacerbation, and enhanced the QOL, especially in those with *P. aeruginosa* infection, although there was no significant improvement in FEV_1.[271] Finally, in a recently published randomized, controlled trial of 90 patients with PCD, thrice

weekly azithromycin therapy was found to reduce exacerbations compared to placebo patients.[272]

Azithromycin also carries risks. In one study there was a nearly threefold increase in macrolide resistance of bacteria in the azithromycin group and significantly higher incidence of abdominal pain and diarrhea, although these gastrointestinal symptoms did not prevent continuation of azithromycin.[273] In addition to the potential increase in antibiotic resistance in pyogenic bacteria, long-term azithromycin may predispose to drug-resistant NTM infections in patients with bronchiectasis.[273] Azithromycin was also shown to inhibit autophagy, a normal homeostatic cell recycling process increasingly recognized as important for the phagosomal killing of intracellular mycobacteria.[273] Other potential serious adverse effects of azithromycin include dysrhythmias and cardiac-related deaths, especially in those with underlying risk factors for cardiovascular disease.[274,275] In sum, at this time, because of their risk of harm, macrolides should probably be considered only in patients who would potentially benefit the most, for example, those with frequent exacerbations.

Inhibition of Neutrophil Elastase

Recurrent exacerbations in bronchiectasis are linked to neutrophilic influx into the airways. Subsequent elaboration of neutrophil serine proteases, including neutrophil elastase, may be at play in both chronic and acute inflammation. Thus, this pathway is postulated to drive recurrent cycles of inflammation and damage in the airways. Clinically, inhibition of these pathways is being explored to reduce the vicious cycle through inhibition of neutrophil elastase, which not only degrades elastin but also has other aforementioned deleterious effects. Recently, a large randomized control trial of a novel oral inhibitor of dipeptidyl peptidase I, a key enzyme in the activation of neutrophil elastase (INS1007, Insmed Corporation), has completed enrollment to demonstrate if this strategy reduces time to next exacerbation and frequency of exacerbation.[276] If successful, this strategy will add to the growing armamentarium for treatment of frequently exacerbating patients.

Recent expert guidelines suggest an integrated approach to treatment of frequent pulmonary exacerbations as outlined in eFig. 69.15.

SURGERY

The role of surgery in the management of bronchiectasis is uncertain. No formal systematic studies of the indications and efficacy of resectional surgery have been conducted among patients with bronchiectasis. Traditional indications for resectional surgery have included chronic disabling infection, recurrent infections of intolerable frequency, or irreversible lung damage distal to a foreign body or benign tumor. Hemoptysis that is life-threatening and/or recalcitrant to bronchial artery embolization may be an indication for surgery. A historical adage has been that surgery does not cure bronchiectasis. If true, it is likely due to our evolving understanding that most cases of bronchiectasis are due to innate risk factors that predispose to recurrence. However, surgery may be an appropriate palliative measure in selected cases, especially with severe localized disease, as not uncommonly seen in patients with NTM lung disease or in those with localized bronchiectasis and recalcitrant or recurrent superimposed infections.

Tracheal reconstruction surgeries, including tracheobronchoplasty or tracheal stenting, may confer symptomatic benefit for patients with Mournier-Kuhn.[277,278] Due to the rare nature of this disease, expert opinion from an experienced airway surgical team is vital for making this decision.

Bilateral lung transplantation has become increasingly recognized for patients who experience severe respiratory failure due to bronchiectasis. Due to the suppurative nature of bronchiectasis, single-lung transplantation is not recommended. Although limited evidence for long-term outcomes are available, single-center studies indicate that adults with bronchiectasis have similar long-term survival and recovery of lung function as other patient populations receiving bilateral lung transplant.[279] However, one study found that underlying immunodeficiency and pretransplantation diagnosis of chronic *Pseudomonas* infection may reduce posttransplantation outcomes.[280] The optimal timing is based on lung allocation scores. Although successful for some cases, there is limited evidence for optimal timing and tailoring of lung allocation scores for non-CF bronchiectasis, an area for future research.

MISCELLANEOUS

Additional measures, such as smoking cessation and vaccination against pneumococcal disease and influenza, are appropriate for all patients. Intuitively, these measures seem particularly important for those with bronchiectasis; however, no systematic information is available to confirm their usefulness in this setting. On the other hand, early recognition and remediation of exercise limitation and sleep-related hypoxia has demonstrated substantial benefits in regard to morbidity and mortality. As with all individuals, it seems sensible to ensure that patients with bronchiectasis have repleted vitamin D levels because this hormone has been shown to induce cathelicidin, an antimicrobial peptide.[281] Recently, it was reported that bronchiectasis patients with vitamin D deficiency have more frequent bacterial colonization (especially *P. aeruginosa*), worse airflow, more frequent exacerbations, higher levels of inflammatory markers in sputa, and more rapid decline in lung function over a 3-year follow-up than those with higher vitamin D levels.[282]

OVERALL APPROACH TO MANAGEMENT

Due to increasing complexity of bronchiectasis management, a thoughtful approach to management is necessary. Recent expert guidelines suggest several approaches. One strategy involves step-up therapy based on patient symptoms and severity of lung function and frequency of exacerbations.[283] In addition, a treatment strategy targeted toward aspects of pathophysiology with frequent reassessment of therapeutic response is a reasonable approach. Individualization of therapeutic approach is necessary and may vary by patient preference. We recommend the strategy outlined in Figure 69.7.

PROGNOSIS

All patients with bronchiectasis are affected by a poorer prognosis than age- and gender-matched healthy control subjects. Recent estimates demonstrate an approximately twofold increase in mortality in those with bronchiectasis

compared to healthy normal subjects.[284] Recently published analyses have identified a host of factors predictive of excessive mortality.[285] Prospective evaluation of these analyses has aided in the development of two propensity scoring systems that assess long-term prognosis in non-CF bronchiectasis: the *FEV_1, Age, Chronic Colonization, Extension, Dyspnea* (FACED) Score[286] and the *Bronchiectasis Severity Index* (BSI).[287] Both identified increased risk of mortality and hospitalization on the basis of worsening lung function, age, presence of *P. aeruginosa*, degree of dyspnea, and extent of radiographic bronchiectasis. Both systems result in similar prediction of outcomes when validated head to head.[288] In addition, the BSI scoring system emphasizes the role of prior hospitalization and frequency of exacerbation in the prediction of risk of subsequent hospitalizations.

In addition to excess mortality attributed to bronchiectasis, many patients experience increased morbidity due to pulmonary and sleep-related complications.[289] Patients also have increased risk of nonpulmonary medical issues, including cardiovascular disease, GER disease, malignancy, and cerebrovascular diseases than age-matched healthy control subjects.[290]

Recent developments of QOL instruments, including the QOL-B, focused on bronchiectasis and have aided the assessment of patients and have served as key clinical trial end points.[291]

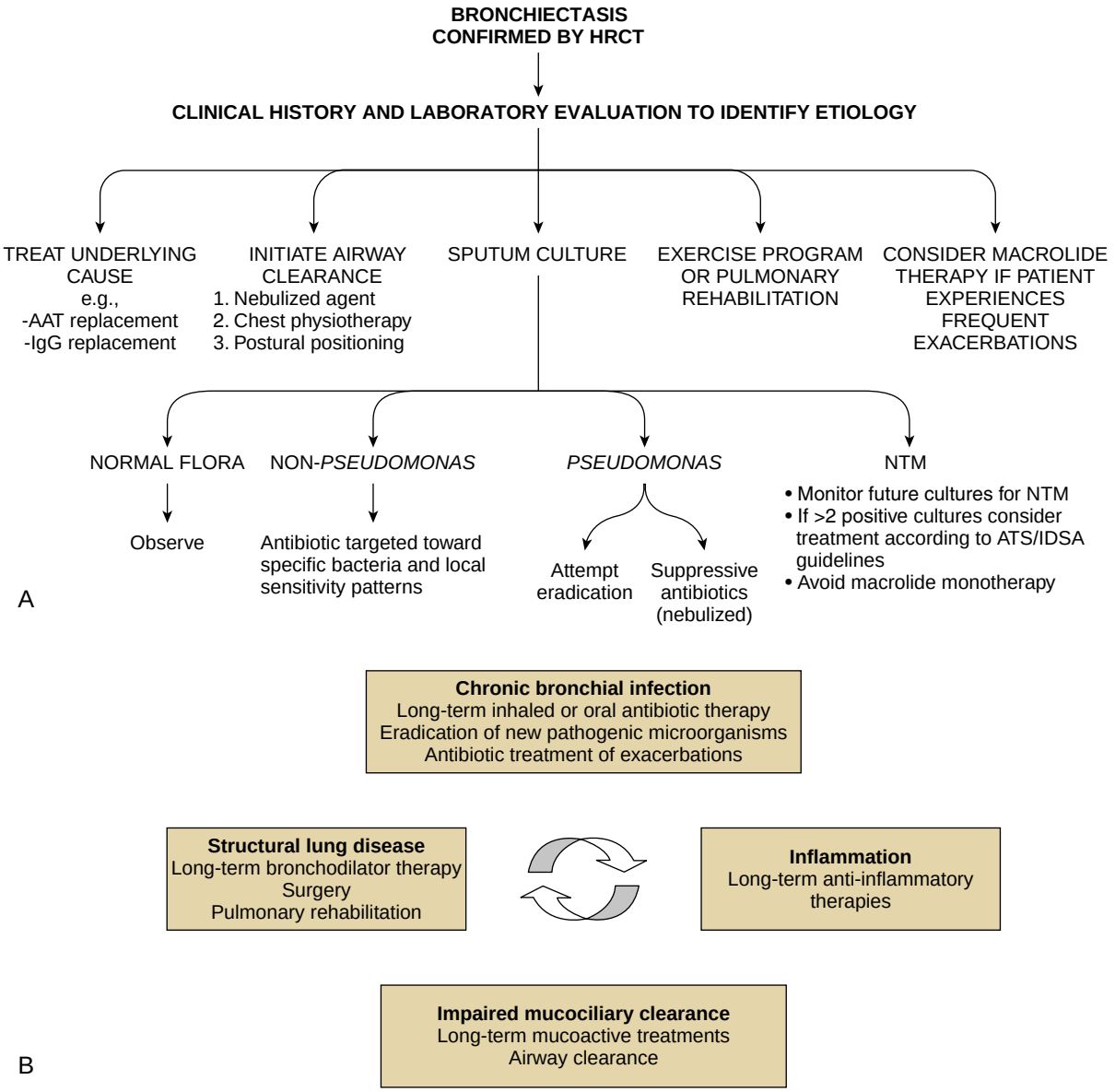

Figure 69.7 Comprehensive management of bronchiectasis. (A) Treatment includes measures that are common to all types and underlying causes of bronchiectasis, such as airway clearance, sputum microbial analysis, and pulmonary rehabilitation. More specific treatments are tailored to the underlying cause, such as *$alpha_1$-antitrypsin* (AAT) augmentation therapy for those with frank AAT deficiency or cystic fibrosis transmembrane regulator modifiers for those with cystic fibrosis. Antimicrobial therapy is based on whether it is for acute treatment or chronic suppressive therapy, and whether the goals are eradication or reducing the bacterial load to limit the symptoms. (B) Treatment strategies shown in the context of the vicious cycle hypothesis of bronchiectasis pathogenesis. ATS, American Thoracic Society; HRCT, high-resolution computed tomography; IDSA, Infectious Diseases Society of America; IgG, immunoglobulin G; NTM, nontuberulous mycobacteria. (A, Modified from McShane PJ, Naureckas ET, Tino G, Strek ME. Non-cystic fibrosis bronchiectasis. *Am J Respir Crit Care Med.* 2013;188(6):647–656; B, modified from Polverino E, Goeminne PC, McDonnell MJ, et al. European Respiratory Society guidelines for the management of adult bronchiectasis. *Eur Respir J.* 2017;50:1700629.)

Key Points

- Bronchiectasis is defined by the presence of permanent dilation of the medium to large bronchi. The main clinical significance of bronchiectasis is recurrent airway infections by bacterial and fungal organisms, resulting in chronic cough, sputum, weight loss, and respiratory compromise.
- Most bronchiectasis is due to a combination of host susceptibility factors, which may be overt or covert, recurrent infections, and the largely neutrophilic, inflammatory response. These factors lead to a vicious cycle of airway inflammation, infection, and mucus obstruction that may result in end-stage lung disease.
- Localized bronchiectasis is most often due to suboptimally treated bacterial infections, although bronchiectasis due to nontuberculous mycobacteria appears increasingly prevalent. Bronchiectasis due to nontuberculous mycobacteria is typically seen in postmenopausal women with lingular and right middle lobe involvement, although other lobes may be affected, and can also be seen in men, especially those with underlying COPD.
- Diffuse bronchiectasis is generally due to an underlying host disorder, such as cystic fibrosis, disorders of immunity, alpha$_1$-antitrypsin anomalies, COPD, primary ciliary dyskinesia, Mounier-Kuhn and Williams-Campbell syndromes, common variable immune deficiency, allergic bronchopulmonary aspergillosis, and chronic inflammatory states.
- Bronchiectasis has been associated with extrapulmonary disorders, such as ulcerative colitis and collagen vascular diseases. Severe fibrotic lung diseases from any cause may also result in a form of bronchiectasis known as traction bronchiectasis.
- The keys to management of bronchiectasis are the timely institution of empirical antimicrobials to treat the most likely pathogens and diligent airway clearance measures to improve symptoms. For patients unresponsive to empirical antibiotics or those with frequent exacerbations, sputum cultures should be obtained, drug susceptibility determined, and treatment tailored to more objective data. Surgical lung resection should also be considered for patients with severe localized disease recalcitrant to medical treatment; bilateral lung transplantation may be necessary for diffuse disease in appropriate patients.
- New approaches to the treatment of initial and chronic *Pseudomonas aeruginosa* infection are important in the consideration of infectious management.
- Prognostic guidelines and understandings of disease severity, including the frequent exacerbator phenotype, have helped to guide new research endeavors targeting appropriate populations.
- Strategies aimed at the vicious cycle of inflammation and infection show promise for improving quality of life and reduction of exacerbations. Anti-inflammatory agents, such as nonsteroidal anti-inflammatory drugs, inhaled corticosteroids, and low-dose intermittent macrolides, show promise in alleviating symptoms and reducing the rate of disease progression, but definitive recommendations for their use remain to be defined. Recent guidelines integrate these therapies for the treatment of patients with frequent exacerbations.

Key Readings

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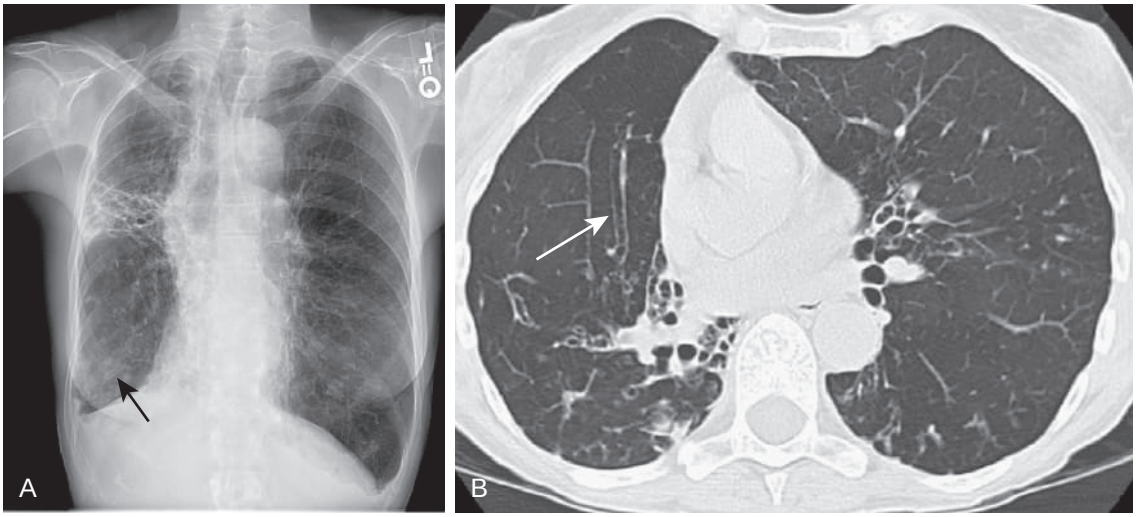
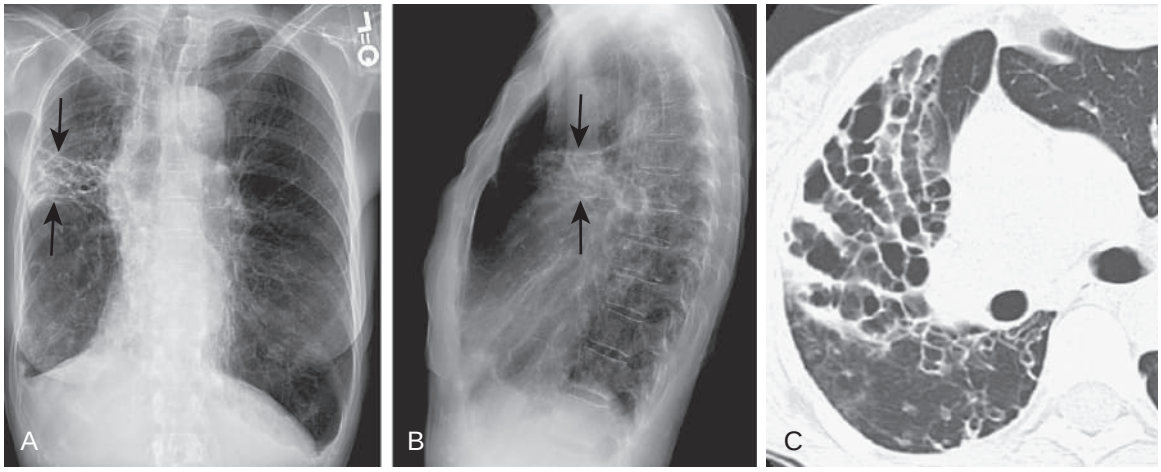
Complete reference list available at ExpertConsult.com.

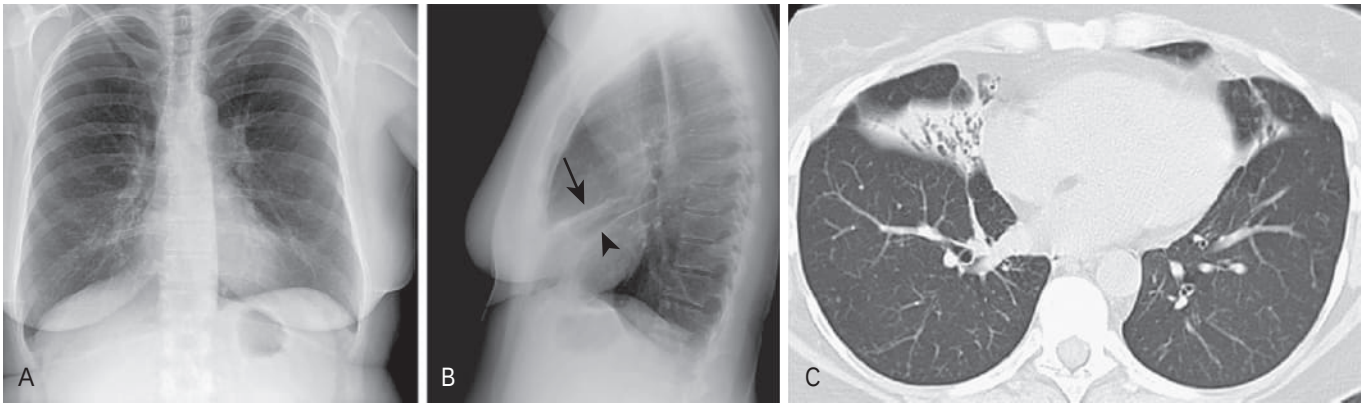
eFIGURE IMAGE GALLERY



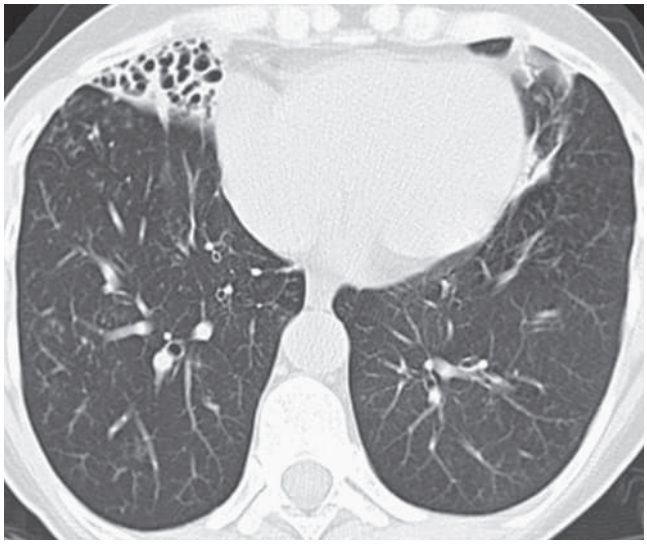
eFigure 69.1 "Tram tracks" on the routine chest radiograph in bronchiectasis, in the same patient as in eFig. 69.2. (A) In the right lower lobe are parallel, nontapering shadows, or "tram tracks" (*arrow*), representing bronchiectasis. (B) The airway is seen as cylindrical bronchiectasis (*arrow*).



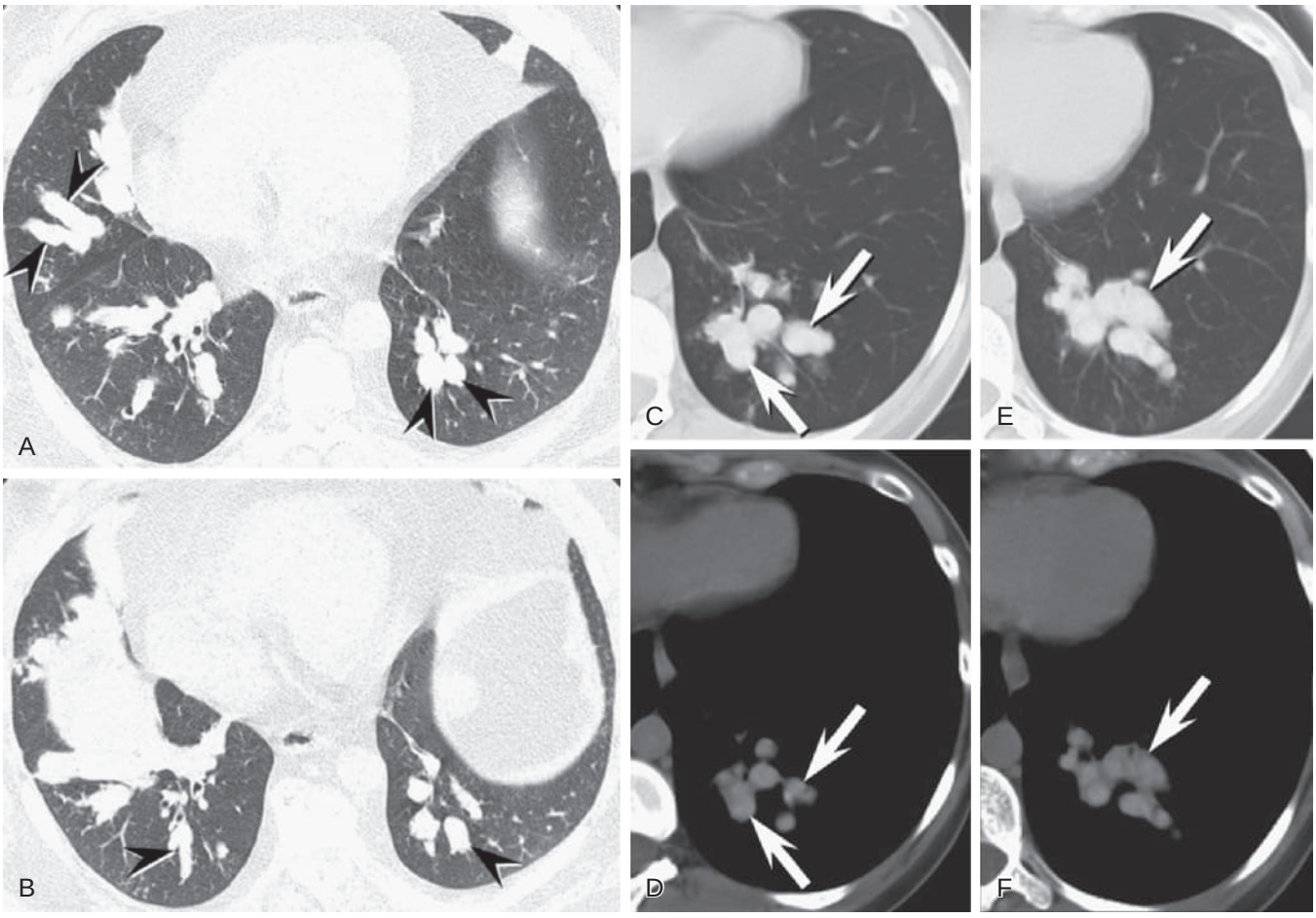
eFigure 69.2 Multiple ring shadows on chest radiography in bronchiectasis in the same patient as in eFig. 69.1. (A) On the posteroanterior view, thin-walled cystic shadowing is seen in the right mid-lung field (*between arrows*). The trachea and mediastinum are shifted to the right, indicating extensive volume loss. (B) The lateral view confirms the presence of multiple ring shadows in the mid-zone (*between arrows*). (C) Computed tomography scan indicates severe varicose bronchiectasis involving the entire right middle lobe and the anterior segment of the right upper lobe.



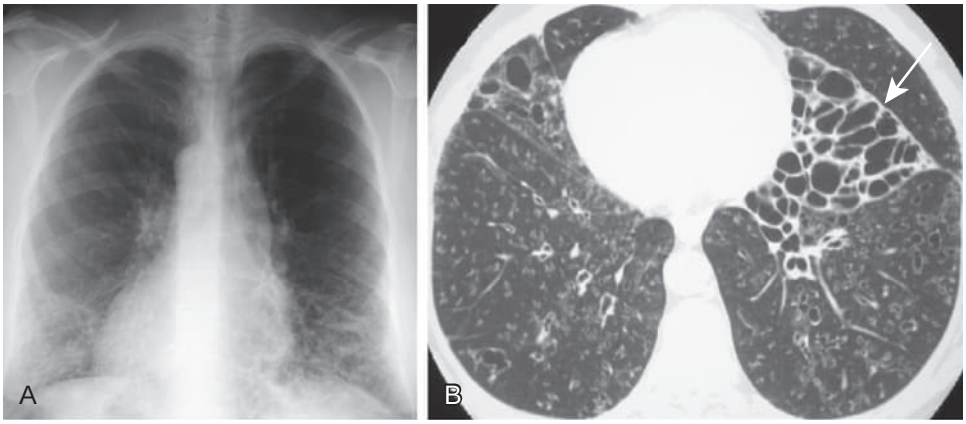
eFigure 69.3 Atelectasis and bronchiectasis involving the right middle lobe and lingula on chest radiographs and a computed tomography scan. This 60-year-old woman has had recurring "pneumonia" throughout life. (A) Posteroanterior view shows subtle effacement of the right heart border and cardiophrenic sulcus as well as a hazy opacity at the left heart border. (B) On the lateral view, there are two oblique densities representing the atelectatic right middle lobe (*arrow*) and lingula (*arrowhead*). (C) Computed tomography scan demonstrates bronchiectasis and atelectasis of the right middle lobe and inferior segment of the lingula.



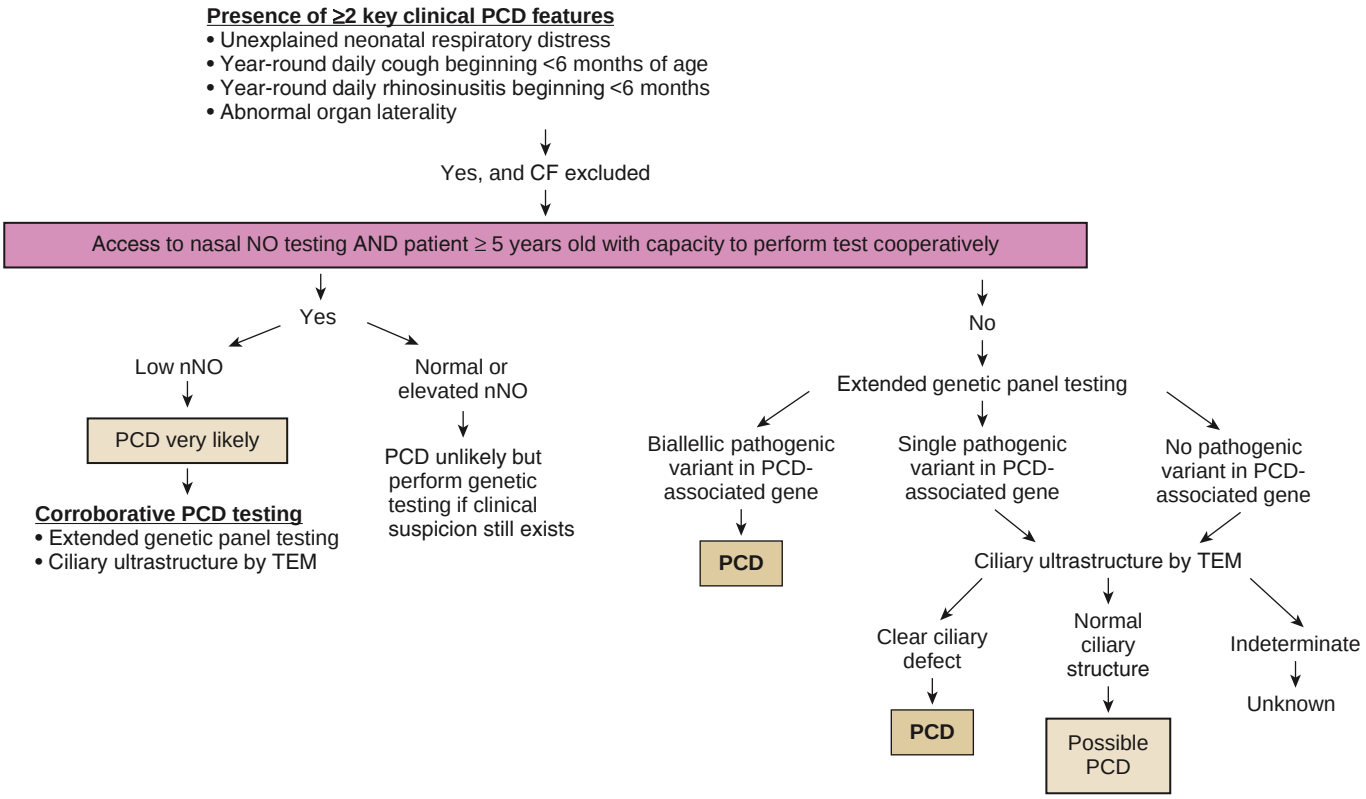
eFigure 69.4 Bronchiectatic consolidation. The inferomedial aspect of the right middle lobe is involved with a coarse cystic process, with essentially no normal remaining lung. Similar changes are often seen in the inferior segment of the lingula. In many cases such findings are associated with nontuberculous mycobacterial infection; however, in this case, the patient was infected only with gram-negative bacilli, including *Pseudomonas aeruginosa* and *Alcaligenes xylosoxidans*.



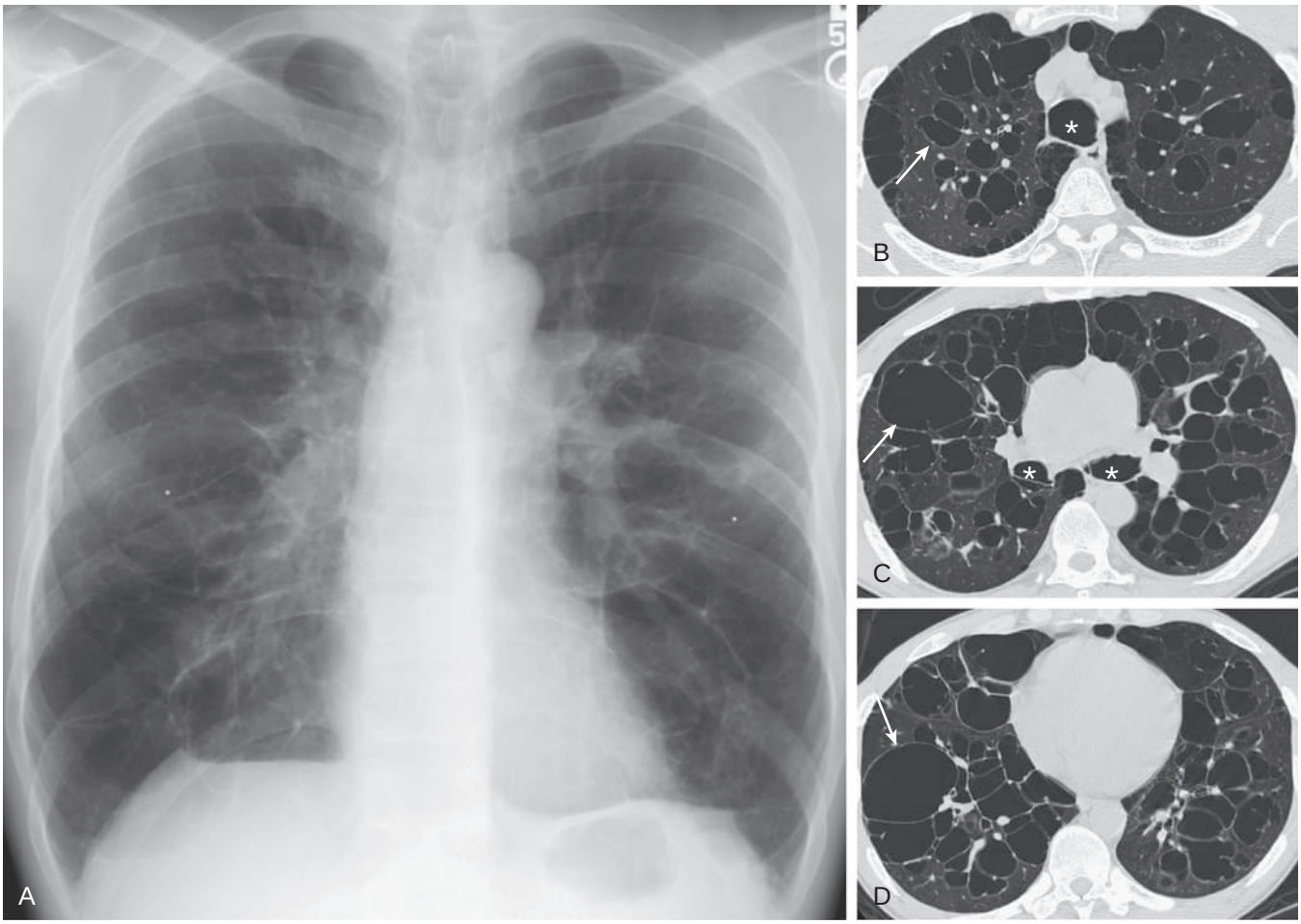
eFigure 69.5 Allergic bronchopulmonary aspergillosis with bronchiectasis and bronchial mucus impaction. (A–B) Axial chest computed tomography displayed in lung windows shows multifocal, bilateral tubular opacities (*arrowheads*) consistent with mucus impaction. (C–F) Axial chest computed tomography from another patient displayed in lung (C and E) and soft-tissue (D and F) windows shows tubular branching opacities (*arrows*) in the left lower lobe consistent with mucus impaction. Note that the opacities show faintly increased attenuation on the soft tissue windows (*arrows* in D and F), representing mucus impaction containing calcium salts and/or metallic ions. (Courtesy Michael B. Gotway, MD.)



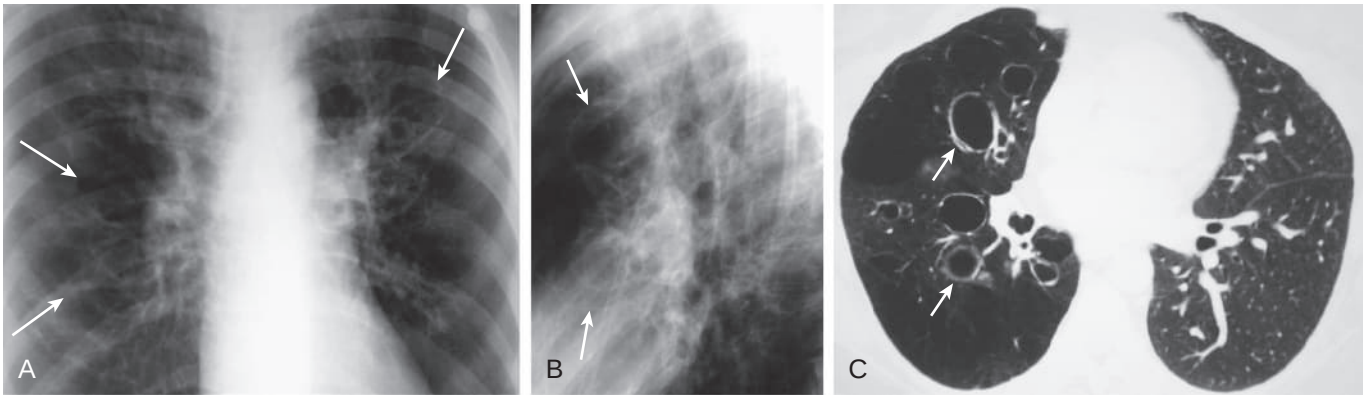
eFigure 69.6 Bronchiectasis: Kartagener syndrome. (A) Frontal chest radiograph shows dextrocardia with basal predominant linear opacities, the latter consistent with bronchial wall thickening and bronchiectasis. (B) Axial chest computed tomography shows dextrocardia and severe cystic bronchiectasis, particularly on the left (*arrow*). Note the left lung shows a morphologic configuration resembling a right middle lobe (same *arrow*). Numerous small nodules are consistent with small airway impaction. (Courtesy Michael B. Gotway, MD.)



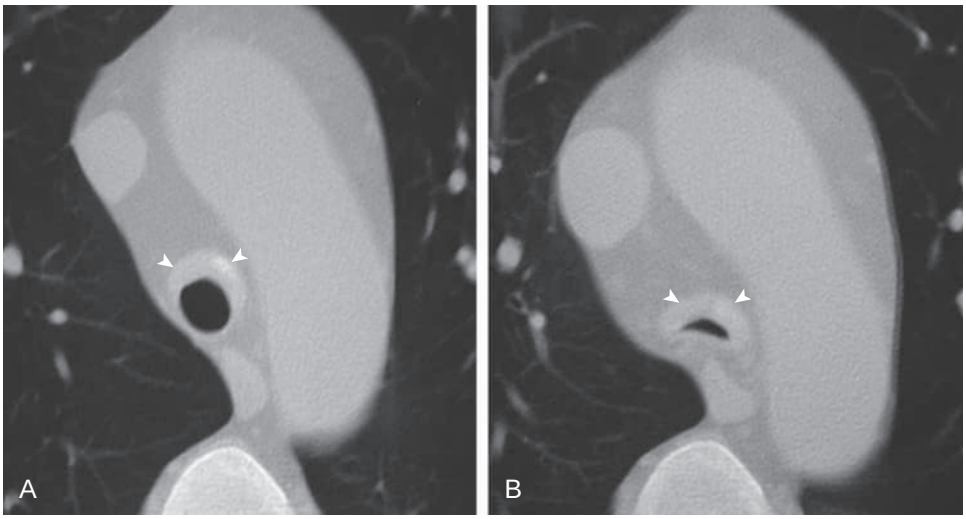
eFigure 69.7 Diagnostic algorithm for primary ciliary dyskinesia. Initial evaluation consists of determining the absence or presence of four predictive clinical parameters. If clinical suspicion is raised, then *nasal nitric oxide* (nNO) is the next screening test; an abnormally low nNO warrants excluding *cystic fibrosis* (CF) first, because a significant minority of CF individuals have low nNO. If testing for nNO measurement is not available, then genetic testing would be required. The traditional gold standards of ultrastructural analysis (by *transmission electron microscopy* [TEM]) and assessment of ciliary beat frequency/coordination require experienced investigators and/or specialized techniques. Ultrastructural analysis suffers from poor sensitivity (i.e., ≈30% of *primary ciliary dyskinesia* (PCD) patients have normal or near-normal TEM features), and video microscopy to assess ciliary movement suffers from low specificity (i.e., ciliary dysfunction may be a feature of chronic infection/inflammation even in the absence of a primary ciliary defect). (Modified from Shapiro AJ, Davis SD, Polineni D, et al. Diagnosis of primary ciliary dyskinesia. An official American Thoracic Society clinical practice guideline. *Am J Respir Crit Care Med*. 2018;197:e24–e39.)



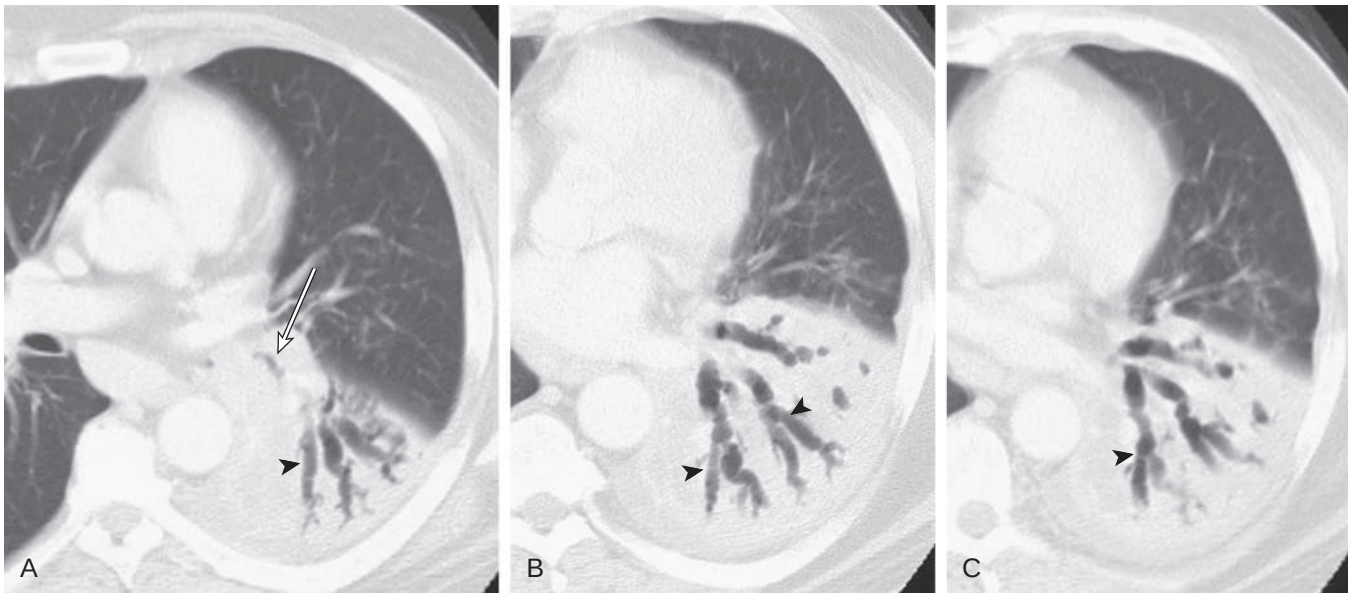
eFigure 69.8 Bronchiectasis: Mounier-Kuhn syndrome. (A) Frontal chest radiograph shows large lung volumes consistent with obstructive pulmonary disease. Bilateral linear and reticular opacities represent the walls of severely dilated bronchi. (B–D) Axial chest computed tomography images show multifocal, thin-walled cystic bronchiectasis (*arrows*) associated with dilated trachea and central bronchi (*asterisks*). The tubular nature of the cystic bronchiectasis can be appreciated best in the right upper lobe (*arrow*, B). In the left upper lobe, note that the cysts are closely associated with pulmonary arteries, which allows the cysts to be identified as bronchial in origin. (Courtesy Michael B. Gotway, MD.)



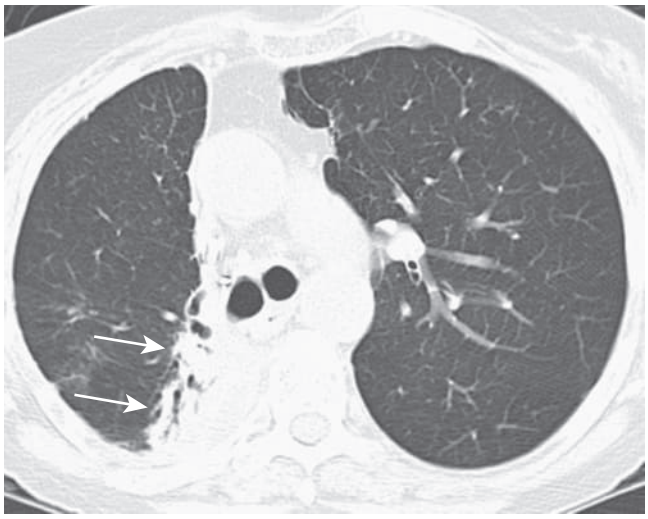
eFigure 69.9 Bronchiectasis: Williams-Campbell syndrome. Frontal (A) and lateral (B) chest radiographs show bilateral linear and reticular opacities (*arrows*) representing the walls of severely dilated bronchi. (C) Axial chest computed tomography after left lung transplantation shows severe cystic bronchiectasis (*arrows*) in the native right lung. (Courtesy Michael B. Gotway, MD.)



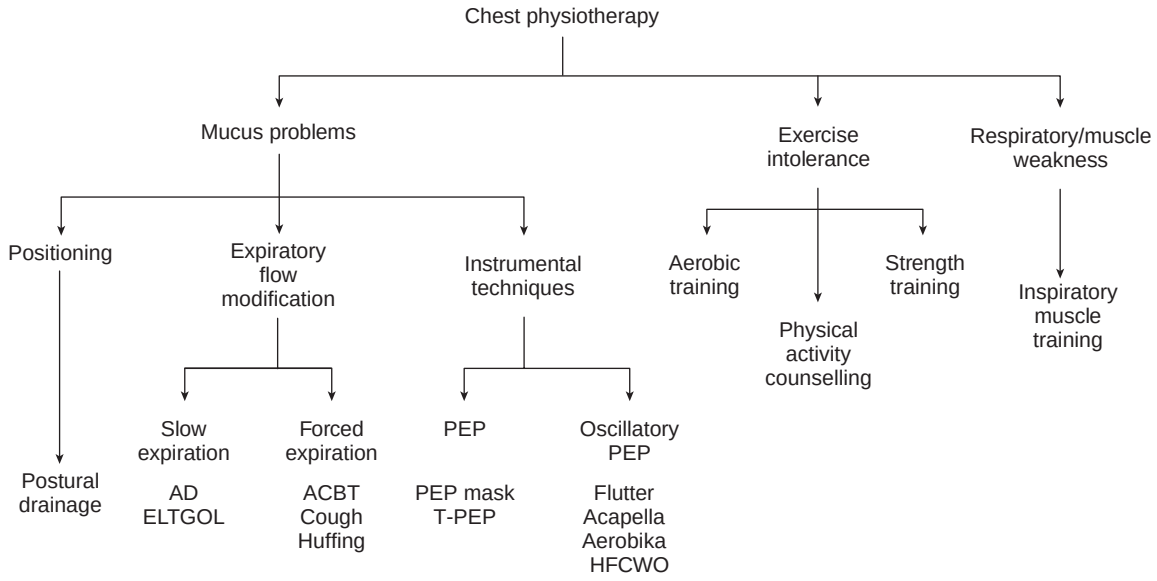
eFigure 69.10 Relapsing polychondritis. (A) Axial inspiratory chest computed tomography shows thickening of the anterior two-thirds of the trachea (*arrowheads*). A tiny focus of calcification is present within the thickened trachea at the 1 o'clock position. (B) Axial chest computed tomography performed after a forced vital capacity maneuver shows excessive trachea collapse (*arrowheads*) consistent with airway malacia. The constellation of findings is typical of relapsing polychondritis. (Courtesy Michael B. Gotway, MD.)



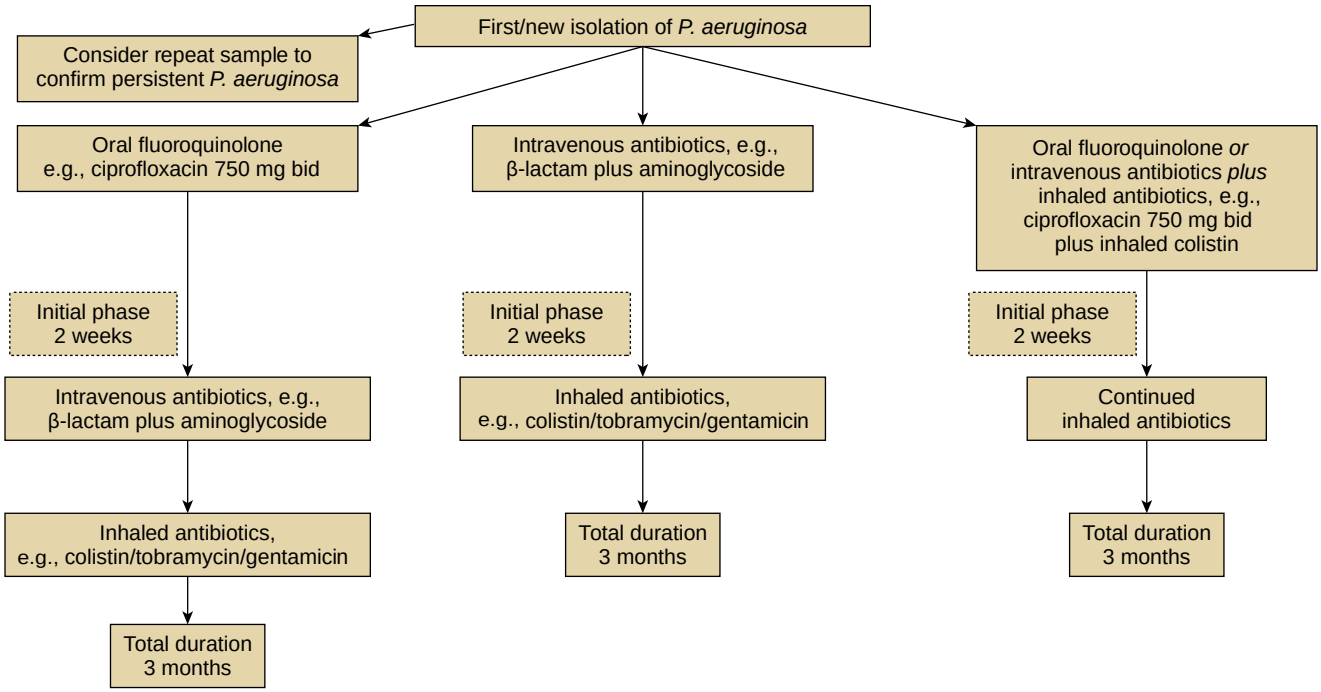
eFigure 69.11 Postobstructive bronchiectasis. (A–C) Axial chest computed tomography shows severe narrowing of the left lower lobe bronchus (*arrow*) due to carcinoid tumor. Multifocal bronchiectatic consolidation (*arrowheads*) is present throughout the left lower lobe. (Courtesy Michael B. Gotway, MD.)



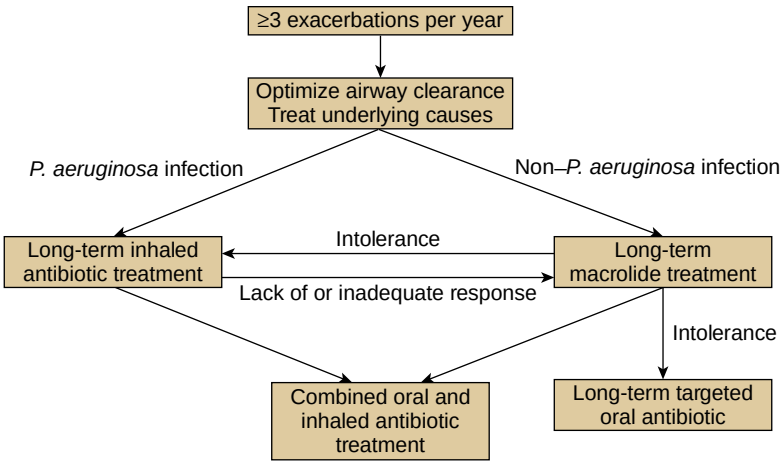
eFigure 69.12 Bronchiectasis in a field of therapeutic x-irradiation. This 68-year-old woman had been diagnosed with a non–small cell carcinoma of the lung. She received radiation therapy to the right hilar region approximately 18 months previously. Her computed tomography scan shows dense fibrosis and bronchiectasis in the radiation field (*arrows*). Inferior to this abnormality, she had a necrotic cavitary process associated with *Mycobacterium avium* complex infection.



eFigure 69.13 Algorithm for chest physiotherapy. ACBT, active cycle of breathing techniques; AD, autogenic drainage; ELTGOL, total slow expiration with open glottis and infralateral position; HFCWO, high-frequency chest wall oscillation; PEP, positive expiratory pressure; T-PEP, temporary positive expiratory pressure. (Modified from Polverino E, Goeminne PC, McDonnell MJ, et al. European Respiratory Society guidelines for the management of adult bronchiectasis. *Eur Respir J.* 2017;50:1700629.)



eFigure 69.14 Three potential *Pseudomonas aeruginosa* eradication pathways. After each step, it is recommended to repeat sputum culture for *Pseudomonas aeruginosa* and to progress to the next step if the culture remains positive. (Modified from Polverino E, Goeminne PC, McDonnell MJ, et al. European Respiratory Society guidelines for the management of adult bronchiectasis. *Eur Respir J.* 2017;50:1700629.)



eFigure 69.15 Summary of recommended long-term antibiotic therapies for bronchiectasis. *P. aeruginosa, Pseudomonas aeruginosa.* (Modified from Polverino E, Goeminne PC, McDonnell MJ, et al. European Respiratory Society guidelines for the management of adult bronchiectasis. *Eur Respir J.* 2017;50:1700629.)

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70 UPPER AIRWAY DISORDERS

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INTRODUCTION

The upper airways extend from the nares to the subglottis and include diverse anatomic structures with a wide variety of functions. Along with assisting in breathing, the structures of the upper airway contain the nerves for the sensory functions of taste and smell, create a functionally safe swallow by separating the process of swallowing from that of breathing, and allow communication through the generation of voice and speech. The nasal cavity has a defined role in filtering and humidifying air for presentation to the lower airway.[1–3] The larynx protects the airway to prevent aspiration and regulates airflow and vocalization. The pharynx and oral cavity assist in these functions by controlling and shaping substances to be swallowed and modulating voiced sounds from the larynx into words and speech. The upper airway is controlled by both voluntary and involuntary mechanisms. Therefore, respiratory function can be affected through uncoordinated or inefficient muscular activity, centrally mediated neurologic reflex activity, and/or humoral or immunologic responses. The exact function of some areas within the upper airway, such as the paranasal sinuses, is unclear.

Pathologic changes in the upper airways are often associated with lower airway disease. Swallowing disorders may result in aspiration, leading to inflammatory and infectious complications in the lungs. Chronic inflammation of the paranasal sinuses is frequently associated with asthma and appears to be driven by similar inflammatory pathways, which has been called the *unified airway theory*.[4–7] This theory posits that the upper and lower airways can be considered one organ, sharing both the mechanisms of injury and the benefits from treatment. Long-standing infection in the sinuses has been implicated as a possible reservoir for recurrent pulmonary infection.[8–10] Laryngeal dysfunction may create symptoms similar to, and mistaken for, asthma. Finally, stenosis of the subglottis or cervical trachea is often misdiagnosed as asthma. This chapter discusses the anatomy and clinical conditions of the upper airway and their influence on lower airway function.

THE NOSE

ANATOMY, HISTOLOGY, AND PHYSIOLOGY

The nose is the initial site of air entry for the majority of breaths. The external nose has important structural components that, when compromised, may inhibit nasal airflow. The nasal dorsum is made up of three structurally distinct subunits (Fig. 70.1). The upper third of the nasal dorsum is supported by the nasal bones. At their distal end, the nasal bones articulate with the upper lateral cartilages in a region known as the keystone area. The upper lateral cartilages define the middle third of the nose. The structure of the lower third, or nasal tip, is defined primarily by the lower lateral cartilages. The nasal septum divides the right and left sides of the nose and provides additional structural support to the lower two-thirds of the nose. The quadrangular cartilage forms the anterior septum. The bone of the vomer, the perpendicular plate of the ethmoid, and the maxillary crest form the posterior and inferior aspects of the septum.

Airflow through the nose may be limited by the cross-sectional area of the external and internal nasal valves (Fig. 70.2). The external nasal valve area is determined by the relationship between the lower lateral cartilage, the septum, and the inferior turbinate. The internal nasal valve is determined by the angle between the upper lateral cartilage and septum. Facial musculature attaching to the upper and lower cartilages of the nose can widen these principal areas of resistance and enhance nasal breathing.[11,12] Patients with narrowing or structural weakness in these regions may suffer from nasal obstruction. The external and internal nasal valves are frequently the target of nasoseptal reconstructive surgery.

Another common area implicated in narrowing of the nasal cavity and subsequent nasal obstruction is the nasal

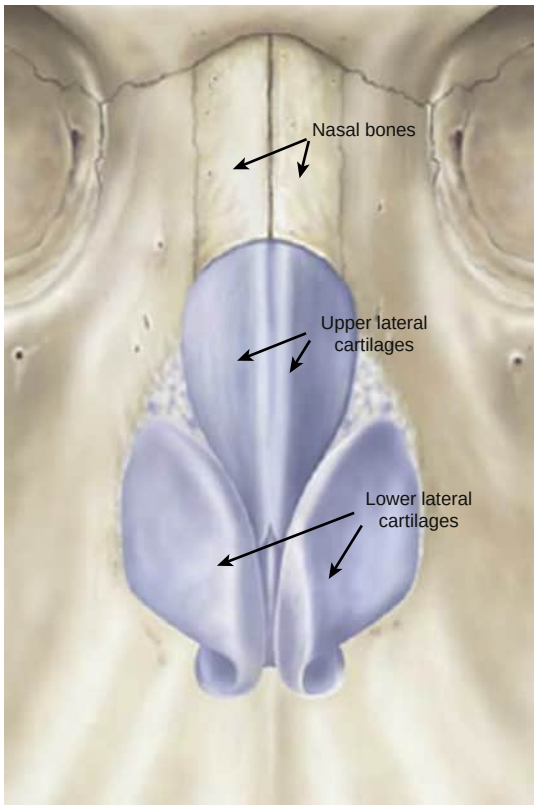

Figure 70.1 Vertical thirds of the nose. The upper, middle, and lower third of the nose are structurally supported by the nasal bones, the upper lateral cartilages, and the lower lateral cartilages, respectively. (From Hafezi F, Naghibzadeh B, Nouhi AH. Applied anatomy of the nasal lower lateral cartilage: a new finding. *Aesthetic Plast Surg.* 2010;342:244–248.)

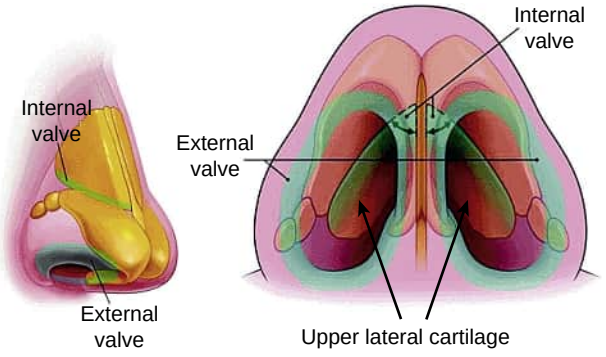

Figure 70.2 The internal and external nasal valves. The external nasal valve exists at the level of the inner nostril and is formed by the caudal edge of the lateral crus of the lower lateral cartilage, the soft tissue alae, the membranous septum, and the sill (the anterior nares) of the nostril. The internal nasal valve accounts for approximately half of the total airway resistance and is bordered medially by the septum, inferiorly by the nasal floor, laterally by the inferior turbinate, and superiorly by the caudal border of the upper lateral cartilage. (From Howard BK, Rohrich RJ. Understanding the nasal airway: principles and practice. *Plast Reconstr Surg.* 2002;109:1128–1146.)

septum. Deviation of the septum diminishes the cross-sectional area of the affected nasal passage and can significantly impact nasal airflow. Most patients have some degree of septal deviation, so anatomic changes in this area must be correlated with clinical findings when determining if a patient would benefit from treatment of a septal deviation. Nasal trauma may lead to septal deviations and spurs; many patients will relate a history of trauma to the nose. Developmental variations are perhaps a more common cause of deviation and of spurs of the nasal septum than is trauma. Overgrowth of the quadrangular cartilage may result in bowing of the cartilage or in forming spurs at the junction of the cartilage and bones that make up the nasal septum. Nasal obstruction related to septal deviation may respond either to surgical or to medical treatment. In patients with concomitant turbinate hypertrophy or chronic rhinitis, treatment with intranasal corticosteroids may diminish mucosal swelling and provide an adequate airway despite the septal deviation. Surgery to straighten the septum has few risks and complications and is an effective method for improving the nasal airway in patients with narrowing secondary to septal deviation. Although implicated as a cause for acute or chronic rhinosinusitis, septal deviation is a very rare cause for inflammatory sinus disease. While a septoplasty may be indicated to improve nasal breathing or enhance surgical access for endoscopic sinus surgery, in the majority of cases, surgical correction of the septal deviation is unlikely to influence the disease course of acute or chronic rhinosinusitis.

Air that enters the nasal sill (or anterior nares) and passes through the internal nasal valve accelerates as it passes through this area of narrowing. There is also a change in direction of airflow because inspired air shifts from a vertical to a horizontal trajectory at this site. This combination of acceleration and change in flow vector causes the majority of airborne particles to be deposited in the anterior nasal cavity.[13,14] Airflow through the nose slows as the nasal passages widen beyond the internal nasal valve.

Upon entry into the nasal cavity the stratified squamous epithelium of the nasal sill quickly transitions to a respiratory epithelium. Located along the lateral nasal wall, the turbinates (or conchae) serve to warm and humidify air passing through the nasal cavity. Rich vasculature, including venous sinusoids, allows the turbinates to enlarge and shrink in response to various stimuli.[15–17] Fenestrated subepithelial capillaries facilitate heat and gas exchange, enhancing humidification during nasal inhalation.[17] Engorgement of the turbinates increases the surface area and mucosal contact with inspired air. The slowing of airflow beyond the internal nasal valve provides prolonged mucosal contact during nasal inspiration and allows efficient humidification and filtration of inspired air so that, even at extremes of ambient temperature and humidity, air that reaches the trachea is very close to body temperature and is at 98% humidity.

The respiratory mucosa of the turbinates contains both goblet cells and seromucous glands. These structures combine to produce a mucus blanket mobilized by coordinated beating of this ciliated epithelium. Nasal irritants, microbes, and other particles are swept through the nasal cavity by this mucociliary clearance mechanism to be swallowed, preventing exposure of the lower airways. The lower airways are further protected by immune function within the nasal mucosa. Both the innate and humoral immune arms of the immune system function within the nasal mucosa, resulting in the secretion of immunoglobulins (primarily immunoglobulin A)[18,19] and microbial toxins, such as lysozyme and lactoferrin.[20,21] Emerging evidence suggests that commensal microbes inhabiting

the mucosal surface or mucus layer of the nasal cavity contribute to the host defense mechanisms within the nasal cavity through competitive colonization and immune regulation.[22,23]

The turbinates are dynamic structures that swell and shrink in response to multiple stimuli. Gravity, nasal irritants, allergic response, and autonomic neural input all regulate the blood supply and venous drainage of the submucosal tissue of the inferior turbinate, resulting in marked fluctuations in turbinate size.[17,24] The size of the inferior turbinate fluctuates throughout the day, with the left and right sides alternately swelling and shrinking in a phenomenon known as the nasal cycle.[24] Pathologic enlargement of the inferior turbinate is one of the most common causes of nasal congestion and nasal obstruction.[25,26]

The tubular structure of the turbinates contributes to a laminar airflow pattern through the nasal cavity.[27,28] Aggressive resection of the turbinates enlarges the cross-sectional area of the nasal cavity but risks paradoxical worsening of nasal obstruction by altering the flow pattern from laminar to turbulent. The humidification function of the turbinates can also be lost with resection, resulting in possible dryness and crusting. This constellation of symptoms after turbinate resection has been referred to as *empty nose syndrome*.[29] A conservative surgical approach to nasal obstruction with turbinate hypertrophy is therefore recommended in patients who do not receive adequate relief from medical therapy.

The superior aspects of the nasal septum, middle turbinate, and superior turbinate are lined with olfactory epithelium. Successful olfaction requires that airborne or mucus-soluble particles reach this epithelium. Odorant-specific receptors of the olfactory epithelium send projections intracranially through the bone of the cribriform plate. Axons from the olfactory epithelium synapse within the olfactory bulb, and these signals are then routed for central processing. Smell disorders may arise from mucosal inflammation and edema that prevent odorant exposure to the olfactory epithelium. This is frequently a reversible condition. Direct viral injury of the olfactory epithelium has also been postulated as a cause for smell loss, which may result in long-term dysfunction.[30,31] Acute smell loss has been identified as a key screening symptom for COVID-19 disease.[32–34] In a prospective tracking study of more than 2.5 million individuals in the United Kingdom and United States, including more than 18,000 who underwent polymerase chain reaction testing for severe acute respiratory syndrome coronavirus-2 infection, loss of smell was the symptom most strongly associated with a positive COVID-19 test, with an odds ratio of 6.4 in the UK cohort and 10.0 in the U.S. cohort. The odds ratio for skipped meals, fatigue, and fever were all less than 3 in both cohorts.[32]

Sneezing is a nonspecific, involuntary response to nasal irritation. Allergens, microbes, and other nasal irritants may precipitate this reaction when they contact the nasal mucosa and trigger histamine release. The trigeminal nucleus coordinates the sneeze reflex, which involves muscles of the pharynx, larynx, oral cavity, and chest wall. The pressure generated from a sneeze may expel irritants and can contribute to spread of infections. In susceptible individuals, sudden exposure to bright light may trigger the sneeze reflex. This photic sneeze reflex is an autosomal dominant trait impacting approximately one-fourth of the human population.[35]

PATHOLOGIC CONDITIONS OF THE NASAL CAVITY

Rhinitis

Rhinitis, or inflammation of the nasal cavity, may result from multiple causes. Rhinitis may be classified by duration (acute vs. chronic) and by cause (allergic vs. nonallergic). Acute rhinitis is a self-limited inflammation, most commonly secondary to viral infection. Many of the clinical features of acute rhinitis may result from the immune response to viral pathogens. Release of inflammatory cytokines and chemokines, including *interleukin* (IL)-6, tumor necrosis factor-α, and interferon-γ, results in tissue edema, increased mucus production, and vascular dilation.[36] The clinical manifestations of these changes are well known as symptoms of the common cold: nasal congestion and obstruction, increased nasal drainage, and diminished sense of smell. Nasal irritants, including perfumes, smoke, and cleaning products, can cause a similar constellation of symptoms, although typically of shorter duration.

Allergic Rhinitis

Epidemiology. *Allergic rhinitis* (AR) is a common disorder estimated to be the sixth most common chronic illness in the United States.[37] The prevalence of AR is 10–20% in the United States and Europe.[38] An estimated 18 million adults in the United States suffer from AR, resulting in significant health care expenditures.[39] A diagnosis of allergic rhinitis adds approximately $1500 per patient per year in direct health care costs.[39] A similar prevalence of AR is evident in children, and AR in this population is associated with a significant decrease in both physical and emotional health, as well as sleep disturbance.[40] Thirteen million Americans in the workforce suffer from AR, and it is estimated that 3.5 million workdays and 2 million school days are lost each year due to this condition.[41,42] Overall, annual direct and indirect costs of AR in the United States have been estimated at $5 to $8 billion and $11 billion, respectively.[43]

The incidence of allergic rhinitis has been rising over the past 3 decades. One explanation for this is the *hygiene hypothesis*, which proposes that early exposure to antigens allows for proper immune system development and a reduced risk for AR and other atopic disease.[44] With improved hygiene and a reduction in exposure to antigens, children may develop an exaggerated immune response, as demonstrated by AR. Early microbial exposure may be particularly important in the prevention not only of atopic but also of autoimmune disease.[45–48]

Diagnosis. AR symptoms may be seasonal or perennial, depending upon the specific allergen. Pollens from trees and grasses are the most common triggers for seasonal symptoms, whereas dust mites and pet dander represent common triggers for perennial disease. Offending allergens may be identified through a variety of approaches. Skin reaction to allergens may be measured through either prick testing or intradermal injection using serial end point dilution techniques. Both approaches carry a rare but important risk for anaphylaxis.[49] Testing centers must have

personnel and equipment to deal with such emergencies. Immunoassays for allergen-specific *immunoglobulin* (Ig) E, such as ImmunoCAP (Phadia AB/ThermoFisher), have largely replaced radioallergosorbent tests as an alternative to intradermal skin testing. Immunoassays demonstrate a similar sensitivity as skin testing. The efficacy of both dermal testing and immunoassays depends on proper antigen selection. Knowledge of local flora is particularly important in patients with seasonal AR. This knowledge is also essential in identifying clinically significant allergens. Identification of offending allergens allows counseling of allergen avoidance and may be used to initiate immunomodulatory therapy.

Pathophysiology. After an initial allergen exposure, inhaled antigens provoke both early and late-phase reactions in the nasal cavity. The early phase is initiated by the recognition of a specific allergen by IgE subunits on the surface of mast cells and basophils. IgE activation results in antibody cross-linking, which, through a series of downstream mediators, causes degranulation of mast cells and basophils with release of preformed mediators, primarily histamine. Tryptase release and de novo formation of leukotrienes may also contribute to nasal inflammation and symptoms. Exposure to inflammatory mediators results in marked tissue edema and mucus secretion, which manifest clinically as rhinorrhea, nasal congestion, and obstruction, frequently in association with sneezing. These symptoms develop within minutes of allergen exposure.

The late phase of AR typically arises 4 to 8 hours after allergen exposure. Nasal congestion is typically the dominant symptom. Chemoattractants and adhesion molecules released in response to the initial inflammatory mediators promote infiltration of leukocytes, eosinophils, basophils, $CD4^+$ lymphocytes, and monocytes. Activation of these cells results in the release of a second wave of inflammatory mediators.[50] The early and late-phase reactions in AR mimic those of allergic asthma.

Priming of the immune response may be important in the pathophysiology of AR. Repeated allergen exposure results in amplification of mucosal hyperresponsiveness. In patients with seasonal AR, the severity of allergic response depends not only on the current pollen count and allergen exposure but also upon the cumulative exposure for a given allergy season. Because of this phenomenon, severe symptoms of AR may persist late in the allergy season despite a waning pollen count. This increased allergen sensitivity may be secondary to both a neural hyperresponsiveness and amplification of the immune response through recruitment of mast cells and basophils. Immune system priming is not an allergen-specific phenomenon; patients also report increased sensitivity to nonspecific nasal irritants, including smoke and perfume.[51,52]

Association With Asthma. AR and asthma are linked through both pathophysiology and epidemiology.[50,52,53] Eighty percent of patients with allergic asthma also suffer from AR. The presence of AR is a risk factor for the future development of asthma. Guidelines suggest screening patients with persistent AR for asthma and evaluating asthmatic patients for rhinitis.[52,53]

The *unified airway theory* suggests that inflammatory cells from an inflamed area within the airway may impact distant airway locations. In patients with AR and asthma, segmental bronchial allergen challenge results in an inflammatory response not only in bronchi, but also in the nasal cavity.[54] When treated with intranasal corticosteroids, these same patients demonstrate a decrease in both nasal and bronchial hyperreactivity.[55,56]

Treatment. There are three primary modalities of treatment for AR: allergen avoidance, pharmacotherapy, and immunomodulatory treatments. Consensus panels suggest evaluating the severity and frequency of AR symptoms to guide treatment. Severity of symptoms is categorized as mild or moderate to severe as determined by the level of impact on daily activities and sleep disturbance. Symptoms are classified as *intermittent* if the duration is less than 4 days per week or for fewer than 4 weeks or as *persistent* if the duration satisfies both of these criteria.[53] Fig. 70.3 depicts a consensus management strategy for AR.[57] The vast majority of patients are effectively treated with pharmacotherapy and allergen avoidance. Saline irrigation results in modest symptomatic improvement and may reduce the need for medications with more significant side-effect profiles. Evidence-based AR treatment recommendations for allergen avoidance, individual medications, and immunotherapy were revised in 2010[58] and again in 2017[59] to incorporate considerations for combination pharmacotherapy options. Recommendations for allergen avoidance strategies for patients with AR are similar to those for patients with allergic asthma and require identification of offending allergens. After identification of clinically significant allergens, environmental precautions may be instituted.

Immunotherapy

Although pharmacologic treatment of AR may be quite effective in managing symptoms, immunotherapy offers the only approach known to impact the natural history of the disease. *Subcutaneous immunotherapy* (SCIT) regimens involve once- or twice-weekly subcutaneous antigen injections with gradual escalation of the antigen dose. This is the most well-studied and commonly used approach in the United States. More recently, *sublingual immunotherapy* (SLIT) has emerged as an option that avoids injection and may be administered at home. The *U.S. Food and Drug Administration* (FDA) has approved four SLIT treatments in the United States: Grastek (ALK-Abelló) for treatment of timothy grass or cross-reactive grass pollens, Oralair (Stallergenes SA) for treatment of five different grass pollens, Odactra (ALK-Abelló) for dust mites, and Ragwitek (ALK-Abelló) for short ragweed pollen.[60] Additional SLIT allergen extracts are approved in Europe and have been used off-label in the United States. The overall treatment course for SCIT or SLIT is 2 to 3 years.

With repeated allergen exposure, a shift in allergen-specific T cells to a regulatory phenotype results in suppression of type 2 T-helper inflammatory cytokines and enhanced production of IL-10 and antigen-specific IgG4. This results in suppression of allergen-specific IgE and mast cells and appears to inhibit antigen capture and presentation to T cells.[61] This immune modulation may also

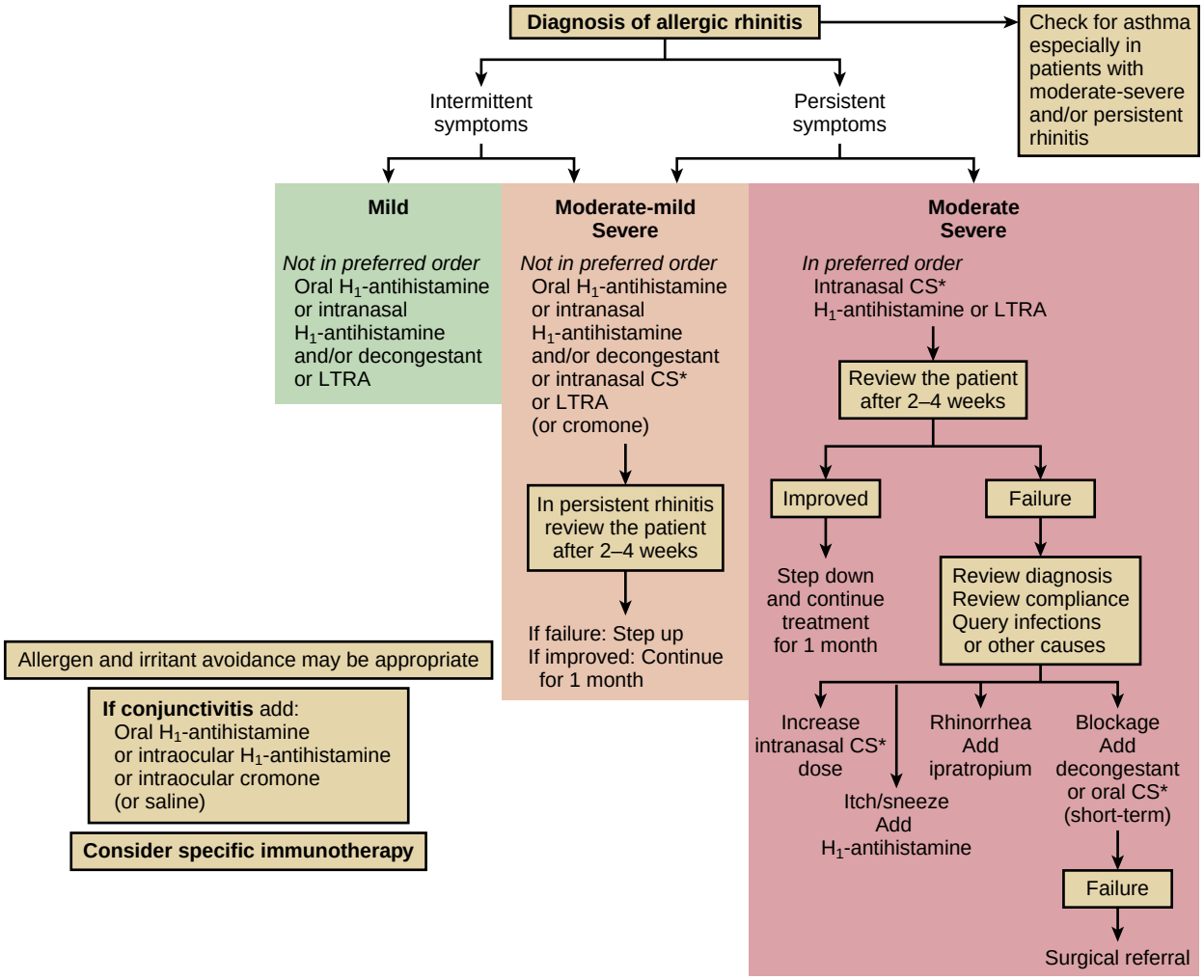

Figure 70.3 Algorithm for the management of allergic rhinitis. CS, corticosteroid; LTRA, leukotriene-receptor antagonist. *Total dose of topical CS should be considered if inhaled steroids are used for concomitant asthma. (From Bousquet J, Schünemann HJ, Samolinski B, et al. Allergic rhinitis and its impact on asthma (ARIA): achievements in 10 years and future needs. *J Allergy Clin Immunol.* 2012;130:1049–1062.)

diminish the onset of additional atopic disorders, such as asthma in patients with AR.

Systemic responses to immunotherapy are rare and typically mild. Nevertheless, deaths have been reported from anaphylactic response during immunotherapy, and vigilance is required. SCIT has a higher, although still very low, incidence of systemic response than SLIT; SLIT has a high rate of mild local (mucosal) side effects that rarely impact the treatment regimen.[62] Practitioners who administer allergy shots require appropriate training and access to emergency equipment to address the rare systemic response. With sublingual administration, patients often self-administer the allergen, and proper patient selection and education are critically important. Multiple trials demonstrate efficacy of both SCIT and SLIT; they appear to have similar efficacy, but head-to-head trials are lacking.[63–65] The determinants of SCIT versus SLIT use are evolving as additional sublingual options receive FDA approval and clinical experience in the United States increases.[66]

Nonallergic Chronic Rhinitis

Overall, nonallergic rhinitis is poorly characterized. *Vasomotor rhinitis* may happen in a subgroup of nonallergic patients thought to have aberrant parasympathetic innervation in the nose. Patients frequently note rhinorrhea in association with eating or a change in the weather. This disorder is more common in elderly patients and may respond well to ipratropium nasal spray. Additional noninflammatory disorders of the nasal cavity, including nonallergic rhinitis with eosinophilia, may improve with nasal steroid treatment. Symptomatic treatment with saline irrigation is another popular treatment for nonallergic rhinitis.

THE PARANASAL SINUSES

ANATOMY, HISTOLOGY, AND PHYSIOLOGY

The paranasal sinuses are aerated cavities within the skull that connect to the nasal cavity. There are four sets of paired sinuses: the maxillary, ethmoid, frontal, and sphenoid. The sinuses are lined with a pseudostratified, ciliated epithelium. Goblet cells within the epithelium produce mucus, and the coordinated action of the cilia moves this mucus through the sinus cavities and into the nose. Once thought to be sterile, it is now known that bacterial communities inhabit the

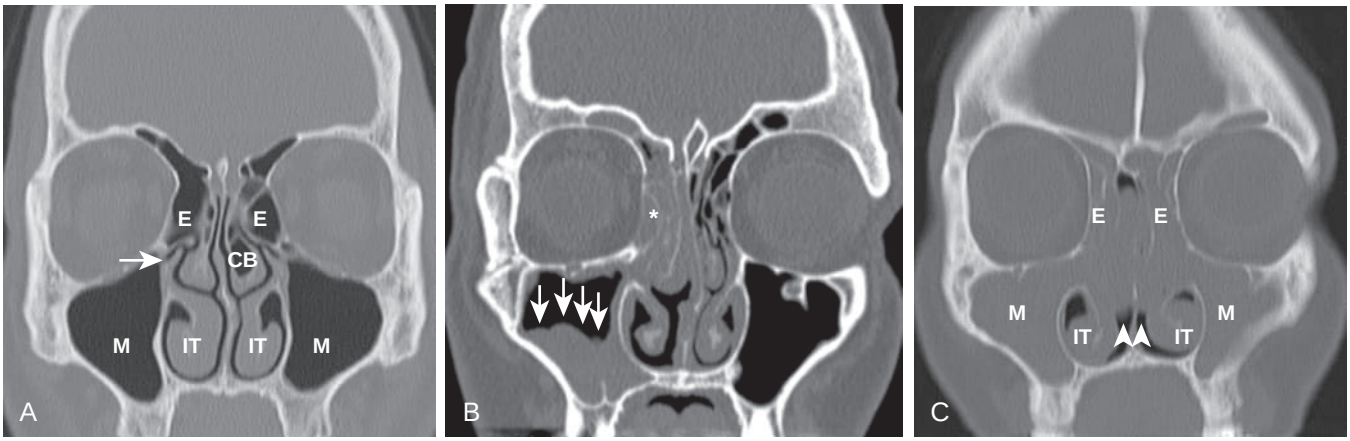

Figure 70.4 Coronal *computed tomography* (CT) imaging of the paranasal sinuses. (A) Normal anatomy, including well-aerated maxillary (M) and ethmoid (E) sinuses bilaterally, patency of the osteomeatal complex (*arrow*), and normal appearance of the inferior turbinates (IT). Incidentally noted is a left concha bullosa (CB), a normal variant involving aeration of the middle turbinate, which arises in approximately 30% of patients. (B) CT findings consistent with acute sinusitis. There is unilateral opacification of the ethmoid sinuses (*asterisk*) and a fluid level within the right maxillary sinus (*arrows*). Acute sinusitis may present with unilateral or bilateral disease, and routine CT imaging is not recommended. (C) Bilateral chronic sinusitis with nasal polyposis. There is complete opacification of the maxillary (M) and ethmoid (E) sinuses bilaterally. *Arrowheads* demonstrate bilateral nasal polyps, a soft tissue density within the nasal cavity and adjacent to the inferior turbinates (IT).

mucosal surfaces of the paranasal sinuses in both health and disease.[22,67,68]

The function of the sinuses has not been clearly established. They may serve a protective role in force dissipation with blunt trauma to the head or face. The paranasal sinuses can impact vocal resonance, which may have aided their evolution. The sinuses may allow for enhanced facial aesthetics. They may play a role in mucus production and immune surveillance in the nasal cavity.

The four paired sinuses are named after the bones they aerate. The maxillary and ethmoid sinuses are the first to develop and are present at birth. The frontal and sphenoid sinuses develop later. A visible frontal sinus is often not present until age 4 or 5 years, and continued aeration and development persist throughout the teenage years.[69] Asymmetric aeration of the sinuses is common, particularly in the later-developing frontal and sphenoid sinuses. The frontal sinus may be absent in up to 10% of normal patients.[70,71] An increased incidence of frontal sinus aplasia and diminished overall paranasal sinus aeration is seen in patients with congenital disorders that impact the sinuses, such as cystic fibrosis.[72]

Mucus produced in the sinuses is propelled into the nasal cavity by coordinated ciliary motion. The maxillary (Fig. 70.4) and sphenoid sinuses are connected to the nasal cavity by discrete ostia, which often have a diameter of no more than 4 mm. The ethmoid sinuses are made up of a labyrinth of small air cells located between the orbit and the nasal septum. The ethmoid sinus typically drains through clefts between air cells rather than through discrete ostia. Collectively, the anterior ethmoid air cells drain through the middle *meatus* located between the middle turbinate and the lateral nasal wall. Whereas the posterior ethmoid air cells drain through the superior meatus, which is located between the superior turbinate and lateral nasal wall, the frontal sinus drainage tract is determined by the variable anatomy of the underlying anterior ethmoid air cells and eventually leads to the middle meatus.

Blood supply to the paranasal sinuses is provided through both the internal and external carotid systems. The *sphenopalatine artery* (SPA) is the terminal branch of the internal maxillary artery, which originates from the external carotid artery. The SPA enters the nasal cavity through the sphenopalatine foramen just behind the posterior wall of the maxillary sinus. The majority of the blood supply to the nasal cavity is provided by the SPA. The blood supply to the superior nasal cavity and to much of the ethmoid system arises from the anterior and posterior ethmoid arteries. These vessels are branches from the ophthalmic artery of the internal carotid system and typically run within the skull base along the roof of the ethmoid sinuses. All of these vessels may contribute to refractory or "posterior" nosebleeds. Epistaxis originating from the SPA is amenable to embolization or surgical ligation of the SPA. The anterior and posterior ethmoid arteries are not amenable to embolization due to their origin from the ophthalmic artery and the associated risk for blindness. In cases of refractory epistaxis, these vessels are amenable to surgical ligation.[73]

PARANASAL SINUS DISEASE

Overall, inflammatory disease of the paranasal sinuses is poorly understood. Sinusitis represents a wide variety of pathologic conditions that may cause either acute or chronic inflammation. Paranasal sinus inflammation is almost inevitably accompanied by inflammation of the nasal cavity, or rhinitis. Thus, the term *rhinosinusitis* is commonly used to describe this condition.

Although the diagnosis of acute rhinosinusitis may be made with clinical symptoms and time course alone, objective evidence of sinus inflammation is required for a diagnosis of chronic rhinosinusitis.[74–76] Table 70.1 demonstrates the diagnostic criteria for acute, chronic, and recurrent acute rhinosinusitis. The duration of symptoms is the primary factor used to differentiate between acute and chronic rhinosinusitis. Acute sinusitis lasts up to 4 weeks. Patients

Table 70.1 Diagnostic Criteria for Rhinosinusitis

Term	Definition
ACUTE	
Acute rhinosinusitis	Up to 4 weeks of purulent nasal drainage (anterior, posterior, or both) accompanied by nasal obstruction, facial pain-pressure-fullness, or both: ■ *Purulent nasal discharge* is cloudy or colored, in contrast to the clear secretions that typically accompany viral upper respiratory infection and may be reported by the patient or observed on physical examination. ■ *Nasal obstruction* may be reported by the patient as nasal obstruction, congestion, blockage, or stuffiness, or may be diagnosed by physical examination. ■ *Facial pain-pressure-fullness* may involve the anterior face, periorbital region, or manifest with headache that is localized or diffuse.
Viral rhinosinusitis (VRS)	Acute rhinosinusitis caused by, or presumed to be caused by, viral infection. A clinician should diagnose VRS when symptoms or signs of acute rhinosinusitis are present for fewer than 10 days and the symptoms are not worsening.
Acute bacterial rhinosinusitis (ABRS)	Acute rhinosinusitis caused by, or presumed to be caused by, bacterial infection. A clinician should diagnose ABRS when: ■ Symptoms or signs of acute rhinosinusitis are present 10 days or more beyond the onset of upper respiratory symptoms, *or* ■ Symptoms or signs of acute rhinosinusitis worsen within 10 days after an initial improvement (double worsening).
CHRONIC AND RECURRENT	

Chronic rhinosinusitis	Twelve weeks or longer of two or more of the following signs and symptoms:
	■ Mucopurulent drainage (anterior, posterior, or both)
	■ Nasal obstruction (congestion)
	■ Facial pain-pressure-fullness *or*
	■ Decreased sense of smell *and*
	■ Inflammation is documented by one or more of the following findings:
	  ■ Purulent (not clear) mucus or edema in the middle meatus or ethmoid region
	  ■ Polyps in nasal cavity or the middle meatus, *and/or*
	  ■ Radiographic imaging showing inflammation of the paranasal sinuses.

Recurrent acute rhinosinusitis	Four or more episodes per year of ABRS without signs or symptoms of rhinosinusitis between episodes. Each episode of ABRS should meet diagnostic criteria.

From Rosenfeld RM, Piccirillo JF, Chandrasekhar SS, et al. Clinical practice guideline (update): adult sinusitis. *Otolaryngol Head Neck Surg*. 2015;152(suppl 2):S1–S39; and Rosenfeld RM. Clinical practice guideline on adult sinusitis. *Otolaryngol Head Neck Surg*. 2007;137(3):365–377.

with signs and symptoms for 12 weeks or longer are diagnosed with chronic sinusitis. Patients with symptoms lasting from 4 to 12 weeks are deemed to have subacute sinusitis, and clinical judgment is recommended in determining whether to manage based on acute or chronic rhinosinusitis guidelines. Whereas the duration of symptoms is used to distinguish between acute and chronic disease, the pathophysiologic features, symptoms, and treatment of these entities are different. *Acute bacterial rhinosinusitis* is an acute infectious disorder, and patients present with fever and facial pain as characteristic symptoms. *Chronic rhinosinusitis* (CRS) is primarily an inflammatory disorder in which the role of microbes is not well established. Patients with CRS typically note nasal congestion, thick nasal drainage, and facial pressure, but fever[77] and pain are uncommon in the absence of acute exacerbations.

Objective findings of rhinosinusitis may be present on routine physical examination during evaluation of the anterior nasal cavity or anterior rhinoscopy. Acute rhinosinusitis may be diagnosed by history and anterior rhinoscopy alone; imaging studies are not recommended for uncomplicated acute sinusitis.[74–76,78] Objective evidence of inflammation in patients with chronic sinusitis is often difficult to establish on anterior rhinoscopy, so nasal endoscopy or imaging of the sinuses is often required to establish the diagnosis. With a nasal endoscope, the middle and superior meatus can be closely examined. Polyps or significant edema in these regions satisfies the objective criteria for inflammation required for a CRS diagnosis. Thick mucus can be sampled under endoscopic guidance to guide antimicrobial therapy. *Computed tomography* (CT) (see Fig. 70.4) is the preferred method of imaging for the paranasal sinuses; radiographs of the paranasal sinuses lack sufficient specificity and sensitivity and have little clinical utility.[78] *Magnetic resonance imaging* (MRI) is not indicated for routine inflammatory sinus disease. MRI, however, is quite useful in the assessment of sinonasal tumors, intracranial complications of sinusitis, and encephaloceles, and in the diagnosis and treatment planning for invasive fungal sinusitis.

ACUTE RHINOSINUSITIS

Epidemiology

Acute rhinosinusitis is extremely common and typically of viral etiology. It is estimated that adults suffer two to five episodes of viral rhinosinusitis (i.e., the common cold) annually. School-age children may suffer 7 to 10 colds per year.[74] In the United States, upper respiratory tract infection is the third most common reason for a primary care provider consultation, with approximately one-third of these attributed to acute rhinosinusitis.[79] Gwaltney and colleagues[80] demonstrated that 60% of viral upper respiratory infections demonstrate radiologic evidence of inflammation within the ethmoid and maxillary sinuses on CT imaging. This study also highlights the futility of CT

imaging for distinguishing between acute viral and acute bacterial rhinosinusitis.

From 0.5–2% of viral rhinosinusitis episodes will progress to *acute bacterial rhinosinusitis* (ABRS).[74] The proposed pathophysiology is that virally mediated mucosal inflammation and edema result in ciliary dysfunction and obstruction of the sinus ostia. This disruption of mucociliary clearance results in mucus stasis and a vulnerability to bacterial superinfection. The most common organisms seen in ABRS are noted in Table 70.2.

Treatment

Distinguishing the self-limited, viral-induced inflammation of the common cold from ABRS is a challenge often faced by primary care physicians. Clinical guidelines suggest that a detailed history is somewhat effective in making this distinction. Patients who do not demonstrate significant clinical improvement after 10 days or experience a worsening of symptoms after 5 days of the onset of symptoms, also referred to as double sickening, are more likely to have ABRS.[75,76,78] In addition, facial pain beyond what is expected from a viral upper respiratory infection or evidence of extrasinus extension of infection, such as periorbital edema, may be used to diagnose ABRS. Although patients who meet these clinical criteria demonstrate decreased duration and severity of symptoms when treated with antibiotics, the magnitude of improvement is relatively small.[75] Watchful waiting and antibiotic therapy are both reasonable options for patients with ABRS. A shared decision-making approach with patients is recommended, and updated guidelines provide patient education materials to help with this decision.[76] Patients who opt for watchful waiting should have access to medical professionals so that they may be treated with antibiotics if their symptoms worsen or fail to improve after 1 week. Patients with suspected complications of ABRS should be treated with antibiotics and referred to an otolaryngologist for urgent evaluation. Amoxicillin with or without clavulanate is recommended as a first-line treatment for uncomplicated ABRS, with trimethoprim-sulfamethoxazole encouraged for penicillin-allergic patients.[76,78] Alternatives for penicillin-allergic patients include doxycycline or a respiratory fluoroquinolone.[76,78,81] Diagnostic imaging, including both radiographs and CT images of the sinuses, do not adequately distinguish between ABRS and acute viral rhinosinusitis and are not recommended unless extrasinus spread of infection is suspected.[76,78]

Table 70.2 Microbiology of Acute Bacterial Rhinosinusitis in Adults

Organism	Range of Prevalence (%)
Streptococcus pneumoniae	20–43
Haemophilus influenzae	22–35
Streptococcus spp	3–9
Anaerobes	0–9
Moraxella catarrhalis	2–10
Staphylococcus aureus	0–8
Other	4

Recurrent acute rhinosinusitis, defined as four or more episodes of ABRS per year, may arise in the context of predisposing anatomic variations, exacerbations of CRS, immune compromise, or without identifiable predisposing factors.[75] Surgical intervention with widening of sinus ostia and removal of ethmoid septations may decrease the frequency and severity of symptoms.[82,83] Balloon sinus dilation, either in the clinic or in the operating room, may also be considered for treatment of recurrent acute rhinosinusitis. Whereas ABRS may be diagnosed without objective (endoscopic or CT) findings of inflammation, CT imaging demonstrating inflammation and elucidating patient anatomy is required before traditional endoscopic surgery or balloon sinus dilation for recurrent acute rhinosinusitis.[84] Although uncommon, complications arising from rhinosinusitis are seen more frequently in acute than in chronic rhinosinusitis. Infection may spread to the orbit or intracranial cavity, a complication more common in children.[85,86] Suppurative complications of acute rhinosinusitis frequently arise from infections of odontogenic origin, particularly from the *Streptococcus milleri* group. Urgent evaluation and treatment, often including surgical drainage of affected sinuses and associated abscesses, is required to minimize the risk for visual loss, seizures, meningitis, and even death.

Invasive fungal sinusitis is a life-threatening condition developing in patients with significant immune compromise. Diabetics with poorly controlled blood glucose levels and patients undergoing bone marrow transplantation are at highest risk. The diagnosis is suspected in this patient population with the development of facial pain, swelling, cranial neuropathies, or unexplained fevers. Imaging studies (CT and MRI) (Fig. 70.5) are helpful in raising suspicion for the diagnosis, particularly if there is loss of contrast enhancement on MRI.[87,88] The diagnosis is established by biopsy demonstrating fungal invasion into the sinus tissues. Frozen section of diseased tissue demonstrates good sensitivity and expedites this analysis.[89,90] Cultures may be helpful to guide antifungal treatment; the morphologic features of fungal elements seen on pathologic evaluation may also assist in identifying the offending fungi. Extrasinus invasion is most common with mucormycosis. Treatment involves surgical débridement, systemic antifungal medications and, when possible, reversal of the underlying immune dysfunction. Even with appropriate medical care, mortality for this condition approaches 50%.[91] Aggressive surgical débridement must therefore be considered in the context of the patient's goals of care.

A slowly progressive, indolent form of invasive fungal sinusitis is seen in patients with less severe immune compromise. Solid-organ transplant recipients and patients with chronic corticosteroid use are at risk for this disorder. *Aspergillus* is the most common pathogen. The treatment principles are the same as for patients with acute invasive fungal sinusitis.

CHRONIC RHINOSINUSITIS

Epidemiology

CRS has an uncertain incidence because the diagnosis often requires both subjective symptoms and nasal endoscopy or CT evaluation. Surveys, which rely only on patient symptom reports, suggest that more than 15% of

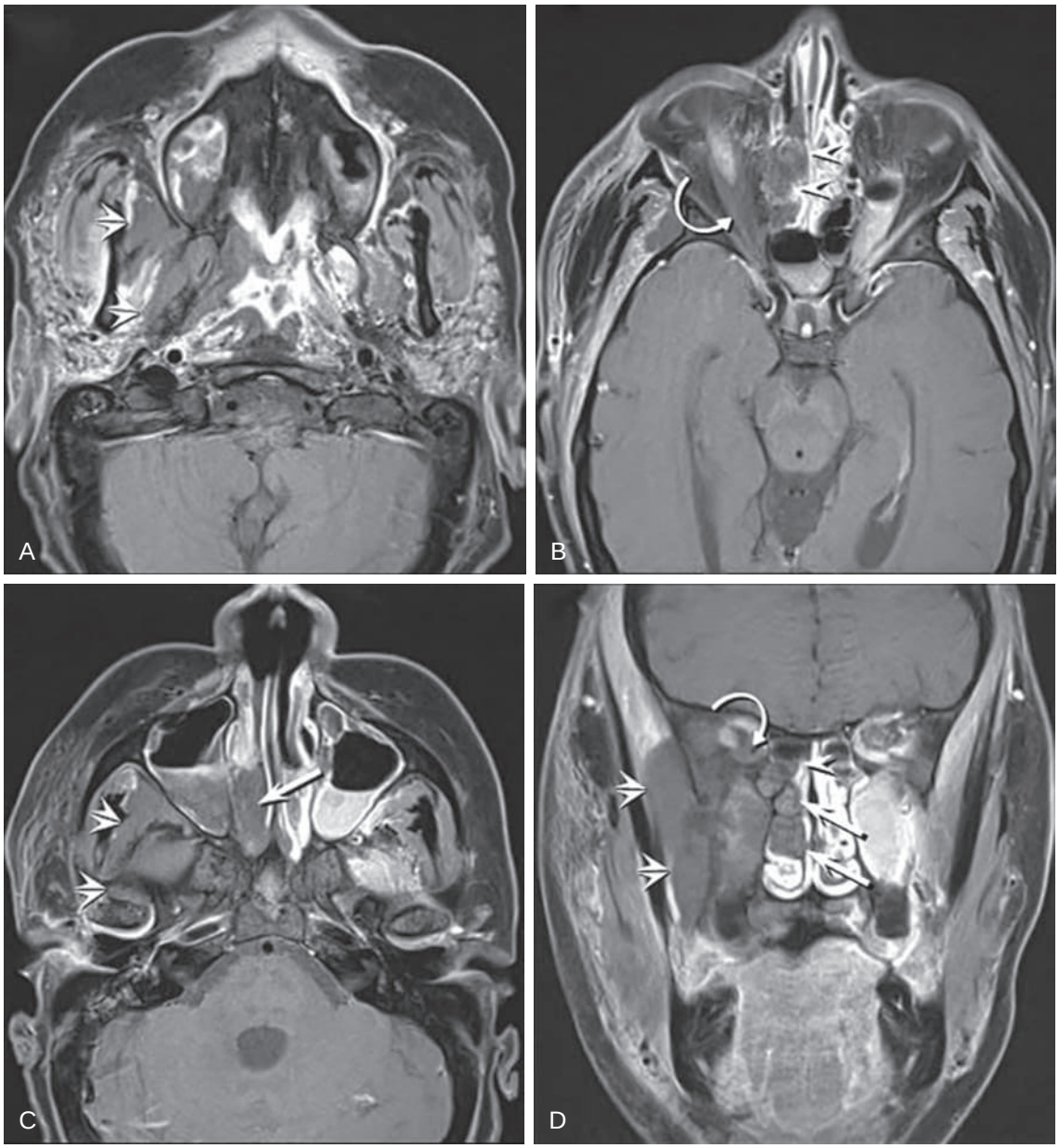

Figure 70.5 Angioinvasive fungal sinusitis. (A–C) Axial and (D) coronal contrast-enhanced fat saturation T1-weighted magnetic resonance images show necrotic tissue with loss of contrast enhancement. The abnormality extends from the right middle/superior turbinates (*arrows*) and posterior right ethmoid region (*arrowheads*) laterally as far as the right infratemporal fossa (*double arrowheads*). Note involvement of the posteroinferior right orbit, particularly the right inferior rectus muscle (*curved arrows*). (Courtesy Joseph M. Hoxworth, MD, Consultant and Associate Professor of Radiology, Department of Radiology, Mayo Clinic College of Medicine.)

the U.S. population suffers from CRS,[92,93] likely a significant overestimation of the true incidence.[74] The prevalence of physician-diagnosed CRS using diagnostic coding reporting in a limited geographic area was closer to 2%.[94] Nonetheless, the impact of CRS on overall quality of life is estimated to be similar to that of COPD and congestive heart failure.[95] In the United States, the overall cost burden for chronic sinusitis is estimated at $8.6 billion per year.[96]

Pathophysiology

CRS is characterized by persistent mucosal inflammation of the paranasal sinuses. The cause of this inflammation is variable and often poorly understood. Numerous theories have been proposed for mechanisms that drive the inflammation in CRS, including systemic immune dysfunction,[97–99] staphylococcal superantigens,[100] pathologic bacterial biofilms,[101–103] aberrant immune response to fungus,[104] and microbial dysbiosis (e.g., imbalance of the resident microbial population).[22,105–108] Several subtypes of CRS have been well established.

The bacteriology of CRS differs from that of acute sinusitis. *Staphylococcus aureus, Pseudomonas aeruginosa,* and anaerobic bacteria are more commonly cultured from patients with chronic disease than with acute disease. Recent studies using culture-independent bacterial identification demonstrate that healthy sinuses contain diverse bacterial communities, which may serve a protective role in the sinuses. Chronically inflamed sinuses are characterized

by a loss of bacterial diversity with overgrowth of a pathologic species[22,105–108] (see also Chapter 17).

Association With Allergy and Asthma

The role of allergy and atopy in CRS is unclear. Studies suggest a higher rate of positive skin tests in patients with CRS[109] but may be confounded by selection bias. Although a causal role for allergy in patients with CRS has not been demonstrated, in atopic patients with CRS, treatment of allergy improves patient outcomes.[110]

CRS with nasal polyps (CRSwNP) demonstrates a more clear association with asthma. Nearly 30–40% of patients with polyps describe wheezing and respiratory discomfort. In addition, 26% of patients with polyps report a diagnosis of asthma compared to 6% of control patients.[111] Patients with asthma also demonstrate a high incidence of sinus mucosal thickening on CT imaging.[112,113] Asthmatic patients also demonstrate a high incidence of nasal polyps; of note, nonatopic asthma is more strongly associated (13%) with nasal polyps than is atopic asthma (5%).[114] As additional evidence of the association of asthma and CRSwNP, asthmatic patients who undergo endoscopic sinus surgery for CRSwNP demonstrate clinical improvement in both upper and lower airway disease.[115–117]

CHRONIC RHINOSINUSITIS WITH NASAL POLYPOSIS

CRS patients are frequently categorized based upon the presence or absence of nasal polyps. A more detailed analysis of the pathophysiology of these patient populations demonstrates that both CRS with and without nasal polyps represents a heterogeneous group of disorders with distinct pathogenic mechanisms. Furthermore, the endotype (i.e., the CRS subtype associated with a pathobiologic mechanism) appears to predict the efficacy of various treatment approaches.[118] Many CRSwNP patients are characterized by type 2 inflammation: inflammatory pathways involving IL-4, IL-5, IL-13, and IgE, which strongly associate with tissue eosinophilia, asthma comorbidity, and severity of sinus disease (see Fig. 70.4C).[119] These patients typically respond well to systemic steroid treatment, which blunts type 2 inflammation, and they are good candidates for biologic therapy targeting IL-4, IL-13, IgE, and IL-5 (see "Treatment" section later).

Conversely, patients with a predominately IL-17–mediated response and neutrophilic inflammation may develop polyps but are generally refractory to corticosteroid treatment.[120] Long-term macrolide therapy has been proposed as an important treatment adjunct for CRSwNP patients with predominately neutrophilic inflammation.[118,121,122]

Although nasal polyps may be visible on anterior rhinoscopy and may even extend to or beyond the nasal vestibule, more frequently nasal endoscopy is required to visualize nasal polyps. Patients typically present with nasal congestion, obstruction, thick nasal drainage, and anosmia. Facial pressure is common. Severe pain, headache, and fever are unusual in the absence of acute exacerbations of chronic disease. Fatigue and difficulty sleeping are also common symptoms.

Patients with asthma and nasal polyps should be queried regarding sensitivity to aspirin and *nonsteroidal anti-inflammatory drugs* (NSAIDs). *Aspirin-exacerbated respiratory disease* (AERD) is found in a subset of CRSwNP patients and is characterized by nasal polyps, asthma, and NSAID sensitivity. Patients with AERD demonstrate abnormalities in arachidonic acid metabolism, characterized by increased production of proinflammatory products of the 5-lipoxygenase pathway after exposure to cyclooxygenase-1 inhibitors, such as aspirin and NSAIDs, which results in shunting through the lipoxygenase pathway and in upper and lower airway inflammation. Patients often develop persistent rhinitis in their late teenage years, with asthma and sinusitis developing over the next several years. Aspirin and NSAID sensitivity may develop at any point along the course of the disease.[123] AERD represents a significant proportion of patients with asthma (9%)[124] and CRSwNP (13%).[114] These patients demonstrate a more refractory clinical course in the treatment of their sinus disease. Aspirin desensitization improves both asthma and sinus disease in this patient population.[125–128]

Patients with unilateral nasal polyps should be evaluated for sinonasal neoplasms with imaging and consideration of biopsy. Before performing a biopsy of a sinonasal mass, the clinician should evaluate the relationship of the mass to the skull base to rule out an encephalocele. Assessment of surrounding vasculature is also critically important because both aneurysms of the carotid artery and juvenile nasal angiofibromas may present as a nasal mass. Biopsy of these entities may lead to severe hemorrhagic complications.

Allergic fungal rhinosinusitis (AFRS) is a distinct category of chronic sinusitis. Unlike the majority of chronic inflammatory sinus disease, AFRS is often unilateral. This diagnosis is established by the presence of nasal polyps, eosinophilic mucus with Charcot-Leyden crystals, and skin or blood testing demonstrating allergy to fungus.[129] The incidence of AFRS is higher in African American patients, and the disorder is more common in humid regions, including the southern United States.[130,131] Bone expansion and erosion may result in initial difficulty distinguishing AFRS from sinonasal neoplasms. In such cases MRI findings are also helpful in the diagnosis of AFRS (Fig. 70.6).

Congenital disorders resulting in impairment of mucociliary clearance have a high incidence of CRS. Because nasal polyps are unusual in pediatric patients, their presence should trigger evaluation for cystic fibrosis and ciliary dyskinesia. Pathologic evaluation of polyps in these patients is likely to demonstrate a neutrophilic infiltrate and a predominately type 1 T–helper cell–mediated inflammatory process.[132,133]

Treatment

Treatment of CRSwNP is challenging. Most patients receive only temporary, if any, benefit from antibiotic therapy.[76,78,134,135] Topical steroid sprays and saline irrigations often provide improvement[135,136] but rarely provide adequate symptomatic relief for patients with a significant polyp burden. Systemic steroid therapy frequently provides significant symptomatic improvement.[76,78,137] Unfortunately, systemic side effects limit long-term use of this medication, and symptoms often recur quickly after

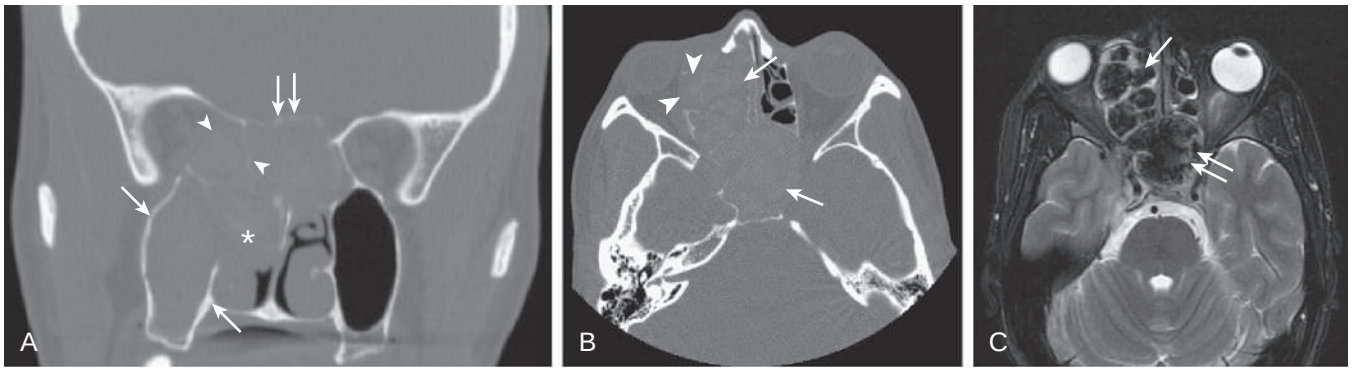

Figure 70.6 Allergic fungal rhinosinusitis. Coronal (A) and axial (B) computed tomography images demonstrate allergic fungal rhinosinusitis. The sinus contents are increased in density and expansile in nature with associated bone remodeling and erosion involving the medial right maxillary sinus (*single arrows*, A), sphenoid sinus walls and ethmoid partitions (*arrows*, B), and anterior skull base (*double arrows,* A). The right lamina papyracea (the medial wall of the orbit) has also been eroded (*arrowheads*, A–B), with the ethmoid contents bowing laterally into the medial right orbit. Lobulated opacity in the right nasal cavity (*asterisk*, A) is consistent with sinonasal polyposis, one of the diagnostic criteria for allergic fungal rhinosinusitis. Axial T2-weighted magnetic resonance imaging (C) demonstrates a loss of signal within the affected sinuses (*arrow*, right ethmoid sinuses; *double arrows*, sphenoid sinuses), which is characteristic of allergic fungal rhinosinusitis. (Courtesy Michael B. Gotway, MD.)

cessation of exogenous glucocorticoids. Initial enthusiasm for antifungal irrigations has waned with the publication of trials that demonstrate not only a lack of efficacy, but worsened symptoms when compared to placebo saline irrigation.[134,138] Current guidelines recommend against use of antifungal irrigations for patients with CRS.[78,139] Endoscopic sinus surgery with removal of polyps and cleaning of mucus and debris from within the sinuses results in significant symptomatic improvement.[140] Systemic corticosteroids are frequently initiated before surgery for CRSwNP to decrease mucosal inflammation, which improves hemostasis and endoscopic visualization during surgery. Corticosteroids also enhance control of asthma during endotracheal anesthesia and the postoperative period. Even in the setting of appropriately performed endoscopic sinus surgery, recurrence of polyps is common. Combining medical and surgical interventions is essential in this patient population. Surgery enhances postoperative access to the sinuses, allowing enhanced penetration of topical steroid irrigations. Steroid-impregnated implantable materials have also been used to extend the duration of symptomatic improvement after surgery.[141–143]

New biologic treatments hold promise for the treatment of CRS. Dupilumab (anti–IL-4 with anti–IL-13 activity) has been approved by the FDA for treatment of CRS with nasal polyps.[144,145] Studies evaluating this treatment focused on patients with severe disease burden and often with concomitant asthma, likely selecting for patients with type 2 inflammation. Concerns related to cost and requirement for continued therapy may limit the clinical utility of this medication. Omalizumab, an anti-IgE monoclonal antibody, has been used to treat refractory asthma and appears also to benefit patients with CRSwNP. Data on the efficacy of omalizumab as a treatment for CRSwNP have been submitted to the FDA with the goal of approval as a treatment for this disorder.[135,146] IL-5 is an important driver of eosinophil differentiation and survival, and anti–IL-5 antibodies (mepolizumab, benralizumab, reslizumab) have been FDA approved for treatment of eosinophilic asthma. Studies targeting patients with asthma have demonstrated some efficacy for CRS.[147,148]

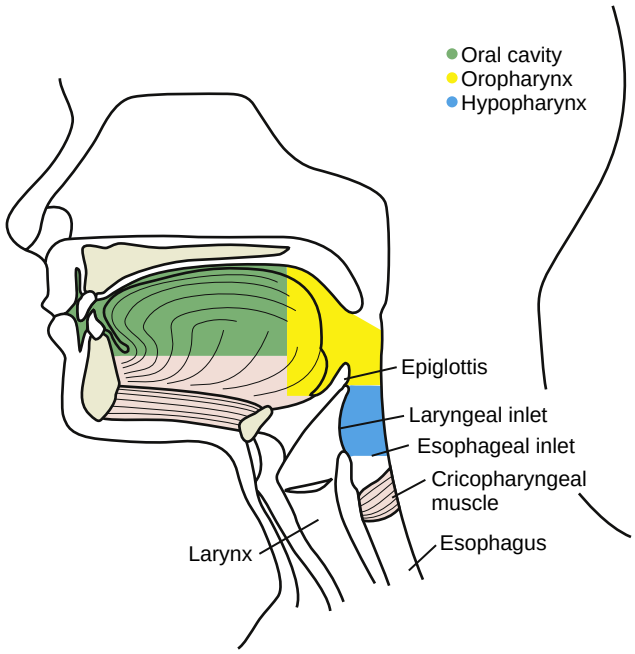

Figure 70.7 Schematic of the oral cavity (*green*), oropharynx (*yellow*), and hypopharynx (*blue*) along with the esophageal inlet and cricopharyngeal muscle.

THE ORAL CAVITY, OROPHARYNX, HYPOPHARYNX, AND LARYNX

ANATOMY, HISTOLOGY, AND PHYSIOLOGY

Oral Cavity

The *oral cavity* is defined as the space from the lips to the end of the hard palate. It contains the teeth, the buccal and gingival mucosa, the mandible and hard palate, the floor of the mouth, and the tongue anterior to the circumvallate papilla (Fig. 70.7). The oral cavity structures are mostly under voluntary control. The oral cavity functions to control the ingestion of food substances. The structures

control the food during mastication and preparation of a bolus suitable for presentation to the oropharynx for reflexive swallowing. Mastication and preparation involve the muscles of mastication for opening and closing of the jaws and the muscles in the lips and cheeks to control the size of the cavity and the muscles of the tongue to move the food particles around the mouth and shape them into the required bolus. In addition to controlling the intake of substances, the structures in the oral cavity are responsible for voluntary modulation of air exhaled from the lungs. This voluntary control is used to control the rate of the air exhaled and to shape the noises created by airflow into speech and song.

Oropharynx

The *oropharynx* is defined as the space from the end of the hard palate to a plane parallel to the top of the epiglottis (see Fig. 70.7). This space includes the structures of the lateral pharyngeal walls, made up by the middle constrictors, the palatoglossus and the palatopharyngeus, the palatine tonsils, the soft palate and uvula, the vallecula, and the base of the tongue. Although these muscles and structures are under voluntary control for assistance in the rate of exhaled air from the lungs and shaping sounds released from the vocal tract, they are under reflexive control for swallowing. Once the sensory nerves are triggered by the exposure to a bolus of solids or liquids, the central nervous system sends a reflexive response to swallow. This reflex leads to an orderly contraction of the tongue base, soft palate, and lateral pharyngeal walls to propel the bolus posteriorly, seal off the nasopharynx, and propel the bolus to the hypopharynx, respectively.

Hypopharynx

The *hypopharynx* is defined as the space from a plane perpendicular to the tip of the epiglottis beyond the superior and lateral aspect of the larynx down to the esophageal inlet (see Fig. 70.7). This includes the structure of the lateral pharyngeal walls, including the inferior constrictors and mucosal membranes, as well as the bilateral pyriform sinuses. As for the oropharynx, the skeletal muscles that make up these structures are under voluntary control for assisting in regulation of airflow out of the lungs and shaping the airflow into speech and as reflexive central nervous system control for swallowing. The distal end of the hypopharynx culminates in the upper esophageal sphincter. This is a region of the pharynx that controls opening of the proximal esophagus to allow passage of food into the alimentary tract and to prevent the inadvertent regurgitation of food or secretions back into the pharynx and upper airway. Although the upper esophageal sphincter is several centimeters in length, the primary portion is made up of the cricopharyngeal muscle (see Fig. 70.7). This circumferential, sling-like skeletal muscle is maintained in a tonic contracted and closed state. The act of swallowing initiates reflexive inhibition of the neural input, resulting in muscular relaxation. As the larynx and pharynx are pulled upward and forward by the actions of other muscles, the relaxed upper esophageal sphincter is stretched open. This allows the passage of the food bolus. The bolus can fail to pass either because of failure of relaxation of the cricopharyngeal muscle segment or failure to stretch the area open through pull of coordinated muscles on the relaxed upper esophageal sphincter segment. Either will result in the retention of foods and secretions, which can then spill into the upper airway.

Larynx

The *larynx* is made of the bone, cartilage, and muscular and mucosal structures from the epiglottis to the bottom of the cricoid ring. It is divided into three regions based on the lymphatic drainage patterns. These regions include (1) the supraglottis from the tip of the epiglottis to the top of the vocal folds (also known as the vocal cords), including the upper part of the arytenoid; (2) the glottis, which includes the tissue from the top of the vocal folds to 1 cm below the top of the vocal folds; and (3) the subglottis, which is below the vocal folds to the first ring of trachea (Fig. 70.8).

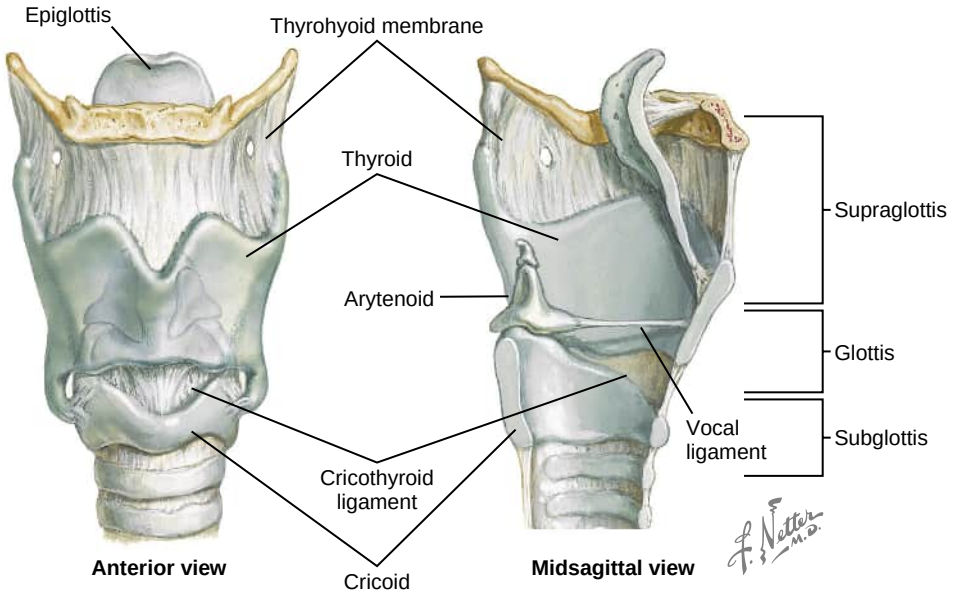

Figure 70.8 Schematic view of the larynx with the cartilage and ligamentous structures. The supraglottis, glottis, and subglottic subdivisions are marked. (Modified from Netter FH. *Atlas of Human Anatomy*. ed 5. Philadelphia: Elsevier; 2010. Netter illustration from www.netterimages.com, ID: 1495. Copyright Elsevier Inc. All rights reserved.)

Bone and Cartilage. The structural bone and cartilages of the larynx include the hyoid bone, paired thyroid lamina, and cricoid ring. These structures have ligamentous and cartilaginous attachments to each other to allow them to function as one organ. Specifically, the hyoid is attached to the thyroid cartilage by the thyrohyoid ligament. The thyroid laminae are attached to the cricoid laterally by the fibrous cricothyroid joint and anteriorly by the cricothyroid ligament and membrane. The hyoid bone is attached to the skull base by the styloglossus muscle, to the mandible by the geniohyoid muscle, and to the tongue base by the hyoglossus muscle. The laryngeal cartilage is attached to the pharyngeal wall through the inferior pharyngeal constrictor muscle and to the cricoid ring by the cricothyroid joint, membrane, ligament, and muscle. The cricoid is attached to the trachea through fibrous attachments. These connections support the airway. Other cartilaginous structures within the larynx include the arytenoid complex cartilages known as cuneiform, corniculate, and arytenoid cartilages and the epiglottic cartilage. The mucosal and muscular structures of the larynx include the aryepiglottic folds connecting the arytenoid complex to the epiglottis; the false vocal folds, running from the body of the arytenoid to the base of the epiglottis; and the true vocal folds, running from the arytenoid to the thyroid cartilage (Fig. 70.9). The laryngeal ventricle is a cleft between the true and false vocal folds. It contains mucus-producing cells and minor salivary glands that lubricate the tissue of the larynx during breathing and speaking. In addition, the shape of the ventricle probably creates turbulence in airflow that is significant for vocal fold vibration during speaking[149] but of relatively little significance for airflow during breathing.

Arytenoid Complex. The arytenoid cartilage is attached to the cricoid ring through a series of anterior and posterior ligaments that form the capsule of the synovial cricoarytenoid joint. The corniculate and cuneiform cartilages have fibrous attachments to the arytenoids and are located on top of and anterior to the arytenoid cartilage, respectively.

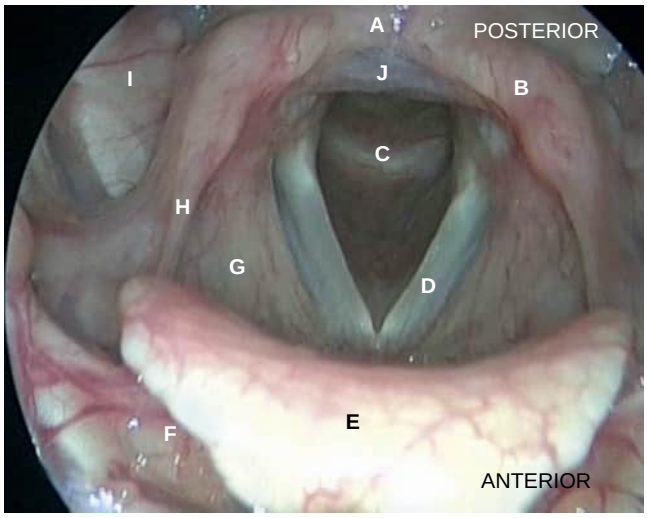

Figure 70.9 Upper airway anatomy: endoscopic view. *A,* Esophageal inlet; *B,* arytenoid; *C,* trachea; *D,* true vocal folds; *E,* epiglottis; *F,* vallecula; *G,* false vocal folds; *H,* aryepiglottic folds; *I,* pyriform sinus; *J,* interarytenoid region.

The true function of these structures is unknown, but they are thought to increase and stiffen the aryepiglottic fold and may therefore aid in prevention of aspiration during swallowing and prevent supraglottic collapse of the airway during breathing. The cricoarytenoid joint allows movement of the arytenoid on the cricoid ring for vocal fold abduction and adduction, which is controlled by the action of the intrinsic laryngeal musculature on the arytenoid. Specifically, the lateral cricoarytenoid muscle attaches from the lateral aspect of the cricoid to the muscular process on the posterolateral aspect of the arytenoid. Contraction of the lateral cricoarytenoid muscle creates inward rotation of the arytenoid on the cricoid and closes the laryngeal airway during swallowing, speaking, and exhalation. This activity is supplemented by the action of the interarytenoid muscle, which runs between the upper bodies of the arytenoids and pulls the arytenoids together. The interarytenoid muscle is probably more important during voice production than during breathing. The posterior cricoarytenoid muscle attaches from the posterior aspect of the cricoid ring also to the muscular process on the posterolateral aspect of the arytenoid. Contraction of the posterior cricoarytenoid muscle creates outward rotation of the arytenoid on the cricoid and opens the airway during inspiration.

Epiglottis. The epiglottis has ligamentous attachments to the hyoid bone (hyoepiglottic ligament) and thyroid cartilage (thyroepiglottic ligament) and fibromuscular attachments to the arytenoid complex (aryepiglottic fold). As the names of these attachments imply (origin to insertion), the epiglottis moves in relation to these supportive structures during breathing and swallowing. This movement is passive. As the tongue base and pharyngeal walls contract and the hyoid and attaching laryngeal supporting framework are pulled upward, the epiglottis tilts posteriorly (passive inversion) to cover the top of the airway and divert the bolus to be swallowed to the outside of the larynx (pyriform sinuses). The epiglottis does not completely cover the airway, but rather steers the bolus through the pyriform sinus and outside of the laryngeal airway. Patients who lose the epiglottis secondary to cancer treatment can be taught to swallow again by strongly contracting the tongue base to pull the larynx forward, thereby partially covering the laryngeal airway. Usually this results in a small amount of residue deposited on the top portion of the larynx and/or vocal folds that then must be cleared out of the larynx into the hypopharynx with a throat clear or cough and swallowed a second time. This is known as a "supraglottic swallowing technique" and is useful in preventing aspiration in cases of epiglottic loss or malfunction.

Mucosal and Fibromuscular Structures. The mucosal and fibromuscular structures include the aryepiglottic folds, false vocal folds, and true folds. As stated previously, the aryepiglottic folds run from the arytenoid complex to the epiglottis. They separate the pyriform sinus of the hypopharynx from the supraglottic larynx and form a sling of tissue around the vocal folds to prevent aspiration during swallowing. They consist of fibrofatty tissue and contain minor salivary glands and mucus-producing cells. If a significant portion of the aryepiglottic fold is removed during surgery, the liquid or food bolus can fall into the larynx and increase the risk for aspiration. At the inferior portion of the

aryepiglottic fold is the false vocal fold. This is a fibrofatty collection of tissue also covered with epithelium containing minor salivary glands and mucus-producing cells. The true function of the false vocal folds is unknown, but they most likely affect the resonance characteristics of the voice rather than the process of breathing or swallowing. The aryepiglottic folds and false vocal folds are part of the supraglottis and can be covered with either respiratory epithelium or squamous epithelium.[150]

The true vocal folds are composed of the *thyroarytenoid* (TA) and *lateral cricoarytenoid* (LCA) muscle covered with mucosa. The mucosa is a stratified squamous epithelium supported by a specialized submucosa or lamina propria differentiated into three layers. This differentiation is likely secondary to use of the vocal folds for phonation, which causes the supporting fibroblasts to produce and secrete proteins and carbohydrates.[151] These extracellular particles are then layered in a particular order, with dense collagen as the deepest layer, an elastin-rich middle layer, and glycosaminoglycans and glycoproteins forming a spongy superficial layer. The middle and deep layer form a transition zone known as the vocal ligament, which runs from the anterior aspect of the thyroid cartilage to the vocal process of the arytenoid. This ligament allows the superficial layers to separate from the deeper layers as the vocal folds vibrate to produce voice and is probably responsible for the relatively wide vocal pitch range that humans are able to produce. The TA-LCA muscle runs from the anterior aspect of the thyroid cartilage and attaches along the body of the arytenoid cartilage. As the TA contracts, it adducts, tenses, shortens, and thickens the vocal fold. This is important because, as the TA-LCA muscle changes tension and shape, it has an indirect effect on the vocal fold mucosa, which is involved in vocal fold vibration. The vibration frequency of an object is related to the driving force for vibration and the tension and mass of the object. Therefore, as we adjust the tension in the vocal fold, through voluntary contraction of the intrinsic skeletal muscle of the larynx, we affect the frequency of vocal fold vibration, which is perceived as the pitch of the voice. In the case of vocal fold tension and mass, the most important muscles are the TA-LCA along with the cricothyroid muscle. As the cricothyroid muscle, which originates on the cricoid ring anteriorly and inserts on the thyroid cartilage, contracts, the thyroid cartilage is subluxed on the cricoid ring. This results in stretching the vocal fold and increasing the tension, which drives up the frequency of vibration and the pitch of the voice.

Pathophysiology. The pharynx and larynx have prominent and complex functions in the upper airway to separate the alimentary tract from the respiratory tract for human survival. For swallowing and breathing, the pharynx and larynx must work in a coordinated manner. If these systems fail to function properly, the airway can be obstructed or pharyngeal contents can be aspirated, leading to lung disease.

DISORDERS OF SWALLOWING

Epidemiology

Disorders of swallowing caused by either neurologic or muscular diseases interrupting the normal sequences of upper airway and pharyngeal activity can lead to the aspiration of pharyngeal contents either directly, during the swallowing act, or indirectly, from refluxed gastric contents. Aspiration of large quantities of liquid material or of large solid substances can lead to airway obstruction with asphyxiation and death. Acute aspiration of small amounts of substances has been shown to produce acute pulmonary inflammation.[152] Aspiration of acidic materials appears to be more inflammatory than aspiration of less acidic materials.[153] If the aspiration is an isolated single event, the inflammation resolves with little consequence.[152] However, repeated aspiration can damage the alveolar lining of cells and capillaries and lead to bacterial invasion, mucosal desquamation, and mononuclear cell inflammation.[153] In lung transplant patients, chronic aspiration of refluxed gastric contents has been associated with increased failure rates of grafts through the development of bronchiolitis obliterans syndrome.[154] Although the exact mechanism is unknown, it appears to be related to fibrosis developing as a response to chronic repeated inflammation. This response may be reduced through the use of agents that reduce inflammation[155] (see also Chapters 43 and 72).

Disorders of swallowing, commonly called dysphagia, affect 2–11% of the general population.[156] The etiology is varied. Dysphagia may arise in response to normal aging due to weakening of the pharyngeal musculature. Dysphagia may also arise from neurologic disease (e.g., stroke), motor neuron disease, or Parkinson disease, due to mistiming of the swallow with poor coordination or to weakness or spasticity of the pharyngeal musculature. Finally, dysphagia often results from medical intervention for the treatment of head and neck disease or after intubation for respiratory failure.

Dysphagia is reported to develop in 40–50% of patients intubated for more than 48 hours.[157–159] Furthermore, the incidence of postextubation dysphagia rises by 14% for each additional day of intubation and is significantly more common in older patients.[158,160] The cause of dysphagia due to prolonged intubation is not completely understood. However, because the incidence is remarkably high, all patients intubated for prolonged periods should be evaluated with at least a bedside swallow examination before the initiation of oral feeding after extubation.[157] Clinical studies have also revealed that aspiration after extubation from prolonged intubation may be silent due to changes in laryngeal and pharyngeal sensation; therefore, some authors recommend more aggressive intervention with *flexible endoscopic examination of swallowing* (FEES) to document aspiration.[160] Silent aspiration can be identified by FEES, but the procedure has no impact on outcomes. Although dysphagia with aspiration does not always lead to pneumonia,[160] dysphagia alone is correlated with prolonged hospital stays.[159] The incidence of postintubation dysphagia can be reduced by using smaller endotracheal tubes and by careful monitoring to prevent excessive endotracheal tube cuff pressure.[161,162]

Symptoms of Disorders of Swallowing

The most common symptoms in patients with disordered swallowing are chronic coughing, weight loss, and repeated episodes of pneumonia. On questioning, patients report that they cough during meals. In general, a greater

difficulty with swallowing liquids is indicative of neurologic dysfunction or muscular weakness, and a greater difficulty with solids is more indicative of obstruction. The examiner should inquire about what substances cause the most difficulty, the timing of the cough in relation to eating, the length of time required to finish a moderate-sized meal, and where food appears to create the greatest difficulty during the swallow.

Coughing early during the act of swallowing indicates poor oral motor control of the bolus. Patients with neurologic disorders may notice that they cannot control the food within the oral cavity so that the food prematurely spills into the oropharynx or hypopharynx before the patient is ready to swallow. Patients find that substances that break apart easily or consist of both liquids and solids are most difficult because portions of the bolus can escape. Coughing during or after the swallow is most indicative of pharyngeal dysfunction due to either disordered reflex timing of the pharyngeal contraction or muscular weakness that prevents the bolus from moving through the pharynx as required.

Prolongation of mealtimes often leads to malnutrition and weight loss. Patients with an intact swallow mechanism can usually finish a complete meal in 15 minutes. Longer mealtimes are suggestive of dysphagia. When patients go beyond 30 minutes for a meal, they typically begin to lose interest in eating. In most cases, this prolongation is socially unacceptable, and dining companions begin to leave the table, forcing the patient to stop eating.

Dysphagia can be roughly divided into pharyngeal phase dysphagia and esophageal phase dysphagia. Patients with pharyngeal phase problems will complain of substances sticking in the back of their "throat" and coughing because of aspiration of retained substances, whereas patients with esophageal phase disorders will complain of food lodging in the chest that needs to be regurgitated or "washed down" with liquids. Cough may also be stimulated at the distal esophagus, but this is after the swallow and is generally nonproductive and not associated with the development of pneumonia.

Evaluation of Dysphagia

Evaluation is best done by a team of physicians and speech-language pathologists interested in disorders of swallowing. After a careful history, the patient can be given a sip of water during palpation of the laryngeal complex. As the patient swallows, the larynx should elevate briskly about 2 cm. In addition, the patient should not cough and should then be able to speak without a wet-sounding voice. If the patient passes this initial screening, then he or she should be asked to take multiple sips to see if the swallowing reflex breaks down. Next, complete head and neck evaluation and indirect endoscopy of the hypopharynx and larynx is undertaken to assess lip and tongue mobility and strength and for patterns of retained secretions or food particles. Patients with normal tongue function should be able to protrude the tongue and move it side to side without associated movement of the mandible. Retention of food particles within the oral cavity or inability to move the tongue freely is indicative of weakness or restricted motion. Indirect endoscopy identifying pooling at the base of the tongue within the vallecula is suggestive of weakness of the tongue base, pooling of secretions within the pyriform sinuses is indicative of pharyngeal weakness, and pooling of secretions in the esophageal inlet is indicative of failure of cricopharyngeal opening or obstruction of the esophagus.

To confirm these patterns of weakness, FEES[163] or modified barium swallowing examination can be performed. These tests are usually performed by a qualified speech-language pathologist. Rather than just being a screening test for aspiration, these examinations should be used to identify which deficits within the swallowing act are responsible for the dysphagia. In addition, during FEES or a modified barium swallow, various adaptive/compensatory swallowing adjustments can be tried. These diagnostic evaluations result in essential treatment approaches and can direct treatment strategies.

Treatment

Treatment for disorders of swallowing involves precise identification of the region and type of the swallowing deficits. If muscular weakness is identified, patients can be given a series of exercises targeting specific areas either of the tongue base[164,165] or of the lateral pharyngeal walls.[166] If neurologic deficits are identified, resulting in reflex timing issues or if the muscular deficits are insurmountable, patients can be taught compensatory strategies to improve the safety of the swallow. These strategies include repositioning of the patient during the swallow so that the bolus is less likely to fall into the airway, chin tuck to keep the bolus in the mouth during mastication, or head turning to close off the weakened side of the pharynx during the swallow act. Finally, if none of these techniques is beneficial and the patient and the family are interested, a feeding tube can be inserted to prevent weight loss and lessen the burden of needing to ingest a sufficient amount of calories orally to maintain weight. If repeated aspiration persists, laryngotracheal separation or narrow field laryngectomy, a less invasive procedure for laryngeal diversion, should be considered.

GASTROESOPHAGEAL AND LARYNGOPHARYNGEAL REFLUX DISEASE

Association with Asthma and COPD

The relationship between reflux disease, asthma, and COPD is complex. Although the association between reflux and severe asthma is well accepted, the empirical evidence for causation of one by the other is lacking. Lung disease may be related to reflux disease by different mechanisms. First, direct microaspiration of contents refluxed into the lungs on a chronic basis may lead to pulmonary remodeling. The extent of injury is related to the amount and characteristics of the aspirate, the frequency of aspiration, and the effectiveness of protective lung-clearance mechanisms. This is one proposed mechanism for the development of bronchiolitis obliterans syndrome in transplant patients. Second, reflux or reduced clearance of food from esophageal dysmotility may cause vagally induced bronchospasm. Vagally induced bronchospasm is associated with increased acidification of the lower esophagus and may be ameliorated by deacidification of the gastric contents in patients with difficult-to-control asthma.[167] Treatment with a *proton pump inhibitor* (PPI) improves asthma control in individuals with symptomatic *gastroesophageal reflux disease* (GERD) but not in those without symptoms.[168,169]

However, as previously stated, the association between reflux disease and lung disease does not prove causation. Medications for the treatment of asthma may increase reflux, as may changes from chronic lung disease. Albuterol is known to lower the resting pressure of the lower esophageal sphincter and decrease esophageal contraction amplitude. These changes may increase the incidence of reflux.[170] Prednisone, which is often prescribed in patients with difficult to control asthma, has been shown to increase esophageal acid exposure times.[171] COPD can lead to hyperinflation with flattening of the diaphragm. The diaphragm, specifically the crura around the esophageal hiatus, forms a critical part of the lower esophageal sphincter, and flattening of the diaphragm decreases the protective reflux barrier of the diaphragm. An increased transdiaphragmatic pressure gradient, as seen in patients with COPD, predisposes to the movement of gastric contents into the esophagus.

Evaluation of Gastroesophageal Reflux Disease and Laryngopharyngeal Reflux Disease

There are no universally accepted physical findings in the upper aerodigestive tract pathognomonic for extraesophageal reflux disease.[172] *Extraesophageal reflux disease* refers to the manifestations of reflux such as laryngitis, dysphonia, cough, and bronchospasm, which are separate from the classic esophageal reflux symptoms such as heartburn. Although attempts have been undertaken to develop a reflux finding score for physical changes in the larynx in patients with presumed extraesophageal reflux,[173] attempts at validation of these findings through correlation with pH studies have been unsuccessful. Therefore, the various laryngeal examination findings previously ascribed to *laryngopharyngeal reflux disease* (LPRD) are nonspecific and must be taken into context of a larger evaluation process.

After a careful history for symptoms of both classic GERD and extraesophageal reflux disease has been completed, most patients will be placed on an empirical trial of antireflux medications in combination with behavioral modification instructions. If the trial results in amelioration of the symptoms, the symptoms are commonly believed to be secondary to reflux disease. This method of evaluation for reflux with an empirical trial of medications is problematic because there may be a considerable placebo effect. Meta-analysis of randomized controlled clinical trials has shown that the effect of medications in alleviating symptoms is not significantly different from the effect of placebo.[174] However, most of these trials did not rely on objective testing for LPRD as entrance criteria. Some clinicians proceed to 24-hour pH monitoring and/or impedance testing. The latter, when combined with pH testing, allows detection of both acid and nonacid reflux. Although 24-hour pH analysis is considered the gold standard for esophageal reflux, pH testing over shorter time periods is often very helpful. Testing of pH within the hypopharynx to assess extraesophageal spillage of gastric contents is an area in its infancy, and there is significant debate as to what constitutes an abnormal finding.[175]

Treatment of Gastroesophageal Reflux Disease

Treatment of GERD or extraesophageal reflux disease causing pulmonary problems is best started with dietary modifications and twice-daily PPI medications. The rationale for these aggressive management strategies is that the pharynx, larynx, and trachea have few, if any, natural protective mechanisms for the neutralization of aspirated gastric contents.[176,177]

If there is strong suspicion of GERD or extraesophageal reflux causing pulmonary disease, consideration can be given to surgical therapies, such as Nissen fundoplication. Studies evaluating the true response of symptoms from extraesophageal reflux disease to surgical intervention show conflicting results. This is due in part to the significant difficulty in diagnosing extraesophageal reflux accurately and in understanding the role extraesophageal reflux may play in the pulmonary disease process.[178] The best results are obtained when classic GERD is identified and surgery, such as Nissen fundoplication, is performed for significant reflux within the lower esophagus.[179–181]

PARADOXICAL VOCAL FOLD MOTION DISORDER AND LARYNGOSPASM

Definition and Diagnosis

Also known as vocal cord dysfunction or inducible laryngeal obstruction, *paradoxical vocal fold motion disorder* (PVFMD) is a descriptive term for inappropriate adduction of the vocal folds during breathing. The mistimed vocal fold closure creates difficulty breathing and is often misdiagnosed as asthma. The diagnosis of PVFMD is made on the basis of history, followed by spirometry and laryngeal examination. Patients present with a constellation of symptoms, including difficulty breathing; a sensation of a foreign body or lump in their throat; a dry, nonproductive cough; and possibly chest tightness. These symptoms can manifest at rest, after talking, or after physical exertion. A distinct subset of this condition is associated with physical exertion and exercise. This has been called exercise-related PVMD or, more recently, exercise-induced laryngeal obstruction. Often the symptoms are exacerbated as the patient increases the intensity of the precipitating behavior. The disease is commonly misdiagnosed as asthma; however, the symptoms are refractory to standard asthma management protocols. In patients with PVFMD, spirometry performed during an episode may reveal flattening of the inspiratory limb of the flow-volume curve, indicative of a variable extrathoracic obstruction[182–184] (see Fig. 32.2, right panel). Flexible laryngoscopy, considered by some to be the gold standard for diagnosis,[182,185,186] may reveal paradoxical closure of the vocal folds during breathing. Typically, paradoxical closure is observed during active inhalation through either the mouth or the nose but is considered pathognomonic by some when seen at the end of a speech utterance.[183] Provocation testing through increased exercise challenge, odor exposure, or even methacholine challenge may increase the sensitivity of laryngoscopy in the identification of paradoxical closure. However, even with these challenges, the sensitivity of endoscopy is still only 60% in patients with symptoms.[187] Therefore, a presumptive diagnosis and empirical treatment may be warranted in all patients with symptoms who do not respond well to medical management for asthma.

Laryngospasm, closing of the vocal folds preventing inhalation, is a physiologic protective reflex to prevent aspiration when foreign particles or liquid (e.g., drowning) stimulate the vocal folds or supraglottic structures. Laryngospasm is most commonly encountered during extubation from general anesthesia. It is managed with positive-pressure

ventilation and small doses of paralytic agents to weaken vocal fold closure. Severe episodes are complicated by postobstructive pulmonary edema, which can require management in the intensive care unit. In the absence of a known stimulus, recurrent episodes of laryngospasm can develop in patients with progressive neurologic disease[188,189] or can be associated with severe forms of PVFMD. These often lead to recurrent trips to the emergency department and can be misdiagnosed as bilateral vocal fold paralysis. Patients with recurrent episodic laryngospasm should undergo a complete neurologic examination to rule out a neurologic disorder. In the absence of neurologic disease, laryngospasm will often respond to the same management strategies used for patients with PVFMD.

Etiology

The etiology of PVFMD is unclear. PVFMD is associated with asthma and GERD.[190] High levels of stress, chronic postnasal drip, and environmental exposure to inhaled or aspirated irritants, allergies, or GERD may lead to laryngeal hyperresponsiveness, which in turn triggers paradoxical laryngeal closure. In one study,[190] when patients with PVFMD were compared with normative data on the Minnesota Multiphasic Personality Inventory, 40% of the patients with PVFMD demonstrated elevation on the hypochondriasis and hysteria scales and minor elevation on the depression scale, in a pattern consistent with conversion disorder. An additional 29% of these patients had significant differences in these scales but did not fit the classic conversion disorder pattern, whereas only 24% of patients had scores suggestive of no psychopathologic conditions.

The association of PVFMD with asthma, GERD, and environmental exposure to irritants raises the possibility of an organic cause in some patients with the disease. Some authors have suggested that, when an organic cause is suspected, the term *irritable larynx* should be used to describe the disorder.[184] In one study of patients with asthma, 19% had coexistent PVFMD, whereas only 5% of asymptomatic control subjects had any evidence of paradoxical vocal fold closure.[191] It is best to consider inappropriate adduction of the vocal fold during breathing as an abnormal physical examination finding with a wide range of etiologies: stress reactivity, GERD/LPRD, environmental exposure, peripheral neuropathy (sensory), or unable to be determined.

Treatment

The first step in the treatment of PVFMD is recognition of the disease. The clinical presentation is often confusing because patients may have coexistent asthma or GERD and may be resistant to the idea that behavioral change could result in any significant reduction in their symptom severity. One study estimated that the association with asthma and GERD is as high as 65% and 51%, respectively.[185] This association, along with a desire to use medication to treat the problems, usually leads to attempted medical trials for asthma management and therapy for GERD. With these strategies, the symptoms may be reduced modestly, but the acute attacks of intermittent dyspnea, cough, and chest tightness can still be difficult to control. Therefore, referral to an otolaryngologist to perform laryngeal endoscopy may be required. If the true coexistence of asthma is questionable because there is little, if any, response to bronchodilator therapy, repeat pulmonary function testing before and after bronchodilator therapy, and possibly with methacholine challenge, is indicated. If test results are positive, management of the reactive airway disease should be maximized. If test results are negative, all medical therapy should be stopped because the asthma medications may be exacerbating the disease by irritating the laryngeal mucosa, increasing patient anxiety, or increasing the risk for gastroesophageal reflux. If symptoms lead to a suspicion that GERD or LPRD is a contributing factor, it is reasonable to treat the patient with dietary modifications and PPI therapy. Dietary modifications include eating small meals, avoiding foods known to cause reflux, and avoiding reclining after eating. Therapy with PPIs should be initiated on a twice-daily basis 30 to 60 minutes before the first and last meal of the day. Reflux that reaches the hypopharynx most frequently happens after meals. Therefore, PPIs should be given before the meal so that a therapeutic serum level can be achieved before the stimulation of acid production by the ingested food. If symptoms have not improved by 2 to 3 months after the initiation of therapy, formal pH impedance testing should be considered. It is also reasonable to consider that acid reflux may not be playing a significant role in the pathogenesis of the patient's disease.

After careful history and endoscopy to rule out other causes of airway obstruction, the treatment of acute episodes of PVFMD includes reassurance, breathing instruction, and possibly the use of a helium and oxygen mixture (heliox) to reduce the turbulence of airflow past an obstruction and thus reduce the pressure needed to generate airflow[192,193] (see also Chapter 39). Often, acute exacerbations will precipitate visits to an emergency department. The patient presents with dyspnea, a rapid respiratory rate, and stridor. Rather than immobile vocal folds or an obstructing mass lesion, endoscopy usually reveals that the vocal folds are held in a paramedian position through inspiration and expiration. If patients are asked to cough or clear their throat, the vocal folds will usually abduct. Vocal fold abduction can be further stimulated by reassuring the patient and attempting to provide a calm, relaxed environment. Inhaling through the nose and exhaling through the nose or pursed lips (metered breathing) may also be beneficial. Alternatively, the patient can be asked to breathe through a straw. Introducing a restriction in the airway with the nose and lips or with a straw facilitates the patient's ability to control his or her breath and promotes laryngeal relaxation with appropriate laryngeal activity. Respiratory control or metered breathing reduces the laryngeal hypersensitivity by reducing either the respiratory rate or breath volume or both. This type of respiratory retraining is the key to management of patients with PVFMD.[194,195]

Difficulties in establishing diagnostic criteria for PVFMD are even greater than for asthma. With asthma, objective pulmonary function measures can document reversible airflow obstruction, or methacholine bronchoprovocation can demonstrate bronchial hyperreactivity. Patients with PVFMD may show flattening of the inspiratory limb of the flow-volume curve, as is seen in patients with variable extrathoracic airway obstruction, but these changes can be transient or mimicked by submaximal inspiratory effort. Therefore, there are no objective measures of the disease, and establishing objective diagnostic criteria is not possible. Treatment may involve placebo effects from medications for other disorders, such as GERD or asthma, or active

respiratory retraining to engage the patient in regaining control of his or her breathing, as described earlier. Due to the difficulty in establishing diagnostic criteria, there have been few randomized controlled trials of respiratory retraining in patients with PVFMD. Limited evidence from case series has shown a reduction in the severity of patient symptoms and improvements in quality of life, which can be maintained through periodic long-term follow-up.[196]

VOCAL FOLD PARALYSIS

Unilateral

Unilateral vocal fold paralysis rarely produces symptoms of airway obstruction other than dyspnea with phonation. Although changes in pulmonary function can be measured during both quiet and active breathing, these are rarely clinically significant.[197] When obstruction is present, the proposed mechanism is either (1) the action of inspiratory airflow producing a Bernoulli effect on the flaccid vocal fold (e.g., pulling the cord inward due to low pressure and thereby increasing obstruction) or (2) inappropriate reinnervation of the paralyzed vocal fold with active signals for adduction during inspiration (e.g., synkinesis).[198] The findings can be corrected through surgery to stabilize the flaccid vocal fold complex, botulinum toxin injections to reduce the effects of the inappropriate reinnervation, or surgery to reduce the nerve supply to the synkinetic vocal fold.[199] It is rare that any of the treatments are required for unilateral vocal fold paralysis.

Bilateral

Bilateral vocal fold paralysis most commonly develops secondary to surgery in the anterior compartment of the neck for thyroid disease.[200] The recurrent laryngeal nerves are either crushed or cut during the intervention, and vocal fold abduction for inspiration and adduction for phonation are lost. Immediately after the onset of the injury, some patients are able to tolerate the loss of vocal fold abduction because the vocal folds are flaccid and immobile in a lateral position. The voice is weak and breathy. However, the recurrent laryngeal nerve contains all axons for abduction and adduction in a single fascicle. As axons regrow, the vocal fold muscles may regain tone without active adduction or abduction. Because of the increased mass of the adductor muscles compared to the abductor muscle, the vocal folds adopt a more medial position. Vocal fold tone recovers in the majority of patients who sustain an injury to the recurrent laryngeal nerve.[201] This process of neural regeneration takes 3 to 9 months and leads to slowly progressive improvement in voice but progressive airway compromise. Patients often adapt to this progressive airway compromise by decreasing their level of activity.

A small percentage of patients develop bilateral vocal fold paralysis secondary to a Chiari malformation with increased intracranial pressure and compression of cranial nerve X in the foramen magnum by the base of the brain as it herniates through the foramen. This condition can be extremely difficult to diagnose. Finally, a small percentage of patients will have an idiopathic etiology. In these instances, the paralysis can develop bilaterally simultaneously or unilaterally, separated by years.[202]

Patients with bilateral vocal fold paralysis typically report minimal voice changes and note marked dyspnea on exertion. Careful history usually reveals the cause as prior surgical intervention,[200] and general examination reveals prolongation of inspiration with mild to moderate inspiratory stridor. Endoscopic examination reveals bilateral vocal fold immobility with possible elongation of the vocal folds on inhalation.[200] Pulmonary function testing demonstrates a classic pattern of variable extrathoracic obstruction with flattening of the inspiratory limb of the flow-volume curve and little change in the expiratory limb (see Fig. 32.2, right panel). When maximal inspiratory flow falls below 1.5 L/sec, most patients are markedly symptomatic, and intervention is warranted. If inspiratory flow is maintained around 2 L/sec, most patients can perform modest activity, such as climbing one flight of stairs or walking on level surfaces.

The treatment of bilateral vocal fold paralysis is aimed at enlarging the airway or bypassing the glottis with a tracheotomy. If patients choose the latter, consideration should be given to the creation of a skin-lined tracheostomy tract. This will reduce the risk for granulation tissue growth at the stoma, provide a safe stable stoma for patients to manage by themselves on a long-term basis, and allow patients to use an appliance that will hold a one-way valve so that digital occlusion is not required for phonation.[203] Bilateral vocal fold paralysis can also be treated by injecting botulinum toxin into the muscles of adduction. This reduces the adductor force and allows improved function of the abductor muscles. The voice is fairly well preserved because the patient can usually override some of the effects of the botulinum toxin. The disadvantage of this treatment option is that it requires repeat injections.[204] Transverse cordotomy or partial arytenoidectomy are also surgical options for treatment designed to remove the posterior portion of the vocal fold or a portion of the arytenoid cartilage, respectively. This enlarges the cartilaginous portion of the laryngeal airway by 1 to 2 mm without interfering too greatly with the anterior vibratory function of the vocal folds. However, because the posterior portion of the airway is enlarged on a static basis, air will leak out during phonation, and the voice will be reduced in volume and be breathy in quality. This is referred to as "the great compromise" because the larger the airway for breathing and activity tolerance, the worse the voice. The patient and surgeon must decide on a balance.[205] In addition, one or both of the vocal folds can be sutured in a lateral position through myriad different techniques referred to as suture lateralization. Some of these techniques are potentially reversible and can be used in patients in whom recovery of function is possible to improve their airway during this period.[206] Finally, experimental surgical strategies for management with electrical stimulation of the abductor muscles (laryngeal pacemaker) to open the glottis are being conducted.[207] Initial results indicate that abduction for breathing can be achieved without compromise of vocal fold closure for voice production. An alternative experimental approach involves surgical reinnervation of the posterior cricoarytenoid muscle to achieve vocal fold abduction. This approach sounds attractive but to date has not achieved consistent results.

LARYNGEAL STENOSIS

Scarring of the larynx, usually in the posterior portion, referred to as *posterior glottis stenosis* (PGS), most commonly

develops secondary to endotracheal tube–related injury. In fact, when patients present with bilateral vocal fold immobility after prolonged intubation, 95% of the time the immobility is secondary to scar formation in and around the cricoarytenoid joints.[200] This is a decidedly different process from bilateral vocal fold paralysis, but clinically and endoscopically it can be difficult to distinguish the two because visual inspection reveals the vocal folds to be immobile in both situations. Helpful clinical clues to diagnosis are the events and timing around the onset of symptoms. The most common events associated with onset are prolonged intubation, multiple intubations, and/or intubation with an excessively large endotracheal tube. As the endotracheal tube rubs against the mucosa of the posterior larynx, the mucosa is eroded and inflammation develops. Reflux may play a role in adding to inflammation or mucosal erosion.[208] Secondary infection of the mucosal ulceration may also play a role in adding to inflammation. After the endotracheal tube is removed, the mucosa heals by secondary intention over a 6-week period. Thus, the patient notices deterioration of breathing more rapidly after a mucosal injury than after a neurologic injury; after a neurologic injury, as described earlier, the difficulty with breathing develops over a 3- to 6-month period as the nerve recovers partial tone.

Examination also reveals subtle differences in patients with PGS from those with bilateral vocal fold paralysis. Careful endoscopic evaluation usually reveals scar tissue over and around the cricoarytenoid joint. This can be subtle, with a relatively normal appearance and only slight reduction in the normal size and shape of the posterior portion of the larynx, or obvious, with overt scar tissue built up in the posterior portion of the glottis.[209] Finally, pulmonary function testing usually reveals a fixed extrathoracic pattern with flattening of both the inspiratory and expiratory limbs of the flow-volume loop.

Distinguishing between PGS and bilateral vocal fold paralysis is clinically significant because treatment options and outcomes are different. Both PGS and bilateral vocal fold paralysis can be treated with tracheotomy. In PGS, the initial surgical treatment should be aimed at release of the scar tissue holding the joint in the fixed position. If this is not possible due to loss or remodeling of the cartilaginous joint structure, portions of the cartilage or vocal fold can be removed. If possible, mucosal advancement flaps should be designed to cover the site of surgical excision. Because the tissue of the posterior glottis is scarred, a simple incision through prior scar tissue is less likely to provide sustained significant release and more likely to heal with recurrent scar. Injudicious surgery can make the problem worse. The majority of patients with either PGS or bilateral vocal fold paralysis can have successful endolaryngeal surgery that will enlarge the airway to prevent a lifetime of tracheotomy dependence.

UPPER AERODIGESTIVE TRACT MALIGNANCIES

Malignancies of the upper aerodigestive tract are a significant cause of morbidity and mortality. Cancers of the upper aerodigestive tract constitute approximately 4% of all malignancies.[210] *Squamous cell carcinoma* (SCC) is the predominant cancer in this location, and smoking and alcohol use are the traditional risk factors. Surgery, radiation, and chemotherapy all play an important role in the treatment of this disease; a thorough discussion of this topic is beyond the scope of this chapter.

In the oropharynx, recent evidence has identified *human papillomavirus* (HPV) as an emerging, and now dominant, cause of malignancies. In all, 80–90% of newly diagnosed SCC of the tonsils or base of the tongue are HPV induced. HPV-associated oropharyngeal SCC represents a distinct clinical entity with a significantly better prognosis than non–HPV-associated oropharyngeal SCC. National Cancer Center Network guidelines now recommend HPV testing for all oropharyngeal malignancies. HPV-16 is identified as the most common HPV subtype associated with oropharyngeal malignancy.[211] In SCC of the oral cavity, oral tongue, and larynx, HPV is less commonly found; in this region, tobacco and alcohol use remain the primary risk factors. Whereas the incidence of these non–oropharyngeal SCCs is declining likely secondary to a decrease in tobacco use, the incidence of oropharyngeal carcinoma is rising, likely due to HPV.

Laryngeal cancers usually present early with voice changes. However, if the cancer arises in the supraglottic area, the subglottis, or pyriform sinus, or if the patient ignores the changes in voice and the diagnosis is otherwise delayed, airway obstruction can be one of the presenting symptoms. In these instances, the diagnosis is made through endoscopic evaluation, and the airway should be managed with endoscopic debulking of the tumor before definitive therapy is undertaken.[212]

SUBGLOTTIS AND CERVICAL TRACHEA

ANATOMY, HISTOLOGY, AND PHYSIOLOGY

The subglottis is the area within the cricoid ring from the bottom of the vocal folds to the top of the first tracheal ring. The latter is the only complete ring in the airway and structurally functions to support the larynx and suspend the trachea. The subglottis is lined with a respiratory mucosa with goblet cells for mucus production and minor salivary glands as well. Mucus and saliva travel upward because of the actions of the ciliated epithelium and airflow and help humidify the airway and lubricate the vocal fold mucosa. In the adult human, the subglottis is the narrowest portion of the airway and ranges from 15 to 18 mm in diameter. It is roughly a round or slightly oval tubular space that is narrowest just below the vocal folds and widens out at the bottom at the transition into the cervical trachea. The space extends for 1 to 2 cm in vertical dimension from the bottom of the vocal folds to the first tracheal ring. The shape of the subglottis is probably important for establishing laminar flow through the glottis. This is important for both the clearance of secretions and generating flow that will efficiently drive vocal fold vibration. Irregularities in the subglottic mucosa often lead to turbulent airflow with crust formation, which can further compromise the airway. Below the subglottis lies the cervical trachea, consisting of the first four or five tracheal rings.

SUBGLOTTIC AND CERVICAL TRACHEAL STENOSIS

Pathophysiology

Because the subglottis is surrounded by a firm cartilaginous structure, and the mucosa lies over the surface with only a normal submucosa for support of the epithelium, the area is particularly prone to injury from surgical manipulation or intubation, reflux disease, and autoimmune disease. Injury to the mucosa by any one of the prior processes can lead to exposure of the perichondrium, which then responds with inflammation and scar tissue formation. The scar tissue impedes airflow and mucus clearance, which can create a fixed extrathoracic airway obstruction.

The cervical trachea is most commonly injured through intervention from prolonged intubation (eFig. 70.1) or tracheotomy. Again, sloughing of mucosa from traumatic manipulation due to a movement of an endotracheal tube or repetitive deep suctioning can lead to exposure of the cartilage with inflammation and secondary collapse. Neoplasia of the minor salivary glands or squamous mucosa can also lead to obstruction.

Diagnosis

The diagnosis of subglottic or cervical tracheal stenosis is made on the basis of the patient's medical history, surgical history, and symptoms. The symptoms are primarily dyspnea on exertion and stridor heard on inspiration and on expiration. If the patient has had a prior intubation or tracheotomy, the possibility of physical obstruction due to scarring should be considered. If a patient has known granulomatosis with polyangiitis, consideration should be given to involvement of the subglottic mucosa with inflammation, vasculitis, and granuloma formation (eFig. 70.2). In the case of idiopathic subglottic stenosis, patients are often treated for reactive airways disease without success.[213] These patients will benefit from early endoscopy/visualization of the subglottic region rather than weeks to months of ineffective treatment. As the name implies, there is no known cause for idiopathic subglottic stenosis. It has been presumed to be autoimmune, and the relationship with extraesophageal reflux disease is established, but the causal nature is unknown.[208,214] Because idiopathic subglottic stenosis is found almost exclusively in women, some authors have proposed a hormonal cause.

High-resolution CT imaging (see eFigs. 70.1 and 70.2) and/or three-dimensional reconstruction of the CT images may help in diagnosis and characterization of the stenotic airway segment. But these imaging modalities are not always available and, even if available, they may miss a short area of obstruction. Pulmonary function tests will demonstrate a characteristic plateau on the flow-volume curve (see Fig. 32.2, right panel), and the measured maximal flow can provide an estimate of the functional diameter of the flow-limiting segment (see eFig 32.3).

The diagnosis of stenosis is confirmed with endoscopic visualization of the area. Endoscopy of the subglottis and cervical trachea for confirmation of stenosis is easily accomplished with a transnasal scope in the office setting using local anesthesia. Lidocaine (4%) can be applied topically to the nose and can also be sprayed onto the vocal fold from above with a curved cannula or from below by injecting it percutaneously into the subglottis and asking the patient to cough. Then the flexible scope can be passed through the vocal folds and the area evaluated.

Treatment

Surgery is the primary mode of treatment of subglottic and cervical tracheal stenosis. The type of surgery, either endoscopic or open, and the use of adjuvant agents, such as steroid injections, or fibroblast activity inhibitors, such as mitomycin C, depend in part on the cause and characteristics of the stenosis. Usually treatment begins with an endoscopic approach. Rigid endoscopy allows palpation of the area to determine the nature of the scar tissue and the length of the segment of the airway that is involved. If the segment is relatively short (<1.5 cm in length), occludes less than 50% of the airway diameter, and is primarily soft tissue in nature, it will likely respond to endoscopic incision and dilation and/or balloon dilation performed in a nontraumatic manner.[215] The incisions, which can be made with either cold steel or a laser, control the area of injury and allow the surgeon to identify the nature of the stenosis without further injury of the cartilaginous airway support. If the laser is used injudiciously, however, the surgeon can create more injury and damage to the cartilage. New-generation lasers have a very short pulse structure, resulting in minimal heat dissipation into the tissue beyond what is seen. Once the extent of the stenosis is identified, the surgeon can use that information to decide on the amount of dilation that the area will accept. The area is then dilated with a balloon to the appropriate size.

For very short stenotic segments or webs, any technique, such as dilation alone, to break up the web usually works after one or two procedures. When performed with the appropriate technique, the area of stenosis should remain dilated after the procedure during visual inspection. If the area collapses immediately after the dilation, it is unlikely that the procedure will have lasting benefits. In addition to endoscopic incision and dilation, short and relatively discrete segments of cartilage collapse, such as may be seen at a tracheotomy site, can be resected endoscopically. Care should be exercised so that no more than 90 to 120 degrees of trachea are treated at one time. This may necessitate staging of the procedures with two or three attempts to resect the area.[216] The primary goal of endoscopy is to characterize the stenotic segment. If the segment is too long, involves too much cartilage, or collapses immediately after completion of the procedure, it is probably wise to proceed to open resection of the segment.

Acknowledgment

We thank Dr. Mark Courey for his contributions to this chapter in a previous edition of this textbook.

Key Points

- The upper airway contains diverse anatomic structures with a variety of functions that contribute to breathing, vocalization, smell, and taste.
- New-onset anosmia is the most specific early symptom of severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2; COVID-19) infection.
- Asthma and chronic rhinosinusitis with nasal polyps are heterogeneous disorders. Subgroups of each disorder are driven by type 2 inflammation and respond to new biologic therapies.
- Allergic rhinitis and asthma are linked in both pathophysiologic and epidemiologic characteristics. Patients with persistent allergic rhinitis should be screened for asthma, and patients with asthma should be evaluated for allergic rhinitis.
- Although multiple medical therapies demonstrate efficacy in the treatment of allergic rhinitis, immunotherapy is the only approach known to alter the natural history of the disease.
- Asthmatic patients with comorbid chronic sinusitis often experience improvement in both upper and lower airway disease after both medical and surgical treatment of chronic rhinosinusitis.
- In swallowing, the oral cavity creates a bolus of the ingested substance and presents this, in an orderly fashion, to the oropharynx and hypopharynx, where the reflexive portion of swallowing takes place. This requires structural and functional integrity and is under control of the central nervous system.
- The larynx is divided into the supraglottis, glottis, and subglottis and functions to regulate inspiratory and expiratory airflow. During swallowing, the larynx is pulled up and forward, to allow the upper esophageal sphincter to open. The bolus passes through the pyriform sinus and into the esophagus.
- During breathing, the vocal folds normally open for inspiration and then close slightly during exhalation to control the rate of air egress. In paradoxical vocal fold motion disease, it is believed that these actions are reversed. The mechanism for this reversal is unknown. However, behavioral interventions designed to retrain breathing are often beneficial in patients demonstrating this finding.
- Paradoxical vocal fold motion disease can often be confused with asthma, but it is typically unresponsive to medical management.
- The contribution of gastroesophageal reflux disease and extraesophageal reflux disease to respiratory disorders is incompletely understood. Most of the evidence supporting an association is derived from studies that measure patient response to empirical therapy.
- Bilateral vocal fold paralysis, posterior glottic stenosis, and subglottic stenosis can often cause airway obstruction that may be misdiagnosed as asthma. Diagnosis requires suspicion based on events in the patient history and endoscopic evaluation. Treatment is usually surgical and is designed to enlarge the airway.

Key Readings

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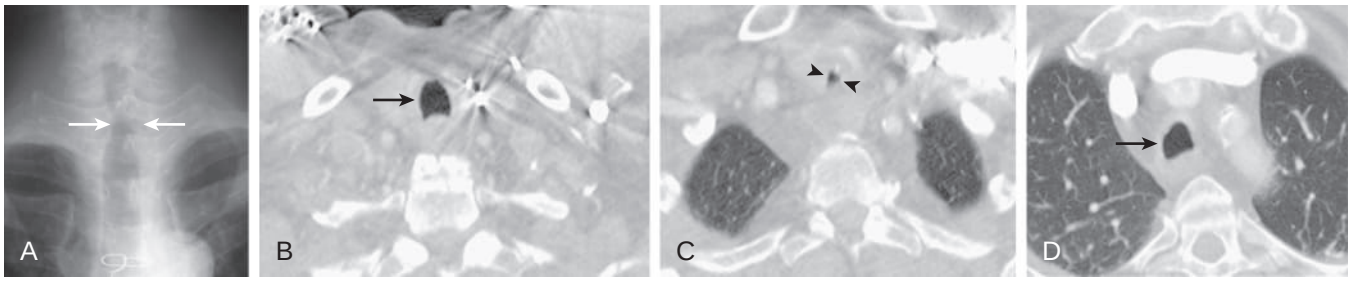
Complete reference list available at ExpertConsult.com.



eFIGURE IMAGE GALLERY



eFigure 70.1 Postintubation tracheal stenosis. (A) Focused image from a frontal chest radiograph of a patient who was intubated for a prolonged interval shows focal narrowing of the trachea (*arrows*) at the thoracic inlet. (B–D) Axial chest computed tomography displayed in lung windows shows a normal-caliber trachea (*arrows*) cranial and caudal to the focally stenotic region (*arrowheads*). (Courtesy Michael B. Gotway, MD.)



eFigure 70.2 Tracheal stenosis due to granulomatosis with polyangiitis. Axial computed tomography through the lower neck shows circumferential tracheal mucosal thickening (*arrowheads*). (Courtesy Michael B. Gotway, MD.)

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71 LARGE AIRWAY DISORDERS

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KEY POINTS

INTRODUCTION

The large intrapulmonary airways are the trachea, mainstem bronchi, and right bronchus intermedius. The trachea is a semirigid tube serving as a conduit for the entire tidal volume with each breath. It begins just below the larynx and extends approximately 10 to 16 cm to the main carina. The trachea is closely associated with the esophagus, which travels toward the gastroesophageal junction along the left posterior tracheal border; the thyroid gland, which sits anterolateral to the proximal cervical trachea; major blood vessels (e.g., aortic arch, innominate artery, superior vena cava, azygos vein); and mediastinal lymph nodes.

Like the trachea, the large bronchi are surrounded by smooth muscle, contain cartilage, and do not participate in gas exchange. The tracheobronchial mucosa consists of a ciliated pseudostratified columnar epithelium containing mucus-producing goblet cells, submucosal gland duct openings, and cough receptors and is one of the initial sites of innate defensive responses against inhaled invaders.

The subglottic, proximal one-third of the trachea is extrathoracic, whereas the distal two-thirds of the trachea is intrathoracic. The trachea contains 16 to 22 C-shaped cartilage rings anteriorly and laterally, which stiffen the trachea and are connected posteriorly by a membranous wall. The trachealis muscle runs longitudinally along the posterior membrane and is innervated by muscarinic output via the vagus nerve. The posterior membrane is somewhat flexible and moves inward during exhalation.

During cough, the flexible tracheal posterior membrane facilitates dynamic compression of the intrathoracic trachea, reducing tracheal cross-sectional area and increasing cough velocity (see Chapter 37). For example, a 50% decrease in tracheal diameter increases mean linear cough velocity fourfold,[1] improving mucus clearance.

Because the large airways contribute to innate airway host defense via cough and mucociliary clearance, are the site of most of the airflow resistance in airways, and are surrounded by critical mediastinal organs, it is no surprise that the manifestations of large airway disorders are protean and can be serious. Unlike the small airways, which are a "silent zone," the large airways are a common source of symptoms and can be evaluated via pulmonary function testing, imaging, and direct visualization (i.e., flexible bronchoscopy).

Large airway disorders can be classified into two general categories: those that are intrinsic, or within the airway or airway wall, and those that are extrinsic, or outside the airway. In intrinsic disorders, the large airways can become narrowed, fibrotic, thickened, or malacic; in extrinsic disorders, they can be compressed or invaded by benign or malignant lesions of surrounding organs, lymph nodes, or vasculature. The roles of the tracheobronchial airways in innate immune host defense are described in Chapter 15. This chapter focuses on the diagnosis and management of intrinsic and extrinsic large airway disorders.

CLINICAL FEATURES

For tracheal disorders, the most serious signs and symptoms are the acute onset of stridor or wheeze (see Videos 18.12 and 18.6) and respiratory distress suggesting possible life-threatening tracheal obstruction. Although the tracheal lumen diameter is often decreased by greater than 75% (to <5 mm) in patients with stridor or dyspnea at rest, these symptoms also depend on patient-specific factors, such as comorbid cardiac and pulmonary disease, functional status, and activity levels.[2] In a patient at risk of tracheal obstruction (e.g., lung cancer, prolonged intubation), these symptoms should prompt immediate evaluation and treatment, with the primary goal of maintaining a patent airway.

For the large airways, the most common symptoms are cough, sputum production, dyspnea, hemoptysis, and wheeze. Because these symptoms are nonspecific and are also found in patients with inflammatory and infectious

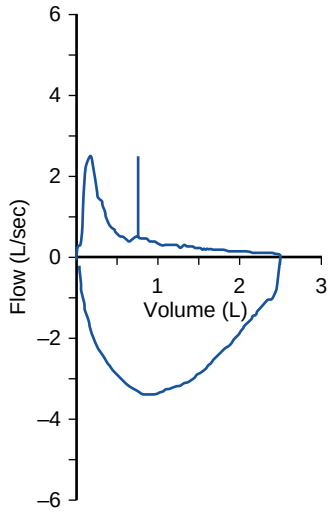

Figure 71.1 Flow-volume loop showing a characteristic rapid decrease in peak expiratory flow due to excessive tracheal collapse. Note that maximal expiratory flow (peak flow) is also reduced. (Courtesy Suil Kim, MD, PhD.)

lower airway diseases (e.g., asthma, COPD, bronchiectasis, pneumonia), large airway disease is often overlooked or misdiagnosed. The key to diagnosing a large airway disorder is having a high index of suspicion. For example, recurrent aspiration, recurrent pneumonia, or cough triggered by eating or drinking should suggest tracheoesophageal fistula in patients with risk factors such as esophageal cancer, tracheal cancer, prolonged intubation, or tracheostomy. In patients with respiratory symptoms suggestive of an obstructive airway disease or infection, the absence of a clinical response to bronchodilators or antibiotics should raise suspicion of a large airway disorder and trigger diagnostic testing rather than additional ineffective treatment.

DIAGNOSTIC APPROACH

The diagnostic approach to a suspected large airway disorder includes spirometry with flow-volume loops, chest imaging, and flexible bronchoscopy.

SPIROMETRY AND FLOW-VOLUME LOOPS

In stable patients, the first step in evaluating a suspected large airway disorder is to obtain spirometry with flow-volume loops, which may reveal plateaus of maximal inspiratory or expiratory airflow that help to localize obstruction (see Chapters 31, 32, and 39). For example, an inspiratory plateau suggests variable extrathoracic obstruction involving the proximal extrathoracic trachea (see Fig. 39.4). An expiratory plateau suggests variable intrathoracic obstruction involving the intrathoracic large airways, as can be seen in tracheobronchomalacia. Plateaus of both inspiratory and expiratory flows suggest fixed tracheal obstruction, as can be seen in tracheal stenosis. Certain features of the flow-volume loop, such as a sudden drop in expiratory flow (Fig. 71.1), plateauing of both inspiratory and expiratory flows, notching of expiratory flow, and oscillations of expiratory flow (see Fig. 39.3), are highly suggestive of large airway disorders.

The classic curves showing the relationship between driving pressure and airflow through a series of critical orifices (see eFig. 32.3) indicate that the diameter of the tracheal lumen must be reduced to less than 8 mm to produce an abnormal flow-volume loop.[2] The FEV_1 is less sensitive than the flow-volume loop in detecting tracheal obstruction, remaining greater than 90% predicted until the orifice diameter is reduced to 6 mm.[3] Of note, in tracheobronchomalacia, airflow limitation on flow-volume loops does not correlate well with *computed tomography* (CT) evidence of tracheal collapse.[4] In clinical practice, the corollary also applies: CT and airway inspection can suggest near total collapse, while the airflow on flow-volume loops is essentially normal. Spirometry and flow-volume loops should be relied upon to determine if tracheal narrowing is physiologically significant.

CHEST IMAGING

After spirometry and flow-volume loops, chest imaging is the next step in evaluating suspected large airway disorders. Chest radiographs can reveal tracheal dilation (i.e., tracheomegaly or Mounier-Kuhn syndrome) or tracheal narrowing (i.e., saber-sheath trachea) but are rarely diagnostic. CT is the imaging test of choice to evaluate the trachea and large bronchi. An axial CT chest scan without contrast is often adequate to localize tracheobronchial pathology and determine if it is focal or diffuse and intrinsic or extrinsic. Contrast is recommended if there is suspicion for mediastinal tissue impinging on the trachea or bronchi, as in fibrosing mediastinitis, or if there is concern for abnormal venous collateral vessels, as in tracheal varices. Multiplanar or three-dimensional reconstructions can create a more complete visualization of tracheal lesions. Magnetic resonance imaging may provide added benefit in characterizing lesions compressing or invading the trachea, such as mediastinal masses or vascular anomalies.[5] If the history, examination, or flow-volume loops suggest tracheobronchial obstruction or collapse, inspiratory, end-expiratory, and/or dynamic CT images should be obtained to evaluate the tracheal lumen at different parts of the respiratory cycle, which is important in diagnosing *tracheobronchomalacia* (TBM) and *excessive dynamic airway collapse* (EDAC).

BRONCHOSCOPY

The definitive procedure for the diagnosis of large airway disorders is visualization of the airways using a flexible bronchoscope. Many large airways disorders cause characteristic mucosal and structural abnormalities that can be identified on white light (standard) bronchoscopy and diagnosed with endobronchial biopsies. Narrow band imaging, which makes blood vessels appear very dark, may be slightly more sensitive than white light bronchoscopy in detecting dysplasia but has not been routinely incorporated into airway inspections.[6]

Radial probe endobronchial ultrasound can be used to evaluate cartilage integrity and wall thickness in tracheobronchomalacia and to determine if malignancies of adjacent structures, such as the esophagus, are invading the

trachea or left mainstem bronchus[7–9] (see Chapter 27). Flexible bronchoscopy can also be used to evaluate the shape and cross-sectional area of the lumen during quiet tidal breathing, forced breathing maneuvers, and cough (a technique termed dynamic bronchoscopy) in patients suspected of having TBM and/or EDAC.[10] For severely obstructed airways, thin and ultrathin bronchoscopes may be able to pass the obstruction safely and allow visualization of the airways distal to the lesion, providing valuable information for planning endobronchial therapy (see Chapter 27). In clinical practice, visual inspection remains the most common method of estimating luminal area and degree of obstruction.[11] Specialized airway sizing tools can be used to measure airway diameter before stent placement.

MANAGEMENT

The decision to treat large airway disease is based on the cause, symptoms, degree of obstruction, and the severity of potential complications. Infections and inflammatory diseases are managed medically unless there is compromise of the airway resulting in respiratory insufficiency. In asymptomatic patients with large airway disorders, regular surveillance is usually indicated. However, significant obstruction, disease progression, and concern for serious complications, such as hemoptysis, should prompt intervention even in patients without symptoms.

Management should be coordinated with a careful strategy to maintain airway patency. Flexible bronchoscopy through a benign or malignant tracheal stenosis can result in complete obstruction and respiratory failure due to edema or bleeding caused by scope trauma or biopsies. Rigid bronchoscopy can minimize these risks by allowing rapid dilation of benign stenosis and coring of malignant obstruction without interruption to ventilation. Endobronchial therapies include laser, microdébrider, electrocautery, airway stents, cryotherapy, and balloon dilation (see Chapter 28). There is growing evidence that endobronchial interventions for simple, benign strictures can produce long-lasting results.[12–15] In patients with life-threatening symptoms, such as massive hemoptysis and respiratory failure due to malignant large airway obstruction, endobronchial therapies can be used to palliate symptoms before definitive surgical resection for early-stage lung cancer or radiation therapy for unresectable disease.

Surgical resection is the definitive treatment for many tracheal diseases such as benign stenosis and localized tracheal tumors. The likelihood of a good surgical outcome depends on the cause of the large airway lesion, the natural history of the disease, whether the surgery is a reoperation, whether there was a previous tracheal appliance, and the location and length of resection (tracheal resections exceeding 4 cm in length are associated with increased anastomotic complications).[16,17]

STENOSIS AND MALACIA

Many large airway disorders decrease the cross-sectional area of the airway lumen, increasing resistance and reducing airflow if driving pressure remains constant.

The term *central airway obstruction* refers to airflow obstruction in the large airways, whereas the terms *tracheobronchial stenosis* and *tracheobronchial malacia* refer to relatively fixed narrowing of the large airways and weakness of the cartilaginous large airway walls, respectively.

STENOSIS

Large airway stenoses can be benign or malignant. They can be intrinsic and caused by exophytic growth into the airways, focal strictures (usually benign), granulation tissue, and airway wall thickening. They can also be extrinsic and caused by compression from structures outside the airways, or they can be both intrinsic and extrinsic (e.g., a combination of exophytic growth and compression). Multiple classification systems for tracheal stenosis based on the degree of obstruction,[18] the location of stenosis,[19] and symptoms, such as dyspnea, change in voice, and dysphagia,[20] or a combination of these features,[21–23] have been developed to facilitate evaluation and treatment of stenosis.

In stenosis, quantifying luminal obstruction is essential for planning interventions, making comparisons over time, and communicating among managing specialists. Numeric visual estimation by bronchoscopy is the most common method for measuring luminal obstruction. CT-based measurements of luminal cross-sectional area reduce interobserver variability and are more reproducible than visual estimates. New machine learning software also improves precision and accuracy of the measurements, but these technologies are not widely available.[11] Because luminal area can vary with the phases of respiration and along the length of the stenosis, it is difficult to measure stenoses reproducibly.

MALACIA

Malacia of the large airways leads to excessive airway collapse, narrowing the airway lumen and reducing airflow. Cartilage weakness causes malacia of the anterolateral cartilaginous walls, whereas laxity of the muscular posterior membrane results in excessive collapse of the posterior wall. Unlike stenosis, malacia of the intrathoracic large airways limits airflow only during expiration. Because standard CT scans are obtained at end-inspiration, and because symptoms of large airway obstruction are nonspecific and can be mistaken for more common obstructive airway diseases such as asthma and COPD, malacia tends to be missed. Suspicion for malacia is often raised by a narrowed tracheal lumen on expiratory CT or by abnormalities in the expiratory flow-volume loop mentioned above (see Figs. 71.1 and 39.3).

Similar to stenosis, the amount of airway collapse due to malacia is measured by CT and visual inspection. Several classification systems have been devised to assist clinicians in diagnosing malacia.[10] However, there may be poor concordance between the degree of collapse, airflow, and symptoms.[24] Thus, malacia can be overlooked in symptomatic patients with airflow limitation and overdiagnosed in patients without these features.

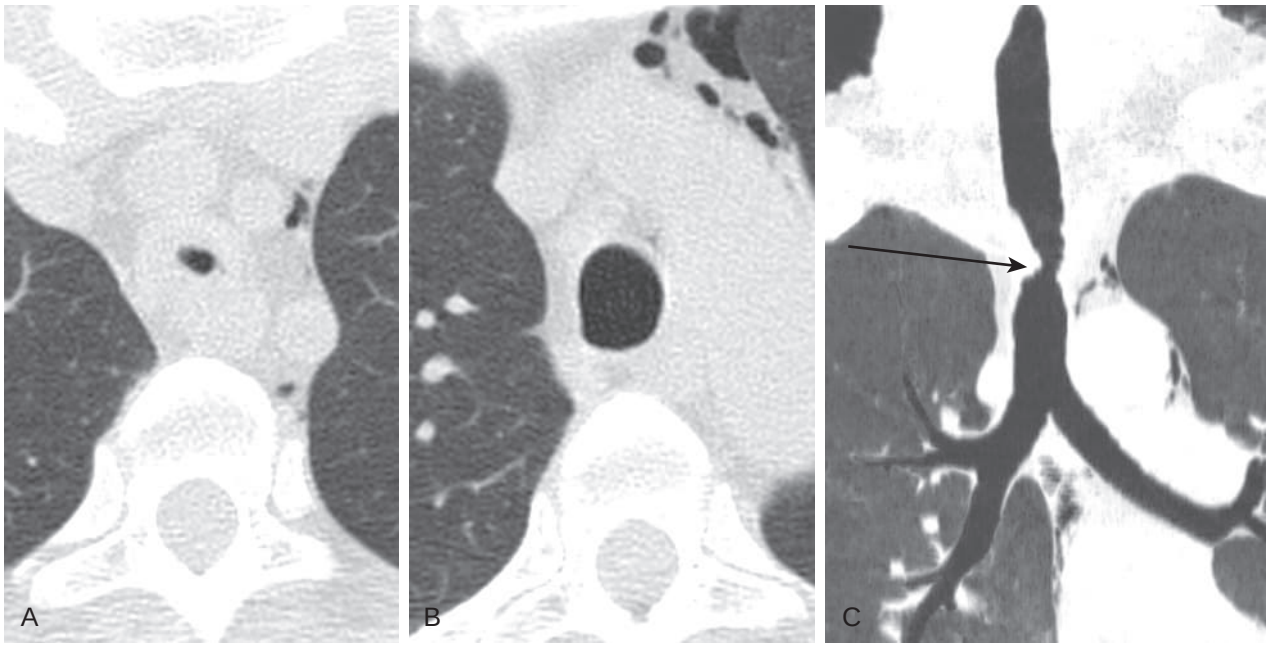

Figure 71.2 Tracheal stenosis. (A) Severe focal narrowing is present in the upper trachea in a patient with postintubation stricture. (B) The tracheal diameter is normal distal to the stricture. (C) Coronal reformatted minimum intensity projection image demonstrates the focal region of narrowing (*arrow*) in the upper trachea. (Courtesy Brett Elicker, MD, Department of Radiology, University of California San Francisco.)

INTRINSIC DISORDERS

For the intrinsic disorders, those primarily causing stenosis or obstruction are discussed before those primarily causing malacia.

BENIGN TRACHEAL STENOSIS

Benign tracheal stenosis is caused by a variety of disorders. Idiopathic laryngotracheal stenosis is characterized by mucosal and submucosal hypertrophy, sparing the cartilage. It is almost exclusively seen in women.[25] Causes of acquired tracheal stenosis include prolonged intubation, tracheostomy, infection, sarcoidosis, and autoimmune disease (e.g., *granulomatosis with polyangiitis* [GPA], ulcerative colitis).

Postintubation tracheal stenosis can result when endotracheal tube cuff pressure exceeds mucosal capillary pressure (≈30 cm H_2O), resulting in mucosal ischemia. If ischemia is prolonged, the mucosa dies via necrosis and becomes fibrotic, causing tracheal stenosis (Fig. 71.2). Risk factors include female sex, obesity, diabetes mellitus, hypertension, and cardiovascular disease.[15]

Posttracheostomy tracheal stenosis results from damage to the tracheal cartilage during tracheostomy placement or from subsequent mucosal injury caused by the tracheostomy tube or cuff. Although the incidence of postintubation tracheal stenosis has decreased with the introduction of low-pressure endotracheal tube cuffs, the incidence of proximal tracheal stenosis has increased as greater numbers of percutaneous tracheostomies are performed.[26] Risk factors include the use of a percutaneous technique, the insertion of a tracheostomy tube size greater than 6, and obesity.[27]

Postinfectious tracheal stenosis is most commonly caused worldwide by tuberculosis. It is estimated that 10–37% of patients with pulmonary tuberculosis develop endobronchial disease at risk of progressing to airway stenosis.[28] Similarly, granulomatous infections with fungus and bacteria such as *Klebsiella rhinoscleromatis*[29] can lead to tracheal stenosis. Infections with human papillomavirus can cause tracheobronchial stenosis as a complication of recurrent respiratory papillomatosis (see later).

Large airway stenosis can be caused by GPA, sarcoidosis, amyloidosis, and inflammatory bowel diseases. The airways are involved in approximately 10–33% of patients with GPA.[30–32] Treatment of stenosis caused by immune or inflammatory disease consists of immune suppression and endobronchial interventions. Surgery can be considered in refractory cases.

When tracheal stenosis is caused by diseases not easily treated medically, the approach depends on several features. First, symptoms such as dyspnea, dysphagia, and dysphonia should be considered as indications for treatment, while asymptomatic patients can often be serially monitored with CT and airway inspection.[19–21] Second, spirometry and flow-volume loops may suggest critical stenosis requiring intervention. Third, CT can define the location and severity of stenosis, which is essential for procedural planning. Finally, flexible bronchoscopy remains the gold standard for characterizing the stenosis and directing therapy.[23]

A decision tool to treat benign tracheal stenosis is shown in Figure 71.3. Simple stenotic lesions (i.e., short-segment concentric stenosis, <1 cm in length, without malacia) can be treated with endobronchial interventions without surgery.[9–12] The optimal treatment for complex stenotic lesions (i.e., many shapes, long segments, >1 cm, with associated malacia) is surgical resection with reconstruction unless the stenosis is located high in the subglottis or is greater than 4 to 6 cm in length.[22] Dilation with or without

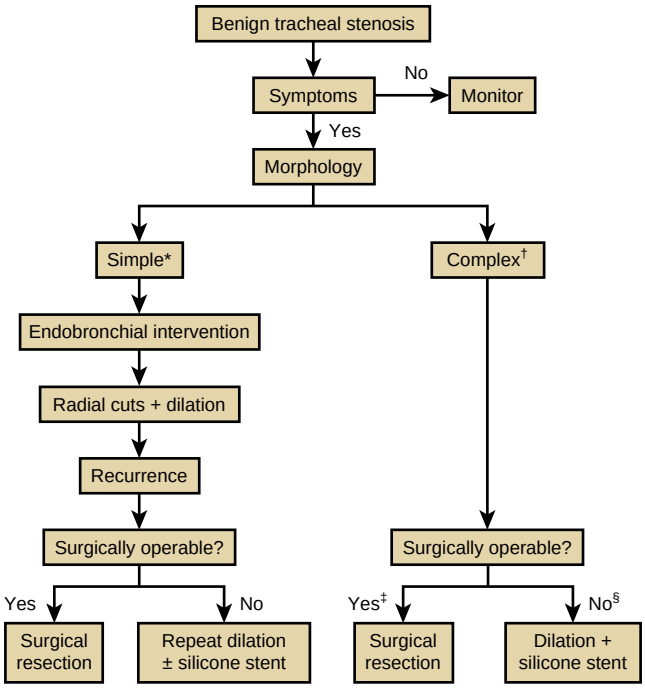

Figure 71.3 Decision tool for benign tracheal stenosis. Management is based on the presence of symptoms, the morphology of the stenosis, and the surgical operability of both the stenotic lesion and the patient. *Simple stenosis: concentric, <1 cm in length, without malacia. †Complex stenosis: many shapes, >1 cm in length, with malacia. ‡1–4 cm in length, not high subglottic, and operable candidate. §>4–6 cm in length, high subglottic, or inoperable candidate.

silicone stent placement may be the only option for patients who are ineligible for or awaiting surgery.

MALIGNANT LARGE AIRWAY DISEASE

Primary tracheal tumors (see Fig. 20.29) are rare, responsible for less than 0.2% of airway neoplasms,[33] and are usually malignant. Squamous cell carcinoma and adenoid cystic carcinoma account for approximately two-thirds of tracheal tumors.[34] Less common primary tracheal tumors include mucoepidermoid carcinoma and pleomorphic adenoma, indolent tumors that can invade locally and metastasize. Pulmonary carcinoid tumors most often arise in major bronchi but can rarely be found in the trachea.[35]

Squamous cell carcinomas generally affect men in their 60s. Adenoid cystic carcinomas show no gender predilection and present in a younger population (≈40s). Of interest, although smoking is associated with the development of squamous cell carcinoma of the trachea, it is not a risk factor for adenoid cystic carcinoma. Patients may be asymptomatic, with the lesion detected incidentally, or have symptoms such as chronic cough unresponsive to standard therapy, sputum production, wheezing, dyspnea, hemoptysis, and obstructive pneumonia. Squamous cell carcinoma of the large airways can invade surrounding structures and cause fistulas.

The approach to large airway tumors has two parts. First, complications such as massive hemoptysis or critical tracheobronchial obstruction should be urgently addressed to stabilize the patient.[36] Second, once the patient is stable, staging with *positron emission tomography* (PET)-CT and invasive lymph node sampling should be expedited to determine optimal treatment. Surgical resection for localized malignant tracheal tumors yields 5- and 10-year survival rates of 39–79% and 18–51%, respectively.[37] For squamous cell carcinoma with nodal involvement, definitive chemotherapy plus radiation is an option. Palliative radiation alone can sometimes relieve symptoms of malignant central airway obstruction. For adenoid cystic carcinoma, the optimal management strategy is not clear, although the cancer is radiosensitive and radiation therapy is used to treat unresectable disease and residual disease after resection. For adenoid cystic carcinoma, complete surgical resection is a more important prognostic factor than nodal staging.[38]

TRACHEOBRONCHOPATHIA OSTEOCHONDROPLASTICA

Tracheobronchopathia osteochondroplastica (TPO) is a benign disorder of the trachea and mainstem bronchi. It is characterized by submucosal cartilaginous or bony nodules that connect to airway cartilage and protrude into the lumen of the large airways, sparing the posterior wall. The exact prevalence is unknown because it rarely causes symptoms and is often detected incidentally on imaging or bronchoscopy performed for other reasons. The etiology remains unknown, although associations with chronic inflammation, atrophic rhinitis, mycobacterial disease, and immunoglobulin A deficiency have been reported.[39–42] When present, symptoms include cough, dyspnea, wheeze, and recurrent airway infections, which may be mistaken for asthma or chronic bronchitis.[43] Large nodules can cause hemoptysis, lobar obstruction, and postobstructive pneumonia.[44] If located in the subglottis, nodules can lead to hoarseness and sore throat.

CT images show calcified nodules arising from cartilage rings in the anterolateral walls of the large airways (Fig. 71.4A). The posterior tracheal wall is spared, a key feature that distinguishes TPO from other causes of tracheal nodules, such as amyloidosis, sarcoidosis, fibromas, and carcinomas. TPO is diagnosed by recognizing submucosal nodules along the cartilaginous tracheal wall during airway inspection (see Fig. 71.4B). Biopsy is not required for diagnosis and is often unsuccessful because the nodules are heavily calcified. If biopsied, nodules reveal cartilaginous and osseous metaplasia.

The goal of treatment is to ameliorate symptoms. In rare cases of severe tracheobronchial obstruction (see Fig. 71.4C), therapeutic options include forceps removal, laser extraction, cryotherapy, external beam radiation, stent placement and, if endobronchial therapies are unsuccessful, surgical resection.[45,46] Tracheostomy has also been performed as a last resort when endobronchial interventions have failed.

TRACHEOBRONCHIAL AMYLOIDOSIS

Amyloidosis is characterized by the extracellular deposition of fibrillar protein in insoluble β-pleated sheets. Causes include chronic inflammation, plasma cell dyscrasias, heritable mutations that promote fibrillogenesis, and senescence

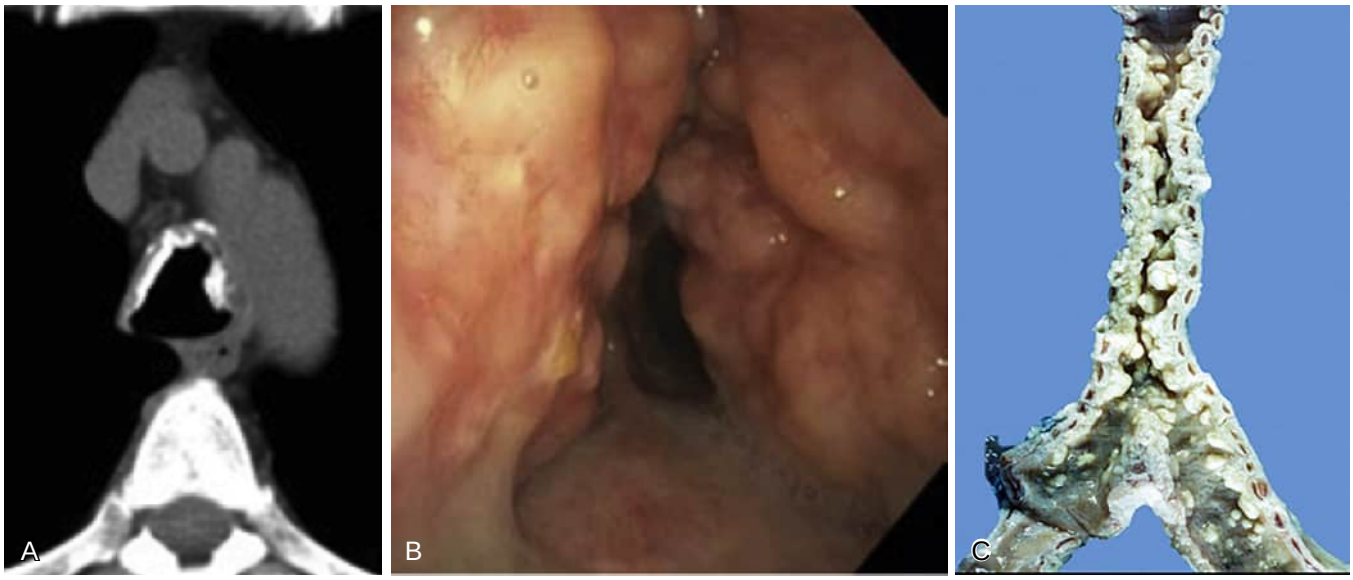

Figure 71.4 Tracheobronchopathia osteochondroplastica. (A) Axial computed tomography displayed in soft tissue windows shows partially calcified nodules involving only the anterior two-thirds of the trachea. (B) Airway inspection in the same patient shows submucosal nodules arising from the anterior tracheal wall and sparing the posterior wall. (C) Gross tracheal specimen from autopsy performed on a different patient shows extensive calcified and ossified nodules throughout the tracheal wall. (A–B, Courtesy Russell Miller, MD, Pulmonary Department, Naval Medical Center, San Diego. C, Courtesy Martha Warnock, MD, Department of Pathology, University of California San Francisco.)

(in senile systemic amyloidosis). Amyloidosis can be systemic or localized to a particular organ.[47] There are few data in the literature to determine the incidence or prevalence of systemic amyloidosis. A small Mayo Clinic study from Olmsted County, Minnesota, cited a yearly incidence of 5.1 to 12.8 per million person-years,[48,49] whereas a study from the United Kingdom estimated the incidence there at just more than 8.0 per million inhabitants per year.[50] Numbers for localized disease are more difficult to acquire.

Amyloid involvement of the respiratory tract is uncommon. Pulmonary amyloidosis can present as one of five subtypes: tracheobronchial, nodular (solitary or multiple), senile pulmonary, mediastinal-hilar, or diffuse interstitial.[51] *Tracheobronchial amyloidosis* (TBA) is a rare idiopathic disorder not typically associated with systemic or lung parenchymal amyloidosis.[52] As such, there is typically no association with other disease entities, such as plasma cell dyscrasias for primary or immunoglobulin light-chain amyloidosis, or inflammatory conditions, such as rheumatoid arthritis for secondary or serum amyloid protein A amyloidosis. Similarly, it is not known if there are any precipitants of this form of amyloid. TBA is estimated to account for only 1.1% of all amyloidoses.[53] The peak age of onset is 50 to 60 years of age, and it is equally prevalent in men and women.[51,54] Symptoms of TBA often go unnoticed because they are nonspecific and can include cough, dyspnea, hoarseness, or hemoptysis, leading to delays in diagnosis. Patients are often treated for recurrent pneumonia, asthma, or tracheobronchitis before the correct diagnosis is made.[47]

Amyloid is deposited in the submucosal tissue plane of the large airway circumferentially and can be associated with calcifications. CT images show diffuse circumferential wall thickening and nodularity of the trachea and mainstem bronchi (Fig. 71.5A).[55] The differential diagnosis includes infectious laryngotracheitis, radiation injury, submucosal tumor spread, and TPO. Flexible bronchoscopy reveals diffuse mucosal edema and hyperemia, friable mucosa, or small nodules or masses occluding the trachea and mainstem bronchi (see Fig. 71.5B).[54] TBA lesions can be sessile, nodular, or polypoid. Sessile lesions are hard, yellow plaques that can cause airway stenosis if distributed diffusely. Nodular or polypoid lesions are firm and nonmobile with overlying hypervascular mucosa, which is friable and is often mistaken for malignancy. Endobronchial biopsy of amyloid lesions reveals amorphous hyaline material, positive Congo red staining, and yellow-green birefringence under polarized light.[52,56]

The goal of TBA treatment is maintaining a patent airway. Endobronchial interventions, such as *neodymium-doped yttrium aluminum garnet* (Nd:YAG) laser, argon plasma coagulation, stent placement, freezing, and resection, can be used singly or in combination to keep the large airways patent (see Chapter 28). Radiation therapy has been shown to slow the progression of TBA and is now considered a first-line therapy in patients with bulky or distal disease not amenable to endobronchial intervention.[56,57] The efficacy of various systemic therapies (e.g., corticosteroids, colchicine, autologous hematopoietic stem cell transplantation) is unclear.[53] Surgical resection should be considered for localized TBA if endobronchial or radiation therapy interventions have failed.

INFECTIONS

Infections can cause large airway obstruction and stenosis as a sequela of acute inflammation and scarring.[58] During the acute phase of infection, edema and necrosis can lead to airway obstruction with thickening of the airway walls and irregular luminal narrowing. Subsequent healing of these infections can result in fibrosis and stenosis. Although numerous agents cause infections in the respiratory tract, few have been linked to the development of tracheal stenosis.

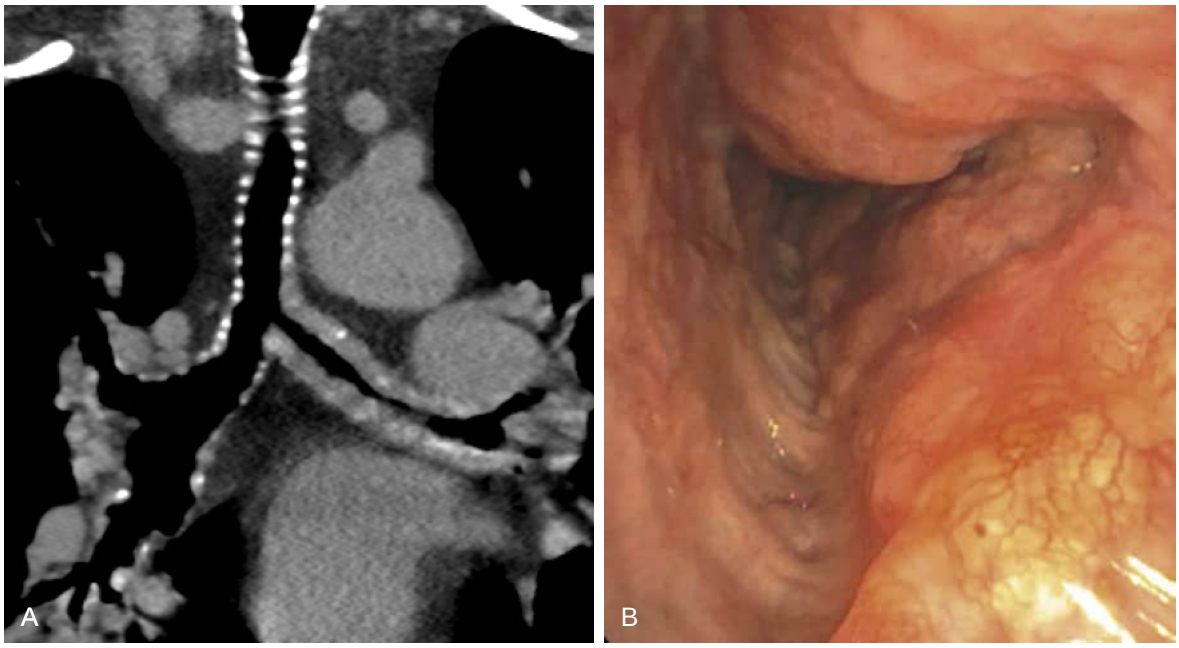

Figure 71.5 Tracheobronchial amyloidosis. (A) Coronal computed tomography displayed in soft-tissue windows shows diffuse circumferential thickening and irregularity of the left mainstem bronchus. (B) Airway inspection in the same patient shows hyperemic and thickened mucosa circumferentially with small nodules and sessile, yellow plaques narrowing the bronchial lumen. (Courtesy Lakshmi Mudambi, MD.)

Tuberculosis

Endobronchial tuberculosis is common,[59] and tracheobronchial stenosis has been reported in up to 90% of patients with endobronchial tuberculosis despite adequate treatment. In rare cases, airway stenosis can be the sole manifestation of infection. The most common symptom of tracheal tuberculosis is intractable cough.[59] CT images show circumferential tracheal thickening, deformation of the tracheal rings, and tracheal stenosis.[60] The presence of mediastinitis suggests active tuberculosis. Airway inspection reveals mucosal ulcers, surrounding erythema and edema, and hyperplastic inflammatory polyps.[61]

Fungal Infections

Fungal infections in immunosuppressed patients also cause large airway stenosis but are difficult to diagnose. *Aspergillus fumigatus* and, to a lesser extent, mucormycosis have been found to cause tracheobronchial infection[58,62] in patients at high risk for fungal infections, such as solid-organ transplant recipients or those with hematologic malignancies or neutropenia, or on immunosuppressive medication.[63] CT images may show parenchymal involvement in addition to irregular tracheal thickening. Flexible bronchoscopy can reveal white plaques, hyperemic mucosa, "sticky" secretions suggestive of fungal disease, and evidence of airway necrosis given the angioinvasive nature of these organisms.[64] White material may represent calcium deposited by the *Aspergillus* (see Fig. 26.3B). Biopsy of the plaques can be diagnostic[65] in the correct clinical setting of a severely immunocompromised patient with respiratory complaints in the absence of other pathogens. If the lesion fails to respond to appropriate antifungals, the resulting stenosis can be treated endobronchially using tracheal balloon dilation,[66] laser therapy, cryotherapy, stent placement, and surgical resection (see Chapter 28).

Bacterial Infections

Bacterial infections localized to the large airways are often overlooked because most instances of tracheitis or tracheobronchitis also involve concomitant infection of the lower respiratory tract. One organism associated with tracheal infections leading to obstruction and stenosis is *Klebsiella rhinoscleromatis*. *K. rhinoscleromatis* primarily infects the nares and paranasal sinuses but can also cause infection in the upper airway and trachea. The diagnosis is made by identifying the pathognomonic Mikulicz cells in the nodules of rhinoscleroma; these cells are round or oval macrophages with small nuclei that contain the causative bacterium, *K. rhinoscleromatis*.[67] This indolent infection is endemic in Africa, South America, and other developing countries and is quite rare in the developed world. Tracheal infection with *K. rhinoscleromatis* can ultimately lead to a chronic granulomatous infection resulting in diffuse tracheal stenosis.[29,68] Treatment may require surgical intervention for obstructing lesions and long-term antimicrobial therapy.

Respiratory Papillomatosis

Recurrent respiratory papillomatosis presents in a juvenile or an adult form (see Chapter 78). The juvenile form is caused by perinatal infection with *human papillomavirus* (HPV) and presents in childhood.[69] It is characterized by multiple benign airway papillomas and recurs frequently. HPV subtypes 6 and 11 cause greater than 90% of cases, whereas infection with subtypes 16 and 18 increases risk of malignant transformation to squamous cell carcinoma (see eFig. 78.25).[70] The adult form is more common in men and in smokers and is caused by HPV transmitted via oral sex.[71] In the adult-onset form, papillomas tend to be solitary or multilobulated and rarely recur after resection (see Fig. 26.3C).

Symptoms are nonspecific and include cough, dyspnea, wheeze and, if the larynx is involved, hoarseness. Rarely,

respiratory papillomatosis can lead to critical tracheal obstruction. Endobronchial resection (see Chapter 28) and adjuvant medical therapy are the mainstays of treatment. Intralesional cidofovir, an antiviral nucleotide analogue, and bevacizumab, a vascular endothelial growth factor inhibitor, have shown promise in the treatment of recurrent, severe, or obstructive tracheobronchial papillomas.[72–74]

INFLAMMATORY

Granulomatous inflammatory diseases, such as sarcoidosis, inflammatory bowel disease, and GPA, and autoimmune conditions, such as relapsing polychondritis, can target the tracheobronchial tree. Scarring often results from the edema and necrosis seen with inflammation, causing stenosis. Chronic airway inflammation can also weaken cartilage, leading to tracheobronchial malacia.

Relapsing Polychondritis

Relapsing polychondritis is a rare autoimmune disorder characterized by inflammation of cartilage in the ears, nose, joints, and large airways. The airways are involved in about 50% of cases and account for about 10% of deaths.[55] The larynx and trachea are the most common sites of airway involvement. Repeated episodes of tracheal chondritis can lead to tracheal obstruction due to tracheomalacia and/or tracheal stenosis. When smaller bronchi are involved, the respiratory phenotype is less severe than with tracheal disease.[75]

Spirometry and flow-volume loops may reveal plateaus of maximal airflow suggestive of tracheal obstruction (see "Diagnostic Approach" earlier), especially when cartilage fibrosis leads to tracheal stenosis. Of note, relapsing polychondritis does not cause a diffusion defect. CT images (see Fig. 20.30) reveal thickened cartilage in the cartilaginous tracheal wall with sparing of the posterior membrane (see Fig. 92.6). The parenchyma is also spared. PET scans may reveal high activity in tracheal cartilage, helping to distinguish between active and fibrotic lesions. Flexible bronchoscopy can delineate the degree of stenosis or malacia.

The mainstay of treatment is immunosuppression with systemic corticosteroids. Biologics have been studied, but the numbers of treated patients are small and the results inconsistent[76] (see Chapter 92). Stepwise treatment with positive pressure ventilation, tracheal stenting, and tracheostomy should be considered if tracheal obstruction due to relapsing polychondritis worsens despite maximal medical treatment.

Sarcoidosis

Sarcoidosis is characterized by the formation of noncaseating granulomas in one or more organs. The lung is involved in greater than 90% of sarcoidosis patients, with endobronchial involvement approaching 70%. In contrast, tracheal involvement is uncommon, seen in only 1–3% of all pulmonary cases.[28,77] In the trachea, sarcoidosis can present as intrinsic granulomatous infiltration or extrinsic compression from enlarged mediastinal lymph nodes. The proximal one-third of the trachea is more commonly affected than the distal trachea or lower airways.[28] Symptoms are nonspecific and include cough, dyspnea, and wheeze. Bronchoscopic findings include cobblestone mucosa and whitish granulomatous material in areas of stenosis (see Fig. 26.2C). Like other forms of sarcoid, tracheal sarcoid is treated with systemic steroids. If there is evidence of reversible airway obstruction on spirometry, inhaled corticosteroids or bronchodilators may be considered[78] (see Chapter 93).

Granulomatosis with Polyangiitis

GPA is a necrotizing granulomatous vasculitis affecting small blood vessels in the upper and lower airways and kidneys (see Chapter 87). GPA has been reported to involve the tracheobronchial tree in 12–23% of patients.[30,31] Of interest, although GPA affects women and men equally, greater than 90% of patients with GPA-related tracheal stenosis are women.[79] The reason for this female predominance is unknown. GPA should also be considered in patients with unexplained hemoptysis (see Chapter 40).

CT images in patients with tracheal GPA show circumferential, smooth, or nodular mucosal thickening (see eFig. 70.2), irregular borders, and ulceration.[80] Although not commonly involved, the cartilage rings can be narrowed and deformed. Flexible bronchoscopy may reveal subglottic stenosis, tracheal stenosis, tracheal ulcers, and inflammatory pseudopolyps. Transbronchial biopsy is insensitive, revealing histopathologic features diagnostic of GPA in less than 20% of specimens.[30,81] In some patients, a presumptive diagnosis of an *antineutrophil cytoplasmic autoantibody*–associated vasculitis, such as GPA, can be made if the clinical picture and positive antineutrophil cytoplasmic antibody argue against an alternative etiology. Treatment depends on the seriousness of the disease. Severe tracheobronchial disease often responds to systemic treatment with the combination of corticosteroids together with either cyclophosphamide or rituximab. If tracheobronchial stenosis persists or recurs despite prolonged immunosuppressive therapy, endobronchial therapies, including tracheal dilation, conservative laser surgery, and stenting, should be considered.[82]

Inflammatory Bowel Disease

Pulmonary manifestations of inflammatory bowel disease are uncommon, and tracheal involvement is even rarer, reportedly as low as 0.2% for ulcerative colitis and 0.4% for Crohn disease.[83] Ulcerative colitis can manifest as a tracheobronchitis, producing dyspnea and hoarseness. CT scanning shows tracheobronchial wall thickening, and flexible bronchoscopy reveals tracheobronchial ulcers in the mucosa, severe luminal narrowing, and cobblestoning. If biopsied, the ulcers show necrosis with submucosal inflammation characterized by lymphoplasmacytic infiltration within the epithelium and lamina propria without granuloma formation.[84] Infection must be excluded. Exacerbations of the gastrointestinal and pulmonary systems often happen simultaneously, quite possibly due to their common embryologic tissue origin.[84] Crohn disease results in extraintestinal manifestations more often than ulcerative colitis but, similarly, pulmonary involvement is rare and can present as tracheitis, tracheobronchitis, or tracheal stenosis.[85] Treatment with high-dose corticosteroids is often successful.

BRONCHOLITHIASIS

Broncholithiasis is characterized by calcified material eroding into the tracheobronchial lumen, leading to inflammation and obstruction of the airway.[86] Most often, the calcified material is a calcified lymph node, often the result of earlier granulomatous infection, endemic fungal diseases such as *Histoplasma capsulatum*, or the result of silicosis.[87,88] Alternatively, broncholiths can originate from aspirated foreign material that has calcified within the tracheobronchial lumen, calcified endobronchial hamartomas, carcinoid tumors, or calcified tracheal cartilage rings that protrude into the lumen.[89] Clinically, broncholithiasis can range from being asymptomatic to causing cough, lithoptysis (expectoration of calcified material), postobstructive pneumonia, and hemoptysis. In severe cases, erosion of the broncholith into the tracheobronchial lumen can lead to a bronchoesophageal fistula.[90] Although chest radiographs may show calcifications within clusters of lymph nodes, diagnosis is most often made by CT scan (see eFig. 56.4). Bronchoscopy can sometimes miss the lesion if the broncholith only partially erodes into the airway.

Treatment is conservative if the patient is asymptomatic or has minimal symptoms, such as an infrequent cough. This involves cough suppression and treatment of any pneumonias. If the symptoms escalate, more definitive therapy is warranted, which can include bronchoscopy to evaluate the broncholith and facilitate its removal. If removal by forceps is not possible, bronchoscopy with Nd:YAG lasers (bronchoscopic lithotripsy) may be effective. If these methods are unsuccessful, surgery can be considered but should be reserved for those who are symptomatic and have not responded to endobronchial therapy.[87,91]

VASCULAR MALFORMATIONS

Tracheal varices are rare but are important to recognize because they are potential sources of massive hemoptysis if biopsied. They can be caused by obstruction of the pulmonary veins or of the superior vena cava due to pulmonary venous hypertension, portal hypertension, congenital cardiac diseases, or mediastinal masses.[92,93] In addition to hemoptysis, patients may present with symptoms of the underlying cause of the varices (e.g., superior vena cava syndrome). Diagnosis is made by bronchoscopy in the setting of hemoptysis or incidentally during bronchoscopy performed for another reason. Airway inspection reveals tracheal varices that appear as polypoid tracheal nodules along with dilated mucosal vessels. Tracheal varices should be suspected in patients with hemoptysis, tracheal nodules, and mediastinal collateral vessels on CT, a feature that distinguishes tracheal varices from other causes of tracheal nodules, such as amyloidosis and sarcoidosis. As mentioned, magnetic resonance imaging may be useful for identifying and mapping vascular abnormalities.

TRACHEOBRONCHOMALACIA AND EXCESSIVE DYNAMIC AIRWAY COLLAPSE

Tracheobronchomalacia (TBM) refers to weakness of the cartilaginous anterolateral walls of the trachea and mainstem bronchi. It is caused by cartilage breakdown that results in loss of structural rigidity and excessive collapse of the trachea and large bronchi during exhalation. In contrast, *excessive dynamic airway collapse* (EDAC) refers to exaggerated bulging of the posterior tracheal membrane into the airway lumen during exhalation. Both TBM and EDAC can cause severe, symptomatic upper airway obstruction and may present individually or together in the same patient.

In adults, TBM is most often acquired. Causes include chronic airway inflammation due to chronic bronchitis,[94] cystic fibrosis,[95] and gastroesophageal reflux[96]; cartilage inflammation due to relapsing polychondritis[97]; chronic extrinsic compression by adjacent structures, such as thyroid goiters[98] or tumors; cartilage necrosis induced by endotracheal and tracheostomy tubes[99]; and radiation. Tracheobronchomegaly (Mounier-Kuhn syndrome) can also cause TBM. In contrast, EDAC, which is mainly found in patients with chronic obstructive airway diseases, is thought to be caused by an increased transmural pressure gradient during exhalation[10] and by weakening of the muscular posterior membrane.[100]

Because symptoms due to TBM and EDAC are nonspecific (e.g., cough, dyspnea, recurrent airway infections), diagnosis requires a high index of suspicion and focused testing. As mentioned, flow-volume loops may show a rapid decline of expiratory flow after a sharp peak suggestive of large airway collapse (see Fig. 71.1) or signs of notching or oscillations of the expiratory flow (Fig. 39.3) to suggest the diagnosis; however, they are not by themselves diagnostic.[101,102] Traditionally, TBM and EDAC have been diagnosed when the cross-sectional tracheal area measured by bronchoscopy or dynamic CT (Figs. 71.6A–B) decreases by greater than 50% during forced exhalation as a result of exaggerated cartilaginous collapse (TBM; see Fig. 71.6C), posterior bulging into the lumen (EDAC; see Fig. 71.6D), or an overlap of both TBM and EDAC.[103–105] However, in many healthy control subjects without these conditions, their trachea collapses posteriorly by 50% or more on forced exhalation,[24] indicating that this threshold is inadequate to define abnormal collapse. Instead, tracheal collapse requiring treatment usually approaches 95–100% during forced exhalation[10,106,107] (see Fig. 39.3). Thus, reduced maximal expiratory flow rates and the appearance of the flow-volume curve, although not diagnostic, may be better indicators of clinically significant collapse than visual assessment.

The decision to treat TBM or EDAC should be based on the presence of symptoms due to excessive tracheal collapse. In an asymptomatic patient, treatment is generally not indicated. In a symptomatic patient, treatment of the underlying cause (e.g., bronchodilators and airway hygiene for COPD, steroids for relapsing polychondritis) may ameliorate symptoms. If medical management is ineffective, continuous positive airway pressure can pneumatically stent the airway open, reducing dynamic airway collapse and facilitating mucus clearance.[108,109] Airway stents[110,111] and surgery,[107] including tracheobronchoplasty (splinting of the posterior membrane with a polypropylene mesh or acellular dermis[113]) or tracheobronchial resection and reconstruction, can be considered in very symptomatic patients who do not respond to noninvasive treatment and have focal tracheobronchial disease. A successful stent trial helps identify patients who will benefit from surgical airway stabilization via tracheoplasty.[107] Successful endoscopic therapy

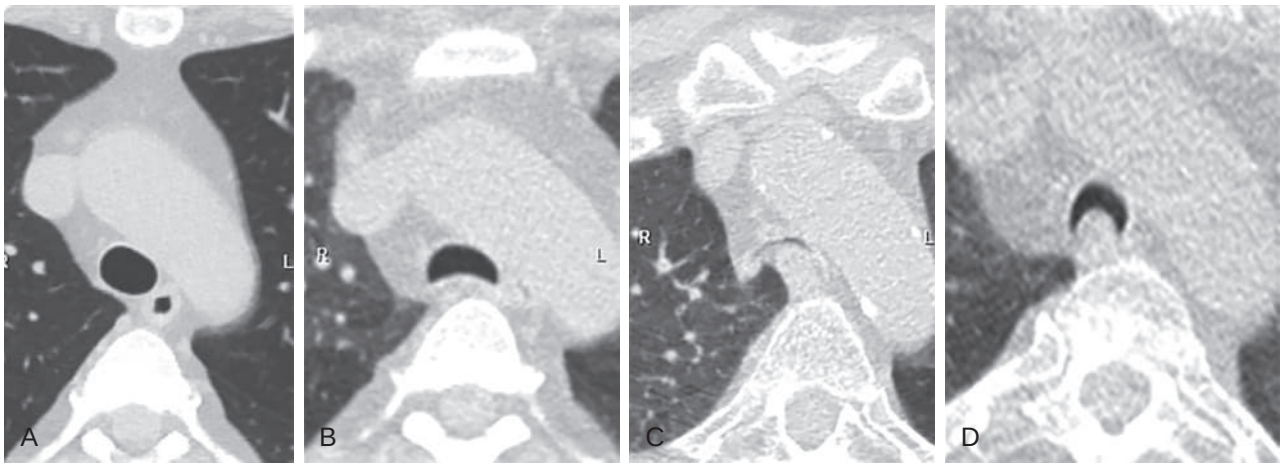

Figure 71.6 Tracheomalacia and *excessive dynamic airway collapse* (EDAC). (A–B) Normal, paired *computed tomography* (CT) images through the midtrachea at the level of the aortic arch show a normal trachea at full inspiration (A) and end-exhalation (B). The posterior tracheal membrane normally bows inward slightly at end-exhalation. (C) Tracheomalacia. The CT image shows excessive flattening of the anterolateral cartilaginous walls at end-exhalation. (D) EDAC. The CT image shows excessive bulging of the posterior membrane into the lumen at end-exhalation. (Courtesy Michael B. Gotway, MD.)

to tighten the posterior membrane with laser has also been reported but requires further study.[114]

EXTRINSIC DISORDERS

FIBROSING MEDIASTINITIS

Fibrosing mediastinitis, also termed sclerosing mediastinitis or mediastinal fibrosis, is a rare disease causing external tracheal compression. It is the result of an exaggerated granulomatous response in mediastinal lymph nodes to a variety of pathogens leading to fibrosis, compression, and invasion of adjacent structures, including the trachea, esophagus, and blood vessels (see Chapter 116). Common triggers include *Histoplasma capsulatum* and, to a lesser extent, *Mycobacterium tuberculosis*.[115] *Aspergillus flavus*, sarcoidosis, and immunoglobulin G4-related disease have also been reported to cause fibrosing mediastinitis.[116,117]

In addition to tracheal compression, the most serious complication of fibrosing mediastinitis is pulmonary arterial and venous obstruction (see Fig. 116.5). Most patients with fibrosing mediastinitis have unilateral disease and can remain undiagnosed for years because symptoms are nonspecific. Chest radiographs can reveal a widened mediastinum due to mediastinal adenopathy and fibrosis, but CT with contrast is indicated to assess the degree of mediastinal involvement along with the extent of airway narrowing and vascular compromise. Bronchoscopy can reveal narrowing of the tracheal lumen and massive tracheal variceal formation along the posterior tracheal wall if superior vena cava syndrome is present. There are no standard treatment options, but therapy focuses predominantly on symptomatic management, including stenting of arteries and veins.

FISTULAS

Tracheoesophageal fistulas (TEFs) are abnormal congenital or acquired connections between the trachea and esophagus. This section focuses on the acquired form, which is most often caused by esophageal or lung cancer. From 5–15% of patients with esophageal cancer and 1% of patients with lung cancer develop TEFs.[118–120] Less common, TEFs are caused by benign conditions, such as prolonged intubation, tracheostomy, surgery, and radiation. Symptoms include cough with eating or drinking, recurrent pneumonia, recurrent aspiration, dysphagia, and malnutrition. In TEF due to cancer, survival has been reported to be a few weeks to months.[121–123]

Airway inspection is indicated in patients when symptoms, barium esophagram, or CT imaging suggest TEF. The fistula may be visible with heaped, irregular margins and secretions from the esophagus escaping into the trachea (Fig. 71.7A) and can be associated with significant tracheal stenosis. Small fistulas may be difficult to identify due to local erythema and edema. In such cases, orally administered methylene blue before bronchoscopy can help identify them.[124]

The goal of treatment is blocking the seepage of esophageal and stomach contents into the airways to prevent aspiration-related airway injury and pneumonia and to improve nutrition. This can be attempted by stenting or surgery. In benign TEF, surgical repair with curative intent is the preferred approach because it can produce good long-term results and because stents, while occasionally placed as a bridge to surgery, cannot be placed indefinitely.[125–127] In malignant TEF or in inoperable benign TEF, stenting of the trachea and/or esophagus can ameliorate symptoms and prolong survival.[7,118,121,122] Surgical repair is normally not attempted in malignant TEF because the underlying condition is incurable and because resection does not yield satisfactory results.[120]

To treat TEF, stents can be placed in the trachea, esophagus, or both. An esophageal stent is indicated in patients with esophageal stenosis and no tracheal obstruction. Side effects of esophageal stent placement include gastroesophageal reflux disease and dietary changes needed to maintain stent patency. On occasion, airway obstruction develops after placement of an esophageal stent, requiring removal or revision with or without placement of a tracheal stent.

Tracheal stenting is performed first if the patient has tracheal obstruction, if there is clinical concern for the development of tracheal obstruction after placement of an esophageal stent, or if the esophageal tumor is not causing stenosis (see Fig. 71.7B–E). Tracheal stents are usually well tolerated but may

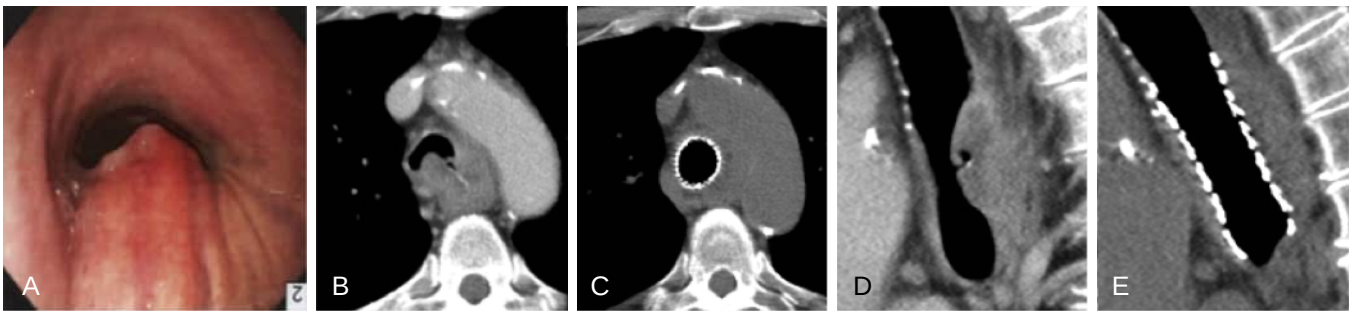

Figure 71.7 Tracheoesophageal fistula. (A) Airway inspection shows a mixed obstruction of the mid-trachea with necrosis and secretions, suggesting a fistula. (B–C) Paired axial computed tomography images show an esophageal mass invading the posterior trachea before (B) and after (C) placement of a covered self-expanding metal stent. (D–E) Paired sagittal computed tomography images clearly show a fistula (D) before stent placement (E). (Courtesy Lakshmi Mudambi, MD.)

produce an intractable cough. Patency is maintained with daily nebulization of bronchodilators and saline solutions.

Double stenting (i.e., placement of a tracheal and esophageal stent) can be considered if the patient has tracheal obstruction and a stenotic esophageal tumor causing dysphagia, a very large fistula not completely occluded by either a tracheal or esophageal stent, or tracheal obstruction that develops after placement of an esophageal stent.[7,128,129] Double stenting can increase the size of the fistula and prevent healing. It should be avoided in patients with potential for cure, surgical correction, or long-term survival.

EMERGING THERAPIES

THREE-DIMENSIONAL PRINTED AIRWAY STENTS

Airway stents are used to maintain tracheal patency and to block fistulous tracts in the trachea (see Chapter 28). In some patients, a deformed trachea can result in poor fit of commercially available stents, leading to complications such as migration, impaired mucus clearance, granulation tissue, and perforation. Three-dimensional printed airway stents address this issue by precisely fitting the patient's trachea. They have recently been approved by the U.S. Food and Drug Administration. The stents are made by injecting medical-grade silicone into a three-dimensional printed mold engineered from three-dimensional CT reconstructions of the patient's trachea.[130] The literature on three-dimensional printed stents is currently limited to case reports, but early results are promising.[131,132]

TRACHEAL REPLACEMENT

Primary tracheal resection with direct end-to-end anastomosis is the definitive treatment for various focal tracheal disorders. The principal limitation is involvement of more than 4 cm of trachea, which significantly increases the risk of anastomotic failure likely due to increased tension on the anastomosis.[16] In patients requiring long tracheal resections, several methods of tracheal replacement (e.g., synthetic prosthetics, allografts, autologous tissue, and tracheal transplantation) have been used to restore function. Currently, none of these methods meets the criteria of an ideal tracheal replacement. Such criteria would include lateral rigidity and stiffness, longitudinal flexibility, air-tightness, support of a functional ciliated respiratory epithelium, biocompatibility, and absence of need for immunosuppression.

Tracheal replacement with synthetic stents,[133,134] aortic allografts reinforced with tracheal stents,[135,136] and cadaveric tracheal allografts[137] has been associated with significant morbidity and mortality. Tracheal allotransplants have been used to reconstruct tracheas in benign tracheal disease.[138,139] This approach is limited by the need for immunosuppression (making it unsuitable for malignant disease), a compromised blood supply (risking necrosis of the transplanted trachea), and the lack of published data on long-term outcomes.[140] In malignant tracheal disease, autologous transplants constructed from fasciocutaneous, omental, or muscle flaps reinforced with strips of cartilage or mesh to simulate cartilage rings have been used in tracheal reconstruction.[141] Artificial tracheas made from biocompatible three-dimensional printed tubular scaffolds and the subject's own pluripotent stem cells have shown promise as tracheal substitutes and are an area of active research.[142]

Key Points

- Because symptoms due to large airway disorders are nonspecific and often mimic those of more common conditions, such as asthma or COPD, the diagnosis of large airway disorders requires a high index of suspicion.
- Spirometry with flow-volume loops, computed tomographic imaging, and flexible bronchoscopy provide complementary information required to evaluate large airway disorders.
- Of the diagnostic tests, flexible bronchoscopy is the gold standard test for the assessment of large airway disorders.
- Surgical resection is the definitive treatment of focal tracheal disease and should be considered in symptomatic patients.
- Endobronchial interventions are first-line therapies for several large airway disorders and can palliate symptoms in nonsurgical disease.
- Intervention for symptomatic tracheal collapse is usually not indicated until collapse approaches 95–100% of cross-sectional area of the trachea during forced exhalation and is supported by finding abnormal expiratory flows on spirometry or flow-volume loop.
- Novel therapeutic approaches, such as three-dimensional printing of tracheal stents and tissue-engineered tracheal replacements, show promise.

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72 BRONCHIOLITIS

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INTRODUCTION

Although other chapters focus on the major diseases primarily affecting the large intrathoracic airways, including asthma, bronchitis, cystic fibrosis, and bronchiectasis, a constellation of entities primarily affect *peripheral* airways. Early diagnosis of these small airway diseases remains difficult, however. Early in the disease course, the large cross-sectional area and reduced airflow of peripheral airways protect patients from symptoms of dyspnea and limit detection of flow abnormalities on functional testing. Diseases affecting the peripheral airways may nonetheless have profound effects on lung function. Because pathologic narrowing of peripheral airways is difficult to detect, these airways may be considered a silent zone of the lung. Although tests to identify peripheral airway obstruction have suffered from a lack of sensitivity, heightened recognition of the entities affecting peripheral airways and diagnostic advances have increased the frequency of diagnosis. Nevertheless, the epidemiology of disorders of the peripheral airways remains largely unknown.[1] This chapter takes into account the heightened clinical recognition and evolving efforts at classification as our understanding of these entities advances. The chapter first reviews the anatomy of the peripheral airways. The predominantly inflammatory and fibrotic bronchiolitis entities are then addressed, with the recognition that there may be substantial overlap in clinical and histologic features.

ANATOMIC AND PHYSIOLOGIC FEATURES

Among other roles, the intrathoracic airways serve as a conduit between the outside environment and alveolar units. Moving distally from the trachea, the bronchi transition to bronchioles and ultimately to the terminal respiratory units. These transitions are defined by changes in the constellation of cell types and by architectural features. Bronchi range in size from 10 down to 1 mm in diameter and are characterized by incomplete cartilaginous rings, ciliated epithelium, goblet cells, submucosal glands, and smooth muscle innervated by muscarinic output via the vagus nerve. Bronchioles are defined by their lack of cartilage; their sparse population of ciliated, simple, columnar epithelium and secretory club cells; and their lack of goblet cells and glands. Bronchiolar smooth muscle is not innervated by the vagus nerve, and the diameter of bronchioles typically ranges from 2 down to 0.5 mm. As bronchioles branch, they go from lobular to terminal and then respiratory segments. Terminal bronchioles are the last divisions of conducting airways, whereas alveoli bud from respiratory bronchioles (Table 1.2; see also Chapter 1).

Because of their relatively small total cross-sectional area, bronchi are responsible for most airflow resistance in the lung. In contrast, bronchioles contribute little to total airflow resistance at high and normal lung volumes. This limited contribution is attributable to dichotomous branching that arranges vast numbers of bronchioles in parallel. Within the conducting region of the lung, bronchioles branch into terminal bronchioles, whereas in the respiratory zone, where gas exchange takes place, respiratory bronchioles branch into alveoli. This branching translates into a much larger total cross-sectional area for bronchioles relative to bronchi. At low lung volumes, the relative contribution of bronchioles to total airflow resistance increases because, as residual volume is approached, the flexible, thin-walled bronchioles, supported only by connective tissue, may collapse. Despite significant disease of the bronchioles, however, *pulmonary function test* (PFT) results may be normal. In advanced disease, PFTs may demonstrate upward concavity (curvilinearity) of the flow-volume curve, especially at low lung volumes, an increased slope of phase III (the alveolar plateau) of the single-breath nitrogen washout test, and air trapping. Although mid–*forced expiratory lung flow* ($FEF_{25\%–75\%}$) had been proposed as an early criterion for post–lung transplantation bronchiolitis, subsequent studies have challenged its predictive utility.[2]

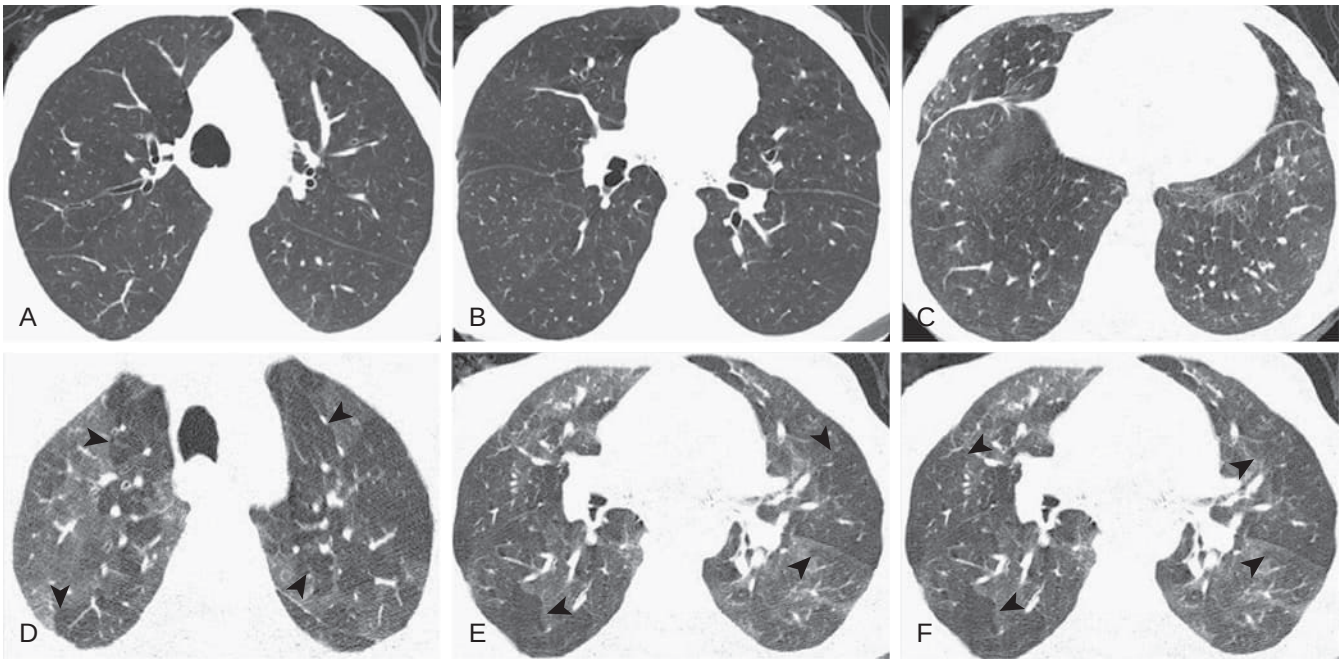

Figure 72.1 High-resolution *computed tomography* (CT) scan demonstrating air trapping during expiration. (A–C) Axial chest CT images performed through the upper (A), mid (B), and lower (C) lungs obtained during inspiration (see Video 140.2) in a bilateral lung transplant recipient show only minimal inhomogeneous lung opacity. Expiratory chest CT images performed through the upper (D), middle (E), and lower (F) lungs show extensive accentuation of the bilateral inhomogeneous opacity (see Video 140.3). The areas of increased attenuation represent normal collapsing lung during exhalation. The areas of relatively decreased attenuation (*arrowheads*) represent air trapping due to constrictive bronchiolitis as a result of chronic rejection.

Computed tomography (CT) scans or magnetic resonance imaging with hyperpolarized gases, similarly, may demonstrate inhomogeneity of ventilation and air trapping (Fig. 72.1, see Video 140.3); see also Chapter 10).

DEFINING BRONCHIOLITIS

Bronchiolitis refers to a nonspecific cellular and mesenchymal reaction of the bronchioles. Developing a straightforward classification, however, is difficult. Perhaps most important, bronchiolitis is a catchall term subsuming several unique clinical syndromes and a histopathologically diverse set of lesions identifiable in many diseases. Next, there are many diseases that, in addition to causing bronchiolitis, also cause disease proximal (e.g., bronchiectasis) or distal (e.g., organizing pneumonia) to the bronchioles. As a result, some avoid defining the precise site of involvement, instead referring to peripheral airways (<2 mm diameter) as small airways. Lastly, clinical bronchiolitis syndromes may demonstrate more than one histologic pattern temporally and spatially. These factors complicate defining a mutually exclusive classification system. Therefore, definitive diagnosis of a specific bronchiolitis entity requires clinical, diagnostic (imaging, PFTs), and frequently histopathologic evaluation. Definitive diagnosis depends on excluding bronchial and alveolar involvement seen in alternative diagnoses. A hybrid classification schema based on both histopathologic findings and clinical syndromes is presented in Fig. 72.2. The early branch points in this schema are driven by histopathologic findings, whereas later branch points are driven by clinical syndromes and exposures.

INFLAMMATORY AND INFECTIOUS BRONCHIOLITIS

This group of bronchiolitis syndromes involve inflammation or infection and are characterized by a predominantly cellular infiltration of the bronchioles. Cellular infiltration can be localized to the wall (mural) or lie within or around the bronchiole (Fig. 72.2).

INFLAMMATORY BRONCHIOLITIS

Infectious Bronchiolitis

Although relatively rare in adults, acute *infectious bronchiolitis* is common in infants and young children. Indeed, within the pediatric population, this entity is referred to simply as bronchiolitis. *Respiratory syncytial virus* infection is the cause of 70% of infectious bronchiolitis, although rhinovirus, metapneumovirus, influenza virus, and other viral and bacterial infections can also cause this syndrome.[3] Infection damages bronchiolar epithelial cells. Edema, epithelial sloughing, ciliary dysfunction, and mucus secretion result in small airway obstruction and atelectasis. In severe cases, there may be peribronchiolar lymphocytic infiltration and even mural necrosis (Fig. 72.3A, see Fig. 72.2 [classified under the category inflammatory bronchiolitis]). Bronchiolitis within the first few years of life can result in protracted wheezing and asthma development, particularly through the first decade and possibly into adulthood. Long-term sequelae appear to be modified by genetic and environmental factors, including environmental tobacco smoke exposure.[4]

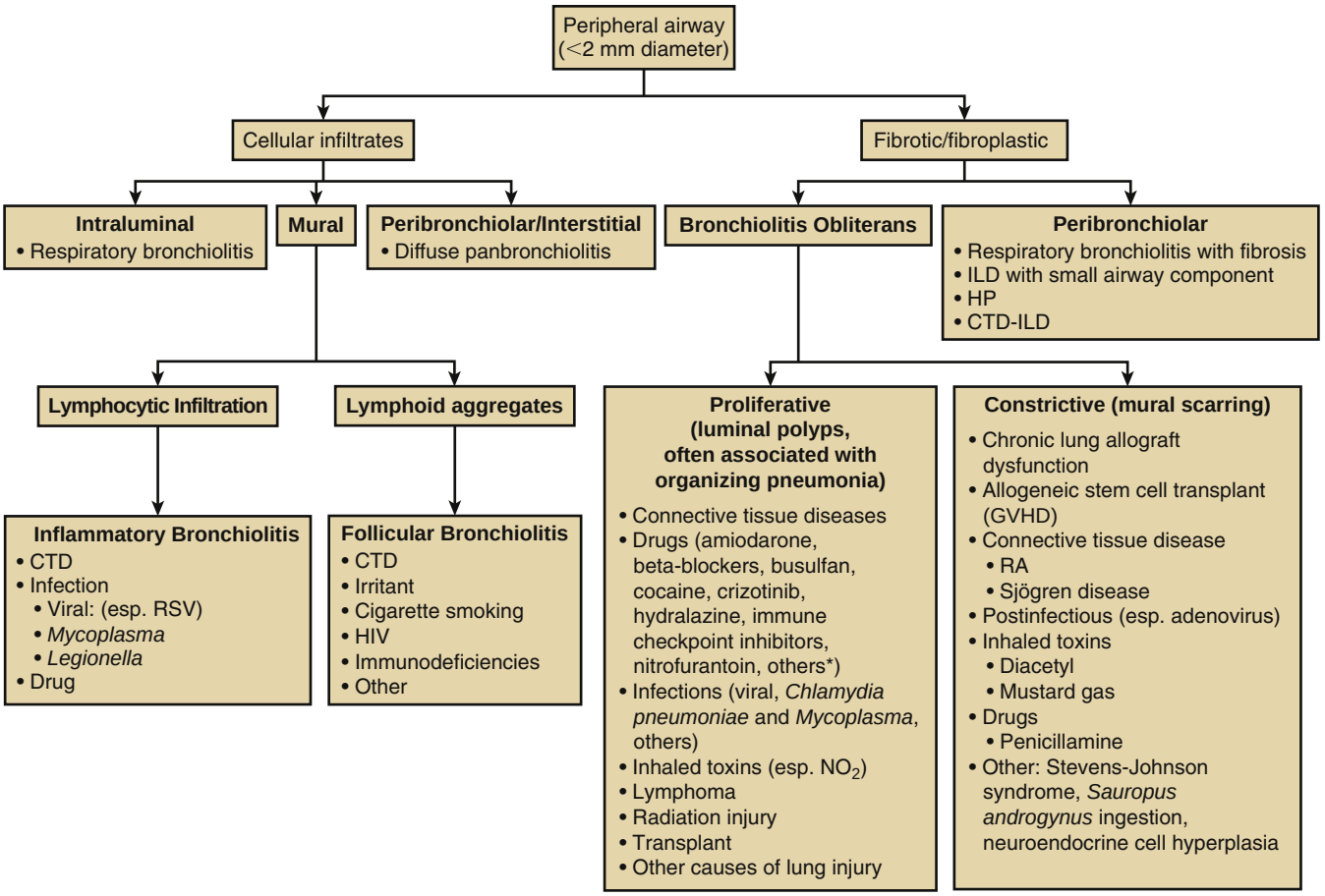

Figure 72.2 Classification schema for bronchiolitis. Traditionally, bronchiolitis has been defined by clinical syndromes and histopathologic lesions, making classification difficult. In this schema, early classification branch points are defined by histopathologic findings (e.g., cellular infiltrates in the small airways vs. fibrosis). Later branch points are defined by specific clinical entities. *See http://pneumotox.com/ for a complete list. CTD, connective tissue disease; esp., especially; GVHD, graft-versus-host disease; HIV, human immunodeficiency virus; HP, hypersensitivity pneumonitis; ILD, interstitial lung disease; NO_2, nitrogen dioxide; RA, rheumatoid arthritis; RSV, respiratory syncytial virus.

Typically affecting children younger than 2 years, bronchiolitis begins as an acute upper respiratory tract infection with rhinorrhea, nasal congestion, and/or cough. Within days the cough worsens, and dyspnea and fever develop. Although wheezing, chest wall retractions, and cyanosis may be seen, respiratory failure is uncommon. Examination typically demonstrates mildly depressed oxygen saturation, tachypnea, mild chest wall retractions, expiratory wheezing, and crackles. In more severe cases, nasal flaring, grunting, pronounced chest wall retractions, prolonged expiratory phase, and cyanosis may be seen. Epithelial sloughing with bronchiolar obstruction may cause hyperinflation and gas exchange abnormalities.[5] In general, infectious bronchiolitis is diagnosed based on clinical signs and symptoms. When obtained, radiographs may be normal or have evidence of pneumonia or bronchitis, whereas focal consolidation may be indicative of bacterial coinfection.[6,7] Outpatient supportive therapy with nasal bulb suctioning and hydration is usually sufficient, but some patients require hospitalization for fluid administration and/or respiratory support. This self-limiting infection typically resolves within weeks. A number of studies have investigated additional therapies and shown no clear evidence of benefit for bronchodilators, corticosteroids, antibiotics, chest physiotherapy, or leukotriene inhibitors.[8,9] Of note, respiratory syncytial virus–specific monoclonal antibody therapies have not proven efficacious for acute management but are recommended as prophylaxis for selected high-risk infants.[8,10]

RESPIRATORY BRONCHIOLITIS

Respiratory bronchiolitis (RB) is a pathologic entity characterized by pigmented alveolar macrophage accumulation in respiratory bronchioles and adjacent alveoli. Peribronchiolar inflammation or fibrosis and epithelial metaplasia extending into adjacent alveoli (i.e., lambertosis) may be present (see Fig. 72.3B). Although nearly universally seen in cigarette smokers, it may also be seen after particulate exposures.[11–13] RB rarely causes symptoms or physiologic abnormalities per se. It is most commonly diagnosed incidentally by imaging (see Fig. 72.2 [classified under the intraluminal category]). In some cases, more extensive fibrosis extends into the alveolar septa and is associated with clinical and radiographic evidence of interstitial pneumonia. In these cases, the term *RB-associated interstitial lung disease* (RB-ILD) is applied (see Chapter 90).[11,12] In

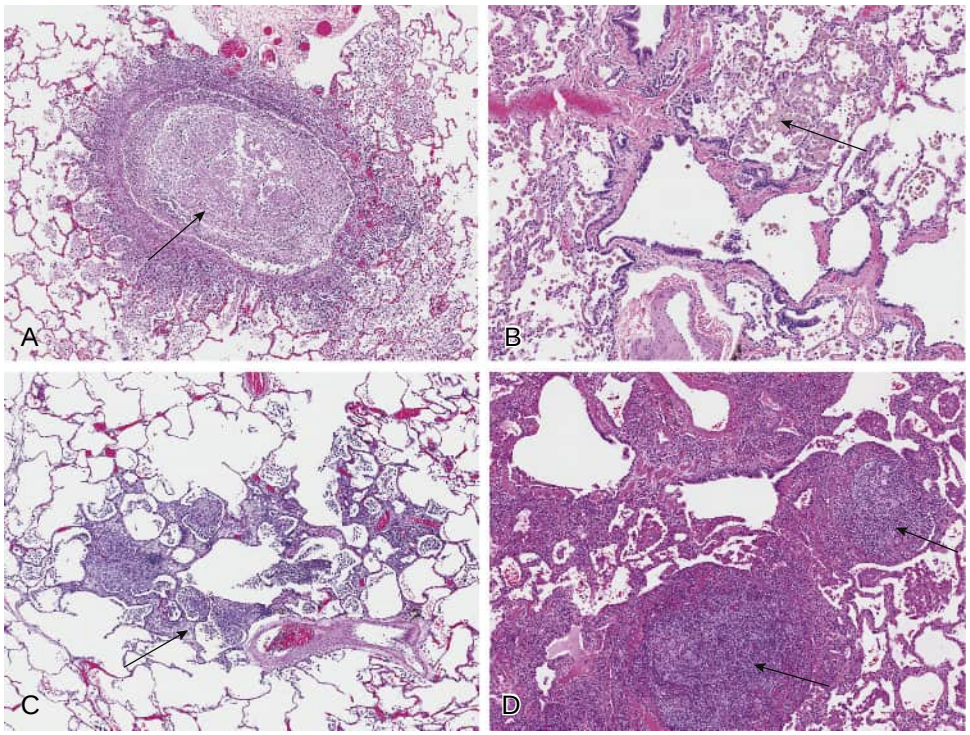

Figure 72.3 Pathologic patterns of bronchiolitis. (A) Infectious bronchiolitis. The bronchiolar wall shows marked acute inflammation with neutrophils and apoptotic debris (*arrow*) extending from the sloughed epithelial surface transmurally to the adjacent alveolar spaces. (B) Respiratory bronchiolitis. The terminal bronchiole and peribronchiolar alveolar spaces show consolidation by lightly pigmented "smoker's" alveolar macrophages (*arrow*). Mild peribronchiolar fibrosis is present. (C) Diffuse panbronchiolitis. The terminal bronchiole shows mural lymphoid inflammation, luminal inflammation and organization, and peribronchiolar interstitial expansion by foamy macrophages (*arrow*). (D) Follicular bronchiolitis. Prominent lymphoid aggregates with well-formed germinal centers (*arrow*) are noted adjacent to bronchioles.

RB-ILD, patients present with subacute cough, dyspnea, and crackles, as well as restriction and reduced diffusing capacity on PFTs.[14] *High-resolution computed tomography* (HRCT) imaging shows a distinctive pattern of bronchial wall thickening, centrilobular nodules, reticulation, and diffuse or patchy ground-glass opacities.[15,16] Smoking cessation leads to resolution or stabilization of disease in most patients, and the risk of progression to respiratory failure and death appears less than is observed with the related smoking-associated ILD—desquamative interstitial pneumonia.[17] Subjective and objective improvements after corticosteroid treatment have been described but not studied prospectively.[17]

DIFFUSE PANBRONCHIOLITIS

Diffuse panbronchiolitis (DPB) is an unusual inflammatory disease of the respiratory bronchioles. Formally described in 1969, a 1982 survey in Japan estimated a prevalence of 11 cases per 100,000 people.[18,19] Although reported outside of East Asia, this entity is predominantly observed among those with Japanese ancestry, which may reflect an increased prevalence of genetic risk factors.[20,21] On histologic examination, DPB is characterized by the triad of bronchiolocentric inflammation, lymphoid hyperplasia, and accumulation of interstitial foam cells (see Fig. 72.2 [classified under the category peribronchiolar/interstitial] and Fig. 72.3C).[22–24] Of note, similar findings are also seen in bronchiectasis, underscoring the importance of developing a diagnostic approach to bronchiolitis that considers clinical, functional, radiographic, and histopathologic findings.

Given the rarity of DPB, epidemiologic data are limited. Clinically, DPB has a slight male predilection, and symptoms manifest in early to mid-adulthood.[19,20,24] Chronic sinusitis is exceedingly common and frequently precedes pulmonary symptoms. Before diagnosis, patients report years of nasal discharge or congestion, cough, dyspnea, and sputum production that exceeds 50 mL/day.[25] Radiographs demonstrate hyperinflation, diffuse small nodular opacities and, in advanced disease, ring shadows and "tram track" opacities consistent with bronchiectasis. In early disease, HRCT findings may include centrilobular nodules, sometimes termed a tree-in-bud pattern, and air trapping on expiratory images. Mosaic perfusion is atypical. In advanced disease, bronchiolar wall thickening, dilation, and cysts are seen.[26,27] PFTs demonstrate a progressive airflow obstruction with reduced diffusing capacity. Less commonly, a mixed obstructive-restrictive pattern may be observed.[21] Although clinical diagnostic criteria have been proposed for Japan, surgical lung biopsy is required in countries and populations in which the disease is rare.[20] If untreated, DPB leads to bronchiectasis, pulmonary hypertension, respiratory failure, and ultimately death. Although the etiology of DPB remains obscure, both genetic and environmental factors are believed to be important.[28–31] *Human leukocyte antigen* (HLA)-Bw54 is associated with a 13-fold increase in risk for diffuse panbronchiolitis.[29] Polymorphisms of the genes

for *interleukin* (IL)-8[30] and mucins[31,32] have been associated with diffuse panbronchiolitis.

Macrolides are the cornerstone of treatment.[33] As with macrolide therapy for other forms of bronchiolitis, their salutary effects likely involve a variety of immunomodulatory mechanisms rather than antimicrobial properties.[34,35] More than 40 studies have described these immunomodulatory effects across a variety of disease states. Within diffuse panbronchiolitis, the most consistently reported effect of macrolides is suppression of neutrophilic airway inflammation, with associated decreases in neutrophil chemoattractants and other proinflammatory cytokines.[36] Of note, 14- and 15-membered lactone ring macrolides (e.g., erythromycin, clarithromycin, azithromycin) are effective in treating DPB, whereas 16-membered lactone ring macrolides (e.g., tylosin, spiramycin) are not. Macrolide therapy is generally continued for at least 6 months.[33] For severe cases, lung transplantation has been performed, although the disease may recur in the allograft.[37]

Originally DPB was a highly fatal disease. In the 1980s, 5- and 10-year survivals were approximately 62% and 33%, respectively. With macrolide therapy, increased disease diagnosis, and early, aggressive treatment of bacterial infections, 10-year survival now exceeds 90%.[34] Recurrent respiratory infections are common, and *Pseudomonas* infection, often arising late in the disease, is associated with markedly increased mortality.[20]

FOLLICULAR BRONCHIOLITIS

Follicular bronchiolitis (lymphoid hyperplasia) is characterized by peribronchiolar hyperplastic lymphoid follicles with germinal centers (see Fig. 72.3D).[38,39] These follicles, which have high endothelial venules, lymphatics, and defined zones with T cells and B cells with follicular dendritic cells, resemble Peyer patches in the gut and are termed *bronchus-associated lymphoid tissue* (BALT).[39] BALT is commonly observed in transbronchial biopsies from lung transplant recipients and is not generally thought to be pathologic in this context. Indeed, in mouse lung transplant models, BALT regulatory T cells were necessary for protection against antibody-mediated rejection.[40]

BALT hyperplasia is pathognomonic for follicular bronchiolitis. Although idiopathic primary pulmonary lymphoid hyperplasia has been described, follicular bronchiolitis commonly indicates pulmonary involvement of a systemic immunologic condition, such as rheumatoid arthritis, Sjögren syndrome, lupus, *coatomer-associated protein subunit alpha syndrome* (COPA), human immunodeficiency virus, Evans syndrome, bronchiectasis, and other infections or immunodeficiencies. It can also be seen in association with smoking or other irritants and other airway or interstitial lung disease states[39,41] (see Fig. 72.2 [classified under the lymphoid aggregates category]).

Clinical symptoms of follicular bronchiolitis are often mild, with cough and dyspnea being most consistently reported.[42,43] PFT findings may show restrictive, obstructive, or mixed patterns. HRCT findings include small (<3 mm) centrilobular or peribronchial nodules and ground-glass opacities.[44] Treatment is directed at the underlying disease.

BRONCHIOLITIS OBLITERANS

Bronchiolitis obliterans can be stratified into constrictive and proliferative bronchiolitis. Although there is some overlap between these entities, this stratification is largely supported by histopathologic and clinical evidence. Unique entities featuring bronchiolitis obliterans are listed in Fig. 72.2; more common entities are discussed in greater detail later.

Histologically, constrictive bronchiolitis defines a submucosal and peribronchiolar fibrotic process that circumferentially and externally compresses the bronchiolar lumen (Fig. 72.4A). Patchy and focal in distribution, progressive fibrosis observed in constrictive bronchiolitis ultimately results in slit-like or completely obliterated bronchiolar lumens. Clinically, patients describe progressive dyspnea and nonproductive cough. Auscultation demonstrates early inspiratory crackles and occasional squeaks. PFTs performed late in the course of disease demonstrate obstruction and air trapping. Radiographs may have normal findings or show hyperinflation. HRCT can demonstrate ground-glass nodules, air trapping and, in advanced disease, bronchiectasis. Currently, the most common presentation of constrictive bronchiolitis is in the context of *chronic lung allograft dysfunction* (CLAD) after lung transplantation.[45]

Histologically, proliferative bronchiolitis is defined by the proliferation of transluminal polypoid organizing fibroblastic tissue, also known as a Masson body (see Fig. 72.4B).[46] Isolated proliferative bronchiolitis is rare, observed only in specific inhalational (e.g., nitrogen gas) exposures or localized injuries. Much more commonly, fibroblastic tissue extends from the bronchioles into adjacent alveoli. The term organizing pneumonia defines this organizing fibroblastic tissue in alveoli. Given the relatively common coexistence of proliferative bronchiolitis and organizing pneumonia, the term *bronchiolitis obliterans with organizing pneumonia* (BOOP) had been used. There is little overlap, however, between the clinical entities featuring constrictive bronchiolitis and those featuring BOOP. Furthermore, BOOP presents as a restrictive pattern on PFTs compared with the obstructive pattern seen in constrictive bronchiolitis. For these reasons, this nomenclature caused confusion and, in response to this confusion, in 2002 the American Thoracic Society and European Respiratory Society jointly recommended abandoning the term BOOP in favor of organizing pneumonia with appropriate qualifiers. When idiopathic, the term cryptogenic organizing pneumonia is used[47] (see Chapter 90). In rare situations, acute injury causing proliferative bronchiolitis may progress into constrictive bronchiolitis.

Despite this evolution in nomenclature, "bronchiolitis obliterans" continues to be used imprecisely in clinical practice and in the biomedical literature. The terms BOOP, bronchiolitis obliterans with intraluminal polyps, and bronchiolitis obliterans applied to both bronchiolitis obliterans and organizing pneumonia persist. Of importance, organizing pneumonia tends to be responsive to corticosteroid treatment, whereas constrictive bronchiolitis is typically resistant. This absence of a precise nomenclature makes studies of the epidemiology, clinical features, and treatment responsiveness of "bronchiolitis obliterans" difficult to interpret. Given the substantial differences in both etiology

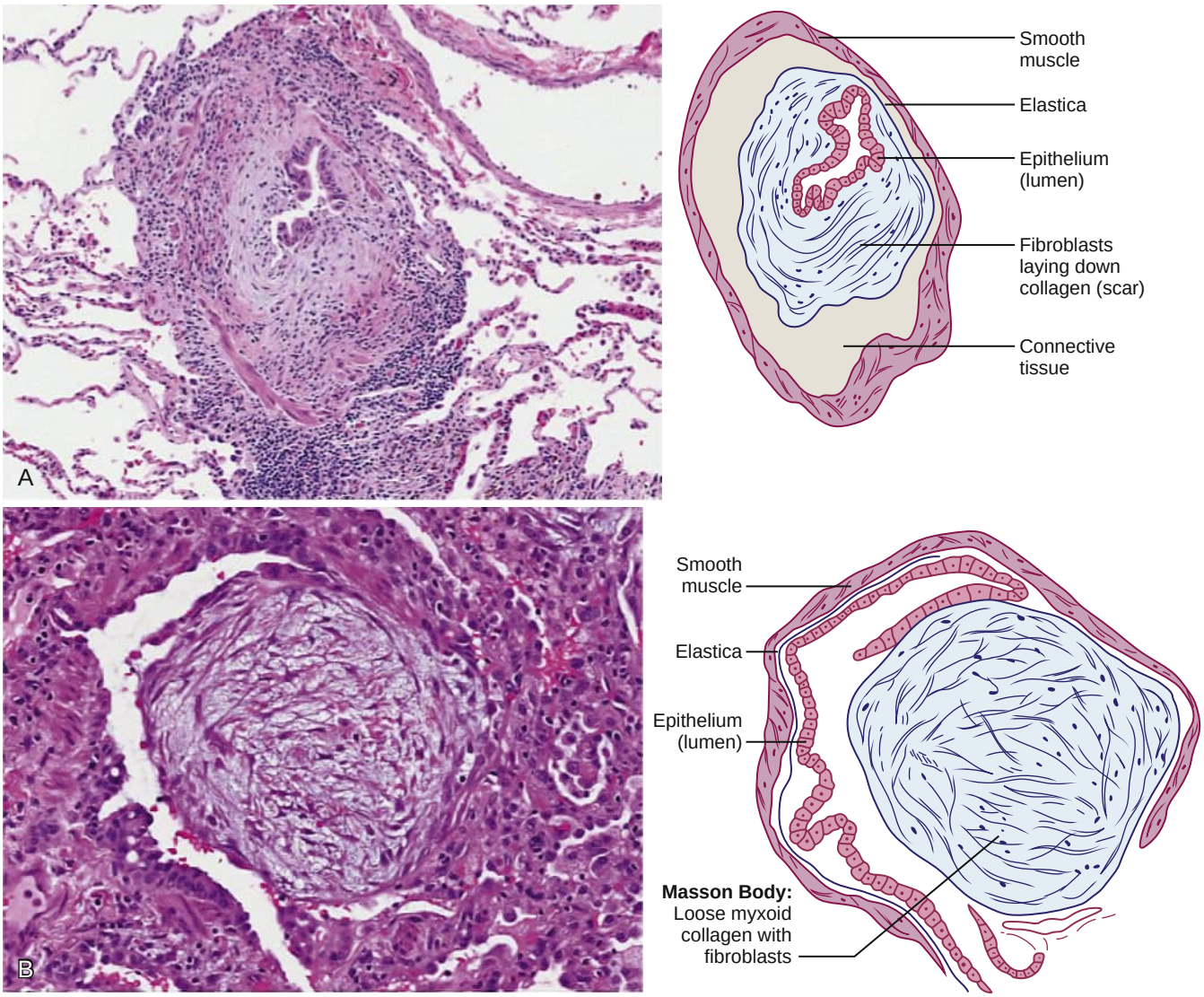

Figure 72.4 Pathologic patterns of bronchiolitis obliterans. (A) Constrictive bronchiolitis. Circumferential subepithelial intramural fibrosis is present. This fibrosis separates the normally approximated epithelium and elastica (the elastin-rich layer of the lamina propria). This scarring results in luminal constriction and narrowing, often with irreversible complete obstruction. (B) Proliferative bronchiolitis. Although the diameter of the airway remains unchanged, the functional area of the lumen is reduced by a rounded intraluminal polypoid plug of granulation tissue, extending from the subepithelium and filling the airway lumen (also known as a Masson body).

and prognosis, we favor using the terms *constrictive* and *proliferative* to define these bronchiolitis subtypes more clearly.

Although these categories are defined histopathologically, in practice, there is a lot of overlap. We will discuss the following entities, which are mostly constrictive but may exhibit proliferative features as well.

CONSTRICTIVE BRONCHIOLITIS AFTER LUNG TRANSPLANTATION (See Chapter 140)

Chronic Lung Allograft Dysfunction

Since the late 1980s, there have been steady increases in the rates of lung transplantation performed, with more than 4500 procedures worldwide in 2016. Although survival rates are improved compared with the pre-2008 era, the median posttransplantation survival is only 6.5 years.[48] The most common cause of death after the first year posttransplantation is *chronic lung allograft dysfunction* (CLAD).[49] CLAD is a clinical syndrome of obstructive or restrictive defects defined by a persistent, greater than 20% decline in *forced expiratory volume in 1 second* (FEV_1) from posttransplantation baseline, with baseline defined as the average of the two best posttransplantation FEV_1 measurements taken more than 3 weeks apart (see Table 72.1). Constrictive bronchiolitis is the most common pathologic feature in CLAD and is thought to be the main cause of decline in FEV_1, particularly for the predominantly obstructive form of CLAD, known as *bronchiolitis obliterans syndrome* (BOS). Registry data show the majority of lung transplant recipients die or develop CLAD within 4 years.[45] The presence of a total lung capacity decline of 10% or more and persistent chest CT opacifications define the restrictive allograft syndrome subtype of CLAD, for which pleural and/or parenchymal fibrotic pathology are also associated.[50]

Adding to the confusion, this terminology has changed over time. Until 2014, BOS was defined as any decline in FEV_1, without regard to *forced vital capacity* (FVC), similar to what is currently called CLAD.[51,52] From 2014 to 2019, CLAD was defined by a decline in FEV_1 *or* FVC.[53] Since 2019, BOS has been considered only the obstructive subtype of CLAD, and CLAD is diagnosed only based on FEV_1.[49] Nonetheless, even in patients meeting criteria for restrictive allograft syndrome, explant tissue typically demonstrates concomitant constrictive bronchiolitis.

Various factors can cause persistent FEV_1 loss in lung transplant recipients, thought to be unrelated to CLAD or constrictive bronchiolitis, including chest wall disease, pleural effusions, pulmonary edema, airway stenosis, obesity, aging, diaphragmatic dysfunction, native lung hyperinflation, or scarring from focal infections. For these, the consensus definition recommends a resetting of the FEV_1 baseline once such factors have been stable for 6 months.[49] Whether or not this FEV_1 baseline is reset in practice, patients with incipient CLAD should undergo an evaluation for these potential confounders, including CT scans and bronchoscopy. Chest CT can also be useful in evaluating for restrictive versus obstructive CLAD, which would be associated with fibrotic changes or air trapping, respectively[54,55] (see Fig. 72.1 and Video 140.3). Transbronchial biopsy can be used to evaluate for acute rejection pathology but only rarely demonstrates histopathologic evidence of constrictive bronchiolitis.

The onset of CLAD is variable based on donor, recipient, and environmental factors (discussed later). Patients report progressive dyspnea and, occasionally, dry cough. In advanced disease with bronchiectasis, the cough is productive. Pulmonary function tests demonstrate irreversible airflow obstruction with reduced diffusing capacity. As CLAD progresses, findings consistent with bronchiectasis may be seen.

Table 72.1 Chronic Lung Allograft Dysfunction Classification System

CLAD 0	FEV_1 > 80% of baseline*
CLAD 1	FEV_1 > 65–80% of baseline
CLAD 2	FEV_1 > 50–65% of baseline
CLAD 3	FEV_1 > 35–50% of baseline
CLAD 4	FEV_1 ≤ 35% of baseline

*Baseline is the average of the two best *forced expiratory volume in 1 second* (FEV_1) measurements that are more than 3 weeks apart but can be adjusted in the case of 6 months of stability for certain non–*chronic lung allograft dysfunction* (CLAD) causes.

Modified from Verleden GM, Glanville AR, Lease ED, et al. Chronic lung allograft dysfunction: definition, diagnostic criteria, and approaches to treatment—a consensus report from the Pulmonary Council of the ISHLT. *J Heart Lung Transplant*. 2019;38:493–503.

Chronic Lung Allograft Dysfunction Pathogenesis. Constrictive bronchiolitis is likely a final histologic lesion resulting from a failure in epithelial cell regeneration in the context of chronic, predominantly alloimmune injury (Fig. 72.5). Emerging evidence suggests that epithelial integrity requires active signaling to prevent proliferation of the adjacent mesenchyme so that when damage to the epithelium

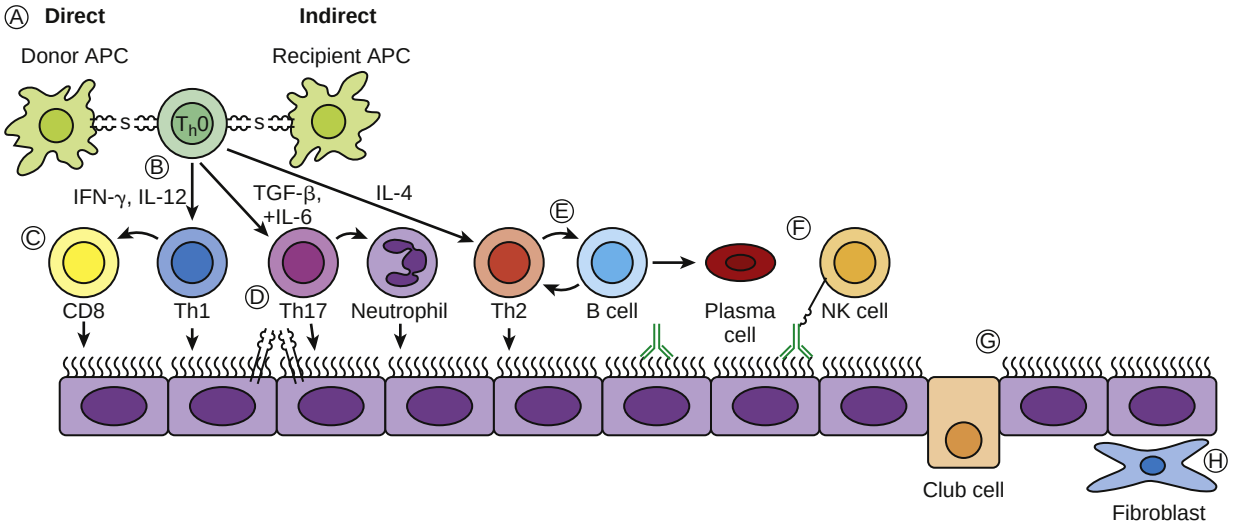

Figure 72.5 Overview of chronic lung allograft dysfunction pathogenesis. (A) Donor antigens are presented on donor *major histocompatibility complex* (MHC) (directly) or on recipient MHC (indirectly) to T cells. (B) T cells differentiate based on the local cytokine milieu into *T helper* (Th)1, Th2, or Th17 subtypes of CD4 cells and activated CD8 cells. (C) These cell types cause direct cytotoxicity in areas of vascular endothelium, manifest as A-grade rejection, and airway epithelium, termed B-grade rejection. (D) Airway injury drives epithelial cell damage responses, such as up-regulation of MHC leading to further amplification of alloimmune responses. (E) B cells interact with T cells and *antigen-presenting cells* (APCs), generating antibodies and differentiating into long-lived antibody-secreting plasma cells. (F) Antibodies also contribute to epithelial cell damage through complement fixation, direct cytotoxicity, or in concert with natural killer (NK) cells via antibody-dependent cell-mediated cytotoxicity. (G) Club cells and other cells responsible for protecting and regenerating the epithelium may initially compensate for the increased epithelial cell turnover but are eventually exhausted, particularly in the setting of compromised vasculature associated with transplantation. (H) Fibroproliferative cells may then replace denuded airway and commit the epithelium to fibrotic replacement via autocrine signaling. Of note, these steps (A–F) of chronic lung allograft dysfunction pathogenesis may not happen in this order or at all in cases. IFN-γ, interferon-γ; IL, interleukin; TGF-β, transforming growth factor-β.

exceeds its capacity for repair, profibrotic cells are activated to patch the denuded airway.[56] This biology may explain why a deficiency of club cells, cells that both protect and repopulate bronchiolar epithelium, is associated with constrictive bronchiolitis.[57,58] Other factors limiting epithelial cell regeneration, such as microvascular injury or telomere dysfunction, are also linked to CLAD risk.[59,60] Similarly, processes that result in airway injury have been linked to CLAD, including primary graft dysfunction[61]; infection with *Pseudomonas,*[62] *Aspergillus,*[63] cytomegalovirus,[64] and other viruses[65,66]; air pollution[67]; and gastroesophageal reflux.[68] Bronchioles might be particularly susceptible to potentiating effects of air pollution because the increase in cross-sectional area related to branching in the bronchiolar region results in a slowing of airflow and a preferential accumulation of airborne particles in this region.[69] Once shunted toward a fibrotic pathway, mesenchymal cells can then become self-perpetuating, further hampering restoration of normal physiology.[70]

Cellular Immune Responses. Among injury responses, alloimmune injury appears most important to CLAD pathogenesis. CLAD risk is linked to acute cellular rejection episodes.[71] Acute cellular rejection of the lung allograft is diagnosed on transbronchial biopsy specimens as perivascular lymphocytosis or lymphocytic bronchiolitis, classified as A-grade and B-grade rejection, respectively, based on *International Society of Heart and Lung Transplantation* (ISHLT) nomenclature (see Chapter 140).[72] Lymphocytic bronchitis (in the large airways) has also been associated with CLAD risk.[73,74] Severity of acute rejection appears important because untreated "minimal" or A1-grade acute cellular rejection does not appear to increase CLAD risk.[74–76]

Enhanced expression of donor *major histocompatibility complex* (MHC) antigens has also been found in bronchiolar and alveolar epithelium of lung transplant recipients with acute rejection and CLAD, likely secondary to type 1 lymphocytic inflammation.[77,78] Donor MHC antigens presenting donor self-antigen are then recognized by the recipient immune system, further propagating alloimmune responses.[79] An increasing burden of donor-recipient HLA mismatches has also been shown to be a CLAD risk factor.[80] In addition to this direct pathway of allorejection, there is also indirect antigen presentation, where recipient antigen-presenting cells present phagocytosed donor antigens.[81] Calcineurin inhibitor–based immunosuppression targets this type 1 immune response. Indeed, the clinical success of lung transplantation is coincident with the advent of calcineurin inhibitors. Of interest, although variability in tacrolimus-based immunosuppression levels has been associated with CLAD, suggesting a detrimental effect of transient lack of immunosuppression,[82] supratherapeutic immunosuppression levels are associated with increased infection risk but no change in rates of acute rejection.[83] Thus, although type 1 immune responses are potentially a potent driver of CLAD, this pathway is effectively inhibited by current immunosuppression strategies, suggesting that other pathways could be responsible for CLAD in practice.

Type 17 and, to a lesser extent, type 2 alloreactive T cell responses are also associated with CLAD and appear to be relatively resistant to calcineurin inhibitors.[84] In particular, type 17 inflammation can recruit neutrophils, and neutrophilic inflammation has been linked to early development of CLAD. A syndrome of greater than 15% neutrophils in bronchoalveolar lavage, combined with a 10% or greater decline in FEV_1, is often reversible with azithromycin treatment, at which point it is termed *neutrophilic reversible allograft dysfunction* (NRAD).[85] Clinical features of NRAD overlap with lymphocytic airway inflammation, which is associated with IL-17 and can reverse after azithromycin treatment.[86] Mechanistically, tacrolimus paradoxically increases the IL-17–dependent production of the neutrophil chemoattractant chemokine IL-8 by airway smooth muscle cells, and this effect can be reversed by azithromycin.[87]

Humoral Immune Responses. Lung transplant recipients may develop antibodies to donor HLA antigens. The de novo development of *donor-specific antibodies* (DSAs), in particular to HLA-DQ, has been linked to more rapid onset of CLAD.[88] A syndrome of *antibody-mediated rejection* (AMR) can manifest as obstructive or restrictive pulmonary function defects; histopathologic features of neutrophil margination, capillaritis, and/or arteritis; complement component 4d deposition on alveolar capillaries; and serologic evidence of DSA. Although some patients present with indisputable AMR, diagnostic uncertainty is common. Thus the ISHLT definition of AMR groups patients into "definite," "probable," and "possible" categories based on the presence of allograft dysfunction and four, three, or two of the following features, respectively: DSA, complement component 4d staining on lung biopsy, compatible lung histology, and exclusion of other causes.[89] Even within this definition, there is disagreement on the criteria for the component features.

Lung transplant recipients with severe AMR have substantial morbidity. Thus, some lung transplantation centers have treated de novo DSA and AMR with combination therapy that includes some or all of the following: corticosteroids, intravenous immunoglobulin, plasmapheresis, monoclonal antibodies to the B cell antigen CD20, proteasome inhibitors, and complement inhibitors.[90] However, there are no randomized controlled trial data to guide therapy. Although clearance of DSA with therapy is associated with freedom from BOS,[91] it is not clear that interventions that result in DSA clearance improve outcomes.[92,93] Crosstalk between alloreactive type 2 and follicular helper T cells and B cells via cytokines and costimulatory molecules results in B cell activation and differentiation into plasma cells. Thus, persistence of DSA may also be a biomarker for alloimmune responses more broadly.

Other Immune Responses. Autoimmune responses may also contribute to the development of CLAD. Lung injury may expose self-antigens that would otherwise be masked from the immune system. Type V collagen and K-α1 tubulin, in particular, are expressed in small airway epithelial cells and exposed during rejection and lung remodeling. Autoantibodies to these proteins are risk factors for CLAD in humans.[94] In rodent models, these autoantibodies can be induced by anti-MHC antibodies, and induction of tolerance to type V collagen can protect from allograft rejection in rodent models.[95]

Finally, innate immune responses play key roles in potentiating adaptive immune responses in the context of lung transplantation. Single nucleotide polymorphisms in innate immune genes, such as *toll-like receptor 4* (TLR4), have been linked to CLAD.[96] Natural killer cells are postulated to play important roles in both amplifying and dampening alloimmune responses, in primary graft dysfunction, in AMR, and in responses to infections.[97]

BRONCHIOLITIS OBLITERANS SYNDROME AFTER ALLOGENEIC STEM CELL TRANSPLANTATION

Although a mismatch between lung and immune system MHC antigens is present in both lung transplantation and allogeneic stem cell transplantation, constrictive bronchiolitis appears less frequent after the latter. In the context of allogeneic stem cell transplantation, the clinical syndrome of constrictive bronchiolitis is termed BOS, and the distinction between restrictive and obstructive forms of chronic lung dysfunction is not generally addressed. The comparison between these two contexts of BOS is complicated by differences in definitions, however. Pulmonary *graft-versus-host disease* (GVHD) resembles constrictive bronchiolitis histologically after lung transplantation. However, surgical lung biopsies are rarely performed to confirm the diagnosis, given the potential surgical risk. Thus, pulmonary GVHD is generally diagnosed as the clinical syndrome termed BOS.

BOS was defined in a 2014 consensus statement by the presence of all four of the following criteria: (1) an obstructive FEV_1/slow vital capacity ratio, (2) FEV_1 less than 75% of predicted with a 10% or greater decline over 2 years, (3) absence of infection, and (4) either evidence of extrapulmonary GVHD or evidence of air trapping by CT or spirometry.[98] With this definition, one study estimated the prevalence of GVHD at about 10% at 36 months after transplantation.[99] Other studies suggest a prevalence of as low as 2–3% at a similar time point after transplantation.[100] More liberal pulmonary GVHD diagnostic criteria have been proposed. For example, post–stem cell transplantation airflow obstruction, defined as greater than 5% per year decline in FEV_1 and minimum FEV_1/FVC of less than 0.8, has a reported prevalence of 26%.[101]

BOS is usually preceded or accompanied by typical findings of GVHD: mucositis, esophagitis, and/or skin rash.[102] Four to 6 months after the onset of GVHD, patients may develop dyspnea and a nonproductive cough that may be severe and rapidly progressive. Physical examination may reveal scattered wheezing and frequently bibasilar crackles. Hypoxemia is common.[100] Spirometry and radiographic findings are similar to those observed in BOS in lung transplantation.

Extrapulmonary GVHD, including skin, gastrointestinal, or hepatic inflammation, is the most significant risk factor for BOS. Other risk factors include a busulfan-containing preparative regimen, stem cells from the peripheral blood, viral infections, lung disease pre–stem cell or post–stem cell transplantation, and ABO blood type incompatibility.[103] Its rarity after autologous stem cell transplantation implies an association with alloimmune responses, but the pathogenesis remains incompletely understood. Quarterly spirometry for at least 1 to 2 years after allogenic stem cell transplantation and with new manifestations of GVHD can aid in early identification of BOS.[103] Mild declines in FEV_1 can be treated with inhaled corticosteroids with or without an inhaled β_2-agonist. With the diagnosis of BOS, treatment with a tapered steroid burst and initiation of fluticasone, azithromycin, and montelukast ("FAM") treatment are recommended.[104] Calcineurin inhibitors, lymphocyte proliferation inhibitors (e.g., mycophenolic acid), or sirolimus for systemic GVHD are generally continued. Additional therapies, including extracorporeal photopheresis and etanercept, have been added in cases of continued progression, without clear evidence of efficacy.[103] A trial of azithromycin for the prevention of post–stem cell transplantation GVHD was stopped early because of increased mortality attributed to the risk of hematologic relapse, so prophylactic azithromycin is generally not recommended.[105]

BRONCHIOLITIS OBLITERANS AND CONNECTIVE TISSUE DISEASES

Constrictive bronchiolitis may present uncommonly with connective tissue or collagen vascular diseases, in particular, rheumatoid arthritis.[106] It predominantly affects women who are at least 10 years out from a rheumatoid arthritis diagnosis. Patients present with rapid onset of progressive dyspnea, nonproductive cough, and spirometric evidence of airflow obstruction. In a case series, all-cause mortality was 27% over a median follow-up of 5 years, with FEV_1 stabilization achieved in the context of (although not necessarily because of) steroids, macrolide antibiotics, and other immunosuppression therapies.[107] Cases of constrictive bronchiolitis have also been reported with Sjögren syndrome.[108] Older literature linking bronchiolitis obliterans and other connective tissue diseases frequently refers to BOOP which, as discussed earlier, is a distinct pathobiology.

BRONCHIOLITIS OBLITERANS AFTER INFECTION

Although acute infectious bronchiolitis is common in children, postinfectious bronchiolitis obliterans is quite rare. The syndrome is defined by persistent airway obstruction, as assessed by symptoms, imaging, and spirometry, subsequent to a lower respiratory tract infection and unresponsive to at least 2 weeks of steroids and bronchodilators.[109] Despite similarity in the names, this disease entity appears distinct from acute bronchiolitis. Postinfectious bronchiolitis obliterans is most common in South America and linked to adenovirus infection, rather than respiratory syncytial virus infection. This epidemiologic difference has been linked to more potent T helper type 1 immune responses associated with adenoviral infection.[110] There are no well-controlled studies to guide management of these patients. Although lung function generally improves in pediatric patients, defects may persist.[111]

BRONCHIOLITIS FROM INHALED OR INGESTED TOXINS

A generalized inflammatory response of the peripheral airways may follow inhalation of toxicants in gases, vapors, fumes, or aerosols (see Chapter 103). The location of damage is determined in part by the toxicant solubility. Highly soluble irritants, such as sulfur dioxide and ammonia,

dissolve in the lining fluid of the upper airway, causing damage primarily there. Less soluble gases, such as oxides of nitrogen, are able to pass into and therefore damage the peripheral airways.[112] Such exposures continue to represent significant industrial and environmental hazards.[113] Nitrogen dioxide for example, may be found in silo gas (silo filler's disease), jet and missile fuel, metal pickling fumes, and certain fires. Exposure results in an acute respiratory distress syndrome that evolves to proliferative bronchiolitis.[114] Acutely, patients may develop cough, dyspnea, cyanosis, hemoptysis, hypoxemia, and loss of consciousness. These symptoms and signs may last hours to weeks before resolving. Corticosteroid therapy is frequently used in the initial management, based on limited evidence.[113] Although most patients recover, some may die from respiratory failure. Finally, some patients develop irreversible obstructive abnormalities 2 to 8 weeks after exposure. Persistent obstruction may even be seen in patients who had no initial illness. Rather, these patients typically have a gradual onset of dyspnea and nonproductive cough that may progress to respiratory failure and death.[115]

Diacetyl and other alpha-diketones used in flavoring food have been linked to proliferative and constrictive bronchiolitis (see Fig. 72.2). These fumes are a particular risk in occupational settings where these chemicals are heated or powdered. In popcorn manufacturing, diacetyl-related constrictive bronchiolitis is termed popcorn lung.[116] Exposed workers are at increased risk for obstructive lung disease that may present with cough, wheeze, or dyspnea.[117] Diacetyl may directly activate fibroproliferative pathways in airway epithelial cells[118] or initiate autoimmune responses through hapten formation.[119] Diacetyl is found in many consumer products, including electronic cigarettes, although constrictive bronchiolitis from exposures outside of industrial settings appears extremely unusual.[116] Minimizing exposure and spirometric screening are reasonable prevention strategies.

Constrictive bronchiolitis has been reported through military exposures. A cohort of Iranian soldiers exposed to mustard gas during the Iran-Iraq war were found to have an increased frequency of chronic respiratory symptoms; a subset of these were diagnosed with constrictive bronchiolitis based on HRCT and, in some cases, lung biopsy. Minimal progression of obstruction was observed on spirometry, with a regimen including inhaled corticosteroid and long-acting β-agonist, azithromycin, and *N*-acetylcysteine.[120] A cohort of soldiers from the United States with otherwise unexplained dyspnea had a high prevalence of constrictive bronchiolitis based on surgical lung biopsy,[121] but subsequent studies have not confirmed this association.[122]

A number of other inhaled and ingested toxins have been linked to constrictive bronchiolitis. Treatment with penicillamine and gold have been linked to constrictive bronchiolitis, although in some cases it may be difficult to distinguish between medication effect and underlying disease.[123] *Sauropus androgynus*, a leafy vegetable popular in Asia and ingested for its slimming properties, has been linked to hundreds of cases of constrictive bronchiolitis.[124] Inhalational exposure during preparation of fiberglass with polymer resin and methylethyl ketone peroxide catalyst has been attributed as the cause of constrictive bronchiolitis among boat workers.[125]

TREATMENT OF CONSTRICTIVE AND PROLIFERATIVE BRONCHIOLITIS

Therapies to reverse the small airway remodeling observed in constrictive bronchiolitis have been largely ineffective. However, therapies to prevent progression of injuries preceding constrictive bronchiolitis have met with some success. In the case of exposure to toxic fumes, for example, corticosteroid therapy for organizing pneumonia or fibroproliferative bronchiolitis appears helpful.[126] In other contexts outside of lung transplantation, a trial of corticosteroids should be considered when there is evidence of these inflammatory bronchiolitis pathologies. If a response is identified, the corticosteroid should be continued for at least 2 to 3 months, then reduced slowly, to minimize the likelihood of relapse. In some cases it may be necessary to continue low-dose or alternate-day therapy for months or years.[127]

In the case of CLAD, azithromycin therapy has demonstrated efficacy in preventing progression and reversing acute airflow obstruction in a randomized trial.[128] This is thought to be particularly true for the subset of patients with NRAD; however, reversal of airway neutrophilia is not consistently linked to efficacy. Separately, prophylactic treatment with azithromycin started at the time of discharge from the initial transplantation was shown to be protective against CLAD development.[129] However, another trial of prophylactic azithromycin did not find evidence of protection from CLAD.[130] Together, these data suggest that macrolide therapy can be important for a subset of lung transplant recipients, but its efficacy for CLAD is modest when compared with its efficacy for diffuse panbronchiolitis.

Substantial attention is paid to identifying and treating other patient-specific risk factors for CLAD. Examples include surveillance bronchoscopy for acute rejection,[131] cytomegalovirus-specific antiviral prophylaxis,[132] reducing aspiration through lifestyle modifications and gastric fundoplication,[133] and treatment of certain community-acquired respiratory viral infections.[134–136]

Intensified corticosteroids do not improve outcomes for lung transplant recipients with CLAD. Of 30 lung transplant recipients randomized to the leukotriene inhibitor monteleukast for CLAD, there was no overall benefit. Additional studies will be needed to determine whether certain subsets, such as those with milder airway dysfunction, might be more likely to benefit.[137] Extracorporeal photopheresis has been used to treat patients with CLAD but without high-quality evidence, and this therapy is the subject of an ongoing clinical trial.[138] Hydroxymethylglutaryl coenzyme A reductase inhibitors have been investigated for CLAD with mixed results.[139] Although there is little evidence that smooth muscle contraction plays a significant role, β-adrenergic agonists are frequently attempted to provide symptomatic relief. Lung transplantation is an option for some patients with CLAD and other forms of constrictive bronchiolitis.[140] After retransplantation, median CLAD-free survival is about 1 year less than after primary transplantation, based on registry data.[141]

Bronchopulmonary dysplasia, which has some features of bronchiolitis, is discussed at ExpertConsult.com.

BRONCHOPULMONARY DYSPLASIA

Bronchopulmonary dysplasia (BPD) is a respiratory complication of premature birth. Since the first description of BPD in 1967,[142] the management of prematurity has evolved, including the use of antenatal glucocorticoids, perinatal surfactant, and modified mechanical ventilation. This evolution has resulted in different clinical and histopathologic entities termed "old" and "new" BPD.

Old BPD was identified in newborn babies with infant respiratory distress syndrome after prolonged treatment with high concentrations of inspired oxygen and positive-pressure ventilation.[143] Characteristic histologic features include unusual abnormalities of the bronchioles, including marked metaplasia, obliteration, and cystic changes.[144] The entity also has been described in adults after acute respiratory distress syndrome[145] and may be more frequent than is currently recognized. The pathologic process includes significant fibrosis of alveolar septa and resembles the honeycombing seen in other fibrotic interstitial lung diseases.[144,146]

New BPD is clinically milder and probably reflects developmental arrest in an immature lung rather than barotrauma and oxygen toxicity.[147] It may be the result of the contemporary management of premature infancy, which has improved survival of increasingly immature infants.[148,149] Histopathologic examination reveals enlarged air spaces with simplified alveolar and alveolar-capillary development. Unlike in the original disease, airway abnormalities are uncommon.[149]

Key Points

- Because of the large cross-sectional area of the peripheral airways, symptoms and physiologic changes of diseases involving the peripheral airways develop late in disease and can be silent.
- Bronchiolitis can be broadly categorized into inflammatory, proliferative, or constrictive subtypes.
- Inflammatory and proliferative bronchiolitis are more likely than constrictive bronchiolitis to be reversible or respond to immunosuppression. Certain bronchiolitis subtypes respond to macrolide antibiotics, especially diffuse panbronchiolitis and neutrophilic reversible allograft dysfunction.
- Constrictive bronchiolitis is the dominant pathology in chronic lung allograft dysfunction. Chronic lung allograft dysfunction is the major long-term limitation to survival after lung transplantation and appears to reflect multiple immune and nonimmune pathobiologies.
- Bronchiolitis obliterans after allogeneic stem cell transplantation results from chronic graft-versus-host disease.

Key Readings

Barker AF, Bergeron A, Rom WN, Hertz MI. Obliterative bronchiolitis. *N Engl J Med*. 2014;370(19):1820–1828.

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SECTION I

NEOPLASMS OF THE LUNG

73 LUNG CANCER: MOLECULAR BIOLOGY AND TARGETS

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INTRODUCTION

Our understanding of lung cancer development has dramatically expanded in the past 20 years. We now understand how *stochastic* (random) events affect the airway epithelium and how they set the stage for a series of processes leading the cells to transformation and invasion of the microenvironment. The hallmarks of cancer have been described[1–4] (Table 73.1) to help understand how cancers evolve to survive and circumvent a series of key regulatory processes. This chapter considers key processes relevant to lung cancer progression. Some of these processes remain largely unknown, such as the mechanisms underlying and linking metabolic reprogramming of the airway epithelium, promotion of genomic instability, and suppression of T cell antitumor function via immune evasion. This discussion includes how point mutations can activate oncogenes or inactivate tumor suppressor genes leading to *driver* mutations that give selective advantage to tumor cells or become *passenger* mutations irrelevant to the progression of the tumor. A series of new concepts (Table 73.2) is examined, including how clonality of the tumorigenic process and tumor evolution over time (including subclonal populations) are being studied to understand the natural history and heterogeneity of tumors. At the same time, the complexity, redundancy, and heterogeneity of these pathways make mutational targeting in *non–small cell lung cancer* (NSCLC) a moving target. Precision medicine-based treatment is successful only in a subset of lung tumors. This indicates the need to characterize clinically related molecular tumor phenotypes, especially those related to driver mutations in tumor suppressor genes and oncogenes.

MOLECULAR BIOLOGY

CARCINOGENS

Both environment carcinogen exposure and natural toxic by-products of cell metabolism cause mutations that lead to cancer. As discussed in Chapter 74, many carcinogens have been studied for their effects on cellular fate. The best understood are tobacco carcinogens and their effect on DNA. Among the many components in tobacco smoke, and in outdoor and indoor air pollution, are *polycyclic aromatic hydrocarbons* (PAHs). Long-term exposure to PAHs may cause lung cancer. PAHs induce phase I metabolic enzymes (e.g., CYP1A1) and phase II enzymes (e.g., glutathione S transferases) that lead to the formation of active carcinogens, such as

Table 73.1 Hallmarks of Cancer

Established 2000[1]	Added in 2011[2]
Sustained proliferation	Metabolic reprogramming
Evasion of tumor suppressors	Genomic instability
Invasion and metastasis	Tumor-promoting inflammation
Replicative immortality	Immune evasion
Angiogenesis	
Resisting apoptosis	

Table 73.2 Key Concepts in Cancer Biology

Clonal and subclonal evolution
Driver mutations
Epithelial to mesenchymal transition
Field of cancerization
Glutamine addiction
Lung cancer stem cells
Mutation signatures
Neoantigens
Spatial and temporal tumor heterogeneity
Immune evasion

diol-epoxides and radical cations. These reactive metabolites produce *DNA adducts*, which are portions of DNA bound to a carcinogenic chemical. Such adducts cause DNA mutations, alterations in gene expression, and eventually tumorigenesis.[5] DNA adducts can alter chromatin structure. They alter the transcription of genes that modify epithelial biology and microenvironment. Key mutations in xenobiotic metabolic enzymes (involved in metabolism and elimination of potentially toxic compounds) as well as the tumor suppressor gene *TP53* and DNA repair machinery are clearly associated with susceptibility to lung cancer. The exact mechanism of action for tumor induction remains unclear. We know that PAHs are metabolized by multiple enzymes into metabolites such as BP-7,8-dihydrodiol-9,10-epoxide that will react with DNA to produce adducts. Specific adducts can cause mismatches in DNA replication and alter promoter methylation and/or binding.[6] These PAHs can also induce formation of protein adducts that trigger elevation of reactive oxidant species that affect DNA, lipids, and proteins as well as their oxidative states to cause altered gene regulation and protein function, leading to carcinogenesis. Much work is being done in an attempt to understand how mixtures of PAHs contribute to tumorigenesis. For example, one potential mechanism involves aryl hydrocarbon receptor–dependent versus –independent pathways because they induce epigenetic alterations that may ultimately regulate the immune response during lung cancer development.[7]

METABOLIC REPROGRAMMING

Tumorigenesis is dependent, at least in part, on the reprogramming of cellular metabolism, which itself is a consequence of oncogenic driver mutations. Metabolic reprogramming constitutes one of the 10 hallmarks of cancer development.[2] We propose that these metabolic derangements predispose cells to develop genomic instability, as discussed below. It is well known that oncogenic drivers regulate metabolic programs and that these oncogenic events need to be supported via increased access to energy facilitated by a bioenergetic upgrade. Deregulated uptake of glucose and amino acids such as glutamine plays a central role in cancer cell reprogramming.[8,9] The tumorigenic process requires enablers such as glutamine and metabolic support to meet increased biosynthetic demand. Glutamine addiction has been recently recognized as a new therapeutic target in cancer.[10] Preliminary studies suggest that metabolic reprogramming happens early in tumorigenesis, while the epithelium still appears normal but demonstrates a number of epigenetic (DNA methylation) and genetic alterations.[11] These alterations may be the consequence of metabolic reprogramming that favors glutamine uptake and that promotes chromosomal instability. Chromatin-modifying enzymes mediate DNA methylation and histone modifications upon recruitment to specific target gene loci in response to various stimuli.[12] In sum, metabolic pathways are reprogrammed early on in the airway epithelium, which may lead to epigenetic alterations and ultimately contribute to genomic instability.

GENOMIC INSTABILITY

Genomic instability refers to the increased propensity to acquire alterations in the genome. It is another hallmark of cancer development[13] and is characteristic of most solid tumors. In hereditary cancers, however, genomic instability results from mutations in DNA repair genes; in sporadic cancer, the mechanism is not well understood.[14] Genomic sequencing data suggest that sporadic carcinogenesis is not due to mutations in either DNA repair genes or mitotic checkpoint genes. Thus, genomic instability in human cancers may be linked to some other mutagenic factor, such as carcinogens or oncogene-induced DNA damage. Genomic instability happens early in tumor development. Multiple specific alterations have been recognized in the at-risk airway epithelium (Figure 73.1), including DNA adducts, DNA methylation,[15] chromatin structure alterations, chromosomal alterations, copy number gains and losses,[16,17] point mutations, expansion of microsatellite regions (a marker of faulty mismatch repair), gene expression alterations,[18] proteomic changes,[19–22] and metabolic changes.[11,23] DNA can be damaged by intrinsic (e.g., germline defect) and extrinsic (e.g., tobacco) mechanisms. Failure of repair, replication, chromosomal segregation mechanisms, and cell cycle checkpoint control may lead to chromosomal, microsatellite, and nucleotide instability.[24]

Cancer starts with mutations in somatic cells, leading to genomic instability and cell transformation. Transformation is followed by dysregulated growth, morphologic remodeling, and changes in metabolism. Genomic instability can also be tracked following spatial and temporal evolution of the genomic changes during tumor progression.[25] Sequencing multiple regions of NSCLCs, researchers have found evidence of branched evolution (subclonal), suggesting truncal mutations are common in the creation of the original malignant clone.

Driver mutations arise before and after progression of the tumor in the form of branches on a tree corresponding to subclones, with unique *driver* (oncogenic) and *passenger* (not functionally relevant) mutations. Environmental carcinogens induce lung cancer by increasing the rate of mutations in airway epithelial cells. The chemical properties of carcinogens

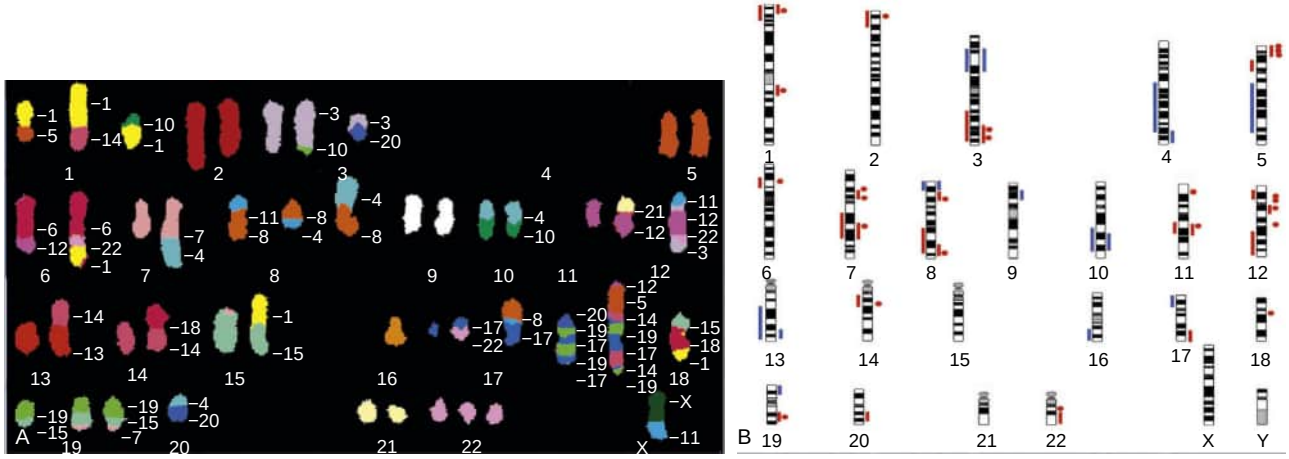

Figure 73.1 Chromosome and genomic changes in lung cancer. (A) Spectral karyotyping of a lung adenocarcinoma showing numerous numerical and structural chromosome changes. In this image, each color is specific to a certain chromosome; therefore, the chromosomes with two or more colors demonstrate rearrangements. In translocations, the origin of the genetic material is listed on the right of the chromosomes. (B) Summary of genomic imbalances reported in lung cancer. Small cell lung cancer is represented on the left of the chromosome idiograms; non–small cell lung cancer is represented on the right. Copy number gain is represented by *red bars*, focal amplification by *red dots*, and copy number loss by *blue bars*. (From Varella-Garcia M. Chromosomal and genomic changes in lung cancer. *Cell Adh Migr*. 2010;4[1]:100-106.)

direct their interaction with DNA, leading to recurrent and recognizable patterns of mutations in the genome called *mutation signatures*.[26] These have been reconstructed from statistical analyses of cancer genomes in smokers[27] and in *small cell lung cancer* (SCLC) in smokers.[28] The contribution of each signature to the mutational profile of individual cancer reveals associations with tobacco exposure and defective DNA maintenance processes such as mismatch repair mechanisms.

Identification of mechanisms underlying oncogenic transformation in epithelial cells remains a major challenge in cancer biology. Gaining insights into early tumor formation is also key to the development of chemopreventive strategies. The influence of smoking status in the clonal history of the tumors is important. The smoking mutation signature (signature 4) is characterized by a high proportion of C→A transversions.[26] Yet, over time, tumors from former and current smokers have shown a decrease in the proportion of C→A transversions in subclonal mutations compared to early clonal mutations, which suggests a relative decrease in the mutational burden attributed to smoking during tumor development.[25,29] The decrease in C→A transversions was followed by an increase in C→T and C→G mutations, which indicates *apolipoprotein B mRNA editing enzyme, catalytic polypeptide-like* (APOBEC) activity.[26] APOBEC proteins are a group of cytidine deaminase enzymes associated with tumor heterogeneity and genome doubling.[30] Doubling of the genome leads to aneuploidy and subsequent chromosomal aberrations and genomic instability. This chromosomal instability mediates tumor heterogeneity and is associated with an increased risk of recurrence or death, as shown in the Tracking Non–Small-Cell Lung Cancer Evolution Through Therapy Consortium.[29] This also suggests that APOBEC mutagenesis may be playing a role in subclonal expansion in these tumors.

The effect of smoking on tumor development can be quite delayed and manifest only after late mutations allow them to emerge. Prolonged tumor latency after smoking has been identified in several studies. In a study conducted by De Bruin and colleagues, a tumor from a patient who stopped smoking 20 years before surgery bore the smoking signature in more than 30% of truncal mutations, which suggests that these events took place within a smoking tumorigenic setting more than 20 years ago.[25] Likewise, Jamal-Hanjani and colleagues reported seven patients who, although they had stopped smoking for several years before surgery, presented with a smoking mutational signature suggesting tumor latency for several years before the cancer manifested.[29] There was an association between the proportion of subclonal genomic alterations and recurrence.[29,31] Finally, many late driver mutations, which correspond to alterations reported in other tumor types, are involved in genome maintenance processes such as DNA damage response, chromatin remodeling, and histone methylation. These late mutations may remove constraints on the neoplastic genome, providing advantages to the emerging subclones, and enabling progression to later stages of the disease.[29]

DNA DAMAGE RESPONSE

The *DNA damage response* refers to the process by which the cell maintains the integrity of the genome after insult. This response engages critical enzymatic activity to recognize DNA damage and correct it. A robust DNA damage response suppresses cancer, whereas a failure in the response has been associated with cancer development. The largest *attributable risk* (i.e., risk explaining the outcome) to lung cancer development at the molecular level is the acquisition of mutations in oncogenic pathways. Mutations happen stochastically over time in the airway epithelium and may eventually modify critical signaling pathways.[32]

The most common DNA lesions from tobacco smoke exposure are DNA adducts (as discussed above) and secondary mutations, *reactive oxygen species* (ROS)-dependent formation of 8-oxo-deoxyguanosine, formation of DNA single and double-strand breaks and phosphorylated histone 2AX foci. Phosphorylated histone 2AX foci can be used as a simple assay indicative of DNA double-strand breaks. These alterations are repaired specifically by 8-oxoguanine glycosylase and base excision repair. A slight infidelity in the DNA replication and repair machinery can lead to a GC to TA *transversion*, a very common somatic mutation in cancer.

(A mutational *transition* is the substitution of similarly shaped bases [e.g., a purine for a purine] whereas a *transversion* is the substitution of differently shaped bases [e.g., a purine for a pyrimidine]). DNA damage may trigger apoptosis or lead to erroneous replication of the damaged DNA, causing mutations. Targeted or whole-exome sequencing can quantify genomic alterations.[33] Deregulated expression of DNA repair proteins, such as *poly (ADP-ribose) polymerase* (PARP), involved in single-stranded DNA break repair, has been studied in lung cancer as a possible biomarker and clinically useful target. Extensive DNA damage can lead to the depletion of intracellular NAD^+ and energy depletion–induced necrosis. PARP is specifically cleaved by caspases, preventing DNA repair and promoting apoptosis. PARP-1 is involved in base excision repair and has targeted therapies available[34] to destroy cancer cells by a *synthetic lethal approach* (i.e., when a combination of deficiencies in the expression of two or more genes leads to cell death; a deficiency in only one of these genes does not).

HOST TUMOR INTERACTION AND INFLAMMATION

Lung cancer can arise from a background of chronic inflammation. Chronic inflammatory mediators favor carcinogenesis, tumor growth, invasion, and metastasis. They can also deplete immune mechanisms that might limit tumor growth. The link between cancer and inflammation depends on pathways controlled by transcription factors such as nuclear factor-κB, STAT-3, and HIF-1 and on accumulation of tumorigenic factors in tumor cells and their microenvironment. STAT-3 and nuclear factor-κB boost tumor-associated inflammation, which can suppress antitumor immune responses. *Interleukin* (IL)-1, IL-6, tumor necrosis factor, and prostaglandin synthases enhance the inflammatory milieu by modulating the expression of tumor-promoting factors. Cancer may be an inflammatory disease after all.

The well-established link between inflammation and lung cancer risk is based on strong epidemiologic evidence that COPD confers a risk for lung cancer independent of smoking history.[35–37] Inflammation gene expression signatures are clearly associated with risk for lung cancer.[18,38,39] The reason some smokers develop COPD, some develop lung cancer, and some develop both diseases remains unclear.[40] Cigarette smoke contains high concentrations of oxidants and ROS together with thousands of different types of particles. Nuclear factor-κB activation and subsequent transactivation of inflammation-related genes appear to play a central role in both COPD and cancer.[41] How some smokers remain free of disease while others develop COPD or cancer may be determined by the activation of specific genes in response to cigarette smoke.[39]

Toll-like receptors (TLRs), which recognize a variety of pathogen-associated molecular patterns, are key to the initiation of the innate and adaptive immune responses. Recent evidence shows that functional TLRs are also expressed on a wide variety of tumors, suggesting that TLRs may play important roles in tumor biology, and are being evaluated as therapeutic targets.[42,43] Activation of tumor cell TLRs not only promotes tumor cell proliferation and resistance to apoptosis but also enhances tumor cell invasion and metastasis by regulating metalloproteinases and integrins. Moreover, the activation of TLR signaling in tumor cells induces the synthesis of proinflammatory factors and immunosuppressive molecules, which enhances the resistance of tumor cells to cytotoxic lymphocyte attack and leads to immune evasion. Thus, the neoplastic process may usurp TLR signaling pathways to advance cancer progression, which suggests that targeting tumor TLR signaling pathways may open novel therapeutic avenues.

Inflammation and tumor-infiltrating inflammatory cells have been shown to induce and help sustain tumor angiogenesis and sustain cellular proliferation.[44] In lung cancer, the chronic airway inflammation of COPD provides support for tumor growth.[45] Chemokines, or inflammatory cytokines, predispose to cancer by activating multiple pathways of tumor progression, including leukocyte recruitment and function, cellular senescence, tumor cell proliferation and survival, invasion, and metastasis.[46] *KRAS*-mutated models have also contributed to a better understanding of this process, because the inflammatory process accounts for immune evasion and aggressiveness of *KRAS*-mutated carcinoma.

Finally, early in tumorigenesis, major histocompatibility complex-1 antigen presentation is down-regulated at the tumor cell surface and becomes functionally impaired, which significantly weakens the ability of $CD8^+$ cytotoxic T lymphocytes to recognize the tumor cells.[47] In addition, *human leukocyte antigen* (HLA) *loss of heterozygosity* (LOH; loss of one functional allele) increases in the progression from adenocarcinoma in situ/minimally invasive adenocarcinoma to lung adenocarcinoma and correlates with loss of chromosome 6p.[48] HLA LOH is found in 40% of NSCLCs and is associated with high subclonal burden of *neoantigens* (i.e., novel antigens specific to the tumor), APOBEC-mediated mutagenesis, upregulation of cytolytic activity, and PD-L1 positivity.[49] The ability of a cancer cell to present neoantigens on its cell surface is required for a tumor-specific T cell–mediated antitumor immune response and successful cancer immunotherapies.[50] Tumor neoantigens are recognized by specific T cell receptors in the context of major histocompatibility complex molecules. They can arise from altered proteins as a result of mutations or from viral proteins. The impairment of tumor neoantigen presentation as a consequence of LOH in HLA class I has been suggested as a mechanism of immune evasion in NSCLC.[49] In that study, both lung adenocarcinomas and squamous cell carcinomas with HLA LOH acquired a higher mutational burden compared to tumors without HLA LOH, with a significant increase in subclonal mutations. Furthermore, tumors harboring HLA LOH were enriched in neoantigens predicted to bind the missing HLA alleles and expressed high PD-L1 staining on immune cells. Thus, HLA LOH may facilitate the subclonal expansion of cells harboring previously antigenic mutations that have become undetectable to the immune system. Taken together, these results suggest that a malignancy derived from epithelial cells needs to be considered as a process taking place within the tissue microenvironment, not within individual cancer cells, and that characterizing HLA LOH may have implications in immunotherapeutic approaches targeting neoantigens.

CELL OF ORIGIN

The study of the cell of origin aims to determine how cancer-initiating stem cells continuously renew and seed distant

sites and to understand the role of these cells in resistance to chemotherapies. Searching for the lung cancer cell of origin is highly controversial because true lung stem cells are still undefined in vivo, although basal cells,[51] club cells, and alveolar type II cells[52] are presumably responsible for the maintenance of the lung epithelium. Putative stem cell populations are identified with pluripotency markers like OCT4, NANAOG, SOX2, and KLF4.[53] Depending on the location in the airways, stem cells may vary. Proximally, the pseudostratified airway epithelium provides most of the cells explaining the development of squamous cell carcinoma. The exact phenotype and precursor have not yet been established, although basal cells are the presumed culprit. Cells expressing cytokeratin 5, cytokeratin 14, nerve growth factor receptor, and TP63 appear to maintain a risk of tumor development after smoking cessation, and we suspect some subpopulations of these cells are the precursors of tumors in the large airways.

Lung cancer primary stem cells are characterized by the expression of markers such as CD133, ALDH1A1, of higher levels of ABC transporters,[54] or of lung developmental pathways such as NOTCH and SHH. These cells have been shown to be tumorigenic and to possess clonogenic activity.[55] Identifying such progenitor cancer cells may uncover therapies to target these populations specifically.

SCLC is thought to develop from pulmonary neuroendocrine cells in the lung. The best evidence for this is from mouse studies in which Rb and p53 are deleted in specific cell types.[56,57] Mouse SCLCs often arise in the lung epithelium, where neuroendocrine cells are located, and the majority of early lesions are composed of proliferating neuroendocrine cells. Mice in which Rb and p53 are deleted in a variety of non-neuroendocrine lung epithelial cells do not develop SCLC.[58] Song et al. developed a genetic tool whereby a fusion protein was expressed specifically in the pulmonary neuroendocrine cells in mice, enabling manipulation of gene activity and lineage tracing of these cells. These cells were shown to form focal tumors with loss of *p53* and *Rb*.[59] This model allowed the careful study of SCLC biology and confirmation of the importance of pulmonary neuroendocrine cells.

Additional publications offer a new and critical molecular characterization of SCLC.[60] Rudin et al. reported a comprehensive genomic analysis of SCLC[61] with high-throughput sequencing techniques; they demonstrated that SCLCs are composed of multiple known and new molecular abnormalities. Exome capture sequencing analysis of 42 SCLC samples paired with normal samples identified 26,406 somatic mutations, 7977 of which would result in altered protein production. They confirmed known SCLC molecular alterations to genes such as *TP53*, *RB1*, *PIK3CA*, *CDKN2A*, and *PTEN*. In addition, they identified other genes coding for proteins with a wide array of cellular functions such as the Ras family regulator, chromatin-modifying enzymes, transcription regulators, kinases, and protein phosphatases of G-protein–coupled receptors. Further genetic mutational clustering identified specific pathways at the epicenter of SCLC pathogenesis, which included *phosphatidylinositol-3′-kinase* (PI3K), Hedgehog, NOTCH, mediator complex, glutamate receptor, DNA repair, and the SRY-related HMG-box genes (SOX) family. This study showed a high mutational frequency of several SOX genes and amplification and overexpression of SOX2 in close to 25% of the SCLCs analyzed. Lastly, they identified new mutations to genes coding for tyrosine kinases such as FLT1, FLT4, KDR, and KIT as well as several fusion proteins such as RLF-MYCL1 that could be potential therapeutic targets.

FIELD OF CANCERIZATION

Whereas lung cancer may originate from only one or a few airway epithelial cells, it is clear that exposure to tobacco smoke increases the risk of the entire bronchial tree to lung cancer, leading to the concept of field cancerization. Field cancerization was first proposed in the 1950s,[62] and its molecular correlates were later confirmed in the airways of human smokers.[63] Exposure to carcinogens, genetic predisposition, and the altered microenvironment contribute to the acquisition of multiple molecular aberrations simultaneously. Because the airway epithelium is the transformative organ in the field of cancerization, there have been multiple efforts to characterize the epigenetic,[64,65] genomic,[39] transcriptomic,[38,66] and proteomic[67] changes contributing to the tumorigenic process in the bronchial epithelium of individuals at risk for lung cancer.

Previously, early proteomic changes acquired in preinvasive lesions were found to be predictive of the presence of a lung cancer in the field of cancerization.[20,21] Yet, very limited information exists about the proteomic determinants of transformation of the bronchial epithelium. Bronchial airway epithelial cells transition from a quiescent state to a proliferative one after prolonged exposure to tobacco smoke. To investigate the mechanisms leading to the transformative events in the normal airway epithelium, changes at the protein level were identified by multidimensional liquid chromatography-tandem mass spectrometry.[11] The investigations demonstrated that the *Warburg effect*, described in the tumor cells more than half a century ago[68,69] as an altered metabolism in which the cells exhibit increased glucose uptake and lactate production even in the presence of oxygen and recognized as a hallmark of cancer,[2] can be identified in the cytologically normal bronchial epithelial cells of at-risk individuals, thereby implicating metabolic reprogramming early on in the pathogenesis of lung cancer. The results demonstrated profound proteomic alterations in the field of cancerization in individuals at high risk for lung cancer and dramatic metabolic reprogramming very early in the process. Dysregulated protein expression provided new insights into the pathogenesis of lung cancer and the hope to stratify at-risk individuals. These findings also may refine the risk assessment and provide new targets to be considered for prevention strategies.

Developing and implementing precision prevention approaches has been constrained by our limited understanding of precancer biology, in contrast to the extensive study of advanced disease. Understanding how precancer leads to cancer is the subject of active investigation and has been accelerated by the PreCancer Atlas initiative.[70,71] The progression of squamous dysplasia (also found in the oropharynx, larynx, esophagus, and cervix) is better understood[72] than that of the preinvasive lesions of the small airways. This is mainly due to the difficulty in accessing the lesions in the distal airways. More recently, the behavior of precursor lesions and early cancers is being

actively investigated,[48,73–76] which may help understand how progression can be stopped at the preinvasive stage. In one such study, it was shown that adenocarcinoma in situ, although preinvasive, has the full genomic alteration profile displayed in invasive lung adenocarcinoma.[76] Some molecular prognostic signatures that will require independent validation were also identified and offer a novel opportunity to study these tumors in detail.

The interplay between the transforming airway epithelium and development of preinvasive lesions happens in a complex immune microenvironment. The interactions between the host and the environment, including airway microbes, are dynamic, and all contribute in shaping an immune response. Recent investigations from Krysan et al. revealed the clonal development of neoantigens among precursor lesions likely to progress into cancer.[75] They used whole-exome sequencing to evaluate potential immunogenic epitopes associated with somatic mutations and demonstrated the presence of significant numbers of premalignancy-associated neoantigens and an altered adaptive immune surveillance in response to them. These observations suggest that the immune system is able not only to recognize early cellular transformation, but also to mount an antitumor immune response. The determinants of this antitumor evasion to progression-associated neoantigens and the relevance of immune surveillance in lung cancer are topics of intense research.

TUMOR HETEROGENEITY

Intratumor heterogeneity represents a major challenge because it can result in inaccurate diagnosis, prognosis, and prediction of response to treatment. Lung cancer is a very heterogeneous disease both spatially and temporally, with one of the highest mutational burdens across different cancer types.[26,77] Tumor heterogeneity can be studied using an evolutionary approach. In 1976, Peter Nowell applied evolutionary models to study tumor progression and treatment failure and proposed a clonal evolution model in which a tumor arises from a single mutated cell ("clone") and progresses as a result of subsequent alterations, in which more aggressive clones replace the original clones.[78] Advances in new sequencing technologies allowing genome-wide sequencing have elucidated a more complex clonal structure than previously thought.[26]

Several models of evolution of mutations have been proposed to understand and attack this constantly shifting heterogeneous process. In *neutral* evolution, all driver alterations are thought to be present in the original neoplastic cell and subsequent alterations are neutral, meaning that there is an absence of selection, and heterogeneity arises from stochastic processes as a by-product of tumor progression.[79] In *punctuated* evolution, it is postulated that tumor heterogeneity is generated in the early development of the neoplasia, followed by neutral evolution.[80,81] *Branching* evolution, also known as the trunk-branch model, is currently the preferred model and is defined by the gradual accumulation of driver mutations in subclonal populations.[82] In this model, the "trunk" of the tumor consists of progenitor clones bearing early somatic alterations driving tumorigenesis. Those early alterations are potentially ubiquitous events. In contrast, later somatic events are heterogeneous events present in the subclones that make up the "branches" of the tumor and that drive tumor progression. Sequencing multiple regions of the same tumor has been the most successful strategy to investigate intratumor heterogeneity and clonal evolution in lung adenocarcinoma to date.[25,29,31] The studies suggest that intratumor heterogeneity and branched evolution might be a universal phenomenon across lung adenocarcinomas.

Molecular analysis of lung tumors also supports the existence of temporal tumor heterogeneity. Most known driver alterations have been mapped to the trunks of the tumors, which suggests that canonical alterations (i.e., changes in well-established pathways) arise early in tumor evolution. Truncal known driver mutations almost always appear before genome duplications, suggesting a particular role in tumorigenesis. On the other hand, truncal genome doubling events take place before subclonal diversification but after the acquisition of driver mutations, which suggests that chromosomal instability may be a crucial step that induces copy number alterations followed by a burst of mutational heterogeneity. Furthermore, the association of drug resistance and relapse with chromosomal instability[83] supports the hypothesis that the ability of chromosomal instability to generate extensive subclonal divergence could be compromising the effectiveness of therapeutic strategies targeting truncal driver mutations.[25] Besides, data from these studies suggest that certain alterations in non-canonical cancer genes (i.e., genes in alternate pathogenic pathways) may also drive tumor development and subclonal diversification.

The study of intratumor and intertumor heterogeneity has also been dramatically enhanced by single cell analysis. This may happen at the transcriptomic (single cell RNA sequence), genomic (single nucleotide variant, copy number variant), or proteomic (mass cytometry) level (Fig. 73.2). These approaches allow the more comprehensive understanding of key changes "cell by cell" rather than at a population level. Subpopulations of cancer cells and immune cells can be identified,[84,85] especially with rare antigen-specific T or B cells, and their unique properties untangled. This field is only beginning and is expected to advance our understanding of tumor biology.

TUMOR INVASION

Invasiveness has been considered a hallmark of cancer because it represents the aggressive nature of tumors. The invasive and metastatic stage of cancer progression correlates with poor clinical prognosis and represents a major barrier to treatment. Metastatic tumor cells go through stages of detachment from the primary tumor sites, invasion into circulation, extravasation into the appropriate secondary site, and establishment of a microenvironment supporting their energetic requirements. The ability of a preinvasive lesion to progress into an invasive disease is determined by a variety of tumor and host factors. *Next-generation sequencing* (NGS) studies have deduced the sequence of events in which cancer cells acquire genomic alterations.[29,86] Key evolutionary alterations in the trajectory of tumors have been identified[87] and include mutations in *TP53, KRAS, EGFR, BRAF*, histone methylation enzymes, APOBEC enzymes, and DNA damage response genes, as discussed earlier. Cell motility and invasion enable tumor cells to penetrate

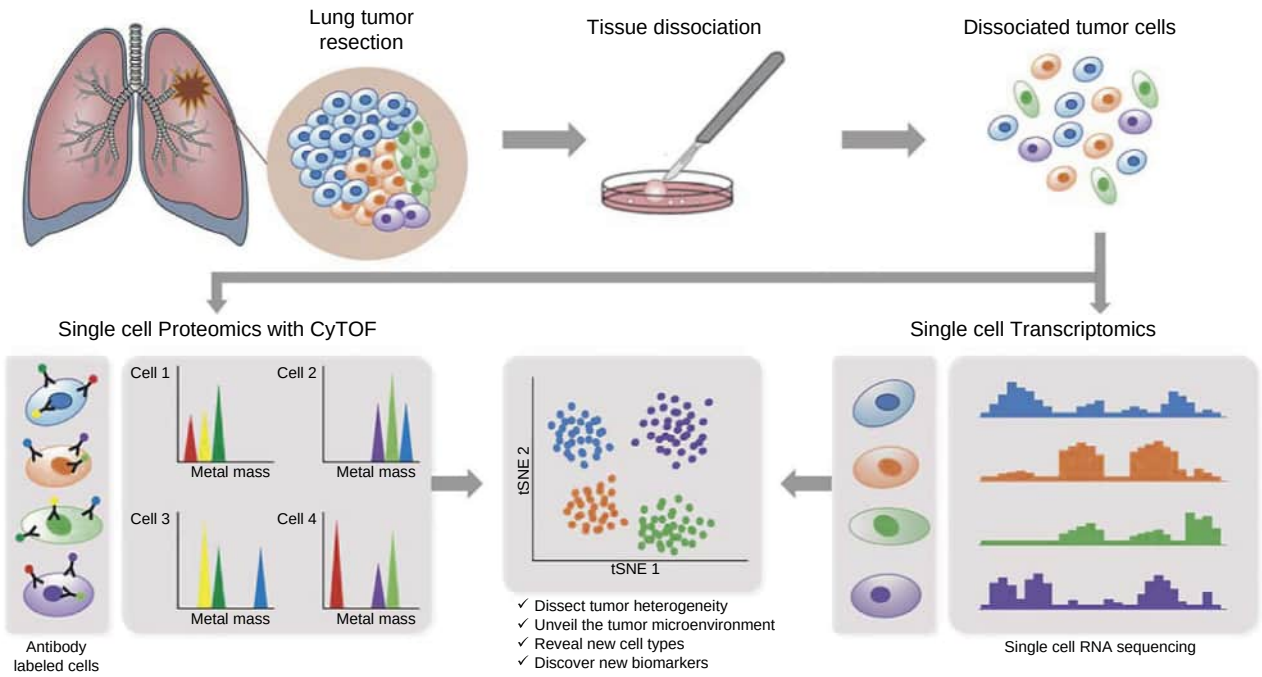

Figure 73.2 Investigating intratumor heterogeneity and the tumor microenvironment with single cell approaches. A lung tumor resection is dissociated into single cell suspension that can be used in different applications. Mass cytometry (CyTOF) uses metal-labeled antibodies to detect a limited number of proteins in cells. Single cell RNA sequencing reveals the transcriptome of each individual cell. Both can be analyzed through computational strategies to dissect intratumor heterogeneity.

basement membranes and extracellular matrices and to migrate into adjacent tissues. Invasive tumor cells have dysregulated adhesion and motility in response to extracellular signals from growth factors and cytokines.

The primary process by which cancer cells are able to migrate and establish a niche is known as *epithelial to mesenchymal transition* (EMT).[88] The reverse process, *mesenchymal-epithelial transition* (MET), allows the cancer to establish in a different microenvironment.[89] Cancer cells activate EMT to enable metastasis and niche formation, events that remain relatively rare in primary tumors.[90] Invasion also involves other cell types, such as macrophages, that contribute to immune suppression and tumor progression. For example, tumor-associated macrophages supply growth factors to cancer cells. Finally, metastasis does not necessarily happen only in the final stages of cancer progression and can also be found before the primary site is discovered. Tumor cells may undergo EMT in the early phases of tumor initiation because tobacco smoke is known to induce EMT.[91] Thus, invasion is a process that may involve EMT at multiple steps in tumor progression.

CLINICALLY RELEVANT MOLECULAR TARGETS IN LUNG CARCINOMA

Tumor heterogeneity is also reflected at the epidemiologic level in the diversity of different targetable driver mutations in lung carcinoma that co-opt signaling mechanisms to drive uncontrolled growth and metastasis. This topic is discussed later in this chapter, as well as how therapeutic targeting of these pathways can lead to improved outcomes in these mutated and targetable areas. Of note, PD-L1 expression is occasionally considered a "targetable" finding, but the theory and practice of immunotherapy are very different from the targetable pathways discussed here. That said, the immune environment in oncogene-driven carcinomas, particularly in never smokers, may be distinct, and immunomodulatory therapy may be less effective in the setting of most mutation-driven lung carcinomas than in the more heterogenous lung tumors without single driver mutations.[92]

Driver mutations are mutations in pathways that confer evolutionary growth and survival advantages to tumors and, once present, are highly clonally preserved. The pathways described below all contain driver mutations or fusions exploiting these pathways for tumor growth and survival. An important point regarding targetable and driver mutations in NSCLC is that they are relatively rare but have a great deal of clinical importance for individual patients with metastatic disease. These mutations also convey dramatically different prognoses and overall survival with treatment than lung carcinomas without these defined drivers. Thus, NGS of every highly locally advanced or metastatic adenocarcinoma has become the standard of care on which to base appropriate treatment decisions.[93] NGS testing is affordable and cost-effective in the upfront setting for metastatic lung adenocarcinoma.[94]

NGS refers to a variety of massively parallel techniques of genetic sequencing that have dramatically reduced cost and increased sequencing speed. In genetic testing of tumor

samples, NGS can sequence up to hundreds of genes of interest and may include RNA sequencing to identify gene fusions or rearrangements, mutations, and copy number alterations. Panel-based NGS is superior to and more cost-effective than single gene testing because it allows for testing of many genes at once in a single test, including rare mutations for which single gene testing may not be available or cost-effective. NGS testing also facilitates clinical trial enrollment for novel targeted therapies by allowing for detection and enrollment or rare mutations. NGS is vital because rare but targetable mutations may make a dramatic difference in treatment options and outcomes.

Tumoral sampling, or alternatively, liquid biopsy (e.g., a blood sample analyzed for circulating tumor DNA by sequencing), for *epidermal growth factor receptor* (EGFR) or other mutation testing needs to be performed both at initial diagnosis and with disease progression. Another important issue with targetable mutations is *central nervous system* (CNS) involvement. Some mutations or fusions such as ALK+ disease have a predilection for metastasizing to the CNS. Also, CNS penetration of targeted therapies may be suboptimal, making the CNS a common "sanctuary" site for recurrence or progression. Figure 73.3 and Table 73.3 summarize the relative contributions of multiple currently targetable and common mutations in NSCLC and note currently available targeted agents.[3] The frequency of specific NSCLC mutations varies significantly by patient population; depending on the population, approximately 50% of non-squamous NSCLC patients have some form of driver mutation present.[13]

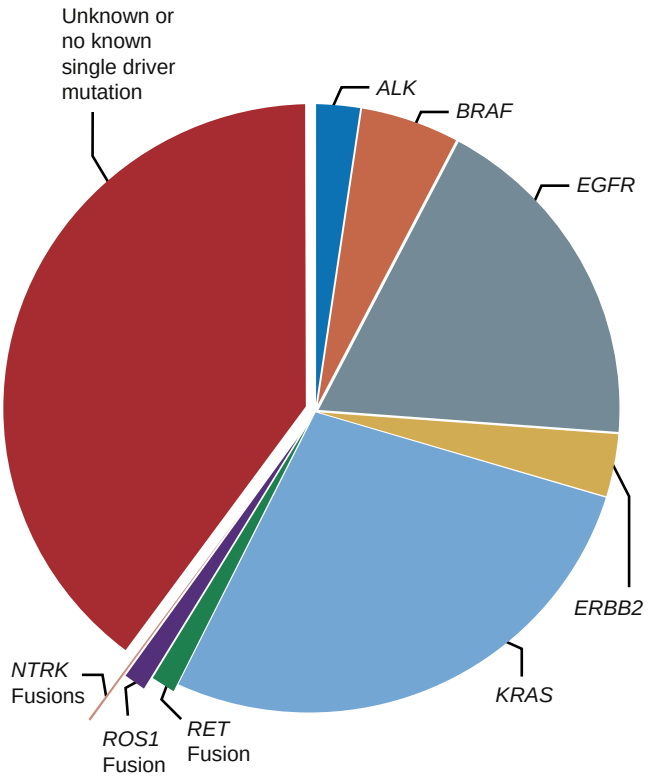

Figure 73.3 Common and targetable mutations/fusions in *non–small cell lung cancer* (NSCLC). Relative percentage of the most common targetable mutations/fusions in NSCLC.[130] This is based on data available from the American Association for Cancer Research Genomics Evidence Neoplasia Information Exchanger (GENIE) consortium. It is important to note that mutational frequency for different targets varies a great deal based on population characteristics including geographic origin, environmental exposures, and tobacco exposure. Approximately 50% of nonsquamous NSCLC have a known driver mutation, but this varies based on sample population.[13]

EGFR/HER2 PATHWAY

The EGFR pathway is the best characterized of the major targetable pathways stimulating lung carcinoma and serves as an excellent example of a targetable mutation with highly effective and specific therapies. As noted in Figure 73.4, EGFR is a receptor-activated tyrosine kinase, which activates a signaling cascade including ERK, Akt, and c-SRC. Constitutive/continuous activation leads to inappropriate production of cyclin D1 and ongoing inappropriate activation of proliferation and survival signals. EGFR (ERBB1) and the related *human epidermal growth factor receptor-2* (HER2; ERBB2), are members of the ERBB family of receptor tyrosine kinases. As with most of the described drivers, EGFR and HER2 serve as predominant drivers of proliferation and are rarely found with other driver mutations in new lung cancer diagnoses. *EGFR (ERBB1)* mutationally driven NSCLC is also the most common targeted mutation in lung cancer, arising in 9–46% of cases depending upon geographic origin and patient characteristics.[95,96] There are multiple primary mutations or genetic alterations that lead to aberrant pathway activation. The most common mutations are *EGFR* L858R (on exon 20) and exon 19 deletions. Mutations in the related gene *HER2 (ERBB2)* also lead to abnormal activation of the pathway via PIK3CA and Akt activation and act as oncogenic drivers. *HER2 (ERBB2)* is mutated in approximately 3% of NSCLC patients.[3] Most common in breast carcinoma, *HER2 (ERBB2)* amplifications are also seen in a rare subset of lung adenocarcinomas and influence initial care options.

Table 73.3 NCCN Recommended Selected Targeted Therapies for Driver Mutation–Driven NSCLC

Driver Genotype	Selected Targeted Therapies
ALK fusions	Alectinib Brigatinib Ceritinib Crizotinib Lorlatinib (second-line therapy)
BRAF	BRAF inhibitor + MEK inhibitor Dabrafenib Trametinib Vemurafenib Cobimetinib
EGFR	Osimertinib Erlotinib Afatinib Dacomitinib Gefitinib
ERBB2	Ado-trastuzumab emtansine
KRAS	AMG 510 (under investigation)
NTRK fusions	Larotrectinib Entrectinib
RET	Selpercatinib Pralsetinib
ROS1 fusions	Crizotinib Entrectinib Ceritinib Lorlatinib (second-line therapy)

NCCN, National Comprehensive Cancer Network; NSCLC, non–small cell lung cancer.

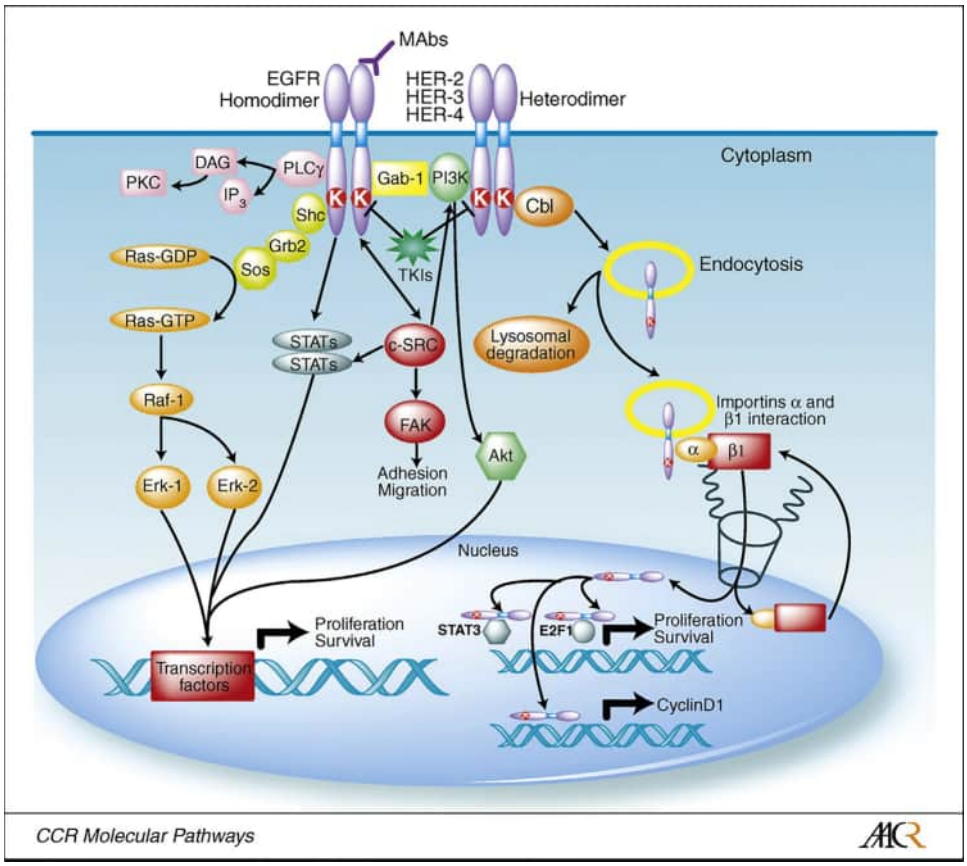

Figure 73.4 Summary of Ras, EGFR, and HER2 signaling. Note the convergent signaling between Ras/KRAS, EGFR, and HER2 signaling pathways as well as downstream ERK and AKT conserved pathways. (From Scaltriti M, Baselga J. Epidermal growth factor receptor pathway: a model for targeted therapy. *Clin Cancer Res*. 2006;12[18]:5268–5272.)

Targeted Agents and Clinical Concerns

EGFR alterations are one of the best-established targets of therapy in mutationally driven lung carcinoma. There are multiple generations of *tyrosine kinase inhibitors* (TKIs) focused on targeting the L858R mutation and exon 19 deletions, which are the primary EGFR-TKI sensitizing mutations. Responses with other less common mutation sites may vary based on the specific mutation site and the specific TKI. First-generation TKIs targeted at EGFR include erlotinib and gefitinib. These reversibly bind the adenosine triphosphate binding site of the receptor and prevent activation. Toxicities include those related to inhibition of wild-type EGFR, such as hand-foot syndrome (i.e., redness, swelling, pain and tingling in the palms and soles), rash, diarrhea, and gastrointestinal upset. Second-generation inhibitors such as afatinib irreversibly bind the adenosine triphosphate binding site; however, their clinical use is limited by their significant and more frequent toxicity. Multiple mechanisms of resistance exist for these first-generation and second-generation medications including most commonly the T790M mutation (responsible for approximately 60% of resistance in this setting).[97] This resistance is thought to be secondary to steric hindrance inhibiting binding of first- and second-generation agents in the EGFR binding pocket. Third-generation TKIs aimed at EGFR have preferential binding characteristics for the mutated receptor. This results in a significantly improved side effect and toxicity profile with improved clinical efficacy and tolerability. Third-generation TKIs, such as osimertinib, are targeted at mutated receptors including that caused by T790M and are highly effective after resistance has developed to first- or second-line TKIs. Recent data have also demonstrated superior performance in the first-line setting as well. Optimal sequencing of therapy still remains somewhat unclear, although the improved tolerability and efficacy favor third-generation TKIs as first-line therapy.[98]

Major mechanisms of resistance include focal mutations in *EGFR* (e.g., T790M, C797S), or amplifications or alterations in the genes coding for other crosstalk pathways (*PIK3CA, KRAS, MET* amplification), or conversion into SCLC. Serial biopsy and NGS are vital to discover the specific mechanism of resistance responsible for growth in an individual patient and to guide further therapy. Strategies to compensate for resistance are being tested in clinical trials, including combination therapy with inhibitors of other pathways, such as MET, alongside EGFR inhibitors. Conversion into SCLC is a mechanism of resistance with a dismal prognosis.

Targeted agents for the related HER2/ERBB2 pathway include trastuzumab, which is primarily used alongside first-line combination chemotherapy. Other agents such as ado-trastuzumab emtansine, a targeted antibody-drug conjugate, are options, though responses are lower in lung cancer compared to breast carcinomas.

Prognosis and Outcomes

Compared to NSCLC with nontargetable mutations, metastatic EGFR-mutated NSCLC has a significantly better prognosis, with most patients with metastatic disease living

longer than 18 months (though still with limited 5-year survival).[99] The frontline use of third-generation inhibitors, with an approximately 19-month median progression-free survival and response rates of approximately 80%, will likely continue to improve outcomes.

KRAS PATHWAY

KRAS and its associated genes are some of the most commonly mutated genes in multiple human carcinomas, including lung, gastrointestinal, and pancreatic carcinomas. *KRAS* is a member of the RAS superfamily (see Figure 73.4). *KRAS* acts as a molecular switch with a guanosine triphosphate (active) and guanosine diphosphate (inactive) state; normally, *KRAS* remains predominately in the inactive state. *KRAS* mutations, seen in approximately 11–30% of lung cancers, lead to increased time in the activated state and the propagation of growth and survival signaling via multiple synergistic mechanisms. *KRAS* signaling also enhances the tumor microenvironment; it can remodel the surrounding stroma and lead to cytokine production impairing immune responses.[100]

Most mutations in *KRAS* are in codons 12, 13, or 61. In lung adenocarcinoma, the most common *KRAS* mutation is the G12C mutation. These mutations are thought to block guanosine triphosphate hydrolysis or to slow or decrease the conversion to the inactive state, and thereby shift the KRAS molecule to an active configuration leading to abnormal proliferation, survival, and stroma modulation favoring tumor growth and comparative immune privilege.

Targeted Agents and Clinical Considerations

KRAS is a challenging and evolving target compared to the other mutations on this list. Unfortunately, there are no *U.S. Food and Drug Administration* (FDA)-approved *KRAS*-targeting drugs, although a novel inhibitor, AMG 510, is undergoing "fast track" evaluation and multiple new medications are in clinical trials.[101,102] AMG 510 is a novel steric inhibitor that binds in a selective and irreversible manner to the *KRAS* G12C[103] protein, maintaining *KRAS* in the inactive state. Data are still preliminary and, as of this writing, in abstract form, but a disease control rate of 100% (stable or partial response to therapy) was observed in the first 23 patients with initial evaluation. CNS progression is a concern, and additional clinical trials are ongoing.

Prognosis and Outcomes

KRAS may be a poor prognostic indicator for chemotherapy response, though the data from retrospective clinical trials are mixed. Recent data seem to indicate that *KRAS* status is less informative than PD-L1 marker status for predicting response to immunotherapy.[104]

ALK/ROS1/NTRK GENE FUSIONS

The *anaplastic lymphoma kinase (ALK)* gene codes for a receptor tyrosine kinase. It is highly expressed in nervous system development, with limited expression in most normal adult tissue.[105] In carcinoma, the *ALK* gene is coupled with a gene rearrangement partner such as *EML4* (most common in NSCLC), and these partner fusions lead to increased expression (via the fusion partner promoter) and increased or constitutive activation (via partner protein domains). These *ALK* fusions are the driver mutations in approximately 3–7% of NSCLC.[106] Of note, the downstream activation pattern may be dependent upon the fusion partner. In lung cancer, with the classic *ALK-EML4* fusion, there is increased downstream proliferation and survival signaling via multiple pathways including ERK, PI3K, AKT, JAK-STAT, RAS, and MEK pathways.

Targeted Agents and Clinical Considerations

Crizotinib, a TKI originally designed to target MET, was the first approved *ALK*-directed therapy, showing excellent initial response rates up to 74% and a *progression-free survival* (i.e., the time after a given treatment that cancer growth remains at least a stable size) of up to 11 months. More potent second- and third-generation *ALK* inhibitors are now available and are preferred in the first-line setting for *ALK* fusions. Outcomes with second-generation *ALK* inhibitor alectinib are excellent, with median progression-free survival of 34 months when given as first-line therapy.[107] Unfortunately, despite excellent initial response rates, the tumor still recurs, though the median survival with appropriate choice and timing of therapy, so-called *treatment sequencing,* after diagnosis of metastatic disease may exceed 7 years. Mechanisms of resistance in *ALK*-mutated tumors most commonly arise from secondary resistance mutations in the *ALK TKI* portion of the fusion. Resistance patterns and susceptibility to second- and third-generation agents vary depending upon the mutation sites. As with *EGFR* mutations, once a tumor progresses, repeat tumor biopsy and NGS are vital to guiding therapy. With NGS, the right therapy can be given at the right time to treat a patient despite mutations leading to resistance to prior drugs. Targeted medications have different resistance mutations, and giving these drugs in the appropriate order (i.e., treatment sequencing) allows for longer-term responses before a tumor is resistant to all available therapies. Given the excellent response rates with treatment, identifying and starting therapy even when patients have poor functional status is vital in these uncommon populations. Even bedbound patients with poor functional status may have dramatic improvement with therapy if their poor functional status is due to their carcinoma.

The *c-ros oncogene (ROS1)* codes for the protein ROS1, a tyrosine kinase receptor with significant homology/similarity to ALK. ROS1 fusions account for 1–2% of NSCLC driver mutations.[3] As an oncogenic driver similar to ALK, it is found as a fusion protein fused to multiple potential gene variant partners, with a greater diversity of fusion variants than is found with ALK.[108,109] Similar to ALK, there are multiple generations of TKIs available in the ROS1+ setting, and crizotinib is a viable first-line option. Initial therapy is usually crizotinib with an initial *overall response rate* (i.e., the percentage of patients whose tumor shrinks in response to treatment) of greater than 70% and a median overall survival of 51 months for metastatic disease, based on the PROFILE trial.[108] This is in stark contrast to the poor prognosis of traditional NSCLC. CNS metastases are a common theme in ALK and ROS1+ disease and remain an issue of concern for long-term prognosis.

Gene fusions leading to aberrant gene activation are a conserved theme in NSCLC and other carcinomas. They are

rare but have a very large impact on treatment options. The most recent example of this is the discovery of *NTRK* fusions in NSCLC. These mutations are very rare and account for only 0.1–1% of NSCLC, but these patients have excellent responses to targeted therapy with two targeted agents recently approved, entrectinib and larotrectinib. These FDA approvals follow a trend in which approvals for targeted therapies are increasingly *disease agnostic*, meaning that they address a specific mutation regardless of the tumor type. This demonstrates a common theme for some oncogenic drivers where mutational signaling, not the cancer histology, drives the disease and patient outcomes.

BRAF

BRAF mutations (most commonly V600E) are present in approximately 1–3.5% of NSCLC.[110] BRAF is an intracellular (not a receptor) protein kinase in the Raf family whose activation leads to downstream *mitogen-activated protein kinase* (MAPK) and MEK activation with Akt and ERK family involvement. The most common currently targetable mutation is the V600E mutation found in some NSLC as well as in many melanomas (≈50%). This mutation allows signal transduction of BRAF as a monomer and dramatically increases its kinase activity by several hundred-fold. These changes lead to constitutive activation and downstream proliferation and survival signaling driving tumor progression.[110] This V600E mutation is a sensitizing mutation for therapy with combined BRAF and MEK inhibition or inhibition of BRAF alone. The strong clinical preference is combined therapy with a MEK inhibitor such as trametinib and a BRAF inhibitor such as dabrafenib. This combination prevents early resistance via changes in MAPK signaling. This MEK blockade also reduces the risks of inadvertent epidermal skin squamous cell carcinoma formation from synergistic skin baseline RAS mutations and paradoxical BRAF inhibitor-induced MAPK signaling in the skin.[111] Clinical outcomes with targeted therapy given as first-line treatment were excellent with a greater than 70% clinical control rate (stable disease + overall response) and median duration of response of approximately 10 months.[112]

MET/PIK3CA

Resistance may be mediated by multiple vital signal transduction pathways that are either independently present or interact with the above targetable mutations. Signaling via MET, a tyrosine kinase receptor, is one such resistance pathway. When phosphorylated, MET activates multiple pathways including PI3K, AKT, and RAS. Of note, the ligand for MET is often expressed by stromal cells and may stimulate activation of wild-type MET. In lung carcinoma, overexpression of wild-type MET has been described as a resistance mechanism for EGFR-mutated lung carcinoma.[113] MET overexpression may be seen in 24–40% of NSCLC.[114,115] Clinical trials are in progress to evaluate MET inhibition alongside EGFR TKIs for management of resistance. The MET inhibitor capmatinib received accelerated FDA approval for the treatment of MET exon 14 skipping mutation-positive lung carcinoma based on the GEOMETRY trial, with an overall response rate of 68% in the first-line setting and a tumor response duration of greater than 12 months.[116] Clinical trials continue with other MET inhibitors for this indication.[117]

The PIK3CA pathway is another highly conserved signaling pathway often with mutations coexisting alongside other patterns of mutation in NSCLC. PIK3CA mutations are highly represented among squamous cell carcinomas, but the full prognostic import is still unclear.[118] PIK3CA and AKT targeting is being explored in clinical trials in NSCLC but there remains a good deal of work to be done.

SCLC has unfortunately lagged behind in the discovery of targetable mutations. SCLC remains best defined by nearly universal alterations in Rb and p53 activity or expression. However, there is ongoing work related to subtyping SCLC cellular subpopulations,[119] including multiple neuroendocrine or mesenchymal-like cells. These cells have differentiation markers such as NEUROD1, YAP, and ASCL1 and may have differential responses to different signaling targets. Expanding our understanding of how these cellular subpopulations survive and interact to contribute to tumor heterogeneity may lead to new targeted therapies for SCLC.

Overall, mutationally targeted therapy, when appropriately selected, has profound advantages in tolerability and efficacy over traditional chemotherapy for appropriate NSCLC patients and serves as a bright star in the NSCLC landscape with improving outcomes and a growing understanding of the complex signaling underpinnings of targeted therapy resistance.

IMMUNOTHERAPY AS TARGETED MOLECULAR THERAPY?

The use of immuno-oncology has been revolutionary in the treatment of lung cancer. In particular, the use of immunomodulatory agents targeting PD-1 and PD-L1 are standard of care therapies in most locally advanced or metastatic lung carcinomas. However, they are not traditionally referenced as targeted therapies because, unlike the targeted therapies noted above, they do not interfere with intrinsic tumoral signaling pathways and disrupt tumor growth or survival signals. Instead, they modulate the patient's overall immune function and disrupt the host-tumoral environment to improve the antitumor immune response. This topic is covered more extensively in Chapter 77, which focuses on lung cancer treatments.

FUTURE CHALLENGES IN TARGETED THERAPY IN LUNG CARCINOMA

Despite dramatic improvements in care, there remain significant challenges in improving targeted therapy for lung carcinoma. The main challenges for this therapy include determining optimal implementation, recognizing tumoral evolution and resistance, early detection of lung cancer, monitoring the patient with lung cancer, and applying targeted therapy to SCLC. These challenges directly link to the molecular biology of lung cancer reviewed above and offer opportunities for the lung cancer researchers of the future.

Implementation remains a challenge in targeted therapy for lung carcinoma. Because of the genomic

instability associated with lung cancer, many different signaling pathways may drive tumor progression. These include rare but targetable mutations such as NTRK or ROS1. Full NGS tumor panel testing is needed to find rare mutations or fusions. Despite National Comprehensive Cancer Network recommendations, these tests are not always performed in community-based oncology practices due to cost considerations.[93] However, NGS panel testing should be offered to all metastatic NSCLC patients.[120] Cost-effectiveness analysis suggests that broad next-generation testing may be more cost-effective than more limited testing, and community-based use of NGS is growing. Outreach for rare but very treatable mutations remains vital.[121] An example would be *NTRK* fusions. These are rare (≈1/1000 patients), and testing can require both DNA and RNA sequencing by NGS panels. Thus, this testing will not benefit 999 out of 1000 lung cancer patients, but it can profoundly improve quality and quantity of life for the one positive lung cancer patient, due to excellent targeted therapies. The challenges of biopsy and re-biopsy can complicate the testing process because many patients may not be good candidates for re-biopsy needed to guide further treatment.[122] This means that patients may receive suboptimal therapy after development of resistance. The lack of biopsies can also limit enrollment for clinical trials to expand treatment options for lung carcinoma. Liquid or plasma-based biopsy with sequencing offers potential to improve options, though it has important limitations of sensitivity depending upon disease burden. This technology is rapidly improving to meet this challenge.

Resistance to therapy is the existential issue in treating lung cancer. The same intra-tumoral heterogeneity that allows for tumor evolution also drives resistance and recurrent disease. Better understanding of how tumor subpopulations shift and communicate at the single cell level may be vital to design better clinical trials using drug combinations for treatment. Without this understanding, structuring appropriate combination therapies in these highly diverse tumors will continue to be challenging. A useful if simplistic analogy may be found in the use of combination therapy in treating tuberculosis and HIV to minimize multidrug-resistant clones and to force the pathogens into genetic changes that are suboptimal for growth.

Early detection of lung cancer is another challenge in this mutationally driven tumor patient population. Although early detection led by low-dose chest computed tomographic screening is a dramatic success story in lung cancer, it has not been able to address the significant populations of light or never smokers who are often affected by lung cancer driven by known oncogenic targets. Implementing lung cancer screening also carries risks of false-positives and increased population morbidity. Liquid biopsy is far less sensitive in the early detection setting.[123] Thus, many patients with targetable mutations are found with metastatic disease. This remains a clinical and scientific challenge.

Monitoring patients for early recurrence is a related problem given the low level of disease. The use of liquid biopsy, however, has become an attractive modality for monitoring disease progression and response to therapy.[124,125] As technology and sensitivity improves, liquid biopsy may contribute to risk stratification for computed tomographic screening,[126] thereby personalizing the management of nodules and reducing the risks of false-positive testing.

SCLC is the most aggressive and rapidly lethal lung carcinoma. Taken by itself, it is the sixth leading cause of cancer death, on par with all of leukemia. Unlike NSCLC, it has initial excellent responses to therapy but almost inevitably recurs with metastatic disease resistant to therapy. Advances have been made with immunotherapy, but mutationally targeted therapy for SCLC lags far behind NSCLC. SCLC is notorious for its cellular plasticity and heterogeneity with multiple coordinating cellular subpopulations supporting metastasis and later chemotherapy resistance.[127–129] Single cell analytic tools are needed to understand how molecular subtypes function and communicate in SCLC in order to disrupt this communication and lead to targeted killing of vital tumor subpopulations.[60]

Acknowledgments

We thank Maria Fernanda Senosain, graduate student in Dr. Massion's laboratory, for providing Figure 73.2.

Key Points

- Lung cancer arises from epithelial cells after a long series of metabolic, epigenetic, and genetic alterations. Mutation signatures, such as those caused by smoking, are associated with the disease process. The cell of origin of lung cancer is still under investigation.
- Most carcinogens damage DNA in a specific manner to induce aberration in the replication machinery and the repair process, causing genomic instability.
- Next-generation sequencing of targetable driver genes is the standard of care in the management and treatment of metastatic *non–small cell lung carcinoma* (NSCLC). Implementation and use of broad panel–based next-generation sequencing of NSCLC is cost-effective and leads to life-changing treatment options for many lung carcinoma patients.
- Targetable mutations in NSCLC can vary in frequency based on population but can have a dramatic impact on optimal treatment options and prognosis.
- Driver mutations direct the malignant process by giving selective advantage to clones of cells; driver mutations are now identified in many receptors and intracellular signaling molecules, including *EGFR/HER2*, *KRAS*, *ALK/ROS1/NTRK* gene fusions, and *BRAF*.
- Repeat liquid or solid biopsy and sequencing of tumors after recurrence are vital in NSCLC with targetable mutations to adjust therapy for specific resistance patterns.
- Prognosis for many targetable mutations in NSCLC is excellent; however, resistance is inevitable and combination or sequential therapy is important to address resistance.
- Small cell lung cancer has no known targetable mutations to date, though it is nearly universally associated with p53 and Rb mutations.

Key Readings

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74 LUNG CANCER: EPIDEMIOLOGY

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INTRODUCTION

Lung cancer is the leading cause of worldwide cancer death, and its mortality is projected to increase sharply from about 1.7 million new deaths per year in 2018 to nearly 3 million deaths per year by 2035,[1] with increases expected in all World Health Organization regions. Lung cancer mortality is anticipated to increase the most in the Western Pacific Region, where deaths are expected to more than double from 750,000 to 1.5 million deaths. The increasing death rates in most of the world, with some notable exceptions in North America[2] and Northern Europe,[3] reflect the ongoing tobacco use epidemic along with aging of the world's populations. Lung cancer remains the most common cause of cancer death in the United States, with an estimated 142,670 deaths expected in 2019. The overall death rate in the United States has decreased by nearly 50% since the peak in 1990, reflecting reductions in harmful exposures from smoking, environmental and occupational exposures, and improvements in earlier detection, management, and treatment of lung cancers.

Despite the reduction in incidence in the United States, lung cancer remains a major public health concern both in the United States and worldwide. Survival following a lung cancer diagnosis remains poor, with a 5-year survival rate of about 20%. The 5-year survival rate has changed little until recently because lung cancers are most often diagnosed at advanced stages when treatment is less effective.[4,5] Only recently has there been evidence that screening for lung cancer using low-dose computed tomography is an effective means of reducing mortality.[6] In 2013 the U.S. Preventive Services Task Force issued a recommendation for lung cancer screening for high-risk individuals.[7] Advances in the treatment of lung cancer have also been slow to improve survival for most patients. Since the early 2000s, treatment targeted to molecular signatures in lung tumors, such as *epidermal growth factor receptor* (EGFR) inhibitors and immune checkpoint inhibitors, has resulted in improved survival in particular subgroups of patients.[8–11] Unfortunately, the development of drug-resistant mutations is a problem that affects overall survival for patients with lung cancer, and continued drug development is crucial. More recently, immunotherapeutic regimens have been developed that greatly improve survival for a selected subset of patients with late-stage lung cancers. To understand the profile of a high-risk individual and aid in the development of chemopreventive agents and targeted treatments, it is essential to understand smoking patterns and the genetics underlying lung cancer development.

GEOGRAPHIC, GENDER, AND ETHNIC VARIABILITY

As shown in Figure 74.1, there is extreme geographic and gender-specific variability in the rates of lung cancer among countries. Shown are the mortality rates in the highest 20 and lowest three countries along with rates in selected other countries. The ratio in rates between genders varies from 11.6 in Belarus to 1.0 in Brazil, with a world average that is three times higher in men than in women.[12] Rates are lowest in sub-Saharan Africa, except South Africa, with rates in most countries less than 10/100,000. Rates are highest in Europe, North America, and Eastern Asia. These highly variable rates among countries and between genders reflect variable exposure patterns and likely relate primarily to variations in smoking patterns across world populations. Studies in the United States, however, show pronounced variation in lung cancer risks among ethnic groups living in the same regions of California and Hawaii, with African Americans and Hawaiians having 20–90% higher risks for lung cancers depending on histology.[13] Historically, African American men have had a higher incidence of non–small cell lung cancer than other groups, despite their lower smoking exposures. *Small cell lung cancer* (SCLC) incidence is particularly elevated in Hawaiians.

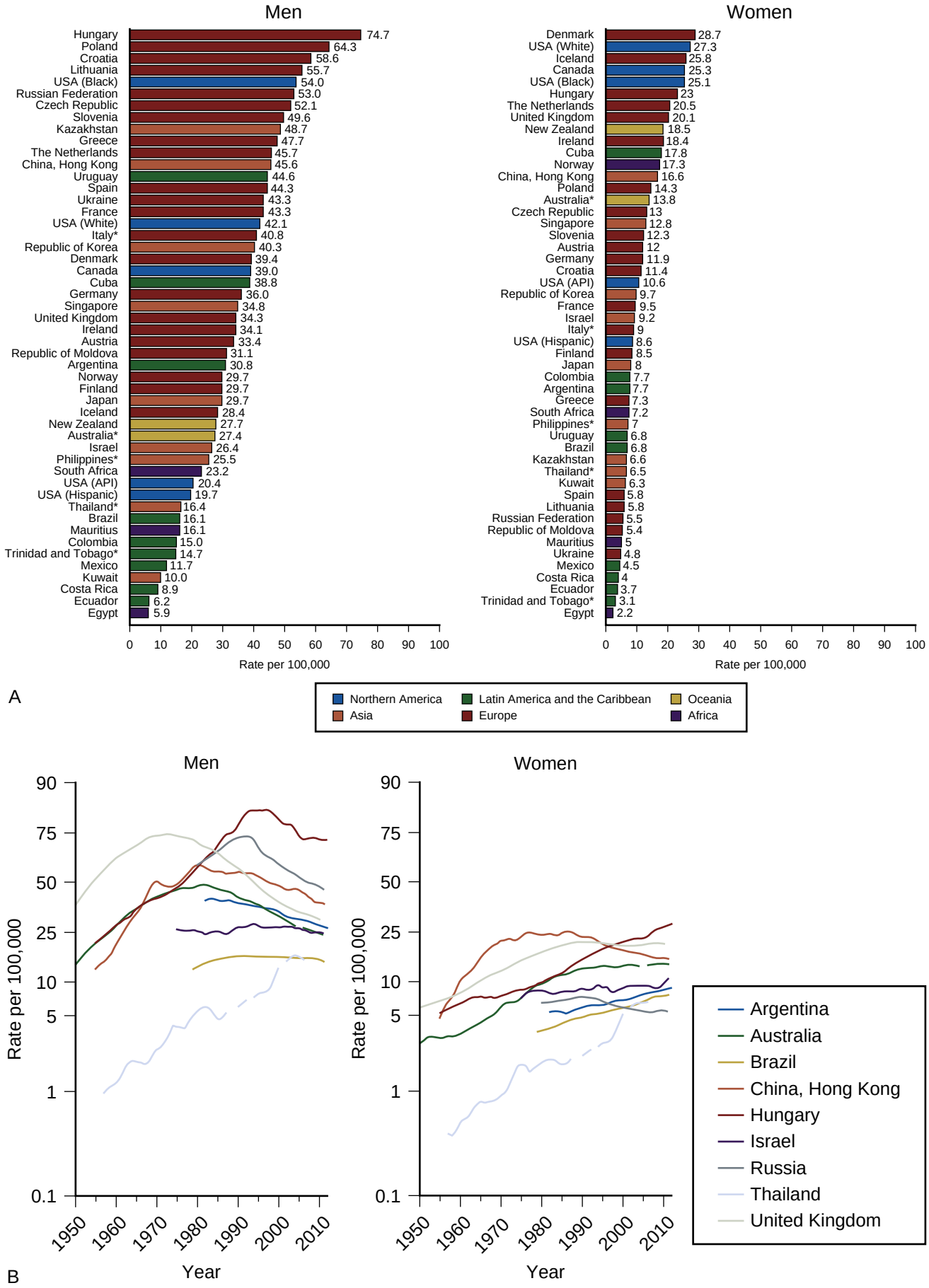

Figure 74.1 Lung cancer mortality rates and trends, by sex. (A) Ranking of age-standardized lung cancer mortality rates for selected countries for all ages, by sex, for the period 2003 to 2007, color-coded by region. Note that the U.S. data vary by gender and major ethnic groups. (B) Lung cancer mortality trends by sex, selected countries, 1950 to 2012. Observed age-standardized lung cancer mortality rates with a 5-year moving average. Global rates can be seen to vary widely among countries and over time. (Data from Forman D, Bray F, Brewster DH, et al., editors. Cancer incidence in five continents, vol. X. IARC Scientific Publication No. 164. Lyon: International Agency for Research on Cancer, World Health Organization, 2014.)

Recent national trends show that populations of African American and European descent in the United States have similar incidence rates due to further decreases in smoking patterns in African Americans.[14]

SMOKING

Lung cancer is a well-established example of a malignancy largely determined by environmental exposure, with risks associated with cigarette smoking,[15–18] with certain occupations such as mining, shipbuilding, petroleum refining, and with asbestos exposure.[4] In Western countries, about 85–90% of the lung cancer risk is attributable to cigarette smoking. However, lung cancer develops in only about 15% of current smokers, suggesting a differential susceptibility to the effects of tobacco carcinogens. In addition, 10–15% of lung cancers arise in never-smokers. Little is understood about risk in never-smokers, although exposure to secondhand cigarette smoke and air pollution certainly contribute to the risk of lung cancer. Secondhand tobacco smoke exposure has been associated with an approximately 30% increased risk for lung cancer in never-smokers, with the increased risk ranging from 20–50%[19,20] depending on the number of years of exposure.[21] In a meta-analysis of 22 studies, the authors reported that exposure to tobacco smoke in the workplace increased the risk of lung cancer by 24%, a risk that was highly correlated with duration of exposure[22] (see also Chapter 65).

There is overwhelming evidence for the carcinogenic effects of cigarette smoking and other environmental exposures and for the association of these exposures with multiple somatic mutations in lung tumors. Known mutations and loss of heterozygosity in oncogenes and tumor suppressor genes involved in lung carcinogenesis accumulate in individual somatic cells during lung tumor initiation and progression.[23–25] In 2016, a comprehensive analysis of mutation profiles in 660 adenocarcinomas and 484 squamous lung cancers was presented as a part of the Cancer Genome Atlas, which found 8.7 and 9.7 mutations per megabase in these cancers.[26] Six mutational signatures were observed, with the most common signature being C to T transversions reflecting smoking exposure.[26] A subset of tumors showed profiles reflecting mismatch repair defects or APOBEC signatures, which can reflect DNA repair after viral exposures. Susceptibility to selected mutations also varies according to host-specific factors. For example, mutations in *EGFR* are much more common in women, Asians, never-smokers, and those with adenocarcinomas,[27] whereas mutations affecting *KRAS* are more common in men, individuals of European descent, smokers, and those with squamous histology.[26] Susceptibility to somatic mutations may be due to individual differences in risk associated with the inhalation of known carcinogens (i.e., individuals differ in their susceptibility to these environmental insults).[28,29] Evidence indicates that allelic variation at genetic loci affects inherited susceptibility to lung cancer. Studies of inherited susceptibility to lung cancer, including major susceptibility loci and loci with less pronounced effects, are described later in this chapter.

SMOKING BEHAVIOR AND RISK FOR LUNG CANCER

In the early 1900s, lung cancer was infrequent. In North America and Europe, the dramatic increase in lung cancer risks beginning after World War I resulted from the confluence of several factors. First, modern automated cigarette production allowed broader distribution of cigarettes, which resulted in a substantial increase in the availability and use of tobacco products. During World War I, tobacco companies targeted the military for distribution of cigarettes, which were viewed as improving the troops' mood and alertness. During World War II, standard rations contained cigarettes. At that time, the causal link between smoking and lung cancer risk was unknown. Establishing the causal relationship between cigarette smoking and lung cancer risk required the development of many of our modern epidemiologic and statistical approaches. Although a correlation between cigarette use and lung cancer was established in the mid-1950s,[15,30] many concerns were raised that this correlation might reflect various biases and poor statistical measures. Berkson argued that the specific association between lung cancer and smoking might reflect bias in studying individuals with prevalent lung cancers, who might survive longer if they smoked.[31] Avoiding Berkson's bias has led to the emphasis on studying incident rather than prevalent cases of a disease when practicable. Fisher argued that some genetic factor might contribute to both smoking and lung cancer risk so that no causal inference could be made.[32] This hypothesis was largely disproved in a study of monozygous twins discordant for smoking behavior,[33] although this study showed lower relative risks than are typically observed in case-control studies, suggesting some evidence for joint effects of genetic factors on both smoking and lung cancer risk.[34] Finally, modern logistic regression techniques were developed for modeling binary factors with covariates to deal with potential confounders that might have influenced the causal inference of smoking on lung cancer risk.[35] Despite the advances in understanding their harm, cigarettes are still made available at low cost to military personnel and were promoted and made readily available to the military during the Gulf War.[36] Causal modeling shows that a large fraction, 35–79%, of the excess veteran deaths due to heart disease and lung cancer are attributable to military-induced smoking.[37]

Notwithstanding the growing evidence in the 1950s and early 1960s that tobacco smoking increases lung cancer risk, progress was slow in the acknowledgement of the association. From 1953 to 1954, smoking rates declined as public awareness of the link between smoking and lung cancer risk emerged, but "filtered" cigarettes were introduced to allay public concerns about smoking and health effects.[38] The 1964 Surgeon General's report used a consensus approach very effectively to consolidate evidence that cigarette smoking increases lung cancer risk. Since 1964, annual reports from the Surgeon General have continued to document the impact of smoking on health in the United States, which has led to a continual decrease in smoking.[38] Although the recognition that smoking is the major determinant in lung cancer risk was a key observation in public health, developing strategies to change behavior and reduce risk has been an ongoing challenge.

The Surgeon General's report in 1964 that linked lung cancer risk to tobacco smoke had an immediate effect in reducing smoking behavior. Given the approximately 20-year lag between exposure to smoking and lung cancer development, the impact of these reductions on lung cancer risk was slow to be realized; however, lung cancer rates have dropped by nearly 50% in U.S. men since their high in 1992.[39] Lung cancer rates in women have shown only a mild decrease, largely because female tobacco smoking trends have been flat. Based on 2018 data, about 34 million adults in the United States smoke cigarettes (16% of men and 12% of women), and every day about 1600 children under the age of 18 smoke their first cigarette.[40]

According to the World Health Organization,[41] the tobacco use epidemic killed 100 million people in the 20th century and could kill 1 billion people in the 21st century without the introduction of population-level approaches to stem its use. A comprehensive review of tobacco control policies is beyond the scope of this chapter and has been comprehensively reviewed elsewhere,[42] but selected policies that are highly effective are briefly described (see also Chapter 66). First, restricting access by adolescents to nicotine-containing products reduces adoption of tobacco smoking and decreases nicotine dependence.[43] Second, nicotine product consumption is sensitive to cost, with higher *elasticity*, meaning a greater sensitivity to cost increases, in younger consumers.[44] Taxation is an acceptable approach to tobacco control for many governments but can increase illicit behavior and smuggling. Research has documented a causal role for marketing of tobacco-containing products in increasing adoption in adolescents and their subsequent use.[45] Finally, clean air laws for public spaces and tobacco smoking bans reduce harm from smoking and also reduce overall smoking behavior.[46] Tobacco control policies in North America, Western Europe, and other higher-income countries have greatly reduced tobacco use by applying a multiple-component approach. In contrast, e-cigarette and noncombustible tobacco use has risen dramatically,[47] particularly in adolescents and young adults. In most regions, e-cigarette use has not been taxed, access for adolescents has not been limited, and marketing has been unregulated. This lack of control has allowed a new epidemic of nicotine dependence to appear. Although the risk for lung cancer among e-cigarette users is likely to be lower than risks from use of combustible tobacco products, harm reduction through the use of these new products remains poorly characterized. A recent meta-analysis showed that e-cigarette users are less likely to have quit smoking successfully than cigarette users who attempted smoking cessation without using e-cigarettes.[48] Also, modeling the potential of decreased harm among smokers and increased adoption of smoking due to dual e-cigarette and combustible smoking shows an increased population-level harm related to adoption of e-cigarettes.[49] Additionally, e-cigarette use has recently led to an outbreak of severe acute lung diseases, including pneumonitis and acute respiratory distress syndrome.[50]

There are 3500 chemical particulate constituents of tobacco smoke, of which more than 70 are known carcinogens.[51,52] These carcinogens include a wide array of compounds, but most undergo activation to more reactive species during the process of conjugation and removal. The activation of *polycyclic aromatic hydrocarbons* (PAHs) and arylamines by cytochrome P-450s (e.g., CYP1A1, CYP1A2, and CYP3A4) leads to the formation of reactive chemical species that can bind covalently to DNA to form carcinogen-DNA adducts.[53] PAHs such as benzo(a)pyrene are first oxidized by aryl hydrocarbon hydroxylase or CYP1A1 (the structural gene for P-450 1A1), resulting in the formation of an arene oxide. This metabolite can be further activated to form a dihydrodiol.[54] Dihydrodiol can then be further metabolized across the olefinic double bond by both cytochrome P-450 (CYP3A4) and other oxidation systems,[55] thus forming a diol epoxide. Diol epoxides are unstable and rearrange to form highly reactive carbocations (carbon atoms bearing three bonds and positively charged). For example, benzo(a)pyrene-7,8-diol 9,10-epoxide forms covalent bonds primarily with the exocyclic amino group of guanosine. This reaction has been shown to be responsible for activating mutations in the *HRAS-1* proto-oncogene in several experimental systems.[56] Alternative and competing routes of metabolism can lead to inactivation of carcinogens (e.g., PAHs) through the formation of conjugates (glutathiones, glucuronides, and sulfate esters) or phenols and tetrahydrotetrols, which facilitate excretion. The balance between metabolic activation and metabolic detoxification, as well as the efficiency of DNA repair mechanisms, has been proposed to affect cancer risk in an individual exposed to PAHs.

Two nicotine-specific nitrosamines that are relatively abundant constituents of all tobacco smoke products are *4-(methylnitrosamino)-1-(3-pyridyl)-1-butanone* (NNK) and *N′-nitrosonornicotine* (NNN). NNK is rapidly converted in biologic systems to the reactive species *4-(methylnitrosamino)-1-(3-pyridyl)-1-butanol* (NNAL)[57] (Fig. 74.2). These compounds can be removed via glucuronidation or can be activated further by cytochrome P-450 metabolism. Genetic analysis has shown that *single nucleotide polymorphisms* (SNPs) in *HSD11B1* and *AKR1C4* associate with NNAL. Variation in CYP2A6, which is the primary cytochrome P-450 involved in metabolizing nicotine and NNAL, is strongly associated with lung cancer risk; it may have roles in both controlling smoking behavior and in modulating risk through NNAL adduct formation.[58] Nicotine-associated nitrosamines have been increasingly associated with lung cancer risk and are not found in cannabis smoke, which to date has not shown a convincing relationship with elevated lung cancer risk.[59] This provides additional indirect evidence that nicotine-specific nitrosamines contribute to the elevated lung cancer risk specifically associated with tobacco smoke.

OCCUPATIONAL AND ENVIRONMENTAL FACTORS

Although the vast majority of lung cancer is the result of environmental exposures, there is a complex interplay between exposure and individual susceptibility. Genetic susceptibility is discussed later. In addition to tobacco smoking, the major environmental causes of lung cancer include occupational exposures and environmental air pollution.

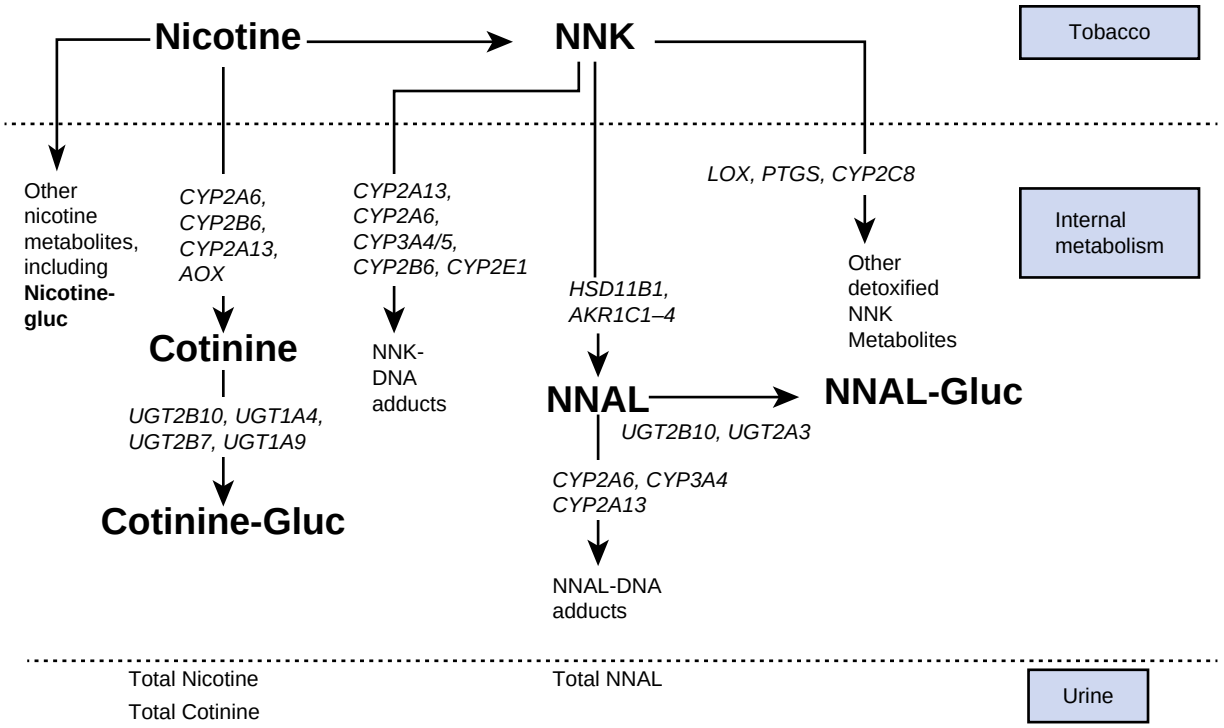

Figure 74.2 Selected genes of NNK to NNAL and of nicotine to cotinine metabolism. Total NNAL, nicotine or cotinine includes their glucuronides. (From Ter-Minassian M, et al. Genetic variability in the metabolism of the tobacco-specific 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanone (NNK) to 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanol (NNAL). *Int J Cancer.* 2012;130:1338-1346.)

OCCUPATIONAL EXPOSURES

Lung cancer has been found to be associated causally with many workplace exposures, including to asbestos, arsenic, beryllium, cadmium, chromium, diesel exhaust, nickel, radiation, silica, and vinyl chloride, in addition to others. Occupational exposure to lung carcinogens has been estimated by case-control studies to account for 9–15% of lung cancer cases.[60] As lung carcinogens have been identified in the workplace and as regulations have been established to prevent workers from being exposed, this proportion has been decreasing over time in the high-income countries, whereas industrial exposures have increased in many low- to moderate-income countries. Cigarette smoking also potentiates the effect of some of the known occupational lung carcinogens, such as asbestos. Some of the most common occupational lung carcinogen exposures are discussed in the following sections.

Asbestos

Asbestos, a well-established occupational carcinogen,[61,62] refers to several forms of fibrous, natural silicate minerals.[63] The epidemiologic evidence that asbestos causes lung cancer dates to the 1950s. In a retrospective cohort study published in 1955, Doll observed that asbestos textile workers at a factory in the United Kingdom had a tenfold elevation in lung cancer risk and that the risk was most heavily concentrated during the timeframe before regulations were implemented to limit asbestos dust in factories.[64] A sevenfold excess of lung cancer was subsequently observed among insulation workers in the United States,[65,66] with peak incidence at 30 to 35 years after the initial exposure to asbestos.[67] The risk of lung cancer has been noted to increase with increased exposure to asbestos[68] and to be associated with each of the principal commercial forms of asbestos.[69] Whether asbestos acts directly as a carcinogen or indirectly, for example, by causing chronic inflammation that eventually leads to cancer, remains controversial.[70–72] For the mechanism of asbestos-induced lung cancer, two competing hypotheses have been proposed: (1) lung cancer arises as a consequence of the asbestos-induced inflammatory lung disease, asbestosis, and (2) lung cancer arises directly from asbestos exposure, while the asbestosis reflects cumulative asbestos dose. Regardless of the mechanism, asbestos is a known lung carcinogen, and the number of exposed workers is increasing in South America, Asia, and the former Soviet Union.[62]

Asbestos and cigarette smoking are independent causes of lung cancer and, in combination, they act synergistically to increase risk. A recent follow-up study of the original Selikoff cohort used to estimate risk has allowed precise quantitative characterization of this synergy (Fig. 74.3).[73] The risk of the combined exposure is much higher than would be expected if one merely added the risks together, showing a strong interaction between the two. In fact, the risks are approximately multiplicative in persons with asbestosis and at least additive in exposed workers without asbestosis who also smoke. Lung cancer mortality was increased by asbestos exposure alone among nonsmokers (rate ratio, 3.6; 95% *confidence interval* [CI], 1.7 to 7.6), by asbestosis among nonsmokers (rate ratio, 7.4; 95% CI, 4.0 to 13.7), and by smoking without asbestos exposure (rate ratio, 10.3; 95% CI, 8.8 to 12.2). The joint effect of smoking and asbestos alone was additive (rate ratio, 14.4 [95% CI, 10.7 to 19.4]) and with asbestosis, supra-additive (rate ratio, 36.8 [95% CI, 30.1 to 45.0]). Insulator lung cancer

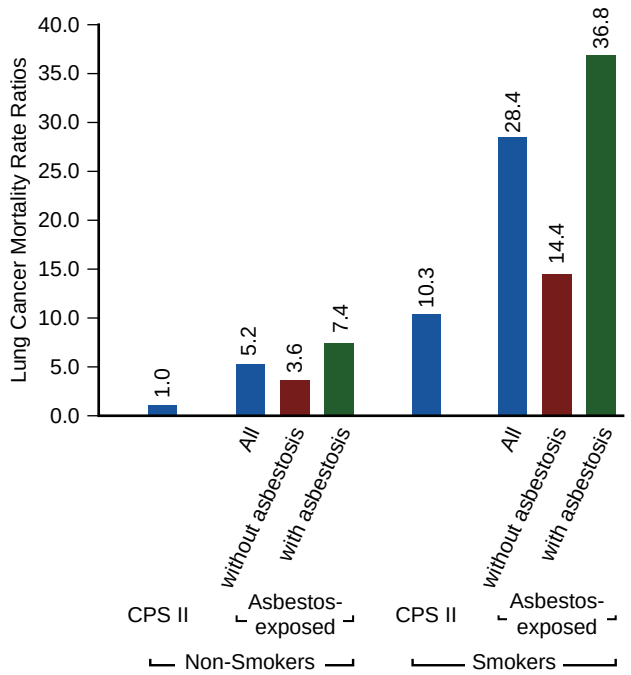

Figure 74.3 Lung cancer mortality rate ratios by asbestos exposure, asbestosis, and smoking status. The risks of smoking and asbestos are approximately multiplicative in persons with asbestosis and at least additive in exposed workers (insulators) without asbestosis who also smoke. CPS II, a control group not exposed to asbestos, from the Cancer Prevention Study II of the American Cancer Society. (From Markowitz SB, Levin SM, Miller A, Morabia A. Asbestos, asbestosis, smoking, and lung cancer. New findings from the North American insulator cohort. *Am J Respir Crit Care Med*. 2013;188[1]:90–96.)

mortality halved within 10 years of smoking cessation and converged with that of never-smokers 30 years after smoking cessation.[73]

Diesel Exhaust

The most definitive study to date evaluating the relationship between quantitative estimates of exposure to diesel exhaust and lung cancer mortality after adjustment for smoking and other potential confounders was the Diesel Exhaust in Miners Study conducted by the National Cancer Institute.[74] The investigators performed a nested case-control study in a cohort of 12,315 workers in eight non-metal mining facilities, which included 198 lung cancer deaths and 562 incidence density-sampled control subjects individually matched on mining facility, sex, race/ethnicity, and birth year (within 5 years), from all workers who were alive before the day the case subject died. They estimated diesel exhaust exposure, represented by *respirable elemental carbon* (REC), by job and year for each subject, based on an extensive retrospective exposure assessment at each mining facility. They observed statistically significant increasing trends in lung cancer risk with increasing cumulative REC and average REC intensity. Cumulative REC, which lagged 15 years, yielded a statistically significant positive gradient in lung cancer risk overall (P [trend] = 0.001); among heavily exposed workers (i.e., above the median of the top quartile [REC ≥ 1005 μg/m^3 per year]), risk was approximately three times greater (*odds ratio* [OR], 3.2; 95% CI, 1.3 to 7.7) than that among workers in the lowest quartile of exposure. Among never-smokers, ORs were 1.0, 1.5 (95% CI, 0.3 to 7.5), and 7.3 (95% CI, 1.5 to 36.6) for workers with 15-year lagged cumulative REC tertiles of less than 8, 8 to less than 304, and 304 μg/m^3 per year or more, respectively. They also observed an interaction between smoking and 15-year lagged cumulative REC (P [interaction] = 0.086) so that the effect of each of these exposures was attenuated in the presence of high levels of the other, all providing further evidence of diesel carcinogenicity in humans.[74,75] The International Agency for Research on Cancer subsequently classified diesel exhaust as a class I known human carcinogen.[76]

Other Occupational Exposures

Population-based studies have reported additional lung cancer associations with the following compounds and/or processes: ionizing radiation (uranium mining), vinyl chloride (pulp and paper workers), arsenic (smelting of ores containing arsenic, pesticide application, wood preservation), beryllium (ceramic workers, missile technicians, nuclear reactor workers, jewelers), chromium (stainless steel production, welding, tanning industries), and nickel (battery makers, ceramic makers, electroplaters, glass workers, jewelers, metal workers, welders).[77] A discussion of occupational exposures to ionizing radiation is included later.

RADIATION

Epidemiologic studies of populations exposed to high doses of radiation show that lung cancer is causally associated with exposure to ionizing radiation. Two types of radiation, classified by the rate of energy transfer to the tissue, are relevant to lung cancer: high-*linear energy transfer* (LET) radiation (e.g., neutrons and radon) and low-LET radiation (e.g., x-rays and γ-rays). High-LET radiation produces ionization of relatively higher density in tissues than low-LET radiation; therefore, in equivalent doses, more biologic damage is produced by high-LET than low-LET radiation.

HIGH-LET RADIATION: RADON

Radon is an inert gas produced naturally from radium in the decay series of uranium. Two of the radon decay products emit alpha particles that can damage the DNA of cells of the respiratory epithelium. Epidemiologic studies of underground miners of uranium and other ores have established exposure to radon daughters as a cause of lung cancer.[78,79] In the underground miners exposed to radon in the past century, very high lung cancer risks were observed; in the miners in more contemporary workplaces, the observed risks have been much less because exposure concentrations have been better controlled, but still show clear evidence of existing cancer risk.[78] Cigarette smoking and radon decay products synergistically influence lung cancer risk, that is, to greater degree than simply adding the risks of each together.[80,81] For this reason, the bulk of the lung cancer burden caused by radon exposure in the general population is concentrated within cigarette smokers.[79]

Radon is of broader societal interest because it is a ubiquitous air pollutant that enters buildings from the underlying

soil and sometimes through the water. On average, indoor exposures to radon for the general population are much less than for occupational groups such as uranium miners; but the results of case-control studies of indoor radon exposure have documented that residential exposure to radon in indoor air is significantly associated with increased lung cancer risk.[82,83]

The assumptions made by the Environmental Protection Agency and the Biological Effects of Ionizing Radiation VI Committee of the National Research Council have led to estimates that approximately 15,000 to 21,000 lung cancer deaths per year in the United States are caused by radon.[84] About 2900 of these cases are estimated in nonsmokers. In the United States, the Environmental Protection Agency has called for testing of all residences and mitigating the exposure when guideline values are exceeded.

LOW-LET RADIATION: X-RAYS AND γ-RAYS

Earlier epidemiologic data relating low-LET radiation to lung cancer stem from three principal populations[85]: (1) the atomic bomb survivors in Japan, (2) patients with diseases such as ankylosing spondylitis or tuberculosis who received multiple radiation treatments, and (3) occupational groups in professions exposed to radiation. The single high-dose exposure of the atomic bomb survivors was associated with significant lung cancer risk.[86] Regardless of age at the time of the blast, the excess of lung cancer appeared when the survivors reached older ages at which cancer usually develops.[87] Quantitative risk models are available that describe how risk increases with radiation dose.[85] Over the past several decades, medical radiation has replaced radon as the leading contributor to the radiation exposure in the population. In general, a substantial proportion of the U.S. population is now exposed to ionizing radiation from medical diagnostics, particularly from computed tomography scans. The exposure is of sufficient magnitude to be of concern as a cause of increased population risk for cancer.[88–90]

The findings from the *National Lung Screening Trial* (NLST) showed that *low-dose spiral computed tomography* (LDCT) screening significantly reduced lung cancer mortality among those at high risk for lung cancer defined by age (55 to 74 years) and smoking history (≥30 pack-year smoking history).[6] Based on the findings of the NLST, the U.S. Preventive Services Task Force recommends annual screening in the high-risk group as defined in the NLST.[91] However, LDCT screening will result in increased exposure of smokers to ionizing radiation. In making their recommendation in support of LDCT screening, the U.S. Preventive Services Task Force acknowledged that there is uncertainty about the magnitude of the radiation-associated risks. Characterizing the magnitude of risks associated with LDCT screening is an important future priority because risk models that have attempted to quantify these risks indicate they are not trivial[92] (see also Chapter 20).

AIR POLLUTION

During a typical day, the average adult inhales about 10,000 L of air. Consequently, even the carcinogens present in the air at low concentrations are of concern as a risk factor for lung cancer (see also Chapter 102).

ATMOSPHERIC AIR POLLUTION

Outdoor (ambient) air can contain a number of hazardous agents. Many of these are generated by the combustion of fossil fuels, including carcinogens such as PAHs and metals such as arsenic, nickel, and chromium.[62] Depending on the pollution sources, the constituents of air pollution vary by locale and over time. Particulate matter, which has multiple sources in urban air, has been studied as a potential lung cancer risk factor. In a study in six U.S. cities, a 40% increase in lung cancer risk was found in residents in the city with the highest concentration of fine particles in the atmosphere compared to the city with the lowest concentration.[93] The data from the American Cancer Society's Cancer Prevention Study II showed that each 10 g/m^3 increase in concentration of fine particles carried an increased lung cancer risk of 14%.[94] A European study of more than 300,000 individuals from nine countries observed that the risk of lung cancer increased significantly as the concentration of particulate matter increased.[95] Further evidence indicating an association between constituents of ambient air pollution and increased lung cancer mortality continues to accrue, with reports from Japan,[96] China,[97] and New Zealand.[98]

INDOOR AIR POLLUTION

Indoor air pollution arises from pollutants that enter from the outside as well as those that originate indoors from tobacco smoking, building materials, soil gases, household products, and combustion from heating and cooking.[99] In the more developed countries, two of the most important indoor pollutants that influence lung cancer risk in never-smokers are passive smoking[91] and radon.[100] In the developing world, the major source of indoor air contamination results from the use of unprocessed solid fuels, notably coal (a fossil fuel) but also biomass fuels, for cooking and space heating.[101] Mumford and coworkers[102] inferred that smoky coal was a major determinant of the geographic distribution of lung cancer in Xuan Wei, China, a finding corroborated by an animal model.[103] Evidence supporting a causal association was subsequently strengthened by studies documenting that switching from use of unvented fire pits to stoves with chimneys[104] or to portable stoves[105] cut the lung cancer risk by half.

Indoor burning of biomass, such as wood, is associated with lung cancer risk, but the association is weaker than for fossil fuel burning. This was illustrated in a pooled analysis of seven case-control studies, in which the risk of lung cancer was strongest for indoor burning of coal in Asia (OR, 4.9; 95% CI, 3.7 to 6.5) and much weaker—but still statistically significant—for indoor burning of wood in Europe and North America (OR, 1.2; 95% CI, 1.1 to 1.4).[106] These findings were corroborated in a meta-analysis of published studies.[107] Indoor burning of solid fuel is a major cause of lung cancer in China and one that is preventable. Based on statistical models, projections indicate that reductions in the indoor burning of solid fuel would substantially reduce lung cancer deaths.[108]

DIET AND OBESITY

The possible role of diet in modifying the risk for lung cancer has been the focus of intensive investigation, driven initially by the rationale that specific micronutrients might have anticarcinogenic activity. The most thoroughly investigated dietary factors are also those that appear to have the greatest implications for prevention: fruits, vegetables, and specific antioxidant micronutrients commonly found in fruits and vegetables.

The results of case-control and prospective cohort studies have tended to show that individuals with high dietary intake of fruits or vegetables have a lower risk for lung cancer than those with a low intake.[110] To understand the basis of this protective association, researchers have grouped fruits and vegetables into classes and examined them individually in relation to lung cancer risk. For example, tomatoes and cruciferous vegetables[110,111] have been associated with a reduced risk for lung cancer in a number of studies. These food-based analyses can help clarify whether protection arises from the complex mixture that composes fruits and vegetables or from specific biochemical constituents present in particular fruits and vegetables.

Fruits and vegetables are the major dietary source of antioxidant micronutrients. Much of the research on diet and lung cancer has been motivated by the hypothesis that diets high in antioxidant micronutrients may protect against oxidative DNA damage and thereby protect against cancer. For example, this was one of the hypothesized roles for β-carotene,[112,113] the focus of now-controversial clinical trials. Two strategies are used to evaluate the relationship of micronutrients to lung cancer risk in observational epidemiologic studies: (1) estimating micronutrient intake from food frequency questionnaires and (2) measuring serum concentrations of micronutrients. Prospective studies of both dietary intake[114] and prediagnostic blood concentrations suggest that carotenoids are inversely associated with lung cancer risk.

However, the protective association predicted between β-carotene and lung cancer on the basis of these observational epidemiologic studies was not confirmed in three randomized, double-blind, placebo-controlled chemoprevention trials.[115–117] In fact, two of these studies with participants at high risk for lung cancer (heavy smokers and asbestos-exposed workers) were stopped early because significantly *increased* risk for lung cancer was observed in the β-carotene group compared with the placebo group.[116] The precise mechanism underlying this clinical trial observation is not known but is postulated to be a disturbance in the balance between cellular oxidants and antioxidants. Specifically, carotene acts as an antioxidant. Tobacco smoking is highly oxidative and decreases plasma carotenoids. The protective effects of β-carotene at dietary intake amounts may be lost or reversed with high-dose supplements because some cellular oxidants are needed for normal homeostasis (such as apoptosis and detoxification reactions by cytochrome P-450 complexes). Hence, high doses of antioxidants such as β-carotene can inactivate more cellular oxidants than necessary and interfere with their protective function.[118,119]

With regard to obesity, disentangling the effects of smoking and lung cancer itself (which can cause cachexia) is difficult when studying incident lung cancer cases and matched controls. Therefore, a causal inference procedure called Mendelian randomization[120] using genetic instruments defined by SNPs that can predict *body mass index* (BMI) has been adopted as an alternative procedure. A Mendelian randomization analysis[121] of multiple cancers showed a positive association between adult BMI, genetic score, and lung cancer (OR, 1.3; 95% CI, 1.1 to 1.5). Additionally, in the consortium, an analysis of 29,266 lung cancer cases and 56,450 controls identified a causative role of higher fasting insulin in the etiology of squamous cell and SCLC but not of adenocarcinoma.[122,123] However, the association of obesity and lung cancer risk remains controversial. A large 12-year pooled analysis of 1.6 million Americans, Europeans, and Asians showed that, whereas increased BMI was generally associated with decreased risk for incident lung cancer, greater waist circumference and waist-hip ratio were shown to increase risk after adjusting for BMI. Central obesity concurrent with overall low BMI may identify a high-risk lung cancer population.[123a]

OTHER CAUSATIVE ASSOCIATIONS

As noted earlier, the results of recent analysis of large-scale consortia studies have allowed assessment of many potential risk factors of relative low risk, but which are significant when considering the numbers of at-risk persons. The consortia have been vital for discovering common genetic traits as well as important complex phenotypic characteristics such as obesity, metabolic disturbances, hormone use, height, and alcohol use.

In an analysis of 22 case-control and cohort studies from the International Lung Cancer Consortium, moderate alcohol consumption was inversely associated with lung cancer risk after adjusting for smoking.[124] Aspirin and nonsteroidal anti-inflammatory drug use conferred modest protection for lung cancer, especially in ever-smokers after appropriate adjustments, but assessment of optimal dosing was not possible.[125] Oral contraceptive use was associated with a reduced lung cancer risk (OR, 0.8; [CI, 0.7 to 1.0]), as was hormone replacement therapy (OR, 0.8 [CI, 0.7 to 0.9]).[126] Both estrogen and combination estrogen-progesterone therapies were associated with decreased risk, with no clear dose-response with years of use. The incidence of lung cancers of all cell types was reduced, with the largest effect in squamous cell (OR, 0.5; [CI, 0.4 to 0.8]), with no interaction with BMI or smoking status.

Lung, bladder, and kidney cancer mortality rates due to arsenic exposure have very long latencies, with increased risks manifesting 40 years after exposure reduction. In fact, arsenic in drinking water may have one of the longest cancer latencies for a human carcinogen.[127]

GENETIC SUSCEPTIBILITY TO LUNG CANCER

In 1963, Tokuhata and Lilienfeld showed familial aggregation of lung cancer.[128,129] After they accounted for personal smoking, the results suggested the possible interaction of

genes, shared environment, and common lifestyle factors in the etiology of lung cancer. In their study of 270 people with lung cancer and 270 age-, sex-, race-, and location-matched controls and their relatives, the authors found a 2.0- to 2.5-fold increased lung cancer mortality among smoking relatives of people with lung cancer compared with smoking relatives of control subjects. Nonsmoking relatives of people with lung cancer were also at higher risk than nonsmoking relatives of control subjects.

Since this study, authors of several other studies have reported familial aggregation of lung cancer.[130,131] In southern Louisiana, authors of case-controlled studies reported an increased familial risk of lung cancer[131] and other smoking-related cancers[132] among relatives of lung cancer cases after accounting for the effects of age, sex, occupation, and smoking history. The risk of lung cancer for parents of cases was fourfold compared with parents of controls. After controlling for the confounding effects of the measured environmental risk factors (occupation and smoking), being a first-degree relative of a lung cancer case conferred a 2.4-fold higher lung cancer risk. The largest single study of familial aggregation involved the evaluation of people with lung cancer and control subjects in Iceland.[133] In this population-based approach, the risk of lung cancer was 2.7-fold higher in parents of lung cancer cases compared to parents of controls and the risk increased to 3.5 for parents of early-stage lung cancer cases (age of onset ≤60 years). The risk to siblings was increased 2.0-fold in general but increased to 3.3-fold for siblings of people with early-onset lung cancer. Studies of risk for lung cancer among relatives of never-smokers are limited[19,134,135] but also show some increased risk, although usually with a weaker association than among lung cancer cases overall, which are predominantly in smokers. Mayne et al. studied never-smokers and former smokers (i.e., those who stopped smoking at least 10 years before they were interviewed) and reported that a positive family history of lung cancer was associated with increased lung cancer risk after adjustment for age and smoking status.[135] Finally, a meta-analysis of 28 case-control and 17 cohort studies found an approximately twofold increased risk of lung cancer associated with family history.[136] Risk was generally higher for relatives of people in whom lung cancer was diagnosed at a young age and when multiple family members were affected.

Overall, these results indicate a similar effect of about twofold higher risk for lung cancer among first-degree relatives of lung cancer cases, similar to what is observed for other common cancers, although this risk is modulated by the smoking patterns of the relatives.

HIGH-RISK SYNDROMES CONFERRING AN INCREASED RISK OF LUNG CANCER

Lung cancer risk is greatly elevated in selected rare syndromes. Leonard et al. reported that survivors of familial retinoblastoma are at increased risk for SCLC.[137] Kleinerman et al.[138,139] reported lung cancer developing among individuals with germline retinoblastoma mutations and a history of heavy smoking.[140] The standardized mortality ratio for lung cancer in those who survived hereditary retinoblastoma was 15-fold.[140] Overall, retinoblastoma survivors tend to smoke less than the general population, suggesting that targeting counseling to avoid this risky behavior in this high-risk population may be effective.[141] The retinoblastoma gene (*RB1*) is inactivated in 90% of SCLCs, indicating the biologic relevance of this gene in SCLC etiology.[142]

Germline mutations in the *TP53* gene cause the inherited Li-Fraumeni syndrome. Individuals with this syndrome are at greater increased risk for many cancers, including breast and lung cancers, sarcomas, leukemias and lymphomas, and adrenocortical tumors. The standardized incidence ratio for lung cancer was estimated at 38 in a prospectively collected cohort of *TP53* mutation carriers.[143] Cigarette smoking was associated with a threefold increase in risk for Li-Fraumeni carriers.

Mutations in the *EGFR* gene are often found in adenocarcinomas of the lung arising in never-smoking women and in Asian populations.[144] One family with multiple lung adenocarcinomas was found to have segregation of an *EGFR* mutation, indicating that rarely inherited mutations of this locus can increase the risk of lung cancer.[145] Gazdar collected data from nine families carrying the very rare inherited T790M mutation of *EGFR* and found that carrying the T790M mutation conveys a very high 31% lifetime risk to never-smokers.[146] This mutation is very rare and, as of September 2019, the GNOMad browser reported the allele frequency of this missense mutation to be 2.8×10^{-5}.[147,148] One Japanese family with an inherited mutation of *MET* associated with lung cancer was found by exome sequencing.[149] In these rare conditions, increased screening is warranted for early lung cancer detection. Both inherited *RB1* and *TP53* mutations make individuals highly susceptible to ionizing radiation, and a targeted prevention strategy using magnetic resonance imaging is encouraged.[150]

Studies of families with multiple relatives affected by lung cancer identified a region on chromosome 6q23-25 harboring a susceptibility region.[151] An updated analysis[152] found strong evidence for this factor only in families with four or more affected relatives in two or more generations. Studying a string of markers called a haplotype, the investigators found that light or heavy smoking conferred high risk, indicating the individuals in these families are particularly sensitive to tobacco exposure. In this chromosomal region, a germline mutation in *PARK2* was linked to lung cancer risk in one family with eight affected family members.[153] The authors found additional evidence suggestive of linkage for regions on chromosomes 1q, 4q, 6p, 6q, 8q, 9p, and 20q.[154,155]

COMMON LOW-PENETRANCE GENES: GENOME-WIDE ASSOCIATION STUDIES

In three articles published at the same time in *Nature* and *Nature Genetics*, researchers using *genome-wide association studies* (GWASs) identified the same region of chromosome 15q as being significantly associated with lung cancer risk.[156–158] The region that the authors identified included a neuronal nicotinic acetylcholine receptor gene cluster comprising *cholinergic receptor nicotine alpha 5* (*CHRNA5*), *CHRNA3*, and *CHRNA4* subunits. Nicotinic receptors are composed of pentamers that include alpha and beta units and are expressed in all tissues, but at higher levels in the brain. In all three studies, the authors identified the 15q region as being associated with an approximately 1.3-fold increased

risk of lung cancer among individuals heterozygous for the mutation and about a 1.8-fold increase for individuals homozygous for the mutation. Since these initial studies, multiple investigations of the 15q region have been conducted.[155] These studies identified novel variants in acetylcholine receptors with a substantial influence on both smoking behavior and lung cancer risk.

Findings from other GWASs led to multiple reports of regions on chromosomes 6p21 and 5p15 being associated with lung cancer risk.[159–161] These regions show considerable variability in the association according to histologic subtype. The *human leukocyte antigen* (HLA) region on chromosome 6p21 is largely associated with squamous cancer,[162,163] although other SNPs show associations only with adenocarcinomas. In the chromosome 5p15 region, variation affecting *cleft lip and palate transmembrane 1-like* (CLPTM1L) influence squamous lung cancer,[161,164–166] whereas variations that influence *human telomerase reverse transcriptase* (hTERT) are more associated with adenocarcinoma risk.[163] Additional regions are associated with squamous cell carcinomas: 12p13 *(RAD52),* 9p21 *(CDKN1B/ANRIL),* and 2q32. Imputation analysis yielded several new loci influencing primarily squamous lung cancer risk in European-descent populations.[167] Notably, an uncommon stop mutation, K3326X, in *BRCA2* found in less than 1% of Europeans was associated with a twofold overall increased risk for lung cancer, a 2.5-fold increased risk for squamous carcinomas, and a twofold increased risk for small cell lung cancer.[168] This increased risk of cancer development has also been noted in other smoking-related cancers, including head and neck[169] and esophageal cancers, along with squamous skin cancer, which is also a highly environmentally influenced cancer. The variant was associated with decreased risk of ovarian cancer among *BRCA1* or *BRCA2* carriers[170] and only confers at 1.3-fold increased risk for breast cancer.[170] Imputation analysis also identified variants of *TP63* influencing lung cancer risk in individuals of European descent and a previously identified[171] rare *CHEK2* variant protective for lung cancer risk.

Additional associations have been noted for adenocarcinomas. Authors of a GWAS conducted in the Han Chinese population found evidence for lung cancer risk associations in the 5p15 region, along with regions not identified in individuals of European ancestry: the 3q28 (*TP63*), 13q12 (*MIPEP-TNFRSF19*), and 22q12 (*MTMR3-HORMAD2-LIF*) regions.[172] With additional samples, Dong et al. identified more regions of risk in the 10p14, 5q32, and 20q13 regions.[173,174] In the Japanese population, Shiraishi et al. replicated the 5p15 and 3q28 findings reported in the Chinese population and the 6p21 findings in individuals with European ancestry and identified a novel region on 17q24.3 at rs7216064 near the *BPTF* gene.[174a]

Insufficient work has been completed to identify susceptibility genes in never-smokers of European descent for lung cancer using a GWAS approach, in part because these individuals are not as common in the population, making it more difficult to identify the numbers of subjects needed for a GWAS. However, this was possible in Asia; in never-smoking women in Asia, Lan et al.[175] replicated the 6p21, 5p15, and 3q28 findings discussed previously and reported new regions of interest in 10q25 and 6q22.77. A large study of individuals with European ancestry further clarified associations of lung cancer in never-smokers with the *hTERT* region.[176] Even fewer studies have been completed in the Black population. Associations between lung cancer risk and SNPs in the 15q25, 5p15, and 6p21 regions identified in individuals of European ancestry were replicated in Black individuals.[177–179] A recent GWAS study of African Americans from multiple U.S. sites did not identify new loci specific to this population but did identify novel African American–specific variants in the CHRNA5 region.[179]

In a review by Bosse and Amos,[180] all the known loci identified through 2018, when the OncoArray project[181] had been completed, were described. This project genotyped about 500,000 individuals for several cancers, including lung. GWAS studies from the OncoArray project identified several novel loci, many of which act as *expression quantitative trait loci*, and genomic loci that influence the expression level of messenger RNA, implicating genetic regulation as drivers of lung cancer risk.[182] Additional studies since 2018 have identified the *LCORL* gene as affecting risk for strongly familial lung cancer,[183] along with a new variant on chromosome 9p, several variants identified by gene-environment interaction analysis,[184] and three regions identified by analysis of gene-gene interactions,[185] including an interaction between *SYNE1* in the chromosome 6 region implicated in familial lung cancer risk with *RNF43.* Additionally, several variants were identified through an integrative study of Chinese- and European-descent populations[186] (eFig. 74.1).

The heritable genetic evidence to date clearly supports the hypothesis of a genetic component to the risk of lung cancer, with multiple genetic loci influencing risk. The aggregation of lung cancer in families remaining after adjustment for smoking history of each relative suggests that a segment of the population is at risk due to inherited mutations. Rarely, high-risk mutations cause greatly increased risk for lung cancer development and individuals with these mutations require careful management to avoid increasing risk from ionizing radiation. The findings from GWASs of more common and lower-penetrance SNPs associated with lung cancer risk contribute information about the biology of lung cancer development. Selected high-risk variants such as the K3326X variant of *BRCA2* convey sufficient risk to suggest implementing screening, in a similar way as would a positive family history of lung cancer. As more genome-wide studies are conducted, we may anticipate that genetic information will become useful for selecting individuals who will benefit from lung cancer screening and precision prevention.

Acknowledgments

This work was supported in part by National Institutes of Health grants U01CA209414 and U19CA203654 and the Cancer Prevention Research Institute of Texas grant RR170048. Dr. Amos is a Research Scholar of the Cancer Prevention Research Institute of Texas. We acknowledge Drs. Jonathan Samet, Anthony Aberg, and Malcolm Brock for earlier chapter contributions, and we thank Rowland Petite for assisting in updating eFig. 74.1.

Key Points

- In the United States, lung cancer remains the leading cause of cancer death for both men and women.
- The predominant cause of lung cancer is exposure to tobacco smoke, with active smoking causing most cases, but passive smoking also contributing.
- The reductions in smoking prevalence in men in the late 1960s through the 1980s will continue to drive lung cancer mortality rates down during the first portion of the 21st century.
- Fortunately, exposures to major occupational respiratory carcinogens have largely been controlled in the United States (though not globally), but the population is still exposed to environmental causes of lung cancer, including asbestos and radon, the second leading cause of lung cancer death.
- Gender similarities and differences exist in lung cancer. The most important fact is that, among smokers, a similar smoking history results in similar lung cancer risk for women and men. Among never-smokers, compared to men, women have a higher overall incidence of lung cancer, particularly of adenocarcinoma with epidermal growth factor receptor mutations.
- Certain heritable genetic risk factors render some individuals more susceptible to environmental carcinogens, especially tobacco. As more genome-wide studies are conducted, genetic information will likely become more useful for selecting individuals who will benefit from lung cancer screening and precision prevention.

Key Readings

American Cancer Society. *Cancer Statistics*. 2020;70(1):7–30.
Bosse Y, Amos CI. A decade of GWAS results in lung cancer. *Cancer Epidemiol Biomarkers Prev*. 2018;27(4):363–379.
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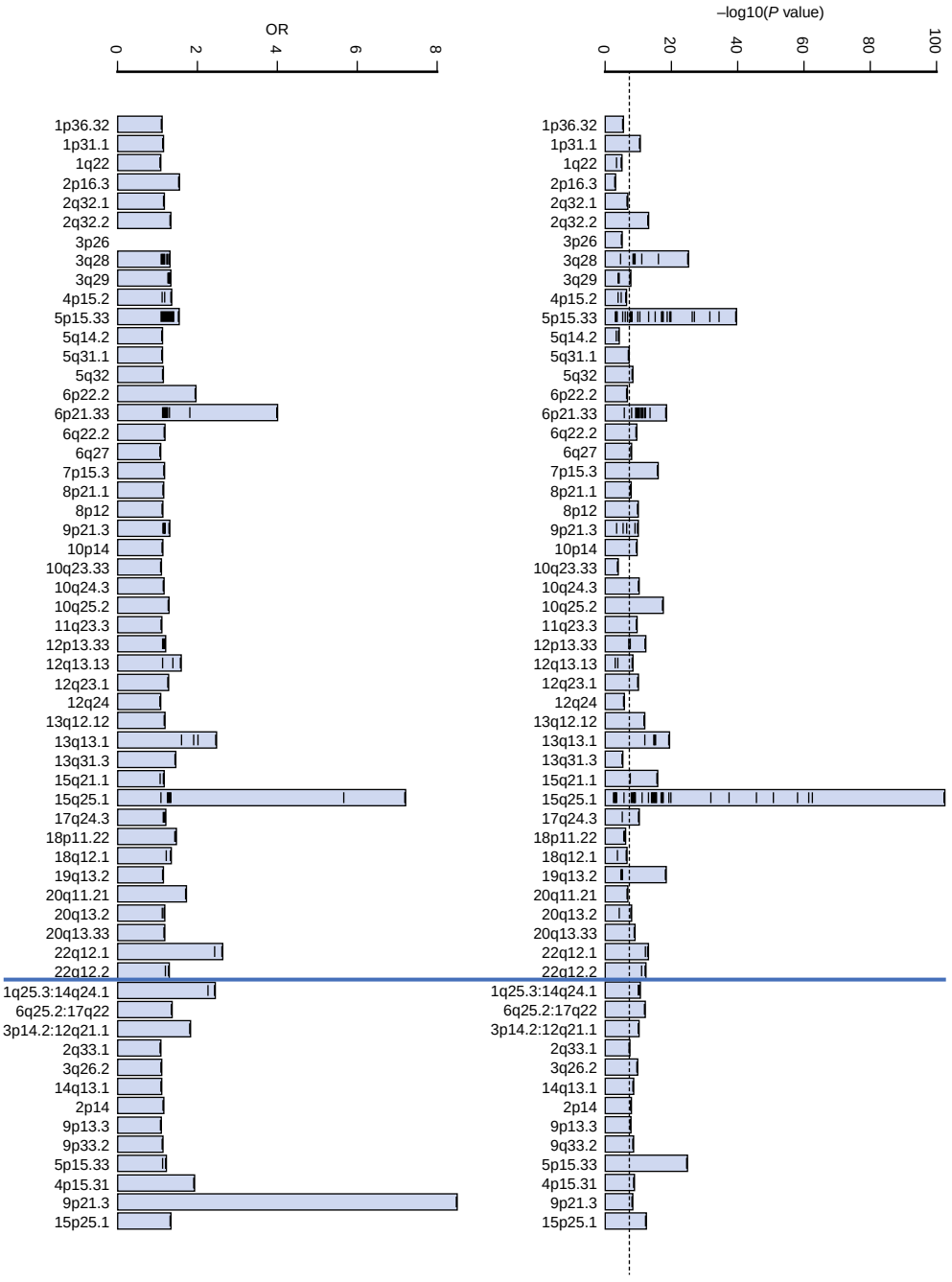
Complete reference list available at ExpertConsult.com.





eFigure 74.1 Magnitude of genetic associations for 58 reported lung cancer susceptibility loci. The *left* and *right* panels show *odds ratio* (OR) and –log10 (*P* values), respectively. The top set of results were previously described by Bosse and Amos,[180] whereas results below the line are newly reported loci. Bars illustrate the smallest *P* values or the maximum OR reported per locus. Tick symbols inside bars are results of the individual studies. *Top,* note that ORs lower than 1 were converted into their reciprocal (1/OR) for illustration purposes. The first three loci below the line are results from gene-gene interaction analyses reported by Li et al.[185]

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75 LUNG CANCER: SCREENING

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INTRODUCTION

Screening for lung cancer using low-dose computed tomography has now been shown to reduce mortality from lung cancer among high-risk individuals. However, in any screening program, attention must be given to the balance of benefit and potential harms from downstream management of screening-detected findings. This chapter discusses the evidence and support for screening and the components of high-quality screening.

EVIDENCE FOR LUNG CANCER SCREENING

The mortality from lung cancer is greater than for prostate, breast, and colon cancer combined. Most individuals are diagnosed when symptomatic at advanced stages of disease when survivorship is worse, making early detection appealing. Screening is the systematic examination of asymptomatic people to detect and treat disease. For screening to be beneficial, the disease must be relatively common, have high mortality, and must be more treatable when detected early, before symptoms develop. In addition, the screening process must benefit those diagnosed with lung cancer without harming the large number of people without the disease. The goal of screening for lung cancer is to detect disease at an earlier stage when it is more treatable (e.g., with surgery); this would indicate that the screening had achieved a favorable stage shift. In the absence of lung cancer screening, 75% of those diagnosed with lung cancer present with advanced disease for which the 5-year survival rate is 6–30%. This is compared to those found with localized disease for which the survival rate is 60%. To prove the benefit from screening, trials must not only be powered to demonstrate improved mortality and stage shift but also must be designed to detect a difference compared to usual care or another screening modality.

Although early cohort studies utilizing regular screening chest radiographs demonstrated an increased prevalence of lung cancers compared to control groups, there was no mortality benefit seen. Sputum cytology alone and in conjunction with chest radiography screening did not affect outcomes. The *Prostate, Lung, Colorectal and Ovarian* (PLCO) trial randomized 154,901 participants ages 55 to 74 to annual chest radiography screening versus usual care at 10 different sites and definitively showed no lung cancer mortality benefit.[1] Screening with *computed tomography* (CT) scan in several single-arm studies found a higher incidence of lung cancer detection at an early stage of disease but could not demonstrate a mortality benefit because of lack of a comparison group. These studies provided the impetus for randomized, controlled trials to assess outcomes from screening with *low-dose computed tomography* (LDCT). LDCT is performed using less ionizing radiation than standard CT scan (8 vs. 32 mSv). (See Chapter 20.)

Several European trials were conducted at single or small numbers of centers. These trials varied in age criteria, smoking history and, in one study, screening interval (annual vs. biennial LDCT), all with a comparison to usual care.[2–5] They were all similar in that they were not powered or designed to detect a difference in lung cancer mortality and therefore could not provide strong enough evidence to support large-scale implementation of lung cancer screening.

The *National Lung Screening Trial* (NLST) addressed these issues. The NLST has been the largest randomized trial of LDCT to date, conducted at 33 centers in the United States.[6] It enrolled 53,454 participants aged 55 to 74 years with at least a 30 pack-year smoking history, with former smokers having quit within the past 15 years.[6] Participants were randomized to annual LDCT for 3 years or annual chest radiograph. The study achieved its primary end point with a 20% lung cancer mortality reduction in the LDCT arm. The all-cause mortality rate was also 6.7% lower in those screened with LDCT. The overall number needed to screen to prevent one lung cancer death was 320.

The *Dutch-Belgian Randomized Lung Cancer Screening* (with the Dutch acronym NELSON) trial was the next largest trial of LDCT powered to detect a mortality difference compared to usual care.[7] Men and women aged 50 to 75 years who were current or former smokers who had quit within 10 years of enrollment with a minimum of 15 pack-years were recruited to participate at four centers. Following a baseline LDCT, participants underwent subsequent screening at 1, 3, and 5.5 years. At 10 years of follow-up, the cumulative rate ratio for death from lung cancer was 0.76 (confidence interval, 0.61–0.94) in the screened group compared to the control group. The decrease in mortality of 24% was similar to that of the NLST. More benefit was seen in women, although this group was relatively small.[7] The trial used computer software to evaluate noncalcified screening-detected nodules according to volume and volume doubling time. Growth between two scans was defined as a volume increase of at least 25%. A nodule identified on a baseline scan was also considered to be negative if the volume was less than 50 mm^3, if there was no growth at 3-month follow-up in nodules 50 to 500 mm^3 in size, or if volume-doubling time was 400 days or more.[8] Using these definitions, the sensitivity of screening following one round was 94.6% with a negative predictive value of 99.9%.[9]

The findings of these two seminal studies have provided definitive evidence in support of screening for early detection and mortality reduction in lung cancer. It is important to recognize, however, that lesions most often detected are benign. Therefore, management of screening-detected nodules is an important consideration because inappropriate management has the potential to lead to downstream harms from invasive diagnostic procedures. This is one of a number of factors that could potentially impact the generalizability of the finding of these large randomized trials.

GENERALIZABILITY

Although the NLST demonstrated a mortality reduction, questions have been raised about generalizability of the results to the eligible U.S. population. There are three main areas that may limit the ability to generalize the NLST results. The *demographics* of the estimated 8 million Americans meeting criteria for screening are considerably different from the NLST participants.[10] In comparison, the NLST participants were younger, healthier, better educated, and less likely to be current smokers. These findings are in line with the "healthy volunteer effect" seen in screening trials in which there is a self-selection of more educated, health-conscious participants with better access to health care.[11] The *expertise* available in the communities where individuals will be screened raises some concern that the results of screening may not be realized. In the NLST, screening was conducted at largely urban, tertiary care hospitals with expertise in all aspects of lung cancer care, including multidisciplinary clinics and dedicated thoracic radiologists. Even though the nodule detection rate was high, the number of participants requiring invasive interventions was quite low. Whether this conservative use of invasive testing will continue at the community level is uncertain. This is of concern because variation in the utilization of CT-guided lung biopsy for diagnosis in incidental nodule management has been demonstrated.[12] Finally, the *surgical outcomes* achieved in the NLST may not be the same for the general U.S. population. The surgical mortality in the NLST was less than 1%. This is less than U.S. national averages, which range from 3–5%, and is likely due in part to the settings where surgery was conducted. The NLST enrollment sites were large centers with dedicated thoracic surgeons performing high volumes of procedures, features associated with better outcomes when compared to centers with a lower volume of procedures.[13,14] Surgical mortality that exceeds that of the NLST could diminish the mortality benefit from screening. As lung cancer screening is more broadly implemented, procedure utilization and outcomes should be collected to address questions of generalizability.

COMPONENTS FOR EFFECTIVE LUNG CANCER SCREENING

Given the evidence to support reduced mortality with lung cancer screening, the *U.S. Preventive Services Task Force* (USPSTF) gave a grade B recommendation in favor of screening.[15] Several professional societies endorse lung cancer screening and have identified essential components that should be part of all programs to ensure high-quality lung cancer screening (Table 75.1). A subset of these topics is covered later in this chapter; radiology aspects are covered in Chapter 20.

PATIENT ELIGIBILITY

Persons deemed eligible for lung cancer screening should be at high enough risk of developing lung cancer that the mortality benefit related to screening outweighs any harms associated with the screening process. As previously discussed, the NLST and the NELSON trials are the only clinical trials to date powered sufficiently to demonstrate a mortality benefit from screening.[6,7] Eligibility for screening in the United States has largely been defined by the entry criteria for subjects participating in NLST, specifically persons aged 55 to 74 years with a smoking history of at least 30 pack-years, currently smoking, or having quit within the past 15 years.[6] Eligibility for screening has also been informed by the *Cancer Intervention and Surveillance Modeling Network* (CISNET) models developed using individual-level data from the NLST and the PLCO trial. CISNET considered 576 different scenarios, with different combinations of ages at which to start and stop screening, intensities of smoking including a range of minimum smoking history and duration of time since quitting, and intervals between screening studies.[16] As would be anticipated, models broadening the criteria to include a larger screening-eligible population averted more lung cancer deaths but required far more screening studies, with an associated increase in the harms associated with screening. Conversely, models that narrowed the criteria required fewer studies to achieve benefit but with benefit limited to a smaller eligible population.

Based on NLST and the CISNET analysis, the USPSTF recommends "annual screening for lung cancer with low-dose computed tomography in adults aged 55 to 80 years who

Table 75.1 Components Necessary for a High-Quality Lung Cancer Screening Program[57]

WHO IS OFFERED LUNG CANCER SCREENING
Programs must confirm that a policy is in place about who will be offered screening that is in line with evidence-based guidelines.
HOW OFTEN, AND FOR HOW LONG, TO SCREEN
Programs must confirm that there is a policy about the frequency and duration of screening that is in keeping with USPSTF recommendations.
HOW THE CT SCAN IS PERFORMED
An LDCT scan should be performed based on the American College of Radiology and Society of Thoracic Radiology technical specifications.
LUNG NODULE IDENTIFICATION
Programs should have a policy about the size and characteristics of a lung nodule to be used to label the test as positive.
STRUCTURED REPORTING
A lung cancer screening program should use a structured reporting system, such as LungRADS, and collect data about compliance with the system.
LUNG NODULE MANAGEMENT ALGORITHMS
Programs must have clinicians with expertise in the management of lung nodules and treatment of lung cancer. The program should have developed lung nodule care pathways with the ability to order additional testing and communicate results to the patient and/or provider. There should be a mechanism to track nodules and collect outcomes.
SMOKING CESSATION
Programs must integrate smoking cessation services for active smokers.
PATIENT AND PROVIDER EDUCATION
Programs are responsible for the oversight and supplementation of provider-based patient education.
DATA COLLECTION
Programs must collect data related to each component of a lung cancer screening program, the outcomes of testing, as well as the cancers diagnosed, and report this data annually to an oversight body.

CT, computed tomography; LDCT, low-dose computed tomography; USPSTF, U.S. Preventive Services Task Force.

have a 30 pack-year smoking history and currently smoke or have quit within the past 15 years."[15] This recommendation was modified by the *Centers for Medicare and Medicaid Services* (CMS), which ultimately endorsed lung cancer screening for the population matching NLST entry criteria (ages 55–74 years), with the exception of increasing the age range to 77 years, acknowledging the upper boundary for age at NLST entry of 74 years and the 3-year duration of LDCT imaging.[17]

The USPSTF and CMS recommendations for screening eligibility should not be interpreted as identifying all individuals at high risk for lung cancer because they are based solely on the stringent NLST entry criteria and the CISNET models. There is concern that individuals at high risk for lung cancer, but who do not meet established eligibility criteria, will not be considered for screening or may have screening declined by insurance providers. The appropriateness of this concern is supported by lung cancer risk prediction calculators such as those used by Tammemagi and colleagues (PLCOm2012) and Katki and colleagues, which include multiple variables beyond age, smoking intensity, and smoking duration in the assessment of clinical risk.[18–20] The PLCOm2012 model includes age, race/ethnicity, education, body mass index, COPD, personal cancer history, family history of lung cancer, and smoking status/intensity/duration/quit time.[21] The use of this PLCOm2012 model in the PLCO dataset resulted in improved sensitivity and positive predictive value for finding lung cancer when compared with application of NLST and USPSTF criteria.[21,22] Arguments supporting targeting of screening to higher-risk individuals identified by using validated risk prediction calculators include a lower rate of false-positive findings, a lower number needed to screen to avert a lung cancer death, and avoidance of screening a lower-risk population less likely to realize benefit.

It is important to recognize that even among persons identified as being at high risk for lung cancer, there are individuals for whom screening should not be recommended. First, screening should be performed in asymptomatic persons. Individuals with symptoms suggestive of lung cancer should undergo usual diagnostic evaluation, as opposed to screening. Second, screening should be performed only in persons whose competing health issues, if present, are not anticipated to limit the benefit gained from early cancer diagnosis.[23] Third, persons undergoing screening should be both able and willing to undergo treatment if a cancer is identified. The USPSTF criteria state that "Screening should be discontinued once a person has not smoked for 15 years or develops a health problem that substantially limits life expectancy or the ability or willingness to have curative lung surgery."[15] Figure 75.1 provides a suggested algorithm for considering patient eligibility for lung cancer screening.

Rigor should be exercised in decisions about screening individuals who do not meet either USPSTF or CMS criteria. In such cases, screening is not recommended. The recommendation against screening is based on the imbalance of benefit, which is unproven in groups other than those meeting the eligibility criteria, and of harm, including the likelihood of false-positive results found more frequently in individuals at low risk, the consequences of evaluation for false-positive results including unnecessary biopsies and surgeries, unnecessary cost, and exposure to radiation. If clinicians continue to have substantial concern about whether to screen because of perceived lung cancer risk, employment of an objective measurement of risk may be useful. For example, the National Comprehensive Cancer Network consensus guidelines recommend lung cancer screening for patients who meet USPSTF guidelines, as well as for another group of younger individuals (age ≥50 years) with less smoking history (≥20 pack-years), and an additional risk factor other than secondhand smoke that increases the risk of lung cancer to 1.3% or more over 6 years.[24] The 2018 CHEST Guideline and Expert Panel Report suggests that a lung cancer risk of 1.51% or more over 6 years, as determined by the PLCOm2012 calculator, could be used as an example of defining "high risk," which could be factored into a decision regarding whether or not to recommend screening for an individual who does not meet USPSTF or CMS criteria.[25]

PATIENT EDUCATION AND SHARED DECISION-MAKING

Shared decision-making (SDM) requires that health care providers collaborate with their patients to make decisions together based on the best available evidence and

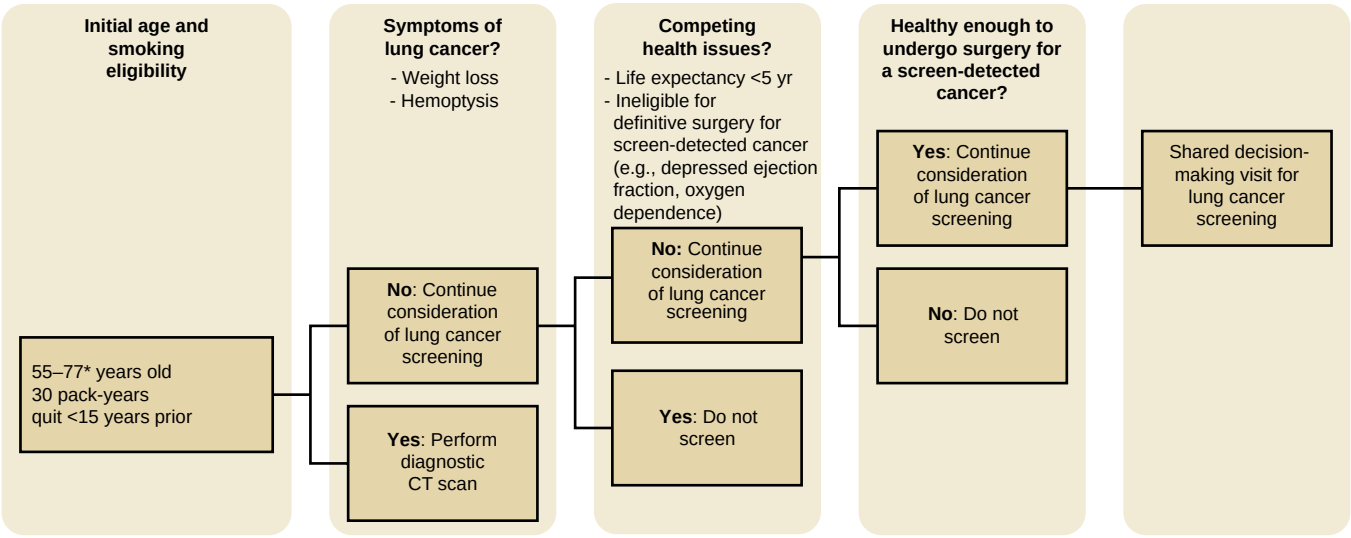

Figure 75.1 Algorithm for considering patient eligibility for lung cancer. *Centers for Medicare and Medicaid Services eligibility criteria. CT, computed tomography.

pertinent patient values and preferences. The goal of SDM for lung cancer screening is to increase the likelihood that patients understand the screening options, benefits, and harms, and are comfortable making decisions aligned with their preferences and values. The lung cancer screening evidence base has informed us about the potential benefit and harms of screening. The balance of benefit and harm varies based on individual characteristics related to the risk of developing lung cancer, the risk of evaluating findings detected by screening, the benefit of finding and treating early-stage lung cancer, and the risk of competing mortality. For a substantial portion of those eligible for lung cancer screening, decisions about whether to proceed with screening are *preference sensitive*, meaning that the risk/benefit ratio is balanced so that there is no right or wrong choice and the decision should be based on patient preference.

For this reason, and with the previously stated goal in mind, CMS coverage of lung cancer screening requires that individuals have a "lung cancer screening counseling and shared decision-making visit" prior to receiving LDCT.[17] The CMS coverage determination lists the components of this visit, which include SDM that incorporates decision aids. Decision aids can be designed as printed handouts or as web/video-based tools. They present information in easy-to-digest graphic or numeric formats to help foster an understanding of the evidence base that empowers those making the decision. Other aspects of the required SDM visit include an assessment of lung cancer screening eligibility, a description of elements of the screening process (e.g., adherence to annual screening, potential need for additional diagnostic evaluation), and counseling about smoking cessation.

Though most concede that the principle of SDM is the ideal result of all clinician-patient interactions, some are concerned that the burden of conducting an SDM visit may reduce the uptake of lung cancer screening without strong evidence that an SDM visit improves traditional lung cancer screening outcomes. Nonetheless, there is accumulating evidence about the benefit of a lung cancer screening SDM visit on knowledge and satisfaction with screening decisions and about the most effective SDM strategies. The use of lung cancer screening decision aids has been shown to increase patient knowledge about LDCT screening and its tradeoffs.[26–29] An SDM visit within a centralized screening program demonstrated that 95% of those who came to the visit went on to complete screening. Knowledge about eligibility criteria, as well as the benefits and harms of screening, was poor prior to the visit, improved immediately after the visit (at the time of the decision), and waned 1 month later. The visit made the patients more comfortable with their screening decision.[30] Others have explored the ideal means of conducting an SDM visit. In one setting, the addition of an informational film to a booklet led to improved knowledge and reduced decisional conflict when compared to the use of the booklet alone, without affecting decisions to undergo lung cancer screening.[31] In another study, an in-person SDM visit was compared to an SDM visit by telephone. Satisfaction with decisions was high, decisional conflict low, and 88% completed the screening exam. These metrics did not differ between the SDM delivery methods.[32]

Despite the growing evidence of benefit, there remain concerns about the uptake and quality of SDM visits. One study of patient-reported physician-patient discussions about lung cancer screening suggested that only 18% of active smokers aged 55 to 74 years discussed lung cancer screening with their provider in 2017.[33] Another study performed a qualitative content analysis of 14 clinician-patient conversations about screening. Using a validated measure of SDM, the Observing Patient Involvement in Decision Making scale, the authors found a low overall quality of the discussions (mean score of 6 on a scale of 0 to 100), and that physicians universally recommended screening and did not discuss the potential harms. Decision aids were not used, and the conversations lasted a mean of 59 seconds.[34] Further efforts will help define the ideal means of conducting and implementing high-quality SDM for lung cancer screening in a variety of settings.

NODULE MANAGEMENT

Lung nodules are commonly identified on LDCT screening exams. The prevalence and incidence of lung nodules vary depending on the definition of what constitutes a positive result. The higher the nodule size threshold for a positive result or the stricter the criteria (e.g., inclusion of growth rate from volumetric imaging), the lower the prevalence and incidence. For reported randomized, controlled trials, the prevalence of a lung nodule has ranged from 1.6% (positive result required growth on 3-month surveillance CT for nodules 50–100 mm^3) to 30.3%, and the cumulative incidence ranged from 6.0–46.1%.[35] Fifty-nine percent of those screened in the Veterans Affairs lung cancer screening demonstration project had a nodule of any size, while 12.7% had a nodule more than 8 mm in diameter.[36] *Subsolid* nodules, which include ground-glass nodules and those that are partly solid, have been reported in up to 16.9% of those screened.[37] Despite these differences, all studies have found that the majority of nodules identified during screening are benign.

Appropriate management of nodules detected by screening is essential to maximizing the benefit and minimizing the harms of lung cancer screening. The goal of nodule management is to minimize testing in those with benign nodules while rapidly identifying and treating those with malignant nodules. To this end, a widely used grading system based on the risk of malignancy has been developed by the *American College of Radiology* (ACR) and is being used to assist with uniform reporting and management of smaller lung nodules. Use of this structured reporting system (Lung-RADS; https://www.acr.org/-/media/ACR/Files/RADS/Lung-RADS/LungRADSAssessmentCategoriesv1-1.pdf?la=en) can help minimize the frequency of surveillance for small benign nodules but may sacrifice a bit of sensitivity for small malignant nodules (see Chapter 41).

Clearly benign nodules (e.g., calcified nodules or subpleural lymph nodes) do not require additional surveillance. (See Fig. 41.1 for examples of benign nodules on CT.) Solid nodules 8 mm or less in diameter are followed with CT imaging (intervals based on the size). Pure ground-glass nodules are monitored until they become more solid, and partly solid nodules are managed based on the size of the solid component of the nodule. Subsolid nodules (i.e., pure ground-glass and partly solid) make up the majority of overdiagnosed cancers. Overdiagnosis, which is an inherent drawback to screening, is the detection of a cancer that would not have otherwise become clinically significant (e.g., life-limiting). Individuals may undergo unnecessary diagnostic procedures and treatments with the potential morbidity and personal distress for a finding that would not have otherwise limited their life expectancy.

Solid nodules more than 8 mm in diameter are managed based on their estimated probability of malignancy (quantitative or qualitative prediction) and features impacting the yield of adjunctive testing (positron emission tomography scanning, transthoracic needle biopsy, bronchoscopic biopsy, or surgical resection). Nodules of this size with a very low probability of malignancy are monitored with serial CT imaging. Those with a low to moderate probability of malignancy, and a low yield from adjunctive testing, are also monitored for growth with serial CT imaging. Those with a low to moderate probability of malignancy and a moderate to high yield from adjunctive testing are further evaluated with positron emission tomography scans or a nonsurgical biopsy (transthoracic needle biopsy or bronchoscopic biopsy). Nodules with a high probability of malignancy may proceed directly to resection or be further evaluated with a nonsurgical biopsy if the results would lead to a change in the need for resection.

Several malignancy risk prediction models have been developed to assist with the estimation of malignancy probability in lung nodules, whether detected by screening or incidentally.[38–43] A model developed in the screening setting and validated in the NLST cohort yielded sensitivity, specificity, positive predictive value, and negative predictive value of 85.3%, 93.9%, 27.4%, and 99.6%, respectively.[43] This model has been shown to have a higher accuracy than the Lung-RADS system and has been incorporated into screening-detected nodule management algorithms.[41] Another model developed in the screening setting increased accuracy over traditional models by including additional nodule measurements.[39]

Low rates of procedures (1.2–6.9% of those screened), major complications (7.8% of procedures), and death potentially related to procedures (0.8% of procedures) have been reported in many trials of lung cancer screening.[35] These rates reflect the quality of nodule management in the sites that participated in clinical trials. It is unclear if systems and processes of care outside of clinical trial settings would produce similar results. Even higher rates of procedures and complications may be seen in other settings.[12] Complication rates (22.2–23.8%) in a population-based community setting were reported to be more than twice as high as those reported by the NLST, with incremental costs of more than $50,000 per major complication.[44]

MANAGEMENT OF OTHER SCREENING-DETECTED FINDINGS

The LDCT screening scan acquires images from the lower neck to the upper abdomen. The current screen-eligible cohort has risk factors (age, smoking history) for other cancers and chronic diseases as well as comorbidities that impact their risk and well-being (hypertension 60%, hyperlipidemia 50%, COPD 30%, coronary artery disease 15%, diabetes mellitus 15%).[45] For these reasons, abnormal findings in organs other than the lungs can be found at the time of screening (Fig. 75.2). Whether these additional findings add value to lung cancer screening or add to the potential for harm is currently unclear. Screening programs must be aware of these potential findings, inform those being screened of this possibility, and have a plan in place to manage them.

The most common abnormal findings include chronic airway disease (36%), emphysema (47%), and coronary artery calcification (51%).[45] The prevalence of interstitial lung abnormalities was 9.7% in one study. At 2-year follow-up, findings of nonfibrotic interstitial lung abnormalities improved in 49% of cases and progressed in 11%. Fibrotic interstitial lung abnormalities improved in 0% and progressed in 37% of cases.[46] Other potentially actionable findings include mediastinal adenopathy, pleural disease including effusions, thyroid and adrenal nodules, and aortic aneurysms (see Fig. 75.2). It is valuable for a screening program to be aware of current guidelines for

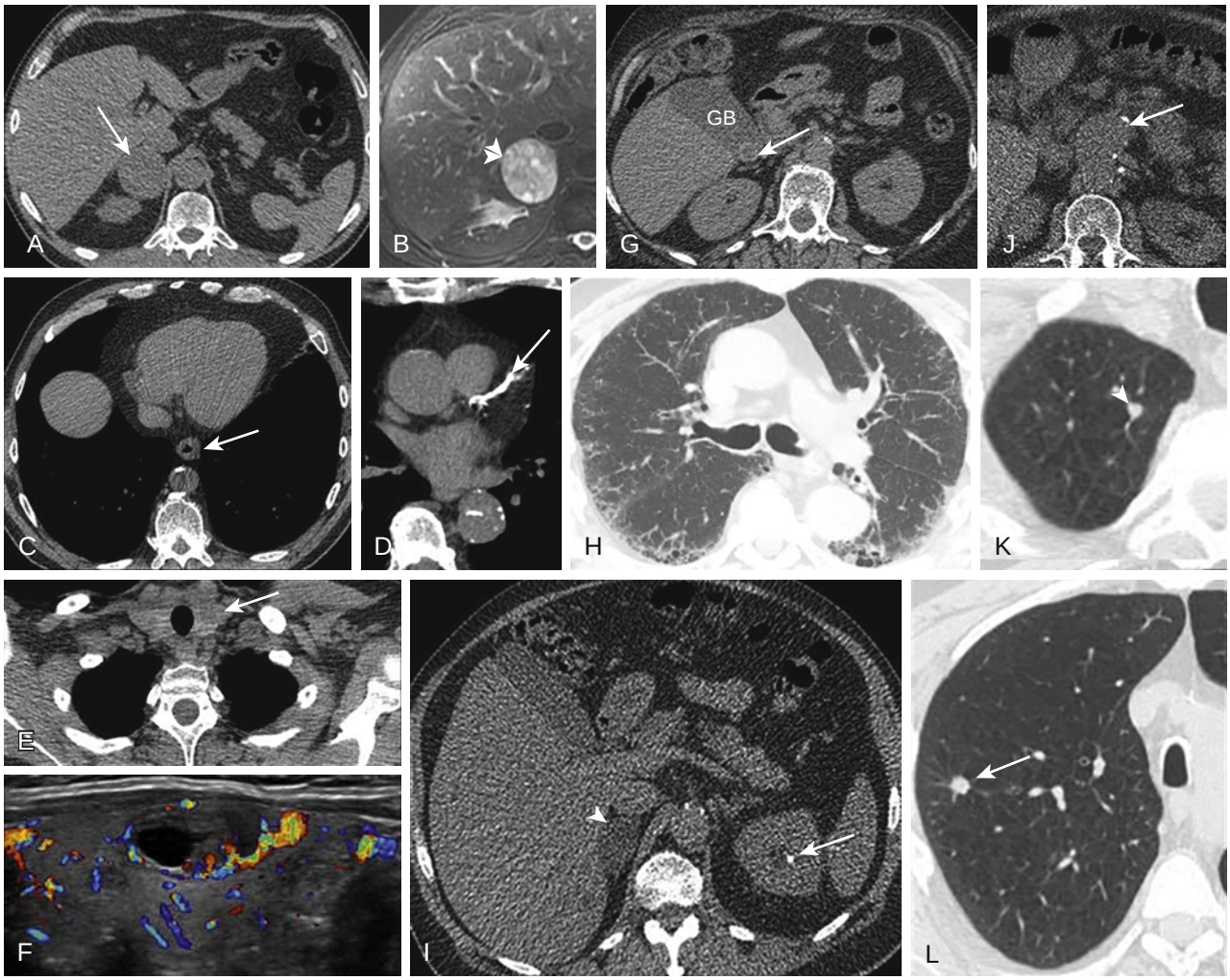

Figure 75.2 Findings, many incidental, on low-dose lung cancer screening computed tomography. (A) Nonspecific right adrenal mass (*arrow*) found on *low-dose lung cancer screening computed tomography* (LDCT). (B) The right adrenal mass shows T2 hyperintensity on dedicated MRI (*double arrowheads*). Resection proved pheochromocytoma. (C) Axial LDCT shows nonspecific thickening of the distal esophagus (*arrow*). Upper endoscopy revealed reflux esophagitis. (D) Axial LDCT (focused on the heart) shows heavy calcification of the left anterior descending artery (*arrow*). (E) Axial LDCT shows incidental left thyroid nodule (*arrow*) measuring 1.6 cm. (F) Thyroid ultrasound shows peripheral vascularity but no features to suggest malignancy; the lesion was considered low-risk and followed for stability. (G) Axial LDCT shows cholelithiasis (*arrow*). (H) Axial LDCT (lung windows) shows bibasilar reticulation and subpleural cystic change, suggesting fibrotic lung disease. (I) Axial LDCT shows a small left-sided nonobstructive renal calculus (*arrow*) and right adrenal adenoma (*arrowhead*), which was lipid-rich and presumed benign. (J) Axial LDCT shows a partially visualized peripherally calcified upper abdominal aortic aneurysm (*arrow*). (K–L) Axial LDCT shows a circumscribed 4.5 mm right upper lobe nodule (*arrowhead*) and mildly irregular more inferiorly located right upper lobe nodule measuring 10 mm (*arrow*) with a background of severe centrilobular emphysema. GB, gallbladder. (Courtesy Michael B. Gotway, MD.)

the management of these findings and to engage with specialists in these areas who can guide the development of management algorithms for the program. Despite the high rate of identifying these abnormalities, less than 5% lead to an invasive diagnostic or therapeutic procedure.[45,47–50] The evaluation of these findings adds to the cost of screening and can account for up to 50% of a screening program's reimbursement, funding that can help support the program.[45,47–49]

SMOKING CESSATION (see Chapter 66)

Smoking cessation reduces lung cancer mortality more effectively than screening. An analysis of the NLST participants randomized to the control arm found that 7 years of abstinence achieved the same 20% mortality reduction seen with LDCT. Furthermore, the combination of smoking abstinence and LDCT screening was additive; those who had quit smoking and undergone screening achieved a lung cancer mortality reduction of 38%.[51] It is currently unclear whether involvement in a lung cancer screening program influences the rate of smoking cessation. Higher rates of smoking cessation at 2 years were found in the screening arm of the UK Lung Screening trial (15% vs. 10%) but not in either the Danish Randomized Lung Cancer Screening Trial (11.9% vs. 11.8%) or the NELSON trials (13.7% vs. 15.5%). There is evidence that smoking cessation rates are higher in those with screening-detected nodules.[52] While there is controversy as to whether smoking cessation counseling is more effective in the context of screening as a "teachable moment," there is no argument that counseling is appropriate and that there are benefits associated with quitting. Smoking cessation improves the impact and cost-effectiveness of lung cancer screening.

CMS requires that smoking cessation counseling be incorporated into the screening process for Medicare-insured patients.[17] Examination of the screening framework readily identifies steps where counseling can be introduced or referrals made to smoking cessation services: by providers at the time of eligibility determination or during SDM visits, in conjunction with the ordering or performance of the screening LDCT, and at the time of delivery of test results.

Currently, smoking cessation interventions applied in the screening setting should follow standard protocols developed in general smoking populations (see Chapter 66). Research is being conducted to determine if alternative or additional measures are more effective in the screening setting.

IMPLEMENTATION

It is widely recognized that achieving reliable cancer screening at a population level is enormously challenging. Even when screening is broadly accepted, known to save lives, and embedded in routine health care, such as is currently the case for breast, colorectal, and cervical cancers, screening processes are often disorganized and inefficient.[53] Guiding principles, such as those outlined above, are fundamental to establishing best practices; successful implementation and maintenance of screening adherent to those principles present practical challenges in real-life settings. It is important that we learn from the long experience of breast, colorectal, and cervical cancer screening about the many barriers that can prevent individuals and populations from being screened, and draw on that knowledge to anticipate predictable pitfalls and to develop processes more likely to be inclusive and sustainable.[54] An online resource sponsored by the *American Thoracic Society* (ATS) and American Lung Association for planning and implementing lung cancer screening programs is available at https://www.lungcancerscreeningguide.org/.

TYPES OF SCREENING PROGRAMS

Designing and implementing a lung cancer screening program demands a keen understanding of local factors, including the type of system in which the program is embedded; the technical capabilities of communication and data systems, including the *electronic health record* (EHR); distribution of resources available to the program; the culture of other institutional screening practices; and the availability as well as willingness of the multiple disciplines involved in lung cancer care to participate.

Screening program structures fall into three general categories: *centralized*, *decentralized*, and *hybrid*. A brief description of centralized and decentralized programs is outlined in Table 75.2; hybrid programs combine aspects of both centralization and decentralization. The structure and extent of a screening program implemented at a given site will be heavily influenced by local resources, which will define the type and scope of program that can be feasibly achieved.

A FRAMEWORK FOR IMPLEMENTATION OF LUNG CANCER SCREENING

Beaber and colleagues proposed a general conceptual screening model for a consortium entitled *Population-based Research Optimizing Screening through Personalized Regimens* (PROSPR), which is intended to unify the screening process across breast, cervical, and colorectal cancer screening.[53] This framework should be generalizable to screening for any cancer, including lung cancer, and can be used as a roadmap to identify where challenges in delivery of screening may be encountered as well as where meaningful

Table 75.2 Types of Screening Programs

Type	Description	Advantages/Disadvantages
Centralized	Screening program assumes responsibility for the entire spectrum of care, from eligibility determination through diagnosis and treatment Feasible for large, comprehensive health care systems capable of providing primary through specialty care internally	**Advantages:** Ability to automate identification and recruit eligible patients Single internal EHR for streamlining communication Standardization of radiographic processes for LDCT performance and result reporting Capability to facilitate and provide comprehensive care for abnormal findings Quality metrics internally measurable **Disadvantages:** Administrative burden Manpower needs for comprehensive care spanning all aspects of screening, evaluation and management
Decentralized	Default process in absence of coordinated comprehensive health care system Screening process steps located in separate systems Reliance on primary care provider to steward screening Most breast and colorectal cancer screening takes place in decentralized settings	**Advantages:** Screening can be performed with existing processes and manpower No requirement for overarching process development or management **Disadvantages:** Fragmented care Communication challenges between sites of care Assessment of quality likely more difficult
Hybrid	Includes components of both centralized and decentralized programs	As outlined above

EHR, electronic health record; LDCT, low-dose computed tomography.

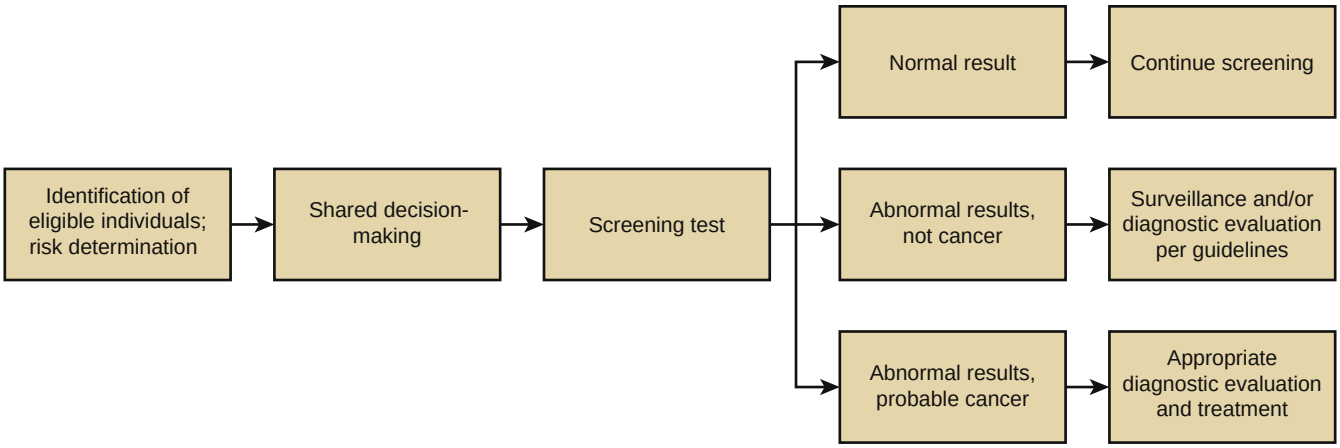

Figure 75.3 Provider-level lung cancer screening process. This model outlines a framework for screening of lung cancer, based on frameworks proposed for breast, cervical, and colorectal cancer screening. The nine elements (boxes) can be addressed individually to target challenges to screening and opportunities for improvement. (Modified from Beaber EF, Kim JJ, Schapira MM, et al. Unifying screening processes within the PROSPR consortium: a conceptual model for breast, cervical, and colorectal cancer screening. *J Natl Cancer Inst.* 2015;107[6]:djv120; and Armstrong K, Kim JJ, Halm EA, Ballard RM, Schnall MD. Using lessons from breast, cervical, and colorectal cancer screening to inform the development of lung cancer screening programs. *Cancer.* 2016;122[9]:1338–1342.)

measures of quality might be targeted. A simplified version of this model is outlined in Figure 75.3, with the notable addition unique to lung cancer screening of the required SDM visit between a practitioner and an individual prior to performance of a screening LDCT.

The framework proposed by the PROSPR consortium helps us understand that lung cancer screening is inherently multidisciplinary. Primary care providers, nurse navigators, radiologists, and thoracic oncology specialists (pulmonary medicine, thoracic surgery, medical oncology, radiation oncology, etc.) all participate in aspects of the flow of patients through screening. Moreover, there must be institutional oversight of the test performance of the actual screening LDCT as well as reporting to a centralized registry. The framework also helps recognize and address important potential pitfalls to successful screening as they arise. In addition, the ATS and *American College of Chest Physicians* (ACCP) have published a policy statement on lung cancer screening program development outlining three main stages to be considered: planning, implementation, and maintenance.[55] This addresses a variety of site-specific strategies to incorporate the nine elements of comprehensive lung cancer screening to fit in with local workflow. The components of screening and potential quality metrics have been discussed previously in detail; the remainder of this section will address a few of the specific areas of the framework that may be useful in the development of sustainable, successful screening programs.

Identification and Engagement of Individuals Eligible for Screening

Although this first step in screening may seem straightforward, differences between existing recommendations may cause confusion about which individuals should be screened and highlight the importance of a program clearly defining the eligibility criteria that will be used. As already noted, the USPSTF criteria for screening are fairly simple: persons aged 55 to 80 years with a 30 pack-year history of smoking, currently smoking or having quit within the past 15 years, and medically fit for treatment with a life expectancy sufficient to reap benefit from treatment.[56] CMS criteria for screening differ slightly in limiting the age range to 55 to 77 years.[17] National Comprehensive Cancer Network and ACCP guidelines suggest that risk assessment using a validated model should be considered for individuals who do not meet USPSTF criteria, with high risk for lung cancer defined as at or more than 1.3%[24] or 1.51%[25] or more over 6 years. A centralized screening program should define a standardized approach to determining eligibility; a decentralized program will have a more difficult task to maintain standardization unless there is gatekeeping at the level of ordering the screening LDCT. In the ACCP and ATS policy statement on components necessary for high-quality lung cancer screening, Mazzone and colleagues recommended that at least 90% of all screened subjects should match a program's stated approach to eligibility.[57]

This first step of identifying and recruiting individuals eligible for screening is critically important. High-risk individuals will benefit from screening only if they can be engaged. Programs may be able to harness the EHR to automate identification of potentially eligible individuals; the decision about the appropriateness of screening based on other medical factors will need to be made by an individual's primary provider. Multiple barriers to engaging eligible individuals include lack of access to primary care, low socioeconomic and/or educational status, poor or absent health insurance, inability to find substitutes for childcare or work, fear of pain or bad news, and cultural or language differences, among others. These are reflected in the imperfect screening rates observed even for screening processes that are embedded in medical practice and widely recognized by the public. In 2015, 71.6% of women aged 50 to 74 years had screening mammography, while 62.9% of adults age 50 to 75 years received colorectal cancer screening.[58,59] In 2015, the first year that lung cancer screening was covered as a Medicare benefit, only 5.8% of eligible adults underwent screening LDCT.[60] Successful implementation will require intentional planning for this first pipeline step in lung cancer screening and should include broad interventions to

increase public awareness of the importance of screening, intensive education of primary care and other front-line providers on the benefit and potential harms of screening and in lung cancer risk assessment, and concerted efforts to address identifiable barriers to care. Special consideration for educating minority populations is advisable because data from the NLST demonstrates that Blacks had a greater mortality benefit from screening than did their white counterparts.[61]

Resources for Ensuring Consistency of the Screening Test

Once an individual is recruited into screening, the next steps of the framework involve the screening test, which can be broken into several components: the SDM visit, the performance of the screening LDCT, and the radiologist's reading of the LDCT, including reporting of results to a central registry. As previously discussed, standardization of all components is important to provide consistent, high-quality screening. Resources for clinical decision support are numerous. Two representative tools include an interactive website supported by the University of Michigan, http://www.shouldiscreen.com/, and a patient-focused print resource from the ATS, https://www.thoracic.org/patients/patient-resources/resources/decision-aid-lcs.pdf. Structured, standardized reading and reporting of LDCT results are crucial to efficient screening, particularly given the high rate of false-positive findings. Lung-RADS, a tool for standardizing reports and management recommendations, is broadly available and was updated in 2019.[62] All screening programs should use Lung-RADS or a similar uniform approach; standardizing reporting and management recommendations should minimize confusion about interpretation and evaluation of true as well as false-positive findings. ACR has published technical specifications for LDCT performed for lung cancer screening, to which diagnostic imaging centers performing screening LDCT should adhere.[63] ACR also maintains the central registry for screening programs or imaging centers to submit data and screening results as required by CMS for Medicare-insured patients.

Communication Across the Screening Process

As with all patient care, communication between points of care essential to achieving best outcomes may present the greatest challenge to a lung screening program. In the PROSPR framework outlined in Figure 75.3, each arrow represents a point of communication. Each point has an inherent risk of misinformation or loss of information between providers or between providers and patients and potential delays in care. During implementation planning, or in reviews of existing screening programs, these should be carefully examined because they represent sites where potential for error or suboptimal care exists and where process improvement may be beneficial.

- In centralized screening programs, where all points of care exist within a single system, uniform access to a single EHR should streamline communication, prevent "leakage" of clinically important information, and facilitate clinical evaluation of results. This does not obviate the burden of navigation and follow-up, but the administrative resources available to manage flow through the screening process should be harnessed to ensure oversight of a patient's journey through screening.
  - Documentation of process steps, including the SDM discussion, the performance, results, and central reporting of the LDCT, and clinical actions based on LDCT results, should be available to any provider or navigator involved in the care of the individual. This should minimize the possibility of information falling through the cracks. It does not, however, ensure that quality care is rendered, which will still require tracking of patient outcomes as well as examination of each step in the screening process by measurements defined by internal program standards or by nationally recommended metrics.
  - Communication of results to patients should be timely and sensitive to patient needs. Large systems may be capable of automated delivery of results directly to patients. If information is sent by letter or via electronic portal in the absence of direct discussion with a provider, care should be taken to state results clearly and provide recommendations to the patient, in order to avoid unintended patient distress.
- In decentralized or hybrid screening programs, points of care may be fragmented and located in separate systems using separate EHRs. Communication of information will depend on the diligence of the sending and receiving parties. Consider the situation of a primary care provider who identifies an eligible patient, engages in a shared decision discussion, and orders a screening LDCT at a freestanding radiology practice. The radiologist should follow ACR technical specifications for performance of the LDCT and use Lung-RADS to report results. The task of reporting to a central registry, which requires specific clinical information as well as the LDCT results, should be assigned to someone. A report is sent to the ordering provider, who is responsible for communicating results to the patient and for follow-up of abnormal pulmonary or extrapulmonary findings, which may require referral of the patient to one or more specialists.
  - Communicating results to patients should follow the same principles as outlined above for a centralized system.
  - Accurate, efficient communication between separate providers who do not share an EHR requires reliable mechanisms to track a patient's progress from evaluation to closure of a specific issue. Accountability is no different than for usual care, with the burden of responsibility for all necessary evaluations assumed by both primary providers and specialists. Achieving efficient, accurate communication in a decentralized or hybrid screening process is as essential but will likely be more challenging than in a centralized program.

For a discussion about the future directions for lung cancer screening, concerning implementation, screening eligibility, and molecular and imaging biomarkers, see ExpertConsult.com.

FUTURE ADVANCES

IMPLEMENTATION

High-quality lung cancer screening programs are being implemented across the country. In the first few years after CMS approval of payment for lung cancer screening in the United States, the uptake of screening was slow. The slow uptake likely reflected the time it takes for knowledge to disseminate and programs to be built. More recent evaluations have suggested that there has been steady growth in access to screening programs. Much work still needs to be done in order to provide broad access to screening, particularly in disadvantaged communities.[64] Efforts to make high-quality screening accessible and equitable for all may be aided by changes in eligibility criteria, technologic advances leading to novel ways to access care, quality metric development and tracking, ongoing education, and the efforts of community outreach programs.

Technology advances may help to accelerate broad implementation of screening. The identification of eligible individuals through electronic health record searches, the ability to connect with eligible individuals through telehealth portals, the initial interpretation of CTs by artificial intelligence platforms,[65] and the prediction of lung nodule risk with deep learning models are all likely to be available over the next decade. Patient management software systems, whose guidance and reminders can optimize compliance with guideline-based care, will be routinely used.

SCREENING ELIGIBILITY

If everyone currently eligible for lung cancer screening were screened, approximately 30–40% of all current lung cancers in the population would be detected.[66] Decades of efforts to minimize cigarette smoking in the population have led to progressively lower smoking rates. The decline in smoking rates will lead to fewer lung cancers overall, and a smaller percentage of all lung cancers will be related to cigarette smoking.[66] If screening eligibility criteria remain the same, a smaller portion of all lung cancers will be detected by screening.

The decline of cigarette smoking will make it more difficult to identify individuals at risk of developing lung cancer. Other tools will be necessary to assist with the selection of screening candidates. Lung cancer risk calculators that include known risk factors, in addition to age and smoking history, have been able to improve accuracy somewhat over current eligibility criteria. The cohort identified may also be at increased risk of complications from the management of screening-detected findings and have higher competing mortality. Additional data from recently completed screening trials and clinical screening registries will help to refine risk models and enhance their clinical utility. Improvement in the management of findings detected by screening and reductions in imaging radiation doses will further minimize screening harms. By improving the balance of benefit and harm, the pool of individuals eligible for screening will be expanded.

MOLECULAR AND IMAGING BIOMARKERS

The development of molecular and imaging biomarkers is likely to influence the future of lung cancer screening. Molecular biomarkers are being developed in hopes of identifying individuals who are most likely to benefit from imaging-based screening. These include genomic, proteomic, and metabolomic markers in the blood, breath, urine, and airway mucosa. Highly specific biomarkers will allow lower-risk individuals with lung cancer to be screened safely, while highly sensitive biomarkers will minimize the risk of testing in the currently screening-eligible (high-risk) cohort.

Molecular biomarkers are also being developed to help guide the management of lung nodules. Biomarkers with high specificity will help to accelerate lung cancer treatment, and markers with high sensitivity will help to minimize procedures for those with benign nodules. Lung nodule risk prediction will also incorporate radiomic models, in which clinical imaging data are mined by computer analysis. The accuracy of these tools may augment or replace traditional risk models and support clinician judgment. Because there is a tradeoff of benefit and harm with the implementation of any test, the clinical utility of both molecular and imaging biomarkers will need to be defined.[67]

Advances in systems, knowledge, and technology will improve the balance of benefit to harm for lung cancer screening, leading to fewer lung cancer deaths.

Key Points

- Lung cancer screening with low-dose computed tomography in individuals at risk based on age and smoking history has been shown to reduce mortality from lung cancer.
- There is variation in eligibility for lung cancer screening among professional society guidelines, the United States Preventive Services Task Force, and the Centers for Medicaid and Medicare Services but, in general, asymptomatic individuals with a 30 pack-year history currently smoking or having quit within the past 15 years, aged 55 to 77 or 80 years, and well enough for curative surgical treatment are eligible.
- Guidelines are in place outlining components needed for high-quality lung cancer screening. These include nodule identification and management, patient and provider education, and smoking cessation.
- Shared decision-making for lung cancer screening aims to increase the likelihood that patients understand the screening options, benefits, and harms, and are comfortable making decisions that are aligned with their preferences and values. A shared decision-making visit should be conducted prior to lung cancer screening.
- The majority of nodules identified by screening are benign. Appropriate management of nodules is essential to maximize benefit and minimize harm.
- Lung cancer screening is multidisciplinary; primary care providers, nurse navigators, radiologists, and thoracic oncology specialists (pulmonary medicine, thoracic surgery, medical oncology, radiation oncology, etc.) will all participate in aspects of the flow of patients through screening. Implementation and type of program depends on resources available.
- Smoking cessation reduces lung cancer mortality more effectively than screening. Smoking cessation programs should be an integral part of every screening program.
- The future of lung cancer screening will include refinement in eligibility criteria, expanded implementation, and the incorporation of molecular and imaging biomarkers.

Key Readings

Aberle DR, Adams AM, Berg CD, et al. Reduced lung-cancer mortality with low-dose computed tomographic screening. *N Engl J Med*. 2011;365(5):395–409.

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76 LUNG CANCER: DIAGNOSIS AND STAGING

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INTRODUCTION

With an estimated 2.09 million new cases globally in 2018, lung cancer remains the most common cause of cancer deaths worldwide.[1] In the United States, lung cancer accounts for an estimated 230,000 cases and more than 140,000 cancer deaths annually.[2] Added together, the number of cancer deaths from breast, colon, and prostate cancer each year would not equal the number of cancer deaths due to lung cancer alone. A common misconception among the general public is that breast cancer accounts for more cancer deaths in women. However, lung cancer is the primary cancer cause of death in women, accounting for 25% of cancer-related deaths among women and, since 1987 in the United States, killing more women than breast cancer. Particularly alarming is the fact that young women are the fastest rising demographic of new cigarette smokers in the United States, with many having made the association between weight control and cigarette smoking. The risk of lung cancer is also 2.5 times more common in female lifetime nonsmokers compared with male nonsmokers. Although more U.S. men died of lung cancer than did women in 2015 (74,000 vs. 61,000), simulation modeling predicts that this gender gap will likely close by 2045. And by 2065, more women will die of lung cancer than will men (26,900 vs. 23,400).[3]

One of the more disturbing trends in lung cancer is the explosion in rates of lung cancer in countries of the developing world. These rates may actually be underestimates of the true rates of lung cancer because many cases may go undiagnosed or unreported in areas where health care is not readily available.[4] An example of how serious this problem has become is found in China, where there were 787,000 new cases and 631,000 deaths in 2015. The age-specific incidence rate in 2014 was 37 per 100,000; there were 457,000 new cases in urban areas, which is 1.4 times higher than in rural areas.[5] Chinese men smoke an average of 11 cigarettes per day, which is equivalent to the highest average rates of smoking ever seen among males in the United States. In fact, the consumption of cigarettes in China alone may surpass that of all developed countries combined.[4,6] Overall, 67% of Chinese men smoke. In view of such statistics, it is imperative that the medical community devotes much of its educational efforts and resources toward the elimination of cigarette smoking worldwide, which would nearly eliminate the development of lung cancer.

This chapter reviews how patients present with lung cancer, the current strategies for diagnosis, the new staging system published in 2017, special cases and concerns, and the importance of palliative care. As much as possible, evidence-based review of the best currently available literature has been included. The role of the pulmonologist is described for every aspect of lung cancer care, from diagnosis to staging to caring for the complications of the disease itself.

PRESENTATION/INITIAL EVALUATION

The symptoms of lung cancer are often nonspecific, thereby delaying recognition and leading to an advanced disease stage at the time of diagnosis. In fact, the major goal of lung cancer screening is to find lung cancer at

an early stage before symptoms develop, when it is more likely to be curable (see Chapter 75). Only a minority of patients in a screened population, but up to 98% of patients in a hospitalized population, will present with symptoms.[7–9] Tables 76.1 and 76.2 list some of the common symptoms and signs associated with the presentation of lung cancer. Most are nonspecific; however, some clues can be gleaned from the history, thus raising the clinician's suspicion that lung cancer is present. Although many smokers cough, lung cancer patients usually admit to a change in the character of their cough. The cough can increase in frequency or strength or may not be relieved with the usual remedies. Chest pain can be present in 25–50% of patients at the time of presentation for evaluation for lung cancer.[8,10] The pain is generally dull in nature, tends to be persistent, remains in the same location, and is not relieved with local measures. Chest pain is usually related to involvement of the pleura but can be related to extension into the mediastinum or chest wall. It is important to note that chest pain in and of itself does not preclude the patient from consideration for surgery with curative intent. Dyspnea is frequently a complaint of patients with bronchogenic carcinoma, described by half of all new patients at presentation.[8] There is a litany of reasons for dyspnea related to lung cancer, including some that may be immediately life threatening, such as pulmonary embolism, hemorrhage, pericardial tamponade, endobronchial obstruction with tumor, postobstructive pneumonia, and stenosis of the central airways due to tumor.

Hemoptysis in a smoker should always raise the suspicion of lung cancer. Hemoptysis can present as blood streaking of the sputum and can be noted over a lengthy period of time before presentation to the physician's office because it is often attributed to smoking-related bronchitis. The clinician should not be led astray, even if the chest radiograph is normal, because up to 5% of those patients with a smoking history and a normal radiograph can harbor lung cancer.[11] Because of the vascular nature of lung cancer, patients can also present with massive hemoptysis. Weight loss, a nonspecific symptom, in the right clinical setting should raise the suspicion of both lung cancer and metastatic disease. Weight loss alone has been correlated with an advanced presentation and poor outcome from lung cancer.[12]

Some presenting signs have particular significance and can direct a workup. Hoarseness can point to involvement of the recurrent laryngeal nerve and should focus attention to that location on *computed tomography* (CT) scanning. An enlarged supraclavicular lymph node can indicate spread of intrathoracic tumor and can lead to a safe and expeditious needle biopsy with concomitant diagnosis and staging at the bedside. Particular attention should also be paid to symptoms and signs suggestive of potential paraneoplastic syndromes. Finally, patients may present with symptoms that warrant immediate referral to palliative care (see also Chapter 141).

Chest imaging may be performed as part of the initial evaluation of nonspecific respiratory symptoms or may incidentally discover lung cancer. Lung cancer may increasingly be detected in the context of lung cancer screening. Chest radiography is the most common imaging modality in the primary care setting to prompt referral to a pulmonologist, but it lacks sufficient resolution to differentiate benign from malignant disease, and a negative result does not exclude lung cancer.

CT is the standard and most common imaging modality for a patient with suspected lung cancer. CT may also be the first test performed, whether the suspicious findings were detected incidentally or in the context of screening, and CT is required at initial evaluation if the lung nodule or mass was initially detected on chest radiography (see comments later). After an abnormality consistent with a lung cancer is detected, attention must turn immediately to the suspected disease stage, and further imaging and invasive testing to confirm the diagnosis should proceed accordingly. In other words, the next steps to diagnosis are guided by determining the most expeditious, safe, and cost-effective way to (1) establish the diagnosis of cancer and (2) simultaneously determine the stage by sampling the suspected site of disease representing the highest stage, when feasible. In addition, ensuring that there is adequate tissue for molecular testing has become

Table 76.1 Presenting Symptoms With Bronchogenic Carcinoma

Symptoms	Patients (%)
Cough	45–75
Weight loss	8–68
Dyspnea	37–58
Hemoptysis	27–57
Chest pain	27–49
Hoarseness	2–18

From Midthun DE, Jett JR. Clinical presentation of lung cancer. In: Pass HI, Mitchell JB, Johnson DH, et al, eds. *Lung Cancer: Principles and Practice.* Philadelphia: Lippincott-Raven; 1996:422.

Table 76.2 Expanded Clinical Evaluation

SYMPTOMS ELICITED IN HISTORY
Constitutional—weight loss > 10 lb
Musculoskeletal—focal skeletal pain
Neurologic—headaches, syncope, seizures, extremity weakness, recent change in mental status
SIGNS FOUND ON PHYSICAL EXAMINATION
Lymphadenopathy (>1 cm)
Hoarseness
Superior vena cava syndrome
Bone tenderness
Hepatomegaly (>13 cm span)
Focal neurologic signs, papilledema
Soft tissue mass
ROUTINE LABORATORY TESTS
Hematocrit < 40% in males
Hematocrit < 35% in females
Elevated alkaline phosphatase, γ-glutamyl transferase, aspartate aminotransferase, calcium

critically important in the era of targeted therapy and immunotherapy.

In summary, patients with lung cancer can present asymptomatically, with relatively nonspecific symptoms or with constitutional symptoms suggestive of metastatic disease. There are often clues in the history that should alert the clinician that lung cancer is a possibility and that further investigation is warranted.

TUMOR-NODE-METASTASIS STAGING OF LUNG CANCER

Pulmonologists play a key role in the diagnostic and staging evaluation of patients with lung cancer.[13] Disease stage portends prognosis and dictates treatment options.

The staging of *non–small cell lung cancer* (NSCLC) has evolved since its inception in 1974.[14] The 1997 classification, proposed by Mountain,[15] was based on a single-institution database of 5319 patients. In contrast, the seventh revision of the staging system, led by the *International Association for the Study of Lung Cancer* (IASLC), was based on an international database of more than 100,000 patients with lung cancer.[16,17] Similarly, the eighth edition is informed by a global database of approximately 95,000 patients treated between 1999 and 2010.[18,19]

The process of developing a staging system is complex and comprehensive. The IASLC is the largest multidisciplinary global organization to study lung cancer, and it appointed a Staging and Prognostic Factors Committee to develop staging guidelines. The eighth edition was based on a very broad collection of data from all modalities of care, 35 institutions, and 16 countries, with the intention to use the database to improve care provided to lung cancer patients. An extensive statistical analysis of the database was performed by the Cancer Research and Biostatistics Group. Outcomes within the database varied by region and type of source data, so stage classifications were made on the basis of the presence (or absence) of differences in prognosis between and within categories and stage groupings that were consistent across multiple comparisons (clinical, pathologic, N0, any N, within a geographic region, histologic type, etc.). Final classifications were made with an understanding of the nature and limitations of the available data, along with clinical and historical considerations to influence how heavily particular analyses were weighed.[19,20] This large database of patient outcomes led to descriptors of more specific tumor characteristics than previously determined. Such characteristics were shown to affect treatment outcomes in subgroups of patients. For example, the more detailed size classifications of patients without nodal and metastatic disease can alter whether adjuvant chemotherapy can be given (based on being stage II rather than stage I) in different subsets of patients with N0M0 disease who receive surgical resection.[21] In the previous seventh edition of lung cancer staging, T2 tumors that were greater than 4 to 5 cm in size and N0M0 were classified as stage IB, whereas in the eighth edition, based on more extensive data, they are classified as stage IIA. Refinements and updates of the staging system will be needed periodically as additional data, new therapies, and scientific discoveries in lung cancer emerge.

Stage classification allows standardized descriptions of the anatomic extent of a cancer and consists of three components: extent of the primary *tumor* (T), involvement of lymph *nodes* (N), and presence or absence of distance *metastasis* (M). This standardized nomenclature facilitates communication about a particular patient, provides an understanding of the extent of disease among patients enrolled in clinical trials, and allows clinicians to make informed treatment decisions.[19]

The following section reviews the eighth edition of the lung cancer staging system, with a focus on changes compared to prior editions. In addition, studies highlighting significant quality gaps in lung cancer staging are reviewed.

EIGHTH EDITION LUNG CANCER STAGE CLASSIFICATION

The eighth edition of the TNM classification of lung cancer became the worldwide standard as of January 1, 2017; it was implemented in the United States and Canada as of January 1, 2018. The TNM system principally guides the staging of NSCLC. In contrast, *small cell lung cancer* (SCLC) is generally classified and managed according to a more simplified system of limited versus extensive disease.

The T, N, and M components of the staging system are divided into several categories. Various characteristics or "descriptors" define what comprises a given T, N, or M category. Specific combinations of T, N, and M categories constitute stage groupings. Tables 76.3 and 76.4 display the eighth edition T, N, and M descriptors and stage groupings. A prefix specifies the type of staging assessment. *Clinical* (c) stage is based on all information available before surgical resection, including symptoms and physical signs, imaging studies, and the results of diagnostic procedures. *Pathologic* (p) stage is defined by the results of surgical resection (including an aborted one) in addition to all clinical information. Of note, most (85%) of the patients included in the global database used to develop the eighth edition of the staging system underwent surgery (± other therapies) and thus added pathologic staging information to the system. Based on survival data of different groupings of patients, several important changes were adopted in the eighth edition of the staging system.

Tumor size remains an important prognostic factor, with T1 and T2 further divided into 1-cm increments. These cutoffs were determined through extensive analysis of survival data, with log-rank tests confirming prior TNM size cutoffs and providing evidence to support further subdivisions into 1-cm increments. T descriptors underwent Cox regression analysis adjusted for age, sex, histologic type, and geography, with results showing a clear difference in 5-year survival and prognosis for each centimeter increase in tumor size between 1 and 5 cm and in larger tumors with worse prognosis (T3: >5 and ≤7 cm, T4: >7 cm).[22] The eighth edition also addresses how size should be measured. The maximal dimension of the solid component (on imaging,

Table 76.3

Definitions for T, N, and M Descriptors in Eighth Staging Classification		Label
T (PRIMARY TUMOR)		
T0	No primary tumor	
Tis	Carcinoma in situ (squamous or adenocarcinoma)	Tis
T1	Tumor ≤3 cm	
T1(mi)	Minimally invasive adenocarcinoma	T1a *(mi)*
T1a	Superficial spreading tumor in central airways*	T1a *ss*
T1a	Tumor ≤1 cm	T1a *≤1*
T1b	Tumor >1 but ≤2 cm	T1b *>1–2*
T1c	Tumor >2 but ≤3 cm	T1c *>2–5*
T2	Tumor >3 but ≤5 cm or tumor involving:	
	visceral pleura†	T2 *Visc Pl*
	main bronchus (not carina), atelectasis to hilum†	T2 *Centr*
T2a	Tumor >3 but ≤4 cm	T2a *>3–4*
T2b	Tumor >4 but ≤5 cm	T2b *>4–5*
T3	Tumor >5 but ≤7 cm	T3 *>5–7*
	or invading chest wall, pericardium, phrenic nerve	T3 *Inv*
	or separate tumor nodule(s) in the same lobe	T3 *Satell*
T4	Tumor >7 cm	T4 *>7*
	or tumor invading: mediastinum, diaphragm, heart, great vessels, recurrent laryngeal nerve, carina, trachea, esophagus, spine	T4 *Inv*
	or tumor nodule(s) in a different ipsilateral lobe	T4 *Ipsi Nod*
N (REGIONAL LYMPH NODES)		
N0	No regional node metastasis	
N1	Metastasis in ipsilateral pulmonary or hilar nodes	
N2	Metastasis in ipsilateral mediastinal/ subcarinal nodes	
N3	Metastasis in contralateral mediastinal hilar or supraclavicular nodes	
M (DISTANT METASTASIS)		
M0	No distant metastasis	
M1a	Malignant pleural/pericardial effusion‡ or pleural/pericardial nodules	M1a *Pl Dissem*
	or separate tumor nodule(s) in a contralateral lobe	M1a *Contr Nod*
M1b	Single extrathoracic metastasis	M1b *Single*
M1c	Multiple extrathoracic metastases (1 or >1 organ)	M1c *Multi*

*Superficial spreading tumor of any size but confined to the tracheal or bronchial wall.
†Such tumors are classified as T2a if >3 cm and ≤4 cm, T2b if >4 cm and ≤5 cm.
‡Pleural effusions are excluded that are cytologically negative, nonbloody, transudative, and clinically judged not to be due to cancer.
M, metastisis; N, node; T, tumor; TX, NX: T or N status not able to be assessed.
From Detterbeck FC, Boffa DJ, Kim AW, Tanoue LT. The eighth edition lung cancer stage classification. *Chest*. 2017;151(1):193–203.

Table 76.4 Lung Cancer Stage Grouping (Eighth Edition)

T/M	Label	N0	N1	N2	N3
T1	T1a *≤1*	IA1	IIB	IIIA	IIIB
	T1b *>1-2*	IA2	IIB	IIIA	IIIB
	T1c *>2-3*	IA3	IIB	IIIA	IIIB
T2	T2a *Cent, Visc Pl*	IB	IIB	IIIA	IIIB
	T2a *>3-4*	IB	IIB	IIIA	IIIB
	T2b *>4-5*	IIA	IIB	IIIA	IIIB
T3	T3 *>5-7*	IIB	IIIA	IIIB	IIIC
	T3 *Inv*	IIB	IIIA	IIIB	IIIC
	T3 *Satell*	IIB	IIIA	IIIB	IIIC
T4	T4 *>7*	IIIA	IIIA	IIIB	IIIC
	T4 *Inv*	IIIA	IIIA	IIIB	IIIC
	T4 *Ipsi Nod*	IIIA	IIIA	IIIB	IIIC
M1	M1a *Contr Nod*	IVA	IVA	IVA	IVA
	M1a *Pl Dissem*	IVA	IVA	IVA	IVA
	M1b *Single*	IVA	IVA	IVA	IVA
	M1c *Multi*	IVB	IVB	IVB	IVB

From Detterbeck FC, Boffa DJ, Kim AW, Tanoue LT. The eighth edition lung cancer stage classification. *Chest*. 2017;151(1):193–203.

clinical stage) or the invasive component (on microscopy, pathologic stage) should be used to assign a T category. Of note, the maximal dimension of the ground-glass or lepidic component should also be recorded[23] (see also Chapter 41).

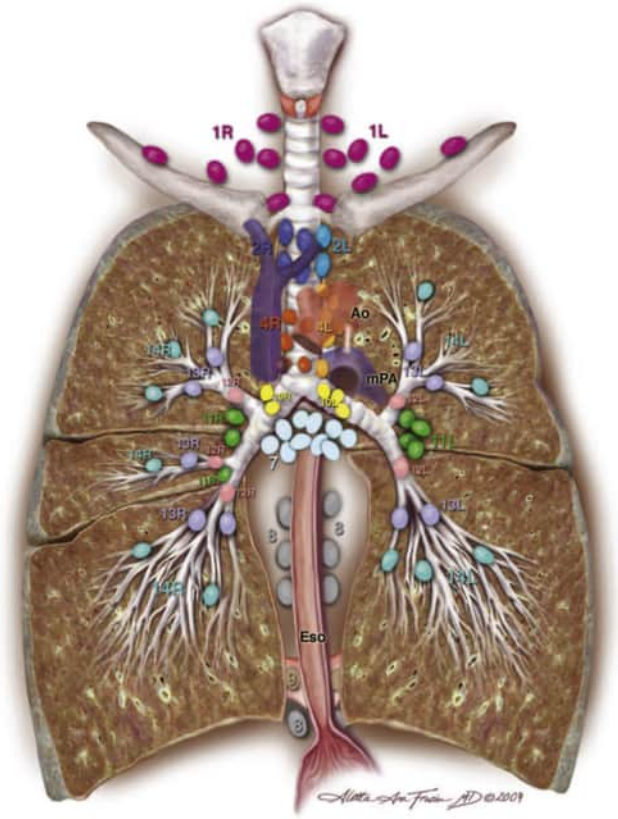
The T category also depends on invasion of adjacent structures. Central tumors involving a main bronchus are considered T2, regardless of distance from, but without involvement of, the main carina. Tumors associated with atelectasis extending to the hilum, whether involving a lobe or the entire lung, are also T2. Involvement of the diaphragm has been reclassified as T4. The classification of additional tumor nodules was maintained from the previous classification. The presence of a satellite nodule in the tumor-bearing lobe defines T3, whereas an additional nodule in a different lobe of the ipsilateral lung defines T4.

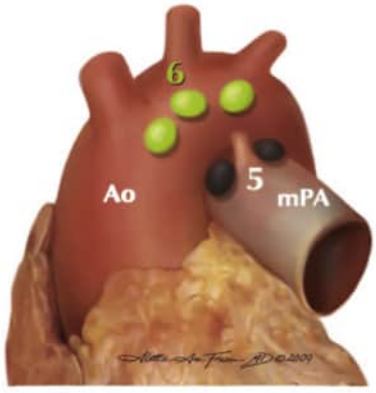
The N category has remained unchanged in the last two iterations of the staging system and is determined by the location of the involved nodes (relative to the primary tumor). The IASLC lymph node map is presented in Fig. 76.1, and the associated nodal definitions with key anatomic borders are detailed in eTable 76.1.

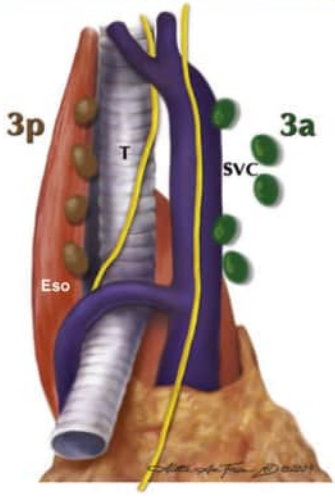
The M category has been further divided into M1a, b, and c, as prognosis was found to worsen increasingly from a to c. Malignant pleural effusions were reclassified as M1a disease in the seventh edition of the staging system, and this has been maintained; the classification of contralateral tumor nodules as M1a disease is also maintained. Single (M1b) versus multiple (M1c) extrathoracic metastases are now distinguished.

The stage groupings in the eighth edition are provided in Table 76.4. Stage IA tumors are subdivided into IA1, IA2, and IA3 according to tumor size. Stage III has been divided into three subgroups, with T3/T4 and N3 tumors now constituting stage IIIC disease. Stage IV has also been divided into stages IVA (M1a or b) and IVB (M1c).

The evaluation of lung cancer patients with multiple pulmonary sites of disease is challenging. In the context of the eighth edition of the TNM staging system, revisions to the classification of lung cancer with multiple pulmonary sites of involvement were proposed. Four







Supraclavicular zone

1 Low cervical, supraclavicular, and sternal notch nodes

SUPERIOR MEDIASTINAL NODES

Upper zone

2R Upper Paratracheal (right)

2L Upper Paratracheal (left)

3a Prevascular

3p Retrotracheal

4R Lower Paratracheal (right)

4L Lower Paratracheal (left)

AORTIC NODES

AP zone

5 Subaortic

6 Para-aortic (ascending aorta or phrenic)

INFERIOR MEDIASTINAL NODES

Subcarinal zone

7 Subcarinal

Lower zone

8 Paraesophageal (below carina)

9 Pulmonary ligament

N1 NODES

Hilar/Interlobar zone

10 Hilar

11 Interlobar

Peripheral zone

12 Lobar

13 Segmental

14 Subsegmental

Figure 76.1 ***International Association for the Study of Lung Cancer*** **(IASLC) lymph node map.** Nodal definitions remain unchanged in the new eighth edition of IASLC lung cancer staging. Ao, aorta; AP, aortopulmonary; Eso, esophagus; mPA, main pulmonary artery; SVC, superior vena cava; T, trachea. (From Rusch VW, Asamura H, Watanabe H, et al; IASLC Staging Committee. The IASLC Lung Cancer Staging Project: a proposal for a new international lymph node map in the forthcoming seventh edition of the TNM classification for lung cancer. *J Thorac Oncol.* 2009;4:568–577. Illustration by Aletta A. Frazier, MD.)

eTable 76.1 IASLC Nodal Anatomic Borders

Nodal Station	Description	Definition
#1 (left/right)	Low cervical, supraclavicular and sternal notch nodes	■ *Upper border:* lower margin of cricoid cartilage ■ *Lower border:* clavicles bilaterally and, in the midline, the upper border of the manubrium 1L and 1R are limited by the midline of the trachea
#2 (left/right)	Upper paratracheal nodes	2R: ■ *Upper border:* apex of lung and pleural space and, in the midline, the upper border of the manubrium ■ *Lower border:* intersection of equal margin of innominate vein with the trachea 2L: ■ *Upper border:* apex of the lung and pleural space and, in the midline, the upper border of the manubrium ■ *Lower border:* superior border of the aortic arch As for #4; in #2 the oncologic midline is along the left lateral border of the trachea
#3	Prevascular and retrotracheal nodes	3a: Prevascular On the right: ■ *Upper border:* apex of chest ■ *Lower border:* level of carina ■ *Anterior border:* posterior aspect of sternum ■ *Posterior border:* anterior border of superior vena cava On the left: ■ *Upper border.* apex of chest ■ *Lower border:* level of carina ■ *Anterior border:* posterior aspect of sternum ■ *Posterior border:* left carotid artery 3p: Retrotracheal ■ *Upper border:* apex of chest ■ *Lower border:* carina
#4 (left/right)	Lower paratracheal nodes	4R: Includes right paratracheal nodes, and pretracheal nodes extending to the left lateral border of trachea ■ *Upper border:* intersection of caudal margin of innominate vein with the trachea ■ *Lower border:* lower border of azygos vein 4L: Includes nodes to the left of the left lateral border of the trachea, medial to the ligamentum arteriosum ■ *Upper border:* upper margin of the aortic arch ■ *Lower border:* upper rim of the left main pulmonary artery
#5	Subaortic (aortopulmonary window)	Subaortic lymph nodes lateral to the ligamentum arteriosum ■ *Upper border:* the lower border of the aortic arch ■ *Lower border:* upper rim of the left main pulmonary artery
#6	Para-aortic nodes (ascending aorta or phrenic)	Lymph nodes anterior and lateral to the ascending aorta and aortic arch ■ *Upper border:* a line tangential to the upper border of the aortic arch ■ *Lower border:* the lower border of the aortic arch
#7	Subcarinal nodes	■ *Upper border:* the carina of the trachea ■ *Lower border:* the upper border of the lower lobe bronchus on the left; the lower border of the bronchus intermedius on the right
#8 (left/right)*	Paraesophageal nodes (below carina)	Nodes lying adjacent to the wall of the esophagus and to the right or left of the midline, excluding subcarinal nodes ■ *Upper border:* the upper border of the lower lobe bronchus on the left; the lower border of the bronchus intermedius on the right ■ *Lower border:* the diaphragm
#9 (left/right)	Pulmonary ligament nodes	Nodes lying within the pulmonary ligament ■ *Upper border:* the inferior pulmonary vein ■ *Lower border:* the diaphragm
#10 (left/right)	Hilar nodes	Includes nodes immediately adjacent to the mainstem bronchus and hilar vessels, including the proximal portions of the pulmonary veins and main pulmonary artery ■ *Upper border:* the lower rim of the azygos vein on the right; upper rim of the pulmonary artery on the left ■ *Lower border:* interlobar region bilaterally
#11	Interlobar Nodes	Between the origin of the lobar bronchi #IIs*: between the upper lobe bronchus and bronchus intermedius on the right #IIi*: between the middle and lower lobe bronchi on the right
#12	Lobar nodes	Adjacent to the lobar bronchi
#13	Segmental nodes	Adjacent to the segmental bronchi
#14	Sub segmental	Adjacent to the subsegmental bronchi

The boundaries delineated in this table are useful when interpreting computed tomography scans and performing bronchoscopy for staging of patients.
*Optional subcategories.
IASLC, International Association for the Study of Lung Cancer.
Data from Rusch VW, Asamura H, Watanabe H, et al; IASLC Staging Committee. The IASLC Lung Cancer Staging Project: a proposal for a new international lymph node map in the forthcoming seventh edition of the TNM classification for lung cancer. *J Thorac Oncol*. 2009;4:568–577.

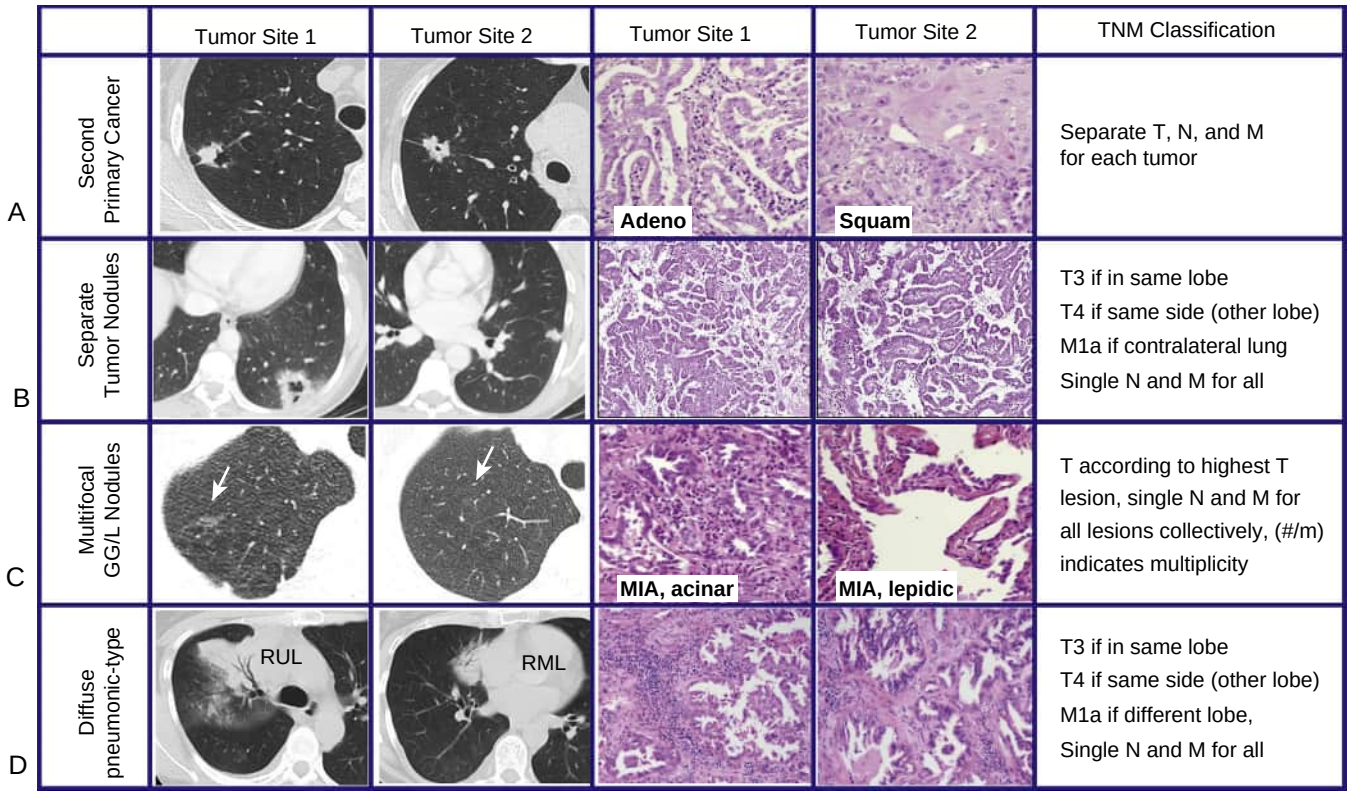


Figure 76.2 Multiple primary lung malignancies: *computed tomography* (CT) patterns. (A) Synchronous primary cancers. A patient with two primary lung cancers in the *right upper lobe* (RUL). CT images of each in the left two panels; corresponding microscopic images showing an *adenocarcinoma* (Adeno) and a *squamous* (Squam) carcinoma in the next two panels. Note that most second primary cancers are of the same (not a different) histologic type. (B) Separate tumor nodules. A patient with a separate tumor nodule of the same histotype as the index tumor. The left panels show CT images of each lesion; the right panels show the corresponding microscopic images. (C) Multifocal GG/L lung cancer. A patient with multifocal GG/L tumors in the right upper lobe who also had other GG/L tumors in other lobes. *Arrows* point to two GG/L tumors on CT in the left two panels; the next two panels show corresponding microscopic images; both were adenocarcinoma with a prominent lepidic component, although with different other adenocarcinoma subtypes. These tumors are classified together as GG/L tumors regardless of such secondary differences. (D) Pneumonic-type lung cancer. A patient with pneumonic-type lung cancer; this patient also had focal sites of disease in the right lower lobe. The left panels show CT images of the RUL and *right middle lobe* (RML) with the typical regional areas with a ground-glass and consolidative appearance. The next panels show the corresponding microscopic images. GG/L tumors, tumors with prominent ground-glass (imaging) or lepidic (histologic) features; M, metastasis; MIA, minimally invasive adenocarcinoma; N, node; T, tumor. (Modified from Detterbeck FC, Nicholson AG, Franklin WA, et al; IASLC Staging and Prognostic Factors Committee. The IASLC Lung Cancer Staging Project: summary of proposals for revisions of the classification of lung cancers with multiple pulmonary sites of involvement in the forthcoming eighth edition of the TNM classification. *J Thorac Oncol.* 2016;11:639–650.)

Table 76.5 5-Year Survival (%) of Patients in the IASLC Database Diagnosed With NSCLC From 1999–2010

Type	IA1	IA2	IA3	IB	IIA	IIB	IIIA	IIIB	IIIC	IVA	IVB
Clinical	92	83	77	68	60	53	36	26	13	10	0
Pathologic	90	85	80	73	65	56	41	24	12	-	-

Average overall survival in the IASLC global database of patients receiving a diagnosis between 1999 and 2010.
IASLC, International Association for the Study of Lung Cancer; NSCLC, non–small cell lung cancer.
From Detterbeck FC, Boffa DJ, Kim AW, Tanoue LT: The eighth edition lung cancer stage classification. *Chest.* 2017;151(1):193–203; with data from Goldstraw P, Chansky K, Crowley J, et al. The IASLC Lung Cancer Staging Project: proposals for revision of the TNM stage groupings in the forthcoming (eighth) edition of the TNM classification for lung cancer. *J Thorac Oncol.* 2016;11(1):39–51.

patterns of disease are distinguished: second primary lung cancers, tumors with a separate solid tumor nodule, multiple tumors with prominent ground-glass (as assessed by imaging) or lepidic (as assessed by pathology, with an appearance of tumor cells spreading along the alveolar surface without distortion) features, and diffuse "pneumonic-type" lung cancers. Fig. 76.2 includes representative examples of these four patterns of disease and the associated application of the TNM classification.

Revisions to the stage classification are based on differences in prognosis. Average 5-year overall survival in the IASLC global database is shown according to the eighth edition TNM staging system in Table 76.5. Although stage has a significant impact on prognosis, it is essential to remember that prognosis is also affected by patient factors, such as age, performance status and comorbidities, and factors related to care (access, quality) and treatment (choice of treatment and response).

STAGING OF SMALL CELL LUNG CANCER

A simpler stage classification exists in SCLC based on a two-stage system of limited and extensive stage disease.[24] However, the TNM staging system is applicable in SCLC and has been shown to have prognostic value in these patients as well.[25,26] Limited stage denotes disease confined to the ipsilateral hemithorax and regional lymph nodes, which can be included in a single tolerable radiation port (broadly corresponding to TNM stages I–III). Extensive stage denotes tumor beyond the boundaries of a radiation port and includes contralateral supraclavicular or hilar involvement, malignant pericardial or pleural effusions, and distant metastasis.

The vast majority of patients with SCLC will not be candidates for surgical resection (35–40% locally advanced and 60–65% metastatic), but stage distinction is important because patients with limited-stage disease are still candidates for chemoradiation with curative intent. Patients with extensive-stage disease are treated with chemotherapy alone and consolidative or palliative radiation if clinically indicated.

QUALITY GAPS IN LUNG CANCER DIAGNOSIS AND STAGING

The importance of diagnosis and accurate staging seems obvious, yet evidence suggests it is often poorly done.[27,28] Studies based on clinical and administrative databases have highlighted significant quality gaps in the diagnosis and staging of lung cancer patients.[29–34]

Suboptimal staging has been associated with worse patient outcomes.[32,33] Farjah and colleagues[33] examined the impact of multimodality mediastinal staging on health outcomes using the Surveillance, Epidemiology, and End Results data. Although a minority of patients underwent multimodality staging (CT ± *positron emission tomography* [PET] ± invasive staging), this was associated with a significantly lower risk of death.[33] Similarly, Ost and colleagues[32] demonstrated that care was consistent with guidelines in only a minority of patients evaluated for lung cancer; yet, when care was consistent, this was associated with significantly fewer complications.[29,32] Navani and colleagues[34] assessed agreement between clinical and pathologic TNM stages among clinical trial (control group) participants with stage I to IIIA NSCLC. The authors found that clinical TNM staging disagreed with pathologic TNM staging in 48% of cases, with the majority of patients being clinically understaged; these discrepancies could have lead to different treatment decisions.[34]

The need for multiple tests and the variable availability of certain tests (PET scan, *endobronchial ultrasound* [EBUS]) may also significantly impact timeliness of care in lung cancer patients. Time to diagnosis and treatment of lung cancer frequently exceeds recommended delays.[35,36] The association between timeliness of lung cancer care and patient outcomes, however, has been variable and at times paradoxical, with a few studies even showing that less timely care was associated with a better survival.[35] Nonetheless, the most recent American College of Chest Physicians guidelines recommend timely investigation of lung cancer patients.[37] In addition, the British National Institute for Health and Care Excellence guidelines recommend rapid access clinics for the investigation of patients with suspected lung cancer.[38] Suggested targets for timeliness may vary among countries; the British guidelines suggest an acceptable delay is 2 months from referral to the beginning of treatment. Quality indicators for the evaluation of patients with lung cancer have also been proposed based on guidelines and links to patient-centered outcomes.[39,40] Mazzone and colleagues[40] have proposed seven quality indicators for the evaluation of patients with lung cancer (eTable 76.2).

HISTOLOGY AND PROGNOSIS

In considering the prognosis for NSCLC, personalized treatment should take into account histologic features and tumor growth patterns in addition to tumor characteristics gleaned from molecular analysis. For example, within the two most common histologic types of NSCLC (adenocarcinoma and squamous cell carcinoma), different growth patterns affect prognosis.[41] The various invasive patterns of adenocarcinomas belong to three prognostic groups with increasing risk metastasis and poorer prognosis: lepidic pattern (grade 1), acinar and papillary pattern (grade 2), and micropapillary and solid pattern (grade 3). In squamous cell carcinoma, which can have keratinizing, nonkeratinizing, or basaloid elements of differentiation, keratinization is associated with a better prognosis.[42] In other instances, mixed histologies, such as adenosquamous, may have similar probabilities of having targetable mutations as a pure adenocarcinoma.[43] In the case of large cell neuroendocrine histology of NSCLC, the survival curve overlaps with that of SCLC, so prognosis is worse than in other NSCLC histologies.[44]

Over the past decade, significant advances have been made in the oncology, molecular biology, pathology, radiology, and surgery for lung adenocarcinomas, which remain the most common type of lung cancer. To address the spectrum of adenocarcinomas, an international multidisciplinary classification of adenocarcinomas was developed to provide uniform terminology and diagnostic criteria, especially for what was formerly called bronchioloalveolar carcinoma. This initiative was meant to improve the overall approach to small nonresection cancer specimens (i.e., needle aspirations, core needle specimens, cytology from body fluids), surgical specimens, and the multidisciplinary strategic management of tissue for molecular and immunohistochemical studies[45] (Table 76.6).

APPROACH TO STAGING

Certain tenets of lung cancer staging must be emphasized. Before classifying a patient within a certain stage, the clinician should make every effort to verify the stage by investigating radiologic abnormalities with tissue sampling if necessary. This is particularly important when surgical resection would be precluded based on abnormal noninvasive radiologic tests. Thus a patient who would otherwise be resectable, except for a single abnormality suspicious for metastasis, should have tissue confirmation of that abnormality before being deemed unresectable. Whenever possible, diagnosis and staging should be achieved in a single procedure (i.e., mediastinal lymph node or other metastatic site sampled) rather than by sampling the primary tumor and then separately biopsying a metastatic site. When obtaining tissue from patients with advanced-stage NSCLC, sufficient tissue should be obtained for molecular testing. Important nuances of noninvasive and invasive staging are described in the next sections of this chapter. As is pointed

eTable 76.2 Assessment of Feasibility and Relevance of Quality Indicators at Three Different Clinical Sites

	SITE 1			SITE 2			SITE 3		
Quality Indicator	**NR (%)**	**Yes (%)**	**Time***	**NR (%)**	**Yes (%)**	**Time***	**NR (%)**	**Yes (%)**	**Time***
1. Percentage of nonsurgical biopsies in patients with clinical stage IV nonsquamous lung cancer from whom obtained an adequate amount of tissue for molecular testing	81	89.5	1.18	82	72.2	2.48	84	62.5	3.13
2. Percentage of patients with clinical stage III or IV lung cancer, or neurologic symptoms who have had brain imaging performed within 3 mo of the initiation of treatment	48	96.2	1.14	46	96.3	2.21	49	88.2	3.5
3. Percentage of patients with evidence of one to three distant metastases who have had an attempt at biopsy confirmation of a site of metastasis or documentation of a reason that this was not possible or necessary	82.5	62.9	1.16	80	50	2.11	67	97.0	3.16
4. Percentage of patients with clinical stage IB or higher, but no evidence of metastatic disease, who have had a mediastinal lymph node sampling procedure performed before the initiation of curative-intent therapy	47.5	95.2	1.24	43.5	96.5	2.11	64	80.6	3.21
5. Percentage of patients with lung cancer who have an AJCC seventh edition clinical lung cancer stage documented before curative-intent therapy	24.5	58.3	1.61	24.5	61.6	1.98	16	76.2	3.77
6. Percentage of active smokers with lung cancer who have had smoking cessation counseling documented	74.5	70.6	1.20	81.5	59.5	1.74	76	75	3.15
7. Percentage of patients with lung cancer in whom a performance status measure is documented in the pretreatment phase	0	100	1.01	0	71	1.54	1	88.9	4.21

Two hundred patients were reviewed at site 1 and site 2, 100 at site 3.

*Time refers to the mean time required to search for the performance of the indicator in the medical record for each patient. Time scale: 1 = very easy (<1-min search), 5 = neither easy nor hard (≈15-min search), 9 = very difficult (>30-min search).

AJCC, American Joint Committee on Cancer; NR, not relevant.

From Mazzone PJ, Vachani A, Chang A, et al., Quality indicators for the evaluation of patients with lung cancer. *Chest*. 2014;146(3):659–669.

Table 76.6 Categories of New Adenocarcinoma Classification Where Former Bronchioloalveolar Carcinoma Concept Was Used

1. Adenocarcinoma in situ, which can be nonmucinous and rarely mucinous
2. Minimally invasive adenocarcinoma, which can be nonmucinous and rarely mucinous
3. Lepidic predominant adenocarcinoma (nonmucinous)
4. Adenocarcinoma, predominantly invasive with some nonmucinous lepidic component (includes some resected tumors, formerly classified as mixed subtype, and some clinically advanced adenocarcinomas formerly classified as nonmucinous bronchioloalveolar carcinoma)
5. Invasive mucinous adenocarcinoma (formerly mucinous bronchioloalveolar carcinoma)

This new classification of adenocarcinomas was developed to provide uniform terminology and diagnostic criteria, especially for what was formerly called bronchioloalveolar carcinoma.

From Travis WD, Brambilla E, Noguchi M, et al. International Association for the Study of Lung Cancer/American Thoracic Society/European Respiratory Society International Multidisciplinary Classification of Lung Adenocarcinoma. *J Thorac Oncol*. 2011;6:244–285.

out, no single imaging study is infallible, so reliance on scans alone to predict malignancy is simply not appropriate.

Patients with stage I and II NSCLC without medical contraindication should be referred for surgical resection, which is considered the gold standard of treatment for lung cancer. Although there are no large randomized controlled trials comparing surgical resection to other modalities, available data show a mortality benefit for surgical resection over radiotherapy alone, chemotherapy alone, or ablative therapies in medically operable patients.

In cases of a solid pulmonary nodule greater than 8 mm in diameter, a surgical diagnosis should be considered when the clinical probability of malignancy is high (>65%), when the nodule is hypermetabolic by PET, when nonsurgical biopsy is suspicious for malignancy, or when a fully informed patient prefers a definitive diagnostic procedure. For surgical diagnosis, video-assisted thoracoscopy is recommended to obtain a diagnostic wedge resection. If malignancy is present on frozen section intraoperatively, then further resection (lobectomy or segmentectomy in selected cases) and lymph node dissection will be pursued as dictated by patient comorbidities and fitness for more extensive surgery. CT-guided transthoracic needle aspiration has a sensitivity of 90% in a high-prevalence population, but there is a risk of nondiagnostic results in about 20% of individuals with malignant nodules,[46] so it lacks adequate negative predictive value to exclude cancer in cases with high probability of malignancy (see Chapter 41). When the risk of malignancy is high, anything other than a definitive benign diagnosis (i.e., inflammation is not definitive) should not prevent further invasive approaches at biopsy. When the clinical probability of malignancy is low or intermediate, nodules can be followed with serial CT scanning over time versus minimally invasive biopsy (CT-guided transthoracic needle or bronchoscopy) depending on clinical setting, growth pattern of the nodule on imaging, and patient preferences.

The question will arise as to which patients with stage I should undergo mediastinal staging before surgery or biopsy of the primary site. In patients with peripheral (outer third of the lung) clinical stage IA tumors (negative nodal involvement by CT and PET), preoperative evaluation of mediastinal nodes is not required. However, even if there is no mediastinal nodal involvement by CT and PET, a central tumor (inner two-thirds of lung), a tumor greater than 3 cm, or a tumor with N1 involvement, the patient should undergo a needle biopsy technique (EBUS, *endoscopic ultrasound* [EUS], or combined EBUS-EUS) instead of surgical staging as the first staging modality because the prevalence of occult mediastinal involvement of tumor is significant (10–30%)[47–50] (Figs. 76.3 to 76.5).

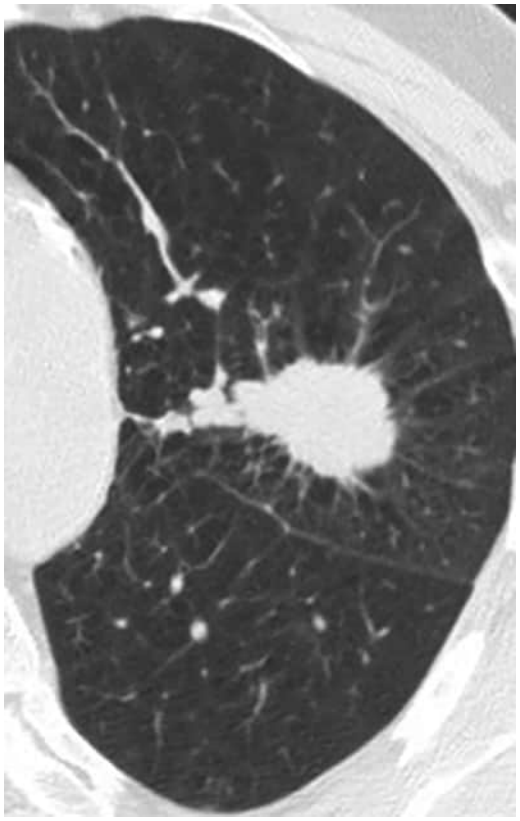


Figure 76.3 Stage I non–small cell lung cancer (3.2-cm mass). If the mediastinum is negative on positron emission tomography–computed tomography, invasive staging of the mediastinum is still recommended due to size of the primary lesion. (Courtesy Dr. Michael B. Gotway.)

Stage III and IV patients may have multiple targets to sample, so the site that would establish the highest stage while maintaining safety and sample quality should be targeted (Figs. 76.6 to 76.8).

SUSPECTED METASTATIC DISEASE

Imaging with ^{18}*F-fluoro-2-deoxy-*D*-glucose* (FDG)-PET scan has greater accuracy than CT for the evaluation of mediastinal lymph node involvement in lung cancer, so it is a widely used adjunct to CT imaging (now commonly a fused CT-PET scan) for the diagnosis and staging of lung cancer. In the appropriate clinical setting, it can be an accurate means of differentiating benign from malignant lesions and identifying unexpected distant metastasis. PET scanning is based on the biologic activity of neoplastic cells, which demonstrate increased cellular uptake of glucose and a higher rate of glycolysis compared with normal cells,[51] resulting in an accumulation of FDG-6-phosphate.[52] The accumulated

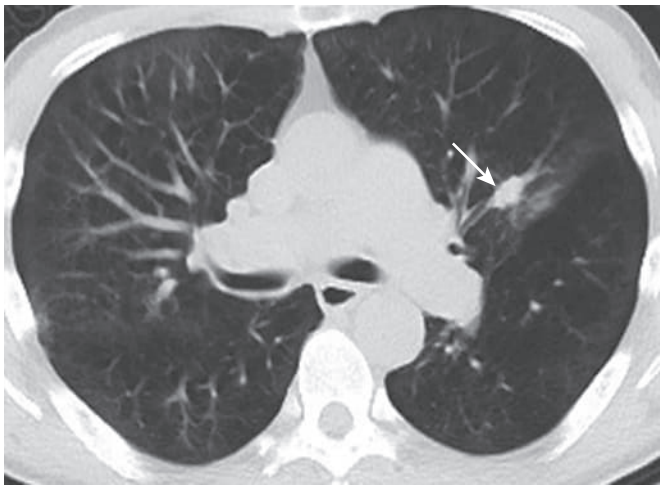


Figure 76.4 Stage I non–small cell lung cancer (central 1-cm nodule). If mediastinum is negative on positron emission tomography–computed tomography, staging is still recommended due to central location of the primary lesion *(arrow)*.

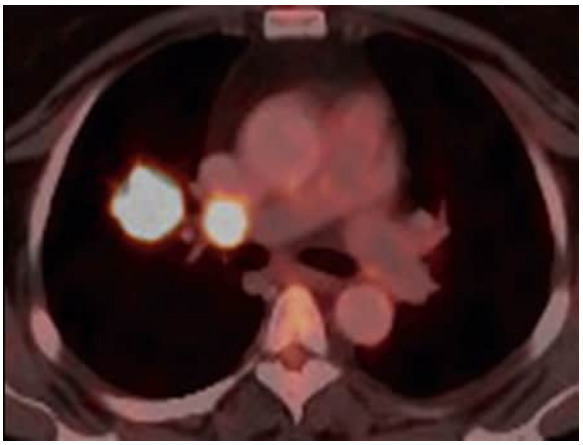


Figure 76.5 Stage IIB non–small cell lung cancer with a 2.9-cm right upper lobe nodule and a positron emission tomography (+) 10R lymph node. This patient needs mediastinal staging for two reasons: because the nodule is centrally located and because there is N1 activity on positron emission tomography–computed tomography.

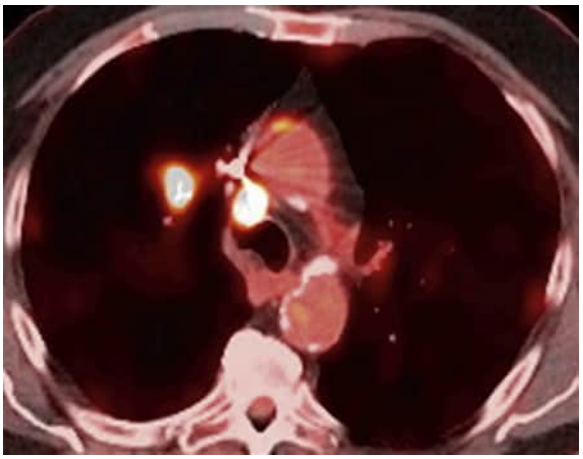


Figure 76.6 Stage IIIA: right upper lobe tumor and a N2 lymph node (station 4R). Mediastinal staging is needed in stage IIIA and should begin on the left with contralateral (N3) lymph nodes sampled in sequence until a positive sample is achieved; in this case 4R was positive.

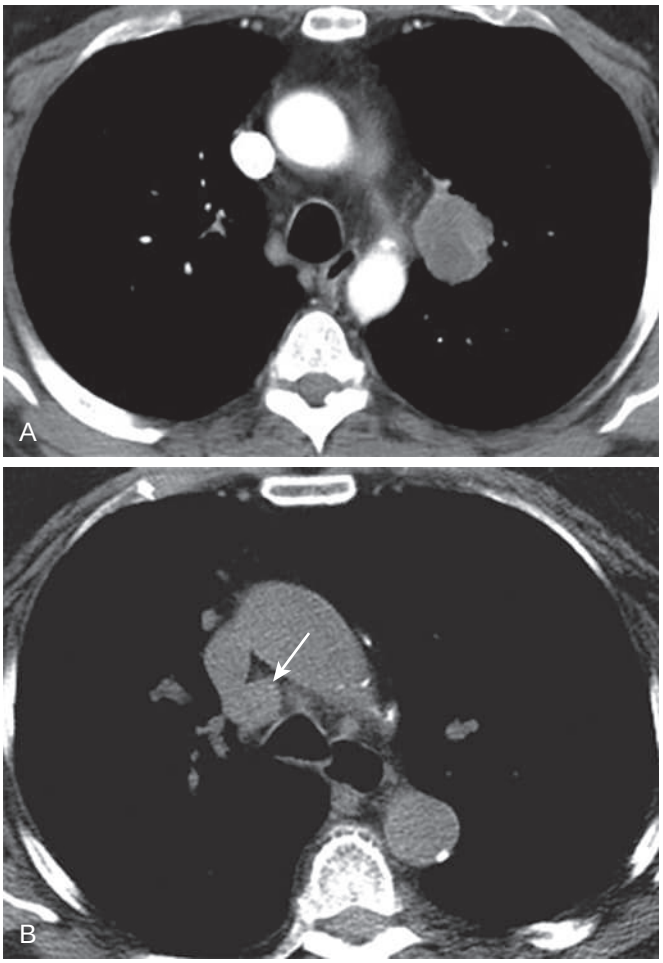


Figure 76.7 Stage IIIB: non–small cell lung cancer. (A) Left upper lobe mass. (B) An N3 lymph node (station 4R). Mediastinal staging is required and should start on the right at 4R *(arrow)* because a positive result there will establish both the diagnosis and the highest tumor stage to define treatment.

isotope is seen using a PET scan camera. A meta-analysis demonstrated a pooled sensitivity of 74% (95% confidence interval, 69–79%) and specificity of 85% (95% confidence interval, 82–88%).[53] There is a low sensitivity of PET for lesions of 1 cm or less, which is likely related to lower metabolic activity in small-nodule lower-grade malignancies.[54] In patients with lung cancer confined to the chest and potentially curable, it is found that the rate of false positives in PET scans is too high to obviate the need for invasive mediastinal staging (transbronchial, transthoracic, or transesophageal needle aspiration; mediastinoscopy; or more extensive surgery).[47]

Brain metastases have long been associated with patients with stage IIIA or higher NSCLC who have neurologic clinical findings and with all patients with SCLC. More recently, data have accumulated showing an association of brain metatasis in patients with asymptomatic stage II to III NSCLC.[55–61] Pooled sensitivity and specificity of nine studies on patients with NSCLC and no neurologic findings on clinical evaluation found a median prevalence of brain metastases of 3% (range, 0–21%).[47] At present, the National Comprehensive Cancer Network guidelines recommend a brain *magnetic resonance imaging* (MRI) with contrast (or contrast CT if MRI is not possible) for stage

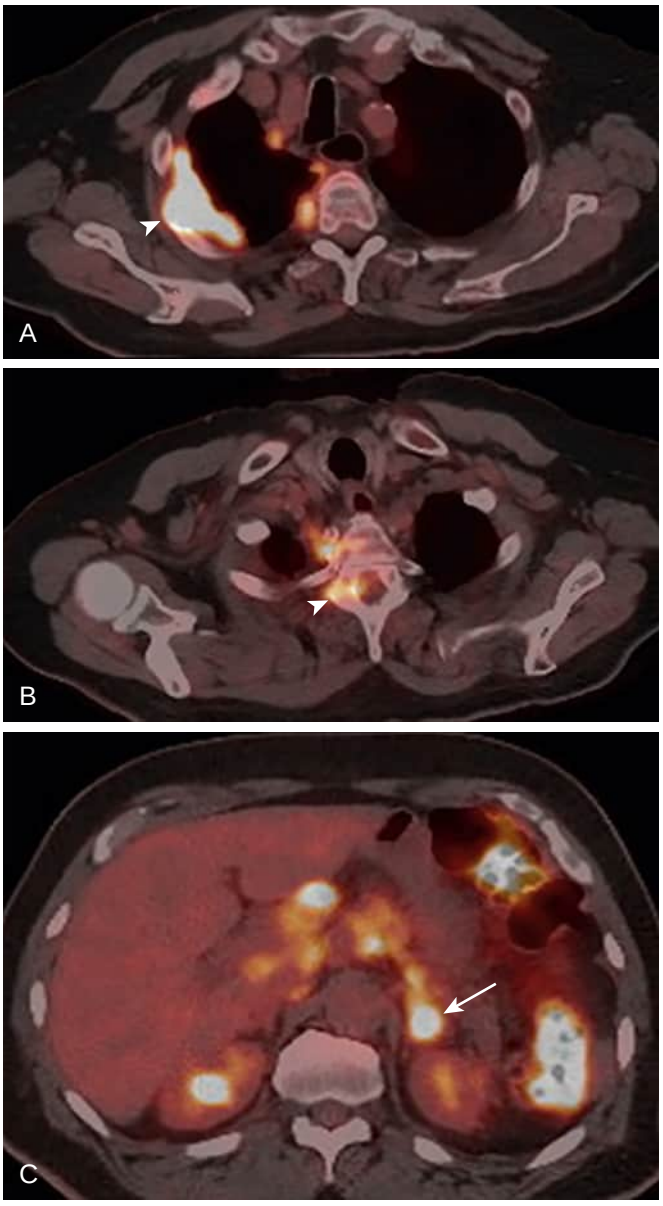


Figure 76.8 Optimized lung carcinoma staging. Endoscopic ultrasound–guided biopsy of the left adrenal gland *(arrow)* (C) was chosen as the safest and highest yield location for diagnosis because, although osseous metastatic disease was present *(arrowheads;* A–B), bone biopsies yield little material for molecular analysis. The diagnosis of adenocarcinoma of the lung was established and confirmed as stage IV. The patient was positive for an anaplastic lymphoma kinase fusion on molecular analysis and was a candidate for an oral tyrosine kinase inhibitor.

II or higher NSCLC,[62] although other guidelines have suggested starting brain imaging with stage III or higher NSCLC. Brain MRI is considered more sensitive than CT scanning of the brain, thus identifying more and smaller lesions; however, some studies have not shown that this difference in sensitivity has led to clinically meaningful survival differences. Therefore, CT scan with contrast is an acceptable alternative in patients who cannot obtain an MRI.[63]

When confronted with a patient suspected of having lung cancer with metastatic disease, tissue confirmation for diagnosis with patient safety in mind is the first step. However, to be accurate, efficient, and minimally invasive, the goal should be to obtain a biopsy from a metastatic site so that both diagnosis and staging may be confirmed in a single procedure. If there is a solitary extrathoracic site that is suspicious for a metastasis, tissue confirmation of that site with a fine-needle aspiration or biopsy should be attempted if feasible. Modalities used for such biopsies may include CT-guided approaches (e.g., commonly for liver, bone, or contralateral lung metastasis), thoracentesis for the diagnosis of a malignant pleural effusion, thoracoscopic biopsy, or EUS fine-needle aspiration of left adrenal metastases. Patient-centered care and risk/benefit ratios factor in to decisions on invasive staging procedures. The pneumothorax risk of CT-guided transthoracic needle lung biopsy was up to 15% in a large population-based study, although less than half required chest tubes (see Chapter 21).[64] Although image-guided liver biopsy carries less risk than lung biopsy, there is a complication rate of 0.5–1% for hemorrhage requiring transfusion, pneumothorax, malignant tract seeding, infection, perforation of viscera, or death.[65] Although a bone biopsy under CT guidance is an even safer procedure, the cellularity may be less than lung or liver biopsies,[66] and the decalcification process required to prepare the specimen may leave insufficient material for molecular analysis. Based on the safety of the proposed procedure to document metastatic disease, there are also situations in which patients have lesions in multiple distant sites suspected of metastases but in whom biopsy of a metastatic site would be technically too difficult or risky, so the diagnosis of the primary lesion should be obtained by the least invasive method.[67]

In addition to choosing a diagnostic procedure that allows concurrent diagnosis and staging of NSCLC, it is now necessary to obtain a sufficient amount of tissue for genetic testing and programmed death-ligand 1 assessment, both of which have potential treatment implications.[68] It is relevant that the majority of patients presenting with lung cancer are diagnosed at an advanced stage when molecular profiling is needed to determine candidacy for targeted therapy and immunotherapy and, in such patients, minimally invasive procedures are recommended for diagnosis and staging. As nonsurgical techniques, such as EBUS–*transbronchial needle aspiration* (TBNA), have emerged as first-line tests; cytology specimens (including pleural fluid)[69] or small-volume biopsies are increasingly being used for molecular testing.[47,70]

LOCALLY ADVANCED DISEASE/ SUSPECTED MEDIASTINAL INVOLVEMENT

In patients with known or suspected NSCLC and no evidence of systemic metastases, attention must immediately turn to mediastinal staging. Accurate staging of the mediastinum is critically important in guiding optimal management. The following section reviews noninvasive staging and invasive staging of the mediastinum.

NONINVASIVE STAGING

CT scanning of the chest is the most widely available noninvasive modality for evaluation of the mediastinum in patients with lung cancer and is recommended as the first test for all patients with suspected or confirmed lung cancer.[71–73] CT scan can define the location, size, and

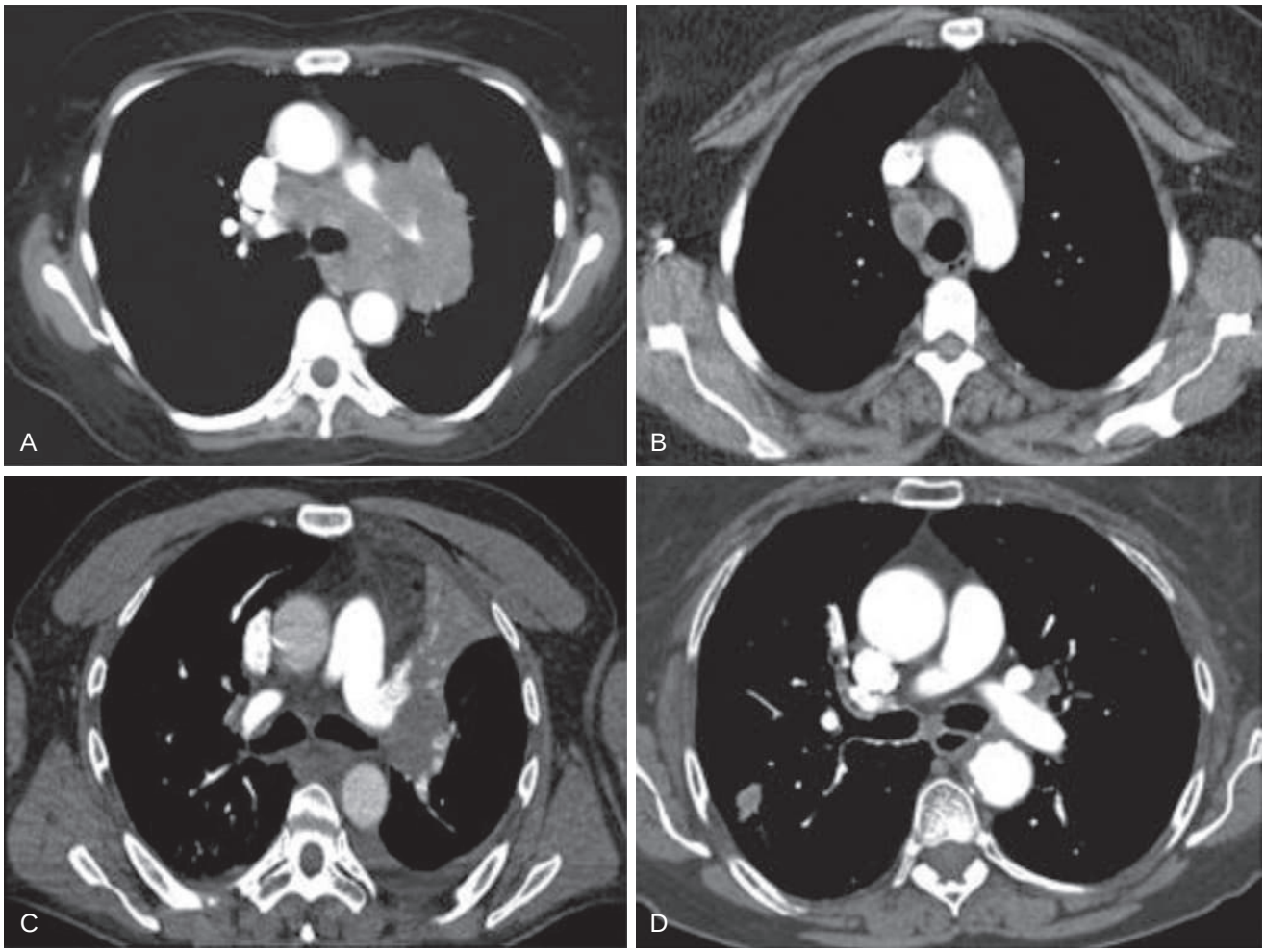


Figure 76.9 American College of Chest Physicians intrathoracic radiographic (computed tomography scan) categories of lung cancer. (A) Mediastinal infiltration by tumor. (B) Enlarged discrete N2 and N3 nodes. (C) A central tumor or a tumor with enlarged N1 nodes but a normal mediastinum. (D) A peripheral small tumor (seen in lower left corner of image) with normal-sized lymph nodes. (From Silvestri GA, Gonzales AV, Jantz, MA, et al. Methods for staging non–small cell lung cancer: diagnosis and management of lung cancer, 3rd ed: American College of Chest Physicians evidence-based clinical practice guidelines. *Chest.* 2013;143:e211S–e250S.)

characteristics of the primary lesion and the anatomic location and size of lymphadenopathy. CT thus provides the necessary information to structure the subsequent diagnostic and staging evaluation, frequently allowing physicians to establish diagnosis and stage with a single invasive procedure. This approach is strongly favored because it streamlines the investigation process and reduces complications.

In the majority of studies evaluating the accuracy of CT for mediastinal staging, CT scans are performed with administration of *intravenous* (IV) contrast material. Although IV contrast is not absolutely necessary when performing CT scans for this indication, it helps to distinguish vascular structures from lymph nodes and to delineate mediastinal invasion by centrally located tumors. The most widely accepted criterion for suspected malignant involvement of mediastinal nodes is a short-axis lymph node diameter greater than or equal to 1 cm on a transverse CT scan.

To help with decisions about mediastinal staging, the American College of Chest Physicians defines four intrathoracic CT radiographic categories of lung cancer, based on the primary tumor and the mediastinum (Fig. 76.9). Group A represents mediastinal infiltration by tumor, in which discrete nodes can no longer be discerned or measured. Group B includes patients with discrete mediastinal node enlargement. Groups C and D comprise patients with normal mediastinal nodes and a central tumor (C) or a peripheral tumor (D). The presence of a centrally located tumor or suspected ipsilateral hilar (N1) disease translates into a 20–25% chance of pathologic node involvement (group C), whereas mediastinal involvement is much less likely in patients with peripheral clinical stage I tumors (group D).[47] This categorization describes patterns of either mediastinal involvement, or lack thereof, that can guide next steps in invasive staging. For example, group A may not need systematic nodal staging by EBUS-TBNA or mediastinoscopy because nodal anatomy is not clearly delineated. Rather, an ultrasound-guided transthoracic needle sample can be obtained from the most easily accessible site in the mediastinum to document disease and potentially obtain material for molecular analysis. Group B is an ideal scenario for systematic EBUS-TBNA evaluation of the mediastinum, starting from the highest station, N3 nodes, and progressing to N2 and potentially N1 nodes. The need for systematic mediastinal staging in groups C and D depends on features mentioned earlier regarding primary tumor size, location, and presence of radiographic N1 disease.

The accuracy of CT scanning for noninvasive staging of the mediastinum in patients with lung cancer was systematically reviewed as part of the third edition of the *American College of Chest Physicians Clinical Practice Guidelines* (Methods for Staging NSCLC).[47] The combined studies yielded 7368 evaluable patients (30% median prevalence of mediastinal metastases). The median sensitivity and specificity of CT scanning for identifying mediastinal nodal metastases were 55% and 81%, respectively. The median positive predictive value was 58% (i.e., >40% of nodes deemed suspicious on CT are actually benign), whereas the median negative predictive value was 83% (i.e., almost 20% of nodes deemed benign by CT criteria are actually malignant). An important message thus emerges: CT scanning can neither reliably rule in nor exclude mediastinal metastases. Despite these important limitations, CT provides important anatomic guidance for selection of biopsy targets, and the most appropriate invasive diagnostic procedures.

PET scanning plays a prominent role in the evaluation of patients with suspected lung cancer. This is also true with regard to mediastinal evaluation, with some important caveats. Standardized quantitative criteria for an abnormal PET scan in the mediastinum are unfortunately lacking. The assessment of nodal uptake is a qualitative one and is based on a comparison of uptake in the node of interest with the background mediastinal activity. Alternatively, a standard uptake value of 2.5 or greater has been used as a threshold level for malignancy. PET is primarily a metabolic examination and has limited anatomic resolution. Integrated PET-CT scanners, however, now provide both anatomic (CT) and functional (PET) images simultaneously. As stated earlier, the sensitivities and specificities are not sufficiently accurate to warrant reliance on PET-CT scanning alone, and tissue confirmation of PET findings is imperative (Fig. 76.10).

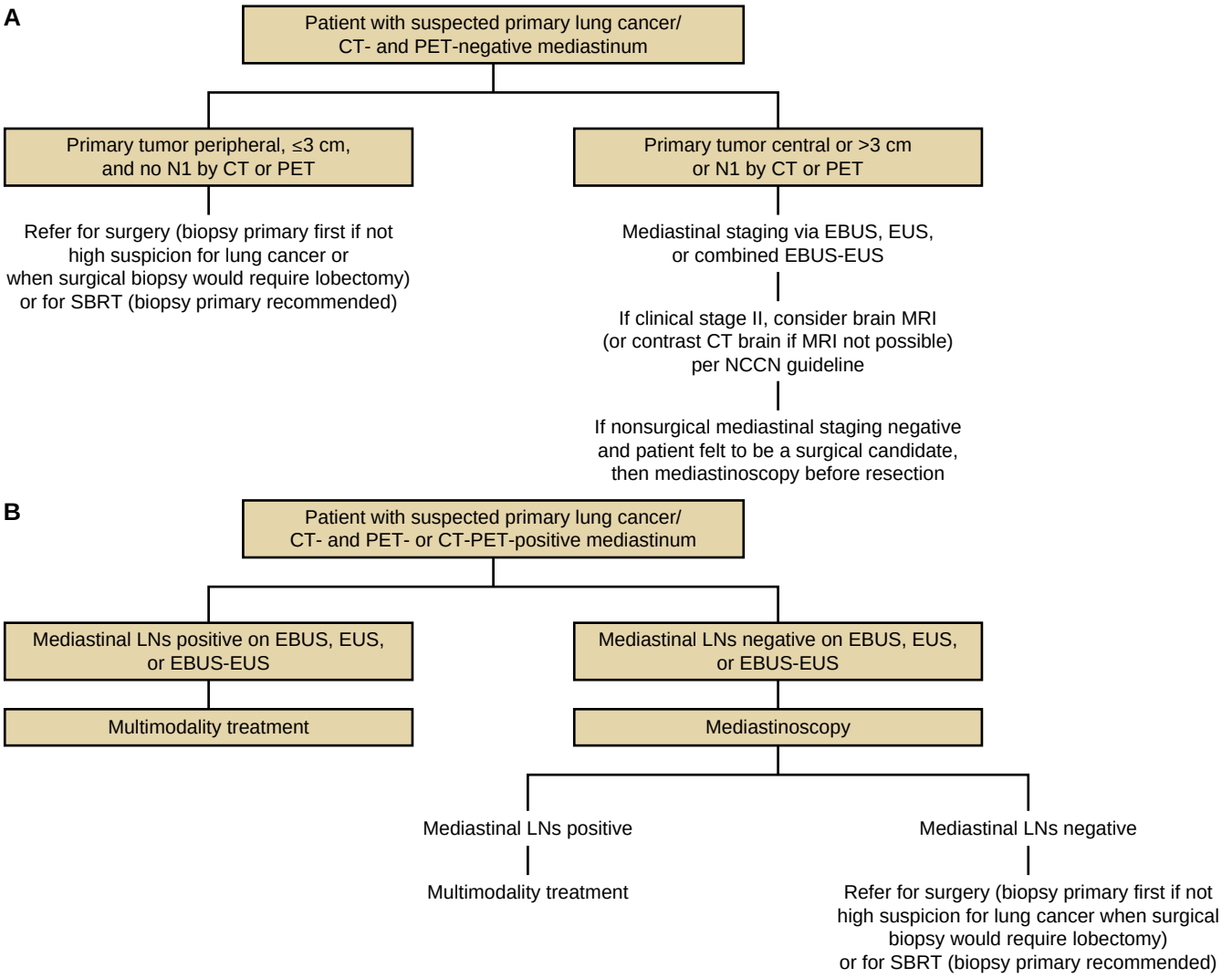


Figure 76.10 Algorithms for preoperative mediastinal node staging in non–small cell lung cancer. Staging algorithm for patients with suspected primary lung cancer (A) with CT- and PET-negative mediastinum and for those (B) with a CT- or PET-positive mediastinum. CT, computed tomography; EBUS, endobronchial ultrasound; EUS, endoscopic ultrasound; LNs, lymph nodes; MRI, magnetic resonance imaging; NCCN, *National Comprehensive Cancer Network*; PET, positron emission tomography; SBRT, stereotactic body radiation therapy. (Modified from De Leyn P, Dooms C, Kuzdzal J, et al. Revised ESTS guidelines for preoperative mediastinal lymph node staging for non–small-cell lung cancer. *Eur J Cardiothorac Surg.* 2014;45[5]:787–798.)

MINIMALLY INVASIVE STAGING: ENDOBRONCHIAL ULTRASOUND, ENDOSCOPIC ULTRASOUND, AND COMBINED ENDOBRONCHIAL ULTRASOUND–ENDOSCOPIC ULTRASOUND

Bronchoscopy with EBUS-guided TBNA has largely surpassed conventional TBNA and mediastinoscopy for the diagnosis and staging of lung cancer. Ultrasound-guided needle techniques, including EBUS, EUS, or combined EBUS-EUS are now recommended as tests of first choice for confirmation of mediastinal involvement in accessible lymph node stations. The sensitivities of these techniques are approximately 89%, 89%, and 91%, respectively[47] (see Chapter 27).

EBUS and EUS may have complementary roles with regard to the lymph node stations that are accessible to each technique. Studies suggest that the combination of the two provides near-complete access to all mediastinal lymph node stations, thus improving the sensitivity for detecting mediastinal nodal metastases and reducing the need for surgical procedures.[74–76] The minor added benefit may not justify adding EUS to EBUS because EBUS can reach and sample all lymph node stations accessible by EUS except stations 8 and 9. It is extremely rare that these two stations are involved in lung cancer without concomitant involvement of stations 2, 4, or 7.[77]

In studies comparing EBUS-TBNA to mediastinoscopy in patients with potentially resectable NSCLC, there were no differences in the diagnostic yield between the two modalities.[78] In addition to superior safety, one of the advantages of EBUS-TBNA compared to mediastinoscopy includes the ability to access N1 lymph nodes, including hilar and interlobar lymph nodes.[79] This is particularly advantageous in staging of clinical stages I and II NSCLC because patients with N1 disease are an intermediate group of patients who have a variable prognosis.[80] If N1 disease is present, such patients can be appropriately excluded from stereotactic body radiation therapy.[81] Alternatively, if N1 nodes that are PET avid are found on biopsy to be benign, the patient can be downstaged and have an opportunity for a more curative treatment paradigm. Using noninvasive staging alone may lead both to inappropriate upstaging and downstaging.[47] The advantages of biopsy in stage III and IV NSCLC are also clear because the sensitivity and specificity of noninvasive radiologic staging are not adequate to exclude or confirm occult mediastinal involvement.

INVASIVE STAGING: MEDIASTINOSCOPY

Mediastinoscopy is the historic gold standard for invasively staging the mediastinum in patients with known or suspected lung cancer, but ultrasound-guided needle techniques (EBUS-TBNA, EUS–fine-needle aspiration, or their combination) are now recommended as the best first invasive diagnostic procedures due to their safety and accuracy. If negative for malignancy in a patient with lung cancer, EBUS or EUS should be followed by another biopsy technique (e.g., CT-guided biopsy) or surgical biopsy (i.e., mediastinoscopy or video-assisted thoracoscopy), particularly in patients with enlarged mediastinal lymph nodes on CT or increased FDG uptake on PET scan.[47,74,82,83]

A section on special considerations in lung cancer is available at ExpertConsult.com, including discussions of superior sulcus tumors and Pancoast syndrome, superior vena cava syndrome, oligometastatic NSCLC, and paraneoplastic syndromes.

Key Points

- When obtaining a careful history and physical examination, physicians should explore symptoms or signs caused by the direct invasion, obstruction, or metastatic effects of tumor and potential paraneoplastic effects.
- A new staging system, the eighth edition of the *tumor-node-metastasis* (TNM) classification for lung cancer of the International Association for the Study of Lung Cancer, based on survival data from a large international population with lung cancer, has changed the T and M but not the N classifications. The revised classifications and stages should predict survival and guide therapy more accurately than the former TNM system.
- Noninvasive staging has limitations. Computed tomography and positron emission tomography can neither reliably rule in nor exclude mediastinal metastases. Despite these important limitations, positron emission tomography–computed tomography provides important anatomic guidance for selection of biopsy targets and the most appropriate invasive diagnostic procedures.
- Ultrasound-guided needle techniques, including endobronchial ultrasound, endoscopic ultrasound, or both, are now the first-line tests for confirmation of mediastinal involvement in accessible lymph node stations in patients with lung cancer.
- In considering where to direct a biopsy, the goal is to maximize the ability to diagnose and stage with the fewest number of biopsies. For example, a biopsy of an involved supraclavicular node can determine a diagnosis of non–small cell lung cancer and its stage with one extremely safe biopsy.
- When obtaining tissue from patients with advanced-stage non–small cell lung cancer, sufficient tissue should be obtained for molecular testing.

Key Readings

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Complete reference list available at ExpertConsult.com.

SPECIAL CONSIDERATIONS IN LUNG CANCER

SUPERIOR SULCUS TUMORS AND PANCOAST SYNDROME

Pancoast syndrome is a constellation of symptoms and signs that includes shoulder and arm pain along the distribution of the eighth cranial nerve trunk and first and second thoracic nerve trunks, Horner syndrome, and weakness and atrophy of the hand.[84–86] The underlying cause is usually local extension of an apical lung tumor located in the superior pulmonary sulcus (Pancoast tumor, eFig. 76.1). The most common cause of this symptom complex is NSCLC, typically squamous cell; however, SCLC and a number of other types of tumors and infections may rarely present in this manner.[84] The most common initial symptom is shoulder pain, which is produced by tumor involvement of the parietal pleura; brachial plexus; vertebral bodies; and first, second, and third ribs. The pain may radiate along the upper back or shoulder into the axilla and along the distribution of the ulnar nerve. Patients are commonly treated for arthritis or bursitis of the shoulder for months before the correct diagnosis is determined. Horner syndrome consists of ptosis, miosis, and anhidrosis and is caused by the invasion of the paravertebral sympathetic chain and the inferior cervical (stellate) ganglion.[84] Pancoast syndrome is present in approximately one-third of patients with superior sulcus tumors reported in the literature. The intrinsic muscles of the hands may become weak and atrophied as the tumor progresses. With further extension through the intervertebral foramina, spinal compression and paraplegia may develop.

The chest radiograph may show an apical tumor, although in some cases a tumor can be identified only on a CT scan of the chest. If the diagnosis is suspected but the chest radiograph is negative, then a CT chest scan should be obtained. CT also provides additional information about the extent of the tumor and is especially helpful in identifying other pulmonary nodules and mediastinal adenopathy. MRI of the chest is considered to be superior for evaluating patients with superior sulcus tumors because of better assessment of invasion through the pleura and subpleural fat, better evaluation of plexus involvement, and better definition of subclavian vessel involvement.[87] Magnetic resonance angiography may give the best assessment of vascular invasion of the subclavian vessels. Bronchoscopy is frequently the first diagnostic test for apical tumors, although it has a diagnostic yield of only approximately 50% for these very peripheral lesions.[88,89] CT-guided transthoracic needle aspiration has a very high diagnostic yield (>90%) even if the bronchoscopy is nondiagnostic.[90] Superior sulcus tumors are usually staged as T3N0M0 (stage IIB) or higher depending on size of the tumor (T3 or T4) and extent of lymph node involvement. In a large series, 25% of patients were stage IIB, 22% were IIIA, and 53% were stage IIIB (T4 or N3).[91] Obviously, some patients are stage IV at diagnosis, but they were excluded from that report. It is estimated that one-third to one-half of all superior sulcus tumors have identifiable distant metastasis at diagnosis. In addition to the stage of disease and performance status, other important poor prognostic factors include weight loss and vertebral body or supraclavicular involvement. The presence of N1 or N2 nodal involvement and incomplete resections have a worse prognosis.[91,92] In patients treated for localized disease (stage IIB or IIIA), the brain is the most common site of relapse.[93] In the past, the most common treatment for localized superior sulcus tumors due to NSCLC was preoperative radiotherapy of 30 to 50 Gy followed by resection. This resulted in a 5-year survival of 25–35%.

More recently, the practice has been to perform neoadjuvant chemoradiotherapy followed by resection. This is based on results of the North America Intergroup Trial in which patients with a negative mediastinoscopy were treated with two cycles of etoposide and cisplatin chemotherapy and concurrent thoracic radiotherapy (45 Gy in 5 weeks). In the resected specimen, a pathologic complete response or minimal microscopic disease was identified in 66% of patients. The overall survival at 5 years was 44% and for those with a complete resection was 54%.[94] In a phase II trial in Japan, chemotherapy with mitomycin, vindesine, and cisplatin with concurrent thoracic radiotherapy led to a 5-year survival of 56%.[95] Data from phase III trials supporting surgery after induction chemoradiotherapy for Pancoast tumors enrolled patients with N0-1 disease, so this same paradigm in patients with N2 disease is controversial.[96] Although the optimal regimen of treatment has not been proved, a reasonable choice is that used in the U.S. Intergroup Trial study described earlier.

SUPERIOR VENA CAVA SYNDROME

The blockage of blood flow in the *superior vena cava* (SVC) results in SVC syndrome.[97] Bronchogenic carcinoma accounts for the vast majority of these cases in older adults.[98,99] In teenagers and young adults, SVC syndrome is usually due to non-Hodgkin lymphoma. Patients report dyspnea and a sensation of fullness in the head and/or light-headedness when bending over. They may also note facial swelling. Cough, pain, and dysphagia are less frequent symptoms. Physical examination findings included dilated neck veins, a prominent venous pattern on the chest, facial edema, and a plethoric appearance. The chest radiograph typically shows widening of the mediastinum or a right hilar mass. On occasion, it may be normal. Dilated veins on the anterior chest wall and compression of the SVC may be demonstrated with a contrast-enhanced CT scan. SVC syndrome is not generally a medical emergency, and patients should not be treated without a tissue diagnosis. Bronchoscopy or mediastinoscopy can be safely performed in the setting of SVC syndrome.[100] SVC syndrome due to SCLC is best treated with chemotherapy. In general, after treatment, symptoms will start to resolve in 5 to 7 days because SCLC is chemosensitive.[101] NSCLC is best treated with concurrent chemoradiotherapy (see earlier discussion of treatment of stage IIIA/IIIB NSCLC). For immediate relief of SVC obstruction, vascular stenting should be strongly considered. A Cochrane meta-analysis reported that SVC stents relieved obstruction in 95% of cases.[101] Stenting has been associated with a complication rate of 3–7%.

OLIGOMETASTATIC NON–SMALL CELL LUNG CANCER

The theory behind oligometastatic disease proposes that cancer metastasis appears along a continuum, from only

local disease to widely metastatic disease. Some patients have a limited number of metastatic tumors in transition between localized and widespread metastatic disease; these tumors are believed to have a more indolent biology, and affected patients have been shown to have longer survival.[102–104] Prospective randomized controlled trials show improved outcomes in other cancers, such as of the colon, when metastasis-directed therapy is added, but data are still emerging in lung cancer.[105,106] For patients with a synchronous resectable N0 primary NSCLC, grade 1C evidence favors resection or radiosurgical ablation of an isolated brain metastasis or resection of an isolated adrenal metastasis[107] (eFig. 76.2).

PARANEOPLASTIC SYNDROMES

Hormonal, neurologic, hematologic, or other remote effects of cancer not related to the direct invasion, obstruction, or metastatic effects of tumor are generally termed paraneoplastic syndromes. Paraneoplastic syndromes related to bronchogenic carcinoma are reported in 10–20% of patients (eTable 76.3).

eTable 76.3 Paraneoplastic Syndromes Associated With Bronchogenic Carcinoma

System	Paraneoplastic Syndrome
Musculoskeletal	Clubbing Hypertrophic osteoarthropathy Polymyositis Osteomalacia Myopathy
Cutaneous	Dermatomyositis Acanthosis nigricans Pruritus Erythema multiforme Hyperpigmentation Urticaria Scleroderma
Endocrinologic	Cushing syndrome Syndrome of inappropriate secretion of antidiuretic hormone Hypercalcemia Carcinoid syndrome Hyperglycemia/hypoglycemia Gynecomastia Galactorrhea Growth hormone excess Calcitonin secretion Thyroid-stimulating hormone
Neurologic	Lambert-Eaton myasthenic syndrome Peripheral neuropathy Encephalopathy Myelopathy Cerebellar degeneration Psychosis Dementia
Vascular/hematologic	Thrombophlebitis Arterial thrombosis Nonbacterial thrombotic endocarditis Thrombocytosis Polycythemia Hemolytic anemia Red cell aplasia Dysproteinemia Leukemoid reaction Eosinophilia Thrombocytopenic purpura
Miscellaneous	Cachexia Hyperuricemia Nephrotic syndrome

MUSCULOSKELETAL EFFECTS

Clubbing of the digits may be a manifestation of lung cancer or other diseases. Clubbing may involve the fingers and toes and consists of selective enlargement of the connective tissue in the terminal phalanges. Physical findings include loss of the angle between the base of the nail bed and the cuticle, rounded nails, and enlarged fingertips. Clubbing is an isolated finding and is usually asymptomatic. Nonmalignant causes of clubbing include pulmonary fibrosis, congenital heart disease, and bronchiectasis. *Hypertrophic pulmonary osteoarthropathy* (HPO) is an uncommon process associated with lung cancer. HPO is characterized by painful arthropathy that usually involves the ankles, knees, wrists, and elbows and is most often symmetrical. The pain and arthropathy are caused by proliferative periostitis that involves the long bones but may also affect metacarpal, metatarsal, and phalangeal bones. Patients may have clubbing of fingers and toes in addition to the painful arthralgias. The pathogenesis of HPO is uncertain, but it may arise from a humoral agent. For patients who smoke and have a new onset of arthralgias, HPO must be considered. A radiograph of the long bones (i.e., tibia and fibula) usually shows characteristic periosteal new bone formation. An isotope bone scan typically demonstrates diffuse uptake by the long bones. Large cell and adenocarcinoma are the most common histologic types associated with HPO. The symptoms of HPO may resolve after resection. For inoperable patients, treatment is with nonsteroidal anti-inflammatory agents. Case reports have observed resolution or marked improvement of symptoms with bisphosphonate treatment.[108]

Although still a topic of debate, population-based studies from Scandinavia suggest a frequency of malignancy of 15–25% in patients with dermatomyositis-polymyositis.[109] The highest risk of malignancy is in the first 2 years after the diagnosis of dermatomyositis-polymyositis. A reasonable approach to cancer surveillance in these patients is a careful history and physical examination, chest radiograph, basic laboratory tests, and age-appropriate cancer screening examinations. Other tests should be based on abnormalities detected during the basic evaluation.

HEMATOLOGIC EFFECTS

Anemia frequently develops in patients who have lung cancer and may be caused by iron deficiency, chronic disease, or bone marrow infiltration. Eosinophilia is more

commonly associated with Hodgkin disease, but it may also be seen in patients who have lung cancer. Production of various cytokines by neoplastic cells may result in eosinophilia, leukocytosis, or thrombocytosis, of which thrombocytosis is by far the most common. The association of deep venous thrombosis and malignancy was described by Trousseau more than a century ago, and lung cancer is the most common malignancy associated with Trousseau syndrome. The causes of the hypercoagulable state remain poorly understood. One large study documented clinically significant association of idiopathic thrombosis and the subsequent development of overt cancer; however, other investigators concluded that the literature does not enable firm recommendations about whether to screen for a malignant neoplasm in patients who have unexplained venous thromboembolism.[109a] Thromboembolism in the patient who has malignancy is often refractory to warfarin treatment. Treatment with *low-molecular-weight heparin* (LMWH) on a chronic basis may be effective. In a randomized trial, patients with cancer and deep vein thrombosis, pulmonary embolism, or both were randomized to receive LMWH (dalteparin) subcutaneously once daily or oral warfarin daily for 6 months.[110] At 6 months, the probability of recurrent thromboembolism was 9% with dalteparin treatment and 17% with warfarin, a difference that was highly significant. The risks of major bleeding or any bleeding were not different in the two groups. The other advantage of LMWH is that it is unnecessary to monitor the anticoagulant effect, except in some patients with renal insufficiency. A 2008 Cochrane analysis concluded that, for long-term treatment in patients with cancer, LMWH reduced venous thromboembolism events, but not death, compared with vitamin K antagonists. There was no significant difference in the risk of bleeding.[111] More recently, direct oral anticoagulants have also shown encouraging results in the treatment of venous thromboembolism in cancer patients and can be considered in this patient population as well.[112–115]

HYPERCALCEMIA

Hypercalcemia in association with malignancy may arise from a bony metastasis or, less commonly, from secretion by the tumor of a *parathyroid hormone–related protein* (PTHrP) or other bone-resorbing cytokine. The most common cancers to cause hypercalcemia are those of the kidney, lung, breast, head and neck, and myeloma and lymphoma. In one study of 690 consecutive lung cancers, 2.5% of cases had tumor-induced hypercalcemia.[116] Squamous cell histology is the most common cell type associated with hypercalcemia, and generally patients have advanced disease (stage III or IV) and are unresectable. Symptoms of hypercalcemia include anorexia, nausea, vomiting, constipation, lethargy, polyuria, polydipsia, and dehydration. Confusion and coma are late manifestations, as are renal failure and nephrocalcinosis. Cardiovascular effects include shortened QT interval, broad T wave, heart block, ventricular arrhythmia, and asystole. Individual patients may manifest any combination of these signs and symptoms in various degrees.

Hypercalcemia of malignancy that is not caused by bony metastases results from accelerated bone resorption, decreased bone deposition, or increased renal tubular reabsorption of calcium. Accelerated bone resorption is caused by activation of osteoclasts by cytokines or PTHrP in most cases. Serum parathyroid hormone levels are usually normal or low, but an elevated level of PTHrP can be detected in the serum in approximately one-half of these patients.[116] Cytokines or PTHrP are secreted autonomously by the tumor. Not only does PTHrP cause renal calcium reabsorption, but also it interferes with renal mechanisms for reabsorption of sodium and water, with resultant polyuria. Polyuria and vomiting result in dehydration; decreases in glomerular filtration further aggravate the hypercalcemia.

Mild elevation of serum calcium may not require treatment, so the decision is based on the patient's symptoms. For patients who have widely metastatic and incurable malignancy, it may be most appropriate to give supportive care only and not treat mild hypercalcemia. The average life expectancy in this situation is 30 to 45 days, even with aggressive treatment.[117] However, most patients who have a serum calcium of 12 to 13 mg/dL or higher are treated.

The four basic goals of treatment are to (1) correct dehydration, (2) increase renal excretion of calcium, (3) inhibit bone resorption, and (4) treat the underlying malignancy. Because of the polyuria, patients with hypercalcemia are volume contracted. Initial treatment is with IV normal saline, using 3 to 6 L per 24 hours as tolerated, with careful attention to volume status. Previously, a loop diuretic such as furosemide or ethacrynic acid was added to maximize calcium excretion, but this has become less common due to the efficacy of the bisphosphonates in inhibiting bone resorption. Thiazide diuretics are not used because they increase calcium reabsorption in the distal tubule. Fluids and diuretics generally result in only a mild decrease of the calcium; additional treatment is needed to inhibit the accelerated bone resorption. The bisphosphonates have a high affinity for bone and inhibit osteoclast activity. Zoledronate, a newer bisphosphonate, is the most effective; the usual dose is 4 mg given IV over 15 minutes.[118] Normal calcium levels are achieved within 4 to 10 days in 85% of patients and last a median of 30 to 40 days. Adverse effects are generally mild and transient and include fever, hypophosphatemia, asymptomatic hypocalcemia, and occasionally renal failure. Calcitonin inhibits bone resorption, increases renal calcium excretion, and has a rapid onset of action, but the duration of action is short lived. Calcitonin is a relatively weak agent and when used alone does not usually normalize the serum calcium of patients who have marked hypercalcemia. Use of calcitonin is appropriate when the calcium is greater than 14 mg/dL or needs to be lowered urgently (onset of action is 4–6 hours) while waiting for the more effective but slower-acting agents to take effect or when relief of bony pain is desired. The effects of calcitonin and bisphosphonates are additive. Tachyphylaxis to calcitonin may be seen after 48 hours. Other agents, such as gallium nitrate or plicamycin, have been used to treat hypercalcemia but have not generally been adopted as first-line therapies because of inconvenience of administration schedules or associated toxicities.

SYNDROME OF INAPPROPRIATE ANTIDIURETIC HORMONE SECRETION

Causes of hyponatremia include tumors, pulmonary infections, central nervous system disorders, and drugs. Although only 10% of patients with SCLC exhibit the *syndrome of inappropriate antidiuretic hormone* (SIADH) secretion, SCLC accounts for approximately 75% of cases of SIADH. Antidiuretic hormone (vasopressin) is secreted in the anterior hypothalamus and exerts its action on the renal collecting ducts by enhancing the flow of water from the lumen into the medullary interstitium, thereby concentrating the urine. The criteria for the diagnosis of SIADH include (1) hyponatremia associated with serum hypoosmolality (<275 mOsm/kg); (2) inappropriately elevated urine osmolality (>200 mOsm/kg) relative to serum osmolality; (3) elevated urine sodium (>20 mEq/L); (4) clinical euvolemia without edema; and (5) normal renal, adrenal, and thyroid function. The serum uric acid is usually low, and the urine osmolality/serum osmolality ratio is frequently greater than 2. The severity of symptoms is related to the degree of hyponatremia and the rapidity of the fall in serum sodium. In one large series of SIADH patients, only 27% had signs or symptoms of hyponatremia despite median sodium of 117 mEq/L (range, 101–129 mEq/L). Symptoms of hyponatremia include anorexia, nausea, and vomiting. With a rapid onset of hyponatremia, symptoms caused by cerebral edema may include irritability, restlessness, personality changes, confusion, coma, seizures, and respiratory arrest. In minimally symptomatic or asymptomatic patients, fluid restriction of 500 to 1000 mL per 24 hours is the initial treatment of choice. Conivaptan is an IV vasopressin receptor antagonist that has been shown to be useful in correcting hyponatremia, but its use is limited to the hospital. Oral vasopressin receptor antagonists[119,120] have also been approved for use in this setting.

If further treatment is needed, oral demeclocycline (900–1200 mg/day) can be considered. Demeclocycline induces a nephrogenic diabetes insipidus and blocks the action of antidiuretic hormone on the renal tubule, thereby increasing water excretion. The onset of action varies from a few hours to a few weeks, so this drug is not recommended for acute emergency treatment. Demeclocycline has potential kidney toxicity. In patients who have more severe or life-threatening symptoms (serum sodium < 115 mEq/L), treatment consists of IV saline, supplemental potassium, and diuresis with loop diuretics, such as furosemide or ethacrynic acid. With severe confusion, convulsions, or coma, it may be appropriate to treat with 300 mL of 3% saline given over 3 to 4 hours in combination with a loop diuretic (saline without a diuretic will not increase the sodium concentration). Rapid correction of the sodium may have life-threatening consequences, and caution is advised.[121] The rate of correction of the sodium is best limited to a maximum of 20 mEq/L/day until a level of 120 to 130 mEq/L is reached. Faster correction has been associated with the development of central pontine myelinolysis, which may result in quadriplegia, cranial nerve abnormalities that manifest as pseudobulbar palsy, alteration in mental status, and subsequent death. In accordance, in the course of treating hyponatremia, the serum sodium must be monitored frequently to ensure that correction is not too rapid. For patients with SIADH due to SCLC, treatment with chemotherapy should be initiated as soon as possible and is likely to result in improvement in the hyponatremia within a few weeks. After an initial response to chemotherapy, SIADH may recur when the tumor relapses.

ECTOPIC CORTICOTROPIN SYNDROME

Ectopic production of corticotropin or corticotropin-releasing hormone with associated Cushing syndrome has been identified in patients who have SCLC, carcinoid tumor (lung, thymus, or pancreas), and neurocrest tumors, such as pheochromocytoma, neuroblastoma, and medullary carcinoma of the thyroid.[122] Of those with ectopic corticotropin secretion, SCLC accounts for 75% of cases, although only 1–2% of patients with SCLC develop Cushing syndrome. Cushing syndrome is seldom caused by NSCLC.

Classic features of Cushing syndrome include truncal obesity, striae, rounded (moon) facies, dorsocervical fat pad (buffalo hump), myopathy and weakness, osteoporosis, diabetes mellitus, hypertension, and personality changes. However, the rapid growth of SCLC means that patients are more likely to present with edema, hypertension, and muscular weakness than with the classic features of Cushing syndrome. Hypokalemic alkalosis and hyperglycemia are usually present. Patients with SCLC and Cushing syndrome appear to have shortened survival compared to those without the syndrome, perhaps because of more frequent opportunistic infections. The best screen for Cushing syndrome is the 24-hour urinary free cortisol measurement. Elevation of cortisol production, lack of suppression with high-dose dexamethasone, and plasma corticotropin levels greater than 200 pg/mL (40 pmol/L) are highly suggestive of ectopic corticotropin as the cause of Cushing syndrome in the absence of a pituitary adenoma. The plasma level of corticotropin is elevated in many, but not all, patients. Treatment of Cushing syndrome due to ectopic corticotropin has included adrenal enzyme inhibitors, such as metyrapone, aminoglutethimide, and ketoconazole, given alone or in combination. Ketoconazole given orally at a dosage of 400 to 1200 mg/day or metyrapone 250 to 750 mg 3 times per day may control hypercortisolism within a few days to weeks, but the response is variable.[123] Dose adjustments are based on achieving normal urinary free cortisol levels or morning plasma cortisols of 7 to 11 μg/mL. Symptomatic hypoadrenalism may result from treatment, and some authorities recommend a replacement dose of glucocorticoid when an enzyme inhibitor is started. When Cushing syndrome arises from SCLC, it is advisable to proceed with appropriate chemotherapy and carefully watch for superimposed infections, as is necessary for any patient receiving high-dose corticosteroids. Cushing syndrome related to a bronchial carcinoid or thymic carcinoid is best treated by surgical resection of the tumor.

NEUROLOGIC EFFECTS

The paraneoplastic neurologic syndromes associated with lung cancer, mostly small cell type, are quite variable and can affect any level of the central or peripheral nervous system. They include *Lambert-Eaton myasthenic syndrome* (LEMS), subacute sensory neuropathy, encephalomyelopathy, cerebellar degeneration, autonomic neuropathy, retinal degeneration, and opsoclonus.[124] The frequency of any of these neurologic syndromes in SCLC is approximately 5%, and neurologic symptoms may precede the diagnosis by months to years.[125,126] Most patients who have SCLC and an associated paraneoplastic syndrome have limited disease–SCLC that may or may not be obvious on initial evaluation. Careful radiographic evaluation of the lungs and mediastinum is indicated in a smoker who has a suspected paraneoplastic neurologic syndrome. In this setting even subtle abnormalities of the mediastinum require a biopsy. A PET scan may help identify an occult lesion and facilitate biopsy confirmation of the diagnosis.[127,128] Many reports have suggested that patients with paraneoplastic neurologic syndromes have a better prognosis than those without the paraneoplastic syndromes with similar stage and histology.

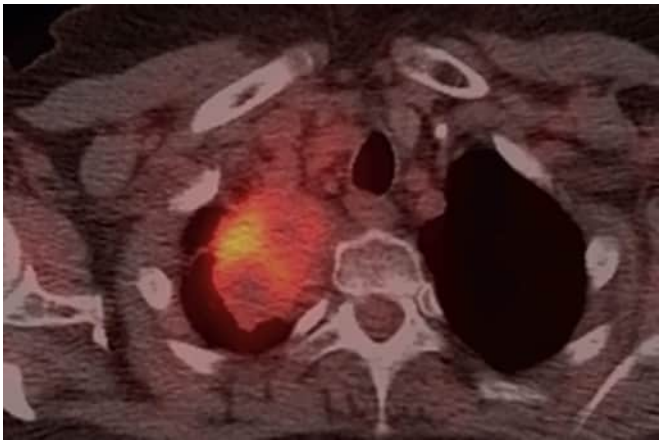
These paraneoplastic neurologic syndromes are thought to be immune-mediated responses against neural antigen abnormally expressed by the tumors. This is based on the identification of antibody and T cell responses against nervous system antigens. A number of onconeural antibodies have been found in the serum that react with both the nervous system and the underlying cancer.[124] However, not all patients with paraneoplastic syndromes have identifiable antibodies in their serum. The literature is confusing because of different names used by various investigators. The anti-Hu antibody is the same as *antineuronal nuclear antibody type 1* (ANNA-1), and the *antiribosomal* (anti-Ri) antibody is identical to ANNA-2. Both of these antibodies, but predominantly ANNA-1, have been associated with SCLC. ANNA-1 binds to the nuclei of all neurons in the central and peripheral nervous system, including the sensory and autonomic ganglia, the myenteric plexus, and cells of the adrenal medulla. Such antibodies should not be confused with the *anti–Purkinje cell antibody* (anti-Yo), which is characteristically found in patients who have subacute cerebellar degeneration as a manifestation of gynecologic malignancy or breast cancer. The *collapsin response-mediator protein-5* (CRMP-5) antibody, also known as anti–CV-2, has been associated with SCLC and thymomas.[124]

In a review of 162 sequential patients who had elevated ANNA-1 (anti-Hu), 142 (88%) were proved to have cancer, 132 of whom had SCLC.[126] In 97% of these cases, the diagnosis of SCLC followed the onset of the associated neurologic syndrome, usually by less than 6 months but, in 20%, by greater than 6 months. Of special note is that 90% of cases had disease limited to the lung or to the lung and mediastinum (limited disease–SCLC). In a report from Europe, 144 patients out of 200 with anti-Hu antibodies had a tumor in the chest.[125] Of these, 111 were proved to be SCLC. In one large series ANNA-1 antibodies were identified in 16% of all patients with SCLC. These antibodies were associated with limited-stage disease, complete response to therapy, and longer survival compared with patients who had SCLC and no ANNA-1 antibody. These neurologic syndromes seldom improve with treatment, so the goal is to prevent progression by starting treatment of the underlying tumor as soon as possible.

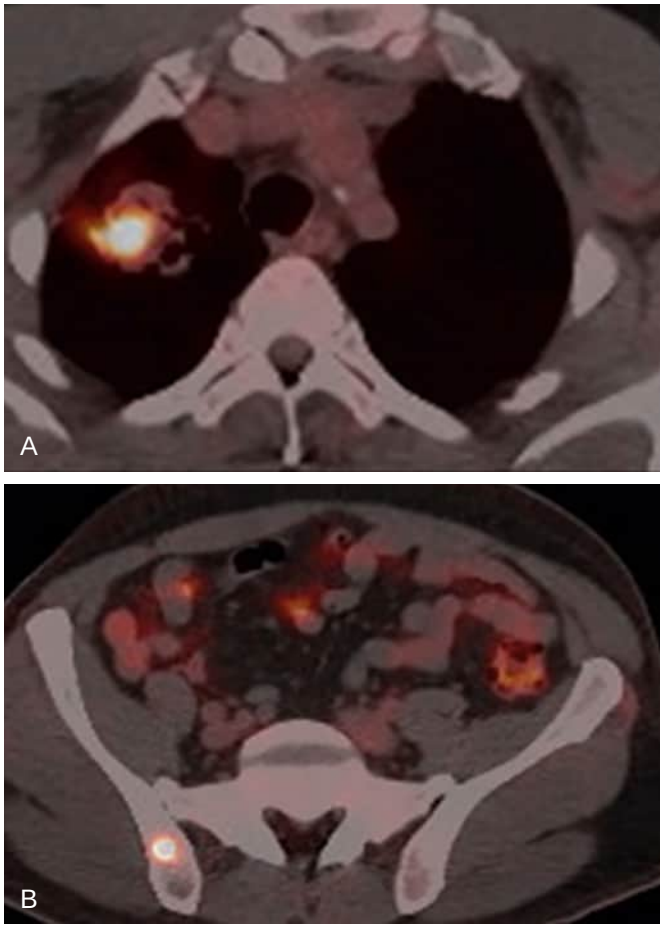
Less common manifestations of neurologic paraneoplastic syndromes are orthostatic hypotension and intestinal dysmotility. The gastrointestinal symptoms may present as nausea, vomiting, abdominal discomfort, or altered bowel habits suggestive of intestinal pseudo-obstruction. Many of these patients present with gastrointestinal symptoms and significant weight loss before the diagnosis of SCLC.

LEMS is characterized by muscle weakness, hyporeflexia, and autonomic dysfunction.[129,130] Cranial nerve involvement may be present and does not differentiate LEMS from myasthenia gravis. LEMS has been strongly associated with antibodies directed against presynaptic anti–voltage-gated calcium channels of peripheral cholinergic nerve terminals. These anti–voltage-gated calcium channel antibodies, identified in greater than 90% of patients with LEMS, block the normal release of acetylcholine at the neuromuscular junction. In contrast, myasthenia gravis is associated with anti–acetylcholine receptor antibodies, which are present in approximately 90% of myasthenic patients. Malignancy is present in approximately one-half of patients who have LEMS, and SCLC is by far the most common malignancy. In a study of 63 patients with SCLC examined prospectively, only 3% had clinical and electrophysiologic signs of LEMS, 8% had elevated anti–voltage-gated calcium channel antibodies, and 26% had other neurologic symptoms unrelated to LEMS.[131] The diagnosis of LEMS is based on characteristic electromyographic findings that show a small amplitude of the resting compound muscle action potential and facilitation with rapid, repetitive, supramaximal nerve stimulation or after brief exercise of the muscle. A single-fiber electromyogram is optimal for making the diagnosis. LEMS is the predominant paraneoplastic neurologic syndrome that may improve with successful treatment of the associated lung cancer. The use of acetylcholinesterase inhibitors is of limited benefit in LEMS.[132] Diaminopyridine enhances the release of acetylcholine and has been used with sustained improvement over months in the majority of patients with LEMS either with or without cancer.[133]

eFIGURE IMAGE GALLERY



eFigure 76.1 A positron emission tomography–computed tomography scan demonstrating a right upper lobe Pancoast tumor.



eFigure 76.2 Oligometastatic disease. This patient was offered surgical resection of the right upper lobe adenocarcinoma (A), followed by stereotactic body radiotherapy to the iliac bone metastasis (B, only site of metastatic disease) and then chemotherapy. Surgical paradigms in oligometastatic lung cancers may be considered in highly selected cases.

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77 LUNG CANCER: TREATMENT

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INTRODUCTION

Worldwide, lung cancer is the leading cause of cancer death and is projected to be a major health problem well through the first half of the twenty-first century, particularly in women and in developing countries, which continue to observe rising incidence rates.[1–3] The main histologic subtype of lung cancer is *non–small cell lung cancer* (NSCLC), which accounts for 85% of cases and includes adenocarcinoma, squamous cell carcinoma, and large cell carcinoma. The other lung cancer cell type is *small cell lung cancer* (SCLC). Survival rates are grouped based on the stage, but additional factors, including cell type (NSCLC vs. SCLC), the presence of actionable mutations, age, and comorbidities can also affect treatment outlook. The 5-year relative survival rate for lung cancer is 19.4% (16% for men and 22% for women) and is higher for NSCLC (23%) than for SCLC (6%).[4] The low survival rate reflects the fact that the majority of patients with lung cancer are diagnosed with advanced stages of disease.

Treatment is primarily based on disease stage and the patient's *performance status* (PS) at the time therapy is initiated. Advances in understanding the molecular pathogenesis of lung cancer underscore the heterogeneity of the disease. Molecular characterization of NSCLC currently serves as a critical guide to treatment in patients diagnosed with metastatic disease and in those who relapse after primary therapy. In general, stage I NSCLC (early stage) is treated with surgery alone. Stage II NSCLC (intermediate between early and locally advanced) is treated with surgery followed by chemotherapy. Stage III disease (locally advanced) treatment is beset with controversy but, in general, includes multimodality therapy with chemotherapy and surgery for resectable stage IIIA or a combination of chemotherapy and radiotherapy followed by immunotherapy. Stage IV NSCLC (metastatic disease) is treated with systemic therapy. However, there are important exceptions to these general rules, which are discussed later in this chapter.

SCLC usually presents with disseminated disease, and treatment strategies have focused on systemic therapy. Although SCLC is highly responsive to both chemotherapy and radiotherapy, it commonly relapses within months despite treatment.

Most patients will require multidisciplinary input over the course of their diagnosis and treatment. Development of multidisciplinary programs supported by members of the major disciplines involved in lung cancer care, namely the pulmonologist, thoracic surgeon, and the medical and radiation oncologists, and a "tumor board," with the addition of chest radiology, pathology, and nursing, is pivotal to ensure patients receive expeditious coordination of care, receive optimal treatment, and are considered for enrollment in clinical trials.

Major advances in lung cancer therapeutics include minimally invasive surgical techniques, refinements in radiotherapy, and a burgeoning of new systemic therapies targeting molecular pathways and the immune system. Systemic therapies and/or radiotherapy can be applied in a neoadjuvant or adjuvant fashion. A few terms used in this chapter are as follows:

- *Neoadjuvant* therapy indicates therapy given before surgery; it has the potential to reduce tumor volume, treat micrometastases, and improve outcomes.
- *Adjuvant* therapy is therapy given after surgery; it is aimed at treating any residual tumor or micrometastases with the aim of preventing tumor recurrence.
- *Concurrent* therapy is therapy given at the same time; for example, when chemotherapy and radiation therapy are given at the same time.
- *Sequential* therapy is therapy given sequentially; for example, when the radiotherapy follows chemotherapy.
- *Definitive* therapy is therapy intended to be curative, not palliative.
- *Consolidation* therapy is given after remission is achieved with the goal to sustain a remission.
- *Maintenance* therapy is given to patients in remission in an attempt to prevent relapse.

Radiotherapy advances include progressing from two-dimensional techniques (where bony landmarks on a patient or radiograph are used to shape a treatment field), to more *conformal* techniques (where *computed tomography* [CT] images are used to design radiation fields to treat a tumor target optimally while sparing other organs).

Treatment conformality and accuracy are also improved with modern techniques that use motion management (to see how a tumor moves with breathing) and customized shaping of radiation beams around a target.

The efficacy of treatments can be assessed by different metrics:

- *Median survival time* (MST) refers to the length of time 50% of the patients survive with a disease after a certain treatment.
- *Progression-free survival* (PFS) is the length of time a patient with lung cancer lives before the tumor progresses.
- *Overall survival* (OS) is the time from diagnosis or treatment until a patient's death.

Outcomes for diseases with excellent prognoses (such as early-stage breast cancer or low-risk prostate cancer) are often reported as percent OS at 5, 10, or 20 years after diagnosis or therapy (5-, 10- or 20-year OS). In contrast, outcomes for lung cancer are often reported as MST, 2-year OS, or PFS, reflecting the higher likelihood of disease recurrence or death.

- *Hazard ratios* (HRs) are used to describe differences in survival between two different treatments and to express survival benefit as a reduction in the risk of death. An HR of 1 for OS means the death rates are the same in both treatment groups while an HR of less than 1 means survival was better in one of the treatment groups. For example, if a study drug compared to placebo resulted in an HR of 0.60, the study drug reduced the risk of dying by 40%.

This chapter describes the current treatment of NSCLC and SCLC. As much as possible, evidence-based review of the best currently available literature has been included.

PROGNOSTIC AND PREDICTIVE FACTORS IN LUNG CANCER

A *prognostic* factor provides information about patient outcomes. Prognostic factors associated with improved survival include good PS (measured on the Karnofsky scale or the *Eastern Cooperative Oncology Group* [ECOG] scale), lesser extent of disease (stage), younger age, absence of weight loss, and female sex.[5–10] Women are diagnosed with less-advanced disease than men and, when adjusted for age, stage, and selected histologic subgroups, have improved outcomes after treatment for lung cancer.[9] Additional factors include the presence or absence of symptoms related to a specific site of metastasis, absence of smoking or smoking cessation, and NSCLC subtype (squamous histology slightly better than nonsquamous histology).[11–15] The maximal standard uptake value of the primary tumor on positron emission tomography has been inversely correlated with survival.[16] In patients with advanced NSCLC treated with platinum-based chemotherapy, absence of Kirsten rat sarcoma *(KRAS)* gene mutation and low or no expression of the DNA excision repair protein ERCC1 is associated with improved prognosis.[17,18] In a meta-analysis, *KRAS* mutations were associated with poorer survival, especially in adenocarcinoma.[17]

A *predictive* factor helps identify patients who will benefit from a specific treatment.[19] Predictive factors include histology (predictive of the benefit of pemetrexed in nonsquamous NSCLC irrespective of the stage),[20] and genomic mutations in the *epithelial growth factor receptor* (EGFR), fusion oncogenes involving *anaplastic lymphoma kinase* (ALK) and rearrangements in the *ROS proto-oncogene 1* (ROS1). Patients with EGFR mutations, ALK-fusion, or ROS1 rearrangement benefit from *tyrosine kinase inhibitors* (TKIs).[21,22] A *tumor proportion score* (TPS) for the expression of *programmed death-ligand 1* (PD-L1) on 50% or more of tumor cells in NSCLC is predictive of patients who will benefit from first-line therapy with an *immune checkpoint inhibitor* (ICI) targeting *programmed death-1* (PD-1).[23] Genomic profiling of cytologic and histologic samples obtained from the primary tumor, lymph nodes, or metastatic lesions is standard practice, because this allows for the best selection of first-line treatment in patients with advanced NSCLC.

TREATMENT OF NON–SMALL CELL LUNG CANCER BY STAGE

This section presents discusses the treatment of NSCLC by stage; Table 77.1 presents an overview of treatment strategies for NSCLC.

STAGE I NON–SMALL CELL LUNG CANCER

In the most recent edition (eighth) of the TNM staging system for NSCLC,[24] stage I is broken down by size of tumor to stage IA (tumors ≤ 3 cm: ≤ 1 cm [T1a (eFig. 77.1A), > 1 cm but ≤ 2 cm [T1b], > 2 cm but ≤ 3 cm [T1c]) and stage IB, which includes tumors between 3 and 4 cm [T2a] (eFig. 77.1B), centrally located and/or involving the visceral pleura (eFig. 77.2A). All stage I tumors are completely surrounded by lung parenchyma greater than 2 cm away from the carina, do not invade the chest wall or parietal pleura, and do not have malignant lymph node or metastatic disease. Thus the TNM classification for stage I is either T1aN0M0, T1bN0M0, or T1cN0M0, (stage IA), or T2aN0M0 (stage IB).[24] Although stage I disease offers the best chance for long-term survival, only 16% of patients with NSCLC present with stage I disease.[4]

The current treatment for stage I lung cancer is surgery alone. The surgical procedure of choice is a lobectomy with mediastinal lymph node sampling. The patient must be a reasonable surgical candidate as determined primarily by cardiopulmonary reserve and secondarily by age and comorbidities. Patients with a postoperative percent predicted forced expiratory volume in 1 second or diffusion capacity less than 40% will have a higher morbidity and mortality following lung cancer surgery. Patients with borderline values preoperatively should be referred for a differential ventilation-perfusion scan for a better prediction of postoperative function. When there is still a question, a cardiopulmonary exercise test can be obtained. Compared with those with a maximum oxygen consumption greater than 20 mL/kg/min, patients with a maximum oxygen consumption between 11 and 19 mL/kg/min have a higher morbidity but no greater mortality and those with a maximum oxygen consumption less than 10 mL/kg/min have both a higher predicted morbidity and mortality.[25] Patients who are "close calls" for surgery should be evaluated by both a pulmonologist and a thoracic surgeon before making a decision on whether the patient is *operable*, meaning that

Table 77.1 Summary of Current Treatment Strategies for Non–Small Cell Lung Cancer

Stage	Surgery	Chemotherapy	Radiotherapy	Chemoradiotherapy	Comments
IA and IB	First line	Adjuvant—tumors ≥4 cm	First line*	No	Role of adjuvant chemotherapy for stage IB not clearly defined but should be considered in tumors ≥4 cm in size and/or high-risk features (vascular invasion, visceral pleural involvement)
IIA and IIB	First line	Adjuvant	No	No	5-year survival improvement with adjuvant chemotherapy about 5%
T3 due to multiple tumor nodules same lobe	Lobectomy to resect primary and satellite nodules				
T3 due to chest wall invasion	En bloc resection				
Superior sulcus tumors					Neoadjuvant chemoradiotherapy improves survival in this subset of stage IIB
IIIA	First line for N0-1	Adjuvant treatment in completely resected IIIA	Neoadjuvant or adjuvant in the setting of N2 nodes	First line for unresectable N2 disease Followed by consolidation immunotherapy	Combined chemotherapy ± radiotherapy followed by surgery is feasible in select N2 disease, but more data are needed to recommend routinely
IIIB and IIIC	No	No	No	First line Followed by consolidation immunotherapy	
IV	No	First line: systemic therapy†: ■ Chemotherapy ■ Targeted therapy ■ Immunotherapy ■ Chemotherapy and immunotherapy	Radiotherapy is used for palliation only	No	All stage IV adenocarcinomas should have mutational analysis, including *EGFR*, *ALK*-fusion, *ROS1*, and *KRAS* All stage IV NSCLC should be tested for PD-L1

*SBRT for patients who are medically unfit or who refuse surgery.
†First-line therapy in stage IV NSCLC is selected based on (1) histology: pemetrexed for nonsquamous cell, gemcitabine for squamous cell and bevacizumab is approved as an adjunct to chemotherapy in the first-line setting in patients with nonsquamous histology and no other contraindications; (2) presence of molecular target guides first-line therapy; (3) PD-L1 expression >50% used to select patients eligible for first-line pembrolizumab.

the patient can tolerate the planned operation. It is important to recognize that patients who are *resectable*, meaning they have a potentially resectable tumor, may not be operable, usually because the patient does not have the pulmonary reserve to tolerate a lobectomy (see Chapter 30).

Stage I tumors located close to the hilum may be amenable to bronchial or vascular sleeve resection as an alternative to bilobectomy or pneumonectomy if the patient does not have sufficient reserve to tolerate the larger resection. Use of video-assisted thoracoscopic surgery has been associated with better postoperative recovery including less pain, shorter length of stay, equivalent long-term survival, and improved quality of life compared to thoracotomy.[26,27]

Patients with T1 tumors less than 2 cm and who are surgically resectable but medically inoperable may be able to tolerate a sublobar resection (wedge resection for peripherally located tumors spanning multiple segments or segmentectomy) as opposed to a lobectomy or pneumonectomy. Margins and lymph node clearance must still be adequate. In the case of wedge resection, the locoregional recurrence rate is higher than that of an anatomic resection (i.e., segmentectomy or lobectomy), but the overall 5-year mortality is no different.[28] Segmentectomy may offer local control, the opportunity for prolonged disease free survival, and OS comparable to lobectomy while preserving lung parenchyma, and so should be offered to patients with inadequate pulmonary function to tolerate lobectomy or those with multiple primary tumors anticipated to need subsequent resection.[29] With segmentectomy, preoperative nodule localization and marking by navigational bronchoscopy can be used to increase the success of a negative margin.[30] Still, whenever possible, a lobectomy or greater anatomic resection is preferred over a lesser resection, primarily because the tumor may be found on pathologic examination to be greater than 2 cm in size or there may be unsuspected positive hilar nodes; both findings would warrant a larger resection than segmentectomy.

The 5-year survival by pathologic stage for surgically resected stage IA (T1a,b,c, N0, M0) NSCLC is 80–90%, whereas the survival for stage IB lung cancer is 73%.[24] Local adjuvant radiation for stage I, after either complete or incomplete resection of the tumor, has not been found to be of any benefit,[31] and adjuvant chemotherapy is associated with worse survival for patients with resected stage IA disease.[32,33] The role of adjuvant chemotherapy in resected stage IB (T2a >3–4 cm) is limited and has yet

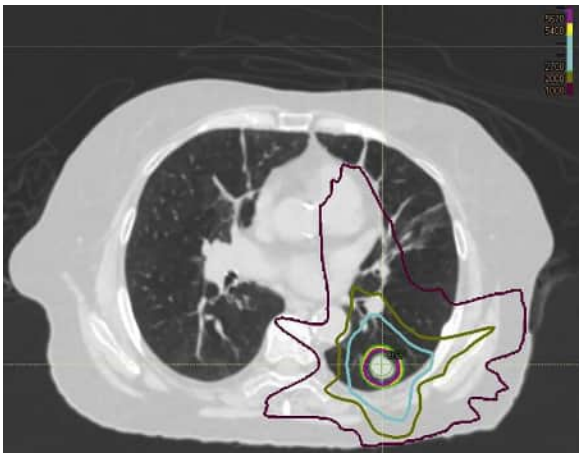

Figure 77.1 Stereotactic body radiotherapy planning. The image shows a typical stereotactic body radiotherapy plan for a peripheral lesion treated with 54 Gy in 3 fractions (yellow isodose line). Rapid dose falloff can be seen, with even a low isodose line (1000 cGy, purple) avoiding the spinal cord and esophagus.

to be defined. In a study of adjuvant chemotherapy in patients with stage IB NSCLC conducted by the Cancer and Leukemia Group B, significant improvement in PFS and OS was noted at 34 months. However, with a longer median follow-up of 74 months, differences in survival were not significant.[34] Subsequent exploratory analysis showed benefit for patients whose tumors were less than 4 cm in diameter (HR, 0.69).[34] This benefit has been reported by others,[35] and current National Comprehensive Cancer Network guidelines suggest adjuvant chemotherapy to treat patients with a tumor greater than 4 cm (particularly if it is poorly differentiated or shows vascular invasion or visceral pleural involvement).[36]

For patients who are deemed medically unfit or who refuse surgery, primary radiotherapy alone with curative intent is typically considered. Historically, nonsurgical candidates with early-stage lung cancer were treated with radiation using conventional fractionation (≈2 Gy per fraction for 6–7 weeks), *two-dimensional* (2D) techniques (without image guidance) and large radiation fields were used to account for tumor motion throughout the breathing cycle. With these relatively crude techniques, local control rates were only in the 30% range.[37] The approach of definitive radiation was further evaluated in a meta-analysis of 1 randomized and 35 nonrandomized trials.[38] The studies were heterogeneous, and the 5-year cancer-specific survival ranged between 13% and 39%. The authors concluded that, even in patients with severe emphysema, radiation therapy can be tolerated if careful planning with *three-dimensional* (3D) conformal techniques is undertaken. *Conformal* indicates that the radiation is designed in 3D to match the shape of the tumor, thereby allowing maximal targeting to the tumor with minimal injury to adjacent normal tissue. The Radiation Therapy Oncology Group conducted a series of dose escalation trials in the 1980s in an attempt to improve outcomes after definitive radiotherapy. Survival improved up to a dose of nearly 70 Gy, yet 2- year survival rates were actually lower at higher radiation doses, likely due to the pulmonary toxicity of high-dose radiation delivered in a nonconformal manner.[39] Consistent with this finding, comparisons of 2D versus 3D conformal radiation plans, of which the latter were based on CT, have demonstrated superior locoregional control with 3D conformal radiotherapy.[37]

More recently, *stereotactic body radiation therapy* (SBRT) has been introduced as a precise and accurate delivery method of highly conformal and dose-intensive radiation to small-volume targets. This method is also referred to as *stereotactic ablative body radiotherapy*. In contrast to conventionally fractionated radiotherapy, which ensures safety for normal body tissues by leveraging principles of radiobiology (small dose each day for many weeks), SBRT spares normal tissue by precise stereotactic localization, image guidance, and motion management to allow a *hypofractionated* course of treatment, in which 5 or fewer radiation treatments are given with larger doses of radiation delivered with each treatment. This technique allows delivery of a higher *biologic effective dose* (BED) with a typical radiotherapy plan (Fig. 77.1) than could previously be achieved using conventional radiotherapy methods.[40] Achieving a BED greater than 100 Gy results in improved local control of early-stage NSCLC, 92% versus 74% for patients receiving a BED less than 100 Gy.[41] Typical SBRT doses and fractionation for lung cancer (54 Gy in 3 fractions, 48 Gy in 4 fractions, and 50 Gy in 5 fractions) all have a BED greater than 100. In a single-arm phase II trial, patients with biopsy-proven stage I NSCLC deemed medically inoperable received SBRT with 60 Gy delivered in three fractions.[41] Long-term follow-up showed 5-year local control of 93%, lobar control 80%, distant failure rate of 31%, and OS 40%.[42] SBRT was typically well-tolerated with minimal toxicity (rates of grade 2 pneumonitis and chest wall pain < 10%).

In this SBRT study, however, the risk of complications was greater in *centrally located* tumors, defined as within 2 cm of the proximal tracheobronchial tree (six patients had treatment-related deaths, and four of those six had central lesions).[42] To improve the safety of SBRT for central lesions, subsequent studies have used a regimen of at least 5 fractions (in contrast to the 3-fraction regimen used for peripheral tumors). In a phase I/II dose escalation study, patients with biopsy-proven, medically inoperable, centrally located NSCLC were treated with 5-fraction SBRT ranging from 10 to 12 Gy delivered over 1.5 to 2 weeks.[43] Three-year local control was approximately 85% and dose-limiting *toxicity* rate in the first year was 7.2%; however, there were four deaths of patients in the higher dose per fraction cohorts—one due to esophageal ulcer and three due to bronchopleural hemorrhages.[43] As such, selection of dose for central lesions is vital to balance local control with risk of severe toxicities. For "ultracentral" tumors, which directly abut an organ at risk (trachea, mainstem bronchus or esophagus), more fractionated non-SBRT regimens (70 Gy in 10 fractions, 60 Gy in 12 fractions) are often used to mitigate toxicity. High local control rate with 60 Gy in 12 fractions has been reported in patients with tumors abutting the trachea or mainstem bronchus but with risk of severe toxicity, with 38% of patients developing a grade 3+ toxicity and 15% grade 5 pulmonary hemorrhage.[44] Thus patients with ultracentral tumors abutting major vessels and trachea are at risk for severe

toxicity even with moderately hypofractionated regimens (10–12 fractions).

STAGE II NON–SMALL CELL LUNG CANCER

Stage II NSCLC is divided into stage IIA T2bN0M0 (tumors >4 cm but ≤5 cm without involved nodes) (see eFig. 77.2B), and stage IIB includes either T3N0 tumors (>5 cm but ≤7 cm, invasion of chest wall or an ipsilobar satellite nodule) without lymph node involvement, or T1a–c or T2a–b tumors with hilar or peribronchial nodes (N1). The 5-year survivals for pathologic stage IIA and IIB are 65% and 56%, respectively.[24] Stage IIA NSCLC is quite uncommon, representing between 1% and 5% of patients treated in several surgical series.[45–48] Stage IIB NSCLC may represent up to 15% of surgically resected cases.[45,48] For stage IIA and IIB NSCLC, surgical therapy is the treatment of choice. NSCLC with invasion of structures such as the chest wall, (T3*inv*N0M0) (eFig. 77.3) is seen in about 5% of all NSCLC but represents about 45% of patients with T3 disease.[49] Adequate surgical treatment requires an en bloc resection of the affected nonvital structures and is designed to include lung, parietal pleura, visceral pleura, and parts of the chest wall, which could include the rib cage and the sternum, and results in a 5-year median survival of about 50%.[50,51] Surgery is also the primary treatment for tumors with satellite nodules in the same lobe (T3*satell*N0M0) and T3N0M0 superior sulcus (Pancoast) tumors.[24] A specific discussion of the evaluation and treatment of Pancoast tumor is discussed later in this chapter.

There is no benefit to postoperative radiotherapy in completely resected stage II and IIB NSCLC.[31] The value of adjuvant chemotherapy after surgery is discussed later (see "Stage IIIA") but, in short, adjuvant chemotherapy is recommended for all patients with resected stage II disease. Immunotherapy holds promise in early stage (stage I–II) NSCLC and is discussed further under "Immunotherapy."

STAGE III NON–SMALL CELL LUNG CANCER

The eighth edition of the TNM staging system expands stage III NSCLC into three subgroups: IIIA, IIIB, and IIIC,[24] which provides a better appreciation of the heterogeneity of stage III NSCLC. When applied retrospectively, each successive stage III subgroup is associated with incrementally shorter survival, ranging from 36% at 5 years for clinical stage IIIA disease to 13% for clinical stage IIIC disease.[24]

Stage IIIA

Stage IIIA NSCLC represents a diverse group of patients and includes those with N2 disease and patients with T3N1 and T4N0-1 disease.[24] The ability to achieve complete resection in stage III NSCLC may be limited by patient-related factors and by tumor characteristics such as large or invasive T4 tumors that cannot be completely resected with negative margins. For carefully selected T4N0-1M0 patients, surgery may be indicated with or without neoadjuvant chemotherapy or neoadjuvant chemoradiotherapy (superior sulcus tumors) (eFig. 77.4).[52] The need for resection of the diaphragm, vertebrae, and even involved areas of the great vessels is no longer considered an absolute contraindication, and a multidisciplinary surgical approach should be considered in these cases. Individuals with T4N0-1 disease due to main carinal involvement have been treated with carinal resection with or without pulmonary resection. Carinal resection carries an operative mortality of 10–15% and 5-year survival of approximately 20% in carefully selected series. Patients who are T4N0 solely due to ipsilateral tumor nodules in a separate lobe (eFig. 77.5) have a 5-year survival of around 20% with surgery alone.[53]

There is no debate that a medically operable patient with T3N1, stage IIIA disease is best treated with surgical resection followed by adjuvant chemotherapy. Occasionally, after complete resection of the lymph nodes and the primary tumor, some patients are incidentally found to have occult N2 metastasis. These patients are best served by a resection of all known disease and consideration for adjuvant chemotherapy.[54] In patients with stage II or IIIA NSCLC who undergo complete resection, adjuvant chemotherapy is recommended with four cycles of a cisplatin-based *doublet* chemotherapy in which cisplatin is given along with a second agent.[32,33] The Lung Adjuvant Cisplatin Evaluation meta-analysis evaluated all stages of totally resected disease and observed a 5.4% overall 5-year survival benefit with adjuvant chemotherapy. The benefit was the greatest for patients with stage II and III disease and those with better PS.[32] The role of postoperative radiation therapy for patients with completely resected stage IIIA (N2) remains controversial; however, because local recurrence rates are very high, some nonrandomized trials suggest possible overall survival benefit from postoperative radiation therapy in patients with N2 disease.[55,56] In a trial, which randomized patients with completely resected stage IB–IIIA to adjuvant chemotherapy or observation, adjuvant radiotherapy was given at the discretion of the treating physicians.[57] In a subset analysis, receipt of adjuvant radiotherapy was associated with worsened OS in patients with N1 disease who received chemotherapy, but was associated with improved OS in patients with N2 involvement regardless of receipt of chemotherapy. A randomized phase III adjuvant radiotherapy trial is underway to evaluate postoperative radiation therapy in these patients.

It is less certain how best to treat patients when N2 (single or multiple station) metastases are documented before thoracotomy. This is a subset of patients who probably benefit the most when the treatment plan is discussed by a multidisciplinary team. Either definitive chemoradiotherapy or neoadjuvant chemotherapy followed by surgery is recommended over either surgery or radiation alone. These recommendations were largely influenced by the two cooperative group trials that evaluated the role of surgery in patients with N2 disease.[58,59] The European trial randomized patients with histologically proven N2 disease to radiotherapy or surgery after neoadjuvant chemotherapy with three cycles of a cisplatin doublet chemotherapy.[59] The MST was 16 months in the surgery arm and 17 months in the radiotherapy arm.[60] The 5-year survival in both arms was 16% and 14%, respectively, and was not significantly different. The North American trial also required pathologic proof of N2 disease and randomized patients to completion radiotherapy (to a cumulative dose of 60 Gy) or surgery

(either lobectomy or pneumonectomy with mediastinal nodal dissection/sampling) after neoadjuvant chemoradiotherapy of two cycles of etoposide plus cisplatin with concurrent thoracic radiotherapy of 45 Gy in 25 fractions over 5 weeks.[58] The MST was 24 and 22 months in the surgery and radiotherapy arms, respectively, with 5-year survivals of 27% and 20%, that were not statistically different. However, the PFS favored the surgery arm. A subset analysis showed that those requiring only a lobectomy (in contrast to a pneumonectomy) after neoadjuvant chemotherapy did better than a matched group receiving only chemoradiotherapy.[58] This was an unplanned subset analysis that weakens the strength of this analysis, though the findings mirror observations in practice that increasingly morbid surgical resection (pneumonectomy) may be poorly tolerated after neoadjuvant chemotherapy. Accordingly, the role of surgery for stage III with discrete N2 disease has not been definitively answered. For patients with stage IIIA disease who are deemed not to be candidates for surgery, the recommended treatment is concurrent chemoradiotherapy followed by consolidation therapy with the PD-L1 inhibitor durvalumab in those who have no evidence of disease progression after definitive treatment. This approach will be discussed in more detail in the next section.

Stage IIIB and Stage IIIC

Stage IIIB is also a heterogeneous group and includes T4N2M0 and T1a–c, T2a–bN3M0 patients. Stage IIIC (new in the eighth edition of TNM staging) includes patients with T3–4N3 disease.[24] The American College of Chest Physicians guidelines used the groupings of *infiltrative stage III* (N2/N3) tumors and stage III with discrete N2 involvement. In infiltrative stage III with N2/N3 involvement, the mediastinal nodes can no longer be clearly distinguished and measured (eFig. 77.6). These patients have extensive tumor infiltration in the mediastinum, which partially surrounds the major structures. In patients with unresectable stage IIIA and infiltrative stage III (N2/N3), good performance score, and minimal weight loss (≤10%), the recommended treatment with curative intent is concurrent chemoradiotherapy.[24,54]

Two multicenter trials concluded that concurrent chemoradiotherapy is superior to sequential therapy (chemotherapy followed by thoracic radiotherapy) in patients with unresectable stage IIIA, IIIB, and IIIC NSCLC.[60,61] Concurrent therapy, however, is associated with a higher rate of severe esophagitis than is sequential therapy. The recommended chemotherapy is a platinum-based regimen that includes etoposide, paclitaxel, or pemetrexed.[58,62] Three cooperative group trials of definitive chemoradiotherapy for unresectable stage III had an MST of 19 to 22 months with 2-year survivals of 40–45%.[58,62,63] Because randomized trials of chemoradiotherapy included both stage IIIA and IIIB disease participants and used the seventh edition of the TNM staging system, it is not possible to separate out the survival of stage IIIB or current IIIC patients specifically.[62,63] In an effort to improve OS in this population, a phase III trial randomized patients with unresectable stage III NSCLC to standard of care chemoradiotherapy (60 Gy in 2 Gy per fraction) versus dose-escalated chemoradiotherapy (74 Gy in 2 Gy per fraction).[64] Surprisingly, the dose-escalated group had worse survival (20 months vs. 29 months MST) than the control arm. Hypotheses for the inferiority of the high-dose arm include increased cardiac dose or worse local failure rates due to tighter treatment margins. There are no phase III randomized trials to date that demonstrate that neoadjuvant chemoradiotherapy followed by surgery for stage IIIB or IIIC disease results in prolonged survival compared with chemoradiotherapy alone.[54]

Unfortunately, most patients with Stage III NSCLC have disease progression after concurrent chemoradiotherapy, with approximately 15–30% of patients remaining alive at 5 years, which corresponds to an MST of no more than 28 months.[65] Although several studies have evaluated the role of adjuvant chemotherapy following concurrent chemoradiotherapy in stage III NSCLC, results are poor with MST ranging from 18 to 23 months.[66–68] More recently, incorporating consolidation therapy with immunotherapy in the treatment paradigm of stage III NSCLC has provided significant promise in survival improvement. Durvalumab is a selective, high-affinity, human IgG1 monoclonal antibody that blocks PD-L1 binding to PD-1 and CD80, thereby allowing T cells to recognize and kill tumor cells.[69,70] It is reported that chemoradiotherapy may up-regulate PD-L1 expression in tumor cells[71,72] and, as such, PD-L1 blockade may result in long-term immune response after chemoradiotherapy. The PACIFIC trial compared durvalumab (anti-PD-L1) to placebo in patients with stage III NSCLC without disease progression after treatment with definitive concurrent chemoradiotherapy.[73] Durvalumab resulted in significantly prolonged PFS compared to placebo, 16.8 months versus 5.6 months, with an HR for disease progression or death of 0.52. Subsequent OS analysis revealed durvalumab significantly improved OS at 24 months as compared with placebo, 66.3% versus 55.6%.[74] On the basis of these positive results, durvalumab is approved for consolidation therapy in unresectable stage III NSCLC patients without disease progression after concurrent chemoradiotherapy.

Occasionally, patients with stage III NSCLC may not qualify for definitive concurrent chemoradiotherapy. These patients can be treated with sequential chemotherapy and radiotherapy with consideration for consolidation immunotherapy. A recent study of patients with locally advanced (stage III disease, who were not candidates for surgery or chemoradiation) or advanced (stage IV) NSCLC (negative *EGFR* and *ALK*, and PD-L1 expression ≥1%) randomized to initial therapy with pembrolizumab versus platinum-based chemotherapy showed pembrolizumab resulted in better median OS, 16.7 versus 12.1 months (HR, 0.81).[75] Although the number of patients with locally advanced disease was small (n=160), subgroup analyses showed a trend toward benefit in these patients[75] and, as a result, pembrolizumab monotherapy was approved in April 2019 for patients with untreated stage III NSCLC who are not candidates for surgery or chemoradiation.

STAGE IV NON–SMALL CELL LUNG CANCER

Stage IV, metastatic or advanced NSCLC, is generally considered treatable but not curable. Approximately 57% of patients with NSCLC are diagnosed with metastatic disease for which the 5-year survival is only 4%.[4] The goal of therapy is to try to control the disease and palliate symptoms.

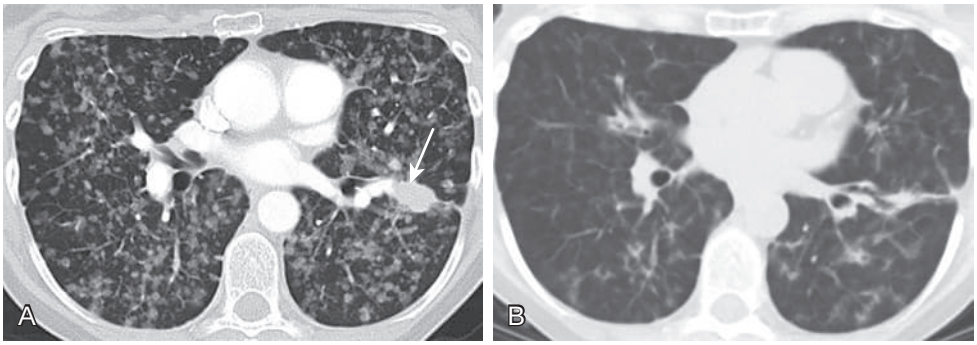

Figure 77.2 Adenocarcinoma of the lung with *ALK* translocation in a nonsmoking woman treated with alectinib. (A) Axial chest computed tomography (CT) displayed in lung windows shows a left lower lobe nodule consistent with adenocarcinoma (*arrow*) with widespread pulmonary metastases. (B) Axial CT following approximately 4.5 months alectinib therapy shows marked reduction in both the primary tumor and metastatic disease.

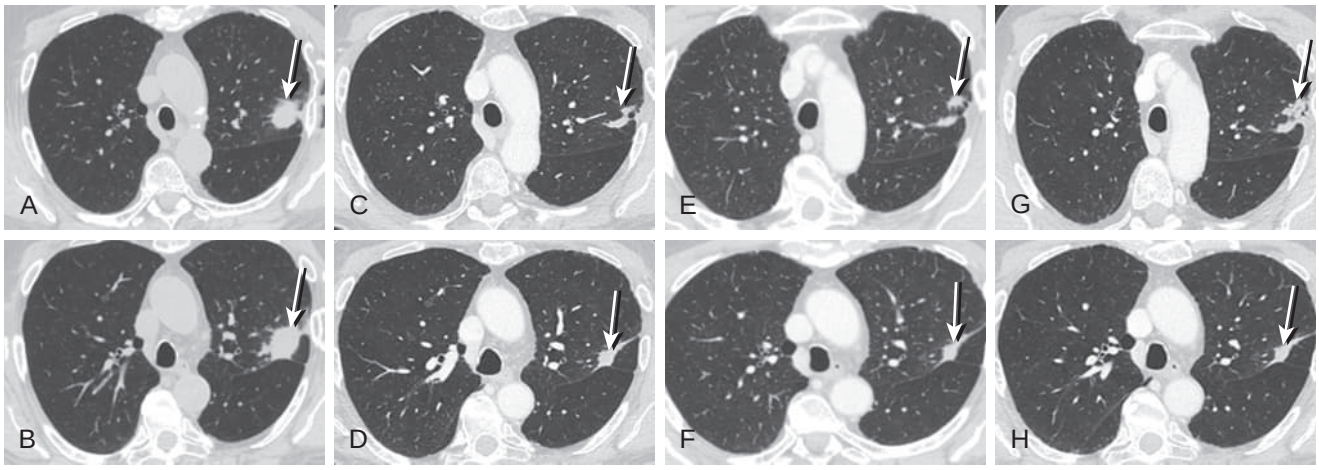

Figure 77.3 *EGFR*-mutated advanced adenocarcinoma of the lung treated with tyrosine kinase inhibitor with development of resistance. (A–B) Axial unenhanced chest computed tomography (CT) at presentation shows a poorly defined subpleural left upper lobe nodule *(arrows),* biopsy-proven to represent adenocarcinoma with *EGFR* mutation with exon 18 and 19 deletions. The lung cancer was stage IV and thus eligible for first-line targeted therapy. (C–D) Axial enhanced chest CT 8 months following presentation and just over 5 months following initiation of afatinib therapy shows reduction in size of the lesion *(arrows),* now with a more scarlike morphology, consistent with a positive response to therapy. (E–F) Axial enhanced chest CT 9 months after initiation of afatinib therapy shows that the main portion of the lesion (*arrow*, F), is similar to the first posttreatment CT (D), but nodularity is increasing along the cranial aspect of the lesion (*arrow*, *E*). (G–H) Axial enhanced chest CT 13 months following afatinib therapy was initiated shows continued growth in the nodularity along the cranial aspect of the lesion (*arrow*, G), while the main portion of the lesion remains stable (*arrow*, H). The patient had developed brain metastases at the time of this scan. (Courtesy Michael B. Gotway, MD.)

First-line treatment options for patients with advanced NSCLC now include chemotherapy, targeted therapy, and immunotherapy. Surgery and radiation can be used in selected cases to palliate symptoms. All patients should be offered access to palliative care services at the time of diagnosis.[76]

Identification of genetic alterations in oncogenes and tumor suppressor genes critical to tumor growth has led to the development of targeted therapies against these actionable mutations[77] and subsequent improvement in patient outcomes (Figs. 77.2 and 77.3). A recent study showed a 5-year survival rate among patients with *EGFR*-mutant metastatic lung adenocarcinoma treated with the TKIs erlotinib or gefitinib to be 14.6%.[78] (This 5-year survival rate can be compared to a 4% 5-year survival before the TKIs.[4]) The Lung Cancer Mutation Consortium demonstrated the potential for multiplex next-generation genomic sequencing in patients with advanced NSCLC and reported a driver mutation was detected in about 64% of genotyped cases.[79] The driver mutations identified include *KRAS* (25%), activating *EGFR* (15%), *ALK*-fusion (8%), *ROS-1* (2%), *BRAF* (2%), *HER2* (2%), *PIK3CA* (1%), and *MET* amplification (1%).[79]

Clinical practice guidelines promote the incorporation of biomarker testing in the diagnostic evaluation of lung cancer,[36,80] and recommend testing for *EGFR* mutations and *ALK* and *ROS1* in metastatic adenocarcinoma, large cell carcinoma, and NSCLC not otherwise specified (NSCLC where the pathologist cannot differentiate between squamous cell or adenocarcinoma). In addition, testing for *EGFR* and *ALK* should be considered in patients with metastatic squamous cell carcinoma or small cell cancer in patients with certain clinical criteria (young age, lack of smoking history) who are never-smokers.[36] The inclusion of additional genes (*HER2*, *MET*, *BRAF*, *KRAS*, and *RET*) is recommended for laboratories that perform next-generation genomic sequencing panels.[80] (See also Chapter 73.)

More recently, harnessing the power of the immune system via inhibition of immune checkpoints has shown significantly improved results and immunotherapy is now integrated into the clinical management of metastatic NSCLC.[81] Improved OS with immunotherapy using the immune checkpoint inhibitor nivolumab in the second-line setting in advanced NSCLCs has been reported, with an estimated 5-year OS rate of 15.6%.[82] Recently, exciting results of improved 5-year OS in a small number of patients with NSCLC treated with first-line pembrolizumab were reported: 15.7% in those with lower PD-L1 staining (TPS of 1–49%) and 29.6% in those

with higher staining (TPS of ≥50%).[83] PD-L1 testing is recommended in all patients with metastatic NSCLC.[36]

The key to realizing the benefits in survival outcomes in advanced NSCLC with precision oncologic therapy is critically dependent on performing genomic profiling and biomarker testing and using the results to guide initial treatment decisions in advanced NSCLC.

First-Line Chemotherapy

In 1995, a landmark meta-analysis evaluated nine randomized trials comparing platinum-based chemotherapy and best supportive care in advanced NSCLC.[84] With best supportive care, the MST was 4 months and the 1-year survival was 15%; with chemotherapy, there was an increase in the MST of 1.5 months and an increase in 1-year survival of 10%.[84] Subsequently, several randomized trials using platinum-based combination regimens demonstrated similar results and, although the survival advantage is modest, it is both clinically and statistically significant.[85] In the 1990s, a number of new chemotherapy agents were introduced, including paclitaxel, docetaxel, irinotecan, vinorelbine, and gemcitabine. Phase III trials incorporating these newer agents in combination with cisplatin have shown an MST of 7.9 months, and 1-year and 2-year survival rates of 33% and 11%, respectively, although no one combination is superior when using survival as the primary measure of outcome.[86] In addition, improved quality of life has been reported for those patients receiving chemotherapy versus best supportive care.[87]

Histology influences response to certain chemotherapeutic agents. A large phase III trial randomized patients to cisplatin plus pemetrexed or cisplatin plus gemcitabine. For the patients with adenocarcinoma, the survival was significantly better with the pemetrexed regimen (MST 12.6 months vs. 10.9 months). Conversely, squamous cell cancers had superior survival with the gemcitabine regimen (MST 10.8 months vs. 9.4 months).[88] Chemotherapy for stage IV NSCLC should be guided by histology and pemetrexed should be limited to patients with nonsquamous NSCLC.[36]

Bevacizumab, a monoclonal antibody that inhibits vascular endothelial growth factor, improves survival when added to platinum-based chemotherapy in some patients. In the ECOG Trial, 4599 patients with nonsquamous histology (bevacizumab is not recommended in squamous cell cancer due to risk of serious, potentially fatal hemorrhage) were randomized to treatment with carboplatin plus paclitaxel with or without bevacizumab. Bevacizumab was continued as maintenance therapy after six cycles of therapy in those responding to treatment or with stable disease.[89] Patients in the bevacizumab arm had a higher response rate (35% vs. 15%) and better survival (MST 12.3 months vs. 10.3 months; 2-year survival 44% vs. 15%). A meta-analysis of four randomized trials of NSCLC patients showed treatment with combination chemotherapy plus bevacizumab demonstrated increased PFS and OS compared with chemotherapy alone.[90]

In brief, treatment of stage IV NSCLC should be guided by histology, molecular pathology, age, comorbidities, PS, and of course, patient preferences. All patients with stage IV NSCLC with a good PS (ECOG 0–2) should be referred to a medical oncologist to discuss systemic therapy. In patients without an actionable mutation (*EGFR*, *ALK*, etc.) and with low PD-L1 expression, platinum-based doublet chemotherapy may be used as first-line therapy. Combination therapy with platinum-based chemotherapy and immunotherapy is emerging as a preferred strategy due to superior results over chemotherapy alone in patients with lower PD-L1 staining (PD-L1 < 50%) and PS 0-1. For PD-L1 staining greater than 50%, immunotherapy alone is the standard of care. This approach will be further discussed in the immunotherapy section.

Maintenance Chemotherapy

In patients with good PS (ECOG 0–2) and with stable or responding nonsquamous NSCLC, maintenance treatment with pemetrexed and/or bevacizumab has been shown to improve PFS and OS. Pemetrexed compared to placebo resulted in significantly improved OS with 22% reduction in the risk of death compared with the placebo group.[91,92] Maintenance therapy with bevacizumab is associated with improved PFS (4.4 vs. 2.8 months) and improved median OS (12.8 vs. 11.4 months) in comparison with placebo.[93] Routine maintenance chemotherapy for advanced squamous cell NSCLC has not been well established, although longer PFS has been reported with immediate versus delayed docetaxel (5.7 vs. 2.7 months) after first-line therapy.[94]

Second-Line Chemotherapy

Eventually, patients with metastatic NSCLC will progress after receiving first-line therapy, with or without maintenance therapy. For those patients who have a good PS (0–2), approved second-line chemotherapy options include docetaxel with or without ramucirumab (monoclonal antibody against vascular endothelial growth factor receptor 2) for all histologies, with pemetrexed for nonsquamous histology and the TKI afatinib for squamous histology.[95–97] Erlotinib represents a potential second- and third-line treatment option, especially in patients not suitable for immunotherapy or second-line chemotherapy, and has been shown in a phase III trial to result in superior survival versus placebo (6.7 vs. 4.7 months).[98] More recently, second-line immunotherapy has been approved for the treatment of metastatic NSCLC after progression on first-line therapy and will be discussed in more detail in the section on immunotherapy.

Targeted Therapy

Driver mutations result in downstream signaling that drives and sustains a tumor and, as opposed to the much more common *passenger* mutations, they render a tumor vulnerable to blockade of that single pathway (see Chapter 73). Driver mutations are detected in about 64% of genotyped NSCLCs,[4] are mutually exclusive of each other, and are more commonly found in adenocarcinoma, and in never-smokers or light smokers (<15 pack-years) but can also be found in smokers.[79,80] Development of drugs directly targeting a driver mutation (Table 77.2) led to the realization of personalized therapy in NSCLC and has resulted in improved PFS and OS in the subset of patients whose tumors harbor a driver mutation.

***EGFR* Mutations.** Activating mutations in the tyrosine kinase domain of EGFR include exon 19 deletions and exon 21 (L858R) substitutions and were the first to be described and to predict response to novel TKIs. Multiple

Table 77.2 Targeted Therapy for Metastatic NSCLC With Molecular Target

Biomarker	First-Line Therapy	Second-Line Therapy	Promising Therapies
EGFR mutations	Erlotinib Gefitinib Afatinib Osimertinib	Osimertinib (after first- or second-generation TKI if T790M)	
ALK-fusion	Crizotinib Alectinib Ceritinib	Lorlatinib Brigatinib	
ROS1	Crizotinib Entrectanib		Repotrectinib
BRAF		Dabrafenib/trametinib	
RET-fusions			LOXO-292 BLU-667
MET exon 14 mutation		Crizotinib	Capmatinib Savolitinib Tepotinib
HER2 dysregulation			Trastuzumab* Ado-trastuzumab*
$KRAS^{G12C}$ mutation			AMG510 MRTX849

*Off-label use.

studies have demonstrated that the phenotype most associated with response to the EGFR-TKIs gefitinib and erlotinib includes adenocarcinoma, never-smoker, female sex, and East Asian descent. Subsequent reports showed that these are the groups most likely to harbor the activating *EGFR* mutations.[99] In a landmark phase III trial in East Asia, patients with untreated stage IV NSCLC were randomized to gefitinib or platinum-based chemotherapy. Of the 437 patient samples tested, 60% were positive for an *EGFR* activating mutation. This subgroup had a significantly better response and PFS after gefitinib than after chemotherapy, and benefit was consistent across all age groups, genders, smoking status, and PS. The subgroup negative for mutations had improved response rates and PFS after chemotherapy.[100]

Multiple phase III trials comparing EGFR-TKIs to chemotherapy in patients with *EGFR*-activating mutations have been conducted. In general the response rate to an EGFR-TKI is 60–80%, the median PFS is 9 to 12 months, and the OS is approximately 2 years.[101] A meta-analysis including 13 studies observed a PFS advantage (HR, 0.43) in patients treated with an EGFR-TKI in the first-line setting.[102] Results were similar when the EGFR-TKI was used in the second-line setting in those with an activating *EGFR* mutation (HR, 0.34 for PFS). As a result of these and other studies, EGFR-TKIs (erlotinib, gefitinib, and afatinib) represent the standard of care in first-line treatment of patients with *EGFR*-mutated advanced NSCLC.

Although the majority of patients with *EGFR*-mutant NSCLC respond to TKIs, resistance will develop in most patients within 9 to 14 months of treatment (see Fig. 77.3).[103] Several mechanisms of resistance have been reported, including *HER2* amplification, *MET* amplification, small cell transformation and, most commonly (seen in more than 50% of patients), a secondary *EGFR* kinase domain mutation in exon 20, the T790M substitution.[104-106] Osimertinib, a third-generation EGFR-TKI, was developed to block *EGFR*-mutant receptors, including the T790M form, whether it arose de novo or as a resistance to prior TKI therapy. Osimertinib has significantly greater efficacy over platinum-based chemotherapy in patients with T790M mutations who progress during first-line treatment with an EGFR-TKI (including those with CNS metastases); with osimertinib, patients realized a median duration of PFS of 10.1 months versus 4.4 months with chemotherapy.[107] As a result of these promising findings, testing for T790M mutations is recommended in patients with *EGFR*-mutant adenocarcinoma who progress after first-line therapy, so they can be considered for osimertinib therapy.[36]

Osimertinib given as first-line therapy has been shown to improve PFS outcomes when compared with gefitinib or erlotinib. In a phase III trial of patients with treatment-naïve, *EGFR*-mutated advanced NSCLC randomized to osimertinib versus gefitinib or erlotinib, osimertinib demonstrated improvement in PFS (18.9 vs. 10.2 months) and duration of response (17.2 vs. 8.5 months).[108] First-line osimertinib is now considered one of the options for patients with metastatic *EGFR*-mutant NSCLC.

***ALK* Translocations.** The *ALK*-fusion gene is found in about 8% of NSCLC[79] and is the second most common driver mutation for which there is an effective TKI. In this mutation, fusion leads to abnormal *ALK* signaling and is opposed by TKIs that target the *ALK* tyrosine kinase. The efficacy of the first-generation ALK-TKI, crizotinib, was demonstrated in a phase I study of 143 patients with advanced-stage IV NSCLC with an *ALK*-fusion that showed an objective response rate of 61%, a median PFS of 9.7 months, and an estimated 12-month survival rate of 75%.[109] Subsequent randomized phase III trials comparing crizotinib to platinum-based chemotherapy as first-line treatment in advanced-stage NSCLC patients with an *ALK*-fusion demonstrated significantly longer PFS (ranging

from 7.7 to 10.9 vs. 3 to 7 months respectively).[22,110] While first-line treatment with crizotinib had been the standard of care for patients with *ALK*-fusion advanced stage NSCLC, the majority of patients eventually progress due to acquired resistance. In addition, crizotinib has negligible CNS penetration, which is unfortunate because *ALK*-fusion NSCLC commonly metastasizes to the brain.[111] The second-generation ALK inhibitors, ceritinib and alectinib, have excellent antitumor activity (see Fig. 77.2). A phase III trial comparing ceritinib to platinum-based chemotherapy in untreated *ALK*-fusion NSCLC resulted in a significant improvement in overall PFS (16.6 months vs. 8.1 months).[112] Furthermore, in patients with CNS metastases, the CNS response rate was superior with ceritinib (72.7%. vs. 27.3%).[112] Two randomized trials comparing first-line alectinib with crizotinib have demonstrated the superior efficacy of alectinib in *ALK*-fusion NSCLC.[113,114] The PFS in the alectinib group was 68.7% compared with 48.7% in the crizotinib group and the HR for disease progression or death was 0.47.[114] Only 12% of patients on alectinib progressed with CNS disease compared with 45% in the crizotinib group. Alectinib is currently the first-line TKI for *ALK*-fusion NSCLC patients.

ROS1. *ROS1* gene rearrangements are observed in approximately 2% of patients with adenocarcinoma of the lung.[4] Many TKIs approved for *ALK*-fusion NSCLC have shown activity in *ROS1*-positive tumors. Crizotinib is currently the standard of care for the treatment of *ROS1*-positive NSCLC.[115]

BRAF. The most common mutation in v-raf murine sarcoma viral oncogene homolog B1 (*BRAF*) is the V600E mutation, which is observed in about 2% of adenocarcinomas and is more common in smokers.[116] Although NSCLC patients with *BRAF*-V600E mutation respond to single-agent BRAF-TKIs, combining dabrafenib (a BRAF inhibitor) and trametinib (a MEK inhibitor) is recommended due to the enhanced efficacy.[117]

Other Targets. Additional mutations include *RET* fusions (2% of NSCLC),[118] *MET* exon 14 skipping mutation (3–4%), *HER2* dysregulation (2%),[4] and *KRAS*, which is the most common mutation, observed in approximately 32% of patients with adenocarcinoma.[4] Several ongoing clinical trials are evaluating the efficacy of TKI inhibitors in patients with *RET* fusions, *MET* mutations, and *HER2* dysregulation with promising results (see Table 77.2). Development of effective targeted therapy against *KRAS* has been disappointing until recently. Results from an ongoing phase I clinical trial with an inhibitor targeted at $KRAS^{G12C}$-mutated NSCLC are promising.[119]

Immunotherapy

Central and peripheral negative regulatory pathways known as immune checkpoints play a crucial role in down-regulating the immune system and protecting against excessive inflammatory responses and autoimmunity. These checkpoints are also used by cancer cells to suppress immune surveillance.[120,121] Immunotherapy targeting those checkpoints has dramatically changed the treatment paradigm in locally advanced and advanced NSCLC and shows promise in early-stage NSCLC and SCLC with extensive disease. Four ICIs have FDA approval in lung cancer: nivolumab and pembrolizumab, targeting the PD-1 receptor and atezolizumab and durvalumab, targeting the ligand PD-L1.[122] An immunohistochemistry-based test to determine PD-L1 expression is needed to guide decisions regarding first-line therapy with immunotherapy and should be routine for all patients with newly diagnosed NSCLC.[80] In addition, patient selection includes assessment of PS and importantly, evaluation for underlying comorbidities such as severe autoimmune disease, solid organ transplant, and interstitial lung disease, which can be associated with increased immune-related adverse events.[123,124]

Pembrolizumab has been established as first-line therapy in untreated patients with advanced NSCLC and PD-L1 expression of 50% or greater. A randomized study of patients with advanced NSCLC and PD-L1 50% or more without *EGFR* mutation or *ALK*-fusion comparing first-line pembrolizumab to platinum-based chemotherapy demonstrated pembrolizumab was associated with higher response rates (44.8% vs. 27.8%), PFS (10.3 vs. 6.7 months), and OS compared to platinum-based chemotherapy. As a result, pembrolizumab was approved as first-line therapy in squamous and nonsquamous advanced NSCLC.[125] An updated analysis revealed the median OS for pembrolizumab was 30 months compared to 14.2 months for chemotherapy (HR, 0.63).[126]

Several trials have evaluated the use of a combination of ICIs with platinum chemotherapy as a first-line regimen in NSCLC irrespective of PD-L1 expression. First-line pembrolizumab plus platinum-pemetrexed in patients with nonsquamous metastatic NSCLC demonstrated significant improvement in 12 months OS (69.2% vs. 49.4%) with similar toxicity profile, compared to chemotherapy plus placebo, irrespective of PD-L1 tumor expression.[127] Similarly, first-line pembrolizumab in combination with carboplatin-taxane in patients with metastatic squamous NSCLC improved survival compared with chemotherapy plus placebo (median OS of 15.9 months vs. 11.3 months).[128] Pembrolizumab in combination with platinum chemotherapy is now approved for first-line treatment in all patients with advanced NSCLC without *EGFR*/*ALK* alterations with PD-L1 tumor expression less than 50%.

Triple therapy with atezolizumab, bevacizumab, and platinum-based chemotherapy in patients with metastatic nonsquamous NSCLC without *EGFR*/*ALK* alterations improved median OS (19.2 vs. 14.7 months) compared with bevacizumab and platinum-based chemotherapy regardless of PD-L1 expression.[129] This triple combination is now approved as another option for first-line treatment for this patient population.

Second-Line Immunotherapy. Second-line therapy is given when first-line therapy either fails or stops working. In two large phase III trials of patients with advanced squamous or nonsquamous NSCLC whose disease had progressed on platinum-based chemotherapy, nivolumab (anti-PD-1), demonstrated improved survival over docetaxel.[130,131] In the trials of squamous cell NSCLC, nivolumab improved outcome in patients with previously treated, advanced squamous cell NSCLC (OS: 9.2 vs. 6.0 months; HR, 0.59).[130] In nonsquamous NSCLC, nivolumab improved outcome when compared to docetaxel (OS: 12.2 months vs. 9.4 months; HR 0.73).[131] As a result, nivolumab is approved

for second-line treatment of patients with advanced NSCLC who progress after first-line therapy.

The use of ICIs in the neoadjuvant setting in early-stage (stage I–IIIA) NSCLC holds promise. Even after curative intent surgical resection and adjuvant chemotherapy, relapse rates are high.[132] In a pilot study of patients with early-stage NSCLC, neoadjuvant nivolumab resulted in a major pathologic response in 45% of resected tumors and did not delay definitive surgery.[133] This approach is further being investigated in ongoing trials.

Adverse Effects. Immune-related adverse events may develop anywhere throughout the body (colitis, thyroiditis, diabetes, neuropathy, myositis, among others) but, in patients with lung cancer, immune-mediated pneumonitis, which may be life-threatening, is a particularly concerning complication. The reported incidence is about 19%.[134] Symptoms are nonspecific and include cough, dyspnea, wheezing, chest pain, and fever, with a range of imaging and pathologic correlates described.[14] Potential risk factors include tumor histology (e.g., risk may be higher with adenocarcinoma), combination therapy with ICIs, COPD, pulmonary fibrosis, autoimmune disease, and previous thoracic radiation.[123,124,134,135] Prompt recognition, withholding immunotherapy, and starting steroid therapy when indicated is essential.

OLIGOMETASTATIC DISEASE

Although metastatic NSCLC is a treatable disease, it has long been considered incurable. A subset of patients with metastatic NSCLC, however, has limited metastases and likely represents a distinct clinical group. This group of patients may possess a more indolent biology and may benefit from prolonged survival after definitive local treatment to all sites of active disease. In 1995, Hellman and Weichselbaum described the biologic spectrum of cancer extending from disease that remains localized, to disease that passes through many intermediate states before becoming systemic. Thus the number of metastatic lesions and sites of metastases may reflect the state of tumor development.[136] They defined oligometastases as "metastases limited to a single or a limited number of organs."[136] The authors subsequently proposed that the oligometastatic state is a distinct clinical entity of intermediate stages of limited metastatic capacity. The oligometastatic state may be more common than previously noted due to more sensitive detection with tools such as positron emission tomography and *magnetic resonance imaging* (MRI) and biomarkers such as circulating tumor DNA.[137]

While the eighth edition of the TNM staging system used M1b disease to identify this important group of patients,[138] the challenge remains that patients with oligometastatic disease represent a heterogenous group because there is currently no consensus on the appropriate cutoff to define the oligometastatic state. The number of metastatic lesions and organs involved in oligometastatic disease is likely cancer dependent and biologically determined.[139] Furthermore, the oligometastatic state can be further defined by number of metastases, organs involved, and rate of progression[140] (Table 77.3).

Table 77.3 Defining Oligometastic Disease

Terms	Definition
Oligometastases	Metastases limited to a single organ or a limited number of organs[176]
Oligometastatic disease	Solitary or few in number (1–5) usually confined to a single organ, more indolent biology and progression at existing sites without widespread metastases[177]
Synchronous	Detected at time of diagnosis of the primary tumor
Metachronous	Developed after treatment of the primary tumor (oligo-recurrent disease) Better prognosis
Oligoprogression	Progression of one or a limited number of metastases (generally five or fewer) while systemic therapy continues to control the primary site and most areas of metastatic disease (seen with acquired mutations to targeted therapy)[178]

Data supporting a curative-intent strategy in oligometastatic NSCLC have been limited to small retrospective studies including patients with 1 to 5 distinct metastases and showing that prognosis is more favorable when patients are treated aggressively with *local ablative therapies* (LAT) compared with palliative intent.[141] When the number of metastases is limited, it is theoretically possible to treat all detectable lesions with curative intent using LAT.[138] It is important to consider that a variety of therapeutic modalities can be explored for LAT, including surgery, SBRT, conventional/moderately hypofractionated radiotherapy, and radiofrequency ablative therapy (see Chapters 21 and 28).

A meta-analysis of 2176 patients with NSCLC and fewer than five metastatic lesions (60% had only metastatic brain lesions) showed that aggressive LAT of all sites of metastatic disease provides improved outcomes with median survival of 19 months and 5-year OS of 23.3%, although survival outcomes were highly variable.[142] In a subsequent meta-analysis of 757 NSCLC patients treated worldwide who had controlled disease at the primary site after definitive treatment and with five or fewer metastatic lesions treated with LAT to all sites of metastatic disease, survival and prognostic factors were evaluated and risk groups were defined by recursive partitioning analysis.[143] The median age was 61, majority had a good PS, 88% had no nodal disease, and the majority had a single brain or lung metastatic lesion (only 3% had multiorgan disease). Median OS was 26 months and 5- and 8-year OS was 29.4% and 23.4%, respectively.[143] Three risk groups were identified: (1) low risk, patients with metachronous disease with 5-year OS of 50%: (2) intermediate risk, patients with synchronous metastasis and no nodal disease with 5-year OS of 36%; and (3) high risk, patients with synchronous metastases and greater than N1 nodal disease with 5-year OS of 14%.[143]

In a recent phase II study patients with stage IV NSCLC with 1 to 3 metastatic lesions and no progression 3 months after first-line treatment were randomized to maintenance therapy or observation versus LAT to all sites of metastasis.[144] The trial was closed after 49 patients were randomized because of a significant benefit with LAT. Compared with maintenance therapy or observation, LAT resulted in a PFS of 14 months versus 4.6 months and an OS of 41.2 months versus 17 months and no increase in grade 3 or higher toxicity.[144] While results of this study are promising,

because of the limited prospective data available in this group of patients, more studies are needed and enrolling patients in clinical trials is recommended.

TREATMENT OF SMALL CELL LUNG CANCER

SCLC accounts for approximately 15% of all lung cancers; it has the strongest association with cigarette smoking and is rarely observed in never-smokers. It is the cell type most commonly associated with paraneoplastic syndromes such as the syndrome of inappropriate (excessive) antidiuretic hormone secretion, ectopic corticotropin secretion, Lambert-Eaton myasthenic syndrome, and sensory neuropathy.

SCLC usually presents as a centrally located mass in the hilum on chest radiograph (eFig. 77.7) and may be associated with obstructive pneumonia. In 5% or fewer cases, SCLC may present as a solitary pulmonary nodule/mass (eFig. 77.8). SCLC is generally staged according to the Veterans Administration Staging System and classified as *limited disease* (LD) or *extensive disease* (ED). LD is confined to one hemithorax, the mediastinum, and the ipsilateral supraclavicular lymph nodes, and the disease can be encompassed adequately in a safe radiation portal.[145] ED is any disease spread beyond these limits. Malignant pleural effusion or disease extending to the contralateral supraclavicular or hilar lymph nodes is generally considered to be ED. It has been proposed that the TNM staging system should also be used for SCLC. When SCLC has been staged via the TNM system, the clinical stage groupings of I to IV have been predictive of OS, and the findings have been validated in a cohort from the Surveillance Epidemiology and End Results registry[146] and the California Cancer Registry.[147] The survival rate for patients with LD with pleural effusions was intermediate between those with ED and LD without pleural effusions. Use of the TNM staging is most helpful in potentially resectable patients with T1–2NO disease. Accordingly, it would be advisable to use the TNM staging system both for tumor registries and for clinical trials to define patients with minimal disease.

In the unusual case in which SCLC presents as a small (T1–2) solitary nodule amenable to sublobar or lobar resection, the treatment of choice is surgical resection followed by adjuvant chemotherapy and, if nodal disease is found incidentally, possibly sequential thoracic radiotherapy. Careful preoperative staging should be performed in these individuals to rule out metastatic disease. Preresection mediastinoscopy should also be performed in all these patients being considered for resection with curative intent. If there are mediastinal node metastases, then surgery should be abandoned, and the patient treated with concurrent chemoradiotherapy as outlined later. The 5-year survival for a small T1–2 solitary SCLC nodule treated with surgery and adjuvant therapy is approximately 40–50%.[147,148]

Approximately one-third of patients with SCLC have LD at diagnosis. LD-SCLC has a response rate of 70–80% with standard chemotherapy and thoracic radiotherapy (eFig. 77.9), and a complete clinical response of 50–60%. Chemotherapy usually consists of a platinum-based regimen. The two most commonly used regimens are etoposide plus cisplatin or etoposide plus carboplatin. Chemotherapy beyond four to six cycles has not been shown to prolong survival. The National Comprehensive Cancer Network and American College of Chest Physicians guidelines recommend treatment with four to six cycles of platinum-based chemotherapy with either cisplatin or carboplatin plus either etoposide or irinotecan.[36,145] Multiple trials have evaluated a number of targeted agents but, to date, none has shown improved outcomes when added to standard treatment of SCLC.[149]

In a meta-analysis of trials with chemotherapy alone versus combined chemotherapy and thoracic radiotherapy, survival was significantly better with combined modality therapy. As a result of the exquisite radiosensitivity of SCLC, it was postulated that fractionating radiotherapy in smaller doses delivered twice daily might be more effective, albeit with a risk of greater acute toxicity. In a phase III trial, patients with LD-SCLC were randomized to receive concurrent chemotherapy with cisplatin/etoposide and 45 Gy radiotherapy delivered daily or 30 fractions delivered twice daily.[150] Although there was more toxicity due to esophagitis, the OS was significantly improved with twice-daily fractionation (5-year OS 16% vs. 26%) and, as such, this twice-daily regimen became standard of care. A more recent trial randomized patients with LD-SCLC to concurrent cisplatin plus etoposide with either 45 Gy radiotherapy delivered twice daily or 66 Gy in daily fractions.[151] Although the study was designed and powered to demonstrate superiority of the once-daily arm, no difference was found in the 2-year OS between the two groups or in toxicity (grade 3 esophagitis was 19% in both groups).[151] As such, twice-daily radiotherapy continues to be the standard of care in LD-SCLC (though once-daily treatment can be considered in situations where the logistics preclude twice-daily radiation).

A meta-analysis evaluated the timing of thoracic radiotherapy.[152] Early thoracic radiotherapy (<9 weeks from the start of chemotherapy) resulted in a 5.2% increase in 2-year survival. The interval from start of treatment to the end of radiotherapy was also identified as an important predictor of outcome.[153] Accordingly, data suggest that thoracic radiotherapy should begin early and be completed quickly.[145]

Patients with LD-SCLC who achieve complete remission after chemoradiotherapy have a 50% chance of developing intracranial metastasis within the next 2 years. A meta-analysis of seven randomized trials of *prophylactic cranial irradiation* (PCI) versus no PCI for patients in complete remission reported a 5.4% increase in absolute survival (20.7% vs. 15.3%) with PCI at 3 years.[154] The major questions raised by the meta-analysis concern the optimal dose of PCI and the neuropsychological sequelae. PCI at 25 Gy in 10 fractions[155] is recommended in patients with LD-SCLC who achieve a complete remission with initial therapy and has also been shown to result in a survival advantage in patients with ED-SCLC who achieve a complete or partial response to initial therapy.[156] However, the true benefit in the setting of ED-SCLC is now in question, because a Japanese randomized study has demonstrated no benefit to PCI if a postchemotherapy brain MRI shows an absence of brain metastases and MRI surveillance is performed.[157]

When patients relapse after initial therapy, the MST is 3 to 4 months. There are no cures with second-line therapy. If a patient has been off treatment for 6 months or longer, then it is reasonable to use the same agents that he or she received initially. If initial therapy did not include a platinum agent, then second-line therapy should use

a platinum-containing doublet. Currently the only drug approved for second-line treatment of SCLC by the FDA is single-agent topotecan.[145,155] Other single agents such as oral etoposide, paclitaxel, docetaxel, irinotecan, gemcitabine, and amrubicin are active but are not yet approved by the FDA for second-line treatment of SCLC. Amrubicin is commercially available and approved for second-line treatment in Japan but is not available in the United States. No molecularly targeted therapy has been approved for SCLC in either the first-line or second-line setting.

The addition of immunotherapy to platinum-based chemotherapy in ED-SCLC holds promise. A phase III trial randomized 403 patients with ED-SCLC to receive carboplatin/etoposide plus the anti-PD-L1 atezolizumab or to receive placebo plus atezolizumab. There was improved median OS and PFS in the group treated with chemotherapy plus atezolizumab, without increased toxicity.[158] Additional studies are ongoing.

PALLIATIVE CARE

Although much of this chapter is devoted to efforts to cure lung cancer, most patients will eventually succumb to their disease. Incorporating palliative care for patients with advanced lung cancer has been shown to improve quality of life and symptom management, reduce use of aggressive medical treatments at the end of life, and increase survival.[76] Current guidelines recommend referral to multidisciplinary palliative care teams within 8 weeks of initial diagnosis of advanced cancer.[159] While pulmonologists are adept at providing supportive care in the intensive care unit, caring for the ambulatory dying patient with lung cancer requires special consideration. There is a vast literature on ambulatory pain management, the use of interventional pulmonary techniques such as tumor ablation and stent placement to relieve malignant airway obstruction, and the use of hospice to provide end-of-life care in the home setting. With the tools now available to physicians, patients need not suffer debilitating cough, nausea, dyspnea, or pain. Pulmonologists are encouraged to provide "aggressive palliation" to lung cancer patients with the same conviction that they provide treatments for critically ill patients in the intensive care unit.[160]

SPECIAL CONSIDERATIONS IN LUNG CANCER

SUPERIOR SULCUS TUMORS AND PANCOAST SYNDROME

Pancoast syndrome is a constellation of symptoms and signs that include shoulder and arm pain along the distribution of the eighth cranial nerve trunk and first and second thoracic nerve trunks, Horner syndrome, and weakness and atrophy of the hand.[161–163] The underlying cause is usually local extension of an apical lung tumor located in the superior pulmonary sulcus (Pancoast tumor). Pancoast syndrome is present in approximately one-third of patients with superior sulcus tumors. The most common cause of this symptom complex is NSCLC; however, SCLC and a number of other types of tumors and infections may rarely present in this manner.[161] The most common initial symptom is shoulder pain, which is produced by tumor involvement of the parietal pleura, brachial plexus, vertebral bodies; and first, second, and third ribs. The pain may radiate along the upper back or shoulder into the axilla and along the distribution of the ulnar nerve. Patients are commonly treated for arthritis or bursitis of the shoulder for months before the correct diagnosis is determined. Horner syndrome consists of ptosis, miosis, and anhidrosis and is caused by the invasion of the paravertebral sympathetic chain and the inferior cervical (stellate) ganglion.[161] The intrinsic muscles of the hands may become weak and atrophied as the tumor progresses. With further extension through the intervertebral foramina, spinal compression and paraplegia may develop.

The chest radiograph may show an apical tumor, although, in some cases, a tumor can be identified only on chest CT (see eFig. 77.4A). If the diagnosis is suspected but the chest radiograph is negative, then a chest CT scan should be obtained. CT also provides additional information about the extent of the tumor and is especially helpful in identifying other pulmonary nodules and mediastinal adenopathy. MRI of the chest is considered to be superior for evaluating patients with superior sulcus tumors because of better assessment of invasion through the pleura and subpleural fat, better evaluation of plexus involvement (see eFig. 77.4B–C), and better definition of subclavian vessel involvement.[164] MR angiography may give the best assessment of vascular invasion of the subclavian vessels. Flexible fiberoptic bronchoscopy may be the first diagnostic test for apical tumors and has a diagnostic yield of approximately 50%.[165] TTNA has a very high diagnostic yield (>90%) even if the bronchoscopy is nondiagnostic.[166] Superior sulcus tumors are usually staged as T3N0M0 (stage IIB) or higher depending on size of the tumor (T3 or T4) and extent of lymph node involvement. In a large series from MD Anderson, 25% of patients were stage IIB, 22% were IIIA, and 53% were stage IIIB (T4 or N3).[167] Some patients who were stage IV at diagnosis were excluded from that report. It is estimated that one-third to one-half of all superior sulcus tumors have identifiable distant metastasis at diagnosis. In addition to the stage of disease and PS, other important poor prognostic factors include weight loss and vertebral body or supraclavicular involvement. The presence of N1 or N2 nodal involvement and incomplete resections have a worse prognosis.[168,169] In patients treated for localized disease (stage IIB or IIIB), the brain is the most common site of relapse.[169]

In the past, the most common treatment for localized superior sulcus tumors due to NSCLC was preoperative radiotherapy of 30 to 50 Gy followed by resection. This resulted in a 5-year survival of 25–35%. The current standard of practice is to perform neoadjuvant chemoradiotherapy followed by resection. This is based on results of the North America Intergroup Trial in which patients with a negative mediastinoscopy were treated with two cycles of etoposide plus cisplatin chemotherapy and concurrent thoracic radiotherapy (45 Gy in 5 wk). In the resected specimen, a pathologic complete response or minimal microscopic disease was identified in 66% of patients. The OS at 5 years was 44% and, for those with a complete resection, 54%.[169] In a phase II trial in Japan, chemotherapy with mitomycin, vindesine, and cisplatin with concurrent thoracic radiotherapy led to a 5-year survival of 56%.[170] Although the optimal regimen of treatment

has not been determined, a reasonable choice is that used in the Intergroup Trial study described earlier.

SUPERIOR VENA CAVA SYNDROME

A blockage of blood flow in the *superior vena cava* (SVC) results in SVC syndrome.[171] Lung cancer accounts for the vast majority of these cases in older adults.[172,173] In teenagers and young adults, SVC syndrome is usually due to non-Hodgkin lymphoma. Patients complain of dyspnea and a sensation of fullness in the head and/or light-headedness when bending over. They may also note facial swelling. Cough, pain, and dysphagia are less frequent symptoms. Physical examination findings included dilated neck veins, a prominent venous pattern on the chest, facial edema, and a plethoric appearance. The chest radiograph typically shows widening of the mediastinum or a right hilar mass. Occasionally, it may be normal. Dilated veins on the anterior chest wall and compression of the SVC may be demonstrated with CT with intravenous contrast. SVC syndrome is not generally a medical emergency, and patients should not be treated without a tissue diagnosis. Bronchoscopy or mediastinoscopy can be safely performed in the setting of SVC syndrome.[174] Because SCLC is chemosensitive, SVC syndrome due to SCLC is best treated with chemotherapy; generally, after treatment, symptoms start to resolve in 5 to 7 days.[175] NSCLC is best treated with concurrent chemoradiotherapy (see earlier discussion of treatment of stage IIIA/IIIB NSCLC), or radiotherapy alone in a patient presenting with SVC syndrome and distant metastatic disease. If there is a need for immediate relief of SVC obstruction, vascular stenting should be strongly considered. A Cochrane meta-analysis reported that SVC stents relieved obstruction in 95% of cases.[175] Stenting has been associated with a complication rate of 3–7%.

Key Points

- Stage I *non–small cell lung cancer* (NSCLC) is treated with surgery alone and, in those who are medically inoperable, stereotactic body radiation therapy is an alternative treatment option. Stage II NSCLC is treated with surgery followed by adjuvant chemotherapy. Stage III represents a heterogeneous group of patients. In carefully selected patients with stage IIIA disease, surgery may be indicated with or without neoadjuvant chemotherapy or neoadjuvant chemoradiotherapy. Unresectable stage III disease is treated with a concurrent chemoradiotherapy followed by consolidation therapy with the immune checkpoint inhibitor, durvalumab. Treatment of stage IV NSCLC is determined by performance status, histology, molecular characterization, and PD-L1 expression and includes chemotherapy, targeted therapy, or immunotherapy alone or in combination with chemotherapy.
- It is imperative that metastatic adenocarcinoma, large cell carcinoma, and NSCLC not otherwise specified undergo molecular testing, preferably with next-generation sequencing, for *EGFR* mutations, ALK-fusion, *ROS1* translocations, and other actionable mutations for which targeted therapies are available or are being developed. Molecular characterization should also be considered in patients with metastatic squamous cell carcinoma who are never-smokers. Patients with actionable molecular targets respond better and have improved progression-free survival and overall survival when treated with targeted therapy.
- Immunotherapy plays a major role in the treatment of patients with stage III and IV NSCLC and has resulted in improved progression-free survival and overall survival. Immunotherapy also shows promise in early stage NSCLC and advanced stage small cell lung cancer.
- Localized small cell lung cancer (disease within one hemithorax that can be encompassed in a radiation port) is treated by chemoradiotherapy; extensive disease is treated with chemotherapy and immunotherapy.
- Patients with stage IV NSCLC who have limited metastases, considered oligometastatic disease, may benefit from definitive treatment to all sites of active disease.
- Immunotherapy-mediated pneumonitis is rare but potentially fatal and requires prompt recognition.

Key Readings

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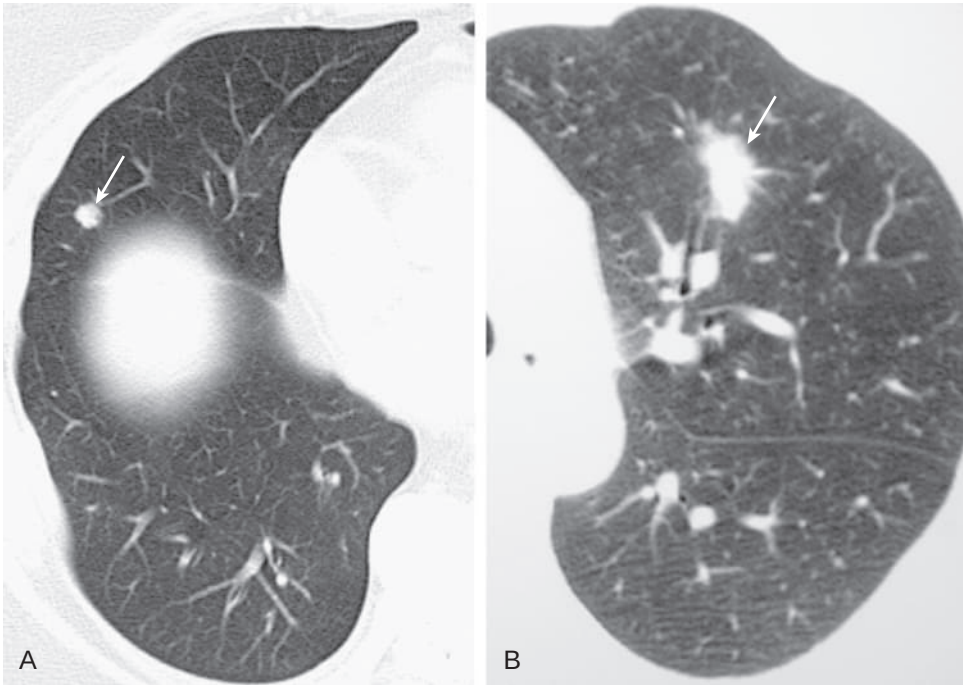
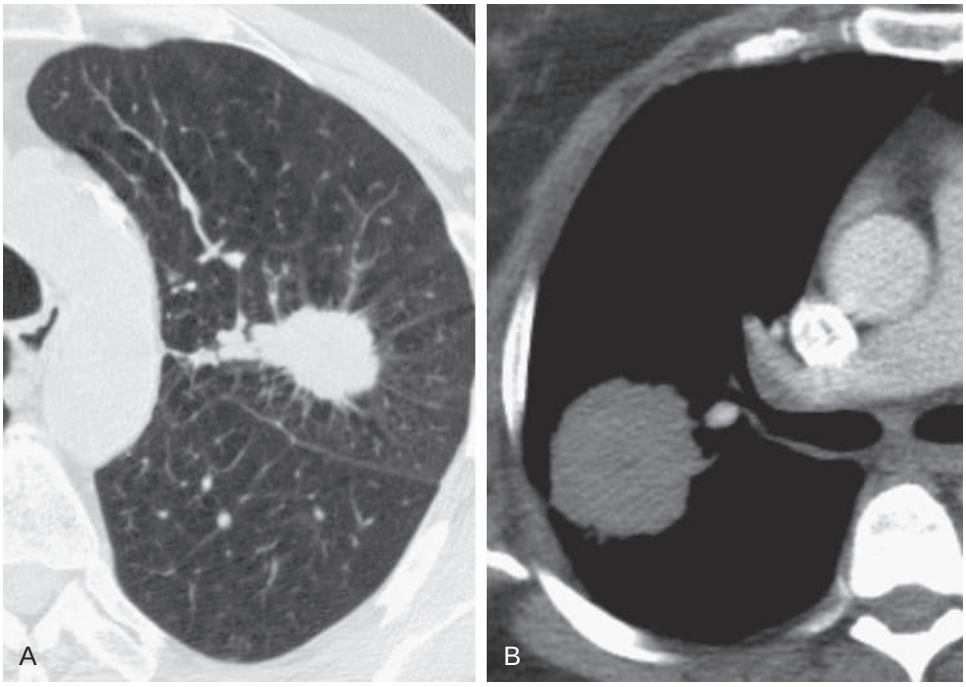
Complete reference list available at ExpertConsult.com.

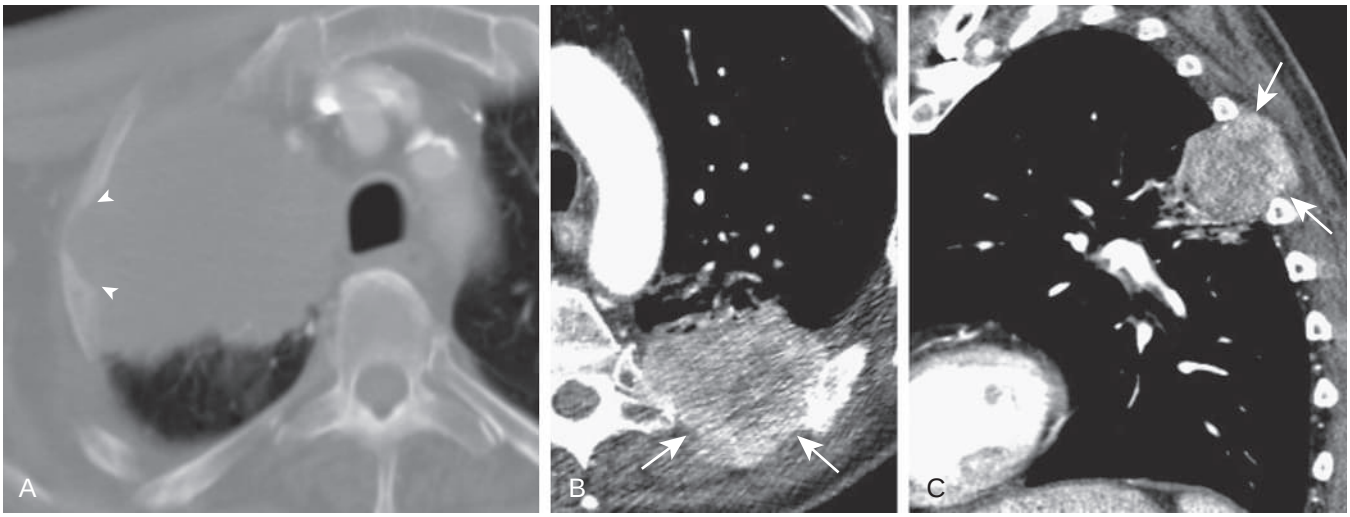
eFIGURE IMAGE GALLERY



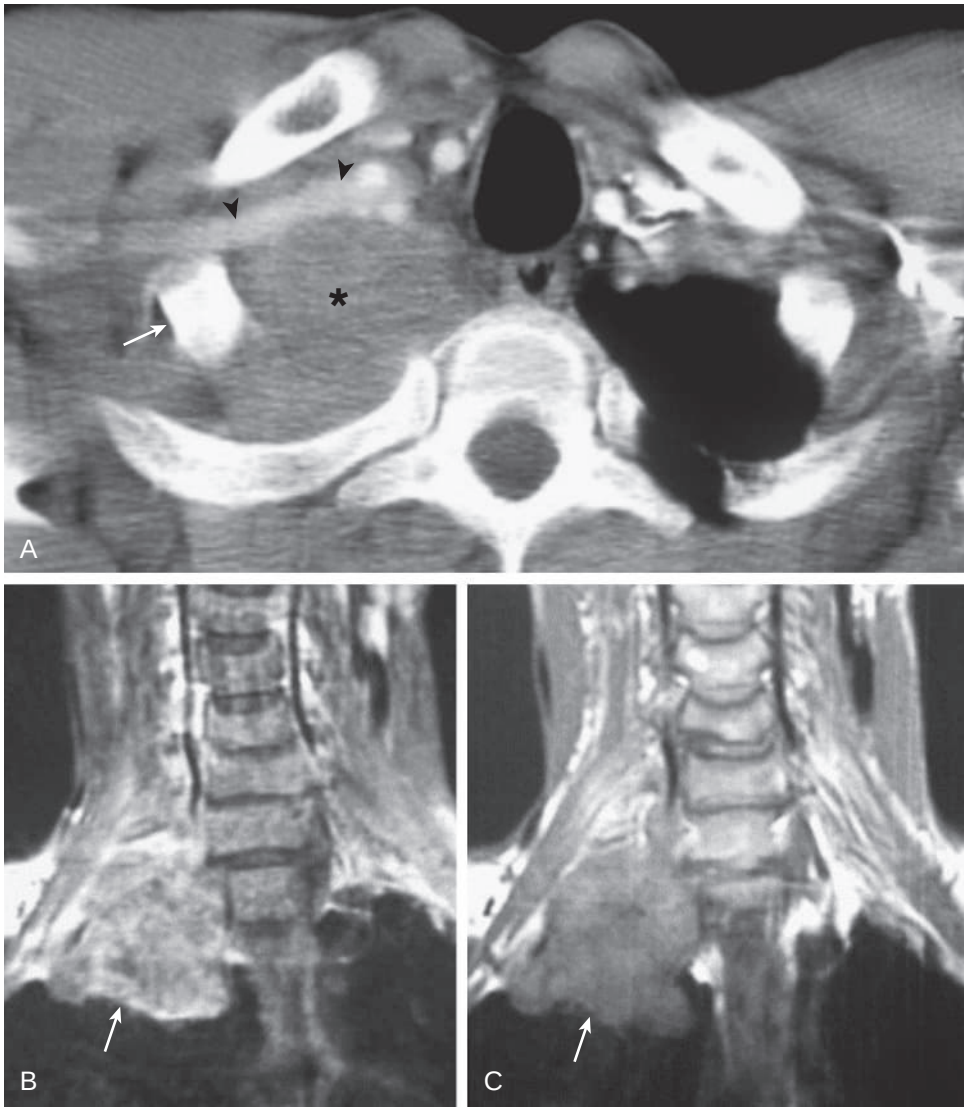
eFigure 77.1 T staging for primary pulmonary malignancy. (A) T1a lung carcinoma: 8-mm lobulated nodule *(arrow)* in the inferior right middle lobe, completely surrounded by lung. (B) T2a lung carcinoma: 3.1-cm spiculated left upper lobe nodule *(arrow),* completely surrounded by lung parenchyma, >2 cm away from the carina, and without chest wall or parietal pleural invasion. (Courtesy Michael B. Gotway, MD.)



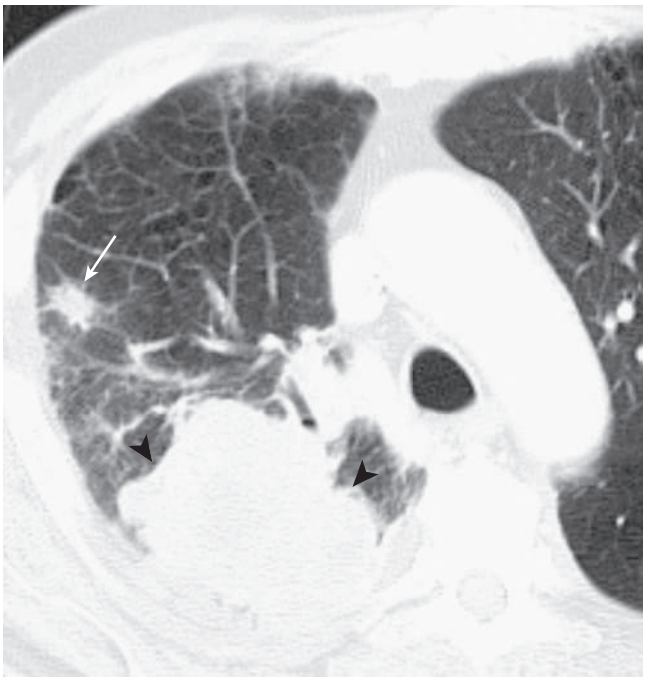
eFigure 77.2 T staging for primary pulmonary malignancy: locally restricted disease. (A) T2a lung carcinoma: 3.8-cm left upper lobe spiculated mass, completely surrounded by lung parenchyma, >2 cm away from the carina, and without chest wall or parietal pleural invasion. (B) T2b 4.8-cm right upper lobe mass, completely surrounded by lung parenchyma, >2 cm away from the carina, and without chest wall or parietal pleural invasion. (Courtesy Michael B. Gotway, MD.)



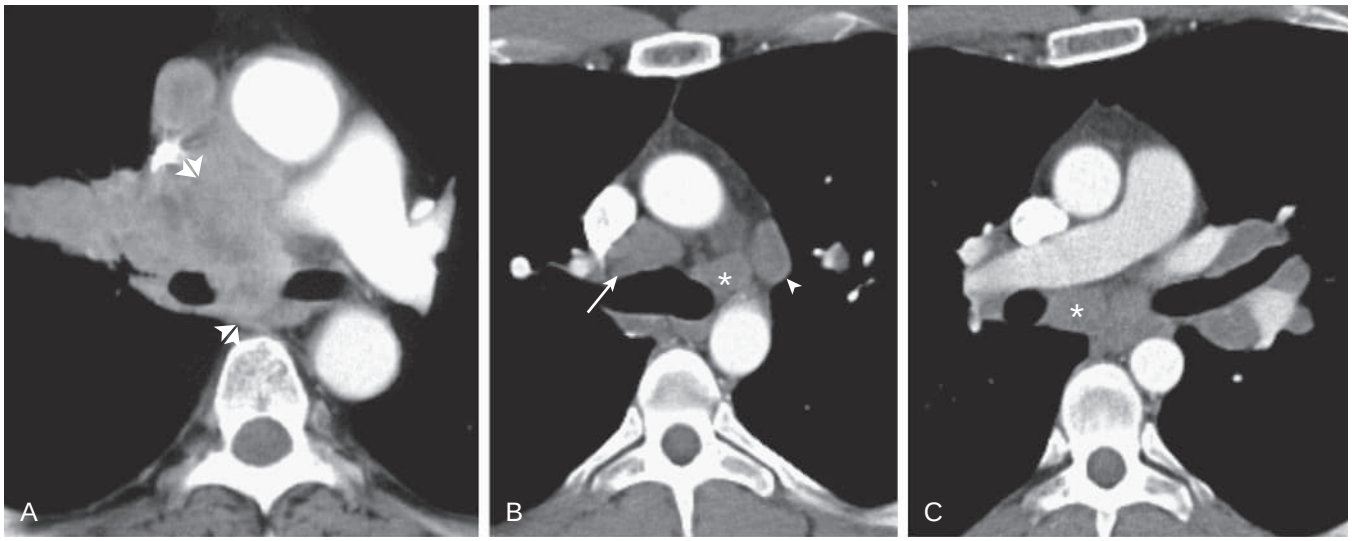
eFigure 77.3 T staging for primary pulmonary malignancy: chest wall invasion (T3). (A) Axial chest computed tomography (CT) displayed in bone windows shows a large right upper lobe mass with clear erosion of the internal cortex of the rib *(arrowheads)*. (B–C) Axial and sagittal enhanced chest CT shows an avidly enhancing subpleural left upper lobe mass extending into the soft tissues of the chest wall *(arrows)*. (Courtesy Michael B. Gotway, MD.)



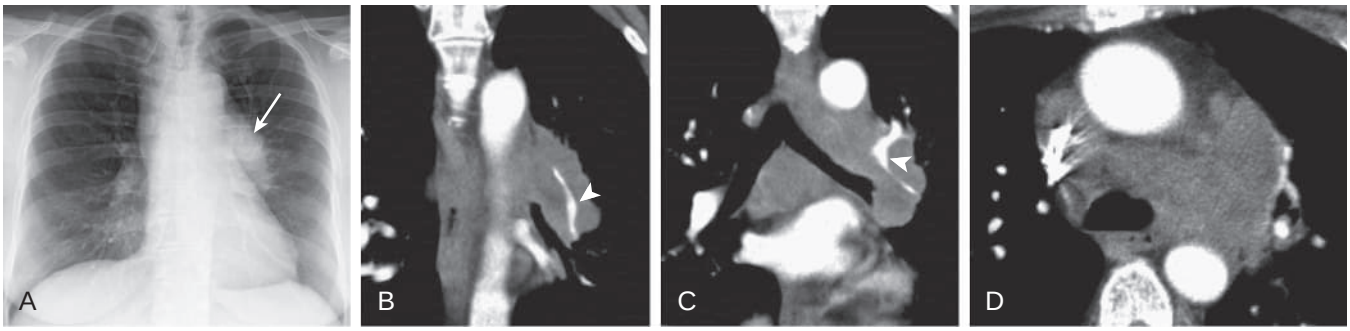
eFigure 77.4 Primary pulmonary malignancy arising in the superior sulcus. (A) Axial enhanced chest computed tomography (CT) shows a mass *(asterisk)* in the superior sulcus. The region of the superior sulcus on axial CT can be readily and quickly identified when the subclavian artery *(arrowheads)* and first rib *(arrow)* are seen. Coronal T2-weighted (B) and T1-weighted (C) magnetic resonance imaging shows the right upper lobe mass *(arrows)* extending cranially into the neck soft tissues, involving the brachial plexus. (Courtesy Michael B. Gotway, MD.)



eFigure 77.5 T staging for primary pulmonary malignancy: locally advanced disease. Axial chest computed tomography shows a large primary pulmonary malignancy *(arrowheads)* in the superior segment of the right lower lobe, with a separate tumor nodule in the right upper lobe *(arrow)* (an ipsilateral nonprimary lobe), consistent with T4 disease and less likely metastasis. (Courtesy Michael B. Gotway, MD.)



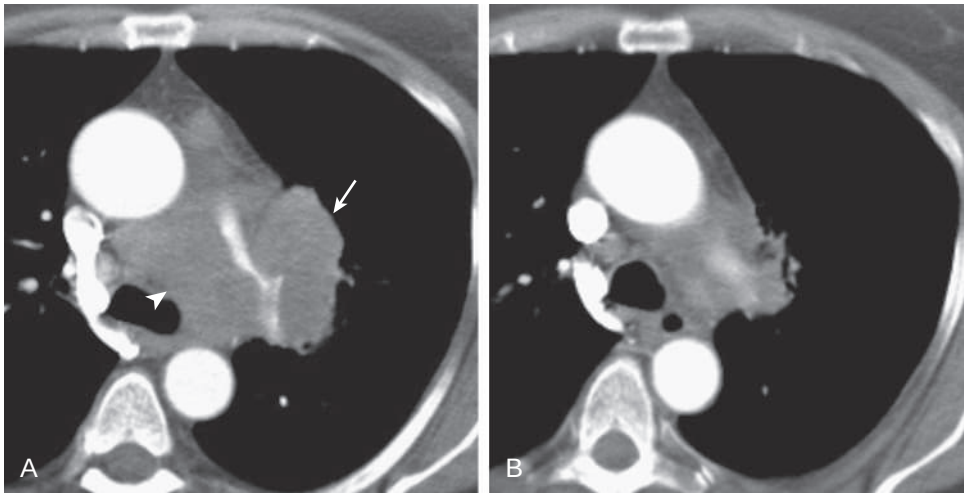
eFigure 77.6 Infiltrating lymphadenopathy versus discrete lymphadenopathy. (A) Axial enhanced chest computed tomography (CT) at the level of the carina shows confluent soft tissue with areas of low attenuation *(arrowheads)* occupying the right paratracheal and subcarinal spaces, extending toward the right peribronchial region. (B–C) Axial enhanced chest CT shows discretely enlarged lymph nodes in the right paratracheal space (station 4R) (*arrow*, B), left tracheobronchial angle (station 4L) (*asterisk*, B), aortopulmonary window region (station 5) (*arrowhead*, B), and subcarinal space (station 7) (*asterisk*, C). (Courtesy Michael B. Gotway, MD.)



eFigure 77.7 Small cell carcinoma: typical imaging appearance. (A) Frontal chest radiograph shows increased density and enlargement of the left hilum *(arrow)*. Coronal (B–C) and axial (D) enhanced chest computed tomography shows confluent soft tissue surrounding and narrowing the left pulmonary artery (*arrowheads*, B–C) and extending into the mediastinum. (Courtesy Michael B. Gotway, MD.)



eFigure 77.8 Small cell carcinoma presenting as a solitary pulmonary nodule. (A) Axial chest computed tomography shows a lobulated peripheral right upper lobe nodule. Appearance suggests pulmonary malignancy, especially adenocarcinoma. (B) Fused axial positron emission tomography shows intense metabolic activity within the nodule. Biopsy revealed small cell lung carcinoma. (Courtesy Michael B. Gotway, MD.)



eFigure 77.9 Small cell carcinoma: treatment response. (A) Axial enhanced chest computed tomography (CT) shows confluent left hilar *(arrow)* and mediastinal *(arrowhead)* lymphadenopathy, proven to represent small cell carcinoma. (B) Axial enhanced chest CT following therapy shows marked regression in the confluent lymphadenopathy. (Courtesy Michael B. Gotway, MD.)

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78 RARE PRIMARY LUNG TUMORS

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INTRODUCTION

Rare pulmonary tumors are defined as malignancies developed in the lung parenchyma with low prevalence and unusual histology and that are different from bronchogenic carcinomas, small and non–small cell lung carcinomas. Rare molecular subsets of non–small cell lung carcinomas, such as *ROS1*-, *RET*-, and *NTRK*-rearranged tumors, are then excluded from the definition, which is mostly based on histologic classification; even so, molecular alterations of therapeutic significance may be identified in rare pulmonary tumors.[1–4] In this setting, rare pulmonary tumors account for less than 1% of all primary lung tumors, whereas they correspond to more than 100 different histologic, molecular, clinical, radiologic, and prognostic entities.[1–4] Some rare lung tumors are specific to the lung, whereas others represent tumors more frequently diagnosed in other organs and are only rarely detected in the lungs, excluding metastases. It is estimated that about 60% of rare primary pulmonary tumors correspond to benign and low-grade lesions and that 40% are malignant.[1,2]

Rare pulmonary tumors are characterized by their low incidence but also by limited clinical and imaging descriptions, by the low number of experienced physicians for each tumor subtype, and by the absence of specific therapeutic data. Recognition of rare pulmonary tumors relies on characteristic clinical and radiologic signs, on a modified diagnostic and imaging strategy, and primarily on the determination of their primary or secondary nature. Of interest, some of those tumors may have a propensity to mimic lung carcinoma and benign orphan lung diseases because they may share clinical, imaging, pathologic, and even molecular features.[4,5] Pseudotumors have further been described in the lung, historically referring to any pseudoneoplasm, but they are now restricted to a specific heterogeneous group of diseases characterized by circumscribed fibrous tissue associated with inflammatory and myofibroblastic cells.[5–7]

The objective of this chapter is to provide the reader with a practical overview of rare pulmonary tumors, highlighting key concepts through the discussion of prototypic entities.

DEFINITION OF RARE PULMONARY TUMORS

Rare cancers are defined as those with an incidence rate less than 6 per 100,000 per year, as per the standard definition proposed in Europe[8]; these correspond to 198 different cancers and ultimately represent 24% of all new cancer cases diagnosed each year (www.rarecancerseurope.org). In the lung, rare tumors account for less than 1% of all lung malignancies and correspond to a wide array of histopathologic, molecular, clinical, and radiologic entities.[1–4] Prevalence ranges from merely uncommon lesions, such as carcinoids, which account for 0.15% of all primary lung tumors, to extremely unusual tumors, such as primary pulmonary melanoma, with fewer than 50 reported cases, even leading to debate about the actual primary pulmonary nature of those lesions. Overall, the most frequent rare malignant primary lung tumors are, in decreasing order of frequency, carcinoid, *mucosa-associated lymphoid tissue* (MALT) lymphoma, and sarcomatoid carcinomas.[1,9]

Most rare lung tumors develop from orthotopic tissues, constitutive of the normal lung parenchyma, or from hematopoietic tissues,[1,2] whereas tumors derived from ectopic tissues are even less frequent.[10] Some rare tumor subtypes arise specifically within the lung, whereas others, such as blastomas and perivascular epithelioid cell tumors, arise in many different tissues of the body, including the lung, and are infrequent wherever they are located. Furthermore, some primary tumors that are uncommon within the lung may be frequent in other locations, including lymph node lymphomas and soft tissue sarcomas, which present with specific histopathologic differentiation when originating in the lung, such as MALT lymphoma and angiosarcoma, respectively.

RARE MALIGNANT PRIMARY PULMONARY EPITHELIAL TUMORS

SARCOMATOID CARCINOMAS

Sarcomatoid carcinomas are a group of poorly differentiated non–small cell carcinomas containing a sarcomatous-like component corresponding to epithelial-mesenchymal transition. In addition to pneumoblastoma, four subtypes are recognized: (1) pleomorphic carcinoma, which corresponds either to the combination of adenocarcinoma, squamous cell carcinoma, or large cell carcinoma with spindle or giant cells; (2) spindle cell carcinoma, which consists exclusively of proliferating fascicular cells; (3) giant cell carcinoma, composed of highly pleomorphic mononucleated or multinucleated cells; and (4) carcinosarcoma, containing a mixture of carcinoma (frequently of epidermoid subtype) and poorly differentiated fibromatous sarcoma.[9,11,12]

Sarcomatoid carcinomas were historically defined in the 1999 World Health Organization classification. These tumors represent 0.3–1.3% of lung tumors, and their specific clinical and radiologic features are rarely reported and may be similar to that of *non–small cell lung cancer* (NSCLC). Sarcomatoid carcinomas develop mostly in men, at a mean age of 65 years at diagnosis.[11–14] Tobacco smoking is described in more than 80% of cases. Radiologic studies usually show a solitary voluminous peripheral heterogenous mass, possibly invading the chest wall in 60% of cases.[15,16] Vascular invasion is observed in 20% of cases. ^{18}*F-fluorodeoxyglucose* (FDG)-*positron emission tomography* (PET) scans show increased uptake.

Histopathologic diagnosis is challenging. The majority of patients present with advanced metastatic disease, and small biopsies are not usually representative of the tumor. In particular, the biopsies may not disclose both the epithelial and the sarcomatous components of the tumor, which is then misdiagnosed as lung cancer in more than 60% of cases.[1]

The sarcomatoid carcinomas, other than pneumoblastoma, are considered to be highly aggressive tumors with early metastatic spread,[17] possibly in unusual sites such as the esophagus, the peritoneum, the kidney, and the subcutaneous tissues. Median overall survival ranges from 6 to 20 months in surgical series.[11–17] The main prognostic factor is staging.[18]

Metastatic sarcomatoid carcinomas are often treated as other NSCLC, with platinum-based chemotherapy considered standard as first-line treatment. In pleomorphic carcinomas, cytotoxic agents (pemetrexed, gemcitabine, or vinorelbine) adapted to the histology of the carcinomatous component (adenocarcinoma versus squamous) may be used.[19] Expression of the immune checkpoint protein programmed cell death–ligand 1 is frequent, but there are only limited data available regarding the use of immune checkpoint inhibitors in the first-line setting.[20] Alternatively, chemotherapy has been reported to follow soft tissue sarcoma regimens.[21] In pleiomorphic carcinomas with an adenocarcinoma component, systematic screening for oncogenic alterations, such as *epidermal growth factor receptor (EGFR), BRAF,* and *MET* alterations, may predict the efficacy of targeted therapies.[22] *MET* alterations, including amplification and exon 14 skipping mutations, are reported in 10–40% of patients, predicting response to MET kinase inhibitors or antibodies.[23,24]

A separate molecularly defined entity within sarcomatoid carcinomas is the tumor with a deficiency of the chromatin remodeling complex SMARCA4 (BRG1).[25] As in the other sarcomatoid carcinomas, patients are usually smokers but are younger and present with larger tumors.[25] Histologically, rhabdoid features may be observed, thyroid transcription factor-1 expression is present, and there is a high tumor mutation burden. The majority of cases are metastatic at the time of diagnosis. Prognosis is poor because chemotherapy or any other standard systemic treatment is poorly effective; bromodomain-modulating agents are under investigation.

PNEUMOBLASTOMA

Pneumoblastoma is a biphasic tumor still classified among the sarcomatoid carcinoma group in the current World Health Organization classification, although corresponding to a separate clinical and biologic entity.[9] Pneumoblastoma contains both an epithelial well-differentiated component, showing tubular architecture resembling the normal fetal lung, and a mesenchymal undifferentiated stroma, defining the blastema-like configuration.[26] It has to be differentiated from pleuropulmonary blastoma, a tumor of early childhood related to other embryonic neoplasms, such as nephroblastoma and neuroblastoma.

Pneumoblastoma most frequently arises in patients age 30 to 45 years, with a marked female predominance (70% of cases) and frequent association with tobacco smoking.[26–28] Imaging shows a solitary circumscribed homogeneous mass,[29] often with cystic and necrotic features. FDG-PET scans show increased uptake. In many cases, the tumor is initially thought to be a bronchogenic carcinoma, and complete surgical resection with mediastinal lymph node dissection ensures both the initial diagnosis and the therapy.[26,27,29] Adjuvant treatment, mostly consisting of radiotherapy, has been reported in a few cases after incomplete resection or in patients with N2 mediastinal involvement, as for NSCLC.[26,30] In unresectable tumors, chemotherapy is based on protocols used for sarcomas, including doxorubicin and ifosfamide-based regimens. In

most recent reports, survival is better than in NSCLC, especially in completely resected cases.[26] Molecular analysis is proposed because oncogenic alterations, such as *ROS1* gene fusions, may be found that would predict the efficacy of targeted agents.[31]

MUCOEPIDERMOID CARCINOMA

Mucoepidermoid carcinoma is the most frequent salivary gland–type tumor arising in the lung; other subtypes include adenoid cystic carcinoma and epithelial-myoepithelial carcinoma. Mucoepidermoid carcinoma is a mixed malignant tumor characterized by the presence of squamous cells, goblet mucin-secreting cells, and cells of intermediate type.[9,32] Identification of these three cellular subtypes in cytologic examination is pathognomonic. Tumors are classified as low-, intermediate-, and high-grade lesions depending on the mitotic index, the degree of cellular atypia, and the degree of necrosis. High-grade tumors contain predominantly squamous and intermediate cells and tend to infiltrate the lung parenchyma. In 60% of cases, molecular analysis may lead to the identification of *CRTC1-MAML2* gene fusions specific to mucoepidermoid carcinomas, which may be associated with better prognosis.[33]

Mucoepidermoid carcinoma in adults mostly develops between the third and fourth decades, with an equal sex distribution.[34] High-grade tumors (30% of cases) are usually diagnosed in older patients. Mucoepidermoid carcinoma is often associated with tobacco smoking. Symptoms, including dyspnea, cough, and hemoptysis, are related to the level of bronchial obstruction (eFig. 78.1). Metastases are found at time of diagnosis in 20% of cases, mainly in the liver, the bone, and the subcutaneous tissues (Fig. 78.1).[35] The lesion is solitary in 40–70% of cases. Hilar involvement is found only for high-grade lesions. There is increased uptake at FDG-PET scanning.[35] Proximal mucoepidermoid tumors can be diagnosed using endobronchial biopsy.

Treatment is historically the same as for NSCLC when the tumor is diagnosed at a limited stage, with extensive surgical resection, including mediastinal lymph node dissection.[32–35] High-grade lesions have often been reported to receive postoperative radiotherapy and chemotherapy, without clear benefit. Chemotherapy of metastatic tumors in most cases is based on cisplatin and/or 5-fluorouracil, as reported for head and neck carcinomas.[36] In cases with *MAML2* gene fusion, deregulation of the EGFR signaling pathway constitutes a rationale for the use of EGFR kinase inhibitors.[37] Prognosis is correlated with the grade of the lesion, the existence of nodal involvement, and the success of the initial surgical resection. Low-grade mucoepidermoid tumors present mostly in children and young adults, usually without hilar involvement, and have a 5-year survival ranging from 70–80%. High-grade tumors have a substantially worse prognosis because of their early disease progression and metastatic spread, with a 5-year survival of only 30–45%.

CARCINOIDS AND LARGE CELL NEUROENDOCRINE CARCINOMA

Carcinoid and large cell neuroendocrine carcinoma share common histopathologic features related to the neuroendocrine origin and correspond to four different clinical and prognostic entities: (1) low-grade typical carcinoids, (2) intermediate-grade atypical carcinoids, and (3) high-grade large and (4) small cell neuroendocrine carcinomas.[9] The *small cell lung carcinomas* (SCLCs) are frequent tumors, accounting for 15–20% of all primary lung malignancies. On the contrary, carcinoids and large cell neuroendocrine carcinomas account for 0.5–2% of lung tumors and are

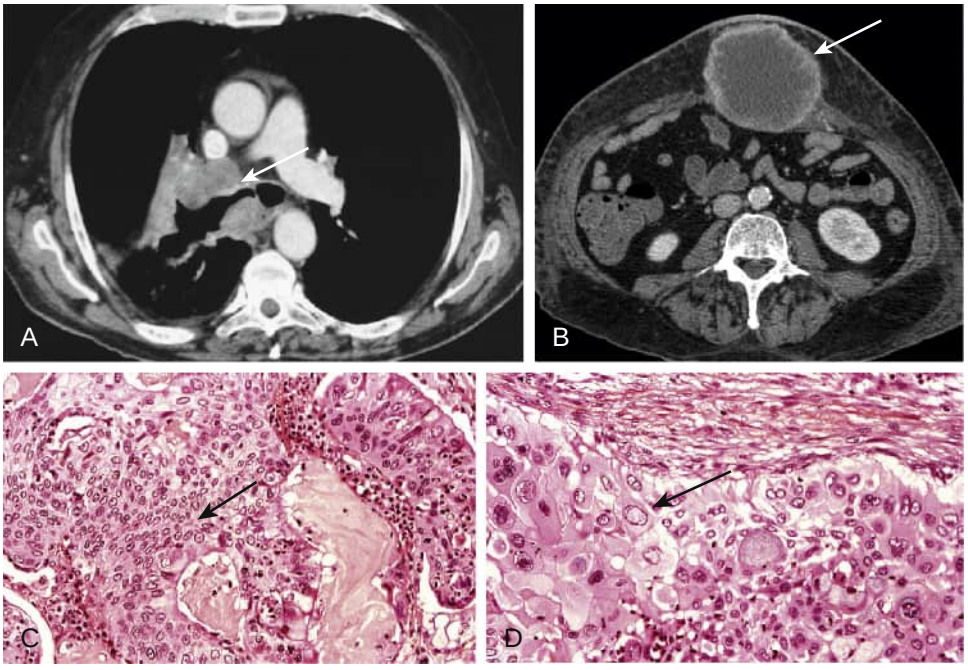

Figure 78.1 Primary pulmonary mucoepidermoid carcinoma. (A) The tumor is located in the right upper lobe and is invading the mediastinum (*arrow*). Radiologic imaging features are identical to those of non–small cell lung cancer. (B) A metastatic mass is discovered on clinical examination of the abdomen. Axial enhanced abdominal computed tomography confirms the location in the anterior abdominal wall (*arrow*). Histopathologic features: a mixture of squamoid (C) and mucin-secreting (D) cells (*arrows*). (C–D, Original magnification ×40.)

thus considered the most frequent lesions among the rare pulmonary tumors.

PATHOLOGIC FEATURES

These tumors share varying degrees of neuroendocrine morphologic features, including organoid nesting, the palisading and trabecular pattern, and rosette-like structures. Classification is mainly based on the mitotic index and the amount of necrosis.[9,38] *Typical* carcinoids exhibit a mitotic index of fewer than two mitoses per 10 high-power fields (2 mm^2), and the absence of necrosis in a tumor that is more than 5 mm in diameter. *Atypical* carcinoids exhibit a mitotic index ranging from 2 to 10, or areas of focal necrosis. Peripheral carcinoids may also be associated with small (<5 mm) neuroendocrine "tumorlets" and/or with diffuse idiopathic pulmonary neuroendocrine cell hyperplasia, which may lead to obstructive lung disease[39] (eFig. 78.2). These lesions may correspond to early-stage in situ carcinoid proliferation. Large cell neuroendocrine carcinomas exhibit a mitotic index higher than 10 (ranging from 70–80 in most cases) and extensive necrosis. Unlike SCLCs, large cell carcinomas have large tumor cells, with moderate to abundant cytoplasm and frequently prominent nucleoli. Immunohistochemically, the expression of at least one neuroendocrine marker, including chromogranin, synaptophysin, or neural cell adhesion molecule (CD56), confirms the diagnosis. The pathologic classification also distinguishes large cell neuroendocrine carcinoma from NSCLC "with neuroendocrine differentiation," a pattern without specific prognostic or therapeutic implications.[40] Recent molecular analyses of large cell neuroendocrine carcinoma have identified two patterns, the first being related to NSCLC, with *KRAS*, *TP53*, and possibly *EGFR* and *BRAF* mutations, and the second being related to SCLC, with *RB1* alterations.[41]

CARCINOID TUMORS

Excluding SCLC, more than 80% of lung neuroendocrine tumors are carcinoids.[42] Carcinoids arise mostly in never-smokers (60–80% of cases). Carcinoids develop in the proximal airways in 60–70% of cases and may produce chronic cough, hemoptysis, and signs of bronchial obstruction. Peripheral carcinoids are asymptomatic, unless they are associated with diffuse hyperplasia of pulmonary neuroendocrine cells or diffuse idiopathic pulmonary neuroendocrine cell hyperplasia (DIPNECH), producing bronchiolar obstruction in 50% of cases and possible airflow obstruction (see eFig. 78.2). Unlike carcinoids in extrathoracic locations, lung carcinoids are small lesions only rarely associated with liver metastases and do not generally produce the carcinoid or Cushing syndrome (<2% of cases).[43] CT shows a peripheral or proximal, circumscribed, solitary nodular lesion in 90% of cases,[42,44] often manifesting as a hilar or perihilar mass (eFig. 78.3). Carcinoid tumors may present as iceberg-like lesions, with a small amount of endobronchial growth (Fig. 78.2) and a prominent parenchymal mass. In some cases, carcinoid tumors may also present as endobronchial lesions, with or without lobar or segmental atelectasis (eFig. 78.4). Calcification (see eFig. 78.3C) may be observed in up to 30% of cases. Regional lymph node invasion is more frequent in atypical carcinoids (40–50% of cases vs. 10–15% of typical carcinoids) (eFig. 78.5), and the tumor-node-metastasis classification, although designed for NSCLC, has been used to stage carcinoids.[45] Although hypervascular (see eFig. 78.3B), carcinoids generally exhibit a low to moderate activity on FDG-PET scanning[46] (eFig. 78.6). Imaging for somatostatin receptors using indium-111–labeled octreotide (eFig. 78.7) is being replaced by gallium-68-DOTA-peptide-PET imaging, which allows three-dimensional analysis with higher sensitivity for diagnosis, staging, and follow-up.[47] The risk of hemorrhage after endobronchial biopsy is less than 1%.[48]

Surgery is the standard treatment for stage I–II and most stage III carcinoids, which account for 75% and 15% of cases, respectively. Typical carcinoids, with a low local recurrence rate, can be treated with limited resection with segmentectomy and regional lymph node dissection; resection followed by endobronchial anastomosis may be used for proximal tumors. This approach is associated with local control and survival rates identical to those after extensive procedures.[42,49] Endobronchial techniques, such as

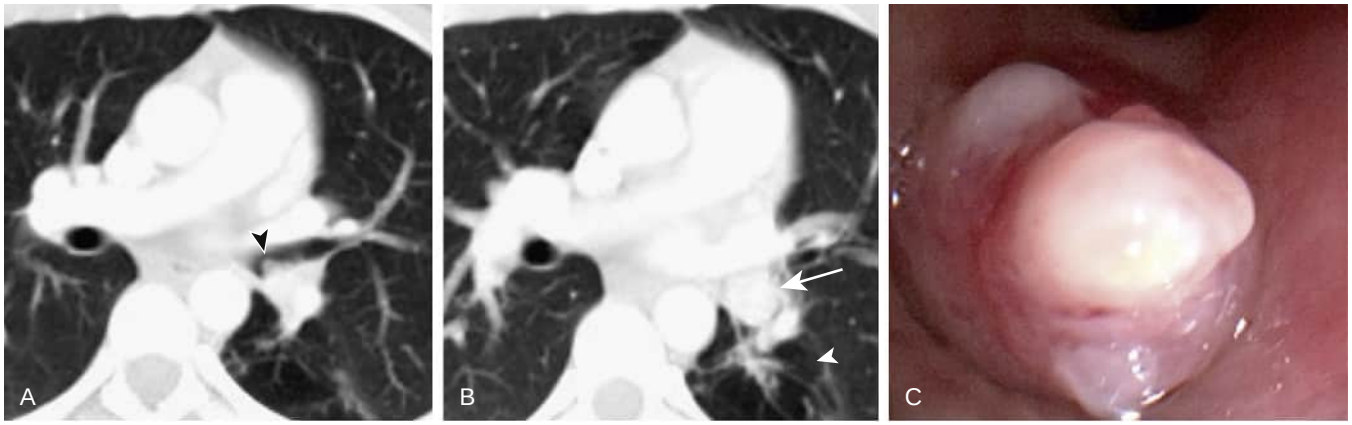

Figure 78.2 "Typical" carcinoid tumor: iceberg-like endobronchial mass. (A–B) Axial chest computed tomography displayed in lung windows in a 32-year-old woman with recurrent pneumonia shows a small portion of tumor protruding into the left mainstem bronchus (A, *arrowhead*), in a manner analogous to the small portion of an iceberg that protrudes above ocean water. There is complete obstruction of the left lower lobe bronchus (B, *arrow*). Left lower lobe postobstructive air trapping (B, *arrowhead*) is present. (C) Bronchoscopic image shows the left lower lobe lesion protruding into the left mainstem bronchus. (Courtesy Michael B. Gotway, MD.)

cryotherapy, have also been reported as an alternative approach for typical carcinoid but fail to ensure accurate counting of the mitotic index and therefore the confirmation of the subtype; this may be reserved for frail patients.[49] Atypical carcinoids, which have a higher local recurrence rate, usually require lobectomy and mediastinal lymph node dissection.[42] Lung carcinoids metastasize in less than 10% of cases; preoperative workup and follow-up should include systematic dedicated liver imaging.[50]

Carcinoids can exhibit quite different growth patterns, as shown in analyses of their molecular and growth characteristics.[50] In fact, some carcinoid tumors, usually with atypical features and high proliferation index, may present with metastases, poor outcome, and rapid progression; they have been defined as *supracarcinoid* tumors, a term that is debated but refers to a peculiar clinical entity. In the setting of metastatic or recurrent disease, cisplatin-based chemotherapy is ineffective, and management is tailored to the growth curve of the tumor lesions.[50] In patients with slow-growing, nonthreatening lesions, it is appropriate to watch and wait; to provide local treatment of oligometastases, which may lead to prolonged remission; or to use somatostatin analogues. In patients with rapidly progressive disease, everolimus may represent the best option.[50] In summary, the most significant prognostic factor is the histopathologic subtype, because 5-year survival rates of typical and atypical carcinoids are 87–98% and 56–73%, respectively.

LARGE CELL NEUROENDOCRINE CARCINOMA

The incidence of large cell neuroendocrine carcinoma has long been underestimated, probably because these tumors are often misdiagnosed as large cell undifferentiated carcinoma either on cytology or on tissue sections in the absence of immunostaining for neuroendocrine markers.[9,51] Large cell neuroendocrine carcinomas are strongly associated with tobacco smoking (90% of cases).[52,53] Clinical and radiologic (eFig. 78.8) features are similar to those of NSCLC and, in most reported series, treatment for early-stage tumors follows recommendations for NSCLC, including perioperative chemotherapy if recommended based on staging.[54] In advanced or metastatic disease, the chemotherapy regimen may be driven by mutation profiles; in the case of an NSCLC-like pattern, platinum-pemetrexed may lead to better outcomes but, in the case of a SCLC-like pattern, platinum-etoposide may be recommended.[55] Ultimately, overall survival is better than in SCLC, with stage being the most significant prognostic factor. Five-year survival rates in stages I–II, III, and IV are 52–88%, 20–45%, and 0–15%, respectively. Clinical trials with immune checkpoint inhibitors are ongoing.

PRIMARY PULMONARY LYMPHOMAS

Primary pulmonary lymphomas are historically strictly defined as lymphomas affecting one or both lungs, without evidence of extrapulmonary involvement at the time of diagnosis.[56–58] However, extrapulmonary lesions are actually found in up to 30% of cases when extensive workup is conducted.[57] Then, pulmonary lymphomas associated with small-sized satellite mediastinal and/or systemic nodes are regarded by clinicians as originating from the lung; similarly, large pulmonary lesions of lymphoma associated with single extrapulmonary lesions are regarded as primary pulmonary lymphoma.[58–61] Overall, primary pulmonary lymphomas are rare, representing 0.4% of all lymphomas. The most frequent subtype is MALT-type lymphoma. Other primary pulmonary lymphoma subtypes are mostly observed in immunocompromised patients. Lymphomatoid granulomatosis is a borderline primary pulmonary lymphoproliferative disorder.

MUCOSA-ASSOCIATED LYMPHOID TISSUE–TYPE LYMPHOMA

Pulmonary MALT lymphoma is referred to as nodal marginal-zone B cell lymphoma, with similar cytopathologic features to other MALT lymphomas, especially gastric lymphoma.[9] These low-grade lymphomas account for 70–90% of primary pulmonary lymphomas. At pathologic examination, MALT lymphoma appears as a diffuse infiltrate of small monomorphic lymphoid cells, with a typical lymphangitic growth pattern spreading along the bronchovascular bundles and interlobular septa and forming solid nodules that fill the alveolar spaces and obliterate the normal lung architecture (Fig. 78.3C–D). Immunohistochemistry forms the basis of the subtype classification, with the expression of the pan–B markers CD20 and CD79 and the absence of staining for CD5 and CD10.[9] The proliferation is monotypic, with surface and/or cytoplasmic expression of *immunoglobulin* (Ig) M and, less frequently, IgG and IgA (see Fig. 78.3E–F). Light chain restriction can be detected in the plasmacytic component using flow cytometry. MALT lymphomas are associated with unique chromosomal translocations, such as t(11;18)(q21,q21), resulting in a fusion of the *API2* and *MALT1* genes; t(1;14)(p22;q32), involving the *BCL10* and *IgH* genes—which is overall much less frequent, more specific to lung locations, and never found in high-grade lymphoma; and t(14;18)(q32;q21), involving the *IgH* and *MALT1* genes.[52,53,62] In cases with t(1;14) (*BCL10*/*IgH*) translocation, immunohistochemistry on paraffin-embedded tissues can detect the strong nuclear overexpression of BCL10. Amplification of the *IgH* gene from paraffin-embedded or cytologic samples with polymerase chain reaction–based assays was demonstrated to be a reliable method to detect monoclonality in greater than 60% of MALT lymphomas. Contrary to extrapulmonary MALT lymphomas, for which a strong relationship has been established with chronic bacterial inflammation related to *Helicobacter pylori* in the stomach and to *Chlamydia psittaci* in the ocular adnexa, no chronic infectious condition has been associated with pulmonary MALT lymphoma, although MALT is absent in the normal bronchial tree and is thought to develop only after long-term inflammation secondary to smoking or to an autoimmune condition.

Clinically, MALT lymphoma has mainly been observed in patients older than 45 years, with a slight male predominance, but it may also arise in younger patients with underlying immunosuppression, especially related to human immunodeficiency virus infection, or with inflammatory conditions such as Sjögren disease or

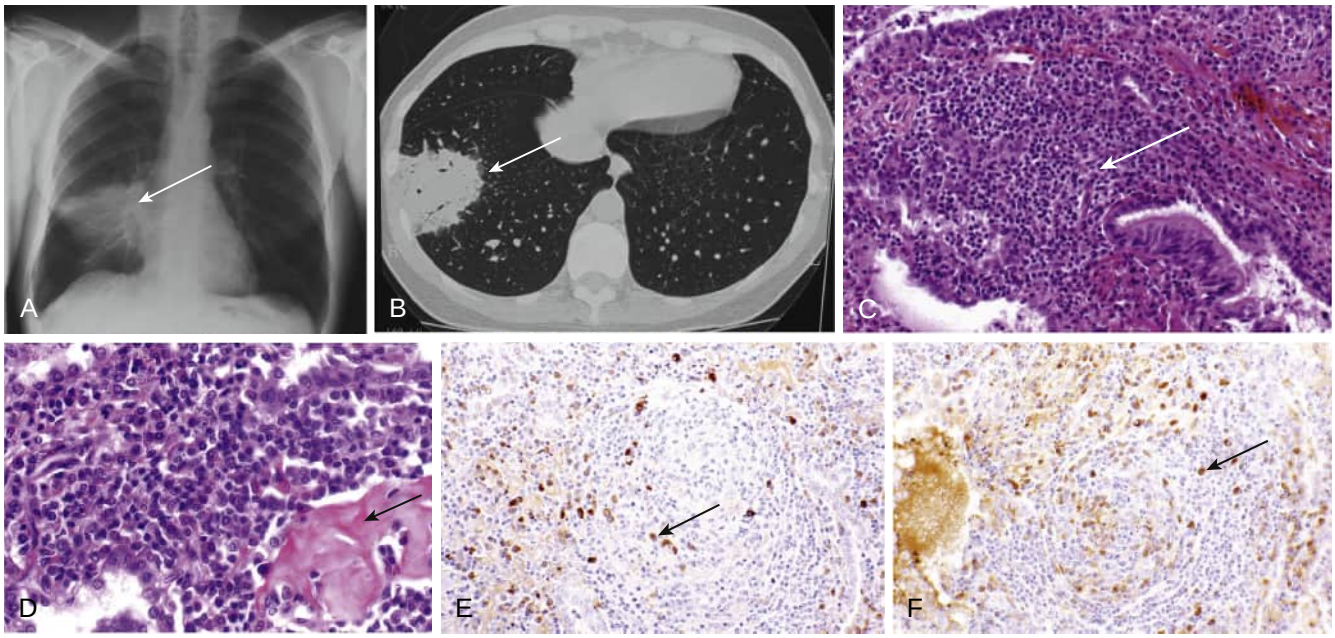

Figure 78.3 Primary pulmonary mucosa-associated lymphoid tissue lymphoma. Chest radiograph (A) and chest computed tomography (B) show a focus of consolidation in the right lower lobe (*arrows*) that persisted despite prolonged antibiotic therapy. (C) Pathologic examination of surgical biopsy showed proliferation of small-sized lymphoid cells infiltrating the bronchial wall. Note a bronchial epithelium encased by destructive lymphoid proliferation (*arrow*). (D) At high magnification, lymphoplasmacytic-like cells of the marginal zone lymphoma are associated with an amyloid deposit (*arrow*). (E) With *immunoglobulin* (Ig) lambda light chain immunostaining, there is a predominance of lambda chain plasma cells (lambda chain restriction; *arrow*). (F) With Ig mu heavy chain immunostaining, there is a predominance of IgM type in plasmacytic and plasma cells (*arrow*). (C, Hematoxylin eosin stain; original magnification ×40; D, original magnification ×100; E–F, original magnification ×40.)

rheumatoid arthritis, or in association with *Epstein-Barr virus* (EBV) infection.[56–65] Less than 50% of patients are symptomatic, with nonspecific symptoms, including cough, dyspnea, and chest pain. Unlike the situation with other lymphomas, systemic signs such as fever, swelling, and weight loss are uncommon. Association with IgM or IgG blood monoclonal gammopathy is observed in 30% of cases.

Radiologically, MALT lymphoma exhibits three imaging patterns on chest radiography and *computed tomography* (CT), which are challenging for differential diagnosis: (1) The most frequent and suggestive is the pneumonia-like alveolar consolidation with air bronchograms (see Fig. 78.3A–B), typically localized in the middle lobe; (2) a tumor-like appearance with a solitary circumscribed nodular opacity (30% of cases) (eFig. 78.9) and possible central air bronchogram; and (3) the "infiltrative" pattern with diffuse, poorly defined ground-glass opacities (eFig. 78.10), assumed to represent early-stage disease before tumor cells invade alveolar spaces.[56–66] The combination of a nodular opacity with peripheral peribronchovascular ground-glass attenuation halo is common. Pleural effusion is unusual. Multiple cystic lesions may be observed, which may be associated with light chain deposition disease. Hence differentiating MALT from infection, cancer, or interstitial diseases may be challenging, leading to frequent misdiagnosis if a complete workup is not conducted.

About one-third of MALT lymphomas are multifocal at the time of diagnosis, a presentation that may hamper the determination of the primary pulmonary origin of the disease.[67] Pulmonary MALT lymphomas are associated with tumor locations in the gastric mucosa in 10–20% of patients and in the bone marrow in 15–20% of patients. Gastroscopy and bone marrow biopsy are then recommended; FDG-PET imaging may not be sensitive enough to exclude extrathoracic disease. The Ann Arbor staging system, although not designed for extranodal lymphoma, may be applied in pulmonary MALT lymphoma, which would be staged as IE (one site, extranodal) in case of lung unilateral or bilateral involvement, IIE (two sites, both above the diaphragm, extranodal) in case of hilar or mediastinal lymph nodes, or IV in case of multiple sites.

Pathologic diagnosis actually requires a large, possibly surgical lung biopsy, because cytologic examination of bronchoalveolar lavage or fine-needle biopsy may show the CD20-positive B cell infiltration but fail to exclude differential diagnoses, such as reactional lymphoid proliferation, follicular bronchiolitis, or lymphoid interstitial pneumonia. *MALT1* gene rearrangements may be identified on bronchoalveolar lavage.[53,62]

Therapeutic options are based on the degree of tumor extension. Surgical resection ensures both the diagnosis and the treatment of nodular lesions, but MALT-type histology is usually unexpected when approaching a lesion thought to be NSCLC. In asymptomatic patients, a watch-and-wait attitude may be preferred to aggressive treatment. In the majority of patients, MALT lymphoma requires more aggressive management, and the standard of care is the combination of rituximab (an anti-CD20 antibody) with chlorambucil.[67] Several alternative options have been described, from single-agent therapy with chlorambucil, fludarabine, or rituximab to combined cytotoxic agents used for diffuse large B cell lymphomas.[68] Whether genomic profiles should drive the chemotherapy regimen is unclear,

even if rituximab alone may be effective in case of t(11;18) translocation.[69]

Prognosis of MALT lymphomas is usually excellent, with an indolent and localized prolonged course and response to chemotherapy. Historical series reported 5-year survival rates greater than 80%, and the more recent availability of rituximab may improve these results. Still, patients may present with recurrences leading to sequential treatment; parenchymal or bronchial sequelae may ensue, leading to chronic obstructive disease or pulmonary fibrosis. Local and systemic recurrences develop in about 50% of cases but are usually controllable with chemotherapy. Evolution to high-grade B cell lymphoma is seen in less than 5% of cases.[65,67] Young age at diagnosis is the most significant favorable prognostic factor.

LYMPHOMATOID GRANULOMATOSIS

Lymphomatoid granulomatosis (LG), previously called "angiocentric lymphoma," is a malignant B cell angiocentric and angiodestructive lymphoproliferative disorder.[9,70] For a long time, LG was considered an inflammatory granulomatous disease owing to a presentation similar to other granulomatoses, such as granulomatosis with polyangiitis and eosinophilic granulomatosis with polyangiitis. Now, LG is recognized as a true EBV-related lymphoid malignancy. Differential diagnosis also includes allergic bronchopulmonary aspergillosis. The lung is the most frequent location, but the disease may also involve the brain, the skin, and the liver.[70–72]

Pathologically, LG forms multiple and confluent nodules composed of an atypical, angiocentric, and polymorphous lymphoid infiltration involving the vascular walls, from the subendothelium to the adventitial zones, with focal lumen obliteration. By immunohistochemistry, these lymphoid cells are characterized mostly as $CD4^+$ T lymphocytes, with scattered atypical cells of B phenotype.[9] Large B cells are infected with EBV in 65% of cases, a fact that correlates with the grade of the lesion. Pulmonary biopsy is required in most cases to exclude other granulomatoses.

LG arises in middle-aged patients between 40 and 50 years of age, with a male predominance.[70,71] Nearly all patients present with respiratory and systemic symptoms, consisting of cough, dyspnea, hemoptysis, chest pain, fever, and weight loss. Peripheral and mediastinal lymphadenopathy is absent. Prolonged immunosuppression is a frequent underlying condition. Hypereosinophilia may be observed in the blood and/or in the bronchioalveolar lavage. The typical radiologic presentation consists of multiple smooth bilateral nodules ranging from 2 to 10 cm, mainly localized in the lower lobes, exhibiting a peribronchovascular pattern, and mimicking multiple metastases (eFigs. 78.11 and 78.12). As in other granulomatoses, convergent nodules may migrate and form cavitated pseudotumoral masses.

LG is considered a low-grade or early-stage lymphoma, and a histopathologic grading system has been developed based on the degree of cellular atypia and necrosis, to predict the risk of evolution to high-grade lymphoma and to select patients for early aggressive treatment.[73] Chemotherapy based on the use of cyclophosphamide with high-dose steroids is the most frequently reported treatment. The additional use of rituximab has been reported.[72] The overall prognosis is grim, with a 5-year survival of 30–40% owing to progression to nodal diffuse aggressive lymphoma in 20–50% of patients.

OTHER LYMPHOMAS AND LYMPHOPROLIFERATIVE DISEASES

Other primary pulmonary malignant lymphoproliferative diseases are very rare and include high-grade, diffuse, large B cell lymphoma; intravascular large cell lymphoma; Hodgkin lymphoma; and plasmacytoma.

Primary pulmonary, diffuse, large B cell lymphoma is likely underrecognized owing to its rapid spread to mediastinal nodes and other extrathoracic sites, which may hide its pulmonary origin.[63] Primary pulmonary high-grade B cell lymphomas typically develop in immunocompetent patients in their sixth to seventh decade. Patients often present with marked respiratory and systemic symptoms. Radiologic studies usually show multiple well-defined rounded solid masses of various sizes, more frequently in the subpleural areas of the lower lobes (see eFigs. 90.33 to 90.35).[74] In younger patients, large B cell lymphoma may be caused by latent EBV infection, which may develop after drug-induced immunosuppression or after human immunodeficiency virus–related immunosuppression. In those patients, reduction of immunosuppression or active antiretroviral therapy, respectively, may lead to the near disappearance of primary pulmonary high-grade lymphomas. Chemotherapy is based on the same multi-agent regimens as those used in high-grade nodal lymphomas; new agents are under development.[75] The overall prognosis is much worse than for MALT lymphoma, with a 5-year survival less than 20%.

Intravascular large cell lymphoma is a variant of non-Hodgkin lymphoma, in which neoplastic lymphoid cells proliferate within the lumen of small- and intermediate-sized blood vessels, resulting in thrombotic and ischemic complications.[9] Clinical manifestations are multiple, but lymphadenopathy is usually absent. Pulmonary imaging features include bilateral ground-glass opacities and/or sometimes migratory atelectatic shadows (eFig. 78.13).

Primary pulmonary plasmacytoma is a solitary lesion composed exclusively of atypical monoclonal plasmocytes, possibly associated with amyloid deposition, without evidence of extrapulmonary myelomatous disease.[76] Again, the apparent decrease of the incidence of primary pulmonary plasmacytoma may be related to the increased sensitivity of biologic and imaging studies for the detection of primary extrapulmonary disease. Moreover, about one-third of patients operated on for pulmonary plasmacytoma were reported to present with multiple myeloma in following years.[76] Surgical resection is, however, recommended for solitary tumors, with a 5-year survival of 60%.[76]

PRIMARY PULMONARY SARCOMAS

Primary pulmonary sarcomas account for 20% of all primary rare lung malignancies and comprise (1) parenchymal lung sarcomas, which usually present as a lung mass, and (2) pulmonary vascular sarcomas, which include pulmonary

artery sarcomas and may mimic chronic pulmonary embolism, and small vessel sarcomas, which may produce interstitial lung disease.

PARENCHYMAL SARCOMAS

Primary lung parenchymal sarcomas show identical pathologic subtypes to those of their soft tissue counterparts, with a wide spectrum of differentiation from low to high grade. Leiomyosarcoma is the most frequent primary lung sarcoma,[77–79] followed by synovial sarcoma.

As in their soft tissue counterparts, pathologic diagnosis relies on morphologic and immunohistochemical features as well as identification of chromosomal translocations such as t(X;18)(p11.2;q11.2), pathognomonic of synovial sarcoma,[9] resulting in the fusion of two genes, *SYT-SSX1* and *SYT-SSX2*. Other subtypes include pleomorphic sarcoma as well as osteosarcoma and chondrosarcoma. Because most mesenchymal malignant tumors have a benign counterpart, pathologic examination must first evaluate the grade of the lesion, according to the three-grade system of the French Federation of Cancer Centers Sarcoma Group[80] and, second, rule out other epithelial tumors with sarcomatoid differentiation, such as sarcomatoid carcinoma, pneumoblastoma, or myofibroblastic tumors. Differential diagnosis also includes the very rare "benign" metastases from uterus (metastasizing leiomyoma) or bone (giant cell tumor).

Compared with their soft tissue counterparts, primary pulmonary sarcomas present in older patients, mainly in the sixth to eighth decade.[77–83] Clinical symptoms are nonspecific and usually consist of cough, dyspnea, and hemoptysis, depending on the size and the location of the lesions. Invasion of the chest wall may be frequent, leading to discussions about the primary parenchymal nature of the lesion. The incidence of radiation-induced sarcoma has decreased because cobalt-based radiotherapy has been abandoned. Unlike metastatic sarcoma, primary pulmonary sarcoma presents as a solitary lesion (eFigs. 78.14 and 78.15), with heterogeneous cystic, necrotic, or hemorrhagic features but with a well-defined circumference. Size ranges from 4 to 25 cm (Fig. 78.4A). FDG-PET scan shows increased uptake (see Fig. 78.4B and eFig. 78.15D) and may be used to rule out primary soft tissue sarcoma metastatic to the lung; attention should be paid to performing full-body (i.e., from skull to foot) scanning. Tumor progression is mainly local, and mediastinal lymph node invasion and systemic metastases are infrequent at the time of diagnosis (<2%).

Surgery is the most effective initial treatment, and complete resection is obtained in 80% of cases.[77–83] Strategies developed in soft tissue sarcoma may not be applicable to primary lung sarcomas; for example, neoadjuvant chemotherapy, based on anthracycline and ifosfamide, is commonly used in soft tissue locations but has been disappointing in primary lung tumors.[84] In the case of unresectable lesions, chemoradiation may be the best therapeutic strategy. As in soft tissue sarcoma, the chemotherapeutic drug trabectedin may be an option for second-line treatment. Prognosis mainly depends on the completeness of initial surgical resection, which, when combined with the grade of the lesion, is the best predictive factor of recurrence-free and overall survival. As is the case for all rare pulmonary tumors, surgery should be discussed in expert multidisciplinary teams. Overall 5-year survival varies from 30–50%.

VASCULAR SARCOMAS

Primary pulmonary vascular sarcomas include pulmonary artery sarcomas and small vessel sarcomas, that is, epithelioid hemangioendothelioma and its high-grade counterpart, angiosarcoma.[9]

Pulmonary artery sarcoma presents as an endoluminal polypoid or nodular mass, which spreads along the intima of the pulmonary artery. Histologic features consist of an undifferentiated spindle cell proliferation, with marked cellular pleomorphism and high mitotic index.[9] Leiomyosarcoma is the most frequent subtype (60% of cases).[85,86] Pulmonary artery sarcomas mainly develop in patients in their fifth to sixth decade.[85–87] Symptoms may mimic pulmonary embolism, with dyspnea, chest pain, cough, and hemoptysis. Failure of anticoagulants in this setting, as well as the presence of symptoms of weight loss and fever (in 40% of cases), may also suggest the diagnosis. Imaging findings also help differentiate between pulmonary artery sarcoma and pulmonary embolism. CT scanning may show a polypoid filling defect in the pulmonary artery, but, in contrast to thromboembolic disease, sarcoma forms a contiguously soft, smooth, tapering tissue, with possible

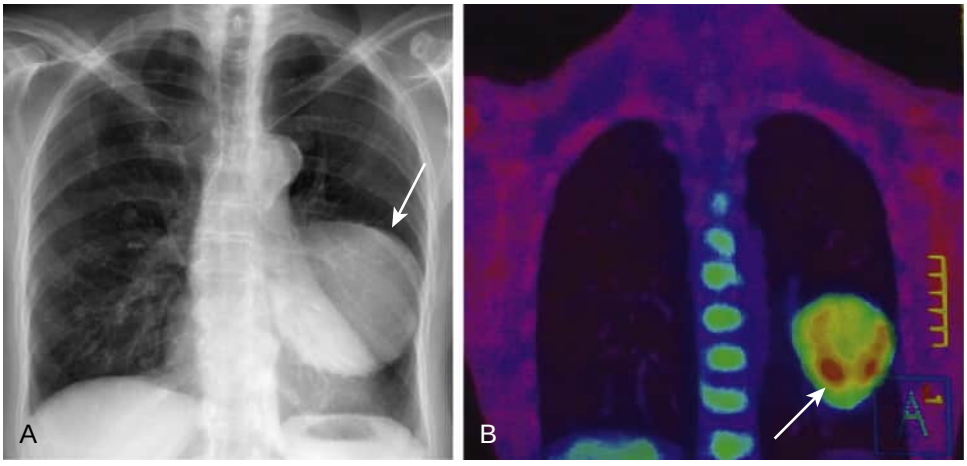

Figure 78.4 Primary pulmonary leiomyosarcoma. (A) Chest radiograph shows a large circumscribed homogeneous mass in the left lung (*arrow*). (B) Coronal positron emission tomography shows marked hypermetabolism within the lesion (*arrow*).

extravascular nodular spread in the parenchyma (40% of cases) (Fig. 78.5A, eFig. 78.16, and Video 78.1) and localized ground-glass opacities (see Fig. 78.5B).[86,87] Sarcoma also presents with a heterogeneous appearance, including areas of necrosis and hemorrhage, and with intense hyperactivity on FDG-PET scanning (see eFig. 78.16F–G). *Magnetic resonance imaging* (MRI) shows intermediate to mildly increased signal on T1-weighted images, often with heterogenous enhancement (eFig. 78.17), and T2-weighted images show intermediate to diminished signal relative to skeletal muscle. Furthermore, the intravascular mass may enhance, a feature not typically encountered with uncomplicated thromboembolic disease. Surgery is the only potentially curative treatment and, even if performed emergently in the setting of acute right-sided heart failure, allows resectability in 60–75% of cases[85–88] (see Fig. 78.5C). Heart and lung transplantation may be an alternative option for unresectable tumors but has rarely been reported. A slight improvement of overall survival has also been reported after adjuvant chemotherapy and/or radiotherapy. Contrary to soft tissue sarcoma, prognosis is mainly related to tumor location, because half of the patients die as a result of the progressive obstruction of the pulmonary trunk.[88] In case of recurrence, reoperation is feasible in 30% of cases; radiation therapy together with chemotherapy may be effective. However, in recent series, overall median survival is as low as 6 to 12 months (eFig. 78.18).[85–88]

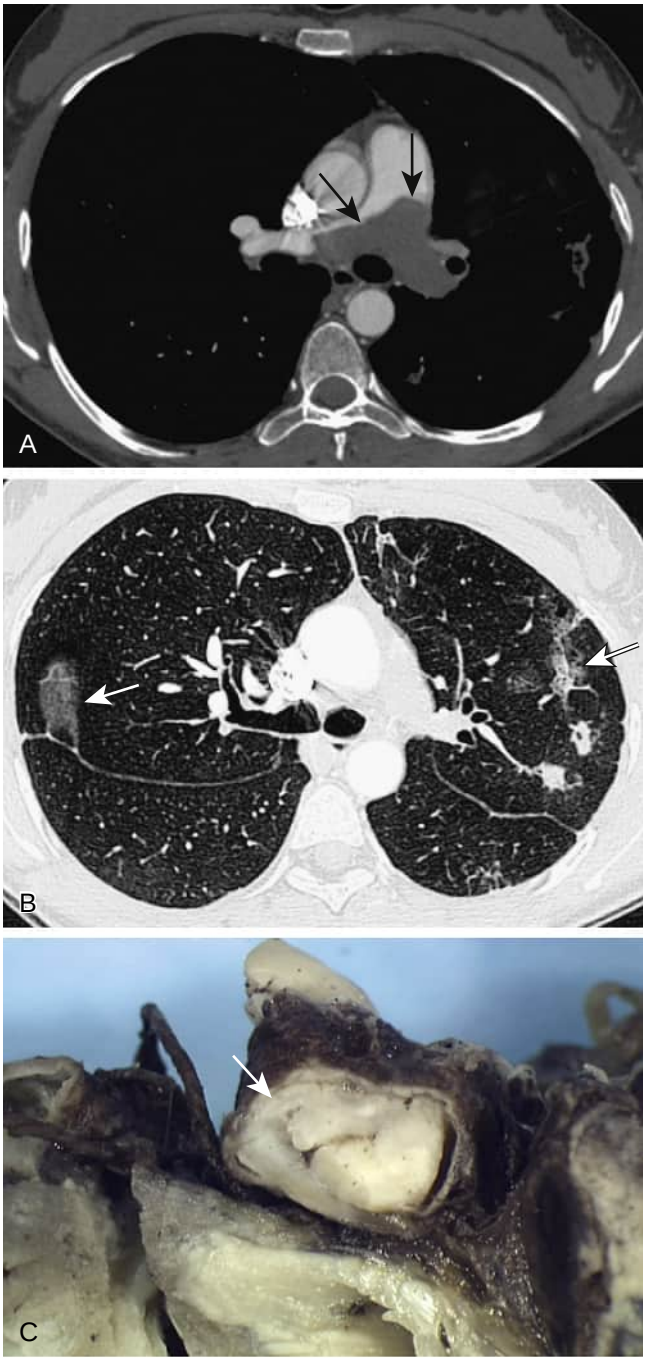

Figure 78.5 Pulmonary artery sarcoma. (A) Computed tomography displayed in soft tissue windows shows a mass filling the pulmonary artery lumen (*arrows*). (B) Computed tomography displayed in lung windows shows peripheral, irregular alveolar opacities (*arrows*) without pleural contact. (C) Specimen at pneumonectomy shows the infiltration of the pulmonary artery wall by the tumor (*arrow*).

Epithelioid hemangioendothelioma (EHE) is a low- to intermediate-grade mixed epithelioid, endothelial, and vascular tumor.[89–92] Lung is the most frequent extrahepatic location (10% of cases); EHE can also arise from the liver (63% of cases), the bone (8% of cases), and the skin (6% of cases).[89–92] EHE is characterized by polypoid nodules, with a central sclerotic paucicellular zone, growing into the alveolar spaces with an angiocentric distribution. Lymphangitic spread may mimic metastatic carcinoma. Around 90% of EHEs are caused by the fusion of *transcriptional coactivator with a PDZ-motif* (TAZ) with *calmodulin-binding transcription activator 1* (CAMTA1), a central nervous system–specific transcription activator; the 10% of EHEs that lack the *TAZ-CAMTA1* fusion instead have a fusion of *yes-associated protein* (YAP) and *transcription factor E3* (TFE3) genes *(YAP-TFE3)*.[93] EBV RNA sequences are detected in 90% of cases. Overlapping entities with IgG4-related disease have been described. Clinically, 80% of cases of EHE are diagnosed in white females.[89–92] The tumor is asymptomatic in 50% of cases; when present, symptoms are nonspecific and include pleuritic chest pain, nonproductive cough, dyspnea, and rarely hemoptysis. By CT imaging, EHE appears either with bilateral, slow-growing, perivascular, multiple nodules, usually located adjacent to small vessels or bronchi, or with predominant infiltrative ground-glass opacities (eFig. 78.19) with a micronodular pattern, mimicking carcinomatous lymphangitis. EHE nodules usually range from 3 to 50 mm, and their number varies from 10 to 20 lesions.[89–92] Nodules in patients with EHE may show increased uptake on FDG-PET scan. Although there are a few reports of spontaneous remission, the complete resection of all pulmonary nodules is the only curative treatment of EHE. Surgery remains effective even in cases of localized recurrence. In contrast, EHE is generally insensitive to chemotherapy (cisplatin based) or radiotherapy. Treatment with rituximab or antiangiogenic kinase inhibitors, such as sorafenib or bevacizumab, have been reported to be effective in isolated case reports.[94,95] In most cases, EHE is a slow-growing tumor that rarely metastasizes and is associated with a median survival of 5 to 6 years. Endobronchial spread, pleural effusion, and extended endovascular disease have been identified as unfavorable prognostic factors.

Angiosarcoma is a high-grade primary pulmonary vascular sarcoma considered a counterpart of EHE. However, no direct transformation from EHE to angiosarcoma has been reported yet.[96] Clinical features of angiosarcoma are similar to EHE, but massive hemoptysis is more frequent. Radiologic features of angiosarcoma include multiple nodules with a typical surrounding halo of ground-glass attenuation, with a specific cauliflower-like appearance on T2-weighted MRI.[97] This aspect may be shared by other disorders, including malignancies (e.g., adenocarcinoma with lepidic pattern [e.g., bronchioloalveolar carcinoma], metastatic sarcomas, choriocarcinoma, melanoma, lymphoma), infectious diseases (e.g., mycobacteriosis, aspergillosis, cytomegalovirus infection), granulomatosis with polyangiitis, and eosinophilic conditions. Distinguishing primary pulmonary angiosarcoma from extrathoracic angiosarcoma metastatic to the lung is crucial. Management of angiosarcoma is not established, because surgical resection is rarely possible owing to local and regional invasion, and because radiotherapy and chemotherapy are poorly effective, as seen for angiosarcoma in other locations. In immunocompromised patients, reduction of immunosuppressive agents may decrease the burden of the disease.

PSEUDOTUMORS AND BORDERLINE ENTITIES

Pseudotumors represent a wide range of etiologic, pathologic, and clinical-radiologic disorders that all share some degree of reactive inflammation and may present with some cancer-related biologic hallmarks. Pseudotumors may mimic the clinical and radiologic features of various intrathoracic diseases.

INFLAMMATORY MYOFIBROBLASTIC TUMOR

Inflammatory myofibroblastic tumor (IMT) is the most representative entity of the pulmonary pseudotumors[6,7,98] and encompasses a wide spectrum of lesions previously called inflammatory pseudotumor, fibroma, fibroxanthoma, fibrous histiocytoma, plasma cell/mast cell/solitary granuloma, plasma cell histiocytoma complex, or pseudosarcomatous tumor.

IMT appears as an intraparenchymatous well-circumscribed mass of variable size.[98–100] Histologically, the tumor is made of irregular proliferation of fibroblasts and myofibroblasts intermixed with an infiltrate of inflammatory cells, mainly lymphocytes and plasma cells. Three distinct histologic patterns are usually recognized[6,7,9,98–100]:

1. Plasma cell variant, also called the lymphoplasmacytic variant, which is composed of inflammatory myxoid proliferation with fascicles of spindled fibroblasts or myofibroblasts, abundant lymphocytes and plasma cells, and minimal fibrous connective tissue.
2. Fibrohistiocytic type, which appears as a compact spindle-cell pattern simulating fibrous histiocytoma characterized by a myxoid proliferation of fibroblasts and myofibroblasts associated with polyclonal plasma cells, xanthoma cells, and rare giant cells.
3. Organizing pneumonia-like type, which has a hypocellular pattern characterized by dense collagen with sparse spindle cells.

The proliferating myofibroblastic cells show no cellular atypia, no necrosis, and only rare mitotic figures. The myofibroblastic cells usually stain for vimentin and smooth muscle actin.

The concept of IMT as a proliferating neoplasm has been questioned.[7] More recently, clonal gene rearrangements have been observed,[101–103] especially involving the *anaplastic lymphoma kinase (ALK)* gene. *ALK* overexpression is observed in 40–70% of IMTs at immunohistochemistry, but *ALK* rearrangement is identified in less than 30% of pulmonary IMT cases and most frequently consists of t(1;2)(q21;p23) translocation, implicating the tropomyosin 3 gene.[101–103] Other translocations have been reported.[101–103] Given the oncogenic nature of *ALK* activation, these data lead some authors to consider IMT as a true malignant neoplasm; *ROS1* translocation has also been described.[103] Other elements further reinforce this concept, including the presence of vascular invasion, the local recurrence rate as high as 25%, and the existence of multifocal lesions.

IMT is also a consequence of immunologic disorders, which consist of EBV and human herpesvirus 8 infection of myofibroblastic cells[6,104] and, of more relevance, IgG4 expression in polyclonal plasma cells extracted from intrathoracic IMTs; such proliferation of IgG4-positive cells has also been associated with autoimmune disorders, including sclerosing pancreatitis and retroperitoneal and mediastinal fibrosis.[105] IMTs may then also be part of IgG4-related disease. Overlap exists between IMT, IgG4-related disorders, and prototypic high-grade inflammatory fibrosarcoma that exhibits prominent cellular atypias and necrosis.

Pulmonary IMTs usually appear before the fourth decade, accounting for more than 50% of pulmonary tumors in children.[6,98–100] IMT appears as a solitary, well-circumscribed, peripheral mass, ranging from 2 to 15 cm in size (Fig. 78.6 and eFig. 78.20). Contrary to its presentation at extrathoracic locations, the pulmonary IMT is usually solitary.[106] Calcifications are observed in 15% of cases. The usual stability

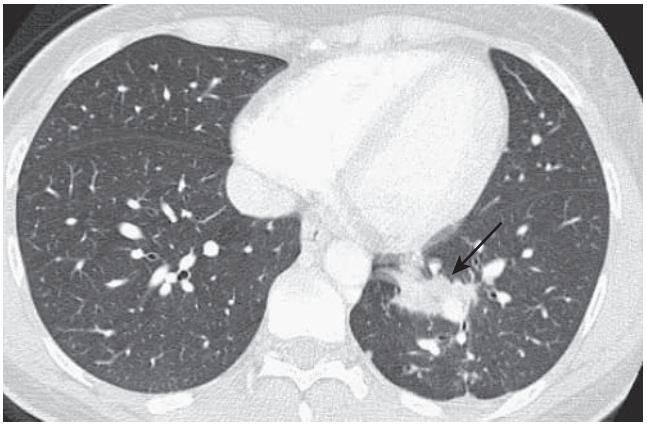

Figure 78.6 Inflammatory myofibroblastic tumor. Computed tomography performed for a 31-year-old man who presented with persistent cough and hemoptysis after infectious pneumonia. A poorly defined infiltrative-appearing opacity is present in the posterior and medial left lower lobe (*arrow*). Percutaneous transthoracic needle biopsy showed polymorphic inflammation without tumor cells.

in size over time is an important imaging feature. Mediastinal invasion is frequent; multifocal and bilateral IMTs are exceptional (eFig. 78.21) and are considered as overlapping forms of low-grade fibrosarcoma or malignant fibrous histiocytoma. IMTs are usually hypermetabolic on FDG-PET scan.

Even if historically considered a benign lesion with possible spontaneous regression, IMT is usually treated by surgical resection due to its tendency to grow, to provoke local complications, including hemoptysis and infection, and to relapse occasionally with lung/pleural and/or mediastinal invasion (15–25% of cases and 3–5% of cases, respectively).[107,108] The need for adjuvant treatment in case of incomplete resection has not been evaluated. In nonoperable patients, focal conformation radiotherapy or corticosteroids may represent an alternative. Corticosteroids are reported to induce objective responses in as many as 50% of cases, especially in predominantly plasma-cell and IgG4-positive tumors. In recurrent or multifocal lesions, chemotherapy may use the same regimens as for soft tissue sarcomas. ALK inhibitors are effective in case of *ALK*-rearranged IMT.[109]

RESPIRATORY TRACT PAPILLOMATOSIS

Some lesions thought to be benign may have a borderline presentation and outcome. One relevant example is recurrent respiratory papillomatosis. Papillomas usually present in the upper respiratory tract but may rarely spread to the lung parenchyma (<5% of cases).[110,111] Histologically, squamous papillomas are usually exophytic with an epithelial layer covering a central fibrovascular core that forms a frondlike architecture protruding into the lumen of the airway. Papillomas may exhibit imaging features similar to those of lung cancer, including heterogeneous, cavitating, or poorly defined masses.

Pulmonary papillomas may be solitary or multiple (eFigs. 78.22 to 78.25); if multiple, these are associated with multiple papillomas of the upper respiratory and aerodigestive tract. As in other locations, the pathogenesis of squamous papillomas is linked with *human papillomavirus* (HPV) infection, often acquired at birth.[112] Specifically, HPV type 11 infection has been reported to bear a high risk of transformation of papilloma to squamous cell carcinoma (Fig. 78.7 and see eFig. 78.25).[113] On a molecular basis, loss of the tumor suppressor genes *TP53, RB,* and *P21* has been reported in squamous cell carcinomas originating from papillomas. Mutation of the *HPV-11* gene with duplication of promoter and oncogene regions has been described in a case responding to vorinostat.[114] FDG-PET scanning may not be useful given the mild hypermetabolism of high-grade papillomas. Given this uncertain malignant potential and the difficult differential diagnosis with lung cancer, complete resection of papillomas is recommended if possible; complete resection may not be possible or may only be temporizing (see eFig. 78.25), in the setting of multiple and bilateral lesions (see Fig. 78.7 and eFigs. 78.22 to 78.24). The role of vaccines, antiangiogenic agents, and antiviral treatment in preventing evolution of pulmonary papillomas is unclear.

PULMONARY LANGERHANS CELL HISTIOCYTOSIS (See Chapter 95)

Pulmonary Langerhans cell histiocytosis (PLCH) is a heterogeneous disease defined by the proliferation of Langerhans cells, corresponding to CD1a-positive histiocytes exhibiting Birbeck granules on electron microscopy.[115–118] These cells of dendritic lineage derive from CD34-positive bone marrow stem cells. If the lung is the sole location of the disease, it is called pulmonary LCH. In less than 15% of cases, LCH is associated with multisystem disease, corresponding to acute disseminated LCH involving the lung, bone, skin, and pituitary gland.[117] The pathogenic concepts about LCH mostly involve an uncontrolled immune response to a yet undetermined stimulus, leading to the recruitment of Langerhans cells in the lung parenchyma. Smoking exposure is found in the majority of patients developing pulmonary LCH and is thought to stimulate this process in the bronchiolar epithelium.[119] The true nature of LCH remains elusive. Strongly favoring the hypothesis of a neoplastic disorder is the observation that Langerhans cells, isolated from patients with either pulmonary or disseminated LCH, are clonal[120] and may harbor activating *BRAF* mutations, as well as mutation of the *MAP2K1* pathway.[120–122] However, the limited proliferation of Langerhans cells, the absence of cellular atypia, the low number of Langerhans cells in high-stage lesions, and the possibility of spontaneous regression argue against a truly cancerous nature of LCH.

Pathologically, LCH lesions are made of Langerhans cells that proliferate and aggregate to form stellate nodules in the interstitium, with a bronchiolocentric pattern and linear distal and proximal spread. High-stage lesions are characterized by disappearance of Langerhans cells, increased amounts of fibrosis, and cavitation of the nodules leading to cyst formation.[115,116]

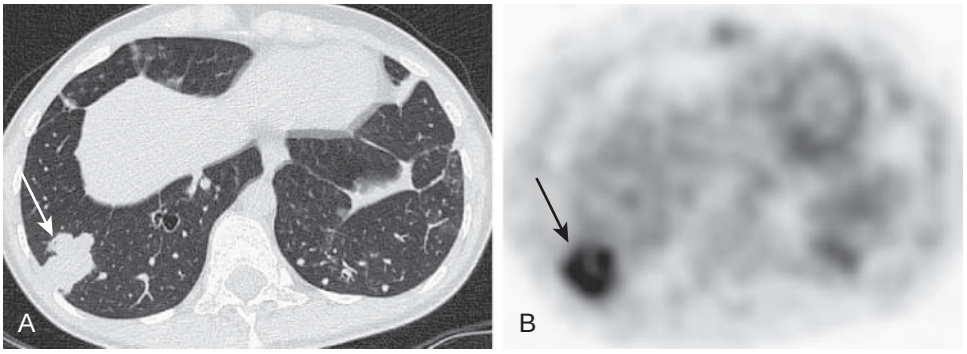

Figure 78.7 Pulmonary squamous cell carcinoma development in a patient with papillomatosis. (A) Chest computed tomography performed for a 32-year-old woman with a history of upper and lower respiratory tract papillomatosis and new complaints of worsening cough and weight loss shows a subpleural mass in the right lower lobe (*arrow*). A thin-walled cyst is also present within the right lower lobe, and small centrilobular nodules are seen in the left lower lobe. (B) Positron emission tomography shows increased metabolism. Percutaneous transthoracic needle biopsy showed squamous cell carcinoma.

Clinically, pulmonary LCH develops in young smokers who present with nonspecific respiratory symptoms, including dyspnea, cough, and chest pain. Pneumothorax may herald the disease in 15% of patients; 10–25% of patients are asymptomatic. The most typical imaging feature is the combination of pulmonary multiple cysts and micronodules sparing the lower zones of the lung. Nodules, ranging from 5 mm to 2 cm in size, are centrilobular and may be solid or cavitated (eFig. 78.26A–C) with smooth or irregular margins. LCH is an active process with predominant nodular aspect at early stages of the disease (see eFig. 78.26A–B), evolving to cavitated nodules, cysts of variable wall thickness (see eFig. 78.26C), and confluent cystic lesions over time (see eFig. 78.26D). Lesions of different age are usually observed. Rarely, pulmonary LCH presents as a single nodule, localized consolidation, or mediastinal disease. Increased uptake on FDG-PET scanning is frequent.

Smoking cessation may lead to regression in as many as 25% of patients. No other treatment has been confirmed to be useful in pulmonary LCH, which may also regress spontaneously. Patients with progressive or multiorgan disease may benefit from chemotherapy with cladribine, which produced a 75% objective response rate in a landmark study of 13 patients[123,124]; cladribine may also reduce the growth and development of cystic lesions. *BRAF* mutations are associated with resistance to chemotherapy but may predict the efficacy of RAF/MEK inhibitors. Supporting the neoplastic hypothesis, pulmonary LCH can recur after lung transplantation.

LESSONS LEARNED FOR THE MANAGEMENT OF RARE PRIMARY PULMONARY TUMORS

CLINICAL STRATEGY

When facing a pulmonary tumor lesion, the primary hypothesis for clinicians is that the lesion represents lung cancer, the main differential diagnosis of rare pulmonary malignancies. The absence of a tobacco-smoking history, especially in men, is more frequently seen for rare lung tumors and pseudotumors than for bronchogenic carcinoma (60% vs. 15%, respectively). Young age at diagnosis is another characteristic to consider because greater than 50% of rare tumors present before the fourth decade. Given the frequent initial suspicion of lung cancer, most patients undergo complete oncologic workup. FDG-PET scan is usually not helpful for differentiating rare primary lung tumors from NSCLC. Preoperative biopsies and intraoperative frozen sections may not be sufficiently representative of the tumor to ensure accurate histopathologic diagnosis, especially in biphasic or composite tumors, for which small-size samples may identify only one cellular component. Frozen specimen collection and storage is mandatory to preserve the tumor for additional analyses.

DISTINGUISHING PRIMARY TUMORS FROM METASTASES

In making the diagnosis of a rare primary lung tumor, one must also consider the fact that most lung tumors with unusual histology represent metastases from extrapulmonary tumors, not primary tumors. The main criteria favoring metastases include a prior history of extrathoracic tumor and the finding of multiple pulmonary lesions. The primary pulmonary nature of some rare tumors may be difficult to establish, either because of early systemic spread, as for EHE, which presents with synchronous pulmonary and hepatic lesions in 20% of cases or because of an ectopic origin, as for melanoma or Hodgkin disease, for which a primary pulmonary origin is highly controversial.

MOLECULAR PROFILING

Sophisticated molecular studies, including flow cytometry and genomic and cytogenetic analyses, may have a critical role in making the accurate diagnosis of rare pulmonary tumors because morphology may not be sufficient for classification and for evaluation of tumor grade. This is especially mandatory for lymphoma, IMT, or sarcomas. Systematic high-throughput genomic analyses, including DNA/RNA sequencing and possibly whole-exome sequencing, is also increasingly used to identify deregulated molecular pathways, which is not possible based on targeted, panel-based analyses designed for frequent tumors; this may lead to discussions of potential treatment strategies based on targeted agents.[125] Family history is of interest to understand possible predispositions and occupational/professional questionnaires to identify potential carcinogens; so far, limited data are available in those areas for rare pulmonary tumors.

TREATMENT PRINCIPLES

In many cases with a localized lesion in the lung parenchyma, initial surgical resection provides the correct diagnosis and the first step of the therapy. However, preoperative diagnosis remains important for specific subtypes, such as lymphoma, for which extensive resection is not warranted, and for sarcoma, which usually does not spread to the mediastinal lymph nodes and thus would not require nodal resection. Surgical biopsy may be required to obtain sufficient tissue material for extensive pathologic and molecular diagnoses, especially when clinical-radiologic presentation is not typical of neoplastic or non-neoplastic disease.

Finally, three main clinical scenarios may arise in the course of evaluation of patients with rare lung tumors:

1. Surgical resection of a tumor assumed to be lung cancer was complete, and pathologic examination disclosed an unusual histopathologic subtype, such as carcinoid or IMT. In this case, usually no adjuvant therapy is recommended; follow-up is adapted to fit the situation.
2. Specific clinical and radiologic signs led to recognition of a rare tumor, such as lymphoma or pulmonary artery sarcoma, followed by specific diagnostic and therapeutic management.
3. Surgery of a pulmonary mass initially thought to be lung cancer led to recognition of a rare tumor subtype for which the therapeutic and prognostic implications are unknown. In those cases, the decision for adjuvant treatment and follow-up is based either on a lung cancer

standard of care or on therapeutic strategies established for a similar tumor subtype in other locations, as is done for lymphoma and sarcoma.

In the absence of evidence-based recommendations, expert consensus is mandatory for selection of a specific therapeutic strategy, possibly based on strategies developed for lesions of similar histology arising in another anatomic location. As discussed, molecularly tailored treatment may be useful, and systematic high-throughput genomic analyses, including DNA/RNA sequencing, are recommended.[125] Also, these issues emphasize the need for multicenter collaboration to generate cohorts and to launch observational studies and clinical trials of rare lung tumors.

NETWORKS

More than their low frequency, the hallmarks of rare lung tumors may be the absence of comprehensive clinical data, the low number of specialized groups for the care of each tumor subtype, and the lack of specific therapeutic recommendations. More than 90% of rare lung tumor observations are published as case reports or small series including fewer than five patients.[1,7] Currently, only carcinoids and large cell neuroendocrine carcinoma, lymphomas, and some sarcomas, among the most frequent of the rare tumor subtypes, have been characterized regarding their clinical, molecular therapeutic, and prognostic features in large retrospective and prospective studies.

Meanwhile, patients with rare lung tumors, like many patients with cancer, tend to go through several stages of grief, including depression, uncertainty, hope, disappointment and, in most cases, physical degradation and social isolation. The rarity of the tumor may also enhance these feelings, owing to the relative lack of information and the increased feeling of isolation; the geographic disparity in access to specific care; the longer duration of the pretherapeutic workup; the involvement of multiple specialists; a feeling of injustice, especially in young and never-smoking patients; and the complex management undertaken in a state of uncertainty.[126] As a result, patients with rare lung tumors may not receive equal care and some may feel "orphaned," being incompletely integrated in the process of care of patients with the more frequent lung cancers.

Ultimately, the management of patients with rare pulmonary tumors requires continuous multidisciplinary expertise at each step of the disease. There has been a dramatic improvement in our knowledge in the last few years through the development of large databases, translational research programs, and clinical trials. Access to innovative strategies represents a major challenge because there is a lack of funding for clinical research in rare cancers, and their rarity precludes the design of robust clinical trials that could lead to specific approval of drugs. In this context, patient-centered initiatives, such as the establishment of dedicated networks, are warranted. International societies and patient advocacy groups provide infrastructure for global collaboration. There are many advantages to having strong regional groups working on the same issue; indeed, there may be regional differences in risk factors, susceptibility, management, and outcomes. The ability to address questions both regionally and globally is ideal to develop a full understanding of rare pulmonary tumors.

In Europe, the recent establishment of the European Reference Network EURACAN provides an infrastructure of more than 70 health care providers with a high level of multidisciplinary expertise for the diagnosis, management, and follow-up of patients with rare cancers, including rare thoracic tumors. The objectives of EURACAN include updating and assessment of current guidelines, development of educational programs, dissemination and communication with patients groups, and the establishment of research projects, from the diagnosis workup of the disease to the therapeutic strategies. Achieving the highest quality of patient care is the main objective of EURACAN, and a multidisciplinary tumor board is hosted by a pan-European online platform called the Clinical Patient Management System. The European network also provides an infrastructure for collaboration with diagnosis and pharmaceutical companies. One example may be the opening of dedicated cohorts in basket trials, in which patients with different tumors but with the same mutation or biomarker receive the same treatment. By using molecular characterization for assessing new drugs, the network allows a better identification of patients and facilitates the recruitment in the trials.

Key Points

- Rare lung tumors are mainly defined as uncommon lung tumors with unusual histology. Rare tumors account for less than 1% of all primary lung tumors, whereas they correspond to more than 100 different histologic entities.
- Rare lung tumors may mimic lung carcinoma or benign orphan lung diseases because they may share clinical, imaging, pathologic, and even molecular features. Awareness is the key to diagnosing rare pulmonary tumors.
- Some rare lung tumors are specific to the lung, whereas others represent tumors more frequently found in other organs and only rarely present in the lungs. Determining whether they are primary or metastatic is a major step in the diagnostic evaluation.
- The most frequent rare malignant primary lung tumors are—in decreasing order of frequency—carcinoid, mucosa-associated lymphoid tissue lymphoma, and sarcomatoid carcinomas.
- Sophisticated pathologic and molecular analyses studies have an increasingly critical role in diagnosis and in therapeutics. High-throughput sequencing is recommended for accurate diagnosis of tumors with complex histology and for deciphering molecular pathways of interest for targeted therapies.
- The management of patients with rare pulmonary tumors requires multidisciplinary expertise at every step of the disease. Dedicated networks are required to ensure high quality care and may provide an infrastructure for collaboration to improve diagnosis and treatment.

Key Readings

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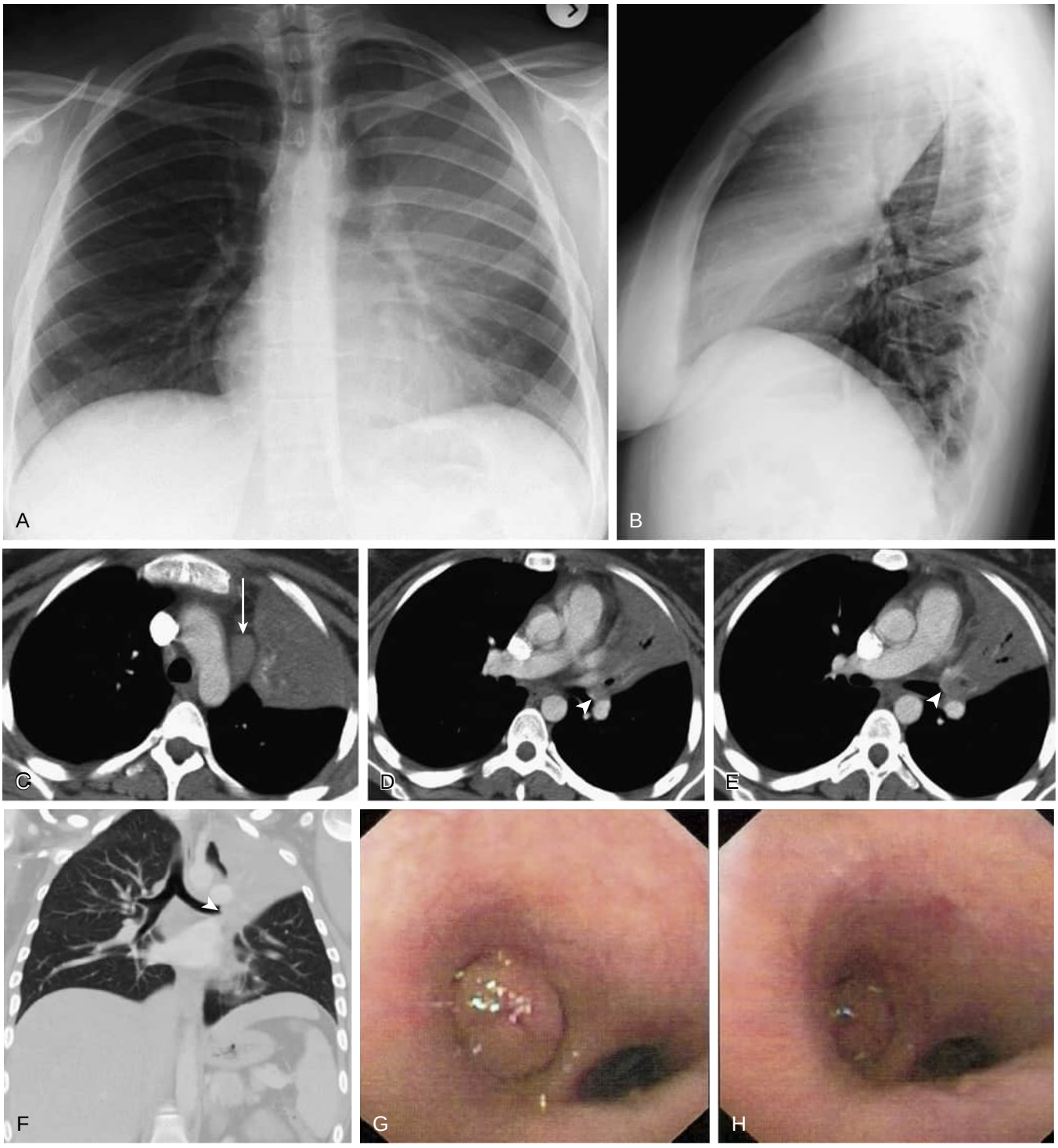
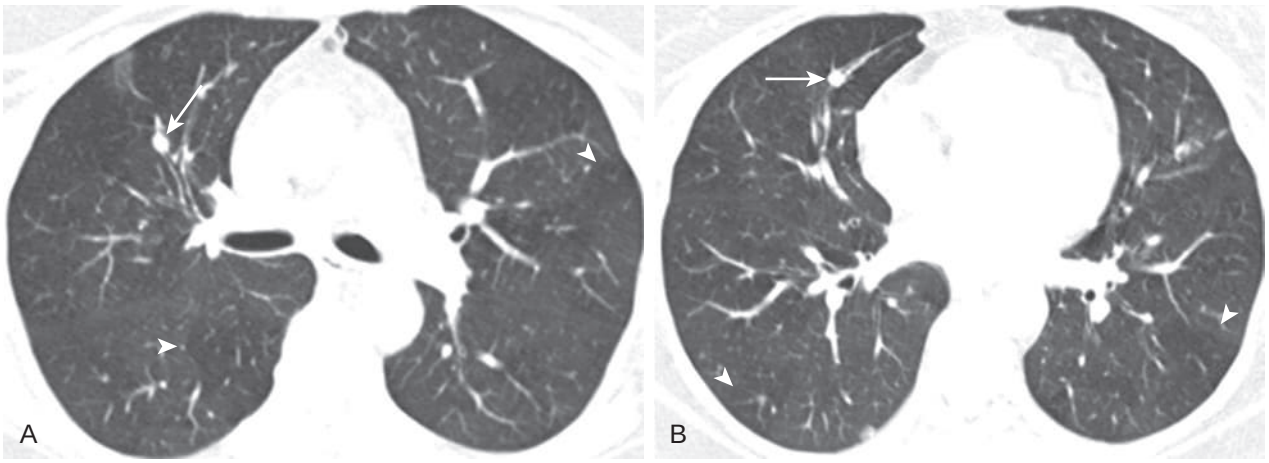
Complete reference list available at ExpertConsult.com.

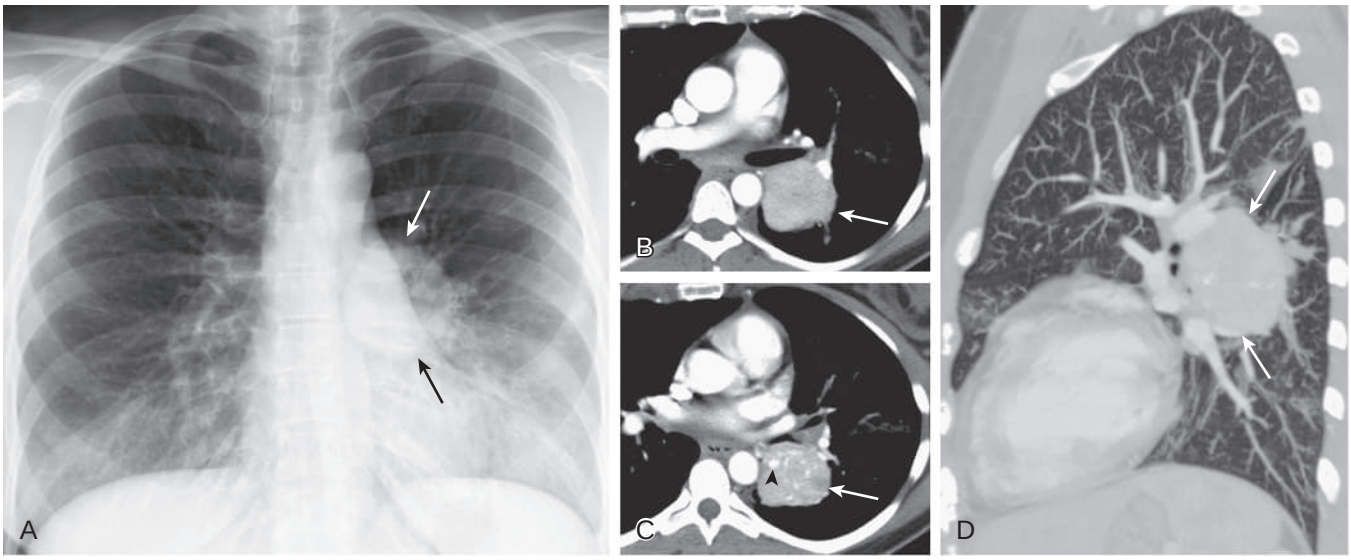
eFIGURE IMAGE GALLEY



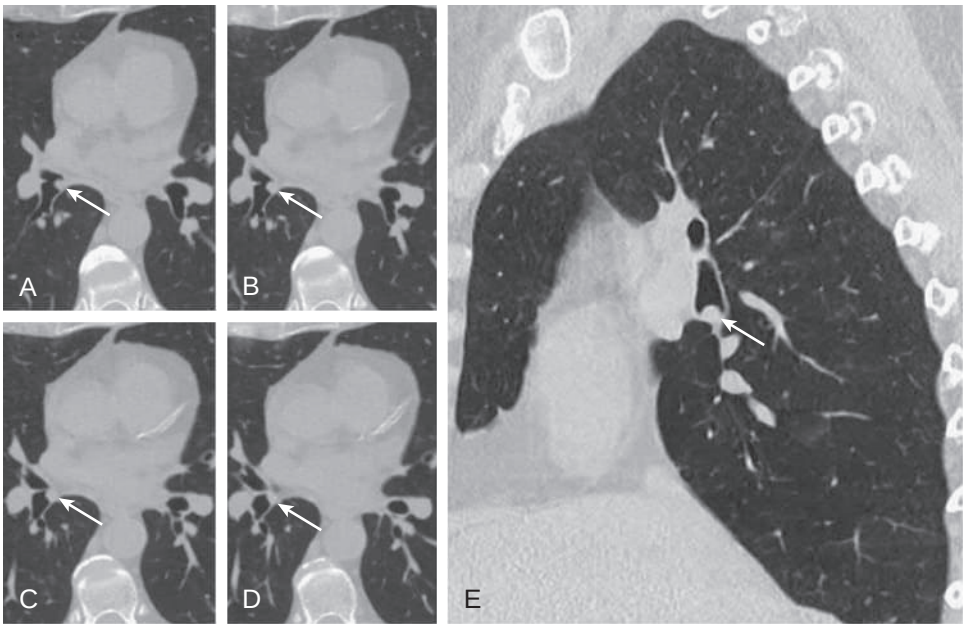
eFigure 78.1 Mucoepidermoid malignancy. Frontal (A) and lateral (B) chest radiographs in a young woman with mucoepidermoid malignancy show the classic chest radiographic appearance of left upper lobe collapse. Left para-aortic lymphadenopathy (C, *arrow*) is present. (C–E) Axial enhanced chest computed tomography scans displayed in soft tissue windows show left upper lobe collapse and reveal the obstructing lesion (D–E, *arrowhead*). (F) Coronal reformatted image displayed in an intermediate window again shows complete left upper lobe collapse and the obstructing lesion within the left upper lobe bronchus (*arrowhead*). (G–H) Bronchoscopic images show the mucoepidermoid tumor completely obstructing the left upper lobe bronchial orifice. (Courtesy Ewa Lupa-Laskus, MD, Arizona Pulmonary Specialists, Scottsdale, AZ.)



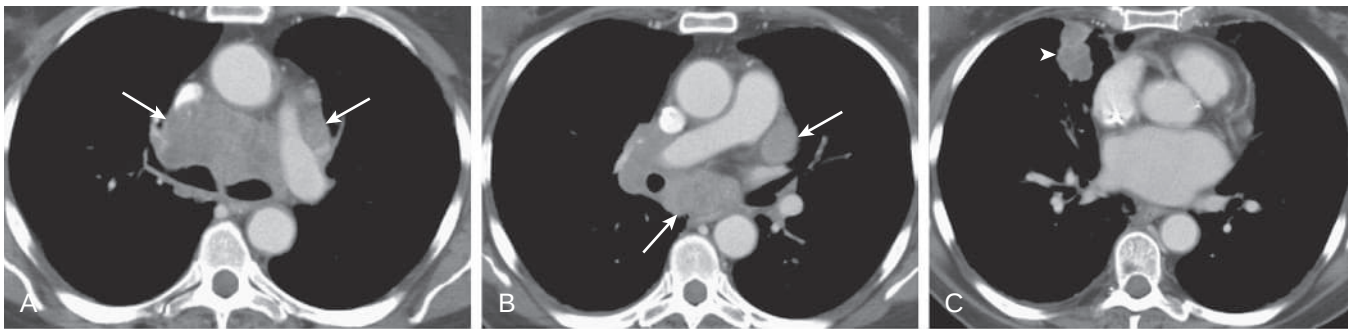
eFigure 78.2 Diffuse neuroendocrine cell hyperplasia. Axial unenhanced chest computed tomography through the middle (A) and lower (B) lungs shows multifocal bilateral inhomogeneous lung opacity with areas of mosaic perfusion manifesting as areas of low attenuation (*arrowheads*); these findings reflect the presence of small airway obstruction. Larger airway-associated nodules (*arrows*), reflecting carcinoid tumors, are present. (Courtesy Michael B. Gotway, MD.)



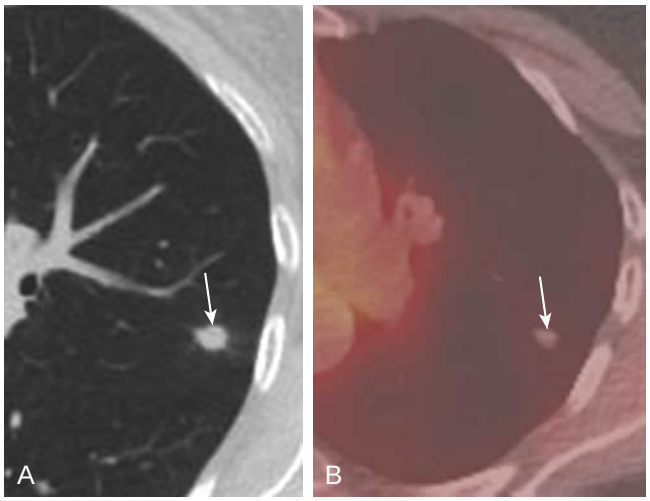
eFigure 78.3 "Typical" carcinoid tumor: hilar mass. (A) Frontal chest radiograph shows a circumscribed left hilar mass (*arrows*). (B–C) Enhanced axial chest computed tomography scans shown in soft tissue windows. (D) Sagittal lung window shows an enhancing mass (*arrows*) arising from and obstructing the left lower lobe bronchus. Calcification (*arrowhead*) is present within the mass. (Courtesy Michael B. Gotway, MD.)



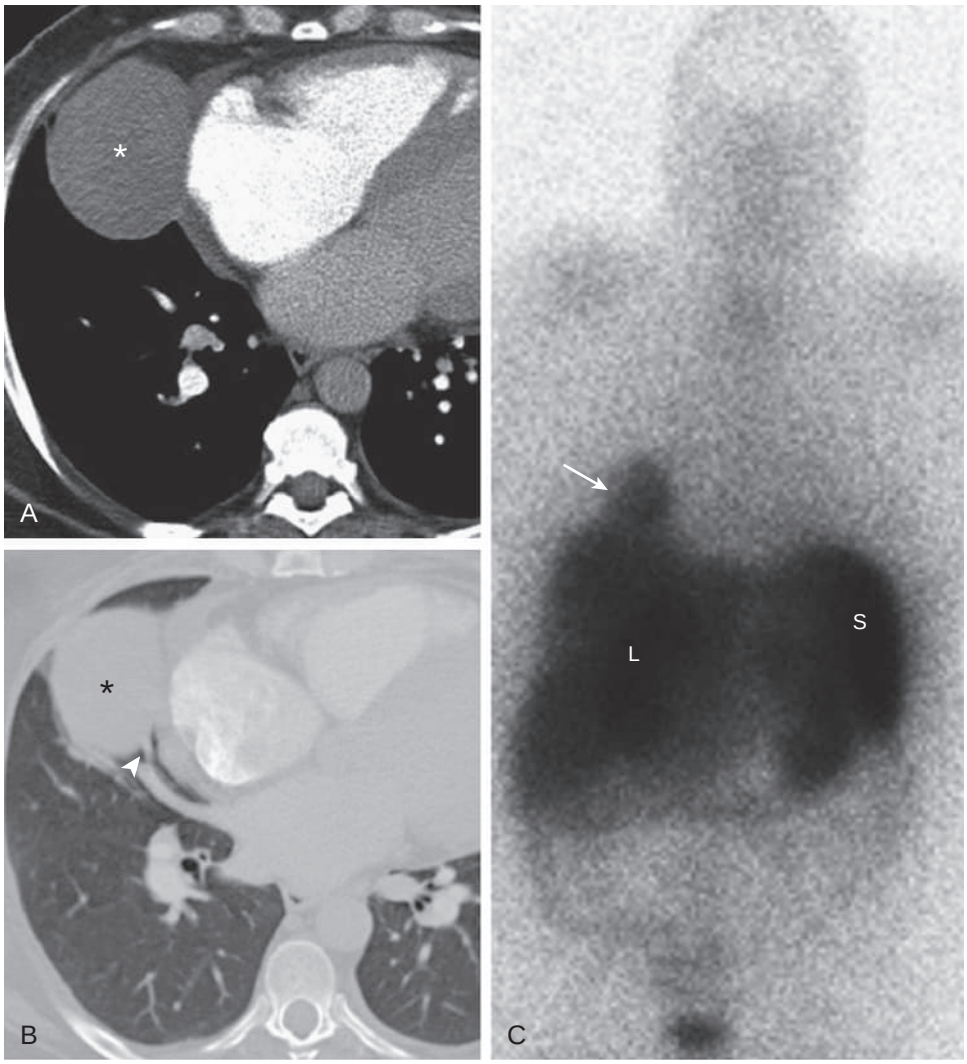
eFigure 78.4 "Typical" carcinoid tumor: endobronchial lesion without postobstructive changes. Axial (A–D) and sagittal (E) unenhanced chest computed tomography images show a small, circumscribed opacity (*arrows*) attached to the medial aspect of the cranial right lower lobe bronchus, unassociated with postobstructive pneumonia or atelectasis. Bronchoscopy and biopsy proved carcinoid tumor. (Courtesy Michael B. Gotway, MD.)



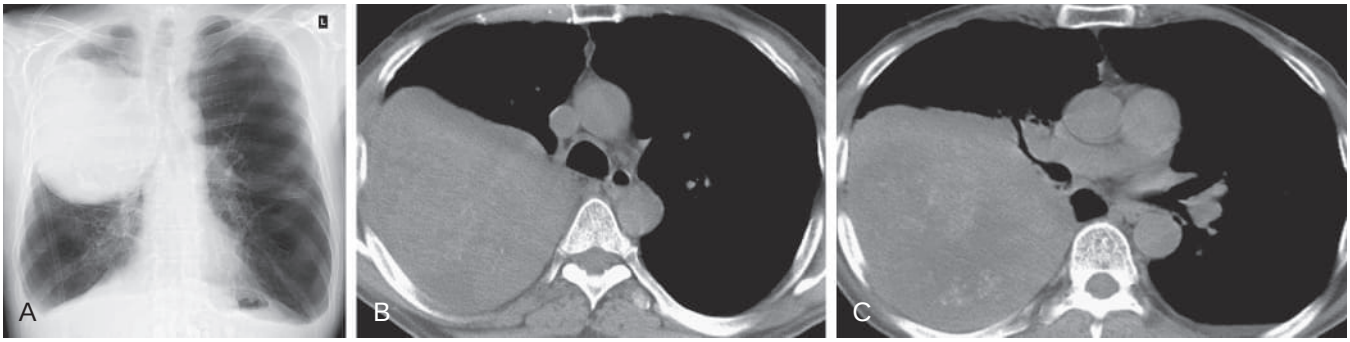
eFigure 78.5 "Atypical" carcinoid tumor. (A–C) Axial enhanced chest computed tomography scans displayed in soft tissue windows show extensive mediastinal lymph node enlargement (A–B, *arrows*) associated with a right middle lobe atypical carcinoid tumor (C, *arrowhead*). The appearance is indistinguishable from bronchogenic malignancy. (Courtesy Michael B. Gotway, MD.)



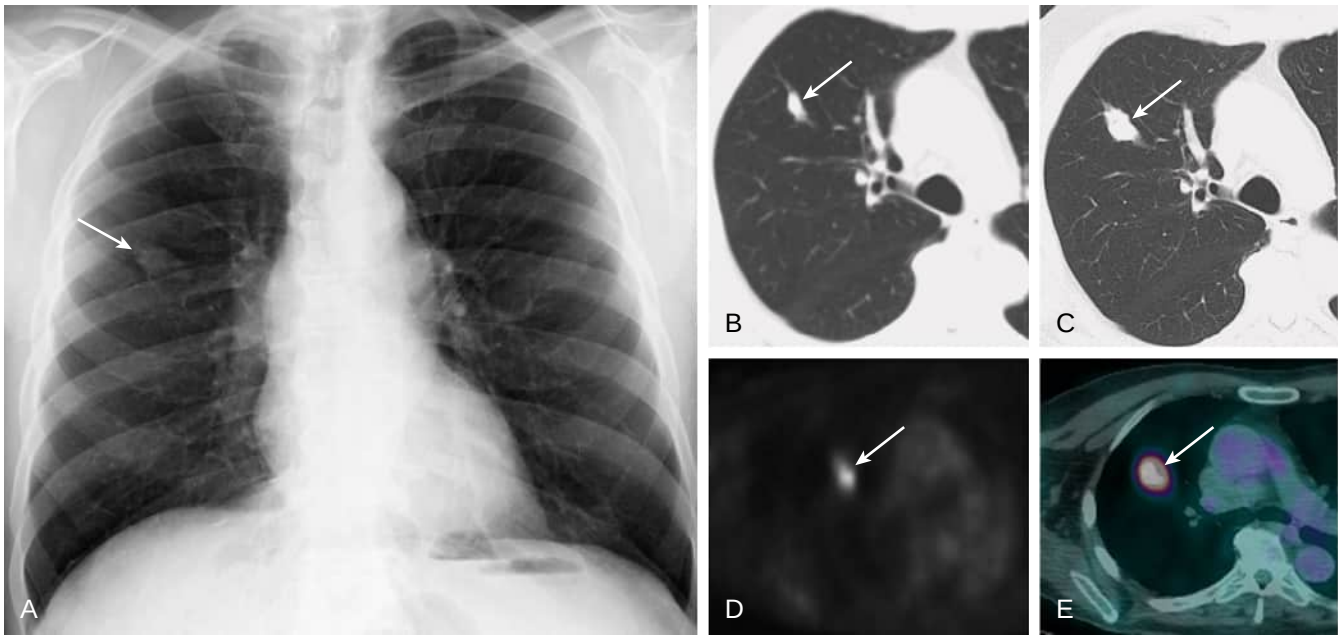
eFigure 78.6 "Typical" peripheral carcinoid tumor at computed tomography and ^{18}*F-fluorodeoxyglucose–positron emission tomography* (FDG-PET). (A) Axial unenhanced chest computed tomography scan displayed in lung windows shows a nonspecific, noncalcified, peripheral, somewhat spiculated left lung nodule (*arrow*). (B) Axial FDG-PET scan shows no tracer utilization within the nodule (*arrow*); compare to tracer activity within the mediastinal blood pool at the left aspect of the image. (Courtesy Michael B. Gotway, MD.)



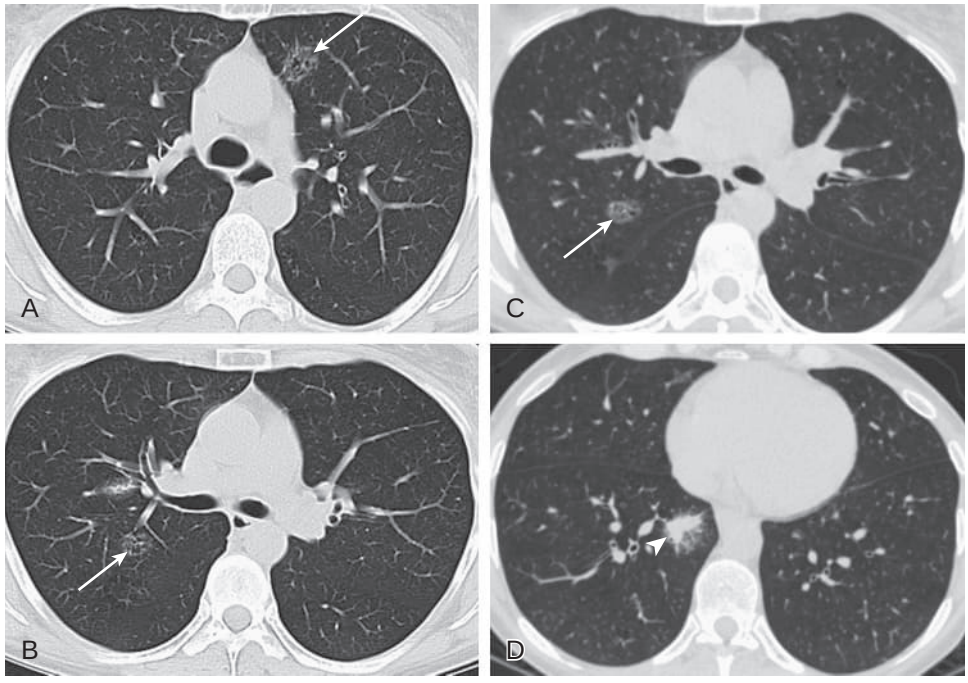
eFigure 78.7 "Typical" carcinoid tumor: somatostatin (octreotide) scintigraphy. Axial enhanced chest computed tomography scans displayed in soft tissue (A) and lung (B) windows show a circumscribed soft tissue mass (*asterisk*) in the right middle lobe, closely associated with bronchi (B, *arrowhead*), proven to represent typical carcinoid tumor. (C) Coronal planar octreotide scan shows tracer uptake within the right middle lobe lesion (*arrow*). Normal physiologic uptake is seen within the liver (L) and spleen (S). (Courtesy Michael B. Gotway, MD.)



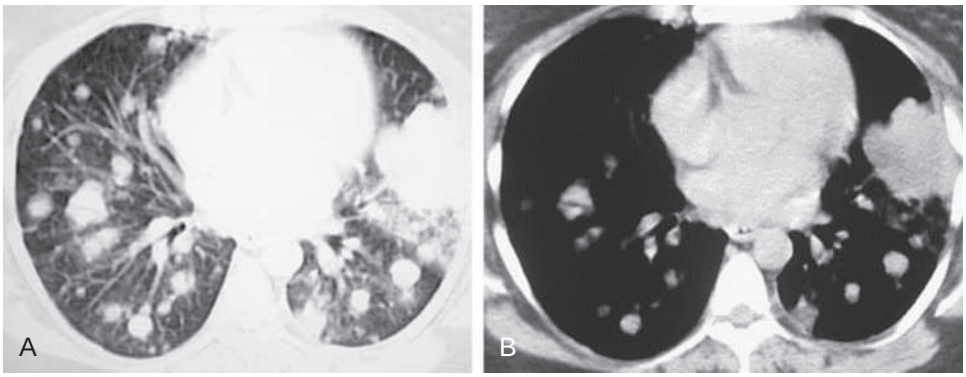
eFigure 78.8 Large cell neuroendocrine neoplasm. (A) Frontal chest radiograph in a patient with biopsy-proven large cell neuroendocrine neoplasm shows a large right upper lobe mass. (B–C) Axial chest computed tomography scans displayed in soft tissue windows show a heterogeneous right upper lobe mass with foci of faint internal hyperattenuation. The appearance is nonspecific and indistinguishable from bronchogenic malignancy. (Courtesy Michael B. Gotway, MD.)



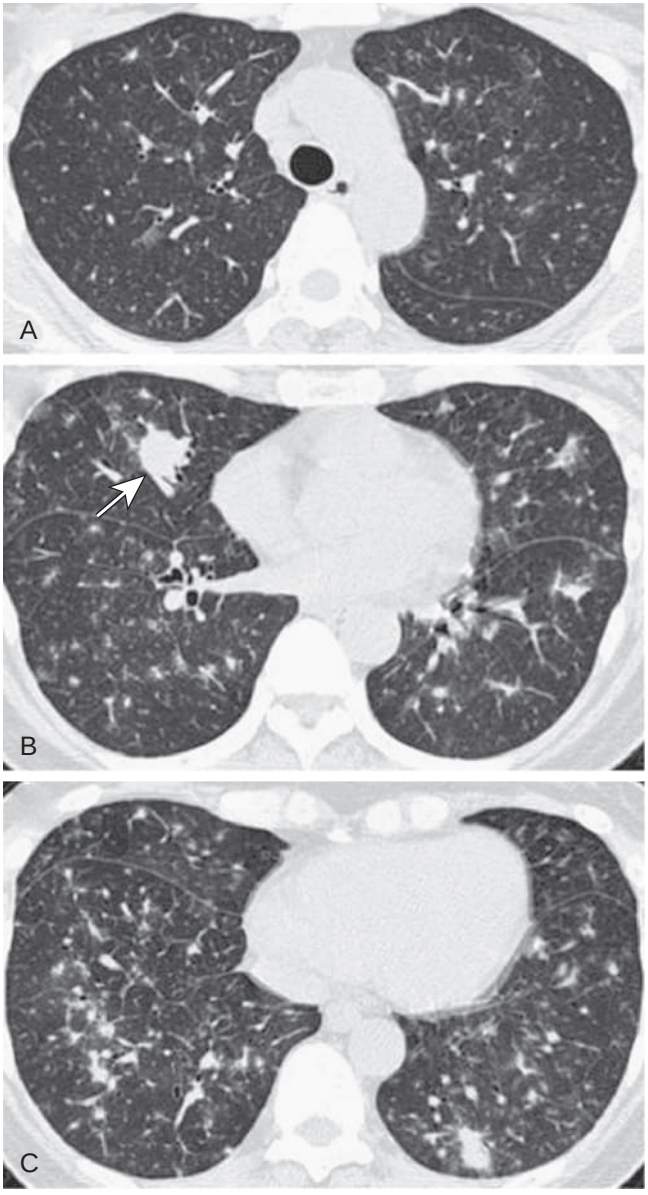
eFigure 78.9 Primary pulmonary mucosa-associated lymphoid tissue lymphoma: solitary pulmonary nodule. (A) Frontal chest radiograph shows a nonspecific, solitary, lobulated right upper lobe pulmonary nodule (*arrow*). (B–C) Axial enhanced chest computed tomography scans displayed in lung windows show rapid growth of the nodule (*arrows*) over a 3-month period. (D–E) *Positron emission tomography* (PET) and fused PET imaging obtained at nearly the same time as the computed tomography studies (B–C) show marked metabolic activity within the nodule (*arrows*). Percutaneous transthoracic fine-needle aspiration and core biopsy showed pulmonary mucosa-associated lymphoid tissue lymphoma. (Courtesy Michael B. Gotway, MD.)



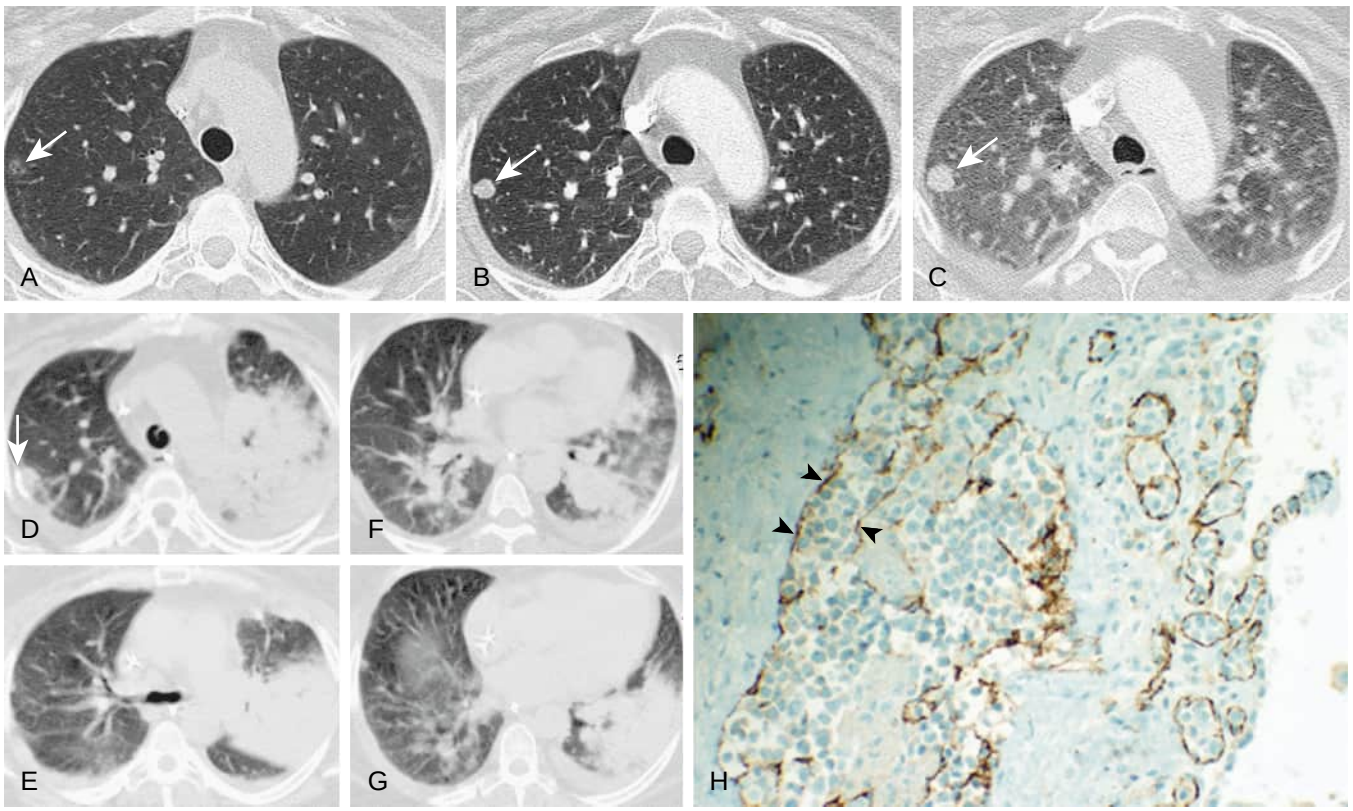
eFigure 78.10 Primary pulmonary mucosa-associated lymphoid tissue lymphoma: multiple nodules. (A–D) Axial chest computed tomography scans displayed in lung windows show multiple ground-glass opacity nodules (*arrows*) associated with small lucent foci. One right lower lobe nodule (*arrowhead*) shows a solid component. Percutaneous transthoracic fine-needle aspiration and core biopsy showed pulmonary mucosa-associated lymphoid tissue lymphoma. (Courtesy Michael B. Gotway, MD.)



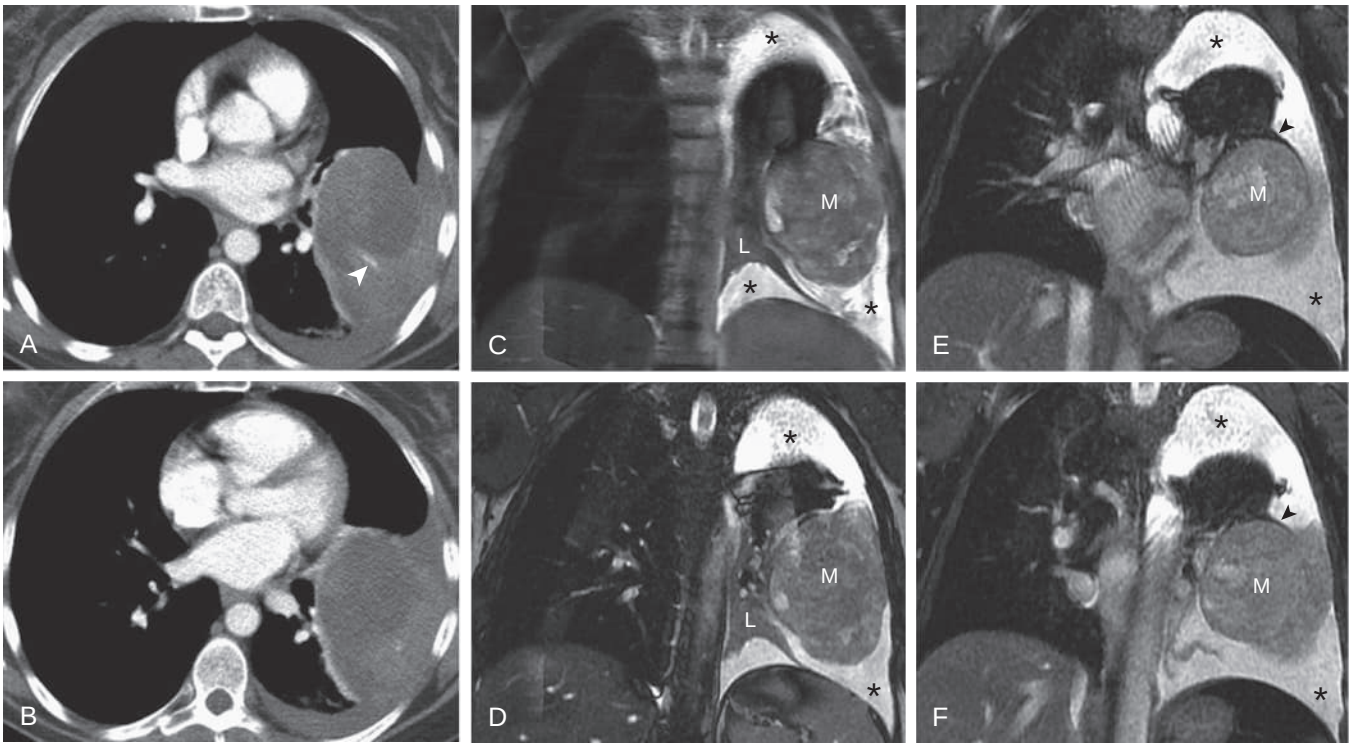
eFigure 78.11 Pulmonary lymphomatoid granulomatosis. Axial chest computed tomography scans displayed in lung (A) and soft tissue (B) windows show multiple, bilateral pulmonary nodules and a lingular mass, shown to represent pulmonary lymphomatoid granulomatosis at biopsy. (Courtesy Michael B. Gotway, MD.)



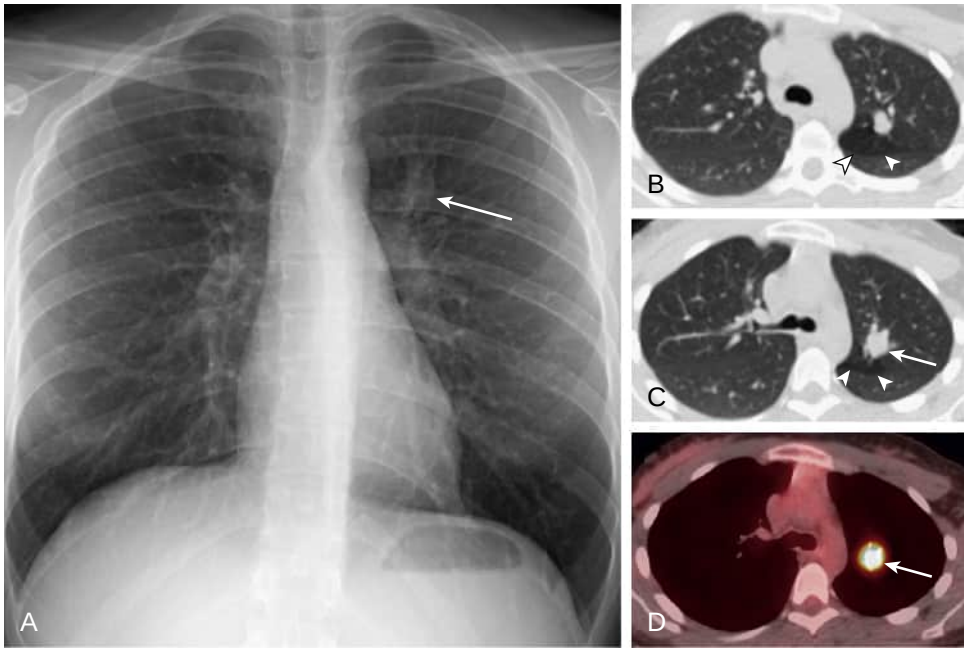
eFigure 78.12 Pulmonary lymphomatoid granulomatosis. (A–C) Axial chest computed tomography scans displayed in lung windows show multiple small nodules distributed along the bronchovascular bundles. A right middle lobe nodule (B, *arrow*) associated with an air bronchogram is present. Surgical lung biopsy showed pulmonary lymphomatoid granulomatosis. (Courtesy Michael B. Gotway, MD.)



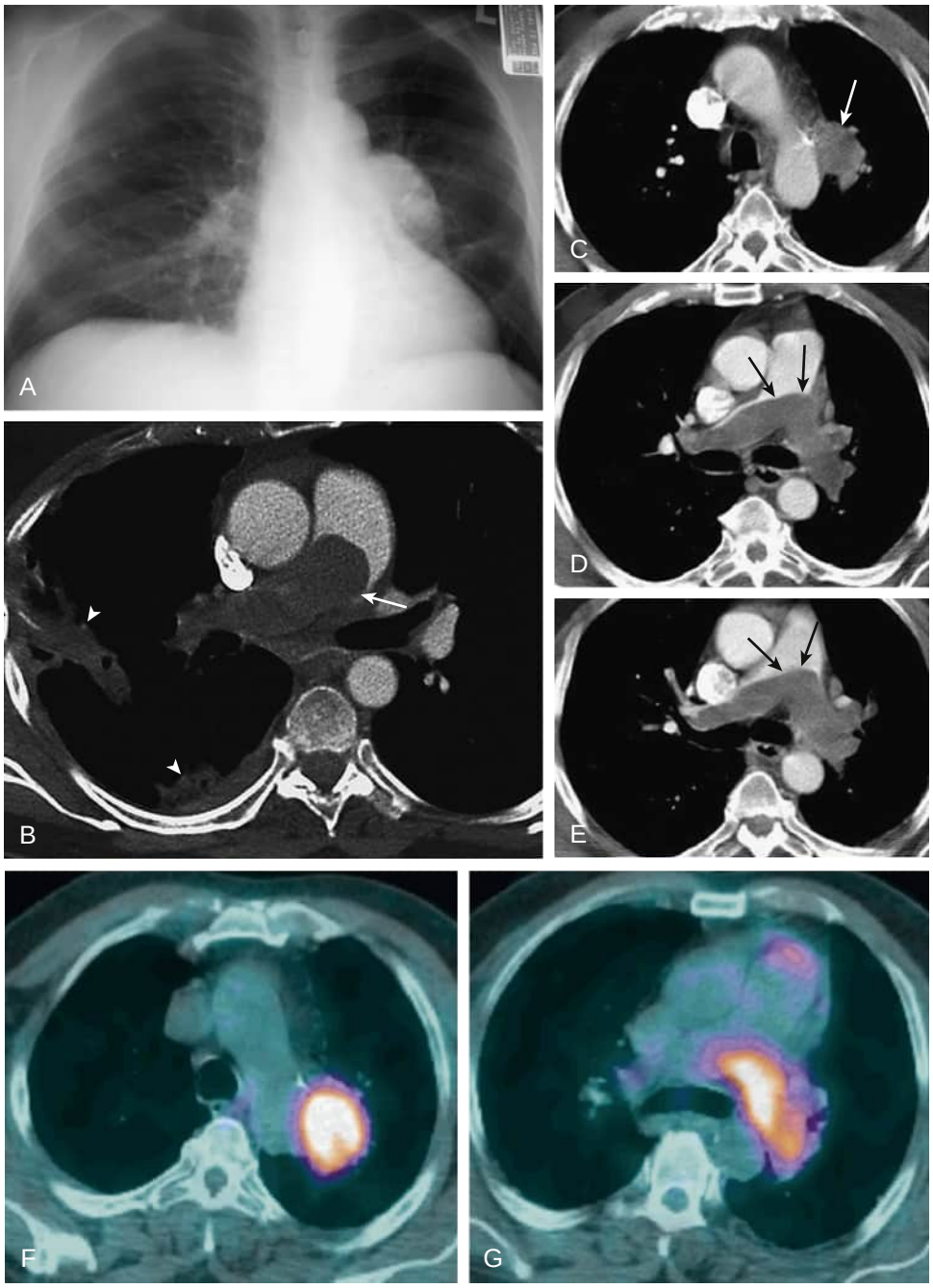
eFigure 78.13 Intravascular large cell lymphoma. (A–C) Axial chest computed tomography scans displayed in lung windows in a 46-year-old woman with sarcoidosis and systemic lupus erythematosus, who reported daily fever and progressive shortness of breath, shows a right upper lobe nodule (*arrow*) growing rapidly over a 2-month period. A corticosteroid therapy burst for 1 week was initiated in addition to the patient's baseline daily dose of 40 mg prednisone, but the patient's symptoms persisted after return to the baseline therapy. (D–G) Axial chest computed tomography scans after return to the baseline prednisone dose of 40 mg shows interval development of multiple, bilateral areas of consolidation and nodularity. A surgical lung biopsy of the right upper lobe nodule, evidenced by right upper lobe suture (*arrow*), was performed. (H) CD31 stain for endothelial cells outlines pulmonary vessels (*brown lined areas, arrowheads*). Note intravascular tumor cells consistent with diffuse, large B cell intravascular lymphoma. (H, Original magnification ×40.) (Courtesy Cristian Jivcu, MD, Cardio-Pulmonary Associates, Monterey, CA, and Michael B. Gotway, MD.)



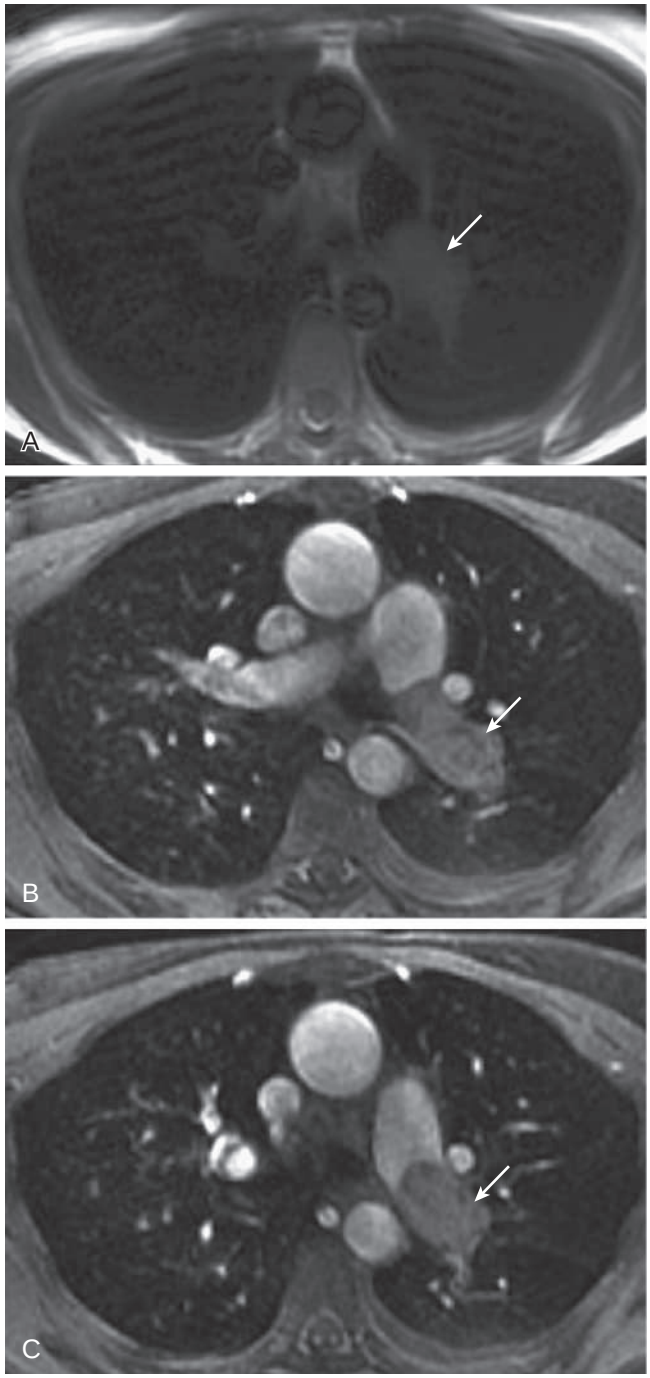
eFigure 78.14 Primary pulmonary leiomyosarcoma. (A–B) Axial enhanced chest computed tomography scans show a large peripheral lung mass associated with a small left pleural effusion. A prominent vessel (A, *arrowhead*) is seen within the mass. (C–F) Coronal magnetic resonance images show a heterogeneous mass (M) with intermediate signal intensity, which reflects the relatively cellular and fibrotic nature of the lesion, arising from the peripheral left lung (L). Some areas of cystic change (the hyperintense foci) are present within the mass. The pulmonary origin of the mass, rather than pleural origin, is suggested by the visible "claw" of lung tissue (E–F, *arrowheads*) surrounding a portion of the lesion. A moderate left pleural effusion (*asterisk*) is present. (Courtesy Michael B. Gotway, MD.)



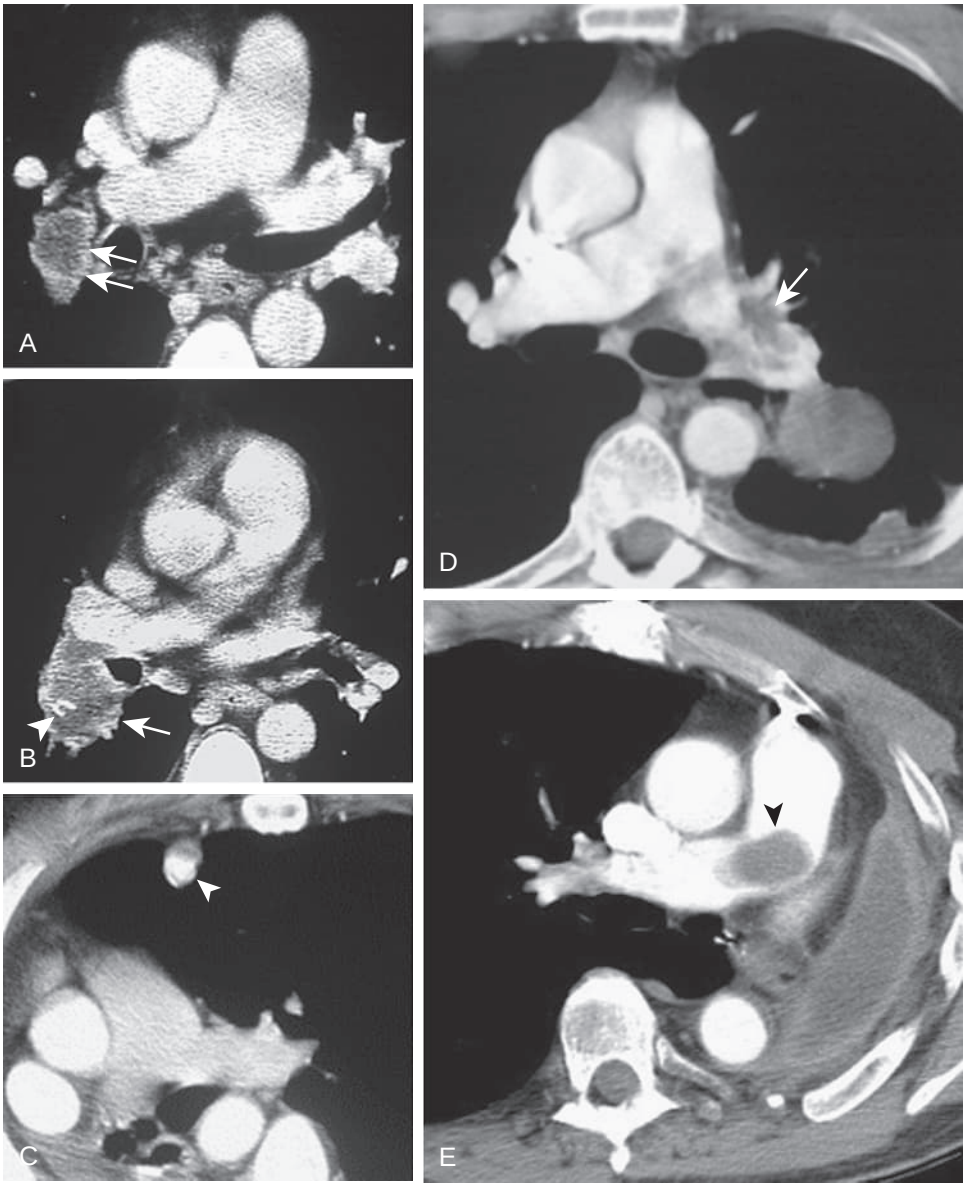
eFigure 78.15 Primary pulmonary leiomyosarcoma: endobronchial origin. (A) Frontal chest radiograph shows a poorly defined medial left upper lobe nodule (*arrow*). (B–C) Axial chest computed tomography scans displayed in lung windows show a circumscribed lesion (*arrow*) in the left upper lobe that could be traced to the apical-posterior segmental left upper lobe bronchus; note presence of hyperlucency distal to the lesion (*arrowheads*), representing postobstructive air trapping. (D) Fused axial positron emission tomography image shows intense metabolic activity within the lesion (*arrow*). (Courtesy Michael B. Gotway, MD.)



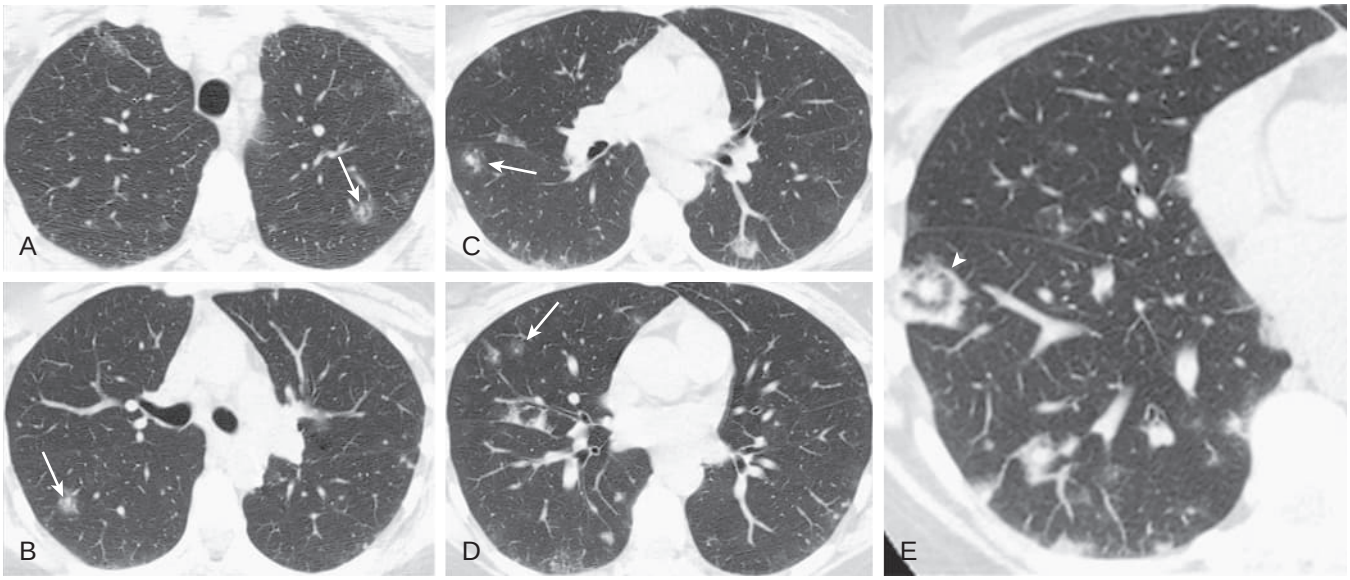
eFigure 78.16 Pulmonary artery sarcoma: imaging appearances. (A) Frontal chest radiograph shows a smoothly enlarged left pulmonary artery associated with left lung oligemia. Whereas pulmonary embolism can result in similar findings, emboli rarely produce findings of this magnitude. (B–E) Axial enhanced chest computed tomography scans in two patients show a large hypoattenuating lesion completely filling the right pulmonary artery (B, *arrow*), associated with pulmonary infarction (B, *arrowheads*). The second patient **(**C–E) shows a large lesion simulating a saddle pulmonary embolism (*arrows*). Both patients were hemodynamically stable and presented with subacute shortness of breath; such a presentation would be exceeding unlikely if pulmonary emboli were the cause of these large, obstructing central intravascular lesions. The full extent of the intravascular lesion and its resemblance to thromboembolic disease is demonstrated in Video 78.1. (F–G) Axial positron emission tomography scan (same patient as in C–E) shows intense hypermetabolic activity within the intravascular lesion, consistent with neoplasm. (Courtesy Michael B. Gotway, MD.)



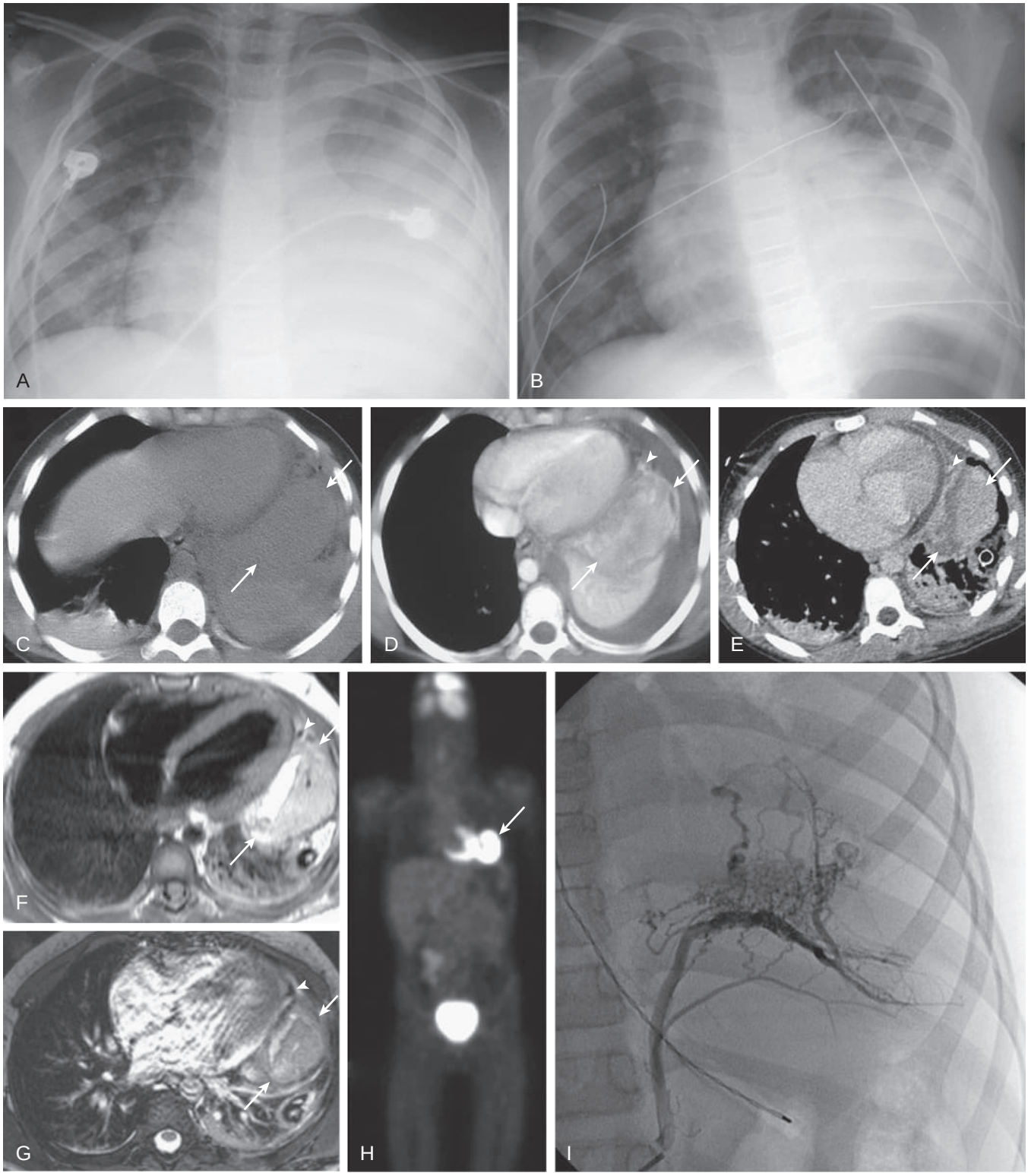
eFigure 78.17 Pulmonary artery sarcoma: magnetic resonance appearance. Axial double-inversion recovery T1-weighted image (A) and axial enhanced fast-spoiled gradient echo images (B–C) show a soft tissue mass (*arrows*) completely filling the left pulmonary artery. Note the faint internal enhancement visible within the intravascular lesion in part B. (Courtesy Michael B. Gotway, MD.)



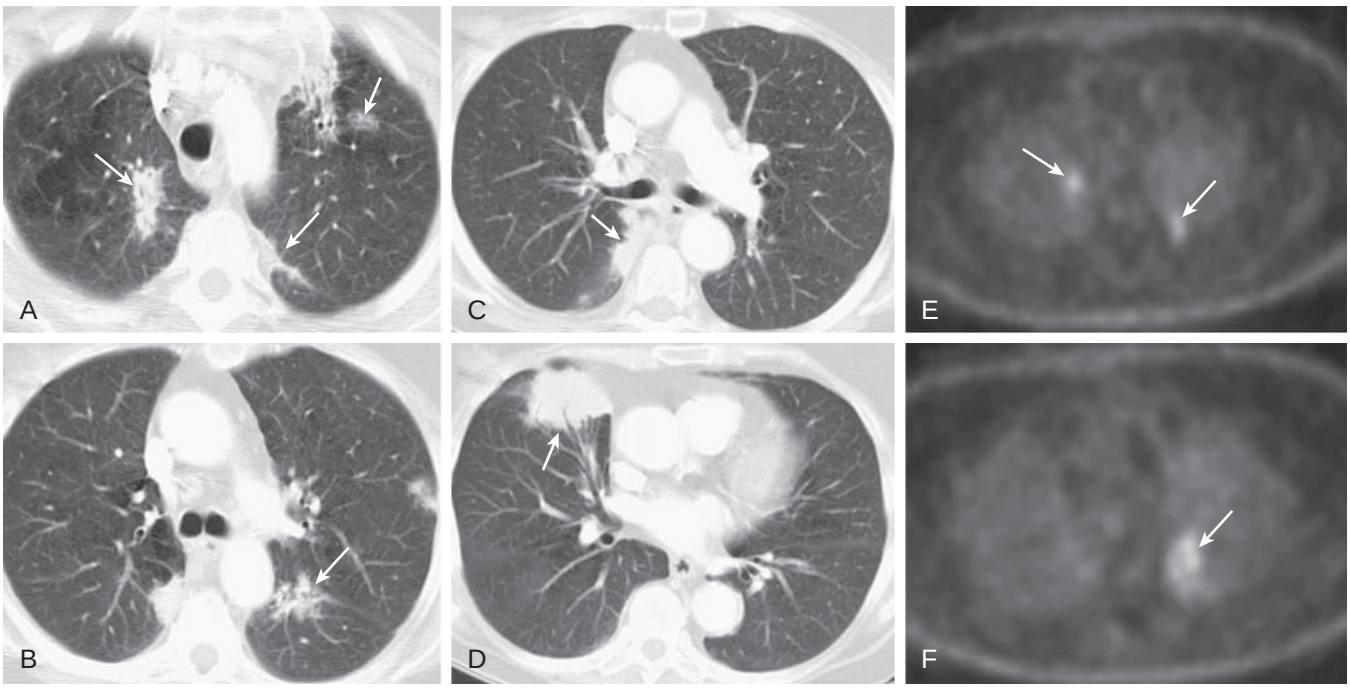
eFigure 78.18 Pulmonary artery sarcoma: tumor recurrence. (A–C) Axial enhanced chest computed tomography scans show right peribronchial lymph node enlargement (A, *double arrows*) associated with a tumor mass arising from the right lower lobe artery (B, *arrow*). Note the small focus of hyperattenuation present within the primary tumor (B, *arrowhead*). The lesion was an osteosarcoma arising with the pulmonary artery. Just over a year after right pneumonectomy, ossified metastatic nodules (C, *arrowhead*) appeared within the left lung. (D–E) In another patient, left pulmonary artery sarcoma (D, *arrow*) is seen, with recurrence (E, *arrowhead*) appearing 1 year after left pneumonectomy. (Courtesy Michael B. Gotway, MD.)



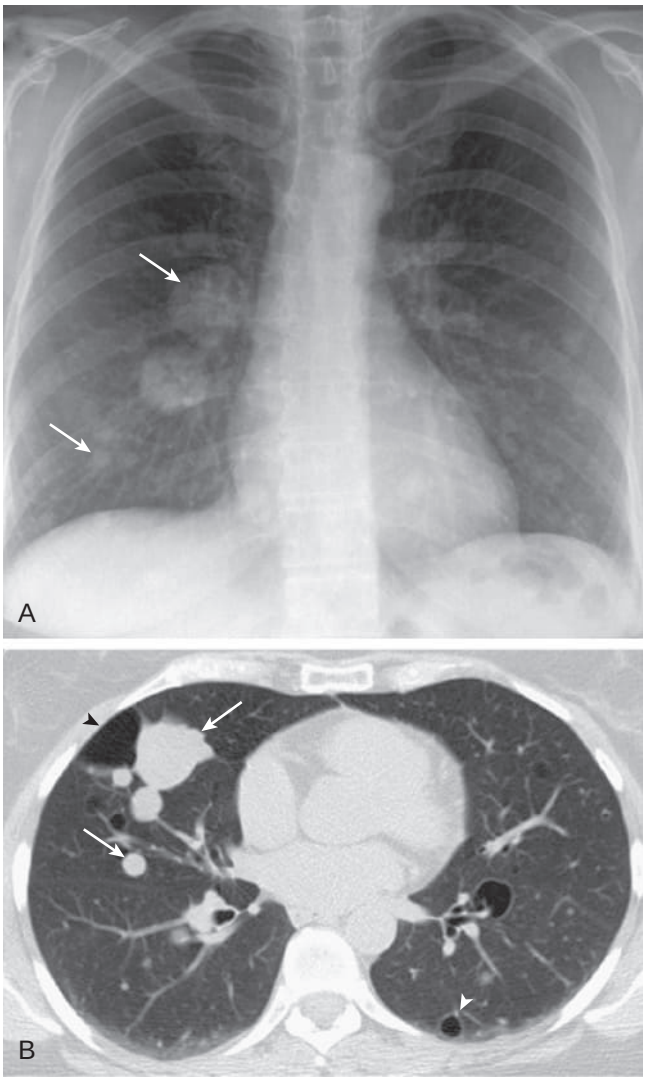
eFigure 78.19 Pulmonary hemangioendothelioma. (A–E) Axial chest computed tomography scans in a 39-year-old woman with cough and hemoptysis displayed in lung windows show multiple, bilateral, variably sized ground-glass opacity nodules with foci of solid nodular internal opacity centrally (*arrows*). One right lower lobe lesion shows peripheral consolidation surrounding ground-glass opacity with a centrally located solid nodular focus (E, *arrowhead*). Surgical lung biopsy proved pulmonary hemangioendothelioma. The lesions have been stable for 1 year during follow-up. (Courtesy Michael B. Gotway, MD.)



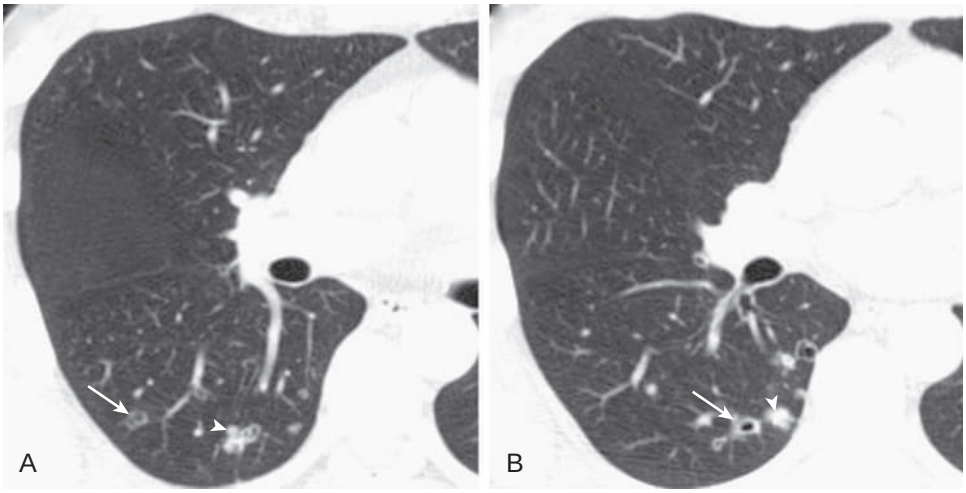
eFigure 78.20 Inflammatory myofibroblastic tumor. (A) Frontal chest radiograph obtained in an 8-year-old boy after being struck by an automobile shows a large left pleural effusion and basal predominant left lung opacity. (B) Frontal chest radiograph obtained after insertion of a surgical thoracostomy tube shows removal of the pleural fluid. During the placement of this tube, the surgeon noted a lesion in the left chest and obtained a small biopsy specimen, but profuse bleeding prevented further assessment. Axial unenhanced (C) and enhanced (D) chest computed tomography shows a left lower anterior chest mass (*arrows*); the mass shows intense enhancement after intravenous contrast administration. A large vessel (D, *arrowhead*) is present in the anterior mediastinum adjacent to the mass. (E) Axial enhanced multislice chest computed tomography again shows the mass (*arrows*) and prominent mediastinal vessel (*arrowhead*). This examination was obtained to search for aberrant systemic arterial supply on the assumption that the lesion might represent a sequestration. No systemic arterial supply arising from the thoracic aorta was seen, but the examination was not extended into the upper abdomen to evaluate the cranial abdominal aorta. Axial T1-weighted (F) and axial gradient echo (G) magnetic resonance images show that the mass (*arrows*) contains high signal in T1-weighted and intermediate to low signal on gradient echo imaging, consistent with hemorrhage. The hypointense structure in the mediastinum adjacent to the mass (*arrowhead*) represents a flow void within a large vessel. (H) Coronal positron emission tomography image shows intense metabolic activity within the lesion (*arrow*). (I) Coronal preoperative angiogram shows aberrant systemic arterial supply to the mass derived from the cranial abdominal aorta; this vessel was embolized to decrease intraoperative blood loss. Inflammatory myofibroblastic tumor was confirmed after surgical resection, and the lesion was noted to be highly vascular and to have invaded the mediastinum at surgery, with the venous drainage of the mass corresponding to the large anterior mediastinal vessel seen on computed tomography (D–E) and magnetic resonance imaging (F–G). (From Gotway MB, Dawn SK. An unusual cause of a pulmonary mass. *Clin Pulmon Med.* 2004;11:266–268.)



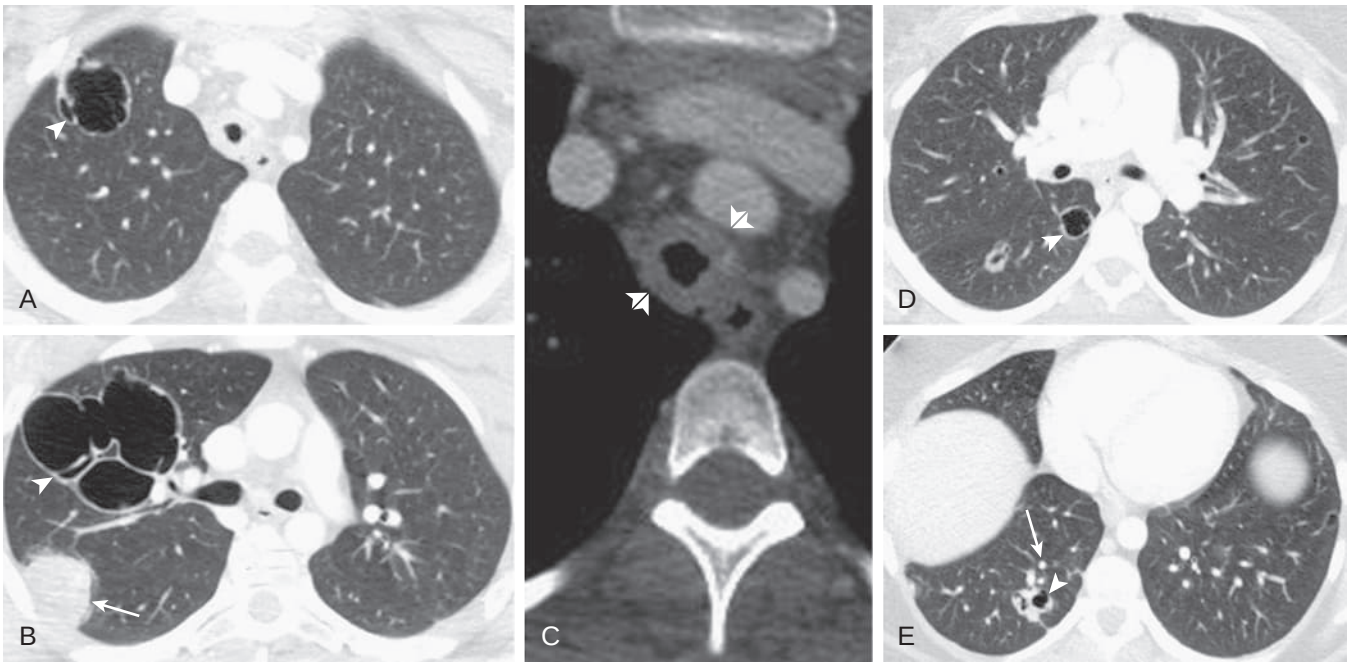
eFigure 78.21 Multicentric inflammatory myofibroblastic tumor. (A–D) Axial chest computed tomography scans displayed in lung windows show multiple, variably sized, poorly defined nodules (*arrows*). (E–F) Axial positron emission tomography images show mildly increased metabolic activity within several of the nodules (*arrows*). The imaging features are ultimately nonspecific, and surgical excision was required to establish the diagnosis. (Courtesy Michael B. Gotway, MD.)



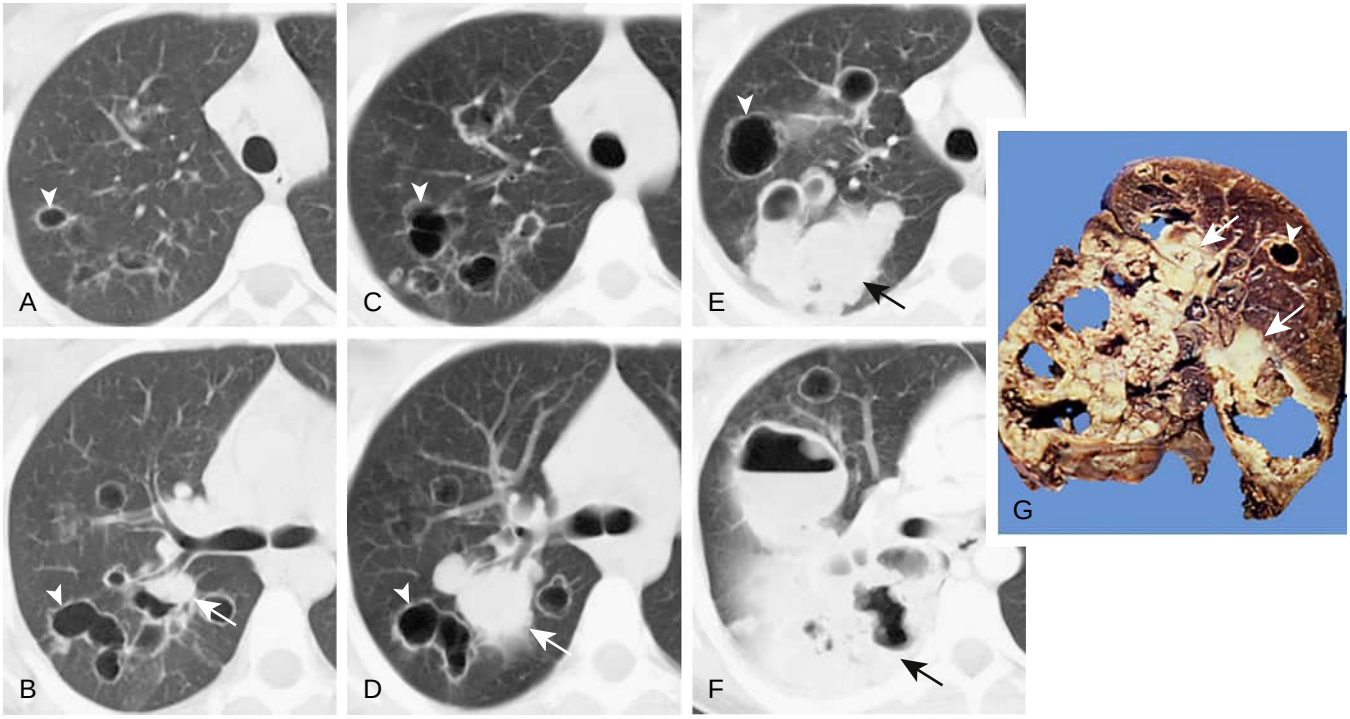
eFigure 78.22 Tracheobronchial papillomatosis: typical chest radiographic and computed tomography findings. (A) Frontal chest radiograph in a patient with tracheobronchial papillomatosis shows several variably sized nodules (*arrows*) bilaterally. (B) Axial chest computed tomography displayed in lung windows shows the typical combination of nodules (*arrows*) and cysts (*arrowhead*). (Courtesy Michael B. Gotway, MD.)



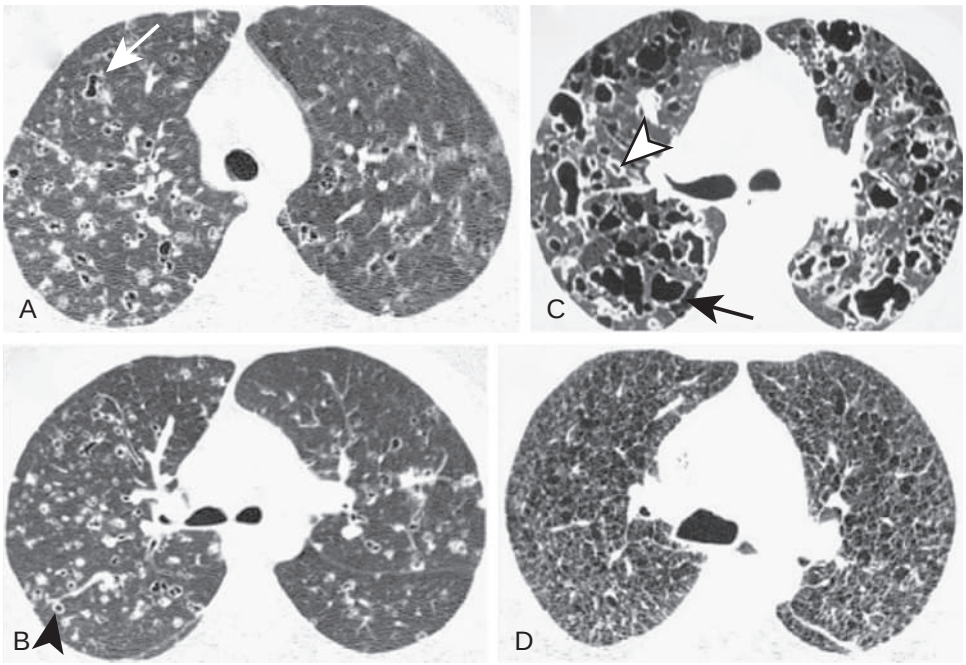
eFigure 78.23 Tracheobronchial papillomatosis: early disease. (A–B) Axial chest computed tomography scans displayed in lung windows show small centrilobular nodules (*arrowheads*) and thin-walled cavities (*arrows*) in the superior segment of the right lower lobe (a relatively dependent distribution). (Courtesy Michael B. Gotway, MD.)



eFigure 78.24 Tracheobronchial papillomatosis. (A–B, D–E) Axial chest computed tomography scans displayed in lung windows show relatively thin-walled, variably sized cysts (*arrowheads*) and nodules (*arrows*). (C) Axial enhanced chest computed tomography displayed in soft tissue windows shows circumferential tracheal wall thickening (*double arrowheads*). (Courtesy Michael B. Gotway, MD.)



eFigure 78.25 Tracheobronchial papillomatosis: progressive disease with malignant transformation. (A–F) Axial chest *computed tomography* (CT) images displayed in lung windows show progressive cyst and cavity enlargement with increasing nodularity related to the cyst walls. (A–B) Axial chest CT scans show mostly thin-walled cyst formation (*arrowheads*) with relatively mild nodularity (B, *arrow*). Axial chest CT scans obtained just over 1 year later shows enlarging cysts (C, *arrowheads*) and marked increase in nodular opacity related to the posterior segment right upper lobe bronchus (D, *arrow*). (E–F) Axial chest CT scans performed just over 2 years after A and B show further enlargement of pulmonary cysts and cavities (*arrowhead*), with marked increase in cavitary nodular right lung opacity (*arrows*). (G) Gross right lung specimen after pneumonectomy shows cystic change (*arrowhead*) with extensive cavitation with internal mural nodularity (*arrows*). The mural nodular opacity represents squamous cell carcinoma development. (Courtesy Michael B. Gotway, MD.)



eFigure 78.26 Langerhans cell histiocytosis. (A–B) Axial chest *computed tomography* (CT) scans displayed in lung windows performed in a 17-year-old patient show features consistent with relatively "early" Langerhans cell histiocytosis: numerous small nodules, some showing cavitation (B, *arrowhead*) and a few developing bizarrely shaped cysts (A, *arrow*). (C) Axial chest CT displayed in lung windows performed in a 30-year-old smoker shows features consistent with more developed Langerhans cell histiocytosis: prominent, bizarrely shaped cysts, with a few small, solid, and cavitating (*arrowhead*) nodules. (D) Axial chest CT displayed in lung windows performed in a 55-year-old smoker shows features consistent with relatively "late," or "burned-out," Langerhans cell histiocytosis: innumerable small cystic areas resembling pulmonary emphysema, which is often coexistent. (Courtesy Michael B. Gotway, MD.)

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79 METASTATIC MALIGNANT TUMORS

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INTRODUCTION

The lung is the most common site for metastasis of malignant tumors from other organs. Logic would suggest that this is because the lung alone receives the entire cardiac output. Indeed, this likely does play a role in the eventual seeding of the lungs when cancers metastasize by the hematogenous route. However, a more detailed understanding of the molecular mechanisms dictating organ-specific metastases has made it clear that specific properties of the primary tumor, as well as the microenvironment of both the tissue of origin and of the lung, all play a significant role in directing the process of metastasis to the lung. Paget[1] initially proposed what became known as the "seed and soil" hypothesis in 1889 based on his observations of the nonrandom nature of breast cancer metastasis. Although we can now begin to define mechanisms of organ-specific metastases at a molecular level,[2,3] and therapeutic tools specifically aimed at preventing metastases have been tested,[4] we still lack effective tools to exploit this emerging knowledge. This chapter reviews the epidemiology of lung metastasis, advances in the knowledge of the pathophysiology of metastasis, approaches to help distinguish metastasis from primary lung cancer, advances in diagnostic methods, and treatment options that vary from palliative therapy to curative surgery.

EPIDEMIOLOGY

Estimates of the incidence of lung metastasis among patients with cancer vary from 20–40%.[5,6] However, these estimates have limitations. Most series focus on a single tumor type as the origin of lung metastases. The incidence of lung metastasis also varies depending on the means used for detection and for follow-up; a lower incidence is reported if the metastases are detected because of respiratory symptoms, and it rises progressively if metastases are detected by routine surveillance with chest radiographs or *computed tomography* (CT) scans or from autopsy data. Not surprisingly, the detection of metastases for any given solid tumor type is greater when ^{18}F-fluorodeoxyglucose *positron emission tomography* (PET) scanning is used as a method of surveillance.[7] Although reports of the proportion of cancers that metastasize to the lung varies, the lung is always among the most common sites of metastasis of solid tumors.[5]

CLINICAL HISTORY

Lung metastases or pleural effusions can be the initial presenting finding of an extrathoracic cancer (*synchronous metastases*, discovered at the same time as the primary tumor), or they can manifest later after diagnosis of an extrathoracic malignancy (*metachronous metastases*). Metastases can be found incidentally in the course of follow-up of a prior malignancy or in the context of new pulmonary symptoms, which are more likely to happen when the metastatic lesion is in the central airways. Because of the large degree of reserve pulmonary function in most individuals, metastases to the periphery of the lung rarely produce symptoms, and patients with even a large metastatic tumor burden can present with minimal or no pulmonary symptoms. When nonspecific symptoms of cough, dyspnea, or chest pain or discomfort can be attributed to metastatic lesions, these symptoms usually result from a very large tumor burden (Fig. 79.1), extensive lymphatic infiltration, airway involvement, and/or a large pleural effusion. The first clue to the presence of lung metastasis most commonly comes from surveillance imaging in patients with known prior cancer. The most classic presentation of lung metastasis is the finding of multiple smooth, rounded nodules in the lower lobes. The finding of an incidental solitary pulmonary nodule as the first sign of an extrapulmonary neoplasm makes the distinction between metastasis and a primary lung tumor challenging. The physical examination is unlikely to disclose evidence of lung metastasis but, in the context of a solitary pulmonary nodule, the examination

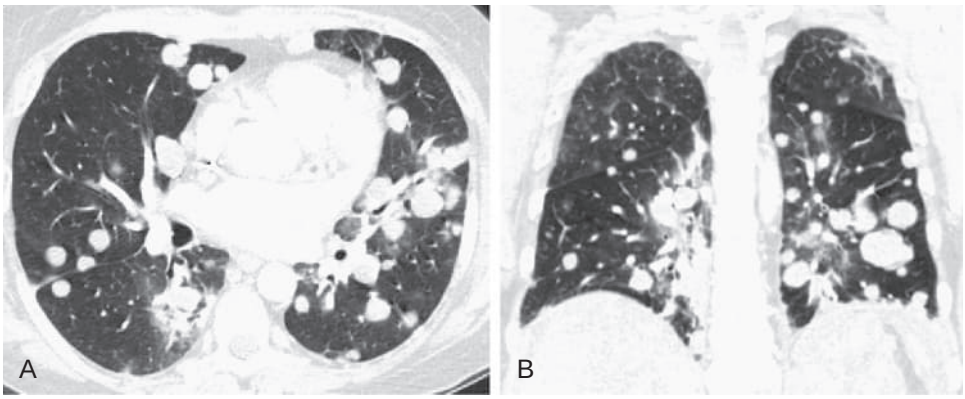

Figure 79.1 Typical appearance of metastatic disease. (A) Axial and (B) coronal thoracic computed tomography displayed in lung windows of a patient with innumerable rounded, lower lobe nodules and a prior history of melanoma. The appearance is typical of metastatic disease. The pretest probability of metastases is so high in such a case that the oncologist may not require a tissue confirmation.

should include a search for malignancy elsewhere in the body (e.g., breast or abdominal masses or enlarged lymph nodes). Rarely, a metastasis can affect the larger central airways and produce localized wheezing that an astute clinician discovers on auscultation. Malignant pleural fluid accumulation produces the physical findings of reduced breath sounds, dull percussion notes, and decreased tactile fremitus.

MECHANISM OF METASTASIS TO THE LUNG

Considering that the lung receives the entire cardiac output, it is perhaps surprising that lung metastases are not even more common among patients with cancer. However, studies show that most circulating cancer cells never form a clinically overt metastatic focus.[8–10] Anatomic access to the pulmonary circulation alone is therefore insufficient to result in clinically evident metastasis. Additional mechanisms must therefore account for the propensity of certain tumors to seed distant organs preferentially.

One of the main processes leading to metastasis involves expression of receptors that bind to ligands in metastatic sites. Chemokines are a group of small cytokines originally discovered as mediators of leukocyte trafficking. Chemokines mediate several important pathologic aspects of tumor biology, including angiogenesis, cell proliferation, invasion, and metastasis.[11] The pattern of constitutive expression of chemokine receptors on cancer cells combined with expression of the corresponding chemokine ligands in various organs may explain the organ-specific pattern of metastasis of a variety of common solid tumor types, including breast, prostate, and lung cancer.[12–14] For example, the chemokine receptors CXCR4 and CCR7 are highly expressed in human breast cancer cell lines, in primary breast tumor samples, and in their metastases. The corresponding ligands for the CXCR4 and CCR7 receptors, CXCL12 and CCL21, are constitutively expressed in organs to which these tumors commonly metastasize (lung, brain, bone, and lymph nodes).[14] In breast cancer cell lines, signaling through the receptors CXCR4 or CCR7 promotes in vitro migration and invasion. Most interestingly, antibodies or small molecule antagonists directed against CXCR4 significantly impaired metastasis of breast cancer cells to regional lymph nodes and lung in vivo. In addition, malignant melanoma, which has a metastatic pattern similar to that of breast cancer but also has a high incidence of skin metastases, showed high expression of the chemokine receptor CCR10 in addition to CXCR4 and CCR7. The ligand for CCR10 (*cutaneous T-cell–attracting chemokine* [CTACK/CCL27]) is highly expressed in normal dermis.[15] Chemokine receptors on cancer cells in concert with tissue-specific expression of their chemokine ligands appear to have a key role in determining the metastatic destination of circulating tumor cells.

Certain molecular processes may specifically increase lung vascular permeability to circulating tumor cells. In a mouse study, transforming growth factor-β was shown to prime breast cancer cells for lung-specific metastasis by up-regulation of the gene *angiopoietin-like 4* (*Angptl4*).[16] Transforming growth factor-β induction of *Angptl4* in breast cancer cells enhanced their subsequent retention in the lungs but not in bone. The investigators in this study showed that tumor cell–derived *Angptl4* disrupted the pulmonary microvascular cell-cell junctions, thereby increasing the permeability of lung capillaries and facilitating the passage of tumor cells into the lung parenchyma. In contrast, in the bone marrow sinusoids, which are normally the more leaky microvascular beds, this mechanism does not confer an advantage.[16]

Other processes may help support the metastatic cell in its lung microenvironment. In another mouse study, tumor cells were preceded into the metastatic niche by bone marrow–derived cells that express the type 1 vascular endothelial cell growth factor receptor. These investigators demonstrated that the receptor-expressing bone marrow–derived cells (1) arrived at the metastatic site before tumor cells, (2) accumulated in the target metastatic organ after either injection of tumor cells or treatment with tumor cell–conditioned media, and (3) established a premetastatic niche in a tumor-specific fashion (i.e., they established a permissive environment for metastasis in an organ-specific pattern that varied depending on the tumor type).[16a] Other investigators demonstrated that the protein metadherin is present on the surface of metastatic breast cancer cells and preferentially facilitated adherence to the pulmonary vascular endothelium.[17]

Although some processes enhance lung-specific metastasis, there are yet other mechanisms by which immune surveillance specifically inhibits lung metastasis. A study by Hanna and colleagues[18] showed that a certain subset of tissue resident monocytes, originally referred to as patrolling monocytes, specifically attenuated the establishment of metastatic foci in the lung in mice receiving experimental intravenous metastases.[19] In summary, tissue-specific metastases arise in a nonrandom fashion determined

by identifiable molecular mechanisms that involve both tumor-derived soluble factors and microenvironment-specific ligand-receptor interactions.

A further refinement in our understanding of the mechanisms of metastasis comes from a study that examined isolated efferent blood from primary tumors in mice. Primary tumors shed tumor fragments, or clusters, consisting of both malignant cells and host stromal fibroblasts. Importantly, the viability of circulating tumor cells was nearly twofold higher in these heterotypic tumor clusters as compared with single tumor cells shed from the primary tumor. These chaperone stromal fibroblasts survived, proliferated, and conferred a survival advantage in lung metastatic deposits. Selective depletion of carcinoma-associated fibroblasts from mice after primary tumor removal significantly inhibited the growth of metastatic deposits.[20] The study further demonstrated that human brain metastases, but not primary brain tumors, contained carcinoma-associated fibroblasts, a finding supporting the hypothesis that the fibroblasts enhanced the metastatic malignant process. This series of experiments, which required modern molecular techniques and cellular-lineage tracking, brought the field back full circle to Paget's seed and soil hypothesis. The study investigators pointed out that the tumor cells facilitated lung metastasis by "…bringing their own soil."[20] These advances are driving the search for new treatments to prevent cancer metastasis. Metastases are nearly universally responsible for cancer mortality and, as these molecular insights are exploited to develop novel strategies for prevention or treatment of metastases, survival *with* cancer (as opposed to a cure *for* cancer) is an attainable goal. Figure 79.2 illustrates some of the potential mechanisms behind tissue-specific metastasis to the lung from extrapulmonary malignancies.

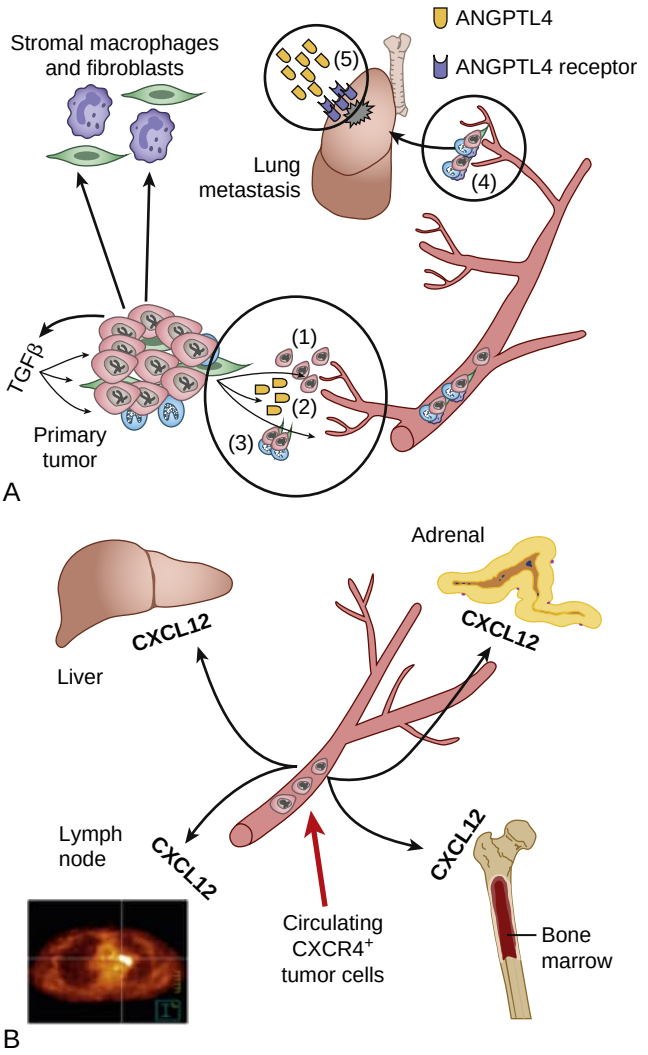

Figure 79.2 Illustration of molecular mechanisms that can drive lung specific metastasis from extrapulmonary malignancy. (A) The primary tumor can release *(1)* single tumor cells, *(2)* soluble substances such as *angiopoietin-like 4* (ANGPTL4), and *(3)* heterotypic tumor fragments, which have a survival advantage that renders them more likely to implant and survive in the lung *(4)*. In the lung, tumor-derived angiopoietin-like 4 creates a microvascular bed that is leaky and conducive to entry of tumor cells in the lung *(5)*. (B) Tumor cells bearing CXCR4, the receptor for the CXC chemokine *CXC chemokine ligand 12* (CXCL12), are preferentially attracted to organs that constitutively produce CXCL12. TGF-β, transforming growth factor-β.

DIAGNOSIS

DIFFERENTIAL DIAGNOSIS

Given the range of diagnostic and therapeutic options in cases of known or suspected lung metastasis, patient care is optimal when delivered within the context of a multidisciplinary team. For example, when deciding whether to perform a biopsy on a lung nodule by bronchoscopy or by using image guidance in a patient with a prior cancer, a chest physician is well served by speaking to the oncologist and/or the surgeon about available therapeutic options and how the results of a biopsy would alter those options. If a patient with a solitary nodule suspected to be an isolated lung metastasis is a surgical candidate, and complete resection is medically and technically feasible, a preoperative tissue diagnosis may not be necessary to undertake resection. Conversely, surgeons may prefer a preoperative tissue diagnosis to improve their discussion of risks, benefits, and alternatives with the patient. Surgeons may also prefer knowing whether a nodule is a metastasis or a primary lung cancer in planning the appropriate surgical procedure, whether a wedge resection, a lobectomy, or an anatomic segmentectomy. With the development of targeted therapy and immune checkpoint inhibitors, the role of and necessity for tissue diagnosis in patients with suspected lung metastases have also changed. Proceduralists and treating oncologists must communicate regarding the need for specific testing for mutations, oncogene rearrangements, or tissue staining to ensure that enough tissue is collected and is processed properly. For these and other reasons, management of these patients is best served by a multidisciplinary discussion.

In general, the patient with a prior history of cancer and a suspected lung metastasis should be managed with knowledge of several interacting factors: the type of prior cancer, its natural history, its propensity to cause lung metastasis, the potential effectiveness of systemic or radiation therapy, and the number and location of lung nodules. A decision to perform a biopsy should consider the likelihood of an alternative diagnosis and whether the results of the biopsy will change the management options.

The diagnostic possibilities for a lung nodule or multiple nodules in the patient with a history of cancer vary with the

type of prior cancer. For example, the implications of finding a cavitary nodule in a patient with prior leukemia after a bone marrow transplant are quite different from the same radiographic finding in an individual with prior head and neck cancer. In general, the differential diagnosis of a lung nodule in a patient with prior cancer includes the same diagnoses found in the general population, with the obvious exception that metastatic disease must be considered as well. Both primary malignant and benign causes, including infectious and noninfectious conditions, should be considered (Table 79.1).

DISTINGUISHING METASTASIS FROM PRIMARY LUNG TUMORS

When a nodule (or nodules) is discovered in a patient with a prior history of cancer, it is important to distinguish lung metastasis from a primary lung cancer because the treatment can be very different. Clues such as the type of prior cancer, radiologic characteristics of the nodule, and the pathologic analysis of biopsy material can be used to guide treatment decisions. Multiple pulmonary nodules with smooth borders located in the lower (dependent) lobes are most likely to be metastatic based on clinical grounds alone. When a single nodule is the only evidence of metastasis, recognizing it as metastatic can be more difficult. In some instances, the origin of the previous cancer can provide a clue to the likelihood of a metastasis versus a primary lung cancer. In a retrospective study of patients with single pulmonary nodules and a prior history of cancer, multiple factors were examined as possible predictors for metastasis, including the histologic characteristics of the original extrapulmonary neoplasm, the patient's age, and smoking history.[21] Of 161 patients with solitary pulmonary nodules, 81 (50%) were determined to have a primary lung cancer, a finding more common in patients with a prior history of cancer of the head and neck, bladder, breast, cervix, bile ducts, esophagus, ovary, prostate, or stomach. Fifty patients (31%) were determined to have metastasis, a finding more common in patients with salivary, thyroid, and adrenal tumors; melanoma; and sarcoma. Primary lung cancer and metastases were equally likely in patients with prior cancer of the colon, kidney, or uterus. In patients with prior lymphoma or leukemia, there was a high proportion of patients with a benign diagnosis (6 of 14), perhaps reflecting the predisposition of these patients to infections.[21] In total, 30 of 161 patients (19%) had benign nodules. The large percentage of benign diagnoses in this study by Quint and colleagues[21] (1994 to 1999) contrasts with a larger but much older study by Cahan and associates[22] (1940 to 1975) in which only 11 of 800 patients (1.3%) proved to have a benign diagnosis. The higher incidence of benign disease in the more recent study can probably be explained by two factors: the greater use of CT scanning and thus higher rate of detection of nodules in the more modern study and the fact that the earlier study was a surgical series in which patients with a high pretest probability of benign disease may have been excluded. A consistent finding in these two studies, representing nearly 40 years from two large centers, was the high proportion of patients with head and neck squamous or esophageal cancers who subsequently developed *primary* lung cancer. Of course, these aerodigestive cancers share common risk factors, and the presence of a smoking history increases the likelihood that a solitary lung nodule in someone with a prior extrapulmonary neoplasm will prove to be lung cancer. These older studies and more recent data[23] confirm that the histologic origin of previously diagnosed cancer can help predict the probability that a pulmonary nodule in a patient with a previously treated cancer is metastatic malignancy, a primary lung cancer, or a benign lesion (Table 79.2).

Table 79.1 Differential Diagnosis of Single or Multiple Pulmonary Nodules in Patients With Prior Cancer

MALIGNANT
Metastasis
Primary lung cancer
BENIGN
Infectious
Fungal infection
Mycobacterial infection
Nocardiosis
Septic emboli
Noninfectious
Rheumatoid nodules
Hamartoma
Carcinoid
Sarcoidosis
Cryptogenic organizing pneumonia
Vasculitis (granulomatosis with polyangiitis)

PATHOLOGY

When a nodule is found to be malignant, the etiology of the nodule can be assessed by comparing the pathologic features

Table 79.2 Probability of Metastasis in a Solitary Pulmonary Nodule Based on a Prior Diagnosis of Cancer

Origin of Prior Tumor	Probability of Metastasis	Probability of Primary Lung Cancer	Probability of Benign Etiology
Head and neck	+	++++	+
Bladder or prostate	+	+++	+
Esophagus, biliary, stomach	+	+++	+
Breast	++	+++	+
Endometrial	++	++	+
Colorectal	++	++	+
Salivary, adrenal, kidney, thyroid, thymus	++	++	+
Melanoma	+++	++	+
Sarcoma	+++	+	+
Germ cell, testicular	+++	+	+
Leukemia or lymphoma	–	+	+++

Relative likelihood of primary cancer, metastatic cancer, or a benign pulmonary nodule from very low (+) to very high (++++) and intermediate (++ or +++).

Data from Quint LE, Park CH, Iannettoni MD. Solitary pulmonary nodules in patients with extrapulmonary neoplasms. *Radiology.* 2000;217:257-261.

of the prior cancer and the lung nodule. The pathologist's approach begins with a knowledge of the prior cancer, its stage and grade (if applicable), and the pretest likelihood of lung metastasis from a tumor with such characteristics. The gross and microscopic patterns of the possible metastasis may be sufficiently similar to the original primary tumor that the diagnosis is rendered on morphologic criteria alone. If the histologic features are not sufficient to distinguish between metastasis and primary lung cancer,[24] immunohistochemical stains are used to help guide the diagnosis (Table 79.3). Lung adenocarcinoma can be identified by specific immunohistochemical markers, including cytokeratin 7, thyroid transcription factor 1 (see eFig. 21.2B), and napsin.[24,25] For example, cytokeratin 7 can be useful for distinguishing adenocarcinoma of the lung from colon cancer metastasis, with cytokeratin 7 favoring lung, and cytokeratin 20 favoring colon.[24] Thyroid transcription factor 1, a nuclear transcription protein expressed in embryonic and adult epithelial cells of the lung and thyroid,[26] is detected in 75% of lung adenocarcinomas, but it is rarely detected in other adenocarcinomas that commonly metastasize to the lungs, except for thyroid cancer.[26] Napsin is an aspartic proteinase present in lung and kidney epithelial cells, and a newer marker for lung adenocarcinoma with similar sensitivity but slightly greater specificity for lung origin than thyroid transcription factor 1. Markers specific for other tumors can of course be used to identify lesions as metastatic; for example, breast cancers can generally be identified if they maintain their original pattern of staining for estrogen receptor or Her-2/Neu, melanomas can be identified by S100 or HMB45 immunoreactivity, and renal carcinoma can be identified by immunostaining for the product of paired box gene 2 or 8. Thus, in instances where the metastatic lesion retains specific markers present in the primary tumor, these stains can be useful for identifying metastases. Squamous carcinoma presents a challenge when attempting to distinguish between a metastasis and a primary lung carcinoma because there are no markers currently capable of distinguishing between squamous tumors of lung origin and those arising from extrapulmonary epithelial tissues. In such situations, the diagnosis relies almost entirely on clinical judgment.

Table 79.3 Immunohistochemical Stains Useful for Distinguishing Primary Lung Cancer From Metastatic Cancer From an Extrapulmonary Primary Cancer

Cancer	Positive Markers	Negative Markers
Lung (adenocarcinoma)	CK7, TTF-1, SP-A, SP-B, napsin	CK20, PAX2, PAX8
Lung (squamous carcinoma)	CK5/6, p63, p40	*
Colon	CK20	TTF-1, napsin
Bladder (urothelium)	S100P, GATA3	TTF-1, napsin
Breast	ER, PR, Her2/Neu	TTF-1, napsin
Prostate	PSA, prostatic acid phosphatase	TTF-1, napsin
Melanoma	HMB45, S100, tyrosine hydroxylase	Cytokeratin†
Thyroid	TTF-1, thyroglobulin	Napsin
Germ cell	Alpha-fetoprotein	TTF-1, napsin
Renal cell	PAX2, PAX8, RCCma	TTF-1, napsin

*There are no accepted stains to distinguish between lung primary and metastatic squamous cancer.
†Fewer than 10% of melanoma metastases stain positively for cytokeratin.
CK, cytokeratin; ER, estrogen receptor; PAX, paired box gene; PR, progesterone receptor; PSA, prostate-specific antigen; RCCma, renal cell carcinoma marker; SP, surfactant protein; TTF, thyroid transcription factor.

MOLECULAR CLASSIFICATION

Progress in molecular characterization of tumors has provided tools to assist in determining the nature of a lung nodule. Giordano and colleagues[27] attempted to develop a molecular classification scheme to discriminate among adenocarcinomas of the lung, colon, and ovary. These investigators identified three groups of 20 differentially expressed genes that correctly identified the origins of all but two of 154 tumors.[27] Other groups of investigators have proposed classifiers for a broader representation of tumors in an effort to categorize the origin of tumors diagnosed as carcinoma of unknown primary. Tothill and colleagues[28] developed a gene array–based classifier, validated with real-time polymerase chain reaction on 229 samples of known origin (a training set). This gene classifier was then able to assign a "tissue of origin" in 9 of 11 cases of carcinoma with unknown primary.[28] The two specimens that the gene classifier failed to classify were squamous carcinomas. Subsequent review of the clinical course of the patients supported the assessment of the gene classifier.[28] In another study, a gene expression–based classifier was devised to distinguish metastases of head and neck squamous carcinoma from primary lung squamous cancer, a task made difficult by both the histologic similarity and the shared risks for both diseases. The expression levels of 10 genes were able to discriminate between tumors of the lung and of the upper aerodigestive origin with high accuracy in both the training and validation samples.[29]

Finding viral antigens may help identify the source of a malignancy. The role of oncogenic strains of *human papillomavirus* (HPV) in squamous carcinogenesis of the cervix and oropharyngeal mucosa had prompted studies to determine whether HPV was involved in the development of lung squamous carcinoma.[30] Investigators using both in situ hybridization and polymerase chain reaction–based genotyping found that, in 132 squamous lung carcinomas, only 5 (1.5%) contained the HPV genome. All five of these patients had prior diagnoses of HPV-related squamous carcinoma in a different tissue, and thus the HPV-positive tumors were considered to be metastatic.[31] This would suggest that the finding of HPV-associated squamous cancer in the lung may serve as an indicator of metastasis, particularly in the setting of a prior HPV-positive extrapulmonary malignancy. Other investigators have used combined characterization of p53 and HPV typing to distinguish metastatic head and neck squamous cancer from primary lung cancer.[32] Molecular techniques such as these may provide new ways of classifying tumors as primary or metastatic when such characterization is needed to determine the best means of treatment.

OPTIONS FOR OBTAINING A TISSUE DIAGNOSIS

A diagnosis may be confidently made without the need for a biopsy when a patient with a history of prior cancer

known to metastasize to the lungs presents with nodules with highly typical characteristics: multiple, new, or growing lower lobe pulmonary nodules with smooth borders. A diagnosis may also be possible without the need for a biopsy in the common situations where measurable diagnostic serum markers exist (e.g., cancer antigen 19-9, cancer antigen 125, carcinoembryonic antigen, alpha-fetoprotein, β-human chorionic gonadotropin, CYFRA21-1 [a fragment of cytokeratin 19]). However, for tumors other than those of germ cell origin, these epithelial markers are not sufficiently specific, and a biopsy is usually warranted to guide therapy. In all cases, before performing a lung biopsy, it is important to search for evidence of metastasis to other sites where a less-invasive biopsy may yield the diagnosis. This should begin with a thorough history and physical examination. In older series, many of the data on tissue biopsies were derived from surgical material, and this remains the gold standard because of the quantity of material available to the pathologist.[22] Surgery, generally video-assisted thoracoscopic surgery, can be used for diagnosis when it is also the appropriate definitive therapy for patients with completely resectable lung metastases from solid tumors. However, there are nonsurgical biopsy options, each with strengths and drawbacks that can be weighed to achieve the best balance of certainty, risk, and cost. Fiberoptic bronchoscopy, percutaneous CT-guided biopsy, and surgical resection are discussed here, with each successive option providing increased accuracy (sensitivity and negative predictive value) but also increased risk and cost.

Bronchoscopy

Fiberoptic bronchoscopy is particularly useful for accessing centrally located lesions and mediastinal lymph nodes. Endobronchial ultrasound–guided transbronchial needle aspiration of enlarged mediastinal lymph nodes is safe and has excellent diagnostic accuracy for malignant involvement of mediastinal lymph nodes (see Chapter 27). In patients with a prior history of cancer, the finding of mediastinal adenopathy still has a very broad differential diagnosis, including benign or inflammatory reactive adenopathy, and pathologic confirmation should almost always be pursued. Endobronchial ultrasound–guided transbronchial needle aspiration is an excellent diagnostic option in such cases.[33] The accuracy of standard bronchoscopy for lung parenchymal lesions declines rapidly as the distance from the main-stem bronchi increases, so that traditional transbronchial sampling techniques have less than 20% sensitivity for peripheral lung nodules.[34] The increasing use and availability of navigational bronchoscopy have allowed biopsy of small peripheral lung nodules with greater accuracy. A multicenter prospective registry study involving more than 1200 patients (with nodules of unknown etiology, including those suspected of representing primary and/or metastatic disease) and experienced navigational bronchoscopists showed a rate of diagnostic yield of 73%. A retrospective analysis of the *American College of Chest Physicians Quality Improvement Registry, Evaluation, and Education* (AQuIRE) by Ost and colleagues[35] showed a wider range of success with navigation bronchoscopy, so navigation bronchoscopy should be reserved for situations in which the available expertise and track record suggest a high probability of a diagnostic result. By using bronchoscopy, multiple samples can be taken from one area or from multiple different nodules in a single procedure without an appreciable increase in the risk for pneumothorax. Given the low risk of pneumothorax (1–5%) and of major bleeding, the chief risk of the bronchoscopic biopsy, even when combined with electromagnetic navigation and real-time radial-probe ultrasound, is that of a nondiagnostic biopsy.[36] In the future, newer robotic-guided bronchoscopy systems may offer the ability to perform biopsies on even smaller, more peripheral nodules with greater accuracy. Sputum cytology, although proven for primary lung cancer, has not been evaluated for its utility in diagnosing metastases.

Computed Tomography–Guided Biopsy (see Chapter 21)

CT-guided biopsy by experienced clinicians has excellent accuracy.[37] This approach has greater sensitivity than bronchoscopy, particularly for peripheral lesions. The sensitivity of CT-guided biopsy of lung nodules varies with the size of the lesion, with a 65–75% accuracy for smaller lesions (<1 cm diameter) and a greater than 95% sensitivity for lesions larger than 1.5 cm in diameter.[38–40] Larger size and a more peripheral location are associated with greater diagnostic accuracy[41] as well as lower risk.[42] Core biopsies can be obtained in addition to or instead of cytologic material (see Fig. 21.3). The major risk of CT-guided transthoracic needle biopsy is pneumothorax, with up to 35% of patients developing pneumothoraces and 10–15% requiring tube thoracostomy or catheter drainage.[43] The risk of pneumothorax appears to increase with the length of the needle tract, with the presence of obstructive lung disease,[41] or with smaller nodules.[42] Less common complications are identifiable only in larger retrospective series. Severe complications of CT-guided biopsy were quite rare. Of 6881 cases, 74 (0.75%) patients were reported with severe complications, including 6 patients with air embolism (see eFig. 21.6), 10 with tension pneumothorax, 6 with severe pulmonary hemorrhage, 9 with hemothorax (see eFig. 21.5), and 6 with seeding of the needle tract. Eight deaths were reported.[44] In general, therefore, CT-guided biopsies are safe and accurate for carefully selected peripheral lesions.

Surgery

Resection of a nodule has the greatest diagnostic yield and may provide both diagnosis and treatment in a single procedure. The selection of patients for whom nodule resection is appropriate is a matter of controversy. There is a lack of randomized data comparing surgical and nonsurgical treatment of lung metastasis, and the data from reported series on surgical treatment of lung metastases lack uniformity in selection criteria. The sensitivity of surgery for diagnosis is likely close to 100% given that it is the accepted gold standard for tissue diagnosis of lung lesions. However, very small lung lesions can be difficult for the surgeon to palpate and may be missed. The risks of surgery include those for general anesthesia in addition to the risks associated with lung resection. A patient's pulmonary function and physical status can also affect the decision whether to perform surgery because noninvasive therapeutic modalities (radiation and ablation) can be used for patients with a high surgical risk. Thoracoscopic surgery is discussed later and is the preferred option when surgery is required for diagnosis.

TREATMENT

MULTIMODALITY THERAPY OF POTENTIALLY CURABLE DISEASE

Treatment of lung metastasis is largely dictated by the tissue of origin (Fig. 79.3). In cases of curable cancers, patients with lung metastases should be treated with appropriate multimodal therapy. Germ cell tumors, neuroblastoma, gestational trophoblastic tumors, lymphoma, and osteosarcoma are included in this category. In patients with nonseminomatous germ cell tumors, resection of residual nodules or masses after systemic chemotherapy is an appropriate approach. In cases of testicular cancer, such residual masses remain after chemotherapy in approximately 40% of patients who had advanced disease but negative serum tumor markers at the conclusion of treatment.[45,46] When resected, approximately one-half of these masses contain only necrotic tissue, a further 25% show a mature teratoma, and the rest contain residual carcinoma. Long-term follow-up studies after chemotherapy suggest that 90% of patients found to have mature teratomas on resection and 50% of those with residual carcinomas are cured by "adjuvant" surgery.[45,46] In patients with other tumors, treatment options are mainly nonsurgical. For patients with lymphoma, for example, in whom treatment alternatives are more numerous and systemic therapy is necessary, biopsy rather than excision is more appropriate. These varied treatment options highlight the importance of undertaking the care of these patients with multidisciplinary input.

STEREOTACTIC RADIOTHERAPY

Often referred to as stereotactic ablative body radiotherapy or *stereotactic body radiotherapy* (SBRT), this mode of therapy is used to deliver a precise and high dose of radiation using a small number of fractions. SBRT combines multiple collimated radiation beams using stereotactic localization on a target lesion or lesions. The multiple lower-dose beams intersect at the target to focus a high dose of radiation at a carefully defined location and to minimize the dose to normal surrounding structures. This technique is gaining favor as a preferred means of local curative or ablative treatment where surgery is either technically or medically inadvisable. In the context of lung metastases, a growing body of evidence suggests that SBRT to treat known sites of metastases, in addition to other supportive care, may result in longer overall survival.[47,48] One study randomized 99 subjects in a 1:2 ratio to receive standard supportive care or supportive care with SBRT to known sites of metastases (up to five).[47] In this study, 53% of patients had lung metastases, and

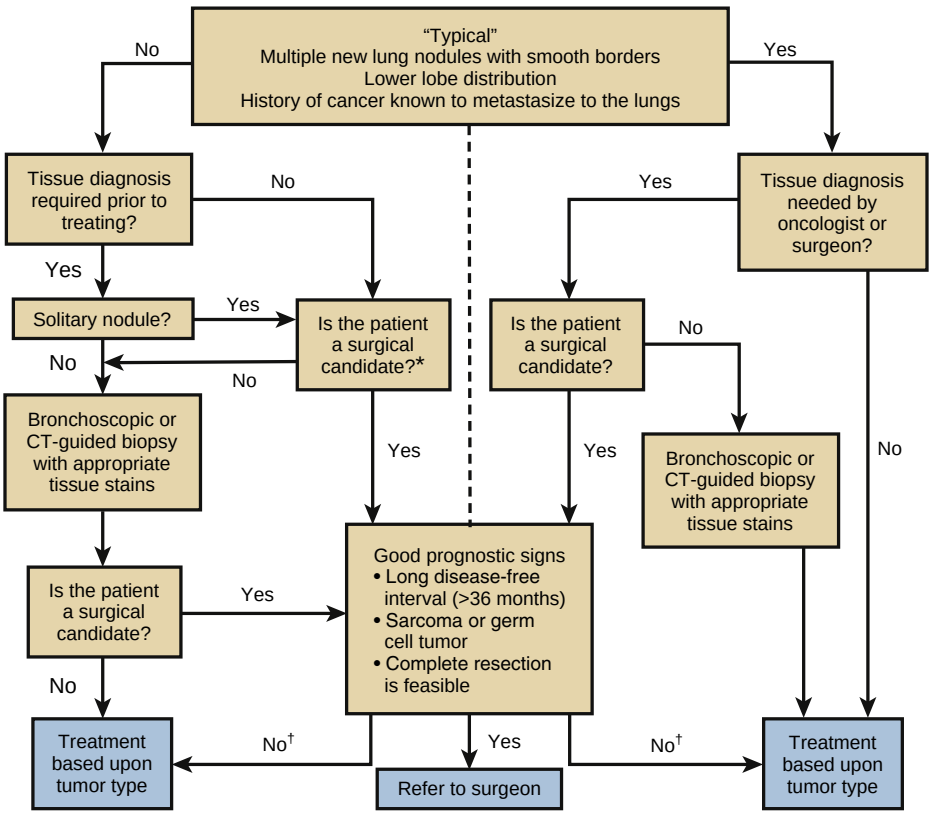

Figure 79.3 Suggested management algorithm for patients with known prior cancer and new lung nodule or nodules. Decisions take into account the typical or atypical appearance of a lung nodule in a patient with prior known cancer, the utility of a tissue diagnosis to the treating physicians, the physiologic fitness of the patient for surgery, and the known prognostic indicators for a favorable outcome after metastasectomy. Each patient should be managed individually, within the context of the skills and experience of local providers with the varied diagnostic and therapeutic options. *Patients at high risk for primary lung cancer may be considered for diagnostic lobectomy, when appropriate. †These are suggested criteria for surgical resection of lung metastases, and multidisciplinary teams should make this decision. Radiofrequency ablation or stereotactic ablative body radiotherapy may also be an excellent choice for these patients. CT, computed tomography.

overall survival was 28 months (95% confidence interval, 19 to 33) in the control group and 41 months (95% confidence interval, 26 to not reached) in the group that received SBRT. Additional prospective studies are ongoing to define the role of SBRT in treating oligometastatic disease.[49]

RADIOFREQUENCY ABLATION

Thermal ablation is a minimally invasive therapy that can be used for local cure or control of either primary or metastatic lung tumors. *Radiofrequency ablation* (RFA), which uses radiofrequency energy to generate frictional heating that leads to cell death, is the most commonly performed thermal ablation procedure used to treat lung tumors. Although the role of RFA is not as clearly defined as other options, the role of RFA in treating lung metastasis is gaining increased acceptance. Although RFA is more commonly performed to treat hepatic and renal tumors, it may be well suited to the lung because of its ability to concentrate thermal energy focally within tumor tissue with little or no energy spread to the adjacent aerated normal lung parenchyma.[51]

Smaller tumors, 3 cm or less in diameter, are more readily treated with RFA than are larger tumors.[52,53] Peripheral tumors surrounded by lung parenchyma and away from hilar structures can be safely treated with RFA (see Fig. 21.5 and eFig. 21.15).[54,55] However, more recent studies report that even tumors contiguous with certain vital structures, such as the thoracic aorta and pulmonary vessels, can be safely treated[56] because the cooling effect of the flowing blood may protect the large vessels from tissue damage. Multiple lesions in the same hemithorax can be treated at one sitting by experienced providers; however, because of the risk of pneumothorax (as high as 50% in one series[57]), bilateral lesions should not be treated during the same setting. Alternative ablative options include cryotherapy and microwave-mediated treatments, although these have not been as well studied as RFA.

SURGICAL RESECTION OF METASTASES

As measured by length of survival and quality of life, surgical resection of pulmonary metastases can be the appropriate choice. As metastasectomy has become more common, surgical registries have identified factors potentially associated with favorable outcomes. In general, the most consistent factor associated with improved survival is complete resection of all metastases. Incomplete resection is associated with survival rates that do not differ from rates in patients with no treatment at all. Another important favorable prognostic factor in numerous large series is a long disease-free interval between initial diagnosis of cancer and the discovery of lung metastasis.[58–60] Five-year survival was 33% when the disease-free interval was 0 to 11 months compared with 45% when the disease-free interval was more than 36 months.[61,62] Although a higher number of pulmonary metastases was once considered a poor prognostic factor, studies do not consistently find higher numbers of these metastases to predict poor outcomes. More accurate prognostic factors must be identified to improve selection of patients for metastasectomy. Suggested selection criteria for pulmonary metastasectomy, taken from various large series,[60,63,64] are shown in Table 79.4. In a retrospective analysis, selection of patients for pulmonary metastasectomy according to these criteria was associated with longer survival times.[60,65–68]

In 1991, the International Registry of Lung Metastases (comprising more than 5000 cases) was established to record and report on the long-term results of pulmonary metastasectomy according to the tissue of origin.[63] Patients with cancers that metastasize exclusively to the lungs have more favorable outcomes from pulmonary metastasectomy than do patients with cancers that metastasize more widely. Malignant diseases in patients with the greatest long-term survival after pulmonary metastasectomy include sarcomas, colorectal cancer, uterine or cervical tumors, head and neck cancer, breast cancer, testicular tumors, renal cell tumors, and melanoma (Table 79.5). Patients undergoing lung metastasectomy for osteosarcoma have some of the best results, but long-term survival after metastasectomy is not limited to patients with sarcoma.[63] Prolonged disease-free

Table 79.4 Suggested Criteria and Indications for Pulmonary Metastasectomy

ABSOLUTE CRITERIA
The patient must be able to tolerate the planned operative procedure.
The primary tumor is (or can be) controlled.
No extrapulmonary metastases exist; or, if present, they must be controllable.
Pulmonary metastases are completely resectable.
RELATIVE INDICATIONS
Pulmonary metastases are symptomatic (e.g. pneumothorax, hemoptysis).
Surgery is necessary to differentiate metastasis from primary lung cancer.
A long disease-free interval separated the metastasis from the primary cancer.

Data from Kondo H, Okumura T, Ohde Y, Nakagawa K. Surgical treatment for metastatic malignancies. Pulmonary metastasis: indications and outcomes. *Int J Clin Oncol.* 2005;10:81–85; and Kaifi JT, Gusani NJ, Deshaies I, et al. Indications and approach to surgical resection of lung metastases. *J Surg Oncol.* 2010;102:187–195.

Table 79.5 Tumor-Specific 5-Year Survival Rates Following Pulmonary Metastasectomy

Primary Malignancy	5-Year Survival (%)
Soft tissue sarcoma[72,86,87]	20–35
Osteosarcoma[88]	25–50
Melanoma[67,89]	5–33
Colorectal[70,90]	13–40
Testis (germ cell)[45,68]	50–80
Renal[71,91]	15–20
Breast[59,92,93]	25–50
Head and neck[69]	30

survival has been reported for patients with colon cancer, breast cancer, prostate cancer, and other malignancies.[58,66–72] Pulmonary metastasectomy for any cancer mandates adherence to certain surgical principles: complete resection must be possible, the primary tumor must be controlled, and there should be no other uncontrolled extrapulmonary metastases.

Surgical resection of pulmonary metastases requires careful planning and preparation. As with any lung resection, the number, location, and size of the lesion or lesions; the patient's pulmonary function; and the general condition of the patient must be considered, as must any evidence of local invasion or the prospects for response to systemic therapy. CT has high sensitivity and accuracy for localizing pulmonary nodules for resection. An emerging strategy is to mark small peripheral tumors before thoracoscopic resection by using guidewires, dye, radioactive tracers, or coils (see Fig. 21.6).[73,74] These markers can be placed either percutaneously or by bronchoscopy (typically using navigational bronchoscopy) before resection. Intraoperative localization of small, nonpalpable nodules can be aided with a sterile ultrasound or radioactivity probe in deflated lung.

In tumors avid for ^{18}F-fluorodeoxyglucose, PET scanning should be performed before pulmonary metastasectomy to exclude the presence of synchronous extrapulmonary metastasis. Increased activity on PET or lymph node enlargement seen on CT suggests the need for confirmation using less invasive biopsy techniques such as mediastinoscopy, transthoracic needle biopsy, and transbronchial needle biopsy (with or without endobronchial ultrasound). Apart from certain germ cell tumors (which may remain curable despite metastatic disease), the finding of synchronous metastasis outside the lung would be a contraindication to pulmonary metastasectomy.

Thoracotomy has been the most frequently used approach for unilateral metastasectomy, primarily because it enables the surgeon to palpate the lung for lesions. Similarly, sternotomy or a clamshell incision has been used for bilateral palpation and metastasectomy. To avoid the morbidity of a thoracotomy or sternotomy, alternate surgical approaches have been sought. Subxiphoid pulmonary metastasectomy has been described.[75] The subxiphoid approach permits palpation of both lungs without transecting large muscles or bone, but it can result in diaphragmatic hernias and has not been widely adopted. Thoracoscopy also allows minimally invasive resection of pulmonary metastases and has now become the gold standard approach. Initially, thoracoscopic pulmonary metastasectomy was criticized for its limited ability to permit palpation of the lungs to identify unknown metastases. However, as the resolution of CT scanning has improved, the likelihood of pulmonary nodules that can be palpated but not visualized on CT scan has decreased dramatically, thus improving the relative utility of thoracoscopic metastasectomy. In addition, instruments and techniques have evolved to allow enhanced visualization and even thoracoscopic palpation of lung parenchyma. Compared with thoracotomy, thoracoscopic metastasectomy has several advantages, including smaller incisions, less pain, earlier recovery, and fewer postoperative adhesions. The last advantage is especially important because repeat pulmonary metastasectomy may be indicated based on the same criteria as the initial metastasectomy.[62,63] Prior thoracotomy was considered a possible contraindication to future thoracoscopy, but the thoracoscopic take-down of adhesions after thoracotomy has proved to be feasible and well tolerated.[76] Indeed, more than 50% of patients who undergo complete pulmonary metastasectomy will develop recurrence. The probability of relapse is higher for sarcoma and melanoma than for epithelial or germ cell tumors. In the International Registry, repeat metastasectomy yielded 44% survival at 5 years and 29% at 10 years,[63] results comparable to those after initial metastasectomy. A retrospective, nonrandomized study comparing outcomes of patients who had undergone metastasectomy with open versus thoracoscopic approaches did not find differences in survival, although fewer complications and shorter hospital length of stay favored the thoracoscopic approach.[77] Thus, the approach for surgical resection should be carefully planned with respect to several criteria, including the number and location of lesions, the surgeon's experience, and the possible need for repeat metastasectomy.

Before any resection, all lung lesions should be identified to plan a resection that minimizes the loss of lung parenchyma. The extent of pulmonary resection is an important consideration. According to the registry data, metastasectomy was achieved by wedge resections in 67%, segmentectomy in 9%, and lobectomy or bilobectomy in 21%.[63] The operation should be planned to remove the least amount of lung parenchyma. Segmentectomy is increasingly favored over lobectomy for central lesions. Wedge resections for peripheral nodules should be the standard. Lymph node dissection is not encouraged given the low incidence of nodal involvement with pulmonary metastasis, associated morbidity, and the poor survival of patients with nodal metastasis regardless of resection. Pneumonectomy or extended resection was rarely used in the registry (3%) and should be reserved for special circumstances when there is acceptable surgical risk and a reasonable likelihood of long-term survival.[63]

The morbidity and mortality associated with pulmonary metastasectomy should be very low. Most series report less than 2% mortality and 10% morbidity.[63] The most common complications are persistent air leak and infection. Preoperative chemotherapy or radiation may increase the risk of respiratory failure after metastasectomy when high fractional concentrations of oxygen are used perioperatively.[46] Anesthesiologists should be alerted to a history of chest irradiation or chemotherapy (particularly with bleomycin used for germ cell tumors) and use the lowest possible fraction of inspired oxygen for these patients.

Most reports regarding the effectiveness of pulmonary metastasectomy have been retrospective. These nonrandomized and uncontrolled series introduce selection and lead-time bias. Reported survival rates of 30–40% at 5 years are encouraging, but the selection criteria used for surgical resection, as well as the nonrandomized design of these studies, must be considered when comparing treatment options. Additional studies are needed to define patients who will receive maximum benefit from metastasectomy. For example, molecular predictors of prognosis have been used in assessing treatment options for patients

with primary tumors, but this approach has been more difficult to incorporate into an algorithm (see Fig 79.3) for treating metastases because of the diversity of origins of primary tumors and the relatively small numbers reported in any given series of metastectomy.[78]

PALLIATIVE CARE

Unfortunately, most adults with pulmonary metastases from solid tumors have incurable disease, and palliative therapy is necessary. For selected cancers, palliative treatment may include radiotherapy, chemotherapy, hormonal, or biologic or targeted therapies. Agents chosen for palliative therapy should balance acceptable levels of toxicity with the expected degree of tumor response and symptom control. Radiation therapy for patients with radiosensitive tumors can provide rapid and effective symptom relief. For patients with endobronchial obstruction, endobronchial tumor ablation using rigid bronchoscopy, brachytherapy, laser, electrothermal cautery, or cryoprobes can be very effective for palliation (see Chapter 28). Because these approaches require specialized training, it is best to seek referral to a center with experience in such techniques when they are needed. Given that most centers may specialize in only one, or at most two, of these interventional methods, direct comparisons of the efficacy and safety of palliative interventions for malignant airway obstruction have not been reported. For patients with end-stage dyspnea, opiates and oxygen therapy may relieve symptoms. In general, for end-of-life care, social, emotional, and physical rehabilitation support measures, as well as hospice services, are valuable.

SPECIAL CASES

AIRWAY METASTASIS

Although rare, large airway involvement with endobronchial metastasis can produce very distressing symptoms of dyspnea and/or hemoptysis. Awareness of the clinical scenario along with available diagnostic and management strategies can be very helpful in palliating these patients. Reported series of patients with endobronchial metastasis are generally small, but they uniformly emphasize the utility of fiberoptic bronchoscopy for diagnosis, as well as interventional methods for symptom control and palliation. In addition to lung cancer, tumors that metastasize to the bronchi include colon, breast, renal cell carcinoma (eFig. 79.1), melanoma, and many others.[79] The tissue origin of airway metastases probably reflects the relative incidence of solid tumors in general rather than a biologic predisposition to seed the airway. Colon cancer can metastasize to the bronchi without involvement of the liver.[80] Radiation can be used for palliation in patients with airway obstruction due to radiosensitive tumors. Mechanical means, including stents, and endobronchial ablative methods (laser, cryoprobe, argon plasma coagulation or physical debridement) can be used for tumors that are relatively radioresistant. (see Chapter 28) These interventions require experienced thoracic surgeons or interventional pulmonologists who can also manage complications of these procedures.

VASCULAR EMBOLIC METASTASIS

A rare but dramatic presentation of lung metastasis is tumor embolism. When it is clinically evident, the symptoms are those of "subacute right heart failure" with dyspnea, edema, elevated jugular venous pressure, and auscultatory evidence of pulmonary hypertension and right ventricular failure. Antemortem diagnosis is difficult unless clinical suspicion is high. Tumor embolism has been reported as the initial presentation of extrapulmonary cancer or as a postmortem finding in those with no antemortem respiratory symptoms.[81] In a series of 214 selected autopsies, 89 patients had evidence of tumor emboli, and only 50 of these had clinical records indicating the presence of respiratory symptoms before death. However, in 29 of the 50 patients, tumor emboli were the recorded cause of death.[82] Tumors arising from the breast, liver, and pancreas accounted for more than 50% of the cases, but many tumor types were represented in this series.[81] Pulmonary arterial tumor emboli may affect larger pulmonary arteries, so-called macroscopic tumor embolization, which may be visible on thoracic CT (eFigs. 79.2 and 79.3). Small pulmonary arteries may also be affected by tumor embolization, a situation referred to as microscopic tumor embolization (eFig. 79.4). Thoracic CT findings (eFig. 79.4A–C) include small centrilobular opacities, possibly with branching configurations (simulating infection), smooth or nodular interlobular septal thickening, and areas of ground-glass opacity or parenchymal consolidation reflecting hemorrhage or infarction. When tumor embolism is suspected, cytologic examination of pulmonary capillary blood obtained through a wedged pulmonary arterial catheter is a possible diagnostic method.[83] Treatment options may be limited to anticoagulation and systemic chemotherapy. Surgical embolectomy is not possible in this setting.

PLEURAL METASTASES

Malignant pleural effusions are usually metastatic and are a significant cause of morbidity in patients with cancer (see Chapter 114). Diagnosis is typically straightforward and can be made in pleural fluid with cytology, though this may require more than one thoracentesis if initial cytology is negative. Flexible or rigid thoracoscopic examination of the pleural space is increasingly used to diagnose pleural metastasis. Metastatic disease to the pleura is incurable, and treatment is directed toward palliation of symptoms of dyspnea. In a randomized study, indwelling tunneled pleural catheters were superior to talc pleurodesis. However, there was no difference in validated quality of life metrics between the two groups, and blockage of the indwelling catheter was a common complication of the group treated with this approach.[84] Clinical practice guidelines have recommended that either indwelling catheters or talc pleurodesis can be used for palliation.[85] Indwelling pleural catheters are particularly useful when there is nonexpendable lung, and they can help dyspnea by reducing the expansion of the chest wall and returning the diaphragm to a more normal position.

Key Points

- Lung metastases are common and arise from most types of solid tumors.
- Metastases are nearly universally responsible for cancer mortality and, as these molecular insights are exploited to develop novel strategies for prevention or treatment of metastases, survival *with* cancer (as opposed to a cure *for* cancer) is an attainable goal.
- In addition to benign causes, a pulmonary nodule in a patient with prior cancer can be a metastasis or a primary lung cancer; the likelihood of metastasis will vary with the original type of cancer and risk factors for primary lung cancer.
- When clinical and/or histologic evaluation cannot distinguish primary lung cancer from a metastasis, immunohistochemistry for tumor-specific markers can be useful. Future directions will include molecular phenotyping.
- The choice of diagnostic method will be determined by the patient's status, the natural history of the prior cancer, the availability of specialized diagnostic methods, and the need, or lack thereof, for a tissue diagnosis before offering therapy.
- Ablation (e.g., radiofrequency, thermal, cryotherapy) is a potential therapeutic option when surgical resection, radiation therapy, or systemic therapy is not.
- Stereotactic body radiotherapy provides local curative or ablative treatment when surgery is either technically or medically inadvisable.
- Surgery for both diagnosis and treatment is appropriate in selected patients. The most important predictor of successful treatment is the ability to address by surgery, radiation, or other modality all visible and palpable lung nodules.

Key Readings

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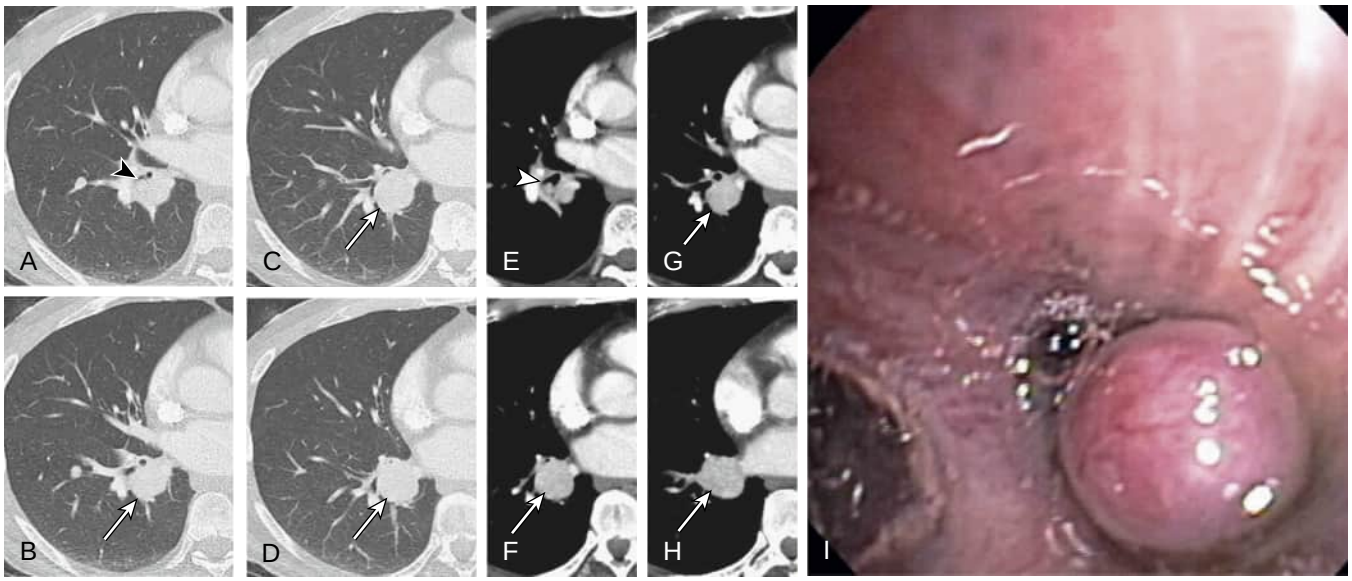
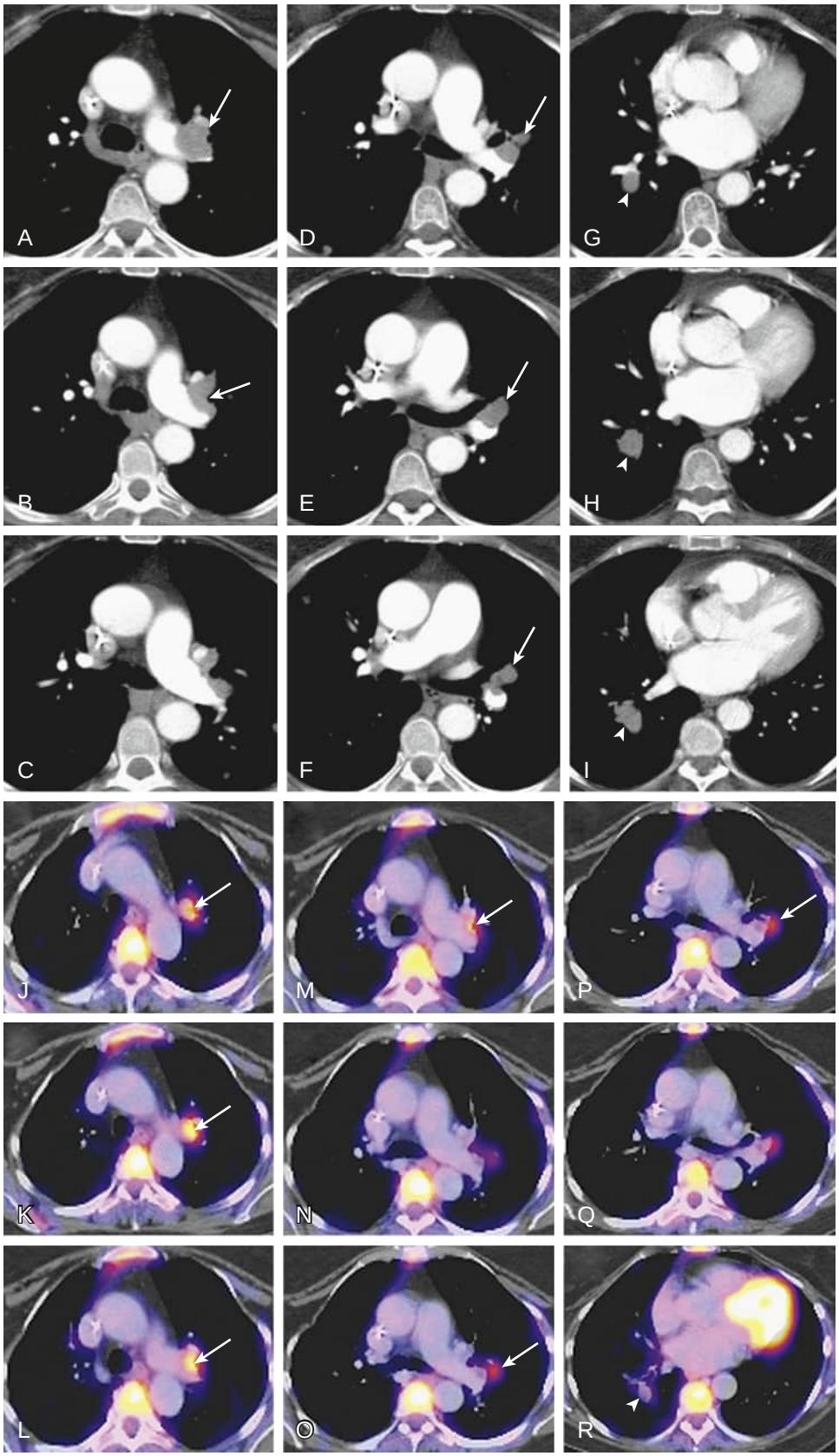
Complete reference list available at ExpertConsult.com.

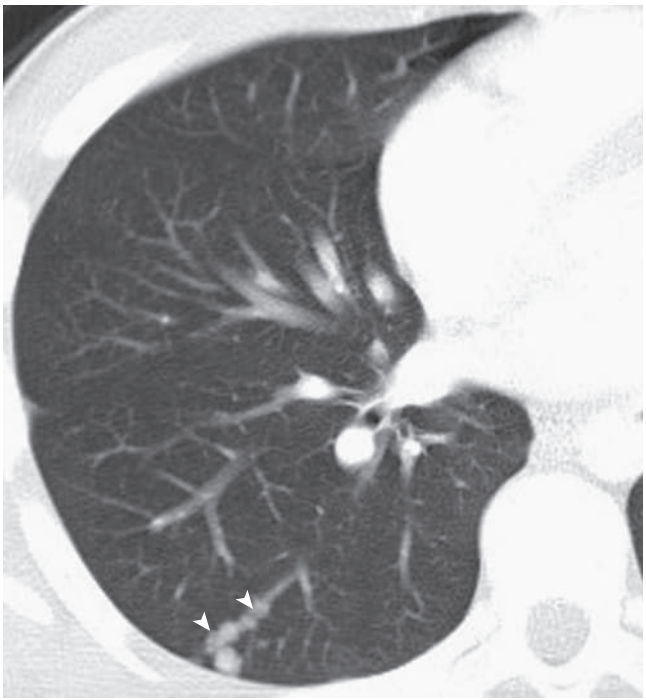
eFIGURE IMAGE GALLERY



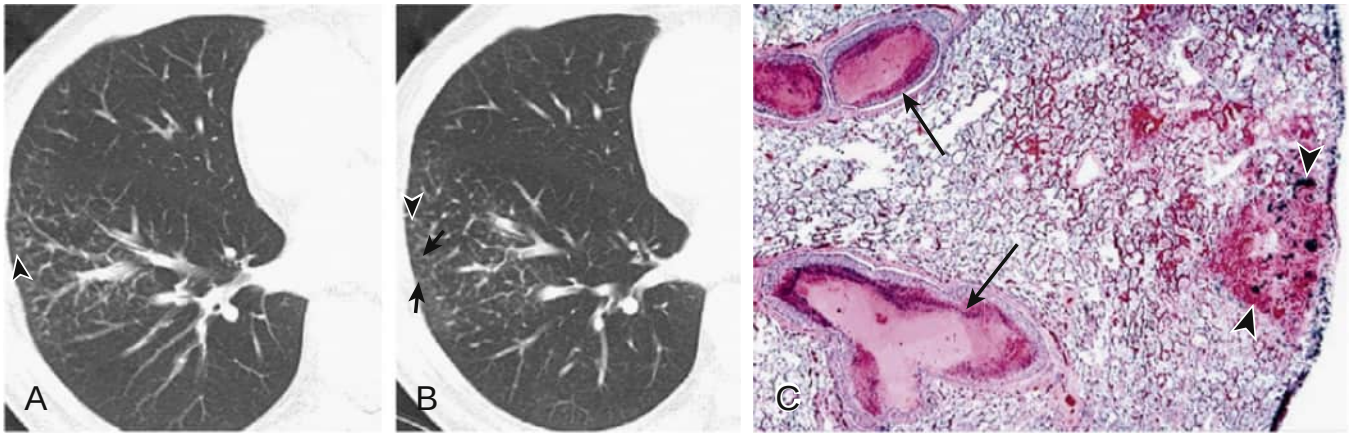
eFigure 79.1 Endobronchial metastasis from renal cell carcinoma. (A–H) Axial enhanced thoracic computed tomography displayed in lung windows (A–D) and soft tissue windows (E–H) shows an enhancing nodule (*arrows,* B–D, F–H) related to the right lower lobe posterolateral basal bronchial trunk. Note displacement of the anterior basal segmental right lower lobe airway (*arrowheads,* A and E). (I) Bronchoscopic image shows the endobronchial tumor protruding into the airway.



eFigure 79.2 Large vessel tumor emboli. (A–I) Axial thoracic computed tomography displayed in soft tissue windows shows low-attenuation filling defects in the left (*arrows,* A–B, D–F) and right (*arrowheads,* G–I) pulmonary arteries, mimicking pulmonary emboli. (J–R) Axial fused ^{18}F-fluorodeoxyglucose positron emission tomography images show metabolic activity with the left (*arrows,* J–M, O–P) and right (*arrowhead,* R) intravascular filling defects, consistent with macroscopic large vessel tumor emboli. These abnormalities did not resolve with anticoagulation and progressed in a fashion similar to other metastatic foci elsewhere. (Courtesy Michael B. Gotway, MD.)



eFigure 79.3 Macroscopic large vessel tumor emboli from Ewing sarcoma. Axial thoracic computed tomography displayed in lung windows shows a "beaded" appearance of a peripheral right lower lobe pulmonary artery (*arrowheads*), characteristic of macroscopic tumor emboli.



eFigure 79.4 Microscopic tumor emboli in a patient with gastrointestinal malignancy. (A–B) Axial thoracic computed tomography images displayed in lung windows show very small centrilobular opacities (*arrowheads,* A–B) and interlobular septal thickening (*small arrows,* B) in a restricted portion of the right lower lobe. (C) Histopathologic specimen shows small pulmonary arterial tumor emboli with necrosis (*arrows*) and subpleural infarction (*arrowheads*). (Courtesy Martha Warnock, MD, Professor Emerita, Department of Pathology, University of California, San Francisco.)

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80 BENIGN LUNG TUMORS

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INTRODUCTION
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Papillomas
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INTRODUCTION

Although in practice the terms "tumor" and "neoplasm" tend to be used interchangeably, there are important and substantial differences between them. A tumor may be regarded as any grossly mass-forming lesion, while a neoplasm is considered an abnormal proliferation of tissues, arising outside of physiologic control. Neoplasms may represent a clonal cell population or be heterogeneous and comprised of multiple cell types. As a result a tumor need not be a neoplasm and a neoplasm may not always be tumefactive. Examples include a localized variant of organizing pneumonia and bone marrow involvement by leukemia, respectively. This chapter reviews the salient clinical and pathologic features of benign lung neoplasms, collections of clonal cells, which generally do not invade or metastasize; these account for only a small fraction of resected lung tumors. Although rare, benign lung neoplasms might mimic more biologically aggressive lesions, posing diagnostic challenges for clinicians, radiologists, and pathologists alike. Localized, non-neoplastic conditions, such as granulomas and organizing pneumonia, that can radiographically resemble neoplasms are not discussed. In addition, rare primary lung tumors are discussed in Chapter 78. When there is overlap between benign and malignant behavior, some of the same entities are discussed in both chapters.

CLINICAL MANIFESTATIONS

Most benign lung tumors present as solitary pulmonary nodules, incidentally discovered on chest radiographs or *computed tomography* (CT) scans performed for other reasons. The majority of individuals are asymptomatic with occasional patients presenting with signs of airway obstruction, bleeding, or compression of surrounding structures. In some cases, a preoperative diagnosis may be possible using a combination of imaging data and transthoracic or endoscopic biopsy. In most cases, however, a diagnosis is recognized only after surgical resection of a lesion for which the possibility of malignancy could not be excluded.[1,2] The decision to proceed with surgical resection in a patient with an unexplained, solitary pulmonary nodule is complex and predicated on analysis of various risk factors, including any prior history of malignancy and radiographic characteristics of the lesion, among others. During the course of evaluation, patients may undergo ^{18}*F-fluorodeoxyglucose positron emission tomography* (FDG-PET) scan. Unfortunately PET scan cannot reliably discriminate between benign and malignant lung neoplasms in a patient with an indeterminate lesion. Therefore, it is rarely informative for patient management in this setting.[3,4] Finally, current recommended approaches to some patients with a solitary lung nodule include watchful waiting.[5,6] Prediction models for assessing the likelihood of malignancy[7–9] and Fleischner guidelines for the management of indeterminate pulmonary nodules[10] are helpful in suggesting watchful waiting for "low risk" nodules (<10% probability of malignancy). The approach to evaluation of a patient with an undiagnosed pulmonary nodule is discussed in detail in Chapter 41.

BENIGN EPITHELIAL LESIONS

PAPILLOMAS

Papilloma refers to a papillary neoplasm, consisting of epithelial-lined, arborizing, fibrovascular fronds (Fig. 80.1). Solitary papillomas are usually exophytic and protrude into conducting airways (eFig. 80.1 and Videos 80.1A–B). Given these features, symptomatic patients commonly present with symptoms due to airway obstruction or hemoptysis. Most solitary papillomas arise in large central airways; rarely, they can develop in smaller bronchioles and present as peripheral nodules.[11,12] Flieder and colleagues divided lung papillomas into three categories based upon the lining epithelium: squamous cell, glandular, and mixed types.[13] More recently, ciliated muconodular papillary tumor has also been described and considered by many to be a variant of glandular papilloma.[14] Of the subtypes, squamous lesions account for nearly 70% of reported cases. Squamous cell papillomas are found more frequently in men than women, and are more often associated with cigarette smoking and *human papillomavirus* (HPV) infection than the other subtypes.[13,15] Malignant transformation of solitary papillomas is very rare and limited to single case reports.[16,17] In the majority of cases initially interpreted as papillomas and later discovered to harbor a frankly malignant component

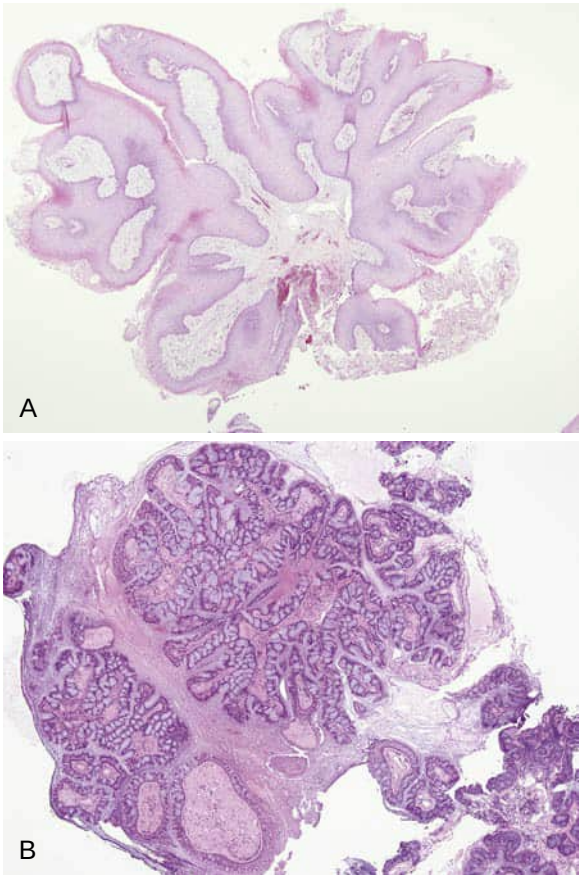

Figure 80.1 Papillomas. Low-magnification photomicrographs illustrate two different solitary endobronchial papillomas from adults. (A) Squamous papilloma showing papillary architecture with central connective tissue stalk covered by benign squamous epithelium with associated keratinous debris. (H&E stain; ×20 original magnification.) (B) Glandular papilloma lined by benign mucinous columnar cells with abundant extracellular mucus. (H&E stain; ×40 original magnification.)

on definitive excision, inadequate sampling at the time of biopsy likely accounts for this discrepancy rather than true malignant transformation. Most patients with solitary papillomas do well regardless of histologic type, and surgical resection is curative. Local recurrences are rare and limited to patients whose papilloma was not completely removed at the time of biopsy or who underwent subtotal bronchoscopic resection.[13] Cytology specimens obtained from these patients, including fine-needle aspirations and exfoliative respiratory specimens, are commonly reported as "atypical" and lack distinguishing cytomorphologic features to establish a diagnosis of benign papilloma with confidence[18]; therefore, endobronchial biopsy or surgical resection is often needed for accurate diagnosis.

Recurrent respiratory papillomatosis (RRP), also referred to as *juvenile laryngeal* or *laryngotracheal papillomatosis,* is a form of HPV-related papillomatosis. RRP is characterized by multiple papillomas that most commonly involve the larynx but can arise anywhere along the respiratory tract.[19] RRP was once considered a disease of children, usually presenting before age 5 years, but it is now recognized in adult patients as well.[20,21] HPV types 11 and/or 6 are implicated in virtually all cases. In children, infection is acquired perinatally through vertical transmission whereas, in adults, it

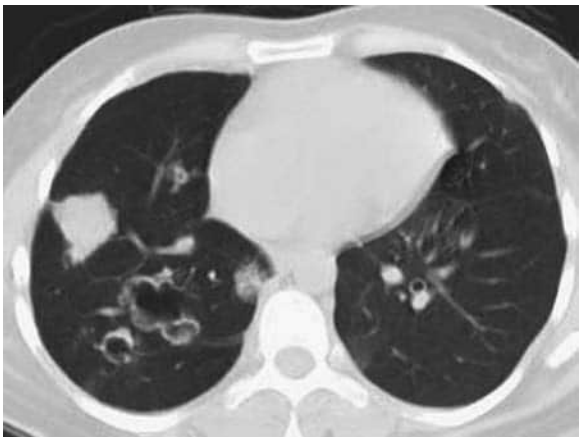

Figure 80.2 Recurrent respiratory papillomatosis. Axial computed tomography of a patient with recurrent respiratory papillomatosis involving her right lung. There are multiple nodules and opacities, the largest measuring 3 cm in greatest dimension. Some of the nodules appear cavitated. (Courtesy Dr. Jay Ryu, Professor of Medicine, Mayo Medical School.)

may be related to new or latent infection.[22–24] Presenting symptoms include hoarseness, stridor, and dyspnea. Surgical excision or laser ablation are the mainstays of therapy for patients with symptomatic disease.[21] Although benign, recurrences are relentless and often necessitate multiple procedures. Squamous cell carcinoma, an infrequent complication, is most often observed in the setting of HPV-11 infection.[25,26]

Papillomas spread to the alveolar lung parenchyma in approximately 3% of patients with juvenile onset RRP. HPV type 11 is disproportionately represented in these patients. For example, HPV-11 is detected in 90% of patients with peripheral lung papillomas.[27] Parenchymal disease typically presents as multiple, asymptomatic radiographic nodules that may be cystic or solid (Figs. 80.2 and 80.3; see eFigs. 78.22 through 78.25).[27–30] The lesions can occasionally show high FDG avidity on PET scan. The histopathologic findings are unique, demonstrating tufts of benign squamous papillomas emanating from distal bronchioles with polypoid extensions into adjacent alveolar spaces (Fig. 80.4). The involved bronchioles are often ectatic, thus mimicking the appearance of cavitation on imaging studies.

Parenchymal lung involvement in patients with RRP is often associated with an aggressive clinical course. There is currently no effective medical therapy, but evidence suggests that HPV vaccination might offer one therapeutic strategy by decreasing disease burden and increasing the time between procedures.[31,32] About 15% of patients with parenchymal disease develop squamous cell carcinoma. The average age of cancer diagnosis is 23 years, with some patients dying of malignancy or progressive lung destruction from RRP (see Fig. 78.7 and eFig. 78.25).[27,33]

ADENOMAS

Whether arising in the peripheral lung or in the central lung as endobronchial lesions, adenomas of the lung are rare and comprise a morphologically heterogenous group of benign epithelial neoplasms. In the peripheral lung, four types are currently recognized, including sclerosing



Figure 80.3 Recurrent respiratory papillomatosis. Gross photograph of left lower lobe excised from a 19-year-old with multiple recurrences of respiratory papillomatosis. The patient had extensive papillomatosis involving his central airways and a large cystic cavity containing innumerable papillomas replacing much of his left lower lobe. (From Kerley SW, Buchon-Zalles C, Moran J, et al. Chronic cavitary respiratory papillomatosis. *Arch Pathol Lab Med*. 1989;113:1166–1169.)

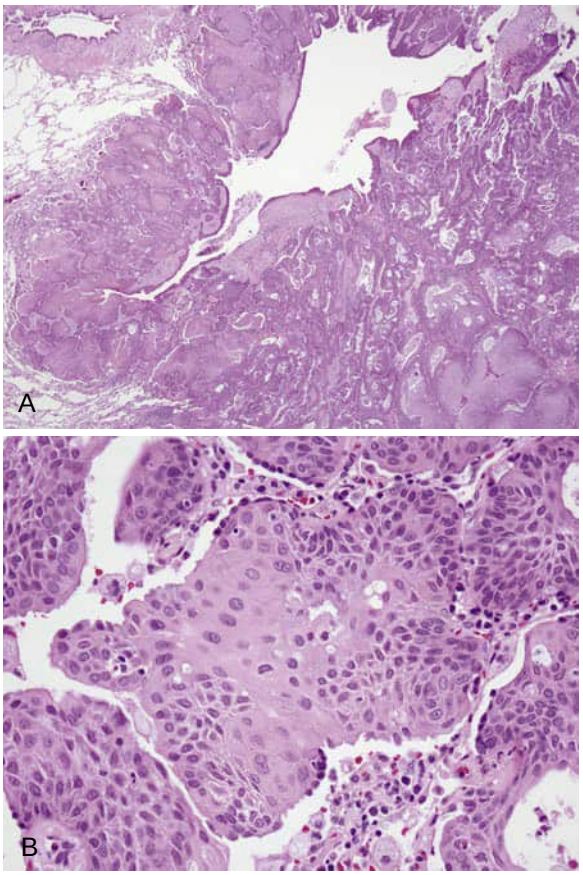

Figure 80.4 Recurrent respiratory papillomatosis. Photomicrographs illustrate lung involvement in a 40-year-old woman first diagnosed with recurrent respiratory papillomatosis at the age of 2 years. She underwent multiple resections of lung nodules starting in her second decade of life. (A) Low-magnification photomicrograph illustrates multiple benign papillomas within an ectatic bronchiole with a centrally dilated lumen. (H&E stain; ×20 original magnification.) (B) High-magnification photomicrograph illustrates cytologically bland, benign appearance of the lung papillomas. (H&E stain; ×400 original magnification.)

pneumocytoma, alveolar adenoma, papillary adenoma, and mucinous cystadenoma.

In the 1999 and 2004 versions of the *World Health Organization* (WHO) classification of lung tumors, *sclerosing pneumocytoma* (SP), historically referred to as sclerosing hemangioma, was considered to be in the "miscellaneous tumors" group, due to its uncertain histogenesis. Now, in the 2015 WHO classification, SP has been moved into the "adenomas" group because it is well recognized to be derived from incompletely differentiated respiratory epithelium.[34] SP has a female predominance, with women comprising up to 80% of patients in some studies. The mean age of diagnosis is the fifth decade of life, but SP has been reported in a wide age range, including children. Most patients are asymptomatic and incidentally discovered to have a solitary pulmonary nodule during imaging studies performed for unrelated problems.[35–41] Multiple lesions are rare but have been reported in up to 5% of patients.[42] CT findings are typically described as showing a well-circumscribed, subpleural, round to oval nodule with smooth margins and inhomogeneous enhancement; associated calcifications are present in about one third of patients (eFig. 80.2).[42–44] PET scans show significant FDG avidity (maximum standard uptake value [SUV_{max}] > 2.5) in half of cases.[45,46]

Resected SP are sharply circumscribed, peripheral nodules averaging 2 to 3 cm in diameter (Fig. 80.5). The histologic hallmark is intratumoral heterogeneity, resulting from both a mixture of cell types and highly variable growth patterns. Two populations of neoplastic epithelial cells are a characteristic feature, and include (1) surface cuboidal cells derived from pneumocytes or club cells and (2) pale stromal round cells with an incompletely differentiated respiratory epithelial phenotype.[37,47–51] Neoplastic cells are arranged in various growth patterns that often include a focally conspicuous sclerotic stroma that is often calcified (Fig. 80.6). Given the expression of the pneumocyte specific marker, TTF-1, by both surface and round cells and frequent papillary configuration, SP represents a potential diagnostic pitfall on fine-needle aspirates and may be misdiagnosed as lung adenocarcinoma.[52–54] "Metastatic" deposits in regional lymph nodes are rare and have no impact on the fundamentally benign behavior of these lesions; patients are considered cured by surgical management alone.[55–57]

Other types of adenomas involving the peripheral lung parenchyma, including alveolar adenoma, papillary adenoma, and mucinous cystadenoma, are even more rare. Of these, *alveolar adenoma* is the most common variant with the largest case series comprised of only 17 patients and the literature otherwise limited to single case reports.[58–63] The average age at diagnosis is between 50 and 55 years. Nearly all patients are asymptomatic at the time of diagnosis. Radiographically, alveolar adenomas present as well-circumscribed, peripheral nodules, averaging just over 2 cm in greatest dimension.[58,59] PET scans reportedly show alveolar adenomas as having no uptake or mild positivity.[60,61] Pathologically, alveolar adenomas are partially cystic nodules in which connective tissue septa are lined by cytologically bland epithelial cells (Fig. 80.7). The epithelial cells are derived from pneumocytes, while the stromal cells are undifferentiated fibroblasts; therefore, both epithelial and stromal components are regarded as neoplastic.[59,62] There is a single case report of papillary adenocarcinoma

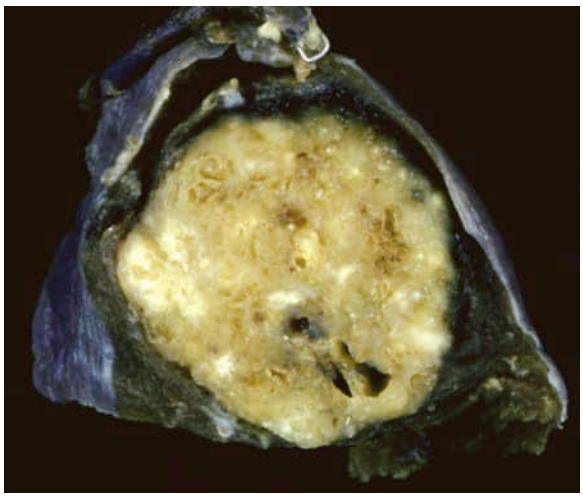

Figure 80.5 Sclerosing pneumocytoma. In this resected specimen, the lobulated nodule is well circumscribed and situated near the visceral pleura. The cut surface betrays the fundamentally heterogeneous nature of these neoplasms, showing a variegated pattern of pale brown and white with both solid and spongy areas.

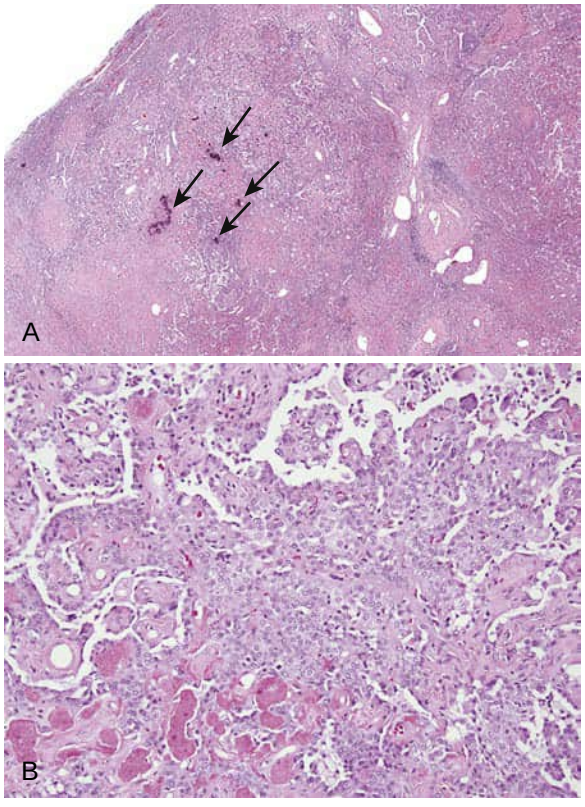

Figure 80.6 Sclerosing pneumocytoma. (A) Low-magnification photomicrograph shows the classic features of sclerosing pneumocytoma in which sclerotic zones with dense collagen deposition and focal calcifications *(arrows)* alternate with variably cellular regions. (H&E stain; ×2 original magnification.) (B) Higher-magnification photomicrograph shows solid and papillary growth patterns. The central area is solid and composed of the pale-staining round cells demonstrating a phenotype consistent with incompletely differentiated respiratory epithelium. (H&E stain; ×400 original magnification.)

arising within an alveolar adenoma; however, whether this case represents true malignant transformation of an alveolar adenoma or whether the two lesions are "true-true, unrelated" is unclear. As in other cases of alveolar adenoma, surgical resection alone was curative.[63]

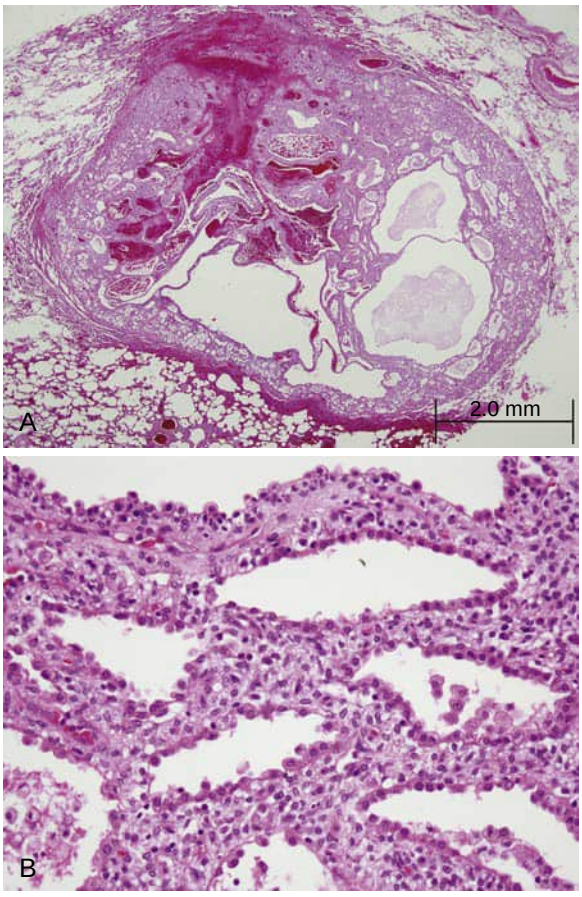

Figure 80.7 Alveolar adenoma. (A) Low-magnification photomicrograph shows a well-demarcated partially cystic mass in a peripheral lung biopsy. (H&E stain; ×20 original magnification.) (B) Higher-magnification photomicrograph illustrates connective tissue septa lined by bland pneumocytes. (H&E stain; ×400 original magnification.)

Papillary adenomas have been described in fewer than 25 patients.[64–70] Of these cases, nearly all patients underwent surgical resection for an asymptomatic solitary peripheral nodule and remained free of disease at follow-up. A single case report details multiple papillary adenomas in a 13-year-old boy with neurofibromatosis type 1; however, there is no established relationship with any specific gene mutation.[69,70] Histologically, papillary adenomas are circumscribed lesions composed of connective tissue fronds lined by cytologically bland type 2 pneumocytes (Fig. 80.8).

Mucinous cystadenoma is a rare lung neoplasm that overlaps with unequivocally malignant mucinous adenocarcinomas.[71–77] Gao and Urbanski proposed separating them into three histologically defined categories: mucinous cystadenoma, mucinous cystic tumor with atypia, and mucinous cystadenocarcinoma.[72] Histologically, benign tumors without atypia accounted for only 13% of reported patients, further emphasizing that this is an extremely rare neoplasm. Patients typically present with slowly growing, well-demarcated, peripheral lung masses that may or may not appear cystic.[73–76] All patients with histologically benign cystadenomas have remained free of disease after surgical resection.

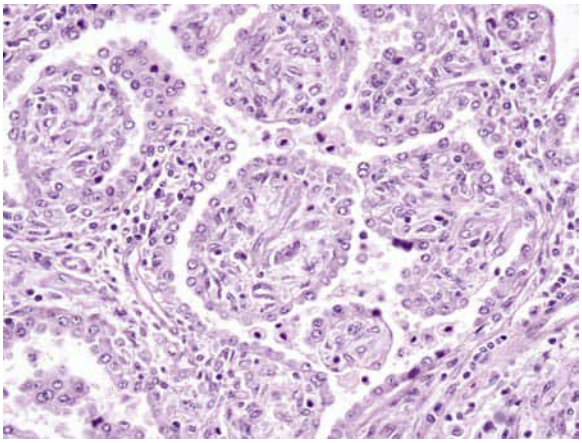

Figure 80.8 Papillary adenoma. High-magnification photomicrograph of a solitary peripheral lung nodule showing papillary connective tissue cores lined by bland cuboidal pneumocytes. (H&E stain; ×400 original magnification.)

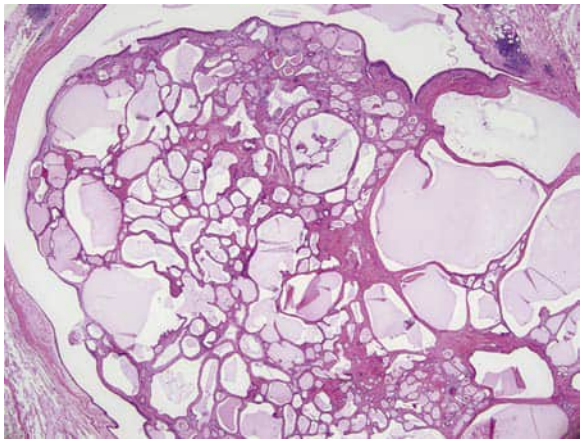

Figure 80.9 Endobronchial mucous gland adenoma. Low-magnification photomicrograph showing that the smooth surface is covered by ciliated respiratory epithelium, whereas the core comprises predominantly cystic spaces lined by variably attenuated columnar mucinous cells. (H&E stain; ×20 original magnification.)

Endobronchial adenomas include two entities analogous to salivary gland counterparts, mucous gland adenoma (cystadenoma), and pleomorphic adenoma, which presumably arise from bronchial submucosal seromucinous glands. As such, virtually all are located within the trachea and cartilaginous bronchi.

Mucous gland adenomas are rare benign tumors affecting a broad age range, including children. These lesions are often polypoid, endobronchial masses arising at the level of lobar or segmental bronchi, many times resulting in luminal obstruction.[78–81] When symptomatic, the most frequent complaints are cough, dyspnea, and wheezing, a combination of findings that can be misconstrued as asthma.[79,80] Chest radiographs may be normal, but more commonly show a solitary pulmonary nodule and/or postobstructive atelectasis or consolidation.[80,81] CT scans show a discrete nodule that may be accompanied by an air-meniscus sign, attesting to an endobronchial location.[81] Moderate PET avidity (SUV_{max} 4.9) is described in one case report.[82] Histologically, mucous gland adenomas are variably solid and cystic, and composed of cytologically bland columnar mucinous cells (Fig. 80.9). Surgical resection, which is often required for diagnosis, is curative.

Pleomorphic adenomas, also termed *benign mixed tumors,* are biphasic neoplasms composed of epithelial elements admixed with a myxoid or chondromyxoid stroma. They usually arise in major salivary glands with few documented cases arising within the lung. Primary pulmonary pleomorphic adenomas have been reported more commonly in women than men (ratio 2:1), with an average age at diagnosis of about 51 years. Cough is the most frequent presenting complaint and is sometimes associated with postobstructive pneumonia; however, one-third of patients are asymptomatic. Eighty percent are found within the larger central airways and appear as polypoid exophytic tumors.[83–86] Chest radiographs and CT scans show a solitary, well-circumscribed, solid mass without distinctive features. PET in a single patient showed high FDG avidity.[85,86] Complete surgical resection with tumor-free margins is curative. As can happen with their salivary gland counterparts, benign pleomorphic adenomas can undergo transformation to malignant carcinoma *(carcinoma ex pleomorphic adenoma)*.[87] Primary pleomorphic adenoma must be distinguished from so-called benign metastasizing pleomorphic adenoma, a term that refers to rare patients in whom histologically benign salivary gland tumors inexplicably metastasize to various sites, including the lung.[88–90]

MICRONODULAR PNEUMOCYTE HYPERPLASIA

Micronodular pneumocyte hyperplasia is an unusual proliferation of alveolar epithelium seen almost exclusively in patients with underlying tuberous sclerosis complex and/or lymphangioleiomyomatosis.[91–95] More than 85% of reported patients are women. Radiologic findings are characterized by scattered nodules that are occasionally numerous and distributed in a miliary fashion with or without the associated cystic changes of the lung parenchyma typical of lymphangioleiomyomatosis (eFig. 80.3).[92,94] The radiologic abnormalities correspond to ill-defined pale peripheral nodules seen either in isolation or in the setting of lymphangioleiomyomatosis (Figs. 80.10 and 80.11). Histologically, micronodular pneumocyte hyperplasia demonstrates circumscribed proliferations of bland pneumocytes cytologically identical to those seen in papillary adenomas, differing in that they are distributed along intact alveolar septa rather than along papillae (Fig. 80.12). These lesions are benign, hamartomatous proliferations that do not progress to carcinoma or require surgical management.

BENIGN NONEPITHELIAL LESIONS

HAMARTOMA AND RELATED LESIONS

Pulmonary hamartoma is the most common benign neoplasm in adults who undergo surgical resection and reportedly accounts for 8% of "coin lesions" seen on chest radiographs.[96–100] Histologically, pulmonary hamartomas are characterized by the presence of least two benign

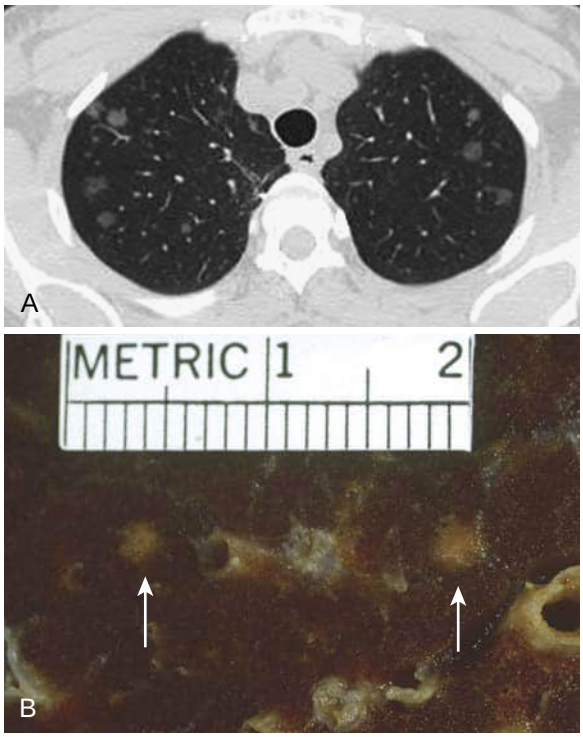

Figure 80.10 Micronodular pneumocyte hyperplasia in tuberous sclerosis complex without lymphangioleiomyomatosis. (A) Axial computed tomography of a 41-year-old woman with tubular sclerosis complex and micronodular pneumocyte hyperplasia shows multiple bilateral nodules characterized by ground-glass attenuation. (B) Photograph of autopsy lung specimen from another patient with tubular sclerosis complex and micronodular pneumocyte hyperplasia *(arrows)*. (A, Courtesy Dr. Jay Ryu, Professor of Medicine, Mayo Medical School.)

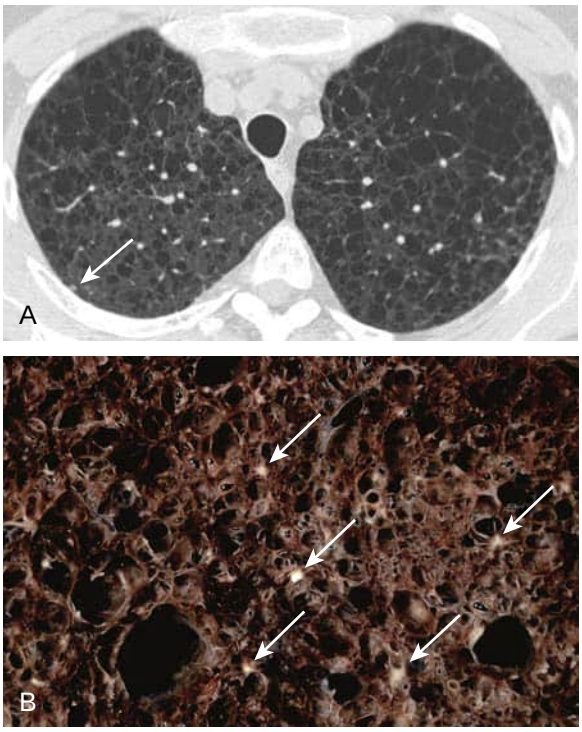

Figure 80.11 Micronodular pneumocyte hyperplasia associated with lymphangioleiomyomatosis. (A) Axial computed tomography scan of a 55-year-old woman with tuberous sclerosis complex and lymphangioleiomyomatosis and a right lung nodule *(arrow)* attributed to micronodular pneumocyte hyperplasia. (B) Photograph of a surgical lung specimen shows a combination of lymphangioleiomyomatosis and micronodular pneumocyte hyperplasia *(arrows)*. (A, Courtesy Dr. Jay Ryu, Professor of Medicine, Mayo Medical School.)

mesenchymal elements (e.g., cartilage, adipose tissue, connective tissue, and smooth muscle) with entrapped, non-neoplastic respiratory epithelium. Although once regarded as a tumor-like malformation, molecular studies have since demonstrated translocations involving chromosomes 6p21 (gene *HMGA1*) or 12q14-15 (gene *HMGA2*), supporting pulmonary hamartoma as a true, acquired mesenchymal neoplasm.[99–101]

Pulmonary hamartomas develop more often in men than women with a peak incidence in the sixth or seventh decade of life. Patients are usually asymptomatic and incidentally discovered to have a solitary lung nodule, most commonly located within the peripheral, subpleural lung parenchyma. Endobronchial hamartomas (eFig. 80.4), which account for about 10% of cases, are the exception; these patients tend to present with obstructive pneumonia and less commonly hemoptysis and cough.[102–105] CT scans show a characteristic combination of calcifications and/or fat, the latter of which is particularly helpful in adding diagnostic specificity for pulmonary hamartomas (Fig. 80.13).[106,107] Pulmonary hamartomas are often negative on PET scans (SUV_{max} <1.5) with mild uptake correlating with larger lesion size.[45,108]

Pulmonary hamartomas usually manifest as well-circumscribed nodules, averaging 1.5 to 2 cm in diameter. A variegated cut surface reflects an admixture of stromal elements (Fig. 80.14). Mature hyaline cartilage is an almost universal component and is typically intermingled with mature fat, fibromyxoid tissue, and rare smooth muscle cells (Fig. 80.15). Any one of the stromal components can predominate, however, resulting in a histologic spectrum of neoplasms that includes *leiomyomas* and *lipomas*.[109–111] Entrapped non-neoplastic respiratory epithelium often results in a characteristically biphasic appearance, a phenomenon that contributes to relatively high rates of false-positive diagnoses of malignancy in fine-needle aspiration biopsies.[112] Although morphology alone is usually sufficient to establish a diagnosis of pulmonary hamartoma on core needle biopsies or surgical resection specimens, an HMGA2 immunohistochemical stain is now available to lend more diagnostic certainty in challenging cases.[113] Resection is curative with rare reports of recurrence or malignant transformation.[114,115]

Pulmonary chondroma is a purely cartilaginous benign lung neoplasm. Although rare cases of sporadic pulmonary chondromas have been described, most arise in patients affected by the Carney triad, a condition characterized by pulmonary chondromas, paragangliomas, and gastric stromal tumors. Pulmonary chondromas develop in three-fourths of patients with the Carney triad and multiple lung tumors are observed in about half of those cases.[116,117] Chondromas are distinct in being purely cartilaginous, devoid of the other stromal and epithelial elements characteristic of hamartoma.[117]

INFLAMMATORY MYOFIBROBLASTIC TUMOR

Inflammatory myofibroblastic tumors (IMTs) have been referred to by a variety of other terms, many of which likely

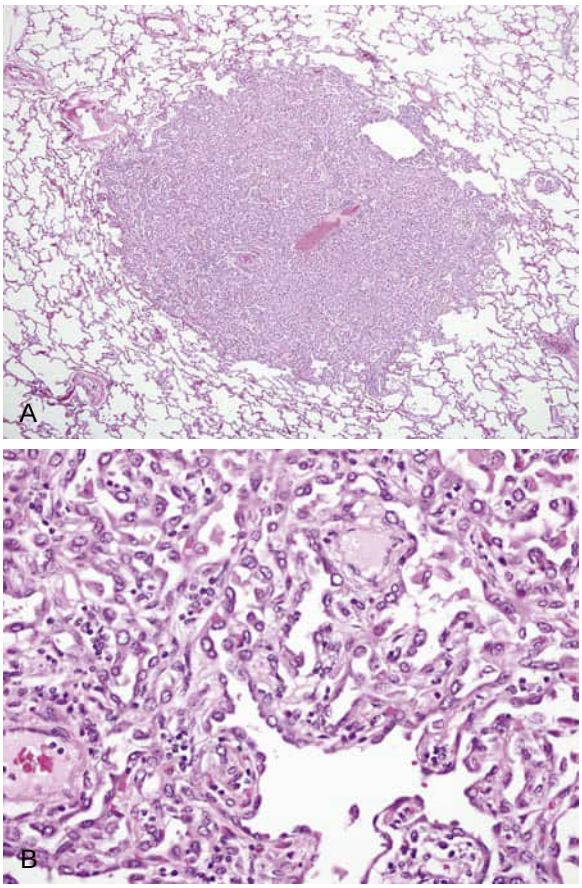

Figure 80.12 Micronodular pneumocyte hyperplasia. Histologic features are shown from the tuberous sclerosis complex patient also illustrated in Figure 80.10B. (A) Low-magnification photomicrograph shows a well-circumscribed nodule. (H&E stain; ×20 original magnification.) (B) High-magnification photomicrograph shows cytologically bland pneumocytes distributed along alveolar septa. (H&E stain; ×400 original magnification.)

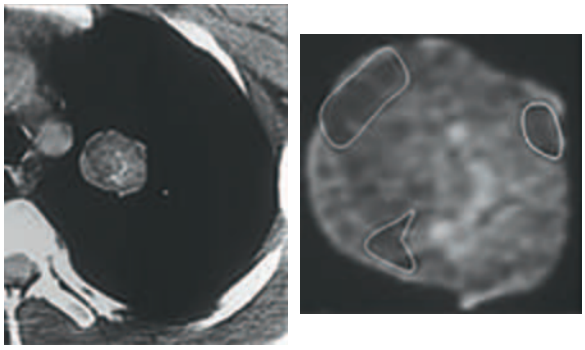

Figure 80.13 Pulmonary hamartoma. Axial computed tomography of a proven hamartoma shows a well-marginated nodule in which there is evidence of intratumoral fat and calcification *(left)*. This combination is characteristic but is seen in only about one-fourth of cases. The low attenuation foci representing fat within the lesion are outlined on the magnified image *(right)*.

represent a spectrum of neoplastic and tumor-like conditions that fall under the broad, descriptive category of "inflammatory pseudotumor." Within this heterogeneous group of lesions, IMT seems to represent a morphologically distinct neoplasm with consistent clonal rearrangements and low to intermediate grade biologic potential, which may recur and can rarely metastasize. Morphologically, IMT is characterized

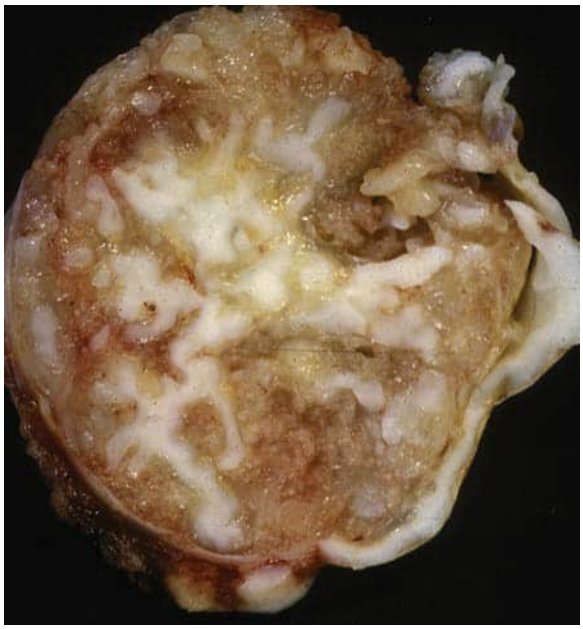

Figure 80.14 Pulmonary hamartoma. In this resected specimen, the cut surface of this well-circumscribed nodule shows glistening irregularly shaped cartilaginous islands alternating with pale yellow adipose tissue. The tumor was 4 cm in greatest dimension.

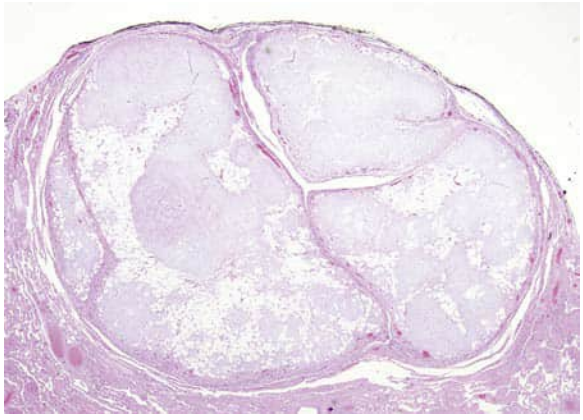

Figure 80.15 Pulmonary hamartoma. Low-magnification photomicrograph of a typical pulmonary hamartoma in which cartilaginous islands are interspersed with adipose tissue resulting in a lobulated appearance. (H&E stain; ×20 original magnification.)

by a proliferation of neoplastic myofibroblastic spindle cells, accompanied by a variably dense chronic inflammatory infiltrate comprised mainly of polyclonal plasma cells (Fig. 80.16). The most common molecular alteration involves translocation of the *ALK* gene locus (chromosome band 2p23) with various fusion partners.[118,119] *ROS1* gene rearrangements account for the majority of cases in which no *ALK* abnormality is detected.[118,120] ALK protein expression by immunohistochemistry is a particularly useful diagnostic tool in small biopsies, including fine-needle aspirates, which may show a spindle cell lesion with broad differential diagnosis that includes both reactive processes and/or malignant neoplasms.[121,122]

IMTs of the lung can arise in any age group but tend to be seen more frequently in children and young adults, with more than half of patients younger than 40 years at the

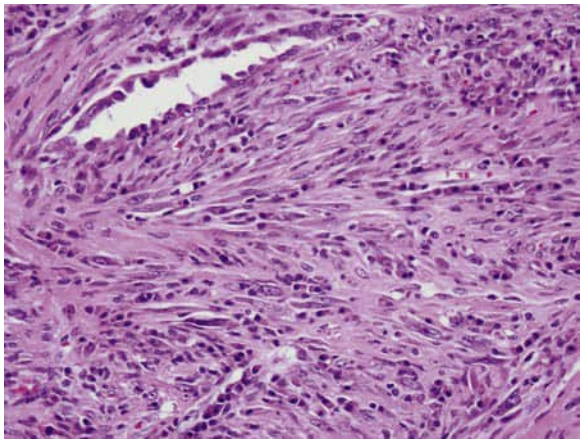

Figure 80.16 Inflammatory myofibroblastic tumor. High-magnification photomicrograph from the tumor illustrated in Figure 80.17. Neoplastic spindle cells are associated with a prominent infiltrate of plasma cells. Non-neoplastic respiratory epithelium *(upper left)* is surrounded by neoplastic spindle cells, resulting in a biphasic appearance, a common phenomenon in benign or low-grade nonepithelial tumors. (H&E stain; ×400 original magnification.)

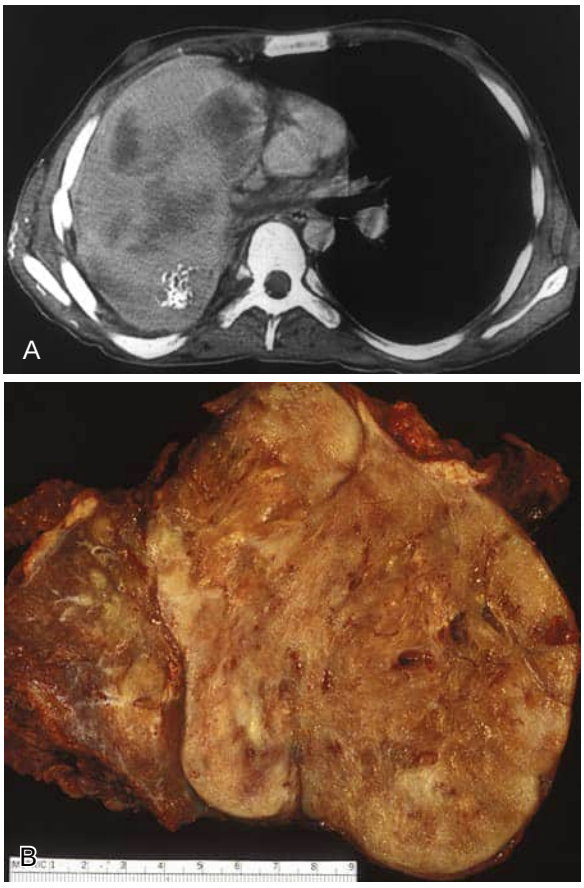

Figure 80.17 Inflammatory myofibroblastic tumor. Large Inflammatory myofibroblastic tumor in a 21-year-old man in whom an intrathoracic mass was first detected at the age of 10 years. (A) Axial computed tomography shows a large mass filling the right hemithorax with heterogeneous attenuation and calcification. (B) Photograph of right pneumonectomy specimen shows a large mass that, despite its size, was well circumscribed without invasion beyond lung parenchyma.

time of diagnosis. *ALK* overexpression and other described clonal gene rearrangements are seen almost exclusively in children and young adults, while tumors in older adults are often fusion-negative.[120,123–125] The absence of *ALK* expression has been associated with a greater risk for aggressive behavior, including distant metastasis.[123] Patients usually present with asymptomatic peripheral lung nodules, averaging 4 cm in greatest dimension.[126–128] Endobronchial tumors (eFig. 80.5) account for about 15% of cases and patients may present with symptoms of cough and dyspnea.[127,129] Chest imaging studies are frequently described as showing a well-circumscribed mass (eFig. 80.6), occasionally accompanied by calcifications, necrosis (Fig. 80.17), and cavitation.[126–128] IMTs can show increased uptake on PET CT (see eFigs. 78.20 and 78.21) and, in one study, accounted for the highest false-positive diagnosis of lung cancer of all benign pathologic entities.[130]

Most primary pulmonary IMTs are cured by surgical resection, with completeness of resection cited as the most significant prognostic factor.[126,131,132] As such, incomplete resection is associated with substantial risk of recurrence and rarely locally aggressive behavior and death.[123,133] In patients with large, unresectable tumors that harbor clonal gene rearrangements, targeted therapy with small molecule tyrosine kinase receptor inhibitors, crizotinib and ceritinib, has shown efficacy in inducing at least partial tumor regression.[134–137]

SOLITARY FIBROUS TUMOR

Solitary fibrous tumors (SFTs), formerly referred to as *localized fibrous mesotheliomas*, are mesenchymal neoplasms that frequently arise from the pleura. SFTs are not unique to the pleura, however, and have been described within the lung parenchyma (intrapulmonary SFT), mediastinum, and numerous extrathoracic sites.[138–142]

Pleural and intrapulmonary SFTs affect men and women equally, with a mean age of diagnosis in the sixth decade of life.[143–147] More than half of patients are symptomatic at the time of presentation with complaints of chest pain, shortness of breath, and/or cough; the severity of symptoms often correlates with tumor size and location. Clubbing has been reported in up to one-fifth of patients.[148] A paraneoplastic syndrome of hypoglycemia (Doege-Potter syndrome) is rare and results from tumor secretion of insulin-like growth factor-2.[149–153]

SFTs frequently measure over 10 cm in maximum dimension (range 1 to ≈40 cm) and are three times more likely to arise from the visceral than the parietal pleura (eFig. 80.7). Those arising from the visceral pleura are frequently pedunculated and attached to the lung surface by a connective tissue pedicle (Fig. 80.18A). Occasionally, SFTs arise within the fissures (Fig. 80.18B), resulting in a radiologic appearance difficult to distinguish from that of an intrapulmonary tumor (see eFig. 80.7). Parietal pleural lesions are more commonly sessile with a broad base of attachment to chest wall, diaphragm, or mediastinum. Regardless of whether the tumor is arising on the visceral or parietal pleura, chest imaging studies are often described as showing a lobulated, sharply delineated mass that compresses and displaces surrounding structures (Fig. 80.19, eFigs. 80.7 through 80.11, and Video 80.2). SFTs are characterized by heterogeneous attenuation and rich vascularization of the tumor resulting in enhancement with contrast administration (see eFigs. 80.8 and 80.10). Calcifications are occasionally present.[154–156]

Histologically, SFTs are variably cellular spindle cell neoplasms with a collagenous stroma and branching blood

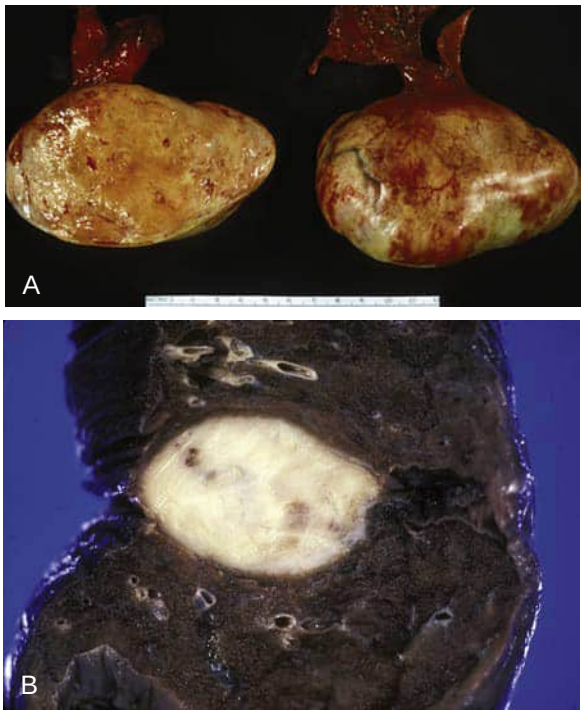

Figure 80.18 Solitary fibrous tumor. Resected solitary fibrous tumor (SFT) arising from the visceral pleura. (A) As demonstrated in this example, most visceral pleural SFTs are attached to the lung by a pedicle and are characterized by a smooth glistening surface *(right)* and an encapsulated homogeneous cut surface without necrosis *(left)*. (B) Less commonly, SFT arises within the fissures, as illustrated in this bilobectomy specimen.

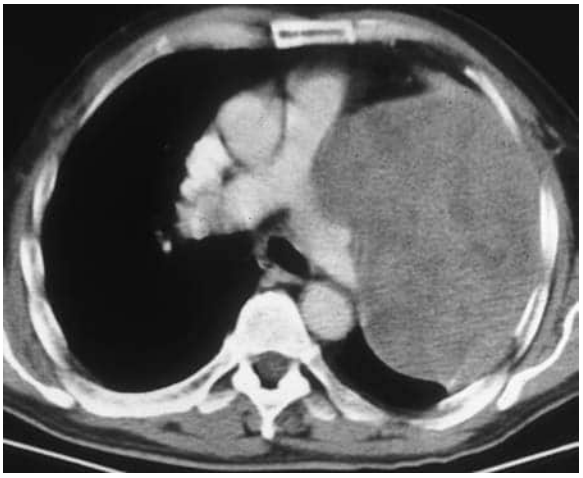

Figure 80.19 Solitary fibrous tumor. Axial computed tomography showing a large solitary fibrous tumor arising from the visceral pleura, nearly filling the left thorax. Together solitary fibrous tumor and inflammatory myofibroblastic tumor are the most likely diagnoses in patients who present with large benign intrathoracic tumors.

vessels. Malignant variants *(malignant SFT)* are more likely to have an invasive growth pattern, increasing cellularity with associated cytologic atypia, higher mitotic rates, and necrosis.[146] SFTs harbor a characteristic *NAB2-STAT6* gene fusion, resulting in overexpression of STAT6, an immunohistochemical finding helpful in distinguishing SFT from its histologic mimics, including in fine-needle aspirates.[157–160]

Most pleural and intrapulmonary SFTs behave as indolent neoplasms and patients are cured with complete surgical excision. A more aggressive course is seen in about 10% of patients, particularly those who undergo incomplete surgical resection or have histologically malignant tumors (eFigs. 80.12 and 80.13). Several risk stratification models have been proposed to predict the risk for recurrence, metastasis, and survival in patients with pleuropulmonary SFT, but, in the absence of indication for systemic therapy, surveillance for these patients remains the mainstay of clinical management.[161]

MENINGOTHELIAL-LIKE NODULES AND INTRAPULMONARY MENINGIOMA

Pulmonary *meningothelial-like nodules* (MLNs), historically termed *chemodectomas*, are a relatively common incidental finding in patients undergoing lung wedge resection for other reasons, usually for removal of a malignant tumor or less commonly for diagnosis of diffuse parenchymal lung disease. MLNs are more frequently seen in women than men and, in about half of patients, the nodules will be multiple.[162–165] A rare syndrome of multiple bilateral MLNs *(diffuse pulmonary meningotheliomatosis)* has been described in women who present in the sixth to eighth decade of life with multiple nodules seen on CT. Half of these patients report dyspnea and/or cough at presentation.[166] Microscopically, MLNs are composed of nests of epithelioid cells histologically and immunophenotypically indistinguishable from meningothelial cells of the central nervous system (Fig. 80.20). Despite this unexplained phenotypic overlap, molecular studies demonstrate significant differences between MLNs and conventional central nervous system meningiomas, raising the possibility that MLNs may be a reactive rather than neoplastic process.[167]

Primary *intrapulmonary meningiomas* are rare solitary lesions unrelated to MLN.[168–170] Men and women are affected equally and typically present in their mid-50s with an asymptomatic solitary lung nodule, averaging 3 cm in greatest dimension. Patients with multiple lesions should be presumed to have metastatic disease from a central nervous system primary until proven otherwise.[171,172] Rare cases of intrapulmonary meningioma show increased uptake on PET scan.[173] Complete surgical resection is curative in patients with WHO grade I meningiomas, while higher grade tumors have a greater risk of recurrence and/or locally aggressive behavior.[174]

OTHER RARE ENTITIES

Granular cell tumors, referred to in older literature as granular cell myoblastomas, are uncommon primary lung neoplasms that typically present as pedunculated or sessile endobronchial tumors (Fig. 80.21, eFig. 80.14).[175,176] Lesions are multiple in a fourth of patients. Symptoms are reported in half and result from airway obstruction. Pulmonary *granular cell tumors* are benign and can usually be managed with conservative excision.

PEComatous tumors refers to groups of tumors thought to arise from *perivascular epithelioid cells* (PECs). In the lung, these tumors may take several forms, including (1) a benign localized mass called *PEComa*, also referred to as *clear cell ("sugar")* tumor, or (2) a diffuse multicystic proliferation known as *lymphangioleiomyomatosis*.[34] PEComas usually present as asymptomatic solitary lung nodules.[177,178] Surgical resection is curative. Lymphangioleiomyomatosis is discussed in detail in Chapter 97.

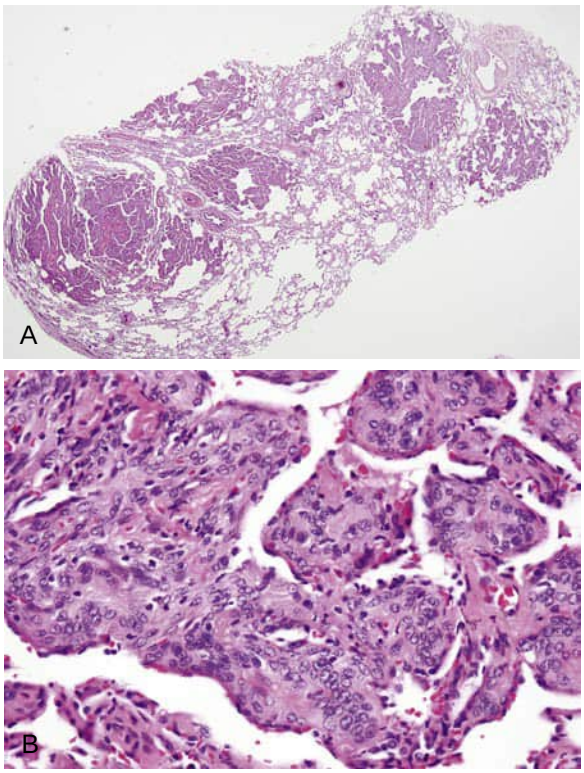

Figure 80.20 Multiple meningothelial-like nodules. Also called *diffuse pulmonary meningotheliomatosis,* the multiple nodules are shown in a surgical lung biopsy from a 56-year-old woman who presented with dyspnea. (A) At low magnification, multiple nodules are seen randomly distributed throughout the biopsy. (H&E stain; ×20 original magnification.) (B) At higher magnification, the nodules comprise bland meningothelial cells arranged in poorly formed nests and expanding the interstitium. (H&E stain; ×400 original magnification.)



Figure 80.21 Granular cell tumor. Cut surface of pneumonectomy specimen in which a granular cell tumor *(arrows)* partially obstructs the lower lobe bronchus.

Key Points

- Most benign lung neoplasms are incidentally discovered as asymptomatic, peripheral lung nodules in adult patients.
- Contrary to expectation, FDG-PET scans may be positive in benign lung tumors.
- Squamous cell papilloma is the most common type of papilloma and is associated with infection by HPV types 11 and/or 6.
- Pulmonary hamartoma is the most common benign neoplasm in patients who undergo resection; it has been shown to have translocations involving chromosomes 6p21 (gene *HMGA1*) or 12q14-15 (gene *HMGA2*).
- Inflammatory myofibroblastic tumor belongs to a heterogenous group of tumors broadly termed "inflammatory pseudotumor" but, within this group, it seems to represent a morphologically distinct neoplasm with common molecular alterations involving the *ALK* gene locus (chromosome band 2p23).
- Solitary fibrous tumors harbor a characteristic *NAB2-STAT6* gene fusion, resulting in overexpression of *STAT6*.
- Solitary fibrous tumor and inflammatory myofibroblastic tumor are the most likely diagnoses in patients who present with large intrathoracic tumors.
- For virtually all benign lung neoplasms, surgical resection is curative with recurrence most often associated with incomplete resection rather than malignant transformation.

Key Readings

Callister MEJ, Baldwin DR, Akram Ar, et al. British Thoracic Society guidelines for the investigation and management of pulmonary nodules. *Thorax*. 2015;70(suppl 2):ii1–ii54.

Can NT, Tretiakova MS, Taxy JB. Natural history and malignant transformation in recurrent respiratory papillomatosis: human papillomavirus (HPV), dysplasia and an autopsy review. *Fetal Pediatr Pathol*. 2015;34:80–90.

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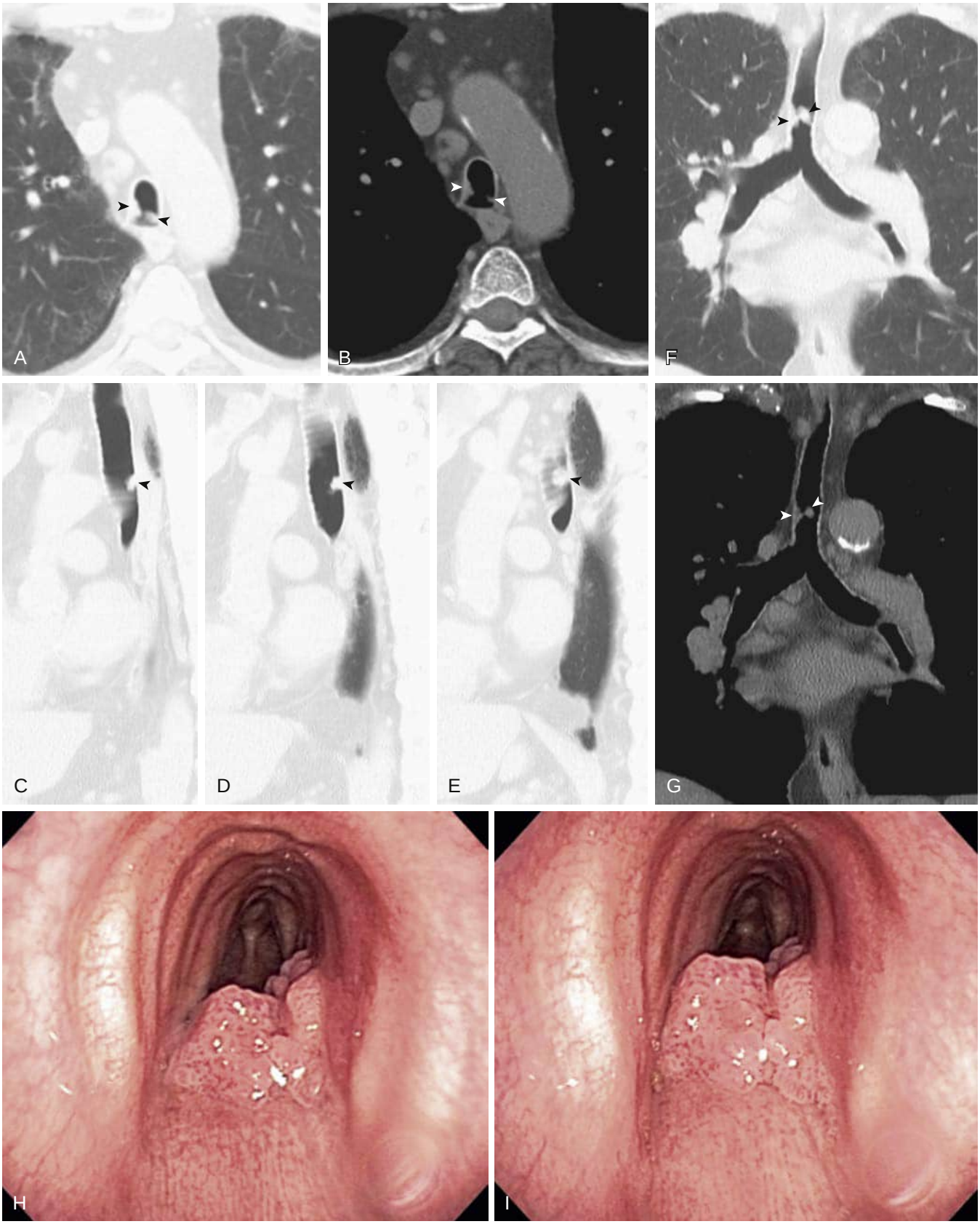
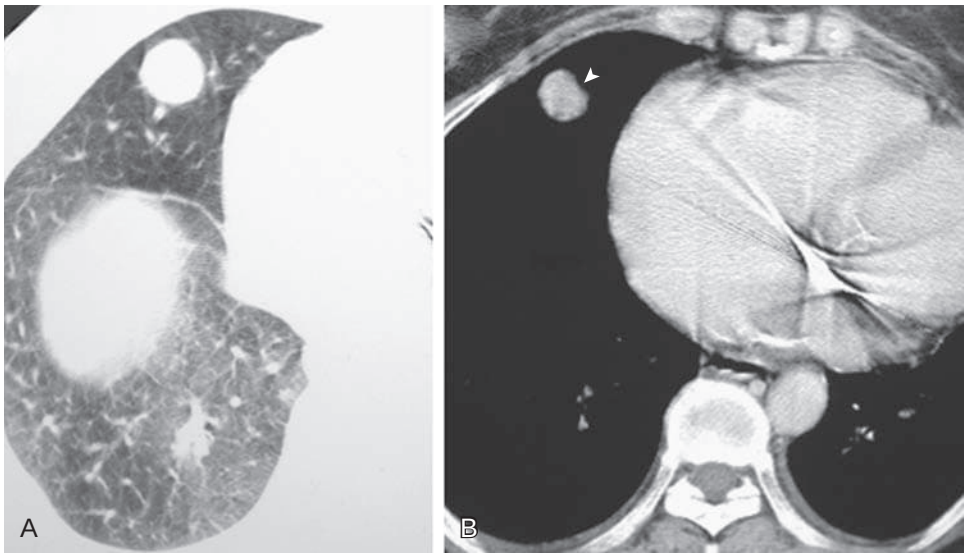
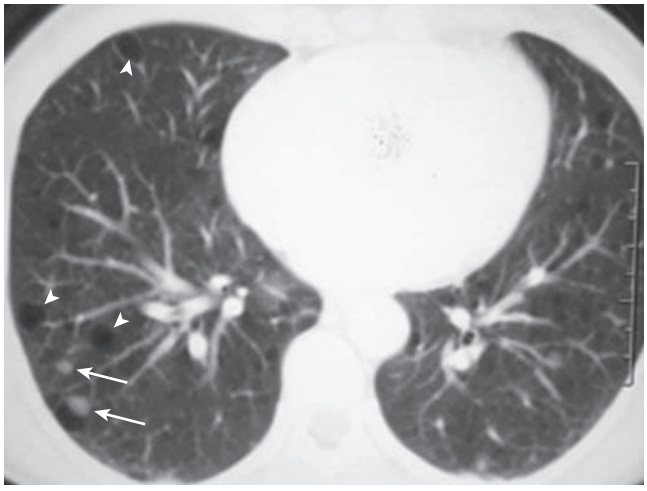


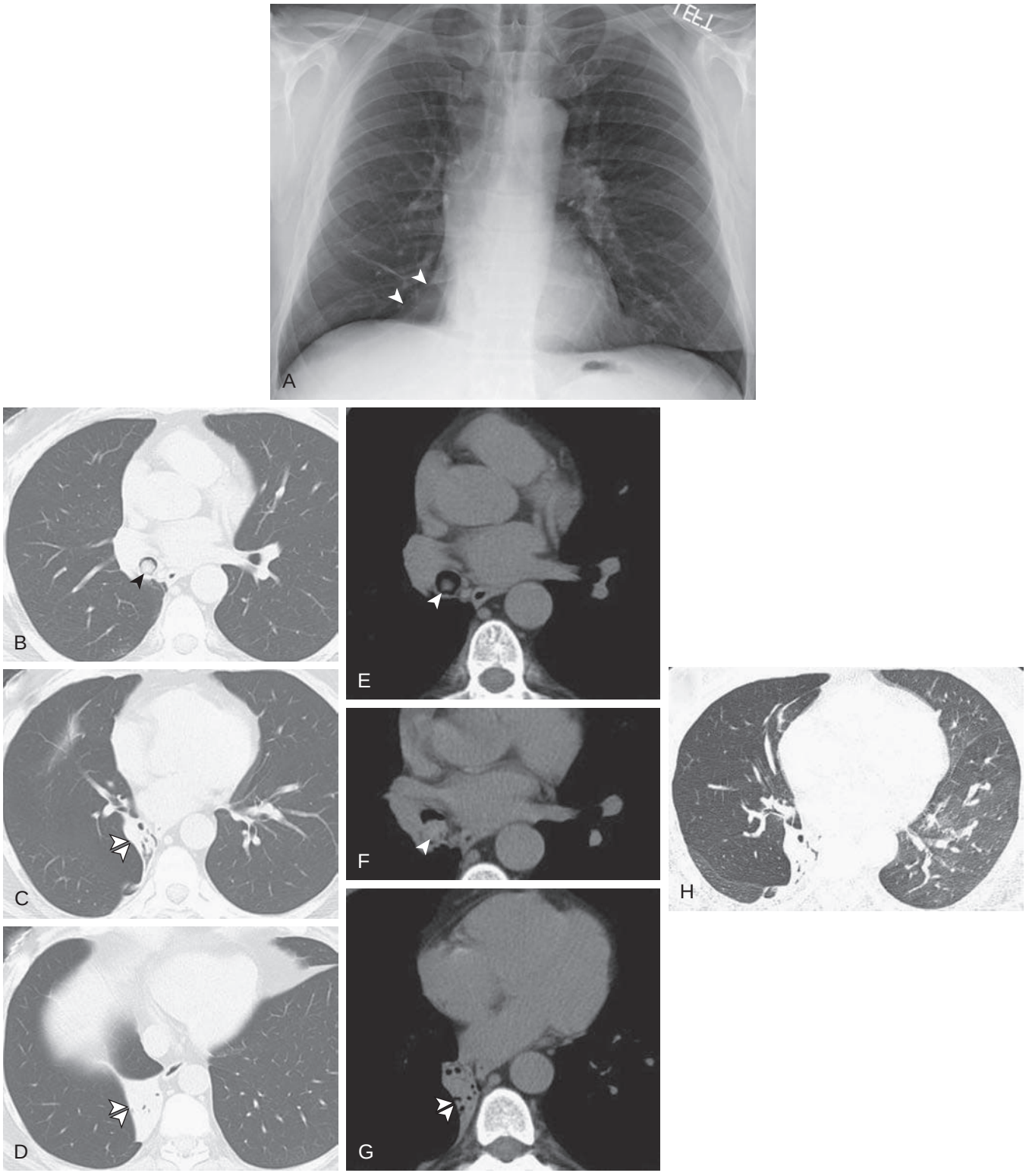
eFigure 80.1 Squamous papilloma of the trachea. Axial chest computed tomography (CT) displayed in lung (A) (see Video 80.1A) and soft tissue (B) windows shows a multilobulated tracheal lesion *(arrowheads)*. (C–E) Sagittal images show the lesion *(arrowheads)* residing along the posterior tracheal wall. Coronal CT images displayed in lung (F) and soft tissue (G) windows show the tracheal lesion *(arrowheads)* arising from the posterior and right lateral wall (see Video 80.1B). (H–I) Bronchoscopic images show a multilobulated posterior tracheal lesion; biopsy confirmed squamous papilloma. (Courtesy Michael B. Gotway, MD; case by Allen Thomas, MD, Veterans Affairs Medical Center, Phoenix, AZ.)



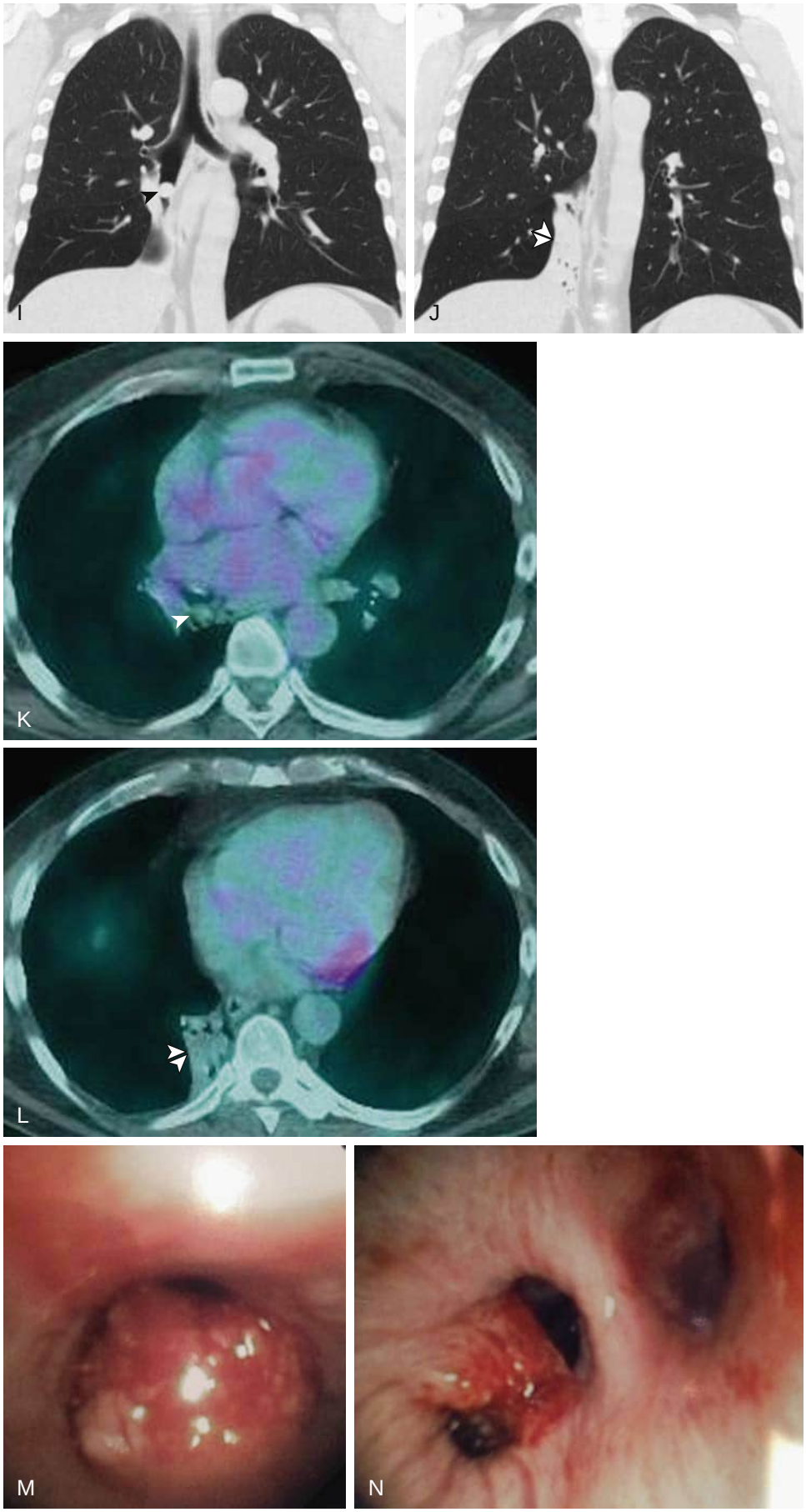
eFigure 80.2 Sclerosing pneumocytoma. Axial enhanced chest computed tomography shown in lung (A) and soft tissue (B) windows shows a nonspecific, enhancing, circumscribed right middle lobe nodule *(arrowhead)* proven on resection to represent sclerosing pneumocytoma. (Courtesy Michael B. Gotway, MD.)



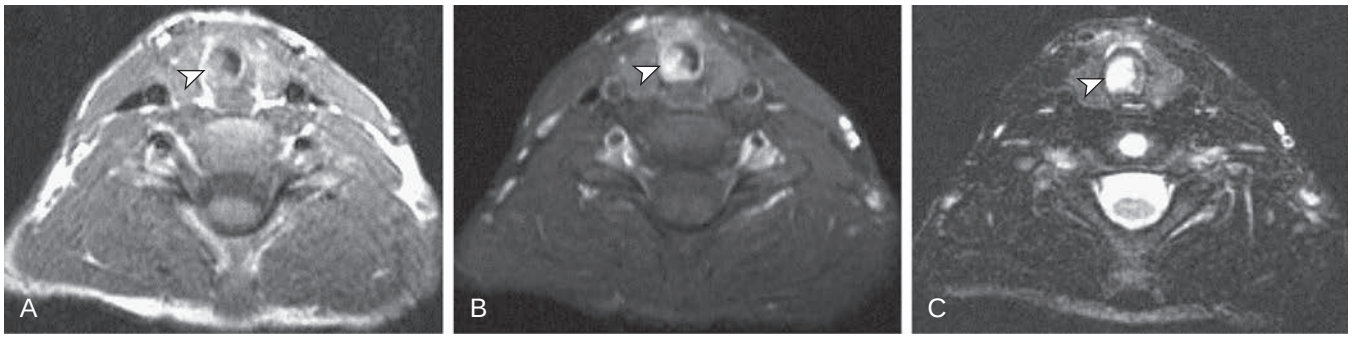
eFigure 80.3 Micronodular pneumocyte hyperplasia in a patient with tuberous sclerosis–lymphangioleiomyomatosis complex. Axial chest computed tomography displayed in lung windows shows several thin-walled cysts *(arrowheads)* associated with small, nonspecific lung nodules *(arrows)*, the latter representing micronodular pneumocyte hyperplasia. (Courtesy Michael B. Gotway, MD.)



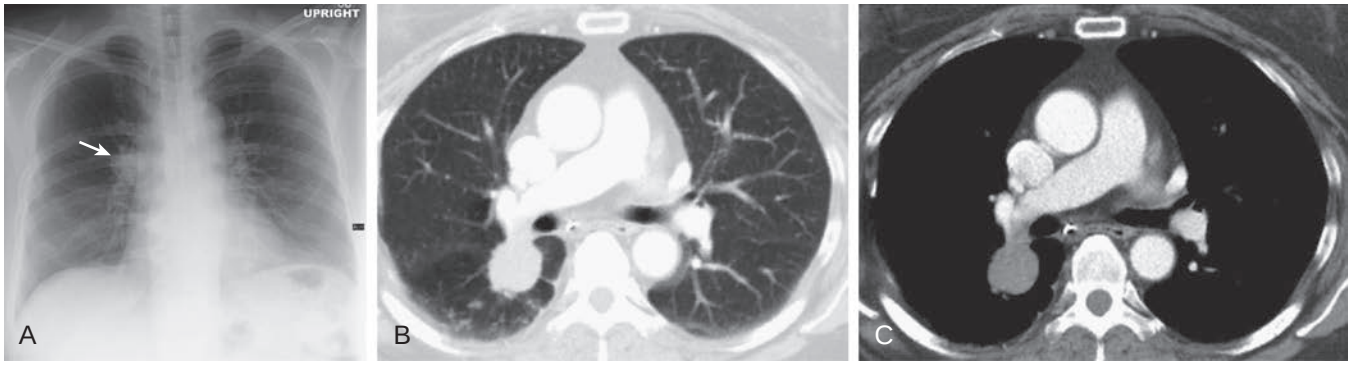
eFigure 80.4 Endobronchial hamartoma. (A) Frontal chest radiograph shows right lower lobe collapse, evidenced by medial and inferior retraction of the right major fissure *(arrowheads)*. Right lung volume is diminished overall compared with the left. Axial unenhanced chest computed tomography (CT) scans displayed in lung (B–D) and soft tissue (E–G) windows show a solid lesion residing within the bronchus intermedius (*arrowheads*, B, E, and F). Right lower lobe collapse (*double arrowheads*, C, D, and G) is present. (H) Axial high-resolution CT shows hyperinflation of the right middle lobe, partially compensating for the right lower lobe collapse.



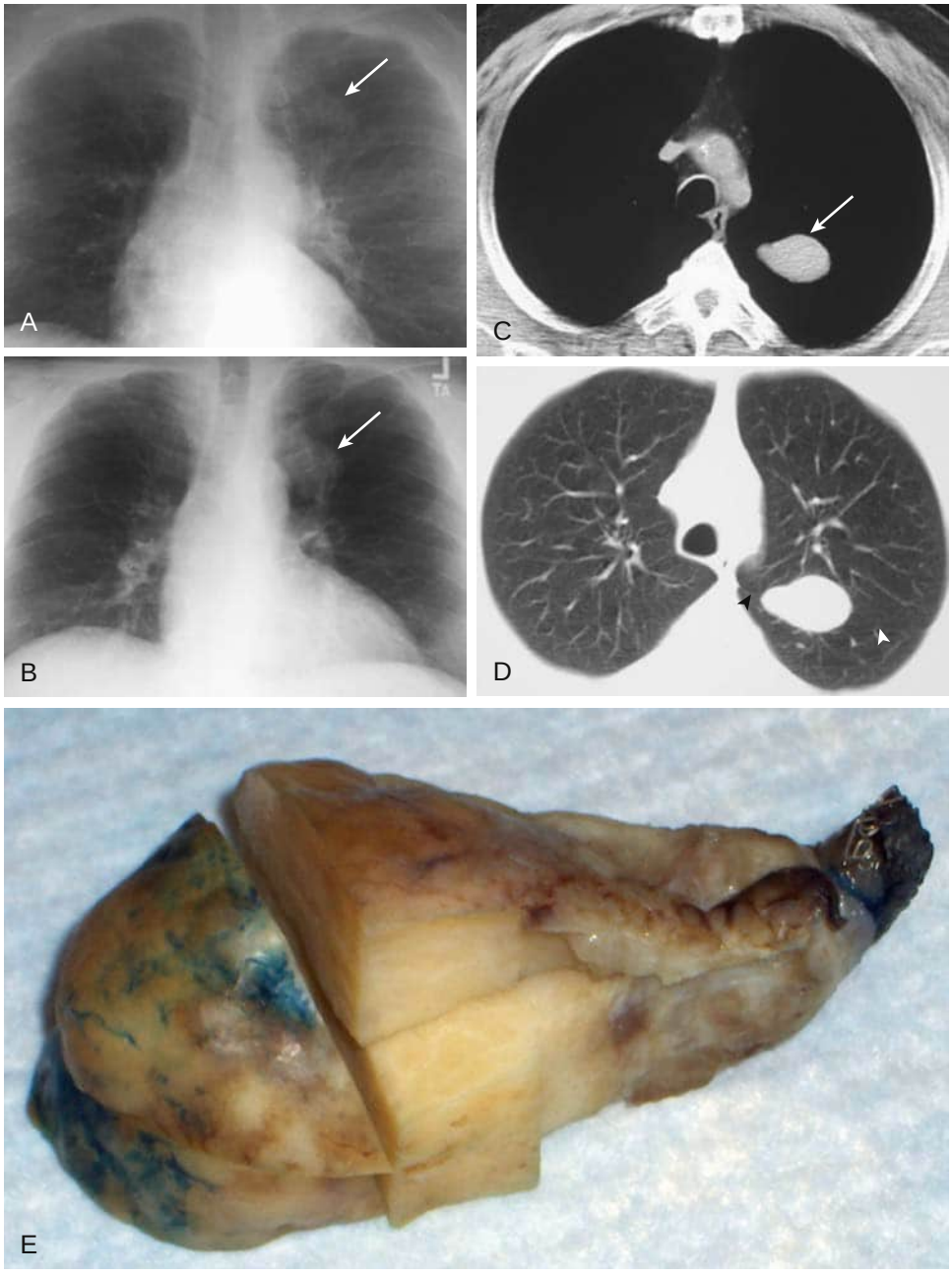
eFigure 80.4—cont'd (I–J) Coronal chest CT images show the endobronchial lesion *(arrowhead)* within the bronchus intermedius and the right lower lobe collapse *(double arrowheads)* to advantage. (K–L) Axial fused positron emission tomography-CT images show no significant tracer accumulation within the bronchus intermedius lesion *(arrowhead)* or the collapsed right lower lobe *(double arrowheads)*. Bronchoscopic images before (M) and after (N) treatment show decrease in size of the lesion, shown on biopsy to represent hamartoma. (Courtesy Andrew H. Goldstein, MD.)



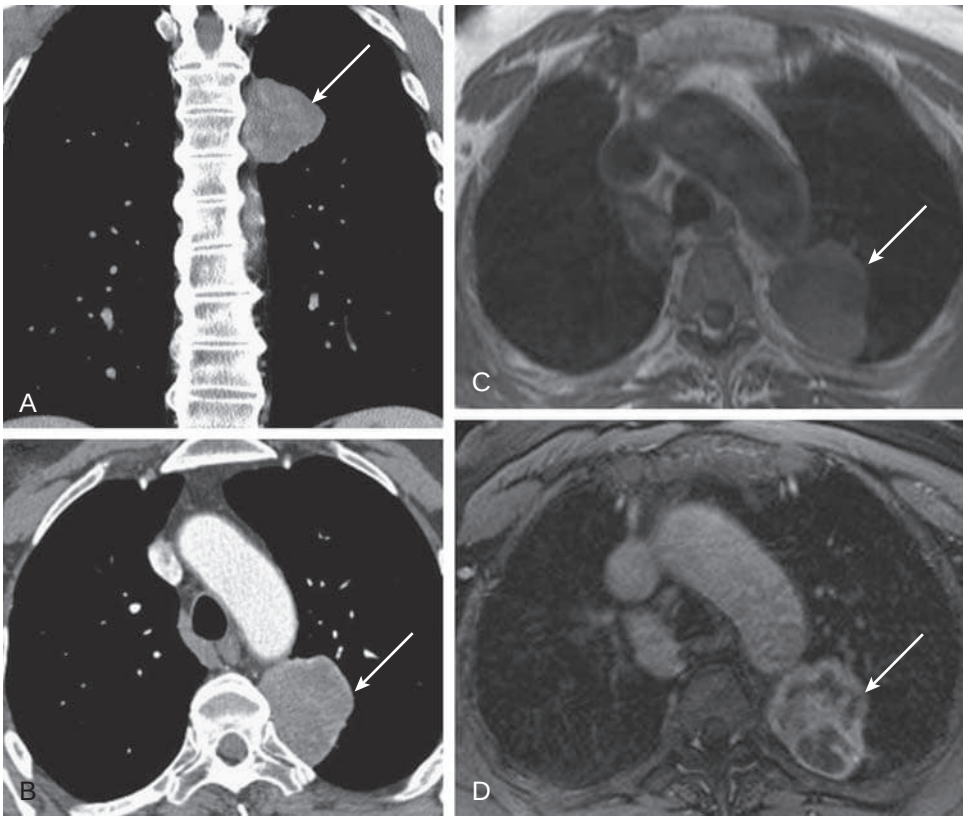
eFigure 80.5 Tracheal inflammatory myofibroblastic tumor. T1-weighted axial magnetic resonance (MR) images before (A) and after (B) intravenous gadolinium administration show an irregular lesion *(arrowheads)* arising from the right lateral tracheal wall. (C) Axial T2-weighted MR image shows high signal within the lesion *(arrowhead)*, consistent with fluid density. Biopsy showed inflammatory myofibroblastic tumor. (Courtesy Michael B. Gotway, MD.)



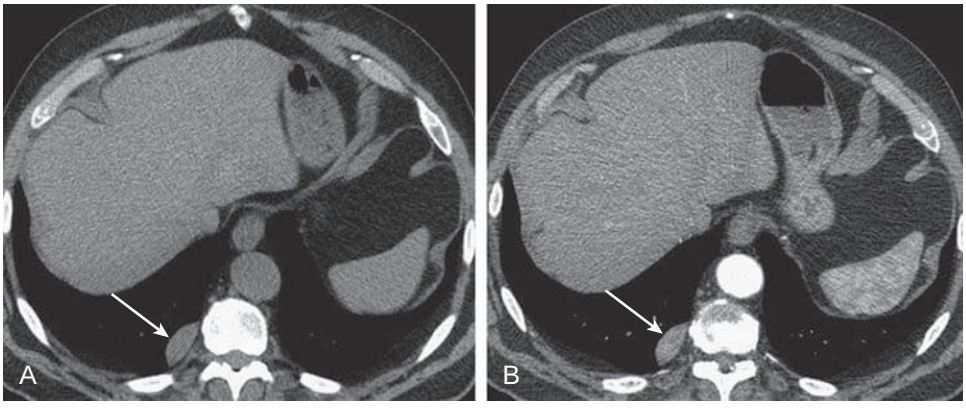
eFigure 80.6 Inflammatory myofibroblastic tumor. (A) Frontal chest radiograph shows a circumscribed nodule *(arrow)* projected over the right hilum. Axial contrast-enhanced chest computed tomography displayed in lung (B) and soft tissue (C) windows shows a finely lobulated superior segment right lower lobe nodule. Small satellite nodules were present more inferiorly. The appearance of the lesion is nonspecific. Biopsy showed inflammatory myofibroblastic tumor. (Courtesy Michael B. Gotway, MD; case courtesy Paul J. Conomos, MD, Arizona Pulmonary Specialists, Phoenix.)



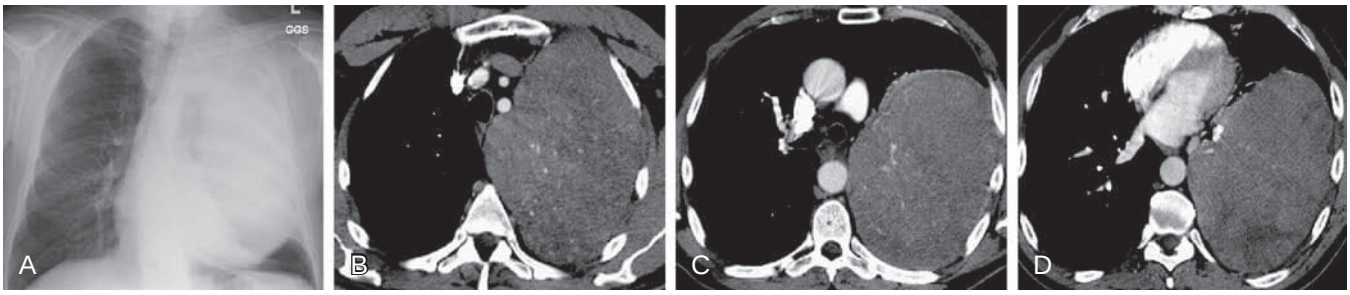
eFigure 80.7 Solitary fibrous tumor of the pleura: visceral pleural origin evident on imaging. (A) Frontal chest radiograph shows a poorly defined left upper lobe opacity *(arrow)*. (B) Repeat frontal chest radiograph 5 years after part A shows slow interval growth in the lesion *(arrow)*. Axial unenhanced chest computed tomography images displayed in soft tissue (C) and lung (D) windows shows a homogeneous, circumscribed, noncalcified lesion (*arrow*, C). On the lung window image (D), the lesion is clearly related to the left major fissure *(arrowheads)*. (E) Specimen following surgical resection was shown to be solitary fibrous tumor of the pleura. (A–D, Courtesy Michael B. Gotway, MD.)



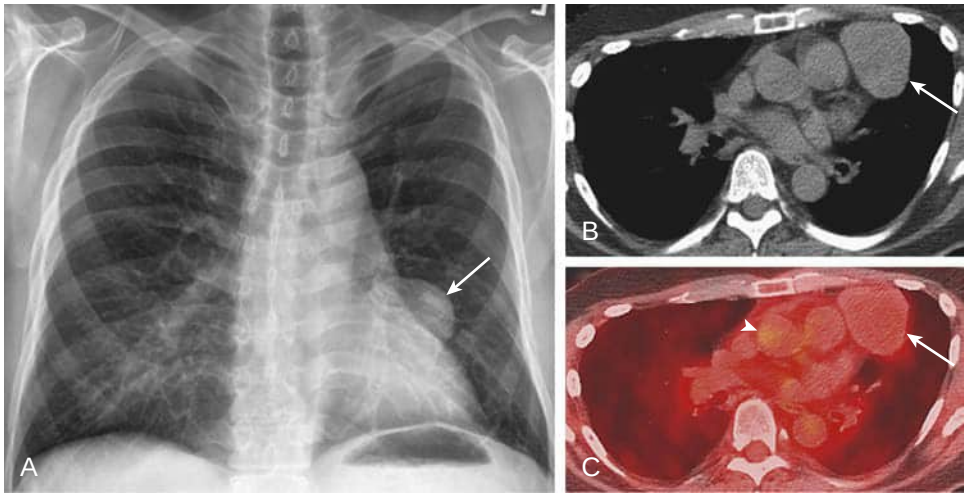
eFigure 80.8 Solitary fibrous tumor of the pleura. Coronal (A) and axial (B) contrast-enhanced chest computed tomography shows an enhancing lesion with extensive mediastinal pleural contact *(arrow)*, suggesting an extrapulmonary origin (see Video 80.2). (C) Axial T1-weighted magnetic resonance image before intravenous contrast administration. (D) Axial contrast-enhanced magnetic resonance image shows extensive peripheral lesion enhancement *(arrow)* as well as enhancement of the internal soft tissue septations within the lesion. Surgical resection proved solitary fibrous tumor of the pleura. (Courtesy Michael B. Gotway, MD.)



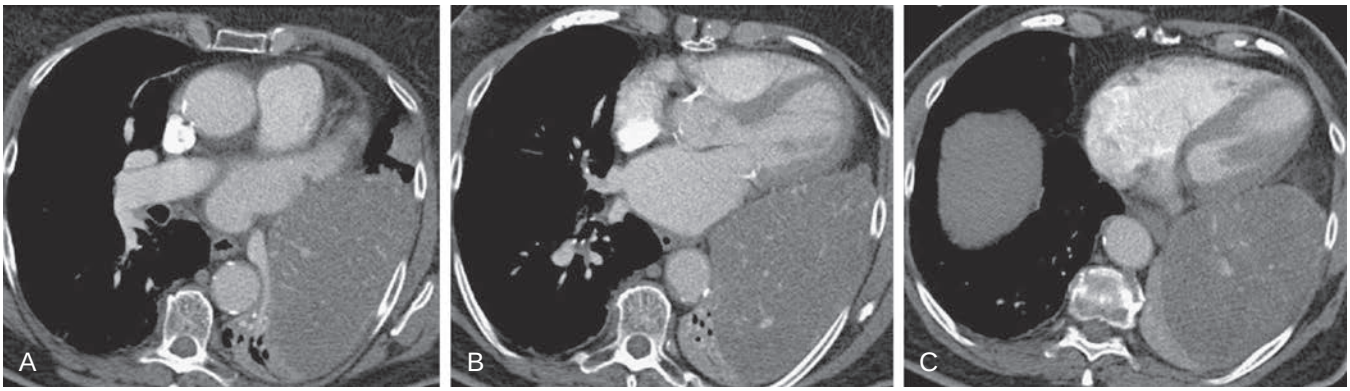
eFigure 80.9 Solitary fibrous tumor of the pleura. Unenhanced (A) and contrast-enhanced (B) chest computed tomography shows the typical appearance of an extrapulmonary lesion *(arrows)*: a circumscribed, lenticular- or oblong-shaped opacity creating obtuse margins with the chest wall. Surgical resection proved solitary fibrous tumor of the pleura. (Courtesy Michael B. Gotway, MD.)



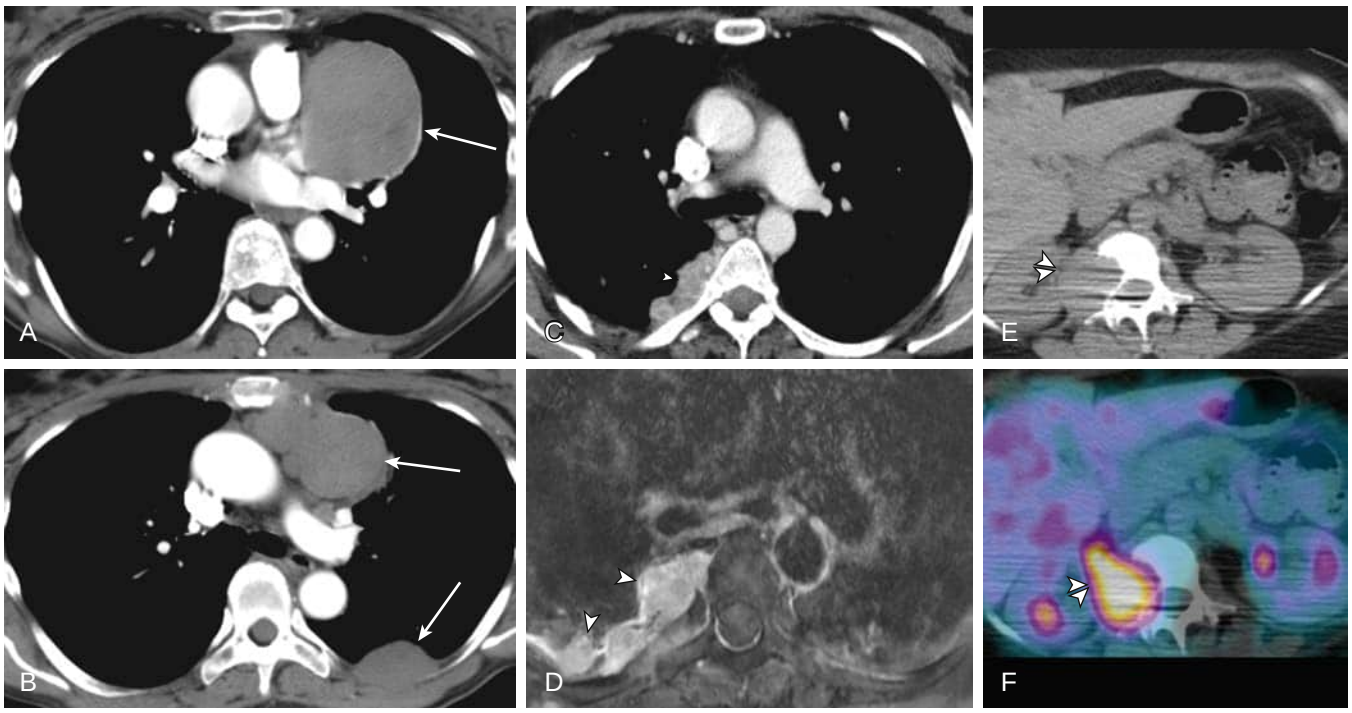
eFigure 80.10 Solitary fibrous tumor of the pleura; large. (A) Frontal chest radiograph shows near complete opacification of the left thorax with slight shift of the cardiomediastinal structures to the contralateral side. (B–D) Axial contrast-enhanced chest computed tomography shows a solid, vascularized lesion occupying much of the left thorax. The large size of the lesion makes determination of the organ of origin difficult, but solitary fibrous tumor of the pleura is a consideration, particularly when no overtly aggressive features, such as a large pleural effusion, rib destruction, or lymph node enlargement, are evident. Surgical resection proved solitary fibrous tumor of the pleura. (Courtesy Michael B. Gotway, MD.)



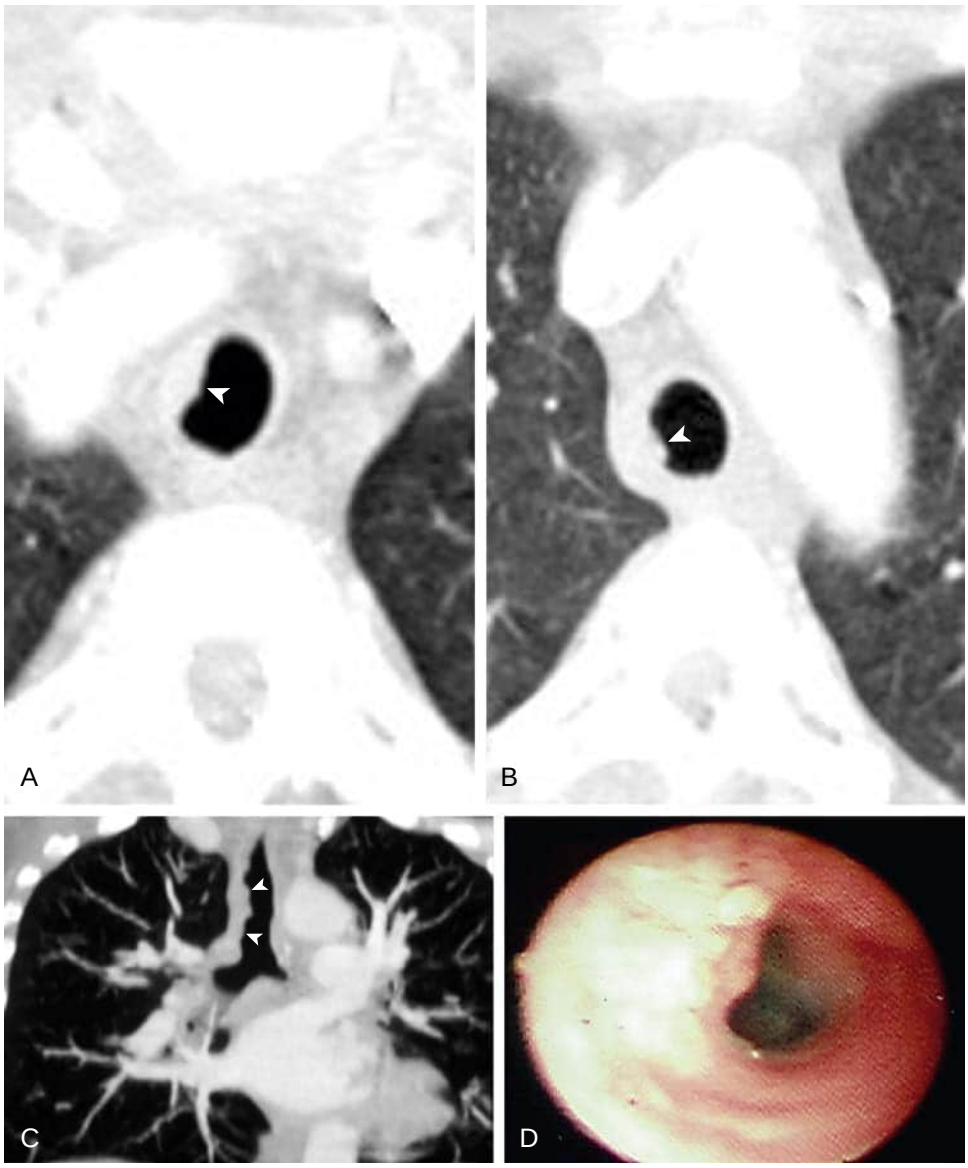
eFigure 80.11 Solitary fibrous tumor of the pleura. (A) Frontal chest radiograph shows a circumscribed mass *(arrow)* along the left heart border. The mediastinal contact, smoothly marginated character of the lesion, and obtuse angles of the lesion at its interface with the lung suggest an extrapulmonary origin. (B) Unenhanced chest computed tomography (CT) shows the lesion *(arrow)* has mildly inhomogeneous attenuation and significantly contacts the left mediastinum and pericardium. (C) Axial fused positron emission tomography-CT image shows little tracer accumulation within the lesion *(arrow)*: note the similarity in tracer uptake between the lesion *(arrow)* and mediastinal blood pool in the aorta *(arrowhead)*. Surgical resection proved solitary fibrous tumor of the pleura. (Courtesy Michael B. Gotway, MD.)



eFigure 80.12 Malignant solitary fibrous tumor of the pleura. (A–C) Axial contrast-enhanced chest computed tomography shows a large, homogeneous, solid, vascularized left-sided mass with broad pleural surface contact. Biopsy showed features consistent with malignant fibrous tumor of the pleura. (Courtesy Michael B. Gotway, MD.)



eFigure 80.13 Malignant solitary fibrous tumor of the pleura. (A–B) Axial contrast-enhanced chest computed tomography (CT) displayed in soft tissue windows shows circumscribed and lobulated soft tissue masses *(arrows)* involving the mediastinal and posterior pleural surfaces, proven on biopsy to represent fibrous tumor of the pleura. Axial contrast-enhanced chest CT (C) and axial T2-weighted magnetic resonance imaging (D) show lobulated soft tissue masses *(arrowheads)* related to the right mediastinal and posteromedial pleural surfaces, again reflecting fibrous tumor of the pleura. Axial unenhanced chest CT (E) and fused positron emission tomography-CT image (F) show a metabolically active lesion involving L1, representing metastatic malignant fibrous tumor of the pleura. This patient originally had a right upper thoracic pleural fibrous tumor arising from the pleura resected in 1997. (Courtesy Diego Ruiz, MD, Palo Alto Medical Clinic, CA, and Michael B. Gotway.)



eFigure 80.14 Granular cell tumor of the trachea. Axial enhanced chest computed tomography (CT) (A–B) and coronal maximum intensity projection (C) performed as part of CT aortography in a patient with chest pain shows the incidental detection of a plaquelike lesion *(arrowheads)* along the right lateral tracheal wall. (D) Bronchoscopic image shows a lobulated lesion corresponding to the computed tomography abnormality. Biopsy proved malignant granular cell tumor. (A–C, Courtesy Michael B. Gotway, MD.)

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SECTION J

DISORDERS OF THE PULMONARY CIRCULATION

81 PULMONARY THROMBOEMBOLISM: PRESENTATION AND DIAGNOSIS

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INTRODUCTION

The one generalization about *venous thromboembolism* (VTE) free from controversy is that many aspects of this disorder remain controversial. There are multiple reasons why VTE continues to engender lively debate. Perhaps the major reason, notwithstanding recent substantial advances, is that a number of fundamental questions continue to exist regarding its pathogenesis, clinical presentation, diagnosis, and therapy.

VTE represents a potentially fatal disease process with a clinical presentation that is often silent or nonspecific and

for which a wide range of diagnostic techniques is available, many with technical and interpretive limitations. Although estimates vary widely, the best available information suggests that there are at least 1 to 5 million episodes of VTE annually in the United States.[1,2] The annual incidence of diagnosed acute *pulmonary embolism* (PE) is approximately 65 to 70 per 100,000.[3–5] Every year, based on discharge diagnosis codes, there are about 676,000 patients with *deep venous thrombosis* (DVT) and about 340,000 with PEs in the United States.[2] One in 12 persons aged 45 years or older will be diagnosed with VTE at some point in their lives, and the incidence increases exponentially through the sixth to ninth decades of life.[6]

Diagnosed cases likely underrepresent the true incidence of acute PE because they account for only those patients in whom the diagnosis was made correctly.[7] Autopsy series suggest that the true number of deaths from acute PE, including patients who died without the diagnosis being made, is at least threefold higher and could be as much as 10-fold higher than reported.[7-11] For this reason, it is likely that most PE-related deaths happen when PE is undiagnosed (and therefore untreated) during life.

Historically, about one in five patients who sustain a PE may die from it.[12] The overwhelming majority of these deaths do not appear to arise from therapeutic failure. The in-hospital mortality rate from acute PE is 2–5% once the diagnosis of embolism is confirmed and appropriate therapy initiated.[5,13,14] Notable exceptions are patients who initially present with hemodynamic impairment[14] and those with recurring PE despite therapy,[15] in whom mortality rates are much higher. Those circumstances notwithstanding, the majority of deaths related to embolism appear to arise from a failure to prevent the disease in at-risk patients and from a failure to make the diagnosis in those afflicted.[7,12]

The incidence of fatal PE declined from the 1970s through the 2000s[16,17] but, over the past 10 years, the number of PE-related deaths and the death rates in the U.S. population have gradually risen.[18] It is noteworthy that these statistics do not account for fatal PE not diagnosed clinically, as described earlier. Balancing these facts are some data that suggest that the increasing reliance on *computed tomographic pulmonary angiography* (CTPA) may be leading to overdiagnosis of PE in some populations.[19] Total admissions and hospital charges for PE have increased in the last 2 decades, which may reflect a trend of admitting patients with less severe PE, although that would not be supported by data showing that population-adjusted deaths during admission for PE have increased.[5] Despite the increase in PE-related hospitalizations, mortality from acute PE remains a substantial public health care problem, possibly because of the demographics of the aging population.[18,20]

Contributing to the debate surrounding VTE is the involvement of a wide range of medical disciplines in its prevention, diagnosis, and management. Thrombosis is not a discrete clinical subspecialty. The problem of VTE involves pulmonologists, cardiologists, hematologists, internists, specialists in vascular disease, radiologists, a range of surgical subspecialists, obstetricians, and others. Because specific prophylactic, diagnostic, and therapeutic strategies within one discipline may not necessarily be applicable to another, a perception of coherence in the clinical approach to this disease process often appears to be lacking.

Many of the long-standing controversies surrounding the natural history, diagnosis, and therapy of VTE have been partially or completely reconciled, resulting in substantial changes in the diagnostic and therapeutic approach to the disease. The persistence of a number of unresolved issues, and the emergence of still others, should not be a cause for cynicism. In the approach to the patient with suspected VTE, an understanding of what is unknown can prove invaluable to the decision-making process.

PATHOGENESIS AND RISK FACTORS

The triad of venous stasis, alterations in coagulation, and vascular injury identified by Virchow in 1856 as primary factors in the pathogenesis of VTE has been supported by a considerable amount of clinical and experimental evidence. Over the past several decades, severe abnormalities of the coagulation and fibrinolytic system, including isolated deficiencies of protein C, protein S, antithrombin III, and plasminogen, as well as the presence of a lupus anticoagulant, have been described and their association with first-time and recurrent VTE confirmed (Table 81.1).[21,22] In addition, there has been increasing recognition of less severe, but more common, inherited thrombophilic conditions capable of shifting the hemostatic balance toward thrombosis and mildly increasing the risk of venous thromboembolic events. They are especially notable among patients with thrombi in unusual locations, such as the upper extremities.[23] Although it is a subject of debate whether they increase the risk of recurrence slightly, the magnitude of the increase is unlikely to warrant changes in therapeutic strategies for patients with those thrombophilias, as discussed later.[6,24]

Factor V Leiden mutation, the most common of the inherited thrombophilic conditions, was first described in 1993 by Dahlback; it is the consequence of a single point mutation in the factor V gene (adenine for guanine) resulting in *activated factor V* (factor Va) with diminished sensitivity to the natural anticoagulant effect of activated protein C.[25] Approximately 5% of whites in Europe and North America are heterozygous for this genetic defect; lower rates of carrier frequency have been reported among Native American, African, and Asian populations.[26,27] Although initially suspected to present in the majority of patients with VTE, a large prospective study of unselected subjects detected the mutation in just over 10% of those who developed VTE.[28] Depending on the population involved, the heterozygous state carries between a twofold and 10-fold increase in lifetime risk for VTE.[6,29,30] Whereas the relative risk among patients homozygous for this mutation is likely much higher, only very small cohorts with this genotype have been followed prospectively, making estimates of absolute risk imprecise.[29–32]

Factor V Leiden mutation appears to be an important risk factor for VTE during pregnancy, in the postpartum

Table 81.1 Thromboembolic Risk Factors

HEREDITARY THROMBOPHILIAS
Protein C deficiency
Protein S deficiency
Antithrombin III deficiency
Factor V Leiden mutation
Prothrombin 20210 G → A variation
Hyperhomocysteinemia
Dysfibrinogenemia
Familial plasminogen deficiency
ACQUIRED SURGICAL PREDISPOSITIONS
Major thoracic, abdominal, or neurosurgical procedures requiring general anesthesia and lasting >30 min
Hip arthroplasty
Knee arthroplasty
Knee arthroscopy
Hip fracture
Major trauma
Open prostatectomy
Spinal cord injury
ACQUIRED MEDICAL PREDISPOSITIONS
Prior venous thromboembolism
Advanced age (>60 yr)
Malignancy
Congestive heart failure
Cerebrovascular accident
Nephrotic syndrome
Estrogen therapy
Pregnancy and the postpartum period
Obesity
Prolonged immobilization
Antiphospholipid antibody syndrome
Lupus anticoagulant
Inflammatory bowel disease
Paroxysmal nocturnal hemoglobinuria
Behçet syndrome

period, and during oral contraceptive use.[31–34] The risk of thrombosis in women who use oral contraceptives and are carriers of the factor V mutation is increased 30-fold compared to women who have neither of these risk factors.[35] However, because the absolute increase in VTE is modest, selective thrombophilia screening based on previous personal or family history of VTE is more cost-effective than universal screening.[32]

Normal prothrombin is overproduced in those with a sequence variation in the prothrombin gene (G20210A). This mutation was described in 1996 and is estimated to exist in approximately 2–4% of the population.[36] Heterozygous prothrombin G20210A is associated with a threefold to fourfold increased relative risk of lower extremity venous thrombosis.[36–38]

Hyperhomocysteinemia had been identified as a potential independent predisposition to VTE, but the evidence supporting its role is quite weak. Elevation of plasma homocysteine levels may be the result of genetic abnormalities, such as the methylene tetrahydrofolate reductase C677T gene polymorphism, nutritional deficiencies of vitamins (B_6, B_{12}, folate), clinical disorders (renal insufficiency, hypothyroidism, inflammatory bowel disease), or a combination of the three. Although retrospective, case-control studies suggested an association between hyperhomocysteinemia and VTE, the results were not consistently confirmed in prospective studies.[39,40] Specifically, there appears to be no association between the methylene tetrahydrofolate reductase C677T gene polymorphism and VTE and, at most, a weak association between elevated homocysteine levels and VTE.[41]

These three common genetic thrombophilias (factor V Leiden, prothrombin G20210A, and hyperhomocysteinemia) may act as independent risk factors for increasing thrombosis risk.[42,43] Although the relative risk for patients with multiple thrombophilic conditions may be higher than for patients with only one, the clinical implications of this possibility are uncertain.

The identification of these risk factors, and the likelihood that others exist, raises the possibility that screening to determine relative thromboembolic risk may be feasible in the future; however, a consensus for such an approach does not currently exist. Despite its prevalence in the general population, screening for factor V Leiden mutation is not advised because the overwhelming majority of patients with this abnormality will never experience a thromboembolic event. Furthermore, the absence of this abnormality should not influence the decision to provide prophylaxis to patients at clinical risk. In addition, there is no evidence that prolonged anticoagulation would be more beneficial for VTE patients with either factor V Leiden[44] or the prothrombin G20210A gene[45] than in VTE patients without these mutations.[24]

The long-term implications for patients with preexisting VTE who are homozygous for factor V Leiden or for prothrombin G20210A are controversial. Although early reports suggested that VTE patients homozygous for factor V Leiden had about twice the risk of recurrence than those who are heterozygous,[46,47] later studies reported no increase in risk for recurrence.[48,49] Studies suggesting higher recurrence for homozygotes differed regarding whether the recurrence risk was limited to provoked VTE (e.g., during subsequent pregnancies without prophylactic anticoagulation)[47] or whether it applied to spontaneous (unprovoked) recurrence.[46]

Similarly, reports have varied regarding whether patients with spontaneous (unprovoked) VTE who are heterozygous for both factor V Leiden and the prothrombin G20210A mutation are at higher risk for recurrence than similar patients without those mutations.[46–48] However, even if the association were to be confirmed, it would not establish a risk-benefit relationship for prolonged anticoagulation in patients with the combination of thrombophilic mutations.

For all the reasons stated, the benefits of screening for the common thrombophilias are controversial. Patient groups in whom screening is likely to yield positive results include those with a history of recurrent VTE or with a confirmed family history of thromboembolism, a first episode of thromboembolism at an early age, spontaneous venous thrombosis, thromboses in unusual anatomic sites, arterial thrombosis, and thromboembolism associated with pregnancy[50,51] or estrogen use. Whether screening should be performed before the initiation of oral contraceptive agents remains a matter of debate.[52,53] The relative risk of VTE is increased approximately fourfold in users of oral

contraceptives, although the increase in absolute risk is modest.[35,54] A policy of routine screening would deny effective contraception to a substantial number of women while preventing only a small number of PEs. A similar situation exists for pregnancy, in which the presence of factor V Leiden or the prothrombin G20210A mutation increases the relative risk of VTE but only slightly increases the absolute risk.[51]

In most patients, even those with an identified thrombophilic state, clinical conditions associated with venous stasis, intimal injury, or both serve as the basis for the thromboembolic event,[55] and adequate prophylaxis may mitigate that risk.[47] In hospitalized patients, the risk of VTE is not limited to patients undergoing surgical procedures; the risk in patients admitted with a wide range of acute medical problems is comparable to that seen in surgical patients.[56–58]

Major acquired risk factors include pelvic or lower extremity fractures, hip and knee surgery, a past history of VTE, acute paralytic stroke or spinal injury, major traumatic injury, open prostatectomy, and abdominal or pelvic surgery for malignant disease. Other factors that enhance risk include prolonged general anesthesia, advancing age, cardiac disease, pregnancy,[50] the postpartum state, the use of estrogen-containing hormone replacement therapy,[59] malignancy, nephrotic syndrome,[60] the presence of a lupus anticoagulant or antiphospholipid antibody, and prolonged immobilization.[61]

Risk factors may be multiplicative,[51,55] and chronic medical conditions not typically listed as thrombophilias may still substantially increase the risk of VTE. For example, the lifetime risk of VTE among patients with sickle cell disease or sickle cell trait is increased at least as high as it is among those with factor V Leiden,[6,62,63] and the risk of VTE during hospitalization is greatly increased in patients with sickle cell disease and sickle cell trait.[64] Patients with chronic liver disease have about twice the lifetime risk of VTE as the general population,[65] and hospitalized patients with cirrhosis have about twice the risk of VTE as other hospitalized patients,[66] despite elevated international normalized ratio values that might be incorrectly interpreted as protective and dissuade clinicians from using prophylaxis.[66–68] Obesity is known to increase the likelihood of VTE during critical illness.[69] It is additionally important to consider the diagnosis of PE in patients with acute exacerbations of COPD because the prevalence of PE in unexplained acute exacerbations of COPD is relatively high, with a pooled prevalence of 16.1% on a systematic review.[70]

Although the risk of posttreatment recurrence depends in part on whether the VTE was provoked by transient risk factors,[71] the distinction between provoked and unprovoked is not entirely dichotomous but, rather, represents a spectrum of risk for recurrence. For example, compared to unprovoked VTE, VTE provoked by a surgical event is one-tenth as likely to result in recurrence, whereas VTE provoked by a nonsurgical transient risk factor is more than half as likely to result in a posttreatment recurrence.[71] Furthermore, there is a great deal of heterogeneity among the nonsurgical provoking factors. For example, a strong risk factor such as acute necrotizing pancreatitis requiring hospitalization is more likely than not to result in VTE.[72] Air travel, on the other hand, is a relatively mild provoking factor, resulting in VTE after about 1 in every 100,000 flights shorter than 4 hours and 1 in every 4700 flights of longer duration.[73] Although the relative risk in fliers is increased compared to nonfliers, the absolute incidence is quite low[73,74] and, in about half of cases, associated with a coexisting risk factor that poses an even higher risk for VTE than the flight itself.[75]

The likelihood that a "provoking" factor was largely responsible for a VTE should weigh heavily in subsequent prognostic and treatment decisions. These types of considerations allow the development of a reasonable risk profile in an individual patient, a profile that should influence the use and intensity of prophylactic intervention.[55] See Chapter 82 for details on prophylaxis.

NATURAL HISTORY: DEEP VENOUS THROMBOSIS

Venous thrombi appear to originate either in the vicinity of a venous valve cusp, where eddy currents arise, or at the site of intimal injury.[76] Platelet aggregation and release of mediators initiate the sequence. With local accumulation of such factors, the coagulation cascade is activated and thrombus develops, composed primarily of fibrin and erythrocytes. As the thrombus extends, local fibrinolytic activity is enhanced. Thus, thrombus behavior becomes a dynamic process that may result in complete dissolution, partial resolution resulting in a variable degree of intimal narrowing and valvular damage, progressive proximal extension, or embolization. In more than half of patients, the venous wall suffers some degree of permanent scarring, which is visible on ultrasound[77]; if the venous wall scarring causes severe obstruction, collateral veins develop.

Extensive autopsy and clinical studies have established that some 90% of clinically apparent PEs arise from venous thrombosis in the deep veins of the lower extremities.[78] In fact, a conservative estimate is that at least one-third of DVT is complicated by symptomatic or asymptomatic PE.[79] Venous thrombi capable of embolization can also arise from other sites. Primary iliac or proximal femoral thrombi may develop in patients undergoing surgery involving the hip, and pelvic vein thrombosis may develop in patients undergoing pelvic or prostatic surgery. Axillosubclavian vein thrombosis may be spontaneous, resulting from congenital abnormalities of the thoracic outlet or may be related to indwelling central venous catheters, pulmonary artery catheters, or transvenous pacing wires.[80–82] Both peripherally inserted central catheters and midline venous catheters are also associated with venous thrombi.[83,84] In patients with dilated right heart chambers or pulmonary arteries, thrombi can form at those sites and embolize distally into the branches of the pulmonary artery. The prevalence of upper extremity DVT is about 3% in a large-scale VTE patient registry. Patients with DVT in the upper extremities were more likely to have a central venous catheter or active malignancy at the time of diagnosis and were less likely to be diagnosed with concomitant PE.[85]

The likelihood of embolism is influenced by the location of thrombi in the veins of the lower extremity. The majority of thrombi originate in the deep veins of the calf (i.e., *distal*) and those that remain limited to the calf veins do not usually result in PE.[86] However, 15–25% of symptomatic

isolated calf thrombi, if left untreated, will extend into the *proximal* deep veins, such as the popliteal vein, femoral vein (which was previously labeled by the misleading term "superficial femoral vein"), common femoral veins, and even more proximal veins.[87] One-third to one-half of patients with proximal extension develop symptomatic or asymptomatic PE.[15,79,88,89] For that reason, a small proportion of patients with distal DVTs are at risk for PE.[79,87,90–92] The risk of proximal DVT and PE after isolated calf DVT is higher in hospitalized patients and in those 60 years of age and older.[91] Symptomatic calf vein thrombosis also poses a risk for recurrence, although the risk is less than for proximal DVT.[87] In one series, about 1 in 10 patients with symptomatic isolated calf vein thrombosis experienced recurrence of VTE, and about half of those recurrences were in the form of proximal DVT or PE.[93]

This natural history of DVT has several important diagnostic and therapeutic implications. First, because the vast majority of emboli arise from thrombi in the veins in the lower extremity, diagnostic approaches to DVT can focus upon techniques that detect lower extremity DVT. Second, techniques that detect above-knee thrombi are of particular value. Finally, although it is true that calf-limited thrombi rarely embolize, many have incorrectly concluded from this information that symptomatic, calf-limited DVT represents a clinically irrelevant condition. As mentioned earlier, calf-limited thrombi may extend proximally, and patients with symptomatic calf vein thrombosis are at risk for PE and recurrence, albeit at a lower risk than proximal vein thrombosis.[87,94]

Although most above-knee thrombi represent extensions from calf thrombi, some do arise in the larger, proximal veins de novo. This appears to be restricted principally to patients with hip fracture or replacement, pelvic surgery (including prostatic resection), and other high inguinal pelvic trauma.

At any time during the thrombotic process, a portion or all of the thrombus can detach as an embolus. This risk is highest early in thrombus development before there is significant fibrinolysis or organization. Beyond this acute phase, the long-term outlook is influenced principally by the extent of residual venous obstruction and valvular damage. If significant obstruction or valvular damage persists, downstream stasis will be present, leading to a risk of recurrent DVT and development of the postphlebitic syndrome.[95,96]

NATURAL HISTORY: PULMONARY EMBOLISM

PE causes a number of consequences to gas exchange and other pulmonary functions.[97] Regional obstruction to pulmonary blood flow and diversion of the flow to unobstructed portions of the lung may alter the ventilation-perfusion balance in both the obstructed and the unobstructed regions.[98,99] In the regions with pulmonary vascular obstruction, alveolar dead space is created.[100] If a region's blood flow is severely obstructed, there may be bronchoconstriction in the airways distal to the area of obstruction as a result of alveolar hypocapnia.[101] This is probably uncommon in patients because they are free to inhale carbon dioxide–rich dead space air into the involved lung regions and because obstruction is rarely total. PE almost always leads to hyperventilation, the mechanism for which remains uncertain.

Hypoxemia is seen to some degree in about 85% of PE patients and is generally caused by the venous admixture due to areas of low ventilation/perfusion ratio or of shunt[98] (see also Chapter 44). Arterial hypoxemia may be worsened when acute increases in *right ventricular* (RV) afterload lower the cardiac output enough to widen the arteriovenous oxygen difference and decrease the oxygen saturation of mixed venous blood.[102] This lowering of the mixed venous oxygen content magnifies the effects of the normal venous admixture, thereby further lowering the resultant *arterial partial pressure of oxygen* (Pa_{O_2}). With more substantial PE, another potential mechanism for hypoxemia is right-to-left shunt, either intrapulmonary or intracardiac.[103] When embolic occlusion is sufficient to increase pulmonary artery pressure, hypoxic vasoconstrictive mechanisms can be overwhelmed, and perfusion may inappropriately increase in poorly ventilated or nonventilated lung regions. On occasion, embolic events massive enough to increase right atrial pressure may result in intracardiac right-to-left shunting through a patent foramen ovale. The final mechanism for hypoxemia relates to the loss of pulmonary surfactant.[104] Surfactant is not lost immediately; loss requires approximately 24 hours of total occlusion and lack of blood flow to develop. At that time or later, surfactant becomes depleted in the obstructed alveolar zones, resulting in atelectasis and edema. If the thrombus resolves, perfusion to this atelectatic region will contribute to hypoxemia.

Pulmonary infarction was once thought to be quite unusual with PE, but advanced CT scan imaging discloses subtle findings consistent with infarction in about 1 in 6 to 1 in 3 patients.[105,106] Still, infarction is uncommon, which is thought to be because the pulmonary parenchyma has three potential sources of oxygen: the pulmonary arteries, the bronchial arteries, and the conducting airways.[107] Of interest, pulmonary infarction is more frequent in the absence of preexisting cardiopulmonary disease and is more frequent in young patients than in elderly patients,[105,106] leading to longstanding speculation that elderly patients or those with preexisting disease may have established collateral flow that protects from infarction.

The cardiac and hemodynamic effects of embolism are related to three factors: the degree of reduction of the cross-sectional area of the pulmonary vascular bed, the preexisting status of the cardiopulmonary system, and the physiologic consequences of both hypoxic- and neurohumorally mediated vasoconstriction.[108–113] Mechanical obstruction of the pulmonary vascular bed by embolism accounts for most of the increase in pulmonary vascular resistance, although resistance is typically worsened by release of vasoconstrictive substances, such as endothelin, thromboxane A_2, and serotonin.[114,115] The combination acutely increases the workload on the RV, a chamber ill-equipped to deal with an acute elevation in pressure load.

In less severe cases, a number of compensatory events minimize adverse hemodynamic consequences. Pulmonary vessels are recruited and become distended, resulting in normal or near-normal pulmonary vascular resistance and pulmonary artery pressure. However, with greater extent

of pulmonary vascular obstruction, pulmonary vascular resistance is increased hyperbolically: It rises modestly as the remaining pulmonary vascular bed expands and recruits available vessels, but it increases precipitously as the vascular reserve is exhausted.[111,116]

PE is termed *submassive* if pulmonary artery resistance and pressure are increased and there are signs of RV strain but the patient is hemodynamically stable. Cardiac output is maintained by increases in heart rate and by increases in RV diastolic volume, which augment stroke volume (the Frank-Starling mechanism).[117] Maintaining cardiac output demands increased work from the RV, which in turn requires increased perfusion of the myocardium itself. The myocardial blood flow depends on the gradient between the coronary artery pressure and the pressure within the myocardium. Unfortunately, the myocardial pressure is greatly increased from the high pressure within the dilated RV lumen and the muscle wall tension required to maintain stroke volume against the pulmonary vascular obstruction.[118] Although a small amount of myocardial enzyme leak is evident clinically under those conditions,[119] the RV can maintain output without a substantial amount of myocardial ischemia. In patients without prior cardiopulmonary disease, the RV can generate mean pulmonary artery pressures of around 40 mm Hg and pulmonary artery systolic pressure of around 70 mm Hg.[110]

In patients with *preexisting* cardiopulmonary disease, the hemodynamic response to acute PE may be considerably different from that in patients without prior disease.[113] In patients without prior cardiopulmonary disease, there is a general relationship between the rise in pulmonary artery pressure and the pulmonary vascular obstruction, whereas in patients with prior cardiopulmonary disease, pulmonary artery pressures may rise disproportionately. As a result, severe pulmonary hypertension may develop in response to a relatively small reduction in pulmonary artery cross-sectional area.[120] In addition, evidence of RV hypertrophy (rather than RV dilation) associated with a mean pulmonary artery pressure greater than 40 mm Hg (pulmonary artery systolic pressure > ≈70 mm Hg) in a patient with suspected embolism should suggest an element of chronic pulmonary hypertension. Preexisting pulmonary hypertension could result from a potentially diverse group of etiologic possibilities (e.g., chronic thromboembolic pulmonary hypertension, left ventricular failure, or valvular disease).

PE is termed *massive* if the compensatory mechanisms are overwhelmed and cardiac output drops. In those cases, a perfect storm of conditions leads to RV failure and hemodynamic instability. Left ventricular diastolic filling is compromised by decreased inflow from the pulmonary circulation and, more importantly, by septal wall displacement from the dilated RV.[121] If the decompensation is severe enough to lower cardiac output and systemic blood pressure, the hypotension worsens the situation by decreasing the coronary perfusion pressure to the already tense RV.[118] The resulting hemodynamic instability can be self-perpetuating. RV ischemia/infarction lowers cardiac output further, which in turn worsens RV myocardial perfusion and magnifies the ischemia/infarction.[118] The mortality of massive PE is greatly increased over less severe manifestations.[122]

About 1 in 10 patients who initially present with submassive PE subsequently develop massive PE,[123,124] although the mechanism of the deterioration is a subject of some controversy. Hemodynamic instability may materialize in normotensive patients with submassive PE later during the day of presentation[124] or several days into treatment.[123] Mechanistically, deterioration reflects either acute recurrence, growth of pulmonary emboli despite appropriate therapy, or progressive RV failure and infarction despite unchanging (or improving) pulmonary vascular resistance. Acute recurrent PE is clinically demonstrable during the first several days of anticoagulant therapy in one-tenth[15] to one-fifth[122] of acute PE patients. If either the existing PE or the residual DVT (or both) are substantial, deterioration within the first few days could reflect a second embolization. Significant growth of emboli during this time frame seems unlikely because serial perfusion scans have disclosed at least some degree of resolution during the first week in almost all acute PE patients treated with anticoagulant therapy.[125] Progressive, continuous RV failure, if it happens, is uncommon because blood troponin levels reflecting RV ischemia peak within a few hours of presentation and then steadily decline over the subsequent hours and days.[126,127] Echocardiographic measurements of RV dysfunction likewise steadily improve over the first few days of therapy.[128]

Thromboemboli resolve in three phases: plasmin-mediated fibrinolysis, cellular infiltration with neutrophils, and monocyte-mediated remodeling with endothelial cells and fibroblasts. In the first phase, polymerized fibrin is degraded by plasmin into degradation products such as D-dimer. Although release of D-dimer into the plasma is evident in 80% of acute PE patients 1 week after diagnosis, it is present in only 40% after 1 month and 13% after 3 months.[129] After about 1 week, thrombus resolution becomes a neutrophil-mediated process dependent on a number of inflammatory cytokines.[130,131] Finally, a much slower phase of resolution is mediated by monocytes recruited from the circulating blood.[132,133] Monocytes[134] and endothelial progenitor cells[135] form channels within the clot to restore the lumen. Interleukin-8,[136] vascular endothelial growth factor,[134,137,138] and basic fibroblastic growth factor[137] stimulate angiogenesis and encourage thrombus resolution.[137,139] Residual lung perfusion defects reflect thrombi that have somehow avoided the full resolution process and have been instead remodeled into scar tissue.

Although there is a great deal of interpatient variability, resolution of PEs typically parallels our understanding of thrombus resolution biology. (The term *resolution* is used here to represent all the phases described in the preceding paragraph.) Resolution tends to be substantial during the first week, somewhat more gradual for the next 4 to 8 weeks, and then very slow thereafter.[100,125,140–144] Typically, about two-thirds of PE-related vascular obstruction resolves over the first month and, in about one-third of patients, resolution is complete by that time.[145] In terms of hemodynamic resolution, a stable pulmonary artery pressure is usually reached at around this time.[128] PEs typically recover more slowly over the subsequent 2 months.[146,147] Nevertheless, nearly one-third of patients with acute PE may have residual perfusion defects, which may be associated with a spectrum of symptoms, including dyspnea,

lower exercise tolerance, and higher pulmonary arterial pressures of various intensities.[148] About 10% of those patients will subsequently develop chronic thromboembolic disease.[149]

CLINICAL PRESENTATION

The most common symptoms and physical findings of venous thrombosis include swelling, pain, erythema, and warmth. "Classic" findings, such as the Homan sign (calf pain with flexion of the knee and dorsiflexion of the ankle), the Moses sign (pain with compression of the calf muscles forward against the tibia), or a palpable cord are infrequent and nonspecific.

As established by multiple investigations, the clinical diagnosis of venous thrombosis is imprecise.[78,150–153] In patients with clinical signs and symptoms suggestive of venous thrombosis, 60–80% will not have the diagnosis by objective testing. Furthermore, and even more disquieting, the majority of high-risk patients who are monitored and who develop DVT will not have signs or symptoms suggesting the diagnosis.[154] Algorithmic clinical models incorporating risk factors, symptoms, and physical signs have been shown to stratify *symptomatic* patients into risk categories, although not to a level in which clinical diagnosis, in the absence of objective testing, can be relied on either to confirm or exclude the diagnosis.[152,155] The differential diagnosis of DVT is extensive and includes cellulitis, arthritis, muscular injury or tear, neuropathy, arterial insufficiency, lymphedema, ruptured Baker cyst, superficial thrombophlebitis, and chronic venous insufficiency.

Similarly, the diagnosis of PE cannot be confirmed or excluded solely on clinical grounds.[156–158] However, recognition of the clinical signs and symptoms associated with PE is valuable because clinical findings and clinical suspicion represent an essential first step in the diagnostic pathway. Although a somewhat arbitrary classification, because presenting symptoms and signs of embolism frequently overlap, the presentation of PE can be categorized into one of three clinical syndromes: (1) isolated dyspnea, (2) pleuritic pain or hemoptysis, and (3) circulatory collapse.[159] Among patients without prior cardiopulmonary disease in the *Prospective Investigation of Pulmonary Embolism Diagnosis* (PIOPED) study, the syndrome of pleuritic pain or hemoptysis was the most common mode of presentation, seen in approximately 60% of patients; isolated dyspnea was noted in approximately 25% and circulatory collapse in 10%.

Overall, the most common presenting symptom of acute embolism is dyspnea.[158–160] However, even dyspnea is not ubiquitous and may be absent in one-fourth of PE patients.[160] Pleuritic chest pain is present in about two-thirds of patients, whereas hemoptysis is much less common. Less than half of patients have cough, leg swelling, or leg pain. Angina as a result of RV ischemia may also be present in the setting of massive embolism. Syncope or presyncope may also be a presenting complaint in major embolic occlusion,[161,162] although it is not consistently associated with a worse short-term outcome.[163,164]

The most common physical examination finding is tachypnea (respiratory rate > 20 breaths/min). Similar to the symptom of dyspnea, however, tachypnea is not universal and is absent in almost one-third of PE patients.[160] Clinical findings noted less frequently include inspiratory crackles, tachycardia, and an increased pulmonic component of the second heart sound (S_2). Fever may develop some hours after the event and often reaches, but rarely exceeds, 38.3°C. Although hemoptysis may be observed and even persist for days, it is usually quite modest in extent. Brisk hemoptysis is rare and is almost never the initial finding. With massive embolism, there may be evidence of RV overload or failure, such as a RV tap along the left sternal border and an accentuated pulmonary valve closure sound. If RV failure develops, there may be narrowed or fixed splitting of S_2, an S_3, and/or an S_4, elevated jugular venous pressure, and cyanosis. Careful examination of the legs may disclose signs suggestive of DVT (unilateral swelling and tenderness) in about 1 in 10 patients, although only about one-third of patients with those signs have demonstrable DVT.[165] However, although PE commonly originates from lower extremity DVT, clinically apparent venous thrombosis remains in only a small proportion of patients at the time of PE presentation.[160]

Obviously, these symptoms and signs are nonspecific. In the PIOPED study,[90,91] none of the presenting symptoms was capable of discriminating between patients with PE and those with other cardiopulmonary problems.[158,159] Also, in terms of presenting signs, only the presence of crackles, an S_4, and an increased pulmonic component of S_2 could differentiate between those with and without PE.[159,160,166] Furthermore, in patients with underlying cardiopulmonary disease, the presenting symptoms and signs frequently may be obscured by manifestations of chronic disease.[157]

It is also important to recognize that the clinical presentation of embolism has been characterized in trials composed of symptomatic patients, although it is known that many PEs do not produce symptoms. In prospective studies of high-risk patients with proximal DVT, PE can be documented in 40% of patients who had no symptoms of PE.[88,156,167] Unsuspected PE and incidental PE are found in about 2% of CT scans evaluating other cardiopulmonary pathology.[168]

It is likely that the frequency and severity of symptoms are influenced by the extent of embolic occlusion and the prior cardiopulmonary status of the patient. Small- or moderate-sized emboli may induce few or no symptoms in an otherwise normal individual.[168] In patients with preexisting cardiopulmonary disease, symptoms are more common and severe.[169]

Owing to the nonspecific presentation of PE, the differential diagnosis is varied and extensive, especially in hospitalized patients with coexisting cardiac or pulmonary disease. Common considerations include congestive heart failure, exacerbation of chronic lung disease, postoperative atelectasis, and viral pleurisy. PE presenting with fever, dyspnea, and chest radiographic abnormalities easily can be confused with a bacterial pneumonia. Fever and leukocytosis (rarely >15,000 cells/μL) are uncommon but well-described accompaniments of VTE.[170,171]

These precautionary statements regarding clinical diagnosis are not meant to suggest that the clinical presentation of VTE or PE cannot be used as a basis for clinical decision making. However, they are meant as a reminder that the clinical presentation of VTE and PE may often be atypical or

subtle and should serve only to generate a suspicion of that diagnosis. A reliance on symptoms and signs considered classic before making the decision to proceed to confirmatory testing may lead to underdiagnosis and unnecessary mortality.

DIAGNOSIS OF VENOUS THROMBOSIS

The proper diagnostic approach to VTE must take into account the central fact that venous thrombosis and PE are manifestations of the same disease process: venous thrombosis representing the source of PE, and PE representing a complication of venous thrombosis.

CLINICAL PREDICTION RULES

Perhaps the most important decision in the diagnostic approach to both venous thrombosis and PE is whether to pursue definitive diagnostic techniques or to exclude patients based on screening tests. The latter choice depends largely on Bayesian analysis, in which the pretest probability of the disease, calculated independently of a particular test result, is evaluated in combination with a test's likelihood ratio (derived from the sensitivity and specificity of that test) to estimate the posttest probability. The posttest probability can then be used as a basis for clinical judgment, either excluding the disease with a certain level of probability or supporting the need for additional diagnostic testing. This approach to diagnosis has proved especially useful for cost-effective medical practice.

Several clinical prediction rules for venous thrombosis based on data obtained during history taking and physical examination have been developed and validated.[172] The most commonly used one is the *Wells score,* which, in its current form (Table 81.2), includes 10 clinical characteristics capable of stratifying outpatients into two groups: "clinically unlikely" (score <2) or "clinically likely" (score ≥2).[173,174] The test was validated in numerous studies of outpatient populations with prevalences of DVT ranging from 5–39%. However, even in the outpatient settings in which the rule was tested, a low score alone is not capable of safely excluding DVT in patients in whom it is clinically suspected.[175] This is especially the case for men, patients outside primary care settings, those with previous DVT, and cancer patients, in whom the lowest possible score (−2) was still associated with a 5% probability of DVT.[175] For this reason, clinical prediction rules for patients suspected of having DVT are best combined with other objective data.

Table 81.2 Wells Clinical Model for Predicting the Pretest Probability of Deep Venous Thrombosis

Clinical Characteristic	Score
Active cancer (patient receiving treatment for cancer within the previous 6 mo or currently receiving palliative treatment)	1
Paralysis, paresis, or recent plaster immobilization of the lower extremities	1
Recently bedridden for 3 days or more, or major surgery within the previous 12 wk requiring general or regional anesthesia	1
Localized tenderness along the distribution of the deep venous system	1
Entire leg swollen	1
Calf swelling at least 3 cm larger than that on the asymptomatic side (measured 10 cm below the tibial tuberosity)	1
Pitting edema confined to the symptomatic leg	1
Collateral superficial veins (nonvaricose)	1
Previously documented deep venous thrombosis	1
Alternate diagnosis at least as likely as deep venous thrombosis	−2

Score	Clinical Assessment Probability
<2 points	Unlikely
≥2 points	Likely, cannot be ruled out

From Wells PS, Anderson DR, Rodger M, et al. Evaluation of D-dimer in the diagnosis of suspected deep vein thrombosis. *N Engl J Med.* 2003;349:1227–1235.

D-DIMER ASSAYS

Of all the available blood tests for VTE, the D-dimer assay has been subjected to the most rigorous clinical evaluation and has performed the best.[176–178] However, to appreciate the practical implications of the D-dimer assay, it is necessary to understand two inherent limitations. "D-dimer" is actually a heterogeneous mixture of fibrinogen derivatives, some (but not all) of which are the result of thrombosis and thrombolysis. The various commercially available tests use different antibodies that bind to different targets that may or may not be present on each D-dimer fragment. That means that the same sample may yield a variety of different D-dimer levels depending on the assays used.[176–178] Equally important is a critical distinction about mass/volume units used to report results. Because the antibodies detect only their specific targets, the "mass" is reported either as *fibrinogen equivalent units* ([FEU], the number of detections multiplied by the mass of an undigested fibrinogen molecule) or *D-dimer units* ([DDU], the number of detections multiplied by the presumed mass of a typical D-dimer fragment, which is half the mass of fibrinogen). To use D-dimer results diagnostically, the clinician must know which standards the local laboratory uses because, for example, 600 ng/mL FEU is the same as 300 ng/mL DDU. For both of these reasons, diagnostic cutoff values may be different among different laboratories.

D-dimer testing is highly sensitive but not specific; that is, elevated levels are present in nearly all patients with thromboembolism but also in a wide range of circumstances, including advancing age, pregnancy, trauma, infections, the postoperative period, inflammatory states, and malignancy. Therefore, the role of D-dimer testing is limited to one of exclusion of VTE. For the technical reasons just listed, D-dimer assay sensitivities can range from 80% to almost 100%.[176–178] The highly sensitive assays and cutoff levels are capable of excluding thromboembolism but are associated with such a high frequency of false-positive results that their clinical utility is limited. Less-sensitive assays and cutoff levels lack the ability to exclude thromboembolism in isolation but have been used successfully in combination with probability-derived clinical prediction rules to exclude

venous thrombosis in certain patients presenting with a low or intermediate clinical likelihood of the disease.[174,179]

A caveat of using D-dimer assays to rule out PE and DVT is that the normal levels of D-dimer in the blood increase as one ages. Multiple clinical studies have demonstrated a higher specificity in patients older than 50 years when age-adjusted D-dimer cutoff values (e.g., age × 10 μg/L FEU) were used rather than a single cutoff value (e.g., 500 μg/L FEU).[180] However, age-adjusted D-dimer cutoff values are subject to the same caveats discussed for single D-dimer cutoff values. For this reason, it is best for the clinician to refer to the local clinical laboratory (U.S. Food and Drug Administration–approved) table of age-adjusted cutoff values, which may differ among laboratories.[181]

COMBINATION OF PREDICTION RULES FOR DVT AND D-DIMER RESULTS

As expected with the Bayesian approach, the combination of independently ascertained clinical likelihood and objective blood test results is particularly useful. In most circumstances, for outpatients falling into the clinically unlikely category (Wells score <2), DVT is reliably excluded when the result of a sensitive D-dimer assay is below the cutoff values described in the previous section, thereby limiting the need for further workup.[174] The ability to exclude venous thrombosis in outpatients using a clinical prediction rule and negative results of a D-dimer assay has been confirmed in other studies.[175,182] The failure rate for the combination of a low Wells score and a low D-dimer is less than 2% in most outpatient populations, although somewhat higher failure rates have been observed for patients with a previous history of VTE and those with malignancy.[175] The fact that fewer than 10% of cancer patients suspected of having DVT fall into the "low score, low D-dimer" category further limits its usefulness in that population. Finally, it should be emphasized that clinical prediction rules constructed and validated in outpatients may not apply seamlessly to an inpatient population. Clinicians should retain the prerogative to perform further objective testing if, in their judgment, DVT remains a plausible risk.

CONTRAST VENOGRAPHY

Although it is rarely used in modern clinical settings, contrast venography (Fig. 81.1) is the gold standard by which many noninvasive techniques were validated.[183] Contrast venography has high sensitivity and specificity but has several shortcomings. It is not easy to interpret, especially in patients with a prior history of venous thrombosis. Venous cannulation may often be difficult and painful, especially in the presence of edema. Injection of contrast material has associated allergic and nephrotoxic risks. Last, it is expensive, and the procedure itself can unfortunately induce venous thrombosis.

Owing to these limitations, noninvasive studies capable of being performed on a sequential basis are much more common in clinical practice. Duplex ultrasonography is the most commonly used. *Magnetic resonance imaging* (MRI) and CT are capable of detecting thrombi, but their widespread use has been limited by cost, access and, in the case of CT, the need for contrast administration.

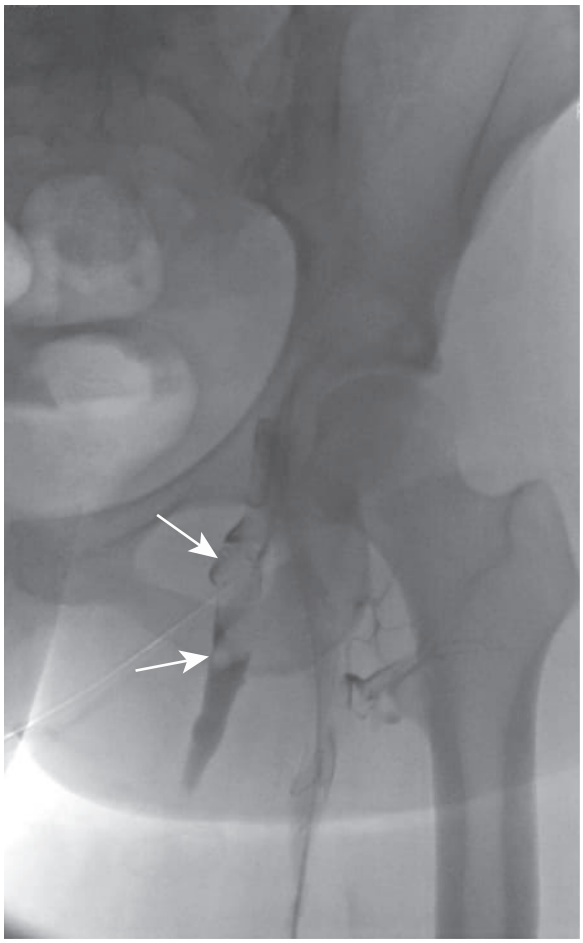

Figure 81.1 Contrast venography of deep venous thrombosis. Contrast venography performed during inferior vena cava filter placement in a patient with acute pulmonary embolism shows filling defects within the proximal femoral artery (*arrows*) representing deep venous thrombosis.

DUPLEX ULTRASONOGRAPHY

Duplex ultrasonography (i.e., the combination of Doppler venous flow detection and real-time B-mode imaging) has assumed a central role in the noninvasive diagnosis of symptomatic lower extremity DVT.[184] A number of criteria are used to diagnose venous thrombosis, the most reliable of which is the noncompressibility of a venous segment (Fig. 81.2 and Video 23.21). Secondary, less reliable criteria include the presence of echogenic material within the venous lumen (eFig. 81.1), venous distention, loss of phasic change with breathing, lack of response at the *common femoral vein* (CFV) to the Valsalva maneuver, lack of augmentation of flow at the CFV with compression of the calf, and diminished or absent color flow with color Doppler sonography (eFig. 81.2). The lack of color flow around a detected DVT is sometimes used to signify an "occlusive DVT," but that distinction has not been shown to influence the potential for PE or other clinical complications of DVT. The two signs showing a lack of increase in flow, either with Valsalva or with calf compression, can mean obstruction of veins between the site of increased pressure and the measured vein. The absence of an echogenic luminal mass cannot be considered useful in excluding the diagnosis of venous thrombosis because acute thrombus may not demonstrate echogenicity (eFig. 81.3).

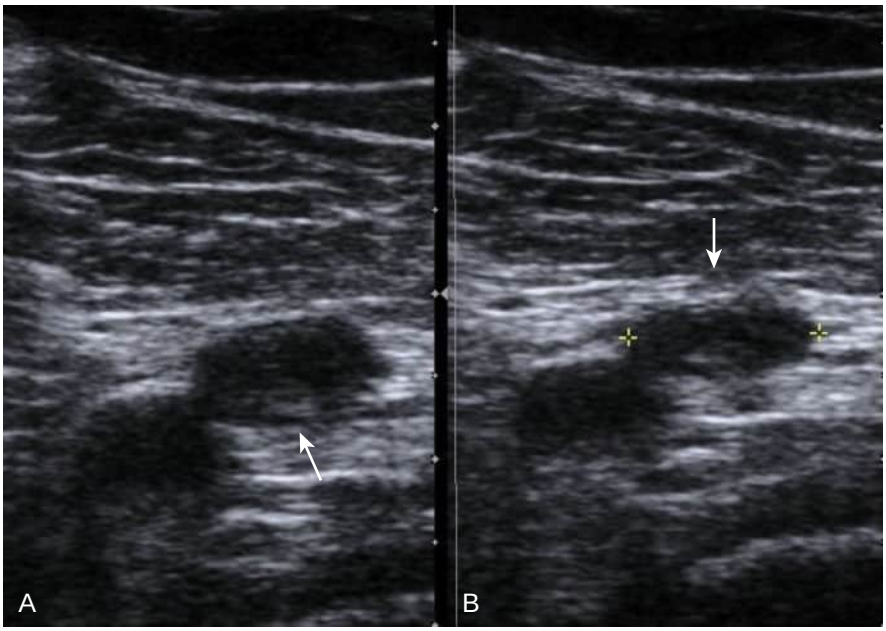

Figure 81.2 Compression ultrasonography for deep vein thrombosis. (A) Rest and (B) compression duplex ultrasonography demonstrates a noncompressible distal femoral vein containing an echogenic mass (*arrow*), consistent with venous thrombosis.

The sensitivity and specificity of duplex ultrasonography exceed 95% for symptomatic patients with proximal venous thrombosis, although asymptomatic and distal venous thrombi are harder to detect. Although simplified compression examinations limited to the symptomatic leg or to the common femoral and popliteal veins (rather than the entire lower extremity venous system) have been suggested, the time saved with such approaches is limited, and a number of isolated femoral vein or calf-limited thrombi may be overlooked.[185–187] Asymptomatic thrombi in the contralateral leg can be detected in approximately 5–10% of patients presenting with symptomatic acute venous thrombosis.[188] Although the detection of asymptomatic, contralateral thrombi has little impact on the immediate management of the patient, it may have long-term consequences when recurrence is suspected. A more prudent and comprehensive approach appears to be a complete examination extending from the inguinal ligament to the popliteal vein and examination of the contralateral extremity if thrombus is detected in the symptomatic leg.

Duplex ultrasonography is less accurate in the detection of symptomatic calf-limited thrombi (sensitivity ≈70%) and in asymptomatic proximal vein thrombi (sensitivity ≈50%), thereby limiting its utility as a screening study in high-risk populations.[189] When duplex ultrasonography is negative in patients with suspected venous thrombosis, a strategy of serial testing has proved to be effective in detecting proximal extension.[190]

MAGNETIC RESONANCE IMAGING

MRI techniques for detecting venous thrombosis include spin-echo magnetic resonance, gradient-recalled-echo magnetic resonance, and magnetic resonance venography. Preliminary reports suggest that MRI is at least as sensitive and specific as duplex ultrasonography.[191,192] A potential advantage of MRI is that the entire length of the venous system, including the pelvic veins, can be evaluated. Disadvantages associated with MRI include cost and limited access, as well as the expertise required to perform and interpret the studies properly.

COMPUTED TOMOGRAPHY

The role of CT as a stand-alone test for venous thrombosis is limited. The sensitivity and specificity of CT venography are comparable with those of ultrasonography but mandate contrast injection with its associated risks and radiation exposure. A diagnostic approach combining CT venography with CTPA, also called indirect CT venography because it does not require additional intravenous contrast, may have a role in patients undergoing evaluation for PE.[193,194] Potential advantages of CT venography, either direct or indirect, include the ability to visualize the pelvic veins (eFig. 81.4) and vena cava (eFig. 81.5). However, the additional scan adds radiation exposure to the pelvis, and nearly all coexisting DVTs discovered in clinical practice by CT venography could have been detected by duplex ultrasound.[195]

DIAGNOSIS OF PULMONARY EMBOLISM

As in the case of DVT diagnosis, clinical evidence is capable of raising the suspicion for PE, but it cannot be relied upon to confirm or exclude the diagnosis entirely. In the appropriate settings, however, clinical prediction rules in combination with noninvasive testing can identify a substantial number of patients in whom the risk is small enough that further diagnostic testing is unnecessary.

CLINICAL PREDICTION RULES

A number of standardized prediction rules for PE have been evaluated and published that range widely in their complexity. Simple, standardized prediction rules (Table 81.3) involve information that can be easily acquired even in an outpatient setting or the emergency department.[196,197]

Complicated prediction rules involve an increased number of clinical variables and require expert interpretation of radiography and *electrocardiography* (ECG) data.[198,199] Alternatively, the clinician may make a subjective ("gestalt") assessment of the probability of PE. So long as it is performed deliberately and independently of subsequent testing, the "gestalt" method appears to have comparable sensitivity to clinical prediction rules, when both are used in combination with sensitive D-dimer testing.[200]

The most commonly used clinical prediction score for acute PE is the *Wells score*, which assigns differential scores for risk factors for VTE (recent surgery or immobilization, previous VTE, malignancy), clinical signs and symptoms of PE and DVT (tachycardia, hemoptysis), and the absence of more likely alternative diagnoses (see Table 81.3).[201] A simplified Wells score, which uses 1 point for each item, appears to have similar accuracy.[202] As an alternative, the *revised Geneva score* uses only objective data (without a subjective evaluation for more likely diagnoses), but is considerably more complex.[203] The *Pulmonary Embolism Rule-Out Criteria* (PERC) is an 8-point clinical score applicable to emergency department patients in whom the diagnosis of

Table 81.3 Prediction Models for Pulmonary Embolism

	SCORING MODEL			
Clinical Variable	**Wells Clinical Model[201]**	**Revised Geneva[203]**	**PERC[205]**	**YEARS[206]**
Patient population in which clinical rule was validated	ED patients suspected of having PE	ED patients suspected of having PE	ED patients at low or very low risk of PE	Outpatients and inpatients suspected of having PE
Clinical signs/symptoms of deep venous thrombosis	3	4	1	1
PE is most likely or as likely as alternative diagnosis	3			1
Heart rate:				
75–94 beats/min		3		
≥95 beats/min		5		
≥100 beats/min	1.5		1	
Immobilization, surgery or trauma in the previous 4 weeks requiring hospitalization or fracture of the lower limb within 1 month (Geneva)	1.5	2	1	
Prior DVT or PE	1.5	3	1	
Hemoptysis	1	2	1	1
Malignancy (on treatment, treated in last 6 months, cured <1 yr or palliative)	1	2		
Sa_{O_2} < 95% on room air			1	
Unilateral lower limb pain		3		
Exogenous estrogen use			1	
Age:				
≥50 years			1	
≥65 years		1		
Clinical assessment probability:				
Low probability	<2 points	0–3 total	0 points*	0 points†
Intermediate probability	2–6 points	4–10 total		
High probability	>6 points	≥11 total		
DICHOTOMOUS WELLS SCORE WITH D-DIMER[446]				
Pulmonary embolism "unlikely"		≤4 points	D-dimer < 500 ng/mL: PE excluded; D-dimer > 500 ng/mL, consider CTPA	
Pulmonary embolism "likely"		>4 points	PE not excluded, consider additional testing with CTPA	
AGE-ADJUSTED D-DIMER CUTOFF FOR VTE[212]:				
Formula for use in patients ≥50 years of age in whom clinical suspicion for PE is low or intermediate				
Units	**Age-Adjusted D-dimer**		**Interpretation/Recommendation**	
FEU (fibrinogen equivalent units)‡	Age × 10 μg/L		Above age-adjusted cutoff: VTE *likely*, consider confirmatory testing	
DDU (D-dimer units) ‡	Age × 5 μg/L		Below age-adjusted cutoff: VTE *unlikely*, consider alternative diagnosis	

*If no criteria are positive and the clinician's pretest probability of PE <15%, PERC criteria is satisfied, and there is <2% chance of PE.
†In patients with no YEARS items and D-dimer < 1000 ng/mL, PE is excluded. In patients with one or more YEARS items, PE is excluded if D-dimer is <500 ng/mL. If PE is not excluded, CTPA is recommended.
‡Must check laboratory closely to ensure correct use of units.
CTPA, computed tomography pulmonary angiography; DVT, deep venous thrombosis; ED, emergency department; PE, pulmonary embolism; PERC, Pulmonary Embolism Rule out Criteria; Sa_{O_2}, arterial saturation of oxygen; VTE, venous thromboembolism.

PE has already been judged as unlikely.[204,205] A modification of the Wells clinical decision rule, called the *YEARS algorithm*, combined an evaluation of three characteristics (clinical signs of DVT, hemoptysis, and whether PE is the most likely diagnosis) with a differential analysis of D-dimer concentrations. In patients with none of the characteristics, D-dimer of less than 1000 ng/mL safely excluded PE; in those with any (or all) of the characteristics, D-dimer less than 500 ng/mL was necessary to exclude PE.[206] Although not a randomized controlled trial, this study did demonstrate that this algorithm was safe and resulted in an absolute decrease of 14% in the number of CTPA examinations across all ages and subgroups.

Although such probability assessments, whether based on scores or overall clinical impression, are incapable of confirming or excluding the presence of PE entirely, they are capable of stratifying patients into categories of likelihood.[196,207] By combining low clinical probability with negative results of a noninvasive diagnostic technique, safe exclusion of embolism can be increased well beyond that achieved by the use of either method alone.[196,207] Clinically, the appropriate application of clinical prediction rules and D-dimer testing can substantially limit the number of patients who require thoracic imaging.[208–210]

D-DIMER TESTING

The utility of D-dimer testing in PE diagnostic pathways is limited by the same shortfalls as those encountered in venous thrombosis pathways: low specificity, which makes it most useful as an exclusionary technique in outpatients, and lack of standardization. However, studies have demonstrated that a normal D-dimer result can safely exclude embolism in patients with a low clinical probability of disease.[196,211,212] Although preliminary data suggest that a highly sensitive assay is capable of excluding embolism at all levels of clinical probability, these results require confirmation.[212]

The sensitivity of D-dimer is similar across age groups, but its specificity decreases markedly with age, which should be considered when interpreting D-dimer values.[213] A retrospective analysis of three large cohorts of patients derived the age-adjusted D-dimer cutoff value based on received operating characteristic curves and found that the clinical usefulness of this age-adjusted value in helping rule out PE, in conjunction with clinical prediction rules, was significantly improved for older patients.[214] When combined with an age-adjusted D-dimer cutoff, a simplified Wells clinical prediction rule worked as well as the original rule and provided a more simple two-tier model of risk (PE likely or PE unlikely).[202] This was prospectively validated by Righini[215] in ADJUST-PE (2014), a multicenter, multinational study that found use of an age-adjusted D-dimer cutoff was associated with a larger number of patients in whom PE could be considered ruled out. A failure rate of age-adjusted D-dimer was found to be 0.3% in this study in patients with low/intermediate or clinically unlikely risk assessment.

STANDARD LABORATORY EVALUATION

Routine laboratory studies cannot make the diagnosis of PE. Although none have the discriminatory power to confirm the diagnosis of embolism, they do provide valuable adjunctive information and support for therapeutic interventions and may confirm the presence of an alternative diagnosis.

The majority of patients with PE have abnormal chest radiographs.[216] However, these abnormalities are usually subtle, nonspecific, and therefore nondiagnostic (Fig. 81.3). In the PIOPED study,[160] the most common radiographic abnormalities were atelectasis and pulmonary opacities. There is some confusion about the diagnostic configuration of radiographic abnormalities due to embolism. Although usually abutting a pleural surface, the opacities can be of any shape, not necessarily wedge shaped. Although pleural effusions are seen in almost half of the patients, the majority of effusions are small and involve only blunting of the costophrenic angle.[158] Findings once considered specific for embolism, such as the *Westermark sign* (focal areas of avascularity, eFig. 81.6), the *Hampton hump* (pleural-based, wedge-shaped opacity, eFig. 81.7), and the *Fleischner sign* (prominence of the central pulmonary artery, eFig. 81.8), have not proved to have discriminatory value. In a patient with hypoxemia or pulmonary complaints, a normal chest radiograph may be quite useful in raising the index of suspicion of embolism and in excluding confounding diagnostic options. The major roles of chest radiography in suspected PE therefore are to exclude competing diagnoses and, if ventilation-perfusion (V/Q) scanning is anticipated, to evaluate the pulmonary parenchyma. Because pleural effusions associated with PE tend to be small, they are generally not amenable to thoracentesis. In the few patients in whom thoracentesis was performed, the effusions were found to be exudative with normal glucose levels and neutrophilic predominance.[217]

Likewise, ECG findings in PE, although frequent, are diverse and nonspecific.[218] The most common abnormalities include nonspecific tachycardia, T-wave inversions in the inferior leads, and abnormalities of the ST segment, although about one-fourth of patients have no ECG changes.[219] With more extensive occlusion, the ECG may reveal the more classic findings of right heart strain, including an $S_1Q_3T_3$ pattern, a pseudoinfarction pattern (Qr in V_1), a complete or incomplete right bundle-branch block, or right-axis deviation.[218,220] T-wave inversions on ECG are common among patients who require hospitalization for acute PE, and S-T segment deviation is common among those with dyspnea, hypotension, cardiogenic shock, and death (see "Risk Stratification" section later).[221] Rhythm disturbances other than sinus tachycardia are uncommon and usually confined to patients with underlying cardiac disease.[218]

Arterial blood gas analysis is helpful, although not definitive.[222] Arterial hypoxemia may be present, and the more massive the obstruction, the more severe the hypoxemia is likely to be. However, many other conditions also cause hypoxemia, and embolism often does not cause hypoxemia or even a widening of the alveolar-arterial P_{O_2} difference. Hypocapnia usually is present with embolism; hypercapnia, conversely, is rare. Hypercapnia appears with embolism only in patients with marked antecedent ventilatory limitation or when such limitation has been imposed because the patient is on controlled mechanical ventilation.

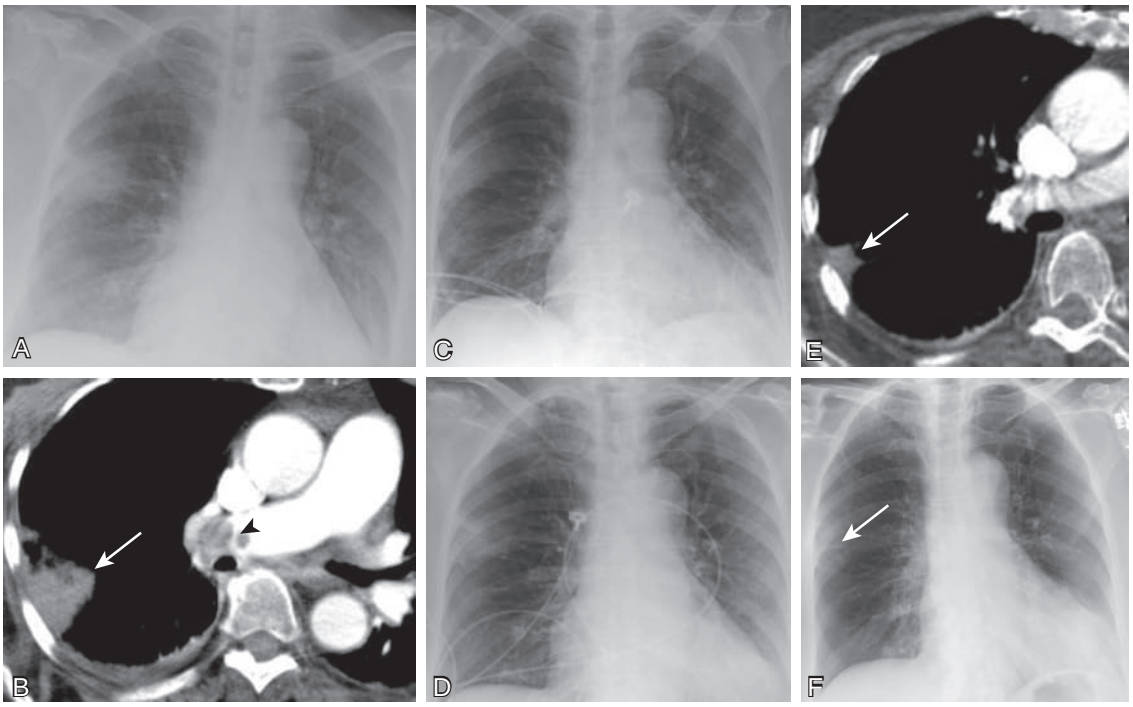

Figure 81.3 Chest radiographic findings in acute pulmonary embolism. (A) Frontal chest radiography at presentation shows a peripheral right upper lobe rounded opacity suggestive of pneumonia. (B) Computed tomography pulmonary angiography shows a right pulmonary arterial filling defect (*arrowhead*) consistent with acute pulmonary embolism. A right upper lobe subpleural wedge-shaped focus of consolidation (*arrow*) is consistent with infarction. (C) Frontal chest radiography obtained several days after presentation shows a more clearly wedge-shaped opacity in the right upper lobe. (D) Frontal chest radiography obtained 2 weeks after presentation shows the right upper lobe opacity is beginning to resolve. (E) Computed tomography pulmonary angiography about 2 weeks after presentation shows the right upper lobe infarct (*arrow*) has decreased in size. (F) Frontal chest radiography performed 5 weeks after presentation shows only linear opacity in the region of infarction (*arrow*), probably reflecting developing scar.

VENTILATION-PERFUSION SCANNING

V/Q lung scanning is typically performed with planar scintigraphic (two-dimensional) images that represent the number and size of lung perfusion defects and the absence or presence of corresponding defects in lung ventilation. The images are compared to differentiate primary vascular obstruction (mismatched defects) from primary parenchymal disorders that result in compensatory pulmonary vasoconstriction (matched defects). A related interpretation strategy relies on the shape and size of the perfusion defects compared to radiographically determined parenchymal lung disease.[223] PE can be diagnosed with either strategy, obviating the need for further studies in many cases.[224]

Despite its limitations, V/Q lung scanning remains a valuable step in the diagnosis of PE if it is interpreted appropriately.[160,225] First, a negative V/Q study (without perfusion defects) excludes the diagnosis of PE with the same degree of certainty as a negative pulmonary angiogram (Fig. 81.4) and has a similar negative predictive value as a negative pulmonary angiogram and negative high-quality CTPA.[226] This conclusion is illustrated by the results of two large prospective clinical trials comparing perfusion scanning to pulmonary angiography, the PIOPED study[160] (performed in the United States), and the *Prospective Investigative Study of Acute Pulmonary Embolism Diagnosis* (PISA-PED) trial[227] (performed in Europe). In both trials, normal pulmonary perfusion scanning was a highly sensitive method for excluding the presence of PE. The value of a normal perfusion scan was not diminished even in a subset of patients who had a high pretest probability for PE[160] or who were critically ill.[228] This was re-demonstrated in a large retrospective study in which patients with normal lung perfusion scans with high clinical pretest probability underwent CTPA confirming the absence of pulmonary emboli, suggesting the negative predictive value of a normal lung perfusion scan approaches 100%.[229] The significance of a normal perfusion scan, as reported by the PIOPED and PISA-PED trials, is consistent with all published longitudinal studies.[230–232] A meta-analysis of diagnostic studies for

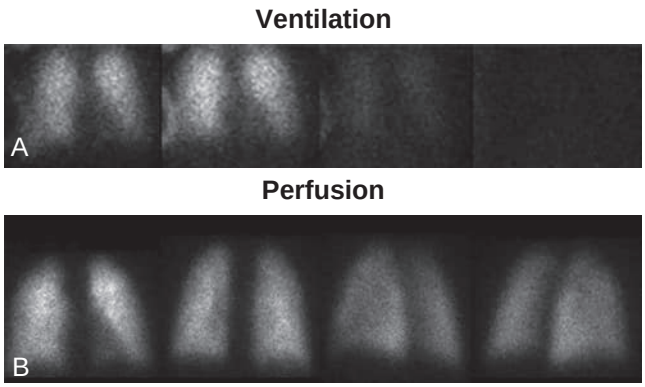

Figure 81.4 Normal ventilation-perfusion scintigraphy. (A) Posterior ventilation images using Tc-99m DTPA shows homogenous tracer distribution and rapid washout. (B) Perfusion imaging in the posterior (*left*), anterior (*middle left*), and oblique (*middle* and *far right*) projections using Tc-99m MAA shows homogenous tracer distribution. No ventilation-perfusion mismatches are present.

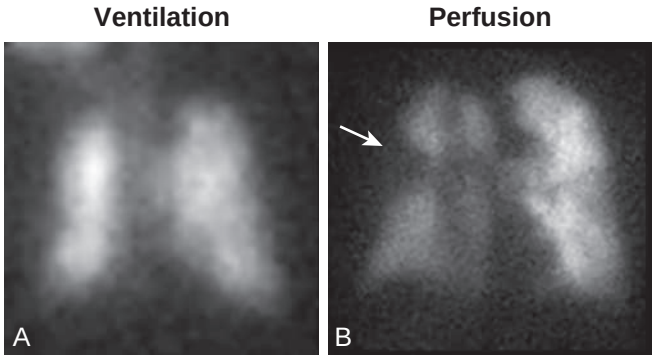

Figure 81.5 High-probability ventilation-perfusion scintigraphy. (A) Anterior ventilation study shows homogeneous tracer distribution. (B) Anterior perfusion study shows several perfusion defects, some clearly peripheral and wedged shaped (*arrow*), in areas of normal ventilation, representing ventilation and perfusion mismatching.

PE calculated the incidence of PE after a normal perfusion scan to be 0.3%.[233] A subsequent case series of consecutive patients followed clinically after objective testing for PE disclosed no pulmonary emboli in 188 patients who had normal perfusion scans.[234]

Conversely, a high-probability V/Q scan (one characterized by multiple, segmental-sized perfusion defects without matching ventilation defects) is associated with embolism in approximately 87% of patients; when coupled with a high clinical probability of embolism, the positive predictive value increased to 96% (Fig. 81.5).[160]

The utility of V/Q scanning is, unfortunately, limited by the fact that the overwhelming majority of patients with suspected embolism do not have scan findings that fall into a high-probability or normal category, the only categories that can be considered definitive.[160] In addition, a clinically significant percentage of patients with scan findings interpreted as "intermediate probability" (33%) or as "low probability" (16%) were subsequently demonstrated to have angiographic evidence of embolism.[160] Because of the latter finding, the term "low-probability scan" is misleading and potentially dangerous because of the frequency of PE in patients exhibiting this scan pattern.[235]

The diagnostic approach to PE in patients with underlying COPD is a particular challenge because the presentation of PE in this population may closely mimic an exacerbation of their underlying disease. Although the positive predictive value of a high-probability scan and the negative predictive value of a normal or near-normal scan in those patients are similar to that in the general population, the proportion of patients whose scans fall into a nondiagnostic category is much higher in patients with COPD than for those without COPD.[236] Given the limitations of V/Q scanning in this population, an approach using chest CTPA or *single-photon emission computed tomography* (SPECT)-V/Q as the initial objective diagnostic study would be appropriate (discussed later).

In critically ill patients in the intensive care unit with suspected PE, despite a large percentage having moderate to severely abnormal chest radiographs, PE may still be diagnosed by high-probability V/Q scan. Portable V/Q scan may be useful in this population with a high incidence of renal failure and hemodynamic instability making CTPA difficult to obtain.[237]

VENTILATION-PERFUSION SCANNING WITH SPECT

SPECT is a nuclear medicine technique that constructs three-dimensional tomographic perfusion and ventilation images from scintigraphic data, in a similar way that CT constructs tomographic images from transmitted x-rays.[238–240] The reported sensitivity of SPECT scanning for embolism has ranged from 62–100%, with a specificity ranging from 88–100%.[241] The tomographic images can identify perfusion defects in areas of the lung hard to visualize with planar V/Q scans because of interposing lung tissue (e.g., the medial basilar segments of the lower lobes).[242] As a result, SPECT-V/Q produces fewer nondiagnostic test results than planar V/Q, which removes one of the major limitations of planar V/Q testing. In fact, nondiagnostic results were reported in only 0.5–3% of SPECT-V/Q studies.[243–245]

SPECT-V/Q avoids the use of iodinated contrast required for CTPA,[246] which poses some risk of radiocontrast-induced nephropathy for older patients and for patients with preexisting renal insufficiency, especially when associated with diabetes mellitus.[247,248] In such patients, SPECT-V/Q may be preferred over CTPA. Another advantage of SPECT-VQ is that it delivers less radiation to breast tissue than CTPA typically delivers.[249] SPECT-V/Q has a high degree of agreement with CTPA in patients suspected of having acute PE.[244] Sensitivities and specificities for PE are typically in the 95–100% range.[244,250,251] Similar to studies with CTPA, the clinical outcomes of patients with negative SPECT-V/Q, in whom anticoagulation was not given, are excellent.[243,245,252] These findings suggest that SPECT-V/Q is highly sensitive for clinically important PE. SPECT-V/Q is less commonly used than other modalities for PE diagnosis, perhaps because the scanners are not present in every nuclear medicine department, and like all nuclear medicine studies, require specially trained personnel who are not always available.

COMPUTED TOMOGRAPHY PULMONARY ANGIOGRAPHY (See Also Chapter 20)

CTPA has substantially advanced the ability to diagnose PE. Unlike V/Q scanning, it provides the ability to visualize emboli directly and to detect parenchymal abnormalities that may support the diagnosis of embolism or provide an alternative basis for the patient's symptoms (Fig. 81.6; Video 81.1). The reported sensitivity of chest CT scanning for embolism has ranged from 57–100%, with a specificity ranging from 73–100%.[241] Factors responsible for this wide divergence relate to the proximal extent of vascular obstruction that can be detected and, in part, to advances in CT technology that allow higher resolution, dramatically faster scanning times, more peripheral visualization, and less motion artifact than that provided by earlier-generation scanners. Sensitivity and specificity of CT scanning for emboli involving the main and lobar pulmonary arteries exceeds 95%. Vascular involvement confined to segmental or subsegmental pulmonary vessels is associated with a lower sensitivity and specificity. In one series the sensitivity of CT scanning for subsegmental arteries reported by two readers ranged from 71–84% even after non-evaluable scans were excluded.[253] Isolated involvement of the subsegmental pulmonary arteries is not

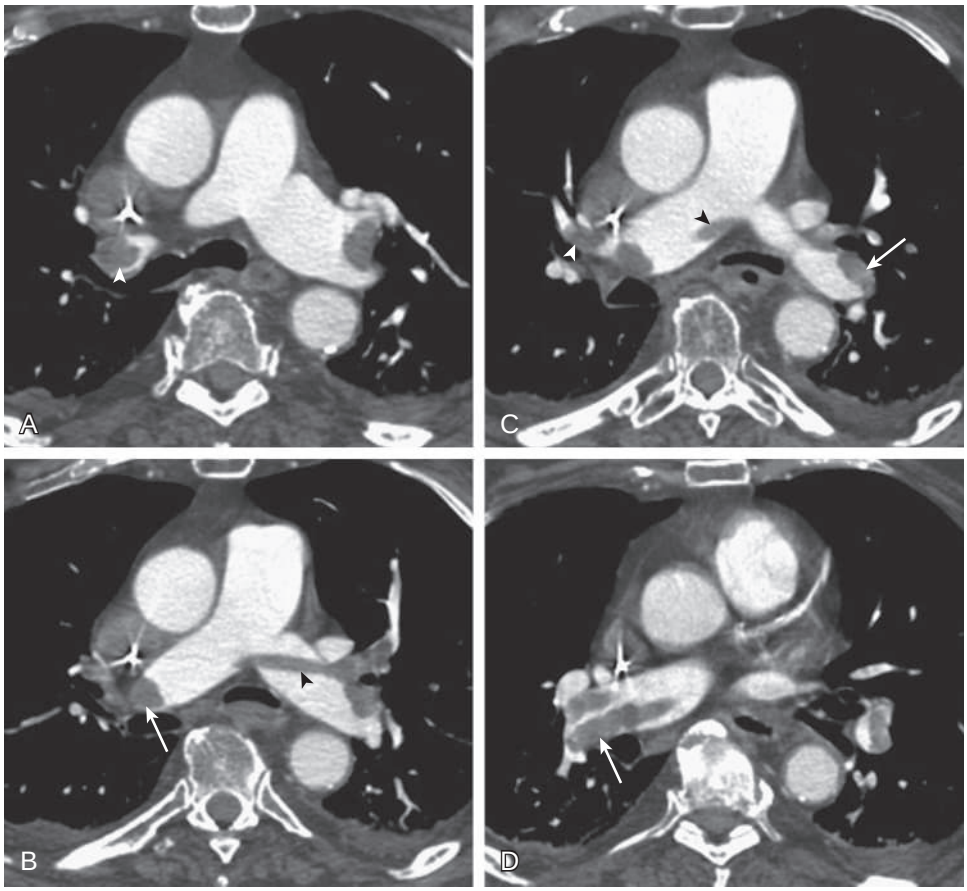

Figure 81.6 *Computed tomography pulmonary angiogram* (CTPA) showing pulmonary emboli. CTPA shows bilateral pulmonary emboli, including a "saddle" embolism (*black arrowheads,* B–C), right upper lobe emboli (*white arrowheads,* A–C), and interlobar emboli (*arrows,* B–D). See Video 81.1 for a clip from the full CT study.

unusual and, depending on the series, may be found in as few as 5% to as many as 30% of patients.[254–256] These findings suggest that filling defects consistent with embolism involving the main or lobar pulmonary arteries can be considered diagnostic of embolism. Depending on the characteristics of the image, defects involving the subsegmental arteries may be considered suggestive of embolism but should be supported by additional objective data.[257,258] The importance of treating patients with CTPA findings suggestive of exclusively subsegmental emboli has been questioned, especially in patients with good cardiopulmonary reserve and no coexisting DVT or persistent risk factors.[256,258] However, no large trials have yet demonstrated the safety of withholding anticoagulants in this patient population.[259,260]

Although CTPA has increased the number of diagnoses of acute PE,[261] it has inherent limitations. The technique requires infusion of intravascular iodinated contrast agents, which can cause the most common serious complications of testing. During CT scanning, the peripherally infused dye fills the lumen of the pulmonary arteries at the same time that the chest is imaged; CT scan images acquired outside that time frame are less accurate.[262] Emboli are detected as focal defects in pulmonary artery filling. When performed and interpreted expertly, CTPA scans are capable of identifying emboli in the segmental or larger pulmonary arteries, as does V/Q scanning.[263,264] However, certain areas, such as the hila, are prone to false positives. Reading emboli in these areas should be done with special care. Perhaps more important, as mentioned, CT scans have difficulty imaging emboli in subsegmental pulmonary arteries.[257,258] Smaller emboli may account for up to 20–30% of PEs[254,265] and represent the very cases in which V/Q scans are the most limited.[160]

The National Institutes of Health–funded PIOPED-2 study highlighted the strengths and limitations of CTPA.[194] Before enrolling the study population of 1090 patients, the investigators excluded 1350 patients because their abnormal creatinine levels reflected some degree of renal dysfunction, which would have increased the risk involved with the administration of contrast dye. An additional 272 patients were excluded because of a history of contrast dye allergy. During the performance of the trial, 6% of the scans were excluded because the images were of poor quality. Even after the inconclusive scans were disregarded, the sensitivity of the CTPA scans was only 83%, although it is difficult to be confident of the gold standard used to compare to CTPA. The PIOPED-2 investigators also excluded another 976 patients from the study because they had history of long-term anticoagulation therapy. This highlights another weakness of CTPA in that luminal filling defects remain long after an acute pulmonary embolic event, so the test cannot easily differentiate between chronic and acute VTE. This is clinically relevant because the rate of recurrence is about 7% during the 6 months after an acute PE and about 3% per year for the subsequent 5 years.[266]

Finally, CTPA can expose patients to clinically significant doses of radiation, and radiation doses may vary widely across countries and institutions.[241,267–271] Current clinical protocols deliver a radiation dose to the female breast ranging from 3 to 10 cGy per scan.[268,270,272] This dose is

especially concerning because most CTPA evaluations are negative, even when the criteria for scanning are rigorously followed.[194,225] In addition, because PE has a relatively high rate of recurrence, patients are commonly reimaged after their first episode. Younger women, who have a known elevated incidence of PE, are particularly at risk from radiation damage to breast and lungs[262] and represent a disproportionate number of patients who undergo CTPA.[273,274]

From a clinical (outcomes-based) perspective, CTPA and V/Q scanning have many similarities, and either can be used to exclude clinically significant PE in stable patients under many circumstances. Prospective outcome studies have demonstrated that withholding anticoagulant therapy in patients with a negative CTPA coupled with a negative lower extremity ultrasound study appears to be a safe strategy except in those patients who present with a high clinical likelihood of embolism.[275,276] Similarly, withholding anticoagulation from patients with non–high-probability findings on V/Q scan coupled with negative lower extremity studies is safe, except in those with inadequate cardiopulmonary reserve.[277,278] A randomized controlled trial comparing CTPA and V/Q for the management of suspected PE found the two studies to be comparable for excluding clinically significant PE.[225] Specifically, the study disclosed no difference in outcome among patients in whom anticoagulation was withheld based on the combination of a negative CTPA and negative leg studies compared with patients in whom anticoagulation was withheld based on the combination of a non–high-probability V/Q scan and negative leg studies or on a normal V/Q scan (without the need for leg studies). Although the value of either study alone (without leg studies) had been controversial,[279] prospective series using modern techniques have disclosed the safety of withholding anticoagulants in patients in whom either CTPA[280] or SPECT-V/Q[281] have ruled out PE. However, it should be emphasized that the outcome studies were done on relatively stable patients. Those with instability or poor cardiopulmonary reserve may require a higher degree of diagnostic certainty to rule out PE.[278]

ECHOCARDIOGRAPHY

Echocardiography may serve a valuable role in the diagnostic approach to PE when RV compromise is suspected. In addition, in some circumstances, the detection of unexplained RV volume (eFig. 81.9A) or pressure overload might suggest the possibility of embolism and lead to confirmatory testing (eFig. 81.9B). A distinct echocardiographic pattern involving akinesia of the mid–free RV wall with apical sparing has been described known as the McConnell sign (Video 81.2).[282,283] Direct visualization of RV chamber emboli is uncommon but possible (Video 81.3). Properly performed *transesophageal* echocardiography may disclose proximal emboli that involve the pulmonary trunk and the right and left main pulmonary arteries.[284] Transesophageal echocardiography has also proven valuable in the evaluation of competing diagnostic possibilities, such as RV infarction, endocarditis, pericardial tamponade, and aortic dissection, in patients with unexplained shock and evidence of elevated central venous pressure.

Echocardiography is not necessary in most cases of low-risk PE.[285] The characteristic findings of RV hypokinesis, dilation, or elevated estimated end-systolic pressure are nonspecific and found in only about half of patients with PE.[286,287] It may be diagnostically useful in patients with suspected massive PE who have no other plausible explanation for RV abnormalities and are unable to be diagnosed by other means. Its most common use, however, is to evaluate evidence of pulmonary hypertension and RV dysfunction in patients with confirmed diagnoses of PE who are hemodynamically unstable.[288] For example, *tricuspid annular plane systolic excursion* (TAPSE) reflects RV systolic function. Among high-risk acute PE patients, even those who are hemodynamically stable, the finding of a decreased TAPSE was associated with elevated systolic pulmonary artery pressures and higher mortality risk.[289] However, there is a great deal of inconsistency among clinicians regarding the use of echocardiography in PE, and higher use is not associated with decreases in PE-related mortality.[290]

CONCURRENT LOWER EXTREMITY VENOUS EVALUATION

Because the majority of PEs arise from the deep veins of the lower extremities, the detection of lower extremity proximal vein thrombosis in a patient suspected of embolism, although not confirming PE, is strongly suggestive of that diagnosis and has an equivalent therapeutic implication. Positive ultrasound findings without symptoms or signs referable to the lower extremities should be interpreted judiciously, especially in patients with low pretest probability of PE, because even a highly specific test can yield false-positive results in some circumstances.[291] Lower extremity ultrasonography has a very low yield in patients without leg symptoms or without risk factors strongly suggestive of thromboembolism.[165,292] Conversely, it is typically positive in only about 10–20% of patients with suspected embolism and in 50% of patients with proven embolism.[293] Therefore, a negative ultrasound finding cannot exclude the diagnosis of PE. Indirect CT venography (see eFig. 81.4) as an adjunct to chest CTPA appears to be capable of detecting femoropopliteal thrombosis with the same accuracy as duplex ultrasonography, while also detecting pelvic and abdominal thrombosis.[193,194] However, the combined CT technique is technically complicated because it must be performed within 2 minutes of the CTPA to use the same contrast injection.[194] It also significantly increases the amount of pelvic radiation exposure to the patient.[267,268,294]

PULMONARY ANGIOGRAPHY

Angiography is uncommonly used due to the utility and availability of the less invasive methods discussed, but it can be considered in patients in whom the diagnosis has not been confirmed or excluded using noninvasive techniques or when the results of diagnostic testing are at such odds with the clinical impression as to warrant the risk of the procedure. Pulmonary angiography can be performed quite safely if certain safeguards are observed and experienced personnel are involved. Because it involves right heart catheterization, it has the additional advantage of providing hemodynamic data.

Like contrast venography, however, pulmonary angiography has a number of limitations as a gold standard. It is invasive and not without risk, especially in patients with acute RV failure. However, experience has demonstrated that the perception of risk associated with angiography outweighs the actual risk.[295,296] Angiography must be performed in a special facility, which may require transport to another hospital. In some institutions, the logistical problems involved are modest; in others, they are substantial. The other limitation is interpretation. The interpretation of pulmonary angiograms is heavily influenced by three factors: the location of the thromboembolic obstruction, the quality of the images, and the experience of the interpreters. Only two angiographic findings are diagnostic of acute embolism: a filling defect and an abrupt cutoff of a vessel (Fig. 81.7). Technical adequacy of the angiogram is essential for accurate identification of both. Flow artifacts can falsely suggest a filling defect. It is essential that good vessel opacification be obtained and that the filling defects be identified as present on a sequence of images.

Although concern about risk should not deter pulmonary angiography, there are noteworthy limitations on its performance and value. Still, it is a rather odd commentary on medical thinking that few would advise against performance of a coronary angiogram in a patient with coronary thrombosis or ischemia because of risk; yet the question of risk often deters pulmonary angiography in a patient in whom embolism is suspected. Given that the case-fatality rate of undiagnosed and untreated embolism exceeds that of myocardial infarction, it is not clear why this disparity exists; it should not exist, given equal competence in the performance and interpretation of these two procedures.

DIAGNOSTIC APPROACH TO PULMONARY EMBOLISM: SUMMARY

A large array of diagnostic techniques is available for patients with suspected VTE. What the clinician at the bedside must understand and accept is that multiple approaches are possible and that a stepwise diagnostic strategy, rather than any single diagnostic technique, may be necessary to confirm or exclude the diagnosis (Fig. 81.8). The initiating point for the diagnostic pathway begins with clinical suspicion, and a subsequent rational approach is essential and potentially lifesaving. Withholding anticoagulation in a patient who has had an embolic event places that patient at risk for recurrent, potentially lethal events; instituting empirical anticoagulant therapy in a patient who has not had an embolic event will involve unnecessary hospitalization and therapy, places the patient at risk for hemorrhagic complications, and establishes a "preexisting" condition that may adversely affect future health care. Finally, the clinician must understand that the use of a clinical prediction rule derived from an outpatient population might have a very different predictive value when applied to a less healthy inpatient population.

MASSIVE PULMONARY EMBOLISM

Massive PE accounts for less than 5% of all diagnosed cases of PE.[5,297] The more than a 15-fold increase in mortality of massive PE in comparison to less severe PE justifies a separate consideration of the diagnostic and therapeutic approach to this problem.[122,298] The definition of massive PE should be based on hemodynamic instability rather than purely anatomic size of the embolus.[299–301] Although anatomically extensive emboli have a greater likelihood of being associated with hemodynamic compromise, they do not all lead to circulatory insufficiency, and the clot burden observed on CTPA is a poor predictor of mortality.[120] Irrespective of the extent of vascular obstruction, patients with PE who present with shock have a several-fold higher mortality rate than more stable PE, regardless of the type of intervention.[14]

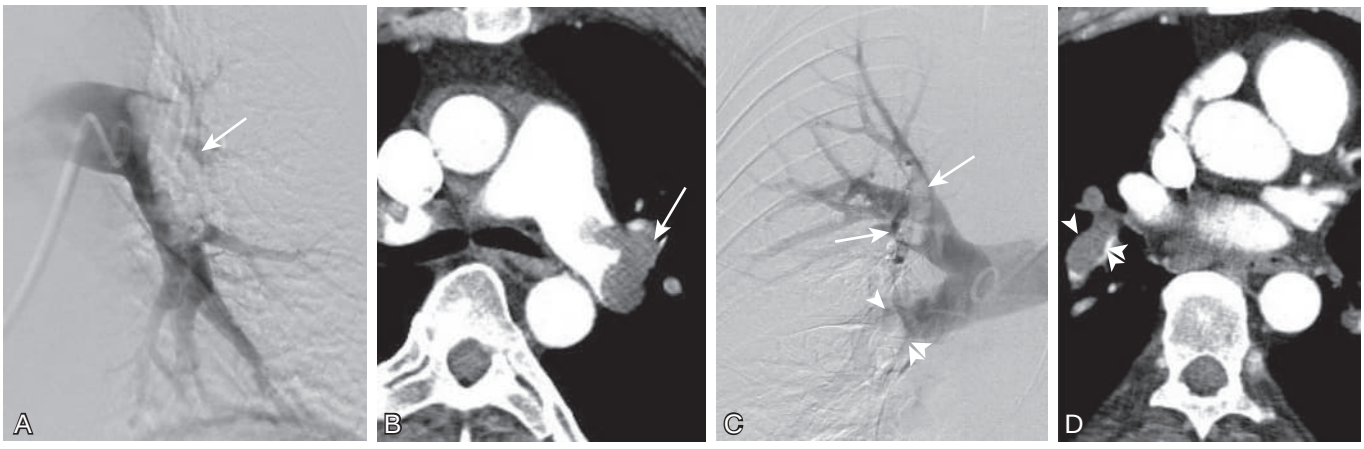

Figure 81.7 Catheter angiographic findings of pulmonary embolism with *computed tomography* (CT) correlation. (A) Catheter digital pulmonary angiography performed via an injection in the left pulmonary artery shows a large intraluminal filling defect within the left pulmonary artery (*arrow*) representing pulmonary embolism. (B) CT pulmonary angiography shows the corresponding left pulmonary arterial embolism (*arrow*). (C) Catheter digital pulmonary angiography performed via an injection in the right pulmonary artery shows several intraluminal filling defects (*arrows*) consistent with acute pulmonary embolism. The right lower lobe artery shows an abrupt vascular cutoff (*single arrowhead*), nearly occlusive, with a thin rim of contrast-opacified blood extending around the right lower lobe embolism along its medial border (*double arrowheads*). (D) CT pulmonary angiography shows the corresponding right lower lobe nearly occlusive pulmonary arterial embolism (*arrowhead*) with the thin stream of contrast extending along the medial border of the embolus (*double arrowheads*).

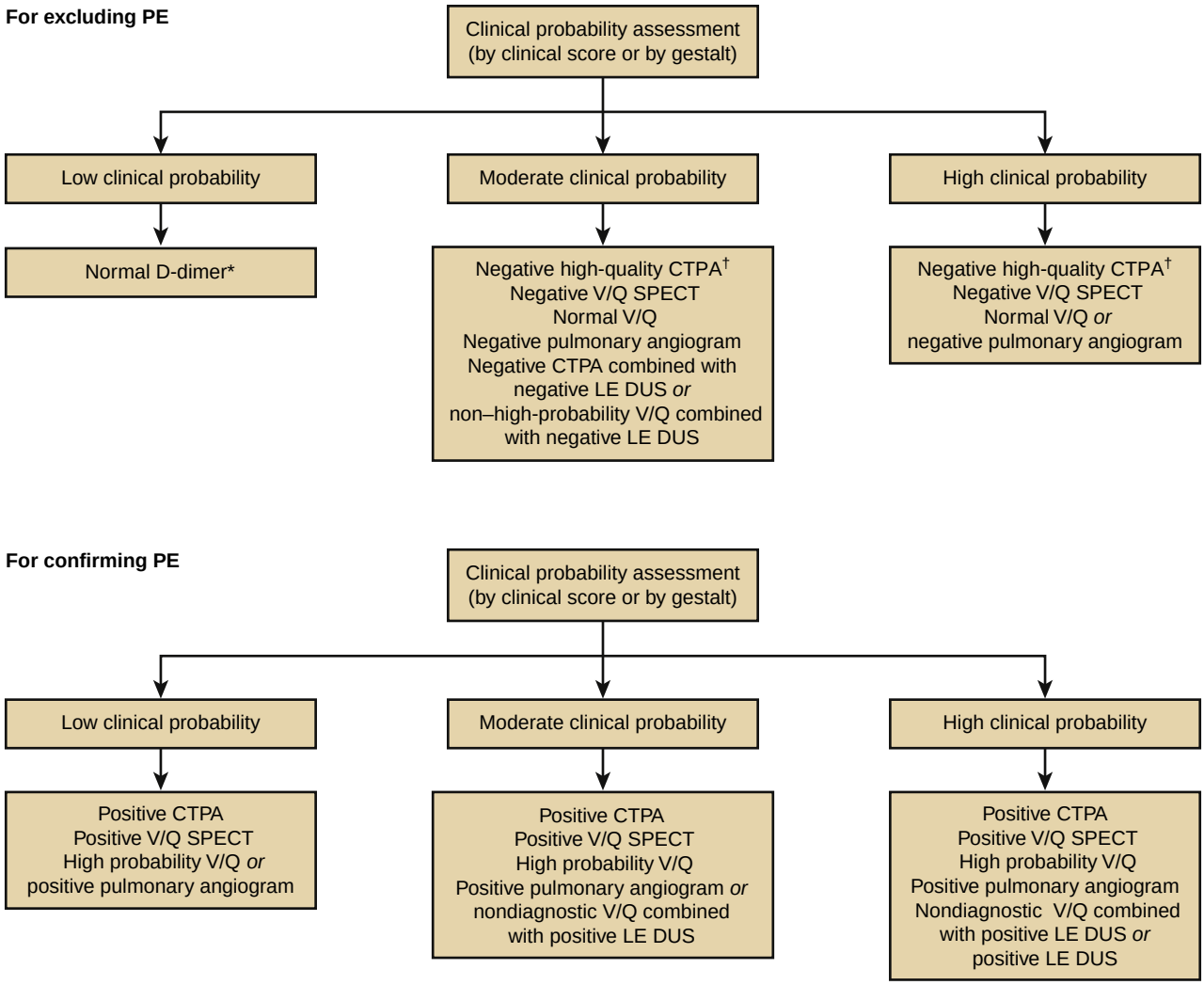

Figure 81.8 Diagnostic strategies capable of excluding or confirming the diagnosis of pulmonary embolism. Depending on the assessed clinical probability, the tests and their results can be used either to exclude or to confirm a diagnosis of pulmonary embolism. CTPA, computed tomographic pulmonary angiography; DUS, Doppler ultrasound; LE, lower extremity; V/Q, ventilation-perfusion scan; V/Q SPECT, ventilation-perfusion scan performed with a SPECT (single-photon emission computerized tomography) protocol. *The limits of normal for D-dimer are best appreciated when the patient's age is taken into account (see text).†Artifacts may interfere with the sensitivity of CTPA, especially in scanners with four or fewer detectors (see text).

RISK STRATIFICATION

The risk of mortality and significant morbidity from acute PE is substantially influenced by the patient's premorbid conditions and clinical presentation.[302] Clinical scoring systems can identify well patients who are at low risk for mortality and who may therefore require less monitoring. However, scoring systems alone typically are not capable of identifying patients at such high risk of PE-related mortality that specialized interventions (fibrinolytics, inferior vena cava filters, embolectomy, etc.) are warranted. The *Pulmonary Embolism Severity Index* (PESI), a risk stratification scoring system derived from patients' demographic characteristics (gender and age), incorporates coexisting illnesses (cancer, heart failure, and chronic lung disease) and physical findings related to cardiopulmonary status (heart rate, systolic blood pressure, respiratory rate, temperature, mental status, and oxygenation).[303,304] The PESI divides PE patients into five distinct classes of risk, and the mortality associated with each class has been shown to be remarkably consistent across several validation populations.[303,304] Mortality is typically 0–1.6% for class I, 2.0–3.5% for class II, 6.5–7.7% for class III, 10.4–12.2% for class IV, and 17.9–24.5% for class V.[303,304] A *simplified version of the PESI score* (sPESI, see Table 82.3), including only age, cancer, chronic cardiopulmonary disease, heart rate, systolic blood pressure, and oxyhemoglobin saturation levels, appears to perform just as well as the more complicated one.[305] An alternative scoring system called the *Bova score* is a 7-point system representing combinations of variables significantly associated with risk of PE-related complications within 30 days, including death from PE, hemodynamic collapse, and recurrent nonfatal PE. The variables include elevated cardiac troponin, tachycardia, RV dysfunction, and hypotension. Patients categorized into low, intermediate, and high-risk groups with this score had acute PE-related mortality of 1.7%, 5.0%, and 15.5%, respectively.[306,307] Regardless of the scoring system used, clinical judgment is paramount. A patient with a low PESI score who nonetheless appears severely ill should be monitored according to clinical judgment, rather than by the score itself.[304]

The ECG provides some information helpful for risk stratification. Increased risk of circulatory collapse and death is seen in patients with the $S_1Q_3T_3$ pattern of RV strain; right bundle-branch block; inverted T waves in the inferior, right sided, or precordial chest leads; S-T segment elevation in aVR; prolonged Q-T interval; Qr pattern in V_1; and tachycardia or atrial fibrillation.[308–313] Widespread T wave inversions predict increased mortality and complications from acute PE,[309] as does the combination of ischemic findings and clinical risk.[312]

Short-term mortality risk in PE is strongly related to the presence of systemic hypotension, a potentially fatal manifestation of RV dysfunction. Systemic hypotension represents the perfect storm of ischemia-related cardiac dysfunction, increased resistance against RV outflow, and hemodynamic instability. For this reason, transthoracic echocardiography[314] and biochemical markers, such as serum troponin[315] or serum brain natriuretic peptide[316] levels, have been investigated as a means of evaluating RV function in patients with embolism. Clinical studies have suggested that, whereas these techniques are reasonably capable of distinguishing patients with a good prognosis from those at risk for death and other adverse events, they lack the predictive power to warrant clinical decision making exclusively on the basis of a single test.[317–319] Moreover, it has not been conclusively established that the potential risks of a more aggressive therapeutic approach (thrombolytics, embolectomy, etc.) in all "high-risk" patients, the majority of whom have a satisfactory outcome when treated with anticoagulation therapy alone, justifies the potential benefit.[320]

OTHER PREDICTORS OF MORTALITY

Other predictors of mortality may reflect the presence of comorbid disease in addition to the effects of PE itself. For example, pleural effusion detected on CT scan at the time of diagnosis of acute PE is associated with increased mortality,[321,322] regardless of whether the effusions were ipsilateral or contralateral to the PE locations.[322] Likewise, hypoalbuminemia[323] and hyponatremia[324] in PE patients are associated with higher mortality, possibly because they reflect coexisting renal disease or malignancy. Renal dysfunction itself in the presence of PE is a poor prognostic factor[325,326] and is associated with a higher incidence of RV injury[327,328] and death.[270]

Bleeding events understandably increase the risk of death in acute PE patients.[270] High red blood cell distribution width, a measure of the variation of red blood cell size, is also associated with mortality,[329,330] although whether that observation reflects recent blood loss or other coexisting conditions is unknown. Other hematologic markers associated with high PE-related mortality, such as high platelet to lymphocyte and high neutrophil to lymphocyte ratios,[331,332] may reflect increased inflammation and thrombogenesis.[333,334]

PULMONARY EMBOLISM DURING PREGNANCY

VTE is a leading cause of maternal mortality.[335] However, PE is confirmed in only about 5% of CTPA scans in pregnant women,[336,337] whereas other findings to explain their symptoms are found in an additional 12% of scans.[337] Because the scans entail the potential risk of radiation exposure to the fetus,[294] a diagnostic approach that limits that exposure is warranted. Therefore, duplex ultrasonography is an appropriate initial diagnostic approach.

Unfortunately, the D-dimer assay and other assays of thrombotic activity are far less useful as screening tools for VTE in pregnant and postpartum women than in the general population. Plasma D-dimer levels in healthy women increase markedly and to variable degrees during pregnancy.[338] The normal increase in plasma D-dimer and other hemostatic markers precludes a specific cutoff value from distinguishing between those with and without VTE.[339–342] However, the combination of low clinical prediction scores and low D-dimer is likely to enable the identification of pregnant women at low enough risk for PE that further workup is not necessary. Specifically, the YEARS algorithm (see the "Clinical Prediction Rules" section), modified for pregnant (not postpartum) women by mandating lower extremity duplex ultrasound in those with leg symptoms, safely excluded PE across all trimesters of pregnancy.[343] The algorithm avoided the need for CTPA in 32% of patients in the third trimester and 65% of patients in the first trimester.[343]

If PE cannot be safely excluded, the diagnostic evaluation should proceed as previously described based on the clinical assessment probability and using CTPA, V/Q scanning, or SPECT-V/Q as the next diagnostic technique. CTPA has a comparable accuracy to planar V/Q for pregnancy-associated PE but may deliver a higher dose of maternal radiation, with wide ranges reported in the literature that may increase with body mass index (1–20 mSv for CTPA vs. 0.9–5.9 mSv for V/Q).[262,344–348] Because of the physiologic changes associated with pregnancy, rates of inconclusive studies for either CTPA or V/Q scanning may be relatively high.[349] Specifically with CTPA, inconclusive studies in pregnant women have been found to be related to motion artifact and low attenuation of the pulmonary artery.[350] Both CTPA and V/Q scanning result in risk of fetal radiation exposure below the safety threshold of 100 mm Gy associated with fetal radiation complications.[349] CTPA may result in less fetal radiation exposure than V/Q scanning[268,351]; however, the breast-absorbed radiation to proliferating breast tissue is significantly higher from CTPA and the long-term implications of this with respect to maternal breast cancer risk remain unknown.[344,346,348] Shielding can be used to reduce radiation to the breast tissue (see Fig. 129.3 and Chapter 129). In the future, MRI may be used to image the pelvic and lower extremity veins and pulmonary arteries; although it would avoid radiation exposure, its accuracy for diagnosis of VTE is not currently known.

RECURRENT PULMONARY EMBOLISM AND DEEP VENOUS THROMBOSIS

The risk of recurrent VTE depends on factors such as the nature of the initial thromboembolic event (spontaneous or associated with a defined clinical circumstance), the type of

initial event (DVT or PE),[352,353] the presence of an ongoing predisposition (either clinical or hereditary), the severity of the initial event,[354] plasma markers reflecting ongoing thrombosis,[355] and residual vascular scars at the thrombotic sites.[356]

Patients whose VTE was associated with clearly defined strong and reversible provoking factors that have subsequently resolved can likely be managed with a short (3- to 6-month) course of therapy with minimal risk of recurrence.[357,358] However, the clinician must evaluate both the strength and the reversibility of provoking factors when evaluating the risk of recurrence because they can vary markedly. For example, VTE provoked by surgery has a recurrence rate of 0.7% per patient-year, whereas VTE provoked by nonsurgical factors has a recurrence rate of 4.2% per patient-year. By comparison, unprovoked VTE has a recurrence rate of 7.4% per patient-year.[71]

Patients without clearly defined strong and reversible provoking factors for thromboembolism (unprovoked VTE) have about a 30–50% risk of recurrence during the subsequent 10 years.[359,360] Recurrence rates are higher in patients with a history of more than one episode of idiopathic DVT or PE[361]; the presence of certain irreversible acquired or hereditary risk factors that strongly predispose toward VTE (active cancer,[362] antiphospholipid antibody syndrome,[363] and hereditary deficiencies of antithrombin III, protein C, or protein S[364]); the presence of extensive residual venous thrombosis[96]; and the presence of extensive residual V/Q scan or CT scan defects.[148,365,366] Although the presence of the heterozygous factor V Leiden mutation or the prothrombin gene mutation individually does not appear to increase the absolute risk of recurrence substantially,[24] the presence of the homozygous factor V Leiden mutation or the heterozygous factor V Leiden mutation in combination with the prothrombin gene mutation does appear to be associated with an increased recurrence risk.[30]

Among unprovoked VTE without the specific risk factors listed in the previous paragraph, a reasonable estimate of recurrence risk may be estimated by various scoring systems (Table 81.4). The *DASH score* is based on the posttreatment D-dimer level, age, sex, and presence or absence of hormone therapy associated with the VTE.[367] The *HERDOO2 system* estimates women (only) at low risk for recurrence if they have no more than one of the following: postthrombotic signs (*h*yperpigmentation, *e*dema, or *r*edness), elevated posttreatment *D*-dimer levels, *o*besity, or *o*lder age.[368] The *Vienna scoring system* constructs a nomogram for risk based on male sex, proximal versus distal DVT, PE versus distal DVT, and elevated posttreatment D-dimer.[356]

A standard for repeating noninvasive testing of either the lungs or the deep veins of the lower extremities at the anticipated time of anticoagulant discontinuation does not exist. Although the cost implications would be substantial, such an approach would be beneficial in establishing a new baseline study that could be used for comparison in the event thromboembolic recurrence was suspected and in identifying patients with pulmonary vascular obstruction of sufficient extent to place them at risk for the development of chronic thromboembolic pulmonary hypertension.

Table 81.4 Prediction of VTE Recurrence in Patients With Prior Unprovoked VTE

Clinical Variable	Scoring System Annual Risk of Recurrence
DASH[367]	
D-dimer 1 mo after stopping anticoagulation	Normal = 0 Abnormal = 2
Age ≤ 50 years	1
Male sex	1
Hormonal therapy at time of initial VTE (female)	−2
Score Interpretation	
≤1	3.1%
2	6.3%
3	10.8%
4	19.9%
HERDOO2[368,*]	
Hyperpigmentation, edema or redness of either leg	1
D-dimer ≥ 250 μg/L while on anticoagulation	1
BMI ≥ 30 kg/m^2	1
Age ≥ 65 years	1
Score Interpretation	
0 or 1	1.6%
≥ 2	14.1%
VIENNA[356]	
Gender	Female = 0 Male = 60
Location of VTE	Distal = 0 Proximal = 70 PE = 90
D-dimer (μg/L) at time anticoagulation discontinued	Quantitative range that correlates with study nomogram
Score Interpretation	
Total points map to a 12-month cumulative recurrence rate nomogram (range, 2–15%) and a 60-month cumulative recurrence rate nomogram (range, 10–50%)	

*To be used in women only, after 5–7 months of anticoagulation.
BMI, body mass index; PE, pulmonary embolism; VTE, venous thromboembolism.

LONG-TERM CONSEQUENCES OF PULMONARY EMBOLISM

After a PE, embolic material in the pulmonary arteries either resolves by fibrinolysis or is remodeled into organized scars. The extent of remodeling and the severity of the resulting vascular obstruction varies among patients; in some, lung perfusion is rapidly restored,[80] although the resolution in the first week is typically incomplete. Embolic remodeling probably continues at a slower pace for the next 1 to 2 months.[247,248] Residual defects commonly persist beyond this period, suggesting that the emboli have been remodeled into permanent vascular scar.[55,74–79,249] Factors associated with poor resolution include large initial PE,[369] unprovoked PE,[370] abnormal fibrinogen subtypes,[369] and elevated fibrinogen levels.[370] Incomplete resolution after acute PE is an important clinical problem.[266,371] An array of chronic manifestations, with considerable overlap, has been described by various authors:

persistent acute pulmonary artery filling defects, residual pulmonary vascular obstruction, post-PE dyspnea, post-PE exercise limitation, post-PE syndrome, chronic thromboembolic disease, and *chronic thromboembolic pulmonary hypertension* (CTEPH) (see also Chapter 86).

Persistent pulmonary artery filling defects refer to intravascular filling defects observed on pulmonary artery contrast studies (CTPA or angiogram).[372–374] Although CTPA findings resolve rapidly in most patients,[145] persistent filling defects have been observed in about 15% of CTPA scans after acute PE and about 50% of scans performed after massive PE.[372,373] About half of those scans disclose central filling defects or complete occlusions similar in appearance to the original PE, another third disclose eccentric defects contiguous with the vessel wall at the site of acute PE, and the remainder disclose filling defects that contain channels of contrast material that suggest recanalization.[372] Acute proximal pulmonary artery PE is more likely to result in persistent pulmonary artery filling defects than distal PE.[372,375] Because of the potential for chronic filling defects to mimic recurrent acute PE, the latter is most confidently diagnosed in patients with prior PE if acute-appearing defects are disclosed in new previously uninvolved regions, such as the contralateral lung or in arteries separate or more proximal than the original PE.[376]

Residual pulmonary vascular obstruction refers to findings on V/Q scan (planar or SPECT) of persistent unmatched perfusion defects.[100,125,140–142,144,377–382] About one-third of acute PE patients will have residual pulmonary vascular occlusion in 10% or more of the lung regions (i.e., in at least two lung segments).[148] In follow-up after acute PE, residual pulmonary vascular obstruction (on V/Q) is about twice as common as persistent pulmonary artery filling defects (on CTPA).[372] SPECT may be more sensitive than planar V/Q for identifying chronic perfusion defects.[383,384]

Residual pulmonary vascular obstruction is associated with respiratory symptoms,[381] hypoxemia[100,140,377] gas exchange deficits,[100,385,386] exercise intolerance,[387] and other serious clinical consequences.[100,140,377,381,385–388] Residual pulmonary vascular obstruction is also associated with an increased risk of CTEPH.[148]

In a substantial proportion of patients, there is post-PE dyspnea and reduced quality of life,[389,390] although it cannot be assumed that such symptoms reflect incomplete resolution of the thromboemboli themselves.[391] Post-PE exercise limitation is a related term that typically implies abnormal results on an objective exercise test.[391,392] Post-PE syndrome is a term used to describe dyspnea or deteriorated quality of life after PE, combined with objective evidence of either cardiac or pulmonary dysfunction (e.g., on echocardiography[393] or cardiopulmonary exercise testing[393,394]). Of interest, a reasonable proportion of patients who fit the definition of post-PE syndrome do not have residual pulmonary vascular obstruction, so their symptoms may reflect comorbid diseases or exercise-limiting conditions, such as obesity or deconditioning.[391,392,395,396]

In many cases, however, post-PE dyspnea is associated with residual pulmonary vascular obstruction on V/Q scan[148] or persistent pulmonary artery filling defects on CTPA.[373] Residual pulmonary vascular obstruction is associated with exertional dyspnea and increased alveolar dead space ventilation and RV dysfunction.[148,397–399] Residual vascular obstruction increases alveolar dead space ventilation in CTEPH, which correlates with severity.[399] Residual vascular obstruction also increases pulmonary arterial resistance and impedes RV stroke volume reserve.[397,398] It may be prudent to evaluate post-PE dyspnea patients with cardiopulmonary exercise testing. V/Q scanning (SPECT or planar) may be used in those with cardiopulmonary dysfunction to search for residual pulmonary vascular occlusion.

CTEPH results from intravascular scar tissue that develops and obstructs the pulmonary arteries sufficiently to cause pulmonary hypertension.[149,400] It arises in a small percentage of "all-comers" after acute PE[388,401–408] but in about one-sixth of patients with residual pulmonary vascular occlusion.[148] The pulmonary hypertension from CTEPH causes significant morbidity and mortality, as described in Chapter 86. CTEPH is distinguished from acute PE on the basis of its chronic presentation, including evidence of pulmonary hypertension and radiographic findings (e.g., intravascular webs, pulmonary artery retraction or dilation, bronchial artery dilation, RV hypertrophy, and interventricular septum flattening[409]). *Chronic thromboembolic disease* is a more recent term used to describe patients with similar findings but in whom pulmonary hypertension is not evident on tests performed at rest, although exercise may induce elevated pulmonary artery pressures or other pathophysiologic changes.[410]

Other forms of embolism are described at ExpertConsult.com.

Key Points

- *Pulmonary embolism* (PE) continues to be a common yet underrecognized cause of morbidity and mortality.
- Most deaths from PE are due to a failure to prevent the disease in at-risk patients and to a failure to make the diagnosis.
- Deep venous thrombosis is best diagnosed by a consideration of clinical probability, D-dimer as a screening test, and then lower extremity Doppler ultrasound.
- Clinical suspicion for PE is the first and most critical step in the diagnosis. Clinical decision rules help determine which patients merit further workup.
- Because D-dimers are highly sensitive but not specific for thromboembolism, the role of D-dimer testing is mainly one of exclusion.
- Recurrence of venous thromboembolic disease is a function of many factors, primarily whether there is an ongoing predisposition to thrombosis.
- Massive PE causes hemodynamic compromise as result of right heart ischemia and failure, caused by increased demand for work, high intraventricular pressures and low systemic blood pressure leading to poor coronary perfusion.
- Long-term outcomes after PE include recurrence as well as a risk of chronic dyspnea.
- The optimal method to screen for and work up prolonged symptoms such as dyspnea after acute PE remains uncertain.

Key Readings

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Complete reference list available at ExpertConsult.com.



OTHER FORMS OF EMBOLISM

Because the lungs receive all of the blood flow returned from the venous system, the pulmonary vascular bed serves as a "sieve" for all particulates entering the venous blood and is the first vascular bed to be exposed to any toxic substance injected intravenously. As a result of its strategic position, the pulmonary vascular bed is therefore exposed to a wide variety of potentially obstructing and injurious agents.

SCHISTOSOMIASIS

Among such agents, the most common on a worldwide basis, although not within the United States, is schistosomiasis. This parasitic disorder may cause pulmonary hypertension by three mechanisms: anatomic obstruction by the organism itself, an intense inflammatory vasculitic response to the components of the organism, and the development of portopulmonary hypertension. In endemic areas, schistosomal disease is the most common cause of RV dysfunction. Limited data suggest that cardiopulmonary schistosomiasis is seen most often in *Schistosoma mansoni* infection. This form of RV dysfunction is always seen with concomitant schistosomal liver disease because the liver is always involved, usually quite extensively, before the lung. The premortem diagnosis of cardiopulmonary schistosomiasis depends on serology and the detection of schistosomal ova in stool or urine along with evidence of hepatic fibrosis and pulmonary hypertension. Treatment with praziquantel can eradicate schistosomal infections with minimal toxicity. However, cardiopulmonary manifestations are not likely to be reversible once chronic fibrosis develops (see Chapter 58).[411]

AIR EMBOLISM

An increasingly common form of nonthrombotic embolism in the United States is air embolism.[412] The increasing frequency of the problem reflects the wide variety of invasive surgical and medical procedures now available, the broad use of indwelling central venous catheters, the use of positive-pressure ventilation with high levels of positive end-expiratory pressure, and the frequency of thoracic and other forms of trauma.[413] The simple inadvertent transection or disconnection of a large-bore *intravenous* (IV) catheter (eFig. 81.10), particularly in the jugular or subclavian vein, can result in ingress of substantial quantities of air. Air bubbles enter the pulmonary vascular bed and, if the air bolus is large enough, can travel from the pulmonary arteries to the pulmonary veins through microvascular shunts and be distributed diffusely throughout the body.[414]

Physiologic consequences of pulmonary air embolism include an abrupt rise in pulmonary artery pressure. Increased permeability (noncardiogenic) pulmonary edema may develop, lung compliance falls, and hypoxemia ensues. The symptoms of air embolism are variable and nonspecific and may include alterations in sensorium, chest pain, dyspnea, or a sense of impending doom. These and other consequences appear to be due to two phenomena: actual lodging of the bubbles in capillary beds, which interferes with nutrient supply to the affected organs, and the formation of platelet-fibrin aggregates, creating diffuse microthrombi.[415] Thrombocytopenia may be seen as a consequence of this latter event. The most serious consequences result from cerebral or coronary artery air embolism, and the severity of the consequences depending upon the volume of air that gains access to the venous circulation.[412]

The best approaches to air embolism are prevention and early detection. Treatment consists of measures designed to restore blood flow and to promote reabsorption of the intravascular air. Measures designed to restore flow include patient positioning (Trendelenburg position with the left side down), removal of air through central venous catheters or direct needle aspiration, and closed-chest cardiac massage. Measures designed to increase absorption include the use of 100% oxygen and the institution of hyperbaric oxygen therapy as early as possible.[416–418] By using such aggressive measures, mortality from air embolism has been dramatically reduced.[419]

FAT EMBOLISM

Another reasonably frequent and dramatic form of nonthrombotic embolism is fat embolism. A rather characteristic syndrome follows entry of neutral fat into the vascular system creating mechanical emboli and focal ischemia, resulting in a triad of symptoms consisting of respiratory distress, petechiae, and altered mental status. There is a variable lag time of 12 to 72 hours in the onset of the syndrome after the inciting event.[420]

By far the most common inciting event is traumatic fracture of marrow-containing long bones; the incidence of fat embolism rises with the number of fractures. However, orthopedic procedures and trauma to other fat-laden tissues (e.g., fatty liver) occasionally are followed by the same syndrome.

The reasons for the variability in incidence of the syndrome after apparently comparable injuries are not clear. Perhaps variations in incidence and severity relate to the amount of fat released. The pathophysiologic consequences appear to derive from two events: (1) actual vascular obstruction by neutral particles of fat and (2) the injurious effects of free fatty acids released by the action of lipases on the neutral fat.[421] The latter effect is probably the more important, causing a diffuse vasculitis with leakage from cerebral, pulmonary, and other vascular beds.[422]

The diagnosis of fat embolism syndrome is a clinical one suggested by the onset of dyspnea, neurologic abnormalities, petechiae, and fever in the proper clinical context (see Fig. 127.2 and eFig. 127.2). Petechiae, typically distributed over the head, neck, anterior chest, and axillae, are present in only 20–50% of cases.[423] Therefore, their absence should not preclude consideration of the disease. No laboratory test is diagnostic of the syndrome.

Although a variety of treatments have been suggested (e.g., IV ethanol, albumin, dextran, heparin), none has proved effective. There is some evidence to suggest that corticosteroid therapy might prevent the onset of fat embolism syndrome after an inciting event, but controlled studies are sparse, and the topic remains controversial.[424] Supportive treatment, including mechanical ventilatory support, when necessary, is the primary approach and, with meticulous supportive care, survival among most cases of fat embolism is common.[425] However, severe fat embolism syndrome, manifested by widespread opacities on chest CT and acute respiratory distress syndrome, is often life-threatening.[426]

AMNIOTIC FLUID EMBOLISM (See Chapter 129)

Another special form of embolism is *amniotic fluid embolism* (AFE), a rare but unpredictable and potentially catastrophic complication of pregnancy with an incidence of approximately 1 in 40,000 pregnancies and accounting for 5–15% of all maternal deaths.[427] This disorder may arise during or after delivery when amniotic fluid gains access to uterine venous channels and, from there, to the pulmonary and general circulations. The delivery may be either spontaneous or by cesarean section; there are case reports of AFE after therapeutic abortion. Unexpectedly and suddenly, the patient may have severe respiratory distress, cyanosis, hypotension, and often cardiovascular collapse. Most cases develop during labor (see Fig. 129.5), but delayed onset of symptoms up to 48 hours after delivery has been reported.[428] Increased risk for AFE is associated with induction of labor, multiparity, advanced maternal age, ethnic minority status, cesarean delivery, placental abnormalities, eclampsia, polyhydramnios, cervical lacerations, uterine rupture, premature placental separation, fetal death, and meconium staining of amniotic fluid.[429,430]

Amniotic fluid contains particulate materials that may cause pulmonary vascular obstruction (see Fig. 129.4), but the major pathogenetic mechanism of the syndrome remains uncertain. Animal models suggest that physical obstruction of the pulmonary capillaries by amniotic fluid is not the main mechanism of AFE.[430] Pulmonary vasoconstriction and increased pulmonary vascular resistance appear to be the drivers of hemodynamic collapse during AFE, leading initially to RV collapse followed by left ventricular failure.[431] Amniotic fluid does have thromboplastic activity that leads to extensive fibrin deposition in the lung vasculature and, occasionally, in other organs. As a consequence of fibrin deposition, a severe consumptive coagulopathy develops, including marked hypofibrinogenemia and thrombocytopenia. After the acute event, there often is an enhanced fibrinolytic state consistent with disseminated intravascular coagulation.[432]

The diagnosis of AFE is based on a compatible clinical picture. Although various forms of therapy have been suggested (e.g., antifibrinolytic agents, such as aminocaproic acid, cryoprecipitate, factor VIIA, pulmonary vasodilators), the best approach is supportive.[430] Even in the setting of aggressive supportive measures, however, maternal mortality is in the range of 20–60%, with many survivors suffering from long-term neurologic disability.[427,433]

SEPTIC EMBOLISM

Septic embolism is another special disorder that, unfortunately, is also increasing in frequency owing to widespread injection drug use and the expanding use of indwelling IV catheters. Previously, septic embolism was almost exclusively a complication of septic pelvic thrombophlebitis secondary to both septic abortion and postpuerperal uterine infection. Although these conditions still lead to septic emboli, injection drug use is now by far the more common cause.[434] An increasingly common cause is iatrogenic: infections secondary to indwelling catheters inserted for a variety of diagnostic or therapeutic purposes.[435,436]

Microscopically, septic phlebitis consists of purulent material admixed with fibrin thrombus. Embolization can result in obstruction of small pulmonary vessels, but the major consequence is pulmonary infection. Characteristically, imaging shows peripherally distributed pulmonary nodular opacities that undergo cavitation (eFig. 81.11). An increasing number of such opacities develop over periods of hours to a few days. Symptoms and signs include a septic temperature course, dyspnea, cough, pleuritic chest pain, and hemoptysis. Initial treatment consists of appropriate antimicrobial drugs. If an indwelling catheter is suspected to be the source of the infection, it should be removed. If there is not a prompt response to this regimen, surgical isolation of the septic vein, if present, should be considered. The role of systemic anticoagulation remains uncertain. Endocarditis may complicate septic phlebitis, or mimic it, particularly in IV drug users.

OTHER EMBOLI

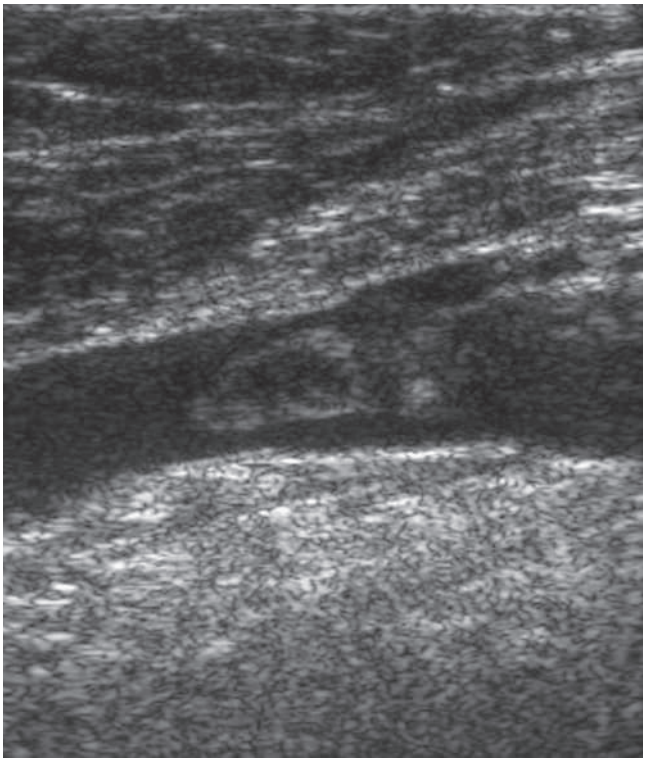
A wide variety of other materials may lodge in the lung, which in effect acts as a sieve for the entire cardiac output.[437] Cancer cells, of course, often find their way into and adhere to the pulmonary vessels; on occasion, tumor emboli (admixtures of thrombus with cells) can lodge in the pulmonary circulation and mimic bland embolization (see eFigs. 79.2 and 79.3). Trophoblastic tissue can escape the uterus and lodge in the pulmonary circulation during evacuation of a molar pregnancy or during hysterectomy for an invasive mole. After head trauma, brain tissue has been found in the lungs; the same is true of liver cells after abdominal trauma and of bone marrow after cardiopulmonary resuscitation. In rare instances, iatrogenic emboli can arise from injection therapy (e.g., treatment of gastric varices) or even procedures such as vertebroplasty (eFigs. 81.12 and 81.13).

In sickle cell disease, pulmonary artery thrombi, either from thromboembolism or from in situ thrombosis, are found in 10–20% of patients with acute chest syndrome.[438] During the acute chest syndrome, pulmonary artery thrombosis may present without clinical findings suggestive of PE, so clinicians would be wise to have a high index of suspicion for this complication. Patients with sickle cell disease may also develop pulmonary artery hypertension.[439] (See Chapter 127 for information about sickle cell disease.)

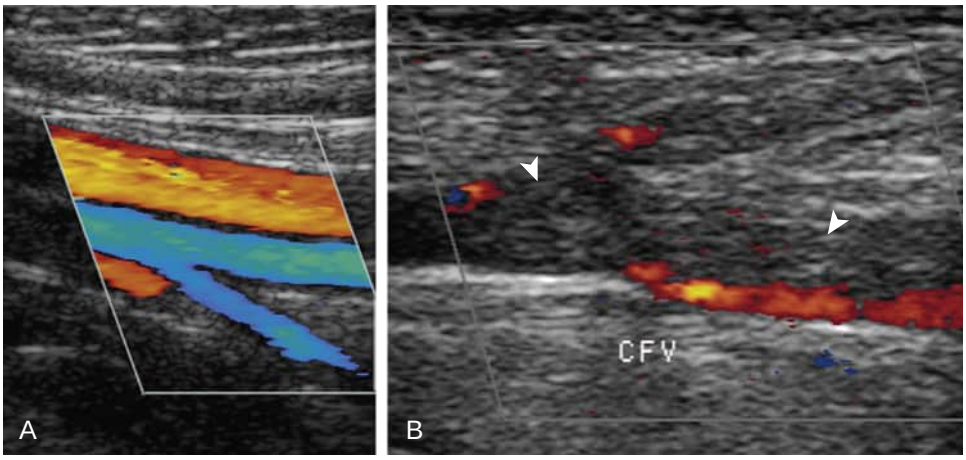
Finally, in this era of injection drug use, noninfectious vasculitic-thrombotic complications are being seen with increasing frequency. Particulate and irritant drug carriers (e.g., talc [see eFig. 99.17], and cellulose [see eFig. 99.16]), and occasionally, the drugs themselves, may cause vascular inflammation and secondary thrombosis.[440] More common, uptake of the talc into the pulmonary interstitium results in fibrosis and advanced emphysema.[441–443]

Mercury, both orally ingested and embolized through the absorption via the gastrointestinal tract and intravenously injected, may embolize to the lungs. Mercury can be used as a homeopathic remedy for pain,[444] injected in the setting of deliberate suicide attempt, for improving athletic or sexual performance, or in the setting of concomitant IV drug abuse. Mercury emboli may have a dramatic radiographic appearance but rarely cause significant respiratory symptoms or decrease in pulmonary function by spirometry.[445]

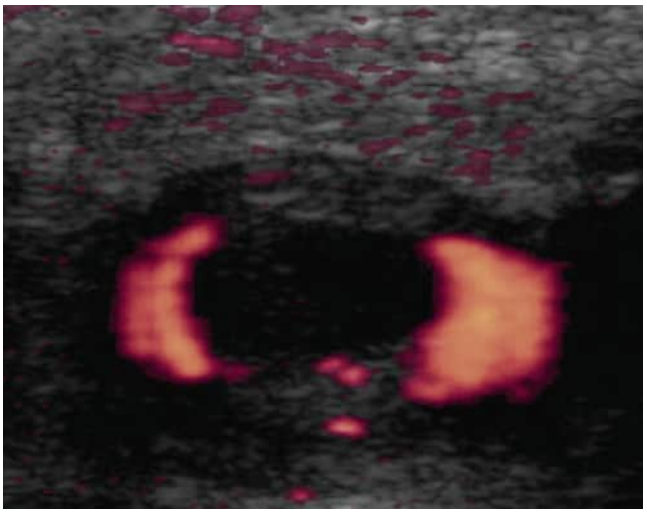
eFIGURE IMAGE GALLERY



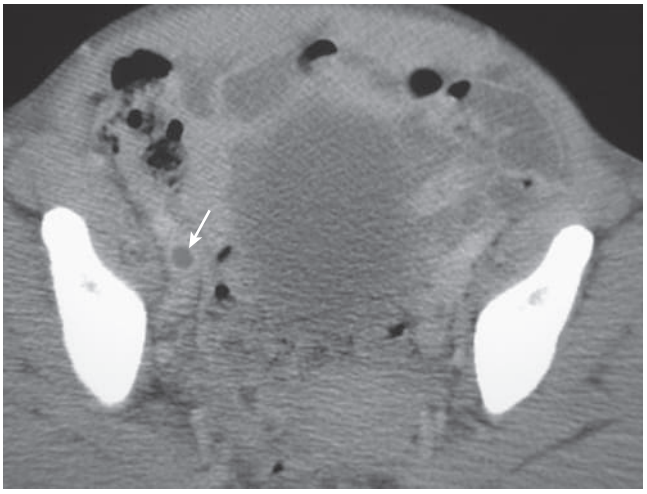
eFigure 81.1 Ultrasound image of deep vein thrombosis. Longitudinal ultrasound image shows mixed echogenicity material within the popliteal vein, consistent with acute deep venous thrombosis. (Courtesy Michael B. Gotway, MD.)



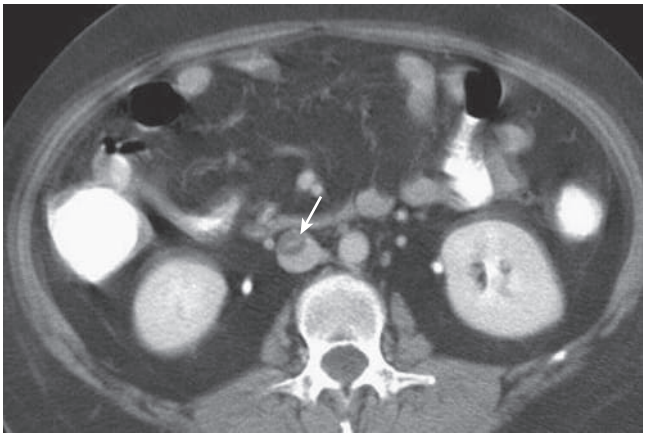
eFigure 81.2 Color Doppler ultrasound of the lower extremity. (A) Normal color Doppler examination of the lower extremity venous and arterial systems. (B) Echogenic material representing deep venous thrombosis (*arrowheads*) is present within the femoral vein, entering the common femoral vein; thrombus can be seen filling the saphenous vein anteriorly at the junction of the femoral veins. Note the displacement of color Doppler flow to the periphery of the thrombosed femoral vein. CFV, common femoral vein. (Courtesy Michael B. Gotway, MD.)



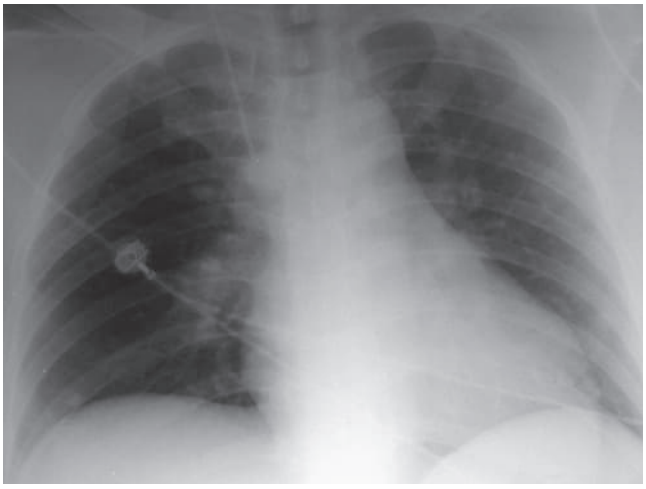
eFigure 81.3 Acute deep venous thrombosis presenting as nearly completely anechoic material filling the venous lumen. Note peripheral displacement of color Doppler signal, marking the remaining patent lateral portions of the common femoral vein. Some echogenic thrombus is seen peripherally both anteriorly and posteriorly as well. (Courtesy Michael B. Gotway, MD.)



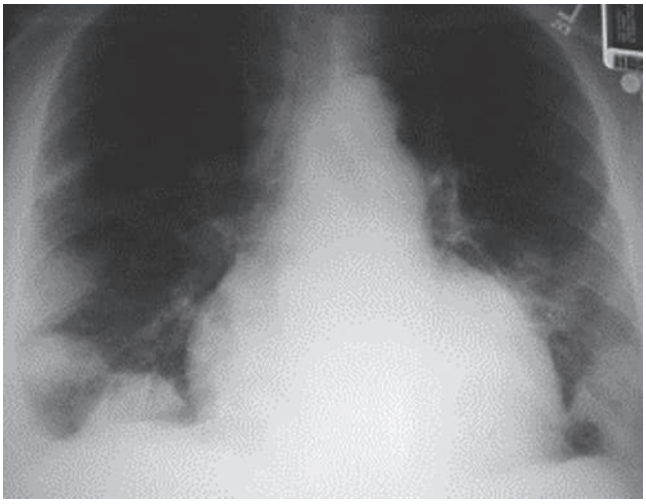
eFigure 81.4 Indirect contrast venography. Axial contrast-enhanced image through the pelvis performed in the course of indirect contrast venography shows a low attenuation filling defect within the right external iliac vein, consistent with deep venous thrombosis (*arrow*). (Courtesy Michael B. Gotway, MD.)



eFigure 81.5 Indirect contrast venography. Axial contrast-enhanced image through the lower abdomen performed in the course of indirect contrast venography shows a low-attenuation filling defect within the inferior vena cava, consistent with deep venous thrombosis (*arrow*). (Courtesy Michael B. Gotway, MD.)



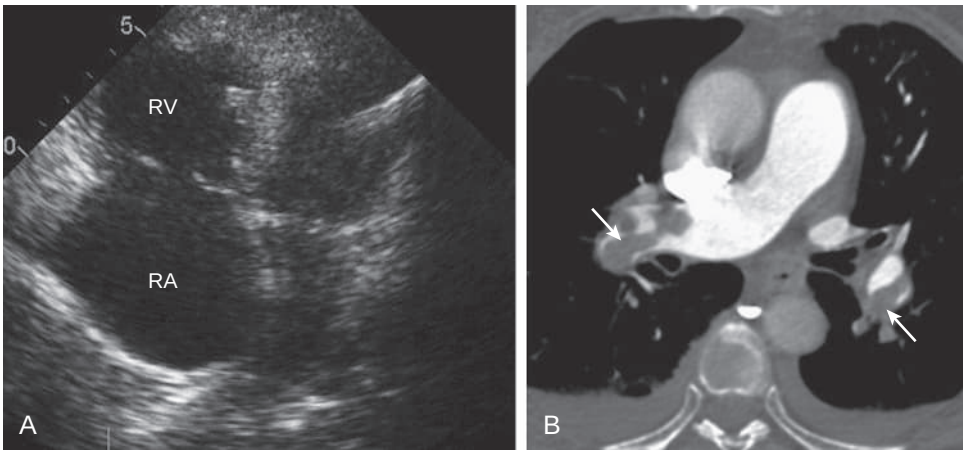
eFigure 81.6 The Westermark sign of pulmonary embolism. Frontal chest radiograph in a patient with acute pulmonary embolism shows hyperlucency of the right thorax compared with the left, consistent with oligemia, representing the Westermark sign. (Courtesy Michael B. Gotway, MD.)



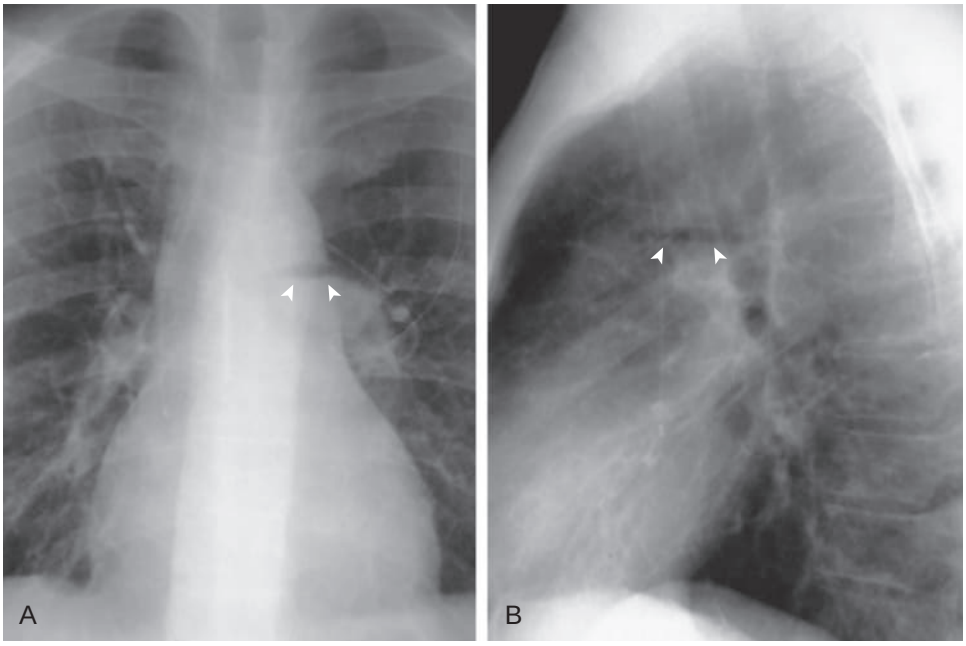
eFigure 81.7 Acute pulmonary embolism. Frontal chest radiograph in a 36-year-old patient with acute pulmonary embolism shows extensive, bilateral, basal subpleural wedge-shaped opacities representing pulmonary infarction (so-called Hampton humps). (Courtesy Michael B. Gotway, MD.)



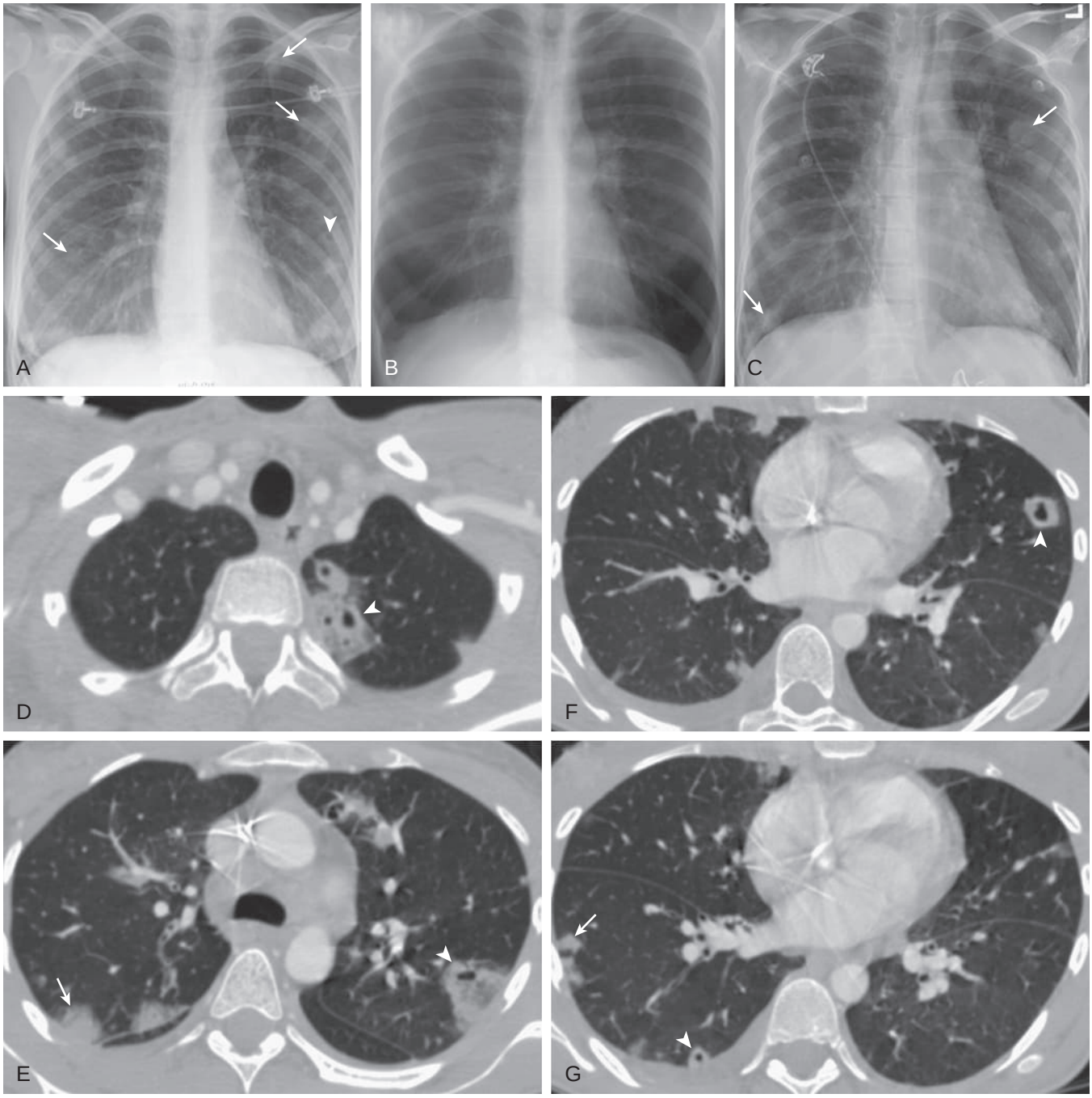
eFigure 81.8 Fleischner and Westermark signs of pulmonary embolism. Frontal chest radiograph in a patient with acute pulmonary embolism shows enlargement of the left pulmonary artery, consistent with the Fleischner sign. Also note the relative hyperlucency of the left thorax compared with the right, consistent with oligemia, representing the Westermark sign. (Courtesy Michael B. Gotway, MD.)



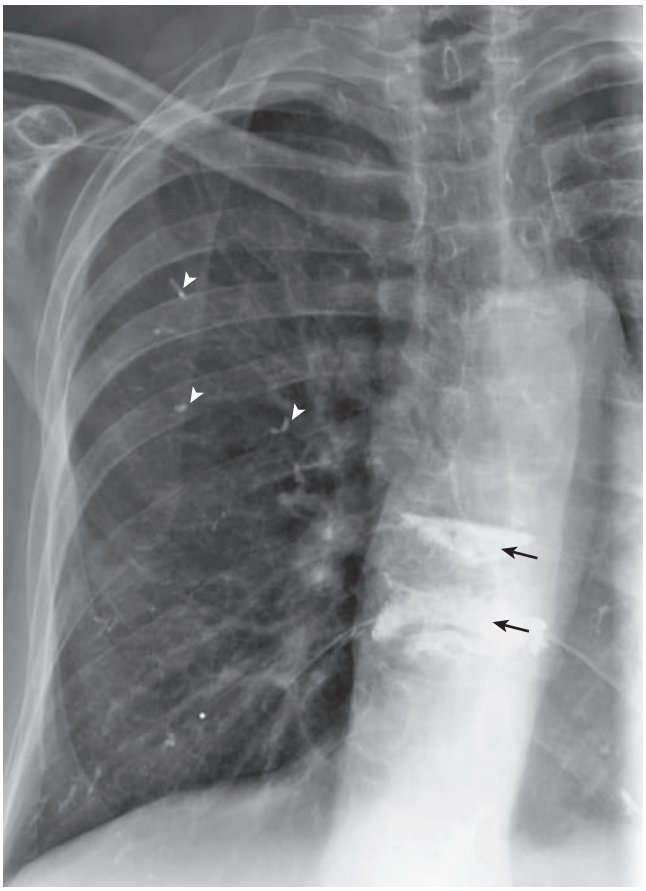
eFigure 81.9 Echocardiogram showing right heart volume overload. (A) Four-chamber echocardiographic image shows enlargement of the right atrium (RA) and right ventricle (RV). (B) Chest computed tomography pulmonary angiography shows bilateral pulmonary emboli (*arrows*), indicating the cause of the right heart chamber enlargement. (Courtesy Michael B. Gotway, MD.)



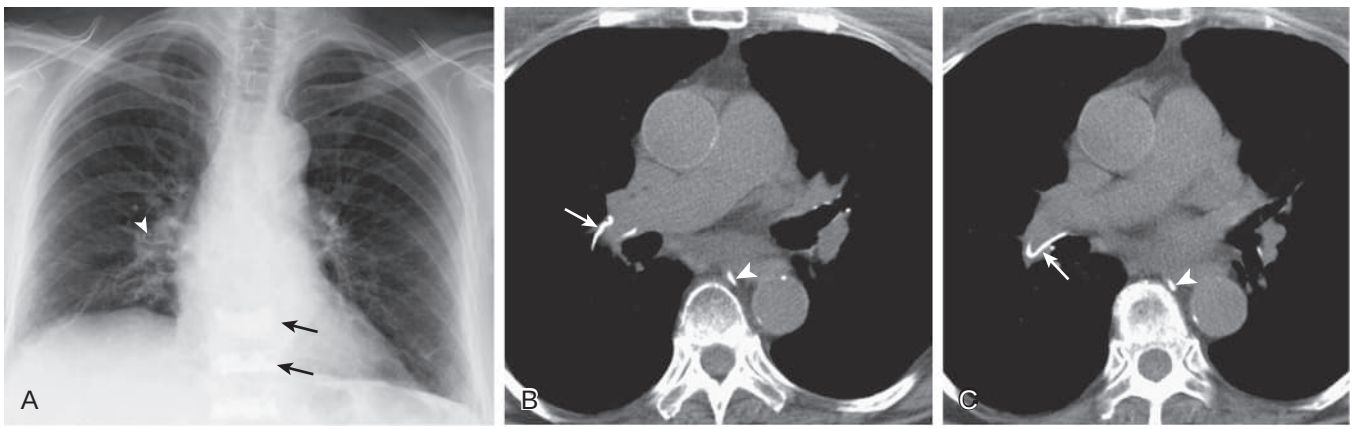
eFigure 81.10 Pulmonary artery air embolism. (A) Frontal and (B) lateral chest radiography performed for acute onset chest pain after manipulation of a central venous catheter shows a gas and fluid level (*arrowheads*) in the main pulmonary artery. This finding resolved without sequelae. (Courtesy Michael B. Gotway, MD.)



eFigure 81.11 Septic embolization. (A) Frontal chest radiography performed in an intravenous drug user with fever shows multiple, bilateral, poorly defined nodular opacities (*arrows*), one of which is cavitary (*arrowhead*). (B) Frontal chest radiography performed 2 years earlier, for comparison, appears normal. (C) Frontal chest radiography performed 1 day after part A shows progression in size of the nodular opacities (*arrows*). (D–G) Axial enhanced thoracic computed tomography confirms the presence of multiple, bilateral, peripherally distributed nodules (*arrows*), many of which are cavitary (*arrowheads*). (Courtesy Michael B. Gotway, MD.)



eFigure 81.12 Methyl methacrylate pulmonary emboli after vertebroplasty. Oblique frontal image of the chest shows thoracic spine vertebroplasty material (*arrows*) with small foci of methyl methacrylate emboli in the right upper lobe (*arrowheads*). (Courtesy Michael B. Gotway, MD.)



eFigure 81.13 Methyl methacrylate pulmonary emboli after vertebroplasty. (A) Frontal chest radiograph shows thoracic spine vertebroplasty material (*arrows*) with a small curvilinear focus of methyl methacrylate in the right interlobar pulmonary artery (*arrowhead*). (B–C) Axial unenhanced thoracic computed tomography confirms high attenuation in the right interlobar pulmonary artery, representing a methyl methacrylate embolism. Methyl methacrylate is also present in the azygos vein (*arrowheads*). (Courtesy Michael B. Gotway, MD.)

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82 PULMONARY THROMBOEMBOLISM: PROPHYLAXIS AND TREATMENT

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INTRODUCTION

Prophylaxis (i.e., primary prophylaxis) and treatment of pulmonary thromboembolism are best achieved with drugs. The primary difference between prophylaxis and treatment is the dosages of anticoagulants used: treated patients receive a higher dosage. This chapter briefly describes the rationales for prophylaxis and treatment and then focuses on the details of each.

PROPHYLAXIS

Because most pulmonary thromboembolism originates in the deep veins, particularly of the lower extremities, the term *venous thromboembolism* (VTE) is often used to describe both *deep venous thrombosis* (DVT) and *pulmonary embolism* (PE). This chapter uses these three terms. Three predisposing factors—hypercoagulability, stasis, and venous injury or inflammation (known as Virchow's triad)—may each contribute to a clot that becomes clinically evident as DVT or PE.

Persons at elevated risk for VTE include the following: patients with lower extremity trauma or surgery, with (total knee replacement) or without (total hip replacement) an intraoperative tourniquet; other patients undergoing prolonged procedures, inpatient or outpatient; lengthy periods of relative immobility (e.g., airplane "economy class syndrome"); diagnosed or undiagnosed high-risk inherited (e.g., homozygous prothrombin gene mutation) or acquired (e.g., antiphospholipid antibody syndrome) thrombophilia; certain cancers (e.g., lung, brain, pancreas, leukemia); and hormonal manipulations (e.g., high-dose fertility injections, hormonal therapy for prostate cancer, certain oral contraceptives).

Because objective tests (e.g., lower extremity venograms and contrast-assisted chest computed tomography) have repeatedly shown that DVT and PE may manifest in patients without symptoms or signs, "primary" VTE drug prophylaxis is undoubtedly administered to some patients who already have established thrombosis.[1] The effect of prophylactic treatment (i.e., low-dose antithrombotic therapy) in these patients is likely partial prevention of clot extension and new clot formation, while endogenous lysing mechanisms resolve the thrombi.

There are two categories of VTE prophylaxis: drug and mechanical. Antithrombotic drugs administered at prophylaxis dosages nonetheless carry risks, such as bleeding, heparin-induced thrombocytopenia, drug interactions interfering with other important therapies, and others. Mechanical prophylaxis, which includes intermittent pneumatic compression and early ambulation, is generally less effective than medical prophylaxis but carries fewer serious risks. Risks include skin injury from improperly applied intermittent pneumatic compression and a potential increase in falls.

BIOAVAILABILITY OF SUBCUTANEOUS ANTICOAGULANTS

The plasma availability for VTE prophylaxis of subcutaneously injected anticoagulants can depend on the patient's other clinical features. A study of mechanically ventilated intensive care unit patients on vasopressors, similar intensive care unit patients not on vasopressors, and surgical ward patients on neither ventilators nor vasopressors, all receiving once-daily subcutaneous prophylactic

nadroparin (a *low-molecular-weight heparin* [LMWH]), measured blood anti–factor Xa levels just before and 3, 4, 6, 8, and 12 hours after a nadroparin dose on the third day of dosing. The patients not receiving vasopressor therapy had expected and satisfactory mean levels of nadroparin at each time point. In contrast, the patients receiving vasopressor therapy had mean nadroparin levels 25–33% of the expected level at each time point, presumably because of peripheral vasoconstriction.[2]

In a 2019 study of adding mechanical prophylaxis to subcutaneous drug prophylaxis in intensive care unit patients that found no added benefit beyond drug prophylaxis alone,[3] only 66% of study participants were on artificial ventilation, and only 35% were receiving vasopressor therapy. Hence, although there is certainty that the bioavailability of subcutaneous drug prophylaxis is markedly reduced in patients receiving vasopressor therapy, an effective countermeasure is not known.

DIFFERING PHILOSOPHIES OF VENOUS THROMBOEMBOLISM PROPHYLAXIS

There are two opposing philosophies to determine which persons warrant VTE prophylaxis. One is *personalized risk stratification*, exemplified by the Caprini[4] risk assessment score for surgical patients and the Geneva Risk and Padua Prediction[5] scores for medical inpatients. The other approach is nearly *universal application within patient groups*,[6] almost akin to society's approach to infant immunization. Proponents of the second approach argue that it simplifies decision-making and recognizes that hospitalization itself is the risk factor provoking prophylaxis consideration. Each approach allows exceptions.

To the extent possible, physicians can share with patients their view of prophylaxis for that individual. We think VTE prophylaxis should be recommended to each patient absent a contraindication. The timing of initiation, duration, drug, and dosage should provide maximum VTE risk protection without undue risk.

VENOUS THROMBOEMBOLISM PROPHYLACTIC DRUGS

Unfractionated Heparin

Unfractionated heparin (UFH) is a mixture of glycosaminoglycans purified from pig intestine. A tanker-truck of pig intestines yields about 8 pounds of UFH. Despite its biologic origin, it is classified as a drug and is standardized by a range of component molecular-weight molecules and activities of anti–factor Xa and anti–factor IIa. Factor Xa is factor X activated by either tissue factor complexed with factor VII (extrinsic pathway) or factor VIII complexed with factor IX (intrinsic pathway). Factor IIa is thrombin, the cleavage-activated product of prothrombin, factor II. Both anti–factor Xa and anti–factor IIa components of UFH have antithrombotic activity. The anti–factor IIa activity of UFH is primarily through binding to catalyze antithrombin, but UFH also has antithrombotic activity in low-antithrombin states, perhaps mostly through its anti–factor Xa molecules. The most sensitive assay for heparin is the anti–factor Xa level, but this level is rarely measured during prophylactic use.

UFH was the first VTE prophylactic drug proven effective, as shown in a study of surgical patients in 1972. When given subcutaneously at 5000 units 2 hours preoperatively and every 8 hours postoperatively for 7 days, autopsy-proven fatal PE was identified in 2 of 2045 patients (0.09%) in the UFH group and in 16 of 2074 (0.8%) in the control group.[7] Currently, UFH prophylaxis is not commonly begun before surgery but is instead given every 8 or 12 hours during the risk period, usually until hospital discharge, assuming reasonable hemostasis. A 2011 meta-analysis showed nonsignificant differences between the two dosing interval regimens for PE, DVT, death, and bleeding.[8]

Subcutaneous UFH is slowly and incompletely absorbed into the circulation, with the circulating amount dependent on the subcutaneously injected dosage; 5000 units UFH administered subcutaneously shows only 15–20% of the area under the curve of activity (measured as anti–factor Xa level) of 5000 units intravenous UFH, with a peak anti–factor Xa level of 0.13 units/mL, and it falls below detection after 4 hours.[9] However, a higher subcutaneous dosage seems to saturate the subcutaneous injection site, and more drug becomes evident in plasma. When 35,000 units UFH is injected subcutaneously in divided doses over 24 hours, more than 90% reaches the plasma. This is the apparent explanation for the treatment efficacy of high-dose subcutaneous UFH and approximate equivalent prophylactic efficacy of 7500 units UFH subcutaneously compared with an LMWH[10]; if more subcutaneous UFH is given, more will find its way into the circulation.

The metabolism and elimination of subcutaneous UFH are complex. Some UFH remains at the injection site. UFH reaching the circulation is partially nonspecifically bound by plasma proteins (acute phase reactants and others) and endothelial cells; these endothelial cells release bound UFH molecules over time. In the liver, reticuloendothelial cells take up and metabolize UFH.

Disadvantages of UFH prophylaxis include bleeding, *heparin-induced thrombocytopenia* (HIT), and heparin resistance. Routine prophylaxis with UFH, as with other antithrombotic drugs, results in an increased frequency of surgical wound hematoma and other bleeding, depending on surgical and patient-specific factors. HIT, seen in an estimated 3% of overall UFH recipients,[11] results from formation of antibodies to complexes of heparin and *platelet factor 4* (PF4); the antibody-heparin-PF4 complex then activates platelets, thus leading to thrombocytopenia and occasionally life-threatening thrombosis. The onset of HIT is usually after 4 to 5 days of UFH administration, but it can rarely begin 1 or 2 days after a single dose.[12] Heparin resistance refers to impaired *activated partial thromboplastin time* (aPTT) elevation despite treatment-level dosing, due to binding and neutralization of UFH by PF4 and plasma proteins, resulting in reduced UFH efficacy.

Low-Molecular-Weight Heparins

Multiple LMWHs (e.g., enoxaparin, dalteparin, nadroparin, tinzaparin) are used in different venues for VTE prophylaxis and treatment. Each is derived from UFH, which is digested to provide smaller fragments of mean molecular weight of approximately 5000 daltons, rather than a mean of approximately 15,000 daltons for UFH. The smaller molecular size

of LMWH provides several therapeutic advantages and a disadvantage. The first advantage is that there is more than 90% absorption of all dosages from subcutaneous injection sites, thereby leading to predictable dose-proportional plasma drug levels. Second, LMWH has minimal nonspecific protein binding in tissue or plasma, so that administered doses are both absorbed and bioactive. Third, LMWH has approximately one-tenth the frequency of causing HIT as UFH, or approximately 3 per 1000 patients.[11] The sole disadvantage of LMWH, besides increased cost compared with UFH, is its nearly total renal elimination. As a consequence, it accumulates in patients with renal insufficiency, who already have impaired hemostasis. Daily LMWH prophylactic dosing in patients with more than minor renal-related impaired hemostasis increases bleeding risk if blood anti–factor Xa levels are not checked and LMWH dosing adjusted or if the patient is not switched to UFH prophylaxis.

LMWHs for prophylaxis are given in fixed dosages or, for two of these drugs, are adjusted for actual body weight. Although LMWHs are all similar, they were developed with different approaches that led to quite differing dosing schemes. The two LMWH prophylactic drugs commonly used in the United States and Canada are enoxaparin, given in a fixed milligram dosage without respect to body weight, and dalteparin, given in a fixed dosage in anti–factor Xa units. Another LWMH, nadroparin, is dosed in units by body weight category or at a fixed dosage, and a fourth, tinzaparin, is dosed in units by actual body weight. Some patients with higher VTE risk situations are given LMWH twice daily in a higher overall dosage than for lower-risk situations. LMWH prophylaxis dosing after hospital discharge is currently given for patients after hip and knee replacement and is used by some higher-risk persons intermittently, such as for long airplane rides.

Fondaparinux

Fondaparinux, also called ultra-LMWH and pentasaccharide, is a synthesized molecule of approximately 1700 daltons molecular weight. Its most important current clinical property is its effectiveness as treatment for HIT,[13] in spite of its ability, like that of UFH and LMWH, to stimulate generation of anti-PF4 antibodies. Despite its generation of PF4 antibodies, fondaparinux molecules are so small that the anti-PF4 antibody bridging and binding are not sufficient to degranulate platelets and cause the HIT syndrome. Therefore, fondaparinux is an excellent treatment for HIT because of its rapid onset of action and effective sustained antithrombotic activity. Absorption from a subcutaneous injection of 2.5 mg, the prophylactic dose, is complete, and elimination is nearly entirely renal, with a prolonged half-life of approximately 18 hours. There is an approximately 20% increase in steady-state blood level with identical daily doses that is reached and stabilized after approximately 5 days in persons with normal renal function; in patients with renal impairment, blood levels may continue to rise.

Oral Anticoagulants

Vitamin K Antagonists. Vitamin K antagonists, or warfarin in the United States and several other countries, was originally used for inpatient, and later extended to outpatient, prophylaxis by some practitioners after lower extremity joint replacement because of several attractive qualities: (1) it took warfarin several days to develop its full antithrombotic effect, thus allowing wound hemostasis to improve; (2) it was orally administered, unlike injected UFH or LMWH; (3) it could be monitored by existing prevalent methods (international normalized ratio) to prevent an overly intense antithrombotic effect; (4) other than bleeding risk, it is quite safe; and (5) it is inexpensive. Warfarin is now uncommonly used because *direct-acting oral anticoagulants* (DOACs) have been extensively studied for the same joint replacement indications and have been judged safe and effective. Warfarin is much less expensive (in the United States) if prophylaxis is to be prolonged (e.g., 5 weeks after discharge). The international normalized ratio target for warfarin in these limited prophylactic indications is not fully settled; some orthopedists target 2.5 (normal, 0.8-1.2), whereas others target a lower range.

Dabigatran (a Direct Oral Anticoagulant). Dabigatran is a direct inhibitor of thrombin. It is *U.S. Food and Drug Administration* (FDA) approved for prophylaxis solely in hip replacement patients, with a half-dose (110 mg) taken 2 hours after awakening from surgery and a full dose (220 mg) taken once daily beginning the next morning for 28 to 35 days. After oral absorption, dabigatran's bioavailability is only 4–7%, irrespective of food intake. A peak level is reached at 2 hours, and the low prophylactic dose effect is nearly gone by 24 hours. There is no significant accumulation with once-daily dosing in patients with normal renal function; because of the drug's renal elimination, drug levels rise with renal insufficiency. Only 35% protein bound, dabigatran can be cleared by dialysis. The prophylactic dose (220 mg once daily) is lower than the treatment dose for VTE and prevention of thromboembolism in patients with nonvalvular atrial fibrillation (150 mg twice daily). The manufacturer reported a statistically significant increased frequency of myocardial infarction compared with warfarin treatment in dabigatran-dosed patients, a finding seen with other direct thrombin inhibitors.[14,15] Hence, among DOACs, dabigatran is a less preferred prophylactic agent. Dabigatran does have a specific antibody antidote,[16] an advantage among DOACs, and is associated with less intracranial bleeding than warfarin. Overdose with hemorrhage can be treated with the antibody antidote and hemodialysis.

In clinical trials, dabigatran was noninferior for VTE prevention to the LMWH enoxaparin, subcutaneously 40 mg/day, the most commonly administered dose in Europe, but inferior to 30 mg subcutaneously every 12 hours, the common North American dose at the time.[17] VTE events were nearly all asymptomatic (>99%) and detected by contrast venography. Bleeding rates were similar.

Rivaroxaban (a Direct Oral Anticoagulant). Rivaroxaban is a direct inhibitor of factor Xa. It is FDA approved for VTE prophylaxis in patients with hip (dosed for 35 days) and knee (dosed for 12 days) replacements, at 10 mg once daily starting 6 to 10 hours after surgery ends and hemostasis is ensured. Absorption and bioavailability are 80–100% at this low dose, although, at higher treatment dosages, they are reduced unless the drug is taken with food to maximize bioavailability (reasons for this are not well understood). Rivaroxaban reaches a peak level in 2 to 4 hours and is measurable in plasma for 16 to

27 hours after ingestion, hence the once-daily dosing for prophylaxis. It has 50% renal elimination and substantial hepatic metabolism, so *significant renal or liver impairment is a relative contraindication to use*. A short-acting competitive inhibitor of rivaroxaban and other anti–factor Xa antithrombotic drugs, andexanet alfa, is an antidote[18] given by infusion; however, it is expensive and not readily available. Restoring depleted clotting factors (including fibrinogen), platelets, and red blood cells, and administering *factor VIII inhibitory bypass activity* (FEIBA), which is sometimes used in patients with hemophilia, can be useful strategies while awaiting the antidote or metabolic elimination of rivaroxaban in a bleeding patient. On prophylactic dosage, the prothrombin time may or may not be prolonged, and the degree of prolongation is not a reliable predictor of rivaroxaban blood level.[19]

Joint Replacement. In clinical trials, rivaroxaban 10 mg/day was superior to the European enoxaparin regimen, 40 mg once daily subcutaneously, in patients undergoing hip and knee replacement for preventing "major VTE," a composite of asymptomatic proximal DVT and symptomatic confirmed DVT and PE. Symptomatic VTE developed in 1% of enoxaparin-treated patients.[20]

Internal Medicine. Rivaroxaban prophylaxis for 45 days was compared with placebo in approximately 12,000 discharged internal medicine patients who were assessed to be at high risk for VTE. Rates of symptomatic VTE or VTE-related death were similar in both groups, at approximately 1%. Clinically relevant bleeding was noted in 2% of rivaroxaban recipients compared with 0.6% of placebo recipients. A previous randomized double-blind trial of medical inpatients compared 10 days of subcutaneous enoxaparin 40 mg once daily with 35 days of rivaroxaban 10 mg. For the first 10 days, symptomatic VTE and clinically relevant bleeding were equivalent. Over 35 days, of those patients receiving only 10 days of enoxaparin, 2% had symptomatic VTE or VTE-related death compared with 1% of patients receiving 35 days of rivaroxaban. However, clinically relevant bleeding was 2.5 times more frequent in rivaroxaban recipients over the first 10-day period compared with the overall 35-day period (4% vs. 1.7%, respectively).[21] A subsequent placebo-controlled study showed no significant difference in efficacy or major bleeding.[22] In 2019, a subgroup reanalysis for regulatory authorities combining subgroup patients from both studies led to U.S. regulatory approval.

Cancer. Prophylaxis with rivaroxaban 10 mg/day for 6 months was compared with placebo in high–VTE risk ambulatory patients with cancer. There was no significant difference in symptomatic VTE overall (approximately 4% in each group) or during the period of randomized treatment (1% for rivaroxaban, 3% for placebo—approximately one-half of patients had discontinued treatment by 6 months), but there were fewer overall VTEs detected in the rivaroxaban group during randomized prophylactic treatment. Clinically relevant bleeding was more frequent in the rivaroxaban group, at 5%, versus 3% in placebo patients.[23]

Apixaban (a Direct Oral Anticoagulant). Another anti–factor Xa drug, apixaban, is begun 12 to 24 hours after hip or knee replacement surgery at 2.5 mg every 12 hours and is continued for 35 days (hip) and 12 days (knee). With or without simultaneous food administration, levels peak at 3 to 4 hours. Bioavailability is approximately 50% and the half-life is approximately 10 hours, close to the time of receiving the next apixaban dose. Thus, although rivaroxaban has a higher peak and lower trough with once-daily dosing, apixaban delivers closer to a steady-state level. There is no known clinical advantage of one property compared with the other. Andexanet alfa is an effective inhibitor antidote to apixaban,[18] as for rivaroxaban, similarly requiring repeat infusions to maintain inhibitory activity. The same approaches to controlling hemorrhage as described for rivaroxaban can be used. In general, antithrombotic activity of apixaban is somewhat reduced compared with rivaroxaban dosing for the same indication[18] (e.g., VTE prophylaxis); for this reason, its lower peak levels, and perhaps its twice-daily dosing, it may be more advantageous to use in patients with increased bleeding risk. As with dabigatran and rivaroxaban, the frequency of intracerebral hemorrhage is reduced compared with similarly effective warfarin dosage.[24]

Joint Replacement. Approximately 1% of hip and knee replacement patients had symptomatic VTE during the trials' observation period, with similar frequencies in the apixaban (40 mg subcutaneously once daily) and enoxaparin (30 mg subcutaneously twice daily) groups.[25] In these recently operated patients, there was a similar extent of clinically relevant bleeding in all treatment groups, at 3–5%.

Betrixaban (a Direct Oral Anticoagulant). Betrixaban is a longer-acting anti–factor Xa drug that is FDA approved for internal medicine patients for VTE prophylaxis of 35 to 42 days' duration, during and after hospitalization. Oral bioavailability is 35% and is reduced by approximately one-half if the drug is taken with food, even within 6 hours of eating. Its half-life is nearly 24 hours. Betrixaban is given at a loading dose of 160 mg, then 80 mg once daily on subsequent days; with this approach, it reaches steady state within 2 to 3 days. Betrixaban can be neutralized by infusion of the antidote andexanet alfa.[26] Because it is only 60% protein bound, an alternative or additional neutralizing therapy is hemodialysis. Betrixaban is metabolized primarily by non–cytochrome P liver enzymes; only 10–15% is eliminated in the urine.

In its sole large clinical trial in hospitalized medical patients, once daily betrixaban for 5 to 6 weeks compared with subcutaneous enoxaparin 40 mg for the first 6 to 14 days reduced the symptomatic VTE rate from 1.5–0.9%. There was an approximate doubling of clinically significant bleeding events in the betrixaban group of 3% compared with 1.6% in the inpatient-only enoxaparin group.[27]

Aspirin. Aspirin, long-recognized for its antiplatelet arterial antithrombotic properties through cyclooxygenase-1 inhibition of thromboxane A_2 production, was also identified early as a DVT prophylactic drug. Platelet activation propagates thrombin generation and thrombosis. Aspirin was found to be approximately as effective as warfarin and superior to placebo in reducing proximal DVT in patients undergoing surgery for hip fracture (9%, 11%, and 30%, respectively).[28] Noncoated oral aspirin is 40–50% absorbed, reaching peak blood levels in 30 minutes, but with a half-life of only 20 minutes. Its effect is prolonged, however, because it irreversibly acetylates circulating platelets; new platelets last 8 to 10 days. The best daily dose of aspirin is uncertain, but less than 300 mg/day produces fewer side effects than higher doses,

without lower efficacy. Some diabetic patients and persons with a high body mass index have more rapid platelet turnover; in these patients, 100 mg aspirin twice daily ensured full inhibition of cyclooxygenase 1.[29] Aspirin at 81 to 100 mg twice daily should be maximally effective in all patients.

Large clinical trials of aspirin for VTE prophylaxis have been limited to patients undergoing hip replacement and hip fracture surgery; these patients had a significant approximately 30% reduction in symptomatic DVT and nonfatal PE compared with patients receiving placebo.[30] Aspirin recipients (160 mg once daily for 35 days) had slightly more clinically relevant bleeding episodes but no more fatal bleeding episodes or reoperations resulting from bleeding. Patients undergoing hip replacement[31] who received 10 days of LMWH (dalteparin 5000 units subcutaneously) and patients undergoing hip and knee replacement[32] who received 5 days of rivaroxaban 10 mg once daily, in separate studies, were then randomized to continue that therapy or switch to 81 mg oral aspirin once daily. In both studies, the patients who transferred to aspirin prophylaxis had outcomes that were nearly identical to those in the comparison group.

Aspirin treatment is so prevalent that some inferences may be drawn from its bystander appearances in other-purposed clinical trials. In a rivaroxaban VTE prophylaxis study of high-VTE risk, discharged medical patients receiving 10 mg rivaroxaban or placebo for 45 days (described earlier), approximately one-half of the patients were taking aspirin up to 162 mg/day. The frequency of symptomatic VTE or VTE-related death in the aspirin-only group and the rivaroxaban-only group was identical, 0.9%, with nearly 3000 patients in each group.[33] Major bleeding was rare in both groups, at 0.2–0.3%; clinically relevant bleeding was not reported. Aspirin use was not randomized, and aspirin users should be assumed to have been self-selected as tolerant to its effects. Overall, aspirin is likely a less potent thromboprophylactic agent than those described earlier, but it may be sufficient for average- and low-risk outpatients in whom prophylaxis is desired.

MECHANICAL PROPHYLAXIS

Options for mechanical prophylaxis include externally applied devices, ambulation, and *inferior vena cava* (IVC) filters. Graduated compression stockings, *intermittent pneumatic compression* (IPC; knee high or thigh high), venous foot pumps, and early ambulation are mechanical. Their primary role is VTE prophylaxis in patients for whom bleeding risk is so high that the aforementioned drug prophylaxis is contraindicated. These devices can also be applied to unoperated lower extremities during operations that carry VTE risk. Mechanical prophylactic devices can be harmful in the following circumstances: if they are improperly applied and thus cause underlying skin, muscle, or vascular injury, if their use impedes ambulation, or if they are ordered in lieu of more effective antithrombotic drugs but are used for only a short time. Interpreting published studies of these approaches is difficult because there is no blinding, and adherence to device use during the study is variable (<50% adherence in one study and as low as 20% in another). Reviews and meta-analyses acknowledging such limitations conclude that some externally applied devices such as IPCs may prevent as many as 16 symptomatic VTEs per 1000 patients undergoing hip and knee replacement or hip fracture surgery.[34]

Fewer studies have been published in hospitalized internal medicine patients, and these studies are inconclusive regarding the benefit of graduated compression stockings (knee high vs. thigh high) and IPC. A 2019-reported intensive care unit–based comparison of IPC added to UFH or LMWH prophylaxis found no difference in symptomatic or asymptomatic VTE.[3] PE was diagnosed in 1% of patients in each group. An earlier study comparing compression stockings alone with IPC added to compression stockings in intensive care unit patients found double the number of patients with asymptomatic distal DVT in patients without IPC but no difference in day 6 outcome in patients with asymptomatic proximal DVT or symptomatic VTE.[35] A larger clinical trial in patients with fresh stroke or transient ischemic attack compared thigh-high IPC with no prophylaxis for 30 days. A total of 67% of patients were taking aspirin or clopidogrel. By day 8, 12% of patients without IPC had duplex ultrasound–proven proximal DVT compared with 8.5% of patients assigned to IPC, a 33% reduction that was significant. There was a borderline significant 18% reduction in death at 30 days.[36]

Considered together, the data suggest that, in orthopedic surgical and medical patients with a contraindication to antithrombotic prophylactic drugs, IPC offers some protection. Conditions should be optimized: a battery-powered rather than corded electric device should be used to optimize compliance, thigh-high devices may be best, there should be regular attention to protecting the skin, and drug prophylaxis should be used when considered safe. Ambulation when safe should be added to every prophylactic regimen.

Vena Cava Interruption

Retrievable IVC filters for primary prevention of PE are primarily used in patients undergoing bariatric surgery at particularly high VTE risk (perhaps 25% of such patients in the United States) and those with serious trauma who may (or may not) have a contraindication to drug prophylaxis. A randomized trial comparing retrievable IVC filter insertion within 72 hours of trauma with no filter insertion resulted in no difference in a composite outcome of symptomatic PE or deaths over a 90-day period. All patients received IPC to uninjured legs. However, among patients whose bleeding risk was too high to receive anticoagulant prophylaxis before day 7, there were fewer PEs in IVC filter recipients at 14 days. These investigators concluded that this latter subgroup could be good candidates for retrievable IVC filters.[37] Although retrievable IVC filters are generally effective in the short term, placement and particularly retrieval involve significant risk of complications—filter migration, filter penetration, tilting, thrombosis—and many filters are never retrieved. As many as 5% of penetration cases require surgery.[38] If IVC filters are used for prophylaxis, they should be limited to temporary use in bariatric and trauma patients.

MANAGEMENT OF PROPHYLAXIS

Table 82.1 presents patient-related categories and recommended approaches to VTE prophylaxis.

We recommend using effective prophylaxis during risk periods unless contraindicated (universal application within patient groups), rather than risk assessing each

Table 82.1 Prophylaxis for Venous Thromboembolism

Patient Category	Prophylaxis	Comment
Internal medicine inpatients	UFH 5000 U SC q8hr or q12hr*	Monitor platelets daily for HIT
	LMWH (e.g., enoxaparin 40 mg SC every morning)	Accumulates with renal insufficiency; HIT less likely, but monitor platelets every 2 days
	Intermittent pneumatic compression	Battery operated, thigh high optimal Use when drug prophylaxis contraindicated
	Retrievable IVC filter	Use when drug prophylaxis contraindicated Expert removal when no longer needed
ICU patients receiving vasopressor therapy	LMWH (e.g., enoxaparin 40 mg SC every morning with intermittent pneumatic compression)	LMWH accumulates with renal insufficiency; optimal IPC thigh high; can monitor anti–factor Xa peak blood levels 3–4 hr after dosing, increase dose if needed to reach 0.25 anti–factor Xa unit/mL
Hip or knee replacement patients	Apixaban 2.5 mg PO 12–24 hr after surgery, then q12hr for 35 days (hip) or 12 days (knee)	
	Rivaroxaban 10 mg PO 6–10 hr after surgery with hemostasis, then daily for 5 days; follow with 81 mg aspirin PO daily for 30 days (after hip replacement) or 9 days (after knee replacement)	Alternatively, rivaroxaban could be continued for the entire duration
	LMWH beginning day after surgery (e.g., enoxaparin 30 mg SC q12hr; dalteparin 5000 U SC daily; tinzaparin 75 U/kg daily) continued for 14 days after knee replacement or 28 days after hip replacement	Could consider stopping SC LMWH after 10 days and starting aspirin 81 mg daily for the remainder of prophylaxis
	Intermittent pneumatic compression	Battery operated, thigh high optimal Use when drug prophylaxis contraindicated, or continue for at least 6 hr after drug prophylaxis was begun
General surgery patients	UFH 5000 U SC q12hr or q8hr after hemostasis	Monitor daily platelets for HIT; start with IPC during surgery, thigh high and bilateral; can discontinue 6 hr after drug prophylaxis is underway
	LMWH (enoxaparin 40 mg SC daily, dalteparin 2500 U SC daily) during hospitalization, after hemostasis	Accumulates with renal insufficiency; HIT less likely, but monitor platelets at least every 2 days; start with IPC during surgery, thigh high and bilateral; can discontinue 6 hr after drug prophylaxis is underway
	Intermittent pneumatic compression	Start during surgery, thigh high and bilateral, until after UFH or LMWH prophylaxis is at least 6 hr underway; continue if drug prophylaxis is contraindicated until contraindication remits
Abdominal or pelvic cancer surgery, high–VTE risk patients	LMWH (enoxaparin 40 mg SC daily, dalteparin 2500 U SC daily) after hemostasis	Accumulates with renal insufficiency; HIT less likely, but monitor platelets at least every 2 days; start with IPC during surgery, thigh high and bilateral, and can discontinue 6 hr after drug prophylaxis is underway; consider extending prophylaxis for 30 days
	UFH 5000 U SC q8hr for 30 days, after hemostasis	Monitor daily platelets for HIT; transition to LMWH for outpatient extended prophylaxis
	Intermittent pneumatic compression	Start during surgery, thigh high and bilateral, until after UFH or LMWH prophylaxis is at least 6 hr underway; continue if drug prophylaxis is contraindicated until contraindication remits
Major trauma patients without intracranial trauma	LMWH (e.g., enoxaparin 40 mg daily) or UFH SC q12hr or q8hr	Start with IPC during surgery, thigh high and bilateral, until after UFH or LMWH prophylaxis is at least 6 hr underway; continue if drug prophylaxis is contraindicated until contraindication remits; LMWH accumulates with renal insufficiency; monitor platelets daily for UFH, every 2 days for LMWH
	Intermittent pneumatic compression	Start during surgery, thigh high and bilateral, unless contraindicated; use in patients for whom drug prophylaxis is contraindicated until contraindication remits
	Consider IVC retrievable filter for trauma patients with or without intracranial trauma who cannot receive drug prophylaxis before day 7 after trauma	Data inconclusive and some risks with IVC filters
Intracranial trauma and/or surgery patients	Intermittent pneumatic compression	Start as soon as possible, thigh high and bilateral; start UFH 5000 units SC q12hr, with platelet monitoring daily, when or if hemostasis and conditions permit

Continued

Table 82.1 Prophylaxis for Venous Thromboembolism—cont'd

Patient Category	Prophylaxis	Comment
Bariatric surgery patients[39]	LMWH (e.g., enoxaparin 40 mg SC q12hr beginning 3 hr before surgery) for 4 wk	May increase intraoperative and postoperative bleeding; accumulation with renal insufficiency; IPC during surgery and postoperatively until fully ambulatory
	UFH 5000 U SC q8hr beginning 3 hr before surgery, for 4 wk	May increase intraoperative and postoperative bleeding; early daily platelet count monitoring followed by close clinical and appropriate laboratory surveillance after discharge; IPC during surgery and postoperatively until fully ambulatory
Outpatients with indwelling central venous catheters	Consider LMWH (e.g., enoxaparin 40 mg SC once daily)	Accumulates with renal insufficiency; increases bleeding risk; may not alter 3-mo mortality; probably superior to low-dose warfarin

*Selection of dosing every 8 hours or every 12 hours should be based on assessment of underlying risk of VTE and bleeding.[41]
HIT, heparin-induced thrombocytopenia; IPC, intermittent pneumatic compression; ICU, intensive care unit; IVC, inferior vena cava; LMWH, low-molecular-weight heparin; PO, orally; SC, subcutaneously; UFH, unfractionated heparin; VTE, venous thromboembolism.

individual to determine whether to use VTE prophylaxis (personalized risk stratification).

Inpatients should generally receive VTE drug prophylaxis unless contraindicated; mechanical prophylaxis can be used until the contraindication remits. Selected groups warrant primary prophylaxis (hip and knee replacement patients). Physicians must be aware of drug prophylaxis risks and monitor accordingly. Maximizing safe ambulation is a part of all VTE prophylaxis strategies.

Patients with a history of VTE are at higher than average VTE risk and particularly warrant prophylaxis. If they are undergoing elective surgery, they need a surgeon comfortable with providing drug prophylaxis. On nonsurgical admissions, these patients need the most effective, safe prophylaxis possible, with close monitoring for complications.

PROPHYLAXIS IN COVID-19 PATIENTS AND SUSPECTS

Numerous reports of coagulopathy, including elevated D-dimer, thrombocytopenia, prolonged aPTT, decreased fibrinogen, objectively diagnosed PE and DVT, and microthromboses at autopsy have characterized cases of COVID-19 in China and the United States.[39,40] Although there is limited evidence, adopting the approach of administering drug thromboprophylaxis unless contraindicated seems wise. Some clinicians recommend higher-dose prophylaxis, as was administered early in North America to joint replacement recipients (e.g., enoxaparin 30 mg subcutaneously every 12 hours rather than 40 mg once daily), if the D-dimer level of the patient with COVID-19 is high and continues to rise or remain elevated. Because thrombocytopenia is not uncommon, using LMWH initially to reduce the HIT risk seems prudent. However, given that progressive renal insufficiency appears common in patients with COVID-19, reducing the frequency of dosing, measuring anti–factor Xa level at peak (4 hours after subcutaneous injection) for a target of 0.2 to 0.35, and switching to UFH may be necessary in these patients to minimize bleeding complications.

TREATMENT OF PULMONARY EMBOLISM

OVERVIEW

Acute PE is a potentially fatal disorder, especially when effective treatment is delayed.[42,43] As such, PE requires prompt diagnosis and effective treatment. Most deaths attributable to PE result from acute *right ventricular* (RV) failure caused by the initial obstruction of blood flow through the pulmonary arteries or from recurrent PE when the diagnosis or treatment of PE is delayed. Death from recurrent PE is uncommon once therapeutic anticoagulation is begun.[44-46]

Treatment of acute PE requires assessment of the risks and benefits of all interventions for each patient. The physician must respond to changes in the patient's condition that alter the risks or benefits of treatment. Understanding the pathophysiology of acute PE is essential.

PATHOPHYSIOLOGY (See Chapter 81)

Acute PE compromises both the circulatory system and the respiratory system.[47]

Circulatory Compromise

Embolic obstruction of the pulmonary arterial tree is the principal cause of circulatory compromise. In the absence of preexisting pulmonary vascular disease, recruitment and distention of pulmonary arteries preserve normal mean pulmonary artery pressure, pulmonary vascular resistance, and cardiac output until more than 25% of the pulmonary arterial tree is obstructed.[48] However, severe embolic obstruction (>50% pulmonary arterial tree) or less severe embolic obstruction combined with preexisting pulmonary vascular disease causes hemodynamic compromise.[47,49-57]

Pulmonary arterial vasoconstriction may combine with vascular obstruction to cause circulatory compromise. Alveolar hypoxia, serotonin and thromboxane released from platelets, and endothelin released from endothelial cells each may contribute to pulmonary vasoconstriction in patients with acute PE.[54,55,58,59]

Increased mean pulmonary artery pressure and pulmonary vascular resistance increase RV afterload. In general, without RV hypertrophy from preexisting pulmonary vascular disease, the right ventricle is unable to generate a mean pulmonary artery pressure higher than 40 mm Hg (RV systolic pressure >70 mm Hg), and cardiac output falls even with catecholamine-induced increases in heart rate and stroke volume.[48,53] Acute right-sided heart failure increases RV end-diastolic pressure and volume, RV wall tension, and myocyte stress. Systemic hypotension and increased RV end-diastolic pressure decrease the pressure gradient, thus reducing blood flow through the coronary arteries and producing RV ischemia.

Respiratory Compromise

Embolic obstruction of the pulmonary arterial tree is also the principal cause of respiratory compromise. Although pulmonary artery obstruction creates dead-space ventilation,[60] compensatory hyperventilation of perfused lung units eliminates carbon dioxide and, in the absence of previous cardiopulmonary disease, acute PE rarely causes hypercarbic respiratory acidosis.[61]

Mild arterial hypoxemia, easily reversed by low-flow oxygen, is common after PE. Redistribution of preserved cardiac output through patent lung vessels creates lung units with low ventilation-to-perfusion ratios.[62,63] Furthermore, investigators have reported qualitative and quantitative changes in pulmonary surfactant following acute PE.[64] Loss of surfactant contributes to alveolar collapse and pneumoconstriction and creates lung units with low ratios of ventilation to perfusion.[65,66]

More severe arterial hypoxemia, refractory to low-flow oxygen, results from right-to-left shunting of venous blood through the lungs, the heart, or both. Right-to-left intrapulmonary shunting can arise in the setting of alveolar hemorrhage, pulmonary edema, and/or atelectasis.[67] Intracardiac shunting usually takes place when venous blood flows from the right atrium to the left atrium through a patent foramen ovale when right-sided heart failure causes right atrial pressure to exceed left atrial pressure.[68] In the setting of a right-to-left shunt, reduction of mixed venous oxygen saturation, resulting from reduced delivery of oxygen to tissues, worsens arterial hypoxemia.[69] (See Chapter 44.)

INITIAL MANAGEMENT OF SUSPECTED PULMONARY EMBOLISM

The initial management of a patient with symptoms or signs that suggest acute PE involves coordination of diagnostic testing, assessment of the patient's risks for morbidity, including major bleeding and mortality, and initiation of treatment (Fig. 82.1).

Pulmonary Embolism Suspected in a Patient With Hypotension, Shock, or Cardiac Arrest

Patients who present with undifferentiated hypotension, shock, or cardiopulmonary arrest are especially challenging (Fig. 82.2). They are often too unstable to transport for imaging studies, and clinicians must use point-of-care tests. Bedside ultrasonography is useful to detect acute RV failure (see Video 24.9), PE in the main pulmonary arteries, PE in transit (Fig. 82.3, Video 81.3), or DVT. However, bedside ultrasonography has limitations. RV free wall hypokinesis with relatively normal contraction of the RV apex (McConnell's sign) is not entirely sensitive or specific for acute PE,[74-82] transesophageal echocardiography can detect only large PE in proximal pulmonary arteries, PE in transit is rarely identified,[83-87] and lower extremity compression ultrasonography detects DVT in less than 50% of patients with acute PE.[88-91] (See Videos 82.1 and 81.2 for McConnell's sign.) These limitations of bedside testing sometimes force clinicians to treat patients with undifferentiated shock or cardiopulmonary arrest for suspected PE without diagnostic confirmation.[92]

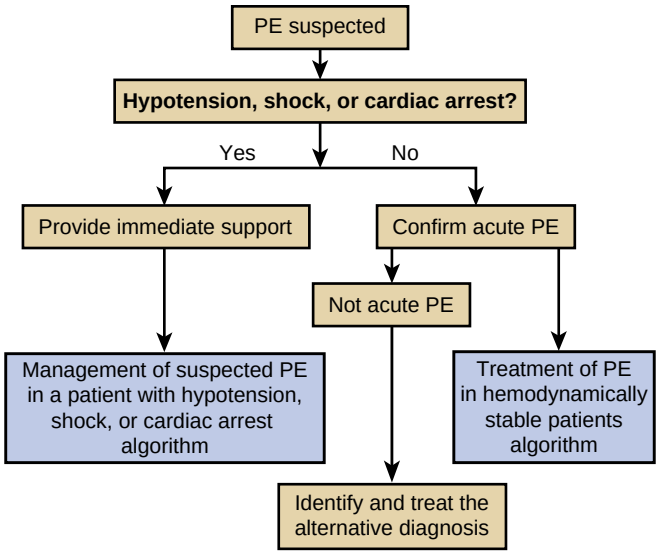

Figure 82.1 The initial management of a patient with symptoms or signs suggesting acute pulmonary embolism. Decision making involves coordination of diagnostic testing, assessment of the patient's risks for morbidity, mortality, and risk for major bleeding, and initiation of treatment. Patients presenting with hypotension, shock, or cardiac arrest require immediate supportive care (see Fig. 82.2), whereas hemodynamically stable patients require prompt confirmation or exclusion of *pulmonary embolism* (PE) combined with judicious initiation of therapy based on individual patient characteristics (see Figure 82.4).

Patients with hypotension, shock, or cardiopulmonary arrest require immediate respiratory and cardiovascular support. Oxygen is essential to reverse arterial hypoxemia, which contributes to RV ischemia, and to reverse hypoxic pulmonary vasoconstriction of pulmonary arterioles. Positive airway pressure is useful to treat intrapulmonary shunting caused by pulmonary edema or alveolar collapse, but positive airway pressure may worsen intracardiac shunting through a patent foramen ovale by increasing pulmonary vascular resistance.[93]

Most experienced clinicians avoid endotracheal intubation, if possible, because narcotics or sedatives depress cardiac function and reduce systemic vascular resistance, thereby leading to hypotension and hemodynamic collapse.[94] Continuous positive airway pressure may allow treatment of arterial hypoxemia without intubation.[95] However, intubation may be necessary when arterial hypoxemia resulting from pulmonary edema and/or pulmonary hemorrhage cannot be reversed by noninvasive means. Care must be taken to avoid hemodynamic instability during tracheal intubation by using anesthetic agents such as etomidate that do not inhibit sympathetic tone or depress myocardial function.

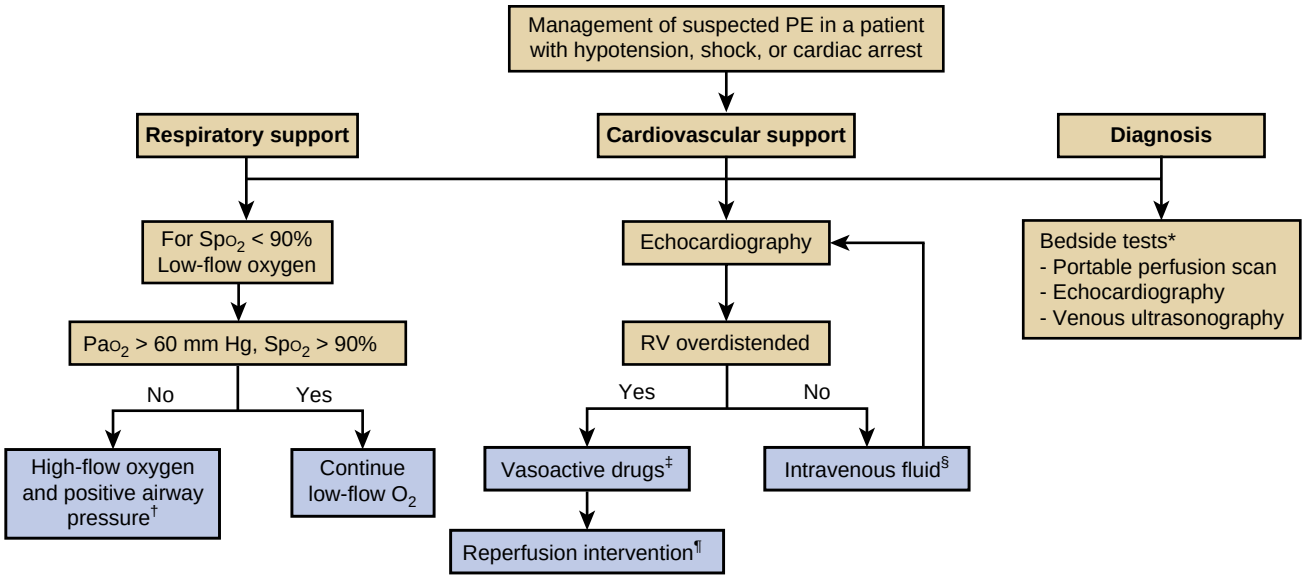

Figure 82.2 Management of a patient with suspected pulmonary embolism and hypotension. Hypotension (defined by systolic blood pressure < 90 mm Hg), shock, and cardiac arrest represent a life-threatening spectrum of hemodynamic compromise, and these conditions often limit diagnostic options. At times, thrombolysis must be tried even though the diagnosis of *pulmonary embolism* (PE) is unproven. *A bedside echocardiogram can support the diagnosis of acute pulmonary embolism (e.g., McConnell's sign) or can provide another diagnosis (e.g., pericardial tamponade), and venous ultrasonography can show deep venous thrombosis. ¶Reperfusion interventions include thrombolysis, surgical embolectomy, and catheter-based treatment. The choice of reperfusion strategy depends on patient-related factors (e.g., bleeding risk and hemodynamic stability) and the institutional resources that can be mobilized (e.g., cardiovascular surgical team). †Suspect right-to-left shunting of venous blood when low-flow oxygen is insufficient. Provide high-flow oxygen. Assess the location of shunting (e.g., atelectasis and/or shunt through the foramen ovale). Provide positive airway pressure with mask ventilation and avoid intubation, if possible, for intrapulmonary shunt, and monitor and manage adverse effects of positive airway pressure on cardiac output. ‡A list of vasoactive drugs is provided in Table 82.2 and is discussed in the text. §Intravenous fluids should be titrated carefully to avoid overdistention of the right ventricle (RV). Pao_2, arterial partial pressure of oxygen; Spo_2, oxygen saturation as measured by pulse oximetry.

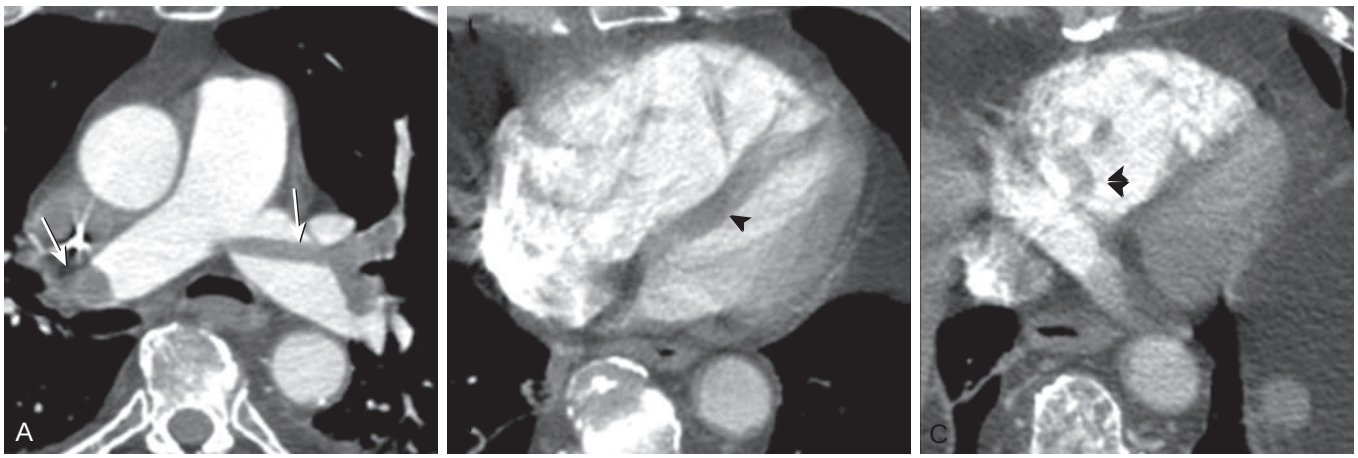

Figure 82.3 Pulmonary embolism in transit. Acute pulmonary embolism with right ventricular embolus and right ventricular strain is seen on computed tomography pulmonary angiography. (A) Imaging through the main pulmonary arterial bifurcation shows a saddle pulmonary embolism (*arrows*). (B) At the level of the tricuspid valve, right ventricular enlargement with leftward bowing of the ventricular septum (*arrowhead*), consistent with elevated right heart pressures, is noted. (C) At the caudal margin of the tricuspid valve and inferior right ventricle, a linear filling defect (*double arrowhead*) is present, representing emboli caught on the papillary muscle and chordae tendineae of the right ventricle. (Courtesy Michael B. Gotway, MD.)

Cardiovascular support involves the judicious administration of intravenous fluids with or without vasoactive agents.[96] The goal of intravenous fluid administration is optimal RV preload to support perfusion of critical organs. Intravenous fluids can improve hemodynamics in patients with acute PE.[97] However, excessive fluid administration may increase RV end-diastolic pressure and, in the setting of low systemic blood pressure, may reduce coronary artery blood flow to the right ventricle. Excessive intravenous fluid also may increase RV wall stress and exacerbate ischemia.[98] A direct comparison of intravenous fluid administration with norepinephrine in an animal model of acute PE demonstrated that even small volumes of intravenous fluid caused RV dysfunction, whereas norepinephrine improved cardiac output.[99,100] Given the physiologic differences of individual patients, administration of intravenous fluids with or without vasoactive agents requires careful monitoring and assessment of each patient's response. Echocardiographic measurement of the ratio of RV to left ventricular end-diastolic axial diameter

Table 82.2 Vasoactive Medications Used to Support Patients With Pulmonary Embolism

Vasoactive Drug	Mechanism	Clinical Effects
Epinephrine	Stimulates α_1, β_1, and β_2 receptors	Increases myocardial contractility and CO
Norepinephrine	Stimulates α_1 and β_1 receptors	Increases myocardial contractility, CO, and coronary flow; use for hypotension to increase coronary flow to RV; high doses may increase PVR
Phenylephrine	Stimulates α_1 receptors	Increases SVR
Dobutamine	Stimulates β_1 receptors	Increases myocardial contractility and CO; increases HR
Dopamine (low dose)	Dopaminergic	Increases myocardial contractility and CO; caution: increases CO and worsens V/Q
Dopamine (high dose)		Increases SVR
Isoproterenol	Stimulates β_1 and β_2 receptors	Increases CO and decreases SVR
Nitric oxide	Vasodilates pulmonary arterioles	Decreases PVR
Milrinone	PDE3 inhibitor	Increases myocardial contractility; decreases SVR
Vasopressin	Stimulates V_1 receptors	Increases SVR; dilates coronary, pulmonary, and cerebral arteries
Levosimendan	Calcium sensitizer	Increases myocardial contractility (no clinical trial data)

CO, cardiac output; HR, heart rate; PDE, phosphodiesterase; PVR, pulmonary vascular resistance; RV, right ventricle; SVR, systemic vascular resistance; V/Q, ventilation-perfusion.

may guide intravenous fluid administration until the ratio is greater than 1.0, whereupon inotropic support replaces fluid administration.[96]

The initial management of shock or cardiac arrest may also require the use of vasoactive medications. Vasopressors differ in their effects on RV function, heart rate, and pulmonary and systemic vascular resistance (Table 82.2).[101] In the absence of well-designed clinical trials, approaches to the choice and dosing of vasopressors differ, with some authors favoring norepinephrine,[102] others favoring dobutamine or dopamine,[94,98] and others advising norepinephrine for hypotensive patients and dobutamine for normotensive patients who have a reduced cardiac index.[103] Assessment of the hemodynamic response to the initial vasoactive medication is essential, so that alternatives can be initiated if blood pressure and perfusion of critical organs are not restored promptly.

The role of thrombolytic therapy for undifferentiated shock or cardiac arrest remains controversial. A randomized double-blind trial of thrombolysis during resuscitation for out-of-hospital cardiac arrest reported no difference in survival at 30 days.[104] However, clinicians have described bolus thrombolysis leading to successful resuscitation of patients with a high pretest probability of PE.[92] These observations suggest that clinicians should avoid thrombolysis for witnessed out-of-hospital cardiac arrest, but they should consider bolus thrombolysis when patients with a high probability for acute PE have cardiopulmonary arrest before diagnostic testing can be completed.

Pulmonary Embolism Suspected in a Patient Without Hypotension, Shock, or Cardiac Arrest

Confirmation of acute PE with specific diagnostic tests is necessary because the clinical manifestations of acute PE are nonspecific, and anticoagulant or thrombolytic therapy increases the risk for major bleeding.[70,71] Computed tomography pulmonary angiography is the preferred imaging modality to confirm PE and to differentiate acute PE from less common abnormalities such as chronic thromboembolic disease and pulmonary artery sarcoma.[72] Correct diagnosis avoids therapeutic misadventures such as the use of thrombolytic therapy to treat these other entities.

When there are no contraindications to anticoagulation, experts recommend initiation of antithrombotic therapy before diagnostic confirmation of PE on the basis of the pretest probability of PE and the time needed to complete diagnostic tests.[73] Specific recommendations for preemptive anticoagulation in this setting include (1) anticoagulation in patients with a high pretest probability of PE before diagnostic testing, (2) anticoagulation in patients with an intermediate pretest probability of PE before tests anticipated to take more than 4 hours to complete, and (3) anticoagulation in patients with a low pretest probability of PE before tests anticipated to take more than 24 hours to complete.

Preemptive anticoagulation reduces delays in treating PE and decreases the risk for recurrent PE. However, preemptive anticoagulation introduces the risk of anticoagulant-induced harm in patients without PE, and it does not address management of patients with either a high risk of bleeding or a contraindication to anticoagulants when delays in completion of diagnostic tests are anticipated. These issues can be addressed by ensuring timely assessment and confirmation of PE in hemodynamically stable patients before initiating treatment.

INITIAL MANAGEMENT OF CONFIRMED PULMONARY EMBOLISM

The initial management of patients with confirmed acute PE requires a clear understanding of the rationale for treatment and evidence basis for management decisions (Fig. 82.4). Treatment is directed at clinically important end points, including death from PE, prevention of recurrent VTE, and avoidance of major or clinically relevant bleeding, rather than intermediate end points such as reversing arterial hypoxemia. Rigorous clinical trials provide the foundation for most management decisions.

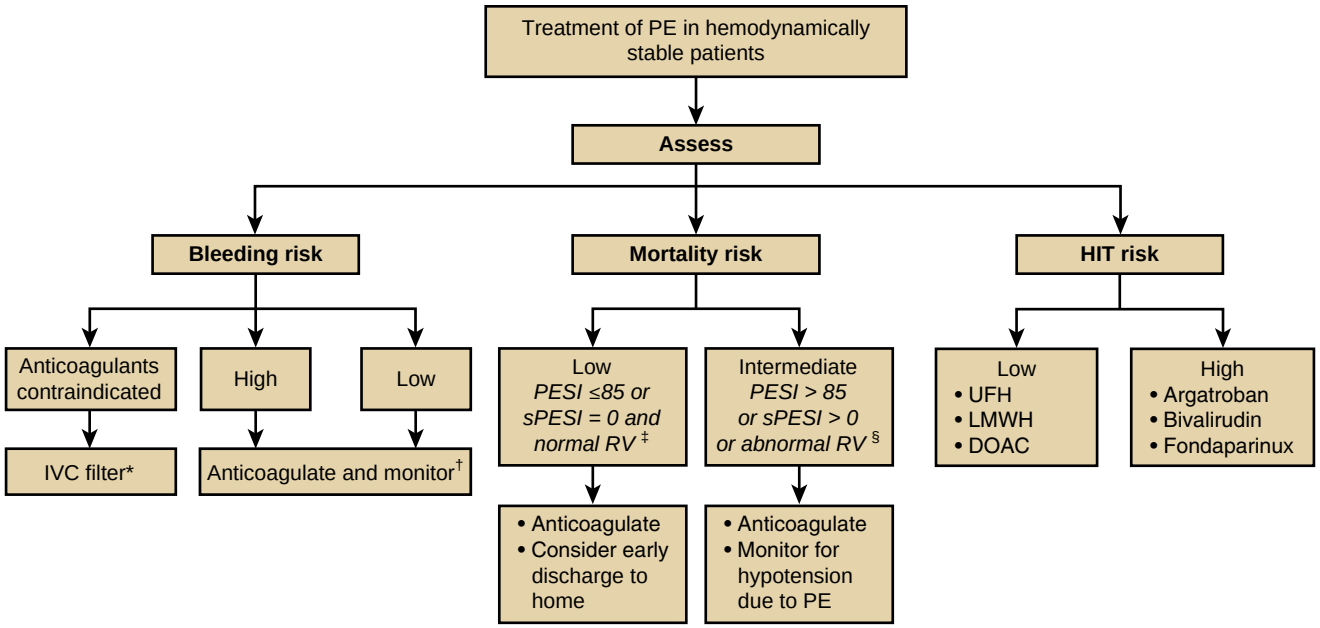

Figure 82.4 Treatment of *pulmonary embolism* (PE) in hemodynamically stable patients. Decisions require assessment of bleeding risk, mortality risk, and risk of *heparin-induced thrombocytopenia* (HIT). *Consider echocardiography to rule out pulmonary embolism in transit (if not already done) before *inferior vena cava* (IVC) filter placement. †See Tables 82.4 and 82.7 for assessment of bleeding risk and recommendations for anticoagulation in patients at high risk for major bleeding. ‡No abnormality of the *right ventricle* (RV) is detected on initial diagnostic testing (e.g., computed tomography pulmonary angiography, echocardiography, troponin). §Obtain an echocardiogram and biomarker test (e.g., troponin or natriuretic peptides) if not done previously. DOAC, direct oral anticoagulant; LMWH, low-molecular-weight heparin; PESI, pulmonary embolism severity index; sPESI, simplified PESI; UFH, unfractionated heparin.

Table 82.3 Simplified Pulmonary Embolism Severity Index (sPESI)[105]*

Variable	Score
Age > 80 yr	1
History of cancer	1
Chronic cardiopulmonary disease	1
Pulse ≥ 110 beats/min	1
Systolic blood pressure < 100 mm Hg	1
Arterial oxygen saturation < 90%	1

*If no variable is met, the mortality risk is considered low. Any score of 1 or more indicates high risk.

Assessment of Pulmonary Embolism Mortality Risk

Assessment of the risk of death from PE is an essential initial step in the management of patients with confirmed acute PE. The risk of death from PE is high for patients who present with hypotension or shock. Death from PE is rare when hemodynamically stable patients with PE receive appropriate therapy.[46] Many patients with PE have advanced comorbidities such as metastatic cancer or severe heart failure, and most deaths within 12 months of acute PE result from these comorbid conditions rather than from PE.[46] Recognition of comorbid conditions with a poor prognosis often negates aggressive intervention to prevent death from PE. In the absence of terminal comorbidities, several algorithms exist to guide management on the basis of the risk of death from acute PE.[103]

Prognostic models offer validated methods to assess mortality risk and guide management. The *pulmonary embolism severity index* (PESI) provides a score to predict 30-day mortality for patients with acute PE who do not present with hypotension or shock. In 2010, investigators reported a simplified version of the original PESI score (sPESI) to facilitate the use of a risk score in clinical practice (Table 82.3).[105] sPESI uses six variables instead of the 11 variables of the original PESI score, with each variable receiving a binary score of 0 or 1, which are then summed for a total score ranging from 0 to 6. An sPESI of 0 combined with a sensitive troponin assay maintains high accuracy in identifying PE patients with a low 30-day mortality risk.[106] Any score of 1 or more indicates high 30-day mortality risk.

Rarely patients with an sPESI score of 0 may have features of increased mortality risk such as the ratio of RV to left ventricular axial diameters greater than 1.0 on computed tomography pulmonary angiography, elevated troponin, or echocardiographic evidence of RV dysfunction on studies done as part of their initial evaluation. Such patients warrant additional testing (e.g., echocardiography and biomarker levels), if not already performed, which may support reclassification to an intermediate mortality risk.

Hemodynamic effects of acute PE, not the appearance of the emboli on imaging studies, are the best predictors of PE mortality.[98] Most algorithms propose that clinicians use systolic blood pressure to differentiate patients with a high risk of death from PE (hypotension defined by systolic blood pressure lower than 90 mm Hg for 15 minutes or longer or a drop of 40 mm Hg or more with end-organ hypoperfusion) from patients with a low risk of death from PE.[98,107] In contrast, the appearance of PE on imaging studies does not predict mortality. For example, most patients who present with "saddle emboli" are hemodynamically stable, and

they usually recover when treated with anticoagulants alone.[108]

An important subpopulation of patients with PE but without hypotension requires special attention because their risk of death from PE falls into an intermediate category (i.e., neither high nor low). These patients have systolic blood pressure higher than 90 mm Hg and evidence of acute RV strain on echocardiography with or without elevated cardiac troponin or natriuretic peptide levels, and they may decompensate abruptly. In the *Pulmonary Embolism International Thrombolysis* (PEITHO) study, 28 of 499 (5.6%) patients with RV strain detected on echocardiography and elevated troponin levels either died or became hypotensive during the first week of treatment.[107] For this reason, patients with RV strain with or without elevated troponin levels require monitoring to detect and treat hypotension resulting from RV failure.[107,109]

Assessment of Bleeding Risk

Assessment of risk for major bleeding in a patient with PE represents another critical step before administration of an anticoagulant or thrombolytic medication. Absolute contraindications to anticoagulants (Table 82.4) and to thrombolytics (Table 82.5) are established when the risk for major bleeding exceeds the benefit of these therapies. In the absence of absolute contraindications, the bleeding risk of anticoagulant or thrombolytic therapy can be estimated from observations reported from pivotal clinical trials.[107,110] Such estimates of the risk for major bleeding may be subject to adjustment on the basis of individual patient characteristics. Additional risk factors include (1) advanced age (>75 years); (2) previous bleeding (if not associated with a reversible cause) or anemia, (3) active cancer, (4) previous stroke, (5) chronic liver or kidney disease, (6) use of antiplatelet or nonsteroidal anti-inflammatory drugs, (7) other serious acute or chronic illness, and (8) poor anticoagulation control. Furthermore, clinicians sometimes must make difficult decisions because the expected benefits of anticoagulation or thrombolysis do not clearly exceed the risk of major bleeding.

Some experienced clinicians choose to give low-dose UFH intravenously without a bolus, although this approach remains unproven. This approach engenders the risk of recurrent VTE because it takes longer to achieve a therapeutic anticoagulant effect. Other clinicians recommend the incorporation of the patient's values into treatment decisions when the risks of major bleeding and recurrent thromboembolism are comparable.[73]

Table 82.4 Contraindications to Anticoagulation

Absolute*	Relative†
Difficult to control active bleeding	Intracranial or intraspinal tumor
Platelet count < 25,000/mL	Aortic dissection
Intracranial bleeding in the last 30 days	Active gastrointestinal bleeding in the last 7 days
	Platelet count < 50,000/mL
	Major surgery‡

*Do not give anticoagulants if any absolute contraindications are present.
†Anticoagulation is strongly discouraged in the presence of relative contraindication(s), but clinicians can assess risk, benefits, and individual patient preferences when they make shared decisions with patients in these difficult circumstances.
‡Major surgery represents a relative contraindication based on the location of the surgery, the time elapsed since the surgical procedure, the degree of hemostasis achieved, and the risk posed by bleeding.

Table 82.5 Contraindications to Thrombolysis

Absolute	Relative
Prior intracranial hemorrhage	History of chronic, severe, poorly controlled hypertension
Structural cerebrovascular lesion	History of ischemic stroke more than 3 mo previously
Known intracranial neoplasm	Traumatic or prolonged (>10 min) cardiopulmonary resuscitation
Ischemic stroke within 3 mo	Major surgery in the past 3 wk
Suspected arterial dissection	Major bleeding in the past 4 wk
Active bleeding or bleeding diathesis	Noncompressible vascular puncture
Significant head trauma within 3 mo	Recent invasive procedure
	Pregnancy or first week postpartum
	Active peptic ulcer
	Pericarditis or pericardial fluid
	Current use of an anticoagulant
	Age > 75 yr
	Diabetic retinopathy

Assessment of Risk for Heparin-Induced Thrombocytopenia

Assessment of the risk for HIT is also necessary before treatment with UFH or an LMWH. Strong risk factors for HIT include the duration of heparin therapy (>5 days), the heparin product (UFH > LMWH > fondaparinux), the clinical setting (surgical and trauma patients at highest risk), and the patient's sex (female > male). A past history of HIT with thrombosis contraindicates initiation of UFH or an LMWH, and it provides justification for anticoagulation with argatroban, bivalirudin, or fondaparinux.[111] Guideline authors recommend intravenous argatroban to treat VTE in patients with HIT and renal insufficiency. Limited evidence suggests that DOACs such as rivaroxaban and apixaban are effective and safe options for treating HIT in selected patients with HIT-induced thrombosis.[112]

Assessment to Determine the Site of Pulmonary Embolism Treatment

Before 2011, hospitalization for the treatment of acute PE was recommended routinely,[113] although randomized clinical trials, completed in 1996, demonstrated that selected patients with symptomatic proximal DVT could be managed safely without a long hospitalization.[114-116] More recent evidence suggests that selected low-risk patients with acute PE can be managed safely with early hospital discharge or without hospitalization.[117-121] However, a Cochrane Database systematic review concluded that only low-quality evidence was available from two published randomized controlled trials on outpatient versus inpatient management of low-risk patients with PE.[122] For this reason, guideline algorithms recommend that clinicians consider early discharge or outpatient treatment for carefully selected patients on the basis of risks (e.g., mortality,

recurrent thromboembolism, bleeding) as well as individual patients' circumstances (e.g., home environment, access to health care, need for pain control). Current algorithms suggest the use of validated risk assessment scores such as the PESI or sPESI score.[103] The Hestia criteria integrate PE severity, comorbidities, and the feasibility of home treatment. If the answer to even one questions is "yes," then the patient cannot be discharged early. In a single-arm management trial that used these criteria to select candidates for home treatment, the 3-month rate of recurrent VTE was 2.0% (0.8–4.3%) in patients with acute PE who were discharged within 24 hours.[120]

Hospitalization remains necessary for most patients with PE. When feasible, tertiary care settings with specialized resources are chosen for patients with an intermediate or high risk for morbidity and mortality from PE or its treatment. Many of these patients require admission to monitored settings with rapid access to reperfusion strategies such as thrombolysis or pulmonary embolectomy.

Telemedicine and Pulmonary Embolism Response Teams

Health care delivery continues to evolve rapidly. The emergence of telemedicine may allow selected patients with PE to receive inpatient monitoring and treatment without immediate transfer to a tertiary care facility.[123] In some institutions, PE response teams direct the initial management of patients with acute PE.[124] PE response teams can offer rapid access to multidisciplinary expertise and skills necessary for a comprehensive assessment of the patient, followed by implementation of a decisive treatment plan.

Initial Treatment of the Patient With Confirmed Pulmonary Embolism and Hypotension, Shock, or Cardiac Arrest

Patients with PE and hypotension, shock, or cardiac arrest require immediate hemodynamic and respiratory support (see Fig. 82.2), combined with treatment to relieve obstruction of the pulmonary arteries.[103] Current reperfusion strategies include thrombolysis and embolectomy.

Systemic Thrombolysis. Systemic thrombolysis is indicated for patients with hypotension, shock, or cardiac arrest resulting from acute PE, provided there is not an absolute contraindication (see Table 82.5). Patients who have stabilized after hypotension require careful monitoring, but previous hypotension, in and of itself, is not an indication for systemic thrombolysis.[109]

Thrombolytic agents lyse thromboemboli more rapidly than endogenous fibrinolysis accompanied by anticoagulation.[125-136] In the setting of life-threatening acute PE, accelerated clot dissolution provided by systemic thrombolysis may be lifesaving,[137] and it justifies the increased risk for major bleeding, especially intracranial hemorrhage, associated with systemic thrombolysis. Current evidence-based guidelines recommend peripheral infusion of 100 mg recombinant tissue plasminogen activator over 2 hours for hypotensive patients and a bolus infusion (0.6 mg/kg up to a maximum of 50 mg recombinant tissue plasminogen activator over 15 minutes) for patients with imminent or full cardiac arrest caused by acute PE.[126,131,134,138]

In contrast, decisions about systemic thrombolysis for patients with acute PE who have an intermediate mortality risk are among the most difficult that a clinician must make. The potential benefit of systemic thrombolysis for normotensive patients with an intermediate mortality risk may not outweigh the risk of intracranial hemorrhage when compared with anticoagulation alone. The PEITHO study randomly assigned 1006 normotensive PE patients with RV dysfunction and myocardial injury to treatment with tenecteplase and heparin or placebo and heparin.[107] Although tenecteplase reduced the primary end point of hemodynamic collapse within 7 days of randomization (2.6% tenecteplase vs. 5.6% placebo), tenecteplase increased the rate of intracranial bleeding (2.0% tenecteplase vs. 0.2% placebo). The all-cause 7-day mortality was low (1.2% tenecteplase vs. 1.8% placebo), and systemic thrombolysis did not alter long-term survival, RV dysfunction on echocardiography, or persistent dyspnea.[139]

Results from PEITHO suggest that patients who meet PEITHO criteria (i.e., patients with PE who are normotensive with RV dysfunction on echocardiography and biochemical evidence of myocardial injury) benefit most from initial anticoagulation with UFH and careful monitoring for hypotension from PE as an indication for systemic thrombolysis, rather than immediate thrombolysis, and this is our recommendation for treating these patients. The PEITHO study also clearly demonstrated the need for new approaches to reduce major bleeding associated with systemic thrombolysis.

Low-Dose Thrombolysis. Low-dose thrombolysis represents an approach to maintain efficacy and reduce the rate of major bleeding complications observed with full-dose thrombolytic regimens when treating life-threatening PE.[134,140] A 2018 retrospective analysis compared propensity score-matched PE cohorts treated with half-dose alteplase with those treated with full-dose alteplase and found no difference in hospital mortality, cerebral hemorrhage, or other major bleeding.[141] Without additional data from well-designed clinical trials, low-dose thrombolysis remains unproven for the treatment of life-threatening PE.

Catheter-Directed Therapies. Catheter-directed therapies aim to establish reperfusion in the setting of life-threatening PE while avoiding the major bleeding complications of systemic thrombolysis. Patients with hypotension from PE and absolute contraindications to thrombolysis may be treated with pigtail or balloon-tipped catheters to fragment PEs or aspiration catheters to suction PEs.

Catheter embolectomy provides an alternative treatment when thrombolysis is contraindicated, unavailable, or has already failed in patients with hypotension, shock, or cardiac arrest from acute PE. This approach also avoids the risks of surgery for patients unlikely to tolerate surgical embolectomy. Investigators have reported several catheter embolectomy techniques.[98,142-149] No randomized controlled trial has compared systemic thrombolysis with catheter-directed thrombolysis, and we do not have comparative data about the choice of catheters, adjunctive thrombolysis, and anticoagulation management in these patients. Thus, this therapy relies on available expertise and

Table 82.6 Trials of Ultrasound-Assisted Catheter-Directed Thrombolysis for Acute Pulmonary Embolism

Reference	Trial	N	Method/Result	Safety
Kucher et al.[185]	ULTIMA	59	RCT in which CDT compared with systemic anticoagulation reduced RV/LV at 24 hr more than UFH alone	0 ICH
Piazza et al.[186]	SEATTLE II	150	Single-arm cohort study finding that USCDT reduced RV/LV at 48 hr	0 ICH
Kuo et al.[187]	PERFECT	54	Registry study finding that MT with CDT reduced PA pressure	1 ICH
Engelberger et al.[188]		52	Retrospective study finding that USCDT reduced mean PA pressure	0 ICH
Tapson et al.[189]	OPTALYSE	101	RCT comparing 4 USCDT regimens in which USCDT reduced RV/LV at 48 hr, but with 1 ICH	1 ICH

CDT, catheter-directed thrombolysis; ICH, intracranial hemorrhage; LV, left ventricle; MT, mechanical thrombectomy; PA, pulmonary artery; RCT, randomized clinical trial; RV, right ventricle; UFH, unfractionated heparin; USCDT, ultrasound-assisted catheter-directed thrombolysis.

resources. However, experts recommend (1) discontinuation of catheter embolectomy once hypotension is reversed and (2) removal of clot only in the main or lobar pulmonary arteries to minimize the risk of perforation or dissection of pulmonary arteries.[98]

In the absence of absolute contraindications to thrombolysis, investigators have attempted direct infusions of thrombolytic drugs into the pulmonary artery or the combination of mechanical fragmentation of PE with local infusion of thrombolytic drugs to improve the benefit of thrombolysis and reduce the risk of major bleeding. In 1988, a randomized clinical trial demonstrated no difference in PE outcomes between a direct infusion of recombinant tissue plasminogen activator into the pulmonary artery and intravenous recombinant tissue plasminogen activator.[150] More recently, investigators have reported experiences with ultrasound-assisted catheter-directed thrombolysis, but all main results are physiologic or anatomic rather than patient-centered outcomes (Table 82.6).

For now, the relative safety and efficacy of all catheter-directed therapies remain to be demonstrated in well-designed clinical trials. However, these approaches deserve consideration for patients with life-threating acute PE who are not candidates for systemic thrombolysis or surgical embolectomy.

Surgical Embolectomy. Surgical embolectomy is an option for patients with hypotension, shock, or cardiac arrest resulting from acute PE who are not candidates for thrombolysis.[151] Embolectomy may also be best for selected patients with mobile intracardiac thrombi when thrombolysis is contraindicated or unsuccessful or when thrombolysis poses a greater risk to the patient than surgical embolectomy.

Reports describe variable survival following surgical embolectomy.[152-155] Patient selection likely accounts for much of the variation in surgical outcomes, although surgical techniques such as limiting extraction to visible clot without blind instrumentation and avoidance of fibrillatory arrest, cardioplegia, and aortic cross-clamping may also contribute to improved survival.[98]

Extracorporeal Membrane Oxygenation or Percutaneous Right Ventricular Assist. Extracorporeal membrane oxygenation and percutaneous RV assist have been reported as life-sustaining treatments that may lead to good outcomes in patients with PE refractory to other therapies.[151,156] Extracorporeal membrane oxygenation has primarily been used in the setting of near cardiac arrest and prolonged hypotension despite volume infusion, vasopressor, and inotropic therapy. The same is true of RV assist (e.g., with Impella PR, a percutaneous microaxial pump providing temporary hemodynamic support).[156] Both extracorporeal membrane oxygenation and percutaneous RV assist require relatively large-bore vascular access by experienced staff. Major hemorrhage is a risk for both extracorporeal membrane oxygenation and percutaneous RV assist but, in settings where they are already used for cardiogenic failure and/or overwhelming respiratory failure, the expertise may exist to deploy such techniques in otherwise treatment-refractory patients.

Initial Treatment of the Patient With Confirmed Pulmonary Embolism Without Hypotension, Shock, or Cardiac Arrest

Anticoagulation. Anticoagulants provide effective initial (day 1 to day 7), long-term (day 7 to 3 months), and extended (beyond 3 months) treatment of PE. The choice of anticoagulant and the anticoagulant dose should match the more intense thrombotic state during the early stages and reductions in the thrombotic state during the long-term and extended stages of treatment. Additional individual patient-related factors also influence the choice of anticoagulants.

In the absence of contraindications, prompt administration of therapeutic doses of an anticoagulant regimen with proven efficacy is indicated. UFH, LMWH, fondaparinux, and direct inhibitors of factor Xa or thrombin are effective.[157,158] Clinical trials have demonstrated the efficacy and safety of these anticoagulants.[159] The choice of anticoagulant and dose often reflects specific clinical circumstances (Table 82.7). For example, UFH is preferable to factor Xa inhibitors for patients with PE who are at increased risk for PE mortality and who may therefore need thrombolysis or embolectomy. UFH also is preferable for patients with renal failure. Other examples include the following: the use of LMWH in patients with liver disease and coagulopathy, in whom oral anticoagulants are contraindicated; avoidance of dabigatran in patients with coronary artery disease, gastrointestinal bleeding, and/or dyspepsia;

Table 82.7 Anticoagulant Treatments for Acute Pulmonary Embolism

Clinical	Initial*	Long-Term*	Extended*
Unstable	UFH† (5+ days)	DOAC or warfarin‡	DOAC or warfarin‡
High risk for bleed§	UFH† (5+ days)	DOAC or warfarin‡	DOAC or warfarin‡
Stable, cancer	Dalteparin 200 IU/kg/day‖ (1 mo)	Dalteparin 150 IU/kg/day	Dalteparin 150 IU/kg/day
Stable, cancer	Enoxaparin 1 mg/kg/bid‖	Enoxaparin 1 mg/kg/bid	Enoxaparin 1 mg/kg/bid
Stable, cancer	Enoxaparin 1 mg/kg bid (7 days)	Edoxaban 60 mg/day¶	Edoxaban 60 mg/day¶
Stable, no cancer	Apixaban 10 mg bid (7 days)	Apixaban 5 mg bid	Apixaban 2.5 mg bid
Stable, no cancer	Rivaroxaban 15 mg bid (21 days)	Rivaroxaban 20 mg qd	Rivaroxaban 20 mg qd
Stable, no cancer	Enoxaparin 1 mg/kg bid (5–7 days)	Dabigatran 150 mg bid	Dabigatran 150 mg bid

*Initial anticoagulant period from day 1 to day 5 to 7 of treatment, followed by long-term anticoagulation from day 5 to 7 to 3 months, with anticoagulation extended beyond 3 months when the risk of recurrent PE exceeds the risk of major bleeding.
†UFH dosed according to a standardized protocol[164]; monitor for HIT.
‡If oral vitamin K antagonist (e.g., warfarin) treatment is planned, begin with 4 to 5 mg once daily and transition entirely to warfarin after all the following criteria are satisfied: (1) at least 5 days of UFH or LMWH; (2) INR > 2.0 for two determinations; (3) PE symptoms and PE-related hypoxemia significantly improved, then monitor INR; and (4) adjust dose to maintain INR in range of 2.0 to 3.0.
§High risk for bleeding as defined by Kearon and colleagues.[73] Some experts advise intravenous UFH 400 U/hr without a bolus and observe for bleeding/hemostasis. After 6 hours with hemostasis, increase to 600 U/hr with continued observation. Keep aPTT < 50 seconds and anti–factor Xa level < 0.5 U/mL. If hemostasis is maintained, then slowly increase UFH dose over 24 hours to 800 U/hr.
‖LMWHs accumulate with renal dysfunction. Titrate doses to produce anti–factor Xa levels of 0.4 to 0.85 U/mL and monitor for HIT.
¶Edoxaban 30 mg once daily for creatinine clearance 15 to 50 mL/min or body weight < 60 kg.
aPTT, activated partial thromboplastin time; bid, twice daily; DOAC, direct oral anticoagulant; HIT, heparin-induced thrombocytopenia; INR, international normalized ratio; LMWH, low-molecular-weight heparin; PE, pulmonary embolism; qd, once daily; UFH, unfractionated heparin.

and the use of an LMWH, apixaban, or edoxaban (a direct inhibitor of factor Xa) for patients with cancer.[160-162]

Unfractionated Heparin. Continuous intravenous UFH provides highly effective treatment of acute VTE.[42] However, proper dosing and monitoring of UFH are essential to prevent recurrent VTE. Approaches not based on a protocol often deliver inadequate doses of UFH.[163] Prompt initiation of continuous intravenous UFH according to dosing protocols proven to achieve a therapeutic anticoagulant effect reduces the risk of recurrent VTE dramatically. Hull and colleagues[43] reported a 15-fold increase in the rate of recurrent VTE in patients who did not have a therapeutic anticoagulant effect within 24 hours of the start of continuous intravenous UFH. A common protocol initiates therapy with an 80-unit UFH/kg bolus, followed by continuous infusion of 18 units UFH/kg/hr, with monitoring of the aPTT and subsequent UFH doses guided by protocol.[164] An aPTT higher than 1.5 times the upper limit of normal provides therapeutic anticoagulation and corresponds to 0.3 to 0.7 unit/mL measured by anti–factor Xa assay. Anti–factor Xa levels, rather than aPTT, guide UFH dose adjustment for patients with circulating lupus anticoagulants or heparin resistance (defined as a requirement for >40,000 units UFH /day).[165]

Low-Molecular-Weight Heparins. LMWHs are at least as effective and safe as UFH for the initial treatment of most patients with acute PE that is not life-threatening. However, LMWHs should not be used to treat PE in patients with unstable renal function or renal failure. Conversely, LMWHs are preferable to UFH, followed by warfarin, for patients with cancer because of improved efficacy in the prevention of recurrence with comparable safety.[160]

Fondaparinux. Fondaparinux is effective and safe to treat acute PE initially.[166] The therapeutic dose depends on the patient's weight (5 mg, 7.5 mg, and 10 mg subcutaneously daily for patients who weigh less than 50 kg, 50 to 100 kg, and more than 100 kg, respectively), and fondaparinux must be given for at least 5 days. Like LMWH, fondaparinux should be avoided in patients with renal failure.

Direct Inhibitors of Factor Xa or Thrombin. DOACs are as effective as vitamin K antagonists for long-term treatment of VTE and are associated with less frequent and less severe bleeding.[157,158] Furthermore, DOACs offer treatment without routine coagulation monitoring, rapid onset and offset of action, and few drug-drug interactions.

Rivaroxaban, a direct inhibitor of factor Xa, is FDA approved for treatment of PE at an initial dose of 15 mg twice daily for 21 days, followed by a reduced dose of 20 mg daily during the long-term and extended phase of treatment. Impaired renal or liver function may alter excretion or metabolism of rivaroxaban and is a relative contraindication to its use. Furthermore, abrupt discontinuation of rivaroxaban in patients with PE and concomitant atrial fibrillation increases the risk of stroke.

Apixaban, a direct inhibitor of factor Xa, is FDA approved for treatment of PE at an initial dose of 10 mg twice daily for 7 days, followed by 5 mg twice daily for 3 months. A dose of 2.5 mg twice daily may be used for extended anticoagulation. Apixaban, 5 mg twice daily, provides effective extended treatment for VTE in patients with advanced cancer.[162]

Edoxaban, a direct oral inhibitor of factor Xa, is FDA approved at a dose of 60 mg/day to treat PE following 5 to 10 days of a parenteral (e.g., intravenous UFH or subcutaneous LMWH) anticoagulant. A lower daily dose (30 mg) is appropriate for patients with renal failure (glomerular filtration rate, 30 to 50 mL/min) or for patients who weigh less than 60 kg. Edoxaban shares the advantage of once-daily dosing, and it can be taken without regard to food. Furthermore, extended treatment with edoxaban prevents

recurrent VTE as effectively as LMWH in patients with advanced cancer.[161]

Dabigatran, an oral direct inhibitor of thrombin, is FDA approved for treatment of PE after 5 to 10 days of a parenteral (e.g., intravenous UFH or subcutaneous LMWH) anticoagulant at a dose of 150 mg twice daily. Caution is advised in patients with concomitant atrial fibrillation because abrupt discontinuation increases the risk of stroke.

Vena Cava Filters. Current guidelines and treatment algorithms consistently recommend the insertion of vena cava filters to treat acute PE when anticoagulants are contraindicated,[73,103] on the basis of observations that suggest reduced mortality from recurrent PE.[167,168] Guideline authors also recommend against the use of IVC filters as an adjunct to anticoagulant treatment of PE accompanied by acute proximal DVT.[103,169,170]

In contrast, guidelines are inconsistent in their recommendations for vena cava filters in other circumstances. For example, the authors of an American College of Chest Physicians guideline recommend against routine use of IVC filters for hemodynamically stable patients with PE who are treated with anticoagulants, but they note that hemodynamically unstable patients with PE may benefit from combining anticoagulants and an IVC filter.[159] In contrast, the authors of the European Society of Cardiology and European Respiratory Society guideline did not recommend IVC filters in combination with anticoagulants for hemodynamically unstable patients, but they do recommend IVC filter placement for patients with objectively confirmed recurrent PE despite therapeutic anticoagulation.[103,107] These discordant viewpoints underscore the importance of integrating additional clinical factors when deciding whether to use an IVC filter in an individual patient.

Most vena cava filters are placed in the IVC below the renal veins and are rarely placed in other locations (e.g., superior vena cava or above the renal veins). Most are retrievable and should be removed after the risk of major bleeding is reduced and anticoagulants are reinstituted. Filter removal reduces the risk of vena cava syndrome (i.e., obstruction of blood flow through the vena cava) and other late complications, including obstruction or perforation of the IVC or fracture of the filter.[171] If vena cava filters are not removed, then clinical surveillance with individualized patient management is necessary.[172]

Duration of Anticoagulant Therapy. Recommendations regarding the duration of anticoagulant therapy have changed over time. There is general agreement that an acute PE requires a minimum of 3 months of full-dose anticoagulation. Estimates of the risk of major bleeding and the risk for recurrent PE are necessary to guide the decision to stop or extend anticoagulation after the first 3 months.

Estimates of the risk of major bleeding incorporate characteristics of the patient and of the anticoagulant medication. Patient-related characteristics that predict an increased risk for major bleeding include advanced age, previous major bleeding not associated with a treatable cause, active cancer, previous stroke, chronic liver or kidney disease, a requirement for antiplatelet or nonsteroidal anti-inflammatory drugs, and/or other serious illnesses (e.g., alcoholism) that increase bleeding risks. The choice of anticoagulant also may influence the risk of major bleeding. For extended treatment, DOACs may offer similar efficacy for prevention of VTE recurrence with a lower risk of major bleeding than vitamin K antagonists.[173]

Estimates of the risk of recurrent PE are derived from clinical and laboratory features of the index PE.[103] Patients with major transient or reversible risk factors for PE, such as a traumatic long bone fracture, have a very low risk (<3% per year) for recurrent PE after 3 months of anticoagulation. The risk of major bleeding during continued anticoagulation exceeds the risk for recurrent PE and justifies discontinuation of anticoagulants for such patients. Patients with a minor transient or reversible risk factor, such as prolonged air travel, or a nonmalignant persistent risk factor, such as inflammatory bowel disease, have an intermediate risk (3–8% per year) for recurrent PE that generally justifies extended anticoagulation in the absence of risks for life-threatening bleeding. In contrast, patients with major ongoing risk factors for recurrent PE, such as active cancer, previous PE without a reversible risk factor, or antiphospholipid antibody syndrome, have a high risk (>8% per year) for recurrent PE. These patients generally require indefinite anticoagulation.

Overall long-term anticoagulant therapy requires an evidence-based plan tailored to the individual patient combined with periodic reassessment of risks and benefits of anticoagulation. For example, PE in a patient with triple-positive antiphospholipid antibody syndrome (i.e., lupus anticoagulant with anticardiolipin and anti–β_2-glycoprotein antibodies) warrants indefinite anticoagulation with warfarin.

SPECIAL PROBLEMS

Isolated Subsegmental Pulmonary Embolism

The rare patient with PE isolated to subsegmental branches of the pulmonary arterial tree requires careful consideration. The natural history of isolated subsegmental PE is not well defined, and there is no evidence from well-designed clinical trials to guide the management of these patients.[159] Overdiagnosis and overtreatment of inconsequential thrombosis represent key risks to be eliminated at the outset. These considerations may lead clinicians to look for evidence of DVT in the legs or elsewhere, if appropriate. Anticoagulation is indicated when DVT is found. Guideline authors recommend anticoagulation when risk factors for recurrent VTE are present and the risk for major bleeding is low.[159] Guideline authors recommend observation without anticoagulation for patients with isolated subsegmental PE, no DVT, and a low risk for recurrent VTE. The absence of DVT on repeat lower extremity venous ultrasonography 5 to 7 days later may be used to confirm the safety of withholding anticoagulants for such patients.

Incidental Pulmonary Embolism

PEs are occasionally identified incidentally on contrast computed tomography examinations in patients with cancer. In retrospect, these patients often have a past history of VTE and nonspecific symptoms of PE such as dyspnea and fatigue.[174] Anticoagulation is indicated in the absence of contraindications.

Hemoptysis

Hemoptysis related to PE and pulmonary infarction generally does not pose an increased risk for major bleeding. However, clinicians should recognize that other serious pulmonary disorders (e.g., lung cancer or bronchiectasis) may substantially increase the risk for major, and even life-threatening, hemoptysis made worse by anticoagulation or thrombolysis. The presence of these conditions may necessitate the use of a vena cava filter if the bleeding risk is high.

Pulmonary Embolism in Transit

PE in transit through the right side of the heart is a rare, but important, clinical problem (see Fig. 82.3). Thromboemboli in transit identify a subgroup of patients with PE who are more likely to have RV dysfunction and who have an increased risk of death from venous thromboembolic disease.[84] Anticoagulation alone is insufficient because of the high risk for the embolus in transit to kill the patient. Thrombolytic therapy is often chosen in the absence of contraindications. However, embolectomy may also be chosen as the first option or as a second option if thrombolysis has failed.[175]

Paradoxical Embolism

Paradoxical embolism (i.e., VTE to systemic vascular beds) may complicate VTE (Fig. 82.5). Patients with acute PE who have a patent foramen ovale are more likely to have an acute ischemic stroke than are patients with PE but without a patent foramen ovale.[176] Similarly, paradoxical emboli may cause myocardial infarction, renal infarction, bowel infarction, or even acute occlusion of systemic arteries. Individual patient circumstances and preferences usually determine the management of paradoxical emboli.

Cancer

Patients with cancer who are treated for PE are at higher risk for recurrent VTE and major bleeding events than are patients without cancer.[177] Extended treatment with LMWH lowers the risk for recurrent VTE when compared with warfarin.[160] Furthermore, several DOACs, including edoxaban,[161] rivaroxaban,[178] and apixaban,[162] have demonstrated efficacy and safety comparable to those of LMWH for treatment of VTE complicating cancer. The DOACs avoid the discomfort, cost, and inconvenience of subcutaneous injections of LMWH, but care is required in choosing which DOAC to use for an individual patient.[179]

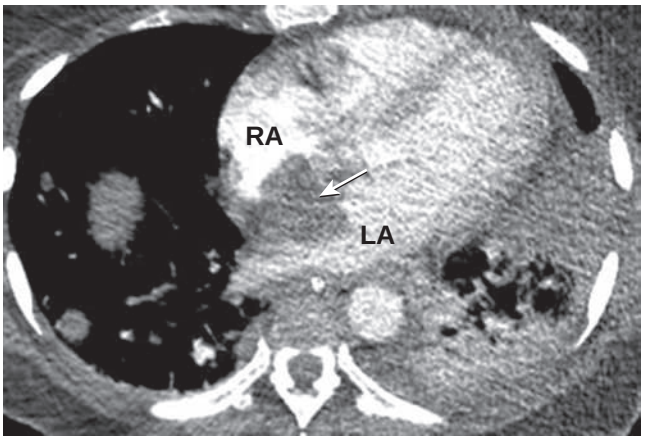

Figure 82.5 Paradoxical embolism. Axial enhanced chest computed tomography in a patient with acute pulmonary emboli shows a dumbbell-shaped filling defect (*arrow*) straddling the interatrial septum, consistent with a pulmonary embolus in transit through a patient foramen ovale. LA, left atrium; RA, right atrium. (Courtesy Michael B. Gotway, MD.)

Pregnancy

Weight-adjusted doses of LMWH are the preferred treatment for uncomplicated PE during pregnancy, provided exposure to LMWH during epidural anesthesia is avoided.[103] Pregnant women should be advised to discontinue anticoagulant therapy on the onset of spontaneous labor. If there is a planned delivery, therapeutic LMWH should be discontinued at least 24 hours before the expected time of epidural analgesia or delivery. LMWH does not cross the placenta, and LMWH is not found in breast milk.[180-183] In contrast, warfarin, fondaparinux, and DOACs are contraindicated for pregnant patients or lactating women. Warfarin causes fetal embryopathies when given in the first trimester, and fetal hemorrhages, as well as placental abruption, may complicate warfarin administration during the third trimester of pregnancy.

UFH also is effective for the treatment of uncomplicated PE during pregnancy, but UFH requires dose adjustments with frequent aPTT monitoring, and UFH also has caused osteoporosis during extended treatment of pregnant women. In pregnant patients with recent PE, many clinicians recommend that LMWH be converted to UFH more than 36 hours before delivery so that the UFH infusion can be stopped 4 to 6 hours before anticipated delivery with a normal aPTT before regional anesthesia.[184] UFH is also preferable for pregnant patients with unstable renal function or renal failure and for pregnant patients at high risk of death who may require thrombolytic therapy.

Thrombolytic agents, typically recombinant tissue plasminogen 100 mg given intravenously over 2 hours, can be given for life-threatening PE during pregnancy; but thrombolysis during the peripartum period poses significant risk for uncontrollable bleeding, and it should be reserved for critical situations.[107]

Recurrent Thromboembolism During Anticoagulant Therapy

Few data are available for this uncommon clinical circumstance. Experts advise several steps: (1) confirm new thromboembolism; (2) confirm bioavailability of the anticoagulant therapy with testing of antithrombotic effect (e.g., anti–factor Xa); (3) confirm that there is no HIT with thrombosis; and, if all three are confirmed, (4) change treatment. If a change of treatment is chosen, treat the new episode as acute, with UFH or a LMWH according to one of the regimens listed in Table 82.7 for initial treatment of PE. Then consider twice-daily subcutaneous LMWH (e.g., enoxaparin 1 mg/kg every 12 hours) for extended treatment.

Key Points

- Venous thromboembolism prophylaxis can be applied to at-risk persons nearly universally unless contraindicated, or it can be applied judiciously after risk assessment of individual patients. The former universal approach is preferred.
- Vasopressor therapy in patients in the intensive care unit reduces bioavailability of subcutaneous low-molecular-weight heparin prophylaxis, so heightened alertness for thrombosis and consideration of monitoring anti–factor Xa levels with upward titration of low-molecular-weight heparin can be considered.
- Anticoagulant prophylactic drugs other than unfractionated heparin undergo significant renal elimination, thus requiring cautious use or avoidance in patients with renal dysfunction.
- Prophylactic use of retrievable inferior vena cava filters is only rarely warranted.
- The initial management of a patient with symptoms or signs that suggest acute pulmonary embolism involves coordination of diagnostic testing, assessment of the patient's risks for morbidity and mortality, risk for major bleeding, and initiation of treatment.
- Treatment of pulmonary embolism is directed at clinically important end points, including death from pulmonary embolism, prevention of recurrent venous thromboembolism, and avoidance of major or clinically relevant bleeding, rather than intermediate end points such as reversing arterial hypoxemia.
- Hypotension, shock, or cardiopulmonary arrest requires immediate respiratory and cardiovascular support. Diagnostic efforts must necessarily await stabilization of the patient.
- Normotensive patients with pulmonary embolism who are at increased mortality risk (i.e., patients in the intermediate mortality risk group) often benefit most from initial anticoagulation with unfractionated heparin and careful monitoring for pulmonary embolism–related hypotension as an indication for systemic thrombolysis, rather than immediate thrombolysis.

Key Readings

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83 PULMONARY HYPERTENSION: GENERAL APPROACH

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INTRODUCTION

Pulmonary hypertension (PH) is a syndrome characterized by elevated pulmonary pressures. Whether acute or chronic, elevated pulmonary pressures lead to increased afterload on the right ventricle that can cause right ventricular failure and death. Of importance, there are numerous causes of elevated pulmonary pressures; thus, a standardized approach to diagnosis and proper classification are imperative to guide appropriate treatment and predict survival. This chapter presents a general approach to the patient with suspected PH and discusses the epidemiology, presenting symptoms, role of screening, diagnostic algorithm, and classification system for PH. Also reviewed is the treatment of certain forms of PH. In-depth reviews of specific forms of PH, such as pulmonary arterial hypertension, PH related to chronic lung disease, and chronic thromboembolic PH, are covered in other chapters (see Chapters 84–86).

DEFINITION OF PULMONARY HYPERTENSION

The *World Symposium on Pulmonary Hypertension* (WSPH) recommends defining PH as a *mean pulmonary artery pressure* (mPAP) greater than 20 mm Hg, measured by *right heart catheterization* (RHC).[1] PH had previously been defined as an mPAP of 25 mm Hg or greater for several decades, but the choice of 25 mm Hg had been arbitrary.[13] The justification for this cut point was based upon the belief that physicians could more easily distinguish between severe PH related to PAH and less severe PH related to underlying lung or heart disease, thus potentially avoiding overdiagnosis and overtreatment of PH.[13] A literature review published in 2009 summarizing the available RHC data from more than 1100 healthy individuals found that normal mPAP was only 14 ± 3.3 mm Hg.[4] Thus, an mPAP greater than 20 mm Hg, two standard deviations above the mean value, would be above the upper limit of normal (the 97.5th percentile) and identify an abnormal pulmonary pressure threshold in an otherwise healthy population.[2]

Mounting data support the threshold of mPAP greater than 20 mm Hg as a clinically relevant cut point. Retrospective cohort studies in specific patient populations, such as those with COPD, idiopathic pulmonary fibrosis, and scleroderma, have demonstrated worse functional status and survival for patients with mildly elevated pulmonary pressures (mPAP, 21–24 mm Hg) compared to those with normal pulmonary pressures.[3–8] Similarly, in unselected referral populations, mildly elevated PAP was associated with poorer survival compared to patients with normal PAP.[9–11] A systematic review that included more than 16,000 patients found that mild PH (defined as a mean PAP between 19 and 24 mm Hg) was associated with an increased risk of all-cause mortality (risk ratio, 1.5; 95% confidence interval, 1.3 to 1.7; $P < 0.001$) compared to the reference group with normal mPAP.[12]

However, despite these observations, it remains to be determined if mildly elevated mPAP leads to poor outcomes or is just an epiphenomenon related to an underlying comorbidity. The impact of mildly elevated pressures on symptoms and functional capacity is not well described, nor is it known whether patients with mildly elevated pressures go on to develop progressive pulmonary vascular disease. Furthermore, there are no approved therapies for patients with mildly elevated pulmonary pressures (between 21 and 24 mm Hg), which complicates the management of patients who now fulfill the new hemodynamic criteria for PH.

Table 83.1 Hemodynamic Definition of PH Based on the 6th World Symposium on Pulmonary Hypertension

Definition	mPAP	PCWP	PVR	WHO Group
Normal hemodynamics	14.0 ± 3.3 mm Hg	8.0 ± 2.9 mm Hg	0.93 ± 0.38 WU	N/A
Precapillary PH	>20 mm Hg	≤15 mm Hg	≥3 WU	1, 3, 4, 5
Isolated postcapillary PH	>20 mm Hg	>15 mm Hg	<3 WU	2 and 5
Combined precapillary and postcapillary PH	>20 mm Hg	>15 mm Hg	≥3 WU	2 and 5

mPAP, mean pulmonary artery pressure; N/A, not available; PCWP, pulmonary capillary wedge pressure; PH, pulmonary hypertension; PVR, pulmonary vascular resistance; WHO, World Health Organization. WU, Wood units.

Data from Simonneau G, Montani D, Celermajer DS, et al. Haemodynamic definitions and updated clinical classification of pulmonary hypertension. *Eur Respir J.* 2019;53(1):1801913.

The hemodynamic definition of PH was significantly revised at the 6th WSPH (Table 83.1), with the new criteria permitting better grouping of patients by the primary hemodynamic perturbation leading to their pulmonary vascular disease. The clinical classification schema underwent more minor revisions.[1] *Pulmonary arterial hypertension* (PAH) remains in group 1 of the schema and includes idiopathic PAH, which represents around half of the PAH population.[13] *Connective tissue disease* (CTD)-associated PAH accounts for about 25% of PAH. Other rare causes, such as heritable PAH, drug- and toxin-induced PAH, *human immunodeficiency virus* (HIV), portal hypertension, congenital heart disease, and schistosomiasis, along with PAH with overt venous/capillary involvement seen in pulmonary veno-occlusive disease, pulmonary capillary hemangiomatosis, and persistent PH of the newborn comprise the remainder (Table 83.2). A new category within group 1 was created to identify PAH with long-term response to *calcium channel blockers* (CCBs), given their unique clinical characteristics. Although many diseases and conditions predispose to the development of PAH, all PAH share the common histopathologic changes of arterial remodeling and inflammation, generally differentiating PAH from other categories of PH. Group 2 is characterized by elevated *pulmonary capillary wedge pressure* (PCWP) and includes patients with PH due to *left heart disease* (LHD), including heart failure with reduced ejection fraction, heart failure with preserved ejection fraction, valvular heart disease, and congenital/acquired cardiovascular conditions leading to postcapillary PH. Group 3 includes PH related to lung diseases and/or hypoxia. Group 4 includes PH related to *pulmonary artery* (PA) obstructions, whereas group 5 includes a heterogenous group of disorders with unclear and/or multifactorial mechanisms for development of PH. Specific details regarding group 2 and group 5 PH are discussed later in this chapter. Group 1, group 3, and group 4 PH are discussed elsewhere (see Chapters 84, 85 and 86, respectively).

EPIDEMIOLOGY

PH affects individuals of all ages and races. Overall, women are affected more frequently than men; the disparity appears to be most pronounced in patients with PAH.[14] Despite increased interest in the syndrome with the advent of certain directed therapies, the incidence and prevalence of PH are poorly described. In part, this is related to incomplete characterization of patients with suspected PH and limitations in the sensitivity and specificity of diagnostic codes used in administrative claims, thereby hindering epidemiologic studies.[15] Most of the data on prevalence of PH results from registries of patients with PAH, which represents the rarest form of PH; estimates for PAH prevalence range from 15 to 50 per 1 million persons.[16–19] Estimates of prevalence in other forms of PH are scant. Recent data generated from Canadian universal health care records show an increase in the prevalence of all forms of PH from 99.8 to 127.3 cases per 100,000 population between 2002 and 2012; only about 20% of the cases had PAH, whereas the majority had PH related to LHD or PH related to lung disease.[20] In a large community study using echocardiography to define PH, PH related to LHD was also found to be the most common form of PH (Fig. 83.1).[21] Extrapolating these estimates of PH to the U.S. population suggests that PH may be as common as multiple sclerosis and more than two times as common as idiopathic pulmonary fibrosis.[22] Still, given the increasing incidence of diseases known to predispose to PH, such as heart failure with preserved ejection fraction and sleep apnea, the prevalence of PH in the United States and in the world is likely to rise.[23–26]

DIAGNOSTIC APPROACH

As noted, PH commonly complicates various cardiopulmonary, vascular, and other diseases and is often associated with poorer outcomes. Given the limited treatment options for most forms of PH, diagnosis of this syndrome will guide clinical management, prompting referral to PH centers and, in some cases, consideration for lung or other organ transplantation. However, evaluation of PH is often undertaken to identify or exclude PAH (WSPH group 1 disease). PAH is distinguished from other PH groups based upon clinical characteristics, putative pathogenesis, and histologic features. PAH portends a poor prognosis, but advances in medical therapies over the past 2 decades provide therapeutic options for this devastating disease. Unfortunately, directed medical therapy does not exist for most other forms of PH other than *chronic thromboembolic PH* (CTEPH). Thus, proper classification of PH is imperative to direct proper therapy. PAH is defined both by hemodynamic criteria: mPAP of 20 mm Hg or greater, PCWP of 15 mm Hg or less, or *pulmonary vascular resistance* (PVR) of 3 or more *Wood units* (WU) and by the absence of alternative causes for elevated pulmonary pressures, including LHD, pulmonary disease, chronic thromboembolic disease, other

Table 83.2 Clinical Classification of PH Based Upon the Sixth World Symposium on Pulmonary Hypertension

GROUP 1: PAH

Idiopathic PAH
Hereditable PAH
Drug and toxin-induced PAH
PAH associated with:
- Connective tissue disease
- Human immunodeficiency virus infection
- Portal hypertension
- Congenital heart disease
- Schistosomiasis

PAH long-term responders to calcium channel blockers
PAH with overt features of venous/capillary (PVOD/PCH) involvement
Persistent PH of the newborn syndrome

GROUP 2: PH DUE TO LEFT HEART DISEASE

PH due to heart failure with preserved left ventricular ejection fraction
PH due to heart failure with reduced left ventricular ejection fraction
Valvular heart disease
Congenital/acquired cardiovascular conditions leading to postcapillary PH

GROUP 3: PH DUE TO LUNG DISEASES AND/OR HYPOXIA

Obstructive lung disease
Restrictive lung disease
Other lung disease with mixed restrictive/obstructive pattern
Hypoxia without lung disease
Developmental lung disorders

GROUP 4: PH DUE TO PULMONARY ARTERY OBSTRUCTION

Chronic thromboembolic PH
Other pulmonary artery obstructions
- Sarcoma (high- or intermediate-grade) or angiosarcoma
- Other malignant tumors
  - Renal carcinoma
  - Uterine carcinoma
  - Germ cell tumors of the testis
- Nonmalignant tumors: uterine leiomyoma

Arteritis without connective tissue disease
Congenital pulmonary artery stenoses
Parasites: hydatidosis

GROUP 5: PH WITH UNCLEAR AND/OR MULTIFACTORIAL MECHANISMS

Hematologic disorders: chronic hemolytic anemia, myeloproliferative disorders
Systemic and metabolic disorders: pulmonary Langerhans cell histiocytosis, Gaucher disease, glycogen storage disease, neurofibromatosis, sarcoidosis
Others: chronic renal failure with or without hemodialysis, fibrosing mediastinitis
Complex congenital heart disease
- Segmental pulmonary hypertension: isolated pulmonary artery of ductal origin, absent pulmonary artery, pulmonary atresia with ventricular septal defect and major aortopulmonary collateral arteries, hemitruncus, other
- Single ventricle: unoperated, operated
- Scimitar syndrome

PAH, pulmonary arterial hypertension; PCH, pulmonary capillary hemangiomatosis; PH, pulmonary hypertension; PVOD, pulmonary veno-occlusive disease.
From Simonneau G, Montani D, Celermajer DS, et al. Haemodynamic definitions and updated clinical classification of pulmonary hypertension. *Eur Respir J.* 2019;53(1):1801913.

predisposing conditions, or exposure to medications implicated in the pathogenesis of PH.[27] Thus, PAH is a diagnosis of exclusion requiring several investigations beyond an RHC to confirm (see later). Of importance, certain diseases

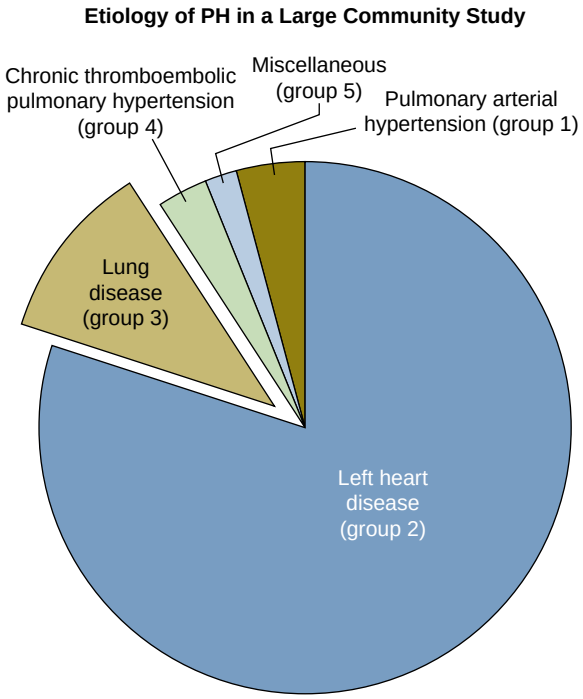

Figure 83.1 Prevalence of *pulmonary hypertension* (PH) by cause in a large community-based study. Note that left heart disease is by far the most common cause of PH, whereas chronic lung disease is the second most common cause. (Data from Strange G, Playford D, Stewart S, et al. Pulmonary hypertension: prevalence and mortality in the Armadale echocardiography cohort. *Heart.* 2012;98:1805–1811.)

and conditions predispose to the development of PAH and, as such, a detailed medical history and laboratory evaluation to evaluate for the presence of these underlying risk factors is integral to the general evaluation of PH (see also Chapter 84).

POPULATIONS AT RISK FOR PULMONARY ARTERIAL HYPERTENSION

Schistomiasis

Although rigorous epidemiologic studies including RHC-proven PAH are lacking, patients with schistosomiasis may represent the largest global population at risk of PAH, with an estimated prevalence of schistosomiasis of more than 200 million and an estimated 40 million of those at high risk of PAH. Of those with schistosomiasis, hepatosplenic involvement imparts the highest risk, with about 10–20% of these patients developing PAH; extrapolating these estimates suggests that 4 to 6 million schistosomiasis patients may have PAH.[28–30]

Scleroderma

Whereas PAH complicates many forms of CTD, it is most prevalent in patients with *systemic sclerosis* (SSc, scleroderma). Cohort studies suggest that from 5–15% of patients with SSc will develop PAH.[31–33] Of importance, SSc is the only at-risk cohort for which data exist supporting routine screening for PAH. The *Detection of PAH in SSc* (DETECT) study, a multinational cross-sectional study of patients with scleroderma, included 488 patients considered at increased risk for PAH due to duration of SSc for more than 3 years

and a predicted *diffusion capacity for carbon monoxide* (DL_{CO}) less than 60% predicted.[34] Patients with a forced vital capacity of less 40% predicted, renal insufficiency, LHD, or pregnancy were excluded. Four hundred sixty-six patients underwent RHC, which revealed PH in 31% and PAH in 19% (6% had group 2 PH based on an elevated PCWP, and 6% had group 3 PH based on greater degree of underlying interstitial lung disease). To identify factors predictive of PH, more than 100 variables, including demographic, serologic, functional, and echocardiographic measurements, were included in a stepwise manner with multivariable logistic regression models. These analyses identified eight clinical variables that, when applied in a two-step algorithm, predicted the presence of PH on RHC with a low rate (4%) of missed PAH diagnoses. Based on these findings, this algorithm has been recommended for implementation in clinical practice by the 6th WSPH statement. However, it should also be noted that implementation of the DETECT algorithm will likely increase identification of patients with mildly elevated pulmonary pressures (mPAP, 21–24 mm Hg) for whom there are no approved therapies.[36]

Other Connective Tissue Diseases

The incidence and prevalence of PAH in other forms of CTD is less well described. *Mixed connective tissue disease* (MCTD) is a CTD characterized by clinical features of several different CTDs, including SSc, *systemic lupus erythematosus* (SLE), *rheumatoid arthritis* (RA), and polymyositis. The distinguishing laboratory feature of MCTD is the presence of antibodies to *uridine-rich* (U1) *ribonuclear protein* (RNP) polypeptides.[37] Although lung disease, including *interstitial lung disease* (ILD) and PH, are commonly found in MCTD, epidemiologic studies defining the incidence and prevalence of such complications are lacking. Estimates of PAH prevalence in MCTD range from 1–50%.[32,38–40] Still, because many patients with MCTD have SSc features, expert consensus recommends yearly screening similar to that used for SSc.[41] The estimated prevalence of PAH in SLE is also poorly defined, ranging from 0.0005–14% of patients.[42–44] A multicenter study designed to determine incidence and prevalence of PH in SLE is currently ongoing and will provide important estimates of PH in this patient population.[45] RA, polymyositis, and Sjögren syndrome have lower estimated prevalence of PAH than either SSc or MCTD. Thus, routine screening for PAH in these populations is not recommended.

Other at-Risk Cohorts

Currently, there are no recommendations for routine screening for PAH in the other known at-risk populations. However, the 6th WSPH suggests that patients with HIV with high-risk features, such as female sex, intravenous drug use, cocaine use, hepatitis C virus coinfection, and known *negative regulatory factor* (Nef) or *transactivator of transcription* (Tat) HIV proteins, as well as U.S. Blacks, should undergo screening for PAH. The frequency and type of screening modalities are not specified. Patients with hereditary hemorrhagic telangiectasia should undergo screening with an echocardiogram if symptoms of dyspnea develop or if heart failure or hepatic arteriovenous malformations develop. Patients with portal hypertension should undergo screening echocardiography, given the reported prevalence of PAH of 2–6% in this population.[46,47] Although patients with congenital heart disease are at risk of PAH, only patients who have undergone surgical correction or who have persistent systemic-to-pulmonary shunts should undergo screening, because their risk of developing PAH is increased compared to other *congenital heart disease* (CHD) patients.[48] This may be due to chronic increased pulmonary blood flow leading to pulmonary vascular remodeling and increased afterload on the *right ventricle* (RV). Patients who have corrected defects and an increased PVR at baseline should undergo yearly testing.

Table 83.3 Drugs and Toxins Associated With PAH

Definite	Possible
■ Aminorex	■ Cocaine
■ Fenfluramine	■ Phenylpropanolamine
■ Dexfenfluramine	■ L-tryptophan
■ Benfluorex	■ St. John's wort
■ Methamphetamines	■ Amphetamines
■ Dasatinib	■ Interferon-α, interferon-β
■ Toxic rapeseed oil	■ Alkylating agents
	■ Bosutinib
	■ Direct-acting antiviral agents for hepatitis C (e.g., sofosbuvir)
	■ Leflunomide
	■ Indirubin (Chinese herb Qing-Dai)

PAH, pulmonary arterial hypertension.
From Simonneau G, Montani D, Celermajer DS, et al. Haemodynamic definitions and updated clinical classification of pulmonary hypertension. *Eur Respir J.* 2019;53(1):1801913.

Heritable Pulmonary Arterial Hypertension

Screening for heritable PAH varies widely by country and is an important practice gap in the evaluation of patients with PAH. Given that PAH mutations are found in nearly 20% of patients with presumed sporadic PAH and nearly 90% of patients with a family history of PAH, genetic testing and genetic counseling should be incorporated into the evaluation of PAH patients.[49] As recommended by the *European Society of Cardiology/European Respiratory Society* (ESC/ERS) guidelines, asymptomatic carriers of genetic mutations should undergo annual echocardiography.[27] Optimal screening strategies for patients with certain gene mutations are currently under investigation (NCT01600898; www.clinicaltrials.gov).

Exposures

Several drugs and toxins are associated with increased risk of PAH, classified as "definite" and "possible" risk factors. Anorexigens, including aminorex fumarate, fenfluramine, fenfluramine/phentermine, and benfluorex, are considered definite risk factors for PAH. Newer chemotherapeutic agents, such as the tyrosine kinase inhibitor dasatinib (definite) and bosutinib (possible), along with immunomodulatory therapies for rheumatologic diseases (leflunomide, possible) and hepatitis C virus (sofosbuvir, interferon-α, and interferon-β, possible) have been implicated as risk factors for PAH.[50–54] Other exposures that may lead to PAH are shown in Table 83.3.

A recent, large cohort study confirmed a strong association between methamphetamine exposure and development of PAH, prompting inclusion of methamphetamines

as a definite risk factor for PAH.[55] Patients with methamphetamine-associated PAH were more likely to be female, have more severe hemodynamic perturbations at diagnosis, and have poorer outcomes than idiopathic PAH patients, demonstrating an increased risk of hospitalizations. Furthermore, pathologic samples showed vascular changes in the pulmonary vasculature similar to idiopathic PAH and features of proliferative capillaritis, similar to pulmonary capillary hemangiomatosis or pulmonary veno-occlusive disease. These findings further strengthen the association between methamphetamine exposure and development of PAH. Even though the 6th WSPH statement recommended heightened awareness of exposures and risk of PAH, no specific screening protocols were endorsed.

Diagnosis

Most patients will not have a risk factor for PAH and thus will not be routinely screened for PAH. Given the multiple potential causes of PH in general, PAH is a diagnosis of exclusion. Therefore, establishing the diagnosis of PAH requires a high index of suspicion and a specific algorithmic approach (Fig. 83.2). This approach is discussed in detail in the following section.

CLINICAL PRESENTATION

The first step in the evaluation of any patient with possible PH is a comprehensive history and physical examination. Symptoms of PH tend to be nonspecific. Most commonly, patients note exertional dyspnea, but fatigue, weakness, chest pain, and light-headedness, and even cough can be prominent.[56] Signs of PH can include peripheral edema; other findings of right heart failure, such as ascites and exertional syncope, tend to present later in the disease course. Other rare manifesting signs include hoarseness related to recurrent laryngeal nerve compression from an enlarged PA (Ortner syndrome) and hemoptysis; as such, PH should be considered in the differential diagnosis of patients who present with these findings.

The physical examination is a key component of the evaluation of patients with suspected PH. An augmented second heart sound (P2 component) is commonly found in patients with established PAH and perhaps other types of PH, although that is not reported.[57] Other findings include jugular venous distension, ascites, and peripheral edema. Cardiac auscultation can elicit a high-pitched systolic ejection click in the second and third intercostal space on the left sternal border and can be followed by a systolic ejection murmur produced by the ejection of blood into the dilated PA. An S3 gallop arising from the right side of the heart may be heard in the fourth and fifth intercostal spaces along the left sternal border. A presystolic S4 can also be heard, reflecting right atrial contraction and expulsion of blood into the dilated RV. More advanced disease may be associated with a palpable thrill over the chest as the pulmonary valve closes. *Tricuspid regurgitation* (TR) is often present and results in a pansystolic murmur at the left sternal border; when PH is severe, the murmur can evolve to include a diastolic component known as a Graham Steell murmur. On the back, a holosystolic murmur between the scapulae can sometimes be heard in patients with CTEPH, resulting from turbulent blood flow across the central pulmonary arteries.

Special attention to identification of conditions that might cause elevated pulmonary pressures, such as underlying heart disease, lung disease, venous thromboembolism, liver or renal disease, or CTD is imperative. These comorbid conditions can also have specific symptoms and signs that suggest certain diseases (e.g., Velcro-like crackles on lung auscultation with ILD, left-sided S3 or S4 gallop with heart failure with reduced ejection fraction) that can focus further evaluation. Similarly, findings such as profound hypoxemia or orthopnea are more likely to be found in patients with PH related to underlying lung disease or LHD, respectively.

DIAGNOSTIC TESTING

BLOOD TESTING

In general, blood testing is not useful to establish the diagnosis of PH but is useful to classify some forms of PH and to assess disease severity. Routine testing, including complete blood count, basic metabolic panel, liver function, and thyroid function, should be performed. Serum *brain natriuretic peptide* (BNP) and *N-terminal pro-BNP* (NT-proBNP) help establish disease severity because both reflect RV dysfunction and predict outcomes in PAH.[58] Patterns of hepatic congestion on liver function testing can also reflect disease severity but alternatively can reflect intrinsic liver disease that may be directly related to development of PAH.

It is imperative to screen for diseases known to predispose to PAH, including CTD, HIV, and hepatitis. Recommended testing for CTD includes antinuclear antibody; if suspicion is high for CTD based upon history and physical examination, additional testing should be considered (see also Chapter 92). For example, if signs of scleroderma are present, additional testing for anticentromere, antitopoisomerase, anti-RNA polymerase III, and U1-RNP antibodies should be undertaken. Given the possibility of overlap with other CTDs, double-stranded DNA (for SLE) and anti-Ro and anti-La (for Sjögren syndrome) should be sent. Of note, many experts consider the presence of U1-RNP antibodies necessary to define MCTD, which is distinct from overlap syndrome in which features of several CTDs may coexist in the same patient but in which U1-RNP antibodies are absent. Because expert consensus recommends that MCTD patients undergo early-detection protocols for PAH similar to SSc patients, proper classification of CTD is important and may require consultation with a rheumatologist.[42]

If there is concern for thrombophilia, additional blood work to screen for coagulopathies and thrombophilia should be undertaken, including testing for anticardiolipin, lupus anticoagulant, and anti-β_2 glycoprotein antibodies.

PULMONARY FUNCTION TESTING

Pulmonary function testing is routinely performed in the evaluation of dyspnea and thus is an important part of the evaluation of PH.[59] Of importance, spirometry alone is insufficient to evaluate for PH; lung volumes and D_{LCO} are key studies to assess for obstructive and restrictive lung disease and effective alveolar-capillary surface area for gas exchange, respectively. Patients with PAH may have mild restrictive lung disease in the absence of obvious parenchymal, thoracic cage, or musculoskeletal disease. Severe

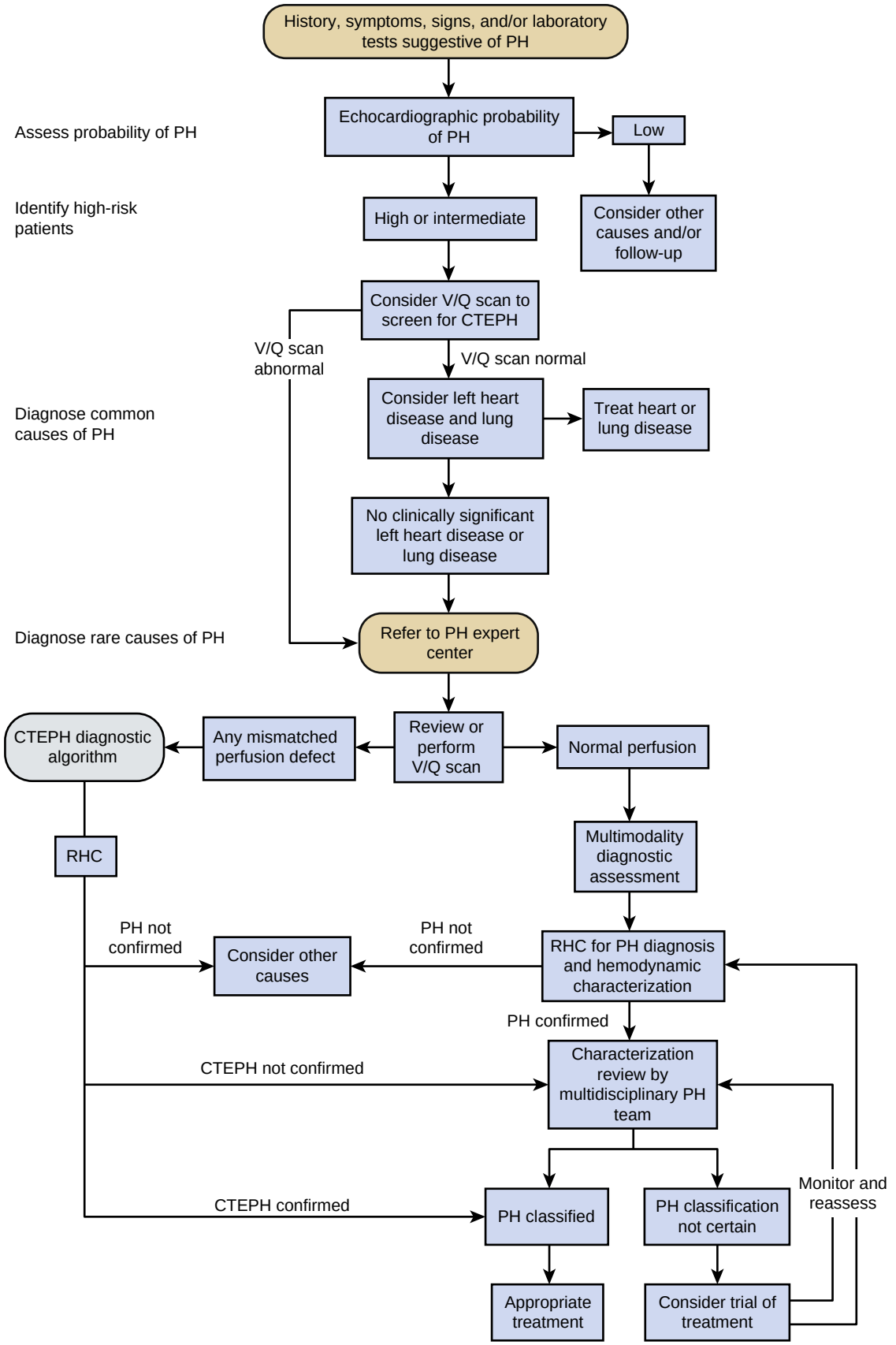

Figure 83.2 Algorithm for the diagnosis of pulmonary hypertension (PH) and its causes. Laboratory tests done locally can include electrocardiography, computed tomography, *ventilation/perfusion* (V/Q) scans, sleep testing, tests to evaluate for left heart disease and chronic lung disease, and blood work. The decision to refer to an expert center versus watchful waiting is based on the probability of PH and the underlying cause (i.e., *chronic thromboembolic pulmonary hypertension* [CTEPH], left heart disease, interstitial lung disease). The patient should be referred to an expert center when no clear cause of PH is identified, when rare causes of PH are identified or suspected, and when further expertise on evaluation and management of PH is needed. RHC, right heart catheterization. (Modified from Frost A, Badesch D, Gibbs JSR, et al. Diagnosis of pulmonary hypertension. *Eur Respir J.* 2019;53[1]:1801904.)

diffusing limitations suggest concomitant parenchymal or airways disease or chronic thromboembolic disease; rare forms of PAH, such as pulmonary capillary hemangiomatosis and pulmonary veno-occlusive disease, may also present with similar reductions in D_{LCO}.[60] Low D_{LCO} also can suggest evolving pulmonary vascular disease in patients with underlying cardiopulmonary disease and may be associated with poor prognosis in patients with *heart failure with preserved ejection fraction* (HFpEF), COPD, and ILD.[61–63]

Arterial blood gases, while not routinely obtained for the evaluation of PH, may be useful in the assessment of patients with established or suspected PAH. Mild hypoxemia and mild hypocapnia are commonly found yet are not strongly associated with hemodynamics. However, hypocapnia and not hypoxemia has been shown to represent an independent marker of mortality in a large cohort of patients with idiopathic PAH.[64] The mechanisms for this finding are not fully understood. Increased ventilatory drive leading to hypocapnia may result from multiple mechanisms: impaired ventilatory efficiency, low cardiac output, and low oxygen delivery. Each of these factors represent worsening cardiopulmonary function that can be linked to the impact of progressive pulmonary vascular disease through worsening dead-space ventilation and RV failure.

SIX-MINUTE WALK TESTING

The *6-minute walk test* (6MWT) is a submaximal exercise test commonly used to evaluate functional capacity in patients with various cardiopulmonary diseases.[65] *Distance achieved during the 6MWT* (6MWD) at the time of diagnosis is a strong predictor of survival in PAH.[66,67] Furthermore, 6MWD was the primary outcome measure for registration trials of novel PAH therapies for most currently available therapies. However, its role in the diagnosis of PH is limited because it lacks sensitivity and specificity for this diagnosis. Rather, the 6MWD provides useful prognostic data and provides a baseline measure of functional capacity that can be followed clinically over time to assess response to therapy and disease progression.[68–70]

NOCTURNAL OXIMETRY AND SLEEP TESTING

Sleep-disordered breathing is a highly prevalent disease, affecting greater than 30% of adult men and 17% of adult women in the United States.[71] Current PH guidelines recommend all patients undergo nocturnal oximetry as a screening test for sleep-disordered breathing because nocturnal hypoxemia is often associated with *obstructive sleep apnea* (OSA). In addition to screening for OSA, overnight oximetry is useful in identifying individuals at risk for nocturnal hypoxemia and hypoventilation in the absence of OSA. Normal sleep is characterized by a mild reduction in arterial P_{O_2} and mild hypoventilation. Individuals with PH who are on the steep portion of the oxyhemoglobin dissociation curve will experience a more profound decrease in arterial oxygen saturation during sleep compared to healthy individuals with normal lung function (see also Chapter 117 and Fig. 117.6). Thus, nocturnal hypoxemia and/or hypoventilation should be a consideration in any individual with a resting, awake, upright oxygen saturation less than 95%.[72] Given the association between OSA and PH and the potential for treatment of OSA to improve cardiopulmonary function, it is important to screen for this disease.[49,73] However, many practitioners do not obtain overnight oximetry despite guideline recommendations.[74] The use of home sleep apnea testing, which includes overnight oximetry, is a validated diagnostic tool for patients with moderate to high pretest probability of having OSA.[75] The use of home sleep apnea testing to screen asymptomatic individuals at a population level is not recommended; individuals with a low pretest probability of having OSA should be referred for in-laboratory sleep testing (polysomnography).[76]

CARDIOPULMONARY EXERCISE TESTING

Cardiopulmonary exercise testing (CPET) is used in the diagnostic evaluation of patients with unexplained dyspnea and, as such, may be useful in the evaluation of patients with suspected PH. In addition, CPET may be used to prognosticate and to assess response to therapy in PAH.[77] However, the utility of CPET is limited by the need for expertise in the conduct and interpretation of study results. Still, even with these caveats, CPET can be a useful tool to evaluate cardiopulmonary disease and assess for possible pulmonary vascular disease in this setting.[49] The role of invasive CPET in the evaluation of PH is discussed later.

ELECTROCARDIOGRAPHY

Electrocardiography (ECG) has an unknown sensitivity and specificity for the diagnosis of PH. Although considered a useful tool to assess for conduction abnormalities and arrhythmias that commonly complicate PH, findings more specific to the diagnosis of PH tend to develop late in the course of the disease (see Fig 85.5). For example, RV hypertrophy, denoted on ECG by tall R waves in V_1, with an R:S ratio of greater than 1, and prominent S waves in V_5 and V_6, with an R:S ratio of less than 1, is found in moderate to severe PH and not a useful screening tool to detect early disease. Other findings, such as right axis deviation, p pulmonale (large-amplitude P waves, typically found in the inferior leads), and large S waves in the inferior leads suggest possible PH as well. In the setting of underlying lung disease such as COPD, the presence of ECG evidence of right heart dysfunction (right axis deviation, p pulmonale, RV hypertrophy) portends a poor prognosis.[78]

TRANSTHORACIC ECHOCARDIOGRAPHY

Transthoracic echocardiography (TTE) is the most important noninvasive screening tool for PH (Fig. 83.3). TTE is widely available, relatively inexpensive, and safe by allowing repeated use without exposure to ionizing radiation. A useful tool to estimate pulmonary pressures and to evaluate cardiac chamber and valvular structure and function, the echocardiogram is often the first test that suggests PH. In addition to estimation of the pulmonary pressures, the echocardiogram is essential to evaluate for nonpulmonary causes of PH. Cardiac disease, including ischemic or nonischemic dysfunction of the *left ventricle* (LV), aortic or mitral valve disease, and CHD with left-to-right shunt, is the most common cause of PH.[79,80]

Of importance, echocardiography is a key component in the evaluation of HFpEF, an emerging epidemic in the United States.[24,81] Patients with HFpEF may be at particularly high risk of developing PH but typically have elevated left-sided

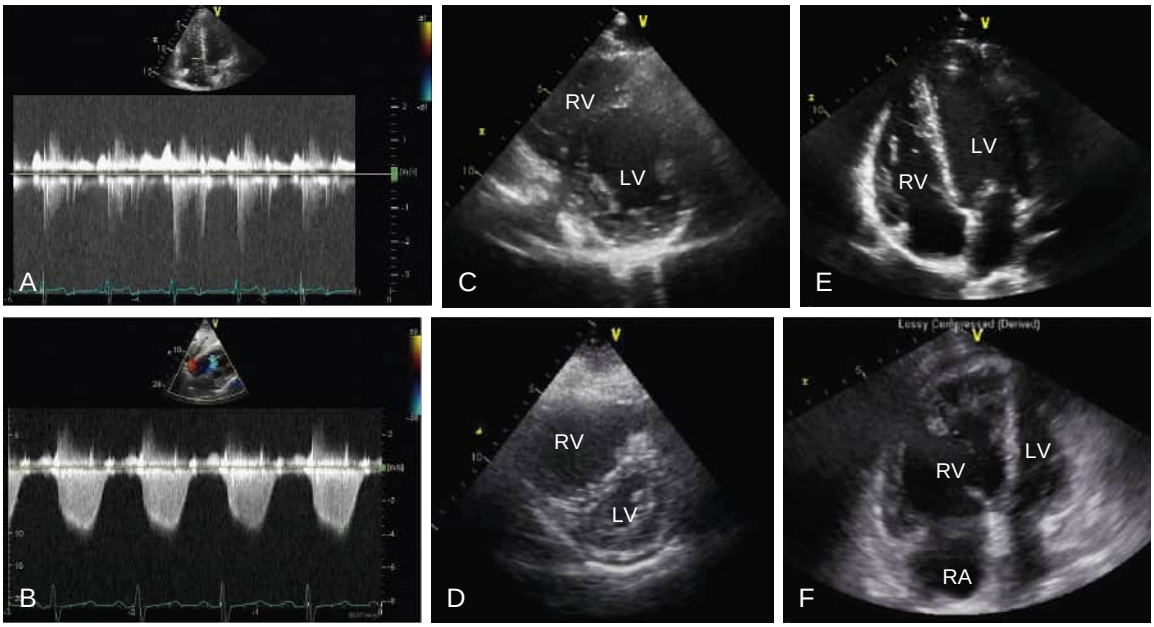

Figure 83.3 Echocardiography in the evaluation of pulmonary hypertension. (A) Poor-quality tricuspid regurgitant jet that cannot be used to estimate *pulmonary artery systolic pressure* (PASP). (B) Good-quality tricuspid regurgitant jet useful for estimating PASP. However, even when a good-quality jet can be obtained, the echocardiographic assessment of PASP may be inaccurate. (C) Short-axis echocardiographic image of a normal heart demonstrating a rounded left ventricle (LV) and normal-appearing right ventricle (RV). (D) Short-axis echocardiographic image from a patient with pulmonary hypertension demonstrating flattening of the interventricular septum and a D-shaped LV during systole and a large RV. (E) Apical four-chamber echocardiographic view of a normal heart demonstrating a normal-sized RV and LV. (F) Apical four-chamber echocardiographic view from a patient with pulmonary hypertension demonstrating a markedly enlarged RV with a small, compressed LV. There is also enlargement of the right atrium (RA) (see Video 83.1).

filling pressures on invasive hemodynamics, thereby fulfilling criteria for postcapillary PH.[82] However, HFpEF patients can also demonstrate combined pre–postcapillary physiology (elevated mean PAP with elevated PCWP and elevated PVR) or even precapillary physiology (elevated mean PAP with normal PCWP and elevated PVR). Thus, patients with evidence of PH and echocardiographic findings of HFpEF require thoughtful and thorough evaluation.

It is important to recognize that there are significant limitations in the diagnostic accuracy of echocardiography, especially for the estimates of *pulmonary artery systolic pressure* (PASP). Often, elevated estimates of PASP on echocardiography prompt the clinician to consider PH. Estimated PASP measurement is based upon the modified Bernoulli equation. This calculation uses the pressure gradient across the tricuspid valve between the right atrium and ventricle (pressure gradient = $4v^2$, where v = peak velocity of the TR jet)[83] and adds this to the right atrial pressure estimate based upon the size and collapsibility of the inferior vena cava to obtain an estimate of the right ventricular systolic pressure, which in the absence of pulmonary valve stenosis equals an estimated PASP. This calculation requires presence of a TR jet, which may not be detectable in up to 60% of patients with RHC-proven PH.[84–86] Presence of underlying COPD, ILD, or obesity affects image quality. For example, in a large series of patients with advanced lung disease, PASP could only be estimated in 44% of patients due to inability to obtain adequate Doppler windows.[87] Further, the correlation between echocardiographic estimates of PASP (when obtained) and invasively measured PASP is only moderate and is often inaccurate (Fig. 83.4).[85,86] Of importance, much of the inaccuracy of the echocardiographically estimated PASP seems to be attributable to right atrial pressure estimates; in one series of patients with PH who underwent echocardiography and RHC within 1 hour, 50% of the overestimation of PASP was due to overestimation of the right arterial pressure (eFig. 83.1).[88] Thus estimates of PASP may be inaccurate and should not be used as the sole echocardiographic measure upon which to determine the likelihood of PH.

Notwithstanding the limitations in the measurement of PASP, echocardiography does provide important structural and functional information about the heart and thereby suggests the presence of PH independent from PASP estimates. For example, evidence of LV systolic dysfunction in the presence of elevated right ventricular systolic pressure estimates imply heart failure with reduced ejection fraction and possible group 2 PH. Dilation of right-sided structures and RV hypertrophy suggest increased RV afterload. Flattening or leftward shift of the interventricular septum during systole and diastole reflect RV pressure and volume overload, respectively, and are consistent with severe RV dysfunction. (See Fig. 83.3D.)

Whereas numerous echocardiographic measurements have been studied to determine their utility in the diagnosis of PH, current guidelines suggest combining the following parameters to stratify the probability of PH: peak velocity of the tricuspid regurgitant jet, RV/LV ratio, RV outflow acceleration time and pattern, PA diameter, inferior vena cava diameter, and right atrial area[27] (Table 83.4). Presence of an elevated TR jet velocity greater than 2.8 m/sec in isolation portends an intermediate probability of PH; additional echocardiographic signs of PH just listed increases this likelihood (eTable 83.1).

Advances in echocardiography offer additional insight into RV structural and functional assessment, such as

eTable 83.1 Echocardiographic Probability of Pulmonary Hypertension (PH) in Symptomatic Patients With a Suspicion of PH

Peak Tricuspid Regurgitant Jet Velocity (m/sec)	Presence of Other Signs of PH on Echocardiography	Echocardiographic Probability of PH
≤2.8 or not measurable	No	Low
>2.8 or not measurable	Yes	Intermediate
2.9–3.4	No	Intermediate
2.9–3.4	Yes	High
>3.4	Not required	High

From Frost A, Badesch D, Gibbs JSR, et al. Diagnosis of pulmonary hypertension. *Eur Respir J.* 2019;53:1801904.

three-dimensional imaging and strain assessment of the RV using speckle tracking echocardiography, in which digital echocardiographic images generated by ultrasound interaction with myocardial tissue are tracked over the cardiac cycle to identify global and segmental myocardial deformation through spatiotemporal displacement.[89] Although these methods may have clinical utility, there remain limitations to their routine application in the assessment of patients with suspected PH, largely related to a lack of data defining normal parameters.[90] Further, despite advances in echocardiographic technology, accurate and reliable noninvasive estimates of left-sided filling pressures and cardiac output remain elusive. Therefore, echocardiography cannot be used to distinguish between precapillary and postcapillary PH. In sum, echocardiography remains the most useful screening tool for PH but is not a reliable tool to diagnose PH or classify PH phenotypes.

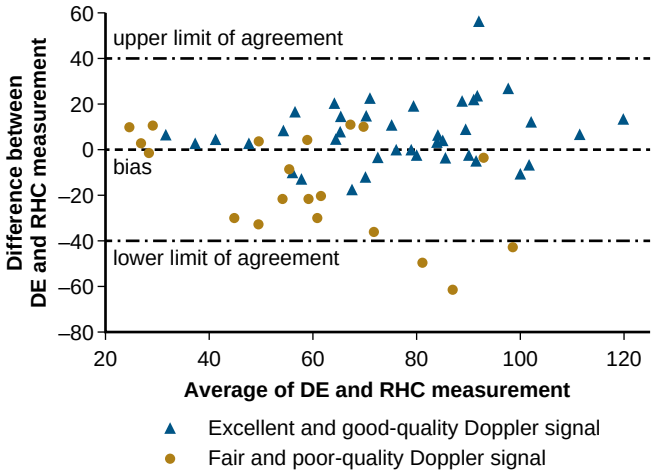

Figure 83.4 Bland-Altman plot of Doppler echocardiographic estimates of pulmonary artery pressure and right heart catheterization (RHC) measurements showing poor correlation between the two methods. Even though the bias (average difference between these two methods) is only –0.6 mm Hg, the 95% limits of agreement are from +38.8 to –40.0 mm Hg. The wide limits of agreement show that echocardiography can both significantly overestimate and underestimate PASP. Poor Doppler imaging of the trans-tricuspid regurgitant jet and inaccurate estimates of right atrial pressure account, in part, for the wide limits of agreement. DE, Doppler echocardiography; PASP, pulmonary artery systolic pressure. (From Fisher MR, Forfia PR, Chamera E, et al. Accuracy of Doppler echocardiography in the hemodynamic assessment of pulmonary hypertension. *Am J Respir Crit Care Med.* 2009;179[7]:615–621.)

CARDIAC MAGNETIC RESONANCE IMAGING

Although it offers superior image resolution and thus a more accurate assessment of the volume, mass, and systolic function of the heart, *cardiac magnetic resonance* (CMR) imaging is not a widely used tool in the screening for PH largely due to its high cost and limited availability. CMR is particularly useful for the diagnosis of CHD, such as partial anomalous pulmonary venous return, atrial septal defect, and other systemic-to-pulmonary shunts, all of which can be associated with PH. CMR has been studied in populations at high-risk of PH, such as scleroderma, in which ventricular mass index (ratio of RV mass to LV mass) demonstrated a high positive and negative predictive value for PH when assessed against invasive hemodynamic measurements.[91] A more recent registry-based study of patients at risk for PH demonstrated acceptable test characteristics for CMR when compared to invasively measured hemodynamics.[92] Larger studies are required to confirm these findings, but there may be a role in the future for CMR in the diagnostic evaluation of PH in at-risk populations.

COMPUTED TOMOGRAPHY

Computed tomography (CT) of the chest is an integral part of the evaluation of a patient with suspected PH. CT assesses the pulmonary parenchyma and can identify disease of the airways, parenchyma, pleura, and mediastinum. CT may identify abnormalities in extrathoracic organs, such as the liver, as a clue to portopulmonary hypertension (Fig. 83.5A–B). CT can establish the diagnosis of ILD (see Fig. 83.5C–D) and identify emphysema. Presence of a dilated esophagus suggests underlying SSc and should prompt careful assessment for this disease. CT scanning may uncover abnormal vascular or cardiac enlargement consistent with extracardiac or intracardiac shunting (see Fig. 83.5E–F). Typical findings of sarcoidosis, ranging from perilymphatic micronodules to pulmonary fibrosis with symmetrical hilar and mediastinal lymphadenopathy, can be seen on a chest CT (see Fig. 83.5G–H). Pleural effusions are rare in PAH and suggest LHD or primary lung disease as the underlying cause of PH. Of importance, rare forms of PAH, such as pulmonary capillary hemangiomatosis or pulmonary veno-occlusive disease, have characteristic CT findings necessary to establish proper diagnosis (see Fig. 83.5I–K). For example, centrilobular ground-glass opacities can be seen in severe idiopathic PAH as a manifestation of cholesterol granulomas

Table 83.4 Echocardiographic Signs Suggesting PH

Ventricles	Pulmonary Artery	Inferior Vena Cava and Right Atrium
RV/LV basal diameter ratio > 1.0 Flattening of the interventricular septum (LV eccentricity index > 1.1 in systole and/or diastole)	Right ventricular outflow Doppler acceleration time < 105 msec and/or midsystolic notching Early diastolic pulmonary regurgitation velocity > 2.2 m/sec Pulmonary artery diameter > 25 mm	Inferior vena cava diameter > 21 mm with decreased inspiratory collapse (<50% with a sniff or <20% with quiet inspiration) RA area (end-systole) > 18 cm^2

Echocardiographic signs from at least two different columns from the list should be present to alter the level of echocardiographic probability of PH.
LV, left ventricle; PH, pulmonary hypertension; RA, right atrium; RV, right ventricle; WSPH, World Symposium on Pulmonary Hypertension.
From Frost A, Badesch D, Gibbs JSR, et al. Diagnosis of pulmonary hypertension. *Eur Respir J.* 2019;53:1801904.

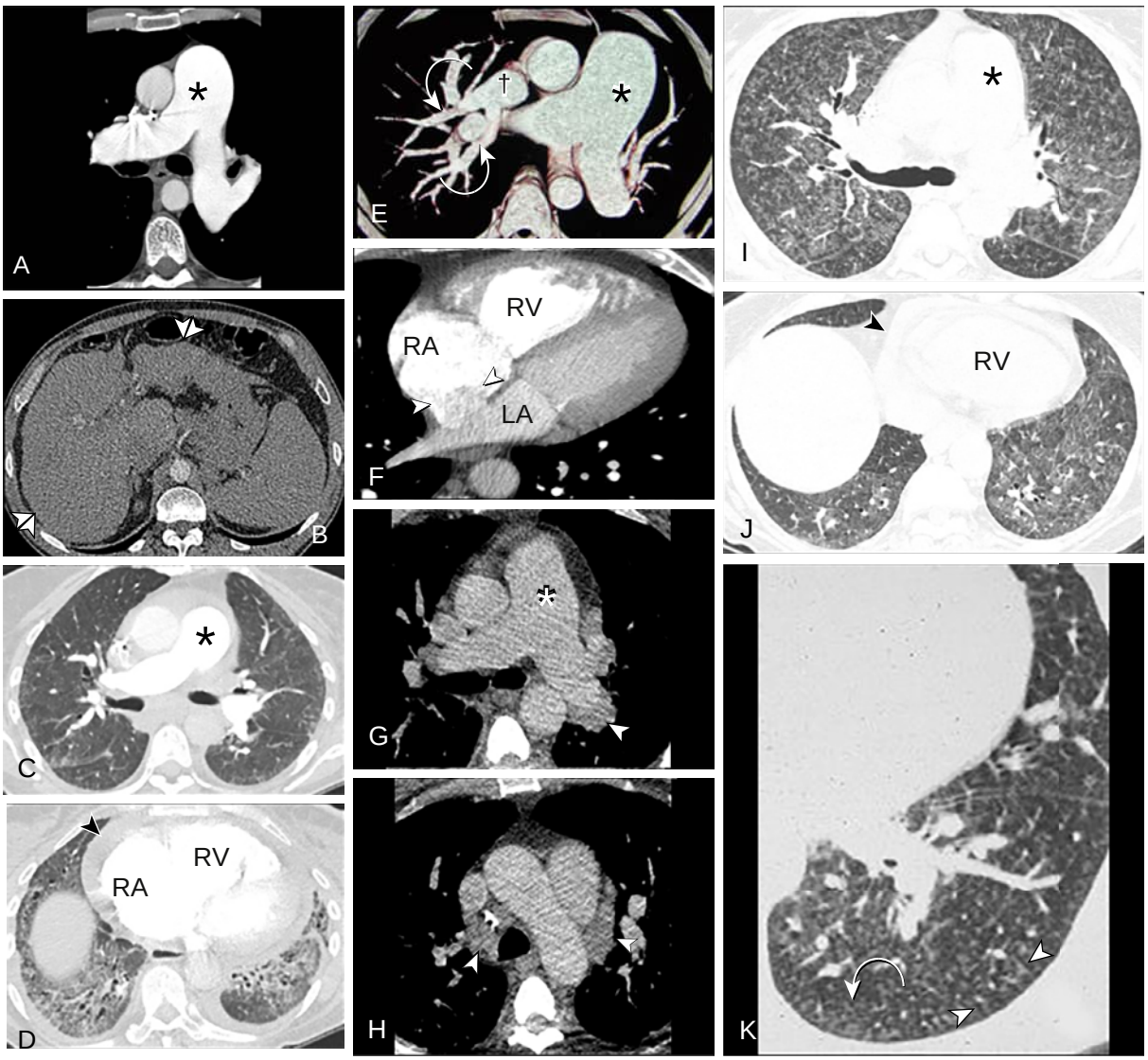

Figure 83.5 ***Computed tomography*** **(CT) imaging leading to diagnosis of disorders producing** ***pulmonary hypertension*** **(PH).** (A–B) Portopulmonary hypertension. Note enlarged main pulmonary artery (*asterisk*) and nodular liver contour (*double arrowheads*), consistent with cirrhosis. (C–D) PH associated with interstitial lung disease. Note enlarged main pulmonary artery (*asterisk*), right atrium (RA), right ventricle (RV), and basilar ground-glass opacity, reticulation, and traction bronchiectasis representing nonspecific interstitial pneumonia in a patient with scleroderma; note that the esophagus is mildly dilated. A small pericardial effusion (*single arrowhead*) is a not-infrequent finding in patients with PH. (E) Pulmonary hypertension due to extracardiac shunt. Axial maximum intensity projected CT shows an enlarged main pulmonary artery (*asterisk*) due to anomalous right upper lobe pulmonary veins (*curved arrows*) draining into the superior vena cava (*dagger*). (F) PH due to intracardiac shunt. Axial enhanced CT shows an enlarged RA and RV with a rightward bowing interatrial septum (*arrowheads*), allowing left-to-right shunt; note how left atrial contrast attenuation appears to extend into the denser right atrial contrast. Quantification of pulmonary-to-systemic flow at magnetic resonance imaging was calculated at 1.6. (G–H) Pulmonary hypertension in sarcoidosis. Note enlarged main pulmonary artery (*asterisk*). Bilateral peribronchial and mediastinal lymph node enlargement (*arrowheads*) is present, showing noncaseating granulomas on biopsy. (I–J) Pulmonary capillary hemangiomatosis. Axial enhanced CT shows multiple poorly defined centrilobular ground-glass opacity nodules. Note enlarged main pulmonary artery (*asterisk*), RV, and small pericardial effusion (*arrowhead*). (K) Pulmonary veno-occlusive disease. Axial thoracic CT displayed in lung windows shows basal smooth interlobular septal thickening (*arrowheads*), and patchy areas of inhomogeneous lung opacity, with some of the areas of increased attenuation consistent with ground-glass opacity, best seen in the medial lung base. Faint ground-glass opacity centrilobular nodules (*curved arrow*) are present. LA, left atrium. (Courtesy Michael B. Gotway, MD.)

resulting from repeated microhemorrhages in the pulmonary vasculature or from profuse proliferation of capillaries as seen in pulmonary capillary hemangiomatosis (see Fig. 83.5I–J).[93–95] Similarly, pulmonary veno-occlusive disease typically presents with interstitial edema, diffuse central ground-glass opacities, intralobular sepal thickening, and mediastinal lymphadenopathy (see Fig. 83.5K).[96] Given the marginal response to pulmonary vasodilator therapies and overall poor prognosis, urgent lung transplantation evaluation should be pursued if this diagnosis is suspected.[97] Thus, parenchymal abnormalities seen on CT chest should alert the clinician to consider rare forms of PAH in the proper clinical context.

CT also provides cardiac images useful in the assessment of PH. Findings of adaptation or failure of the right-sided cardiac structures, such as right atrial enlargement, RV enlargement (RV to LV diameter ratio greater than 1 at the midventricular level), RV hypertrophy (wall thickness > 4 mm), straightening or bowing of the interventricular septum, pericardial effusion, and dilation of the inferior

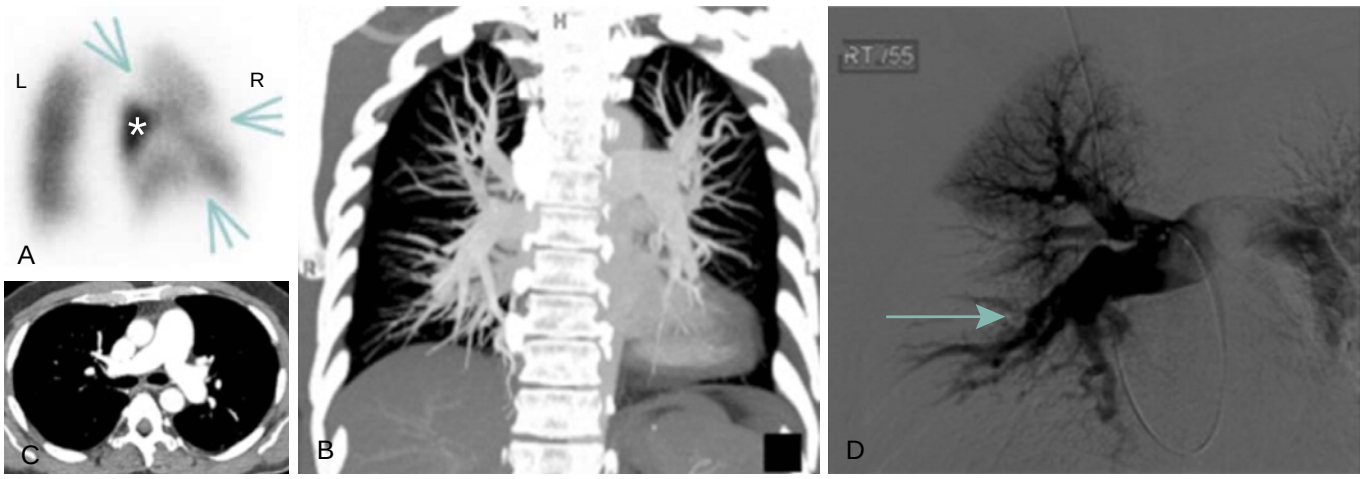

Figure 83.6 An example of discordant findings of thromboembolic disease between ventilation-perfusion scanning and *computed tomography* (CT) with angiography of a single patient. (A) Perfusion image obtained after injection of technetium-99m macroaggregated albumin in right posterior oblique view showing perfusion defects in the right upper lobe, right middle lobe, and right lower lobe (*arrows*). There is an area of increased intensity in the superior segment of the right lower lobe that represents artifact from insignificant clotting of the Tc-99m macroaggregated albumin (*asterisk*). The ventilation scan was completely normal. (B) Coronal maximum intensity projection CT pulmonary angiogram shows tortuous and dilated pulmonary arteries but no pulmonary arterial filling defects or other signs of chronic thromboembolic disease within the pulmonary arteries. (C) Axial CT pulmonary angiography shows a dilated main pulmonary artery but no filling defects within the proximal pulmonary arteries and no other signs of chronic thromboembolic disease. (D) Pulmonary angiogram confirmed the abnormalities by revealing a truncated and pruned right middle lobe segmental pulmonary artery (*arrow*) and wedge-shaped area of hypoperfusion. (From Furfaro D, Azadi J, Housten T, et al. Discordance between imaging modalities in the evaluation of chronic thromboembolic pulmonary hypertension: a combined experience from two academic medical centers. *Ann Am Thorac Soc.* 2019;16[2]:277–280.)

vena cava and hepatic veins can be seen in PH. Congenital cardiac defects, such as anomalous pulmonary venous drainage and intracardiac shunt, can also be identified (see Fig. 83.5E–F). Thus, CT imaging is imperative to evaluate for underlying cardiopulmonary conditions associated with PH.

With the addition of intravenous contrast, acute and chronic thromboembolic disease can be identified as well. Although not as sensitive for the diagnosis of chronic thromboembolic disease as *ventilation-perfusion* (V/Q) scan (see later), the *CT pulmonary angiogram* (CTPA) provides important information regarding the operability of the lesions with pulmonary endarterectomy or to guide balloon pulmonary angiography. In addition, CTPA can identify webs, obstructions, bands, intimal irregularities, and bronchial artery dilations consistent with chronic thromboembolic disease.[98] Other findings include parenchymal abnormalities, such as scars from prior infarction, mosaic pattern of perfusion, and cylindrical bronchial dilations.

The utility of PA size in the diagnosis of PH has been studied extensively, with varying results.[99–105] These studies have examined the PA diameter in isolation, the ratio of the PA to aortic diameter, the ratio of segmental PA size to bronchus, and PA diameter in combination with other noninvasive modalities such as echocardiography. Findings of a main PA diameter greater than or equal to 29 mm or a main PA diameter to aorta diameter ratio greater than 1 suggest possible PH with sensitivity and specificity ranging from 57–89%. However, progressive dilation of the PA may be a function of disease duration rather than disease severity and thus limit the utility of using PA size metrics as screening tools.[106] Thus, despite advances in CT technology and extensive clinical research, CT chest findings can only suggest possible PH; establishing the diagnosis of PH requires additional testing, including RHC.

VENTILATION-PERFUSION SCANNING

V/Q scans are an integral part of the evaluation for PH (Fig. 83.6). The role for V/Q scanning as a mandatory study to establish the proper classification of PH was confirmed at the 6th WSPH.[49] V/Q scans detect chronic thromboembolic disease more consistently than CT angiograms.[107,108] Prior studies have suggested a negative predictive value of nearly 100%, making V/Q scans extremely useful to rule out chronic thromboembolic disease.[107] In a more recent multicenter study, there was discordance between the V/Q scan and CTPA regarding presence of chronic thromboembolic disease in greater than 30% of patients who had both studies performed and who had RHC and pulmonary angiogram-proven CTEPH.[109] In all cases of discordance, the CTPA was negative, whereas the V/Q scan was positive for chronic thromboembolic disease, highlighting the limitations of CTPA. Despite these studies supporting the utility of V/Q scanning in the evaluation of PH, data suggest that few providers actually perform V/Q scans. A large observational study of 60 academic and community practices in the United States, the *Pulmonary Arterial Hypertension-Quality Enhancement Research Initiative* (PAH-QuERI), demonstrated that fewer than 60% of patients evaluated for PH underwent V/Q scanning.[74]

The decision to pursue RHC for the definitive diagnosis of PH should be based upon the clinical suspicion for PH as a result of the completion of the recommended evaluation algorithm (see Fig. 83.2). As discussed earlier, results from each of the tests inform the likelihood of the presence of PH, the contributors to PH if present, and potential treatment options. Unfortunately, as shown in the PAH-QuERI study, only a minority of patients diagnosed with PAH completed the entire diagnostic evaluation.[74] The most commonly missed tests were overnight oximetry (completed in 41.5% of patients) and V/Q scanning (completed in 57.2% of

patients). Overall, only 6% of patients carrying a diagnosis of PAH underwent all the recommended studies to rule out other PH etiologies. There are significant implications of an incomplete evaluation for PH as demonstrated in a study by Deaño and colleagues[110] in which a cohort of 98 patients with a pre-referral diagnosis of PH underwent reevaluation for PH at tertiary referral centers. The authors found that 33% of patients with a pre-referral diagnosis of PH had an incorrect diagnosis. Of importance, of the 42 patients with a pre-referral diagnosis of PAH who were receiving pulmonary vasodilator therapy, only 23 (54.8%) had confirmed PAH after completing the recommended evaluation. This study highlights the impact of incomplete evaluation leading to incorrect diagnoses and, more important, to inappropriate use of PAH-specific therapy. Given the high cost and potential toxicity of PAH-specific medications, use of these agents should be carefully considered and prescribed in accordance with regulatory body guidelines. Further, referral of patients to centers of excellence for the management of PH is strongly encouraged by consensus guidelines.

RIGHT HEART CATHETERIZATION

RHC is the test of choice for the diagnosis of PH and is mandatory for any patient in whom PH treatment is being considered. RHC allows accurate measurement of PAP and important prognostic features, such as RA pressure and cardiac output, exclusion of LHD-associated PH, and assessment of vasoreactivity in certain subgroups. Although RHC is an invasive test, it is safe, with a low risk of complications when performed by experienced providers. In the largest multicenter description of RHC safety, the percentage of serious adverse events was 1.1% of 7218 RHCs performed in PH patients at expert centers.[111] Twenty-nine serious adverse events were due to venous access (e.g., hematoma), 22 due to placement of the catheter (e.g., supraventricular tachycardia), 15 due to vasoreactivity testing (e.g., systemic hypotension), and 6 related to pulmonary angiography (e.g., pulmonary edema). There were four fatal events in association with RHC, resulting in an overall procedure-related mortality of 0.055%.[111]

Performance

RHC is recommended in patients who have clinical features suggestive of PH with an echocardiogram that has intermediate or high probability of PH. RHC is generally performed either through the internal jugular or femoral vein using a balloon flotation catheter. The catheter is advanced under fluoroscopic guidance into the RA, RV, and PA with waveforms as shown in Figure 83.7. In general, the external pressure transducer should be zeroed at the level of the left atrium, which is at the midthoracic line halfway between the anterior sternum and the surface of the bed in a supine patient.[112] All pressure measurements should be made at the end of a normal expiration.[113]

Accurate measurement of PCWP, an estimate of *left atrial pressure* (LAP), is essential for proper PH group classification. PCWP is obtained with the catheter balloon inflated and advanced until the characteristic waveform is visualized (see Fig. 83.7). Blood gas analysis with the balloon inflated may be used to confirm that the catheter is properly placed. Common pitfalls in PCWP measurement include either a wedged location too proximal, which creates a

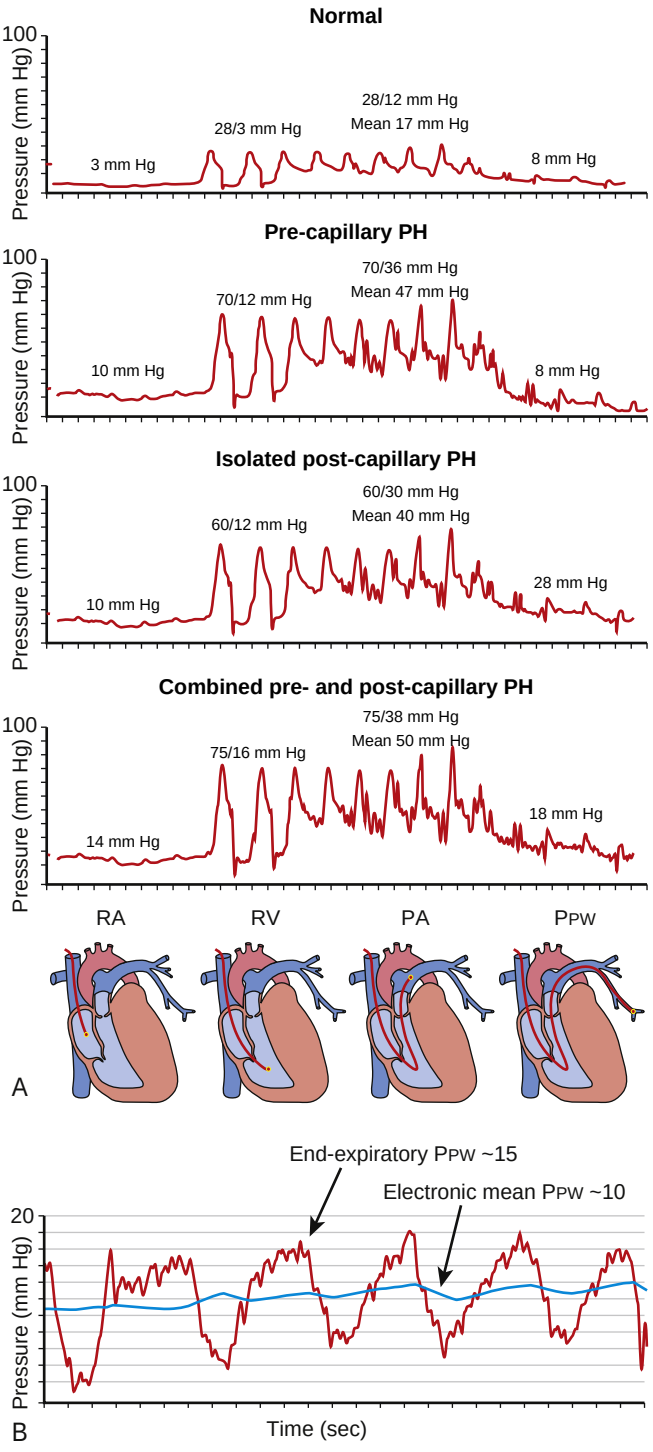

Figure 83.7 Tracings from *right heart catheterization* (RHC) in patients with *pulmonary hypertension* (PH). (A) RHC waveforms are obtained as the catheter passes from the right atrium (RA) through the right ventricle (RV), pulmonary artery (PA), and into the pulmonary capillary wedge position in a normal individual and in individuals with precapillary PH, isolated postcapillary PH, and combined precapillary and postcapillary PH. (B) Pulmonary artery wedge pressure (PPW) tracing from a patient with chronic lung disease demonstrating marked respiratory variation in the wedge pressure. Abrupt rise in pressure in some respiratory cycles at the end of expiration likely represents forceful expiration, which is sometimes seen in patients with lung disease. It is important to identify and measure the pressure at end-expiration correctly. Use of the computer-measured mean wedge pressure is misleading because the mean wedge pressure is calculated to be normal (~10 mm Hg), whereas the actual end-expiratory wedge pressure is elevated (~15 mm Hg), suggesting a diagnosis of pulmonary hypertension from left heart disease. Normal pressures are provided.

hybrid pressure tracing between the PAP and PCWP, or too distal, which results in overwedging with subsequent improper measurement of PCWP and risk for PA rupture. Although PCWP should approximate LAP, and therefore *left ventricular end-diastolic pressure* (LVEDP), studies have demonstrated relatively poor concordance between PCWP and LVEDP. In 3926 patients with PH who underwent simultaneous right and left heart catheterization, PCWP underestimated LVEDP by an average of 2.9 mm Hg (eFig. 83.2).[114] This may have significant clinical implications because almost half of patients diagnosed as having precapillary PH based on a PCWP less than or equal to 15 mm Hg actually had an LVEDP greater than 15 mm Hg, consistent with postcapillary disease.[114] Similar findings were described from another center; older age was associated with a PCWP measurement that underestimated LVEDP, whereas atrial fibrillation, rheumatic valve disease, and left atrial enlargement were associated with overestimation of LVEDP.[115] Recent guidelines from the 6th WSPH recommend direct measurement of LVEDP in patients who have a low probability of LHD-associated PH but a PCWP greater than 15 mm Hg on RHC.[116] Another potential strategy to "unmask" occult LHD is using provocative measures, such as exercise or fluid loading.

Cardiac output (CO) is a critical parameter measured during RHC because it is used in the calculation of PVR and is recognized as an independent predictor of outcome in PAH.[117,118] Thermodilution, performed by injecting a known volume of saline into the RA and measuring temperature change in the PA, should be measured in triplicate to calculate CO.[113] This method agrees strongly with CO calculated by the direct Fick method (the gold standard for CO measurement) and is unaffected by low CO or severe TR.[119] (The *indirect* Fick method, which includes assumptions of normal oxygen consumption, agrees poorly with thermodilution CO and is an inferior prognostic measurement[120] and thus is not recommended for CO estimation.)

Chronic left-to-right shunting, which can be seen with some forms of CHD, may cause PH and can be evaluated during RHC. Blood samples are obtained from the vena cava and multiple positions in the RA, the RV, and the PA. An increase in oxygen saturation between the vena cava and the PA indicates a left-to-right shunt and allows quantification. Shunt quantification should be performed only in patients on 30% or less supplemental oxygen because higher concentrations may invalidate pulmonary blood flow estimates.[121]

Provocative Maneuvers

Vasoreactivity Testing. Vasoreactivity testing during RHC to determine acute responsiveness to a pulmonary vasodilator is not recommended in all types of PH and is not used to determine responsiveness to vasodilators other than CCBs. It is recommended only in patients with idiopathic PAH, heritable, and drug-induced PAH because these are the only patients who may have a durable response to CCBs, and it may change management in these subgroups.[83,122] A positive acute vasoreactivity test requires (1) reduction of mPAP by 10 mm Hg or more to an absolute mPAP of 40 mm Hg or less with (2) an increased or unchanged CO. Inhaled nitric oxide is the preferred agent for vasoreactivity testing, but intravenous epoprostenol or intravenous adenosine are alternatives.[83] CCBs should not be used to gauge acute response because high-dose calcium channel blockade can acutely lead to hypoxemia and worsened RV function.[123]

In the era before availability of PAH-specific medications, patients who had an acute response to vasodilation had dramatically improved survival when treated long-term with CCBs.[124] Although about 10% of idiopathic, heritable, and drug-induced PAH patients will be responsive, half of them are expected to lose responsiveness over time for unclear reasons. A large series of idiopathic PAH patients demonstrated that an acute vasodilator response was found in 12.5%, but only approximately 6.8% of the overall group had a durable long-term response.[125] Therefore, although long-term response to CCB is rare in PAH, it is important to perform vasoreactivity testing to identify this subgroup because it dramatically changes prognosis and treatment.

Exercise. Exercise can be used during RHC to provoke changes in patients with normal resting hemodynamics, assess for occult left heart disease, and provide additional prognostic data in PAH patients. An exercise-induced rise in mPAP was taken out of the definition of PH in 2008 due to uncertainties about what constitutes a normal pulmonary vascular response to exercise. Although still not incorporated into the diagnosis of PH,[83] recent research has further elucidated normal and abnormal exercise responses. Rather than relying on a single mPAP at maximum exercise, using a combination of mPAP and the slope of change in mPAP and CO, or *total pulmonary resistance* (TPR = mPAP/CO) is recommended. A current suggested diagnosis of exercise-induced PH is a normal mPAP (<21 mm Hg) at rest but a maximal exercise mPAP greater than 30 mm Hg *and* TPR greater than 3 WU.[126] This definition, however, is unable to differentiate between exercise-induced increases in mPAP resulting from a primary pulmonary arteriopathy and increases in mPAP resulting from PCWP due to left heart disease. PCWP is difficult to measure during exercise due to large respiratory swings and technical challenges in wedging the catheter. A suggested upper limit of normal for exercise PCWP is 25 mm Hg, although this varies with age, and some have described a CO-adjusted measure of PCWP as potentially useful, with a proposed cutoff of a PCWP/CO slope of greater than 2 mm Hg/L/min as abnormal.[127] In patients with PAH, exercise can be used to prognosticate survival. The ability of the RV to increase pressure depends on preserved ventricular-pulmonary vascular coupling and the capacity to increase stroke volume during exercise without RV dilation. PAH patients who are unable to increase their PAP with exercise have reduced RV functional reserve,[128] which corresponds to worse outcomes.[129,130]

Fluid Challenge. Another provocative maneuver that can be used to unmask occult LHD (i.e., a PCWP of 15 mm Hg or less with an intermediate or high pretest probability of LHD) is a fluid challenge during RHC. In the presence of impaired LV diastolic compliance, a fluid challenge will lead to an increase in PCWP, generally to greater than 18

to 20 mm Hg.[131] In patients with PAH[132] and SSc-PAH,[133] a 500-mL bolus of normal saline resulted in an elevated PCWP in 22% and 46% of patients, respectively, although a subsequent study reported this in only 6% of precapillary PH patients.[134] Fluid challenge during RHC can be helpful to identify occult HFpEF and is recommended when patients with an intermediate to high probability of PH due to HFpEF have a PCWP of 13 to 15 mm Hg.[79]

TESTING TO DETERMINE PROGNOSIS

Once the diagnosis of PH is established by RHC, numerous modalities can determine the patient's prognosis, including biomarkers, echocardiography, cardiac magnetic resonance, and exercise testing. In general, a multiparameter prognostic approach, such as the REVEAL risk score[135] or the ESC/ERS risk assessment strategy,[113] performs better than any one test alone.

BIOMARKERS

The most common clinically used biomarkers for PAH are BNP and NT-proBNP. ProBNP is released from left- and right-sided cardiac myocytes in response to ventricular stretch/stress and then cleaved into NT-proBNP (inactive) and BNP (active). This compensatory mechanism is exploited as a prognostic test in PH, with higher BNP levels corresponding to higher RA pressure and RV dysfunction.[136] Elevation of both NT-proBNP[137] and BNP[138] levels at the time of PAH diagnosis are predictors of poor long-term survival. Changes in BNP after initiation of therapy seems to predict survival with better accuracy than baseline measurements.[138,139]

IMAGING

As described earlier, echocardiography forms the basis for PH screening by measuring estimated PASP and determining the probability of PH. Echocardiography is also useful for the functional assessment of the RV, which is a strong predictor of outcomes. Imaging of the RV with echocardiography is difficult due to the complex anatomy of the RV. *Tricuspid annular plane systolic excursion* (TAPSE) measures the displacement of the tricuspid annulus in the longitudinal plane towards the RV apex (Video 83.1)[140] and strongly correlates with RV ejection fraction[141] and stroke volume index.[142] Lower TAPSE corresponds to worse RV function, with a cutoff of 1.8 cm demonstrating an increased risk of death of almost sixfold.[142] A newer modality, RV strain imaging via speckle-tracking echocardiography, is emerging as an accurate noninvasive measure of RV function and prognosis. As mentioned earlier, this technique measures myocardial deformation of the RV, both globally and regionally. A meta-analysis of 1001 patients with precapillary PH demonstrated that RV strain is a strong predictor of mortality and may outperform TAPSE.[143] Pericardial effusion, which may develop in PH partially from elevated RA pressure limiting pericardial fluid drainage into the RA, is most common in patients with CTD-associated PH[144] and is an independent predictor of mortality in PAH.[135,144] Any attempt at drainage for significant pericardial effusions without hemodynamic decompensation in PAH patients should be approached cautiously because drainage in this population is associated with a high mortality.[145] Rapid removal of pericardial effusion via pericardiocentesis can lead to rapid enlargement of the RV and subsequent compression of the LV that can lead to hemodynamic collapse.[146] In situations of hemodynamic stability with large pericardial effusions, a more conservative approach with diuresis and systemic blood pressure support if needed is recommended. However, in situations of hemodynamic instability due to tamponade physiology, a pericardiocentesis with slow, controlled drainage through a pericardial drain may be necessary.[147]

Cardiac magnetic resonance (CMR) overcomes many of the limitations of echocardiography and is the gold standard for measurement of right-sided cardiac function and size.[148] CMR allows for accurate measurement of RV ejection fraction, RV hypertrophy, RV/RA dilation/enlargement, flattening of the interventricular septum, and PA stiffness. Phase-contrast imaging also permits quantification of CO, RV stroke volume, and intracardiac shunts.[149] Of note, PAP cannot be measured by CMR and requires RHC. Numerous CMR parameters, including RV stroke volume,[150] PA stiffness,[151] RV size,[150–152] RV hypertrophy,[153] and decreased LV filling[150] are independent predictors of mortality in PAH.

EXERCISE TESTING

6WMD is a key parameter used in the management of PH patients to establish prognosis and gauge changes over time. The 6MWD strongly corresponds to patient-reported functional class and moderately correlates to *maximum oxygen consumption* ($\dot{V}O_{2max}$).[154] Baseline 6MWD,[154,155] as well as oxygen desaturation during the 6MWT,[156] independently predicts mortality in patients with idiopathic PAH. The 6MWT is routinely repeated in PAH patients to gauge response to therapy. The minimal important difference in 6WMD is approximately 33 m in PAH patients.[157] Studies have suggested that a worsening of 6WMD over time is strongly associated with poor prognosis,[158] but an improvement in 6WMD may not correlate with improved outcomes.[158,159]

CPET (see also Chapter 33) can be safely[160] applied to patients with PH and may give additional prognostic value and uncover complications of PH (e.g., exercise-induced right-to-left shunt). Patients with PH characteristically have a reduced aerobic capacity (low maximum $\dot{V}O_2$), early anaerobic threshold, reduced ventilatory efficiency (increased ventilation needed to eliminate carbon dioxide [CO_2], [$\dot{V}E/\dot{V}CO_2$], and elevated $\dot{V}E/\dot{V}CO_2$ slope), abnormal V/Q ratio (decreased *end-tidal CO_2 partial pressure*, $PETCO_2$) at anaerobic threshold, and desaturation during exercise.[160,161] PH patients with more severe functional impairments have a greater reduction in $PETCO_2$ and $\dot{V}E/\dot{V}CO_2$ slope,[162] and PAH patients with lower maximum $\dot{V}O_2$ and higher $\dot{V}E/\dot{V}CO_2$ slope have worse survival.[155] CPET can also be used to detect exercise-induced right-to-left shunting, which can be recognized by an abrupt and sustained decrease in end-tidal CO_2 with associated oxygen desaturation.[163]

GROUP 2: PULMONARY HYPERTENSION

As detailed earlier, the 6th WSPH updated the clinical classification of PH, as detailed in Table 83.2. It is essential to assign patients to the proper WSPH clinical classification group by the workup described earlier because patients with groups 1 and 4 have specific treatments proven to be effective, whereas those in groups 2, 3, and 5 generally do not benefit from PAH-specific therapy. Detailed discussions for group 1, group 3, and group 4 PH epidemiology, clinical characteristics and treatment, and outcomes are discussed elsewhere (see Chapters 84–86, respectively).

Group 2 PH includes the PH due to cardiac disease. LHD is by far the most common cause of PH in the developed world, with one study finding that 69% of patients with an elevated PA pressure on echocardiogram have LHD-PH.[164] In general, patients with LHD may develop PH due to heart failure with preserved or reduced *left ventricular ejection fraction* (LVEF) or valvular heart disease. Most patients with LHD-PH have *isolated postcapillary PH* (Ipc-PH), in which the elevated LAP causes a proportional rise in PAP. However, some patients experience an elevation in PAP out of proportional to the increase in LAP, which is termed *combined precapillary and postcapillary PH* (Cpc-PH). In contrast to patients with Ipc-PH, those with Cpc-PH (defined as a PVR ≥3 WU) have a worse survival, with every 1 WU increase in PVR corresponding to a 9% increase in likelihood of death.[165]

HFpEF is a very common cause of PH; estimates vary of the prevalence of PH in HFpEF but, in one large community-based study, 83% of HFpEF patients had an elevated estimated PAP on echo.[166] Differentiating HFpEF from PAH is a diagnostic challenge because many patients with PAH have cardiovascular risk factors,[167] and the echocardiographic assessment of diastolic function is imprecise. Even PCWP, the parameter used to differentiate precapillary from postcapillary PH, has limitations, which may necessitate direct measurement of LVEDP and/or provocative RHC maneuvers. The first step in the assessment of potential HFpEF-PH is to judge the pretest probability. Compared to patients with PAH, those with HFpEF are significantly older,[166,168] with a higher incidence of comorbidities,[168] including features of metabolic syndrome.[169] The next step is incorporation of echocardiographic features that increase or decrease the likelihood of HFpEF-PH. In patients with low probability of HFpEF-PH or an intermediate probability with RV abnormalities, RHC is recommended for accurate diagnosis.[116]

Heart failure with reduced LVEF (HFrEF) is complicated by PH in 16–63% of patients, depending on which criteria are used and what population is being studied.[170–173] Compared to HFrEF patients without PH, HFrEF-PH patients have more obesity, diabetes, and atrial fibrillation, as well as more severe diastolic abnormalities and mitral regurgitation on echocardiogram.[174] Patients with HFrEF-PH are less likely to have Cpc-PH than their HFpEF-PH counterparts,[175] although HFrEF-PH patients have worse RV function.[176,177] The presence of PH in HFrEF clearly worsens outcomes, with a significant increase in mortality in multiple studies.[171,173,174] In addition, HFrEF patients with Cpc-PH have significantly worse survival than those with Ipc-PH, with a 56% increase in mortality.[174]

All forms of left-sided *valvular heart disease* (VHD) may cause PH, with estimated prevalence as displayed in eFig. 83.3[178]; in general, mitral valve disease causes more severe PH than does aortic valve disease. Identifying PH in VHD is essential because it affects prognosis and may impact timing of intervention. In many cases, PH is reversible with intervention. *Aortic stenosis* (AS) leads to PH by causing LV pressure overload, which then results in diastolic dysfunction and elevated LAP. In fact, in patients with AS, the degree of PH correlates best with diastolic dysfunction, not with AS severity.[178] The impact of PH on survival in AS is controversial,[179,180] but improvements in PAP after treatment of AS are associated with better long-term outcomes.[181] PH may be caused by aortic regurgitation through LV volume overload and subsequent diastolic dysfunction, and most patients have normalization of PAP after valve surgery.[182] However, PH has been relatively understudied in aortic regurgitation, and valve replacement is not indicated solely for elevated PAP.[178] *Mitral stenosis* (MS) has long been recognized as a classic cause of PH by directly increasing LAP. It is important to intervene before the onset of severe PH in patients with MS because outcomes after mitral valve intervention are worse in MS patients with severe PH. However, most patients have resolution of PH after intervention.[178] In primary mitral regurgitation, the rate of PH correlates with severity of mitral regurgitation.[183] Even if patients are asymptomatic with preserved LV function, those with PH have worse survival. For this reason, resting PH with an estimated systolic PA pressure greater than 50 mm Hg should be considered for mitral valve repair.[178]

TREATMENT CONSIDERATIONS FOR GROUP 2 PULMONARY HYPERTENSION

There is a strong recommendation against treating LHD-PH with PAH-specific medications[116] because there are no multicenter *randomized controlled trials* (RCTs) that show benefit in this group. In patients with HFrEF-PH, intravenous epoprostenol versus standard care (diuretics, digoxin, angiotensin-converting enzyme inhibitor) was investigated in a large RCT but was terminated early due to a signal of higher mortality in the epoprostenol group.[184] The only study to date targeting the Cpc-PH subgroup in HFpEF was the MELODY-1 study, which was a multicenter RCT randomizing 63 patients to 12 weeks of macitentan (an endothelin receptor antagonist) or placebo. The main outcome of fluid retention or functional class worsening was more common in patients randomized to macitentan, with no signal of benefit in secondary outcomes.[185] In patients with corrected VHD, sildenafil was investigated in a multicenter RCT by randomizing 200 patients to 6 months of treatment or placebo. The primary end point (a composite of death, hospitalization for heart failure, functional class, and quality of life) was significantly worse in the group given sildenafil, with no improvement in 6MWD, NT-proBNP, or echocardiographic measurements of PAP.[186]

There are smaller single-center RCTs in HFrEF-PH[187,188] and HFpEF-PH[189] that suggested some potential benefit to phosphodiesterase-5 inhibitors but, taken together, the data do not support a role for pulmonary vasodilator therapy in the management of group 2 PH and suggest possible harm in certain forms of group 2 PH. As such, pulmonary

vasodilator therapy for group 2 PH is not recommended in the 6th WSPH statement.[79]

There are no clinical RCTs to guide the use of targeted interventions for LHD-PH. Thus, individualized management of underlying LHD is left to the discretion of the treating physician but without supporting evidence that these treatments will impact PH.

GROUP 5: PULMONARY HYPERTENSION

Group 5 PH comprises a wide range of diseases that predispose to the development of PH through unclear or multifactorial mechanisms. This heterogeneous group includes common disorders, such as renal disease, and rare disorders, such as chronic hemolytic anemia and rare forms of ILD. Overall, little is known regarding the epidemiology of PH within these disorders, therapeutic options, or outcomes.

HEMATOLOGIC DISORDERS (See Chapter 127)

Chronic hemolytic anemias associated with PH include *sickle cell disease* (SCD) and β-thalassemia. PH in SCD may develop related to intravascular hemolysis and subsequent inhibition of nitric oxide signaling and impairment in endothelial function, thrombosis, high CO from chronic anemia, and hypoxia.[190] Repeated episodes of acute chest syndrome do not appear to increase risk for PH in SCD.[191-193] Whereas an elevated TR jet velocity is found in 27–40% of SCD patients screened with echocardiography,[193,194] the true rates of PH based on RHC are lower. In three major cohort studies, the prevalence of an mPAP of 25 mm Hg or greater has been described in SCD patients undergoing screening. In SCD patients screened for PH, based on TR jet velocity with[192] or without[193,194] symptoms and low 6MWD, 5–10% had an mPAP of 25 mm Hg or greater on RHC, with a roughly even distribution of precapillary and postcapillary PH patients. Another key finding of these studies is what constitutes "normal" hemodynamics in SCD. Patients who did not have PH on RHC had a high CO and therefore a lower than normal PVR. Patients with SCD-PH were characterized by a PVR only mildly above the PH definition threshold of 3 WU. Despite this, patients with SCD-PH have significantly worse functional class and 6MWD and a mortality twofold higher than SCD patients without PH.[191,192] Risk for death is closely tied to hemodynamic markers of precapillary PH.[192] Screening echocardiography is recommended every 1 to 3 years, with further workup if indicated.[195] Special note is made of their recommended PVR cutoff for PH, which is 2 WU, below the standard threshold of 3 WU. However, this recommendation was not included in the 6th WSPH statement.

β-Thalassemia appears to be another risk factor for PH, although it is less well studied than SCD.[196] Two major variants of β-thalassemia exist: thalassemia major and thalassemia intermedia. The prevalence of PH in β-thalassemia is unknown, but there appear to be echocardiographic differences between the variants, with thalassemia intermedia patients more likely to develop an elevated estimated PAP and thalassemia major patients more likely to have LV dysfunction.[197]

Myeloproliferative disorders (MPDs), including chronic myeloid leukemia, polycythemia vera, essential thrombocytosis, and myelofibrosis, may be complicated by PH. Possible mechanisms include chronic thromboemboli in association with prothrombotic states and splenectomy,[176] pulmonary veno-occlusive disease,[198] portal hypertension,[199] and drug-induced PH. Although some studies using echocardiographic definitions have shown a PH prevalence of up to 48% of MPD patients,[200] larger series found a lower estimated prevalence of approximately 4–5%.[201,202] There appears to be an association between treatment with the tyrosine kinase inhibitor dasatinib and development of PAH; dasatinib is now listed as a definitive cause of PAH in the WSPH guidelines,[83] possibly by causing endothelial dysfunction and oxidative stress.[203] In a series of 21 MPD patients taking dasatinib with RHC-confirmed PAH, most patients were functional class III or IV with a median mPAP of 45 mm Hg.[204] Of importance, discontinuation of dasatinib was associated with significant improvements in functional class, 6WMD, and hemodynamics, with 63% of patients normalizing their mPAP.[204]

SYSTEMIC AND METABOLIC DISORDERS

Pulmonary Langerhans cell histiocytosis (PLCH) is a rare sporadic smoking-related cystic lung disease characterized by infiltration of bronchioles by $CD1a^+$ Langerhans-like cells.[205] Case series have demonstrated that PLCH may be complicated by severe precapillary PH.[205,206] It appears that PLCH may directly affect the pulmonary vasculature, as suggested by a lack of correlation with pulmonary function parameters and PH severity. In addition, histopathology demonstrates a proliferative vasculopathy, prominently in venules, even in lung parenchyma that is otherwise normal.[206]

Gaucher disease is a rare inherited disorder in which glucocerebroside is deposited in cells of the macrophage-monocyte system, leading to multisystem involvement. Symptomatic PH is more common in patients with type 1 Gaucher disease who have a history of splenectomy and have not been treated with enzyme replacement therapy,[207,208] and concurrent hepatopulmonary syndrome has been described in some patients.[208]

Glycogen storage diseases, rare genetic conditions characterized by enzyme deficiencies that impair either glycogen synthesis or breakdown, may be complicated by PH, particularly in type 1a glycogen storage disease.[209] Although the mechanisms underlying PH in glycogen storage diseases are unknown, abnormal serotonin handling may be involved.[210]

Neurofibromatosis type 1 (i.e., von Recklinghausen disease) is an autosomal dominant genetic disorder that causes multisystem disease, including skin lesions, neurofibromas, gliomas and, rarely, severe PH.[211] Cases described in the literature suggest a female predominance and median age of PH diagnosis of 57 years, with 75% of patients presenting with functional class III or IV symptoms.[211] PH may present in patients with or without parenchymal lung involvement, which is also a well-described complication of neurofibromatosis.[211] Case reports demonstrate a limited response to PAH-specific therapy and overall a poor prognosis; if patients are candidates for lung transplantation, this should be considered when the diagnosis of PH is made.

Lymphangioleiomyomatosis is a disorder that mostly affects young or middle-aged women and is caused by proliferation of smooth muscle–like cells along lymphatic channels. Pulmonary involvement includes a diffuse cystic lung disease and precapillary PH. A recent description of 20 lymphangioleiomyomatosis patients who underwent RHC showed that the average mPAP was 32 ± 6 mm Hg with a PVR of 4.7 ± 2.3 WU, and the presence of PH was associated with worse hypoxemia and exercise capacity.[212]

Sarcoidosis is a multisystem granulomatous disease of unknown cause. Sarcoid-associated PH is covered in Chapter 93.

Others

Chronic renal failure (CRF) is commonly associated with PH which, in most cases, is due to concomitant LHD. The exact prevalence of PH in CRF is difficult to determine because most reports rely on echocardiographic estimates of PAP for PH diagnosis; prevalence estimates range from 13–48%.[213] The *Prevalence of Precapillary Pulmonary Arterial Hypertension in Patients With End-Stage Renal Disease* (PEPPER) study[214] used RHC to determine hemodynamics in patients with CRF who had persistent dyspnea despite hemodialysis. In the dialysis group, the prevalence of PH was 72%, which dropped to 60% when mPAP was remeasured after a hemodialysis session. In patients with CRF who were not yet receiving hemodialysis, the prevalence was 72%. In both groups, the vast majority of patients with PH had postcapillary disease with a PCWP greater than 15 mm Hg. Other potential mechanisms for CRF-associated PH include *arteriovenous* (AV) fistula creation and poorly defined mechanisms, such as the inflammation, oxidative stress, and endothelial dysfunction associated with CRF and HD.[213] It has been posited that AV fistula creation may lead to a high cardiac output state, which may cause pulmonary vascular remodeling and PH. However, data are mixed concerning any association of AV fistula and PH in CRF, with some studies showing an association between AV fistula creation and PH[215,216] and others demonstrating no such relationship.[217,218] Whatever the cause, patients with CRF undergoing hemodialysis who have PH had a twofold higher all-cause mortality, independent of other risk factors.[219]

Fibrosing mediastinitis is caused by benign proliferation of fibrous tissue in the mediastinum with encasement of mediastinal structures, including the vasculature. Common causes of fibrosing mediastinitis include histoplasmosis, sarcoidosis, tuberculosis, and radiation therapy. PH may result from compression of the pulmonary arteries and/or veins. In a French series of 27 patients with RHC-proven PH from fibrosing mediastinitis, the average mPAP was 42 mm Hg with a PVR of 6.2 WU, with most patients having a precapillary phenotype. Functional capacity was significantly impaired with a 5-year survival of only 56%[220] (see also Chapter 116).

COMPLEX CONGENITAL HEART DISEASE

The complex CHD category represents a heterogeneous group of pediatric patients who are challenging to define and manage. Interested readers are directed to the 6th WSPH article by Rosenzweig and colleagues.[221]

TREATMENT CONSIDERATIONS FOR GROUP 5 PULMONARY HYPERTENSION

Although case reports and open-label studies have reported varying degrees of clinical improvement associated with treating PH patients with glycogen storage disease,[222] Gaucher disease,[223] PLCH,[205] neurofibromatosis, lymphangioleiomyomatosis,[212] β-thalassemia,[224] and CRF,[225] there are no RCTs of PAH-specific medications in these conditions and such treatment is not recommended by the recent guidelines. PH appears to improve in CRF patients who undergo renal transplantation, which seems to be due to significant improvements in LV function.[226] Patients with fibrosing mediastinitis may be cautiously considered for endovascular/surgical stenting or bypass of obstructed vessels,[227,228] and corticosteroids have been associated with variable success in sarcoidosis-associated fibrosing mediastinitis.[229]

RCTs of PAH-specific medications have been conducted in SCD and sarcoidosis, with variable reports of success. There have been RCTs of PAH-specific therapy in SCD-associated PH, but none have provided definitive results. The ASSET-1 and -2 studies randomized a total of 26 patients with precapillary ($n = 14$) or postcapillary ($n = 12$) SCD-PH to either bosentan or placebo.[230] Due to slow enrollment, both studies were terminated early and no analysis of the primary end point was conducted. The WALK-PHaSST study randomized 74 SCD subjects with an elevated TR jet velocity on echocardiogram to sildenafil or placebo and was stopped early due to safety concerns.[231] Although the sample size was limited, there was no treatment effect on 6MWD or NT-proBNP, but there was an increased risk of hospitalization for pain crisis in the sildenafil-treated patients. There have been case reports of prostacyclins[232] and the soluble guanylate cyclase stimulator riociguat[233] in SCD-PH, but neither has been tested in an RCT. Although there are concerns about risk of sickling with cardiopulmonary bypass and hypothermia, SCD patients with CTEPH appear to improve with pulmonary thromboendarterectomy surgery.[234]

Key Points

- *Pulmonary hypertension* (PH) is defined as a mean pulmonary artery pressure of greater than 20 mm Hg on right heart catheterization and can be further characterized based on pulmonary artery capillary pressure and pulmonary vascular resistance as precapillary, isolated postcapillary, or combined precapillary and postcapillary PH.
- It is essential to assign patients to the proper *World Symposium on Pulmonary Hypertension* (WSPH) clinical classification group because patients with groups 1 and 4 have specific treatments proven to be effective, whereas those in groups 2, 3, and 5 generally do not benefit from PAH-specific therapy.
- Populations at risk for *pulmonary arterial hypertension* (PAH) (WSPH group 1) include patients with connective tissue disease (especially systemic sclerosis), human immunodeficiency virus, portal hypertension, and certain drug or toxin exposures (e.g., methamphetamines).

- Symptoms of PH are nonspecific and include dyspnea on exertion, fatigue, chest pain, and light-headedness.
- Transthoracic echocardiography is the screening test of choice for PH, which can be used to estimate systolic pulmonary artery pressure, assess right heart size and function, and evaluate for signs of left heart disease or congenital heart disease.
- In patients with suspected PH, ventilation-perfusion scanning is imperative to rule out chronic thromboembolic PH.
- Computed tomography can reveal clues to the diagnosis and show parenchymal abnormalities characteristic of interstitial lung disease or of rare forms of PH.
- Right heart catheterization is mandatory for establishing the diagnosis of PH and for determining the proper clinical classification.
- Prognosis should be assessed at baseline and every 3 to 6 months by measuring laboratory biomarkers, echocardiography and/or cardiac magnetic resonance imaging, and exercise testing. A multimodal risk assessment incorporating these and other parameters is superior to any individual prognostic test.
- Group 2 PH is the most common cause of PH in the developed world and is caused by heart failure with preserved or reduction ejection fraction, as well as left-sided valvular heart disease.
- Group 5 PH is a heterogeneous group of disorders, including chronic hemolytic anemias, myeloproliferative disorders, metabolic (e.g., Gaucher disease) and systemic (e.g., sarcoidosis) diseases, chronic renal failure, fibrosing mediastinitis, and complex congenital heart disease.

Key Readings

D'Alto M, et al. Strengths and weaknesses of echocardiography for the diagnosis of pulmonary hypertension. *Int J Cardiol*. 2018;263:177–183.

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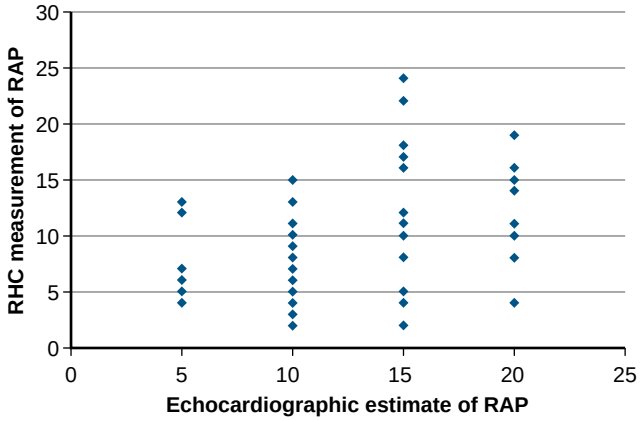
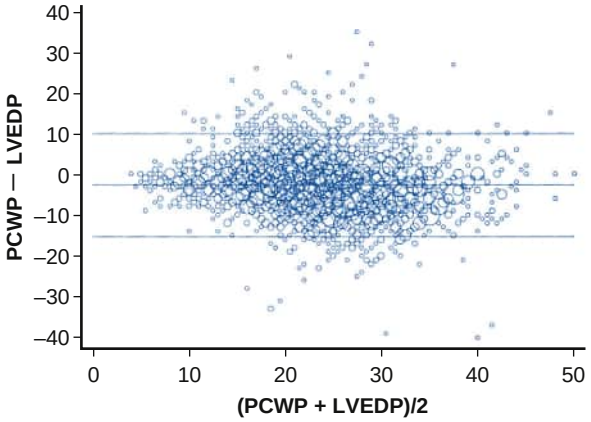
Complete reference list available at ExpertConsult.com.

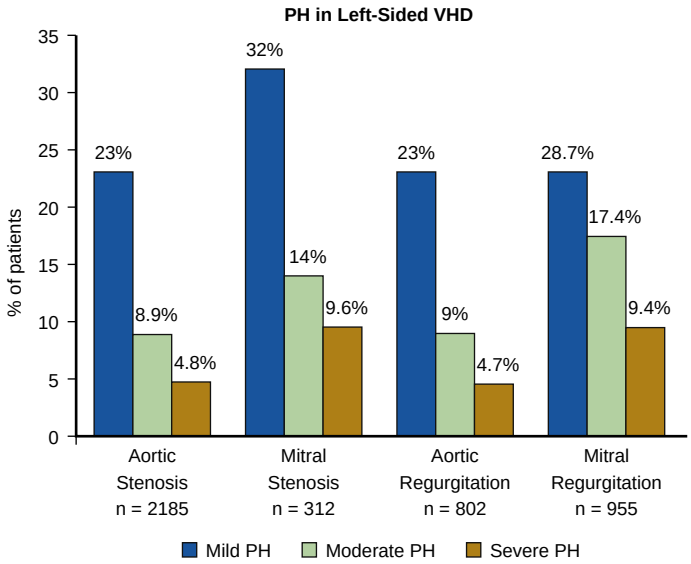
eFIGURE IMAGE GALLERY



eFigure 83.1 Comparison of *right atrial pressure* (RAP) as estimated by Doppler echocardiography and *right heart catheterization* (RHC). Comparison of right atrial pressure as estimated by Doppler echocardiography and RHC demonstrating poor correlation. For example, for echocardiographic estimates of right atrial pressure of 15 mm Hg, corresponding directly measured RHC right atrial pressure ranged from 2 to 24 mm Hg. (From Fisher MR, Forfia PR, Chamera E, et al. Accuracy of Doppler echocardiography in the hemodynamic assessment of pulmonary hypertension. *Am J Respir Crit Care Med.* 2009;179[7]:615–621.)



eFigure 83.2 Bland-Altman plot of *pulmonary capillary wedge pressure* (PCWP) and *left ventricular end-diastolic pressure* (LVEDP) among 3926 patients with pulmonary hypertension. The *y*-axis shows the difference between PCWP and LVEDP (PCWP – LVEDP). The *x*-axis shows the average of these measures: (PCWP + LVEDP)/2. The graph describes the agreement between these two quantitative measures. On average, PCWP underestimated LVEDP by 2.9 mm Hg (bias –2.9 mm Hg; confidence interval, –3.0 to –2.7); limits of agreement of –15.2 to 9.5 mm Hg. *Larger circle*s indicate identical observations among multiple patients. (From Halpern SD, Taichman DB. Misclassification of pulmonary hypertension due to reliance on pulmonary capillary wedge pressure rather than left ventricular end-diastolic pressure. *Chest* 2009;136[1]:37–43.)



eFigure 83.3 Prevalence of mild, moderate, and severe *pulmonary hypertension* (PH) according to left-sided *valvular heart disease* (VHD) etiology. PH was diagnosed by right heart catheterization in all patients. Mild, moderate, and severe PH were defined as a mean pulmonary artery pressures: 25–34, 35–44, and ≥45 mm Hg, respectively. As seen, mitral valve disease causes more severe PH than does aortic valve disease. (From Magne J, Pibarot P, Sengupta PP, et al. Pulmonary hypertension in valvular disease: a comprehensive review on pathophysiology to therapy from the HAVEC Group. *JACC Cardiovasc Imaging.* 2015;8[1]:83–99.)

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84 PULMONARY ARTERIAL HYPERTENSION: GROUP 1

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INTRODUCTION

Group 1 *pulmonary arterial hypertension* (PAH) is characterized by elevated pulmonary arterial pressures, normal left heart filling pressures, and no evidence of significant lung disease, chronic thromboembolic disease, or one of the conditions that can cause pulmonary hypertension due to unclear and/or multifactorial mechanisms. The most common causes of PAH include *idiopathic PAH* (IPAH), drugs and toxins, *connective tissue disease* (CTD), and *congenital heart disease* (CHD). Genetic variants, *human immunodeficiency virus* (HIV), and portal hypertension are important but less common causes, while schistosomiasis is an important cause in countries where it remains prevalent. These conditions have many similarities in pathobiology, presentation, hemodynamics, prognosis, and response to therapies. However, differences are large enough that familiarity with each individual subtype is required for optimal patient care.

PATHOBIOLOGY

The primary abnormalities in IPAH involve the pulmonary vasculature, particularly the distal muscular-type arteries with a size of 70 to 500 μm. These small arteries develop intimal and adventitial fibrosis, medial hypertrophy/hyperplasia, in situ thrombotic lesions, and plexiform lesions.[1] Smaller precapillary pulmonary arterioles ranging in diameter from 20 to 70 μm are also abnormal and reveal luminal obliteration, abnormal muscularization, and perivascular inflammation (Fig. 84.1 and eFig. 84.2).

Pathologic findings in IPAH, drug/toxin PAH, and CHD-PAH are essentially indistinguishable from each other, while CTD-PAH may have all of these findings plus more pronounced interstitial fibrosis and inflammation (eFig. 84.2A–D).[2] Hemodynamic findings correlate only moderately with intimal and medial thickening and with the presence and number of plexiform lesions.[2] Due to the risk associated with this procedure, lung biopsy does not currently play a role in assessing PAH type or severity, although some centers do occasionally utilize biopsy in the diagnosis of pulmonary veno-occlusive disease. Chest radiographs may show enlarged pulmonary arteries and right atrial and right ventricular dilation, particularly in advanced disease (eFigs. 84.1, 84.3, and 84.4). In contrast, chest radiographs may be normal or near normal in milder or well-compensated disease. With computed tomography, the above findings may be seen in greater detail. Additionally, parenchymal ground-glass abnormalities have also been described in up to 40% of patients, most often in a centrilobular pattern.[3]

Pulmonary veno-occlusive disease (PVOD) is characterized by extensive venous involvement, including obstruction of pulmonary venules and veins by loose, fibrous remodeling of the intima that may totally occlude the lumen, in addition to arterial changes. PVOD is often accompanied by *pulmonary capillary hemangiomatosis* (PCH), and both pathologic patterns are now thought to be different manifestations of the same disease process, classified as PVOD/PCH (eFig. 84.2E–H). Venous remodeling may also be seen in other forms of PAH, most notably scleroderma-associated PAH, where clinical findings suggestive of PVOD are associated with worse outcomes.[4]

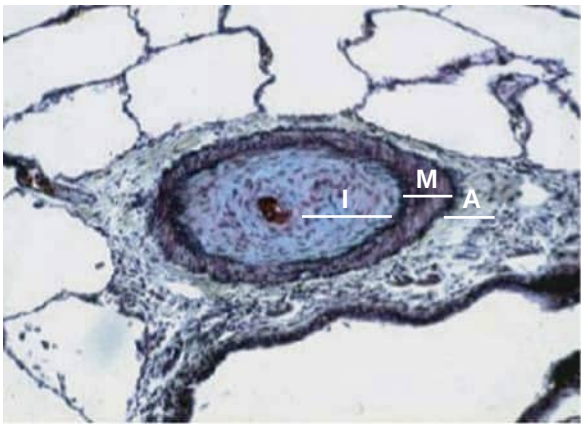

Figure 84.1 Typical advanced pulmonary arteriopathy in idiopathic pulmonary arterial hypertension. Note the proliferative changes in all three vessel layers, including intimal hyperplasia (I), medial hypertrophy (M), and adventitial fibrosis (A).

PULMONARY ARTERIAL HYPERTENSION SUBGROUPS

IDIOPATHIC

Approximately 48% of all patients diagnosed with PAH have no discernable risk factors and are therefore deemed idiopathic.[5] All ages may be affected, but it is more common in women, and the median age at diagnosis is around 50 years.[6] Without treatment, median survival for IPAH is approximately 2.8 years, based on results from the United States National Institutes of Health registry conducted from 1981 to 1985.[7] Modern treatment can improve survival and delay the time to clinical worsening, with median survival of up to 7.8 years.[5,6,8]

HERITABLE

As early as 1954, it was reported by Dresdale et al. that PAH may present in multiple family members.[9] However, it was not until 2000 that genetic analysis was able to implicate heterozygous mutations in the *bone morphogenetic protein receptor 2 (BMPR2)* gene in the development of PAH. Abnormalities in *BMPR2* are found in 70–80% of families with PAH and 10–20% of patients diagnosed with IPAH.[10] *Heritable PAH* (HPAH) is autosomal dominant but with incomplete penetrance; 14% of men and 42% of women with the *BMPR2* mutation will develop disease.[11] PAH patients who carry the *BMPR2* mutation develop disease sooner than noncarriers and have an accelerated course with increased risk of death or lung transplantation.[12] A number of less-common mutations have also been identified as risk factors for the development of PAH: *EIF2AK4*, *TBX4*, *ATP13A3*, *GDF2*, *Smad 9*, *CAV1*, and *KCNK3*.[10] HPAH is also recognized to run in families with the autosomal dominant disorder *hereditary hemorrhagic telangiectasia* (HHT). Mutations in HHT-related HPAH are found in both the *ACVRL1* (activin receptor-like kinase 1) and *ENG* (endoglin) genes.[13] Genetic counseling and screening is recommended for patients with IPAH or a family history of pulmonary hypertension. Because of incomplete penetrance, testing of asymptomatic relatives should be offered only with genetic counseling.

DRUGS AND TOXINS

The effects of drugs and toxins on the human pulmonary circulation have been demonstrated historically. Between 1967 and 1970 in Switzerland, Austria, and Germany, a 20-fold increase in pulmonary hypertension was observed after the introduction of aminorex, an appetite suppressant resembling epinephrine and amphetamine.[14] The pulmonary lesions produced by this agent resembled plexogenic pulmonary arteriopathy in every respect. Pulmonary hypertension was subsequently also associated with the appetite suppressants fenfluramine (eFig. 84.5) and dexfenfluramine.[15] Other stimulants have been suspected of causing pulmonary hypertension, based on both pharmacologic similarities with the anorexigens as well as case reports, case series, and case-control studies.[16,17] The link with methamphetamine has been strongest, and some centers recommend drug testing on all newly diagnosed PAH patients.[18] Other medications suspected of causing pulmonary hypertension include chemotherapeutic agents, reported mainly in association with PVOD,[19] and dasatinib, a tyrosine kinase inhibitor associated with the development of PAH.[20]

PULMONARY VENO-OCCLUSIVE DISEASE/ PULMONARY CAPILLARY HEMANGIOMATOSIS

PVOD/PCH is characterized by virtually identical hemodynamic findings as IPAH, but with significant venous and/or capillary involvement. The venous/capillary involvement results in clinical findings of a lower *diffusing capacity for carbon monoxide* (D_{LCO}), more hypoxemia, and more abnormal chest imaging than in most patients with IPAH. These abnormalities arise because blood flow is obstructed at or beyond the capillary, leading to elevated pressures for all upstream vessels and resulting in a tendency towards pulmonary edema. Chest radiographs may show prominent Kerley B lines in the absence of other signs of left-sided heart failure, and computed tomography scanning may reveal interlobular septal thickening, pleural effusions, and enlarged pulmonary arteries (Fig. 84.2 and eFig. 84.6). These findings should lead to a clinical suspicion of PVOD/PCH at the time pulmonary hypertension is diagnosed, although individual findings are neither sensitive nor specific. Suspicion may be further increased following a trial of PAH therapies, because this can lead to worsening hypoxemia, abnormal computed tomography findings, and occasionally overt pulmonary edema due to pulmonary arterial vasodilation in the setting of a mostly fixed obstruction in the capillaries and veins (Fig. 84.2C–D). PVOD/PCH may develop in association with viral syndromes, toxin exposure, and chemotherapy, but most cases are idiopathic.[21] A familial form of PVOD/PCH involves the *EIF2AK4* gene, which is inherited in an autosomal recessive fashion.[20] Biallelic mutations in the *EIF2AK4* gene have also been identified in around 1% of patients diagnosed with IPAH. These patients appear to have at least some characteristics typical of PVOD/PCH, and possibly a worse prognosis.[2,22] Because response to PAH therapies in these patients is often poor, any use of such therapies should be undertaken with extreme caution, and early referral for transplant evaluation is recommended.

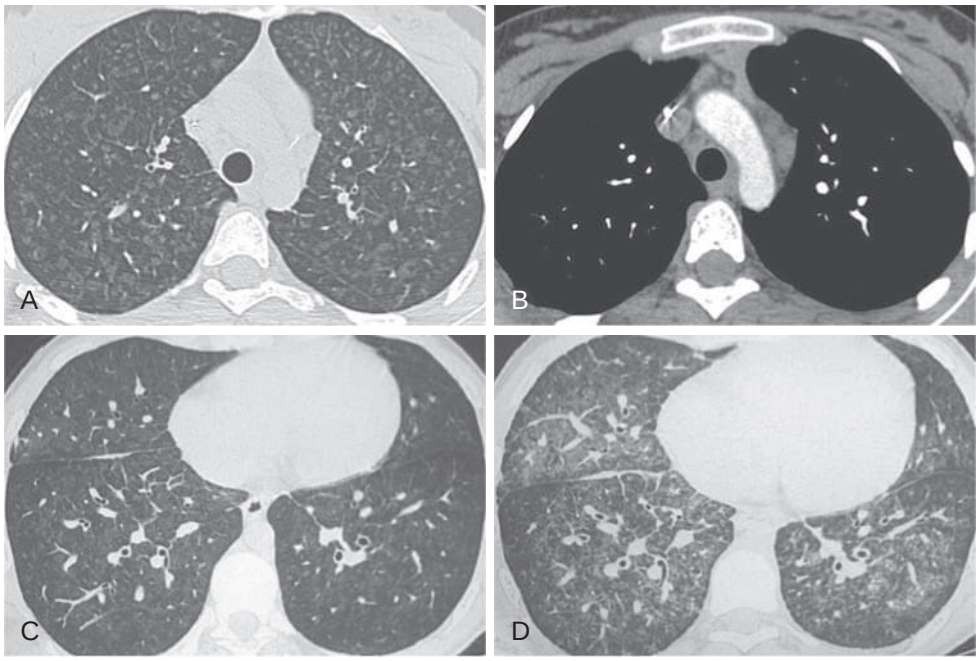

Figure 84.2 Imaging in pulmonary veno-occlusive disease/pulmonary capillary hemangiomatosis. (A) Ground-glass opacities with centrilobular pattern, poorly defined nodular opacities, and septal lines. (B) Mediastinal lymph node enlargement. (C) Imaging before initiation of specific therapy for PAH showed mild abnormalities with septal lines and ground-glass opacities. (D) After therapy with an endothelin receptor antagonist, imaging showed an increase in radiologic abnormalities consistent with pulmonary edema. (Modified from Montani D, Girerd B, Jais X, et al. Clinical phenotypes and outcomes of heritable and sporadic pulmonary veno-occlusive disease: a population-based study. *Lancet Respir Med*. 2017;5[2]:130.)

CONNECTIVE TISSUE DISEASE

CTD-associated PAH (CTD-PAH) is associated with several connective tissue diseases, particularly scleroderma and closely related conditions. Current guidelines recommend screening for PAH in scleroderma and utilizing echocardiography, pulmonary function testing with D_{LCO}, and biomarkers.[23,24] Survival rates for scleroderma-associated PAH are lower than for patients with IPAH. However, the treatment response, meaning relative improvement compared to no therapy, is robust. For example, in the CTD-PAH subgroup in the AMBITION study, up-front combination therapy with ambrisentan and tadalafil significantly reduced the risk of clinical failure compared to the pooled monotherapy group (hazard ratio, 0.43; 95% confidence interval, 0.24 to 0.77)[25]; similarly, in the GRIPHON trial, selexipag significantly reduced the risk of mortality/morbidity events in this subgroup (hazard ratio, 0.59; 95% confidence interval, 0.41 to 0.85, eFig. 84.7).[26] Other CTDs associated with PAH, albeit less commonly, include systemic lupus erythematosus, mixed CTD, Sjögren disease, polymyositis/dermatomyositis, and rheumatoid arthritis[27] (see Chapter 92).

CONGENITAL HEART DISEASE

CHD is a well-recognized risk factor for development of PAH (eFig. 84.8). In 1958, Paul Wood coined the term Eisenmenger's complex to describe pulmonary hypertension due to high *pulmonary vascular resistance* (PVR)[28] with reversed shunting through a large ventricular septal defect. Subsequently, the term has been used to describe pulmonary hypertension with cyanosis coupled with any systemic to pulmonary circulatory shunt. Compared to PAH associated with other shunts, PAH due to true Eisenmenger syndrome is associated with more preserved right ventricular compensation and therefore longer periods of clinical stability. The defect itself may provide a protective mechanism, providing a route for blood to reach the underfilled left ventricle and therefore off-loading right ventricular pressure/volume overload. However, right heart failure does eventually develop in most patients, and once it develops prognosis is poor.[29] Patients with PAH arising after closure of a congenital defect have been included in many PAH clinical trials and are treated following the usual algorithm. Patients with a very small defect may be classified as "PAH with small/coincidental defects" and are also treated similarly.[24] For those with large, uncorrected defects, the BREATHE-5 clinical trial found that treatment with bosentan led to improvement in exercise capacity compared with placebo,[30] while macitentan treatment in the MAESTRO clinical trial failed to improve *6-minute walk distance* (6MWD), the primary end point, but did lead to improvement in functional class, *N-terminal pro b-type natriuretic peptide* (NTproBNP) levels and, in a hemodynamic substudy, a trend towards improvement in PVR index (PVR relative to body surface area).[31] Observational studies have also suggested improvement following PAH therapies, and current CHD guidelines recommend their use.[32] Closure of the defect is not generally recommended once significant PAH has developed, though a small number of patients have tolerated late closure after improvement in PVR with PAH therapies.[33]

PORTAL HYPERTENSION

Portopulmonary hypertension (POPH) is similar to other types of PAH histologically and is characterized hemodynamically by elevations in pulmonary arterial pressure and PVR (eFig. 84.9). Incidence is estimated at 0.73% of all patients

with portal hypertension, based on a large autopsy study,[34] and rates of up to 5% have been reported in patients undergoing workup for liver transplantation.[35,36] Hemodynamic assessment in end-stage liver disease is complicated by the frequent coexistence of a high cardiac output related to splanchnic vasodilation and by concomitant volume overload and/or diastolic heart failure.[36] As a result, patients with POPH tend to have higher cardiac outputs and lower PVR than other World Health Organization Group I PAH patients.[37] Despite their more favorable hemodynamics, patients with POPH have 3.6 times the risk for 1-year mortality when compared to patients with other types of PAH.[38] Interestingly, the severity of the POPH does not correlate with the severity of the liver disease.[39]

A retrospective study evaluating screening right heart catheterization in POPH patients treated at the Mayo Clinic revealed the highest 5-year survival for patients who were medically treated for POPH and then underwent liver transplantation, at 67%.[40] In contrast, 5-year survival for patients treated with PAH medication alone, liver transplant alone, or neither were 45%, 25%, and 14%, respectively. Still, the mortality risk for patients with severe PAH who undergo liver transplantation has been reported to be as high as 36% historically, particularly in patients who were untreated for PAH or had severe disease.[41] These data regarding better long-term outcomes balanced by surgical risk for POPH patients have led to development of aggressive strategies for screening and treatment of these patients prior to transplantation, including recommendations for echocardiography in all patients being evaluated for liver transplant, right heart catheterization for patients whose estimated right ventricular systolic pressure exceeds 50 mm Hg, treatment of patients whose pulmonary hypertension is due to PAH, and liver transplantation of these patients only if treatment is successful in lowering the mean pulmonary arterial pressure to below approximately 35 mm Hg.[36,40]

HUMAN IMMUNODEFICIENCY VIRUS

Although a strong association between HIV and PAH has been shown, the etiology remains unclear (eFig. 84.10). Prevalence in studies requiring catheterization is as high as 0.5%,[42,43] but high rates of concomitant illicit intravenous drug use and/or methamphetamine use complicate the association.[44] Additionally, some studies with even higher prevalence rates relied on echocardiographic findings, potentially including some left heart disease–associated PH. Pulmonary hypertension can present in all stages of HIV, including in patients with no detectable viral load. Clinical and hemodynamic features of HIV-associated pulmonary hypertension are similar to those of IPAH.[45] Treatment is also similar, with extra precautions due to potential drug interactions with HIV medications.

SUPPORTIVE THERAPIES

EXERCISE AND PHYSICAL ACTIVITY

Although data are limited, consensus guidelines support the benefits of exercise in PAH patients.[24] Patients should avoid activities that lead to undue symptoms such as severe dyspnea, chest pain, lightheadedness, or syncope. Small studies have demonstrated that exercise training can be safe and lead to measurable improvements in fatigue, exercise capacity, and quality of life compared with untrained controls.[46,47] No significant safety concerns were identified, but training was generally highly supervised, often in an inpatient setting. There were also no significant changes in echocardiographic measures of right heart function or in BNP levels.[48]

HYPOXIA AND HIGH ALTITUDE

The benefits of supplemental oxygen for PAH patients, unlike for patients with pulmonary hypertension associated with lung diseases such as COPD,[49,50] are not clear. In fact, most PAH patients are not hypoxemic at rest. Mild hypoxemia, when present, is likely on the basis of reduced mixed venous oxygen saturation caused by low cardiac output with mild ventilation/perfusion inequality (see Chapter 44). The presence of more profound hypoxemia in a PAH patient should raise suspicion for underlying parenchymal lung disease, systemic to pulmonary shunting, PVOD/PCH, or pulmonary arteriovenous malformations as may be seen in pulmonary hypertension due to HHT. Additionally, a patent foramen ovale, present in more than 20% of the normal population, can contribute to hypoxemia in pulmonary hypertension by allowing shunting to develop after right heart pressures rise.

Given the known pulmonary vasodilatory effects of oxygen, there is a general consensus to recommend supplemental oxygen for patients with an arterial P_{O_2} less than 60 mm Hg or systemic arterial O_2 saturation less than 90% at rest. There are also limited data suggesting that oxygen may lead to improvements in exercise capacity in PAH patients with normal resting and only borderline reduced oxygen saturation with exercise.[51] One exception to this approach is in patients with Eisenmenger syndrome, with hypoxemia due to right-to-left shunting. In this group, the use of supplemental oxygen may have negligible benefit both on symptoms and on the pulmonary vasculature (because alveoli are not the cause of the hypoxemia).[52,53]

For travel, studies on the need for O_2 during prolonged flights in PAH are lacking, but guidelines suggest it should be considered for those with an arterial PO_2 less than 60 mm Hg.[24] Similarly, patients with these levels should avoid traveling to elevations above 5000 feet without supplemental oxygen[54] (see Chapter106).

PREGNANCY AND BIRTH CONTROL

Pregnancy is risky in patients with PAH, with a high peripartum mortality rate that peaks in the 3 months postdelivery.[55] Published case series do suggest some improvement in outcomes; for example, mortality rates in the 12–25% range were seen in three multicenter series,[56–58] an improvement compared with the 30–50% mortality rates seen in earlier studies. This likely relates to the availability of PAH therapies as well as the development of specialized teams to care for these patients. However, decompensation during pregnancy remains common and unpredictable due to the increased blood volume and cardiac output demands placed on the cardiovascular system. Therefore, it is strongly recommended that women with childbearing potential use

appropriate methods of birth control to avoid pregnancy; none of the highly effective methods is absolutely contraindicated in PAH, though surgical procedures (sterilization) may be too high risk for many patients. Additionally, some experts recommend avoiding estrogen-containing hormonal contraceptives in favor of progestin-only contraception or intrauterine devices to avoid the procoagulant activity of estrogens. This is particularly important in patients who are not anticoagulated[59] (see Chapter 129).

ORAL ANTICOAGULANTS

Until recently, anticoagulation was recommended for all patients with idiopathic, heritable, and anorexigen-associated PAH based on both observational studies and tissue studies showing microscopic thrombotic lesions in the pulmonary vasculature of PAH patients. However, more recent observational studies have shown variable results,[60,61] and current guidelines have lowered this to a class IIb recommendation (i.e., may be considered; usefulness is less well established by evidence/opinion).[24] Some experts recommend anticoagulation in patients treated with intravenous prostanoids due to the indwelling central venous catheters. Conversely, anticoagulation is generally not recommended in patients with other forms of pulmonary hypertension due to a lack of evidence as well as the increased bleeding risk, which is particularly a concern in patients with concomitant liver disease, CTD, or CHD.

DIURETICS

Diuretics have long been a mainstay of therapy for heart failure, including right ventricular failure. Both total-body and intravascular volume overload are common in PAH patients. In pivotal trials of PAH drugs, the majority of patients were on chronic diuretic therapy.[62,63] Volume overload of the right ventricle can cause compression of the left ventricle and contribute to decreased cardiac output and prerenal azotemia, symptomatic peripheral edema, and renal[64] and hepatic congestion. Thus, it is a common observation that, in decompensated PAH patients, aggressive diuresis leads to clinical and physiologic improvements.

A loop diuretic is frequently used first. Although furosemide is often the loop diuretic of choice, there is some evidence that torsemide might be more efficacious without increased side effects.[65] In addition, in patients with marked extravascular fluid accumulation and poor intestinal absorption, intravenous diuretic therapy is frequently needed. Anti-aldosterone drugs (e.g., spironolactone, eplerenone) are commonly combined with loop diuretics in PAH patients. Whether data suggesting a morbidity and mortality benefit of spironolactone in left-sided heart failure can be extrapolated to right-sided heart failure is not known.[66] In some cases, the addition of a thiazide diuretic to the regimen is appropriate. Although it is possible that in some PAH patients the right ventricle is preload dependent and therefore over-diuresis can be detrimental, this has not been our experience. More often in decompensated patients, aggressive diuresis (1 to 3 L negative fluid balance per day) leads to improvement in renal function and blood pressure.

CALCIUM CHANNEL BLOCKERS

Calcium channel blockers are effective in less than 7% of patients with IPAH[67] and are considered only in patients with IPAH, HPAH, and drug-induced PAH who respond to a vasodilator challenge in the catheterization lab. They are not recommended in other PAH subgroups regardless of vasodilator testing results due to a lack of long-term efficacy data. Vasodilator testing is typically performed using inhaled nitric oxide, intravenous adenosine, or intravenous epoprostenol. Advantages of inhaled NO include its rapid onset, short half-life, and lack of the systemic side effects seen with the other agents. A positive vasodilator test is defined as a decline of at least 10 mm Hg to a level below 40 mm Hg, with no decrease in cardiac output.[67] Patients with a positive response may be initiated on a calcium channel blocker at an initially low dose, with subsequent uptitration to the maximal tolerated dose. Close monitoring is required because patients with worsening PAH should be transitioned to other PAH therapies. Importantly, a "trial" of calcium channel blockers in nonresponders should not be attempted because this may lower systemic blood pressure and, if PAH severity prevents a concomitant increase in cardiac output, can lead to decompensation and death.

TARGETED THERAPIES

PAH-specific therapies have been available since 1995, when intravenous epoprostenol was approved by the U.S. *Food and Drug Administration* (FDA) based on the first prospective randomized, controlled trial in PAH. Since then, 12 therapies have been FDA approved for PAH (eTables 84.1 to 84.3) targeting three major pathways to offset the imbalance in endothelial-derived mediators seen in PAH: excessive endothelin-1 production, low nitric oxide production, and deficient prostacyclin (Fig. 84.3). Excessive endothelin-1 is addressed by *endothelin-receptor antagonists* (ERAs); the low nitric oxide is addressed by *phosphodiesterase-5 inhibitors* (PDE5Is) or soluble guanylyl cyclase activators, which activate the guanylate cyclase pathway, the major mediator of vasodilation by nitric oxide; and deficient prostacyclin is addressed by prostacyclin analogues. Evidence in favor of combination therapy has grown considerably, and most patients are now treated with two or more drugs, often started simultaneously soon after diagnosis. This is discussed in more detail in the "Combination Therapy" section that follows the discussion of individual medications.

ENDOTHELIN RECEPTOR ANTAGONISTS

In humans, two *endothelin* (ET)-1 receptor subtypes are found, ET-A and ET-B. Antagonism of one or both receptors has been shown to be an effective treatment strategy for PAH, with three FDA-approved ERAs: bosentan,[63,68] ambrisentan,[69] and macitentan.[70] ERAs improve exercise capacity and reduce risk of clinical worsening events. They are well tolerated by most patients but can cause nasal congestion and anemia. Additionally, significant peripheral edema was noted during the clinical trials, particularly in older patients. This has also been seen at higher rates in patients with three or more risk factors for or findings of

eTable 84.1 Short-Term Randomized Controlled Clinical Trials in PAH: Majority of Patients Not on Background Therapy

Study	Medication	Background PAH Rx (%)	N	Weeks	Δ6MWD vs. Placebo (m)		FC	QOL	Catheterization	CW or Death	NTproBNP
PROSTACYCLINS											
Barst[62]	Epoprostenol	0	81	12	47	Y*	Y	Y	Y	Y	—
Badesch[78]	Epoprostenol	0	111	12	108	Y*	Y	—	Y	—	—
Simonneau[83]	Treprostinil SC	0	470	12	16	Y*	—	Y	Y	—	—
Olschewski[91]	Iloprost inhaled	0	203	12	36	Y†	Y†	Y	Y	N	—
Jing[93]	Treprostinil PO	0	349	12	26	Y*	N	—	—	N	—
ERA											
Channick[68]	Bosentan	0	32	12	76	Y*	Y	—	Y	Y	—
Rubin[63]	Bosentan	0	213	16	44	Y*	Y	—	—	Y	—
Galie, FC II[120]	Bosentan	16	185	24	35	N†	Y	Y	Y†	Y	Y
Galie[121]	Ambrisentan	0	202	12	5 mg = 31 10 mg = 51	Y*	Y	N	—	N	Y
Galie[121]	Ambrisentan	0	192	12	5 mg = 59	Y*	N	Y	—	Y	Y
PDE-5 INHIBITORS											
Galie[72]	Sildenafil	0	93‡	12	45	Y*	Y	—	Y	N	—
UNREPAIRED CHD											
Galie[30]	Bosentan	0	54	16	53	Y	—	—	Y*	—	—
Gatzoulis[31]	Macitentan	27	226	16	–5	N*	N	—	N	—	Y

Includes 12- to 24-week studies with >100 patients where a majority of patients were not on background therapy, plus pivotal early studies (epoprostenol, bosentan) that included fewer patients.
Y, statistically significant ($P < 0.05$); N, not significant ($P > 0.05$); —, not reported.
*Primary end point.
†Coprimary or combined primary endpoint.
‡Substudy.
6MWD, 6-minute walk distance (results for approved dose[s] only); CHD, congenital heart disease; CW, clinical worsening; ERA, endothelin-1 receptor antagonist; FC, functional class; NTproBNP, N-terminal pro b-type natriuretic peptide; PAH, pulmonary arterial hypertension; PDE-5, phosphodiesterase-5; PO, oral; QOL, quality of life; SC, subcutaneous.

eTable 84.2 Short-Term Randomized Controlled Clinical Trials in PAH: Majority of Patients on Background PAH Therapy

Study	Medication	Background PAH Rx (%)	N	Weeks	Δ6MWD vs. Placebo (m)		FC	QOL	Catheterization	CW or Death	NTproBNP
Simonneau[102]	Sildenafil	100	267	16	29	Y*	—	Y	Y	Y	—
Galie[73]	Tadalafil	53	93‡	16	33	Y*	N	Y	Y	Y	—
McLaughlin[92]	Treprostinil inhaled	100	235	12	20	Y*	N	Y	—	N	Y
Tapson[95]	Treprostinil PO	100	350	16	11	N*	N	—	—	N	—
Tapson[94]	Treprostinil PO	100	310	16	10	N*	N	N	—	N	N
Ghofrani[77]	Riociguat	50	443	12	36	Y*	Y	N	Y	Y	Y

Includes 12- to 24-week studies with >100 patients with at least 50% of patients on PAH background therapy.
Y, statistically significant ($P < 0.05$); N, not significant ($P > 0.05$); — not reported.
*Primary end point.
‡Substudy.
6MWD, 6-minute walk distance; CW, clinical worsening; FC, functional class; NTproBNP, N-terminal pro b-type natriuretic peptide; PAH, pulmonary arterial hypertension; PO, oral; QOL, quality of life.

eTable 84.3 Long-Term Outcome-Based Randomized Controlled Clinical Trials in PAH

Study	Medication	Background PAH Rx (%)	N	Weeks*	Δ6MWD vs. Placebo (m)		FC	QOL	Catheterization	Composite CW End Point	NTproBNP
Pulido[101]	Macitentan	64	742	85, 104	22	Y	Y	Y	Y†	Y ↓45%‡	Y
Galie[99]	Ambrisentan, Tadalafil	0§	500	69,79	25	Y	N	N	—	Y↓50%‡	Y
Sitbon[97]	Selexipag	80	1156	64,71	12	Y	N	—	—	Y↓40%‡	Y
McLaughlin[122]	Bosentan	100	334	115,133	22	Y	N	—	—	N↓17%‡	Y

Includes long-term studies with composite clinical events as the primary end point.
Y, statistically significant ($P < 0.05$); N, not significant ($P > 0.05$); — not reported.
*Weeks: median duration for placebo or monotherapy group is listed first, followed by the median duration for the study drug or combination therapy group.
†Substudy, N = 145.
‡Primary end point.
§AMBITION included treatment naive patients, all of whom received one or two therapies with ambrisentan alone, tadalafil alone, or both ambrisentan and tadalafil (randomized 1:1:2).
6MWD, 6-minute walk distance; CW, clinical worsening; FC, functional class; NTproBNP, N-terminal pro b-type natriuretic peptide; PAH, pulmonary arterial hypertension; QOL, quality of life.

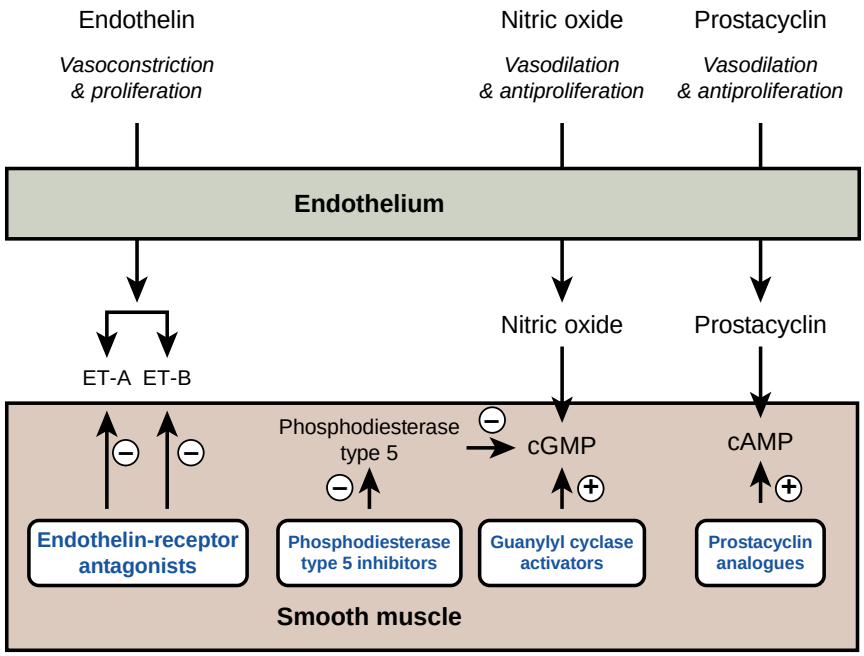

Figure 84.3 Schematic of three abnormal endothelial mediator pathways targeted by current therapies. The endothelin-1 pathway acts via two receptor subtypes (ET-A and -B) as a vasoconstrictor/proliferator pathway and is inhibited by the endothelin receptor antagonists. The nitric oxide and prostacylin pathways are vasodilatory and anti-proliferative; these are enhanced by either inhibition of an inhibitory process (phosphodiesterase type 5 inhibitors) or by more direct activation. +, stimulation; –, inhibition; ET-A, endothelin receptor A; ET-B, endothelin receptor B; cAMP, cyclic adenosine monophosphate; cGMP, cyclic guanosine monophosphate.

left heart disease, such as systemic hypertension, diabetes, atrial fibrillation, coronary artery disease, and obesity.[71] Close monitoring of volume status is therefore indicated during drug initiation and up-titration.

ERAs as a class are considered teratogenic; therefore women of childbearing potential require monthly pregnancy testing and the use of two reliable forms of birth control during therapy. Increases in liver aminotransferases greater than eight times the upper limit of normal were also noted with bosentan therapy during randomized controlled clinical trials; as a result, all patients receiving bosentan are required to undergo monthly liver function testing. The rate of liver function test abnormalities with ambrisentan and macitentan administration has been found to be similar to that of the general population, but periodic liver function testing and hemoglobin monitoring are still recommended. All three ERAs also have significant drug interactions that should be checked prior to prescribing. Notably, bosentan increases the metabolism of oral contraceptive pills, thereby reducing their effectiveness. (See package inserts for additional details on monitoring, pregnancy prevention, and drug interactions.)

PHOSPHODIESTERASE TYPE 5 INHIBITORS

The PDE5Is, sildenafil and tadalafil, are selective inhibitors of *cyclic guanosine monophosphate* (cGMP)-specific PDE5, an enzyme that promotes the breakdown of cGMP; by enhancing cGMP, the PDE5Is increase nitric oxide signaling. Both sildenafil and tadalafil are usually well tolerated, and no significant laboratory abnormalities were noted during the pivotal clinical trials. Sildenafil (Revatio) was evaluated in the SUPER-1 (Sildenafil Use in Pulmonary Arterial Hypertension) trial, a 12-week randomized, double-blind, placebo-controlled trial comparing placebo, 20 mg, 40 mg, and 80 mg 3 times daily.[72] Significant improvement was seen in exercise capacity, functional class, and hemodynamics but not in the incidence of clinical worsening. Walk distance improvement was similar across the three doses. However, hemodynamic improvement was greater with higher doses of sildenafil, as was the percentage of patients with improved functional class. Despite these trends, the only dose approved by the U.S. FDA and European Medicines Association is 20 mg tid PO, though higher doses are sometimes used clinically. Tadalafil (Adcirca) was approved in 2009 based on the PHIRST trial, a 16-week study of 2.5 mg, 10 mg, 20 mg, and 40 mg tadalafil or placebo.[73] Tadalafil 40 mg led to improvement in exercise capacity, quality of life, hemodynamics, and time to clinical worsening. Smaller improvements in walk distance were seen with 10 mg and 20 mg.

Common adverse events during the clinical trials included headache, myalgias, flushing, epistaxis, and dyspepsia. Both drugs can be initiated at their approved dose (sildenafil 20 mg tid or tadalafil 40 mg daily), but tadalafil is often started at 20 mg PO daily for the first week in an attempt to lessen headaches and other side effects.

Rare potential adverse effects with sildenafil and tadalafil include impaired vision and hearing. Mild vision changes including particularly color vision changes are thought to relate to cross-reactivity with and inhibition of retinal phosphodiesterase-6. More severe vision changes including sudden vision loss have also been reported, and hearing loss has been reported as well; both are of unclear mechanism.[74] Patients should discontinue use and seek immediate medical attention in the event of sudden loss of vision in one or both eyes or with sudden changes in hearing.

SOLUBLE GUANYLYL CYCLASE ACTIVATORS

Riociguat is a direct activator of guanylyl cyclase, increasing levels of cGMP by stimulating its synthesis.[75] It was studied in the PATENT phase III randomized controlled

clinical trial. Improvement was seen in the primary end point, change in 6MWD at 12 weeks, and in a number of secondary end points including PVR, NT-BNP level, and World Health Organization functional class.[76,77] Riociguat cannot be given concurrently with PDE5Is due to the risk of hypotension and should instead be substituted for this class of medication. It is also teratogenic, with pregnancy testing and birth control requirements similar to the ERAs.

PROSTACYCLIN ANALOGUES

Prostacyclin synthase is under-expressed in endothelial cells in the lungs of PAH patients, and epoprostenol (prostaglandin I2, prostacyclin) was the first therapy shown in randomized controlled clinical trials to be beneficial in PAH. With prostacyclin analogs now available in oral, inhaled, subcutaneous, and intravenous forms, this class of medications remains a key component of PAH therapy. Management can be complicated due to the variable dosing schemes as well as the frequent side effects. "Prostacyclin-type" side effects including jaw pain, nausea, vomiting, headache, diarrhea, and leg pain are seen universally with medications in this class. In general, prostanoid medications are started at a low starting dose and then gradually up-titrated until reaching either the target dose or the maximum tolerated dose, as limited by symptoms. Other class effects include the potential to lower systemic blood pressure and reduce platelet function. Clinically significant hypotension is uncommon except in the presence of other systemic antihypertensives, though mild hypotension may also be seen with combinations of PAH therapies. Side effects are most often manageable with a symptom-based approach, and abrupt cessation should be avoided because pulmonary hypertension can rebound, leading to worsening symptoms and potentially death.

Epoprostenol

Epoprostenol was the first prostanoid to be developed. Continuous intravenous infusions of prostacyclin (prostaglandin I2, epoprostenol) produce sustained improvement in hemodynamics and exercise tolerance and prolonged survival. In the first randomized, prospective study of epoprostenol,[62] 81 patients with *New York Heart Association* (NYHA) class III or IV symptoms despite treatment with conventional therapy were randomized to either continuous intravenous epoprostenol plus conventional therapy or conventional therapy alone for 12 weeks. At 12 weeks, 6MWD, the primary end point, had improved by 32 meters in the continuous intravenous epoprostenol group and decreased by 15 meters in the conventional therapy group. There were also significant improvements in the epoprostenol group in hemodynamics, quality of life, and NYHA functional class. Eight patients died during the 12-week study, all in the conventional treatment group. Notably, this is the only randomized controlled PAH trial to show a significant effect on survival. A subsequent study found significant improvements in 6MWD, functional class, and exercise capacity in patients with scleroderma-associated PAH.[78]

Long-term follow-up studies have shown sustained benefits, including improved functional class and survival, compared with historical controls. Five-year survival of greater than 60% was reported in two large series[79,80] compared with a median survival of less than 3 years in the "pre-epoprostenol" era, and even better outcomes have been reported with epoprostenol in combination with other therapies.[81,82] Despite its clear benefits, chronic use of epoprostenol is complex and requires an indwelling central venous catheter, continuous infusion pump, and daily preparation of the medication. In addition, prostacyclin-type side effects are nearly universal and require both careful dose titration as well as focused symptom management.

Subcutaneous and Intravenous Treprostinil Sodium

Treprostinil sodium is an analogue of prostacyclin with a longer half-life of approximately 4 hours compared with the 3- to 6-minute half-life for epoprostenol. Treprostinil's initial approval was for continuous subcutaneous delivery, based on a double-blind, randomized controlled trail that included 470 patients with IPAH (58%), CTD-PAH, or CHD-PAH.[83] Treprostinil led to improvements in 6MWD, dyspnea indices, and hemodynamics. Walk distance improvement among treprostinil-treated patients varied by dosing quartile, with the greatest improvement seen in patients in the highest dosing quartile (>13.8 ng/kg/min). Infusion site pain was the major adverse event, with 200 (85%) patients in the treprostinil group reporting site pain versus 62 (27%) in the placebo arm. Intravenous treprostinil was subsequently approved based on bioequivalence with subcutaneous treprostinil, intended for use in patients not tolerating subcutaneous infusion. Small, mostly open-label studies suggest good tolerability and sustained hemodynamic response, including both patients newly started on intravenous treprostinil as well as those transitioned from epoprostenol.[84–86] Prostacyclin-type side effects are similar to those seen with epoprostenol.

Epoprostenol and Treprostinil Dosing

Intravenous epoprostenol is typically initiated in the hospital setting at 1 to 2 ng/kg/min and titrated up to approximately 4 to 8 ng/kg/min prior to discharge, aiming to reach an effective dose as quickly as possible while also avoiding excessive side effects. After the initial inpatient up-titration, patients continue to up-titrate at home at approximately 3- to 7-day intervals until a target dose is reached. Initiation of subcutaneous or intravenous treprostinil is similar, but doses are often 1.5- to 2-fold greater.[86,87] Typical maintenance doses are often reached by 3 to 6 months, and are in the 20 to 40 ng/kg/min range for epoprostenol and 20 to 80 ng/kg/min range for treprostinil.[24,88] Although evidence to support specific dosing strategies is limited, subcutaneous treprostinil doses greater than 40 ng/kg/min were associated with improved survival in the long-term extension study of the subcutaneous treprostinil clinical trial (N = 230; 28% reached this dose).[89] However, excessive doses of prostacyclins can lead to an abnormally high cardiac output and severe side effects.[90] Therefore, dosing must be individualized, and periodic hemodynamic monitoring is recommended for all patients on parenteral prostacyclins, particularly following significant dose adjustments.[88,90]

Inhaled Iloprost and Treprostinil

Two prostacyclin analogues, iloprost and treprostinil, are approved for use in inhaled formulations. Inhaled iloprost is delivered via ultrasonic nebulizer 6 to 9 times daily. In the Aerosolized Iloprost Randomized study, patients receiving inhaled iloprost for 12 weeks were more likely to reach the composite end point of improvement in functional class

and greater than 10% increase in 6MWD compared with patients receiving placebo (17% vs. 5%).[91] Inhaled treprostinil is administered four times daily via the Tyvaso Inhalation System, an ultrasonic nebulizer, and a dry powder inhaler is currently under investigation. In the TRIUMPH-1 study, inhaled treprostinil led to improvement in 6MWD (primary end point) as well as quality of life and NTproBNP compared with placebo.[92] Unlike prior studies, TRIUMPH-1 enrolled only patients receiving background therapy with either an ERA or a PDE5I. Theoretical benefits for inhaled administration include direct delivery to the pulmonary vasculature and potentially fewer systemic side effects.

Oral Treprostinil and Selexipag

Although parenteral prostacyclins are widely considered to be the "strongest" therapies for pulmonary hypertension, the delivery of the drug has traditionally been cumbersome. In the last few years, two oral medications in this class have been approved by the FDA.

Oral treprostinil was approved in 2013 on the basis of the pivotal FREEDOM-M trial. FREEDOM-M included 349 patients who were naive to PAH therapy. Subjects were randomized to oral treprostinil versus placebo, and 6MWD at 12 weeks was improved by 23 meters in the treatment group. Larger improvements were seen in those with longer drug exposure and higher dosages.[93] Two other pivotal trials (FREEDOM-C and FREEDOM-C2) of oral treprostinil in PAH patients who were stable on background ERA, PDE5I, or ERA plus PDE5I therapy failed to meet their primary end point.[94,95] However, a third study evaluating longer-term outcomes as well as 3 times daily dosing (compared with twice daily in the earlier studies) found a 26% relative reduction in clinical worsening events compared with placebo patients (hazard ratio, 0.74, $P = 0.03$) as well as improvement in functional class and NT-proBNP levels.[96]

Oral treprostinil causes the aforementioned prostacyclin side effects and aggressive management of these to allow up-titration to an effective dosage is often required.

Selexipag is not a prostacyclin but rather a prostacyclin receptor agonist. It was FDA approved for the treatment of PAH in 2015. The pivotal clinical trial, GRIPHON, enrolled 1156 patients randomized to selexipag versus placebo with a primary end point that was a composite of death, hospitalization, or disease progression. Subjects could be naive to PAH therapy, on background monotherapy with an ERA or PDE5I, or on background combination therapy with both. At the end of 3 years the treatment group had a 40% reduction in the risk of disease progression. The side effect profile is consistent with the prostacyclin class of medications and often requires symptom management to allow uptitration.[97]

COMBINATION THERAPY

There is strong rationale for combining drugs to treat PAH, and current guidelines now recommend combination therapy for nearly all patients with PAH.[24,98] The combination of an ERA and a PDE5I has been best studied as up-front or add-on two-drug therapy,[99,100] while the addition of a prostacyclin is often considered if response is inadequate.

A small residual role for monotherapy remains, particularly in patients who are more likely to have a negative response to therapy, patients suspected of having PVOD/PCH, and patients older than 75 years or with multiple risk factors for heart failure with preserved ejection fraction. Patients with very mild disease and stable patients with a low-risk profile while on long-term monotherapy may also be appropriate candidates for continued monotherapy.[98]

The AMBITION clinical trial published in 2015 set the standard for initiating dual therapy in treatment naive patients with PAH.[99] The trial was composed of three arms comparing the initiation of ambrisentan monotherapy, tadalafil monotherapy, and ambrisentan plus tadalafil up-front dual therapy with a primary end point of time to first clinical failure. The trial enrolled 500 patients and followed them for over 3.5 years. The dual-therapy group exhibited a 50% improvement in time to clinical worsening compared to the pooled monotherapy group. The dual-therapy group also had more improved 6MWD (49 meters vs. 24 meters) and lower NTproBNP levels.[99] Adverse events were more common in the up-front dual-therapy group and were most commonly headache, nasal congestion, edema, and anemia.

The dual ERA macitentan was studied in SERAPHIN, a long-term event-driven, randomized, double-blind, placebo-controlled trial. The primary end point was the time to first significant morbidity or mortality event, and patients were followed for 3 years. The majority (64%) of patients enrolled were on background therapy, most often with a PDE5I. There was a 45% risk reduction in the primary end point in the macitentan treatment group.[101]

Selexipag has also been well studied as an add-on therapy for patients with an inadequate response. In the pivotal GRIPHON trial, the majority of patients enrolled were already taking background PAH medication, with 15% on an ERA alone, 32% on a PDE5I alone, and 33% taking both an ERA and a PDE5I.[97] Additional positive studies that included large numbers of patients receiving combination therapy are shown in eTables 84.2 and 84.3, including the pivotal trials for both inhaled treprostinil and riociguat.

Although most studies involving parenteral epoprostenol and treprostinil were completed in the monotherapy era, there is evidence supporting combination therapy with prostacyclins as well. PACES (Pulmonary Arterial Hypertension Combination Study of Epoprostenol and Sildenafil) was the largest of these, evaluating the addition of sildenafil or placebo in 267 patients already receiving epoprostenol. Subjects were randomized to either sildenafil 80 mg orally tid or placebo for 16 weeks.[102] The trial demonstrated improvement in 6MWD, hemodynamics, and time to clinical worsening for the sildenafil plus epoprostenol group. Although mortality was not a prespecified end point, there were seven deaths during the 16-week clinical trial, all within the placebo plus epoprostenol group.

Maximal medical therapy is currently considered to be triple therapy including an intravenous or subcutaneous prostanoid infusion, and nearly all patients with an inadequate response to oral therapies including oral treprostinil or selexipag should be considered for treatment with an intravenous or subcutaneous prostanoid.[98] Although long-term randomized controlled clinical trials are lacking, observational studies suggest greater hemodynamic benefits with prostanoid infusion combinations as well as improved long-term outcomes compared to historical controls.

To wit, in 19 patients with IPAH treated in the French registry, up-front triple therapy including a prostacyclin infusion led to a 71% decline in PVR and a 95% transplant-free survival rate at 3 years; this compares favorably to monotherapy and dual-combination therapy patients treated at the same center.[81,82] In another study involving 196 patients with IPAH, CTD-PAH, or CHD-PAH at two U.S. medical centers, the subset of patients receiving triple therapy including parenteral infusion showed the largest declines in PVR compared to baseline. Further, among patients transitioning from nonparenteral triple therapy (i.e., triple therapy with an inhaled or oral prostanoid), the initiation of a parenteral prostanoid led to an additional 36% decline in PVR.[103]

ATRIAL SEPTOSTOMY AND POTTS SHUNT

Balloon atrial septostomy may be considered after failure of medical therapy or as a bridge to transplantation in a subset of patients. Balloon atrial septostomy is a percutaneous procedure in which a right-to-left intracardiac shunt is created by puncture of the interatrial septum and subsequent balloon dilation. Because the right-to-left shunt will induce some degree of hypoxemia, it can only be utilized in patients without baseline hypoxemia. Although the procedure can reduce right ventricular pressure/volume overload and improve cardiac output, there is a risk of periprocedural mortality, and it should be performed at an experienced center.[104]

A transcatheter Potts shunt is an alternative procedure also designed to decompress the failing right heart. It involves the creation of an anastomosis between the left pulmonary artery and the descending aorta. A theoretical advantage of this procedure is that its anatomic placement avoids directly exposing the brain and myocardium to deoxygenated blood. Benefit has been demonstrated in small case series of patients with decompensated PAH, but periprocedural mortality remains a concern.[105]

MECHANICAL SUPPORT

Indications for mechanical cardiovascular support in patients with PAH remain a subject of debate. Mechanical support as a bridge to lung or heart/lung transplantation is the indication best supported by the literature.[106] Other indications require a careful discussion of the risks and benefits of mechanical support among the patient, the patient's family, and the medical team. Such relative indications include patients who have a reversible cause of decompensation with reasonable chance of recovery, as may be the case in postoperative acute-on-chronic right ventricular failure or with an acute, reversible condition such as sepsis. Because failure to wean from mechanical support is a significant risk, mechanical support is contraindicated in patients without a reasonable chance of recovery or without the option of transplantation.

Extracorporeal membrane oxygenation is currently the preferred method of mechanical support for decompensated patients with PAH who have not responded to medical therapy. Because of the failure of the right ventricle, an arteriovenous configuration is preferred to a venovenous configuration in the majority of patients.[107] Extracorporeal membrane oxygenator flows of 2.5 to 4 L/min are appropriate for PAH patients and allow unloading of the right ventricle, preservation of pulmonary blood flow, and adequate systemic oxygen delivery while avoiding overload of the left heart, which may have secondary dysfunction in patients with severe right ventricular failure,[106,108]

Pulmonary artery–left atrium oxygenators, or lung-assist devices, are also available for mechanical support of PAH patients. These pumpless devices utilize the patient's right ventricle but decrease the afterload on the right ventricle by bypassing the pulmonary circulation. An advantage of this approach is that avoidance of a femoral approach allows ambulation of the patient. One disadvantage is that the cannulation itself is a more involved surgical procedure with a median sternotomy or thoracotomy and is therefore less practical in a patient with cardiogenic shock.[106,109]

Right ventricular assist devices have been attempted in patients with right ventricular failure due to PAH, with disappointing results published in case reports. Complications such as increased pulmonary pressures with the increased flow, hemorrhage, and pulmonary edema have been reported. Although some of the complications may be mitigated by using lower flows with the device, extracorporeal membrane oxygenation or extracorporeal lung support remain the preferred mechanical devices in patient with PAH.[110-112]

LUNG TRANSPLANTATION

In patients not responding to maximal medical therapy, lung transplantation remains the primary option. According to the International Society of Heart and Lung Transplantation, current recommendations for consideration of transplantation in PAH include persistent NYHA class III or IV on maximal medical therapy, low or declining 6MWD, no response to therapy with intravenous epoprostenol, cardiac failure with cardiac index less than 2 L/min/m^2, and elevated right atrial pressure (>15 mm Hg).[113] Additionally, all patients with PVOD should be referred for transplant evaluation at the time of diagnosis. After transplantation, PAH patients have increased risk of early mortality due to higher rates of hemodynamic instability. However, among those surviving 1 year, median survival is better for PAH patients than for patients with most other lung transplant indications.[114–116]

RISK ASSESSMENT

Risk assessment is important in evaluating prognosis and for deciding on specific PAH therapy. Modern treatment algorithms for PAH reflect this priority, with treatment recommendations focused on future mortality risk rather than patient symptoms alone. Goals include achieving and then maintaining a low-risk profile for early mortality. Although the PAH disease process involves the pulmonary vasculature, symptoms and disease progression associate strongly with cardiac function. Therefore, laboratory, hemodynamics, and imaging measures of cardiac function are included in the assessment of prognosis.

The best studied individual measures of prognosis are shown in Table 84.1, with suggested cutoffs for each measure that associate with lower, intermediate, and higher

Table 84.1 European Society of Cardiology/European Respiratory Society Risk Table

Determinants of prognosis[a] (estimated 1-year mortality)	Low risk <5%	Intermediate risk 5–10%	High risk >10%
Clinical signs of right heart failure	Absent	Absent	Present
Progression of symptoms	No	Slow	Rapid
Syncope	No	Occasional syncope[b]	Repeated syncope[c]
WHO functional class	I, II	III	IV
6MWD	>440 m	165–440 m	<165 m
Cardiopulmonary exercise testing	Peak $\dot{V}O_2$ >15 mL/min/kg (>65% pred.) $\dot{V}E/\dot{V}CO_2$ slope <36	Peak $\dot{V}O_2$ 11–15 mL/min/kg (35–65% pred.) $\dot{V}E/\dot{V}CO_2$ slope 36–44.9	Peak $\dot{V}O_2$ <11 mL/min/kg (<35% pred.) $\dot{V}E/\dot{V}CO_2$ slope ≥45
BNP and NT-proBNP plasma levels	BNP <50 ng/L NT-proBNP <300 ng/L	BNP 50–300 ng/L NT-proBNP 300–1400 ng/L	BNP >300 ng/L NT-proBNP >1400 ng/L
Imaging (echocardiography, CMR imaging)	RA area <18 cm^2 No pericardial effusion	RA area 18–26 cm^2 No or minimal pericardial effusion	RA area >26 cm^2 Pericardial effusion
Hemodynamics	RAP <8 mm Hg CI ≥2.5 L/min/m^2 $S\bar{v}O_2$ >65%	RAP 8–14 mm Hg CI 2.0–2.4 L/min/m^2 $S\bar{v}O_2$ 60–65%	RAP >14 mm Hg CI <2.0 L/min/m^2 $S\bar{v}O_2$ <60%

[a]Most of the proposed variables and cutoff values are based on expert opinion. They may provide prognostic information and may be used to guide therapeutic decisions, but application to individual patients must be done carefully. Also note that most of these variables have been validated mostly for idiopathic PAH, and the cutoff levels used above may not necessarily apply to other forms of PAH. Furthermore, the use of approved therapies and their influence on the variables should be considered in the evaluation of the risk.

[b]Occasional syncope during brisk or heavy exercise or occasional orthostatic syncope in an otherwise stable patient.

[c]Repeated episodes of syncope, even with little or regular physical activity.

6MWD, 6-minute walking distance; BNP, brain natriuretic peptide; CI, cardiac index; CMR, cardiac magnetic resonance; NTproBNP, N-terminal pro B-type natriuretic peptide; PAH, pulmonary arterial hypertension; pred, predicted; RA, right atrium; RAP, right atrial pressure; $S\bar{v}O_2$, mixed venous oxygen saturation; $\dot{V}E/\dot{V}CO_2$, ventilatory equivalents for carbon dioxide; $\dot{V}O_2$, oxygen consumption; WHO, World Health Organization.

From Joint Task Force for the Diagnosis and Treatment of Pulmonary Hypertension of the European Society of Cardiology (ESC) and the European Respiratory Society (ERS). 2015 ESC/ERS Guidelines for the diagnosis and treatment of pulmonary hypertension. *Eur Respir J*. 2015;46:903-975.

mortality risk. Lower risk findings include functional class I or II, 6MWD greater than 440 meters, right atrial pressure less than 8 mm Hg, and cardiac index greater than 2.5 L/min/m^2, among others (Fig. 84.4). Although not initially intended as a scoring system, the number of lower risk measures at both baseline and first follow-up was strongly associated with survival in a French registry study (eFig. 84.11).[117] Obtaining the average of the European Society of Cardiology/European Respiratory Society risk measures also provides good risk stratification, as shown in the COMPERA registry.[118] Benefits of this approach are the ability to include a larger number of prognostic measures as well as allowing for assessment of prognosis even when some measures are not available.

Finally, another risk calculator is the REVEAL equation, developed from the large U.S.-based REVEAL registry.[119] The most recent update, REVEAL 2.0, includes 13 variables (eFig. 84.12). Although the inclusion of nonmodifiable risk factors (PAH subtype, male older that 60 years), has been criticized, this does improve the overall accuracy of the prognostic assessment. Another advantage of the REVEAL calculator is the diverse PAH patient population studied, making it broadly applicable for Group 1 PAH patients.

Whichever risk stratification strategy is utilized, a patient on treatment who is doing well will generally have functional class I or II symptoms, good exercise capacity, a low BNP or NT-proBNP level, and a normal cardiac index and right atrial pressure at catheterization. Cardiac imaging with echocardiography or magnetic resonance imaging will typically show a normal or near normal right atrial and right ventricular size and function and a lack of significant left ventricular compression, pericardial effusion, or tricuspid regurgitation.[24,118] Achieving a lower PVR, particularly a PVR less than 5 Wood units, has also recently been found to associate with improved long-term outcome.[8,80,119]

APPROACH TO THERAPY

Decisions about therapy are made based on many factors, including severity of illness, comorbidities, route of administration, and anticipated side effect profile. Many patients are treated with a combination of an ERA and a PDE5I, either as up-front or sequential therapy, while some patients with severely abnormal hemodynamics may receive up-front triple therapy, including a parenteral prostanoid. Current guidelines recommend serial reassessments and escalation of therapy when appropriate in patients failing to achieve low risk clinical findings.

An additional point to remember is that most clinical trials in PAH have included IPAH, CTD-PAH, and repaired CHD and,

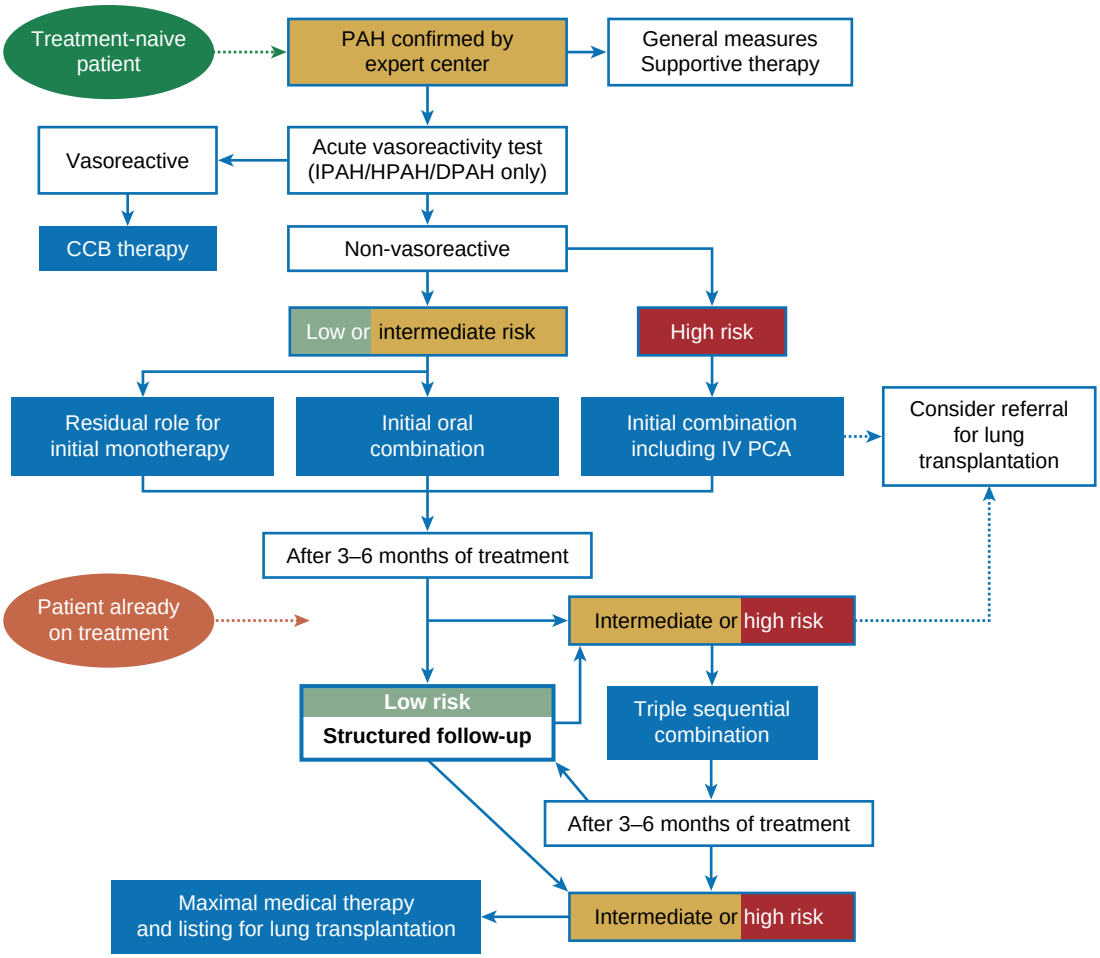

Figure 84.4 Treatment algorithm from the 2015 European Society of Cardiology/European Respiratory Socieity Pulmonary Arterial Hypertension Guidelines. Acute vasoreactivity testing is recommended for idiopathic *pulmonary arterial hypertension* (IPAH), *heritable PAH* (HPAH), and *drug-induced PAH* (DPAH). For those with a negative response as well as for those with other forms of PAH, treatment is chosen partially based on risk stratification. Recommendations include use of combination therapy in most patients, either as oral therapy or, for higher-risk patients, combination therapy that includes a parenteral prostanoid. CCB, calcium channel blocker; PCA, prostacyclin analogues. (From Galiè N, Channick RN, Frantz RP, et al. Risk stratification and medical therapy of pulmonary arterial hypertension. *Eur Respir J.* 2019;53[1]:1801889.)

as a result, considerable evidence of the optimal treatment strategies exists for these subgroups. In contrast, a much smaller number of studies have included POPH, HIV, and unrepaired CHD, and no randomized studies have included PVOD/PCH.

When combining PAH therapies, several principles should be kept in mind. First, PAH therapies have not been found to be beneficial in studies of PAH associated with left heart disease or lung disease. While most patients with these forms of PAH can be excluded after the usual diagnostic algorithm, occasional patients may have atypical features and/or marked volume excess at diagnosis, making it difficult to be certain. In such patients, in whom a Group 1 diagnosis is felt to be most likely and where PAH therapy is planned, monotherapy is sometimes considered. This allows assessment of tolerability and can be followed by repeating key diagnostic tests after 3 to 6 months in order to characterize the severity and overall disease process. Second, initiation of multiple medications together may increase the risk of certain adverse reactions; this may not necessarily be reduced by staggering initiation by a week or two, but this does at least allow assessment of tolerability as each medication is added.

In summary, the prognosis for patients with PAH continues to improve with the development of new treatments and the evolution of treatment strategy. Multiple long-term clinical trials have now confirmed the benefits of PAH therapies alone and in combination with more robust clinical end points, including morbidity and mortality measures. Treatment strategy is evolving towards early double- and triple-combination therapy, with goals of preventing or reversing right heart failure and improving symptoms and quality of life. This proactive treatment algorithm is best utilized when a correct diagnosis is diligently and expediently pursued. Early diagnosis and watchful, goal-directed follow-up will ensure the best possible patient outcomes as PAH research and best practices continue to emerge.

Acknowledgement

We thank Drs. Lewis Rubin and Richard Channick for their work on earlier versions of this chapter.

Key Points

- Group 1 *pulmonary arterial hypertension* (PAH) includes idiopathic and heritable PAH as well as PAH associated with drugs and toxins, connective tissue disease, congenital heart disease, portal hypertension/liver disease, human immunodeficiency virus, and *pulmonary veno-occlusive disease/pulmonary capillary hemangiomatosis* (PVOD/PCH).
- Significant remodeling in the small pulmonary arteries can be found in all forms of PAH. In addition, PVOD/PCH also has remodeling of pulmonary capillaries and/or small pulmonary veins.
- Mutations in *BMPR2* are the most common cause of heritable PAH. Inheritance is autosomal dominant with variable penetrance; mutations have been identified in 70–80% of families with PAH and 10–20% of patients diagnosed as idiopathic PAH.
- The basis for treatment of idiopathic PAH stems from its known abnormalities: excess endothelin-1, defective nitric oxide release, and deficiencies in prostacyclin.
- PAH-targeted therapies include endothelin-1 receptor antagonists, phosphodiesterase type 5 inhibitors and guanylate cyclase stimulators, and prostacyclin analogues. Treatment has been shown to lead to improvements in symptoms, exercise capacity, clinical functioning, and survival.
- Combination therapy has been shown to be superior to monotherapy in improving PAH outcomes. This includes up-front combination therapy (two-drug combination) with an endothelin-1 receptor antagonist and phosphodiesterase type 5 inhibitor and add-on therapy with various combinations, including triple therapy, for patients with an inadequate response to in initial therapy.
- Maximal medical therapy is considered three-drug combination therapy including a parenteral prostanoid.

Key Readings

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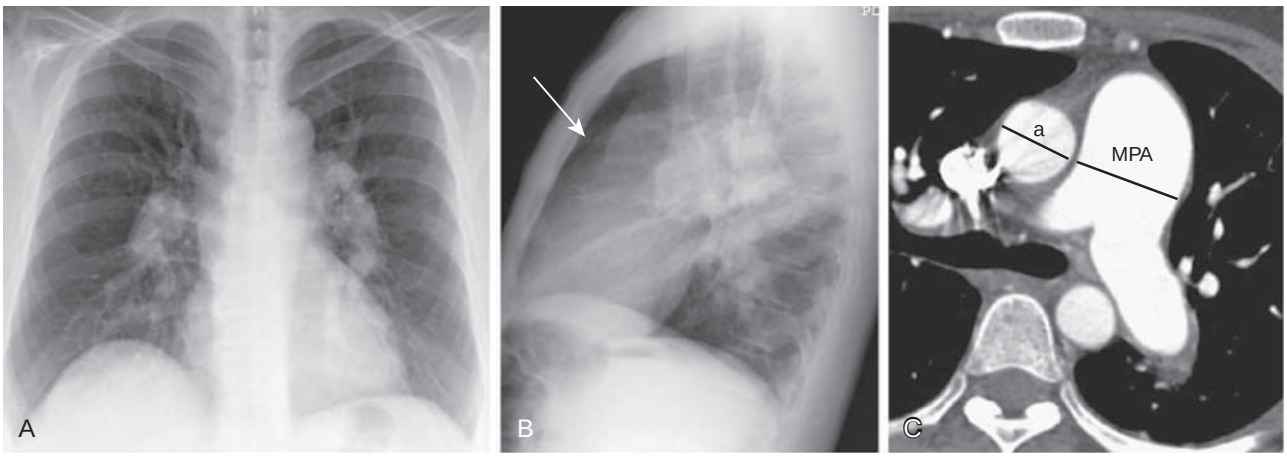
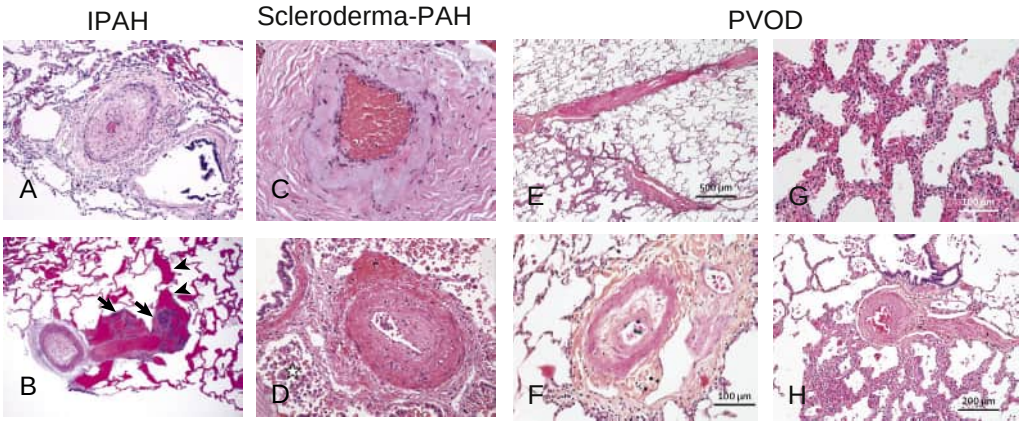
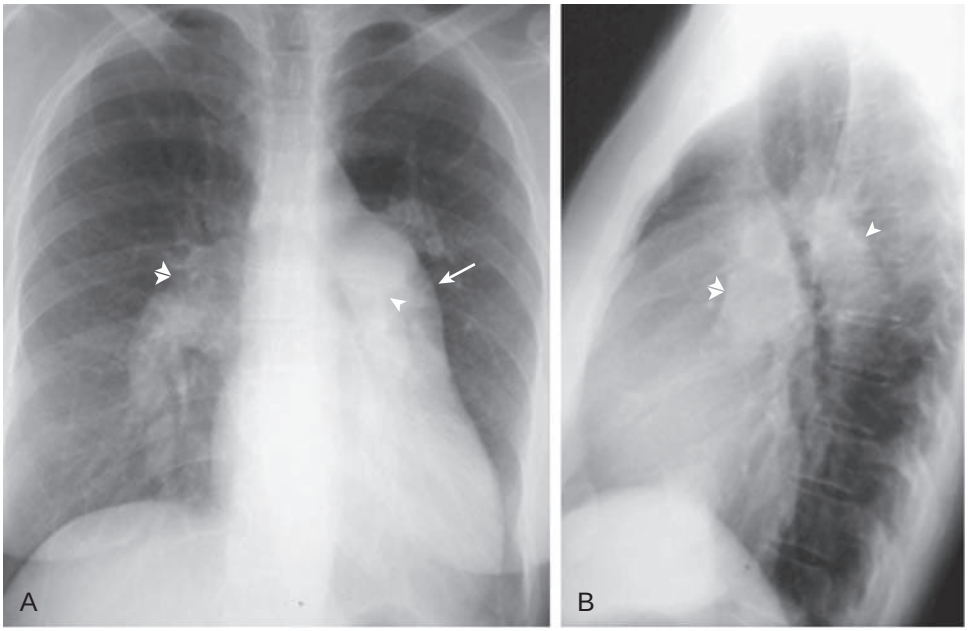


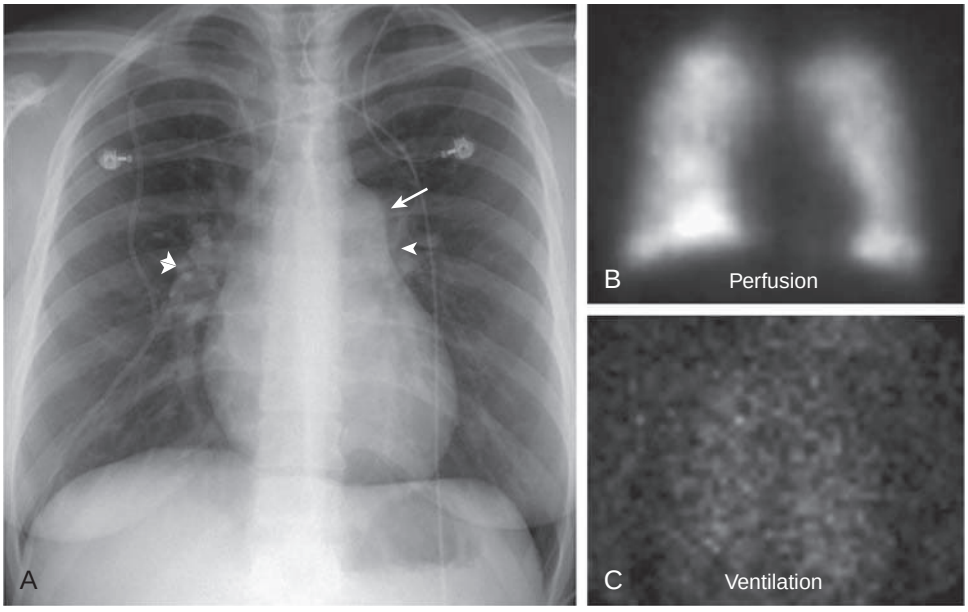
eFigure 84.1 Idiopathic pulmonary arterial hypertension: chest radiographic and chest computed tomography (CT) findings. Frontal (A) and lateral (B) chest radiographs show bilateral, symmetrical central pulmonary arterial enlargement. The lateral radiograph (B) reveals "filling" of the substernal regions (the "retrosternal clear space"), representing enlargement of the right ventricular outflow tract (*arrow*). (C) Axial enhanced chest CT shows enlargement of the *main pulmonary artery* (MPA), consistent with elevated pulmonary arterial pressure. The MPA is measured as indicated, typically at the widest portion of the vessel at or near the level of the bifurcation: ≥29 mm in transverse diameter is considered abnormal. Alternatively, the size of the MPA may be compared with the ascending aorta (*a*) at the same level. Assuming the aorta is not pathologically enlarged, the MPA may be considered abnormally enlarged if its diameter, typically measured at the MPA bifurcation, exceeds the ascending aortic diameter at the same level, as is seen in this case. (Courtesy Michael B. Gotway, MD.)



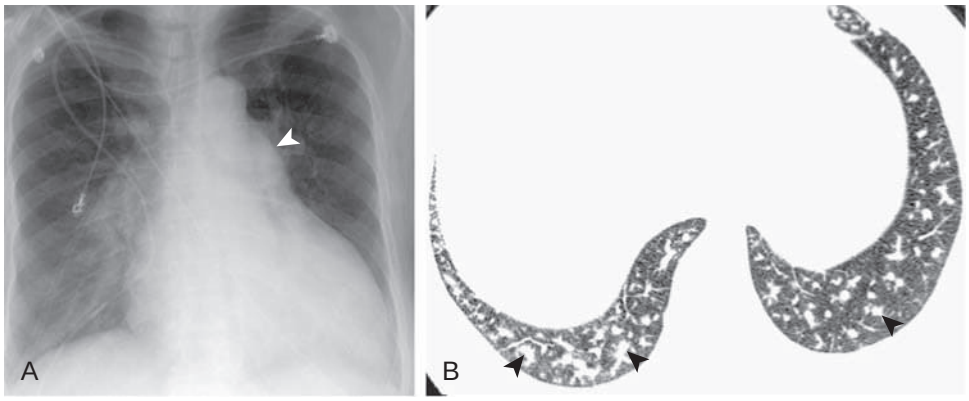
eFigure 84.2 Histopathologic patterns in *pulmonary arterial hypertension* (PAH). (A) Concentric intimal fibrosis. B, Plexiform lesions (*arrows*) downstream of a branch point with associated dilation of vessels (*arrowheads*). (C–D) Scleroderma PAH. (C) There can be marked perivascular collagen deposition in the adventitia of vessels in patients with collagen vascular disease–associated pulmonary hypertension. This histologic feature is usually most prominent in the vessels of CREST/scleroderma patients. (D) Small pulmonary artery displaying pronounced intimal fibrosis, as typically seen in PAH (Group 1). Note alveolar hemorrhage and numerous intra-alveolar macrophages (*star*). Magnification ×200. (E–H) Pulmonary veno-occlusive disease. (E) Severely remodeled septal vein with fibrous intimal occlusion. (F) Preseptal muscularized venule with constrictive loose intimal fibrosis, identified by green dye in its lumen previously injected into hilar veins. (G) Magnification of patchy foci with alveolar septal thickening with a multiplication of alveolar capillaries and scattered inflammatory cells. (H) Pulmonary artery (*center*) with its adjacent bronchiole (*top*) showing eccentric intimal fibrosis and pulmonary capillary hemangiomatosis-like focus adjacent to the pulmonary artery (*bottom*). (A–B, From Husain AN. *High-Yield Pathology*. Philadelphia: Elsevier; 2012. C, From Cool CD. Vascular diseases. In Zander DS, Farver CF, editors. *Pulmonary Pathology*, ed 2. Philadelphia: Elsevier; 2018. D, From O'Callaghan DS, Dorfmuller P, Jaïs X, et al. Pulmonary veno-occlusive disease: the bête noire of pulmonary hypertension in connective tissue diseases? *Presse Med*. 2011;40[1 Pt 2]:e65-e78. E–H, From Montani D, Girerd B, Jais X, et al. Clinical phenotypes and outcomes of heritable and sporadic pulmonary veno-occlusive disease: a population-based study. *Lancet Respir Med*. 2017;5[2]:125-134.)



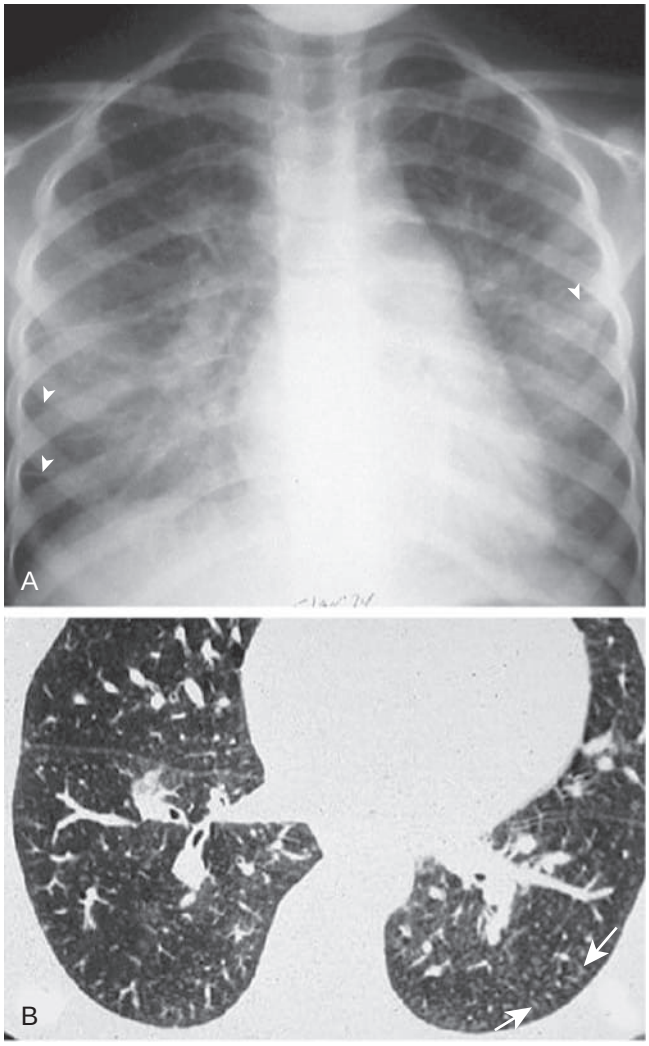
eFigure 84.3 Idiopathic pulmonary arterial hypertension: chest radiographic findings. Frontal (A) and lateral (B) chest radiographs show an enlarged main pulmonary artery (*arrow*) and enlargement of the right (*double arrowheads*) and left (*single arrowheads*) pulmonary arteries. The peripheral pulmonary arteries appear rather small, particularly given the marked central pulmonary arterial enlargement. The imaging findings are consistent with pulmonary hypertension, although the findings are not specific for the underlying etiology. (Courtesy Michael B. Gotway, MD.)



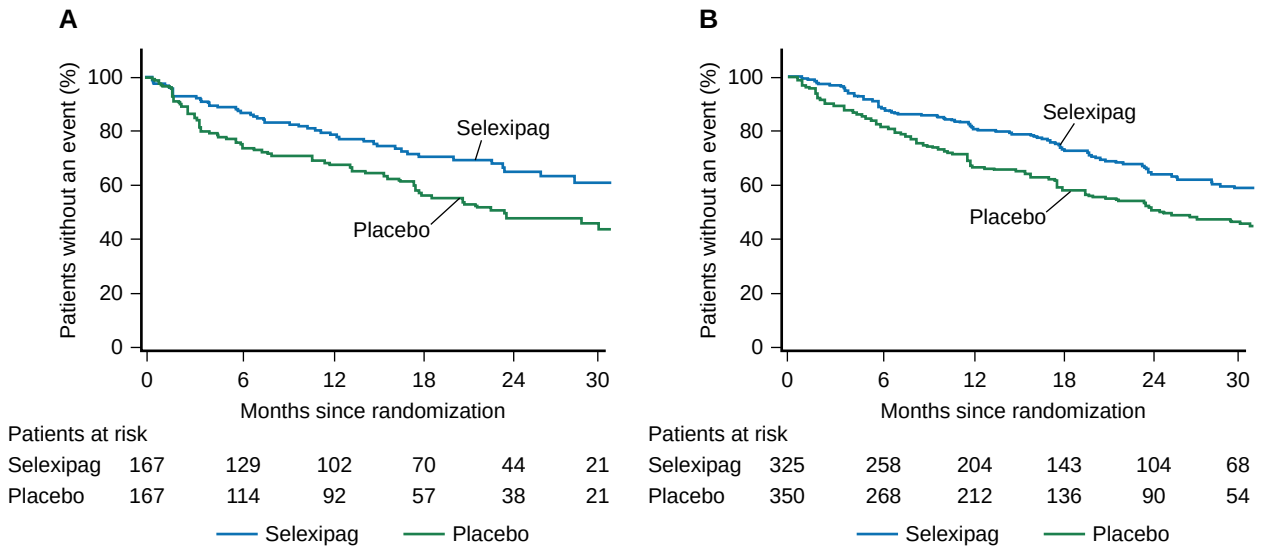
eFigure 84.4 Idiopathic pulmonary arterial hypertension: chest radiographic and ventilation-perfusion scintigraphy findings. (A) Frontal chest radiograph shows an enlarged main pulmonary artery (*arrow*) and enlargement of the right (*double arrowheads*) and left (*single arrowhead*) pulmonary arteries. The peripheral pulmonary arteries appear rather small, particularly given the marked central pulmonary arterial enlargement. The imaging findings are consistent with pulmonary hypertension, although the findings are not specific for the underlying etiology. Ventilation-perfusion scintigraphy shows fairly homogeneous perfusion (B) and ventilation (C), consistent with a low probability study. The patient subsequently underwent bilateral lung transplantation. (Courtesy Michael B. Gotway, MD.)



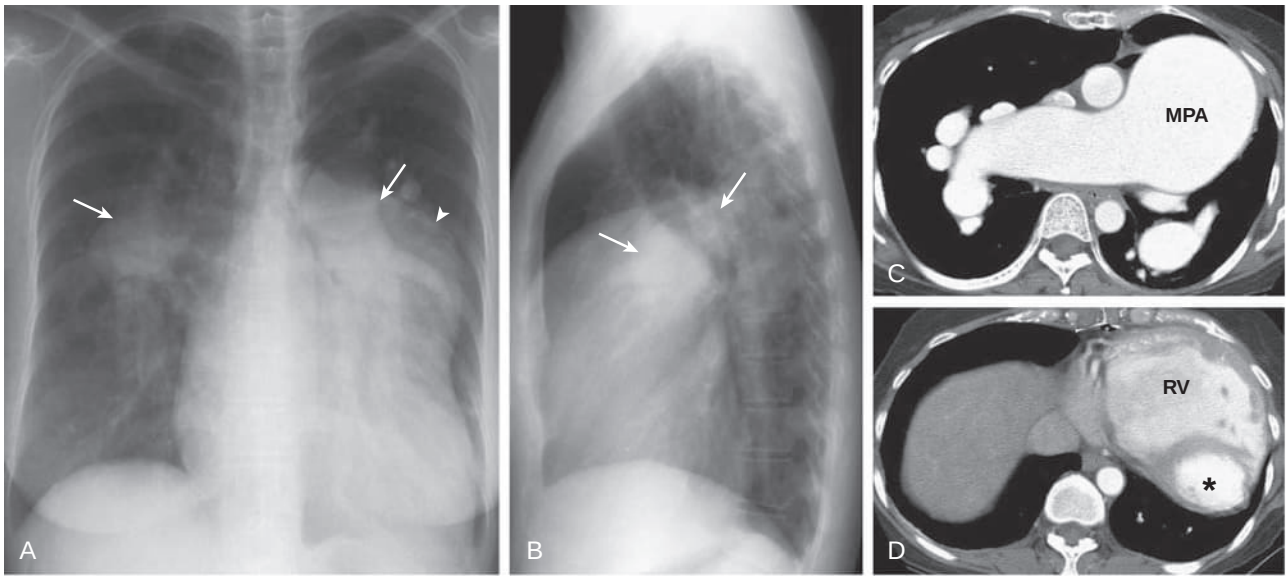
eFigure 84.5 Pulmonary hypertension associated with fenfluramine use. (A) Frontal chest radiograph shows enlarged central pulmonary arteries (*arrowhead,* main pulmonary artery). (B) Axial chest computed tomography through the lung bases displayed in lung windows shows enlarged peripheral pulmonary arteries (*arrowheads*). The imaging findings are consistent with pulmonary hypertension, although the findings are not specific for a particular etiology. (Courtesy Michael B. Gotway, MD.)



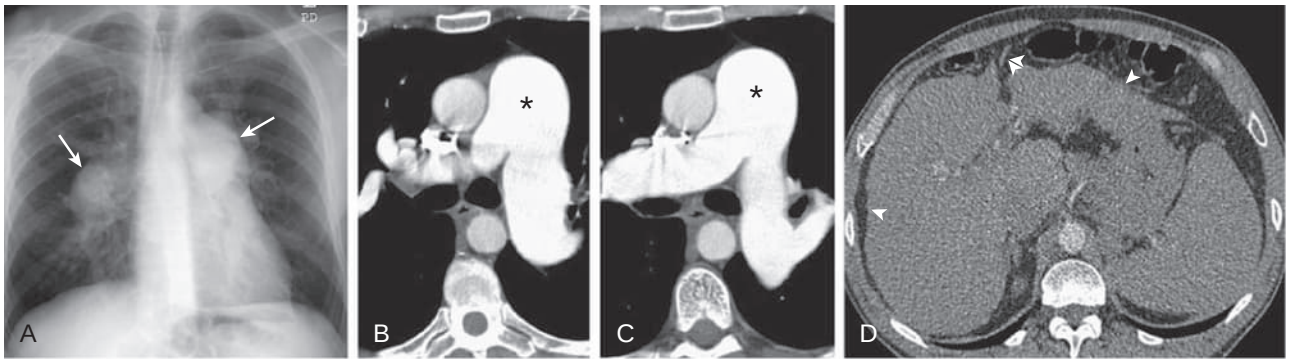
eFigure 84.6 Pulmonary veno-occlusive disease. (A) Frontal chest radiograph shows central pulmonary arterial enlargement, consistent with pulmonary hypertension. Central increased opacity is noted, with a background of linear opacities, some of which are consistent with interlobular septal thickening (also called Kerley B lines, *arrowheads*). (B) Axial chest computed tomography displayed in lung windows shows patchy areas of inhomogeneous lung opacity, with some areas of increased attenuation consistent with ground-glass opacity, best seen in the medial lung bases. Faint peripheral linear opacity and interlobular septal thickening (*arrows*) is present. The patient eventually was treated with bilateral lung transplantation. (Courtesy Michael B. Gotway, MD.)



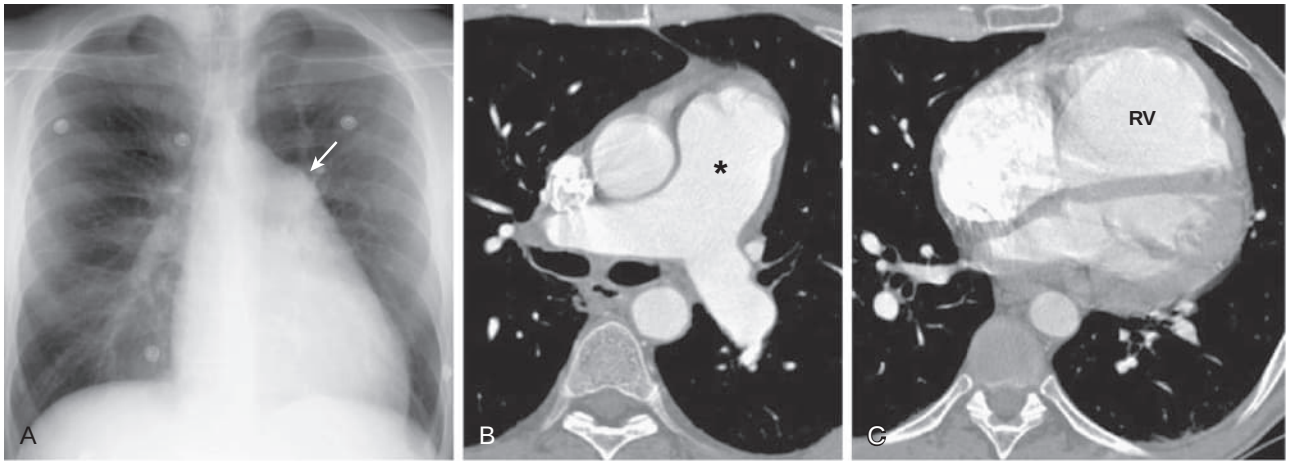
eFigure 84.7 Effect of selexipag on the primary composite end point of morbidity/mortality. (A) In patients with pulmonary arterial hypertension (PAH)–connective tissue disease or (B) in patients with idiopathic PAH/heritable PAH. (From Gaine S, Chin K, Coghlan G, et al. Selexipag for the treatment of connective tissue disease-associated pulmonary arterial hypertension. *Eur Respir J.* 2017;50[2].)



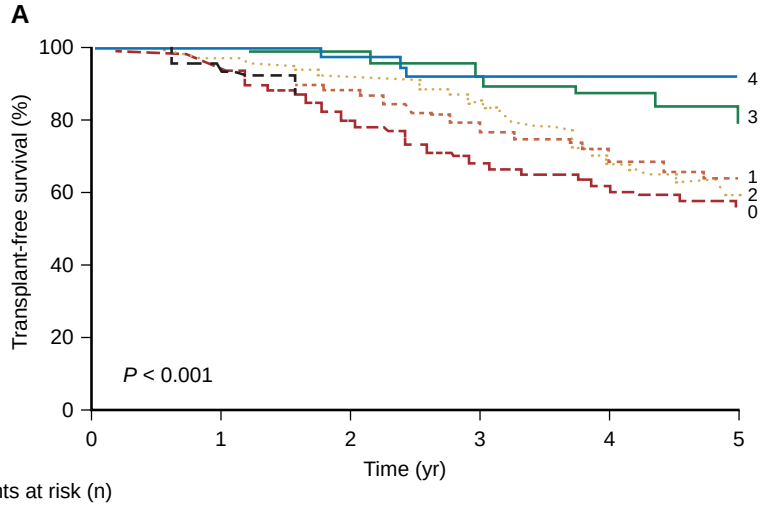
eFigure 84.8 Pulmonary hypertension with Eisenmenger syndrome due to an atrial septal defect. Frontal (A) and lateral (B) chest radiographs show massive enlargement of the right and left (*arrows*) pulmonary arteries and main (*arrowhead*) pulmonary artery. (C–D) Axial contrast-enhanced chest computed tomography shows massive enlargement of the main pulmonary artery (MPA). The right ventricle (RV) is enlarged with muscular hypertrophy. The left ventricle is noted by the *asterisk*. (Courtesy Michael B. Gotway, MD.)



eFigure 84.9 Portopulmonary hypertension: imaging findings. (A) Frontal chest radiograph shows enlarged central pulmonary arteries (*arrows*). (B–C) Axial enhanced chest computed tomography shows an enlarged main pulmonary artery (*asterisk*); the imaging findings are consistent with pulmonary hypertension, although the findings are not specific for the underlying etiology. (D) Axial enhanced computed tomography through the abdomen shows a scalloped liver contour (*single arrowheads*), consistent with cirrhosis. An enlarged ("recanalized") paraumbilical vein (*double arrowheads*) consistent with portal hypertension is present. (Courtesy Michael B. Gotway, MD.)

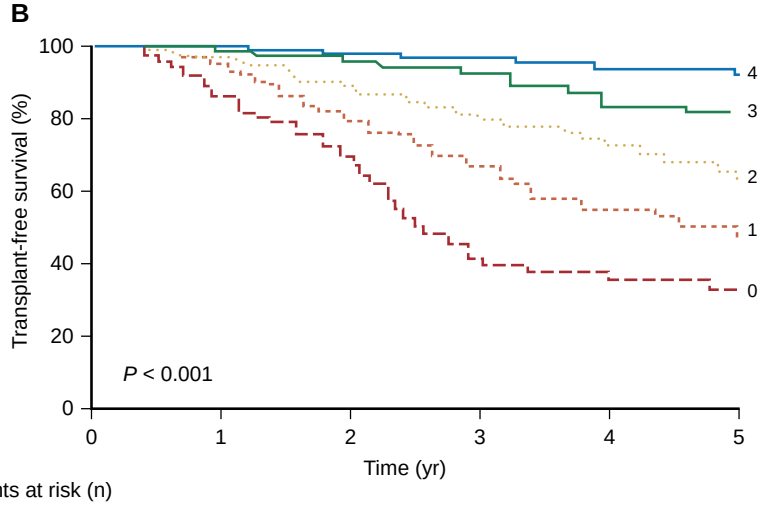


eFigure 84.10 Pulmonary hypertension in human immunodeficiency virus: imaging findings. (A) Frontal chest radiograph shows an enlarged main pulmonary artery (*arrow*). (B–C) Axial enhanced chest computed tomography shows an enlarged main pulmonary artery (*asterisk*) and right ventricle (RV); the imaging findings are consistent with pulmonary hypertension, although the findings are not specific for the underlying etiology. (Courtesy Michael B. Gotway, MD.)



Patients at risk (n)

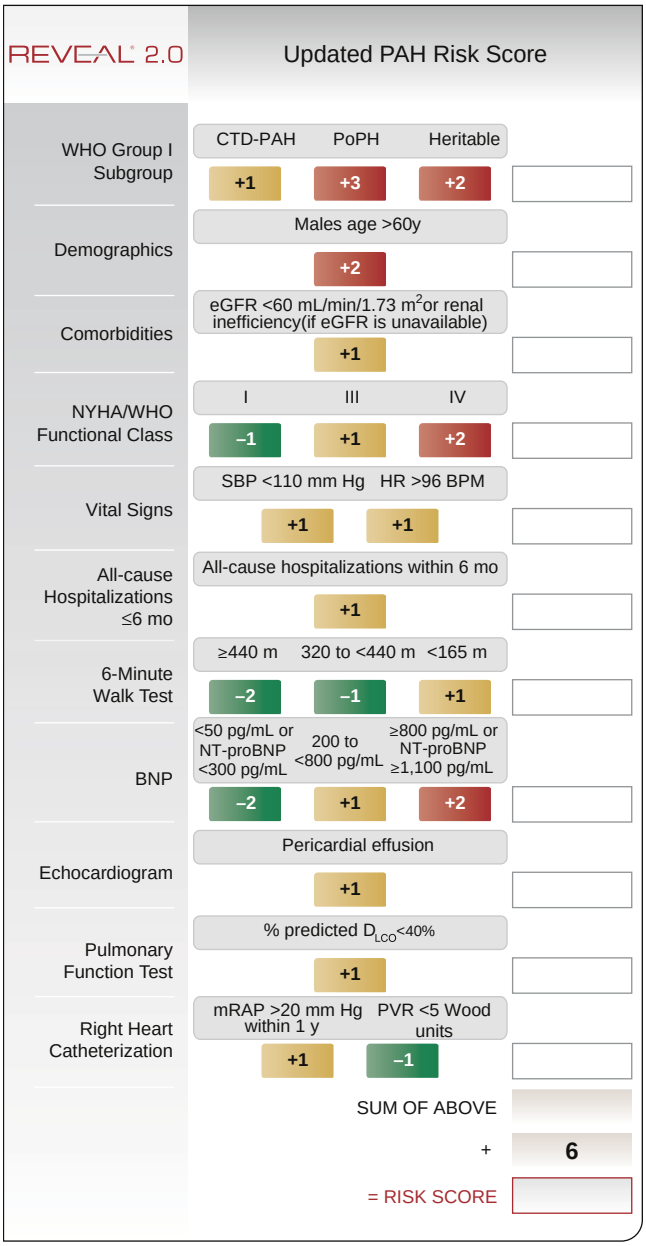
4 criteria	59	52	46	35	26	20
3 criteria	112	94	74	59	36	26
2 criteria	217	173	149	104	63	45
1 criterion	371	302	233	176	128	89
0 criteria	258	212	158	117	76	53



Patients at risk (n)

4 criteria	175	153	128	102	63	48
3 criteria	247	204	175	140	102	72
2 criteria	275	219	171	122	78	49
1 criterion	225	183	128	91	62	45
0 criteria	95	61	44	22	18	14

eFigure 84.11 Outcomes by number of European Society of Cardiology/European Respiratory Society risk criteria in pulmonary arterial hypertension. Outcome based on functional class I/II, 6-minute walking distance >440 m, right atrial pressure <8 mm Hg, cardiac index ≥2.5 L/min/m^2 (A) at diagnosis and (B) at first follow-up within the first year after diagnosis. (From Boucly A, Weatherald J, Savale L, et al. Risk assessment, prognosis and guideline implementation in pulmonary arterial hypertension. *Eur Respir J*. 2017;50.)



eFigure 84.12 REVEAL 2.0 calculator. Low risk is considered ≤6 points, intermediate risk is 7 or 8 points, and and high risk is ≥9 points, associated with mortality risk at 1 year of ≤2.6%, 6.2–7%, and ≥10.7%. (From Benza RL, Gomberg-Maitland M, Elliott CG, et al. Predicting survival in patients with pulmonary arterial hypertension: the REVEAL Risk Score Calculator 2.0 and comparison with ESC/ERS-based risk assessment strategies. *Chest*. 2019;156[2]:323-337.)

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85 PULMONARY HYPERTENSION DUE TO LUNG DISEASE: GROUP 3

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INTRODUCTION

This chapter focuses on group 3 *pulmonary hypertension* (PH) *due to chronic lung disease* (CLD-PH). This is a common and significant clinical complication of chronic lung disease, and it differs from other types of PH both in causation and therapeutic approach. The current (2019) Updated Clinical Classification of Pulmonary Hypertension (see Chapter 83, Table 83.2) serves to define the terminology used in this chapter and in Chapter 83.[1] Note that the term *pulmonary arterial hypertension* (PAH) refers specifically to diseases in group 1, including idiopathic PAH. PH is used in reference to groups 2, 3, 4, and 5. PAH is covered in Chapter 84, and group 4 PH (chronic thromboembolic PH) is covered in Chapter 86.

The development of PH in patients with chronic lung disease is clinically important because it can lead to subsequent *right ventricular* (RV) failure (previously referred to as *cor pulmonale*[2,3]) and is associated with increased morbidity and mortality. In one large community-based series, CLD-PH was the second most common cause of PH after left heart disease[4] (see Fig. 83.1). PH develops in most types of advanced lung disease. However, patients with COPD and *idiopathic pulmonary fibrosis* (IPF) and sleep-disordered breathing are the focus of this chapter. As in all patients with PH, a thorough and exhaustive diagnostic evaluation is essential to determine the primary cause of PH and to identify comorbid, potentially treatable conditions that might worsen PH and right heart failure. The different groups of PH affect different areas of the pulmonary circulation (Fig. 85.1). Distinguishing between group 3 CLD-PH and group 1 PAH is especially important because these diseases are pathologically and clinically distinct and respond differently to treatment. The best treatment of patients with CLD-PH remains optimal management of the underlying lung disease, correction of hypoxemia, and timely consideration for lung transplantation. Trials in CLD-PH have generally shown that PAH medications lack efficacy and may cause harm; however, early results of a recent trial suggest benefits of inhaled PAH medications in CLD-PH. Due to the need for larger trials to guide the management of CLD-PH, patients diagnosed with CLD-PH should be offered enrollment in clinical trials.

EPIDEMIOLOGY

PREVALENCE

Numerous studies have sought to establish the prevalence of CLD-PH but have suffered from significant limitations, including inconsistent definitions of PH and frequent use of echocardiography rather than right heart catheterization to assess hemodynamics. Additionally, patient cohorts have often been heterogeneous, and comprehensive assessments to exclude other important and common comorbid causes of PH (e.g., chronic thromboembolic PH and left heart disease) were not generally performed. Recommendations from the 2019 Sixth World Symposium on Pulmonary Hypertension incorporate the findings from a large retrospective study which concluded that the upper limit of normal *mean pulmonary artery pressure* (mPAP) in heathy individuals is 20 mm Hg.[5] Adoption of this change in the

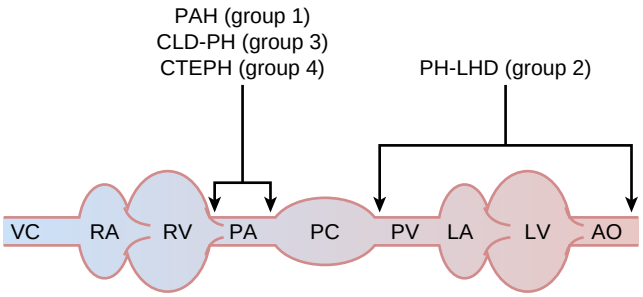

Figure 85.1 Localization of abnormalities in pulmonary hypertension. Pathologic changes that result in *pulmonary hypertension from group 3 chronic lung disease* (CLD-PH) primarily target pulmonary arterioles, the same location as abnormalities in group 1 *pulmonary arterial hypertension* (PAH) and group 4 *chronic thromboembolic pulmonary hypertension* (CTEPH). Abnormalities that result in PH in group 2 *left heart disease* (PH-LHD) are found mostly on the venous side of the pulmonary circulation. AO, aorta; LA, left atrium; LV, left ventricle; PA, pulmonary arteries; PC, pulmonary capillaries; PV, pulmonary veins; RA, right atrium; RV, right ventricle; VC, vena cava.

Table 85.1 Hemodynamic Definitions of Chronic Lung Disease–Pulmonary Hypertension: Recommendations From the Sixth World Symposium on Pulmonary Hypertension

CLD *without* PH: mPAP < 21 mm Hg, or mPAP 21–24 mm Hg with PVR < 3 WU
CLD *with* PH: mPAP 25–34 mm Hg, or mPAP 21–24 mm Hg with PVR ≥ 3 WU
CLD *with severe* PH: mPAP ≥ 35 mm Hg, or mPAP ≥ 25 mm Hg with low cardiac index (<2.0 L/min/m²).

CLD, chronic lung disease; PH, pulmonary hypertension; mPAP, mean pulmonary artery pressure; WU, Wood units, PVR, pulmonary vascular resistance.

From Nathan SD, Barbera JA, Gaine SP, et al. Pulmonary hypertension in chronic lung disease and hypoxia. *Eur Respir J.* 2018;53:1801914.

hemodynamic definition of PH will result in many more patients being classified as having PH[6] (Table 85.1).

COPD

The lung disease most frequently associated with PH is COPD (COPD-PH), accounting for more than 80% of all cases of CLD-PH.[7] However, the estimated prevalence of PH in patients with known COPD varies dramatically, from 2.7–90.8%,[8,9] depending on the definition of PH, whether right heart catheterization or echocardiography is used to establish the diagnosis, and the study population.

The most commonly used definition of PH in studies on COPD-PH, as in other populations, is an mPAP greater than 25 mm Hg, although some studies of CLD-PH have used different cutoff values (e.g., 20 mm Hg). An early study of right heart catheterization in 175 patients with severe COPD showed that 35.4% of patients had an mPAP of 20 mm Hg or greater, and 9.7% had a mPAP greater than 30 mm Hg.[10] In another study, invasive hemodynamic values were assessed in 120 patients with severe airflow obstruction (mean FEV_1 27% of predicted) at the time of enrollment in the National Emphysema Treatment Trial. In this cohort, 90.8% of patients had an mPAP greater than 20 mm Hg, but only 5% had an mPAP greater than 35 mm Hg. Importantly, *pulmonary artery wedge pressure* (PAWP) was

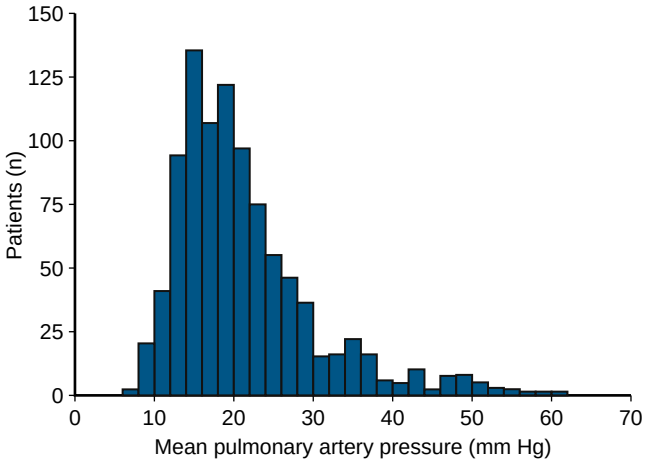

Figure 85.2 Severity of pulmonary hypertension in patients with COPD in a large French cohort. Although elevation in pulmonary artery pressure is common in patients with COPD, severe pulmonary hypertension is unusual. For many of the patients with severe pulmonary hypertension in this cohort, another medical problem such as left heart disease or chronic thromboembolic disease was judged to be the primary cause of pulmonary hypertension. (From Chaouat A, Naeije R, Weitzenblum E. Pulmonary hypertension in COPD. *Eur Respir J.* 2008;32:1371–1385.)

greater than 12 mm Hg in 61.4% of patients and greater than 20 mm Hg in 6.4% of patients, suggesting that left-sided heart failure was an important contributor to PH in this population.[9] To assess the prevalence of PH in an outpatient population with stable COPD, echocardiography was performed in 159 patients to estimate *pulmonary artery systolic pressure* (PASP). Tricuspid regurgitation was adequate to estimate PASP in 105 patients and, of those, 60% had a PASP of 35 mm Hg or greater and were classified as having PH.[11] Patients with PASP of 35 mm Hg or greater were older and had lower FEV_1 and *diffusing capacity for carbon monoxide* (D_{LCO}) values.

In one well-designed study,[8] 998 patients underwent right heart catheterization at a referral center in France as part of an evaluation for chronic respiratory failure; severe PH, defined as mPAP of 40 mm Hg or greater, was diagnosed in 27 patients (2.7%) (Fig. 85.2). Another cause of PH was found in 16 of those patients, resulting in a final diagnosis of PH secondary to COPD in only 11 patients (1.1%). Compared to a control group of patients with COPD, the patients with severe PH had lower D_{LCO} and arterial P_{CO_2} and P_{O_2} values. Patients with severe PH also had lower cardiac indices and higher right atrial pressures, suggesting reduced right ventricular function.

These studies demonstrate that mild PH is common among stable outpatients with COPD. Importantly, more severe hemodynamic abnormalities were observed only in a very small number of patients and, among those patients, other causes of PH were common.

Examining cohorts of patients undergoing evaluation for lung transplantation is useful because they include a relatively homogenous patient population with complete hemodynamic data; however, they represent a cohort with particularly advanced lung disease in whom PH might be expected to be more frequent and more severe. A retrospective study used right heart catheterization data from the Organ Procurement and Transplantation Network

database to study PH in 4930 patients with COPD listed for lung transplantation.[12] The prevalence of mild and moderate PH, defined as an mPAP of 25 mm Hg or greater and less than 35 mm Hg with a PAWP of 15 mm Hg or less, was 30.4%, and the prevalence of severe PH defined as an mPAP of 35 mm Hg or more with a wedge pressure 15 mm Hg or less was 4.0%. A significant number of patients, 17.2%, had an mPAP of 25 mm Hg or more but also had a PAWP greater than 15 mm Hg. Moreover, the PAWP was greater than 15 mm Hg in about 50% of the patients with mPAP of 31 mm Hg or greater, demonstrating that elevated left heart filling pressures (group 2 PH) are common in this population and may contribute significantly to PH. Findings were similar in another study of 409 patients with COPD undergoing evaluation for lung transplantation in Denmark.[13] In this study, 36% of patients had PH with an mPAP of 25 mm Hg or greater and a PAWP of 15 mm Hg or less, and 13% had an mPAP of 25 mm Hg or greater but also had a PAWP greater than 15 mm Hg. Only 6 (1.5%) patients had an mPAP of 40 mm Hg or greater. In this population, PH was associated with the presence of more severe hypoxemia and lower FEV_1 values. In both studies, many patients being evaluated for transplantation had elevations in mPAP; however, there was a low prevalence of severe PH, and a significant proportion of patients had elevated PAWP, which indicates that comorbid group 2 PH is common and may be the primary factor causing PH.

There are limited longitudinal data concerning COPD-PH; however, the progression of PH in these patients appears to be slow.[14] Among patients who are found to have normal PAP at rest, changes in pulmonary hemodynamics are frequently minimal over time. For example, in a group of 61 patients without initial PH, all of whom had arterial hypoxemia, a second right heart catheterization almost 8 years later revealed an average change in mPAP from 15.5 ± 2.4 mm Hg to 19.6 ± 7.0 mm Hg.[15] In a second group of 32 patients who had PH on their first catheterization, there was a nonsignificant rise in mPAP, from 27.7 ± 6.0 mm Hg to 31.0 ± 9.3 mm Hg, after 5 years.[16] An increase of 5 mm Hg or more was seen in approximately one-third of patients and was clearly related to worsening hypoxemia.

In patients with COPD, the presence of PH is clinically important because it is associated with worse exercise tolerance and survival compared to COPD patients without PH. In the retrospective organ procurement database study, *6-minute walk distance* (6MWD) was on average 28 m less in patients with PH compared to those with normal hemodynamics; in addition, mPAP was an independent predictor of a low 6MWD in a multivariate model. In this study, adjusted risk for death on the transplant list was significantly increased in patients with PH (hazard ratio, 1.27).[12] Findings were similar in a study of 362 patients at a single center undergoing transplant evaluation. In multivariate analysis, higher mPAP was associated with a shorter 6MWD, including a reduction of 11 m for every 5 mm Hg increase in mPAP.[17] In the Danish cohort, PH did not affect 6MWD but did affect the survival rate; the survival rate at 5 years was 37% for patients with PH compared to 63% in patients without PH ($P = 0.016$). In this cohort, the presence of PH did not affect outcomes following lung transplantation.[13] Among the 11 patients with severe PH in the French COPD cohort, exertional dyspnea was significantly worse and survival was significantly shorter compared to patients without severe PH.[8] In another study, the effects of PH on survival were assessed in a cohort of 84 patients who underwent hemodynamic evaluation before institution of long-term oxygen therapy. Adjusted 5-year survival rate was 62% for patients with an initial mPAP of 25 mm Hg or less, whereas it was only 36% in the 40 remaining patients who had an initial mPAP higher than 25 mm Hg. In this cohort, initial mPAP was a better prognostic indicator than either the FEV_1, the degree of hypoxemia, or the level of hypercapnia.[18] A study of 101 patients with PH and COPD at a PH referral center came to similar conclusions. Survival at 3 years was 33% in patients with mPAP of 40 mm Hg or greater versus 55% in patients with mPAP of 25 to 39 mm Hg. In a multivariate analysis, age, DL_{CO}, mixed venous oxygen saturation, and World Health Organization functional classification were independent predictors of survival.[19] These findings suggest that even mild PH may have a significant negative impact on exercise tolerance and survival and that the presence of PH may be a more important prognostic factor than the severity of lung disease.

IDIOPATHIC PULMONARY FIBROSIS

Most of the available data regarding *PH associated with IPF* (IPF-PH) come from patients undergoing evaluation for lung transplantation. In a study of 79 patients with IPF referred for lung transplantation who had a right heart catheterization, 32% (25 of 79) had PH documented by an mPAP greater than 25 mm Hg.[20] In another cohort of 124 patients undergoing evaluation for lung transplant at the Cleveland Clinic, 44% (54 of 124) had an mPAP of 25 mm Hg or greater.[21] A study of 101 Japanese patients with IPF who underwent right heart catheterization showed similar results with a prevalence of mPAP greater than 25 mm Hg of 15% (15 of 101).[22] These studies show an overall high rate of IPF-PH in patients with advanced IPF.

The presence of IPF-PH is associated with worsening symptoms, functional impairment, and increased morbidity and mortality.[20,23–25] In a retrospective study of 136 patients with IPF, the median survival of those with estimated PASP of greater than 50 mm Hg by echocardiography was less than 1 year ($P = 0.009$) compared to 4.1 years for patients with mild PH (PASP 36 to 50 mm Hg), and 4.8 years for patients without PH (PASP < 35 mm Hg).[24] The 1-year survival rate in 79 patients undergoing lung transplant evaluation was lower (72%) in those patients with PH compared to IPF patients without PH (94.5%; $P = 0.002$).[20] Furthermore, patients with PH who had lower DL_{CO} values were more likely to require supplemental oxygen, to have shorter 6MWD, and to exhibit a lower arterial oxygen saturation nadir. In one study of 78 patients with IPF-PH, using a cutoff based on a receiver operating curve, the 5-year survival rate was 17% for the group ($n = 24$) with mPAP values greater than 17 mm Hg ($P < 0.001$) and 62% for the group ($n = 37$) with mPAP values less than 17 mm Hg. The relative risk for death was significantly higher at 2.2 for the high-mPAP group.[21] According to an analysis of 2972 patients with advanced IPF listed for lung transplantation between 1995 and 2004, those with PH were 1.6 times

more likely to die after being listed for transplantation compared to those without PH.[25] These data suggest that, similar to patients with COPD-PH, the consequences of IPF-PH are serious and that even mild increases in mPAP are associated with increased mortality.

The presence of pretransplantation PH in patients with IPF may even have a significant effect on posttransplantation outcomes. In a cohort of 126 patients, those who developed primary graft dysfunction had high pretransplantation mPAP values, and each 10 mm Hg increase in mPAP was associated with an increase in the odds of primary graft dysfunction by 1.64.[26]

Combined emphysema and pulmonary fibrosis imparts a greater risk for developing PH and having poorer outcomes. The prevalence of PH in these patients has been described as 30–50%; this group had markedly reduced survival.[27,28] In one retrospective series of 40 patients with combined emphysema and pulmonary fibrosis, elevated mPAP above 40 mm Hg was present in 48% of patients.[29] Patients had severe symptoms, 85% with New York Heart Association functional class III or IV, and an average 6MWD of 244 m. Outcomes in this population were poor. For those with a *pulmonary vascular resistance* (PVR) above the median value, 1-year survival was 48%, whereas for those with a PVR below the median, 1-year survival was 100%.

SLEEP-DISORDERED BREATHING, OBESITY HYPOVENTILATION, AND HIGH ALTITUDE

In patients without parenchymal lung disease, hypoxemia from high altitude, *obstructive sleep apnea* (OSA), and *obesity hypoventilation syndrome* (OHS) are important independent causes of PH by themselves, or they may contribute significantly to PH from other causes.

High altitude affects a large number of individuals globally. Thus, environmental hypoxemia related to altitude may be one of the most common causes of PH worldwide.[30,31]

OSA appears to be an increasingly common cause of PH. In multiple studies of patients with OSA, the prevalence of PH ranges from 20–40%, typically with mild elevation in mPAP (23 to 32 mm Hg).[32] Multiple mechanisms contribute to PH in patients with OSA, including elevated left heart filling pressures (pulmonary venous hypertension), hypoxic pulmonary vasoconstriction, reduced intrinsic vasodilators, and increased vasoconstrictors and inflammatory mediators.[32] Interestingly, this PH may be reversible. One well-designed prospective trial showed that treatment with *continuous positive airway pressure* (CPAP) over 6 months reduced mPAP in patients with OSA.[33] Another more recent study showed improvement in right ventricular function with treatment of OSA.[34]

OHS, which is increasingly common worldwide, also causes PH. The prevalence of mPAP greater than 20 mm Hg among 29 patients with OHS was 59% in a cohort of untreated patients.[35] In another study of 21 patients with OHS treated with noninvasive positive pressure ventilation, the prevalence of mPAP greater than 20 mm Hg was 81%, although only three patients (14%) had severe PH with mPAP greater than 35 mm Hg. In this study, mPAP correlated negatively with use of noninvasive positive pressure ventilation and, by multivariate regression, the presence of PH was an independent predictor of poor physical functioning.[36] The use of CPAP compared to bilevel positive airway pressure treatment for OHS was evaluated in the Pickwick trial.[37] In this short-term trial, bilevel positive airway pressure reduced PASP more than CPAP and only bilevel positive airway pressure reduced left ventricular hypertrophy and improved 6MWD (see also Chapter 137).

SCLERODERMA INTERSTITIAL LUNG DISEASE

Scleroderma interstitial lung disease (SSc-ILD) complicated by PH is a particularly challenging clinical entity. Patients with scleroderma are at high risk of developing group 3 PH from SSc-ILD and also group 1 PAH secondary to connective tissue disease. A recent study found that, in a cohort of patients with SSc-ILD, 31.2% of patients also had PH.[38] Three-year survival after a diagnosis of SSc-ILD was 97%, and survival following a diagnosis of PH was 91%. However, comparison to other previously analyzed cohorts is difficult because the PH cohort included patients with group 1, group 2, and group 3 PH, and patients who were included may have had less severe disease. A retrospective cohort study comparing patients with SSc and group 1 PAH versus SSc group 3 PH found survival in the SSc group 3 PH patients at 1, 2, and 3 years to be 82%, 46%, and 39%, respectively, consistent with a fivefold higher risk of death in the SSc group 3 PH patients.[39]

OTHER LUNG DISEASES

Case reports and small series have described PH as a complication of a variety of other lung diseases, including sarcoidosis, pulmonary Langerhans cell histiocytosis, lymphangioleiomyomatosis, adult bronchopulmonary dysplasia, and cystic fibrosis. These conditions are discussed in other chapters (see also Chapters 83 and 94). Limited published data suggest that development of PH in all of these conditions is associated with worse outcomes.[40–42]

PATHOLOGIC CHANGES AND PATHOGENESIS

Although the mechanisms underlying the development and progression of PH in patients with lung disease are incompletely understood, they appear to be multifactorial and to vary with the underlying lung disease. Early vascular endothelial injury is likely caused by factors such as hypoxemia and inflammation, leading to endothelial dysfunction and subsequent vascular remodeling. These abnormalities lead to an increase in PVR and a subsequent increase in PAP.

PULMONARY VASCULAR REMODELING

Many of the individual elements of pulmonary vascular remodeling seen in CLD-PH are similar to those seen in PAH. The primary differentiating pathologic feature is the absence of plexiform lesions in CLD-PH.[43] The development of the vascular pathologic features observed in CLD-PH is likely multifactorial.[44,45]

A variety of pathologic vascular changes described in CLD-PH vary with the type of lung disease and overlap significantly with the changes seen in PAH (Fig. 85.3). Knowledge about pathologic changes in CLD-PH comes from autopsy series and studies of explanted lungs at the time of transplant. A characteristic feature often seen in CLD-PH and also seen in PAH is the extension of smooth muscle into small pulmonary arterioles less than 80 μm, which is not found in healthy lungs. This is termed "muscularization" and is characterized by circularly oriented smooth muscle cells between the two layers of elastic lamina.[46] Muscularization may result from hypertrophy and proliferation of existing smooth muscle and from development of new smooth muscle cells. Another common finding in lungs from patients with CLD-PH that overlaps with PAH is proliferation of the intimal layers of the pulmonary arterioles. Inflammation and thrombosis in situ may also be seen.

Pathologic changes unique to CLD-PH are associated with the underlying lung disease. In COPD-PH, destruction of alveoli and concomitant destruction of the associated pulmonary vasculature reduces pulmonary vascular cross-sectional area and increases PVR.[47] In IPF-PH, a unique finding is that vascular changes are seen both in areas of lung fibrosis and in areas of normal lung, though the vascular changes in areas of normal lung are less severe and found in a smaller proportion of vessels. Also, in IPF-PH, much more than in PAH, there are occlusive pathologic changes of pulmonary veins. In general, in IPF-PH, large portions of the pulmonary vascular bed may be destroyed or obliterated from progressive parenchymal fibrosis, inflammation, perivascular fibrosis, and/or thrombotic angiopathy.[48–50]

The severity and extent of structural changes correlate variably with the degree of hemodynamic abnormalities seen in CLD-PH. A recent study compared the structural changes observed in pulmonary arterioles from patients with COPD with and without PH undergoing transplant. Even without PH, patients with COPD frequently had muscularization and medial thickening of the pulmonary arterioles. Severity of pathologic changes worsened as the hemodynamic abnormalities worsened.[51] In another study of tissue from COPD patients who died during the National

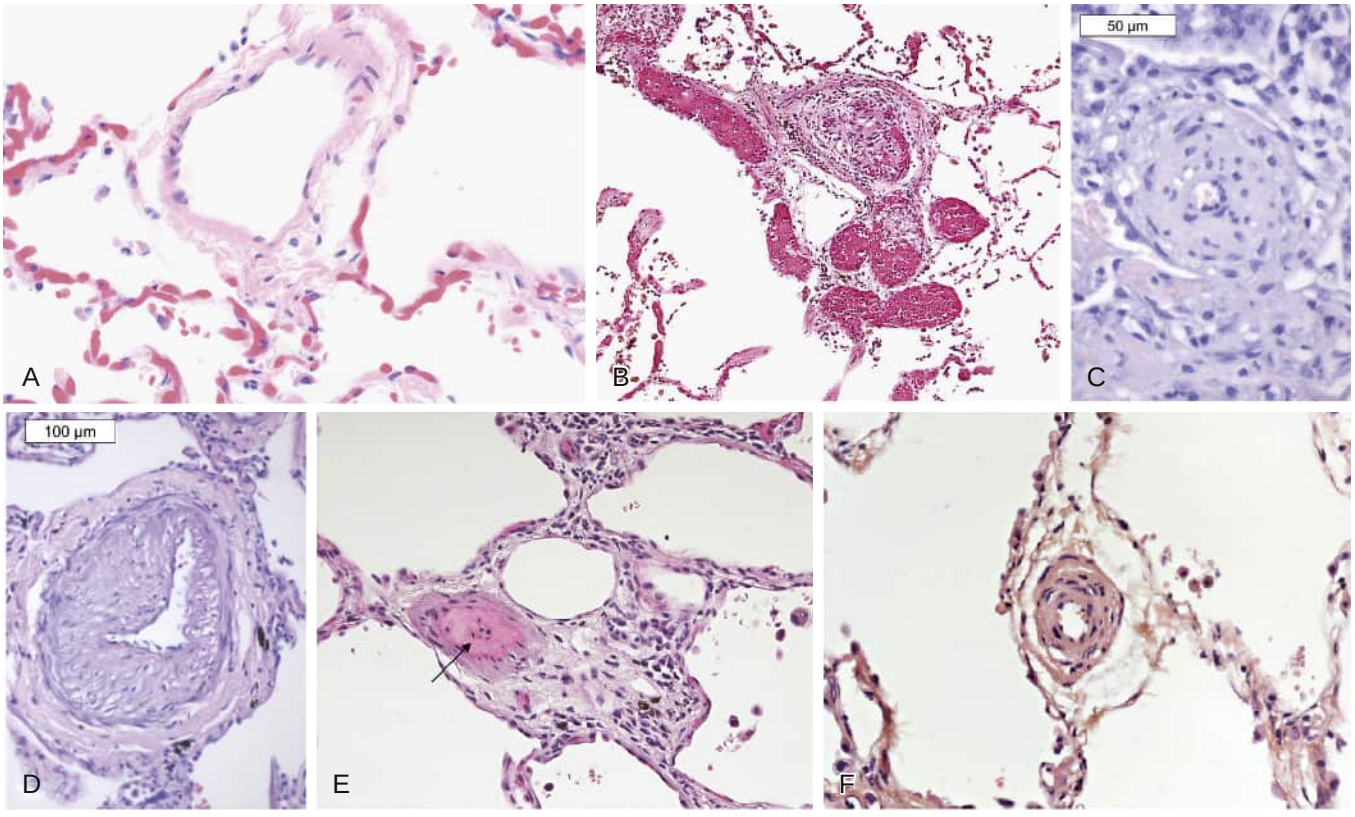

Figure 85.3 Histologic appearance of normal and abnormal pulmonary arterioles. (A) Normal pulmonary arteriole. Characteristic features include a large lumen relative to wall thickness, a single elastic lamina, and the absence of medial smooth muscle. (B) Typical plexiform lesion from a patient with pulmonary arterial hypertension. (C) Pulmonary arteriole from a patient with pulmonary hypertension from COPD showing cellular intimal proliferation in small muscular arteries. (D) Pulmonary arteriole from a patient with pulmonary hypertension from COPD showing medial hypertrophy and concentric laminar intimal fibrosis. (E) Pulmonary arteriole from a patient with pulmonary hypertension from idiopathic pulmonary fibrosis showing vascular intimal fibrosis with luminal obliteration (*arrow*) in a region of interstitial fibrosis and chronic inflammation. (F) Pulmonary arteriole from a patient with pulmonary hypertension from idiopathic pulmonary fibrosis showing muscularization of a small pulmonary arteriole. (A, Courtesy Dr. Philip Ursell, University of California San Francisco. B, From Leslie KO, Wick MR. *Practical Pulmonary Pathology: A Diagnostic Approach: A Volume in the Pattern Recognition Series*. 2nd ed. Philadelphia: Elsevier; 2011. C–D, From Carlsen J, Andersen KH, Boesgaard S, et al. Pulmonary arterial lesions in explanted lungs after transplantation correlate with severity of pulmonary hypertension in chronic obstructive pulmonary disease. *J Heart Lung Transplant.* 2013;32:347–354. E, Courtesy Dr. Rubin Tuder, Baltimore, MD. F, From Colombat M, Mal H, Groussand O, et al. Pulmonary vascular lesions in end-stage idiopathic pulmonary fibrosis: histopathologic study on lung explant specimens and correlations with pulmonary hemodynamics. *Hum Pathol.* 2007;38:60–65.)

Institutes of Health Nocturnal Oxygen Therapy Trial, there was no correlation between the histologic appearance of pulmonary arterioles and severity of PH.[52]

Several studies suggest that vascular remodeling in patients with mild COPD without concomitant hypoxemia is a component of early-stage disease as evidenced by increased inflammatory cell density in the adventitia and increased pulmonary artery intimal thickening.[53,54] Furthermore, endothelial lesions have been shown to be present in cigarette smokers without chronic airflow obstruction.[55] These findings suggest that, although the pathologic changes in the pulmonary vasculature predominate, other abnormalities appear to contribute to the development of clinically relevant PH. It is also important to note that pathologic findings are not used clinically in the management of patients with CLD-PH.

PATHOGENESIS

Multiple mechanisms may contribute to the pathogenesis of CLD-PH, including hypoxic pulmonary vasoconstriction, vasoconstrictive neurohormones, and inflammation.

Hypoxic Pulmonary Vasoconstriction

Among all the mechanisms leading to PH in lung disease, the most potent and most important is alveolar hypoxia.[56] *Hypoxic pulmonary vasoconstriction* (HPV) is a normal physiologic response to alveolar hypoxia, first demonstrated in isolated cat lungs[57] and subsequently confirmed in healthy human volunteers[58] (see also Chapters 6 and 10). This effect is unique to the pulmonary circulation. Whereas acute hypoxia in the systemic circulation induces vasodilation, acute hypoxia in the pulmonary circulation causes constriction. The constriction of precapillary pulmonary arterioles effectively shunts blood away from poorly ventilated lung units to preserve optimal ventilation-perfusion matching.[59]

HPV is thought to result from hypoxia-mediated inhibition of voltage-gated potassium channels in pulmonary artery smooth muscle cells. Hypoxia inhibits the outward flow of potassium through these channels, resulting in depolarization of the membrane and entry of calcium, which causes smooth muscle cell contraction and sustained vasoconstriction.[59] When activated, this mechanism results in smooth muscle contraction within seconds of exposure to hypoxia. Smooth muscle contraction is augmented by the activity of RhoA and Rho-associated kinase. Hypoxia signals through the G protein RhoA stimulating Rho-associated kinase to increase phosphorylation of smooth muscle cell myosin light chain and to augment smooth muscle cell contraction, regardless of the level of intracellular calcium.[59]

Even brief periods of hypoxia may result in persistent hemodynamic abnormalities. In six healthy volunteers exposed to 8 hours of hypoxia, there was an increase in PVR, which did not return to normal after 2 hours of normoxia.[60]

Long-term hypoxia–induced structural changes in the pulmonary arterioles were demonstrated in an invasive hemodynamic study of 11 high-altitude natives, which showed that hemodynamics did not normalize even after 2 years at low altitude.[61] Structural changes in the pulmonary vasculature similar to those observed in COPD and IPF patients are present in the lungs of animals and humans exposed to hypoxia. In an autopsy series of tissues from Andean subjects born and living at high altitude who died without cardiac or pulmonary disease, medial hypertrophy of the pulmonary arteries was seen.[31]

The degree of increase in PAP in humans exposed to hypoxia varies widely among individuals from absent to very intense, with a rise to an mPAP of 40 mm Hg in 1–2% of healthy individuals.[62,63] These differences may be due to heritable differences in sensitivity to hypoxia or in pulmonary vascular reactivity, or both. Such differences may help explain why some patients with lung disease develop PH whereas others do not.[64]

Hypoxia is not the sole factor in generating PH.[65] This conclusion is supported by the finding that oxygen therapy in patients with lung disease has an inconsistent effect and does not normalize PAP.[66,67] In addition, hypoxia is not necessary to produce vascular changes; pulmonary vascular structural changes have been observed in patients with mild COPD who do not have hypoxemia (and thus do not have alveolar hypoxia), and structural changes seen in the pulmonary vasculature in patients with IPF are more extensive than can be explained by hypoxia alone.[52]

The development of hypercapnia may be one reason patients with lung disease develop more PH than individuals exposed to environmental hypoxia, such as those living at high altitudes. In patients with COPD-PH, hypoxemia is often accompanied by hypoventilation and hypercapnia, causing acidosis, which worsens HPV and PVR. This is in contrast to high-altitude dwellers such as healthy Andeans who have chronic hypoxia but generally have hyperventilation with resultant hypocapnia. Despite the presence of hypoxia, the high-altitude dwellers generally do not develop PH, suggesting that hypercapnia and acidemia are important contributing elements.

Neurohormones

Neurohormonal abnormalities and increased sympathetic nervous system activation are observed in patients with CLD-PH and contribute to development of hemodynamic abnormalities. Plasma catecholamine levels generally rise in patients with RV failure in a manner comparable to that seen in patients with heart failure secondary to primary myocardial disorders. It is clear that increased sympathetic activity is present with RV failure from CLD-PH, resulting in high plasma levels of circulating catecholamines and stimulation of the renin-angiotensin-aldosterone system.[68] Vasopressin levels have been shown to be higher in patients with RV failure due to COPD-PH than in patients with heart failure not associated with COPD.[69] Because cardiac output is often normal or may even be increased in decompensated RV failure, it is likely that the decrease in *systemic vascular resistance* (SVR) resulting from both hypercapnia and hypoxia leads to a reflex increase in circulating catecholamines and other neural hormones. Increased arterial P_{CO_2} may also directly activate the sympathetic nervous system and worsen pulmonary vascular constriction.

Angiotensin. Angiotensin II is a potent vasoconstrictor of the pulmonary vascular bed. The pulmonary vasculature appears to be more sensitive to the vasoconstrictor effects of angiotensin II than is the systemic vascular bed.[70] This is noteworthy because increased circulating levels of

angiotensin II and aldosterone are found in patients with RV failure secondary to COPD who have hypoxemia and hypercapnia.[71] Activation of the renin-angiotensin-aldosterone systems, together with hypoxemia, is probably an underlying pathophysiologic mechanism responsible for the elevation in PVR observed in patients with decompensated RV failure.

Angiotensin induces a dose-response increase in PVR in normal subjects.[72] Angiotensin II inhibitors have been shown to lower PVR and to be beneficial in patients with CLD-PH, especially in patients with IPF. In healthy human subjects, inhibition of angiotensin-converting enzyme has been demonstrated to attenuate the pulmonary pressor response to HPV.[73] Angiotensin II receptor blockade has resulted in similar reductions in HPV.[74] However, studies performed to date have not clarified a role for angiotensin-converting enzyme inhibitors or angiotensin II receptor antagonists in the treatment of CLD-PH.

Endothelin. *Endothelin-1* (ET-1) is a 21–amino acid peptide secreted by vascular endothelial cells in response to stimuli, including pulsatile stretch, sheer stress, neurohormones, cytokines, growth factors, thrombin, and hypoxemia. Endothelin-1 is a potent vasoconstrictor and mitogen. The effects of ET-1 are mediated by both *endothelin A* (ET_A) and *endothelin B* (ET_B) receptors. ET_A is localized on vascular smooth muscle cells, and ET_B is expressed on vascular smooth muscle cells, endothelial cells, and fibroblasts. Activation of ET_B receptors on endothelial cells mediates release of prostacyclin (prostaglandin I_2) and of *nitric oxide* (NO), a pulmonary vasodilator and inhibitor of fibrosis; both mediators exert vasodilatory and antiproliferative effects while also inhibiting ET-1 production by endothelial cells. Furthermore, the pulmonary endothelial ET_B receptors are responsible for the pulmonary clearance of up to 50% of circulating ET-1.[75] Despite these potential benefits of ET_B activation, the dominant effects of ET-1 are those primarily mediated by the ET_A receptor, including vasoconstriction, hyperplasia, hypertrophy, fibrosis, and increased vascular permeability.[76]

Increased ET-1 production has been described in patients with PAH, and both increased ET-1 levels and increased expression of receptors have been shown to be present in plexiform lesions of the lung in patients with PAH.[75,77] Furthermore, high plasma levels of ET-1 correlate with disease severity and adverse prognosis.[77–81] ET-1 concentration is also elevated in the sputum and urine of patients with COPD compared to normal subjects, and urinary levels have been shown to increase further during COPD exacerbations.[82,83] In addition, plasma ET-1 levels are increased in subjects who exhibit exertional and nocturnal hypoxemia.[84,85] In another study, patients with COPD-PH were shown to have elevated transpulmonary ET-1 levels.[86] Increased plasma levels and lung tissue expression of ET-1 have also been identified in patients with IPF with or without PH.[87]

Inflammation

Inflammation has been hypothesized to play a significant role in the development of the vascular changes seen in CLD-PH because increased markers of inflammation and inflammatory mediators have been observed in patients with CLD-PH. However, the exact role of inflammation in CLD-PH remains controversial.[88] Increased numbers of $CD8^+$ T lymphocytes have been observed in the walls of pulmonary vessels of patients with COPD. Furthermore, the presence of these cells was correlated to the enlargement of the intimal layer.[53] Similar findings have been observed in the lungs of smokers without COPD or PH, suggesting that cigarette smoke might induce these inflammatory markers. In another study, elevated serum levels of inflammatory cytokines, including C-reactive protein and tumor necrosis factor-α, were seen in patients with COPD-PH.[89] In patients with IPF-PH, elevated levels of multiple inflammatory mediators have been seen, including thromboxane A_2, tumor necrosis factor-α, platelet-derived growth factor, transforming growth factor-β, and fibroblast growth factor.[66,90,91] Studies of gene expression suggest that inflammatory mediators are overexpressed in patients with IPF-PH.[92] Further studies are needed to determine the causal nature of these changes and whether antagonizing inflammation could be of therapeutic value.

RIGHT VENTRICLE

The pattern of development of RV structural and functional abnormalities is similar in patients with CLD-PH and PAH and is secondary to the increased afterload on the RV resulting from the increase in PVR. RV afterload generally increases slowly in patients with chronic lung disease as PAP and PVR rise, leading to progressive RV hypertrophy, which minimizes wall stress. The RV eventually dilates so that the normal crescent shape of the RV is progressively transformed into a more spherical structure better able to generate an increased stroke work. RV dilation and wall thinning result in increased RV wall stress that, along with increased heart rate, leads to further increases in myocardial oxygen consumption, decreased myocardial perfusion, and RV ischemia. As the RV dilates, severe tricuspid regurgitation may develop, further compromising RV cardiac output and *left ventricle* (LV) filling. RV dilation in the setting of an intact pericardium compromises LV filling by shifting the interventricular septum toward the LV and reducing LV filling and cardiac output.[74] Nevertheless, several studies of end-diastolic pressure-volume relationships suggested well-preserved RV contractility in patients with COPD.[93] The additional presence of acidemia or infection can precipitate RV failure. When chronic hypercapnia with acidosis is present in patients with alveolar hypoventilation, the ability of the RV to increase its work appears to be impaired significantly, and RV end-diastolic pressure increases.

There may be subtle changes before elevations in PAP can be detected. For example, even before the development of significant elevations in PAP, RV hypertrophy and pathologic remodeling has been observed in patients with chronic lung disease. This was studied by echocardiographic and invasive hemodynamic evaluation of the RV in a group of 98 patients with stable moderate to severe COPD and no known heart disease.[94] Compared to 34 healthy controls, patients with COPD but without PH had increased RV wall thickness, RV size, and outflow tract dimension, as well as functional abnormalities assessed by myocardial performance index, RV isovolumic acceleration, and RV strain. In another study of patients with COPD, pulmonary artery compliance was reduced before PVR was significantly elevated, suggesting that decreases in compliance may be an early marker of hemodynamic compromise. In patients with lung disease, it is likely that early destruction of the

pulmonary vascular bed, though not sufficient to increase PVR, significantly reduces pulmonary artery compliance and contributes to early increases in RV afterload and subsequent RV hypertrophy.[95]

This impairment of myocardial contractility in the presence of hypercapnia probably plays a significant role in producing decompensated pulmonary heart disease in response to acute increases in arterial P_{CO_2} associated with exacerbations of COPD and accompanying decreases in alveolar ventilation. The development of RV volume overload with ventricular dilation results in a decreased RV ejection fraction; however, stroke volume tends to be maintained close to the normal range even in decompensated right heart failure.[96,97] With exercise, patients with COPD significantly raise their RV afterload, which causes further increases in RV end-diastolic volume and decreases in ejection fraction. It is likely that this deterioration in hemodynamic performance with exercise is a major factor limiting the exercise capacity of such patients.

LUNG MECHANICS

In healthy individuals, ordinary inspiration causes a small reduction of 3 to 5 cm H_2O in pleural pressure that is adequate to generate a normal tidal volume with only a small transmission of intrathoracic pressure affecting the heart and pulmonary vasculature. Increased stiffness of the chest wall or the lung parenchyma means that patients with obesity or obstructive or restrictive lung diseases must generate more negative pleural pressures to achieve an adequate tidal volume. Additionally, patients with COPD often have lung hyperinflation secondary to airflow obstruction, loss of elastic lung parenchyma, or dynamic hyperinflation. These abnormalities in pulmonary mechanics may contribute significantly to the pathophysiologic features of PH.

Lung hyperinflation affects RV function through changes in RV preload and afterload. Increased lung volumes in diseases such as COPD can passively compress alveolar vessels directly, increasing PVR and RV afterload,[98] and, in some cases, hyperexpanded lungs may even directly compress the heart with negative effects on cardiac performance.[99] Exaggerated swings in intrathoracic pressure such as those seen in patients with OSA can result in increased right-sided venous return, which causes acute RV enlargement and in turn impedes LV filling and cardiac output. At the same time, reductions in intrathoracic pressure increase LV afterload, which may be transmitted backward and result in transient increases in PAP.[100] In patients with acute bronchospasm, echocardiographic studies have shown acute inspiratory RV dilation and simultaneous reduction in LV cavity size that reverse during expiration, resulting in increased PVR from hyperinflation and increased RV wall tension from exaggerated negative pleural pressure. Importantly, the clinical significance of these effects may depend largely on the cardiovascular reserve of the specific patient.[98]

CLINICAL PRESENTATION

A diagnosis of CLD-PH should be considered and an appropriate investigation initiated when the degree of exercise impairment is greater than expected given ventilatory abnormalities and imaging findings or when signs and symptoms of right heart failure are present (Fig. 85.4). At times, the underlying cause of PH may be difficult to establish, and often the cause of PH is multifactorial. As described earlier, one large study showed that 59% of patients with COPD and elevated PAP had another cause of PH, including left heart disease, chronic thromboembolic PH, connective tissue disease, portal hypertension, drug use, and OSA.[7] When evaluating a patient with a new diagnosis of PH, an exhaustive evaluation is required to identify all possible causes of increased PAP (see Chapter 83).[101] The prognosis and treatment of PH vary dramatically with the cause so that a complete and accurate understanding of the underlying cause or causes of PH is required for prognostication and treatment selection.

SYMPTOMS AND SIGNS

The first step in the evaluation of a patient in whom CLD-PH is suspected is a comprehensive history and physical examination to identify any conditions that might cause PH (see Chapter 83, "Clinical Presentation"). In patients already diagnosed with lung disease, it is important that the lung disease be well characterized and that definitive diagnostic studies have been performed and are reviewed. Studies to exclude daytime hypoxemia with exercise and nocturnal hypoxemia secondary to OSA or hypoventilation should be performed. Left-sided heart disease is the most common cause of PH[4] and should always be considered as a potential contributor to PH. Although echocardiography is useful to detect reduced LV ejection fraction and valvular abnormalities, heart failure with preserved ejection fraction can be missed and may be detected only during comprehensive invasive hemodynamic assessment.[9,12]

Mild CLD-PH reflected in small chronic elevations in RV pressure generally causes minimal, if any, clinical, radiologic, or electrocardiographic findings. When moderate or severe CLD-PH develops (mPAP > 35 mm Hg), symptoms are often similar to those associated with the underlying pulmonary disease. Most commonly, these are dyspnea on exertion, chronic cough productive of mucoid sputum, wheezing, and occasional cyanosis. Clubbing of the fingers may be present. In addition to exertional dyspnea and fatigue, some patients experience dizziness or exertional syncope, attributable to the inability to increase cardiac output during exercise in the face of an increased PVR. Furthermore, these patients may have chest pain owing to RV ischemia or stretching of the main pulmonary artery.

When resting PAP is sufficiently elevated, patients may eventually reach a point at which the RV cannot meet the need for increased stroke work without a significant increase in right heart filling pressures. The resultant increase in central venous pressure is associated with developing symptoms of right-sided heart failure, such as peripheral edema, right upper quadrant discomfort, nocturia, and easy fatigability.

On examination, the patient with severe RV failure often appears dyspneic and tachypneic, with prominent use of the accessory muscles. In COPD, pulsus paradoxus may be present, the chest is often hyperinflated, and otherwise mild wheezing may be audible. Sinus tachycardia is often present; atrial and ventricular arrhythmias are

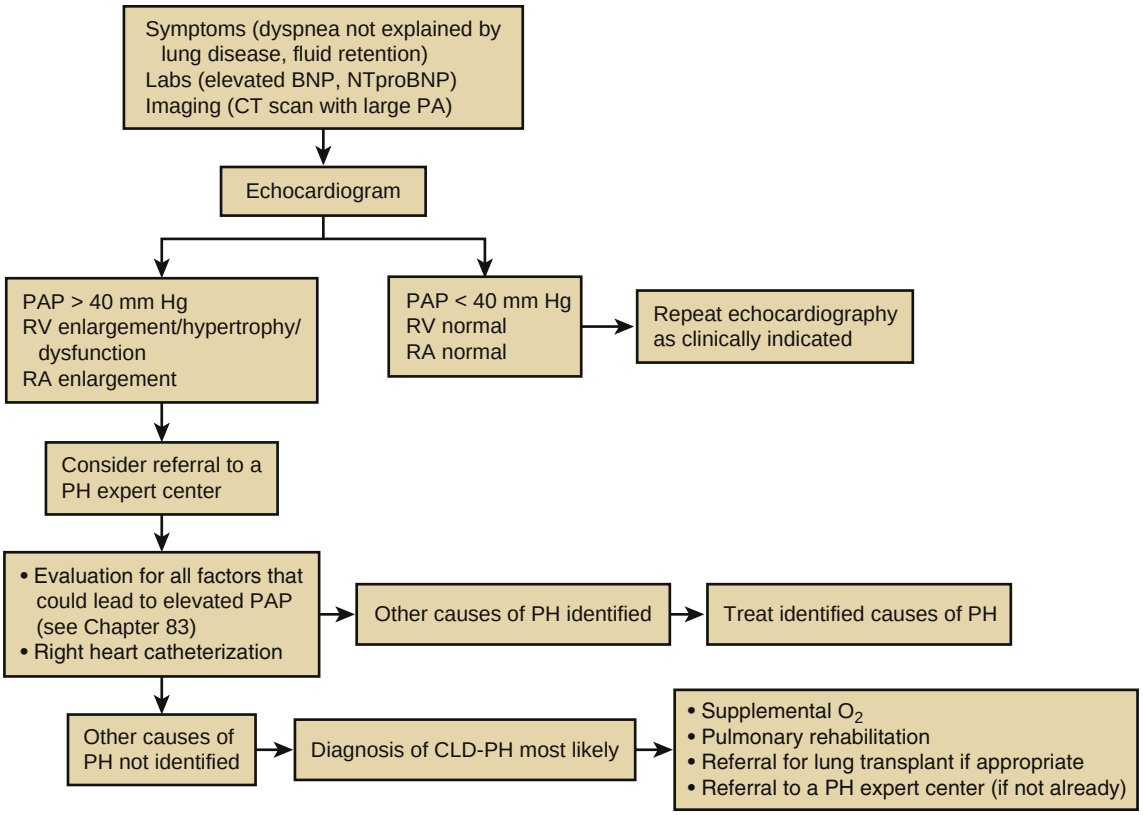

Figure 85.4 Approach to evaluation of patients with chronic lung disease with possible pulmonary hypertension. *Pulmonary hypertension* (PH) should be suspected in patients with *chronic lung disease* (CLD) who have worsening symptoms of dyspnea that cannot be attributed to known lung disease or who develop symptoms or signs of right heart failure, such as fluid retention. Elevated *B-type natriuretic peptide* (BNP) or increased pulmonary artery diameter on *computed tomography* (CT) scan may also suggest the development of PH. An echocardiogram should then be performed to estimate *pulmonary artery pressure* (PAP) and to assess *right ventricular* (RV) structure and function. In patients with elevated PAP or right heart abnormalities, referral to a PH expert center is appropriate. The evaluation proceeds with right heart catheterization to define hemodynamics as well as studies to identify all factors that could cause elevated pulmonary artery pressure, which should then be treated. If no other causes of PH are found, then treatment should be directed at optimization of lung disease, including consideration for lung transplant. It is important to take into consideration the severity of the underlying lung disease as assessed by pulmonary function testing and imaging. If the severity of parenchymal lung disease (i.e., not severe enough to cause hypoxemia) does not explain hemodynamic abnormalities, then a diagnosis of group 1 pulmonary artery hypertension with comorbid lung disease should be considered. NTproBNP, N-terminal pro–B-type natriuretic peptide; PA, pulmonary artery; RA, right atrium.

also common.[102] The cardiac examination is similar to patients with PAH (see Chapter 84). Findings of a parasternal lift, a loud second heart sound, and a right-sided S_3 and S_4 suggest right ventricular enlargement and elevated right ventricular filling pressures. Evidence of fluid retention may include dependent edema and ascites. The liver may be enlarged and tender to palpation and may be pulsatile, reflecting the presence of severe tricuspid regurgitation. Similarly, the neck veins may be distended and, when tricuspid regurgitation is present, show a large *c-v* wave with rapid *y* descent. Signs of volume overload secondary to RV dysfunction must be distinguished from sympathetically mediated renal salt and water retention without RV dysfunction, which can also develop in patients with lung disease.[103]

B-TYPE NATRIURETIC PEPTIDES

Measurement of *B-type natriuretic peptides* (BNPs) may be useful in the assessment of patients with lung disease and possible PH if there are no other reasons for elevated BNP values. In one study, plasma BNP was measured in 176 consecutive patients with a variety of pulmonary diseases[116]; elevated BNP levels identified PH (defined as PASP > 35 mm Hg) with a sensitivity of 0.85 and a specificity of 0.88 and predicted mortality. In both univariate and multivariate analysis, BNP was found to be a risk factor for death independent of pulmonary function impairment or hypoxemia.[116]

ELECTROCARDIOGRAPHY

Findings on the electrocardiogram may suggest the presence of PH; however, they are insensitive and cannot be used to rule out the presence of PH and RV abnormalities. Characteristically, the P wave of the electrocardiogram has a "p pulmonale" pattern with right-axis deviation resulting in an increase in its amplitude in leads II, III, and aVF to more than 2.5 mm (Fig. 85.5). The P wave may also be tall in the right precordial leads. The QRS vector in the frontal plane often shifts to the right and, if lung hyperinflation is present, a low-voltage QRS complex is common. Prominent S waves are seen in leads I, II, and III. An incomplete right bundle-branch block pattern is also frequently observed. When PH is moderate or severe, the more classic findings of RV hypertrophy may dominate the electrocardiogram,

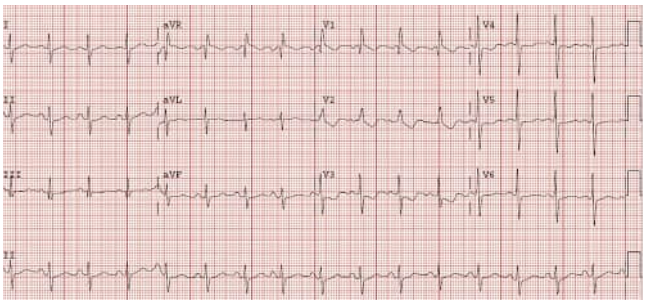

Figure 85.5 Electrocardiogram from a patient with pulmonary hypertension. Findings include a prominent "p pulmonale" and increased R wave voltage in the anterior precordial leads suggestive of right atrial and right ventricular abnormalities.

including tall R waves in V_1 with an R/S ratio of more than 1, and a prominent S wave in V_5 and V_6 with an R/S ratio of less than 1. The presence of electrocardiographic evidence of RV abnormalities in patients with COPD is a poor prognostic sign.[104]

CHEST RADIOGRAPHY

Similar to the ECG, the chest radiograph is insensitive for the detection of PH. There may be enlargement of the main pulmonary artery as well as enlargement of the right and left descending pulmonary arteries. Abrupt tapering of the peripheral vessels may result in disproportionately large central pulmonary arteries and attenuated distal vessels. A right descending pulmonary artery with a diameter greater than 16 mm suggests PH.[105] Enlargement of the RV may be seen on the lateral projection of the chest radiograph as a reduced retrosternal space. If hyperinflation of the lungs is present, the overall diameter of the cardiac silhouette may not be increased, although the heart may have a globular appearance.

The chest radiograph should be carefully evaluated for evidence of left heart failure. Pleural effusions are seldom seen in patients presenting with CLD-PH and right heart failure unless coexisting left ventricular dysfunction and failure are also present.[106] Radiographic findings of pulmonary edema also point to left heart failure as a likely cause of PH. Additionally, a diagnosis of pulmonary veno-occlusive disease should be considered in patients with PH and pleural effusions.

ECHOCARDIOGRAPHY

An echocardiogram should be performed in any patients with a clinical presentation that is suggestive of PH (see Chapter 83). Echocardiography is a useful tool for estimating PAP and evaluating RV structure and function and it can be repeated for serial assessments (see Fig. 83.3, Video 83.1). The echocardiogram is important in assisting the clinician in eliminating various nonpulmonary causes of PH, such as LV systolic dysfunction, aortic or mitral valve disease, and congenital heart disease.

Echocardiographic estimates of PASP are subject to important limitations, especially among patients with parenchymal lung disease. The presence of hyperinflation of the lungs impairs the transmission of ultrasound and can result in suboptimal image quality so that an adequate tricuspid regurgitant jet cannot be measured; in one large series of patients with advanced lung disease, a satisfactory PASP could be estimated in only 44% of patients.[107] The sensitivity and specificity of echocardiography to predict the presence of PH range from 0.79 to 1.0 and from 0.6 to 0.98, respectively.[108] However, when compared to invasive assessment, the echocardiographic estimate of PASP shows only moderate correlation and is often inaccurate.[107,109,110] Therefore, in patients with symptoms or clinical signs that are concerning for PH, right heart catheterization should be considered even if the estimated PASP by echocardiography is normal.

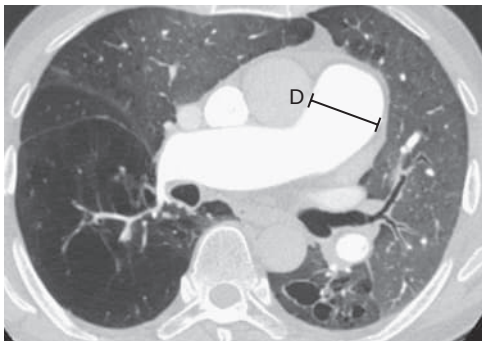

Figure 85.6 Chest computed tomography scan in a patient with interstitial lung disease demonstrating enlargement of the main pulmonary artery. Enlargement of the main pulmonary artery suggests the diagnosis of pulmonary hypertension. D = 36.4 mm, whereas the mean main pulmonary artery diameter in healthy controls is 25.1 ± 2.8 mm.[183]

COMPUTED TOMOGRAPHY

Chest *computed tomography* (CT) is important to evaluate the extent of parenchymal lung disease. It is important that the findings on the CT scan be consistent with the abnormalities detected on PFTs and, if they do not agree, that further investigation be performed to determine the true severity of parenchymal lung disease. Additionally, using this imaging modality, the size of the pulmonary artery can be measured and, in patients with moderate to severe PH, enlargement of the main pulmonary artery or an increased diameter of the pulmonary artery (>29 mm) may be documented (Fig. 85.6). This finding may have prognostic significance and, in a study of 3464 patients with COPD, a pulmonary artery/aorta ratio greater than 1 was associated with future severe COPD exacerbations (odds ratio, 3.44; $P < 0.001$).[111] However, in a study of 65 patients with advanced IPF, main pulmonary artery diameter on chest CT failed to differentiate between those who did or did not have PH diagnosed by right heart catheterization.[112] Other findings, such as dilated right-sided heart chambers on contrast-enhanced CT imaging, are suggestive but not diagnostic of CLD-PH in patients with severe parenchymal lung abnormalities.

CARDIAC MAGNETIC RESONANCE IMAGING

Currently, magnetic resonance imaging is the most accurate method for assessing the characteristics of the RV, including its volume, mass, and systolic function. Additionally,

phase-contrast magnetic resonance imaging has the capability to calculate accurate flow characteristics, including cardiac output, valvular regurgitant fraction, and both right- and left-sided shunt fractions. Magnetic resonance imaging has significant advantages over echocardiography in that it can image in any desired imaging plane, has a large field of view, and is not limited by acoustic windows. Although high cost, relatively long image acquisition time, and lack of widespread availability limit its use compared with echocardiography, cardiac magnetic resonance imaging is increasingly being used as the standard method for evaluating RV structure and function in patients with PH (see also Chapter 83).[113,114]

RIGHT HEART CATHETERIZATION

A discussion about the optimal technique for a right heart catheterization is found in Chapter 83 and applies to patients with CLD-PH. Of particular importance in the hemodynamic assessment of CLD-PH is how to perform pressure measurements, especially measurement of the PAWP in patients who may have large variation in pressure secondary to large swings in intrathoracic pressure during breathing. Incorrect pressure determination could lead to misclassification of the type and the severity of PH. There is no consensus on the best approach to measure pressures during right heart catheterization. It has been recommended that measurements should be made at end-expiration, when gas flow is minimal and transthoracic pressure is zero, to assess hemodynamics without respiratory influence.[115] However, such measurements can be technically challenging; the Sixth World Pulmonary Hypertension Symposium Proceedings suggest that, in CLD-PH, a floating average over several breaths (without a breath hold) should be obtained for measurement of mean pressures, including the PAWP.[6] Regardless of the technique used, it is important to review the hemodynamic tracings carefully and to consider the measurements in the context of the patient's overall clinical picture. Acute vasodilator testing should only be performed in the evaluation of patients with CLD-PH at a PH center to ensure patient safety and appropriate technique (see "Treatment" section).

SUMMARY

There is no single test that can be used to make a diagnosis of CLD-PH. It is important that all of the data described earlier, in particular, a comprehensive assessment of the severity of lung disease, be considered together to determine the most likely etiology of PH in any individual patient. Differentiating group 1 PAH from CLD-PH in a patient with lung disease is a common clinical dilemma that often requires evaluation at a PH specialty center.[117]

TREATMENT

In the vast majority of patients with CLD-PH, optimal treatment of the underlying lung disease according to established guidelines is by far the best approach to managing PH. Comorbidities that worsen PH and are amenable to treatment, such as left-sided heart disease, valvular disease, pulmonary emboli, and sleep-disordered breathing, should also be sought and aggressively treated. Because PH portends a poor prognosis in patients with lung disease, early referral for lung transplantation evaluation is imperative. Although it may be tempting to treat patients who have CLD-PH with therapies proven useful in group 1 PAH, these treatments have not been shown to be useful, and some have been harmful in patients with lung disease. Updated guidelines strongly discourage using treatments for PAH in patients with CLD-PH.[118,119] We recommend consultation at a center of excellence with experience in the evaluation and management of CLD-PH disease before initiation of PAH-specific therapy; if warranted, patients should be enrolled in prospective treatment trials.

Table 85.2 Therapeutic Strategies for Pulmonary Hypertension Due to Chronic Lung Disease

FOR ALL PATIENTS
Treatment of underlying lung disease
Lifestyle modification
Smoking cessation
Sodium restriction
Weight loss
Judicious exercise training
Structured rehabilitation and breathing training programs
Avoidance of overexertion
Avoidance of pregnancy
Avoidance of high altitudes
Supplemental oxygen
Diuretics
Treatment of sleep-disordered breathing and alveolar hypoventilation disorders (CPAP, BPAP, surgery)
Lung transplantation
FOR SELECTED PATIENTS
Lung volume reduction surgery
Phlebotomy
Iron supplementation
PAH-specific therapies (use discouraged except in highly selected circumstances and when managed by a pulmonary hypertension referral center)

BPAP, bilevel positive airway pressure; CPAP, continuous positive airway pressure; PAH, pulmonary arterial hypertension.

TREATMENTS USEFUL IN ALL PATIENTS WITH PULMONARY HYPERTENSION DUE TO CHRONIC LUNG DISEASE

In patients with CLD-PH, optimal treatment directed at the specific underlying pulmonary disorder is mandatory and is the subject of most of this textbook. The overall therapeutic strategies for CLD-PH and RV failure are shown in Table 85.2.[120,121]

Lifestyle Modifications

In the management of CLD-PH, diet and lifestyle modifications are crucially important. Smoking cessation is the most important of all preventive lifestyle interventions, especially considering the possible harmful effect of cigarette smoke on the pulmonary vasculature.[54] Other interventions consist of sodium restriction, weight loss, and exercise training to improve functional performance. Structured rehabilitation programs and breathing training have been shown to

be useful.[74,122] Patients with severe PH or RV dysfunction, especially those with a history of syncope, should avoid overexertion, pregnancy, and high altitudes (>1220 m [4000 feet]).

Oxygen

Alveolar hypoxia may make a major contribution to the genesis of CLD-PH, and aggressive treatment with supplemental oxygen to correct hypoxia is central to optimal treatment. Controlled trials evaluating long-term oxygen administration in COPD showed improvement in survival. Oxygen administration may have beneficial effects on hemodynamics,[123,124] RV function,[125] and exercise tolerance.

The effects of oxygen supplementation in CLD-PH have been studied in two major randomized trials. First, in the British Medical Research Council evaluation of long-term home oxygen in chronic hypoxic RV dysfunction, long-term oxygen administration for at least 15 hr/day lessened mortality and appeared to prevent further increases in PAP, compared with no oxygen administration in control patients.[126] Second, in a National Institutes of Health–sponsored study in the United States, continuous oxygen therapy was better than nocturnal therapy alone; furthermore, continuous oxygen lessened the mortality rate at 2 years[127] and decreased PVR in comparison with the group receiving only nocturnal therapy. These findings were confirmed in two more recent studies, both showing stabilization of PAP with long-term oxygen therapy.[128,129] There are other beneficial effects of oxygen therapy, including relief of renal vasoconstriction and improvement in oxygen delivery to critical organs such as the heart and brain.[130]

Based on the results of these studies, it is clear that hypoxemic patients with COPD should receive supplemental oxygen therapy. Additionally, there is evidence that oxygen improves functional class and symptoms in patients with IPF so that, in these patients, maintenance of arterial oxygen saturation at or slightly over 90% at rest and especially with activity has been recommended.[91] It must be remembered, however, that the acute administration of excessive concentrations of oxygen to a patient can have adverse effects on ventilation, particularly in patients with evidence of chronic hypercapnia. Patients given oxygen need to be observed closely when they are initially instructed on the use of this therapy to ensure that arterial oxygen saturation actually increases, but not too high: flow rates of 1 to 3 L/min generally suffice. Further information about the long-term use of oxygen in pulmonary rehabilitation is provided in Chapter 139.

Diuretics

Diuretic therapy to optimize volume status alleviates dyspnea, hepatic congestion, and peripheral edema. Decompression of the RV with diuretics may also improve RV performance by reducing preload and wall stress and reducing tricuspid regurgitation. Judicious diuresis may reduce intrapericardial pressure and potentially attenuate interventricular septal shift toward the LV, resulting in increased LV filling and improved systemic cardiac output.

Treatment of Sleep-Disordered Breathing

Sleep-disordered breathing is common in patients with COPD and can contribute to nocturnal hypoxemia and hypercapnia, leading to increased pulmonary vasoconstriction. As described in Chapter 120, CPAP exerts its beneficial effects by maintaining patency of both upper and lower airways and improving gas exchange. Patients diagnosed with OSA should be treated with CPAP and supplemental oxygen as required; in patients with OSA, CPAP is associated with improved ventricular function and survival and reduced hematocrit level.[131,132] In patients who have nocturnal hypoxemia without evidence of OSA, supplemental oxygen alone may be adequate. In some patients, such as those with obesity-hypoventilation syndrome, bilevel positive airway pressure may be more appropriate (see Chapters 122 and 136).

Lung Transplantation

There is a clear role for lung transplantation in patients with CLD who develop PH.[133] Because development of PH and right heart failure in patients with lung disease portends a poor prognosis and there are no effective medical therapies, timely referral for evaluation for lung transplantation is essential. Early referral to a transplantation center is preferred so that candidacy can be determined and barriers to transplantation can be identified and addressed. Recovery of RV function and good long-term prognosis have been demonstrated in patients following both single- and double-lung transplant for PH.[134,135]

There is conflicting evidence regarding the effects of pretransplantation hemodynamics on posttransplantation mortality in patients with CLD-PH. A retrospective study of 830 patients treated with lung transplant for IPF found that 90-day posttransplantation mortality increased with increasing pretransplant mPAP.[136] Another retrospective study showed that, in COPD patients undergoing lung transplantation, a preoperative echo-estimated PASP of 45 mm Hg or higher was associated with increased intensive care unit length of stay and duration of mechanical ventilation but was not associated with reduced survival.[137] The degree of pretransplantation RV dysfunction is potentially more important than PAP and may be considered by the transplantation team when determining risk and transplantation candidacy and the optimal surgical approach (single or double lung, on-pump or off-pump).[138] In patients with more advanced RV dysfunction, use of mechanical support such as extracorporeal membrane oxygenation during the perioperative period has been used to provide hemodynamic support and permit transplantation in patients with right heart failure[139,140] (see Chapter 138).

TREATMENTS THAT MAY BE CONSIDERED IN SELECTED PATIENTS

Lung Volume Reduction Surgery

The effects of *lung volume reduction surgery* (LVRS) on pulmonary hemodynamics remain controversial. LVRS has been shown to improve symptoms and quality of life in patients with emphysema and may improve pulmonary hemodynamics by improving oxygenation and reducing hyperinflation; by contrast, pulmonary hemodynamics may be worsened by removing or altering the pulmonary vasculature. Results of retrospective studies have shown variable effects of LVRS on hemodynamics; some have shown improvement in RV function[141] and reduction in wedge

pressure,[142] whereas others have found an increase in PAP and PVR.[143,144] The prospective cardiovascular substudy of the National Emphysema Treatment Trial attempted to clarify the hemodynamic effects of LVRS by randomizing 110 patients to either LVRS or medical therapy.[145] Six months after treatment, hemodynamics were similar in both groups, with the exception of a small reduction in wedge pressure in the LVRS group. Based on these results, LVRS is not currently recommended for routine treatment of CLD-PH.

Phlebotomy for Polycythemia

If severe polycythemia is present, phlebotomy may be helpful, although clinicians are frequently reluctant to undertake this type of therapy today. An elevated hematocrit above 40% is known to increase viscosity and PVR (see eFig. 85.1). Phlebotomy in patients with polycythemia and chronic hypoxemia may also improve RV ejection fraction, exercise tolerance, and neuropsychological function.[74] For those with an elevated hematocrit (e.g., above 55%), phlebotomy should be considered and, if the patient benefits, repeated as needed to maintain a lower hematocrit.[146–148]

Iron Supplementation

Experiments in animals and human tissue cells have revealed that the hypoxia-inducible factor family of transcription factors is integral to regulation of the pulmonary vascular response to hypoxia.[149] Hypoxia-inducible factor is primarily regulated by oxygen-dependent proteasomal degradation, a process that is up-regulated or down-regulated based on iron availability. A study in humans showed that intravenous iron infusions into healthy iron-replete volunteers blunted the pulmonary vasoconstrictor response to hypoxia, whereas a reduction in available iron through chelation to those same volunteers enhanced the pulmonary vasoconstrictor response to hypoxia.[150]

In a follow-up study, PAP was assessed by echocardiography in 22 healthy volunteers at sea level.[151] Subjects were then taken to 4340 m for 3 days and treated with either intravenous iron or saline; repeat assessment showed a reduction in PASP in iron-treated patients compared to controls. Another trial evaluated the effects of standard therapy, phlebotomy, followed by iron infusion or saline infusion in 11 patients with chronic mountain sickness.[151] Following phlebotomy, all patients developed iron deficiency with an increase in PASP of 9 mm Hg that did not reverse acutely with intravenous iron treatment. Further randomized trials are needed; however, these studies suggest that evaluation for and correction of iron deficiency in patients with CLD-PH may be beneficial.

Pulmonary Arterial Hypertension–Specific Therapies

Multiple therapies are now available with proven efficacy in the treatment of PAH (see Chapter 84). Elevated PAP in patients with CLD-PH is an appealing target of therapy given the poor outcomes associated with the development of CLD-PH and availability of PAH-specific medications. Acute hemodynamic benefits in CLD-PH have been demonstrated with some of these agents[152,153]; however, adverse effects, including worsening hypoxemia from reversal of physiologic ventilation-perfusion matching and reduction in systemic blood pressure from peripheral vasodilator effects, have been described.[153,154] Randomized studies of IPF patients treated with *endothelin receptor antagonists* (ERAs) and the soluble guanylate cyclase agonist riociguat have resulted in worse outcomes compared to placebo.[155–157]

Current guidelines discourage the use of PAH-specific therapy in CLD-PH patients because of a lack of efficacy and risk for adverse effects.[118,119] However, the INCREASE trial of inhaled treprostinil in ILD-PH, published in early 2021, showed that, compared to placebo, 12 weeks of inhaled treprostinil improved 6MWD, lowered levels of NT-proBNP, and reduced clinical worsening.[157a] This small brief trial is important because it is the first to show a benefit of PAH-specific therapy in CLD-PH. Additional trials will be needed to clarify the effects of this treatment on more consequential long-term outcomes and to show how it should be incorporated into patient management decisions.[157b] This and other PAH-specific therapies might be considered in selected patients with CLD-PH such as those who also have evidence of concomitant group 1 PAH or group 4 chronic thromboembolic PH and to manage right heart failure in CLD-PH patients awaiting lung transplant. If treatment with PAH-specific therapies is considered, we recommend consultation at a PH center of excellence before initiating therapy and, if possible, enrollment in a clinical trial.

Of major concern in patients with CLD-PH is that pharmacologic reversal of HPV with vasodilators may increase pulmonary blood flow to poorly ventilated or nonventilated alveoli and cause arterial P_{O_2} to fall despite a drop in PAP. Ventilation-perfusion mismatching also affects carbon dioxide elimination; therefore minute ventilation may increase to compensate for the retention of carbon dioxide, although arterial P_{O_2} may still fall.[158] Another practical problem limiting the use of pulmonary vasodilators is that very often they also act as systemic vasodilators and cause significant hypotension.

A comprehensive review of the studies of PAH-specific treatment in patients with CLD-PH can be found at ExpertConsult.com.

TREATMENT OF DECOMPENSATED RIGHT VENTRICULAR FAILURE

Management of patients with decompensated RV failure must focus on improvement of the underlying pulmonary disorder.[120] The precipitating event for decompensation in patients with stable chronic right heart failure from either COPD or interstitial lung disease is often an upper respiratory infection. Increased secretions and infection are likely to tip the balance toward further arterial hypoxemia, hypercapnia, and acidemia, which aggravate PH and worsen ventricular contractility, resulting in cardiac decompensation.

Improvement in RV performance is best accomplished not only by correcting acidemia, but also by reducing the afterload of the RV (i.e., reducing mPAP). Correction of arterial hypoxemia through the administration of an increased concentration of oxygen lowers PAP in patients with HPV. Improvement in alveolar ventilation with mechanical or noninvasive positive-pressure ventilation helps eliminate the acute hypercapnia and acidemia that depress myocardial contractility.

Calcium Channel Blockers. Calcium channel blockers are not useful in the treatment of CLD-PH. In a study of 53 patients with COPD and PH, treatment with nifedipine reduced PVR at baseline by 23% at rest and 35% during exercise, but the benefits were no longer seen after an average of 13 months of treatment.[152] Another study randomized 20 patients with COPD and mild PH to either placebo or nifedipine. There were no acute improvements with the first dose of nifedipine, and 18 months later cardiac output was slightly higher in nifedipine-treated patients accompanied by a nonsignificant reduction in arterial Po_2. In another study of felodipine in 13 patients, hemodynamics were improved and gas exchange remained stable at 12 weeks compared to baseline, but exercise tolerance was not improved.[159] Due to the lack of long-term benefits and potential side effects from calcium channel blockers (worsening hypoxemia, systemic hypotension, and peripheral edema), we recommend against attempts to treat CLD-PH with calcium channel blockers.

Endothelin Receptor Antagonists. Three ERAs are approved by the Food and Drug Administration for the treatment of PAH. Bosentan and macitentan are dual ET_A and ET_B receptors, and ambrisentan is a selective ET_A receptor antagonist.[160] Studies of ERAs in lung disease have been designed to evaluate the effects of endothelin blockade on lung fibrosis and have not specifically included patients with CLD-PH.

BUILD 3 (Bosentan Use in Interstitial Lung Disease) was a large, randomized trial of bosentan to reduce the rate of IPF worsening or death. Results of BUILD 3 showed no significant difference in the primary end point of rate of IPF worsening or death in the 407 patients treated with bosentan versus the 209 in the placebo group. Another study evaluated the effects of bosentan on exercise capacity in patients with severe or very severe COPD; at the end of 12 weeks, only 16 of 20 patients randomized to bosentan remained in the treatment group, with the remainder dropping out because of adverse effects.[161] There was no difference in exercise capacity in the bosentan-treated group compared to the placebo group, and, in addition, there was a significant reduction in arterial oxygenation and quality of life in the bosentan-treated patients.

In Artemis-IPF, the largest study of ET_A receptor antagonists in the treatment of IPF, ambrisentan was studied in patients with IPF with minimal lung fibrosis.[155] The study was terminated early because interim analysis suggested a low likelihood of meeting the primary end point. Analysis of data from patients who were enrolled showed that those in the ambrisentan group were more likely than control subjects to experience disease progression (27.4% vs. 17.2% in the placebo group); this end point was primarily driven by higher rates of hospitalization in the ambrisentan group.

The effect of macitentan on forced vital capacity was studied in patients with IPF in the MUSIC trial, in which 178 subjects were randomized to macitentan or placebo. Hemodynamic assessments were not reported in this study. After 12 months there was no difference in change from baseline forced vital capacity, but there was a trend toward a higher rate of worsening of IPF in the macitentan group.[157]

In summary, in patients with lung disease, no benefits to treatment with ERAs have been demonstrated, and the Artemis-IPF and MUSIC studies show ERAs may be harmful in this population. From these findings, we conclude that ERAs should not be used to treat CLD-PH, and further studies of ET_A receptor antagonists in patients with lung disease seem unlikely.

Prostacyclin and Its Analogues. Prostanoids such as epoprostenol are potent pulmonary vasodilators normally synthesized by the pulmonary vascular endothelium, and exogenous prostanoids have a central role in the treatment of PAH.[162] Studies in animals and humans have shown that hypoxemia results in relative prostanoid deficiency[163,164]; however, studies in patients have not found treatment with prostanoids to be uniformly beneficial in CLD-PH.

Intravenous epoprostenol was studied in a small number of patients with respiratory failure secondary to COPD. Those treated with epoprostenol experienced significant reductions in arterial Po_2, most likely from nonselective pulmonary and systemic vasodilation, resulting in a worsening ventilation-perfusion relationship.[165] Several small case series suggest improvements in hemodynamics and right ventricular function of parenteral prostanoids in patients with IPF-PH and with ILD-PH in patients with scleroderma,[166] but these findings have yet to be recapitulated in larger studies. Studies of inhalational prostanoids were performed because it was thought they might cause less nonselective pulmonary vasodilation, preserving ventilation-perfusion relationships and minimizing hypoxemia. Beneficial effects using inhaled prostanoids were shown in several early trials. In one small study, treatment with aerosolized iloprost resulted in preferential pulmonary vasodilation and significant reduction in mPAP and PVR.[167] Another study evaluated the effects of a single dose of inhaled iloprost in 10 patients with COPD-PH and right ventricular abnormalities; patients had a statistically significant improvement of 49.8 m on the 6MWD without a significant change in arterial Po_2 and without adverse hemodynamic effects.[168]

The same beneficial effects of inhaled prostanoids were not seen in a more recent randomized double-blind crossover trial of inhaled iloprost in COPD patients with right heart catheterization–confirmed PH.[169] In this study, placebo, 10 μg, and 20 μg of iloprost were studied in 16 patients during three separate study visits. There was no difference in 6MWD after either dose of iloprost compared to placebo. A significant reduction in arterial So_2 was seen at rest, and a nonsignificant reduction was seen with exercise. The subgroup of 3 participants with right ventricular abnormalities and more severe PAP did have an improvement in exercise tolerance.

More recent trials have utilized inhaled treprostinil, which is delivered via a more user-friendly device and requires less frequent treatments. The INCREASE trial of inhaled treprostinil in ILD-PH demonstrated that after 16 weeks of treatment, the difference between the treprostinil group and the placebo group in the change from baseline in peak 6MWD was 31.1 m ($P < 0.001$).[157a] This trial is important because it is the first to show a benefit of a PAH medication and therapy target elevated PAP in patients in ILD-PH. However, the trial was small and was not designed to evaluate the effects of treatment on long-term outcomes including survival. Additional trials are needed to further

define the role of this therapy in the management of ILD-PH. The PERFECT trial of inhaled treprostinil in COPD-PH is ongoing (ClinicalTrials.gov Identifier: NCT03496623).

Nitric Oxide. NO is produced by the enzyme NO synthase within endothelial cells and activates guanylate cyclase, increasing smooth muscle cell cyclic guanosine monophosphate, which causes pulmonary vasodilation.[170,171] A possible role in the treatment of CLD-PH has been suggested based on data demonstrating that NO reverses HPV in healthy volunteers.[172,173] Similar to inhaled prostanoids, inhaled NO would be expected to cause less nonselective dilation of the pulmonary vasculature and less ventilation-perfusion mismatch than systemic vasodilators. Furthermore, inhaled NO is inactivated before it reaches the systemic circulation so that less systemic hemodynamic effect would be expected. Only limited, conflicting data are available regarding the effects of NO on hypoxemia in advanced COPD; one small study reported a decrease[174] and another no change[175] in arterial Po_2 after inhaled NO. However, because treatment with NO is technically challenging, costly, and associated with a variety of potential adverse effects, clinical use remains impractical at this time.

Phosphodiesterase Type 5 Antagonists. Sildenafil and tadalafil are selective inhibitors of cyclic guanosine monophosphate–specific phosphodiesterase type 5 and cause pulmonary arteriolar smooth muscle cell relaxation and vasodilation. Additionally, sildenafil has antifibrotic activity that has been tested in patients with lung disease.

The acute effects of sildenafil on hemodynamics and oxygenation were studied at rest and with exercise in 20 patients with COPD and mild PH after a single dose of 20 mg or 40 mg of sildenafil.[153] There was a significant 21% reduction in resting mPAP 1 hour after sildenafil that was accompanied by worsening gas exchange with a reduction in arterial Po_2 of 9%. A similar reduction in mPAP was seen during exercise with no significant change in oxygenation; concomitant studies showed that worsening hypoxemia was related to worsening of ventilation-perfusion matching after sildenafil.

Three studies have attempted to address the effects of sildenafil on exercise tolerance in patients with COPD. In the first, sildenafil was administered to 15 COPD patients for 3 months; compared to baseline, there was no difference in the RV stroke volume measured by magnetic resonance imaging or in exercise tolerance measured by cardiopulmonary exercise testing and the 6MWD.[176] In a second study, the effects of sildenafil on exercise capacity were studied in 10 patients in a randomized, double-blind placebo-controlled crossover study.[177] Patients with PH were specifically excluded from this study. After 14 days of sildenafil treatment, there was no difference in exercise capacity, but there was worsening of oxygenation and quality of life with increasing symptoms and adverse events in the sildenafil group. The third study randomized 63 patients with COPD and moderate PH documented by echocardiography to treatment with sildenafil for 3 months during pulmonary rehabilitation; in this study, sildenafil had no effect on exercise capacity or oxygenation.[178]

The acute effects of sildenafil have also been evaluated in patients with interstitial lung disease. Sixteen hospitalized patients with pulmonary fibrosis were treated with inhaled NO and then randomized to receive open-label intravenous epoprostenol (mean dose 8 ng/kg/min) or a single dose of oral sildenafil 50 mg.[154] All three agents reduced the PVR index to a similar extent. However, only inhaled NO and sildenafil reduced the PVR-to-SVR ratio. Intravenous epoprostenol also decreased mean systemic arterial pressure and Po_2 values owing to ventilation-perfusion mismatching. By contrast, during treatment with inhaled NO and sildenafil, ventilation-perfusion matching was maintained. Therefore, among patients in this study, sildenafil exerted a selective pulmonary arterial vasodilatory effect without worsening hypoxemia.

The effects of sildenafil on exercise tolerance in patients with IPF-PH were examined in two studies. In one small open-label study, 14 patients with IPF and mild PH received sildenafil 20 to 50 mg three times daily for 12 weeks.[179] At the end of the study, of the 11 patients who completed the 6MWD, 9 demonstrated an improvement in the mean 6MWD of 49 m (90% confidence interval, 17.5 to 84 m). The second study, STEP-IPF (Sildenafil Trial of Exercise Performance in Idiopathic Pulmonary Fibrosis), was the largest study of sildenafil in patients with IPF to date.[180] In this study, patients with IPF were randomized to either sildenafil ($n = 89$) or placebo ($n = 91$) for 12 weeks of treatment without any assessment for the presence or severity of PH. The primary end point of improvement in 6MWD was not met; however, patients taking sildenafil had improved dyspnea, quality of life, and less deterioration in oxygenation.

Overall, the results of these studies are highly variable but suggest that, in certain patients with lung disease, sildenafil might confer some early hemodynamic and symptomatic improvement, potentially at the expense of worsening ventilation-perfusion matching and worsening oxygenation and without any clear long-term benefits. Further well-designed studies are needed to determine if there is a role for these agents in CLD-PH.

Riociguat. Riociguat is a soluble guanylate cyclase agonist approved by the Food and Drug Administration in 2013 for the treatment of PAH; it was also studied in patients with CLD-PH. In an open-label trial, riociguat was studied in 23 patients with interstitial lung disease who also had PH with an mPAP above 30 mm Hg and no more than mild airflow obstruction. At 12 weeks, there were small but statistically significant improvements in cardiac output, PVR, and SVR compared to baseline. The PVR-to-SVR ratio remained largely unchanged, and the mPAP was increased in some patients, suggestive of an increase in blood flow that may be attributable to reduction in the SVR. There was also statistically significant worsening of oxygenation. The subsequent RISE IIP randomized controlled trial of riociguat versus placebo in patients with idiopathic interstitial pneumonia was terminated early due to increased serious adverse events (37% riociguat group vs. 23% placebo) and mortality and no improvement in the 6MWD in the riociguat group.[156] These findings suggest that riociguat should not be considered in patients with CLD-PH.

In the setting of severe acute RV decompensation with hypoperfusion, intravenous dopamine and dobutamine or milrinone may improve cardiac output, blood pressure, and renal perfusion. Low-dose dopamine infusion (2 to 5 mg/kg/min) can increase cardiac output, reduce PVR, and improve oxygen delivery.[181] Higher infusions of dopamine (10 mg/kg/min) have been shown to increase diaphragmatic blood flow and contraction.[182] Although they are effective in acute decompensated RV failure, the value of these agents in CLD-PH is yet to be determined.

Key Points

- *Pulmonary hypertension* (PH) is present in approximately 25% of patients with *chronic lung disease* (CLD-PH) and is associated with significantly worsened symptoms, functional impairment, and increased morbidity and mortality.
- Mild PH is common among patients with COPD. Severe hemodynamic abnormalities are found in a very small number of patients and, among those patients, other causes of PH are common.
- PH secondary to sleep-disordered breathing may be reversible if it is adequately treated with continuous positive airway pressure or bilevel positive airway pressure.
- The pathogenesis of CLD-PH involves both hypoxic pulmonary vasoconstriction and pulmonary vascular remodeling, which are related to anatomic restriction and/or obliteration of the pulmonary vascular bed from alveolar destruction, fibrosis, inflammation, thrombosis, and the effects of mitogenic mediators specific to the underlying lung disease.
- The diagnostic work-up of patients with CLD-PH should include a comprehensive evaluation to identify any other medical conditions that can elevate pulmonary arterial pressure, including sleep-disordered breathing, left heart disease, and chronic thromboembolic pulmonary hypertension.
- The optimal approach to management of patients with CLD-PH and right heart failure includes aggressive treatment of the underlying lung disease and administration of supplemental oxygen.
- Group 1 PAH-specific treatments, with the exception of inhaled treprostinil, have not shown benefit in patients with CLD-PH and may cause harm.
- Currently, there are no U.S. Food and Drug Administration–approved therapies for the treatment of CLD-PH apart from the administration of oxygen; accordingly, early referral for evaluation of lung transplantation is important and, if specific treatment for PH is warranted, expert consultation before initiating therapy is recommended.
- Pulmonary hypertension practices and centers accredited by the Pulmonary Hypertension Association can be found at: https://phassociation.org/patients/doctorswhotreatph/

Key Readings

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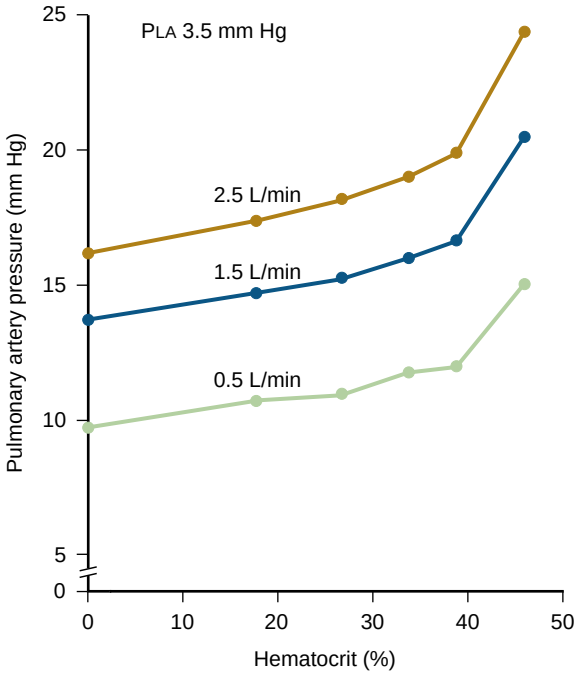
Complete reference list available at ExpertConsult.com.

eFIGURE IMAGE GALLERY



eFigure 85.1 Effect of hematocrit on pulmonary artery pressure at three levels of blood flow (0.5, 1.5, and 2.5 L/min). *Left atrial pressure* (Pla) was held constant at 3.5 mm Hg. As the *hematocrit* (Hct) is increased at constant levels of pulmonary flow, pulmonary artery pressure increases, reflecting the higher vascular resistance caused by increased blood viscosity. With an increase in Hct above 40%, the pressure and resistance rise rapidly. (From Murray JF, Karp RB, Nadel JA. Viscosity effects on pressure-flow relations and vascular resistance in dogs' lungs. *J Appl Physiol*. 1969;27:336-341.)

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86 PULMONARY HYPERTENSION DUE TO CHRONIC THROMBOEMBOLIC DISEASE: GROUP 4

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INTRODUCTION

Chronic thromboembolic pulmonary hypertension (CTEPH) is one of the five *World Health Organization* (WHO) classifications of *pulmonary hypertension* (PH). This disease, classified in WHO Group 4, is often under-recognized, and may represent a larger population than *pulmonary arterial hypertension* (PAH), in WHO Group 1. CTEPH is unique among the various forms of PH due to the potential for surgical cure with *pulmonary thromboendarterectomy* (PTE). CTEPH is preceded by an incident PE in approximately 75% of patients. The acute thrombosis is replaced by chronic intravascular scar, which can ultimately lead to PH due to increased flow shunted from the obstructed vasculature through the open vascular beds. This chapter reviews the pathogenesis, epidemiology, diagnostic algorithm, and treatment options for CTEPH.

EPIDEMIOLOGY AND RISK FACTORS

The precise incidence of CTEPH is difficult to establish. In the literature, estimates are either based on small registries in which patients were prospectively followed after acute PE to identify CTEPH or based on the discovery of CTEPH at specialized PAH centers. Given these limitations, current estimates of the incidence of CTEPH after acute PE range from 0.1–8.8% within 2 years of the incident PE.[1]

Based on the incidence of PE in the United States and the natural history learned from well-done prospective follow-up cohorts after acute PE, the expected incidence of CTEPH is much higher than is currently seen. Approximately 300,000 acute pulmonary emboli are diagnosed in the United States annually.[2] In the largest, most rigorous follow-up studies, the observed rate of persistent perfusion defects after 6 months of anticoagulation ranges from 30–50% of all patients with unprovoked PE.[3,4] Persistent perfusion defects are required for the development of CTEPH, although the majority of patients with residual defects do not have resting PH. Approximately 10–15% of patients after acute PE experience dyspnea due to chronic perfusion defects with no evidence of resting PH.[4] Approximately 4% of patients after acute PE developed CTEPH.[5] Based on the incidence of acute PE and a conservative estimate of the rate of persistent perfusion defects and development of CTEPH, approximately 30,000 will have symptomatic dyspnea on exertion and at least 3000 patients per year will be diagnosed with CTEPH. The total number of pulmonary thromboendarterectomies, balloon pulmonary angioplasties, and referrals for medical therapy for CTEPH is much lower than expected by this projected incidence. Furthermore, these estimates of CTEPH incidence do not take into account the approximately 25% of patients who are diagnosed with CTEPH but who do not have a history of a preceding PE.[6]

Some features of the acute PE presentation may increase the likelihood for subsequent CTEPH. A common presenting feature among patients with CTEPH is a delay in diagnosis in which symptoms began more than 2 weeks prior to the onset of anticoagulation.[7] Compared to patients who completely resolved their PE, those with CTEPH had elevated circulating biomarkers, such as heart-type fatty acid binding protein or an *N-terminal pro B-type natriuretic peptide* (NT-proBNP), and more evidence of PH (i.e., massive or submassive presentations of their acute PE) at the time of diagnosis.[8] The presence of an initial right ventricular systolic pressure by a transthoracic echocardiogram of greater than 50 mm Hg at the time of PE diagnosis was associated with a 3.3 times higher odds ratio of PH at 1 year.[9]

Several medical conditions have been associated with the development of CTEPH. Chronic inflammation plays a key

role in the development and persistence of chronic thrombi, and a number of inflammatory conditions, including staphylococcal infection, osteomyelitis, and inflammatory bowel disease, have been linked to increased risk for CTEPH development.[1] DNA from *Staphylococcus* has been isolated from thromboendarterectomy specimens in patients with venoarterial shunts, suggesting a component of chronic infection.[10] Similarly, patients with infected intravascular devices such as pacemakers are associated with increased risk for CTEPH.[11]

Hypothyroidism is seen with increased prevalence in CTEPH patients compared to the general population.[12] The mechanism by which hypothyroidism might mediate CTEPH development has not been delineated, but hypothyroidism is associated with increased risk for *venous thromboembolism* (VTE) development compared to euthyroid controls. Malignancy also is more common in patients with CTEPH than in patients with PAH.[13] Cancer induces a hypercoagulable state associated with increased risk for VTE; certain chemotherapies and high doses of steroids may further amplify this risk. Additionally, many patients with malignancy require chronic intravascular access for chemotherapy infusions; these catheters may lead to small, subclinical PE and have been associated with chronic thromboembolic disease at a distal level.

CTEPH is usually preceded by PE but, interestingly, most of the hypercoagulable states that increase the risk for acute PE are not over-represented in patients with CTEPH (Table 86.1). The notable exceptions are lupus anticoagulant/anticardiolipin antibodies,[14] elevated clotting factor VIII,[15] elevated von Willebrand factor,[16] and certain dysfibrinogenemias[17] (i.e., presence of the fibrinogen Aa chain Ala312 allele[18]), which increase both the risk for acute PE and the persistence of chronic thrombus leading to CTEPH.

PATHOGENESIS

The first step in the pathogenesis of CTEPH is the failure of the initial PE to resolve completely. With anticoagulation, resolution of perfusion defects after acute PE may range from complete restoration of perfusion to long-term persistence of perfusion defects with chronic clot.[19] Several pathways have been implicated in the failure of thrombus resolution. The initial phase of thrombus clearance is dictated by neutrophils and marked by increases in interleukin-1β and transforming growth factor-α.[20] In a rat model of CTEPH, neutropenia leads to failure of thrombus clearance and increased deposition of collagen in the vessel wall.[21] Beyond the first few days after a PE, neutrophils give way to monocytes, which create a fibrotic milieu with elevated levels of vascular endothelial growth factor and transforming growth factor-β, which in turn lead to increased collagen deposition.[22] Over the ensuing weeks, the original fibrin-rich thrombus is remodeled into an intravascular, collagen-rich scar with neovascularization.

Beyond these inflammatory changes that favor thrombus persistence, impaired fibrinolysis has been implicated in thrombus persistence as well. In some cases, patients with CTEPH have fibrin resistant to plasmin-mediated fibrinolysis.[23] This resistance to lysis has been associated with several novel fibrinogen variants that have bulky side chains

Table 86.1 Selected Risk Factors and Univariate Odds Ratios for the Development of Chronic Thromboembolic Pulmonary Hypertension

	Risk Factor	Comparator	OR (95% CI)
Risk factors related to the acute pulmonary embolism	Unprovoked PE[7]	Resolved PE	20.0 (2.7 to >100)
	Massive/submassive PE[65]	IPAH	13.0 ($P = 0.004$)*
	Symptoms >2 weeks prior to PE diagnosis[7]	Resolved PE	7.9 (3.3–19.0)
	RV dysfunction at diagnosis[7]	Resolved PE	4.1 (1.4–12.0)
	Age >60 years[7]	Resolved PE	2.9 (1.2–7.2)
Medical risk factors for CTEPH	VTE history[65]	IPAH	49.0 ($P < 0.001$)*
	Recurrent VTE[66]	IPAH	45.0 (21.0–114.7)
	Splenectomy[66]	IPAH	22.1 (3.0–2824)
	VA shunt[66]	IPAH	19.5 (2.5–2520)
	Prior VTE[66]	IPAH	19.4 (11.7–33.8)
	Thyroid replacement[66]	IPAH	5.4 (2.7–12.2)
	Hypothyroidism[7]	Resolved PE	4.3 (1.4–13.0)
	APS/lupus AC[66]	IPAH	3.3 (1.6–7.5)
	Non–blood group O[65]	IPAH	3.1 ($P < 0.001$)*
	Malignancy[66]	IPAH	2.0 (1.0–4.3)

*Adjusted for age and sex.

AC, lupus anticoagulant; APS, antiphospholipid antibody syndrome; CI, confidence interval; CTEPH, chronic thromboembolic pulmonary hypertension; IPAH, idiopathic pulmonary arterial hypertension; OR, odds ratio; PE, pulmonary embolism; RV, right ventricular; VA, veno-arterial, VTE, venous thromboembolism;

Modified from Fernandes T, Auger W, Fedullo P. Epidemiology and risk factors for chronic thromboembolic pulmonary hypertension. *Thromb Res*. 2018;164: 145–149.

or post-translational modifications that may obscure the tissue plasminogen activator binding site.[24] The presence of fibrin-rich clot in the pulmonary artery modulates the endothelial and mesenchymal cells, which mediate the formation of an intravascular scar and drive the neoangiogenesis in the residual chronic clot.[25]

The persistence of perfusion defects is necessary, but not sufficient, for the development of CTEPH. Most patients with persistent perfusion defects do not manifest overt resting PH, and what mediates the development of PH is not clear. In vessels obstructed by chronic clot, the distal vascular bed is preserved but the flow is diverted to the unobstructed vascular beds. Over time, this increased flow to the unobstructed vascular beds leads to shear stress on the endothelial walls.[26] Ultimately, the unobstructed vascular bed is remodeled to an appearance similar to that of PAH, with smooth muscle proliferation and endothelial dysfunction.[27] As the pulmonary vasculature remodels, the afterload on the right ventricle increases, culminating in right ventricular remodeling (i.e., dilation, hypertrophy) and, if left untreated, right ventricular failure.

If patients have chronic perfusion defects but no resting PH, they may still be symptomatic due to these defects, a condition called *chronic thromboembolic disease* (CTED). The dyspnea that patients with CTED experience is due either to exercise-induced PH or dead space ventilation.[28] The natural history of CTED and whether these patients would develop overt resting PH in the future is unknown. The management of these patients is somewhat controversial, but many experienced centers offer *pulmonary endarterectomy* (PTE) or *balloon pulmonary angioplasty* (BPA) to selected CTED patients with significant dyspnea and few comorbidities.[29]

DIAGNOSTIC EVALUATION

The key to the diagnosis of CTEPH is having a high index of suspicion for this condition (Fig. 86.1). Most commonly, CTEPH presents in patients with a history of previous PE whose dyspnea did not completely resolve and whose function did not return to baseline. The expectation after a PE should be that the patient returns to the pre-PE level of dyspnea; if there is worsening dyspnea compared to baseline, an investigation should be undertaken to exclude CTEPH as the cause.[30] The other group in whom CTEPH should be considered is patients with unexplained dyspnea, because about 25% of patients with CTEPH do not recall a preceding PE.[6] Finally, all patients who are being evaluated for PAH should be screened for CTEPH prior to initiation of medical therapy.[31]

VENTILATION-PERFUSION SCANNING, ECHOCARDIOGRAPHY, AND EXERCISE TESTING

Ventilation-perfusion (V/Q) scintigraphy and echocardiography are the initial recommended screening tests for CTEPH (Fig. 86.2). V/Q scanning remains the preferred first-line test for CTEPH due to its superior sensitivity compared to *computed tomography pulmonary angiography* (CTPA) (V/Q sensitivity >96% compared to CTPA sensitivity of 51%).[32] The advantage of the high sensitivity of V/Q scanning is that a normal V/Q scan can exclude CTEPH; an abnormal V/Q scan requires further follow-up imaging with either a high-quality CTPA or a conventional angiogram. Transthoracic echocardiography is indicated to assess right ventricular function and estimate right ventricular systolic pressure. However, it is important to note that a normal echocardiogram does not exclude CTEPH as the etiology of the dyspnea. Right heart catheterization should be performed to confirm the diagnosis of PH. (See Chapter 83 for further details regarding the hemodynamic assessment of PH.) Assessment of hemodynamics with exercise can be particularly useful in identifying symptomatic patients with normal resting hemodynamics but an abnormal hemodynamic response to exercise. Cardiopulmonary exercise testing may serve as a complementary tool in assessing symptomatic patients who have a normal resting echocardiogram or right heart catheterization. The hallmark finding in CTED is ventilator inefficiency with elevated dead space ventilation due to pulmonary vascular obstruction.[28] Details regarding the role of cardiopulmonary exercise testing in evaluating dyspnea are described in Chapter 33. Exercise studies have shown that CTEPH patients, when compared to patients with PAH, have higher ventilatory demands at anaerobic threshold and peak exercise, higher minute volume of ventilation/volume of CO_2 exhaled per unit time slope, greater physiologic dead space, and a lower end-tidal CO_2 at anerobic threshold.[33]

Perfusion imaging is performed using ^{99m}Tc-radiolabeled macroaggregated human albumin particles that are injected in a peripheral vein and lodge in precapillary arterioles and capillaries, providing an image of lung perfusion. A ventilation scan is also performed following inhalation of radiolabeled compounds to define lung borders and increase specificity by identifying matching ventilation defects and other pulmonary disorders such as airway obstruction or parenchymal lung disease. Ventilation is usually preserved in segments affected by PE; regional absence of perfusion, when paired with normal ventilation in the same region, defines the V/Q mismatch suggestive of PE. The V/Q scan in CTEPH typically demonstrates one or more segmental or larger mismatched perfusion defects (see Fig. 86.2).[34,35] This is in contrast to the perfusion scan in disorders of the smaller vessels, such as PAH, which typically have a normal or mottled appearance (see eFig. 84.4). Compared to the appearance in acute PE, perfusion defects may be more subtle in CTEPH due to partial recanalization of thromboemboli, resulting in areas of reduced rather than absent perfusion; thus a perfusion scan can under-represent the amount of chronic thromboembolic vascular obstruction.[36] This is why, when there is a suspicion of CTEPH, any degree of abnormality on the V/Q scan is considered sufficient to proceed to further anatomic evaluation.

Although V/Q scanning is a valuable screening test to exclude CTEPH, it cannot distinguish acute from chronic PE. In addition, it cannot distinguish CTEPH from other diseases that can cause mismatched perfusion defects on V/Q imaging, such as pulmonary artery sarcoma, large vessel arteritis, veno-occlusive disease or extrinsic vascular compression from adenopathy, tumor, or fibrosing mediastinitis. For this reason, further radiologic imaging is required to determine the etiology of the perfusion defects.

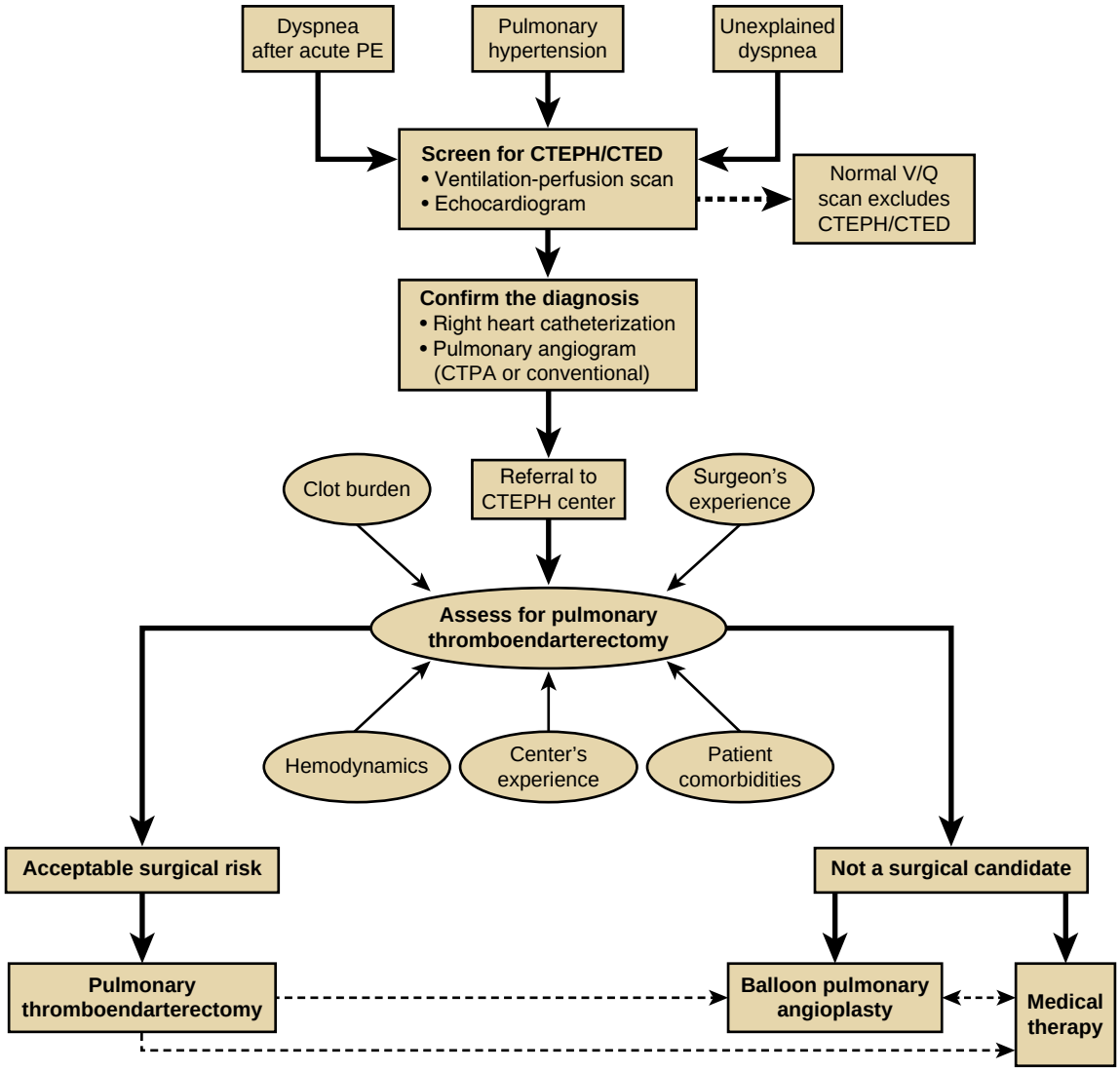

Figure 86.1 Approach to the diagnosis of chronic thromboembolic pulmonary hypertension and determination of operability. Patients with residual dyspnea after acute *pulmonary embolism* (PE), pulmonary hypertension, or unexplained dyspnea should be screened for *chronic thromboembolic pulmonary hypertension* (CTEPH). Initial screening is done with a *ventilation-perfusion* (V/Q) scan (to look for perfusion defects) and an echocardiogram (to screen for resting pulmonary hypertension). The diagnosis of CTEPH is confirmed with right heart catheterization to assess hemodynamics and pulmonary angiography to determine the amount and proximity of the chronic thrombotic material. Once the diagnosis is established, the key is referral to a CTEPH center where both *pulmonary thromboendarterectomy* (PTE) surgery and *balloon pulmonary angioplasty* (BPA) are offered. The first management decision the CTEPH center makes is determining whether the patient is a surgical candidate. Clot burden, location of disease, hemodynamics, comorbidities, and experience of both the surgeon and the center factor into the decision. PTE surgery is offered to all patients with an acceptable risk/benefit ratio because PTE is curative in the majority of patients. In those with residual pulmonary hypertension following PTE, BPA and/or pulmonary hypertension–targeted therapy can be considered. For those deemed not to be surgical candidates (either due to disease that is too distal or to an unacceptable PTE risk/benefit ratio), therapeutic options include BPA, medical therapy, or a combination of both. All patients with CTEPH require lifelong anticoagulation to prevent recurrent thrombosis; CTED, chronic thromboembolic disease.

RADIOLOGIC IMAGING

Digital subtraction angiography has long been considered the gold standard for the diagnostic confirmation and preoperative evaluation of CTEPH (Fig. 86.3). In digital subtraction angiography, an initial "mask" image is taken via fluoroscopy and saved. After contrast is injected, the saved precontrast mask is subtracted from the contrast images. In effect, the background is digitally subtracted, allowing the vessels to be seen clearly. Preferably, both anterior-posterior and lateral images should be obtained in a cine mode; the right and left pulmonary artery should be separately evaluated. Classic digital subtraction angiography findings of CTEPH include pouching defects, webs or bands, intimal irregularities, abrupt vascular narrowing, and complete vascular obstruction.[37] When required, more selective lobar or segmental injections can enhance visualization of more distal segmental and subsegmental arteries, which has recently become more accessible with the advances in more distal endarterectomy and the advent of BPA as a therapeutic option for distal disease. A right heart catheterization can be performed at the same time to determine hemodynamics, which will influence the decision making among PTE, BPA, and medical management. However, expertise in performing and interpreting conventional pulmonary angiography is becoming more limited in many radiologic practices as it is increasingly replaced by noninvasive and easily accessible CTPA.

CTPA findings are often subtle. Chronic thrombi can appear quite different from acute PE and are thus often

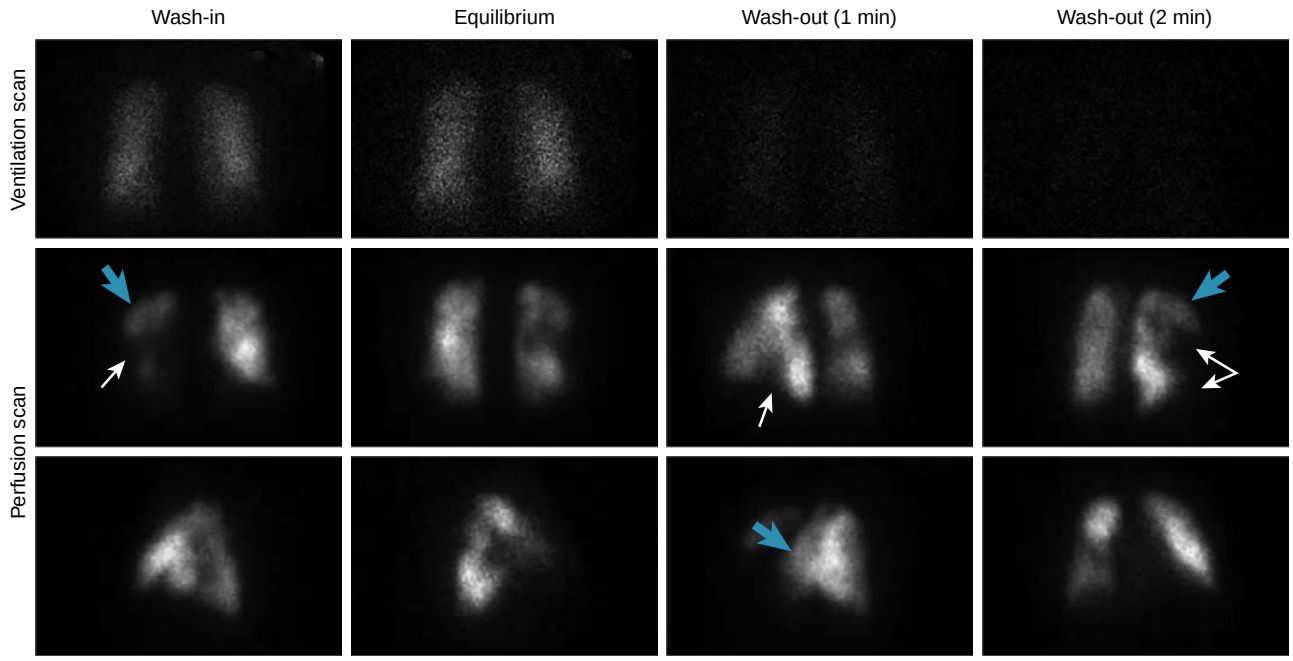

Figure 86.2 Ventilation-perfusion scan. Xenon ventilation scan (posterior view) in a patient with chronic thromboembolic pulmonary hypertension depicted in the top row with wash-in, equilibrium, and wash-out images at 1 and 2 minutes. Perfusion scan images in the bottom two rows demonstrate areas of absent perfusion (*white arrows*) and areas of relative hypoperfusion (*blue arrows*).

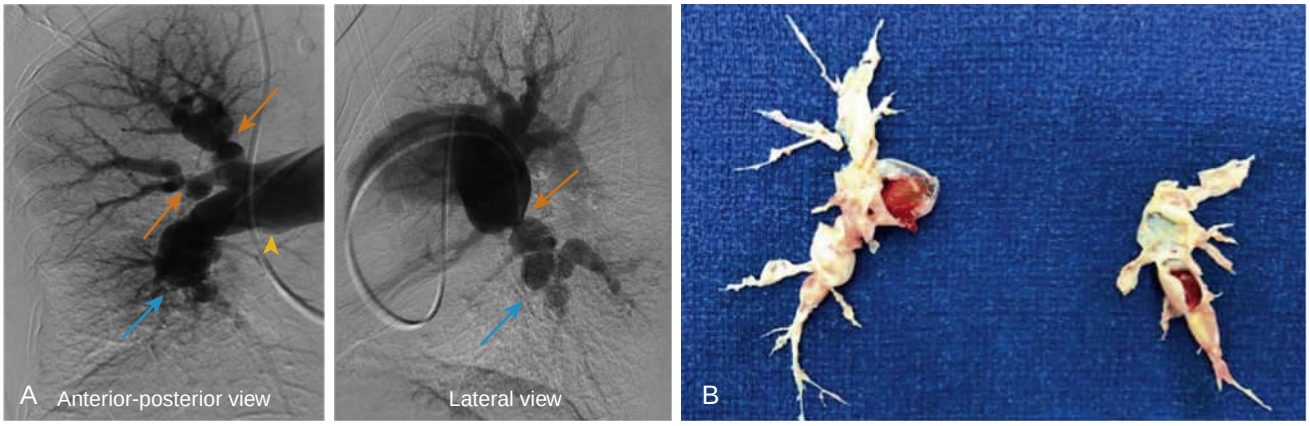

Figure 86.3 Digital subtraction pulmonary angiogram. (A) Right pulmonary digital subtraction angiogram demonstrating luminal irregularities in the distal main pulmonary artery (*arrowhead*), bands with poststenotic dilation (*orange arrows*), and pouch deformity in the right lower lobe (*blue arrow*). (B) Surgical specimen from the same patient.

overlooked, resulting in a delay in diagnosis (Fig. 86.4). Acute PE may appear as central filling defects surrounded by contrast, eccentric filling defects that form acute angles with the artery wall, or complete vessel obstruction associated with normal size or distended vessel caliber. In contrast, chronic emboli can cause complete vessel obstruction with vessel contraction or can cause partial recanalization, forming eccentric defects that form obtuse angles to the arterial wall. Other characteristic features include laminated thrombi that may be calcified, intimal irregularities, and intravascular bands or webs appearing as delicate lines crossing the vessel that may cause stenoses of the vessel. Additional supportive findings include mosaic attenuation of the lung parenchyma, with hyperperfused areas showing more attenuation (possibly even appearing as ground-glass opacities) and areas of hypoperfusion appearing dark. Right ventricular hypertrophy and bronchial artery dilation are other features of CTEPH.[34,35] CTPA can also provide additional ancillary information regarding thoracic abnormalities that may impact surgical candidacy, such as parenchymal lung disease. For example, mechanical interventions such as PTE or BPA should not be pursued if the parenchyma that would be revascularized has significant fibrotic changes. CTPA can also identify alternative diagnoses to CTEPH such as fibrosing mediastinitis, large vessel arteritis, or pulmonary artery sarcoma.

With technological improvements and experience, the sensitivity of CTPA in detecting thromboembolic disease has improved, especially in the setting of more central lobar disease (97–100%), although sensitivity is a bit lower at the segmental level (86–100%).[38–40] However, it must be emphasized that a negative CTPA does not exclude CTEPH, especially in the presence of more distal disease or with an inexperienced reader.[41] In addition, the finding of chronic

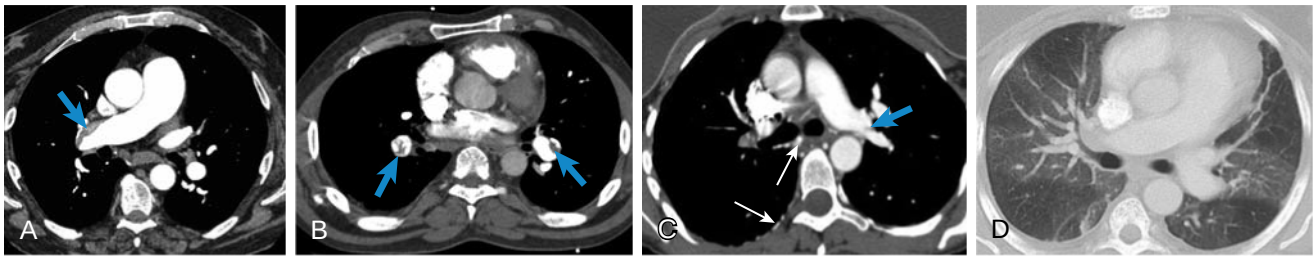

Figure 86.4 Computed tomography pulmonary angiography. (A) Eccentric lining thrombus (*arrow*) in the right main pulmonary artery. (B) Web (*arrows*) in the right and band in the left descending pulmonary artery. (C) Abrupt narrowing of the proximal left descending artery with a visible band (*blue arrow*). Numerous systemic to pulmonary artery collaterals are seen in the mediastinum and along the pleura (*white arrows*). (D) Mosaic perfusion pattern with hypoperfused segments appearing darker than the normal or hyperperfused segments.



Figure 86.5 University of California San Diego classification of pulmonary endarterectomy disease levels. Typical surgical specimens classified based on the most proximal level of obstruction, levels I to IV. (From Madani MM. Surgical treatment of chronic thromboembolic pulmonary hypertension: pulmonary thromboendarterectomy. *Methodist Debakey Cardiovasc J.* 2016;12[4]:213-218.)

clot on CTPA does not alone confirm the diagnosis of CTEPH. A common diagnostic pitfall is the presence of in situ thrombosis, chronic clot seen lining the vessel walls in the massively dilated pulmonary arteries in congenital heart disease with right-to-left shunt and in other forms of advanced PH. In this case, the chronic clot is not causing PH but is a *consequence* of PH. Proposed mechanisms for the formation of thrombus in this setting include shear stress on the vessel wall, endothelial damage, and chronic stasis in the aneurysmal dilated arteries. In situ thrombosis can be distinguished from CTEPH by the absence of mismatched perfusion defects on the V/Q scan, because in situ thrombosis is nonobstructive.[42]

DETERMINING OPERABILITY

Once the diagnosis of CTEPH has been established, patients should be referred to an experienced center capable of PTE and BPA (see Fig. 86.1).[43,44] A multidisciplinary team first determines whether the CTEPH is technically operable, a decision based on the location of the disease and the expertise of the surgeon.[43] Concordance of the amount of surgically accessible disease and the severity of the PH is important; severe PH in the setting of limited accessible disease suggests coexisting small-vessel arteriopathy and less-favorable surgical outcome. The patient's comorbidities, including age, functional status, body habitus, and coexisting medical conditions, must also be evaluated.

PULMONARY THROMBOENDARTERECTOMY

The definitive management of CTEPH is PTE, a surgical procedure that is quite distinct from pulmonary embolectomy performed for acute PE. This invasive surgery entails median sternotomy, cardiopulmonary bypass, deep hypothermia to about 20°C, and then circulatory arrest for multiple intervals of approximately 20 minutes each.[43] While the patient is on circulatory arrest, the surgeon opens the pulmonary artery and identifies the plane between the intima and the media (Video 86.1). Once this plane is found, a true endarterectomy is completed using an eversion technique of the pulmonary artery, and the plane of dissection is continued into each of the subsegmental vessels. The freed specimen is never cut, to allow dissection of long tails into distal vessels beyond the field of view. After completing the endarterectomy on the right pulmonary artery tree, the left pulmonary artery is dissected in a similar fashion.

The surgical specimens removed are classified by the University of California San Diego level (Fig. 86.5).[43] Level I disease refers to proximal disease with the place of dissection beginning in the right or left main pulmonary artery. Level II disease connotes a dissection plane that begins at the level of the lobar pulmonary arteries. Level III and IV are considered distal resections. In Level III disease, the plane of dissection starts in the segmental arteries whereas, in level IV disease, this plane begins at the subsegmental level only. These distal resections are more technically challenging and should be reserved for surgeons and centers with extensive experience with PTE surgery. In the European CTEPH Registry, the overall postoperative mortality was 4.7%.[6] At the most experienced centers, the perioperative mortality is even lower, in the range of 1–2%, despite higher-risk patients and more distal resections.[45]

Immediately after surgery, the hemodynamics are improved, and the expectation is that the *pulmonary vascular resistance* (PVR) should be normalized in the vast majority of patients. The PVR is reduced on average by about 65%. In the International CTEPH

Registry, the mean PVR was reduced from about 800 to 250 dynes•sec•cm^{-5} (normal 100 to 200 dynes•sec•cm^{-5}).[6] This improvement in the hemodynamics is associated with reductions in dyspnea and an improvement in functional ability, as measured by 6-minute walk distance.

There are three immediate potential complications specific to PTE of note: pulmonary hemorrhage, reperfusion lung injury, and residual PH. Due to the delicate nature of the operation on the pulmonary arteries, there is a risk of pulmonary hemorrhage. This happens in less than 5% of patients, but the risk appears to be slightly higher with the more technically challenging distal resections. Pulmonary hemorrhage management ranges from simply withholding anticoagulation to the use of endobronchial blockers to requiring venoarterial or venovenous *extracorporeal membrane oxygenation* (ECMO) life support. The second specific complication of PTE is reperfusion lung injury. The newly endarterectomized arteries become the vessels with the least resistance, and flow preferentially shifts to these vessels and is shunted away from the previously open vascular beds, referred to as *pulmonary vascular steal*.[46] Approximately 20% of patients post-PTE experience an inflammatory, noncardiogenic pulmonary edema resulting in focal opacities in the territory of the newly opened vessels. The high-permeability edema combined with pulmonary vascular steal shunting blood to the edematous lung regions can result in profound hypoxemia with relatively subtle changes on the chest radiograph. The risk of reperfusion lung injury is highest in patients with higher preoperative PVR and right ventricular failure. Treatment is typically supportive but, when more severe, may include steroids or ECMO support.[47]

Although most patients benefit from PTE, residual PH remains a leading cause of morbidity and mortality after surgery. Persistent PH following PTE surgery may be due to inadequate endarterectomy, small vessel arteriopathy, or reversible factors such as hypercarbia, hypoxemia, and/or reperfusion edema. Postoperative residual PH is associated with increased perioperative mortality, although it has improved over time. A study from a single institution showed that patients with a postoperative PVR of greater than 500 dynes•sec•cm^{-5} had a mortality rate of 10.3% compared to those with a postoperative PVR less than 500 dynes•sec•cm^{-5} who had a mortality rate of only 0.9%.[45] Treatment of persistent PH in the immediate perioperative period focuses on minimizing oxygen consumption, reversing hypoxemia and hypercarbia, optimizing right ventricular preload, and providing inotropic support. Systemic administration of pulmonary artery vasodilators is typically avoided in the early postoperative period due to the potential to contribute to systemic hypotension and exacerbate V/Q mismatching and hypoxemia. ECMO may be required in severe cases as a bridge to lung transplant or support during recovery.

Modest residual PH is not uncommon following PTE surgery, but the majority of these patients experience significant functional and symptomatic improvement with no apparent adverse effect on medium-term survival.[48,49] Until recently, no data were available to guide when to evaluate and how to define meaningful residual PH after PTE surgery. A large, single-center cohort of 880 post-PTE patients found only a moderate correlation between the immediate postoperative hemodynamics and those obtained 3 to 6 months after surgery. Longer-term follow-up revealed 51% of the patients had a mean pulmonary artery pressure greater than 25 mm Hg on right heart catheterization at 3 to 6 months post-PTE, but the majority of patients maintained a good functional status over the long term. However, those with a mean pulmonary artery pressure of 30 mm Hg or greater were more likely to have PH therapy initiated and a mean pulmonary artery pressure of 38 mm Hg or greater and PVR of 425 dynes•sec•cm^{-5} or greater at reassessment correlated with a worse long-term survival.[50] Hence, it seems reasonable in most postoperative PTE patients with residual PH to wait at least 3 months and reassess functional status and pulmonary hemodynamics with right heart catheterization before initiating PH-targeted therapy.

Despite these complications, overall outcomes are quite good. Refinements in technique have resulted in the ability to remove more distal disease while also reducing perioperative morbidity and mortality at experienced centers. Long-term studies have demonstrated PTE surgery results in sustained improvement in cardiopulmonary hemodynamics, functional class, and 6-minute walk distance.[6,51–53] Three-year survival is better in those who undergo PTE surgery compared to those who elect against surgery,[54] and postoperative long-term survival rates are 82% at 5 years and 75% at 10 years.[45]

INOPERABLE DISEASE

Even at experienced surgical centers, nearly one-third of patients with CTEPH will be deemed inoperable, for reasons such as distal disease, comorbidities, or PH out of proportion to the surgically accessible clot burden.[6] PH-targeted medical therapy and BPA have potential therapeutic value in these patients.

MEDICAL THERAPY

Lifelong anticoagulation is advised for all CTEPH patients to prevent recurrent thrombosis. The largest and longest experience has been with vitamin K antagonists. Although direct oral anticoagulants have proven to be effective in the treatment of acute VTE, a large prospective study has not yet been done to compare vitamin K antagonists to direct oral anticoagulants in the CTEPH population.[55]

Drugs found to be effective in the treatment of PAH have been used off-label for many years to treat patients with CTEPH who are inoperable or suffer from residual or recurrent PH following PTE surgery. Histologic changes in the distal vascular bed, similar to those seen in PAH patients, have been demonstrated in specimens from CTEPH patients.[27,56,57] CTEPH is not only a macroscopic disease of proximal obstructing chronic thrombi, it is also associated with more distal small-vessel remodeling, which likely explains residual PH in patients who have otherwise undergone a complete endarterectomy. The presence of these small-vessel changes provides the rationale for PH-targeted therapy in patients with inoperable CTEPH and those with residual or recurrent PH. Previous unblinded cohort trials (Table 86.2) have assessed PH-targeted medical therapy in various subpopulations of CTEPH patients using endothelin

Table 86.2 Summary of Key Trials of Pulmonary Hypertension: Targeted Medical Therapy in Inoperable CTEPH

Study	Medication	Study Design	Participants	Primary End Point	Conclusions
CHEST-1[59]	Riociguat	Randomized placebo-controlled trial	261 patients (functional class II–III; 72 with residual PH post-PTE)	Change in 6MWD at 16 weeks	Significant placebo-adjusted mean change by 46 m; improvement in secondary end points including PVR and CI
CTREPH[61]	Treprostinil (subcutaneous)	Randomized trial of low-dose (targeting 3 ng/kg/min) vs. high-dose (targeting 30 ng/kg/min)	105 patients (functional class III–IV, inoperable or residual PH)	Change in 6MWD at 24 weeks	Significant treatment effect (40.7 m) in high-dose group; safe, with most common adverse event being infusion site pain
MERIT[60]	Macitentan	Randomized, placebo-controlled trial	80 patients with inoperable CTEPH	Change in PVR at 16 weeks	Significant treatment effect on PVR; PVR reduced to 73% of baseline
BENEFiT[58]	Bosentan	Randomized, placebo-controlled trial	157 patients with CTEPH (functional class II–VI; 41 with residual PH post-PTE)	Co-primary end points at 16 weeks: change in 6MWD; percent reduction in PVR from baseline	No significant improvement in 6MWT (2.2 m); significant 24% reduction in PVR from baseline
Suntharalingam et al.[67]	Sildenafil	Randomized, placebo-controlled trial	19 patients, all with inoperable CTEPH	Change in 6MWD at 16 weeks	No significant improvement in 6MWT (+17.5 m); PVR reduced 197 dynes • sec • cm^{-5}
Cabrol et al.[68]	Epoprostenol	Retrospective cohort study	27 patients with inoperable CTEPH	Improvements in NYHA class, 6MWT, or hemodynamics	At 3 months, 48% improved NYHA class; 6MWT increased by 66 m; mPAP reduced 5 mm Hg

6MWD, 6-minute walk distance; 6MWT, 6-minute walk test; CI, cardiac index; CTEPH, chronic thromboembolic pulmonary hypertension; mPAP, mean pulmonary arterial pressure; NYHA, New York Heart Association; PH, pulmonary hypertension; PTE, pulmonary thromboendarterectomy; PVR, pulmonary vascular resistance.

receptor antagonists (e.g., bosentan), nitric oxide agonists (e.g., sildenafil), and prostacyclin analogs (e.g., epoprostenol, treprostinil, and iloprost). Each demonstrated measurable pulmonary hemodynamic effects. The first randomized, placebo-controlled trial in inoperable CTEPH was the BENEFIT trial, in which 157 patients were randomized to either bosentan or placebo.[58] After 16 weeks of therapy, there were two co-primary end points: change in PVR and improvement in 6-minute walk distance. After 16 weeks of treatment, bosentan significantly reduced PVR 24% from baseline compared to placebo but failed to improve the 6-minute walk distance.

Riociguat, a soluble guanylate cyclase stimulator acting in the nitric oxide pathway, is the first and currently only U.S. Food and Drug Administration–approved therapy for inoperable CTEPH based on the CHEST-1 trial, which demonstrated both an improvement in functional capabilities (6-minute walk distance) as well as significant gains in secondary pulmonary hemodynamic end points.[59] In the CHEST-1 trial, 261 patients with CTEPH (189 of whom were deemed inoperable) were randomized to 16 weeks of either riociguat (starting at 1 mg and titrated to 2.5 mg or the maximum tolerated dose) or placebo. At 16 weeks, there was a 46-m placebo-adjusted improvement in 6-minute walk distance as well as significant reductions in PVR and levels of NT-proBNP.

In addition to riociguat, there is emerging evidence from randomized controlled trials for the efficacy of both macitentan and subcutaneous treprostinil in selected patients with inoperable CTEPH. In the MERIT trial, macitentan was compared with placebo in reduction of PVR at 16 weeks; there was a significant treatment effect, with macitentan reducing PVR to 73% of baseline.[60] In the CTREPH trial, two doses of subcutaneous treprostinil were compared, a very low dose (3 ng/kg/min) and the typical therapeutic dose (30 ng/kg/min). Patients in the higher-dose group, but not the lower-dose group, experienced a significant improvement in 6-minute walk distance.[61] There are little data about the benefit of combination therapy for inoperable CTEPH, but many providers apply the same principles used in the management of PAH to the management of CTEPH. Furthermore, while many will manage these patients in a similar fashion to PAH, there is not a consensus about the optimal follow-up and goals for treatment of inoperable CTEPH.

BALLOON PULMONARY ANGIOPLASTY

In addition to medical therapy, BPA has emerged as an option for selected patients with inoperable CTEPH or patients with residual PH following PTE surgery. BPA is a percutaneous interventional procedure using telescoping catheters placed in the pulmonary arteries, through which wires and balloons are used to disrupt chronic clot mechanically and relieve pulmonary vascular obstruction (Video 86.2).[62] Initial attempts at BPA for CTEPH were associated with high complication rates (namely hemoptysis and reperfusion edema) and untenably high mortality.[63] Several innovations were made to the technique that brought these complication rates down to an acceptable range. First, BPA now is performed over multiple sessions

to achieve the hemodynamic end points targeted. With the first pass, the balloons are inflated to improve the caliber of the vessel. Opening the lumen to the normal caliber is reserved for later sessions.[64] Second, target lesions are selected to achieve benefit without excessive risk for complications; pouch defects or totally occluded vessels should not be targeted with BPA. Finally, imaging techniques (such as optical coherence tomography or intravascular ultrasound) or pressure wires (which measure the intravascular pressure proximal and distal to an area of stenosis to assess the fractional flow reserve) are used to help choose target lesions and maximize both the safety and efficacy of BPA.[64] Contemporary observational case series from multiple centers worldwide have demonstrated improvement in pulmonary hemodynamics, functional class, and 6-minute walk distance with this approach. As with PTE surgery, BPA should be performed at a center with expertise in the treatment of CTEPH.

Key Points

- About 30% of patients with *pulmonary embolism* (PE) do not have perfusion completely restored despite adequate anticoagulation, and about 4% of all patients with PE will develop *chronic thromboembolic pulmonary hypertension* (CTEPH).
- Identified risk factors for development of CTEPH after acute PE include recurrent PE, history of splenectomy, unprovoked PE, presence of symptoms for more than 2 weeks prior to PE diagnosis, right ventricular dysfunction at the time of PE diagnosis, and hypothyroidism. All patients with PE should be expected to return to their pre-PE baseline; in those who have residual dyspnea, an evaluation for CTEPH should be undertaken.
- Approximately 25% of patients with CTEPH will not have a known prior PE, and CTEPH should be included in the differential for any patient with unexplained dyspnea.
- The *ventilation-perfusion* (V/Q) scan remains the screening test of choice; an abnormal V/Q scan should be followed with an angiogram (either digital subtraction angiography in the catheterization lab or a CT pulmonary angiogram).
- *Pulmonary thromboendarterectomy* (PTE) is the treatment of choice for patients with surgically accessible chronic thromboembolic disease and favorable surgical risks. PTE surgery uses a median sternotomy approach for cardiopulmonary bypass, deep hypothermia to allow circulatory arrest, and a true endarterectomy with removal of pulmonary artery intimal lining with adherent chronic thromboembolic disease.
- For patients with distal, surgically inaccessible disease or in whom risks preclude PTE, options for management include pulmonary hypertension-targeted medical therapy (at this time, only riociguat is U.S. Food and Drug Administration approved for inoperable CTEPH) and balloon pulmonary angioplasty. Lung transplant is an option if all other interventions fail.
- The presence of chronic thromboembolic disease increases the risk for recurrent PE; CTEPH is an indication for indefinite anticoagulation.

Key Readings

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87 PULMONARY VASCULITIS

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INTRODUCTION AND DEFINITIONS
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INTRODUCTION AND DEFINITIONS

Pulmonary vasculitis is a clinicopathologic term encompassing a wide variety of individual disease entities, all of which share the presence of inflammation and destruction of blood vessels within the lung. More specifically, these disorders are characterized histopathologically by the presence of a variety of types of cellular infiltration within vessel walls, vessel destruction, and ultimately tissue necrosis. Specific clinical features are determined by the site, size, and type of vessel involved, as well as the relative amounts of vessel inflammation, destruction, and tissue necrosis. While simple to define, the recognition, diagnosis, and management of the pulmonary vasculitides are among the most demanding challenges in pulmonary medicine. Protean in their presentation and variable in their clinical evolution, their signs and symptoms fully overlap with pulmonary or systemic infection, adverse medication reaction, other connective tissue diseases, and malignancy. Even in patients with known pulmonary vasculitis, separating clinically active vasculitis from infection, drug toxicity, or some combination thereof will challenge the most astute clinician. Increasing the stakes, all of these diseases impair quality of life, limit functional status, and shorten survival. Even with improvements associated with currently available treatment, the long-term survival among patients with *antineutrophil cytoplasmic antibody* (ANCA)-positive *ANCA-associated vasculitis* (AAV) is shortened—approaching 90% survival at 1 year and 75% survival at 5 years, with a 2.7-fold increase in the standardized mortality ratio compared to the general population.[1] Despite this, the clinician can make the diagnosis, initiate and manage therapy, and minimize complications by keeping some broad concepts in mind.

CLASSIFICATION

The major clinical benefit of classification is to provide a framework that allows for an appreciation of clinically relevant features of disease and the ability to distinguish among specific conditions. The 2012 Revised International Chapel Hill Consensus Conference nomenclature[2] remains broadly accepted and is based on clinicopathologic presentations (Table 87.1). Because it was developed prior to the widespread use of ANCA testing and is not based on disease mechanism or response to therapy, it should be used cautiously to establish a diagnosis or to initiate management. In the near future, the Diagnostic and Classification in Vasculitis Study (a multinational, observational study designed to develop diagnostic criteria and update classification in vasculitis) is likely to replace the Chapel Hill nomenclature. Draft revised criteria for AAV incorporating diagnostic criteria have been proposed (Table 87.2).

Recognizing the variety and complexity of the clinical presentations of these disorders, a broad diagnostic approach is required. A common scheme focuses on clinical manifestations associated with specific vessel size (large, medium, and small). Large vessels are made up of the aorta, its largest branches (e.g., carotid, cerebral, iliac, subclavian, and femoral vessels), and the main pulmonary arteries. Medium vessels are the main visceral arteries (the renal, hepatic, coronary, and mesenteric vessels). Small vessels are the capillaries, venules, and arterioles. In any group of disorders, there is often some overlap, with specific vasculitides that generally affect either the large or small vessels also involving medium-sized arteries, though large and medium vessel vasculitides generally do not involve vessels smaller than arteries.

A second and commonly utilized classification scheme uses ANCA. The identification of these antibodies in the 1980s revolutionized diagnosis and pathogenesis (see

Table 87.1 Classification of Vasculitis[1,125,126]

PRIMARY IDIOPATHIC

Small Vessel

- Granulomatosis with polyangiitis
- Eosinophilic granulomatosis with polyangiitis
- Microscopic polyangiitis
- Idiopathic pauci-immune glomerulonephritis
- Idiopathic capillaritis

Medium Vessel

- Polyarteritis nodosa
- Kawasaki disease

Large Vessel

- Takayasu arteritis
- Giant cell arteritis

PRIMARY IMMUNE COMPLEX-MEDIATED

- Anti-glomerular basement membrane disease (Goodpasture syndrome)
- IgA vasculitis (formerly Henoch-Schönlein purpura)
- Cryoglobulinemic vasculitis
- Hypocomplementemic urticarial vasculitis

SECONDARY

- Classic autoimmune disease
- Systemic lupus erythematosus
- Rheumatoid arthritis
- Anti-phospholipid antibody syndrome
- Infection
- Paraneoplastic
- Drug-induced (e.g., propylthiouracil)
- Inflammatory bowel disease

IgA, immunoglobulin A.

below). The vasculitides that pulmonologists are most likely to encounter, the primary idiopathic small vessel vasculitides, are also AAV. These include *granulomatosis with polyangiitis* (GPA), *eosinophilic granulomatosis with polyangiitis* (EGPA), and *microscopic polyangiitis* (MPA).

A third approach defines the vasculitides by the presence or absence of granulomatous inflammation. Two of the ANCA-associated vasculitides, GPA and EGPA, as well as the large vessel vasculitides, Takayasu arteritis, and giant cell arteritis, are characterized histopathologically by granulomatous inflammation.

Regardless of the classification scheme or diagnostic approach, ultimately the diagnosis of pulmonary vasculitis requires the clinician to recognize both general and specific patterns of clinical, imaging, laboratory, and pathologic features and to determine whether or not the available evidence is adequate to support a specific diagnosis.

EPIDEMIOLOGY

The true overall incidence and prevalence of vasculitis is difficult to gauge, because the available epidemiologic studies contain significant limitations that prevent general applicability. The available data are rarely geographically or ethnically diverse, and the case definitions and data acquisition methodology often vary from study to study. With these caveats in mind, giant cell arteritis remains the most frequently recognized systemic vasculitis in those over the age of 50 yeras, with an annual incidence of 150 to 350 per million persons in those of northern European extraction. Those of non-Caucasian ethnicity appear to be at much lower risk. The primary systemic vasculitides have an overall prevalence estimated at between 90 and 300 per million in European populations.

The annual incidence of all forms of AAV combined ranges from 6 to 32 per million. The epidemiology of the AAV differs among ethnicities in both ANCA specificity and clinical manifestations. GPA is most common in Europe while MPA is more common in East Asia. Among the individual disorders, the annual incidence ranges from 4.9 to 10.5 per million for GPA, 0.5 to 4.2 per million for EGPA, and 2.7 to 11.6 per million for MPA. Their prevalence ranges from 24 to157 per million for GPA, 7 to 38 per million for EGPA, and 0 to 66 per million for MPA. Among the secondary vasculitides, the best data are for *systemic lupus erythematosus* (SLE)-associated vasculitis (incidence of 3.6 per million) and rheumatoid arthritis–associated vasculitis (incidence of 12.5 per million), though the latter incidence appears to have fallen dramatically with the advent of biologic therapy.[3]

NORMAL VASCULAR ANATOMY AND HISTOLOGY

In order to understand the presenting clinical features of the pulmonary vasculitides, it is useful to understand the normal location and histologic characteristics of the arterial and venous blood supplies. The lung has a dual blood supply: the pulmonary and the bronchial circulations. The bronchial arteries arise from the systemic circulation (aorta and intercostal arteries) and form a plexus in the bronchial wall. The bronchial veins associate closely with the bronchial arteries. Neither are commonly affected in vasculitis.

During embryogenesis, the pulmonary arterial system forms in tandem with the branching bronchial buds and is recognized by its close proximity to the corresponding bronchi or bronchiole (Fig. 87.1A). In the normal lung, arteries and adjacent airways (either bronchi or bronchioles) are similarly sized, so significant size differences may be an indication of pathology.[4] The arterial system consists of four components: elastic arteries, muscular arteries, arterioles, and capillaries. The elastic arteries are larger than 0.5 to 1.0 mm in diameter and can be recognized macroscopically. They are composed of an endothelial cell lining layer, a smooth muscle medial layer, and have well-developed, multiple elastic laminae. Muscular arteries are between 100 and 500 μm in diameter, and are composed of an endothelial lining, a smooth muscle media bound by two elastic laminae (inner and outer), and a collagenous adventitia (see Fig. 87.1B). The smooth muscle layer progressively decreases in thickness down to the arterioles, which are defined by the absence of a muscular media and a diameter of less than 100 μm; however, these may become muscularized in a variety of diseased states. The arterioles transition into capillaries, characterized by the presence of a

Table 87.2 Draft classification criteria for the ANCA-associated vasculitides

GPA		EGPA		MPA	
c-ANCA or PR3 antibody	+5	Eosinophil count ≥1 × 10^9/L	+5	p-ANCA or MPO-antibody positive	+6
Bloody nasal discharge, ulcers, crusting, congestion or blockage, or septal defect/ perforation	+3	Obstructive airways diseases	+3	Fibrosis or ILD on chest imaging	+3
		Nasal polyps	+3	Pauci-immune glomerulonephritis	+3
Cartilaginous involvement*	+2	Extravascular eosinophilic predominant inflammation/ eosinophils in bone marrow	+2	c-ANCA or PR3 antibody	−1
Granuloma, extravascular granulomatous inflammation, or giant cells on biopsy	+2			Bloody nasal discharge, ulcers, crusting, congestion or blockage, septal defect/ perforation	−3
Nodules, mass, cavitation on chest imaging	+2	Mononeuritis multiplex or motor neuropathy	+1	Eosinophil count ≥1 × 10^9/L	−4
Inflammation, consolidation, or effusion of the nasal/paranasal sinuses on imaging	+1	Microscopic hematuria	−1		
Conductive or sensorineural hearing loss	+1	c-ANCA or PR3 antibody	−3		
p-ANCA or MPO antibody	−1				
Eosinophil count ≥1 × 10^9/L	−4				
Total score of ≥5 is needed for classification		Total score of ≥5 is needed for classification		Total score of ≥6 is needed for classification	
Sensitivity 93%, specificity 94%		Sensitivity 88%, specificity 98%		Sensitivity 87%, specificity 96%	

*Cartilaginous involvement: inflamed ear or nose cartilage or hoarse voice/stridor, endobronchial involvement, or saddle nose deformity.
ANCA, antineutrophil cytoplasmic antibodies; c-ANCA, cytoplasmic ANCA; EGPA, eosinophilic granulomatosis with polyangiitis; GPA, granulomatosis with polyangiitis; ILD, interstitial lung disease; MPA, microscopic polyangiitis; MPO, myeloperoxidase; p-ANCA, perinuclear ANCA; PR3, proteinase 3.
From Robson J, Grayson P, Ponte C, et al. Draft classification criteria for the ANCA associated vasculitides. *Annal Rheum Dis*. 2018;77:60-61.

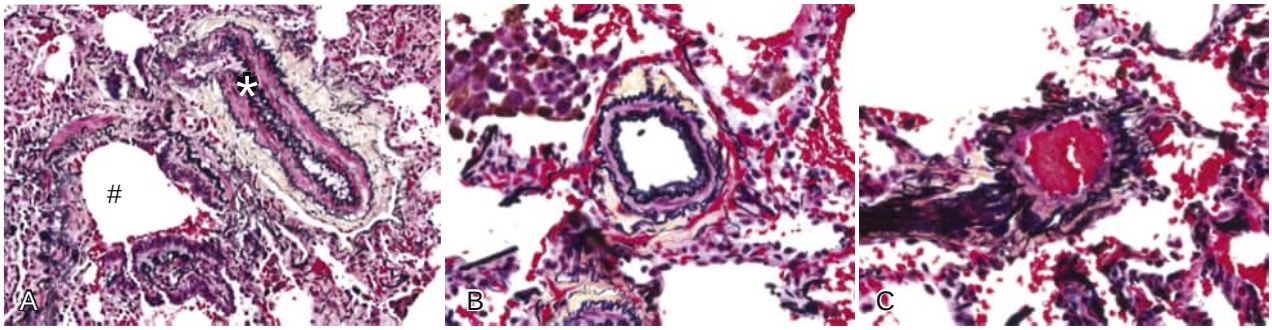

Figure 87.1 Normal appearance of pulmonary artery, small muscular pulmonary artery, and vein. (A) A pulmonary artery (*asterisk*) and bronchiole (#) are shown in close proximity (pentachrome/Movat stain). (B) Muscular pulmonary artery in the peripheral lung showing internal and external elastic lamina in black (pentachrome/Movat stain). (C) Small pulmonary vein in peripheral lung showing one elastic lamina in black (pentachrome/Movat stain).

single layer of endothelial cells and an underlying basement membrane. They form part of the alveolar septa and are the most commonly affected vessels in pulmonary vasculitis. On hematoxylin and eosin stains of surgical lung biopsies, identifying the capillaries may be difficult because a number of cell types including endothelial cells, fibroblasts, and mononuclear cells, are normal occupants of the alveolar septa.

The location of the pulmonary veins in the mature lung is typically within interlobular septa, because the embryonic pulmonary veins form branches that grow into the mesenchyme surrounding the lung buds. Although pulmonary veins can be distinguished from pulmonary arteries by their single elastic lamina (see Fig. 87.1C), in the diseased lung, there can be reduplication of the elastic lamina, causing "arterialization" of the pulmonary veins, and anatomic location may be the only indicator of vessel type.

HISTOPATHOLOGY OF VASCULITIS

Although the diagnosis of vasculitis never relies on histopathology alone, both the general diagnosis and subclassification can often be suggested based on the size and location of the affected vessels (Fig. 87.2). Histopathologic findings common to all the pulmonary vasculitides are inflammatory cell infiltration (inflammation) of the vessel wall with destruction of elastic laminae (in the case of arteries and veins) and often, an accompanying fibrinoid necrosis of the associated tissue. The lining endothelial cells may show abnormalities, with subendothelial inflammation

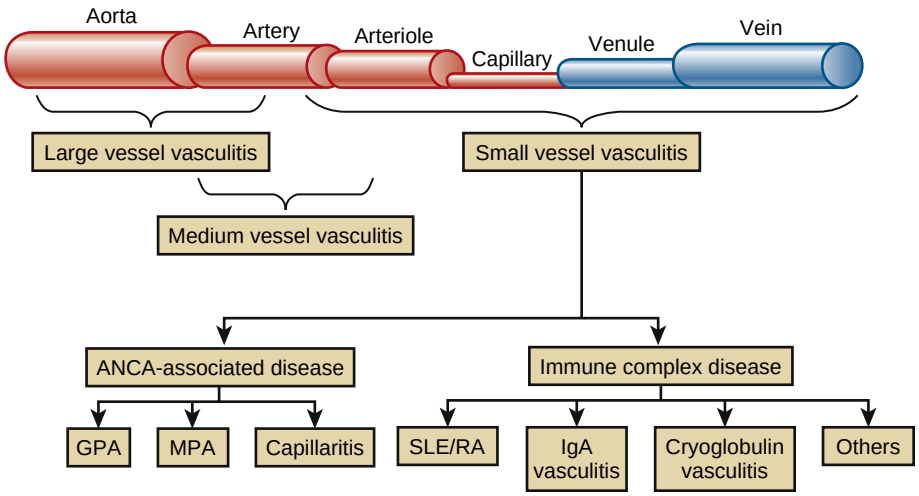

Figure 87.2 Relationship between vessel size and mechanism. The small vessel vasculitides are diagrammed as antineutrophil cytoplasmic antibody–associated disease and immune complex disease. ANCA, antineutrophil cytoplasmic antibodies; GPA, granulomatosis with polyangiitis; IgA, immunoglobulin A; MPA, microscopic polyangiitis; SLE/RA, systemic lupus erythematosus/rheumatoid arthritis.

with regenerative/hyperplastic endothelial cells ("endothelialitis"), cellular disruption, and even loss of endothelial cells. The type of inflammation varies widely: neutrophilic, eosinophilic, lymphoplasmacytic, or mixed infiltrates can all be seen. Granulomatous inflammation, consisting of poorly formed granulomas or multinucleated giant cells and/or epithelioid histiocytes, is of particular importance because one classification approach is based on its presence or absence (see above).

The term *capillaritis* is used to describe vasculitic involvement of the capillaries; however, it is often difficult to identify vasculitic involvement on routine hematoxylin and eosin stains, much less to identify the endothelial disruption necessary to make the diagnosis. Therefore, identifying neutrophils and nuclear debris (evidence of cellular apoptosis) within alveolar septal walls is used as an indirect sign.

Beyond the size and type of the affected vessel, changes to the associated lung parenchyma may provide additional clues. For example, a nodular parenchymal opacity is commonly seen in GPA, with microabscesses, necrosis, eosinophilic pneumonia, organizing pneumonia, and/or hemorrhage. The specific pathologic findings associated with each entity are discussed in more detail below.

PATHOGENESIS

Most of the vasculitic syndromes are hypothesized to be the result of immunopathogenic mechanisms responding to antigenic stimuli. Why some patients develop vasculitis, while others do not, is unknown. The etiology is almost assuredly multifactorial, and likely includes genetic predisposition, epigenetic factors, environmental exposures (e.g., drugs, infections, airborne pollutants), and individual immune responses. Genome-wide association studies have found both major histocompatibility complex and non–major histocompatibility complex associations with both an increased and decreased risk of AAV, confirming a genetic contribution to disease development. The strongest associations are with major histocompatibility complex class II genes.[5] Three broadly defined mechanisms have been proposed: pathogenic autoantibody formation with neutrophil activation and endothelial damage, immune complex deposition, and pathogenic lymphocyte responses. For each of these mechanisms, some combination of direct immunologic attack and endothelial and vascular wall response appears responsible for the subsequent clinical and pathologic findings.[6]

A large variety of autoantibodies have been described, including the antiglomerular basement membrane (collagen type IV) antibodies seen in *anti-glomerular basement membrane disease* (anti-GBM disease, formerly called Goodpasture syndrome), antiendothelial cell antibodies, antilaminin antibodies, antiphospholipid (β2-glycoprotein 1) antibodies, and ANCA, among others. Of these, the best-studied mechanism is that proposed for AAV. While the clinical syndrome was described in the 1930s,[7–9] it was not until 1982 that specific autoantibodies, now known as ANCA, were described.[10] ANCA are recognized biomarkers and have pathogenic potential, with considerable in vitro, in vivo, and clinical evidence supporting their pathogenicity. Proinflammatory cytokines generated from a variety of insults result in neutrophil priming and activation, causing them to express antigens (e.g., *proteinase 3* [PR3] and *myeloperoxidase* [MPO]) on their cell surface. ANCA can bind to these cell surface antigens as well as to Fc receptors on the neutrophil, resulting in further neutrophil activation. This over-activation of the neutrophil results in cytokine production, release of reactive oxygen species, lytic enzymes, and neutrophil extracellular traps, all of which can cause extensive endothelial damage through a variety of complex mechanisms. In particular, excessive neutrophil extracellular trap formation and persistence are thought to play key roles. Separately, lymphocyte differentiation and complement activation are also recognized as important. Additional data suggest that ANCA are associated with the severity and persistence of disease activity. These data include the link between the presence of these autoantibodies and the development of systemic vasculitic complications and prognosis, the effectiveness of the anti-CD20 monoclonal antibody rituximab at reducing ANCA titers and controlling disease activity, and the finding that

patients who become ANCA negative appear to be at significantly decreased risk of clinical relapse.

The trigger for initial ANCA production and persistence is an area of active investigation. A role for active infection/inflammation in the disease pathophysiology has been proposed because there is evidence that chronic or concurrent infections can lead to disease exacerbation or relapse.[11–13] ANCA positivity has also been directed against a variety of antigens seen with viral, fungal, bacterial, and protozoal infection, as well as subacute bacterial endocarditis and cystic fibrosis.[14,15] It has been hypothesized that infections may give rise to ANCA through molecular mimicry and may contribute to their persistence through T- and B cell stimulation by microbial superantigens. For example, some patients with AAV have been shown to elaborate antibodies against *lysosome-associated membrane protein-2* (LAMP2) found in neutrophils. The LAMP2 protein bears close homology to the bacterial adhesin FimH protein expressed in gram-negative bacteria, and antibodies against LAMP2 and FimH are capable of producing glomerulonephritis in animal models.[16]

Aberrant lymphocyte responses are hypothesized to contribute to both the granulomatous inflammation seen in GPA and EGPA (T cells) as well as the production of ANCA (B cells). Activated T cells may be found in the peripheral blood of patients with GPA, even when the disease is in remission, and markers of T cell activation appear to correlate with disease activity.[17] Further, there appears to be an increase in Th17-positive T cell populations (believed to promote autoimmunity) and reduced regulatory T cell functionality, suggesting a loss of tolerance.[17–20] Finally, there is increased elaboration of Th1 cytokines in patients with GPA (tumor necrosis factor-α, *interleukin* (IL)-1 and IL-8), whereas there is increased elaboration of interferon-gamma, IL-4, IL-5, and IL-13 in patients with EGPA.[21,22]

Other potential mechanisms for the development of vasculitis include the direct invasion of the vessel wall by infectious organisms (e.g., bacterial, mycobacterial, spirochetal, rickettsial, fungal, viral) leading to an acute, direct inflammatory response as well as deposition of circulating immune complexes in the blood vessel wall. This deposition of immune complexes can lead to complement activation, anaphylatoxin production, and mast cell degranulation. Mast cell degranulation leads to release of vasoactive substances and the anaphylatoxins can act as chemotactic agents for neutrophils, eosinophils, and mononuclear inflammatory cells. The prototypical disease for this mechanism is SLE, in which complexes of nuclear antigens such as DNA, immunoglobulins, and complement proteins lead to vascular injury.[23,24] Other immune complex–mediated vasculitides include rheumatoid vasculitis, IgA vasculitis, and cryoglobulinemic vasculitis.

INITIAL DIAGNOSIS

CLINICAL SCENARIOS SUGGESTIVE OF VASCULITIS

The importance of the initial history in the evaluation of a patient with suspected vasculitis cannot be overemphasized. Symptoms that initially appear of only minor importance and unrelated may need to be explored fully because both vasculitis and its mimics (connective tissue diseases, infection, malignancy, drug toxicity, etc.) present with and evolve through a variety of confusing clinical manifestations. Similarly, a careful physical examination may reveal otherwise asymptomatic disease that suggests the presence of a systemic disorder. In particular, the identification of particular clinical scenarios can suggest the presence of a systemic vasculitis.[25]

Chronic and/or Destructive Upper Airway Lesions

Chronic refractory sinusitis, otitis, and/or subglottic stenosis may be relevant to a diagnosis of vasculitis, particularly when infectious, allergic, traumatic, and anatomic causes have been excluded and/or when soft tissue injury (chronic ulceration) or bone lesions are present.

Chest Imaging Findings of Cavitary or Nodular Disease

While a wide variety of nonspecific findings may be seen on chest imaging in the vasculitides, the presence of nodular or cavitary disease should raise concern. Whereas infection and malignancy are the most common causes of nodular or cavitary opacities, in the correct clinical context, pulmonary vasculitis (particularly an AAV) should be considered. Cavities are found in 35–50% and nodules in 55–70% of patients with GPA.[26,27]

Diffuse Alveolar Hemorrhage (See Chapter 94)

Diffuse alveolar hemorrhage (DAH) refers to the presence of diffuse intra-alveolar bleeding, generally from the alveolar capillaries, and less frequently from the precapillary arterioles and postcapillary venules. Whereas patients classically present with hemoptysis, diffuse alveolar opacities, and a drop in hematocrit, DAH must be considered in all patients with unexplained air space disease. Hemoptysis can be difficult to identify because it is generally only intermittent. Up to one-third of patients with DAH will not present with hemoptysis. The alveolar opacities do not have to be diffuse, and a fall in the hematocrit can be difficult to document. Because of these caveats, DAH should be considered in patients with otherwise unexplained diffuse alveolar opacities, particularly when these opacities are associated with symptoms of a connective tissue disease or new-onset renal insufficiency. While an increase in the diffusion capacity of more than 30% over baseline can be suggestive, it is rare for this information to be available.

DAH is diagnosed by bronchoalveolar lavage. With the bronchoscope in a wedged position, serial aliquots (30 to 60 mL in volume) of sterile saline are instilled and aspirated (for a total volume of 100 to 300 mL). If the serial aliquots of fluid reveal an increasingly hemorrhagic or even a persistently bloody return, the diagnosis of DAH is made. It must be recognized that DAH is not diagnostic of vasculitis. Although differential diagnoses include diseases associated with the histopathologic small vessel vasculitis (including both primary and secondary vasculitides) (Fig. 87.3), DAH can result from both diffuse alveolar damage and bland hemorrhage (eTable 87.1, see also Table 94.1). When DAH is a complication of an AAV, capillaritis is almost always present, though its absence in no way excludes the diagnosis, particularly if treatment has been initiated. When DAH with pathologic pulmonary capillaritis is the only clinical

eTable 87.1 Causes of Diffuse Alveolar Hemorrhage[127,128]

WITH CAPILLARITIS (CLASSIC VASCULITIDES)

Primary idiopathic small vessel vasculitis

- ANCA associated: GPA, EGPA, MPA
- Isolated pauci-immune pulmonary capillaritis

Immune Complex Mediated

- Anti-glomerular basement membrane disease (Goodpasture syndrome)
- IgA vasculitis (formerly Henoch-Schönlein purpura)
- Cryoglobulinemic vasculitis

Secondary Vasculitis

- Defined autoimmune disease
  - Systemic lupus erythematosus
  - Primary anti-phospholipid antibody syndrome
  - Other (e.g., rheumatoid arthritis, scleroderma)
- Hematopoietic stem cell transplantation
- Drug-associated disease (chemotherapeutic agents, diphenylhydantoin)
- Behçet's disease

WITHOUT CAPILLARITIS (BLAND HEMORRHAGE)

Idiopathic pulmonary hemosiderosis
Coagulopathy
Mitral stenosis
Inhalation injury
Drug-associated disease (chemotherapeutic agents, penicillamine, trimellitic anhydride, amiodarone, nitrofurantoin)

ANCA, antineutrophil cytoplasmic antibodies; IgA, immunoglobulin A; EGPA, eosinophilic granulomatosis with polyangiitis; GPA, granulomatosis with polyangiitis; MPA, microscopic polyangiitis.

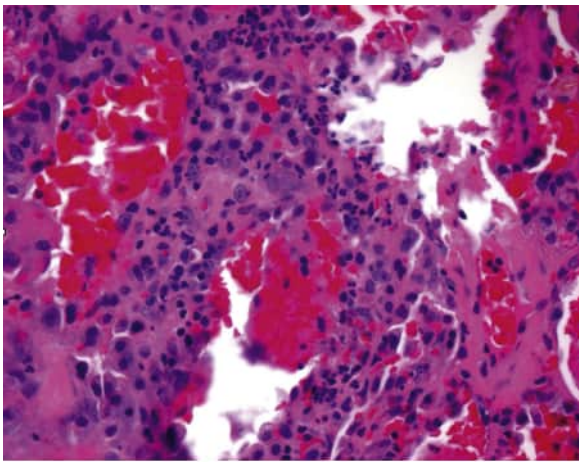

Figure 87.3 Capillaritis. The alveolar septa are disrupted by infiltrates of neutrophils and nuclear debris. The septal borders are indistinct, indicating wall damage.

manifestation of a vasculitis, the term idiopathic pauci-immune pulmonary capillaritis may be used, and this syndrome is classified in the family of primary idiopathic, small vessel vasculitis regardless of ANCA status.

Acute Glomerulonephritis

Rapidly progressive glomerulonephritis (RPGN) is recognized by the identification of an active urinary sediment on urinalysis, including hematuria (especially with dysmorphic red cells), red cell casts, and proteinuria (>500 mg/d) in the setting of a rising blood urea nitrogen and serum creatinine. The microscopic examination of the urine needs to be performed on a fresh urine sample because red cell casts and dysmorphic red cells degenerate within 30 to 60 minutes in a freshly voided sample. Once RPGN is identified, the differential diagnosis includes ANCA-associated vasculitis, idiopathic pauci-immune glomerulonephritis (isolated small vessel renal vasculitis), SLE, anti-GBM disease, postinfectious glomerulonephritis, IgA nephropathy, IgA vasculitis (formerly Henoch-Schönlein purpura), essential cryoglobulinemia, and membranoproliferative glomerulonephritis.[28–31]

Pulmonary-Renal Syndrome

Pulmonary renal syndromes are classically defined as the presence of both DAH and RPGN. However, whenever a destructive airway lesion or chest imaging findings of nodules and/or cavities exist in the setting of renal insufficiency, vasculitis should be considered. When this happens, the primary differential should include AAV, anti-GBM disease, and SLE.

Palpable Purpura

The presence of palpable purpura on physical examination implies a small vessel, cutaneous vasculitis.[32] The most common explanation is a cutaneous (hypersensitivity) vasculitis secondary to a drug reaction; however, AAV, cryoglobulinemia, connective tissue diseases, infections, and malignancy all should be considered. Other evidence of a cutaneous vasculitis, particularly with systemic features, should raise concerns.

Mononeuritis Multiplex

Defined by neuropathic symptoms in two or more independent peripheral nerve distributions, either simultaneously or sequentially, mononeuritis multiplex should raise suspicion for a vasculitis, particularly those disorders that affect the small or medium-sized arteries.[33,34] The underlying vasculitic process affects the vessels supplying the nerves, causing ischemia of the nerves. A variety of central or peripheral nervous system symptoms can be seen, including pain, numbness, paresthesias, weakness, or loss of function (e.g., sudden onset of a foot drop or wrist drop).

Eye Findings

Ocular findings are common in some vasculitides. Approximately one-quarter of patients with giant cell arteritis and GPA will have ocular manifestations as part of their disease. Intermittent or persistent scleritis, retinal vein occlusion, optic neuropathy, or a retro-orbital mass might be seen.

Multisystem Disease

Unusual combinations of signs and symptoms that involve multiple organ systems either simultaneously or over time should raise the possibility of a vasculitis. This requires a high index of suspicion from the clinician because symptoms and/or signs such as constitutional symptoms (e.g., fever of unknown origin), unusual "rashes," migratory polyarthritis, or "chronic sinus disease" may be relevant when the primary clinical presentation is breathlessness, renal failure, or abnormal chest imaging.

SPECIFIC TESTING

Antineutrophil Cytoplasmic Antibodies

ANCAs were initially described in 1959 in patients with chronic inflammation. The first relationship with vasculitis was recognized in 1982, with a pattern of diffuse immunofluorescent staining of ethanol-fixed neutrophils. In 1985, they were identified by *indirect immunofluorescence* (IIF) in a population with GPA, and it was appreciated that they produced a cytoplasmic staining pattern (c-ANCA). Autoantibodies that produce a perinuclear staining pattern (p-ANCA) were then reported in patients with systemic arteritis and glomerulonephritis. These antibodies are closely associated with the small vessel vasculitides of the lung, GPA, EGPA, and MPA. These AAV all involve the small vessels and share a number of clinical features including, when present, pauci-immune, crescentic, and focal necrotizing GN. However, whereas ANCA positivity is common in these disorders, it is by no means universal.

Three staining patterns on IIF are often described, *cytoplasmic* (c-ANCA) (Fig. 87.4A), *perinuclear* (p-ANCA) (see Fig. 87.4B), and *atypical* (a-ANCA). c-ANCA are primarily, but not exclusively, directed against PR3 (in azurophilic granules), while p-ANCA is most commonly directed against MPO (also in azurophilic granules), but they have a wider group of potential intracellular targets. Specific immunoassay testing for PR3 and MPO are now widely available, and a 2016 multicenter *European Vasculitis Study* (EUVAS) Group evaluation demonstrated good diagnostic performance of current antigen-specific immunoassays for ANCA detection in patients with GPA and MPA and,

separately, quite variable results among laboratories in the performance of IIF. Based on this, revised international consensus recommendations are that high-quality immunoassays for PR3-ANCA and MPO-ANCA are the preferred methods for the diagnostic evaluation of patients with AAV, without the categorical need for IIF.

The diagnostic utility of ANCA testing is dependent upon the sensitivity, specificity, and positive predictive value of c-ANCA (or PR3-ANCA) for GPA and p-ANCA (or MPO-ANCA) for MPA and EGPA. When testing is applied indiscriminately, the positive predictive value of the testing declines dramatically. As noted by Mandl et al., the use of clinical guidelines to identify patients with a higher pretest possibility of vasculitis increases the positive predictive value of the tests without reducing sensitivity.[35]

Current consensus guidance provides recommendations for diagnosing AAVs by utilizing high-quality, antigen-specific PR3-ANCA and MPO-ANCA assays as the primary screening method (Fig. 87.5). If results for both PR3-ANCAs and MPO-ANCAs are negative and there is still a strong suspicion of small vessel vasculitis, repeating these assays or using other immunoassays and/or IIF may be helpful to increase sensitivity. It is important to note that a diagnosis of AAV cannot be excluded on the basis of negative PR3-ANCA and MPO-ANCA results; a positive PR3-ANCA and/or MPO-ANCA test contributes to the diagnosis but is not diagnostic by itself. The frequency of ANCA positivity in AAV is noted in Table 87.3.

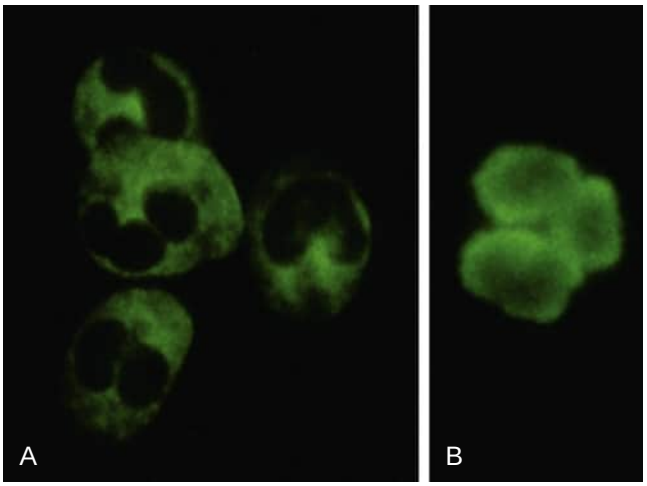

Figure 87.4 Indirect immunofluorescent staining patterns of neutrophils with *antineutrophil cytoplasmic antibodies* (ANCA). Indirect immunofluorescence showing the cytoplasmic pattern of c-ANCA (A) and the perinuclear pattern of p-ANCA (B).

Both the immunoassay for PR3-ANCA and IIF for c-ANCA are quite sensitive in active systemic GPA but less so in limited disease, and even less so for GPA in remission.[36] In the proper clinical setting, with a very high pretest probability of disease, a positive PR3-ANCA may have a sufficient positive predictive value for the diagnosis to obviate the need for tissue biopsy.[37] On the other hand, MPO-ANCA, while generally as specific, is less sensitive due to a wider group of potential intracellular targets, and a negative test may provide no more than supportive evidence of MPA, pauci-immune RPGN, or EGPA.[38] It should be emphasized that the absence of a positive test does not rule out a diagnosis of vasculitis. Indeed, while the concept of ANCA association applies to the patient population as a whole, it must be emphasized that an individual patient may well be ANCA negative and still have what is described as an AAV. In fact, there is a subgroup of ANCA-negative pauci-immune vasculitis, best recognized as renal-limited disease, but assuredly involving the lung as well. In patients who are both PR3-ANCA and MPO-ANCA positive, drug-induced disease should be considered.

Considerable attention has been focused on the utility of ANCA to assess disease activity, particularly the role of rising ANCA titers in predicting relapse.[39,40] Unfortunately there appears to be no clear relationship between antibody titers and disease activity. In a prospective interventional study in which PR3-ANCA levels were routinely obtained, decreasing ANCA titers did not predict time to remission and increasing titers did not predict relapse. Increasing titers were associated with a relapse in only 40% of patients

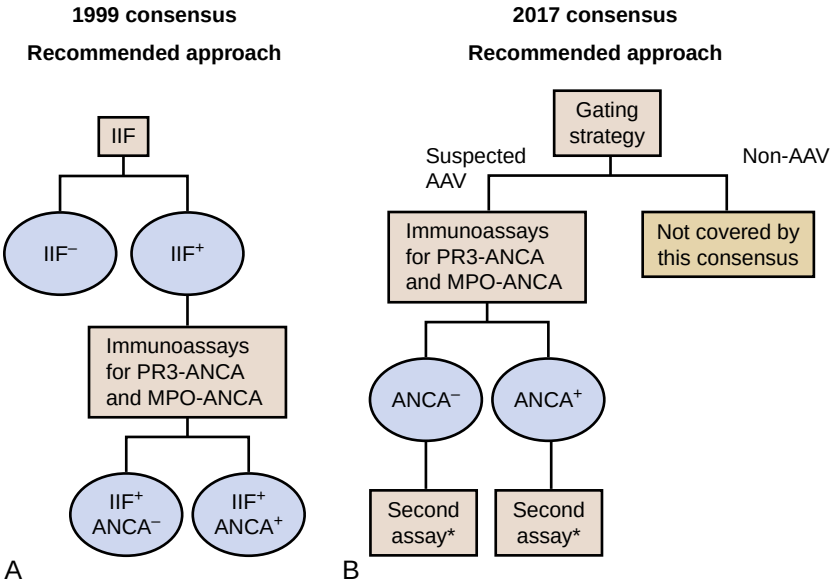

Figure 87.5 Newer recommended algorithm using immunoassays as the first screening method for *granulomatosis with polyangiitis* (GPA) and *microscopic polyangiitis* (MPA). (A) In the 1999 consensus document, the recommended approach for *antineutrophil cytoplasmic antibody* (ANCA) detection was to screen for ANCA by *indirect immunofluorescence* (IIF) and to test for proteinase 3 (PR3)-ANCAs and myeloperoxidase (MPO)-ANCAs in IIF-positive samples; the ideal approach was to perform IIF and immunoassays on all samples (not shown). (B) In the 2017 consensus, the use of high-quality immunoassays is recommended as the preferred first screening method for ANCA detection in patients suspected of having the ANCA-associated vaculitides (AAV), GPA and MPA. IIF is no longer deemed suitable as the first screening test. ANCA detection for non-ANCA-associated vasculitis conditions is not included in this consensus. *A second PR3- and MPO-ANCA or IIF can be considered for negative results in patients with a high clinical suspicion (to increase sensitivity) or in case of low antibody levels (to increase specificity). Take the antibody level into account. (From Bossuyt X, Cohen Tervaert JW, Arimura Y, et al. Position paper: revised 2017 international consensus on testing of ANCAs in granulomatosis with polyangiitis and microscopic polyangiitis. *Nat Rev Rheumatol*. 2017;13[11]:683–692.)

Table 87.3 Clinical Findings in the ANCA-Associated Vasculitides

	GPA	EGPA	MPA
Constitutional	Common. Includes fatigue, malaise, fevers and weight loss.	Common. Weight loss, fatigue, fevers, myalgias and arthralgias.	Very common. Generally precedes renal disease by months.
Pulmonary	70–95% of patients with respiratory symptoms or chest imaging abnormalities. Tracheobronchial and endobronchial disease in 10–50%.	Asthma essentially universal. Patchy, heterogenous radiographic infiltrates in >70%.	10–30% with diffuse alveolar hemorrhage.
Renal	50–90% of patients.	20–50% of patients.	RPGN almost universal.
Upper airway	70–95% of patients. Destructive or ulcerating lesions are suggestive.	Sinusitis, polyposis, and/or rhinitis in ≥70% of patients. Generally not destructive.	5–30%, with sinus disease most common.
Musculoskeletal	Arthralgias, synovitis and myalgias in up to 80%.	Arthralgias and myalgias in up to 50%.	Arthralgias and myalgias in at least 50% of patients.
Eyes	25–60% of patients. Vision-threatening disease including uveitis, ocular ulcers.	<5%	0–30% of patients. May be clinically silent.
Cardiac	5–25% of patients. Conduction delays or other ECG abnormality, systolic or diastolic dysfunction, pericarditis, or coronary artery vasculitis.	30–50% of patients and a major cause of mortality. Conduction delays or other ECG abnormality, systolic or diastolic dysfunction, pericarditis, or coronary artery vasculitis.	10–20%. CHF and pericarditis have been described.
Gastrointestinal	<10%	30–50% of patients and a major cause of morbidity and mortality. Hemorrhage, abdominal pain, infarct or perforated viscus.	35–55% of patients. Findings similar to PAN. Pain, bleeding, and ischemia. Rare visceral aneurysms.
Dermatologic	Up to 60%. Palpable purpura, ulcers, nodules or vesicles.	50–70% purpura, nodules, papules, leukocytoclastic vasculitis with or without eosinophils.	35–60% of patients with purpura common.
Neurologic	Both central and peripheral nervous system involvement.	Mononeuritis multiplex in 50–75%. CNS in 5–40%.	Mononeuritis multiplex in 10–50%.
Chest Imaging	Abnormal in >80%. Alveolar, interstitial or mixed infiltrates, often with nodular and/or cavitary disease.	Infiltrates in >70%. Airways disease common (airway wall thickening, hyperinflation).	Infiltrates in 10–30%. Pleural effusions in 5–20%.
ANCA	ANCA positive > 90% (PR3-ANCA 75%, MPO-ANCA 20%).	ANCA positive in 50% (PR3-ANCA 5%, MPO-ANCA 45%).	ANCA positive in 90% (PR3-ANCA 30%, MPO-ANCA 60%).

ANCA, antineutrophil cytoplasmic antibodies; CHF, congestive heart failure; CNS, central nervous system; ECG, electrocardiography; EGPA, eosinophilic granulomatosis with polyangiitis; GPA, granulomatosis with polyangiitis; MPA, microscopic polyangiitis; MPO, myeloperoxidase; PAN, polyarteritis nodosa; PR3, proteinase 3; RPGN, rapidly progressive glomerulonephritis.
Data from references 26, 31, 42, 44, 47, 62, 64, 66, 72, 81, 84, 123, 129–143, 152.

over a 12-month period. Therefore, the decision to modify therapy in patients with ANCA-associated vasculitis must be a clinical decision based on clinical evidence of disease activity independent of ANCA titers.[36]

Other Laboratory Studies

Cultures of blood and other potentially affected organs (when tissue is obtained) should be performed to exclude infection. Routine laboratory tests (complete blood count with differential, chemistries, liver function tests, blood urea nitrogen, and creatinine) should be obtained, though the findings are generally nonspecific. The erythrocyte sedimentation rate and C-reactive protein are commonly elevated but lack specificity. Urinalysis with microscopy should be performed on a fresh sample in all patients, because proteinuria and microscopic hematuria are common early findings in GPA and MPA. Anti-GBM antibodies should be obtained in all patients with pulmonary hemorrhage or a pulmonary-renal syndrome. Antinuclear antibodies and rheumatoid factor can be positive, although high titers—especially with the presence of disease-specific antibodies (e.g., dsDNA, SS-A/SS-B, anti-RNP, anti-Scl-70, anti-centromere antibodies, anti-Jo1)—favor a connective tissue disease. Immunoglobulin E and circulating eosinophil counts should be obtained when EGPA is being considered.

Chest Imaging

Plain chest radiographs and *computed tomography* (CT) scanning is often abnormal even in the absence of symptoms, and over 80% of patients with GPA and EGPA will have some radiographic abnormalities. Specific findings are best described in GPA and include nodular opacities (Fig. 87.6) and masses, particularly those that cavitate (eFig. 87.1), diffuse ground-glass opacification (eFig. 87.2) (especially when DAH is a possibility), consolidation (eFigs. 87.3 and 87.4), atelectasis, and airway complications such as stenoses (eFig. 87.5) and ulcerations (eFig. 87.6). Pleural involvement is much less common, seen in 10–20% of patients. Effusions are frequently present with pleural

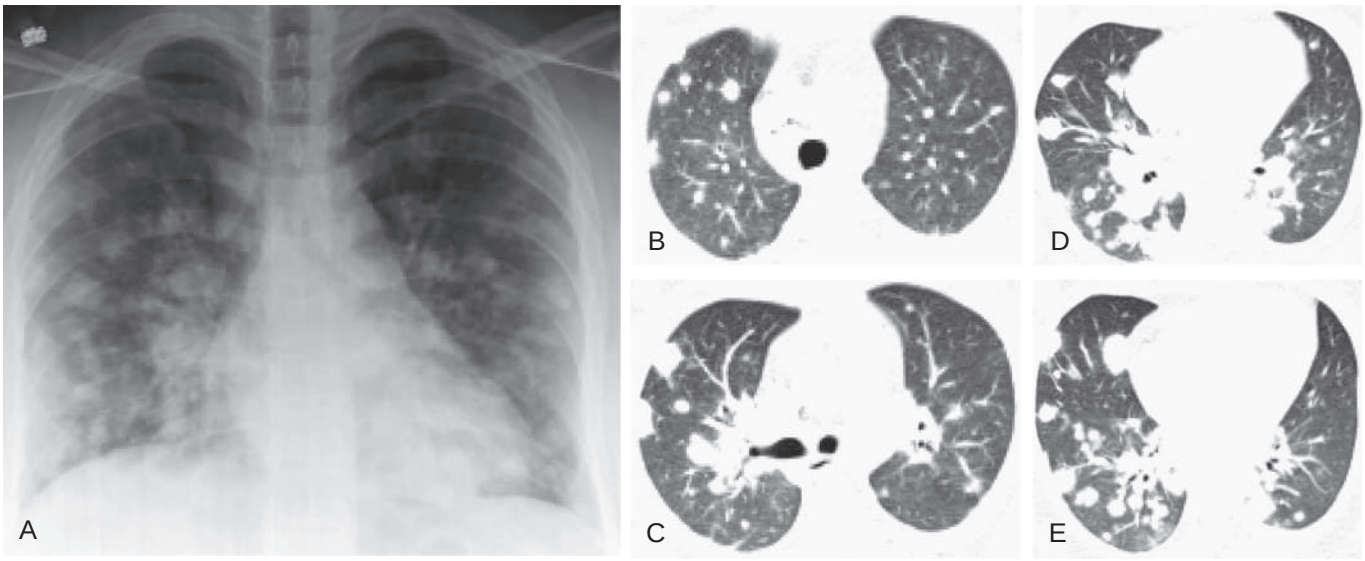

Figure 87.6 Granulomatosis with polyangiitis: nodules. (A) Frontal chest radiograph in a patient with granulomatosis with polyangiitis shows numerous bilateral, variably sized pulmonary nodules. (B–E) Axial chest computed tomography displayed in lung windows confirms the presence of numerous nodules without cavitation. (Courtesy Michael B. Gotway, MD.)

thickening, while nodularity or pneumothorax are quite rare. Adenopathy can be seen (eFig. 87.7) but is not common and is more suggestive of infection or malignancy. [41] Patients with EGPA commonly demonstrate patchy, heterogeneous ground glass opacities or consolidation as well as evidence of airways disease.

Other Imaging Studies

CT imaging of the sinuses (see eFig. 87.6) demonstrates abnormalities in a majority (70–90%) of patients with GPA and EGPA and may help identify destructive or ulcerating disease in patients with GPA. Although both echocardiography and cardiac *magnetic resonance imaging* (MRI) can evaluate for cardiac abnormalities, cardiac MRI is preferred when cardiac involvement is suspected to assess for myocardial inflammation, structure, and function. Although the heart is involved in only 5–15% of patients with GPA, the heart is affected in 30–50% of patients with EGPA and potentially carries a high attributable mortality. Additional imaging or functional studies are determined by the clinical scenario and the signs and symptoms present in the individual patient (e.g., abdominal CT, brain CT/MRI, nerve conduction studies).

Bronchoscopy

Bronchoscopy is primarily used to look for malignancy, infection, stenotic or ulcerative upper airway or endobronchial lesions, pulmonary eosinophilia, and alveolar hemorrhage. Bronchoalveolar lavage should be grossly examined for evidence of alveolar hemorrhage, and sent for culture (bacterial, fungal, and mycobacterial), cytology, and a differential cell count. Transbronchial biopsies may provide important information that helps exclude infection or malignancy; however, they are rarely useful in making a positive diagnosis of vasculitis. When Hoffman et al.[42] performed 59 transbronchial biopsies in 48 patients with GPA, only four provided useful diagnostic features. Schnabel et al.[43] found that transbronchial biopsies supported a diagnosis of GPA in only 2 of 17 patients, while otolaryngologic examination and biopsy of the clinically involved areas of the upper respiratory tract yielded useful information in 13 of 19 GPA patients.

Diagnostic Biopsy. Whereas a confident diagnosis may occasionally be made without tissue, diagnostic tissue biopsy remains necessary for a definitive diagnosis and is recommended when establishing a new diagnosis and for further evaluation of patients suspected of having relapsing vasculitis. Biopsy of the skin or upper airway is generally safe and these sites are easily accessible, but they less commonly yield diagnostic tissue when compared with a needle biopsy of the kidney or a surgical biopsy of the lung. When Hoffman et al.[42] examined 82 open lung biopsies in patients with small vessel vasculitis, diagnostic features were found in 90%. Renal biopsy is often performed to determine the cause of an acute glomerulonephritis. Specific features indicative of vasculitis such as granulomatous inflammation or vascular necrosis are rarely found; however, the presence of focal, segmental necrotizing glomerulonephritis without immune deposits (pauci-immune) strongly suggests a systemic vasculitis.[42,44-46]

The pathologic features of vasculitis often overlap with the pathologic findings seen in other disorders such as necrotizing infections. Separately, some typical histopathologic features that one may expect to see in vasculitis may be absent because of the timing of the biopsy and/or modification of the histology secondary to prior treatment, particularly with corticosteroids. Because of this, it is essential that the surgeon, pulmonologist, and pathologist have a coordinated plan prior to the biopsy. The clinical differential will dictate the appropriate specimens to collect, including fresh tissue for culture and immunofluorescence (the presence of characteristic immunofluorescence patterns, such as IgA deposition in IgA vasculitis, linear IgG deposition in anti-GBM disease, and irregular immunoglobulin and complement deposition in SLE can be diagnostic) as well as for formalin fixation.

SPECIFIC CLINICAL DISORDERS

Because the majority of the vasculitides are systemic disorders, essentially all of them can involve the lung. Pulmonary involvement can range from DAH to cavitary nodules, parenchymal inflammation, pleural disease, vascular aneurysms, and thrombotic and thromboembolic phenomena. A full accounting of each described disorder and their pulmonary manifestations is beyond the scope of this chapter. However, the primary idiopathic small vessel vasculitides deserve special attention.

GRANULOMATOSIS WITH POLYANGIITIS

GPA is the most common of the ANCA-associated small vessel vasculitides, can present at any age (generally 40 to 60 years), and affects the sexes equally. It is clinically recognized by its ability to involve the upper airway (e.g., chronic sinusitis and/or otitis, upper airway ulceration and/or structural deformity, subglottic, tracheal, or endobronchial stenosis), lower respiratory tract (e.g., chest symptoms of cough, chest pain, shortness of breath, hemoptysis, and/or chest imaging abnormalities), and kidney (e.g., glomerulonephritis) (see Table 87.3). However, involvement of all three sites is neither necessary nor common at presentation. For example, even though 80–90% of patients may ultimately develop some renal disease, as few as 40% will have renal involvement at initial presentation.[47–49] Constitutional symptoms, skin, eye, musculoskeletal, peripheral and central nervous system disease, and vascular thrombosis are not rare.[31,47–49]

Chest imaging is abnormal in the majority of patients, with nodular (see Fig. 87.6) or cavitary disease (see eFig. 87.1), or alveolar, mixed, or interstitial opacities (see eFigs. 87.2 through 87.4).[26,27] A positive c-ANCA is seen in 90–95% of those with active systemic disease but in only 60–65% of those with limited disease (disease mostly of the airways, not considered organ- or life-threatening).[39,50–52] The histopathology on surgical lung biopsy is dependent on the stage of the disease and whether there has been prior immunomodulatory treatment. A small and medium-sized vessel necrotizing vasculitis with granulomatous inflammation and parenchymal necrosis, often with a geographic appearance, is characteristic (Fig. 87.7A).[53–57] The pathologic manifestations can be divided into major and minor histologic features. The three major features include (1) lung parenchymal necrosis, either in the form of geographic necrosis or neutrophilic microabscesses; (2) vasculitis (generally involving small to medium-sized arteries, but also veins and capillaries) (see Fig. 87.7B–C); and (3) granulomatous inflammation (see Fig. 87.7D). Although the inflammation in GPA is typically described as granulomatous, it is often mixed and includes granulomas, giant cells, neutrophils, lymphocytes, plasma cells, histiocytes, and eosinophils. The minor histologic criteria include organizing pneumonia (70% of cases), DAH (10% of cases), eosinophilia, and bronchocentric granulomatosis (1% of cases).[53,58] The earlier the biopsy is performed, the more likely it is that some of the classic histologic findings will be absent. With prior treatment, there may be no significant cellular inflammatory infiltrates and the only histopathologic clue may be scarring of arteries and/or airways.[59] A distinctive, but uncommon, histologic appearance is isolated capillaritis (see Fig. 87.3).

With current therapy, there is a 5-year survival rate of 74–91%, with a significant improvement noted over the past 25 years. The mortality risk of patients diagnosed from 1997–2004 and those diagnosed from 2005–12 has declined from a hazard ratio of 5.6 to 2.3, though the increased mortality risk persists beyond 5 years. Overall, there was excess mortality due to cardiovascular disease but not cancer. So, while it is commonly assumed that active vasculitis itself accounts for all the excess mortality, the actual cause of death can result from a variety of causes including cardiac disease, thromboembolic disease, infection, renal failure, malignancy, and drug toxicity.[60] Historically, a leading cause of death among patients with AAV is infection, which is linked to the intensity of immunosuppression, particularly cyclophosphamide. Poor outcomes correlate with advanced age; *lack* of ear, nose and throat involvement; more severe renal impairment; pulmonary involvement (particularly with alveolar hemorrhage); cardiac involvement; and high-level PR3-ANCA positivity.[61]

EOSINOPHILIC GRANULOMATOSIS WITH POLYANGIITIS (see Chapter 96)

EGPA is a specific ANCA-associated small vessel vasculitis clinically distinct from GPA and MPA (see Table 87.3). EGPA affects adults of all ages, and both sexes equally. Its presentation often overlaps with the eosinophilic lung diseases (chronic eosinophilic pneumonia, allergic

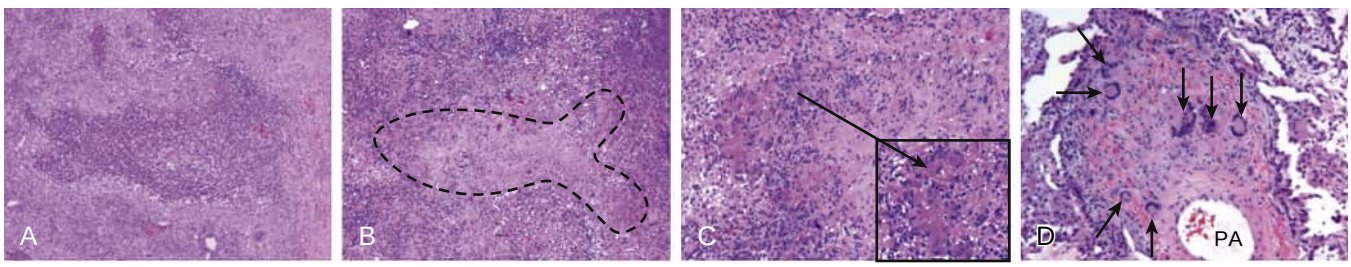

Figure 87.7 Granulomatosis with polyangiitis. (A) Irregular outlines of geographic necrosis are typical of the parenchymal necrosis found in granulomatosis with polyangiitis. (B) Low-power view of a branching vessel (*dashed line*) demonstrating necrotizing vasculitis (hematoxylin and eosin). (C) Higher power views of same vessel shown in part B. Note the basophilic necrosis (*arrow*) accompanied by chronic inflammation and vague granulomas (*inset*). (D) Granulomatous inflammation, including giant cells (*arrows*), of the adventitia of a pulmonary artery (PA). (A, Courtesy Dr. Christopher Bee.)

bronchopulmonary mycosis, drug reactions, hypereosinophilic syndrome, parasitic infection, asthma/atopic disease), and difficult to control asthma/atopy.

The syndrome has a triad of (1) asthma, (2) hypereosinophilia, and (3) necrotizing vasculitis that classically has a three-phase presentation with the initial presence of atopy/rhinitis/sinusitis/asthma, followed by an eosinophilia, and finally a vasculitic phase. However, the three phases may not happen sequentially, and the asthma may even postdate the vasculitis. Asthma is essentially universally found and, whereas EGPA may present with any degree of asthma severity and duration, severe (steroid-requiring) asthma is common. Patients may have the airways disease for 7 to 10 years prior to the diagnosis of vasculitis. The upper airway is commonly involved with chronic rhinitis and sinusitis (with or without nasal polyposis) as well as laryngeal involvement, although generally without any of the destructive features associated with GPA and therefore not as characteristic.

Chest imaging is abnormal in more than two-thirds of patients. Most commonly, waxing and waning parenchymal opacities (ground-glass attenuation and consolidation) (eFig. 87.8) and less commonly nodules, are seen on CT imaging of the chest. Pleural effusions can be seen in 10%. In contrast to GPA and MPA, pulmonary hemorrhage and glomerulonephritis are much less common.[62–66] Significant neurologic, cardiac (conduction abnormalities, systolic or diastolic dysfunction, intracavitary thrombus, pericarditis), or gastrointestinal disease (perforation, ischemia, bleeding) are dreaded, but well-recognized, complications. ANCA is positive in a perinuclear IIF pattern (p-ANCA) in 30–70%, with peripheral eosinophilia (absolute eosinophil count >1500/μL) almost universal at some point in the course.

Recently, it has been recognized that patients with EGPA segregate into two distinct clinical phenotypes. One subset is characterized by a greater incidence of neurologic, renal, gastrointestinal, and cutaneous involvement and is more commonly ANCA- or MPO-positive (i.e., shares a high degree of overlapping features with GPA and MPA). The other subset typically shares features with the hypereosinophilic syndromes, namely cardiac manifestations, migratory lung opacities (eosinophilic pneumonia), and an ANCA-negative/MPO-negative serologic profile.[66–68] These subgroups may have differing underlying genetic predispositions. Both ANCA-positive and ANCA-negative groups carry variants in Th2 response, eosinophil proliferation, and eosinophil survival genes; however, the ANCA-positive group is strongly associated with variants in HLA, suggesting a role for HLA class II–associated autoimmunity, while the ANCA-negative patients show variants in interferon regulatory factor-1/IL-5 and a gastrointestinal and bronchial mucosal/barrier protein, suggesting abnormal mucosal function in the lung and gastrointestinal tract.

Pathologically, patients with EGPA will demonstrate both a necrotizing, small vessel vasculitis and an eosinophil rich cellular infiltrate.[69,70] The diagnostic findings on lung biopsy include eosinophilic pneumonia, necrotizing vasculitis, and granulomatous inflammation (Fig. 87.8A–B). The vasculitis consists of artery, vein, or capillary wall infiltration by lymphocytes and eosinophils. The granulomas often show central areas of necrosis with abundant necrotic eosinophils, surrounded by palisaded histiocytes and multinucleated giant cells. Findings highly suggestive of EGPA include eosinophilic pneumonia and parenchymal necrosis.[70]

Mortality is generally due to cardiac complications (up to half of EGPA-related deaths), gastrointestinal complications, or status asthmaticus and respiratory failure.[62,63,71] While mortality rates of up to 40% were described in the 1970s, more recent data suggest that, when adequately treated, patients may have a normal lifespan.[72] A recent single center study demonstrated that a comprehensive vasculitis center–based management strategy of patients with EGPA without heart failure had a survival rate no different than a matched general population.[73] Overall 5-year survival rates have been estimated at 60–97%.[61]

In the late 1990s, an association between the use of leukotriene inhibitors and EGPA had been suggested in

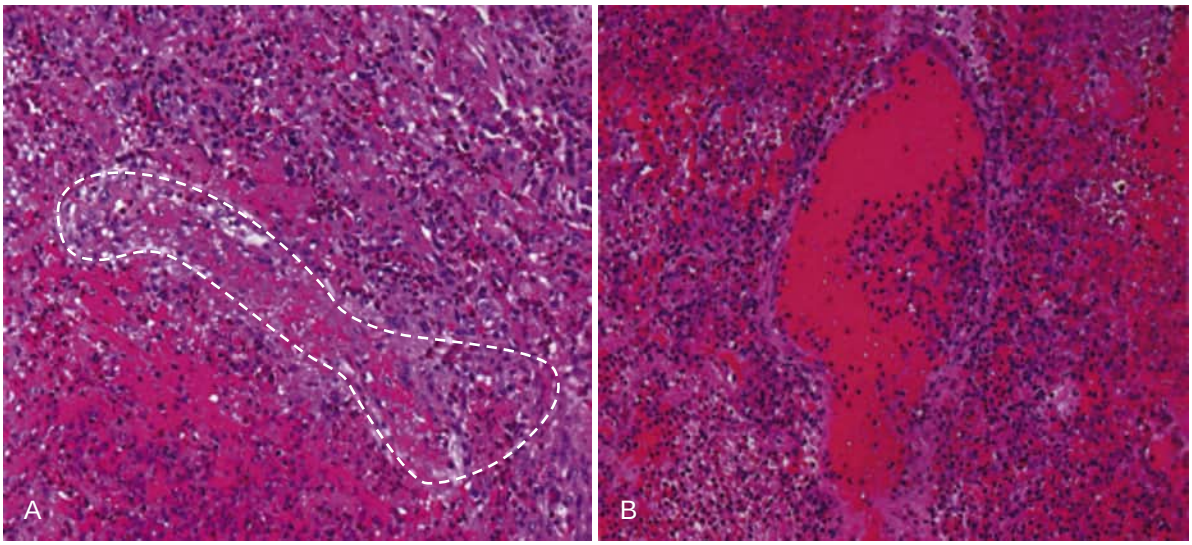

Figure 87.8 Eosinophilic granulomatosis with polyangiitis. (A) Outline (*dashed line*) of a destroyed vessel. Note the marked eosinophilic infiltration. (B) A small vein showing destruction of its wall by eosinophils. There is an accompanying eosinophilic pneumonia characterized by numerous clusters of eosinophils within the air spaces. Hemorrhage is also present.

a number of case reports and case series.[74,75] This led to the concern that leukotriene inhibitors may help promote the biologic conversion of severe asthma/atopic disease to EGPA.[76] However, analyses of postmarketing surveillance data and a number of patient cohorts over the mid-2000s argued against this relationship, and hypothesized that these excess cases were due to either reporting bias or to the unmasking of EGPA precipitated by withdrawal of corticosteroids in patients with improved control of their asthma.[72,77–79] However, in 2010, an analysis of the Food and Drug Administration Adverse Event Reporting Database found that only 36% of cases of EGPA in patients treated with leukotriene inhibitors had preexisting clinical evidence suggesting possible EGPA or an associated tapering of the patient's corticosteroids, hence, the majority of cases of EGPA associated with leukotriene antagonists could not otherwise be explained.[80] Similar findings were identified in the United Kingdom's Committee on Safety of Medicines "yellow card" scheme. As such, the pendulum has swung back towards favoring a very small but potentially real relationship between the use of leukotriene antagonists and the development of EGPA.

MICROSCOPIC POLYANGIITIS

MPA is an ANCA-associated small vessel vasculitis generally heralded by weeks to months or longer of profound constitutional symptoms (fever, asthenia, fatigue, malaise, myalgias, arthralgias) followed by the development of renal disease, generally RPGN (see Table 87.3). MPA is more common in men, with an average age of onset in the sixth decade. Its clinical manifestations overlap with those of polyarteritis nodosa, explaining the decades of confusion over their relationship. The glomerulonephritis is essentially universal, whereas the lungs are involved in a minority of patients (10–30%).[81–83] In patients who develop lung disease, DAH/capillaritis is the most common manifestation (eFig. 87.9). Pulmonary fibrosis is uncommon but associated with a high mortality rate. The skin is involved in over half of patients, most commonly with purpura. The peripheral nervous system (most commonly with mononeuritis multiplex) is involved more frequently than the central nervous system, and the gastrointestinal tract can be involved, with bleeding and ischemia.[84] MPO-ANCA and a perinuclear pattern on IIF is positive in 50–75%. Pathologically, a focal, segmental necrotizing vasculitis and a mixed inflammatory infiltrate without granulomata are seen. Pathologically, this vasculitis affects venules, capillaries, and arterioles. Neutrophilic capillaritis (see Fig. 87.3) is the classic histologic finding in the lung, with pulmonary alveolar hemorrhage and hemosiderin-laden macrophages (Fig. 87.9). As the lesions heal, plugs of organizing pneumonia may fill air spaces, resulting in an organizing pneumonia–like pattern. Unlike the other small vessel vasculitides, MPA lacks granulomatous inflammation. The overall 5-year survival rate has been estimated to be approximately 45–76%, with higher mortality rates in those greater than 65 years old or those with significant renal impairment.[61] Relapses after successful induction therapy are common (25–33%)[81] but usually less severe and responsive to therapy.

SMALL VESSEL VASCULITIS RELATED TO IMMUNE COMPLEXES

There are a number of small vessel vasculitides that involve the lung and are pathophysiologically defined by the deposition of

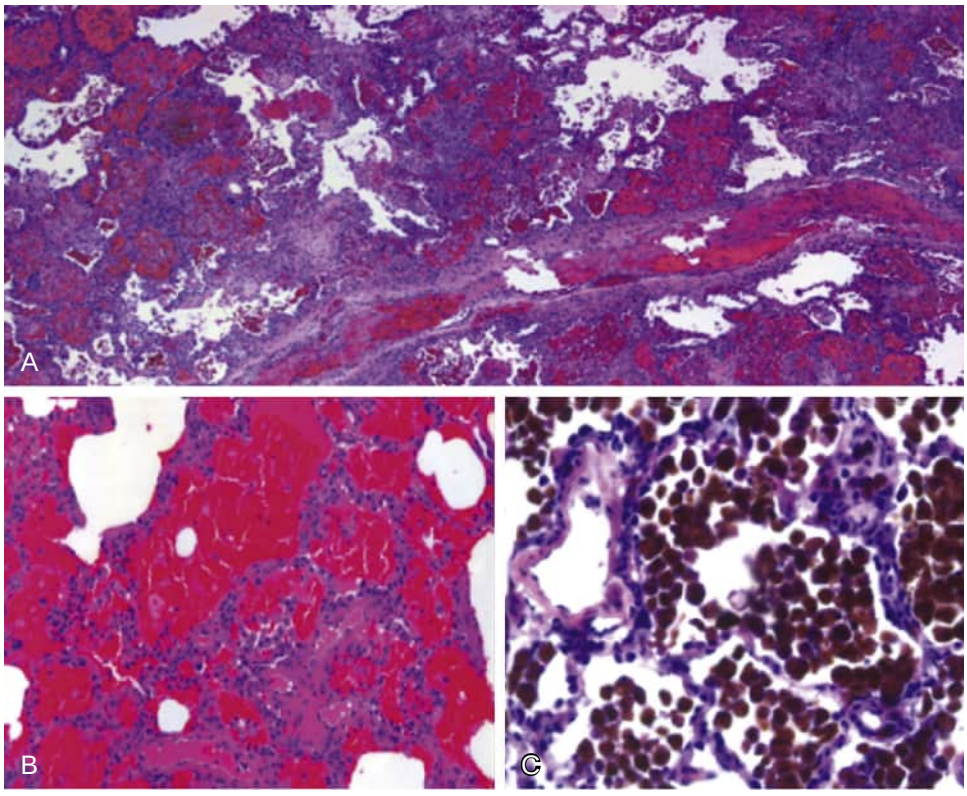

Figure 87.9 Microscopic polyangiitis. (A) Low-power view of diffuse alveolar hemorrhage. The air spaces are filled with red blood cells and the alveolar septa show concomitant inflammatory thickening. (B) Alveolar hemorrhage demonstrating the smudged, homogeneous appearance of the disrupted red blood cells in the air spaces. Occasional hemosiderin-laden macrophages can be seen in the center. (C) Hemosiderin-laden macrophages within the air spaces indicating chronic alveolar hemorrhage.

immunoglobulins and/or complement in the wall of the small vessels. These include *anti-glomerular basement membrane disease* (anti-GBM disease), hypocomplementemic (anti-C1q) urticarial vasculitis, cryoglobulinemic vasculitis, and IgA vasculitis. All are quite rare, variably affect the lung, frequently involve the kidney, and can be identified by the presence of specific circulating antibodies and pathologic findings.

Anti-GBM disease is a rare, small vessel vasculitis that results from antibodies that target domains on the alpha-3 chain of type IV collagen. Because these chains are most highly expressed in the glomerulus and the alveolar basement membrane, immune complex deposition in the small vessels of the kidney and lung define the clinical manifestations. It is a classic pulmonary-renal syndrome, presenting with RPGN and alveolar hemorrhage. Once alveolar hemorrhage and RPGN are identified, the differential includes ANCA-associated vasculitis, anti-GBM disease, IgA vasculitis, cryoglobulinemic vasculitis, and SLE. Up to 50% of patients with anti-GBM disease will also have positive ANCA; even in patients with known anti-GBM disease, ANCA should be measured because the antibodies are associated with clinical manifestations and outcome. Whereas renal disease is almost universal, lung disease is present in up to 60% of patients. The pulmonary presentation is generally that of alveolar hemorrhage, with cough, dyspnea, and sometimes, but not always, hemoptysis. Chest imaging is abnormal with diffuse ground-glass opacities with occasional consolidation. Active hemorrhage may be associated with an increased diffusing capacity for carbon monoxide. Treatment is with plasmapheresis (to remove circulating antibodies) and immunomodulatory therapy (to decrease new antibody production), generally a combination of glucocorticoids and cyclophosphamide. Alternatives to cyclophosphamide include mycophenolate mofetil and rituximab. A response to therapy is measured by serum creatinine, urine output, and hemoglobin. Outcome is generally dictated by renal disease. Monitoring anti-GBM antibodies is common, and they should become undetectable with efficacious treatment.

Hypocomplementemic urticarial vasculitis is clinically characterized by the presence of obstructive airways disease, urticaria, arthralgia/arthritis, glomerulonephritis, low complement levels, and anti-C1q antibodies. Treatment is based upon disease severity and generally includes glucocorticoids. Cryoglobulinemic vasculitis (mixed, types II/III) is most often secondary to hepatitis C infection or an underlying connective tissue disease. Symptomatic respiratory involvement is rare, but when present includes cough and dyspnea associated with airflow limitation. Pulmonary hemorrhage is exceedingly rare. Treatment depends upon the underlying cause and disease severity. Both glucocorticoids and rituximab have been used. IgA vasculitis is a systemic vasculitis with deposition of IgA1 predominant immune complexes affecting mostly the small vessels. Skin (palpable purpura), gastrointestinal (pain), joint (arthralgia/arthritis), and renal disease are the classic presenting tetrad. Lung involvement is rare.

TREATMENT

GENERAL PRINCIPLES

Therapy of the pulmonary vasculitides, particularly the AAV, generally involves aggressive immunomodulation with varying combinations of cytotoxic agents, biologic agents, and corticosteroids. Most treatment approaches have been defined using GPA as the most common of the AAV, though treatment of MPA is similar. EGPA is somewhat unique given the prominence of eosinophils in the pathophysiology and the availability of eosinophil-specific therapy. Given the risks associated with therapy, the intensity of immunosuppression should be titrated to the severity of the disease, therefore the choice, dose, and duration of therapy is not driven by the clinical diagnosis alone, but rather by the combination of the diagnosis and its severity. The goal is disease control while minimizing the risk of treatment-related adverse events.

A variety of disease severity and activity scoring systems have been utilized. The French Vasculitis Study Group has validated the *five-factor score* (FFS) in EGPA and subsequently across the AAV.[85] The FFS is calculated by adding 1 point for the presence of each of the following: (1) renal insufficiency, (2) clinically significant gastrointestinal disease, (3) cardiac symptoms, (4) the *absence* of upper airway (ear, nose, and throat) involvement (because involvement may define a more limited phenotype), and (5) age 65 years or older. Five-year mortality rates for scores of 0, 1, and 2 or greater are 9%, 21%, and 40%, respectively.[85]

More recently and conveniently, disease severity has been divided into two groups: non–organ-threatening disease and organ- or life-threatening disease (including the specific subset of rapidly progressive renal failure or pulmonary hemorrhage) (Table 87.4). Non–organ-threatening disease may have a variety of signs or symptoms such as rhinosinusitis without bone or cartilage involvement or hearing loss, exanthem without ulceration, or pulmonary nodules with hemoptysis, but it does not have evidence of active renal disease (i.e., an abnormal serum creatinine, proteinuria or red cell casts on urinalysis), cardiac disease (i.e., pericarditis or myocarditis), central or peripheral neurologic involvement (i.e., cerebral vasculitis, meningeal disease, progressive neuropathy), gastrointestinal bleeding (with or without mesenteric involvement), or orbital pseudotumor. In contrast, organ- or life-threatening disease includes rapidly progressive renal disease, pulmonary hemorrhage, pulmonary cavitary disease, motor neuropathy, and cardiac involvement among a variety of others.

Ongoing monitoring of disease activity and persistent damage is also important. Complete remission does not mean all evidence of disease activity must fully resolve, because there may be irreversible injury due to vasculitis, even early in the disease, and other potential causes (e.g., infection) may be responsible for some manifestations of disease. For example, nasal ulcers and other upper airways signs and symptoms are unlikely to respond rapidly to therapy and are not considered resistant or refractory disease. To improve interobserver reliability and to make disease activity and vasculitic damage scoring more objective, reliable, and reproducible, specific instruments have been developed. The Birmingham Vasculitis Activity Score (version 3.0) is an inventory of signs, symptoms, and laboratory findings associated with AAV that is commonly used in clinical trials to grade and quantify vasculitic disease activity objectively.[86] The instrument quantifies the history, examination, review of systems, and routine laboratories obtained by the bedside clinician caring for the patient. The Vasculitis Damage Index similarly quantifies vasculitic

Table 87.4 Disease Severity and Proposed Treatment Options for Induction and Maintenance

Disease Class	Treatment Options for Induction
New non–organ-threatening disease	Methotrexate + glucocorticoids *or* Rituximab + glucocorticoids *or* Cyclophosphamide + glucocorticoids
New organ- or life-threatening disease	Cyclophosphamide + glucocorticoids *or* Rituximab + glucocorticoids
Major relapse of organ-threatening or life-threatening disease	Rituximab + glucocorticoids *or* Cyclophosphamide + glucocorticoids
RPGN with serum creatinine >500 mmol/L (5.7 mg/dL) *or* Diffuse alveolar hemorrhage	Consider plasma exchange *plus* Cyclophosphamide (or rituximab) + glucocorticoids
Refractory disease	Referral to a center with specialized expertise in the management of vasculitis when feasible. Switch from cyclophosphamide to rituximab or from rituximab to cyclophosphamide.
Maintenance of remission for a minimum of 24 months	Azathioprine ± low-dose glucocorticoids *or* Methotrexate ± low-dose glucocorticoids *or* Rituximab ± low-dose glucocorticoids

RPGN, rapidly progressive glomerulonephritis.
Data from references 90–92, 98, 99, 111, 113, 116, 131, 144–151, 153.

damage.[87] Both of these instruments are well validated and commonly used in the conduct of clinical trials.

Similar to cancer therapy, treatment is divided into two phases, an initial remission-induction phase to control active disease and a maintenance phase to maintain disease remission while lowering treatment-related risk. Regardless of the phase of therapy, both disease-specific and drug-specific monitoring is required and should focus on the early identification of disease activity and adverse events (e.g., infection and drug toxicity). Clinicians should be familiar with the common toxicities associated with each drug utilized and have a standard protocol to monitor for potential treatment-related adverse effects during both remission-induction and maintenance therapy. Not to be forgotten, oxygen therapy (when needed), the treatment of comorbid disease, appropriate vaccinations, *Pneumocystis jirovecii* prophylaxis (as appropriate), physical and occupational therapy, a regular exercise regimen to maintain conditioning, proper nutrition along with achieving and maintaining ideal body weight, proper sleep hygiene, supporting bone health, and psychosocial support should be provided because they reduce morbidity associated with these diseases.

INDUCTION OF REMISSION

Fauci's early studies[48] of cyclophosphamide plus corticosteroids dramatically changed the field of vasculitis therapy. The combination of oral cyclophosphamide plus oral corticosteroids in this initial study yielded a remission rate of greater than 90%. Prior to the advent of this regimen, the prognosis for patients with AAV was uniformly poor, with 5-year mortality rates as high as 85%.

Glucocorticoids have been the mainstay of treatment for the vasculitides, while their adverse effects have been a primary driver of the early study of the addition of cyclophosphamide. There is general disagreement among experts regarding the appropriate dosing and tapering regimens in the treatment of AAV. Pulse methylprednisolone (7 to 15 mg/kg to a maximum dose of 500 to 1000 mg/day) for 3 days is often recommended for those with severe pulmonary disease and/or necrotizing or crescentic glomerulonephritis, but whether it should be used in those with less severe disease is unknown. After initial pulse intravenous therapy, oral prednisone therapy of 1 mg/kg per day, to a maximum of 80 mg/day, is generally started. The tapering regimen is then dictated by clinical response with a goal of 20 mg/day or less by the end of 2 months. The use of glucocorticoids beyond 6 months may be associated with a significantly higher incidence of infections. The results of the recent PEXIVAS trial suggest that standard induction with pulse methylprednisolone followed by oral doses less than 60% of standard dose is noninferior in terms of all-cause mortality or end-stage kidney disease. This more rapid tapering of therapy, starting in the second week of therapy, is likely to become standard.

In an attempt to reduce the side effects and toxicity associated with oral cyclophosphamide induction therapy while preserving high rates of disease remission, a number of clinical trials have been performed looking at alternative regimens. Pulsed intravenous cyclophosphamide has been compared head-to-head with oral cyclophosphamide in the EUVAS-sponsored CYCLOPS trial (daily oral versus pulse cyclophosphamide for renal vasculitis).[88–90] While the investigators found that intravenous cyclophosphamide was as effective as oral cyclophosphamide at inducing disease remission and was associated with fewer side effects, long-term follow-up data found that the risk of relapse was higher (29.5% vs. 20.8%).[90,91] On the other hand, no significant differences were found between the two groups in regard to survival, renal function, or adverse events. The EUVAS sponsored Methotrexate versus Cyclophosphamide for "Early Systemic Disease" trial showed oral methotrexate to be as efficacious as oral cyclophosphamide in the induction of disease remission at 6 months (84% vs. 83%), albeit with a longer time to remission (5.2 months vs. 3.2 months).[92–94] The methotrexate side effect profile was also more favorable, though the rate of relapse in this group was also higher (74% vs. 42%).[95] The EUVAS study group has also shown that *mycophenolate mofetil* (MMF) was noninferior to cyclophosphamide for remission induction in AAV, but resulted in a higher relapse rate. One hundred forty newly diagnosed patients were randomly assigned to MMF or pulsed cyclophosphamide. All patients received the same oral glucocorticoid regimen and were switched to azathioprine following remission. Noninferiority was demonstrated for the primary remission end point, 67% in the MMF group and 61% in the cyclophosphamide group. There were more relapses in the MMF group (33%) than in the cyclophosphamide group (19%). In MPO-ANCA patients, disease relapsed in 12% of the cyclophosphamide group and

in 15% of the MMF group. In PR3-ANCA patients, disease relapsed in 24% of the cyclophosphamide group and in 48% of the MMF group. Serious infections were similar between groups (26% MMF group, 17% cyclophosphamide group).

Because B cells have also been implicated in the pathogenesis of AAV, the anti-CD20 monoclonal antibody rituximab was tested and has been shown to be a safe and effective therapy. After a number of promising case series, two large randomized, multicenter controlled clinical trials were performed comparing rituximab to cyclophosphamide for the induction of disease remission.[96,97] The RAVE trial compared rituximab to daily oral cyclophosphamide. In this study, rituximab was shown to be noninferior to cyclophosphamide as measured by the primary end point of disease remission plus successful tapering of corticosteroids at 6 months.[98] Subgroup analysis found no difference in efficacy for the treatment of alveolar hemorrhage and that rituximab may be superior for the treatment of relapsing disease. No differences were noted in the rate of adverse events. Similar findings were found in the RITUXVAS trial in which rates of sustained remission, median time to remission, and adverse events were similar between the two treatment groups.[99]

In Non–Organ-Threatening Disease

Patients with non–organ-threatening disease may have a variety of signs or symptoms but do not have evidence of active renal or cardiac disease, central or peripheral neurologic involvement, gastrointestinal bleeding, or orbital pseudotumor. For this group of patients with comparatively mild disease, glucocorticoids in combination with methotrexate, cyclophosphamide, rituximab, and MMF have all been evaluated. Current recommendations suggest the combination of glucocorticoids and methotrexate as first-line therapy with the combination of glucocorticoids with rituximab for those patients with contraindications to the use of, or intolerant to, methotrexate. For patients unresponsive to methotrexate or who progress despite an initial response, cyclophosphamide or rituximab should be considered.

In Organ-Threatening or Life-Threatening Disease

Organ- or life-threatening disease will manifest with active renal disease (i.e., an abnormal serum creatinine, proteinuria or red cell casts on urinalysis), cardiac disease (i.e., pericarditis, myocarditis, cardiomyopathy), central or peripheral neurologic involvement (i.e., cerebral vasculitis, progressive neuropathy), pulmonary involvement with aggressive cavitary disease or DAH, and gastrointestinal bleeding or orbital pseudotumor, among others. In this group of patients, aggressive immunomodulation with the combination of either glucocorticoids plus cyclophosphamide or glucocorticoids plus rituximab is indicated.

In Rapidly Progressive Renal Failure, DAH

Plasma exchange (PEX) has been considered a reasonable treatment option for patients with rapidly progressive renal failure in the setting of new or relapsing disease or DAH. This approach was based on data from the MEPEX trial in a cohort of patients with severe renal disease. In this small study, the addition of plasma exchange therapy to the standard cyclophosphamide plus corticosteroid regimen was found to be superior to high-dose, pulsed intravenous steroids as measured by dialysis-free survival (69% vs. 49%).[100–106] Based upon a 20-patient case series and number of case reports, this strategy was also thought to be effective for the treatment of DAH.[105] However, the recently published PEXIVAS trial changes this thinking. In this trial, PEX and two regimens of oral glucocorticoids were tested in patients with severe ANCA-associated vasculitis (defined by renal disease or DAH). Patients underwent either PEX (seven plasma exchanges within 14 days after randomization) or no PEX. Among patients with severe ANCA-associated vasculitis, the use of PEX did not reduce the incidence of death or end-stage kidney disease. In addition, the reduced-dose regimen of glucocorticoids was noninferior to a standard-dose regimen. In the reduced-dose group, oral glucocorticoids were reduced by approximately 50% at the start of the second week. The dose in the standard-dose group was tapered more gradually, starting in week 3. At 6 months, the cumulative dose of glucocorticoids in the reduced-dose group was less than 60% of that in the standard-dose group.

Additional therapies described at the case report level for patients with unresponsive DAH include activated human factor VII to control ongoing, refractory hemorrhage in patients with respiratory failure[107,108] and extracorporeal membrane oxygenation, which has been used to treat refractory hypoxemic respiratory failure in patients with severe hemorrhage until other interventions have had a chance to work.[109]

After Relapse of Organ- or Life-Threatening Disease

Historically, up to 50% of patients with an ANCA-associated vasculitis have suffered at least one relapse despite active treatment. Relapses are more common among patients with GPA (40–65%) and less common among patients with EGPA (15–25%).[57,110] The features of clinical deterioration during a relapse may be similar to the patient's original presentation or may present with novel symptoms and signs and in previously unaffected organs.

For a major relapse of organ- or life-threatening disease in AAV, it is recommended that treatment be approached as if the disease were newly diagnosed, with a combination of glucocorticoids and either cyclophosphamide or rituximab. Given the risks associated with cumulative doses of cyclophosphamide, rituximab may be the preferred choice.

In Refractory Disease

According to European League Against Rheumatism definitions, refractory disease is persistent or increased disease activity in acute AAV after 4 weeks of treatment with standard therapy or a lack of response (defined as <50% reduction in the activity score of the Birmingham Vasculitis Activity Score) after 6 weeks of treatment. Chronic, persistent disease is defined as the presence of at least one major or three minor items on the disease activity score after greater than 12 weeks of treatment. Questions to be asked prior to the diagnosis of refractory disease include: Is the diagnosis correct? Has the correct treatment been given? Is the disease actually active? and Is the measured activity due to AAV or due to infection, drug toxicity, malignancy, or other comorbidity?

For patients with refractory disease, it is recommended that therapy be switched from cyclophosphamide to rituximab or from rituximab to cyclophosphamide. In particular, for patients who are PR3-ANCA positive, rituximab may be a better choice. Other considerations include intravenous immunoglobulin and antithymocyte globulin.[111] Patients with presumed refractory disease should be cared for in centers with specialized expertise in the management of vasculitis when feasible.

MAINTENANCE

Maintenance therapy is designed to control the disease while reducing the risk or severity of medication-related adverse effects. Options during this phase of treatment include azathioprine, rituximab, methotrexate, and MMF.[92,93,112–115] The choice may be informed by initial induction regimen and ANCA status. In patients with GPA or MPA in remission, azathioprine and methotrexate appear to have similar efficacy. Among patients who are PR3-ANCA positive, rituximab may be superior to both of these. As with all therapy, any of these agents must be introduced with drug-specific monitoring to identify adverse effects as early as possible. In particular, persistent unexplained hematuria in patients with prior exposure to cyclophosphamide should be investigated and serum immunoglobulins should be tested prior to each course of rituximab and in those with recurrent infection.

The timing of transition from the induction to maintenance therapy had been a subject of debate with one school of thought arguing that patients should be treated until there was clinical evidence of response and another school of thought arguing that they should have defined courses of therapy to "consolidate" the induction of remission. Transitions determined by clinical evidence of response tend to be earlier than those determined by fixed courses of therapy. The results of a European Vasculitis Study Group trial demonstrated that patients with active generalized vasculitis may be transitioned from oral cyclophosphamide to azathioprine at the time of clinical remission (using defined criteria; generally within 3 to 6 months). Patients in the clinically determined (early) transition group demonstrated no increase in the rate of relapse, disease activity scores, or change in renal function, suggesting that this approach is as safe and effective as fixed-course therapy.[116]

Maintenance therapy should continue for at least 24 months following the induction of remission.[117] The EUVAS-sponsored REMAIN trial prospectively compared two different durations of maintenance immunosuppressive therapy for the prevention of relapse in AAV. After cyclophosphamide/prednisolone-based induction followed by azathioprine/prednisolone maintenance therapy, patients were randomized (1:1) to receive continued azathioprine/prednisolone to 48 months from diagnosis (continuation group) or to withdraw azathioprine/prednisolone by 24 months (withdrawal group). The primary end point was relapse, from randomization to 48 months from diagnosis. It was found that prolonged remission-maintenance therapy with azathioprine/prednisolone beyond 24 months after diagnosis reduced relapse risk out to 48 months and improved renal function. This study supports the use of prolonged maintenance therapy to minimize the risk of relapse.

Another point of controversy has been the optimal dosage and duration of the corticosteroid component of the treatment regimen. While there is general agreement that "high-dose" corticosteroids should be introduced in patients with active disease as part of their induction therapy (e.g., 1 mg/kg/day of oral prednisone or equivalent), and that this should be "slowly tapered" (e.g., 3 months) towards a "low" maintenance dose (e.g., 5 to 10 mg of oral prednisone per day or equivalent), there is no validated, widely accepted corticosteroid protocol. However, the recent PEXIVAS study showed that a reduced dose approach with an early taper starting in week 2 is noninferior to the higher, "standard dose" taper. Whether the corticosteroids should be tapered off or remain at a low dose for a prolonged period of time remains controversial, with advocates on both sides of the argument. That said, a meta-analysis of 13 large clinical trials has suggested that patients maintained on some dose (i.e., "non-zero") of corticosteroids have a lower rate of disease relapse than patients who are weaned entirely off (14% vs. 43%). Still, this has not been replicated in a well-designed, prospective clinical trial and even low-dose corticosteroids carry a risk of adverse side effects.

Finally, trimethoprim/sulfamethoxazole[13,118] may have an adjunctive (but not sole) role in the management of AAV and reduces the risk of relapse in GPA.[12,119] Studies have demonstrated a reduced frequency of disease relapse in patients who are maintained on trimethoprim/sulfamethoxazole compared to those without,[118] with additional work suggesting that this is related to *Staphylococcus aureus* nasal carriage.[12,119] For those with nasal *S. aureus*, mupirocin may be considered. Regardless, trimethoprim/sulfamethoxazole should be considered for *P. jirovecii* prophylaxis in patients maintained on cyclophosphamide or other aggressive immunosuppression regimens barring a sulfa allergy or other contraindication.

SPECIFIC TREATMENT ISSUES IN EGPA

While grouped with the AAV, EGPA is unique in that eosinophils are recognized as pathophysiologically important and responsible for multiple clinically relevant features of the disease. With the availability of specific anti-eosinophilic biologic therapy, the treatment of EGPA (particularly more severe disease) often includes one of these newer agents.

Similar to the other AAV, therapy depends upon underlying disease severity, which can be scored using the FFS (see above). Glucocorticoids alone are the usual remission induction therapy for EGPA, generally at doses of 0.5 to 1.0 mg/kg. More severe disease may be treated with intravenous pulse methylprednisolone. In patients with mild disease, remission rates above 90% have been described using glucocorticoid therapy alone. Once remission is achieved, a glucocorticoid taper is planned for 12 to 18 months, though the majority may need prolonged, low-dose steroids.

Additional immunomodulatory therapy is generally reserved for patients with more severe disease, refractory disease, or disease that continues to flare with steroid tapers. Cyclophosphamide is the preferred choice, particularly for patients with an FFS score of 2 or more, with cardiac or central nervous system involvement, and with a positive ANCA. Cyclophosphamide is associated with improved survival in severe EGPA patients with a higher FFS. In those with milder disease who need additional therapy, methotrexate or azathioprine are recommended.

Large retrospective studies suggested the efficacy of azathioprine as maintenance therapy, though a randomized controlled trial (CHUSPAN2) for nonsevere vasculitides, including an EGPA subset ($n = 51$), showed that azathioprine was not superior to placebo in preventing relapse. Ultimately, the role of long-term azathioprine maintenance therapy for EGPA is still unclear. Other maintenance therapy has included methotrexate and leflunomide.

Mepolizumab, a humanized monoclonal antibody against IL-5 (a cytokine with major effects on eosinophil differentiation and survival), has also been studied in EGPA. MIRRA was a randomized placebo-controlled trial of mepolizumab in addition to standard care, in relapsing or refractory EGPA patients. Mepolizumab was associated with more weeks of remission than placebo (28% vs. 3% of the participants had ≥24 weeks of accrued remission; $P < 0.001$) and a higher percentage of participants in remission at both week 36 and week 48 (32% vs. 3%; $P < 0.001$). Minimal adverse effects were noted. However, it also appears that mepolizumab alone or with less than 5 mg/day of prednisolone does not maintain remission in the majority of patients. Mepolizumab is considered a good choice in EGPA, especially in patients whose disease is not controlled with glucocorticoids alone, have a low FFS, and in ANCA-negative EGPA patients. Reslizumab, another anti-IL-5 monoclonal antibody, and benralizumab, an anti-IL-5 receptor monoclonal antibody, are now being investigated for EGPA.

Rituximab has also been evaluated for treatment of EGPA. A recent retrospective review of EGPA patients who received rituximab for mostly refractory EGPA or in whom cyclophosphamide was contraindicated were reviewed. In this population, rituximab led to improvement (response and partial response with a reduction in prednisolone requirement) in 76.8% of patients at 6 months, 82.8% at 12 months, and 93.2% by 24 months, while there were relapses (particularly asthma and ENT) in 54% by 24 months. The ANCA-positive subset appeared to have a more sustained response on isolated asthma/ENT exacerbations. Currently, there are two randomized placebo-controlled trials (REOVAS and MAINRITSEG) evaluating the efficacy of rituximab as remission induction therapy compared to cyclophosphamide and as remission maintenance therapy compared to azathioprine, respectively.

Additional therapies have been evaluated including, interferon-α and the anti–immunoglobulin E monoclonal antibody, omalizumab. It has shown effectiveness for asthma in EGPA patients. Intravenous immunoglobulin has been approved for refractory EGPA in Japan since 2010. The underlying asthma is often difficult to control and should be managed using standard guidelines.

MONITORING FOR COMPLICATIONS

Monitoring for complications is mandatory in order to minimize the morbidity and mortality of both the disease and its treatment. When there is clinical deterioration, infection, drug toxicity, disease relapse, thromboembolic disease, and disease processes unrelated to the underlying vasculitis[120] should all be considered (Table 87.5).

Infection is the leading cause of morbidity and mortality in patients with vasculitis. Infection may present with atypical clinical features or atypical organisms and is frequently difficult to separate from disease activity. Infection may also contribute to triggering or increasing disease activity, and the immune dysfunction associated with disease activity appears to place patients at increased risk for infection, so that infections may accompany disease flares. Ultimately, infection accounts for 13–48% of deaths in patients with vasculitis.[2,121,122] Combining high-dose glucocorticoids with cytotoxic or rituximab therapy puts patients at especially high risk for infection. Measuring immunoglobulins (particularly IgG and IgM) in those on active rituximab therapy as well as those with recurrent infection is recommended, because profound hypogammaglobulinemia increases infection risk.

Drug toxicity is also common. In GPA patients treated with cyclophosphamide, cystitis is described in up to 12%, myelodysplastic syndrome in 8%, and solid malignancy in 5%.[123] Ultimately, the bedside clinician must be familiar with the adverse effects associated with the therapies used and have a system in place for the monitoring of cytotoxic/immunosuppressive therapies to identify toxicity as early as possible. Evidence-based clinical practice guidelines have been developed by the American College of Chest Physicians to assist with monitoring practices.[124]

Thromboembolic disease is an under-recognized complication of vasculitis, particularly of GPA. Patients with GPA have the same rate of venous thromboembolism as patients with a known prior history of venous thromboembolism, 7.0 events per 100 person years. As such, venous thromboembolism must also be considered in the differential diagnosis of a patient with new chest or lower extremity symptoms. The rate of venous thromboembolism in MPA and EGPA has yet to be defined.

Table 87.5 Common Complications in the Management of Vasculitides

Common Complications	Potential Interventions
■ Infection ■ Drug toxicity ■ Disease recurrence or relapse ■ Comorbid disease ■ Osteoporosis ■ Venous thromboembolism ■ Deconditioning ■ Psychosocial distress	■ Pneumocystis prophylaxis ■ Vaccination ■ Tailor treatment intensity to disease severity ■ Drug-specific standardized monitoring ■ Disease-specific monitoring, as appropriate for specific disease ■ Bone mineral testing and prophylaxis as appropriate for corticosteroid dose ■ Physical therapy, occupational therapy, routine aerobic exercise, nutrition ■ Patient support groups

Key Points

- Pulmonary vasculitis describes a variety of disorders characterized by their ability to cause vascular inflammation, destruction, and tissue necrosis in the lung.
- The presentation, clinical features, and evaluation overlap with more common disorders including infection, other characterized autoimmune disorders, and drug toxicity.

- A confident diagnosis may occasionally be made without tissue biopsy; however, diagnostic biopsy remains necessary for a definitive diagnosis and is generally recommended when establishing a new diagnosis and for further evaluation of patients suspected of relapse.
- The antineutrophil cytoplasmic antibody–associated vasculitides—granulomatosis with polyangiitis, eosinophilic granulomatosis with polyangiitis, and microscopic polyangiitis—are the most commonly encountered pulmonary vasculitides.
- A large number of high-quality randomized, controlled therapeutic trials have defined evidence-based treatment recommendations and generally allow for confidence in initial therapy.
- Because most treatment approaches involve aggressive immunosuppression, treatment-related complications are common and can be severe. Common complications that arise during the course of disease include infection, adverse drug reactions, disease relapse, comorbid disease, and venous thromboembolism.

Key Readings

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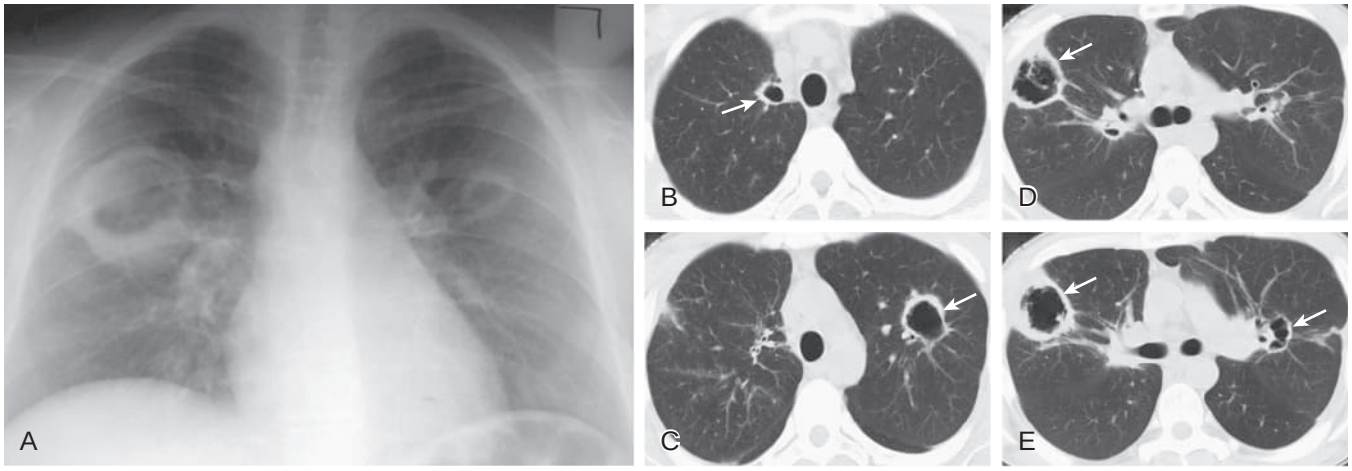
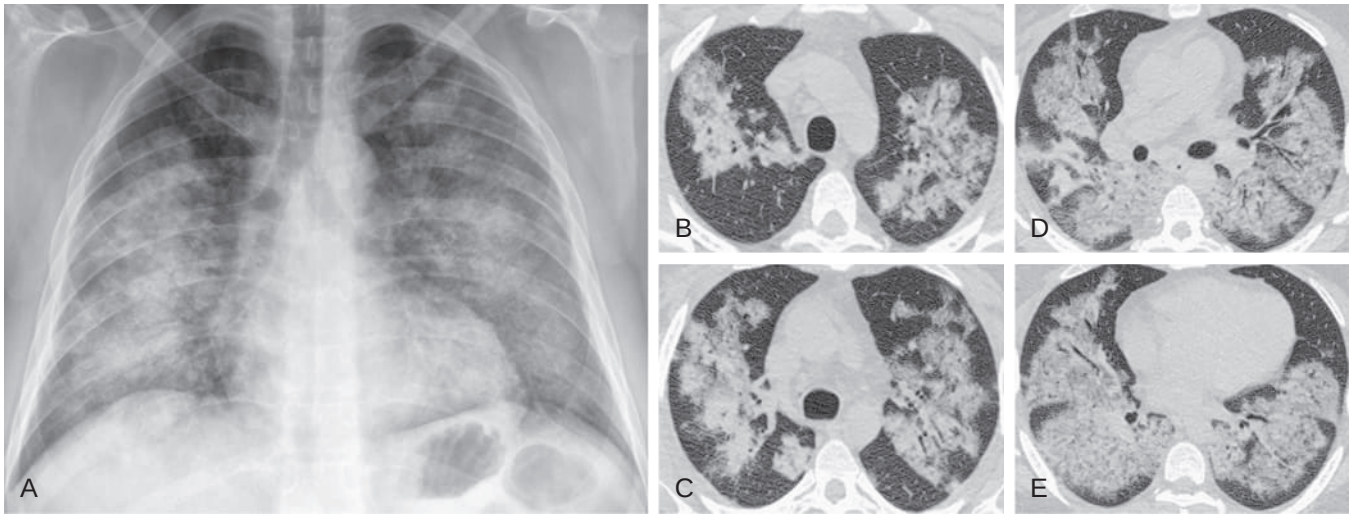
Complete reference list available at ExpertConsult.com.

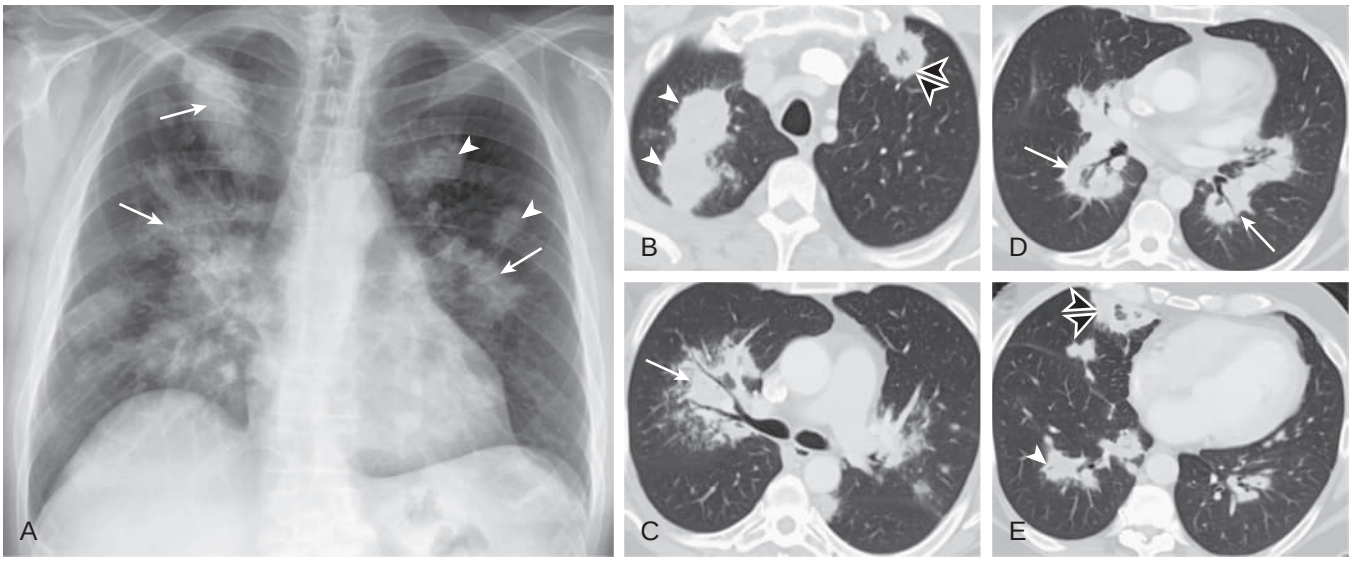
eFIGURE IMAGE GALLERY



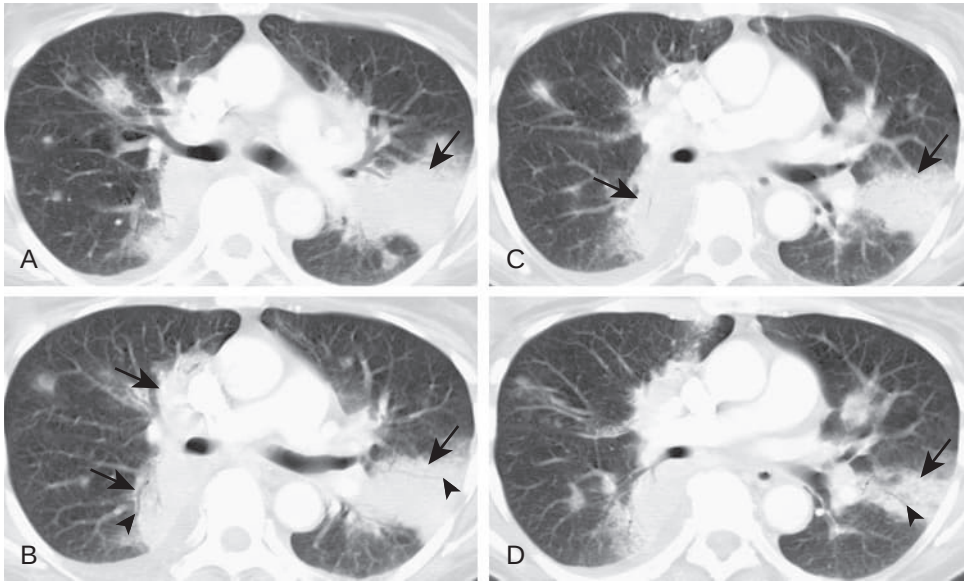
eFigure 87.1 Granulomatosis with polyangiitis: cavities. (A) Frontal chest radiograph in a patient with granulomatosis with polyangiitis shows bilateral, variably sized pulmonary cavities. (B–E) Axial chest computed tomography displayed in lung windows confirms the presence of numerous cavities (*arrows*) with variable wall thickness; some contain internal opacity, but without air-fluid levels. (Courtesy Michael B. Gotway, MD.)



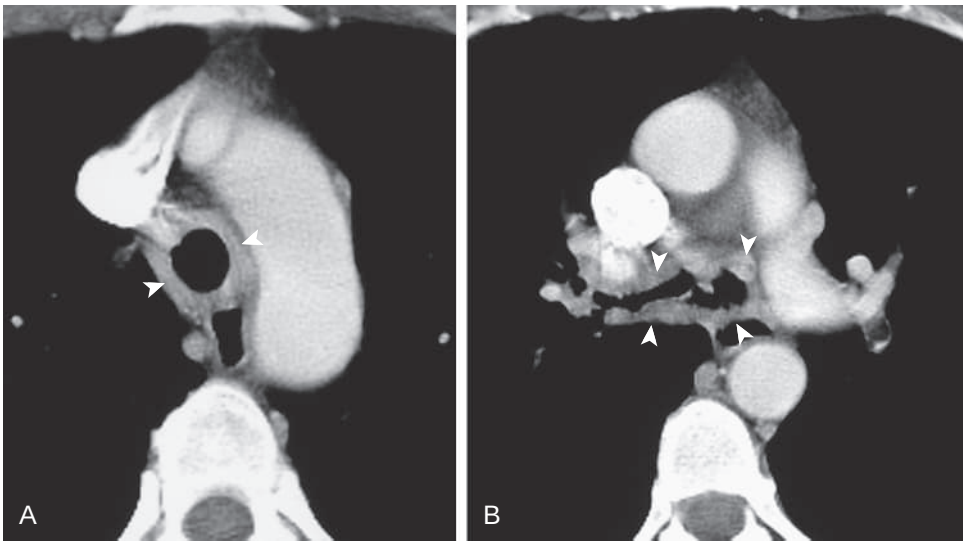
eFigure 87.2 Granulomatosis with polyangiitis: diffuse pulmonary opacities due to pulmonary hemorrhage. (A) Frontal chest radiograph in a patient with granulomatosis with polyangiitis shows multifocal, bilateral, ground-glass opacity and consolidation. (B–E) Axial chest computed tomography displayed in lung windows shows multifocal ground-glass opacity associated with linear and reticular opacities; prominent peribronchial localization of these opacities is visible in the upper lobes, with numerous air bronchograms as well. These findings are consistent with pulmonary hemorrhage, but are nonspecific. (Courtesy Michael B. Gotway, MD.)



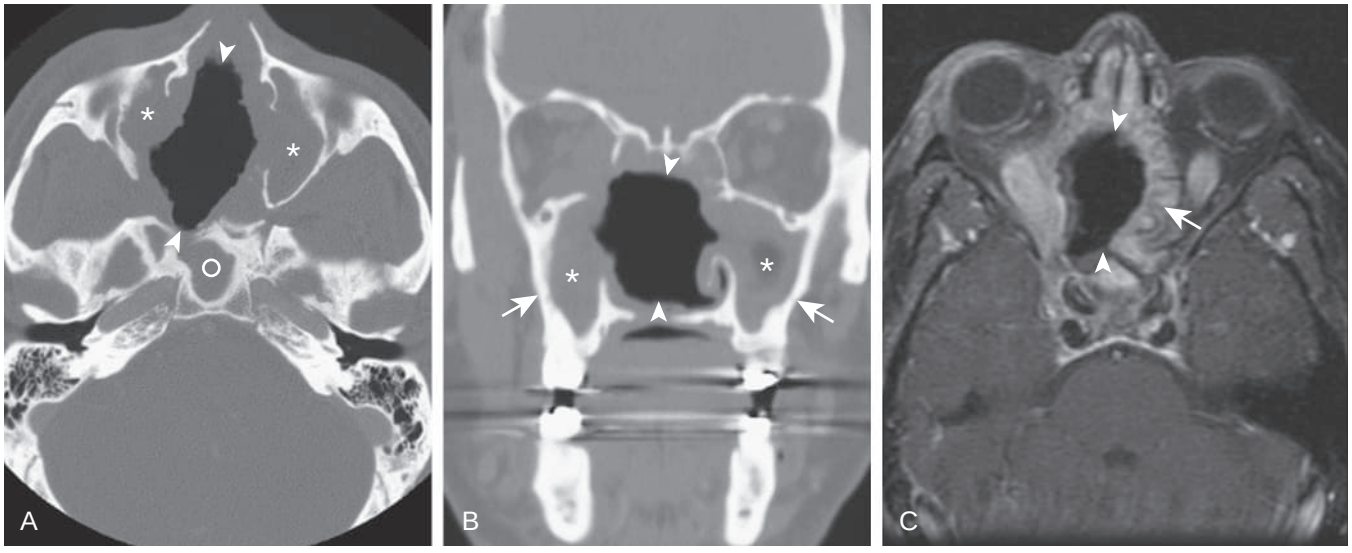
eFigure 87.3 Granulomatosis with polyangiitis: consolidation. (A) Frontal chest radiograph in a patient with granulomatosis with polyangiitis shows several nodular and masslike areas (*arrowheads*) as well as foci of consolidation (*arrows*). (B–E) Axial chest computed tomography displayed in lung windows shows nodules and masses (*arrowheads*), with areas of increased opacity and air bronchograms (*arrows*) consistent with consolidation. Some of the masses show internal ground-glass opacity surrounded by consolidation (*double arrowheads*), representing the reverse ground-glass halo (or "atoll") sign, representing areas of pulmonary infarction in this clinical context. (Courtesy Michael B. Gotway, MD.)



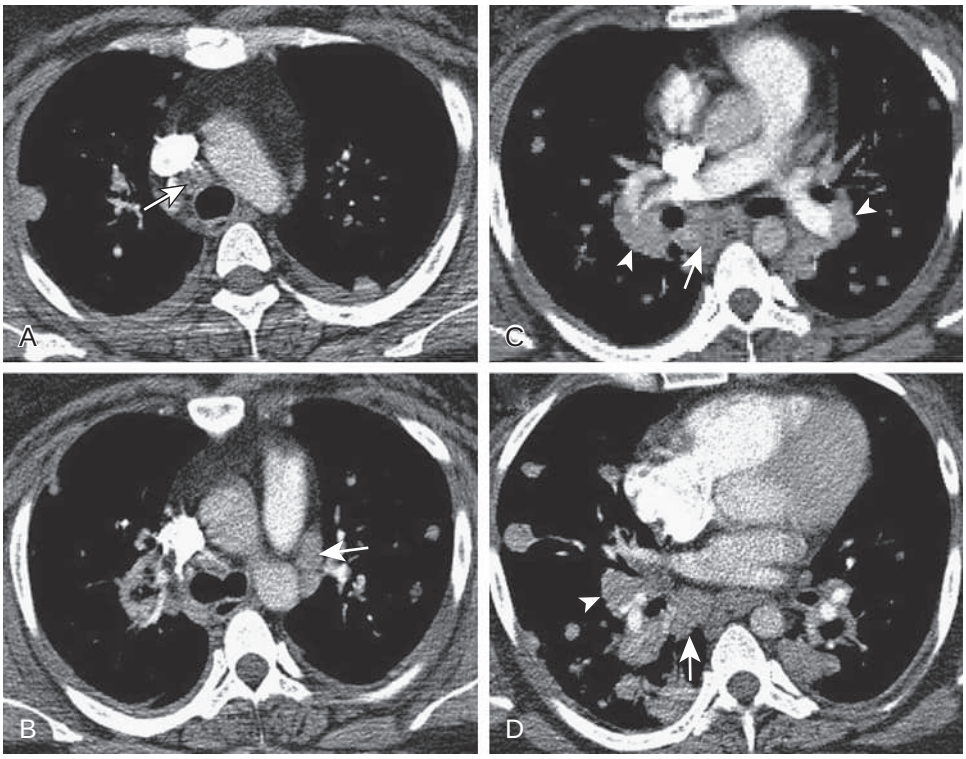
eFigure 87.4 Granulomatosis with polyangiitis: consolidation. (A–D) Axial chest computed tomography displayed in lung windows in a patient with granulomatosis with polyangiitis shows multifocal consolidation (*arrows*), somewhat resembling organizing pneumonia. Note presence of air bronchograms in some of the opacities (*arrowheads*). (Courtesy Michael B. Gotway, MD.)



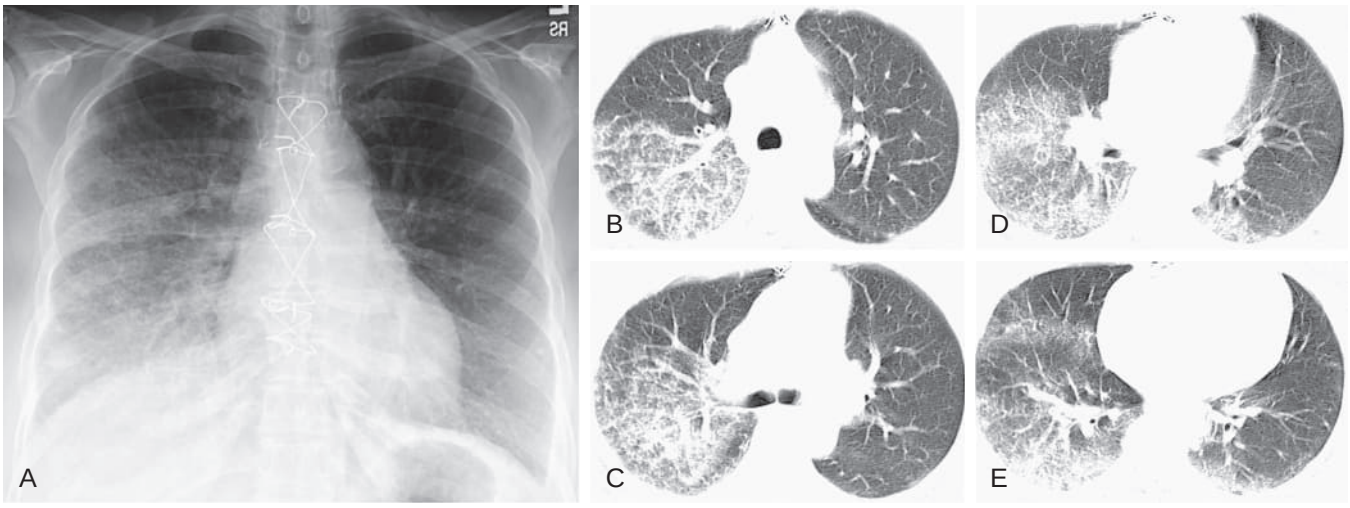
eFigure 87.5 Granulomatosis with polyangiitis: tracheobronchial stenoses. (A–B) Axial chest computed tomography displayed in soft tissue windows in a patient with granulomatosis with polyangiitis shows nodular, circumferential thickening of the trachea and bilateral mainstem bronchi (*arrowheads*). (Courtesy Michael B. Gotway, MD.)



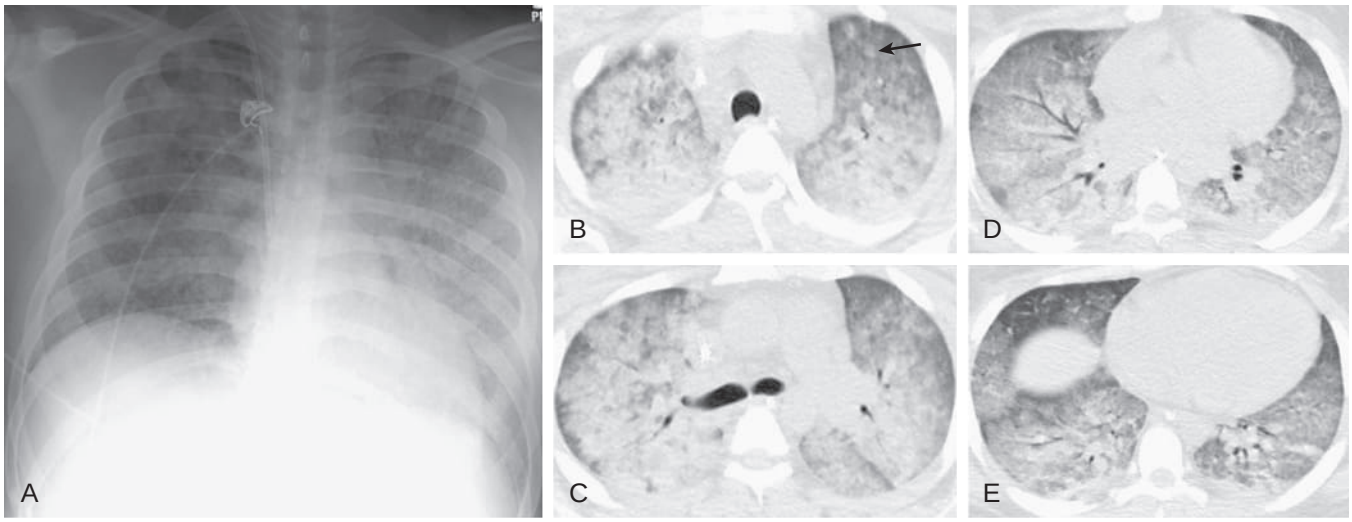
eFigure 87.6 Granulomatosis with polyangiitis: upper respiratory tract ulceration. Axial (A) and coronal (B) sinus computed tomography in a patient with granulomatosis with polyangiitis shows opacification of the maxillary sinuses bilaterally (*asterisk*) and the sphenoid sinus (*open circle*). The nasal septum is completely eroded and essentially absent (the nasal septum should normally be located approximately between the two *arrowheads*). (C) Axial contrast-enhanced axial T1-weighted magnetic resonance imaging with fat saturation shows extensive inflammatory tissues in the nasopharynx (*arrow*) as well as absence of the nasal septum (the nasal septum should normally be located approximately between the two *arrowheads*). (Courtesy Michael B. Gotway, MD.)



eFigure 87.7 Granulomatosis with polyangiitis: lymphadenopathy. (A–D) Enhanced chest computed tomography shows bilateral peribronchial (*arrowheads*) and mediastinal (*arrows*) lymph node enlargement in a patient with granulomatosis with polyangiitis. Lung nodules are also visible (same patient as in eFig. 87.1). (Courtesy Michael B. Gotway, MD.)



eFigure 87.8 Eosinophilic granulomatosis with polyangiitis. (A) Frontal chest radiograph shows multifocal hazy increased attenuation associated with a background of linear and reticular opacities, primarily affecting the right lung. (B–E) Axial chest computed tomography displayed in lung windows shows multifocal ground-glass opacity associated with linear and reticular opacities; these findings are consistent with pulmonary hemorrhage, but are ultimately nonspecific. (Courtesy Michael B. Gotway, MD.)



eFigure 87.9 Microscopic polyangiitis. (A) Frontal chest radiograph shows multifocal, bilateral hazy increased attenuation associated with a background of linear and reticular opacities, the latter best seen in the left lung. (B–E) Axial thoracic computed tomography displayed in lung windows shows multifocal ground-glass opacity, faintly forming poorly defined centrilobular nodules (*arrow*) in some locations, associated with linear and reticular opacities; these findings are consistent with pulmonary hemorrhage, but are ultimately nonspecific. (Courtesy Michael B. Gotway, MD.)

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88 PULMONARY VASCULAR ANOMALIES

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INTRODUCTION

Pulmonary vascular anomalies are a diverse group of blood vessel anomalies that can lead to pulmonary hemorrhage and/or other complications, such as shunting. The anomalies are often rare and can be congenital, inherited, or acquired. The most common and well characterized are the pulmonary arteriovenous malformations, whereas sequestrations, pulmonary arterial aneurysms, venous varices, and anomalies of systemic supply are more rare. These typical anomalies are described, including their imaging and clinical presentations, as well as treatment, as relevant.

PULMONARY ARTERIOVENOUS MALFORMATIONS

DEFINITION AND EPIDEMIOLOGY

Pulmonary arteriovenous malformations (PAVMs) consist of a direct pulmonary artery to pulmonary vein connection, with resulting right-to-left shunting. These most frequently arise as a complication of *hereditary hemorrhagic telangiectasia* (HHT). In fact, as HHT has become more recognized and diagnosed and genetic testing has become available, the proportion of PAVMs reported to be associated with HHT has risen steadily from 30–90%.[1-5] Most other cases are *idiopathic*[6] and presumed to be congenital. Other causes,[7] as described remotely in the literature, are exceedingly rare and may have represented unrecognized HHT, with the detection of PAVMs in these cases predating the diagnosis of HHT. The prevalence of PAVMs has been previously estimated at 38 in 100,000 based on a lung cancer *computed tomography* (CT) screening study,[8] although this rate has not been confirmed in other studies and may be an overestimate because not all cases were confirmed.

HEREDITARY HEMORRHAGIC TELANGIECTASIA

HHT is an autosomal dominant disorder with an estimated prevalence of 10 to 20 per 100,000 HHT is characterized by the presence of malformations with direct artery-to-vein connection. The larger lesions, arteriovenous malformations, typically are found in the lungs of 40–50% of HHT patients.[9] Arteriovenous malformations are also present in the brain in approximately 10%, in the pancreas in 15%, and rarely in other organs (small bowel in 5%, kidney in 1%, and spine in 1%). Smaller shunting lesions, or telangiectasias, can be seen typically on the nasal mucosa, oral mucosa, and skin of the face and hands, with multiple lesions noted in 90% of adults older than 50 years. Telangiectasia also develops in the liver in 75% and gastrointestinal tract in 30%.

The genetics of HHT have been largely elucidated over the past 30 years. In studies of patients from several countries, 80% of families were found to have a pathogenic mutation in either the *ENG* (endoglin) gene, the *ACVRL1* (activin receptor-like kinase 1) gene[10-12] or the *SMAD4* gene.[13,14] All three genes are members of the transforming growth factor-β signaling pathway. Depending on the locations worldwide, the distribution of genotype varies widely, with a predominance of endoglin families in the United States,[12,15] a predominance of *ACVRL1* families in France and Italy,[9] and roughly equal proportion in Canada and the Netherlands.[16]

Approximately 40% of HHT patients have PAVMs,[17,18] and PAVMs are significantly more frequent among HHT patients with an endoglin mutation compared to those with a mutation of *ACVRL1*.[9,15,16,19,20] However, patients with mutations in *ACVRL1* or *SMAD4* genes also have PAVMs, and therefore screening recommendations for PAVMs in HHT have not been limited to endoglin families.[21] The International HHT Guidelines recommend screening all HHT patients for PAVMs,[21] given the risk of debilitating and life-threatening complications from untreated PAVMs and the availability of low-risk preventative treatment.

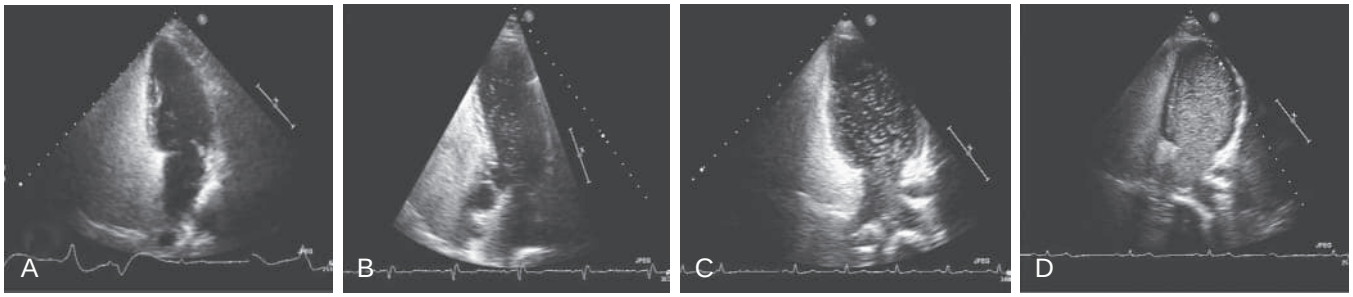

Figure 88.1 Contrast echocardiography showing different grades of left ventricular opacification. The grades shown are minimal (A), moderate (B), extensive (C), and extensive with endocardial definition (D). The likelihood of detecting a pulmonary arteriovenous malformation on chest computed tomography increases with higher grades of abnormality. (From Parra JA, Bueno J, Zarauza J, et al: Graded contrast echocardiography in pulmonary arteriovenous malformations. *Eur Respir J.* 2010;35:1281-1285. Courtesy the European Respiratory Society.)

CLINICAL PRESENTATION

PAVMs are often asymptomatic until they present with neurologic or hemorrhagic complications. At the usual time of diagnosis of PAVM, typical patients are in their 40s and have already had a stroke or transient ischemic attack (30%), cerebral abscess (10%), massive hemoptysis (10%), or spontaneous hemothorax (10%). Only 10% of PAVM patients present with classical features such as cyanosis, clubbing, and pulmonary bruit. Approximately 50% of patients with PAVMs experience exertional dyspnea,[22,23] but this is nonspecific and often unrecognized. In other words, patients with PAVMs are at risk of debilitating and life-threatening complications and often have no warning symptoms.[24,25]

PAVMs occasionally come to attention when a "nodule" is discovered on chest radiograph or CT. This is often how idiopathic PAVMs are first detected, though their clinical presentations are similar to HHT-related PAVMs,[6] and neurologic complications can also be the first presentation of an idiopathic PAVM.[26]

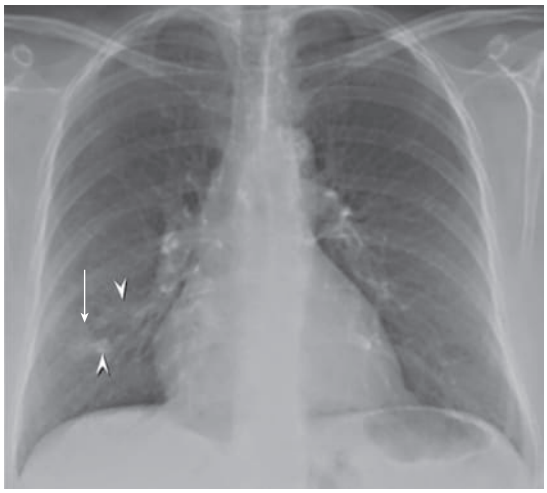

Figure 88.2 Pulmonary arteriovenous malformation. Chest radiograph shows a large lobulated pulmonary arteriovenous malformation (*arrow*). Note the serpiginous-appearing vessels (*arrowheads*) faintly seen leading toward the malformation.

SCREENING AND DIAGNOSIS

Transthoracic contrast echocardiography, using agitated saline, has emerged as the first-line screening test of choice[21] for PAVMs, given its high sensitivity of 93–97%[23,27,28] as well as its accessibility and low risk to patients. Grading of right-to-left shunt on contrast echocardiography predicts the presence of PAVM and guides the next steps for diagnostic confirmation[29,30] (Fig. 88.1). Chest radiography is not sensitive for detecting PAVMs, even in experienced hands,[23] though larger lesions can be detected (Fig. 88.2). Measurement of right-to-left pulmonary shunt fraction while breathing 100% oxygen also has a low sensitivity, detecting only approximately 50% of patients with right-to-left shunt found on contrast echocardiography; even large right-to-left shunts on contrast echocardiography could be missed on shunt testing.[31] Positional oximetry, in an attempt to detect orthodeoxia (i.e., a fall in oxygen saturation of 2% or more upon standing, as evidence of the redistribution of blood flow to the base where PAVMs are more common), had even lower sensitivity.[22] Of the patients with PAVMs in this prospective study, only 29% (n = 79) demonstrated orthodeoxia, and none described platypnea (i.e., dyspnea on standing).

The recommended diagnostic confirmatory test is chest CT[21] (Fig. 88.3A–B; see also eFig. 20.18A), which demonstrates a fistulous lesion with a feeding artery, aneurysm, and draining vein. Lesions are often multiple and peripheral in location. Varied protocols are used, with contrast-enhanced CT angiogram the most reliably sensitive and specific across centers of variable experience. However, many experienced centers routinely use non-contrast low-dose protocols[32] to minimize radiation and contrast risk for patients.[33] Pulmonary catheter angiography is rarely required for diagnosis given the current high resolution of CT imaging, but it is typically performed at the time of treatment (Fig. 88.4A, Videos 88.1 to 88.3; also see eFig. 20.18B). Contrast-enhanced magnetic resonance imaging has also been described for screening and confirmation of PAVMs[34] in HHT, but its operating characteristics are less well studied and access remains more limited.

TREATMENT

Transcatheter embolization is the treatment of choice for PAVMs, given its high success rate and low complication rate.[2,35] Embolization is recommended for all PAVMs, regardless of symptoms, with the goal of preventing

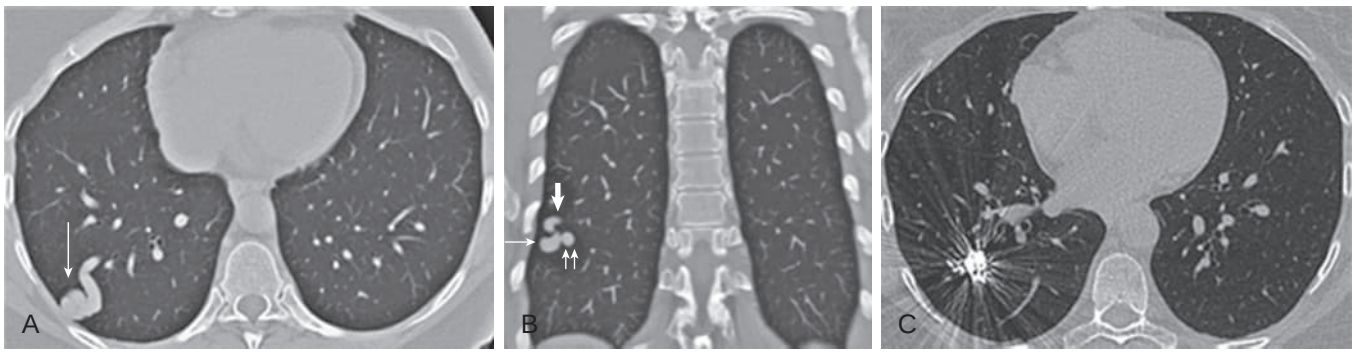

Figure 88.3 Pulmonary arteriovenous malformation before and after embolization. Axial (A) unenhanced and coronal (B) computed tomography with maximum intensity projection shows the lobulated pulmonary arteriovenous malformation (*thin arrow*), feeding artery (*double arrow*), and draining pulmonary vein (*thick arrow*). (C) One year after embolization, axial unenhanced computed tomography shows complete involution of the aneurysmal segment, with streak artifact from the embolic material.

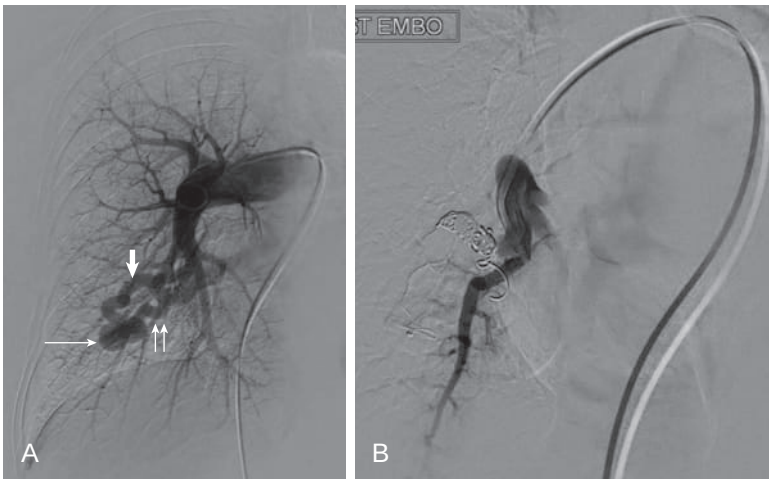

Figure 88.4 Pulmonary arteriovenous malformation before and after embolization. Catheter angiogram before (A) and after embolization (B) shows the lobulated pulmonary arteriovenous malformation (*thin arrow*), feeding artery (*double arrow*), and draining pulmonary vein (*thick arrow*). Postembolization, the lobulated aneurysm and draining vein are no longer visible.

neurologic and hemorrhagic complications.[21,36] Typically, embolization (see Fig. 88.4B, Video 88.1B) is performed with coils or Amplatzer vascular plugs,[2,37-40] with the patient under sedation and with local anesthesia of the femoral vein access site. The decision to treat a PAVM is based on the diameter of the feeding artery, generally at 3 mm or greater, although targeting PAVMs with a feeding artery of 2 to 3 mm may also be appropriate. Embolization is generally well tolerated and is often done as an outpatient procedure, with the most common complication being postembolization pleuritic chest pain in approximately 30%. The pain is usually self-limited, lasting an average of 7 to 10 days, and is treated with nonsteroidal anti-inflammatory drugs as needed. Other complications are rare in experienced centers, including hemoptysis (5%), device migration into the systemic circulation (1%), and very rare (<1%) reports of complication by angina pectoris, transient ischemic attack, or stroke.[41] Embolization device migration through a PAVM (paradoxical device embolization) is a complication at the time of embolization, but not after. The migrated device can usually be retrieved with a catheter by the interventional radiologist during the same procedure. The published series of PAVM outcomes are all from experienced centers; outcomes may be less favorable from inexperienced centers because of the rarity of the disease.

Long-term follow-up after embolization is recommended to ensure ongoing occlusion of the embolized PAVMs and also to follow growth of untreated small PAVMs. The reported long-term PAVM reperfusion rate after embolization ranges from 7–30%[35,37,42] and is generally via recanalization of the embolized feeding artery, and less frequently through a previously unrecognized additional feeding artery. Reperfused PAVMs are typically retreated with embolization with outcomes similar to the initial embolization.[43,44] Clinical follow-up after embolization is typically performed initially at 1 to 2 months after the procedure, with the goal of early confirmation of success of the procedure. On chest radiograph, visible involution of the aneurysmal sac and/or draining vein distal to the embolization material is reassuring, as is improvement in arterial P_{O_2} (room air and/or on 100% oxygen where available). HHT Guidelines[21] recommend that PAVMs should then be reassessed at 1 year postembolization with unenhanced chest CT to confirm involution of the aneurysm and of the draining vein of the embolized PAVMs (Fig. 88.3C). If there is not sufficient involution (<50%), reperfusion is suspected and retreatment should be considered. Further follow-up after initial confirmatory CT should be performed every 3 years with unenhanced chest CT using a low-dose protocol as feasible.

PAVM precautions should be recommended for all patients, even after treatment. These include antibiotic prophylaxis for bacteremic procedures, an air-eliminating intravenous filter when there is intravenous access, and

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avoidance of scuba diving.[21,45] The rationale for antibiotic prophylaxis is the high rate of brain abscess in these patients[2,24,46] and the presumed mechanism of paradoxical embolization of biofilms of bacteria through pulmonary shunting vessels. The air-eliminating filter is perhaps an overly cautious precaution but is easily administered, with the goal of preventing transient ischemic attack from iatrogenic paradoxical air embolism. Finally, scuba diving should be avoided based on the evidence that decompression from any depth, even within recommended limits, leads to nucleation of circulating nitrogen bubbles[47] that may lead to transient ischemic attack in a diver with PAVM[48] (see Chapter 107).

PULMONARY SEQUESTRATION

Pulmonary sequestration, also called bronchopulmonary sequestration, is a condition with aberrant lung tissue that has no normal connection to the bronchial tree or with the pulmonary arteries and is supplied by a systemic artery. This condition was first described in 1946 by Pryce,[49] who divided this condition into intralobar and extralobar types. In intralobar sequestration, the aberrant tissue is contained within the normal lung; in extralobar sequestration, the aberrant tissue is contained within its own pleural lining. Pulmonary sequestration usually is a congenital abnormality secondary to failure of obliteration of one of the systemic arterial connections to the base of the developing fetal lung, although intralobar sequestration may possibly also be acquired from chronic infection.[50]

INTRALOBAR

Intralobar sequestration is the more common variety and accounts for 75–85% of cases, frequently presenting in adult life as an abnormality detected on imaging or as a cause of recurrent pneumonia. It is usually seen in the lower lobes in the posterior basal segment, more frequently on the left side. In a subset of patients, the intralobar sequestration is associated with partial anomalous venous return, called scimitar syndrome; in this setting, right-sided lesions are more common.[51]

Imaging

Imaging appearances are varied, with two major patterns described depending on the degree of aeration and presence or absence of associated infection. Some of these appear as a solid water-density mass or an area of consolidation; others present as an air-containing single or multicystic lesion. Air likely enters the sequestrated tissue from the surrounding parenchyma through collateral ventilation. With underlying infection, an air-fluid level may be seen on radiograph or cross-sectional imaging. Enhanced CT (Fig. 88.5; also see eFig. 20.21) or magnetic resonance imaging shows the abnormal systemic artery in the majority of these cases. CT also demonstrates the architecture of the sequestrated lung. In some cases, the systemic artery is not seen on cross-sectional imaging and catheter angiography may be required for diagnosis.

EXTRALOBAR

Extralobal sequestration is less common and is seen in 15–25% of cases. It typically manifests in early infancy or in the newborn. The sequestrated segment is most often seen in the left hemithorax between the lower lobe and the diaphragm, although it can be found in the mediastinum, within the diaphragm, or below the diaphragm. Associated congenital anomalies are more frequent with extralobar than with intralobar sequestrations. These happen in approximately 50–60% of patients and may include congenital diaphragmatic hernia, congenital cystic adenomatoid malformation, vertebral defects, congenital heart disease, tracheoesophageal fistula, pulmonary hypoplasia, bronchogenic cyst, and congenital megacolon.

Imaging

Chest radiography shows a well-defined homogenous area of increased opacity in the lower chest silhouetting the posterior medial hemidiaphragm. The diagnosis is usually made on cross-sectional imaging with demonstration of the anomalous feeding artery and draining vein. Usually there is no air bronchogram. Extralobar sequestration may be identified in the mediastinum, pericardium, upper chest, and rarely subdiaphragmatic areas. Communication with the stomach or esophagus has been described and may be demonstrated on an upper gastrointestinal contrast study.

Routine prenatal imaging studies have led to the diagnosis in utero. Ultrasound is useful in the neonatal infant, where typical findings of a uniformly echogenic mass with a hyperechoic rim are demonstrated. Duplex scanning may demonstrate the aberrant arterial and venous connections. On CT,

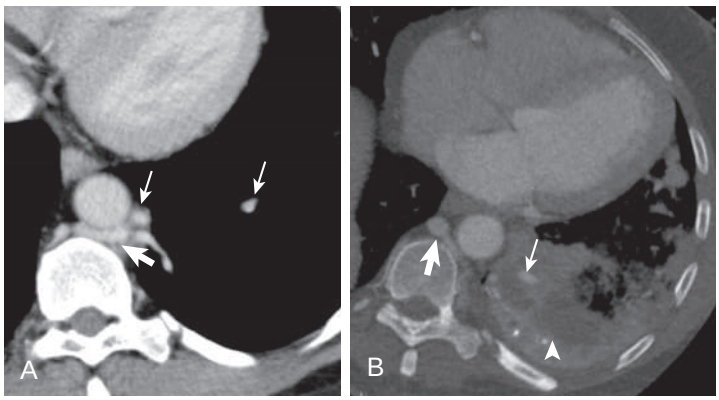

Figure 88.5 Intralobar sequestration. (A) Asymptomatic patient. (B) Symptomatic patient with consolidation (*arrowhead*), a complication of sequestration. *Thin arrows* show the systemic artery arising from the aorta, and the *thick arrows* show the venous drainage.

the extralobar sequestration presents as a homogenous, well-defined mass with soft tissue attenuation (Fig. 88.6), occasionally accompanied by emphysema in the adjacent lung.

TREATMENT

Surgery, usually requiring lobectomy or segmentectomy, is the treatment of choice.[52] Approximately half of adults diagnosed with pulmonary sequestration are asymptomatic. In patients with hemoptysis,[53] selective systemic artery embolization can be helpful preoperatively to decrease intraoperative bleeding.[54] Perinatal management of pulmonary sequestration is typically performed in a hospital environment equipped to provide resuscitation and appropriate treatment for pulmonary hypoplasia.

PULMONARY VEIN VARIX

Pulmonary vein varix (PVV) is defined as focal dilation of a pulmonary vein without an anomalous arterial connection.[55] This condition may be either congenital or acquired. The acquired subtype may be secondary to trauma or increased pulmonary vein pressure resulting from mitral regurgitation, aortic dilation, congenital heart diseases, cirrhosis, or emphysema. When secondary to mitral regurgitation, the right inferior pulmonary vein is most commonly affected, probably due to the direction of the jet, and the dilation may regress after repair of the mitral valve.

CLINICAL PRESENTATION

PVVs are almost always asymptomatic and detected incidentally on imaging. Hemoptysis secondary to rupture or systemic embolization secondary to thrombosis is very rare.[55] PVVs are very rarely clinically significant, but they often require diagnostic imaging to confirm the diagnosis and differentiate the PVV from a PAVM.

IMAGING

Chest radiographs may show a well-defined nodular opacity without calcification or a tortuous tubular structure close to the hilum. As such, the PVV may be mistaken for mediastinal adenopathy.[56] This condition is usually diagnosed on CT (Fig. 88.7) and magnetic resonance imaging.[55-57] If performed, conventional catheter angiography demonstrates a normal pulmonary artery with the tortuous pulmonary varix opacifying at the same rate as normal pulmonary veins, with the varix draining into the left atrium with no left-to-right shunt (Fig. 88.8 and eFig. 88.1, Video 88.4). Although it opacifies at the same time as other veins, the varix usually drains later than normal pulmonary veins.

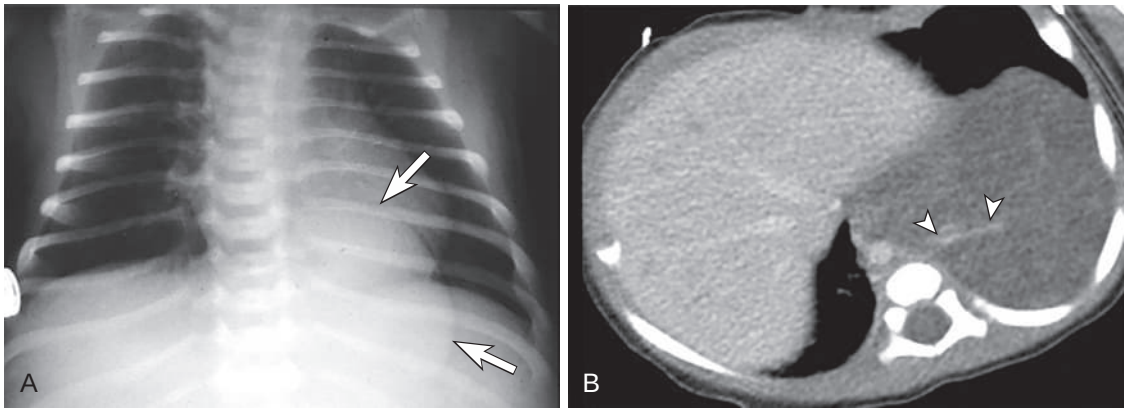

Figure 88.6 Extralobar sequestration. (A) Frontal chest radiograph shows a mass (*arrows*) at the medial left base. (B) Axial enhanced computed tomography shows a homogeneous soft tissue mass in the left posteromedial thorax. Note anomalous systemic artery (*arrowheads*), derived from the descending thoracic aorta, supplying the mass. (Courtesy Michael B. Gotway, MD.)

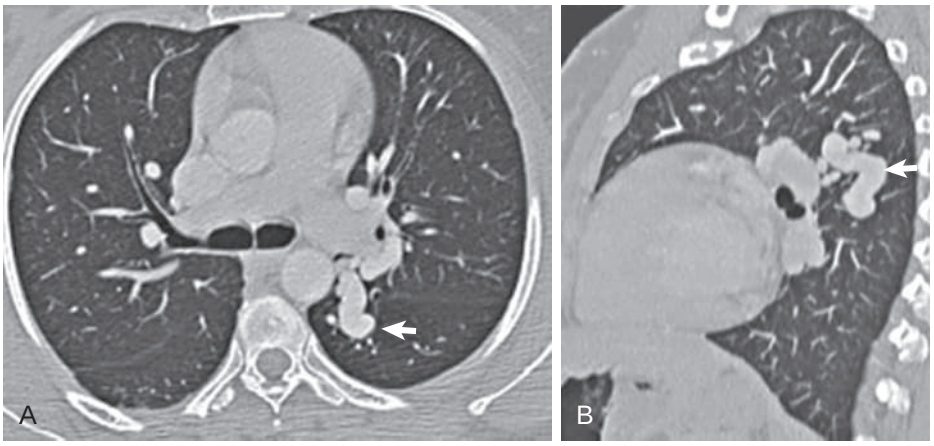

Figure 88.7 Pulmonary vein varix. Axial (A) and sagittal (B) computed tomography shows a varix of a pulmonary vein (*arrow*). It is a dilated tortuous channel draining the left upper lobe via the inferior left pulmonary vein.

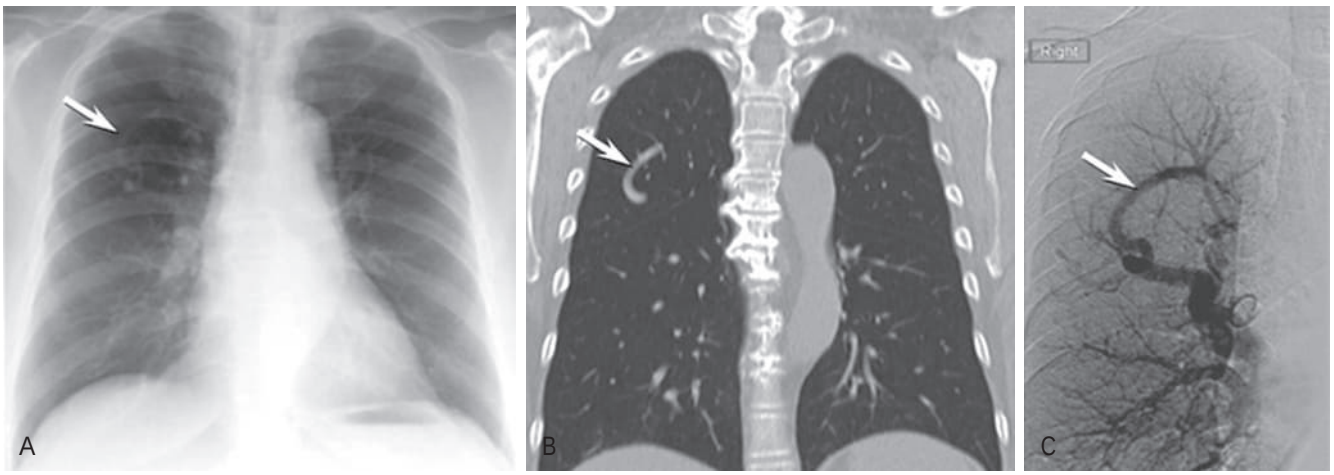

Figure 88.8 Pulmonary vein varix. (A) Frontal chest radiograph, (B) coronal computed tomography, and (C) conventional catheter pulmonary angiogram in the pulmonary venous phase demonstrate a dilated vascular structure. Curvilinear opacity in the right upper lobe with no arterial connection and no shunting is in keeping with pulmonary vein varix.

TREATMENT

Most cases are asymptomatic, considered benign, and require no specific treatment. Rare symptomatic patients may require surgical resection.[56,57]

PULMONARY ARTERY ANEURYSM

Pulmonary artery aneurysm (PAA) is defined by a dilation of the pulmonary artery to at least 1.5 times the normal diameter, involving all three layers of the vessel wall. PAA is an uncommon finding, with an estimated prevalence of 1 in 14,000.[58,59] When fewer than three layers are involved, it is defined as a pseudoaneurysm and is associated with a higher incidence of rupture.[60] Spontaneous dissection or rupture of PAA is rare, although it is described as a complication of catheterization. PAA can be a feature of a broad range of diseases, as detailed in Table 88.1.[61,62]

CLINICAL PRESENTATION

Patients with PAA are typically asymptomatic, and the diagnosis is made incidentally on imaging. Rarely, patients present with hemoptysis.

IMAGING

Chest radiographs have limited value in diagnosis but may demonstrate hilar enlargement or a lung nodule. Cross-sectional imaging, typically CT, is the imaging modality of choice and demonstrates focal pulmonary artery dilation (Figs. 88.9 and 88.10A). Associated mural calcification suggests chronic pulmonary hypertension or calcified intramural thrombus. There may be pulmonary artery wall thickening if the underlying condition is vasculitis. Ground-glass opacities in the adjacent parenchyma suggest associated pulmonary hemorrhage. Other parenchymal changes, including scarring, bronchiectasis, and granulomas, can indicate underlying lung disease. Conventional catheter angiography is generally not required for diagnosis but typically is performed if endovascular treatment is planned (see Figs. 88.10B–C and 88.11).

Table 88.1 Etiology of Pulmonary Artery Aneurysm

VASCULAR
▪ Pulmonary arterial hypertension
▪ Pulmonary valvular or post–valvular stenosis and regurgitation
▪ Cystic medial degeneration
INFECTIOUS
▪ Tuberculosis (Rasmussen aneurysm)
▪ Syphilis
▪ Mycotic (intravenous drug users); may be multiple
TRAUMATIC
▪ Penetrating or blunt thoracic trauma
▪ Iatrogenic, following chest tube insertion and most commonly from Swan-Ganz catheters
AUTOIMMUNE/VASCULITIS
▪ Behçet disease and its variant Hughes-Stovin syndrome; usually multiple
▪ Giant cell arteritis
IDIOPATHIC
CONGENITAL
▪ Left-to-right shunts, most commonly patent ductus arteriosus

TREATMENT

Routine treatment usually involves management of the underlying cause. PAA associated with vasculitis may regress with immunosuppressive treatment. If the patient presents with hemoptysis, emergency management includes airway stabilization followed by endovascular treatment, usually embolization (Figs. 88.10C and 88.11B). Central or large PAA may need surgical treatment, including excision and patch angioplasty. Endovascular management, including use of stent grafting, has been described.

ANOMALIES OF SYSTEMIC ARTERIAL SUPPLY

Systemic arterialization of the lung without bronchopulmonary sequestration is a rare form of anomalous systemic arterial supply[63] to the lung. It is characterized

by an aberrant systemic arterial branch arising from the descending thoracic aorta and, less commonly, from the upper abdominal aorta or its branches, with a normal bronchial system (i.e., pseudosequestration). The etiology[64] of this anomaly is considered to be a persistent remnant of the embryonic connection between the aorta and the pulmonary parenchyma. The normal lung can be supplied either by an entirely systemic arterial source or by both systemic plus pulmonary arterial sources (dual supply). Anomalous systemic arterial supply may also be seen in patients with chronic pulmonary parenchymal inflammation.[65] In these patients, in addition to hypertrophy of the preexisting connection[66] between the bronchial and pulmonary arteries (eFig. 88.2), transpleural systemic to pulmonary artery anastomoses develop, especially in the presence of pleural adhesions (Fig. 88.12).

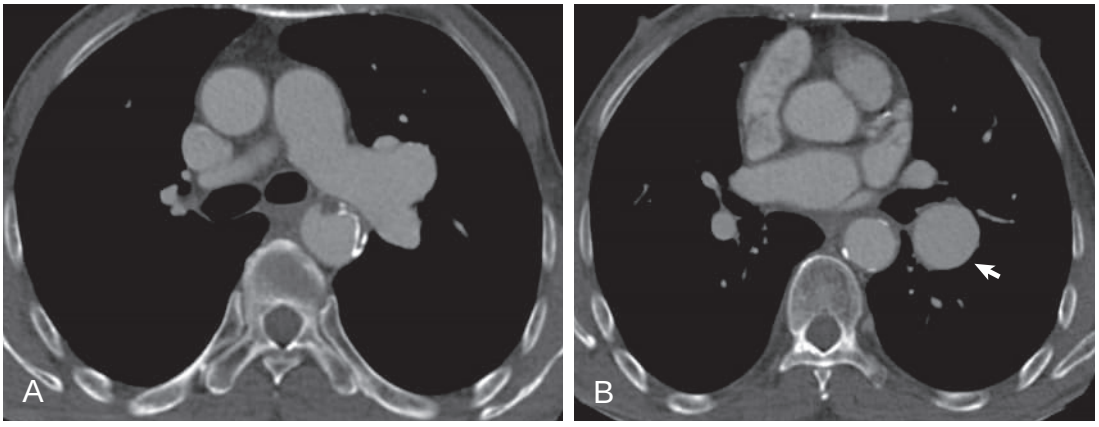

Figure 88.9 Pulmonary artery aneurysm. Axial computed tomography at the level of left hilum (A) and at the left atrial appendage level (B) shows aneurysmal dilation of the left pulmonary artery (*arrow*) in a patient with pulmonic stenosis.



Figure 88.10 Pseudoaneurysm (Rasmussen aneurysm). (A) Axial enhanced computed tomography shows a pseudoaneurysm (*arrow*) arising from an upper lobar branch of the left pulmonary artery, bulging into a large cavity. (B–C) Catheter angiogram confirms the pseudoaneurysm (*arrow*, B), which was occluded using several coils.

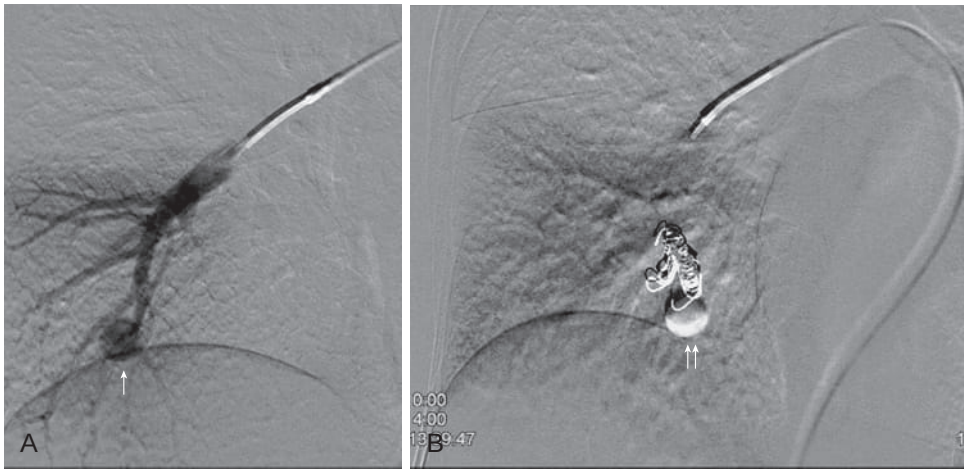

Figure 88.11 Pulmonary artery aneurysm. Catheter pulmonary angiogram shows a pulmonary artery aneurysm (*arrow*) that was embolized using coils. Note the stagnant pool of contrast in the sac (*double arrows*).



Figure 88.12 Systemic arterial supply. Selective bronchial angiogram in a patient with remote tuberculosis and aspergilloma presenting with hemoptysis. Note extensive parenchymal vascularity with hypertrophied right bronchial artery (*thick arrow*) and very prominent pulmonary artery shunting (*thin arrow*).

CLINICAL PRESENTATION

Most patients are asymptomatic and the anomaly is noted incidentally on imaging. When symptomatic, the typical presentation is massive hemoptysis and, less frequently, hemothorax. The proposed explanation for the hemoptysis is the higher pressure of systemic circulation generated in the abnormally perfused segments, resulting in intra-alveolar hemorrhage. Rarely, patients may present with dyspnea, a bruit over the chest, or cardiac symptoms related to left-to-right shunting. These lesions are not typically associated with right-to-left shunting and its related complications.

IMAGING

Chest radiographs may demonstrate tortuous vessels, but only when the anomalous systemic arterial supply vessel is large in caliber. CT is the most common imaging modality and can confirm the diagnosis and the specific vascular anatomy (see Figs. 88.13A and 88.14). Catheter angiography may be needed for confirmation (Figs. 88.13B–C and eFig. 88.3, Video 88.5). Anomalous systemic arterial supply

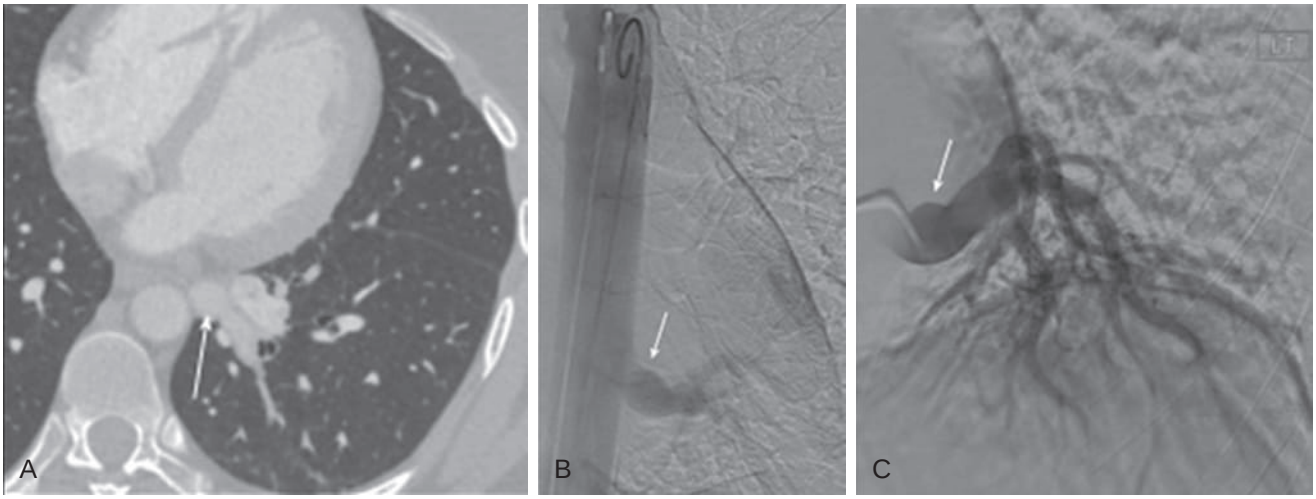

Figure 88.13 Systemic arterial supply to the left lower lobe. (A) Axial contrast-enhanced computed tomography shows an aberrant artery (*arrow*) arising from the descending thoracic aorta with normal bronchial tree. (B) Flush descending thoracic catheter angiogram and (C) selective angiogram show the aberrant artery arising from the aorta (*arrow*) and supplying the lung parenchyma.

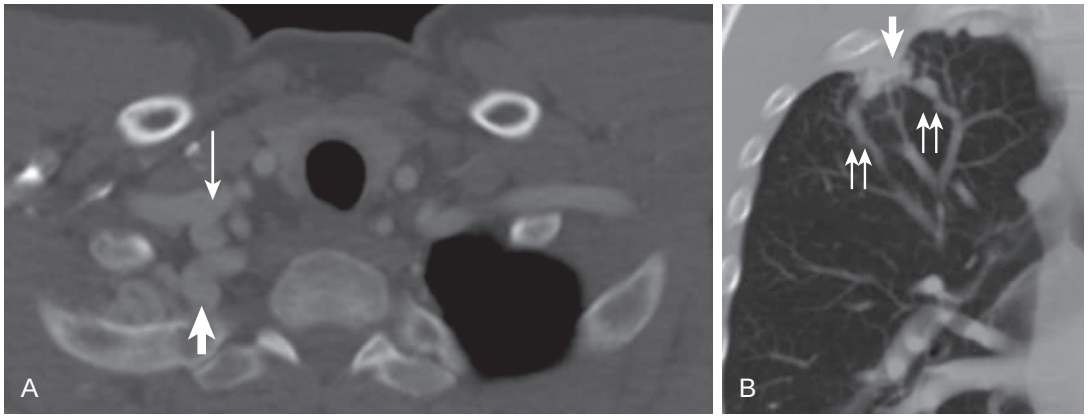

Figure 88.14 Systemic arterial supply. Contrast-enhanced axial (A) and coronal (B) computed tomography shows the right subclavian artery (*thin arrow*) and, from it, an anomalous systemic branch (*thick arrow*) drains into the pulmonary artery branch (*double arrows*).

can mimic a PAVM, although the anatomy can usually be clarified on CT. When pulmonary arterial supply is suspected, contrast echocardiography (as described above) can be helpful in ruling out right-to-left shunting. Echocardiography can also be helpful in ruling out pulmonary hypertension and associated cardiac anomalies.

In cases of massive hemoptysis, CT may help localize the site of bleeding and may also identify the underlying cause, as well as the presence of hypertrophic bronchial or systemic arteries supplying the parenchyma.[67]

TREATMENT

Asymptomatic systemic (bronchial) to pulmonary artery shunt rarely requires treatment. Surgical or endovascular treatment has been used in symptomatic cases. Usual indications for treatment include hemoptysis, heart failure, and high-flow pulmonary hypertension. Angiography with embolization of the abnormal vessels is the preferred method of management.[68,69] Although rare, inadvertent spinal artery embolization resulting in transverse myelitis is a potential serious complication, typically when there is an unrecognized spinal artery arising from the intercostal or bronchial arteries. In 80–90% of cases, control of hemoptysis is achieved with embolization, with 20% rebleeding in the first 6 months and another 50% on longer follow-up.[70] Although this procedure is not curative and there is always a risk for further bleeding, embolization can be repeated several times if needed. Surgery is reserved for selective cases, such as mycetoma, and may involve segmentectomy, lobectomy, or pneumonectomy.[71]

Key Points

- Pulmonary vascular anomalies are diverse, but can lead to massive hemoptysis or specific complications related to shunting.
- *Pulmonary arteriovenous malformation* (PAVM) is the most common anomaly, and the vast majority are due to underlying hereditary hemorrhagic telangiectasia.
- PAVM often presents with complications of the right-to-left shunting of blood, including stroke, transient ischemic attack, or brain abscess; in addition, it may present with massive hemoptysis or spontaneous hemothorax.
- Transthoracic contrast echocardiography is the first-line screening test for PAVM, with chest computed tomography recommended for confirmation.
- Transcatheter embolization is the treatment of choice for PAVM. Patients should be followed for reperfusion of PAVM, which is seen in up to 30% of cases. Even after treatment, precautions include antibiotic prophylaxis, air-eliminating intravenous filters for intravenous catheters, and avoidance of scuba diving.
- Less common causes of pulmonary vascular anomaly include pulmonary sequestration (intralobar and extralobar), pulmonary vein varix, and systemic arterial supply to the lung.

Key Readings

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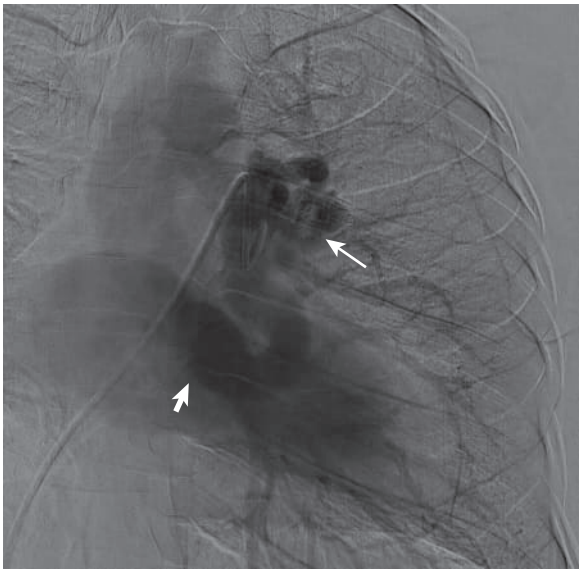
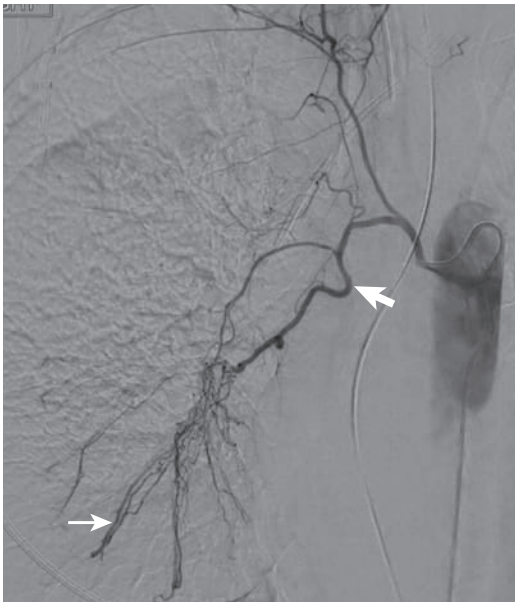
Complete reference list available at ExpertConsult.com.

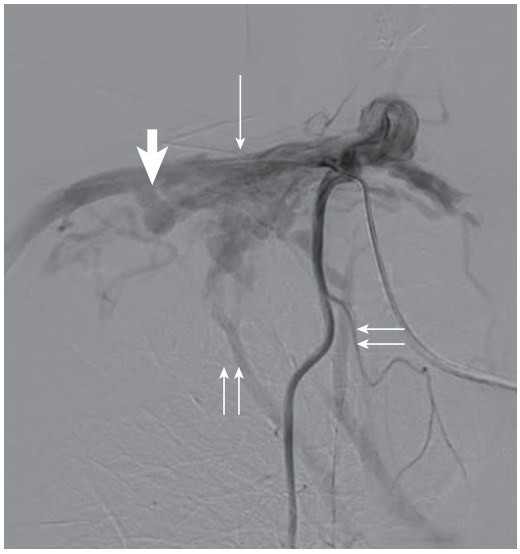
eFIGURE IMAGE GALLERY



eFigure 88.1 Pulmonary vein varix. Pulmonary venous phase of the catheter pulmonary angiogram shows the dilated varix (*thin arrow*) draining into the inferior left pulmonary vein (*thick arrow*). The superior left pulmonary vein is absent.



eFigure 88.2 Systemic arterial supply. Selective bronchial angiogram shows a normal bronchial artery (*thick arrow*) with connection to branches of the pulmonary artery (*thin arrow*).



eFigure 88.3 Systemic arterial supply. Catheter angiogram shows the thoracic vascular anomaly supplied by a branch (*thick arrow*) of the right subclavian (*thin arrow*) and draining into the branches of the right pulmonary artery (*double arrows*).

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SECTION **K**

INFILTRATIVE AND INTERSTITIAL LUNG DISEASES

89 *IDIOPATHIC PULMONARY FIBROSIS*

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INTRODUCTION

This first chapter in the section on infiltrative and interstitial lung diseases is focused on *idiopathic pulmonary fibrosis* (IPF), a disease characterized by progressive parenchymal fibrosis of unknown cause. The term *interstitial lung disease* (ILD) refers to a heterogeneous group of diffuse parenchymal infiltrative disorders that impair the gas exchange function of the lung by disrupting the alveolar walls. In many ILDs, lung regeneration fails and interstitial fibrosis resulting from fibroblastic proliferation and excessive collagen deposition is the dominant pathologic process as a reparative response to injury of the gas-exchanging units. However, nonfibrotic processes can also cause ILDs by abnormal infiltration of the lung parenchyma (interstitium and/or alveolar spaces) by cells (e.g., eosinophils, histiocytes) or substances (e.g., amyloid). Thus ILDs comprise a broad spectrum of disorders of varying etiology with some similarities in clinical, imaging, physiologic, and pathologic features. In most ILDs, the pathologic involvement is not restricted to the "interstitium" (i.e., the anatomic space between the basement membranes of the alveolar epithelium and capillary). Some develop from identifiable causes or arise in the context of systemic diseases, such as connective tissue disease, whereas others remain idiopathic.

The exact prevalence and incidence of ILDs are unknown. Studies suggest a prevalence of 81 in 100,000 for men compared with 67 in 100,000 for women.[1,2] Similarly, the overall incidence of ILD is slightly higher in men (32 per 100,000 annually) than in women (26 per 100,000 annually) and increases with age. In the United States, the mortality rate from ILDs increased twofold from 1980 to 2014.[3]

Classification of ILDs can be based on several parameters including etiology, clinical features, histopathology, or pattern of radiologic abnormalities. A classification of ILDs based on the presence or absence of an identifiable cause (including underlying systemic disease) is likely the most practical option for clinicians and is shown in Table 89.1.[4] Alternative methods of classifying ILDs based on clinical, histopathologic, or radiologic parameters are less clinically useful because similar features can result from different ILDs (see Table 90.2). For example,

Table 89.1 Classification of Interstitial Lung Diseases

Known Cause	Unknown Cause
Connective tissue disease-related ILDs Environmental and occupational ILDs Drug- and radiation-related ILDs Smoking-related ILDs Rare forms (lymphangioleiomyomatosis, pulmonary alveolar proteinosis, amyloidosis, alveolar microlithiasis, heritable disorders, etc.)	Idiopathic pulmonary fibrosis and other IIPs Sarcoidosis Idiopathic eosinophilic pneumonias Vasculitis Rare forms (IgG4-related disease, Erdheim-Chester disease, etc.)

Ig, immunoglobulin G; IIP, Idiopathic interstitial pneumonia; ILD, interstitial lung disease.

the histopathologic pattern of *usual interstitial pneumonia* (UIP), a hallmark of IPF, can be seen in other ILDs such as chronic hypersensitivity pneumonitis, drug-induced ILD, connective tissue disease–associated ILD, and asbestosis. In other words, multiple clinical entities may result in similar histologic appearances.

A specific diagnosis can be made in many patients presenting with ILD based on the results of a careful history, physical examination, laboratory tests, and imaging findings.[4,5] Although the diagnosis of ILD due to occupational exposure, a medication, or a connective tissue disease may be obvious, idiopathic ILDs can be more difficult to diagnose using clinico-radiologic parameters alone. Bronchoscopy with *bronchoalveolar lavage* (BAL) and transbronchial biopsy can be useful in the diagnosis of some ILDs.[6] In some cases, surgical lung biopsy (thoracoscopic or open) may be required for a definitive diagnosis.[7-9] The goal of the diagnostic evaluation is to determine the cause or underlying disease whenever possible or, if not, at least a working diagnosis that allows reasonable prognostication and a management plan for the individual patient.

APPROACH TO PATIENTS WITH SUSPECTED INTERSTITIAL LUNG DISEASE

The hallmarks of an ILD are progressive dyspnea and cough, abnormal chest imaging, and impaired pulmonary function results.[4,5] The initial evaluation of a patient with suspected ILD is focused on confirming the presence of ILD, gauging the tempo of the process (duration of symptoms), and obtaining clues as to the underlying cause.[4] This is performed by assessment of demographics and findings gathered from history taking, physical examination, chest imaging, and laboratory tests. It should be noted that 5–10% of symptomatic patients eventually diagnosed as having ILD have normal chest radiographs at the time of presentation. There are also dyspneic patients with or without abnormal chest radiographs in whom routine pulmonary function tests (flows, volumes, and diffusing capacity) are normal. Some patients with ILD (e.g., sarcoidosis) on chest imaging may have no associated symptoms or pulmonary function abnormalities.

CLINICAL ASSESSMENT

Taking a careful history is of paramount importance in identifying the clinical manifestations and their temporal evolution as well as potential cause for the lung disease including exogenous agents and hereditary disorders. Persistent cough and progressively worsening exertional dyspnea are common presenting symptoms but are nonspecific and can be a feature of many pulmonary and nonpulmonary disorders. The presence of extrapulmonary symptoms may lead to the diagnosis of connective tissue disease–associated ILD. Symptoms of *gastroesophageal reflux* (GER) may suggest aspiration-related ILD.[10,11]

There are some clinical presentations characteristic of certain ILDs. For example, spontaneous pneumothorax can be the presenting manifestation or *pulmonary Langerhans cell histiocytosis* (PLCH) (see Chapter 95) or lymphangioleiomyomatosis (tuberous sclerosis–related or sporadic forms) (see Chapter 97). Hemoptysis is typical for the diffuse alveolar hemorrhage syndromes (see Chapter 94).

Symptoms in many patients with ILDs are present for months to years (i.e., chronic) and progress at varying rates. However, some ILDs are acute (days to several weeks) in presentation and often misdiagnosed as community-acquired or atypical pneumonia. Examples of acute ILDs include acute interstitial pneumonia (Hamman-Rich syndrome) (see Chapter 90), acute eosinophilic pneumonia, diffuse alveolar hemorrhage syndromes, and acute presentations (acute exacerbation) of IPF, hypersensitivity pneumonitis, drug-related ILDs, cryptogenic organizing pneumonia, and connective tissue disease–associated ILD.

Eliciting a history of tobacco use as well as of electronic cigarettes is important. Most adults presenting with PLCH, respiratory bronchiolitis, or desquamative interstitial pneumonia are smokers.[12,13] Smoking is a risk factor for rheumatoid arthritis-related ILD.[13] A subset of acute eosinophilic pneumonia is smoking-related.[14] Conversely, hypersensitivity pneumonitis infrequently appears in the active smoker.[15]

The occupational and environmental history is of obvious importance. It should be thorough and detailed because a long latency period (e.g., asbestosis) may occasionally exist between exposure and the appearance of clinical impairment and disability. Hypersensitivity pneumonitis (see Chapter 91) can manifest either as recurrent acute or subacute pneumonitis or as an insidious chronic form with slowly progressive dyspnea.

A review of the medications used in the recent and distant past is important. Uncommonly, lung disease may appear weeks to years after the drug has been discontinued (see Chapter 99). The medication history should include over-the-counter medications. For example, the nocturnal use of oily nose drops or use of mineral oil as a laxative should lead to the consideration of exogenous lipoid pneumonia.[16]

Family history is relevant for recognizing ILDs related to hereditary disorders such as tuberous sclerosis, and neurofibromatosis. Familial associations have also been identified in cases of IPF (see "Familial Pulmonary Fibrosis" later) and sarcoidosis.[17] Niemann-Pick disease, Gaucher disease, and Hermansky-Pudlak syndrome are inherited in an autosomal recessive fashion.[18]

There are ILDs with a sex predilection. Sporadic lymphangioleiomyomatosis arises almost exclusively in women. In addition, many connective tissue diseases (see Chapter 92) more commonly affect women. Occupation-related pneumoconioses are more likely in men. However, transmission of inorganic dust, either from clothes or by living in the vicinity of a manufacturing or mining facility, has resulted in asbestosis and chronic beryllium disease in women, children, and men not employed in the industry. IPF is usually encountered in middle-aged to elderly subjects and is unusual in those younger than 50 years, while sarcoidosis is typically seen in younger patients.

The most common physical finding in patients with ILD is bibasilar inspiratory crackles. For example, nearly all patients with IPF will manifest this finding. Crackles are less likely in granulomatous diseases such as sarcoidosis. Clubbing of the digits, which in most cases indicates advanced fibrotic disease, is a common finding in patients with IPF. However, the new appearance of digital clubbing in a patient with an established case of ILD could indicate an underlying bronchogenic carcinoma. With advanced fibrosis causing chronic hypoxemia, clinical signs of pulmonary hypertension and right heart dysfunction appear. Attention to extrapulmonary physical findings such as skin lesions or cardiac findings may lead to a specific diagnosis.

CHEST IMAGING

Although standard chest radiography is not as sensitive for detection of ILD as the *high-resolution computed tomography* (HRCT) scan, it is the logical starting point and the initial way of identifying and defining disease. Chest radiography allows for the initial assessment of pattern and distribution of parenchymal abnormalities and associated features such as pleural effusion or mediastinal lymphadenopathy. The predominant type of parenchymal abnormalities can be categorized as reticular or linear, nodular (small nodules), combination of linear opacities and nodules ("reticulonodular" opacities), consolidation (characterized by confluent opacities with ill-defined outer borders, air bronchograms, and obliteration or silhouetting of normal structures such as the diaphragm, heart, and intrapulmonary blood vessels), ground-glass (hazy increased opacity in which pulmonary vessels are visible but indistinct), and cystic. Linear or reticular interstitial changes are seen in most ILDs, including IPF, and are generally more prominent in the lower lung zones (Fig. 89.1).

Aside from the dominant pattern of parenchymal abnormalities, the distribution and associated findings may provide clues as to the diagnosis. For example, some ILDs characteristically present with radiographic changes that are more prominent in the upper lung zones.[4,19,20] These ILDs include sarcoidosis, PLCH, silicosis, coal worker's pneumoconiosis, and carmustine-induced pulmonary fibrosis.[4,20] Pneumothorax is often the presenting manifestation of PLCH or lymphangioleiomyomatosis. Calcified pleural plaques in a patient with interstitial opacities is indicative of asbestos-related lung disease. Pleural thickening and pleural effusion may complicate the course of the connective tissue–associated ILDs.

In patients with suspected ILD, HRCT of the chest (see Chapter 20) is more sensitive than chest radiography and enables better visualization of parenchymal details, their distribution, and associated findings (e.g., mediastinal lymphadenopathy).[4,21,22] In some ILDs, the clinical context and characteristic features seen on HRCT may be sufficient to establish a diagnosis without the need for a lung biopsy. For example, the presence of rounded, thin-walled cysts diffusely throughout both lungs in a woman with tuberous sclerosis complex is diagnostic of lymphangioleiomyomatosis and histopathologic confirmation is not necessary.



Figure 89.1 Frontal chest radiograph in a patient with idiopathic pulmonary fibrosis. Peripheral basal predominant reticulation is seen consistent with fibrotic lung disease. Note diminished lung volumes. (Courtesy Michael B. Gotway, MD.)

PULMONARY FUNCTION TESTING

Assessment of ventilatory function and the mechanical properties of the lungs, as well as gas exchange, particularly during exercise, are vital components of the initial evaluation of patients with suspected ILD (see Chapters 31–33). Although limited in diagnostic usefulness, the pulmonary function results are an important component of assessing the severity of ILD. In addition, serial measurements of function enable the physician to determine progression of the disease and the response to therapeutic interventions.

Most patients with ILDs manifest a restrictive pulmonary impairment with a reduced *diffusion capacity for carbon monoxide* ($D_{L_{CO}}$). In most patients, gas exchange is disturbed during exertion, even in those with normal gas exchange at rest. In early or mild ILD, however, pulmonary function results may be entirely normal. Obstructive pattern of impairment is commonly seen in some ILDs, including PLCH, lymphangioleiomyomatosis, sarcoidosis, and ILD superimposed on preexisting COPD/emphysema.

LABORATORY TESTS

Laboratory tests performed in patients with suspected ILD generally include a complete blood count with differential leukocyte counts, metabolic panel, and urinalysis. Anemia is frequently seen in patients with diffuse alveolar hemorrhage syndromes. Peripheral eosinophilia raises suspicion for eosinophilic pneumonias or drug reactions.

Hypercalcemia is often seen in patients with sarcoidosis. Abnormal urinary sediment suggests possible pulmonary-renal syndrome such as systemic vasculitis.

Serologic testing for connective tissue disease, vasculitis, or hypersensitivity pneumonitis may be useful depending on the clinical context and imaging findings. Serologic results should be interpreted judiciously. For example, elevated serum precipitins to certain environmental fungi indicate exposure and sensitization but do not confirm the diagnosis of hypersensitivity pneumonitis. Similarly, positive autoimmune serologic results need to be correlated to the clinical context to decipher their relevance.

BRONCHOALVEOLAR LAVAGE

BAL is a technique used to sample the distal airways via the instillation of sterile saline through a wedged fiberoptic bronchoscope (see Chapter 26). After aspiration, the contents, which are thought to represent the cellular, immunologic, and biochemical milieu of the alveolar structures, can be analyzed. The results of BAL for the evaluation of ILD have been difficult to interpret because of the prior lack of standardized techniques for both the performance of the procedure and the subsequent analysis of the data.[23-25] Furthermore, in some of the earlier studies, correlative data between BAL and lung biopsies were not obtained. Often, the treatment or smoking status of the patient was not considered.[26]

BAL can be a useful tool in evaluation of ILDs depending on the clinical context.[25] Cytologic analysis of BAL fluid can be diagnostic for malignancies and infections that mimic ILD in presentation. The finding of cloudy BAL fluid containing numerous periodic acid-Schiff–positive lipoproteinaceous bodies is seen in pulmonary alveolar proteinosis. Increased number of Langerhans cells (>5%) in BAL fluid supports the diagnosis of PLCH.[25,27] In cases of diffuse alveolar hemorrhage, red blood cells and hemosiderin-laden macrophages dominate the BAL specimen.

The differential cell profile in BAL has limited value in diagnosing specific ILDs.[25] For example, BAL lymphocytosis (>15% lymphocytes) predominates in some ILDs including sarcoidosis and hypersensitivity pneumonitis but can also be seen in many other entities including lymphocytic interstitial pneumonia, cryptogenic organizing pneumonia, pulmonary lymphoma, chronic beryllium disease, and some drug-induced or connective tissue disease–related ILDs.[25] An eosinophil level in BAL of 25% or more (normal, <2%) suggests eosinophilic pneumonia.

Other attempted applications of BAL in ILDs have included assessment of disease activity, therapeutic responsiveness, and prognosis. For example, some studies have correlated BAL lymphocytosis with a cellular histology (as opposed to fibrosis) and an improved response to treatment.[23-26] However, more recent data indicate that BAL cellular analysis has very limited value in predicting response to therapy or prognosis.[25]

LUNG BIOPSY

The final step in the evaluation of a patient with ILD is to decide whether histologic evaluation is necessary for diagnosis. As previously noted, the diagnosis of connective tissue, occupational, or drug-related ILD is often obvious after a careful history has been taken. In cases of idiopathic ILDs (see Table 89.1), the diagnosis may not be easily reached. If the clinical, imaging, and laboratory results are inconclusive, lung histopathology may be needed to reach a specific ILD diagnosis (see Table 90.3).

Transbronchial biopsy (see Chapter 26) has traditionally been performed using forceps via flexible bronchoscope and yields specimens that measure in the range of 2 to 3 mm in diameter. This procedure is relatively safe and often diagnostic in certain ILDs including sarcoidosis, diffuse malignancy, pulmonary alveolar proteinosis, and eosinophilic pneumonias.[6] Other entities, such as IPF, are less frequently confirmed by this procedure.

In recent years, a new method of bronchoscopic lung biopsy has emerged. Transbronchial cryobiopsy employs a cryoprobe and has the advantage of yielding larger specimens (≥5 mm) with less crush artifact.[28-30] However, this procedure is associated with a higher rate of bleeding and pneumothorax compared to forceps biopsy. Although the role of transbronchial cryobiopsy in the evaluation of ILD remains to be clarified, it seems likely that the use of this procedure will expand in the coming years.

The definitive method of obtaining lung tissue in the diagnostic evaluation of ILD is surgical lung biopsy, more commonly performed via video-assisted thoracoscopic surgery than thoracotomy.[4,5,31-33] However, the use of surgical lung biopsy for evaluation of ILD has been declining in recent years, in part due to concerns regarding associated morbidity and mortality.[34,35] The benefits and risks of surgical lung biopsy need to be weighed in individual patients with consideration of their personal preferences in reaching a decision regarding this procedure.

IDIOPATHIC PULMONARY FIBROSIS

Among ILDs, there is a subset of disorders referred to as *idiopathic interstitial pneumonias* (IIPs) (see Chapter 90) that comprise a heterogeneous group of diffuse parenchymal lung diseases characterized by varying patterns of inflammation and fibrosis.[32,36] Although each IIP manifests characteristic histopathology, it is crucial to be aware that the histologic pattern underlying these IIPs can also be encountered in subjects with known causes for their lung disease (e.g., connective tissue diseases, smoking, drugs). Thus the UIP pattern can be seen not only in patients with IPF but also in patients with rheumatoid arthritis (i.e., rheumatoid arthritis–related ILD (see Table 90.4).[36,37] Some interstitial pneumonia patterns are more specific with respect to etiology. For example, respiratory bronchiolitis–associated ILD in most patients is caused by smoking.[32]

IPF is the most common form of IIP and accounts for 20–30% of ILDs.[2,38,39] It is associated with characteristic clinical, radiographic, physiologic, and pathologic manifestations but is also a diagnosis of exclusion.[33,40,41] Epidemiologic studies indicate steadily increasing mortality from IPF worldwide.[42]



Figure 89.2 Usual interstitial pneumonia pattern often shows a striking subpleural distribution. This low-power photomicrograph is from an area without the usual remodeling of the lung architecture with cystic (honeycomb) changes. The visceral pleura is at the bottom of the image. (Courtesy Thomas V. Colby, MD, Mayo Clinic, Scottsdale, AZ.)

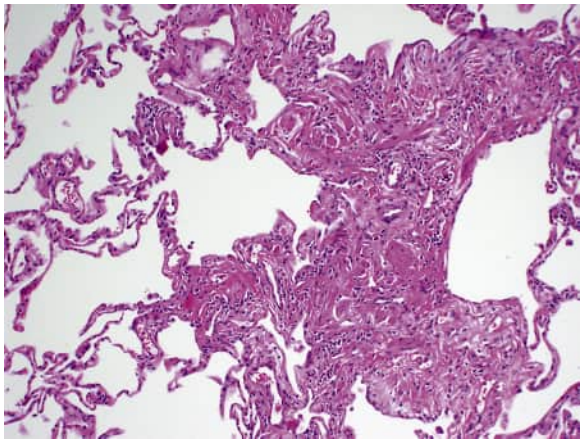

Figure 89.3 Photomicrograph of usual interstitial pneumonia. Residual lymphoplasmacytic inflammation and collagen deposition are seen broadening alveolar walls. (×10 original magnification.)

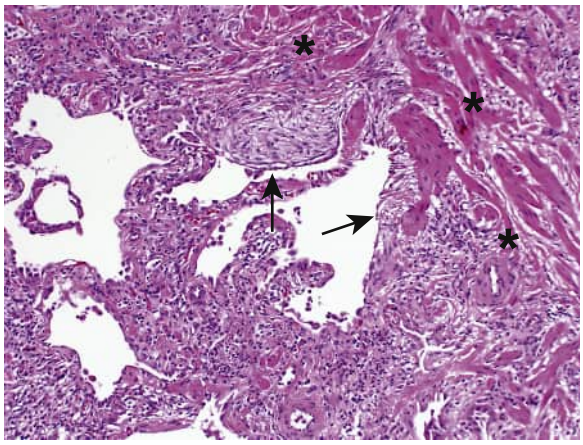

Figure 89.4 Photomicrograph of usual interstitial pneumonia. Two fibroblastic foci of loose organizing connective tissue *(arrows)* are seen adjacent to an area of dense fibrosis *(asterisks).* (Courtesy Thomas V. Colby, MD, Mayo Clinic, Scottsdale, AZ.)

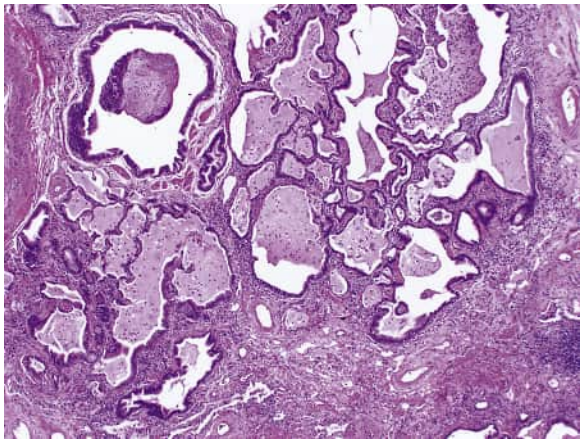

Figure 89.5 Photomicrograph of honeycomb lung in idiopathic pulmonary fibrosis. There is total disruption of the lung architecture by bands of fibrous tissue forming cystic spaces. The spaces are lined by metaplastic epithelium. (×10 original magnification.)

EPIDEMIOLOGY

The incidence and prevalence of IPF are not fully defined. A systematic review analyzing data from population-based studies in 1968 to 2012 estimated an incidence range of 3 to 9 cases per 100,000 per year for Europe and North America.[43] In a study using "narrow" case-finding criteria, the incidence of IPF in the United States was estimated to range from 0.4 to 27 per 100,000 persons; comparable figures for prevalence were 0.8 to 65 per 100,000 persons.[39] Both the incidence and the prevalence of IPF increase markedly with age, particularly over 75 years.[39]

GROSS APPEARANCE AND HISTOPATHOLOGY

The gross appearance of the lungs in IPF reveals a distinctive nodular pleural surface, sometimes resembling cirrhosis of the liver, due to contraction of the fibrotic septa. Cut sections show scarring and often abnormal cystic regions of honeycombing, typically with a lower lung zone and subpleural distribution. The histopathologic pattern seen in IPF is UIP. UIP is characterized by a pattern quite distinguishable even on low-power magnification because of its characteristic heterogeneous, predominantly subpleural and paraseptal distribution (Fig. 89.2). This striking heterogeneity is characterized by the presence of regions of residual normal or nearly normal lung tissue interspersed among extensively scarred parenchyma, which may show microscopic (i.e., not obvious grossly) honeycombing characterized by enlarged air spaces lined by bronchiolar epithelium, often filled with mucin and variable numbers of acute inflammatory cells. Abutting more densely (i.e., older) scarred areas of lung, one finds discrete active (i.e., more recent) proliferations of fibroblasts and myofibroblasts (Figs. 89.3 to 89.5).[33,36,37] These discrete areas of fibroblastic proliferation have been termed *fibroblastic foci* and are essential to the histopathologic diagnosis of UIP[37] (see Fig. 89.4), and are a reflection of active and ongoing fibroplasia. Fibroblastic foci are composed of small convex or dome-shaped collections of spindle-shaped fibroblasts and

myofibroblasts within myxoid stroma, covered by hyperplastic alveolar lining cells. Generally, interstitial chronic inflammation away from foci of honeycombing is minimal in UIP; if chronic interstitial inflammation is present in significant amounts, the diagnosis of IPF should be reconsidered and other causes of a UIP pattern such as chronic HP and collagen vascular disease should be considered. However, chronic inflammation, lymphoid aggregates with germinal centers, and even acute inflammation may be prominent around honeycomb areas, likely related to poor clearance from the areas of scarred lung.[37]

ETIOLOGIC FACTORS AND PATHOGENIC MECHANISMS

A widely held hypothesis is that IPF develops in susceptible individuals following some unknown stimulus that initiates an uncontrolled epithelial-driven cascade of events that evolve to the fibrotic process.[44] Several potential risk factors for the development of IPF have been identified. Smoking presents the most significant association with IPF, particularly for individuals who were ever smokers, with odds ratios varying from 1.6 to 9.4.[45] The same association has been found in familial pulmonary fibrosis.[46] Some occupational and environmental exposures—primarily to wood and metal dusts—have also shown increased association with IPF.[45] The presence of Epstein-Barr virus found in some patients has led to speculation that chronic viral infection might play a role in the etiology of IPF,[47] but this virus has also been found in other fibrotic lung diseases, as well as in many controls. The lungs of patients with IPF have higher bacterial loads and substantial differences in the composition and diversity of their microbiota compared with control subjects. However, the role of bacteria in the development and/or progression of IPF remains unclear.[48] A higher incidence of GER has been found in patients with IPF.[49] GER is frequent, however, in the normal population, as well as in patients with other advanced lung diseases, including cystic fibrosis, COPD, and fibrosis associated with scleroderma.[50]

The role of host genetic factors and their interactions with environmental factors leading to IPF is being elucidated. The first gene association revealed that a common polymorphism in the promoter region of the *MUC5B* gene increased the risk for sporadic IPF as well as familial pulmonary fibrosis, although the link with disease pathogenesis is unclear.[51,52] Paradoxically, it has been suggested that this polymorphism in *MUC5B* may be associated with improved survival.[53]

After this discovery, several large genome-wide association studies have revealed and confirmed a number of gene variants as risk factors, including in *MUC5B*, components of telomerase (telomerase reverse transcriptase, telomerase *ribonucleic acid* [RNA]), desmoplakin, and toll interacting protein, indicating that genes involved in host defense, epithelial integrity, DNA repair, and senescence increase the risk of developing the disease.[54-57]

One of the intriguing observations regarding IPF is that the disease is clearly associated with aging; it usually appears in individuals older than 50 years, reaching a peak in subjects of 60 to 65 years old.[44] Actually, most of the hallmarks that characterize the aging process have been identified in IPF lungs, including abnormal shortening of telomeres, genomic instability, mitochondrial dysfunction, increased oxidative stress, loss of proteostasis (i.e., homeostasis of proteins in the cell), and cellular senescence, supporting the notion that aging is a driving force of the disease.[58,59] These alterations have been revealed primarily in epithelial cells. For example, severely short telomeres, dysmorphic and dysfunctional mitochondria, and accumulation of damaged DNA have been found in alveolar epithelial cells, indicating that these cells may be the main culprit in this pathologic process.[58-61] Telomeres play a central role in cell fate and aging by adjusting the cellular response to stress and growth stimulation on the basis of previous cell divisions and DNA damage; their shortening has been associated with aging and several diseases.[62]

An important advance in our understanding of ILD has been the recognition that UIP appears to be a distinct pathophysiologic entity characterized by minimal inflammation and chronic fibroproliferation due to abnormal parenchymal wound healing.[63] This paradigm suggests that the pathologic process of UIP is the result of persistent remodeling (abnormal wound healing) of the lung parenchyma. Multiple "microinjuries" damage and activate alveolar epithelial cells, which in turn provoke a profibrotic microenvironment.[58,63] Single-cell RNA sequencing has identified unique differentiation states and gene expression patterns of epithelial cells in this disease with the up-regulation of several profibrotic pathways including HIPPO/YAP, TGF-β, and PI3K/AKT signaling pathways.[64] Accordingly, alveolar epithelial cells secrete growth factors and induce migration and proliferation of fibroblasts and differentiation into myofibroblasts. Aggregates of subepithelial fibroblasts-myofibroblasts (fibroblastic foci) and alveolar epithelial cells produce matrix-metalloproteinases 2 and 9 that may increase basement membrane disruption and allow fibroblast-myofibroblast migration into the alveolar spaces. In addition, alveolar epithelial cells induce an antifibrinolytic environment in the alveolar spaces, enhancing wound clot formation. Current evidence suggests that the epithelial assembly of the tissue factor complex (TF/FVIIa/FX) leading to factor X activation is the predominant mechanism by which the coagulation cascade is locally activated in the lungs of patients with pulmonary fibrosis.[64] Both intra-alveolar and interstitial myofibroblasts secrete extracellular matrix proteins, mainly collagens. Matrix stiffness and mechanical forces play critical roles in the progression of IPF contributing to the direct activation of myofibroblasts through mechanotransduction signaling pathways, and by integrin-mediated activation of latent TGF-β1.[65,66]

Signals responsible for myofibroblast apoptosis seem to be absent or delayed in UIP, increasing cell survival.[67] In addition to extracellular matrix proteins, these myofibroblasts produce angiotensinogen and hydrogen peroxide, which have been implicated in alveolar epithelial cell death, further impairing reepithelialization.[68,69] Although the molecular mechanisms that lead to end-stage pulmonary fibrosis are poorly understood, data support this "abnormal wound healing" hypothesis in UIP. At least in part, the abnormal communication between alveolar epithelial cells and myofibroblasts may be provoked by an aberrant recapitulation of embryologic programs.[59,70-72]

FAMILIAL PULMONARY FIBROSIS

While most cases of IPF are sporadic, pulmonary fibrosis in two or more first-degree relatives within the same biologic family may account for 2–20% of the cases overall.[73] Importantly, *familial pulmonary fibrosis* (FPF) has been associated with multiple pathologic subsets of idiopathic interstitial pneumonias (e.g., UIP [the most frequent in adults], *nonspecific interstitial pneumonia* [NSIP], and unclassifiable lung fibrosis), as well as to nonidiopathic interstitial pneumonias such as hypersensitivity pneumonitis, and connective tissue disease–related interstitial fibrosis. Moreover, discordant forms of interstitial lung disease have been found in affected individuals from 50–80% of studied families.[46,74]

The clinical, radiographic, physiologic, and morphologic manifestations of familial IPF/UIP are indistinguishable from the sporadic form of the disease, although those associated with mutations affecting telomere biology tend to present it at a younger age.[75] Geographic clustering of patients with familial IPF has been noted, suggesting a "recent founder effect," the nonrandom genetic sampling when a population derives from a small number of individuals.[76,77]

Several rare variants (defined as those with minor allele frequency of <0.1%) have been found associated with FPF. However, at present, only around 30% of the mutations associated with FPF have been identified. The most frequent gene mutations identified so far are those related to telomere biology and include rare variants in telomerase reverse transcriptase, human telomerase RNA component, dyskerin, telomere interacting factor 2, regulator of telomere elongation helicase, and nuclear assembly factor 1.[78-82] Pathogenic variants in these genes are associated with extremely short age-adjusted telomere length that may result in apoptosis or senescence.

Familial studies have also identified FPF-associated variants related to the integrity and function of alveolar epithelial cells such as genes encoding surfactant protein C and A *(SFTPC, SFTPA1, SFTPA2),* ATP-binding cassette-type 3, and thyroid transcription factor 1.[83] In general, these mutations lead to accumulation of misfolded protein resulting in increased endoplasmic reticulum stress and activation of the unfolded protein response. As mentioned for telomere-related genes, the presence of different pathologic diagnoses is also observed in patients with mutations in surfactant proteins genes. Thus NSIP, DIP, and other histopathologic disorders have been diagnosed in affected relatives sharing the same mutation, suggesting that these diseases may represent pleiotropic manifestations of the same central pathogenesis.[83-85]

Most FPF patients appear to have an autosomal dominant inheritance pattern with incomplete penetrance, indicating a significant role for rare gene variants of large effect. Evidence of aggregation of disease was highly significant among sibling pairs, and 20 pedigrees demonstrated vertical transmission, consistent with autosomal dominant inheritance.[46] Certainly, environmental factors also play a role and, for example, in one study of FPF it was found that older age, male gender, and having ever smoked cigarettes were associated with the development of IIP.[46]

CLINICAL FEATURES

IPF is generally a disease of middle-aged or older subjects, most commonly encountered in those between 60 and 75 years of age. Patients with familial pulmonary fibrosis tend to present at a younger age, as already described; otherwise, it is quite uncommon for a patient to present before the age of 40 years.[46,86,87] The typical patient presents with the insidious onset of exertional breathlessness and a persistent nonproductive cough. In some patients, cough can be debilitating. Constitutional symptoms are uncommon, but weight loss, fever, fatigue, myalgias, or arthralgia is occasionally present. Although some patients may present with only a nonproductive cough, all patients experience dyspnea with exertion as the disease progresses. Most patients have these symptoms for months to years before definitive evaluation leading to diagnosis, usually around 12 to 30 months.[88,89,89a]

The physical examination is rarely normal. Most patients have bibasilar late inspiratory fine crackles (Velcro crackles) on chest auscultation. Clubbing of the fingers is seen in 40–75% of patients and is a finding late in the disease course. Cardiac examination is usually normal except in the later stage of the disease, when findings of pulmonary hypertension (e.g., augmented P2, right-sided lift, tricuspid regurgitation, and S3 gallop) and right heart dysfunction may become evident. Similarly, cyanosis is a late manifestation indicating advanced disease. Spontaneous pneumomediastinum or pneumothorax happens rarely.

BLOOD AND SEROLOGIC STUDIES

In the diagnostic evaluation of patients with suspected IPF, laboratory tests are used to exclude other diagnostic possibilities rather than to confirm the suspected diagnosis. These other diagnostic entities include connective tissue disease–related interstitial lung disease, chronic hypersensitivity pneumonitis, and vasculitis-associated pulmonary fibrosis. Thus serologic testing relevant to these disorders is frequently sought.

It is not uncommon for such screening serologic studies for autoimmune diseases and hypersensitivity pneumonitis to yield positive results. However, positive serologic results do not necessarily confirm a diagnosis and need to be interpreted in the context of presenting clinico-radiologic findings (see Chapters 91 and 92). An elevated erythrocyte sedimentation rate, positive low-level antinuclear antibodies titer, and elevated rheumatoid factor have been identified in some patients with IPF.[90,91] The hemoglobin level, leukocyte and differential counts, and metabolic panel are usually normal.

CHEST IMAGING

Chest Radiography

The typical finding in patients with IPF is peripheral reticular opacities with a netlike appearance of linear or curvilinear densities, with predominance at the lung bases (Fig. 89.1). A coarse reticular pattern or multiple cystic or honeycombed areas (i.e., coarse reticular pattern with cystic translucencies measuring 0.3 to 1 cm in diameter, best seen in the lower and peripheral lung zones) are radiographic



Figure 89.6 Frontal chest radiograph showing characteristic features of honeycomb lung. A network of 2- to 3-mm cystic spaces is distributed throughout the lung fields. This patient with end-stage idiopathic pulmonary fibrosis also had pulmonary hypertension and was receiving oxygen through a transtracheal catheter.



Figure 89.7 Advanced idiopathic pulmonary fibrosis. High-resolution computed tomographic image shows extensive honeycomb changes.

findings that correlate with advanced fibrotic disease and poor prognosis (see Figs. 89.1 and 89.6). Reduced lung volumes are usually evident unless there is associated obstructive airway disease, as can be seen in smokers.

Pleural abnormalities are uncommon in IPF; their presence should suggest another diagnosis, such as connective tissue disease (especially rheumatoid arthritis or systemic lupus erythematosus), mitral valve disease, congestive heart failure, asbestos-related lung disease, infection, drug-induced lung disease, or lymphangitic carcinomatosis.

High-Resolution Computed Tomography

CT plays a major role in the evaluation of ILDs, including IPF.[33,40,41,92,93] HRCT is useful in the differentiation of IPF from other ILDs and the determination of the extent and severity of disease.

HRCT findings in IPF include a predominantly peripheral (subpleural) and basal distribution of the interstitial opacities.[33,40] This involvement is patchy, with areas of reticulation intermingled with areas of normal tissue, often associated with traction bronchiectasis and cystic spaces 3 to 5 mm in diameter that share walls and frequently stack on one another in several layers (i.e., honeycombing; Fig. 89.7).[40,92] Early disease may manifest as mainly patchy subpleural reticular opacities without discernible honeycombing (eFig. 89.1).[40,92] The predominantly basal nature of these abnormalities is readily appreciated with reconstructed coronal imaging (eFig. 89.2). The presence of honeycomb cysts in a bibasilar subpleural distribution is a key finding in achieving a radiologic diagnosis of IPF (eFig. 89.3). Ground-glass opacities are common but of mild severity and characteristically much less extensive than the reticular opacities.

A typical or definite UIP pattern is characterized by the combination of findings that include the *presence* of a reticular pattern with associated traction bronchiectasis, honeycombing, basal and subpleural dominant distribution with the *absence* of features that suggests an alternative diagnosis.[33,40] An alternative diagnosis would be considered if findings include extensive consolidation or ground-glass opacities, extensive mosaic attenuation with air trapping on expiratory views, diffuse nodules or cysts, pleural plaques, predominant distribution involving the upper, mid or peribronchovascular lung zones. For the diagnosis of definite UIP, the presence of honeycombing is key. If the CT demonstrates all the aforementioned features except for honeycombing, it is classified as "probable" UIP pattern.[33,40]

In some patients, radiologic features of lower lobe pulmonary fibrosis may be combined with significant upper lobe emphysema and is referred to as *combined pulmonary fibrosis and emphysema* syndrome (Fig. 89.8, eFig. 89.4, Video 89.1,).[94-96] Patients with this entity have a smoking history and are more commonly men with a mean age of 65 years. These patients manifest relatively preserved lung volumes but marked reductions in D_{LCO} on pulmonary function testing. These patients with IPF and coexisting emphysema are more likely to require long-term oxygen therapy due to severe gas exchange impairment, to develop pulmonary hypertension, and to have a worse outcome than those without emphysema.[94,97]

Other Imaging Techniques

Magnetic resonance imaging (MRI) provides inferior resolution of lung parenchyma compared to HRCT but has several advantages, including the lack of ionizing radiation and the ability to identify tissue characteristics at a nuclear level that may allow for novel assessments of lung function and microstructure.[98,99] Although MRI is not ready for use in clinical practice, MRI may eventually find a role in differentiating between inflammation and fibrotic changes in ILDs.

Functional imaging using *^{18}F-fluorodeoxyglucose* (FDG) positron emission tomography scans may have a role in IPF.[100-102] In general, the lungs of patients with IPF appear to show increased FDG uptake. Higher scores of FDG uptake in the lung seemed to correlate with severity of disease and predict worse progression-free survival.[102] Some studies have suggested that cis-4-^{18}F-fluoro-L-proline may be a reliable marker for fibrosis formation. This radioligand has been tested in patients with IPF who manifested disappointingly low pulmonary uptake, perhaps because of the slow

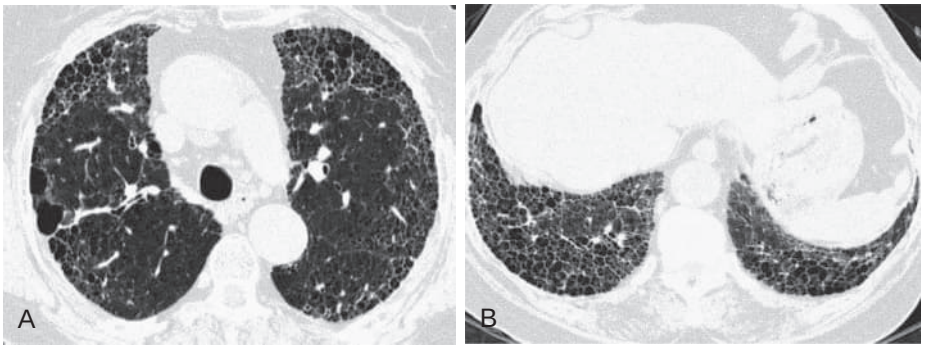

Figure 89.8 Combined pulmonary fibrosis and emphysema. Computed tomographic images from a 69-year-old woman with a 12-month history of worsening cough and dyspnea. She was a current heavy smoker. (A) Upper zones of the lungs show emphysema and mild patchy peripheral reticular opacities. (B) Lower zones of the lungs show emphysema and architectural distortion with patchy peripheral reticular opacities and extensive honeycombing lesions.

nature of fibrogenesis or the low doses of agent that must be used; as a result, this technique did not seem suitable for assessing the activity of fibrogenesis.[103]

PULMONARY FUNCTION TESTS

In most cases, IPF is associated with a restrictive pattern of pulmonary impairment with a decreased D_{LCO}. Early in the disease process, the lung volumes may be normal. As mentioned previously, smokers with emphysema who develop IPF can also manifest normal or near-normal lung volumes, even in advanced disease.[94-96] The decrease in D_{LCO} results from both a loss of the pulmonary capillary volume and the presence of ventilation-perfusion abnormalities. Resting arterial blood gases are often abnormal, revealing hypoxemia and respiratory alkalosis. The major cause of resting hypoxemia is ventilation-perfusion mismatching. With exercise, the alveolar-arterial P_{O_2} difference widens, and the arterial P_{O_2} and oxygen saturation fall. During maximal exercise, 20–30% of the exercise-induced widening of the alveolar-arterial P_{O_2} difference may be caused by a limitation of diffusion.

In patients with IPF, a significant correlation has been reported between the *6-minute walk distance* (6MWD) test and D_{LCO}, as well as maximal oxygen consumption; the 6MWD is a strong predictor of mortality.[104,105] The 6MWD test is difficult to perform in patients with advanced lung disease, however, and variability is common.

DIAGNOSIS

The diagnosis of IPF is achieved by establishing the presence of UIP by HRCT or lung biopsy in the absence of an identifiable cause, in other words, by establishing the diagnosis of idiopathic UIP.[33,40] Although surgical lung biopsy has been considered the most definitive method of obtaining diagnostic lung specimens, it should again be noted that the histopathologic findings of UIP can be seen in patients with non-IPF ILDs such as chronic hypersensitivity pneumonitis and connective tissue disease–related ILDs.[105a] Thus the clinical and HRCT features must be compatible with the diagnosis of IPF and not include findings inconsistent with this diagnosis, such as diffuse mosaic attenuation or upper lung predominance of abnormalities depicted on HRCT.

If HRCT findings represent typical/definite UIP (reticular opacities, honeycombing, and traction bronchiectasis with subpleural/basal predominant distribution) or probable UIP (reticular opacities, and traction bronchiectasis with subpleural/basal predominant distribution but without honeycombing) pattern, the diagnosis of IPF can be made without histopathologic confirmation in the presence of appropriate clinical context (i.e., age >60 years, absence of significant inhalational or medication exposure, no evidence of connective tissue disease).[40,106-109] Overall, approximately half of patients with IPF can be diagnosed without lung biopsy,[33,110-115] but this number may increase as radiologic criteria are refined.

When the findings on the HRCT study combined with clinical and laboratory features do not yield a clear diagnosis of IPF or another disorder, histopathology obtained by lung biopsy may be needed. Transbronchial lung biopsy is unlikely to yield the amount of lung tissue needed to recognize the features of UIP. However, recent reports suggest transbronchial cryobiopsy may be more informative in such patients, but requires validation and is not currently recommended by international guidelines.[28,30] In addition, molecular classifiers are becoming available that may allow a confident diagnosis of UIP on bronchoscopic biopsy specimens.[116] Surgical lung biopsy (thoracoscopic or open) is the most reliable method of obtaining adequate tissue to identify the underlying histopathologic pattern. As previously described, however, surgical lung biopsy is associated with increased in-hospital mortality.[34] Age and comorbidity are main risk factors for in-hospital mortality related to surgical lung biopsy, but a provisional diagnosis of IPF also increases this risk.[34]

Because the diagnosis of IPF requires correlation of clinical, radiologic, and sometimes histopathologic findings, a multidisciplinary discussion among clinicians, radiologists, and pathologists improves interobserver agreement and enhances diagnostic specificity.[117] As previously discussed, the presence of UIP alone, whether by HRCT or lung biopsy, does not automatically translate to the diagnosis of IPF.

THERAPEUTIC APPROACH

IPF is a progressive and fatal disorder without spontaneous remission and, until the recent introduction of antifibrotic therapy, no therapy had been shown to be effective.[118] Nonetheless, IPF remains a progressive lung disease in most patients even in the era of antifibrotic therapy. Thus it is essential that the prognostic aspects, management options, and goals of care be thoughtfully discussed with patients and family members, taking into account their individual contexts, values, and preferences. This discussion should

include advanced care planning to avoid treatments such as mechanical ventilation that may be unwanted by patients.

Era Before Antifibrotic Therapy

Although corticosteroids alone were the mainstay for the treatment of IPF for many years, there was never any randomized, placebo-controlled study to support their use.[119,120] The use of anti-inflammatory therapies in this disease was based on the earlier concept that a chronic inflammatory infiltrate led to progressive extracellular matrix deposition. However, the response to corticosteroid treatment in IPF has been almost uniformly poor.[121] In addition, significant complications can result from corticosteroid therapy, affecting the quality of life.

Because of the poor responsiveness of IPF to corticosteroids, various immunomodulatory agents (alone or in combination with corticosteroids) were tried and suggested possible benefit.[122-125] Combination therapy with prednisone, azathioprine, and *N-acetylcysteine* (NAC) was suggested for patients with mild to moderate disease and seemed to be associated with preserved *forced vital capacity* (FVC) and D_{LCO} when compared to standard therapy of prednisone plus azathioprine after approximately 1 year of follow-up.[126] However, in a subsequent study, this combination therapy (prednisone, azathioprine, and NAC) was shown to be associated with an increased rate of death and hospitalizations compared with placebo.[127] The comparison of NAC alone versus placebo also yielded negative results with no significant benefit in preventing FVC decline in patients with IPF with mild-to-moderate impairment in lung function.[128] A subsequent study suggested that toll interacting protein polymorphisms may influence the response to NAC in patients with IPF.[129]

A number of other immunosuppressive or putative antifibrotic agents have been reported in individual cases or in small groups of patients with IPF but lack evidence to support their efficacy. These agents include colchicine,[130-132] penicillamine,[132] captopril,[133] and etanercept.[134] Based on positive results from in vitro studies, animal experiments,[135] and a preliminary open, randomized trial,[136] interferon γ-1b in IPF was investigated in two large, controlled trials but yielded no difference in the primary end point (progression-free survival) or in secondary end points compared to placebo.[137-139] Similarly, bosentan, a dual endothelin-1 receptor antagonist (ET_A and ET_B), was investigated in two large, randomized, multinational, double-blind, placebo-controlled trials in patients with IPF but failed to demonstrate a benefit in primary end points (time to worsening or death) or other end points, including health-related quality of life or dyspnea.[140,141] Other agents that have failed to show efficacy in clinical trials include imatinib, a competitive tyrosine-kinase inhibitor capable of blocking the TGF-β pathway,[142] and anticoagulant therapy with warfarin.[143]

Current Era

On the basis of accumulating knowledge about the pathogenic mechanisms involved in IPF, newer antifibrotic agents have been developed and tested in patients with IPF.

Pirfenidone. Pirfenidone (5-methyl-1-phenyl-2-[1H]-pyridone) is a novel antifibrotic agent that inhibits the progression of fibrosis in animal models. Several clinical trials showed promise in stabilizing lung function and reducing the number of patients with IPF who experienced acute exacerbation.[144,145] In a randomized clinical trial from Japan, the high-dose pirfenidone group had better progression-free survival than the placebo group.[146] Two international randomized clinical trials of pirfenidone enrolled 435 and 344 IPF patients, respectively.[147] In one of these trials, pirfenidone achieved the primary end point of reducing decline from baseline in percent-predicted FVC. The second trial did not meet this primary end point. A subsequent phase III randomized, double-blind, placebo-controlled trial evaluating pirfenidone in patients with IPF observed reduced disease progression as reflected by lung volume, exercise tolerance, and progression-free survival.[148]

As a result of these positive trials, pirfenidone is approved for the treatment of IPF in the United States, Canada, Europe, Japan, and many other countries. The usual dosing is 267 mg 3 times daily by mouth, which is increased weekly to 801 mg 3 times daily by the third week. The main adverse effects are gastrointestinal and hepatic; patients often develop a photosensitivity skin rash.

Nintedanib. Nintedanib (BIBF-1120) is a tyrosine kinase inhibitor that targets the platelet-derived growth factor receptor, vascular endothelial growth factor receptors, and fibroblast growth factor receptors.[149] A 12-month, randomized, double-blind, placebo-controlled, phase II trial with 432 IPF patients included four groups assigned to different doses of nintedanib.[150] The primary end point was the annual rate of decline in FVC. A trend toward a reduced decline of lung function with fewer acute exacerbations and preserved quality of life was associated with the highest-dose (150 mg twice daily) regimen. In two subsequent replicate phase III, multinational, randomized, placebo-controlled, parallel-group trials (INPULSIS-1 and INPULSIS-2), nintedanib slowed disease progression by significantly reducing the rate of decline in FVC.[151]

As a result of these data, nintedanib has been approved for the treatment of IPF in the United States, Canada, Europe, Japan, and many other countries. The usual dosing of nintedanib is 150 mg by mouth twice a day. The main adverse effects are gastrointestinal and hepatic.

In sum, both pirfenidone and nintedanib reduce the rate of FVC decline by approximately 50% over 1 year of treatment in patients with IPF. Pooled data analyses and post hoc analyses suggest these drugs may improve quality of life, reduce the rate of hospitalizations and acute exacerbations, and prolong survival.[152-156] A recent real-world retrospective cohort analysis using a large insurance database suggested the use of these medications reduced risk of all-cause mortality (hazard ratio 0.77) for up to 2 years with no significant difference between the two drugs.[157] Studies to date suggest the adverse effects of these medications are manageable for the majority of patients with a reasonable long-term tolerability profile.[155,158,159] Combination therapy with both pirfenidone and nintedanib is being explored.[160]

There are additional pharmaceutical agents currently being investigated as potential therapies for IPF. A phase II study of recombinant human pentraxin 2, an inhibitor

of monocyte differentiation into profibrotic fibrocytes and TGF-β1 production, has shown some early promising results in slowing the decline of lung function in patients with IPF.[161] GLPG1690 (Galapagos), a potent inhibitor of autotaxin, an enzyme thought to play a role in fibrogenesis, is currently undergoing clinical trials.[162]

Lung Transplantation (see Chapter 140)

Since the late 1980s, lung transplantation has been used for the management of a wide range of severe lung disorders with progressive impairment unresponsive to pharmacologic treatment, with evidence supporting an improved quality of life and survival benefit.[163-165]

Given the scarcity of donors, along with the age considerations and comorbidities seen in IPF patients, transplantation is indicated only in carefully selected patients. The International Society for Heart and Lung Transplantation has published updated guidelines for the selection of IPF patients who should be considered potential transplant candidates.[166] Early referral for consideration of transplant is highly desirable, particularly for those who have progressive disease (including oxygen desaturation at rest or with exercise). It allows an orderly process for assessment, management of issues of concern, and patient education before active listing. Extracorporeal membrane oxygenation may be an option for selected patients who have developed acute respiratory failure and are candidates for lung transplantation.[167]

According to the 2012 International Society for Heart and Lung Transplantation/United Network of Organ Sharing International Registry, the 1- and 5-year survival rates following lung transplantation for IPF were 84% and 48%, respectively.[168] Telomere length less than the tenth percentile may be associated with worse survival and shorter time to onset of chronic lung allograft dysfunction.[169] Survival after lung transplantation for IPF appears to be worse than for other indications, and some studies have suggested that survival may be improved by double-lung transplant.[170] However, a study using registry data showed no difference between patients who had single- and double-lung transplant when adjusted for baseline differences.[171]

MANAGEMENT OF COMORBIDITIES AND PALLIATIVE CARE

The clinical course and management of patients with IPF may be complicated by comorbidities. These include GER disease, pulmonary hypertension, sleep-related breathing disorder, lung cancer, and other issues.

Gastroesophageal Reflux

Although GER is common in patients with IPF, it is not clear how aggressively to pursue this diagnosis and to treat GER in patients with IPF.[172-175] There is some evidence suggesting a clinical benefit in those patients with IPF treated with proton-pump inhibitors or histamine 2 receptor blockers.[49,176-178] However, other studies have cast doubt on the beneficial effects of antacid therapy in IPF.[173,179-182] A randomized, controlled trial (n = 58) assessed the effect of laparoscopic antireflux surgery in patients with IPF and abnormal acid GER and found a lower rate of acute exacerbation, respiratory-related hospitalization, and death in the surgery group (n = 29), but the difference was not statistically significant compared to the nonsurgery group (n = 29) in this small study.[182a] It is unknown if other measures used in the management of GER, such as lifestyle modifications (e.g., small meals, avoidance of certain foods and alcohol), and other pharmaceutical interventions (e.g., prokinetics) have a role in the treatment of patients with IPF.[178,183]

Pulmonary Hypertension

Pulmonary hypertension due to IPF (PH-IPF) is relatively common (32–85% of patients) and may contribute substantially to functional status, quality of life, morbidity, and mortality (see Chapter 85).[184-189] As previously described, patients with combined pulmonary fibrosis and emphysema syndrome are at increased risk for the development of PH.

The most appropriate method to detect PH noninvasively is transthoracic (Doppler) echocardiography. However, echocardiography may be inaccurate in estimating pulmonary arterial systolic pressure in patients with ILD.[190,191] Right heart catheterization is the gold standard for the hemodynamic evaluation of the pulmonary circulation and the diagnosis of PH. Abnormalities in gas exchange and exercise capacity seem to have a significant association with PH-IPF. Thus exaggerated exercise-related oxygen desaturation and out-of-proportion reduction of D_{LCO} should raise suspicion of PH.[184,189] Brain natriuretic peptide concentration may also be helpful in predicting the presence of moderate to severe PH in patients with IPF.[192,193] In addition, a ratio of the main pulmonary artery to ascending aorta diameter greater than 1 on chest CT images also raises the suspicion for PH.[194,195]

Supplemental oxygen is the most obvious choice for prevention or treatment of PH; however, there are no data supporting favorable effects of oxygen on survival in PH-IPF. Vasoactive agents are being studied, but one must recognize that decreased physiologic vasoconstriction in low ventilation-perfusion lung units may worsen shunt and hypoxemia in IPF.[187,189,196] To date, pulmonary vasoactive agents, including ET-1 receptor antagonists, prostacyclin (prostaglandin I_2) analogs, and phosphodiesterase-5 inhibitors, have been associated with short-term functional improvement in some studies, but long-term benefits including improved survival have not been demonstrated.[196-201]

Sleep-Related Issues

Many patients with IPF, especially those with low daytime arterial oxygen saturation or a history of snoring during sleep, develop sleep disturbances characterized by reduced rapid eye movement sleep, lighter and more fragmented sleep, and hypoxemia during rapid eye movement sleep.[202-204] The prevalence of obstructive sleep apnea is increased in the IPF population.[202] An increased body mass index and a significant impairment in pulmonary function testing may be predictors of obstructive sleep apnea in these patients.[205] However, severe hypoxemia can be seen in the absence of obstructive sleep apnea or changes in breathing pattern. Nocturnal hypoxemia is common in patients with IPF and has an adverse effect on

quality of life.[202,206] It may also contribute to the development of PH. Identification and correction of the sleep disturbance may reduce morbidity and improve quality of life and patient survival.

Lung Cancer

Bronchogenic carcinoma (all histologic types; most commonly squamous cell carcinoma) has been identified with increased frequency in advanced IPF (eFig. 89.5).[207-213] These cancers tend to arise in peripheral lung zones involved with fibrosis.[207,212-214] It has been postulated that carcinoma arises from the metaplastic bronchiolar epithelium found in these patients, but the pathogenic mechanisms are unclear.[208] The risk of lung cancer in patients with IPF is several-fold higher compared to the general population.[211,212] One recent study identified a smoking history of 35 pack-years or more and coexisting emphysema as risk factors for the development of lung cancer in these patients.[212] Not surprisingly, the development of lung cancer increases the risk of death.[215-217] Furthermore, surgical resection and nonsurgical therapies are associated with a high prevalence of adverse events, including acute exacerbation of IPF.[215,218,219]

Other Comorbidities

Because most patients with IPF are of older age, there are other commonly encountered comorbidities, including cardiovascular diseases such as ischemic heart disease and venous thromboembolism.[216,220,221] These comorbidities need to be identified and managed appropriately because they may shorten survival and worsen quality of life.[216,217,222,223]

Rehabilitative and Palliative Care

In recent years, more attention has been focused on rehabilitative therapy and palliative care in the management of patients with IPF.[223a] Participation in a pulmonary program has been shown to improve dyspnea, fatigue, 6MWD, and quality of life.[224-230] The beneficial effects of pulmonary rehabilitation appear to be more pronounced in patients with worse baseline functional status.[229,231]

Cough can be a debilitating symptom for patients with IPF. A systematic review on the management of cough in ILDs noted a paucity of antitussive treatment options for these patients and suggested gabapentin, opiates, and speech therapy as possible options.[232] In a small crossover trial, thalidomide improved cough in patients with IPF.[233] A pilot clinical trial suggested a reduction in cough with omeprazole therapy compared to placebo in patients with IPF.[234] In an uncontrolled observational study, pirfenidone treatment was associated with improvement in measures of cough.[235] Further research is needed in assessing the efficacy of these agents for antitussive effects in IPF.

Similarly, breathlessness is a common source of suffering for patients with ILDs. Moderate doses of opioids and benzodiazepines can be used in patients with ILDs to relieve distressing symptoms, including breathlessness.[236] In a progressive disease such as IPF, early institution of integrated palliative care may help both the patients and their caregivers by improving the quality of life as well as the quality of dying.

PROGNOSIS

Although the natural history of IPF has not been fully defined, data thus far suggest the median survival after diagnosis is approximately 3 years.[33,41,93,237-241] Long-term survival in IPF is distinctly poor, with only a 20–35% survival 5 years after diagnosis.[237,240-242] Clinical deterioration in patients with IPF is expected, even in patients on antifibrotic therapy (although it may be slower in this group). Most patients experience episodes of worsening shortness of breath, decreased exercise tolerance, or other declines in functional status during the course of their illness.[237,239,242,244] Disease progression may be difficult to distinguish from disease-associated complications and adverse effects of therapy.[245-247] Frequent hospitalizations for respiratory problems are common events and are often associated with death.[239,242,248]

In a study of 42 consecutive IPF patients who died over a 9-year period, autopsies showed that IPF by itself was the immediate cause of death in half of the patients either from an acute exacerbation (see "Acute Exacerbations of Idiopathic Pulmonary Fibrosis" later) or from the gradual progression of the disease.[247] Other respiratory causes of death included pneumonia and aspiration. Cardiovascular disease including arrhythmia, myocardial infarction, and severe right heart dysfunction, was found to be the cause of death in 20% of subjects. Evidence of pulmonary hypertension was present on autopsy in 45% of patients and was the immediate cause of death in two of them. Pulmonary embolism appears to be relatively common in IPF lung transplant recipients, although its prevalence is unknown.[249] Importantly, it has been shown that patients with IPF have a higher prevalence of coronary artery disease.[250] Also, patients with clinically stable IPF exhibit not only right ventricle diastolic and systolic dysfunction but also impaired left ventricle diastolic filling, while the systolic function is preserved.[251]

Staging of IPF and Predicting Outcome

The rate of progression is variable among patients with IPF.[239,248,252] Thus prognostication for individual patients diagnosed to have IPF is difficult. Various parameters, singly or in combination, have been correlated with prognosis.

Demographic and clinical factors have been correlated with prognosis. Mortality rates are higher in men, higher with increasing age, and highest in the winter, even when infections are excluded.[239,252–254,254a] The *Medical Research Council* (MRC) Chronic Dyspnea Score estimated at the time of diagnosis is predictive of survival and may aid clinicians in assessing the prognosis of new cases of IPF.[255]

Immunologic markers, including autoantibodies, elevated sedimentation rates, circulating immune complexes, and increased serum immunoglobulins, have not been shown to correlate with the overall natural history of IPF. Serum surfactant protein (SP)-A and SP-D may have prognostic value for mortality in patients with IPF.[256] One study showed that after controlling for known clinical predictors of mortality, an increased serum SP-A level is a strong and independent predictor of early mortality among patients with IPF. A prediction model containing SP-A and SP-D was substantially superior to a model with clinical predictors alone.[257] Also, serum chemokine

ligand 18 concentrations seem to have a predictive value in IPF with higher mortality observed in patients with concentrations above 150 ng/mL.[258] At present, however, there is no biomarker signature proven to be predictive of outcome in this disease.

Chest imaging features have also been correlated with prognosis. Chest radiography is relatively insensitive in detecting progression in IPF and may demonstrate no changes despite clinically apparent physiologic deterioration. Another major problem with using chest radiography to follow the disease course or to estimate the stage of disease is that there is considerable interobserver variability in the interpretation of these studies. However, HRCT scanning in IPF depicts anatomic details better and may be useful in assessing and staging disease. The finding of a greater extent of ground-glass opacities and a lower extent of reticular opacities on the initial HRCT identifies those patients with early disease who are the most likely to survive longer[259] compared to those with a typical HRCT appearance of UIP (including honeycombing) who experience higher mortality.[260] In addition, a greater extent of fibrosis visually scored on HRCT predicts greater short-term mortality.[261,262] More recently, computer-based quantification of disease on HRCT has been investigated to aid in prognostication and has shown promise in this regard.[263-265]

Physiologic assessment with pulmonary function testing is a common component of determining disease severity at baseline and during the clinical course, allowing the assessment of response to therapy. Reductions in the vital capacity correlate with the degree of fibrosis present and show a relationship with the overall histologic derangements.[239,252,266] In general, severe pulmonary function impairment at baseline as assessed by FVC and D_{LCO} predict a higher mortality rate.[239,252,266] A marked reduction of the D_{LCO} and resting hypoxemia are associated with pulmonary hypertension and decreased survival.[187] Likewise, changes in D_{LCO}, total lung capacity, FVC, arterial P_{O_2}, oxygen saturation, and alveolar-arterial P_{O_2} difference during follow-up are predictive of survival time after adjustment for baseline values.[267,268]

BAL constituents may reflect the state of the pulmonary inflammatory response. IPF is characterized by a several-fold increase in the total number of inflammatory cells with an increase in the percentage of neutrophils and eosinophils.[25] However, studies evaluating the association of BAL fluid cellular constituents and mortality have yielded conflicting results and were limited by the size of the study cohort and duration of follow-up. In one study, it was found that SP-A in BAL is reduced in IPF, and decreases in its concentration referenced to total phospholipid (a marker of surfactant to normalize to the surface sampled by lavage and recovery) predict an adverse clinical outcome and poorer survival.[256] At present, evaluation of BAL fluid constituents has no role in determining the prognosis in IPF.

Histologic features, other than end-stage fibrosis and honeycombing, have not been shown to correlate with survival in UIP.[269] It has been proposed that an early and characteristic manifestation of active and ongoing lung injury in UIP is the presence of multiple fibroblastic foci.[37] The prognostic significance of these aggregates of fibroblasts and myofibroblasts in surgical lung biopsies from patients with IPF is unclear, and several studies quantifying them have given contradictory results.[270-274] The effect of sample size, tissue sampling bias, and the different techniques for assessing the number of foci may account for these results. Overall, detailed quantification of fibroblast foci on surgical lung biopsies may not be a useful or consistent predictor of patient survival in this disease.

Composite prediction models have been designed to help predict the clinical course and prognosis of IPF.[252,266,269,275–277] Some of these composite models require detailed radiographic analysis or exercise physiologic measurements, neither of which is readily available to many physicians and limit their utility in clinical practice.[269,275] Ley and colleagues[266] proposed a multidimensional prognostic staging system (GAP model) for IPF using only commonly measured clinical and physiologic variables (age, gender, FVC, and D_{LCO}). A simple-to-use staging system such as this may help estimate prognosis and guide management decisions such as those about the appropriate timing of lung transplantation. The CT fibrosis score may be able to replace the D_{LCO} measurement in this model.[278] In addition, including comorbidities in the GAP model may improve the discriminative performance in assessing the risk of death.[217]

Acute Exacerbations of Idiopathic Pulmonary Fibrosis

Some patients with IPF (as well as other chronic ILDs) may experience a rapid deterioration in respiratory status after a period of relative stability.[239,279,280] This acute worsening, termed *acute exacerbation,* may be related to viral or bacterial infection, aspiration, or thromboembolism. However, many of these acute clinically significant episodes do not have an identifiable trigger. The incidence of acute exacerbations in the IPF population has been reported to range from 4–15% at 1 year.[242,279,281,282]

An International Working Group Report updated the definition and diagnostic criteria for acute exacerbation of IPF.[279] This revised definition is "an acute clinically significant respiratory deterioration characterized by evidence of new widespread alveolar abnormality." The diagnostic criteria include (1) previous or concurrent diagnosis of IPF, (2) acute worsening or development of dyspnea typically less than 1 month duration, (3) CT with new bilateral ground-glass opacity and/or consolidation superimposed on a background pattern consistent with UIP pattern (eFig. 89.6A–F), and (4) deterioration not fully explained by cardiac failure or fluid overload.[279] In contrast to an earlier definition of acute exacerbation,[283] the updated definition allows for inclusion of episodes with an identifiable trigger including respiratory infection, aspiration, drug toxicity, and surgical procedures. Histologic evaluation is not required to diagnose acute exacerbation; however, when tissue is encountered by biopsy or autopsy in this setting, it typically shows diffuse alveolar damage superimposed on underlying UIP. Occasionally, other patterns of acute lung injury may be seen, such as organizing pneumonia and extensive fibroblastic foci.[284–287]

Although some acute exacerbations, as currently defined, have an identifiable trigger such as pneumonia, the etiology and pathogenesis of this phenomenon remain mostly unclear.[279] A role for occult viral infection and

microaspiration has been suggested.[279,288–290] Disordered epithelial cell integrity, acute inflammation, excessive cytokines and matrix metalloproteinases, and an antifibrinolytic alveolar milieu are all likely involved.

Once infections and other treatable causes of worsening have been excluded, management of acute exacerbation has generally consisted of enhanced immunosuppression with pulse doses of methylprednisolone (0.5 to 1 g/day), sometimes combined with another immunosuppressive agent, such as cyclophosphamide or cyclosporine, but no convincing evidence of benefit has been demonstrated.[279,291–293] There have been reports of potential benefit from the use of direct hemoperfusion with a polymyxin B–immobilized fiber column,[294] which would bind circulating endotoxin, cytokines and growth factors, and neutrophil elastase inhibitors.[293] Unfortunately, no data from controlled trials have proved the efficacy of any treatment for this condition.[279,295]

Key Points

- *Interstitial lung diseases* (ILDs) comprise a heterogeneous group of diffuse infiltrative lung diseases that disrupt the alveolar-capillary interface, leading to hypoxemia.
- ILDs are encountered in diverse clinical settings; the majority of patients will have an identifiable cause, including occupational, environmental, drug or other exogenous exposures, connective tissue diseases, and hereditary disorders, while others remain idiopathic.
- In some patients with ILDs, correlation of the clinical context (detailed history and examination along with relevant laboratory results) and radiologic features can establish the likely diagnosis; in others, histopathologic examination of lung tissue may be necessary to identify a specific diagnosis.
- *Idiopathic pulmonary fibrosis* (IPF) is one of the most common ILDs and is progressive, irreversible, and usually fatal, with a portion of these deaths attributed to the phenomenon of "acute exacerbation."
- Antifibrotic agents, pirfenidone and nintedanib, have been shown to slow progression in IPF and have been approved by the U.S. Federal Drug Administration for the treatment of IPF. In contrast, anti-inflammatory agents, such as corticosteroids, have not been of benefit.
- Comprehensive care of patients with IPF, a progressive disorder, includes management of comorbidities and counseling of patients and family members regarding prognostic aspects, management options, and goals of care that take into account their individual contexts, values, and preferences.

Key Readings

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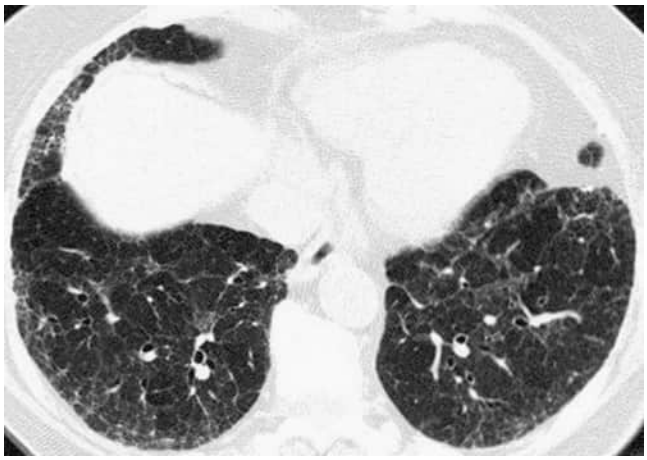
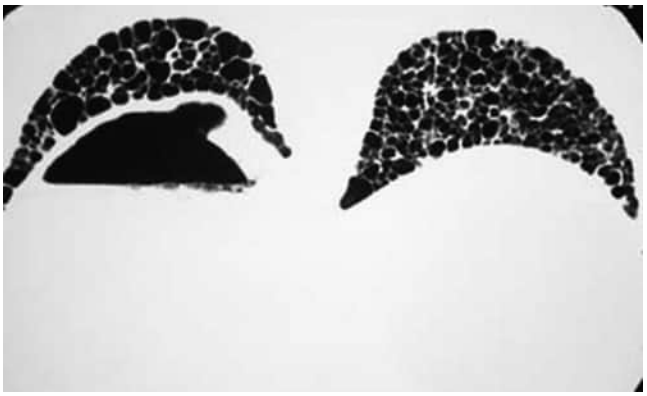
Complete reference list available at ExpertConsult.com.

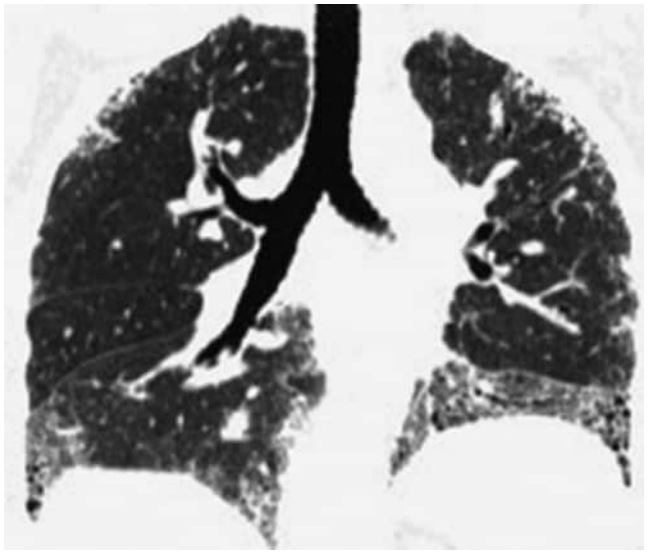




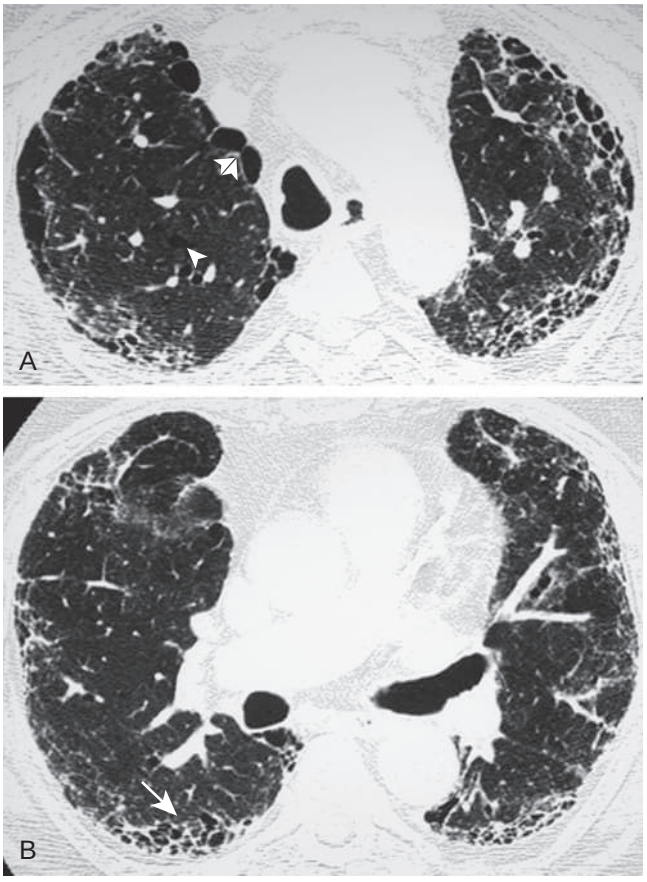
eFigure 89.1 Computed tomography of "early" usual interstitial pneumonia/idiopathic pulmonary fibrosis. Axial chest computed tomography through the lung bases shows subpleural reticulation and architectural distortion with areas of traction bronchiectasis, but no discrete honeycombing is visualized. (Courtesy Michael B. Gotway, MD.)



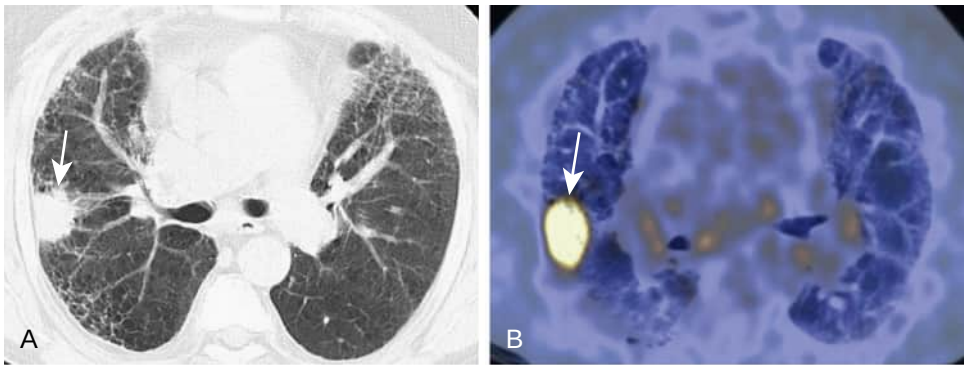
eFigure 89.3 Honeycombing on high-resolution computed tomography in usual interstitial pneumonia/idiopathic pulmonary fibrosis. Axial prone chest computed tomography through the lung bases shows extensive subpleural cystic change consistent with honeycomb lung. Note how the cyst walls are visible, are mildly thickened (measuring 1 to 2 mm), and share walls with one another. (Courtesy Michael B. Gotway, MD.)



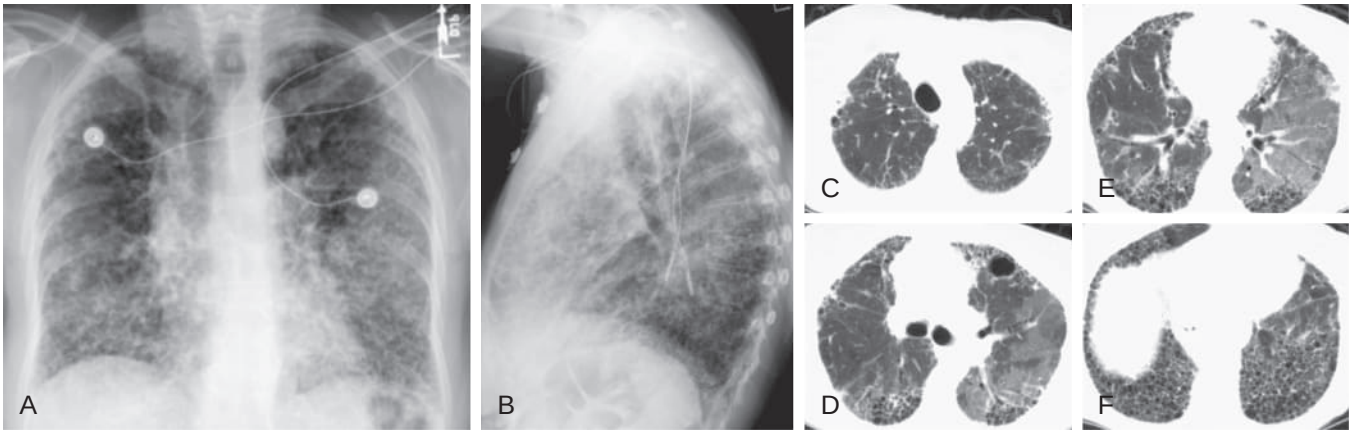
eFigure 89.2 Value of coronal computed tomography for demonstrating the basal distribution of pulmonary findings in interstitial pneumonia/idiopathic pulmonary fibrosis. Coronal chest computed tomography shows subpleural reticulation and basal predominant honeycombing. This single image captures the basal predominant nature of the high-resolution computed tomography findings in patients with idiopathic pulmonary fibrosis. (Courtesy Michael B. Gotway, MD.)



eFigure 89.4 Combined pulmonary fibrosis and emphysema. Axial chest computed tomography through the upper lungs (A) and lung bases (B) shows centrilobular *(single arrowhead)* and paraseptal *(double arrowheads)* emphysema, with basal predominant reticulation, architectural distortion, and honeycombing (*arrow*), the latter consistent with interstitial pneumonia/idiopathic pulmonary fibrosis. (See Video 89.1 for another example from a different patient.) (Courtesy Michael B. Gotway, MD.)



eFigure 89.5 Computed tomography (CT) and positron emission tomography (PET)-CT in idiopathic pulmonary fibrosis with coincident lung carcinoma. Axial chest CT (A) shows basal, subpleural reticulation and traction bronchiectasis representing idiopathic pulmonary fibrosis. A subpleural nodule (*arrow,* A) is present, representing lung carcinoma. Fused image from PET-CT (B) shows increased tracer utilization within the nodule (*arrow,* B), as well as faint tracer uptake within the areas of fibrotic lung disease. (Courtesy Michael B. Gotway, MD.)



eFigure 89.6 Chest radiography and computed tomography of acute exacerbation in idiopathic pulmonary fibrosis. Frontal (A) and lateral (B) chest radiographs show multifocal, bilateral reticular abnormalities, with cystic change most evident in the posterior and inferior lung bases on the lateral radiograph (B), consistent with fibrotic changes in a patient with idiopathic pulmonary fibrosis. In addition to these findings, more widespread areas of increased attenuation as well as a generalized nodular appearance are evident. Axial chest computed tomography images in the upper (C), mid (D), and lower (E) lungs, as well as the extreme lung bases (F), show peripheral predominant fibrotic changes consistent with idiopathic pulmonary fibrosis. However, extensive areas of ground-glass opacity are evident, particularly in the left mid (D) and lower (E) lungs, and are consistent with an acute lung injury pattern and not fibrosis. (Courtesy Michael B. Gotway, MD.)

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90 NONSPECIFIC INTERSTITIAL PNEUMONITIS AND OTHER IDIOPATHIC INTERSTITIAL PNEUMONIAS

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INTRODUCTION
MAJOR IDIOPATHIC INTERSTITIAL PNEUMONIAS
Nonspecific Interstitial Pneumonia
Cryptogenic Organizing Pneumonia
Acute Interstitial Pneumonia
Respiratory Bronchiolitis–Associated Interstitial Lung Disease and Desquamative Interstitial Pneumonia
RARE IDIOPATHIC INTERSTITIAL PNEUMONIAS
Idiopathic Lymphocytic Interstitial Pneumonia
Idiopathic Pleuroparenchymal Fibroelastosis
KEY POINTS

INTRODUCTION

The *idiopathic interstitial pneumonias* (IIPs) are a heterogeneous group of eight diffuse parenchymal lung diseases characterized by varying patterns of inflammation and fibrosis.[1,2] *Idiopathic pulmonary fibrosis* (IPF), the most common IIP, is discussed in detail in Chapter 89. This chapter describes the remaining seven IIPs with a focus on the distinct clinical, radiologic, and histopathologic patterns of each disease.

The classification, diagnosis, understanding of the pathogenic mechanisms, and management of IIPs continue to evolve.[1,3,4] The classification was most recently updated in 2013 in a joint statement by the American Thoracic Society and the European Respiratory Society.[1] In this update, the IIPs were classified into major and rare IIPs, with the major IIPs further categorized by disease behavior (Table 90.1). The IIPs have overlapping but ultimately distinct presentations (Tables 90.2 and 90.3), and they can be distinguished from other forms of *interstitial lung disease* (ILD) by clinical methods including history, physical examination, chest radiologic and laboratory studies, and histopathology. Establishing an accurate diagnosis is crucial because, despite their similarities, each of these diseases has a different treatment and prognosis.

Accurate diagnosis of any IIP can be challenging. Clinicians must be aware that the radiologic and histopathologic patterns seen in the IIPs can be encountered in patients with known, identifiable causes of their lung disease (Table 90.4). For example, *usual interstitial pneumonia* (UIP) on histopathology can be seen not only in patients with IPF but also in patients with rheumatoid arthritis as a form of rheumatoid arthritis–associated ILD.[5,6] In addition, the interstitial pneumonia patterns are associated with varying degrees of specificity with respect to etiology. For example, *respiratory bronchiolitis–associated ILD* (RB-ILD) in most patients is caused by smoking, whereas *organizing pneumonia* (OP) can be associated with a broad spectrum of causes, including infections, aspiration, drug reactions, connective tissue disorders, eosinophilic lung disease, and many others.[7-12]

This chapter presents an approach for the evaluation of patients with an emphasis on the IIPs. Despite the challenges, a specific diagnosis can be made in many patients by integrating the results of a careful history, selected laboratory results, and radiologic and histopathologic data. A dynamic, integrated approach to diagnosis through a *multidisciplinary discussion* including clinicians, radiologists, and pathologists is considered the gold standard for the diagnosis of ILDs and can be particularly helpful to diagnose IIPs.[1,13,14]

MAJOR IDIOPATHIC INTERSTITIAL PNEUMONIAS

NONSPECIFIC INTERSTITIAL PNEUMONIA

Idiopathic *nonspecific interstitial pneumonia* (NSIP) was recognized first as a provisional diagnosis in 2002 and subsequently as a distinct disease state in 2008.[13,15] Originally, NSIP referred to a histopathologic categorization reserved for surgical lung biopsies that did not demonstrate a clearly identifiable histologic pattern consistent with another IIP.[16] Although the histopathologic pattern of NSIP is found in a wide variety of diseases of known cause (e.g., hypersensitivity pneumonitis, drug-related disorders, acquired immunodeficiency syndrome, and collagen-vascular diseases),[15] idiopathic NSIP is a specific disease entity with a unique clinical presentation and overall good prognosis. Many

Table 90.1 Classification of Idiopathic Interstitial Pneumonias

MAJOR IDIOPATHIC INTERSTITIAL PNEUMONIAS			
Chronic Fibrosing IPs	**Acute/Subacute IPs**	**Smoking-Related IPs**	**RARE IDIOPATHIC INTERSTITIAL PNEUMONIAS**
Idiopathic pulmonary fibrosis (see Chapter 89) Nonspecific interstitial pneumonia	Cryptogenic organizing pneumonia Acute interstitial pneumonia	Respiratory bronchiolitis–associated interstitial lung disease Desquamative interstitial pneumonia	Idiopathic lymphocytic interstitial pneumonia Idiopathic pleuroparenchymal fibroelastosis

IPs, interstitial pneumonias.

patients diagnosed with idiopathic NSIP meet the case definition of undifferentiated connective tissue disease, a finding suggesting that idiopathic NSIP may actually be a form of autoimmune disease.[17,18] In addition, it is estimated that up to 15–20% of patients with newly diagnosed ILD either have an occult connective tissue disease or subsequently develop a clinically overt connective tissue disease. In this group of patients, the initial clinical presentation may be essentially indistinguishable from that of several IIPs, especially NSIP.[19]

Clinical Features

The presentation with respect to time course and symptoms is quite similar to that of other forms of IIPs (see Tables 90.2 and 90.3). Most patients are middle-aged adults with a subacute onset of symptoms approximately 8 months before diagnosis.[15,16,20] In contrast to IPF, up to two-thirds of the patients are female, and 70% are never smokers.[15] Cough and dyspnea are the main clinical manifestations.

Laboratory Features

Serologic abnormalities (antinuclear antibodies and rheumatoid factor) are common. *Bronchoalveolar lavage* (BAL) findings do not discriminate between UIP and NSIP and have no prognostic value.[21]

Pulmonary function testing typically shows a restrictive ventilatory defect and gas-exchange abnormalities.

Radiologic Features

Chest Radiography. In patients with early NSIP, the chest radiograph may be normal. In advanced disease, bilateral reticular or hazy opacities (eFig. 90.1) are the most prominent abnormalities. The lower lung lobes are more frequently involved, but an obvious apical-basal gradient, as seen in UIP, is often absent.[15,16]

Computed Tomography. The characteristic radiologic features of idiopathic NSIP are lower lung-zone–predominant reticular opacities, traction bronchiectasis, and lobar volume loss.[15] Ground-glass attenuation is present in nearly one half of the cases (Fig. 90.1). Other findings in advanced NSIP include subpleural cysts (eFig. 90.2). Compared with those of UIP, these cysts are smaller and limited in extent.[22] The major *computed tomography* (CT) differential diagnosis for NSIP is UIP. Favoring the diagnosis of NSIP are the following findings: homogeneous lung involvement without an obvious apical-basal gradient, extensive ground-glass opacities, a finer reticular pattern, and micronodules. NSIP, as compared with UIP, can also demonstrate subpleural sparing in 20% of cases.[15] Importantly, during follow-up, ground-glass opacities in patients with NSIP usually do not evolve to areas of honeycombing. By contrast, progression of ground-glass opacities to honeycombing is common in UIP and indicates irreversible fibrosis.[23] If honeycombing is present, an alternative diagnosis should be considered.

Histopathologic Features

The histopathologic pattern of NSIP is characterized by temporally and spatially homogeneous lung involvement. This homogeneity is a key feature in differentiating the NSIP pattern from the UIP pattern. It is characterized by varying degrees of inflammation and fibrosis, with some patients having a primarily chronic inflammatory or cellular pattern (cellular NSIP) but most cases revealing a mixed cellular-fibrotic pattern (fibrotic NSIP)[15,16] (Figs. 90.2 and 90.3). Cellular NSIP exhibits uniform alveolar septal infiltrates of lymphocytes and plasma cells. Neutrophils, eosinophils, and histiocytes are inconspicuous. Although NSIP may be associated with significant fibrosis, it is temporally uniform, with the underlying alveolar architecture most often preserved; fibroblastic foci and honeycombing, if present, are rare.[15,24] Fibrotic NSIP can be difficult to distinguish from UIP, and interobserver variability among expert pathologists is significant.[25]

Differential Diagnosis

Clinically, the most common diagnosis confused with fibrotic NSIP is IPF.[3,15,16,20] It is essential that the pathologist not use terms such as UIP or NSIP unless the defined criteria are met because some degree of fibrosis and inflammation is common in many ILDs, and sampling error can be an issue, especially in small or inadequate surgical



Figure 90.1 Nonspecific interstitial pneumonia. High-resolution chest computed tomography image shows bilateral, patchy, ground-glass opacities without evidence of subpleural honeycombing.

Table 90.2 Contrasting Clinical Features of Idiopathic Interstitial Pneumonias

Features	IPF	NSIP	COP	AIP	RB-ILD	DIP	LIP	PPFE
Mean age at onset (yr)	60s	50s	50s	50s	40s	40s	40s	50s
Sex distribution	2:1 M:F	1:1.5 M:F	1:1 M:F	1:1 M:F	2:1 M:F	2:1 M:F	Female predominance	1:1 M:F
Onset	Insidious	Subacute, insidious	Acute or subacute	Acute	Insidious	Insidious	Insidious	Insidious
History of cigarette smoking	About two-thirds	Uncommon	About one-half	Not known	Most	Most	Unknown	Uncommon
Pulmonary function testing	Restrictive defect with reduced D_{LCO}	Restrictive defect with reduced D_{LCO}	Restrictive defect with reduced D_{LCO}	Not typically performed	May be normal; mild to moderate restriction with normal or mildly reduced D_{LCO}	May be normal; mild to moderate restriction with normal or mildly reduced D_{LCO}	Restrictive defect with reduced D_{LCO}	Restrictive defect with reduced D_{LCO}
HRCT pattern	Bilateral, symmetrical, lower lung zone reticular opacities with traction bronchiectasis and honeycombing	Bilateral, symmetrical, lower lung zone ground-glass and reticular opacities with traction bronchiectasis; subpleural sparing may be present; honeycombing is rare or absent	Peripheral patchy air space consolidation, small nodular opacities and bronchial wall thickening; slight lower lung zone predominance; migratory over time; reticular opacities with progressive disease	Symmetrical, bilateral, diffuse ground-glass opacity and consolidation; evolving fibrosis later in the disease state with traction bronchiectasis and reticular opacities	Bronchial wall thickening, centrilobular nodules and diffuse or patchy ground-glass opacities; honeycombing is rare or absent	Bilateral, symmetrical, peripheral, basilar ground-glass opacities; tiny thin-walled cysts may be present within the ground glass opacities; honeycombing is rare or absent	Ground-glass opacity with few, mid-lung zone, thin-walled perivascular cysts, typically ≤3 cm, centrilobular nodules, reticular opacities; one-third progress to diffuse fibrosis	Bilateral upper lobe dense, subpleural consolidation, traction bronchiectasis, architectural distortion, and volume loss
Survival rate*	<50%	75–85%	75–80%	<50%	>75%	>75%	Unknown for idiopathic LIP	60%
Response to steroids	Poor	Good	Excellent	Poor	Good†	Good†	Good	Poor
Complete recovery possible	No	Yes	Yes (≥70% of patients)	Yes, rarely	Yes	Yes	Yes	No

Also see references 1–3, 8–10, 16, 25, 26, 33, 47, 57, 59, 62, 69, 86, 106, 108, 113, 120–125.

*Survival rate is the estimated percentage of patients alive 5 years after diagnosis.

†If accompanied by smoking cessation.

AIP, acute interstitial pneumonia; COP, cryptogenic organizing pneumonia; DIP, desquamative interstitial pneumonia; D_{LCO}, diffusing capacity for carbon monoxide; HRCT, high-resolution computed tomography; IPF, idiopathic pulmonary fibrosis; LIP, lymphocytic interstitial pneumonia; M:F, male/female; NSIP, nonspecific interstitial pneumonia; PPFE, pleuroparenchymal fibroelastosis; RB-ILD, respiratory bronchiolitis–associated interstitial lung disease.

Modified from Katzenstein AL, Myers JL. Idiopathic pulmonary fibrosis: clinical relevance of pathologic classification. *Am J Respir Crit Care Med.* 1998;157:1301-1315; and King TE Jr. Idiopathic interstitial pneumonia. In: Schwarz MI, King TE Jr, eds. *Interstitial Lung Diseases*. 4th ed. Hamilton, Canada: BC Dekker; 2003:701-786.

Table 90.3 Contrasting Histopathologic Features of Idiopathic Interstitial Pneumonias

Features	UIP	NSIP	COP	AIP	RB-ILD	DIP	LIP	PPFE
Temporal appearance (age of lesion)	Variegated	Uniform	Uniform	Uniform	Uniform	Uniform	Uniform	Uniform
Interstitial inflammation	Scant	Usually prominent	Usually moderate	Scant	Scant	Scant	Dense	Scant
Fibrosis	Subpleural and patchy	Variable: cellular vs. fibrotic patterns	No	Typically no, but may evolve	Variable, focal, mild	Variable, diffuse, moderate	Variable	Subpleural; visceral pleural involvement
Fibroblast proliferation	Fibroblast foci prominent	Rare fibroblast foci	Within airways and air spaces (Masson bodies)	Diffuse	No	No	Variable	Rare
Honeycomb change	Yes	Rare, typically absent	No	No	No	No	Rare	No
Intra-alveolar macrophage accumulation	Occasional, focal (smokers)	Occasional, patchy	Foamy macrophages common	No	Peribronchiolar	Yes, diffuse	Rare	No
Hyaline membranes	No	No	No	Occasional, focal	No	No	No	No

Also see references 106, 108, 113, and 120.

AIP, acute interstitial pneumonia; COP, cryptogenic organizing pneumonia; DIP, desquamative interstitial pneumonia; PPFE, pleuroparenchymal fibroelastosis; LIP, lymphocytic interstitial pneumonia; NSIP, nonspecific interstitial pneumonia; RB-ILD, respiratory bronchiolitis–associated interstitial lung disease; UIP, usual interstitial pneumonia.

Modified from Katzenstein ALA, Myers JL. Idiopathic pulmonary fibrosis: clinical relevance of pathologic classification. *Am J Respir Crit Care Med.* 1998;157:1301-1315; and King TE Jr. Idiopathic interstitial pneumonia. In: Schwarz MI, King TE Jr, eds. *Interstitial Lung Diseases.* 4th ed. Hamilton, Canada: BC Dekker; 2003:701-786.

Table 90.4 Histologic Patterns in the Idiopathic Interstitial Pneumonias and Other Disease Associations

Histologic Patterns	Clinical Associations
Usual interstitial pneumonia	Idiopathic pulmonary fibrosis; connective tissue diseases (uncommon); asbestosis; hypersensitivity pneumonitis; chronic aspiration pneumonia; chronic radiation pneumonitis; Hermansky-Pudlak syndrome; neurofibromatosis
Nonspecific interstitial pneumonia	Idiopathic; connective tissue diseases; drugs; hypersensitivity pneumonitis; resolving diffuse alveolar damage; AIDS; infections
Diffuse alveolar damage	Acute interstitial pneumonia (Hamman-Rich syndrome); acute respiratory distress syndrome; drugs (cytotoxic agents, heroin, cocaine, paraquat, ethchlorvynol, aspirin); toxic gas inhalation; radiation therapy; oxygen toxicity; connective tissue disease; infections (*Legionella, Mycoplasma,* viral)
Organizing pneumonia	Cryptogenic organizing pneumonia; organizing stage of diffuse alveolar damage; organizing infections (e.g., influenza) as part of diffuse alveolar hemorrhage; drugs (amiodarone, cocaine); infections; connective tissue diseases; hypersensitivity pneumonitis; eosinophilic pneumonia; granulomatosis with polyangiitis
Desquamative interstitial pneumonia or respiratory bronchiolitis	Cigarette smoking; idiopathic; connective tissue diseases; primary pulmonary Langerhans cell histiocytosis; asbestosis; hard-metal pneumoconiosis (cobalt); Gaucher disease; Niemann-Pick disease; Hermansky-Pudlak syndrome; drugs (nitrofurantoin, amiodarone)
Lymphocytic interstitial pneumonia	Idiopathic; hypogammaglobulinemia; autoimmune diseases, including Hashimoto thyroiditis, systemic lupus erythematosus, primary biliary cirrhosis, Sjögren syndrome, myasthenia gravis, chronic active hepatitis; AIDS; allogeneic bone marrow transplantation

AIDS, acquired immunodeficiency syndrome.

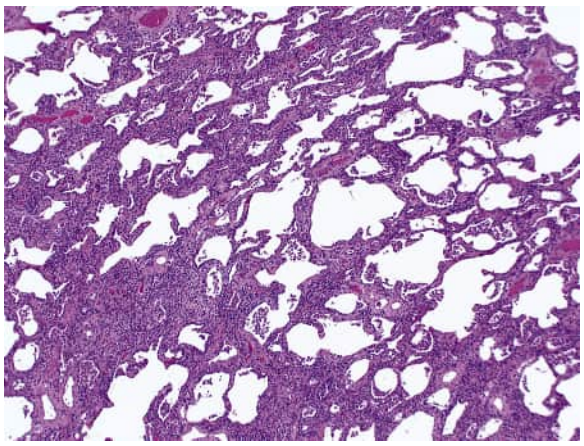

Figure 90.2 Photomicrograph of nonspecific interstitial pneumonia. Note the lymphoplasmacytic cells expanding the interstitial compartment. Alveolar macrophages are present also. (Original magnification ×10.)

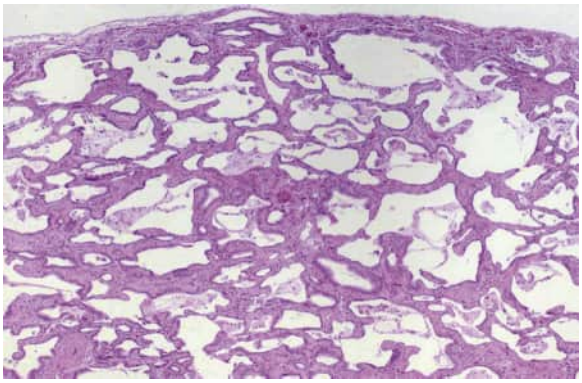

Figure 90.3 Photomicrograph of nonspecific interstitial pneumonia with a mixed cellular-fibrotic pattern. The alveolar walls are thickened by dense collagen and a few lymphocytes and plasma cells. The fibroblastic foci that are commonly found in the usual interstitial pneumonia pattern are not present in this lesion.

biopsies. Importantly, most biopsies showing an NSIP pattern are seen in patients who may have other conditions: an ill-defined or inadequately evaluated connective tissue disease, drug-induced ILD, chronic hypersensitivity pneumonitis, resolving acute lung injury (pneumonia or acute respiratory distress syndrome), or OP.[2,26-31] The NSIP pattern on surgical lung biopsy should prompt the clinician to revisit the clinical data and to look carefully for these conditions; a diagnosis of idiopathic NSIP should be given only after review by multidisciplinary discussion.

Clinical Course and Outcome

Several retrospective studies indicate the survival rate of patients with idiopathic NSIP is significantly higher than in patients with UIP.[15,16,20,25,32] This difference persists even after adjusting for age, sex, smoking history, and physiologic variables. Those patients with a purely cellular pattern on biopsy demonstrate the longest survival, a finding suggesting that this pattern may be more responsive to treatment, and overall prognosis depends primarily on the extent of fibrosis.[15,26] In those patients with an NSIP pattern in one lobe and a UIP pattern in another, the survival is similar to that in patients with UIP. In NSIP, corticosteroids combined with a steroid-sparing agent may be more effective than corticosteroids alone. The optimal dose and treatment duration remain unknown.

CRYPTOGENIC ORGANIZING PNEUMONIA

OP can be cryptogenic (i.e., COP), or it can result from various forms of lung injuries, termed *secondary OP* (e.g., postinfectious, drug-related, connective tissue disease–related, post-transplant, or related to hypersensitivity pneumonitis, radiation, or aspiration of particulate matter). COP is a specific clinicopathologic syndrome characterized by a pneumonia-like illness, with excessive proliferation of granulation tissue inside the alveolar spaces associated with chronic inflammation in the surrounding alveoli.[2,5,11] The process may also involve the small airways (bronchiolitis obliterans with organizing pneumonia).

COP and secondary OP have no major differences in clinical features.[33-35] OP may also be seen accompanying other histopathologic patterns (e.g., UIP, NSIP) but should not be a prominent finding when making the diagnosis of an alternative IIP. The diagnosis of COP is reserved for isolated OP in patients without an identifiable associated disease. Historically, the term *idiopathic bronchiolitis obliterans with organizing pneumonia* encompassed COP, but the term is no longer used for this idiopathic condition. This change in taxonomy was recommended by the American Thoracic Society and the European Respiratory Society consensus classification of IIPs in 2002 in part to avoid confusion with constrictive bronchiolitis obliterans.[2] (See Chapter 72.)

Clinical Features

The incidence of COP is similar in both men and women.[34] The mean age at presentation is about 50 to 55 years (range, 21 to 80 years). Patients with COP are frequently specific about the timing of their disease onset. This is because the disease onset is recent (usually <2 months) and is often dramatic, with the development of a flulike illness characterized by cough, mild dyspnea, fever, malaise, fatigue, and weight loss. Physical examination usually discloses focal sparse crackles but may be normal. Finger clubbing is rare.

Laboratory Features

Routine laboratory studies are nonspecific. Leukocytosis without an increase in eosinophils is seen in approximately half the patients. The initial erythrocyte sedimentation rate is frequently elevated in patients with COP.

Pulmonary function is usually impaired, with a restrictive defect being most common. An obstructive defect (ratio of *forced expiratory volume in 1 second to forced vital capacity ratio* [FEV_1/FVC] <70% of predicted) is found in almost one-fifth of subjects with COP, mostly in current or former smokers.[34,36] Gas-exchange abnormalities are extremely common, with hypoxemia at rest and with exercise. The *diffusing capacity for carbon monoxide* (D_{LCO}) is reduced (<80% of predicted) in three-fourths of patients.

The most common differential cell count on BAL shows an increase in lymphocytes (20–40%), neutrophils (10%), and eosinophils (5%), with the level of lymphocytes higher than that of eosinophils.[34] BAL lymphocytes are activated, and the CD4/CD8 ratio is usually decreased. An increase in plasma cells and/or mast cells may also be seen.

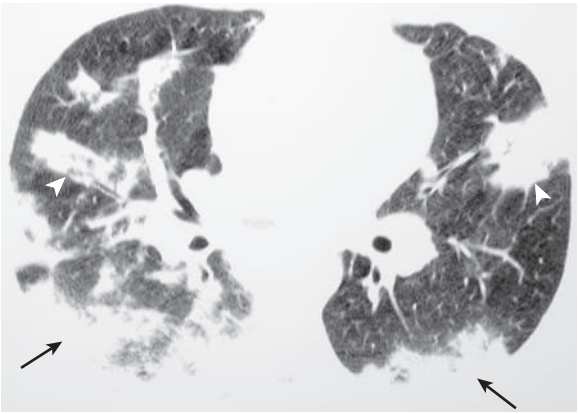

Figure 90.4 Cryptogenic organizing pneumonia. Axial computed tomography shows areas of peripheral *(arrows)* and peribronchial *(arrowheads)* consolidation. (Courtesy Michael B. Gotway, MD.)

Radiologic Features

Chest Radiography. The radiographic manifestations are distinctive, usually including unilateral or bilateral patchy consolidations that resemble pneumonic opacities in the presence of normal lung volumes (eFig. 90.3).[37,38] A peripheral distribution of the opacities, similar to that thought to be "virtually pathognomonic" for chronic eosinophilic pneumonia, is commonly seen in COP.[35,39,40] Irregular linear or nodular interstitial opacities are rarely present as the only radiographic manifestation (eFig. 90.4).[41] Honeycombing is rare and is seen only as a late manifestation in the few patients with progressive disease. Other radiographic abnormalities, such as pleural effusion, pleural thickening, hyperinflation, and cavities, are uncommon.

Computed Tomography. CT scans of the lung reveal patchy air space consolidation, small nodular opacities, and bronchial wall thickening and dilation, most frequently in the periphery of the lung and often in the lower lung zones[38,39,41,42] (Fig. 90.4, Video 90.1). Frequently, the CT findings are far more extensive than are expected by review of the chest radiograph. These opacities tend to migrate and decrease in size, even without treatment (eFig. 90.5). The CT finding of consolidation is associated with partial or complete resolution, whereas reticular opacities are associated with persistent or progressive disease (eFig. 90.6).[43] Sometimes, COP has unique findings such as the reverse halo sign (eFig. 90.7), which is defined as central ground-glass opacity surrounded by denser air space consolidation of crescentic and ring shapes. This sign is seen in approximately 20% of patients with COP.[44] The presence of enlarged lymph nodes is less common in COP than in the other IIPs.[45]

Focal OP has been described as a discrete form of COP and manifests as an isolated focal lesion on chest imaging.[46-48] Many of these patients are asymptomatic, and the lesion may be discovered incidentally by chest radiography or CT performed for other indications. It may be suspected to be a putative lung cancer because most patients with focal OP have a smoking history and are middle aged or older.[48]

Histopathologic Features

The diagnosis of COP depends on both the clinical setting and the finding of characteristic histopathologic features.

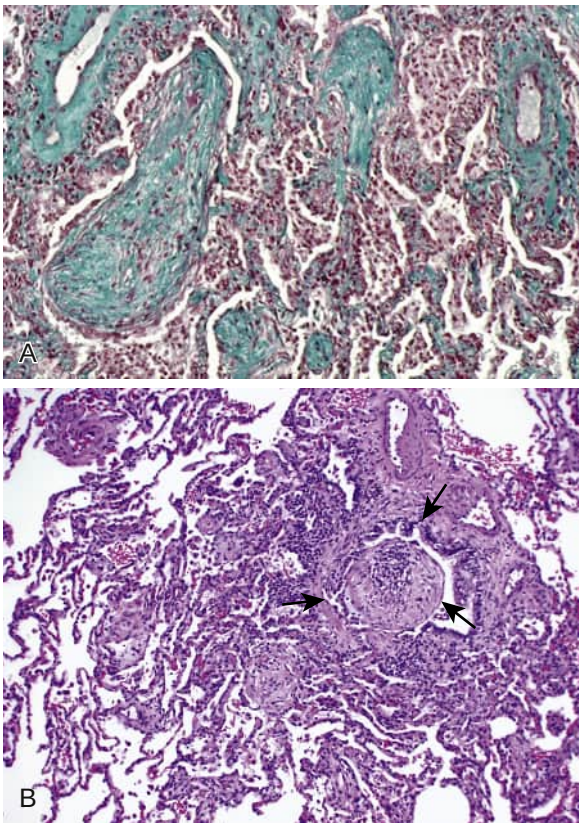

Figure 90.5 Photomicrographs of organizing pneumonia. (A) Immature connective tissue and proliferating fibroblasts (also called Masson bodies) appearing blue-green are present in alveolar ducts and alveolar spaces, as is an interstitial infiltrate consisting of mononuclear cells. (Pentachrome stain; original magnification ×40.) (B) A typical inflammatory polyp extends into the lumen of a terminal bronchiole *(arrows)*. (Original magnification ×40.)

Intraluminal fibroblastic buds, also called *Masson bodies*, seen in respiratory bronchioles, alveolar ducts, and alveoli, are the most prominent features.[2,32,49] Other histopathologic features include foamy cells in the alveolar spaces, prominent alveolar epithelial type 2 cell hyperplasia, interstitial infiltrates, and fibrinous exudates.

The characteristic Masson bodies appear in the small airways as intraluminal collections of proliferating fibroblasts and myofibroblasts in a mucopolysaccharide-rich matrix. They are most prominent in the alveolar ducts but extend distally to the alveolar lumina and proximally to the bronchioles (Fig. 90.5A). Masson bodies may also extend from one alveolus to the next through the interalveolar pores, thus creating a characteristic butterfly pattern.[34] OP can also have an interstitial lymphoplasmacytic infiltrate and hyperplasia of the alveolar epithelial type 2 cells. The organizing process, which may extend into the bronchioles, produces an intraluminal polypoid bronchiolitis obliterans (Fig. 90.5B). OP represents a common reparative response to injury seen in a variety of ILDs, infectious pneumonias, and many other processes. If the injury is unresponsive to treatment, the organizing process can progress to irreversible fibrosis and a honeycombed lung.

Clinical Course and Outcome

Corticosteroid therapy results in complete clinical, radiologic (eFig. 90.8), and physiologic recovery in two-thirds

of patients.[34] The other one-third demonstrates recurrent or persistent disease. Secondary OP is less likely to respond to corticosteroids. In general, clinical improvement is rapid, within several days or a few weeks. Occasionally, recovery is quite dramatic. When corticosteroids are withdrawn, patients can experience a relapse, usually within 1 to 3 months. Most patients with relapses improve when retreated with corticosteroids.[50] It has been suggested that COP may also respond to macrolide therapy, but studies are scant.[51] A few patients may improve spontaneously over 3 to 6 months.[34,52] A seasonal (early spring) presentation of COP with relapse every year during the same period has been reported.[53] Few patients with COP die as a result of this illness, but those with a rapidly progressive, fatal form of OP have a clinical course similar to that of patients with *acute interstitial pneumonia* (AIP).[54] In such patients, the diagnosis is usually delayed or missed. Focal OP is generally cryptogenic, does not recur after surgical resection, and does not require corticosteroid therapy.[48,55,56]

ACUTE INTERSTITIAL PNEUMONIA

AIP is a rare, fulminant form of lung injury that manifests acutely (days to weeks from onset of symptoms), usually in a previously healthy person.[57-59] AIP likely represents a subset of cases of idiopathic acute respiratory distress syndrome and is what Hamman and Rich[60] described and termed *acute diffuse interstitial fibrosis.*

Clinical Features

Most patients are older than 40 years (mean age, 50 years; range, 7 to 83 years).[57,58] Men and women are equally affected, and cigarette smoking does not seem to increase the risk. A prodromal illness, usually lasting 7 to 14 days before presentation, is common. The clinical signs and symptoms include fever, cough, and shortness of breath. Routine laboratory studies are nonspecific and generally not helpful.

Radiologic Features

Chest Radiography. Diffuse, bilateral, air space opacification is seen on the chest radiograph (eFig. 90.9).[61-63]

Computed Tomography. The typical *high-resolution CT* (HRCT) features of AIP are bilateral, multifocal, or diffuse areas of ground-glass opacity and consolidation, usually without pleural effusion (eFig. 90.10).[37,61,64,65] A predominantly subpleural distribution may be seen. These radiographic findings are similar to those seen in acute respiratory distress syndrome; however, patients with AIP are more likely to have a symmetrical, bilateral distribution with a lower lobe predominance.[66] In the early phase of AIP, ground-glass opacities and less extensive areas of consolidation make up the dominant CT pattern, reflecting the presence of alveolar septal edema and hyaline membranes.[64] During the organizing phase of the disease, HRCT findings consistent with evolving fibrosis are often present, including traction bronchiectasis, reticular opacities, and architectural distortion.[67] In this phase, consolidations resulting from intra-alveolar fibrosis may also be present, along with mild honeycombing, usually involving less than 10% of the lung.[61]

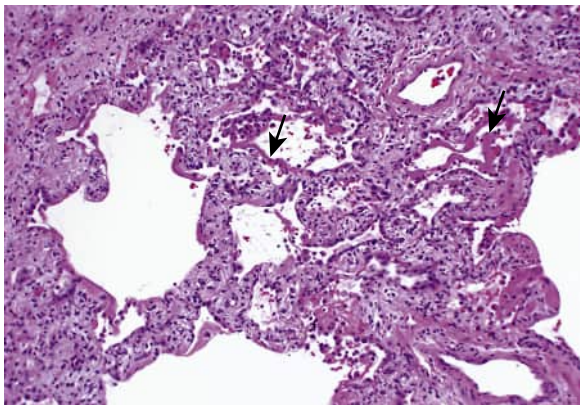

Figure 90.6 Photomicrograph of acute interstitial pneumonia shows diffuse alveolar damage. Note the hyaline membranes *(arrows)* within alveolar spaces and edema and inflammatory cell infiltration of the alveolar wall. (Original magnification ×10.)

Histopathologic Features

A surgical lung biopsy is required to confirm the diagnosis of AIP.[2,57,68] The histopathologic pattern seen in AIP is *diffuse alveolar damage* (DAD), which can be categorized into an early exudative phase, an organizing phase, and a chronic phase, depending on the timing of the biopsy in relation to the lung insult. DAD develops after an acute injury to the alveolar capillary basement membranes.[57,59] DAD is common and may be seen on biopsy in many settings, including in immunosuppressed patients who have received cytotoxic drugs or in patients who have diffuse infectious pneumonias.[69-71]

After the endothelial-epithelial injury, serum proteins and red blood cells leak into the alveolar spaces. The alveolar epithelium becomes necrotic and is sloughed, and the interstitium becomes edematous. Hyaline membranes, recognized as eosinophilic debris and consisting of necrotic epithelial cells, protein, and fibrin, form within alveolar spaces (Fig. 90.6). In the reparative or organizing stage of DAD, proliferation and hyperplasia of the alveolar epithelial type 2 cells are noted, often showing nuclear enlargement and prominent nucleoli. Extensive fibroblast proliferation is a dominant finding in the organizing phase; proliferating fibroblasts and myofibroblasts within a myxoid basophilic matrix may be seen within alveolar septa or in the alveoli, a picture resembling OP.[68] Fibrin thrombi are often present. In some cases, these changes may resolve but, in others, perhaps because of protracted or repeated parenchymal injury, they may progress to irreversible fibrosis and honeycomb lung.

Clinical Course and Outcome

Treatment is largely supportive and consists of mechanical ventilation and oxygen supplementation.[57,58,63,69] Corticosteroids seem to be effective in the early phase of disease. According to most studies, the mortality from AIP appears to be high (>50%), with the majority of patients dying within 3 months of presentation.[57-59,63] Most survivors of AIP experience recurrences and chronic, progressive ILD.[63] However, a lower hospital mortality (12.5%) with no evidence of either recurrent or progressive disease has been also described.[72]

RESPIRATORY BRONCHIOLITIS–ASSOCIATED INTERSTITIAL LUNG DISEASE AND DESQUAMATIVE INTERSTITIAL PNEUMONIA

RB-ILD and *desquamative interstitial pneumonia* (DIP) are related and, in some cases, inseparable conditions because most cases appear to represent different stages of the same process.[73-76]

These diseases represent a distinct clinical syndrome found in current heavy smokers. The term RB-ILD is more anatomically accurate because it conveys important pathogenic implications compared with the older term DIP. Both (primarily RB-ILD) account for 15–20% of patients with IIPs who have undergone biopsies.[68,77] Importantly, respiratory bronchiolitis is an accurate histologic marker of cigarette smoking, and it may be found many years after smoking ceases.[78] The level of cytoplasmic pigmentation of macrophages and the presence of peribronchial fibrosis correlate with the smoking history in pack-years.[78] Moreover, it has been reported that persons with significant lifetime secondhand smoke exposure, especially in the previous 12 months, have significant increases in ground-glass opacities on HRCT, a finding suggesting early or subclinical respiratory bronchiolitis and DIP.[79] Furthermore, RB- and DIP-like histologic changes (1) are exceedingly common in pulmonary Langerhans cell histiocytosis, (2) may be sufficiently severe to cause the appearance of ground-glass opacities on HRCT, and (3) correlate with the cumulative exposure to cigarettes smoked.[80]

Although cigarette smoking is considered the main cause of RB-ILD and DIP, genetic abnormalities of surfactant function, including mutations in the genes coding for surfactant protein B and C, account for an increasing number of ILDs, including DIP.[81,82] In addition, DIP can be observed in various occupational or drug exposures.[9,77,83]

Clinical Features

RB-ILD and DIP primarily affect cigarette smokers between the third and the sixth decades of life.[9,10,77] RB-ILD and DIP have a male preponderance, with men affected nearly twice as often as women. Patients with either RB-ILD or DIP commonly present with insidious exertional dyspnea and persistent nonproductive cough. Less frequently, patients with DIP experience fatigue and weight loss. Coarse, bibasilar end-inspiratory crackles are frequent findings on physical examination, whereas finger clubbing is uncommon.

Laboratory Features

BAL fluid in patients with RB-ILD and DIP is characterized by mild to moderate increases in total cell numbers, moderate to marked eosinophilia (a feature that, in the absence of a biopsy, could raise the consideration of chronic eosinophilic pneumonia), and moderate neutrophilia.[84,85]

Pulmonary function testing may be normal but usually shows mild to moderate restriction, normal or slightly reduced diffusing capacity, and mild hypoxemia.[9,10,85] A mixed obstructive-restrictive pattern is common, although there may be an isolated increase in residual volume.

Radiographic Features

Chest Radiography. The chest radiograph is insensitive for detection of RB-ILD and is often normal.

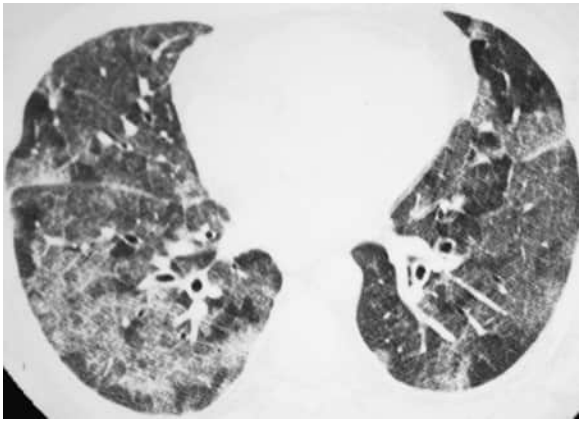

Figure 90.7 Desquamative interstitial pneumonia. Axial high-resolution computed tomography shows patchy, multifocal ground-glass opacity associated with areas of interlobular septal thickening and intralobular interstitial thickening. (Courtesy Michael B. Gotway, MD.)

Sometimes, bronchial wall thickening or reticular opacities can be seen (eFig. 90.11). Chest radiographs of DIP (eFig. 90.12) are nonspecific and usually reveal bilateral ground-glass opacities. Middle and lower lung field involvement with normal-appearing lung volumes predominates.[9,10,77] Air bronchograms can be found when the disease process surrounds the airways. The honeycomb pattern is rare.

Computed Tomography. The key HRCT features of RB-ILD include central bronchial wall thickening proximal to segmental bronchi, peripheral bronchial wall thickening distal to segmental bronchi, centrilobular nodules (eFig. 90.13), and areas of ground-glass opacity.[75,86,87] Ground-glass opacifications may be diffuse or patchy, without basal or peripheral predominance.[75,87,88] The predominant abnormality in DIP (eFig. 90.14) is the bilateral, moderately symmetrical, peripheral, and predominantly basal ground-glass attenuation Fig. 90.7, eFig. 90.14). Tiny thin-walled cysts (eFig. 90.15) are noted within the ground-glass opacities in 30–60% of cases.[84,89,90] A honeycomb pattern is rarely found.[9,84,87,90] Appearances between RB-ILD and DIP occasionally overlap, although the ground-glass attenuation of DIP is usually more extensive, and nodules are infrequent or absent.[85]

Histopathologic Features

The cardinal feature of RB-ILD is the accumulation of alveolar macrophages within the bronchioles, including the terminal and respiratory bronchioles, variably extending into alveolar ducts and alveoli.[8,68,78,91] In contrast to RB-ILD, DIP shows a much more widespread and uniform filling of all alveoli, although in any given biopsy one can find low-power fields showing only RB-ILD–type changes and others typical of DIP. This histologic observation supports the close association of RB-ILD and DIP. Macrophages are characterized by glassy eosinophilic cytoplasm, usually with brown and finely granular pigmentation (representing constituents of cigarette smoke).[2,68,85,91] A chronic inflammatory cell infiltrate in bronchiolar and surrounding alveolar walls is often noted. The changes of RB-ILD are patchy at low magnification and have a distinctly bronchiolocentric

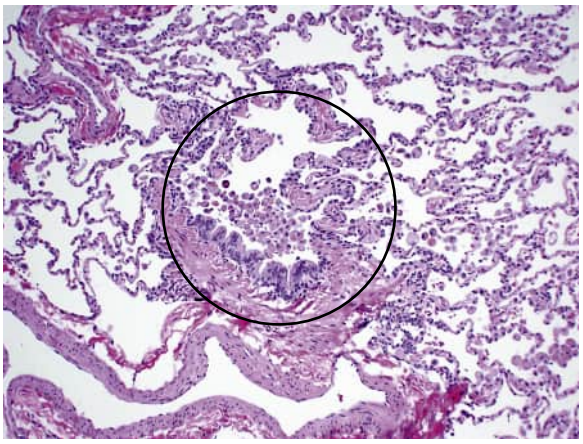

Figure 90.8 Photomicrograph of respiratory bronchiolitis. An ectatic small airway *(circle)* is visible, with thickened walls and extension of the bronchiolar metaplastic epithelium into the immediately surrounding alveoli. Intraluminal macrophages are also present within the peribronchiolar alveolar spaces.

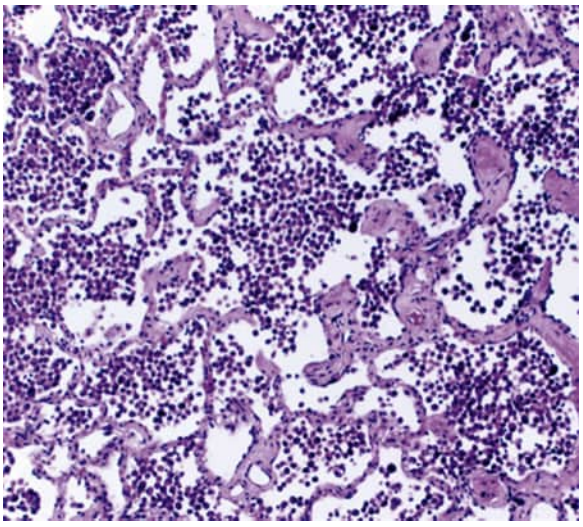

Figure 90.9 Photomicrograph of desquamative interstitial pneumonia. Characteristic dense collections of macrophages are seen filling alveolar lumina. (Original magnification ×100.)

distribution without the associated diffuse involvement and interstitial pneumonia necessary for a diagnosis of DIP (Fig. 90.8).[68]

As mentioned, the histologic hallmark of DIP is the uniform filling of the alveolar spaces by cohesive clusters of numerous pigmented alveolar macrophages, including occasional multinucleated cells, eosinophils, and lymphocytes (Fig. 90.9).[68,92] Alveolar septa are thickened by a sparse inflammatory infiltrate and lined by uniform hyperplastic alveolar epithelial type 2 cells. Peribronchiolar lymphoid hyperplasia is seen in the majority of cases.[68,92] Most DIP cases show a difference in the degree of pathologic change from one lobule to the next in a given biopsy specimen. Some degree of architectural destruction is usually observed. Akira and colleagues[90] have pointed out the presence of dilated alveolar ducts and bronchioles and/or pulmonary cysts, which corresponded to cystic spaces on HRCT.[84]

Bedrossian and coworkers[93] coined the term *DIP-like reaction* to identify prominent intra-alveolar macrophage accumulation around space-occupying pulmonary lesions. This DIP-like reaction can be seen in a number of other processes, including pulmonary Langerhans cell histiocytosis, drug reactions (e.g., amiodarone), chronic alveolar hemorrhage, eosinophilic pneumonia, pneumoconioses (e.g., talcosis, hard-metal disease, asbestosis), obstructive pneumonias, and exogenous lipoid pneumonia.[92,94] In these cases, however, the DIP-like reaction is usually focal, without the uniform involvement of lung parenchyma seen in true cases of RB-ILD and DIP.

Clinical Course and Outcome

Because there has not been a longitudinal study of a large group of participants, the clinical course and prognosis of patients with RB-ILD are unknown. Most studies suggest a favorable response to smoking cessation and the use of corticosteroids, with documented improvement in lung function and chest radiographs[91]; few deaths secondary to progressive lung disease have been reported.[10]

Patients with the DIP stage of this process also have a good prognosis, particularly with early smoking cessation. Five-year survival rates of more than 75% have been reported with mean follow-up times in these small studies ranging from 5 to 10 years.[9,83,91] Additional prospective studies with a larger number of participants will be necessary to confirm these results. In another study, symptomatic improvement (i.e., improved cough, dyspnea, or both) with prednisone treatment was noted in 24% of patients with DIP and in 55% of patients with RB-ILD.[9] Objective improvement with prednisone treatment, as evidenced by improvement in pulmonary function measurements or parenchymal opacities seen on chest radiography or CT scans, was noted in 33% of patients with DIP and in 64% of patients with RB-ILD.[9] Unfortunately, these positive responses tended to be transient in half of the patients, with recurrence of disease following tapering and discontinuation of prednisone treatment. Patients can regress to their original disease status even in the absence of smoking.[9]

Nevertheless, because smoking plays a major role in the pathogenesis, smoking cessation is always indicated in these patients. With smoking cessation, there can be significant improvement in clinical symptoms and D_{LCO}, as well as in radiologic features including ground-glass opacities and centrilobular nodules.[95] Corticosteroids may be required in refractory or recurrent cases but are not recommended if the patient continues to smoke.

RARE IDIOPATHIC INTERSTITIAL PNEUMONIAS

IDIOPATHIC LYMPHOCYTIC INTERSTITIAL PNEUMONIA

Lymphocytic IP (LIP) is an uncommon pathologic pattern characterized by the presence of widespread, monotonous sheets of lymphocytic infiltration in the interstitium of the lung.[96-98] Idiopathic LIP is rare and, in addition to being differentiated from other IIPs, it must

Table 90.5 Diseases Associated With Lymphocytic Interstitial Pneumonitis

AUTOIMMUNE DISEASE
Sjögren syndrome
Primary biliary cirrhosis
Myasthenia gravis
Hashimoto thyroiditis
Pernicious anemia
Autoimmune hemolytic anemia
Systemic lupus erythematosus
DYSPROTEINEMIAS
Hypogammaglobulinemia
Polyclonal gammopathy
INFECTIONS
Human immunodeficiency virus
Epstein-Barr virus
HTLV-1
Legionella
Tuberculosis
MISCELLANEOUS
Celiac sprue
Phenytoin
Allogeneic hematopoietic stem cell transplantation
Surfactant protein C deficiency

HTLV-1, human T cell lymphotrophic virus type 1.
Modified from Cosgrove GP, Fessler MB, Schwarz MI. Lymphoplasmacytic infiltrations of the lung. In: Schwarz MI, King TE Jr, eds. *Interstitial Lung Diseases*. 4th ed. Hamilton, Canada: BC Decker; 2003:827.

be distinguished from other lymphocytic infiltrations in the lung, notably lymphomas and ILDs associated with prominent lymphoid infiltrates such as collagen vascular diseases (especially Sjögren syndrome), dysproteinemia, drug reactions, hypersensitivity pneumonitis, immunodeficiency syndromes (e.g., human immunodeficiency virus infection, combined variable immunodeficiency), and hematopoietic stem cell transplantation. The LIP pattern is seen far more commonly as a secondary disease in association with systemic disorders than it is as the idiopathic disease described here. Most of the earlier reports on LIP included secondary cases (Table 90.5).[99-102]

Clinical Features

Patients most commonly present with progressive dyspnea and cough, although they may also have weight loss, pleuritic pain, arthralgias, and fever.[96-98] Bibasilar crackles can be heard on auscultation in most patients. Digital clubbing is usually absent, and cyanosis is a rare physical finding. Because LIP is more commonly a secondary process found in association with a primary underlying disease, close attention to extrapulmonary findings that may assist in diagnosing a primary condition is of utmost importance.

Laboratory Features

In idiopathic LIP, results of laboratory studies are likely to be normal. If laboratory results are abnormal, they may reflect an underlying disease state leading to secondary LIP. Dysproteinemia may be found, usually a polyclonal gammopathy. Pulmonary function testing shows a restrictive defect, reduced D_{LCO}, and hypoxemia.[96-98] If performed, the differential cell count on BAL demonstrates striking T cell lymphocytosis.[97]

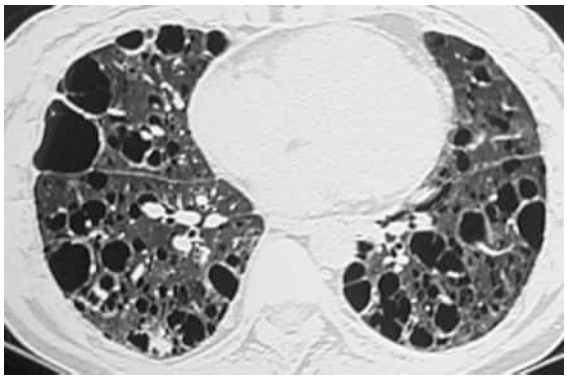

Figure 90.10 Lymphocytic interstitial pneumonia. High-resolution computed tomography image shows diffuse, randomly distributed round cysts, many of which lie near vessels.

Radiologic Features

Chest Radiography. The chest radiograph is nonspecific, with reticular opacities (eFig. 90.16) the most frequent abnormality. A mixed alveolar-interstitial pattern appears as the disease progresses because of the coalescence of the opacities. Cysts, honeycombing, and signs of pulmonary hypertension are also late manifestations.[103] Pleural effusions are infrequent and suggest a complicating lymphoma.

Computed Tomography. The main parenchymal abnormalities on CT scan consist of ground-glass opacities (eFig. 90.17), thickening of interlobular septa, centrilobular nodules (eFig. 90.18), thin-walled perivascular cysts (Fig. 90.10), and air space consolidation (see eFig. 90.17).[42,101] In contrast to the subpleural, lower lung cystic changes seen in UIP, the cysts of LIP are usually within the lung parenchyma throughout the mid-lung zones and presumably result from air trapping secondary to peribronchiolar cellular infiltration.[101-103] The cysts that may be seen in up to 80% of patients are typically scant and measure less than 3 cm in diameter. On follow-up CT, most patients show improvement in the extent of parenchymal abnormalities.[102] Cystic changes are not reversible, and some patients have enlarging cysts or develop new cysts over time (eFig. 90.19). New cysts often develop in areas with centrilobular nodules on initial CT. Although uncommon, honeycomb change in areas of previous air space consolidation has been observed on follow-up imaging.[102]

Histopathologic Features

Surgical lung biopsy is generally required for the diagnosis. The lymphocytic infiltration is usually extensive and severe, involving the alveolar septa and peribronchiolar and perivascular interstitium[2,5,96] (Fig. 90.11). Reactive lymphoid follicles are often present and distributed along the peribronchiolar regions. The lymphocytes are polytypic (both B and T cells may be found), distinguishing

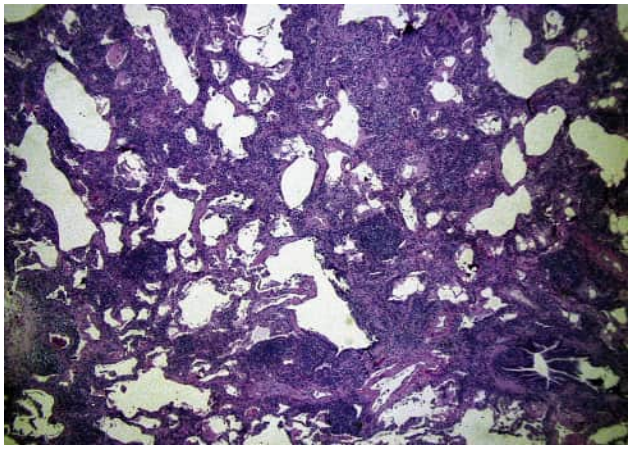

Figure 90.11 Photomicrograph of lymphocytic interstitial pneumonia. A diffuse lymphoid infiltrate extends through the pulmonary interstitium. (Original magnification ×10.)

them from the monotypic lymphocytic infiltrates characteristic of pulmonary lymphoma. Immunohistochemistry and molecular analysis may also be helpful to distinguish LIP from pulmonary lymphomas. The number of plasma cells and macrophages is also increased in these infiltrates. LIP is distinguished from DIP and NSIP by the marked density of the lymphoid infiltrate in LIP, although no precise criteria exist.[2,5,96] Other features of LIP include the interstitial accumulation of macrophages, noncaseating granulomas, perivascular amyloid deposits, and germinal lymphoid centers.

Clinical Course and Outcome

Because of the rarity of idiopathic LIP, its clinical course is unknown. When LIP is associated with another disease, the underlying disease largely determines the outcome. In many case reports, marked improvement or complete resolution has followed corticosteroid therapy.[97-99] However, the disease can progress to pulmonary fibrosis, right heart failure, and death of the patient despite therapy. Infection is a common complication, especially in patients with associated dysproteinemia.[97-100] Progression to pulmonary or systemic lymphoma appears to be rare, and it is likely that, in this group of patients, malignant lymphoma was present from the outset.[98,100,104,105]

IDIOPATHIC PLEUROPARENCHYMAL FIBROELASTOSIS

Idiopathic *pleuroparenchymal fibroelastosis* (PPFE) is another rare form of IIP and is characterized by an upper lung zone predominant fibrotic process involving the visceral pleura and adjacent subpleural parenchyma.[106-109]

A similar presentation of upper lobe subpleural fibrosis has been described in patients following bone marrow transplantation,[110] after lung transplantation, and in association with several different chemotherapeutic drugs.[111]

Radiologic PPFE-like lesions have also been found in patients with connective tissue–associated ILD, especially in patients with systemic sclerosis and primary Sjögren's syndrome.[112] Many patients diagnosed with PPFE also demonstrate radiographic or histopathologic features of a second IIP. It is important to follow these patients closely to determine the best therapeutic strategy, depending on the evolution of either IIP.

Clinical Features

The presentation of patients with PPFE is similar to that in patients with other IIPs, with progressive dyspnea on exertion the most commonly reported symptom. Cough may or may not be present. Most patients are adults in the sixth decade of life, and men and women are equally affected.[106,108] Most patients are nonsmokers and report a history of recurrent pulmonary infections in the past.[108] Patients may also present with spontaneous pneumothorax or pneumomediastinum or develop these disorders in the course of their illness.[108,113] The pulmonary examination is often normal, although a "flat chest" has been described in which the ratio of the anteroposterior to the transverse diameter is abnormally low; whether this arises congenitally or from the fibrosis of the underlying lung is not known, but it may worsen over time with disease progression.[114]

Laboratory Features

Results of pulmonary function tests are consistent with a restrictive defect and may show a decrease in FVC out of proportion to that of the D_{LCO}. Arterial blood gas analysis in the early stages of disease may show hypercapnia and a normal alveolar-arterial oxygen tension difference, possibly because, in the early stages, the major pathophysiologic defect is pleural fibrosis and an extrapulmonary restrictive defect.[115,116]

Radiologic Features

Chest Radiography. In patients with early PPFE, chest radiography may be normal. With disease progression, bilateral, irregular pleural thickening at the apices may be apparent. The hilar structures are often pulled up as a result of upper lobe volume loss and architectural distortion.[117,118]

Computed Tomography. The characteristic CT scan findings are dense, subpleural consolidations with associated traction bronchiectasis and architectural distortion in the bilateral upper lobes (Fig. 90.12).[106,108,119] The pleura is typically thickened in the areas of the subpleural fibrotic changes. A characteristic feature of PPFE is a clear delineation between areas of fibrosis and normal lung. Volume loss and architectural distortion with upward retraction of the hila and cysts and bullae may also be present. Coexistent lower lobe interstitial changes in a UIP-like or NSIP-like pattern are increasingly reported.[116]

Histopathologic Features

The histopathologic features of PPFE include subpleural, intra-alveolar fibrosis with septal elastosis and the deposition of elastic fibers with intervening collagen within the alveolar septa (Fig. 90.13).[106-108] The visceral pleura appears densely fibrotic in an upper lung zone predominance, but all lung zones may be involved histologically even if involvement is not apparent on CT

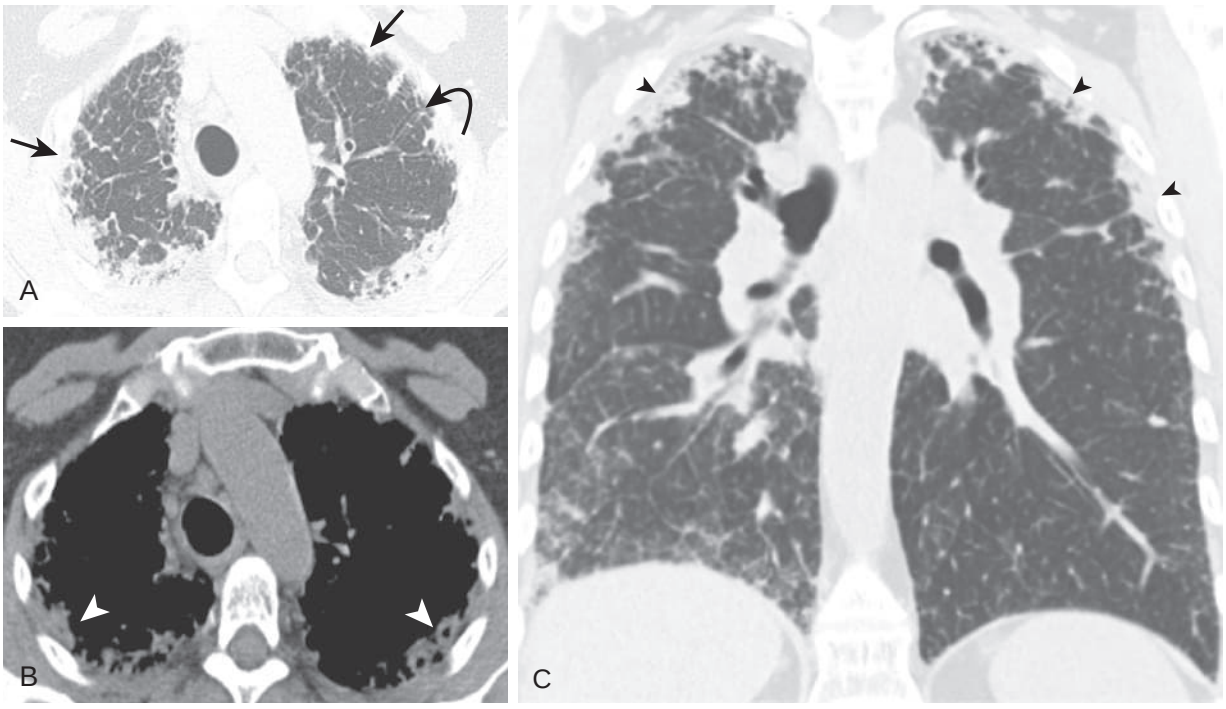

Figure 90.12 Computed tomography of idiopathic pleuroparenchymal fibroelastosis. (A) Axial image of the lung apices in lung windows demonstrates fibrosis characterized by reticulation *(straight arrows)* and traction bronchiectasis *(curved arrow)*. (B) Soft tissue windows show areas of marked pleural thickening *(arrowheads)*. (C) Coronal images in lung window demonstrate apical predominant fibrosis, resulting in volume loss and upward retraction of the hila. Marked pleural thickening is present *(arrowheads)*. (Courtesy Tami Bang, MD.)

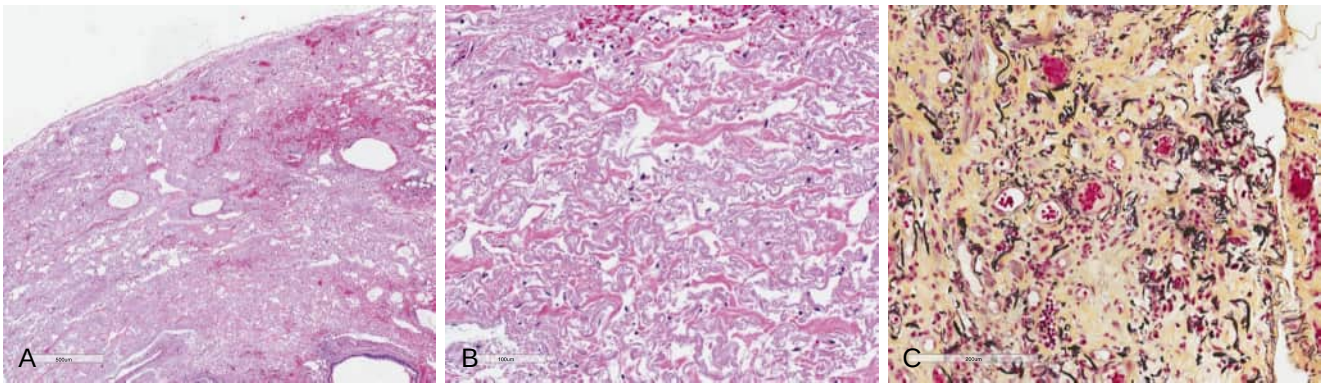

Figure 90.13 Photomicrograph of idiopathic pleuroparenchymal fibroelastosis. (A) Hematoxylin and eosin–stained section demonstrating the characteristic subpleural-pleural fibroelastosis consisting of pink collagenous fibrous tissue and disordered elastic fibers. (B) Higher-power view showing bright pink fibrous tissue (collagen) interspersed with disordered, purple elastic fibers. (C) Pentachrome (Movat) stain highlights the mature collagen (yellow) and irregular, fragmented elastic tissue fibers (black). (Courtesy Carlyne Cool, MD.)

imaging. The subpleural space demonstrates homogeneous fibroelastosis with a sharp delineation between the involved subpleural region and normal lung parenchyma. Rare fibroblastic foci may be found at the leading edge of the fibrotic changes adjacent to normal parenchyma.[113]

Clinical Course and Outcomes

Most patients with idiopathic PPFE experience disease progression. In a case series of 12 patients with PPFE, prednisone treatment, even with additional immunosuppressive therapy, did not appear to have a beneficial effect.[108] In a series of 52 patients with idiopathic PPFE diagnosed after multidisciplinary discussion, the 5-year mortality was reported to be 42%.[120] In patients with another coexisting IIP, particularly with lower lobe UIP, the clinical course may be more rapidly progressive.[116]

ACKNOWLEDGMENT

We acknowledge the contributions of Drs. Jay H. Ryu, Moisés Selman, and Thomas Colby to the writing of this chapter.

Key Points

- Idiopathic interstitial pneumonias are a subgroup of interstitial lung diseases of unknown etiology and are associated with variable radiologic features, response to therapy, and clinical course.
- The gold standard for diagnosis of any idiopathic interstitial pneumonia includes multidisciplinary discussion including clinicians, radiologists, and pathologists with specific expertise in interstitial lung disease.
- Nonspecific interstitial pneumonia is characterized by diffuse, temporally and geographically homogenous cellular infiltrates (cellular nonspecific interstitial pneumonia) or fibrosis (fibrotic nonspecific interstitial pneumonia). Finding a histopathologic pattern of nonspecific interstitial pneumonia on biopsy should prompt additional evaluation to identify an underlying cause because idiopathic nonspecific interstitial pneumonia is uncommon. In general, patients with nonspecific interstitial pneumonia (especially cellular nonspecific interstitial pneumonia) have a better prognosis than patients with idiopathic pulmonary fibrosis.
- Cryptogenic organizing pneumonia is characterized by patchy, migratory pulmonary opacities that are often mistaken for pneumonia. Cryptogenic organizing pneumonia is very steroid responsive but may relapse following tapering or discontinuation of steroids.
- Acute interstitial pneumonia is a rapidly progressive cause of acute respiratory failure characterized by diffuse alveolar damage and hyaline membranes on histopathology. Mortality is high.
- Respiratory bronchiolitis–associated interstitial lung disease and desquamative interstitial pneumonia are smoking related in most patients. Smoking cessation is the cornerstone of treatment for most patients with or without corticosteroids.
- Idiopathic lymphocytic interstitial pneumonia is a rare diagnosis, and clinicians should perform additional diagnostic evaluation to rule out an underlying condition.
- Idiopathic pleuroparenchymal fibroelastosis is a progressive disease with no known treatments. Standardization of diagnostic criteria and prospective research are needed in this disease.

Key Readings

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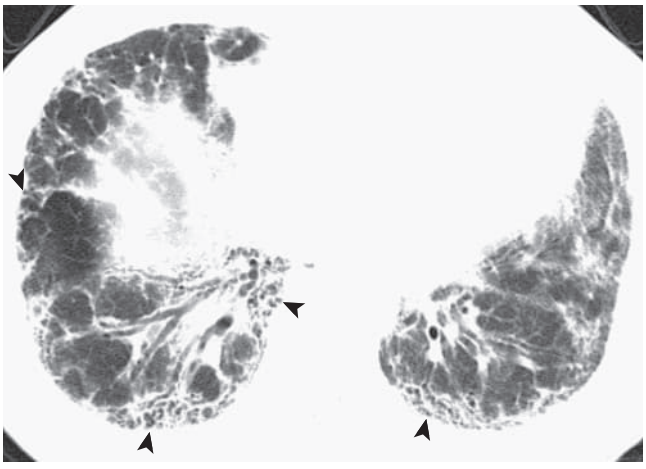
Complete reference list available at ExpertConsult.com.



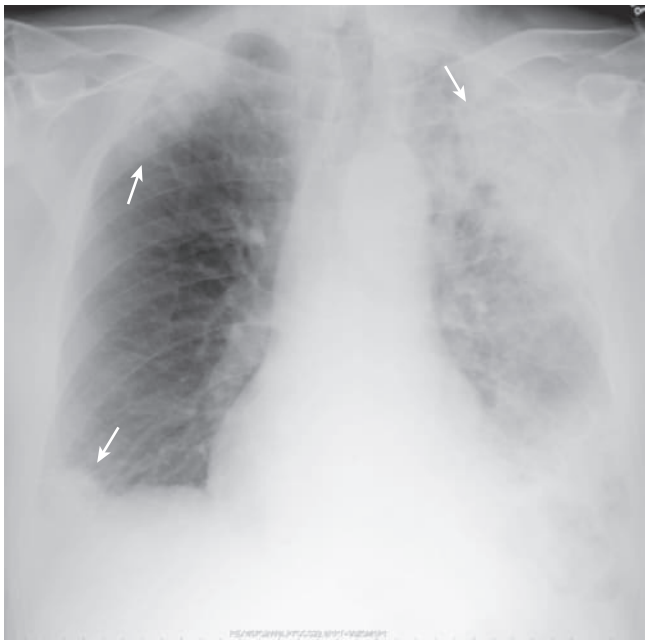
eFIGURE IMAGE GALLERY



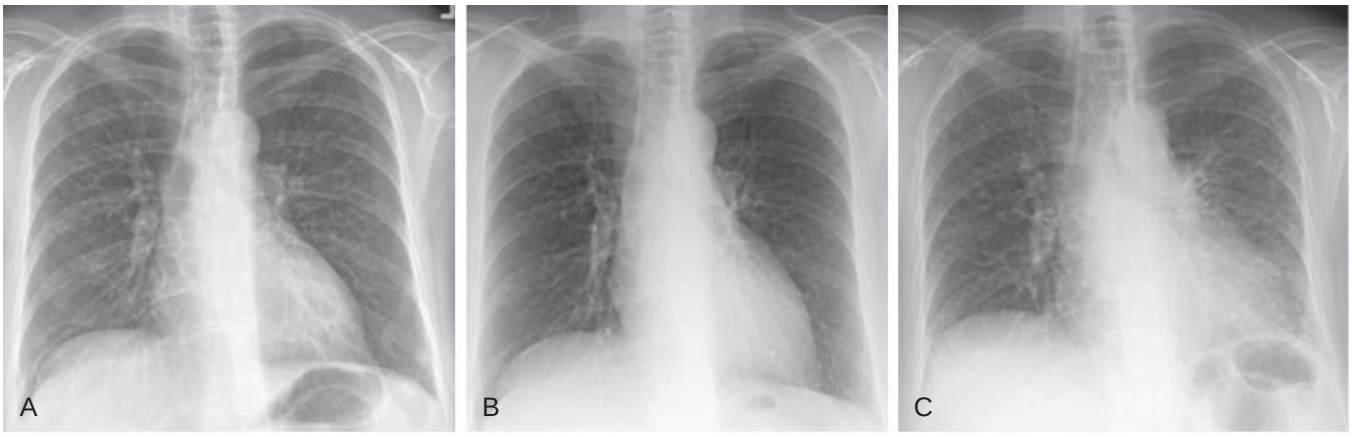
eFigure 90.1 Chest radiography of nonspecific interstitial pneumonia. Frontal chest radiograph shows patchy, bilateral areas of increased attenuation associated with faint areas of underlying reticulation; lung volumes are relatively preserved. (Courtesy Michael B. Gotway, MD.)



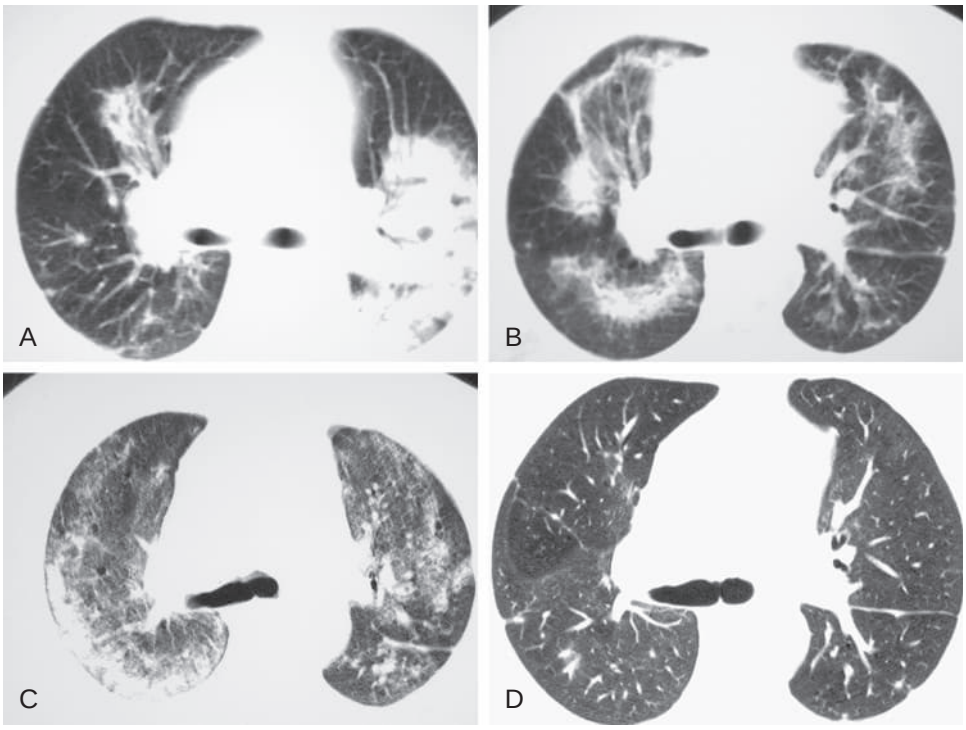
eFigure 90.2 Computed tomography showing subpleural cystic change in nonspecific interstitial pneumonia. Axial chest computed tomography performed through the lung bases in a patient with fibrotic nonspecific interstitial pneumonia shows coarse peripheral reticulation, traction bronchiectasis, and peripheral cystic change (*arrowheads*). (Courtesy Michael B. Gotway, MD.)



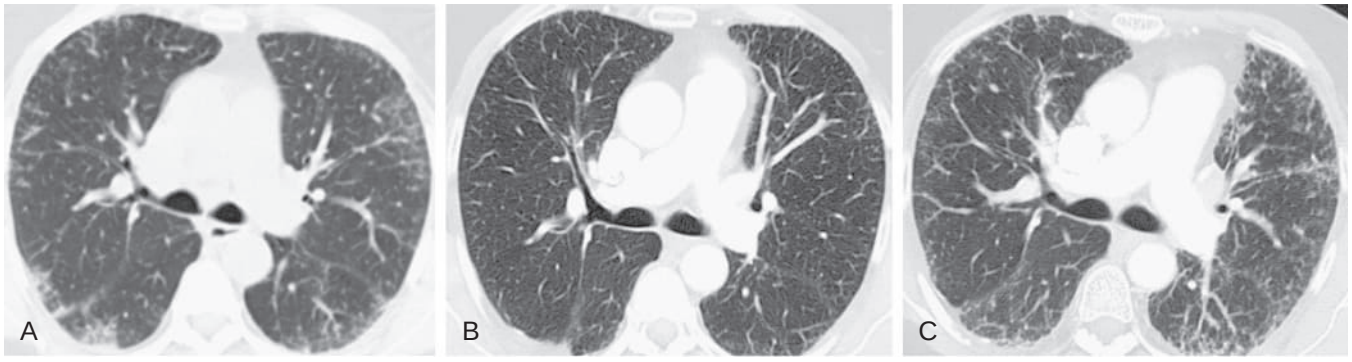
eFigure 90.3 Chest radiography of cryptogenic organizing pneumonia. Frontal chest radiograph shows multifocal, bilateral, peripherally distributed areas of consolidation (*arrows*). (Courtesy Michael B. Gotway, MD.)



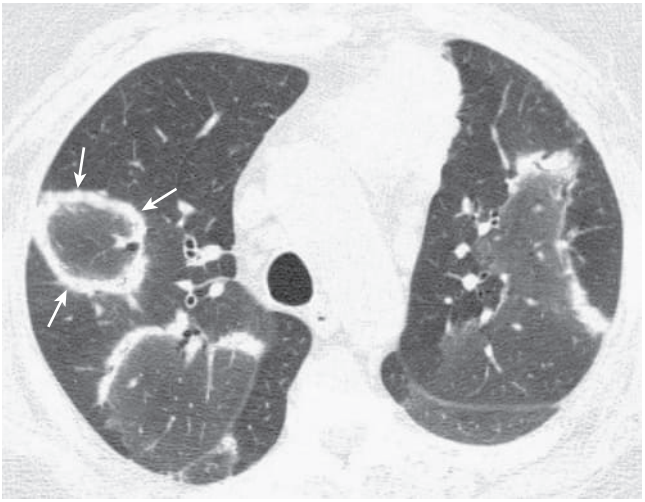
eFigure 90.4 Reticular appearance on chest radiography in cryptogenic organizing pneumonia. Frontal chest radiographs obtained (A) at presentation, (B) 2 years later following corticosteroid therapy, and (C) 4 years following presentation and after corticosteroid therapy withdrawal show (A) peripheral reticulation and interstitial thickening at presentation that (B) regresses following corticosteroid therapy. After withdrawal of corticosteroid therapy, when the patient again presented with symptoms, the reticulation and interstitial thickening have recurred. See computed tomography of the same patient in eFig. 90.6. (Courtesy Michael B. Gotway, MD.)



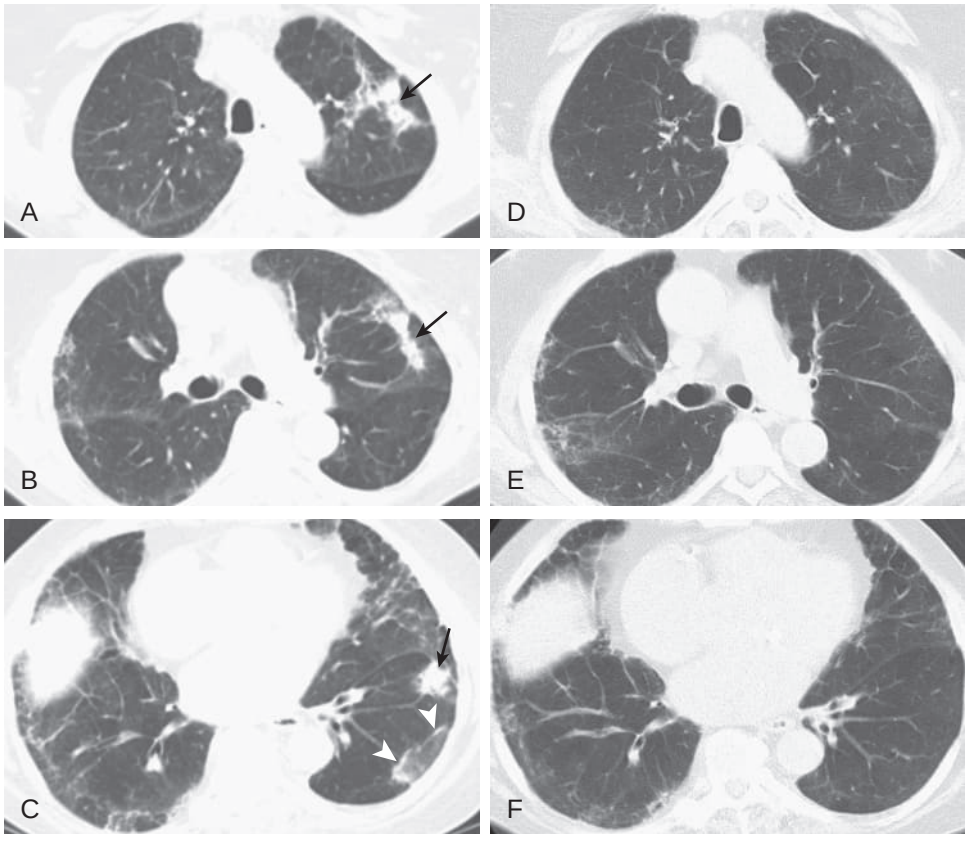
eFigure 90.5 Computed tomography of migratory opacities in cryptogenic organizing pneumonia. (A) Axial chest computed tomography at presentation obtained through the mid-lungs shows extensive left lung consolidation and mild right lung consolidation. (B) Six months after presentation, the left lung abnormalities have regressed and new right lung opacity is now present; note how the opacities have migrated peripherally. (C) Image obtained 1 year following presentation shows that the right lung consolidation has migrated into a frankly subpleural position. (D) Image obtained following corticosteroid therapy shows complete resolution of lung opacity. (Courtesy Michael B. Gotway, MD.)



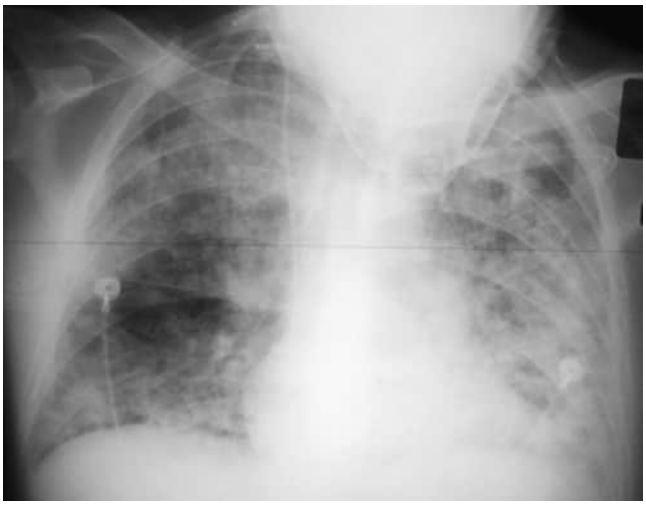
eFigure 90.6 Reticular appearance on computed tomography in cryptogenic organizing pneumonia. Axial chest computed tomography performed through the mid-lungs, obtained (A) at presentation, (B) 2 years later following corticosteroid therapy, and (C) 4 years following presentation and after corticosteroid therapy withdrawal shows (A) peripheral reticulation and interstitial thickening at presentation that (B) regresses following corticosteroid therapy. After withdrawal of corticosteroid therapy, when the patient again presented with symptoms, the reticulation and interstitial thickening have recurred. See chest radiograph of the same patient in eFig. 90.4. (Courtesy Michael B. Gotway, MD.)



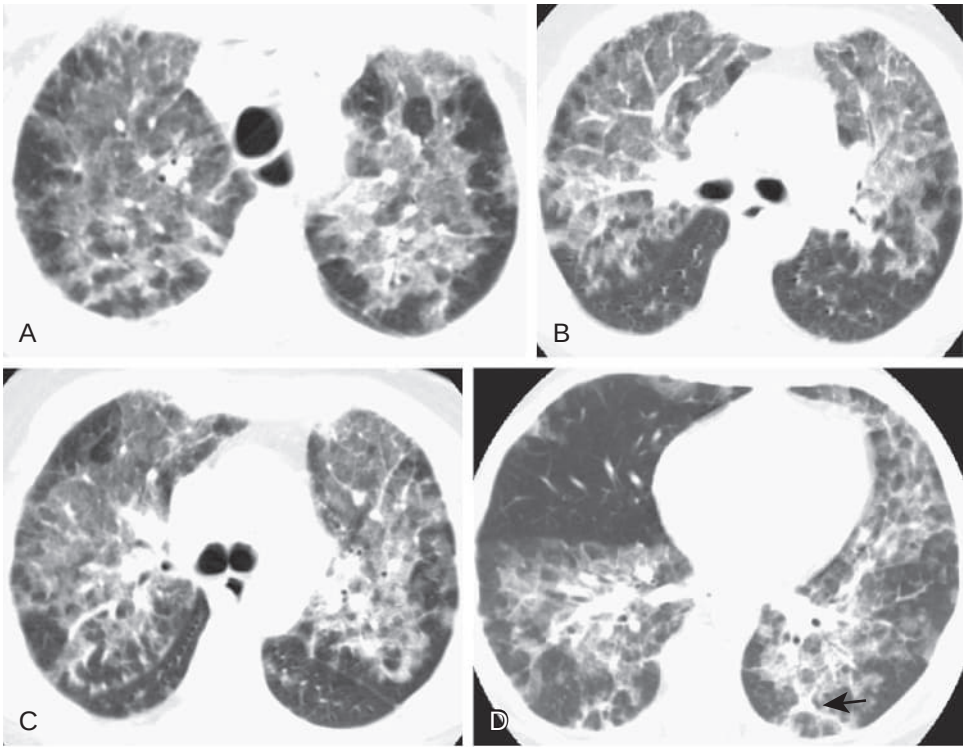
eFigure 90.7 Computed tomography of the reverse ground-glass halo ("atoll" sign) in organizing pneumonia. Axial chest computed tomography performed though the mid-lungs shows bilateral opacities characterized by peripheral consolidation with internal mild increased attenuation, the latter representing ground-glass opacity. One of the opacities shows a complete ring of peripheral consolidation *(arrows),* whereas other opacities show a partial ring or curvilinear appearance. (Courtesy Michael B. Gotway, MD.)



eFigure 90.8 Computed tomography of organizing pneumonia following corticosteroid therapy. Axial chest computed tomography performed through (A) the upper, (B) middle, and (C) lower lungs at presentation shows patchy bilateral reticular opacities with foci of bandlike (*arrows* in A and B) and nodular (*arrow* in C) consolidation, representing foci of organizing pneumonia. Note the left lower lobe reverse ground-glass halo ("atoll" sign) (*arrowheads*) (C). Axial chest computed tomography performed through (D) the upper, (E) middle, and (F) lower lungs following corticosteroid therapy shows resolution of the foci of consolidation. (Courtesy Michael B. Gotway, MD.)



eFigure 90.9 Chest radiography in acute interstitial pneumonia. Frontal chest radiograph shows extensive, multifocal, bilateral consolidation. The imaging appearance is nonspecific and could be caused by numerous conditions. (Courtesy Michael B. Gotway, MD.)



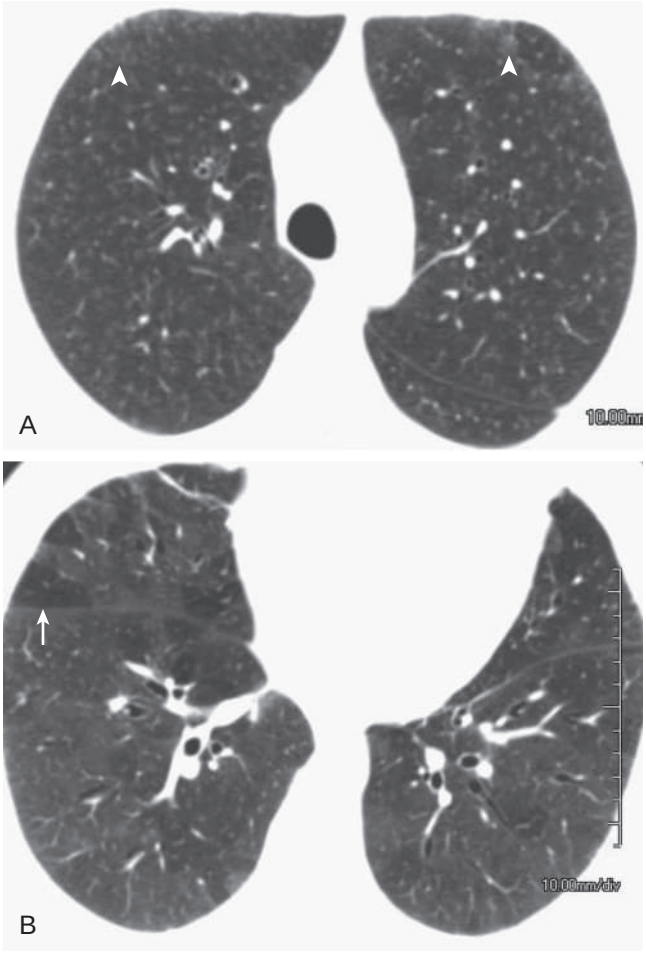
eFigure 90.10 Computed tomography of acute interstitial pneumonia. Axial chest computed tomography images obtained through the (A) upper, (B–C) middle, and (D) lower lobes show extensive, multifocal bilateral areas of bronchovascular thickening, ground-glass opacity, reticulation, and areas of bandlike consolidation (*arrow*). The imaging appearance is nonspecific and could be caused by numerous conditions. (Courtesy Michael B. Gotway, MD.)



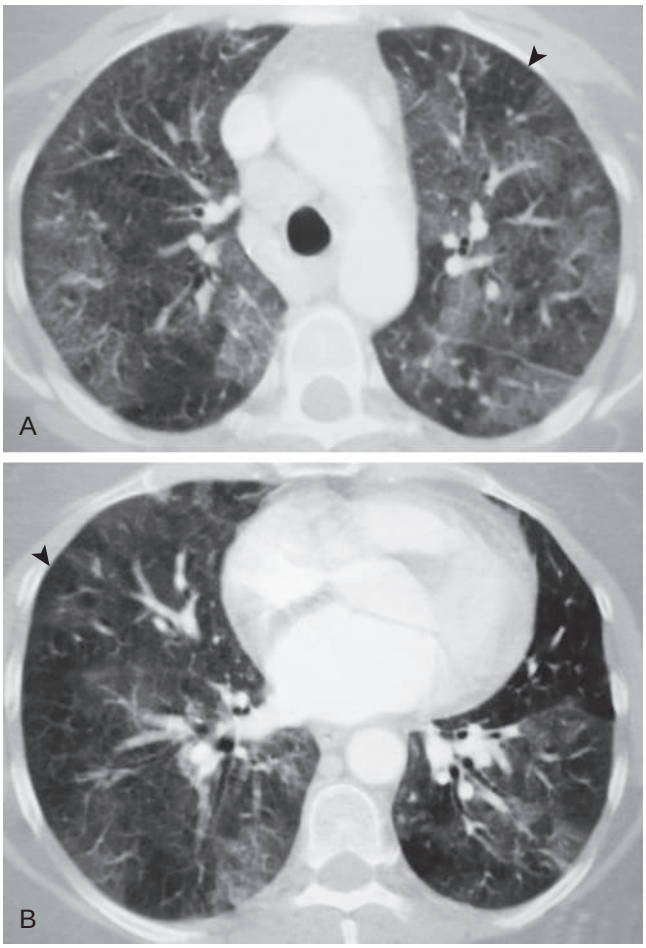
eFigure 90.11 Chest radiography of respiratory bronchiolitis–associated interstitial lung disease. Frontal chest radiograph shows multifocal, bilateral, linear, and reticular abnormalities predominating in a perihilar and infrahilar distribution. Lung volumes are preserved. The appearance is nonspecific. (Courtesy Michael B. Gotway, MD.)



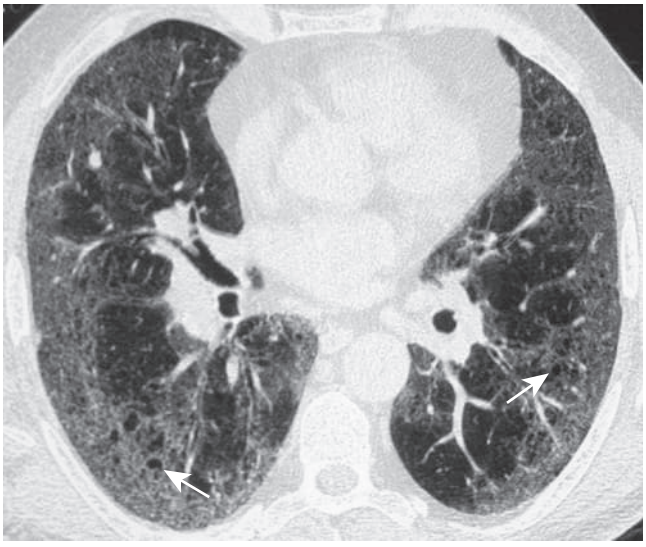
eFigure 90.12 Chest radiography of desquamative interstitial pneumonia. Frontal chest radiograph shows multifocal, bilateral, peripherally distributed linear and reticular abnormalities associated with peripheral left mid-lung consolidation. The appearance is nonspecific. (Courtesy Michael B. Gotway, MD.)



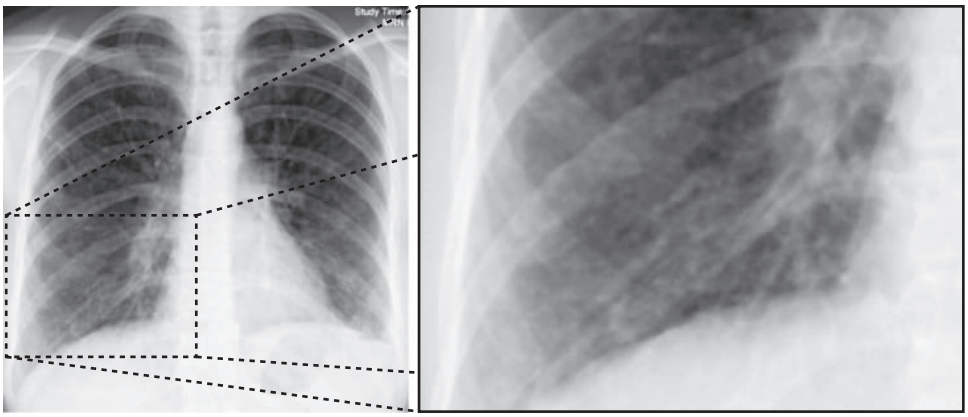
eFigure 90.13 Computed tomography of respiratory bronchiolitis–associated interstitial lung disease. Axial chest computed tomography performed through the (A) upper and (B) lower lobes shows small, centrilobular ground-glass opacity nodules (*arrowheads* in A) predominantly in the upper lobes. Patchy, bilateral inhomogeneous lung opacity is visualized in the lower lobes, consisting of some mild increased attenuation, representing ground-glass opacity, and areas of decreased attenuation, representing mosaic perfusion, resulting from lobular air trapping (*arrow* in B). (Courtesy Michael B. Gotway, MD.)



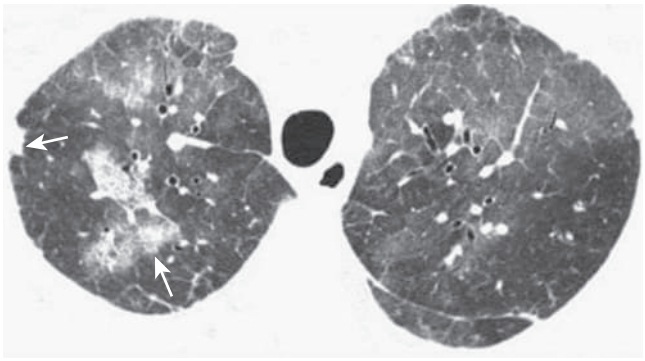
eFigure 90.14 Computed tomography of desquamative interstitial pneumonia. Axial chest computed tomography performed though the (A) upper and (B) lower lobes shows multifocal, patchy areas of ground-glass opacity associated with fine reticular opacities. Areas of lobular low attenuation are present (*arrowheads*). (Courtesy Michael B. Gotway, MD.)



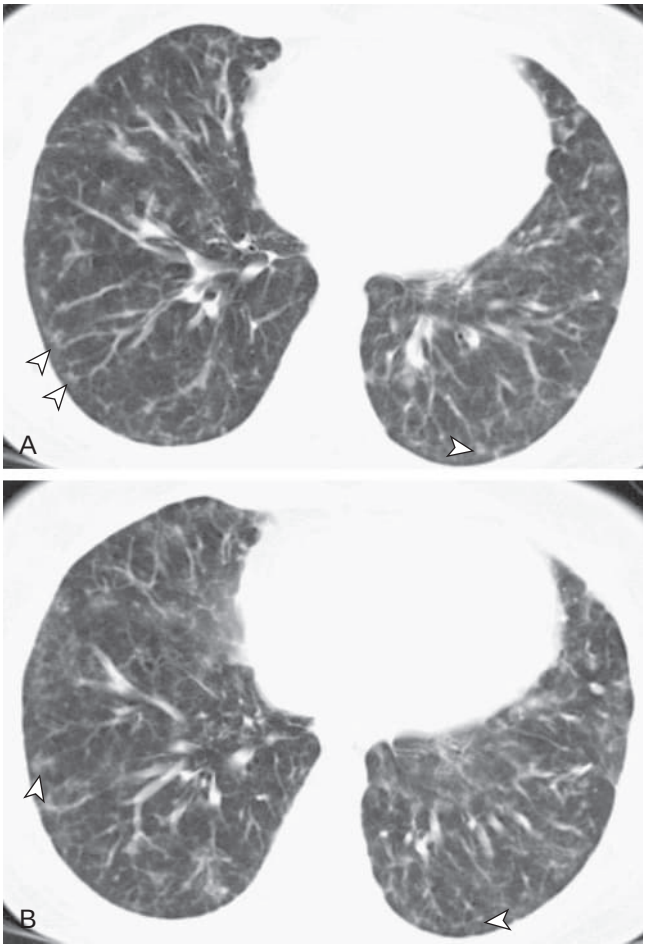
eFigure 90.15 Computed tomography showing small cystic foci in desquamative interstitial pneumonia. Axial chest computed tomography shows multifocal, patchy areas of peripherally located ground-glass opacity associated with fine reticular opacities. Small cystic foci (*arrows*) are present. (Courtesy Michael B. Gotway, MD.)



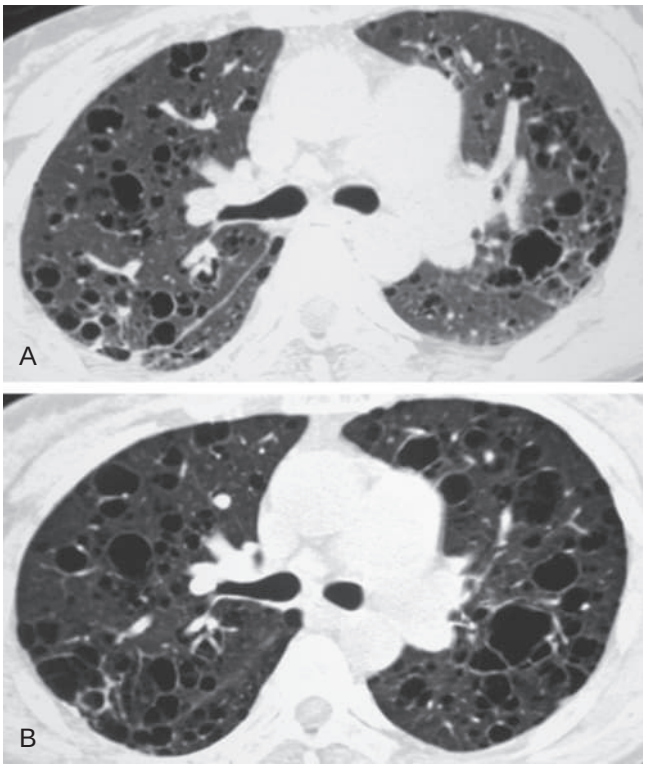
eFigure 90.16 Chest radiography of lymphocytic interstitial pneumonia. Frontal chest radiograph shows bilateral perihilar and infrahilar linear and reticular abnormalities with relative preservation of lung volumes. These findings are best appreciated in the detail of the right lower lobe. The imaging appearance is nonspecific and could result from numerous conditions. (Courtesy Michael B. Gotway, MD.)



eFigure 90.17 Computed tomography showing ground-glass opacity and consolidation in lymphocytic interstitial pneumonia. Axial chest computed tomography performed through the upper lobes shows patchy, multifocal, bilateral areas of ground-glass opacity and consolidation *(arrows)*. The imaging appearance is nonspecific and could result from numerous conditions, including infection, hypersensitivity pneumonitis, and hemorrhage, among other possibilities. (Courtesy Michael B. Gotway, MD.)



eFigure 90.18 Computed tomography showing ground-glass opacity centrilobular nodules in lymphocytic interstitial pneumonia. (A–B) Axial chest computed tomography performed through the lower lobes shows patchy, bilateral bronchovascular thickening as well as small, ground-glass opacity centrilobular nodules (*arrowheads*). (Courtesy Michael B. Gotway, MD.)



eFigure 90.19 Computed tomography showing progression of cysts in lymphocytic interstitial pneumonia. (A) Axial chest computed tomography performed through the mid-lungs shows numerous, variably sized, thin-walled cysts. (B) Axial chest computed tomography performed almost 2 years later shows progression in cyst size and number. (Courtesy Michael B. Gotway, MD.)

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91 HYPERSENSITIVITY PNEUMONITIS

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INTRODUCTION

Hypersensitivity pneumonitis (HP) is a complex inflammatory and/or fibrotic *interstitial lung disease* (ILD) seen in susceptible individuals due to an immunologically mediated reaction to one or more inciting inhaled antigens. HP can arise after exposures in occupational, avocational, residential, or environmental settings. Due to its heterogeneous clinical course and overlap with other ILDs, diagnosis and management can be challenging. Recognizing HP requires a high index of suspicion and should be on the differential diagnosis whenever a patient presents with a syndrome suggestive of ILD.

HP is diagnosed through the integration of clinical, radiologic, and histopathologic findings consistent with the disease. As with all forms of ILD, the diagnostic gold standard is based on review of all available information in a *multidisciplinary discussion* (MDD). Recently, international consensus guidelines have been published for the diagnosis of HP.[1] These developments will help better characterize HP, ultimately improving our understanding and management of this entity. HP is currently classified into two groups, nonfibrotic (or inflammatory) and fibrotic HP. For consistency with prior terminology, acute and chronic HP may be used throughout this chapter synonymously with the nonfibrotic and fibrotic forms of disease, respectively.

CLASSIFICATION

HP is a complex lung disease arising in susceptible individuals caused by the repeated inhalation of a variety of organic or low-molecular-weight agents. For many years, a time-based classification of the clinical-radiologic-histopathologic presentation and disease behavior of HP (i.e., acute, subacute, and chronic) had been used for descriptive purposes.[1a] However, it has become evident that this classification of HP does not provide prognostic precision. A cluster analysis of a large prospective multicenter cohort study showed that most HP cases at presentation fit best into a two-cluster model.[2] This study also showed that subacute HP is particularly difficult to define because the clinical, functional, and imaging findings in this subset overlap with both the acute and chronic forms of disease. Thus, there has been a shift from a solely time-based classification to a stratification of the disease based on characteristics known to improve diagnostic certainty and prognosis, as described next.

Among patients with HP, determining the presence or absence of an inciting antigen exposure is essential for patient counseling and disease management. Furthermore, during the diagnostic workup, the identification of an inciting antigen exposure is the strongest predictor of the likelihood of HP.[3] Also, findings on chest *high-resolution computed tomography* (HRCT) can be prognostic. The initial evaluation of patients presenting with HP or any ILD requires HRCT of the chest before considering invasive testing (e.g., lung biopsy); thus, the evidence supports classifying HP according to the presence or absence of radiographic pulmonary fibrosis. Irrespective of the background pattern of involvement, the radiographic presence of fibrosis (i.e., reticulation, bronchiectasis, or honeycombing) and its extent have been consistently shown to predict a poor outcome.[4–7] The current ontologic approach to HP is conceptualized into two broad categories: inflammatory or nonfibrotic, and fibrotic HP. In general, inflammatory or nonfibrotic HP is expected to normalize with antigen remediation and/or pharmacologic treatment with immunosuppressive drugs. A nonfibrotic form of HP should result in no long-term sequelae. Conversely, patients with fibrotic HP will not have normalization of their lung function, chest imaging, or symptoms and may not achieve disease stabilization.

EPIDEMIOLOGY

HP is one of the most common diagnoses encountered at ILD referral centers worldwide. Population-level databases have helped improve our understanding of disease burden attributable to HP. However, in contrast to work-related HP, nonoccupational HP cases are not reportable and therefore likely underrepresented.[8]

Several factors influence estimates of HP frequency. First, several lines of evidence suggest aging-related mechanisms in HP pathogenesis since its prevalence increases with increasing age. In an analysis of a large U.S. health care database with 150 million unique enrollees, the prevalence of HP increased with age from 0.95 per 100,000 in children aged 0 to 9 years to 11.2 per 100,000 in adults older than 65 years.[9] Second, it is known that environment-specific variations in HP frequency can indicate differences in occupational exposures. The most convincing evidence of the impact of the occupation and the risk of HP comes from epidemiologic studies focusing on *farmer's lung disease* (FLD) and HP among pigeon breeders.[10] Also, there are numerous reports of occupational outbreaks in specific settings such as after exposure to various low-molecular-weight chemicals and contaminated metalworking fluids, ventilation, and water humidification systems.[11] Third, the duration or frequency of exposure to the antigen and weather conditions may contribute to the prevalence and environmental distribution of HP in populations at risk. For example, FLD is prevalent during late winter and the early spring cattle feeding period and after the harvest season, when farmers may be reexposed to a heavy spore concentration from stored moldy hay.[12,13] Similarly, in Japan, the incidence rate of summer-type HP has been reported to increase in years with increased rainfall and decreased daylight hours.[14]

The epidemiologic impact of fibrotic HP (representing a subgroup at high risk for disease progression) was highlighted in an administrative claims-based analysis carried out from 2004 through 2013 that found the 1-year prevalence rate of HP ranged from 1.7 to 2.7 per 100,000 persons. From 56–68% of HP cases in each year were classified as chronic (prevalence, 0.9–1.7 per 100,000 persons). Moreover, up to 25% of cases met the criteria set for fibrotic HP (prevalence ranged 0.4–0.8 per 100,000 persons), which was associated with a higher mortality rate.[15]

Only two countrywide studies have evaluated trends in HP mortality, both from the United States. The overall age-adjusted HP-related mortality rate increased from 0.1 per 1,000,000 in 1988 to 0.7 per 1,000,000 persons in 2016, equating to an average annual percentage increase in mortality rate of 5.6%. Mortality rates increased with increasing age and rates were highest in men and in those from the farming states of the Midwestern United States.[16] Using the same database, an earlier study identified a similar mortality trend over time, observing a significant increase in overall age-adjusted mortality rate between 1980 and 2002 from 0.1 to 0.3 per million.[17] It is unknown whether these trends were caused by an increase in true incidence or disease-related mortality, or by an increase in disease recognition.

ETIOLOGY

More than 200 sources of exposure have been implicated in HP, and new exposures continue to be reported. These causes are frequently named according to the setting in which the patient was exposed (e.g., hot tub lung, cheese washer's lung), but there is significant overlap with the specific antigenic agents implicated in disease. HP antigens can be grouped according to three main categories: microbes, animal proteins, and chemical sensitizers. These exposures can take place in residential, occupational, avocational, or environmental settings, highlighting the importance of a thorough and comprehensive exposure assessment. Importantly, in up to 50% of chronic HP patients at tertiary referral centers, no causative antigen can be identified despite a comprehensive assessment and exhaustive search.[5,18] The prevalence of HP without an identified antigen suggests that either there are unrecognized causes of HP and/or current exposure assessment and identification tools have limited ability to identify the inciting antigen source. Table 91.1 provides a list of commonly reported causes of HP. More comprehensive summaries of the causes of HP are available elsewhere.[19,20]

MICROBES

Microbial organisms such as bacteria and fungi flourish in both indoor and outdoor environments. Many microbes are ubiquitous, and their inhalation may initiate sensitizing diseases of the lung, including HP. Several species of bacteria are known to cause HP. Thermophilic actinomycetes are causally associated with FLD. These bacteria thrive in hot temperatures and damp conditions, secreting enzymes that digest agricultural products, and can cause FLD when inhaled in large quantities, such as by pitching moldy hay. Thermophilic actinomycetes are also found in moldy sugar cane and mushroom compost. Water sources such as humidifiers, showerheads, and swamp coolers have been associated with multiple forms of bacteria causing HP, including *Thermoactinomyces vulgaris* and *Mycobacterium avium complex*. In metalworking fluid used in several industrial work environments, contamination by nontuberculous mycobacteria led to isolated cases and outbreaks.[21–23] Mycobacterial exposures have also been reported to cause HP from exposures to contaminated water sources such as swimming pools (lifeguard's lung) and hot tubs (hot tub lung).[24–26]

Fungal antigen exposure can cause some forms of HP via the inhalation of airborne spores, mycelial fragments, metabolites, and toxins of different fungi.[27] Multiple fungi have been cultured from these environments, highlighting the general point that sensitizing and inciting exposures may not be single, but may be multiple with additive or even synergistic effects. Indoor environments ripe for fungal growth include garbage containers, food storage areas, wallpaper, curtains, carpeting, and areas of moisture such as shower curtains, damp basements, air conditioners, and emissions from cool mist vaporizers.[28,29] Several different fungal species are implicated in causing HP. *Aspergillus* species have been associated with HP in esparto lung, caused by exposure to esparto grass fibers and often seen in plasterers.[30] *Penicillium* species can cause HP in cheese washers, cork workers, sausage makers, and tree cutters. Summer-type HP is the most common form of HP reported in Japan, caused by residential mold contamination with

Table 91.1 Common Causes of Hypersensitivity Pneumonitis (HP)

Disease	Antigen	Scenario/Source
MICROBES		
Farmer's lung	Thermophilic actinomycetes, *Faeni rectovirgula*	Moldy hay, silage, grain
Humidifier lung	*Thermoactinomyces vulgaris*, *T. sacchari*, *T. candidus*	Contaminated forced air systems, water reservoirs
Hot tub lung	*Mycobacterium* avian complex spp	Contaminated hot tubs
Wind instrument lung	*Fusarium* sp, *Penicillium* sp, *M. chelonae*, *Candida* sp, *Cryptococcus* sp	Contaminated trombone, bagpipe, saxophone
Metalworking fluid lung	*M. immunogenum, Pseudomonas* sp	Aerosolized metalworking fluid
Summer-type HP	*Trichosporum cutaneum*	Contaminated old houses
Mushroom worker's lung	*T. sacchari*	Mushroom compost
Suberosis	*T. viridis, Aspergillus fumigatus, Pseudomonas* spp	Cork molds
Esparto lung	*Aspergillus fumigatus*	Moldy *Stipa tenacissima* grass
Woodworker's lung	*Alternaria* sp wood dusts	Moldy oak, cedar, mahogany
ANIMAL PROTEINS		
Pigeon breeder's lung	Pigeon droppings, feathers, serum	Pigeons, domestic and environmental
Bird fancier's lung	Avian droppings, feathers, serum	Parakeets, budgerigars, love birds, cockatiels, chickens
Duvet lung	Avian feathers	Pillows, duvets, sleeping bags stuffed with feathers
Animal handler's lung	Rats, gerbils	Urine, pelts, serum, proteins
Bat lung	Bat proteins	Bat droppings
CHEMICAL SENSITIZERS		
Chemical worker's lung	Isocyanates	Spray paints, polyurethane foams, glues
Epoxy resin lung	Phthalic anhydride	Heated epoxy resin
Pauli's reagent alveolitis	Sodium diazobenzene sulfate	Laboratory reagent

Trichosporon sp, typically in wood flooring.[31–33] The most common cause of HP in Australia is domestic fungal exposure from decaying wood and damp walls in urban dwellings.[34] Contaminated wind instruments (e.g., trombones, saxophones) can harbor multiple different microbes, including *Penicillium* sp, *Fusarium* sp, and mixed fungi.[35–37]

ANIMAL PROTEINS

Inhaled particulates from a wide variety of animals have been associated with HP. Bird exposure is the most frequently reported animal cause of HP. Avian antigens are high- and low-molecular-weight proteins found in the serum, droppings, and feathers and are highly immunogenic. Bird "bloom" is a fine respirable dust that coats bird feathers. It is composed of keratin and immunoglobulins and is highly immunogenic. Flying birds such as pigeons and parakeets can produce a considerable amount of bloom and are the birds most often associated with HP. Bird antigen exposure is at its highest level with activities such as cleaning out cages and coops. Duvet lung is an established form of HP, reported in patients using feather down duvets and bedding.[38–40] Down products also are used as filler for pillows, coats, and high-end furniture, including sofas or decorative cushions. There appears to be cross reactivity across sources of bird antigens, with HP exacerbations after exposure to down bedding in hotels or guest rooms.[41] Patients with *bird-exposure HP* (BHP) should avoid all potential sources, including feathers and down products.

Avoidance or complete removal of bird antigens can be very difficult, particularly in a home environment. Despite thorough cleaning, bird antigen can persist in residential dust samples for years and may explain why some patients continue to have progressive disease despite apparent remediation.[42] Moreover, some patients with bird exposure may be reluctant to remove the family bird from the home and are at risk of persistent exposure.

Animal handlers, laboratory workers, and veterinary workers can develop HP after sensitization and subsequent inhalational exposure to animal proteins in pelts, serum, and feces of rodents, including rats and gerbils. Those involved in the production of silks can develop HP from larval and cocoon particulates, while production workers exposed to mollusk shells can develop HP from the shell dust during cutting and polishing shells to make buttons.[43]

CHEMICAL SENSITIZERS

HP is caused less commonly from low-molecular-weight chemical sensitizers than by microbes and animal proteins, but these exposures are widespread across many industries and present risk for occupational HP. Isocyanates are used in large-scale production of polyurethane polymers for foams, adhesives, paints, and surface coatings and are recognized as a cause of HP.[44,45] Acid anhydrides used in plastics, paints, and epoxy resins have been reported to cause HP.[46] There are rare reports of HP from exposure to the pesticide pyrethrum, Pauli's reagent in chromatography, copper sulfate in fungicides used in vineyards, and the enzyme

phytase used as an additive in cattle feed.[47] Other chemicals reported to cause HP include styrene, formaldehyde, and dimethyl phthalate.[48,49]

IMMUNOPATHOGENESIS

The pathobiology of HP is complex and incompletely characterized for both the inflammatory and fibrotic forms of the disease. Overall, the development of HP appears to involve (1) inhalational antigen exposure, (2) host sensitization to the antigen, and (3) immune-mediated lung damage. The lung damage may regress or progress depending on host factors and/or ongoing antigen exposure. Antigenic exposure assessment is challenging for several reasons, including the unknown latency period between exposure and clinical disease and the lack of a clearly defined dose-response relationship. This makes it difficult to identify the timing of sensitization or exposure, particularly in cases of fibrotic HP.

Both humoral and cellular mechanisms are likely important in the development of HP, and their relative activity may influence the phenotype of disease (e.g., nonfibrotic vs. fibrotic). Early reports suggested a role of immune complexes in the development of HP, but the lack of immune complexes in *bronchoalveolar lavage* (BAL) fluid and the fact that HP develops in the presence of hypogammaglobulinemia indicate this to be an unlikely mechanism.[50,51] T cell–mediated delayed-type hypersensitivity appears to play a key role in the pathogenesis of HP. This is supported by the increased number of T cells in BAL fluid, lymphokine production by antigen-stimulated T cells of the lung, and the transferability of disease via sensitized T cells in animal models.[52–54]

In acute HP, BAL fluid cellular profiles show an alveolitis in which neutrophilic influx peaks 48 hours after exposure followed by a subsequent lymphocytic alveolitis. $CD4^+$ lymphocytes predominate early, between 48 and 72 hours, due to redistribution from peripheral blood and due to local lymphocyte proliferation. An influx of $CD8^+$ lymphocytes typically lags that of the $CD4^+$ cells, although the CD4:CD8 ratio can be unpredictable. Activated alveolar macrophages contribute to the production of reactive oxygen species, leading to damage of alveoli. The lymphocytes and antigen-presenting cells release inflammatory chemokines and cytokines, further perpetuating the inflammatory response.

In persistent forms of HP, the adaptive immune response is characterized by a profound BAL lymphocytosis comprised of $CD4^+$ and $CD8^+$ cells. A cell-mediated type IV hypersensitivity reaction is essential to its pathogenesis. Lymphocytes accumulate in the interstitium and peribronchial tissue, leading to the formation of poorly formed granulomas. Granuloma formation is supported by *type 1 T helper* (Th1) lymphocyte and macrophage secretion of cytokines including interferon-γ, tumor necrosis factor-α, and interleukin 18 (see also Chapter 16).

The pathobiology of fibrotic HP is not clear. After induction by the antigen and promoting factors that drive inflammation, progression factors promote fibrosis and chronicity.[55] Chronic lower-level antigen exposure may contribute to a smoldering low-grade subclinical inflammation that leads to fibrosis. Conversely, this form may be driven by profibrotic aberrant wound healing and not arise from unsuppressed inflammation, as seen in the acute form of HP. Again, the BAL cellular profiles provide insight into the pathophysiology of the disease. In fibrotic HP, there is a shift toward a profibrotic pathway with a loss of effector T cell function, and increases in the Th2 lymphocyte profile and CD4:CD8 ratio.[56] Polarization of $CD4^+$ lymphocytes to a Th2 phenotype may be important for the fibrotic response. Mice genetically programmed for enhanced Th2 response were more likely to develop lung fibrosis.[57] It remains unclear how host factors, antigen exposure, and immunologic reactivity interact to drive the chronic and progressive form of the disease.

HOST FACTORS AND GENETICS

The development of HP depends not only on the type, intensity, and duration of exposure to an inciting antigen but also on individual susceptibility. Only a small proportion of any population of exposed individuals develops HP, suggesting a prerequisite for an underlying susceptible genetic predisposition. Studies have reported familial clustering of patients with chronic HP in different environments and the development of summer-type HP in monozygotic twins.[58] Also, early studies showed an increased relative risk for the development of HP in subjects with specific polymorphisms of major histocompatability class I (A2, A11),[59] class III (tumor necrosis factor-α),[60] class II (DP, DQ, DR) antigens,[60–62] and transporters associated with antigen processing and antigen loading on major histocompatability class I.[63] Variations in immune responses may also be important determinants of the clinical phenotype of HP. Human and animal studies suggest that patients with chronic HP may lose effector T cell function, exhibit skewing toward Th2 and/or Th17 activity, and exhibit a decrease in gamma-delta T cells (implicated in the regulation of the immune response generated against microbial pathogens and allergens), which may be involved in the fibrotic response that characterizes this clinical form.[56,64]

Genomic factors have been examined to help stratify risk and provide insights into the pathogenesis of HP. In familial pulmonary fibrosis associated with abnormal telomere-related genes, 12% of affected individuals have chronic HP even if the index case or affected family member has a different diagnosis of fibrotic ILD such as *idiopathic pulmonary fibrosis* (IPF).[65,66] Thus, a family history should be obtained to identify potentially familial forms of ILD because this may help identify underlying genetic drivers of disease.

A *MUC5B* promoter variant and mutations in the telomere reverse transcriptase gene and telomere attrition have been associated with an increased risk for the development of fibrotic HP.[67] The prevailing hypothesis is that the *MUC5B* promoter variant may impair mucociliary clearance, mucosal host defense, and alveolar repair and contribute to lung injury and inflammation. In turn, persistent inflammation in chronic HP may promote accelerated alveolar epithelial cell turnover, contributing to telomere shortening in these cells and increasing the risk for lung remodeling and fibrosis. In a multicenter study of patients with chronic HP, short telomere length (<10th percentile for age) in peripheral blood

leukocytes and the *MUC5B* promoter variant were associated with radiographic fibrosis. Short telomere length was also strongly associated with histopathologic features typical of *usual interstitial pneumonia* (UIP) and reduced survival.[67] Furthermore, in chronic HP, the presence of protein-altering variants in telomere-related genes, which are associated with short peripheral blood telomere length, are found in approximately 10% of chronic HP patients and correlate with reduced transplant-free survival.[68]

In addition to inherent biologic susceptibility, external risk factors may modify the development and expression of HP.

Tobacco Use

Interestingly, smokers are less likely than nonsmokers to develop HP, attributed to a reduced immune response to inhaled antigenic exposure. In an animal model of HP, nicotine exposure reduced cellular responses, lymphocyte and total cell counts in BAL, and overall lung inflammation. Pigeon fanciers who smoked had lower levels of *immunoglobulin* (Ig) A and IgG antibodies to pigeon proteins compared to former and nonsmokers, suggesting that smoking reduces T cell–dependent and –independent responses to inhaled antigens.

However, despite the apparent preventive effect of smoking, smoking has a harmful effect on those who already have HP. Patients with chronic HP who are cigarette smokers at diagnosis have a worse prognosis even after adjusting for the presence of fibrosis.[18] In a case-control study, patients with chronic FLD who were current or former smokers had a lower survival rate compared with nonsmokers.[69] As in IPF, a subset of patients with significant smoking history might present with simultaneous fibrotic HP and emphysema. Such patients can present with significant hypoxemia and a marked reduction in the *diffusing capacity of the lungs for carbon monoxide* (D_{LCO}) out of proportion to relatively preserved lung volumes on pulmonary function tests.

Viral Infections

Viruses are known to enhance the pathology of experimental HP induced in mice by repeated exposures to causative HP antigens.[70] Similarly, common respiratory viruses have been isolated from the lower airways of patients with acute HP.[71]

Pathogen Virulence

In a mouse HP model of exposure to different mycobacterial genotypes belonging to three different species, the extent of the inflammatory cell response on BAL and extent of disease is highly dependent on the type of bacteria. This suggests that, in addition to host susceptibility, differential immunogenicity of mycobacteria strains may also impact the development of disease.[72]

HISTOPATHOLOGY

The hallmarks of histopathology in HP have been referred to as "the triad of four." This includes (1a) a diffuse lymphoplasmacytic interstitial infiltrate, (1b) with bronchiolocentric accentuation, (2) poorly formed granulomas, and (3) foci of organizing pneumonia (Fig. 91.1).[73] The

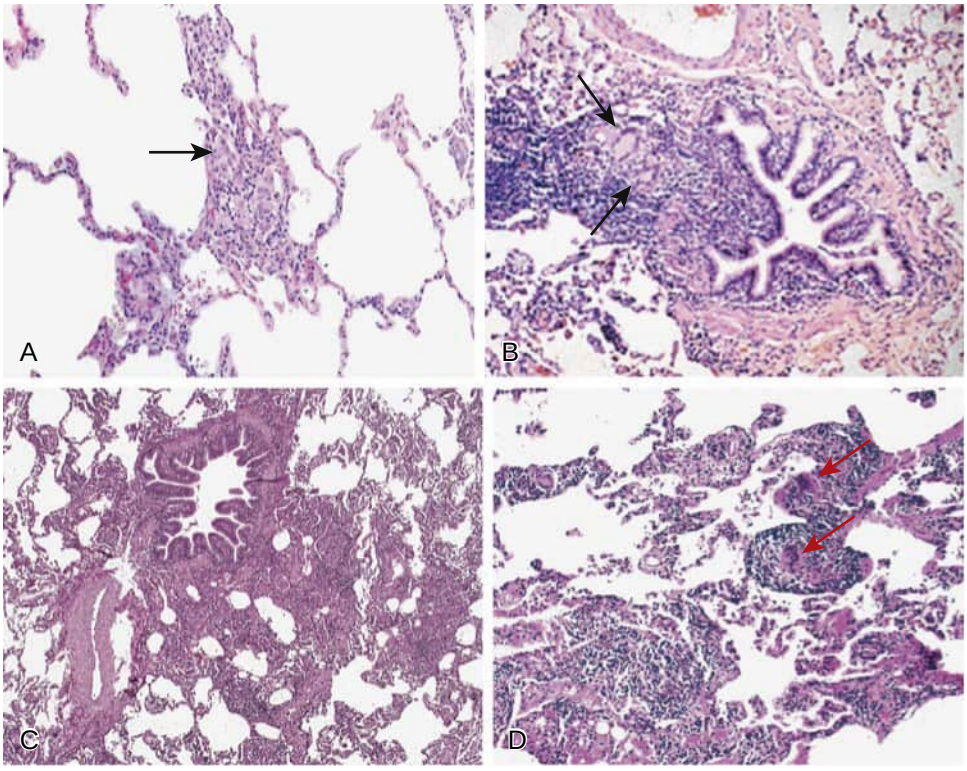

Figure 91.1 Granulomatous involvement seen in hypersensitivity pneumonitis. (A) Several poorly formed non-necrotizing granulomas are present (*arrow*). (B) Airway-centered interstitial fibrosis is seen together with giant cells (*arrows*). (C) A bronchiolocentric distribution may be evident, as indicated either by the presence of a terminal bronchiole or by some degree of nodularity to the infiltrates at low magnification. (D) Multinucleate giant cells (*arrows*) may also be seen in the interstitium and constitute a helpful feature at low magnification in drawing the eye to features meriting closer examination.

poorly formed granulomas of HP consist of loose aggregates of epithelioid histiocytes with or without multinucleate giant cells. Not all features of the triad may be identified on lung biopsy, especially depending on the stage of disease and type of biopsy performed (surgical vs. transbronchial). Cholesterol clefts in the interstitium are a common but nonspecific finding in HP. Giant cells with cholesterol clefts can be found in the airways in obstructive lung disease but, when present in the interstitium, are suggestive of HP.

Specific histologic findings of acute or nonfibrotic HP are poorly understood, given the infrequent rate of surgical lung biopsy in this clinical context. Biopsies generally show lymphocytic interstitial infiltrates and a neutrophilic and lymphocytic alveolitis, similar to the BAL findings in the acute phase. Focal areas of eosinophilic infiltration may also be found. As the disease progresses in nonfibrotic HP, the lymphocytic infiltrate may become most prominent in peribronchiolar areas and may resemble the *nonspecific interstitial pneumonitis* (NSIP) pattern with a uniform distribution. The presence of poorly formed granulomas may be a helpful distinguishing feature. The exception to this is in hot tub lung, where granulomas may be more well formed, although smaller and more loosely organized than those found in sarcoidosis.[74] Granulomas in HP rarely hyalinize; thus they can resolve after disease remission and antigen remediation. Focal areas of organizing pneumonia and constrictive bronchiolitis may be observed.

With increasing fibrosis in chronic HP, features of the triad may be identified, but other patterns can exist. Bridging fibrosis may be seen between perilobular and peribronchiolar areas, and granulomatous inflammation may or may not be present. Organizing pneumonia, cellular or fibrotic NSIP, and UIP with honeycombing and fibroblastic foci have all been described in chronic HP.[75] In the UIP-like pattern, a bronchiolocentric distribution of disease raises the likelihood of HP over IPF. More recent data suggest, however, that fibrotic bronchiolocentricity may also be identified in patients with IPF and is not as specific for HP as previously thought.[76] That no single feature is pathognomonic for HP reinforces the importance of incorporating pathologic data into the overall clinical and radiologic context, which should then be reviewed in an experienced MDD.

DIAGNOSIS

No single test can confidently establish or exclude a diagnosis of HP. Multiple domains, including clinical, radiologic, and histopathologic information, must be incorporated into the diagnostic pathway (Fig. 91.2). Because there are no universally agreed-upon diagnostic criteria for HP, clinical prediction models have been developed to discriminate HP from other forms of non-HP ILD.[77–80]

EXPOSURE ASSESSMENT

Identifying a potential causative exposure in HP relies upon the application and interpretation of a host of clinical tools. Most HP diagnostic algorithms start with antigen identification, because it is essential in establishing a confident diagnosis. Nevertheless, a positive exposure history or serologic testing does not necessarily imply disease causality, and judgment must be applied when interpreting findings. Furthermore, an unidentified antigen does not rule out the diagnosis of HP because antigen indeterminate status may signify exposure to an unrecognized or to a novel, as of yet unidentified, antigen. HP can present in patients with autoimmune features[81,82]; therefore, the presence of autoimmune features or positive serology does not necessarily exclude a diagnosis of HP.

History

The first step towards identifying a potentially relevant exposure is taking a comprehensive history aimed at identifying the antigen. This can be achieved through direct questioning or by the completion of HP-specific questionnaires, the latter of which may be helpful because they are less dependent on the clinician's memory. To date, no such questionnaire has been validated for clinical use, and many exposures vary geographically, seasonally, and/or culturally. Therefore, a focused history should be contextualized to relevant exposures in the current environment. The history should focus on current and previous occupations, with detailed descriptions of work settings and exposures. Questions should cover the home environment, with a focus on contaminated water sources or mold, including musty odors and previous water damage. It is also essential to ask about current and past bird and down exposures, with detailed histories of pet birds and bird-related activities, as well as use of down-stuffed bedding or furniture, as well as about hobbies such as woodworking, spray painting, musical instruments, and those that include use of glues or resins. Consultation with an occupational medicine expert should be considered, particularly when the exposure is thought to arise in a workplace setting or when a home or avocational setting requires a more thorough evaluation than can be addressed by clinical history alone.

Antibody Testing

Serum-specific antibody tests are neither sensitive nor specific for the diagnosis of HP but may identify immunologic reactivity by measuring the patient's IgG reaction to specific antigens.[83] There are two main methods of serum IgG testing: qualitative IgG measurement using double diffusion (i.e., serum precipitins) and quantitative IgG measurement (e.g., enzyme-linked immunosorbent assay). In some circumstances, when the inciting antigen is known, positive antibodies may support the diagnosis. In a study of French farmers, serum antibody tests had good sensitivity and specificity for distinguishing those with HP from those without.[27] Antibody testing should not be used as a screening tool given the high false-positive rate in those exposed to the antigen but without evidence of disease. In a large study of bird fanciers, 92% of those with BHP had positive antibodies, but so did 87% of control bird fanciers without HP.[84]

There are important limitations to the use of antibody tests, and their results must be interpreted with care. Serum antibodies can wane over time with decreased exposure or may be undetectable with chronic low-level exposure. Antigens included in standard HP panels may not be applicable to the individual patient's environment,

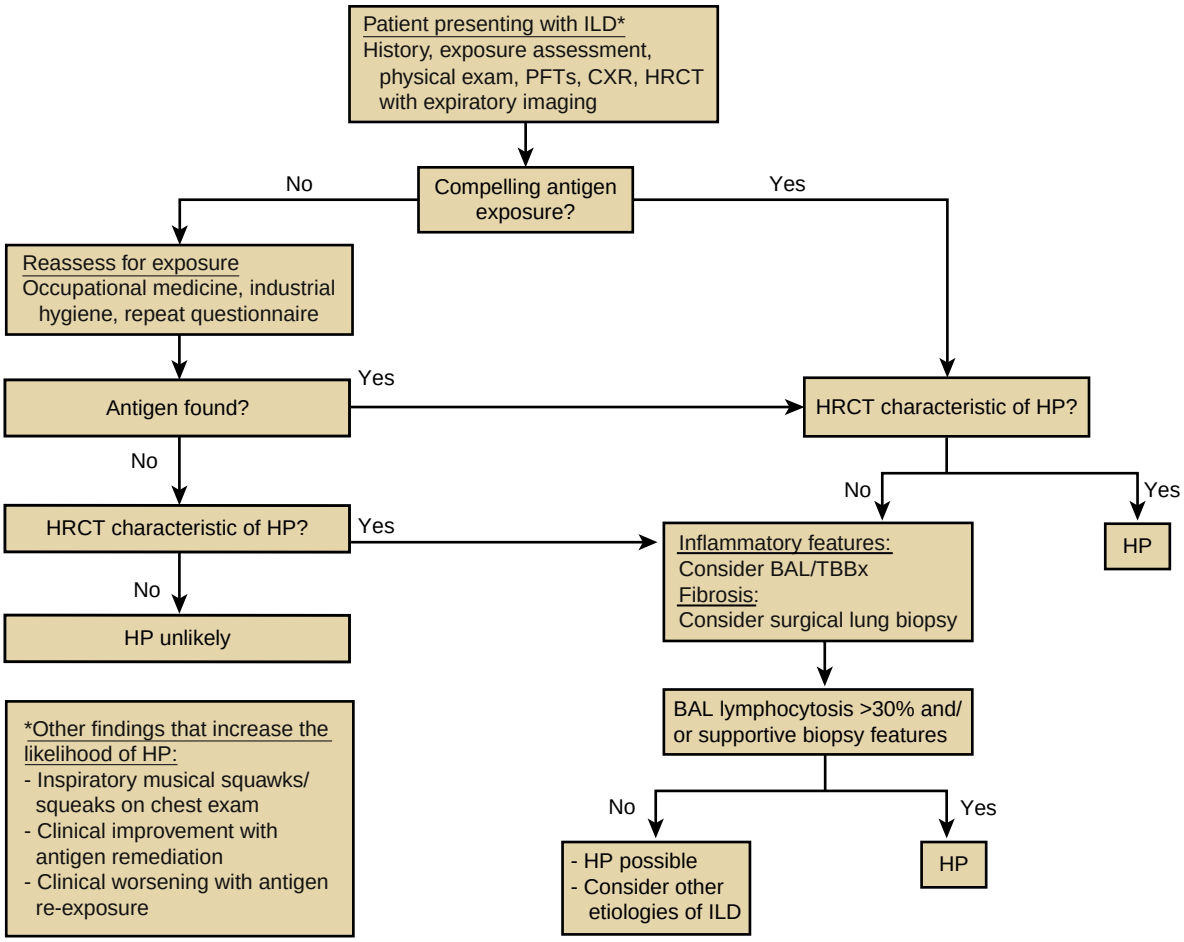

Figure 91.2 Approach to the diagnosis of *hypersensitivity pneumonitis* (HP). The diagnostic HP approach requires thorough exposure evaluation, exclusion of alternative etiologies, and multidisciplinary evaluation. The first and most crucial step in determining the likelihood of diagnosis is characterizing the occupational and environmental exposure by a comprehensive history and/or exposure questionnaire. Because the identification of the inciting antigen source and mitigation are critical, referral to an occupational medicine specialist or industrial hygienist may be helpful, especially when a more detailed investigation is needed. The combination of the clinical context, exposure history, and chest *high-resolution computed tomography* (HRCT) pattern inform the degree of diagnostic certainty: confident vs. working diagnosis vs. unlikely. For patients with a working diagnosis, on a case-by-case basis and in the setting of multidisciplinary discussion, further testing including *bronchoalveolar lavage* (BAL)/*transbronchial biopsy* (TBBx) and/or surgical lung biopsy may be considered. After the HP diagnosis is made, if not previously done in a patient with suspected HP, removal of the inciting antigen and careful reevaluation for possible ongoing reexposure are vital. CXR, chest radiograph; ILD, interstitial lung disease; PFTs, pulmonary function tests.

presenting a risk of false-negative results.[85] On the other hand, a positive result confirms that the patient has been exposed to that antigen, but it does not necessarily equate to causation of disease. Results may be most informative if antigens are prepared from a direct sample of the patient's environment, although this requires highly specific expertise and the cost and effort required make it largely prohibitive at present.[85,86]

Inhalational Challenge

Skin tests for immediate and delayed hypersensitivity reactions are not recommended in the diagnostic testing for HP.[87] *Specific inhalational challenge* (SIC) exposes the patient to the suspected inciting antigen via an inhalational circuit, and the physiologic reaction is measured. A positive SIC can support the diagnosis of HP and implicate the causative agent,[80,88–90] but SIC testing requires skilled personnel and specialized equipment and is performed at only a few centers worldwide. It remains unclear what SIC adds beyond a positive exposure history because the causative antigen must be suspected in the first place to select the exposure reagent. In vitro lymphocyte proliferation testing has been described in avian HP but is not widely available, and its diagnostic performance characteristics remain unclear and is therefore not recommended.[91,92]

CLINICAL FEATURES

Signs and Symptoms

The clinical presentation of a patient with HP varies substantially depending on the type, duration, and intensity of exposure and whether the patient has an acute or chronic illness (Table 91.2). Symptoms of acute HP typically arise 4 to 8 hours after the exposure and consist of a flulike syndrome with malaise, fever, and chills.[93] Respiratory symptoms include nonproductive cough and dyspnea. Symptoms usually resolve within 24 to 48 hours but may recur upon reexposure to the antigen. The presentation of chronic HP

Table 91.2 Typical Features and Differential Diagnosis of Hypersensitivity Pneumonitis

	Nonfibrotic	Fibrotic
Time course of presentation and inciting antigen exposure	▪ Acute symptom onset ▪ Exposure to antigen ▪ Temporal relation of symptoms to exposure usually recognized ▪ Chronic presentations are less common	▪ Chronic, insidious symptom onset ▪ Inciting antigen may not be recognized ▪ Unclear relation between exposure and symptoms
Symptoms	▪ Cough, dyspnea at rest and/or with exertion ▪ Systemic symptoms including fever, chills, myalgias	▪ Dyspnea on exertion ▪ Cough, typically nonproductive
Physical examination	▪ Fever, tachypnea, hypoxemia ▪ Crackles on chest exam ▪ Inspiratory musical squeaks/squawks ▪ May have normal exam	▪ Inspiratory Velcro crackles ▪ Inspiratory musical squeaks/squawks ▪ Hypoxemia on exertion ▪ May have normal exam
HRCT chest imaging	▪ Diffuse ground-glass opacities ▪ Centrilobular nodules ▪ Bronchovascular distribution ▪ Mosaic attenuation ± air trapping on expiratory imaging ▪ Mixed interstitial (ground-glass opacities or high-attenuation areas) and obstructive (mosaic changes or low-attenuation areas), i.e., "headcheese" sign	▪ May have similar findings as acute HP, but also: ▪ Fibrosis—reticulation, traction bronchiectasis or bronchiolectasis, honeycombing
Bronchoalveolar lavage fluid analysis	▪ Lymphocytosis (lack of this finding does not exclude HP)	▪ Lymphocytosis less common (lack of this finding does not exclude HP)

Histopathologic findings	▪ Neutrophilic and lymphocytic infiltrates involving bronchioles and alveolar interstitium
	▪ Poorly formed granulomas
	▪ Lymphocytic bronchiolitis
	▪ Foci of organizing pneumonia
		▪ Features seen in acute HP, plus:
		  ▪ Peribronchiolar fibrosis
		  ▪ Interstitial fibrosis ± bridging features
		  ▪ UIP-like pattern with honeycombing and fibroblastic foci

Differential diagnosis	▪ Viral, atypical pneumonia
	▪ CTD-ILD
	▪ Drug reaction
	▪ Inhalational fever (e.g., organic dust toxic syndrome)
	▪ Toxic fume inhalation
	▪ Asthma
	▪ Sarcoidosis
	▪ Mycobacterial infection
	▪ Aspiration pneumonitis
	▪ Bronchiolitis obliterans
	▪ Organizing pneumonia
	▪ Acute fibrinous and organizing pneumonia
	▪ Granulomatous-lymphocytic interstitial lung disease
		▪ Other ILD:
		  ▪ CTD-ILD
		  ▪ NSIP
		  ▪ IPF
		▪ Sarcoidosis
		▪ Familial ILD
		▪ Pleuroparenchymal fibroelastosis

CTD, connective tissue disease; HP, hypersensitivity pneumonitis; ILD, interstitial lung disease; HRCT, high-resolution computed tomography; IPF, idiopathic pulmonary fibrosis; NSIP, nonspecific interstitial pneumonitis.

has a more insidious onset with nonproductive cough and exertional dyspnea being the most common symptoms. The presentation frequently overlaps with other fibrotic ILDs such as IPF. Symptoms may be episodic or situational in relation to exposure or persistent due to low-level chronic exposure.

Patients with acute HP may have a normal physical examination or demonstrate inspiratory crackles or expiratory wheeze. They may have low-grade fever, tachycardia, and tachypnea. Oxygen saturation may be low at rest or solely with exertion. Patients with fibrotic HP typically have inspiratory Velcro-like crackles but may have clubbing and other findings associated with fibrotic ILD such as right heart dysfunction. Notably, patients with HP may demonstrate high-pitched inspiratory musical squeaks or squawks in the chest corresponding to bronchiolitis and small airways involvement.[94] In a study of 14 patients with ILD and inspiratory squawks, nine had HP.[95] HP-related squawks were of shorter duration and higher frequency and were heard later in inspiration. They are localized most commonly in the upper lobes but may be heard anywhere in the chest.[96] The sensitivity and specificity of these auscultatory findings have not been studied within clinical prediction models but may serve to identify HP and are an important physical exam finding.

Lung Function

Pulmonary function tests (PFTs) should be obtained on every patient presenting with suspected HP. PFTs can demonstrate an obstructive, restrictive, or mixed defect, often with a reduced D_{LCO}. Spirometry and lung volumes may be preserved, with an isolated low D_{LCO}, or in some cases PFTs may be within normal limits. Exercise testing may reveal normal oxygen saturation at rest with isolated exertional desaturation. Nonspecific bronchial hyperreactivity has been described in HP and identified on methacholine challenge testing. In patients diagnosed with HP, longitudinal serial PFTs should be conducted to monitor for disease stability or progression. As in other forms of ILD, exercise oxygenation studies should also be conducted periodically, because new-onset exertional desaturation may herald disease recurrence or progression.

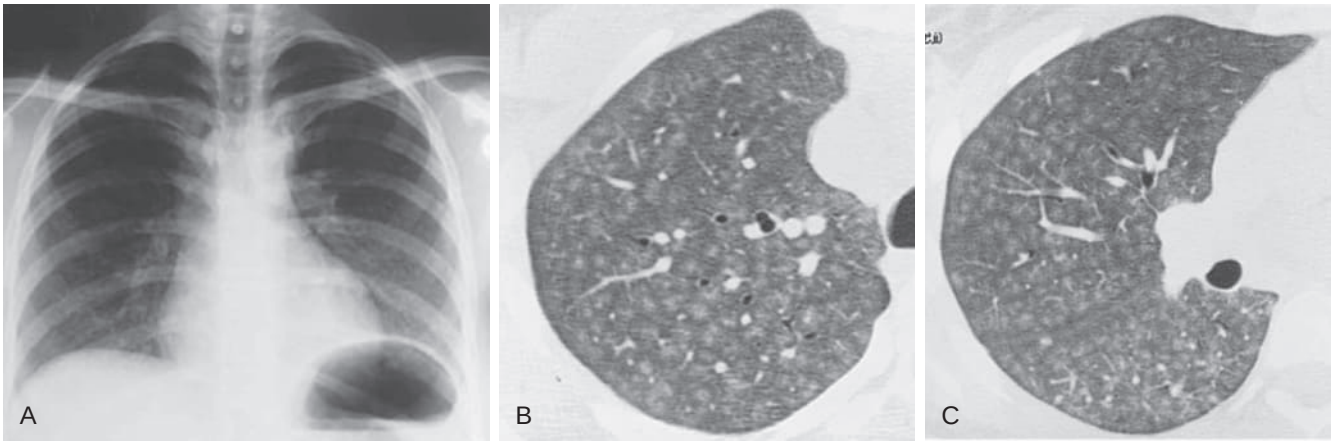

Figure 91.3 Nonfibrotic hypersensitivity pneumonitis. (A) Chest radiograph of a patient with hypersensitivity pnemonitis shows diffuse poorly defined nodular opacities. (B) *High-resolution computed tomography* (HRCT; 1.5-mm thin section) image through the lung of the same patient shows profuse centrilobular ground-glass opacity nodules. (C) HRCT scan of a different patient with bird breeder's lung shows diffuse ground-glass attenuation with reticular opacities and centrilobular ground-glass opacity nodules.

Bronchoalveolar Lavage

BAL fluid cellular analysis may be performed as part of the diagnostic workup of patients with suspected HP. It is a relatively safe, minimally invasive procedure that can identify alveolitis and help support a diagnosis. However, BAL findings are neither sensitive nor specific for HP. Antigen-exposed but healthy individuals can have a BAL alveolitis, and HP patients can demonstrate persistent alveolitis despite a lack of ongoing exposure to the inciting antigen or even when in disease remission.[97] Classically, a marked lymphocytosis with greater than 50% lymphocytes is highly suggestive of HP, although this degree of lymphocytosis can also be seen in other entities such as cryptogenic organizing pneumonia and NSIP.[98]

Patients with fibrotic HP may not demonstrate active alveolitis. In a large epidemiologic study of chronic HP from Japan, the median BAL lymphocyte rate was 24.5%, with substantial variability across individuals and etiologies.[99] Of 86 patients with bird fancier's lung, 15 (17%) had the fibrotic form of disease.[84] BAL was performed in a subset of patients (7/15), finding a BAL lymphocytosis greater than 20% in 6 of 7 (85%), but these findings may not be generalizable to an unselected population. In a study of 139 HP patients where 41 of 139 (29.5%) had chronic disease, the mean lymphocyte percentage was elevated in all forms of disease but was significantly lower in chronic HP than in acute HP.[100] In a study of 72 HP patients, 44 of whom had histopathologic fibrosis, the average BAL lymphocyte count was significantly lower in fibrotic HP compared to nonfibrotic HP (15 ± 31 vs. $46 \pm 31 \times 10^6$ cells/mL).[101] A systematic review and meta-analysis found that BAL lymphocyte percentage was higher in patients with chronic HP (42.8%) compared to patients with IPF (23.1%), non-IPF IIP (23.4%), and CTD-ILD (23.4%) but not sarcoidosis (31.2%).[101a] Using individual patient data, the optimal performance of BAL lymphocyte percentage was at a threshold greater than 20%, differentiating chronic HP from other forms of ILD with a sensitivity of 68.1% and a specificity of 64.8%. The presence of radiographic fibrosis is generally associated with the absence of BAL lymphocytosis in ILD[102] and, in advanced fibrotic HP with a histologic pattern resembling UIP, BAL lymphocytosis is unlikely.[91] Older age and a positive smoking history are also associated with lower BAL lymphocyte percentage in chronic HP.[101a] Overall, BAL fluid lymphocytosis is less likely to be present with increasing fibrosis and/or with remote or uncharacterized antigen exposure. The CD4:CD8 ratio is often elevated in HP, particularly in comparison to sarcoidosis, but the diagnostic performance characteristics of this test are unclear, particularly in chronic HP, and it is not recommended. BAL measurement of interleukins, matrix metalloproteinases, and other chemokines and cytokines is currently considered a research tool.[20,103]

Chest Imaging

HRCT is an essential tool for the evaluation and diagnosis of HP. It is more accurate than chest radiography in capturing the variety of different patterns and distribution of abnormalities observed in HP, such as areas of inspiratory mosaicism, ground-glass attenuation, and poorly defined centrilobular nodules (Fig. 91.3 and eFig. 91.1). Early in the course of HP, these abnormal imaging features are frequently seen next to areas of normal attenuation and generally observed in the mid to upper and peripheral lung zones with a diffuse and/or peribronchiolar distribution. Regardless of smoking history, these features may sometimes coexist with zones of predominantly upper lung and centrilobular emphysema.[104] As part of the standard evaluation of a subject with suspected ILD, the HRCT protocol needs to include end-expiratory images for evaluation of air trapping, which may be indicative of small airway disease, a finding suggestive of the diagnosis of HP. Air trapping appears as areas of decreased attenuation resulting from the presence of trapped gas (eFig. 91.2).

In subjects presenting with acute clinical manifestations living in areas where HP is highly prevalent, an HRCT demonstrating diffuse and symmetrical homogenous ground-glass opacities or nodules with a centrilobular distribution and absence of fibrotic findings has an estimated sensitivity of 66–74%, specificity of 90–96%, and likelihood ratio of 7.7 to 16 for the diagnosis of HP.[105] Therefore, in the correct clinical context and, after excluding other known causes of ILD, the combination of characteristic HRCT findings and a temporal pattern of environmental exposure to

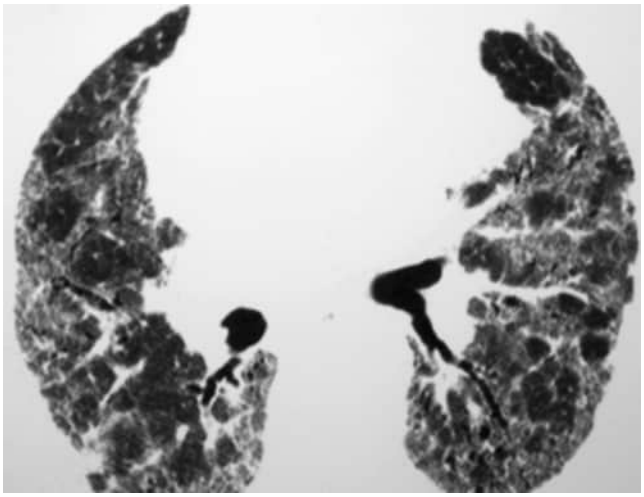

Figure 91.4 Fibrotic hypersensitivity pneumonitis. Areas of ground-glass opacity admixed with a few small areas of fairly normal appearing lung are associated with extensive reticulation, traction bronchiectasis, and architectural distortion.

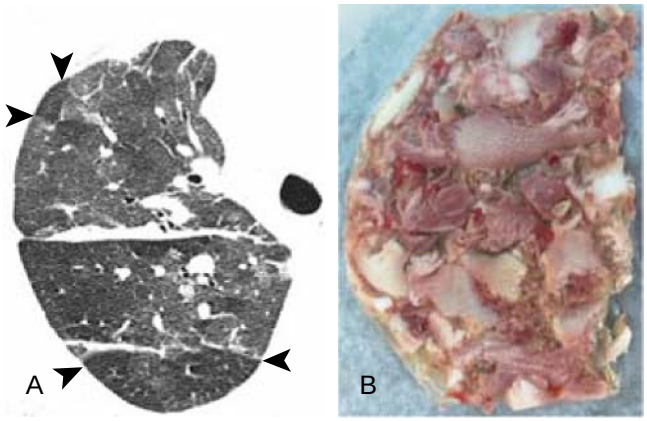

Figure 91.5 The "headcheese" sign at *computed tomography* (CT) in hypersensitivity pneumonitis. (A) Axial high-resolution chest CT image shows multifocal ground-glass opacity with areas of mosaic perfusion manifesting as lobular low attenuation (*arrowheads*) on the same inspiratory scan image. This scan pattern reflects the simultaneous presence of an infiltrative (ground-glass opacity) and obstructive (mosaic perfusion) abnormality and suggests the diagnosis of hypersensitivity pneumonitis. The mixed restrictive and obstructive process creates a variegated appearance at CT that has been likened to headcheese (B), a terrine or meat jelly typically made with flesh from the head of a pig or calf, less commonly from a cow or sheep, frequently encased in a savory jelly made from meat stock set in a mold, referred to as aspic. (A, Courtesy Michael B. Gotway, MD. B, From Shroff GS, Marom EM, Godoy MCB, et al. CT signs in the lungs. *Semin Ultrasound CT MRI.* 2019;40[3]:265–274.)

a relevant antigen or antigens can often lead to a confident diagnosis without the need for lung biopsy.

For chronic HP, classic radiologic appearances can help in the diagnosis. A subgroup of subjects with disease progression develop chest imaging features of pulmonary fibrosis, which include peripheral reticulation, traction bronchiectasis and/or bronchiolectasis, honeycombing, architectural distortion, and volume loss, findings that often coexist with nonfibrotic findings (Fig. 91.4). A peribronchiolar disease distribution of fibrotic features, the presence of the aforementioned nonfibrotic findings, and the absence of lower-zone predominance help distinguish fibrotic HP from fibrotic NSIP and IPF.[106] Among subjects with chronic HP, the presence of nonfibrotic CT features and the distribution of disease outperform fibrotic findings in discriminating HP from other fibrotic lung diseases.[106,107] For example, in HP, mixed interstitial (ground-glass opacities or high-attenuation areas) and obstructive (mosaic changes or low-attenuation areas) findings next to areas of normal attenuation (normal lung) on thin-section CT can give rise to the "headcheese" sign (Fig. 91.5). The headcheese sign was found to be moderately sensitive (49%) and highly specific (93%) for a high confidence diagnosis of fibrotic HP.[107] In a study that included a derivation cohort comprised of 124 subjects (35% of which had HP) and a validation cohort comprised of 66 subjects (33% of which had HP), a diagnostic predictive model that included patient age, a history of down feather and/or bird exposure, the presence of diffuse craniocaudal ground-glass opacity, and mosaic perfusion on HRCT had a sensitivity of 48% and a specificity of 91% for the diagnosis of chronic HP.[108] Similarly, another study that analyzed a derivation cohort comprised of 356 subjects (34% of which had HP) and a validation cohort comprised of 424 subjects (16% of which had HP) showed that, when radiologic mosaic attenuation or air trapping (Videos 91.1A and 91.1B) is more extensive than reticulation, and the disease has a diffuse axial distribution, the specificity for an HP diagnosis is high at 90% (with a sensitivity of 65%).[79] It should be noted that these predictive models were derived in patients diagnosed after review in an MDD, and patients did not necessarily undergo lung biopsy.

Lung Biopsy

The decision to pursue lung biopsy should be made in the context of all other available data and based on the need to establish a confident diagnosis and/or guide management. A diagnosis of HP can be established in the absence of histopathology; thus, biopsy is not necessary in every case. Lung biopsy can be performed using transbronchial biopsy, *transbronchial lung cryobiopsy* (TBLC), or *surgical lung biopsy* (SLB) using video-assisted thoracic surgery or an open approach. The decision to pursue lung biopsy should be reached only after consideration of the anticipated risks of the procedure, experience of the proceduralist/surgeon, and patient preference.

Transbronchial biopsy may be informative in nonfibrotic HP, although the diagnostic yield is not well characterized.[109] Histologic findings supportive of HP can preclude the need for more invasive testing such as SLB. The absence of typical histologic findings does not exclude HP, and finding normal lung tissue or nonspecific abnormalities may be due to sampling error. Small blind forceps biopsies may miss the pathologic pattern in a patchy or heterogeneously distributed disease such as HP. SLB should be considered if a confident diagnosis cannot be established based on all other available data, if the findings of biopsy will influence treatment decisions, or if it is necessary to exclude other forms of fibrotic ILD such as IPF. Ideally, patients will be reviewed in a formal MDD before referral for SLB to confirm that biopsy is indicated.[110] The biopsy findings should then be reviewed in the MDD, taking all other clinical and radiologic data into consideration. TBLC has been used in the evaluation of patients with chronic HP, with most studies reporting

on diagnostic yield in cohorts of patients presenting with unspecified ILD.[108] No studies have evaluated the ability of TBLC to diagnose chronic HP accurately. The largest study to date assessed diagnostic accuracy in 65 patients with ILD deemed to have an indication for SLB.[111] Of the 65 patients who underwent concurrent TBLC and SLB, 15 were diagnosed with chronic HP after MDD that incorporated results of the TBLC, while 18 were diagnosed incorporating findings of SLB, suggesting higher sensitivity of SLB. Overall agreement between SLB and TBLC for the specific histopathologic pattern as well as MDD-based final diagnosis was good, suggesting a role for TBLC in experienced centers in an appropriately selected group of patients with ILD. However, international societies have not taken a formal stance on the role of TBLC in the evaluation of chronic HP.

MULTIDISCIPLINARY DISCUSSION

There is no test specific for the diagnosis of HP and histologic diagnosis is no longer regarded as the gold standard for the diagnosis. Several diagnostic criteria for HP have been proposed, most characterizing acute HP but not the complex nature of chronic HP. The MDD has been shown to increase the level of confidence in ILD diagnosis and to help determine whether additional, invasive procedures are necessary to support or confirm a diagnosis.[112] Given the complex clinical presentation and disease course, integrating the radiographic and histopathologic findings in the context of the exposure history by a multidisciplinary team to arrive at a diagnosis of HP is recommended.[113] Formal MDD may not be available at each center, but we would encourage all clinicians to collaborate with exposure assessment, radiology, and pathology experts where available when considering a diagnosis of HP. Inter-MDD agreement on a diagnosis of HP is fair when comparing one MDD to the next.[114] The lack of standardized diagnostic criteria has surely contributed to this low level of agreement, and it is hoped that upcoming consensus criteria for HP will improve the agreement between groups, ultimately improving the accuracy of diagnosis.

PROGNOSIS AND DISEASE BEHAVIOR

The natural history of patients with HP is variable. While patients may encounter periods of clinical, radiologic, and functional stability after removal of the inciting antigen, a subgroup of patients with HP without a known exposure develops chronic disease and often progressive pulmonary fibrosis. The significant morbidity and mortality in the latter group has prompted a search for baseline markers of disease progression. Several clinical, physiologic, and radiologic prognostic factors of disease severity and mortality in HP have been identified (eTable 91.1).

Age has an impact on outcome in these patients because the prevalence and mortality of HP increase with age regardless of the severity of disease.[9] In addition, men have a prognosis worse than women.[16] Baseline auscultatory crackles on lung examination are an independent predictor of time to death or lung transplantation.[5] A history of cigarette smoking is associated with worse survival.[18,115]

Identifying an antigen and avoiding it are associated with better prognosis. In patients with chronic HP, while the disease can progress even after eliminating relevant antigenic exposure, avoidance of inciting antigen exposure is associated with a better prognosis. In a cohort of 142 consecutive adult patients with clinical-radiologic-pathologic chronic HP (47% with an unidentified exposure), after adjusting for the presence of fibrosis, patient age, pulmonary function, and smoking history, survival was longer for patients with an identified inciting antigen exposure than for those without an identified inciting antigen exposure (median survival of 8.8 years vs. 4.9 years).[18] In a study of 202 patients with HP, 41 (20%) had an unidentified inciting antigen; a trend towards worse survival was reported for patients with no identified inciting antigen exposure after multivariate correction for age, gender, and baseline percentage of *forced vital capacity* (FVC) (hazard ratio, 2.1).[116] In a cohort of 112 patients with fibrotic HP, 25 experienced clinical improvement after antigen avoidance (characterized as a decrease in dyspnea and cough in two consecutive visits); clinical improvement after antigen avoidance was associated with a decreased mortality (hazard ratio, 0.14).[117] Such findings emphasize the importance of finding an antigen if possible.

On chest imaging, HRCT features of fibrosis (e.g., bronchiectasis, reticulation, honeycombing) and the extent of fibrosis evaluated by semiquantitative scoring have been associated with shortened survival.[5–7] Other CT measures with negative prognostic significance include the presence of inspiratory mosaic attenuation and expiratory air trapping, and an increased pulmonary artery/aorta ratio.[4,118,119] Baseline pulmonary physiologic measures of disease severity, particularly FVC and D_{LCO}, have been shown to be predictors of early mortality. The ILD-GAP index is a metric for evaluation of prognosis that integrates gender (G), age (A), and physiology (P), (e.g., FVC and D_{LCO}) that has been shown to predict mortality across different forms of chronic ILD, including HP.[120] Also, a more rapid longitudinal decline in FVC has been associated with shorter survival. Patients with 10% or greater decline in predicted FVC after 6 to 12 months had a significantly increased risk of all-cause mortality (median survival, 53 months vs. 139 months).[117] Such prognostic indicators may help guide timing of therapy, referral to a lung transplantation program, and patient expectations. They may also be useful for cohort enrichment in clinical trials of therapeutics.

MANAGEMENT

ANTIGEN AVOIDANCE

Management of HP is primarily aimed at antigen identification and avoidance (Fig. 91.6). Antigen avoidance is the only nonpharmacologic measure known to improve the clinical course and survival of patients with HP. Organic antigen sources (e.g., bacteria, fungi, mycobacteria, animal proteins) are a frequent cause of nonoccupational HP. BHP can be particularly difficult to manage given the persistent nature of exposure in the home despite apparent remediation. In a study of patients with BHP that measured the amount of avian antigen and collected questionnaires on the

eTable 91.1 Baseline Prognostic Indicators of Disease Severity and Mortality in Hypersensitivity Pneumonitis

Demographics	■ Male sex ■ Older age
Physical exam	■ Auscultatory crackles
Pulmonary physiology	■ Low FVC % ■ Low DL_{CO} %
High-resolution computed tomography	■ Increased fibrosis ■ Honeycombing ■ Traction bronchiectasis ■ Inspiratory mosaic attenuation and expiratory air trapping ■ Increased pulmonary artery/aorta ratio
Pathology	■ Increased fibrosis ■ Fibroblast foci
Genomic factors	■ Mucin 5B rs35705950 single nucleotide polymorphism ■ Shorter telomere length (<tenth percentile for age)
Composite measures	■ Abnormal ILD-GAP index
Other	■ No known inciting antigen exposure ■ Smoking ■ Acute exacerbation ■ Pulmonary hypertension

DL_{CO}, diffusing capacity for carbon monoxide; FVC, forced vital capacity; GAP, gender, age, physiology; ILD, interstitial lung disease.

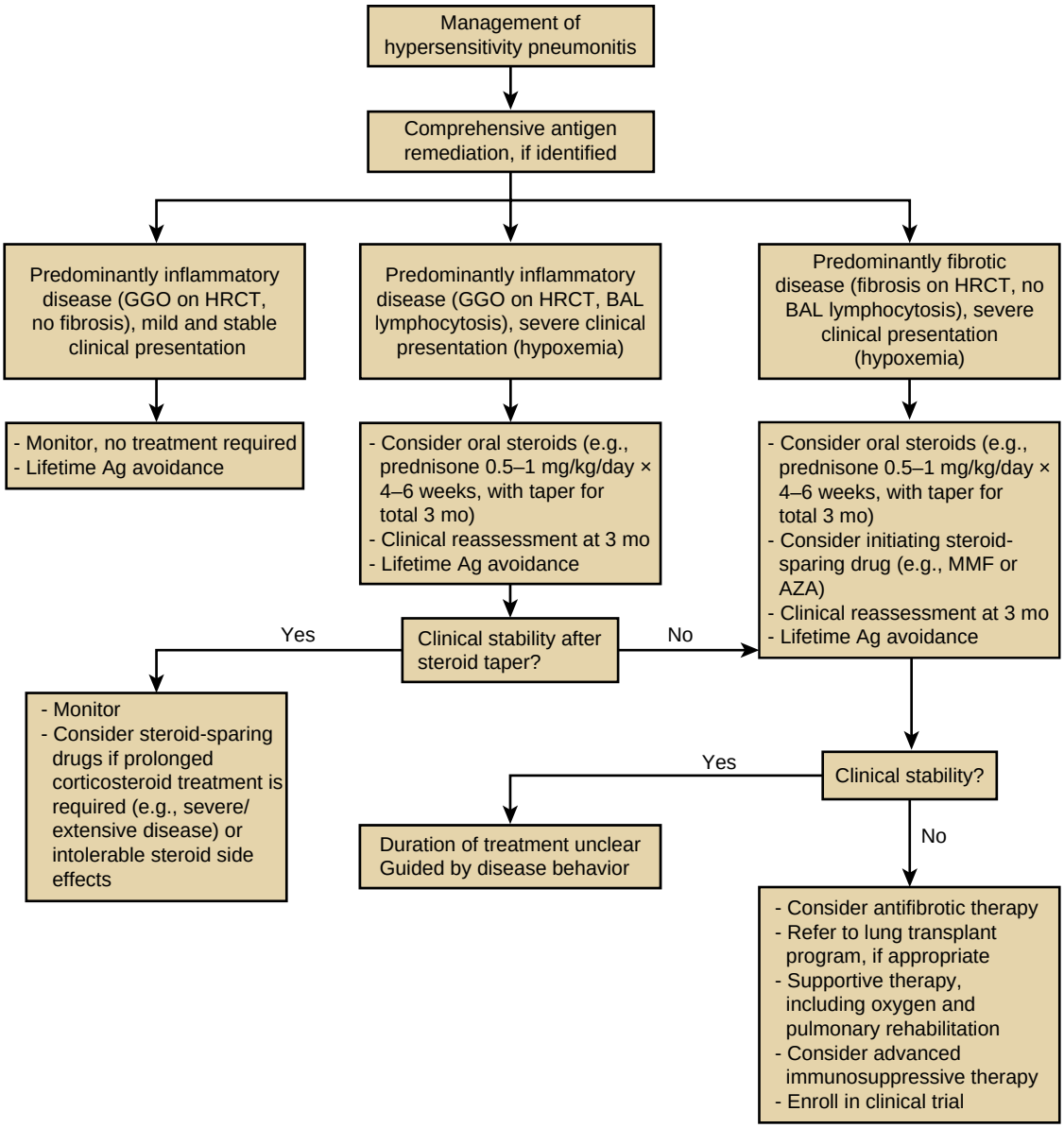

Figure 91.6 Approach to the management of *hypersensitivity pneumonitis* (HP). Pharmacologic therapy is often initiated when clinically significant disease progression is recognized despite comprehensive inciting antigen remediation or avoidance. Initial treatment is often with systemic corticosteroids in the form of prednisone with a tapering schedule. Patients require monitoring and management of corticosteroid adverse reactions as well as assessment for clinical, physiologic, and/or radiographic response before considering coadministering and/or transition to corticosteroid-sparing agents. The multidisciplinary approach to HP includes symptom management, supplemental oxygen for hypoxemic patients, pulmonary rehabilitation, smoking cessation, appropriate vaccinations, referral for lung transplant evaluation if indicated, treatment of comorbid conditions, and palliative/end-of-life care. Ag, antigen; AZA, azathioprine; BAL, bronchoalveolar lavage; GGO, ground-glass opacity; HRCT, high-resolution computed tomography; MMF, mycophenolate mofetil.

environmental conditions of their homes, patients exposed to a higher amount of avian antigen in household dust samples had a worse trajectory of disease over 1 year of follow-up than patients with a lower amount.[121] Furthermore, subtle exposures to avian antigens such as sleeping with feather duvets and pillows may cause HP.[122,123] The risk of disease is more likely with prolonged exposure. The potential for a fibrotic response of the lungs emphasizes the importance of screening and questioning for occult exposure to avian antigens in the patient's environment.

When action to reduce and prevent a known antigen exposure is not feasible or if the source of exposure is unknown, removing the patient from the likely antigen-containing environment should be considered, especially when HP is severe and progressive over time. However, this may not be feasible in all cases and can be particularly challenging with occupational HP. Therefore, close clinical surveillance and/or workplace monitoring by an occupational hygienist is essential to ensure that prevention strategies are effective.

PHARMACOLOGIC THERAPY

There are few data guiding the use of therapeutics in patients with HP. Immunosuppression with systemic corticosteroids is a frequently employed adjunctive management strategy for HP. A few early reports in FLD demonstrated short-term improvements in symptom resolution and D_{LCO}, but no sustained differences in long-term outcomes were detected in prednisolone-treated versus nontreated groups.[124,125] No prospective studies have evaluated the efficacy of corticosteroids in treating fibrotic HP. Frequently, corticosteroids are given when there is evidence of active inflammation or severe physiologic impairment. Corticosteroids carry important potential risk and side effects. Therefore, their empiric use in treating HP is not recommended and should be reserved for cases where the anticipated benefits outweigh the potential risks.

Steroid-sparing agents such as *azathioprine* (AZA) and *mycophenolate mofetil* (MMF) have been used to treat chronic HP in an effort to reduce steroid dose while preserving lung function. Two retrospective observational studies have evaluated the role of AZA or MMF in treating chronic HP. In a multicenter study of 70 chronic HP patients treated with AZA or MMF, there was no improvement in FVC but an increase in D_{LCO} at 1 year, and a reduction in prednisone dose.[126] In a study of 131 patients with chronic HP in which 93 received immunosuppression, treated patients had worse lung function and survival than those not treated, suggesting that sicker patients are more likely to be treated with immunosuppressing drugs.[127] There were no survival or longitudinal lung function differences among those treated with AZA, MMF, or prednisone. The AZA and MMF groups had fewer treatment-related adverse events compared to the prednisone group. In both studies, more patients switched from AZA to MMF than vice versa, citing either a failure of therapy or drug intolerance.

Rituximab is another steroid-sparing agent utilized in patients with progressive disease despite apparent antigen remediation and treatment with prednisone, AZA, or MMF. In a retrospective report of six patients whose chronic HP progressed despite immunosuppression who were then treated with rituximab infusion, three patients stabilized at 1 year while three had disease progression and died.[128] Antifibrotic therapies have been investigated as treatments for non-IPF forms of progressive fibrosing ILD, including fibrotic HP. In the INBUILD trial, nintedanib was effective at slowing the rate of disease progression as measured by a change in FVC percentage over 52 weeks, with a between-group difference of 107 mL/year (95% CI, 70.8 to 185.6; $P < 0.001$).[128a] Subgroup analysis demonstrated that this difference was consistent across diagnostic categories, including for patients with HP.[128b]

LUNG TRANSPLANTATION

Lung transplantation should be considered for patients with progressive disease despite comprehensive management. The indications for a lung transplant in patients with chronic HP are similar to those for other forms of fibrotic ILD.[129] Chronic HP patients undergoing lung transplantation have excellent outcomes posttransplantation, with better survival than patients with IPF.[130] The risk of HP recurrence in the allograft lung appears low. However, patients with chronic HP may have worse health-related quality of life than patients with IPF, even after accounting for disease severity, and these issues are important to address and support.[131] The relationships among the impacts of chronic lung disease and age, sex, and socioeconomic factors deserve further study. Other supportive management approaches include infection prevention, pulmonary rehabilitation, oxygen supplementation, education, symptom management, and palliative care where appropriate.

PREVENTION AND OUTBREAK IDENTIFICATION

Recognition of an index case of HP is often a sentinel health event indicating an inciting antigen exposure and a population at risk, particularly in occupational settings. When one or more individuals develop HP in a shared environment, measures must be taken to protect the individuals from further exposure, identify the potential antigen sources, and modify the environment to prevent additional exposure. For example, interventions taken to minimize the risk of metalworking fluid HP have included the enclosure of machining operations, improved ventilation and engineering controls that decrease aerosolization of metalworking fluids, and worker education.[132]

Indoor microbe contamination is often associated with poor moisture control. Thus, source control should be implemented where appropriate to reduce indoor contamination. Source control involves preventing water intrusion, removing standing water sources (e.g., humidifiers, hot tubs), and keeping indoor relative humidity below 60%. Humidifiers and other water sources should follow factory-recommended maintenance schedules, with water frequently changed to prevent microbial growth. Work practices recommended to prevent FLD include drying of hay and grains before storage, use of mechanized feeding systems, improving ventilation in farm buildings, and education of workers on safe work practices.

Personal protective equipment may be helpful in reducing exposure to inciting antigens. In bird breeders with HP, serum antibody levels declined by 65% over 14 months in those using respirators, with no decline in those without respirators.[133] However, no data compared changes in symptoms or physiology between the two groups; therefore the clinical relevance is unknown. In another study of bird breeders, high-efficiency respirator masks nearly normalized lung function and serologic responses upon antigen rechallenge.[134] The long-term safety or feasibility of these masks is unknown, and compliance with masks is often poor due to discomfort and their cumbersome nature. Dust respirators and simple face masks can reduce the volume of particulate exposure but, given the minimal exposure needed to trigger a response in a sensitized individual, they may not provide adequate protection to at-risk individuals. A high index of suspicion and early recognition can reduce the subsequent risk to the index case and prevent future cases of the disease in at-risk individuals.

Key Points

- *Hypersensitivity pneumonitis* (HP) is a complex pulmonary syndrome caused by an immunologic reaction to an inhaled inciting antigen. The diagnosis of HP requires a high index of suspicion given its heterogeneous presentation. HP should be considered whenever a patient presents with an undifferentiated interstitial lung disease.
- HP is classified into nonfibrotic or fibrotic disease, depending on the presence of radiographic or histopathologic fibrosis, with an identifiable, indeterminate, or unidentifiable inhaled antigen exposure. The terms acute, subacute, and chronic HP have fallen out of favor because this arbitrary time classification does not stratify the disease based on characteristics known to improve diagnostic certainty and prognosis.
- Combinations of variables must be integrated to establish a confident diagnosis of HP. Exposure to an inciting antigen plus a high-resolution computed tomography pattern consistent with HP can establish the diagnosis in the appropriate clinical context. In some cases, bronchoscopy with bronchoalveolar lavage or lung biopsy may be necessary for diagnosis.
- Nonfibrotic HP lacks radiographic or histologic fibrosis, and the patient is anticipated to improve with antigen removal and, if indicated, systemic corticosteroid therapy.
- Fibrotic HP commonly does not normalize, and the patient may develop progressive pulmonary fibrosis despite apparent antigen remediation. Systemic immunomodulatory and/or antifibrotic therapy may be required, but a subset of patients will progress nonetheless.

Key Readings

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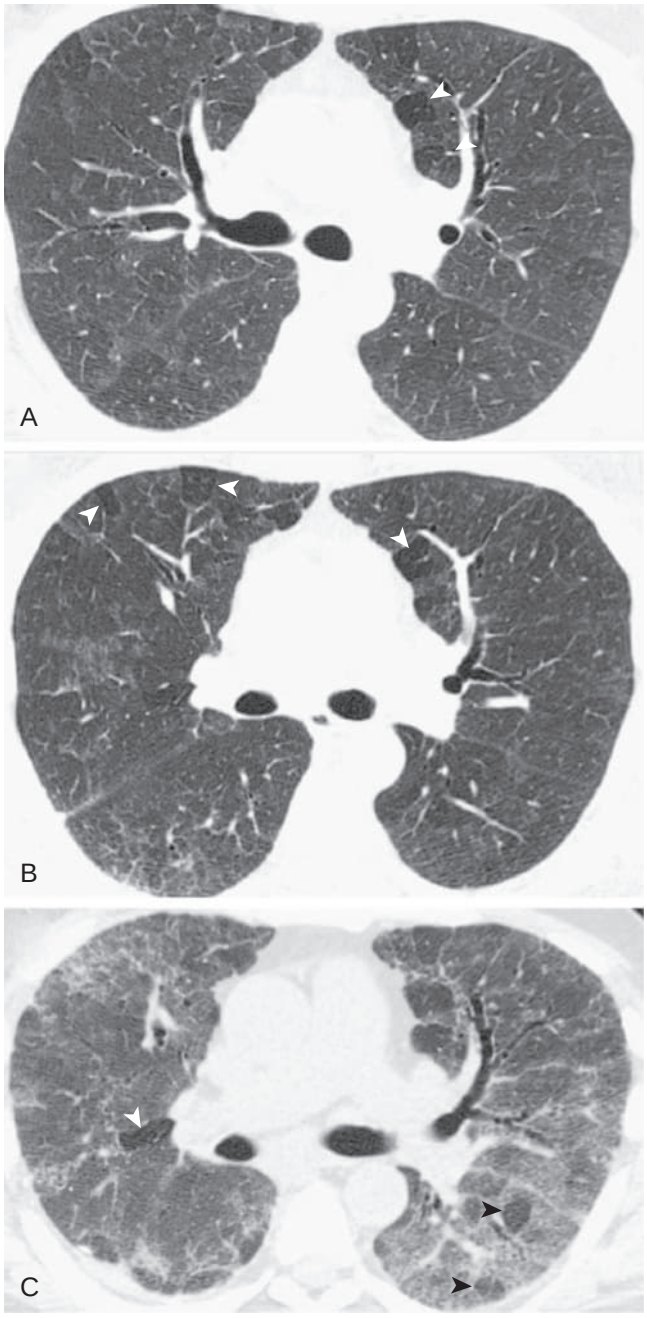
eFIGURE IMAGE GALLERY



eFigure 91.1 Progression of hypersensitivity pneumonitis over time from alveolitis toward fibrotic lung disease. (A) Axial *high-resolution computed tomography* (HRCT) image shows minimal bilateral inhomogeneous lung opacity with a few areas of faintly seen lobular low attenuation (*arrowheads*), which may suggest a small airway obstructive process, but the findings are subtle. (B) Axial HRCT image performed 2 years later shows more apparent inhomogeneous lung opacity with more clearly visible areas of lobular low attenuation (*arrowheads*); faint ground-glass opacity is also developing. (C) Axial HRCT performed 4 years the first image shows extensive ground-glass opacity and reticulation associated with areas of lobular low attenuation (*arrowheads*).



eFigure 91.2 Hypersensitivity pneumonitis. Bilateral, diffuse ground-glass opacities with mosaic perfusion reflect alveolitis and bronchiolitis, respectively.

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92 CONNECTIVE TISSUE DISEASES

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INTRODUCTION

The lung may be involved in all *connective tissue diseases* (CTDs). The involvement is often subclinical, but its true extent may be masked by exercise limitation due to musculoskeletal features of the CTD. Patterns of lung involvement vary considerably within each CTD.[1] The differential diagnosis is made even wider by inclusion of drug-induced pulmonary reactions and opportunistic infections secondary to therapy for lung disease, which may present with features indistinguishable from diffuse lung disease.

It is not surprising that the lung is involved frequently in CTDs because these are systemic syndromes, but it is disappointing that so little is known about the true incidence and prevalence of lung disease because of a dearth of well-controlled, prospective, unselected series. Imprecision of nomenclature has also confused the issue. With this background, the aims of this chapter are to highlight the ways in which the lung may be involved in the most common CTDs and to indicate, when appropriate, the most usual pattern of lung disease for each CTD, with an emphasis on approaches to diagnosis and efficient management.

Interstitial lung disease (ILD) has been evaluated in much more detail in *systemic sclerosis* (SSc) than in other CTDs, probably because patients with SSc tend to be managed at referral centers. The broad approach to clinical presentation, prognostic evaluation, and management of ILD in the setting of CTD is outlined before discussing the specific data available for disease subgroups.

APPROACH TO DIAGNOSING AND TREATING CONNECTIVE TISSUE DISEASE–INTERSTITIAL LUNG DISEASE

CLINICAL FEATURES

Patients with CTD-ILD are more likely to be younger, female, and nonsmokers compared to those *with idiopathic interstitial pneumonia* (IIP).[2] A thorough clinical examination to identify extrathoracic manifestations, including Raynaud phenomenon, inflammatory arthritis, pleuropericardial involvement, sicca symptoms, and esophageal dysmotility, is recommended for any patient with suspected CTD-ILD.

RADIOLOGIC FEATURES

All radiologic patterns of IIP can be present in a patient with CTD-ILD (Table 92.1).[3] Overall, the most frequent radiologic pattern is *nonspecific interstitial pneumonia* (NSIP), characterized by homogenous ground-glass opacity, reticulation, and traction bronchiectasis, often with a peribronchovascular distribution.[4] A patient with radiographic NSIP should always be comprehensively investigated for an underlying CTD, which may present later in the disease course.[5] *Usual interstitial pneumonia* (UIP) is the second most common radiologic pattern seen in CTD-ILD and the most common pattern identified in *rheumatoid arthritis* (RA).[3] The

Table 92.1 Prevalence and Radiologic/Histologic Pattern for ILD in Major Connective Tissue Diseases

CTD Type	Prevalence of ILD	Radiologic/Histopathologic Pattern
SSc	40–75% with clinically significant disease (at least moderate impairment on pulmonary function) Up to 70% with detectable interstitial changes on HRCT	Most common: NSIP Other: UIP
RA	Detectable on HRCT: 30–60% Clinically evident 10–30%	Most common: UIP Other: NSIP, OP, LIP
SLE	3–11% chronic diffuse interstitial disease Up to 30% with detectable interstitial changes on HRCT Need to distinguish from acute pneumonitis (1–10%) and alveolar hemorrhage (rare)	Most common: NSIP Other: LIP, OP, UIP
SS	10–30% Need to exclude pulmonary lymphoma	Most common: NSIP Other: LIP, OP, UIP
PM/DM	30–50%	Most common: NSIP Other: UIP, OP, DAD
MCTD	20–85%	Common: NSIP Other: UIP

CTD, connective tissue disease; DAD, diffuse alveolar damage; HRCT, high-resolution computed tomography; ILD, interstitial lung disease; LIP, lymphocytic interstitial pneumonia; MCTD, mixed connective tissue disease; NSIP, nonspecific interstitial pneumonia; OP, organizing pneumonia; PM/DM, polymyositis/dermatomyositis; RA, rheumatoid arthritis; SSc, systemic sclerosis; SLE, systemic lupus erythematosus; SS, Sjögren syndrome; UIP, usual interstitial pneumonia.
From Jee A, Adelstein S, Bleasel J, et al. Role of Autoantibodies in the diagnosis of connective-tissue disease ILD (CTD-ILD) and interstitial pneumonia with autoimmune features (IPAF). *J Clin Med*. 2017;6:51.

UIP pattern seen in CTD-ILD is often indistinguishable from that of *idiopathic pulmonary fibrosis* (IPF) and is characterized by honeycombing, reticulation, and traction bronchiectasis in a subpleural basal distribution.[3,6] Other radiologic patterns seen in CTD-ILD include *organizing pneumonia* (OP), most commonly associated with *polymyositis/dermatomyositis* (PM/DM), mixed NSIP with OP overlap pattern and, less commonly, *lymphocytic interstitial pneumonia* (LIP), a pattern most closely associated with Sjögren syndrome.[4,6]

Radiologic features that may be more suggestive of an underlying CTD include multicompartment involvement, such as esophageal dilation and pleural and/or pericardial involvement; subpleural sparing and extensive honeycombing are rare.[4,7,8]

HISTOPATHOLOGIC FEATURES

Surgical lung biopsy is usually not required in the setting of CTD-ILD because the underlying histopathologic pattern has little impact on management and prognosis.[9,10] In cases where surgical lung biopsy has been performed, NSIP is the most common histopathologic pattern, except in RA, where UIP predominates (see Table 92.1).[11] Other patterns include OP, LIP, diffuse alveolar damage, and overlap patterns.[12] Specific features suggestive of an underlying CTD include involvement of airways, vasculature, or pleura; evidence of inflammation with follicular bronchiolitis; or lymphoplasmacytic inflammation.[12,13]

ROLE OF AUTOANTIBODIES IN THE DIAGNOSIS OF CTD-ILD

Distinguishing CTD-ILD from idiopathic ILD is essential and has major implications for prognosis and management. The role of autoantibodies in the diagnosis and management of patients with ILD is highlighted in the 2018 *American Thoracic Society* (*ATS*), *European Respiratory Society* (*ERS*), Japanese Respiratory Society, and Latin American Thoracic Society guidelines for the diagnosis of IIP, which recommend testing for *antinuclear antibody* (ANA), anti–cyclic citrullinated peptide, and *rheumatoid factor* (RF) in all patients, even in those without overt features of CTD.[14] More specific tests, including extractable nuclear antigen antibodies (e.g., anti–Sc-l70, SSA/Ro, SSB/La, *ribonucleoprotein* [RNP], and Sm antibodies) and selected myositis antibodies (e.g., anti-Jo1, PL7, and PL12), are recommended only in selected cases (eTable 92.1).[14–16]

Repeat serologic testing is also recommended. A study of 1044 Chinese CTD-ILD patients demonstrated seroconversion in 51.2% of patients at follow-up, 32% of which were initially given an alternative ILD diagnosis, most likely due to the absence of autoantibodies and overt rheumatologic features at first assessment.[17]

APPROACH TO TREATMENT OF CTD-ILD

The goal of treatment in CTD-ILD is to maximize lung function and minimize symptom burden. Often, stability of disease reflects successful treatment, and improvement is possible only in a smaller subset. Not all patients will require therapeutic intervention. The decision to treat is often difficult, requiring consideration of the severity of the ILD, rate of progression, age, comorbidities, underlying CTD-ILD subtype, and time since onset of CTD. A summary of the therapeutic agents considered in the management of CTD-ILD is given in eTable 92.2.

eTable 92.1 Autoantibodies in Connective Tissue Disease With the Percentages Positive in Different Disease Settings

CTD	Autoantibody	Target	Comments
SSc	Anticentromere	Centromere proteins (CENP A–F)	20–40% positive in total SSc, wide racial variation 70–80% positive in limited cutaneous variant with pulmonary hypertension
	Scl-70	DNA topoisomerase 1	28–70% total SSc, wide racial variation; >30% diffuse cutaneous disease with ILD
	PM-Scl	—	Scleroderma-myositis overlap syndromes
	Antinucleolar	RNA polymerase-1	8–20% SSc suggests poorest 10-yr survival, renal crisis
	Ku	DNA binding proteins	Scleroderma-myositis overlap syndromes
Rheumatoid arthritis	Rheumatoid factor	IgG	Seropositive disease more frequent with pulmonary nodules
	Antinuclear antibody	—	—
	Histone	Histone proteins	5% rheumatoid vasculitis
SLE	dsDNA	dsDNA	50–75%, strong association with nephritis
	ANA	—	90–95%
	Ro/La	RNA transcription factors	60%/20%
	Histone	Histone proteins	>90% drug-induced lupus, 20–30% primary SLE
	Sm	—	10% whites and 30% Blacks and Chinese
	Lupus anticoagulant	Phospholipid	20–30%
Antiphospholipid syndrome	Anticardiolipin Lupus anticoagulant	Membrane phospholipids	Disease diagnosis depends on presence of clinical features
Sjögren syndrome	Ro (SS-A) La (SS-B)	RNA transcription factors	40–50% primary Sjögren syndrome (25–30% SLE) 50% Sjögren (10% SLE)
PM/DM	Jo-1	Histidyl tRNA synthetase	20–30% inflammatory myopathy but 50–100% when associated with diffuse fibrosing lung disease
	PL-7	Threonyl tRNA synthetase	<3% antisynthetase syndrome
	PL-12	Alanyl tRNA synthetase	<3% antisynthetase syndrome
	EJ	Glycyl tRNA synthetase	<2% antisynthetase syndrome
	OJ	Isoleucyl tRNA synthetase	<2% antisynthetase syndrome
	Mi-2	Nuclear proteins	<8% DM, associated with acute onset of classic DM
	Ku	Nuclear proteins	Associated with myositis-CTD overlap syndromes
	Anti-CADM140 (MDA5)	Cytoplasmic proteins	Clinically amyopathic PM/DM ILD; poor prognosis
MCTD	U1-RNP	Small nuclear proteins	Myositis overlap syndromes (10% SSc)
	U2-RNP	—	Myositis, SLE, SSc
Relapsing polychondritis	Anticartilage Anticollagen	Cartilage Collagen	Unknown sensitivity

Percent (%) range indicates the percentage of patients with the listed disease who are positive for the antibody listed.
ANA, antinuclear antibody; CTD, connective tissue disease; dsDNA, double-stranded DNA; IgG, immunoglobulin G; ILD, interstitial lung disease; MCTD, mixed connective tissue disease; PM/DM, polymyositis/dermatomyositis; RNP, ribonuclear protein; Scl, scleroderma; SLE, systemic lupus erythematosus; Sm, Smith; SSc, systemic sclerosis; tRNA, transfer RNA.

eTable 92.2 Common Drugs Used in the Treatment of the Major Pulmonary Complications of Connective Tissue Diseases

Drug	Dose	Duration	Comments	Monitoring
IMMUNOSUPPRESSIVE AGENTS				
Azathioprine	2.5 mg/kg/day, max 200 mg/day	Continuous	Maximal effect may not be evident for 6–9 mo but has better adverse effect profile than cyclophosphamide May be used long term Starting dose, 50 mg daily with monitoring full blood count in case of thiopurine methyltransferase deficiency; maintenance dose from 1 mo	Full blood count Liver function tests
Cyclophosphamide, oral	2 mg/kg/day	Variable	May be used continuously or substituted at 3 mo for azathioprine because of more favorable adverse effect profile in DLD	Full blood count Liver function tests Urinalysis for blood
Cyclophosphamide, IV	15 mg/kg monthly for 1–6 mo	Variable	IV therapy for rapid induction of remission at 2–4 mg/kg/day for 3–4 days, especially for vasculitis Pulsed IV cyclophosphamide may be given at 1- to 3-mo intervals with better adverse effect profile and lower long-term cumulative dose, particularly in nonvasculitic disease	Full blood count Liver function tests Urinalysis for blood
Cyclosporin A	5 mg/kg/day	Continuous	Bioavailability variable, thus blood monitoring necessary May be used in combination with prednisolone	Blood pressure Urea and creatinine Cyclosporin A level
Mycophenolate mofetil	1–3 g/day	Continuous	Increasingly favored as best second-line therapy, usually in combination with low-dose prednisolone Usually well tolerated with gastrointestinal symptoms as the major side effects	Full blood count Liver function tests
Methotrexate	7.5–25 mg/wk	Continuous	Little information to support use except as second-line therapy Pulmonary toxicity may be limiting	Full blood count Liver function tests
Prednisolone	1 mg/kg/day or 20 mg alternate days	Continuous	Prednisolone used alone in high dose for cellular DLD and then titrated to control Low-dose regimen is used in conjunction with immunosuppressants	Blood pressure Blood glucose Weight Bone densitometry
Methylprednisolone	500–1000 mg	3–5 days	Used for aggressive induction of remission, particularly for vasculitis or acute pneumonitis, then followed by maintenance therapy of prednisolone or prednisolone plus immunosuppressive agent	
BIOLOGIC AGENTS				
Rituximab	1g IV	Induction and maintenance regimen	Usually reserved for rapidly progressive and resistant CTD-ILD, although clinical trial of up-front therapy with rituximab is ongoing	Full blood count Electrolytes Liver function tests Immunoglobulins
Tocilizumab	162 mg/wk SC	Maintenance	Used for RA joint disease; recent study suggesting a reduction in decline in FVC in SSc-ILD needs confirmation	Full blood count Electrolytes Liver function tests
ANTIFIBROTIC AGENTS				
Nintedanib	150 mg bid	Maintenance	42% reduction in the rate of decline of FVC in SSc-ILD patients; ongoing study including other CTD-ILD	Full blood count Electrolytes Liver function tests
Pirfenidone	801 mg tid	Maintenance	Ongoing studies for SSc-ILD and RA-ILD and unclassifiable ILD (including IPAF) at present	LOTUSS Trial: IPAF; ongoing

bid, twice daily; CTD, connective tissue disease; DLD, diffuse lung disease; FVC, forced vital capacity; ILD, interstitial lung disease; IPAF, idiopathic pneumonia with autoimmune features; IV, intravenous; RA, rheumatoid arthritis; SC, subcutaneous; SSc, systemic sclerosis; tid, three times daily.

SYSTEMIC SCLEROSIS (SCLERODERMA)

The preliminary criteria for classification of SSc require that one major or two or more of three minor criteria be present (Table 92.2).[18] The skin changes may affect the entire extremity or the face, neck, and trunk (thorax and abdomen). Scleroderma is traditionally classified on the basis of the extent of skin disease. Limited disease can involve the face, but the trunk and limbs proximal to the elbows and knees are spared. Diffuse disease can involve any part of the body. Nail fold capillaroscopy, a noninvasive technique in which a magnifying lens is used to assess the nail bed microcirculation,[19] is now included in current *European League Against Rheumatism* (EULAR) classification criteria for SSc diagnosis. Characteristic findings include decreased capillary density, neovascularization, and microhemorrhages.[20,21]

Table 92.2 Systemic Sclerosis (Scleroderma)

CRITERIA FOR DIAGNOSIS*
Major
Thickening of the skin of the hands
Minor
Sclerodactyly (i.e., the changes of the major criterion but limited to the fingers)
Digital pitting scars or loss of substance from the finger pad: depressed areas at tips of fingers or loss of digital pad tissue as a result of ischemia
Bibasilar pulmonary fibrosis
LUNG MANIFESTATIONS
Interstitial pulmonary fibrosis
Organizing pneumonia
Isolated pulmonary vascular disease
Aspiration pneumonia (secondary to esophageal dysmotility)
Chest wall restriction

*The major or ≥2 minor criteria required for diagnosis.
From Jee AS, Corte TJ. Current and emerging drug therapies for connective tissue disease–interstitial lung disease (CTD-ILD). *Drugs*. 2019;79(14):1511–1528.

EPIDEMIOLOGY AND RISK FACTORS

The incidence of SSc is approximately 2 to 20 per 100,000 per year, with a peak incidence in the fourth to sixth decades. The prevalence is 30 to 120 per 100,000, with a 3:1 to 8:1 female preponderance. Mortality rates have been remarkably consistent over the years, varying from 0.9 to 1.5 per million for men and 2.1 to 3.8 per million for women in the United States. The disease is present worldwide.

Although scleroderma clusters in families with other autoimmune disease, there are few reports of first-degree relatives having SSc. The importance of genetics to SSc is illustrated by a study of Choctaw Indians residing in southeastern Oklahoma. The prevalence of SSc in full-blooded Choctaws is roughly 1:200, which is significantly higher than is found in non–full-blooded Choctaws (1:3000) and strikingly higher than the prevalence of SSc in other Native Americans in Oklahoma (1:10,000).[22]

Genetic involvement in the disease has been determined by the identification of chromosomal abnormalities and by studies of the major histocompatibility complex genes. Although many of the early studies were serologic, more recently, polymerase chain reaction technology has been used. With this latter approach, an association between diffuse lung disease and *human leukocyte antigens* (HLAs)—HLA-DR3, HLA-DR52a, HLA-DRB1*11, and HLA-DPB1*1301—has been recognized.[23,24]

CHEMICALLY INDUCED SCLERODERMA-LIKE DISORDERS

A variety of agents are known to induce SSc-like disease, often with lung involvement, including D-penicillamine, tryptophan, bleomycin, pentazocine and, particularly in men, the industrial agents vinyl chloride, benzene, toluene, and trichloroethylene. Silica exposure increases the relative risk of developing SSc, and silicosis increases the risk even further.[25] The toxic oil syndrome, first recognized in Madrid in 1981, results from ingestion of an adulterated cooking oil containing rapeseed oil denatured with aniline.[26] This provokes a scleroderma-like syndrome with pulmonary involvement. An association with silicone breast implants is unproved.

PULMONARY MANIFESTATIONS

More is known about the pulmonary complications associated with SSc than with any other CTD. Pulmonary involvement has emerged as the major cause of excess morbidity and mortality in SSc.[27] The patterns of lung disease with which SSc may present are variable and are shown in Table 92.1.

Interstitial Lung Disease

Pathogenesis

Predisposition. Individuals may be predisposed genetically to develop SSc, and there are emerging markers that define risks for diffuse lung disease. Class II major histocompatibility complex associations increase the risk of ILD in SSc. The relative risk is increased if the anti-DNA topoisomerase (Scl-70) antibody is present. There may also be an association between Scl-70 and an allele of the major histocompatibility complex *DPB1* gene.

The genetic susceptibility for SSc probably results in injury and an immune response. It has been shown that there are highly restricted T-cell responses to epitopes of DNA topoisomerase 1, both in healthy individuals and in those with SSc. Thus, in individuals with Scl-70–responsive T-cell clones, the autoantibody may be responsible for driving the immune response. In the lung, there is an accumulation of "memory-type" CD45 Ro lymphocytes and secondary lymphoid follicles with true germinal centers within lung biopsy samples.[28] Furthermore, the T cells present within the lung express cytokines of both the *T helper 1* (Th1) and *T helper 2* (Th2) subsets.[29] Genetic susceptibility is also relevant to noninflammatory mediators on the basis of genome-wide association studies.[30,31]

Inflammation Amplification. A wide variety of cytokines identified in *bronchoalveolar lavage* (BAL) fluid clearly contribute to the cascade of inflammation in the lungs.[32] The most striking of these are *interleukin* (IL)-8 (neutrophil chemoattractant and activator), *tumor necrosis factor*-α (TNF-α; an early cytokine involved in many pathologic processes), macrophage inflammatory protein-1α (important in neutrophil chemotaxis), and RANTES (*regulated on activation normal*

T-cell expressed and secreted; important in T-cell and eosinophil recruitment and activation). It is clear that the downstream events of the initiation result in the release of a number of proinflammatory cytokines responsible for further recruitment and activation of inflammatory cells at disease sites.

Fibrogenetic Factors. The hallmark of SSc in both lung and skin is the accumulation of connective tissue matrix cells and proteins.[33,34] Many factors have been studied in this regard, and a wide variety of growth factors have been identified. Perhaps the most striking of these is connective tissue growth factor, which appears to depend on *transforming growth factor-β* (TGF-β) for up-regulation and has a potent effect on collagen production, as evidenced by collagen gel retraction studies. TGF-β is found in high amounts in the lungs of patients with SSc[35] and, when TGF-β signaling is perturbed, minor epithelial injury leads to extensive fibrosis.[36] *Endothelin* (ET)-1 and coagulation cascade proteins are also present in high amounts in BAL fluid.[37] Fibroblasts from patients with lung disease exhibit dysregulated type I collagen biosynthesis and impaired messenger RNA downregulation. The balance of ET receptors (A and B) is modified in the lungs of patients with SSc, with a consistent decrease in ETA and an increase in ETB receptors.[38] ET-1 may contribute to epithelial-mesenchymal transition of airway epithelial cells, resulting in fibrosis.[39]

Epithelial Damage. Although a key pathogenic event in idiopathic ILD, epithelial damage has been relatively underemphasized in disease models of pulmonary fibrosis in CTD. The intratracheal instillation of normal saline in a mouse strain with SSc features, including skin fibrosis and other universal characteristics, leads to lung injury and fibrosis, with evidence of epithelial injury on electron micrographic studies, attenuated alveolar epithelial type 2 cell proliferation, and persistence of the myofibroblast population after injury.[40,41] Chronic microaspiration, believed to happen in many patients with SSc,[42] is a plausible trigger of recurrent epithelial injury.

A number of parallel events result in the development of lung injury and subsequent fibrosis, and there seems little doubt that the key cytokines in the cascade include TNF-α, because it appears early in disease and has been shown in animal models to be a pivotal factor in lung fibrosis,[43] and TGF-β receptor, which up-regulates collagen gene expression and is important in connective tissue growth factor release. Other important cytokines may include hepatocyte growth factor and insulin-like growth factor-II.[44,45] The balance of Th1 to Th2 cytokines is also key because, when the shift is in favor of Th2 cytokines, such as in IPF, the prognosis is worse and there is a much higher eosinophil influx into the lung compared with patients with SSc, in whom the Th1/Th2 ratio is balanced and there is less eosinophil influx per unit of lung involvement.[29]

Clinical Features

Dyspnea is present in 21–80%.[46] Cough, a less frequently reported symptom, tends to be dry and nonproductive. Hemoptysis is rare but may complicate carcinoma or bronchial telangiectasia.[47] Fine crackles are heard at the lung bases and are of a "Velcro" character. Digital clubbing is extremely rare. Secondary pulmonary hypertension with appropriate clinical features of right ventricular strain, raised jugular venous pressure, and ankle edema may be seen during the terminal stages of the disease.

The lung is involved more commonly in patients with diffuse rather than limited cutaneous SSc, but the extent of skin involvement does not correlate with lung function changes. Patients can often be asymptomatic, even with moderate pulmonary function impairment, whereas, in other cases, patients can have exertional dyspnea when ILD is trivial or absent due to pulmonary vascular limitation, cardiac involvement, musculoskeletal problems, general debility, loss of fitness, or a variable combination of these factors. Rarely, scleroderma of the chest wall may cause extrathoracic restriction.

Lung disease may be the first manifestation of SSc and thus may not be recognized as a CTD-ILD. In this setting, a history of Raynaud phenomenon is often helpful. In addition, careful examination of the capillaries in the nail beds reveals the typical feature associated with scleroderma: abnormal loops associated with capillary "dropout" (Fig. 92.1A). The presence of autoantibodies, particularly ANAs, is helpful in suggesting a CTD etiology (see eTable 92.1).

Imaging

Chest radiographic abnormalities are present in 25–67% of patients, and lung function is impaired in up to 90%, although a large subset of patients has only a minor reduction in gas transfer or *diffusing capacity for carbon monoxide* (DL_{CO}). Chest radiography typically shows a reticular pattern in the lung bases and periphery in early disease (see

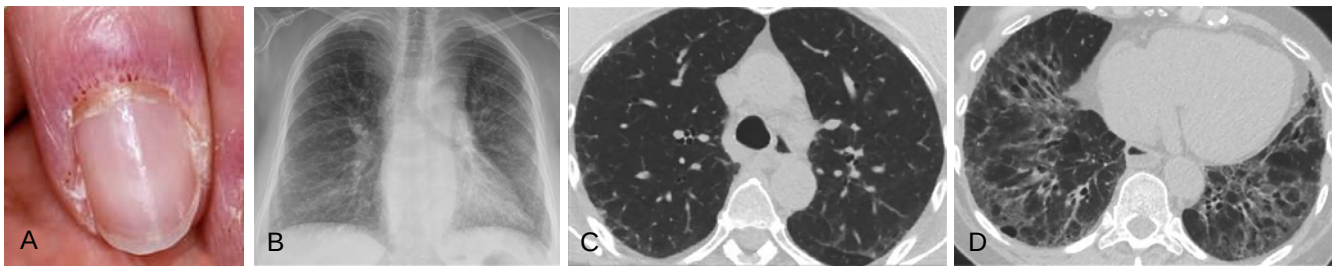

Figure 92.1 Imaging of systemic sclerosis. (A) Nail bed showing abnormal capillary loops in the cuticle. (B) Frontal chest radiograph shows bilateral, symmetric, fine linear and reticular opacities with a basal predominance. (C–D) Axial chest computed tomography through the middle (C) and lower (D) lungs shows nonsegmental, peripheral, and fine reticulation reflecting intralobular interstitial thickening, with a clear basal predominance. The reticulation is associated with ground-glass opacity in the bases and traction bronchiectasis is present in this region as well. Mild gas and fluid distension of the esophagus is visible and commonly visible with computed tomography in patients with systemic sclerosis. The dilated esophagus indicates that this disease is likely to be part of systemic sclerosis. (A, Modified from Iaccarino L, Ghirardello A, Bettio S, et al. The clinical features, diagnosis and classification of dermatomyositis. *J Autoimmun.* 2014;48–49:122–127. B–D, Courtesy Michael B. Gotway, MD.)

Fig. 92.1B). There is obvious loss of volume with more extensive reticular shadowing in more advanced disease. In this situation honeycombing may be present.

High-resolution computed tomography (HRCT) has revolutionized the interpretation of the pattern and extent of disease. Disease is localized to the lung periphery, appearing earliest at the bases and posteriorly (see Fig. 92.1C–D, eFigs. 92.1 to 92.3). As disease becomes more advanced, it progresses superiorly, centrally, and anteriorly. Esophageal dilation is common (see Fig. 92.1C–D).[48] The pattern may be ground-glass (reflecting either fine intralobular fibrosis or a more cellular histopathology) or an overtly fibrotic reticular pattern consisting of intersecting linear abnormalities, often associated with traction bronchiectasis.[49] Honeycomb change is present in up to one-third of cases but is usually limited in extent.[50] HRCT extent correlates moderately well with lung function variables, particularly measures of D_{LCO}.[51] In the absence of overt pulmonary hypertension, individuals with SSc are less hypoxemic than those with IPF, once the extent of disease on HRCT has been taken into account, which has been ascribed to a relative absence of new and abnormal vessel formation in SSc lung.[52]

Gallium scans and technetium-99m–labeled diethylenetriaminepentaacetic acid clearance provide little additional prognostic benefit.

Pulmonary Function Tests

The interstitial pulmonary fibrosis of SSc is characterized by a restrictive ventilatory defect, which results in reduced pulmonary compliance, vital capacity, and total lung capacity. Residual volume is decreased. D_{LCO} is reduced and may be the only abnormality in early disease. Arterial blood gas analysis usually reveals a normal or reduced arterial oxygen partial pressure, reflecting regional vasoconstriction in diseased lung, with a normal or low arterial carbon dioxide partial pressure. In the absence of pulmonary hypertension, hypoxemia is seldom marked until late in the disease process.

There have been a number of studies of the rate of decline of lung function in SSc.[53,54] In one study of 38 patients with SSc, the mean loss of vital capacity was 100 mL/yr; 20 to 30 mL/yr is the normal rate of decline.[55] A second study showed that vital capacity loss was greater in patients who had evidence of an active alveolitis on BAL.[44] Lower *forced vital capacity* (FVC) within 3 years of disease onset predicts decline in pulmonary function,[55] which in turn is associated with increased mortality.[56] Rates of decline are often higher within the first few years of onset of SSc, emphasizing the importance of identifying lung disease early and initiating therapy.

On cardiopulmonary exercise testing (see Chapter 33), ventilation-perfusion mismatching and diffusion abnormalities increase, resulting in hypoxemia and widening of the alveolar-arterial oxygen tension difference. Minute ventilation increases generally as a consequence of increased respiratory rate rather than tidal volume. Dead space ventilation may increase with exercise, with a rise in the dead space/tidal volume ratio. For a given degree of lung involvement defined by CT, abnormalities on exercise gas exchange are less severe in patients with interstitial pulmonary fibrosis of SSc than in those with IPF.[52]

Bronchoalveolar Lavage

BAL may identify alveolitis in SSc before the onset of pulmonary symptoms.[57] A neutrophil alveolitis has been described by some authors to predict more progressive disease.[53,58,59] However, it has been shown that an increase in neutrophils reflects an increase in the extent of disease on CT, particularly of the reticular pattern; thus this increase is likely to be a marker of more extensive disease rather than an independent index of progressive disease.[38,46,47] BAL should not be used alone to determine whether treatment should be started. Many patients with apparently normal BAL findings may exhibit progressive disease. BAL is therefore not recommended routinely for the diagnosis or monitoring of SSc-related interstitial disease.

Biopsy

Surgical lung biopsy is virtually never required in the diagnosis of SSc-related interstitial disease unless clinical and CT findings are atypical for ILD in SSc and an alternative diagnosis is suspected. Furthermore, transbronchial biopsy or transbronchial cryobiopsy provide no useful information. Pathologically, the most prevalent pattern is NSIP[59] (eFig. 92.4). Less commonly, a UIP pattern is seen, or indeed a combination of patterns.[60] Crucially, outcome does not differ materially among these patterns. In idiopathic disease, the UIP pattern of injury is associated with a worse outcome compared with the NSIP pattern.[61] However, in SSc, outcome was not related to the histologic pattern in the largest series,[59] although there is evidence in a smaller series that some patients with a UIP pattern have a more progressive course.[62] Overall, biopsy does not provide sufficient prognostic information to justify the procedure in SSc.

Electron microscopy shows early endothelial and epithelial cell injury, even without abnormalities on light microscopy. Autopsy studies show diffuse lung disease in up to 80% of cases and pulmonary vascular disease in up to 30% (see eFig. 92.4C). In some patients with a more accelerated course of disease, histopathologic examination has shown a diffuse alveolar damage pattern.[63]

Serologic Investigations

Although SSc is traditionally defined on the basis of the extent of the skin disease, as outlined previously, the pattern of autoantibodies appears to be a much stronger determinant of the associated internal organ involvement.[64,65] ANAs are found in 90–100% of patients with SSc, although even normal individuals often have positive ANAs (roughly 30% of normal individuals have an ANA titer of 1:40). Three major autoantibodies include anticentromere, seen in 57% of patients with limited cutaneous disease; Scl-70, seen in 40% of patients with diffuse disease; and PM-Scl, seen in a small fraction of cases in association with the PM overlap syndrome. It is rare to have both Scl-70 and anticentromere antibodies. Diffuse lung disease is rare in the presence of anticentromere antibodies, and a protective role for this autoantibody has been argued but not substantiated. IPF is strongly associated with the Scl-70 antibody and with diffuse scleroderma. Limited cutaneous disease associates with vascular disease and the anticentromere antibody. Both forms of lung disease may progress to pulmonary

hypertension. Other autoantibody studies have shown associations with organ involvement, including a nucleolar pattern associated with diffuse lung disease and pulmonary hypertension[66]; the antibody against B23, a nucleolar phosphoprotein associated with pulmonary hypertension and the presence of the antifibrillarin antibody; and anti-Th/To antibodies associated with pulmonary hypertension and diffuse lung disease.

Prognosis

Crude mortality rates are 3.9% per year for men and 2.6% per year for women, and lung disease remains the most common cause of death in patients with SSc.[67] In one series, lung disease accounted for 21% of all deaths.[68] There is also an increased risk of lung cancer in SSc. With the widespread use of HRCT, mild ILD (see eFigs. 92.1 and 92.3) is detected in many SSc patients, leaving the clinician with difficult decisions as to whether to introduce therapy or to observe carefully without immediate intervention. In overtly severe ILD, the decision to treat is straightforward. However, the majority of SSc patients have milder lung involvement, and a reliable means of discriminating between stable and progressive ILD would be useful in management. On the basis of clinical series and accumulated experience, prognostic evaluation should focus on three main considerations: the extent of disease at presentation, the duration of systemic disease, and recent progression of disease.[69]

Extent of disease at the time of presentation is the strongest consideration in the decision to treat patients with SSc. The extent of disease is best judged by lung function tests, particularly FVC and D_{LCO}, and the extent of disease on CT. A simple staging system using CT extent (above and below 20%) and FVC at presentation (above and below 70%), the *United Kingdom Raynaud's and Scleroderma Association* (UKRSA) staging system, is highly discriminatory for both progression and death (eFig. 92.5).[70] The prognostic value of the UKRSA staging system has been confirmed,[71] and the severity thresholds were virtually identical to those found to identify the likelihood of a treatment effect in the first controlled study of oral cyclophosphamide in SSc.[72]

Duration of systemic disease is also an important consideration in the decision to treat. The greatest risk of ILD progression is during the first 4 years of SSc. Early declines in FVC are strongly predictive of subsequent severe ILD,[73] which most often develops in the first 4 years.[74] Put simply, in SSc and other CTDs, the early development of mild to moderate ILD is a marker of likely rapid disease progression, which should reduce the threshold for initiating therapy.

Finally, recent disease progression is an important justification for treatment. It should be acknowledged that the long-term prognostic value of observed disease progression has not been quantified in SSc or, indeed, in other CTDs. However, declines in lung function variables, especially FVC, have consistently been predictive of long-term mortality in other forms of pulmonary fibrosis, and these observations can reasonably be extrapolated to CTDs.

Although no overall treatment algorithm of ILD has been devised to integrate extent of disease, duration of systemic disease, and evidence of recent progression, consideration of all three factors provides a basis for rational treatment decisions. More recently, attention has focused on refining the selection of appropriate SSc patients with pulmonary fibrosis to participate in controlled treatment trials. For treatment effects to be demonstrated, it is necessary to enroll patients with progressive disease: The UKRSA staging system has been endorsed for this purpose by an expert group.[75] Biomarker data might, in principle, be used both for clinical prognostication and for selecting patients for trial involvement but, at present, despite promising preliminary data, no single biomarker is currently fit for routine use.

Treatment

The treatment paradigm for SSc-ILD is rapidly changing. The Scleroderma Lung Study demonstrated a small but significant benefit of oral cyclophosphamide compared with placebo for FVC, skin scores, and quality of life and dyspnea scores at 12 months.[72] The oral cyclophosphamide treatment regimen used most commonly is 2 mg/kg/day orally, up to a maximum of 150 mg with moderately low dosages of prednisolone at 10 mg/day or 20 mg every other day. Close scrutiny with full blood counts, liver function tests, and urine testing for evidence of hemorrhagic cystitis is necessary.

Intravenous (IV) cyclophosphamide may have a better safety profile.[76] Studies of IV cyclophosphamide (750–1000 mg/m^2) given at 2- to 4-week intervals for 6 to 12 months tended toward significance, as judged by CT and pulmonary function data.[77,78] The similarity in the amplitude of treatment effects in the Scleroderma Lung Study[72] and a smaller placebo-controlled trial of IV cyclophosphamide[78] prompted the EULAR to state that "in view of the results from two high-quality RCTs and despite its known toxicity, cyclophosphamide should be considered for treatment of SSc-ILD."[79] However, careful selection of patients with severe or progressive lung disease is required given the toxicity associated with intense immunosuppressive therapy.

In controlled trials[72,78] treatment effects largely consisted of stopping or slowing progression of lung disease, as judged by serial lung function trends, with the greatest benefit seen in patients with extensive fibrotic disease.[72] This endorses the important principle of intervention in apparently irreversible fibrotic lung disease, with the primary aim of achieving stabilization, as opposed to regression of disease. However, in the Scleroderma Lung Study, after the cessation of active treatment, therapeutic benefits were transient.[79] Longer-term treatment approaches have not been evaluated in controlled studies.

Other less toxic immunosuppressive agents have been widely used, including azathioprine, methotrexate, and *mycophenolate mofetil* (MMF), on the basis of accumulated clinical experience and small retrospective case series.[80–82] In one retrospective series of 100 CTD-ILD patients, treatment with MMF was well tolerated and was associated, on average, with stabilization of pulmonary fibrosis over a number of years.[83] The Scleroderma Lung Study 2 demonstrated similar treatment effects between MMF over 1 to 2 years to cyclophosphamide for 1 year, followed by placebo. Patients were able to tolerate MMF significantly better, and it is considered by many as a first-line therapy for SSc-ILD.[84]

The SENSCIS study evaluated an antifibrotic agent, nintedanib, in patients with mild to moderate SSc-ILD. Nintedanib, a tyrosine kinase inhibitor, was found to reduce the rate of decline of FVC at 52 weeks by 41 mL/yr, which is a relative reduction of 44%.[85] This effect appears to be additive to background MMF, which also had a benefit in slowing FVC decline.

Tocilizumab is an anti–IL-6 receptor monoclonal antibody used for the treatment of RA, and also studied in SSc, including in a subset of patients with SSc-ILD. A phase II study (FaSScinate)[86] demonstrated that, over 48 weeks, more patients on placebo demonstrated a decline in FVC greater than 10% compared to those receiving tocilizumab. Similar results were shown in a phase III study (focuSSced); there was no change in the primary end point (modified Rodnan skin scores), but patients with SSc-ILD had a significant reduction in FVC decline.[87]

The question of *Pneumocystis* prophylaxis has not been resolved. Some medical centers use cotrimoxazole three times a week if immunosuppressive agents are being given.

Steroid therapy is associated with scleroderma renal crisis, a life-threatening complication due to rapidly progressive renal failure. This complication has been seen both with moderate- to high-dose therapy (≥15 mg/day prednisone or equivalent)[88] and, more recently, with prednisolone doses of less than 10 mg daily.[89] However, confounding by severity cannot be excluded because patients with more aggressive systemic disease are more likely to receive corticosteroids, nonetheless, occasional cases of renal crisis are undoubtedly linked to high-dose corticosteroid therapy.[90]

Hematopoietic stem cell transplantation (HSCT) can now be considered for the treatment of selected patients with rapidly progressive SSc at risk of organ failure (EULAR SSc treatment recommendations, 2017).[91] In principle, HSCT may work to "reset" the immune system. The Autologous Stem Cell Transplantation International Scleroderma Trial compared nonmyeloablative HSCT with monthly IV cyclophosphamide in patients with early diffuse SSc. Despite higher early treatment-related mortality, there was superior long-term event-free and overall survival.[92] The Scleroderma: Cyclophosphamide or Transplantation Trial compared monthly IV cyclophosphamide with HSCT using a lower dose of pretransplant cyclophosphamide and fully myeloablative total-body irradiation conditioning.[93] HSCT demonstrated superiority in the primary outcome of global rank composite score at 54 months. Autologous HSCT has demonstrated long-term survival and lung function benefit in carefully selected SSc patients with rapidly progressive disease at risk of organ failure.

Single-lung transplantation has been offered to those with end-stage lung disease, provided there is no evidence of disease activity in other organs and no major esophageal dysfunction. With careful selection of patients, outcome with transplantation may differ little from that in individuals with idiopathic diffuse lung disease, although it should be understood that perceived contraindications to lung transplantation due to systemic disease activity vary widely between transplant units.

In terminal disease, consideration must be given to oxygen therapy, treatment of supervening heart failure, and infection and advanced care planning, with palliative care specialists often having an invaluable input.

PULMONARY VASCULAR DISEASE

Pulmonary arterial hypertension (PAH; World Health Organization Group 1) may develop in patients with SSc. Unlike the other CTDs, vascular involvement in SSc is caused by concentric fibrosis of small arterioles replacing the normal intima and media, but the plexiform lesions and fibrinoid necrosis of idiopathic PAH are not seen. Isolated vascular disease arises mainly in the limited form of SSc. Associated features are those of the CREST syndrome (calcinosis, Raynaud phenomenon, esophageal dysmotility, sclerodactyly, and telangiectasias) with prominent telangiectasia, esophageal disease, abnormal nail fold capillaries (dilated capillaries and dropout of capillary loops), and a positive anticentromere antibody. Lung function studies show an isolated or disproportionate fall in D_{LCO}, quantified by a decline in D_{LCO} adjusted for the alveolar volume (D_{LCO}/alveolar volume or carbon monoxide transfer coefficient) or a rise in the FVC/D_{LCO} ratio. Although routine annual echocardiography has been advocated in all SSc patients, the stated gas transfer variables can reasonably be used to select patients for echocardiography.[94] When damage to the pulmonary vascular bed is extensive (D_{LCO} < 50% of predicted), the risk of pulmonary hypertension increases.[95] Mortality rates increase with increasing pulmonary hypertension[96,97] (see also Chapter 84).

Doppler echocardiography has been shown to correlate with measurements of pulmonary artery pressures made at right heart catheterization. Qualitative features found on echocardiography may also suggest pulmonary hypertension even when the absence of a tricuspid regurgitant jet precludes measurement of the gradient across the tricuspid valve and thus an estimate of pulmonary artery pressure. These qualitative features include right ventricular dilation and right ventricular hypertrophy. Overall, echocardiography is moderately sensitive for the diagnosis of PAH (47–88%).[98,99] However, echocardiography is less accurate at borderline and mild levels of pulmonary hypertension. Stress (exercise) echocardiography may be able to identify preclinical PAH.[100,101] N-Terminal pro–brain natriuretic peptide, released from cardiac ventricles in response to stretch, is elevated in SSc and inversely related to D_{LCO}. Elevated N-terminal pro–brain natriuretic peptide levels may predict the development of pulmonary hypertension in SSc.[102,103] Worse functional class and impaired D_{LCO} predict worse outcomes in scleroderma-associated PAH.[104]

Although there are a number of emerging therapeutic options, optimal treatment of pulmonary vascular disease (see Chapter 84) in SSc has not yet been defined.[1,105]

OTHER PULMONARY COMPLICATIONS

Classical aspiration pneumonia is uncommon, particularly considering the prevalence of esophageal dysfunction in SSc. It is not yet clear whether microaspiration from reflux may in some cases serve as an important cofactor leading to progression of lung disease and therefore whether active treatment of symptomatic reflux is advisable. Pleural disease is uncommon. Rarely, the extent of skin tightness over the chest wall produces an

extrinsic restriction of ventilation. On occasion the first manifestation of pulmonary parenchymal disease is OP. This responds well to corticosteroid therapy, as does OP in other contexts.

RHEUMATOID ARTHRITIS

The American Rheumatism Association revised criteria for the classification of RA require that at least four of the criteria listed in Table 92.3 be satisfied for a minimum of 6 weeks.[106]

EPIDEMIOLOGY AND RISK FACTORS

The reported incidence of RA ranges from 0.2 to 3 per 1000 person-years (<0.5/1000 person-years in most surveys), with a rising incidence with increasing age into the seventh decade. In white adults, the prevalence of RA ranges from 0.5–2%, with a male-to-female ratio between 1:2 and 1:4. Depending on disease severity, as judged by disability scales and the need for long-term corticosteroid therapy, the age-matched mortality rate of RA is up to twofold higher than in the general population, with this increased mortality being attributed to cardiorespiratory complications.[107,108] The prevalence of RA is similar throughout the world. Evidence in support of a genetic predisposition includes familial and twin clustering and associations between RA and HLA-DRB1 alleles.[109] Hormonal factors may play a role, judging from the female preponderance of RA and a reduced incidence during pregnancy. Infectious agents and socioeconomic factors have not been shown to be etiologically important.

PULMONARY MANIFESTATIONS

Pleuropulmonary manifestations are multiple and are listed in Table 92.3 and shown in Fig. 92.2.

Interstitial Lung Disease

The interstitial pulmonary fibrosis of RA has a male predominance (male/female ratio of 3:1).[110] High titers of RF[111] and the presence of rheumatoid nodules[112,113] are associated with an increased prevalence of pulmonary fibrosis in RA. Smoking is a risk factor for the development of overt pulmonary fibrosis in RA, predisposes to the phenotype of combined pulmonary fibrosis and emphysema,[114,115] and has also been associated with subclinical disease.[116,117] In the presence of HLA-DR susceptibility genes, smoking is strongly associated with development of anti–citrulline-positive RA.[114,117–119] It has been suggested that the seropositive RA actually starts in the lungs.[120] The *MUC5B* promoter variant gene was found to be associated with the presence of RA-associated ILD in a population of RA patients, suggesting an underlying genetic susceptibility to developing ILD, and specifically UIP, in these patients.[121]

In early disease, a lymphocytic interstitial infiltrate is often the predominant abnormality,[122] and prominent peribronchiolar follicles, containing aggregates of lymphocytes with germinal centers, are often seen.[123] In long-standing disease, fibrosis predominates, often resulting in cystic changes or honeycombing. Both NSIP and UIP are present in significant proportions of patients with interstitial fibrosis[124,125] (eFig. 92.6A). UIP is associated with a better outcome in CTD than in an idiopathic setting.[60,126,127] In RA, UIP is associated with a worse outcome than NSIP.[128,129] Furthermore, UIP has a worse outcome in RA than in other CTDs.[130]

In RA patients with UIP, with HRCT appearances similar to classical IPF (consisting of predominantly basal subpleural honeycomb change and little or no ground-glass attenuation; see Fig. 92.2A), average short to intermediate outcomes are similar to those with IPF.[131] However, approximately 25% of these RA patients with a CT pattern of UIP have a good long-term outcome.[132]

Minor pulmonary fibrosis is common in RA; in one open-lung biopsy series performed in the previous century in volunteers with RA (some without clinical evidence of ILD), pulmonary fibrosis was seen in 60% of patients.[133] Reductions in D_{LCO} are found in 40% of unselected RA patients.[134] However, radiologically overt pulmonary fibrosis is found in only 1–5% of RA patients, based on three large chest radiographic series.[112,115,135] In the largest prospective series reported to date, 150 consecutive patients were screened for pulmonary disease.[136] Of these, 19% had CT evidence of interstitial fibrosis, which was often subtle; 43% of those with interstitial abnormalities also had emphysematous bullae. Chest radiography identified abnormalities in only 14% of the whole cohort, but physiologic abnormalities were seen in 82% (D_{LCO}) and 14% (restrictive pattern of ventilatory defect).[136] Disease severity as judged by CT generally reflects functional impairment.[137–139]

The most frequent symptom is exertional dyspnea, although this may be masked by a general loss of mobility due to systemic disease. The clinical picture is usually

Table 92.3 Rheumatoid Arthritis

CRITERIA FOR DIAGNOSIS*
Morning stiffness (lasting at least 1 hour)
Arthritis (soft tissue swelling or fluid) of three or more joints (PIP, MCP, wrist, elbow, knee, ankle, MTP joints)
Arthritis of hand joints (swelling of at least one wrist, MCP, or PIP joint)
Symmetrical arthritis (i.e., simultaneous arthritis of the same joints on both sides of the body)
Rheumatoid nodules
Serum rheumatoid factor positivity (at a level such that <5% of normal controls are positive)
Radiographic hand or wrist changes typical of rheumatoid arthritis
LUNG MANIFESTATIONS
Interstitial pulmonary fibrosis
Organizing pneumonia
Obliterative bronchiolitis
Follicular bronchiolitis
Bronchiectasis
Vasculitis
Nodules
Pleural disease
Lymphocytic interstitial pneumonia
Drug induced

*At least four criteria for a minimum of 6 weeks.
MCP, metacarpophalangeal; MTP, metatarsophalangeal; PIP, proximal interphalangeal.

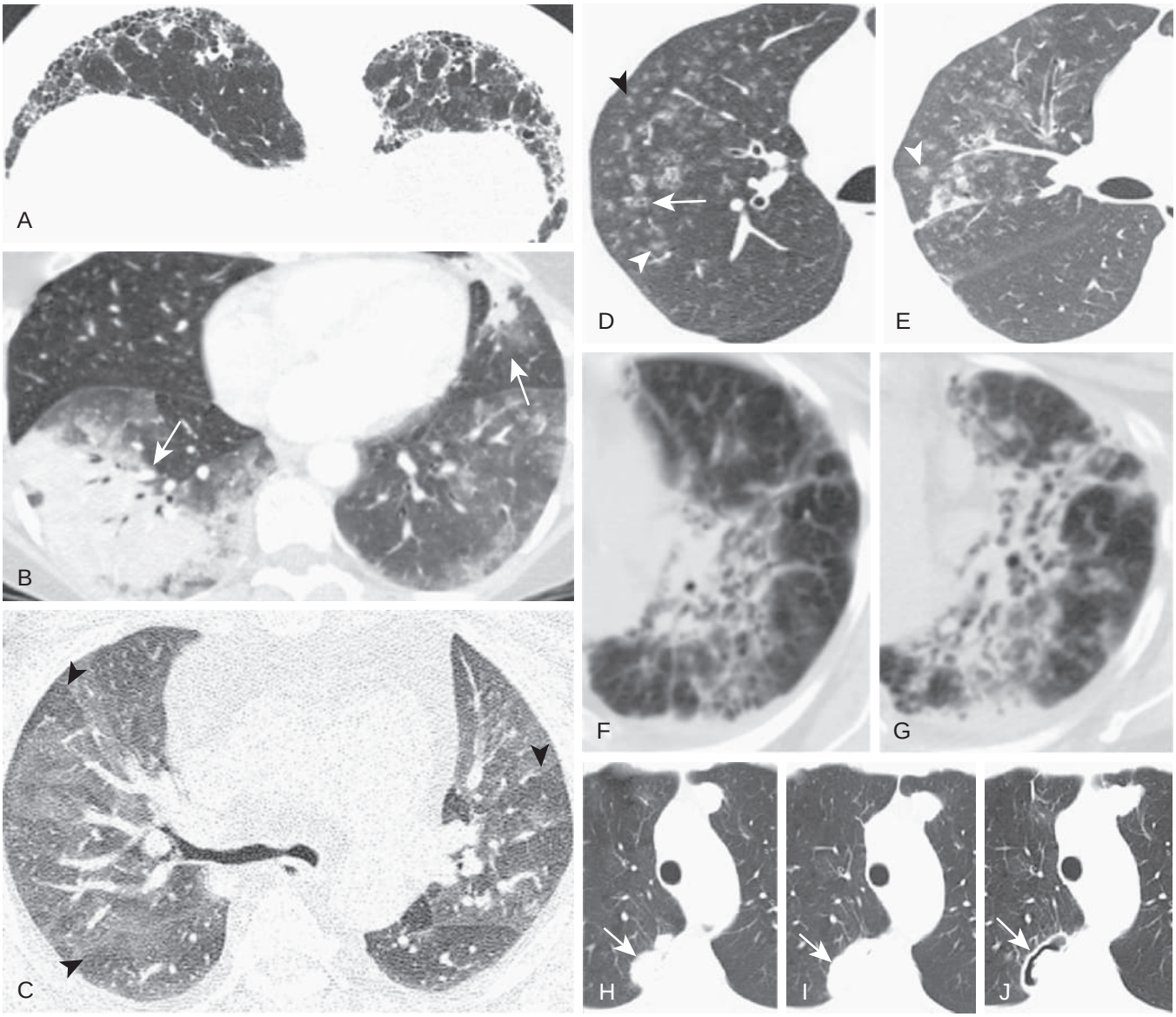

Figure 92.2 Rheumatoid arthritis–associated pulmonary abnormalities shown on axial chest computed tomography. (A) Usual interstitial pneumonia pattern. Axial prone *high-resolution computed tomography* (HRCT) image shows basal and subpleural coarse reticulation, architectural distortion, and honeycombing identical to the interstitial pneumonia pattern in patients with idiopathic pulmonary fibrosis. (B) Organizing pneumonia. Axial HRCT image shows bilateral peripheral consolidation (*arrows*). (C) Bronchiolitis obliterans. Axial supine HRCT image shows extensive, multifocal, bilateral areas of low attenuation (*arrowheads*) reflecting air trapping due to small airway obstruction. (D–E) Axial supine HRCT images show centrilobular ground-glass opacity nodules (*arrowheads*) in the right upper lobe, some of which show early cavitation (*arrow*), shown on biopsy to represent follicular bronchiolitis. (F–G) Axial supine HRCT images show bronchiectasis in the left upper lobe, progressing over the 4-year interval between the two studies. (H–J), Axial supine HRCT images show progressive enlargement of a rheumatoid nodule (*arrows*) over 1 year (H–I), with cavitation developing 3 years later (J). (Courtesy Michael B. Gotway, MD.)

identical to that of IPF, with bilateral, predominantly basal crackles and tachypnea; cyanosis; and right heart failure in advanced disease. Finger clubbing, which is occasionally striking, is more prevalent than in other CTDs. Severe progressive disease requiring hospitalization may be associated with right heart dysfunction and respiratory failure and has a poor prognosis, with a 5-year survival rate of less than 50%.[66] A subgroup of patients has more indolent disease that progresses little during prolonged follow-up. A strong predictor of clinical decline is a $D_{L_{CO}}$ less than 55% of predicted at presentation.[140]

Organizing Pneumonia

OP is characterized by plugs of granulation tissue in the air spaces distal to and including the terminal bronchioles, associated with lymphocytic infiltration within well-preserved bronchiolar walls and the surrounding lung interstitium. OP has a very different profile from the entity of *bronchiolitis obliterans* (BO; also found in RA); in OP, there is a clinical presentation of pneumonia (as opposed to airflow obstruction), multifocal consolidation on chest radiograph and CT (see Fig. 92.2B), a restrictive functional defect, and a much higher chance of responsiveness to corticosteroids than BO, with a good outcome in 15 of the first 17 reported cases.[141]

OP is more common in RA than in other CTDs, with the exception of inflammatory myopathy and *mixed connective tissue disease* (MCTD).

Bronchiolitis Obliterans

BO, synonymous with obliterative bronchiolitis and constrictive bronchiolitis, is characterized histologically by destruction of the bronchiolar wall by granulation tissue and eventual replacement of the bronchiole by fibrous tissue. In some cases BO may be preceded by an inflammatory exudate; prominent bronchiolar inflammation may be found in patients with the shortest symptomatic course.[142] The expression of HLA antigens B40 and DR1 is increased in BO associated with RA but not in isolated BO.[143]

There is great heterogeneity in the speed of progression, with some patients having indolent disease and others a rapidly progressive and fatal course[144]; the use of CT in RA patients with suspected pulmonary complications has now identified a subgroup with occult bronchiolitis (see Fig. 92.2C), often admixed with ILD. The prevalence of unsuspected BO in unselected RA patients remains uncertain, with unexplained airflow obstruction identified in a significant minority, including many nonsmokers in one study,[145] but no increase in the prevalence of pulmonary function abnormalities suggestive of isolated small airway disease in two subsequent controlled series.[146,147]

Two major associations with the development of BO in RA have been reported. It is likely that secondary Sjögren syndrome is an important predisposing factor.[144] Because the presence or absence of Sjögren syndrome is not documented in many case reports of BO in RA, the etiologic importance of Sjögren syndrome in this context remains uncertain. More contentious is the reported association between BO and the use of penicillamine, first reported in the late 1970s.[148] After a number of case reports and small series, a significantly higher prevalence of BO was identified in RA patients who took penicillamine (3 of 133) than in other RA patients (0 of 469) in a large cohort.[142] It is possible that the development of BO and the use of penicillamine are both markers of more aggressive RA and are linked for this reason; however, BO developed less than 1 year after penicillamine was begun in 19 of the first 20 cases,[142] and thus the association is unlikely to be entirely spurious. Because BO has been reported in many RA patients not taking penicillamine, it is likely that an underlying predisposition to BO in RA is unmasked by penicillamine, which disrupts collagen linkage and thus interferes with tissue repair. A relationship between BO and gold therapy has been suggested but is not endorsed by clinical experience.

Follicular Bronchiolitis

Follicular bronchiolitis (FB) is characterized by external compression of bronchioles by hyperplastic lymphoid follicles, with variable lymphocytic infiltration of the bronchiolar wall (see eFig. 92.6B). FB is associated more commonly with RA than with other CTDs[149] and is often found incidentally at lung biopsy in RA patients with interstitial pulmonary fibrosis. No causative mechanism has been identified, and it is unclear whether FB predisposes to the subsequent development of BO. When found in isolation, FB simulates ILD, with reticular or nodular opacities on chest radiography and a pattern of functional impairment that may be restrictive or obstructive. Clinically significant isolated FB is rare in RA, but its recognition is important because a response to corticosteroid therapy, although not the rule, is much more likely than in BO; in six of the first nine reported cases, disease stabilized or regressed with treatment.[141] In a CT study of patients with histopathologically proven FB, the most prominent features were centrilobular (see Fig. 92.2D–E) and peribronchial nodules, together with patchy ground-glass increases in attenuation in a bronchocentric distribution.[150]

Bronchiectasis

The prevalence of bronchiectasis is higher in RA than in other CTDs. One literature review identified 289 patients with bronchiectasis associated with RA reported since 1928; however, because respiratory symptoms preceded the systemic manifestations of RA in 90%, it is likely that chance association accounts for a high proportion of early reported cases.[151] Although associated with long-standing RA in one study,[152] on prospective evaluation of 50 RA patients, bronchiectasis was present on 30% of CT scans (see Fig. 92.2F–G).[153] Bronchiectasis in RA is not associated with more aggressive systemic disease and is often clinically silent, with little or no sputum production and a less progressive and disabling course than in patients with idiopathic bronchiectasis.

Pulmonary Vasculitis

There is a relatively high prevalence of systemic vasculitis in patients with RA. Pulmonary hypertension resulting from pulmonary vascular disease, as opposed to extensive pulmonary fibrosis, is uncommon, although occasional cases of pulmonary vasculitis have been found at autopsy.[149] Similarly, diffuse alveolar hemorrhage is a rare complication of RA.

Pulmonary Rheumatoid Nodules

Pulmonary rheumatoid nodules may be single or multiple, are found on chest radiography in less than 1% of RA patients,[113] and are usually associated with rheumatoid nodules elsewhere in the body.[154] On occasion, pulmonary rheumatoid nodules precede the development of systemic disease. Nodules are circumscribed, with central necrotic material contained by palisading epithelioid cells and surrounded by fibrosis and lymphocytic infiltration (see eFig. 92.6C). Nodule cavitation occasionally causes hemoptysis, and pneumothorax may result from the rupture of subpleural nodules. Diffuse infiltration by small nodules, leading to respiratory failure, has been reported.[155] However, nodules generally present as asymptomatic abnormalities on imaging (see Fig. 92.2H–J) and may vary in size according to underlying rheumatoid activity; thus, when solitary, their growth as judged by chest radiography may simulate malignancy. Caplan syndrome consists of the association of single or multiple nodules with coal workers' pneumoconiosis, which is often trivial, in keeping with the suggestion that nodule formation results from a hypersensitivity reaction to inhaled coal dust, perhaps amplified by immunologic overactivity.

Pleural Disease

Pleural disease is seen at autopsy in approximately 50% of patients,[113] and 20% give a history of pleuritic chest pain[156] (see eFig. 92.6D). However, pleural effusions are found in less than 5%,[111,112] usually in men,[154] and are frequently asymptomatic, often being identified on routine chest radiography. In a minority, pleuritic pain and fever are prominent, and the exclusion of empyema, which may be more prevalent in RA, is required. On occasion, effusions may develop acutely in association with pericarditis or exacerbations of arthritis; more typically, radiographic abnormalities are chronic, often remaining unchanged for years. The fluid is an exudate, with a low glucose level, correlating poorly with serum glucose,[157] a low pH, and usually a predominant lymphocytosis, although a neutrophilia is occasionally found. Pleural fluid RF levels tend to mirror serum levels, and the clinical utility of measuring RF in pleural fluid is not clear.

Other Pulmonary Complications

Other pulmonary complications of RA are rare. *Lymphocytic interstitial pneumonia* (LIP) is an occasional finding at lung biopsy and responds variably to corticosteroid therapy. Apical fibrosis mimicking the lung disease ankylosing spondylitis has been reported.[158] Extensive apical cavitation in the absence of nodules or other causes of fibrocavitary disease, including tuberculosis, has been described in a handful of cases and may follow a fulminant course.[159] Pulmonary amyloidosis has been reported occasionally. The incidence of secondary pulmonary hypertension increases with time from diagnosis.[160] Lower respiratory tract infection is increased in frequency in RA; bronchopneumonia is a common terminal event, accounting for 15–20% of deaths in RA patients.[161,162] An increase in lung cancer has been reported in RA.[163]

Drug-Induced Pulmonary Disease

Drug-induced pulmonary disease is a particular problem in RA because of the widespread use of methotrexate in routine clinical practice, and lung disease has been reported in 3–18% of RA patients treated with methotrexate.[164,165] Methotrexate pneumonitis is potentially life-threatening. It presents with cough, dyspnea, fever, widespread crackles, and pulmonary opacities on chest radiography and CT (see eFig. 99.4), which may be focal or diffuse.[166] Although the presentation is sometimes explosive, more often the onset is subacute, with symptoms evolving for up to 2 months before diagnosis[166]; 50% of cases are diagnosed within 4 months of initiation of methotrexate therapy. Because the clinical and radiographic features are nonspecific, methotrexate-induced lung disease should always be suspected in the treated patient presenting with progressive lung disease. Unfortunately, histologic findings are nonspecific, although finding a prominent lymphocytic infiltration increases the likelihood of methotrexate pneumonitis.[167] There is conflicting evidence on whether preexisting lung disease predisposes to lung injury caused by methotrexate, but the published evidence does not suggest that functional impairment is an absolute contraindication to its use, although particular caution is warranted when pulmonary reserve is grossly compromised. Patients with previous methotrexate toxicity should not be retreated.[166,168] Pulmonary methotrexate toxicity is associated with a mortality rate of 15–20%.[166] Because the lymphocytic component of disease is wholly or partially reversible, immediate withdrawal of methotrexate and the early institution of steroid therapy are warranted.

Pulmonary toxicity in RA has also been documented with sulfasalazine, gold therapy, and penicillamine (discussed earlier; see also Chapter 99). Pulmonary opacities (due to OP) associated with sulfasalazine most commonly present in the upper lobes; this side effect is rare in RA, with only a handful of cases reported (most cases were reported in ulcerative colitis).[169] Pulmonary disease induced by gold takes the form of alveolar opacities adjacent to bronchovascular bundles, best demonstrated by HRCT, and often associated with fever or skin rash, relatively low RF titers, and a BAL lymphocytosis.[170] In most patients with sulfasalazine or gold toxicity, lung disease largely regresses with withdrawal of the agent and corticosteroid therapy.

There have been a number of reports of rapidly progressive ILD associated with anti–TNF-α and other biologic therapies, including etanercept, infliximab, and rituximab (an anti-CD20 B-cell–depleting monoclonal antibody), although there are divergent views on whether these reports are truly indicative of drug toxicity or reflect the selective use of these therapies in more aggressive RA. The scope of reported toxicity ranges from infection (with particular focus on reactivation of tuberculosis), undoubtedly a true association, to interstitial disease and vasculitis.[171,172] Leflunomide has also been associated with pulmonary rheumatoid nodules and interstitial disease.[173,174]

Acute Exacerbations of Interstitial Lung Disease

Acute exacerbations of ILD, representing the development of diffuse alveolar damage, are less prevalent in CTD than in IPF. In both settings, presenting features include worsening dyspnea over 2 to 4 weeks, new ground-glass opacities on HRCT (eFig. 92.7), and the absence of infection or other overt causes of decline.[175] Acute exacerbations are more common in RA than in other CTDs, with a high early mortality.[176–178] Triggers of acute exacerbations have not been identified in RA and there is currently no proven therapy, although high-dose corticosteroid therapy is usually given.

PULMONARY FUNCTION TESTS

Patterns of functional impairment in RA have been variable in unselected populations. Predominant airflow obstruction was a frequent finding in one cohort,[145] and reductions in D_{LCO} were ascribed to occult interstitial fibrosis in at least 40%.[134] Inconsistencies in published data can be ascribed to the confounding effects of smoking and variations in the type and severity of associated pulmonary disease. Airflow obstruction may result from bronchiectasis or BO. Interstitial pulmonary fibrosis, OP, and LIP give rise to restrictive defects.

RADIOLOGIC FEATURES

In chest radiographic series of unselected patients with RA, appearances indicative of ILD are found in 1–5% of cases.[111,112,135,138] In interstitial pulmonary fibrosis, appearances are indistinguishable from IPF in a minority of cases, with symmetrical basal interstitial opacification in limited disease and diffuse coarse reticular abnormalities in extensive disease. In the majority of cases, CT appearances are intermediate between those of IPF (see Fig. 92.2A) and NSIP or are suggestive of the latter pattern.[179] Ground-glass opacity, consisting of a patchy or diffuse increase in lung density, is likely to denote inflammatory histologic appearances or fine intralobular fibrosis, as in other fibrosing lung diseases. Rheumatoid nodules (see Fig. 92.2H–J) are usually radiologically discrete and small but are often multiple and may reach up to 7 cm in diameter; in Caplan syndrome, nodules appear in crops, often grow rapidly, and may cavitate. Other chest radiographic findings in RA include focal consolidation (in OP [see Fig. 92.2B], infectious pneumonia, and lung disease induced by methotrexate); focal areas of hyperinflation (in BO; see Fig. 92.2C); and pleural thickening or effusion.

The cardinal CT feature of OP is patchy bilateral air space consolidation, often with associated ground-glass attenuation, which is often predominantly subpleural[180] but may have a bronchovascular distribution (see Fig. 92.2B).[181] Small nodules (≤1 cm in diameter) are common in OP; small pleural effusions and limited fibrosis, probably resulting from prolonged untreated inflammation, are occasional findings.

In bronchiolitis, bronchiolar structures are occasionally visualized directly on CT as centrilobular (see Fig. 92.2D–E) micronodular opacities and peripheral branching structures, denoting marked thickening of the bronchiolar wall; this appearance may be most frequent in FB.[182] In BO, areas of reduced lung density in a patchy distribution ("mosaic perfusion"; see Fig. 92.2C) are associated with a reduction in the caliber of pulmonary vessels in areas of decreased attenuation, indicative of regional hypoxic vasoconstriction in areas of severe bronchiolitis. Bronchiectasis and bronchial wall thickening on CT are common in constrictive bronchiolitis.

TREATMENT OF PULMONARY COMPLICATIONS

The treatment of ILD has usually consisted of corticosteroid therapy, with or without immunosuppressive agents, extrapolated from the SSc-ILD literature. However, when CT appearances are similar to those of IPF, immunomodulation, and especially high-dose corticosteroid therapy, should be used with caution due to the major toxicity with this approach in IPF.[183] It can reasonably be argued that, in this context, high-dose steroid therapy should be largely confined to those with suspected supervening drug-induced lung toxicity or diffuse alveolar damage. Owing to small numbers, regimens have remained anecdotal. Evaluation of the role of antifibrotic agents in RA-ILD is being evaluated in ongoing clinical trials (pirfenidone in TRAIL and nintedanib in IN-BUILD), although the use of antifibrotic agents is currently not approved for the management of RA-ILD.[184,185] Tocilizumab appears to slow progression of decline in lung function.[186] Rituximab has an uncertain role, although it may slow progression of physiologic decline.[187,188] Abatacept was associated with stabilization of lung function in some patients.[189]

Lung function may improve in response to treatment in interstitial pulmonary fibrosis, but a more realistic goal in most cases is to prevent further progression of disease, especially when lung disease is extensive. OP and methotrexate pneumonitis often respond well to treatment. Regression of disease is highly variable in FB and LIP and is virtually never seen in BO.

SYSTEMIC LUPUS ERYTHEMATOSUS

Systemic lupus erythematosus (SLE) is an inflammatory multisystem disorder of unknown etiology with protean clinical and laboratory manifestations and a variable course and prognosis. The 1982 revised American College of Rheumatology criteria for the diagnosis of SLE require that a minimum of four of the criteria listed in Table 92.4 be satisfied, although SLE is sometimes diagnosed with fewer than four criteria.[190]

EPIDEMIOLOGY AND RISK FACTORS

SLE appears throughout the world; the reported prevalence ranges from 12 to 50 per 100,000 population, and the incidence ranges from 1.8 to 7.6 per 100,000 population per year.[191] There is a 6- to 10-fold female excess, and the disease is three times more common in Blacks than in whites. The 5-year survival rate exceeds 90%, but the mortality rate is three times higher than in the general population. Support for a genetic contribution to disease includes a high prevalence in monozygotic twins, familial clustering, and associations among SLE and HLA-DR2, HLA-DR3, and the C4A null allele.[192] No infectious or other environmental factor has been shown to play a major etiologic role.

PULMONARY MANIFESTATIONS

Pleuropulmonary manifestations are common in SLE, with 50–70% of SLE patients experiencing pleuropulmonary complications at some point in their disease course. Pleuropulmonary manifestations of SLE are listed in Table 92.4.

Diffuse Lung Disease

Diffuse lung disease on lung biopsy or at autopsy has been reported in 4%, 33%, and 70% of SLE patients.[193–195] These striking inconsistencies undoubtedly reflect major variations in the histologic diagnostic criteria. In the series with the highest prevalence, trivial interstitial thickening was categorized as "pulmonary fibrosis" but likely represented the minor residuum of infection or inflammatory complications of SLE. Only 3% of SLE patients have clinical evidence of diffuse lung disease at the onset of systemic disease, and a disease resembling interstitial pulmonary fibrosis (eFig. 92.8) develops during follow-up in less than 5%.[196] Risk factors for pulmonary fibrosis in SLE include increasing

Table 92.4 Systemic Lupus Erythematosus

CRITERIA FOR DIAGNOSIS*
Malar rash
Discoid rash
Photosensitivity skin rash
Oral or nasopharyngeal ulceration
Nonerosive arthritis involving ≥2 peripheral joints
Serositis (pleuritis or pericarditis)
Renal disorder (persistent proteinuria or cellular casts)
Neurologic disorder (unexplained seizures or psychosis)
Hematologic disorder (hemolytic anemia, leukopenia, lymphopenia, or thrombocytopenia)
Immunologic disorder (positive LE cell, anti-DNA antibody, anti-Sm antibody, false-positive syphilis serology)
Elevated antinuclear antibodies
LUNG MANIFESTATIONS
Acute lupus pneumonitis
Interstitial pulmonary fibrosis
Pulmonary vasculitis
Diffuse alveolar hemorrhage
Pulmonary hypertension
Shrinking lung syndrome
Antiphospholipid antibody syndrome
Organizing pneumonia
Pleural disease

*Minimum of four criteria required.
LE, lupus erythematosus; Sm, Smith.

age, a history of pneumonitis, and the presence of anti-RNP antibodies.[197]

Interstitial Lung Disease. ILD is uncommon in SLE, affecting only 1–15% of patients. It is usually mild, with slow progression or stability over time. ILD is most commonly seen in patients with long-standing SLE, in patients older than 50 years, and in patients with scleroderma-like features. The clinical presentation (dyspnea, cough, predominantly basal crackles, a restrictive lung function defect or isolated reduction in D_{LCO}, basal opacities on chest radiography) is similar to idiopathic ILD. Features suggestive of SLE include pleuritic pain, functionally severe lung fibrosis, and the frequent presence of enlarged peribronchiolar lymphoid follicles at lung biopsy. OP, NSIP, and LIP are the ILD patterns usually seen in ILD associated with SLE, although a UIP pattern can be seen less commonly. Partial regression of disease with corticosteroids in 9 of 14 cases in one series[198] suggests that an empirical trial of therapy is usually warranted.

Acute Lupus Pneumonitis. Although seen in approximately 1–4% of SLE patients, acute lupus pneumonitis is often life-threatening, with a mortality rate of more than 50% (once respiratory failure has supervened) despite treatment.[199] It can be clinically difficult to distinguish from severe infection and acute respiratory distress syndrome, particularly when it is the first presentation of SLE. The predominant histologic feature of diffuse alveolar damage is nonspecific, and it has been argued that acute lupus pneumonitis is merely a manifestation of aspiration, bacterial infection, or cardiac dysfunction.[193] However, striking responses to corticosteroids and immunosuppressive agents after antibiotic failure suggest strongly that the disorder is a true, albeit rare, entity.

Acute lupus pneumonitis is not to be confused with OP, discussed elsewhere in this chapter and reported in only a handful of adult patients with SLE, or with LIP, described in a small number of patients with SLE.

Shrinking Lung Syndrome

Extrapulmonary restriction, resulting in exertional dyspnea, a restrictive functional defect, and marked decrease of D_{LCO}, is a well-recognized complication of SLE but seen in less than 1% of SLE patients. The shrinking lung syndrome was first described in patients with severe restriction and a marked reduction in lung volume on chest radiography and is associated with progressive breathlessness on exertion and pleuritic chest pain. Lung function tests show reduced lung volumes in a restricted pattern with a normal D_{LCO} when corrected for carbon monoxide transfer coefficient. Chest radiography usually shows reduced lung volumes with raised hemidiaphragm and may also show pleural effusions or atelectasis.

The pathophysiology of shrinking lung syndrome is not clear, and it is generally ascribed to respiratory muscle weakness (Fig. 92.3).[200] However, the use of sniff pressures to evaluate diaphragmatic strength may be confounded by concurrent lung restriction or airflow obstruction; in one study, with the use of alternative methods to evaluate diaphragmatic function, the characteristic restrictive defect was attributed to an "unspecified restriction in chest wall expansion."[201] Pleural inflammation and/or adhesions and pain are also potential contributors to the pathophysiology of shrinking lung syndrome. No treatment of proven efficacy currently exists, although a handful of patients have improved in association with corticosteroid or immunosuppressive therapy.[202] The disorder is almost always self-limited, although sometimes it is severe.

Diffuse Alveolar Hemorrhage (see Chapter 94)

Although seen more frequently in SLE than in other CTDs, *diffuse alveolar hemorrhage* (DAH) is a rare but serious complication of SLE. DAH develops in 1.5–4% of SLE patients, usually early in the disease course. It is more common in patients with active SLE, particularly in those patients with active lupus nephritis.

The typical presentation of DAH with acute dyspnea over hours to days, fever, and extensive pulmonary opacities on imaging (eFig. 92.9) may mimic acute lupus pneumonitis, especially in the absence of hemoptysis, which is only present in 30% of patients.[203] A fall in hemoglobin is common, as is elevation of the D_{LCO}.

DAH is often life-threatening, with a mortality rate of approximately 50%, similar to that of acute lupus pneumonitis. Poor prognostic markers include renal involvement, thrombocytopenia, and the need for assisted ventilation.

Treatment for DAH is not clear but usually includes high-dose corticosteroids, cytotoxic therapy, and plasmapheresis in resistant cases. Treatment responses in both acute lupus pneumonitis and DAH have been observed with IV immunoglobulins, plasmapheresis, and rituximab.[204–207] Patients with SLE have underlying defects in most arms of the immune system and are at added risk of fulminant infection with the use of corticosteroids or immunosuppressive agents.[204] In this context, a misdiagnosis of acute lupus

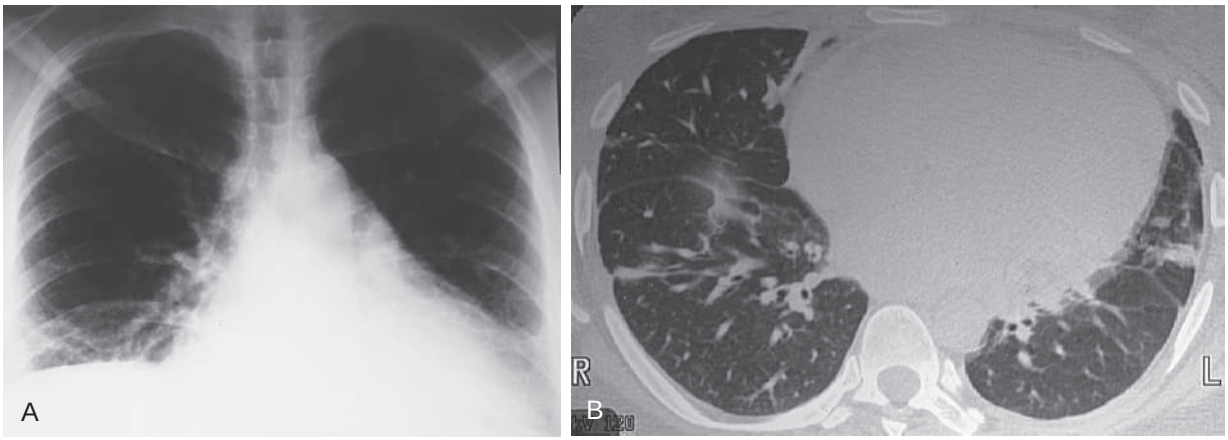

Figure 92.3 Systemic lupus erythematosis. (A) Chest radiograph from a patient with systemic lupus erythematosus shows elevation of both hemidiaphragms, in keeping with shrinking lung syndrome. (B) On a computed tomography scan from the same patient as in part A, linear abnormalities are seen that denote subsegmental atelectasis resulting from regional hypoventilation due to diaphragmatic weakness. The heart is enlarged.

pneumonitis or DAH may lead to a potentially disastrous increase in immunosuppression. Thus the performance of BAL to exclude opportunistic infection may be crucial in SLE patients with unexplained extensive pulmonary opacities.

Pulmonary Arterial Hypertension

PAH was once considered rare in SLE, but it is now reported with a frequency of 0.5–17.5%[208] and has a 2-year survival rate of less than 50% in severe disease. PAH usually affects younger women who have been diagnosed with SLE for more than 5 years. PAH is more common in those with a history of Raynaud phenomenon and serositis and with the presence of anticardiolipin and RNP antibodies. PAH presents with exercise-induced breathlessness and decreased exercise tolerance. Echocardiography can estimate the pulmonary arterial pressure, but the definitive diagnostic test is a right heart catheterization.[209]

The pathophysiology of PAH in SLE is largely related to pulmonary vasoconstriction. Important alternative mechanisms for pulmonary hypertension include vasculitis and thromboembolism.[210] Thromboembolism has a high prevalence in SLE, especially in patients with antiphospholipid antibodies, which cross-react with coagulation factors.[211,212] In a 1993 study of 842 SLE patients, immunoglobulin G anticardiolipin antibodies were present more frequently than immunoglobulin M antibodies (24% vs. 13%), but both were associated with a 30% prevalence of thrombosis as opposed to 10% in SLE patients without these antibodies.[213] Patients with antiphospholipid antibody syndrome also have a higher incidence of impaired lung function than normal control patients.[214]

In view of the multiplicity of mechanisms potentially responsible for pulmonary hypertension, vasodilators and anticoagulation have all been advocated empirically for patients with the pulmonary vascular disease of SLE. Corticosteroid or immunosuppressive agents may be effective therapy for SLE-associated pulmonary hypertension.[210] With the availability of PAH-specific therapies, including prostanoids, endothelin receptor antagonists, and phosphodiesterase-5 inhibitors, outcomes have improved.

Pleural Disease

Pleural disease is the most common pulmonary manifestation of SLE. Clinical or radiographic evidence of pleural involvement is seen in 20% of patients at the onset of systemic disease and in at least 50% at some time,[215] with pleural abnormalities at autopsy in 50–100%. Pleural disease is often asymptomatic, but pleuritic pain may be recurrent or intractable. Acute pleurisy may present with chest pain, dyspnea, fever, and cough. Pleural effusions are often small and bilateral in 50% of patients. Pleural fluid is usually serosanguineous (but occasionally hemorrhagic) and exudative, with a neutrophilia in patients with pleurisy but a predominant lymphocytosis in chronic effusions.[215] The nonspecific histologic appearance of fibrinous pleuritis is not diagnostically useful. The identification of lupus erythematosus cells has largely fallen out of favor because technical difficulties greatly reduce the sensitivity of the test in confirming that a pleural effusion is due to SLE.[216] The measurement of pleural fluid ANA titers may be more diagnostically useful when the etiology of pleural disease is in doubt[217] (see also Chapter 108). Drug-induced lupus also often has pleural involvement, including acute pleurisy and pleural effusions requiring cessation of the offending drug.

SJÖGREN SYNDROME

Sjögren syndrome is an autoimmune disorder characterized by mononuclear cell (primarily lymphocyte) infiltration of the lacrimal, salivary, conjunctival, and pharyngeal mucosal glands, with variable involvement of extraglandular tissue. The cardinal clinical features of keratoconjunctivitis sicca (dry eyes) and xerostomia (dry mouth) may exist in isolation (primary Sjögren syndrome, typically seen in women older than 40 years) but are more often associated with CTDs, such as RA, SSc, or SLE (secondary Sjögren syndrome). Sicca symptoms (e.g., dry eyes and mouth) are common in lung disease, however, and such patients need to be carefully evaluated for the presence of subclinical Sjögren syndrome.[218] Variable diagnostic criteria are used internationally; in one proposed diagnostic algorithm, sicca

symptoms are mandatory, with supportive evidence including ocular signs (positive Schirmer test for testing reduced tear formation, rose bengal score greater than 3 for staining of damaged conjunctiva and cornea), typical histologic appearances on salivary gland biopsy, antibodies to Ro (SS-A) or La (SS-B), or reduced salivary flow.[219]

EPIDEMIOLOGY AND RISK FACTORS

Primary Sjögren syndrome has a reported annual incidence of 6.9 per 100,000 with a prevalence of 60.8 per 100,000. Reported prevalence rates vary, largely due to differences in diagnostic criteria used, but range from 4.2 per 100,000 in a cohort in Minnesota to 93 per 100,000 in a Greek study.[220,221] Some evidence suggests a genetic predisposition, including familial clustering and an association with HLA-Dw2 and HLA-Dw3, but no environmental triggers have been identified. Primary Sjögren syndrome is more common in women and presents at two age peaks: at 20 to 30 years and older than 50 years.

PULMONARY MANIFESTATIONS

Pulmonary involvement is common in Sjögren syndrome. In early series, primary and secondary Sjögren syndromes were combined; it is likely that many of the pulmonary abnormalities seen in secondary Sjögren syndrome were ascribed to the underlying CTD. Careful evaluation of patients with primary Sjögren syndrome has shown that cough and dyspnea are common,[222] with objective evidence of pulmonary abnormalities in approximately one-fourth of cases.[223] Lung involvement usually consists of lymphocytic infiltration similar to that seen in salivary glands and resulting in tracheobronchial disease or ILD, depending on whether involvement is limited to secretory glandular tissue or is more widespread. However, population studies of respiratory involvement in Sjögren syndrome have been hampered by variations in diagnostic criteria, failure to discriminate between primary and secondary Sjögren syndrome, and failure to control for confounding features, such as drug treatment and smoking. Lung manifestations include diffuse lung disease and tracheobronchial disease.

In a CT study of 35 patients, the most prevalent findings were large and/or small airway disease ($n = 19$) and diffuse lung disease ($n = 12$, including 7 in whom the features were suggestive of LIP). The patterns of physiologic abnormalities were consistent with the predominant CT pattern.[224]

Interstitial Lung Disease

Although often asymptomatic, clinically significant ILD in Sjögren syndrome may develop in 8–27% of patients and, when present, ILD is associated with a poorer quality of life and increased mortality. ILD is more common in older, male patients with a history of smoking and positive antinuclear antibody testing.[225] ILD tends to develop early in the disease course, with a cumulative incidence of 10% at 1 year after the diagnosis of systemic disease.[223]

ILD usually presents with cough, increasing dyspnea on exertion, crackles on auscultation, reticular or nodular opacities on chest radiography, and a restrictive pattern of functional impairment. ILD frequently takes the form of fibrotic NSIP with lung biopsies showing an NSIP pattern in 45.5% of patients (eFig. 92.10A–B) and, less commonly, UIP or LIP (eFig. 92.10C and E), OP or pulmonary amyloidosis, or lymphoma.[226] Although ILD associated with Sjögren syndrome is usually regarded as clinically insignificant, Gardiner and coworkers[227] found that patients with primary Sjögren syndrome reporting dyspnea (≈10%) have a high prevalence of histologic abnormalities (fibrosis or lymphocytic infiltration) on transbronchial biopsy.[227] In one study, the 5-year survival rate of patients with ILD associated with Sjögren syndrome was 84%.[217]

Lymphocytic interstitial infiltration may take the form of LIP, pseudolymphoma (extensive pulmonary lymphocytic infiltration with the formation of lymphoid follicles; see eFig. 92.10E), or pulmonary lymphoma (see eFig. 92.10F–G). LIP is characterized by a diffuse lymphocytic infiltrate, with or without histiocytes and multinucleated giant cells, most prominent around bronchioles. Regression of disease with corticosteroids, in isolation or in combination with immunosuppressants, is highly variable. There are anecdotal reports of responses to rituximab. Pseudolymphoma, characterized by pulmonary infiltration, may regress spontaneously and often responds well to corticosteroid therapy; however, some patients progress to pulmonary lymphoma. The prevalence of lymphoma is increased 40- to 50-fold in Sjögren syndrome[228]; pulmonary lymphoma has a highly variable clinical and radiographic presentation, with the spectrum of disease ranging from diffuse interstitial involvement to discrete (often perihilar) masses (see eFig. 92.10F–G).

OP has been reported in Sjögren syndrome (see eFig. 92.10D) but is less common than in RA or PM. A response to corticosteroid therapy is usual but not invariable.

Tracheobronchial Disease

Tracheobronchial disease may take the form of loss of mucous secretion in the trachea (xerotrachea), chronic bronchitis, or small airway disease. Xerotrachea develops in up to 25% of patients with primary Sjögren syndrome and consists of atrophy of tracheobronchial mucous glands in association with a lymphoplasmacytic infiltrate, manifesting clinically as a relentless dry cough and endobronchial inflammation at bronchoscopy.[229] It is likely that similar histologic abnormalities in bronchi and bronchioles account for an increased prevalence of bronchial hyperresponsiveness, reported in 40–60% of patients with primary and secondary Sjögren syndrome.[230]

Subclinical bronchiolitis may be common in Sjögren syndrome. In the ILD of Sjögren syndrome, lymphocytic infiltration is more prominent around small bronchioles, resulting in a BAL lymphocytosis[231]; thus it is likely that the occasional cases of isolated lymphocytic bronchiolitis, presenting with a clinical picture of COPD, represent a more limited form of Sjögren syndrome involving only the airways. The evaluation of airflow at low lung volumes in unselected patients with primary and secondary Sjögren syndrome has demonstrated a high prevalence of small airway dysfunction[222]; aerosol penetration from central airways to the lung periphery is reduced, indicating small airway obstruction.[232] These abnormalities lead to cough, bronchial hyperreactivity in up to 60% of patients, bronchitis, and bronchiectasis. There may be evidence of either BO or mucous plugging, which

may contribute to an increased prevalence of bronchopneumonia but not evolve into severe BO, which is not generally a feature of Sjögren syndrome, except in occasional cases with associated RA. FB has been reported in a handful of patients with primary Sjögren syndrome but may be more frequently seen in secondary Sjögren syndrome; in a number of reported cases of FB associated with RA, the presence of Sjögren syndrome is not explicitly excluded. FB and diffuse bronchiolar lymphocytic infiltration may be part of the same spectrum of disease, but the relationship between the two disorders is uncertain.

Due to the association between Sjögren syndrome and bronchial reactivity, some have postulated that asthma and COPD may be more common in patients with Sjögren syndrome. Indeed, studies have demonstrated that the incidence of asthma and COPD was 1.6-fold and 1.4-fold higher, respectively, compared to matched control patients.[233,234] Of interest, inhaled anti-inflammatories, including inhaled budesonide and inhaled cromoglycate, appear to have no effect on patients with Sjögren syndrome and bronchial hyperreactivity.

POLYMYOSITIS AND DERMATOMYOSITIS

The defining criteria for PM and DM are listed in Table 92.5. For PM, a definite diagnosis is made if the first four features are present, a probable diagnosis is made if any three of the first four features are present, and a possible diagnosis is made if any two of the first four features are present. For DM, the typical rash must be present, plus any three of the first four for a definite diagnosis, two of the first four for a probable diagnosis, and one of the first four for a possible diagnosis (the Bohan and Peter criteria).[235]

Skin problems of DM include the presence of scaly cutaneous eruptions affecting extensor surfaces of the finger joints (Gottron tubercles or papules) (see Fig. 92.4A) and the characteristic edema and violaceous or purplish, heliotrope rash that involves and surrounds the eyelids (see Fig. 92.4B). Proximal muscle weakness tends to be insidious, progressive, and painless, affecting head, neck, and limb girdles and eventually involving the muscles of the tongue and pharynx and the respiratory muscles. Pulmonary complications arise in approximately 45% of patients and are the most frequent cause of death.

EPIDEMIOLOGY AND RISK FACTORS

The inflammatory myopathies are relatively rare, affecting 2 to 10 per 100,000 population, with a female-to-male predominance of 2.5:1 and with a bimodal age distribution peaking in childhood and in the fourth to fifth decades. PM associates with HLA-B8/DR3 and in Blacks with HLA-B7 and HLA-DRw6,[236] whereas DM appears to have a higher expression of HLA-B8/DR3, HLA-B14, and HLA-B40. There are multiple manifestations of lung disease, as listed in Table 92.5. The presence of diffuse lung disease has been associated with two specific HLA haplotypes.[237] In combined series, the prevalence of diffuse lung disease can be up to 64%. The disease may also present with pulmonary symptoms; in one series, this was the case in 21 of 70 patients.[238] The prevalence of lung disease varies from series to series, and the respiratory symptoms often are masked by muscle fatigue. Nonetheless, pulmonary complications of the disease can be a frequent cause of death.

Table 92.5 Polymyositis and Dermatomyositis

CRITERIA FOR DIAGNOSIS*
Symmetrical proximal muscle weakness
Muscle biopsy specimen showing myositis
Elevation of serum skeletal muscle enzymes
Characteristic electromyographic pattern of myositis
Typical rash of dermatomyositis
LUNG MANIFESTATIONS
Interstitial pulmonary fibrosis
Acute pneumonitis (with diffuse alveolar damage)
Organizing pneumonia
Aspiration pneumonia
Pulmonary vasculitis and alveolar hemorrhage
Respiratory muscle weakness

*For defining criteria, see text.



Figure 92.4 Skin changes seen in dermatomyositis. (A) Gottron papules. A discrete scaly rash is seen over the extensor surfaces of the joints. (B) Heliotrope rash. Named after a lilac-like flower with purple petals, this purplish rash and associated edema particularly involve the eyelids. (Modified from Iaccarino L, Ghirardello A, Bettio S, et al. The clinical features, diagnosis and classification of dermatomyositis. *J Autoimmun.* 2014;48–49:122–127.)

PULMONARY MANIFESTATIONS

Interstitial Lung Disease

ILD is the most common problem encountered in the context of PM and DM and may develop in up to 32% of patients.[239] This has been described as antisynthetase syndrome when

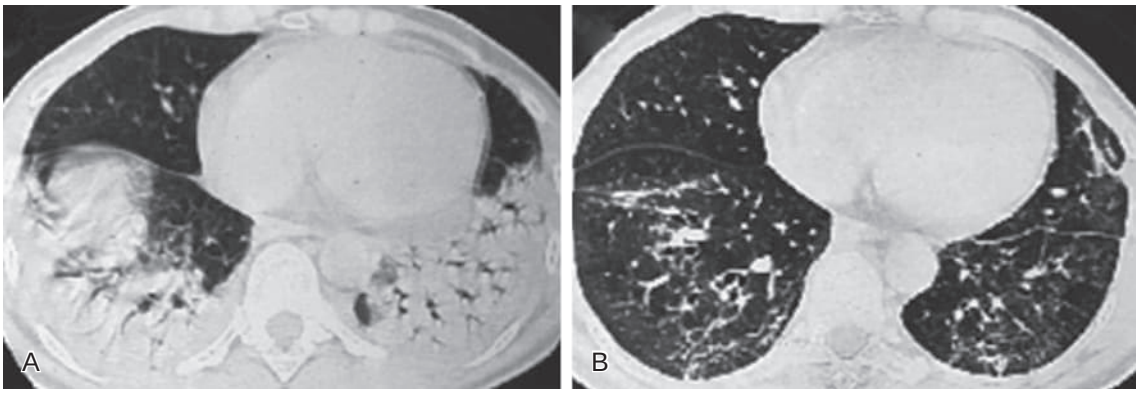

Figure 92.5 Organizing pneumonia in polymyositis. (A) Computed tomography scan shows dense consolidation that denotes organizing pneumonia in a patient with polymyositis. As shown in this example, the disease tends to be most prominent posteriorly in the lower lobes. (B) After treatment, the dense consolidation has regressed, but there is extensive residual linear opacification, representing residual fibrosis and resulting in traction bronchiectasis on the right and a restrictive functional defect. (Courtesy Michael B. Gotway, MD.)

associated with an anti–*transfer RNA* (tRNA) antibody. The prevalence of diffuse lung disease may be less common in patients with amyotrophic DM, a small subgroup of patients with the rash of DM but not the muscle involvement, and is three to five times more common in women than men, most commonly presenting in the fifth decade. The pattern of diffuse lung disease is most often that of NSIP. In many cases, a major component of OP, admixed with fibrotic abnormalities, is a prominent early feature, both histologically and on HRCT[240–242] (Fig. 92.5). However, in a distinct minority of cases with supervening diffuse alveolar damage (eFig. 92.11), the onset is subacute, rapidly progressive, and often resistant to treatment.[243] The histopathologic features associated with these forms of presentation include NSIP, UIP, and OP, and diffuse alveolar damage in the acute setting.[244–246] In a large series of 70 patients, Douglas and colleagues[238] reported that 82% of patients who were biopsied had an NSIP pattern. One report described an acute presentation of pulmonary capillaritis with alveolar hemorrhage in association with PM.[247]

Clinical Features. The clinical features of diffuse lung disease in PM and DM depend on the nature of the lung process. Dyspnea and nonproductive cough are the most common presenting symptoms. Breathlessness on exertion without wheeze is common and, if the myopathy is severe, orthopnea may be striking. Hemoptysis may develop if there is capillaritis. Pleural disease is uncommon. Pulmonary involvement can develop before the systemic disease or at any time in the disease course. There is no correlation between the severity of pulmonary parenchymal involvement and the systemic musculoskeletal manifestations. Rarely, patients present acutely with, or progress rapidly to, acute respiratory failure.

Imaging. Chronic diffuse lung disease is associated with peripheral reticular opacities, particularly in the lung bases. Acute pneumonitis can result in ground-glass opacification on chest radiography and alveolar hemorrhage with areas of consolidation.

HRCT is more sensitive and specific than chest radiography at highlighting the distributions of the different processes. CT findings include thickened interlobular septa, linear opacities, ground-glass opacification (see eFig. 92.11), and patchy consolidation. A combination of consolidation with a peripheral reticular pattern is highly characteristic.[248] Traction bronchiectasis and honeycombing are less common. The consolidation may evolve into a reticular pattern.[249] PM and DM are well-recognized paraneoplastic phenomena, so it is sometimes difficult to determine which condition presented first.[250] Screening for occult carcinoma is recommended with mammography, abdominal CT, pelvic ultrasonography, tumor markers and, in some settings, positron emission tomograpy.

Pulmonary Function. Lung function tests show a restrictive ventilatory defect with reduced D_{LCO}. With recent hemorrhage or marked myopathy, there may be a disproportionate preservation of the D_{LCO}. However, it must be remembered that acute hemorrhage can present in the context of previous chronic disease, so the D_{LCO} may be normal or subnormal but elevated from a level that was previously lower. Severe reduction in D_{LCO} is associated with increased mortality.

Bronchoalveolar Lavage. BAL lymphocytosis and neutrophilia have been described in diffuse lung disease associated with PM/DM. The significance of BAL is debated, but it appears that neutrophilia on BAL is associated with clinical deterioration.[251]

Laboratory Tests. Several studies have reported no association between creatine kinase levels and respiratory disease. In fact, the presence of a low creatine kinase has been associated with more rapidly progressive diffuse lung disease.[252,253] Studies of autoantibodies have highlighted the association between the presence of antibodies to aminoacyl-tRNA synthetases, inflammatory myopathies, and diffuse lung disease.[252] These antibodies help to define the clinical antisynthetase syndrome: the coexistence of myositis, diffuse lung disease, and arthritis (Table 92.6). The most common autoantibody is Jo-1 (a cytoplasmic antihistidyl tRNA synthetase), found in 20–30% of patients with inflammatory myopathy and correlating strongly with the presence of diffuse lung disease. Jo-1 antibodies are present in 50–100% of cases of inflammatory myopathy and diffuse lung disease, in contrast to less

Table 92.6 Antisynthetase Syndrome

Patient must have:
Positive anti-tRNA antibody
Plus one or more of the following:
Myositis by Bohan and Peter criteria
ILD by ATS criteria
Arthritis by clinical examination, radiographic findings or patient self-report
Unexplained, persistent fever
Raynaud phenomenon
Distal digital fissuring ("mechanic's hands")

ATS, American Thoracic Society; ILD, interstitial lung disease; tRNA, transfer RNA.

Modified from Connors GR, Christopher-Stine L, Oddis CV, Danoff SK. Interstitial lung disease associated with the idiopathic inflammatory myopathies: what progress has been made in the past 35 years? *Chest*. 2010;138(6):1464–1474.

than 5% of patients without diffuse lung disease. A variety of novel autoantibodies have been described with affinity for other tRNA synthetase molecules: PL-12, PL-7, EJ, OJ, Ku, and melanoma differentiation–associated gene 5 (see eTable 92.1).[254] Melanoma differentiation–associated gene 5 antibodies are associated with rapidly progressive forms of ILD.[255]

OTHER PULMONARY MANIFESTATIONS

Muscular weakness may lead to aspiration pneumonia in up to 20% of patients and is usually associated with dysphagia. Respiratory muscle weakness and hypercapnic respiratory failure develop in up to 25% of patients, although severe respiratory failure requiring ventilatory support is less common. Bilateral diaphragmatic paralysis has been reported.

TREATMENT OF PULMONARY COMPLICATIONS

Diffuse lung disease is a serious complication of PM/DM and is associated with increased mortality.[256] The clinical course and prognosis of PM/DM-associated diffuse lung disease is heterogeneous and depends on the histologic pattern of disease. The decision to treat and the choice of therapy therefore needs to be individualized. Corticosteroids are the preferred initial therapy. Oral prednisolone (0.75–1 mg/kg/day) is usual, but IV corticosteroids are required in more severe or rapidly progressive disease. Immunosuppressive therapy may be used in patients who are steroid resistant or experiencing adverse effects from corticosteroids. There are some reports of efficacy of cyclophosphamide,[257,258] cyclosporin A,[259] azathioprine, mycophenolate, and tacrolimus, a calcineurin inhibitor.[260,261] In refractory cases, IV immunoglobulin should be considered. Rituximab is a promising treatment for the antisynthetase syndrome,[262] including for patients with life-threatening disease refractory to other immunomodulatory therapies.[263] Retrospective studies demonstrate stabilization of CTD-ILD with rituximab. Patients with myositis-associated ILD may represent the subgroup of CTD-ILD with the greatest response to rituximab.[264]

MIXED CONNECTIVE TISSUE DISEASE

MCTD is defined by the presence of features of SLE, SSc, and PM (Sjögren syndrome may also be seen) in association with high titers of autoantibody (>1:1600) directed against the ribonucleoprotein U1-RNP.[265,266] Criteria that have been suggested for the diagnosis of MCTD include the presence of antibody to U1-RNP, together with the clinical features of hand edema, synovitis, Raynaud phenomenon, acrosclerosis, and myositis. At least three of these clinical features are needed in addition to the autoantibody finding. A fourth clinical feature is required if the initial three are Raynaud phenomenon, edema, and acrosclerosis. The difference between MCTD and an overlap syndrome may be semantic, but the former often presents more acutely and with greater specificity for U1-RNP. MCTD may differentiate into specific rheumatologic diseases. This differentiation may be genetically determined.[267]

Overlap syndromes are reported in which clinical features of more than one CTD are present in the same patient. Although MCTD tissue disease remains the most clearly definable, other overlap syndromes are seen both with and without typical autoantibody association. Of the former, overlapping clinical features found in association with U2-RNP and U3-RNP and the tRNA synthetase–associated diseases (see earlier) can be considered to be part of an overlap syndrome. Antibodies to PM-Scl, KU, and U2-RNP are associated with overlaps of SSc and PM.[266]

The prevalence of MCTD is unclear, but it is estimated at 1 in 10,000, with a 9:1 female preponderance, most frequently presenting in the fourth decade. Pleuropulmonary complications are seen in 20–85% of patients, but diffuse lung disease, most commonly with an NSIP CT pattern, is the most common lung complication.[268] In a CT study of 41 patients, the major abnormalities were ground-glass opacities in all, subpleural micronodules in 40 of 41, and nonseptal linear opacities in 32 of 41.[269] Pleural effusions develop in patients with other clinical features of SLE and are usually small, exudative, and often resolve spontaneously. Pulmonary hypertension may also develop.[270] Respiratory muscle weakness, DAH, and small airway disease are less common complications.

Survival is difficult to quantify owing to the heterogeneity of disease. The individual disease course tends to be similar to that of the CTD most closely resembled in that patient. Survival is better for those with CTD-ILD if the diffuse lung disease is associated with U1-RNP positivity than with no U1-RNP. Treatment depends on the nature of the lung disease and is identical to the approaches used for the other CTDs. Pleural effusions are often responsive to corticosteroids. A combination of low-dose prednisolone and an immunosuppressant, such as cyclophosphamide or azathioprine, is generally used to treat interstitial fibrosis, with an approach similar to that for SSc.

IDIOPATHIC PNEUMONIA WITH AUTOIMMUNE FEATURES

Although most patients with CTD-ILD will develop an ILD in the context of a previously diagnosed CTD, in some cases,

ILD can be the first and/or only manifestation of CTD.[271] CTD is eventually diagnosed in approximately 15% of patients presenting with idiopathic interstitial pneumonia[272,273] and in 30% of patients with idiopathic NSIP.[274] It is now recognized that there is a cohort of patients with ILD meeting some, but not all, diagnostic criteria for CTD. This group has now been defined by an ATS/ERS taskforce, and termed *idiopathic pneumonia with autoimmune features* (IPAF).[275] To fulfill criteria for IPAF, patients must have (1) presence of an interstitial pneumonia (by HRCT or surgical lung biopsy), (2) exclusion of alternative etiologies, (3) incomplete features of a defined CTD, and (4) at least one variable from at least two of three domains (clinical, serologic, and morphologic; Table 92.7).[275] IPAF is currently a provisional entity, pending validation by ongoing clinical studies.

Table 92.7 Classification Criteria for Interstitial Pneumonia With Autoimmune Features

Clinical domain	▪ Distal digital fissuring (i.e., "mechanic's hands") ▪ Distal digital tip ulceration ▪ Inflammatory arthritis or polyarticular morning joint stiffness ≥60 min ▪ Palmar telangiectasia ▪ Raynaud phenomenon ▪ Unexplained digital edema ▪ Unexplained fixed rash on the digital extensor surfaces (Gottron sign)
Serologic domain	▪ ANA ≥ 1:320 titer, diffuse, speckled, homogeneous patterns *or* ANA nucleolar pattern (any titer) *or* ANA centromere pattern (any titer) ▪ RF ≥ 2 × ULN ▪ Anti-CCP ▪ Anti-dsDNA ▪ Anti-Ro (SS-A) ▪ Anti-La (SS-B) ▪ Anti-ribonucleoprotein ▪ Anti-Smith ▪ Antitopoisomerase (Scl-70) ▪ Anti-tRNA synthetase (e.g., Jo-1, PL-7, PL-12, others are: EJ, OJ, KS, Zo, tRS) ▪ Anti–PM-Scl ▪ Anti-CADM (MDA-5)
Morphologic domain	Suggestive radiology patterns by HRCT: ▪ NSIP ▪ OP ▪ NSIP with OP overlap ▪ LIP Histopathology patterns or features by surgical lung biopsy: ▪ NSIP ▪ OP ▪ NSIP with OP overlap ▪ LIP ▪ Interstitial lymphoid aggregates with germinal centers ▪ Diffuse lymphoplasmacytic infiltration (with or without lymphoid follicles) Multicompartment involvement (in addition to IPAF): ▪ Pleural effusion or thickening (not otherwise explained) ▪ Pericardial effusion or thickening (not otherwise explained) ▪ Small airways disease (by PFTs, imaging or pathology) ▪ Pulmonary vasculopathy

ANA, antinuclear antibody; anti-CCP, anti–cyclic citrullinated peptide; anti-dsDNA, anti–double-stranded DNA; CADM, clinically amyopathic dermatomyositis; HRCT, high-resolution computed tomography; IPAF, interstitial pneumonia with autoimmune factors; LIP, lymphocytic interstitial pneumonitis; MDA-5, melanoma differentiation–associated gene 5; NSIP, nonspecific interstitial pneumonia; OP, organizing pneumonia; PFTs, pulmonary function tests; RF, rheumatoid factor; Scl, scleroderma; ULN, upper limit of normal.

From Fischer A, Antoniou KM, Brown KK, et al. An official European Society/American Thoracic Society research statement: interstitial pneumonia with autoimmune features. *Eur Resp J*. 2015;46:976–987.

RELAPSING POLYCHONDRITIS

Relapsing polychondritis is a rare disease characterized by recurrent progressive cartilaginous inflammation. The episodic and painful inflammation results eventually in the widespread degeneration of cartilaginous structures. The diagnosis of relapsing polychondritis requires the presence of three or more of the following clinical features[276]: bilateral auricular chondritis, nonerosive seronegative inflammatory polyarthritis, nasal chondritis, ocular inflammation, respiratory tract involvement (either upper or lower respiratory tract); cochlear involvement with or without vestibular abnormality; and a positive biopsy specimen. The presence of anticartilage antibodies may be helpful in the diagnosis. (See Chapter 71.)

The condition affects men and women equally and has a peak incidence between ages 40 and 60 years. It is considered an autoimmune process, and autoantibodies have been found directed against cartilage and type II collagen. A weak association with HLA-DR4 has been reported.[277] Diagnosis is chiefly clinical but can be confirmed by biopsy of affected cartilage, including tracheal rings.

Relapsing polychondritis is usually multifocal, affecting cartilage of the ear (85–94%), nose (54–57%) (see Fig. 92.6A–B), upper respiratory tract (31–48%), and ribs. In addition, patients frequently have ocular inflammation, nonerosive arthropathy (52%), and vestibulocochlear dysfunction.[276,278] Relapsing polychondritis may be associated with a wide range of other conditions, especially CTD and vasculitis. Approximately 30% of patients have a preexisting CTD.

Respiratory involvement probably accounts for around 10% of deaths in this condition. Up to 25% of cases present with focal or generalized respiratory tract involvement. The larynx and upper trachea are the most common focal areas involved, but large or small airways may also be affected. Laryngotracheal involvement is a poor prognostic determinant. Destruction and obstruction of the glottis, trachea, and bronchi may lead to airway stricture, lobar collapse/consolidation, and distal infection.[279] Pulmonary parenchymal disease is rare, with the exception of pulmonary vasculitis.

The site of cartilaginous involvement determines the clinical presentation. Upper airway involvement typically presents with wheezing and hoarseness. Lung function testing shows diminution in maximal inspiratory (large, extrathoracic airways) and expiratory (smaller, intrathoracic airways) flow rates, suggesting airway collapse. Static recoil pressures are preserved. Chest radiography may show ectopic airway cartilage calcification or large airway narrowing (see Fig. 92.6C) but is often insensitive. However, HRCT scanning shows tracheal ring thickening,

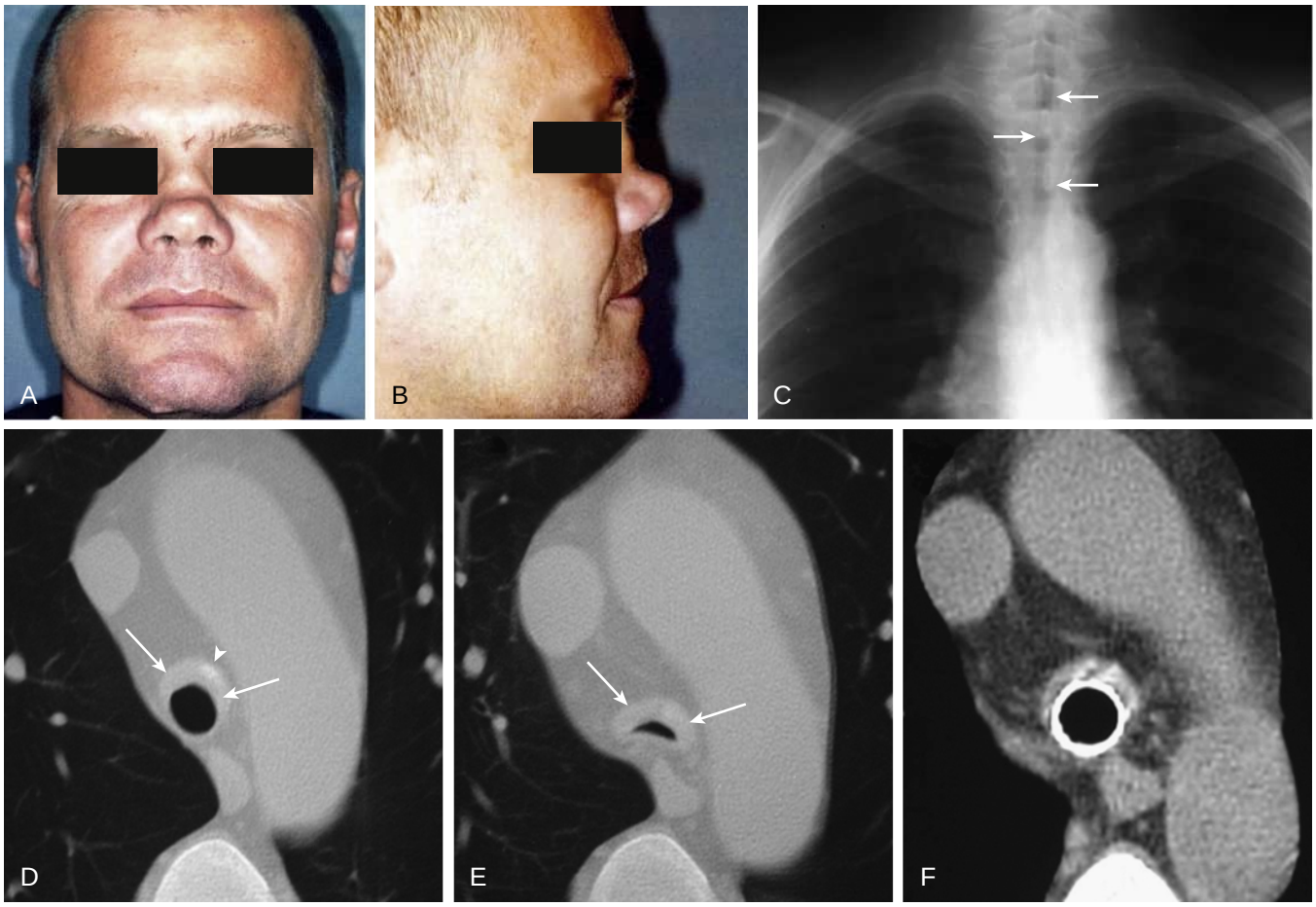

Figure 92.6 Relapsing polychondritis. (A–B) Saddle nose deformity indicating loss of cartilage of the nose due to inflammatory deterioration of cartilage structure. In this 42-year-old man, destruction of the nasal septum led to restriction of ventilation, with collapse of the internal nasal valves during a rapid inspiration. (C) Focused frontal chest radiograph shows smooth sagittal narrowing of the trachea (*arrows*). (D) Axial unenhanced chest computed tomography shows thickening of the anterior two-thirds of the trachea (*arrows*), with sparing of the posterior tracheal membrane; this pattern is typical of relapsing polychondritis. A small focus of calcification is present in the anterior tracheal wall at the 1 o'clock position (*arrowhead*). (E) Axial postexpiratory high-resolution computed tomography image shows extensive tracheal collapse (*arrows*) consistent with tracheomalacia and typical of relapsing polychondritis. (F) Treatment of relapsing polychondritis with a self-expandable endoluminal metallic stent shows patency of the tracheal lumen. (A–B, From Haug MD, Witt P, Kalbermatten FD, et al: Severe respiratory dysfunction in a patient with relapsing polychondritis: should we treat the saddle nose deformity? *J Plast Reconstr Aesthet Surg.* 2009;62:e7–e10. C–F, Courtesy Michael B. Gotway, MD.)

airway wall attenuation, and calcification (see Figs. 92.6D and Fig. 20.30). Postexpiratory CT scanning, using either scanning at the completion of an FVC maneuver (see Fig. 92.6E) or cine scanning during such a maneuver, shows extensive tracheobronchial collapsibility and can help to localize the large airway disease.[280] Bronchoscopy may show endobronchial inflammation or stenosis and is useful in the exclusion of mechanical obstruction. Endobronchial biopsy may be diagnostic but is insensitive. Laryngoscopy and bronchoscopy are associated with risk of acute airway compromise, however.[279]

Treatment depends on disease severity. Mild cases may be controlled with nonsteroidal anti-inflammatory drugs, but troublesome relapses may require short-term high-dose corticosteroid therapy. In acute airway involvement, high-dose IV corticosteroid is used. In one large review of 159 reported cases, three-fourths of the patients required chronic corticosteroid therapy, which, in that series, decreased the frequency, duration, and severity of flare-ups but did not prevent disease progression.[281] Steroid-resistant lesions have been treated with immunosuppressive agents such as cyclophosphamide. Despite short-term improvement with steroid and immunosuppressive therapy, relapse and disease progression are common. There have also been a number of reported responses to biologic agents, including TNF-α antagonists, anti–IL-6 therapy, and rituximab, with efficacy or partial efficacy in more than half of cases.[282,283] Currently, biologics cannot be recommended as first-line therapy but may have an important role in cases refractory to corticosteroids and as steroid-sparing agents. Tracheostomy and stenting are occasionally indicated, but other surgical treatment is difficult owing to the diffuse nature of involvement and risk of relapse.[284] In one study, the use of multiple, self-expandable stents (see Fig. 92.6F) via fiberoptic bronchoscopy in five patients requiring mechanical ventilation resulted in improvement in four patients who were all able to live without mechanical ventilation for up to 20 months.[285] Newer self-expanding silicone stents have been used with variable effect in palliative cases.[286] Intraluminal stents may be complicated by hemorrhage, tracheal erosion, ulceration, or airway obstruction, however. Survival has been reported at 94% at 8 years.[287]

Table 92.8 Behçet Syndrome

CRITERIA FOR DIAGNOSIS
Major (Required)
Recurrent aphthous ulceration at least three times in a 12-mo period
Minor (Two of Four)
Recurrent genital ulceration
Ocular disease
Skin lesions (erythema nodosum, skin ulcers)
Positive pathergy test (a 2-mm erythematous papule or pustule at the prick site 48 hr after the application of a sterile hypodermic 20- to 22-gauge needle that obliquely penetrated avascular antecubital skin to a depth of 5 mm)

Data from Cambrey AD, Harrison NK, Dawes KE, et al. Increased levels of endothelin-1 in bronchoalveolar lavage fluid from patients with systemic sclerosis contribute to fibroblast mitogenic activity in vitro. *Am J Respir Cell Mol Biol* 1994;11:439–445; and Shi-Wen X, Denton CP, McWhirter A, et al. Scleroderma lung fibroblasts exhibit elevated and dysregulated type I collagen biosynthesis. *Arthritis Rheum*. 1997;40:1237–1244.

BEHÇET SYNDROME

Behçet syndrome is found predominantly in the countries bordering the Mediterranean Sea. Prevalence estimates approach 80 to 370 per 100,000 population in Turkey. Men and women are affected equally, and age of onset is usually in the second or third decade. There is an association between the HLA-B51 allele and Behçet syndrome; the relative risk of HLA-B51 carriers for Behçet syndrome is roughly 13:1. Herpes simplex type 1 and streptococci have been suggested as causative agents.[288] Diagnosis requires the development of recurrent oral ulceration at least three times in a 12-month period and the presence of two of the four minor features listed in Table 92.8.[289] Mucocutaneous ulceration is the clinical hallmark, with aphthous oral and genital ulceration seen in almost all patients. Other cutaneous features include erythema nodosum, an acneiform rash, and papular lesions of cutaneous vasculitis. Uveitis is the major cause of morbidity, but systemic vasculitis may affect all systems.

Pulmonary involvement is seen in 1–7% and tends to affect HLA-B51–positive younger men (<25 years) more severely. The major pulmonary manifestations are pulmonary vasculitis,[290] pulmonary artery aneurysms, arterial and venous thromboses, pulmonary infarction, OP, and pleurisy.[291] Symptoms include dyspnea, chest pain, and recurrent hemoptysis that can be massive and fatal.[292]

The cardinal histologic feature is vasculitis affecting arterial and venous vessels of all sizes. Pulmonary arterial aneurysms are surrounded by inflammatory infiltrates and have thickened intima and degeneration of the elastic lamina with thrombosis. Behçet syndrome may be accompanied by arterial and venous thromboses, pulmonary infarcts and, on occasion, pleural effusion.[293] The radiographic abnormalities are nonspecific but may include the features of small airway disease, pulmonary hemorrhage, vascular occlusion, or mass lesions representing arterial aneurysm(s) (see eFig. 94.2).[294,295] Prognosis is variable. The disease course is relapsing remitting. Pulmonary artery aneurysm carries the worst prognosis, with a 2-year survival of 70%.

Treatment is complex and depends on presentation. Steroids and immunosuppressive agents are used to control vasculitis, particularly in cases of pulmonary artery aneurysm, in which eventual regression is sometimes observed. Cyclosporin A and tacrolimus have been successful in some patients.[291] Anticoagulants may be required for control of thrombosis but should be used only if immunosuppression is insufficient because there is a significant risk of hemorrhage. However, controlled data are lacking, and accumulated experience mostly relates to the treatment of systemic disease, including orogenital ulceration, and must be applied to pulmonary disease with caution. Acknowledging this caveat, the major change in treatment has been the increasing use of anti-TNF therapy, found to be efficacious for oral ulceration and skin lesions in a randomized controlled trial[296] and endorsed for eye disease, neurologic disease, and gastrointestinal disease by a position paper, based on a definitive review of uncontrolled treatment data.[297] For pulmonary artery aneurysms, pulmonary embolization and surgical resection have been reported to be successful, but surgical treatment of aneurysms can result in aneurysms at the anastomosis site.[298]

ANKYLOSING SPONDYLITIS

Ankylosing spondylitis (AS) is a seronegative spondyloarthritis developing in 0.05–1.5% of the general population and is associated with the major histocompatibility antigen HLA-B27.[299] The prevalence of AS is higher in white men, with a male-to-female ratio of 10:1. The cardinal site of disease is the vertebral column. As the disease progresses, inflammation leads to fibrosis and ossification, with ankylosis of the vertebral joints. Peripheral joint arthritis is seen in approximately one-third of patients, and extra-articular features include aortic regurgitation, uveitis, pulmonary disease, and extrapulmonary restriction.

Lung disease, mainly upper zone fibrosis, can be present in up to 30% of case series, but fibrobullous disease is less common (see eFigs. 131.4 and 131.6). In a series of 2080 patients with AS, this pattern was seen in only 1–2% of patients.[300] Limited ILD, small airway disease, bronchiectasis, and paraseptal emphysema are frequently present even when chest radiographic appearances are normal.[301–303] In another study, abnormalities were seen in 15 of 21 patients, comprising thickened interlobular septa (33%), bronchial wall thickening (29%), pleuropulmonary abnormalities (29%), and linear septal thickening (29%).[304] Pulmonary involvement, often subclinical, is an early manifestation of AS.[305]

A subclinical lymphocytic alveolitis may be evident with BAL.[306] Histologically, lung abnormalities consist of a variable mixture of lymphocytic infiltration, fibrosis, and bullous change. On chest radiography, diffuse reticular opacities in the upper zones are usually symmetrical and are seldom extensive except in patients with severe spinal disease[307] or a long history of AS.[300] However, apical fibrosis occasionally may precede the development of extrapulmonary disease. No proven treatment exists to prevent the development of apical fibrosis; resistance to corticosteroid therapy is the rule.

Cavities may develop within distorted fibrotic apical tissue and are sometimes colonized by mycobacteria or fungi, especially *Aspergillus fumigatus* (see eFig. 131.6), which are

isolated in up to 60% of AS patients with apical cavitation.[308] Life-threatening hemoptysis is an occasional complication of mycetoma formation within cavities and may be controllable by bronchial artery embolization; the resection of a mycetoma is a treatment of last resort owing to the high prevalence of postoperative bronchopleural fistula or empyema. Advanced apical fibrosis is often associated with apical pleural thickening, but pleural disease is seldom seen adjacent to normal lung parenchyma elsewhere in the thorax. There is an increased (≤10%) prevalence of pneumothorax in AS patients with apical fibrosis,[300] probably due to subpleural bullous degeneration in advancing disease.

Extrapulmonary restriction due to immobilization of the chest wall with costovertebral ankylosis is an occasional complication of AS. Extrapulmonary restriction is often asymptomatic and associated with surprisingly little impairment in pulmonary function, perhaps because the diaphragm is able to make a major contribution in the presence of a high resting volume. Lung volumes may be mildly reduced, but the D_{LCO} is almost always preserved in the absence of parenchymal disease.[309]

MARFAN SYNDROME

Marfan syndrome (MS) is an autosomal dominant condition of variable penetrance affecting approximately 5 per 100,000 population. MS is characterized by abnormalities of fibrous connective tissue with abnormal type I collagen, in some cases due to mutations on chromosome 15, especially in the skeleton (long limbs, arachnodactyly, pectus excavatum, kyphoscoliosis), eyes (subluxation of the lens), and cardiovascular system (aortic or mitral regurgitation, aortic aneurysm). The reduced life expectancy of MS is largely attributable to cardiac complications; there is no effective treatment to reverse disease or slow progression.

Respiratory complications can be subdivided into pulmonary and extrapulmonary abnormalities. From 10–15% of patients with MS have pulmonary involvement. The most common pulmonary complication is pneumothorax, often recurrent and bilateral. The high prevalence of pneumothorax in MS of 5–10%[310] (>100-fold higher than in the general population) can be ascribed to the rupture of subpleural bullae. Localized bulla formation with a predilection for the lung apex[311] is an occasional striking finding in young patients. Emphysema is present on chest radiography in the majority of MS patients with pneumothoraces.[310,312] Lung histologic appearance in MS is poorly characterized but, in a small series of patients with absent or minimal smoking histories, a pattern of distal acinar emphysema was evident in all cases.[313] Generalized emphysema in nonsmoking patients with MS may become evident at any age and is sometimes fatal in childhood.[314] Underlying apical fibrosis has been reported in a handful of cases. Other less frequent parenchymal manifestations include congenital malformations of the middle lobes, which may be absent or rudimentary, and an increased prevalence of bronchopneumonia.[310]

Thoracic cage involvement is present in greater than 50% of MS patients. Isolated pectus excavatum in MS is seldom associated with significant impairment in lung function. However, on occasion, kyphoscoliosis is associated with fatal right heart failure.[315] It is likely that nocturnal desaturation amplifies hypoxemia from the kyphoscoliosis. Increased upper airway collapsibility during sleep is common in MS, accounting for an association between MS and obstructive sleep apnea.[316]

Key Points

- In *connective tissue diseases* (CTD), the lung can be involved by a wide variety of patterns of pathology, from the trachea to the parenchyma to the pleura.
- Sometimes, pulmonary manifestations may precede the systemic features of CTD.
- The true extent of lung involvement is often masked by exercise limitation due to musculoskeletal features of the CTD.
- Often, combinations of patterns exist that raise the likelihood that CTD is the underlying problem. Some patterns of lung disease are more common in one CTD than the others. Specific pathologic entities seen in these diseases do not generally follow the same course as their idiopathic counterparts.
- Distinguishing CTD–interstitial lung disease from idiopathic interstitial lung disease is essential and has major implications for prognosis and management. Therefore serologic testing and repeat testing, if needed, are recommended to distinguish these two entities.
- Common drugs used in the treatment of CTD may result in major pulmonary complications.
- Increasing recognition of the pulmonary manifestations of these protean disorders is resulting in better outcomes.

Key Readings

Arida A, Fragiadaki K, Giavri E, et al. Anti-TNF agents for Behçet's disease: analysis of published data on 369 patients. *Semin Arthritis Rheum*. 2011;41:61–70.

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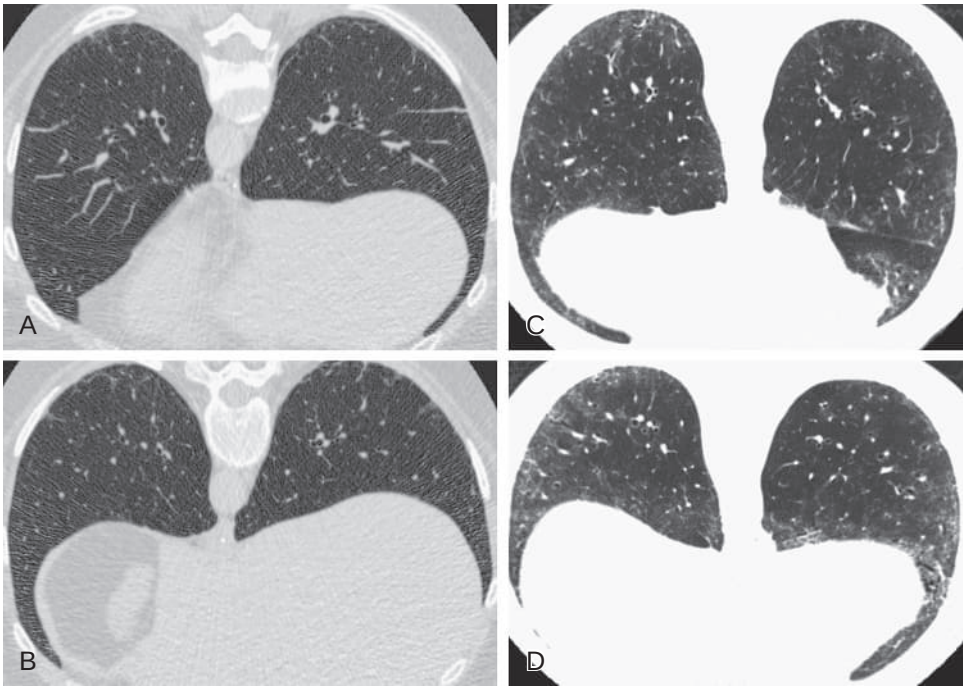
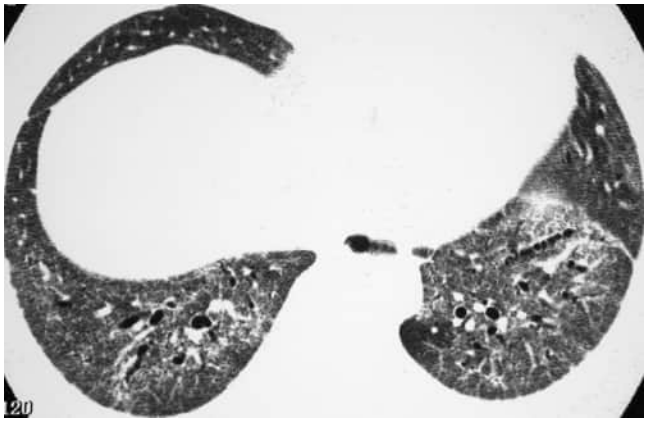
Complete reference list available at ExpertConsult.com.

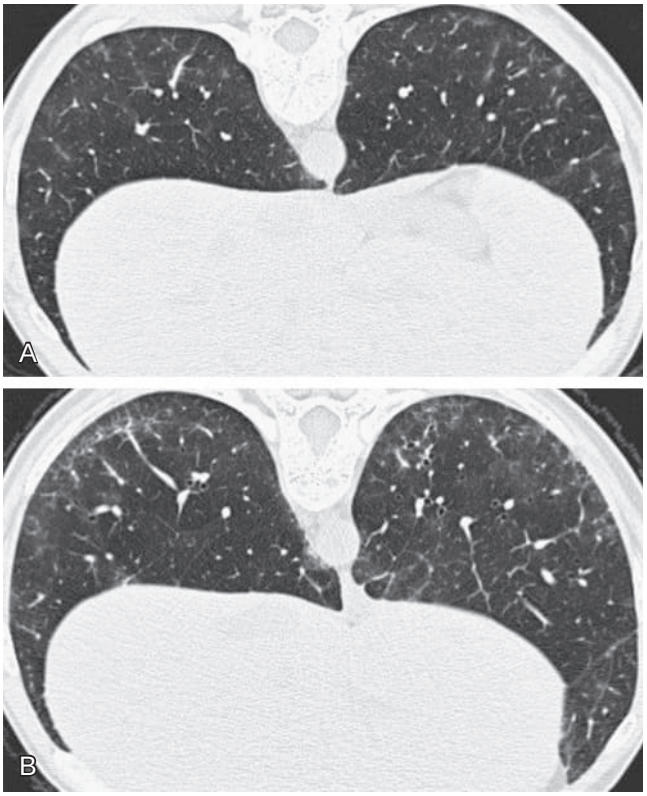
eFIGURE IMAGE GALLERY



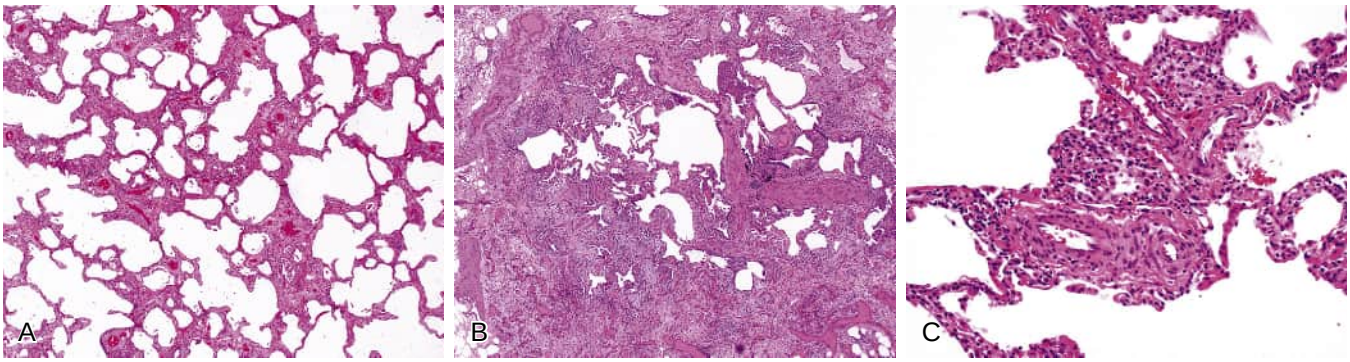
eFigure 92.1 High-resolution computed tomography of mild systemic sclerosis lung disease. (A–B) Axial prone imaging in a patient with scleroderma shows mild, faint reticulation. (C–D) Axial prone imaging in a patient with scleroderma shows some faint reticulation, with more prominent subpleural ground-glass opacity. (Courtesy Michael B. Gotway, MD.)



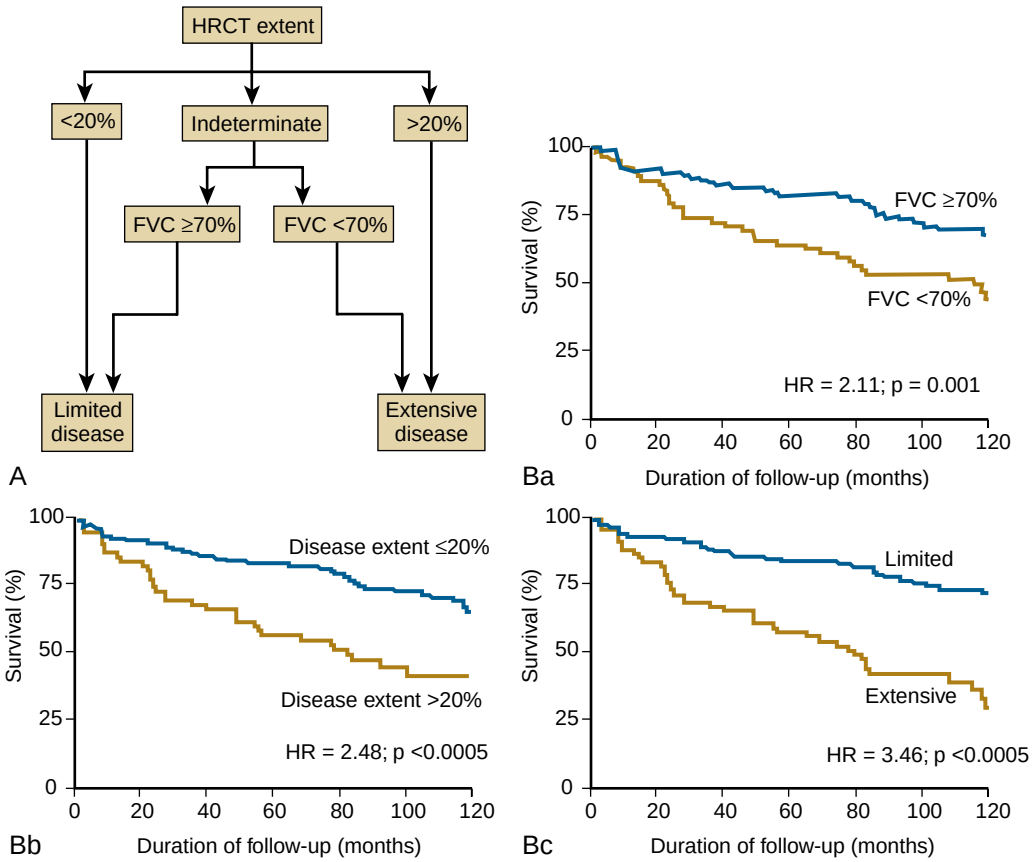
eFigure 92.2 High-resolution computed tomography of moderate systemic sclerosis lung disease. Axial supine imaging shows moderate basal, subpleural ground-glass opacity associated with reticulation. The pattern is identical to idiopathic nonspecific interstitial pneumonia. (Courtesy Michael B. Gotway, MD.)



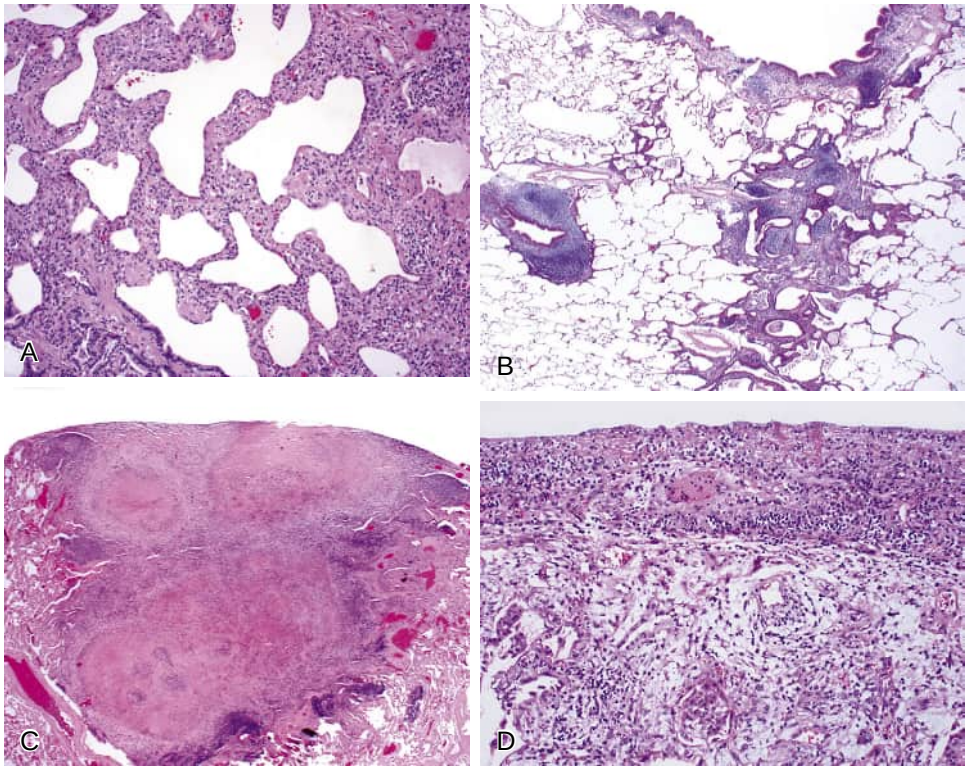
eFigure 92.3 High-resolution computed tomography of progressive systemic sclerosis lung disease. (A) Axial prone imaging shows faint, subpleural basal ground-glass opacity. (B) Axial prone imaging 1 year after part A shows worsening of basal subpleural ground-glass opacity and reticulation. (Courtesy Michael B. Gotway, MD.)



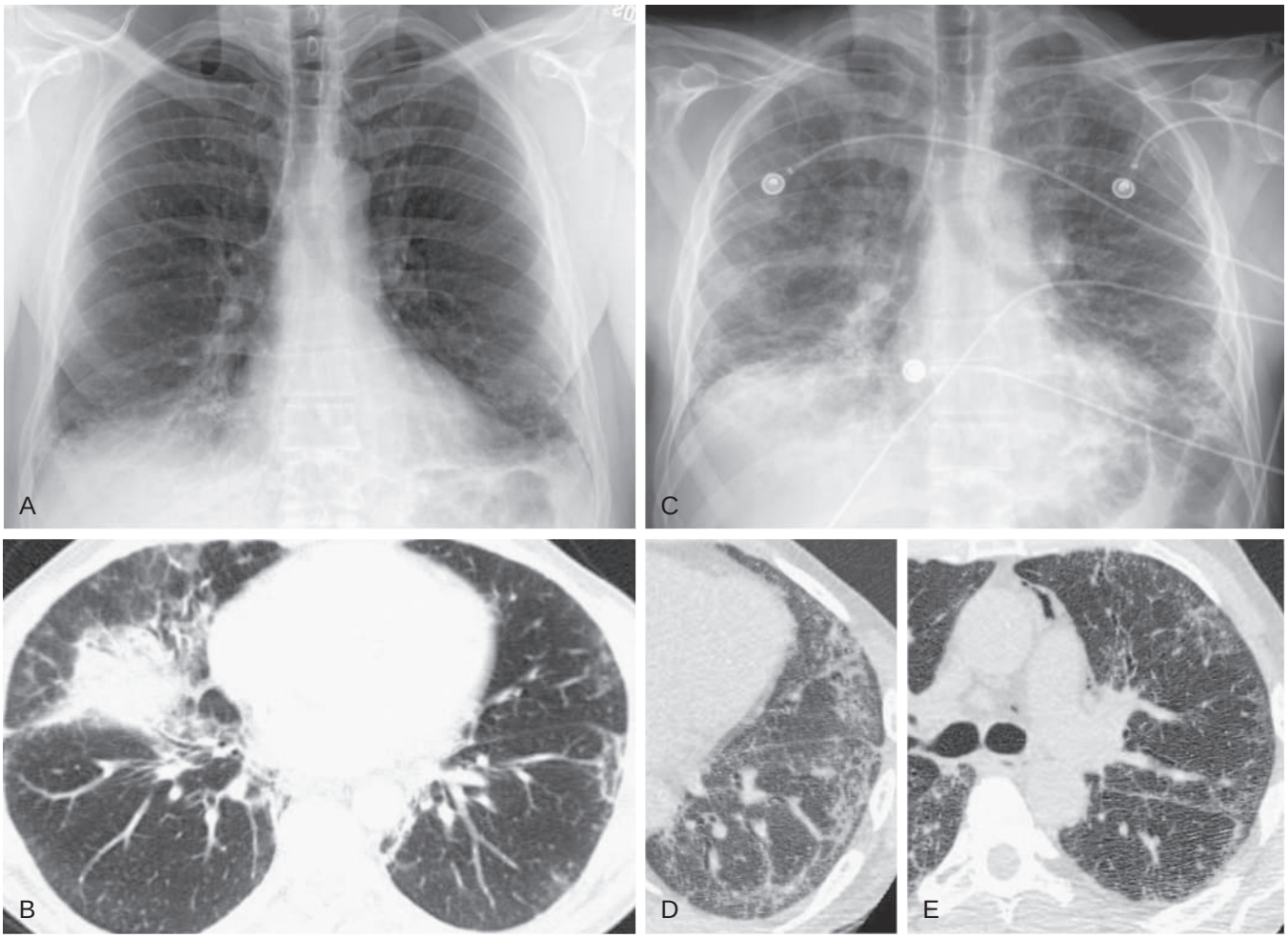
eFigure 92.4 Progressive systemic sclerosis. (A) The interstitial fibrosis of progressive systemic sclerosis is typically paucicellular and diffuse, with preservation of underlying lung architecture. (B) When fibrosis is more advanced, distinction from usual interstitial pneumonia (of idiopathic pulmonary fibrosis) may be difficult on morphologic grounds. (C) Pulmonary hypertensive changes may be present and deserve careful attention because this is a major cause of mortality in scleroderma patients with lung disease. (From Leslie KO, Wick MR. *Practical Pulmonary Pathology: A Diagnostic Approach*, ed 2. Philadelphia: Elsevier; 2011.)



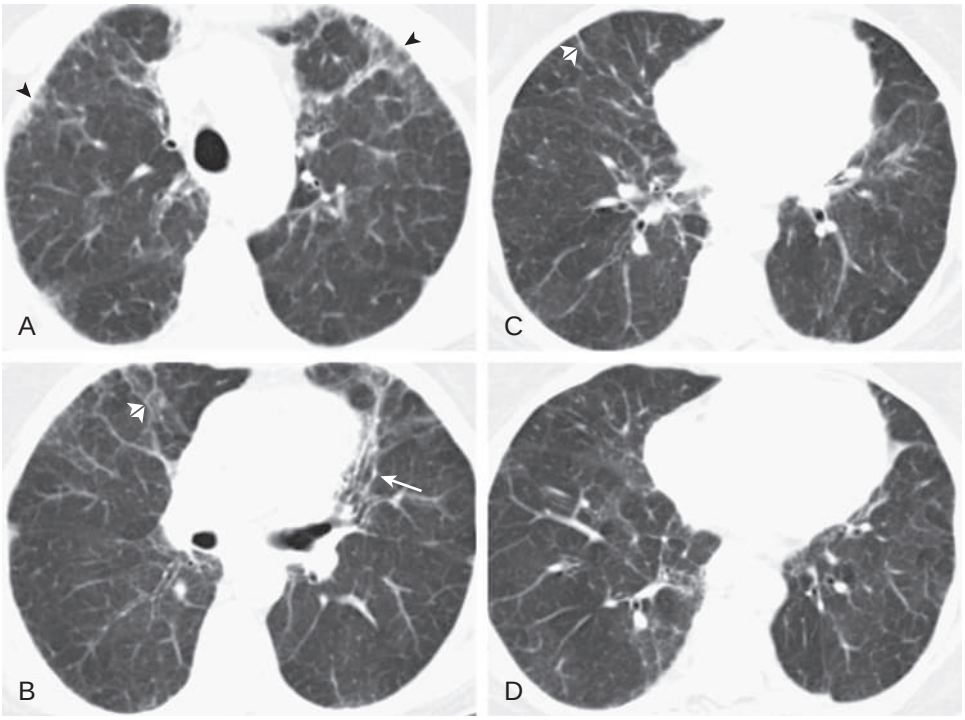
eFigure 92.5 Staging algorithm for interstitial lung disease due to systemic sclerosis. (A) Flow diagram of limited/extensive staging system with use of high-resolution computed tomography (HRCT) scores and pulmonary function test data. Identification of overtly minimal/limited disease is based on a disease extent threshold of 20% on HRCT vs. severe/extensive disease that is identified by HRCT disease extent greater than 20%. In cases with an indeterminate extent of disease on HRCT, a forced vital capacity (FVC) threshold of 70% is used to separate the cases into limited or extensive disease. The HRCT scans are scored at five levels for total disease extent, extent of reticulation, proportion of ground-glass, and coarseness of reticulation. (B) Survival compared between patient subgroups with (Ba) FVC levels above and below a threshold value of 70%; (Bb) HRCT disease extent above and below a threshold value of 20%; and (Bc) limited disease (HRCT extent ≤ 10%, or when HRCT extent was 10–30%, FVC ≥ 70%) vs. extensive disease (HRCT > 30%, or when HRCT extent was 10–30%, FVC < 70%). **HR, hazard ratio.** (Data from Goh NS, Desai SR, Veeraraghavan S, et al. Interstitial lung disease in systemic sclerosis: a simple staging system. *Am J Respir Crit Care Med.* 2008;177:1248–1254.)



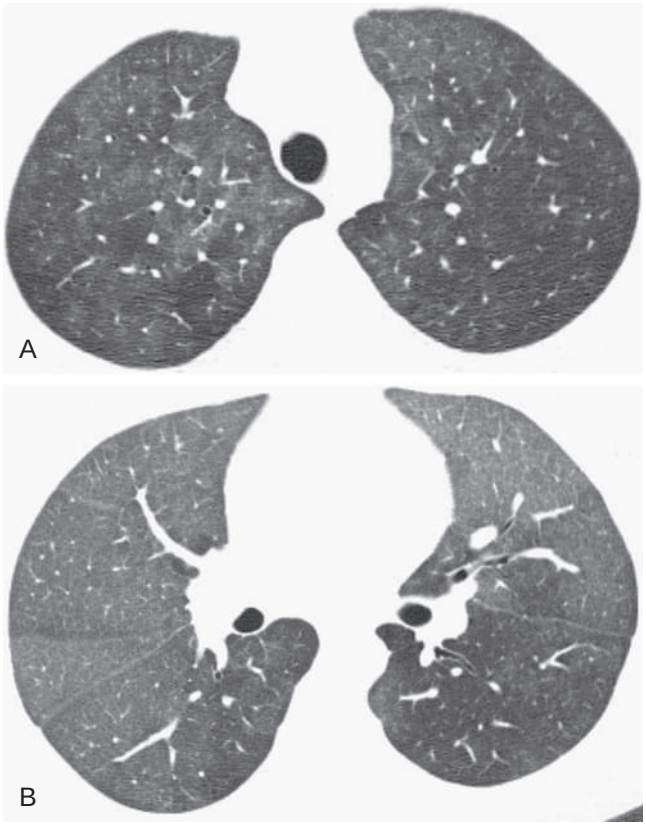
eFigure 92.6 *Rheumatoid arthritis* (RA) lung disease. (A) Variable interstitial fibrosis is typical and often resembles the fibrotic form of nonspecific interstitial pneumonia. (B) Most of the lymphoid aggregations in RA are present around the terminal airways ("follicular bronchiolitis" when lymphoid germinal centers are prominent), but lymphoid follicles may also be present in the pleura. (C) Typical rheumatoid nodules may appear in the RA lung and must be distinguished from lesions seen with infection and in granulomatosis with polyangiitis. (D) The presence of chronic pleuritis should always raise the possibility of RA in the differential diagnosis. (From Leslie KO, Wick MR: *Practical Pulmonary Pathology: A Diagnostic Approach,* ed 2. Philadelphia: Elsevier; 2011.)



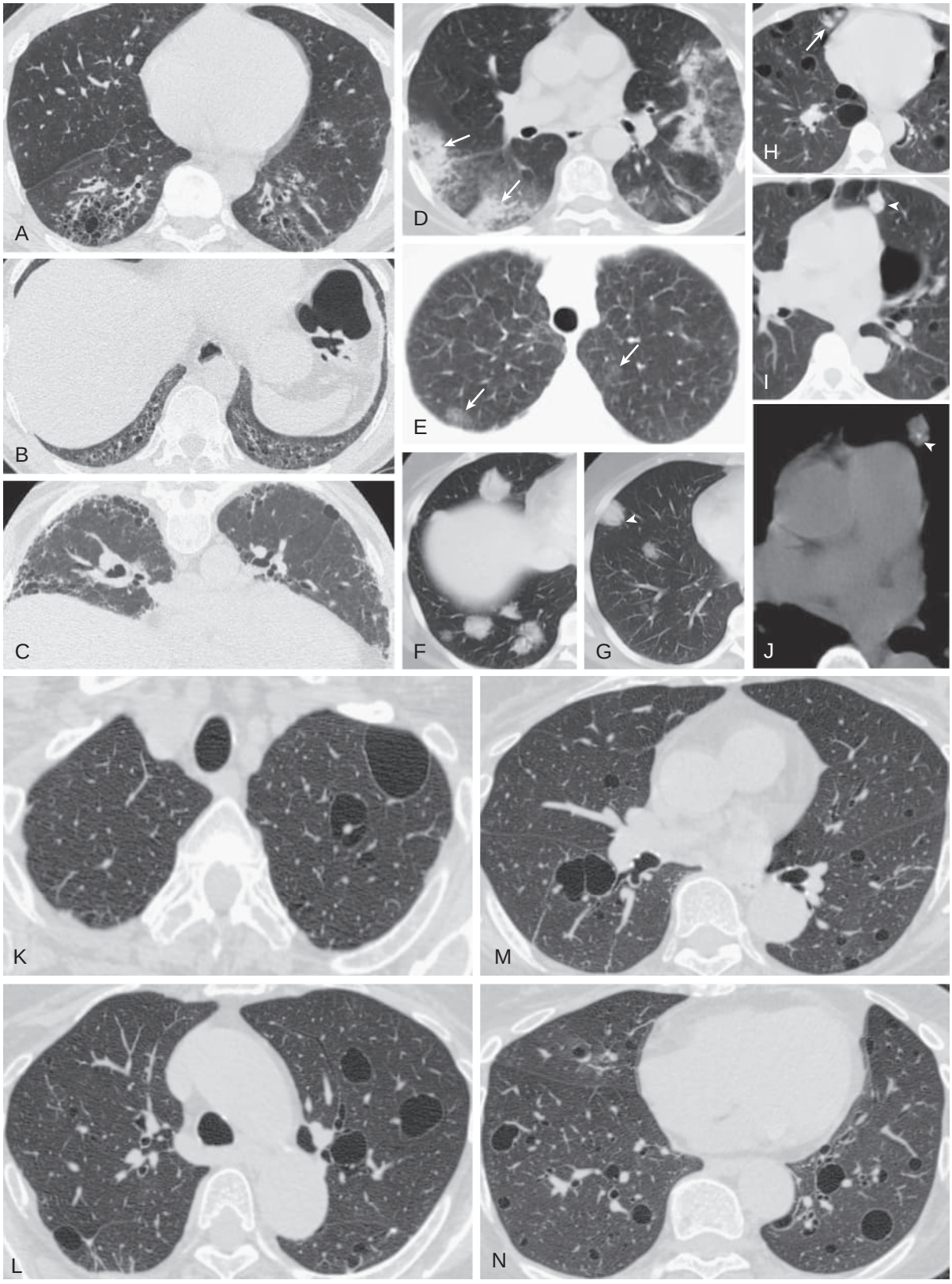
eFigure 92.7 High-resolution computed tomography of accelerated interstitial pneumonia in a patient with rheumatoid arthritis. (A) Frontal chest radiography shows basal reticulation and linear opacities consistent with interstitial lung disease in the setting of rheumatoid arthritis. (B) Axial supine image shows basal reticulation, patchy subpleural ground-glass opacity, and traction bronchiectasis. (C) Frontal chest radiography performed several years after parts A and B, when the patient developed severe shortness of breath, shows diminished lung volumes with development of extensive bilateral opacities. (D) Axial supine image focused on the left base shows progression of the basal lung abnormalities seen previously; similar findings were now also present in the mid and upper lungs (E). Surgical lung biopsy showed diffuse alveolar damage. The pneumomediastinum was postoperative in nature. (Courtesy Michael B. Gotway, MD.)



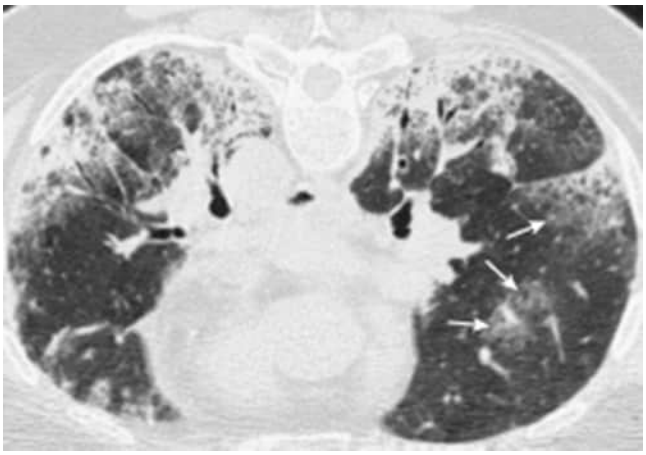
eFigure 92.8 High-resolution computed tomography of diffuse interstitial fibrosis in systemic lupus erythematosus. (A–D) Axial supine images show multifocal, bilateral, patchy areas of reticular and linear opacities, including interlobular septal thickening (white arrowheads), associated with ground-glass opacity (black arrowheads) and mild architectural distortion. Mild traction bronchiectasis (arrow) is evident. The findings are nonspecific, but surgical lung biopsy showed features suggestive of a connective tissue disorder (enlarged peribronchiolar lymphoid follicles). (Courtesy Michael B. Gotway, MD.)



eFigure 92.9 High-resolution computed tomography of diffuse alveolar hemorrhage in systemic lupus erythematosus. (A–B) Axial supine images show multifocal bilateral ground-glass opacity, with a somewhat centrilobular nodular appearance in the upper lobes (A). (Courtesy Michael B. Gotway, MD.)



eFigure 92.10 High-resolution computed tomography showing spectrum of Sjögren-related pulmonary abnormalities. (A–B) Axial supine images show basal reticulation, mild ground-glass opacity, and traction bronchiectasis in the subpleural lower lobes, consistent with a nonspecific interstitial pneumonia pattern. (C) Axial prone image shows coarse basal reticulation, subpleural cystic change, and traction bronchiectasis, consistent with a usual interstitial pneumonia pattern. (D) Axial supine image shows peripheral consolidation (*arrows*) consistent with an organizing pneumonia pattern. (E) Axial supine image shows several poorly defined ground-glass opacity nodules (*arrows*), representing lymphocytic interstitial pneumonia. This appearance is nonspecific and can be seen with other lymphoproliferative disorders that may be encountered in Sjögren patients, including follicular bronchiolitis, nodular lymphoid hyperplasia, and even *mucosa-associated lymphoid tissue* (MALT) lymphoma. (F–G) Axial supine image shows multiple, bilateral poorly defined pulmonary nodules found to represent MALT lymphoma. Note the air bronchograms associated with one of the nodules (*arrowhead*), indicating the bronchiolocentric nature of the process. (H–I) Axial supine images show multiple thin-walled cysts and small nodules (*arrow*), one of which shows a small focus of calcification (*arrowhead*) on the images displayed in soft tissue windows (J). (K–N) Axial supine images in a patient with Sjögren syndrome show multiple, bilateral, thin-walled cysts with normal intervening lung parenchyma. (Courtesy Michael B. Gotway, MD.)



eFigure 92.11 Diffuse alveolar damage superimposed on pulmonary interstitial abnormalities in a patient with polymyositis-dermatomyositis. Axial prone high-resolution computed tomography image shows patchy, subpleural reticulation and areas of consolidation, consistent with a mixture of nonspecific interstitial pneumonia and organizing pneumonia injury patterns. Patchy areas of ground-glass opacity *(arrows)*, spatially separated from the subpleural process, represent areas of diffuse alveolar damage. (Courtesy Michael B. Gotway, MD.)

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93 SARCOIDOSIS

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INTRODUCTION

Sarcoidosis has been defined as a multisystem granulomatous disorder of unknown cause.[1] Histologic evidence of granulomatous inflammation is inadequate for the diagnosis of sarcoidosis because alternative causes of granulomatous inflammation need to be excluded. Additionally, with some exceptions (see later), clinical findings without histologic confirmation of granulomatous inflammation are inadequate to confirm a diagnosis of sarcoidosis. Sarcoidosis affects the lung in more than 90% of cases, but it can affect any part of the body. For many patients, the disease is self-limited and resolves within 2 to 5 years.[2] However, a chronic form of the disease can lead to significant morbidity and some mortality.[3,4] Glucocorticoids are usually effective for treating the disease. However, because long-term treatment may be required, steroid-sparing agents are often used.[5]

EPIDEMIOLOGY

Sarcoidosis is a worldwide disease. However, it is more common in some parts of the world and within certain ethnic groups. Figure 93.1 summarizes the reported rates of sarcoidosis around the world.[6,7] Sarcoidosis is rare before adulthood.[8] When it does manifest in childhood, there is a different clinical phenotype with more eye, skin, and joint involvement than seen in adult sarcoidosis.[9,10]

Although sarcoidosis was previously thought to be a disease mostly of young adults, it has been increasingly diagnosed in older patients. In more recent studies, more than half the patients are diagnosed when they are more than 40 years of age.[7,11,12] Sarcoidosis is believed to be more common in women than in men, at a ratio of almost 2:1.[8,13] In the United States, it is more common in African Americans than in whites and less common in Hispanics and Asians.[7,14] The disease seems to be more common in the eastern third of the United States,[7] but that finding may reflect the distribution of African Americans.

ETIOLOGY, IMMUNOLOGY, AND GENETICS

ETIOLOGY

Although sarcoidosis was first described as a distinct clinical entity more than 140 years ago, its cause still remains unknown. By extension from other granulomatous diseases, sarcoidosis is thought to be caused initially by an antigen processed by an *antigen-presenting cell* (APC). The APC then presents the antigen through a *human leukocyte antigen* (HLA) class II molecule to a restrictive set of T cell receptors on a T lymphocyte, usually of the $CD4^+$ class.[15,16] This interaction results in a polarization of the T lymphocytes to a T helper phenotype and is followed by monocyte recruitment, T cell proliferation, and differentiation leading to the development of the sarcoidosis granuloma. In this process, a myriad of cytokines and chemokines are released to maintain granuloma integrity (see Chapter 16).

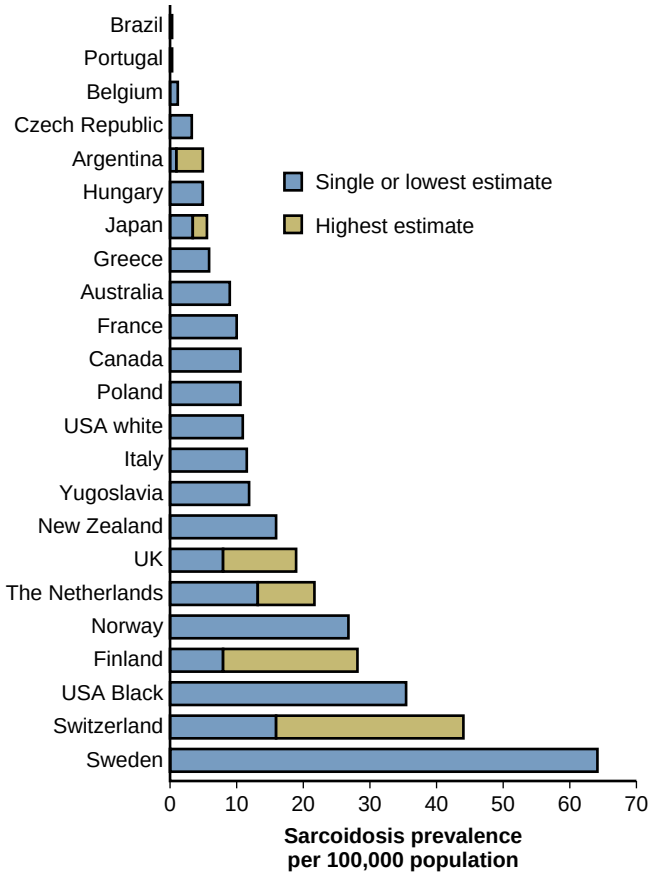

Figure 93.1 Prevalence of sarcoidosis around the world. (Modified from Denning DW, Pleuvry A, Cole DC. Global burden of chronic pulmonary aspergillosis complicating sarcoidosis. *Eur Respir J.* 2013;41:621-626.)

Infectious pathogens have been implicated as the source of antigen leading to sarcoidosis because many infections induce a granulomatous response. For example, remnants of bacterial components of propionibacteria and mycobacteria have been detected in sarcoidal tissues.[17-20] Subsequent studies have demonstrated a T-lymphocyte response to a mycobacterial protein, mKatG, both in the peripheral blood and in *bronchoalveolar lavage* (BAL) samples of sarcoidosis patients.[18,21,22] One problem with viewing sarcoidosis as an invasive infectious disease is that sarcoidal inflammation usually improves with immunosuppressive therapy. Moreover, sarcoid granulomas are typically nonnecrotizing. Although there is no consensus on whether sarcoidosis represents an autoimmune disease,[23] evidence is accumulating that autoimmunity may play a role in some forms of sarcoidosis. The immunologic phenomenon referred to as molecular mimicry is a mechanism that could explain an association between sarcoidosis and infectious microorganisms. Molecular mimicry is initiated by stimuli, often infectious or chemical, that trigger inflammation leading to exposure of self-peptides.[24] Immunologic similarities between the "foreign" trigger and the "self" peptide promote autoreactive T or B cells in a susceptible individual. In such a scenario, the inflammation can be self-limiting or prolonged, depending on the balance of mediators that favor resolution versus persistence of the inflammation. Although there are reports of autoimmune phenomenon and mycobacterial infections,[25] the best evidence for autoimmunity is the self-limiting form of Löfgren syndrome associated with individuals who carry the *HLA-DRB1*03* allele.[26,27] Most of these patients develop a clonal expansion of $CD4^+$ T cells expressing the T cell receptor α chain variable segment Vα2.3 in the lungs.[28,29] Independent groups have identified vimentin as a possible autoantigen in these patients by using proteomic techniques on lung macrophages and homogenized spleen tissue.[30-34] Follow-up studies on blood and lung samples from these patients have demonstrated antivimentin antibodies and functional T cell responses to vimentin.[31,35] Although these data are compelling, it may be that these observations are the effect of ongoing inflammation and not part of the trigger causing the disease.[36] The role of autoimmunity in sarcoidosis may be an area of research deserving of more attention.

Other triggers associated with the etiology of sarcoidosis include certain environmental and occupational exposures.[37,38] Sarcoidosis has been reported in individuals with heavy exposure to combustible wood products[39,40] and with the particulates and chemicals from the World Trade Center disaster.[41,42] There are reports of sarcoidosis in the metal industry with exposure to titanium,[43] metal working, metal machining,[43] and photocopier toner (which contains silicates, iron, and copper).[44] Analysis of lung biopsy specimens from sarcoidosis patients has revealed metals, including silicates, aluminum, and titanium.[45] Sarcoidosis has also been associated with occupations and exposures, including hairdressers,[46] health care workers,[47] agricultural employment,[38] insecticide use at work,[38] work environments with mold or mildew,[38] industrial organic dust exposure, educators, and workers of suppliers of building materials, hardware, and gardening materials.[37] Many of these exposures may, in and of themselves, cause granulomas. Sarcoidosis associated with environmental exposure to respirable material is often isolated to the lung.[48] It is not clear whether these are cases of sarcoidosis or sarcoid-like conditions.

IMMUNOLOGY AND GENETICS

Clues to mechanisms causing sarcoidosis may eventually be revealed as we understand the molecular interactions that initiate granulomatous reactions. Although rare, granulomatous reactions in patients treated with programmed cell death protein 1 and/or cytotoxic T lymphocyte–associated protein 4 blockade may offer mechanistic insights.[49-51] Molecular targets can also be discovered using large genome-wide association studies. [52-61] Putting genetics together with environmental triggers, the current paradigm is that sarcoidosis develops in an immunogenetically susceptible host after exposure to a particular antigen.[62] One reason that no common antigen has been found in sarcoidosis is that granulomatous inflammation is likely a final pathway for many different types of antigen exposures. Thus, in some sense, sarcoidosis may represent a collection of diseases with diverse genetic susceptibility loci and diverse environmental antigen triggers.[63,64]

Immunologically, the sarcoid granuloma is a complex structure, and its integrity depends on the interaction of innate and adaptive immunity (see Chapters 15 and 16). Studies of targeted cell types involved in granuloma formation have opened up new areas of research that may provide opportunities for new therapies. Novel research tools

have facilitated studies of mouse and human dendritic cell populations.[65] A Scandinavian study of patients with newly diagnosed sarcoidosis found that, unlike in healthy individuals, myeloid dendritic cells from the lung and blood of the sarcoid patients were activated.[66] Blood dendritic cells from the patients induced *tumor necrosis factor-α* (TNF-α) production in co-culture experiments with allogenic naive $CD4^+$ T cells, whereas dendritic cells from unaffected control samples did not. This finding suggests that dendritic cells are functionally capable of contributing to sarcoidal inflammation and, if so, the availability of current reagents that affect dendritic cell function may lead to future therapies. Another notable discovery has provided a new perspective about mechanisms contributing to granuloma formation; in a mouse model of constitutively active mammalian target of rapamycin complex 1 restricted to myeloid cells (macrophages), granulomas formed spontaneously in the lung and liver.[67] A genetic link with the target of rapamycin signaling pathway was then identified in a study of five French families with autosomal transmission of non-Löfgren sarcoidosis.[68] There has also been progress in the development of in vitro human granuloma models. A model using peripheral blood mononuclear cells from sarcoid patients revealed up-regulation of genes related to *interleukin* (IL)-13 signaling pathways when the cells were incubated with polystyrene beads coated with purified protein derivative.[69,70] The results were corroborated using immunohistochemical methods that identified intense staining for a marker, CD163, in macrophages and giant cells from granulomatous tissue sections from patients with sarcoidosis compared with tuberculosis.[71] These findings and others related to $CD4^+$ type 2 T helper cell (Th) inflammation[72] raise many new questions about granuloma biology in sarcoidosis.

There have also been complementary studies performed on lymphocytes providing additional insight into how they contribute to granuloma biology. Using a combination of transcription factors and/or chemokine receptors to identify blood and lung $CD4^+$ cells, studies from independent sarcoidosis cohorts suggest that cells that produce higher amounts of IL-17 relative to interferon-γ are associated with better clinical outcomes in patients with Löfgren syndrome compared with chronic sarcoidosis.[73-75] These studies have provided evidence for Th17 cell plasticity[76] in sarcoidosis through identification of a subset of $CD4^+$ T cells, called Th17.1, in lung lavage expressing the transcription factors T-bet and RORγt and chemokine receptors CXCR3 and CCR6. Cell-based in vitro co-culture experiments have revealed hypoxia-inducible factor-1α as a possible regulator of IL-17 production by activated $CD4^+$ T cells.[77] Although few studies related to other types of lymphocytes have been conducted, the available data suggest that there may be activation or dysfunction of B cells,[78-80] CD8 T cells,[81] and T-regulatory cells,[82,83] which deserves further attention. Collectively, these findings highlight the complexity of roles that lymphocytes play in sarcoidal inflammation.

DIAGNOSTIC APPROACH

GENERAL CONSIDERATIONS

Figure 93.2 outlines the approach to the diagnosis of sarcoidosis. In general, this process involves a review of clinical information and histologic examination of tissue for the presence of granulomatous inflammation. At every step, it is important to consider and exclude other known causes of granulomatous inflammation.[84] This diagnostic approach is discussed here.

One can never be certain of the diagnosis of sarcoidosis. Similar to other diseases, sarcoidosis may be considered a probable diagnosis if clinical data exceed a certain threshold, thus making the diagnosis plausible. Table 93.1 outlines clinical findings that are often used to gauge the likelihood of the diagnosis of sarcoidosis. For most patients, the clinical information suggests the diagnosis, but a tissue biopsy is usually indicated to enhance the probability of sarcoidosis.

Patients with sarcoidosis may present with no symptoms, a feature more common in white than Black patients.[85] Therefore, sarcoidosis should be considered not only in symptomatic patients but also in asymptomatic patients with hilar adenopathy, mediastinal adenopathy, and/or diffuse parenchymal opacities on lung imaging.[85-87] An inquiry should be made about a family history of sarcoidosis because the prevalence rate of sarcoidosis is much higher in first-degree relatives of sarcoidosis patients than in the general population.[53] Sarcoidosis is more common in nonsmokers in most, but not all, studies.[38,88,89]

Alternative causes of granulomatous inflammation should be reasonably excluded before a diagnosis of sarcoidosis is rendered. A history of active tuberculosis, latent tuberculosis, and tuberculosis exposure should be obtained. *Chronic beryllium disease* (CBD) can mimic sarcoidosis radiographically[90] and histologically.[91,92] CBD has been misdiagnosed as sarcoidosis in up to 40% of cases.[93] Because most patients are unaware of potential exposures to beryllium, it is important to ask about work where exposure to beryllium is plausible, including work in aerospace, nuclear weapons, electronics, jewelry, sporting goods, ceramics, and dental industries.[94] Furthermore, minimal beryllium exposure may lead to significant disease.[95,96] Hypersensitivity pneumonitis is a granulomatous pulmonary disease that may mimic sarcoidosis. Although it may result from exposure to numerous agents, hypersensitivity pneumonitis is most commonly caused by antigens from birds and hot tubs (see also Chapters 91 and 101).

EXTRAPULMONARY INVOLVEMENT

At presentation, 90% of sarcoidosis patients will have clinical evidence of pulmonary involvement, and more than 40% have evidence of involvement in the skin, liver, peripheral lymph node, or eye.[11,97] Therefore, evaluation for involvement of these organs should be performed in any patient being assessed for possible sarcoidosis. Specific criteria for individual organ involvement have been proposed.[98] A diagnostic scoring system (Sarcoidosis Diagnostic Score) has been developed, which emphasizes that the higher the number of organs involved, the more confident one can be of the diagnosis.[99]

RADIOGRAPHIC FINDINGS

Bilateral hilar adenopathy on chest radiograph suggests the diagnosis of sarcoidosis, especially if the patient has no

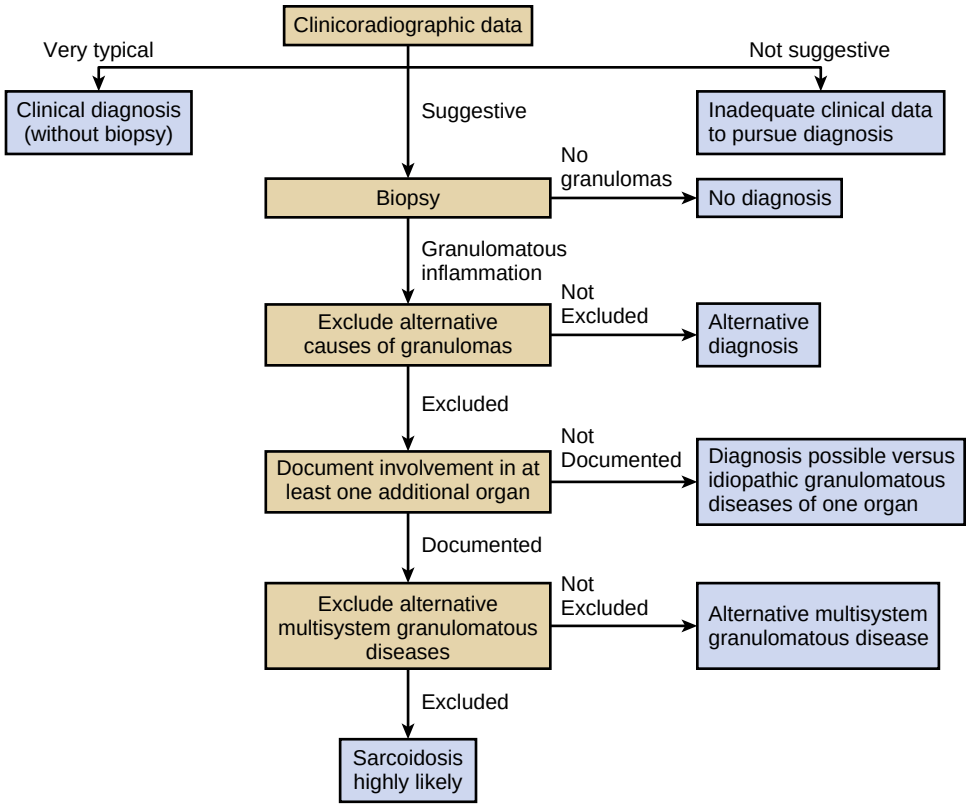

Figure 93.2 Diagnostic algorithm for sarcoidosis. The diagnostic approach for sarcoidosis with consideration of clinical information and tissue biopsy demonstration of granulomatous inflammation as well as exclusion of known causes of granulomatous inflammation (see text for details). (Modified from Judson MA. The diagnosis of sarcoidosis. *Clin Chest Med.* 2008;29:415-427.)

Table 93.1 Clinicoradiographic Data Supporting or Weakening the Likelihood of Sarcoidosis

	Supports	Weakens
Demographics	▪ U.S. African American ▪ Northern European	▪ Age <18 years
Medical history	▪ Nonsmoking ▪ No symptoms (in patients with CXR findings) ▪ Positive family history of sarcoidosis ▪ Symptoms involving ≥2 organs commonly involved with sarcoidosis (e.g., lung and eyes)	▪ Exposure to tuberculosis ▪ Exposure to organic bioaerosol ▪ Exposure to beryllium ▪ Intravenous drug abuse
Laboratory data	▪ Elevated SACE, especially if >2× ULN ▪ Elevated serum calcium ▪ Elevated serum alkaline phosphatase ▪ Leukopenia	
Radiographic findings	▪ CXR: bilateral hilar adenopathy (especially if without symptoms) ▪ HRCT: disease along the bronchovascular bundles	

CXR, chest radiograph; HRCT, high-resolution computed tomography; SACE, serum angiotensin-converting enzyme; 2× ULN, twice the upper limit of normal. Modified from Judson MA. The diagnosis of sarcoidosis. *Clin Chest Med.* 2008;29:415-427.

fever, night sweats, or weight loss.[86,87] The chest radiograph often demonstrates bilateral enlargement of the hilar lymph nodes, as well as concomitant enlargement of the right paratracheal lymph nodes[100] (Fig. 93.3). Scadding defined four patterns of chest radiographic findings: stage 1, with adenopathy alone (see Fig. 93.3); stage 2, with adenopathy and parenchymal opacities (Fig. 93.4); stage 3, with opacities alone (Fig. 93.5); and stage 4, with fibrosis (see Fig. 93.11).[101]

Findings on *high-resolution chest computed tomography* (HRCT) are likely more specific for the diagnosis of sarcoidosis than findings on chest radiography. Typical HRCT findings that suggest sarcoidosis include the presence of parenchymal nodules and opacities that represent conglomerations of these nodules and their location in a perilymphatic distribution along the bronchovascular bundles, as well as in subpleural locations[102-104] (see Fig. 93.4).

SERUM MARKERS

Angiotensin-converting enzyme (ACE) is produced in the epithelioid cell of the sarcoid granuloma,[105] and *serum ACE* (SACE) levels may reflect the total sarcoid granuloma

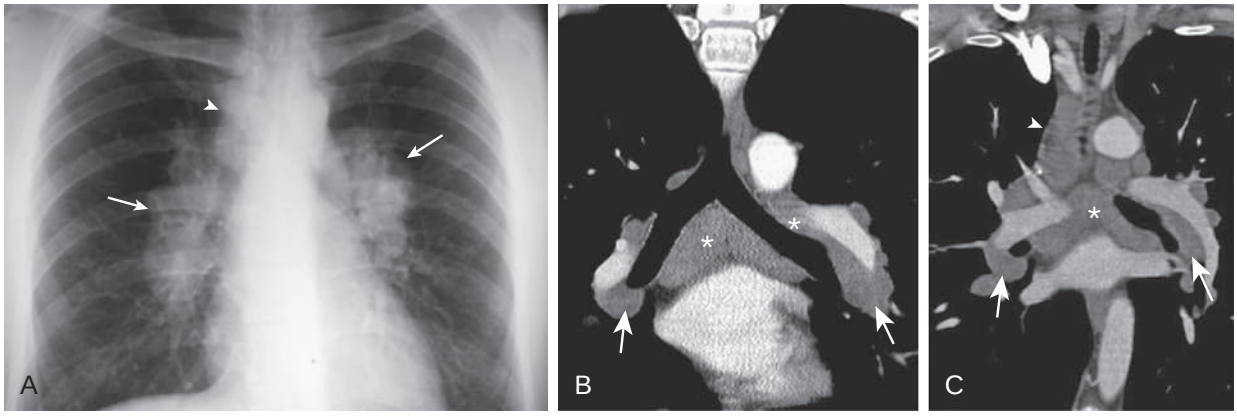

Figure 93.3 Sarcoidosis: Scadding stage 1. (A) Frontal chest radiograph shows symmetrical, bilateral peribronchial *(arrows)* and right paratracheal lymphadenopathy *(arrowhead),* typical of sarcoidosis. (B–C) Contrast-enhanced chest computed tomography confirms the presence of symmetrical, bilateral peribronchial *(arrows)* and right paratracheal *(arrowhead)* lymphadenopathy, as well as enlargement of other mediastinal lymph nodes *(asterisks).* (Courtesy Michael B. Gotway, MD.)

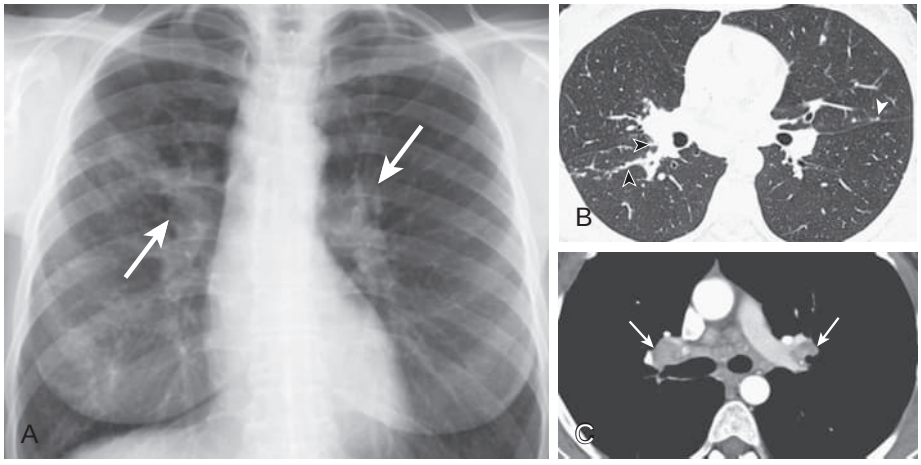

Figure 93.4 Sarcoidosis: Scadding stage 2. (A) Frontal chest radiograph shows symmetrical, bilateral peribronchial lymph node enlargement *(arrows)* as well as small, well-defined nodules best visualized in the right suprahilar region. The oblong opacity in this area represents a conglomeration of granulomatous inflammation. (B–C) Axial enhanced chest computed tomography (CT) in lung (B) and soft tissue (C) shows small, circumscribed nodules distributed along the fissural surfaces *(white arrowhead),* as well as along the more central peribronchovascular interstitium *(black arrowheads),* the latter resulting in a "beaded" appearance of the pulmonary vessels. Chest CT also confirms the presence of peribronchial lymph node enlargement (*arrows*, C). (Courtesy Michael B. Gotway, MD.)

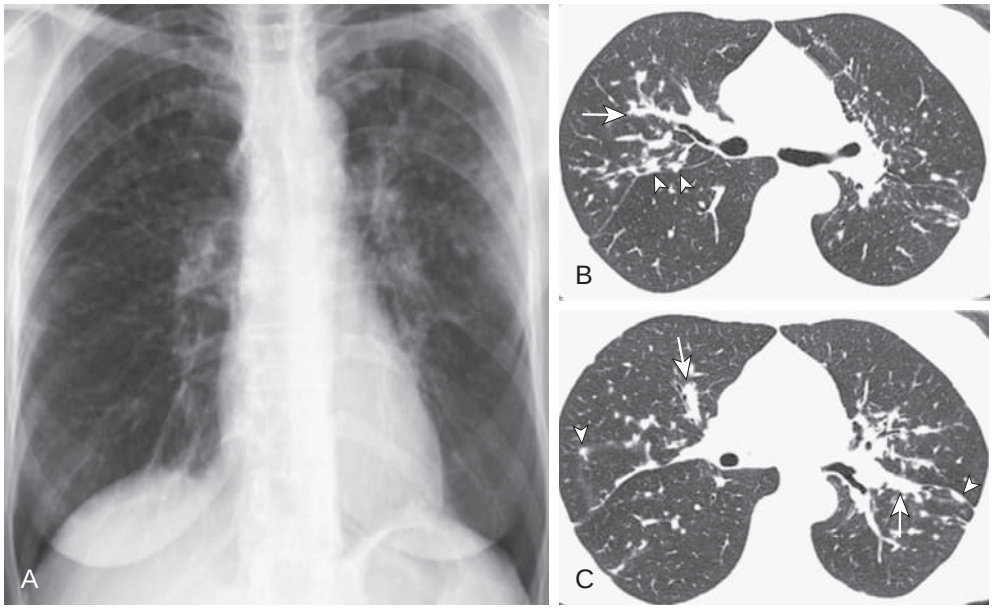

Figure 93.5 Sarcoidosis: Scadding stage 3. (A) Frontal chest radiograph shows upper lobe–predominant nodular opacities with little evidence of architectural distortion to suggest associated parenchymal fibrosis. No clear evidence of peribronchial or mediastinal lymph node enlargement is present. Mild prominence of the left hilum is the result of parenchymal opacity projected over this region, as shown on chest *computed tomography* (CT). (B–C) Axial chest CT displayed in lung windows shows small, circumscribed nodules distributed along the fissural surfaces *(arrowheads),* as well as along the more central peribronchovascular interstitium *(arrows),* the latter resulting in a "beaded" appearance of the pulmonary vessels. Additional chest CT images also confirmed the lack of significant peribronchial and mediastinal lymph node enlargement. (Courtesy Michael B. Gotway, MD.)

burden.[105] Although SACE has been suggested as a diagnostic test for sarcoidosis,[106] elevated SACE levels in isolation are inadequately sensitive or specific either to diagnose or to exclude the disease. In a review of 14 studies encompassing 4195 patients concerning the diagnostic accuracy of SACE for sarcoidosis, the sensitivity was 77% (range, 41–100%), and the specificity was 93% (range, 83–99%).[107] The likelihood of sarcoidosis increases with higher SACE levels,[107,108] and SACE levels greater than twice the upper limits of normal are rarely seen in other diseases and are not seen in cancer or lymphoma.[106,109] Polymorphisms of the ACE gene also influence the SACE.[110] However, none of these polymorphisms has been shown to be associated with increased incidence or worsening of the disease.[111]

Other serum markers have been studied in sarcoidosis. Chitotriosidase, an enzyme produced by activated macrophages, has been described in sarcoidosis, and higher levels within the serum may be associated with a worse prognosis of the disease.[112,113] The soluble IL-2 receptor, a marker of T cell activation, has been found to be elevated in sarcoidosis patients.[113,114] In small studies, the level of this receptor was an effective measure of disease activity.[102,114] The value of these biomarkers regarding diagnosis and prognosis needs to be verified by larger, multinational trials.

HISTOLOGIC EXAMINATION

With the exception of the rare instances where the clinical findings are highly specific for sarcoidosis, the diagnosis requires a tissue biopsy demonstrating granulomas (Fig. 93.6). Our approach to the selection of a biopsy site is summarized in Figure 93.7. It is in the patient's best interest for the biopsy to be minimally invasive and associated with the least morbidity. For these reasons, biopsy of superficial sites is preferred to biopsy of visceral organs.[115] Even in patients suspected to have sarcoidosis on the basis of obvious thoracic or abdominal disease, a thorough skin, conjunctival, lacrimal gland, and peripheral lymph node examination should be performed. The patient should be questioned about the presence of scars or tattoos because skin nodules of sarcoidosis have a predilection to form in these areas (see Fig. 93.10).

When there is no clinical evidence that a superficial site is involved with sarcoidosis, a biopsy is usually attempted in an organ where sarcoidosis involvement is suspected. This is very often the lung because the lung is involved in more than 90% of sarcoidosis patients early in the course of the disease.[11,116] Bronchoscopy is the most commonly used procedure to obtain tissue from the lung. More invasive techniques such as mediastinoscopy are reserved for cases in which bronchoscopy was not diagnostic. Video-assisted thoracoscopic biopsy is rarely needed to confirm the diagnosis of sarcoidosis.

Fiberoptic bronchoscopy allows for several different samples, including the *transbronchial lung biopsy* (TBLB), endobronchial biopsy, and *transbronchial needle aspirate* (TBNA) of a mediastinal lymph node. The yield of TBLB for the diagnosis of pulmonary sarcoidosis ranges from 60–97%, depending on the number of biopsies taken and the presence of parenchymal disease on chest

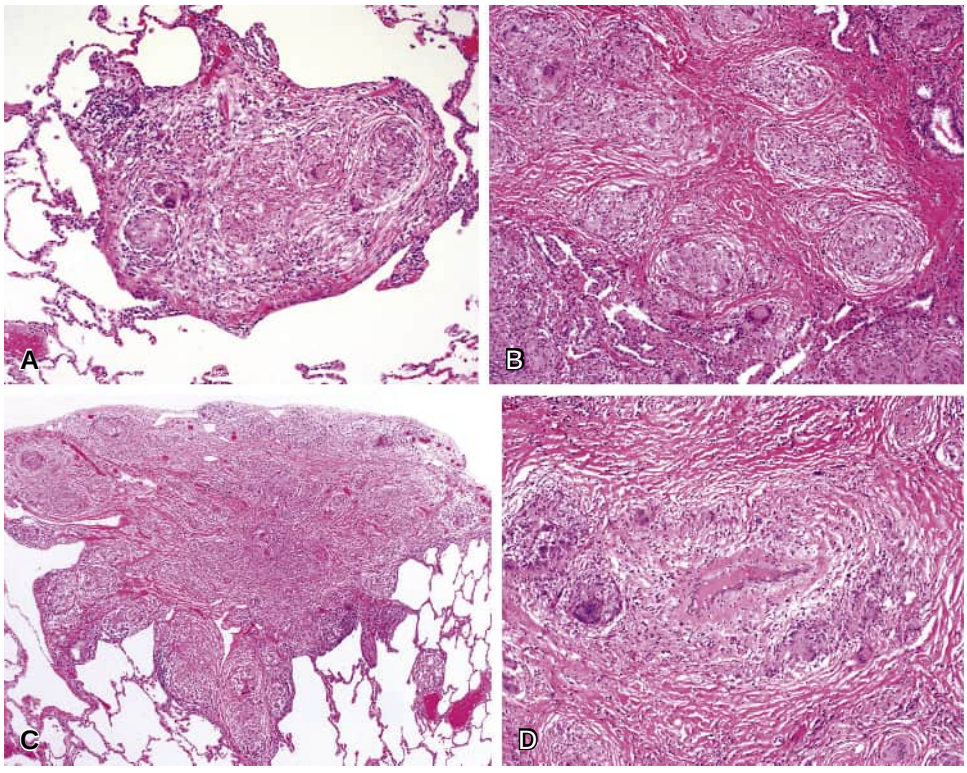

Figure 93.6 Sarcoidosis. (A) The characteristic pathologic lesion of pulmonary sarcoidosis is the non-necrotizing (immune) granuloma. (B) Granuloma within sclerotic fibrosis. (C) Granulomas distributed along lymphatic routes in the pleura, within the intralobular septa, and along the bronchovascular bundles. This image is diagnostic of sarcoidosis, but berylliosis should always be included as a diagnostic possibility. (D) Perivascular granulomas embedded in sclerosis are commonly seen. Despite this potential for vasocentric growth, pulmonary hypertension is an uncommon complication of sarcoidosis. (Modified from Leslie KO, Wick MR. *Practical Pulmonary Pathology: A Diagnostic Approach.* 2nd ed. Philadelphia: Elsevier; 2011.)

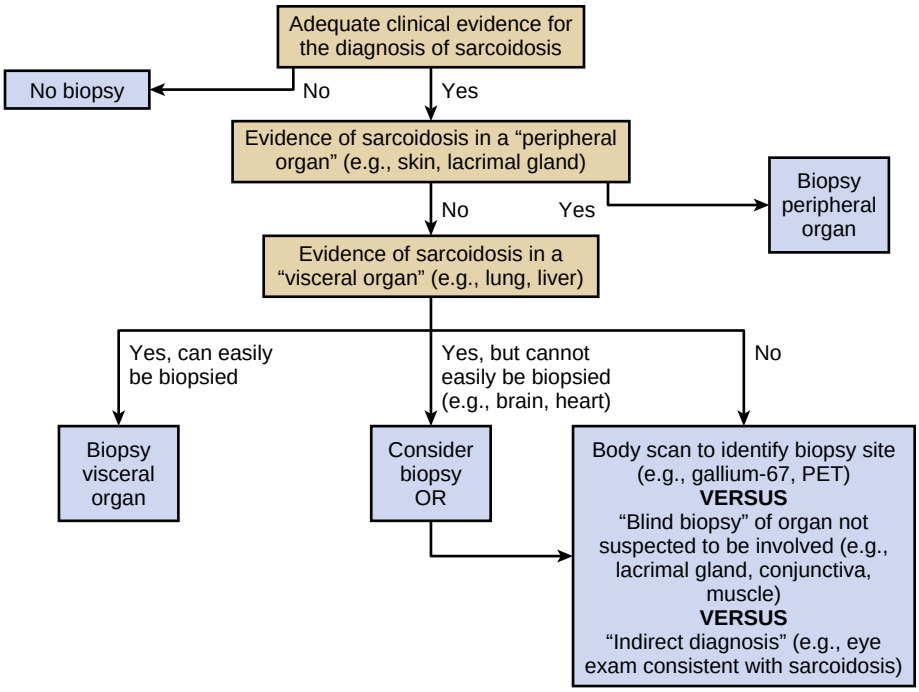

Figure 93.7 Diagnostic approach to selecting a biopsy site for pathologic confirmation of granulomatous inflammation consistent with sarcoidosis. This approach emphasizes selection of a relatively noninvasive biopsy site when possible, biopsy of a site suspected to be clinically involved unless the biopsy would be highly invasive, and various approaches when no obvious organ involvement is demonstrated or only organs requiring very invasive biopsies demonstrate potential involvement. PET, positron emission tomography.

radiograph.[117-119] Endobronchial biopsy results may be positive in up to 60% of patients with pulmonary sarcoidosis.[120,121] Biopsy results are more frequently positive in individuals with abnormal-appearing airways.[120] Furthermore, endobronchial biopsy can be performed at the time of TBLB and increases the yield for sarcoidosis above biopsy using TBLB alone.

Endobronchial ultrasound (EBUS) was shown to be superior to blind TBNA for obtaining diagnostic material in two randomized trials.[122,123] The yield for EBUS or TBNA is much higher for patients with adenopathy on chest radiograph (stage 1 or 2), whereas the yield for TBLB is higher for patients with a stage 3 chest radiograph.[123,124] The use of on-site cytopathology allows for rapid review of the EBUS-TBNA specimen, and the bronchoscopist may not require TBLB.[125] In a meta-analysis, it was found that EBUS had a significantly higher diagnostic yield than TBLB alone. However, the combination of EBUS, TBLB, and endobronchial biopsy had a significantly higher yield than EBUS alone.[126] The addition of cryobiopsy may further enhance the diagnostic yield.[127]

BAL is sometimes used to examine inflammatory cells as a complementary test for the diagnosis of pulmonary sarcoidosis.[128] The diagnostic accuracy of the percentage of lymphocytes and of the CD4/CD8 lymphocyte subpopulation ratio in BAL has been assessed. In general, BAL lymphocytosis (>15% lymphocytes) has a 90% sensitivity for the diagnosis of sarcoidosis,[128-130] although the specificity is lower. Other conditions that lead to BAL lymphocytosis must be excluded, including infections such as tuberculosis and fungal infections, lymphoma, and hypersensitivity pneumonitis.[130,131] BAL lymphocytosis of more than 60% and the presence of mast cells are more common with hypersensitivity pneumonitis than sarcoidosis.[129] The BAL CD4/CD8 ratio is greater than 3.5 in 50–60% of pulmonary sarcoidosis patients. However, the specificity of the BAL CD4/CD8 ratio criterion has approached 95% in some,[130-132] but not all,[133] studies. Some investigators have advocated that the BAL CD4/CD8 criterion is diagnostic of sarcoidosis when there are concomitant chest imaging findings compatible with sarcoidosis[128]; however, these criteria not been formally tested. BAL samples can be tested along with bronchial washings for evidence of fungal or mycobacterial infection.[134]

Tissue biopsy can be used to detect granulomas in any organ involved with sarcoidosis.[115] However, biopsy of neural tissue and biopsy of the heart raise serious concerns because of the potential morbidity associated with these procedures. Because patients with neurosarcoidosis have extraneural sarcoidosis nearly 90% of the time,[135] an extraneural biopsy site can usually be found. In addition, although endomyocardial biopsy is a fairly specific test for cardiac sarcoidosis in the proper clinical setting, its sensitivity is very low.[136] For this reason, endomyocardial biopsy is rarely performed for the diagnosis of sarcoidosis. Often, imaging studies are used as surrogate tests for the diagnosis of neurosarcoidosis (e.g., *magnetic resonance imaging* [MRI] with gadolinium enhancement) and cardiac sarcoidosis (e.g., ^{18}F-fluorodeoxyglucose *positron emission tomography* [PET] or MRI with gadolinium enhancement). Cardiac MRI and PET are often performed to evaluate nonischemic cardiomyopathy. Although these tests may suggest cardiac sarcoidosis, such studies should be interpreted cautiously because their specificity depends on associated clinical evidence for sarcoidosis, which should almost always include previous biopsy confirmation of granulomatous inflammation of unknown cause in another organ (see earlier).

When a confirmatory biopsy is performed for sarcoidosis, a meticulous histologic examination with appropriate

Table 93.2 Clinical Presentations That May Be Assumed to Be Sarcoidosis Without Tissue Confirmation as Long as Additional Data Do Not Suggest an Alternative Diagnosis

- Lupus pernio
- Löfgren syndrome[26]
  - Bilateral hilar adenopathy on chest radiograph
  - Erythema nodosum skin lesions
  - Periarticular inflammation or arthritis of the ankles with or without erythema nodosum
- Heerfordt syndrome[138]
  - Uveitis
  - Parotitis
  - Fever (often)
- Bilateral hilar adenopathy on chest radiograph without symptoms
- Positive panda sign (parotid and lacrimal gland uptake) and lambda sign (bilateral hilar and right paratracheal lymph node uptake) on gallium-67 scan[141]

Modified from Judson MA. The diagnosis of sarcoidosis. *Clin Chest Med.* 2008;29:415-427.

staining should also be performed to search for known causes of granulomatous inflammation, such as mycobacteria, fungi, parasites, and foreign material (e.g., talc). Although no specific histologic features are diagnostic of sarcoid granulomas, certain features suggest this diagnosis. The sarcoid granuloma usually consists of a compact (organized) collection of mononuclear phagocytes (macrophages and epithelioid cells).[137] Typically, there is no necrosis within the sarcoid granuloma; however, on occasion, a small to moderate amount of necrosis is present. Usually, giant cells fuse within the sarcoid granuloma to form multinucleated giant cells (see Fig. 93.6). These granulomas are typically surrounded by lymphocytes in the periphery. A variety of inclusions may be present within the sarcoid granuloma, including asteroid bodies (star-shaped inclusions), Schaumann bodies (lamellated calcified inclusions), birefringent crystals, and Hamazaki-Wesenberg bodies (pigmented oval inclusions); however, these inclusions are neither specific nor diagnostic of sarcoidosis[137] (eFig. 93.1). In particular, birefringent crystals within the sarcoid granuloma may lead to a misdiagnosis of talc granulomatosis.[92] Care must be taken to ensure that the crystal morphology and size are compatible with intravenously injected talc before making the diagnosis of talc granulomatosis.

DIAGNOSIS OF SARCOIDOSIS WITHOUT CONFIRMATORY BIOPSY

In some cases, the clinical presentation of sarcoidosis is so specific that the diagnosis can be made without performing a confirmatory tissue biopsy. These presentations are listed in Table 93.2.[84] In patients with these presentations, performing bronchoscopy can be considered to exclude other possible causes, including infection. In patients whose bronchoscopy findings are not diagnostic, the presence of factors shown in Table 93.2 may help bolster the confidence of the diagnosis

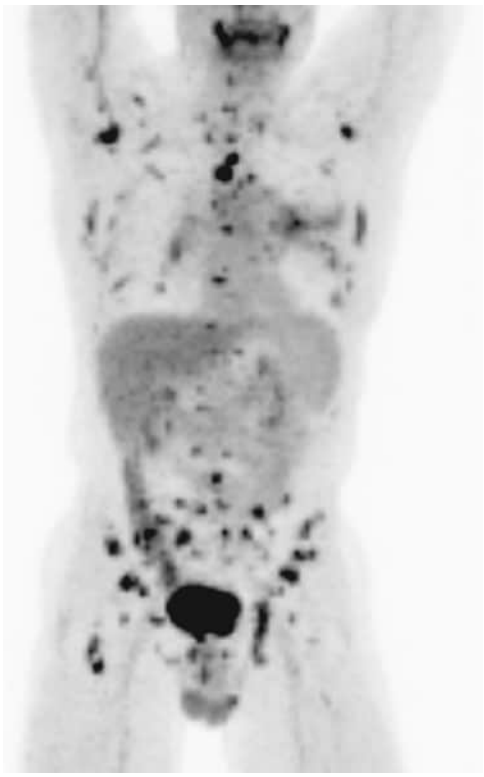

Figure 93.8 Positron emission tomography scan demonstrating both lung parenchymal and mediastinal nodal uptake. Also demonstrated are several extrapulmonary lymph nodes and other areas with increased activity.

of sarcoidosis. Löfgren syndrome initially included only patients with erythema nodosum of lower legs or forearms (eFig. 93.2). However, periarticular inflammation or arthritis of the ankles with or without erythema nodosum has been added to the expanded definition of Löfgren syndrome.[26] Uveoparotid fever, also known as Heerfordt syndrome, is an uncommon, specific manifestation of sarcoidosis that establishes the diagnosis without the need for a confirmatory biopsy.[138]

On some occasions, the diagnosis of sarcoidosis is suspected on clinical grounds although no specific organ is identified to biopsy. This would include patients presenting with disease of the eye, brain, or heart that is consistent with sarcoidosis but who have no organ that can be safely sampled by biopsy. There is no established approach for this situation. Total body imaging using ^{18}F-FDG-PET[139,140] or gallium-67 scanning[141] has been proposed in such cases to identify an organ for biopsy (Fig. 93.8), although no rigorous analysis of this approach has been undertaken. Another suggested approach in this situation is to perform a biopsy in organs that are commonly affected, even in the absence of symptoms or of other clinical findings suggestive of sarcoidosis. Conjunctival biopsies have been performed in this situation, and the yield has ranged from 27–55% in patients without ocular symptoms.[142-145] In vivo confocal microscopy of the conjunctiva can detect multinucleated giant cells without the need for a biopsy, and this has also been advocated as a noninvasive way to confirm granulomatous inflammation in sarcoidosis

patients.[146] Liver biopsy demonstrates granulomas in 24–78% of sarcoidosis patients, even when they have no symptoms attributable to the liver and have normal serum liver function test results.[147,148] However, hepatic granulomas are not specific for sarcoidosis, so clinical evidence of extrahepatic sarcoidosis must be present for the diagnosis to be secure.[149] A gastrocnemius muscle biopsy was shown to reveal granulomas in patients without muscle symptoms who had bilateral hilar adenopathy on chest radiograph.[150] However, most of these patients had strong clinical evidence of sarcoidosis; furthermore, this procedure is fairly invasive.

As a mostly historical test, the Kveim test involved the intradermal inoculation of a suspension of splenic tissue from spleen that was involved with sarcoidosis.[151] If a skin nodule developed at the inoculation site in 4 to 6 weeks, it was sampled by biopsy. A biopsy demonstrating nonnecrotizing granulomatous inflammation was considered highly specific for the diagnosis of sarcoidosis.[152] The Kveim test had a false-negative rate of approximately 20–40%. At present, the Kveim test is rarely performed because of lack of properly prepared Kveim reagent and concern for transmission of an infectious agent.

CONTROVERSIES CONCERNING THE NUMBER OF ORGANS TO SAMPLE BY BIOPSY

Sarcoidosis has been defined as multisystem granulomatous disorder of unknown cause.[1] For this reason, it has been stated that the diagnosis of sarcoidosis requires demonstration of granulomatous inflammation in at least two organs.[1] This diagnostic criterion is controversial.[153] Sarcoidosis is clearly a systemic disease by virtue of its association with specific inflammatory syndromes such as anergy,[154] erythema nodosum,[26] and the recurrence of sarcoidosis in organ transplant recipients with sarcoidosis.[155] The presence of sarcoidosis in a second organ increases the specificity of the diagnosis by excluding conditions involving a single organ such as idiopathic granulomatous hepatitis[156,157] and localized granulomatous skin reactions. However, some clinical presentations are adequately specific for sarcoidosis that the diagnosis can be established on the basis of granulomatous inflammation in one organ. This belief is consistent with the National Institutes of Health *A Case Control Etiology of Sarcoidosis Study* (ACCESS), in which 50% of the sarcoidosis cohort enrolled by sarcoidosis experts had evidence of sarcoidosis in only one organ.[11]

Other multiorgan granulomatous syndromes should be considered in the differential diagnosis of sarcoidosis. These include infections such as tuberculosis. There are also some idiopathic multiorgan granulomatous diseases. Blau syndrome consists of granulomatous iritis, arthritis, and skin rash.[158,159] Blau syndrome may be distinguished from sarcoidosis because it is a genetic disorder[160] with an autosomal dominant pattern of inheritance with variable penetrance[158,159]; it has a lack of visceral (e.g., pulmonary) involvement, and it usually manifests before 12 years of age.

Necrotizing sarcoid granulomatosis is a type of systemic granulomatous vasculitis.[161,162] Because of vascular involvement, necrosis is a prominent feature, unlike in most cases of sarcoidosis. Although the lung is commonly involved, extrapulmonary involvement is also common.[163] It is debated whether necrotizing sarcoid granulomatosis is a distinct clinical entity or a form of systemic sarcoidosis.[163-165]

In summary, the diagnosis of sarcoidosis is never secure. Clinical criteria, including the presence of multiple organ involvement as reflected by a high Sarcoidosis Diagnostic Score, may provide sufficient confidence in the diagnosis.[99] The presence of granulomas in one or more organs further enhances the diagnostic certainty.

EVALUATION OF PULMONARY DISEASE

IMPORTANCE OF SYMPTOMS AND QUALITY OF LIFE

The evaluation of pulmonary disease in sarcoidosis patients relies on three major determinants: pulmonary function, chest imaging, and symptoms. The clinician often focuses on pulmonary function testing and chest imaging as methods to assess lung involvement. However, the patient's major concerns are how they feel and how their lung disease affects their quality of life, and clinicians need to understand that maximizing quality of life is of greater importance to the patient than maximizing an objective assessment of lung involvement or function. Dyspnea and cough are the major reasons for treatment of pulmonary sarcoidosis.

PULMONARY FUNCTION TESTING

Sarcoidosis is classically a restrictive lung disease with reduction of lung volumes, including *forced vital capacity* (FVC). However, many sarcoidosis patients have obstructive lung disease.[166,167] In fact, a significant proportion of sarcoidosis patients will have a normal FVC at the time of diagnosis.[11,116] Over time, some of these patients will develop more restrictive disease.[3,168] The *diffusing capacity for carbon monoxide* (D_{LCO}) is a more sensitive measure of early interstitial lung disease. Abnormalities in D_{LCO} are found in less than half of sarcoidosis patients.[169] These reduced values of D_{LCO} often predict a reduction in exercise capacity.[169,170] A disproportionately reduced D_{LCO} may also be an indicator of sarcoidosis-associated pulmonary hypertension.[171,172]

Clinical pulmonary exercise testing may be useful in assessing dyspnea and functional limitation in sarcoidosis patients.[169] Patients with normal lung function testing may still have abnormalities in exercise testing.[173] However, exercise testing is not well standardized and is relatively cumbersome to perform.

The *6-minute walk distance* (6MWD) test has been widely used to assess exercise capacity.[174] In sarcoidosis, reduction in 6MWD has been found to correlate with reduced FVC, fatigue, and quality-of-life measures.[175] Reduced 6MWD and oxygen desaturation have been found in patients with sarcoidosis-associated pulmonary hypertension.[175,176]

However, several factors besides cardiopulmonary function influence the 6MWD, including muscle strength, joint disease, neurologic symptoms, and the degree of motivation.[174,177]

LUNG IMAGING

The routine chest radiograph has been characterized by stages, originally proposed by Scadding, as described earlier.[101] The Scadding stage correlates with prognosis of the chest radiograph, but not with sarcoidosis itself. Patients with stage 1 (see Fig. 93.3) have a more than 80% chance of resolution of hilar adenopathy 2 to 5 years after presentation, whereas those with stage 3 (see Fig. 93.5) have a less than a 30% chance of resolving to a normal chest radiograph. Fibrotic changes (stage 4) do not resolve. The difficulty with chest radiographic staging is that it does not characterize extrapulmonary manifestations of sarcoidosis. In addition, there is significant variability in the classification of radiographic stage even among experienced radiologists.[178]

Comparing chest radiographs over time is an alternative to assessing the chest radiograph by Scadding staging. This comparison reading is commonly done in clinical practice. The change in the chest radiograph has been shown to have good reproducibility and correlates with changes in pulmonary function.[179,180] In one study, the interobserver agreement for comparison reading was superior to that using the Scadding scoring system.[178]

Another method used for assessing the chest radiograph is similar to a scoring system for pneumoconiosis.[181] This system scores the radiograph in four categories: reticulonodular opacities, mass opacities, confluence, and fibrosis. It was shown that the "reticulation" portion of this score detected changes after corticosteroid therapy[182] and after treatment with infliximab[183] versus placebo. The scoring system was reproducible with a good interobserver agreement.[178] However, the scoring is tedious and does not appear practical for routine clinical practice.

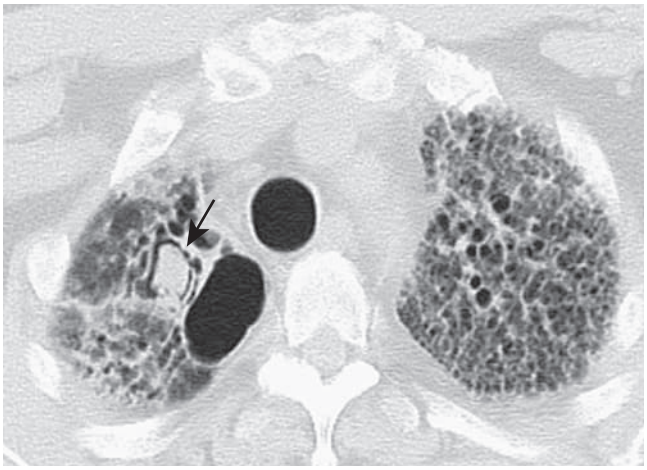

Figure 93.9 Aspergilloma in a patient with sarcoidosis. High-resolution computed tomography demonstrating upper lobe fibrosis with presence of an aspergilloma in the right upper lobe (*arrow*).

As noted earlier, chest CT imaging, including HRCT, has proved useful in the diagnosis of sarcoidosis (see Fig. 93.4).[184] A scoring system for CT scans in sarcoidosis has been described,[102] and it has been suggested to assess severity of disease.[185] However, it is unclear what features of the CT scan are important for management of the disease. Some HRCT scan features correlate with physiologic impairment in sarcoidosis, such as honeycombing, which is associated with reduced D_{LCO} and increased alveolar-arterial oxygen tension difference,[186,187] and peribronchial thickening, which may lead to airway obstruction and air trapping.[188,189] HRCT is useful in defining the extent of bronchiectasis and the presence of complications, such as aspergilloma (Fig. 93.9).[190] The extent of pulmonary fibrosis can be estimated from HRCT findings. Patients with more than 20% pulmonary fibrosis have increased mortality rates.[191,192]

Radionuclide scanning has been used as an aid in the diagnosis of sarcoidosis and the assessment of organ involvement.[140] Early studies focused on the gallium scan as a method of identifying inflammation.[193,194] The presence of extrapulmonary disease was often useful in identifying potential biopsy sites. In addition, uptake in the parotid and lacrimal glands ("panda sign") and/or right paratracheal and bilateral hilar areas ("lambda sign") was highly supportive of the diagnosis of sarcoidosis.[141] Octreotide scanning,[195] as well as somatostatin receptor scintigraphy,[140,195] has also been used as a marker of lung inflammation in sarcoidosis.

PET scan activity can be quite enhanced in sarcoidosis and can demonstrate diffuse activity in the lungs, mediastinal lymph nodes, and other parts of the body (see Fig. 93.8).[139,140] The PET scan proved useful in identifying potential biopsy sites in suspected sarcoidosis.[139] It has also been found to demonstrate ongoing activity in patients who are receiving immunosuppressive therapy and may suggest that the patient will have a relapse when therapy is withdrawn.[196,197] In a study comparing PET with gallium scan, the PET scan was found to be more sensitive and reproducible.[198]

PET may also provide clinically useful information. Patients with positive PET uptake demonstrated evidence of active disease by virtue of a significant improvement in their FVC and D_{LCO} with an increased immunosuppressive regimen and a significant fall in the D_{LCO} when therapy was not changed.[199] Additionally, a negative PET scan result was associated with a stable FVC and D_{LCO} without therapy.[199] The intensity of PET activity can be expressed as the *maximal standardized uptake value* (SUV_{max}) in a region of interest. In patients treated for pulmonary sarcoidosis, a linear relationship was shown between the reduction of SUV_{max} and improvement in FVC.[200] A fall in SUV_{max} has also been demonstrated with successful treatment of pulmonary sarcoidosis with a variety of immunosuppressive agents.[201-203]

Imaging of the heart with either PET or MRI scanning can detect cardiac involvement in sarcoidosis.[204] Cardiac MRI appears to be more sensitive and specific.[205] However, cardiac MRI requires special expertise to interpret properly and is contraindicated if an implanted defibrillator or pacemaker is not MRI compatible.

HEALTH-RELATED QUALITY OF LIFE

Sarcoidosis has been associated with impaired health-related quality of life.[206-208] In a survey of more than 1800 European patients with sarcoidosis, quality of life and functional status were more important to the patients than blood tests or pulmonary function test results.[209] These data have influenced sarcoidosis clinicians to focus more on patient priorities and less on objective test measurements of granulomatous inflammation or physiologic changes.[210] Health-related quality of life has been measured in sarcoidosis patients by using instruments that are not disease specific, such as the Short Form 36 (SF-36)[208,211,212] and the Saint George Respiratory Questionnaire.[213,214] Three sarcoidosis-specific quality-of-life instruments have been developed: the Sarcoidosis Health Questionnaire,[215] the King's Sarcoidosis Questionnaire,[206] and the Sarcoidosis Assessment Tool.[216]

Fatigue is a common complaint in sarcoidosis patients.[217,218] It has been reported by more than half of sarcoidosis patients in both Europe and the United States.[219] Although fatigue is a complaint in patients with pulmonary sarcoidosis, it is more common in those with extrapulmonary involvement.[220] Fatigue may persist long after other evidence of disease has regressed.[218] Several fatigue scales that have been used for sarcoidosis are not disease specific.[217,220,221] The Fatigue Assessment Scale and Sarcoidosis Assessment Tool fatigue module are sarcoidosis-specific fatigue questionnaires.[216,222]

SARCOIDOSIS-ASSOCIATED PULMONARY HYPERTENSION

Sarcoidosis-associated pulmonary hypertension (SAPH) can be caused by a variety of mechanisms, including left ventricular diastolic dysfunction, pulmonary arterial vasculitis, pulmonary veno-occlusive disease, pulmonary fibrosis, and hypoxia.[223] The overall incidence of pulmonary hypertension in sarcoidosis appears to be 5–15%.[171,176,224,225] However, in patients with moderate to severe pulmonary symptoms, the rate of pulmonary hypertension has been reported to be 50% or greater.[172,226-228] Precapillary pulmonary hypertension is the most common cause of SAPH, but left ventricular diastolic dysfunction is a cause in a significant proportion of cases.[225,228] More than one-third of SAPH patients have moderate to severe pulmonary hypertension, with a mean pulmonary artery pressure greater than 35 mm Hg.[229,230] The survival of patients with precapillary SAPH is significantly worse than in patients with SAPH and diastolic dysfunction.[228]

Table 93.3 Organ Involvement in Sarcoidosis*

	Charleston	Cincinnati
Women	66%	71%
African American	66%	43%
SPECIFIC ORGAN INVOLVEMENT		
Lungs	89%	88%
Eye	23%	33%
Skin	32%	33%
Liver	20%	13%
Neurologic	9%	14%
Cardiac	4%	5%

*For a total of 2700 patients, organ involvement was determined to be definite or probable by standardized criteria.

Charleston data from Judson MA, Boan AD, Lackland DT. The clinical course of sarcoidosis: presentation, diagnosis, and treatment in a large white and black cohort in the United States. *Sarcoidosis Vasc Diffuse Lung Dis*. 2012;29:119-127; Cincinnati data from personal communication.

EVALUATION FOR EXTRAPULMONARY DISEASE

GENERAL CONSIDERATIONS

Sarcoidosis is a multiorgan disease. Pulmonary involvement has been reported in more than 90% of cases in most large series.[11,116,231] However, several other organs are commonly affected with the disease. Table 93.3 lists organ involvement as detected by two large clinics in the United States including a total of more than 2700 patients.[231] Both groups used the same standardized criteria for organ involvement and listed only those organs with definite or probable disease.[232]

EYE

The eye is involved in about one-third of patients in the United States and Europe. Eye disease is more common in African Americans and women.[11,231] In Japan, up to 80% of patients with sarcoidosis have eye disease.[233] Table 93.4 lists some of the more common ocular manifestations of sarcoidosis.[234] Uveitis is the most common manifestation of ocular sarcoidosis and at times can be clinically silent.[235] It is recommended that all sarcoidosis patients undergo an ocular examination by a specialist at the time of initial evaluation.[1] Patients with ocular sarcoidosis may develop complications from eye involvement such as sicca syndrome, glaucoma, and cataracts. Cataracts and glaucoma can also be complications of local or systemic corticosteroid treatment.

Table 93.4 Areas of Eye Involvement in Sarcoidosis

Uveitis: anterior, intermediate, posterior
Optic neuropathy
Adnexal and orbital disease
Lacrimal glands: enlargement, sicca, dacrocystitis (blockage of duct)
Orbital mass
Scleral involvement
Glaucoma
Cataracts

Modified from Baughman RP, Lower EE, Kaufman AH. Ocular sarcoidosis. *Semin Respir Crit Care Med*. 2010;31:452-462.



Figure 93.10 Multiple skin lesions associated with chronic cutaneous sarcoidosis. (A) Lupus pernio. Violaceous nodular plaques on the nose, cheek, and lip. (B) Lupus pernio. Violaceous swelling of the distal digits. (C) Papular sarcoidosis. Multiple papules in a periorbital distribution. (D) Cutaneous sarcoidosis manifesting as pink, indurated areas within and around a tattoo.

SKIN

The skin is involved in about one-third of sarcoidosis patients.[236] Skin manifestations include maculopapular lesions, papules, hyperpigmentation, and hypopigmentation (Fig. 93.10).[237] Lupus pernio is a disfiguring facial lesion specific for sarcoidosis.[238] It is more common in African Americans . It is usually chronic,[239] and it can be resistant to usual therapy.[240] Erythema nodosum, as noted earlier, is often, but not always, associated with a good prognosis.[26] In particular, African Americans with erythema nodosum often have chronic disease.[241] In addition, a study of Scandinavian patients with Löfgren syndrome found that those who had the HLA DRB1*03 polymorphism uniformly had an excellent prognosis, whereas those lacking this antigen had unresolving disease almost half the time.[26]

NERVOUS SYSTEM

Neurologic disease can develop centrally, affecting the spinal cord, causing meningitis, or involving the cranial nerves.[242-244] The most sensitive method of detecting neurologic disease is with an MRI scan with gadolinium contrast because neurologic lesions often enhance.[244,245] Spinal fluid analysis may demonstrate lymphocytosis and elevated protein levels.[245] An elevated level of ACE in spinal fluid has been reported to be specific for neurosarcoidosis, but the sensitivity is as low as 50%.[246] In patients suspected of having neurosarcoidosis, especially those who present with isolated disease,[247] multiple sclerosis should be considered as an alternate diagnosis.[248] As in multiple sclerosis, patients with sarcoidosis can develop optic neuritis with or without uveitis.[249] It is important to distinguish patients with neurosarcoidosis from those with multiple sclerosis because neurosarcoidosis patients often improve with treatment, including anti-TNF treatments such as infliximab.[249,250]

HEART

The heart can be affected by sarcoidosis with two major manifestations: arrhythmias and reduced ejection fraction. The detection of cardiac sarcoidosis can be quite difficult.[251] The presence of cardiac symptoms, including palpitations and syncope, is as good as or better than any single screening test for cardiac sarcoidosis.[204,252] Rhythm monitoring and echocardiography are useful supplemental tests for screening.[204] Currently, imaging with MRI and/or PET scanning is believed to be the most specific for diagnosing cardiac sarcoidosis.[251] Arrhythmias, especially ventricular arrhythmias, remain a potential cause of death in cardiac sarcoidosis.[253] However, the use of implantable defibrillators has markedly reduced the mortality from this manifestation.[254,255] The role of prophylactic defibrillators is controversial but, at a minimum, patients with potential cardiac sarcoidosis should be screened for ventricular arrhythmias.

LIVER

Liver involvement is common in sarcoidosis.[256] The usual pattern of serum chemistry markers includes elevated alkaline phosphatase, but elevated transaminases have been seen.[147,257] Imaging of the liver with contrast CT scan can support the diagnosis. Liver biopsy usually detects granulomatous disease, even in patients with no symptoms or blood chemistry abnormalities.[147,257,258] Liver sarcoidosis can lead to end-stage hepatic fibrosis, but this is uncommon.

VITAMIN D DYSREGULATION

Hypercalcemia or hypercalcuria has been reported in up to 30% of sarcoidosis patients.[259,260] The most common mechanism is from excessive levels of $1,25\text{-}(OH)_2$ vitamin D_3 secondary to autonomous 1-α-hydroxylase activity.[261,262]

Table 93.5 Treatment for Sarcoidosis

	Grade
ANTI-INFLAMMATORY TREATMENT	
Acute Disease	
Glucocorticoids	1A
Hydroxychloroquine	2B
Methotrexate	2A
Chronic Disease	
Glucocorticoids	1B
Methotrexate	1A
Azathioprine	1B
Leflunomide	1B
Mycophenolate	1C
Infliximab	1A
Adalimumab	1A
Hydroxychloroquine	2B
Refractory Disease	
Infliximab	1A
Adalimumab	1A
FIBROTIC DISEASE	
When Criteria for Treatment Are Met	
Oxygen therapy	1C
Lung transplantation	1B
Pulmonary rehabilitation	1C
COMPLICATIONS OF DISEASE	
Pulmonary Hypertension	
Bosentan	1A
Ambrisentan	2B
Sildenafil	1B
Tadalafil	2B
Inhaled iloprost	2B
Prostacyclin	1B
Fatigue	
Methylphenidate	1C
d-Methylphenidate	1A
Armodafinil	1A
COMPLICATIONS OF DISEASE OR THERAPY	
Aspergillomas	
Azole therapy	1C
Intracavitary amphotericin	1B
Resection (when tolerated)	1C

*The grading scheme classifies recommendations as strong (grade 1) or weak (grade 2), according to the balance among benefits, risks, burdens, and possibly cost, and the degree of confidence in estimates of benefits, risks, and burdens. The system classifies quality of evidence as high (grade A), moderate (grade B), or low (grade C) according to factors that include the study design, the consistency of the results, and the directness of the evidence.

From James WE, Baughman R. Treatment of sarcoidosis: grading the evidence. *Expert Rev Clin Pharmacol*. 2018;11:677-687.

Levels of 1,25-$(OH)_2$ vitamin D_3 may be elevated despite low levels of 25-(OH) vitamin D_3.[259] There are other causes of hypercalcemia in sarcoidosis, including hyperparathyroidism.[259] Hypercalcemia in sarcoidosis patients can be associated with renal failure, which may reverse with treatment of the hypercalcemia.[263]

PARASARCOIDOSIS SYNDROMES

Besides specific sarcoidosis organ involvement, sarcoidosis may also cause symptoms or abnormalities not directly related to granulomatous tissue invasion or fibrosis. These entities are collectively known as *parasarcoidosis syndromes.*[264] Parasarcoidosis syndromes include sarcoidosis-associated fatigue, small fiber neuropathy, pain syndromes, depression, cognitive impairment, Löfgren syndrome, and vitamin D dysregulation. Because many of these syndromes are not directly related to granuloma formation, the treatment of many of them requires nonstandard therapies.

TREATMENT

GENERAL CONSIDERATIONS

The treatment of sarcoidosis requires consideration of sarcoidosis-related inflammation, the consequences of the disease, and the consequences of therapy. Table 93.5 lists these aspects of the disease and potential treatments that have been reported, with a level of evidence to support their use in sarcoidosis.[265-267]

ANTI-INFLAMMATORY AGENTS

General Comments

Because sarcoidosis patients are frequently asymptomatic and many have spontaneous resolution of their sarcoidosis within 6 months of diagnosis,[182] not all patients require initial therapy.[182,268,269] Usually, the decision to treat patients is based on symptoms and, when sarcoidosis involves the lungs, on a decline in pulmonary function.[268]

Corticosteroids

Corticosteroids remain the most widely used, well-documented, and most effective treatments for sarcoidosis; however, many patients require treatment for a prolonged time (>1 year), and steroid-sparing medications should be considered early in treatment.[5,270,271]

The reported initial dose of corticosteroids varies widely. In one retrospective study of patients with exacerbations of pulmonary sarcoidosis, a short course of prednisone (20 mg/day) led to a significant improvement in FVC and pulmonary symptoms in less than 1 month.[272] Whatever dose of steroid is selected, once the patient has shown improvement, the dose of drug is usually tapered to minimize toxicity but maintain benefit from the initial induction of response. In some cases, the patient may have a relapse as treatment is being reduced, thus leading to a return to a higher

dosage.[273] Slow withdrawal over the course of months is usually recommended.[274] Even those patients treated with glucocorticoids for 2 or more years have at least a 50% chance of relapse when drug is withdrawn.[275,276]

Patients who do not respond to the equivalent of prednisone 40 mg daily are considered refractory to standard treatment and should be considered for alternative therapy. However, such patients are relatively rare.

Rationale for Corticosteroid-Sparing Agents

For patients who are started on therapy, a significant percentage will require long-term treatment beyond 2 years.[182,268,269,274,277] Corticosteroid-sparing agents and alternative agents are often considered in sarcoidosis patients who require corticosteroids for more than 1 year because significant cumulative toxicities from corticosteroids are common. Evidence-based recommendations have been published regarding monitoring patients while being treated for pulmonary disease for many of the nonsteroidal immunosuppressive agents.[278]

Antimalarial Agents

The antimalarial agents chloroquine and hydroxychloroquine are effective in treating certain aspects of extrapulmonary disease,[279,280] especially cutaneous and sinonasal disease.[279,281] They have also proved useful in treating hypercalcemia,[282] and they may be more effective in treating sarcoidosis-associated fatigue than other anti-inflammatory agents.[219] The major toxicity encountered with antimalarial agents has been ocular. Hydroxychloroquine appears to have a lower rate of ocular toxicity. However, routine screening is still recommended.[283-285] For most patients, a hydroxychloroquine dose of less than 5 mg/kg of real body weight appears to be safe.[286]

Antimetabolites

Methotrexate is a commonly used steroid-sparing cytotoxic agent for sarcoidosis.[270,287] Methotrexate has been shown to be effective in remitting and persistent disease, as well as in ocular,[234,288] cutaneous,[289-291] sinus,[292,293] and neurologic disease.[294,295] A major potential toxicity of methotrexate and other cytotoxic drugs is bone marrow suppression. The effect is dose dependent. Evidence-based and expert opinion recommendations for monitoring patients while receiving methotrexate therapy have been published.[278,296]

Azathioprine is another cytotoxic agent commonly used in chronic sarcoidosis. Limited data suggest that it is as effective as methotrexate, but it results in greater toxicity.[297] It has been shown to be effective in pulmonary[298] and extrapulmonary disease.[292,299,300] Compared with other cytotoxic agents, azathioprine is associated with a greater risk for malignancy and myelodysplastic syndrome.[301]

Leflunomide is an antimetabolite similar in action to methotrexate originally developed for treating rheumatoid arthritis.[302] It has been reported to be effective in treating sarcoidosis either alone or in combination with methotrexate.[303,304] Compared with methotrexate, the drug has less gastrointestinal toxicity but a similar rate of liver function test abnormalities.[302] Although pulmonary toxicity with leflunomide is less common than with methotrexate, leflunomide can still cause pulmonary toxicity.[305,306] Leflunomide can also cause peripheral neuropathy that usually resolves with discontinuation of the drug.[307,308]

Mycophenolate analogues have been increasingly used to treat inflammatory lung diseases.[309,310] They have been reported to be effective as steroid-sparing agents for patients with persistent disease, especially neurosarcoidosis.[311,312] In a retrospective report of neurosarcoidosis patients, mycophenolate was associated with a higher rate of relapse than methotrexate.[313] Although mycophenolate treatment is associated with less bone marrow and hepatotoxicity, it is associated with significant gastrointestinal and infectious complications.[314]

Tumor Necrosis Factor Antagonists

Infliximab is a chimeric monoclonal antibody directed against TNF. It was first shown to be effective in treating refractory sarcoidosis in 2001.[315,316] The drug has been widely used for various forms of refractory disease, including pulmonary, skin, eye, and neurologic disease.[317-321] Two double-blind placebo-control trials demonstrated a benefit of infliximab as additional therapy to maintenance therapy.[183,212] The drug has also proved to be effective for some patients with extrapulmonary disease.[322,323] In a large retrospective study of patients with lupus pernio, infliximab was superior to all other treatment options[240] and was superior to placebo in a randomized trial.[324] It has also proved to be useful in treating refractory neurosarcoidosis.[325,326] Adverse effects of the drug may be considerable, and a high rate of relapse has been reported within a year after the drug is withdrawn.[327]

The toxicity of infliximab includes an allergic reaction to the chimeric antibody that can manifest as an acute reaction, including anaphylaxis, vasculitis, or a subacute, lupus-like reaction.[328] Infliximab has also been associated with a high risk for reactivation of tuberculosis.[329] This risk for reactivation can be significantly reduced by adhering to guidelines for screening and treating latent tuberculosis.[330] Testing for latent tuberculosis with skin testing may not be adequate in sarcoidosis because anergy is common and can interfere with the skin test. [331] A quantitative interferon-γ test seems to be more reliable for screening for latent tuberculosis in anergic or immunosuppressed patients.[332] The anti-TNF treatments are believed to be relatively contraindicated in advanced congestive heart failure because one large study demonstrated increased mortality in patients with advanced heart failure who were treated with infliximab.[333] However, infliximab has been used successfully in treatment of cardiomyopathy secondary to sarcoidosis.[334-336] The potential increased risk for malignancy with the use of anti-TNF agents is still unclear. In rheumatoid arthritis, a meta-analysis found an increased incidence only of nonmelanoma skin cancers.[337] However, another study suggested a potential increased risk for lymphoma, although the relative risk was not significantly increased compared with control subjects.[338] The risk for developing cancer in sarcoidosis patients treated with anti-TNF therapy is unknown, and one should remain cautious regarding this risk when using this class of drugs.

Adalimumab, a totally humanized anti-TNF antibody, has been reported to be effective in treating some sarcoidosis cases.[321,339-341] In a randomized trial, it was superior to placebo for chronic cutaneous disease.[342] Compared

with infliximab, adalimumab appears to have a lower response rate and takes longer to demonstrate effectiveness.[320] This finding may reflect the relatively lower doses of drug initially used. For example, adalimumab was shown to be more effective in treating Crohn disease when a higher induction and maintenance dose was used.[343] This higher dose of the anti-TNF antibody may be necessary to achieve clinical response in sarcoidosis, but it remains unclear how often these increased doses are required.[344] Golimumab, another humanized monoclonal anti-TNF antibody, failed to demonstrate efficacy for the treatment of lung and skin sarcoidosis, possibly as the result of an inadequate dosing regimen.[345] Etanercept is a TNF-receptor antagonist and has been reported to be effective in some cases of refractory sarcoidosis.[346] However, the drug was not found to be effective in an open-label trial of pulmonary sarcoidosis[347] or in a placebo-controlled, double-blind randomized controlled trial of ocular sarcoidosis.[348]

Interestingly, patients treated with anti-TNF therapy can develop a granulomatous disease indistinguishable from sarcoidosis.[349,350] The mechanism of this reaction is unknown, but one possible mechanism is through T regulatory cells.[351] As noted earlier, abnormalities of T regulatory cells have been described in sarcoidosis.[83,352] There are several new anti-inflammatory therapies being evaluated in sarcoidosis.[5]

Given the high cost of anti-TNF therapy, there is a recent interest in the use of biosimilars of these agents for the treatment of sarcoidosis. A recent retrospective report found a biosimilar to infliximab to be effective in advanced sarcoidosis.[202] We suspect that biosimilars will be more frequently used for the treatment of sarcoidosis in the future.

APPROACH TO EXTRAPULMONARY DISEASE

In general, the treatment of extrapulmonary disease is similar to the treatment of pulmonary disease. However, there are a few special considerations. For ocular sarcoidosis, local therapy with topical steroids, periocular steroid injections, and steroid implants may be sufficient to control disease.[234] However, use of corticosteroids may cause cataracts or glaucoma. Therefore, the use of cytotoxic agents such as methotrexate should be considered early in the management of chronic ocular sarcoidosis.[288,321] For cutaneous sarcoidosis, patients may often respond to hydroxychloroquine or local corticosteroid therapy.[281,353] However, lupus pernio requires long-term therapy, with infliximab proving to be superior to corticosteroid or cytotoxic therapy.[354] Neurologic disease often requires more intense treatment with either higher doses of corticosteroids or cytotoxic treatments.[294] Anti-TNF treatment may be particularly helpful in the treatment of refractory neurosarcoidosis.[312,355]

FIBROTIC SARCOIDOSIS

Patients with significant pulmonary fibrosis from sarcoidosis have increased mortality.[187,191,192] The fibrosis usually appears in the upper lobes and can lead to airway distortion and cystic changes (Fig. 93.11 and eFig. 93.3). Radiographic and histologic data suggest that the fibrosis in sarcoidosis is derived from the granulomatous inflammation.[356,357] To date, there is limited understanding of the pathophysiologic mechanisms that underlie fibrosis, and no specific therapy is known to be effective for the fibrotic component of sarcoidosis.[358] Supportive care is the mainstay of therapy for these patients. This includes

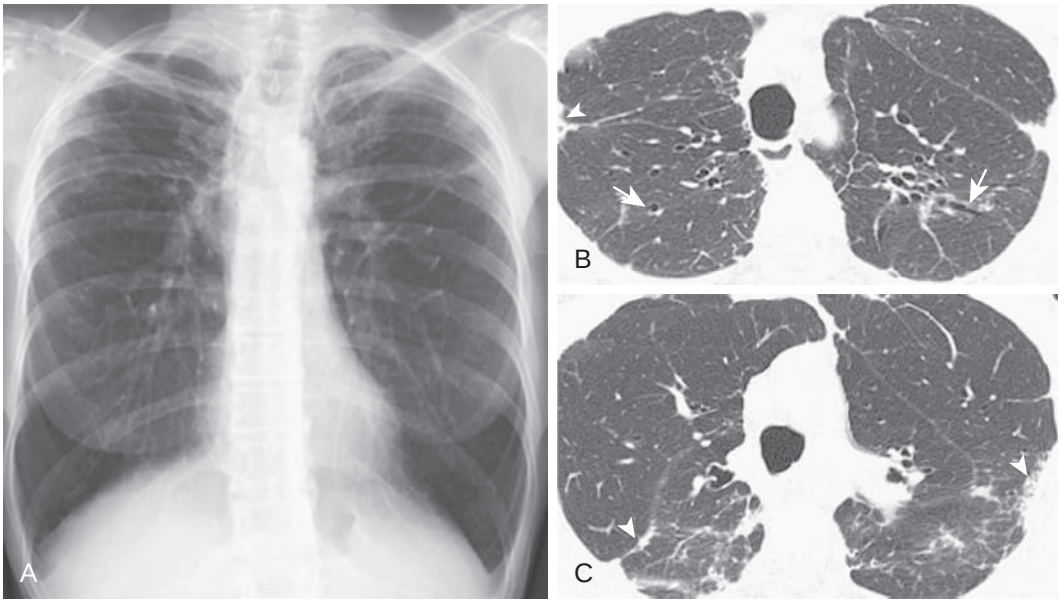

Figure 93.11 Sarcoidosis: Scadding stage 4. (A) Frontal chest radiograph shows upper lobe linear and reticular opacities associated with architectural distortion consistent with a fibrosing process; note bilateral superior hilar retraction. Little pleural abnormality is noted; this image is typical of granulomatous inflammation secondary to sarcoidosis, as opposed to granulomatous infections. (B–C) Axial chest computed tomography in lung windows shows patchy, upper lobe linear opacities associated with architectural distortion and traction bronchiectasis *(arrows)*. Subpleural and perifissural nodular opacities *(arrowheads)* are present. (Courtesy Michael B. Gotway, MD.)

Table 93.6 Treatment of Sarcoidosis-Associated Pulmonary Hypertension

Class	Therapy	Significant Improvement	Improvement Seen in Some Cases
Prostanoids	Epoprostenol[363,364]		Improved hemodynamics
	Iloprostenol[365]		Improved hemodynamics and HRQoL
Endothelin-receptor antagonists	Bosentan[369]	Improved hemodynamics	
	Ambrisentan[366]		Improved HRQoL
Phosphodiesterase-5 inhibitors	Sildenafil[370]		Improved hemodynamics
Combination therapy	PAH-specific therapy[390]	Improved hemodynamics	Improved 6MWD

HRQoL, health-related quality of life; 6MWD, 6-minute walk distance.

facilitation of mucociliary clearance and treatment of infections associated with bronchiectasis, supplemental oxygen, and pulmonary rehabilitation when appropriate.[359] Focus should be on the treatment of superimposed infections because they are common complications of the bronchiectasis seen in fibrotic sarcoidosis. These infections may be among the events leading to acute decompensation.[360]

LUNG TRANSPLANTATION

Lung transplantation has been successfully performed in sarcoidosis patients.[361] Patients may develop granulomas in the transplanted lung.[155] The clinical outcome of transplant recipients is seldom altered by recurrence, however, because posttransplant immunosuppression is often adequate treatment for the sarcoidosis. [360,362]

PULMONARY HYPERTENSION

For precapillary *sarcoidosis-associated pulmonary hypertension* (SAPH), several pulmonary hypertension agents have been studied. Table 93.6 lists some of the studies that were specifically designed to determine the efficacy of treatment, including the prostanoids, including intravenous prostacyclin (epoprostenol)[363,364] and inhaled iloprost.[365] Long-term use of intravenous epoprostenol was associated with prolonged clinical improvement in some cases.[363] The endothelin-receptor antagonists have also been reported to be safe in treating SAPH.[366-368] A double-blind, placebo-controlled study demonstrated significant improvement of pulmonary hemodynamics for SAPH patients treated with bosentan but not for those treated with placebo.[369] Sildenafil has also been shown to improve hemodynamics in patients with SAPH.[370]

For several of the studies cited in Table 93.6, the response to treatment for SAPH was in pulmonary hemodynamics and/or quality of life.[365,366,370] In part, that was because the studies examined patients only after a relatively short period, usually 4 months. In one study that evaluated SAPH patients after more prolonged therapy, there was not only improvement in hemodynamics, but also improvement in 6MWD.[367] However, that improvement in 6MWD was seen only in patients with mild to moderate restrictive disease and was unusual in patients with an FVC of less than 50% of predicted value. In one large series, SAPH treatment usually improved hemodynamics, but it did not improve 6MWD.[230]

FATIGUE

As noted earlier, fatigue is a common manifestation of sarcoidosis.[217] Fatigue can be associated with several factors, including diabetes, depression, sleep apnea, and corticosteroid withdrawal.[371,372] Sleep apnea is a common problem in sarcoidosis patients, especially those patients who have been treated with glucocorticoids.[372-374] However, even after treatment of sleep apnea, fatigue may persist.[375]

The neurostimulants such as methylphenidate appear to be effective in treating sarcoidosis-associated fatigue.[376] The benefits associated with treatment of fatigue should always be weighed against the risks associated with the side effects of neurostimulants. In a double-blind, placebo-controlled crossover trial of d-methylphenidate, sarcoidosis-associated fatigue was 30% lower during active treatment versus placebo.[221] A limitation of methylphenidate is the short half-life of the drug that often requires an afternoon dose, which may lead to insomnia. Long-acting preparations of methylphenidate may be preferred for this reason. Armodafinil is a neurostimulant-like drug. In a double-blind, placebo-controlled crossover trial, armodafinil was found to reduce fatigue significantly more than placebo.[375]

SMALL FIBER NEUROPATHY

Small fiber neuropathy is common with sarcoidosis,[377] and there is a relationship between small fiber neuropathy and fatigue.[378] Several agents have been used with varying success in sarcoidosis-associated small fiber neuropathy. Although drugs for neuropathic pain are often the initial medications of choice, these agents have limited efficacy, and anti-TNF therapy and intravenous gamma globulin have been found to be more effective.[377,379]

MYCETOMA

Fungal infections, especially aspergillomas, are complications of advanced fibrotic sarcoidosis usually associated with immunosuppressive therapy.[6,187,380-382] Aspergillomas may be associated with fatal hemoptysis. The risks and benefits of medical and surgical therapy vary with the manifestations of disease and the patient's pulmonary status. Therefore, the approach to therapy must be individualized. For the acute management of massive hemoptysis, bronchial artery embolization may be effective, at least in the short term.[383] In patients with good pulmonary function, surgical resection is offered to prevent or treat potentially life-threatening hemoptysis, and it is usually curative. The

medical treatment of aspergillomas includes azole therapy.[6,384,385] The evidence regarding the efficacy of long-term antifungal therapy for chronic cavitary pulmonary aspergillosis is based on small case series and open-label, noncomparative studies.[384,386] Limited data suggest that intracavitary amphotericin may be effective on a short-term basis in treating selected cases of aspergillomas in sarcoidosis patients.[387]

BONE HEALTH

Because sarcoidosis patients often have high levels of 1,25-$(OH)_2$ vitamin D_3 there usually is no reason for supplementation of vitamin D.[388] However, osteopenia or osteoporosis may improve with bisphosphonates.[389]

Key Points

- Sarcoidosis is characterized by an enhanced granulomatous response to an unknown antigen or antigens, although autoimmunity related to molecular mimicry may also be involved.
- Although many patients with sarcoidosis have resolution of their disease within 2 years, a significant proportion will have chronic disease—with roughly a quarter of all patients still requiring systemic therapy more than 2 years after diagnosis.
- The diagnosis of sarcoidosis relies on recognition of a clinical pattern consistent with disease, exclusion of other conditions that can cause granulomatous inflammation and, in most cases, a biopsy demonstrating granulomas.
- Identification of extrapulmonary disease is important not only to identify other potential causes of morbidity in sarcoidosis but also to help bolster confidence in the diagnosis.
- Quality of life and functional status are more important issues for patients than quantitative measures of organ function. Fatigue, chest discomfort, and depression are conditions that lead to poor quality of life for patients with chronic sarcoidosis.
- Systemic treatment of sarcoidosis, usually initially with glucocorticoids, is indicated when the patient has symptoms. Steroid-sparing agents are most useful for patients with chronic disease or those encountering toxicity with glucocorticoids.
- Treatment of sarcoidosis also includes therapy for any nongranulomatous aspects of disease, including fatigue, small fiber neuropathy, and pulmonary hypertension.

Key Readings

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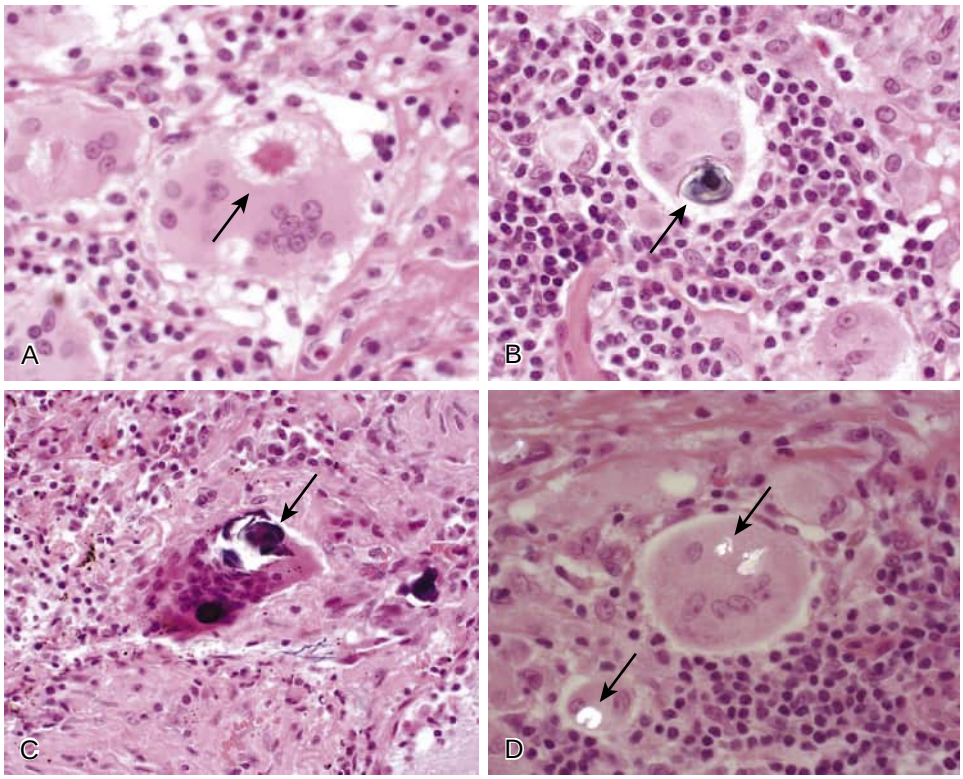
Complete reference list available at ExpertConsult.com.

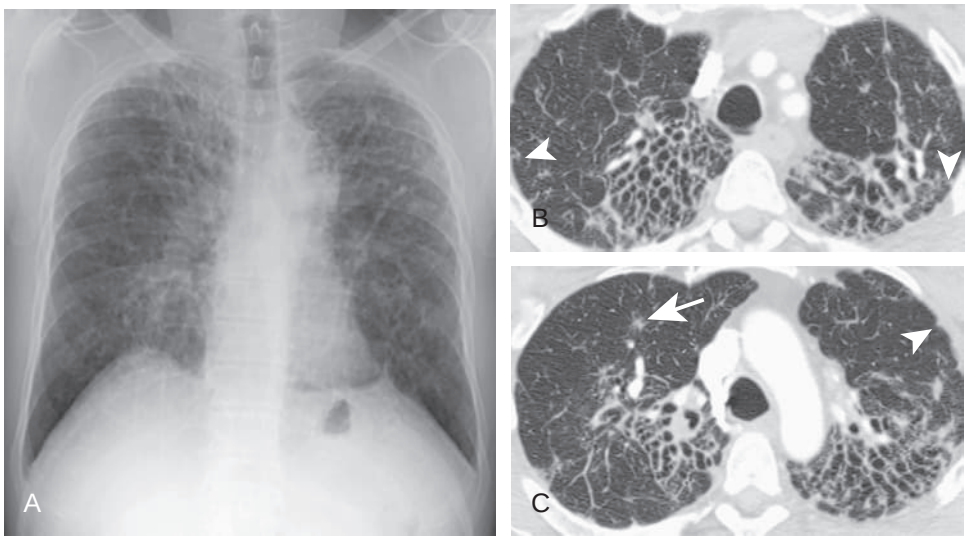
eFIGURE IMAGE GALLERY



eFigure 93.1 Sarcoidosis. Multinucleate giant cells characteristically are present, often accompanied by a variety of distinctive (but not specific) cytoplasmic inclusions. (A) Asteroid body. (B) Schaumann body. (C) Schaumann (conchoidal) bodies. (D) Schaumann body in polarized light. (Modified from Leslie KO, Wick MR. *Practical Pulmonary Pathology: A Diagnostic Approach.* 2nd ed. Philadelphia: Elsevier; 2011.)



eFigure 93.2 Erythema nodosum. Tender red nodules or lumps, usually seen on both shins, are caused by inflammation of the fat cells under the skin.



eFigure 93.3 Sarcoidosis: Scadding stage 4. (A) Frontal chest radiograph in a patient with advanced lung parenchymal fibrosis related to sarcoidosis shows extensive upper lobe linear and reticular opacities associated with architectural distortion, again without significant pleural abnormality. Nodular interstitial thickening is also evident. (B–C) Axial chest computed tomography in lung windows shows extensive biapical traction bronchiectasis with peribronchovascular interstitial thickening *(arrow)* and perifissural nodularity *(arrowheads)*. (Courtesy Michael B. Gotway, MD.)

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94 DIFFUSE ALVEOLAR HEMORRHAGE

MARVIN I. SCHWARZ, MD • SCOTT MATSON, MD

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INTRODUCTION

Diffuse alveolar hemorrhage (DAH) is a life-threatening condition characterized by widespread intra-alveolar hemorrhage originating from the pulmonary microcirculation (arterioles, capillaries, and venules). DAH can arise as a complication of many disease states and often as the initial manifestation. Unlike the more common forms of pulmonary bleeding resulting from focal lesions (e.g., necrotizing pneumonia, bronchitis, bronchiectasis, malignancy, pulmonary infarction, arteriovenous malformation), DAH involves the majority of the alveolar capillary surface. DAH is a medical emergency that often results in acute respiratory failure and death. Pulmonologists must be prepared to identify DAH promptly, diagnose the underlying disease causing it, and institute appropriate medical therapy. DAH is defined on clinical grounds, including radiographic findings of diffuse pulmonary opacities, varying degrees of respiratory failure, a falling hemoglobin level, and progressively bloody return (increasing red blood cell counts) on sequential *bronchoalveolar lavage* (BAL) specimens.

CLASSIFICATION

There is no consensus classification schema for DAH, although clinical, histopathologic, and etiologic approaches have all been suggested.[1,2] One approach is presented here (Table 94.1). The various causes of DAH are diverse; any source of injury to the alveolar microcirculation may contribute. The most common causes of DAH are the systemic vasculitides, in particular *granulomatosis with polyangiitis* (GPA) (Fig. 94.1). Other vasculitides are also implicated, including *microscopic polyangiitis* (MPA) and isolated pulmonary capillaritis. A review of 34 cases of DAH found that vasculitis accounted for about one-half of the cases, followed by *anti–glomerular basement membrane disease* (anti-GBM disease, formerly Goodpasture syndrome) (13%), *idiopathic pulmonary hemosiderosis* (IPH; 13%), and connective tissue disease (13%).[3]

CLINICAL PRESENTATION

The clinical presentation of DAH includes hemoptysis, alveolar opacities on chest radiograph, and anemia.[1] However, some cases show only one or two of these features; the absence of classic features does not exclude DAH. In up to 33% of cases, hemoptysis is initially absent.[4] Other symptoms are nonspecific (e.g., dyspnea, cough, chest pain, fever), although, in some cases, disease-specific symptoms (e.g., sinusitis, rash, arthritis) may be present. In general, symptoms are usually of short duration, manifest from days to several weeks, and may be recurrent. The lung examination is nonspecific, with inspiratory crackles common but not universal. There may also be physical findings suggesting a systemic disease.

LABORATORY FINDINGS

Laboratory evaluation usually reveals anemia and leukocytosis. Serum creatinine levels may be elevated. BAL reveals a bloody return that, with each aliquot obtained from the same location, becomes progressively bloodier (Fig. 94.2). BAL shows increased sequential red blood cell counts even in patients who do not report hemoptysis. The reason for this increasing red blood cell count is not known, but it may be caused by increased sampling with each aliquot of the bleeding at the most distal area of the lung; bleeding at a more proximal site (e.g., bronchial bleeding) may instead be diluted with each aliquot. On examination of the BAL sediment, there is a predominance of red blood cells and hemosiderin-containing macrophages.

RADIOLOGIC FEATURES

The chest radiograph in DAH shows varying degrees of diffuse alveolar opacities (Fig. 94.3; see also eFigs. 87.3A,

Table 94.1 Causes of Diffuse Alveolar Hemorrhage

VASCULITIS
Granulomatosis with polyangiitis
Microscopic polyangiitis
Eosinophilic granulomatosis with polyangiitis
Isolated pulmonary capillaritis
Mixed cryoglobulinemia
Behçet syndrome
Henoch-Schönlein purpura
Pauci-immune glomerulonephritis
Antiphospholipid antibody syndrome
IMMUNOLOGIC DISORDERS
Anti-GBM disease (Goodpasture syndrome)
Connective tissue disease associated
Immune complex–associated glomerulonephritis
Acute pulmonary allograft rejection
COAGULATION DISORDERS
IDIOPATHIC PULMONARY HEMOSIDEROSIS
OTHER CAUSES
Drugs and toxins
Diffuse alveolar damage
Mitral stenosis
Pulmonary veno-occlusive disease
Pulmonary capillary hemangiomatosis
Lymphangioleiomyomatosis/tuberous sclerosis

GBM, glomerular basement membrane.

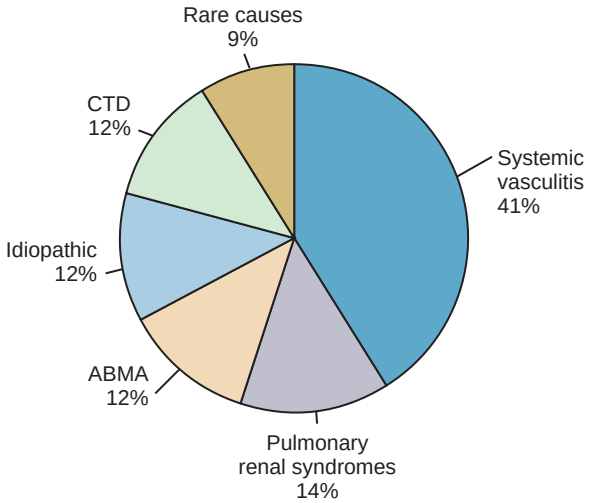

Figure 94.1 Causes of diffuse alveolar hemorrhage. A retrospective review of 34 cases of diffuse alveolar hemorrhage found systemic vasculitis to be the most common cause (14 cases: 5 definite granulomatosis with polyangiitis, 6 probable, and 3 unclassifiable), followed by unclassifiable pulmonary renal syndromes (5 cases), anti–glomerular basement membrane disease (Goodpasture syndrome; 4 cases), idiopathic (4 cases), *connective tissue disease* (CTD; 4 cases: 2 systemic lupus erythematosus, 1 rheumatoid arthritis, 1 juvenile rheumatoid arthritis), and other rare causes (3 cases: 2 idiopathic glomerulonephropathy, 1 immunoglobulin A nephropathy). ABMA, anti–glomerular basement membrane antibody. (Data from Travis WD, Colby TV, Lombard C, Carpenter H. A clinicopathologic study of 34 cases of diffuse pulmonary hemorrhage with lung biopsy confirmation. *Am J Surg Pathol.* 1990;14:1112–1125.)

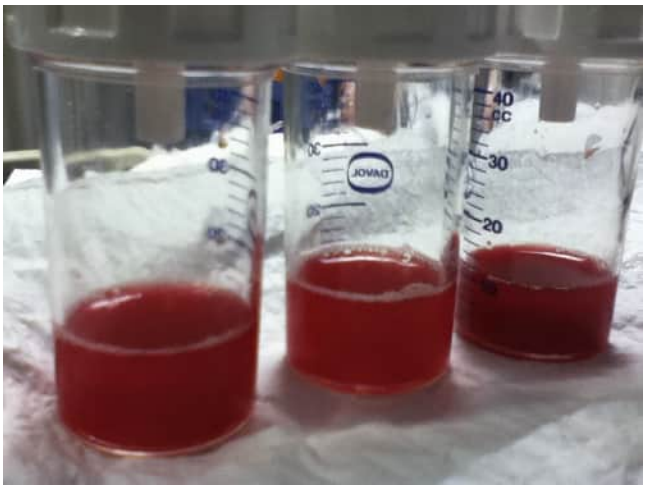

Figure 94.2 Sequential bronchoalveolar lavage specimens showing increasing bloody appearance diagnostic of diffuse alveolar hemorrhage. These bronchoalveolar lavage specimens, sequential in order from left to right, were obtained from the same location of the lung in a patient with granulomatosis with polyangiitis. (Courtesy Dr. Sixto Arias, Johns Hopkins University.)

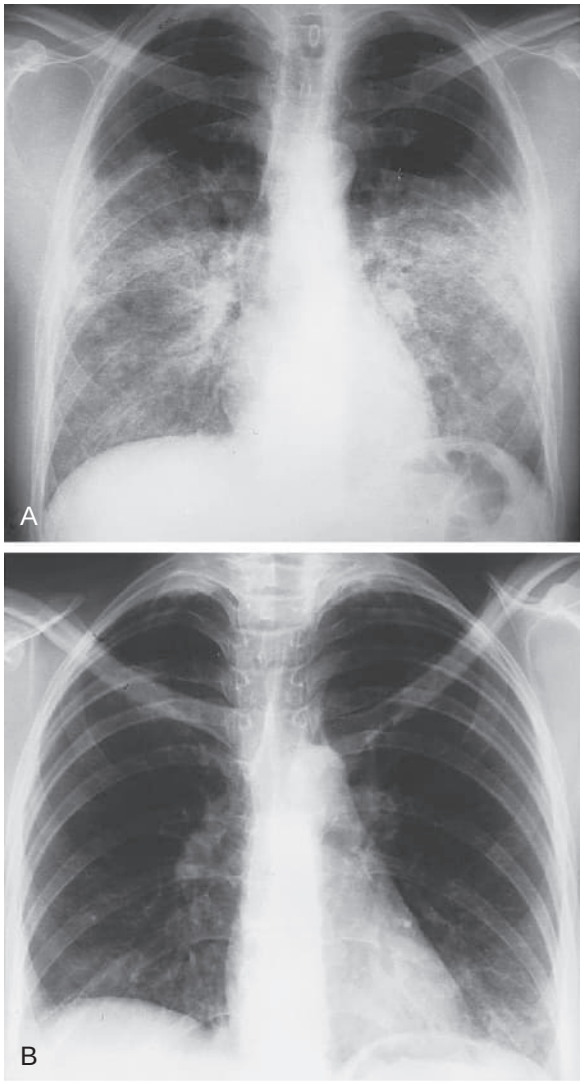

Figure 94.3 Diffuse alveolar hemorrhage. Chest radiographs show diffuse alveolar opacities in a patient with microscopic polyangiitis (A) and in a patient with granulomatosis with polyangiitis (B).

87.9A, and 87.10A).[5] *High-resolution computed tomographic* (HRCT) imaging is more sensitive for radiographic abnormalities and generally shows bilateral ground-glass opacities or patchy consolidation and occasionally centrilobular nodules. Nonetheless, it is important to recognize that the HRCT appearance of pulmonary hemorrhage is variable and not specific for a particular cause or for DAH itself (Fig. 94.4; see also eFigs. 87.3B–E, 87.9B–E, and 87.10B–E, and Fig. 125.4). With recurrent and chronic disease, reticulation may appear, providing evidence of interstitial fibrosis. Interlobular septal thickening (Kerley B lines) (eFig. 94.1) may occasionally be present in cases of mitral stenosis and *pulmonary veno-occlusive disease* (PVOD).

PHYSIOLOGIC FEATURES

When measured, there are features of a restrictive lung disease with gas exchange abnormalities. In acute DAH, an increase in the diffusing capacity for carbon monoxide can be present, attributed to the increased binding of carbon monoxide to intra-alveolar hemoglobin.[6] This will generally resolve in 48 to 72 hours, as hemoglobin is degraded

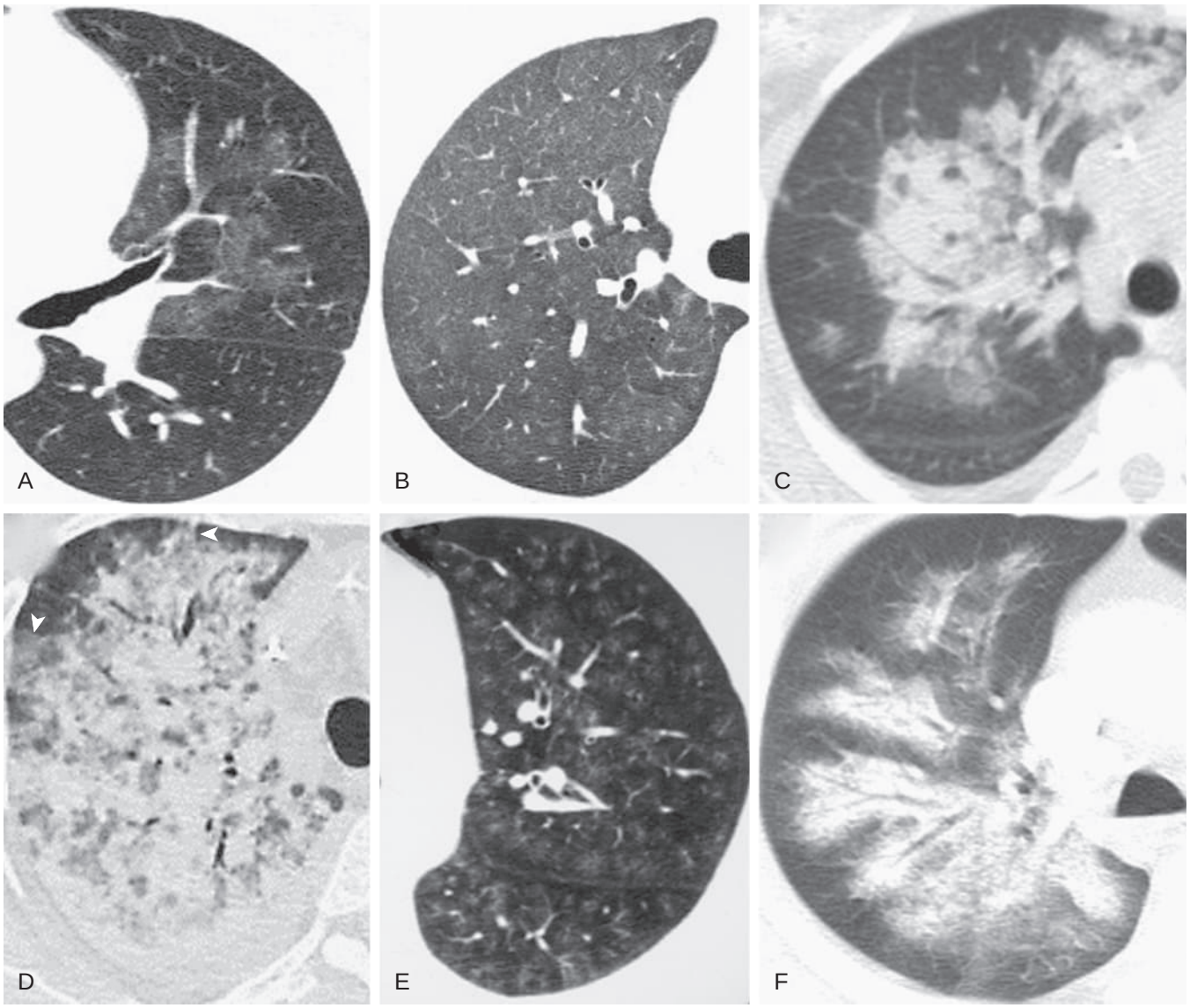

Figure 94.4 High-resolution computed tomographic appearance of diffuse alveolar hemorrhage. Axial chest computed tomographic images in different patients with various causes of diffuse alveolar hemorrhage showing the variable computed tomographic manifestations of pulmonary hemorrhage. The features of diffuse alveolar hemorrhage on high-resolution computed tomography are nonspecific and can be seen with any cause. (A) Patchy, geographic ground-glass opacity in a patient with granulomatosis with polyangiitis. (B) Vague, extensive multifocal ground-glass opacity in a patient with systemic lupus erythematosus. (C) Dense consolidation with air bronchograms in a patient with microscopic polyangiitis. (D) Consolidation and ground-glass opacity with a background of linear opacities representing interlobular septal thickening (*arrowheads*) in an overly anticoagulated patient undergoing antiplatelet therapy. (E) Hazy ground-glass opacity in a patient with hemosiderin-laden macrophages on bronchoalveolar lavage, with presumed idiopathic pulmonary hemosiderosis. (F) Extensive peribronchovascular thickening and peribronchial consolidation and ground-glass opacity in a patient with granulomatosis with polyangiitis. Solid centrilobular nodules can also be manifestations of pulmonary hemorrhage. (Courtesy Michael B. Gotway, MD.)

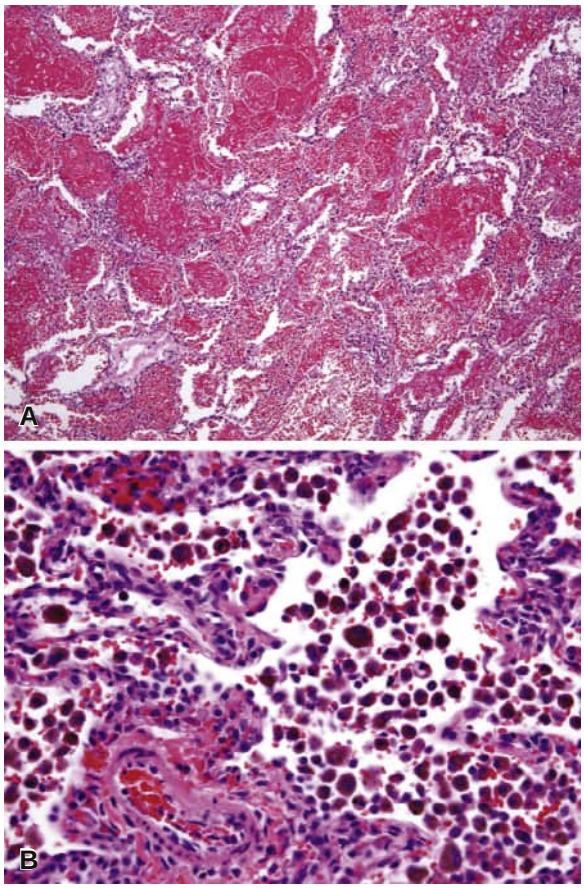

Figure 94.5 Histopathologic findings of diffuse alveolar hemorrhage. (A) In acute diffuse alveolar hemorrhage, the alveoli show filling and distention by red blood cells admixed with fibrin. (B) Chronic alveolar hemorrhage shows numerous hemosiderin-filled macrophages within air spaces. The alveolar septa may show mild fibrosis. (Courtesy Dr. Kirk Jones, University of California, San Francisco.)

into hemosiderin.[7] Varying degrees of hypoxemia result from the ventilation-perfusion abnormalities produced by the alveolar hemorrhage, and patients often require ventilatory support.

HISTOPATHOLOGIC FEATURES

The pathologic process is characterized by the intra-alveolar accumulation of erythrocytes (Fig. 94.5). There is often histologic evidence of previous bleeding represented by the accumulation of intra-alveolar hemosiderin-containing macrophages, erythrophagocytosis, and loci of free interstitial hemosiderin,[3,8,9] findings that help distinguish DAH from acute biopsy-related bleeding. Other histologic features of DAH include hyperplasia of the alveolar epithelial type 2 cells, intra-alveolar organization as seen in organizing pneumonia, mononuclear cell infiltration of the alveolar interstitium, and small thrombi in the alveolar capillaries and venules.[3,8–11]

Patients with DAH may demonstrate neutrophilic inflammation of the alveolar interstitium known as pulmonary or alveolar capillaritis (Fig. 94.6).[12] Capillaritis represents a small vessel vasculitis of the lung and is central to the pathogenesis of many cases of DAH. The

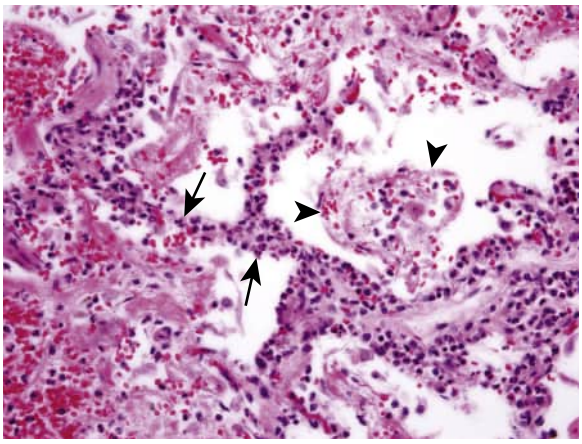

Figure 94.6 Histopathologic findings of diffuse alveolar hemorrhage accompanied by pulmonary capillaritis. Capillaritis is identified by accumulation of neutrophils (*arrows*) within alveolar septa with accompanying fibrinoid necrosis and adherent alveolar fibrin within air spaces (*arrowheads*). (Courtesy Dr. Kirk Jones, University of California, San Francisco.)

small vessel injury and necrosis lead to the loss of integrity of the shared epithelial-endothelial alveolar basement membrane, resulting in endothelial edema, injury, localized fibrinoid necrosis, and extravasation of red blood cells into the alveolar lumina.[10] Characteristically, there is infiltration of the alveolar septa with neutrophils, many of which are undergoing leukocytoclasis and appear fragmented and pyknotic. Fragmentation of these cells leads to accumulation of nuclear dust in the lung parenchyma.

The pathogenesis of DAH due to capillaritis is thought to result from one of the following scenarios: (1) the direct effects of autoantibodies on the alveolar capillary endothelium, as in GPA or MPA; (2) the effects of antibody directed against the alveolar basement membrane (e.g., anti-GBM disease); (3) immune complex–mediated injury (e.g., *systemic lupus erythematosus* [SLE], Henoch-Schönlein purpura); or (4) direct alveolar injury.[13]

DAH can also result from all causes of *diffuse alveolar damage* (DAD) (i.e., cytotoxic drug, allogeneic [bone marrow transplantation]) as well as from bland (noninflammatory) injuries (i.e., mitral stenosis, coagulation disorders).

DIAGNOSIS OF DIFFUSE ALVEOLAR HEMORRHAGE

The diagnostic considerations for patients presenting with DAH are broad. A thorough history and physical examination looking for evidence of potential associated conditions (e.g., connective tissue disease, symptoms/signs of systemic vasculitis, anticoagulant medications) are essential, and initial studies should include an HRCT scan of the chest, complete blood count, and examination of the urine sediment. If DAH is suspected, fiberoptic bronchoscopy should be performed immediately.

Bronchoscopy with BAL is essential to the accurate identification of DAH. Sequential BAL specimens should be obtained and sent for cell count and differential, with an increasing red blood cell count considered consistent with the diagnosis. BAL specimens should be obtained after

the bronchoscope is wedged into a terminal bronchus; the selection of site does not matter because this is a diffuse condition throughout all segments of the lung. Sterile saline is then instilled through the bronchoscope in 30- to 60-mL aliquots to achieve a 20-mL return after each instillation. Qualitative evaluation by the performing clinician can often differentiate those samples, which become progressively bloodier, and is adequate to diagnose DAH. However, samples can also be sent in the nonheparinized sample tubes to the laboratory to evaluate cell counts in each sample to determine the degree or presence of serial red blood cell elevation in the samples.

Quantitative scoring of the hemosiderin concentration in alveolar macrophages obtained by BAL cytologic examination also has sensitivity for the diagnosis of DAH.[14] Importantly, BAL serves to rule out other diagnostic considerations such as infection, acute eosinophilic pneumonia, and pulmonary alveolar proteinosis.

DIAGNOSIS OF UNDERLYING ETIOLOGY

Once DAH is identified, the underlying cause is sought. Table 94.2 summarizes the differential clinical and laboratory features of some of the more common causes of DAH. In some cases, the cause is clear (e.g., history of SLE, drug exposure). In others, a detailed laboratory evaluation is required.

The presence of proteinuria and abnormal urinary sediment (red blood cells and red blood cell casts) suggests underlying glomerulonephritis consistent with the diagnosis of systemic vasculitis, anti-GBM disease, connective tissue disease or, rarely, infection.[15]

Vasculitis is often associated with the presence of *antineutrophil cytoplasmic antibodies* (ANCAs) directed against either proteinase 3 (*cytoplasmic ANCA* [c-ANCA]) or myeloperoxidase (*perinuclear ANCA* [p-ANCA]).[16] Elevation of the c-ANCA level is seen in GPA, whereas elevation of p-ANCA is seen with MPA, pauci-immune glomerulonephritis, eosinophilic GPA, and sometimes isolated pulmonary capillaritis.[17]

The diagnosis of anti-GBM disease is established by the presence of serum anti-GBM antibodies. DAH caused by SLE is accompanied by reduced serum complement levels as well as the presence of antinuclear and native anti-DNA antibodies in the serum. Henoch-Schönlein purpura is characterized by the formation of immunoglobulin A immune complexes present in the circulation and also bound to tissue.[18]

ROLE OF SURGICAL LUNG BIOPSY AND RENAL BIOPSY

To establish the presence of DAH, BAL is generally sufficient. For identifying the underlying cause of the DAH, clinical and confirmatory serologic findings are usually sufficient.[3] Surgical biopsy of the lung may be useful but is often nonspecific; it should be strongly considered when a patient has isolated DAH without an obvious cause because treatment is based on the etiology of the hemorrhage. For patients with DAH without positive serologic findings and with an echocardiogram excluding mitral valve stenosis, a lung biopsy should be strongly considered if the clinical scenario allows. For instance, lung biopsy is required for the diagnosis of isolated pulmonary capillaritis and PVOD, and treatment differs in these conditions.

When serologic findings are equivocal and vasculitis or anti-GBM disease is under consideration, renal biopsy may be appropriate because these conditions are more easily confirmed on renal tissue, even in the absence of clinically apparent involvement.[19] Moreover, renal biopsy may provide useful information regarding the activity and chronicity of renal involvement that may help guide therapy.

Table 94.2 Clinical Differentiation of Common Diffuse Alveolar Hemorrhage Syndromes

Syndrome	Renal	Arthritis	Skin	ANA	dsDNA	C	ABMA	c-ANCA (PR3)	p-ANCA (MPO)	Histopathology; IF
Granulomatosis with polyangiitis	+	+	+	±	±	Nl	–	+	–	Capillaritis; ± granular IF
Microscopic polyangiitis	+	+	+	±	±	Nl	–	–	+	Capillaritis; no IF deposits
Isolated pulmonary capillaritis	–	–	–	–	–	Nl	–	–	±	Capillaritis; no IF deposits
Anti-GBM disease (Goodpasture syndrome)	+	–	–	–	–	Nl	+	–	–	Bland or capillaritis; linear IgG
Systemic lupus erythematosus	+	+	±	+	+	Low	–	–	–	Bland or capillaritis; granular IgG
Idiopathic pulmonary hemosiderosis	–	–	–	–	–	Nl	–	–	–	Bland; no IF deposits

ABMA, anti–glomerular basement membrane antibody; ANA, antinuclear antibody; C, complement; c-ANCA (PR3), cytoplasmic antineutrophil cytoplasmic antibody (anti–proteinase 3); dsDNA, anti–double-stranded DNA antibody; GBM, glomerular basement membrane; IF, immunofluorescence; IgG, immunoglobulin G; Nl, normal; p-ANCA (MPO), perinuclear antineutrophil cytoplasmic antibody (anti-myeloperoxidase).

THERAPEUTIC APPROACH

The first steps in management are to identify the underlying cause and begin specific treatment. Initial treatment may include stopping suspected drugs or exposures, treating infection, and reversing excess anticoagulation. Patients with severe hemoptysis require general supportive therapy based on the degree of bleeding. Finding an underlying capillaritis is paramount because mortality in these groups without appropriate therapy is very high. Picard and colleagues[20] validated a clinical scoring system to evaluate risk for immune-mediated DAH that can help guide early clinical decisions.

Systemic glucocorticoids, with additional immunosuppressive therapy including plasma exchange therapy, are the mainstays of therapy for the DAH syndrome associated with systemic vasculitis, connective tissue disease, anti-GBM disease, and isolated pulmonary capillaritis. The common approach is to begin intravenous pulse methylprednisolone (500 to 1000 mg in divided doses daily) for up to 5 days followed by gradual tapering and then maintenance on an oral preparation. The decision to add immunosuppressive therapy (e.g., cyclophosphamide, azathioprine, or rituximab) is dependent on the severity of the illness, the responsiveness to glucocorticoids, and the underlying disease.

Plasma exchange has typically been used in the treatment of DAH associated with anti-GBM disease, vasculitis syndromes, or connective tissue disease if patients require intensive care unit level care or are initially refractory to intravenous corticosteroid administration.[21–25] The role of intravenous immunoglobulin or rituximab in patients with DAH remains to be defined; however, these therapeutic interventions have been shown to have significant success in patients with SLE-related DAH and rheumatoid arthritis–related DAH.[26–30] Recombinant activated factor VII has been given intravenously, by nebulizer, or via bronchoscopy in refractory DAH with variable success.[31–36]

The role of advanced cardiopulmonary support such as *extracorporeal membrane oxygenation* (ECMO) has been explored successfully in a few patients with DAH. However, the use of ECMO in this disease state remains controversial given the need for anticoagulation in current ECMO circuits and the subsequent risk of worsening the underlying hemorrhage. Several centers have reported their success in treating refractory DAH with typical ECMO circuits.[37,38] Of note, a single center reported their experience supporting a patient with DAH in a circuit without systemic anticoagulation.[39] Given the reversibility of many of the causes of DAH, ECMO as a supportive measure or salvage therapy should be considered early in the disease course, and clinicians should facilitate transfer of patients with life-threatening DAH to ECMO-capable centers.

SPECIFIC CAUSES

VASCULITIS (See Chapter 87)

Granulomatosis With Polyangiitis

GPA is a systemic vasculitis that commonly involves the upper and lower respiratory tracts and kidneys. Other organs (e.g., eyes, skin) may be involved. The typical histologic features of GPA are granulomatous inflammation, small and medium vessel vasculitis, and parenchymal necrosis in a geographic pattern (e.g., involving areas sharply demarcated from other uninvolved areas). DAH secondary to pulmonary capillaritis can either complicate an established case of GPA or represent the initial manifestation of the disease. Surgical lung biopsy specimens from 87 patients with GPA revealed pulmonary capillaritis in 31%, but only in three patients was it an isolated finding.[11] In another series, capillaritis was present in 17% of 35 patients, but never as an isolated finding.[40] In a postmortem study of 22 patients, capillaritis was the sole histologic feature in three patients and was seen in conjunction with the more typical granulomatous vasculitis in seven cases.[41] When DAH is present alone (see eFig. 87.3), without the characteristic histologic features, sinusitis (see eFig. 87.7), or nodular or cavitary lung lesions (see eFigs. 87.1, 87.2 and 87.4), differentiation from MPA is difficult.

The specific diagnosis depends on the ANCA pattern, with c-ANCA suggesting the diagnosis of GPA. If the cytoplasmic pattern of ANCA immunofluorescence is present, most laboratories will perform reflex testing for the specific *immunoglobulin G* (IgG) class ANCA directed at the proteinase 3 of neutrophils and monocytes because proteinase 3 positivity is also more typical of GPA.[42] The characteristic histologic and clinical features of GPA may appear months to years after the initial presentation of DAH and capillaritis.[43]

Alveolar hemorrhage is often subclinical and recurrent in GPA (as well as in MPA), suggested by the presence of hemosiderin-laden macrophages on BAL. This pattern of frequently recurring DAH is more typical of the ANCA-associated vasculitides and SLE than of nonvasculitic diseases such as rheumatoid arthritis.[44]

More than 40 cases of GPA with only DAH and pulmonary capillaritis without the other features of GPA have been described. Early mortality is 37% and is most often the result of acute respiratory or renal failure.[11,40,41,43,45,46] Renal disease in the form of focal segmental necrotizing glomerulonephritis (Fig. 94.7), cutaneous leukocytoclastic vasculitis, and arthritis often accompanies the DAH.

Treatment with high-dose corticosteroids and cyclophosphamide or rituximab has been the recommended

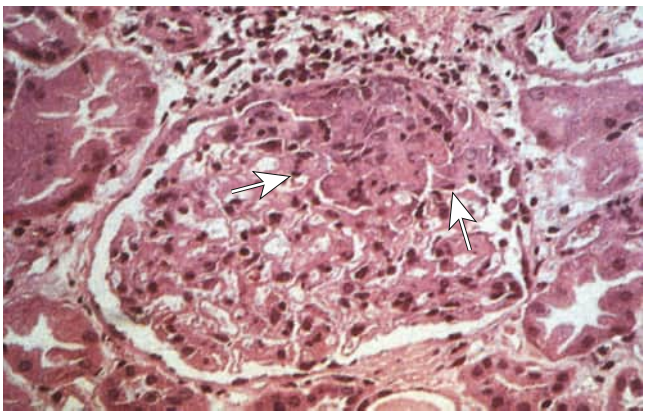

Figure 94.7 Granulomatosis with polyangiitis. Histopathologic findings of a renal biopsy specimen demonstrate focal segmental necrotizing glomerulonephritis. The focal lesion represents an area of fibrinoid necrosis (*arrows*) (×40 original magnification).

initial therapy for GPA with DAH.[47–52] Therapeutic plasma exchange is typically initiated for patients with DAH with impaired oxygen exchange or patients requiring mechanical ventilation, as well as cases of GPA with renal failure, typically followed by rituximab therapy.[22–25] In a large randomized controlled trial of plasma exchange for induction therapy in ANCA-associated vasculitis with renal disease, plasma exchange was not associated with benefit.[53] However, because this trial was not expressly designed to evaluate the role of plasma exchange in ANCA-associated pulmonary hemorrhage, plasma exchange remains a mainstay of therapy in ANCA-associated DAH.[53]Azathioprine may be substituted for cyclophosphamide after remission.[54]

Exacerbations of DAH and other disease manifestations with tapering treatment are to be expected. Disease activity can be monitored by erythrocyte sedimentation rate, ANCA level, serial diffusing capacity for carbon monoxide determination, and microscopic urine examination. As previously stated, in the setting of DAH, the differentiation of GPA from MPA is at times difficult because the clinical presentation, lung histologic features (e.g., capillaritis), and serologic findings can be identical.[55] In fact, the response to treatment and the tendency to recurrence are similar. The differentiation can be established only after the development of the more typical upper airway disease and pathologic features of GPA.

Microscopic Polyangiitis

MPA is distinguished from GPA by the absence of granuloma formation and is typified by a necrotizing vasculitis. When present, it is a frequent cause of pulmonary capillaritis and DAH (see eFig. 87.10).[10,12,43,56–59]

The most consistent pathologic feature in MPA is a focal segmental necrotizing glomerulonephritis, the renal lesion common to all systemic vasculitides. The lungs are involved by capillaritis in 20–30% of cases.[31] The alveolar hemorrhage tends to be severe and is often life-threatening. Other manifestations include fever, weight loss, cutaneous vasculitis, myalgias, arthralgias, diarrhea, and gastrointestinal bleeding from mucosal vasculitis (often visible by direct examination), peripheral neuropathy, and, in a few cases, sinusitis.[59,60,61]

As with other vasculitides, the erythrocyte sedimentation rate is elevated, and nonspecific increases of serum rheumatoid factor and antinuclear antibody levels are possible. Although circulating immune complexes are present in 45% of cases, tissue localization of these complexes is difficult to detect (i.e., pauci-immune). Anti-DNA antibodies and hypocomplementemia, findings suggestive of SLE, are absent. A positive serum p-ANCA result supports the diagnosis, and serology is typically notable for positivity to ANCA myeloperoxidase.[42] Antibodies to hepatitis B and C antigens are present in 33% of cases.[62]

Treatment consists of either oral or intravenous corticosteroids combined with cyclophosphamide or rituximab.[54,47–52] Adjuvant treatment with therapeutic plasma exchange is recommended for patients with MPA who are experiencing hypoxemic respiratory failure or renal failure.[59,53] In one reported case of uncontrolled DAH, intravenous factor VIIa was used successfully with dramatic effects.[63]

Outcome with early initiation of therapy for MPA is generally good, with a 65% rate of 5-year survival. However, the presence of DAH contributes to an early mortality rate of 25%.[10,12,43,56–59] There is a tendency to recurrence with tapering of the medications.

The transition to pulmonary fibrosis and restrictive ventilatory impairment after recurrent DAH has been described,[7] and fibrotic lung disease has been reported as the presenting manifestation of MPA.[64] There have been three cases of persistent, severe, irreversible airway dysfunction after recurrent episodes of DAH that complicated MPA.[65]

Isolated Pulmonary Capillaritis

Isolated pulmonary capillaritis is a small vessel vasculitis confined to the lungs and without concomitant systemic involvement.[66] There are two forms: one with serum p-ANCA positivity and the other without positive serologic testing.[66,67] In one series, the latter type was the most frequent cause of pulmonary capillaritis and DAH.[66] In that series, results of direct immunofluorescence studies of the lungs in these patients were negative (pauci-immune). Although respiratory failure necessitating ventilator support was frequent, response to corticosteroids and cyclophosphamide was good, and only one of eight patients died. Recurrences appeared in two subjects. In another series, patients with biopsy-proven isolated pulmonary capillaritis were followed for a median duration of 116 months; during that follow-up period, no clinical or serologic evidence for a systemic vasculitis or connective tissue disease appeared, and all patients achieved remission following immunosuppressive therapy.[68] There have been case reports of successful treatment of this condition with rituximab after failure of traditional glucocorticoid and cyclophosphamide regimens.[69]

Isolated forms of pulmonary capillaritis causing DAH must be distinguished from IPH, which is not associated with pulmonary capillaritis, as well as from lung-limited forms of anti-GBM disease, initial presentations of a collagen vascular disease, primary antiphospholipid antibody syndrome, and mitral stenosis. Thus, all patients who present with unexplained DAH should have an echocardiogram and, if possible, undergo surgical lung biopsy to differentiate these possible causes.

Mixed Cryoglobulinemia

Mixed cryoglobulinemia is a systemic vasculitis recognized by the presence of purpura, arthritis, hepatitis, and glomerulonephritis. It is thought to be an immune complex–induced disease, with most cases linked to hepatitis C (and less commonly hepatitis B) viral infection. Cutaneous vasculitis appearing as raised purpura is the clinical hallmark of this disease. Histologically, a perivascular polymorphonuclear infiltration with tissue extravasation and fragmentation in the dermis termed leukocytoclastic vasculitis are noted. The renal disease is a proliferative glomerulonephritis with positive granular immunofluorescence. Interstitial lung disease consisting of inflammation and fibrosis of the alveolar walls is the most common pulmonary manifestation.[70] There are two published cases of DAH with pulmonary capillaritis that complicated mixed cryoglobulinemia.[71,72] DAH associated with mixed cryoglobulinemia is treated with an immunosuppressive strategy combining

high-dose steroids with intravenous rituximab, which has shown efficacy in treating the underlying condition.[31,73,74]

Behçet Syndrome

Behçet syndrome is a chronic relapsing illness characterized by oral and genital ulceration, iridocyclitis, thrombophlebitis, and a multisystem disease consisting of a cutaneous vasculitis, arthritis, and meningoencephalitis.[72] Immune complexes have been identified in the serum of active cases as well as in the lung and other organs.[75,76]

The thorax is involved in 5–10% of cases of Behçet syndrome. The pulmonary disease is typically a small vessel vasculitis affecting capillaries, venules, and arterioles. The renal disease is a focal segmental necrotizing vasculitis, as is seen in other systemic vasculitides. Immune complexes composed of IgG and complement have been identified in small pulmonary vessels in several cases.[75,76] In addition to alveolar hemorrhage, involvement of larger vessels can lead to aneurysms of the pulmonary (eFig. 94.2) and bronchial arteries, the latter potentially eroding into bronchi, thereby causing massive pulmonary hemorrhage and death.[77,78] Another potential cause of pulmonary hemorrhage in Behçet syndrome is pulmonary arterial occlusion with infarction.[76] A review of 28 cases of pulmonary involvement in Behçet syndrome emphasized two points: pulmonary signs and symptoms consisting of cough, hemoptysis, chest pain, and fever were more common in men than in women, and 39% of patients died of pulmonary hemorrhage, usually within 6 years of the first episode of hemoptysis.[79] Other studies have confirmed the seriousness of this complication regardless of its cause.[77,78] Treatment consists of corticosteroids and immunosuppressive therapy.[80] Treatment with intravenous anti–tumor necrosis factor therapy has shown dramatic results in case reports and is supported in systemic manifestations of Behçet syndrome by European society guidelines.[81,82]

Henoch-Schönlein Purpura

Henoch-Schönlein purpura, primarily a disease of children, can also be seen in adults.[83] Adults typically present with palpable purpura caused by leukocytoclastic vasculitis and glomerulonephritis.[18] The joints and gastrointestinal tract are commonly involved. Pulmonary involvement is unusual. In several large series, pulmonary disease, except for transient chest radiographic opacities, was not mentioned.[18] There have been documented cases of DAH with pulmonary capillaritis in patients with Henoch-Schönlein purpura.[84–86] In one case, immunoglobulin A immune complexes were present in the alveolar septa.[84] It is postulated that immunoglobulin A immune complexes, which are present in the serum and kidneys of these patients, are responsible for the tissue damage that results in the clinical syndrome.[87] Corticosteroids were used in both cases and are generally recommended.

Pauci-Immune Glomerulonephritis

Pauci-immune glomerulonephritis is one of three types of vasculitides with renal predominant manifestations associated with DAH (the other two being immune complex–mediated glomerulonephritis and anti-GBM disease). Pauci-immune glomerulonephritis lacks any immunoreaction product (i.e., no antibody is detected in serum or on histologic examination except for the minimal accumulation of fibrin). The glomerulonephritis is histologically and immunologically similar to that of MPA and GPA and is considered to represent a form of renal-limited vasculitis.[43] Up to 50% of affected patients develop pulmonary capillaritis and DAH, and a smaller number will develop a full-blown systemic vasculitis indistinguishable from MPA. Another indication that pauci-immune glomerulonephritis represents a limited form of vasculitis is the presence of serum p-ANCA. Because clinical manifestations are often limited to the lung and kidney, the disorder can be confused with anti-GBM disease.[43,87] Pauci-immune glomerulonephritis is distinguished by the absence of circulating basement membrane antibodies in the serum and by the negative findings on renal immunofluorescence studies. Treatment with high-dose corticosteroids and immunosuppressive therapy with cyclophosphamide is recommended. In patients who present with hypoxemic respiratory failure or require intensive care unit admission, treatment should also consist of therapeutic plasma exchange given the possibility of an unidentified plasma antibody.[88]

IMMUNOLOGIC DISORDERS

Anti–Glomerular Basement Membrane Disease (Goodpasture Syndrome)

Whether the case reported by Goodpasture in 1919[89] describes the syndrome that bears his name is questionable. He described an 18-year-old man who died 6 weeks after an influenza infection and was found to have DAH, pleuritis, glomerulonephritis, splenic infarctions, and vasculitis of the small intestines. In 1965, an *anti–glomerular basement membrane antibody* (ABMA)—now identified as an antibody against the NC1 domain of the α3 chain of type IV collagen—was identified in the kidneys and lungs of some patients with DAH and glomerulonephritis.[90,91] The diagnosis of anti-GBM disease is reserved for cases of DAH and glomerulonephritis in which this antibody appears in the serum and is seen to bind to kidney and/or lung basement membranes in a linear manner by immunohistochemical staining.[43,92]

The level of ABMA is not generally considered an accurate index of disease activity, although higher levels have been associated with more severe renal disease. In 60–80% of cases, the lung and renal disease appears simultaneously; in 5–10%, only the lung is affected; and in the remainder, renal disease exists by itself.[93,94] It is clear that ABMA is pathogenic; however, the stimulus for its production remains unknown. The clinical onset of anti-GBM disease has been temporally related to infection with influenza A2 as well as other respiratory infections, hydrocarbon exposure, and tobacco use.[95–97] The presence of histocompatibility human leukocyte antigens DRw2 and B7 (90% and 60%, respectively) in patients with anti-GBM disease indicates that susceptible individuals are predisposed to disease.[98,99] In some experimental models, the introduction of ABMA produced renal but not pulmonary disease; for the antibody to deposit in the lung, an additional injury was required that increased alveolar-capillary permeability.[100,101]

Men are more commonly affected (60–80% of patients), with the highest incidence between the ages of 20 and

30 years.[102,103] In older patients, the sex distribution is equal, and the disease tends to be limited to the kidney.[96] Interestingly, DAH is more common in patients who smoke.[96] The alveolar permeability is increased in most smokers, which is thought to be an important factor leading to DAH.[95] In one study, 100% of smokers with anti-GBM disease developed both DAH and glomerulonephritis, whereas only 20% of nonsmokers developed DAH.[96] Resumption of cigarette smoking by patients who are in remission can result in recurrent episodes of DAH. Exposure to volatile hydrocarbons (e.g., petroleum products, turpentine, toluene, and pesticides) is associated with initiation and exacerbations of DAH.[93,94,104,105]

Symptoms most often refer to the lungs and consist of hemoptysis, cough, and dyspnea. Fatigue caused by iron-deficiency anemia and renal failure may predominate. Microscopic hematuria, proteinuria, and increases in the serum creatinine level are often present, but gross hematuria with hypertension is unusual. The diffusing capacity may be increased during periods of active bleeding and is considered to be a useful monitor of new or recurrent DAH.[106] An increase of 30% above baseline is highly suggestive of an intra-alveolar hemorrhage, and this increase may precede pulmonary symptoms or radiographic changes.

Chest radiography often reveals patchy air space abnormalities (eFig. 94.3A–B). Computed tomographic scanning (see eFig. 94.3C) typically shows ground-glass opacities and consolidation and is more sensitive for DAH than is chest radiography.[107]

The usual histologic appearance is bland pulmonary hemorrhage, although pulmonary capillaritis is present in some cases.[105] Alveolar wall necrosis, which is seen with systemic vasculitis, is not a feature of anti-GBM disease. The renal histologic findings consist of a focal segmental necrotizing glomerulonephritis with crescent formation. The major distinction between anti-GBM disease and the other rapidly progressive glomerulonephritides is the presence of an uninterrupted linear deposition of immunoglobulin and complement along the glomerular basement membrane (Fig. 94.8). Identical findings are present on alveolar basement membranes.[108] Even when DAH dominates the clinical picture (i.e., there is no evidence of renal disease), renal biopsy usually reveals the typical linear staining.[109]

If there is no evident renal involvement, DAH responds to oral or intravenous corticosteroids. However, if glomerulonephritis is present, the hemorrhage associated with anti-GBM appears resistant to corticosteroid monotherapy. The combination of therapeutic plasma exchange, corticosteroids, and cytotoxic drugs is effective, particularly in patients who do not have anuria and do not require dialysis.[110–114] The combination of cyclophosphamide or azathioprine with corticosteroids leads to a dramatic fall in circulating ABMA, and oliguric dialysis-dependent subjects have responded to the point at which dialysis could be discontinued.[114,115] However, anuric patients do not respond well to this combination therapy, and dialysis and renal transplantation are often necessary.[115] Case reports of successful treatment of refractory, life-threatening anti-GBM disease with mycophenolate mofetil and rituximab have been reported.[116,117]

The survival rate in anti-GBM disease has improved from 80% mortality at 6 months, with one-half of patients dying of DAH and the rest dying of renal insufficiency, to approximately 50% at 2 years.[103] With the aggressive treatment approach described previously, it is estimated that the 5-year survival rate exceeds 80%, and less than 30% of patients require long-term dialysis. DAH is the usual cause of death, often precipitated by a concomitant infection.[94] There has been spontaneous remission in patients without clinical evidence of renal disease, although this is not usual.[118] The most useful prognostic information comes from the kidney. Clinically, oliguric or anuric renal failure reduces the survival rate to 50% at 6 months. Histopathologically, less than 30% involvement of the glomeruli on biopsy predicts significant therapeutic response and improved survival. When 70% or more of glomeruli have formed crescents in conjunction with renal insufficiency, renal failure is progressive and often unresponsive to therapy, and patients eventually require dialysis.[115]

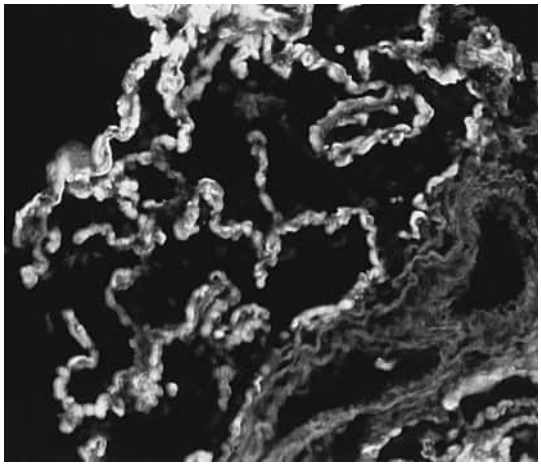

Figure 94.8 Anti–glomerular basement membrane disease (formerly Goodpasture syndrome). Immunofluorescence study demonstrates linear staining of immunoglobulin G in the alveolar walls in a patient with anti–glomerular basement membrane disease (×10 original magnification).

Connective Tissue Disease

Systemic Lupus Erythematosus. Among the connective tissue diseases, SLE is the most common cause of DAH (eFig. 94.4).[43,119–121] It is unusual for DAH to be the initial pulmonary manifestation of SLE; the more common initial manifestation is acute lupus pneumonitis.[122,123] Most patients with DAH have active lupus nephritis.[120] The onset of alveolar hemorrhage can be dramatic, producing severe gas exchange abnormalities and necessitating mechanical ventilation. Reduced complement levels and increased serum titers of serum antinuclear antibodies confirm the diagnosis.

DAH must be distinguished from other causes of hemoptysis in SLE, specifically acute lupus pneumonitis. Acute lupus pneumonitis manifests with fever, cough, and dyspnea and, in 50% of cases, this is the initial manifestation of SLE.[123] It is an inflammatory condition characterized histologically by organizing pneumonia, DAD, cellular nonspecific interstitial pneumonia, and occasionally intra-alveolar hemorrhage. Although hemoptysis may accompany acute lupus pneumonitis, significant reductions of the hemoglobin level are not expected. Unlike in DAH, pleural and pericardial effusions

are common in acute lupus pneumonitis. Other diagnostic considerations in the patient with suspected DAH include infectious pneumonias and pulmonary infarction associated with pulmonary emboli with or without a circulating lupus anticoagulant.[124,125]

Histopathologic examination of the lung in patients with DAH resulting from SLE generally reveals capillaritis, but bland pulmonary hemorrhage and DAD have been described.[123,126] Granular deposits of IgG and complement (C3) are commonly found in the alveolar interstitium and within the walls of intra-alveolar blood vessels (Fig. 94.9).[119,126–128] Capillaritis and immune complex deposition do not necessarily overlap. In one series of four patients with SLE and massive DAH associated with pulmonary capillaritis, only two demonstrated immune complexes by light and electron microscopic techniques.[129]

Treatment of DAH caused by SLE includes high-dose intravenous corticosteroids as well as azathioprine or cyclophosphamide. Rituximab has been shown to be an effective treatment strategy; in some cases, it limits the need for high-dose steroids or other typical chemotherapy regimens.[26–29] Recombinant activated factor VII administered by the local intrapulmonary route may also be an effective treatment option for DAH in patients with SLE.[32] Therapeutic plasma exchange has been combined with chemotherapy in some cases,[22] but its utility is not as clear as in the ANCA-associated vasculitidies.[120,130] Broad-spectrum antibiotic coverage is recommended because of some evidence that infection may trigger the hemorrhage.[120] DAH is associated with a 50% mortality rate in SLE and can be recurrent in survivors.[122,126–129,131] Death is caused by massive hemorrhage, concurrent infection, or renal or central nervous system disease.

Antiphospholipid Syndrome. *Antiphospholipid syndrome* (APS) can manifest as a primary disorder; however, it is commonly seen in the setting of other underlying autoimmune diseases such as SLE. The DAH seen in APS is commonly typified by a diffuse capillaritis (eFig. 94.5)[132]; however, this was seen in only 50% of biopsy specimens in one series.[133] The presence of anticardiolipin antibodies, anti–β_2-glycoprotein 1, and/or a lupus anticoagulant is consistent with APS.[134] The diagnosis of APS is generally made by the presence of one of the aforementioned antibodies in the clinical setting of vascular thrombosis or pregnancy morbidity; however, an atypical manifestation such as DAH may be the initial presenting feature of APS.[135] These patients typically respond to high doses of glucocorticoids, although the role of other steroid-sparing agents or long-term options for remission induction or maintenance remains unclear.[135] DAH in APS remits following corticosteroids in nearly one-half of patients, whereas the other half require a steroid-sparing agent such as cyclophosphamide or rituximab.[133]

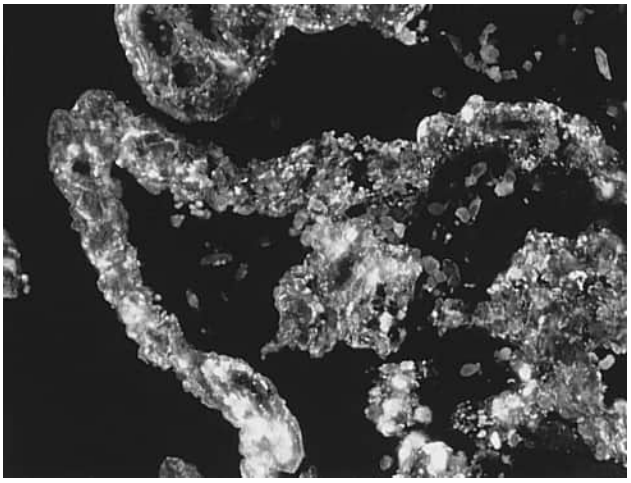

Figure 94.9 Systemic lupus erythematosus. Immunofluorescence study demonstrates granular deposition of immunoglobulin G in the alveolar walls of a patient with systemic lupus erythematosus and diffuse alveolar hemorrhage (×40 original magnification).

Other Connective Tissue Diseases. Other connective tissue diseases such as rheumatoid arthritis, polymyositis, dermatomyositis, scleroderma, and mixed connective tissue disease can cause DAH but are much less common causes than are APS and SLE.[136–142] Isolated DAH with capillaritis has been described in polymyositis, rheumatoid arthritis, and mixed connective tissue disease.[143,144] In polymyositis, DAH was the presenting manifestation and, in rheumatoid arthritis and mixed connective tissue disease, DAH and capillaritis followed the primary diagnosis by 2 to 20 years.[143,144] The therapeutic approach in these cases is similar to that used in the management of SLE, with the use of high-dose corticosteroids with a second agent such as cyclophosphamide or rituximab.

Immune Complex–Related Crescentic Glomerulonephritis

Immune complex–related crescentic glomerulonephritis is rarely accompanied by capillaritis and DAH.[3,145] Although the kidneys demonstrate granular immune deposits, immune complexes are not found in lung tissue.

Acute Pulmonary Allograft Rejection

Pulmonary capillaritis and DAH have been reported after lung transplantation and may represent an acute vascular rejection.[146] The capillaritis can develop weeks to months after the transplantation and may be the only histopathologic manifestation of allograft rejection. This condition represents a serious immunologic complication that threatens survival. In addition to standard anti-inflammatory therapy with corticosteroids and cytotoxic agents, therapeutic plasma exchange may be effective.

COAGULATION DISORDERS

Coagulation disorders associated with DAH include disseminated intravascular coagulation,[147] idiopathic thrombocytopenic purpura,[148] thrombotic thrombocytopenic purpura,[149] and acquired vitamin K deficiency.[150]

All anticoagulant medications have been associated with DAH, including warfarin and its derivatives,[151–153] thrombolytic agents,[154–156] agents targeting the platelet glycoprotein IIb/IIIa,[157–159] and clopidogrel[160] as well as direct oral anticoagulant therapies.[161,162] In most iatrogenically anticoagulated patients, correction of the coagulation defect resolves the DAH. It has been suggested that patients using coumarin with confirmed DAH are at risk for the development of fibrosing interstitial pneumonitis.[163]

DAH can be seen in patients with acute leukemia who have undergone induction chemotherapy and are thrombocytopenic (eFig. 94.6).[164–166] Although thrombocytopenia surely contributes to the DAH, these patients also have evidence of DAD resulting from chemotherapy, oxygen toxicity, and infection that likely plays a central role.

IDIOPATHIC PULMONARY HEMOSIDEROSIS

IPH is predominantly a disease of children, but adults represent about 20% of cases.[165,166] It is a diagnosis of exclusion,[167,168] and efforts to rule out other causes of DAH are essential. Among adults, men are more often affected, and there are reports of familial cases.[169]

The pathogenesis of IPH is not understood. Some cases may be secondary to environmental exposures, such as exposure to *Stachybotrys chartarum,* a toxigenic fungus that has been potentially linked to several cases of otherwise idiopathic alveolar hemorrhage.[170] There are reports of an association between IPH and celiac disease, which is referred to as Lane-Hamilton syndrome. As can be seen with celiac disease, serum immunoglobulin A levels are increased in 50% of cases.[171,172] Serologic testing for immunoglobulin A anti–tissue transglutaminase should be undertaken, and then dietary avoidance of gluten should be initiated to prevent DAH recurrence because some series show total remission of DAH in these cases.[162,173–175]

Recurrent hemoptysis resulting from DAH is the rule, ranging from intermittent blood-streaked sputum to life-threatening hemorrhage. Fever, cough, substernal chest pain, and fatigue secondary to iron-deficiency anemia are also reported. In selected pediatric cases, lymphadenopathy and hepatosplenomegaly are found. Renal disease is absent. In chronic recurrent disease, progressive dyspnea, finger clubbing, inspiratory crackles, and pulmonary fibrosis appear.

Pulmonary function testing reveals a restrictive ventilatory defect with an increase in the diffusing capacity for carbon monoxide during periods of active bleeding. Chest imaging reveals diffuse ground-glass opacity (eFigs. 94.7 and 94.8) and ill-defined centrilobular nodules, the typical appearance of pulmonary hemorrhage of any cause.[176]

In adult cases, lung tissue is required to exclude the entity of isolated pulmonary capillaritis. Histologic examination of the lung in IPH reveals bland alveolar hemorrhage with hemosiderin accumulation.[168,177] There is hyperplasia of alveolar epithelial type 2 cells with capillary dilation and tortuosity. The iron content of the lung is increased, and it is the hemosiderin deposition in the interstitium that is thought to be the basis for collagen proliferation and parenchymal fibrosis. Electron microscopic studies indicate degeneration of alveolar epithelial type 1 cells with exposure of and breaks in the basement membrane and discontinuity of the alveolar capillary structure.[170,176] Although nonspecific, these findings indicate a form of DAD.

Clinical benefit and recovery from the acute hemorrhage after corticosteroid therapy have been reported, but long-term benefit is unlikely.[168,178] Azathioprine has been successful in several cases.[177,179,180] Approximately 25% of patients are free of disease after the initial episode. Another 25% are free of active disease but have persistent dyspnea and anemia, and another 25% have persistent disease activity that leads to fibrosis and severe restrictive lung disease. The rest have unresponsive disease with continued hemorrhage and death from respiratory failure. In patients with persistent disease, the average survival is 3 to 5 years.[168,178] Adults have a better prognosis than children. Lung transplantation is controversial in this disease because IPH has been reported to recur after bilateral lung transplantation.[181]

MISCELLANEOUS CAUSES

Drugs and Toxins

There are many drugs that have been reported to cause DAH.[182] Anticoagulant agents have been discussed previously. Most cases of DAH resulting from drugs or toxins are associated with DAD. This has been reported with abciximab, amiodarone, azathioprine, carbamazepine, cyclosporine, cytosine arabinoside, dextran, docetaxel, fludarabine, hydralazine, methotrexate, radiographic contrast media, retinoic acid, sirolimus, tumor necrosis factor-α, and valproate.[183]

A few drugs have been associated with DAH and capillaritis, including tretinoin, propylthiouracil, phenytoin, and mitomycin.[184–188] DAH resulting from these drugs may also be associated with crescentic glomerulonephritis and elevated ANCA levels.

Penicillamine can result in DAH and an immune complex–mediated glomerulonephritis. Glomerular capillaries display a granular (as opposed to a linear) immunofluorescent pattern for IgG and complement (C3).[189–191] Cases have appeared after as much as 20 years of treatment. Treatment with immunosuppressive therapy and even plasma exchange may be required.[192]

Trimellitic anhydride, used for the manufacture of paints, epoxy resins, and plastics, has caused DAH after the inhalation of fumes or dry powder, generally during spraying of this product on heated surfaces.[193–195] Antibodies to trimellitic anhydride in the serum and a latent period of 1 to 3 months both support an immunologic basis for this syndrome. Long-term physiologic impairment is unusual if further exposure is avoided.

Cocaine inhalation is associated with acute pulmonary toxicity, referred to as "crack lung."[196–198] Crack lung reflects a constellation of findings associated with DAD and hemorrhagic vasculitis, which, in autopsy series, has been associated with DAH.[199] The inhaled particulates used as cocaine adulterants or cocaine-induced acute pulmonary vasoconstriction likely play roles in the acute presentation of DAH in cocaine users. In addition to supportive care, cocaine-related DAH is treated mainly by avoidance of further exposure to cocaine; there are case reports of successful treatment of DAH with glucocorticoids.[200] Vaping and marijuana use have also been reported to cause DAH.[200a,200b]

Diffuse Alveolar Damage

DAD is the underlying histopathologic feature of acute lung injury, and it has a variety of causes (Table 94.3). In DAD, the interstitium of the lung becomes edematous, and the alveolar epithelial type 1 cells are sloughed. There is neutrophilic inflammation and fibroblastic proliferation, but the neutrophilic inflammation in DAD-associated DAH is not as intense as it is in pulmonary capillaritis. Hyaline

Table 94.3 Causes of Diffuse Alveolar Damage

ACUTE RESPIRATORY DISTRESS SYNDROME
Sepsis
Pneumonia (e.g., bacterial, viral, *Pneumocystis jirovecii*)
Trauma
Aspiration
Massive transfusion
Drugs (e.g., cytotoxic/chemotherapeutic agents, antibiotics)
CONNECTIVE TISSUE DISEASE
DIFFUSE LUNG DISEASE
Acute interstitial pneumonia
Acute exacerbation of idiopathic pulmonary fibrosis
RADIATION THERAPY
TOXIC INHALATION
Smoke
Ozone
Heavy metal fumes

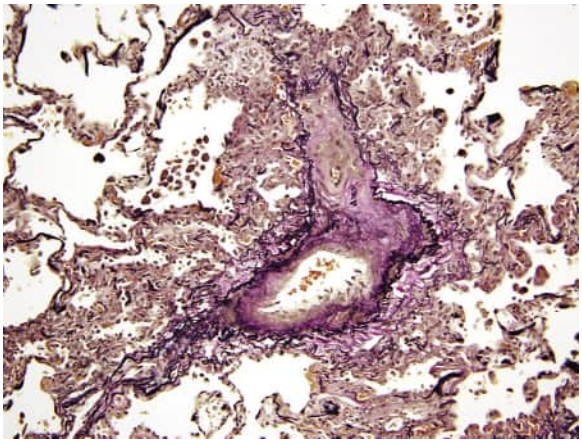

Figure 94.10 Histopathologic findings of pulmonary veno-occlusive disease. An elastic tissue stain (elastic van Gieson) shows marked intimal sclerosis with venous narrowing. These cases may show mild interstitial chronic inflammation and air space accumulation of hemosiderin-filled macrophages (hemosiderosis). (Courtesy Dr. Kirk Jones, University of California, San Francisco.)

membranes consisting of eosinophilic strands of necrotic cells, protein, and fibrin develop adjacent to the injured alveolar walls. In severe cases, the injury to the alveolar-capillary interface leads to leakage of red blood cells into alveolar space that results in DAH.

Mitral Stenosis

Mitral stenosis can be clinically silent and, over time, can result in substantial pulmonary venous hypertension. In some cases, this can lead to the development of DAH.[201] The presentation can be dramatic, with massive hemoptysis arising from the rupture of engorged bronchial varicosities that develop as a result of long-standing left atrial hypertension. Less severe DAH may be recurrent and is often misdiagnosed, leading to chronic interstitial fibrosis. Radiographic findings consist of central ground-glass abnormalities and, in chronic cases, reticular abnormalities (eFig. 94.9).[202] Repair or replacement of the stenotic mitral valve prevents recurrence.

Pulmonary Veno-occlusive Disease

PVOD is a rare cause of *pulmonary hypertension* (PH) resulting from fibrous obliteration of small pulmonary veins and venules. PVOD affects men and women equally and involves all age groups, most commonly children and young adults.[203–205] Patients with PVOD present with dyspnea, syncope, and, when severe, physical findings suggestive of right ventricular overload or failure. Because PVOD is a postcapillary cause of PH, paroxysmal nocturnal dyspnea, orthopnea, and DAH can be seen.

Right-sided heart catheterization cannot easily distinguish PVOD from precapillary PH because the pulmonary capillary wedge pressure is measured in veins distal to the obstructive process, and is generally normal. Chest imaging shows signs of PH; in some cases, interstitial opacities with septal thickening (see Fig. 84.2) suggesting congestion, as well as ground-glass abnormality from alveolar hemorrhage, may be seen. Pleural effusions are common.

Pulmonary function studies reveal a reduced diffusing capacity for carbon monoxide with preservation of lung volumes, a physiologic picture similar to that found in other causes of PH.

Definitive diagnosis is achieved by lung biopsy, which demonstrates fibrous intimal obliteration of small pulmonary veins and venules, acute or recanalized thrombi, and hemosiderosis (Fig. 94.10).

PVOD is usually idiopathic, but it has been reported after chemotherapy (e.g., carmustine, mitomycin, bleomycin), after bone marrow transplantation, and in association with connective tissue disease.[206–213] A mutation in the *bone morphogenic protein receptor II gene* (*BMPR2*), a gene associated with many cases of primary PH, has been identified in a patient with idiopathic PVOD, suggesting an etiologic role.[214]

The use of pulmonary vasodilators in the treatment of PVOD is complicated and potentially harmful. Modest improvements with nifedipine and epoprostenol have been reported, but there have also been cases of these agents precipitating massive pulmonary edema and death.[215,216] Any trial of vasodilator therapy should be performed during right-sided heart catheterization in an appropriate hospital setting. A few patients have had clinical responses to prednisone and azathioprine.[217,218] Anticoagulation for PVOD has been recommended based on the potential role of thrombosis in the pathogenesis of PVOD and on limited data suggesting efficacy in patients with primary PH. However, anticoagulant agents should generally be avoided in patients who have had DAH.

Pulmonary Capillary Hemangiomatosis

Pulmonary capillary hemangiomatosis (PCH) is a rare cause of PH that can be associated with severe and recurrent DAH.[219–221] It is seen across ages and sexes. Patients universally present with dyspnea, often with evidence of right-sided heart failure. Hemoptysis develops in roughly one-third of cases during the course of the disease.[219]

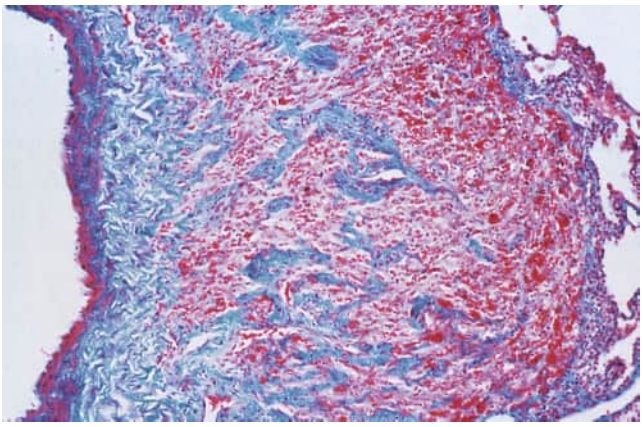

Figure 94.11 Histopathologic findings of pulmonary capillary hemangiomatosis. There is capillary proliferation in the wall of this large pulmonary vein (×100 original magnification).

Chest imaging findings are nonspecific. Chest radiography often shows nonspecific diffuse or bibasilar predominant reticular (eFig. 94.10A) and nodular opacities, with interlobular septal thickening less common than seen with PVOD. Chest computed tomography may show multifocal or diffuse, poorly defined centrilobular ground-glass opacities (eFigs. 94.10B–E and 94.11) and evidence of PH.

Pulmonary function test results are mixed, with both obstructive and restrictive changes described.[219] As with PVOD, right-sided heart catheterization generally reveals a normal pulmonary capillary wedge pressure.

Histologically, PCH is characterized by a proliferation of pulmonary capillaries, which infiltrate the interstitial, bronchial, and vascular structures of the lung (Fig. 94.11).[220] The exact mechanism of PH and DAH is unclear, but mechanical rupture of hemangiomatous vessels in the setting of pulmonary arterial and venous occlusion and/or thrombosis is likely responsible.

Treatment of PCH with pulmonary vasodilators is generally contraindicated because worsening pulmonary edema and death have been reported.[222,223] In a few reports, treatment with recombinant interferon-alfa-2a may have led to stabilization or improvement.[219,224] Mean survival after diagnosis is usually 3 years, although successful treatment with lung transplantation has been reported.[219]

Lymphangioleiomyomatosis and Tuberous Sclerosis

Lymphangioleiomyomatosis and tuberous sclerosis share common pathobiologic features involving proliferation of smooth muscle in pulmonary interstitial, lymphatic, bronchial, and vascular structures (see Chapter 97 for a full discussion of these diseases).[225–227] Involvement of the pulmonary vasculature commonly results in episodes of alveolar hemorrhage. This alveolar bleeding is often focal; DAH is unusual. Pathologic specimens of the lung in lymphangioleiomyomatosis and tuberous sclerosis typically demonstrate focal areas of hemorrhage and hemosiderin deposition.

Key Points

- Diffuse alveolar hemorrhage is a medical emergency that often results in acute respiratory failure and death.
- The classic clinical presentation of diffuse alveolar hemorrhage includes dyspnea, hemoptysis, alveolar opacities on chest radiograph, and anemia. Importantly, in as many as one-third of patients with diffuse alveolar hemorrhage, hemoptysis may not be a presenting symptom.
- Many of the disorders causing diffuse alveolar hemorrhage appear to be immunologically mediated, either through injury to the capillary basement membrane by specific autoantibodies or through deposition of immune complexes.
- Bronchoscopy with serial bronchoalveolar lavage showing a sequential increase in red blood cell counts or bloody appearance is essential to confirm diffuse alveolar hemorrhage.
- Many cases of diffuse alveolar hemorrhage demonstrate neutrophilic inflammation of the alveolar interstitium known as capillaritis.
- The presence of proteinuria and an abnormal urinary sediment (red blood cells and red blood cell casts) suggests underlying glomerulonephritis consistent with the diagnosis of systemic vasculitis or anti–glomerular basement membrane disease (formerly Goodpasture syndrome).
- Accurate diagnosis is essential because, in some of the causes of diffuse alveolar hemorrhage, aggressive treatment with corticosteroids, cytotoxic agents, rituximab, and plasma exchange (alone or in combination) is often helpful.

Key Readings

de Prost N, Parrot A, Cuquemelle E, et al. Diffuse alveolar hemorrhage in immunocompetent patients. Etiologies and prognosis revisited. *Respir Med.* 2012;106:1021–1032.

Frankel S, Schwarz MI. The pulmonary vasculitides. *Am J Resp Crit Care Med.* 2012;186:216–224.

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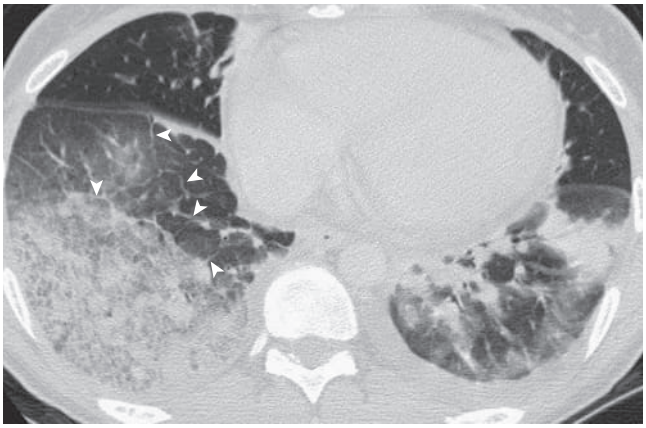
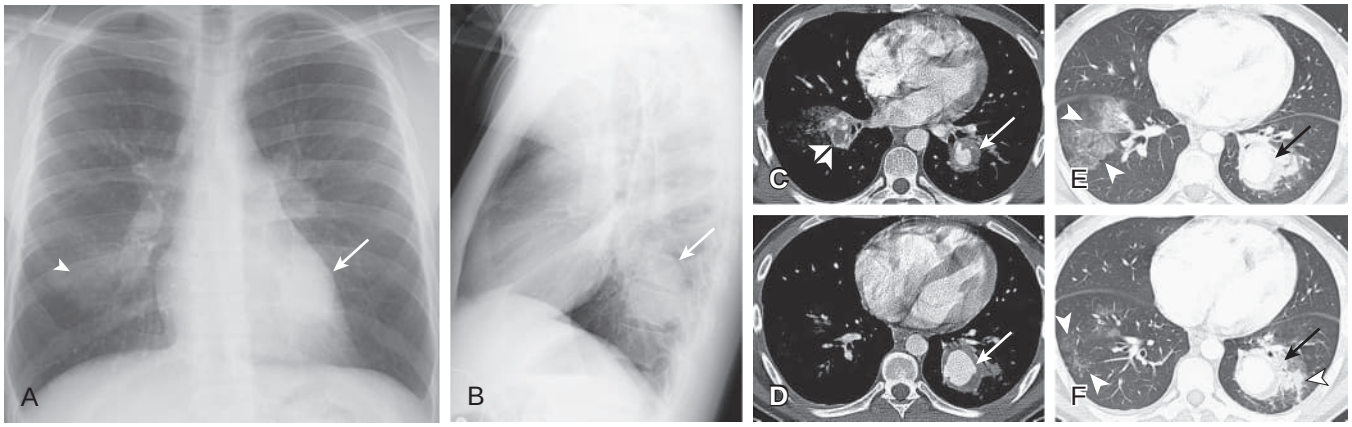
Complete reference list available at ExpertConsult.com.

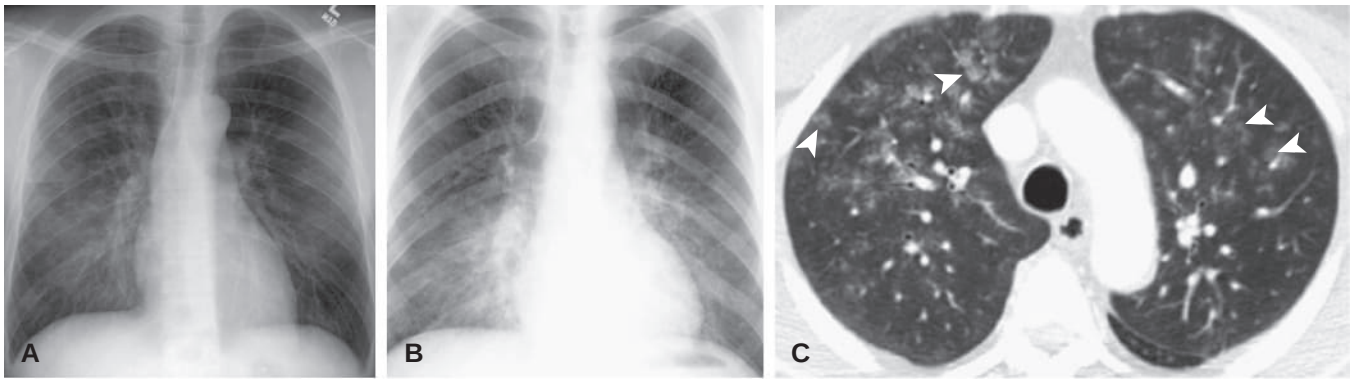
eFIGURE IMAGE GALLERY



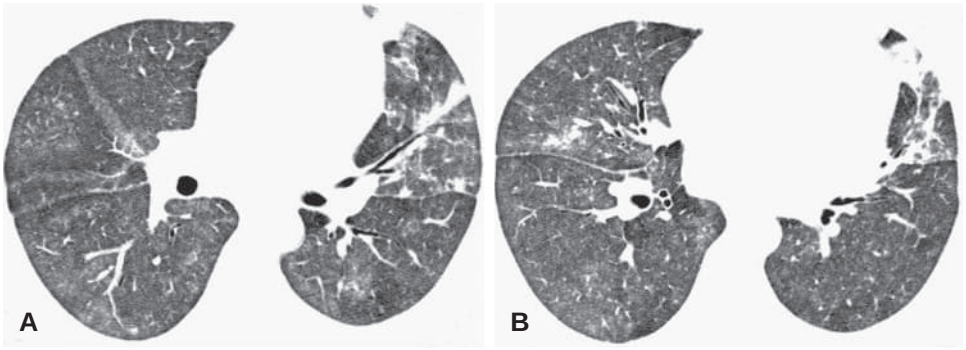
eFigure 94.1 Diffuse alveolar hemorrhage with smooth interlobular septal thickening. Axial chest computed tomographic image displayed in lung windows shows multifocal ground-glass opacity and consolidation associated with smooth linear opacities (*arrowheads*), representing interlobular septal thickening. (Courtesy Michael B. Gotway, MD.)



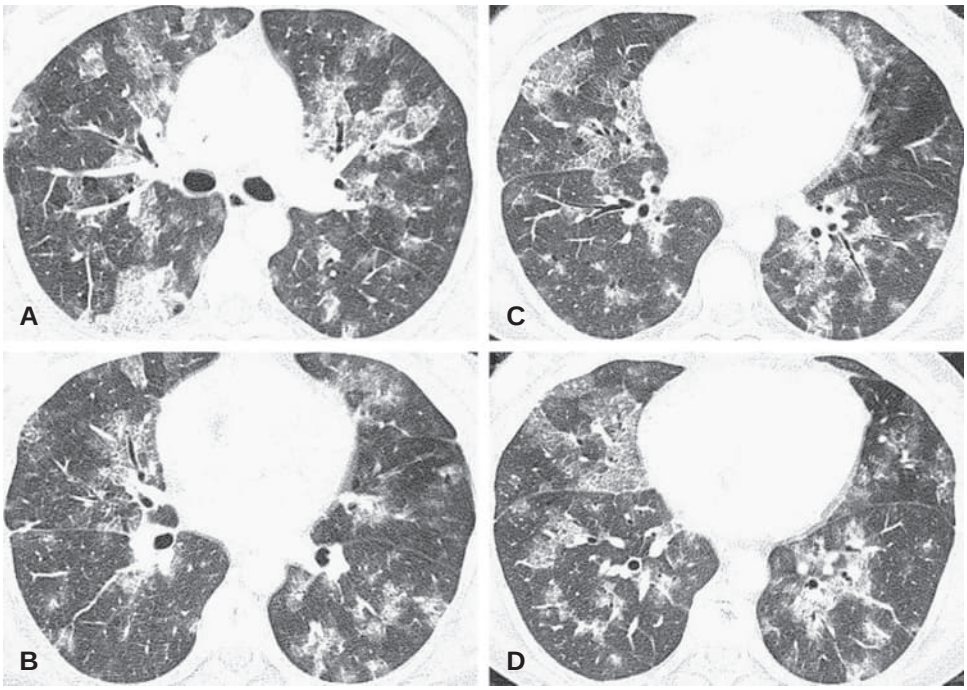
eFigure 94.2 Behçet disease: chest radiographic and chest computed tomographic manifestations. (A) Frontal and (B) lateral chest radiographs show left hilar enlargement associated with a left lower lobe mass (*arrow*) representing a pulmonary artery aneurysm as well as patchy areas of ground-glass opacity best seen in the right lower lobe (*arrowhead*), reflecting pulmonary hemorrhage. (C–F) Axial enhanced chest computed tomography displayed in soft tissue (C–D) and lung (E–F) windows shows a left lower lobe pulmonary artery aneurysm (*arrow*). Thrombosis is seen in the caudal portion of a right pulmonary artery aneurysm (*double arrowhead*, C). Ground-glass opacity (*arrowheads*, E–F) represents hemorrhage surrounding the pulmonary artery aneurysms. (Courtesy Michael B. Gotway, MD.)



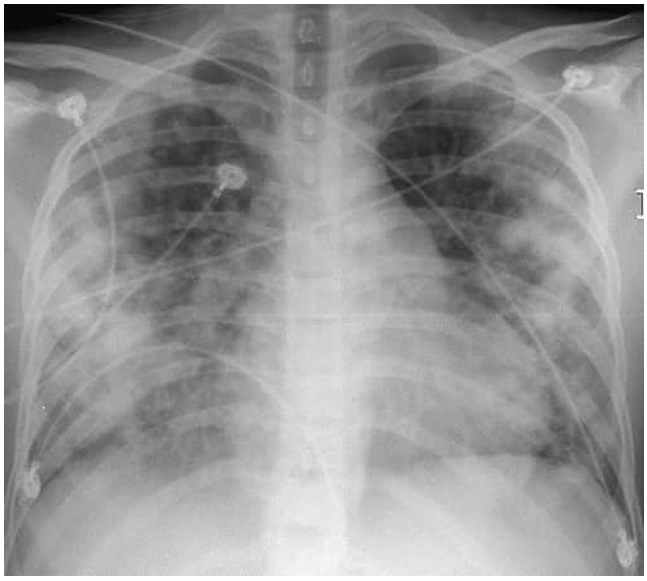
eFigure 94.3 Diffuse alveolar hemorrhage in anti–glomerular basement membrane disease (formerly Goodpasture syndrome). Chest radiography and chest computed tomographic findings. (A–B) Frontal chest radiographs of two different patients with anti–glomerular basement membrane disease show multifocal bilateral, hazy ground-glass opacity representing pulmonary hemorrhage. These findings are slightly denser and more prominent in the perihilar area in the second patient (B). (C) Axial chest computed tomography displayed in lung window (same patient as in A) shows multifocal, poorly defined ground-glass opacity and centrilobular nodules (*arrowheads*), reflecting recurrent pulmonary hemorrhage. (Courtesy Michael B. Gotway, MD.)



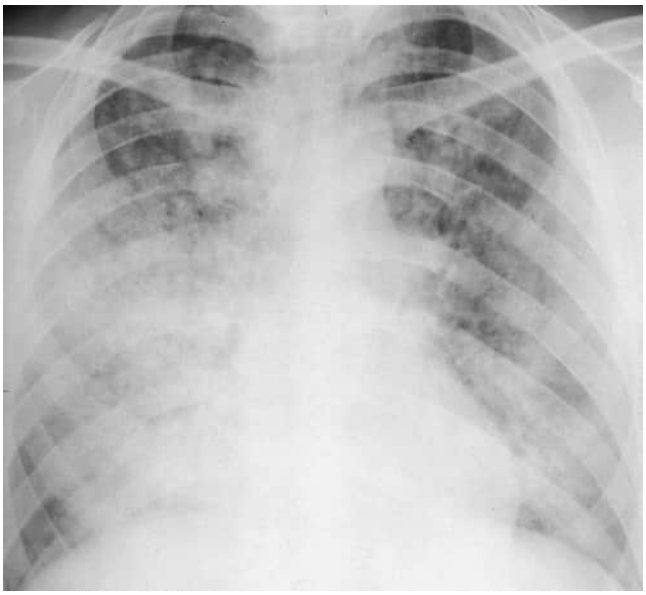
eFigure 94.4 Diffuse alveolar hemorrhage in systemic lupus erythematosus. (A–B) Axial chest computed tomography displayed in lung windows shows multifocal, poorly defined ground-glass opacity and lingular consolidation, reflecting pulmonary hemorrhage. The findings are not specific for the cause of the hemorrhage because diffuse alveolar hemorrhage of any cause can manifest in this fashion. (Courtesy Michael B. Gotway, MD.)



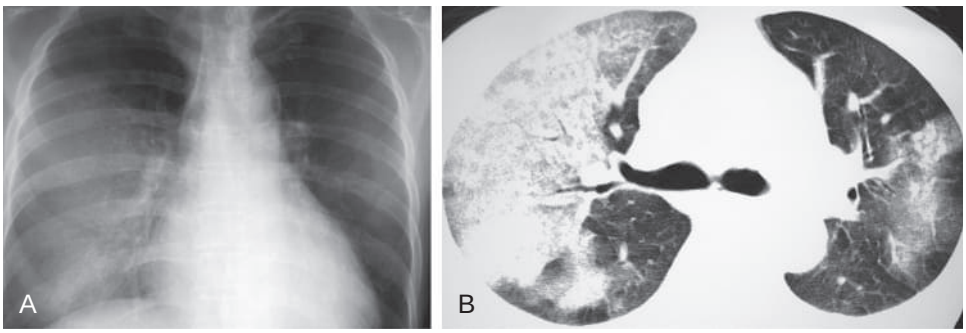
eFigure 94.5 Diffuse alveolar hemorrhage in antiphospholipid antibody syndrome. (A–D) Axial chest computed tomography displayed in lung windows shows multifocal, poorly defined ground-glass opacity associated with mild, smooth interlobular septal thickening, reflecting multifocal pulmonary hemorrhage. (Courtesy Michael B. Gotway, MD.)



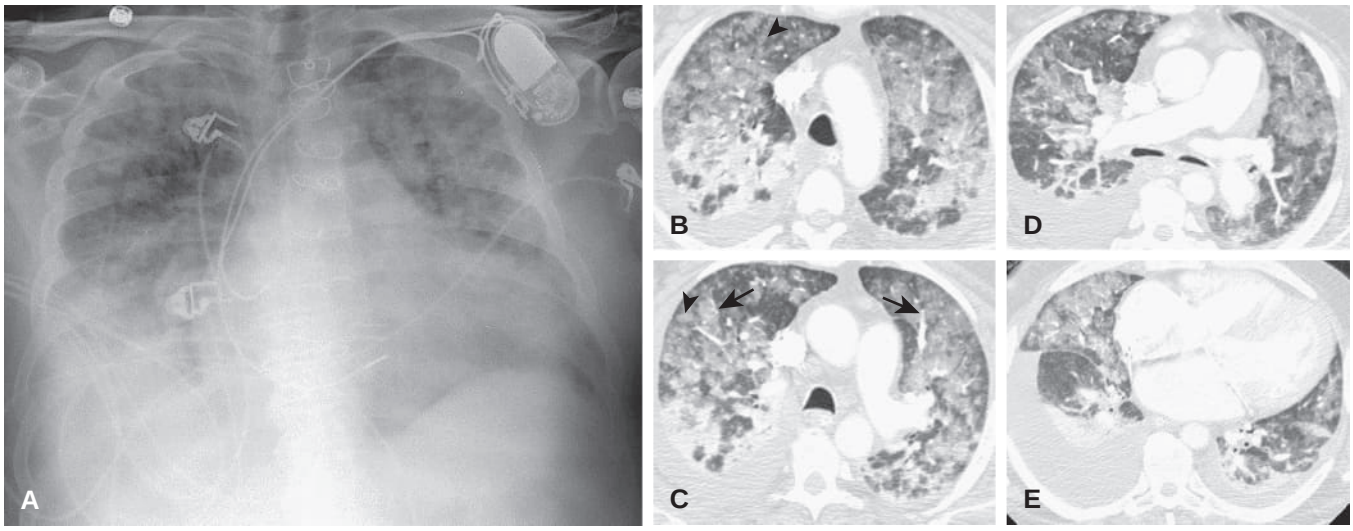
eFigure 94.6 Diffuse alveolar hemorrhage in acute leukemia. Frontal chest radiograph shows multifocal, bilateral, peripherally predominant consolidation, proven to represent diffuse alveolar hemorrhage. (Courtesy Michael B. Gotway, MD.)



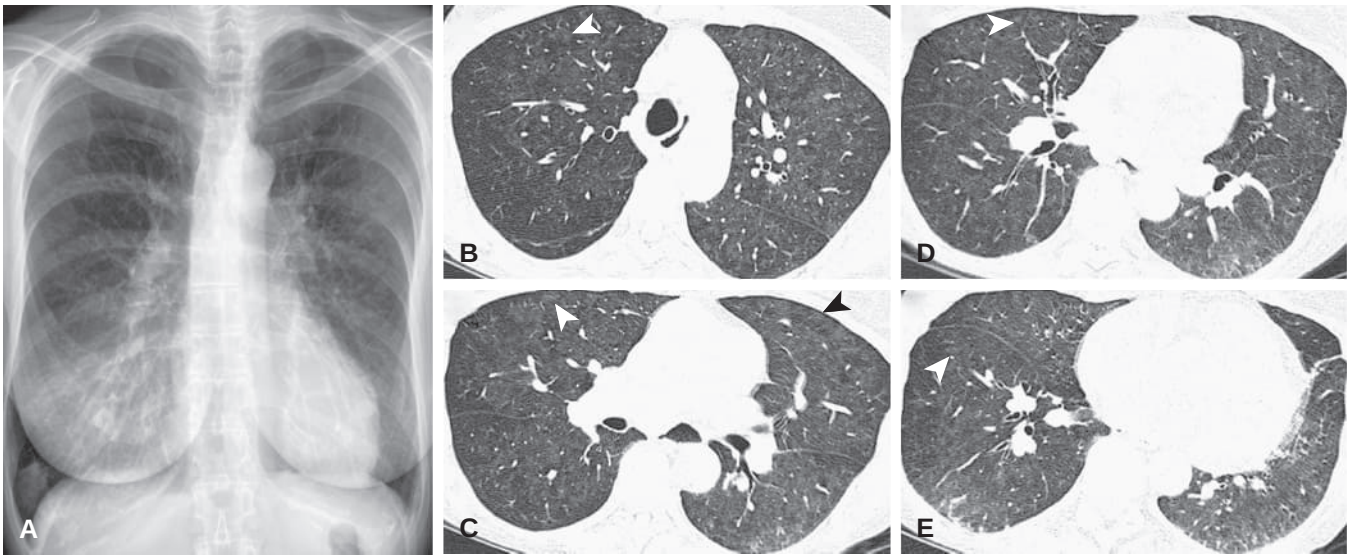
eFigure 94.7 Idiopathic pulmonary hemosiderosis syndrome. Frontal chest radiograph shows multifocal, bilateral, dense consolidation, proven to reflect diffuse alveolar hemorrhage. (Courtesy Michael B. Gotway, MD.)



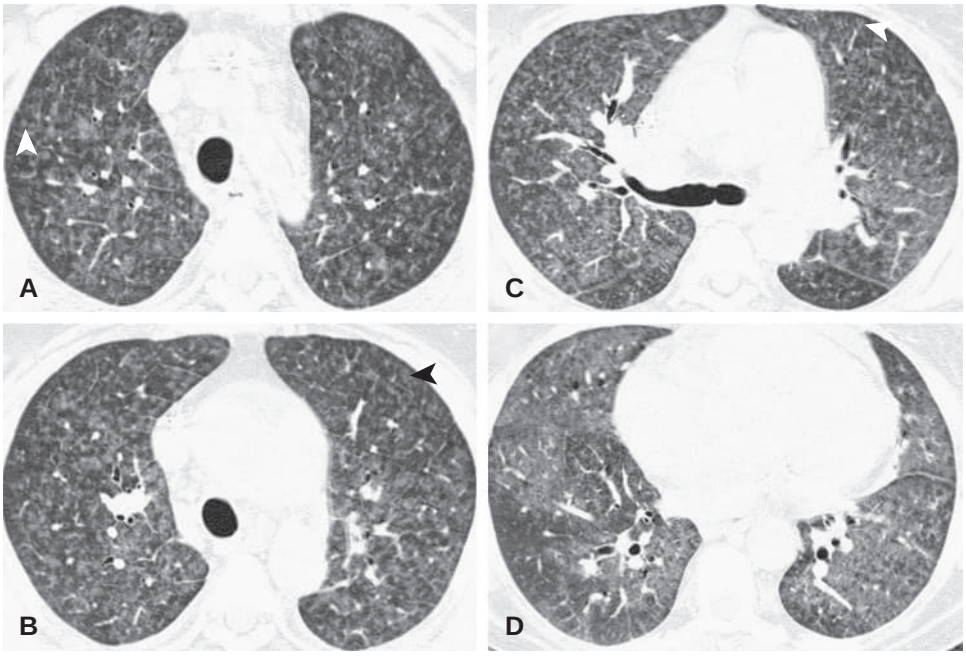
eFigure 94.8 Idiopathic pulmonary hemosiderosis syndrome: chest radiography and chest computed tomographic findings. (A) Frontal chest radiograph shows multifocal, bilateral, right-greater-than-left ground-glass opacity found to reflect pulmonary hemorrhage. (B) Axial chest computed tomography displayed in lung window shows multifocal, bilateral ground-glass opacity associated with smooth interlobular septal thickening, typical of alveolar hemorrhage, correlating with the chest radiographic findings. (Courtesy Michael B. Gotway, MD.)



eFigure 94.9 Diffuse alveolar hemorrhage in a patient with mitral stenosis. (A) Frontal chest radiograph shows extensive bilateral consolidation and peribronchovascular infiltration in a patient with cardiomegaly and sternotomy. (B–E) Axial chest computed tomography displayed in lung windows shows multifocal areas of ground-glass opacity, in some areas centrilobular (*arrowheads*) and in others more lobular (*arrows*). Areas of consolidation and pleural effusions are also present. The appearance is very suggestive of, although not specific for, pulmonary hemorrhage. (Courtesy Michael B. Gotway, MD.)



eFigure 94.10 Pulmonary capillary hemangiomatosis: findings on chest radiography and chest computed tomography. (A) Frontal chest radiograph shows patchy right infrahilar opacity. (B–E) Axial chest computed tomography images displayed in lung windows show multifocal, bilateral ground-glass opacity, in some areas with a centrilobular appearance (*arrowheads*). (Courtesy Michael B. Gotway, MD.)



eFigure 94.11 Pulmonary capillary hemangiomatosis: chest computed tomographic findings. (A–D) Axial chest computed tomography displayed in lung windows shows multifocal, bilateral ground-glass opacity centrilobular nodules (*arrowheads*). The ground-glass opacity appears more confluent in the bases (D). (Courtesy Michael B. Gotway, MD.)

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PULMONARY LANGERHANS CELL HISTIOCYTOSIS AND OTHER RARE DIFFUSE INFILTRATIVE LUNG DISEASES

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INTRODUCTION

Histiocytic disorders are associated with organ infiltration and inappropriate activation of myeloid cells belonging to the monocyte-macrophage and dendritic cell lineage.[1] Individual histiocytic syndromes vary widely in natural history and clinical behavior.[1] *Langerhans cell histiocytosis* (LCH) is a subgroup of the histiocytic syndromes characterized by organ infiltration with myeloid cells expressing surface CD1a and intracellular Birbeck granules.[1] In adults, LCH may affect the lungs in isolation (as pulmonary LCH) or as part of a multisystem disease.[2]

PULMONARY LANGERHANS CELL HISTIOCYTOSIS

EPIDEMIOLOGY

Pulmonary Langerhans cell histiocytosis (PLCH) is an uncommon cause of diffuse lung disease and represents approximately 3% of all cases referred for evaluation of interstitial lung disease.[3] The disease is seen principally in adults between the ages of 20 and 40 years.[2,4] Men and women are affected in equal proportion.[2,5] PLCH, particularly when isolated to the lung, is a smoking-related lung disease.[2,5-10] At least 90% of adults with isolated PLCH are active or former smokers,[2] and cigarette smoking has been reported to precipitate the onset of PLCH in adolescents previously in remission from disease earlier in childhood, a finding suggesting that smoking may be a critical factor in disease induction.[6] The role of smoking is less clear when LCH arises in the context of a multisystem disease.

PATHOLOGY

Inspection of the surface of the lungs at the time of autopsy or during surgery reveals cysts. When the lung is sectioned, nodules of varying sizes (0.1 to 1.5 cm) may be seen.[11] In advanced disease, the predominant finding may be bullous and cystic destruction of the middle and upper lung regions.[5,11,12] In early-stage disease, PLCH is an inflammatory type of bronchiolitis with varying degrees of interstitial infiltration.[5,11,13] Some patients have extensive alveolar macrophage infiltration in the air spaces.[14] In addition to bronchiolar, interstitial, and varying degrees of alveolar involvement, some cases may be associated with extensive vascular infiltration.[5,15-17] An appreciation of the different pulmonary compartments that the disease involves is important because the extent of airway, interstitial, and vascular involvement may vary greatly from one patient to another, and it helps to explain the variability observed in clinical findings and lung function testing.[2]

Histologic examination of lung biopsy samples shows loose cellular nodules adjacent to small airways and scattered throughout the lung parenchyma.[5,11,18] The nodules consist of a mixed population of inflammatory cells including T lymphocytes, monocytes, plasma cells, eosinophils, and myeloid cells, which share morphologic features with cutaneous antigen-presenting cells known as Langerhans cells (identifiable by typical morphologic features on light microscopy and surface CD1a staining).[5,11,19,20] The histologic findings may sometimes be confused with respiratory bronchiolitis or desquamative interstitial pneumonia because of the extent of macrophage accumulation in small airways and alveolar and interstitial spaces.[11,14] The bronchiolocentric lesions often form symmetrical stellate shapes with central scarring.[11]

The stage of evolution of the process influences the pathologic findings. In early stages, numerous cells accumulate adjacent to terminal or respiratory bronchioles, thus resulting in the destruction of the bronchiolar wall and the adjacent alveolar structures. In more advanced disease, cellularity may diminish considerably, and fibrotic changes predominate.[11]

Cystic lesions are characteristic of PLCH. These lesions do not represent necrosis of the nodules but rather progressive dilation of the small airways and eventual fibrosis as the peribronchial lesions destroy the bronchiolar walls.[11,13] Injury to the small airways with subsequent dilation and scarring leads to the formation of irregular parenchymal cystic lesions.

PATHOGENESIS

The cell believed to be primarily responsible for disease pathogenesis is a myeloid cell that shares several morphologic features with cutaneous Langerhans cells.[1] Given their location and close association to airway epithelial cells, it is very likely that these myeloid cells are recruited, or possibly develop in situ, in response to epithelial signals that arise in the context of certain inhalational challenges such as cigarette smoking.

Accumulation of CD1a-expressing myeloid cells in a subepithelial distribution is postulated to be the earliest lesion to develop in the natural history of PLCH.[21] Cigarette smoking may lead to recruitment of these cells through the induction of certain cytokines and chemokines such as tumor necrosis factor-α, *granulocyte-macrophage colony-stimulating factor* (GM-CSF), and transforming growth factor-β from airway epithelial cells.[22,23] These putative mechanisms of myeloid cell accumulation in subepithelial regions are supported by immunohistochemical techniques that identify abundant GM-CSF protein expression in the epithelium of bronchioles affected by the inflammatory lesions of PLCH, which colocalizes with the presence of numerous $CD1a^+$ myeloid cells in proximity.[21] A pathogenic role for GM-CSF is further suggested by the observation that the expression of GM-CSF is substantially lower in bronchioles not affected by disease.[21] In addition to epithelial cells, alveolar macrophages and other lung cells may be important sources of secreted factors that recruit myeloid as well as other inflammatory cells that ultimately lead to nodular lesions.

Although the link between smoking and PLCH appears strong, the disease develops in a very small percentage of smokers, thereby indicating that in addition to exogenous factors, there must be some inherent host genetic (or additional environmental) factors that lead to PLCH. Extensive analyses have failed to identify candidate viruses.[24,25] It is possible that somatic mutations affecting the *mitogen-activated protein kinase* (MAPK) pathway may be the critical endogenous factor that predisposes smokers to PLCH development.[26]

Whether PLCH is a reactive or a clonal neoplastic process has been a subject of debate.[27] The low frequency of mitotic figures or cytogenetic abnormalities in the lesional $CD1a^+$ myeloid cells, reports of "spontaneous" resolution, and the inflammatory nature of the nodules were considered arguments favoring a reactive immune granulomatous reaction. Conversely, the occasionally aggressive natural course of PLCH in some patients with progressive disease and the efficacy of chemotherapy in certain severe forms of PLCH favored a neoplastic mechanism. The argument was fueled further by discordant findings in two molecular studies: one supported a clonal nature of infiltrating lesional $CD1a^+$ myeloid cells,[28] whereas another study reported a polyclonal process in most cases.[27]

The identification of recurrent genetic abnormalities in the lesional $CD1a^+$ cells provides the strongest argument to date in support of the neoplastic nature of PLCH.[29] Both *B-raf proto-oncogene* (BRAF) and *neuroblastoma RAS viral oncogene* (NRAS) mutations have been found in PLCH lesions and in circulating myeloid $CD1a^+$ cells.[30,31] The $BRAF^{V600E}$ mutation results in a modified kinase domain of the protein that leads to constitutive activation of the MAPK pathway.[29] This mutation is found in 35–50% of people with PLCH.[31,32] Although at least one-half of PLCH patients have a wild-type BRAF status, evidence of activation of the MAPK pathway by immunohistochemical studies can be shown in all patients.[29] This finding implies additional mechanisms for MAPK pathway activation in the absence of $BRAF^{V600E}$ mutations. At this time, and although strongly supportive of a neoplastic biology, the clinical significance of MAPK pathway mutations in PLCH is not fully known. Additional studies are needed to evaluate the impact of MAPK mutations and the associated clinical phenotype, as well as the potential for these mutations to guide individualized treatment approaches with targeted inhibitors of the MAPK pathway.[26]

RADIOGRAPHIC FINDINGS

The chest radiograph is abnormal except in mild or very early disease (Fig. 95.1). Nodular and reticulonodular opacities predominate in early disease, whereas cystic abnormalities and hyperinflation are typical in advanced disease.[33] Unusual findings on chest radiographs include discrete pulmonary nodules[34] and pleural effusions.

High-resolution computed tomography (HRCT) scans should be obtained in every patient suspected of having PLCH. As with the chest radiograph, abnormalities described on HRCT vary depending on when it is obtained relative to the natural course of the disease. In disease of recent onset, nodules are very common: these vary in size from a few millimeters to up to 2 cm in size, and they may show central cavitation.[35] In more advanced disease, lung cysts tend to predominate.[36] The combination of nodular and cystic changes may result in a highly characteristic radiographic appearance (see Fig. 95.1). The lung cysts often vary in size, have thin walls, and tend to be pleomorphic (unlike the more uniform-appearing cysts reported in lymphangioleiomyomatosis and described in Chapter 97 and Fig. 97.3).[2,37]

PLCH lesions are frequently fluorodeoxyglucose avid, and positron emission tomography scanning may be helpful to determine the extent of thoracic disease activity, as well as to detect occult extrapulmonary disease, present in approximately 10–15% of patients.[38]

PULMONARY FUNCTION TESTING

Results of pulmonary function testing may be normal in up to 20% of patients at the time of diagnosis.[2] The most

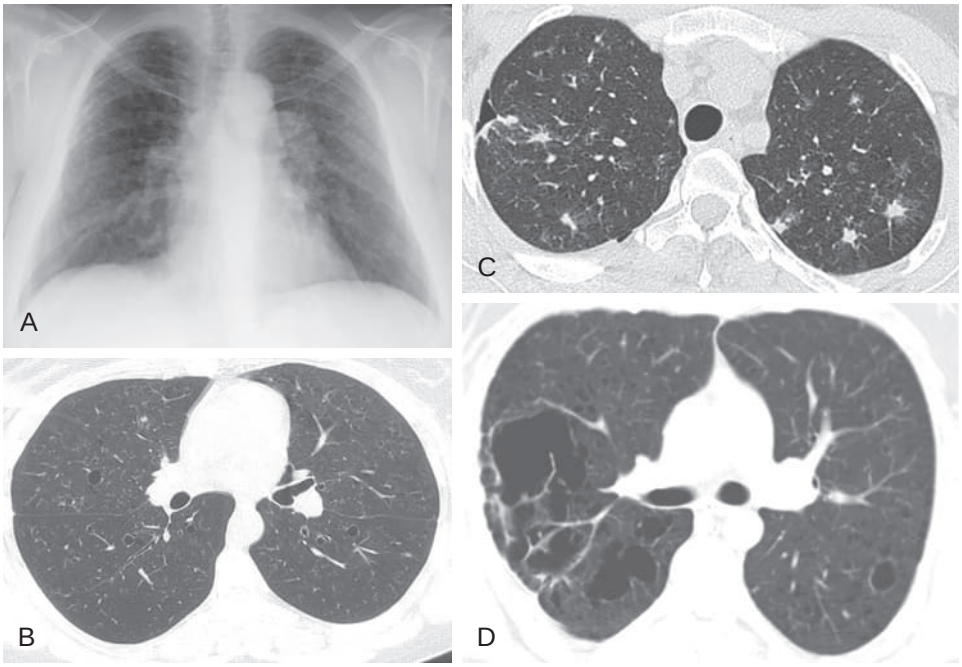

Figure 95.1 Pulmonary Langerhans cell histiocytosis. (A) Chest radiograph from a 48-year-old woman with biopsy-proven *pulmonary Langerhans cell histiocytosis* (PLCH) showing diffuse interstitial opacities with an upper lobe predominance and prominent pulmonary arteries resulting from coexistent secondary pulmonary hypertension. (B) Representative high-resolution chest *computed tomography* (CT) image from a 23-year-old woman with biopsy-proven PLCH showing discrete, thin-walled cysts in both upper lobes. (C) Representative chest CT image from the upper lobes of a 35-year-old woman with PLCH. Several nodules can be appreciated in both lungs. A tiny, right-sided pneumothorax and focal area of consolidation along a suture line are present in the right upper lobe laterally, at the site of recent surgical lung biopsy. (D) Representative chest CT image from a 50-year-old patient with PLCH showing pleomorphic cystic changes, particularly in the right lung.

common abnormality at the time of diagnosis is a reduction in *diffusing capacity for carbon monoxide* (DL_{CO}).[2,5] Lung function testing may also reveal obstructive, restrictive, or mixed physiologic abnormalities.[2,5] The various patterns of lung function abnormalities are manifestations of the different degrees of interstitial, airway, and vascular involvement in PLCH. In a series of 23 patients with presumed early disease, lung function testing showed normal or restrictive physiology,[39] whereas another cohort reported restriction in 37 of 81 patients (46%) at the time of diagnosis.[2] Obstructive physiology manifested by increased lung volumes, air trapping, and diminished *forced expiratory volume in 1 second* (FEV_1) relative to the *forced vital capacity* (FVC), is present in at least one-third of patients at the time of diagnosis and becomes more prevalent later in the natural course of disease.[2,14,40]

CLINICAL FEATURES AND DIAGNOSTIC EVALUATION

Two-thirds of patients have symptoms at the time of presentation, usually cough and dyspnea.[2] Chest pain secondary to pneumothorax can happen in 10–20% of patients, and it may be recurrent.[41,42] Complications of PLCH include pneumothorax, hemoptysis, and pulmonary vascular disease.

Physical examination of the pulmonary system is usually unremarkable. Auscultation of the chest may be normal or may reveal evidence of airflow limitation. There are no diagnostic blood tests, and most patients have normal hematologic indices.

PLCH should be suspected in any smoker with diffuse lung opacities. HRCT of the chest should be obtained in all patients suspected of having PLCH. In asymptomatic patients or those with mild disease, HRCT may be sufficient to enable a provisional diagnosis. Further evaluation and definitive diagnosis with lung biopsy should be pursued when the HRCT findings are consistent with, but not highly suggestive of, PLCH, and whenever treatment is contemplated. The yield of transbronchial lung biopsy is relatively low,[5,43,44] and the identification of greater than 5% $CD1a^+$ *bronchoalveolar lavage* (BAL) cells has high specificity but low sensitivity and is infrequently used as a diagnostic test.[45-49]

Surgical lung biopsy may establish the diagnosis if transbronchial lung biopsy is nondiagnostic. In patients with multisystem LCH, the diagnosis may be established by biopsy of other involved sites, such as bone or skin. With the recognition of specific mutations associated with LCH, and the potential for these mutations to guide treatment decisions, biopsy confirmation of disease is recommended whenever possible. Although a provisional diagnosis may be established on the basis of clinical features and consistent imaging findings, analysis of biopsy tissue for specific mutations should be considered whenever possible.

MANAGEMENT

The management of PLCH should be individualized. Active smokers should be offered the best current smoking cessation approaches. Abstinence from smoking leads to stabilization of symptoms in many patients, and it may be the only medical intervention necessary

for sustained remission.[10,50] Unfortunately, the lung function of patients may not improve or even stabilize following smoking cessation. In addition, some patients are unable to quit smoking and develop progressive disease. Because the decline in FEV_1 and D_{LCO} predict adverse outcome,[2,40] a practical approach to detect patients at risk of progressive disease is to establish longitudinal follow-up every 3 to 6 months with pulmonary function testing.

Oral corticosteroids are often prescribed for PLCH, but there is limited evidence in support of their use.[7,51-53] The presumed efficacy of corticosteroids, as suggested by retrospective studies, is difficult to ascertain because of the confounding effect of smoking cessation, which may in itself lead to objective improvement. Given the potential for side effects and limited evidence to support efficacy, as well as the availability of alternative therapies, it is now quite uncommon to use corticosteroid therapy for the treatment of PLCH.

Various chemotherapy agents have been reported to induce disease remission in patients with isolated progressive pulmonary disease or multisystem LCH with lung involvement.[54-58] Cladribine, a purine nucleoside commonly used in the treatment of hairy cell leukemia, seems to have efficacy in both multisystem and isolated PLCH.[55,59-61] Of interest have been anecdotal reports of responses to cladribine associated with reduction in the dimension of lung cysts.[62] However, the long-term bone marrow toxicity of cladribine in young patients is not well defined, and treatment with this agent should be undertaken only by specialized centers.

Another treatment option for patients with mutated $BRAF^{V600E}$ is the use of the targeted inhibitors of the BRAF/MAPK/MEK pathways, vemurafenib and tramatenib.[63] Use of these agents should be restricted to patients with documented $BRAF^{V600E}$ mutation and only in those with progressive disease despite smoking cessation. One report suggested that in patients who have BRAF wild type and have progressive disease, use of inhibitors of the downstream MEK pathway may also be a potential alternative therapy.[64] The role of these agents in the management of isolated PLCH is not well established at this time and, given their potential toxicity, they should be used only after careful consultation with centers that have expertise in managing rare histiocytic disorders.

The management of PLCH also includes screening for *pulmonary hypertension* (PH) by transthoracic echocardiography, particularly in patients with dyspnea that seems out of proportion to measured pulmonary function, or in patients with progressive decline in D_{LCO}. In patients with signs of possible PH, it is recommended to proceed to right-sided heart catheterization to confirm the presence and severity of the PH and to measure the hemodynamic response to a vasodilator trial (see Chapter 83).[16]

Lung transplantation is an option for patients with severe respiratory impairment and should be considered in the patient with rapidly declining lung function or with a severe limitation unresponsive to smoking cessation or a trial of immunosuppressive therapy.[65-68a] It is imperative that patients stop smoking before lung transplantation because the disease may recur in the transplanted lung if smoking is resumed.[69] There are also reports of recurrence in the transplanted lung in spite of presumed abstinence from tobacco use.[57,70,71]

OUTCOMES AND PROGNOSIS

The overall prognosis is good for most patients, particularly if they stop smoking early in the course of disease. Factors associated with a worse prognosis include multisystem involvement, extensive cysts, markedly reduced D_{LCO}, low FEV_1/FVC ratio, and a high ratio of residual volume to total lung capacity.[2,40,72] As mentioned, some patients develop progressive disease. It is difficult to determine how many patients with PLCH progress to respiratory failure because some of these patients have associated emphysema caused by long-standing tobacco abuse.

Pregancy in women with PLCH appears to be safe. One study reported that 10 healthy children were delivered by a cesarean section in eight women with PLCH.[73] In that cohort, pregnancy did not significantly influence pulmonary function or the distance and arterial oxygen saturation in the 6-minute walk test.[73] One patient did experience bilateral pneumothorax in the third trimester. Accordingly, although limited data exist, pregnancy does not appear to trigger deterioration of pulmonary function in PLCH.[73] Anecdotally, complete remission of cutaneous and lymph node involvement by LCH during pregnancy has been reported.[74] Although PLCH is not a contraindication to pregnancy, patients with PH require very careful monitoring and counseling.[75]

PLCH patients also appear to have an increased risk of secondary malignant diseases, including lymphoma, multiple myeloma, myelodysplastic syndrome, and other cancers.[2] These cancers may either predate or follow the diagnosis of LCH. It is important for clinicians to recognize this association because of the implications in follow-up and counseling of these patients.

RARE INFILTRATIVE DISORDERS OF THE LUNG

This is a collection of diseases with very low incidence, associated with different genetic mechanisms and characterized by multisystemic involvement, including the lungs. In most of these disorders, no clear treatment options are recognized. Most affected individuals tend to be young, and appropriate recognition and diagnosis are essential. In many instances, given the relatively young age of persons affected by these rare infiltrative disorders, lung transplantation referral should be considered.

NEUROFIBROMATOSIS

Neurofibromatosis (NF) is a genetic condition characterized by multiorgan involvement with compromise of skin, central and peripheral nervous system, bone, and eyes. The more common form is NF type 1 (NF1), formerly known as von Recklinghausen disease. It is an autosomal dominant disorder; however, 50% of cases arise sporadically from spontaneous mutations. The *NF1* gene is located on the long arm of chromosome 17 (at locus 17q11.2). Its protein product, neurofibromin, is a negative regulator of the proto-oncogene Ras, which could explain the higher

incidence of neoplasia,[76] with reported coexistence of different malignant tumors in the same patient,[77,78] along with rare cases of primary lung carcinosarcoma[79] and primary lung rhabdomyosarcoma.[80] The loss of neurofibromin protein accelerates the production of Ras proteins, which play a central role in cell differentiation and growth, resulting in the development of benign neurofibroma-type tumors, and perhaps interstitial lung disease, potentially because of increased fibroblast proliferation.[81] Moreover, proliferation and migration of endothelial cells cause pronounced pulmonary arterial remodeling and uniform wall thickening in cases associated with PH.[82]

The most common manifestations include café au lait macules, neurofibromas, Lisch nodules (present in 95% of patients), and axillary or inguinal freckling (present in 70% of patients). NF is fully penetrant in adults, but many manifestations of the disease increase in frequency and severity with age, with full criteria eventually recognized by the age of 10 years.[83]

Abnormal chest CT findings are documented in 15% of patients with NF1.[84] The more common abnormal radiologic findings are subcutaneous and skin nodules, with rates of cystic changes and emphysema approximately 15% and 18%, respectively.[84,85] The presence of emphysema seems to be related to a positive smoking history.[84,86] Cysts and bullous disease are common, particularly in the upper lobes, with sizes ranging between 8 and 25 mm; some of these cystic and bullous lesions may have thicker and more sharply defined walls than similar lesions observed in cases of smoking-related emphysema (Fig. 95.2).[84-86] Mediastinal masses are present in 15% of cases; 50% correspond to neurofibromas, and others are malignant peripheral nerve sheath tumors, meningoceles, and other causes.[84,87,88] Positive radiologic findings were related to symptoms and abnormal pulmonary function test results in most of the patients in two small case series.[85,86]

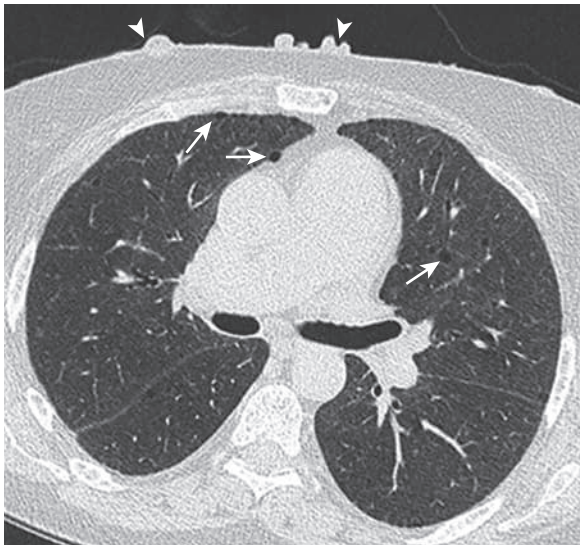

Figure 95.2 Neurofibromatosis. Axial computed tomography image of the chest demonstrates a few small (2- to 3-mm) lung cysts *(arrows)* with a random pattern of distribution in this patient with neurofibromatosis type 1. Also note cutaneous neurofibromas in the anterior and posterior chest walls *(arrowheads)*.

An additional complication is PH, categorized as group 5 (unclear and/or multifactorial mechanisms). The described cases to date have shown female predominance and presentation late in the course of NF, with median age at diagnosis of 57 years. Most patients have severe functional impairment (New York Heart Association functional class III or IV) at the time of diagnosis, with average mean pulmonary arterial pressure values of 49 mm Hg. There are no clear recommendations for this group for the use of PH-approved drugs.[82,89,90] Evidence of capillary hemangiomatosis has been described, and questions about a relatively high prevalence of pulmonary veno-occlusive disease have been raised, given the development of respiratory failure following the initiation of vasodilators.[91] The limited response to specific PH therapies and the poor prognosis of PH associated with NF1 indicate the need for prompt referral to lung transplantation centers following diagnosis.[90]

HERMANSKY-PUDLAK SYNDROME

Hermansky-Pudlak syndrome (HPS) is a rare autosomal recessive genetic disorder characterized by oculocutaneous albinism, bleeding diathesis, and granulomatous colitis. Ten subtypes have been recognized; among them, HPS-1, HPS-2, and HPS-4 are associated with pulmonary fibrosis and generally manifest with more severe disease.[91a] HPS affects approximately 500,000 to 1 million people worldwide. Puerto Rico has the highest prevalence, with 1 in 1800 in the northwest of the island, representing 50% of cases globally, most of them subtypes 1 and 3.[92,93]

The HPS genes encode proteins that form complexes termed *biogenesis of lysosome-related organelles complexes* (BLOCs), which are critical regulators of protein trafficking to lysosome-like organelles, such as melanosomes and platelet dense granules, thus explaining many of the syndrome manifestations. The *HPS1* gene product is a component of BLOC3, and *HPS1* mutations cause highly penetrant pulmonary fibrosis.[92,93] Evidence indicates that macrophage-mediated inflammation precedes pulmonary fibrosis.[93]

The diagnosis of HPS, regardless of the type, includes albinism and a functional platelet disorder resulting from a storage pool deficiency. Other manifestations include strabismus, nystagmus, and transillumination of the iris. *Idiopathic pulmonary fibrosis* (IPF) and HPS-related pulmonary fibrosis share the *usual interstitial pneumonia* (UIP) pattern but, in HPS, it is characterized by giant lamellar body formation in alveolar epithelial type 2 cells.[94] Virtually all patients with HPS-1 develop pulmonary fibrosis, typically around the fourth decade of life (in contrast to IPF, which usually manifests after the age of 60 years), with an average survival following the onset of pulmonary fibrosis of 10 years. Although the pattern of the fibrosis associated with HPS shares some similarities with IPF, there are distinct differences, particularly a greater frequency of ground-glass opacities, more common subpleural thickening, and generally less honeycombing (Fig. 95.3).[95] There are no Food and Drug Administration–approved treatments for HPS pulmonary fibrosis. Whether antifibrotic therapies such as pirfenidone or nintedanib have efficacy in HPS-associated pulmonary fibrosis is not well established at this time.[96] Despite the bleeding diathesis, patients with HPS-associated IPF have undergone lung transplantation successfully. Given the potential need

for lung transplantation in their future, patients should be managed with care to avoid alloimmunization from platelet transfusions that could prevent finding a suitable match.[97]

DYSKERATOSIS CONGENITA

Dyskeratosis congenita (DC) is a congenital premature aging syndrome and bone marrow failure disorder characterized by abnormal skin pigmentation, nail dystrophy, and oral leukoplakia. These abnormalities are secondary to short telomeres; in fact, telomere-mediated diseases were initially identified in the context of DC.[98] More recently, similar telomere mutations have been documented in adults with IPF.[99] These telomere-mediated disorders are now recognized as syndromes of telomere shortening, characterized by manifestations in multiple organs with the highest morbidity and mortality related to failure of the bone marrow, liver, and lung; indeed, the coexistence of bone marrow, liver, and lung dysfunction should alert clinicians to this diagnosis.[98,100,101]

Pulmonary fibrosis develops in a proportion of patients with DC, and lung function decline may be detected early in life, usually associated with cytopenias and the onset of bone marrow failure. Certain genotype abnormalities are linked with bone marrow failure, and studies are ongoing to determine whether these correlations also link with pulmonary complications, thus suggesting a possibility for early detection.[101] Histopathologic findings on lung biopsy include interstitial fibrosis with pneumocyte hypertrophy, intra-alveolar foamy macrophages, and honeycombing. Radiologic findings have been characterized as atypical UIP with frequent involvement of middle and upper lobes (Fig. 95.4).[101,102] Pulmonary involvement is usually progressive (eFig. 95.1). Rarely, lung disease may be complicated by the hepatopulmonary syndrome.[103] There are no known effective therapies for the interstitial lung disease in DC, and early referral for lung transplantation should be considered.

NIEMANN-PICK AND GAUCHER DISEASES

Niemann-Pick (NP) disease and Gaucher disease are rare lysosomal storage diseases, inherited in an autosomal recessive manner, that result in accumulation of lipid compounds in various organs. NP disease is associated with acid sphingomyelinase deficiency, and Gaucher disease is associated with deficient activity of the lysosomal enzyme glucocerebrosidase; these diseases cause accumulation of sphingomyelin and glucocerebroside, respectively. In both disorders, lipid-laden macrophages (called NP or Gaucher cells for the respective eponymous disorder) accumulate in different organs, including liver, spleen, bone marrow, brain, and lung.

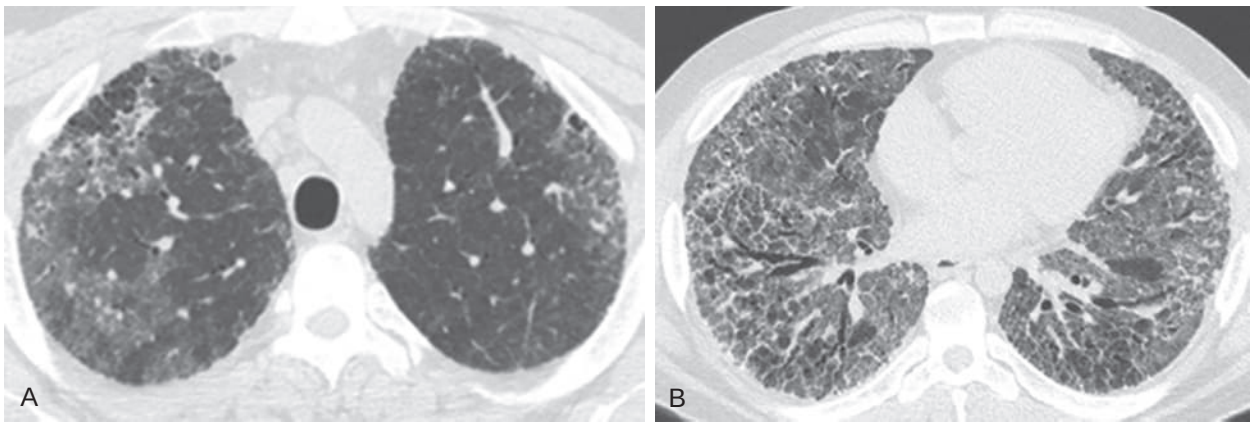

Figure 95.3 Hermanksy-Pudlak syndrome. Axial computed tomography images of the chest at the level of the (A) upper and (B) lower lobes demonstrate extensive reticulation, bronchiectasis, and ground-glass opacities with lower lobe predilection and with no definite honeycombing.

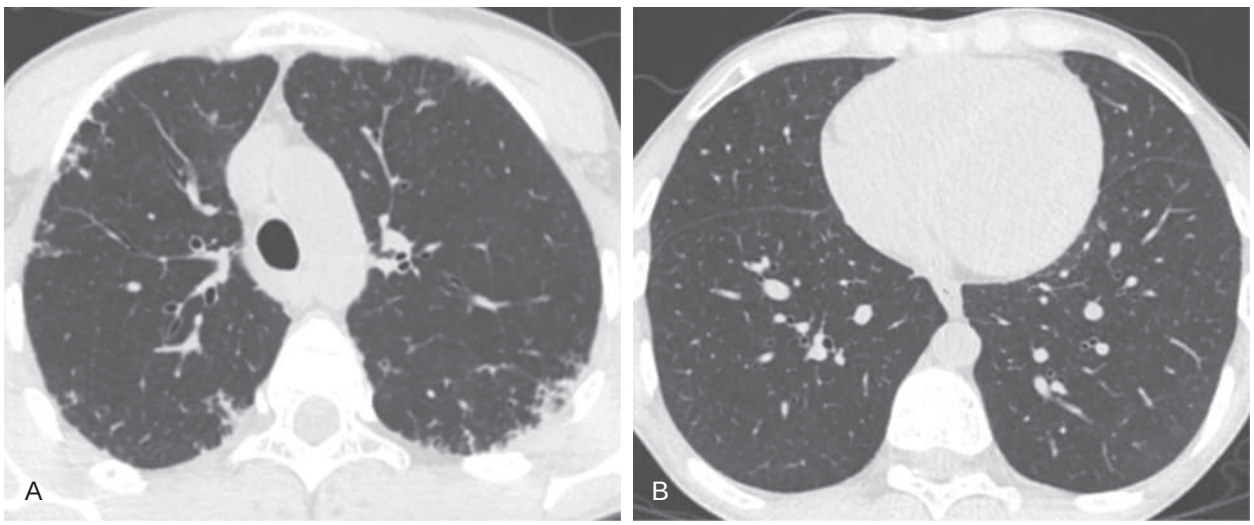

Figure 95.4 Dyskeratosis congenita. Axial computed tomography images of the chest at the level of the (A) upper and (B) lower lobes demonstrate subpleural reticulation with an upper lobe predilection and with no honeycombing.

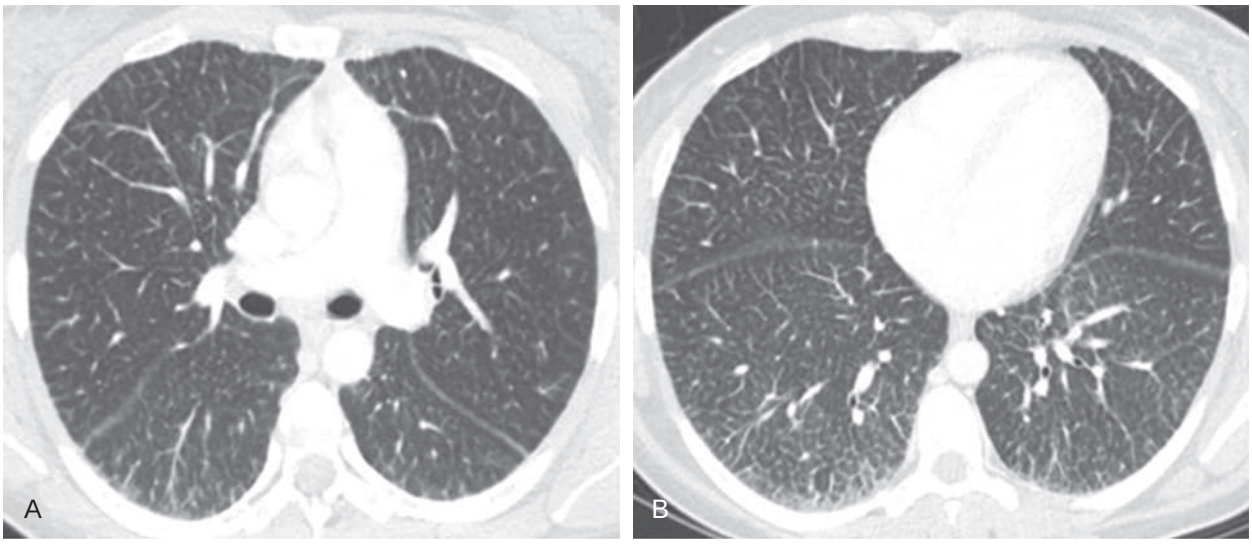

Figure 95.5 Niemann-Pick disease. Axial computed tomography images of the chest (A) immediately below the level of the carina and (B) lower lobes demonstrate interlobular septal thickening and ground-glass opacities, predominantly at the lung bases.

Each disease has different recognized subtypes. In NP disease, A and B subtypes are associated mostly with neurologic involvement. The A subtype is fatal during infancy, whereas the B subtype is associated with milder disease. The lung can be involved in all subtypes, but it is more common in type B, which causes chronic lung and bone marrow compromise without significant neurologic manifestations. Pulmonary involvement is detected mostly in adults, sometimes incidentally with an abnormal chest CT (Fig. 95.5 and eFig. 95.2) although, in some cases, it can progress to respiratory failure.[104,105] Of the three recognized subtypes of Gaucher disease, pulmonary disease is seen in type 1, usually in the more severe form of the disease. In both NP and Gaucher diseases, recurrent pulmonary infections are common.[106-108]

PH and hepatopulmonary syndrome have been documented in both NP and Gaucher diseases but seem to be more prevalent in the latter. The hepatopulmonary syndrome usually develops in the setting of long-standing liver disease and is associated with intrapulmonary shunting (intrapulmonary vascular dilations), with invariable association with splenomegaly. PH is not consistently related to the severity of the disease because it has been reported in cases of mild Gaucher disease.[110]

A presumptive diagnosis can be established in the setting of clinical symptoms, abnormal radiologic findings, and associated hepatosplenomegaly. The diagnosis of NP disease may be confirmed by genetic testing or determination of sphingomyelinase activity in peripheral blood leukocytes or cultured skin fibroblasts.[81,104] Analysis of bone marrow biopsy specimens may also reveal accumulations of lipid-filled macrophages.[109] BAL reveals lipid-laden macrophages. Lung biopsy shows foamy histiocytes in the alveolar space and interstitial tissue.[104] The diagnosis of Gaucher disease is confirmed by the finding of reduced glucocerebrosidase activity, usually in peripheral leukocytes, or detection of relevant mutations in peripheral blood cells.

Management is challenging and should include the usual supportive measures (vaccination, treatment of hypoxemia, pulmonary rehabilitation). Enzyme replacement therapy can ameliorate some of the manifestations, and cases of successful lung transplantation have been reported.[111]

PULMONARY ALVEOLAR MICROLITHIASIS

Pulmonary alveolar microlithiasis (PAM) is a rare autosomal recessive disorder characterized by widespread intraalveolar accumulation of calcium phosphate deposits called microliths. The disorder is linked to mutations in the type IIb sodium-dependent phosphate cotransporter, which results in an inability of alveolar epithelial type 2 cells to clear phosphorus ions from the alveolar space, thus leading to microlith or calcospherite formation in the extracellular fluid.[112,113]

The average age at the time of diagnosis is 40 years. There is no sex predilection. It is seen in all continents, but mostly in Europe and Asia, and particularly in Turkey and China.[114] Most patients are asymptomatic, with PAM diagnosed incidentally on the basis of radiologic findings. Slow progression follows in most cases (usually 10 to 20 years), with subsequent development of dyspnea, dry cough, chest pain and, in some cases, weight loss. Clubbing is present in most patients with advanced disease, and pneumothorax has been seen as a complication.[114]

Clinicoradiologic dissociation is an important characteristic, with minimal symptoms in the setting of abnormal or advanced radiologic changes. The *sandstorm sign* is characteristic of PAM. It is seen in both chest radiography and chest CT and consists of diffuse, scattered, bilateral areas of micronodular calcifications, involving the dependent portions of the lung, followed by the middle and upper areas (eFig. 95.3). The vascular tree and borders of the heart and diaphragm are often obscured ("vanishing heart" phenomenon).

A linear radiolucency at the pleural boundaries abutting the heart, diaphragm, and pleura on HRCT is also characteristic, and it has been named the *black pleural sign.* This characteristic imaging finding is likely secondary to the development of subpleural cystic changes, as reported in cross-sectional imaging and pathologic specimens.[112]



Figure 95.6 Pulmonary alveolar microlithiasis. (A) Chest radiograph showing the widespread intraalveolar deposition of calcium-containing microliths, with a lower lobe predominance. (B–C) Axial computed tomography images of the chest at the level of the (B) upper and (C) lower lobes demonstrate extensive alveolar granular calcifications in both lungs. Note the subpleural sparing giving the appearance of a "black pleura" sign, characteristic of alveolar microlithiasis.

This pattern can also be observed in mediastinal window images because calcification is present along the interlobular septa. One of the main differential diagnoses is miliary tuberculosis, given its similar radiologic appearance (Fig 95.6).[113-115]

At autopsy, the lungs are enlarged, heavy, and nonbuoyant, with a granular appearance of the pleural surface. The microliths are periodic acid–Schiff positive and form calcareous concentric lamellae around a central nucleus[113,114] (eFig. 95.4). The diagnosis is usually established in the setting of a characteristic radiologic appearance. Microliths can be isolated from BAL and even from sputum. Lung biopsy can be considered as well; transbronchial biopsy may be sufficient to provide the diagnosis.[116]

Currently, there is no recognized medical or gene therapy. Calcium-chelating agents, diphosphonates, and serial BAL have been ineffective. Lung transplantation should be considered.[114,117,118]

Key Points

- *Pulmonary Langerhans cell histiocytosis* (PLCH) is a smoking-induced diffuse lung disease that usually affects young adults and may cause varying degrees of bronchiolar, interstitial, and pulmonary vascular dysfunction.
- Analyses of PLCH tissues have identified activating mutations, particularly *BRAF*^{V600E}. For that reason, and because it can respond to chemotherapeutic agents such as cladribine, PLCH is currently considered a myeloid neoplasm with inflammatory characteristics.
- The natural history of PLCH is unpredictable: many patients have remissions or stabilize following smoking cessation, whereas others develop progressive lung disease.
- Smoking cessation is essential but not sufficient for all patients with PLCH. For a select subgroup, additional therapy with chemotherapy or *BRAF* inhibitor therapy may be necessary.
- Lung transplantation may extend life expectancy and improve quality of life in advanced PLCH, as well as in other rare infiltrative disorders discussed in this chapter, and it should be considered in patients with severe pulmonary involvement.
- Given the rarity of these disorders, referral to specialized centers and participation in clinical trials are recommended.
- Pulmonary hypertension group 5 (unclear and/or multifactorial mechanisms) may complicate the course of PLCH, neurofibromatosis, Niemann-Pick disease, and Gaucher disease.
- Hepatopulmonary syndrome can develop in patients with dyskeratosis congenita, Niemann-Pick disease, and Gaucher disease.

Key Readings

Allen CE, Merad M, McClain KL. Langerhans-cell histiocytosis. *N Engl J Med*. 2018;379:856–868.

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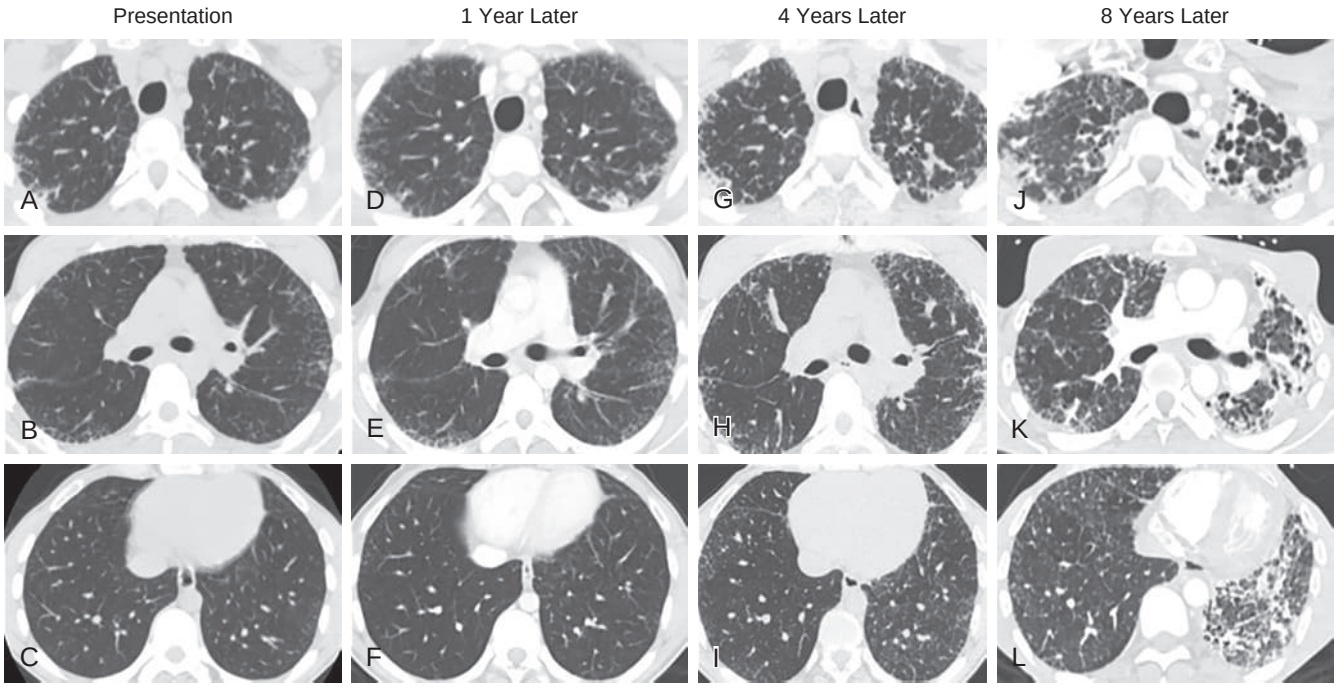
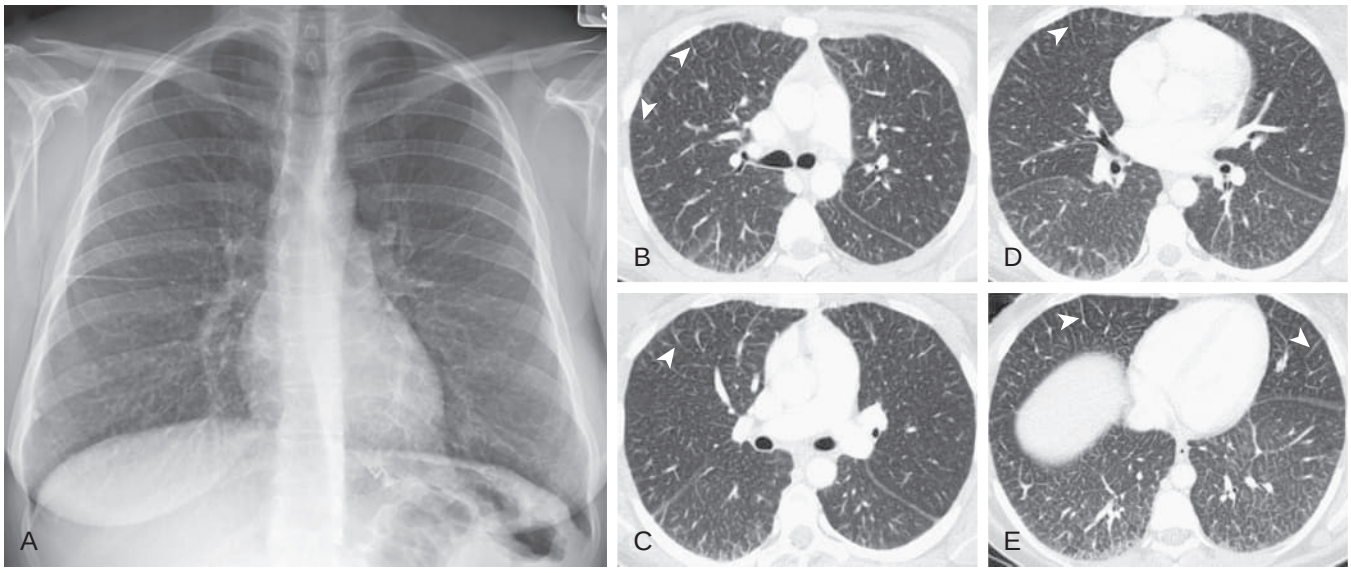
Complete reference list available at ExpertConsult.com.

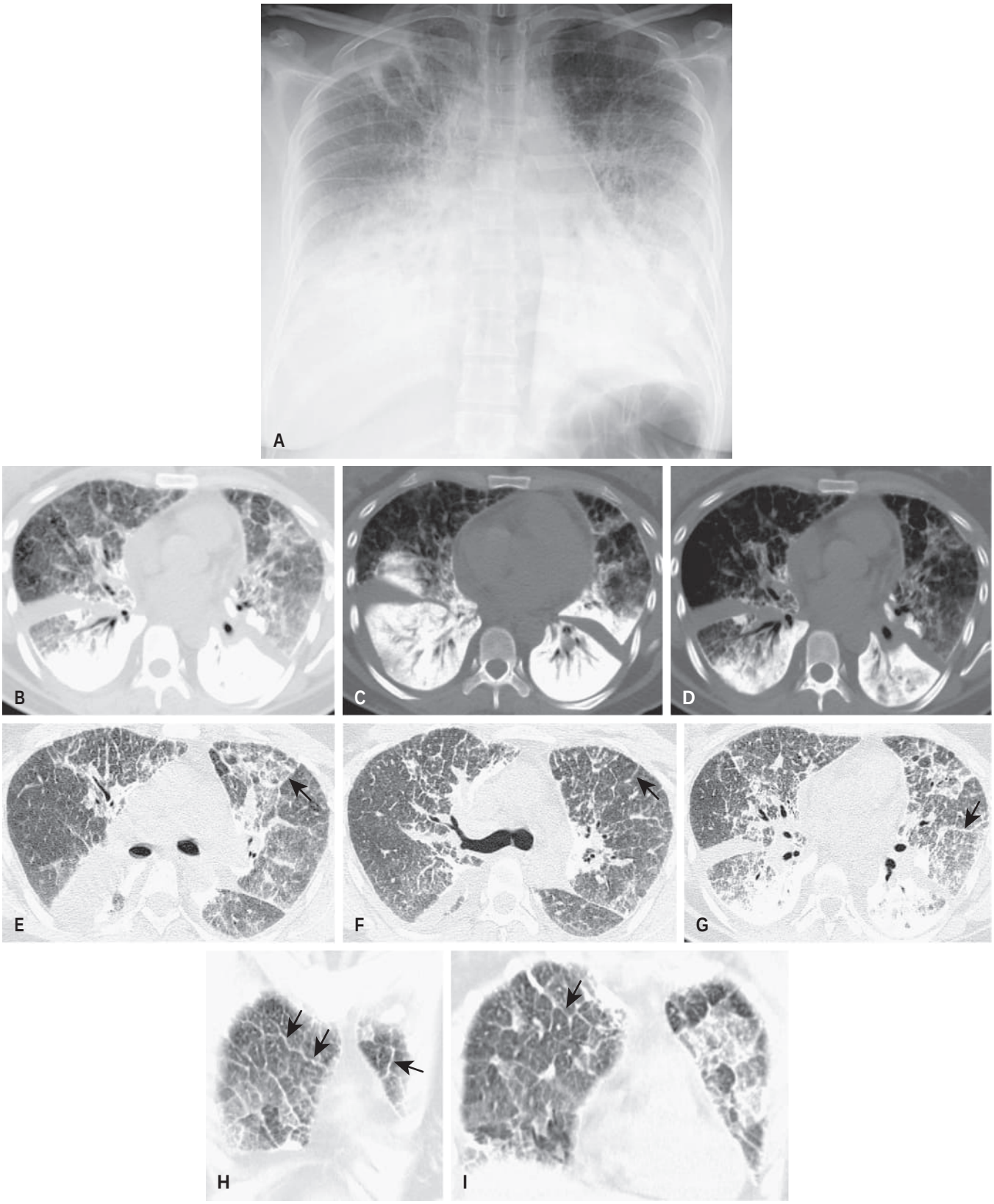
eFIGURE IMAGE GALLERY



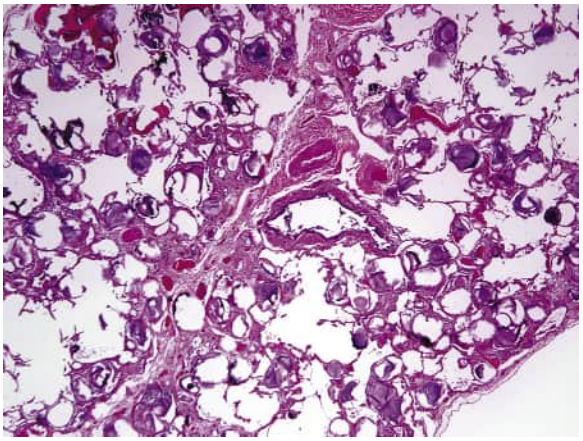
eFigure 95.1 Fibrotic lung disease secondary to dyskeratosis congenita. (A–C) Axial chest *computed tomography* (CT) through the (A) upper, (B) middle, and (C) lower lungs in a 30-year-old man at presentation shows upper lobe peripheral reticulation without honeycombing; only mild architectural distortion is present. (D–F) Axial chest CT through the (D) upper, (E) middle, and (F) lower lungs 1 year following presentation shows slightly more apparent upper lobe predominant reticulation. (G–I) Axial chest CT through the (G) upper, (H) middle, and (I) lower lungs shows progression 4 years after presentation. (J–L) Axial chest CT through the (J) upper, (K) middle, and (L) lower lungs 8 years after presentation shows severe upper lobe fibrotic disease with frank honeycombing in the left apex. Fibrosis at the bases, particularly the left, has also worsened, but the abnormalities remain most severe in the upper lobes. (Courtesy Michael B. Gotway, MD.)



eFigure 95.2 Niemann-Pick disease: chest radiographic and chest computed tomography findings. (A) Frontal chest radiograph in a 34-year-old patient with Niemann-Pick disease type B shows fine, symmetrical, basal-predominant reticulation. Lung volumes are normal, and no pleural disease is evident. (B–E) Axial chest computed tomography displayed in lung windows shows smooth interlobular septal thickening *(arrowheads),* becoming particularly pronounced in the bases bilaterally. (Courtesy Dr. Eric A. Jensen, Mayo Clinic, AZ, and Michael B. Gotway, MD.)



eFigure 95.3 Pulmonary alveolar microlithiasis: chest radiographic and chest computed tomography findings. (A) Frontal chest radiograph shows bilateral, extensive, hyperattenuating basal consolidation associated with extensive linear opacity radiating from the hila. A right apical cavity (a finding unrelated to pulmonary alveolar microlithiasis) is present. (B–D) Axial chest *computed tomography* (CT) displayed in (B) lung and (C–D) bone windows shows calcified basal consolidation. Extensive interlobular septal thickening, in some areas hyperattenuating, is present. (E–G) Axial high-resolution chest CT displayed in lung windows shows extensive interlobular septal thickening *(arrows),* which is also seen to advantage in the coronal reformatted images (H–I; *arrows).* (From Panse PM, Jensen EA, Gruden JF, Gotway MB. Pulmonary parenchymal consolidation at thoracic CT: clues to a specific diagnosis. *Clin Pulm Med.* 2014;21:104-106.)



eFigure 95.4 Histopathologic findings of pulmonary alveolar microlithiasis. Alveolar spaces are filled by lamellated, rounded microliths. (Courtesy Dr. Kirk Jones, University of California San Francisco.)

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96 EOSINOPHILIC LUNG DISEASES

VINCENT COTTIN, MD, PHD

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INTRODUCTION

The eosinophilic lung diseases are a group of disorders characterized by the presence and presumed pathogenetic role of eosinophils. They are mainly represented by the eosinophilic pneumonias, defined by a prominent infiltration of the lung parenchyma by eosinophils, which respond dramatically to corticosteroid treatment and generally heal without significant sequelae. The other eosinophilic lung diseases mainly involve the airways, as in the allergic bronchopulmonary mycoses and hypereosinophilic obliterative bronchiolitis. The eosinophilic endotype of asthma is not discussed in this chapter (see Chapter 60).

EOSINOPHIL BIOLOGY

PHYSIOLOGIC ROLE OF EOSINOPHILS

Identification of the multifunctional properties of the eosinophil has changed the view of eosinophils from terminal effector cells in allergic airway diseases to being involved in the initial stages of nonimmune and immune responses and disease.[1,2] Eosinophils are leukocytes implicated in innate and adaptive immunity, including numerous inflammatory reactions to parasitic helminth, bacterial, and viral infections.[3,4] They have been credited with a beneficial role against migratory nematode larvae in parasitic infestation through a strong *type 2 T-helper* (Th2) lymphocytic immune response and a non–antigen-specific host defense response mediated by group 2 innate lymphoid cells expressing *interleukin* (IL)-5.[5] In addition to their role in host protection, eosinophils have a role in tissue regeneration and repair after injury, metabolic homeostasis, immune homeostasis, angiogenesis, fibrosis, steady-state development of intestine and mammary gland, and tumor rejection.[1]

Many biologic properties of the eosinophil are directed by Th lymphocytes, but the eosinophil interacts in many allergic or inflammatory processes with other cells, including mast cells and basophils, endothelial cells, macrophages, platelets, and fibroblasts.[1,3,4,6] Eosinophils are

capable of regulating mast cell function and histamine release. Activated eosinophils express the major histocompatibility complex II protein *human leukocyte antigen* (HLA)-DR and possess the ability to participate in numerous immune functions, including antigen presentation and secretion of an array of cytokines capable of promoting effector T cell proliferation. Eosinophils are implicated in the regulation of Th1/Th2 balance through the synthesis of IL-4; the promotion of IL-4, IL-5, and IL-13 secretion by $CD4^+$ T cells; and the synthesis of indoleamine 2,3-dioxygenase (indirectly promoting Th1 apoptosis) (see also Chapters 15 and 16).

DIFFERENTIATION AND RECRUITMENT OF EOSINOPHILS TO THE LUNG

The eosinophil[3,4,6] matures in the bone marrow under the action of cytokines and especially of IL-5 (involved in the differentiation of eosinophil precursors), and, to a lesser extent, IL-3 and *granulocyte-macrophage colony-stimulating factor* (GM-CSF), the receptors of which use a common beta-chain, and the activation of transcription factors, including Δdbl-GATA-1. The eosinophil then circulates in the blood for about 1 day before being attracted into tissues by complex processes, including adhesion and chemoattraction, diapedesis, and chemotaxis, where it undergoes apoptosis unless survival factors are present. Recruitment of the eosinophil to the lung mostly implicates IL-5 and the eotaxin subfamily of chemokines (eotaxin is regulated by the Th2 cell–derived IL-13 cytokine).[7] IL-5 is mainly produced by Th2 cells but also by group 2 innate lymphoid cells implicated in the homeostatic homing of eosinophils to tissues, including the lungs.[8–10]

RELEASE OF PREFORMED PROTEINS

The release of proteins stored in intracellular granules is a major function of eosinophils and contributes to dysfunction and tissue damage.[11] Crystalline core-containing granules can release toxic cationic granule proteins (especially eosinophil peroxidase and eosinophil major basic protein-1[3]) and lipid mediators.[12] Granules also contain preformed cytokines that can be secreted by classical exocytosis, piecemeal degranulation, or cytolysis with granule release in a process that is rapid, stimulus dependent, and highly specific in terms of which cytokines are secreted.[1] For example, stimulation of eosinophils by eotaxin-1 leads to the rapid and specific release of granule-stored IL-4.[13] Vesicle-associated membrane proteins are implicated in the regulation of granule fusion in eosinophils.[6]

In addition to eosinophil-specific cationic proteins and cytokines, eosinophils release arachidonic acid–derived mediators, enzymes, reactive oxygen species, and matrix metalloproteases. They express a variety of surface proteins, including adhesion molecules, apoptotic signaling molecules, chemokines, complement receptors, chemotactic factor receptors, cytokine receptors, and immunoglobulin receptors.

The release of toxic substances contributes to the pathophysiology of eosinophilic disorders.[3] Eosinophilic cationic proteins have direct toxicity to the heart, brain, and bronchial epithelium.[11] Activated, degranulated eosinophils and cationic proteins can be found in the *bronchoalveolar lavage* (BAL)[14,15] and the lung tissue[16–18] of patients with eosinophilic pneumonia, and in cardiac lesions in the hypereosinophilic syndrome or in tropical eosinophilia.[19,20] Eosinophil-derived neurotoxin can be found in the urine in patients with active eosinophilic disease.[21,22]

Although histopathologic lesions in eosinophilic pneumonias are largely reversible with treatment, there may be tissue damage and remodeling with fibrosis partly through the release by eosinophils of transforming growth factor-β, especially in the bronchial mucosa, as in allergic bronchopulmonary aspergillosis and in *eosinophilic granulomatosis with polyangiitis* (EGPA).

TARGETING THE EOSINOPHIL CELL LINEAGE

Corticosteroids are the most effective agents for dramatically reducing eosinophilia in the blood and tissues by shortening the half-life of cytokines, such as eotaxins, and by inhibiting the cytokine-dependent survival of eosinophils; however, corticosteroids lack specificity.[23] Because IL-5 is involved at all stages of eosinophil differentiation, priming, activation, degranulation, and mediator secretion, monoclonal antibodies targeting the IL-5 pathway have been developed to target this cell lineage selectively,[24] first in humans with asthma[25–28] and later in various eosinophilic disorders.[29,30] Several other biologic therapies are already licensed to suppress type 2 inflammation via *immunoglobulin* (Ig)E and IL-4 receptor α.[31] Other targets for therapy more specific for eosinophils are being investigated, including eotaxins, which drive eosinophil recruitment into tissues, CD2-binding protein, and eosinophil surface-expressed inhibitory receptors,[1] especially Siglec-8.[32]

GENERAL FEATURES OF EOSINOPHILIC PNEUMONIAS

HISTORICAL PERSPECTIVE

In 1952, Reeder and Goodrich[33] published a series of cases describing pulmonary "infiltration with eosinophilia," including probable *idiopathic chronic eosinophilic pneumonia* (ICEP) and EGPA. In the same year, Crofton and coworkers[34] published a series of 16 cases of "pulmonary eosinophilia" with a review of 450 cases from the literature and proposed a classification of clinical presentations, including a description of simple pulmonary eosinophilia (Loeffler syndrome), defined by mild symptoms and transient opacities and, of interest, they mentioned "a continuum from the Loeffler syndrome to the severe and often fatal manifestations of polyarteritis nodosa." Churg and Strauss had reported in 1951[35] the eponym syndrome of "allergic granulomatosis, allergic angiitis, and periarteritis nodosa," now EGPA, and Carrington and colleagues[36] described in 1969 the syndrome of ICEP. McCarthy and Pepys[37] later reported 27 cases of "cryptogenic pulmonary eosinophilias," two of which developed systemic vasculitis. Idiopathic acute eosinophilic pneumonia was described by Davis and colleagues

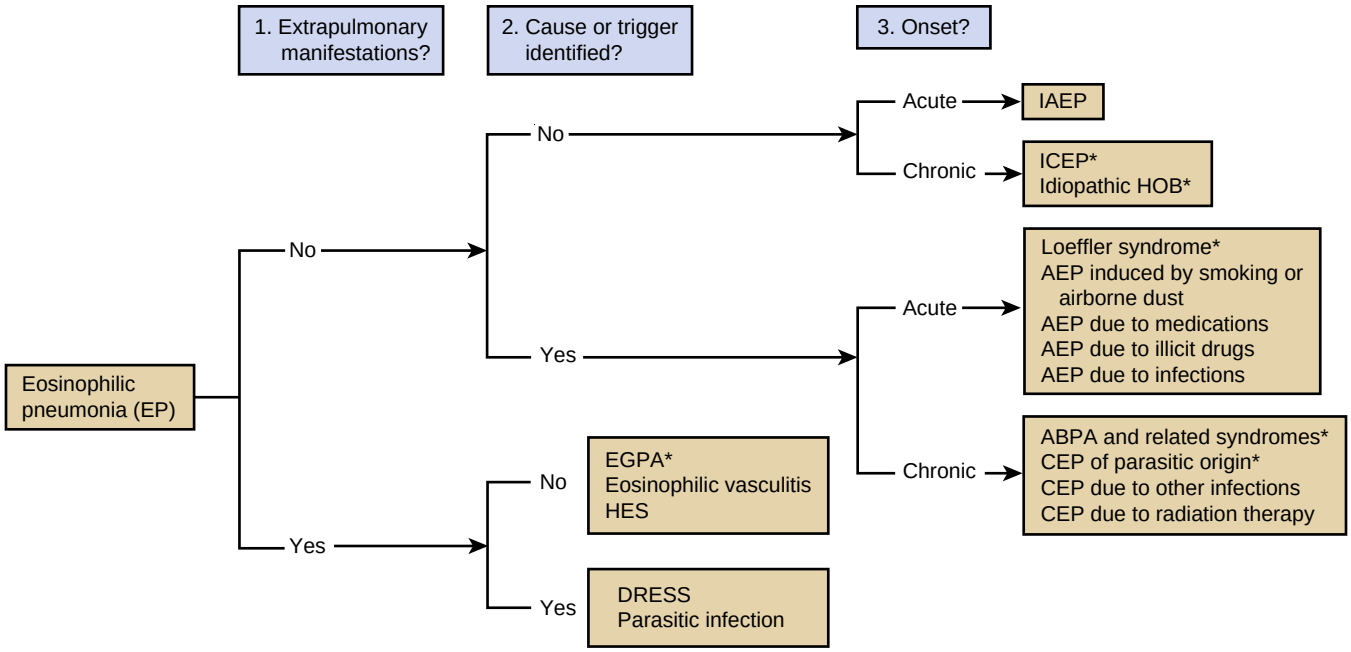

Figure 96.1 Diagnostic algorithm for eosinophilic pneumonia. The initial diagnostic question is whether there are extrapulmonary manifestations. *Conditions commonly associated with asthma or airflow obstruction. ABPA, allergic bronchopulmonary aspergillosis; AEP, acute eosinophilic pneumonia; CEP, chronic eosinophilic pneumonia; DRESS, drug reaction with eosinophilia and systemic symptoms; EGPA, eosinophilic granulomatosis with polyangiitis; HES, hypereosinophilic syndrome; HOB, hypereosinophilic obliterative bronchiolitis; IAEP, idiopathic acute eosinophilic pneumonia; ICEP, idiopathic chronic eosinophilic pneumonia.

in 1986,[38] then by Badesch and colleagues[39] and Allen and colleagues in 1989.[40] Hypereosinophilic bronchiolitis[41] and EGPA limited to the lung[42] were described recently.

CLINICAL PRESENTATION

Eosinophilic pneumonia is a pneumonia in which, on histopathologic examination, eosinophils are the most prominent inflammatory cells. Other inflammatory cells, especially lymphocytes and neutrophils, are often associated, but eosinophils clearly predominate. In clinical practice, eosinophilic pneumonias may be separated into two main etiologic categories: (1) those in which a definite cause is found or (2) those of undetermined origin (idiopathic), with the eosinophilic pneumonia being either solitary or included in a systemic disorder such as EGPA. A definite cause must be carefully investigated in any patient with eosinophilic pneumonia because it has practical consequences (e.g., stopping a drug responsible for iatrogenic eosinophilic pneumonia or treating a parasitic infection) (Fig. 96.1).

PATHOLOGY

Histopathologic studies of eosinophilic pneumonia have mainly been done in patients with ICEP,[36,43,44] which was initially diagnosed by open-lung biopsy. The pathologic features described in ICEP may be considered as a common denominator of all categories of eosinophilic pneumonias, whatever their origin. Additional features may be seen in other conditions, such as a distinctive distribution of lesions (e.g., bronchocentric distribution in *allergic bronchopulmonary aspergillosis* [ABPA], angiocentric distribution in EGPA), the presence of causal agents such as parasites or fungal hyphae, or necrotizing vasculitis in EGPA.[42]

In ICEP, the alveolar spaces are filled with eosinophils (Fig. 96.2A). Macrophages are also present, with some multinucleated giant cells scattered in the infiltrate; these may contain eosinophilic granules or *Charcot-Leyden crystals*, which are microscopic crystals composed of the eosinophil protein galectin-10.[36] An associated proteinaceous and fibrinous exudate and an interstitial inflammatory cellular infiltrate consisting of eosinophils, lymphocytes, plasma cells, and histiocytes are present. Some eosinophilic microabscesses may be observed as foci of necrotic intra-alveolar eosinophils surrounded by macrophages or epithelioid cells with palisading arrangement. The global architecture of the lung remains intact.

Organization of the alveolar inflammatory exudate is common,[36] suggesting some possible overlap between ICEP and organizing pneumonia. However, in ICEP, intraluminal organization in the distal air spaces is only sparse and never prominent and mucus plugs obstructing the small airways may be present.[36] A mild *non-necrotizing* vasculitis involving both small arteries and venules is common, with perivascular cuffing and a few cells infiltrating the arterial media (see Fig. 96.2B). The hilar lymph nodes associated with ICEP contain many eosinophils, and lymphoid hyperplasia is present.[36]

In *idiopathic acute eosinophilic pneumonia* (IAEP), the pathologic pattern includes intra-alveolar and interstitial eosinophilic infiltrates, diffuse alveolar damage, intra-alveolar fibrinous exudates, organizing pneumonia, and non-necrotizing vasculitis (Fig. 96.3).[45]

DIAGNOSIS

In clinical practice, the diagnosis of eosinophilic pneumonia is suspected in patients presenting with respiratory

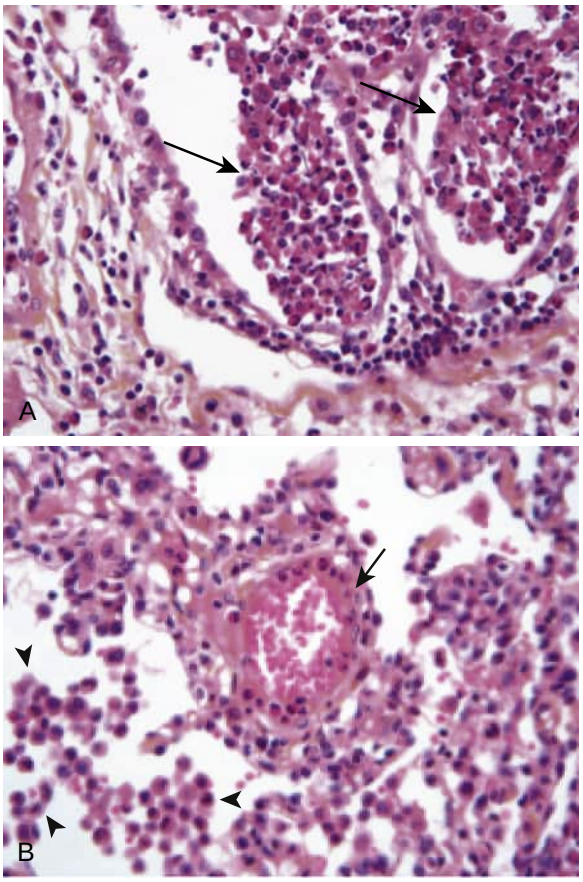

Figure 96.2 Eosinophilic pneumonia. (A) There is an accumulation of eosinophils (*arrows*) within the alveoli. (B) Eosinophils have infiltrated the arteriolar wall (non-necrotizing vasculitis) (*arrow*) and are present within the alveoli (*arrowheads*). (Courtesy Françoise Thivolet-Béjui, MD, Department of Pathology, Louis-Pradel Hospital and Claude Bernard University, Lyon, France.)

symptoms (dyspnea, cough, or wheezing), pulmonary opacities on chest imaging, and the demonstration of eosinophilia in the peripheral blood or, preferably, in the lung. Of importance, *blood eosinophilia* is defined by an eosinophil blood count greater than 0.5×10^9/L (500/μL) and *hypereosinophila* by an eosinophil blood count greater than 1.5×10^9/L (1500/μL) on two examinations at least 1 month apart, and/or tissue hypereosinophilia.[46]

Lung biopsy is seldom necessary to confirm the diagnosis of eosinophilic pneumonia. Transbronchial forceps lung biopsy may show characteristic features, but the small size of the specimen usually does not allow morphologic evidence of a possible etiologic process. Transbronchial cryobiopsy may be useful in difficult cases.[47,48]

BAL is recommended to confirm the diagnosis of eosinophilic pneumonia in most cases. BAL is a widely accepted noninvasive surrogate of lung biopsy for the diagnosis in a patient with *high-resolution computed tomography* (HRCT) features of eosinophilic pneumonia, although no study has definitely established a correlation between increased eosinophils at BAL and the finding of eosinophilic pneumonia at lung pathology. In normal subjects, BAL eosinophils comprise less than 1% of cells.[49,50] In contrast, BAL eosinophilia greater than 40% is found mainly in patients with chronic eosinophilic pneumonia, whereas BAL eosinophilia from 3–25% (and especially from 3–9%) may be found in various conditions, such as idiopathic pulmonary fibrosis, interstitial lung disease associated with connective tissue disorders, hypersensitivity pneumonitis, sarcoidosis, radiation pneumonitis, asthma, pneumoconioses, and infection.[51]

A conservative cutoff of 40% of eosinophils in the BAL has been adopted for the diagnosis of ICEP in clinical studies,[52,53] and a cutoff of 25% has been proposed for the diagnosis of IAEP.[54] For clinical practice, a diagnosis of eosinophilic pneumonia is supported by alveolar eosinophilia when the eosinophils (1) are the predominant cell population (macrophages excepted) and (2) represent more than 25% of the differential cell count in the BAL.[50]

Although BAL is usually useful and safe in patients with suspected eosinophilic pneumonia, it may not always be mandatory in typical cases with both pulmonary opacities on imaging and markedly elevated peripheral blood eosinophilia (>1×10^9/L and preferably 1.5×10^9/L [1500/μL]). However, BAL also contributes to alternative diagnoses in cases of bacterial or parasitic pneumonia or when pulmonary opacities are related to Hodgkin disease. BAL is generally omitted in Loeffler syndrome. Conversely, peripheral blood eosinophilia may be missing in patients who have already received systemic corticosteroids, and it is often absent at presentation in IAEP.

Once the diagnosis of eosinophilic pneumonia has been made, a thorough evaluation is necessary to investigate possible causes, such as parasitic infection or drug or toxic exposure, and to classify the case into one of the possible clinical entities (see Fig. 96.1).

IDIOPATHIC CHRONIC EOSINOPHILIC PNEUMONIA

CLINICAL FEATURES

ICEP was first described in detail by Carrington and colleagues[36] in a series of nine patients and further confirmed and detailed by several series.[44,52,55–59] It is the most frequent cause of eosinophilic pneumonia is Western countries. Current diagnostic criteria of ICEP are listed in Table 96.1.

ICEP is characterized by a progressive onset of symptoms over a few weeks or months with cough, increasing dyspnea, malaise, and weight loss. ICEP arises predominantly in women (with a 2:1 female/male ratio). It is rare before the age of 20 years,[60] and incidence is highest in the fourth decade.[44,52] A vast majority of patients are nonsmokers.[44,52,56,58] A prior history of atopy is found in about half of the patients, with allergic rhinitis in 12%[44] to 24%,[52] drug allergy in about 10%,[44,52] nasal polyps in 5–13%,[44,52] urticaria in 10%,[52] and eczema in 5%.[52]

Prior asthma is present at diagnosis of ICEP in two-thirds of the patients, develops concomitantly with the diagnosis of ICEP in 15% of patients, and can develop after ICEP in 13%.[53] The presentation of ICEP is similar in asthmatic and nonasthmatic patients, with the exception of higher total IgE in asthmatics.[53] Allergic desensitization is not considered to trigger ICEP. Asthma often gets worse after the development of ICEP and requires long-term oral corticosteroid

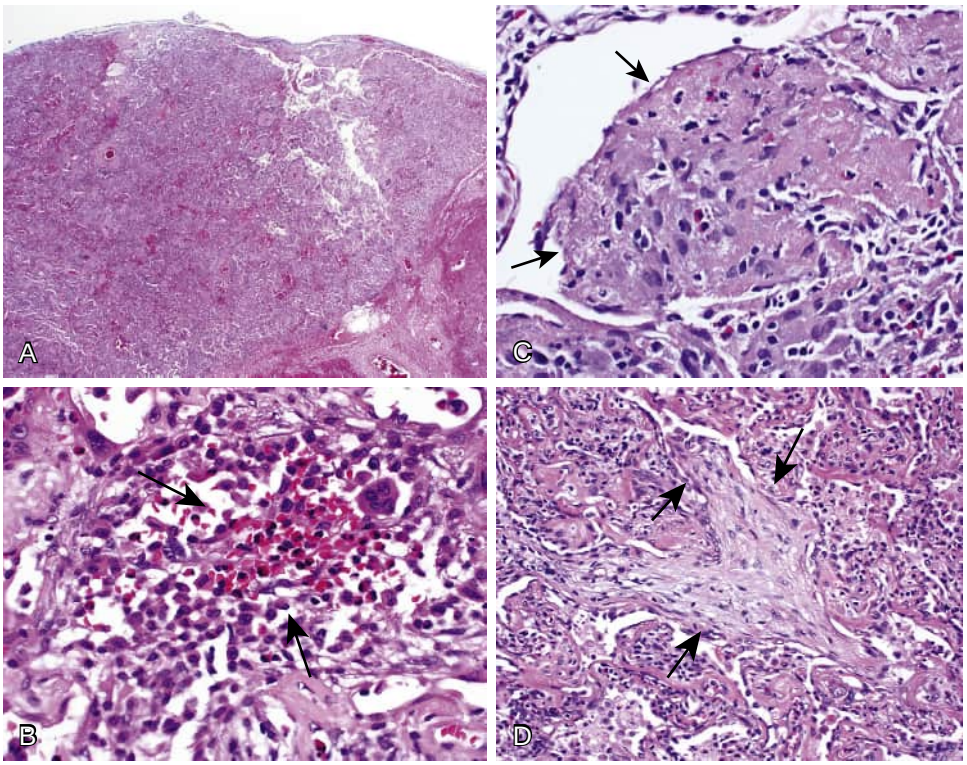

Figure 96.3 Acute eosinophilic pneumonia. (A) In acute eosinophilic pneumonia, the alveolar spaces are diffusely filled with eosinophils and plump eosinophilic macrophages, sometimes with an associated mild interstitial pneumonia. In this low-power view, multiple alveolar spaces are completely filled, up to the pleural surface. (B) Eosinophilic microabscesses (*arrows*) may be present. (C) Fibrinous air space exudates (*arrows*) are commonly present, typically with admixed eosinophils, as seen in this specimen. (D) Organizing pneumonia pattern with repair may also be seen (*arrows*). (From Leslie KO, Wick MR. *Practical Pulmonary Pathology: A Diagnostic Approach: A Volume in the Pattern Recognition Series.* ed 2. Philadelphia: Elsevier; 2011.)

Table 96.1 Distinctive Features of Idiopathic Chronic Eosinophilic Pneumonia and Idiopathic Acute Eosinophilic Pneumonia

	Idiopathic Chronic Eosinophilic Pneumonia	Idiopathic Acute Eosinophilic Pneumonia
Onset	>2–4 wk	<1 mo
History of asthma	Yes	No
Smoking history	10% are smokers	Two-thirds are smokers; often recent initiation
Respiratory failure	Rare	Usual
Initial blood eosinophilia	Yes	Often no (typically delayed)
BAL eosinophilia	>25%	>25%
Chest imaging	Homogeneous peripheral air space consolidation	Bilateral patchy areas of ground-glass attenuation, airspace consolidation, interlobular septal thickening, bilateral pleural effusion
Relapse	Yes	No
Diagnostic criteria	1. Diffuse pulmonary alveolar consolidation with air bronchogram and/or ground-glass opacities at chest imaging, especially with peripheral predominance 2. Eosinophilia at BAL differential cell count ≥ 40% (or peripheral blood eosinophils ≥ 1000 /mm^3) 3. Respiratory symptoms present for at least 2–4 wk 4. Absence of other known causes of eosinophilic lung disease (especially exposure to drug susceptible to induce pulmonary eosinophilia)	1. Acute onset with febrile respiratory manifestations (≤1 mo, and especially ≤7 days' duration before medical examination 2. Bilateral diffuse opacities on imaging 3. Pa_{O_2} on room air ≤ 60 mm Hg (8 kPa), or Pa_{O_2} /F_{IO_2} ≤ 300 mm Hg (40 kPa), or oxygen saturation on room air <90% 4. Lung eosinophilia, with ≥25% eosinophils at BAL differential cell count (or eosinophilic pneumonia at lung biopsy when done) 5. Absence of determined cause of acute eosinophilic pneumonia, including infection or exposure to drugs known to induce pulmonary eosinophilia. Recent onset of tobacco smoking or exposure to inhaled dusts may be present

BAL, bronchoalveolar lavage; F_{IO_2}, fractional concentration of oxygen in inspired gas; IAEP, idiopathic acute eosinophilic pneumonia; ICEP, idiopathic chronic eosinophilic pneumonia; kPa, kilopascal; Pa_{O_2}, arterial P_{O_2}.

treatment even in the absence of recurrence of the eosinophilic pneumonia.[53]

The onset of ICEP is progressive, with a mean interval between the onset of symptoms and the diagnosis of several weeks, and up to 4 months in one series.[52] However, the disease may be severely symptomatic at the time of diagnosis, and the definition of "chronic" may create some ambiguity. Fever, weight loss (>10 kg in about 10%), asthenia, malaise, fatigue, anorexia, weakness, and night sweats are also common.[52,58] The most common respiratory symptoms

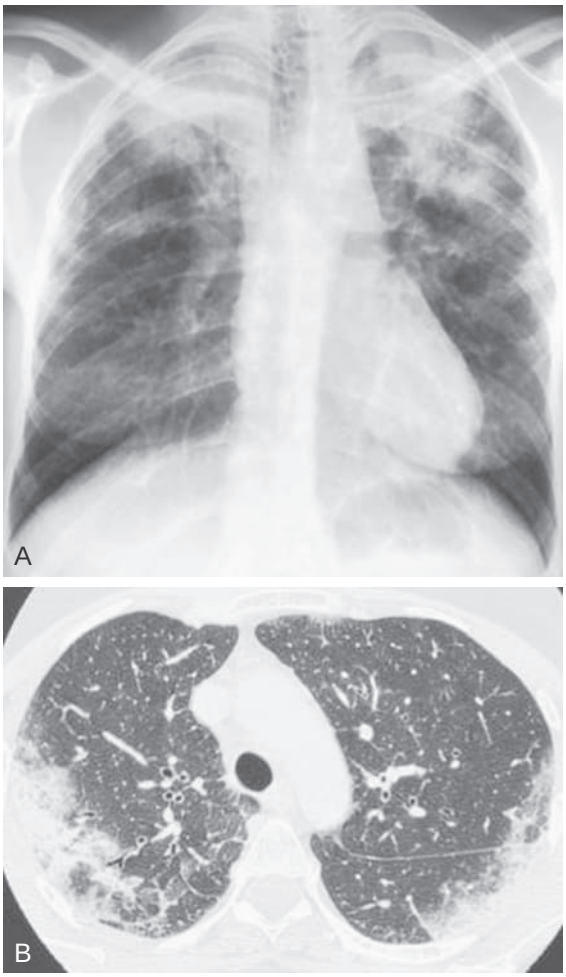

Figure 96.4 Idiopathic chronic eosinophilic pneumonia. (A) Chest radiograph of a patient with idiopathic chronic eosinophilic pneumonia shows bilateral alveolar opacities predominating in the upper lobes. (B) Axial chest computed tomography scan of a patient with idiopathic chronic eosinophilic pneumonia shows bilateral symmetrical peripheral alveolar opacities.

are cough, dyspnea, and chest pain.[44,52] Dyspnea is usually not severe initially, although respiratory failure has been reported.[61,62] Hemoptysis is rare (<10% of cases).[44,52] Wheezes at physical examination are found in one-third of patients[44] and crackles in 38%.[52] Upper respiratory tract symptoms of chronic rhinitis or sinusitis are present in about 20% of patients.[52]

IMAGING

The imaging features of ICEP are characteristic, although they may overlap with those found in cryptogenic organizing pneumonia. Peripheral opacities on chest radiography are present in almost all cases[36,44,52] and are migratory in a one-fourth of the cases.[52] They usually consist of alveolar opacities with ill-defined margins, with a density varying from ground-glass to consolidation (Fig. 96.4A, eFig. 96.1). The classic pattern of "photographic negative or reversal of the shadows usually seen in pulmonary edema,"[63,64] which is highly suggestive of ICEP,[63] is seen in only one-fourth of patients.[44]

The characteristic imaging features of ICEP are better described at HRCT (see Fig. 96.4B). Whereas the opacities are bilateral in at least 50% of cases at chest radiography,[44,56] the proportion of bilateral opacities may increase up to 97.5% at HRCT.[52] Characteristic opacities predominate in the upper lobes[44,52,65] and are peripheral, with generally coexisting ground-glass and consolidation opacities (Video 96.1).[52,66–69] Midzone distribution of opacities and centrilobular nodules are present in less than 20% of cases.[68] Lower lung zone involvement is infrequent.[58] Consolidation with segmental or lobar atelectasis may be seen.[66] Septal line thickening is common (see Video 96.1).[67] On corticosteroid treatment, consolidation and ground-glass opacities rapidly show a decrease in size and extent (eFig. 96.2), with possible change from consolidation to ground-glass opacities or inhomogeneous opacities and later to streaky or bandlike opacities parallel to the chest wall.[66] Cavitary lesions are extremely rare and should lead to reconsideration of the diagnosis. Contrary to organizing pneumonia, the reverse halo or atoll sign (i.e., central ground-glass opacity surrounded by denser consolidation in a crescentic circle or ring) is rare. Mediastinal lymph nodes are enlarged in 15–20%.[52,58] Compared with IAEP, in which pleural effusions are seen in the majority (see later), small pleural effusions are present in only 10% of cases of ICEP at HRCT.

LABORATORY STUDIES

Peripheral blood eosinophilia is almost always present, with the exception of cases where treatment has been initiated before the test. The mean percentage of blood eosinophils at differential count is generally greater than 20%,[44] and the mean blood eosinophilia is often greater than 5×10^9/L (5500/μL).[52,58] C-reactive protein level is elevated.[44,52,56] Total blood IgE level is increased in about half of cases and is greater than 1000 IU/mL in 15% (normal < 100 IU/mL) but lacks specificity.[52] Fractional exhaled nitric oxide is increased in ICEP and has been proposed as a way to monitor eosinophilic parenchymal inflammation.[70] Measurement of urinary excretion of eosinophil proteins and leukotrienes has been proposed for monitoring disease activity[21,71]; however, it is not widely available.

BRONCHOALVEOLAR LAVAGE

BAL is generally recommended for the diagnosis of ICEP. Alveolar eosinophilia is always present, with a differential cell count greater than 25% (mean value, 38% and 58% in two large series). A value greater that 40% is considered most consistent with a confident diagnosis of ICEP in the appropriate clinical setting.[52,58] Alveolar eosinophilia may also be associated with an increased percentage of neutrophils, mast cells, and lymphocytes.[52] BAL eosinophil cell count drops within a few days under corticosteroid treatment.[72] Sputum eosinophilia may also be present.[34,57]

Eosinophils with features of degranulation, activation and suppression of apoptosis (defined by in vitro studies), and eosinophil cationic proteins and various mediators are present in BAL fluid[15,73–88] and lung tissue[89] of patients

with ICEP. Of note, BAL lymphocytes are characterized by an accumulation of $CD4^+$ T cells that express activation surface antigens of memory T cells ($CD45RO^+$, $CD45RA^-$, $CD62L^-$)[90] and may present clonal rearrangement of the T cell receptor repertoire.[91,92]

DIFFERENTIAL DIAGNOSIS

Parasitic infection and drug-induced lung disease must be excluded. Although ICEP is not a systemic disease, isolated and moderately severe extrapulmonary manifestations, including arthralgias, repolarization (ST-T) abnormalities on the electrocardiogram, pericarditis, altered liver biologic tests, or eosinophilic lesions at liver biopsy, have been reported occasionally.[36,52] More significant manifestations, such as mononeuritis multiplex, skin nodules, or eosinophilic enteritis, suggest misclassification or overlap between ICEP and EGPA. Because eosinophilic pneumonia similar to ICEP may be a presenting feature of EGPA,[93–95] a thorough clinical evaluation is warranted, especially for clinically silent cardiac or renal involvement by EGPA, particularly in patients who have already received corticosteroids, which might prevent the development of overt systemic vasculitis.

PULMONARY FUNCTION TESTS

Pulmonary function tests (PFTs) in ICEP show an obstructive ventilatory defect in about half the patients[44,52] and a restrictive ventilatory defect in the other half.[52] An arterial partial pressure of oxygen of 75 mm Hg or less was present in 64% of patients in one series.[52] *Diffusion capacity for carbon monoxide* (D_{LCO}) may be decreased due to restrictive physiology, but the transfer coefficient (D_{LCO}/unit alveolar volume) is impaired in only one-fourth of cases.[52] An increased alveolar-arterial oxygen tension difference has been reported in 90% of cases.[44]

With treatment, PFTs normalize rapidly in most patients.[44] However, asthma frequently gets worse after the diagnosis of ICEP and may require long-term oral corticosteroids.[53] A persistent obstructive ventilatory defect may develop over time in one-third of patients,[58] especially those with a markedly increased BAL eosinophilia[96] or with airflow obstruction[58] at initial evaluation.

TREATMENT AND PROGNOSIS

Because ICEP is generally symptomatic, most patients are treated, although spontaneous resolution has been reported.[44,52] Response to oral corticosteroids is dramatic and rapid, with symptomatic improvement within 48 hours in about 80% of cases.[52] Death directly resulting from ICEP is exceedingly rare. Pulmonary opacities on chest radiography clear rapidly (eFig. 96.3), within 1 week of treatment in the majority of patients.[52]

The initial dose of corticosteroids usually varies between 20 and 60 mg/day. In an open-label, parallel group study, patients with ICEP were randomized to receive oral prednisolone for either 3 months or 6 months, with an initial dose of prednisolone of 0.5 mg/kg/day, which was then tapered and discontinued at either 3 or 6 months.[97] The primary end point was relapse during the follow-up period. No significant difference was found in the cumulative rate of relapse, and all relapses improved rapidly upon resumption of prednisolone. Our group starts with 0.5 mg/kg/day of prednisone, with slow tapering down to 5 to 10 mg/day over 3 months based on clinical evaluation and blood eosinophil cell count.

The clinical series in which follow-up is reported clearly show that most patients need very prolonged corticosteroid treatment due to the high frequency of relapse (>50%) below a daily dose of 10 to 15 mg/day of prednisone, or after stopping the corticosteroid treatment.[44,52,55] Relapses respond well to resumed corticosteroid treatment; a dose of 20 mg/day of prednisone is usually sufficient to treat the relapses.

Respiratory symptoms may be due to asthma or to a relapse of ICEP. Relapses of ICEP may be less frequent in patients with asthma, possibly because they often receive inhaled corticosteroids after stopping oral corticosteroids.[52,53] Inhaled corticosteroids might thus help in reducing the maintenance dose of oral corticosteroids, although they are not sufficient when given as monotherapy.[98] Alternate-day oral prednisone may reduce the adverse effects of systemic glucocorticoids. Long-term steroid use may lead to osteoporosis.

Omalizumab, a recombinant humanized monoclonal antibody against IgE, has been suggested in case reports to prevent recurrence of ICEP and to spare oral corticosteroids[99–101]; however, caution must be exerted given recent reports of omalizumab-associated EGPA.[102,103]

Successful off-label use of mepolizumab,[104,105] a monoclonal antibody against IL-5, and benralizumab,[47,104,106] an IL-5 receptor antagonist, were reported in case reports of ICEP. Because of the exquisite sensitivity of ICEP to corticosteroids, medications targeting the IL-5 pathway should be used with caution in patients with ICEP, pending further studies. Cases considered refractory to corticosteroids should lead the clinician to reconsider the diagnosis of ICEP.

IDIOPATHIC AND SMOKING-RELATED ACUTE EOSINOPHILIC PNEUMONIA

IAEP differs from ICEP by its acute onset; the severity of hypoxemia; the usual lack of increased blood eosinophils at presentation, contrasting with frank eosinophilic alveolitis at BAL (BAL differential count with ≥25% eosinophils); and the absence of relapse after clinical recovery.[38–40,45,54,57,107–109] Because fever and bilateral opacities on chest radiograph are present in nearly all patients, IAEP is often misdiagnosed as infectious pneumonia, and its frequency may therefore be underestimated[54] (see Table 96.1).[110]

CLINICAL FEATURES

IAEP presents acutely in previously healthy young adults,[111–113] with an average age at presentation of 30 years.[54,109,114,115] It is very rare in children.[116] A second peak has been reported in individuals age 60 years or older.[117] In contrast with ICEP, IAEP predominates in men,[112,115,118] and most patients have no prior asthma history.[57]

Symptoms at presentation consist of acute onset of cough, dyspnea, fever, and chest pain. IAEP may also develop subacutely over a few weeks (up to 1 month).[45,109] Abdominal complaints and also myalgias have been reported.[54] At physical examination, tachypnea and tachycardia are present, with crackles or, less often, wheezes on auscultation.

EXPOSURE AND TRIGGERS

AEP can be due to identifiable causes, including medications (see later) and inhalational exposures, especially cigarette smoke. Most patients diagnosed with IAEP seem to have been exposed to dust or cigarette smoke within the days before onset of disease,[119–123] and challenge with cigarette smoking was positive in some of them.[119–124] Tolerance may develop in patients who resume smoking.[120–122] Flavoring components of smoked cigars have been suspected.[125] Recent alterations in smoking habits within the previous month (e.g., beginning to smoke, restarting, or increasing the number of cigarettes smoked daily) is a frequent trigger.[112,115,123,126,127] Passive smoking has also been reported to cause AEP.[128] It is likely that inhalation of tobacco smoke or of other nonspecific injurious agents may initiate or contribute to the development of IAEP in individuals intrinsically prone to develop eosinophilic reactions to inhaled nonspecific causative agents. Increased levels of β(1→3)-D-glucan, a major component of the cell wall of most fungi and also one of the components of cigarette smoke, have been reported in BAL fluid of patients with IAEP,[129] suggesting that inhaled β(1→3)-D-glucan may be involved in the mechanisms of pulmonary inflammation in patients with IAEP.

Some patients reported peculiar prior outdoor activities, such as cave exploration, plant repotting, wood pile moving, smokehouse cleaning, motocross racing in dusty conditions, indoor renovation work, gasoline tank cleaning, and exposure to an exploding tear gas bomb,[54,109] which may explain why IAEP predominates in young patients during the summertime.[117] IAEP was reported in military personnel exposed to airborne dust and recent onset of tobacco smoking.[111–113,130–133] One case was also reported in a New York City firefighter exposed to World Trade Center dust.[134]

IMAGING

The chest radiograph shows bilateral opacities, with mixed alveolar or interstitial opacities (eFig 96.4A–B, G).[54,107–109] In contrast with ICEP, bilateral pleural effusion and Kerley B lines are common.[54] The chest radiograph returns to normal within 3 weeks (see eFig. 96.4L),[54,107] with pleural effusions being the last abnormality to disappear.[54]

At chest CT imaging, ground-glass opacities and air space consolidation are the most common patterns of parenchymal lesions, with poorly defined nodules and interlobular septal thickening seen in a majority of patients; pleural effusion is present in at least two-thirds of patients and is usually bilateral (see eFig. 96.4C–F, H–K).[54,107,109,113,135,136] Bilateral pleural effusion and interlobular septal thickening are highly characteristic of IAEP in a patient with eosinophilic pneumonia; in addition, they should raise the suspicion of IAEP in a patient considered to have infectious pneumonia.

LABORATORY STUDIES

In contrast with ICEP, the white blood cell count at presentation usually shows an increased leukocyte count with a predominance of neutrophils, with eosinophils only rarely higher than 0.3×10^9/L (300/μL). The eosinophil count often rises to high values later during the course of disease,[54,57,109,113] a retrospective finding suggestive of IAEP. Compared with medication-related and idiopathic AEP, smoking-related AEP is less likely to be associated with peripheral eosinophilia at presentation.[137] Eosinophilia is also present in the pleural fluid[113,121] and sputum.[57] Patients with peripheral blood eosinophilia[131,133,137] at onset or high BAL eosinophilia[133] may have milder disease.

The serum level of IgE may be increased,[113] and the serum level of IgG may be decreased,[138] but both lack specificity. Serum biomarkers were proposed[114,139–149] but with uncertain clinical relevance.

BRONCHOALVEOLAR LAVAGE

Given the usual lack of initial blood eosinophilia, BAL is the key to the diagnosis of IAEP,[115] showing an average percentage of 37%[54] to 65%[114] eosinophils on the differential cell count, with sterile bacterial cultures. Lymphocyte and neutrophil counts can be moderately increased. Eosinophilia greater than 25% at BAL establishes the diagnosis of AEP and obviates the need for lung biopsy. Bronchoscopy may show inflamed mucosa of the trachea.[127] A careful search for a cause of AEP is mandatory, and infectious agents must be sought for in BAL fluid by cultures and appropriate staining.[150–154] Drug-induced AEP must also be carefully excluded.

PULMONARY FUNCTION TESTS

Hypoxemia may be severe and refractory to breathing 100% oxygen, suggesting right-to-left shunting.[40,109] A majority of patients fit the definition of acute respiratory disease syndrome.[155] More than half of patients present with acute respiratory failure.[112] Noninvasive ventilation or mechanical ventilation is necessary less frequently in recent series[112,113,115,133,137] than in earlier reports.[54,109] In contrast with acute respiratory disease syndrome, shock is extremely unusual,[156,157] and extrapulmonary organ failure is not seen. Within a few hours of steroid treatment, it may be possible to decrease the fractional concentration of oxygen in inspired gas in many patients initially requiring oxygen.[54]

When performed in less severe cases, PFTs have shown a restrictive ventilatory defect, reduced D_{LCO},[45,109,111,116] and increased alveolar-arterial oxygen tension difference.[54] PFTs performed after recovery are normal in most patients, with possible ventilatory restriction in some of them.[54,158]

LUNG BIOPSY

When BAL is performed, lung biopsy is seldom necessary. When done, lung biopsies show acute and organizing

diffuse alveolar damage together with interstitial alveolar and bronchiolar infiltration by eosinophils, intra-alveolar eosinophils, and interstitial edema.[45,54,59,156]

TREATMENT AND PROGNOSIS

Recovery without corticosteroid treatment has been reported.[109,114] However, most patients diagnosed with IAEP receive corticosteroid treatment, with a starting dose of 40 to 60 mg of oral prednisone. For those with respiratory failure, intravenous methylprednisolone (60–125 mg every 6 hours) is given until respiratory failure resolves.[112] The patient generally responds to corticosteroids within 3 days (see eFig. 96.4L)[112] and can be rapidly weaned from the ventilator and from oxygen supplementation. The chest radiograph normalizes within 1 week in 85% of patients, but mild pulmonary opacities and pleural effusion may still be present on chest CT at 2 weeks.[112] A treatment duration of 2 weeks is sufficient.[112] Fatal cases are very rare,[111,156] and therefore prognosis is far better than that of acute respiratory disease syndrome.

The disease does not relapse after corticosteroid treatment is stopped, in contrast with ICEP. Identification of causative tobacco or environmental exposures is crucial to preventing rare recurrences that, in most cases, are due to resumption of cigarette smoking after smoking cessation.

EOSINOPHILIC GRANULOMATOSIS WITH POLYANGIITIS

HISTORY AND NOMENCLATURE

Although the first cases were reported by Lamb in 1914,[159] and by Rackemann and Greene in 1951,[160] J. Churg and A. Strauss[35] described the syndrome, mainly from autopsied cases. They described characteristic pathologic features consisting of granulomatous extravascular lesions, as well as necrotizing, inflammatory, and granulomatous vascular changes, with an inflammatory exudate rich in eosinophils. The most frequent site of inflammation was the heart. In approximately half of the cases, a pneumonic process was found.

In 2012, the disease was renamed eosinophilic granulomatosis with polyangiitis at the International Chapel Hill Consensus Conference.[161] EGPA is a systemic disease associated with asthma, blood eosinophilia, and eosinophil-rich and granulomatous inflammation involving the respiratory tract and a small-vessel, necrotizing, small- to medium-sized vessel necrotizing vasculitis.[161] Because EGPA is associated in about 30–40% of cases with *antineutrophil cytoplasmic antibodies* (ANCA) positivity, it belongs to the group of ANCA-associated vasculitides, together with granulomatosis with polyangiitis and microscopic polyangiitis.[161] Yet, in most cases, circulating ANCAs are absent,[162,163] and robust criteria of documented systemic vasculitis (polyangiitis) are not always present.[164] (See also Chapter 87.)

PATHOLOGY

Because the diagnosis is now made earlier in the course of disease, lung biopsy is seldom necessary, and patients may receive corticosteroids before overt vasculitis has developed. The pathologic lesions of EGPA currently observed[165–167] only rarely comprise all the characteristic features on a single biopsy from one organ. When typical features are present, both vasculitis (necrotizing or not, involving mainly the medium-sized pulmonary arteries) and granulomatous eosinophilic infiltration are seen (Fig. 96.5A–B).[42] The extravascular granuloma consists of palisading histiocytes and giant cells (see Fig. 96.5C). Diffuse pulmonary hemorrhage with capillaritis can develop (see Fig. 96.5D). When present, the eosinophilic pneumonia in EGPA is similar to ICEP. The early (prevasculitic) phase of EGPA is characterized by eosinophilic infiltration of the tissues without vasculitis (perivascular eosinophils are commonly found).

CLINICAL FEATURES

EGPA predominates in the fourth or fifth decade, with no gender predominance,[163,164,168–178] which contrasts with allergic asthma predominating earlier in life and in women. EGPA also presents earlier in life than other ANCA-associated vasculitides. It has occasionally been reported in children and adolescents.[179–185]

Asthma, generally severe and corticosteroid dependent, presents at a mean age of about 35 years.[169] It may precede the onset of vasculitis by 3 to 9 years.[169–172] However, the interval between asthma and the onset of vasculitis may be much longer in rare cases,[172] or they may be contemporaneous.[170] Asthma severity, however, may attenuate after the onset of the vasculitis,[169,172,186] possibly due to the effect of systemic glucocorticoids prescribed for vasculitic manifestations.[186–188]

Chronic rhinitis is present in about three-fourths of cases of EGPA[169,189,190] and is often accompanied by relapsing paranasal sinusitis and/or polyposis,[163,186,191,192] with eosinophilic infiltration seen on histopathology.[193–195] Crusty rhinitis may be present, but the rhinitis in EGPA is distinctly much less severe than in granulomatosis with polyangiitis, with septal nasal perforation being rare. Mild to moderate hearing impairment is frequent.[191]

Asthenia, weight loss, fever, arthralgias, and myalgias often herald the development of the extrapulmonary manifestations of vasculitis.

Heart damage, which may be severe and lead to cardiac failure with long-term sequelae or sudden death,[169-173,196–198] results especially from eosinophilic myocarditis[196] and much less commonly from coronary arteritis[199–201] or endomyocarditis.[202] It is often insidious and asymptomatic and thus may be recognized only when left ventricular failure and dilated cardiomyopathy have developed. Heart failure may require heart transplantation.[203] Because marked improvement may be obtained with corticosteroid treatment without resolving the cardiac risks, any patient suspected of having EGPA should undergo a systematic cardiac evaluation,[204] including electrocardiogram, echocardiography, and serum levels of troponin I and N-terminal pro–brain natriuretic peptide. In case of clinical suspicion, cardiac *magnetic resonance imaging* (MRI) is the preferred method to confirm heart involvement, by demonstrating late enhancement of the myocardium[197,198,204–209]; however, it remains difficult to differentiate irreversible lesions representing scarring from active inflammation requiring intense

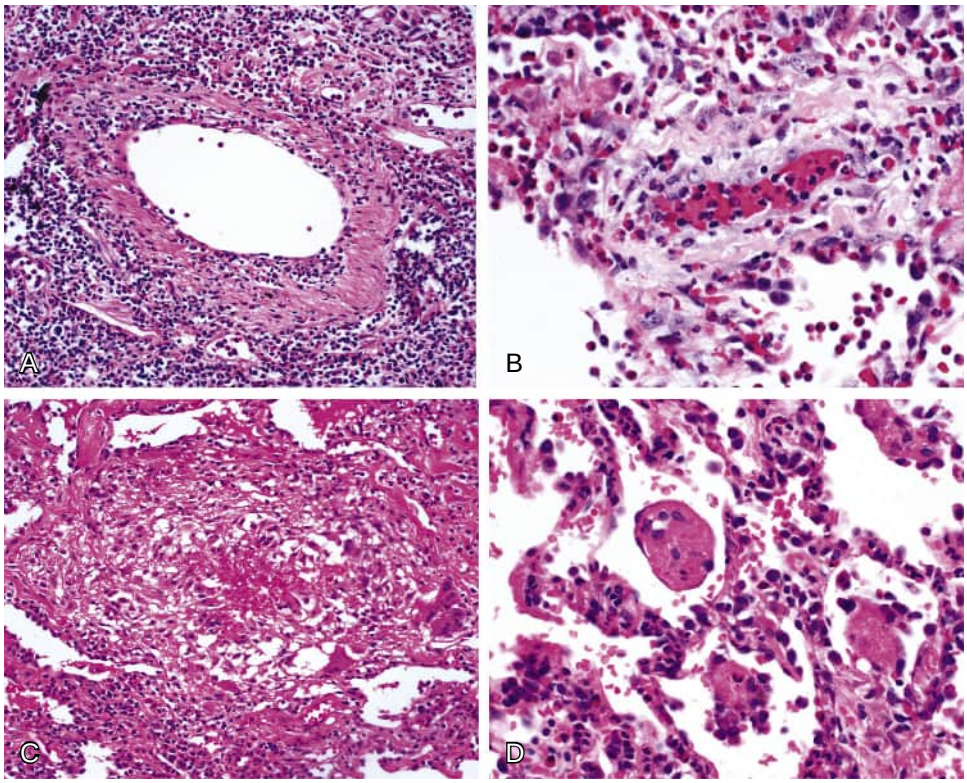

Figure 96.5 Eosinophilic granulomatosis with polyangiitis. (A) Vasculitis. A medium-sized artery infiltrated by eosinophils and scattered lymphocytes. (B) Vasculitis. A venule infiltrated by eosinophils. Note fibrin and eosinophils in surrounding air spaces. (C) Eosinophilic granulomas. Characteristic "allergic granuloma" is readily apparent. Note the vaguely palisaded histiocytes at the periphery of eosinophilic necrosis (*center*). Multinucleate giant cells may be present and typically have a brightly eosinophilic cytoplasm. (D) Pulmonary hemorrhage. Diffuse pulmonary hemorrhage with capillaritis can be seen in eosinophilic granulomatosis with polyangiitis. Capillaritis is demonstrated here, associated with aggregated air space fibrin and eosinophils. (From Leslie KO, Wick MR. *Practical Pulmonary Pathology: A Diagnostic Approach: A Volume in the Pattern Recognition Series.* ed 2. Philadelphia: Elsevier; 2011.)

immunosuppression.[197,205,210–212] The combination of cardiac MRI with positron emission tomography may be useful but deserves further study.[213] Pericarditis with limited effusion at echocardiography is common, but tamponade is rare.[214] In contrast with the idiopathic hypereosinophilic syndrome, endomyocardial involvement is not a common feature. Patients with EGPA are at increased risk of venous thromboembolic events,[215,216] in part through activated eosinophils.[217–219]

Virtually all organs may be involved with varying frequency.[220] Peripheral neurologic involvement consists mainly of sudden onset of mononeuritis multiplex, present in three-fourths of patients.[163,221–224] Cranial nerve palsies and central nervous system involvement are rare.[225] Gastrointestinal tract involvement is present in 31% of cases[163] and usually manifests as isolated abdominal pain, but intestinal or biliary tract vasculitis may be present. Other gastrointestinal manifestations include diarrhea, ulcerative colitis, gastroduodenal ulcerations, perforations (esophageal, gastric, intestinal), digestive hemorrhage, and cholecystitis.[226] Cutaneous lesions, which present in about half of patients,[163] mainly consist of palpable purpura of the extremities, subcutaneous nodules (especially of the scalp and extremities), erythematous rashes, and urticaria. Renal involvement presents in one-fourth of cases and is usually mild,[163,171,227,228] in contrast with the other ANCA-associated vasculitides. Alveolar hemorrhage is rare.[163,229–233]

IMAGING

Pulmonary opacities corresponding to eosinophilic pneumonia represent the most typical abnormalities present in 37–72% of cases on chest radiograph.[169,234] The chest radiograph may be normal throughout the course of the disease. The pulmonary opacities usually consist of ill-defined opacities, sometimes migratory, transient, and of varying density.[169,172,235–237] Pulmonary cavitary lesions are extremely unusual. Pleural effusion (usually mild) and phrenic nerve palsy may be observed.

The abnormalities on thin-section chest CT may predominate in the airspaces or in the airways, corresponding to eosinophilic pneumonia, or to bronchiolar and bronchial involvement, respectively.[185,237,238] Airspace abnormalities consist of ill-defined opacities, with a density varying from ground-glass attenuation to airspace consolidation (Fig. 96.6). They typically predominate in the lung periphery and upper zones of the lung, or have a random distribution, and can be migratory as in ICEP.* Airway abnormalities include centrilobular nodules, bronchial wall thickening, and occasionally bronchiectasis or a tree-in-bud pattern.[68,135,186,237] Interlobular septal thickening, mediastinal lymphadenopathy, and pleural or pericardial effusion (eFig. 96.5) can rarely be observed.[68,235,237,239,242]

LABORATORY STUDIES AND BRONCHOALVEOLAR LAVAGE

Peripheral blood eosinophilia is a major feature of EGPA and usually parallels the activity of the vasculitis. Blood eosinophils are generally between 5 and 20 × 10^9/L (5000–20,000/μL), but they may reach higher values.[163,169,186] Blood eosinophilia often disappears

*References 169, 171, 172, 186, 234–237, 239–242.

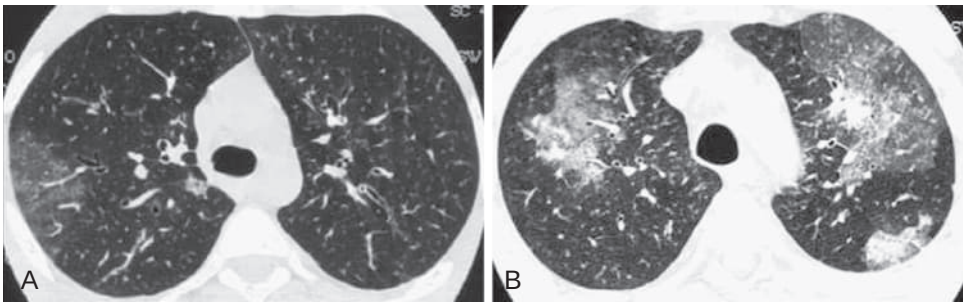

Figure 96.6 Eosinophilic granulomatosis with polyangiitis. Axial chest computed tomography scan of patients with eosinophilic granulomatosis with polyangiitis shows ground-glass opacity of the right upper lobe (A) and bilateral central and peripheral opacities with varying density (B).

dramatically after the initiation of corticosteroid treatment. Eosinophilia, sometimes greater than 60%, is found on BAL differential cell count[186,243] and in pleural fluid when present.[244] The bronchial mucosa may look macroscopically inflammatory at bronchoscopy, with occasional whitish granulations[186,245–247] reminiscent of what is seen in hypereosinophilic bronchiolitis.[41]

Serum IgE levels are increased[186] but lack specificity for the diagnosis. The C-reactive protein level is increased, and anemia is common. Rheumatoid factor may be associated with more frequent gastrointestinal lesions.[180] None of the proposed biomarkers has been validated.[22,248–258]

ANTINEUTROPHIL CYTOPLASMIC ANTIBODIES

The ANCAs reported in 30–40% of patients are mainly *perinuclear antineutrophil cytoplasmic antibodies* (p-ANCAs) with myeloperoxidase.[162,164,170,171,259,260] ANCA status characterizes two distinct clinical phenotypes in EGPA, although with some overlap.[162,163,259–262] Patients *with* ANCA, representing approximately 40% of patients, have a *vasculitic phenotype* of disease, with more frequent glomerular renal disease, peripheral neuropathy, palpable purpura, and biopsy-proven vasculitis. Conversely, patients *without* ANCA have a *tissue* phenotype of disease, with more frequent cardiac (eosinophilic myocarditis), fever, and pulmonary involvement (eosinophilic pneumonia). The latter might conceivably represent a variant of the hypereosinophilic syndrome with systemic manifestations.[263] A genetic predisposition may affect the phenotype of EGPA.[264–266] ANCAs have been found in the sputum of patients with EGPA, including in some without circulating ANCAs.[267] However, measurement of ANCAs in the sputum is not recommended in clinical practice.

PATHOGENESIS

Deciphering the pathogenesis of EGPA is challenging due to its dual categorization as a hypereosinophilic condition and an ANCA-associated systemic vasculitis.[268] It is unclear whether the two subsets of EGPA have unique pathogenic mechanisms.[268]

EGPA, when associated with ANCAs, is considered an autoimmune process involving a Th2-mediated inflammatory response.[269–271] A genetic predisposition to EGPA has been demonstrated in patients carrying the major histopathology complex DRB4 and the DRB1*04 and *07 alleles[264] and perhaps in certain families.[272] Genetic predisposition may affect the presence of ANCA and the clinical phenotype of disease.[266,273,274] In patients with EGPA without ANCA, IL-10 promoter polymorphisms have been found to be associated with increased serum levels of IL-10 (a cytokine that inhibits the Th1-type T cell response).[265]

Possible defects have been identified in regulatory T cell lymphocytes.[275,276] Also, dysregulation of Th17,[269] clonal expansions of $CD8^+/V\beta^+$ T cells with effector memory phenotype expressing markers of cytotoxic activity, and rearrangement of the *T cell antigen receptor (TCR)-γ* gene[277–279] and *T-cell receptor-C β* gene have been reported.[280] The pathogenic relevance of these observations is unclear. The hypothesis of defective apoptosis pathways in eosinophils has not been confirmed.[281]

Exogenous and environmental risk factors were suspected to play a role in the pathogenesis of EGPA, including vaccines, allergens, desensitization, medications,[282,283] some infections *(Aspergillus,* allergic bronchopulmonary candidiasis, *Ascaris*), or exposure to silica,[284] birds, or smoked cocaine. Evidence of allergy (demonstration of specific IgE with corresponding clinical history) is present in less than one-third of patients with EGPA, mainly consisting of perennial allergies, especially to *Dermatophagoides*.[285]

Drug-induced eosinophilic vasculitis with pulmonary involvement has been reported in the past with sulfonamides used together with antiserum[286] and later with diflunisal,[287] macrolides,[288] diphenylhydantoin,[289] mesalazine,[290] propylthiouracil,[291] masitinib,[292] and immune checkpoint inhibitors.[293] The association between leukotriene-receptor antagonists (montelukast, zafirlukast, pranlukast) and EGPA is generally considered to be related to reducing oral or inhaled corticosteroids, allowing them to unmask smoldering EGPA,[170,294–301] although a direct causal relationship cannot be totally excluded.[262,294,296,302,303] It is probably wise to avoid these medications in any asthma patient with eosinophilia or suspected EGPA. EGPA has also been reported in asthmatic patients treated with inhaled corticosteroids[304] or with omalizumab, an anti-IgE antibody, probably through better control of asthma manifestations, allowing a reduction in corticosteroids.[103,305–310]

DIAGNOSIS

The evolution of EGPA usually follows three stages: asthma and rhinitis, tissue eosinophilia (such as a pulmonary disease resembling ICEP), and extrapulmonary eosinophilic disease with vasculitis. Diagnostic difficulties thus largely depend on the stage of disease at which the patient is seen. Exceptional cases without asthma have been described[311,312]; however, no lung function was reported.

Table 96.2 Cottin and Cordier[316,317] Diagnostic and Classification Criteria of Eosinophilic Granulomatosis With Polyangiitis

Asthma
Peripheral blood eosinophilia > 1500 /mm^3 and/or alveolar eosinophilia > 25%
Extrapulmonary clinical manifestations of disease (other than rhinosinusitis), with at least one of the following: ■ Systemic manifestation typical of the disease: mononeuritis multiplex, cardiomyopathy confidently attributed to the eosinophilic disorder, or palpable purpura ■ Any extrapulmonary manifestation with histopathologic evidence of vasculitis as demonstrated especially by skin, muscle, or nerve biopsy ■ Any extrapulmonary manifestation with evidence of ANCA with antimyeloperoxidase or antiproteinase 3 specificity

When a single extrarespiratory manifestation attributable to the systemic disease is present, disease may be called a forme fruste of EGPA syndrome.
ANCA, antineutrophil cytoplasmic antibodies; EGPA, eosinophilic granulomatosis with polyangiitis.

Although systemic disease is necessary to consider a diagnosis of EGPA, it is extremely important that the diagnosis be established before severe organ involvement (especially cardiac) is present. In addition, *formes frustes* of EGPA[313,314] or EGPA limited to a single organ,[313] including the lungs, have been described.[42,315]

Diagnostic and classification criteria for EGPA are present in Table 96.2, including pragmatic criteria taking into account the presence of ANCA[316,317]; additional criteria are included in eTable 96.1. Of importance, the classification criteria of the American College of Rheumatology[318] are applicable only in a patient with proven systemic vasculitis.

A pathologic diagnosis of EGPA is desirable, but not mandatory, in patients with characteristic clinical features and marked eosinophilia. The skin, nerve, and muscle are the most common sites where a pathologic diagnosis of vasculitis may be obtained. Biopsy of the cutaneous lesions is the most common and simple procedure to obtain pathologic evidence of vasculitis. Lung biopsy is seldom done. Transbronchial biopsies usually do not show vasculitis or granulomata.

Idiopathic systemic eosinophilic vasculitis[319] is a recently described entity. Pathologically, the vasculitis, which may be necrotizing or not, is without granulomas. By definition, patients do not have a history of asthma. The lung may be involved,[320] although this has not yet been described in detail. Although idiopathic systemic eosinophilic vasculitis appears distinct from EGPA, it may be part of a common spectrum.[320]

Cases of EGPA overlapping with ICEP,[36,93,94] ABPA,[321–324] granulomatosis with polyangiitis,[325–328] polyarteritis nodosa,[329] temporal arteritis,[330–335] IgA glomerulonephritis,[336] unclassified systemic eosinophilic disease, idiopathic hypereosinophilic syndrome,[337,338] and infections[339] have been described. Rare infections can masquerade as EGPA.[340,341] Careful clinical analysis, the presence of ANCA, serology for *Aspergillus*, the finding of a vasculitis and granulomas on biopsy, and molecular biologic analysis (in the cases of idiopathic hypereosinophilic syndrome) help in determining the final diagnosis.

TREATMENT AND PROGNOSIS

Glucocorticoids are the mainstay of treatment and are sufficient to control the disease in the majority of cases. Oral prednisone is initiated at a dose of 1 mg/kg/day for 3 to 4 weeks, then tapered to reach 5 to 10 mg/day by 12 months of therapy. Initial methylprednisolone bolus (15 mg/kg/day for 1–3 days) may be indicated in the most severe cases,[342] especially in case of myocardial involvement. Management should be multidisciplinary,[343] avoiding any delay which may impact prognosis.[344]

For remission induction, the immunosuppressant cyclophosphamide (three intravenous infusions of 0.6 g/m^2 each at day 1, 15, 30; then three additional infusions of 0.7 g/m^2 every 3 weeks)[345–347] should be added to glucocorticoids in patients with features of poor prognosis (so-called five-factor score: i.e., cardiomyopathy, severe gastrointestinal involvement, renal insufficiency with serum creatinine greater than 150 μmol/L [1.7 mg/dL], proteinuria > 1 g/day, central nervous system involvement).[348,349] (The dose of cyclophosphamide may be reduced to 500 mg fixed-dose intravenous pulses, every 2 to 3 weeks, in individuals older than 65 years.[352])

Predictors of poor prognosis have been updated and now include age older than 65 years, cardiac symptoms (based on easily detectable clinical parameters), gastrointestinal involvement, renal insufficiency, and absence of ear, nose, and throat symptoms.[163,350,351] In addition, severe alveolar hemorrhage, eye involvement (e.g., scleritis), and/or fulminant mononeuritis multiplex also warrant the prescription of immunosuppressants. In the absence of criteria of poor prognosis, corticosteroids alone are sufficient and, in a randomized placebo-controlled trial, azathioprine failed either to increase remission rate or prevent relapses.[353]

Once remission has been achieved, prolonged maintenance therapy is necessary to prevent relapses. In the absence of criteria of poor prognosis, maintenance generally consists of glucocorticoids alone, with tapering doses.[354] Immunosuppressive therapy, especially azathioprine or methotrexate, is occasionally used as a corticosteroid-sparing agent in this situation, particularly in subjects who require 10 mg/day of prednisone or more; however, it may now be less frequently used due to availability of eosinophil-targeted therapy. In patients with poor prognostic criteria, maintenance therapy is generally based on azathioprine for 18 to 24 months. Mycophenolate mofetil may be less effective than azathioprine to prevent relapses.[355] Methotrexate, 0.25 mg/kg/week, is an alternative to azathioprine.[356]

Mepolizumab, a human monoclonal antibody that binds to IL-5 and prevents its interaction with its receptor on the eosinophil surface, consistently reduces eosinophil cell counts in peripheral blood, and improves severe eosinophilic asthma.[26,27,357–359] After promising preliminary results in isolated cases,[29,360,361] the efficacy and safety of mepolizumab was evaluated in a Phase III randomized trial as add-on therapy versus placebo in subjects with relapsing or refractory EGPA,[30] in many patients due to difficult to control asthma. Compared to placebo, mepolizumab (300 mg every 4 weeks) led to an increased proportion of patients achieving remission, an increased duration of remission, a lower rate of relapse, and a lower average daily dose of oral corticosteroids.[30] Mepolizumab is indicated as adjunctive

eTable 96.1 Variously Published Diagnostic and Classification Criteria of Eosinophilic Granulomatosis With Polyangiitis

LANHAM AND COLLEAGUES[169]
Asthma
Eosinophilia
Evidence of vasculitis involving at least two organs
AMERICAN COLLEGE OF RHEUMATOLOGY*[318]
Asthma
Eosinophilia > 10%
Mononeuropathy or polyneuropathy
Pulmonary infiltrates, nonfixed
Paranasal sinus abnormality
Extravascular eosinophil infiltration on biopsy findings
2012 CHAPEL HILL CONSENSUS CONFERENCE DEFINITION[161]
Eosinophil-rich and necrotizing granulomatous inflammation, often involving the respiratory tract ■ *and* necrotizing vasculitis predominantly affecting small to medium vessels ■ *and* associated with asthma and eosinophilia
ANCA is more frequent when glomerulonephritis is present
DIAGNOSTIC CRITERIA USED IN TRIAL NCT02020889[30]
History or presence of asthma plus eosinophilia ($1.0 \geq 10^9$/L and/or >10% of leukocytes) plus at least two of the following additional features of EGPA: ■ A biopsy showing histopathologic evidence of eosinophilic vasculitis, perivascular eosinophilic infiltration, or eosinophil-rich granulomatous inflammation ■ Mononeuropathy or polyneuropathy (motor deficit or nerve conduction abnormality) ■ Pulmonary infiltrates, nonfixed ■ Sinonasal abnormality ■ Cardiomyopathy (established by echocardiography or MRI) ■ Glomerulonephritis (hematuria, red cell casts, proteinuria) ■ Alveolar hemorrhage (by bronchoalveolar lavage) ■ Palpable purpura ■ ANCA-positive (MPO or PR3)

*Diagnosis is probable when four of the six criteria are present (sensitivity of 85%, specificity of 99.7%); these are classification criteria that may be used when the diagnosis of systemic vasculitis has been established by histopathology.

ANCA, antineutrophil cytoplasmic antibodies; EGPA, eosinophilic granulomatosis with polyangiitis; MPO, myeloperoxidase; MRI, magnetic resonance imaging; PR3, proteinase 3.

therapy in subjects with relapsing or refractory EGPA; however, many questions remain regarding its optimal use and timing in EGPA. It is anticipated that it may also be beneficial in cases with persistent severe asthma when the vasculitis is in remission.

Reslizumab, another monoclonal antibody against IL-5, is beneficial in uncontrolled asthma with peripheral blood eosinophilia[362,363] but has not been studied in EGPA. Benralizumab, a monoclonal antibody directed against the α-subunit of IL-5 receptor, has demonstrated a sparing effect of oral glucocorticoids in severe asthma,[364] especially eosinophilic asthma[365]; its potential effect in EGPA[366–369] remains to be determined in prospective trials.

Other treatments have been used successfully in a few cases refractory to glucocorticoids, including omalizumab,[370–373] subcutaneous interferon-α,[374–377] high-dose dose intravenous immunoglobulins,[378,379] cyclosporine-A,[380] tacrolimus,[381] tumor necrosis factor-α inhibitors,[382] and rituximab.[383–395] These treatments, however, are not routinely used. Whether rituximab may reduce the need for cyclophosphamide in patients with severe forms of EGPA, especially those with ANCAs,[393] or to reduce the risk of relapse,[396] is currently being evaluated; however, severe bronchospasm has been reported after the first infusion.[397] Plasma exchanges are not beneficial.[398,399]

The 5-year overall survival in EGPA is currently greater than 90%.[163,176] Most deaths during the first years of treatment are due to cardiac involvement,[163,400] gastrointestinal bleeding, renal insufficiency, or central nervous system involvement.[348,350]

Distinguishing relapse or persistence of so-called difficult asthma from relapse or persistence of EGPA requires precise evaluation, with consideration of the levels of blood eosinophils (generally <1000/μL in asthma without EGPA relapse)[349] and occasionally new systemic manifestations. Nearly half of patients experience at least one episode of disease worsening, consisting of asthma exacerbation with peripheral eosinophilia (two-thirds of cases), or of new-onset systemic manifestations (one-fourth to one-half of patients).[163,186,351,354] The risk of relapse of the vasculitis is higher in patients with ANCA[163] and lower in patients with baseline eosinophils greater than 3×10^9/L (>3000/μL).[351]

Because most patients continue to take oral corticosteroids over the long term, treatment-related side effects cause significant morbidity.[176,186,401] In addition, persistent airflow obstruction due to uncontrolled asthma is present despite corticosteroids in nearly half the patients during follow-up.[186–188,401–404] In the future, treatment indications based on phenotypes, endotypes, and possibly genotypes may help tailor the choice of medications and reduce the risk of adverse events associated to corticosteroids.[186,405]

ALLERGIC BRONCHOPULMONARY ASPERGILLOSIS AND RELATED SYNDROMES

ABPA is distinct from the other pulmonary manifestations caused by the fungus *Aspergillus*, such as invasive pulmonary aspergillosis developing in immunocompromised patients,[406] aspergilloma developing in preexistent pulmonary cavities,[407] or *Aspergillus fumigatus*–associated asthma.[408,409] However, ABPA may be associated with chronic necrotizing aspergillosis.[410]

PATHOGENESIS

ABPA is characterized by asthma, eosinophilia, and bronchopulmonary manifestations with bronchiectasis secondary to a complex allergic and immune reaction to the presence of *Aspergillus* colonizing the airways in susceptible hosts who are unable to clear the respiratory epithelium of inhaled fungal spores.[411] ABPA presents almost exclusively in subjects with a prior history of chronic bronchial disease. ABPA develops in approximately 2.5% of adults with previous asthma[412,413] and in up to 7–10%[414,415] of patients with cystic fibrosis. ABPA is exceedingly rare in patients with COPD despite their impaired mucociliary clearance.[416–418] ABPA has also been reported in Kartagener syndrome,[419] in hyper-IgE syndrome,[420] in Crohn disease,[421] in workers in the bagasse-containing sites in sugar cane mills,[422] in sarcoidosis after infliximab therapy,[423] and, rarely, in the absence of asthma or bronchial lung disease.[424]

Persistence of *A. fumigatus* is hypothesized to be caused partly by defects in innate and adaptive immunity.[409,425] The immunologic response in ABPA includes an early allergic response mediated by IgE antibodies and late-phase lung injury in response to repeated exposure to *Aspergillus* antigens with the participation of IgG and IgA antibodies, and of a Th2 $CD4^+$ T cell–mediated immune response accompanied by sustained IL-17 expression.[426–428] The Th2 response causes a profound inflammatory reaction with influx of neutrophils and eosinophils and synthesis of IgE (total and *A. fumigatus*–specific). A defect in regulatory T cell response has been documented.[429] Over time, the associated inflammatory reaction, with secretion of a variety of inflammatory cytokines and recruitment of inflammatory cells, results in damage to the bronchial epithelium, submucosa, and adjacent pulmonary parenchyma.[425,430,431]

Interaction of luminal eosinophils with *A. fumigatus* causes cytolysis of eosinophils, leading to the release of filamentous chromatin fibers and the creation of extracellular traps. Eosinophil extracellular traps are composed of stable and condensed chromatin fibers and thus might contribute to the high viscosity of eosinophilic mucus.[427] Eosinophils accumulated in the airways release toxic cationic proteins, as seen by the presence of Charcot-Leyden crystals,[432] causing epithelial damage and further decreasing mucus clearance. Airway mucus plugging, a hallmark of ABPA, is therefore key to the pathogenesis of this condition.

Genetic susceptibility to ABPA has been well demonstrated[425] and includes mutations and polymorphism in a variety of genes coding for HLA DR4, DR5, DR7, DR2, DR2/DR5, DRB1*1501, DRB1*1503, DRB1*0701, DQB1*0602, DQB1*0201, mannose-binding lectin (10q11.2-q21), surfactant protein A2 (10q22.3), toll-like receptor 9 (3p21.3), IL-4Ra (16p12.1-p11.2), IL-10 (13q13), transforming growth factor-β (19q13.1, 13.2), cystic fibrosis transmembrane regulator (7q31.2), and chitinase 1 (1q31–32)[433–437] (as previously reviewed).[425,438] Familial cases may represent up to 5%.[439]

CLINICAL FEATURES AND DIAGNOSIS

Patients with ABPA experience chronic cough, dyspnea, expectoration of brown or tan sputum plugs, low-grade fever, and chronic rhinitis, with a chronic course of disease and repeated exacerbations.[440] The current staging system of ABPA includes seven stages: stage 0: asymptomatic; stage 1: acute (with or without mucoid impaction); stage 2: response; stage 3: exacerbation; stage 4: remission; stage 5a: treatment-dependent ABPA; stage 5b: glucocorticoid-dependent asthma; and stage 6: advanced ABPA.[425] Pulmonary opacities or peripheral blood eosinophilia may be present only during the acute phase or recurrent exacerbations of the disease.

Diagnostic criteria, which encompass the spectrum of disease manifestations, can be found in Table 96.3.[425] Finger clubbing is rare.[425] A high index of suspicion should be maintained in patients with particularly severe asthma.

PFTs may show airflow obstruction; however, normal spirometry results do not exclude ABPA.[441] Bronchial provocation with *Aspergillus* antigens is not recommended.[425]

ABPA may be associated with allergic *Aspergillus* sinusitis, which has been considered as a sinus equivalent of ABPA and results in a syndrome called *sinobronchial allergic aspergillosis.*[442–453] Diagnosis is based on demonstration of eosinophilic mucin and fungal hyphae in the specimens obtained from the paranasal sinuses[449] and of hyperattenuating mucus and/or bony erosion on a paranasal CT scan. Hyperattenuation (increased attenuation on CT images and decreased signal intensity on T1- and T2-weighted MR images) is a feature of *Aspergillus* infection due to the fixation of calcium by the organism and to the high protein and low free water content in mucin, along with the presence of air and paramagnetic metals (iron, magnesium, manganese).[453a–c]

LABORATORY STUDIES

The total IgE level is particularly high in ABPA, indicating that a normal serum IgE (in the absence of systemic corticosteroid therapy) generally excludes active ABPA. However, no consensus cutoff value exists, and different units may be used.[425] The IgE level generally increases during exacerbations of ABPA. Peripheral eosinophilia greater than 1000/μL is present in fewer than half the patients at diagnosis,[454] and a normal blood eosinophil count does not rule out ABPA.

An immediate cutaneous hypersensitivity to *A. fumigatus* antigens, as demonstrated by a skin prick test, is the hallmark of ABPA, and denotes the presence of IgE specific for *A. fumigatus*. An elevated level of IgE antibodies specific to *A. fumigatus* is considered a characteristic finding of ABPA,[441] more sensitive than prick tests,[455,456] however, also lacking specificity because it may be found in patients with *Aspergillus* sensitization or severe asthma with fungal sensitization.[425] Specific IgE to recombinant antigens rAsp f4 and rAsp f6 have better reproducibility, consistency, and specificity compared to antibodies against crude antigens.[457] They may differentiate ABPA from asthma with *Aspergillus* sensitization[458–461] or infection.[462] High levels of *Aspergillus* IgG are more suggestive of chronic pulmonary aspergillosis than of ABPA.[463] Serum levels of thymus- and activation-regulated chemokine were proposed for identification and monitoring of ABPA because of animal studies linking an antifungal immune response with the promotion of Th2-mediated hypersensitivity to *A. fumigatus*.[464,465]

Sputum and expectorated plugs contain eosinophils and Charcot-Leyden crystals.[466] Sputum cultures are positive for *A. fumigatus* in only 40–60% of cases with ABPA,[467] despite the presence of detectable *Aspergillus* DNA in the sputum or in mucus plugs.[468] Increasing the number of specimens examined may increase the rate of positive results.[425]

Table 96.3 Diagnostic Criteria for Allergic Bronchopulmonary Aspergillosis

MINIMAL ESSENTIAL DIAGNOSTIC CRITERIA OF ABPA[488]	
Patients with asthma and central bronchiectasis	1. Asthma 2. Central bronchiectasis (inner two-thirds of chest CT field) 3. Immediate cutaneous reactivity to *Aspergillus* 4. Total serum IgE concentration > 417 IU/mL (1000 ng/mL) 5. Elevated serum IgE—*Aspergillus fumigatus* and/or IgG—*A. fumigatus* (opacities on chest radiograph and serum precipitating antibodies to *A. fumigatus* may be present but are not minimal essential diagnostic criteria)
Patients with asthma (ABPA-seropositive)	■ Patients with the above criteria 1, 3, 4, 5 (opacities on chest radiograph may be present but are not a minimal essential diagnostic criteria)
Patients with cystic fibrosis	■ Clinical deterioration (increased cough, wheezing, exercise intolerance, increase sputum, decrease in pulmonary function) ■ Immediate cutaneous reactivity to *Aspergillus* or presence of IgE—*A. fumigatus* ■ Total serum IgE concentration ≥ 1000 IU/mL ■ Precipitating antibodies to *A. fumigatus* or serum IgG—*A. fumigatus* ■ Abnormal chest radiograph (opacities, mucus plugging, or a change from earlier films)
NEWLY PROPOSED DIAGNOSTIC CRITERIA[425]	
Predisposing conditions	■ Bronchial asthma ■ Cystic fibrosis
Obligatory criteria (both should be present)	■ Type I *Aspergillus* skin test positive (immediate cutaneous hypersensitivity to *Aspergillus* antigen) or elevated IgE levels against *A. fumigatus* ■ Elevated total IgE levels (>1000 IU/mL)*
Other criteria (at least two of three)	■ Presence of precipitating or IgG antibodies against *A. fumigatus* in serum ■ Radiographic pulmonary opacities consistent with ABPA† ■ Total eosinophil count > 500 cells/μL in steroid naïve patients (may be historical)

*If the patient meets all other criteria, an IgE value <1000 IU/mL may be acceptable.

†The chest radiographic features consistent with ABPA may be transient (i.e., consolidation, nodules, tram-track opacities, toothpaste/finger-in-glove opacities, fleeting opacities) or permanent (i.e., parallel line and ring shadows, bronchiectasis and pleuropulmonary fibrosis).

ABPA, allergic bronchopulmonary aspergillosis; CT, computed tomography; IgE, immunoglobulin E; IU, international units.

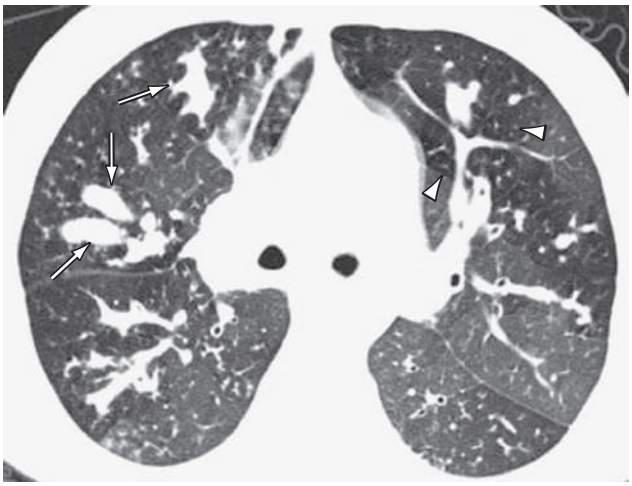

Figure 96.7 Allergic bronchopulmonary aspergillosis. Axial computed tomography scan of a patient with allergic bronchopulmonary aspergillosis shows central bronchiectasis with mucoid impaction (*arrows*), representing the "finger-in-glove" appearance typical of this disease. Diffuse bilateral inhomogeneous lung opacity is present, with areas of low attenuation throughout the pulmonary parenchyma (*arrowheads*) representing mosaic perfusion resulting from a combination of large and small airway inflammation. (Courtesy Michael B. Gotway, MD.)

Infection with nontuberculous mycobacteria may be seen with increased frequency in patients with ABPA.[469] Sputum cultures are often positive for *Pseudomonas aeruginosa* and *Staphylococcus aureus*, especially in individuals with bronchiectasis.

IMAGING

The initial stage of ABPA is characterized on imaging by either fleeting opacities due to eosinophilic pneumonia or mucus plugging with ensuing segmental, lobar, or even whole-lung atelectasis and bronchial wall damage.[470] Mucoid bronchial impaction is typically characterized by a V-shaped lesion with the vertex pointing toward the hilum and by atelectasis.[471,472] High-attenuation mucus defined as mucus visually denser than paraspinal skeletal muscle is considered pathognomonic for ABPA (see eFig. 69.5).[473–477] MRI is a promising technique to identify mucoid impaction.[478]

Proximal bronchiectasis predominates in the upper lobes on chest CT[479–482]; however, it lacks both specificity and sensitivity, especially in early disease.[425] Bronchiectasis may extend to the periphery of the lung.[441,480,482] Mucoid impaction of high attenuation, mosaic attenuation, centrilobular nodules, and tree-in-bud opacities are also commonly seen (Fig. 96.7 and eFig. 69.5). In asthmatic patients, the presence of bronchiectasis affecting three or more lobes, centrilobular nodules, and mucoid impaction on CT scan is highly suggestive of ABPA.[135,483] The CT imaging pattern may be classified as serologic ABPA (without bronchiectasis), ABPA with bronchiectasis, ABPA with high-attenuation mucus, and ABPA with pleuropulmonary fibrosis.[425] However, central bronchiectasis does not always develop during follow-up.[484]

Features of bronchiolitis are common, with centrilobular nodules with a tree-in-bud pattern.[441,483] Although surgery is seldom warranted, eosinophilic pneumonia may be found in resected specimens from patients with asthma and ABPA with chronic pulmonary consolidation or masses.[479,485–487]

TREATMENT

In addition to conventional treatment of severe asthma (i.e., high-dose inhaled corticosteroids and long-acting bronchodilators), the treatment of ABPA mainly relies on oral corticosteroids during exacerbations, with long-term corticosteroids maintained only in patients with frequent symptomatic attacks or evidence of progressive lung damage. Treatment is initiated at 0.5 mg/kg/day of prednisone for 1 or 2 weeks, then tapered over a total duration of about 12 weeks (short regimen),[488] or at 0.75 mg/kg/day for 6 weeks, then tapered over a total duration of 6 to 12 months (long regimen).[441,489] Treatment of episodes of pulmonary consolidation may prevent the progression of ABPA to the fibrotic end stage.[490] Inhaled corticosteroids may reduce the need for long-term oral corticosteroids.

Antifungal therapy to attenuate the fungal load in the airways is a useful adjunct to corticosteroids. However, prednisolone alone is more effective than itraconazole monotherapy in the acute stage of treatment-naïve ABPA.[491] Oral itraconazole reduces the doses of corticosteroids[492–495] and decreases sputum eosinophils, sputum eosinophil cationic protein levels, serum IgE levels, serum IgG levels to *A. fumigatus,* and the number of exacerbations. Uncontrolled studies further suggest that itraconazole is potentially useful in ABPA patients with cystic fibrosis.[496,497]

The duration of itraconazole therapy is not standardized; however, treatment is generally continued for a minimum of 4 to 6 months.[425] Serum levels of itraconazole should be monitored. Itraconazole interacts with many medications and may also induce adrenal insufficiency.[498,499] To reduce interactions, oral prednisone and inhaled beclomethasone or ciclesonide are preferred to oral methylprednisolone and budesonide or fluticasone.[497] Measuring the total serum IgE level may be helpful for monitoring therapy. Clinical and radiologic improvement along with a 25% or greater decline in serum total IgE level signifies a satisfactory response to therapy.[425]

Treatment with the anti-IgE recombinant antibody omalizumab may be useful,[500–504] with possibly fewer episodes of exacerbation and with a reduction of steroid dose. The appropriate dosing, however, is unknown in the setting of ABPA with IgE levels that exceed 1000 IU/mL. Pulses of intravenous corticosteroids have also been used to treat exacerbations.[505–508] Mepolizumab, benralizumab,[509–519] and dupilumab[520] have been used successfully in isolated cases. Bronchoscopy to remove mucus plugs may improve symptoms and lung function.[521]

Experience with the newer agents, voriconazole[522–531] and posaconazole,[527,532–534] is still moderate in ABPA, with cases reported especially in cystic fibrosis. In an open-label, randomized trial, voriconazole was as effective as oral corticosteroids in patients with acute ABPA.[523] In the absence of proven benefit compared with itraconazole, these medications are indicated in patients intolerant to itraconazole or in itraconazole failures.[425] Sustained improvement has been reported after administration of nebulized liposomal amphotericin B in patients with ABPA that was difficult to control using the standard treatment regimen.[535,536]

OTHER ALLERGIC BRONCHOPULMONARY MYCOSES

A similar syndrome of allergic bronchopulmonary disease may be produced by other fungi or yeasts.[537–540] The diagnosis is difficult due to the necessity to document sensitization to the specific fungi. The frequency of this condition is far less than that of ABPA, which may be due to the small size (3–6 μm) of the conidia of *A. fumigatus*,[541] their high dispersibility due to their remarkable hydrophobicity,[542,543] induction of the *MUC5AC* gene and mucus production in bronchial epithelial cells,[544] and higher serine protease activity, which activates membrane-bound tumor necrosis factor-α–converting enzyme and transforming growth factor-α, stimulating epidermal growth factor receptors.[544,545]

BRONCHOCENTRIC GRANULOMATOSIS

Bronchocentric granulomatosis described by Liebow[546] is defined pathologically as an inflammatory and destructive process beginning within the bronchiolar walls and further extending into the surrounding parenchyma.[547] The granulomatous inflammatory process destroys both the mucosa and the walls of the bronchioles, and the necrotic areas resulting from the destroyed bronchioles are often surrounded by palisading histiocytes and a dense inflammatory infiltrate, mostly composed of eosinophils. Scattered fungal hyphae may be demonstrated by the Grocott silver stain. Vascular inflammation and mucoid impaction may be present.[547,548]

About half the patients are asthmatics, who present with fever and cough. A peripheral blood eosinophilia is common, generally greater than 1000/μL.[547,548] The radiographic features consist of masses (eFig. 96.6), alveolar opacities or pneumonic consolidation, or reticulonodular opacities, which predominate in the upper lobes and are unilateral in a majority of patients.[470,549] Most of these patients fulfill the criteria for ABPA, and those treated with corticosteroids have an excellent prognosis, although recurrences are common.[547] Eosinophilia is usually not conspicuous.

HYPEREOSINOPHILIC SYNDROMES

DEFINITION AND CLASSIFICATION

Since the historical description of "idiopathic" *hypereosinophilic syndrome* (HES) by Hardy and Anderson,[550] then by Chusid and colleagues,[551] the definition of HES has been refined,[552] although it remains a heterogeneous entity. After a consensus statement,[46] the diagnosis of HES is now considered in patients with (1) absolute eosinophil count of 1500/μL or greater and clinical manifestations attributable to eosinophilia or (2) tissue hypereosinophilia with blood eosinophilia (eosinophil count above the upper limit of normal for the reference laboratory). HES is further divided into six clinical variants[553,554]: myeloid variant HES (myeloproliferative HES), lymphocytic variant HES, overlap HES corresponding to eosinophilic disease restricted to a single organ (including ICEP or IAEP) or defined eosinophilic syndromes (including EGPA), HES associated with a known cause (including infection with helminths, drug reactions, and immunodeficiency), familial HES, and idiopathic HES. This section reviews, especially, pulmonary manifestations associated with myeloproliferative HES or lymphocytic HES (so-called primary HES).

PATHOGENENESIS

In contrast with common hypereosinophilia, which is usually a reactive nonclonal process (as in parasitic disorders), several studies demonstrated that HES may result from the clonal proliferation of the eosinophil cell lineage itself (myeloproliferative HES, including the *chronic eosinophilic leukemia*) or from a clonal proliferation of lymphocytes producing eosinophilopoietic chemokines (lymphocytic HES).[554] The term *idiopathic* HES or HES of unknown significance[554,555] is used in cases that cannot at present be classified in either category despite appropriate diagnostic tools, including the quantitative assessment of the *Wilms tumor (WT1)* gene transcript (a molecular marker useful for the detection of clonal myeloid disorders) in peripheral blood.[556]

Myeloproliferative HES (or chronic eosinophilic leukemia), considered to account for 20–30% of cases, is caused primarily by a constitutively activated tyrosine kinase fusion protein created by fusion of the genes *FIP1-like 1 (FIP1L1)* and *platelet-derived growth factor receptor-α* (*PDGFRA-α)* as a consequence of an interstitial chromosomal deletion in 4q12. The fusion gene *FIP1L1-PDGFRA* is not detectable by karyotype analysis but can be demonstrated by reverse transcriptase polymerase chain reaction analysis[557,558] or by fluorescence in situ hybridization on peripheral blood or peripheral bone marrow aspirate.[559] The tyrosine kinase of PDGFRA is constitutively activated in the fusion protein, transforms hematopoietic cells, and is inhibited by imatinib.[557] Clonal eosinophilia in patients presenting with clinical features of HES can also be related to other uncommon, imatinib-sensitive *PDGFR* fusions, including *KIF5B-PDGFRA* and *ETV6*-PDGFRB[560–562] and to point mutations in *PDGFRA*.[563] Clonal eosinophilia has been described in chronic eosinophilic leukemia–not otherwise specified, in *D816V KIT*–positive systemic mastocytosis,[564] and in mixed lymphoid/myeloid neoplasms with rearrangements of *FGFR1* or *JAK2*.[565–567] Hepatomegaly, splenomegaly, mucosal ulcerations, severe cardiac manifestations resistant to corticosteroid treatment, anemia, thrombocythemia, increased serum vitamin B_{12}, leukocyte alkaline phosphatase and serum tryptase level, atypical mast cells, and circulating leukocyte precursors are common and suggestive of the diagnosis, whereas cutaneous manifestations are infrequent.[567–569]

Lymphocytic HES,[570,571] which may account for up to 30% of patients with HES, results from the production of chemokines, especially IL-5, by clonal Th2 lymphocytes bearing an aberrant immunologic phenotype, such as $CD3^-$ $CD4^+$.[570,572–578] Lymphocyte phenotyping should be performed on peripheral blood (or bone marrow) to detect a phenotypically aberrant T cell subset by flow cytometry and analysis of the rearrangement of the *TCR* genes in search of T cell clonality. The observation of increased IL-5 expression from cultured T cells can also demonstrate that the observed eosinophilia is caused by an expanded population

of T cells.[559] There is no sex predominance. Patients present with a high prevalence of skin and soft tissue manifestations, elevated serum IgE (as a consequence of IL-4 and IL-13 production by Th2 lymphocytes),[570,579] and thymus- and activation-regulated chemokine levels.[580] Most reported patients are recruited from dermatology clinics and have papules or urticarial plaques. The disease may progress to overt lymphoma or leukemia in 5–25% of cases.[570,576,581]

CLINICAL AND IMAGING FEATURES

The pulmonary involvement in HES has not been studied extensively in cases classified according to the previously discussed variants. Clinical manifestations mainly comprise fatigue, weight loss, and nonrespiratory involvement, especially targeting the skin, mucosa, heart, and nervous system.[573,582] In older series, nonspecific respiratory manifestations, such as cough and dyspnea, present in up to 40% of patients, and patchy ground-glass attenuation, consolidation, and small nodules are seen at chest imaging.[551,583,584]

In more recent studies using current diagnostic standards, respiratory manifestations are generally of mild severity, with rare eosinophilic pneumonia, if any.[585] Chest CT may show pleural effusion, pulmonary emboli, small nodules with or without a halo of ground-glass attenuation, and focal areas of ground-glass attenuation mainly in the lung periphery.[135,586,587] Chronic dry cough can be remarkable and may be a presenting or the only feature.[588–590]

Cardiovascular involvement is a major cause of morbidity and mortality.[591–593] Fibrotic thickening of the endocardium by collagen-rich connective tissue (endomyocardial fibrosis) is characteristic of cardiac disease in HES,[583,594] which differs from the cardiac involvement seen in EGPA. Endomyocardial fibrosis is preceded by an initial acute necrotic stage followed by a thrombotic process[595,596] (eFig. 96.7). Cardiac manifestations include dyspnea, congestive heart failure, mitral regurgitation, and cardiomegaly.[583,597,598] Echocardiography demonstrates mural thrombus, ventricular apical obliteration, and involvement of the posterior mitral leaflet.[599]

TREATMENT AND PROGNOSIS

In myeloproliferative HES, imatinib, a tyrosine kinase inhibitor, is the first-line therapy when the *FIP1L1-PDGFRA* fusion protein or rearrangement of *PDGFRB* is present.* Imatinib should be started together with corticosteroids. Testing for the presence of *FIP1L1-PDGFRA* is recommended every 3 to 6 months in patients on a stable imatinib dose because of possible relapses.[603] Imatinib can be stopped without relapse in some patients, whereas in others, low-dose imatinib is necessary to maintain long-term remission.[555,569] Alternative tyrosine kinase inhibitors may be used in case of imatinib resistance.[567]

In lymphocytic HES, corticosteroids are the first-line therapy (with response in only about half of the patients); however, doses of 30 to 60 mg of prednisone per day may be required.[567] Imatinib may also be beneficial in lymphocytic HES.[604] The anti–IL-5 antibody mepolizumab has been shown to be beneficial as a corticosteroid-sparing agent in HES patients negative for the *FIP1L1-PDGFRA* fusion gene.[25,605–609] Other treatments include chemotherapeutic agents (hydroxyurea, vincristine, etoposide), cyclosporin A,[584,591,595] and interferon-α either as monotherapy[610–614] or in association with hydroxyurea, particularly in the myeloproliferative variant.[615,616] A detailed description of treatment can be found elsewhere.[567]

*References 557, 558, 564, 567, 569, 573, 600–602.

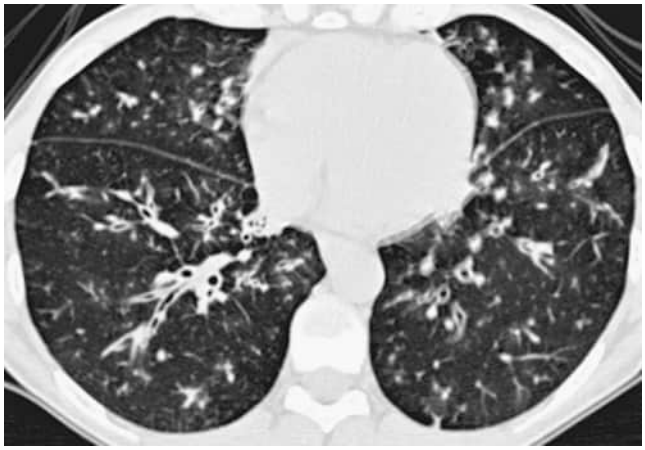

Figure 96.8 Idiopathic hypereosinophilic obliterative bronchiolitis. Axial chest computed tomography scan of a patient with idiopathic hypereosinophilic bronchiolitis shows bronchial wall thickening, peripheral tree-in-bud and branching pattern, and central bronchiectasis with mucoid impaction.

IDIOPATHIC HYPEREOSINOPHILIC OBLITERATIVE BRONCHIOLITIS

Hypereosinophilic obliterative bronchiolitis is a distinct entity defined by the following provisional working criteria: (1) blood eosinophil cell count greater than 1×10^9/L (>1000/μL) and/or BAL eosinophil count greater than 25%, (2) persistent airflow obstruction despite high-dose inhaled bronchodilators and corticosteroids, and (3) eosinophilic bronchiolitis at lung biopsy, and/or direct signs of bronchiolitis (centrilobular nodules and branching opacities) on chest CT[41] (Fig. 96.8). Before this description, some biopsy-proven isolated cases of eosinophilic bronchiolitis had been reported,[617–620] and a few cases have been reported since then.[621,622] The blood eosinophil cell count is elevated (with a mean of 2.7×10^9/L (2700/μL), and the mean eosinophil differential percentage at BAL was 63% in our series.[41] Airflow obstruction is often severe but reversible with oral corticosteroid therapy in all cases. Whitish tracheal and bronchial granulations or bronchial ulcerative lesions can be present with prominent eosinophilia at bronchial biopsy.[41] Clinical and functional manifestations often recur when oral prednisone is tapered to less than 10 to 15 mg/day. It is hypothesized that unrecognized and/or smoldering hypereosinophilic obliterative bronchiolitis might be a cause of irreversible airflow obstruction in chronic eosinophilic respiratory diseases. In addition to the idiopathic presentation, a similar condition of hypereosinophilic obliterative bronchiolitis can be encountered in patients with asthma, ABPA, or EGPA or may be induced by drugs, especially minocycline[41] or sulfasalazine.[623] Mepolizumab may be beneficial.[624]

EOSINOPHILIC PNEUMONIAS OF PARASITIC AND INFECTIOUS ORIGIN (See Also Chapter 58)

The eosinophilic pneumonias related to parasite infestation[625–627] probably represent the most common cause of eosinophilic pneumonia in the world and in travelers and refugees.[628–630] Parasitic eosinophilic pneumonia arises mainly in humans after infection by helminths (large multicellular worms) and especially nematodes (roundworms). The parasites may or may not be found at pathologic examination of the lung when performed. Due to frequent chronic infection, echocardiography is advised to assess endomyocardial and valvular disease.[631]

TROPICAL PULMONARY EOSINOPHILIA

Tropical pulmonary eosinophilia,[632–635] caused by the filarial nematodes *Wuchereria bancrofti* and *Brugia malayi,* is endemic in the tropical and subtropical areas of Asia and Africa. It presents mainly in young adults, with a male predominance.[630,632,636–639] Presenting manifestations include dry, hacking cough exacerbated at night and often associated with dyspnea and expiratory wheezing masquerading as asthma.[640] Associated fever, weight loss, and anorexia are common. Eosinophils, and sometimes Charcot-Leyden crystals, are present in the sputum. Clinical features of lymphatic filariasis (e.g., adenolymphangitis or dermatolymphangioadenitis) are usually absent because tropical pulmonary eosinophilia results from an immune response of the host to the parasites trapped in the lung vasculature.

The chest radiograph can reveal patchy bilateral opacities and small nodules (see Fig. 58.2 and eFig. 58.2).[639] Prominent blood eosinophilia is high at the early stage (<2 weeks) of pulmonary disease[634] but may be missing.[641] Eosinophilic pneumonia with eosinophilia at BAL[20,642] is seen later (1–3 months). Cases left untreated for 5 years or more eventually show pulmonary fibrosis with histiocytic infiltration, with possible restrictive and reversible obstructive ventilatory defects.[643,644]

Because microfilariae are not detectable in the blood, the diagnosis is made by the combination of cough worse at night, residence in a filarial endemic area, and laboratory features, including blood eosinophilia persisting for weeks with an absolute eosinophil count in the blood greater than 3×10^9/L (3000/μL), IgE levels exceeding 4200 IU/mL (normal < 100 IU/mL), and markedly increased antifilarial IgG. Diagnosis is further supported by a clinical and hematologic response to diethylcarbamazine,[645] which is the only effective drug. Corticosteroids in addition to diethylcarbamazine may be beneficial.

ASCARIS PNEUMONIA

Ascaris lumbricoides is the most common helminth infecting humans, especially children, in tropical and subtropical areas. The disease is transmitted through food or water contaminated by human feces. The infective larvae formed within eggs develop in the small intestine, penetrate through the intestinal wall, and migrate via the venous circulation to the lungs, where they break out into the alveoli. They then migrate through the bronchi and trachea, are swallowed, and mature into adult worms in the small intestine.

Pulmonary manifestations develop during larval migration to the lungs. Usually, pulmonary symptoms are mild, with cough and wheezing, transient pulmonary opacities (Loeffler syndrome), and blood eosinophilia that can be higher than 20×10^9/L (20,000/μL).[646] There may be transient fever and pruritus. Symptoms spontaneously resolve in a few days, whereas blood eosinophilia may remain elevated for several weeks. The diagnosis may be made by finding larvae in the sputum or gastric aspirates but is more usually made by the delayed finding of the worm or ova in the stool within 3 months of the pulmonary manifestations. Intestinal ascariasis is treated with oral mebendazole, 100 mg twice a day for 3 days, or albendazole, 400 mg once, or ivermectin.[647]

EOSINOPHILIC PNEUMONIA IN LARVA MIGRANS SYNDROME

Visceral larva migrans[635,648] is a zoonotic infection caused in humans by *Toxocara canis,* a parasite infecting dogs and found in all areas of the world. Children playing in areas contaminated by infected dogs may become infected, especially when they practice geophagia.[649] Ingested eggs hatch in the intestine, migrate through the portal circulation, and invade the liver, lung, and other organs. However, in humans, the development of the parasite is blocked at the larval stage.

Visceral larva migrans presents predominantly in children, the majority of whom remain asymptomatic and undiagnosed. When symptomatic, patients may present with fever, fatigue, pulmonary manifestations, and seizures. Pulmonary manifestations in about 80% of cases consist of cough, wheezes, and dyspnea; pulmonary opacities on chest radiography are present in approximately half the patients with pulmonary symptoms.[635] Although uncommon in adults, toxocariasis may be severe.[650–652] Blood eosinophilia may be present initially or may develop only in the following days.[653] Eosinophils are increased in the BAL differential cell count.

The diagnosis of toxocariasis is difficult because a positive serodiagnosis may be caused by residual antibodies that do not have any diagnostic significance. IgM antibodies can be found throughout the course of helminthiasis and are not diagnostic of recent infection.[654] Visceral larva migrans usually requires only symptomatic treatment, with the use of antihelminthics being controversial. Corticosteroids seem beneficial in cases with severe pulmonary involvement.[650]

STRONGYLOIDES STERCORALIS INFECTION

Strongyloides stercoralis is an intestinal nematode that may cause severe autoinfection in immunocompromised patients. It is widely distributed in the tropics and subtropics and is especially diagnosed in travelers returning from tropical countries.[655–658] Human infection is acquired through the skin by contact with the contaminated soil. Eosinophilia is usually present in recently infected

patients, but it is often absent in disseminated disease.[659] *S. stercoralis* infection may persist for years and give rise to severe disseminated strongyloidiasis, which may affect all organs (hyperinfection syndrome),[659,660] especially after treatment with corticosteroids or with immunosuppression from any cause.[661]

Loeffler syndrome develops when larvae migrate through the lungs after acute infection.[659] Rhabditiform larvae may be recovered by BAL or bronchial washing (eFig. 96.8A)[662,663] or in the sputum.[664] Diagnosis of strongyloidiasis depends on the demonstration of larvae in the feces or in sputum or BAL fluid (see Fig. 58.1C). Immunodiagnostic assays by enzyme-linked immunosorbent assay may be useful for diagnosis and screening. All infected patients should be treated when diagnosed (ivermectin, 200 µg/kg daily for 2 days and repeated 2 weeks later).

EOSINOPHILIC PNEUMONIAS IN OTHER PARASITIC INFECTIONS

In early acute schistosomiasis, due to either *Schistosoma haematobium* or *Schistosoma mansoni* (see eFig. 96.8B), patients may develop transient, multiple, small pulmonary nodules on chest radiography (best seen on chest CT scan) and eosinophilia.[628,665,666] Chronic infection can cause pulmonary hypertension. Eosinophilic pneumonitis resulting from parasitic antigen release may follow treatment.[667]

The dog hookworm *Ancylostoma brasiliense*, the human hookworms *Ancylostoma duodenale* and *Necator americanus*, the filarial parasite of dog *Dirofilaria immitis*[635] (the pulmonary fluke) (eFig. 96.8C, see Fig. 58.3), *Paragonimus westermani*[668] (see Fig. 58.4 and eFig. 58.3), *Trichomonas tenax*,[669] *Capillaria aerophile*,[670] and *Clonorchis sinensis*[671] are other possible causes of Loeffler syndrome or other pulmonary manifestations with eosinophilia.

EOSINOPHILIC PNEUMONIAS OF OTHER INFECTIOUS CAUSES

Pulmonary infection with eosinophilia has been reported with the fungi *Coccidioides immitis*, *Bipolaris australiensis*, *Aspergillus niger*, and *Bipolaris spicifera*. BAL eosinophilia has been reported in *Pneumocystis jirovecii* pneumonitis in patients with acquired immunodeficiency syndrome. Bacterial or viral pulmonary infection (e.g., tuberculosis, brucellosis, respiratory syncytial virus, influenza infection), or the ingestion of *Ulomoides dermestoides* larvae ("Chinese beetles")[672] may occasionally be a cause of eosinophilic pneumonia.

DRUG-, TOXIC AGENT-, AND RADIATION-INDUCED EOSINOPHILIC PNEUMONIAS

MEDICATIONS AND ILLICIT DRUGS (see also Chapter 99)

An iatrogenic cause must be systematically considered in patients with eosinophilic pneumonia.[673] More than 80 drugs have been reported to cause eosinophilic pulmonary opacities and especially acute eosinophilic pneumonia. However, the cause has not been established in many case reports, and thus the number of drugs that can reliably be considered as a common cause of drug-induced eosinophilic pneumonia is much smaller.

Drugs causing eosinophilic pneumonia are mainly nonsteroidal anti-inflammatory drugs, antibiotics, and cardiac medications.[674,675] The online database www.pneumotox.com is a reliable reference in the evaluation of suspected cases. All the drugs taken in the weeks or months preceding the clinical syndrome must be carefully recorded in any patient presenting with eosinophilic pneumonia, including illicit drugs such as cocaine, crack, heroin; marijuana/cannabis use (i.e., smoking, vaping, eating, or dabbing),[674,676–679] the intake of which is often denied by the patient; and noncigarette smoking products, including vaping and water pipe smoking.[680–682] Historical toxic causes also include the eosinophilia-myalgia syndrome, related to the intake of contaminated preparations of L-tryptophan in 1989 in the United States,[683–686] and the toxic oil syndrome, a scleroderma-like disorder that affected about 20,000 people in Spain in 1981.[687]

Drug-induced eosinophilic lung disease may present in three scenarios: (1) patients taking a drug for several months (or years) who develop symptoms, (2) asymptomatic patients who are found to have incidental imaging abnormalities, and (3) patients who present with acute respiratory manifestations, sometimes severe.

Presentation of eosinophilic drug-induced pneumonia is generally nonspecific, including manifestations of simple pulmonary eosinophilia (Loeffler syndrome); chronic eosinophilic pneumonia with the association of pleural effusion and extrapulmonary manifestations, including cutaneous rash, which is suggestive of drug-induced pneumonia; and acute eosinophilic pneumonia, with possible overlap in presentation.[688] Associated extrapulmonary manifestations, especially cutaneous rashes, fever, or nausea, may be present. Severe cases may present as *drug reaction with eosinophilia and systemic symptoms* (DRESS),[689,690] which consists of a multiorgan sensitivity reaction to an eliciting drug with a genetic predisposition, together with an antiviral immune response to reactivated human herpesvirus-6 in the majority (>70%) of these patients.[691–693] Drug-induced systemic eosinophilic vasculitis involving the lung has also been reported (see earlier).

The regression of eosinophilic lung disease after stopping the drug is the best clue for an iatrogenic reaction. However, this may take a long time and, therefore, in many reported cases, corticosteroids have been given concomitantly with drug withdrawal, so the responsibility of the drug cannot be definitely established. The only absolute proof of the drug responsibility would be obtained by its reintroduction with ensuing relapse of pneumonia, but this may be dangerous and thus is strongly discouraged.

RADIATION THERAPY

Chronic eosinophilic pneumonia may develop after radiation therapy for breast cancer.[694] It was seen in women with a history of asthma or allergy, at a median time of

3.5 months and up to 10 months after completion of radiotherapy for breast cancer (one case was reported 6 years after completion of radiation therapy).[695–697] Dyspnea and cough were the main presenting symptoms, with pulmonary opacities at imaging being unilateral (involving the irradiated lung) or bilateral and possibly migratory. All patients had blood eosinophilia of 1.0×10^9/L (1000/μL) or greater and/or eosinophilia greater than 40% on the BAL differential cell count. Patients rapidly improved with oral corticosteroids without sequelae, but some patients relapsed after treatment withdrawal. Cases have also been reported after radiation therapy for lung cancer.[698,699]

This syndrome is similar to the organizing pneumonia syndrome primed by radiation therapy to the breast,[700] with eosinophilic pneumonia developing preferentially in patients with asthma or atopy. Eosinophilic pneumonia may also develop on radiation therapy preferentially in patients with a preexisting Th2-oriented lymphocyte response,[694,701,702] together with yet unidentified additional factors.

EOSINOPHILIC BRONCHITIS

Eosinophilic bronchitis is distinct from bronchial asthma. Eosinophilic bronchitis (without asthma) with a high percentage of eosinophils (about 40%) in sputum is a cause of chronic cough responsive to corticosteroid treatment, with normal lung function and absence of bronchial hyperreactivity.[705–711] It is not accompanied by eosinophilic pneumonia. The observed values of sputum eosinophils and of various chemokines are often much higher in eosinophilic bronchitis than in asthma,[707,712] although levels of IL-5 in sputum and pathologic findings are comparable.[713,714] Chest imaging is normal.[715] The *FIP1L1-PDGFRA* fusion gene has been reported in some patients with eosinophilic bronchitis.[588,589] Bronchoscopy may show diffuse nodules in the tracheobronchial mucosa causing obstruction that does not respond to bronchodilators.[716] Rare cases may be due to drugs[717] or occupational exposure to acrylates,[718] welding fumes and formaldehyde,[719] isocyanate, or flour.[720]

Treatment is based on inhaled corticosteroids.[706,721–723] Treatment with an antagonist of the eotaxin tissue receptor CCR3, the receptor for eotaxin and other chemokines, may be beneficial.[724] It generally is a benign condition,[725,726] although it may in rare cases evolve to irreversible airflow obstruction without asthma or to genuine asthma.[727–729]



See ExpertConsult.com for a discussion of other lung diseases associated with eosinophilia, including hypereosinophilic asthma, idiopathic interstitial pneumonias, and pulmonary Langerhans cell histiocytosis.

Key Points

- Eosinophilic lung disease may manifest clinically with varying severity, ranging from chronic or transient opacities with mild symptoms to the acute severe eosinophilic pneumonia resembling acute lung injury or acute respiratory distress syndrome and necessitating mechanical ventilation.
- Blood eosinophilia greater than 1×10^9 eosinophils/L (and preferably $>1.5 \times 10^9$/L or 1500/μL) is of considerable help for suggesting the diagnosis. However, blood eosinophilia may be absent (as in the early phase of idiopathic acute eosinophilic pneumonia or when patients are already taking corticosteroids).
- On bronchoalveolar lavage, high eosinophilia (>25%) may be considered diagnostic of an eosinophilic pneumonia in a compatible setting.
- Inquiry concerning drug intake must be meticulous (www.pneumotox.com), and any suspected drug should be withdrawn.
- Consideration of parasitic causes must consider the travel history or residence and the epidemiology of parasites.
- When present, extrathoracic manifestations raise the suspicion of a systemic eosinophilic disease, such as eosinophilic granulomatosis with polyangiitis or hypereosinophilic syndrome.
- Airflow obstruction can be found in hypereosinophilic asthma, allergic bronchopulmonary aspergillosis, idiopathic chronic eosinophilic pneumonia, eosinophilic granulomatosis with polyangiitis, or in hypereosinophilic obliterative bronchiolitis.
- Corticosteroids remain the cornerstone of symptomatic treatment for eosinophilic disorders, with a generally dramatic response, but relapses are common when tapering the doses or after stopping treatment. Cyclophosphamide is necessary in patients with eosinophilic granulomatosis with polyangiitis and poor prognostic factors.
- Medications targeting the interleukin-5 pathway play an increasing role in eosinophilic lung diseases.
- Imatinib, a tyrosine kinase inhibitor, has proved effective in the treatment of myeloproliferative hypereosinophilic syndrome.

Key Readings

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HYPEREOSINOPHILIC ASTHMA

Eosinophilic inflammation in asthma is beyond the scope of this chapter. However, some patients present with asthma and important blood hypereosinophilia (i.e., >1 and especially >1.5 × 10^9/L (1500/μL) or alveolar eosinophilia (>25% and especially >40%), a condition tentatively labeled hypereosinophilic asthma.[703,704] Hypereosinophilic asthma is generally severe, frequently requires high-dose inhaled or even oral corticosteroids, and may progress to EGPA, ABPA, or ICEP. To what extent hypereosinophilic asthma differs from the eosinophilic endotype of asthma has not been formally studied.

IDIOPATHIC INTERSTITIAL PNEUMONIAS

Organizing pneumonia may have imaging features that closely mimic ICEP, especially with migrating alveolar opacities. Organizing pneumonia can also overlap with ICEP pathologically, with foci of organizing pneumonia in ICEP, and eosinophils in organizing pneumonia.[36,730,731] In some cases, organizing pneumonia may represent the evolution of an untreated CEP.[732] Cryptogenic organizing pneumonia may also have eosinophilia in BAL, but it is usually less than 20% at differential cell count.

The other idiopathic interstitial pneumonias, including idiopathic pulmonary fibrosis[733–735] and nonspecific interstitial pneumonia,[736] may exhibit mildly increased levels of eosinophils in BAL and/or focal lesions of eosinophilic pneumonia at biopsy. In series of pulmonary fibrosis that predated the current definitions, increase of BAL eosinophils was associated with a poor outcome,[737–740] which may reflect eosinophil-fibroblast interaction.[741] Desquamative interstitial pneumonia may show eosinophilia at BAL[742,743]; however, peripheral blood eosinophilia is unusual.

PULMONARY LANGERHANS CELL HISTIOCYTOSIS

The pulmonary pathologic lesions of Langerhans cell histiocytosis (also designated as eosinophilic granuloma) consist of nodules composed of Langerhans cells with variable numbers of eosinophils, plasma cells, and lymphocytes. Eosinophils usually present in the initial active stage of disease contribute to the eosinophilic granuloma. Numerous in about one-fourth of cases, they are usually situated at the periphery of the lesions.[744] The eosinophils are rare or absent at the chronic stage of disease. Blood eosinophilia is generally absent.

OTHER CONDITIONS

In lung transplant recipients, eosinophilic alveolitis may be indicative of acute rejection[745] or may result from drugs or infectious agents such as *Aspergillus, Pseudomonas,* or coxsackievirus. BAL eosinophilia of 2% or greater is associated with a poor outcome in lung transplantation.[746] In patients with graft-versus-host disease after hematopoietic stem cell transplantation, the significance of eosinophilia at BAL is unclear.[747]

In sarcoidosis, blood eosinophilia and tissue eosinophilia may be present but are usually mild.[748,749] Pulmonary eosinophilia developed in two patients after transplantation for sarcoidosis, with bronchiolitis obliterans syndrome developing after resolution of pulmonary eosinophilia.[750] Eosinophilic pneumonia was reported as a paraneoplastic manifestation in patients with colon adenocarcinoma,[751] and in gastric cancer producing GM-CSF and IL-5.[752]

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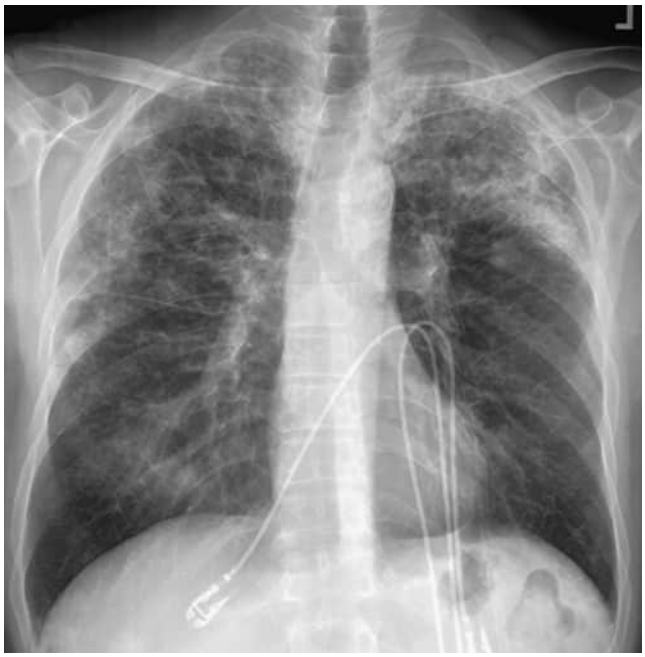
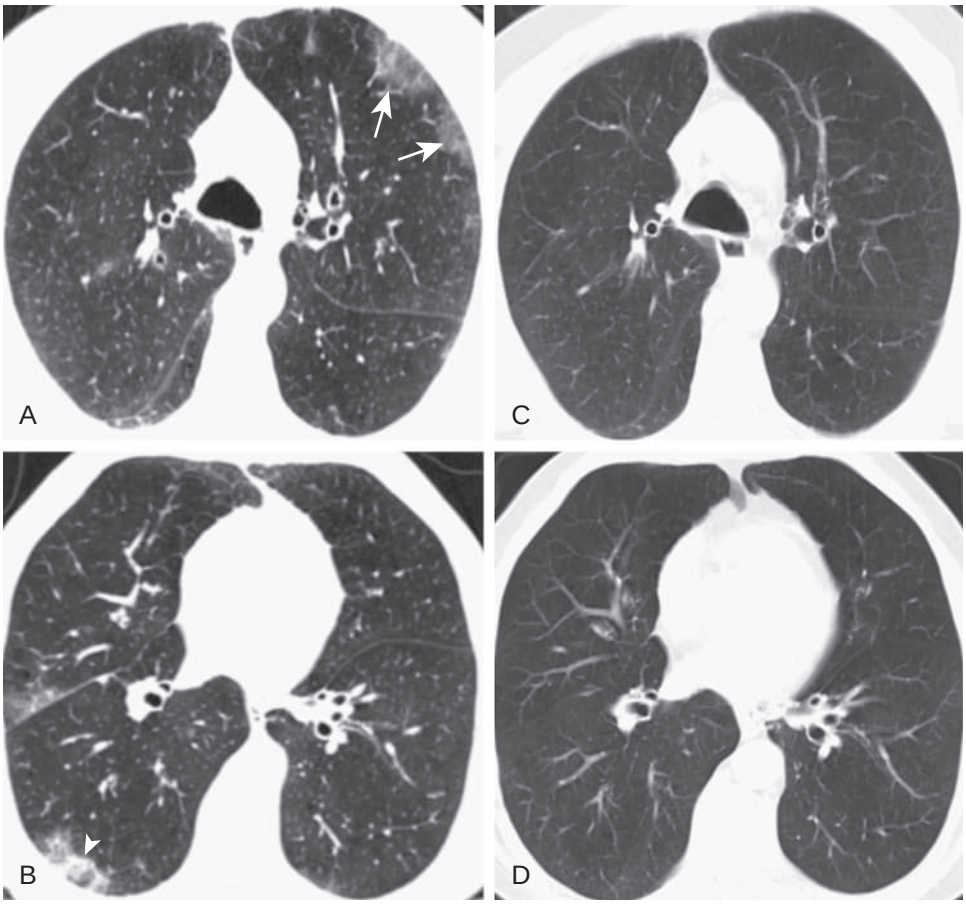
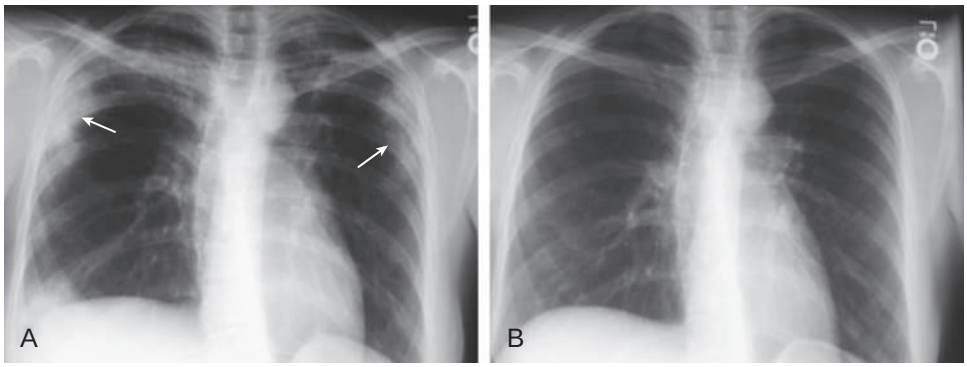
eFIGURE IMAGE GALLERY



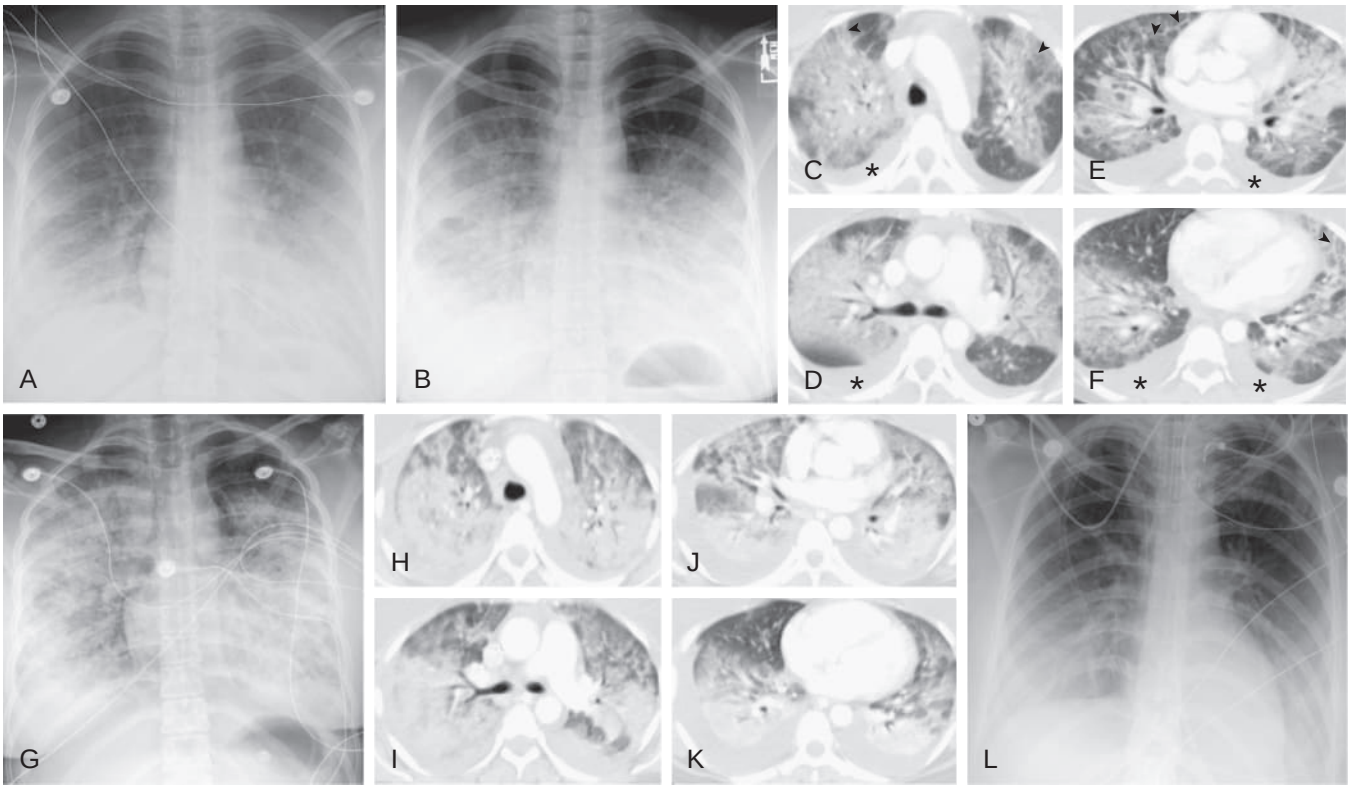
eFigure 96.1 Idiopathic chronic eosinophilic pneumonia: chest radiographic findings. Frontal chest radiograph in a patient with chronic eosinophilic pneumonia shows bilateral, upper lobe predominant peripheral consolidation and bronchovascular thickening (see Video 96.1 for chest computed tomography for this patient). (Courtesy Michael B. Gotway, MD.)



eFigure 96.2 Idiopathic chronic eosinophilic pneumonia: clearing after corticosteroid therapy at chest *computed tomography* (CT). (A–B) Axial chest CT in a patient with chronic eosinophilic pneumonia, displayed in lung windows, shows patchy, bilateral areas of subpleural ground-glass opacity (*arrows*) and consolidation (*arrowhead*). (C–D) Axial chest CT displayed in lung windows after corticosteroid therapy shows resolution of the areas of ground-glass opacity and consolidation. (Courtesy Michael B. Gotway, MD.)



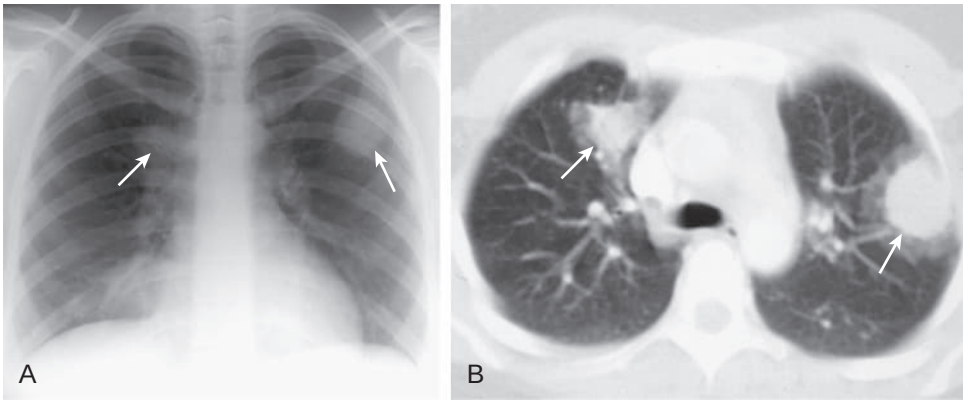
eFigure 96.3 Idiopathic chronic eosinophilic pneumonia: clearing after corticosteroid therapy at chest radiography. (A) Frontal chest radiograph in a patient with chronic eosinophilic pneumonia shows the typical appearance of upper lobe, bilateral, subpleural consolidation (*arrows*). (B) Frontal chest radiography after corticosteroid therapy shows clearing of the consolidation. (Courtesy Michael B. Gotway, MD.)



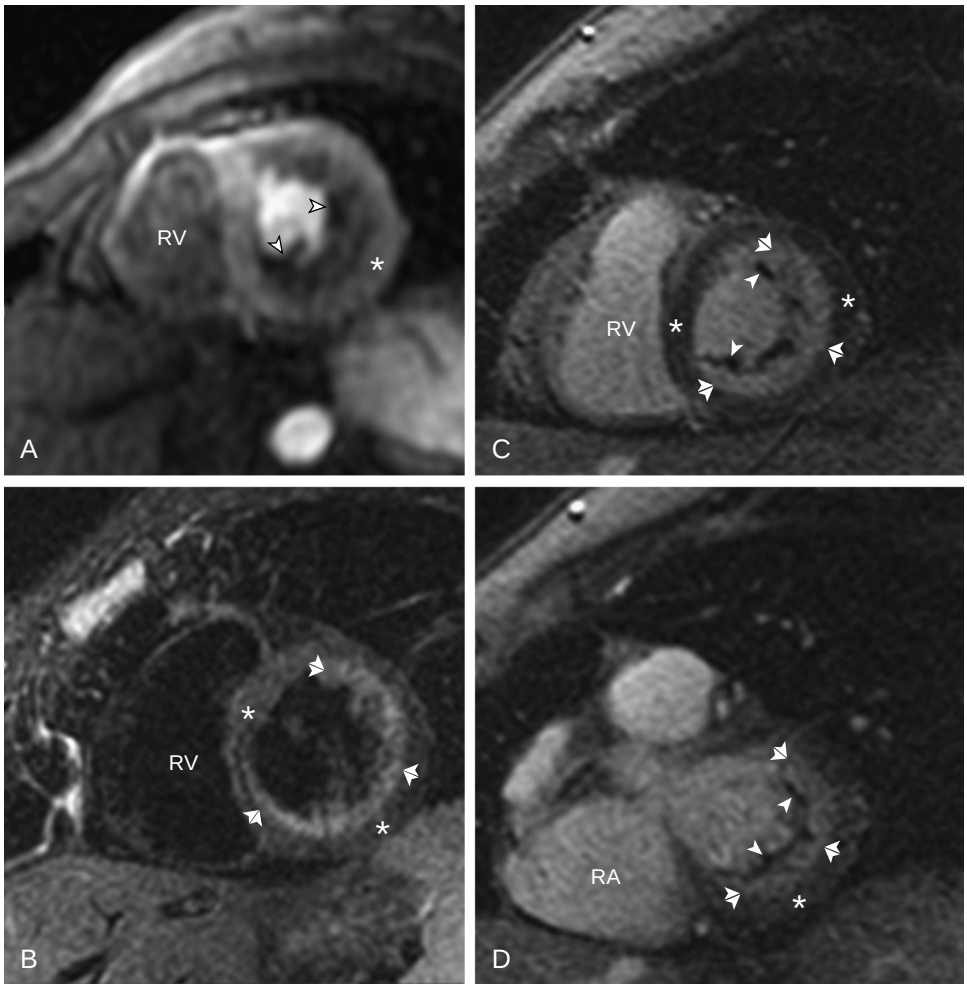
eFigure 96.4 Idiopathic acute eosinophilic pneumonia: chest radiographic and chest *computed tomography* (CT) findings with evolution. (A) Frontal chest radiograph in a 31-year-old previously healthy, immunocompetent, nonsmoking woman performed on the first day of hospitalization shows bilateral, symmetrical, middle and lower lung–predominant opacities with preserved lung volumes, normal mediastinal width, and no clear pleural effusions. The patient initially reported cough and was treated with broad-spectrum antibiotics, but her condition worsened and she developed shortness of breath and fever. (B) Frontal chest radiograph performed on the second day of hospitalization shows progression of the bilateral pulmonary opacities. (C–F) Axial chest CT displayed in lung windows on the third hospital day shows symmetrical, bilateral, diffuse air space consolidation and ground-glass opacity with a background of smooth interlobular septal thickening (*arrowheads*). Small symmetrical bilateral pleural effusions (*asterisks*) are seen. (G) Frontal chest radiograph on the third hospital day shows continued progression in bilateral and now extensive air space consolidation. (H–K) Axial chest CT displayed in lung windows after the patient developed profound oxygen desaturation, which required transfer to the intensive care unit and intubation, shows progression in the bilateral ground-glass opacity and consolidation with slight enlargement of the pleural effusions. (L) Frontal chest radiograph performed 6 days after hospitalization, after administration of corticosteroids initiated after bronchoscopy with bronchoalveolar lavage revealed eosinophilia, shows marked clearing of the bilateral air space opacities. The patient remains intubated, but her respiratory status continued to improve rapidly. She was subsequently extubated and discharged home 5 days later. (From Gotway MB, Conomos PJ. Rapidly progressive pulmonary opacities on thoracic imaging studies. *Clin Pulmon Med.* 2008;15:300–303. Courtesy Paul Conomos, MD, Arizona Pulmonary Specialists, Phoenix.)



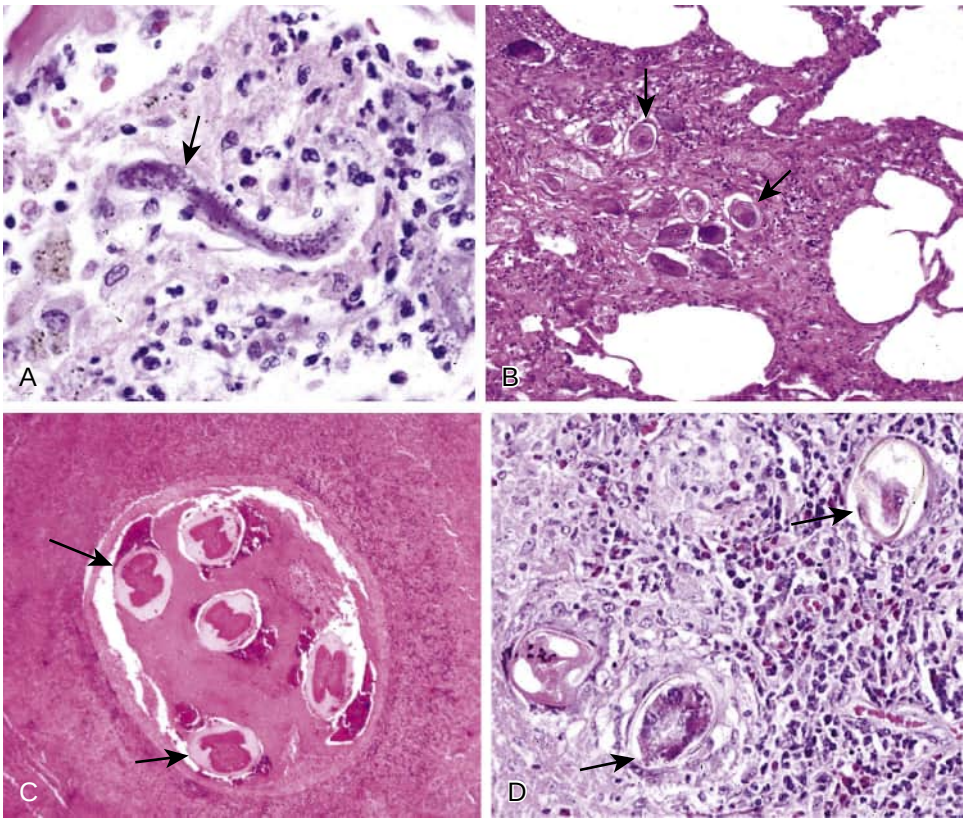
eFigure 96.5 Eosinophilic granulomatosis with polyangiitis. Axial chest computed tomography scan of a patient with eosinophilic granulomatosis with polyangiitis, with lung consolidation and ground-glass opacities corresponding to eosinophilic pneumonia. In addition, pericardial effusion and bilateral pleural effusions are present due to cardiomyopathy.



eFigure 96.6 Bronchocentric granulomatosis: chest radiographic and chest computed tomography findings. (A) Frontal chest radiograph performed in a 20-year-old nonsmoking woman with pleuritic chest pain shows bilateral, upper lobe pulmonary nodules and masses (*arrows*). (B) Axial chest computed tomography displayed in lung windows shows the lesions at chest radiography to be somewhat poorly defined, with faint, surrounding ground-glass opacity halos (*arrows*). Percutaneous biopsy of the dominant left upper lobe lesion showed only necrotizing granulomatous inflammation without evidence of malignancy. Surgical lung biopsy was performed and showed bronchocentric granulomatosis. The patient's symptoms and lesions resolved after corticosteroid therapy, and she had no recurrences during 5 years of follow-up. (Courtesy Michael B. Gotway, MD.)



eFigure 96.7 Cardiac involvement in hypereosinophilic syndrome. Cardiac magnetic resonance imaging findings showing the characteristic three-layered appearance of endomyocardial fibrosis. (A) Short-axis, first-pass perfusion image shows extensive low-signal, nonenhancing thrombus (*arrowheads*) within the left ventricle, adjacent to the enhanced left ventricular cavity, internal to the left ventricular muscle (*asterisk*). (B) Short-axis triple inversion recovery image (a fluid and inflammation-sensitive sequence) shows diffuse high signal involving the severely thickened endomyocardium (*double arrowheads*) internal to the normal-appearing, intermediate signal left ventricular musculature (*asterisk*). (C–D) Short-axis, inversion–recovery-prepared, fast-gradient echo late gadolinium enhancement images (obtained 10 minutes after the intravenous administration of gadolinium) at the base of the heart show the hypointense thrombus (*single arrowheads*) associated with extensive enhancement of the inflamed (and possibly fibrotic) and markedly thickened endomyocardium (*double arrowheads*), interposed between the low-signal thrombus (*single arrowheads*) and normal-appearing left ventricular muscle (*asterisk*). **RA, right atrium; RV, right ventricle.** (Courtesy Philip A. Araoz, MD, Department of Radiology, Mayo Clinic, and Michael B. Gotway, MD.)



eFigure 96.8 Parasites in the lung. (A) Filariform larva of *Strongyloides stercoralis* (*arrow*) penetrating into alveolar space with associated inflammation. (B) Schistosome eggs in lung parenchyma (*arrows*). (C) Dirofilarial nodule, with worm remnants (*arrows*) in organizing thrombosed vessel. (D) *Paragonimus westermani* with yellowish refractile eggs (*arrows*) in eosinophil-rich exudates. (Modified from Leslie KO, Wick MR. *Practical Pulmonary Pathology: A Diagnostic Approach: A Volume in the Pattern Recognition Series.* ed 2. Philadelphia: Elsevier; 2011.)

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97 LYMPHANGIOLEIOMYOMATOSIS

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INTRODUCTION

Lymphangioleiomyomatosis (LAM) is a rare neoplastic disease characterized by a genetic association with the neurocutaneous syndrome *tuberous sclerosis complex* (TSC), marked female sex predominance, cystic destruction of the lung, and progressive respiratory failure. Symptoms and signs include dyspnea on exertion, recurrent pneumothoraces, abdominal tumors including renal *angiomyolipomas* (AMLs) and lymphangioleiomyomas, and chylous fluid accumulation in the chest and abdomen.[1]

LAM was first reported in a patient with TSC who presented with bilateral spontaneous pneumothorax in 1918[2] and in a patient without TSC in 1937.[3] In the 1950s and 1960s, solitary case reports or small case series fostered a varied and confusing pathologic nomenclature in the early literature.[4] Since the late 1970s, larger case studies and registry-based studies have better defined the natural history, pathologic classification, and clinical presentation of LAM.[5-16] Moreover, in the past 2 decades, synergistic interactions among pulmonary investigators, TSC geneticists, *Drosophila* biologists, molecular biologists, and patient advocacy groups have resulted in truly remarkable progress in the understanding of the molecular and cellular basis of LAM,[17,18] as well as the development of a diagnostic serum test, clinical practice guidelines, and a targeted therapy.[19]

EPIDEMIOLOGY

LAM is seen both in the setting of TSC (TSC-LAM) and in a sporadic form in patients who do not have germline mutations in TSC genes or the clinical syndrome of TSC (*sporadic LAM* [S-LAM]) (Table 97.1).[1] TSC is an autosomal dominant genetic disorder associated with cognitive impairment, seizures, and the development of hamartomas and dysplastic lesions in several organs, including cortical tubers, giant cell astrocytomas, and subependymal nodules in the central nervous system; angiofibromas, shagreen patches, and ash leaf macules of the skin; and AMLs and cysts of the kidney.[20,21]

The cystic lung changes seen in patients with TSC are typically presumed to be caused by LAM, and several cases of biopsy-proven LAM have been reported in women and men with TSC.[22-24] Lung biopsies are not routinely performed in the TSC population, however, and other causes of cystic change in TSC patients are possible, including smoking,[25] alpha$_1$-antitrypsin deficiency, Sjögren syndrome,[26] and as yet unclassified forms.[27]

In cross-sectional studies from tertiary referral centers, TSC-LAM has been reported in approximately 10% of men and 30% of women with TSC,[28-30] although a screening study suggested that age-dependent development of cystic change in women with TSC results in an estimated LAM prevalence of up to 80% by the age of 40 years.[31] Symptomatic TSC-LAM is almost entirely restricted to women, with a few rare exceptions.[23,24,32]

In S-LAM, lesions of the skin and brain are absent, and manifestations that accompany the pulmonary cystic changes include only renal and extrarenal AMLs, infiltration and obstruction of the lymphatic system, and occasional sclerotic bone lesions.[33] A clinical presentation consistent with S-LAM, including biopsy documentation and negative germline TSC mutation analysis, has been reported in a single male patient without clinical evidence of TSC.[34] However, it is possible that limitations of the genetic

Table 97.1 Comparison of Tuberous Sclerosis Complex–Associated Lymphangioleiomyomatosis and Sporadic Lymphangioleiomyomatosis

	TSC-LAM	S-LAM
Estimated number of patients worldwide	150,000	10,000-30,000
Reported in male patients	++	+ (1)
Reported in children	+	+
Ascertainment	Screening, dyspnea, pneumothorax	Dyspnea, pneumothorax, chylothorax, incidentally on CT
Germline *TSC* mutations	+	–
Inheritable	+	–
TSC1 or *TSC2* mutations reported	33%/66%	0%/100%
Renal angiomyolipomas Bilateral Multiple	93% 81% 60%	33% 19% 6%
Hepatic angiomyolipomas	33%	2%
Lymphangiomyomas	9%	29%
MMPH	+ (~12%)	Very rare, if ever (~1%)
CNS, skin, eye, or cardiac lesions	+	–
Sclerotic bone lesions One or more Four or more	 98% 88%	 30% 3%
Retroperitoneal, thoracic adenopathy	Rare	39%
Dyspnea	Less common	More common
Chylothorax	Uncommon	20%
Pneumothorax	Less common	66%
Respiratory failure	Less common	More common

CNS, central nervous system; CT, computed tomography; MMPH, multifocal micronodular pneumocyte hyperplasia; S-LAM, sporadic lymphangioleiomyomatosis; TSC-LAM, tuberous sclerosis complex–associated lymphangioleiomyomatosis.

methods available at the time may have precluded identification of underlying *mosaicism* for TSC in this case, whereby there may be two genotypes in the same individual. In support of this notion, mosaicism for *TSC2* mutations has been described in two male patients with apparent S-LAM who did not meet diagnostic criteria for TSC.[35,36]

Careful epidemiologic analyses of the ethnic and racial distribution of LAM have not been performed. Although the biases introduced by the rarity of the illness, the protean presentation, and the disproportionate reporting of patients with LAM in large series from the United States, Europe, and Asia may suggest a predilection of the disease for whites and Asians, it is likely that all races are affected and that countries and populations with the greatest access to health care resources and the Internet are overrepresented in these studies.

Harknett and colleagues[37] determined that LAM was diagnosed in 3.4 to 7.8 women per million across seven different countries. These investigators did not stratify patients by the presence or absence of TSC, but it is likely that both S-LAM and TSC-LAM populations were included in the estimate. Extrapolation of this prevalence range to the approximately 3.8 billion women on Earth results in a predicted global LAM population ranging from 13,000 to 30,000 diagnosed patients.

It is likely that LAM is severalfold more common than these numbers suggest. The live birth prevalence of TSC ranges between 1 in 6000 and 1 in 13,000 persons.[38] TSC affects both sexes equally,[39] and the estimated worldwide prevalence of TSC is approximately 0.6 million to 1.25 million people (assuming a world population of 7.6 billion people), with roughly half of them being women. If one estimates that cystic pulmonary changes consistent with LAM are found in one-third of women with TSC,[28-30] the global prevalence of TSC-LAM is estimated to be approximately 100,000 to 200,000 women.

Although screening of TSC populations identifies a subset of LAM patients who have a range of cystic change in the lung from very mild to severe, the degree of cystic profusion is most often mild or moderate,[31] and pulmonary manifestations appear to reach clinical significance in only approximately 5–10% of patients with TSC-LAM.[40] TSC-LAM is certainly underrepresented in large trials, registries, and databases: patients with TSC-LAM made up only about 14.7% of the 230 patients who enrolled in the *National Heart, Lung and Blood Institute* (NHLBI) LAM Registry.[11] Although TSC-LAM is predicted to be 10-fold more common than S-LAM, most patients with LAM (85–90%) who seek medical attention with adult pulmonary specialists have S-LAM. This observation is consistent with the notion that TSC-LAM identified through screening is often milder than S-LAM, which most typically reaches attention through progressive dyspnea, pneumothorax, or chylothorax. It is also possible that other TSC comorbidities may overshadow the pulmonary manifestations of TSC-LAM and hinder TSC-affected patients from seeking medical care for their lung disease.

GENETIC AND MOLECULAR BASIS OF TUBEROUS SCLEROSIS COMPLEX AND LYMPHANGIOLEIOMYOMATOSIS

INHERITANCE

Approximately two-thirds of new TSC cases arise from de novo mutations that take place during embryogenesis. Familial TSC, which results from inheritance of germline mutations, accounts for one-third of new cases.[41] There have been several reports of familial TSC-LAM,[28,42] but mother-daughter transmission of S-LAM has never been reported.

MOLECULAR PATHOGENESIS

LAM is a neoplastic and metastatic process caused by mutations in TSC genes.[43] Dysregulation of the PI3 (phosphatidylinositol-3)/Akt signaling pathway leading to

constitutive activation of the *mechanistic* (or *mammalian*) *target of rapamycin* (mTOR) complex plays a central role in abnormal LAM cell growth, proliferation, and survival.[18,44] The metastatic and destructive effects of the disease are aided by the combination of abnormal lymphangiogenesis mediated by lymphangiogenic growth factors such as *vascular endothelial growth factors* (VEGF-C and VEGF-D),[45,46] matrix degradation by proteolytic enzymes,[47] antiapoptotic effects of sex steroids such as estrogen,[48] and immune evasion strategies.[49-51]

Tumor Suppressor Proteins Control Cell Growth

Clinicians have long recognized that the cystic lung disease in women with TSC is pathologically indistinguishable from that in women with S-LAM.[4,52] However, the demonstration that S-LAM and TSC-LAM are genetically linked was delayed, in part, by the failure to appreciate that a nonfamilial disease could share a common genetic basis with a heritable disease.[53] There are several precedents for this phenomenon among the class of diseases known as tumor suppressor syndromes (including neurofibromatosis and von Hippel–Lindau disease), of which TSC is a member.

Tumor suppressor proteins regulate orderly cell growth and differentiation by sensing the surrounding environment, transmitting signals to the nucleus, and directly affecting transcription, translation, survival, or cell division. In the classic "two-hit" paradigm,[54] a mutant copy of a tumor suppressor gene is inherited from one parent, and a tumor or dysplastic lesion develops when the second "good" parental copy of the tumor suppressor gene is inactivated through a random, somatic mutation. This first (inherited) hit, often a point mutation or a small insertion or deletion, results in heterozygosity for the allele (i.e., one good copy and one mutant copy). The second mutational event is usually a large deletion, resulting in the loss of a chromosomal segment and *loss of heterozygosity* (LOH) (i.e., two mutant copies). When both copies of a tumor suppressor gene contain damaging mutations, the protein produced by the gene becomes defective or deficient, protein function is lost, and cell growth, survival, and synthetic function become dysregulated.

Tuberous Sclerosis Complex Proteins Regulate Signaling Through the Akt Pathway

TSC is caused by inactivating mutations in either of the two known TSC loci, *TSC1* on chromosome 9q34[55] or *TSC2* on chromosome 16p13.[56] The proteins encoded by *TSC1* and *TSC2* are hamartin and tuberin, respectively. Hamartin has no informative homologies with other proteins in the National Center for Biotechnology Information database, whereas tuberin has a domain with *guanosine triphosphatase* (*GTPase)-activating protein* (GAP) homology.[57]

Until recently, little was known about the function of TSC proteins other than that they modulate cell growth. In 1999, it was reported that the enlarged eye cell phenotype of the mutant fruit fly, *Gigas,* was the result of genetic inactivation of the fly homologue for tuberin.[58] Several laboratories subsequently reported that tuberin and hamartin regulate signaling through the phosphatidylinositol-3-kinase/PKB (Akt)/S6K pathway, which controls cellular size and proliferation.[59-61]

Tuberin and hamartin associate into a complex that functions as a master regulator for mTOR through an intermediate G protein called Rheb.[62,63] The intact tuberin-hamartin complex acts as a GAP for Rheb, thus maintaining the protein in an inactivated, nonphosphorylated state (Rheb–guanosine diphosphate). Phosphorylation of tuberin by Akt inactivates the GAP activity of the tuberin-hamartin complex, increases the abundance of Rheb–guanosine triphosphate, drives association of mTOR with raptor (and mLST8 and PRAS40, not shown) to form the mTORC1 complex, and results in phosphorylation and activation of downstream kinases mTOR, S6K, and the initiation factor *4E-binding protein* (4E-BP1) (Fig 97.1). The association of mTOR with rictor (and mSIN1 and mLST8, not shown) to form mTORC2 results in activation of ROCK and rho kinase, cytoskeletal rearrangement, and cell movement.

Genetic mutations that result in the absence or dysfunction of tuberin or hamartin, such as is seen in patients with TSC and LAM, ultimately cause constitutive activation (phosphorylation) of S6 and eIF4E, two proteins intimately involved in the regulation of protein translation, as well as Rho kinase, which regulates intracellular trafficking, cell adhesion, and cell movement. Constitutive activation of the mTOR pathway causes inappropriate cell growth and proliferation by promoting anabolic metabolism in a pleiotropic fashion, leading to increased protein, lipid, and nucleotide synthesis in a balanced and coordinated manner.[64-68] Disruption of this balance in the anabolic pathway activation may yield a future therapeutic strategy. Multiple mTOR effectors and mTOR itself are found to be highly phosphorylated in tumors of rats,[69] mice,[70] and humans[71] with mutations in TSC genes. Sirolimus, a microbial product that inhibits mTOR activity, extinguishes staining for phosphorylated S6 and causes regression of TSC-deficient rat renal tumors.[69]

Tuberous Sclerosis Complex Mutations Are Found in the Lung and Kidney Lesions of Patients With Sporadic Lymphangioleiomyomatosis

Patients with tuberous sclerosis have germline mutations in TSC genes, but patients with S-LAM do not.[72] Whether patients with S-LAM represent generalized low-level mosaics for TSC gene mutations remains a possibility, at least in some individuals.[35,36] Smolarek and coworkers[43] first implicated TSC genes in the pathogenesis of S-LAM by finding that LOH for *TSC2* was present in the renal AMLs and lymph nodes of patients with S-LAM. Proof that the loss of tuberin function was responsible for lung disease in LAM was provided by Carsillo and colleagues,[53] who demonstrated the presence of missense and protein truncating *TSC2* mutations associated with LOH in the abnormal lung and kidney tissue of patients with S-LAM. Samples taken from the normal regions of lung and the kidney in those patients did not exhibit TSC mutations.[72] These findings were subsequently confirmed in 21 patients by Sato and associates.[73] Whereas both *TSC1* and *TSC2* mutations have been described in patients with TSC-LAM,[28,74] to date only *TSC2* mutations have been described in patients with S-LAM.[53,73,75]

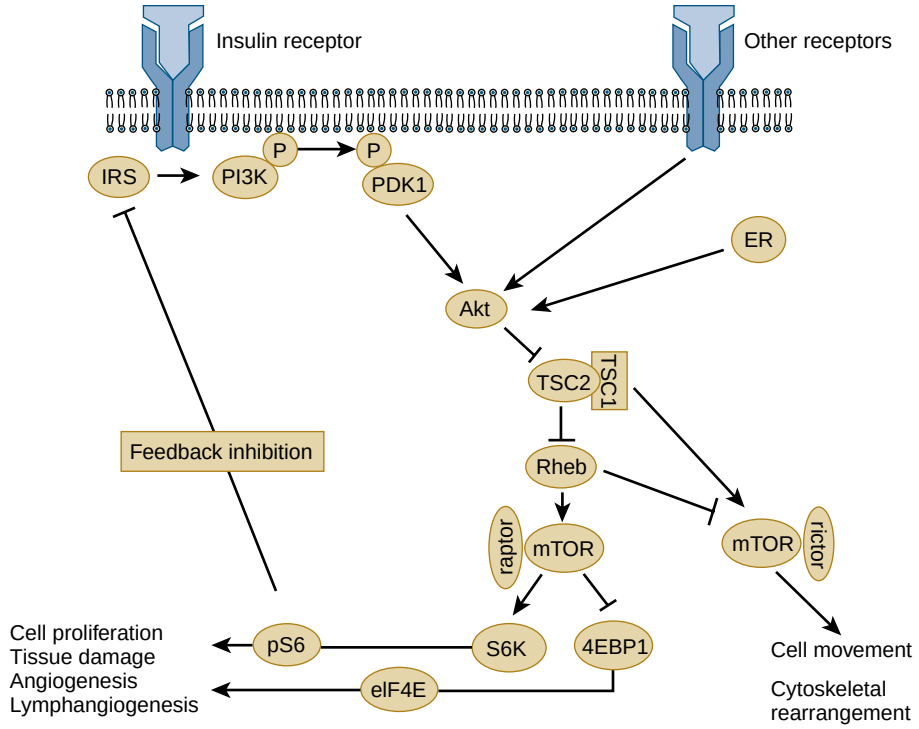

Fig. 97.1 Tuberous sclerosis proteins regulate signaling through the Akt growth and protein translation pathway. The binding of a ligand to a growth factor receptor (e.g., the insulin receptor) activates *phosphatidylinositol-3-kinase* (PI3K) followed by PDK1 and Akt. Activated pAkt phosphorylates *tuberous sclerosis complex-2* (TSC2), which blocks its *guanosine triphosphatase–activating protein* (GAP) activity. When not phosphorylated, TSC2 complexed with TSC1 functions as a GAP for Rheb, thus maintaining Rheb in an inactivated Rheb–guanosine diphosphate state. Activated Rheb (Rheb–guanosine triphosphate [GTP]) is therefore abundant when TSC1 or TSC2 is missing or defective or when TSC2 is phosphorylated. Rheb-GTP activates *mechanistic target of rapamycin* (mTOR) in a manner that is potentiated by the availability of amino acids, phosphatidic acid, and adenosine triphosphate and is blocked by the absence of these substrates or the presence of sirolimus. Activated mTOR complexed with raptor phosphorylates downstream targets S6K and *4E-binding protein* (4E-BP1). pS6K phosphorylates S6, and 4E-BP1 releases eIF4E, which together activate the cellular translational machinery and promote cell growth. S6 also feeds back to inhibit upstream signaling, which restrains cell growth and "malignant" cellular behavior. Activated mTOR complexed with rictor signals through a divergent pathway to control cytoskeletal dynamics and cell movement through Rho kinases. ER, estrogen receptor; IRS, insulin receptor substrates. (Modified from Kwiatkowski DJ. Rhebbing up mTOR: new insights on TSC1 and TSC2, and the pathogenesis of tuberous sclerosis. *Cancer Biol Ther.* 2003;2:471-476.)

GENETIC EVIDENCE SUGGESTS THAT LYMPHANGIOLEIOMYOMATOSIS IS A METASTATIC NEOPLASM

Cornog and Enterline[4] were the first to suggest that, despite their benign appearance, cells that make up the LAM lesion represent a clonal, neoplastic proliferation of smooth muscle cells. The demonstration of LOH in the lung, kidney, and lymph node lesions in patients with LAM 3 decades later proved that their suspicions were correct.[43] Carsillo and colleagues[53] further demonstrated that the mutations present in the cells of the kidney tumor and lung lesion of a given individual with S-LAM were identical, thus suggesting that they arise from a common precursor.

A model for LAM has been proposed in which the lung is infiltrated as a consequence of benign metastasis of LAM cells from a remote and as yet unidentified source such as the lymphatic system,[46] the uterus,[76,77] or AMLs.[78] Reports of recurrence of LAM in the donor lung of patients with LAM who had undergone lung transplantation are also consistent with this metastatic theory[79-82]; in two cases, the source of lung metastases was proven to arise from the recipient by genetic and molecular techniques.[80,83] Cells containing LOH for TSC genes have been isolated from the blood and chylous fluid of patients with LAM,[84,85] a finding consistent with dissemination through the systemic circulation and lymphatics.

ROLE OF LYMPHANGIOGENESIS AND LYMPHATIC SPREAD IN DISSEMINATION OF LYMPHANGIOLEIOMYOMATOSIS

Approximately 30% of patients with LAM have axial abdominal or thoracic lymphadenopathy.[86] In some cases, LAM is restricted to the retroperitoneum, abdomen, or pelvis, with normal lung parenchyma or only a very few lung cysts, consistent with regional spread from a subdiaphragmatic source.[87] Valensi[88] showed that clusters of cells can be found in the chylous pleural fluid of patients with LAM. Itami and coworkers[89] demonstrated that the clusters originated in the dilated lymphatic system and were composed of α-smooth muscle actin–positive spindle cells enveloped by a single layer of endothelial cells (eFig. 97.1). Data from Japan provide additional evidence that the mechanism of spread of LAM may be through the lymphatic circulation.[45,46]

Induction of lymphangiogenesis appears to play an important role in this process, on the basis of abundant expression of lymphatic endothelial markers such as *podoplanin* (D2-40), LYVE-1, *VEGF receptor 3* (VEGFR-3),

VEGF-C, and VEGF-D.[45] Several laboratories have reported that VEGF-D is elevated more than threefold to eightfold in the serum of patients with LAM, a finding useful for distinguishing LAM from other cystic lung diseases and for predicting response to therapy.[90-99]

LAM clusters are found in the lymphatic lumen, in regions between axial lymph nodes (retroperitoneal, mediastinal, and the left venous angle [junction of the left internal jugular and subclavian veins]) that are infiltrated with LAM cells, and in chylous fluid of patients with chylous ascites and chylothorax.[45,46,100,101] LAM cell clusters enter the venous circulation at the insertion of the thoracic duct into the junction of the left internal jugular and subclavian veins and disseminate throughout the pulmonary capillary bed. LAM cell clusters impacted in the lung vasculature proliferate and invade or perhaps establish themselves in the lung by an "invasion-independent" mechanism by which the cluster lodges and becomes enveloped by the capillary wall without actually invading it, a process described by Sugino and colleagues.[102,103]

ROLE OF ESTROGEN IN THE PATHOGENESIS OF LYMPHANGIOLEIOMYOMATOSIS

Estrogen may play a role in LAM cell migration, infiltration, proliferation, survival, or secretion of destructive proteases. Hormonal fluxes during the menstrual cycle and estrogen-containing drugs have been implicated in LAM progression.[104,105] Estrogen regulates the transcription of many genes, and some evidence indicates that estrogen can modulate signaling through the Akt pathway.[106,107] Estrogen-mediated activation of the ERK pathway promotes activation of the late response gene *FRA1*, which is associated with epithelial-mesenchymal transition.[108] Akt activation, in turn, enhances the efficiency of *FRA1* translation through the phosphorylation of the S6K1-dependent eukaryotic translation factor 4B.

Estrogen was shown to promote pulmonary metastases and enhanced survival of TSC2-deficient cells in mice.[48] Prizant and colleagues[109,110] created a uterine-specific Tsc2 knockout mouse model and demonstrated that loss of Tsc2 leads to increased mTORC1 activity that drives uterine myometrial proliferation and pulmonary metastasis. Elimination of sex steroid production by either ovariectomy or aromatase inhibition was shown to decrease mTORC1 activity and inhibit myometrial proliferation. The myometrial growth was restored by addition of estrogen and not progesterone, thus suggesting that estrogen is the major sex steroid regulating myometrial growth and proliferation.[109] Tsc2-null myometrial lesions exhibited increased expression of matrix-degrading proteases such as *matrix metalloproteinases* (MMP-2 and MMP-9), as well as neutrophil elastase, and the expression of these proteases was dependent on estrogen signaling.[110] In another preclinical model of LAM, administration of fulvestrant ([Faslodex] an estrogen receptor antagonist) was shown to reduce estrogen-induced MMP up-regulation and block pulmonary metastasis of Tsc2 null xenograft tumors.[111] Collectively, these data suggest that targeting the estrogen-ERK pathway in combination with the mTORC1 pathway may be an effective combination therapy for LAM.

IMMUNE EVASION AS A MECHANISM FOR LYMPHANGIOLEIOMYOMATOSIS CELL PROLIFERATION

Escaping detection by the host immune system is a key survival mechanism used by a variety of human neoplasms.[112] LAM cell clusters in the lumen of conducting lymphatics and chylous pleural effusions are enveloped by a single layer of (presumably nonmutant) lymphatic endothelial cells, which may shield the mutant LAM cells from immune detection.

Another major modality of immune evasion involves expression of ligands such as PD-L1, PD-L2, and B7-H3 on the surface of neoplastic cells that down-regulate T cell–mediated cellular responses through binding to cognate receptors on the T cell surface, such as *cytotoxic T lymphocyte antigen-4* (CTLA-4), *programmed cell death 1* (PD-1), and *T cell immunoglobulin and mucin receptor 3* (TIM-3). Blocking these interactions through the use of targeted monoclonal antibodies against these receptors or their corresponding ligands (e.g., PD-L1) results in the de-repression of antitumor T cell responses.[113-117] Increased expression of PD-1 on the T cells within LAM nodules, and treatment with anti-PD-1 antibody alone or in combination with anti–CTLA-4 antibody, results in a substantial reduction in tumor burden in an animal model of TSC-LAM.[50] In another study, immunohistochemical analysis revealed evidence of increased PD-L1 expression in LAM nodules, and treatment with anti–PD-1 antibody resulted in prolonged survival in a mouse model of TSC-LAM.[51]

Another common host defense mechanism against tumors involves the *natural killer* (NK) cells, which recognize ligands (NKG2D ligands) such as the *major histocompatibility class* (MHC) *class I chain-related* (MIC) molecules MICA and MICB and the family of UL-16 binding proteins on the surface of neoplastic cells leading to deployment of antitumor defenses such as cytolytic granules. Shedding of soluble NKG2D ligands is a well-characterized decoy mechanism used by tumor cells to evade immune detection. Pulmonary LAM cells were found to express multiple NKG2D ligands by immunohistochemistry, and soluble NKG2D ligands were elevated in the serum of LAM patients. The presence of the NKG2D ligands *UL16 binding protein 2 and 3* (ULBP-2 and ULBP-3) was correlated with the rate of lung function decline.[49] Taken together, these data support the role of immune system evasion in the pathogenesis of LAM and suggest immunotherapy as a potential treatment strategy.

MECHANISMS OF MATRIX REMODELING IN LYMPHANGIOLEIOMYOMATOSIS

Proteases are believed to play a major role in the cystic destruction of the lung parenchyma in LAM. The spectrum of metalloproteinases that are aberrantly expressed in LAM has not been fully characterized, but MMP-2 is the most abundant of those studied to date. Overexpression of MMP-1, MMP-9, MT1-MMP, and MMP-14 has also been reported,[118] and serum levels of MMP-9 are elevated in patients with LAM.[119] MMP-1, MMP-2, and MMP-9 are able to degrade elastin, consistent with the loss and degradation of elastic fibers seen in LAM.[118] Zhe and associates proposed that increased expression of serum response factor

may lead to MMP activation and down-regulation of *tissue inhibitor of metalloproteinase* (TIMP-3) in LAM cells,[120,121] thus resulting in an imbalance of proteases and protease inhibitors.[47,120-122]

Abundant expression of cathepsin K has been reported in LAM, a finding suggesting a possible pathogenic role for this protein in tissue destruction.[123] Extracellular matrix remodeling proteins such as fibronectin, von Willebrand factor, and kallikrein III were found to be differentially expressed in the serum of LAM patients as compared with healthy controls in a small case-control analysis.[124]

Multiple growth factors and cytokines are abundantly expressed in LAM, and they induce proliferation, suppress apoptosis, and support fibrosis. *Basic fibroblast growth factor* (bFGF) is a potent mitogenic factor for smooth muscle cells, myofibroblasts, and fibroblasts. LAM lesions have also been reported to contain abundant tryptase-positive mast cells, which express bFGF and receptors Bek (FGFR-2) and Flg (FGFR-1), as well as chymases, renin, angiotensin-converting enzyme, and angiotensin receptors type I and type II.[125-127] *Insulin-like growth factors* (IGFs) are involved in normal pulmonary development and in the pathogenesis of smooth muscle cell proliferation. IGF-I, IGF-II, IGF-I receptor, *IGF-binding protein* (IGFBP)-1, IGFBP-2, IGFBP-4, IGFBP-5, and IGFBP-6 are expressed in lung tissue of patients with LAM.[128] Carelli and coworkers[129] showed that $TSC2^{-/-}$ human smooth muscle cells derived from AMLs express the apoptosis inhibitor protein, survivin, when exposed to IGF-1. Transforming growth factor-β_1, a profibrotic cytokine, is enriched in highly cellular areas of the LAM lesion.[130] Increased prostaglandin biosynthesis has been reported in preclinical models of LAM, and increased levels of prostaglandin metabolites prostaglandin E_2 and prostacyclin are found in the serum of LAM patients.[131,132] Targeting the systems that promote proteolytic and fibroproliferative responses are possible therapeutic strategies for the future.

CLINICAL FEATURES

LAM usually manifests during the reproductive years, with a mean age at the onset of symptoms in the early to mid-30s.[6,9,14,133] Although new diagnoses of LAM have been reported in patients as young as 12 years,[134,135] documented cases of the disease before menarche are rare. Several reports in the literature describe women in whom the diagnosis was made after menopause and at ages through the ninth decade of life.[6,8,9,136-138] LAM does not appear to be smoking related because most patients in the largest case series were nonsmokers.[8,9,11]

Because LAM is rare and the symptoms are often nonspecific, the diagnosis is often delayed, with a mean interval between the onset of symptoms and diagnosis of 5 to 6 years.[6,8,15,139] Initial incorrect diagnoses typically include bronchial asthma, emphysema, chronic bronchitis, COPD, sarcoidosis, diffuse panbronchiolitis (in Asia), and even idiopathic interstitial pneumonias, including idiopathic pulmonary fibrosis.

The most common reasons for patients with LAM to present for initial evaluation include complaints of dyspnea on exertion, an episode of spontaneous pneumothorax, or an incidental discovery of pulmonary cystic change on imaging performed for unrelated reasons.[10,11,140] During the course of the illness, dyspnea develops in the majority of patients, and pneumothorax happens in approximately two-thirds.[8,14,141] Among patients with a pneumothorax, the first pneumothorax precedes the diagnosis of LAM in 82% of patients; in fact, most patients have two pneumothoraces before the diagnosis is made.[141] Pneumothorax in LAM has a very high (>70%) risk of recurrence.[8,14,141,142]

Other signs and symptoms of LAM, which may be present at the onset or may develop during the course of the disease, include fatigue (frequent and can be disabling), cough (uncommon), hemoptysis (rarely massive), chest pain, and symptoms related to movement of chylous fluid into pleural locations (~20% of patients) and extrapleural locations, such as the peritoneum (chylous ascites) or pericardium (chylopericardium), airway (chyloptysis), and genitourinary tract (chyluria and chylous metrorrhea). Fistulous communication with the gut can result in chyle in stool and protein-losing enteropathy. Chylous pulmonary parenchymal congestion is likely the result of retrograde chylous reflux and manifests with ground-glass opacities or interstitial or reticular changes in the lung. This diagnosis should be considered in LAM patients with crackles and subacute worsening of oxygenation or shortness of breath.[143] It is likely that the chylous complications of LAM result from obstruction of lymphatic channels secondary to infiltration by LAM cells and/or lymphatic remodeling that causes leaking of chylous material into various potential spaces. A history of chylous discharge from visceral organs resulting in such findings as the expectoration of plugs from the bronchi (e.g., plastic bronchitis) or the appearance of white material in urine, stool, or vaginal discharge is often overlooked and should be actively sought in every LAM patient.

AMLs, unusual hamartomas composed of fat, smooth muscle, and abnormal blood vessels, may arise in virtually any location in the chest and abdomen but are most common in the kidney (eFig. 97.2). Approximately 29–33% of patients with S-LAM have renal AMLs, compared with approximately 88–93% of patients with TSC-LAM.[11,28] AMLs are more commonly unilateral and solitary in patients with S-LAM, and they are more commonly bilateral and multiple in patients with TSC-LAM (see eFig. 97.2).[86] Blood vessels in AMLs are often tortuous and aneurysmal and are composed of cells with normal genotype and cells with TSC mutations.[144] Spontaneous hemorrhage into AMLs may produce severe flank or abdominal pain, acute hypotension, and/or anemia, occasionally in association with circulatory collapse.[145]

Renal cysts are seen occasionally in patients with LAM; in TSC-LAM, polycystic kidney disease may develop as a result of a contiguous gene deletion of *PKD1* that is immediately adjacent to *TSC2* on chromosome 16.[146]

Lymphangioleiomyomas (also known as lymphangiomyomas) are tumor-like masses composed of smooth muscle–like LAM cells and endothelial proliferations within lymphatic vessels and lymph nodes in the mediastinum, retroperitoneum, and lung. Not uncommonly, LAM manifests as retroperitoneal masses, including cystic lymphangiomyomas (eFig. 97.3) or lymph nodes with hypodense centers, which mimic necrotizing lymphomas, ovarian or renal cancers, or other malignant tumors.[147,148]

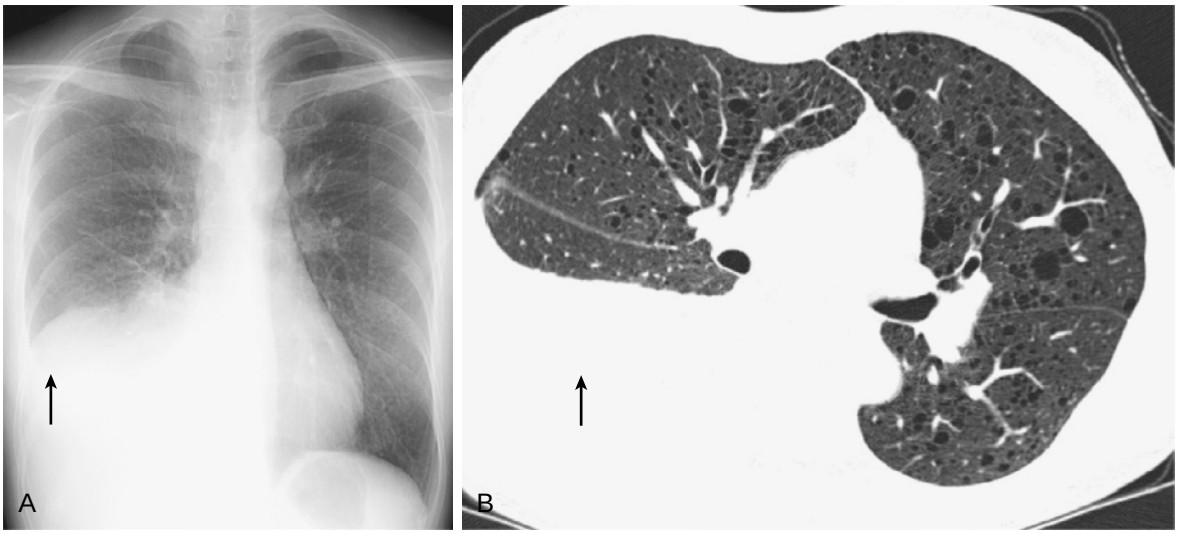

Fig. 97.2 Sporadic lymphangioleiomyomatosis with chylothorax. (A) Chest radiograph and (B) high-resolution computed tomography of a 40-year-old woman with sporadic lymphangioleiomyomatosis. Diffuse cystic changes and right-sided chylothorax *(arrows)* are present.

PHYSICAL EXAMINATION

The physical examination in LAM is often nonspecific. Lung auscultation is usually uninformative but may reveal rhonchi or wheezing in some patients.[8,9,15] Crackles are unusual and, if present, should raise suspicion of chylous pulmonary congestion. Clubbing is not a feature of LAM, even though it was reported in 3% and 5% of patients in two larger case series.[9,15] Physical examination may also reveal evidence of pleural effusion, ascites, or pneumothorax, if present. Careful dermatologic, ocular, and dental surveys should be performed for evidence of TSC, including facial angiofibromas, subungual fibromas, palpable dysplastic cutaneous lesions called shagreen patches, hypomelanotic macules including those with ash leaf or confetti configurations, retinal hamartomas, and dental pitting.[20,21,39]

IMAGING STUDIES

The chest radiograph in patients may appear relatively normal (eFig. 97.4), even late in the disease, or may suggest hyperinflation only. As the disease progresses, the chest radiograph often demonstrates diffuse, bilateral, and symmetrical reticular or nodular opacities (eFig. 97.5), cysts (eFig. 97.6), bullae, or a "honeycomb" or somewhat "pseudofibrotic" appearance (eFig. 97.7).[8,9] Pleural effusion (Fig. 97.2) and pneumothorax (eFig. 97.8) may also be apparent. Preservation of lung volumes in the presence of increased interstitial markings is a radiographic hallmark of LAM that helps distinguish it from most other interstitial lung diseases (see eFigs. 97.4A, 97.5, 97.6A, and 97.7A), in which increased lung elastic recoil decreases lung volumes.

The *high-resolution computed tomography* (HRCT) chest scan is much more sensitive than the chest radiograph in detecting cystic parenchymal disease and is the gold standard radiologic approach to establish the diagnosis of LAM. The typical CT scan shows diffuse round, bilateral, thin-walled cysts of varying sizes ranging from 1 to 45 mm in diameter (see Fig. 97.2; eFigs. 97.2C, 97.3C, 97.4B–D, 97.6B, 97.7B, and 97.8B).[142,149] The numbers of cysts vary in LAM from a few (see eFig. 97.8B) to almost complete replacement of the normal lung tissue (see eFig. 97.6B). The profusion of cysts tends to be milder in patients with TSC-LAM than S-LAM, perhaps explained in part by identification of patients with TSC-LAM earlier in the disease process through screening.[86]

Advances in image analyses enable the quantification of cystic change in patients with LAM,[150-153] and they provide an opportunity to develop imaging-based biomarkers to follow disease progression and treatment response in LAM. For instance, in a post hoc quantitative volumetric analysis of the CT scans obtained during the *Multicenter International Lymphangioleiomyomatosis Efficacy and Safety of Sirolimus* (MILES) trial, Argula and colleagues[151] demonstrated a reduction in CT image–derived residual volume in the sirolimus group and suggested the reduction in air trapping as a potential mechanism for the beneficial physiologic effect of sirolimus. Gopalakrishnan and associates[154] analyzed the pulmonary parenchymal texture on CT scans of LAM patients being evaluated at the NHLBI and identified unique CT-based texture properties that correlated with cyst scores and therapeutic response to sirolimus. Perhaps the greatest barrier to widespread use of serial quantitative CT scans to monitor disease progression and/or treatment response is the risk of cumulative ionizing radiation exposure. Hu-Wang and associates[155] used model-based iterative reconstruction to perform ultralow-dose radiation CT scans on 105 LAM patients at the NHLBI. Radiation exposure was reduced by more than 90%, to levels similar to that of a plain chest film, with sufficient retention of resolution to define the degree of cystic lung destruction.[155] Further validation and widespread clinical availability of these techniques are high-priority future needs in LAM.

The morphology of the cysts is useful in differentiating LAM from other cystic lung diseases (Fig. 97.3). LAM cysts are characterized by their relatively uniform size and thin walls; they also tend to be distributed evenly in a diffuse manner and are separated by normal-appearing lung parenchyma. Blinded expert radiologists can correctly

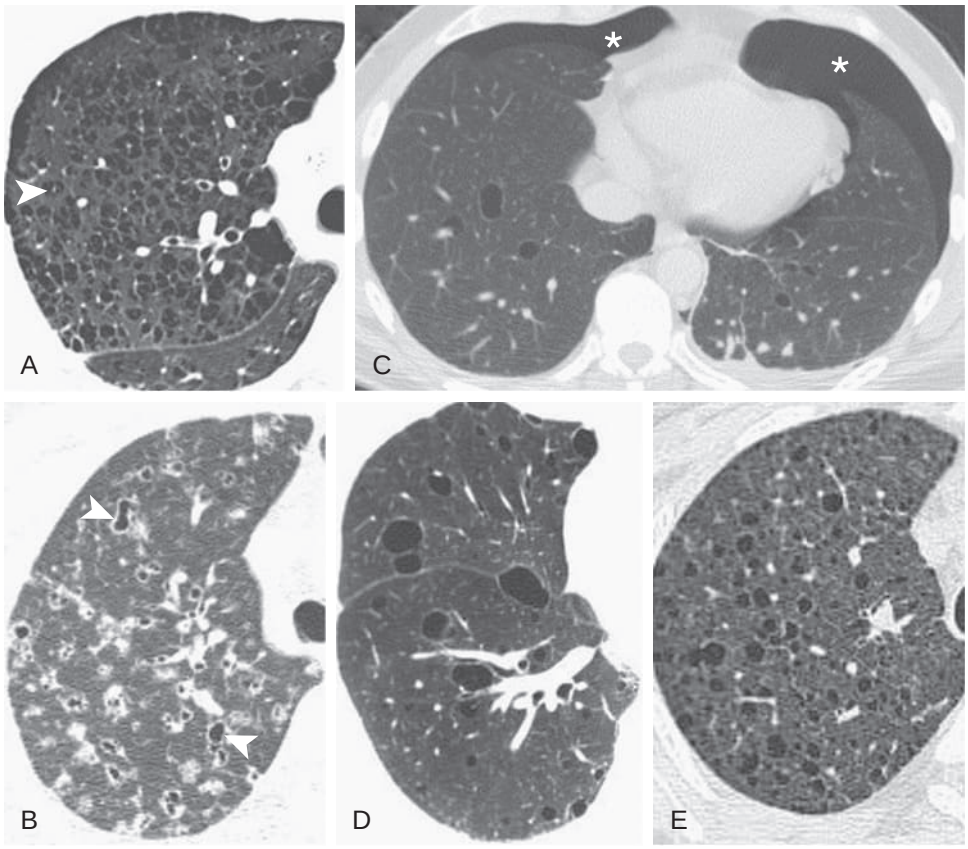

Fig. 97.3 Lymphangioleiomyomatosis cystic lung disease mimics. (A) Centrilobular emphysema—note the lack of a true cyst wall and the presence of the centrilobular artery *(arrowhead)* within the cystic region. (B) Pulmonary Langerhans cell histiocytosis—note unusually shaped cysts *(arrowheads)* and numerous nodules. (C) Birt-Hogg-Dubé syndrome—note lower lobe predominance of cysts. Spontaneous pneumothorax *(asterisks)* is present bilaterally. (D) Lymphocytic interstitial pneumonia—the cysts in this disorder may closely simulate lymphangioleiomyomatosis, particularly when no other infiltrative parenchymal findings coexist. (E) Lymphangioleiomyomatosis, presented for comparison. Note the relatively uniform, thin-walled appearance of the cysts with normal-appearing intervening lung parenchyma. (Courtesy Michael B. Gotway, MD.)

differentiate LAM from other cystic lung diseases approximately 80% of the time when provided with a pool of chest CT scans without accompanying clinical data.[142,149,156,157] Pleural effusions are found on CT in 12% of patients with S-LAM and in 6% of patients with TSC-LAM. Other CT features include linear densities (29%), hilar or mediastinal lymphadenopathy (9%), pneumothorax, lymphangiomyomas (see eFig. 97.3), and thoracic duct dilation.[8,15] Ground-glass opacities (12%) may suggest the presence of interstitial edema secondary to lymphatic congestion (Fig. 97.4). Views that include the abdomen may reveal AMLs.

In patients with TSC, nodular densities on HRCT may represent *multifocal micronodular pneumocyte hyperplasia* (MMPH) or clusters of hyperplastic type 2 pneumocytes[31,158-160] (Fig. 97.5; see also eFig. 80.2). MMPH may be present in male or female patients with TSC in the presence or absence of LAM, but it is typically not seen in patients with S-LAM.[30,161] MMPH is not generally associated with physiologic or prognostic consequences,[162] but one case of respiratory failure from MMPH has been reported.[163]

Chu and associates[15] reported that ventilation-perfusion scans were abnormal in 34 of 35 women with LAM. The most common abnormality was nonspecific diffuse heterogeneity of the ventilation and perfusion scans, with the defects usually grossly matched. These investigators also described an "unusual speckling pattern" on the ventilation scans in 74% of patients, consisting of "small, often peripheral collections of radioisotope" (eFig. 97.9). Using hyperpolarized xenon-129 magnetic resonance imaging ventilation scans on 22 LAM patients, Walkup and colleagues[164] found ventilation abnormalities and alveolar airspace dilation in all subjects, even in patients with normal spirometry; the magnetic resonance imaging abnormalities correlated well with pulmonary function testing. This technology may become useful for identifying the earliest evidence of airway changes in LAM and tracking treatment response. LAM and AML lesions do not typically exhibit increased uptake of ^{18}F-fluorodeoxyglucose on positron emission tomography scanning.[165] Other neoplasms (or sources of inflammation) should therefore be considered



Fig. 97.4 Interstitial pulmonary edema secondary to lymphatic obstruction or congestion. In patients with cystic change seen on high-resolution computed tomography that is otherwise typical for lymphangioleiomyomatosis, the ground-glass appearance *(arrows)*, often together with chylous effusions, lymphadenopathy, and/or lymphangiomyomas, may be indicative of pulmonary lymphatic congestion resulting from chylous reflux.

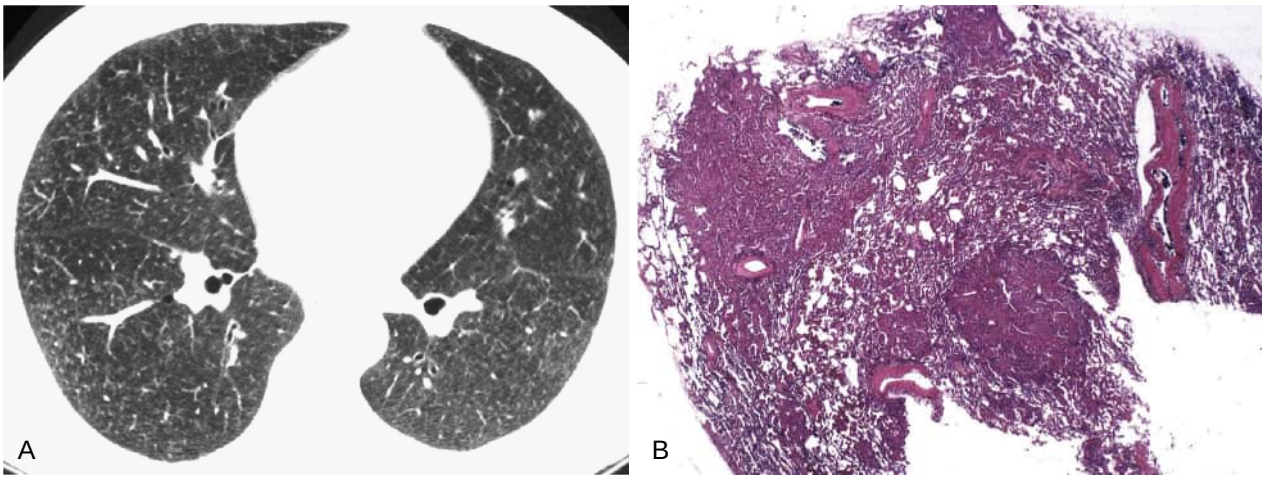

Fig. 97.5 Radiographic and histopathologic presentation of multifocal micronodular pneumocyte hyperplasia. (A) High-resolution chest computed tomography of a patient with multifocal micronodular pneumocyte hyperplasia reveals miliary nodules throughout both lungs. (B) The low-power view of a lung biopsy sample from a patient with multifocal micronodular pneumocyte hyperplasia reveals diffuse nodular proliferation of alveolar type 2 cells (×10 original magnification).

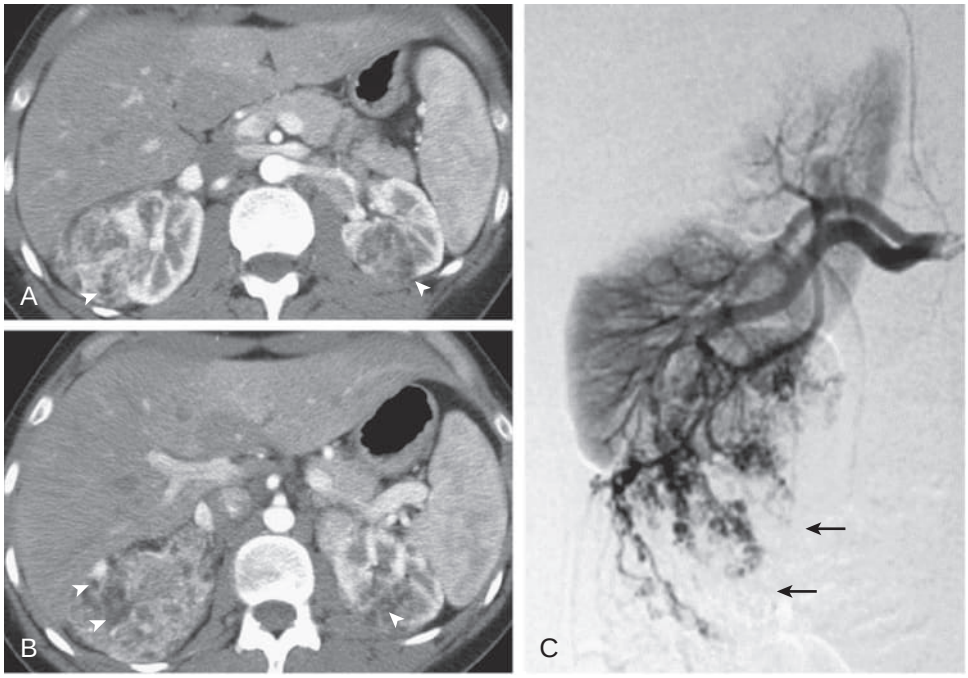

Fig. 97.6 Angiomyolipoma. (A–B) Axial abdominal computed tomography scans and (C) angiography of a renal angiomyolipomas (hypoattenuating foci bilaterally; *arrowheads*) in a 16-year-old girl with sporadic lymphangioleiomyomatosis. Note the tumor neovascularity *(arrows)* in the right kidney. (Courtesy Dr. Shoji Samma, Nara Prefectural Nara Hospital, Nara, Japan.)

in known or suspected LAM cases with positive positron emission tomography results.[165]

Abnormalities on abdominal imaging, such as renal AML (Fig. 97.6 and see eFig. 97.2A–B) and enlarged lymphatic structures, are also common in LAM (Fig. 97.7). Fat density within a renal mass is pathognomonic of AMLs (see eFig. 97.2A–B). AMLs are more prevalent and more frequently bilateral and large in patients with TSC-LAM than in patients with S-LAM, and AML size roughly correlates with the prevalence of pulmonary cysts in patients with TSC.[28] Avila and associates[86] reported the results of CT imaging in 256 patients with S-LAM and 67 patients with TSC-LAM who were referred to the National Institutes of Health. Renal AMLs were present in 32% of patients with S-LAM and in 93% of patients with TSC-LAM. Hepatic AMLs (eFig. 97.2A) were present in 2% of patients with S-LAM and in 33% of patients with TSC-LAM. Ascites was uncommon, seen in fewer than 10% of patients with S-LAM and very rarely in TSC-LAM. Abdominal lymphangiomyomas (see eFig. 97.3B), often containing both cystic and solid components, were seen in 29% of patients with S-LAM and in 9% of patients with TSC-LAM.[86]

Central nervous system abnormalities, such as cortical tubers, subependymal nodules, and astrocytomas, are common in patients with TSC, including those with TSC-LAM, but these abnormalities are not found in women with S-LAM. Moss and associates[166] reported that women with S-LAM and TSC-LAM may have an increased incidence of meningioma, but the significance of that finding has been challenged.[167]

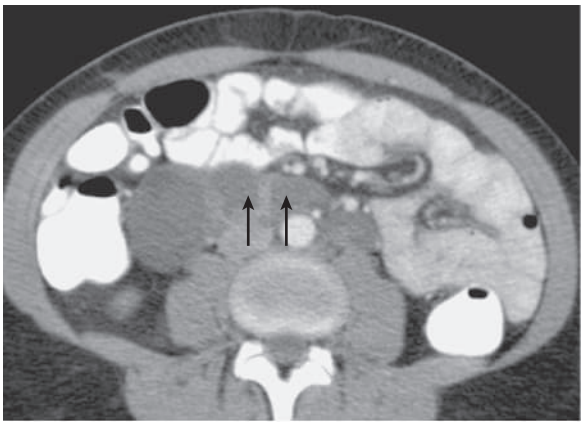

Fig. 97.7 Enlarged lymphatic structures. Abdominal computed tomography of cystic lymphangiomyomas *(arrows)* and retroperitoneal lymphadenopathy in a patient with lymphangioleiomyomatosis.

PULMONARY FUNCTION TESTING

Pulmonary function tests (PFTs) in patients with LAM may be normal or may reveal obstructive, restrictive, or mixed patterns, with obstructive physiology the most common abnormality. Quality-controlled lung function data were collected prospectively by the NHLBI Registry, a 5-year study of patients with LAM in centers around the United States.[11] Spirometry revealed obstructive changes in approximately 57% of patients and normal results in 34%. Restriction, defined as a total lung capacity less than the lower limit of normal, was seen in 11%. Hyperinflation was unusual, present in approximately 6%. The average residual volume was 125% of predicted when measured by plethysmography, but it was only 103% of predicted determined with gas dilution methods, a finding suggesting significant air trapping in noncommunicating air spaces.[11] Approximately 25% of patients with obstructive physiology may demonstrate bronchodilator responsiveness.[13] The obstructive physiologic defect in LAM is primarily attributable to airflow obstruction and, to a lesser degree, to a modest increase in lung compliance.[168]

The earliest and the most common finding on initial PFTs in various case series was abnormal gas transfer, as assessed by the *diffusing capacity for carbon monoxide* ($D_{L_{CO}}$), described in 82–97% of patients.[6,8,9,15] It is not unusual for $D_{L_{CO}}$ to be reduced out of proportion to *forced expiratory volume in 1 second* (FEV_1).[13]

Crausman and colleagues[169] studied the mechanism of exercise limitation in 16 patients with LAM. These investigators concluded that poor exercise performance was primarily the result of airflow obstruction and increased dead-space ventilation caused by pulmonary vascular disease or extensive cystic change. Cardiopulmonary exercise testing in a much larger cohort of patients with LAM revealed a reduced *maximal oxygen consumption* ($\dot{V}O_{2max}$) and anaerobic threshold in 217 patients.[170] Exercise-induced hypoxemia was found even in patients who did not have resting abnormalities in FEV_1 and $D_{L_{CO}}$. In most patients, exercise was thought to be limited by abnormalities in ventilation caused by airflow obstruction and increased dead-space ventilation.

Disease progression is usually accompanied by a progressive obstructive ventilatory defect, and decline in FEV_1 is the most commonly used parameter to monitor disease progression. Although resting pulmonary hypertension appears to be unusual in LAM, pulmonary arterial pressure often rises with low levels of exercise, related in part to hypoxemia.[171] Zafar and colleagues[172] reported an increase in intraparenchymal shunts in dyspneic patients with LAM that may contribute to resting and exercise hypoxemia.

Taveira-DaSilva and coworkers[13] correlated PFTs with lung histologic features in 74 patients. These investigators reported that a positive bronchodilator response was associated with a predominantly solid pattern of LAM lesions, as opposed to a cystic pattern. They also found that the $D_{L_{CO}}$ correlated with the lung histology score, a quantification of the extent of involvement with cystic lesions and LAM cells. FEV_1 and $D_{L_{CO}}$ were the best predictors of $\dot{V}O_{2max}$.

PATHOLOGY

Grossly, LAM lungs are enlarged and diffusely cystic, with dilated air spaces ranging from mild distention of alveolar spaces to bullous lesions of several centimeters in diameter (Fig. 97.8).[7,173] Microscopic examination of the lung reveals foci of smooth muscle cell infiltration of the lung parenchyma, airways, lymphatics, and blood vessels associated with areas of thin-walled cystic change. LAM lesions often contain an abundance of lymphatic channels, forming an anastomosing meshwork of slitlike spaces lined by endothelial cells. LAM cells generally expand interstitial spaces without violating tissue planes, but they have been observed to invade the airways, the pulmonary artery, the diaphragm, aorta, and retroperitoneal fat, to destroy bronchial cartilage and arteriolar walls, and to occlude the lumen of pulmonary arterioles.[7,174,175]

The two major cell morphologic types in the LAM lesion are cuboidal epithelioid cells and small spindle-shaped cells. The cuboidal cells within LAM lesions react with a monoclonal antibody called HMB-45, developed against the premelanosomal protein gp100, an enzyme in the melanogenesis pathway.[176] This immunohistochemical marker is very useful diagnostically because other smooth muscle–predominant lesions in the lung do not react with the antibody.[177] The spindle-shaped cells of the LAM lesion are more frequently proliferating cell nuclear antigen-positive than the cuboidal cells, a finding consistent with a proliferative phenotype.[176] Compared with cigar-shaped normal smooth muscle cells, spindle-shaped LAM cells contain less abundant cytoplasm and are less eosinophilic. In addition to staining for the typical smooth muscle markers such as actin, vimentin, and desmin, LAM lesions also express estrogen and progesterone receptors (Fig. 97.9).[178-180]

LAM lesions express lymphatic markers LYVE-1, PROX1, podoplanin, and VEGFR3.[181] The smooth muscle–like cells of AMLs are morphologically and immunohistochemically similar to LAM cells, with reactivity to antibodies directed against HMB-45 as well as against estrogen and progesterone receptors.[182,183] Unlike the dilated air spaces in emphysema, the cystic spaces found in LAM may be partially lined with hyperplastic type 2 cells in a discontinuous manner.[184]

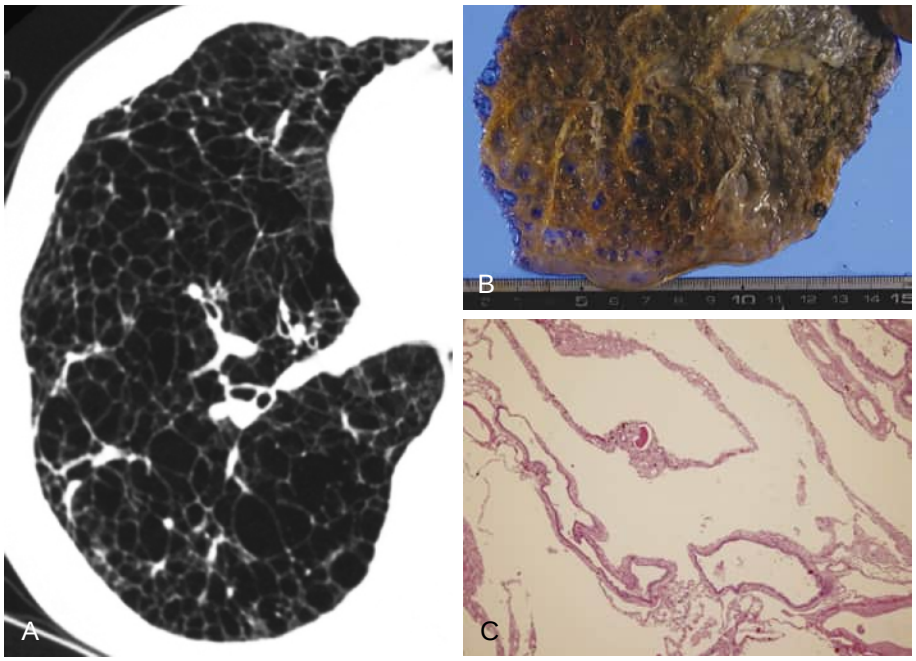

Fig. 97.8 Pathologic appearance of lymphangioleiomyomatosis. (A) High-resolution computed tomography and (B) pathologic gross specimen of the autopsied lung of a 57-year-old woman with sporadic lymphangioleiomyomatosis. (C) Microscopy with low magnification. (Hematoxylin and eosin stain; ×10 original magnification.) Extensive cystic changes are evident in the terminal stages of lymphangioleiomyomatosis. (Courtesy Dr. Masanori Kitaichi, National Hospital Organization, Kinki-Chuo Chest Medical Center, Osaka, Japan.)

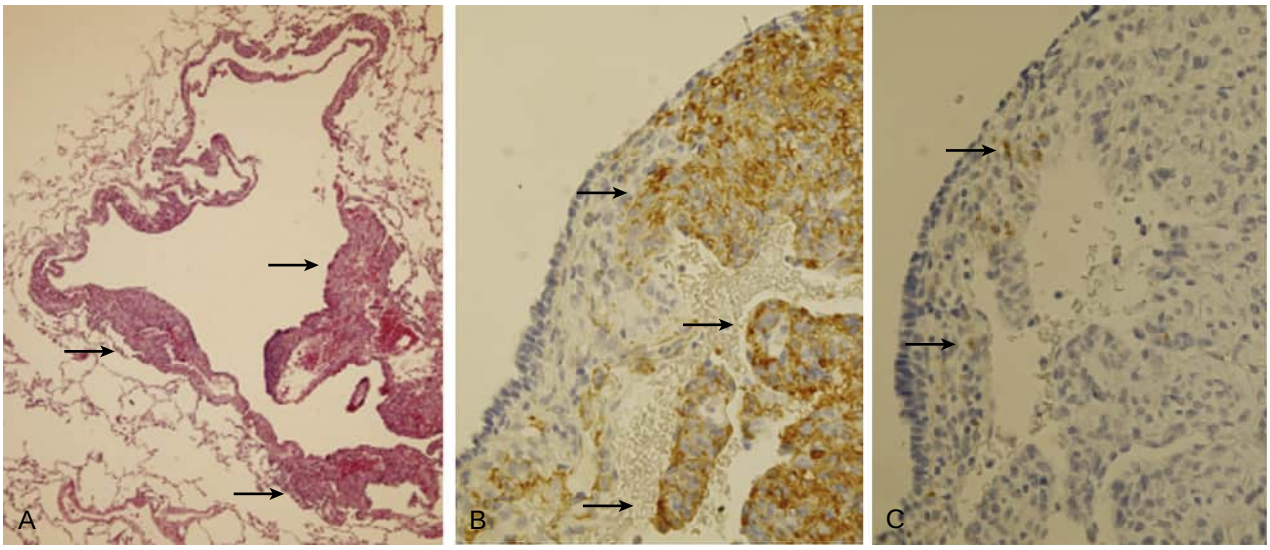

Fig. 97.9 Histopathology of a lung specimen from a 32-year-old woman with sporadic lymphangioleiomyomatosis. (A) Smooth muscle cell proliferation *(arrows),* cystic change, and distorted pulmonary architecture characteristic of lymphangioleiomyomatosis. (Hematoxylin and eosin stain; ×10 original magnification.) (B) Lymphangioleiomyomatosis nodule *(arrows).* (Immunostained with α-smooth muscle actin; ×40 original magnification.) (C) Scattered positive lymphangioleiomyomatosis cells *(arrows).* (Immunostained with HMB-45; ×40 original magnification.) (Courtesy Dr. Masanori Kitaichi, National Hospital Organization, Kinki-Chuo Chest Medical Center, Osaka, Japan.)

DIAGNOSIS

The diagnosis of LAM usually follows CT scanning of the chest showing characteristic cystic change (Table 97.2). The differential diagnosis of cystic change on CT scan is broad (Table 97.3 and eFigs. 97.10 to 97.14), and critical review of the radiologic features is central to achieving the correct diagnosis.[1,185,186]

Besides LAM, the most common cystic lung diseases encountered in clinical practice include atypical emphysema, Birt-Hogg-Dubé syndrome (see Fig. 97.3C and eFig. 97.14), pulmonary Langerhans cell histiocytosis, and lymphoid interstitial pneumonia or follicular bronchiolitis typically secondary to underlying Sjögren syndrome or systemic lupus erythematosus. In rare circumstances, LAM and Sjögren syndrome may coexist in the same patient.[26] Typical demographic, clinical, laboratory, radiologic, and pathologic findings of these disorders are presented in Table 97.4.

Typical diffuse, thin-walled cystic change on HRCT is a prerequisite for the diagnosis of pulmonary LAM, but it is not sufficient to establish a definitive diagnosis.[142] Instead, an algorithmic, "least invasive" approach is advised (Fig. 97.10),[142] beginning with a detailed history and physical examination to determine whether TSC is present or absent. Pulmonary cystic change in a nonsmoking woman with TSC that is consistent with LAM does not usually

Table 97.2 Summary of the Joint American Thoracic Society and Japanese Respiratory Society Lymphangioleiomyomatosis Clinical Practice Guidelines

DIAGNOSIS
■ High-resolution chest CT findings should not be used in isolation to establish a confirmed diagnosis of LAM.
■ Serum VEGF-D is a highly specific diagnostic biomarker for LAM, which can obviate the need for more invasive diagnostic procedures.
■ Transbronchial lung biopsy has a >50% diagnostic yield with a reasonable safety profile, and it should be considered before performing surgical lung biopsy.
PHARMACOLOGIC TREATMENT
■ Hormonal agents should not be routinely used to treat LAM.
■ Doxycycline should not be routinely used to treat LAM.
■ Sirolimus is a safe and effective treatment for LAM and should be the first-line treatment for patients with abnormal lung function (FEV_1<70%), symptomatic chylous effusions, rapidly declining lung function (FEV_1 decline rates >90 mL/yr), or substantial disease burden (abnormal D_{LCO}, significant air trapping, resting or exertional hypoxemia).
PLEURAL DISEASE MANAGEMENT
■ Patients with LAM are at a high risk of developing recurrent spontaneous pneumothoraces, and pleurodesis should be offered following the first episode of spontaneous pneumothorax.
■ Prior pleurodesis is not a contraindication to future lung transplantation.

CT, computed tomography; D_{LCO}, diffusing capacity of the lung for carbon monoxide; FEV_1, forced expiratory volume in 1 second; LAM, lymphangioleiomyomatosis; VEGF-D, vascular endothelial growth factor-D.

require biopsy for a clinically confident diagnosis, although some cases of non-LAM cystic disease have been reported in patients with TSC.[25,27]

In the absence of TSC, careful review of the imaging and confirmatory procedures (e.g., thoracentesis to document chylothorax) should be performed to determine whether renal AMLs, chylous fluid collections, lymphadenopathy, or lymphangioleiomyomas are present; any one of these findings can establish the diagnosis in the setting of typical cystic change on HRCT. In the absence of these clinical features, serum VEGF-D levels higher than 800 pg/mL found in approximately 60–70% of the patients with LAM are almost 100% specific for the diagnosis of LAM, thus obviating the need for further invasive testing.[91-93]

Although in most patients (approximately 75–80%) a clinically confident diagnosis of LAM can be made by noninvasive means, the diagnosis is most definitively established by lung biopsy. HMB-45 staining is highly specific for LAM and can be used to differentiate LAM from other causes of smooth muscle proliferation in the lung, including idiopathic pulmonary fibrosis, benign metastasizing leiomyoma, and leiomyosarcoma. Bronchoscopic diagnosis, using transbronchial biopsies with appropriate immunohistochemical staining and expert interpretation, was shown to be safe in small series with a diagnostic yield of 50–60%, and it is recommended before performing surgical lung biopsy.[8,142,187-191] Transbronchial cryobiopsy is an emerging technique for establishing bronchoscopic diagnoses of diffuse parenchymal lung diseases, and it has been successfully used to diagnose LAM in isolated cases.[192-194] Although the diagnostic

Table 97.3 Classification of Diffuse Cystic Lung Diseases

NEOPLASTIC
■ Lymphangioleiomyomatosis, sporadic as well as associated with tuberous sclerosis
■ Pulmonary Langerhans cell histiocytosis, and non–Langerhans cell histiocytoses including Erdheim-Chester disease
■ Other primary and metastatic neoplasms (e.g., sarcomas, adenocarcinomas, pleuropulmonary blastoma) (see eFigs. 97.11, 97.12, and 97.13)
GENETIC, DEVELOPMENTAL, OR CONGENITAL
■ Birt-Hogg-Dubé syndrome (see eFig 97.14)
■ Proteus syndrome, neurofibromatosis, Ehlers-Danlos syndrome
■ Congenital pulmonary airway malformation, bronchopulmonary dysplasia, and others
ASSOCIATED WITH LYMPHOPROLIFERATIVE DISORDERS
■ Lymphoid interstitial pneumonia
■ Follicular bronchiolitis
■ Amyloidosis
■ Light chain deposition disease
INFECTIOUS
■ *Pneumocystis jiroveci* pneumonia
■ Staphylococcal pneumonia
■ Recurrent respiratory papillomatosis
■ Endemic fungal diseases especially coccidioidomycosis
■ Paragonimiasis
■ Tuberculous and other nontuberculous mycobacterial disease
ASSOCIATED WITH INTERSTITIAL LUNG DISEASES
■ Hypersensitivity pneumonitis (see eFig 97.10)
■ Desquamative interstitial pneumonia
■ Follicular bronchiolitis/lymphoid interstitial pneumonia associated with connective tissue disorders such as Sjögren syndrome
SMOKING RELATED
■ Pulmonary Langerhans cell histiocytosis
■ Desquamative interstitial pneumonia
■ Respiratory bronchiolitis
OTHER AND MISCELLANEOUS
■ Posttraumatic pseudocysts
■ Fire-eater's lung
■ Hyper-IgE syndrome
CYST MIMICS
■ Emphysema
■ $Alpha_1$-antitrypsin deficiency
■ Bronchiectasis
■ Honeycombing seen in late-stage scarring interstitial lung diseases

Certain diseases have overlapping features and can be classified in more than one category. Pulmonary Langerhans cell histiocytosis is classified both as a neoplasm and a smoking-related cystic lung disease. Similarly, desquamative interstitial pneumonia is classified under the category of interstitial lung disease, as well as a smoking-related cystic lung disease. Although classified as a lymphoproliferative disorder, light chain deposition disease can also be considered under the neoplastic category.

IgE, immunoglobulin E.

Modified from Gupta N, Vassallo R, Wikenheiser-Brokamp KA, McCormack FX. Diffuse cystic lung disease. Part I. *Am J Respir Crit Care Med*. 2015;191:1354-1366.

Table 97.4 Summary of Demographic, Clinical, Laboratory, Radiologic, and Pathologic Characteristics of the Major Cystic Lung Diseases

	LAM	BHD	PLCH	LIP/FB
Personal history	Pneumothorax, angiomyolipomas, and cortical tubers, seizures, skin lesions if TSC	Pneumothorax, skin lesions, renal tumors	Pneumothorax, smoking	HIV, autoimmune diseases, sicca symptoms, Raynaud phenomenon
Family history	TSC	Pneumothoraces, skin lesions, renal cancers	Not relevant	Not relevant
Sex predilection	Women >> men	Women = men	Women = men	Women > men
Extrapulmonary manifestations and other associations	Renal angiomyolipomas, chylous ascites, TSC manifestations	Renal tumors, skin fibrofolliculomas	Diabetes insipidus, cutaneous and osteolytic bone lesions	SS and other CTDs, HIV, EBV, CVID
Laboratory testing	Elevated serum VEGF-D	Genetic testing for *FLCN* mutations	Serum and urine studies for diabetes insipidus	ANA, SS-A, SS-B, RF, polyclonal dysproteinemia
Typical CT chest findings	Round, thin-walled cysts, distributed uniformly across all lung fields	Round-lentiform thin-walled cysts, predominantly located in the basilar, subpleural areas or abutting the pulmonary vasculature	Both thin-walled cysts and thick-walled cavities and nodules; cysts often have bizarre shapes; findings more prominent in the upper lobes with characteristic costophrenic angle sparing	Cysts of variable size, distributed uniformly across all lung fields with slight lower lobe predominance; cysts often have internal septations or eccentric vessels; may have associated ground-glass attenuation or nodules in the adjacent parenchyma
Diagnostic yield of bronchoscopy (BAL, TBB)	>50%	0	30–50%	Low yield
Consider surgical lung biopsy	Yes	No	Yes	Yes
Pathologic findings	Infiltration by HMB-45–positive LAM cells with smooth muscle phenotype	Intraparenchymal and subpleural cysts abutting interlobular septa and lacking abnormal cell proliferations or significant fibroinflammatory component	S100, CD1a-positive Langerhans cells with intracellular Birbeck granules by electron microscopy; stellate fibrotic scars in late stages	LIP: Diffuse interstitial polyclonal lymphocytic infiltrate FB: Peribronchiolar polyclonal follicular lymphoid hyperplasia with germinal centers
Genetic testing	Germline TSC mutations in TSC-LAM but not S-LAM, usually not clinically indicated	Germline *FLCN* gene mutation	Lesional MAP kinase pathway mutations such as BRAF, NRAS, MAP2K1	No
Inheritance	Autosomal dominant or sporadic	Autosomal dominant	Not inheritable	Not inheritable
Treatment	Sirolimus	None available	Smoking cessation, immunosuppression, cladribine, MEK inhibitors	Corticosteroids and other immunosuppressive agents

ANA, antinuclear antibody; BAL, bronchoalveolar lavage; BHD, Birt-Hogg-Dubé syndrome; CT, computed tomography; CTD, connective tissue disorders; CVID, common variable immunodeficiency; EBV, Epstein-Barr virus; FB, follicular bronchiolitis; HIV, human immunodeficiency virus; LAM, lymphangioleiomyomatosis; LIP, lymphoid interstitial pneumonia; MAP, mitogen-activated protein; MEK, MAP/ER kinase; PLCH, pulmonary Langerhans cell histiocytosis; RF, rheumatoid factor; SS, Sjögren syndrome; SS-A and SS-B, Sjögren syndrome antibodies A and B; TBB, transbronchial biopsy; TSC, tuberous sclerosis complex; VEGF-D, vascular endothelial growth factor-D.

Modified from Gupta N, Vassallo R, Wikenheiser-Brokamp K, McCormack FX. Diffuse cystic lung diseases: part II. *Am J Respir Crit Care Med*. 2015;192:17-29.

yield of transbronchial lung cryobiopsy for LAM should be equivalent or superior to that of traditional transbronchial forceps lung biopsy, the safety of this technique with regard to the risk of pneumothorax and bleeding needs to be more thoroughly investigated before widespread implementation. Video-assisted thoracoscopic lung biopsy remains the gold standard for making the diagnosis of LAM.

Criteria for establishing a confirmed diagnosis of LAM and a proposed diagnostic algorithm are presented in Table 97.5 and Figure 97.10, respectively. Clarity regarding the diagnosis of LAM facilitates discussions on life planning, pregnancy, birth control, pneumothorax management, and candidacy for trials, and it is increasingly important in the era of therapies that are effective but also prone to side effects.

MANAGEMENT

PHARMACOLOGIC TREATMENT

Hormonal Agents

The remarkable sex restriction in LAM, although incompletely explained, provided the rationale for the empirical antiestrogen strategies that had dominated the approach

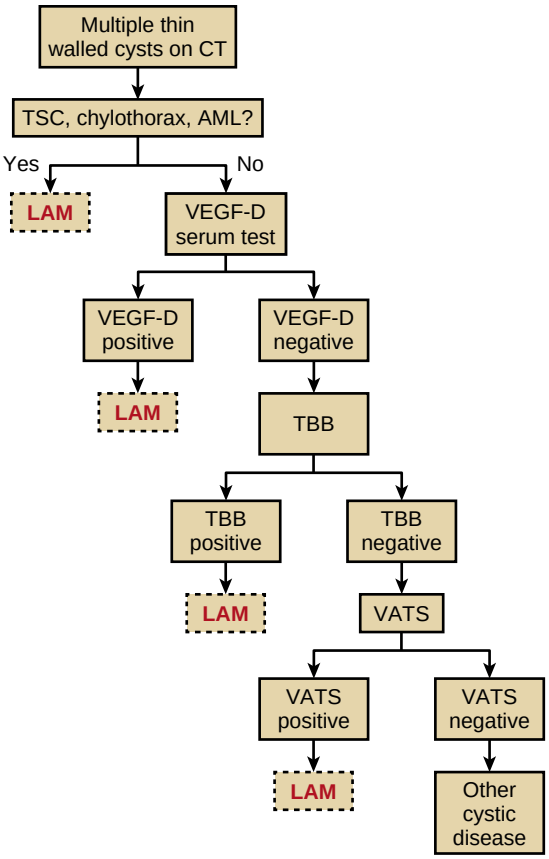

Fig. 97.10 Proposed diagnostic algorithm for lymphangioleiomyomatosis. *Lymphangioleiomyomatosis* (LAM) should be considered in the differential diagnosis of thin-walled multicystic lung disease. In a patient with typical *computed tomography* (CT) changes, a confident clinical diagnosis of lymphangioleiomyomatosis can be made if *tuberous sclerosis complex* (TSC), chylothorax, lymphangiomyoma, or *angiomyolipoma* (AML) is present. For patients without these features, a serum *vascular endothelial growth factor-D* (VEGF-D) level greater than 800 pg/mL is also diagnostic for lymphangioleiomyomatosis. If VEGF-D test results are negative, *transbronchial biopsy* (TBB), cytologic examination of pleural fluid, or thin needle biopsy of abdominal or thoracic masses can be useful for obtaining a pathologic diagnosis without surgery. Biopsy by means of *video-assisted thoracoscopic surgery* (VATS) can be used if the aforementioned approaches are uninformative, and it will distinguish lymphangioleiomyomatosis from other mimics including emphysema, Langerhans cell histiocytosis, and lymphocytic interstitial pneumonitis or follicular bronchiolitis.

to management of LAM for several decades. The results had been generally disappointing and, because proper trials with hormonal therapies have not been conducted, there remain no proven therapies for LAM based on antagonism of estrogen action. Bilateral oophorectomy has not been demonstrated to slow the rate of decline in lung function in LAM.[6,8,9]

Enthusiasm for the use of progesterone, which became the standard of care following a single positive outcome published in a case report in 1987,[180] has similarly waned over time. In a retrospective study of 275 patients, Taveira-DaSilva and associates[139] found that progesterone treatment had no impact on the decline in FEV_1 and was associated with an accelerated rate of decline in D_{LCO} compared with that in untreated patients. This finding was possibly explained by the statistical limitation "confounding by indication"—that is, patients taking progesterone were likely prescribed progesterone therapy because the disease was progressing more rapidly at enrollment.

Table 97.5 Criteria for Establishing a Confirmed Diagnosis of Lymphangioleiomyomatosis

1. Definite diagnosis of LAM can be established if a patient with compatible clinical history and characteristic HRCT of the chest has one or more of the following features:
   - Presence of TSC
   - Renal angiomyolipoma(s)*
   - Elevated serum VEGF-D >800 pg/mL
   - Chylous effusion (pleural or ascites) confirmed by tap and biochemical analysis of the fluid
   - Lymphangioleiomyomas (lymphangiomyomas)*
2. Demonstration of LAM cells or LAM cell clusters on cytologic examination of effusions or lymph nodes
3. Histopathologic confirmation of LAM by lung biopsy or biopsy of retroperitoneal or pelvic masses

*Angiomyolipoma may be diagnosed on the basis of radiographic appearance of characteristic fat-containing lesions either on computed tomography scan or magnetic resonance imaging. Contrast is not typically required unless the vascular characteristics of the tumor need to be analyzed, such as for evaluation of the potential for hemorrhage or planning for embolization. Similarly, lymphangioleiomyomas can typically be diagnosed on the basis of their characteristic radiographic appearance.

HRCT, high-resolution computed tomography; LAM, lymphangioleiomyoma; TSC, tuberous sclerosis complex; VEGF-D, vascular endothelial growth factor-D.

Modified from Gupta N, Finlay GA, Kotloff RM, et al. Lymphangioleiomyomatosis diagnosis and management: official American Thoracic Society and Japanese Respiratory Society clinical practice guidelines: high-resolution chest CT, transbronchial lung biopsy, and pleural disease management. *Am J Respir Crit Care Med*. 2017;196:1337-1348.

In another study, the rate of decline in FEV_1 and D_{LCO} was no different in patients treated with the gonadotropin-releasing hormone agonist triptorelin for 3 years than in a well-characterized cohort of historical control subjects.[195] Other case reports and case series of gonadotropin-releasing hormone agonist treatment have yielded conflicting results.[196-199]

The only randomized controlled trial of hormonal therapy in LAM, a comparison of an aromatase inhibitor versus placebo in postmenopausal women with LAM, demonstrated the safety of this approach but failed to meet the enrollment target needed to assess efficacy.[200] Thus, although there is a strong rationale for the use of hormonal therapy (e.g., aromatase inhibitors, gonadotropin-releasing hormone agonists) for this steroid-responsive neoplasm, this approach is not currently recommended,[201] pending the successful execution of pivotal trials.

Doxycycline

Doxycycline is a tetracycline antibiotic that inhibits the production and activity of several MMPs.[202] On the basis of data demonstrating expression of MMPs in LAM,[47,119,122] and a single case report suggesting dramatic improvement in lung function following administration of doxycycline,[203] there was considerable interest in the potential therapeutic role of doxycycline in patients with LAM. Two uncontrolled studies and an underpowered double-blind clinical trial showed no efficacy in the rate of decline in FEV_1, D_{LCO}, walk distance, or quality of life scores.[204-208] Current guidelines recommend against the routine use of doxycycline for treatment of LAM.[201]

Sirolimus

The discovery of the importance of the mTOR pathway in LAM and preclinical studies in TSC animal models formed the basis for phase I/II trials of sirolimus in patients with tuberous sclerosis and LAM (*Cincinnati Angiomyolipoma Sirolimus Trial* [CAST]; NCT00457964).[209] In CAST, an open-label study, 25 patients with AMLs, including 6 patients with S-LAM, 12 with TSC-LAM, and 7 with TSC alone, were treated for 1 year with sirolimus and followed with serial magnetic resonance imaging studies of the kidneys, chest CT scans, and PFTs. Of the patients still enrolled at 1 year, AML volume shrank by an average of 47% (n = 20). A remarkable and unexpected finding in this study was the improvement in lung function: in 11 of the patients with LAM, the FEV_1 and *forced vital capacity* (FVC) increased by 118 mL and 390 mL, respectively. The residual volume fell by 440 mL, and cyst volume percent, a measurement of the fraction of the pulmonary parenchyma occupied by cysts, tended to decline on therapy.[150] Parameters that did not change included total lung capacity, 6-minute walk distance, and D_{LCO}. There were a number of *adverse events* (AEs) while patients were taking the study agent, including mouth ulcers, cholesterol elevations, and hospitalizations for pneumonia, diarrhea, cellulitis, pyelonephritis, palpitations, and mucositis.[209]

In the second year of the trial, patients were observed off the study agent at 6-month intervals. At the 2-year point, the average AML volume had increased again to 86% of baseline, although, in 25% of patients, tumor volumes remained lower than 70% of baseline. FEV_1 and FVC declined in the observation year but remained 62 mL and 364 mL above baseline, respectively, and residual volume remained 333 mL below baseline, indicative of durable reduction in gas trapping. Similar results were seen in subsequent trials.[210,211]

On the basis of the unexpected lung function improvement in the 11 patients with LAM, and a higher than expected rate of AEs, a pivotal trial was designed to determine the risks and benefits of sirolimus in patients with LAM. The MILES trial was a randomized, double-blind, controlled trial of sirolimus that enrolled 89 women with LAM and abnormal lung function (FEV_1 <70% predicted).[19] During the 1-year treatment period, lung function (FEV_1) stabilized on sirolimus while declining by about 11% in the placebo group. Sirolimus also improved some measures of quality of life and functional performance. In the observation year off therapy, FEV_1 decline resumed in the sirolimus group and paralleled that in the placebo group. At baseline, serum VEGF-D was elevated in both groups. VEGF-D remained stable in the placebo group throughout the study, but it decreased by 50% during the first year on sirolimus. When sirolimus was withdrawn, VEGF-D increased toward baseline again, showing that the effect was temporary, consistent with the known cytostatic action of the drug.[94] The sirolimus-induced decreases in VEGF-D are intriguing in light of the strong lymphangiogenic phenotype observed in LAM and the striking effect of sirolimus on improving chylous effusions and decreasing the volume of lymphangioleiomyomas.[212-214] AEs were common during the treatment period, including acne, mucositis, nausea, diarrhea, hypercholesterolemia, and lower extremity edema, and they were more prevalent in the sirolimus group, especially during the first 3 months on the drug.[95] There was no increase in risk of infection, however, and the frequency of serious AEs was balanced between the groups.[19]

The beneficial effect of sirolimus and another mTOR inhibitor, everolimus, on lung function in LAM has subsequently been replicated in multiple other reports.[215-218] Collectively, these data affirm that treatment with sirolimus provides effective suppression of disease activity and stabilization of lung function in patients with LAM. However, durable disease control requires long-term, perhaps even lifelong, treatment with sirolimus.[217,218] The long-term safety and efficacy of sirolimus in LAM are the subjects of an ongoing, prospective observational study titled *Multicenter International Durability and Safety of Sirolimus in LAM* (MIDAS; NCT02432560). Sirolimus as a treatment of LAM has now been approved by the United States *Food and Drug Administration* (FDA), as well as by regulatory agencies in 39 other countries to date, including Brazil, Japan, Russia, South Korea, Uruguay, and all members of the European Union.

On the basis of the results of the MILES trial,[19] and several other open-label studies,[213,219] the joint *American Thoracic Society* and *Japanese Respiratory Society* (ATS/JRS) guidelines recommend initiation of sirolimus to treat LAM in the following circumstances: FEV_1 lower than 70% predicted, symptomatic chylous effusions, rapidly declining lung function (FEV_1 decline rates ≥ 90 mL/yr), or other parameters that could suggest substantial disease burden, such as abnormal DL_{CO}, air trapping, and exertional or resting hypoxemia[201] (eAppendix 97.1).

The sirolimus dose used in the MILES trial was 2 mg/day, titrated to maintain blood trough levels between 5 and 15 ng/mL, resulting in a mean sirolimus trough level of 7.2 ng/mL.[95] Subsequent open-label data from Japan suggest that lower-dose sirolimus (1 mg/day, blood trough ~2 ng/mL) has similar efficacy.[212] Many physicians around the world have since adopted this low-dose approach.

Serial postbronchodilator spirometry should be obtained at frequent intervals after initiation of sirolimus (every 3 to 4 months for the first 12 months) to assess treatment efficacy and ensure stability of FEV_1. Safety laboratory tests such as trough sirolimus levels, complete blood count, liver and renal function tests, urinalysis, and lipid panel should be monitored periodically, perhaps every month for the first 3 months and every 3 months thereafter.[220] Early administration of long-term, low-dose suppression with sirolimus is an appealing strategy to prevent progression of LAM, and a randomized, placebo-controlled study to determine the safety and efficacy of this approach is ongoing (*Multicenter Interventional LAM Early Disease* [MILED] trial; NCT03150914).

Although sirolimus has been successfully used to treat recurrent LAM after lung transplantation,[221] its use in the immediate postoperative period has been associated with bronchial anastomotic dehiscence,[222] and the FDA has issued a black box warning against sirolimus as first-line immunosuppression postoperatively. Some transplantation centers therefore recommend against the use of sirolimus in listed LAM patients; a practice that has resulted in precipitous lung function decline in some women.[223] On the basis of these experiences, and a review of the evidence that

indicates that most episodes of dehiscence take place more than 6 weeks after surgery, long after the drug would have washed out if stopped on the day of surgery, many centers now allow sirolimus use in patients on the waiting list.[224] In some cases, the therapeutic agent is changed from sirolimus to everolimus, to take advantage of the shorter half-life (11 hours vs. 60 hours) and the faster washout.[225,226]

High serum VEGF-D levels are associated with baseline markers of disease severity, including need for oxygen, bronchodilator responsiveness, and reductions in FVC and D_{LCO}. Higher baseline VEGF-D levels also predict disease progression and treatment response.[94] In the MILES trial, patients with serum VEGF-D levels higher than 600 pg/mL tended to have a faster rate of decline in FEV_1 in the placebo group and better treatment response in the sirolimus group.[94,95] On the basis of these observations, with all other things being equal, a high baseline VEGF-D may tip the balance toward treatment in a patient being considered for sirolimus therapy. Post hoc analysis of the MILES data has shown that sirolimus had a beneficial therapeutic effect regardless of underlying race (Asian vs. white), menopausal status (premenopausal vs. postmenopausal), type of LAM (TSC-LAM vs. S-LAM), bronchodilator responsiveness, or baseline FEV_1.[95]

OTHER THERAPEUTIC CONSIDERATIONS

A trial of bronchodilators should be considered in patients with LAM because up to 17–25% of patients with LAM have bronchodilator-responsive airflow obstruction.[11,15] Oxygen should be administered to maintain oxyhemoglobin saturations at 90% or higher with rest, exercise, and sleep.

All LAM patients should be vaccinated against influenza and against pneumococcus, including both the 13-valent and 23-valent preparations. Patients taking or considering mTOR inhibitors should receive the recombinant shingles vaccine. Live vaccines should be avoided in patients taking mTOR inhibitors (eAppendix 97.2).

Bone densitometry should be considered in all patients who are immobilized and/or receiving antiestrogen therapies, and appropriate therapy should be instituted for osteoporotic patients. Proper attention should be paid to cardiovascular health following natural or induced menopause. Pulmonary rehabilitation was shown to improve exercise capacity, dyspnea, and quality of life in women with LAM in a single-center, parallel-group study in Brazil.[227]

The LAM Foundation, an active patient advocacy organization for LAM, is a useful resource for both patient and provider education (www.thelamfoundation.org). The LAM Foundation also maintains 64 worldwide clinics, including 36 sites within the United States, as a referral network for expert care and access to research studies.

GENERAL RECOMMENDATIONS

SCREENING

Sporadic Lymphangioleiomyomatosis

Spontaneous pneumothorax is the second most common mode of presentation in LAM after dyspnea on exertion. A spontaneous pneumothorax in a woman should prompt consideration of LAM because primary spontaneous pneumothorax is most commonly seen in men who smoke cigarettes. Obtaining a chest CT scan in women presenting with a spontaneous pneumothorax can facilitate a timely diagnosis of LAM and was shown to be cost effective in two separate decision analysis models.[228,229] We recommend HRCT screening in women with spontaneous pneumothorax.

Tuberous Sclerosis–Associated Lymphangioleiomyomatosis

HRCT screening of women with TSC identifies cystic changes in approximately 20% of subjects younger than 30 years of age and in 80% of subjects older than 40 years of age.[31] The Tuberous Sclerosis Alliance[230,231] and the European Respiratory Society[232] recommend a screening chest CT scan in women with TSC after the age of 18 years. For women without pulmonary symptoms, the chest CT scan should be repeated every 5 to 10 years.[231] Once cysts are detected, the pace of TSC-LAM progression should be determined by periodic chest CT screening testing (perhaps every 2 to 3 years, preferably with low–radiation dose algorithms) accompanied by annual PFTs (and in patients with moderate cyst profusion, the 6-minute walk test), at least until trends are established.[231] The percentage of women with TSC and cystic change on CT who become symptomatic because of LAM is generally thought to be small, probably less than 10%, but in a single-center analysis of a large TSC clinic, LAM was found to be the second leading cause of death in the overall clinic population and the leading cause of death in adult women with TSC. These data highlight the importance of vigilance in pulmonary screening and disease management in the TSC population.[32] Although cystic changes consistent with LAM are found in approximately 10% of adult men with TSC,[233,234] symptomatic LAM in men is very rare,[23] and routine screening is not recommended.

PREGNANCY

Patients should be advised that pregnancy has been reported to result in exacerbations of LAM in some cases.[8,235-238a] In a group of 69 patients with sporadic LAM, pulmonary symptoms began during pregnancy in 9 of the 46 patients (20%) with a history of pregnancy before or at the time of diagnosis.[8] In this same group, a marked exacerbation of previously diagnosed LAM was observed in two (14%) patients during pregnancy.[8] In a natural history study of 89 women with LAM in Japan, the frequency of pregnancy was higher in the patients who exhibited a progressive decline in FEV_1 as compared with the subgroup of patients who did not have such a decline.[133] Women in whom LAM is diagnosed during pregnancy have higher rates of pneumothorax, miscarriage, and premature birth.[239] However, risk associated with pregnancy in LAM has not been rigorously studied, and decisions regarding the advisability of pregnancy should be made on an individual basis.[240] Unfortunately, the more pressing question of whether pregnancy accelerates the decline in lung function in LAM may never be rigorously addressed because so few women with a known LAM diagnosis choose to become pregnant, and patients in whom LAM is diagnosed during pregnancy rarely have baseline PFTs available. One recent study addressed this question: in 16 women with LAM, lung function was measured before and after pregnancy. During the pregnancy, pneumothorax was frequent; during

and after the pregnancy, the decline in FEV_1 was also high. The authors conclude that women with LAM should be counseled about the risk of pneumothorax and loss of lung function with pregnancy.[238a] Sirolimus is an FDA pregnancy category C drug and, although there is some experience with use of the drug in pregnant transplant recipients (TransplantPregnancyRegistry.org) and at least one reported LAM patient,[241,242] the safety and efficacy of sirolimus for mother and child have not been well established for pregnant women with LAM.

AIR TRAVEL (see Chapter 106)

Whether patients with LAM are at increased risk for pneumothorax during air travel is controversial. Pollock-BarZiv and coworkers[243] found that 35% of patients with LAM had been advised by their physician to avoid air travel because of the theoretical risk for lung cyst rupture associated with atmospheric pressure changes during flight. In a survey of 276 patients who answered a LAM Foundation questionnaire, there were eight cases of radiographically documented pneumothorax associated with 454 flights. In five cases, however, symptoms that were consistent with pneumothorax may have been present before boarding. Other on-board symptoms and signs noted in 10–20% of flights included anxiety (22%), chest pain (12%), shortness of breath (14%), cyanosis (2%), and hemoptysis (0.4%). The conclusion from the study was that, although there were AEs during flight, air travel is well tolerated by most patients with LAM.

A study of 281 patients with LAM who had routine chest radiographs after traveling to the National Institutes of Health for semiannual study visits identified seven patients with acute pneumothorax. There was no difference in the incidence of pneumothorax in patients who traveled by ground versus air, however. These investigators concluded that pneumothorax with air travel was related to the high incidence of pneumothorax in the disease rather than the air travel itself.[244] Another survey-based study conducted in LAM patients based in Europe revealed 6 episodes of pneumothorax related to air travel from a total of 178 flights. In contrast to prior studies that focused on events in the immediate peritravel period, the European study included any pneumothorax detected within 30 days of air travel as "air travel related."[245]

In summary, the risk of air travel–related pneumothorax in women with LAM is approximately one episode per 100 flights. In advising patients with LAM about air travel, it is reasonable to consider several factors, including a history of frequent or recent pneumothoraces, and the overall extent of cardiopulmonary impairment. Patients with poor cardiopulmonary reserve may tolerate even small pneumothoraces poorly. It is prudent for patients with LAM to seek medical evaluation, including a chest radiograph, before boarding a plane if pleuritic chest pain or unexplained shortness of breath is present. Hypoxemia during flight presents other risks, and patients should consult with their physicians regarding recommendations for on-board oxygen use. In most cases, however, air travel in patients with LAM should not be routinely restricted.

PLEURAL DISEASE (see Chapters 110 and 111)

Pneumothoraces in patients with LAM tend to recur, especially after conservative management such as observation, simple aspiration, or tube thoracostomy (eAppendix 97.3). More than 65% of patients with LAM develop pneumothorax during the course of their illness, averaging 3.5 pneumothoraces per affected patient over a lifetime.[141] The incidence of pneumothorax in LAM has been estimated to be approximately 5% per year following the diagnosis of LAM, and 8% per year following the first onset of symptoms attributable to LAM, compared with an incidence of 0.006% for women in general.[245] Risk of pneumothorax appears to correlate with premenopausal status, age younger than 50 years, and larger size of cysts.[141,246,247]

The ATS/JRS LAM Guideline Committee recommended a pleural symphysis procedure with the first pneumothorax, given the greater than 70% chance of recurrence.[142] Chemical sclerosis, mechanical abrasion, talc poudrage, and pleurectomy have been effective in patients with LAM. However, for reasons that are not well explained, failure rates after pleurodesis are surprisingly high (~35%) compared with other diffuse lung diseases known to be associated with secondary pneumothorax.[141]

Total pleural covering (TPC) is a newer technique from Japan in which the entire visceral pleura is reinforced by sheets of bioabsorbable mesh. This procedure can be accomplished under video-assisted thoracoscopic surgery guidance and does not induce pleural symphysis. In a single-center retrospective analysis involving 43 LAM patients with a spontaneous pneumothorax, TPC reduced the pneumothorax recurrence rate to approximately 25% with an acceptable safety profile.[248] Lack of validation and operator experience with this technique limits its current worldwide applicability; nevertheless TPC holds promise as a minimally invasive way of reducing recurrent pneumothoraces in LAM without creating pleural adhesions, and it warrants future investigation. The role of sirolimus in preventing recurrent pneumothoraces is not clear, but a small case series from China suggested potential benefit.[249]

Chyle does not generally cause pleural inflammation or fibrosis, and small stable chylous effusions are generally well tolerated. Effusions large enough to cause shortness of breath require intervention. The ATS/JRS LAM guidelines recommend treatment with sirolimus as the first-line therapy for symptomatic chylous effusions (see eAppendix 97.3).[201] Although thoracentesis may be required for the relief of acute symptoms, sirolimus therapy has significantly reduced the need for tube thoracostomy and pleural symphysis procedures for control of chylous complications in LAM. It is important to realize that, with sirolimus therapy, complete resolution of chylous effusions and ascites can take up to 6 months.

LUNG TRANSPLANTATION (see Chapter 140)

The first reported lung transplant in a patient with LAM was a combined heart-lung transplant in 1984.[250] Since then, post–lung transplant experience and outcomes in LAM have been reported in various studies from around the world.[8,141,224,226,251-257] Although some estimates suggested that post–lung transplantation survival in LAM was similar to that in other lung diseases,[252,253,256] more recent analyses suggest that LAM patients may fare better.[224,226,258] Khawar and associates[258] analyzed outcomes in 134 LAM patients registered with the *United Network for Organ Sharing* (UNOS) in the United States who underwent lung transplantation

between January 2003 and June 2017. Most patients (109 of 134; 81%) underwent bilateral sequential lung transplantation. The median time spent on the transplant wait list was 257 days, which was reduced to 148 days after the introduction of the lung allocation score in 2005. The median post–lung transplant survival in LAM was 12 years, with 1-, 5-, and 10-year survival rates of 94%, 73%, and 55%, respectively. These survival rates exceed those in patients with other diseases who underwent lung transplantation in the same time frame ($P < 0.0001$).[258] Similar post-transplantation survival outcomes have been reported from a study evaluating 57 LAM patients who underwent lung transplantation in Japan, with 1-, 3-, and 5-year survival rates of 87%, 82%, and 74%, respectively.[226]

Several case reports of recurrence of LAM in the donor allograft have been published.[80-83] The risk of graft compromise from bronchiolitis obliterans and other forms of chronic rejection is much higher than from recurrent LAM, and the latter should not be a dominant factor when judging candidacy for lung transplantation. More than half of patients with LAM who have undergone lung transplantation have a prior history of unilateral or bilateral pleural fusion procedures and, although postoperative bleeding risk is increased, the operative mortality and long-term survival do not appear to be adversely affected.[141,252] According to the ATS/JRS LAM Guidelines and the International Society for Heart and Lung Transplantation Guidelines, a history of prior pleurodesis is not a contraindication to future lung transplantation.[142,259] As with other obstructive lung diseases, referral for lung transplantation should be considered when the FEV_1 falls to less than 30% of the predicted value. Some patients who fail to meet this criterion may qualify on the basis of other factors that profoundly affect quality of life, such as disabling dyspnea or problems maintaining oxygen saturation despite high levels of supplemental oxygen.

ANGIOMYOLIPOMAS

Renal AMLs may require embolization or cauterization for control of bleeding, a complication thought to be more common when the diameter of the tumor exceeds 3 to 4 cm.[260-262] However, the validity of size-based cutoffs to determine bleeding risk in AMLs has been questioned.[263] The extent of aneurysmal change and the rate of growth of AMLs may also influence bleeding risk.[262,264] Serial abdominal imaging should be performed to assess AML size at 6- to 12-month intervals, at least until trends in growth are established. Nephron-sparing partial resections may be considered for very large tumors.[265] Nephrectomy is sometimes required for tumors with intravascular extension or life-threatening hemorrhage, but it is rarely the approach of choice because most AMLs can be managed by less invasive means. The FDA has approved everolimus for the treatment of AMLs.[266] Guidelines for management of AMLs have been published by the Tuberous Sclerosis Alliance.[230,231]

DISEASE PROGRESSION

Progressive airflow obstruction develops in most patients with LAM. In a cohort of patients in the United Kingdom, 10 years after symptom onset, 55% of 77 patients were breathless when walking on flat ground, and 10% were housebound.[267] The average annual rates of decline in FEV_1 and D_{LCO} in 217 patients studied in the NHLBI LAM Registry were 89 ± 53 mL and 0.81 ± 0.20 mL/min/mm Hg, respectively.[12] In other series from Europe, the rate of decline in FEV_1 was considerably higher, estimated at approximately 100 to 120 mL/yr,[8,268,269] whereas the rate of decline in FEV_1 was estimated to be only approximately 50 mL/yr in a natural history analysis in Japan.[133] In the MILES trial, annual loss of FEV_1 in patients in the placebo group was 134 mL, or approximately 11% of their lung function.[19]

There appears to be a clear relationship between menopausal status and the rate of decline in lung function. For instance, the rate of FEV_1 decline was higher in premenopausal women in the NHLBI Registry cohort as compared with postmenopausal women (118 mL/yr vs. 74 mL/yr; $P = 0.003$).[12] Similarly, in the placebo cohort from the MILES trial, the rate of decline in premenopausal patients was fivefold higher than the rate in postmenopausal patients (200 mL/yr vs. 40 mL/yr; $P = 0.003$).[95] A positive bronchodilator response, which was associated with a lower FEV_1, was found to be a predictor of more rapid rate of decline in FEV_1 in some studies,[12,13] but not in the placebo cohort of the MILES trial.[95] Neither a history of pneumothorax nor the total number of pneumothoraces appears to be associated with a higher rate of decline in FEV_1.[12]

Although TSC-LAM is often considered a milder form of disease, after matching for baseline disease severity, the rate of decline in FEV_1 appears to be similar in patients with TSC-LAM as compared with S-LAM.[12,95,270] High baseline VEGF-D also correlates with faster disease progression and better treatment response[92,94,95]; these data indicate that in addition to its utility as a diagnostic tool, serum VEGF-D can be useful for making treatment decisions.

PROGNOSIS

Survival estimates vary widely, appear to be dependent on mode of presentation or ascertainment, and have generally trended upward over the past few decades, probably because of earlier recognition through more widespread use of CT scanning and screening of TSC populations. The data from early, large case series indicated that 38–78% of patients were alive at 8.5 years from the time of disease onset.[6,9] Urban and associates[8] reported a 91% probability of survival at 8.5 years, 79% at 10 years, and 71% at 15 years.

For Japanese patients who presented with pneumothorax as the sentinel event, Hayashida and colleagues[10] reported that 5-, 10-, and 15-year survival probabilities were 95%, 89%, and 89%, respectively, whereas for patients who presented with dyspnea, survival rates were only 85%, 60%, and 47%. Matsui and coworkers[271] found that the actuarial survival rate, based on time from lung biopsy to death or transplantation, was 85% and 71% after 5 and 10 years, respectively. These investigators also developed a lung histology scoring system based on semiquantitative analyses of smooth muscle cell infiltration and cystic change, which correlated with survival. Other negative prognostic indicators include reduced FEV_1/FVC, increased total lung capacity, and predominantly cystic, rather than nodular, histologic features.[9]

In a population-based cohort ascertained by surveying patients registered with the LAM Foundation, the median

survival was 29 years.[140] Gupta and colleagues[12] performed a longitudinal analysis of the NHLBI LAM Registry data set to determine long-term outcomes in patients with LAM. Of the 217 patients who enrolled in the study in the late 1990s, 69 had progressed to death or lung transplantation by the censure date of December 31, 2014. The median transplant-free survival was more than 20 years from the time of diagnosis, with actuarial 5-, 10-, 15-, and 20-year estimates of 94%, 85%, 75%, and 64%, respectively. Postmenopausal status and baseline disease severity as assessed by FEV_1 and D_{LCO}, were the most important determinants of future progression to death or transplantation.[12] These data apply primarily to the presirolimus era (before 2011), and it is not yet clear whether sirolimus will affect mortality or the need for lung transplantation.

Although no robust prognostic data are available for TSC-LAM, the survival of patients identified through screening is almost certainly more favorable than that of patients who present with dyspnea. Zak and associates[32] analyzed long-term outcomes in a large single-center TSC clinic and reported that TSC-LAM is the second leading cause of death overall in the overall TSC population and the leading cause of death among adult women with TSC. The average life expectancy of women with TSC-LAM was 63 years, which was 7.5 years less than women with TSC who did not have LAM.[32]

FUTURE CLINICAL TRIALS

The most tangible and immediate research priorities in LAM include refinement and optimization of the use of mTOR inhibitors by studying the long-term safety and efficacy of sirolimus in LAM (MIDAS; NCT02432560), determining whether early administration of low-dose sirolimus can prevent future disease progression in a prophylactic manner (MILED; NCT03150914), and developing dosing biomarkers that can help personalize mTOR inhibitor-based treatment strategies for individual LAM patients.

Progress in understanding the genetic and molecular basis of LAM has led to several potential candidate therapies beyond allosteric mTOR inhibitors that may be appropriate for single-agent or combination therapy–based testing in clinical trials (eFig. 97.15). Examples of next-generation clinical trials either underway or recently completed include the following: combined hydroxychloroquine and sirolimus (NCT01687179),[272] combined sirolimus and simvastatin (NCT02061397),[273] combined resveratrol and sirolimus (NCT03253913), celecoxib (NCT02484664), imatinib (NCT03131999), and nintedanib (NCT03062943). Other potential promising treatment strategies include phosphatidylinositol-3-kinase pathway inhibitors, Rheb and Rho inhibitors (e.g., farnesyltransferase inhibitors and statins), estrogen antagonists (e.g., gonadotropin-releasing hormone agonists), selective estrogen response modifiers, selective estrogen receptor down-regulators (e.g., fulvestrant [Faslodex]), prolactin axis inhibitors, purine and pyrimidine synthesis inhibitors, angiogenesis inhibitors (e.g., bevacizumab), and lymphangiogenesis inhibitors (e.g., anti–VEGF-D antibody, VEGFR3 antibody, pazopanib). Many agents in these categories have already been approved by the FDA or are in development for other indications.

Key Points

- Lymphangioleiomyomatosis is a progressive cystic lung disease that is most prevalent in women and most commonly manifests with dyspnea on exertion and/or pneumothorax and less commonly with chylothorax, hemoptysis, or incidentally discovered abdominal masses or pulmonary cysts.
- Lymphangioleiomyomatosis is a metastasizing neoplasm, arising from an unknown source, associated with infiltration of lung with benign-appearing smooth muscle–like cells and cystic parenchymal destruction.
- The diagnosis of lymphangioleiomyomatosis can be established on clinical grounds, using consensus guidelines in an algorithmic, least invasive, stepwise approach that comprises abdominal imaging for lymphangioleiomyomatosis-related masses, measurement of the diagnostic biomarker, serum vascular endothelial growth factor-D, transbronchial biopsy, cytologic evaluation of chylous fluid, thin needle aspirates from abdominal lesions, or, less commonly, surgical tissue confirmation.
- Lymphangioleiomyomatosis is associated with tuberous sclerosis complex mutations that activate mechanistic target of rapamycin and promote growth and lymphangiogenesis, whether the mutations are in the germline in the heritable genetic disease tuberous sclerosis complex or exclusively somatic (nongermline) mutations in the sporadic form of the disease.
- Sirolimus is an effective treatment for lymphangioleiomyomatosis that should be considered in patients with abnormal lung function, rapid decline in forced expiratory volume in 1 second or diffusing capacity of the lung for carbon monoxide, recurrence after lung transplantation, or symptomatic chylous complications.
- The clinical course of lymphangioleiomyomatosis is highly variable, but it is generally slowly progressive, with 10-year survival of approximately 80–90% and a median survival after the onset of symptoms approaching 30 years.

Key Readings

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Complete reference list available at ExpertConsult.com.

eAppendix 97.1

SIROLIMUS PRESCRIBING GUIDE

INITIATION

1. Obtain baseline laboratory tests: complete blood count, comprehensive metabolic profile, lipid profile, urinalysis.
2. Begin drug at 1 to 2 mg daily.

MAINTENANCE

1. Instruct patients to take the drug at the same time every day.
2. After 2 to 4 weeks of treatment, perform a serum trough level. Instruct patients to wait 24 hours (20 to 28 hours) after taking the medication (just before the next dose) before drawing a serum trough level.
3. Check sirolimus level, complete blood count, comprehensive metabolic profile, lipid profile, and urinalysis every month for the first 3 months, and if OK, extend repeat testing to every 3 months.
4. Inquire about other adverse effects such as acne, oral ulcers, or worsening of pulmonary symptoms (to evaluate for drug-induced pneumonitis) at every visit.
5. Encourage patients to have annual influenza vaccinations, recombinant shingles vaccine, as well as pneumococcal prophylaxis, including both *23-valent pneumococcal polysaccharide vaccine* (PPSV) and *13-valent pneumococcal conjugate vaccine* (PCV). Avoid live vaccines while taking sirolimus.
6. Hold drug for at least 1 to 2 weeks before and 1 to 2 weeks after a surgical procedure or injury.

OTHER USEFUL TIPS

1. **Dosing**: We typically begin with low-dose sirolimus (1 mg daily) for most patients, unless disease is rapidly progressive or in an advanced stage. In general, most patients respond well with stabilization of lung function with a trough around 5 ng/mL or less, and caregivers should strive to determine the lowest effective dose to minimize adverse effects, given the need for long-term treatment. For patients with rapidly progressive or advanced disease, it may be better to start at 2 mg per day and titrate downward once stability is ensured.
2. **Oral ulcers**: In general, oral ulcers are uncommon and mild at low sirolimus doses. Corticosteroid-based topical applications are very effective in treating sirolimus-induced oral ulcers. Swish and spit dexamethasone is most effective. For topical gels, fluocinonide or clobetasol is preferred over triamcinolone (Kenalog).
3. **Acne**: Acne is not common in patients taking low-dose sirolimus. Over-the-counter medications such as benzoyl peroxide and salicylic acid are quite effective and are reasonable first-line treatment options for acne.
4. **Hyperlipidemia**: Treatment of hyperlipidemia should follow existing guidelines, including dietary modifications and statins.
5. **Common interactions**:
   a. Over-the-counter medications such as St John's wort
   b. Grapefruit juice
   c. CYP3A4 inducers (e.g., rifampin, carbamazepine, barbiturates, phenytoin)
   d. CYP3A4 inhibitors (e.g., ketoconazole, clarithromycin)

OTHER ADVICE

1. Use sunscreen, hats, and so forth because of the enhanced risk of skin cancer.
2. Do not split tablets.
3. Hold sirolimus for fever requiring antibiotics or for serious infections.
4. Hold sirolimus for any event that requires optimal wound healing, such as an accident with injuries.
5. Spirometry should be obtained at regular intervals that vary on the basis of disease progression, from every 3 months for those with worsening to every year or so for stable patients.
6. Consider obtaining serum vascular endothelial growth factor-D levels at least annually.

eAppendix 97.2

VACCINATIONS IN PATIENTS WITH LYMPHANGIOLEIOMYOMATOSIS

Patients with lymphangioleiomyomatosis (LAM) should maintain appropriate vaccinations. Live vaccines should be avoided in patients taking immunosuppressive agents, so the vaccination recommendations given here differ between LAM patients who are receiving mechanistic target of rapamycin (mTOR) inhibitors and those who are not.

For LAM patients who are *not* taking mTOR inhibitors, we recommend:

1. Annual influenza vaccination with the inactivated vaccine. Flumist (live attenuated influenza vaccine) is not recommended in LAM patients because diffuse lung disease is a relative contraindication.
2. Vaccination against pneumococcus:
   a. All patients should receive 13-valent PCV, one dose in a lifetime; ideally given before 23-valent PPSV, but at least 1 year after 23-valent PPSV.
   b. All patients should receive 23-valent PPSV, one dose every 5 years; given at least 2 months after 13-valent PCV.
3. Shingles (herpes zoster) vaccination:
   a. Shingles (herpes zoster) vaccination with recombinant zoster vaccine (RZV) is preferred over the live attenuated zoster vaccine (ZLV).
   b. RZV is recommended for all LAM patients over the age of 50 years.
   c. It requires a two-dose administration series at zero and 2 to 6 months.
4. Hepatitis (A and B) vaccines are recommended for all patients.
5. Tetanus vaccine is recommended for all patients.

For LAM patients who *are* taking mTOR inhibitors, we recommend:

1. Annual influenza vaccination with the inactivated vaccine. Flumist (live attenuated influenza vaccine) should not be used in immunocompromised LAM patients taking mTOR inhibitors.
2. Vaccination against pneumococcus:
   a. All patients should receive 13-valent PCV, one dose in lifetime; ideally given before 23-valent PPSV, but at least 1 year after 23-valent PPSV.
   b. All patients should receive 23-valent PPSV, one dose every 5 years; given at least 2 months after 13-valent PCV.
3. Shingles (herpes zoster) vaccination with RZV should be given to all LAM patients who are either currently taking or about to start taking mTOR inhibitors, regardless of age.
4. Hepatitis (A and B) vaccines are recommended for all patients.
5. Tetanus vaccine is recommended for all patients.
6. Avoid other live virus vaccines:
   a. Measles, mumps, rubella
   b. Oral polio
   c. Smallpox
   d. Rotavirus
   e. Yellow fever
   f. Rabies

GENERAL COMMENTS

Inactivated or recombinant flu vaccines should not be used in anyone with prior severe allergy without consulting an allergist, and they should be used with caution in patients with moderate or severe acute illness with or without fever, patients with a history of Guillain-Barré syndrome within 6 weeks of previous influenza vaccination, or people with egg allergy.

Minor illnesses (such as diarrhea, mild upper respiratory infection with or without low-grade fever, other low-grade febrile illness) are not contraindications to vaccination. Adults with egg allergy of any severity can receive inactivated vaccines with the same indications as those without egg allergy because the new preparations contain much smaller quantities of egg products.

Contraindications to 23-valent PPSV and 13-valent PCV include severe prior allergic reaction and moderate or severe acute illness. Patients with a documented true allergic reaction (rather than a history of egg allergy) to 13-valent PCV or 23-valent PPSV should seek the advice of an allergist.

eAppendix 97.3

PLEURAL DISEASE IN LYMPHANGIOLEIOMYOMATOSIS

The two most common pleural complications encountered in patients with lymphangioleiomyomatosis (LAM) are (1) spontaneous pneumothorax and (2) chylous pleural effusions.

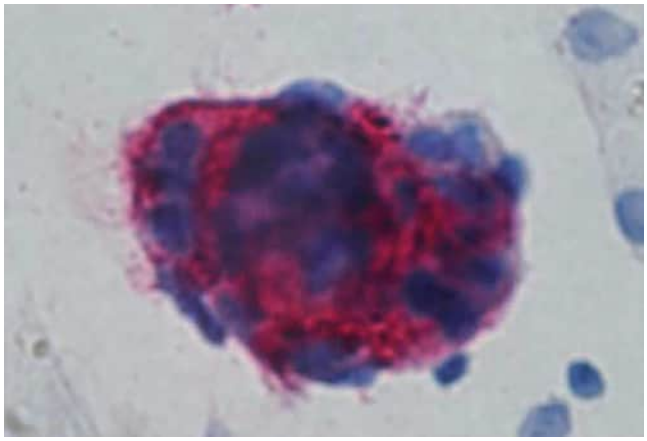
SPONTANEOUS PNEUMOTHORAX

1. Almost two-thirds of women with LAM experience at least one episode of spontaneous pneumothorax in their lifetime.
2. Patients who have a sentinel pneumothorax have a greater than 70% chance of recurrence.
3. Pleurodesis (chemical or surgical) reduces the risk of recurrence to approximately 30%.
4. Because of the high recurrence rate, patients with LAM should be offered pleurodesis after their initial episode of pneumothorax, rather than waiting for a recurrent event.
5. Although the preferred mode of pleurodesis varies among different centers depending on individual practices and experiences, we recommend video-assisted thoracoscopic surgery–guided mechanical abrasion as the preferred modality for pleurodesis, rather than instillation of talc or other sclerosing agents.
6. Whenever possible, pleurodesis should be handled by clinicians experienced in managing pleural complications of LAM.
7. Prior pleurodesis is not a contraindication to future transplantation.
8. All patients should be educated about the signs and symptoms of spontaneous pneumothorax at the time of initial diagnosis and advised to seek immediate medical attention if they experience any of these symptoms.
9. The risk of spontaneous pneumothorax associated with air travel is approximately 1 to 2 episodes per 100 flights. In general, it is safe for LAM patients to undertake air travel. Patients should be advised to seek medical attention and not board an airplane if they experience new or worse pleuritic chest pain and/or dyspnea before undertaking air travel.
10. Although there is no direct evidence, patients with LAM should be advised against scuba diving because of the potential increased risk of spontaneous pneumothorax related to atmospheric pressure changes.

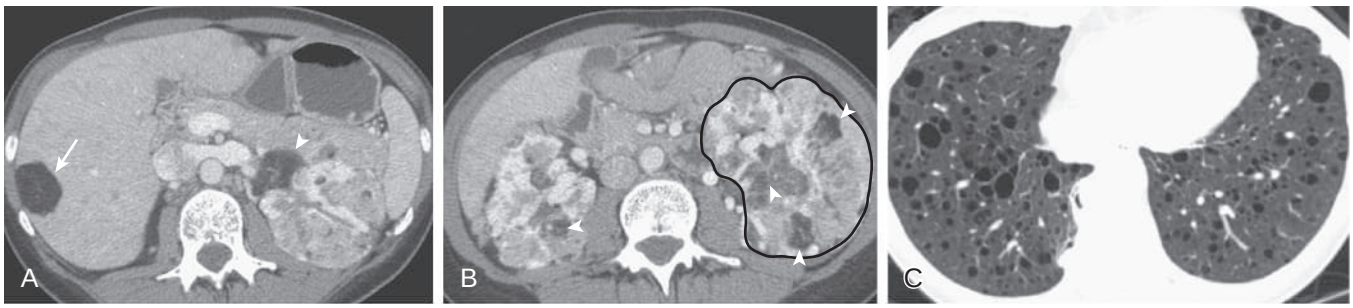
CHYLOUS PLEURAL EFFUSIONS OR CHYLOTHORAX

1. Chylous pleural effusions can be seen in 10–30% of patients with LAM.
2. If large enough to be tapped safely, chylous effusion should be confirmed with diagnostic thoracentesis. The presence of chylous effusion in a patient with characteristic cystic changes on high-resolution computed tomography is diagnostic of LAM. Pleural fluid obtained from diagnostic thoracentesis should be investigated for the presence of LAM cells. The demonstration of LAM cells on pleural fluid cytologic examination further strengthens the diagnosis of LAM.
3. Sirolimus is effective in managing chylous effusion, and it should be the first-line treatment option for patients with chylothorax, as compared with invasive treatment modalities.
4. In patients with persistent chylous leaks, dedicated lymphatic imaging such as heavy T2-weighted magnetic resonance imaging and dynamic contrast-enhanced magnetic resonance lymphangiogram should be performed to study the lymphatic anatomy and to determine if transcatheter embolization is feasible before pursuing invasive options such as pleurodesis.
5. Treatment with sirolimus may take a few months (even up to 6 to 12 months or longer) to be effective in managing chylous effusions. Because chyle does not typically produce pleural inflammation or fibrothorax, it may be prudent to wait for sirolimus to take peak effect before considering invasive treatment options.
6. Invasive management such as thoracic duct embolization should be performed by clinicians who have expertise in managing lymphatic complications in patients with LAM.

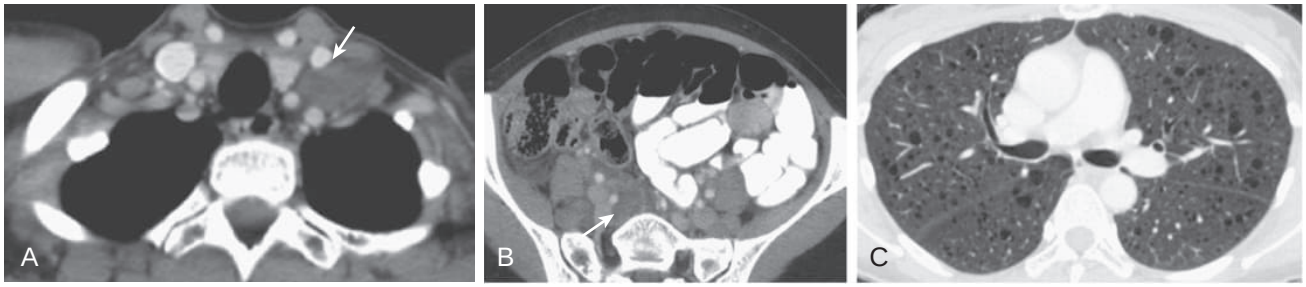
eFIGURE IMAGE GALLERY



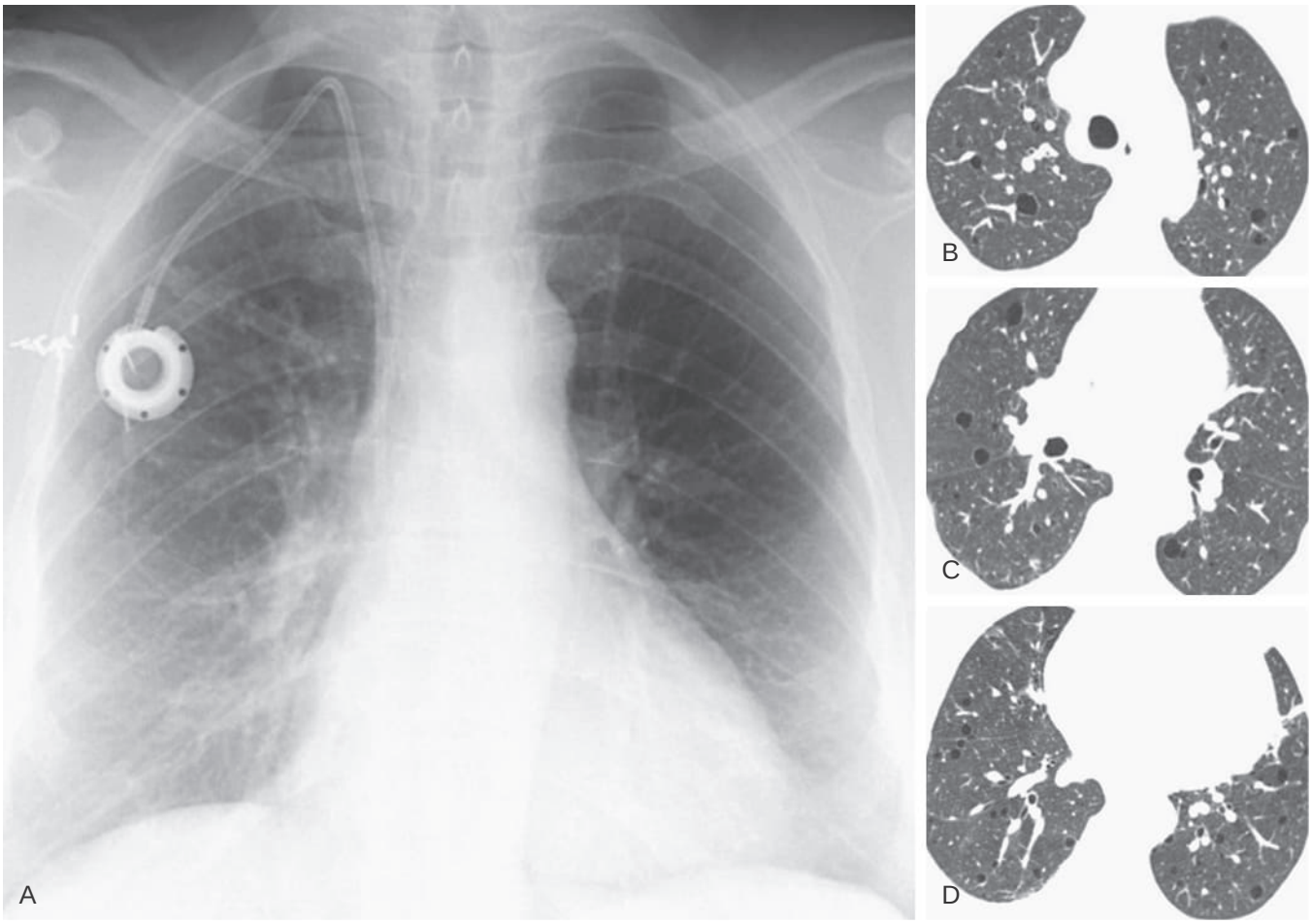
eFigure 97.1 Immunocytochemistry for *lymphangioleiomyomatosis* (LAM) cell cluster in chylous effusion. LAM cells in the clusters were strongly positive for α-smooth muscle actin, but the thin, flat cells surrounding the LAM cells were negative. (Smear; ×3400 original magnification.) (From Kumasaka T, Seyama K, Mitani K, et al. Lymphangiogenesis-mediated shedding of LAM cell clusters as a mechanism for dissemination in lymphangioleiomyomatosis. *Am J Surg Pathol.* 2005;29:1356-1366.)



eFigure 97.2 Angiomyolipomas in lymphangioleiomyomatosis. (A–B) Axial contrast-enhanced chest computed tomography through the upper abdomen shows bilateral renal enlargement (left kidney outlined in B). Numerous areas of fat density (*arrowheads,* A and B) representing angiomyolipomas are present. Hepatic angiomyolipomas (*arrow*, A) are also evident. (C) Axial chest computed tomography displayed in lung windows shows numerous bilateral, uniform-appearing, thin-walled cysts with relatively normal-appearing intervening lung, findings typical of lymphangioleiomyomatosis. (Courtesy Michael B. Gotway, MD.)



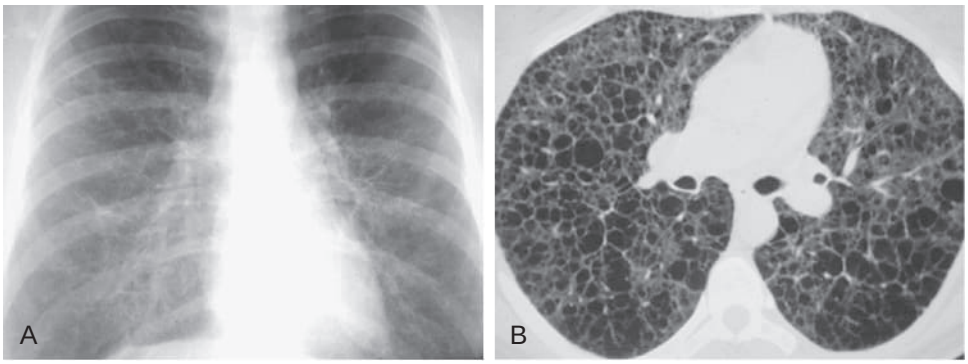
eFigure 97.3 Lymphangiomyomas in lymphangioleiomyomatosis. Axial chest computed tomography through (A) the upper thorax and (B) the pelvis show circumscribed, faintly septated, low-attenuation structures *(arrows)* representing lymphangiomyomas. (C) Axial chest computed tomography displayed in lung windows shows numerous bilateral, uniform-appearing, thin-walled cysts with relatively normal-appearing intervening lung, typical of lymphangioleiomyomatosis. (Courtesy Diego Ruiz, MD, Palo Alto Medical Clinic, Palo Alto, CA.)



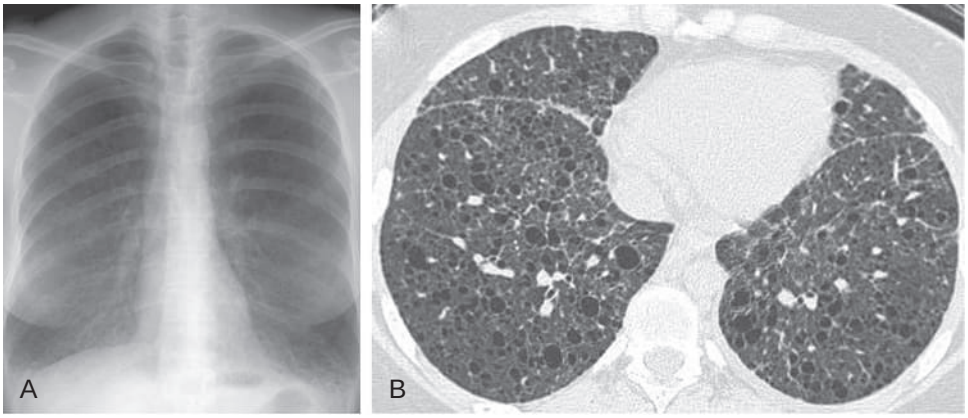
eFigure 97.4 Relatively unremarkable chest radiographic appearance in *lymphangioleiomyomatosis* (LAM). (A) Frontal chest radiograph in a patient with LAM shows relatively few abnormalities, with no findings specifically suggesting the diagnosis of LAM. Nonspecific mild right perihilar linear and reticular opacities are present. (B–D) Axial chest computed tomography displayed in lung windows shows bilateral, uniform-appearing, thin-walled cysts with relatively normal-appearing intervening lung, typical of LAM. The presence of comparatively fewer and smaller cysts in this patient likely contributes to the understated nature of the appearance on the chest radiograph (compare with eFigs. 97.5, 97.6A, and 97.7A). (Courtesy Michael B. Gotway, MD.)



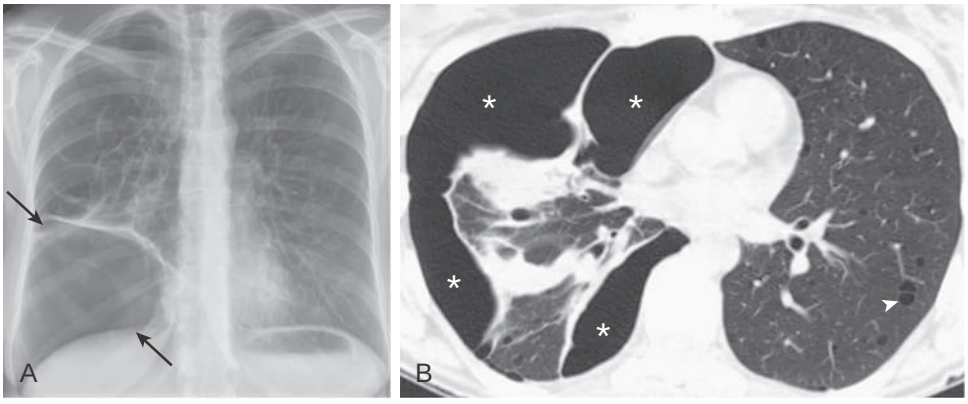
eFigure 97.5 *Lymphangioleiomyomatosis* (LAM)—linear or reticular appearance on chest radiograph. Frontal chest radiograph in a patient with LAM shows diffuse, bilateral, symmetrical linear and reticular opacities suggesting a disorder infiltrating the pulmonary interstitium. The appearance of interstitial lung disease on chest radiograph in patients with LAM may result from superimposition of the walls of the cysts characteristic of this disorder, in addition to actual interstitial space expansion resulting from lymphatic dilation and diffuse nodular proliferation of alveolar type 2 cells. (Courtesy Michael B. Gotway, MD.)



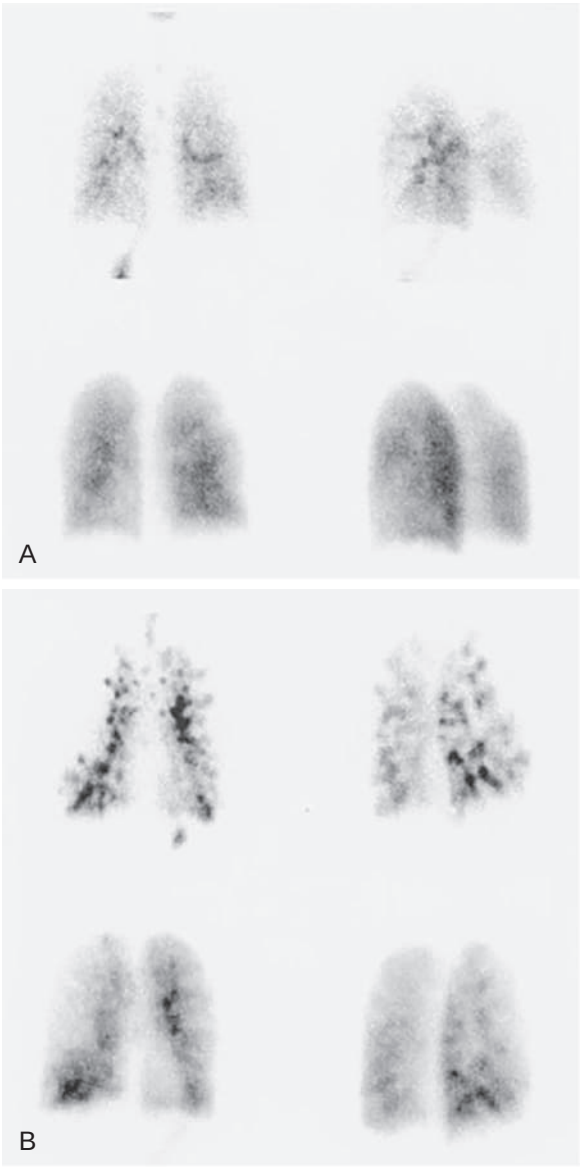
eFigure 97.6 *Lymphangioleiomyomatosis* (LAM)—typical imaging appearance. (A) Frontal chest radiograph in a patient with LAM shows increased lung volumes associated with bilateral linear and reticular opacities, faintly seen to represent the walls of the cysts typical of LAM. (B) Axial chest computed tomography shows numerous bilateral, uniform-appearing, thin-walled cysts with relatively normal-appearing intervening lung, typical of LAM. (Courtesy Michael B. Gotway, MD.)



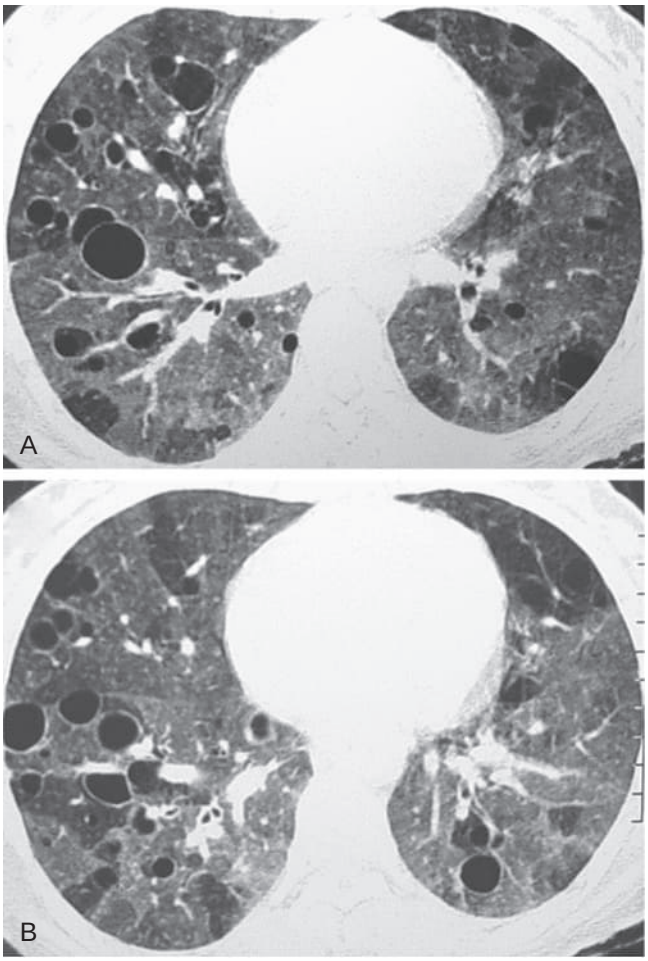
eFigure 97.7 "Honeycomb" or "pseudofibrotic" appearance of lymphangioleiomyomatosis at imaging. (A) Frontal chest radiograph shows bilateral linear and reticular opacities, somewhat resembling interstitial or fibrotic lung disease, especially in the bases. The large lung volumes, however, strongly argue against fibrotic interstitial pneumonia. (B) Axial chest computed tomography displayed in lung windows shows numerous bilateral, uniform-appearing, thin-walled cysts with relatively normal-appearing intervening lung, typical of lymphangioleiomyomatosis. The numerous overlapping cyst walls contribute to the "interstitial" appearance on radiography. This appearance in the bases can superficially resemble fibrotic lung disease. (Courtesy Michael B. Gotway, MD.)



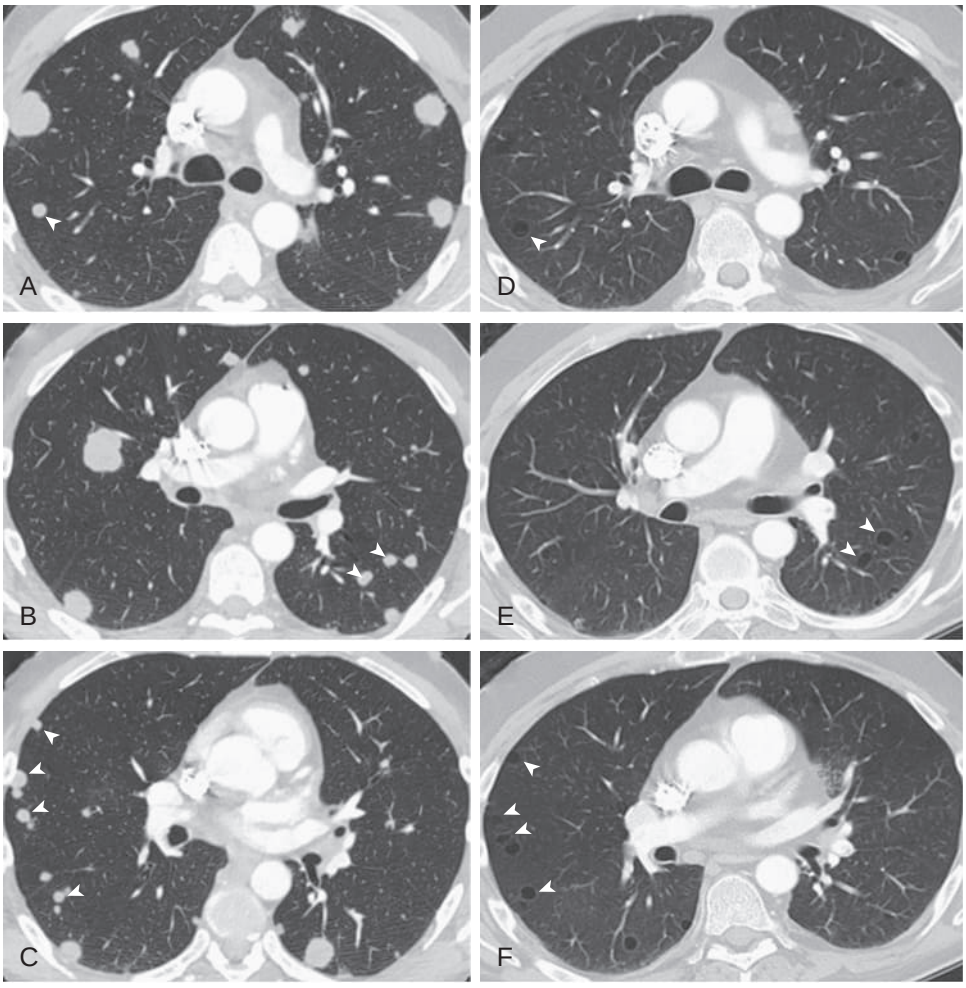
eFigure 97.8 Spontaneous pneumothorax in lymphangioleiomyomatosis. (A) Frontal chest radiograph shows a basal predominant right-sided pneumothorax *(arrows).* (B) Axial chest computed tomography displayed in lung windows shows the pneumothorax *(asterisks);* thin-walled left lower lobe cysts *(arrowhead),* typical of lymphangioleiomyomatosis, are present. (Courtesy Michael B. Gotway, MD.)



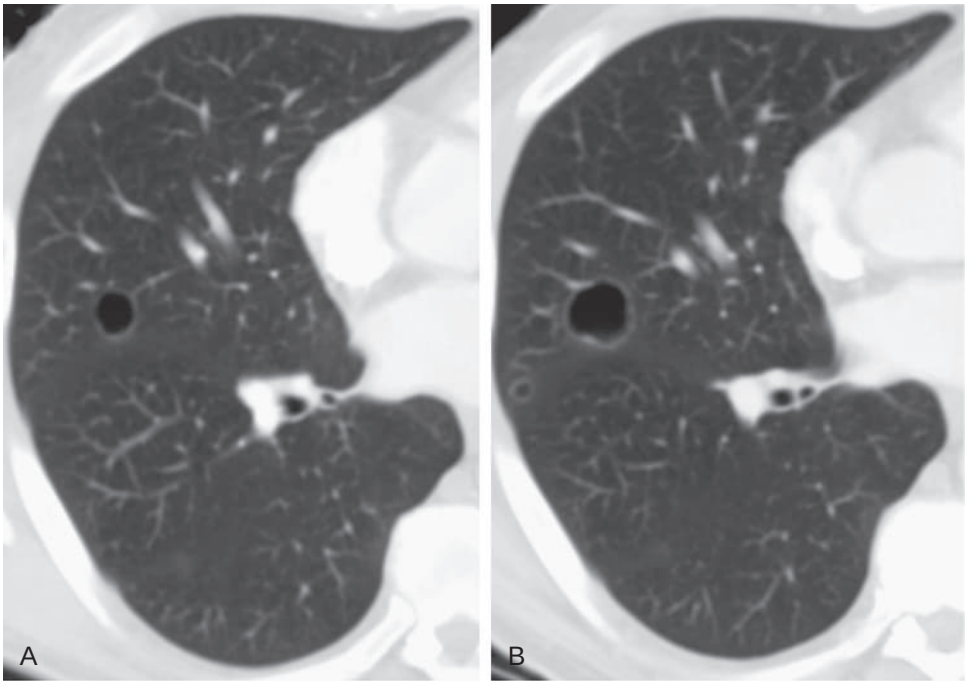
eFigure 97.9 Ventilation-perfusion scans of two patients with lymphangioleiomyomatosis. (A) Mild speckling. Posterior *(left)* and left posterior oblique *(right)* views of ventilation *(upper)* and perfusion *(lower)* scans show diffuse mild heterogeneity with mild speckling. A moderate amount of central clumping is also seen on the ventilation images. (B) Severe speckling. Anterior *(left)* and right posterior oblique *(right)* views of ventilation *(upper)* and perfusion *(lower)* scans show severe speckling and a significant degree of heterogeneity throughout. (From Chu SC, Horiba K, Usuki J, et al. Comprehensive evaluation of 35 patients with lymphangioleiomyomatosis. *Chest.* 1999;115:1041-1052.)



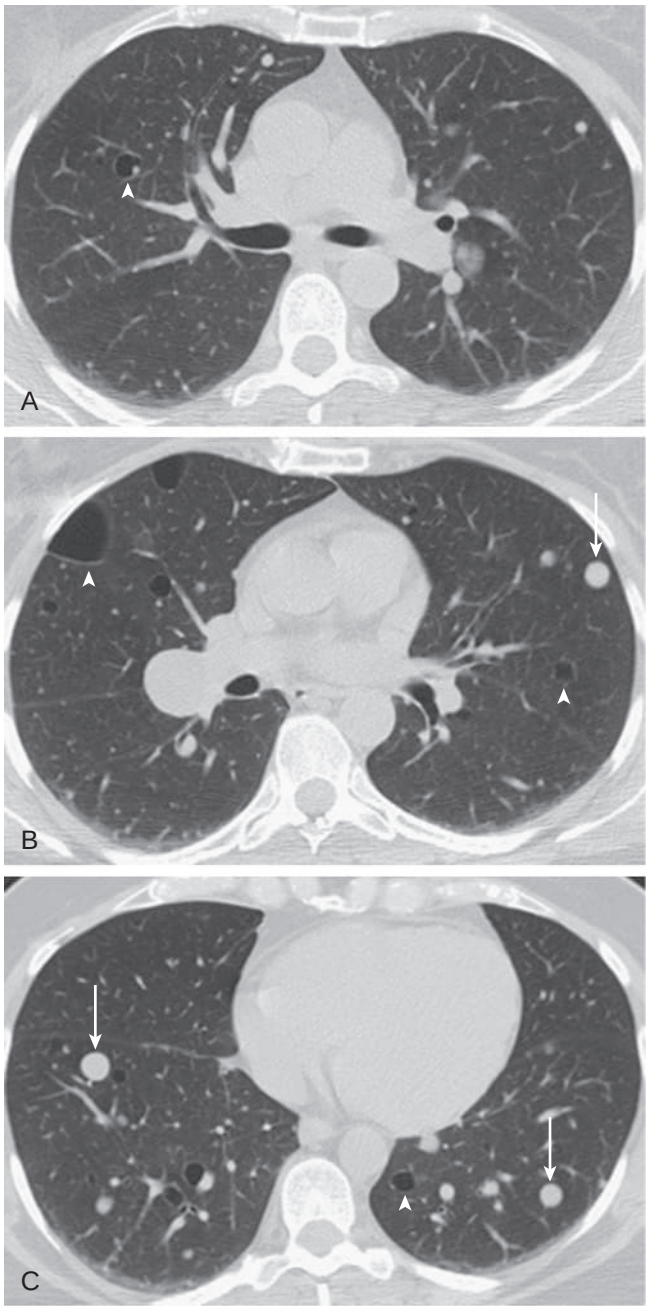
eFigure 97.10 Thin-walled cystic lung disorders simulating lymphangioleiomyomatosis: diffuse cystic lung disease in hypersensitivity pneumonitis. (A–B) Axial chest computed tomography displayed in lung windows shows patchy areas of ground-glass opacity associated with numerous thin-walled cysts in a patient with proven hypersensitivity pneumonitis. (Courtesy Alejandro Gómez-Gómez, Faculty of Medicine, Dr. Ignacio Morones Prieto Central Hospital, San Luis Potosí, Mexico.)



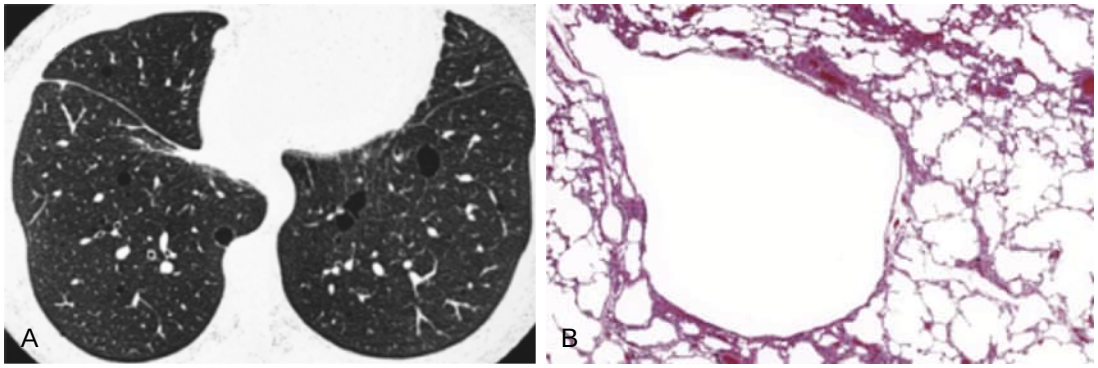
eFigure 97.11 Thin-walled cystic lung disorders simulating lymphangioleiomyomatosis: cystic metastatic disease. (A–C) Axial chest computed tomography displayed in lung windows at diagnosis shows numerous, variably sized, bilateral solid lung nodules *(arrowheads),* representing pulmonary metastatic disease from testicular carcinoma. (D–F) Axial chest computed tomography following therapy for metastatic testicular carcinoma shows many of the solid nodules have evolved into thin-walled cysts *(arrowheads).* Although the appearance at follow-up (D–F) may simulate more common causes of diffuse cystic lung disease, such as lymphangioleiomyomatosis and lymphocytic interstitial pneumonia, the clinical context (particularly the sex in this particular circumstance) and serial evolution from nodular lung disease readily provide differentiation from typical cystic lung disorders. (Courtesy Michael B. Gotway, MD.)



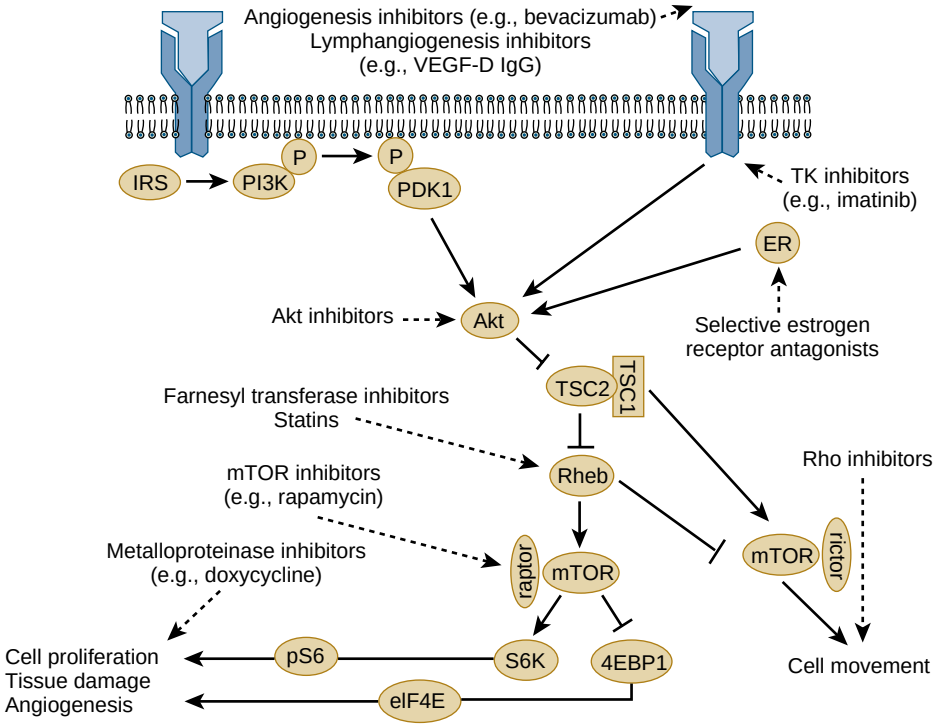
eFigure 97.12 Thin-walled cystic lung disorders simulating lymphangioleiomyomatosis: cystic metastatic disease. (A–B) Axial chest computed tomography displayed in lung windows in a patient with metastatic angiosarcoma shows several thin-walled cysts, ultimately shown to reflect metastatic angiosarcoma. (Courtesy Diego Ruiz, MD, Palo Alto Medical Clinic, Palo Alto, CA.)



eFigure 97.13 Thin-walled cystic lung disorders simulating lymphangioleiomyomatosis: cystic benign metastasizing leiomyoma. (A–C) Axial chest computed tomography displayed in lung windows shows several bilateral thin-walled cysts *(arrowheads)* and solid, circumscribed nodules *(arrows)*. The cysts evolved from solid nodules on serial examinations. Biopsy showed benign metastasizing leiomyoma. (Courtesy Michael B. Gotway, MD.)



eFigure 97.14 Birt-Hogg-Dubé syndrome. (A) High-resolution computed tomography and (B) histopathologic presentation of the lung cysts. (B, Hematoxylin and eosin stain.) This 58-year-old patient had repeated bilateral pneumothoraces and a family history of pneumothorax in a brother, son, and daughter. In the cyst wall, there is a lack of smooth muscle infiltration. (Courtesy Dr. Takashi Ogura, Kanagawa Cardiovascular and Respiratory Center, Kanagawa, Japan; and Tamiko Takemura, Japanese Red Cross Medical Center, Tokyo, Japan.)



eFigure 97.15 Future therapeutic targets for lymphangioleiomyomatosis. Knowledge of the signaling pathways that are dysregulated in patients with lymphangioleiomyomatosis has revealed several promising molecular targets for intervention. The constitutive activation of mechanistic target of rapamycin (mTOR) drives the inappropriate phosphorylation of S6 (pS6) when the *TSC1* or *TSC2* gene is missing or defective, as is seen in patients with lymphangioleiomyomatosis. pS6 (and eIF4E) drives protein translation and inappropriate cellular proliferation, but it also feeds back to inhibit the activation of immunoreactive secretin (IRS) and the downstream effector Akt. This feedback loop control can be defeated by the activation of Akt through other routes, such as the *platelet-derived growth factor* (PDGF) and estrogen receptor pathways (which may partly explain the sex restriction in lymphangioleiomyomatosis). In this regard, *tyrosine kinase* (TK) inhibitors such as imatinib and selective estrogen antagonists may have special utility in lymphangioleiomyomatosis to block alternative activation of Akt. mTOR inhibitors such as sirolimus and everolimus block mTOR signaling, and statins and farnesyl transferase inhibitors block Rheb translocation to the membrane by inhibiting the lipid modification of the protein. Patients with lymphangioleiomyomatosis express elevated levels of the lymphangiogenic growth factor, *vascular endothelial growth factor-D* (VEGF-D), which is currently being studied as a target in metastatic malignancy trials. Angiogenesis inhibitors such as bevacizumab and anti–VEGF-D or VEGF receptor 3 (VEGFR-3) antibody may block blood and lymphatic vessel recruitment required for tumor maintenance, respectively, and metalloproteinase inhibitors such as doxycycline may block lung matrix degradation that plays a role in tumor implantation, spread, and tissue destruction. Cell migration, infiltration, and metastasis are controlled by a rapamycin-insensitive mTOR pathway, but they may be susceptible to inhibition by rho kinase inhibitors. eIF4E, eukaryotic translation initiation factor 4E; ER, estrogen receptor; IgG, immunoglobulin G; PI3K, phosphatidylinositol-3-kinase; PDK, phosphoinositide-dependent kinase; S6K, ribosomal protein S6 kinase; TSC, tuberous sclerosis complex; 4EBP1, 4E-binding protein.

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98 PULMONARY ALVEOLAR PROTEINOSIS SYNDROME

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INTRODUCTION

Pulmonary alveolar proteinosis (PAP) is a rare syndrome characterized by abnormal alveolar surfactant accumulation and hypoxemic respiratory insufficiency presenting in a heterogeneous group of mechanistically distinct diseases usefully divided into disorders of surfactant clearance or surfactant production.[1–3] The *clearance* disorders can be further divided into primary PAP, caused by disruption of *granulocyte-macrophage colony-stimulating factor* (GM-CSF) signaling, and secondary PAP, caused by another disease or condition that disrupts alveolar macrophage surfactant clearance. The *production* disorders include *pulmonary surfactant metabolic dysfunction* (PSMD) disorders, caused by mutations in genes encoding surfactant proteins or genes encoding proteins involved in surfactant production.

Recent advances, including reports of several large cohorts,[4–7] have greatly improved our understanding of PAP pathogenesis, epidemiology, clinical subtypes, prognosis, and natural history and have resulted in new methods to diagnose, evaluate, and treat patients (see review[8]). Of importance, research on this rare and fascinating syndrome has uncovered the critical role of GM-CSF in alveolar macrophage ontogeny, pulmonary surfactant homeostasis, alveolar structural integrity, lung function, host defense, pulmonary and systemic inflammation, and autoimmunity. Further, studies involving GM-CSF–deficient mice have identified new treatment approaches for common diseases, such as asthma, rheumatoid arthritis, and others. This chapter reviews the pathogenesis, classification, epidemiology, presentation, and therapy of PAP and focuses on the disorders of surfactant clearance. These produce the characteristic pattern of PAP in adults. The disorders of surfactant production are mostly, but not exclusively, in children and only occasionally produce a proteinosis pattern.

PATHOGENESIS

SURFACTANT COMPOSITION AND HOMEOSTASIS

Surfactant is a complex mixture of roughly 80% phospholipids, 10% cholesterol, and 10% surfactant proteins that functions at the air-liquid–alveolar wall interface to reduce surface tension, thereby preventing alveolar collapse. It is produced in alveolar epithelial type 2 cells, secreted into the alveolar space, and cleared either by recycling or catabolism in type 2 cells or by uptake and catabolism by alveolar macrophages. Surfactant composition, production, and homeostasis are reviewed in Chapter 3. Studies in animals and humans have identified GM-CSF as a critical regulator of surfactant homeostasis (Fig. 98.1).

GRANULOCYTE-MACROPHAGE COLONY-STIMULATING FACTOR

GM-CSF is a 23-kD cytokine that signals via cell surface receptors comprising a GM-CSF–binding, low-affinity α chain (CDw116) and a nonbinding, affinity-converting β chain (CD131).[9,10] Although neither chain has intrinsic signaling activity,[9] the β chain constitutively binds *Janus activating kinase* (JAK),[11] a tyrosine kinase involved in cytokine signaling.

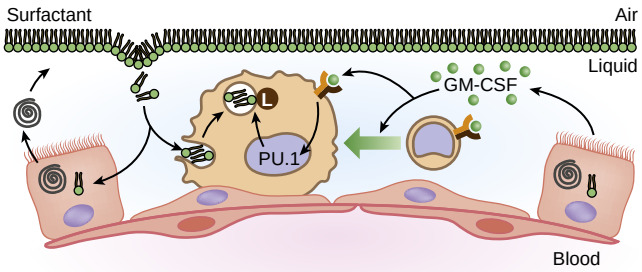

Figure 98.1 Schematic of pulmonary surfactant homeostasis within an alveolus of a healthy individual. Surfactant lipids and proteins are synthesized in alveolar epithelial type 2 cells and secreted into the intra-alveolar space. Extracellular surfactant contributes to the surfactant layer present at the air-liquid-tissue interface, which plays a critical role by reducing surface tension within the alveolus. Surfactant lipids and proteins are removed from the extracellular surfactant by uptake and recycling in type 2 cells or by uptake and catabolism in alveolar macrophages. *Granulocyte-macrophage colony-stimulating factor* (GM-CSF), a critical regulator of surfactant catabolism in alveolar macrophages, functions by binding to heterologous receptors on alveolar macrophages and stimulating surfactant catabolism via the transcription factor PU.1. GM-CSF is also critical for stimulating the terminal differentiation of precursors into mature alveolar macrophages (via *large green arrow*).

Ligand binding causes the formation of αβJAK2 multimers and the activation of JAK2, resulting in phosphorylation of α[12] and β chains, activation of other kinases,[11] and initiation of signaling via multiple pathways,[11,13] including the *signal transducer of activation and transcription-5* (STAT5).[14]

MURINE MODELS OF DISORDERED SURFACTANT HOMEOSTASIS

Abnormal Surfactant Clearance

GM-CSF–deficient (*Csf2*KO) mice provided the first clue to PAP pathogenesis. Although neither production of surfactant by alveolar epithelial type 2 cells nor its uptake by alveolar macrophages was altered,[15,16] surfactant clearance by alveolar macrophages was impaired.[17] Pulmonary GM-CSF,[18,19] acting via the transcription factor PU.1,[20] coordinately regulated surfactant catabolism; expression of Fc receptors, mannose receptors, and other receptors; phagocytosis; bacterial killing; and toll-like receptor-4 signaling[20] and identified pulmonary GM-CSF as a critical regulator of the terminal differentiation of alveolar macrophages in mice.

Mice deficient in either the GM-CSF receptor α chain (*Csf2ra*KO) or the β chain (*Csf2rb*KO) develop PAP indistinguishable from that observed in GM-CSF–deficient mice.[21] Transplantation of wild-type bone marrow corrected PAP in these mice, identifying myeloid cells and not lung epithelial cells as the cellular site of pathogenesis.[22] A biomarker of PAP in these mice (increased serum GM-CSF) suggested the means that led to identification of hereditary PAP caused by *CSF2RA* and *CSF2RB* mutations in children.[23–25] Of importance, *Csf2ra*KO and *Csf2rb*KO mice and children with *CSF2RA* or *CSF2RB* mutations develop a lung disease that is identical in every respect, including lung pathology (surfactant-filled alveoli, preserved architecture), cytopathology (oil-red-O–stained macrophages, cell debris), alveolar macrophage biomarkers (reduced messenger RNA for PU.1, *peroxisome proliferator-activated receptor* (PPAR)-γ, *ATP-binding cassette G subfamily1* (ABCG1), bronchoalveolar lavage biomarkers (increased surfactant proteins/lipids, turbidity), cytokines (GM-CSF, *macrophage colony-stimulating factor* [M-CSF], monocyte chemoattractant protein-1), and clinical course (progressive surfactant accumulation). Studies in these mice have identified pulmonary macrophage transplantation as a novel therapeutic approach for hereditary PAP.[26]

A more recent development has been the demonstration of a murine model of autoimmune PAP, using the *Rasgrp1*-deficient mouse. RasGRP1 is a guanine exchange factor expressed by B and T cells that activates *Ras* downstream of antigen receptor stimulation; mice deficient in RasGRP1 are prone to autoimmune features. *Rasgrp1*-deficient mouse lungs display the characteristic histopathology of PAP and reduced lung compliance.[27]

Mice deficient in ABCG1, a transmembrane protein mediating cellular cholesterol efflux, accumulate cholesterol in alveolar macrophages and alveolar epithelial type 2 cells and develop pulmonary lipidosis, indicating ABCG1 may be important in surfactant homeostasis.[28] Of importance, ABCG1 expression is decreased in alveolar macrophages from GM-CSF–deficient mice and patients with autoimmune PAP,[29] and from GM-CSF receptor–deficient mice and patients with hereditary PAP (unpublished data). Conditional disruption of *PPAR-γ* (a known transcriptional regulator of ABCG1), specifically in alveolar macrophages, also disrupts surfactant clearance.[30]

Together, murine studies suggest the pathogenesis of autoimmune and hereditary PAP may involve disruption of a pathway, including GM-CSF, PU.1, PPAR-γ, and ABCG1, that is essential for surfactant clearance by alveolar macrophages.

Several models have shed light on the pathogenesis of secondary PAP. In one, reduction of alveolar macrophage numbers by chemical depletion increased surfactant pool size.[31] In another, inhalation of respirable silica resulted in extensive alveolar proteinosis.[32] These models both support the concept that decreasing the number and/or functions of alveolar macrophages can cause the development of secondary PAP.

Abnormal Surfactant Production

Murine models of PSMD develop lung diseases faithfully recapitulating their respective human diseases, which are clinically, histologically, and biochemically distinct from PAP in the GM-CSF–deficient mice, and have improved understanding of surfactant homeostasis. For example, SP-B–deficient mice develop respiratory failure at birth. Studies in these mice showed that SP-B is essential for the posttranslational processing of SP-C, organization of surfactant phospholipids in lamellar bodies, formation of tubular myelin in alveoli, generation of surfactant films capable of reducing surface tension, and lung function during the early postnatal period.[33–35] Expression of mutant SP-C in mice causes a severe interstitial lung disease phenotype.[36] ABCA3-deficient mice develop respiratory failure at birth.[37] Studies in these mice established ABCA3 as critical to lamellar body formation and pulmonary surfactant biogenesis.[38]

Murine models of abnormal surfactant production that develop a PAP-like phenotype provide insights to surfactant homeostasis, including severe combined immunodeficiency,[39] pulmonary overexpression of *interleukin* (IL)-4[40] or IL-13,[41] and SP-D deficiency.[42]

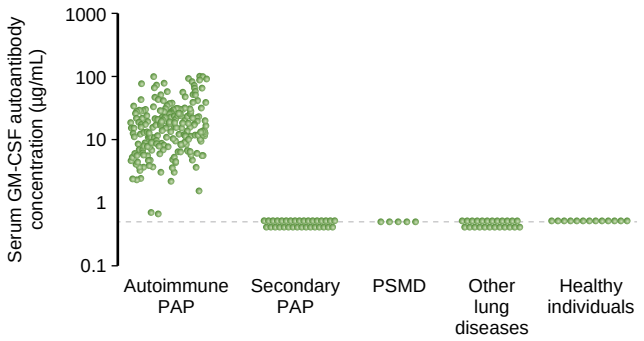

Figure 98.2 Serum antibodies to *granulocyte-macrophage colony-stimulating factor* (GM-CSF) are elevated in autoimmune *pulmonary alveolar proteinosis* (PAP). Serum GM-CSF autoantibody levels in individuals with autoimmune PAP ($n = 223$), secondary PAP ($n = 33$), *pulmonary surfactant metabolic dysfunction* (PSMD) ($n = 5$), other lung diseases ($n = 24$), and in healthy control subjects ($n = 13$). The detection limit of the assay was 0.5 μg/mL of serum. (Data from Inoue Y, Trapnell BC, Tazawa R, et al. Characteristics of a large cohort of autoimmune pulmonary alveolar proteinosis patients in Japan. *Am J Respir Crit Care Med.* 2008;177:752–762.)

ROLE OF GM-CSF AUTOANTIBODIES

In 1999, Nakata's group first identified neutralizing GM-CSF autoantibodies in the *bronchoalveolar lavage* (BAL) fluid and serum of idiopathic PAP patients.[43,44] Multiple subsequent studies confirmed that high levels of GM-CSF autoantibodies are associated with idiopathic PAP but not with secondary PAP, PSMD disorders, other lung diseases, or healthy individuals (Fig. 98.2).[1,2,4,45,46] In one study, the concentration of GM-CSF autoantibodies in 158 idiopathic PAP patients was 113 ± 7 μg/mL,[1,45] whereas levels were less than 1 μg/mL in patients with secondary PAP, PSMD disorders, or other lung diseases.[1] GM-CSF autoantibodies are composed of *immunoglobulin* (Ig) G, predominantly of the IgG1 and IgG2 subclasses; are highly specific for GM-CSF; have a very high binding affinity (20 ± 7.5 pM); and are capable of neutralizing GM-CSF at levels up to many thousands times higher than the physiologic concentrations of GM-CSF in vivo.[43,45,47] Notwithstanding these important observations suggesting a role of these antibodies in PAP, GM-CSF autoantibodies had been reported at low frequency in healthy people, in patients with autoimmune diseases without evidence of PAP, and to comprise the dominant anticytokine activity in pharmaceutical Ig prepared from healthy individuals.[48,49] In a more recent study using multiple detection methods, GM-CSF autoantibodies were demonstrated in all of 72 healthy individuals with no prior exposure to exogenous GM-CSF, albeit at a low level (median [interquartile range] = 1.0 [0.6–1.7] μg/mL serum).[47] Another confusing observation was that serum GM-CSF autoantibodies did not correlate with disease severity.[46]

To prove that GM-CSF autoantibodies were critical to the pathogenesis of idiopathic PAP and not a related but unimportant epiphenomenon, GM-CSF autoantibodies from these patients were isolated in pure form (i.e., a single band on sodium dodecyl sulfate gels) and used for passive immunization of healthy nonhuman primates. Results demonstrated unequivocally that GM-CSF autoantibodies reproduced the cardinal molecular and cellular features of PAP, including surfactant-filled alveoli with preserved wall architecture, foamy alveolar macrophages, cellular biomarkers of PAP (reduced PU.1, PPAR-γ, and ABCG1 messenger RNA), and BAL biomarkers (increased SP-D, turbidity).[50,51] GM-CSF autoantibodies isolated from the immunized primates or directly from patients had similar bioactivity.[50] Together with the clinical studies in humans, these data provided strong evidence that GM-CSF autoantibodies were in fact the pathogenic driver in idiopathic PAP, which is now recognized as autoimmune PAP.[50] Neutrophils from the immunized primates also had impaired phagocytosis similar to defects reported in these patients, GM-CSF–deficient mice, and normal human neutrophils incubated with purified GM-CSF autoantibodies in vitro.[52] Using the CD11b stimulation index assay (see later), GM-CSF signaling in immunized primates was found to decrease inversely with GM-CSF autoantibody concentration at values below 5 μg/mL and was zero at higher values, thus defining a critical threshold concentration needed to block GM-CSF signaling.[51] In a translational study using this assay, a similar relationship and threshold were observed in humans.[47] Thus seemingly discrepant observations (i.e., the critical role of GM-CSF autoantibodies in PAP pathogenesis and the lack of correlation between their concentration and disease severity) were reconciled by the hypothesis that a critical threshold level of GM-CSF autoantibodies was needed to reduce GM-CSF bioactivity sufficiently to impair surfactant clearance.[49]

GM-CSF autoantibodies are polyclonal and directed at epitopes throughout the GM-CSF molecule.[45] Evaluation of 19 monoclonal autoantibodies from six patients demonstrated that they use multiple V genes and targeted at least four nonoverlapping epitopes on GM-CSF, suggesting that GM-CSF drives the autoantibodies and not a B cell epitope on a pathogen cross reacting with GM-CSF.[53]

The observations that GM-CSF stimulation of neutrophil functions is impaired in autoimmune PAP and GM-CSF–deficient mice provides a further explanation for the increased infection risk in PAP caused by disruption of GM-CSF signaling. Further, the inverse correlation between GM-CSF autoantibody levels and neutrophil function (phagocytosis) in healthy people suggests that GM-CSF autoantibodies may have a physiologic role, such as in scavenging free GM-CSF, which can function as a proinflammatory cytokine. Supporting this concept, using methods capable of detecting GM-CSF whether it is bound by GM-CSF autoantibody or not, serum GM-CSF concentrations in healthy people are much higher than previously reported, and more than 99% is bound to GM-CSF autoantibodies in healthy individuals and in PAP patients.[47]

GENETIC FACTORS

Hereditary PAP

A series of reports established hereditary PAP as a recessive disease caused by genetic mutations in *CSF2RA* and *CSF2RB,* which encode GM-CSF receptor α or β chains, respectively (eFig. 98.1).[23–25,54,55] In some cases, the genes have been cloned and the defects reproduced in vitro, the signaling abnormalities studied in detail,[23–25] and results used to develop several novel biomarker-based diagnostic tests (see later). One particularly useful test, measurement of serum GM-CSF, was used to identify a number of patients

with hereditary PAP and is capable of identifying patients with defects in either chain.[23,24,25,56] Of importance to understanding the pathogenesis of PAP, in families with two siblings carrying the same function-impairing GM-CSF receptor gene mutation, the older sibling had minimal disease, whereas the younger sibling had severe disease, suggesting another factor besides loss of GM-CSF signaling is important in determining disease severity in hereditary PAP.[24]

Pulmonary Surfactant Metabolic Dysfunction Disorders

Mutations in three genes encoding surfactant proteins, *SFTPB, SFTPC,* and *ABCA3,* disrupt surfactant production and function and cause respiratory disease in neonates, children, and older individuals.[57–60] SP-B and SP-C are hydrophobic peptides that reside within the surfactant phospholipid layer, which functions to reduce surface tension at the alveolar wall–liquid-air interface,[35] whereas ABCA3 likely transports lipids, including phosphatidylcholine, cholesterol, sphingomyelin, and phosphatidylglycerol, into lamellar bodies in alveolar epithelial type 2 cells where the surfactant complex is assembled, processed, and stored.

SFTPB is a small gene (9.7 kb) encoding a 79–amino acid, hydrophobic protein. Infants homozygous for recessive loss-of-function mutations in *SFTPB* develop respiratory failure and die shortly after birth.[61,62] In contrast, individuals heterozygous for *SP-B*–deficiency alleles have normal lung function.[63] More than 30 mutations have been identified to date in fewer than 100 infants with SP-B deficiency.[60,64] Two-thirds have an insertional frameshift mutation caused by the replacement of a single nucleotide by three nucleotides at codon 121 (designated 121ins2). Among infants with SP-B deficiency, approximately 60% are homozygous for the 121ins2 mutation, 25% are heterozygous for this and another function-altering allele, and 15% have other mutations. SP-B deficiency is associated with the aberrant processing and secretion of an immature SP-C peptide, which may contribute to the respiratory failure associated with hereditary SP-B deficiency.[65]

SFTPC is a small gene (3 kb) encoding a 35–amino acid hydrophobic protein. Known mutations in *SFTPC* are expressed in a dominant fashion and are associated with interstitial lung disease in neonates, children, and adults.[60,66–69] Twenty-five percent of individuals with SP-C–associated lung disease have a point mutation in *SFTPC* causing the substitution of threonine for isoleucine at codon 73 (I73T).[67] Immunohistochemical analysis of lung tissue from an infant with the I73T mutation demonstrated normal staining patterns for pro–SP-B, SP-B, and pro–SP-C. Although infants with this mutation can present with respiratory distress syndrome, most children with the mutation become symptomatic with interstitial lung disease beyond the newborn period.[67,70]

ABCA3 is a large gene (80 kb) encoding a 1704–amino acid protein. Autosomal recessive mutations in *ABCA3* can result in fatal surfactant deficiency in neonates[71,72] and chronic respiratory insufficiency in older children.[69] Function-altering mutations in *ABCA3* result in surfactant that is deficient in phosphatidylcholine and has decreased function, suggesting that *ABCA3* has an important role in pulmonary surfactant phospholipid homeostasis.[73] A relatively common missense point mutation in *ABCA3,* causing the substitution of a valine for glutamic acid at codon 292 (E292V), is associated with chronic interstitial lung disease in older children who are heterozygous for this and a different function-altering mutation on the other *ABCA3* allele.[74]

NKX2.1 (also known as thyroid transcription factor 1 or TTF1) is a transcription factor essential for expression of SP-B, SP-C, and ABCA3. Haploinsufficiency of *NKX2.1* causes a complex phenotype in neonates that includes, albeit variably, hypothyroidism, brain abnormalities, and acute and chronic lung disease.[75,76]

Although the lung diseases associated with mutations in *SP-B, SP-C, ABCA3,* and *NKX2.1* disrupt surfactant homeostasis, cause varying degrees of surfactant accumulation (i.e., PAP), and are often cited as congenital forms of PAP in the medical literature, they are distinguished from disorders of surfactant clearance by their surfactant dysfunction (i.e., functionally abnormal surfactant), histopathologic abnormalities (gross parenchymal derangement and interstitial disease), and their clinical course. In consequence, the term *pulmonary surfactant metabolic dysfunction* (PSMD) disorders has been proposed for this group of genetic disorders.

DISEASE ASSOCIATIONS

PAP has been reported in association with various medical conditions believed to cause PAP, resulting in use of the term secondary PAP.[1,2,8] Systemic disorders associated with secondary PAP include malignant and other hematologic diseases, nonhematologic malignancies, immune deficiency syndromes, chronic inflammatory syndromes, and chronic infections (Table 98.1). In the past, chronic myelogenous

Table 98.1 Underlying Systemic Disorders Reported in Association With PAP Syndrome

HEMATOLOGIC DISORDERS
Acute lymphocytic leukemia
Acute myeloid leukemia
Aplastic anemia
Chronic lymphocytic leukemia
Chronic myeloid leukemia
Myelodysplastic syndromes
Multiple myeloma
Lymphoma
Waldenström macroglobulinemia
NONHEMATOLOGIC MALIGNANCIES
Adenocarcinoma
Glioblastoma
Melanoma
IMMUNE DEFICIENCY AND CHRONIC INFLAMMATORY SYNDROMES
Acquired immunodeficiency syndrome
Agammaglobulinemia
Amyloidosis
Fanconi syndrome
Juvenile dermatomyositis
Juvenile idiopathic arthritis
Methionyl-tRNA synthetase mutations
Renal tubular acidosis
Severe combined immunodeficiency disease
CHRONIC INFECTIONS
Cytomegalovirus
Mycobacterium tuberculosis
Nocardia
Pneumocystis jirovecii

PAP, pulmonary alveolar proteinosis; tRNA, transfer ribonucleic acid.

leukemia and myelodysplastic syndrome were the most frequently reported hematologic disorders associated with PAP.[2,77–79] In one single-institution study, PAP developed in 5.3% of patients with hematologic malignancies and in 8.8% of those who were neutropenic.[78] Of pathogenic significance, 9 of 10 patients in one study were neutropenic when PAP developed and, in most, PAP resolved spontaneously after bone marrow engraftment. In another, PAP developed during a period of neutropenia that resolved after treatment with granulocyte colony-stimulating factor.[80] In a third report, PAP developed in three patients with acute myeloid leukemia with GM-CSF receptor abnormalities, including reduced levels of the β chain (3 of 3) and undetectable α chain (2 of 3).[81] PAP arises in about 10% of patients with lysinuric protein intolerance, an ultrarare inherited disorder caused by defective cationic amino acid transport.[82,83] Secondary PAP has been reported in association with various forms of immunodeficiency, including thymic alymphoplasia,[84] IgA deficiency,[85] solid-organ transplantation,[86] acquired immunodeficiency syndrome,[87] and mutations in methionyl-tRNA synthetase.[88]

Although the mechanism(s) responsible for secondary PAP are poorly studied, two common themes have emerged when considered in the context of the critical role of alveolar macrophages in surfactant homeostasis. Conditions reducing either the numbers or functions of alveolar macrophages would be expected to reduce the capacity of resident alveolar macrophages to clear surfactant from the lung surface.

ENVIRONMENTAL FACTORS

PAP has been associated with inhalation exposure to environmental agents, including cigarette smoke and a wide variety of organic and inorganic dusts, fumes, and gases (Table 98.2). Epidemiologic studies (see later) document that PAP is more common in smokers. Five of the 27 original patients reported by Rosen and colleagues[89] had been exposed to wood dust. Most reports implicating other environmental exposures are single cases or small retrospective series and, in general, have not established a causal relationship between the exposure and development of PAP. One early report of 138 PAP patients found that half had significant exposure to dust and fumes, of which the most common exposure was to inhaled silica.[90] With the advent of occupational protective equipment in the workplace, this form of "acute silicoproteinosis"[91,92] is rare. Other case reports document the association of PAP with exposure to aluminum dust,[93] cellulose fibers, cement dust, titanium dioxide,[94,95] indium-tin oxide,[96] and nitrogen dioxide. The link between silica and PAP is supported by studies in rats demonstrating that inhalation of silica particles disrupts surfactant homeostasis resulting in increased surfactant accumulation.[32,97] In an analysis of 1045 PAP patients from five separate large series,[2,4–7] a history of dust exposure, when data were available, was present in 26–54% of patients.[7] Further research is needed to determine what role environmental inhalation exposure plays in the pathogenesis of PAP, although one can speculate that the dust alters macrophage clearance functions.

Table 98.2 Pulmonary Exposures Reported to Be Associated With PAP Syndrome

INORGANIC DUSTS
Aluminum
Cement
Indium
Silica
Titanium
ORGANIC DUSTS
Agricultural
Bakery flour
Fertilizer
Sawdust
FUMES
Chlorine
Cleaning products
Gasoline/petroleum
Nitrogen dioxide
Paint
Synthetic plastic fumes
Varnish

PAP, pulmonary alveolar proteinosis.

MECHANISMS OF DISRUPTION OF SURFACTANT HOMEOSTASIS

Primary Pulmonary Alveolar Proteinosis

In mice, a series of observations has established GM-CSF as a critical regulator of pulmonary surfactant homeostasis, including the following: (1) surfactant homeostasis requires the presence of GM-CSF in the lung, and PAP develops in the absence of either pulmonary GM-CSF or its receptor; (2) surfactant accumulation in GM-CSF–deficient mice is caused by decreased clearance by alveolar macrophages, and not an increase in surfactant production; (3) pulmonary GM-CSF is required for normal expression of transcription factor PU.1 in alveolar macrophages, and enforced (i.e., retroviral mediated) expression of PU.1 restores surfactant catabolism in alveolar macrophages from *Csf2*KO mice; and (4) surfactant homeostasis can be restored in *Csf2rb*KO mice by transplantation of bone marrow from a wild-type mouse.

In humans, studies elucidating the pathogenesis of autoimmune and hereditary PAP show that GM-CSF effects on macrophages are also essential for surfactant homeostasis. Supportive data include (1) GM-CSF autoantibodies are present at high levels only in autoimmune PAP and, when isolated in pure form, cause PAP after injection into healthy primates[50,98]; (2) GM-CSF autoantibodies neutralize vastly higher amounts of GM-CSF than is present physiologically[45]; (3) in PAP patients, PU.1 expression is reduced in alveolar macrophages and increased by GM-CSF therapy[99]; (4) disruption of GM-CSF signaling by *CSF2RA or CSF2RB* mutations cause lung disease histopathology indistinguishable from that of GM-CSF knockout mice and autoimmune PAP in humans[23–25,54,55]; (5) reduced expression of GM-CSF receptor β on leukocytes is associated with PAP in children and with development of PAP in leukemia patients[81]; and (6) disorders that transiently reduce numbers and/or functions of alveolar macrophages are temporally related to the development and resolution of secondary PAP in humans.[80]

Available evidence suggests that GM-CSF regulates myeloid cell functions similarly in humans and mice. GM-CSF knockout mice and autoimmune PAP patients have remarkable

similarity in (1) pulmonary histopathologic appearance of the lung, (2) cytologic and ultrastructural appearance of alveolar macrophages, (3) elevation of certain cytokines (monocyte chemotactic protein-1, macrophage colony-stimulating factor), (4) the pattern of differential impairment of various neutrophil functions, and (5) the increased incidence of pulmonary and extrathoracic secondary infections.

The pathogenic mechanism in primary PAP is disruption of GM-CSF signaling to alveolar macrophages, either by the absence of GM-CSF (observed in mice, but not yet in humans), disruption of GM-CSF signaling by mutations in the GM-CSF receptor proteins (in mice and humans), or an autoimmune attack targeted at GM-CSF that neutralizes GM-CSF, eliminating GM-CSF bioactivity and myeloid cell stimulation in vivo (in humans and nonhuman primates). GM-CSF, via PU.1, regulates catabolism of surfactant in alveolar macrophages (in mice and possibly humans). Surfactant accumulation in PAP is due to reduced clearance in alveolar macrophages, but the precise mechanism is unknown. Because pulmonary surfactant is internalized into macrophages by endocytosis and catabolized in phagolysosomes, it is possible that interruption of GM-CSF signaling blocks the translocation of endocytosed surfactant to lysosomes. Such a mechanism has been demonstrated for adenovirus internalized by macrophages from GM-CSF–deficient mice, in which PU.1 redirects adenovirus-containing endosomes to lysosomes for destruction. Alternatively, GM-CSF deficiency may result in a key enzyme deficiency. Potentially supporting this possibility are data related to PPAR-γ, a ligand-activated transcription factor regulating genes involved in lipid metabolism and other pathways.[100] PPAR-γ messenger RNA and protein are expressed in alveolar macrophages in healthy individuals, decreased in PAP patients, and increased by GM-CSF therapy of PAP patients.[99] CD36, a lipid scavenger receptor regulated by PPAR-γ, is regulated in a similar pattern. PPAR-γ deficiency has been noted in several other disorders, including sarcoidosis, acute respiratory distress syndrome, and asthma, where there have been reports of surfactant abnormalities.[101] Further studies are required to determine the mechanism by which interruption of GM-CSF signaling leads to reduced clearance of surfactant by alveolar macrophages.

Recent findings have revealed the importance of macrophage cholesterol clearance in maintaining surfactant homeostasis and alveolar macrophage function. In animal models of PAP and in PAP patient-derived macrophages, the capacity of alveolar macrophages to clear surfactant is impaired due to reduced cholesterol clearance, which is the rate-limiting step causing macrophage dysfunction in primary PAP.[102] Abnormal GM-CSF signaling results in reduced *PPAR-γ* gene expression in macrophages, resulting in lower expression of the cell surface cholesterol transporters ABCG1 and ABCA1. This, in turn, leads to reduced cholesterol clearance in alveolar macrophages, altering their ability to uptake and clear surfactant, resulting in alveolar surfactant accumulation. In patients with primary PAP, the foamy alveolar macrophages have elevated cholesterol content, and there is a corresponding increase in the ratio of cholesterol to phospholipid in BAL fluid.[103]

Secondary Pulmonary Alveolar Proteinosis

The mechanisms involved in secondary PAP, although less well supported by experimental data, likely involve reduced numbers or functions of alveolar macrophages. This would decrease the surfactant clearance capacity of resident alveolar macrophages and is supported by data demonstrating a temporal relationship of the onset and resolution of PAP with myeloid-cell suppression and its resolution in hematologic disorders. Other secondary mechanisms of PAP, for example, due to inhalation of toxic fumes and dusts, are less clear. Presumably, they would involve a reduction in the ability of alveolar macrophages to clear surfactant. However, because overexpression of certain cytokines (IL-4, IL-13) or decreased expression of some surfactant proteins (SP-D) also increases surfactant production in mice, other potential mechanisms appear possible.

Pulmonary Surfactant Metabolic Dysfunction

Mechanisms of PSMD involve mutations in genes of the surfactant synthetic pathway, including *SFTPB, SFTPC, ABCA3,* and likely others, and result in the production of biochemically and functionally abnormal surfactant. These disorders exhibit a lung histopathology and clinical course markedly different from PAP caused by interruption of GM-CSF signaling. Furthermore, the pathophysiology arises from surfactant deficiency and/or dysfunction rather than surfactant excess as in PAP. Thus, it seems appropriate to consider these disorders as distinct from PAP and not part of a spectrum of PAP.

NOMENCLATURE AND CLASSIFICATION

Since PAP was first described as a lung disease "of the filling of the alveoli by a periodic acid–Schiff–positive proteinaceous material, rich in lipid,"[89] it has become recognized as a syndrome caused by distinct diseases[1,8] and is reported in the medical literature using numerous terms, resulting in a nomenclature that is redundant, inconsistent, and confusing. Terms have been based on the biochemical characteristics of the accumulated material (e.g., alveolar proteinosis, phospholipidosis), pathogenesis (e.g., silicoproteinosis, idiopathic), disease category (e.g., primary vs. secondary), and timing of symptom onset (e.g., congenital, acquired) and are redundant (e.g., idiopathic PAP, acquired PAP, pulmonary alveolar lipoproteinosis, phospholipoproteinosis, alveolar lipoproteinosis, alveolar proteinosis, alveolar phospholipidosis, and alveolar lipophosphoproteinosis). Confusion arises from use of the same term for different diseases. For example, the term *congenital PAP* is used for the disease caused by mutations in *SFTPB* that is uniformly fatal at birth and caused by surfactant deficiency, and also for the disease caused by GM-CSF receptor deficiency that presents in children, is caused by surfactant accumulation, and can be treated successfully.

The foregoing discussion underscores the need for a classification and nomenclature that will facilitate clear communication about disorders of homeostasis necessary for clinical training, disease management, and research. Based on initial discussions of a global task force assembled by the Rare Lung Diseases Consortium, a simplified classified scheme is proposed (Table 98.3).

Disorders of surfactant homeostasis are separated into disorders of reduced clearance (PAP) or abnormal production (PSMD). PAP is further subdivided into primary and

Table 98.3 Classification of Diseases Associated With Disruption of Surfactant Homeostasis

PRIMARY PULMONARY ALVEOLAR PROTEINOSIS
GM-CSF autoimmunity
CSF2RA mutations
CSF2RB mutations
GM-CSF mutations (mice)
SECONDARY PULMONARY ALVEOLAR PROTEINOSIS
Hematologic disease
Nonhematologic malignancy
Immune deficiency syndromes
Chronic inflammatory syndromes
Chronic infections
PULMONARY SURFACTANT METABOLIC DYSFUNCTION DISORDERS
SFTPB mutations
SFTPC mutations
ABCA3 mutations

ABCA3, ATP-binding cassette subfamily A3; CSF2RA, colony-stimulating factor 2 receptor subunit alpha; GM-CSF, granulocyte-macrophage colony-stimulating factor; SFTPB, surfactant protein B; SFTPC, surfactant protein C.

secondary categories, depending whether it is due to a primary disturbance of GM-CSF signaling or secondary to another disease. Primary PAP is composed of several specific disease mechanisms: an autoimmune disease caused by GM-CSF autoantibodies (autoimmune PAP) or a genetic disease caused by mutations in the genes coding for the GM-CSF receptor, *CSF2RA* or *CSFR2B.* A third disease, caused by GM-CSF deficiency, has been described in mice and is predicted but not yet observed in humans. Secondary PAP arises in association with several disease categories, including hematologic disorders, malignancy, immunodeficiency syndromes, chronic inflammatory disorders, chronic infections (see Table 98.1), and in association with certain inhalation exposures, especially silica (sandblasters) (see Table 98.2). On the other hand, PSMD disorders are those arising from mutations in genes of the surfactant synthesis pathway, including *SFTPB, SFTPC, ABCA3, NKX2.1,* and likely others that have yet to be identified.[58] These disorders are included in a new classification of interstitial lung disease in young children.[104]

The plethora of terms used to report on the PAP syndrome are not recommended for continued use and should be replaced with the term *pulmonary alveolar proteinosis.* Terms referring to clinical presentation (i.e., acquired PAP, congenital PAP) should not be used when the underlying disease is known. For example, "SP-B deficiency" is far more informative than "congenital PAP" and more consistent with its pathogenesis as a disorder of surfactant deficiency (PSMD) rather than excessive surfactant accumulation (PAP). When the cause is unknown, the term "unclassified PAP" is preferred over "idiopathic PAP" because the latter is currently understood to be the disorder caused by a high level of GM-CSF autoantibodies and should be called autoimmune PAP.

EPIDEMIOLOGY

Disorders of surfactant homeostasis are found in worldwide distribution but are quite rare. Since the initial description of PAP, more than 1000 separate cases of PAP[2,4–6,23,89,105,106] and substantially fewer cases of PSMD* have been reported in the medical literature (eTable 98.1). A comprehensive meta-analysis of 410 separate cases of PAP representing all clinical subtypes and most or all cases of PAP reported in the medical literature through 1998 found that patients were more likely to be male (male/female ratio = 2.65:1.0) and that men predominated among smokers (male/female ratio = 2.78:1.0) but not among nonsmokers (male/female ratio = 0.69:1.0).[2] These results suggested that the high proportion of men among PAP patients may be explained by their higher frequency of tobacco use. More recent evaluations have refined these estimates for individual diseases. Consequently, the epidemiology of each is considered individually.

Autoimmune PAP has been studied worldwide. In a large national, multicenter, registry-based study of PAP conducted in Japan, 223 patients were identified with autoimmune PAP.[4] This study reported a male predominance (male/female ratio = 2.1:1.0) and that men predominated among smokers (male/female ratio = 9.3:1.0) but not among nonsmokers (male/female ratio = 0.6:1.0). The median age at the time of diagnosis was 53 years (52 years in men and 55 years in women). The prevalence was similar in nine nonoverlapping geographic regions encompassing the entirety of Japan, and the case rate correlated closely with the regional population size. An intensive screening within the Niigata prefecture in Japan (population 2.41 million) estimated the incidence and prevalence of autoimmune PAP to be 0.5 ± 0.1 and 6.2 per million, respectively.[4] This registry found that, among noncongenital cases of PAP, 89.9% of cases were autoimmune, 9.7% were secondary, and 0.4% were unclassified. In a meta-analysis of 1045 primarily adult PAP patients in five center-based series,[7] the mean age at diagnosis was similar in four of five series (range, 39–43 years) and slightly older in the Japanese series (mean age, 51 years). In all series, men prevailed over women, with a ratio ranging from 1.3:1 to 6:1. The interval between onset of symptoms and diagnosis was similar (range, 7–11 months). Of importance, 21–43% of PAP patients were never-smokers, indicating that PAP is not simply a smoking-related disease. A more recent study in the United States, using a medical insurance claims database to examine the records of 15 million patients, estimated the prevalence of PAP syndrome at 6.9 per million people.[110] It is likely these rates are all underestimated; indeed, a recent report from Japan using a Poisson distribution with the number of cases diagnosed annually estimated that the true incidence and prevalence of autoimmune PAP is roughly four times higher than previously estimated, at 1.7 and 26.6 per million, respectively.[111] In summary, PAP can present in men, women, and children of all ethnic backgrounds in all geographic locations and has an estimated overall prevalence of 7 to 20 per million in the general population.

Hereditary PAP is caused by various genetic mutations in *CSF2RA* or *CSF2RB* and usually presents in children between the ages of 1.5 and 11 years, although it has been reported to present in adults aged 29 to 35 years.[23–25,54,55]

*References 57–60, 66, 67, 69, 71, 74, 107, 108.

eTable 98.1 Comparison of Demographic and Epidemiology Data Among Five Large Series of PAP Patients

	Seymour[2] (*n* = 410)	Inoue[4] (*n* = 233)	Xu[5] (*n* = 241)	Bonella[6] (*n* = 70)	Campo[7] (*n* = 81)
Age at diagnosis (mean, range)	39 (30–46)	51 (41–58)	42 (N/A)	43 (18–78)	40 (26–54)
Ratio (male/female)	2.6	2.0	2.2	1.3	2.0
Primary PAP (%)	N/A	90	N/A	91	90
Secondary PAP (%)	N/A	10	N/A	9	3.7
Time to diagnosis (months)	7 (3–19)	10 (4–36)	N/A	9 (1–36)	11 (0–27)
Spontaneous remitters (%)	6	5	N/A	5	7
Smoking habits (%)					
Never	28	43	—	21	36
Previous	N/A	29	—	30	42
Current	N/A	29	—	49	22
Dust exposure (%)	N/A	26	N/A	54	32
Whole-lung lavage	54%	N/A	59%	90%	54%

N/A, not available; PAP, pulmonary alveolar proteinosis.

Secondary PAP accounts for no more than 10% of all PAP cases in adults[2,4,8,112] and develops as a consequence of an underlying disease (see Table 98.1) or environmental exposure (see Table 98.2). The prevalence of secondary PAP is estimated to be approximately 0.3 per 100,000 individuals in the general population. Historically, hematologic malignancy was the most common cause of secondary PAP, accounting for up to 5.3% of cases.[78] However, in a recent study, myelodysplastic syndrome accounted for 65% of cases.[112] Secondary PAP arises as a function of the underlying clinical disorder and, in some cases, can resolve with successful treatment of the underlying disorder.

PSMD disorders are found in individuals with mutations in the genes involved in surfactant synthesis, such as *SFTPB, SFTPC, ABCA3,* and *NKX2.1,* as discussed earlier. The incidence of SP-B deficiency is estimated to be approximately 1 per 1.5 million births. Among infants with respiratory distress syndrome of unknown etiology, mutations appear more commonly in *ABCA3* than in *SFTPB*.[58] The prevalence of the common disease-associated mutations in the *SFTPB* (121ins2), *SFTPC* (I73T), and *ABCA3* (E292V) genes are not well established. However, a recent study in ethnically diverse cohorts from Missouri, Norway, South Korea, and South Africa (n = 420) found the population-based frequencies of these mutations to be rare (<0.4%). However, E292V was present in 3.8% of newborns with respiratory distress syndrome, suggesting it imparts an increased genetic risk for this syndrome.[57]

CLINICAL PRESENTATION

PULMONARY ALVEOLAR PROTEINOSIS

Autoimmune PAP presents as progressive dyspnea of insidious onset unless secondary infection is also present, in which case fever, cough, and, rarely, hemoptysis may also be present. The frequency of various symptoms was recently evaluated in a large contemporaneous cohort in Japan (Table 98.4). This nonspecific presentation may lead to months or years of misdiagnosis as "asthma" or "chronic bronchitis." The symptoms are frequently milder than expected from the radiographic findings, which should raise the suspicion of PAP. The physical examination is nonspecific and is frequently normal despite a grossly abnormal chest radiograph but may include basilar crackles. Cyanosis is seen in severe cases; hemoptysis and fever are rare. Clubbing is not a feature of autoimmune PAP or hereditary PAP caused by *CSF2RA* or *B* mutations. In the Japanese national PAP registry cohort, 31% of patients with marked radiologic manifestations were asymptomatic.[4]

Table 98.4 Frequency of Symptoms Among Patients With Autoimmune PAP*

Symptom	Frequency (%)
Dyspnea	54
Cough	23
Sputum production	4
Other	4
None (asymptomatic)	31

*Data for a contemporaneous group composed of 220 patients.
PAP, pulmonary alveolar proteinosis.
From Inoue Y, Trapnell BC, Tazawa R, et al. Characteristics of a large cohort of autoimmune pulmonary alveolar proteinosis patients in Japan. *Am J Respir Crit Care Med.* 2008;177:752–762.

Hereditary PAP caused by mutations in GM-CSF receptor genes (*CSF2RA* or *CSF2RB*) usually presents as progressive dyspnea of an insidious nature, as in autoimmune PAP, but more commonly in children than in adults.[23–25,54,55] Thus, although this disease is newly described, ultrarare, and less well studied, it appears quite similar to autoimmune PAP, except that it is mostly a disease of children.

Secondary PAP usually arises in an individual with an underlying systemic disorder, such as a hematologic malignancy or disease.[77,78,80,106,113,114] It can develop in the context of neutropenia or myeloid-cell dysfunction related to the underlying disorder and can resolve with successful treatment of the underlying disorder.

PULMONARY SURFACTANT METABOLIC DYSFUNCTION

PSMD disorders can present as a spectrum of lung disease, ranging from respiratory distress syndrome in neonates and infants to interstitial lung disease in children, adolescents, and adults, depending on the exact nature of the underlying genetic mutations. SP-B deficiency typically presents as respiratory distress immediately after birth.[61,70,115] *ABCA3* mutations can result in fatal respiratory distress syndrome in neonates and interstitial lung disease in infants, children, and adolescents.[71,74,108,116] SP-C mutations can present as interstitial lung disease in children and adults.[60,66,68,117]

EVALUATION AND DIFFERENTIAL DIAGNOSIS

This section describes the evaluation of PAP disorders, which are better defined and reported compared to the PSMD disorders.

RADIOGRAPHIC APPEARANCE

The chest radiograph in autoimmune PAP and secondary PAP of hematologic origin typically reveals patchy bilateral air space disease similar in appearance to that of pulmonary edema but without the other radiographic signs of left heart failure[89,118] (Fig. 98.3 and eFig. 98.2). Other patterns can include mixed alveolar, interstitial, or nodular opacities and asymmetrical or focal abnormalities (eFig. 98.3). Adenopathy, cardiomegaly, and effusions are not features of PAP. The chest radiography findings in hereditary PAP are similar but may be normal early in the clinical course or in mild cases.[23] The diagnostic value of the plain chest radiograph is limited by its lack of specificity.

Conventional 7- to 10-mm collimation chest *computed tomography* (CT) scans demonstrate bilateral areas of consolidation with poorly defined margins (Fig. 98.4).[119,120] High-resolution chest CT is superior to both conventional CT and chest radiography in the assessment of the pattern and distribution of abnormalities and may demonstrate lesions even when the radiograph is normal. The distribution of disease is variable and may reflect heterogeneity of underlying disease-causing PAP (Fig. 98.4). Several features are noteworthy.

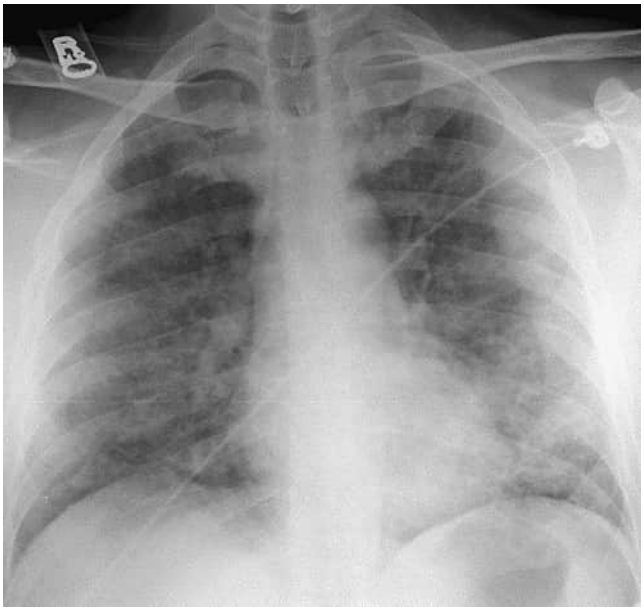

Figure 98.3 Pulmonary alveolar proteinosis: typical chest radiographic findings. Frontal chest radiograph shows multifocal, bilateral, poorly defined, somewhat linear-appearing opacities suggesting a diffuse interstitial lung process. (Courtesy Michael B. Gotway, MD.)

Areas of ground-glass opacification often have sharply defined straight and angulated margins, giving them a "geographic" appearance (Fig. 98.4 and eFig. 98.4). The sharp margination usually reflects lobular or lobar boundaries. A pattern of fine overlapping lines forming 3- to 10-mm polygonal shapes is seen in the majority of cases. Superimposition of these two patterns gives an appearance that has been described as "crazy paving," which is characteristic but not diagnostic of PAP (eFig 98.5).[121] Of note, crazy paving also happens in hypersensitivity pneumonitis, *Pneumocystis jirovecii* pneumonia, minimally invasive adenocarcinoma/lepidic invasive adenocarcinoma (formerly bronchioloalveolar carcinoma), lymphangitic carcinomatosis, cardiogenic pulmonary edema/acute lung injury, and lipoid pneumonia (eFig 98.6). One study reported that, among patients with PAP, a geographic appearance with crazy paving is more commonly seen in autoimmune than secondary PAP.[122]

Findings on the chest radiograph and high-resolution chest CT correlate with a restrictive ventilatory defect, reduced *diffusing capacity for carbon monoxide* (DL_{CO}), and hypoxemia.[120] An algorithm for quantitative assessment of longitudinal changes in ground-glass opacification, lung weight, and gas volume in patients with PAP has been reported.[123]

PULMONARY FUNCTION TESTING

The results of pulmonary function testing may be normal or, in more advanced disease, may show a restrictive ventilatory defect with mild impairment of the forced vital capacity and total lung capacity. There may be a disproportionate, severe reduction of the DL_{CO}.[2,4] Arterial blood gases show mild to severe hypoxemia; an increased *alveolar-arterial* Po_2 *difference* [(A–a)Po_2]; compensated respiratory alkalosis, depending on the degree of disease progression; and absence of hypercarbia. The shunt fraction is elevated compared to patients with other diffuse lung diseases.[124]

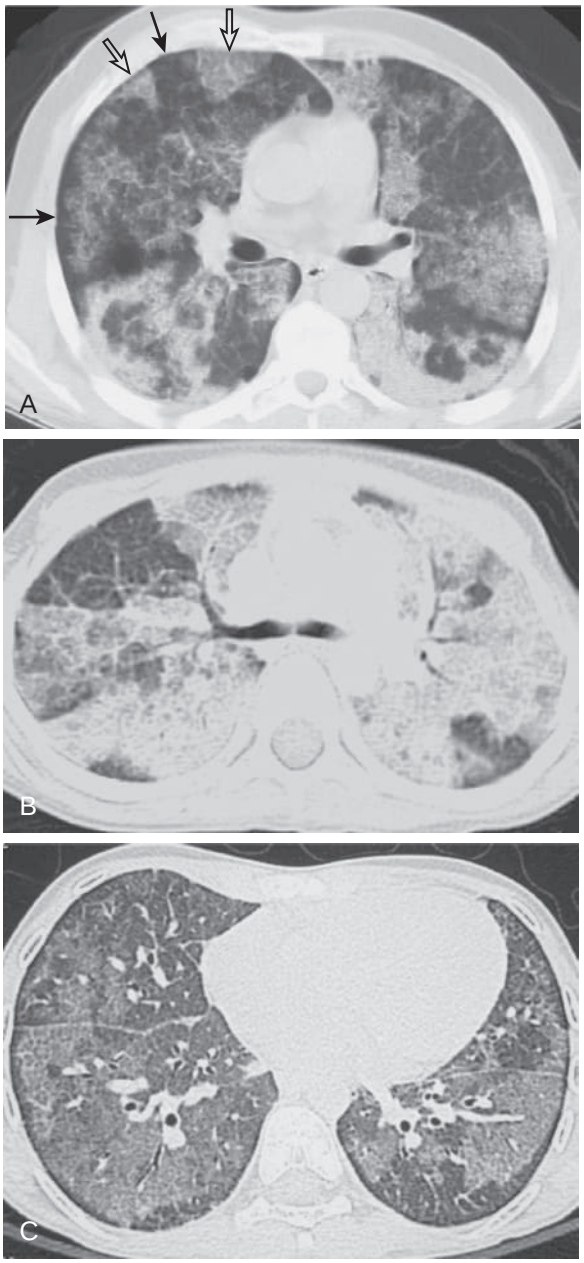

Figure 98.4 Computed tomography of the lungs in *pulmonary alveolar proteinosis* (PAP). Computed tomography of the chest illustrating differences in the radiographic appearance of the lungs in autoimmune PAP (A), hereditary PAP due to granulocyte-macrophage colony-stimulating factor receptor (α chain) dysfunction (B), and secondary PAP in a child with lysinuric protein intolerance (C). Note the juxtaposition of highly abnormal secondary lobules (*open arrows*), adjacent to more normal-appearing secondary lobules (*solid arrows*). This is referred to as a "geographic" pattern and is common in autoimmune PAP and is also present in hereditary PAP. More homogeneous and less geographic opacities are more common in secondary PAP (C).

Six-minute walk testing typically reveals early desaturation and, depending on disease severity, a reduction in the baseline saturation of peripheral oxygen (Spo_2).

BRONCHOSCOPY, BRONCHOALVEOLAR LAVAGE

Bronchoscopy is performed to obtain specimens to rule out infection and to identify the characteristic alveolar material



Figure 98.5 Whole-lung lavage. Gross appearance of the whole-lung lavage fluid from a patient with autoimmune pulmonary alveolar proteinosis demonstrating the milky appearance and dense sediment (*right*) compared to normal saline (*left*). The lavage fluid was allowed to settle overnight in a refrigerator.

of PAP. The BAL specimens reveal characteristic gross, cytopathologic, and biochemical findings highly suggestive or diagnostic of PAP. In autoimmune, hereditary, and secondary PAP (but not PSMD), the BAL fluid has a milky or waxy appearance, and sediment forms upon standing (Fig. 98.5). Cytologic examination of periodic acid–Schiff–Papanicolaou-stained specimens of BAL fluid and sediment reveals granular, acellular, lipoproteinaceous material,[125] cells, and fat globules. Strikingly, cytospin preparations reveal alveolar macrophages engorged with intracytoplasmic lipid droplets imparting a foamy appearance by light microscopy (Fig. 98.6). Electron microscopic examination of the sediment reveals the presence of tubular myelin, lamellar bodies, and fused membrane structures characteristic of pulmonary surfactant. The BAL cell differential in autoimmune PAP may be normal or reveal the presence of increased pulmonary lymphocytes composed of increased numbers of $CD4^+$ and $CD8^+$ cells.[126]

Biochemical analysis of BAL fluid reveals increased amounts of phospholipids and proteins, similar in composition to that of surfactant from healthy individuals,[127] except for an increase in the relative proportion of cholesterol.[127a] Surfactant proteins are variably increased in the BAL fluid in PAP.

LUNG BIOPSY

Macroscopically, the cut surface of lung biopsy specimens in autoimmune and hereditary PAP reveals a geographic pattern of 2 to 3 cm grayish-yellow regions of firm consolidation that exudes fatty material (eFig. 98.7). Microscopically, alveoli and terminal airways are filled with a fine eosinophilic material that stains strongly for surfactant proteins with periodic acid–Schiff reagent (see Fig. 98.6). The alveolar wall and interstitial architecture are relatively well preserved, but lymphocyte infiltration and, occasionally, fibrosis can be seen. The vasculature appears normal. Electron microscopy, which is seldom necessary, reveals characteristic, concentrically laminated surfactant structures (lamellar body inclusions) within the granular material and in alveolar macrophages.[128] Of importance, although a lung biopsy can establish the presence of PAP syndrome, it cannot identify the disease responsible, such as autoimmune or hereditary PAP (see Fig. 98.6E–F, respectively), which has important implications for newer therapies. However, it should be noted that biopsy can have a significant false-negative rate due to the patchy distribution of disease and can fail to identify the histopathologic changes of PAP syndrome.[129]

LABORATORY STUDIES

Routine laboratory studies are usually normal in PAP. Serum lactate dehydrogenase is typically elevated in proportion to lung disease severity, although this finding is nonspecific.[2,124] Serum levels of SP-A, SP-B, SP-D, C-reactive protein, and *Krebs von den Lungen protein-6* (KL-6), a mucin-like protein secreted by alveolar epithelium, are increased in PAP and correlate with lung disease severity.[4,46,130] However, these biomarkers can be elevated in other lung diseases.[131,132] Thus, although not useful in diagnosis, these biomarkers may be useful in monitoring disease activity in patients with PAP. For example, KL-6 has been reported to outperform *arterial partial pressure of oxygen* (Pa_{O_2}) and lactate dehydrogenase in predicting disease progression and need for therapy in autoimmune PAP.[133]

Several biomarker-based tests are effective for disease-specific PAP diagnosis. The most well established is the serum-based GM-CSF autoantibody *enzyme-linked immunosorbent assay* (ELISA) test.[1,45,52,134–136] Although serum GM-CSF autoantibodies are present at low levels in healthy people,[47] a high serum level is diagnostic of autoimmune PAP. In a validation study (MICEPAP) conducted in the United States, Germany, Italy, and Japan, both the sensitivity and specificity of an improved assay were found to be 100%.[136,137] Furthermore, an international monoclonal GM-CSF autoantibody reference standard was developed to help standardize test results from the few laboratories that currently perform the test. Measurement of GM-CSF signaling in whole blood is useful for confirming the functionality of GM-CSF autoantibodies for levels close to the diagnostic threshold and can be done by measuring the ability of exogenous GM-CSF to bind GM-CSF receptors on leukocytes and stimulate an increase in cell surface CD11b (the *CD11b stimulation index test* [CD11b-SI])[52] or an increase in STAT5 phosphorylation (the *STAT5-phosphorylation index* [STAT5-PI] test).[51] Both assays give similar results—a robust increase in healthy people and no change in autoimmune PAP. Measurement of the concentration of GM-CSF (not of the autoantibodies) in serum by ELISA is a useful screening test to identify patients with hereditary PAP because, in these patients, GM-CSF signaling is disrupted not by GM-CSF autoantibodies but by GM-CSF receptor dysfunction.[23,138] Receptor dysfunction results in the accumulation of GM-CSF due to reduced clearance. Various molecular and genetic tests are available to determine the specific abnormality in hereditary PAP and PSMD.[24,25]

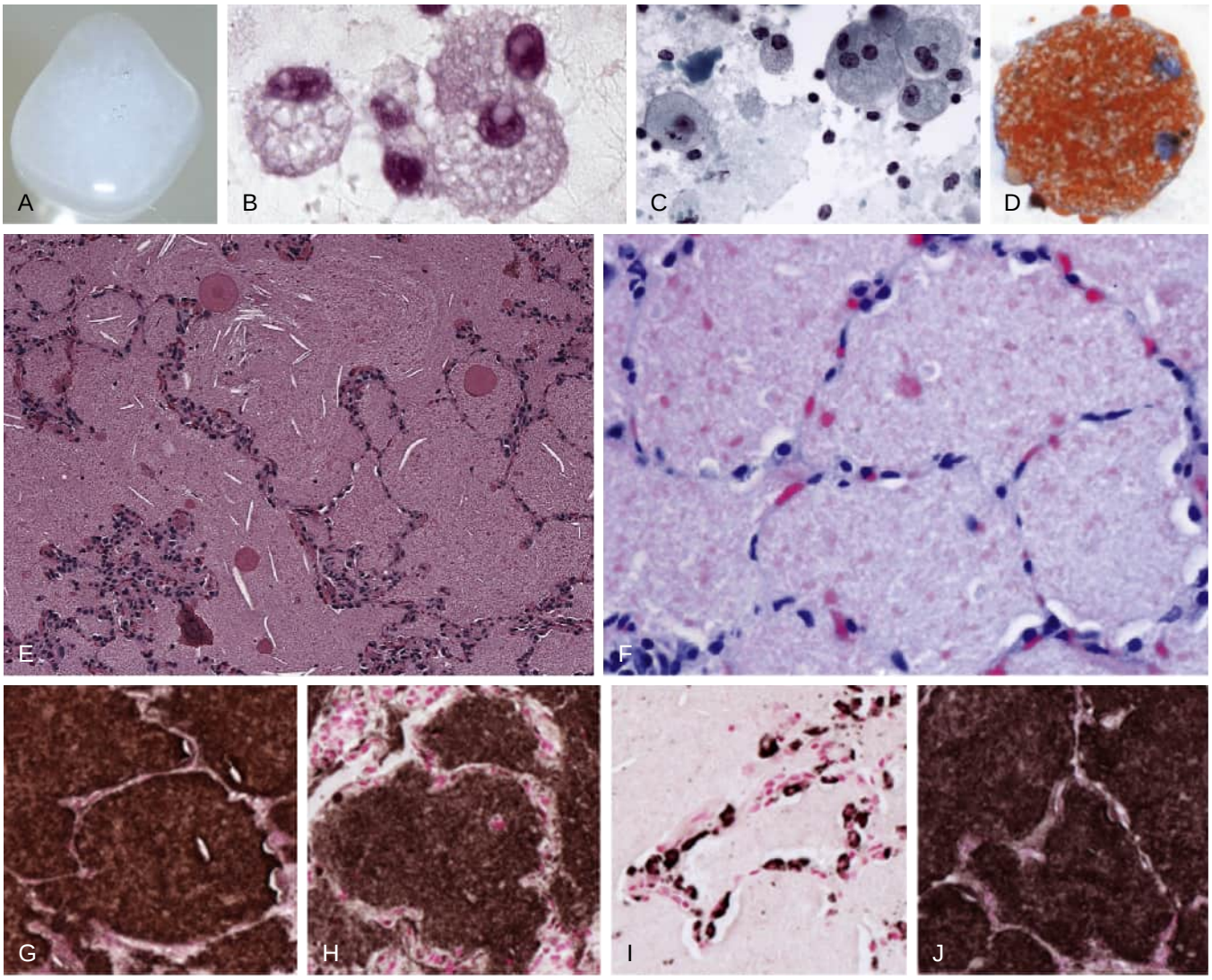

Figure 98.6 Appearance of the sputum, sputum cytology, and lung histopathology in *pulmonary alveolar proteinosis* (PAP) due to disruption of granulocyte-macrophage colony-stimulating factor signaling. (A) Gross appearance of freshly expectorated sputum from a patient with uncomplicated autoimmune PAP. (B) Sputum smear after staining with periodic acid–Schiff reagent. (C) Sputum smear after staining with Papanicolaou reagent. Note the appearance of large, foamy-appearing alveolar macrophages (B–C). (D) Alveolar macrophage stained with oil red-O. (E) Histopathologic appearance of an open-lung biopsy in autoimmune PAP after periodic acid–Schiff staining. Alveoli are filled with amorphous, acellular eosinophilic material as well as cholesterol clefts and eosinophilic bodies. Alveolar wall architecture is well preserved. (F–J) Histopathologic appearance of an open-lung biopsy in hereditary PAP caused by *CSF2RA* gene mutations after staining with hematoxylin and eosin (F), or immunostaining for SP-A (G), mature SP-B (H), pro–SP-C (I), or SP-D (J). (F–I, From Suzuki T, Sakagami T, Rubin BK, et al. Familial pulmonary alveolar proteinosis caused by mutations in *CSF2RA*. *J Exp Med.* 2008;205:2703–2710.)

APPROACH TO DIAGNOSIS

Timely diagnosis of PAP requires a high degree of clinical suspicion and should be suspected in patients with dyspnea of insidious onset and typical chest CT findings. In previously healthy adults with these findings, an abnormal serum GM-CSF autoantibody test is usually sufficient to establish the diagnosis of autoimmune PAP.[137] An abnormal STAT5-PI (or CD11b-SI) test confirms the diagnosis. Pulmonary function testing may be helpful if the disease is moderate or severe but is normal (except for D_{LCO}) in many patients.[4] Although surgical or transbronchial lung biopsy or BAL cytology can establish the presence of a PAP syndrome, none can identify the underlying disease.[106,139] An open-lung biopsy is usually not necessary. However, if the diagnosis is still unclear or if secondary PAP is suspected, a lung biopsy may help rule out disorders that have radiologic, cytologic, or pathologic features similar to PAP.

In younger patients in whom PAP is suspected, the presentation can be helpful. Autoimmune PAP has presented in children as young as 3 years and can readily be diagnosed by blood test without the need for a lung biopsy. Hereditary PAP can often present in children between the ages of 1.5 and 11 years but can present as late as 35 years. In hereditary PAP, the serum GM-CSF autoantibody test is normal, and the STAT5-PI (CD11b-SI) and serum GM-CSF test results are abnormal.[23–25] These blood-based tests are useful in evaluating young patients and should be used to minimize the use of more invasive procedures. PSMD disorders more commonly present in young patients: SP-B deficiency presents as respiratory failure at birth; ABCA3

dysfunction can present similarly or as interstitial lung disease in infants, children, and adolescents; and SP-C dysfunction presents as interstitial lung disease in children and adults.

The diagnostic workup of individuals with disorders of surfactant homeostasis, including PAP and PSMD disorders, consists of routine clinical evaluations, a series of biomarker evaluations, and genetic tests capable of distinguishing among autoimmune PAP, secondary PAP, hereditary PAP caused by receptor dysfunction, and PSMD disorders (Fig. 98.7).

NATURAL HISTORY

No longitudinal studies of the clinical course of PAP have been reported. However, cross-sectional evaluations of PAP cohorts in Japan, China, Germany, and Italy have been reported (see eTable 98.1).[4–7] In Seymour and Presneill's comprehensive meta-analysis of PAP, the actuarial survival rates for 343 patients with "acquired," probably autoimmune, PAP were 78% ± 8% at 2 years, 75% ± 8% at 5 years, and 68% ± 9% at 10 years. More than 80% of the deaths attributable to PAP during a 5-year observation period took place during the first 12 months after diagnosis. This study reported that, of the 69 deaths, death was caused by respiratory failure from PAP in 47 patients (72%), uncontrolled infection in 13 (20%), and unrelated causes in 5 cases (8%). In a contemporaneous cross-sectional cohort study of 223 autoimmune PAP patients in Japan, no deaths were recorded over the 5-year period of the study.[4] Autoimmune PAP follows one of three patterns: progressive deterioration, stable disease, or spontaneous resolution.[2] A recent study of 40 individuals with secondary PAP diagnosed premortem reported a median survival of less than 20 months from diagnosis, a prognosis far worse than for those with autoimmune PAP.[112]

SECONDARY INFECTIONS

Multiple reports document increased infections in PAP by microbial pathogens ranging from community- and hospital-acquired organisms to *Nocardia* spp. (eFig 98.8), mycobacteria (eFig 98.9), or opportunistic organisms.[2,52] GM-CSF–deficient mice also have increased mortality from infection and increased susceptibility to a wide variety of microbial pathogens, including bacteria, fungi, and mycobacteria. Further, myeloid cells from both patients with autoimmune PAP and GM-CSF–deficient mice have defects in innate immune functions, including phagocytosis, generation of reactive oxygen species, inflammatory signaling, and bacterial killing.[20,47,52,134,140] The finding of infections at extrathoracic locations in PAP patients and GM-CSF–deficient mice is consistent with a

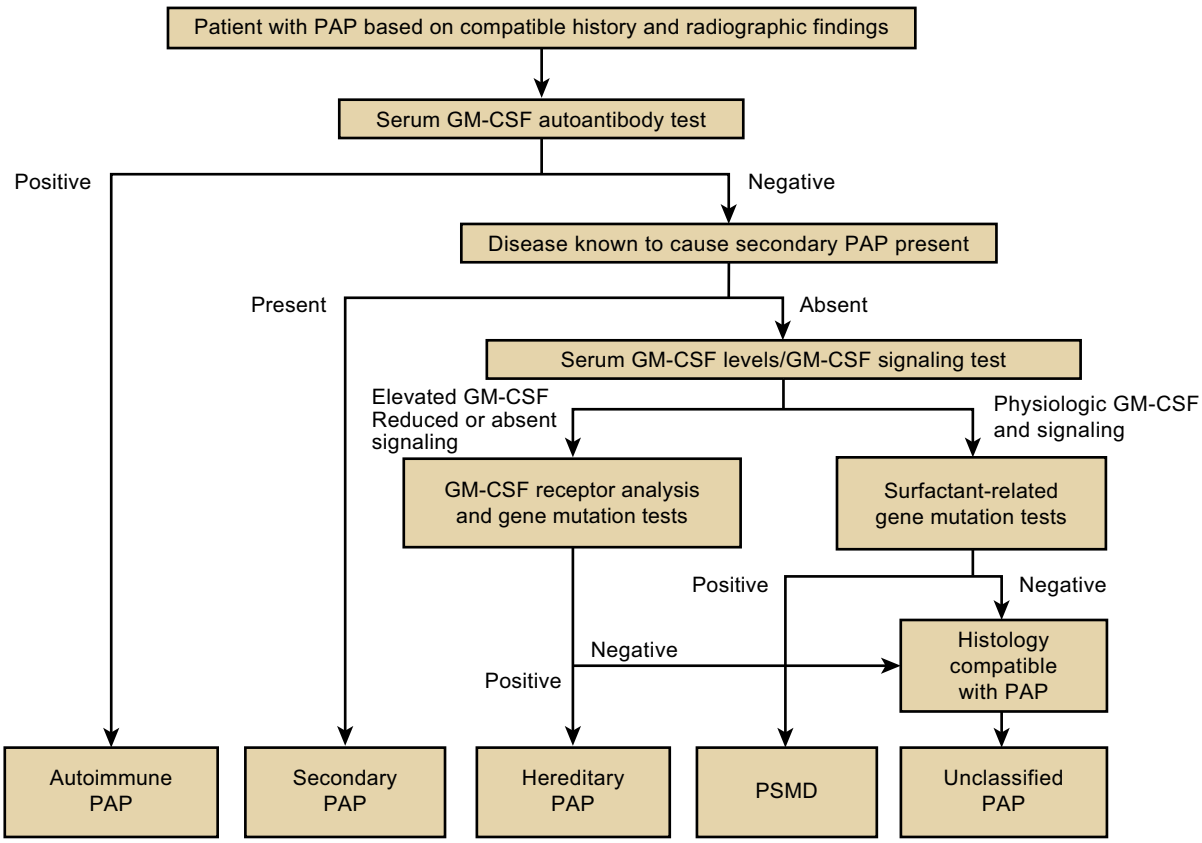

Figure 98.7 Diagnostic algorithm for evaluation for individuals with *pulmonary alveolar proteinosis* (PAP) syndrome. In hereditary PAP caused by mutations in *granulocyte-macrophage colony-stimulating factor* (GM-CSF) receptor genes *CSF2RA* or *CSF2RB,* further GM-CSF receptor function tests are needed to confirm and identify the specific nature of the defect. See text for details. PSMD, pulmonary surfactant metabolic dysfunction. (Modified from Trapnell BC, Nakata K, Bonella F, et al. Pulmonary alveolar proteinosis. *Nat Rev Dis Primers*. 2019;5:16.)

systemic immune defect caused by disruption of GM-CSF signaling.

PULMONARY FIBROSIS

Pulmonary fibrosis has been reported in association with PAP and has been reproduced in animal models of exposure to inhaled silica.[32,128] Further, exposure to oxygen or repeated *whole-lung lavage* (WLL) have been suggested as potentially contributing to fibrosis. However, although not adequately studied, "end-stage lung disease" or irreversible scarring of the lung is not commonly associated with PAP.

SPONTANEOUS RESOLUTION

Spontaneous improvement of PAP was noted in Rosen's initial report,[89] in subsequent case series, and in Seymour's comprehensive meta-analysis of 303 patients, where it was observed in 7.9% of patients (eFig 98.10). Recent cohorts in Japan, China, Germany, and Italy confirmed this value with estimates for spontaneous resolution ranging from 5–7% among 735 additional PAP patients (see eTable 98.1).[4–7]

TREATMENT

AUTOIMMUNE PULMONARY ALVEOLAR PROTEINOSIS

Whole-Lung Lavage

Originally developed by Ramirez in the early 1960s, WLL is a procedure performed under general anesthesia in which large volumes (up to 50 L) of saline are infused into each lung to "wash out" the accumulated surfactant lipids and proteins, while the other lung is mechanically ventilated.[141–143] A number of procedural variations have been tested (although none systematically), including the use of mechanical chest percussion, prone positioning, variation in the volume of infusate, and use of a hyperbaric chamber. Despite changes, WLL has not been standardized with respect to the method (i.e., volume infused, use of mechanical percussion, or the endpoint of an individual lavage procedure), indications for its use, methods for evaluating the treatment effectiveness, or timing of repeated procedures. The endpoint used clinically for terminating lung lavage in the operating room is an improvement in visual clearing of the lavage effluent. No studies have systematically evaluated the procedure, its use in clinical practice, or the efficacy or durability of clinical responses. Notwithstanding, WLL is widely held among practitioners to improve symptoms, radiographic findings, and gas exchange in PAP patients.[144,145]

Although WLL is safe in the vast majority of individuals, complications can include hypoxemia, pneumonia, sepsis, hydropneumothorax, acute respiratory distress syndrome, and pneumomediastinum (eFig. 98.11). The procedure should not be performed in a patient with an active bacterial lung infection because this can result in sepsis and shock. Bronchoscopic segmental or lobar lavage has been proposed as a safe alternative in patients in whom WLL under general anesthesia is considered risky due to severe hypoxemia.[146] Other alternatives include performance in a hyperbaric chamber[147] and use of complete cardiopulmonary bypass.[148]

A comprehensive literature review identified 231 individuals for whom sufficient WLL data were available and reported that lavage was associated with increased overall 5-year survival (94 ± 2% with lavage [n = 146] vs. 85 ± 5% without lavage [n = 85]; P = 0.04).[2] This study also reported that the median number of WLL procedures performed was two and that 70% of patients underwent the procedure within 5 years of diagnosis. Among 55 individuals undergoing the procedure, the median duration of benefit was 15 months, and only 20% of patients remained stable at 3 years. Among 41 patients with adequate available data, arterial Pao_2 improved by 20.1 mm Hg after WLL (see eTable 98.2). The improvement in other pulmonary function test parameters was less impressive. More than 95% of patients respond to WLL; however, a small fraction of patients did not respond despite aggressive lavage. Treatment-related improvement results from the physical removal of the accumulated surfactant can happen within hours of completion of therapy.

In practice, the indications for WLL therapy include dyspnea, exercise intolerance, and a desire to reduce the requirement for supplemental oxygen therapy. Reasonable indications for performing the procedure may include dyspnea-limiting activities of daily living, arterial Pao_2 less than 60 mm Hg while breathing room air, significant desaturation (>5%) on exercise,[7] and a shunt fraction greater than 10–12%.

Granulocyte-Macrophage Colony-Stimulating Factor

Subcutaneous recombinant GM-CSF therapy of PAP was first attempted in a single patient in 1995.[149] A follow-up open-label study of subcutaneous GM-CSF administered in escalating doses (5–20 μg/kg/day) to 14 autoimmune PAP patients over a 3-month period reported a therapeutic response rate of 43%.[150] In another open-label study, subcutaneous GM-CSF administered in escalating doses (5–18 μg/kg/day) to 21 autoimmune PAP patients over a 6- to 12-month period reported an overall response rate of 48%.[151] In these studies, a positive response was defined by a 10 mm Hg improvement in $(A–a)Po_2$ measured on room air. Several other case studies and small series reported similar findings. Together, results of these studies indicate that (1) daily subcutaneous GM-CSF therapy of autoimmune PAP improves the lung disease in approximately 50% of patients, (2) the therapeutic benefit varies among patients and is dependent on the dose and duration of administration, and (3) there may be a delay of at least 8 weeks before a therapeutic response is observed.

Inhaled aerosolized GM-CSF therapy of autoimmune PAP was first demonstrated in three patients in 2005.[152] In a retrospective unblinded evaluation in 12 patients receiving doses of inhaled GM-CSF, ranging from 125 to 500 μg per patient per day, all patients were found to have a positive response.[153] In a subsequent open-label study involving 50 patients, 39 patients with unremitting or progressive lung disease during a 3-month observation period received inhaled GM-CSF at a relatively higher dose during an induction period, and subsequently 35 of these patients received a relatively lower dose during a subsequent maintenance period.[154] The overall response rate was 62% based on intention-to-treat analysis, and no treatment emergent or drug-related adverse events were noted. A randomized, double-blinded study of inhaled GM-CSF therapy was conducted in 64 patients with mild to moderate autoimmune PAP (Pao_2 < 75 mm Hg but > 50

eTable 98.2 Therapeutic Response to Whole-Lung Lavage Therapy of Adults With PAP

Parameter	*N*	Mean Change ± SD	95% CI of the Mean	*P* Value*
Arterial Po_2 (mm Hg)	41	20.1 ± 14.3	15.6 to 24.6	<0.0001
(A–a)Po_2 (mm Hg)	21	−30.6 ± 18.0	−38.8 to −22.4	<0.0001
FEV_1 (L)	33	0.26 ± 0.47	0.09 to 0.42	<0.0034
VC (L)	40	0.50 ± 0.54	0.33 to 0.67	<0.0001
DL_{co} (mL/mm Hg/min)	25	4.4 ± 4.5	2.6 to 6.3	<0.0001

*Value is for the comparison of paired postlavage to prelavage data for individual patients for each parameter for only those patients with available data, using a two-sample *t*-test.

(A–a)Po_2, alveolar-arterial Po_2 difference; CI, confidence interval; DL_{CO}, diffusing capacity of carbon monoxide; FEV_1, forced expiratory volume in 1 second; PAP, pulmonary alveolar proteinosis; Po_2, partial pressure of oxygen; SD, standard deviation; VC, vital capacity.

From Seymour JF, Presneill JJ. Pulmonary alveolar proteinosis: progress in the first 44 years. *Am J Respir Crit Care Med*. 2002;166:215–235.

mm Hg), who received either sargramostim (recombinant human GM-CSF produced in yeast; 125 μg twice daily for 7 days on alternating weeks) or placebo for a total of 24 weeks. Compared to placebo, inhaled GM-CSF therapy had a significantly greater reduction in $(A–a)Po_2$ (0.2 ± 10.5 vs. −4.5 ± 9.0 mm Hg; $P = 0.02$) and a reduction in lung densitometry in the chest CT, which reflects the degree of abnormal surfactant accumulation, but clinical benefit was not demonstrated.[155] A global phase III randomized, double-blind, placebo-controlled study of inhaled GM-CSF therapy in autoimmune PAP (IMPALA trial) was recently conducted in 138 patients, who received either molgramostim (recombinant human GM-CSF produced in *Escherichia coli*) 300 μg daily (continuous group) or daily on alternating weeks (intermittent group) or placebo for 24 weeks.[156] Daily administration of inhaled molgramostim resulted in greater improvements in pulmonary gas transfer and functional health status than placebo and was more beneficial when given daily than when administered on alternating weeks.[157]

Combined WLL and inhaled GM-CSF therapy of autoimmune PAP has been evaluated in an 18-patient, open-label study in Italy. A preliminary report indicated patients receiving WLL, followed by inhaled GM-CSF (sargramostim, 250 μg daily every other week), had a greater improvement in D_{LCO} percent predicted, forced vital capacity, total lung capacity, and $(A–a)Po_2$ compared to patients receiving WLL alone.[158] In this study, GM-CSF also resulted in a reduction in the requirement for further WLL therapy.

Together, results from a number of open-labeled and randomized, blinded, controlled trials indicate that GM-CSF is effective as therapy of autoimmune PAP, inhaled delivery is more effective than subcutaneous delivery, and no important safety concerns have been identified. Notwithstanding, neither the optimal dose nor time required to achieve a maximal treatment benefit has yet been identified.

Targeting GM-CSF Autoantibodies

Other therapeutic strategies aimed at reducing the level of GM-CSF autoantibodies have been tried, including plasmapheresis and B lymphocyte depletion. One small study of a single cycle of rituximab therapy in 10 patients gave promising results,[159] with seven of nine patients demonstrating a slight improvement in $(A–a)Po_2$. However, this improvement was minimal after 6 months of follow-up. A retrospective report of 13 patients showed no improvement 6 months after treatment.[160] Although these strategies are theoretically attractive, their lack of definitive efficacy may reflect the lack of correlation between circulating GM-CSF autoantibody levels and disease severity.[46]

Targeting Cholesterol Homeostasis

The revelation of the pathogenic role of cholesterol clearance in determining surfactant clearance by alveolar macrophage has unlocked several therapeutic possibilities and the consideration of small molecules to target this pathway. In mouse models of PAP, the use of a PPAR-γ agonist (pioglitazone) was demonstrated to improve PAP lung disease,[102] resulting in a phase I/II trial of pioglitazone in autoimmune PAP (ClinicalTrials.gov identifier: NCT03231033). Furthermore, statins (3-hydroxy-3-methylglutaryl coenzyme A reductase inhibitors) have been shown to increase alveolar macrophage cholesterol homeostasis, resulting in improved lung disease in mouse models of PAP.[103] Although not established, statin-induced reduction in intracellular cholesterol accumulation leads to improved surfactant uptake and clearance by alveolar macrophages. Indeed, a case series of autoimmune PAP patients treated with statins demonstrated resolution of PAP lung disease with improvements in lung function, oxygenation, and radiologic findings.[103] These studies support the possibility of targeting cholesterol homeostasis as a novel pathogenesis-based therapeutic approach for autoimmune PAP and possibly other types of PAP syndrome. Carefully designed trials are required to investigate these potential strategies.

HEREDITARY PULMONARY ALVEOLAR PROTEINOSIS

WLL is the standard therapy for hereditary PAP caused by *CSF2RA* or *CSF2RB* mutations.[23,24] Bone marrow transplantation has been tried without success in one child.[55] Gene correction and pulmonary macrophage transplantation have shown promising results in mouse models of hereditary PAP.[21,161] Studies in mice have demonstrated that a single administration of wild-type or *Csf2ra*- or *Csf2rb*-gene–corrected macrophages results in nearly complete resolution of the lung disease, normalizes disease-specific biomarkers for more than 1 year, and increases the life span of the treated mice. Results also show that transplanted macrophages have a marked survival advantage over endogenous alveolar macrophages and replace them over the course of several months after transplantation, reaching wild-type levels at 1 year. Of interest, after pulmonary macrophage transplantation, transplanted macrophages remain in the lungs permanently. Furthermore, it is possible to correct the relevant genes in macrophages from patient-derived induced pluripotent stem cells,[161,162] allowing the possibility of translating this approach into human clinical trials in hereditary PAP.

SECONDARY PAP

Secondary PAP, in most cases caused by hematologic disorders, can resolve with resolution of the underlying disorder. There have been several case reports of effective resolution after stem-cell, cord-blood, and bone marrow transplantation.[163] Secondary PAP caused by a reduction in the number or functional capacity of alveolar macrophages can be treated with WLL; however, those associated with fibrosis (i.e., silicoproteinosis) are less responsive to this therapy.

SURFACTANT METABOLIC DYSFUNCTION DISORDERS

Therapy of these disorders depends on the disease and presentation; care is generally supportive and includes assessment of need for supplemental oxygen and nutritional support. In very young children, WLL is extremely challenging and of uncertain efficacy, and an adapted technical approach to airway management is required during lavage.[164] Neonates may show transient improvement with exogenous surfactant administration. Lung transplantation is particularly considered in cases of SP-B deficiency and in severe and progressive disease from *ABCA3* mutations.

Key Points

- *Pulmonary alveolar proteinosis* (PAP) syndrome presents in a group of clinically and mechanistically heterogeneous diseases and is characterized by surfactant accumulation in alveolar macrophages and alveoli due either to impaired surfactant clearance by alveolar macrophages or to abnormal surfactant production.
- The molecular pathogenesis is now known in most cases: Mechanisms include disruption of *granulocyte-macrophage colony-stimulating factor* (GM-CSF) signaling by GM-CSF autoantibodies (autoimmune PAP, ≈85% of cases) or GM-CSF receptor mutations (hereditary PAP, ≈5% of cases), a disease reducing alveolar macrophage numbers or functions (secondary PAP, ≈5% of cases), and mutations resulting in abnormal surfactant production (pulmonary surfactant metabolism dysfunction, ≈5% of cases).
- PAP can present in men, women, and children; of all ethnic backgrounds; in all geographic locations; and has an estimated overall prevalence of 7 to 20 per million in the general population.
- The clinical presentation is typically progressive dyspnea of insidious onset with or without cough. If infection is also present, depending on its nature, location, and severity, there may also be symptoms of fever, diaphoresis, or hemoptysis.
- The presence of relatively mild symptoms in the setting of abnormal chest imaging should raise the suspicion of a PAP syndrome.
- The natural history depends on which PAP-causing disease is present. In autoimmune PAP, the clinical course varies and includes respiratory failure and death in a small fraction, slowly progressive/stable disease in most and spontaneous improvement in 6–8% of patients.
- Characteristic (but nondiagnostic) chest computed tomography findings and transbronchial or surgical lung biopsy results can be used to diagnose PAP syndrome but cannot identify the underlying disease causing it. However, new blood tests (GM-CSF autoantibody levels, STAT5-phosphorylation index test, GM-CSF serum levels, and others) currently available as clinical research tests can identify the underlying disease in greater than 95% of cases, reducing the need for lung biopsy.
- Whole-lung lavage is the current standard therapy for autoimmune PAP, hereditary PAP, some (myelodysplasia) but not all (silica-induced) forms of secondary PAP and is usually not useful in pulmonary surfactant metabolic disorders.
- Inhaled GM-CSF and cholesterol-targeted therapy are promising experimental approaches under active study. Other potential therapies include pulmonary macrophage transplantation, bone marrow transplantation, and stem-cell transplantation (for hereditary PAP). Lung transplantation is a therapeutic option for multiple PAP-causing diseases when clinically indicated (usually by extensive fibrosis).

Key Readings

Bonella F, Bauer PC, Griese M, Ohshimo S, Guzman J, Costabel U. Pulmonary alveolar proteinosis: new insights from a single-center cohort of 70 patients. *Respir Med*. 2011;105:1908–1916.

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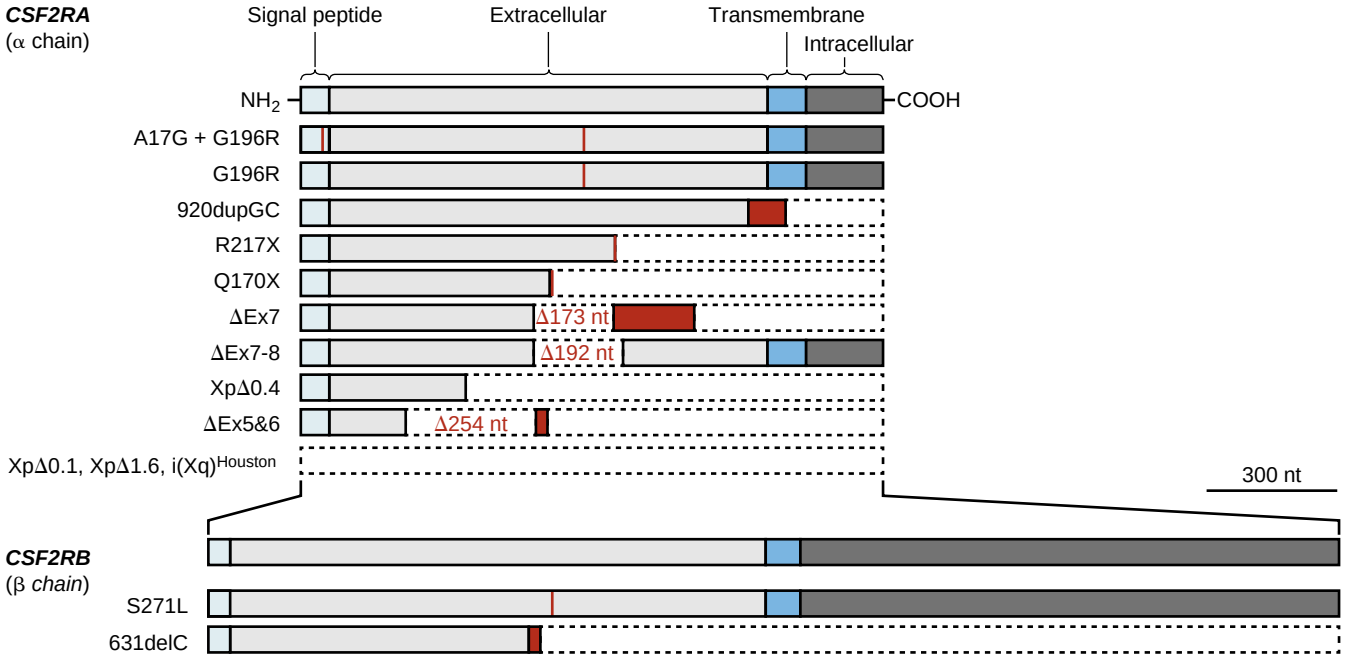
Complete reference list available at ExpertConsult.com.

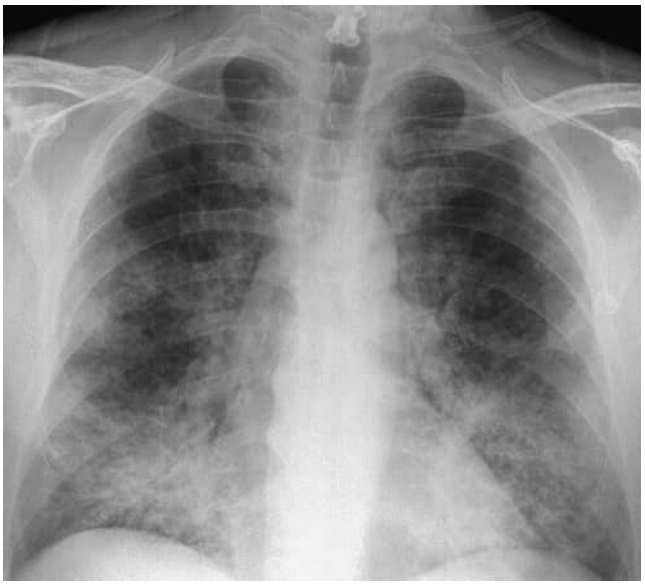
eFIGURE IMAGE GALLERY



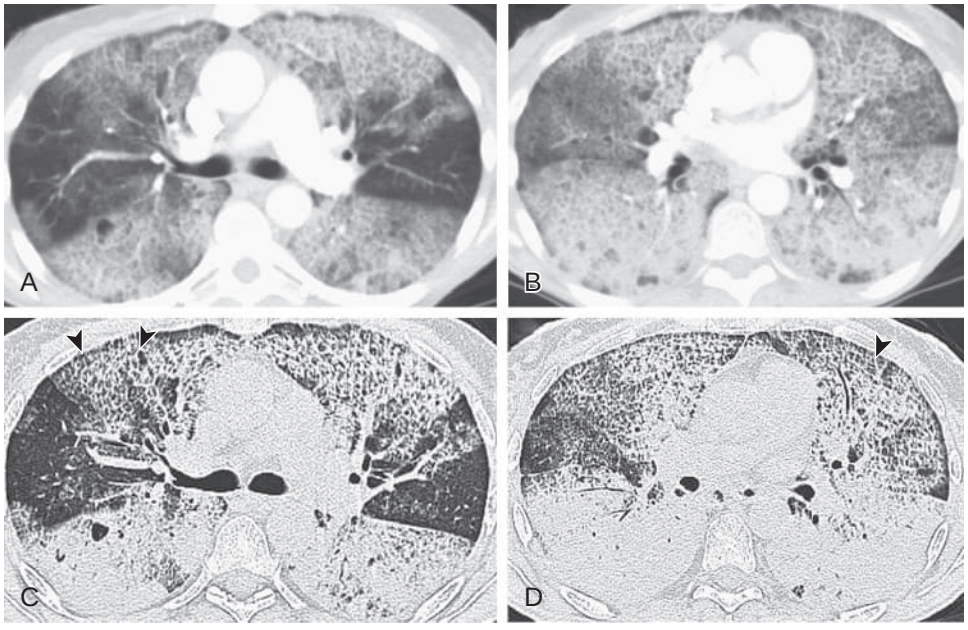
eFigure 98.1 Genetic mutations in *CSF2RA* and *CSR2RB* and corresponding granulocyte-macrophage colony-stimulating factor receptor α and β chain abnormalities associated with the development of hereditary pulmonary alveolar proteinosis. For each gene, a schematic of the normal protein is shown above to indicate regions corresponding to the signal peptide, extracellular domain, transmembane-spanning domain, and intracellular domain. Shown below each normal protein are the abnormal proteins caused by genetic mutations (indicated) known to cause hereditary pulmonary alveolar proteinosis. nt, nucleotides. (Data from Suzuki T, Sakagami T, Young LR, et al. Hereditary pulmonary alveolar proteinosis: pathogenesis, presentation, diagnosis, and therapy. *Am J Resp Crit Care Med.* 2010;182:1292–1304.)



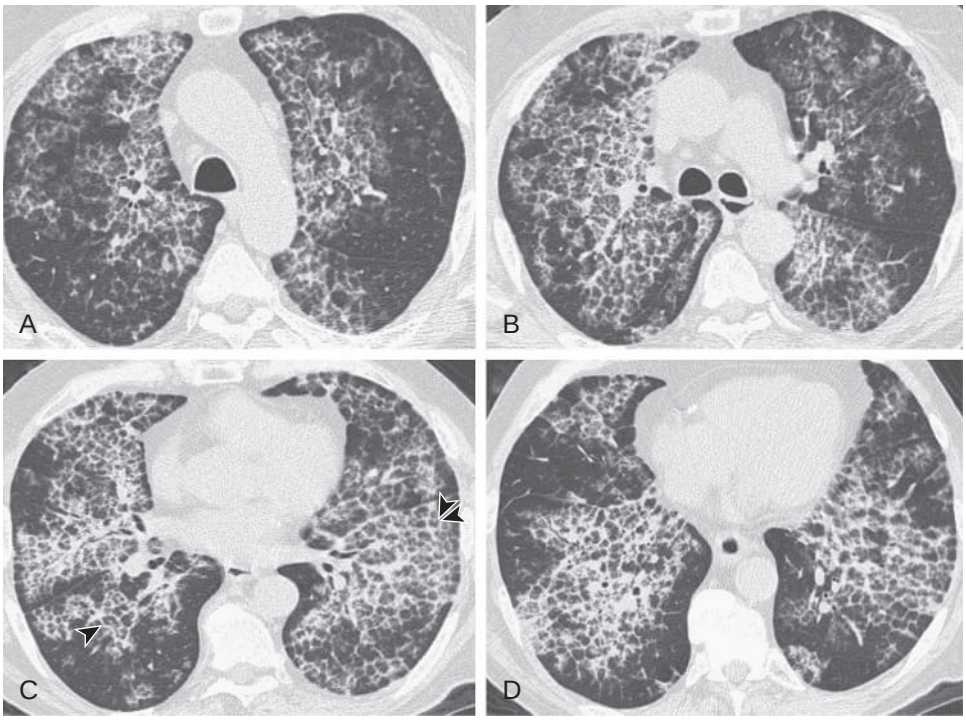
eFigure 98.2 Pulmonary alveolar proteinosis: typical chest radiographic findings. Frontal chest radiograph shows bilateral ground-glass opacity associated with a prominent, underlying linear and reticular pattern. Note the normal heart size and mediastinal width, both of which argue against increased pressure pulmonary edema. (Courtesy Michael B. Gotway, MD.)



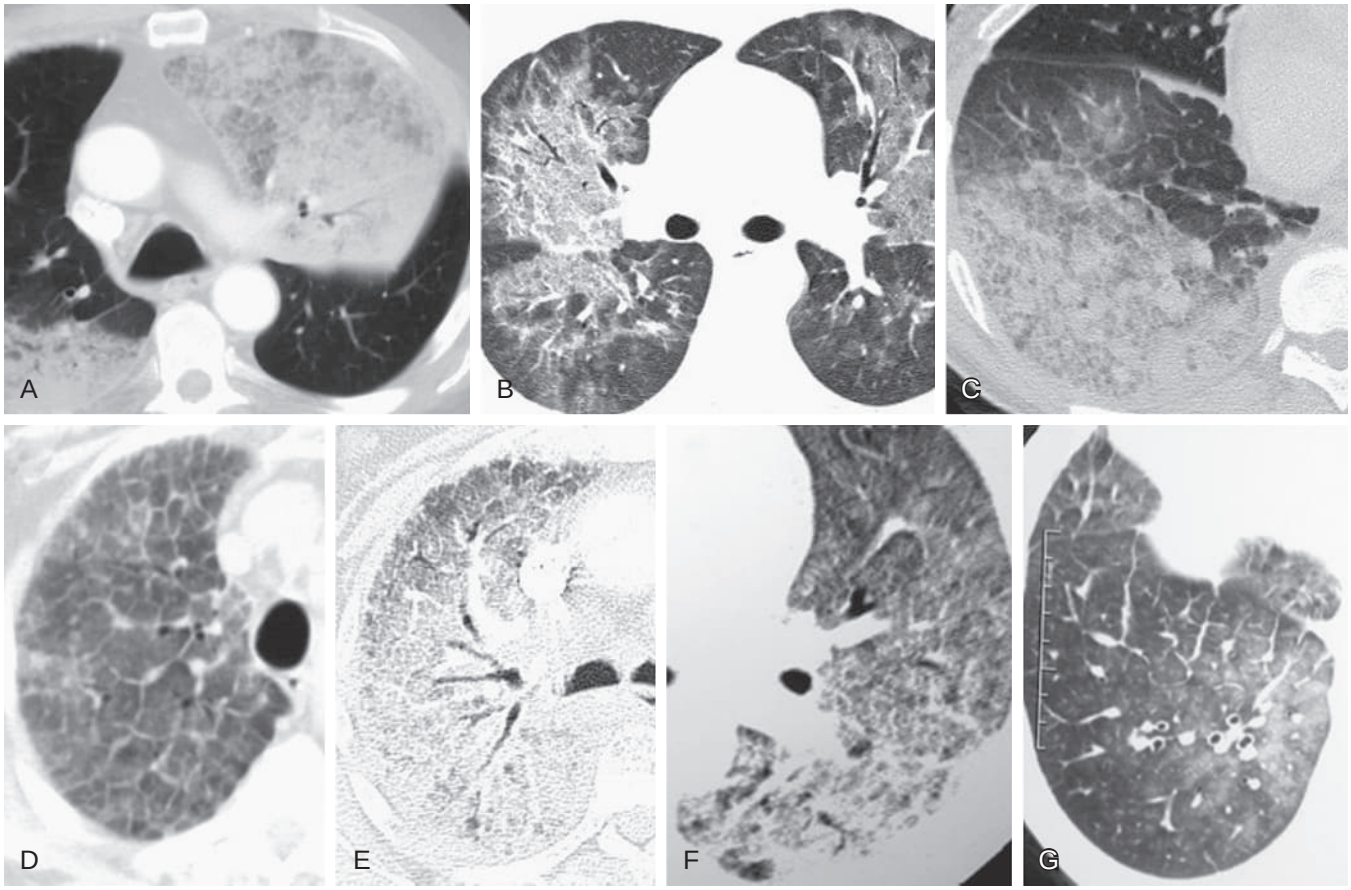
eFigure 98.3 Pulmonary alveolar proteinosis: somewhat atypical chest radiographic findings. Frontal chest radiograph shows multifocal bilateral linear opacities and peribronchovascular thickening, with more focal opacity in the right lung base. High-resolution computed tomography of this patient is shown in eFig. 98.5. (Courtesy Michael B. Gotway, MD.)



eFigure 98.4 Pulmonary alveolar proteinosis: "routine" versus high-resolution chest *computed tomography* (CT) findings. (A–B) Axial chest CT reconstructed at 5 mm–section thickness displayed in lung windows shows multifocal, bilateral, ground-glass opacity associated with interlobular septal thickening. (C–D) Axial high-resolution chest CT performed 24 hours after parts A and B shows the smooth interlobular septal thickening, associated with fine intralobular opacities (*arrowheads*), to advantage. The combination of ground-glass opacity and smooth interlobular septal thickening is consistent with a "crazy paving" appearance. (Courtesy Michael B. Gotway, MD.)



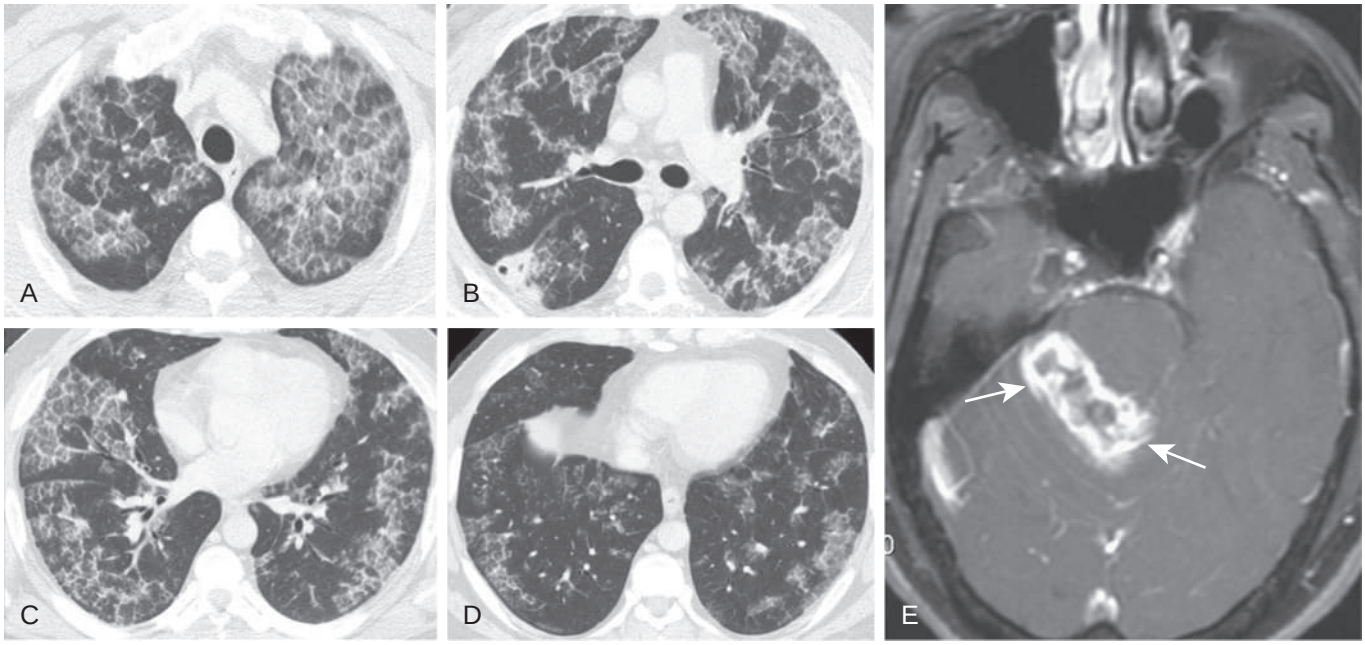
eFigure 98.5 Pulmonary alveolar proteinosis: high-resolution chest *computed tomography* (CT) findings. (A–D) Axial high-resolution CT displayed in lung windows shows patchy, multifocal, bilateral areas of ground-glass opacity associated with smooth interlobular septal thickening (*arrowhead*, C) associated with fine intralobular lines, with a sharp, geographic, often nonanatomic demarcation between normal- and abnormal-appearing lung, consistent with the "crazy paving" pattern. Note the appearance of "polygons" (*double arrowhead,* C), representing the secondary pulmonary lobule outlined by the smoothly thickened interlobular septa. (Courtesy Michael B. Gotway, MD.)



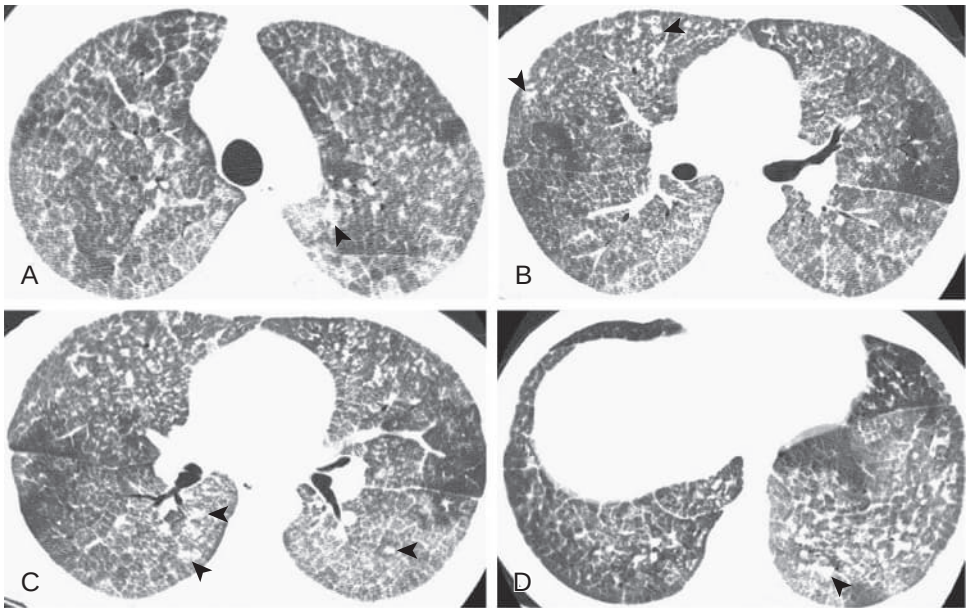
eFigure 98.6 "Crazy paving" mimics at chest *computed tomography* (CT). (A) Invasive mucinous adenocarcinoma with lepidic growth (formerly referred to as multicentric mucinous bronchioloalveolar carcinoma), (B) lipoid pneumonia, (C) pulmonary hemorrhage, (D) acute fibrinous and organizing pneumonia, (E) noncardiogenic edema, (F) acute eosinophilic pneumonia, and (G) increased pressure pulmonary edema. To some extent, all these cases show the combination of ground-glass opacity with smooth interlobular septal thickening, consistent with crazy paving, although, as is often the case, conditions other than pulmonary alveolar proteinosis that produce a crazy paving pattern at chest CT have a qualitatively distinct appearance. Compare these CT images with eFigs. 98.4, 98.5, 98.8A–D, and 98.10. (Courtesy Michael B. Gotway, MD.)



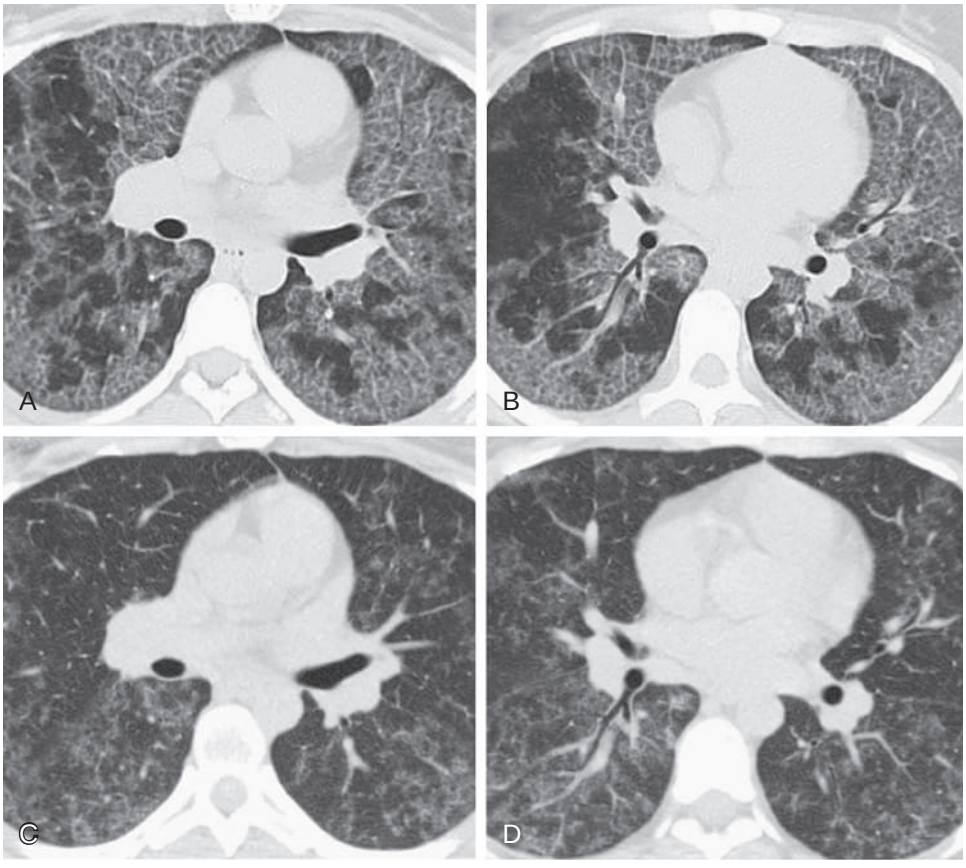
eFigure 98.7 Pulmonary alveolar proteinosis: gross pathologic findings. Multifocal focal areas of yellowish firm consolidation (*arrows*) are present, representing an exudate of fatty material. These findings are associated with smoothly thickened interlobular septa (*arrowheads*).



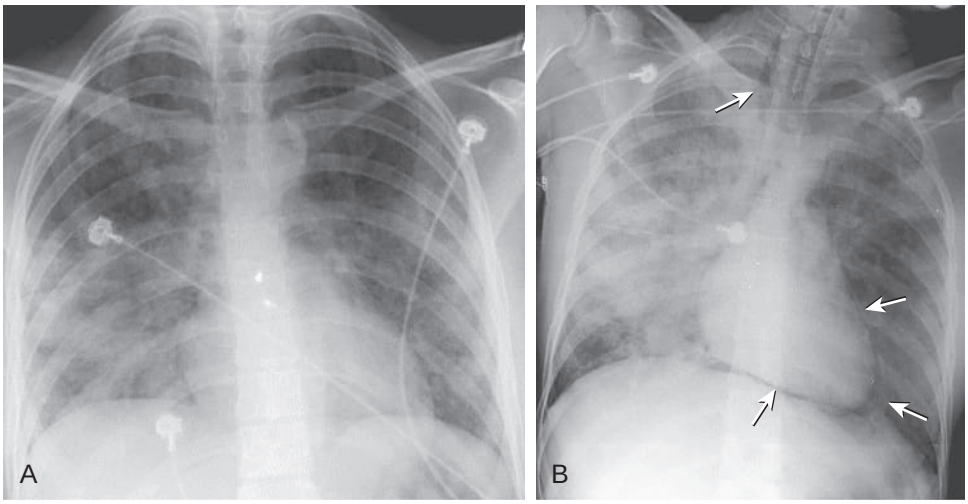
eFigure 98.8 Pulmonary alveolar proteinosis: infectious complications. (A–D) Axial high-resolution computed tomography displayed in lung windows shows the classic "crazy paving" appearance of pulmonary alveolar proteinosis. (E) Axial contrast-enhanced brain magnetic resonance imaging shows a peripherally enhancing lesion in the right cerebellopontine angle (*arrows*), representing a *Nocardia asteroides* brain abscess. (Courtesy Michael B. Gotway, MD.)



eFigure 98.9 Pulmonary alveolar proteinosis: infectious complications. (A–D) Axial chest computed tomography displayed in lung windows shows the classic "crazy paving" appearance of pulmonary alveolar proteinosis, with numerous superimposed small nodules (*arrowheads*), the latter reflecting disseminated nontuberculous mycobacterial infection. (Courtesy Michael B. Gotway, MD.)



eFigure 98.10 Spontaneous improvement in a patient with pulmonary alveolar proteinosis. (A–B) Axial high-resolution computed tomography obtained at the time of initial diagnosis shows the typical appearance of "crazy paving." (C–D) Axial chest computed tomography obtained 1 year after parts A and B shows spontaneous reduction in multifocal ground-glass opacity; the patient had not undergone any specific therapy for pulmonary alveolar proteinosis. (Courtesy Michael B. Gotway, MD.)



eFigure 98.11 Pulmonary alveolar proteinosis: whole-lung lavage complication. (A) Frontal chest radiograph obtained before whole-lung lavage shows multifocal, patchy bilateral ground-glass opacity and consolidation associated with linear and reticular abnormalities, consistent with pulmonary alveolar proteinosis. (B) Frontal chest radiograph obtained after whole-lung lavage procedure shows development of pneumomediastinum (*arrows*). (Courtesy Michael B. Gotway, MD.)

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99 DRUG-INDUCED PULMONARY DISEASE

ANDREW H. LIMPER, MD

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INTRODUCTION

Adverse drug reactions have been the object of intense scrutiny since the early 1990s and have been recognized as a top safety priority by health care quality improvement organizations.[1] Medical errors, including medication errors, may be responsible for 250,000 patient deaths per year in the United States.[2] Specifically, medication errors and preventable adverse drug events may injure 1.5 million people and cost billions of dollars annually. Up to 2–5% of hospitalized patients may have nonpreventable adverse drug reactions.[3] The classification of drug reactions includes allergic or hypersensitivity reactions, overdosage, intolerance, idiosyncratic reaction, and secondary side effects such as bronchospasm or cardiovascular suppression.

We know relatively little about the pharmacokinetic properties of drugs in individual patients. Indeed, only a small percentage of the population develops pulmonary toxicities to otherwise successful medications. Nevertheless, drug-induced pulmonary diseases represent a significant problem and are likely underrecognized.[1] The number of drugs associated with pulmonary toxicity is steadily increasing.[4] By 2019, more than 450 drugs had been identified as causes of adverse pulmonary reactions. These reports are of various types and quality, ranging from clear toxicities established in large series to isolated case reports. Some of these medications are listed in Table 99.1. To minimize mortality and significant morbidity, it is incumbent on the clinician to keep in mind at least the more common drugs that may induce pulmonary disease.[5-8]

Four mechanisms of drug injury to the lungs are recognized: (1) oxidant injury, such as during long-term nitrofurantoin ingestion; (2) direct cytotoxic effects (and these effects may be aggravated by oxidant injuries); (3) deposition of phospholipids within cells, such as those produced by cationic amphophilic drugs (e.g., amiodarone); and (4) immune-mediated injury through drug-induced *systemic lupus erythematosus* (SLE) reactions and immune checkpoint inhibitor toxicities.[6,9-13]

ONCOLOGY AGENTS

Chemotherapeutic agents are used extensively in solid and hematologic malignant diseases but are also increasingly used for their immunosuppressive properties in various inflammatory disorders. It remains a diagnostic challenge to determine the responsibility of the chemotherapeutic agent for a given toxicity. Diagnosis is usually made on the basis of exclusion of competing diagnoses, especially infection and recurrent malignant disease.

Oncology patients are prone to numerous pulmonary complications irrespective of their chemotherapy regimen, including opportunistic infections, atypical presentations of common lung infections, radiation-induced lung injury, cardiogenic or noncardiogenic pulmonary edema, and, of course, metastatic lung involvement. The various presentations of drug-induced pulmonary disease must be rapidly differentiated from these other causes whose clinical presentations, including fever and diffuse radiographic

Table 99.1 Classification of Drug-Induced and Related Pulmonary Diseases by Type of Medication

ONCOLOGY AGENTS

Cytotoxic
- Azathioprine
- Bleomycin
- Busulfan
- Chlorambucil
- Cyclophosphamide
- Etoposide
- Interleukin-2
- Melphalan
- Mitomycin C*
- Nitrosoureas
- Procarbazine
- Vinblastine
- Zinostatin

Noncytotoxic
- Bleomycin*
- Cytosine arabinoside*
- Gemcitabine*
- Methotrexate*
- Procarbazine*

Immunomodulatory
- Pembrolizumab*
- Nivolumab*
- Ipilimumab*

Molecularly Targeted
- Bevacizumab*†
- Cetuximab*
- Trastuzumab*
- Rituximab*
- Gefitinib,* erlotinimb,* imatinib*
- Ceritinib*

ANTIBIOTIC AGENTS
- Amphotericin B*
- Nitrofurantoin (short term,* long term)
- Sulfasalazine

ANALGESIC AGENTS
- Ethchlorvynol (Placidyl)*
- Propoxyphene*
- Salicylates*

CARDIOVASCULAR AGENTS
- Amiodarone*
- Angiotensin-converting enzyme inhibitors
- Anticoagulant agents
- β-Blockers*
- Dipyridamole
- Flecainide
- Protamine*
- Tocainide

ILLICIT AGENTS
- Heroin*
- Methadone*
- Methylphenidate
- Cocaine
- Talc granulomatosis

INHALANT AGENTS
- Aspirated oil
- Oxygen*

INTRAVENOUS AGENTS
- Blood products*
- Sodium morrhuate*
- Ethiodized oil (lymphangiogram)

MISCELLANEOUS AGENTS AND CONDITIONS
- Appetite suppressants
- Bromocriptine
- Complement-mediated leukostasis*
- Dantrolene
- Hydrochlorothiazide*
- Methysergide
- Radiation
- Systemic lupus erythematosus (drug-induced)
- Tocolytic agents*
- Tricyclic antidepressants*
- L-Tryptophan

*Typically manifesting as acute or subacute respiratory insufficiency.
†Can induce severe hemorrhage in patients with lung cancer.

Table 99.2 Selected Chemotherapeutic Agents With Associated Pulmonary Toxicities

ANTIBIOTIC-DERIVED AGENTS
- Bleomycin
- Mitomycin C

ALKYLATING AGENTS
- Busulfan
- Cyclophosphamide
- Chlorambucil
- Melphalan

ANTIMETABOLITES
- Methotrexate
- 6-Mercaptopurine
- Azathioprine
- Cytosine arabinoside
- Gemcitabine
- Fludarabine

NITROSOUREAS
- Bischloroethyl nitrosourea
- Chloroethyl cyclohexyl nitrosourea
- Methyl–chloroethyl cyclohexyl nitrosourea

PODOPHYLLOTOXINS
- Etoposide
- Paclitaxel
- Docetaxel

NOVEL ANTITUMOR AGENTS
- All-*trans* retinoic acid (ATRA)
- Gefitinib (Iressa)
- Erlotinib (Tarceva)
- Imatinib (Gleevec)
- Dasatinib

IMMUNOMODULATORY AGENTS USED IN MALIGNANT DISEASE
- Immune checkpoint inhibitors
- Interferons
- Interleukin-2
- Tumor necrosis factor-α

OTHER MISCELLANEOUS CHEMOTHERAPY AGENTS
- Procarbazine
- Zinostatin
- Vinblastine

abnormalities, may be extremely similar to drug-induced pulmonary reactions. Chemotherapy-associated pulmonary reactions have become a major problem, particularly in relation to therapeutic regimens containing bleomycin, methotrexate, cyclophosphamide, and a host of newer agents (Table 99.2).

Consistent criteria for drug-induced lung disease have not been officially established. Confirmation with rechallenge is generally avoided because it is often neither practical nor generally ethical. Hence the diagnosis of cytotoxic lung damage rests on an appropriate history of drug exposure, histologic evidence of lung injury, and the exclusion of other causes of the lung damage. No single diagnostic test or tissue biopsy can definitively confirm the diagnosis of chemotherapy-associated lung disease. A careful and thorough evaluation to eliminate the possibility that other conditions, particularly infections, may be producing these effects is warranted.[8,14] Thus the clinician should maintain a high index of suspicion and carefully screen for other competing causes of pulmonary injury that may affect these immunocompromised patients.

The clinical presentation of many chemotherapy drug effects is quite similar, with the exception that some effects manifest more acutely, whereas others tend to be more insidious in their onset. In general, nonproductive cough, dyspnea, and often fever begin weeks to years after the agent is first administered. Occasionally, symptoms may manifest acutely, as in the case of hypersensitivity reactions or infusion reactions. Symptoms may also manifest years after discontinuation of the drug, perhaps reactivated by radiotherapy. Fever is common with most chemotherapeutic drug-induced pulmonary injury, but it may not be consistently present, and chills are usually absent. Weight loss may be present. The chest radiograph in patients with chemotherapy-induced lung disease may be unremarkable for days or weeks before it shows typical changes of a diffuse interstitial infiltrative pattern. Alternatively, there may be a diffuse mixed alveolar-interstitial pattern, which may occasionally be useful in recognizing early drug effects (Fig. 99.1). Auscultation of the lungs frequently reveals crackles, which are also nonspecific. In some instances, pleural effusions may be present during adverse drug reactions, but not consistently.

Results of pulmonary function studies are abnormal in almost all patients compared with pretreatment testing. The *diffusing capacity for carbon monoxide* (D_{LCO}) may decrease before reduced volumes are detected. In addition, this decrease in D_{LCO} may precede the onset of symptoms and radiographic changes by days or weeks.[14,15]

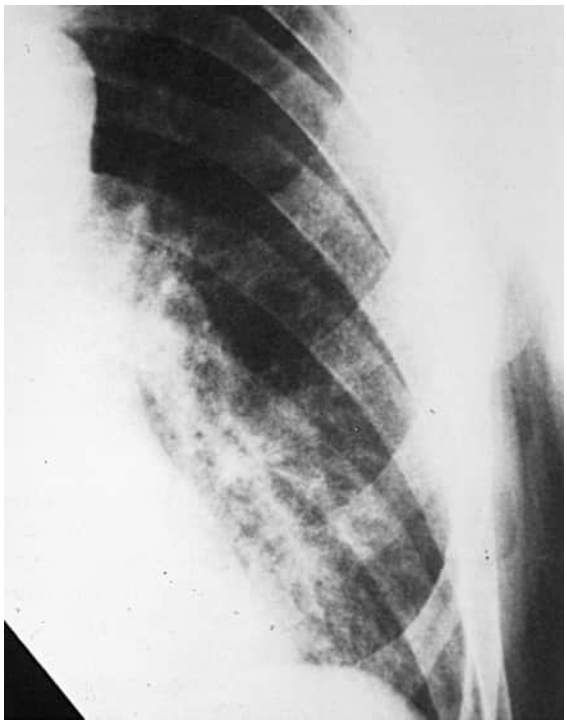

Fig. 99.1 Cytotoxic pattern of drug-induced lung disease. A close-up chest radiograph showing an alveolar interstitial pattern that is characteristic but not diagnostic of cytotoxic lung disease.

Bronchoalveolar lavage (BAL) may be another means of assessing early lung damage from these drugs; however, the results are often variable. In general, the greatest utility of BAL is to exclude infection.

ANTIBIOTIC-DERIVED AGENTS

Bleomycin

Bleomycin is an antibiotic chemotherapeutic agent whose pulmonary toxicity was recognized early, and this toxicity has since been one of the main factors limiting the use of this drug in the clinical setting. The incidence of bleomycin lung toxicity ranges anywhere from 0–46%; pulmonary function testing and chest radiographs reveal that 20% of patients treated with bleomycin develop overt pulmonary disease, and up to 3% die of pulmonary consequences of bleomycin therapy.[14,16]

Bleomycin exerts direct cytotoxic effects, prevents neoangiogenesis by the tumor, stimulates production of various cytokines, and generates free radicals by formation of a complex between ferrous iron and oxygen.[17-20] This last effect may explain increased bleomycin toxicity with high fractions of inspired oxygen, often during anesthesia and postoperative recovery.[21,22] This sensitivity to supplemental oxygen may persist for months and even years after discontinuation of the drug.

Perhaps one of the most consistent features of bleomycin-induced lung disease is cumulative toxicity. The incidence of pulmonary toxicity is significantly greater in patients who have received a cumulative bleomycin dose greater than 450 units, and a 10% death rate has been noted in patients who received a total dose greater than 550 units. However, doses as low as 50 units may occasionally be enough to cause pulmonary toxicity, especially when other synergic factors are present. Rapid rates of delivery by the intravenous route may also play a role, and slower infusion rates, as well as intramuscular injections, have been recommended.

Bleomycin is metabolized primarily by the kidneys. Hence renal failure predisposes patients to impaired metabolism of the drug and increased toxicity. The drug is also inactivated by an enzyme, bleomycin hydrolase, present in most tissues except for the lungs and skin. Radiotherapy is itself a common cause of pulmonary complications and is also thought to promote the generation of free radicals, toxic to both the tumor cells and the surrounding tissues. The concomitant use of bleomycin and radiotherapy may be synergistic. Treatment with bleomycin may reactivate prior radiation-induced lung disease *(radiation recall)*, as an example of a delayed drug reaction. Pulmonary toxicity is also increased in patients older than 70 years of age and in patients with preexisting lung disease. Good evidence indicates that pediatric patients may also be at increased risk; in one study, 70% of children treated with bleomycin for rhabdomyosarcoma developed pulmonary toxicity.[23] Impaired or immature ability to process free radicals and inadequate kidney function may explain these differences.

Although of uncertain value, determination of pretreatment D_{LCO} and its frequent monitoring have been suggested in an attempt to predict subsequent clinical deterioration.[24] Vital capacity and pulmonary capillary blood volume (Vc) may be better predictors of lung toxicity.[25] In addition, the enhanced sensitivity of *computed tomography* (CT) scanning may also be useful in establishing an early diagnosis of bleomycin pneumonitis.[26]

Other forms of bleomycin-induced lung disease have been described less commonly. Hypersensitivity reactions (eFig. 99.1) are possible with an association of fever and peripheral blood or BAL eosinophilia.[14,15] Discontinuation of bleomycin and initiation of corticosteroids usually bring about rapid reversal of this hypersensitivity variant of bleomycin pneumonitis.

An additional rare, but clinically important, presentation of bleomycin pneumonitis is that of nodular pulmonary lesions mimicking tumor metastasis (Fig. 99.2).[27] These reactions to bleomycin may require surgical biopsy to differentiate bleomycin-associated lung injury from recurrence of the primary malignant disease. Although bleomycin pulmonary toxicity may reflect diffuse alveolar damage (eFig. 99.2A), these nodular lesions from bleomycin often exhibit the histologic pattern of organizing pneumonia (eFig. 99.2B).[6]

In suspected cases of bleomycin lung toxicity, discontinuation of the drug is warranted. Administration of corticosteroids is often recommended. It would seem prudent to pay particular attention to avoid high fractions of inspired oxygen and concomitant radiotherapy and to monitor kidney function carefully during the duration of treatment. One study demonstrated that if the patient survives the acute injury from bleomycin,

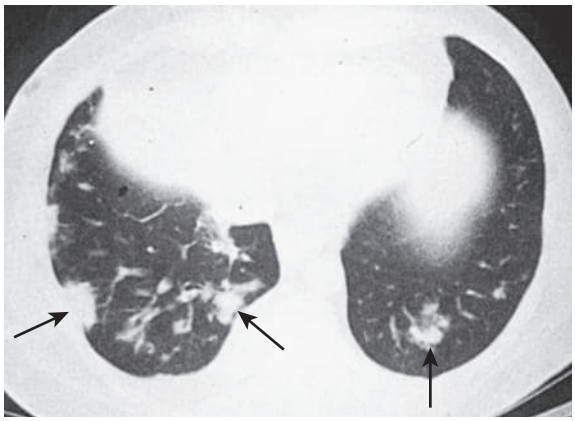

Fig. 99.2 Bleomycin-induced lung disease. A chest computed tomography scan of bleomycin pneumonitis showing a nodular pattern *(arrows)*. The histologic features of this form of bleomycin-induced lung injury are typical of organizing pneumonia.

pulmonary findings may improve substantially over time (see eFig. 99.1).[28] However, if significant fibrosis is present, the process may progress insidiously despite the administration of corticosteroids.

Mitomycin C

Mitomycin C is another antibiotic chemotherapeutic agent associated with pulmonary toxicity, which shares features similar to the toxic effects induced by bleomycin. The incidence of mitomycin-induced pneumonitis may range from 8% to as high as 39%.[29,30] Similar to bleomycin-induced lung toxicity, the cumulative dose appears to be associated with the incidence of pulmonary manifestations, with pulmonary fibrosis unlikely at doses less than 30 mg/m^2. Again, a high fraction of inspired oxygen and radiotherapy may exacerbate this phenomenon. Concomitant administration of other chemotherapeutic agents such as bleomycin, doxorubicin, or cyclophosphamide may also enhance pulmonary toxicity. The symptoms, imaging abnormalities, and histologic findings of mitomycin-induced pneumonitis are similar to those of other alkylating drug toxicities.[30] A favorable response to corticosteroid therapy has also been quite dramatic in many patients, possibly greater than in other forms of chemotherapy-associated lung injury.

In addition, there are reports of an unusual reaction to mitomycin C consisting of microangiopathic hemolytic anemia with associated noncardiogenic pulmonary edema and renal failure, taking the form of a hemolytic uremic syndrome. This develops in particular when mitomycin C is administered with 5-fluorouracil.[31] Most of these patients developed this hemolytic uremic syndrome between 6 and 12 months after beginning mitomycin C. Up to one-half of these patients also develop the *acute respiratory distress syndrome* (ARDS), with mortality as high as 95%. The mortality in patients with mitomycin C–associated hemolytic uremic syndrome who do not develop ARDS is still in the range of 50%. In some instances, this unusual drug reaction appears to be precipitated by blood transfusions. Microangiopathic changes are present in the lungs and kidneys. Treatment is essentially supportive, with initiation of plasma exchange with or without dialysis and corticosteroids when deemed appropriate.

ALKYLATING AGENTS

Busulfan

Busulfan can be responsible for significant pulmonary toxicity. The average duration from the initiation of therapy to the onset of respiratory symptoms is roughly 3.5 years, ranging between 8 months and as late as 10 years. However, busulfan pulmonary toxicity can develop as soon as 6 weeks following initiation of therapy. The incidence of busulfan pulmonary toxicity is estimated to be 6%, with a reported range of 3–43%.[32]

Dyspnea, fever, and cough begin in a more insidious fashion in busulfan toxicity than in many other chemotherapy-related lung toxicities. Such symptoms have even been reported to begin months after busulfan therapy has been discontinued. The chest radiograph in busulfan toxicity reveals a combined alveolar and interstitial process to a greater degree than in other chemotherapy reactions. This is likely the result of a high degree of desquamation of injured epithelial cells into the alveolar spaces. This alveolar debris may be so extensive as to suggest pulmonary alveolar proteinosis. Busulfan-induced pulmonary toxicity is also characterized by the presence of acute lung injury, with associated atypical alveolar epithelial type 2 cells with markedly enlarged pleomorphic nuclei and prominent nucleoli (eFig. 99.3).

The mortality rate is extremely high, in the range of 80%.[23] No effective therapy has been identified, but discontinuation of the drug with or without initiation of corticosteroid therapy is recommended.

Cyclophosphamide

Cyclophosphamide is widely included in combination chemotherapy for hematologic malignant diseases and solid tumors. It is also used in the treatment of granulomatous polyangiitis. The incidence of pulmonary toxicity is estimated at approximately 1%, although accumulating evidence suggests that the disorder may be much more common. A case series from a large tertiary referral center identified only 6 patients older than 20 years of age in whom cyclophosphamide was the only factor contributing to pulmonary injury.[33]

Clinical features of cyclophosphamide-associated pulmonary toxicity include fever, dyspnea, cough, gas-exchange abnormalities, parenchymal opacities, and pleural thickening. Two patterns of cyclophosphamide-induced lung toxicity have been described. First, there can be early-onset pneumonitis within the first 1 to 6 months after institution of therapy. This form generally responds to withdrawal of cyclophosphamide. In contrast, there may also be late-onset pneumonitis that develops after months or even years of therapy and results in progressive lung fibrosis and bilateral pleural thickening. This late-onset variety unfortunately has minimal response to withdrawal of cyclophosphamide or to corticosteroid therapy.[33] The dose of cyclophosphamide and the development of lung disease are not clearly related. Supplemental oxygen and radiotherapy may increase the likelihood of lung manifestations.

Chlorambucil

The clinical presentation, chest radiographic abnormalities, and histologic features of chlorambucil-associated pneumonitis are remarkably similar to those described in other alkylating agent–induced pulmonary toxicities.[8] Cumulative doses in excess of 2 g seem to increase the risk significantly. The presentation is usually insidious, beginning 6 months to a year or more after the start of therapy. Surveillance of lung function, particularly D_{LCO}, may be of benefit in anticipating which patients will have a deteriorating condition and will require discontinuation of the agent. Few data are available on the efficacy of corticosteroid therapy in chlorambucil-related lung toxicity.

Melphalan

Melphalan also has resulted in well-documented cases of pulmonary toxicity.[34] The course of melphalan-associated pulmonary injury varies from acute to subacute in tempo. Patients present with insidious to abrupt onset of dyspnea, cough, and frequently fever. There are no particular clues for predicting which patients will develop side effects. The incidence of pulmonary side effects from melphalan must be generally low because this agent has been widely used in the long-term management of myeloma.

Other Alkylating Agents

Procarbazine is rarely associated with interstitial pneumonias, which are sometimes characterized by significant eosinophilia suggesting a hypersensitivity reaction. Progression to widespread and irreversible fibrosis seems rare.[35]

Oxaliplatin has been associated with laryngeal dysesthesia and was thought to be responsible for the development of diffuse alveolar damage, often in association with 5-fluorouracil. More typically, there can be severe anaphylactic reactions during infusion of the drug in approximately 1.3% of the cases. Eosinophilic pneumonia has also been rarely reported.[36,37]

Temozolomide is a second-generation alkylating agent. Few respiratory side effects have been described, mainly pharyngitis, sinusitis, cough, upper respiratory tract infection, and dyspnea. Pneumonitis was found in up to 4.8% of patients in Phase II trials. One case of organizing pneumonia that resolved after discontinuation of treatment was described.[38]

ANTIMETABOLITES

Methotrexate

Methotrexate is present in many combination regimens for malignant diseases and is also used extensively for nonmalignant conditions, including psoriasis and rheumatoid arthritis. It interferes with the metabolism of folic acid, hence specifically targeting replicating cells and leading to a variety of well-described adverse effects, including bone marrow suppression, mucositis, alopecia, and gastrointestinal manifestations. Pulmonary toxicity is thought to develop in approximately 10% of all patients treated but is fortunately rarely fatal. Dyspnea, nonproductive cough, and fever usually commence a few days to several weeks after initiation of therapy. However, in rare cases, symptoms may be observed a few months or years after the onset of therapy.[39]

Methotrexate-associated pneumonitis (eFig. 99.4) is generally reversible with or without the addition of corticosteroids. Eosinophilia is seen in at least one-half of cases, and the disease is therefore believed to represent a hypersensitivity reaction.[14] The intriguing feature of this reaction is that the drug may be reinstituted following resolution of methotrexate pneumonitis without necessarily triggering a subsequent recurrence of symptoms or findings.[40] In about one third of patients, poorly formed granulomas are identified in lung biopsy; this finding is unusual in other forms of chemotherapy-associated lung disease (eFig. 99.5).[6] Hilar lymphadenopathy is occasionally present, and this may mimic sarcoidosis. There is no cellular atypia, such as is seen in many other cytotoxic drug toxicities.

The chest radiograph tends to reveal a homogeneous opacity throughout all lung fields. Hilar adenopathy or pleural effusion is seen in at least 10–15% of patients with methotrexate lung toxicity. In distinct contrast to most of the other chemotherapy-induced pulmonary toxicities, prospective investigations of patients receiving methotrexate have not demonstrated a diminished D_{LCO} that could predate subclinical toxicity. In addition, pulmonary toxicity in response to methotrexate does not appear to be dose related. Two other important manifestations associated with methotrexate should be mentioned. Opportunistic infections related to T cell deficiency need to be excluded, in particular *Pneumocystis* pneumonia.[41] Peculiar Epstein-Barr virus–related lymphomas that typically resolve after discontinuation of treatment have also been reported and may be directly related to an alteration in immune surveillance induced by methotrexate.[41]

Azathioprine and 6-Mercaptopurine

More than two dozen case reports of azathioprine-associated pneumonitis have been reported. However, the net overall incidence must be low, considering the widespread use of this agent for neoplastic and nonneoplastic conditions.[34] Nevertheless, the possibility of azathioprine pneumonitis must be considered in any individual receiving this agent. Azathioprine is metabolized to 6-mercaptopurine, and a handful of reports detailed cytotoxic interstitial pneumonitis in association with this metabolite.[5] However, most of these patients also received other agents that potentially could be implicated in the lung injury described.

Cytosine Arabinoside

Cytosine arabinoside (ara-C) is a cytotoxic agent used to induce remission in acute leukemia and other hematologic malignant diseases before bone marrow transplantation. Intensive ara-C treatment regimens have been associated with rapidly fatal noncardiogenic pulmonary edema (Fig. 99.3).[5] Histologic examination of lung tissue during ara-C pulmonary toxicity reveals substantial accumulation of intra-alveolar proteinaceous material without the cellular atypia and mononuclear infiltration described with other cytotoxic drugs. In two large series, 13–28% of the patients with toxicity developed respiratory distress

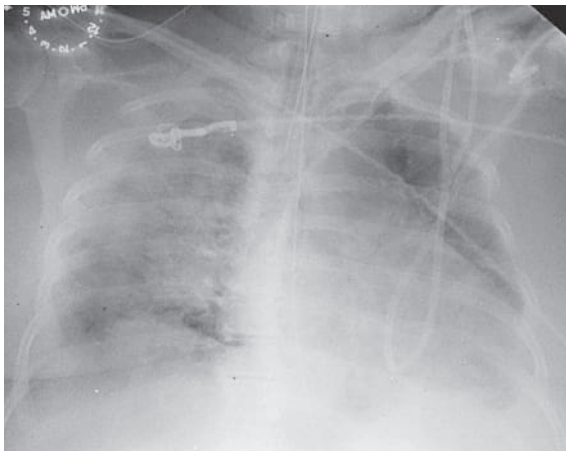

Fig. 99.3 Cytosine arabinoside–induced lung disease. A chest radiograph of a 44-year-old woman showing acute noncardiogenic pulmonary edema that resulted from cytosine arabinoside–induced lung disease. Histologic examination typically demonstrates intense intraalveolar proteinaceous material forming hyaline membranes, but little other reaction.

with administration of the drug. The mechanism underlying this reaction is unknown, and the associated mortality is high. Treatment for ara-C pulmonary toxicity is largely supportive.

Gemcitabine

Gemcitabine is a pyrimidine analogue, with structure and activities similar to ara-C. The incidence of respiratory complications has probably been underestimated. Dyspnea has been reported in 10% of treated patients, with severe dyspnea reported in up to 5%.[42-44] Noncardiogenic pulmonary edema is thought to develop in 0.1–7% of all patients treated.[45] There are three major patterns of respiratory involvement in gemcitabine-related pulmonary toxicity. The first pattern is a nonspecific, self-limiting dyspnea reported within hours to days of treatment. A second, relatively uncommon, pattern is that of an acute hypersensitivity reaction with bronchospasm. A third pattern of severe respiratory involvement is occasionally seen. This is a severe idiosyncratic reaction with profound dyspnea and pulmonary opacities that may progress to life-threatening respiratory insufficiency within hours of infusion (Fig. 99.4). Most cases of gemcitabine-related pulmonary toxicity resolve with discontinuation of this drug. In cases of severe symptoms, discontinuation of the agent along with institution of corticosteroids, careful fluid management, and diuretic therapy may be warranted.[42] Cases of diffuse alveolar hemorrhage, pulmonary veno-occlusive diseases, and thrombotic microangiopathy have also been described.

Fludarabine

The incidence of pulmonary toxicity related to fludarabine, another nucleoside analogue, was estimated to be approximately 8.6% in a series of 105 patients.[46-48] Affected individuals experience dyspnea as early as 3 days after the first round of chemotherapy, although later onset of pulmonary symptoms has also been reported. The chest radiograph reveals either interstitial

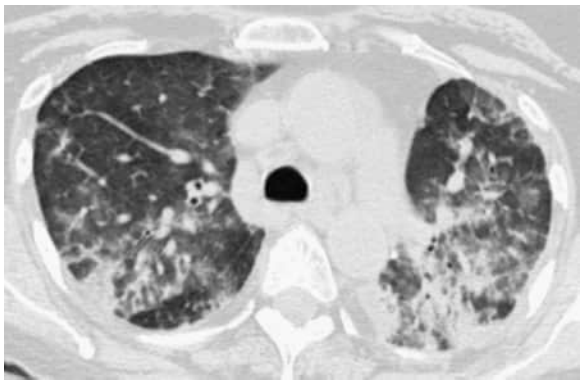

Fig. 99.4 Gemcitabine-induced lung disease. A chest computed tomography image of an individual with gemcitabine-induced lung disease. The pattern is a mixed alveolar and interstitial infiltration.

or mixed alveolar-interstitial opacities. Nodular opacities have also been described. Most patients respond to discontinuation of the drug and receive symptomatic and objective benefits from additional corticosteroid therapy.

Nitrosoureas

Pulmonary toxicity related to nitrosoureas is well recognized.[49] In particular, *bischloroethyl nitrosourea* (BCNU, carmustine) has been described to induce both acute-onset pulmonary injury (see eFig. 125.12) and delayed-onset pulmonary fibrosis, with a predilection for the upper lobes.[49] The incidence of pulmonary toxicity associated with the administration of BCNU varies from 2–20% and is dose related, with an incidence of lung disease of up to 50% in patients receiving a total dose of greater than 1500 mg/m^2. However, there have also been reports of pulmonary effects with much lower doses. The duration of therapy before the onset of pulmonary toxicity for the acute variant of nitrosourea lung injury has generally ranged from 6 months to 3 years. The outcome may be unpredictable and sometimes fatal. There have been fewer case reports of pulmonary toxicity with *methyl-chloroethyl cyclohexyl nitrosourea* (methyl-CCNU) and *chloroethyl cyclohexyl nitrosourea* (CCNU). Apparently, fever is less commonly associated with this form of pulmonary toxicity than with many other chemotherapeutic drugs. Therapy usually consists of withholding the offending agent and starting corticosteroids, which has variable and often only transient beneficial effects.[50]

A long-term complication of BCNU toxicity is upper lobe fibrosis that may appear many years after the completion of chemotherapy. O'Driscoll and colleagues[51] followed 17 patients for up to 17 years, and 12 (71%) developed delayed upper lobe fibrosis. The fibrosis is insidious in onset and, once discovered, appears to be intractably progressive. Corticosteroid therapy has not proven to be effective.

Cases of pulmonary fibrosis have been reported with several nitrosourea agents, including lomustine (CCNU), semustine (methyl-CCNU), fotemustine (CENU), bendamustine, and chlorozotocin (DCNU). Pneumothoraces have rarely been described with these agents.

PODOPHYLLOTOXINS

Etoposide and Teniposide

Etoposide (VP-16), a topoisomerase II inhibitor, has been widely used in combination chemotherapy for non–small cell and small cell lung carcinoma. Despite its extensive use, only a few cases of etoposide-associated pulmonary toxicity have been reported.[52] Toxicity may become apparent shortly after the first round of chemotherapy, although most patients present after prolonged treatment. Therapy consists of withdrawal of the agent and administration of corticosteroids, which provide variable improvement. Teniposide, another podophyllotoxin agent, is also associated with hypersensitivity reactions in 3.6–6.5% of cases. This toxicity may manifest with dyspnea, bronchospasm, and hypertension.[53]

Paclitaxel

Well-documented cases of pulmonary toxicity induced by paclitaxel can be found in the literature, but the frequency is unclear. Patients may report respiratory symptoms including cough, dyspnea, wheezing, and chest tightness within minutes of administration of the drug, thus suggesting a type I hypersensitivity reaction.[54] This reaction may be seen in up to 30% of patients, and premedication with corticosteroids is sometimes considered. Reticular and nodular opacities have been reported on chest radiographs.[55] Cases of transient pulmonary opacities and suspected interstitial pneumonitis have also been described (eFig. 99.6). The true incidence of lung toxicity directly related to paclitaxel is not well understood. A prospective study of lung function in 33 patients receiving paclitaxel with carboplatin (an agent with little lung toxicity) in the setting of nonthoracic malignant disease revealed an isolated decrease in D_{LCO} without other clinical or radiographic evidence of pulmonary toxicity.[56] In other studies, conducted in patients with lung carcinoma, significant early and late pulmonary toxicity has been noted in 10% and 68% of patients, respectively.[57,58] Therefore, clinicians should be aware of the potential of paclitaxel to impair pulmonary function.

Docetaxel

Docetaxel (Taxotere), another taxane, infrequently causes pulmonary toxicity based on a hypersensitivity reaction.[59] These patients have responded rapidly to corticosteroid therapy. The combination of docetaxel and gemcitabine may have particular propensity to induce severe pulmonary toxicity.[60] Some patients may develop capillary leak syndrome with peripheral edema, noncardiogenic pulmonary edema, and/or pleural effusions.[61,62] The severity of fluid retention can be reduced by prophylactic treatment with corticosteroids.[63]

ALL-*TRANS* RETINOIC ACID AND DIFFERENTIATION SYNDROME

All-trans retinoic acid (ATRA) has been used in acute promyelocytic leukemia, in which it promotes differentiation of myeloid precursors and stimulates the maturation of leukemic cells, thereby promoting remission. It has also been reported to reduce disseminated intravascular coagulation and hemorrhagic complications during promyelocytic leukemia. The main complication limiting its use is the development of the differentiation syndrome (previously called retinoic acid syndrome) in up to 25% of patients treated. This syndrome consists of diffuse edema, pleuropericardial effusions, and noncardiogenic pulmonary edema that may evolve into a generalized capillary leak syndrome (eFigs. 99.7 and 99.8). Hypotension and acute renal failure are commonly present. Toxicity may manifest suddenly between days 2 and 21 of treatment. Its pathogenesis remains elusive, but it is thought to result from a massive release of cytokines from newly mature myeloid cells and adhesion of granulocytes to the pulmonary endothelium. Indeed, high leukocyte counts have been associated with an increased incidence of the syndrome in some, but not all, studies. In addition, multiple hemorrhagic complications have also been described. One study reported that 9 of 35 patients with promyelocytic leukemia receiving ATRA developed respiratory distress.[64] Intravenous corticosteroid therapy seemed to be of benefit to these patients. The mortality associated with ATRA-induced pulmonary toxicity is estimated at approximately 9%.[65] Differentiation syndrome in acute promyelocytic leukemia has also been observed in patients receiving arsenic trioxide.

MOLECULARLY TARGETED THERAPY

Monoclonal Antibodies

Bevacizumab. Bevacizumab, a monoclonal antibody targeting vascular endothelial growth factor, is designed to inhibit tumoral neoangiogenesis. It is associated with hemorrhagic complications, including fatal pulmonary hemorrhage thought to result from extensive tumor necrosis. These complications have been predominantly seen in patients with squamous cell lung cancer. Although it may seem counterintuitive, bevacizumab is thought to increase the incidence of thromboembolic disease. This may be secondary to vascular injury with secondary exposure of the underlying endothelium and activation of the coagulation cascade. Cases of thrombotic microangiopathy with hypertension and acute renal failure have also been described. Tracheoesophageal and bronchoesophageal fistulas have been reported in patients treated with bevacizumab for lung cancer.[66-69]

Cetuximab and Panitumumab. Cetuximab and panitumumab are two monoclonal antibodies directed against the *epidermal growth factor receptor* (EGFR). Both have been associated with rare pulmonary toxicity. Interstitial lung disease has been reported in 0.4% of patients with cetuximab, and there may be infusion reactions with bronchospasm and hoarseness in 23% of the cases. With panitumumab, patients may have similar infusion reactions, which may be severe in 1% of the cases. Panitumumab has now been associated with interstitial lung disease and pulmonary fibrosis. The interstitial lung disease has been found to be fatal in some cases, so if toxicity develops, panitumumab should be stopped and steroids considered.[70,71]

Trastuzumab and Ado-trastuzumab Emtansine. Trastuzumab selectively binds the *human epidermal growth factor receptor-2* (HER-2) protein and is an

adjuvant treatment for metastatic HER-2–positive breast cancer. As with other monoclonal antibodies, infusion reactions may present in 15% of the cases and are potentially associated with angioedema, fever, and bronchospasm. Trastuzumab reactions may also manifest as acute or subacute interstitial pneumonia in approximately 0.5% of patients, with a mortality rate estimated at 0.1%.[72] Interstitial pneumonia is a rare toxicity of trastuzumab.

Ado-trastuzumab emtansine is an antibody-drug conjugate that contains trastuzumab and a cytotoxic microtubule inhibitor, emtansine. It is also used in breast cancer and has been associated with acute pneumonitis. The incidence is low, at 0.8–1.2%, but the toxicity may be life-threatening, so if pneumonitis develops, ado-trastuzumab should be discontinued.[73]

Rituximab. Rituximab is an anti-CD20 chimeric monoclonal. The most common side effect of rituximab is an infusion reaction in more than 50% of patients. Symptoms include fever, chills, dyspnea, hypotension, rhinitis, urticaria, pruritus, and a sensation of throat and tongue swelling. Slowing or stopping the rituximab infusion may help resolve the symptoms. Corticosteroids are occasionally required. Other pulmonary complications of rituximab appear fairly rare overall. Rituximab can also cause interstitial lung disease.[74]

Tyrosine Kinase Inhibitors

Gefitinib. Gefitinib is a selective EGFR tyrosine kinase inhibitor. Acute interstitial pneumonia has been associated with this drug, and the overall incidence of gefitinib-associated interstitial lung disease may be in the range of 1%, with a mortality rate approaching 30%.[75,76] The most common presentation is acute dyspnea with or without cough or fever.[75] The median onset of symptoms is 24 to 42 days.[75] Diffuse ground-glass opacities and multifocal airspace consolidation have been reported on CT scan.[77] Tissue examination demonstrates diffuse alveolar damage, interstitial inflammation with or without fibrosis, and organizing pneumonia.[76,78-80] Although some patients respond to withdrawal of the agent and institution of corticosteroid therapy, others progress to fulminant respiratory insufficiency. Hence the clinician should discontinue the agent if symptoms and radiographic abnormalities develop.

Erlotinib. Erlotinib is another EGFR antagonist. Erlotinib has also been rarely associated with pulmonary toxicity, including fatalities.[81-83] Patients who have undergone lung biopsy have shown organizing pneumonia or diffuse alveolar damage.[83] The presentation is similar to that of most drug-induced lung injury, with dyspnea, cough, and low-grade fever. The median time to toxicity is 47 days.[81] Treatment is supportive with removal of the drug. The benefit of corticosteroids is unclear.

Imatinib. Imatinib is an inhibitor of the BCR-ABL, KIT, and *platelet-derived growth factor receptor* (PDGFR) tyrosine kinases.[84] Fluid retention causing peripheral, periorbital, and pulmonary edema is a common complication.[85-87] There have been cases reported of pulmonary infiltration with eosinophilia or acute interstitial pneumonia.[84,88-91] Symptoms of dyspnea, cough, and low-grade fever develop at a median time of 49 days.[92] Radiographic studies have shown ground-glass opacities, consolidation, or nodular opacities. BAL findings demonstrate lymphocytes, foamy macrophages, and, in some cases, eosinophilia.[91,93,94] Peripheral eosinophilia has also been demonstrated.[93] Lung biopsies have demonstrated interstitial inflammation and fibrosis, alveolitis, and pulmonary alveolar proteinosis.[93-95] Treatment consists of removal of the drug and administration of corticosteroids. Rechallenge of the drug does not always cause recurrence of the lung injury, so physicians must carefully consider alternative agents and the risk and benefit of rechallenge.[93,96]

Dasatinib. Dasatinib is another BCR-ABL tyrosine kinase inhibitor. Dasatinib is associated with pleural effusions, pulmonary hypertension, and pulmonary parenchymal abnormalities. Pleural effusions have been reported in 10–35% of patients treated.[97-100] Effusions are mostly lymphocytic and exudative. Concomitant lung disease and higher initial daily dose are reported risk factors for development of pleural effusions.[99] Treatment of the pleural effusions is unclear but has included glucocorticoids, diuretics, thoracentesis, and discontinuation of dasatinib.[97,99,101,102] Pulmonary arterial hypertension is a rare complication of dasatinib use with symptom onset after 8 to 48 months of therapy.[103-107] Presenting symptoms include tachypnea, exertional dyspnea, fatigue, and peripheral edema.[103-107] Dasatinib therapy should be discontinued if pulmonary hypertension develops, and there should not be a rechallenge.[103-107] Pneumonitis is another rare complication of dasatinib. In a study of patients treated with dasatinib, 40 (23%) developed a lung abnormalitiy.[108] The lung changes resolved or partially resolved in all nine patients with parenchymal abnormalities.[108] Discontinuation of dasatinib resulted in resolution in five patients, and glucocorticoids were used in one patient with complete resolution.[108]

Sunitinib and Sorafenib. Sunitinib and sorafenib are small molecule tyrosine kinase inhibitors that block the intracellular domain of the vascular endothelial growth factor receptor. Sunitinib has been reported to cause dyspnea and cough.[109] Pulmonary embolism has also rarely been reported. Sorafenib is used to inhibit angiogenesis. Pulmonary toxicity has been reported during sorafenib use, with diffuse pulmonary opacities, dyspnea, cough, and fever.[110] Although a rare toxicity, it was fatal in some patients, so the drug should be stopped immediately if pulmonary toxicity is suspected.[110]

Anaplastic Lymphoma Kinase Inhibitors. Ceritinib, alectinib, crizotinib, and brigatinib are inhibitors of *anaplastic lymphoma kinase* (ALK) and are used for treatment of advanced non–small cell lung cancer. These agents have been reported to induce interstitial opacities and organizing pneumonia. These reactions can be severe, and treatment cessation is recommended. [111,112]

IMMUNOMODULATORY AGENTS

INTERFERONS

Interferons (α, β,and γ) have been used in a wide variety of malignant, infectious, and inflammatory disorders. Administration of interferons has been associated with a variety of pulmonary reactions. For instance, interferon-α has been linked to severe exacerbation of bronchospasm in patients with preexisting asthma.[113] In addition, a granulomatous reaction indistinguishable from sarcoidosis (eFig. 99.9) has been described in relation to interferon therapy.[114] These toxicities usually respond to either reduction or withdrawal of the interferon treatment with or without the addition of corticosteroids. Noncaseating granulomas have been documented in the lung, lymph nodes, liver, and skin of affected patients.

Interferon-associated interstitial lung disease has also been reported.[115] Dyspnea and cough are observed, and bilateral opacities are present on chest radiography. In some cases, interferon therapy has also been associated with an organizing pneumonia pattern.[116] Most affected patients respond to discontinuation of the interferon and administration of corticosteroids. Interferon-γ has been used in idiopathic pulmonary fibrosis. In one series, four patients with advanced idiopathic pulmonary fibrosis developed acute hypoxemic respiratory failure during interferon-γ treatment.[117] This respiratory failure was not responsive to corticosteroids and was fatal in three cases. Interferon-γ is also associated with a high incidence of severe radiation pneumonitis when it is used in multimodality therapy for non–small cell lung carcinoma.

RAPAMYCIN ANALOGUES

Sirolimus is an inhibitor of the *mammalian target of rapamycin* (mTOR), with antiproliferative and immunosuppressive properties, which has become an important treatment for lymphangioleiomyomatosis[118] (see Chapter 97). Several patterns of drug toxicity have been described with sirolimus, including the subacute onset of interstitial pneumonitis (eFig. 99.10) (which usually resolves after discontinuation of therapy), an organizing pneumonia pattern, and diffuse alveolar hemorrhage. Rare cases of alveolar proteinosis and granulomatosis have also been reported. Typically, these pulmonary complications are reversible after discontinuation of therapy.[119]

Everolimus is a similar inhibitor of the mTOR pathway. Several types of pulmonary toxicity have been described, including organizing pneumonia and the subacute onset of interstitial pneumonitis.[120] The interstitial pneumonitis has been reported in varying severity. In one report of interstitial lung disease in patients receiving everolimus, four patients underwent BAL, which demonstrated lymphocytosis; two patients also had increased eosinophil counts.[121] Transbronchial biopsy samples from three of the patients demonstrated interstitial lymphocytic inflammation and septal thickening.[121] Treatment may involve observation in mild cases but can require discontinuation of the drug and initiation of glucocorticoids in severe cases.[122,123] The use of glucocorticoids is of unclear benefit. Temsirolimus is yet another mTOR inhibitor with similar patterns of lung toxicity.[124-126]

IMMUNE CHECKPOINT INHIBITORS

Immune checkpoint inhibitors are potent immunomodulatory antibodies that enhance host T cell responses to help eliminate tumor cells and have become first-line therapies for many cancers, either as monotherapy or combined with chemotherapy.[127] The primary targets are the cytotoxic T lymphocyte–associated antigen 4 (e.g., ipilimumab), the programmed cell death-1 receptor (e.g., nivolumab and pembrolizumab), and the programmed cell death ligand-1 (e.g., atezolizumab). These agents are approved for metastatic melanoma and advanced non–small cell lung cancer, but they are increasingly used in other malignant diseases. Despite potent and often durable antineoplastic activities of these drugs, the release of normal immune checkpoint controls is associated with immune-related adverse events in a wide variety of organ systems. Accordingly, these agents are associated with immune-related toxicities in the skin, gastrointestinal tract, liver, thyroid, and lung.[128-130] Immune-related adverse events in total have been reported in up to 12% of treated patients.[131,132]

A spectrum of lung toxicities has been reported, including focal or diffuse pneumonitis and diffuse interstitial lung disease, seen in approximately 5% of treated patients.[131,132] In addition, immune checkpoint inhibitors have also been associated with the development of organizing pneumonia[133-135] (Fig. 99.5). These lung toxicities range from asymptomatic (grade 1), mildly symptomatic (grade 2), and severely symptomatic (grade 3) to life-threatening (grade 4). In most cases, lung infection should also be excluded. These

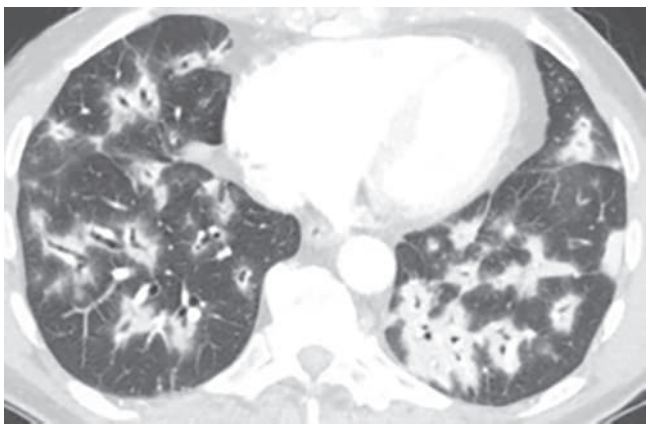

Fig. 99.5 Pembrolizumab-induced-pneumonitis with an organizing pneumonia pattern. Chest computed tomography through the lung bases in a patient with non–small cell lung carcinoma treated with pembrolizumab shows multifocal, bilateral extensive consolidation with a striking peribronchovascular distribution. Note the opacities are primarily distributed along the airways. Following discontinuation of the drug and use of corticosteroid therapy, the areas of consolidation regressed leaving some areas of architectural distortion suggesting scarring. (From Gotway MB. Medical image of the week: pembrolizumab-induced pneumonitis. *Southwest J Pulm Crit Care.* 2017;15:118-119.)

toxicities often respond to withholding the agents and instituting corticosteroids. Grade 1 lung toxicities involve 25% of the lung fields and usually respond well to withholding the immune checkpoint inhibitor. Grade 2 lung toxicities involve 25–50% of the lung fields and require withholding the immune checkpoint inhibitor, often with the addition of prednisone. Antibiotics are also frequently provided empirically to cover for potential infection. In grade 1 or mild grade 2 toxicities, consideration is sometimes given to reinstituting the immune checkpoint inhibitor, thus balancing the risk of recurrent malignancy against the potential risk for recurrent lung toxicity. In contrast, grade 3 toxicities involve more than 50% of lung fields or require hospitalization for oxygen and supportive care, and grade 4 toxicities involve urgent intervention for severe respiratory compromise. Grade 3 and 4 toxicities require permanent withdrawal of immune checkpoint inhibitors with hospitalization, bronchoscopy to exclude infection, empirical antibiotics, and high-dose corticosteroids (of at least 100 mg of prednisone equivalent per day). [136] Refractory cases are challenging to manage; some investigators have suggested the use of intravenous immunoglobin in such cases, although definitive data are lacking.[136] Overall, the checkpoint inhibitor–associated pneumonitis may have an adverse effect on survival in patients receiving immune therapy for non–small cell lung carcinoma.[137]

ANTIMICROBIAL AGENTS

NITROFURANTOIN

Acute Reaction

Nitrofurantoin pneumonitis is one of the most common drug-induced pulmonary diseases.[138-140] Acute pulmonary reactions are underestimated. The incidence has been estimated to be anywhere from 1 in 550 to 1 in 5400 individuals.[140] The mechanism of the acute nitrofurantoin reaction is unknown. The typical reaction begins a few hours to several days after initiation of therapy. It appears to be more common in women, perhaps because of the increased use of this drug in women. Fever, dyspnea, and cough are present in most cases. Other incidental findings include leukocytosis and eosinophilia in one third and an elevation in sedimentation rate in nearly one-half of cases. Imaging shows either an alveolar or an interstitial process or both. The reaction is generally most prominent at the bases. Pleural effusion has been found in one third of patients, most commonly unilaterally. Bronchospasm has been reported in some cases, but its incidence is unknown; it may happen in the absence of pulmonary parenchymal or pleural disease.[140]

The treatment consists of discontinuing the medication and providing supportive care. It is not known whether corticosteroids accelerate the resolution. Nitrofurantoin-induced SLE with pleuropulmonary disease and a positive antinuclear antibody test result has also been reported.

Chronic Reaction

There is no clinical overlap between the acute and chronic pulmonary reaction to nitrofurantoin. Chronic reactions are far less common than acute pulmonary reactions. In chronic reactions, fever and eosinophilia are much less common.[139-141] The onset of dyspnea and cough is usually insidious, beginning after 6 months to many years of continuous or intermittent use of nitrofurantoin. Chest imaging shows a diffuse interstitial process. There is no associated bronchospasm or obstructive airway disease. Pulmonary function testing demonstrates a restrictive pattern. BAL usually shows a lymphocytic reaction. Histologic analysis of lung tissue shows inflammatory cells and fibrosis. Clinically, radiologically, and histologically, this condition often mimics other forms of interstitial lung disease, including usual interstitial pneumonia or nonspecific interstitial pneumonia patterns (eFig. 99.11).

The literature on the utility of corticosteroids varies. Our experience is that these drugs are almost always required for significant resolution. Other investigators imply that the opacities resolve spontaneously on discontinuation of the medication.[141] Our policy is to observe the patient for 2 to 4 months after discontinuing nitrofurantoin and then repeat the imaging and pulmonary function studies. If there is no improvement, a trial of corticosteroids is given.[142]

SULFASALAZINE

Sulfasalazine is an antimicrobial drug used for its anti-inflammatory activity.[143] There appear to be two separate types of adverse pulmonary reactions: one is a pulmonary opacity with eosinophilia, and the other is an organizing pneumonia pattern of pulmonary injury. After 1 to 8 months of continuous therapy, patients experience the onset of cough, dyspnea and, in about one-half of cases, fever. The chest radiograph shows a variable pattern of lung opacities, ranging from upper lobe alveolar opacities to a diffuse interstitial process (eFig. 99.12). More than one-half of the patients have significant blood eosinophilia. Resolution is seen within 1 week to 6 months after discontinuing the drug and, if necessary, adding corticosteroids. Sulfasalazine is metabolized to 5-aminosalicylic acid and sulfapyridine, both of which have been implicated in eosinophilic pneumonitis. In cases of suspected sulfasalazine-associated pulmonary disorders, it is important to keep in mind that inflammatory bowel disease has been associated with a variety of pulmonary abnormalities independent of sulfasalazine use. Inflammatory bowel disease has been independently linked to airway inflammation, interstitial lung disease including an organizing pneumonia pattern of pulmonary injury, neutrophilic necrotic pulmonary nodules, and serositis. Most of these disorders respond to corticosteroid therapy.

ILLICIT DRUGS

HEROIN AND METHADONE

Heroin-induced pulmonary edema may be the most common drug-induced pulmonary disease worldwide. There are several postulated mechanisms to explain heroin-induced noncardiogenic pulmonary edema. These include the following: a direct toxic effect on the alveolar-capillary

membrane, leading to an increased permeability and extravasation of fluid into the alveolar spaces; a neurogenic response to central nervous system injury; an allergic or hypersensitivity reaction; and an acute hypoxic effect on the alveolar-capillary membrane in association with secondary increased permeability.

Up to 40% of addicts hospitalized for acute drug overdose have acute pulmonary edema with severe hypoxemia and hypercapnia. The noncardiogenic pulmonary edema is indistinguishable from other forms of ARDS. The pulmonary capillary wedge pressure is usually normal. Typically, symptoms of dyspnea and somnolence begin within minutes of the intravenous "push," but reports of delayed onset of hours and even a few days have been published. The patient hypoventilates and becomes hypoxemic and hypercapnic. The pupils are small. Imaging (see Fig. 133.6) typically shows changes of noncardiogenic pulmonary edema.

Up to one-half of these patients vomit and aspirate, which may complicate interpretation of the chest radiograph and later lead to bacterial infection. Infection should be suspected if the pulmonary opacities do not clear within 24 to 48 hours of treatment. Other pulmonary abnormalities may include septic emboli from infected thrombophlebitis or tricuspid endocarditis. Treatment consists of assisted ventilation using positive end-expiratory pressure, oxygen, and intravenous naloxone to reverse the respiratory depression. This is usually sufficient treatment for the noncardiogenic pulmonary edema, which will reverse with time. Corticosteroids are unnecessary. Appropriate use of antimicrobial drugs is indicated.

Bronchiectasis and necrotizing bronchitis in chronic heroin users have been reported. These may be more likely to be sequelae of recurrent gastric aspiration than of the heroin itself. In long-term users of heroin and other illicit intravenous drugs, pulmonary function abnormalities are more likely to be related to talc granulomatosis (see later) than to sequelae of a single acute injury.

Methadone has been reported to have similar pulmonary effects as heroin. Treatment is the same as for heroin-induced sequelae. Noncardiogenic pulmonary edema has been reported in cases of both oral and intravenous overdose of methadone.

METHYLPHENIDATE

Methylphenidate can be taken either intravenously or orally. In a series of patients who injected methylphenidate, all 22 patients had chest pain and wheezing, and most had abnormal pulmonary function test results and hemoptysis.[144] In another series, severe panlobular emphysema (eFig. 99.13) was found in 7 patients at autopsy.[145]

COCAINE

Cocaine use is associated with increasing reports of adverse pulmonary effects from both intravenous and inhalational use of the drug. These are over and above the known cardiac effects of cocaine, which produces left ventricular failure with pulmonary congestion and edema. The principal effects of cocaine are infection and aspiration, noncardiogenic pulmonary edema (eFig. 99.14), particulate embolization, talcosis, diffuse alveolar damage, diffuse alveolar hemorrhage (eFig. 99.15), intra-alveolar eosinophilic infiltration, lung mass with or without cavitation, and an organizing pneumonia pattern of lung injury (Table 99.3).[146,147]

Table 99.3 Principal Effects of Cocaine on the Lung

Infection and aspiration leading to noncardiogenic pulmonary edema
Particulate embolization
Talcosis
Diffuse alveolar damage
Alveolar hemorrhage*
Intra-alveolar eosinophilic infiltration
Lung mass with or without cavitation
Organizing pneumonia
Vasculitis*

*Also can be caused by the adulterant levamisole.

Illicit drugs such as cocaine are very frequently altered by the addition of other agents. These adulterants are commonly added to cocaine and have also been associated with causing lung disease. Levamisole, a white powder used in veterinary medicine, can add to the bulk of cocaine and may also add to its effects.[148] It has been detected in up to 70–80% of cocaine sources tested. Levamisole can induce an antineutrophil cytoplasmic antibody vasculitis, with pulmonary vasculitis and rarely diffuse alveolar hemorrhage.[149]

TALC GRANULOMATOSIS

Talc (magnesium silicate) and other agents, such as cellulose, are used as fillers in many medications intended for oral use. Addicts who inject oral medications such as meperidine, methadone, methylphenidate, and amphetamines often crush tablets and mix them with various solutions before injecting them intravenously. This results in the insidious onset of granulomatous interstitial fibrosis, granulomatous pulmonary arterial occlusion, or both.[150] In a large series of consecutive autopsies performed on addicts, depending on the type of addiction, the incidence of talc granulomatosis ranged from 15–80%.

Dyspnea is the major symptom, with cough in some patients; in more advanced stages, pulmonary hypertension may manifest with exercise-induced syncope, right-sided heart failure, and even sudden death. Chest radiography may be normal in up to one-half of patients with proven talc granulomatosis. Pulmonary function studies characteristically show a low D_{LCO}. Imaging in patients with injection granulomatosis may show diffuse micronodular densities varying in size between 1 and 3 mm (eFig. 99.16), which may mimic alveolar microlithiasis or hypersensitivity pneumonitis. Pulmonary opacities resulting from injection talcosis may show hyperattenuation on chest CT (eFig. 99.17). Therapy with corticosteroids provides little consistent improvement.

Histologically, the pulmonary tissue demonstrates granulomatous changes, with multinucleated giant cells, mononuclear inflammatory cells, lymphocytes, and fibrosis. Talc is detected by the presence of strongly birefringent crystals

(using polarized light) within the granulomas (eFig. 99.18). BAL fluid shows increased lymphocytosis and sometimes contains intracellular and free talc.

CARDIOVASCULAR DRUGS

ANGIOTENSIN-CONVERTING ENZYME INHIBITORS

Angiotensin-converting enzyme (ACE) inhibitors are widely used for control of hypertension and congestive heart failure. Dry cough develops in 5–20% of patients on ACE inhibitors and is reported with virtually all ACE inhibitors. The mechanism of ACE inhibitor–induced cough likely involves accumulation of kinins and substance P, which are normally degraded by ACE and other endopeptidases. The cough generally is reported in the first few weeks after beginning therapy but may not be appreciated for several months. ACE-induced cough is usually benign but can be quite annoying, and it causes the discontinuation of these agents in one-half of the patients affected. Exacerbation of bronchospasm has been rarely associated with ACE inhibitors. Cough generally abates within 4 days of discontinuation of the agent, thus providing confirmation of the diagnosis. Rechallenge with a different ACE antagonist is not recommended because cough usually returns. Of note, selective angiotensin receptor antagonists have much lower incidence of dry cough compared with ACE inhibitors and may represent a therapeutic option for many patients.

Compared with cough, angioedema from ACE inhibitors is much less common, arising in 0.1–0.2% of patients. This complication usually arises within hours to, at most, 1 week after initiating therapy, and it can be life-threatening. Treatment is supportive and consists of airway protection. Although frequently used, epinephrine, antihistamines, and corticosteroids are of unclear value. The ACE inhibitor must be discontinued and future use avoided.

AMIODARONE

Amiodarone has significant benefit for ventricular and supraventricular dysrhythmias in patients who do not respond to other antiarrhythmic agents. This drug is associated with certain side effects, which include the following: corneal microdeposits; peripheral neuropathy; liver dysfunction; thyroid dysfunction, including hypothyroidism and hyperthyroidism; and bluish pigmentation of the skin. The most serious side effect is interstitial pneumonitis, which develops in up to 6% of patients and may be fatal.

The toxicity is dose related and has distinctive histologic features. The histologic findings generally include foamy alveolar macrophages and alveolar epithelial type 2 cells containing lamellar inclusions. The incidence of pulmonary toxicity from amiodarone varies widely but probably averages 4–6% of those patients.[11,151] Symptoms consist of insidious dyspnea, nonproductive cough, and occasionally a low-grade fever without chills, followed by subtle chest radiographic findings, which initially may be asymmetrical or even limited to the upper lobes. If the drug is continued, the process may diffusely involve the lungs with an interstitial or alveolar process. Pleural effusion is uncommon. Pleuritic chest pain exists in approximately 10% of patients. Crackles may be heard, but it is difficult to be certain whether these are caused by pulmonary edema during congestive heart failure. In approximately 20% of patients with amiodarone pneumonitis, the presentation is acute, mimicking pneumonia (eFig. 99.19).

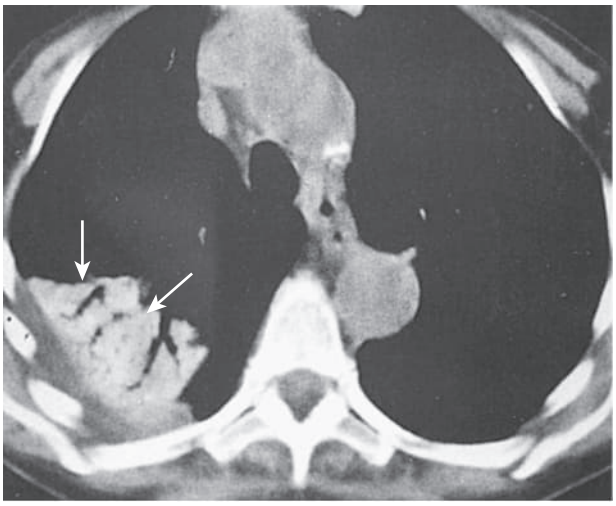

Fig. 99.6 Amiodarone-induced lung disease. A chest computed tomography scan showing confluent pulmonary masses *(arrows)* from amiodarone pneumonitis. Note that the masses are appreciably denser than the surrounding soft tissue in the chest wall in this scan without contrast; the reason for the increased density is that amiodarone is iodinated and thus is radiopaque.

On laboratory studies, there is a normal to mildly elevated leukocyte count, generally no eosinophilia, and an elevated sedimentation rate, with little or no reactivity to antinuclear antibody. Pulmonary function studies disclose a decrease in the total lung capacity and $D_{L_{CO}}$, as well as hypoxemia. There may be an increased predisposition to amiodarone pneumonitis if either pulmonary function test results or imaging studies are abnormal before administration of the drug.

Most patients who develop amiodarone pneumonitis have been taking the drug for at least a month, and some for a few years. Most are receiving at least 400 mg/day. However, there have been some reports of amiodarone pneumonitis in patients taking as little as 200 mg/day. There are also reports of patients receiving 200 mg/day for months or years and not developing amiodarone pneumonitis until the dose is boosted for better control of the arrhythmia. Generally, the systemic side effects of amiodarone, such as peripheral neuropathy and liver dysfunction, correlate with the serum levels, but this is not necessarily the case with pulmonary toxicity. The diagnosis of amiodarone pneumonitis is one of exclusion.

Normally, amiodarone pneumonitis is thought to be primarily an interstitial or alveolar process (or both) sometimes mimicking eosinophilic pneumonitis with peripheral opacities (eFig. 99.20), but some reports have noted confluent lesions and other patterns. Many of these lesions represent an organizing pneumonia injury pattern (eFig. 99.21A–B; see also eFig. 99.23D).[152,153] Chest CT imaging can further define these processes because amiodarone, being an iodinated compound, is radiopaque and, on a CT scan, the amiodarone pneumonitis lesions are denser than the surrounding soft tissue in the chest wall (Fig. 99.6, eFig. 99.22). This finding may help support the diagnosis.

Table 99.4 Drugs or Treatment Associated With the Induction of Organizing Pneumonitis

Amiodarone	Mitomycin C
Bleomycin	Nivolumab
Cocaine	Pembrolizumab
Cyclophosphamide	Penicillamine
Gold	Radiation
Interferons	Sulfasalazine
Methotrexate	

Treatment consists of drug withdrawal and leads to a variety of responses. Some patients who were not treated with corticosteroids have died of pulmonary fibrosis and respiratory failure. Others have died in spite of corticosteroids. The majority respond to discontinuation of the drug and addition of corticosteroids (see eFigs. 99.19 and 99.21), which are usually required for a period of at least 2 months and perhaps 6 months or longer. There are many case reports of patients who continued on amiodarone because it was the only drug that controlled their arrhythmia and who were given corticosteroids to suppress their pneumonic reaction.[154]

Tissue confirmation is occasionally needed to establish a diagnosis, although stopping the drug and adding corticosteroids may offer a presumptive diagnosis if the process clears. BAL produces variable results.[11] The presence of foamy macrophages in lavage fluid or on biopsy confirms exposure to the drug, whereas their presence alone does not necessarily indicate amiodarone toxicity. However, their absence does exclude the diagnosis. Although not used frequently in recent years, a positive gallium scan can be highly suggestive of an inflammatory pneumonitis rather than heart failure. If the diagnosis has not been established, the clinician must decide whether to proceed with a lung biopsy to rule out other disease processes or to consider diminishing the dose or discontinuing the drug, or adding corticosteroids, or both. A lung biopsy usually reveals the foamy macrophages and epithelial cells, as well as variable inflammatory cell infiltration (eFig. 99.23). The histopathologic patterns of amiodarone-induced pulmonary injury vary, and the most common pattern of injury is cellular interstitial pneumonia (see eFig. 99.23). However, some patients may exhibit an organizing pneumonia injury pattern (Table 99.4, see eFig. 99.23D). Reductions in the erythrocyte sedimentation rate following discontinuation of amiodarone or reduction of the dosage may help support the diagnosis.

There are reports that patients receiving amiodarone can develop postoperative ARDS, an injury that begins 18 to 72 hours after surgery.[155,156] In a population-based study, amiodarone was responsible for approximately 2.7% of cases of acute lung injury. It has been postulated that the high fraction of inspired oxygen given during the operation and postoperative period contributes to this complication.

β-ADRENERGIC ANTAGONISTS

β-Adrenergic antagonists are among the most commonly prescribed drugs. β-Adrenergic receptors can be divided into excitatory β_1-receptors, located in the heart, and inhibitory β_2-receptors, located in the bronchi. The β-adrenergic blockers, or β-blockers, are competitive antagonists.

Propranolol was the first β-adrenergic antagonist introduced. It was quickly recognized to have adverse effects on individuals with known obstructive lung disease, and was shown to increase airway resistance in patients with nonasthmatic COPD.[157] Thus, this agent should be avoided in patients with known obstructive lung disease when possible. The following β-adrenergic antagonists, presented in decreasing order of bronchoprovocation potential, are available for clinical use in the United States: propranolol, timolol, nadolol, metoprolol, atenolol, and labetalol.[158]

Two features of β-adrenergic antagonists predict their potential for bronchoprovocation: their cardioselectivity and their intrinsic sympathomimetic activity. Generally, cardioselectivity is the more important of the two in avoiding bronchoconstriction; if the drug is cardioselective, it has little effect on the inhibitory β-receptors located in the bronchial walls. Propranolol, timolol, and nadolol have essentially no cardioselectivity and thus a higher bronchoprovocation potential. Metoprolol has some cardioselectivity, and atenolol and labetalol have considerable cardioselectivity, making them the drugs of choice in an individual with obstructive airway disease who needs a β-adrenergic antagonist. Thus, among the drugs listed, atenolol and then metoprolol or labetalol are the three that can be used with relative safety in persons with obstructive lung disease, if absolutely necessary. However, these drugs should always be given in conjunction with an aerosolized β_2-adrenergic agent.

The same findings have been described in asthmatic patients receiving timolol eye drops for glaucoma.[159] Topically applied timolol is absorbed through the conjunctiva and bypasses the liver, thus resulting in a higher serum concentration than when given orally. A novel ocular β-adrenergic antagonist, betaxolol, has been shown to be safer in patients with known airway disease. There are scattered reports of β-blocker–associated interstitial pneumonitis.[160] Propafenone is an additional membrane-stabilizing antiarrhythmic agent that is structurally similar to propranolol and has the potential to aggravate bronchospasm.[161]

TOCAINIDE AND FLECAINIDE

Tocainide is used in the treatment of refractory ventricular arrhythmias. There are more than 100 known cases of acute interstitial pneumonitis beginning 3 weeks to several months after initiation of therapy.[162] The response to discontinuing the drug is good; corticosteroids may be necessary in some cases.

Flecainide, another antiarrhythmic agent, has been reported to be associated with ARDS and interstitial lymphocytic pneumonitis.[35,163]

ANTI-INFLAMMATORY AGENTS

ASPIRIN

Anti-inflammatory agents are among the most commonly used drugs, and many have pulmonary side effects. Aspirin is the most commonly used drug in the world. It is estimated that up to 5% of asthmatic patients are sensitive to

aspirin; ingestion may cause fatal aggravation of bronchospasm.[164] The exact cause of aspirin-sensitive asthma is unknown. One theory is that, by inhibiting cyclooxygenase, aspirin and similar compounds prevent the generation of cyclooxygenase products such as the prostaglandins. If certain individuals are reliant on the bronchodilator activity of prostaglandins such as prostaglandin E_2, then prostaglandin inhibition could cause bronchospasm. The aspirin-asthma triad consists of asthma, rhinitis, and nasal polyposis. Almost always there are other associated side effects, such as cutaneous rashes and gastrointestinal symptoms. These adverse reactions are not dose related and can develop with very small doses. Salicylates can induce noncardiogenic pulmonary edema in cases of overdose when the serum salicylate level is greater than 40 mg/dL.

OTHER NONSTEROIDAL ANTI-INFLAMMATORY DRUGS

Most of the nonsteroidal anti-inflammatory agents can produce the same side effects as aspirin, including aggravation of asthma, noncardiogenic pulmonary edema, drug-induced SLE, and pulmonary opacities with eosinophilia.[165] A few agents can cause hypervolemia and, in turn, pulmonary edema through the mechanism of increased sodium retention through the kidneys.

PENICILLAMINE

Penicillamine is used to treat Wilson disease, rheumatoid arthritis, and cystinuria and has been associated with pulmonary toxicity. There are three possible pulmonary complications with the use of penicillamine, with no apparent overlap: penicillamine-induced SLE, bronchiolitis obliterans, and *anti–glomerular basement membrane disease* (anti-GBM disease; formerly Goodpasture syndrome). Penicillamine-induced SLE may induce pneumonitis, alveolitis, and sometimes pleural effusion. Penicillamine-associated bronchiolitis obliterans is probably underestimated in its incidence and severity. Corticosteroids have little benefit in treating this condition, which usually manifests in an advanced state. There have also been several reports of penicillamine-associated anti-GBM disease with diffuse alveolar hemorrhage.[166] If this disorder is recognized early enough, appropriate therapy with hemodialysis, plasmapheresis, and immunosuppression may prevent a serious outcome.

LEFLUNOMIDE

Leflunomide is currently used to treat rheumatoid arthritis and psoriatic arthritis. It is a pyrimidine synthesis inhibitor, which exerts mainly an immunomodulating effect, although it was also found to exert significant anti-inflammatory effects. Its main described adverse effect is liver toxicity, and it may act synergistically with methotrexate. Several patterns of lung injury have been observed with leflunomide, mostly consisting of hypersensitivity reactions. In postmarketing surveillance, significant lung toxicity was identified in 61 of 5053 patients, with 24 patient deaths directly related to pulmonary complications.[166a] Preexisting lung disease and, to a lesser degree, loading dose, a smoking history, and low body weight were identified as independent risk factors for lung toxicity. A case-control study also showed a higher incidence of lung toxicity in patients with prior lung disease but suggested that the reason was that higher-risk patients were more likely to receive leflunomide.[167] True hypersensitivity pneumonias have also been reported in case series, as defined by interstitial opacities associated with ill-defined granulomas.[168] Nonspecific opacities with or without eosinophilia have also been reported. Diffuse alveolar hemorrhage and pulmonary alveolar proteinosis are rarely encountered. Cholestyramine washout therapy has been shown to treat leflunomide-induced pneumonitis; oral cholestyramine binds the drug and its metabolites, removes them from the body, and greatly shortens their otherwise long half-life.[169]

BIOLOGIC AGENTS

These agents have revolutionized the management of chronic inflammatory conditions such as rheumatoid arthritis, inflammatory bowel disease, and psoriasis. *Anti–tumor necrosis factor-α* (anti–TNF-α) medications such as infliximab (a chimeric monoclonal antibody targeting TNF-α), etanercept (a soluble TNF-α receptor), or adalimumab (recombinant monoclonal antibody targeting TNF-α) have been used in these conditions.

Not unexpectedly, infections are a major complication of these treatments. Tuberculosis, in particular, may easily reactivate in a context of impaired immunity. Tuberculosis skin tests or interferon-γ release assays for *Mycobacterium tuberculosis* are mandatory before treatment begins. Other opportunistic infections, including fungal lung infections, are also described with these agents.

Multiple patterns of lung injury have been described with infliximab, including acute hypersensitivity reactions with or without eosinophilia, nonspecific interstitial pneumonitis, lung fibrosis, or exacerbation of rheumatoid arthritis–associated usual interstitial pneumonia and vasculitis.[170]

Etanercept and adalimumab (eFig. 99.24) have also been described in association with pulmonary fibrosis, but these associations are relatively weak.[171,172] Etanercept has also been associated with pulmonary granulomatous inflammation.[173]

LEUKOTRIENE ANTAGONISTS

The leukotriene antagonists, zafirlukast, montelukast, and pranlukast, have been associated with *eosinophilic granulomatosis with polyangiitis* (EGPA).[174-176] A systematic review of the cases reported in the literature identified 62 cases of EGPA after initiation of leukotriene antagonists.[176] Although some of the patients may have had preexisting EGPA, many demonstrated a temporal relationship with the leukotriene antagonist.[176] Because these agents are added to a treatment regimen for asthma, corticosteroids are frequently tapered, thus suggesting that some of the effects are actually the result of tapering the corticosteroids. However, a few of these reported patients were not receiving oral or inhaled corticosteroids at the time the medication was added. EGPA has developed 6 to 18 months after initiation of these drugs. Remission of the signs and symptoms have been noted on removal of the leukotriene antagonist with or without escalation of corticosteroids.[176] The pulmonary reaction usually responds to discontinuation of the leukotriene antagonist and reinstitution of corticosteroids.

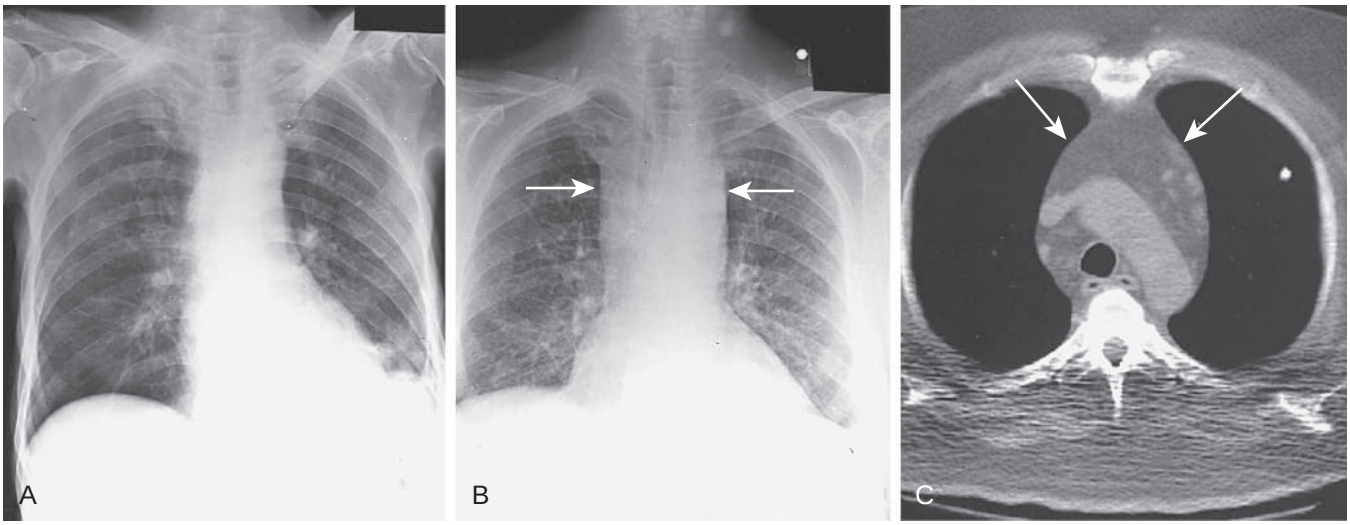

Fig. 99.7 Mediastinal lipomatosis in response to corticosteroids. (A) Chest radiograph before systemic corticosteroid administration. (B) Chest radiograph after corticosteroid administration shows a widened mediastinum *(arrows)*. (C) Chest computed tomography scan shows mediastinal lipomatosis, with radiographic fat density *(arrows)* surrounding the great vessels and tracheal shadows.

CORTICOSTEROIDS

Corticosteroids are well known for predisposing to opportunistic infections. A most unusual adverse effect of corticosteroids is mediastinal lipomatosis, the deposition of mediastinal fat, which produces a widening of the mediastinum that mimics lymphadenopathy or other neoplasms (Fig. 99.7). The chest radiograph does not show the lumpiness usually expected with adenopathy. Chest CT can usually make this diagnosis by establishing fat density throughout the mediastinal mass. Mediastinal lipomatosis does not necessitate tapering corticosteroids because the fat does not compromise vital structures.

DRUG-INDUCED SYSTEMIC LUPUS ERYTHEMATOSUS

Of more than 75 drugs associated with SLE, only five regularly induce antinuclear antibodies (hydralazine, procainamide, isoniazid, phenytoin, and penicillamine), and only a few patients taking these drugs develop the clinical lupus-like syndrome.[176a] It is thought that patients who develop antinuclear antibodies to these drugs are *slow acetylators,* with a slower rate of metabolism of the offending drug. Symptoms almost always begin insidiously after the patient has been taking the drug for many months or years. Systemic signs and symptoms of polyarthralgia, myalgia, fever, pleurisy, and cutaneous lesions are common. Renal disease is uncommon in the drug-induced form of SLE.

The antinuclear antibody assay is positive in all patients with drug-induced SLE. However, the test result for antinative (anti–double-stranded) DNA is negative. The complement level may or may not be abnormal. An elevated erythrocyte sedimentation rate and hypergammaglobulinemia are common nonspecific findings.

The chest radiographic findings of the drug-induced form of the disease are indistinguishable from spontaneous-onset SLE and include pleural effusions, basilar opacities, pneumonitis with atelectasis, and apparent cardiomegaly from pericardial effusion. Pleural fluid glucose is normal or at least correlates with the blood glucose levels. The symptoms usually resolve once the drug is discontinued. However, occasionally it is necessary to add corticosteroids.

OXYGEN

Exposure to high concentrations of oxygen may contribute to or aggravate ARDS. High fractions of inspired oxygen induce formation and release of free oxidant radicals. These short-lived molecules damage DNA, destroy lipid membranes, and inactivate intracellular enzymes.[177] Hyperoxia can also produce direct injury to endothelial cells and alveolar epithelial type 1 cells that results in alveolar-capillary leak.[178] Studies in volunteers breathing 100% oxygen for 24 hours produced variable effects, but some participants developed tracheobronchitis, with symptoms of substernal burning, chest tightness, nonproductive cough, and reduction in vital capacity and D_{LCO}.[179]

The sequelae of oxygen toxicity are separable into two phases, the acute exudative phase and the subacute proliferative phase. However, there is considerable overlap between the two phases. The exudative phase begins within 48 to 72 hours, depending on the fraction of inspired oxygen, and is associated with perivascular, interstitial, and alveolar edema with atelectasis, as well as alveolar hemorrhage. This phase appears to be reversible.

The proliferative phase begins after the fourth to seventh day and is characterized by progressive resorption of exudates and hyperplasia of alveolar epithelial type 2 cells. This is followed by the deposition of collagen and elastin in the interstitium and hyaline membrane deposition. This is usually an irreversible phase. Clinically, hypoxemia and diminished compliance progress, requiring a greater fraction of inspired oxygen with assisted ventilation, thus further aggravating the problem. Imaging shows an alveolar-interstitial pattern in an irregular distribution, with evidence of moderate loss of volume from patchy atelectasis.

There is no clinical way of diagnosing oxygen toxicity. A lung biopsy specimen may show changes consistent with

oxygen toxicity, but the primary value of the biopsy is to exclude other causes of lung injury. Keeping the arterial partial pressure of oxygen at less than 80 mm Hg or the inspired fraction of oxygen to less than 0.40 to 0.50 minimizes the likelihood of oxygen toxicity. Barotrauma and ventilator-induced injury may accompany and be indistinguishable from oxygen toxicity

MISCELLANEOUS DRUGS AND AGENTS

TOCOLYTIC-INDUCED PULMONARY EDEMA

Tocolytic drugs are agents that have been widely used in the treatment of premature labor. The most commonly used drugs are terbutaline, albuterol, ritodrine, and other β-mimetic drugs. There are many reports of these agents inducing pulmonary edema in otherwise healthy women. The incidence varies from 0.5–5%. Predisposing factors include the use of corticosteroids, twin gestation, fluid overload (particularly with saline), and anemia. The β-mimetic drugs typically stimulate β_2-adrenergic receptors, increase the maternal pulse rate and cardiac output, and produce peripheral vasodilation. Hemodilution can be detected by a drop in the hemoglobin, hematocrit, and albumin values. The blood pressure may drop as a result of the peripheral vasodilation.

A typical clinical scenario is as follows. In spite of the tocolytic agent, labor continues; the tocolytic agent is then stopped, and corticosteroids are added to accelerate fetal lung maturation. With the discontinuation of the tocolytic, the vasodilated vessels return to normal tone. During delivery, uterine contractions lead to autotransfusion. The increased venous tone and the increased blood volume can then lead to pulmonary edema, usually in the postpartum period.

The treatment consists of oxygen and diuresis. In certain cases, consideration has been given to resuming the tocolytic agent to recreate the previous peripheral vasodilation. Corticosteroids aggravate the situation by their mineralocorticoid effect, which promotes fluid retention. The differential diagnosis includes aspiration of gastric contents, left-sided heart failure, amniotic fluid embolism, and excessive transfusion.

HYDROCHLOROTHIAZIDE

Some cases of acute onset of diffuse pulmonary opacities are associated with hydrochlorothiazide.[180] It may begin with the first dose or days later; 90% of cases have been reported in women who take the drug intermittently rather than daily, presumably for fluid retention. Symptoms consist of fairly rapid onset of dyspnea that clears 48 to 72 hours after discontinuing the drug. A low-grade fever may be present. Eosinophilia and antinuclear antibodies are not present. The chest radiograph shows diffuse bilateral alveolar-interstitial opacities.

METHYSERGIDE, BROMOCRIPTINE, AND CABERGOLINE

Methysergide, bromocriptine, and cabergoline are structurally similar and produce similar pleuropulmonary reactions. Methysergide is now rarely used to treat vascular headaches because better alternative drugs are available. Bromocriptine and cabergoline have been used for Parkinson disease. The pleuropulmonary disease produced by both these agents has an insidious onset. The predominant features are pleural thickening and effusion, which are reversible by discontinuing the medication. Effusions are rarely large, are not commonly associated with pleuritic pain, and may show lymphocytosis.[181]

AMPHETAMINERGIC AGENTS

In the 1960s, excess cases of pulmonary hypertension were associated with the potent anorexigen, aminorex fumarate. More recently, pulmonary hypertension has been associated with dexfenfluramine, fenfluramine, and phenteramine.[182] Valvular heart disease has also been associated with these agents.[183] A careful drug history must be taken to exclude this possibility in patients presenting with dyspnea, cardiovascular symptoms, or heart murmurs because manifestations typically persist despite discontinuation of the drugs. A retrospective study of 340 patients with pulmonary hypertension identified a history of stimulant use in 29%; drugs included methamphetamine, amphetamine, and cocaine, thus emphasizing the importance of seeking a drug history that may not be easily volunteered by the patients.

Key Points

- The frequency of drug-induced pulmonary toxicity may be underestimated because the diagnosis is one of exclusion in most cases. Clinicians must maintain a high index of suspicion that unexplained pulmonary disease may be caused by medications.
- Most associations are based on anecdotal reports and circumstantial evidence.
- Potential mechanisms of lung injury include (1) oxidative injury, (2) direct cytotoxic effect, (3) accumulation of phospholipids, and (4) immune-mediated injury.
- Chemotherapy-induced lung toxicity should always be considered in the differential diagnosis of diffuse lung opacities because virtually all histopathologic presentations have been described.
- Even when cumulative toxicity is an issue, screening with serial imaging or physiologic studies is rarely helpful.
- Most drug-induced pulmonary reactions are reversible if the drug is stopped. If necessary, additional measures such as judicious use of corticosteroids may be helpful.
- Rechallenging the patient with the suspected drug is often dangerous and is generally not indicated.
- Many additional medications, more than space permits in this chapter, are associated with respiratory toxicities. If there is a question about whether a medication may be the cause of a particular pulmonary abnormality, one option is to call the medical director of the drug manufacturer, listed in the *Physicians' Desk Reference.* In addition, a useful online resource can be accessed at http://www.pneumotox.com.

Key Readings

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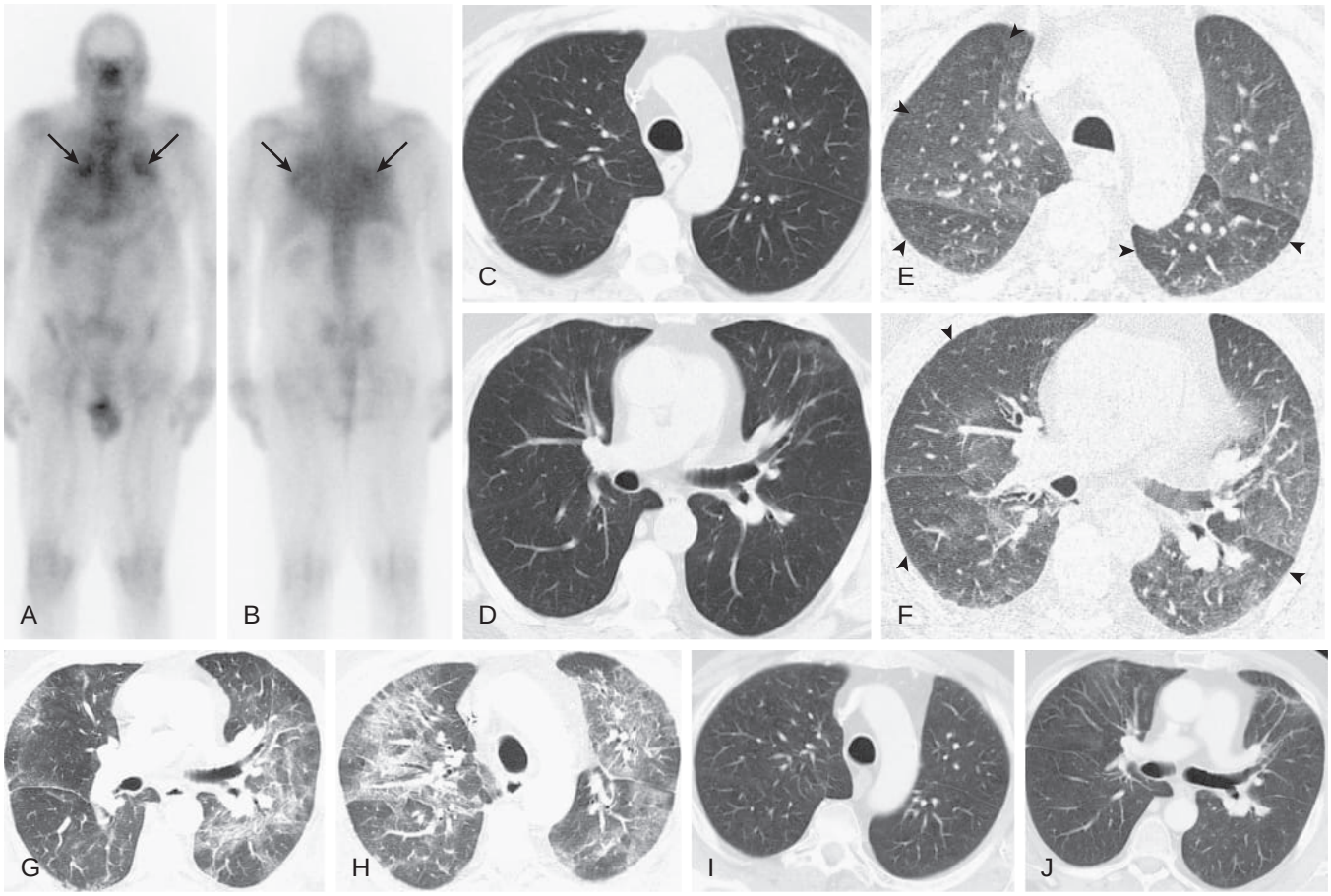
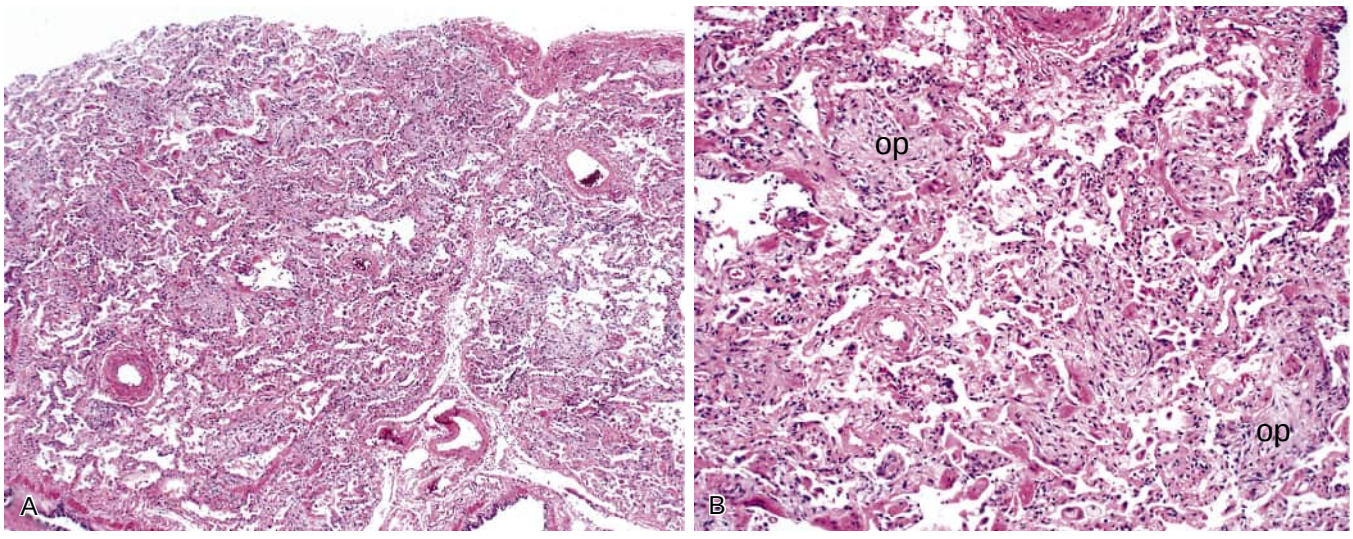
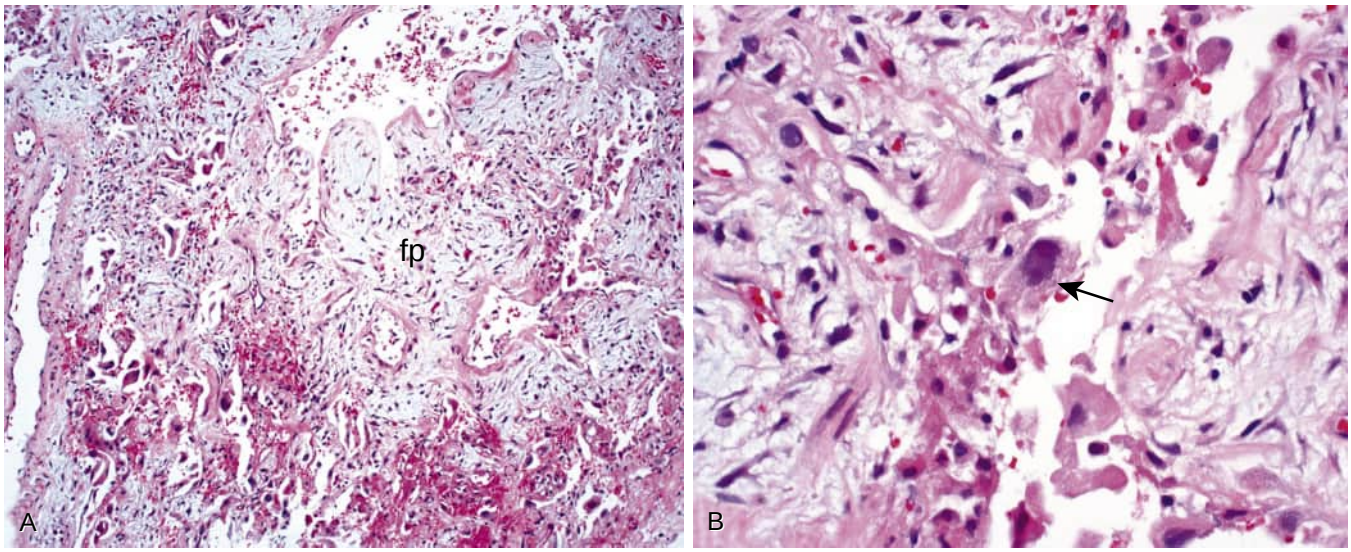


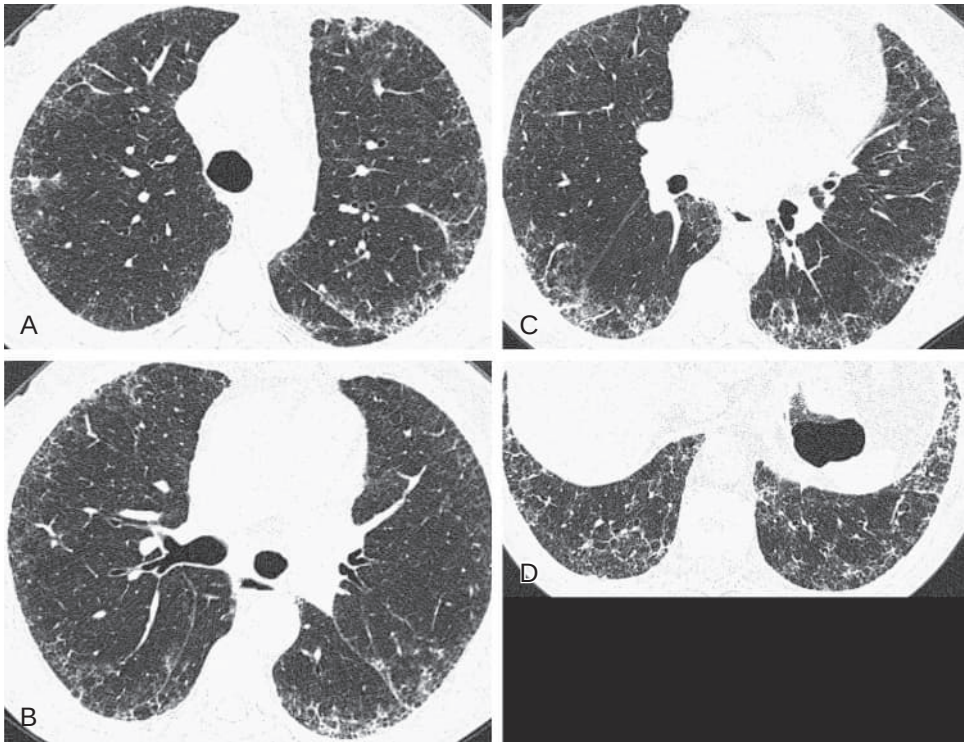
eFigure 99.1 Bleomycin-induced lung injury; hypersensitivity reaction. Anterior (A) and posterior (B) planar gallium-68 scintigraphic images in a patient with Hodgkin lymphoma treated with bleomycin shows increased uptake in the lungs *(arrows)* in a symmetrical, bilateral distribution. (C–F) Axial chest computed tomography obtained at the same time as the nuclear study (A–B) shows little evidence of an infiltrative abnormality on inspiratory images (C–D). On expiratory imaging, areas of decreased lung attenuation (E–F, *arrowheads*) are evident, representing air trapping and suggesting a small airway obstructive process. This pattern suggests bronchiolitis obliterans but can rarely be seen with hypersensitivity reactions. (G–H) Axial chest computed tomography obtained 2 weeks following (C–F) shows interval development of multifocal, bilateral areas of ground-glass opacity and reticulation; this pattern is consistent with an acute lung injury pattern, although the presence of the small airway obstruction, as shown on the initial computed tomography (C–F), suggests a combined infiltrative and obstructive disorder, which is typical of a hypersensitivity reaction. Evaluation for infection and pulmonary hemorrhage was unrevealing. (I–J) Axial chest computed tomography following withdrawal of bleomycin, obtained 4 months after (C–F), shows clearing of the infiltrative lung opacity with minimal anterior lung scarring remaining. (Courtesy Michael B. Gotway, MD.)



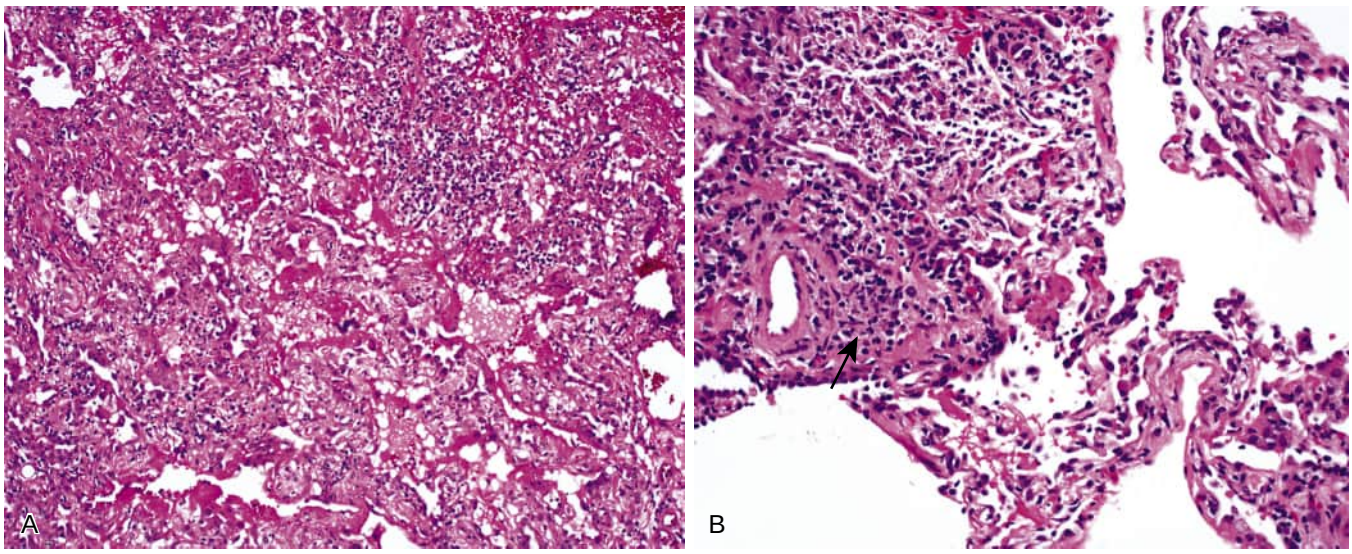
eFigure 99.2 Histopathologic patterns of bleomycin-induced pulmonary injury. (A) Diffuse alveolar damage from bleomycin toxicity. (B) Reactive alveolar epithelial type 2 cells and organizing pneumonia *(op)* are commonly found. (From Cheung Y, Graziano P, Leslie KO. Acute lung injury. In: Leslie KO, Wick MR, eds. *Practical Pulmonary Pathology: A Diagnostic Approach: A Volume in the Pattern Recognition Series.* 2nd ed. Philadelphia: Elsevier; 2011:117–137.)



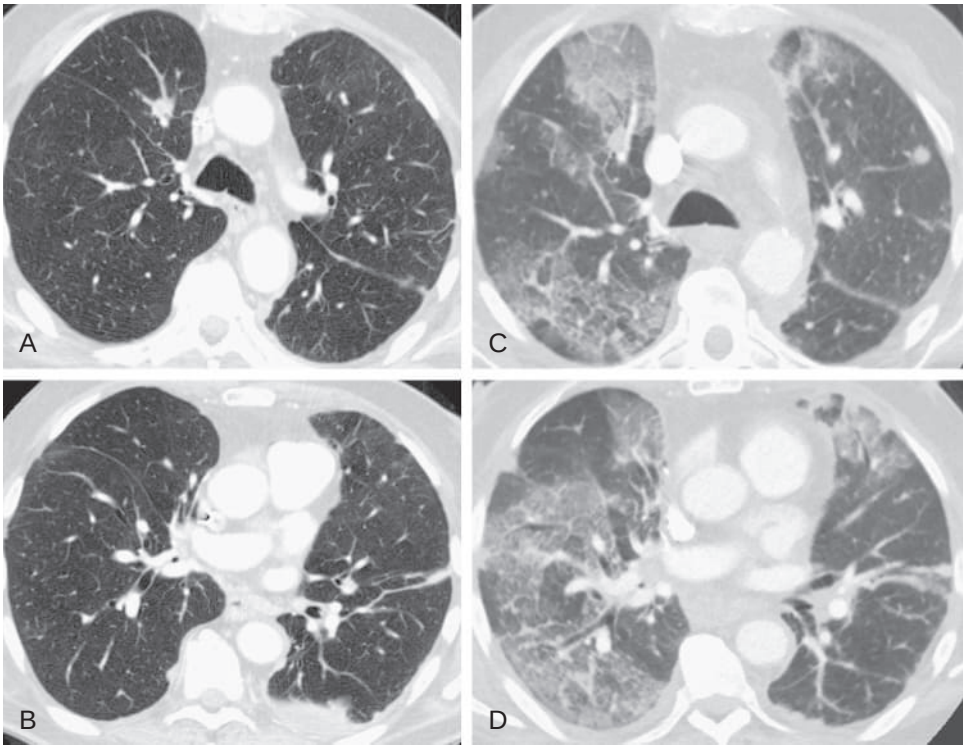
eFigure 99.3 Diffuse alveolar damage from busulfan toxicity. (A) Busulfan can produce diffuse injury characterized by the presence of prominently atypical alveolar epithelial type 2 cells. In this case, prominent interstitial organization with edematous fibroblastic proliferation *(fp)* is seen, and hyaline membranes are evident. (B) Reactive alveolar epithelial type 2 cells may appear alarmingly atypical *(arrow)*. (From Cheung Y, Graziano P, Leslie KO. Acute lung injury. In: Leslie KO, Wick MR, eds. *Practical Pulmonary Pathology: A Diagnostic Approach: A Volume in the Pattern Recognition Series.* 2nd ed. Philadelphia: Elsevier; 2011:117–137.)



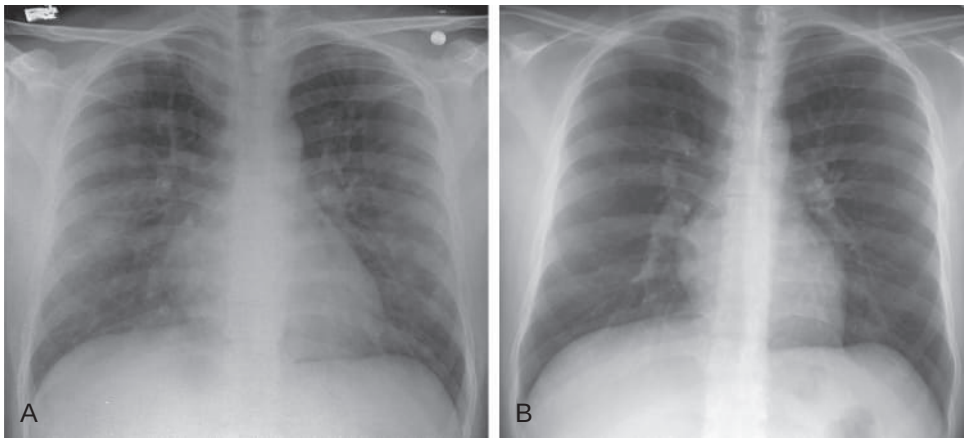
eFigure 99.4 Methotrexate-induced lung injury; non-specific interstitial pneumonia pattern. (A–D) Axial chest computed tomography in a patient receiving methotrexate shows bilateral basal and peripheral predominant linear and reticular abnormalities associated with architectural distortion and mild traction bronchiolectasis; the pattern resembles fibrotic nonspecific interstitial pneumonia. (Courtesy Michael B. Gotway, MD.)



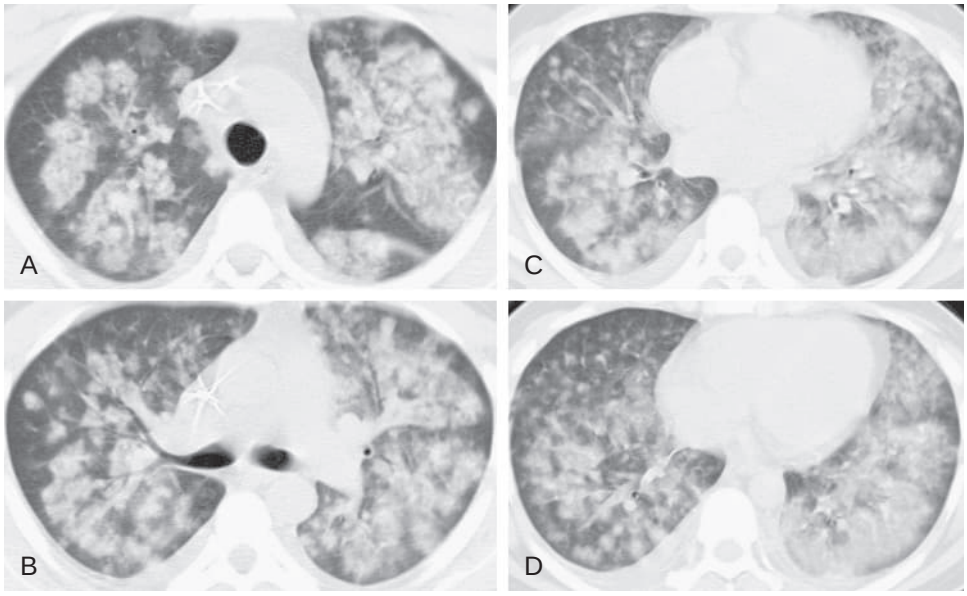
eFigure 99.5 Diffuse alveolar damage from methotrexate toxicity. (A) Methotrexate produces small, poorly formed granulomas in subacute and chronic manifestations of lung toxicity. (B) Early aggregations of macrophages may be seen resembling poorly formed granulomas in cases in which diffuse alveolar damage is the manifestation of injury, but these are not required for the diagnosis *(arrow).* (From Cheung Y, Graziano P, Leslie KO. Acute lung injury. In: Leslie KO, Wick MR, eds. *Practical Pulmonary Pathology: A Diagnostic Approach: A Volume in the Pattern Recognition Series.* 2nd ed. Philadelphia: Elsevier; 2011:117–137.)



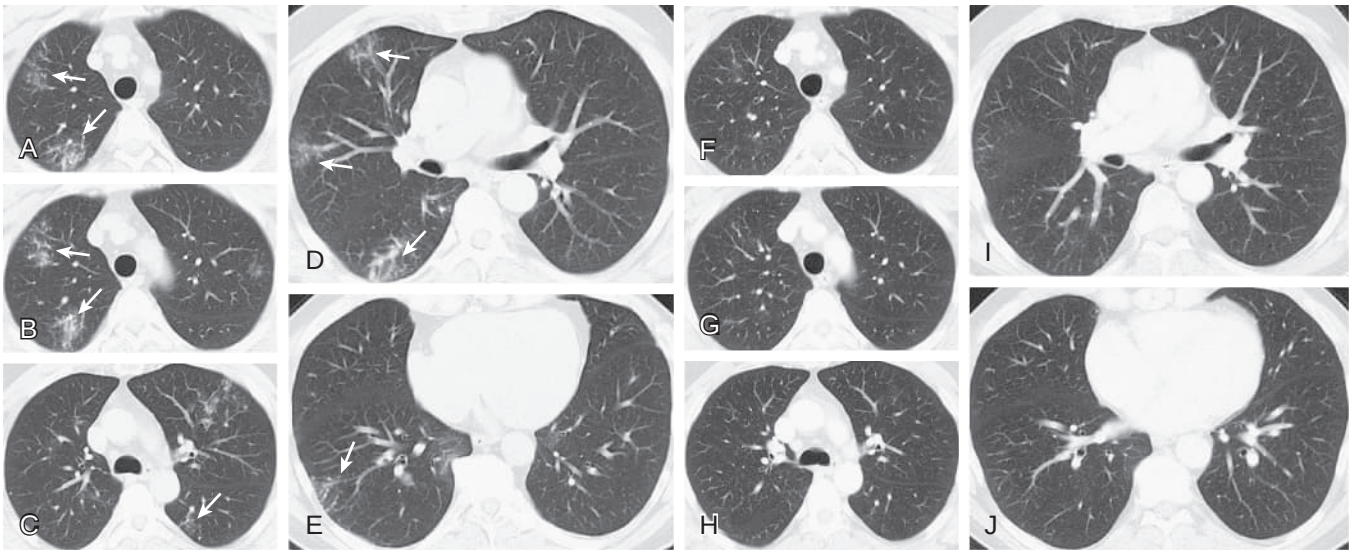
eFigure 99.6 Paclitaxel-induced pulmonary injury. (A–B) Axial chest computed tomography in a patient with non–small cell lung carcinoma at the onset of paclitaxel therapy. (C–D) Axial chest computed tomography performed 2 weeks following initiation of paclitaxel therapy shows interval development of multifocal ground-glass opacity associated with reticulation. No evidence of infection or pulmonary hemorrhage could be found. The computed tomography appearance is consistent with an acute lung injury pattern. (Courtesy Michael B. Gotway, MD.)



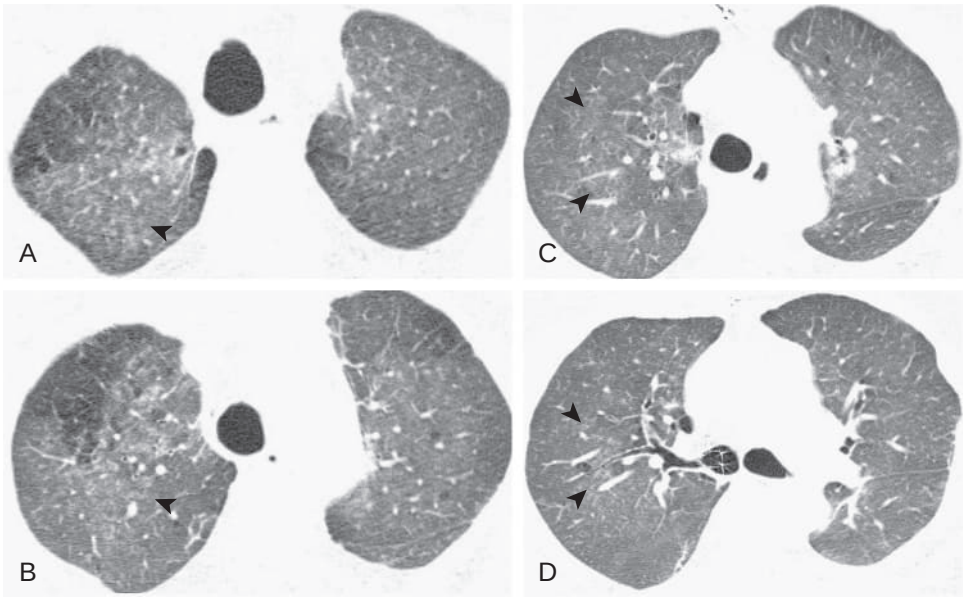
eFigure 99.7 All-*trans* retinoic acid syndrome in a patient treated for acute promyelocytic leukemia: chest radiographic findings. (A) Frontal chest radiograph performed shortly following initiation of therapy, when the patient developed renal insufficiency and peripheral edema, shows multifocal bilateral opacities consistent with an acute lung injury, or "capillary leak," pattern. (B) Frontal chest radiograph following withdrawal of therapy and corticosteroid treatment shows resolution of findings. (Courtesy Michael B. Gotway, MD.)



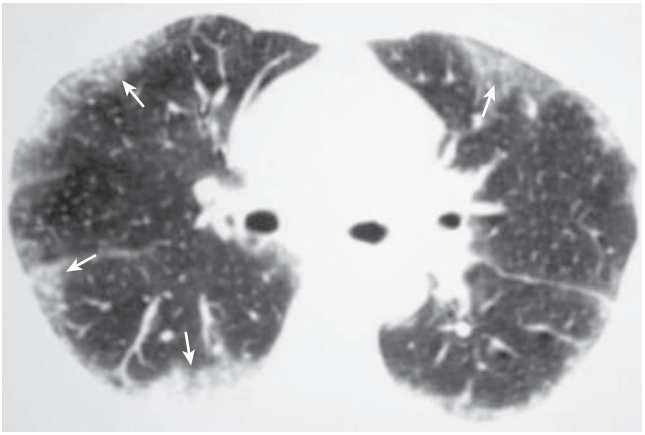
eFigure 99.8 All-*trans* retinoic acid syndrome in a patient treated for acute promyelocytic leukemia: chest computed tomography findings. (A–D) Axial chest computed tomography displayed in lung windows shows multifocal, bilateral areas of nodular ground-glass opacity resembling pulmonary hemorrhage, although no hemorrhage was found at bronchoscopy. The pattern is nonspecific but consistent with acute lung injury. The abnormalities resolved following cessation of all-*trans* retinoic acid therapy and corticosteroid treatment, and no infection was ever found. (Courtesy Michael B. Gotway, MD.)



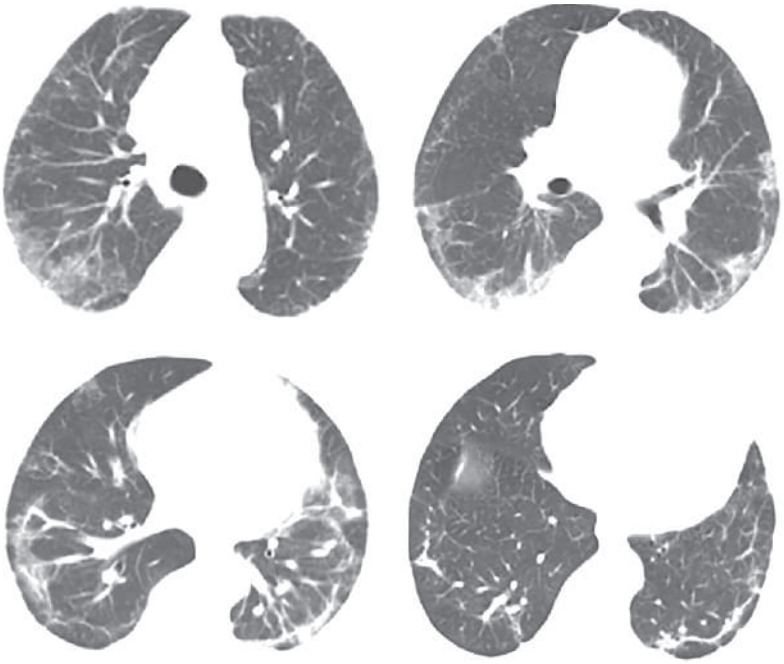
eFigure 99.9 Interferon-induced sarcoid-like reaction. (A–E) Axial chest computed tomography in a patient with renal cell carcinoma treated with interferon-alfa shows multifocal, bilateral, patchy nodules *(arrows)* distributed along the bronchovascular bundles and fissural surfaces, typical of the appearance of sarcoidosis. No infectious cause was found, and the findings worsened on repeat evaluation. (F–J) Axial chest computed tomography performed following withdrawal of interferon-alfa therapy shows resolution of the small nodules. (Courtesy Michael B. Gotway, MD.)



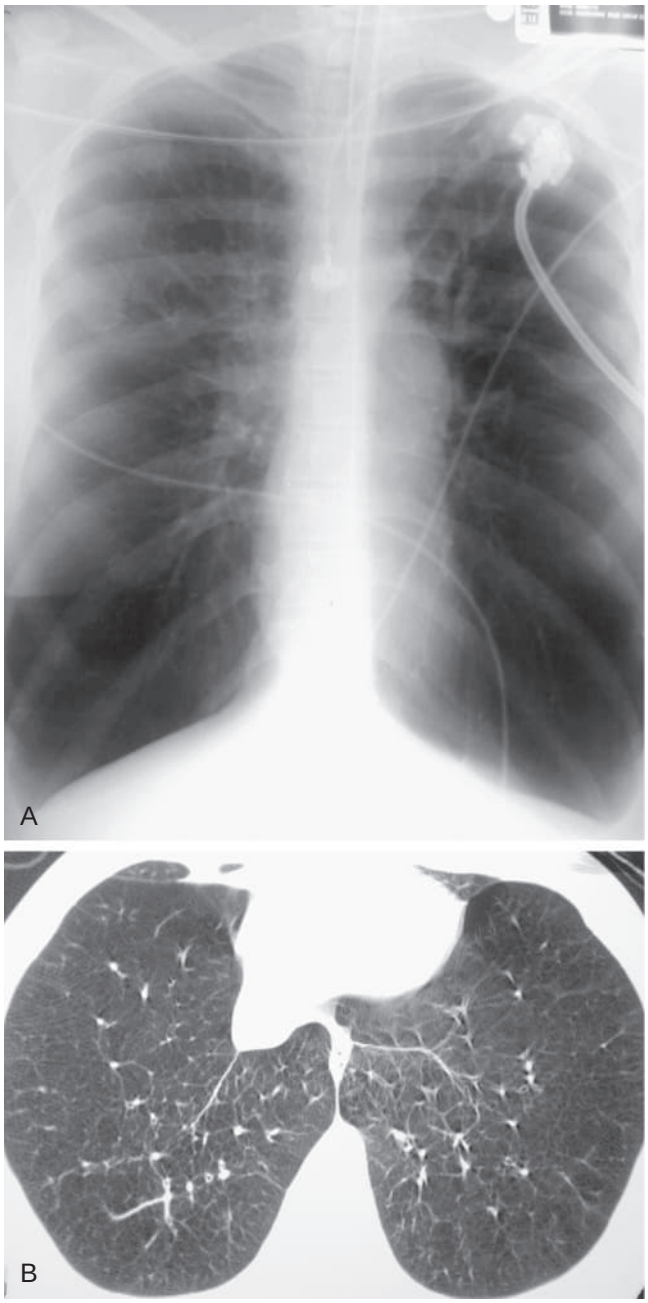
eFigure 99.10 Sirolimus-induced interstitial pneumonitis in a lung transplant recipient. (A–D) Axial chest computed tomography shows poorly defined, faintly nodular areas of ground-glass opacity *(arrowheads)* in the middle and upper lungs bilaterally. Extensive evaluation revealed no evidence of infection or hemorrhage, and the abnormalities resolved following withdrawal of sirolimus therapy. (Courtesy Michael B. Gotway, MD.)



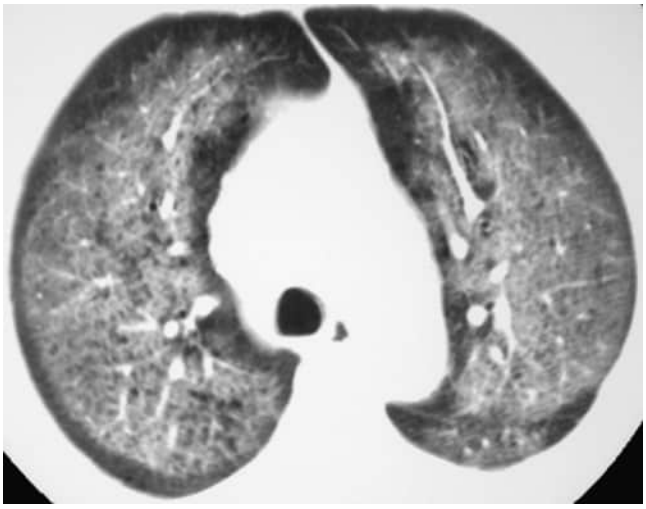
eFigure 99.11 Nitrofurantoin-induced interstitial pneumonitis. Axial chest computed tomography in a patient undergoing nitrofurantoin therapy shows bilateral, patchy, subpleural ground-glass opacity and reticulation *(arrows)* consistent with a nonspecific interstitial pneumonia lung injury pattern. (Courtesy Michael B. Gotway, MD.)



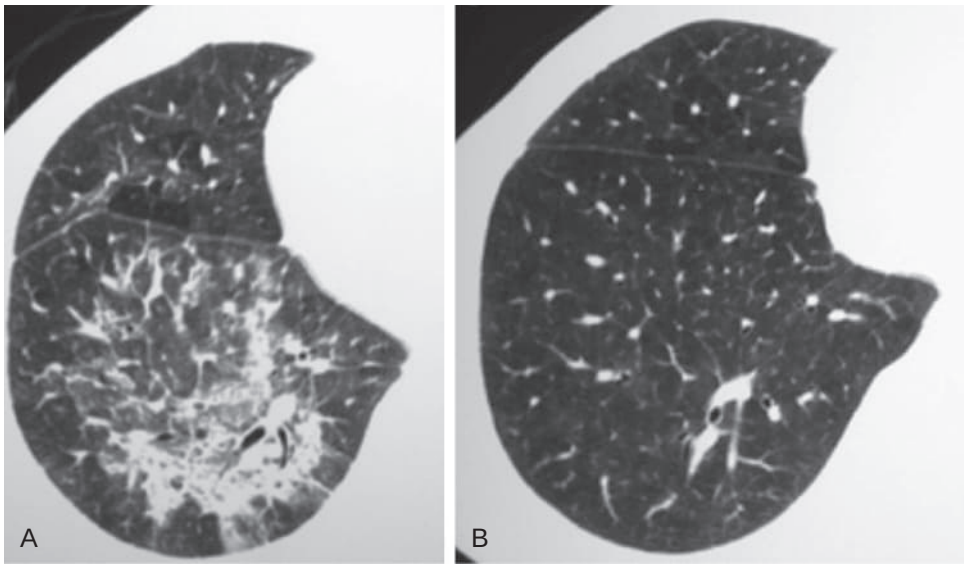
eFigure 99.12 Eosinophilic pneumonia pattern resulting from sulfasalazine. The patient was a 66-year-old woman who had taken sulfasalazine for inflammatory bowel disease. She developed cough and shortness of breath. The computed tomography images demonstrate patchy subpleural ground-glass opacity and consolidation bilaterally in a nonspecific pattern. Bronchoscopic biopsy confirmed eosinophilic pneumonia, which responded to withdrawal of sulfasalazine and corticosteroid therapy. (Courtesy Michael B. Gotway, MD.)



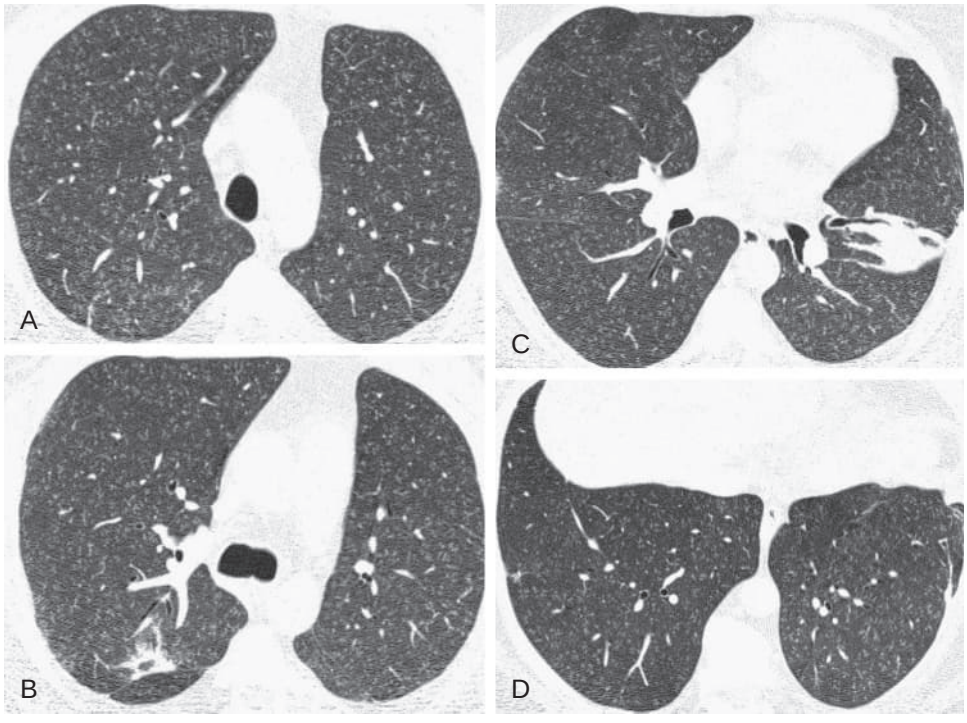
eFigure 99.13 Panlobular emphysema in a patient abusing methylphenidate. (A) Frontal chest radiograph in a 40-year-old woman with respiratory failure who was known to inject methylphenidate intravenously shows enormous lung volumes. Note diaphragmatic flattening. (B) Axial chest computed tomography through the lung bases shows diffuse low attenuation and simplification of pulmonary architecture, consistent with panlobular emphysema. (Courtesy Michael B. Gotway, MD.)



eFigure 99.14 Noncardiogenic edema following cocaine inhalation. Axial chest computed tomography performed in a patient who developed severe shortness of breath and cough following crack inhalation shows multifocal bilateral ground-glass opacity with peripheral sparing. No evidence of infection was noted. (Courtesy Michael B. Gotway, MD.)



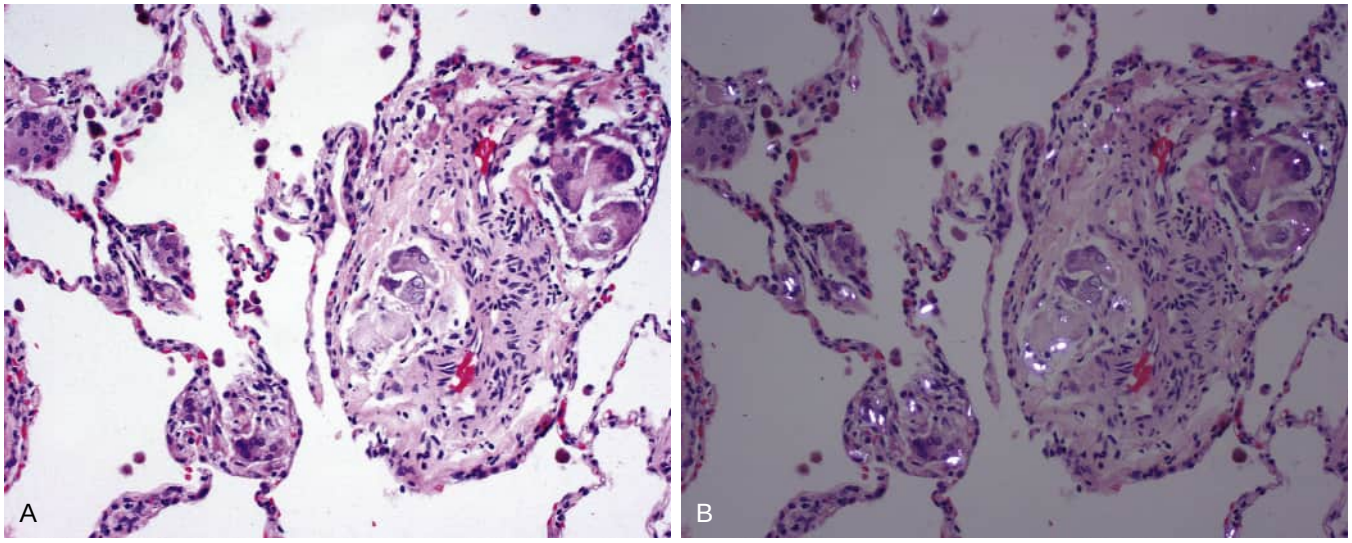
eFigure 99.15 Pulmonary hemorrhage following cocaine inhalation. (A) Axial chest computed tomography performed in a patient reporting shortness of breath and cough following crack inhalation shows patchy right lower lobe ground-glass opacity with interlobular septal thickening, consistent with hemorrhage; the latter was confirmed at bronchoscopy. (B) Repeat axial chest computed tomography 3 weeks later shows clearing of the right lower lobe pulmonary hemorrhage. (Courtesy Michael B. Gotway, MD.)



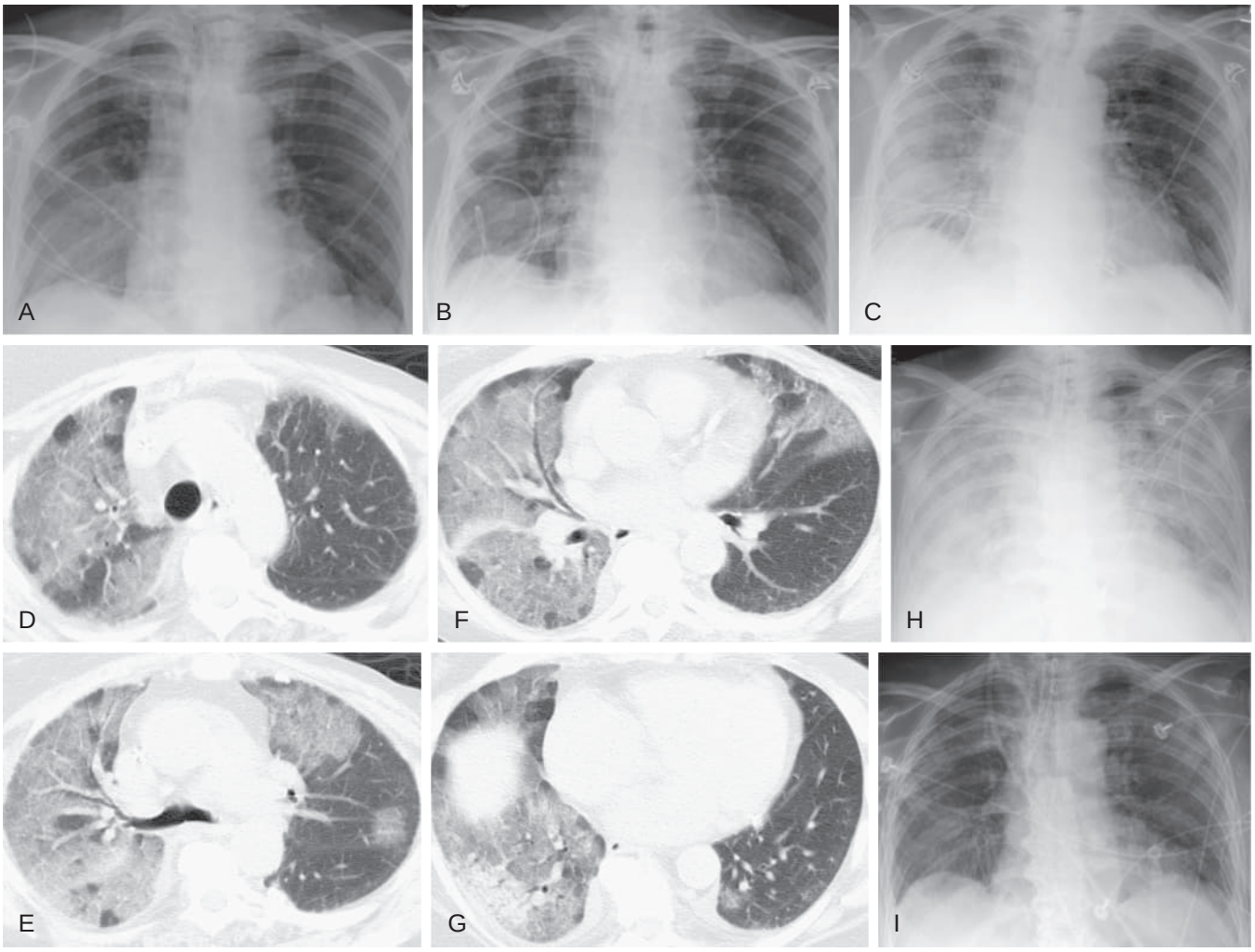
eFigure 99.16 Injection cellulose granulomatosis in a patient injecting Vicodin tablets intravenously. (A–D) Axial chest computed tomography in an injection drug user shows numerous, diffusely distributed, bilateral ground-glass opacity nodules; the appearance closely resembles subacute hypersensitivity pneumonitis. Surgical lung biopsy showed a perivascular foreign body giant cell reaction with granulomas and polarizable refractive crystals consistent with cellulose. (Courtesy Michael B. Gotway, MD.)



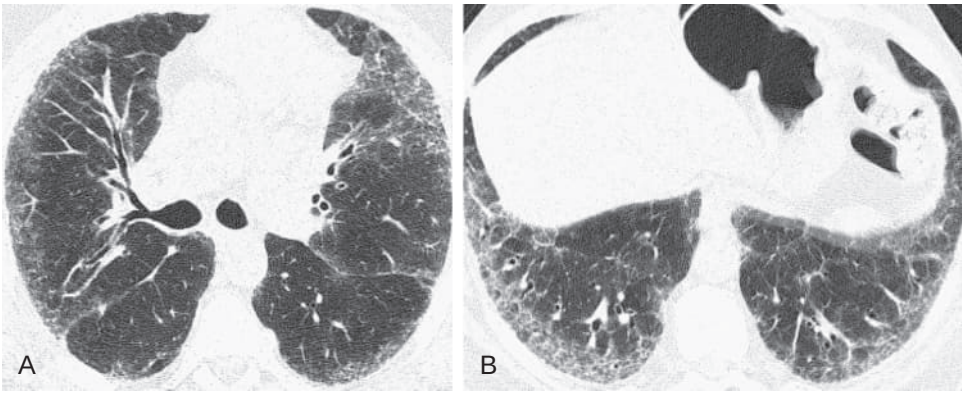
eFigure 99.17 Injection talcosis. Axial chest computed tomography displayed in soft tissue windows performed on an intravenous drug user shows bilateral masslike opacities consistent with injection talc granulomatosis. (Courtesy Michael B. Gotway, MD.)



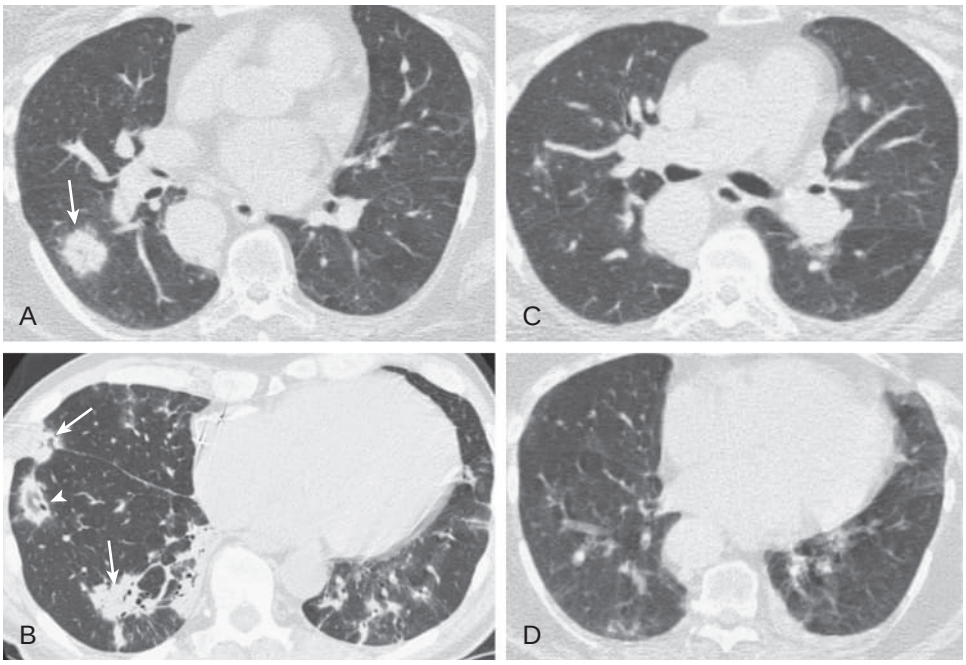
eFigure 99.18 Intravenous drug use-induced particulate foreign body reaction. (A) Normal light microscopy appearance. (B) Polarized light. A perivascular interstitial foreign body–type granulomatous reaction is associated with prominent vascular changes, as shown. (From Cheung Y, Graziano P, Leslie KO. Acute lung injury. Leslie KO, Wick MR, eds. *Practical Pulmonary Pathology: A Diagnostic Approach: A Volume in the Pattern Recognition Series.* 2nd ed. Philadelphia: Elsevier; 2011:117–137.)



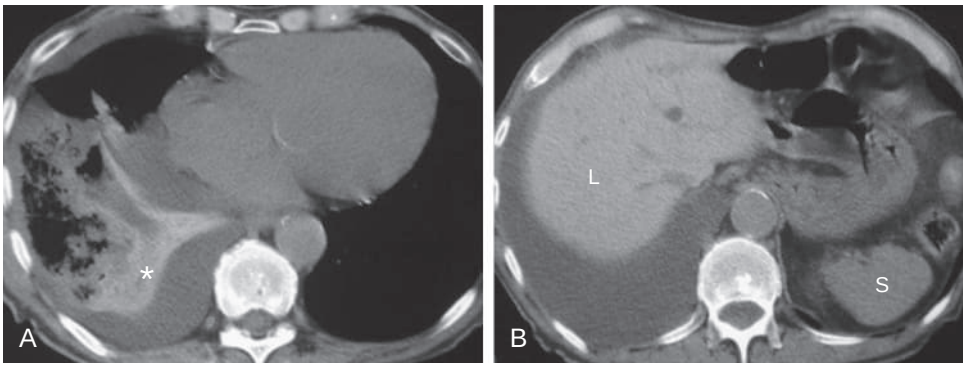
eFigure 99.19 Acute amiodarone pulmonary toxicity. (A) Frontal chest radiograph performed in a patient with supraventricular tachycardia recently loaded with amiodarone shows right lower lung opacity thought to reflect pneumonia. The patient was treated presumptively for pneumonia with broad-spectrum antibiotics. (B) Frontal chest radiograph performed several days following (A) shows slight improvement in right lower lung opacity, but new right upper lobe opacity is now present. (C) Follow-up frontal chest radiograph shows progression of the right lung abnormalities despite a normal intravascular volume and broad-spectrum antibiotic therapy. (D–G) Axial chest computed tomography displayed in lung windows shows multifocal, bilateral ground-glass opacities associated with fine reticulation and subpleural right lower lobe consolidation, but no features to suggest fibrosis. The findings are consistent with alveolitis or hemorrhage but are nonspecific. (H) Follow-up frontal chest radiograph shows continued worsening of bilateral lung opacities. (I) Frontal chest radiograph performed several days following discontinuation of amiodarone shows significant improvement in bilateral lung opacities. (Courtesy Michael B. Gotway, MD.)



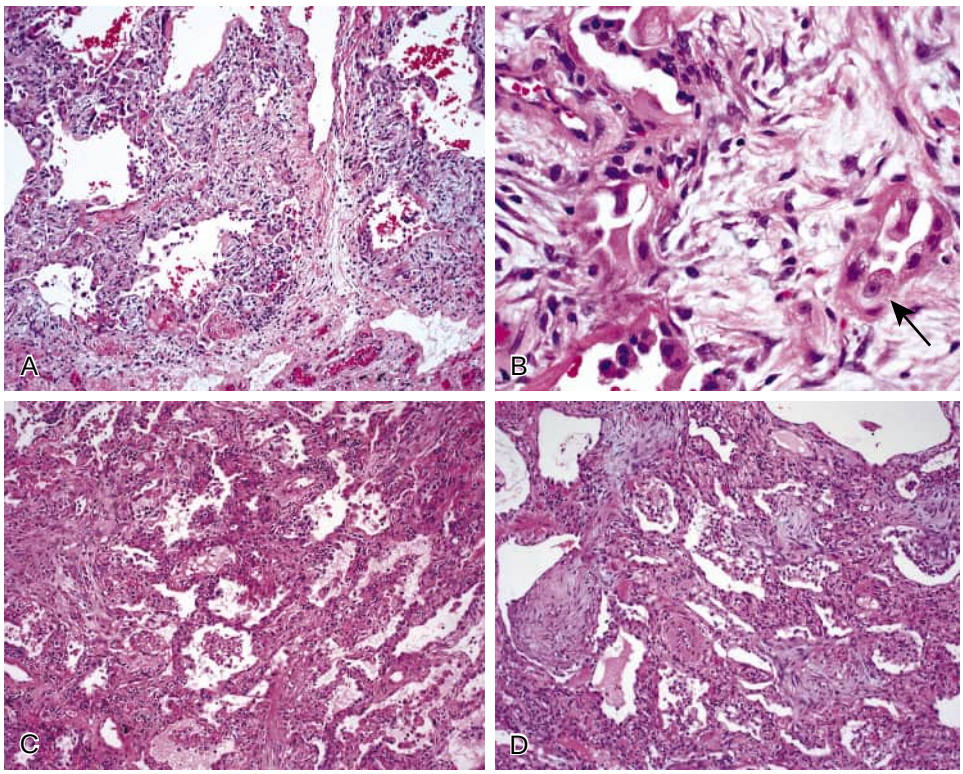
eFigure 99.20 Amiodarone pulmonary toxicity: nonspecific interstitial pneumonia pattern. (A–B) Axial chest computed tomography displayed in lung windows performed in a patient receiving long-term amiodarone therapy shows bilateral, subpleural fine intralobular interstitial thickening and ground-glass opacity; the appearance resembles a nonspecific interstitial pneumonia lung injury pattern. (Courtesy Michael B. Gotway, MD.)



eFigure 99.21 Amiodarone pulmonary toxicity: nodular organizing pneumonia pattern. (A–B) Axial chest computed tomography displayed in lung windows performed in a patient receiving long-term amiodarone therapy shows right lung nodules *(arrows)* associated with air bronchograms; one nodule shows ground-glass opacity surrounded by consolidation (B, *arrowhead*), consistent with the "reverse ground-glass halo" sign, or "atoll" sign, suggestive of organizing pneumonia. (C–D) Axial chest computed tomography performed following discontinuation of amiodarone therapy and implementation of corticosteroid treatment shows nearly complete resolution of the nodules. (Courtesy Michael B. Gotway, MD.)



eFigure 99.22 Amiodarone exposure: high-attenuation lung consolidation. (A) Axial chest computed tomography performed in a patient taking amiodarone for an atrial arrhythmia shows high-attenuation right lower lobe consolidation *(asterisk),* consistent with amiodarone exposure. (B) Axial chest computed tomography through the upper abdomen shows increased attenuation of the liver parenchyma (L) relative to the spleen (S), also consistent with amiodarone exposure. (Courtesy Michael B. Gotway, MD.)



eFigure 99.23 Amiodarone toxicity. (A) Scanning magnification of amiodarone-induced diffuse alveolar injury. (B) The finely vacuolated macrophages in alveolar epithelial type 2 cells are clearly evident *(arrow)*. (C) The most common pathologic change seen in amiodarone toxicity is cellular interstitial pneumonia associated with prominent intra-alveolar macrophages whose cytoplasm shows fine vacuolation. (D) In some patients with amiodarone toxicity, an organizing pneumonia pattern develops, resulting in a mass effect on thoracic imaging studies. (From Cheung Y, Graziano P, Leslie KO. Acute lung injury. Leslie KO, Wick MR, eds. *Practical Pulmonary Pathology: A Diagnostic Approach: A Volume in the Pattern Recognition Series.* 2nd ed. Philadelphia: Elsevier; 2011:117–137.)



eFigure 99.24 Adalimumab-induced lung injury. (A–C) Axial chest computed tomography in a patient with rheumatoid arthritis undergoing adalimumab therapy shows multifocal bilateral ground-glass opacity with reticulation, consistent with an acute lung injury pattern. (Courtesy Michael B. Gotway, MD.)

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SECTION L

ENVIRONMENTAL AND OCCUPATIONAL HAZARDS

100 ASTHMA IN THE WORKPLACE

CATHERINE LEMIÈRE, MD, MSC • OLIVIER VANDENPLAS, MD, PHD

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INTRODUCTION

DEFINITIONS OF ASTHMA IN THE WORKPLACE

Work-related asthma (WRA) is a major public health concern because of its high prevalence and societal burden. WRA is a broad term indicating that asthma is worsened by the workplace.[1] WRA encompasses *occupational asthma* (OA), which is asthma caused by a specific agent at the workplace, and *work-exacerbated asthma* (WEA), which corresponds to asthma exacerbated by, but not caused by, nonspecific stimuli in the workplace[2] (Fig. 100.1). WRA is prevalent; the Centers for Disease Control estimates that among the 9% of adults with asthma, 15.7% have work-related cases. This proportion of adults with WRA varies according to state from 9–23%.[3]

OA includes two main entities: sensitizer-induced OA and irritant-induced asthma. Several definitions of OA have been proposed. The American College of Chest Physicians defines OA as follows[4]:

…de novo asthma or the recurrence of previously quiescent asthma (i.e., asthma as a child or in the distant past that has been in remission) induced by either sensitization to a specific substance (e.g., an inhaled protein [high-molecular-weight protein of >10 kd] or a chemical [low-molecular-weight agent]), at work, which is termed sensitizer-induced OA, or by exposure to an inhaled irritant at work, which is termed irritant-induced OA.

Sensitizer-induced OA has also been defined as "asthma with a latency period," suggesting the presence of an underlying immunologic mechanism responsible for a latency period from the beginning of the occupational exposure to the onset of asthma symptoms.[5]

Irritant-induced (occupational) asthma (IIA), also called OA without a latency period or nonimmunologic OA, encompasses a wide spectrum of asthma phenotypes related to irritant mechanisms, as opposed to OA caused by immunologic mechanisms. The rapid onset of asthma within a few hours after a single exposure to very high levels of irritant substances (i.e., acute-onset IIA or *reactive airways dysfunction*

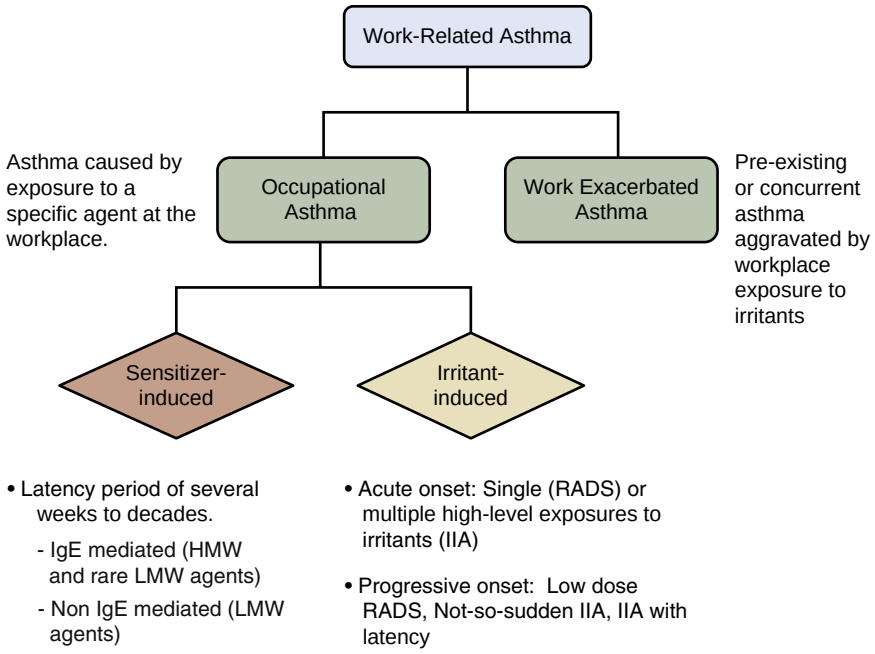

Figure 100.1 Categorization of work-related asthma into subsets based on the cause and timing of the asthma. HMW, high molecular weight; IgE, immunoglobulin E; IIA, irritant-induced (occupational) asthma; LMW, low molecular weight; RADS, reactive airway dysfunction syndrome.

syndrome (RADS) is the best characterized phenotype of IIA, whereas other clinical phenotypes (e.g., low-dose reactive airways dysfunction syndrome, not-so-sudden IIA, or IIA with latency)[6-11] are mainly described in epidemiologic studies because the causal relationship with workplace irritant exposures is difficult to establish at the individual level.

WEA has received growing attention. The latest definition of WEA was proposed by the American Thoracic Society Task Force on Work-Exacerbated Asthma[2] and consists of four criteria:

- There is preexisting or concurrent asthma. The asthma may have begun either before the current employment or while at the worksite of interest, but it was not caused by specific exposures within that workplace.
- An increased frequency of asthma symptoms, medication use, or health care use is temporally associated with work. Medical test results may document more frequent abnormalities.
- Workplace exposures or conditions exist that can exacerbate asthma.
- OA (asthma caused by a specific, identified workplace exposure) is unlikely.

In spite of these clear definitions, differentiating those conditions is often difficult in clinical practice. An accurate diagnosis is crucial because the diagnosis of this condition can result in a change of career and/or financial compensation. This chapter reviews the epidemiology, pathophysiology, diagnosis, management, prevention, and socioeconomic impacts of sensitizer-induced OA, IIA, and WEA.

SENSITIZER-INDUCED OCCUPATIONAL ASTHMA

EPIDEMIOLOGIC ASPECTS

Estimates of the frequency of OA have been derived from various sources, including cross-sectional and longitudinal studies of high-risk workforces, occupational disease registries, voluntary notification programs, and population-based surveys. A pooled analysis of data published up until 2007 indicated that 17.6% of all adult-onset asthma is attributable to workplace exposures.[12]

Cross-sectional surveys of workforces exposed to sensitizing agents reported highly variable prevalence rates of OA, but these estimates were largely affected by the criteria used to identify the disease and by selection biases. Prospective cohort studies reported incidence rates ranging from 1.8 to 4.1 cases of OA per 100 person-years among workers exposed to laboratory animals,[13] wheat flour,[14] and latex gloves.[15] Incidence rates derived from notification schemes and compensation statistics in various countries ranged from 24 to 174 new cases per million active workers per year.[16-22] Differences from one country to another may result from geographic differences in industrial activities, as well as from the heterogeneity in diagnostic criteria and in data collection procedures.

The European Community Respiratory Health Survey II provided higher estimates of 250 to 478 incident cases of work-attributable asthma per million people per year.[23,24] These data suggest that the disease remains largely unrecognized, although population surveys are affected by the lack of confirmation of OA through objective tests.

Assessing mortality related to WRA is challenging because WRA does not usually have a specific *International Classification of Diseases* (ICD) code.[25]

CAUSAL AGENTS

Many substances (more than 400) used at work can cause sensitizer-induced OA.[26] They are usually categorized as *high-molecular-weight* (HMW) or *low-molecular-weight* (LMW) agents (Table 100.1). HMW agents are (glyco)proteins originating from plants and animals, whereas LMW agents include chemicals, metals, and wood dusts. The intrinsic characteristics of occupational agents that determine their sensitizing potential remain largely uncertain. However, LMW agents causing OA are typically highly reactive electrophilic compounds capable of combining with hydroxyl, amino, and thiol

Table 100.1 Principal Agents Causing Occupational Asthma

Agent		Occupation or Industry
HIGH-MOLECULAR-WEIGHT AGENTS		
Cereals, flour	Wheat, rye, barley, buckwheat	Flour mills, bakers, pastry makers
Latex	Proteins from the *Hevea* tree	Health care workers, laboratory technicians
Animals	Mice, rats, cows, seafood	Laboratory workers, farmers, seafood processing
Enzymes	α-Amylase, maxatase, alcalase, papain, bromelain, pancreatin	Baking product production, bakers, detergent production, pharmaceutical industry, food industry
LOW-MOLECULAR-WEIGHT AGENTS		
Isocyanates	Toluene diisocyanate, methylene diphenyldiisocyanate, hexamethylene diisocyanate	Polyurethane production, plastic industry, insulation, molding, spray painting
Metals	Chromium, nickel, cobalt, platinum	Metal refinery, metal alloy production, electroplating, welding
Biocides	Formaldehyde, glutaraldehyde, quaternary ammonium compounds	Health care workers, cleaners
Persulfate salts	Hair bleach	Hairdressers
Acrylates	Cyanoacrylates, methacrylates, diacrylates, and triacrylates	Adhesives, dental and orthopedic materials, sculptured fingernails, printing inks, paints and coatings
Acid anhydrides	Phthalic, trimellitic, maleic, tetrachlorophthalic anhydrides	Epoxy resin workers
Reactive dyes	Reactive black 5, pyrazolone derivatives, vinyl sulfones, carmine	Textile workers, food industry workers
Woods	Red cedar, iroko, obeche, oak, and others	Sawmill workers, carpenters, cabinet and furniture makers

functionalities on airway proteins. Quantitative structure-activity relationship models have identified certain reactive groups associated with a high risk of respiratory sensitization (e.g., isocyanate [N=C=O], carbonyl [C=O], and amine [NH_2]), particularly when two or more groups are present within the same molecule.[27]

Actually, a handful of agents (i.e., flour, diisocyanates, latex, persulfate salts, aldehydes, animals, wood dusts, metals, and enzymes) usually account for the majority (50–90%) of reported cases of OA.[22,28] A large European multicenter study reported the frequency of OA attributed to those occupational agents in Europe (Table 100.2).[29] Nevertheless, the distribution of causal agents may vary widely across geographic areas, depending on the pattern of industrial activities.[16-22] The highest incidence of OA is seen in bakers and pastry makers, other food processors, spray painters, hairdressers, wood workers, health care workers, cleaners, farmers, laboratory technicians, and welders.

PATHOPHYSIOLOGY

The pathophysiology of sensitizer-induced OA often involves an *immunoglobulin E* (IgE)–dependent mechanism. This mechanism is encountered mainly with HMW agents. Although specific IgE has also been encountered in OA caused by some LMW agents (e.g., platinum salts, trimellitic anhydride, and other acid anhydrides), the production of specific IgE antibodies or the up-regulation of IgE receptors has not been identified in the majority of cases of OA induced by LMW agents.[30]

Immunologic, Immunoglobulin E–Mediated Occupational Asthma

The pathophysiology of OA induced by IgE-dependent agents is similar to allergic asthma unrelated to work. HMW agents are proteins; they act as complete antigens and induce the production of specific IgE antibodies. Subepithelial immature dendritic cells residing within the airway walls take up the antigen and migrate to the regional lymph nodes for maturation. They express antigenic peptide on their surface in conjunction with major histocompatibility complex type II molecules. Dendritic cells interact with $CD4^+$ T cells expressing high-affinity receptors for the antigen–major histocompatibility complex II complex. Type 2 T helper (Th2) cells, attracted by chemokines, eventually reach the airways. With future exposures in the airways, CD4 T cells may react to antigen presentation,[31] thereby releasing *interleukin* (IL)-4, IL-5, and IL-13. With help from Th2 cells, B cells switch isotype and produce IgE. IgE binds to a number of cells through both high- and low-affinity receptors. On subsequent exposure to an antigen, mast cells and basophils release mediators inducing bronchospasm and airway inflammation.

LMW occupational agents are less likely to induce specific IgE antibodies because they act as haptens and have to bind with proteins to form functional antigens. OA caused by platinum salts or anhydride acid is clearly IgE mediated. Demonstrating the presence of specific IgE to platinum salts or anhydride acid is useful in the diagnosis of OA related to those agents. In contrast, the role of specific IgE is still controversial in isocyanate-induced asthma.[32] The presence of specific IgE to isocyanates seems a good predictor of isocyanate-induced OA (specificity, 89–100%),[4] whereas specific *immunoglobulin G* (IgG) seem to be mostly associated with exposure to isocyanates.[33] However, whether isocyanate-induced asthma is an IgE-mediated disease is still a matter of debate.[32]

Immunologic, Non–Immunoglobulin E–Mediated Occupational Asthma

Cell-mediated reactions are probably important in OA caused by LMW agents. The predominant immune response to chemical respiratory allergens may be of the Th2 type, but other cells are also likely to play important supportive or regulatory roles. CD4 and $CD8^+$ T cells, as

Table 100.2 Frequency of Agents Causing Sensitizer-Induced Occupational Asthma According to a Large European Multicenter Study

HMW Agents	n (%)*	LMW Agents	n (%)*
Flour/grains	369 (31.3)	Isocyanates	206 (17.4)
Latex	36 (3.0)	Persulfate salts	78 (6.6)
Enzymes	26 (2.2)	Metals	42 (3.6)
Storage mites	12 (1.0)	Quaternary ammonium compounds	38 (3.2)
Rodents	11 (0.9)	Acrylate compounds	35 (3.0)
Cow dander	11 (0.9)	Wood dusts	35 (3.0)
Fish and seafood	8 (0.7)	Welding fumes	30 (2.5)
Insects and derived products	6 (0.5)	Cleaning products or disinfectants (NOS)	27 (2.3)
Ornamental plants	6 (0.5)	Epoxy resins	18 (1.5)
Molds	5 (0.4)	Aldehydes	17 (1.4)
Soybean flour	3 (0.2)	Drugs	16 (1.4)
Spices	3 (0.2)	Metalworking fluids	15 (1.3)
Vegetable gums	3 (0.2)	Resins, glues, or paints (NOS)	15 (1.3)
Various plant-derived products	26 (2.2)	Acid anhydrides	11 (0.9)
Various animals and derived products	18 (1.5)	Amines	10 (0.8)
		Colophony	4 (0.3)
Total:	543 (46.5)	Styrene	3 (0.2)
		Reactive dyes	2 (0.2)
		Triglycidyl isocyanurate	2 (0.2)
		Other low-molecular-weight agents (NOS)	21 (17.8)
		Total:	624 (52.9)

*Percentage of total identified agents ($n = 1167$); the causal agent was not precisely identified in 13 subjects.
HMW, high molecular weight; LMW, low molecular weight; NOS, not otherwise specified.
From Vandenplas O, Godet J, Hurdubaea L, et al. Are high- and low-molecular-weight sensitizing agents associated with different clinical phenotypes of occupational asthma? *Allergy*. 2019;74:261-272.

well as different cytokines such as IL-1, IL-4, IL-5, IL-6, and IL-15, have been found in biopsy specimens,[34] bronchoalveolar lavage samples, and the sputum of patients with isocyanate-induced asthma.[33] In murine models of toluene diisocyanate "asthma," the presence of both CD4 and CD8 cells seems necessary to produce airway hyperresponsiveness and Th2-type inflammation. IL-4 and IL-13 are major determinants of the pathobiology. Innate lymphoid cells and lineage negative cells contribute to type 2 cytokine production in the airways in response to nonallergenic stimuli. Although few in number, these type 2 innate lymphoid cells may produce significant quantities of IL-5 and IL-13.

IL-13 has the ability to affect epithelium, smooth muscle, and immune cells, and it may possibly drive allergic asthma or even irritant-induced asthma. Neutrophils are also likely to be involved in isocyanate-induced asthma, as shown by an increase in myeloperoxidase and IL-8 after exposure to toluene diisocyanate.[35] Mixed Th1-Th2 cytokine production has been observed in subjects with red cedar–induced asthma.[36] Furthermore, a specific inhalation challenge test induced a mixed Th2/Th1 response in which $CD8^+$ cells were the main producers of interferon-γ.[37]

Isocyanates may stimulate human innate immune responses by up-regulating immune pattern-recognition receptors of monocytes and increasing the chemokines that regulate monocyte and macrophage trafficking (macrophage migration inhibitory factor, monocyte chemoattractant protein-1).[38]

RISK FACTORS

OA results from the complex interaction between environmental and individual susceptibility factors (Table 100.3).[28]

Environmental Factors

The intensity of exposure to sensitizing agents is currently the best identified and the most important environmental risk factor for the development of OA. Strong evidence supports a dose-response relationship between the level of exposure to HMW agents and the development of IgE-mediated sensitization and OA. Such a dose-response relationship has also been documented for some LMW agents, such as platinum salts, acid anhydrides, and isocyanates. Exposure-response relationships may be affected by individual susceptibility factors and the timing of exposure. For instance, the role of genetic susceptibility markers, such as certain *human leukocyte antigen* (HLA) class II alleles, may become more apparent at low levels of exposure to occupational agents.[39] The incidence of WRA symptoms is consistently higher within the first 1 to 4 years of exposure to HMW agents, and exposure-response gradients are more clearly documented in this early period of exposure.[13]

Cigarette smoking can increase the risk of IgE-mediated sensitization to some HMW and LMW agents, but the evidence supporting an association between smoking and the development of clinical OA is still weak. The role of other environmental cofactors, such as nonrespiratory routes of exposure and concomitant exposure to endotoxin and pollutants at work, remains largely uncertain.

Host-Related Factors

Atopy has been consistently demonstrated to be an important host risk factor for the development of IgE sensitization and OA, but only for HMW agents. Preexposure sensitization to common allergens structurally related to workplace allergens, such as exposure to pets in laboratory animal workers, could be a stronger risk factor for OA than atopy.

Table 100.3 Potential Risk Factors for Occupational Asthma

Risk Factor	Evidence	Agents or Settings
ENVIRONMENTAL FACTORS		
High level of exposure	Strong	HMW agents
	Moderate	LMW agents: platinum salts, acid anhydrides, isocyanates
Cigarette smoking	Moderate	For IgE sensitization: laboratory animals, snow crab, prawn, salmon, psyllium, green coffee, enzymes, acid anhydrides, platinum, reactive dyes
	Weak	For clinical OA: laboratory animals, enzymes
Skin exposure	Weak	Isocyanates
HOST-RELATED FACTORS		
Atopy	Strong	HMW agents
	Weak	LMW agents: platinum, acid anhydrides
Genetic markers:		
HLA class II alleles	Moderate	LMW agents: isocyanates, red cedar, acid anhydrides, platinum salts HMW agents: laboratory animals, latex
Antioxidant enzymes*	Moderate	Isocyanates
SNPs of alpha-T catenin	Moderate	Isocyanates
TLR4 polymorphisms	Weak	Laboratory animals
IL-4 receptor alpha and IL-13 polymorphisms	Weak	Isocyanates
Preexisting nonspecific bronchial hyperresponsiveness	Moderate	HMW agents: laboratory animals, flour, latex
Work-related rhinitis	Strong	Laboratory animals
Sex (female)	Weak	Snow crab processors

*Glutathione-S-transferase and N-acetyltransferase.
HLA, human leukocyte antigen; HMW, high molecular weight; IgE, immunoglobulin E; IL, interleukin; LMW, low molecular weight; OA, occupational asthma; SNPs, single nucleotide polymorphisms, TLR4, toll-like receptor-4.

Prospective cohort studies suggest that the presence of nonspecific bronchial hyperresponsiveness[40,41] and rhinitis[41,42] before exposure to HMW occupational agents is an independent risk factor for subsequent IgE sensitization to these allergens. Conversely, strong evidence indicates that the development of occupational rhinitis during exposure is associated with an increased risk for the development of OA.[43,44] However, the proportion of persons with occupational rhinitis who will develop OA remains unknown. Among workers exposed to laboratory animals, the predictive value of work-related nasal symptoms on the subsequent development of probable OA was only 11.4% over a follow-up period of 30 to 42 months.[45]

Certain HLA class II molecules (i.e., HLA-DR, HLA-DQ, and HLA-DP alleles), which are involved in the presentation of processed antigens to T lymphocytes, were found to confer either susceptibility to or protection against OA caused by various LMW and HMW occupational allergens.[46] There is also some suggestion that genes associated with Th2-cell differentiation (i.e., polymorphism of the IL-4 receptor alpha-chain, IL-13, and CD14 [C159T] genes) could play a role in the development of OA. Genes involved in the protection against oxidative stress, such as *glutathione-S-transferase* (GST) and *N*-acetyltransferase, have been associated with an increased risk of isocyanate-induced OA (i.e., GSTM1 null genotype and slow *N*-acetylator phenotypes) or a protective effect (i.e., GSTP1*Val/Val allele).[47] Overall, the currently available information indicates that genetic markers have a low predictive value in identifying susceptible workers. In addition, there is convincing evidence that a wide variety of environmental factors can interact with genetic determinants to affect disease susceptibility.

DIAGNOSIS

The diagnosis of OA is difficult to establish. A comprehensive and integrated approach, including the assessment of occupational history, clinical symptoms, and functional and inflammatory characteristics at baseline and in response to exposure to occupational agents, is needed to achieve an accurate diagnosis. This approach is summarized in Figure 100.2. Each step of the investigation has substantial limitations that may be avoided by combining several tests.[48] The validity of the different diagnostic tests and their practical limitations and advantages are summarized in Table 100.4.

OA should be suspected in every adult with new-onset asthma. Although the respiratory symptoms (e.g., wheezing, dyspnea, chest tightness, cough, and sputum production) are similar to those encountered in *non–work-related asthma* (NWRA), in OA, their appearance and severity are usually modulated by the work exposure. The symptoms can start at the beginning of the work shift or toward its end or even after work, with remission or improvement during weekends and holidays. Rhinitis is associated with respiratory symptoms in the majority of cases of OA and often precedes the respiratory symptoms, especially with exposure to HMW agents. Although a thorough clinical and occupational history must be carefully recorded, the diagnosis of OA cannot be made only on the basis of a compatible history, which has a low positive predictive value.[49] Some clinical characteristics seem to be associated predominantly with exposure to HMW compared with exposure to LMW agents. For example, atopy, work-related rhinitis, conjunctivitis, and an immediate asthmatic reaction seem to be the hallmarks of OA caused by HMW agents, whereas chest tightness, sputum production, and a late asthmatic reaction are more common in patients with OA caused by LMW agents.[50]

A good occupational history must detail not only current employment and exposure, but also past employments and exposures. Work history (current and past employments), symptoms (nature and temporal relationship with work), and potential risk factors need to be recorded.[51] The substances to which the worker is potentially exposed at work can be checked against a comprehensive list of

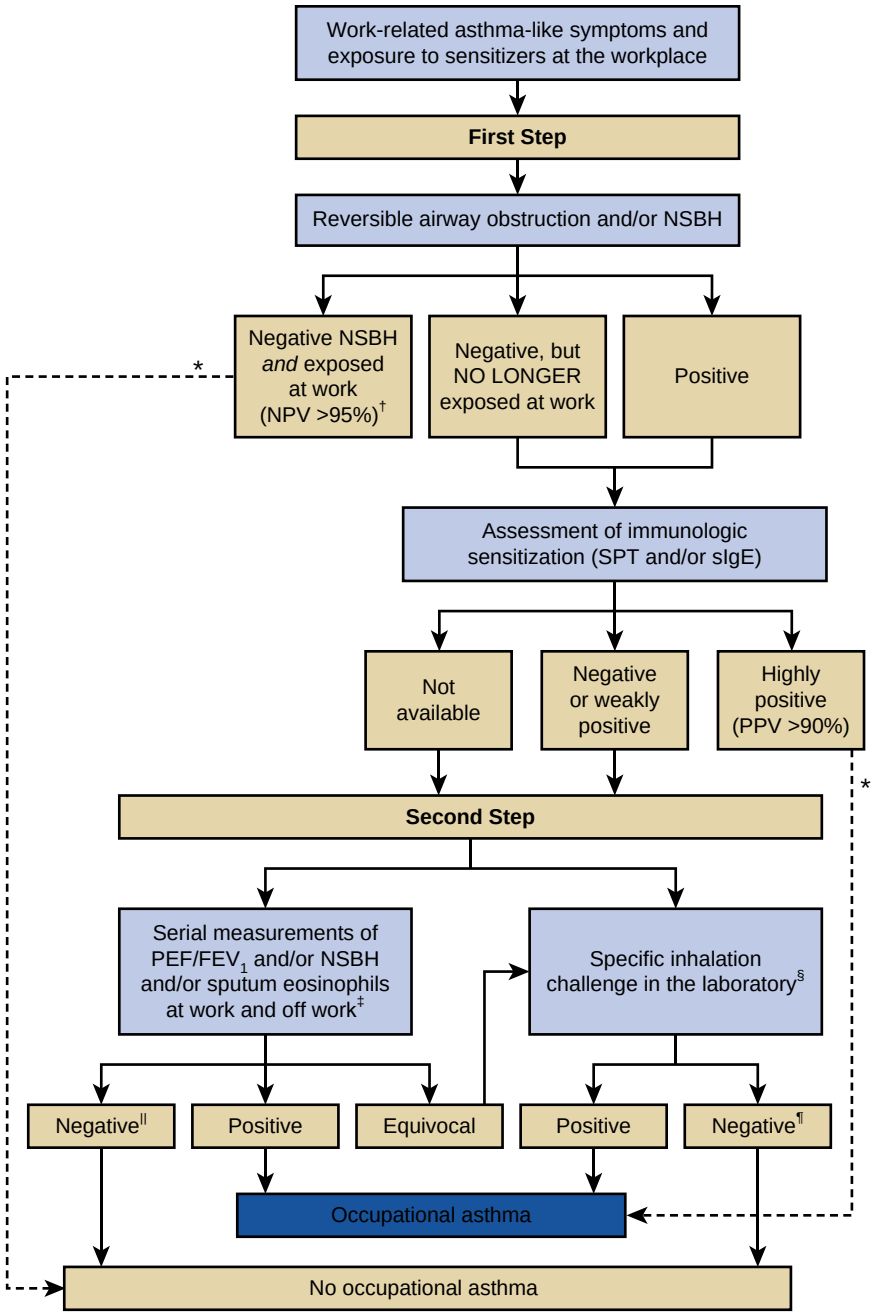

Figure. 100.2 Diagnostic approach to the investigation of sensitizer-induced occupational asthma. *High *negative predictive value* (NPV) and *positive predictive value* (PPV) have been established in selected populations with a high pretest probability of occupational asthma and may be applicable only in those populations. †Consider assessing sputum eosinophil counts to identify occupational asthma. ‡Especially useful when the patient is exposed to multiple potential sensitizers at work and no agent known to cause occupational asthma has been identified at work, specific inhalation challenge is not easily available, or the conditions of exposure at work cannot be reproduced in the laboratory. §Especially useful when specific inhalation challenge can be performed efficiently and safely, the patient is no longer exposed at work, the highest level of diagnostic accuracy is required, there is a need to identify a particular agent, and peak expiratory flow rate records are inconclusive. ‖Consider specific inhalation challenge if the clinical history is highly suggestive of occupational asthma. ¶Consider workplace inhalation challenge if the clinical history is highly suggestive of occupational asthma. FEV_1, forced expiratory volume in 1 second; NSBH, nonspecific bronchial hyperresponsiveness; PEF, peak expiratory flow; sIgE, serum-specific immunoglobulin E; SPT, skin prick test.

agents recognized as causing OA, and the person's employment can be searched on the list of at-risk occupations.[4] Material safety data sheets can be requested from the workplace and may be of help in clarifying the presence of a workplace sensitizer. However, if the content of the causal agent is less than 1%, it may not be listed. If available, the occupational health record and the industrial hygiene record from the company should also be reviewed. A list of agents responsible for OA can be found at https://www.csst.qc.ca/en/prevention/reptox/occupational-asthma/Pages/occupational-asthma.aspx. A list of occupations in which exposure to those agents is encountered can be found at https://www.csst.qc.ca/en/prevention/reptox/occupational-asthma/Documents/Occupational%20Asthma%20-%20Agents%20by%20occupation.pdf.

Once the history has been obtained, the diagnosis of asthma should be confirmed by documenting reversible airflow limitation and/or airway hyperresponsiveness. However, the lack of airway hyperresponsiveness does not exclude the diagnosis of OA in persons who have been removed from exposure.

Assessing airway responsiveness is an important step in the investigation of OA. Finding airway hyperresponsiveness can confirm the diagnosis of asthma; finding a reduction of airway hyperresponsiveness after a period away from work can support the diagnosis of OA. Normal airway responsiveness after a period at work at which time the workers experience their respiratory symptoms makes the diagnoses of OA and asthma improbable. The negative predictive value of normal airway responsiveness for OA while the worker is exposed to the offending agent at the workplace has been reported to be as high as 98%.[52] In this case, an alternative diagnosis should be investigated.[4]

Table 100.4 Advantages and Limitations of Diagnostic Tests for Occupational Asthma

Diagnostic Tests	Advantages and Limitations
Assessment of nonspecific bronchial hyperresponsiveness	■ Simple, low cost ■ Confirms the diagnosis of asthma ■ Low specificity for diagnosis of OA. The absence of airway hyperresponsiveness does not exclude the diagnosis of OA in patients who have been removed from the workplace
Immunologic tests	■ Easy to perform, low cost ■ Commercial extracts are available (skin prick tests or specific IgE for HMW agents) ■ Measurement of specific IgE available for some LMW agents (anhydrides, acids, isocyanates, aldehydes) but low sensitivity ■ Lack of standardization for most occupational allergens except for latex ■ Can identify the sensitization but not necessarily the disease
PEF monitoring	■ Low cost ■ Requires workers' collaboration ■ Low adherence (<60%) ■ Possible falsification of results ■ Requires 2 weeks at and away from work (not always possible) ■ Impossible to perform when the worker has been removed from work ■ No standardized method for interpreting the results ■ Interpretation of the results requires experience
Specific inhalation challenges in the laboratory	■ Confirmation of the diagnosis of OA when test result is positive ■ False-negative test results are possible ■ Costly ■ Available in only a few centers worldwide
Specific inhalation challenges at the workplace	■ Exclude diagnosis if negative when performed in the usual work conditions ■ Require usual work conditions ■ Costly
Noninvasive measures of airway inflammation	Sputum cell counts ■ Impossible to falsify ■ Bring additional evidence to the diagnosis of OA ■ Costly ■ Not widely available ■ Does not allow confirmation or exclusion of the diagnosis of OA by itself Exhaled NO ■ Easy to perform ■ Inconsistent results ■ Difficult to interpret ■ Affected by many different factors

HMW, high molecular weight; IgE, immunoglobulin E; LMW, low molecular weight; NO, nitric oxide; OA, occupational asthma; PEF, peak expiratory flow.

Immunologic testing is useful in demonstrating sensitization of the worker to the suspected agent. Although the negative predictive value of these tests is high in the case of HMW, these tests are limited by the lack of standardized commercially available reagents for skin and in vitro tests. Skin prick tests are seldom useful when LMW agents are suspected.[53]

The work relatedness of asthma should be assessed through two additional tests: serial measurements of *peak expiratory flow* (PEF) and/or nonspecific bronchial hyperresponsiveness at work and off work and/or specific inhalation challenges in the laboratory or at the workplace.

Serial measurement of PEF at work and away from work has been found to be useful in confirming OA.[51] The minimum period of PEF monitoring should be 2 weeks at work with a significant exposure to the suspected causative agent and a similar period away from work, unless significant changes are recorded earlier at work. However, a study using analytic software showed that reasonable sensitivity and specificity can be achieved within a shorter period of time.[54] Asthma treatment should be kept constant throughout the period of monitoring. However, as in common asthma, compliance with PEF monitoring has been shown to be poor, and the results may be falsified if an electronic PEF meter is not used.[55,56]

Specific inhalation challenge tests consist of exposing the subjects to the suspected occupational agent in the laboratory and/or at the workplace.[57,58] These tests are considered the reference tests, but they are time-consuming and require specialized facilities available in only a few centers. Specific inhalation challenge tests are useful when (1) the diagnosis of OA remains in doubt after serial monitoring of PEF or airway responsiveness, (2) a patient clearly has OA but the causal agent needs to be identified, (3) a new agent is suspected of causing OA, and (4) the patient cannot be returned to the incriminated workplace. A false-negative response may be obtained if the wrong agent is used or if the exposure conditions are not comparable to those in the workplace.

Noninvasive Measures of Airway Inflammation

Noninvasive measures of airway inflammation are increasingly used during the investigation of OA.

Although there is limited evidence in the literature, the eosinophil count in the peripheral blood does not seem to be an effective tool to aid the diagnosis of OA.[59] However, the percentage of eosinophils in *sputum* increases during periods at work and decreases after removal from exposure in subjects with OA.[60,61] In settings where this tool is available, sputum eosinophil counting complements the

investigation of OA during the investigation both at and away from the workplace in addition to serial PEF measurement, as well as during specific inhalation challenges before and after exposure to the offending agent.

Although the measurement of *fractional exhaled nitric oxide* (FeNO) is easier to obtain than sputum differential cell counts, the current evidence does not show a clear benefit of using FeNO in the investigation of OA.[62] The interpretation of increased FeNO is more difficult than that of sputum differential cell counts because of the lack of specificity, as well as the potential confounding factors that may influence the results (i.e., inhaled corticosteroid treatment, smoking). However, evidence shows a high specificity of FeNO in subjects exposed to HMW agents.[63] The use of FeNO may be more useful in patients exposed to HMW agents where an IgE-dependent reaction is involved.[64]

The predictive values of those tests at baseline, while the patient is not exposed to the offending agent, is modest at best. The combination of several biomarkers improves the accuracy of the diagnosis of OA. The combination of sputum eosinophil differential cell counts[59,65] or FeNO levels[65] with measurement of airway responsiveness improves the sensitivity of the methacholine or histamine challenge alone. The combination of the changes in sputum eosinophil differential cell counts and airway responsiveness after exposure to the offending agents improves the diagnostic accuracy for the diagnosis of OA.[59]

OUTCOME AND MANAGEMENT

According to systematic reviews of the existing data, complete avoidance of exposure to the causal agent remains the optimal treatment of sensitizer-induced OA.[66,67] Although a reduction of exposure to the agent can be considered an alternative option, the limited available evidence indicates that this option is less beneficial than complete cessation of exposure because it is associated with a lower likelihood of asthma improvement and a higher risk of asthma worsening.[68,69]

Immunotherapy has been tested only in workers with allergy and/or OA to HMW agents for which an IgE-dependent reaction has been demonstrated, mainly in health care workers allergic to latex.[70] Although immunotherapy can reduce cutaneous and respiratory symptoms in health care workers allergic to latex, this treatment can induce systemic reactions in a large number of treated subjects.[71] Small or uncontrolled studies have reported an improvement of allergic and respiratory symptoms after immunotherapy to some selected agents (cereal,[72] sea squirt,[73] laboratory animal,[74] and wood[75]). However, whether immunotherapy can alter the course of OA in the long term remains to be determined. Further studies need to be conducted before immunotherapy can be recommended for the treatment of OA to HMW agents.

A few case reports have suggested that treatment with the anti-IgE agent omalizumab could improve asthma control in subjects with flour-induced OA who remain exposed to the causal work environment, although further prospective investigations are required in persons who choose to continue exposure.[4]

Clinicians should be aware that OA is not always reversible after cessation of exposure to the sensitizing agent. Asthma symptoms and airway hyperresponsiveness persist in approximately 70% of the patients with OA even several years after removal from the offending environment.[76] Besides environmental interventions, the pharmacologic treatment of OA should follow the clinical practice guidelines for asthma.

PREVENTION

Primary prevention aims at preventing the development of immunologic sensitization to workplace agents and subsequent OA.[4,77] Primary preventive strategies should focus on the control of workplace exposures because strong evidence supports a dose-response relationship between the level of exposure to sensitizing agents and development of OA. The control of exposure can be achieved through a panel of measures that include the elimination of agents with a known sensitizing potential whenever feasible: (1) the modification of sensitizing materials (e.g., encapsulation of detergent enzymes), (2) the substitution of highly sensitizing agents by materials with lower asthmagenic potential (e.g., nonvolatile oligomers of diisocyanates, latex gloves with a lower content in powder and protein allergens), (3) engineering changes to the workplace (e.g., exhaust ventilation, enclosure of industrial processes), (4) information and education of workers and employers on safe work practices, and (5) the use of personal protective equipment for specific tasks.[78,79] Another approach is to identify susceptible individuals at the time of preemployment examination and exclude them from employment or from high-risk jobs. However, this strategy is inefficient and unduly discriminatory because the currently identified markers of individual susceptibility (see Table 100.3) offer only a low positive predictive value for the development of OA, especially when these markers, such as atopy, are highly prevalent in the general population.[4] Nevertheless, physicians caring for adolescents with asthma and allergic diseases may offer useful advice regarding careers in which their underlying atopic status increases the risks for work-related sensitization to HMW agents.[80]

Secondary prevention of sensitizer-induced OA involves the detection of the disease process at an early (preferably preclinical) stage to modify the disease process through appropriate interventions to eliminate exposure. The rationale underlying secondary prevention is the consistent finding that the outcome of OA is better with an early diagnosis and with milder disease at the time of removal from exposure.[75,81] Increasing awareness of the disease among workers and health professionals is a key step to enhance the recognition of OA because the condition still remains underdiagnosed and inappropriately investigated.[82] Evidence indicates that appropriately designed surveillance programs are effective in identifying OA in persons with less severe asthma, thereby leading to a more favorable outcome.[83]

A few observational studies and historical data indicate that prevention is effective in reducing the incidence of OA and occupational rhinitis caused by natural rubber latex in health care workers,[84] enzymes in the detergent industry,[85] flour,[86] laboratory animals,[87] and isocyanates.[83] However, available data do not distinguish among the relative effects of the diverse components of prevention strategies, given that they are usually implemented as multicomponent

programs targeting education, control of exposure, and medical surveillance.

SOCIOECONOMIC IMPACT

Studies worldwide have shown that OA is associated with substantial financial consequences for affected workers and society as a whole.[88,89] Growing evidence indicates that WRA is associated with more severe asthma,[90-92] and with higher health care resource use,[93] as compared with asthma unrelated to work. In addition, OA generates higher indirect costs than asthma that is not OA because OA most often requires job changes either to avoid or to reduce exposure to the causative agent.[94] Follow-up studies of workers with OA have consistently documented that the condition is associated with a high rate of prolonged unemployment, ranging from 18–69%, and a reduction in work-derived income in 44–74% of affected workers.[95] A poorer socioeconomic outcome is associated with the need for complete avoidance of exposure to the sensitizing agent, a lower level of education, older age, and lack of effective job retraining programs.[95]

Because the specific bronchial hyperreactivity to occupational agents hardly ever completely disappears, workers with OA should be considered permanently and completely disabled for jobs involving exposure to the sensitizing agent that caused their OA.[96] They should be thoroughly informed about the possibilities for compensation, and established cases should be reported to the appropriate public health authorities, according to national regulations. Evaluation of physiologic impairment should consider the characteristic features of asthma and should be based on the level of airway obstruction, the degree of nonspecific bronchial hyperresponsiveness, and the intensity of medication required for controlling asthma.[4]

IRRITANT-INDUCED ASTHMA

EPIDEMIOLOGIC ASPECTS

Surveillance programs conducted in various countries have indicated that RADS and IIA account for 5–18% of all reported cases of WRA.[97] However, few population-based surveys have addressed the impact of acute inhalation incidents on the global burden of asthma. The longitudinal part of the European Community Respiratory Health Survey found that reported acute inhalation incidents were associated with a higher risk of new-onset asthma.[24] Several cross-sectional studies revealed that asthmatic individuals more often report a history of a single high-level exposure to irritant cleaning products than do healthy control subjects.[98-100] A longitudinal study of rescue and recovery workers exposed to high levels of alkaline dust during and after the World Trade Center disaster showed an increased risk of new-onset asthma in the follow-up period of 5 to 6 years, particularly in the first months after exposure.[101]

Longitudinal workforce-based studies have documented an increased risk of asthma among workers with repeated exposures to high levels of chlorine, ozone, and sulfur dioxide in metal production and among pulp mill workers.[102-104] Exposures to high levels of irritants in the workplace are called "gassings" and are often recalled by workers in epidemiologic studies. Few epidemiologic studies have supported the role of repeated and/or long-term exposure to lower levels of irritant compounds at work in the development of asthma, except for workers exposed to cleaning agents.[105] In these workers, the frequent use of chlorine bleach and ammonia has been associated with an increased risk of asthma.[98] A spectrum of exposures to irritant agents is likely to induce different clinical presentations of asthma ranging from RADS, when workers are exposed to high concentrations of irritants, to "low-dose reactive airways dysfunction syndrome," "not-so-sudden IIA," or "IIA with latency" when workers are exposed to irritants at lower concentrations. However, "low-level" IIA cannot currently be reliably diagnosed in the individual worker.

Table 100.5 Examples of Exposures Causing Acute Irritant-Induced Asthma

Exposure	Examples
Gases	Chlorine (e.g., released by mixing sodium hypochlorite with acids), chloramines (released by mixing sodium hypochlorite with ammonia), sulfur dioxide, nitrogen oxides, dimethyl, sulfate
Acids	Acetic, hydrochloric, hydrofluoric, hydrobromic acids
Alkali	Ammonia, calcium oxide (lime), hydrazine
Biocides	Formalin, ethylene oxide, fumigating agents, insecticides (sodium methyldithiocarbamate, dichlorvos)
Halogenated derivatives	Bromochlorodifluoromethane (fire extinguisher), trifluoromethane, chlorofluorocarbons (CFC, thermal degradation products of freons), uranium hexafluoride, hydrogen, and carbonyl fluoride
Solvents	Perchloroethylene
Fumes	Diesel exhaust, paint fumes, urea fumes, fire smoke, iodine compounds (iodine and aluminum iodide, hydrogen iodide), diethylaminoethanol (corrosion inhibitor)
Sprays	Paints (not specified), floor sealant (aromatic hydrocarbons)
Dusts	World Trade Center alkaline dust, calcium oxide (lime)
Potential sensitizers	Isocyanates, phthalic anhydride

PATHOPHYSIOLOGY

Several factors may influence the pulmonary responses to irritants, such as intensity of exposure, physical properties (e.g., vapor pressure and solubility), and chemical reactivity.[106] Although many irritants are odorous and pungent, it is worth remarking that odor is not related to toxicity. The resulting biologic effect depends on the deposition of the irritant in the upper and/or lower airways. Water-soluble irritants and particles with an aerodynamic diameter larger than 5 μm are predominantly deposited in the upper respiratory tract and proximal airways. Water-insoluble agents and particles measuring 0.5 to 5 μm can reach the distal airways and alveoli, often without causing much sensory irritation (see Chapters 13 and 103).

The development of acute IIA has been associated with a wide variety of high-level exposures to irritant fumes, gases, sprays, or even dusts (Table 100.5).[107] Typically, the

exposure is caused by spills of volatile compounds, accidental releases of irritants under pressure, accidental fire with release of complex mixtures of thermal degradation products, or inadvertent reduction of the air ventilation rate in a confined space.[106] The nature and concentrations of inhaled irritants generated during workplace exposure incidents are most often unavailable.

Inhaled irritants provoke epithelial cell damage and persistent inflammatory response and airway remodeling, although the precise pathophysiologic mechanisms leading to persistent asthma remain largely speculative.[106] Bronchial biopsy samples obtained after a high-level exposure to irritants revealed marked epithelial desquamation, inflammatory changes with predominance of lymphocytes, airway remodeling, and collagen deposition in the bronchial wall.[107,108] Similar changes have been described in animal models.[109-112] Two studies provided information on the long-term outcome of airway inflammation and remodeling in a large series of subjects with acute IIA.[109,113] Both studies showed an inflammatory profile similar to what has been described in sensitizer-induced OA after removal from exposure, with an increase of eosinophils in some patients or neutrophils in others. However, in patients with IIA, subepithelial fibrosis was more prominent than in patients with sensitizer-induced OA. Altogether, in IIA, the pathologic changes observed during the acute phase are consistent with an acute toxic injury, whereas those observed during the long-term phase are consistent with sensitizer-induced OA.

RISK FACTORS

The environmental and host factors that determine the initiation and persistence of IIA remain largely unknown. A relationship between the level of exposure assessed qualitatively by industrial hygienists and the prevalence of nonspecific bronchial hyperresponsiveness has been documented in subjects who had been exposed to a spill of acetic acid.[114] In a follow-up survey of pulp mill workers exposed to high levels of chlorine, the severity of gassing incidents, as evidenced by hospital *emergency department* (ED) visits, was a more significant risk factor for the persistence of nonspecific bronchial hyperresponsiveness than was the number of incidents.[115] The development of IIA did not appear to be associated with smoking and atopy.[114,115] Among the World Trade Center rescue and cleaning workers, the main risk factors for the development of a respiratory disease were the presence on the site during the first 48 hours and the duration of exposure during rescue and cleaning.[116] Smoking was a predisposing or an additive risk factor, whereas atopy was identified as a risk factor for upper, but not lower, airway disease.

DIAGNOSIS

RADS (i.e., acute IIA) is characterized by the onset of asthma symptoms within 24 hours after a single, most often accidental, high-level exposure to a wide variety of irritant substances in subjects without preexisting asthma. Brooks and coworkers proposed stringent clinical and functional criteria for the diagnosis of this condition (Table 100.6).[4,117] The presence of asthma should be substantiated by spirometry demonstrating airflow limitation with a significant bronchodilator response or nonspecific bronchial hyperresponsiveness to methacholine or histamine. Conditions with similar clinical manifestations, such as irritant-induced vocal cord dysfunction, should be carefully considered.[4] The causal role of the workplace exposure can be documented with a reasonable level of confidence by the strong temporal association between an inhalation accident and the rapid onset of asthma symptoms. Such cases should be considered as "definite" IIA. Nevertheless, the World Trade Center tragedy brought new insights by suggesting that asthma can develop insidiously over a few months after a massive exposure to a complex mixture of alkaline dust and combustion products.[118,119] In persons who reported multiple high-level exposures to irritants, although less clearly massive than those that cause RADS, the causal relationship can be supported by the documentation of repeated symptomatic inhalation accidents requiring medical care or of reports to first aid units or occupational health services. These subjects should be regarded as having "probable" IIA.

Table 100.6 Diagnostic Criteria for the Reactive Airways Dysfunction Syndrome (i.e., Acute-Onset Irritant-Induced Asthma)

Absence of preexisting asthma symptoms or a history of asthma in remission
Onset of asthma symptoms after a single specific inhalational exposure or accident
Exposure to an irritant vapor, gas, fume, or smoke in very high concentration
Onset of asthma symptoms within minutes to hours and less than 24 hours after the exposure
Presence of airflow limitation with a significant bronchodilator response or nonspecific bronchial hyperresponsiveness to histamine or methacholine
Exclusion of other pulmonary disorders that can explain the symptoms or simulate asthma

Modified from references 4, 106, 117.

Some clinical features clearly distinguish acute IIA from sensitizer-induced OA. Unlike sensitizer-induced OA, acute IIA does not require a latency period of exposure before the appearance of asthma, but an apparent latency period can be present in IIA that develops after multiple high-level exposures. Persons with IIA do not develop WRA symptoms after reexposure to low concentrations of the irritant that initiated the symptoms because they are not "sensitized" to the offending agent. However, persons with acute IIA may experience WRA symptoms because their nonspecific bronchial hyperresponsiveness makes them more susceptible to irritant stimuli at work. The development of specific bronchial hypersensitivity has been documented after a single, intense exposure to some LMW chemicals.[120] Conversely, known sensitizers can induce IIA when inhaled at very high concentrations.[121,122] In such instances, it may be difficult to differentiate sensitizer-induced OA from IIA; specific inhalation challenges with the suspected agent may be useful in distinguishing between those two conditions.

In clinical reports that described the onset of asthma after repeated, often daily exposure to "moderate" levels of respiratory irritants at work, the evidence supporting the work

relatedness of asthma was very weak and relied on the following findings: (1) a history of adult-onset asthma (or even the reactivation of a previously quiescent asthma[7]), (2) a history of repeated exposure to irritants, and (3) the absence of an identified sensitizer in the patient's working environment. Distinguishing IIA attributed to repeated, moderate level exposures from coincidental asthma that is not work related is difficult in any individual case. The possibility of "chronic–delayed-onset IIA" can be inferred only from epidemiologic studies documenting an increased risk of adult-onset asthma in certain occupations associated with frequent moderate-to-excessive exposures to irritant compounds.

OUTCOME AND TREATMENT

The outcome of IIA is thought to be quite similar to what has been described in patients with sensitizer-induced OA after avoidance of exposure to the causal agent. Nonspecific bronchial hyperresponsiveness can improve over several years after an acute symptomatic inhalation accident.[115,123] Over the long term, however, about three quarters of subjects with acute IIA show persistent nonspecific bronchial hyperresponsiveness and require treatment with inhaled corticosteroids.[124]

Limited data exist on the management of IIA, mainly from case reports of acute IIA.[125] There is some evidence that subjects with IIA benefit rapidly from treatment with oral and/or inhaled corticosteroids, although the dose and duration of treatment remain unknown. Unlike workers with sensitizer-induced OA, workers with acute IIA may be able to continue in their usual jobs with appropriate asthma management, although they may subsequently experience worsening of their asthma symptoms on exposure to irritants at work that may substantially reduce their capacity to work in polluted or dusty environments. The management of IIA may be further complicated by associated disorders, such as chronic rhinitis, perceived intolerance to multiple chemicals, and posttraumatic stress syndrome, which can result from an accidental exposure to irritant substances at work.[101,124,126]

PREVENTION

Prevention of IIA should be primarily aimed at eliminating the risk of high-level exposures that can cause asthma. Such strategies should be directed toward the control of exposures to safe levels by occupational hygiene measures such as containment and adequate ventilation. Continuous monitoring of airborne concentrations of potential respiratory irritants and alarm systems to detect peak exposures may be appropriate in some settings. An important component of prevention is the implementation of workers' educational programs on safe handling of chemicals, effective use of personal protective equipment, and measures to take in the event of an accident at work.

WORK-EXACERBATED ASTHMA

EPIDEMIOLOGIC ASPECTS

The prevalence of WEA reported in the literature varies according to the definition and the type of setting (clinical vs. epidemiologic) in which the WEA was assessed. Twelve studies provided overall estimates of prevalence of WEA.[127] These studies were conducted in the general population or in general health care settings in seven countries. The definition of asthma was not consistent and included physician-diagnosed asthma, as determined from self-reports or medical records, or a diagnosis based on an objective measurement of pulmonary function.[128,129] Some of the studies reported prevalence as a percentage of all adults with asthma, and others reported prevalence as a percentage of all working adults with asthma. The prevalence of WEA from these 12 studies ranged from 13–58% of adults with asthma, with a median of 21.5%. In the study where WEA was diagnosed according to changes in PEF between periods at and away from work, the prevalence of WEA was 14% in asthmatic workers.[130] The most recent systematic review of the literature estimated that 21.5% of the cases of asthma were exacerbated by conditions at the workplace.[2] Data from Michigan, Oregon, and Minnesota showed that 53% of the asthmatic adults surveyed reported that their work worsened or caused their asthma.[131] WEA was suspected in 41% of an Italian cohort of 893 asthmatic patients and in 50% of asthmatic patients exposed to gas, fumes, and dust.[132] Therefore, although the prevalence varies quite widely from one study to another because of the definition and the population of interest, the prevalence of WEA can be estimated to be approximately 20% of adults with asthma.

PATHOPHYSIOLOGY

The pathophysiology of WEA is likely to be largely dependent on the type of triggers inducing asthma exacerbations. There is no reason to believe that the pathophysiology of WEA is different from the pathophysiology of asthma exacerbations observed in NWRA when the triggers are common allergens. When triggers consist of irritant agents, the pathophysiology probably resembles what is seen in IIA. An airway epithelial injury is likely to play a pivotal role, and the intensity of the injury to the epithelial layer may be correlated with the respiratory function impairment, as demonstrated in New York firefighters who responded to the September 11 terrorist attacks.[133] In murine models of chlorine exposure, oxidative stress plays a pivotal role in the pathogenesis of this condition, and the administration of antioxidants can mitigate the epithelial damage.[134] Furthermore, chlorine exposure induces Th2 airway inflammation in ovalbumin-sensitized mice.[135,136] As shown in animal models of chlorine exposure, the extent of damage is likely to depend on the dose of the irritant agent inhaled.

WORK EXPOSURES ASSOCIATED WITH WORK-EXACERBATED ASTHMA

The exposures associated with WEA have been identified either in studies that recorded the agents to which the subjects with WEA were exposed in clinical settings, in surveillance programs, or in worker compensation programs or by using a risk-set approach, in which associations between occupational exposures and WEA were tested while controlling for potential confounders. The

studies assessing individual cases of WEA were performed mainly in North America[137-145] or in Europe.[146] The most commonly described agents were chemicals, dust, smoke, paints, and cleaning products. Although less frequently encountered than these agents, physical factors, such as exercise,[145] temperature,[137] or emotional stress,[138] have also been reported to be associated with WEA. Exposures to gas, smoke, dust, dampness and mold, cold, LMW agents, or physically strenuous work seem to be associated with asthma exacerbations in asthmatic workers.[147]

DIAGNOSIS

WEA should be suspected in all patients whose asthma is difficult to control, in patients who report worsening of their symptoms, or in patients who require an increase in their asthma medication when at work.[4]

Before establishing a diagnosis of WEA, the diagnosis of asthma needs to be confirmed by objective measures. Most asthma guidelines recommend the performance of spirometry, both before and after bronchodilator use, to show an increase in forced expiratory volume in 1 second of 12% with an absolute increase of at least 200 mL.[148] In the absence of reversible airflow limitation, the measurement of airway hyperresponsiveness can confirm the diagnosis of asthma. The lack of objective confirmation of the diagnosis of asthma can lead to misdiagnosis in 30% of cases.[149] Furthermore, nonspecific respiratory symptoms are frequent and can mimic asthma in workers exposed to a dusty or irritant environment.[150]

The diagnosis of WEA relies on the demonstration of (1) a relationship between asthma exacerbations and occupational exposures or (2) poor asthma control during periods at work, along with (3) the determination that OA is unlikely. Asthma exacerbations or loss of asthma control can be documented by a change in the frequency and severity of asthma symptoms or by the need for an increase in asthma medications. Asthma exacerbations can also be documented by the need for ED visits or hospitalizations or by changes in respiratory function at work. Serial PEF monitoring can show increased variability during periods at work compared with periods away from work.[151] Identifying the factors that trigger asthma symptoms is important not only to confirm the diagnosis of WEA, but also to decrease or remove the adverse environmental conditions at the workplace. Identifying multiple triggers is common because the workers are frequently exposed to several agents concomitantly.

Although data on the management of WEA are limited, professional organizations have advised minimizing exposures at work and optimizing standard medical management for asthma (e.g., pharmacologic treatment and avoidance of symptom triggers).[4,152] Clear evidence indicates that persistent exposure to the occupational agent that caused their asthma is detrimental for workers with OA,[66] but the impact of continuing exposure to triggers for WEA has not been well studied and thus is unknown at this time. There is limited evidence that workers with OA may have a greater improvement in their lung function and better asthma control than workers with WEA when removed from exposure.[153-155]

DIFFERENTIATING WORK-EXACERBATED ASTHMA FROM NON–WORK-RELATED ASTHMA OR OCCUPATIONAL ASTHMA

A few studies have compared workers with WEA with adults with NWRA. The clinical characteristics of workers with WEA did not differ greatly from those of adults with NWRA. Some studies reported that workers with WEA tended to be older,[153,156] and they had a higher rate of smoking.[93] No specific risk factors have been clearly identified for WEA.

Workers with WEA are often very difficult to differentiate from asthmatic patients with OA, especially in workers who report a new onset of asthma while in the current workplace. The studies that compared persons with WEA and OA report discrepant findings that can be explained by the different populations studied (general population vs. tertiary clinics). Based on cases in the United States that fulfilled the surveillance case definitions set by the *Sentinel Event Notification System for Occupational Risks* (SENSOR), Goe and colleagues[157] found that patients with WEA were more likely to be female, young, nonwhite, and nonsmokers. These findings were not confirmed in the studies in which WEA cases came from a referral clinic and were defined by a worsening of asthma symptoms when at work and a negative result of a specific inhalation challenge to the suspected agent or agents.[61,158]

The occupational exposures encountered in patients with WEA tend to differ from those found in patients with OA. Whereas occupational exposures of patients with WEA are mainly composed of irritants, chemicals, fumes, mineral dust or particles, patients with OA tend to be exposed to sensitizers such as enzymes or animal-derived dust.[159]

Lemière and associates[155] found that, after adjusting for age, asthma control, and forced expiratory volume in 1 second, the diagnosis of WEA was associated with more frequent prescriptions of inhaled corticosteroids, a noneosinophilic phenotype, and a trend toward a higher proportion of smokers than the diagnosis of OA.

The timing of the onset of asthma with respect to the start of employment at the workplace does not necessarily differentiate WEA from OA; for example, Larbanois and colleagues[158] defined WEA by the presence of WRA symptoms and a negative specific inhalation challenge test result and showed that only 7% of the 71 patients with WEA had asthma before employment. In addition, the onset of asthma before employment in the workplace of interest does not preclude the diagnosis of OA. Workers with previously diagnosed asthma can become sensitized to a new agent at their workplace and develop OA. An increase in asthma symptoms or severity is usually noticed at this time.

In both WEA and OA, asthma symptoms worsen at work and improve when the patient is removed from exposure. Serial PEF monitoring can show a greater variability during periods at work compared with periods away from work in both types of cases, and the PEF variability is greater in persons with OA than with WEA.[151] However, in clinical practice, the difference in the magnitude of PEF variability does not differentiate WEA from OA.

Specific inhalation challenge testing can be performed to diagnose OA, with a positive result considered indicative of OA. Although there can be false-negative test results, a negative challenge test result favors the diagnosis of WEA. In

Table 100.7 Characteristics of Work-Exacerbated Asthma Compared With Non–Work-Related Asthma and Occupational Asthma

Characteristics	Compared With Adults With Non–Work-Related Asthma	Compared With Adults With Occupational Asthma
Sex	Similar,[153,156] or predominance of men in subjects with WEA[93]	Similar,[93] or greater number of women in subjects with WEA[157]
Age	Older[153,156]	Similar or younger[157]
Race	More nonwhite[153]	More nonwhite[157]
Education	Less[153]	N/A
Smoking habits	More likely to have smoked cigarettes[153]	More smokers[93]
Asthma severity	More asthma exacerbations requiring ED visits or hospitalizations in workers with WEA[93] More days with asthma symptoms, more severe asthma based on self-report[153]	Same number of asthma exacerbations requiring ED visits or hospitalizations[155] Greater need of ICS in subjects with WEA[155]
Functional characteristics	Similar FEV_1, PC_{20}[93]	Less PEF variability when at work in subjects with WEA compared with OA[151] PC_{20} may be lower in subjects with WEA[158]
Airway inflammation	Neutrophilic inflammation inconsistently found depending on the study[60,61]	Less likely to have eosinophilic airway inflammation[61,155]

ED, emergency department; FEV_1, forced expiratory volume in 1 second; ICS, inhaled glucocorticoids; N/A, not applicable; OA, occupational asthma; PC_{20}, provocative concentration of methacholine; PEF, peak expiratory flow; WEA, work-exacerbated asthma.

several clinical studies, the definition of WEA or OA relied on the negativity or positivity, respectively, of specific inhalation challenge test results.[61] However, those tests are not available in most settings.

An eosinophilic phenotype is more frequently found in subjects with OA compared with WEA. Workers with OA usually show an increase in eosinophilic inflammation when they are exposed to the agents to which they are sensitized. In contrast, one report found that workers with WEA had no increase in eosinophilic inflammation when at work compared with periods away from work or during exposure to the suspected agents in the laboratory.[61]

Table 100.7 summarizes demographic, clinical, functional, and inflammatory differences among patients with WEA, NWRA, and OA.

SOCIOECONOMIC IMPACT

WRA has a major impact on workers and society as a whole. The workers tend to experience asthma symptoms that interfere with their work productivity and cause absenteeism. Although there are no current data on absenteeism in persons with WEA, the cost related to reduced workforce participation, restrictions in job duties, loss of work days ("absenteeism"), or decreased effectiveness while at work ("presenteeism") is likely to be substantial. *Presenteeism* is the term used to describe employees who are physically present at their jobs but who have decreased productivity because of illness or other barriers to performance; such workers seem to represent even higher costs than workers who are absent. In addition to decreased work productivity, these workers must seek medical care, go to the ED, or be hospitalized.

When examining all cases of WRA, the 2001 and 2002 data from Breton and associates[160] showed that patients who reported having WRA in the United States were 4.8 times more likely to report having an asthma exacerbation, 4.8 times more likely to visit the ED at least once, and 2.5 times more likely to visit their physician for an asthma exacerbation in the previous 12 months compared with individuals with NWRA. Lemière and associates[93] confirmed these data and showed that 341 subjects with WRA who were followed in a tertiary Canadian clinic had more visits to the clinic for asthma (4.1 vs. 1.2; $P < 0.05$) and more hospitalizations for asthma (0.04 vs. 0.008; $P < 0.05$) during the year preceding their diagnosis than 381 subjects with NWRA. In a more recent cohort study of subjects with WRA followed in two Quebec tertiary clinics, Lemière and colleagues[155] showed that the health care–related costs were similar between WEA and OA but were 10-fold greater than the costs related to NWRA in the year preceding the assessment of those patients in tertiary clinics.

Although the cost of OA decreased significantly after the diagnosis was made and the patients were removed from exposure, the cost of WEA following the diagnosis did not decrease significantly because most workers with WEA remained at their workplace. In the few studies in which the work disruption of persons with WEA was evaluated, it was reported to be similar to that seen in OA.[154,158] There is a high rate of unemployment in workers with WEA (30–50%)[158,161] equivalent to patients with OA. Job changes are frequent in workers affected with WEA, but the reduction in earnings seems to be similar in WEA and OA.[158] WEA is likely to have a negative impact on the psychological state of the workers. A small Canadian study showed a trend toward higher depression and anxiety scores in subjects with WEA compared with subjects with OA.[162] Overall, WEA exerts a large socioeconomic impact on workers and society by using a large amount of health care resources and inducing substantial disruption of work.

Key Points

- The workplace environment can lead to the development of different types of work-related asthma, including occupational asthma (i.e., asthma caused by work through either immunologic [sensitizer-induced] or nonimmunologic [irritant-induced] mechanisms) and work-exacerbated asthma (i.e., preexisting or coincident asthma exacerbated by nonspecific stimuli at work).
- Work-related asthma represents a significant public health concern because of its high prevalence, long-term respiratory health consequences, and socioeconomic consequences for affected workers.
- Sensitizer-induced occupational asthma should be diagnosed with the highest level of accuracy by comprehensive investigations to avoid unwarranted removal from exposure and the associated socioeconomic consequences.
- For patients with sensitizer-induced occupational asthma, the recommended treatment is complete avoidance of the causal agent, although the rate of recovery is low, especially when the diagnosis is delayed.
- Irritant-induced asthma is characterized by early onset after exposure; however, irritant-induced asthma can also develop insidiously over a few months after massive exposure to a complex mixture of alkaline dust and combustion products, as shown in the World Trade Center disaster.
- Unlike patients with sensitizer-induced occupational asthma, those with irritant-induced occupational asthma do not develop work-related asthma symptoms after reexposure to low concentrations of the irritant that initiated the symptoms.
- Work-exacerbated asthma should be suspected in all patients whose asthma is difficult to control, in patients who report a worsening of their symptoms, or in those who require an increase in their asthma medication when at work.
- Workers with work-exacerbated asthma are often very difficult to differentiate from asthmatic patients with occupational asthma, especially in individuals who report a new onset of asthma while in the current workplace.

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KEY POINTS

INTRODUCTION

The pneumoconioses are a class of entirely preventable diseases caused most commonly by workplace exposures to fibrogenic mineral dust. In 2005, the World Health Organization estimated that the most important of these diseases, silicosis, asbestosis, and coal workers' pneumoconiosis, respectively, caused 486,000, 376,000, and 366,000 disability-adjusted years of life lost globally.[1] Pneumoconiosis is caused by the inhalation of respirable dust, which accumulates in the lungs and results in pathologic tissue reactions. Although occupational exposures are the main cause (Figs. 101.1 and 101.2), environmental pneumoconioses may also be seen.

PATHOGENESIS AND EXPOSURE-RESPONSE RELATIONSHIPS

Dust deposition in the lungs depends on the size, geometry, and aerodynamic properties of the inhaled dust particles. Their clearance is determined by the mucociliary escalator and cellular mechanisms, particularly engulfment by macrophages. The balance of dust deposition and its clearance determines dust accumulation in the lungs. Tissue reactions to dust are generally determined by the quantity and duration of exposure to accumulated dust, the surface physicochemical properties of the dust particles, and host responses.

In epidemiologic studies, the cumulative exposure to dust is estimated using a job exposure matrix, which combines information taken from the worker's job and task history with industrial hygiene environmental measurements. These diseases generally follow clear exposure-response relationships. However, given the variability in host susceptibility, there may be heavily exposed individuals who remain unaffected and less severely exposed individuals with disease. Therefore, a clinician should not reject the diagnosis of pneumoconiosis solely because exposure is believed to be too remote, too brief, or of too low a level. Workplace data demonstrating compliance with regulatory limits may not reflect the totality of a worker's exposure and do not account for workers who are especially susceptible, had an unusual exposure profile, or retained more dust than other workers who were similarly exposed.

CHEST IMAGING

Chest radiographs have been the cornerstone of surveillance for pneumoconiosis in the workplace given wide international availability, portability, and low cost. The International Labour Office International Classification of Radiographs of Pneumoconioses[2] provides a widely accepted framework for evaluation of posteroanterior chest radiographs taken for medical surveillance of occupational lung disease. The system requires users to compare the images of the subject with standard calibration radiographs to classify the shape, size, and profusion (or abundance) of pneumoconiotic opacities. This system improves consistency in the reading of pulmonary parenchymal and pleural disease, and places an individual case in the context of available epidemiologic information.[2,3]

High-resolution computed tomography (HRCT) is more sensitive than chest radiographs and is used primarily in



Figure 101.1 Underground longwall coal miners in Ukraine. Note the miner in foreground with skin and clothing heavily soiled with coal mine dust, who, despite earlier respirator use, has significant dust deposition around his nose and mouth. Individuals performing work in dusty conditions are at significant risk of pneumoconioses despite engineering controls such as dust suppression technologies and personal protective equipment such as respirators. (Courtesy Robert Cohen, MD.)



Figure 101.2 Engineered stone fabricator. Worker cutting engineered stone, a composite material high in content of silica along with resins and pigments. Note highly dusty work conditions with lack of dust suppression measures. The primary control for respiratory disease prevention in this worker's case is use of a respirator, which is generally less effective than measures limiting overall respirable dust, such as wet cutting of the stone product. Similar workers are at considerable risk for silicosis. (Courtesy Ling Mao, MD, PhD.)

a diagnostic clinical setting to characterize lung, mediastinal, and pleural lesions. HRCT is not widely applied in disease surveillance, although reductions in cost and radiation exposure raise the possibility of future application in this setting. A classification system for HRCT similar to the International Labour Office system for chest radiographs has been proposed.[4]

Magnetic resonance imaging is of limited value, but it can be useful in differentiating benign pleural thickening from mesothelioma.[5] Positron emission tomography is also of limited utility because pneumoconiotic lesions and lymph nodes may demonstrate metabolic activity similar to that of neoplastic lesions.[6–8]

CLINICAL ISSUES, LUNG FUNCTION, AND PRINCIPLES OF DIAGNOSIS

The clinician is faced with two main tasks when evaluating a case of suspected pneumoconiosis. *First,* the clinician must assess the nature of the disease process, as well as determine whether it has decreased the worker's capacity to perform his or her job. Assessment of *impairment* is based on symptoms and measurements of pulmonary function at rest and during exercise where indicated (see Chapters 32, 33, and 35). Assessment of *disability* is made in the wider context of whether subjects' impairment makes them unfit for work and thus requires detailed knowledge of the job tasks and exertional requirements. Pneumoconiosis may be associated with normal lung function or with obstructive, restrictive, or mixed patterns of impairment. Lung function measurements in the normal reference range may be misleading given that persons who undertake heavy labor may have higher initial lung function measurements than the general population, on which most reference values are based.[9]

Second, the clinician needs to determine whether there has been environmental or occupational exposure of sufficient duration and intensity to be a significant contributing cause of the patient's condition. For this task, the key tool is the occupational exposure history, provided by the worker, who generally possesses extensive knowledge of the materials, processes, and exposure controls involved. Reliance on job titles for determining exposures is insufficient because individuals often perform job tasks not indicated by the job classification. A complete exposure history, including student summer jobs, military service, avocations, and short-term jobs, is of vital importance. On occasion, it may be necessary to establish occupational exposure through analysis of biologic material (e.g., sputum, *bronchoalveolar lavage* [BAL], or lung biopsy specimens) for the putative dust or its breakdown products, particularly in cases in which the exposure is remote or the exposure history is incomplete.

In the discussion that follows, the pneumoconioses caused by silica, coal mine dust, asbestos, and beryllium are considered separately with respect to occupations at risk, epidemiology, and pathophysiology, as well as the clinical issues of diagnosis, prognosis, and management. Lists of occupations and jobs at risk are never exhaustive for a given exposure but are a guide for use in general office practice. Less frequently encountered pneumoconioses, including those resulting from nonasbestos silicates such as talc and mica, hard metal dust exposure, and silicon carbide, are outside the scope of this chapter.

SILICOSIS

DEFINITION

Silicosis is a fibrotic lung disease caused by the inhalation of *respirable crystalline silica* (RCS) usually in the form of quartz and, less commonly, as cristobalite and tridymite.[10,11] Amorphous silica is relatively nontoxic.

INDUSTRIES AND OCCUPATIONS AT RISK

Silicosis is an ancient disease, with outbreaks and associated deaths that continue to be reported worldwide.[1]

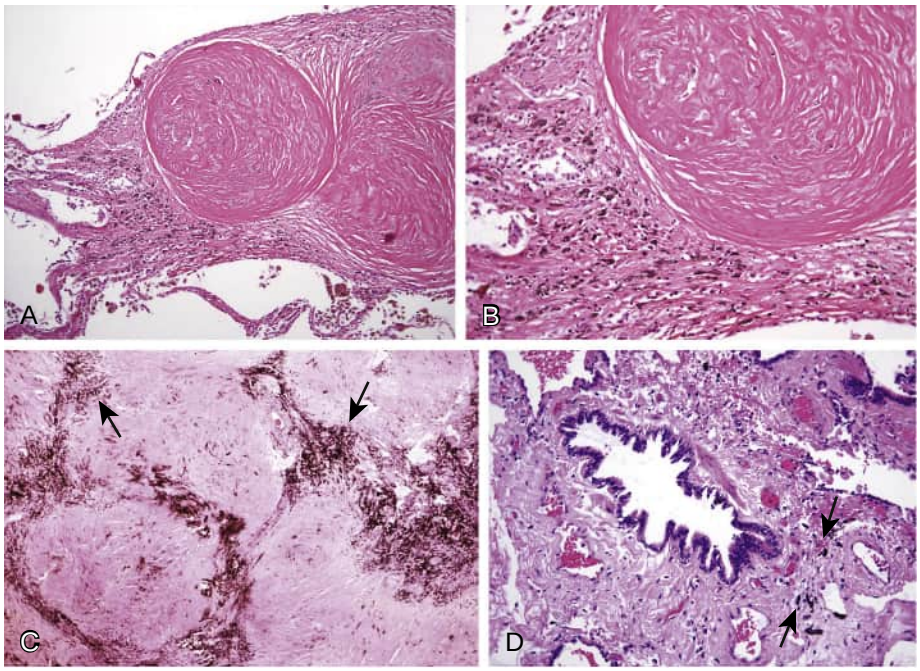

Figure 101.3 Pathologic lesions of chronic silicosis. (A) Silicotic nodule characterized by a central zone of a cellular hyalinized collagen with a whorled appearance and a peripheral zone of dust-laden macrophages. (B) Silicotic nodule at higher magnification to show these characteristics to better advantage. (C) Progressive massive fibrosis showing confluent silicotic nodules and aggregates of dust-laden macrophages *(arrows).* (D) Mineral dust small airways disease characterized by peribronchiolar fibrous tissue containing a moderate amount of pigment *(arrows).* (Courtesy National Institute for Occupational Health, South Africa.)

Despite significant improvements in dust control regulations, silicosis continues to be reported in workers from a variety of industries in the 21st century. Silicosis cases are likely to be underreported as is often the case in chronic occupational illnesses.[12] Construction, surface and underground mining, tunneling, and foundry work are major sources of silica dust exposure.[12a] Reports have shown a severe silicosis risk for workers fabricating artificial or engineered stone countertops[13–15,15a,15b] (see Fig. 101.2) and stonemasons. Workers who repair or demolish concrete structures,[16] including roads, have significant risk of disease.[17] Less common occupational groups associated with silicosis include workers producing stressed denim by sandblasting,[18] stone carvers,[19] dental technicians,[20] and jewelers using chalk molds.[21] Many of the current cases of silicosis come from industries using relatively new technology that, if unaccompanied by modern dust controls, results in exposures to finer dust particles than in traditional industries and jobs. Cases of silicosis have also been reported following environmental exposure to dust storms or volcanic particulate,[22,23] as well as in agricultural workers.[24,25]

PATHOLOGY

Three clinicopathologic types of silicosis have been described. *Chronic silicosis* is the most common form of the disease, and it typically follows exposure measured in decades rather than years. The pathologic hallmark of chronic silicosis is the silicotic nodule, a well-circumscribed lesion and one of the few agent-specific lesions in pathology (Fig. 101.3A–B; eFig. 101.1). Silicotic nodules are believed to develop first in the hilar lymph nodes,[26] and they may be confined to this area; they may become encased in calcification and impinge on or erode into airways. The disease process next involves the lung parenchyma. It is usually bilateral, predominantly involving the upper lung zones. The silicotic nodules may grow or become confluent with disease progression, leading to the development of *progressive massive fibrosis* (PMF) (Fig. 101.3C), also known as *complicated silicosis.* These lesions, which are larger than 1 cm in diameter (and often significantly larger), frequently involve the upper lobes. They may cause substantial scarring and volume loss. Rarely they cavitate, which may be an indication of tuberculosis (see later and eFig. 101.7).[27]

Accelerated silicosis differs from chronic silicosis in the earlier development of silicotic nodules, usually after 3 to 10 years of more intense RCS exposure. The nodules may be more widely distributed in the lung and are more cellular than fibrotic. PMF may develop in accelerated silicosis as well.

Acute silicosis follows intense exposure to RCS, such as that caused by sandblasting, for periods measured in months rather than years.[27] This form has many features of pulmonary alveolar proteinosis (see Chapter 98), and it is also known as silicoproteinosis. Silica particles and various biomarkers of tissue reaction can be identified in BAL material.[28]

Rheumatoid nodules may occasionally develop in the setting of silicosis and may be seen in patients with rheumatoid arthritis or high levels of circulating rheumatoid factor.[27] There may be silicotic nodules in the background. Silicotic nodules may also develop in the cervical and abdominal lymph nodes and, occasionally, in the liver, spleen, and bone marrow.

PATHOGENESIS

The toxicity of silica dust is dependent on the physical and chemical properties of the particles, as well as the cellular mechanisms that initiate and drive the process of inflammation and fibrosis. Animal studies have shown that the mechanisms likely involve activation of inflammasomes that induce the secretion of proinflammatory cytokines, including interleukin-1β, interleukin-18, tumor necrosis factor-α, and interferon-β from antigen-presenting

cells that lead to fibrosis.[29,30] Growth factors, including transforming growth factor-β, are important in fibrogenesis and also have been implicated in carcinogenesis in association with silica.[31,32] Reviews have described the immune response to silica in more detail, including the role of innate and adaptive immunity.[33,34] There is agreement that freshly fractured silica, such as that generated during drilling, cutting, and blasting, is more toxic to the alveolar macrophages than is "aged" silica, presumably because of its increased redox potential.[35,36] Other minerals, particularly clay components, may adhere to the surfaces of silica particles and produce "coated" silica that is less toxic than uncoated silica dust. Although the major determinant of silicosis is the level of exposure to silica-containing dust, individual susceptibility to the disease may play a role in its development and severity.[37–39]

AIRFLOW OBSTRUCTION, CHRONIC BRONCHITIS, AND EMPHYSEMA

COPD and chronic bronchitis are common manifestations of long-term occupational exposure to environments contaminated by silica dust and can develop in silica-exposed individuals with or without silicosis.[40–45] *Mineral dust airways disease* refers to disease of small airways, including fibrosis and pigmentation of respiratory bronchioles (see Fig. 101.3D), and it is seen in association with exposures to a variety of mineral dusts, including silica.[46] In a study of adolescents and young adults working in a stone-crushing plant, lung function changes were interpreted as evidence for impaired lung growth attributed to their high RCS exposure.[47] Additionally, smoking can potentiate the effect of silica dust on airflow obstruction.[40]

CONNECTIVE TISSUE DISEASES, RENAL DISEASE, AND CARDIOVASCULAR DISEASE

Silica exposure has been associated with connective tissue diseases. The relative risk of rheumatoid arthritis, systemic lupus erythematosus, and systemic sclerosis is substantially higher in silica-exposed populations.[41,48,49]

Renal disease has also been reported in silica-exposed workers. Some studies have implicated an immune complex–mediated glomerulonephritis or a direct toxic effect of silica.[41,50,51] Silicosis has been linked with antineutrophil cytoplasmic antibody positivity and possibly with vasculitis.[48,52] Cardiovascular disease may also be associated with silica exposure. A report of a cohort of 74,040 silica-exposed workers found an increased risk of mortality compared with nonexposed workers; cardiovascular disease was the major cause of death.[53]

LUNG CANCER

The association between silicosis and lung cancer is well established. Silica was classified as a known human carcinogen by the International Agency for Research on Cancer in 1997 and again in 2012.[54,55] A review of large epidemiologic studies and analysis of pooled data have established that silica, as well as silicosis, conferred increase risks for lung cancer in occupationally exposed cohorts.[56,57]

TUBERCULOSIS

The association between silicosis and tuberculosis has long been recognized. Rates of active tuberculosis in silicotic subjects range from 2- to 30-fold higher than rates in the same workforce without silicosis.[58] Workers with acute and accelerated silicosis are at even greater risk for tuberculosis.[10] Other risk factors include high prevalence of tuberculosis in the local population, older age, smoking, poor general health, and HIV-positive status.[58–62] Exposure to silica, without silicosis, may also predispose individuals to tuberculosis.[58,59]

In most areas, *Mycobacterium tuberculosis* is the more frequent mycobacterial pathogen in the setting of silicosis. However, in areas where tuberculosis is less prevalent, nontuberculous mycobacterial infections are more common.[50,63] Some evidence suggests that persons with silicosis are also at increased risk for fungal infections.[64]

CLINICAL FEATURES

Workers with silicosis commonly present with shortness of breath. Cough and sputum production are common symptoms and usually relate to chronic bronchitis, but they may reflect the development of tuberculosis or lung cancer. Patients with abnormal radiographs found during medical surveillance may be asymptomatic. Chest pain is not a feature of silicosis. Systemic symptoms such as fever and weight loss should be attributed to tuberculosis or lung cancer until proved otherwise. Clubbing is also not a common feature of silicosis and should raise concern for lung cancer. Accelerated silicosis and acute silicosis cause a more rapid onset of breathlessness developing over months or a few years rather than decades, and they often cause severe impairment in gas exchange.

RADIOGRAPHIC FEATURES

Chronic simple silicosis and accelerated silicosis are characterized by small rounded opacities on the chest radiograph. Silica exposure has been associated with rounded opacities that are between 3 and 10 mm in diameter,[65] although smaller or irregular opacities may be seen. In general, there is good correlation among cumulative dust exposure, the retained dust in the lungs, the presence and severity of lung disease, and the chest radiograph.[66] However, occasionally, even histologically confirmed advanced silicosis may not be apparent on a chest radiograph.[67]

Silicotic nodules are usually symmetrically distributed and tend to appear first in the upper zones and later, although not invariably, involving other zones (eFig. 101.2). Enlargement of the hilar nodes may precede the development of the parenchymal lesions. Eggshell calcification of lymph nodes, when present, is strongly suggestive, although not pathognomonic, of silicosis (eFig. 101.3).

PMF is characterized by the coalescence or growth of small rounded opacities to form larger lesions (eFig. 101.4, Videos 101.1 and 101.2). With time, the mass lesions tend to contract, usually to the upper lobes, and leave hyperlucent zones at their margins (eFigs. 101.5 and 101.6) and often at the lung bases. In this process, small rounded opacities, previously evident, may disappear, sometimes resulting in a picture that must be distinguished from sarcoidosis

or tuberculosis. The rapid development of several large lesions may indicate rheumatoid silicosis or concomitant tuberculosis.

In contrast to chronic and accelerated silicosis, acute silicosis is characterized by diffuse changes that usually display an air space and interstitial pattern. Findings include consolidation with or without calcification, centrilobular nodules, and ground-glass opacification.[68]

LUNG FUNCTION

The lung function profile is determined by the extent of silicosis, as well as by the associated airway and vascular changes. In chronic silicosis, spirometric tests usually reflect airflow limitation. Reduction in single-breath carbon monoxide uptake (*diffusing capacity for carbon monoxide* [D_{LCO}]) is generally apparent in more advanced chronic silicosis and may reflect dust-related fibrosis and/or associated emphysema.

In the accelerated and acute forms, functional changes are more marked, and progression is more rapid. In acute silicosis, lung function shows a restrictive defect and impairment of gas exchange, which can lead to respiratory failure.

DIAGNOSIS AND COMPLICATIONS

Silicosis is diagnosed on the basis of the history of exposure and characteristic radiographic changes. Problems arise when the history of exposure is remote, forgotten, or missed, or when the exposure took place outside a recognized occupation. The duration and intensity are important factors used to calculate cumulative dose. Short periods of intense exposure are also important. The physician should never dismiss the diagnosis of silicosis when that diagnosis is suggested by clinical and radiologic features but exposure appears to have been insignificant or in an occupation not known to be associated with silicosis.

HRCT scanning is superior to plain chest radiography in detecting the presence and profusion of silicotic opacities (Fig. 101.4), as well as early conglomeration (see eFig. 101.4B–E). Occasionally, the radiologic features are unusual; examples include diffuse irregular interstitial fibrosis, hilar lymphadenopathy, or large lung opacities in the absence of typical small nodules.

Detection of silica in BAL fluid may suggest the diagnosis. Lung biopsy may be necessary to distinguish PMF or other atypical features from lung cancer, tuberculosis, and other diagnoses. Biopsy material should be reviewed under polarizing light microscopy or submitted for mineralogic analysis.

Less common complications include right heart dysfunction, spontaneous pneumothorax, broncholithiasis, and tracheobronchial obstruction from enlarged calcified hilar nodes. The presence of cough, hemoptysis, weight loss, fever, or any new radiologic feature, such as cavitation, should be pursued with further evaluation, including culture and histologic examination of tissue, to exclude tuberculosis or malignancy (eFig. 101.7, Video 101.3).

MANAGEMENT AND CONTROL

Once established, the fibrotic process of chronic silicosis is thought to be irreversible. Management of the individual case is therefore focused on preventing disease progression or complications. Removal from exposure to silica or other respiratory hazards should be advised. Although the disease may progress without further exposure, the rate of deterioration may be reduced.

Interventions to interrupt the inflammatory process that leads to chronic silicosis have not been shown to be successful. There has been interest in the use of whole-lung lavage to remove silica from the lung, but a favorable impact on progression of acute or chronic silicosis has not been clearly demonstrated.[69,70]

Patients with silicosis should be monitored for mycobacterial disease and other infections, and they should be treated for latent tuberculosis infection (see Chapters 42 and 51). This is especially true for patients with acute or accelerated silicosis, as well as for those with silicosis who are infected with human immunodeficiency virus.

The interaction between silica exposure and smoking in the development of COPD, tuberculosis, and lung cancer makes it important to implement smoking-cessation programs in the workplace. Patients with severe disease may be considered for lung transplantation (see Chapter 140).

The most important aspect of the management of silicosis relates to its prevention. Each patient with silicosis represents not only a sick patient, but also potentially a sick workplace. Such cases should be considered sentinel events and reported to public health authorities. More recent deaths from silicosis in younger subjects in the United States have been reported after exposure in the construction and manufacturing sectors. Deaths of young persons who sandblasted denim or worked with engineered stone are reminders that there is often a lack of awareness of the hazards of silica outside the occupations traditionally associated with silicosis.

COAL MINE DUST LUNG DISEASE

DEFINITION

Coal mine dust lung disease (CMDLD) is a spectrum of chronic lung diseases caused by prolonged excessive exposure to coal mine dust.[71] Classic *coal workers' pneumoconiosis* (CWP) is one manifestation, with findings of small nodules or masslike lesions and obstructive lung disease. In addition, coal mine dust exposure may contribute to other phenotypes, including COPD, as well as pulmonary fibrosis, termed *dust-related diffuse fibrosis* (DDF). The diversity of these manifestations reflects variation in host responses as well as variation in coal mine dust composition.

COMPOSITION OF COAL MINE DUST

Coal is a heterogeneous material that is high in carbon content, but contains a number of other substances, including silica, silicates such as mica and kaolinite, metals, and volatile compounds such as hydrocarbons. Coal is extracted using underground or surface mining techniques.

Coal miners are exposed to mixed dusts during the mining process. *Respirable crystalline silica* (RCS) is an important component of coal mine dust. RCS is created as miners cut through siliceous layers above, below, and within the coal seams. Dust exposure may also vary within a mine as a result of differences in local ventilation and dust-control

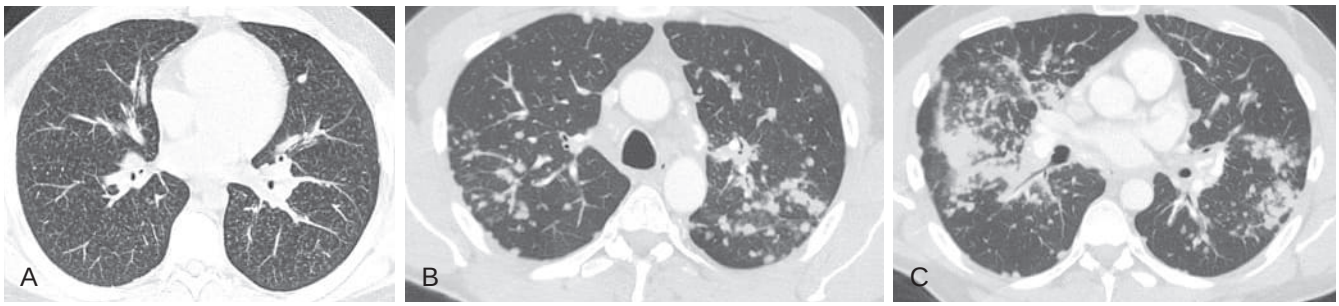

Figure 101.4 Imaging appearance of lesions in silicosis. (A) Axial chest computed tomography from an artificial stone countertop fabricator with heavy respirable crystalline silica exposure, with innumerable centrilobular ground-glass micronodules. (B) Axial chest computed tomography from a stonemason demonstrating somewhat larger, well-circumscribed nodules consistent with simple silicosis. (C) Axial chest computed tomography from the same individual seen in (B), demonstrating larger opacities >1 cm in long-axis dimension, consistent with progressive massive fibrosis. (A, Courtesy David Deller, MD. B–C, Courtesy Robert Cohen, MD.)

techniques.[71a] Coal miners working close to the mining face, particularly when downwind of production, are often exposed to greater concentrations of respirable dust than other workers at the same mine.

The introduction of modern mining technology has likely changed coal mine dust composition. Unlike the older technology of drilling and blasting, newer, more powerful mining equipment pulverizes rock layers, thereby generating large quantities of RCS. Newer coal preparation plant technology permits large amounts of coal to be separated from waste rock. These innovations may increase worker exposure to noncoal dust, possibly increasing the risk of lung disease. Specific job tasks, such as roof bolting (in which workers drill bolts upward into the roof of the mine to stabilize it) and the operation of continuous mining machines, have been frequently associated with CMDLD.

PATHOLOGY

Histologically, simple CWP may initially manifest as a *coal macule*, a collection of dust-laden macrophages containing reticulin and collagen (Fig. 101.5A). These macules are located within the wall of respiratory bronchioles and may be surrounded by centrilobular or focal emphysema. Compared with coal macules, coal nodules contain a greater degree of collagen and are not confined to respiratory bronchioles (Fig. 101.5A). The nodules may grow or coalesce into lesions larger than 1 cm, indicating progression to PMF (Fig. 101.5B). PMF lesions may necrose and cavitate, raising the possibility of superimposed mycobacterial or fungal infection.[72] The lesions may be irregular in shape, in some cases mimicking usual interstitial pneumonia[73] (Fig. 101.5C). Silicotic nodules may also be identified when there has been significant RCS exposure.[74]

EPIDEMIOLOGY AND NATURAL HISTORY

Radiologic surveillance has been the primary tool used in public health programs to identify coal workers with CWP and to evaluate the prevalence and progression of disease. A meta-analysis of studies published from 2001 to 2011 concluded that the prevalence of radiologic CWP in Chinese miners was approximately 6%.[75] In the United States after the institution of modern dust-control regulations, the Coal Workers' X-Ray Surveillance Program operated by the National Institute for Occupational Safety and Health reported a decline in prevalence from nearly one-third of working miners with 25 years of tenure in the 1970s to a low of less than 5% in the 1990s. More recently however, simple CWP prevalence has increased to more than 10% of surveyed workers nationally and 20% of workers in the central Appalachian states of Kentucky, Virginia, and West Virginia. Disturbingly, the rate of PMF in central Appalachia has also increased to levels not seen since the institution of modern dust controls.[76–78]

DISEASE PHENOTYPES

Classic Coal Workers' Pneumoconiosis

CWP may be diagnosed in an individual with compatible radiographic findings and a history of coal mine dust exposure of at least 10 years, although shorter-duration exposures of high intensity may be associated with disease. Typical chest imaging findings of CWP may include nodular or masslike opacities, areas of hyperlucency consistent with emphysema, and, in more advanced disease, architectural distortion of neighboring anatomic structures resulting from loss of lung volume.

The likelihood of developing disease depends on multiple factors, the most important of which is cumulative coal mine dust exposure.[79,80] In addition, increasing coal rank—reflecting greater carbon content of the coal—is believed to be a factor.[80,81] Exposure to dust with a high component of RCS is also a significant contributor to disease. Although the chest radiograph is insensitive for detecting early lesions of CWP,[82] it remains a useful tool in the assessment of severity of CWP because the number of small opacities correlates well with the number of small lesions observed on pathologic examination.[83]

Like silicosis, CWP is divided into "simple" or "complicated" disease on the basis of the size of the radiographic or pathologic lesions. The abnormalities in simple CWP are often rounded and upper zone predominant (eFig. 101.8), although data from large studies of surveillance radiographs show that significant proportions of affected workers have irregular and lower zone–predominant lesions.[65] Increasing

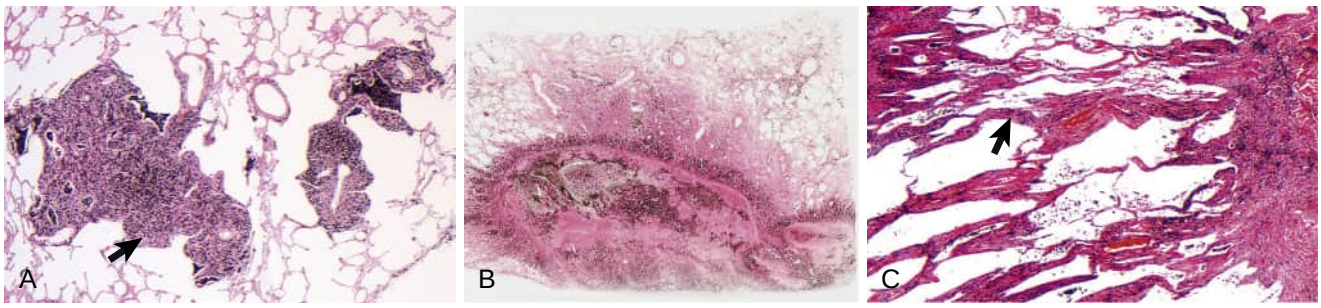

Figure 101.5 Pathologic lesions of coal mine dust lung disease. (A) Coal macule and micronodule *(arrow)* with associated emphysema. (B) Lesion of progressive massive fibrosis formed from enlargement and coalescence of two lesions, with pigmented dust deposition, central necrosis, and cholesterol clefts. (C) Dust-related diffuse fibrosis *(arrow)* bridging two coal nodules. (From Petsonk EL, Rose C, Cohen R. Coal mine dust lung disease. New lessons from an old exposure. *Am J Respir Crit Care Med.* 2013;187:1178–1185. Courtesy Dr. Francis Green.)

profusion of simple pneumoconiotic opacities is associated with reduced lung function, contrary to prior dogma.[84]

Complicated lesions or PMF lesions have a long-axis diameter exceeding 10 mm. These lesions are often located in the upper zones and frequently become bilaterally distributed with progressive disease. Lower lobe and asymmetrical distribution of these large opacities has been reported.[85] PMF is always associated with a background of smaller opacities, although their profusion may be low because many nodules are subsumed into these larger scars. Additionally, with severe disease, there may be emphysema, volume loss, and distortion of thoracic architecture. The risk of development of PMF increases with older age and greater cumulative dust exposure,[86] as well as with a higher baseline profusion of the small opacities of simple CWP in a miner.[86,87]

Rapidly Progressive Pneumoconiosis

In the United States, rapidly progressive pneumoconiosis, defined as radiographic progression of more than one International Labour Office profusion subcategory within 5 years or the development of PMF after 1985, has been observed with increasing frequency.[88] Histologic examination of lung tissue from miners with rapidly progressive disease demonstrated lesions of silicosis and mixed-dust pneumoconiosis.[74] The distribution of this disease entity appears concentrated in the central Appalachian region of the United States.

Dust-Related Diffuse Fibrosis

Although less common than CWP, interstitial pulmonary fibrosis is a recognized disease among workers exposed to coal, silica, and mixed mineral dusts.[73] This entity, DDF, typically manifests radiographically with lower lung zone–predominant reticular disease with or without honeycombing. There also may be a background of nodular interstitial opacities. Pathologically, the observed fibrosis may be pigmented or unpigmented,[89] with a lobular distribution similar to that of usual interstitial pneumonia. Examination of the histologic specimen with polarized light microscopy or scanning electron microscopy with energy dispersive x-ray spectroscopy may demonstrate silica and other minerals within the lung tissue.[90]

Overall, the clinical course of DDF is thought to be less aggressive than that of *idiopathic pulmonary fibrosis*.[91] Distinguishing DDF from idiopathic pulmonary fibrosis sometimes poses a diagnostic challenge. However, it is imperative to bear in mind that the diagnosis of idiopathic pulmonary fibrosis requires the exclusion of other known causes of interstitial lung disease, including occupational and environmental exposures.[45]

Chronic Bronchitis, Emphysema, and Lung Function Impairment

Chronic cough and sputum production resulting from chronic bronchitis are commonly encountered among coal miners.[92,93] The prevalence of chronic bronchitis increases with increased cumulative coal mine dust exposure. Symptoms of chronic bronchitis are also associated with significant declines in the *forced expiratory volume in 1 second* (FEV_1).[94]

Coal mine dust is also an important cause of emphysema (Fig. 101.6).[95–97] Emphysema severity scores are strongly associated with increased lung dust content.[98,99] Centrilobular emphysema is the most common type of emphysema associated with coal mine dust exposure and can develop in nonsmoking miners as well as smoking miners.[98] The effect of cigarette smoking on emphysema is additive to that of coal mine dust exposure.[95] All pathologic types of emphysema, including centriacinar, panacinar, and bullous emphysema, are associated with both dust exposure and cigarette smoking.[100]

Coal mine dust exposure is associated with impairment in lung function as measured by spirometry, even in the absence of radiographic evidence of CWP.[101] Examination of multiple cohorts of miners is notable for evidence of an excess lifetime risk of significant loss of lung function attributable to dust exposure.[102] After adjusting for age and smoking status, the magnitude of decline in lung function is proportional to estimated cumulative coal mine dust exposure.[103–106] The correlation between the rate of decline in FEV_1 and cumulative coal mine dust exposure is greater in nonsmokers,[106] and it is the same order of magnitude as that caused by exposure to tobacco smoke. In addition to being a marker for respiratory symptoms, the magnitude of FEV_1 decline is associated with increased risk of death from cardiovascular and nonmalignant respiratory disease.[107]

Asthma may be caused or exacerbated by exposure to the coal mine atmosphere. Mines contain contaminants that may contribute to asthma, including isocyanates[108,109] and diesel exhaust particulate.

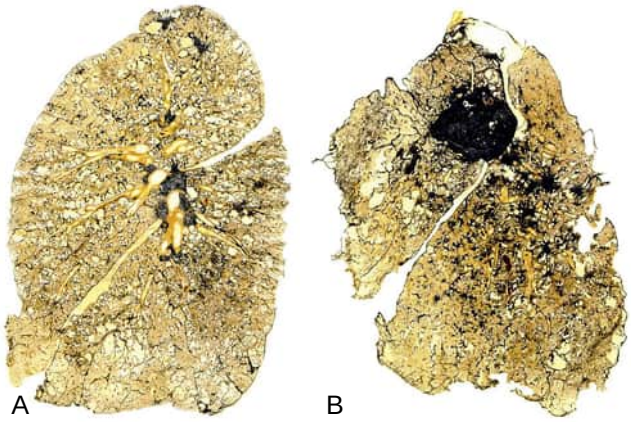

Figure 101.6 Coal mine dust lung disease. (A) Whole-lung section from a never smoker with 28 years of coal mining experience, showing macular and nodular coal workers' pneumoconiosis and a background of severe emphysema, predominantly centriacinar. (B) Whole-lung section from a never smoker with 36 years of coal mining experience, showing progressive massive fibrosis and moderately severe emphysema. (Modified from Kuempel ED, Wheeler MW, Smith RJ, et al. Contributions of dust exposure and cigarette smoking to emphysema severity in coal miners in the United States. *Am J Respir Crit Care Med.* 2009;180:257–264.)

Rheumatoid Pneumoconiosis

Eponymously known as Caplan syndrome, rheumatoid pneumoconiosis is the association of rheumatoid arthritis with CWP.[110] This is an uncommon manifestation of CMDLD, observed in less than 1% of autopsied cases.[111] The chest radiograph typically demonstrates large, well-defined nodules or masses, ranging from 5 to 50 mm in diameter, typically without a background of smaller opacities. Pulmonary tuberculosis and fungal infections may need to be considered in some cases, particularly when nodules cavitate.

LUNG CANCER

Historically, coal mine dust exposure was not believed to be associated with increased risk of bronchogenic lung cancer.[112] However, more recent studies with longer follow-up suggest that there may be an association between coal mine dust exposure and lung cancer.[113–115] This may reflect the heterogeneous composition of coal mine dust, with the presence of multiple other carcinogenic coal mine dust constituents, including silica and diesel exhaust particulate.

CLINICAL FEATURES

Respiratory symptoms of CMDLD include dyspnea, wheezing, and cough with or without chronic sputum production. Symptoms develop insidiously; they may often begin when the worker is still being exposed to coal mine dust or may instead begin or progress after the worker is no longer exposed. The degree of radiographic involvement may not always correlate with symptoms. The worker may be asymptomatic at the time of discovery, such as when radiographic abnormalities are identified during medical surveillance. There is no specific laboratory test for CMDLD, although levels of angiotensin-converting enzyme,[116] antinuclear antibodies,[117] or rheumatoid factor may be abnormal.

CHEST IMAGING

Plain chest radiography is discussed earlier, under the disease phenotype of CWP. HRCT scanning is a more sensitive means of identifying certain CMDLD manifestations, including emphysema[118,119] and early pulmonary fibrosis. HRCT is also useful in evaluating other radiographic features that may coexist with CMDLD, including lung neoplasms. HRCT may be most useful in the evaluation of symptomatic workers with normal or borderline chest radiographs,[120] or for the evaluation of radiographic lesions atypical for CWP.

Similar to PMF observed in the setting of silicosis, PMF in the setting of CMDLD may sometimes be difficult to distinguish from other lesions, particularly neoplastic disease and granulomatous infections. Malignant disease should be distinguished from PMF, particularly when there is a paucity of background small opacities, or when disease is unilateral. Prior imaging may be helpful in estimating the doubling time of growth of the lesion. Increased ^{18}F-fluorodeoxyglucose uptake at the time of positron emission tomography scanning may not be useful because PMF lesions may also exhibit increased uptake.[7]

The likelihood of developing tuberculosis has been observed to be variably increased in coal miners,[121,122] a finding that may reflect their silica exposure. Histoplasmosis and miliary tuberculosis may be alternative explanations for profuse small opacities and should be kept in mind.

LUNG FUNCTION

Given the heterogeneous nature of the manifestations of CMDLD, there is no characteristic pattern of physiologic abnormality in CMDLD.[98,123] Spirometry may demonstrate obstructive, restrictive, or mixed ventilatory defects. Diffusion impairment may be observed,[94,124] even in the absence of spirometric abnormalities. Abnormalities on spirometry and of D_{LCO} are associated with increased emphysema on chest HRCT and profusion of small nodules on chest radiography.[118,125] Cardiopulmonary exercise testing may be useful in the assessment of individuals with dyspnea whose resting pulmonary function test results do not explain the severity of their symptoms.

DIAGNOSIS

As in silicosis, the diagnosis is most commonly made on the basis of the exposure history and chest imaging findings. Lung biopsy should not be used routinely in the diagnosis of CMDLD in an exposed individual with typical radiographic findings. Surgical biopsy may be appropriate if there is diagnostic uncertainty, such as concern for neoplasm. The clinician must keep in mind the variety of manifestations of CMDLD and be careful to include this in the differential diagnosis in coal miners with COPD or diffuse fibrotic lung disease.

MANAGEMENT

There is currently no specific treatment for CMDLD. Therapy should be directed at specific manifestations of the disease spectrum, such as by prescribing bronchodilators

for patients with COPD. Secondary prevention by avoiding further exposure to respiratory hazards is recommended. Smoking cessation is imperative. Treatment is otherwise supportive, with some patients eventually requiring oxygen supplementation and potentially lung transplantation. Similar to silicosis, whole-lung lavage has been advocated as a potential treatment through removal of coal mine dust and possibly inflammatory mediators and cells, but there is insufficient evidence to support routine treatment.[69]

As discussed earlier, CMDLD may progress after cessation of exposure. CWP may become more profuse or even initially develop after an individual has stopped working as a coal miner. Physiologic abnormalities also may develop or worsen after cessation of exposure. This likely reflects incomplete clearance and retention of coal mine dust within the lungs. Therefore, former coal mine workers with and without disease should be monitored with regular physiologic and radiographic evaluation.

ASBESTOS-RELATED FIBROSIS OF THE LUNGS (ASBESTOSIS) AND PLEURA

Asbestosis and asbestos-related pleural disease are fibrotic lung and pleural reactions caused by the inhalation of respirable asbestos fibers. *Asbestos* refers to naturally present mineral silicates of the serpentine and amphibole group. These silicates are characterized by their natural formation in bundles from which fibers can be easily separated. Humans have utilized asbestos from prehistoric times because of its durability, heat resistance, and fibrous nature, which enabled it to be spun. Asbestos is currently banned in 55 countries, although 2 million tons are still consumed globally each year, with the result that significant human exposure will continue into the foreseeable future.[126,126a] Although asbestos mining is banned in the United States, its use is not[127]: more than 1000 metric tons per year are imported for domestic manufacturing, and an estimated 1.3 million American workers continue to be exposed.[128]

INDUSTRIES AND OCCUPATIONS AT RISK

Workers involved in the mining, milling, transporting, or manufacturing of asbestos products, as well as those who perform maintenance or demolition of structures containing asbestos materials, are at risk of exposure. More recently, workers involved in asbestos abatement operations or disposal of industrial waste have been exposed.

Domestic exposure is less common in recent years than previously, and it happened when workers brought home fiber-laden work clothes. This exposure mainly resulted in pleural disease. Environmental and residential exposure may take place as a consequence of living within proximity of asbestos mines, mills, or plants or from living in homes with asbestos tile roofing.[129,130] Mining of nonasbestos products has also led to significant environmental asbestos exposure. Vermiculite mined near Libby, Montana was found to be contaminated by amphibole asbestos. In addition to asbestos exposure among vermiculite miners, use of contaminated material in landscaping and other applications led to widespread environmental asbestos exposures in Libby.[131] Beyond Libby, exposure to waste piles of Libby vermiculite in Minneapolis[132] and other US locations led to significant environmental asbestos exposure.

PATHOGENESIS

The toxicity of asbestos fibers depends on the cumulative dose, fiber dimensions, and fiber durability in lung tissue.[133–135] Clearance of fibers from the lung is greater for short and chrysotile fibers than for long and amphibole fibers.[136] Fibers equal to or less than 3 μm are phagocytosed by activated macrophages and then are translocated to lymphatic channels. Longer fibers are incompletely phagocytosed, often by more than one macrophage, and become the core of what were originally called *asbestos bodies* because of their association with asbestos exposure. Although most coated fibers in human lungs have been shown to contain asbestos (usually amphibole), the term *ferruginous bodies* has been suggested to underline the fact that other mineral fibers may undergo coating in human lungs. Far more uncoated fibers, which are visible only on electron microscopy, are present in an exposed individual than ferruginous bodies, which are visible by light microscopy.[137]

For many years, the asbestos body has been considered the hallmark of exposure, no doubt because of its distinctive structure and because it is readily visible under the light microscope. The presence of more than one coated fiber has been cited (and challenged) as a necessary criterion for the pathologic diagnosis of asbestosis, even in a person with an appropriate exposure history.[137]

Epidemiologic studies have consistently demonstrated exposure-response relationships for asbestos-related parenchymal lung fibrosis.[138] Mineralogic analysis has also shown that the degree of fibrosis correlates with fiber concentration. Additional relevant factors in fibrogenesis and probably in carcinogenesis are the solubility of the fibers, their surface properties and electrical charge, and their length-to-width aspect ratio.[27,139] For asbestos-related pleural disease, exposure-response relationships can also usually be demonstrated, but the residence time of the dust in the lungs is more important than the cumulative exposure,[134,140] possibly reflecting the time required for fibers to move to and accumulate in the pleura.

ASBESTOSIS (PULMONARY PARENCHYMAL FIBROSIS)

Pathology

Asbestosis tends to be most prominent in the lower lobes and subpleural areas. The lesions of mild asbestosis are found at scattered sites and usually consist of foci of peribronchiolar fibrosis with local chronic interstitial inflammation, accumulation of macrophages in the air spaces, and proliferation of alveolar epithelial type 2 cells. Second- and third-order bronchioles and alveolar ducts tend to be involved as the disease progresses and the fibrosis spreads to involve the alveolar interstitium (Fig. 101.7A). When disease is advanced, the lungs are small, with streaks of fibrosis outlining lobar and interlobar septa, and the visceral pleura is thickened. Honeycombing may be prominent subpleurally and in the lower lobes. Advanced asbestos-related fibrosis

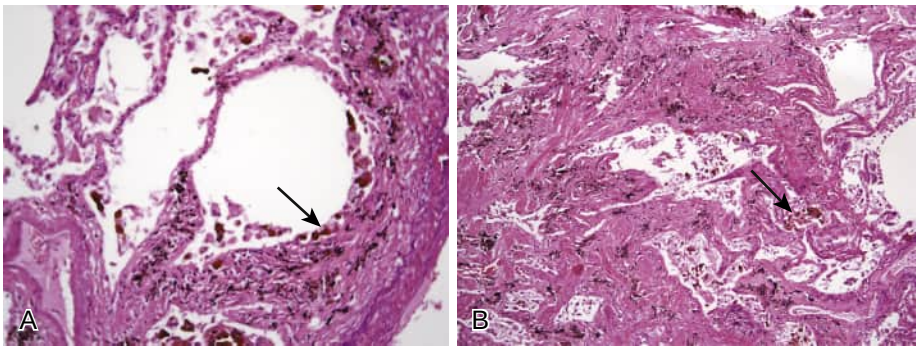

Figure 101.7 Pathologic features of asbestosis: examples from South African asbestos workers. (A) Asbestos *bodies (arrow)* with commencing fibrosis. The architecture of the surrounding lung parenchyma is preserved. (B) Diffuse interstitial fibrosis with destruction of the lung architecture and honeycombing; asbestos bodies are seen in the air spaces and interstitial tissue *(arrow).* (Courtesy National Institute for Occupational Health, South Africa.)

is distinguishable from advanced fibrosis from any other cause only by the presence of asbestos bodies or uncoated asbestos fibers seen on light microscopy or mineralogic analyses (Fig. 101.7B).[27]

In general, the degree of pulmonary fibrosis relates to the fiber burden carried by the lungs.[27] On the basis of animal and human data,[27,141,142] asbestosis is thought to commence with alveolitis that may resolve if the fiber burden is low and the fibers are cleared. If the fiber load is low but retained, mineral dust–induced peripheral airway disease, a nonprogressive distal airway lesion, may develop.[136,139,141–143] If the retained dust load is high and phagocytosis of fibers by macrophages is incomplete, fibroblasts are recruited to the site of the injury, where they proliferate and lay down collagen. If sustained, this leads to irreversible damage, loss of alveolar spaces, and the development of chronic interstitial lung fibrosis, asbestosis.[136]

Epidemiology and Natural History

Clinical asbestosis is becoming less frequent and less severe as exposure levels in workplaces around the world are increasingly meeting currently recommended control levels.[134,144] It is estimated that there are up to 255,000 deaths each year from asbestos-related diseases.[126,145] In the United States, the rate of asbestosis increased possibly by as much as 10-fold between 1968 and 1999 and plateaued, remaining relatively constant through 2010.[128,146] A similar trend was apparent in Australia.[147] With low-level exposure to asbestos, the interval between exposure and disease increases.[134] Exposure at a young age is an independent determinant of both attack and progression rates of parenchymal and pleural radiologic abnormalities, a finding suggesting that residence time of dust in the lung is important in their pathogenesis.[134,148,149] Other determinants of progression are intensity and duration of exposure, cumulative exposure, and fiber type; asbestosis is more frequent after exposure to the amphiboles, or mixtures of amphibole and chrysotile, than exposure to chrysotile alone.[134] This may reflect the comparatively low biopersistence of chrysotile compared with the amphiboles.[150]

Asbestosis may initially appear after exposure ceases, and it may progress without further exposure. In a study of chrysotile miners and millers in Quebec, appearance and progression rates of 31% and 9%, respectively, were observed for pleuroparenchymal disease over an average follow-up period of 17 years after exposure.[134,148] Genetic features appear to play a role in determining the development and extent of asbestos-induced lung fibrosis.[134,151,152] Pathologic studies do not show evidence of an association between asbestosis grade and smoking,[153] although evidence suggests that smoking enhances the retention of fibers in the lungs.[27,153]

Clinical Features

Workers with asbestosis commonly report shortness of breath and dry cough. Acute asbestos-associated pleural reactions may cause chest tightness or pain. Basal crackles, which are early and distinctive features of asbestosis, are fine, crisp, persistent sounds, often heard first over axillary and basal regions and then more generally as the disease advances.[154] Other sounds, including coarse crackles and rhonchi, reflect airway disease that may be related to cigarette smoking or to dust in the occupational environment.[155] Digital clubbing develops in some subjects. Late manifestations include respiratory and circulatory failure, and these conditions, along with cancer, are common causes of death attributable to asbestos.

Radiographic Features

As for coal workers, the posteroanterior chest radiograph remains a key tool in the health surveillance of asbestos-exposed workers and in the initial identification of asbestosis. The irregular, reticular parenchymal opacities associated with this disease are usually seen first in the lower lateral zones (eFig. 101.9). The coarse linear opacities at the bases can blur the heart border, thus giving a "shaggy heart" sign (eFig. 101.10). Small rounded opacities are unusual when the exposure has been primarily to fibers, and they may rather suggest mixed-dust exposures (e.g., silica).[17]

Early fibrotic changes are better visualized by HRCT (eFig. 101.11).[156] Visceral pleural thickening of the interlobar fissures is common.[140] Changes in the parietal pleura are also common, and the presence of pleural plaques or thickening provides additional evidence that the parenchymal disease is asbestos related. HRCT can also identify coexisting lung disease such as emphysema, identify the pattern of rounded atelectasis (see later), and distinguish subpleural fat from pleural thickening and plaques (eFigs. 101.12 to 101.14, Video 101.4).

Lung Function

Patients with asbestosis may demonstrate restrictive, obstructive, or mixed patterns of impairment, often associated with diffusion impairment.[148,157]

Diagnosis

As with disorders related to coal and silica, the clinical diagnosis of asbestosis depends on establishing the appropriate exposure history, typically 20 to 30 years between

initial asbestos exposure and detection of disease, although this period may be shorter or longer. Given an appropriate exposure history with compatible chest imaging findings, histopathologic evaluation is generally unnecessary.[158] In the absence of a clear history of exposure, it may be reasonable to perform a biopsy of the lung to establish the nature of the disease and the presence of asbestos fibers in the lung.

PLEURAL PLAQUES, PLEURAL FIBROSIS, AND VISCEROPARIETAL REACTIONS

Pathology and Pathogenesis

Pleural plaques are smooth, white, raised lesions with irregular borders usually found on the parietal pleura and rarely on the visceral pleura (eFig. 101.15). Common sites are the posterolateral midzones, where they may follow the rib contour, and on the diaphragm. They are less commonly found on the pleura adjacent to the mediastinum and pericardium and are only rarely located in the apices and costophrenic sulci.[140]

Pleural plaques are thought to develop after asbestos fibers move into the pleural space. Once the fibers are within the pleural space, macrophage and cellular interactions may determine plaque formation. On microscopic section, pleural plaques consist of avascular, acellular, laminated collagen fibers arranged parallel to the surface or in whorls, with hyaline changes and occasional fibroblasts. Calcifications are common. Fine asbestos fibers can be seen on electron microscopy.[140]

Like pleural plaques, pleural fibrosis and visceroparietal pleural reactions may be localized or diffuse and may vary in thickness from a milky discoloration of the lung surface to a thick, white peel encasing much of one or both lungs. The interlobar fissures are commonly involved. Visceral pleural disease may be severe even in the presence of minimal parenchymal reaction.[137,140] Occasionally, a localized pleural reaction may fold on itself and the surfaces adhere, trapping the underlying lung and leading to a well-defined pleuroparenchymal lesion or pseudotumor, also called *rounded atelectasis*[140] (eFig. 101.13). Asbestos bodies and fibers are usually found in the visceral pleura, the underlying parenchyma, or both,[140] and the lung dust burden usually reflects the occupational exposure, although fiber counts are considerably less than those seen in asbestosis.

Epidemiology

Pleural plaques continue to be the most frequent and often the only manifestations of asbestos exposure in individual cases,[140,159,160] and asbestos exposure is the most common cause of pleural plaques. Bilateral pleural plaques are more likely to be associated with asbestos exposure than unilateral plaques, for which other causes, such as trauma or prior infection, should be considered.[154] Age and residence time of dust in the lungs are determinants of these distinctive pleural lesions.[140] Domestic, residential, and environmental exposures have been implicated in the development of pleural plaques.

Of greater concern to the patient and the clinician is the prognostic significance of plaques. In one study, they were associated with alveolitis, as reflected in BAL cell counts,[161] and, by implication, with an increased likelihood of developing parenchymal disease. The results of a Swedish cohort mortality study involving 1596 men were interpreted as showing that pleural plaques on the chest radiograph indicated significant exposure to asbestos, as well as an increased risk of mesothelioma and possibly also lung cancer.[162] This risk raises the question of radiographic screening for malignancy in patients with pleural plaques, a topic that remains controversial in the absence of clear evidence of benefit.[154,162,163]

Pleural fibrosis and visceroparietal reactions may also be found in the absence of radiologic parenchymal fibrosis, and they have increased in frequency.[140] Latency is usually long, 34 years in one report,[164] reflected in the finding that these reactions relate to time since first exposure and not to cumulative exposure dose.[140] Pleural fibrosis, like other manifestations of asbestos-related pleural disease, has been reported in association with environmental asbestos exposures.[165,166]

Clinical Features and Diagnosis

Pleural plaques, in the absence of parenchymal disease, typically do not cause abnormal signs and symptoms and are usually detected as an incidental finding on a routine chest radiograph (eFigs. 101.9, 101.10, 101.12A). Only modest proportions of pleural plaques seen at autopsy are detected on posteroanterior chest radiographs. CT scans can identify pleural plaques (Fig. 101.8, eFigs. 101.12B and 101.13) at an earlier, less well-developed stage and can differentiate plaques from extrapleural fat pads. The lung volumes of patients with pleural plaques are on average modestly reduced,[167,168] whereas the D_{LCO} is generally normal.[137,148,169] Increasingly, it is recognized that, in some individuals, pleural plaques may be associated with respiratory disability.[170] The underlying mechanism may be inhibition of inspiratory capacity during exercise that results in an increase in the work of breathing.

Pleural fibrosis (eFig. 101.14) is less specific for asbestos exposure than are pleural plaques, and other causes need to be considered in the differential diagnosis. Clinical presentation, like that of pleural plaques, is often as an incidental abnormality detected on a routine chest radiograph (see Fig. 101.8). After careful inquiry, a remote history of exposure, often quite brief but usually heavy, can be obtained from the patient. In the absence of associated parenchymal disease, clinical signs may be minimal, even though functional impairment is detectable. Impairment may be modest even in the presence of severe pleural disease.[140,148,171] In one study, the presence of pleural plaque or pleural thickening was associated with an average FEV_1 deficit of 0.22 L and a forced vital capacity deficit of 0.40 L,[170] but pleural fibrosis occasionally becomes severe enough to precipitate respiratory and cardiac failure and to require pleurectomy.[140,172] (See Chapter 112.)

Given a history of exposure, obliteration of the costophrenic angle is likely to represent the residuum of asbestos pleural effusion.[140] Some subjects present with breathlessness, chest pain, or both, with or without a history of acute episodes, attributable to benign pleural effusions. In rounded atelectasis, the CT scan is particularly useful in delineating the relationship of the rounded lesion to other pleural changes (see Fig. 101.8).[173] Nevertheless, the

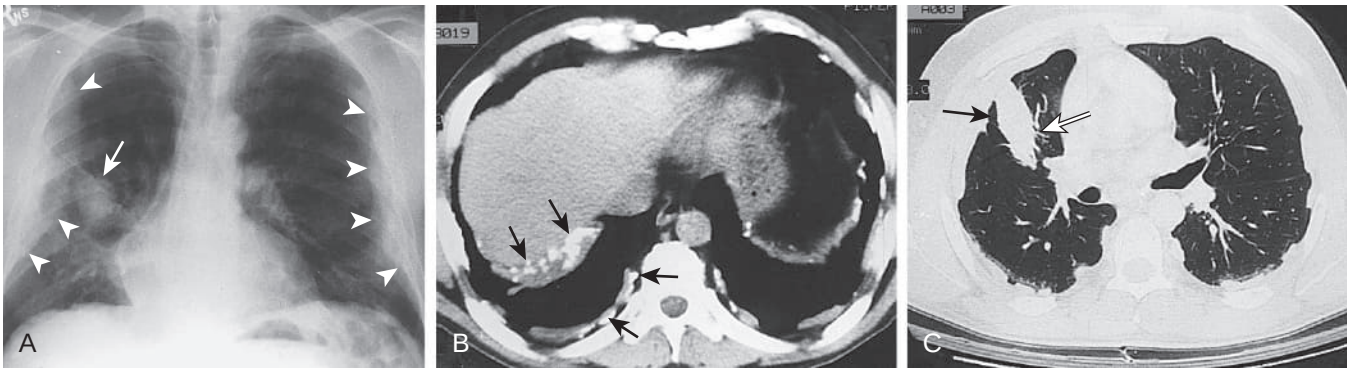

Figure 101.8 Asbestos-related pulmonary parenchymal and pleural disease (bilateral pleural fibrosis and atypical rounded atelectasis) in a 50-year-old man. The patient had worked as an electrician from the age of 17 years, first in construction for 10 years (with known exposure to asbestos), then briefly on naval ships during World War II, and in a chemical plant (with known exposure to talc) for the past 20 years. His only complaint was a dry cough. Chest radiographic abnormalities had been noted 4 years previously. (A) Posteroanterior chest radiograph shows bilateral diaphragmatic plaques, extensive bilateral pleural thickening *(arrowheads),* and a circumscribed lesion in the right midlung zone *(arrow).* (B) On computed tomography, the pleural plaques were shown to be much more extensive than appeared from the chest radiograph. Many plaques *(arrows)* were calcified. In addition, high-resolution computed tomography revealed bands of subpleural fibrosis related to the pleural plaques or thickening, or both. Lung volumes and carbon monoxide diffusing capacity were normal. (C) Axial computed tomography shows the circumscribed lesion also shown in (A) *(arrows).* Because the lesion had enlarged over the past year, it was removed surgically. The lesion consisted of pleural, subpleural, and interstitial fibrosis. Analysis of lung digest revealed 36 asbestos bodies/mg of dry lung tissue and 7570 fibers/mg of dry lung tissue, more than one-half of which were asbestos fibers and less than 1% of which consisted of talc. These findings implicated his earlier, rather than his more recent, occupational exposures as the cause of his pleural disease. (Courtesy Dr. J. Kosiuk, Department of Radiology, Royal Victoria Hospital, Montreal, Canada, who carried out the radiographic studies; and Dr. A. Dufresne, School of Occupational Health, McGill University, Montreal, Canada, who performed the lung dust analyses.)

differential diagnosis of rounded atelectasis includes lung cancer and, in some cases, the diagnosis can be established only by tissue biopsy.

BENIGN ASBESTOS-RELATED PLEURAL EFFUSIONS

Benign asbestos-related pleural effusions may arise without evidence of prior pleural involvement from asbestos exposure or may mark an increase in the extent or severity of an already present pleural reaction. The term "benign" does not imply a lack of clinical significance but rather that the effusion is not associated with mesothelioma.[140]

Benign asbestos-related pleural effusions usually appear within 15 years of the first exposure, often after exposure has ceased.[140] The episodes are usually transient and may be silent, or they may be associated with chest tightness and, occasionally, pleural pain, fever, and dyspnea.[140] Frequently, other benign asbestos-related pleural disease, including pleural plaques and diffuse pleural thickening, are encountered.[174,175]

The effusion is usually small, exudative, and blood tinged.[27] Asbestos bodies are rarely found in the fluid.[176] The sedimentation rate is often raised.[176] Diagnosis is by exclusion, and suggested criteria include (1) an exposure history, (2) the absence of other causes, and (3) absence of tumor on a 3-year follow-up.[136] Because cytologic examination of the pleural fluid is rarely conclusive, a thoracoscopic biopsy is usually required for the following reasons: to exclude other causes; to establish the presence of fibers in the pleural fluid (rarely demonstrable), pleura (sometimes demonstrable), or the underlying lung parenchyma (more frequently demonstrable); and to rule out malignancy, in particular malignant pleural mesothelioma. The usual pathologic findings in benign asbestos-related pleural effusions are those of chronic fibrous pleurisy with minimal cellularity.

The prognosis of benign asbestos-related pleural effusions is generally good because most effusions clear spontaneously. They may recur on the opposite side. Although pleural effusion is a common form of presentation for mesothelioma, there is no evidence that a benign effusion signals a future pleural malignancy. It appears rather to represent a stage in the evolution of asbestos-related pleural fibrosis and carries an associated risk of development of parenchymal fibrosis (asbestosis).[134]

MANAGEMENT, PREVENTION, AND HEALTH MONITORING

No active treatment measures have been shown to influence the course of asbestosis. Patients with end-stage asbestosis have been the recipients of lung and heart-lung transplants, but technical difficulties may arise because of associated pleural disease. The presence of asbestosis is associated with an increased risk for lung cancer.[177,178]

For the nonmalignant asbestos-related pleural disorders, the evidence is reasonably clear that patients with pleural fibrosis are at greater risk for parenchymal fibrosis in the future.[134] The presence of pleural fibrosis or pleural plaques indicates significant asbestos exposure and, consequently, indicates that the patient is at increased risk for malignant pleural mesothelioma and lung cancer.[162] Workers with a history of occupational exposure to asbestos and smoking should be considered for low-dose CT scanning even with lower smoking histories than used for non–asbestos-exposed workers.[179,180] A document from the American College of Chest Physicians highlights areas in which there is and is not consensus regarding the health effects of asbestos exposure.[181]

Smoking cessation is an important preventive measure. The possible role of smoking in the initiation and progression of fibrotic parenchymal disease and its established role

in multiplying the risk of lung cancer in asbestos-exposed individuals are strong indications for smoking cessation.

It is important to make the appropriate notification of a case of asbestos-related disease. Employment advice should be guided by knowledge of the impact of further exposure on the natural history of the disease,[137,140,148] as well as by the risks for developing additional asbestos-related disease. It is important to emphasize that, even in the absence of any further exposure, all nonmalignant asbestos-related diseases may progress because of the dust load already in the lungs. Working in a dusty occupation also puts the worker at risk for developing COPD.[157]

BERYLLIUM LUNG DISEASE

BERYLLIUM: USES, HUMAN TOXICITY, AND EXPOSURES

Beryllium is a rare metal that has many applications in modern industry because of its light weight, tensile strength, high melting point (1500°C), excellent alloying properties (beryllium-copper alloys are the most widely used), good thermal and electrical conductivity, resistance to corrosion, and ability to reduce the speed of nuclear fission.

Workers can be exposed to beryllium in a wide variety of industries, including the manufacture of alloys, ceramics, radiographic equipment, and vacuum tubes and in the extraction and smelting of beryllium. At least 134,000 current US workers are estimated to be exposed to beryllium, and more are at risk when former, contract, and construction workers are added to the list.[182] Industries that actively use beryllium alloys and salts include foundries, aerospace, automotive parts, electronics, ceramics, metal smelting and recycling, nuclear (reactors, weapons), telecommunications, tool and die, and welding.[183,184] Environmental exposure to beryllium has been reported in residents living near a beryllium manufacturing facility.[185] Individuals with trivial exposures, including security guards, secretaries, and bystanders, have been reported to develop disease, thus indicating that there may not be a clear dose-response relationship.

PATHOLOGY AND IMMUNE PATHOGENESIS

Chronic beryllium disease (CBD) is a multisystem disorder characterized by the formation of noncaseating granulomas throughout the body, although their primary manifestation is in the lung.[183] On pathologic examination, CBD is characterized by the presence of a lymphocytic (helper/inducer T cells) alveolitis, as well as of noncaseating epithelioid granulomas indistinguishable from those of sarcoidosis (eFig. 101.16). There is a variable amount of fibroblastic activity that progresses to interstitial fibrosis as the lesions mature. Granulomatous lesions may occasionally be found in other sites, including thoracic and abdominal lymph nodes, spleen, liver, kidneys, and adrenal glands.

Beryllium enters the body by inhalation and, occasionally, through the skin, where it acts as a specific antigen, alone or as a hapten. Subsequently, beryllium-specific $CD4^+$ lymphocytes proliferate and release lymphokines. There is a wide range in the reported prevalence of beryllium sensitization, from less than 1% to as high as 20% of exposed individuals,[186] and this range appears to be related to the level of beryllium exposure. Progression to CBD develops in a smaller number of sensitized individuals, 6–8% in some studies, with the highest risk in the first few years after exposure.[187,188] Because the agent persists in the lung, its slow release over time explains the appearance and progression of disease, even without further exposure.[27] There is evidence for an underlying genetic basis for susceptibility to beryllium disease, linked to a major histocompatibility complex class II marker (human leukocyte antigen $DP\beta\text{-}1^{Glu69}$) carrier status. A review of the immunology and genetic susceptibility summarizes current understanding of these complex gene-environment interactions.[189]

CLINICAL FEATURES

Acute beryllium disease is now uncommon. The disorder is associated with high, and usually accidental, exposure, and it may manifest with an acute syndrome with features of the acute respiratory distress syndrome or in a subacute form with features of pneumonitis.[190]

CBD may follow acute beryllium pneumonitis but more usually develops in individuals with low-level long-term exposure. The clinical features of CBD are similar to those of pulmonary sarcoidosis, although extrapulmonary manifestations, including hilar and mediastinal lymphadenopathy and splenomegaly, are less common.[190,191] There may be no associated symptoms,[192] but symptoms when present often include dyspnea, cough, chest pain, weight loss, fatigue, and arthralgias. Physical signs may include crackles, but signs of lung disease are often absent.

The usual radiographic findings are ill-defined nodular or irregular opacities (eFig. 101.17A–B, Video 101.5). Hilar lymphadenopathy (eFigs. 101.17C–D) is seen in approximately 40% of cases but is usually mild.[183] In the later stages of the disease, patchy fibrosis is seen, with adjacent hyperinflation or distortion and extensive honeycombing.

Obstruction is the most commonly encountered pulmonary function abnormality, but restriction, a mixed process, or an isolated reduction in D_{LCO} may also be observed.[193] The clinical course of CBD is variable; some cases remain stable, some relapse and remit, and some relentlessly progress.[183]

DIAGNOSIS AND MANAGEMENT

Suspicion for possible beryllium exposure, sarcoidosis, or interstitial lung disease should prompt a thorough occupational history, one that spans the worker's lifetime as a result of the latency between exposure and disease. Seemingly minimal exposure to beryllium has been reported in cases of CBD.[194,195]

Evidence for delayed hypersensitivity to beryllium may be assessed by the in vitro *beryllium lymphocyte proliferation test* (BeLPT) on lymphocytes from blood or BAL fluid.[196,197] Diagnosis of beryllium sensitization or beryllium-related lung disease requires demonstration of a beryllium-specific immune response, which is confirmed by one of the following: two abnormal peripheral blood BeLPT results, one abnormal and one borderline peripheral blood BeLPT result, one abnormal BAL BeLPT result, or a positive skin patch

test result.[193] The BeLPT has allowed for the introduction of three categories of beryllium-associated disorders: beryllium sensitization (positive BeLPT result with negative biopsy or absence of clinical or radiologic features of beryllium-related lung disease), subclinical beryllium disease (positive BeLPT result and biopsy without clinical or radiologic features of the disease), and CBD (positive BeLPT result and biopsy with clinical and radiologic features of disease).[198]

Despite the generally lower beryllium exposures since the 1950s and its decreasing frequency, CBD should remain in the differential diagnosis of sarcoidosis because of the long latency time of disease. Clusters of suspected sarcoidosis in a workplace should alert the clinician to the possibility that these represent examples of CBD. In this context, note should be made of the wide range of occupations associated with potential exposure to beryllium. Additionally, beryllium is considered a human carcinogen, especially in the presence of beryllium lung disease; in 1993, the International Agency for Research on Cancer classified beryllium as a class 1 human carcinogen.[199]

The most important step in case management in the setting of beryllium sensitization is to consider complete cessation of further exposure to beryllium because of the risk of progression to CBD. Regular medical surveillance is indicated in these individuals. There is limited evidence that CBD will improve with removal of the worker from additional beryllium exposure.[193] Although there is no randomized clinical trial to evaluate this treatment, corticosteroid therapy has been recommended in CBD,[200] initiated on the basis of symptoms, imaging, and pulmonary function test results. Long-term steroid therapy is believed to alter the course of the disease favorably.[193] A small trial with infliximab showed improvement in immune response, quality of life, and a trend toward improved D_{LCO} in the subgroup of patients with low D_{LCO} at baseline.[201]

Acknowledgments

We thank Robert Cowie, MD, and Margaret Becklake, MBBCh, MD, for their contributions to earlier versions of this chapter.

Key Points

- Workplace and environmental exposure to disease-causing dust is a common cause of lung disease. Therefore, a detailed history that includes current and prior occupations should be part of every respiratory assessment.
- Chest imaging and physiologic evaluation are the cornerstones of evaluation for pneumoconiosis. Lung biopsy may be necessary in selected cases.
- In addition to classic pneumoconioses caused by silica, coal mine dust, and asbestos, exposed workers may develop a spectrum of disease that includes obstructive lung diseases, lung cancer, connective tissue diseases, and infections such as tuberculosis.
- Silicosis has long been associated with exposure to toxic respirable crystalline silica in construction, mining, tunneling, and foundry work. Silicosis has more recently been described in newer industries and tasks, such as sandblasting of denim, fabrication of engineered stone products, and jewelry production.
- Coal mine dust lung disease is a spectrum of lung diseases caused by a mixture of dust constituents including coal, silica, silicates, and diesel exhaust particulate. The condition may manifest not only as classic coal workers' pneumoconiosis, but also as obstructive lung disease and pulmonary fibrosis, known as dust-related diffuse fibrosis.
- Despite well-known health risks, asbestos remains a widely used mineral resource, including in the United States. As a result, workers remain at risk for asbestos-related diseases, including asbestosis, pleural plaques, pleural mesothelioma, and lung cancer. Given the long latency times for these disease manifestations, asbestos-related disease will remain clinically relevant in the decades to come.
- Pneumoconioses are untreatable and cause significant long-term impairment, disability, and death. Therefore, prevention of pneumoconioses should be a primary public health concern.

Key Readings

Adverse effects of crystalline silica exposure. American Thoracic Society Committee of the Scientific Assembly on Environmental and Occupational Health. *Am J Respir Crit Care Med.* 1997;155:761–768.

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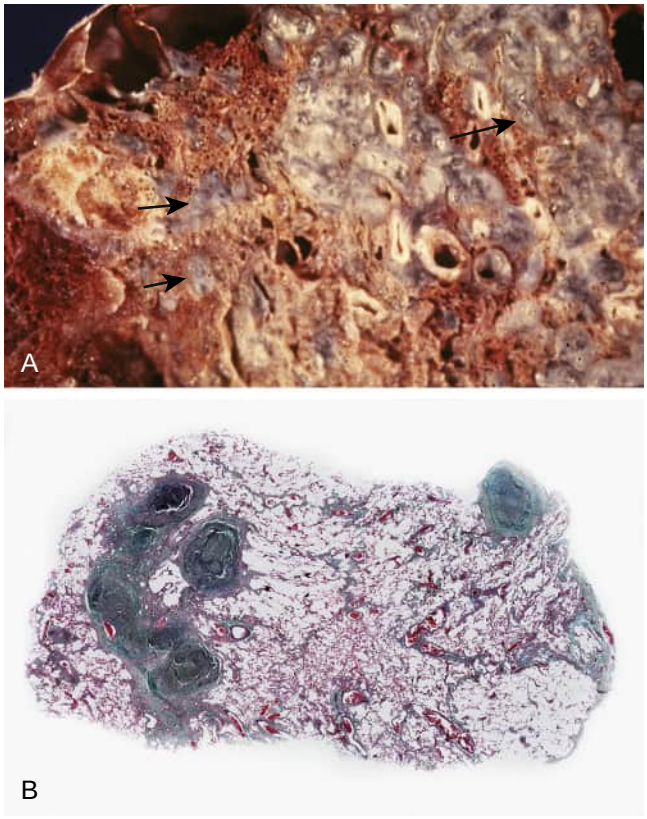
Complete reference list available at ExpertConsult.com.

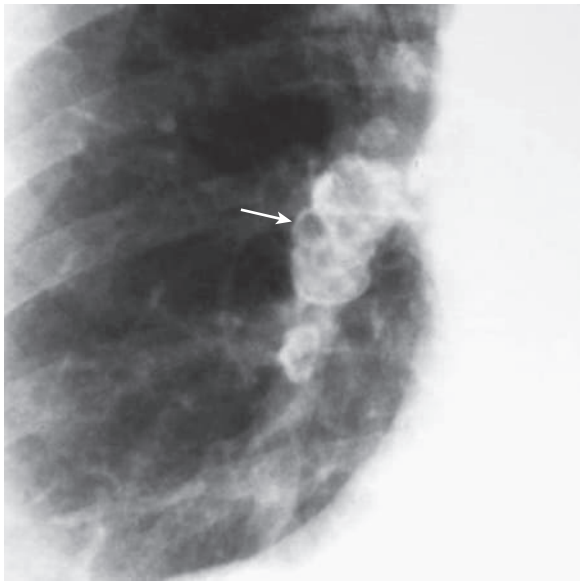
eFIGURE IMAGE GALLERY



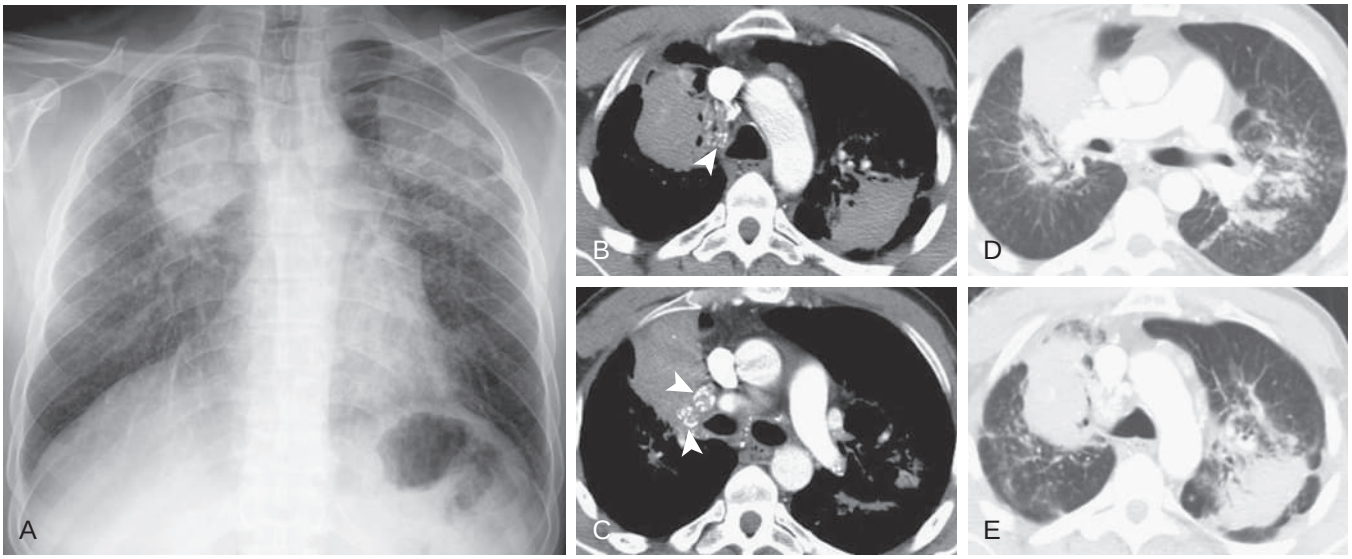
eFigure 101.1 Silicosis: gross images. (A) In this gross specimen, circumscribed areas of nodular fibrosis are slate gray and of firm consistency *(arrows).* (B) At low magnification, silicotic nodules are sharply circumscribed and densely collagenous (Masson trichrome stain). (Modified from Butnor KJ, Roggli VL. Pneumoconioses. In: Leslie KO, Wick MR, eds. *Practical Pulmonary Pathology: A Diagnostic Approach: A Volume in the Pattern Recognition Series.* 2nd ed. Philadelphia: Elsevier; 2011:311–338.)



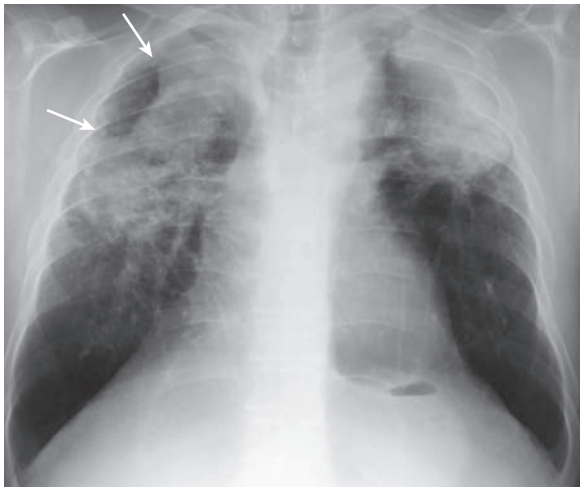
eFigure 101.2 Silicosis on chest radiograph. Frontal chest radiograph in a patient with silicosis shows a somewhat atypical distribution of small, round lung opacities. In this patient, opacities are best seen in the middle and lower lungs, rather than the more typically encountered upper and posterior lung location. (Courtesy Michael B. Gotway, MD.)



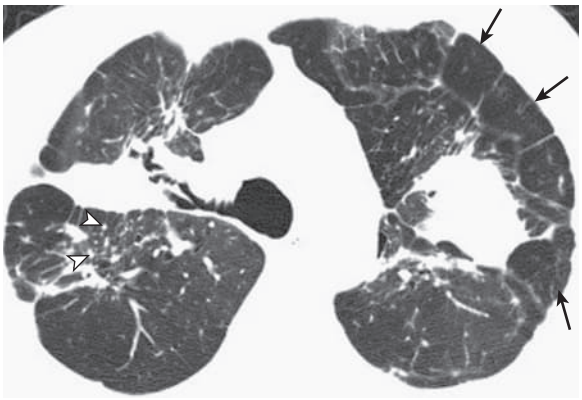
eFigure 101.3 Silicosis with eggshell calcification of hilar lymph nodes. Detail of a frontal chest radiograph in a patient with silicosis shows the typical appearance of "eggshell" lymph node calcifications *(arrow).* (Courtesy Michael B. Gotway, MD.)



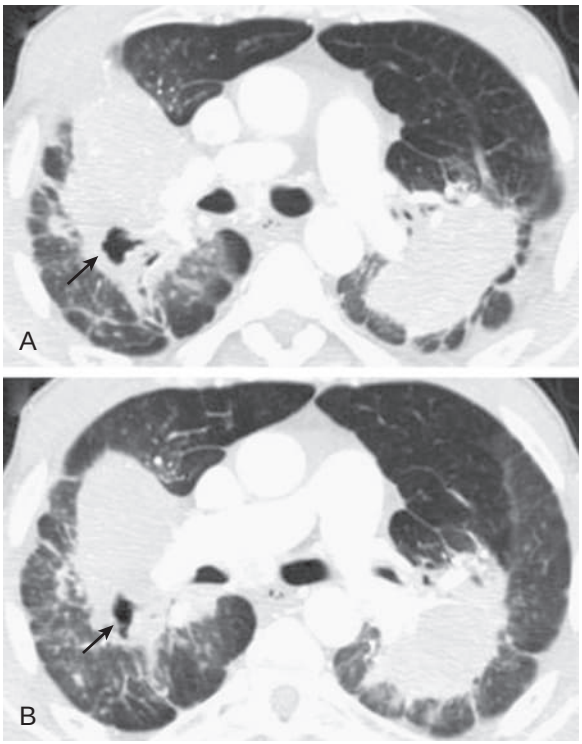
eFigure 101.4 Complicated silicosis: progressive massive fibrosis on chest radiograph and chest computed tomography. (A) Frontal chest radiograph shows upper lobe masses with a background of small nodules and linear and reticular opacities. Axial chest computed tomography in soft tissue (B–C) and lung windows (D–E) shows the upper lobe masses and background of small, circumscribed nodules and lymph node calcifications *(arrowheads)*. The associated videos (see Video 101.1, soft tissue windows, and Video 101.2, lung windows) highlight the presence of calcification within the upper lobe masses as well as the upper lobe distribution of the lung opacities. (Courtesy Michael B. Gotway, MD.)



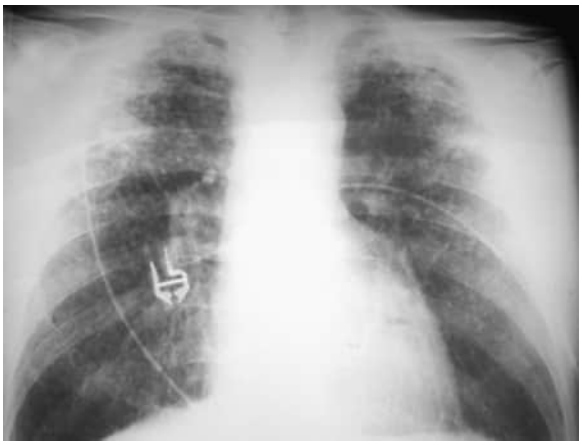
eFigure 101.5 Silicosis: progressive massive fibrosis on chest radiograph. Frontal chest radiograph in a patient with silicosis and progressive massive fibrosis shows bilateral upper lobe opacities with areas of hyperlucency (*between arrows*) left in the "wake" of the migration of the opacities toward the hila. (Courtesy Michael B. Gotway, MD.)



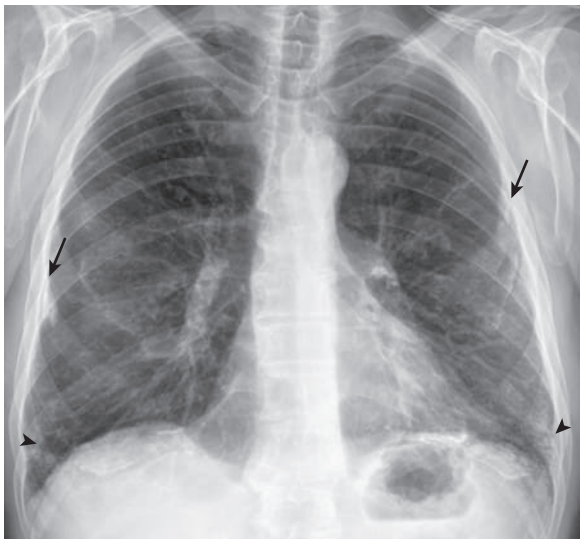
eFigure 101.6 Silicosis: progressive massive fibrosis on axial chest computed tomography. Chest computed tomography in a patient with silicosis and progressive massive fibrosis shows small nodules in the posterior upper lobes *(arrowheads)* consistent with silicosis, as well as upper lobe opacities representing progressive massive fibrosis. Note the area of hyperlucency and irregular air space enlargement *(arrows)* left in the "wake" of the migration of these opacities towards the hila. (Courtesy Michael B. Gotway, MD.)



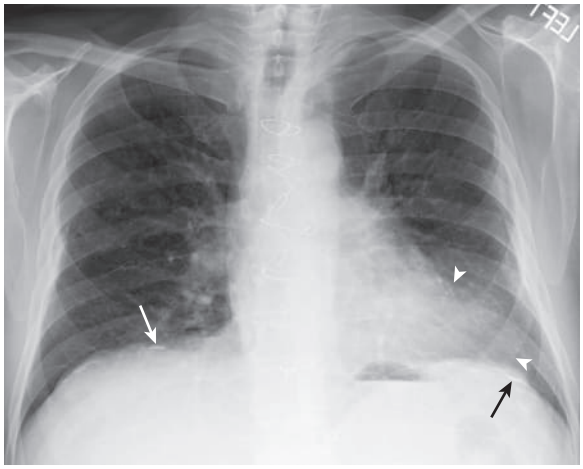
eFigure 101.7 Silicosis: superimposed infection in area of progressive massive fibrosis. (A–B) Chest computed tomography in a patient with silicosis and progressive massive fibrosis (same patient as eFig. 101.5, at a later time) shows development of cavitation within the posterior margin of the right upper lobe opacity *(arrows)* resulting from superimposed mycobacterial infection. See Video 101.3. (Courtesy Michael B. Gotway, MD.)



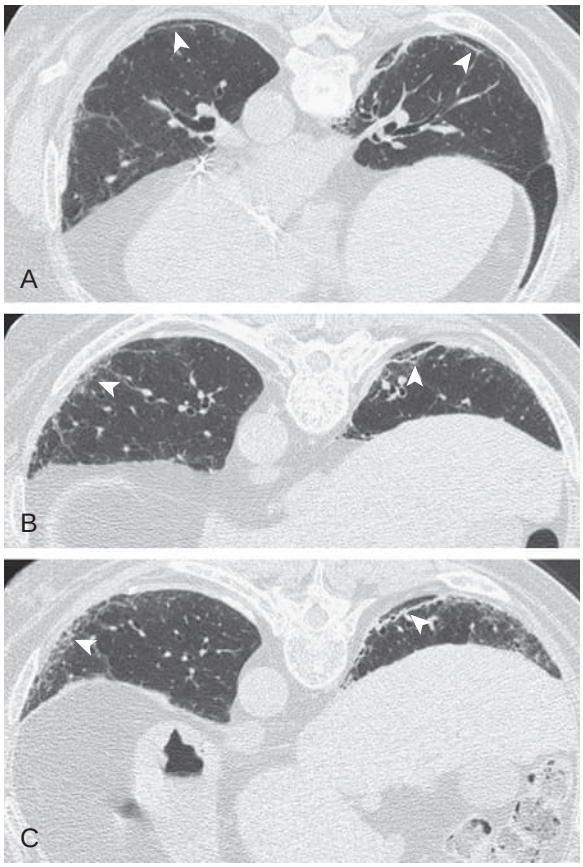
eFigure 101.8 Coal workers' pneumoconiosis: chest radiograph. Frontal chest radiograph in a patient with simple coal workers' pneumoconiosis shows upper lobe–predominant, circumscribed small nodules. The nodules are somewhat larger than is often seen in coal workers' pneumoconiosis, especially in the upper lobes, thus raising the possibility of superimposed silicosis. (Courtesy Michael B. Gotway, MD.)



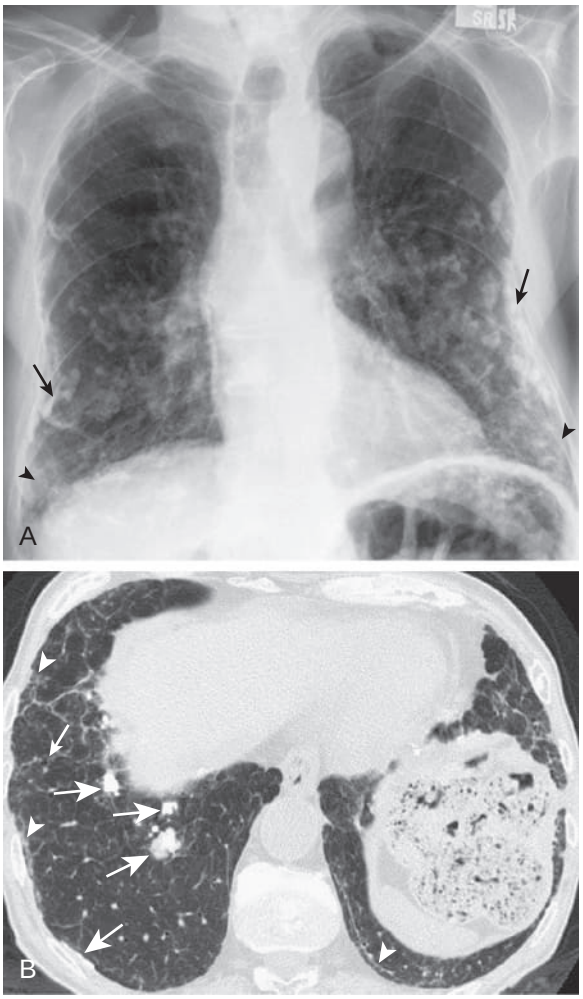
eFigure 101.9 Asbestosis: chest radiograph. Frontal chest radiograph in a patient with asbestos exposure shows bilateral calcified pleural plaques *(arrows)* and fine, subpleural, bibasal linear and reticular opacities *(arrowheads)* consistent with fibrotic lung disease. (Courtesy Michael B. Gotway, MD.)



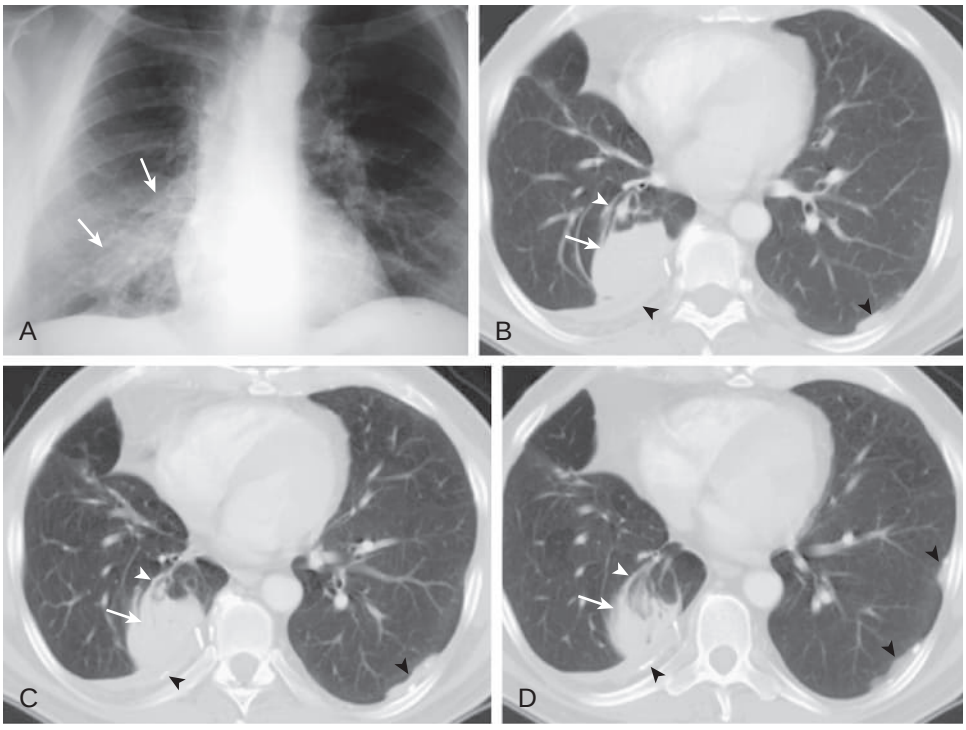
eFigure 101.10 Asbestosis: the "shaggy heart" sign on chest radiograph. Frontal chest radiograph in a patient with asbestos exposure shows bilateral calcified pleural plaques *(arrows)* and obscuration of the left cardiac border *(arrowheads),* representing the "shaggy heart" border sign in asbestosis. (Courtesy Michael B. Gotway, MD.)



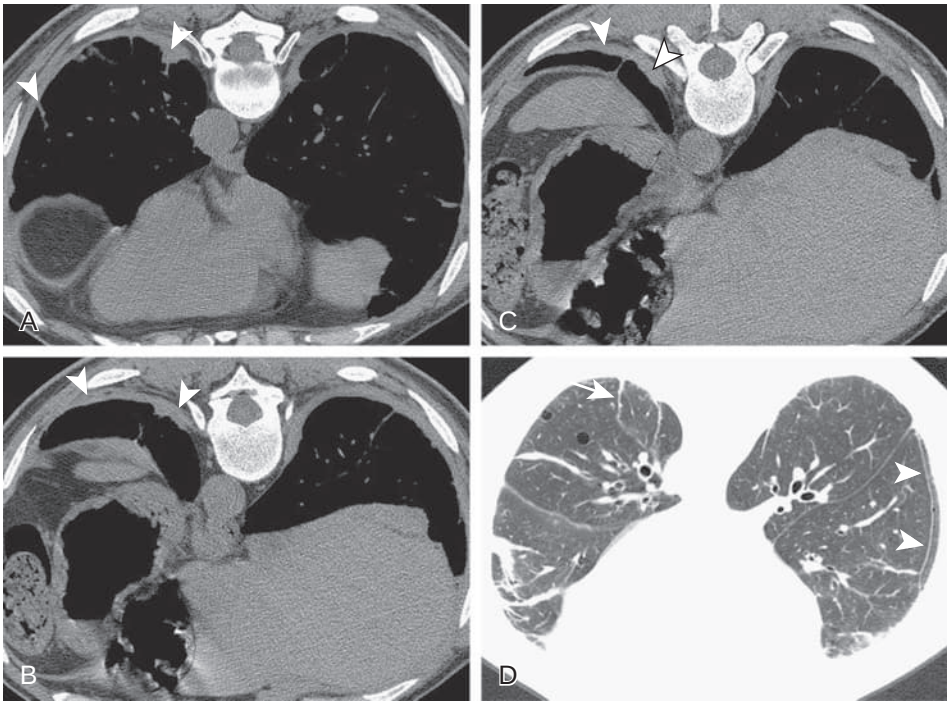
eFigure 101.11 Asbestosis: axial chest computed tomography. (A–C) Axial prone high-resolution computed tomography of the lung through the bases in a patient with asbestos exposure shows bilateral, subpleural linear, and reticular opacities *(arrowheads)* consistent with asbestosis. (Courtesy Michael B. Gotway, MD.)



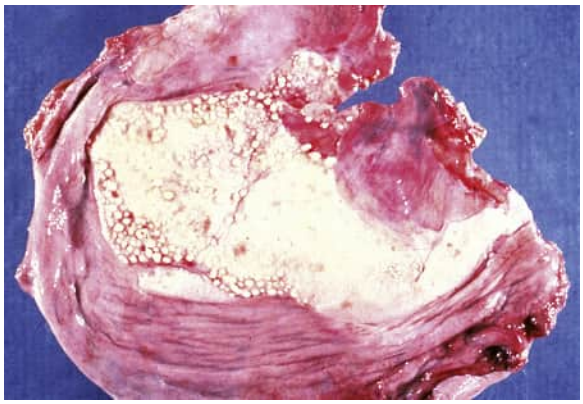
eFigure 101.12 Asbestosis with calcified pleural plaques: chest radiograph and axial chest computed tomography. (A) Frontal chest radiograph in a patient with asbestos exposure shows bilateral calcified pleural plaques *(arrows)* and faint basal linear and reticular abnormalities *(arrowheads)* suggesting possible fibrotic lung disease. The heavy pleural calcification limits assessment. (B) Axial chest computed tomography through the lung bases shows pleural calcifications *(large arrows)* and peripheral linear and reticular opacities *(arrowheads)* with mild traction bronchiectasis *(small arrow),* confirming fibrotic lung disease. (Courtesy Michael B. Gotway, MD.)



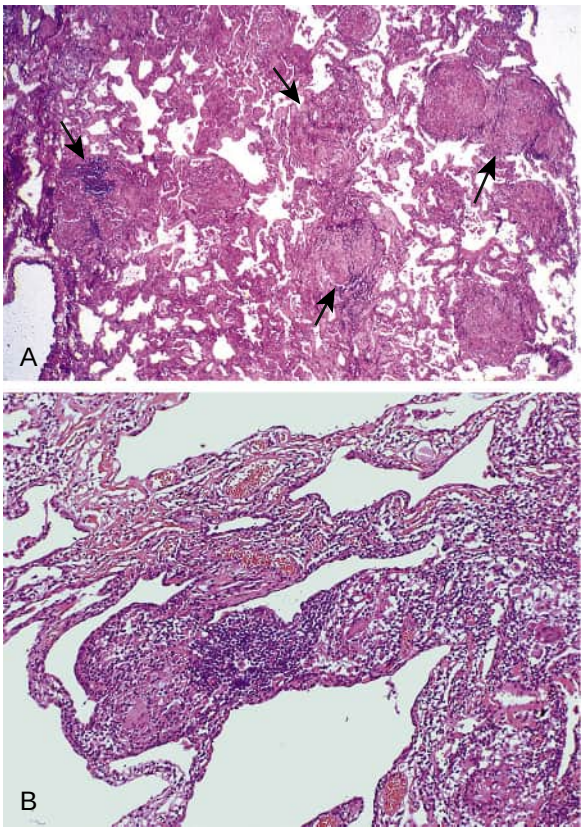
eFigure 101.13 Asbestos-induced pleural plaques and rounded atelectasis: chest radiograph and axial chest computed tomography. (A) Frontal chest radiograph in a patient with asbestos exposure shows a poorly defined right lower lobe opacity *(arrows).* (B–D) Axial chest computed tomography through the lung bases shows calcified and noncalcified pleural plaques *(black arrowheads)* and confirms the right lower lobe subpleural mass *(arrows).* The mass is in contact with abnormal pleura and is associated with a spiraling configuration of the bronchovascular bundles *(white arrowheads)* leading to the mass, as well as right lower lobe volume loss—these features are consistent with rounded atelectasis (see Video 101.4). (Courtesy Michael B. Gotway, MD.)



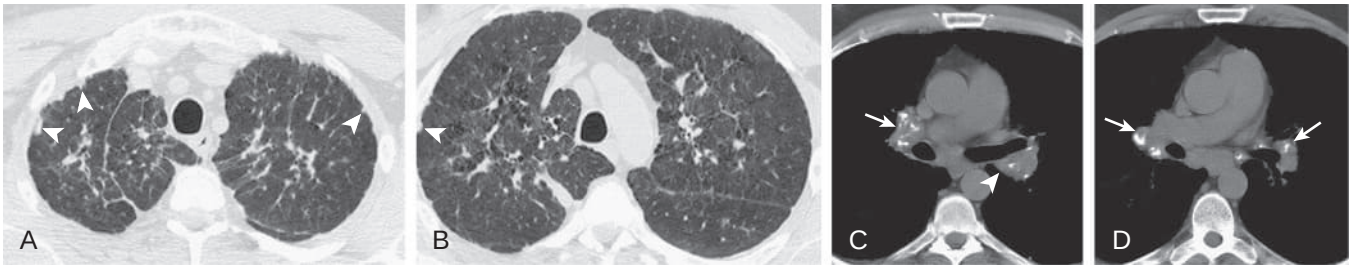
eFigure 101.14 Diffuse pleural thickening related to asbestos exposure: axial chest computed tomography. Axial prone chest computed tomography in soft tissue (A–C) and lung windows (D) shows extensive contiguous pleural thickening (*arrowheads*, A–C) extending continuously from the posteromedial thorax along the right lateral thorax. (D) Image displayed in lung windows shows other pulmonary parenchymal findings associated with asbestos exposure, such as parenchymal bands *(arrow)* and a subpleural line *(arrowheads).* (Courtesy Michael B. Gotway, MD.)



eFigure 101.15 Pleural plaque: gross appearance. The whitish plaque has been resected along with surrounding tissue and is viewed en face. Its gross appearance has been likened to that of candle wax drippings. (From Butnor KJ, Roggli VL. Pneumoconioses. In: Leslie KO, Wick MR, eds. *Practical Pulmonary Pathology: A Diagnostic Approach: A Volume in the Pattern Recognition Series.* 2nd ed. Philadelphia: Elsevier; 2011:311–338.)



eFigure 101.16 Chronic beryllium disease: pathology. (A) The presence of numerous granulomas is characteristic of chronic beryllium disease *(arrows)*. (B) In addition to granulomatous inflammation, there is a chronic interstitial inflammatory infiltrate. (From Butnor KJ, Roggli VL. Pneumoconioses. In: Leslie KO, Wick MR, eds. *Practical Pulmonary Pathology: A Diagnostic Approach: A Volume in the Pattern Recognition Series.* 2nd ed. Philadelphia: Elsevier; 2011:311–338.)



eFigure 101.17 Chronic beryllium disease: axial chest computed tomography. (A–B) Axial chest computed tomography shown in lung windows shows subpleural nodules (*arrowheads*) associated with central bronchovascular thickening and architectural distortion. The appearance resembles sarcoidosis. (C–D) Axial chest computed tomography shown in soft tissue windows shows mild, symmetrical, bilateral calcified lymph node enlargement *(arrows)*. An uncalcified, mildly enlarged left retrobronchial lymph node (*arrowhead*, C) is present. The appearance is identical to that of sarcoidosis. Video 101.5 shows the upper lobe distribution of the pulmonary parenchymal abnormalities to advantage. (Courtesy Michael B. Gotway, MD.)

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102 INDOOR AND OUTDOOR AIR POLLUTION

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INTRODUCTION

Catastrophic air pollution events in the Meuse Valley of Belgium (1930)[1]; Donora, Pennsylvania (1948)[2]; and London (1952)[3] arose when air stagnation caused high levels of ambient pollutants, especially sulfur dioxide and particles. In each case there was a marked increase in respiratory symptoms and mortality. These "fog disasters" provided incontrovertible evidence that air pollution can have immediate lethal consequences. Since that time, scientific investigations have uncovered myriad adverse respiratory health effects of air pollution, ranging from asthma exacerbation to respiratory mortality.

Because it is the portal of entry for air pollutants, the respiratory system suffers the major consequences of air pollution. This chapter reviews the key air pollutants, which are termed *criteria pollutants* by the *U.S. Environmental Protection Agency* (EPA), and how they affect the airways and lungs (Table 102.1). Both indoor and outdoor air pollution are considered. Respiratory health conditions most strongly linked with air pollution are reviewed. Although evidence is accumulating that links air pollution to noncardiopulmonary outcomes (e.g., adverse birth outcomes, metabolic dysfunction, cognitive development, and dementia), these topics are not considered.

AIR POLLUTANTS

POLLUTANTS: WHAT THEY ARE AND WHY THEY MATTER

Air pollution involves the contamination of the atmosphere by chemicals, particles, or biologic materials that cause human morbidity and mortality; damage other living organisms, such as plants; or adversely affect the natural environment, such as by reducing visibility. Pollutants can be emitted from mobile sources (e.g., vehicles), stationary sources (e.g., factories, power plants, refineries), and indoor sources (e.g., building materials, gas stoves, passive smoking, cleaning products).[4,5]

The major types of air pollutants affecting the respiratory system are *particulate matter* (PM), *sulfur dioxide* (SO_2), *nitrogen dioxide* (NO_2), and *ozone* (O_3) (Table 102.2).[4,5] These pollutants arise directly from mobile and stationary sources. O_3 is a secondary pollutant that arises from the action of sunlight on nitrogen oxides and hydrocarbons present in motor vehicle exhaust. It is a major component of photochemical pollution, or smog. The respiratory health effects of these pollutants are considered later in this chapter. Two other air pollutants, *carbon monoxide* (CO) and lead, which also enter via the respiratory tract, have primarily nonpulmonary toxicity and are not discussed in this chapter. Toxic air pollutants (*air toxics*) are a subset of air pollutants that may cause cancer or other serious health effects, such as birth defects. These substances, such as benzene and cadmium, also produce primarily nonrespiratory effects despite entering the body via the respiratory tract; as a result, they are also not discussed in this chapter.

Carcinogens are also found in outdoor air, including the known lung carcinogens *polycyclic aromatic hydrocarbons* (PAHs), *n*-nitroso compounds, and asbestos. Their concentrations in ambient air, however, are quite low. Diesel exhaust, in particular, contains particles with PAHs as constituents. Epidemiologic studies have provided consistent evidence of an excess risk of lung cancer in workers exposed to diesel exhaust; it is listed by the International Agency

on Cancer Research as a known human carcinogen.[6–9] Several large population-based epidemiologic studies have also linked lung cancer to long-term exposure to PM and traffic-related air pollution.[10,11]

As levels of outdoor ambient air pollution have decreased in many areas throughout the United States, the relative impact of indoor air pollution has increased. Moreover, North American residents spend the majority of their time indoors, increasing their exposure to indoor air pollutants.[12,13] At the same time, changes in home and office building construction have resulted in lower air exchange rates, increasing the levels of pollutants emitted indoors. In the developing world, indoor air pollution due to biomass smoke from domestic cooking and heating is a major source of morbidity and mortality.[14] Biomass smoke is a mixture of gases and PM similar to tobacco smoke, with the exception that it does not contain nicotine. In the developed world, emissions from cooking may also be an underappreciated source of morbidity. Both indoor and outdoor pollution must be considered when assessing the total health effects of air pollution.

Table 102.1 National Primary Air Quality Standards in the United States (Criteria Pollutants)

Pollutant	Standard*	Averaging Period
Particulate matter < 10 μm (PM_{10})	150 μg/m³	24 hr
Particulate matter < 2.5 μm ($PM_{2.5}$)	12 μg/m³ 35 μg/m³	1 yr 24 hr
Sulfur dioxide	75 ppb (214 μg/m³) 500 ppb (1430 μg/m³)	1 hr 3 hr
Nitrogen dioxide	100 ppb (188 μg/m³) 53 ppb (100 μg/m³)	1 hr 1 yr
Ozone	70 ppb (100 μg/m³)	8 hr
Lead	0.15 μg/m³	Rolling 3-mo average
Carbon monoxide	9 ppm (10 mg/m³) 35 ppm (40 mg/m³)	8 hr 1 hr

*Where two standards are listed, the first is the primary air quality standard set by the U.S. Environmental Protection Agency to protect health. The second standard listed is the so-called secondary standard, which is set to protect the public welfare (i.e., to protect against decreased visibility and damage to animals, crops, vegetation, and buildings).
ppb, parts per billion; ppm, parts per million.

GENERAL PROPERTIES, SOURCES, AND DISTRIBUTION OF POLLUTANTS

Particulate matter (PM) is an important pollutant. In the western United States and many other areas of the world, particulate pollution is not driven by the combustion of sulfur-containing fuels. Atmospheric particulate air pollution arises from a variety of sources, including both natural (e.g., sea spray, windblown dust) and synthetic (e.g., power plants, motor vehicles) sources. Moreover, PM that enters the atmosphere can be primary (particles emitted directly) or secondary (particles formed by complicated chemical reactions happening in the atmosphere and involving gas-phase precursors, such as SO_2 and nitrogen oxides). In North America, secondary particles comprise most of the fine-particle pollution.

In epidemiologic studies, researchers have defined the size of particles in terms of aerodynamic diameter because most particles have irregular shapes with geometric diameters not easily measured. The aerodynamic diameter is the diameter of a perfect sphere of unit density (1 g/mL) with the same aerodynamic properties (e.g., settling velocity) as the particle in question. Larger particles are filtered in the nose and throat, but particles less than 10 μm in diameter (PM_{10}) can be deposited in the respiratory tract. Fine particles, which are less than 2.5 μm in diameter ($PM_{2.5}$), penetrate to the alveoli, and ultrafine particles ($PM_{0.1}$) can pass through the alveoli and spread to other organs.

Size also determines how far particles travel and persist in the environment. Coarse particles (>2.5 to 10 μm) travel for rather short distances and have atmospheric half-lives of minutes to hours. Fine particles can travel for long distances and remain in the atmosphere for days to weeks.

Table 102.2 Major Pollutants Associated With Adverse Pulmonary Effects

Pollutant	Outdoor Sources	Indoor Sources	Adverse Effects
Particulate matter	Motor vehicle exhaust, power plants	Tobacco and wood smoke	Exacerbations of asthma and COPD, increased cardiopulmonary mortality
Sulfur oxides	Power plants, oil refineries, smelters	Kerosene space heaters	Bronchoconstriction
Nitrogen oxides	Motor vehicle exhaust, power plants, oil refineries	Gas stoves and furnaces, kerosene space heaters	Airway injury (respiratory bronchiolitis), impaired lung defenses, enhanced response to allergens
Ozone	Motor vehicle exhaust	Aircraft cabins, welding, copiers, ozone generators	Airway injury (respiratory bronchiolitis), decreased lung function, exacerbations of asthma, enhanced response to allergen
Radon	None	Residential basements	Lung cancer
Polycyclic aromatic hydrocarbons	Diesel exhaust	Tobacco smoke	Lung cancer

Ultrafine particles are typically generated from combustion processes and, due to their high reactivity, have short atmospheric half-lives due to physical agglomeration and chemical growth. For example, the concentration of ultrafine particles emitted from motor vehicles on a major roadway rapidly decreases with distance from the roadway; the concentration returns to the background level at or beyond 300 m.[15]

Fine particles ($PM_{2.5}$) are composed mainly of varying amounts of water and several major components (sulfates, acids, nitrates, elemental carbon, organic carbon, and trace metals) depending on their sources.[16] They are directly emitted during combustion but are also formed from gases by nucleation, condensation, or liquid-phase reactions. Coarse particles ($PM_{10-2.5}$) are composed primarily of crustal (rock, soil), biologic (pollen, spores), and industrial components; they are formed primarily by mechanical processes that produce small particles from larger particles.

Sulfur dioxide (SO_2) is produced by the combustion of sulfur contained in fossil fuels, such as coal and crude oil. The major sources of SO_2 pollution are power plants, oil refineries, smelters, and paper pulp mills. A newly recognized source of exposure to SO_2 associated with acute health effects is volcanic emissions.[17] For example, the major source of SO_2 exposure on the island of Hawai'i is the Kilauea Volcano, which has been erupting for nearly 40 years, sometimes emitting up to 12 kilotons in a day.[17] Although eruption events are impressive, global satellite data suggest that passive degassing of SO_2 from nonerupting volcanoes is the major global source, with 63 kilotons emitted daily worldwide.[18] In the United States, SO_2 levels are generally higher in the Northeast and Midwest because sulfur-containing coal is used in power plants. SO_2 itself is a clear, highly water-soluble gas, so it is effectively absorbed by the mucosal surfaces of the upper airways. Only a small proportion of inhaled SO_2 reaches the distal regions of the lungs, but susceptible persons, such as those with asthma, may still suffer adverse respiratory health effects.[19] The SO_2 released into the atmosphere does not, however, remain uniquely in the form of a gas; rather, it undergoes chemical reactions with water, trace metals, and other pollutants to form particulate aerosols. The nature of particles generated from sulfur-containing fuels varies geographically, but sulfuric acid and various metallic, acidic, and ammonium sulfates are commonly present. The mixture of sulfur oxides and small particles may be blown great distances from its source, undergoing continuous transformation from a gas to a particle phase and ultimately becoming acid rain.

Nitrogen dioxide (NO_2) is rapidly generated from nitrogen oxides, which are produced whenever there is combustion. Motor vehicles and power plants are the major sources of this pollutant. The areas with the highest concentrations of NO_2 tend to be the downtown cores of large cities, where there are major roadways and traffic congestion. Because NO_2 tracks well with traffic emissions, it is often considered a marker of traffic-related air pollution in epidemiologic studies. NO_2 reacts with oxygen to generate O_3 and nitric oxide, but this is a bidirectional reaction so that O_3 levels tend to be lower in areas where NO_2 is concentrated. Thus, O_3 levels tend to be lower in neighborhoods adjacent to major roadways. High concentrations sometimes found in silos are well known to cause the acute and sometimes lethal pulmonary edema of silo filler's disease.[20] However, the much lower levels of NO_2 in outdoor air were not linked to adverse health effects in epidemiologic studies until the late 20th century.

Ozone (O_3) arises primarily from the action of sunlight on emissions from internal combustion engines of motor vehicles.[21] The most important of these emissions are unburned hydrocarbons (so-called *volatile organic compounds* [VOCs]) and nitrogen oxides. In the atmosphere farther away from traffic sources, ultraviolet irradiation of the mixture of VOCs and NO_2 results in a complex series of chemical reactions, producing O_3, alkyl nitrates, peroxyacyl nitrates, alcohols, ethers, acids, peroxyacids, and other organic and inorganic compounds that exist in both gas and particulate aerosol phases.[21] This mixture of pollutants typifies the smog found in areas with large numbers of automobiles and abundant sunlight, such as the Los Angeles basin.

Because O_3 and NO_2 are the gases present in the highest concentration in smog and cause toxic effects in animals and humans, they have been the oxidant pollutants most extensively studied. Both gases are relatively insoluble and poorly absorbed by the upper airways. A high proportion of the inhaled dose therefore reaches the peripheral portion of the lungs and can cause injury at any site from the upper airways to the alveoli.

MECHANISMS OF DEFENSE AGAINST AIR POLLUTION–RELATED RESPIRATORY EFFECTS

The respiratory system, which encounters myriad particles and gases daily, has evolved an effective defense system for removing impurities from inhaled air. The various mechanisms of defense are interrelated and work in a coordinated manner. A perturbation of any defense mechanism, whether because of congenital deficiency, disease, or the effect of an inhaled pollutant itself, may result in the breakdown of the coordinated defense system and the development of disease.

DEPOSITION OF AND CLEARANCE OF PARTICLES (see Chapter 13)

The size of particles determines their site of deposition in the respiratory tract.[23] Large particles (diameter > 10 μm) are efficiently removed in the nose by simple filtration via the cilia. Those particles not removed by filtration will largely be deposited by a process termed impaction. The pathway through the nose, mouth, and branching airways is tortuous. Because inhaled particles cannot easily change direction to follow the abrupt changes in the pathway of airflow, they impact on the mucosa of the upper and lower respiratory tract. Airway bifurcations are especially prone to particle impaction. The complementary mechanisms of filtration and impaction are efficient; therefore, few particles more than 10 μm in diameter reach the lower respiratory tract.

Smaller particles are less affected by filtration and impaction; the sites of their deposition are more determined by the processes of sedimentation and diffusion.[23] Sedimentation is the tendency for particles to fall at a constant rate under the influence of gravity. It is strongly influenced by particle density, particle diameter, and the viscosity of the surrounding gas. As air moves deeper into the lung, the airflow rate decreases, and particles fall out of the air stream under the influence of gravity. Sedimentation is the predominant mechanism for deposition of particles of intermediate size (0.5 to 3.0 μm) in the smaller bronchi, bronchioles, and alveoli.

The smallest particles (<0.5 μm), however, are deposited by the mechanism of diffusion. These particles have random (Brownian) motion and will impact the airway mucosa in the terminal bronchioles and alveoli, removing them from the stream of inspired air.

The pattern of breathing can influence the deposition of particles. A higher respiratory rate increases the velocity of airflow, promoting impaction of particles in the more proximal airways. Conversely, increased tidal volume results in deeper lung penetration by particles; when the respiratory rate is slow, there is more time for diffusion and sedimentation to deposit particles in the distal airways and alveoli. In exercise, the increase in tidal volume will have a larger effect than the effect of increased velocity, resulting in higher overall deposition into the deep lung despite some increased airway impaction.

In the larger, more central airways, cough is the most effective mechanism for clearing particles. It is provoked by stimulation of afferent nerves located most densely in the mucosa of the larynx and branching points of the tracheobronchial tree, sites at which particles are most likely to be deposited.[24]

In the proximal trachea down to the terminal bronchioles, the "mucociliary escalator" is the critical system for clearing particles. The mucus blanket is the product of secretion by goblet cells and serous cells of the epithelium and by the mucus cells and serous cells of the submucosal glands. The mucus blanket is propelled toward the mouth by the coordinated beating of epithelial cell cilia. The effective removal of particles by the mucociliary system thus requires secretion of glycoproteins by specialized secretory cells, maintenance of liquefaction by the transport of water and solute by airway epithelial cells, and coordinated function of airway cilia. Impairment of any of these functions, whether by congenital or acquired conditions affecting mucus or water secretion (e.g., cystic fibrosis, chronic bronchitis) or ciliary function (e.g., dysmotile cilia syndrome, tobacco smoking), leads to longer residence of particles in the airway and a greater likelihood of adverse health effects.

In the distal airway and alveoli, particles are beyond the reach of the mucociliary escalator. The central mechanism for clearing these particles involves the alveolar macrophage, which phagocytoses particles deposited in the gas-exchanging parts of the lung and either digests them or removes them as it migrates to the respiratory bronchiole and ascends the mucociliary escalator. A smaller number of particle-laden macrophages migrate to peribronchial or perivascular connective tissue, a slow method of clearance that takes many weeks. Because macrophages are the primary phagocyte for inhaled PM, the carbon content of macrophages has been used as a biomarker of exposure to particulate pollution in epidemiologic studies.[25]

GASES: DEPOSITION AND DAMAGE ARE FUNCTIONS OF SOLUBILITY

For gaseous pollutants such as SO_2, NO_2, and O_3, the site of deposition in the respiratory tract is largely a function of water solubility. For highly soluble gases, the nose serves an important defensive function because the air inhaled transnasally is passed over the large, irregular surface of the turbinates. The promotion of turbulent flow prolongs contact with the mucosal surface, increasing adsorption. Under conditions of quiet breathing, when most air is inspired transnasally, the concentration of SO_2 that reaches the glottis is less than 2% of the concentration inspired at the nose.[26] As the inspiratory flow rate increases, the proportion of SO_2 reaching the glottis increases. Compared to the nose, the mouth is substantially less efficient at adsorbing gases, and the proportion of air inhaled through the mouth increases as the ventilatory demands of exercise rise. Therefore, the dose of a soluble pollutant delivered to the lower airways is increased by exercise for three reasons: the inspiratory flow is higher, the proportion inhaled through the mouth is increased, and the total quantity inhaled over time is greater. The importance of the level of ventilation, which depends on the level of exercise, and of the oral-nasal distribution of breathing has perhaps best been shown in studies of the bronchoconstrictor response to SO_2, in which the responses are greatest during oral breathing and smallest during nasal breathing.[27] In addition, people with obstructive nasal disease also appear to be at greater risk for adverse respiratory effects of soluble pollutant gases.

OXIDATIVE STRESS

Air pollution, especially involving particles and O_3, can increase the oxidative burden to the lung. To minimize oxidant damage to biologic molecules, the human lung has an integrated antioxidant system of enzymatic and expendable soluble antioxidants. This system includes several antioxidant defense mechanisms that detoxify reactive products or convert them to products quenched by other antioxidants. If the oxidant burden is sufficiently great, the reactive species may overwhelm or inactivate the antioxidant system. An imbalance between the production of reactive oxygen species and reactive nitrogen species and antioxidant capacity leads to a state of oxidative stress that contributes to the pathogenesis of respiratory and cardiovascular diseases.[28–30]

When imbalance exists, the excess oxygen species induce a cellular stress response that activates a number of the redox-sensitive signaling cascades. This initial response is mediated in large part through the transcription factor nuclear factor erythroid 2–related factor 2, which leads to transcriptional activation of antioxidant and detoxification

enzymes collectively known as the phase 2 response.[30] Examples of phase 2 enzymes include heme oxygenase 1, glutathione-*S*-transferase isoenzymes, reduced nicotinamide adenine dinucleotide phosphate–quinone oxidoreductase, catalase, superoxide dismutase, and glutathione peroxidase. If phase 2 responses fail to prevent a further increase in reactive oxygen species production, major cellular components, including membrane lipids, protein, carbohydrates, and DNA, will be damaged and inflammation and tissue damage may ensue.

Oxidative stress–induced proinflammatory effects are mediated by the redox-sensitive cascades responsible for the expression of cytokines, chemokines, and adhesion molecules.[30] Cytotoxic effects are associated with mitochondrial membrane damage, which leads to a release of factors that induce apoptosis of lung cells. Pathophysiologic consequences of pollutant-induced oxidant injury include airway inflammation, leading to clinical exacerbation of asthma, increased susceptibility to infection, enhanced allergic responses and, if repetitive or chronic, airway remodeling and systemic effects.[29,30]

METHODS OF STUDYING THE HEALTH EFFECTS OF AIR POLLUTION

To develop sound public policy aimed at protecting the public from the adverse health effects of pollutants, scientific studies are necessary both to elucidate the health effects of various pollutants and to define the threshold level at which the risk substantively increases. The scientific basis of public policy is based on several lines of evidence: epidemiologic studies of the association between air pollution and disease in the population, controlled human exposure studies conducted in the laboratory, studies of the effects of pollutants on lung structure and function in animals, and in vitro studies of toxicity. Each of these study designs has advantages and disadvantages, and none alone can provide irrefutable proof of harmful effects from a particular pollutant under realistic conditions of exposure (Table 102.3).

According to the 1970 Clean Air Act, air quality standards are set to provide a margin of safety to protect susceptible subgroups of the general population. For each putative pollution-related health effect, evidence must be compiled from published literature, synthesized, and evaluated for the likelihood of a causal association. Traditionally, the EPA uses a weight-of-the-evidence approach to assess the strength, consistency, and specificity of the association; coherence with related health effects; biologic plausibility; and exposure-response relationship. Epidemiologic studies are required because they evaluate the impact of real-world air pollution on respiratory health outcomes among the general population. However, epidemiologic studies have limitations (see later).[31]

EPIDEMIOLOGIC STUDIES

The strengths of epidemiologic studies include the ability to evaluate a wide array of health effects, longer durations of exposure, and representative sampling of the larger population. Epidemiologic studies, crucially, allow the study of questions that could not ethically or feasibly be addressed via a randomized controlled trial. Although their weaknesses must also be understood, they remain a valuable source of scientific information. Because epidemiologic studies do not provide mechanistic data, other studies providing human, animal, and cellular toxicologic data are required to understand mechanistic pathways.

One challenge of epidemiologic studies is the risk of confounding or other sources of bias. To make causal inferences regarding air pollutant exposures, the issue of confounding must be addressed in epidemiologic studies of air pollution–related health effects. It is often difficult to be sure that all confounders (e.g., cigarette smoking, occupational exposures, socioeconomic status) have been identified and controlled.

Another challenge of epidemiologic studies is that most environments include a complex mixture of pollutants.

Table 102.3 Methods for Studying Air Pollution

Method	Strengths	Weaknesses
Epidemiologic study	▪ Representative sample of general population ▪ Naturalistic exposure ▪ Broad range of pollutants ▪ Wide range of health outcomes ▪ Study of susceptible subgroups	▪ Chance, bias, confounding are threats to study validity ▪ Difficulty separating effects of individual pollutants when present as multipollutant mixtures ▪ Usually no information on biologic mechanisms
Controlled human exposure study	▪ Rigorous experimental design ▪ Elimination of bias and confounding ▪ Systematic control of exposure levels ▪ Study of susceptible subgroups	▪ Acute effects do not necessarily predict chronic effects ▪ Limited range of exposures and outcomes evaluated
Animal study	▪ Best method for evaluating impact of pollutants on structure and function of lung ▪ Dose-response relationship (from minimal level producing health effects to death)	▪ Large interspecies response to pollutants ▪ Applicability to humans often uncertain
In vitro study	▪ Elucidate cellular mechanisms ▪ Rigorous experimental control	▪ Limited to available cell lines ▪ Applicability to intact human organism often uncertain

Assessing the effects of individual pollutants, one by one, might miss the effects of the mixture. A related issue is multicollinearity, which arises because air pollutant concentrations are correlated with one another, making it difficult to parse out the individual health effects of each pollutant. Sophisticated statistical modeling attempts are used to address these potentially confounding issues, but they remain challenges to valid inferences.[22]

Another major challenge to air pollution epidemiologic studies is exposure assessment. Many studies estimate individual exposure by mapping each individual subject's home (and sometimes schools or workplaces) relative to stationary pollution monitors. Recent advances have also allowed investigators to conduct land-use regression modeling, personal monitoring of exposure to specific pollutants, and the use of remote-sensing satellite data.[32] Choosing the metric of exposure most relevant to disease causation requires careful consideration. With O_3, for example, the 8-hour average from 10 AM to 6 PM may be most appropriate because the EPA air quality standard uses an 8-hour averaging time, and these hours reflect the impact of photochemistry on O_3 precursors emitted from motor vehicles during the morning commute. In contrast, with SO_2, shorter peak exposures would be more appropriate for assessing its effect on exacerbations of asthma. Whether a time lag between onset of exposure to the pollutant and onset of the health outcome (e.g., one or several days) should be considered is also an important question.

CONTROLLED HUMAN EXPOSURE RESEARCH

Experimental studies expose human subjects to pollutants under carefully controlled conditions. Such studies can rigorously evaluate the impact of a single pollutant or a mixture such as diesel exhaust on acute responses, such as lung function or airway inflammation. In addition to documenting the acute health effects of pollution, controlled human exposure studies can evaluate the minimal concentration of a pollutant that causes reduction in lung function or other acute responses. These studies can also evaluate the effects of pollutants on susceptible subgroups of the population, such as on adults with asthma. Moreover, measurement of biomarkers of inflammation, oxidative stress, and other pathophysiologic processes can provide mechanistic insights.

A major advantage of controlled human exposure studies is the (near) elimination of confounding and bias because exposures are experimentally induced and carefully controlled. Because these studies evaluate acute effects, however, they cannot, by themselves, be easily extrapolated to the effects of more chronic or recurrent exposure. The finding that a brief exposure to O_3 causes acute decrements in lung function does not, for example, necessarily indicate that prolonged or repeated exposure will lead to the development of COPD. However, controlled human exposure studies, when combined with epidemiologic and animal toxicologic studies, can provide important data for establishing the causal effect of pollution on a respiratory health outcome.

ANIMAL RESEARCH

Animal studies offer the most effective way to investigate the impact of air pollution on lung structure. In addition, animal studies permit assessment of the effects of a range of concentrations so that a dose-response curve can be constructed for outcomes ranging from the first measurable change in lung function or structure until death. Animal studies also afford a unique opportunity to dissect the pathogenetic mechanisms of pollution-related health effects.

The major limitation of animal studies is the large interspecies variations in response to pollutants. As such, applicability of animal studies to humans, especially for dose-response relationships, may not always be clear. Rodents, for example, can tolerate relatively high levels of O_3 without developing structural injury to the lungs, whereas rhesus monkeys develop injury at levels approaching ambient concentrations.[33] Moreover, common human lung diseases, such as asthma and cystic fibrosis, have not been fully reproduced in animals, precluding study of these susceptible subgroups for pollution-related effects.

IN VITRO RESEARCH

Exposure of cell and model tissue cultures to specific air pollutants has helped to elucidate the mechanisms of lung injury, inflammation, and other adverse respiratory health effects. Specifically, cell culture systems have been used to study the impact of particulate and other air pollutants on inflammatory cytokines, oxidative stress, DNA damage, and cytotoxicity.[34–37,39] Cultures of bronchial and alveolar epithelial cells, monocytes, dendritic cells, and other cell lines have been useful for studying the mechanisms of air pollution on the respiratory system.[37] Models of respiratory epithelium using air-liquid interface exposures can be used to mimic in vivo air pollutant exposures.[37,39]

OUTDOOR AIR POLLUTION: STANDARDS AND ADVERSE RESPIRATORY EFFECTS OF SPECIFIC POLLUTANTS

In the United States, the EPA has established regulatory standards for the criteria air pollutants (PM, O_3, NO_2, SO_2, CO, and lead) (see Table 102.1). Each standard provides a concentration that should not be exceeded, which is intended to be health protective, as well as an averaging time, which ranges from 1 hour to 1 year. Brief, high spikes in air pollutant levels can be obscured in longer-term data; if a pollutant level was near zero most days of the year, a few days of very high levels may not increase the annual average much, even though those days could provoke acute health effects. Thus, for some pollutants, shorter-term standards have been introduced. Because high spikes can be obscured in long-term data, even though these shorter-term standards are often at higher concentrations, they are *more* health protective than the lower concentration standards with longer averaging times. Globally, the World

Health Organization guidance levels are used as a target for protecting human health; these are lower than EPA levels, although there is no regulatory enforcement associated with these.

PARTICULATE MATTER

Since the catastrophic air pollution events of the Meuse Valley, Donora, and the London Fog, hundreds of epidemiologic studies have examined the health impacts of particulate air pollution. There is strong and consistent evidence that particulate pollution causes premature death, principally from cardiovascular and respiratory causes.[38,40–43] Both short-term exposure, measured as daily fluctuation of particulate pollutant levels, and longer-term chronic exposures have been linked with mortality.[44] In particular, the Harvard Six Cities Study[38] and the American Cancer Society study[41] have provided key insights into the long-term health impacts of particulate air pollution. Evidence linking PM_{10} and $PM_{2.5}$ to mortality is robust but is particularly strong for $PM_{2.5}$.

PM increases respiratory symptoms. For example, exposure to PM has been associated with lower respiratory tract symptoms in children, such as cough, wheezing, or shortness of breath.[45,46] Children with asthma are especially vulnerable.[47,48] Adults with asthma who are exposed to higher levels of PM have an increased risk of exacerbations.[49]

PM is also associated with poorer lung function, both in children and in adults. The Children's Health Study conducted in Southern California, which has followed thousands of children over many years, found that fine-particulate pollution was linked to a reduced rate of lung function growth but, with improved air quality over time, growth of lung function improved.[50,51] In adults, particulate pollution has also been linked to poorer lung function and increased risk of COPD, which may reflect decreased growth of lung function in childhood or accelerated decline subsequently.[52] In support of a link between particulate pollution and COPD, other studies have linked ambient particle exposure to a greater risk of hospitalization and death from COPD.[53,54]

Of importance, a reduction in particulate air pollution translates to improved pulmonary function and a longer life span for the population. A Swiss study (SAPALDIA) examined the association between the change in air quality over 11 years and the decline in lung function among a large sample of adults.[55] A reduction in PM_{10} of 10 $\mu g/m^3$ was associated with a decreased rate of annual decline of *forced expiratory volume in 1 second* (FEV_1). To address the impact of declining $PM_{2.5}$ levels on mortality, another study examined 211 metropolitan counties throughout the United States from approximately 1980 to 2000.[42] A decrease in $PM_{2.5}$ of 10 $\mu g/m^3$ was associated with a mean increase in life expectancy of 0.61 years, after taking into account measures of sociodemographic and smoking factors. During the 2 decades of the study, the average life expectancy increased 2.72 years. The authors estimated that up to 15% of this improvement in life span could be attributed to declining particulate pollution levels. In the Harvard Six Cities Study, declining fine particle levels were also shown to be associated with reduced mortality in the United States.[40]

Diesel exhaust is another important component of particulate pollution. Diesel exhaust from heavy-duty trucks and diesel-engine cars is a major contributor to particulate air pollution in many parts of the world. Diesel exhaust particles have a central carbon core and adsorbed organic compounds, including PAHs and other known carcinogens. Occupational exposure to diesel exhaust among truck drivers, railroad workers, and miners has been associated with an elevated risk of lung cancer.[6–8] Toxicologic studies have confirmed the carcinogenic properties of diesel exhaust.[9]

Diesel exhaust exposure can cause acute deterioration of lung function among persons with asthma. A randomized crossover study randomly assigned adult subjects with mild to moderate asthma to walk for 2 hours at lunchtime along Oxford Street in London (the busiest shopping street, in which only diesel-powered buses and taxis are allowed) or in Hyde Park.[56] Fine and ultrafine particle levels were approximately three times higher on Oxford Street than in Hyde Park. The maximal decline in FEV_1 was much greater for subjects during and after a single 2-hour walk on Oxford Street than in Hyde Park, and sputum biomarkers of neutrophilic inflammation were also increased. A second study, including older subjects with COPD, also showed a lung function response while walking for 2 hours on Oxford Street.[57] Other studies indicate that diesel exhaust may favor a type 2 T helper cell (lymphocyte) immune response, further connecting this form of particulate pollution with allergic disease and asthma.[58] Diesel exhaust contains PAHs that have been shown to worsen asthma outcomes, potentially through an epigenetic mechanism decreasing T regulatory cell function.[59]

SULFUR DIOXIDE

Bronchoconstriction is the primary acute effect of SO_2 and is likely mediated by chemosensitive receptors in the tracheobronchial tree. In particular, persons with asthma are most sensitive to the effects of SO_2, which may result from preexisting airway inflammation that leads to enhanced release of mediators, alterations in the autonomic nervous system, and exaggerated response of the chemosensitive receptors. Multiple controlled human exposure studies have observed symptomatic bronchoconstriction in exercising asthmatics after 5- to 10-minute exposures to SO_2 at concentrations similar to those found in ambient air.[60,61] In the published studies, 5–30% of relatively healthy asthmatic subjects experienced moderate or greater decrements in lung function (>100% increase in specific airway resistance or >15% decrease in FEV_1) with exposures to SO_2 concentrations of 200 to 300 *parts per billion* (ppb) during exercise.[60] A clear concentration-response relationship has been demonstrated after exposures to SO_2 at concentrations between 200 and 1000 ppb, with increases in both the severity of effect and the proportion of asthmatic individuals affected. Individuals without asthma do not typically experience bronchoconstriction at these levels.[61]

The results of multiple epidemiologic studies show associations between short-term exposures (generally 24-hour averages) to ambient SO_2 and respiratory morbidity. Several multicity studies and single-city studies have found an association between 24-hour average SO_2 concentrations

and respiratory symptoms in children, particularly those with asthma.[62,63] Generally consistent associations have also been observed between ambient SO_2 concentrations and lung function decrements and health care utilization for all respiratory causes, particularly among children and older adults (≥65 years), and for asthma.[19,63] Because SO_2 and $PM_{2.5}$ are both emitted from the combustion of sulfur-containing fuels, such as coal and heating oil, studies of SO_2 need to address potential confounding by coexposure to PM. This is often statistically difficult because these exposures are related to each other, so many studies use only single-pollutant models. The use of complex statistical methods to consider mixtures is expected to provide further insights in the future.

The observed associations of asthma symptoms and lung function changes with 24-hour average SO_2 exposures in epidemiologic studies may be due to short-term peak exposures similar to the 5- to 10-minute exposures that have produced symptomatic bronchoconstriction in controlled human exposure studies. In other words, the effects of SO_2 on respiratory symptoms and lung function observed in human experimental studies using peak exposures are coherent with the increased emergency department visits and hospital admissions observed in epidemiologic studies. In the initial EPA standards, SO_2 exposures were regulated only in 24-hour and annual averages. This meant that very high short-term exposures, which could trigger acute bronchoconstriction, could be allowed as long as the overall average was low. In 2010, to protect asthmatic individuals from acute episodes of bronchoconstriction, the EPA added a 1-hour ambient air quality standard for SO_2 of 75 ppb.

Several studies have assessed the effects of decreases in SO_2 concentrations on respiratory symptoms due to air quality regulations. In eastern Germany, a marked decline in ambient SO_2 concentrations (90% across the decade of the 1990s) was associated with a decrease in the prevalence of respiratory symptoms.[64] During the study period, however, concentrations of other ambient air pollutants also decreased, including that of PM, which was approximately 60% lower. In a similar study of the effect of a 1990 regulation requiring use of low-sulfur fuel for power generation and on-road vehicles in Hong Kong, large reductions in ambient SO_2 concentrations of up to 80% were associated with reduced respiratory symptoms; in this study, reductions in ambient PM were less than 20%.[65] Although the improved respiratory symptoms observed in both of these intervention studies may be partially attributable to declining concentrations of air pollutants other than SO_2, the results nevertheless provide support for a causal relationship between SO_2 and respiratory health.

NITROGEN DIOXIDE

Controlled human exposure studies provide evidence for increased airway responsiveness to both nonspecific and specific challenges in asthmatic subjects after short-term exposure to NO_2. The results of several older studies suggested that short-term (30- to 60-minute) exposures to NO_2 at concentrations in the range of 100 to 300 ppb may cause increased airway responsiveness to nonspecific bronchoconstrictor agents, such as methacholine and histamine.[66] Other studies involving allergen challenge in asthmatics suggest that NO_2 may enhance both allergen-induced bronchoconstriction and inflammatory responses after exposures as low as 260 ppb NO_2 for 30 minutes during rest.[67,68]

Evidence from a number of epidemiologic studies supports an association between ambient NO_2 and respiratory morbidity, especially among persons with asthma. Multiple epidemiologic studies have shown positive associations between short-term ambient NO_2 concentrations and emergency department visits and hospital admissions for respiratory causes, especially asthma.[19,69] These associations are particularly consistent for children and older adults (age 65+ years) when considering all respiratory diseases and, for children and adults of all ages, when considering asthma.

In addition to the epidemiologic evidence that short-term exposure to ambient NO_2 can cause respiratory morbidity, long-term exposure to NO_2 has been associated with decreased rate of growth of lung function. Results from the longitudinal Children's Health Study indicated that decrements in lung function growth were substantial for boys and girls who lived in southern California communities with higher annual average ambient NO_2,[50] even though the mean annual NO_2 concentrations in these communities ranged from approximately 5 to 40 ppb, well below the current EPA national ambient air quality standard of 53 ppb as an annual average. Similar associations have also been found for PM, inorganic (mostly nitric) acid vapor, and proximity to traffic (<500 m) in this cohort; the high correlation among traffic-related pollutants makes it difficult to determine the independent effect of NO_2 on lung function growth.[70] As noted previously for PM, Children's Health Study investigators have demonstrated improved lung function growth with improved air quality in their study communities.[51]

Of interest, the results of several studies, including two from the Children's Health Study, suggest that long-term residential exposure to NO_2 is associated with increased risk of developing asthma in children.[71–73] However, it may be that NO_2 itself is not the causal agent, but rather that NO_2 concentrations are a good marker of exposure to the traffic pollution mixture.[72] A recent follow-up analysis from the Children's Health Study showed decreased risk of incident asthma with improved air quality in southern California.[74]

Because short-term exposures to NO_2 can induce greater airway responsiveness among asthmatic subjects in human experimental studies and are associated with respiratory outcomes, especially asthma, in epidemiologic studies, there is coherent evidence to support a short-term averaging time for air quality standards to control this pollutant. To protect individuals with asthma from acute exacerbations, the EPA promulgated a new 1-hour ambient air quality standard for NO_2 of 100 ppb in 2010.

OZONE

Although O_3 has long been associated with southern California smog, many other areas of North America also experience high concentrations of this pollutant, especially Houston, Mexico City, and cities in the eastern United States and Canada during the summer months. In these areas,

there are many days each year when the current EPA national ambient air quality standard for O_3 is exceeded.

O_3 is a potent oxidant and is capable of reacting with a variety of extracellular and intracellular molecules. When O_3 reacts with unsaturated lipids, free radicals and toxic intermediate products are generated that can lead to cellular damage or cell death.[75] Direct cytotoxicity is a major mechanism of O_3-induced tissue injury; secondary damage from the inflammatory response likely also plays a role.

Dosimetric studies indicate that much of the inhaled O_3 is deposited in the upper and proximal lower airways.[76] However, because of its relative water insolubility, a considerable fraction will penetrate to the distal airways and alveoli. At these sites, there is a clear relationship between cumulative dose and epithelial injury.[77] Increased inspiratory flow, as would be seen with exercise, may overwhelm the upper airway "scrubbing mechanisms" and cause greater deposition of O_3 in the distal lung.[78]

Most of the research on the health effects of O_3 has focused on short-term exposure. In controlled human exposure studies, O_3 inhalation by healthy subjects causes decrements in FEV_1 and forced vital capacity that correlate with concentration, exposure duration, and minute ventilation.[79,80] These decrements in lung function are primarily a result of decreased inspiratory capacity rather than airway obstruction. The mechanism of the decreased inspiratory capacity appears to be a neurally mediated involuntary inhibition of inspiratory effort involving stimulation of C fibers in the lungs.[75] Somewhat surprisingly, older subjects demonstrate lower O_3-induced decrements in pulmonary function than younger, healthy subjects.[81] The acute decrements in pulmonary function induced by O_3 usually resolve within 24 hours. Statistically significant decrements in FEV_1 have been demonstrated in healthy subjects with exposures during exercise to concentrations below the current U.S. air quality standard.[82]

Respiratory symptoms (e.g., substernal chest discomfort, cough, wheeze, dyspnea) are correlated with these decrements in pulmonary function. Another adverse effect of short-term exposure to O_3 is enhanced airway responsiveness to nonspecific stimuli, such as methacholine and histamine. This effect may persist longer than the acute decrements in lung function and may be seen even in individuals who do not experience a decline in their FEV_1.

O_3 exposure may induce adverse respiratory consequences through a variety of mechanisms. These include nasal inflammatory changes, injury to alveolar epithelial type 1 cells, ciliated airway epithelial cell injury, infiltration of the airway mucosa by neutrophils, and increased bronchoalveolar lavage fluid neutrophils and inflammatory mediators.[75] Airway inflammation has been demonstrated after exposure to ambient concentrations with exercise, including levels below the current U.S. air quality standard.[81,82]

The effects of *chronic* O_3 exposure in humans have not been adequately defined. It has been hypothesized that chronic exposure would lead to structural changes; however, to date, most toxicologic studies involving rodents have failed to demonstrate structural damage after long-term exposure to ambient concentrations. However, studies with rhesus monkeys have shown that O_3 exposure of neonatal rhesus monkeys led to abnormal development of conducting airways, especially with coexposure to house dust mites.[33] In addition, some epidemiologic studies, but not all, suggest that long-term residence of children in a high ambient O_3 environment can lead to remodeling of the small airways.[50,83,84]

Multiple epidemiologic studies show that high ambient O_3 concentrations are associated with an increased rate of asthma attacks and increased respiratory-related hospital admissions/emergency department visits for respiratory disease.[19,66] The biologic plausibility of these findings is supported by the results of controlled human exposure studies showing that O_3 increases nonspecific airway responsiveness, asthmatic subjects have a greater inflammatory response to exposure, and specifically sensitized asthmatic subjects have enhanced bronchoconstrictor responses to inhaled allergen.[85] In addition to the exacerbation of preexisting asthma, some evidence exists that exposure to O_3 could induce new cases of asthma. For example, children playing outdoor sports in polluted areas of the Los Angeles basin have a threefold to fourfold increased risk of asthma compared to children not playing outdoor sports, but this association was not present in areas with lower O_3 levels.[86]

Both short-term and long-term exposures to O_3 have been associated with increased risk of mortality, as reported in Europe and the United States.[87–92]Although this effect was first reported for respirable PM, both O_3 and fine PM are capable of generating oxidative stress and inflammation deep in the lung. Similar to what has been observed in PM mortality studies, it appears that elderly people with preexisting heart and lung disease represent the group at greatest risk for O_3-related death. If excess oxidative stress is a critical step in a pathway that leads to early mortality in individuals with heart and lung disease, it is not surprising that exposure to both ambient O_3 and PM is associated with increased risk. Of additional concern, several studies have suggested that young adults living in southern California have increased oxidative stress and cytogenetic damage compared with those living in northern California, perhaps related to differential exposure to O_3.[93,94]

In summary, tens of millions of persons in the United States are exposed to levels of O_3 above the current U.S. national ambient air quality standard. This exposure is capable of inducing both acute decrements in lung function and respiratory symptoms. Although these effects are transient, acute respiratory tract injury and inflammation can also be induced by short-term exposure to ambient concentrations of O_3. Exacerbations of asthma and increased risk of death of the elderly appear to be the most important health effects of short-term exposure. The long-term consequences of O_3-induced acute injury and inflammation are not well understood, but there is epidemiologic evidence that O_3 can lead to airway remodeling.

INDOOR AIR POLLUTION

Indoor air quality has been increasingly recognized as an important determinant of human health. Because levels of outdoor ambient air pollution have decreased throughout the developed world and because residents of these countries spend the majority of their time indoors, the relative

impact of indoor air pollution has increased.[12] In low- and middle-income countries, cooking and heating with solid fuels and lighting with kerosene cause household air pollution. To characterize personal exposure to air pollution, indoor air quality must be taken into account (Table 102.4).

SOURCES OF INDOOR POLLUTION

The concentrations of indoor air pollutants depend on both indoor and outdoor emission sources (Fig. 102.1).[12] Outdoor emission sources determine outdoor pollution concentrations, which, in turn, affect indoor air quality. The degree of penetration of outdoor pollution into the indoor environment depends largely on the rate of air infiltration from outdoors to indoors.[95] The rate of air infiltration is a complex function of the "tightness" of building construction and insulation, building location and orientation, number of exterior walls and windows, surrounding terrain and barriers, wind speed and direction, indoor-outdoor temperature gradient, and type and efficiency of ventilation system (e.g., heating, ventilation, air-conditioning).[95]

Time-activity patterns influence personal exposure. The relative time spent indoors versus outdoors affects the contribution of indoor pollutants to total personal exposure. Time spent in specific locations within the home affects exposure to particular pollutants because the distribution of indoor pollutant concentrations varies among different zones of a building, especially for pollutants generated indoors.[95] In addition, activity level affects metabolic rate and ventilatory rate, which also influence personal exposure to indoor pollutants.

Table 102.4 Indoor Air Pollutants

Category of Pollutant	Indoor Pollution Source
Combustion (e.g., NO_2, CO, $PM_{2.5}$, PAHs)	Secondhand smoke Gas stoves, ovens, heaters, and fireplaces Wood smoke (stoves, fireplaces) Kerosene heaters Candles and incense
Building materials (e.g., formaldehyde, volatile organic compounds)	Plywood Particle board Carpeting Paints
Cleaning materials (e.g., ammonia gas, chlorine gas, choramine)	Bleach, ammonia, detergents

CO, carbon monoxide; NO_2, nitrogen dioxide; PAHs, polycyclic aromatic hydrocarbons; $PM_{2.5}$, particulate matter less than 2.5 μm in diameter.

INDOOR COMBUSTION: MAJOR SOURCE OF INDOOR AIR POLLUTION

The major source of indoor pollution is from combustion, particularly *secondhand tobacco smoke* (SHS) exposure, gas stove use, and solid fuel (dung, crop waste, wood, charcoal, coal) burning in stoves and fireplaces. Kerosene space heaters and wick lamps are also an important source of indoor air pollution. Table 102.4 shows the major indoor

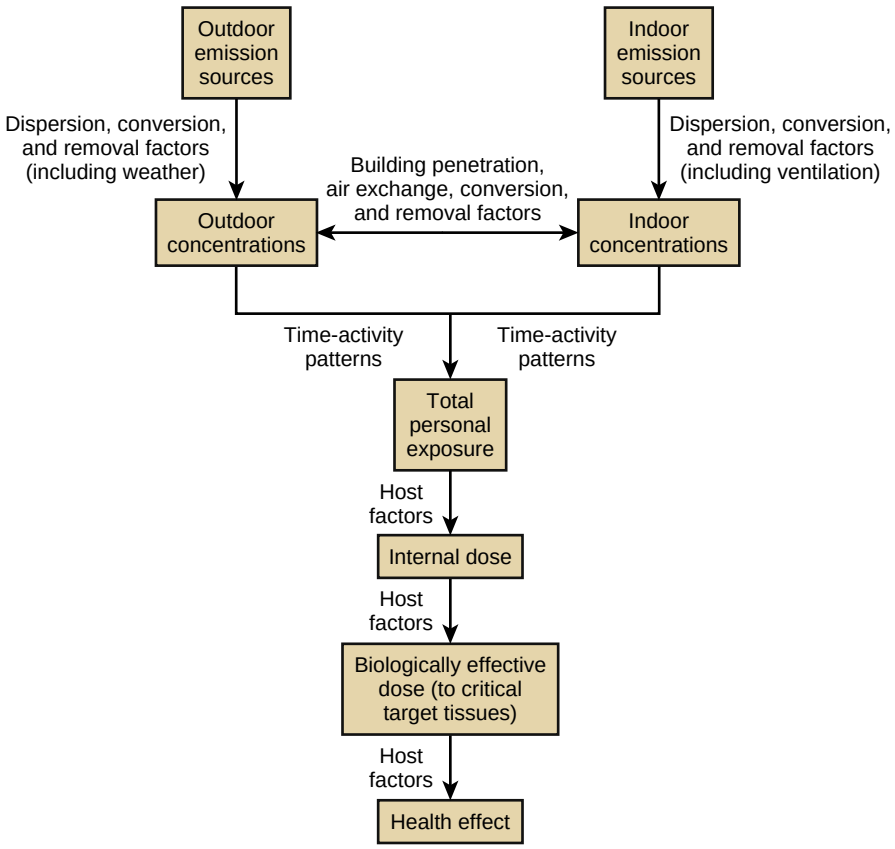

Figure 102.1 Relationships among outdoor pollution, indoor pollution, and health effects.

pollutants released from these sources and are associated with adverse pulmonary effects.

SECONDHAND SMOKE AND OBSTRUCTIVE LUNG DISEASE

SHS is perhaps the best known and studied indoor pollutant. Strong evidence implicates it as a cause of lung cancer, coronary heart disease, and decreased life span.[96,97] In addition to these adverse health effects, SHS contains respiratory irritants, such as SO_2, ammonia, acrolein, and formaldehyde. SHS is a complex mixture containing thousands of gas-phase and particulate substances. In homes where smoking is allowed, $PM_{2.5}$ levels are found up to 10 times higher than in nonsmoking homes.[98] Workplace exposures can be even higher, especially in bars and casinos.

Passive smoking has also been linked with allergic phenomena, such as elevated serum immunoglobulin E levels.[99,100] As a consequence, SHS has the potential to induce new cases of asthma through irritant or sensitizing mechanisms. The results of multiple studies provide evidence that SHS exposure is causally associated with new-onset asthma among children.[101]

Exposure to SHS also appears to be associated with new-onset asthma in adulthood. Cross-sectional, case-control, and cohort studies have suggested a link between SHS exposure and adult-onset asthma.[102] SHS exposure in the workplace, in particular, appears to be related to adult asthma induction.[103]

Beyond asthma induction, SHS exposure is a likely cause of asthma exacerbation in both children and adults.[104] Parental smoking causes increased symptoms, poorer pulmonary function, and other indicators of worsened asthma control among children with established asthma.[105] Similarly, SHS exposure, both at home and at work, appears to cause asthma exacerbation among adults.[106] Moreover, the negative impact of SHS exposure on pulmonary function appears to be greater among adults with asthma than in the general population.[107]

Exposure to SHS may also cause respiratory symptoms and impaired lung function among nonasthmatic individuals.[106] In a cohort of older adults, lifetime home and workplace exposure to SHS was associated with a more rapid decline of lung function during a decade of follow-up.[108] Studies of bartenders and restaurant workers with high occupational exposures to SHS have revealed a strong link between SHS and poorer respiratory health; smoke-free workplace laws have led to a reduction of respiratory symptoms and improved lung function in such workers.[109]

Emerging evidence now suggests that SHS exposure may also be a cause of COPD independent of personal cigarette smoking.[110,111] Population-based studies from multiple countries have found that both cumulative home and work SHS exposures were associated with a greater risk of COPD, controlling for potential confounders.[112] Among patients with established COPD, SHS exposure may increase the risk of respiratory symptoms, poor health status, and disease exacerbations.[113]

GAS STOVE EXPOSURE: CAUSE OF ASTHMA EXACERBATION?

When it became apparent that indoor concentrations of NO_2 often exceeded outdoor concentrations, particularly in homes equipped with gas stoves, research interest focused on the possibility that exposure to NO_2 in indoor air might increase the frequency of respiratory infections, in part because of animal studies showing that exposure increased risk of infection.[114]

In fact, the 2015 Institute of Medicine report concluded that short-term high NO_2 levels are associated with airway responsiveness, and that there is suggestive evidence for an association with asthma exacerbations.[115] In childhood, there appear to be consistent deleterious respiratory effects of living in a home with gas appliances. A recent meta-analysis demonstrated a summary odds ratio of 1.32 for asthma among children living in households with gas stoves.[116] When considering interventions, a study that evaluated the effect of reduced indoor exposure to NO_2 from gas heaters provided evidence of improvement in respiratory symptoms in asthmatic children,[117] and a nationally representative study in which parents were queried about cooking ventilation use showed higher rates of asthma, wheezing, and cough in households that did not use the stove hood.[118,118a]

In adults, the findings have been less consistent.[119–121] Overall, the evidence has not been sufficient to implicate gas stove use as an exacerbating factor in preexisting adult asthma. Among children with asthma, however, there is stronger evidence of a deleterious effect of indoor NO_2 exposure and poorer asthma control.[122,123]

WOOD SMOKE EXPOSURE: RESPIRATORY HEALTH EFFECTS

Wood smoke, which is produced from domestic fireplace or wood stove use, contains potent respiratory irritants, such as formaldehyde, acrolein, nitrogen oxides, and SO_2. It is also a major source of particulate air pollution.[124] Exposure to extremely high wood smoke levels has been linked with respiratory problems. After a work shift, forest firefighters experience an acute decrement in pulmonary function.[125] Similarly, wildland fires have been associated with increased respiratory symptoms and health care utilization for respiratory problems.[126] In developing countries, wood smoke from domestic cooking and heating in poorly ventilated homes has been associated with chronic bronchitis and COPD.[14,127] The exposure levels in such settings are extremely high and are likely the major cause of COPD in women in the developing world because women in these regions tend not to smoke cigarettes.[128] Cooking with other biomass fuels, such as crop residues or dung, and with coal can also lead to chronic respiratory symptoms and airflow obstruction.[129] Cooking with wood and/or charcoal has been associated with risk of COPD in developed countries as well.[124]

As opposed to COPD, asthma is not as clearly associated with biomass smoke exposure. Previous studies have reported conflicting results.[14,130] However, an analysis from the International Study of Asthma and Allergy in Children, which included more than 250,000 children from more than 31 countries, did find an association between use of an open fire for cooking and prevalence of asthma symptoms and reported asthma.[131] Exposures to wood smoke in developed countries are usually at much lower levels than in countries where a large proportion of the population cooks on open fires, so it is less clear how such exposures contribute to asthma burden. That said, wood smoke in communities that rely on burning wood for home heating or in which

fireplaces are frequently used during winter months can contribute to asthma exacerbations.[124]

RESPIRATORY EFFECTS OF KEROSENE HEATER USE

Kerosene heaters can substantially increase indoor levels of fine particles ($PM_{2.5}$), sulfate aerosol (SO_4^{2-}), and acidic aerosol (H^+), as well as CO.[132] Kerosene is similar to diesel fuel in chemical composition. The existing evidence, however, is inconclusive about whether kerosene heater use is a cause of respiratory and asthma symptoms in developed countries. In developing countries, where kerosene may also be used for lighting, using inefficient wick lamps, this fuel has been associated with increased risk of respiratory infections, especially tuberculosis.[133,134]

OTHER INDOOR POLLUTANTS: "TOXIC" INDOOR ENVIRONMENT

Besides indoor combustion, there are many other sources of indoor pollutants. Building materials, such as plywood or particle board, and carpeting can emit formaldehyde; furniture may release formaldehyde and VOCs; paints, cleaning compounds, and photocopiers may release VOCs; and radon can arise from soil sources.[135] Cleaning with disinfectants, such as bleach or quaternary ammonia compounds, can release airway irritants. A combination of bleach and ammonia or other nitrogen sources can also produce chloramine, which may induce upper and lower respiratory tract symptoms.[136,137] Indoor radon exposure has been associated with lung cancer[138] (see also Chapters 74 and 103).

Key Points

- Epidemiologic studies, taken together with controlled human exposure studies, animal studies, and in vitro studies, have delineated many of the serious respiratory and cardiovascular health effects of air pollution.
- The major types of air pollutants affecting the respiratory system are particulate matter, sulfur dioxide, nitrogen dioxide, and ozone.
- In developing countries, a major source of air pollution is biomass smoke from domestic heating and cooking, which may be the world's leading cause of obstructive lung disease among women.
- Exposure to air pollutants can decrease the normative growth of lung tissue and lung function during childhood and adolescence, with the potential for life-long effects.
- Great progress has been made in clearing the air in the United States and other developed countries, but levels of indoor and outdoor pollutants remain higher than is desirable for human health.
- Despite progress, significant questions remain about the impact of multiple pollutants acting together, the effect of pollution on susceptible populations, and the minimum ambient levels at which the risk of health effects increases. Further research is needed to answer these important questions.

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103 ACUTE RESPONSES TO TOXIC EXPOSURES

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INTRODUCTION

This chapter focuses on the acute effects on the lung after exposure to toxic substances. For most acute toxicant exposures, inhalation is the route of delivery leading to the lung injury. Importantly, *target organ* does not equate with *route of exposure.* In some instances, inhalation may be the route of exposure for the toxicant, and yet the primary target organ is not the lung (e.g., solvent inhalation that causes central nervous system depression). Inhalation exposures leading to nonpulmonary illnesses are not addressed here.

As used in this chapter, *acute* indicates short-term exposures (minutes to hours), with the initial onset of pulmonary responses within a similarly rapid time period. Generally, the relevant toxicant exposures are of high intensity, far in excess of recommended safety limits for population-wide environmental levels.

Because ingestion may also lead to lung injury, paraquat and hydrocarbon, examples of ingested toxins with severe acute target organ effects on the lung, are included in this chapter.

Moreover, this chapter does not address brief exposures, inducing acute responses mediated by anamnestic (i.e., allergic or other immune-mediated) mechanisms. These responses require prior exposures that already have led to sensitization, such as *hypersensitivity pneumonitis* (HP) (see Chapter 91) or occupational asthma (see Chapter 100). Although there is overlap with certain specific exposures that at far lower levels are also relevant to ambient air pollution (such as oxides of nitrogen, ozone, and sulfur dioxide), these are addressed at the population level in the chapter on air pollution (see Chapter 102).

Finally, some toxicants cause unusual pulmonary syndromes after subacute (days to months) exposure. Some of these syndromes have emerged in recent years associated with new technologies or novel toxicants, such as diacetyl-caused popcorn worker's lung and other flavor industry workers' diseases linked to this chemical,[1–3] "flock worker's lung" caused by short synthetic textile fibers,[4–6] and "Ardystil lung," a dye chemical–induced organizing pneumonia.[7,8] Some of these syndromes are discussed elsewhere in this text.

PATHOGENESIS OF LUNG INJURY FROM INHALED TOXICANTS

PATTERNS OF RESPONSE TO IRRITANT INHALATION

Acute lung toxicity results from a variety of exposures but nonetheless is manifest by a narrow repertoire of injury (Table 103.1). Irritant toxicants can be encountered in various physical states relevant to their inhalational properties. Such states include *gases, vapors* (i.e., the gaseous form of a substance that is a liquid or a solid at normal temperatures and pressures), and *fumes* (i.e., solid material, often metals, of small particle size suspended in a gaseous medium [most <1.0 μm and many <0.1 μm in diameter]). *Aerosols* encompass a mix of potential states (i.e., liquid droplets or fine particulates dispersed in a gaseous medium; *smoke* is a subset of aerosols from incomplete combustion).

These various classes of exposures include heterogeneous toxicants capable of causing extensive cell injury throughout the upper and lower respiratory tract. The primary location of respiratory tract injury and the onset of clinical symptoms partly depend on the solubility of the gas, vapor, fume, or aerosol involved and, in the case of fumes or aerosols, on the physical characteristics of the particle or droplet. Other factors that determine the injury pattern following exposure include (1) the amount of the toxicant inhaled, (2) the duration of exposure to the inhalant, (3) the concentration of the inhalant in the ambient air, (4) other physical properties (such as pH or chemical reactivity), and

Table 103.1 Major Clinical Scenarios of Pulmonary Responses Shortly After Acute Toxicant Exposure

Clinical Scenario	Exemplar Exposures	Additional Comments
Mucous membrane and airway irritation (burning eyes, nose, and throat; laryngospasm and bronchospasm) with or without lower lung injury (pulmonary edema, diffuse alveolar damage)	Chlorine, chlorine dioxide, chloramine; bromine; sulfur dioxide; acid aerosols (sulfuric, hydrochloric, hydrofluoric); ammonia; zinc chloride (smoke bombs)	At low exposures, mucous membrane irritation may be the sole effect; with heavy exposure, lower lung injury may be seen
Lower lung injury (pulmonary edema, diffuse alveolar damage) with little or no mucous membrane irritation or airway effects	Nitrogen dioxide, phosgene, ozone, cadmium fume, mercury vapor, nickel carbonyl, fluorocarbon (waterproofing)	Exposure can be inadvertent or occult with presentation delayed 24–48 hr
Self-limited flulike illness with fever and leukocytosis beginning 6–12 hr after a clear exposure history	Zinc oxide fume, heavy organic dust inhalation, polymer fume, endotoxin	The presence of hypoxemia or lung injury indicates another diagnosis
Foreign substance ingestion followed by pneumonitis	Hydrocarbon aspiration, exogenous lipoid pneumonia, paraquat fibrosis	Heavy aerosol inhalation can cause lipoid pneumonia; paraquat can also be absorbed through the skin

(5) a variety of host factors, such as age, genetics, use of respiratory protection, and comorbid illness. Overwhelming exposures to any irritant inhalant, however, can cause extensive damage throughout the respiratory tract.

Ammonia[9] and sulfur dioxide[10] are examples of substances that are highly soluble in water. Such highly soluble substances cause immediate irritation of the conjunctival mucosa and upper airways. This immediate onset of irritant effects provides warning symptoms that may prompt the victim to flee, thereby limiting exposure. In contrast, oxides of nitrogen,[11] ozone,[12] and phosgene[13] have relatively low water solubility. For this reason, exposure to one of these agents may *not* be characterized by immediate symptoms of mucous membrane irritation. This may lead to more prolonged exposure and delay in seeking medical attention. Both more-soluble and less-soluble irritant exposures can lead to distal lung injury but, in the case of highly soluble materials, a history of severe upper respiratory symptoms should precede the presentation of distal airway and alveolar damage.[14]

Irritants reaching the lower respiratory tract, either because of their inherent physical characteristics or because of exposures that overwhelm the absorptive capacity of the upper airway, can injure both the lung epithelium and its endothelium. Irritant injury at this level leads to a nonspecific pattern of *diffuse alveolar damage* (DAD) similar to that seen from a variety of different causes (see Chapter 8). The pathologic changes in fatal cases of irritant lung injury include focal and confluent areas of edema with protein-rich fluid in the alveolar spaces, hyaline membrane formation, and denudation of the alveolar epithelium. In addition, mucous membranes of the bronchial and bronchiolar walls may be denuded or destroyed. Pulmonary hemorrhage may be seen in irritant lung injury but is typically not the dominant clinicopathologic manifestation; prominent pulmonary hemorrhage should raise suspicion of other toxicant- or non–toxicant-mediated syndromes[15] (see Chapter 94).

On the cellular level, respiratory tract injury may be mediated through the deposition or formation of an acid, alkali, free radical, or other reactive chemical species. The precise cellular mechanisms of injury from irritant inhalants have not been fully delineated, even for relatively common irritants such as chlorine or the chemical warfare agent phosgene, substances for which extensive human and experimental animal data exist.[16–19]

OTHER PATTERNS OF RESPONSE

Acute irritant inhalation injury is the predominant, but not the only, pathophysiologic mechanism underlying acute toxicant-caused lung syndromes. In contrast to the anatomic distribution commonly seen in water-soluble, irritant chemical–related inhalant injury, it may be difficult to delineate a descending, hierarchical pattern from upper airway to lower lung injury following exposure to a diverse group of other agents. Many of these exposures, as with the water-soluble irritants, also lead to acute lung injury through nonimmunologic mechanisms (clinically, *acute respiratory distress syndrome* [ARDS]; pathologically, DAD), as detailed subsequently in this chapter. Other toxicant exposures produce various other syndromes of respiratory tract injury, such as heavy metal pneumonitis,[20] hydrocarbon aspiration,[21] or paraquat lung injury.[22,23] The inhalation fever syndromes are exceptions in that they do not involve obvious lung injury; the pathophysiology of this group of self-limited acute lung syndromes appears to be cytokine mediated.[24]

GENERAL MANAGEMENT PRINCIPLES

Symptoms and signs of acute inhalation injury can be delayed in onset. Following removal of the patient from exposure while safeguarding the rescuing personnel, the next most important management decisions include protection of the airway (i.e., preemptive intubation may be required to prevent precipitous airway obstruction from progressive airway edema) and treatment of hypoxemia. The nasopharynx and larynx may manifest injuries earliest because they are exposed to the highest concentrations of inhaled water-soluble toxicants. The upper airway may also be a primary target organ as a result of angioedema in selected toxicant ingestions.[25] Within a few hours of exposure, progressive airway edema, mucopurulent sputum production, and bronchorrhea may develop. Bronchoconstriction, peribronchial edema, and bronchial mucosal sloughing may produce atelectasis. In the distal airways and alveoli, epithelial and endothelial injury leads to permeability-induced edema, which can manifest ranging from mild interstitial edema to DAD. Pulmonary edema may be rapid following high-concentration toxicant exposure or may be delayed

up to 24 to 48 hours. Pneumothorax and pneumomediastinum can be acute complications of respiratory tract injury resulting from chemical toxicants.[26–31]

Acute toxicant lung injury manifest as DAD should be managed consistent with the basic management of acute lung injury from other causes. This includes utilizing lung-protective ventilation strategies for patients with ARDS and avoiding fluid overload.[32,33] Concomitant airway injury with acute bronchospasm often warrants treatment with bronchodilators because of the airway obstruction.

A beneficial role for systemic corticosteroids in the acute phase of irritant and other chemically mediated forms of acute injury to the lungs has not been established, either by controlled trials in humans or through studies using experimental animal models.[34,35] Inhaled steroids are more likely to have a better risk-benefit ratio in the therapy of acute inhalation injury (e.g., in the context of bronchospasm and concomitant use of bronchodilators, taking acute smoke inhalation injury as a paradigm).[36] Despite the lack of controlled evidence of efficacy, anecdotal reports of benefits of systemic corticosteroid use continue to appear.[30] For example, systemic corticosteroids may have a beneficial effect in the treatment of lung injury following zinc chloride inhalation.[31,37] Prophylactic antibiotic drugs have not proved to be efficacious in toxicant-induced lung injury; antibiotics should be reserved for those patients with clinical evidence of infection, including ventilator-associated pneumonia.[38,39] To date, convincing data do not support the use of other pharmacologic agents, such as antioxidants, in the generic treatment of toxic chemical lung injury, although this is the subject of experimental research.[34,40,41]

Certain exposure-specific management issues do occasionally arise. In paraquat-induced lung injury, for example, oxygen toxicity is a particular concern because of the specific mechanism of action of paraquat (i.e., high concentrations of oxygen may lead to more severe lung injury).[22] In addition, in paraquat-induced lung injury, immunosuppressive therapy has yielded some promising data but remains to be confirmed in randomized controlled studies.[23] Biologic therapy utilizing an anti-C5a antibody also has demonstrated promise for the treatment of paraquat-induced lung injury and the associated systemic inflammatory response.[42] In the case of certain metal toxins, chelation may have a therapeutic role, as is addressed later in relation to the specific exposures involved. Inhalation fever is self-limited, so the principal clinical management issue is to exclude other exposures with more serious outcomes.[24]

Nonspecific treatments for toxic lung injury include interventions to clear the airways of mucus, denuded mucosal tissue, and cellular debris. Such interventions may include chest physiotherapy, intrapulmonary percussive ventilation, inhalation of isotonic saline, aerosolized mucolytic agents such as *N*-acetyl cysteine, and, in some settings, therapeutic bronchoscopy.[43] Although a detailed discussion of mass casualty events is beyond the scope of this chapter, large-scale release of toxicant chemicals may result in widespread chaos and confusion that has the potential to overwhelm the public emergency system, including first responders and emergency departments (see also Chapter 59). A surge of highly exposed, acutely ill victims along with lower–exposure risk but anxious patients may present significant challenges to prehospital care and hospital-based emergency care.[44,45]

Companion animals (e.g., dogs, cats, and birds) often show symptoms and signs in advance of humans. An example of historical interest is that of coal miners bringing canaries into coal mines. This phenomenon may allow the clinician to identify occult exposure, test, and treat while human disease is mild or still subclinical.[45a]

CHRONIC SEQUELAE AND RESIDUAL EFFECTS

Persons surviving symptomatic exposure to acute irritants may have persistent structural and functional effects. Long-term consequences to the upper airways (nose, pharynx, and larynx) can be sequelae of acute inhalational exposures; upper airway complaints, including chronic rhinitis (reactive upper airway dysfunction syndrome, anosmia, and vocal cord dysfunction), have been reported.[46–50] Follow-up studies of more homogeneous populations evaluated after inhalation injury (with only a minority experiencing severe injury) suggest that airflow obstruction and nonspecific airway hyperresponsiveness are the most common persistent abnormalities of the conducting airways after irritant injury. Even so, epidemiologic data suggest that only a minority of those exposed will experience these outcomes.[51–53] The term *reactive airway dysfunction syndrome* has been applied to the persistence of airway reactivity after acute exposure to respiratory irritants.[54–57] The more general term *irritant-induced asthma* has also been used to describe this condition.[58,59] Insofar as this can represent a form of work-related asthma, it is addressed in Chapter 100.

Chronic injuries to the lower airways and lung parenchyma are unusual sequelae of acute inhalational exposure. Long-term follow-up evaluation after recovery from ARDS resulting from heterogeneous causes (predominantly associated with sepsis) suggests that residual deficits in lung volumes, airflow, and gas exchange may persist long after recovery.[60] *Bronchiolitis obliterans* (BO),[61–69] bronchiectasis,[9,68,70–73] and organizing pneumonia[74,75] may all develop, but are rare complications. Irritants, in particular nitrogen oxide and related exposures, have long been known to cause BO.[76] Yet even with nitrogen dioxide, BO is an infrequent event; for example, only one case was found in a series of 20 moderate to severe exposures.[62] The histologic manifestations of exposure-related bronchiolitis can include various subtypes.[63] Pathologically, acute or subacute irritant-induced bronchiolitis is usually characterized histologically as either proliferative bronchiolitis with organizing pneumonia (that is, a histologic pattern of organizing pneumonia) or constrictive bronchiolitis. The latter appears to be the pathologic correlate of diacetyl-caused popcorn worker's lung[2] and has been reported in one case of BO following exposure in the World Trade Center disaster,[77] in a case series of Iraq and Afghanistan military veterans (although no single toxic exposure has been implicated),[78] and in association with styrene-fiberglass boat construction, presumably with more indolent exposure, rather than acute exposure.[79] In addition to residual obstructive ventilatory deficits, restrictive deficits may also result from severe irritant inhalation injury.[70,80] There is also some indication that an isolated reduction in residual volume may be noted in the follow-up of such cases.[81,82] Finally, nonspecific respiratory signs and symptoms after

Table 103.2 Selected Toxic Agents Causing Pulmonary Responses After Acute Exposure

Agent	Common Exposure Scenarios	References
Acid aerosols	Plating; microelectronics; other manufacturing	123, 149–153
Acrolein	Structural or wildland fires; other combustion	292, 293
Ammonia	Industrial refrigeration leaks; fertilizers	9, 322, 326
Brevetoxin	Aerosolization of "red tide" toxin	311, 313
Bromine	Water treatment; chemical manufacturing	69, 328–331
Cadmium fume	Flame cutting of soldered or sheet metal materials	186–190
Chloramines and nitrogen trichloride	Bleach + ammonia mix; chlorination + ammonia	101–103
Chlorine gas	Gas leak; water treatment; bleach + acid mix	16, 87–96
Chlorine dioxide	Pulp paper bleaching	130, 131
Crowd-control agents (tear gas)	Military and police training and operations	174–177
Dimethyl sulfate	Industrial chemical yielding sulfuric acid	137, 138
Fluorocarbon polymers	Overheating polymers	145, 217, 223
Fluorocarbon sprays	Waterproofing and related aerosol sprays	256–260
Hydrocarbons	Aspiration of low-viscosity materials, "fire eating"	21, 267, 269, 275, 278
Hydrogen sulfide	Sewers and manure pits; fossil fuel and geothermal production	336, 340–342
Mercury vapor	Gold extraction, heating cinnabar	192–199
Methyl bromide	Pesticide fumigant	334, 335
Methyl isocyanate	Pesticide manufacturing	343, 345
Methyl isothiocyanate	Breakdown product of metam sodium fumigant	346, 347
Mustard gas	Chemical warfare agent	70, 155–157
Nickel carbonyl	Nickel processing, metal reclamation	200–204
Nitrogen dioxide	Silage; combustion; explosives; welding; nitric acid mixes	11, 62, 117, 118, 121
Organic dusts or aerosols	Contaminated dust or bioaerosol generation	24, 237, 242, 243
Organophosphates	Pesticide application; chemical warfare	170, 307
Ozone	Bleaching; water treatment; plasma welding	12
Paraquat	Herbicide skin contamination or ingestion	22, 282
Phosgene	Chlorinated solvent breakdown by-product	13, 18
Phosphine	Fumigation with aluminum or zinc phosphide, microelectronics	364–366
Sulfur dioxide	Refrigeration; cement manufacture; mining; pulp paper mills	10, 132–134
Tributyltin (bis[tributyltin] oxide)	Paint additive for mold inhibition	215
Vanadium	Ore processing; fossil fuel by-product, catalyst use	211, 212
Zinc chloride	Smoke bombs ("white smoke")	179, 183
Zinc oxide fume	Welding galvanized steel; brass casting	218, 219, 236

acute inhalation events can be somatic manifestations of psychological processes and can be further complicated by posttraumatic stress disorder comorbidity.[83–86]

SPECIFIC EXPOSURES

See Table 103.2 for a list of selected toxic agents causing pulmonary responses after acute exposure.

CHLORINE, CHLORAMINES, HYDROCHLORIC ACID, AND RELATED CHEMICALS

Among toxicants causing pulmonary responses, *chlorine* is a common and potent irritant inhalant accounting for substantial human morbidity.[17,87,88] Common forms of exposure include industrial leaks,[89,90] environmental releases primarily during transport,[91,92] water purification,[93] swimming pool–related events,[94,95] household cleaning product misadventures,[96] and even homemade chemical bombs[97] or intentional terrorist use.[98]

In the form of a yellow-green acrid gas, industrial and environmental releases typically have clear-cut exposure histories. Because the gas is heavier than air, higher contamination can be expected in low-lying areas (hence, its use in trench warfare in World War I).[99] Other environmental conditions, however, may supervene. Examples include one well-documented case of the gas rising along the heated outside wall of a factory where rooftop workers were exposed.[89] In another case, chlorine initially collected in a basement but then was sucked up into the central heating system of a dormitory.[100]

The history of exposure to chlorine may be less straightforward when the chlorine is generated after de novo generation from chlorine-containing products. Chlorine gas can be generated from liquid bleach containing hypochlorite or from dry powdered bleach containing chlorinated phosphate. In either liquid or powdered bleaches, the chlorine gas is liberated on contact with acids, which can be common in other household products (such as those containing muriatic [i.e., hydrochloric], phosphoric, or hydrofluoric acid[96]) or in industrial settings.[53] In contrast, mixing chlorine-containing products with ammonia leads to release of chloramines (monochloramine [NH_2Cl] and dichloramine [$NHCl_2$]) and related chemicals, especially nitrogen trichloride (NCl_3), chemicals whose irritant effects are attributed to in situ pulmonary reactions releasing chlorine, hypochlorous acid, and ammonia.[96,101,102] In aquatic venues, including swimming pools, inadvertent mixing of the chlorinated water with nitrogen donors can also happen, with potential irritant effects attributed to nitrogen trichloride in particular.[101,103] A report of a public aquatic venue mishap found that inadvertent mixing of sodium hypochlorite and hydrochloric acid led to toxic chlorine gas release resulting in a constellation of adverse health effects, including vomiting, coughing, and eye irritation, among several dozen affected bathers.[104] Chloramines evolved from mixing chlorine and ammonia should not be confused with Chloramine-T (sodium-*N*-chlorine-*p*-toluene sulfonamide), a disinfectant that can act as a chemical sensitizer leading to allergic asthma and other anamnestic responses.[105]

Irritant effects after inhalation of *hypochlorite* aerosols in confined spaces without a history of combining products (not an uncommon scenario when cleaning bathrooms) can also be associated with irritant effects. Similarly, in certain industrial operations, hydrochloric (hydrogen chloride in water) or hypochlorous acid aerosols are also respiratory irritants.

Chlorine exposure can also take place in specific industrial processes that use inorganic chlorine derivatives. Worthy of particular mention are chlorine dioxide (used in pulp paper processing),[106] chlorinated silanes (gases used in microelectronics),[107] reactive metal halides (e.g., titanium or antimony chlorides),[20] and thionyl chloride (which breaks down to yield hydrogen chloride and sulfur dioxide).[65,108]

For chlorine and related chemicals, there is a dose-dependent exposure-response relationship; that is, lung injury is largely a function of the dose of irritant gas entrained into the respiratory system. For chlorine, as for irritant gases generally, the dose response has been presumed to be equivalent for any given cross-product of concentration and exposure time (Haber's law), although experimental data indicate that this relationship may be more variable.[109]

All of these compounds appear to share a final common toxic pathway. As noted in the general discussion of acute toxicant inhalation, water solubility is an important determinant of the dose reaching the lower airways. For chlorine, chlorine dioxide, chloramines, and nitrogen trichloride, their lower solubility favors deeper penetration with a more effective delivered dose compared with an equivalent inhalation of agents with a higher solubility such as acid aerosols. Nonetheless, exposure to any of these compounds is associated with some degree of immediate mucous membrane and upper airway irritation. In fact, the absence of acute irritant effects is not clinically consistent with chlorine gas or related exposures.

Chlorine inhalation may manifest any of the full spectrum of respiratory tract irritant effects, from minor mucosal responses to upper airway responses to DAD.[89–99,110,110a] Persistent airway hyperresponsiveness after irritant exposure has been associated particularly with chlorine gas and chlorine-containing products, although this association may have more to do with the frequency of chlorine exposures than with any particular effect of chlorine on the airways.[16,43,58,59] Human experimental studies have provided inconsistent results about whether persons with underlying airway hyperreactivity may be more responsive to chlorine.[111,112]

Use of inhaled bronchodilators and inhaled steroids may be indicated for both acute and residual bronchospasm following chlorine inhalation, consistent with the general principles of management addressed previously. Although several case reports and series have touted the potential benefits of nebulized sodium bicarbonate inhalation in the acute treatment of chlorine or chloramine inhalation, the efficacy of this intervention has never been assessed in a controlled trial.[102,112,113] One small controlled trial administered inhaled bicarbonate 3 months or more after exposure in irritant-induced asthma and described some benefit.[114] Other potential therapeutics have been reported on the basis of published animal and human data, including intramuscular sodium nitrite, intramuscular ascorbic acid/deferoxamine, and sevoflurane (an inhalational anesthetic agent), although the efficacy of such interventions remains to be established.[115]

OXIDES OF NITROGEN, OZONE, SULFUR DIOXIDE, AND ACID AEROSOLS

These inhalants are major air pollutants; the effects of low-level exposure are discussed in detail in Chapter 102. When inhaled in high concentrations, these irritants can cause acute lung injury. Because of their lower solubility and thus their lower incidence of upper airway symptoms, ozone[12] and, even more commonly, nitrogen dioxide may be associated with a longer exposure with a greater predilection for lung injury.[116] With sulfur dioxide and acid aerosols, despite their high solubility, a sufficient intensity of exposure can also lead to DAD.

High-intensity exposure to *oxides of nitrogen* can take place through decomposition of organic matter and other sources. Examples of exposure scenarios include the following: nitrogen dioxide–induced lung injury among farmers (also known as silo filler's disease)[52,117,118]; use of internal combustion engines in enclosed spaces (with large outbreaks associated with ice resurfacing equipment used in indoor skating rinks)[11,119–121]; thermal degradation of polymers (e.g., in structural fires)[38]; toxicant gas produced by the detonation of explosives[67,122]; the release of gas through reactions of nitric acid breakdown in air or in reaction with metals or organic materials[123–125]; welding by-products, particularly when "gas-shielded" techniques are used (manual inert gas welding or tungsten inert welding)[124]; and the release of compressed nitrogen dioxide gas.[126] Historically, the detonation of explosives has been one of the most important sources of exposure to nitrogen oxides.[122] Work-related exposure to a mixture of nitric acid

and hydrofluoric acid, known as "pickling paste," used to clean welding joints in welded stainless steel construction, has been reported as a cause of ARDS.[127] Nitric oxide, an inhalant used therapeutically, breaks down to nitrogen dioxide in the presence of oxygen and thus must be monitored with appropriate delivery devices to avoid exposure to the potentially toxic nitrogen dioxide.[128]

High-intensity occupational ozone exposure is unusual, but it can happen with welding conditions similar to those associated with oxides of nitrogen.[129] More recently, ozone in water treatment and in pulp paper bleaching has also emerged as a health issue; in the latter industry, there is often concomitant exposure to chlorine dioxide.[130,131]

Important sources of exposure to high-level sulfur dioxide include mining and ore refining,[10] portland cement manufacturing,[132] sulfur treatment of fruit,[133] and industrial releases.[134] Sulfur dioxide has been and continues to be important in sulfite process pulp paper processing, where acute gas releases are superimposed on long-term lower-level exposure.[130,131,135] In the past, sulfur dioxide was also a common refrigerant.[136]

In ambient air pollution, sulfuric acid is an acid aerosol of primary concern; in various occupations, sulfuric acid can also be encountered at high levels. Workers can be exposed to sulfuric acid through both direct use and the breakdown of a highly toxic industrial chemical, dimethyl sulfate.[137,138] Certain other inorganic and organic acid vapors and aerosols are also important potential causes of acute lung injury, including chromic,[139] acetic,[140] formic,[141] and hydrofluoric acids.[125,142,143] *Hydrofluoric acid* (hydrogen fluoride) inhalation, in addition to nonspecific irritant effects, can induce clinically significant hypocalcemia, which is thought to result from the formation of insoluble calcium fluoride.[144] Persons can be exposed to hydrofluoric acid in manufacturing of both microelectronics and phosphate fertilizers, in household use of hydrofluoric acid rust removal agents (the mixture of which with hypochlorite bleach can evolve both chlorine and hydrogen fluoride), and in the incomplete combustion (pyrolysis) of fluorinated polymers.[145] Exposure to hydrogen fluoride is a long-term problem in the aluminum smelting industry.[146] Hydrogen fluoride is also released as a breakdown product of sulfur hexafluoride, an electrical insulating liquid chemical used in circuit breakers, cables, capacitors, and transistors.[147]

MILITARY AND CROWD-CONTROL AGENTS

Unfortunately, chemical warfare agent exposures are not of mere historical interest.[99,148,149] Not only can sporadic exposures result from contact with a discarded ordnance,[150] but also, and more importantly, exposure can be widespread through the use of chemical warfare agents in acts of terrorism or in conventional military conflicts. Such risks have raised the specter that the diagnosis and management of such toxicants will again become clinically relevant. Several reviews have addressed general aspects of this question.[151–153] The goal of this section is to address individual chemical agents, including other military and crowd-control agents that are not warfare chemicals per se, with a focus on their respiratory toxicity. Biologic warfare agents of relevance to the respiratory tract are covered elsewhere (see Chapter 59).

Sulfur Mustard

Of the major World War I chemical weapons, only sulfur mustard (so called "mustard gas," although not a true gas in physical state) has subsequently been used in warfare. Classified as a vesicant because of blistering induced by skin contact, mustard gas inhalation causes severe respiratory injury. Largely on the basis of the Iranian experience of their Iraqi war veterans, sulfur mustard survivors can exhibit residual tracheobronchitis, asthma, bronchiectasis, bronchotracheomalacia, BO, and fibrosis.[70,154–157] Nitrogen mustards were sulfur mustard derivatives originally developed for military purposes but later applied medically; nonetheless, occupationally related acute lung injury has been reported through industrial release.[158]

Phosgene

Another World War I toxicant gas, phosgene, currently is encountered as a chemical industry process chemical and as a thermal breakdown product or ultraviolet photoreactant of chlorinated solvents (e.g., methylene chloride).[13,159] An occult cause of exposure can be inadvertent phosgene production from welding metals "degreased" with solvents.[129] Phosgene is the prototypical deeply penetrating inhalant exhibiting a delayed onset of symptoms (12 to 24 hours after exposure).[19,32,160–162] Even victims of phosgene exposure who eventually develop fulminant respiratory failure may exhibit only mild initial symptoms and have a normal chest radiograph in the first 2 hours after exposure.[163] Methyl chloroformate ($C_2H_3ClO_2$) has chemical and structural similarities to phosgene ($COCl_2$), is used in industrial chemical synthesis, and is also a potent inhalation irritant associated with severe lung injury.[164]

Chloropicrin

Chloropicrin, another World War I gas, is a low-threshold irritant currently encountered in chemical manufacturing and as a component of fumigants; it is added to fumigants for its irritant warning properties to deter persons from entering and remaining in structures during or soon after fumigation.[165–167]

Neurotoxicants

The modern chemical warfare armamentarium is dominated by systemic toxicants developed from organophosphate pesticides (which are discussed later in the section "Pharmacologic Syndromes"); the nerve agent VX is prototypical.[168,169] These highly lethal neurotoxins have important respiratory effects, including manifestations of both muscarinic receptor stimulation (bronchorrhea and bronchospasm) and nicotinic receptor depolarization blockade (respiratory muscle paralysis); treatment is based on reversing enzyme inhibition and countering the effects of acetyl cholinesterase excess.[170]

Chloroacetophenone (Mace), Other Tear Gas Agents, and Zinc Chloride

Crowd-control agents ("tear gases"), as opposed to the war gases, are intended to incapacitate persons through immediate mucous membrane irritation.[171] The agents in greatest use worldwide are chloroacetophenone ("mace") and orthochlorobenzamalonitrile.[172,173] In addition to their

mucous membrane effects, these agents have also been implicated in lower respiratory injury and even in persistent effects following high-intensity exposures (e.g., in enclosed buildings).[174–177] Unlike tear gas, exposure to smoke bomb releases (sometimes referred to as "white smoke") can cause severe lower respiratory injury by exposure to the potent respiratory irritant, zinc chloride fume, created through a pyrotechnic reaction between hexachloroethane and zinc oxide.[178,179] Military, police, and others who are exposed, often during ill-conceived training exercises, are at risk.[29,178–183] In an analysis of 15 cases of overexposure to a hexachloroethane–zinc chloride smoke bomb during a military exercise, the serum zinc level correlated with later lung function impairment, a finding suggesting that serum zinc may serve as a biomarker of high exposure that may predict outcomes.[184]

TOXIC METALS

Inhalation of certain metal fumes or metal vapors can cause acute pneumonitis.[20] Dangerous exposures to toxic metal fumes arise in part because these agents are not immediately irritating, analogous to the delayed symptoms after phosgene or nitrogen oxide gas inhalation. Patients typically present in respiratory distress 12 to 48 hours after exposure. Indeed, the exposure history often remains occult unless aggressively pursued. Metal pneumonitis from these materials also can include fever as a clinical manifestation of this toxic syndrome. However, the term *metal fume fever* should not be used in this context.[185] The toxic mechanism generalizable in heavy metal pneumonitis is presumed to be inhibition of enzymatic and other critical cellular functions.

Cadmium, Mercury, and Nickel

The three metals most important in clinical lung injury are cadmium, mercury, and nickel (nickel in the form of nickel carbonyl). *Cadmium* exposure typically takes place through welding, brazing (high-temperature soldering), or flame-cutting metal, or in working with molten metal under conditions of inadequate ventilation.[186–189] In welding, brazing, and flame-cutting, the usual source of cadmium is the welding rod, brazing solder, or a metal coating, rather than the base metal itself.[129] In areas of the world where jewelry is made at a cottage industry level, cadmium use in silver working can present a particular exposure risk.[190,191]

Mercury is relatively volatile, and high levels can be generated effectively from many nonenclosed operations, most notably through heated metal reclamation processes (e.g., home refining of mercury-gold amalgams or reclaiming of mercury from electronic equipment).[192–199] Exposure has also been reported after burning mercury sulfide (Chinese red cinnabar) and mercuric oxide for medicinal purposes.[197] Chelation treatment for elevated systemic mercury typically is begun after the onset of pneumonitis, but its efficacy in ameliorating mercury pneumonitis has not been studied.[196]

Nickel carbonyl is an organic metal derivative and potent pulmonary toxicant, with exposure described during nickel refining, during manufacturing processes in which it is used as a catalyst or intermediate, and during metal recycling or reclaiming operations.[200–204] Cases of severe nickel fume inhalation from metal spraying operations that were nickel carbonyl free suggests that, under certain conditions, inorganic nickel also can cause acute lung injury.[205,206] The agent dithiocarb (diethyldithiocarbamate) has been used as a chelating antidote for nickel carbonyl pneumonitis, on the basis of supportive animal data, although its benefits are most clear-cut when it is administered soon after exposure (e.g., before the time clinical illness would be manifested); disulfiram has been suggested as a potential alternative treatment, although experimental data to support this practice are also weak.[207]

Other Metals

Other metals, including antimony, manganese, and beryllium, are sometimes cited as causes of acute lung injury consistent with metal pneumonitis, but there are few reports in the past 50 years providing documentation of such disorders.[9] A case report implicated copper dust inhalation as a cause of acute lung injury.[208] Osmium tetroxide is a potent respiratory irritant with terrorist weapon potential; fortunately, experience with human inhalation exposure has been limited.[209] Cerium oxide is another metallic exposure of theoretical concern because of its potential use as a fuel additive and its capacity to cause acute inhalation injury experimentally.[210]

Two other metal compounds are well-documented bronchial irritants in humans. Vanadium (typically as a metal oxide), which is encountered in metal processing and, in lower concentrations, as a fossil fuel by-product, causes acute bronchitis.[211] Among boilermakers, vanadium-rich fuel oil ash is suspected to be a key exposure related to acute respiratory symptoms.[212] In a single case report, high-intensity exposure to ash from an oil-burning furnace was associated with DAD; although vanadium was detectable in the residue, the toxic mechanism in this case was unclear.[213] In another case report, vanadium (as vanadyl pyrophosphate) was linked to pneumonitis.[214] Tributyltin (bis[tributyltin] oxide) is an organotin compound, which is an organic compound with one or more molecules of tin. Tributyltin, which is used as a mildew and mold retardant, is also an acute airway irritant.[215]

METAL FUME FEVER, POLYMER FUME FEVER, ORGANIC DUST TOXIC SYNDROME, AND OTHER INHALATION FEVERS

Certain febrile flulike pulmonary syndromes reflect similar clinical responses to a diverse group of acute inhalational exposures.[24,216] Their hallmarks are chills, fever, malaise, and myalgia, with onset 4 to 8 hours after intense inhalation of fumes or organic dusts.[24,185,217] Common respiratory signs and symptoms include cough or mild dyspnea, but chest radiographic opacities or hypoxemia are not seen and would be inconsistent with this disorder. Peripheral leukocytosis usually accompanies the syndrome; bronchoalveolar lavage shows a marked influx of neutrophils.[218–220] These syndromes are self-limited, resolving clinically within 12 to 48 hours. Inhalation fevers share a common feature of tachyphylaxis, with a blunted response to daily repeated inhalation (and hence the name "Monday morning fever" among both brass founders and cotton mill workers).[24,221,222]

Signs or symptoms of pneumonitis should suggest alternative, more serious diagnoses, such as cadmium pneumonitis,[187,188] HP (see Chapter 91), active infection (in the case of water-source aerosols), or inhalation of more toxic temperature-dependent fluoropolymer combustion by-products (which include hydrogen fluoride and perfluoroisobutylene, which is more toxic than phosgene).[223–225] Toxic pneumonitis caused by fluorocarbon-containing aerosol sprays is an exposure scenario distinct from polymer fume fever resulting from exposure to fluoropolymer combustion by-products or from acute lung injury and is dealt with separately (see the following section).

Metal fume fever is associated with zinc oxide inhalation from welding galvanized metal or brass working.[226] There is only limited clinical evidence that other metals (magnesium and copper) are capable of causing a similar response,[185,227] and experimental data further discount magnesium as a potential cause of fume fever.[228] Zinc oxide fume rarely has also been purported to cause an acute lung injury pattern in case reports of welding-related illness, but the likelihood of cadmium or nitrogen dioxide coexposures makes this uncommon association questionable.[229] Further, controlled experimental human exposure data do not support this disorder as a zinc oxide inhalation effect.[219]

Polymer fume fever is associated with thermal breakdown products of fluoropolymers (e.g., polytetrafluoroethylene [Teflon] and related materials).[217,230–232] The pathophysiologic mechanisms underlying the metal and polymer fume fever syndromes have not been established, but research suggests that pulmonary cytokines may play a key role.[233–236]

Organic dust toxic syndrome (ODTS) is associated with inhalation of materials contaminated with thermophilic bacteria and fungal spores, including wood chips,[237] straw,[238] silage,[239] seeds,[240] grains and flour,[241] and textile raw materials.[222] The increasing industrialization of agricultural processes, especially the use of animal confinement techniques or so-called *concentrated animal feeding operations*, is an additional source of exposure leading to ODTS, although these same settings also can produce irritant gases such as hydrogen sulfide and ammonia.[242,243] ODTS has gone by various names, including pulmonary mycotoxicosis,[244] silo unloader's syndrome,[239] and mill fever.[245] One of the best documented historical outbreaks of ODTS was among individuals who worked with contaminated cotton mattresses.[222] Inhalation of aerosols from contaminated water sources produces a self-limited febrile syndrome similar to ODTS. Some of these outbreaks are attributable to inhalation of *Legionella* species without actual infection (i.e., without clinical evidence of pneumonia) and are referred to as "Pontiac fever."[246–248] Contaminated aerosols causing inhalation fever syndromes can originate from saunas or hot tubs,[249,250] commercial (industrial) humidifying systems,[251,252] and metal machining cooling fluids.[253] Along with these heterogeneous exposure scenarios, various different names have been used for these syndromes, including humidifier fever,[252] sump bay fever,[254] and bath water fever.[249] Many of the same occupational and environmental exposures that cause ODTS can cause HP and respiratory tract infections, thus complicating diagnosis and treatment. Certain features help to distinguish ODTS from HP or infection. For one, ODTS is self-limited, typically resolving spontaneously. For another, ODTS has a relatively high attack rate over a fairly short time period; that is, in contrast to HP in which host susceptibility, including sensitization, plays a role in disease pathogenesis, ODTS does not require sensitization and may develop in a high proportion of all exposed individuals. As with metal fume fever and polymer fume fever, cytokines are presumed to be key mediators of the ODTS and water-borne aerosol–related inhalation fevers, with endotoxin and related factors being key exposure variables.[24,255]

FLUOROCARBON AEROSOL SPRAY PNEUMONITIS

Acute lung injury following inhalation exposure to commercial fluorocarbon-containing aerosol products is an important emerging syndrome first reported in the early 1990s.[256] This syndrome is distinct both from fluoropolymer fume fever, as previously discussed, and from exposure to irritant by-products from higher-temperature thermal breakdown of such polymers. A key feature of fluorocarbon aerosol pneumonitis is the onset of symptoms within several hours after using a spray product containing fluorocarbon polymers. Exposure can take place in an occupational setting (e.g., construction) or, commonly, from home use of over-the-counter products. These exposures can be relatively brief, with varying degrees of ventilation; importantly, exposure need not be in an enclosed space. Victims usually do not recall previous exposure; there is nothing in the condition to suggest a hypersensitivity mechanism. Application of multiple types of fluorocarbon-containing products has been linked to outbreaks; although waterproofing leather and fabric sprays have dominated the reports, other products include floor stain protector, rustproofing spray, grout sealer, and ski wax.[256–263] The clinical presentations manifest a range of severity consistent with varying degrees of nonspecific acute lung injury, including ARDS.[264] Management is based on standard supportive care. The various descriptive labels for this condition, such as "horse rug lung" and "hill walkers' lung," can obscure the consistent pattern of the syndrome.[259,265]

HYDROCARBON PNEUMONITIS AND FIRE-EATER'S LUNG

Hydrocarbon pneumonitis can follow oral ingestion of hydrocarbons and associated hydrocarbon aspiration. In the pediatric high-risk age group, aspiration can take place during ingestion from non–tamper-proof containers typically involving mineral spirits, mineral seal oil (common in furniture polish), lamp oil, kerosene (paraffin), turpentine (pine oil), gasoline, and lighter fluid.[21,266–268] In adults, hydrocarbon aspiration associated with fuel syphoning represents an occupational hazard among diesel-powered heavy equipment and tractor operators.[269–271] Even though these substances have systemic toxic effects such as central nervous system depression, life-threatening complications of ingestion are predominantly the result of concomitant hydrocarbon aspiration and subsequent pulmonary compromise, making the lung the target organ of concern in hydrocarbon ingestion. Pneumatocele is a recognized complication of hydrocarbon pneumonitis.[272] In contrast

to aspiration hydrocarbon pneumonitis, the toxicity of hydrocarbon (solvent) vapor inhalation manifests primarily in either the central nervous system or the heart. Major pulmonary damage associated with acute hydrocarbon exposure by inhalation is unusual but has been reported.[273] Importantly, the lung also appears to be the target organ for the toxicity of intravenously administered hydrocarbons, an unusual but well-documented suicidal scenario.[274]

Fire-eater's lung is an important variant of hydrocarbon pneumonitis.[275–277] This syndrome typically involves adolescents or young adults who become exposed through mishap during flame-blowing performances using a variety of different flammable materials. In addition to kerosene and gasoline, the toxicants include jet fuel and, in France, an aromatic hydrocarbon-enriched petroleum-distillate called "kerdan."[278,279] There has also been a case of citronella oil aspiration in a fire-eater.[275] As with hydrocarbon pneumonitis in children, fire-eater's lung can also be complicated by pneumatocele.[280] Although the term *acute lipoid pneumonia* has been used to refer to the fire-eater's lung syndrome, as well as in other acute aspirations, this is a misnomer.[281]

In both childhood and adult pneumonitis, hydrocarbons are aspirated at the time of the initial ingestion or subsequently with vomiting. The low viscosity of an ingested hydrocarbon is considered a major factor promoting aspiration, presumably for mechanical reasons.[21,267] Although it has been theorized that hydrocarbon toxicity may involve disruption of surfactant, the chemical pneumonitis of the syndrome appears to be nonspecific.

PARAQUAT

Paraquat is a widely used herbicide and a potent toxin. Ingestion, rather than inhalation, is the typical route of exposure associated with human toxicity. There have been systemic reactions following skin exposure after direct exposure to the skin (e.g., soaking of the skin with paraquat) or when the skin integrity has been breached (e.g., preexisting skin lesions or burn). The theoretical risk of smoking contaminated materials has never been established.

Most paraquat deaths result from suicidal intent.[22,282,283] Paraquat ingestion is a relatively uncommon method of suicide in the United States, but its incidence is greater in a number of other countries, perhaps related to patterns of crop utilization and ease of access.[282,284] Although paraquat ingestion leads to acute gastrointestinal tract necrosis and multiorgan failure, the lung is the target organ for toxicity among those surviving the immediate postingestion period. Diquat, a related dipyridyl herbicide, does not cause the lung injury associated with paraquat, although poisoning can lead to renal failure and cerebral hemorrhage.[285]

The pulmonary toxicity of paraquat, in contrast to its gastrointestinal effects, does not reflect caustic irritant injury. The major lung effect of paraquat toxicity is the development of pulmonary edema, usually observed 24 to 48 hours after ingestion. The pulmonary edema may evolve to a condition resembling ARDS, associated with histopathologic findings similar to those of DAD, which may progress to an accelerated, chemically induced pulmonary fibrosis. After stabilization following acute multiorgan toxic effects, disease progression is marked by rapidly worsening respiratory distress, hypoxemia, and a restrictive ventilatory defect, with decreased lung compliance and diffusing capacity, ending in death from ventilatory failure within days to weeks.[22,282] Survivors may demonstrate modest and slow improvement in lung function.[286]

The mechanism of paraquat toxicity is attributed to the generation of superoxide radicals that may be partly iron dependent. Consistent with an oxidant mechanism, supplemental oxygen and radiation therapy may worsen the outcome; there are no known antidotes for paraquat poisoning, and enhanced elimination such as by hemoperfusion has not demonstrated a clear benefit.[22,282] Plasma paraquat levels can be determined and may have a use in predicting outcome.[287] Data suggest a possible therapeutic benefit from immunosuppression, but this awaits confirmation through controlled clinical trials.[23,282] Death results from multiorgan failure, which usually happens within 1 to 2 weeks but may be observed up to 6 weeks after ingestion.

SMOKE INHALATION

The generic term *smoke inhalation* includes potential exposure to a wide array of substances because of the complex chemistry of heat decomposition and pyrolysis.[38,288] *Pyrolysis* refers to the thermal decomposition of organic material without the involvement of oxygen and is a common component of burning buildings where oxygen is limited. Pyrolysis produces a variety of gases and a physical product such as charcoal. Although anoxia from carbon monoxide, cyanide, and oxidants represents a major manifestation of toxic insult from acute smoke inhalation, this nonpulmonary target organ effect is not covered here. Nonetheless, some chemical irritants produced as pyrolysis by-products do have significant potential pulmonary toxicity. In contrast to thermal injury to the respiratory tract, which typically is limited to upper airways, with laryngeal edema the major potential medical management problem,[289,290] inhalation of the smoke from fires can affect the entire respiratory tract through irritant injury.

In certain cases, irritant chemicals are released in fires as preformed substances, but, most commonly, the toxins are formed de novo. These irritants are produced by the thermal degradation of both natural and synthetic polymers. The predominant by-products of heat breakdown are determined by the nature of the polymers consumed, the temperature of the fire, and the availability of oxygen.[291]

Generally, polymers do not break down to their monomer precursors, although residual monomers can evolve under certain circumstances. For example, when polyvinyl chloride is burned, hydrogen chloride is released rather than the monomer, vinyl chloride. Many of the specific chemical irritants that can be released as common thermal breakdown by-products are addressed elsewhere in this chapter. These include the following: hydrochloric acid (hydrogen chloride), hydrofluoric acid (hydrogen fluoride), and other acids; ammonia; phosgene; and oxides of nitrogen. The zinc chloride "smoke" of smoke bombs (in contrast to the heterogeneous character of "natural smoke") was discussed previously.

Aldehydes merit specific attention. They are a common cause of high-intensity irritant lung injury from the smoke from fires. These chemicals include formaldehyde,

acetaldehyde, and acrolein. The most severe irritant, *acrolein* (CH_2=CHCHO), is least familiar to health care providers. Acrolein, a highly reactive chemical and key toxicant in smoke inhalation injury, is formed as an important pyrolysis product of both synthetic (e.g., acrylic) and natural polymers.[292,293] In addition to de novo formation as a combustion by-product, acrolein is also intentionally manufactured and used as a pesticide; its use as an aquatic herbicide to facilitate water flow in irrigation canals can lead to human inhalation exposure with irritant effects.[294]

The general considerations concerning irritant exposure discussed previously, including air concentration and water solubility, come into play in smoke inhalation. These factors are further complicated by the potential interactive effects of multiple simultaneous exposures, as well as the modifying impact of physical cofactors such as airborne respirable particulates (e.g., soot) that may serve as adsorbent carriers facilitating deep lung penetration of toxicants. In practice, detailed exposure data delineating the irritant contents of a specific smoke exposure are rarely available. Information that may help to elucidate exposure conditions include identity of the products involved (e.g., specific synthetic polymers, if known), history of inhalation within an enclosed or confined space, evidence of thermal injury, and carboxyhemoglobin and methemoglobin levels as markers of inhalation severity based on other concomitant exposures (carbon monoxide and oxidants, respectively).

Firefighters (both urban and wildland) and nonoccupationally exposed victims of irritant smoke inhalation have proved to be important groups in which to study acute inhalational syndromes. Large-scale conflagrations (e.g., urban "wildland" fires[295,296]) can expose substantial numbers of persons to irritant combustion by-products, as can smoke drift from intentional burning of agricultural residue. Wildfire health hazards can be expected to increase as climate change creates longer, warmer, and drier seasons. Studies of such populations after smoke inhalation have demonstrated acute and persistent airflow obstruction and increased nonspecific airway hyperresponsiveness.[297–305] Bronchiectasis and BO have both been associated with combustion by-product exposure.[66,68] The acute respiratory effects and potential sequelae of exposure to the plume generated by the destruction of the World Trade Center may relate to other factors such as alkaline (high-pH) dust from concrete, gypsum, and glass fibers, rather than to standard smoke particulate.[306]

PHARMACOLOGIC SYNDROMES

Certain natural and synthetic chemical exposures affect the lung by specific mechanisms consistent with known pharmacologic actions. These chemicals are site specific for key cellular functions leading to adverse respiratory effects. As noted previously, the most potent chemical warfare agents act through acetyl cholinesterase inhibition, with profound impacts on respiratory function.[168,169] Similar, albeit less potent, agents have widespread uses as agricultural chemicals. Both organophosphate and carbamate pesticides lead to respiratory compromise as a principal toxic effect. For example, in one case series, a considerable number of poisonings from these pesticides led to respiratory failure, accompanied by a high case-fatality rate; in contrast, all the patients without concomitant respiratory failure survived.[307]

Inhaled capsaicin, of interest as a research tool to study substance P–mediated effects, is associated with cough in occupational settings (e.g., in chili pepper processing).[308] When used as a personal defense spray, respiratory irritation has been reported, although ocular problems are more common.[309,310]

Brevetoxin is a toxin produced by dinoflagellates associated with "red tides." Environmental inhalation exposure from airborne aerosols of red tide resulting from wind and surf action causes cough, sneeze, and wheeze.[311–313] For lifeguards, brevetoxin health effects represent a source of occupational respiratory morbidity, including work loss.[314] The toxin appears to act by stimulating sodium channels in the lung.

Palytoxin is another natural toxin produced by certain dinoflagellates, as well as by sea anemones and zoanthid corals. Human exposure may result from ingestion, dermal contact, or inhalation. Respiratory illness attributable to palytoxin inhalation has been described among aquarium hobbyists and among individuals in proximity to algal blooms in ocean water.[315] The palytoxin inhalational toxic syndrome includes dyspnea, cough, fever, and tachycardia.[316]

Respiratory irritation may also be a manifestation of *Pfiesteria* dinoflagellate toxin inhalation (although potential neurotoxicologic effects have been of greater concern).[317,318]

OTHER INHALANT EXPOSURES

Ammonia

Anhydrous ammonia is a gas at room temperature and ambient pressure, although ammonia is more commonly encountered in aqueous form, as in cleaning solutions. Potential sources of ammonia gas exposure include incidents in the chemical industry and in hazardous transportation, commercial refrigeration systems, and farming (e.g., fertilizer).[9,318–323] Anhydrous ammonia has also been released from illicit methamphetamine laboratory operations, although such exposures are often in the context of conflagrations with concomitant thermal burns and other coexposures.[324,325]

Ammonia has prominent irritant properties, such as burning eyes, that warn the exposed individual to escape. It is linked with lung injury chiefly in settings of overwhelming exposure or where immediate escape has not been possible. Both asthma and bronchiectasis have been documented after ammonia exposure.[9,322] Acute ammonia exposure has also been reported to have residual upper airway effects, including decreased olfactory acuity.[46] Death may result from laryngeal edema and airway obstruction, acute pulmonary edema, or complications of the pneumonic process (e.g., bacterial superinfection). Lung transplantation following ammonia inhalation has been reported, including in a patient who had severe lung injury following an explosion in a poultry plant.[326,327]

Bromine and Methyl Bromide

Bromine is an irritant halogen. It is usually handled as a liquid rather than as a gas, but it vaporizes readily. Sources of bromine exposure other than environmental releases include chemical synthesis and water purification.[69,328–331] Bromine is a more potent irritant than chlorine and is approximately 100 times more irritating than ammonia.[332] In a murine model of bromine-induced lung injury, high heme levels, possibly released from dead inflammatory cells or sloughed epithelial cells, correlated with a spectrum of adverse sequelae, including lung edema, increased airway resistance, and lung inflammation. Therapeutic reduction of heme levels improved lung function and survival, thus suggesting a potential role for heme attenuation as a treatment for victims of bromine inhalation, although this has not been studied in humans.[333]

Methyl bromide is a major industrial fumigant with far-greater potential for public exposure. Methyl bromide is also a potent respiratory irritant, but the central nervous system may represent the more important target organ in typical exposures.[334,335]

Hydrogen Sulfide

Hydrogen sulfide is a common by-product of petroleum extraction and refining, as well as a potential hazard from the breakdown of organic materials (hence, its common name, "sewer gas"); overexposure can result from work in confined spaces, submersion in manure pits,[336] or proximity to geothermal or volcanic sources.[337] Asphyxial death of several tourists exploring a volcanic crater was attributed to inhalation of mixed gases containing both hydrogen sulfide and carbon dioxide.[338] Hydrogen sulfide is a respiratory irritant, but it is an even more potent cytotoxic asphyxiant, impairing cytochrome oxidase and cellular respiration. Therefore, in cases of severe hydrogen sulfide exposure, rapid cardiovascular collapse and death often overshadow any pulmonary organ effects, although an acute lung injury pattern can be present in persons surviving long enough to receive intensive supportive care; irritant symptoms as a predominant feature may be of greater relevance in lower-intensity exposures.[337,339–342]

Methyl Isocyanate and Methyl Isothiocyanate

Methyl isocyanate (MIC) use is restricted to a narrow industrial application in the synthesis of pesticides. The mass fatalities at Bhopal, India, make MIC an important toxin for historical reasons. The toxicity of MIC was the result of its severe irritant properties leading to pulmonary edema.[343–345] No cyanide-mediated mechanism was involved. *Methyl isothiocyanate*, a breakdown product of the soil fumigant metam sodium, is an irritant chemically related to MIC that was also involved in a mass exposure episode, although less severe than the MIC release at Bhopal, and has also been associated with respiratory symptoms following agricultural application.[346,347] The isocyanates associated with urethane, such as toluene diisocyanate, diphenylmethane diisocyanate, and hexamethylene diisocyanate, are pulmonary irritants but are primarily of concern because of their induced sensitization (see Chapter 100).

MISCELLANEOUS EXPOSURES

Numerous other occupational and environmental agents result in acute pulmonary syndromes. Examples of such exposures include the following: diethylaminoethanol and cyclohexylamine (both anticorrosive boiler additives)[348,349]; amitrole and glyphosphate (both common herbicides)[350,351]; thiram (used as a fungicide in agriculture and as a vulcanization accelerator in the rubber industry)[351a]; sodium azide (used in a variety of chemical applications but important as a potential inhalant through automobile airbag deployment)[352]; diazomethane, which is explosive but also highly toxic to the lung, with a delayed onset similar to that of nitrogen dioxide[353,354]; diborane (an irritant gas used in manufacturing microelectronic equipment)[355,356]; barium (inhalation can cause bronchospasm and respiratory muscle weakness in addition to life-threatening hypokalemia)[357]; and hydrogen selenide (an irritant gas used in several industrial processes, as well as being a potential metal processing by-product).[358,359]

An outbreak of severe lung injury in Korea, particularly among young, peripartum women, was linked to treatment of room humidifier water with two biocides: polyhexamethylene guanidine and oligo(2-(2-ethoxy)ethoxyethyl) guanidinium chloride.[360,361] The overall mortality rate in what has been labeled "humidifier disinfectant–associated lung injury" is reported to be more than one-third of cases, with three-fourths of those patients requiring mechanical ventilation dying of their injuries.[362] After the original offending product was removed from the market, humidifier disinfectant–associated lung injury was described in twin sisters exposed to chloromethylisothiazolinone and methylisothiazolinone, thus broadening the spectrum of disinfectants associated with toxic lung injury.[363]

Phosphine is an important agricultural fumigant with pulmonary and systemic toxicity, which is generated on site as a gas given off by moisture coming in contact with solid-form aluminum or zinc phosphide (e.g., in grain storage facilities or railway grain transport cars, where bystanders can be exposed).[364,365] Ingestion of the parent material by animals can also lead to exposure among treating veterinary personnel.[366] Phosphine also has industrial applications, particularly in the production of microelectronics.

Acetic anhydride (used in making epoxy and other resins) has also been associated with acute lung injury following acute inhalation.[367] A distinctly different pattern of injury is associated with a related epoxy chemical, trimellitic anhydride, which causes severe pulmonary hemorrhage after subacute exposure.[15]

Carbon dioxide, although a bulk asphyxiant and not a respiratory irritant, causes shortness of breath and induces tachypnea; persons can be exposed through natural geologic sources and dry ice sublimation in an enclosed space.[368–370]

Baby (talcum) powder inhalation can cause pediatric acute pneumonitis within hours of heavy exposure; infant inhalation of nontalcum powders has also led to pneumonitis.[371–373]

Paraphenylenediamine is a dye used to color hair and can also be admixed with henna as a temporary tattooing agent; its ingestion as an agent of self-harm is common in

TABLE 103.3 Useful Resources for Information About Specific Toxins

- The Household Products Database (https://healthdata.gov/dataset/household-products-database) is a consumer guide that provides information on the potential health effects of chemicals contained in more than 7000 common household products used inside and around the home.
- WISER (Wireless Information System for Emergency Responders) (http://wiser.nlm.nih.gov) is a system designed to assist first responders in hazardous material incidents.
- The EPA CompTox Chemicals Dashboard (https://comptox.epa.gov/dashboard/) provides access to multiple types of data, including physicochemical properties, environmental fate and transport, exposure, usage, in vivo toxicity, and in vitro bioassay.
- The ECOTOXicology knowledgebase (ECOTOX (https://cfpub.epa.gov/ecotox/) is a comprehensive knowledgebase providing single-chemical environmental toxicity data on aquatic life, terrestrial plants, and wildlife.
- The ATSDR Toxic Substances Portal (https://www.atsdr.cdc.gov/) provides information on toxic substances and their health effects.

Asia and Africa. In addition to rhabdomyolysis and renal damage, this chemical has a particular propensity to cause angioedema leading to airway obstruction.[25]

Naturally occurring sources of exposure can also be associated with acute and subacute lung responses, although these syndromes are poorly characterized. Epidemiologically, *Stachybotrys chartarum (atra)* mold growth in water-damaged residential structures was initially linked to a cluster of cases of pulmonary hemorrhage in infants, although the association was later retracted in a follow-up review by the U.S. Centers for Disease Control and Prevention.[374,375] Other case reports have occasionally linked other molds or mold by-products with lung injury (as opposed to self-limited ODTS, discussed previously).[376]

Lycoperdonosis is a potentially severe, acute pulmonary syndrome following intentional inhalation (sometimes as a natural medicinal treatment) of puffball mushroom *(Lycoperdon)* spores; in addition to human illness, fatal inhalation in pet dogs is a well-characterized veterinary syndrome.[377–379] The pathophysiology of the syndrome is not understood, but its high attack rate with heavy exposure suggests a toxic rather than an allergic or infective mechanism.

Beginning in 2019, acute lung injury associated with "vaping" (use of electronic cigarettes or e-cigarettes) began to be widely observed.[380,381] These devices work by heating liquids to produce an inhalable aerosol. Such aerosols can contain multiple intended and unintended component toxicants, including potential thermal breakdown materials. The topic of vaping, as well as classic cigarette smoking lung effects, is covered in Chapter 65.

Additional information about toxicants and their effects can be accessed online from a variety of resources (Table 103.3).

Key Points

- Short-term inhalation exposures to toxicants have important effects on the lung as the target organ for damage.
- Acute lung toxicity results from a variety of exposures but nonetheless is manifest by a narrow repertoire of injury.
- Although modified by the solubility and other physical properties of the toxicant, injury largely depends on the intensity and duration of exposure.
- Extensive injury can lead to acute pulmonary edema and diffuse alveolar damage.
- Specific exposures of importance include chlorine, oxides of nitrogen, sulfur dioxide, acid aerosols, toxic metal fumes, and pyrolysis by-products.
- Aside from acute irritant or toxic lung insult leading to airway injury and diffuse alveolar damage, other patterns of acute responses include the inhalation fevers (which are self-limited and appear to be cytokine mediated) and certain target-specific effects, such as those elicited by cholinesterase inhibition.
- Exposure by *ingestion* of some substances (e.g., hydrocarbons and paraquat) can cause important acute pulmonary target organ toxicity.

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104 TRAUMA AND BLAST INJURIES

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THORACIC TRAUMA

INTRODUCTION

Among trauma victims, thoracic trauma is the second most common cause of death in the field and the third most common cause of death in patients who make it to the hospital. In civilian trauma, the most common mechanism is blunt trauma, and the most frequently encountered injuries (i.e., hemothorax and pneumothorax) are seen in 20% of patients.[1] The majority will require only tube thoracostomy for definitive treatment. However, up to 15% of these patients will require operative intervention,[1] whether immediate (resuscitative), urgent, or delayed. Overall mortality in patients with thoracic trauma is approximately 10%, with a low Glasgow Coma Scale score exerting the strongest influence on mortality.[1] Additional predictors of poor outcomes include increasing age, mechanism of blunt injury, increasing number of ribs fractured, and concomitant long bone extremity fractures.[1]

RESUSCITATIVE THORACOTOMY

Patients who arrive without signs of life may benefit from *emergency department thoracotomy* (EDT) or "resuscitative" thoracotomy, depending on the amount of time elapsed since the loss of vital signs (<15 minutes for penetrating trauma; <10 minutes for blunt trauma).[2,3] The goal of this procedure is to restore spontaneous circulation by rapid repair of intrathoracic injuries or release of pericardial tamponade and by occlusion of the descending thoracic aorta to divert perfusion to the brain and heart. Internal cardiac massage with injection of intracardiac medications may also be indicated. In cases of bronchovenous air embolism, clamping of the pulmonary hilum prevents further propagation. Because patients who undergo resuscitative thoracotomy should always proceed to the operating room for definitive repair, EDT should not be attempted without a surgeon immediately available. Rhee and colleagues[4] reported that the overall survival rate after EDT is 7.4%, with a survival rate of 15% among all patients with penetrating injuries and 35% among patients with penetrating cardiac injuries. In contrast, survival rates after EDT are very low (2%) after blunt traumatic arrest.[4]

It is important to perform an initial cardiac ultrasound examination because EDT can be considered futile if asystole is the presenting rhythm and pericardial tamponade is absent.[3] In patients with appropriate indications, aggressive efforts are justified because functional long-term outcomes in survivors are excellent. More than one-half of survivors are discharged home from the hospital, and more than 75% have normal cognition, are ambulatory, and have no posttraumatic stress disorder.[5] However, inappropriate EDT results in no survival benefit, wasted use of resources, and exposure of health care workers to needle-stick and bone fragment injuries.[6]

URGENT THORACOTOMY

Commonly accepted indications for urgent thoracotomy include any of the following: initial chest drain output of 1500 mL, greater than 1500 mL output in the first 24 hours after injury, more than 200 mL bloody output per hour for 3 consecutive hours, massive air leak (present during all phases of respiration associated with inability to reexpand the lung or affecting ventilation secondary to loss of tidal volume), or hemodynamic instability.[7] Rarely, a patient has sudden cardiovascular collapse or new neurologic symptoms, typically after the patient is placed on positive-pressure ventilation, which are consistent with air embolism, and require urgent thoracotomy.

DELAYED THORACOTOMY

Delayed thoracotomy is performed several days after injury in stable patients, usually for retained hemothorax, trapped lung, persistent air leak, or rib fixation (see also Chapters 110, 112, and 113).

THORACIC CAGE INJURIES

Rib Fractures

Rib fractures are seen in 10% of hospitalized trauma patients.[8,9] The morbidity of rib fracture pain is underappreciated; one-third of patients require hospitalization for pain control, and pneumonia develops in another one-third.[10] The true incidence of rib fractures is likely higher; a supine chest radiograph is 50% sensitive (at best) for detecting rib fractures. Chest *computed tomography* (CT) (eFig. 104.1) is much more sensitive and can also evaluate for other occult injuries.[8] In general, ribs tend to fracture at their weakest structural point (the posterior angle) or directly at the point of impact.[11] They are rarely the sole injury, and 50% of patients with rib fractures have other significant injuries.[10] In a patient with lower rib injury (ribs 9 through 12), abdominal solid organ injury (spleen or liver) should be considered.

Pressley and colleagues[12] developed a simple scoring system that was based on initial clinical findings (age, number of fractured ribs, severity of *pulmonary contusion* [PC], and unilateral vs. bilateral rib fractures) to predict the likelihood of requiring intubation and mechanical ventilation or *intensive care unit* (ICU) admission (Table 104.1). These investigators found that a patient with a total score greater than 7 had a high probability of death, need for ICU admission, and need for mechanical ventilation. Similarly, a total score greater than 4 predicted the need for a longer hospital stay and prolonged mechanical ventilation. Other studies have also found that an increasing number of rib fractures correlates with increasing ICU *length of stay* (LOS), hospital LOS, and mortality.[13,14] Additionally, vital capacity lower than 30% is independently associated with increased odds of pulmonary complication,[15] whereas a low incentive spirometry volume (500 mL or less) is predictive of acute respiratory failure.[16]

Treatment for most patients with rib fractures is supportive care, consisting of aggressive pain control and pulmonary rehabilitation. Deep breathing facilitates clearance of secretions to reduce the incidence of pneumonia. Analgesic options include oral analgesics (including opioids), intermittent intravenous analgesics, patient-controlled analgesia, *thoracic epidural analgesia* (TEA), intrapleural blocks, intercostal blocks, and *thoracic paravertebral blocks* (TPVBs).[17,18] Nonopioid analgesic options include acetaminophen, nonsteroidal anti-inflammatory drugs (including ketorolac), anticonvulsant agents such as gabapentin, and topical lidocaine patches.[19] Numerous small, single-center trials have reported that, compared with intravenous opioids, TEA results in less pain, improved pulmonary function, fewer ventilator days, fewer infections, fewer pulmonary complications, shorter ICU LOS, and shorter hospital LOS.[20–27] Furthermore, TEA may also attenuate the postinjury inflammatory response.[25–28]At present, TEA is the preferred analgesic modality for pain secondary to blunt thoracic injury.[29,30] However, there are other considerations. For one, TEA is underused, with studies reporting its use in less than 30% of eligible patients.[31] For another, epidural analgesia is not without risk; side effects include hypotension, epidural hematoma, urinary retention, and epidural abscess. Finally, TEA may be of benefit only in selected patients. For example, one pooled meta-analysis did not find any benefit of TEA for decreasing the duration of mechanical ventilation, ICU LOS, hospital LOS, or mortality.[32] For epidural analgesia to be of benefit, appropriate patient selection is paramount. Although the absolute number of fractured ribs is predictive of the need for TEA, it is important to examine the patient carefully to determine whether pain is severe enough to cause respiratory embarrassment. In fact, one review reported that, in older patients, epidural analgesia was associated with *increased* complications and prolonged LOS.[33] In sum, based on the existing evidence, the Eastern Association for the Surgery of Trauma conditionally recommends epidural analgesia and multimodal analgesia for patients with severe pain resulting from traumatic rib fractures.[29]

Another underused analgesic option is the TPVB or paravertebral block, which is easy to perform, has a greater than 90% success rate, and has a low incidence of side effects.[34,35] When successful, TPVB has been shown to improve pain scores and pulmonary function tests.[36] TPVB provides only unilateral pain relief and thus is usually used only for patients with unilateral rib fractures; however, it is also useful when there are contraindications to TEA, such as coagulopathy, spinal fractures, or altered mental status.

In addition to pain control, a formalized multidisciplinary pathway that includes aggressive respiratory therapy and nutritional support has been shown to decrease ventilator days, LOS, infectious morbidity, and mortality among patients older than 45 years of age and with more than four fractured ribs.[37]

Older patients with rib fractures are at especially high risk for complications: 15% require intubation, and pneumonia develops in up to 31%[31,38–40] (Fig. 104.1). In patients older than 45 years of age, morbidity sharply increases when more than four ribs are fractured.[41] Bulger and coworkers[31] reported that patients older than 65 years of age with fractured ribs have double the morbidity and mortality rates compared with younger patients with similar injuries. Bedside vital capacity measurement can predict hospital LOS and identify those patients requiring discharge to an extended care facility.[42]

Table 104.1 Chest Wall Trauma Scoring System*

Age (y)	Number of Rib Fractures
<45 = 1 point	<3 = 1 point
45–65 = 2 points	3–5 = 2 points
>65 = 3 points	>5 = 3 points
Score: _____	Score: _____
Pulmonary Contusion	**Bilateral Rib Fractures**
None = 0 points	No = 0 points
Mild = 1 point	Yes = 2 points
Severe = 2 points	Score: _____
Bilateral = 3 points	
Score: _____	
	Total Score: _____

*Total score is the sum of the scores of each of the 4 categories. A score >4 predicts a longer hospital length of stay; a score >7 predicts increased risk for mortality, admission to the ICU, and intubation/mechanical ventilation.
From Pressley CM, Fry WR, Philp AS, Berry SD, Smith RS. Predicting outcome of patients with chest wall injury. *Am J Surg.* 2012;204:910–914.

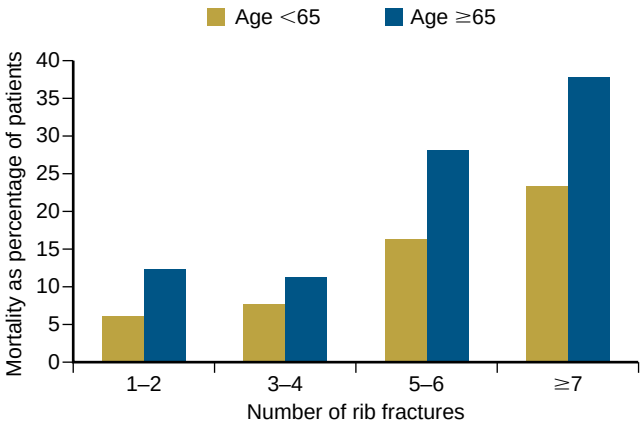

Figure 104.1 Relationship between the number of rib fractures and mortality. In a retrospective study of patients admitted to trauma centers, mortality increased with increasing number of rib fractures, an easily quantifiable measure of trauma severity. At each number of rib fractures, mortality for those patients older than 65 years was greater than that for those younger than 65 years. (From Stawicki SPG, Michael D, Hoey BA, et al. Rib fractures in the elderly: a marker of injury severity. *J Am Geriatr Soc.* 2004;52:805–808.)

Rib fractures continue to cause significant pain and disability long after hospital discharge. Typically, follow-up demonstrates that significant proportions of patients have chronic persistent pain and impairment of both work and personal life.[43,44] In one study, patients with rib fractures had more disabilities at 30 days after injury than did patients with chronic medical illness. These patients with rib injuries missed an average of 70 days of work.[45] Two months after injury, more than 75% of patients with rib fractures reported some form of disability.[46] Of patients who had blunt chest trauma and were admitted to the ICU, more than 60% reported chronic pain (requiring regular use of analgesics) 3 months after hospital discharge.[47] Interestingly, the single most important predictive factor for long-term disability after rib injury was the initial intensity of pain. The total number of rib fractures and the presence of bilateral injury was not predictive.[46]

Flail Chest. A flail chest, also known as stove-in or crushed chest, is the most severe form of blunt thoracic injury (see Chapter 131). The mortality associated with flail chest is as high as 40%.[48] Radiographically, it is defined as three or more consecutive ribs fractured in at least two locations. Clinically, a flail chest manifests as paradoxical incursion (rather than excursion) of the floating segment of chest wall during inspiration (Videos 104.1 and 104.2). Given the significant energy required to produce this injury, flail chest is almost universally accompanied by PC. Complications, especially pneumonia and *acute respiratory distress syndrome* (ARDS), are very common in this morbid condition.[49]

The management of flail chest has evolved over the past 50 years. Previously, it was believed that the paradoxical chest wall movement was the cause of the respiratory failure and hypoxemia. Now, it is understood that the respiratory impairment is secondary to the underlying pulmonary parenchymal injury. Historically, efforts were focused on correcting the paradoxical motion through external stabilization ("sandbagging") and, later, by internal pneumatic stabilization (i.e., positive-pressure ventilation).[50,51] Hence, in the mid-20th century, the predominant treatment method for all patients with flail chest was mechanical ventilation. Starting in the mid-1970s, some physicians found that these patients could be adequately managed without ventilatory support. At this time it was recognized that the underlying PC, rather than the chest wall instability, was the driving factor in outcome.[52] Currently, less than half of patients with flail chest require mechanical ventilation.[53] Abnormal gas exchange, not chest wall movement, should drive the decision to initiate mechanical ventilation.[54]

In the modern management of flail chest, optimal pain control is paramount. According to the Eastern Association for the Surgery of Trauma practice management guidelines,[55] TEA is the preferred pain treatment modality in the treatment of flail chest. When an epidural catheter is contraindicated, TPVB may be considered. If mild to moderate respiratory compromise is present, a trial of noninvasive ventilation in conjunction with TEA may be considered before proceeding to endotracheal intubation. However, in the absence of respiratory embarrassment, mechanical ventilation to treat paradoxical chest wall motion is not recommended.

The long-term outcome of flail chest managed nonoperatively is marked by disability, with 70% of patients reporting dyspnea and more than 50% reporting chronic chest wall pain.[55,56] Less than half of patients managed conservatively are able to return to work.[57] Surgical fixation of the floating chest wall segment has been practiced for decades in Europe and Asia, but it is underused in the United States, likely because of a combination of relative unfamiliarity with the procedure itself and unfamiliarity with the evidence supporting the procedure. In a survey of trauma surgeons, orthopedic surgeons, and thoracic surgeons, only 26% had ever performed or assisted on the procedure, and most were unaware of the published randomized trials supporting its use.[58] More recently, the use of surgical fixation for rib fractures has been increasing, although this change is inconsistent and varies according to region and by trauma center designation level.[59] Numerous techniques are described for rib fracture fixation, including the use of wire suture, staples, metal or absorbable plates, and screws.[10] A case-control study reported by de Moya and colleagues[60] concluded that rib fracture fixation significantly decreased the need for analgesia. Infection of rib fixation hardware is uncommon, reported to be approximately 2%.[10]

To date, three randomized controlled studies and a meta-analysis evaluating surgical fixation in patients with flail injury have been published supporting rib fracture fixation.[50] Tanaka and colleagues[61] reported that patients who underwent internal fixation of their fractured ribs had a shorter duration of mechanical ventilation, a lower incidence of pneumonia, a shorter ICU LOS, improved pulmonary function, and quicker return to employment. Granetzny and coworkers[62] also reported that patients randomized to surgical fixation had a decreased need for mechanical ventilation, a shorter ICU LOS, and a lower incidence of pneumonia. More recently, Marasco and associates[53] demonstrated that patients randomized to operative repair had a decreased ICU LOS and a reduced need for tracheostomy, with no difference in the duration of invasive mechanical ventilation. The optimal time for operative intervention is currently unknown, although a

multicenter observational study reported that early surgical fixation (<1 day) compared with late fixation (3 to 10 days after injury) was associated with decreased operative time and lower rates of pneumonia, prolonged mechanical ventilation, and tracheostomy.[63] No trial has compared surgical fixation with nonoperative management with TEA and chest physiotherapy. An economic analysis based on reported incidences of complications and outcomes concluded that, despite the additional cost of surgery, rib fixation for flail chest remained cost-effective compared with nonoperative management.[64] Long-term survey follow-up of patients treated by rib fixation revealed very high rates of satisfaction and return to work.[65]Currently, rib fixation is conditionally recommended by the Eastern Association for the Surgery of Trauma for the treatment of flail chest.[66]

Sternal Fractures. The most common cause of sternal fracture is motor vehicle crash (eFig. 104.2).[67] The presence of sternal fractures has traditionally been considered a marker of injury severity, especially in previous decades when seatbelt use was not as widespread. As such, some investigators advocate for hospital admission and close monitoring to rule out other serious injuries, such as blunt cardiac injury. Others report that sternal fracture by itself is not a significant cause of morbidity or mortality, and many believe that morbidity is mainly attributable to other associated injuries.[67–71] With increasing seatbelt use and more frequent use of diagnostic CT scanning, the incidence of sternal fractures has increased, whereas mortality has decreased.[72–74]

In the initial workup of a patient with sternal fracture, it is important to rule out a blunt cardiac injury by obtaining a 12-lead electrocardiogram and serum troponin level. A normal electrocardiogram and a normal initial troponin level essentially exclude the diagnosis of blunt cardiac injury, and no further workup is recommended.[75] However, arrhythmias, ST-segment changes, heart block, signs of ischemia, and elevated troponin levels are considered abnormal screening test results and should be followed by a confirmatory formal echocardiogram. Nuclear medicine studies are not useful in the diagnostic workup of blunt cardiac injury. As was discussed for rib fractures, adequate pain control is paramount for the treatment of sternal fractures. However, with isolated sternal fractures, pain can usually be treated on an outpatient basis.[76] Sternal fracture fixation is rarely indicated.

Clavicle Fractures. The clavicle is an S-shaped bone that acts as a strut between the shoulder and the axial skeleton. It protects the apex of the lung, brachial plexus, and subclavian vessels. Clavicle fractures follow direct impact to the extremity or chest and account for 44% of all fractures to the shoulder girdle.[77]

Fractures of the middle third are the most common, accounting for 69–81% of all clavicular fractures.[77] Diagnosis of clavicle fractures requires some type of imaging, usually radiography, although many fractures are visualized only on CT. Special radiographic views can be ordered to improve the evaluation for subtle fractures, fracture displacement, or sternoclavicular joint dislocations (eFigs. 104.3 and 104.4). These views include axillary views, 45-degree cephalic tilt, or a serendipity view, which is a 40-degree cephalic tilt.

Treatment generally is nonoperative, with a sling or figure-of-eight brace, and 2 to 6 weeks of immobilization, as well as avoidance of heavy lifting and contact sports for 4 to 6 months. Operative treatment is indicated for all open fractures, for skin tenting indicating a break that may result in an open fracture, and for any case with neurovascular compromise. A Cochrane meta-analysis of eight trials involving 555 patients examined the difference between conservative treatment and surgical fixation among patients with fractures of the middle third of the clavicle.[78] Unfortunately, because of heterogeneity between the studies and the overall high risk of bias, no strong conclusions could be made, and the investigators concluded that the decision to operate must be made on a case-by-case basis.[78]

LUNG PARENCHYMA INJURIES

Pulmonary Contusion

PC is a common injury, with an incidence of 30–75% in patients with blunt thoracic injury[55] and up to 17% of all trauma admissions. PC is most common after a blunt mechanism of injury, but it can also manifest adjacent to a missile tract through lung parenchyma. At the microscopic level, the contused lung displays edema, alveolar and intraparenchymal hemorrhage, and atelectasis, which results in intrapulmonary shunting, ventilation-perfusion mismatch, and decreased lung compliance.[79] This manifests as hypoxemia, hypercarbia, and increased work of breathing. The full effects of PC may not be obvious immediately; however, clinically significant PC becomes apparent within 24 hours. The natural history of PC is progressive dysfunction over the first few days and resolution within a week.[80]

Severe PC can produce systemic effects. Animal studies demonstrate that unilateral contusion can lead to capillary leak in *both* ipsilateral and contralateral sides, with increased edema and accumulation of inflammatory cells.[81] Inflammatory cytokines are increased both locally and systemically, and there is evidence of global immune dysfunction.[82–85] Additionally, PC may prime the immune system for an exaggerated response to a subsequent second hit, such as infection[81,86] (Fig. 104.2). Trauma patients with PC have twice the rate of ventilator-associated pneumonia as those without PC.[87] At 6 years after injury, more than half of patients with PC have evidence of lung fibrosis on CT scan,[88] and long-term lung function can be compromised.[43]

Because not all PCs are clinically significant, several groups have attempted to identify factors predictive of outcome. De Moya and associates[89] developed a simple scoring system, combining the initial CT findings, Glasgow Coma Score, and number of fractured ribs, to predict the need for mechanical ventilation. Interestingly, in this study, less than one-third of all PCs were evident on the initial chest radiograph (eFig. 104.5).[89] Other investigators have questioned the significance of occult PC (i.e., apparent only on CT; eFig. 104.6). In a prospective study of 255 patients with PC, Deunk and colleagues[90] reported that patients with occult PC fared no worse than those without PC, whereas patients with PC seen on both chest radiograph and chest CT scan had significantly worse outcomes. Others have attempted to correlate PC size (as a percentage of total lung volume) with outcomes. Studies have demonstrated that patients with PC volume greater than 20% of total lung volume are at increased risk for requiring mechanical ventilation, developing pneumonia, and developing ARDS.[91]

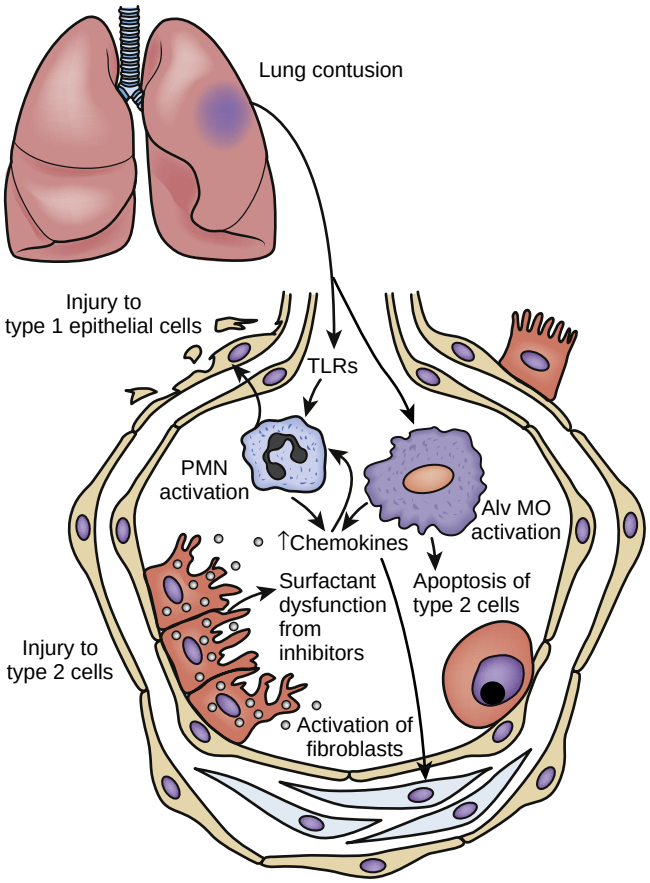

Figure 104.2 Inflammatory effects following pulmonary contusion. In the diagram, the potential interactions of the cells and mediators of the innate inflammatory response to contusion are shown. Although this inflammatory mechanism may amplify the injury of the contusion, it may also provide potential targets for therapeutic intervention. Alv MO, alveolar macrophage; PMN, polymorphonuclear neutrophil; TLRs, toll-like receptors. (Modified from Raghavendran K, Notter RH, Davidson BA, et al. Lung contusion: inflammatory mechanisms and interaction with other injuries. *Shock*. 2009;32:122–130.)

At this time there is no well-supported intervention to treat PC, and management consists mainly of supportive care and avoidance of iatrogenic injury. Steroids are not recommended, and prophylactic antibiotics are strongly discouraged. In 1973, Trinkle and coworkers[92] recognized that crystalloid administration increased the size of the contusion, whereas diuresis decreased it. Pharmacologic therapies being investigated include arginine vasopressin and dexmedetomidine.[93] In an animal study using a model of PC, dexmedetomidine infusion improved hemodynamic parameters, decreased inflammatory infiltration, and limited the extent of lung damage and pulmonary edema.[94] In patients with early, severe hypoxemia (ratio of arterial Po_2 to fractional concentration of oxygen in inspired gas <200), a trial of noninvasive ventilation may be attempted to avoid intubation; however, the development of pneumothorax must be carefully monitored.[95,96] In animal studies, the application of positive end-expiratory pressure has been shown to decrease the size of PCs. Small clinical studies have reported that recruitment maneuvers are successful in improving aeration ("open lung" strategy).[97] In patients with PC, the use of airway pressure release ventilation has been reported to decrease the incidence of ventilator-associated pneumonia; however, experience and evidence are limited.[87] For severe unilateral PC, lung isolation ventilation may be considered.[98] Although traumatic injury (with the attendant risk of bleeding complications) was previously considered a contraindication to *extracorporeal membrane oxygenation* (ECMO), increasing experience with ECMO without anticoagulation[99] and demonstration of improved outcomes compared with conventional mechanical ventilation for severe hypoxemic respiratory failure have made ECMO (with or without systemic anticoagulation) a viable rescue therapy in experienced centers.[100–103] The use of other rescue therapies such as high-frequency oscillatory ventilation and surfactant administration for the treatment of PC is poorly studied and considered experimental at this time.[104,105]

In sum, for the management of PC, the patient should be resuscitated to maintain signs of adequate tissue perfusion and achieve usual end points of resuscitation. Once this has been achieved, however, meticulous attention should be paid to the avoidance of excessive fluid administration, to the point of using a pulmonary artery catheter if necessary to help guide diuretic therapy.[55] Aggressive pulmonary toilet and adequate analgesia are extremely important in preventing pneumonia.

Pulmonary Laceration

Pulmonary laceration is the tearing of the pulmonary parenchyma, which disrupts the alveolar walls. Pulmonary lacerations result from several mechanisms, such as alternate compression and decompression of the chest wall or from a sudden, rapid increase in intrathoracic pressure with a closed glottis leading to high intra-alveolar pressure that produces shearing of pulmonary parenchymal tissue. Alternatively, pulmonary laceration may also result from direct puncture of lung tissue by a fractured rib, missile, or stab wound or from shearing of lung tissue fixed by previously formed pleural adhesions. The disrupted pulmonary tissue fills with blood and/or air and manifests on thoracic imaging as one or more pulmonary parenchymal cavities (eFig. 104.7), appearing as gas-fluid levels, frequently with surrounding pulmonary consolidation and ground-glass opacity related to hemorrhage and atelectasis.

Although only a small fraction of patients with thoracic injury will ultimately require urgent thoracotomy, of those patients who proceed to surgery, approximately one-third may require lung resection, usually to remove severely injured lung tissue, to control hemorrhage, or to remove irreparable proximal bronchus injuries.[106] The extent of resection can range from simple, nonanatomic wedge resection, to formal anatomic lobectomy, to the extremely morbid pneumonectomy.[107] For the majority of penetrating injuries, lung-sparing techniques such as simple suture or "tractotomy" (in which the tract of a penetrating injury is opened and damaged bronchi and vessels are ligated) are sufficient[106,108,109] (Fig. 104.3). Not surprisingly, there is a stepwise increase in mortality with increasing extent of lung resection for trauma: wedge resection (19%), lobectomy (27%), and pneumonectomy (53%).

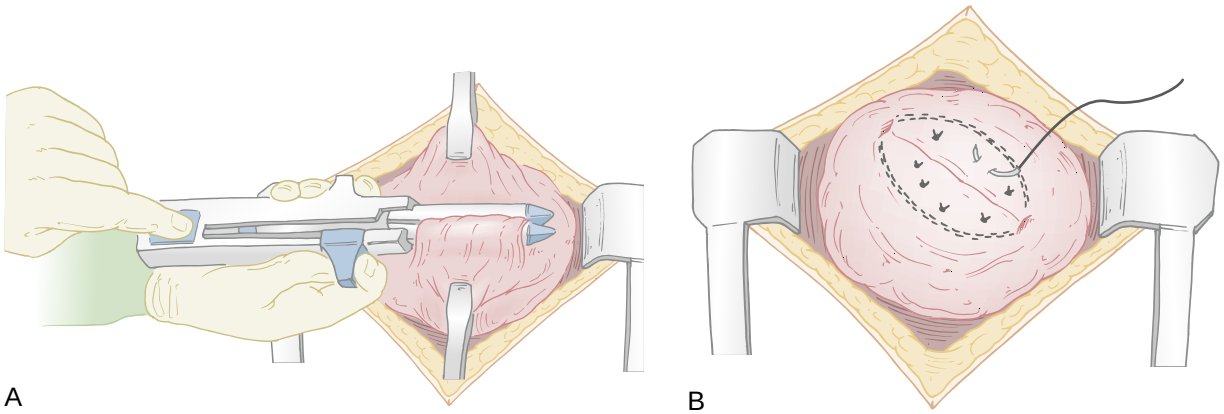

Figure 104.3 Lung-sparing "tractotomy" in which the tract of the penetrating injury is rapidly opened and injured vessels and bronchi are ligated. (A) The stapling device is advanced through the orifices of the entry and exit wound and is then closed and fired to staple the lung on either side and to open the tract ("tractotomy") for visualization of the injured vessels and bronchi. (B) The tractotomy exposes the bleeding vessels, which are then selectively ligated. The tractotomy approach preserves lung by avoiding wedge resection, lobectomy, or pneumonectomy. (From Asensio JA, Demetriades D, Berne JD, et al. Stapled pulmonary tractotomy: a rapid way to control hemorrhage in penetrating pulmonary injuries. *J Am Coll Surg.* 1977;185:486–487.)

Although most previously healthy patients who have experienced trauma can easily tolerate a minor wedge resection or even formal lobectomy, pneumonectomy can impose a tremendous physiologic burden to the unstable trauma patient, and patients often succumb to right ventricular failure.[110] Using a porcine model of hemorrhagic shock, Cryer and colleagues[111] demonstrated that pulmonary vascular resistance increases up to 500% within 4 hours after pneumonectomy. This phenomenon was not seen in animals subjected to pneumonectomy without preceding major blood loss.[111] Inhaled nitric oxide and prostacyclin have been demonstrated to restore pulmonary vascular resistance back to baseline and improve right ventricular function and oxygenation.[112,113] Postoperative complications in survivors are common and include pneumonia, bronchopleural fistula, empyema, or erosion into the pulmonary artery.

Bronchopleural Fistula

A bronchopleural fistula is a direct connection between the bronchus and the pleural space. Although most fistulas heal spontaneously, a persistent bronchopleural fistula may seriously impair the ability to ventilate a patient secondary to loss of tidal volume through the fistula. It is believed that air flowing through the fistula impedes healing, and therefore medical therapies are aimed at reducing bronchopleural fistula air flow.

Nonsurgical treatments include minimizing airway pressures (via lower tidal volumes, positive end-expiratory pressure, and inspiratory time), isolated contralateral lung ventilation, dependent positioning of the side with the bronchopleural fistula, and use of high-frequency oscillatory ventilation.[114–116] Bronchoscopy is useful to identify the injury directly (proximal) or the affected bronchial segment (distal). A balloon is used to occlude the segments sequentially until a reduction in air leak is noted. Once the affected bronchus is identified, agents such as silver nitrate, cyanoacrylate-based agents, gelatin, fibrin, and even fishing weights have been applied to occlude the bronchial segment and close the fistula.[117–121] Bronchopleural fistula refractory to medical therapy for more than 7 days may require pleurodesis, an endobronchial valve,[122,123] or operative intervention.

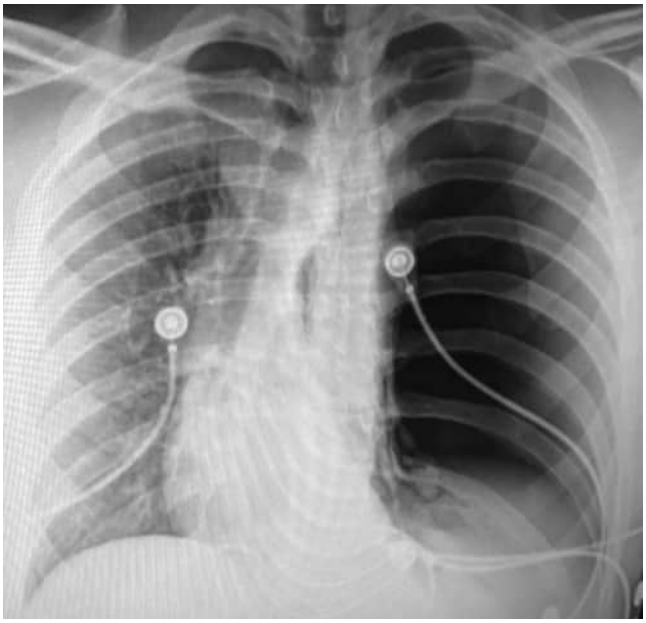

Figure 104.4 Chest radiograph showing tension pneumothorax. The free air in the left hemithorax is associated with a shift of the mediastinum into the right side of the chest, depression of the hemidiaphragm, and widening of the intercostal spaces. Hypotension follows as a result of impairment of venous return to the right side of the heart, both by the high intrathoracic pressure and perhaps by mechanical compression or kinking of the superior vena cava. Immediate decompression is required.

PNEUMOTHORAX

Pneumothorax, air within the pleural cavity, is present in 40% and 20% of patients with blunt and penetrating thoracic trauma, respectively (see Chapter 110).[124] The clinical consequence of pneumothorax ranges from asymptomatic to the most life-threatening manifestation, tension pneumothorax, whereby progressive air trapping in the thorax results in a contralateral mediastinal shift, compression or kinking of the superior and inferior vena cavae, and a precipitous drop in preload and cardiac output (Fig. 104.4). Clinically, this form of "obstructive" shock manifests as hypotension and hypoxia, although the mode of

presentation depends on the ventilator status of the patient. In a comprehensive review of the literature, Roberts and colleagues[125] reported that hypoxemia was nearly universal (92%) in ventilated patients with pneumothorax but present in only 50% of patients breathing unassisted. In those patients breathing unassisted, tension pneumothorax rarely progressed to respiratory arrest or cardiac arrest. Regardless of ventilator status, when diagnosed, tension pneumothorax should be treated with immediate thoracic decompression, either with needle thoracostomy or with tube thoracostomy. Current recommendations from the Advanced Trauma Life Support program[126] are to use longer needles and to insert the needle between the fourth and fifth intercostal space, the midaxillary line, instead of the traditional mid-clavicular line at the second intercostal space. This is because cadaver studies have shown that the midaxillary fourth and fifth intercostal space has higher likelihood of entering the thoracic cavity when compared with the mid-clavicular second intercostal space[127] because of decreased chest wall thickness in this location and greater needle stability during transport.[128,129] A systematic review of 15 studies describing chest wall thickness concluded that a 5-cm angiocatheter would have a significantly lower failure rate if inserted into the anterior axillary line at the fourth to fifth intercostal space compared with the mid-clavicular line at the second intercostal space (13% vs. 38%).[130] Additionally, lateral needle insertion avoids potentially life-threatening hemorrhagic complications such as laceration of the internal mammary artery, subclavian artery, or pulmonary artery.[131,132] Other investigators recommend inserting a chest tube at the outset instead of a needle because of frequent failure rates associated with the latter.[133]

An open pneumothorax, or sucking chest wound, is a special form of pneumothorax whereby a defect in the chest wall permits air entry through the wound with diaphragmatic movement. If the size of the wound approaches the size of the trachea, this may significantly hamper ventilation because air may preferentially enter through the wound rather than through the native airway.[134] Before operative repair, the wound should be covered with a one-way flutter (Heimlich) valve or an occlusive dressing with one side open to allow air egress.

For less severe pneumothorax, the decision to drain the pleural cavity should be made based on the degree of respiratory compromise and the potential for enlargement to a tension pneumothorax. In asymptomatic patients with a small (<2 cm in the largest dimension on upright chest radiograph) pneumothorax, selective conservative management without tube thoracostomy has been reported to have a high success rate.[135] Clinical significance of a pneumothorax depends not only on the absolute size of the pneumothorax, but also on the preinjury condition of the patient (e.g., presence of COPD) and other associated injuries.

Chest tube insertion is not without risk, and modern series report a 15–20% incidence of tube-related complications.[136] Complications can be broadly classified into one of five categories: insertional; positional; removal; infective and immunologic; and instructional, educational, or equipment related[137,138] (Fig. 104.5). The decision to place an additional chest tube should be based on

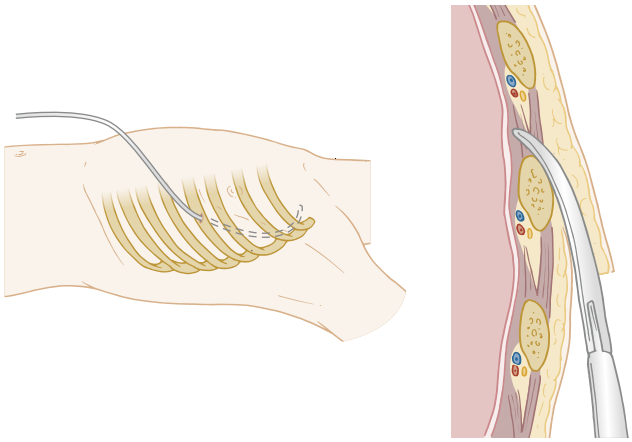

Figure 104.5 Diagrams illustrating tube thoracostomy placement. The thoracostomy tube is placed in the midaxillary line; the tube is directed anteriorly for drainage of pneumothorax. (From Van Way CW III, Buerk CA. *Surgical Skills in Patient Care.* St. Louis: Mosby; 1978.)

inadequate function of the initial chest tube, not based on the radiographic appearance of the trajectory.[139] As long as the sentinel port is within the thoracic cavity, nonkinked malpositioned tubes seem to function just as well as those with an "ideal" trajectory.[140] One rare complication following pneumothorax drainage is reexpansion pulmonary edema[141] (Fig. 104.6). Prophylactic antibiotics for the duration of dwell time of the chest tube are not recommended.[142] Accumulating evidence suggests that smaller, 14- to 16-French pigtail catheters are equally effective as traditional large-bore chest tubes (28 to 40 French), require less dissection, can be placed by the Seldinger technique, and may be less painful.[143,144]

An occult pneumothorax is defined as a pneumothorax that can be visualized only on chest CT scan; it is not detectable on chest radiograph, nor is it suspected on clinical examination (Fig. 104.7). Occult pneumothorax is present in up to 12% of seriously injured patients,[145,146] and it comprises more than 50% of all pneumothoraces diagnosed in injured patients.[147] Supine portable chest radiographs have been consistently shown to be only 50% sensitive for the detection of pneumothorax. Subtle findings on supine chest radiograph suggestive of pneumothorax include the deep sulcus sign (Fig. 104.8). Access to ultrasonography has increased dramatically, with most hospital areas having good access to ultrasound machines. As such, ultrasound is increasingly used to detect pneumothorax, especially because ultrasonography has higher sensitivity than chest radiography for its detection.[148–157]

The management of occult pneumothorax has evolved since the 1990s from mandatory tube thoracostomy for all occult pneumothoraces, progressing to selective drainage for only those patients undergoing positive-pressure ventilation,[158] to routine observation for all patients with selective drainage only for those demonstrating significant pneumothorax enlargement on chest radiograph or developing respiratory symptoms such as tachypnea or hypoxemia.[145,158] In a large, multicenter observational study of 569 patients with occult pneumothorax across 16 trauma centers, Moore and colleagues[159] reported that 21% required immediate tube thoracostomy. Of the remaining patients, observation failed in only 6% overall, and these patients required tube thoracostomy for pneumothorax

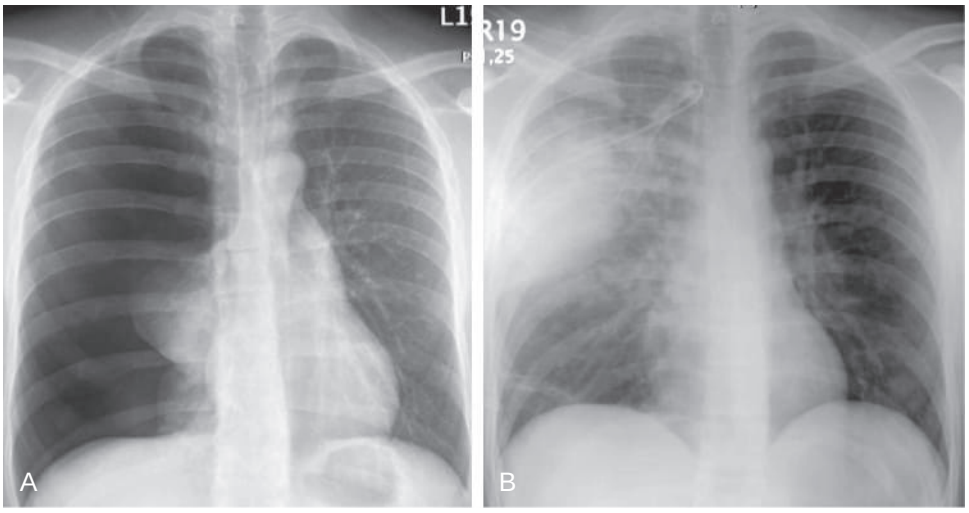

Figure 104.6 Chest radiographs showing pneumothorax and reexpansion pulmonary edema following evacuation of the pneumothorax. (A) Right-sided pneumothorax can be seen with subtotal lung collapse. (B) The same patient after expansion of the lung following placement of a thoracostomy tube. Peripheral right upper lobe opacity is now present, consistent with the development of reexpansion injury and edema in that region of lung. (From Malota M, Kowarik MC, Bechtold B, Kopp R. Reexpansion pulmonary edema following a posttraumatic pneumothorax: a case report and review of the literature. *World J Emerg Surg.* 2011;6:32.)

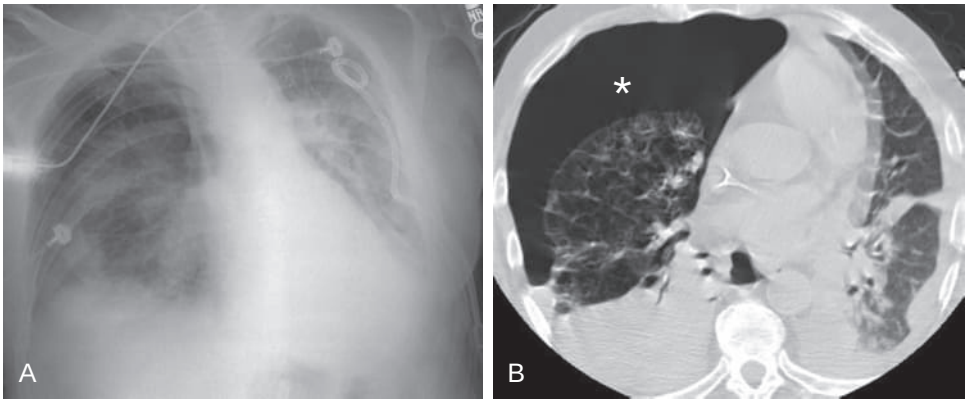

Figure 104.7 Imaging of radiographically occult pneumothorax. (A) Frontal chest radiography shows patchy bilateral opacity with a left-sided thoracostomy tube. No right pneumothorax is visible. (B) Axial chest computed tomography displayed in lung windows shows a moderate right-sided pneumothorax *(asterisk),* as well as basal lung opacity and pleural effusion bilaterally. (Courtesy Michael B. Gotway, MD.)

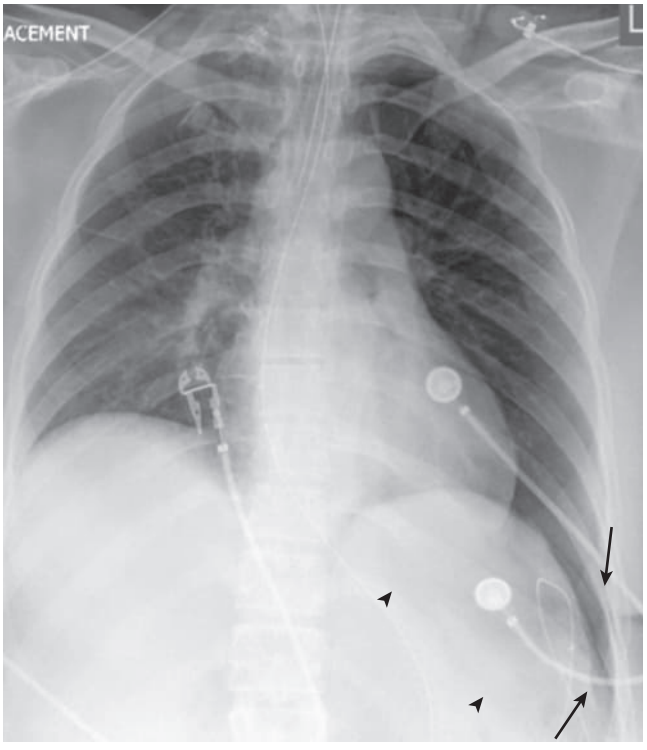

Figure 104.8 Deep sulcus sign on supine chest radiograph. In this supine patient, a pneumothorax on the left can be recognized by the depth of the diaphragmatic sulcus on the left compared with the right *(arrows)*. There is also lucency overlying the left hemidiaphragm that represents air anterior and lateral to the left hemidiaphragm and is seen as an air-tissue interface *(arrowheads)*.

enlargement, respiratory distress, or development of hemothorax. In this series, only 14% of patients undergoing positive-pressure ventilation required tube thoracostomy. Importantly, no patient in whom observation failed experienced an adverse event resulting from delay of chest drainage.[159] Thus, occult pneumothorax can be managed safely with observation, even in patients undergoing positive-pressure ventilation.

After drainage, standard management of the chest tube entails serial chest radiographs to document resolution of the pneumothorax. A bedside clinical examination should be performed to rule out an ongoing air leak, which is usually secondary to persistent alveolar-pleural fistula.[160] Air leaks may be graded according to increasing severity: forced expiratory, expiratory, inspiratory, and continuous. Most posttraumatic air leaks in stable patients are forced expiratory (coughing) or expiratory, and almost all resolve with time and patience.[160] Typically, the chest tube is placed at −20 cm H_2O suction and is advanced to water seal before removal.[161] In the trauma setting, chest tubes are generally not clamped. It is customary to obtain a chest radiograph after transitioning to water seal and after chest tube removal to monitor for pneumothorax reappearance. Pneumothorax recurs after chest tube removal in 11–24% of cases; however, if the pneumothorax is small and stable and the patient is asymptomatic, observation is frequently successful.[162–164] It is common practice to allow up to 24 hours between changes in chest tube management; however, Schulman and associates[165] reported that changes may be made at shorter intervals because clinically significant recurrent pneumothorax appeared within 3 hours.

After successful radiographic resolution of a pneumothorax, current guidelines from the Aerospace Medical Association[166] and the British Thoracic Society[167] recommend waiting at least 2 weeks before commercial airline travel, based on low-quality evidence (case reports and expert opinion) and the rationale that hypobaric conditions may cause expansion of a pneumothorax by up to 30%, thus potentially leading to life-threatening tension pneumothorax. However, a prospective study challenged these conservative recommendations. Majercik and colleagues[168] enrolled 20 patients with traumatic pneumothorax and submitted them to hypobaric conditions (554 and 471 mm Hg) within 48 hours of chest tube removal or resolution with high-flow oxygen therapy alone. Although an "in-flight" chest radiograph demonstrated an average pneumothorax expansion of 0.5 cm, no patients experienced cardiorespiratory symptoms, and all pneumothoraces returned to baseline within 4 hours after returning to normobaric conditions.[168] Zonies and associates[169] performed a retrospective review of patients transferred between medical facilities by air medical transport a median of 2.5 days after chest tube removal. Of the 73 patients (40% mechanically ventilated during flight), none experienced an in-flight emergency, and none experienced post-flight radiographic or clinical recurrences.[169]

HEMOTHORAX (See Chapter 113)

A hemothorax is blood in the pleural cavity. It can cause a wide range of consequences, from minor to life-threatening (eFig. 104.8). In general, a hemothorax evident on supine chest radiograph in the trauma bay is usually drained immediately, especially in the presence of hemodynamic instability. In stable patients, hemothorax is often diagnosed on CT of the thoracic cavity. Similar to occult pneumothorax, occult hemothoraces also exist, and the decision to drain the hemothorax should take into consideration the amount of blood present and the morbidity of chest tube insertion. For small (<300 mL) hemothoraces, initial observation without drainage in selected patients (younger age, no concomitant pneumothorax) is safe and may result in better outcomes.[170]

The initial treatment of hemothorax is tube thoracostomy. Based on the volume of initial output, the next step may be either urgent thoracotomy or observation. If the source of bleeding is the pulmonary parenchyma, hemostasis can sometimes be achieved simply through complete expansion of the lung. Because the pulmonary circulation is a low-pressure circuit, full inflation of the lung tissue can easily compress minor venous bleeding or raw surface oozing. However, bleeding from lacerated intercostal or internal mammary arteries is likely to persist and may require urgent thoracotomy for definitive hemostasis. Indications for urgent thoracotomy include hemodynamic instability, 1500 mL initial chest tube output, greater than 1500 mL over a 24-hour period, or greater than 200 mL/hr blood drainage for 3 consecutive hours.[171] Hemothorax secondary to major thoracic vascular structures (e.g., aorta, pulmonary artery) almost universally requires emergency thoracotomy for hemodynamic instability. Although some investigators have advocated for reinfusion ("autotransfusion") of blood collected from a hemothorax,[172] traumatic hemothorax blood may become hypercoagulable once remixed with the patient's own plasma.[173] Thus, caution should be applied when considering this practice.

Assuming adequate drainage and resolution of the hemothorax, it is customary to advance the chest tube to water seal before removal, similar to the chest tube management for a simple pneumothorax (see earlier). An additional factor to consider is the daily volume of bloody chest tube drainage. Although there are no standardized guidelines or recommendations, most trauma surgeons advance a chest tube once the daily output decreases to between 100 and 300 mL per day. A randomized trial comparing various thresholds after elective thoracic surgery did not show any difference in major pleural fluid accumulation or thoracocentesis rates when a threshold of 200 mL was used to trigger chest tube removal.[174]

The evacuation of a hemothorax may be incomplete in up to 20% of cases and can be a frustrating situation.[163,175,176] Untreated, a retained hemothorax may evolve into empyema; in one prospective observational trial of more than 300 patients with traumatic retained hemothorax, empyema developed in 26% and was more likely in patients with a greater number of rib fractures, a higher injury severity score, and a need for more interventions to drain the hemothorax.[177] Additional chest tube placement is usually ineffective for clot evacuation. For retained hemothorax, early *video-assisted thoracic surgery* (VATS) (<5 days after injury), compared with delayed operation or additional chest tubes, has been reported to decrease hospital LOS and decrease conversion to open thoracotomy.[178,179] Compared with open thoracotomy, VATS has significant advantages and should be considered as first-line operative treatment in the absence of contraindications.[180] According to the Eastern Association for the Surgery of Trauma guidelines,[181] there is level 1 evidence that a retained hemothorax should be treated with early VATS, not insertion of a second chest

tube. VATS should be considered within 3 to 7 days of hospitalization because this reduces the risk for infection and the requirement for thoracotomy (level 2 evidence). Retained hemothorax less than 300 mL by chest CT scan may be observed.[181] Currently, intrapleural thrombolytic agents are considered second-line treatment after VATS and can be considered in patients with subacute hemothoraces to improve drainage.[182,183] As a preventive measure, thoracic irrigation with 1 L of warmed sterile saline at the time of chest tube insertion may be considered to reduce the rate of retained hemothorax.[184,185]

Over the past decade, there has been a trend toward using smaller chest tubes for evacuating hemothorax.[186] When comparing the standard 36- to 40-French chest tube with 28- to 32-French tubes, Inaba and colleagues[186] found that the initial drainage volume and total indwelling time were similar, and there were no differences between groups in tube-related complications or the need for additional interventions. Animal studies of flow dynamics provide even further evidence that smaller tube size is equally effective for hemothorax evacuation. Niinami and coworkers[187] reported that a 19-French silicone drain is capable of draining 11 L/hr, and Russo and associates[188] demonstrated no significant difference in percentage of drainage when comparing a 14-French pigtail catheter with a 32-French chest tube. In that study, the pigtail catheter was able to drain almost 200 mL of fresh blood *per minute*. In human patients, a 14-French pigtail catheter seems to drain blood as effectively as larger-bore traditional chest tubes, with a similar incidence of complications.[189]

CHYLOTHORAX (See Chapter 111)

Traumatic chylothorax is an uncommon entity that results from disruption of the thoracic duct. Chylothorax manifests as a milky pleural effusion on resumption of oral intake, and the diagnosis is confirmed by finding fluid triglyceride levels greater than 110 mg/dL with or without lymphocytes predominating.[190] Initial treatment involves lung reexpansion and parenteral nutrition, with the possible addition of octreotide. If these measures fail, thoracic duct embolization or operative intervention is warranted.[191] However, the optimal duration of nonoperative management is unknown.

PNEUMATOCELE OR INTRAPARENCHYMAL HEMATOMA

Also termed a *posttraumatic pulmonary pseudocyst*, a pneumatocele is a traumatic cavitary lesion within the parenchyma following a pulmonary laceration (eFig. 104.9). Asymptomatic patients may be managed expectantly, and most pneumatoceles resolve within several weeks. For infectious complications, antibiotics and CT-guided catheter drainage may be attempted. Operative resection (VATS or thoracotomy) may be necessary if less invasive measures fail.

TRACHEOBRONCHIAL INJURIES

Tracheobronchial injuries are most commonly caused by penetrating injury,[192,193] and surgical intervention is usually required for the airway injury or for associated injuries in the neck or chest.[194] Tracheobronchial injuries from blunt trauma, conversely, manifest in one of two ways, depending on site, size, and communication with the pleural cavity: they are either immediately apparent, requiring immediate attention, or they are very subtle and difficult to diagnose.[195,196] Most are unrecognized for the first 24 hours and, in a few patients, there is no evidence of thoracic injury on physical examination or radiographs.[195] In those patients with delayed diagnosis, there is no discernible morbidity associated with delayed repair. Death is usually not from the tracheobronchial injury itself, but instead from fatal injuries to adjacent vascular structures.[197] Even with complete transection, the robust peritracheal connective tissue can splint the tracheal fragments, thus maintaining airway continuity. Blunt force likely injures the tracheobronchial tree by one of three mechanisms: rupture from tracheal compression against the rigid vertebral column, rupture from increased airway pressures secondary to compression of the chest with a closed glottis, or laceration from shearing forces.[198]

Most tracheobronchial injuries take place within 2.5 cm of the carina, with mainstem bronchial injuries comprising the majority (86%).[193,195,198] Clinically, the patient may have dyspnea or tachypnea (the most common symptom), hoarseness, stridor, hemoptysis, crepitus, or respiratory distress.[194] Radiographically, the "fallen lung" sign, first described by Oh and associates in 1969, is a highly specific finding for this injury.[199] This sign manifests when the patient has a pneumothorax. When pneumothorax is present without tracheobronchial injury, the lung falls *toward* the hilum (central displacement), whereas with tracheobronchial injury, the transected lung falls *away* from the hilum (peripheral displacement)[200] (Fig. 104.9). CT scanning may demonstrate bronchial wall discontinuity (eFig. 104.10 and Video 104.3) or mediastinal emphysema.[201] A tracheal or proximal bronchus injury should be suspected in a patient with pneumomediastinum or with a pneumothorax refractory to chest drainage. Bronchoscopy is the most effective method of diagnosis.[194]



Figure 104.9 "Fallen lung" sign seen on chest radiograph. Chest radiograph obtained 6 hours after initial presentation of acute dyspnea in an 8-year-old boy. Bilateral pneumothorax, more prominent on the right, is seen. Pneumomediastinum and soft tissue emphysema are observed. The right lung is seen to be collapsed inferior to the hilum ("fallen lung" sign), usually a sign of complete rupture of the main bronchus. A thoracostomy tube has been inserted on the right, yet a large right pneumothorax remains. (From Savas R, Alper H. Fallen lung sign: radiographic findings. *Diagn Interv Radiol.* 2008;14:120–121.)

Although the treatment for large or life-threatening tracheobronchial injuries is immediate repair, selective intubation beyond the injury alone (or even observation alone) may be successful in carefully selected patients with small or partial-thickness injuries.[7,202,203]

Delayed complications of unrecognized injury include bronchopleural fistula, bronchial stricture, atelectasis, bronchiectasis, and postobstructive pneumonia, as well as more serious sequelae such as mediastinitis or cervical abscess.[204]

DIAPHRAGM INJURIES

Diaphragmatic injury is a rare but morbid injury, manifesting in less than 1% of blunt trauma cases, and it is associated with a 21% overall mortality rate.[205] More than 90% of these injuries are seen after motor vehicle crashes. Two-thirds of diaphragm injuries develop on the left, perhaps because the liver cushions the impact on the right side. Because of the significant force required to rupture the diaphragm, these injuries are almost universally accompanied by other organ injuries, such as lung (77%), liver (52%), spleen (32%), and stomach (19%).[205]

The physical examination is inaccurate for the diagnosis of diaphragmatic injuries. For most victims of penetrating injury, there is no sign or symptom unique to diaphragmatic injury. For patients following blunt trauma, dyspnea and pain are common but nonspecific. Chest radiography is diagnostic in fewer than half of those patients with injury to the left hemidiaphragm (eFig. 104.11) and in only 17% of those with injury to the right hemidiaphragm[206] (Fig. 104.10). CT scan has a very high sensitivity for blunt diaphragmatic rupture. Imaging signs of injury include a nasogastric tube terminating above the diaphragmatic contour, discontinuity of the hemidiaphragm, herniation of the viscera into the thorax (eFig. 104.12), diaphragmatic thickening, the hump sign, the band sign, the dependent viscera sign (eFig. 104.13), the collar sign (eFig. 104.14), and the dangling sign.[207,208]

All acute diaphragmatic injuries should be surgically repaired. The natural history of traumatic diaphragmatic hernias is poorly studied, but it is presumed that the tendency of these hernias is to enlarge over time, with progressive herniation of abdominal viscera into the chest in response to the negative intrathoracic pressure and positive intra-abdominal pressure. For patients with left-sided penetrating thoracoabdominal wounds, if there is no immediate indication for operative exploration, it is recommended to perform diagnostic laparoscopy, because 20% of these patients will have diaphragm injuries.[209,210]

BLAST LUNG INJURY

INTRODUCTION

An increasing frequency of terrorist bombing attacks worldwide has resulted in a large number of civilian blast injuries.[211] Blast victims require a standard trauma workup as recommended by Advanced Trauma Life Support. Additionally, such victims may also present with a set of pulmonary injuries unique to the blast mechanism.[212]

Victims of blast injuries have different injuries depending on the type of the bomb, the location of detonation, and whether the targets were military or civilian. Typically, military victims have different injuries from civilian victims. Military personnel are young and healthy, and they usually have body armor that protects their thoracic and abdominal organs, whereas civilian victims range from children to older adults, and they are not wearing body protection. Thus, civilian victims present with more thoracic or lung and abdominal injuries than military victims. As a general rule, blast injury victims have multiple blunt and penetrating injuries, including traumatic amputations. Injuries from blast detonations are classified into the following categories: (1) primary, (2) secondary, (3) tertiary, and (4) quaternary.[212]

PRIMARY BLAST INJURIES

Primary blast injuries result from overpressure effects of the blast wave (see later). The blast typically injures organs that have interfaces between different densities, such as air and tissue or water and air. Examples include pulmonary barotrauma, tympanic membrane ruptures, gastrointestinal contusions or perforations, and traumatic amputations. Previously, tympanic membrane rupture was used as a marker of severity of illness from the blast wave. However, later studies showed that tympanic membrane rupture is not a reliable marker of severity because it has demonstrated poor sensitivity and specificity.[213] Instead, markers of severe blast injury include the following: (1) burns over more than 10% of total body surface area, (2) skull or facial fractures, and (3) penetrating injuries to the head or torso.[213]

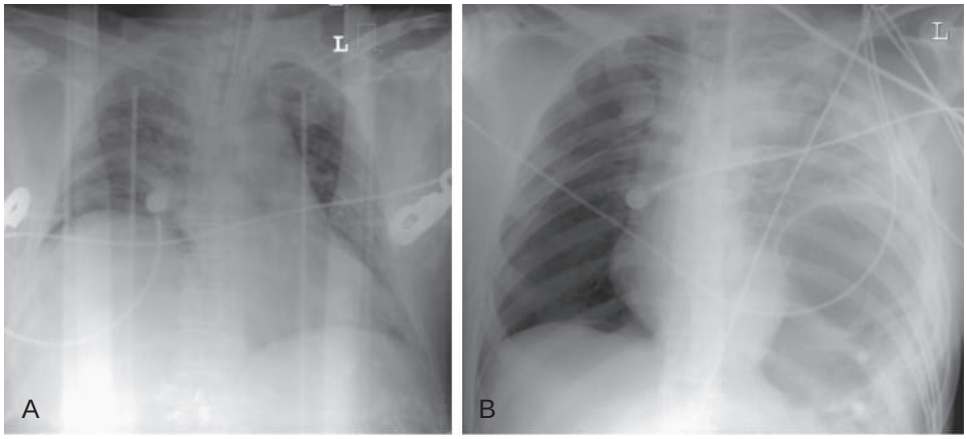

Figure 104.10 Hemidiaphragmatic injury in the setting of trauma. (A) Right hemidiaphragmatic injury. Frontal chest radiograph shows apparent elevation of the right hemidiaphragm, generally a nonspecific finding. However, in the setting of trauma, diaphragmatic injury with herniation of the liver into the thorax manifests similarly, as in this example. (B) Left hemidiaphragmatic injury. Frontal chest radiograph shows herniation of the stomach into the left thorax, consistent with a large tear of the left hemidiaphragm. *L*, Left.

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SECONDARY BLAST INJURIES

Secondary blast injuries result when penetrating injuries are caused by flying debris, such as bomb fragments from the explosive device and fragments of bone and teeth from the bomber and victims. There are case reports of these biologic fragments transmitting hepatitis B.[214,215]

TERTIARY BLAST INJURIES

Tertiary blast injuries result when victims are physically propelled into hard surfaces by the force of the blast wave. Crush injuries from falling debris also fit into this category.

QUATERNARY BLAST INJURIES

Quaternary blast injuries encompass all other explosion-related effects such as burns, asphyxia, radiation poisoning, toxins, psychological trauma, and exacerbation of underlying medical conditions.

PHYSICS OF THE BLAST WAVE

Explosions result when a chemical reaction transforms a solid or liquid into gas within a very short time period and thus results in a massive release of energy. The explosion releases most of its energy as a blast wave, a positive-pressure front that travels faster than the speed of sound.[216] As a result, victims feel the blast wave before hearing the explosion. In the open air, the blast wave behaves in a predictable manner based on the physics of wave motion.[217]

Detonations within confined spaces or underwater cause blast waves that are accentuated and deadlier.[212,214] Under these conditions, blast waves are reflected back from surfaces with a different density, such as walls or air-water interfaces. The reflected wave superimposes and amplifies the outgoing blast wave, thereby causing a higher-intensity and much deadlier blast wave. Furthermore, the blast wave can reflect back from surfaces at an angle greater than 40 degrees, augmenting the incoming wave and creating a new blast wave. This phenomenon is known as a "mach stem formation."[218] Studies have shown that explosions detonated in corners can result in explosions that are up to eight times deadlier than explosions in the open air.[214]

The human body is damaged when the blast wave transmits energy directly to the body. This energy is transmitted unevenly through body tissues and, as described, reflects back when encountering changes in density. As a result, the majority of damage is done at interfaces of different tissue densities. For example, pulmonary blast injuries result when the blast wave rapidly changes in amplitude on entering and exiting the multiple air- and fluid-filled structures within the lungs. Other air-tissue interfaces include the gastrointestinal tract, tympanic membranes, and extremities, where greatly disparate density planes (e.g., air, soft tissue, and bone) all reside within a small space. The mechanisms causing these injuries can be classified physiologically into distinct categories: (1) spalling forces, (2) implosion forces, and (3) inertia forces.[212,217]

Spalling Forces

Spalling forces result when the blast wave displaces and fragments one tissue into another tissue, usually the higher-density tissue into the lower-density tissue. For example, spalling forces cause the forcible movement of blood from the capillaries into the alveoli, thus causing alveolar hemorrhage.

Implosion Forces

Implosion forces result when the highly compressed edge of the blast wave enters the victim. This results in gas that rapidly compresses and reexpands, causing injury. For example, implosion forces cause barotrauma by compressing and reexpanding the air in the alveoli. Furthermore, this rapid change in air density can cause an air embolism by forcing air into the circulatory system.

Inertia Forces

Inertia forces result when the blast wave causes the different tissue densities to absorb different amounts of energy. This results in different tissues moving at different velocities. The resulting shearing of tissue planes causes massive injuries, typically traumatic avulsions or amputations.

Results of Blast Injury

Blast lung injury results from the combination of all the forces described previously. The initial damage to the architecture of the alveoli leads to pulmonary hemorrhage. The free hemoglobin in the alveoli leads to the formation of free radicals, thereby worsening edema and an early inflammatory response.[219,220] This leukocyte accumulation and release of inflammatory cytokines cause further epithelial cell damage over 12 to 24 hours, as well as endothelial cell damage over 24 to 56 hours. This inflammatory cascade results in a lung injury syndrome similar to ARDS. Histologic examination of the lung damaged by blast injury reveals perivascular edema, extensive alveolar hemorrhage during the first 12 hours, and then further epithelial cell damage and detachment from the basement membrane.[219,220]

MANAGEMENT

Initial management of patients with blast lung injury should follow standard local trauma protocols and Advanced Trauma Life Support teaching. Pulmonary blast injury is the most common injury found in scene fatalities,[4] and survivors of the blast wave with primary blast lung injury represent a group of patients with very severe injuries. Clinical features include shortness of breath, cough, chest pain, hemoptysis, cyanosis, and tachypnea. Hypoxemia is a typical finding, but it may not develop until after the first few hours following presentation. One case series found that only 28% of patients had hypoxemia on initial presentation.[220]

All patients with suspected blast lung injury should receive a chest radiograph as soon as possible. Radiographic findings of blast injury may include not only the classic "bat wing" appearance on chest radiograph but also subcutaneous emphysema, pneumothorax, pulmonary interstitial emphysema, pneumopericardium, pneumomediastinum, and pneumoperitoneum.

The general treatment for patients with primary blast lung injury is similar to the treatment for patients with ARDS. This includes limiting fluid administration to reduce the chance of pulmonary edema and using low–tidal

volume lung-protective ventilation with permissive hypercapnia to minimize peak and plateau airway pressures.[221] Patients with refractory cases can be considered for rescue treatments for ARDS, such as inhaled nitric oxide, inhaled prostaglandins, and open-lung ventilation strategies. The underlying pathophysiology of blast lung involves alveolar hemorrhage, and the coagulopathy and anticoagulation usually started with ECMO can result in catastrophic pulmonary hemorrhage.[222] With increased use of ECMO, there is more experience in managing ECMO circuits safely without anticoagulation.[223] This opens up the possibility of using ECMO in patients with severe respiratory failure from blast injuries. However, caution should be taken because the ECMO circuit itself can lead to coagulopathy and an increased risk of bleeding, even without anticoagulation.[224]

In the rare case of air embolism from the blast lung injury, treatment aims to prevent further air emboli. The patient is placed in the left lateral decubitus position, with the head down and feet up in an attempt to contain the air embolism at the apex of the left ventricle. Peak pressures during positive-pressure ventilation should be minimized, and hyperbaric therapy should be considered. The diagnosis is clinical because CT scans, echocardiograms, and observations of retinal air bubbles on funduscopic examinations are unreliable.[212]

Patients who survive blast lung injury typically have excellent long-term pulmonary outcomes. One study found that, 1 year after the injury, survivors had normal pulmonary examinations, with minimal pulmonary complications.[225]

Key Points

- The majority of patients with pneumothorax and hemothorax may be adequately managed by tube thoracostomy alone.
- The cornerstone of treatment for rib fractures and flail chest is pain control.
- Pulmonary contusion is a major driver of morbidity and can cause systemic immune dysfunction.
- Occult pneumothorax may be safely managed with observation, even in patients undergoing positive-pressure ventilation.
- Blast lung injury is a unique form of lung injury most commonly seen in survivors of closed-space explosions.
- The diagnosis of blast lung injury is based on clinical observations and confirmed by plain chest radiograph.
- Management of blast lung injury is predominantly supportive and closely approximates the treatment of acute respiratory distress syndrome.

Key Readings

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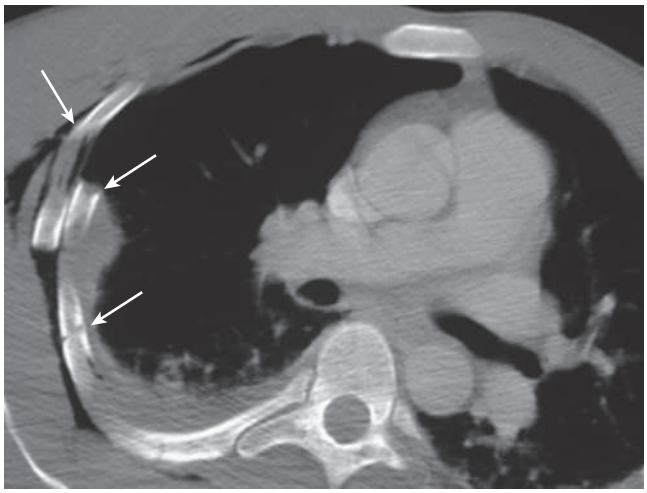
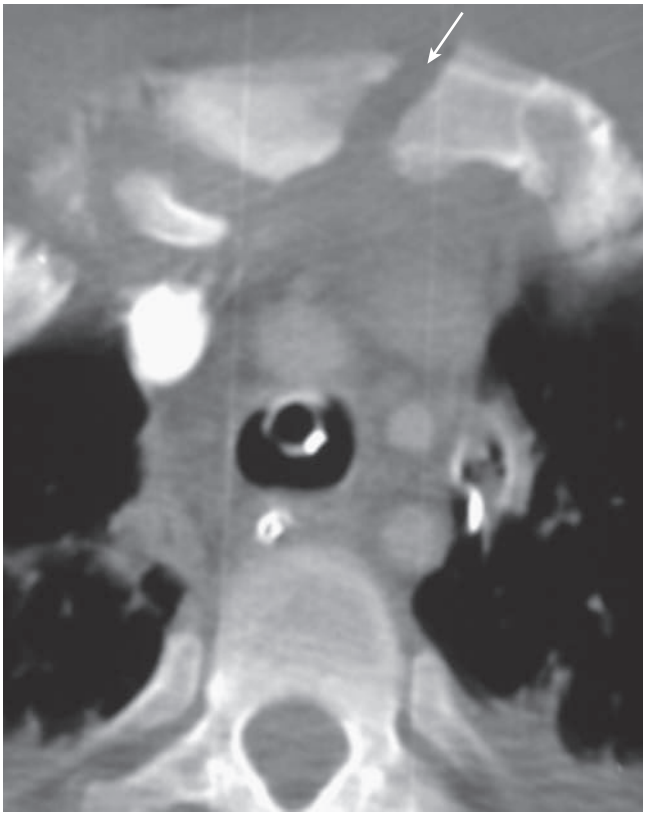
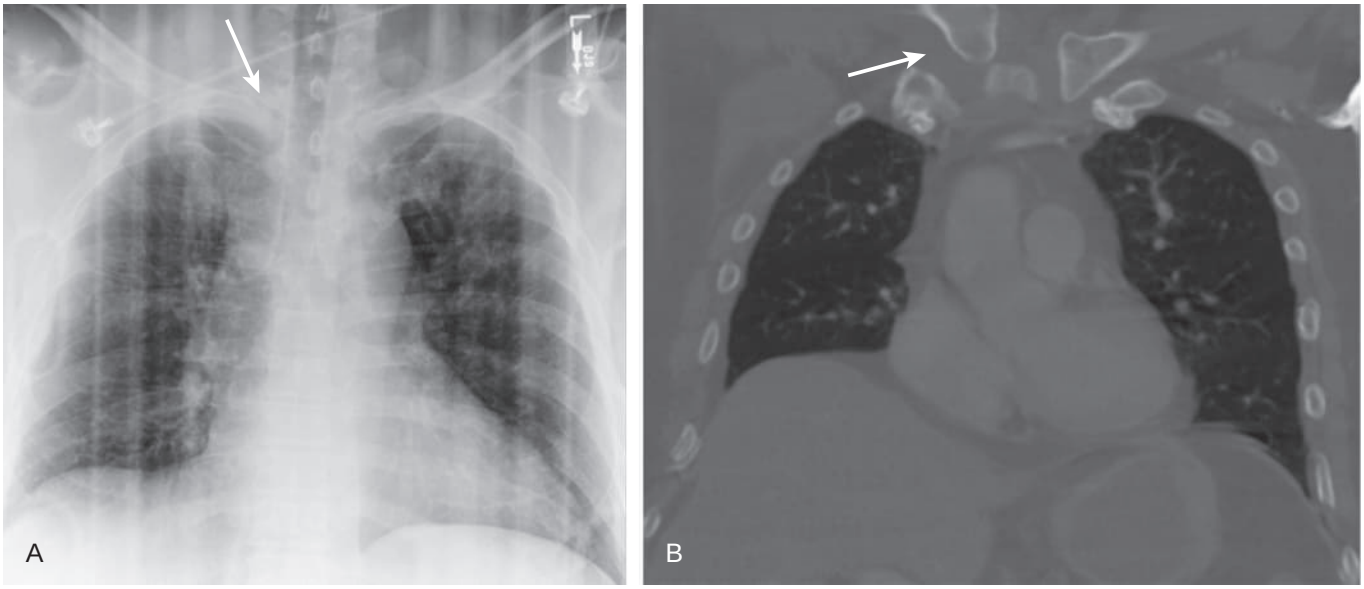
eFIGURE IMAGE GALLERY



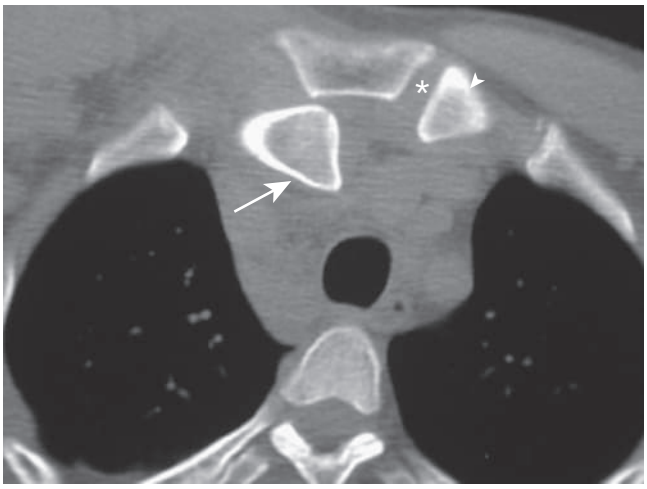
eFigure 104.1 Blunt thoracic traumatic injury: rib fracture. Axial enhanced chest computed tomography scan shows displaced right-sided rib fractures *(arrows).* (Courtesy Michael B. Gotway, MD.)



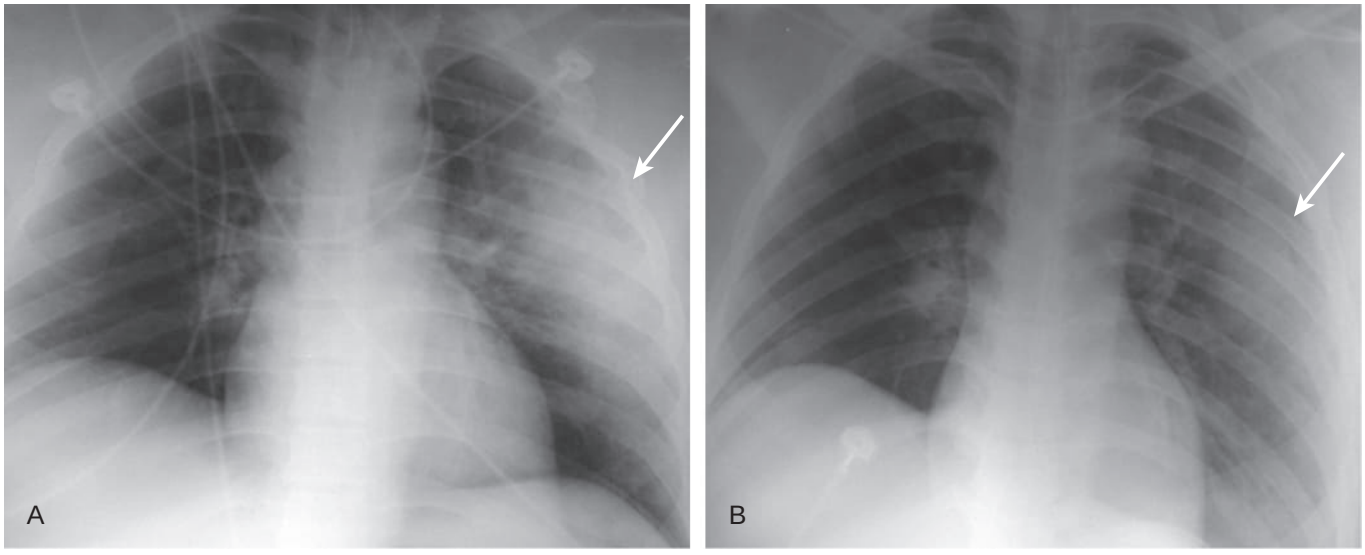
eFigure 104.2 Blunt thoracic traumatic injury: manubrial fracture. Axial chest computed tomography scan shows a fracture line *(arrow)* through the manubrium resulting from a motor vehicle collision. (Courtesy Michael B. Gotway, MD.)



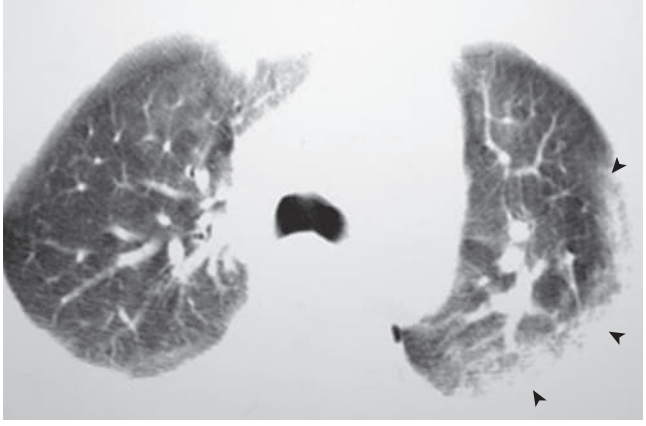
eFigure 104.3 Blunt thoracic traumatic injury: sternoclavicular dislocation. (A) Frontal chest radiograph of a patient who fell from height shows subtle displacement of the medical head of the right clavicle *(arrow);* compare with the normally positioned left clavicular head. (B) Coronal enhanced chest computed tomography scan displayed in bone windows shows superior dislocation of the medial head of the right clavicle *(arrow).* (Courtesy Michael B. Gotway, MD.)



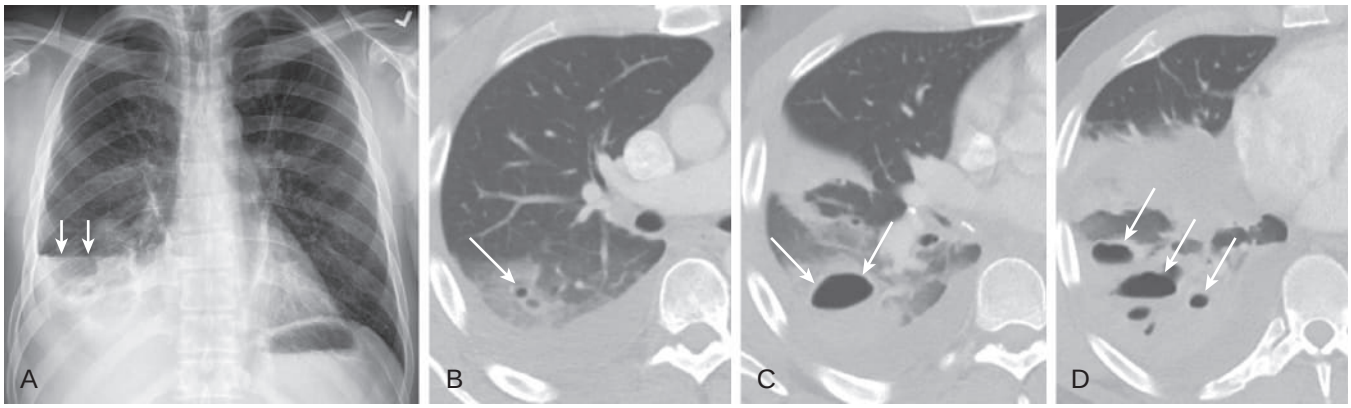
eFigure 104.4 Blunt thoracic traumatic injury: sternoclavicular dislocation. Axial chest computed tomography scan in a patient following a motor vehicle collision shows posterior dislocation of the right clavicular head *(arrow).* Note the normally positioned left clavicular head *(arrowhead)* and the normal sternoclavicular joint space *(asterisk).* (Courtesy Michael B. Gotway, MD.)



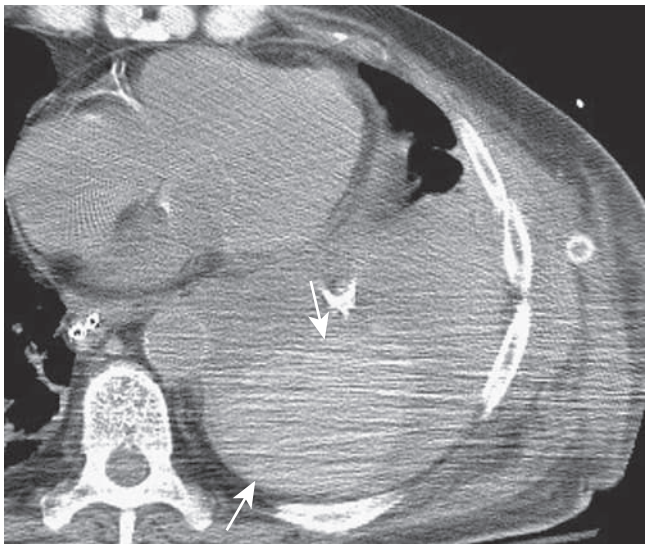
eFigure 104.5 Blunt thoracic traumatic injury: pulmonary contusion on chest radiograph. (A) Frontal chest radiograph performed on emergency room presentation in a patient following a motor vehicle collision shows homogeneous peripheral left lung consolidation *(arrow),* consistent with contusion. (B) Frontal chest radiograph performed 24 hours following presentation (A) shows significant improvement in the left lung contusion *(arrow).* (Courtesy Michael B. Gotway, MD.)



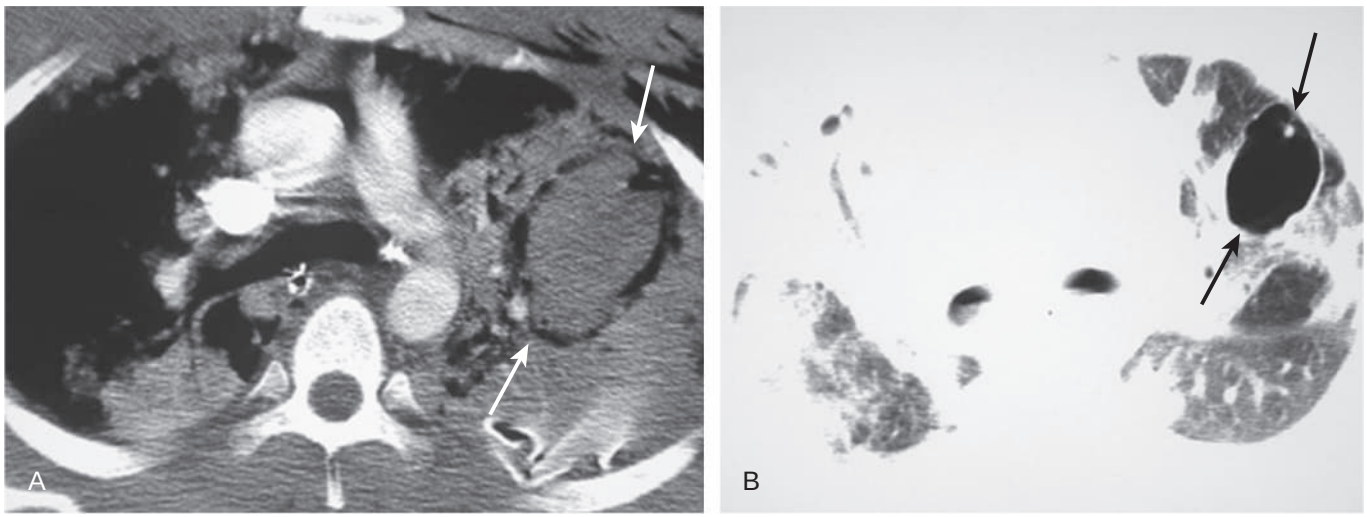
eFigure 104.6 Blunt thoracic traumatic injury: pulmonary contusion on chest computed tomography scan. Axial chest computed tomography scan performed in a patient following blunt traumatic thoracic injury shows homogeneous, nonsegmental, peripheral left upper lobe ground-glass opacity and consolidation *(arrowheads),* typical of pulmonary contusion. (Courtesy Michael B. Gotway, MD.)



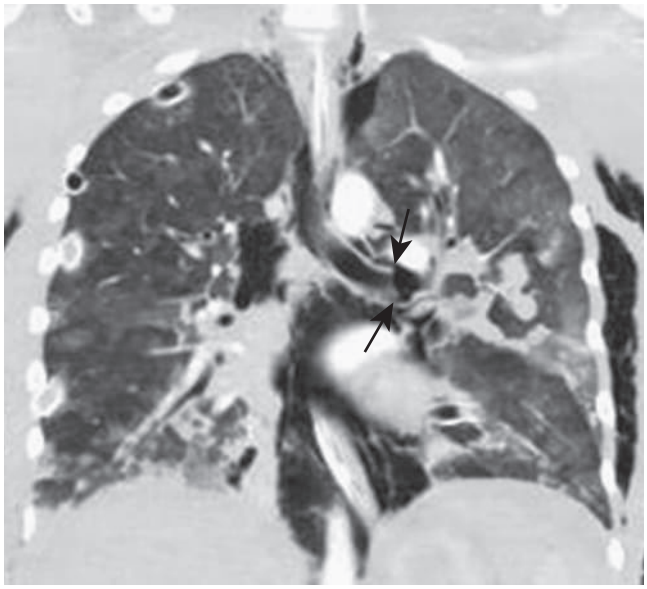
eFigure 104.7 Blunt thoracic traumatic injury: pulmonary laceration. (A) Frontal chest radiograph performed in a patient following a motor vehicle collision shows right lower lobe consolidation containing an air-fluid level *(arrows).* (B–D) Axial chest computed tomography scan displayed in lung windows shows numerous right lower lobe areas of cavitation *(arrows)* associated with surrounding consolidation, consistent with pulmonary laceration. (Courtesy Michael B. Gotway, MD.)



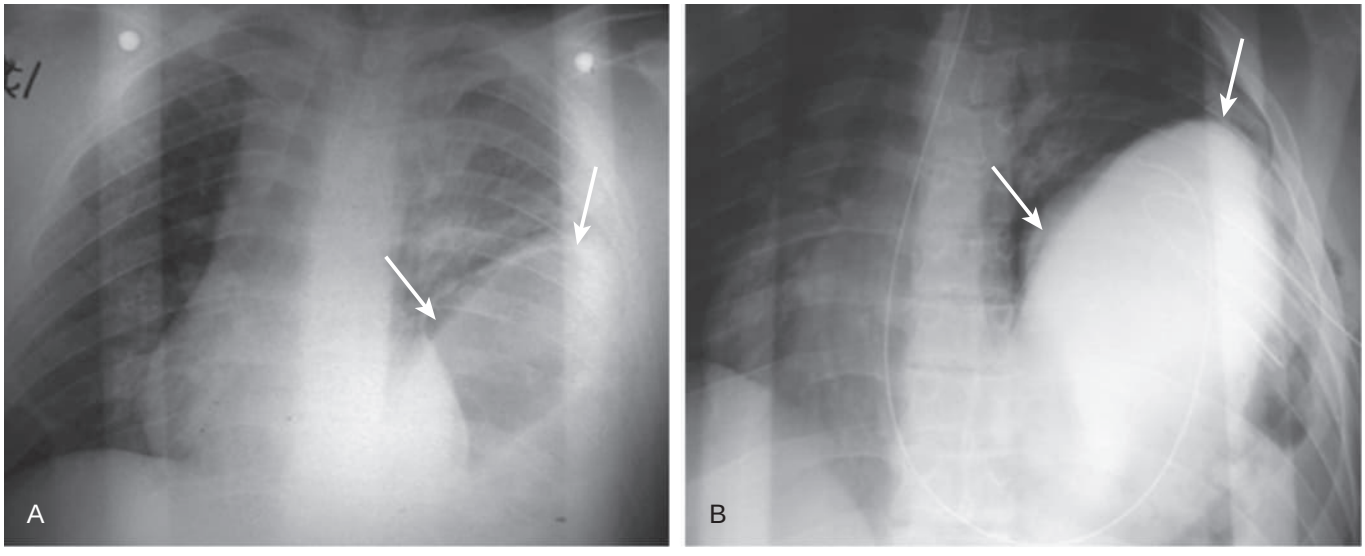
eFigure 104.8 Blunt thoracic traumatic injury: hemothorax. Axial chest computed tomography scan shows a left pleural effusion containing a masslike area of high attenuation *(arrows),* representing retracting clot within a hemothorax. (Courtesy Michael B. Gotway, MD.)



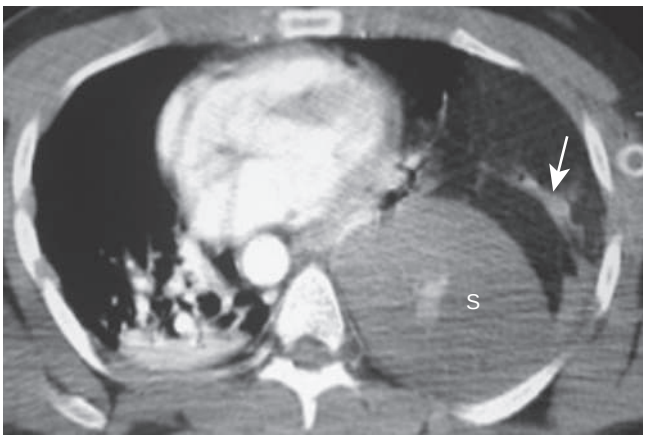
eFigure 104.9 Blunt thoracic traumatic injury: hematoma with pneumatocele development. (A) Axial chest computed tomography scan performed in a patient following blunt traumatic thoracic injury shows a left upper lobe mass *(arrows)* with surrounding lucency, the latter consistent with cavitation. The material within the cavity is blood, consistent with hematoma. (B) Axial chest computed tomography displayed in lung windows performed 3 weeks following (A) shows evacuation of the contents of the left upper lobe cavity, revealing a thin-walled cyst *(arrows).* This lesion spontaneously closed over the ensuing month, consistent with a pneumatocele. (Courtesy Michael B. Gotway, MD.)



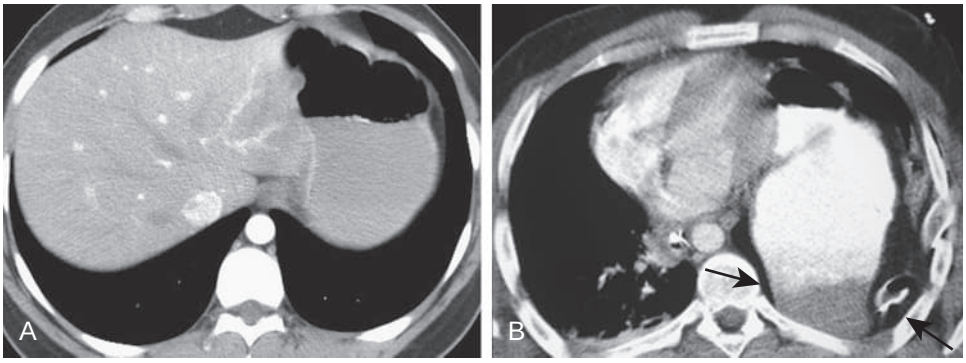
eFigure 104.10 Blunt thoracic traumatic injury: tracheobronchial injury. Coronal chest computed tomography displayed in lung windows performed in a patient following a high-speed motor vehicle collision shows extensive subcutaneous emphysema and pneumomediastinum, both hallmarks of airway injury. The left mainstem bronchus is fractured (*arrows*), with gas collecting around the area of airway injury. The associated video (see Video 104.3) shows the extensive pneumomediastinum, subcutaneous emphysema, and medial left apical pneumothorax as well as multifocal lung parenchymal injuries. (Courtesy Michael B. Gotway, MD.)



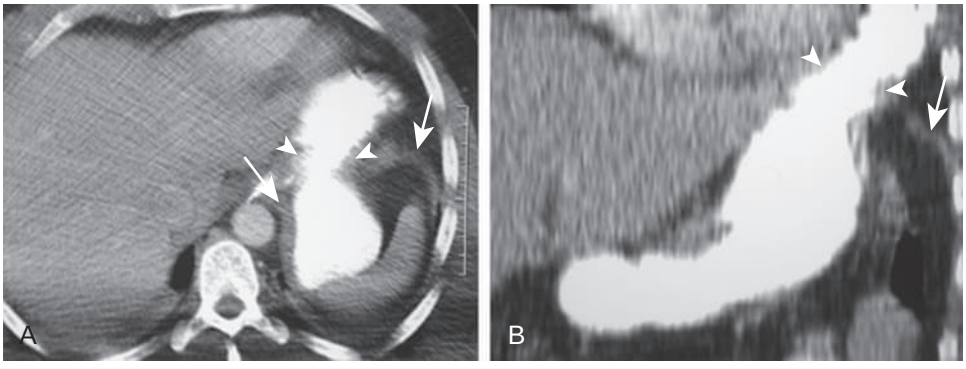
eFigure 104.11 Blunt thoracic traumatic injury: diaphragmatic injury on chest radiography. (A) Front chest radiograph obtained in a patient after a motor vehicle collision shows intrathoracic herniation of the stomach *(arrows).* (B) Frontal chest radiograph obtained following chest computed tomography, for which an oral contrast agent was administered, shows the contrast medium filling the intrathoracic stomach *(arrows).* (Courtesy Michael B. Gotway, MD.)



eFigure 104.12 Blunt thoracic traumatic injury: diaphragmatic injury manifesting as intrathoracic visceral herniation. Axial chest computed tomography scan performed in a patient following blunt traumatic injury shows intrathoracic herniation of the spleen (S) as well as other contents of the left upper quadrant, including the colon *(arrow),* consistent with a very large left diaphragmatic tear. (Courtesy Michael B. Gotway, MD.)



eFigure 104.13 Blunt thoracic traumatic injury: diaphragmatic injury manifesting as the "dependent viscera" sign. (A) Normal computed tomography appearance of the thoracoabdominal junction. Note the abdominal contents are positioned within the central portion of the image at this level, with the thoracic contents positioned peripherally. (B) Axial chest computed tomography scan performed in a patient following blunt traumatic injury shows the abdominal viscera (stomach and left upper quadrant fat, *arrows*) resting against the posterior chest wall. Normally, as shown in (A), the lung parenchyma and pleura occupy this location. The positioning of abdominal viscera against the posterior chest wall near the thoracoabdominal junction on chest computed tomography is referred to as the "dependent viscera" sign and represents intrathoracic visceral herniation, usually secondary to fairly large diaphragmatic tears. (Courtesy Michael B. Gotway, MD.)



eFigure 104.14 Blunt thoracic traumatic injury: diaphragmatic injury manifesting as the "collar" sign. (A) Axial enhanced chest computed tomography scan shows focal constriction of the stomach *(arrowheads)* as it enters the thorax through a small left hemidiaphragmatic tear (*arrows,* left hemidiaphragm). (B) Coronal reformatted computed tomography image shows the focal constriction of the stomach as it passes through the small diaphragmatic defect *(arrowheads)* to advantage; this focal constriction is referred to as the "collar" sign (*arrow,* left hemidiaphragm). (Courtesy Michael B. Gotway, MD.)

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105 HIGH ALTITUDE

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INTRODUCTION

Nearly 100 million persons live at altitudes greater than 2500 m across North America, South America, Asia, and Africa. These individuals have developed the ability to live and reproduce at elevations as high as 5000 m but, in some cases, they develop chronic medical problems attributable to their high-altitude residence. In addition, millions of lowlanders venture to high altitude for work and recreation each year, where they face a risk of acute altitude illness or altitude-related exacerbations of preexisting diseases. Given these large numbers of persons exposed to high altitude on a short- or long-term basis, medical providers must be able to provide guidance about minimizing risks and managing problems related to being in this environment.

This chapter reviews the adaptive and maladaptive responses to high altitude. Acute and chronic adaptation is discussed, and changes in common activities are explored, including sleep and exercise. The consequences of maladaptation—the acute and chronic illnesses of high altitude—are reviewed, as are strategies for managing these situations. Finally, an approach to the traveler with underlying medical problems who is planning a trip to high altitude is discussed.

ACCLIMATIZATION TO HIGH ALTITUDE

As altitude increases and barometric pressure declines (Table 105.1), the partial pressure of oxygen (P_{O_2}) decreases at each point of the oxygen transport chain from air to tissues. Compensatory processes involving ventilation, ventilation-perfusion matching, circulatory transport, oxygen diffusion from blood into tissues, and mitochondrial metabolism take place at each step at different rates to raise P_{O_2}, maintain oxygen delivery, and improve tolerance of the hypoxic environment.

The process of altitude acclimatization is vitally important to survival. Whereas a person who suddenly ascends from sea level to the summit of Mt. Everest (8848 m) by helicopter would become unconscious within minutes and die soon thereafter, some climbers using an appropriate ascent rate can complete the climb without supplemental oxygen because of adaptation to hypoxia. These adaptive responses been reviewed extensively elsewhere,[1,2] and a summary of the key features is provided in the following subsections.

PULMONARY ACCLIMATIZATION

Control of Ventilation

Acute Response. On acute hypoxic exposure, ventilation increases. This *hypoxic ventilatory response* (HVR), the magnitude of which varies among individuals, minimizes the drop in alveolar P_{O_2} (Fig. 105.1) and is mediated by carotid body peripheral chemoreceptors, which respond in a hyperbolic fashion to decreasing arterial P_{O_2}.[3] Ventilation increases immediately in response to a constant hypoxic stimulus (Fig. 105.2). With the initial rise in ventilation, the arterial partial pressure of carbon dioxide (P_{CO_2}) at medullary chemosensors decreases and partially depresses this ventilatory response.[4] In a process referred to as *ventilatory acclimatization*, ventilation then begins a steady rise over a period of days to weeks.[5] The classic explanation for this ongoing increase was the return of arterial pH toward normal through renal compensation and development of metabolic acidosis. However, the hypocapnic alkalemia persists as ventilation increases, thus suggesting that other mechanisms beyond renal compensation must be responsible for increasing ventilation. It was proposed that a relative cerebrospinal fluid acidosis at the medullary chemosensors triggers increased ventilation, but lumbar cerebrospinal fluid remains alkaline at 3100 m for 3 weeks, whereas hyperventilation persists even when arterial P_{CO_2} and blood and cerebrospinal fluid pH returns toward normal following descent.[6] Brain interstitial and intracellular fluid pH measurements also failed to show changes accounting for the increase in ventilation.[7] These results suggest that some mediators other than hydrogen

Table 105.1 U.S. Standard Atmosphere: Altitude, Barometric Pressure, and Inspired P_{O_2}*

Altitude (m)	Altitude (Feet)	Barometric Pressure (mm Hg)	Inspired P_{O_2} (mm Hg)
0	0	760	159
1000	3280	674	141
2000	6560	596	125
3000	9840	526	110
4000	13,120	463	97
5000	16,400	405	85
6000	19,680	354	79
8000	26,240	268	56
8848	29,028	253	43

*Values except 8848 m are taken for mid latitude (45°N). There is greater variation at higher latitudes.

Modified from Altman PL, Dittmer DS, eds. *Respiration and Circulation*. Bethesda, MD: Federation of American Societies for Experimental Biology; 1971:12–13.

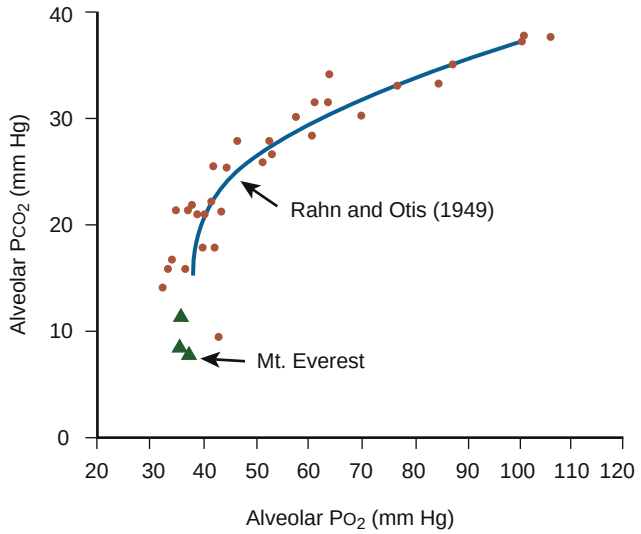

Fig. 105.1 Oxygen–carbon dioxide diagram demonstrating the alveolar gas composition in acclimatized subjects at high altitude. *Circles* represent data collected by Rahn and Otis (Rahn H, Otis B. Man's respiratory response during and after acclimatization to high altitude. *Am J Physiol.* 1949;157:445-449), and the *triangles* are measurements from three altitudes on Mt. Everest. At extreme altitudes, marked hyperventilation maintains alveolar P_{O_2} at approximately 35 mm Hg. (From West JB, Hackett PH, Maret KH, et al. Pulmonary gas exchange on the summit of Mt. Everest. *J Appl Physiol.* 1983;55:678–687.)

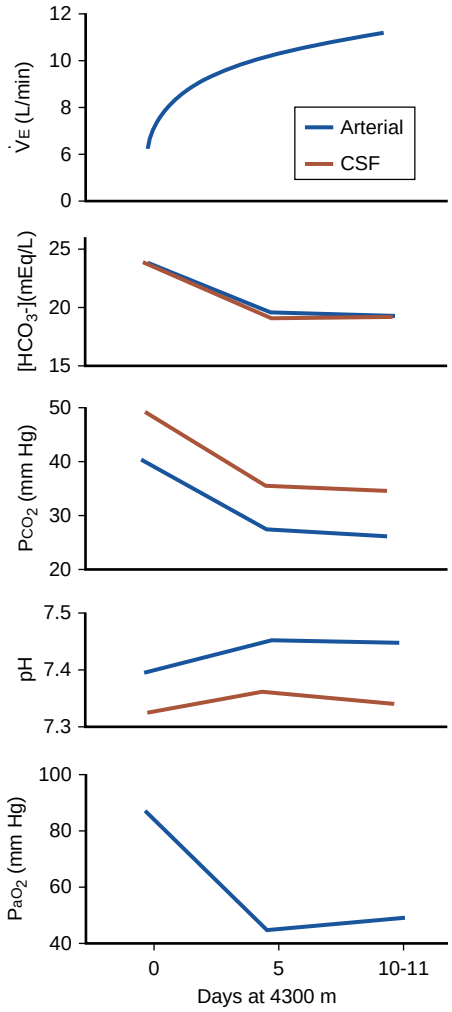

Fig. 105.2 Ventilatory acclimatization during 10- to 11-day sojourn to 4300 m. Ventilation continues to increase as cerebrospinal fluid (CSF) acid-base alterations parallel plasma changes. HCO_3^-, bicarbonate; P_{aO_2}, arterial P_{O_2}; $\dot{V}_E$, minute volume of ventilation. (From Forster HV, Dempsey JA, Chosy LW. Incomplete compensation of CSF [H^+] in man during acclimatization to high altitude [4300 m]. *J Appl Physiol.* 1975;38:1067–1072.)

ion sustain hyperventilation with ongoing hypoxic exposure. Other possible mechanisms include *erythropoietin* (EPO) signaling in the brain via EPO receptors,[8] carotid body hypertrophy,[9] or increases in carotid body sensitivity to hypoxia.[10]

Chronic Ventilatory Adaptation. High-altitude residents have lower ventilation and higher arterial P_{CO_2} than acclimatized lowlanders at the same elevation and have blunted ventilatory responses to acute hypoxia.[11] The blunted response develops despite carotid body hypertrophy and may be an adaptive phenomenon in which the disadvantages of lower arterial P_{O_2} are offset by decreased work of breathing associated with lower ventilation.

Pulmonary Function and Mechanics

Vital capacity decreases on acute ascent,[12] potentially as a result of a variety of mechanisms including airway narrowing and gas trapping secondary to interstitial fluid accumulation,[12] pulmonary vascular engorgement,[13] decreased respiratory muscle strength,[14] and decreased lung compliance caused by hypocapnia.[15] In contrast, in high-altitude residents, vital capacity is increased compared with nonnative residents,[16] with larger changes seen in those born and raised at high altitude compared with those who move to high altitude later in life.[17]

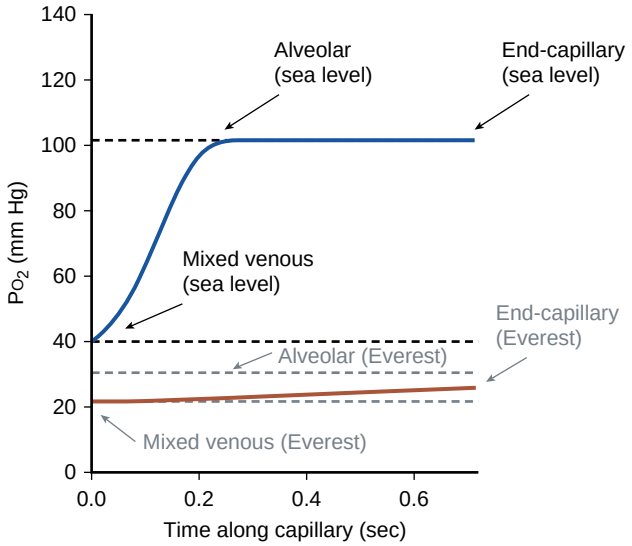

Fig. 105.3 Altitude-related diffusion limitation. Comparison of the calculated time course of P_{O_2} in the pulmonary capillary of a climber at rest on the summit of Mt. Everest (*orange line:* barometric pressure, 250 mm Hg; inspired P_{O_2}, 43 mm Hg; oxygen consumption, 250 mL/min; diffusion capacity of the alveolar capillary membrane, 40 mL/mm Hg) with sea-level values (*blue line:* barometric pressure, 760 mm Hg; inspired P_{O_2}, 150 mm Hg; oxygen consumption, 300 mL/min; diffusion capacity of the alveolar capillary membrane, 40 mL/mm Hg). At sea level, there is adequate time for equilibration of alveolar and end-capillary oxygen, whereas at extreme altitude, even at rest, when transit time for the red blood cell is presumably similar to that at sea level, full equilibration is not realized, resulting in end-capillary blood that is not fully saturated. (Modified from West JB, Wagner PD. Predicted gas exchange on the summit of Mt. Everest. *Respir Physiol.* 1980;42:1–16.)

Airway resistance is also reduced,[18] presumably because of decreased air density counteracting airway narrowing in response to hypoxia and hypocapnia.

Gas Exchange

Ventilation and Perfusion Matching. Increased ventilation during acute hypoxia is accompanied by greater cardiac output and pulmonary perfusion. Additionally, alveolar hypoxia triggers *hypoxic pulmonary vasoconstriction* (HPV), which increases *pulmonary vascular resistance* (PVR). These changes redistribute blood flow to recruit areas of the lung that are usually less well perfused during rest at sea level, thus potentially improving ventilation-perfusion matching and optimizing gas exchange. With exercise at high altitude, however, ventilation-perfusion matching is not improved by HPV.[19]

Diffusion. Hypobaria lowers alveolar P_{O_2}, which, in turn, decreases the pressure gradient for diffusion across the alveolar-capillary barrier so that, at altitudes higher than 2500 m, the estimated pulmonary capillary transit time at rest of 0.75 seconds may not be adequate for end-capillary oxygen equilibration (Fig. 105.3). This phenomenon is further exacerbated during exercise as a result of shortened capillary transit time and greater fall in mixed venous P_{O_2}. Because the low P_{O_2} lies on the steep portion of the oxygen-hemoglobin dissociation curve, a small decrease in arterial P_{O_2} causes a proportionately greater drop in arterial oxygen content than at sea level.[20] West and Wagner[20] modeled these factors for the summit of Mt. Everest (barometric pressure ~250 mm Hg) and demonstrated that alveolar-capillary oxygen equilibration is far from complete.

With many weeks at altitude and long-term residence, diffusing capacity has been shown to increase, possibly due to changes at the alveolar-capillary membrane from increased sympathetic activity.[21] Compared with sojourners, highland residents have a lower (A–a)P_{O_2} difference, increased diffusing capacity and, despite lower ventilation, a higher arterial P_{O_2} at rest and during exercise.[22,23]

CARDIOVASCULAR ACCLIMATIZATION

Cardiac Response

With acute hypoxia, cardiac output increases to maintain oxygen delivery, but the cardiac output-work relationship returns to sea level values over 1 to 2 weeks as hematocrit and arterial oxygen content rise. Increased cardiac output is largely the result of increases in heart rate rather than a change in stroke volume. In fact, stroke volume declines with ascent and remains lower than sea-level values despite acclimatization. The lower stroke volume is not caused by depressed myocardial function because contractility is maintained in hypoxia[24]; instead, it likely results from a decrease in plasma volume and venous return. Variable changes in systemic blood pressure have been reported following ascent, with some individuals experiencing small increases secondary to increased sympathetic stimulation and others experiencing either no change or a small decrease.[25–28]

Pulmonary Vascular Response

With ascent, *pulmonary artery* (PA) pressure increases because of HPV. This response is minimal until the arterial P_{O_2} drops to less than 70 mm Hg, at which point a more pronounced rise ensues (Fig. 105.4), although the magnitude of the response varies markedly among individuals.[29,30]

HPV remains relatively unchanged for several weeks,[31] but thereafter PVR and PA pressure rise further in response to the additional factors of polycythemia-induced hyperviscosity and vascular remodeling caused by smooth muscle hypertrophy and collagen proliferation. The time course of these changes is not clear. In a 40-day simulated ascent of Mt. Everest, Groves and associates[32] exposed individuals to progressively lower pressure of inspired oxygen and demonstrated a more than threefold increase in PVR after 40 days. PVR did not return to sea-level values on breathing 100% oxygen, a finding suggesting possible vascular remodeling. Depending on the severity of changes, particularly the degree of intimal fibrosis, reversal of pulmonary hypertension may require months or years at low altitude.[33]

HEMATOLOGIC ACCLIMATIZATION

Erythropoiesis

Hemoglobin concentration increases within 1 to 2 days of ascent and continues to rise over several weeks. The initial rise is caused by hemoconcentration from an early diuretic response, with further changes resulting from increased *red*

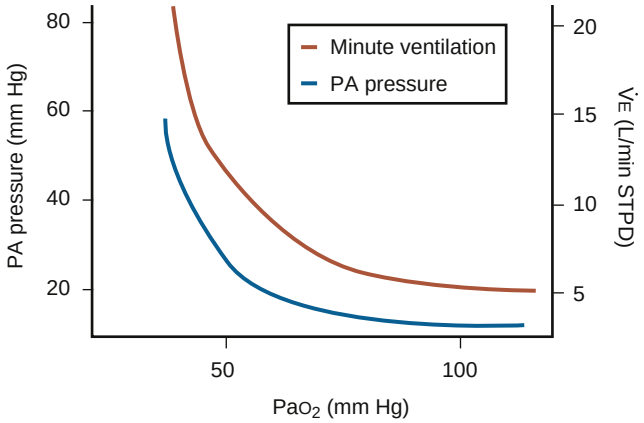

Fig. 105.4 Relationship of arterial P_{O_2} with minute ventilation and pulmonary arterial pressure. Although there is variability among individuals, both the ventilatory and the pulmonary vascular response do not increase until arterial P_{O_2} (P_{aO_2}) falls to less than 70 mm Hg. PA, pulmonary artery; STPD, standard temperature, standard pressure, and dry (conditions); $\dot{V}_E$, minute volume of ventilation. (From Reeves JT, Wagner WW Jr, McMurtry F, et al. Physiological effects of high altitude on the pulmonary circulation. In: Robertshaw D, editor. *International Review of Physiology: Environmental Physiology III.* Baltimore, MD: University Park Press; 1979:289–310.)

blood cell (RBC) production secondary to hypoxia-mediated renal EPO release and a hypoxia-mediated prolongation of RBC survival.[34] Although polycythemia augments arterial oxygen content, it may impair oxygen delivery if the hematocrit rises to more than 60%, because hyperviscosity can impair cardiac output and microvascular perfusion. Serum EPO increases within 24 to 48 hours before declining over 3 weeks as the hematocrit rises.[35] Erythrocytosis ceases on descent and the hematocrit returns to lowland values in approximately 3 weeks as a result of decreased RBC production and neocytolysis, a reactive oxygen species–mediated destruction of the youngest circulating RBCs.[36]

There is interindividual variability in the erythropoietic responses of both sojourners[37] and highlanders.[38] Similar variability is seen among different highland populations[39] because Andean natives demonstrate greater erythropoiesis than Himalayan or Ethiopian highlanders.[40] Whether greater erythropoiesis in Andean natives is secondary to genetic factors,[41] environmental exposures such as cobalt in mining regions,[42] or an up-regulation of the erythropoietic response to the renal sensing of hypoxia[43] is not clear. In Tibetan and Sherpa populations, the lower hematocrit results from a partial loss of function in the hypoxia inducible factor-2α gene responsible for renal EPO production.

Oxygen-Hemoglobin Affinity

A critical feature of oxygen transport at high altitude is that the hemoglobin-oxygen dissociation curve is much steeper as arterial P_{O_2} falls to less than 60 mm Hg. On ascent, with the P_{O_2} on the steep portion of the curve, arterial oxygen saturation (arterial S_{O_2}) falls precipitously with only a small decrease in P_{O_2}. Potential impacts on oxygen delivery are mitigated by adaptations in the dissociation curve. Because of the increase in ventilation and resulting respiratory alkalosis, the curve shifts leftward, enhancing oxygen loading and increasing arterial oxygen content, but at the expense of decreased tissue oxygen off-loading. Over several days, the dissociation curve shifts back rightward as RBC 2,3-diphosphoglycerate increases,[44] and the pH decreases because of renal compensatory responses.

Coagulation

There has long been a question whether acute hypoxia provokes a procoagulation state, and various studies have reported conflicting results regarding platelet function, bleeding times, and markers of thrombin and fibrin formation.[45–48] This uncertainty may be explained by the finding that most of the studies on this question have typically examined isolated portions of the coagulation process. In contrast, when thromboelastography, a functional test of all aspects of the clotting system, was used, Martin and colleagues[49] found evidence of slowed coagulation.

TISSUE ACCLIMATIZATION

The final stage of oxygen delivery is the movement of oxygen from the plasma to intracellular sites of oxidative phosphorylation. Driving pressures of 10 mm Hg may be needed for movement from plasma to the cytoplasm, whereas only 1 to 2 mm Hg will be necessary for diffusion from cytoplasm to the mitochondria. At extreme altitudes, capillary P_{O_2} may fall to levels at which diffusion from plasma to the cytoplasm and then to the mitochondria is impaired. Structural and biochemical responses may mitigate the effects of the low capillary P_{O_2}, including diminished muscle fiber size and reduced diffusion distance from blood to mitochondria, increased myoglobin concentration, and increased levels or activity of enzymes involved in oxidative metabolism favoring glucose utilization over fatty acid. Within mitochondria, changes in the oxidative cytochromes and a down-regulation of mitochondrial uncoupling protein increase mitochondrial oxygen utilization efficiency.[50] Much of this structural and metabolic adaptation may be driven by gene transcription via hypoxia inducible factor-1 and hypoxia inducible factor-2, which regulate nearly 1000 genes involved in hypoxia tolerance, such as EPO.[51] In addition, many cells express cytoglobins, heme oxygen binding proteins with transport characteristics similar to myoglobin.[52]

CENTRAL NERVOUS SYSTEM ACCLIMATIZATION

Cerebral Blood Flow and Other Changes

Acute hypoxia causes increased *cerebral blood flow* (CBF) that is partially offset by hypocapnic-mediated cerebral vasoconstriction. The net result is a modest increase in CBF[53] equally distributed between white and gray matter.[54] The acute response may be biphasic, with an initial decrease in CBF resulting from acute hypocapnia and the subsequent increase triggered by arterial hypoxemia.[55] After 4 to 5 days, CBF decreases but remains higher than at sea level.[53] Along with cytoglobin, intracerebral neuroglobin, another heme oxygen binding protein, is up-regulated during hypoxia and may limit neuronal dysfunction or injury.[56]

Cerebral Function

Motor, sensory, and complex cognitive abilities progressively decline with ascent. New tasks are learned with difficulty at 3048 m and, at 6100 m, sensory, perceptual, and motor performance suffers. Short-term memory is impaired

with ascent to greater than 8500 m without oxygen.[57] Even acute, modest decreases in arterial S_{O_2} to 85% impair mental concentration and fine motor coordination; further decreases to 75% cause poor judgment, irritability, and decreased muscle function.

Predicting who will develop neurologic dysfunction in hypoxia is difficult, but data from actual and simulated ascents of Mt. Everest demonstrate that individuals with a higher HVR and arterial S_{O_2} have more pronounced neuropsychometric dysfunction,[58] potentially because persons with greater HVR have more hypocapnic cerebral vasoconstriction and consequently lower oxygen delivery. Evidence suggests the transient deterioration in learning, memory, and verbal expression return to baseline within 1 year, although fine motor dyscoordination may persist.[58,59]

Whether these changes in cerebral function can be traced to structural changes in the brain following ascent is not clear. Fayed and colleagues[60] performed brain magnetic resonance imaging in climbers who ascended to between 5895 and 8848 m and demonstrated subcortical lesions suggestive of small infarctions. However, the investigators did not correlate these findings with evidence of neurologic dysfunction, nor did they perform follow-up studies to determine whether the lesions resolved.

FLUID HOMEOSTASIS AND RENAL FUNCTION

Diuresis and natriuresis happen after ascent, with a 10-fold variability in magnitude among individuals over the first 24 to 48 hours of exposure.[61,62] The mechanism underlying these responses does not relate to changes in renin, angiotensin, aldosterone, or atrial natriuretic peptide, but rather to a peripheral chemoreceptor response not involving renal sympathetic nervous tone.[61] Acute hypoxia causes a two- to threefold increase in urinary protein that increases further with acute altitude illness.

CHANGES IN COMMON SEA-LEVEL ACTIVITIES AT HIGH ALTITUDE

SLEEP

Difficulty sleeping is a common problem at high altitude. In studies examining pharmacologic prophylaxis of acute mountain sickness, for example, more than 70% of persons receiving placebo reported poor-quality sleep.[63] There is also objective evidence of poor sleep, with increased arousals, changes in sleep architecture, and an increased incidence of periodic breathing (Video 105.1).[64] In addition, all individuals experience an increase in hypoxemia during apneic periods.

Periodic breathing, one of the cardinal features of altered sleep at high altitude, develops from abnormalities in the feedback control system that governs ventilation. As a result of increases in ventilation, arterial P_{CO_2} falls below the apnea threshold, thus leading to a cessation of respiratory effort. With apnea, arterial P_{CO_2} rises and pH falls. In conjunction with decreases in arterial P_{O_2}, this leads to increased central and peripheral chemoreceptor stimulation. Excessive central chemoreceptor responses lead to overly large increases in ventilation, thereby lowering the arterial P_{CO_2} too far and initiating another cycle of apnea. As ventilatory acclimatization proceeds, periodic breathing diminishes over several days at moderate altitudes (<3000 m) but, at higher altitudes or with ongoing ascent, this breathing can persist.[65,66]

Periodic breathing can be eliminated by breathing supplemental oxygen (Fig. 105.5), and it can be reduced by using respiratory stimulants such as acetazolamide.[67] Acetazolamide may also improve overall sleep quality,[63,68] as can pharmacologic agents such as temazepam, zolpidem, and zaleplon. Of these agents, temazepam decreases periodic breathing,[65] whereas the latter two have no effect on this phenomenon.[69,70] Although periodic breathing is not dangerous by itself, it interferes with sleep quality.

EXERCISE

Exercise at high altitude is different in many respects from exercise at sea level.

Maximal Work

With acute and sustained hypoxia, maximal oxygen consumption and work capacity decrease relative to sea-level values,[71,72] at an approximate rate of about 10% per 1000 m of altitude gain. Because maximum oxygen uptake is decreased at high altitude, maximum minute ventilation and heart rate at end-exercise are also reduced compared with their sea-level values (Fig. 105.6).[71]

Ventilation

For any given work rate, minute ventilation is higher at high altitude than at sea level, with the magnitude of change varying as a function of both the altitude attained and the strength of the individual's HVR.[73] However, the increase in ventilation comes at a price because, at extreme altitude, the oxygen cost of breathing during exercise may be as high as 40% of the overall metabolic rate and may result in allocation of cardiac output to respiratory muscles instead of to muscles of locomotion. Extreme dyspnea with exercise may also limit the intensity and duration of exercise.

Gas Exchange

Unlike at sea level, where arterial S_{O_2} remains constant with increasing work, arterial S_{O_2} at high altitude decreases with exercise following either short[74] (Fig. 105.7) or long exposures.[71] Alveolar hypoxia decreases the gradient for

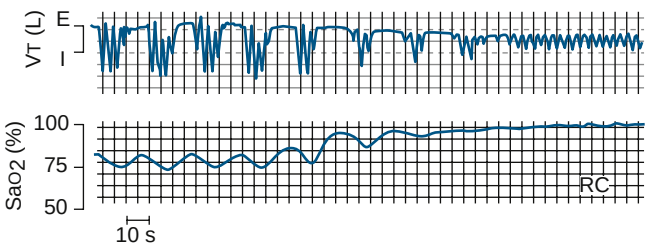

Fig. 105.5 Effect of altitude on breathing during sleep. Periodic breathing in a lowlander at 5400 m during sleep while breathing ambient air (*left half* of tracings) and oxygen (*right half* of tracings). *Top panel,* tidal volume (V_T, inspiration downward); *bottom panel,* arterial oxygen saturation (Sa_{O_2} [%]). (From Lahiri S, Maret K, Sherpa MG. Dependence of high-altitude sleep apnea on ventilatory sensitivity to hypoxia. *Respir Physiol.* 1983;52:281–301.)

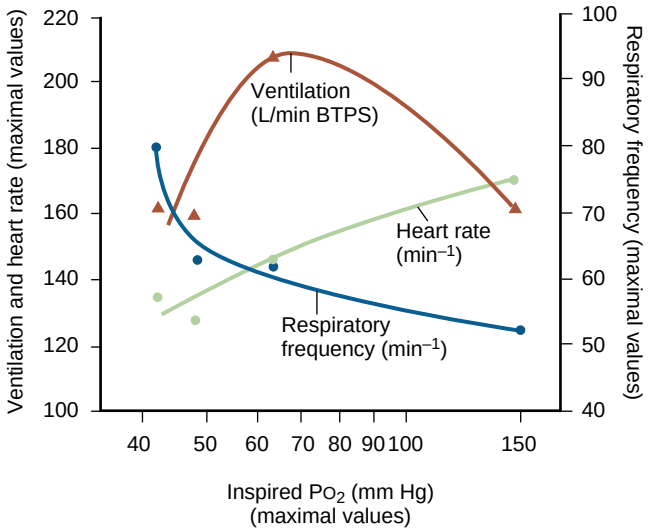

Fig. 105.6 Maximal ventilation, respiratory frequency, and heart rate versus inspired P_{O_2}. At a P_{O_2} of 64 mm Hg, equivalent to about 6300 m, maximal ventilation is increased because of the stimulation to ventilation from hypoxia, as well as a decreased density of the inspired air whereas, at a P_{O_2} of 43 mm Hg, equivalent to an altitude higher than 8000 m, maximal ventilation is decreased, probably as a result of a diminished metabolic demand from low work rates. Frequency continues to increase. Maximum heart rate decreases with increasing altitude. BTPS, body temperature ambient pressure, saturated with water vapor. (From West JB, Boyer SJ, Graber DJ, et al. Maximal exercise at extreme altitudes on Mount Everest. *J Appl Physiol.* 1983;55:688–702.)

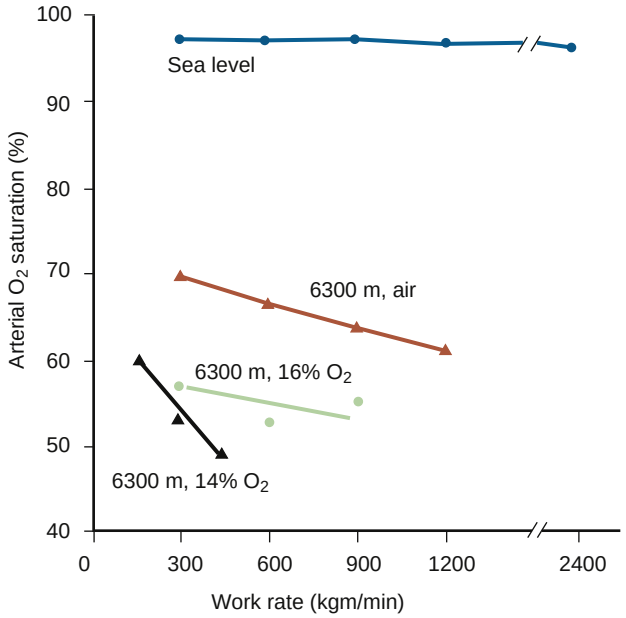

Fig. 105.7 Arterial oxygen saturation and altitude. Arterial oxygen saturation does not decrease with exercise at sea level but drops progressively with higher workloads at lower inspired P_{O_2}. At the 16% and 14% O_2 conditions, the inspired P_{O_2} was equal to that at 8050 m and 8848 m (the summit of Everest), respectively. The steep fall in O_2 saturation with the increasing work rate can be explained by diffusion limitation of oxygen transfer across the blood gas barrier. (From West JB, Boyer SJ, Graber DJ, et al. Maximal exercise at extreme altitudes on Mount Everest. *J Appl Physiol.* 1983;55:688–702.)

diffusion, while pulmonary capillary transit time is shortened as a result of the increase in cardiac output, thereby creating a true diffusion limitation (see Fig. 105.3). Ventilation-perfusion mismatching may also contribute to the observed gas exchange abnormalities[74] because nonuniform HPV may cause interstitial pulmonary fluid accumulation that, in turn, worsens ventilation-perfusion heterogeneity and impairs gas exchange.

Cardiovascular Response

For any given *submaximal* work rate, cardiac output and heart rate are higher during exercise on initial ascent compared with sea level. With acclimatization, cardiac output at submaximal workloads returns to sea level values, whereas heart rate remains elevated. However, because *maximum* exercise capacity is reduced, peak heart rate and cardiac output at altitude are lower than at sea level. Because acclimatization does not restore maximal exercise capacity to sea-level values, maximum cardiac output, heart rate, and stroke volume all remain decreased as well, despite acclimatization.[24]

PA pressure reaches high levels during exercise at high altitudes.[32] Whether this response limits exercise capacity at altitude is not clear. Because cardiac output is maintained at levels appropriate for the work rates attained, the increase in PVR in healthy sojourners to high altitude would not appear to limit exercise. However, in a field study of acclimatized individuals at 5245 m,[75] administration of the phosphodiesterase inhibitor sildenafil before a maximum exercise test lowered PA systolic pressure and improved maximum exercise capacity compared with placebo. This result has not been confirmed in other studies,[76] however, and it remains unresolved whether the rise in PA pressure contributes to exercise limitation at high altitude.

Exercise Performance at High Altitude

The effect of moderate altitude on exercise performance varies based on the type of activity and the duration of stay at high altitude. For running and throwing events of less than 2 minutes' duration, performance at high altitude is not impaired at altitudes lower than 3000 m and may even slightly improve because of decreased air density and resistance. However, for longer-duration events, performance is predictably diminished and can be restored only in part to sea-level capacity with prolonged stays at high altitude. Finally, as noted earlier, maximum oxygen consumption, peak heart rate, and minute ventilation are reduced at high altitude and do not return to sea level values regardless of the duration of stay or intensity of training.

Training at High Altitude

Ever since the 1968 Olympics in Mexico City (2200 m), there has been considerable interest in whether residence and training at high altitude improves performance at lower elevations. In the past, many elite endurance athletes relocated to and trained at moderate altitudes above 2000 m, but the beneficial effects on performance after return to sea level were generally not realized because, at high altitude, athletes could not attain the same maximum speeds and power output as when training at sea level. This problem led to interest in using intermittent hypoxia as an alternative means to apply the benefits of high-altitude acclimatization to sea-level performance. In a landmark study, Levine and Stray-Gundersen[77] used a randomized, controlled design and demonstrated that a combination of residence at high altitude (~3000 m) and training at lower elevation

(~1350 m) was associated with improvements in performance compared with those who lived and trained either at high altitude or at low elevation. This advantage was presumably the result of the modestly elevated hemoglobin from the altitude exposure, because there was individual variability in the erythropoietic response that correlated with improvement in performance.[78]

Because access to high altitude is limited for many athletes, interest has focused on "bringing the mountain to the athlete,"[79] by having the athlete spend time each day in oxygen-depleted tents that can be set up in the home or training center. Key questions that persist, however, are what "dose" of hypoxic exposure and what level of fitness are necessary to see a benefit in sea-level performance. A review concluded that athletes needed to reside at 2000 to 2500 m for 4 weeks or longer and for 22 hours or more per day to derive benefits from the live high–train low model,[79] but a subsequent placebo-controlled trial in which elite athletes were blinded to whether they were "living high" found no benefit to this strategy.[80] Approaches to altitude training and the data regarding their utility have been reviewed extensively elsewhere.[81,82]

MALADAPTATION

The physiologic adaptations described earlier give most individuals the ability to tolerate high-altitude exposure. However, regardless of the ultimate altitude achieved, individuals ascending too rapidly to altitudes higher than 2500 m may manifest maladaptive responses and develop one of three forms of acute altitude illness: *acute mountain sickness* (AMS), *high-altitude pulmonary edema* (HAPE), and *high-altitude cerebral edema* (HACE). Although long-term residents are not susceptible to these acute problems, several forms of chronic altitude illness—chronic mountain sickness and right heart failure—can affect these populations and represent important public health concerns.

PROBLEMS OF LOWLANDERS ON ASCENT TO HIGH ALTITUDE

Susceptibility to Altitude Illness

The incidence and severity of acute altitude illness depend on several factors, including the rate of ascent, the length of stay, and individual susceptibility. A trip to and from high altitude on the same day poses much less risk than an overnight stay because alveolar hypoxia is accentuated during sleep and because the overnight stay prolongs the duration of exposure. Susceptibility to altitude illness varies considerably among individuals but, for a single individual, the symptoms are often reproducible if the rate and other circumstances of the ascent remain roughly similar. Any individual who ascends too high and too fast can develop altitude illness, even if the person has never been sick at high altitude before.[83] Of note, being in good physical condition is not protective.[84]

At present, there is no way to predict who will get sick on ascent. Variables such as the HVR[85] and arterial S_{O_2} during hypoxic exposure[86] have been proposed as useful predictors for developing AMS, but they have not been validated in further studies, and specific genetic markers that predict susceptibility have not yet been identified.[87] Richalet and associates[88] derived and validated a model to identify patients with risk factors for severe high-altitude illness, but this model requires the use of cardiopulmonary exercise testing under hypoxic conditions to identify susceptible individuals and, as a result, is difficult to implement on a wide basis.

HAPE-susceptible individuals have been shown to have intense HPV and exaggerated pulmonary vascular responses to resting hypoxia and normoxic exercise,[29,89] but the presence of such responses alone is not sufficient to cause HAPE.[90] In the end, the only useful predictive tool remains the patient's prior experience at high altitude, particularly when the ascent rate and altitude of the prior and planned sojourns are similar.

Acute Mountain Sickness

AMS is the most common form of acute altitude illness, affecting 22–50% of travelers to altitudes between 1850 and 4240 m.[91,92] Given the increased awareness of the risks of altitude illness among the general population, the incidence of AMS has fallen in commonly traveled regions,[93,94] but very high rates (up to 70%) continue to be reported with rapid ascents to high elevations in certain regions such as Mt. Kilimanjaro.[95]

Clinical Presentation. AMS is marked by the presence of headache in addition to one or more other symptoms, including lassitude, anorexia, nausea, dizziness and, in severe cases, vomiting, although recent debate has developed on whether headache is required for diagnosis.[96,97] Difficulty with sleep was previously considered a primary symptom of AMS but was removed from the revised Lake Louise Acute Mountain Sickness Scoring System[98] after systematic studies showed it was not closely related to AMS.[99] Symptoms do not start immediately on ascent and instead come on over many hours following arrival at altitudes higher than 2400 m (8000 feet); the elevation at which symptoms begin varies significantly among individuals.

There are no characteristic physical examination findings, although mild increases in body temperature, crackles on auscultation, and peripheral edema have been documented in some reports.[100–102] S_{O_2} may be lower in individuals with AMS compared with those who remain healthy,[103,104] but AMS can still be seen in persons with what would be considered normal oxygenation.

The symptoms and signs of AMS are nonspecific, and other items must be considered in the differential diagnosis, including dehydration, hypothermia, hyponatremia, exhaustion, alcohol hangover, carbon monoxide poisoning, and central nervous system infection. The diagnosis is based solely on the clinical history, and there are no confirmatory laboratory tests. For a diagnosis of AMS, instead of HACE, the patient must have a normal neurologic examination and normal mental status.

Time Course of Symptoms. Symptoms develop after 6 to 10 hours at a given elevation, not immediately. In a study of a general tourist population traveling to 1900 to 2950 m in Colorado, Honigman and colleagues,[91] for example, reported that 65% developed symptoms within 12 hours of arrival at altitude, whereas 34% developed symptoms

between 12 and 36 hours following arrival. Onset after 36 hours at a given elevation is uncommon and should prompt a careful evaluation for alternative causes.

Symptoms are typically self-limited and resolve without treatment over a period of 1 to 4 days as the body acclimatizes to hypoxia although, in rare cases of individuals with very poor altitude tolerance, symptoms may persist for longer periods[100] and resolve only on descent. Even though symptoms resolve in most cases, they may recur with subsequent large gains in elevation if the individual does not take appropriate precautions. A small percentage of those with AMS proceed to develop HACE or HAPE, especially if ascent is continued despite illness.

Pathophysiology. Despite a considerable amount of research in this area, there is no coherent, unified explanation for why individuals develop AMS. Beyond the finding that hypoxemia is the key inciting factor that sets in motion a series of physiologic responses and pathophysiologic processes that ultimately cause AMS, the causal pathway leading from hypoxemia to that end point remains unclear. One challenge in interpreting the literature is that, although many studies have established associations between various physiologic derangements and AMS, they have failed to establish a causal relationship.

Because headache is the cardinal symptom of AMS, investigations of AMS pathophysiology often revolve around the pathophysiology of headache, with one of the leading concepts being the role played by trigeminovascular activation.[105] A long-standing concept in the literature is that symptom onset is related to the development of intracranial hypertension; however, increased intracranial pressure has not been consistently demonstrated in patients with AMS by using either direct or surrogate measures such as optic nerve sheath diameter. The *tight fit hypothesis*, which posits that individuals with a lower ratio of cerebral spinal fluid to blood and brain tissue volume have decreased ability to compensate for cerebral swelling or increased intracranial blood volume,[106] has long been an appealing theory from a theoretical standpoint, but supportive data are lacking. Various other factors have been considered to play a causal role, including ventilatory responses to hypoxemia,[107] alterations in CBF[108] or cerebral autoregulation,[109] subclinical pulmonary edema, abnormal fluid balance,[110,111] inflammation,[112] alterations in cerebral venous outflow,[113] and differences in mediators such as vascular endothelial growth factor,[114] free radicals, or reactive oxygen species.[115] Each of these factors may contribute in some way to the development of AMS, but as noted earlier, the particular causal links remain unclear.

Prevention. The pharmacologic and nonpharmacologic approaches to prevention and amelioration of AMS have been described in published guidelines.[116] Because overly rapid ascent to high elevation is the leading risk factor for altitude illness, gradual ascent, with rest days for acclimatization, is the single best way to prevent all acute altitude illness. Once higher than 3000 m, individuals should increase their sleeping elevation by no more than 300 to 500 m per night and should take an acclimatization day and sleep at the same elevation for two or more nights every 3 to 4 days or after any large gain in elevation. Although only a single study has demonstrated the benefits of slow ascent in a randomized, controlled manner,[117] considerable observational data support this approach. Strict adherence to published recommendations may be difficult, however, for a variety of logistic factors. Travelers should avoid overexertion and refrain from heavy alcohol consumption or opiate medication use, particularly before bedtime, to avoid hypoventilation, which can exacerbate hypoxemia. These strategies have not been systematically studied but represent common sense measures in light of the known physiologic changes at altitude. Staged ascent, in which an individual spends several days at a moderate elevation before ascending to the higher target elevation,[118,119] or preacclimatization, in which an individual undertakes repeated hypoxic exposures in the days and weeks before the planned ascent,[120,121] may be useful for preventing AMS. However, the precise recipe for implementing these strategies is unclear, and they can be logistically challenging to implement in practice.

Pharmacologic measures can also be used to prevent AMS in individuals deemed to be of moderate to high risk for AMS based on a prior history of the problem and/or features of their ascent profile[116] (Table 105.2). The most commonly used medication for this purpose is acetazolamide. Its principal action is renal carbonic anhydrase inhibition, which causes bicarbonate diuresis and metabolic acidosis, which, in turn, stimulates ventilation, increases alveolar Po_2, and enhances oxygen off-loading in the tissues. In effect, the drug speeds natural acclimatization by accelerating ventilatory acclimatization. Actions of acetazolamide on carbonic anhydrase elsewhere in the body, such as the peripheral and central chemoreceptors, may also contribute to its preventive role.[122] Acetazolamide is well tolerated, with the most common side effects being paresthesia involving the hands, feet, and lips and altered taste of carbonated beverages secondary to inhibition of hydration of carbon dioxide on the palate. Acetazolamide has a sulfonamide moiety and shares the cautions common to all sulfa drugs. The likelihood of cross-reactivity is very low,[123] but case reports do describe fatal anaphylaxis in persons with documented sulfa allergy who received acetazolamide.[124] For patients who do not tolerate or cannot take acetazolamide, dexamethasone is an effective alternative to AMS prophylaxis.[125] Although equally effective as acetazolamide,[126] dexamethasone does not hasten acclimatization, and symptoms may recur with abrupt discontinuation.[127] Attention has also focused on a potential prophylactic role for ibuprofen,[128] but it has yet to be proven equivalent to acetazolamide,[129] and it is not part of standard protocols at this time.[116]

Treatment. Descent leads to resolution of all forms of altitude illness, but patients with mild AMS usually recover by simply resting at the same elevation for a period of time. Descent is indicated in more severe cases or when symptoms fail to resolve with appropriate interventions and should continue until symptoms resolve. Logistic and other factors sometimes preclude descent, and alternative treatments may be necessary. Severely ill patients can be administered supplemental oxygen if gas tanks or oxygen concentrators are available or "low altitude" can be brought to the patient through the use of lightweight portable hyperbaric chambers (eFig. 105.1). These chambers, which can be pressurized to 2 psi and mimic a descent of approximately 1500 m,

Table 105.2 Dosing and Use of Altitude-Illness Medications

Medication	Indication	Route	Dosage
Acetazolamide	AMS, HACE prevention	Oral	125 mg q12h Pediatrics: 2.5 mg/kg q12h (maximum, 125 mg/dose)
	AMS treatment	Oral	250 mg q12h Pediatrics: 2.5 mg/kg q12h (maximum: 125 mg per dose)
Dexamethasone	AMS, HACE prevention	Oral	2 mg q6h or 4 mg q12h Pediatrics: Should not be used for prophylaxis
	AMS, HACE treatment	Oral, IV, IM	AMS: 4 mg q6h HACE: 8 mg once then 4 mg q6h Pediatrics: 0.15 mg/kg/dose q6h (maximum: 4 mg per dose)
Ibuprofen	AMS prevention	Oral	600 mg q8h
Nifedipine	HAPE prevention	Oral	30 mg ER version q12h or 20 mg ER version q8h
	HAPE treatment	Oral	30 mg ER version q12h or 20 mg ER version q8h
Tadalafil	HAPE prevention	Oral	10 mg q12h
Sildenafil	HAPE prevention	Oral	50 mg q8h

AMS, acute mountain sickness; ER, extended-release; HACE, high-altitude cerebral edema; HAPE, high-altitude pulmonary edema; IM, intramuscular; IV, intravenous.

have been shown to improve symptoms of AMS,[130,131] but they can be difficult to use with claustrophobic individuals or those who are vomiting. Relief of symptoms can be seen with as little as 1 hour of treatment, but the effects are not durable with such short treatment courses.[130]

Affected individuals can use aspirin,[100] acetaminophen, nonsteroidal anti-inflammatory drugs,[132] and antiemetics to relieve AMS symptoms. Individuals not responding to these conservative measures or persons with more severe AMS can add either acetazolamide[133] or dexamethasone[127,134,135] (see Table 105.2). The relative efficacy of these agents has not been studied, but clinical experience suggests that dexamethasone is a faster and more reliable intervention than acetazolamide.[116] Dexamethasone should never be taken to suppress symptoms of AMS while continuing to ascend.

High-Altitude Cerebral Edema

HACE is a potentially fatal form of acute altitude illness defined by the onset of mental status changes or ataxia in a person with AMS or by the presence of both neurologic signs in a person without AMS who has recently ascended to high altitude. It usually develops at altitudes higher than 3000 to 4000 m, although cases have been seen in conjunction with HAPE at more moderate altitudes in Colorado (~2500 m).[136] Although incidence rates of 0.26–1% have been reported,[92,137] the true incidence is difficult to assess because the boundary of progression from AMS is difficult to define, and the symptoms and signs may be similar to those of cerebral hypoxia secondary to severe hypoxemia from pulmonary edema. If HACE is not recognized and treated promptly, coma and death may ensue.

Based on findings on brain magnetic resonance imaging (discussed later), it has long been thought that HACE develops as a result of vasogenic, rather than cytotoxic, edema. More recent studies suggest that patients may progress from maladaptive ion transport to vasogenic edema and, in severe cases, hemorrhagic conversion,[138] whereas preliminary research suggests that the glymphatic system, consisting of a series of periarterial and perivenous channels associated with glial cell aquaporin channels, may also play a role in disease pathophysiology.[139]

In addition to symptoms of AMS, the most common signs include ataxia and altered mental status. Altered mental status may initially be subtle and include problems such as apathy, irritability, lassitude, and inability to eat or care for oneself before more obvious signs appear, including confusion, somnolence and, in the most severe cases, coma. Most cases are preceded by AMS but, in rare instances, HACE develops without preexisting AMS symptoms.

The physical examination demonstrates signs of global neurologic dysfunction rather than focal neurologic deficits, although the latter have been documented, along with abnormal reflexes, anisocoria, hallucinations, clonus, cranial nerve palsies, and seizures.[100,137,140,141] Retinal hemorrhages have been reported in HACE,[137] but they are common in otherwise healthy individuals at very high elevation,[142] and they are not a harbinger of the development of AMS or HACE. Hypoxemia is common in HACE and results from either poor ventilatory acclimatization or concurrent HAPE.

Because HACE is a global encephalopathy marked by onset over a period of hours, a sudden onset, and/or the presence of focal neurologic deficits, high fevers, or neck stiffness should prompt consideration of alternative diagnoses, including all other causes of encephalopathy, such as carbon monoxide poisoning, hypertensive crisis, hypoxic encephalopathy secondary to HAPE, meningitis, hypoglycemia, moderate to severe hypothermia, and severe migraine headache. Diagnosis in the field is based on clinical history and physical examination. Heel-to-toe walking along a straight line is an effective test for ataxia (see Video 105.2). When advanced diagnostic modalities are available, head computed tomography scans show nonspecific changes of diffuse edema, whereas magnetic resonance imaging reveals a pattern of reversible increased T2-weighted signal predominantly in the splenium and genu of the corpus callosum.[143] Microhemorrhages are common and specific findings,[143–145] and they may be present for up to 50 months following resolution of HACE, thus providing an

opportunity to confirm the diagnosis after symptoms have resolved following descent.[136,145]

Descent is the definitive treatment for HACE, although recovery in severe cases may take several weeks.[136,141] If descent is not feasible, oxygen and portable hyperbaric therapy (see eFig. 105.1) may be lifesaving temporizing measures. Although very early reports documented the use of furosemide and betamethasone,[100] dexamethasone is now the standard pharmacologic intervention for HACE (see Table 105.2). Mannitol and hypertonic saline are difficult to use safely in the field because of a lack of adequate monitoring, and they should be used only in a hospital or clinic setting.

High-Altitude Pulmonary Edema

The most common cause of death from high-altitude illness, HAPE was historically misdiagnosed as pneumonia, bronchitis, or congestive heart failure until reports by Hultgren and colleagues[89] and by Houston[146] revealed it to be a distinct form of noncardiogenic pulmonary edema.

Clinical Presentation. Typically manifesting within 2 to 4 days of ascent to altitudes higher than 2400 m, persons with HAPE usually present in the early stages with decreased exercise performance and increased time to recover from exertion, as well as fatigue, weakness, a persistent dry cough, and, in some cases, symptoms of AMS. As the disease worsens, individuals are dyspneic on minimal exertion and, in the most severe cases, dyspneic at rest. Even in the absence of concurrent HACE, severe hypoxemia may produce mental changes, ataxia, and altered levels of consciousness.

On physical examination, patients may have a low-grade fever to 38.5°C as well as tachycardia, tachypnea, and decreased oxygen saturation by pulse oximetry (Spo_2). Generalized pallor and cyanosis are often present, whereas crackles are initially heard in the right mid-lung fields and then more diffusely as the disease worsens. Radiographs[147] and computed tomography scans show patchy, alveolar opacities, which may be limited to one area (the right lung field predominating initially) or generalized, depending on illness severity (Fig. 105.8). Arterial blood gas measurements reveal severe hypoxemia. In a study at 4559 m, for example, individuals with HAPE had a mean arterial Po_2 of 23 ± 3 mm Hg and an average arterial So_2 of 48 ± 8% versus 40 ± 5 mm Hg and 78 ± 7%, respectively, for healthy control subjects.[148] Although not used as part of diagnostic protocols, right heart catheterization performed in a research setting demonstrates increased PA and pulmonary capillary pressure, but normal pulmonary capillary wedge pressure consistent with normal left ventricular function.[89,149]

Possible Mechanisms. HAPE is a form of noncardiogenic pulmonary edema marked by normal left ventricular function. Unlike the situation with AMS and HACE where the precise pathophysiologic mechanisms are unclear, it is well established that elevated PA pressure plays a key role in development of HAPE, because multiple investigations have shown that affected individuals have markedly elevated PA pressures compared with healthy controls.[89,149,150]

HAPE-susceptible individuals have exaggerated HPV, which likely accounts for their elevated PA pressures; multiple studies demonstrate that HAPE-susceptible individuals have abnormally high PA pressure responses during hypoxic breathing, during normoxic and hypoxic exercise, and on ascent to high altitude before the onset of edema.[29,30] The reasons for this exaggerated response are not entirely clear but may be related to differences in hypoxic ventilatory responsiveness,[151,152] lung volumes,[153] increased sympathetic tone,[154] or alterations in circulating vasoactive mediators including endothelin, nitric oxide, and free radicals.[155–159]

Given the central importance of elevated PA pressure in the pathogenesis of HAPE, the question is how this elevated pressure causes fluid accumulation when patients with severe pulmonary arterial hypertension at sea level do not typically have pulmonary edema. Hultgren[160] has suggested that edema results from uneven hypoxic vasoconstriction, leading to overperfusion of the microvasculature in areas of the lung where arteriolar vasoconstriction fails to protect downstream vessels. Uneven perfusion is suggested clinically by the typical patchy radiographic appearance (see Fig. 105.8) and by magnetic resonance imaging studies in persons breathing hypoxic gas mixtures,[161] which demonstrate more heterogeneous perfusion in HAPE-susceptible subjects.

Earlier work suggested that the leak in overperfusion edema was the result of *capillary stress failure* in which high shear forces cause biomechanical stress and injury in the precapillary arterioles and capillaries,[162,163] but other investigators[164] have argued that high pressures and shear

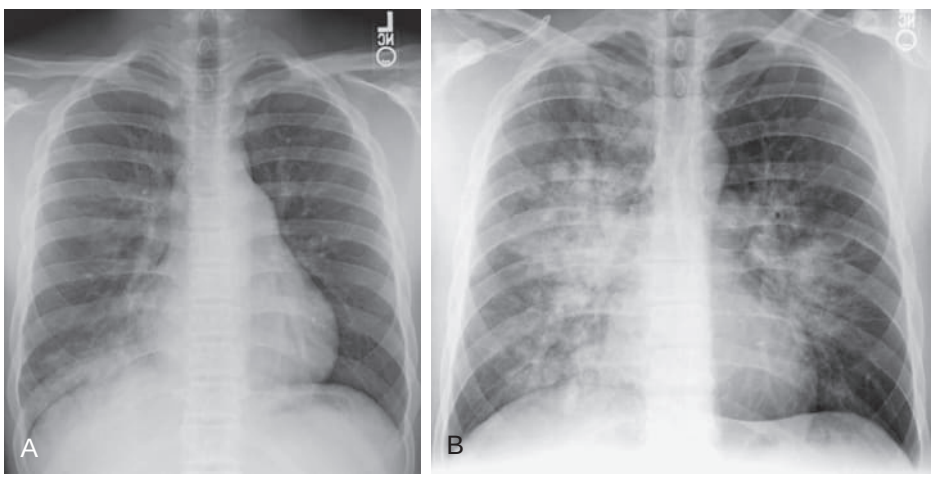

Fig. 105.8 Radiographs of high-altitude pulmonary edema. (A) Typical chest radiographic appearance of high-altitude pulmonary edema in a 15-year-old boy. Note that the edema is predominantly right sided. (B) Severe high-altitude pulmonary edema in a 27-year-old man. Note the normal heart size and the presence of bilateral opacities in this case. (Courtesy Peter Hackett.)

stress lead to a high permeability–type leak along a continuum of pressure-related phenomena by which plasma and even RBCs move from the intravascular space to the interstitium and subsequently into the alveolar space. At lower levels of pressure elevation, stretch on collagen and other supporting extracellular matrix elements may induce dynamic and quickly reversible changes in barrier permeability[165] that, with greater duration and further pressure elevation, may lead to capillary rupture and alveolar hemorrhage, as seen in severe HAPE.

Although the data largely establish a mechanical basis for HAPE, a role for inflammation was suggested by bronchoalveolar lavage studies in patients with HAPE that demonstrated increased cellularity and the presence of chemotactic (leukotriene B_4) and vasoactive (thromboxane B_2) mediators compared with control subjects.[166] Swenson and associates[150] further clarified the role of inflammation by performing bronchoalveolar lavage in HAPE-susceptible individuals and normal control subjects within the first 24 hours of arrival at 4559 m, earlier than the lavage samples obtained in the earlier studies. The lavage fluid demonstrated high protein and RBC content, the levels of which correlated with PA pressure estimated by echocardiography (eFig. 105.2), but no evidence of cytokine expression or neutrophil recruitment. These findings solidified the notion that HAPE arises from high intravascular pressure, rather than from inflammation. Inflammation may, however, play a role in certain situations, because viral respiratory infections may predispose children to HAPE,[167] and anecdotal reports suggest a similar role of viral infections in adults. These infections may trigger inflammation, which makes the capillary endothelium more vulnerable to increased pressures. This phenomenon may explain the cases of HAPE seen at atypically low altitudes (1500 to 2400 m).[168] Alterations in the alveolar epithelium may also contribute to HAPE. Hypoxia, for example, decreases alveolar transepithelial sodium transport[169] and fluid clearance,[170] with potential effects on alveolar fluid balance. In human studies, transepithelial potential differences across the nasal mucosa were studied as a model of alveolar epithelial function. In these studies, lower transepithelial nasal potentials in normoxia were indicative of decreased epithelial sodium channel transport in HAPE-susceptible individuals compared to control subjects.[171] A subsequent study confirmed the difference in nasal potential between HAPE-susceptible individuals and control subjects in normoxia, but the study could not attribute these differences to alterations in epithelial sodium channel activity.[172] Transalveolar sodium transport can be increased by β_2-receptor stimulation, and a field study reported successful prevention of HAPE with inhalation of the long-acting β_2-agonist salmeterol.[171] However, given the multiple actions of this drug, including increased ventilatory response to hypoxia, and tightening of cell-to-cell contacts, the contribution of enhanced alveolar fluid clearance to the study's positive outcome remains uncertain.[173]

Allemann and colleagues[174] documented an increased incidence of patent foramen ovale in HAPE-susceptible individuals at low and high altitude compared with healthy control subjects and argued that the presence of this anomaly may increase the risk of HAPE. It is not clear, however, whether the patent foramen ovale causes HAPE or is a sequela of prior marked rises in PA pressure during sojourns to high altitude or during normoxic exercise seen in HAPE-susceptible individuals.[175]

Prevention. The nonpharmacologic preventive measures previously described for AMS also apply to HAPE, with a slow ascent being the most important strategy. HAPE-specific pharmacologic prophylaxis is reserved for persons known to be HAPE susceptible based on a prior history of the disease (see Table 105.2). The mainstay of prevention is nifedipine, presumably via its action as a potent vasodilator, which was shown in a small study to be effective in individuals with a past history of the illness.[176] More recently, Maggiorini and colleagues[177] demonstrated that another vasodilator, the phosphodiesterase inhibitor tadalafil, can also prevent HAPE in known susceptible individuals. An unexpected finding of this study was that dexamethasone was also effective in this regard. Subsequent studies showed that dexamethasone decreases estimated PA pressure following ascent to 4559 m[178] but, because the mechanism of action remains unclear and clinical experience with dexamethasone for HAPE prophylaxis is limited, it is not part of standard HAPE prevention protocols.[116] A single study also established that inhaled salmeterol augments alveolar fluid clearance and may prevent HAPE,[171] but very high doses (2.5 times those used in asthma) were used in the study and may be associated with side effects that affect patient tolerance. For this reason, it is also not recommended as a primary option for HAPE prophylaxis.[116]

Treatment. Proper treatment depends on the severity of the illness and the clinical setting. In remote locations with limited access to care, the first priority is descent to lower elevation. Exertion should be limited during descent because this may increase PA pressure and worsen pulmonary edema. With early diagnosis, recovery is rapid with descents of only 500 to 1000 m, and the individual may be able to reascend cautiously 2 or 3 days later. If descent is not possible because of weather or other factors, supplemental oxygen or portable hyperbaric therapy should be initiated. If neither option is available, expiratory positive airway pressure may improve oxygenation, although the effect on outcomes has not been established.[179]

Given the reduced margin for error in remote settings, use of a pulmonary vasodilator such as nifedipine is warranted regardless of whether supplemental oxygen is available. The data supporting this practice are limited,[180] however, and the recommendation is based largely on extensive clinical experience. Other pulmonary vasodilators such as tadalafil and sildenafil have not been studied for HAPE treatment, but reports document their use, often in conjunction with calcium channel blocker therapy.[181,182] However, given the absence of data supporting benefit and the risk of provoking systemic hypotension, concurrent use of two pulmonary vasodilators should be avoided. Diuretic agents were used in the past,[183] but they are now avoided because patients with HAPE are typically volume depleted at the time of diagnosis and at risk for hypotension.

Individuals who can access well-supported medical facilities can typically be treated with bed rest and oxygen without the need for evacuation to lower elevation.[184,185] Well-selected patients with mild disease and adequate

support by family or friends can often be sent home or to their hotel with supplemental oxygen.[186] Addition of nifedipine or other pulmonary vasodilators to supplemental oxygen may not yield additional benefit,[185,187] and this treatment is generally reserved for those patients not responding appropriately to supplemental oxygen. A single series documented the use of continuous positive airway pressure to relieve dyspnea in HAPE,[168] but there are no controlled data demonstrating improved outcomes. Because fevers up to 38.5°C have been described in HAPE, a finding of elevated temperature should not prompt administration of antibiotics unless the clinical picture is consistent with pneumonia. Patients who do not improve with appropriate therapy should be investigated for other causes of hypoxemia and radiographic opacities.

PROBLEMS OF HIGH-ALTITUDE RESIDENTS

Chronic Mountain Sickness

First described in Andean dwellers by Monge[188] in 1928 and often referred to as Monge's disease, *chronic mountain sickness* (CMS) is a commonly described form of chronic altitude illness. It is seen in persons born and living at high altitude, as well as in lowlanders who move to high altitudes and stay for more than 1 year. Excessive erythrocytosis, defined as a hematocrit higher than 60–70% or more than two standard deviations above the average value for healthy residents at a given high altitude, is an essential characteristic of this syndrome. There are geographic and ethnic differences in the prevalence of CMS. It is rarely found in natives of the Tibetan plateau and Ethiopian highlands but is frequently encountered in the Andes, in the North American Rockies, and in other mountainous regions where lowlanders have moved as, for example, in Han Chinese who have been relocated to Tibet.[189–191] The reason for these regional differences is unclear, but they may relate to genetic polymorphisms affecting factors such as hypoxic pulmonary vasoconstriction and erythrocytosis that arose as a result of differences in duration of existence at high elevations between the Tibetan and Ethiopian highlanders compared with that of the Andeans and others who are more susceptible to the disease.

Clinical Presentation. Symptoms of CMS resemble those found in persons with polycythemia at low altitude: headache, dizziness, lethargy, impaired memory and mentation, decreased exercise tolerance, arthralgias, and poor sleep. Physical examination reveals deep cyanosis of the lips, mouth, and throat, digital clubbing, plethoric appearance, and hyperemic conjunctivae, whereas laboratory studies show the characteristic elevated hematocrit and hemoglobin concentration.[192] Chest radiography typically demonstrates enlargement of the right atrium and ventricle and pulmonary arteries, whereas electrocardiography reveals P pulmonale and right-axis deviation, among other findings.[193] The diagnosis is established by eliminating all other causes of polycythemia. Indeed, much confusion in the literature regarding incidence and other aspects of CMS may reflect inadequate validation of the diagnosis. For example, several studies have found evidence of respiratory disease in a high percentage of CMS patients in both Peru and Colorado.[189,194] The Qinghai score, which is based on the hemoglobin concentration and other signs and symptoms, can be used to quantify the severity of disease.[195]

Pathophysiology. The likely initiating factors for CMS are a blunted HVR and relative hypoventilation. Hypoventilation increases alveolar hypoxia and arterial hypoxemia. Alveolar hypoxia, in turn, triggers more HPV and greater pulmonary hypertension, whereas arterial hypoxemia leads to increased EPO secretion and more RBC production.[193,196,197] Serum EPO concentration may account for some of the excessive erythrocytosis because some CMS patients have EPO values that resemble those of healthy highlanders, rather than the low values one would expect in the setting of polycythemia, and thus they may not be able to "turn off" their EPO.[192] Instead of considering EPO levels, perhaps EPO availability, assessed as the ratio of serum EPO to its soluble receptor, an endogenous antagonist of EPO action, is the key factor.[198]

The precise cause and effect relationships among hypoventilation, polycythemia, and CMS are not entirely clear, however. For example, polycythemia has been shown to blunt ventilation and ventilatory responses,[199,200] whereas hypoxemia itself may contribute to the ventilatory depression, as evidenced by an increase in ventilation in some natives with CMS when given supplemental oxygen. Moreover, HPV may not be solely a function of increased alveolar hypoxia because CMS patients have also been noted to have accentuated PA pressure responses to modest exercise when compared with healthy individuals living at the same elevation,[201] a phenomenon also seen in HAPE-susceptible individuals.

Although the excessive polycythemia of CMS is likely the result of greater hypoxemia, the actual hematocrit is often higher than expected for the measured arterial So_2,[202] a finding suggesting that affected individuals have exaggerated erythropoietic responses to a given hypoxic stimulus.[196] Severe nocturnal desaturation may also contribute to the development of polycythemia because investigations in the Rocky Mountains revealed greater hypoxemia during sleep in patients with CMS compared with healthy controls.[203] Finally, Jefferson and associates[42] found that a majority of subjects with the most severe CMS and the greatest degree of excessive erythrocytosis in an Andean mining community had detectable serum concentrations of cobalt, a heavy metal known to stimulate renal EPO production. This may help explain the higher incidence of CMS in high-altitude regions where mining is common.

Once present, polycythemia may also contribute to the pulmonary vascular issues noted earlier because the increase in viscosity increases PVR. Along with impaired gas exchange and pulmonary vascular changes resulting from HPV, the onset of polycythemia represents a turning point in CMS that ultimately leads to the clinical deterioration and demise of these patients.[193,204]

Treatment. The keys to treating CMS are to reduce the hypoxic stimulus for RBC production and to decrease RBC mass. Although relocation to a lower altitude is the definitive means to achieve these goals, it is often not feasible, and other treatments are necessary. Phlebotomy with or without isovolumic hemodilution reduces symptoms and improves oxygenation and hematocrit,[205] but concerns exist about provoking iron deficiency with its potential effects on

PA pressure,[206] as well as a rebound effect on hematocrit whereby the hematocrit subsequently rises above the pretreatment values with return of symptoms.[192] Mild exercise may also be of benefit,[192] but care must be taken to avoid worsening pulmonary hypertension[201] or interstitial fluid accumulation.[207] Pharmacologic measures also have a role in treatment. Although studies have assessed the impact of angiotensin-converting enzyme inhibitors, medroxyprogesterone, and almitrine on oxygenation and hemoglobin concentration, the most promising agent appears to be acetazolamide, which has been demonstrated to reduce hemoglobin and serum EPO, as well as improve oxygenation, sleep disordered breathing, and PVR.[208,209]

High-Altitude Pulmonary Hypertension

An alternative form of altitude-related disease in long-term residents has also been described in areas outside the Andes Mountains. Referred to as high-altitude pulmonary hypertension, it is marked by pulmonary hypertension and right heart dysfunction *without* polycythemia. Based on consensus criteria,[195] high-altitude pulmonary hypertension is present if a resident at altitudes higher than 2500 m has a mean PA pressure greater than 30 mm Hg or a systolic PA pressure greater than 50 mm Hg, right ventricular hypertrophy, right heart failure, and moderate hypoxemia without excessive erythrocytosis (hemoglobin <21 g/dL in men and <19 g/dL in women). There is considerable overlap between this disease and subacute mountain sickness, a syndrome of pulmonary hypertension and right heart failure seen in lowlanders after weeks to months at high altitude,[210] with the major difference being the time spent at high altitude. There is also some debate about whether this truly represents a separate entity from CMS or is simply a variant of the same disease.[193]

Affected individuals manifest dyspnea, cough, cyanosis, peripheral edema, and physical examination findings consistent with right heart failure. Right-axis deviation, right ventricular hypertrophy, and P pulmonale may be present on the electrocardiogram, whereas chest imaging reveals right ventricular and right atrial enlargement and prominence of the pulmonary arteries.[195] The pulmonary hemodynamic findings are similar to those seen in patients with CMS.[193] The optimal treatment for the disorder is relocation to lower elevation, but that may not be feasible for many patients. A small placebo-controlled trial demonstrated that a 3-month course of the phosphodiesterase inhibitor sildenafil modestly lowered PA pressure (~6 to 7 mm Hg) and improved 6-minute walk distance,[211] but larger studies of this and other pulmonary vasodilators have not been performed, and there are no clear treatment guidelines.

Reentry and Resident Pulmonary Edema

Long-term residents who descend to lower altitudes may develop HAPE on reascent. Referred to as reentry HAPE, this phenomenon was originally described in Peru. In fact, many of the original cases of HAPE described in the literature were of the reentry variety. Since then, cases have also been widely reported in Colorado,[212] but only infrequently in the Himalayas.[213,214] No systematic studies have addressed the best means for prevention, but acetazolamide is commonly used for this purpose in children with history of reentry HAPE in Colorado.[215] No treatment trials have been conducted for reentry HAPE, and the disorder should be managed in the same way as for HAPE in unacclimatized lowlanders.

One report suggested that high-altitude residents may also be at risk for pulmonary edema even in the absence of a change in elevation. Ebert-Santos[216] documented multiple cases of high-altitude residents presenting to a clinic at 2800 m with hypoxemia and chest radiographs consistent with HAPE despite not having traveled to lower or higher elevations. All cases of what they referred to as mountain resident HAPE were seen in young children (ages 2 months to 15 years) and resolved readily with supplemental oxygen administration, although a few patients required up to 10 days of oxygen. The role of preceding viral infections in the development of pulmonary edema was not clear from this report, and physiologic data such as estimated PA pressure were not reported.

PREEXISTING ILLNESS AND HIGH ALTITUDE

Given the prevalence of many common diseases, such as hypertension and COPD, in the general population, it is likely that many high-altitude travelers have some underlying medical condition. This situation raises two important questions: (1) Will the underlying disease predispose these individuals to high-altitude illness? and (2) Will the stress of hypoxia at high altitude worsen control of their disease? To date, few studies have examined what happens to persons with respiratory and other diseases when they visit high-altitude destinations, and even fewer data are available on how to treat them before and after their exposure. Several major categories of respiratory diseases are discussed in the following subsections, whereas other major disease categories, including heart disease,[217–219] chronic kidney disease,[220] diabetes,[221,222] solid organ transplantation,[223] and chronic liver disease,[224] are reviewed elsewhere.

RESPIRATORY DISEASES

High-altitude exposure poses several challenges to patients with lung disease that have been reviewed extensively elsewhere.[225] Several important lung diseases are considered briefly here.

Chronic Obstructive Pulmonary Disease

Patients with COPD are at risk for exaggerated hypoxemia[226] and decreased exercise capacity[227] following ascent to high altitude. Spirometric measures of pulmonary function are unchanged,[226] and the risk of pneumothorax does not appear to be increased in those with bullous disease.[228,229] Patients with moderate to severe COPD (forced expiratory volume in 1 second <1.5 L) should undergo pretravel assessment of their risk of hypoxemia and need for supplemental oxygen. One of several published prediction rules can be used,[230,231] but the overall accuracy of these rules is not clear. A better test is the hypoxia altitude simulation test,[232] which allows one to observe actual physiologic responses to hypoxia. This approach is limited, however, by the short duration of exposure relative to the length of a high-altitude sojourn and the degree of hypoxia to which the patient can be exposed in a clinical testing environment. Those at risk for severe hypoxemia should travel with a portable oxygen concentrator or a

prescription for home oxygen that they can fill at their destination (e.g., a ski resort town). An alternative strategy in less severe disease is to monitor pulse oximetry following arrival and fill a prewritten home oxygen prescription if their saturation falls below a prespecified threshold.[233] Patients should travel with their controller medications and a supply of rescue medications in the event of an exacerbation.

Interstitial Lung Disease

Patients with various forms of interstitial lung disease are also at risk for exaggerated hypoxemia at high altitude that will worsen with even mild exertion.[231,234] From a theoretical standpoint, such patients may also have difficulty related to underlying pulmonary hypertension (described further later) and reduced lung compliance that may make it difficult to increase and maintain ventilation in response to hypoxemia at high altitude. Patients with severe restrictive physiology (total lung capacity <50% predicted) or a preexisting oxygen requirement should probably avoid high-altitude travel altogether, whereas those with less severe disease can travel to high altitude with adequate pretravel assessment to determine the need for supplemental oxygen.

Asthma

Changes in air temperature, humidity, and density may alter lung mechanics and airflow obstruction in patients with asthma, but field data demonstrate that patients with mild, well-controlled asthma have decreased bronchial hyperresponsiveness at elevations as high as 5000 m[235] and tolerate ascents as high as 6410 m without significant changes in their symptoms.[236,237] Asthma must be under good control before any trip to high altitude, and patients should travel with both their controller medications and an adequate supply of rescue inhalers and prednisone for use in the event of an exacerbation.

Pulmonary Vascular Disease

Only two studies have examined PA pressure responses to hypoxic exposure in patients with pulmonary hypertension. One study showed an increase in PA systolic pressure without deterioration in right heart function,[238] and the other showed no significant changes in mean PA pressure, PVR, or cardiac output.[239] Although these studies are somewhat reassuring, they involved very short exposures (≤20 minutes) to hypoxia, and multiple reports have documented HAPE in patients with various causes of pulmonary hypertension following ascent to high altitude.[240] Patients with New York Heart Association functional class III or IV symptoms or those who require continuous intravenous vasodilator therapy should avoid high altitude altogether. If travel is necessary, strong consideration should be given to using supplemental oxygen to blunt the rise in PA pressures. Patients with less severe disease may avoid problems but should consider adding or increasing the intensity of pulmonary vasodilator therapy and should monitor symptoms and pulse oximetry following arrival. Patients with congenital absence of a PA should also avoid high-altitude travel because these individuals are known to be susceptible to HAPE.[241,242]

Sleep Apnea

Although the decrease in barometric pressure and air density at high altitude could lead one to expect a decrease in the severity of obstructive sleep apnea following ascent, field studies suggest that obstructive sleep apnea persists following ascent to 2950 m and is accompanied by a marked increase in the number of central apneas, as well as impaired performance on simulated driving tasks, increased systolic blood pressure, and more frequent cardiac arrhythmias.[243] Given these issues, persons with moderate to severe obstructive sleep apnea should travel to high altitude with their continuous positive airway pressure machine when possible, assuming that reliable access to power sources can be arranged. In addition, for those using autotitrating continuous positive airway pressure, the addition of acetazolamide has been shown to improve the apnea-hypopnea index by decreasing the number of central sleep apneas and to improve nocturnal oxygenation.[244]

Thromboembolic Disease

Although many case reports document arterial or venous thromboembolic events at high altitude, many of the cases were in persons with underlying coagulopathy.[225] There remains no compelling evidence that the risk of thromboembolism is increased in normal individuals at high altitude. As a result, there is no need to screen for thrombophilia in asymptomatic persons before high-altitude travel and no indication to start anticoagulation in patients not previously taking such medication. Efforts should be made to maintain mobility and good hydration throughout a trip. The international normalized ratio may change with trips to and from altitude,[245] and patients taking warfarin should obtain follow-up values on returning from a long sojourn or periodically during prolonged stays at a new altitude. An alternative approach is to change to a direct oral anticoagulant agent for the sojourn, although reversal of coagulopathy is more challenging with those agents compared with warfarin.

UNDERLYING MEDICAL PROBLEMS AND ALTITUDE ILLNESS MEDICATIONS

The efficacy and safety of acetazolamide, dexamethasone, nifedipine, and the phosphodiesterase inhibitors in managing acute altitude illness have largely been established based on studies in healthy individuals with no underlying medical disease. However, given the increasing numbers of persons traveling to high altitude, it is possible that many of those using the foregoing medications for management of altitude illness will have underlying medical problems or will be using other medications that cause adverse drug interactions. Practical guidelines for the selection and dosing of the altitude illness medications in such patient populations have been reviewed elsewhere.[246]

Key Points

- At high altitude, important adaptations at every step of the oxygen transport chain maintain oxygen delivery in the setting of lower ambient oxygen levels. However, the magnitude of these changes varies among individuals and affects individual tolerance of this environment.
- Various aspects of sleep, including respiratory patterns, sleep architecture, and subjective impressions of sleep quality, are altered and contribute to poor sleep at high altitude.
- Maximum exercise capacity is reduced at high altitude and does not recover to sea-level baseline values even with prolonged time and acclimatization at high altitude.
- An overly rapid ascent to high elevation is the primary reason persons develop acute altitude illness, and a gradual ascent is the best nonpharmacologic means for prevention. Pharmacologic options are available to prevent or treat specific illnesses and can include acetazolamide, dexamethasone, or pulmonary vasodilators.
- Acute mountain sickness is the most common form of acute altitude illness and is marked by the onset of headache in addition to one or more other symptoms, including lightheadedness, gastrointestinal upset, and fatigue several hours following ascent.
- High-altitude cerebral edema and high-altitude pulmonary edema are uncommon and potentially fatal forms of severe acute altitude illness that can be avoided with prompt recognition and initiation of treatment.
- Long-term high-altitude residents are susceptible to two forms of chronic altitude illness, namely chronic mountain sickness and high-altitude pulmonary hypertension, for which the optimal form of treatment is relocation to a lower elevation.
- High-altitude travelers with underlying medical problems should undergo pretravel assessment to evaluate whether the underlying disease process may be worse at high altitude. The choice and dose of prophylactic medications may require adjustment based on the patient's underlying medical issues.

Key Readings

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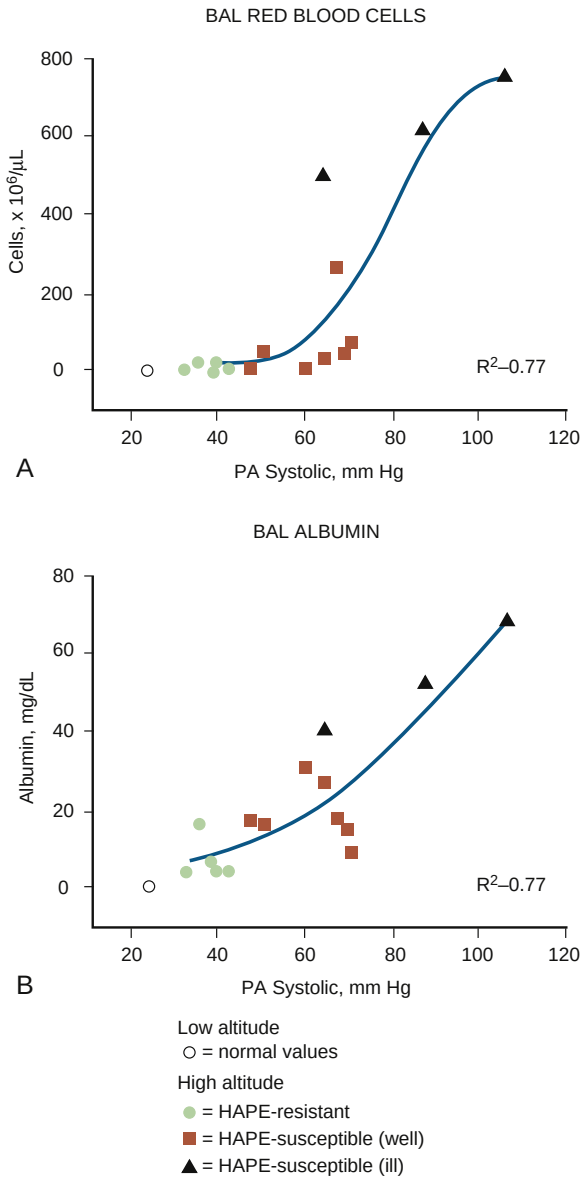
Complete reference list available at ExpertConsult.com.





eFigure 105.1 Portable hyperbaric chamber used to treat severe altitude illness when supplemental oxygen is unavailable or descent is impossible. The sick individual is placed in the bag, which is then closed using an air-sealed zipper. (A) A hand pump is used to inflate the bag and increase the barometric pressure within it. Some products use a foot pump instead. Once inflated to the target pressure, the bag must be pumped on a continual basis to maintain the target pressure and ensure adequate ventilation. (B) Altimeter watch held outside the portable hyperbaric chamber before inflation, showing 2439 m altitude. (C) Altimeter watch held by an individual inside the portable hyperbaric chamber after inflation to 1.5 psi, now showing 1343 m altitude. (Courtesy Andrew Luks, MD.)



eFigure 105.2 Bronchoalveolar lavage findings at high altitude (4559 m). The relationship between *pulmonary artery* (PA) pressure measured by echocardiography and (A) the number of red blood cells and (B) the concentration of albumin in *bronchoalveolar lavage* (BAL) fluid of normal and high-altitude pulmonary edema–susceptible individuals at sea level and at 4559 m. The *open circles* show normal values for red blood cells and albumin at low altitude (490 m). Correlation coefficients are provided for the best fit curves of the data at high altitude. (Data from Swenson ER, Maggiorini M, Mongovin M, et al. Pathogenesis of high-altitude pulmonary edema: inflammation is not an etiologic factor. *JAMA*. 2002;287(17):2228–35.)

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106 AIR TRAVEL

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INTRODUCTION

As air travel increases as part of the fabric of modern life and as more individuals with lung disease—perhaps most commonly COPD—travel by air, pulmonologists are increasingly called upon to assess their patients' fitness to fly. Also, when air travel is endorsed, pulmonologists must advise patients about how to avoid the hazards of travel and manage their supplemental in-flight oxygen prescription, when needed. In this context, the current chapter reviews pulmonary aspects of commercial air travel. First, the epidemiology of air travel and concomitant risks are discussed. Then, based on the physiologic effects of high-altitude exposure discussed in Chapter 105, the physiologic impact of air travel (e.g., on gas exchange) is discussed. Attention then turns to evaluating fitness to fly, followed by assessing in-flight oxygenation. When and how to prescribe supplemental in-flight oxygen is discussed next, including recommendations for oxygen-naive patients and also for those already using supplemental oxygen at home. Equipment to provide in-flight supplemental oxygen is then reviewed, as is the process of prescribing in-flight oxygen. The chapter concludes with a discussion of the risks of air travel on infection transmission, venous thromboembolism, and pneumothorax, followed by issues regarding air travel that pertain to individuals with a spectrum of diagnoses beyond COPD (e.g., lymphangioleiomyomatosis, pulmonary hypertension) and a discussion of practical aspects of assessing a patient with pulmonary symptoms in flight.

EPIDEMIOLOGY AND GENERAL RISKS OF AIR TRAVEL

Travel is integral to modern life and, in the context of increasing affordability and facilitative technology (e.g., *portable oxygen concentrators* [POCs], mobility-enhancing devices), travel by air is increasingly common, even for individuals with chronic medical conditions. World Bank data suggest that 3.7 billion individuals traveled by air in 2016, up from 2.1 billion in 2006.[1]

Even though individuals with chronic medical illnesses are flying more frequently, medical emergencies associated with commercial air flight are relatively uncommon. Death in flight has been estimated to take place in 0.3% of in-flight emergencies, which happen in 1 of every 604 flights or for 1 of every 33,600 to 39,600 passengers.[2,3] The worldwide estimated frequency of in-flight medical emergencies is 1:40,000 passengers[4] and a *U.S. Federal Aviation Administration* (FAA) study[5] estimated that there were 1132 in-flight medical events in 140,000 plane trips between 1996 and 1997. Though not all in-flight medical events prompt calls for ground-based medical assistance, among calls from commercial aircraft for ground-based medical advice, syncope or presyncope was most common (37.4% of cases), followed by respiratory symptoms in 12.1% and nausea and vomiting in 9.5%. Cardiac symptoms (7.7%), stroke (2%), and cardiac arrest (0.3%) were less common. Having respiratory symptoms in-flight was associated with a twofold increase in risk of admission to the hospital after landing.[2]

Diversions of commercial air flights due to onboard medical emergencies are expensive and result in significant inconvenience for other passengers. Recent estimates suggest a cost of diversion ranging from US $50,000 to over US $600,000, depending on factors like fuel costs, passenger rebooking, and accommodations.[6] Approximately 7–13% of all in-flight medical events led to a diversion, and respiratory symptoms were the third most common reason for diversion.[4,7]

Table 106.1 Hypobaric Conditions at Increasing Altitude

Altitude (ft)	Barometric Pressure (mm Hg)*	Atmospheric P_{O_2} (mm Hg)*	Tracheal P_{O_2} (mm Hg)	Gas Density†	Gas Volume‡
0 (sea level)	760	159	149	1	1
2000	707	148	138	—	—
4000	656	137	128	0.9	1.1
5000	632	132	122	0.8	1.2
8000	564	118	108	—	1.4
10,000	523	109	100	0.7	1.5
15,000	428	89	80	0.6	1.9
30,000	226	47	38	0.3	4
40,000	141	29	20	0.2	7.6

*Fall in ambient pressure and PO_2 at increasing altitude. However, during air travel in commercial airliners, pressurization of the cabin limits the reduction in cabin pressure, thereby limiting the reduction in inspired PO_2.
†Ratio of density at altitude to density at sea level.
‡Ratio of volume occupied by a fixed amount of gas at altitude to the volume occupied at sea level.
Modified from Gong H. Advising COPD patients about commercial air travel. *J Respir Dis*. 1990;11:484.

PHYSIOLOGIC IMPACT OF COMMERCIAL AIR TRAVEL

Commercial airplanes characteristically travel at altitudes of 30,000 to 40,000 feet, posing risks of hypobaric hypoxia and changes in gas density related to altitude.[8] Because exposure to such ambient altitudes is life-threatening, airplanes are pressurized to provide so-called cabin altitudes (the altitude equivalent inside the airplane) that are tolerable. The degree of pressurization reflects structural features of the airplane (e.g., fuselage diameter, airplane construction materials, and their ability to withstand transmural pressure gradients) and in-flight cabin altitudes are uniformly higher than sea level. By FAA regulations,[9] cabin altitude must be maintained at 8000 feet (2438 meters) with rare diversions to 10,000 feet (3048 meters) for safety (e.g., weather avoidance). Measured peak cabin altitudes on 207 U.S. domestic flights using 17 different aircraft was 4528 to 8154 feet, with only 11.2% of measurements showing altitude measurements greater than 8000 feet, indicating good regulatory compliance.[10]

The physiologic impact of exposure to cabin altitudes of 8000 to 10,000 feet largely relates to the decreased ambient pressure (which prompts a decrease in the partial pressure of oxygen) and to the increasing volume of trapped gas as ambient pressure decreases (Boyle's law [see Chapter 107]). As discussed later (see "Transmission of Respiratory Infections During Air Travel"), a third effect of exposure to the environment of a commercial airliner cabin relates to the internal cabin air quality.

The impact of high altitude on inspired oxygen tension (P_{IO_2}) is defined by the equation:

$$P_{IO_2} = F_{IO_2} \times (P_{atm} - P_{H_2O})$$

where P_{atm} is the atmospheric pressure (760 mm Hg at sea level and 564 mm Hg at 8000 feet).

In the context of the oxyhemoglobin dissociation curve (see Chapter 10), the consequence of this hypobaric hypoxia at a cabin altitude of 8000 feet is that the in-flight P_{IO_2} is generally between 108 and 122 mm Hg and the arterial P_{O_2} of healthy individuals is generally 53 to 75 mm Hg (7–10 kPa). In general, exposure to the hypobaric hypoxia of commercial air travel causes the sea-level oxygen saturation to decrease by 3–4%, maintaining values of 90% or above (arterial P_{O_2} of 60–70 mm Hg)[4] in most healthy individuals.

Physiologic responses to the hypobaric hypoxia of commercial air flight include increased minute ventilation, increased heart rate, increased cardiac output to maintain tissue oxygen delivery, and pulmonary vasoconstriction to preserve ventilation-perfusion matching and oxygenation. With regard to the impact of cabin altitude exposure on gas density (Boyle's law), gas trapped in confined spaces (e.g., in noncommunicating bullae, within congested middle ear) expands, causing sequelae like pneumothorax and ear pain. Consider the progressive distension of a bag of potato chips or the cover on a container of yogurt as the plane ascends.[11] At a constant temperature, 1 L of gas at sea level expands to approximately 1.3 L at 1500 m and to approximately 1.4 L at 2450 meters (≈8000 feet).[4,12] The expected changes in gas volume and pressure at various altitudes are summarized in Table 106.1.[13] Such gas expansion can also pose risks for wound dehiscence in patients who have recently undergone surgery[14] or vision loss after intraocular gas injections. Cabin humidity is characteristically low (10–20% humidity), which may prompt dryness and precipitate bronchospasm in asthmatics.

The effects of hypobaric hypoxia and of decreased gas density during commercial air travel are relatively mild among normal subjects. For example, an in-flight study of 84 passengers with no history of lung disease showed a reduction in oxygen saturation from 97% (93–100%) at ground level to 93% (85–98%) during commercial flights.[15] Another study of 502 normal subjects exposed in a hypobaric chamber simulating a cabin altitude of 8000 feet showed an approximately 4.4% reduction in oxygen saturation with mild discomfort after 3 to 9 hours of exposure.[16]

In contrast, individuals with lung disease may experience more profound degrees of desaturation during commercial

air flight. A study of 18 individuals with COPD exposed to a mean cabin altitude of 6000 feet for a 5 hour, 40 minute flight showed that saturation declined at rest by 6% (i.e., from 96 ± 1% to 90 ± 4%) and declined further during walking in the aisle of the plane (to 87 ± 4%).[17] Similarly, Kelly et al. reported that in 13 subjects with COPD, oxygen saturation decreased from 95 ± 1% at ground level to 86 ± 4% in flight at rest, worsening further to 78 ± 6% with in-flight activity.[18]

The risks of gas expansion in noncommunicating cavities (e.g., in bullae in COPD or in lung cysts in lymphangioleiomyomatosis) pose risk for in-flight pneumothorax (see "Lymphangioleiomyomatosis" later).

Notwithstanding these physiologic effects, commercial air travel is generally well tolerated among patients with lung disease who are evaluated for travel; the prevalence of in-flight medical events among such individuals is relatively low. Coker et al. prospectively studied 616 patients with lung disease who planned air travel on a commercial airline.[19] The cohort included patients with COPD (39%), diffuse parenchymal lung disease (23%), asthma (15%), bronchiectasis (8%), sarcoidosis (7%), and various other conditions (8%). In the subset of 431 travelers who completed air travel, fewer than 1% required in-flight medical assistance and, although 18% reported some respiratory difficulty in flight, there were no flight diversions or deaths.

Table 106.2 Assessing Fitness to Fly

FEATURES WARRANTING PREFLIGHT ASSESSMENT
History of significant respiratory symptoms associated with air travel
Severe COPD (FEV_1 <30% predicted), bullous lung disease, difficult-to-control asthma, cystic fibrosis, or pulmonary tuberculosis
Severe restrictive disease (vital capacity <1 L), including interstitial lung, chest wall, and respiratory muscle disease, especially if associated with hypoxemia and/or hypercapnia
Presence of a comorbidity with conditions made worse by hypoxemia (e.g., cerebrovascular disease, cardiac disease, pulmonary hypertension)
Recent pneumothorax or within 6 weeks of an acute respiratory illness
Risk of, or previous history of, venous thromboembolism
Preexisting requirement for oxygen, continuous positive airways pressure or ventilator support
CONTRAINDICATIONS TO AIR TRAVEL
Infectious tuberculosis
Ongoing pneumothorax with persistent air leak
Major hemoptysis
Need for supplemental oxygen at sea level with requirements exceeding 4 L/min

Modified from Shrikrishna D, Coker RK. Managing passengers with stable respiratory disease planning air travel: British Thoracic Society recommendations. *Thorax*. 2011;66(9):831-833.

PREFLIGHT ASSESSMENT OF FITNESS TO FLY

The goal of preflight assessment is to optimize the patient's fitness to fly and to minimize the risk of an in-flight adverse medical event. Careful assessment registers the prospective traveler's comorbidities, past experience of flying, and oxygenation, particularly as estimated in flight.

The first consideration regards which travelers require preflight assessment for fitness to fly. Table 106.2 lists the clinical features that warrant preflight assessment according to the *British Thoracic Society* (BTS).[20]

Practice varies in assessing patients for air travel. In the series reported by Coker et al.,[19] tests used in preflight assessment included pulse oximetry, pulmonary function tests, high-altitude simulation testing, and walking tests. Assessment of oxygenation, usually by pulse oximetry, is almost universally employed.

ASSESSING FOR IN-FLIGHT HYPOXEMIA IN PATIENTS WITH RESPIRATORY DISEASE

Once the traveler is deemed fit to fly, assessing for in-flight hypoxemia should proceed. Various methods for assessing in-flight hypoxemia have been reported, including predictive equations (frequently based on sea-level pulse oximetry oxygen saturation, pulmonary function test results, health status, and sometimes arterial blood gases) and *high-altitude simulation testing* (HAST; also called hypoxic challenge testing or hypoxia altitude simulation testing). HAST is performed most commonly by having a patient breathe a hypoxic gas mixture (i.e., normobaric hypoxia testing) and, less frequently, by hypobaric chamber testing (i.e., hypobaric hypoxia testing). Predictive equations have largely fallen out of favor, based on poor accuracy in determining in-flight oxygenation,[21,22] leaving HAST as the primary method for assessing in-flight hypoxemia when indicated (Fig. 106.1; see also following text).

The purpose of HAST is to assess whether the traveler's in-flight arterial Po_2 will be less than 50 mm Hg or oxygen saturation 85% or less, which are the threshold values at which supplemental in-flight oxygen is generally recommended. The Aerospace Medical Association sets this threshold at arterial Po_2 55 mm Hg.[23] Hypobaric chamber testing is perhaps the gold standard for HAST but is not commonly available and usually reserved for treating diving-related injuries or osteonecrosis, or for training personnel who will perform tasks at high altitudes. Thus, HAST usually involves administering a hypoxic gas mixture and assessing oxygenation. Inhaling a gas mixture of 15.1% oxygen (fractional concentration of oxygen in inspired gas 0.151) simulates the oxygen concentration at a cabin altitude of 8000 feet. The HAST is generally performed by providing 15.1% oxygen through a mouthpiece or tight-fitting face mask with a nonrebreathing valve for 20 minutes or, alternatively, placing the patient in a body box chamber containing 15.1% oxygen for the same duration. An infrequently used alternative involves using a 35% Venturi mask with nitrogen as the driving gas because this produces an oxygen mixture of 15–16%. Estimates of oxygenation using HAST with 15.1% oxygen compare favorably with hypobaric chamber testing in identifying patients who need in-flight oxygen.[24] Also, the results of normobaric hypoxic high-altitude simulation correlate well, though imperfectly, with actual in-flight measurements ($r = 0.84$).[18,21,22] However, the effects of in-flight hypobaric conditions (i.e., lower gas density and

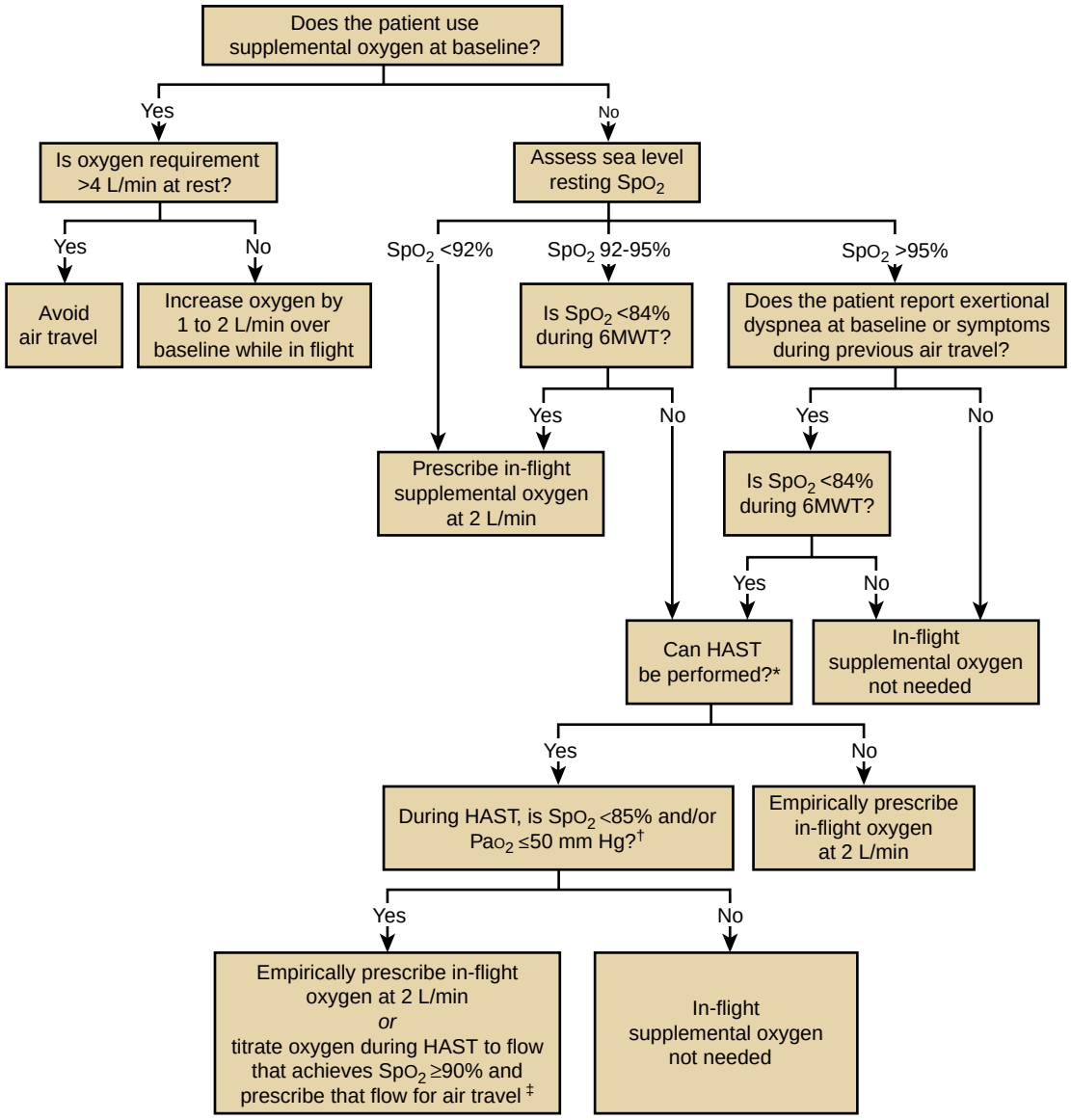

Figure 106.1 Algorithm to assess the need for supplemental oxygen before commercial air travel. The testing algorithm portion that applies to patients who are not on supplemental oxygen demonstrated 100% sensitivity and 80% specificity in identifying the need for in-flight oxygen when tested prospectively in 50 COPD patients.[25] Thus, using this algorithm allowed accurate identification of all patients who needed supplemental in-flight oxygen and led to overprescription of oxygen in 20% of the patients who did not need supplemental in-flight oxygen.[25,26] *HAST may not be covered by medical insurance. †During *high-altitude simulation testing* (HAST), assessment of arterial Po_2 is preferred if available. ‡HAST is less accurate than hypobaric testing but is more readily available. Determining exact supplemental oxygen requirement during HAST is technically difficult and may underestimate supplemental oxygen requirements. 6MWT, 6-minute walking test; Spo_2, oxygen saturation measured by a pulse oximeter. (Data from Stoller JK. Evaluation of patients for supplemental oxygen during air travel. In: Post TW (Ed). *UpToDate*. Waltham, MA: UpToDate; Akerø A, Christensen CC, Edvardsen A, Ryg M, Skjønsberg OH. Pulse oximetry in the preflight evaluation of patients with chronic obstructive pulmonary disease. *Aviat Space Environ Med*. 2008;79(5):518-524; and Edvardsen A, Akerø A, Christensen CC, Ryg M, Skjønsberg OH. Air travel and chronic obstructive pulmonary disease: A new algorithm for pre-flight evaluation. *Thorax*. 2012;67[11]:964-969.)

increased volume) can only be assessed preflight by using a hypobaric chamber.

ASSESSING FOR IN-FLIGHT HYPOXEMIA IN PATIENTS NOT USING SUPPLEMENTAL OXYGEN AT SEA LEVEL

The BTS guidelines suggest using pulse oximetry at sea level to identify individuals who need further assessment for supplemental in-flight oxygen.[20] These recommendations can be summarized as follows:

1. Patients with oxygen saturation less than 92% can forego further testing and be prescribed in-flight oxygen
2. Patients with oxygen saturation 92–95% at rest should undergo further testing with a *six-minute walk test* (6MWT) and HAST.
3. Patients with oxygen saturation greater than 95% do not require further testing and can usually fly without oxygen supplementation.

The first criterion (i.e., travelers whose sea-level oxygen saturation is less than 92% can forego further testing

and should be prescribed supplemental in-flight oxygen) is based on the observation that 83% of patients under this threshold desaturate during HAST.[25] Similarly, although a sea-level oxygen saturation greater than 95% generally predicts an in-flight arterial Po_2 greater than 50 mm Hg, thereby obviating the need for supplemental in-flight oxygen, up to 23% of patients with resting oxygen saturation greater than 96% still experience desaturation during HAST.[19] Therefore, clinicians should have a low threshold for ordering HAST for those patients with sea-level oxygen saturation greater than 95% who have additional risk factors for desaturation, such as a low diffusion capacity or previous respiratory symptoms during air travel.

Because exercise desaturation and aerobic capacity also correlate with in-flight desaturation, algorithms[26,27] for preflight assessment of in-flight hypoxemia often combine multiple tests to determine the need for in-flight supplemental oxygen (Fig. 106.1). The algorithm in Figure 106.1 suggests the following conclusions:

- Patients who have a sea-level oxygen saturation greater than 95% and 6MWT oxygen saturation 84% or greater can fly without oxygen and do not require further testing.
- Patients with a resting oxygen saturation less than 92% and those with a resting oxygen saturation 92–95% plus a 6MWT oxygen saturation less than 84% should be prescribed supplemental oxygen for air travel without further testing.
- Patients with a resting oxygen saturation of 92–95% and a 6MWT oxygen saturation 84% or greater or with a resting oxygen saturation greater than 95% and a 6MWT oxygen saturation less than 84% require further assessment with a HAST.

When the use of supplemental oxygen is recommended in flight, an oxygen flow rate (using continuous flow) of 2 L/minute generally suffices to assure adequate in-flight oxygenation.[28] A second study[29] suggested that providing oxygen in flight at 1.5 L/minute sufficed to reverse hypoxemia at a cabin altitude of 10,000 feet. Alternatively, the flow rate for supplemental in-flight oxygen can be determined by administering oxygen through nasal cannula during the HAST, though this method may underestimate the in-flight oxygen need.

PRESCRIBING SUPPLEMENTAL IN-FLIGHT OXYGEN IN PATIENTS ALREADY USING SUPPLEMENTAL OXYGEN AT SEA LEVEL

Patients who use long-term supplemental oxygen can fly with appropriate precautions. Management of their underlying lung disease should be optimized, of course. While the required liter flow for in-flight oxygen can be assessed during normobaric hypoxic testing (i.e., by administering oxygen through nasal cannula), supplemental oxygen needs are often underestimated in this manner.[30] As a practical matter, either doubling the sea-level flow rate during flight[20] or increasing the sea-level supplemental oxygen flow rate by 1 to 2 L/min will usually suffice. Notably, it is generally accepted that an oxygen requirement greater than 4 L/min at rest at sea level is a contraindication to air travel.

PROVIDING SUPPLEMENTAL IN-FLIGHT OXYGEN

The U.S. Department of Transportation's "Nondiscrimination on the Basis of Disability in Air Travel" final rule permits the use of respiratory assist devices, including POCs, on airplanes.[31] To date, over 20 POCs have been approved by the FAA.[32] The list will likely evolve over time, and prospective travelers are encouraged to check the FAA website for current approvals.[31] Passengers who need in-flight oxygen and who travel frequently may elect to buy a POC that is FAA approved. Travelers are also strongly encouraged to check with the individual airline to ensure their device is approved by the airline for use onboard their aircraft. For those not wishing to purchase a POC, the devices are often available for rental by the airlines and/or durable medical equipment providers. Notably, because POCs differ in performance characteristics, the weight, battery life, and maximum possible oxygen output should be considered when choosing a suitable system.[33] Furthermore, if the traveler plans to use pulsed flow during travel, preflight testing to determine the required in-flight flow rates should be performed with the traveler's own device.

Personal oxygen cylinders cannot be brought on board airplanes and are now very infrequently used for providing in-flight oxygen with the advent of POCs. When needed, oxygen cylinders that can be secured are sometimes provided by the airlines with prenotification by the traveler and with physician authorization. Charges may apply and may vary widely across carriers[34] so that the traveler hoping to use an oxygen cylinder should become well informed. Because policies regarding the use of in-flight oxygen and allowable equipment vary and may be confusing, various resources are available to the traveler in helping to plan air travel. In addition to individual airline sites, Table 106.3 lists websites available to help the traveler.

Clinicians should be aware of several practical considerations for the traveler and must be prepared to discuss these issues with their patients who are preparing to fly. These are summarized in Table 106.4.

CONSIDERATIONS REGARDING SPECIFIC LUNG DISEASES AND AIR TRAVEL

In addition to the challenges of traveling with COPD, other lung diseases pose specific issues for the affected air traveler. Table 106.5 summarizes some of these considerations according to BTS guidelines. Specific considerations are discussed below.

PNEUMOTHORAX

Pneumothorax may develop during air travel because of the expansion of gas at increasing altitude (see Table 106.1).

Table 106.3 Available Resources to Help Travelers Manage In-Flight Supplemental Oxygen

Source	Web Site	Type of Travel Advice Offered
Aerospace Medical Association	www.asma.org	Health tips for passengers and health professionals
Alpha-1 Foundation	www.alpha1.org	Free patient information line on all aspects of life with COPD for patients with alpha$_1$-antitrypsin deficiency
American Association for Respiratory Care	http://www.aarc.org/resources/clinical-resources/oxygen-resources/	Detailed information on oxygen therapy
British Lung Foundation	https://www.blf.org.uk/support-for-you/going-on-holiday/flying-with-a-lung-condition	General information and travel tips for patients with lung disease
British Thoracic Society	www.brit-thoracic.org.uk	Patient information leaflet
Centers for Disease Control	www.cdc.gov/travel	Travelers' health website for individuals and health care providers
Civil Aviation Authority	www.caa.co.uk/	Medical information for passengers and health care providers
European Federation of Allergy and Airways Diseases Patients' Associations	http://www.efanet.org/images/2015/20151118_EFA_Booklet_Enabling_Air_Travel_with_Oxygen_Updated_2015_FINAL.pdf	Enabling air travel with oxygen in Europe (an EFA booklet for patients with chronic respiratory disease); EFA booklet for steps for passengers flying with medical oxygen
European Lung Foundation	https://www.europeanlung.org/en/lung-disease-and-information/air-travel/	Information and medical tips for air travel
International Air Transport Association	http://iata.org	Medical manual for air travel
International Civil Aviation Organization	www.icao.int	Manual of civil aviation medicine for flying personnel and health care
International Society of Travel Medicine	www.istm.org	Online learning programs for health care providers
Transportation Security Administration	www.tsa.gov/travel/special-procedures	Crucial information regarding security screening procedures for patients with disabilities who intend to travel by air

Modified from Ergan B, Akgun M, Pacilli AMG, Nava S. Should I stay or should I go? COPD and air travel. *Eur Respir Rev*. 2018;27(148):180030. Tab 2.

Table 106.4 Checklist for the Clinician to Inform Patients About Traveling on Commercial Airlines with Supplemental Oxygen

1. Inform the airline carrier of their intent to bring a POC on board at least 2 weeks in advance.
2. Ensure that the POC satisfies the maximum weight and dimension criteria of the airline and is labeled appropriately.
3. Inform the TSA official during screening about the POC.
4. Carry a clinician's letter or TSA notification card that describes the underlying lung condition, prescribed oxygen liter flow, instructions on when oxygen would be used (continuously or only during flight).
5. Ensure that the particular POC is approved for use in flight by the U.S. Federal Aviation Administration and the airline.
6. Bring enough batteries for the POC to last 1.5 times the anticipated duration of flight.
7. Ensure that arrangements for supplemental oxygen have been made at the destination if a delivery means other than a POC is planned (e.g., oxygen cylinders).
8. Bring adequate supplies of prescribed medications and medications that may be needed for emergencies (e.g., bronchodilators, corticosteroids, antibiotics). Such medications should be brought in the traveler's carry-on, and NOT in checked bags.
9. Identify local health care providers and hospitals at the destination in case of need.

POC, portable oxygen concentrator; TSA, Transportation Security Administration.

Though potentially dangerous during air travel, pneumothorax during air travel has only infrequently been reported. For example, an early FAA report documented only one confirmed and one suspected episode of pneumothorax among 2322 in-flight emergencies over 2 years.[35] No instance of pneumothorax was reported among a series of 431 travelers with lung disease[19] or in a series of 11,920 in-flight medical emergencies managed by a physician-directed medical communication center.[2] In-flight pneumothorax is also fortunately exceedingly rarely fatal; in a review of in-flight pneumothorax by Hu et al.,[36] only a single instance of fatal in-flight pneumothorax (in a woman with tension pneumothorax complicating treated tuberculosis) was reported. (see also Chapter 110).

Pneumothorax risk during air travel relates to the expansion of air within noncommunicating air collections, commonly present in cystic lung diseases or when mucous plugging obstructs communicating airways.[36–38] Specific conditions predisposing to pneumothorax include subpleural blebs,[39] *lymphangioleiomyomatosis* (LAM),[40–42] Birt-Hogg-Dubé syndrome,[43] congenital pulmonary airway malformation,[44] and bullae due to emphysema,[45] alpha$_1$-antitrypsin deficiency,[46] and tuberculosis.[47] As reviewed in Table 106.5, the BTS guidelines proscribe travel for patients with current pneumothorax and recommend delaying travel for 1 to 2 weeks following complete resolution of a prior pneumothorax.

Table 106.5 Disease-Specific Considerations and Recommendations for Air Travel

Condition	Considerations	Recommendation
Asthma and COPD	Hypoxemia, acute bronchospasm, or infectious exacerbation	■ Patients to use own bronchodilator (brought aboard with the traveler).
Bronchiectasis	Hypoxemia, infectious exacerbation	■ Nebulized bronchodilators and antibiotics not generally required.
Cancer	Risks related to anemia, neutropenia, pleural effusion	■ Correct symptomatic anemia before travel. ■ Pleural effusions should be drained before air travel, assuring no pneumothorax post-thoracentesis. ■ Travel within 24 hours of a seizure is not permitted.
Cardiac disease	Hypoxemia and tachycardia can increase risk	■ Patients who are status post percutaneous cardiac intervention may fly 2 days postprocedure. ■ Patients at low risk after STEMI (e.g., restored TIMI grade 3 flow, absence of heart failure and arrhythmia), can fly after 3 days; others may travel after 10 days unless awaiting revascularization or device implantation. ■ Patients may fly within 14 days following coronary artery bypass graft but should undergo a chest radiograph to exclude a pneumothorax. ■ Patients with unstable angina should not travel and those with stable angina at rest should be discouraged from traveling.
Cystic fibrosis	Hypoxemia	■ Assessment of in-flight oxygenation is recommended.
Interstitial lung disease	Hypoxemia	■ Careful preflight assessment is needed. ■ Supplemental oxygen is often needed, both in flight and on arrival at high-altitude destinations.
Neuromuscular disease and kyphoscoliosis	Hypoxemia	■ Assess for the need for in-flight supplemental oxygen.
Obstructive sleep apnea	CPAP machine use, availability of power to run machine	■ CPAP machines should travel with the passenger in the cabin; a physician's letter is often required. ■ Because A/C power may not be available in flight, dry cell batteries should be used. Also, ensure availability of a power source on arrival. ■ Avoid alcohol and sedatives during travel.
Pneumothorax	Risk of barotrauma and gas expansion	■ Patients with a closed pneumothorax should not travel (with the exception of a loculated or chronic localized air collection that has been carefully assessed). ■ Patients who have had a pneumothorax must have a chest radiograph to confirm resolution before flight; another 7 days should ideally elapse before air travel. ■ In the case of traumatic pneumothorax, a delay of 2 weeks after full resolution is recommended. ■ Definitive surgical intervention via thoracotomy is likely to be entirely successful and permit travel; intervention by video-assisted thoracoscopic surgery is also expected to have a high success rate but is not deemed definitive. ■ Patients undergoing other forms of pleurodesis are unlikely to experience recurrence, but consequences of recurrence precipitated by flight could be severe (e.g., tension pneumothorax); the risk of recurrence is higher in those with coexisting lung disease and does not fall for at least 1 year. Those not undergoing definitive treatment of prior pneumothorax may wish to consider alternative forms of travel. ■ Patients with lymphangioleiomyomatosis should be apprised of increased risk of pneumothorax and that any symptoms of chest pain or dyspnea should preclude travel until fully evaluated.
Pulmonary arteriovenous malformation	Hypoxemia, embolization	■ Considered to be at moderate or high risk of venous thromboembolism. ■ Patients with prior venous thromboembolism or history of embolic stroke should receive a single dose of low-molecular weight heparin before the flight. ■ If embolization is planned, defer long-haul travel until embolization is complete.
Pulmonary hypertension	Worsened pulmonary hypertension with hypoxemia	■ Those in NYHA class I or II can often fly without oxygen. ■ Those in NYHA class III or IV should receive in-flight oxygen. ■ Severe pulmonary hypertension is a contraindication to air travel.
Sinus and middle ear disease	Risks of barotrauma	■ Adults at risk for sinus or middle ear barotrauma should receive an oral decongestant before travel and a nasal decongestant during flight before descent. ■ Women in the first trimester of pregnancy may use intranasal steroids instead of topical decongestants. ■ Passengers who develop sinus barotrauma after flying should receive topical and oral decongestants, analgesics, and oral steroids. ■ Antibiotics are advised if bacterial sinusitis is thought to be the trigger and antihistamines if allergic rhinitis is suspected. ■ Symptoms and signs of barotrauma should have resolved before flying again; this usually takes a week and may take up to 6 weeks.

Data from Nicholson TT, Sznajder JI. Fitness to fly in patients with lung disease. *Ann Am Thorac Soc*. 2014;11(10):1614-1622; and Shrikrishna D, Coker RK. Managing passengers with stable respiratory disease planning air travel: British Thoracic Society recommendations. *Thorax*. 2011;66(9):831-833.

CPAP, continuous positive airway pressure; NYHA, New York Heart Association; STEMI; ST-segment elevation myocardial infarction; TIMI, Thrombolysis in Myocardial Infarction.

In general, the rarity of severe consequences of in-flight pneumothorax suggest that conservative in-flight management is appropriate (i.e., using supplemental oxygen and advising descent as soon as feasible). In the rare instance of suspected tension pneumothorax in flight, needle placement to decompress the pneumothorax may be needed. Given the scarcity of appropriate tools and the rarity of fatalities, needle decompression or use of improvised chest tubes should be reserved as a last resort and in the context of high diagnostic certainty.

LYMPHANGIOLEIOMYOMATOSIS

LAM (see Chapter 97) poses a significant (55–73%) lifetime risk of pneumothorax[48] and the risk associated with air travel has been estimated. Specifically, prevalence estimates of pneumothorax risk during air travel range from 1.1–2.8% per flight.[40–42] These rates are twofold higher than those observed in LAM patients traveling by car and the risk ratio of suffering a pneumothorax within 30 days of air travel in LAM patients was 3.6 (95% confidence interval, 1.4 to 7.5) compared to nonflight periods.[42] The BTS guidelines (see Table 106.5) specifically advise LAM patients with chest pain or dyspnea to seek evaluation in order to exclude a pneumothorax before traveling by air.

BIRT-HOGG-DUBÉ SYNDROME

Birt-Hogg-Dubé syndrome is also strongly associated with spontaneous pneumothorax; up to 24–38% of Birt-Hogg-Dubé patients experience a pneumothorax, with a 75% chance of recurrence.[49] The prevalence of pneumothorax within 30 days of air travel has been estimated to be 0.12–0.63% per flight.[43,49]

PULMONARY HYPERTENSION

Travelers with *pulmonary hypertension* (PH; see Chapter 83) may be particularly prone to the adverse effects of hypoxic pulmonary vasoconstriction.[50] Specifically, acute increases in pulmonary artery pressure may predispose to right ventricular failure and hemodynamic compromise.[51] Indeed, mean systolic pulmonary artery pressure, as estimated by echocardiography, increased by 6 mm Hg in healthy air travelers.[52] In a patient with increased hypoxic pulmonary vasoconstriction (due to a mutation leading to Chuvash polycythemia), an inflight echocardiogram showed the mean systolic pulmonary artery pressure increased by 15 mm Hg in response to a relatively mild reduction in oxygen saturation to 96% during a commercial flight.[53] Notwithstanding these theoretical risks, air travel has generally not been associated with severe complications in PH patients.[54,55] In a survey of 179 air travelers with PH,[54] most of whom were in *New York Heart Association* (NYHA) class II and III functional class (86%) and receiving pH-specific monotherapy or combination therapy (78%), only 20 (11.2%) of the travelers reported having in-flight symptoms (i.e., dyspnea, peripheral edema, exhaustion, palpitations or chest pain). Seven of the 20 required medical attention, and one patient required intensive care unit admission. In a second study of 34 air travelers,[55] most of whom (62%) carried a diagnosis of pulmonary arterial hypertension and who were receiving combination therapy (59%), nine (26%) of the patients experienced oxygen desaturation with a nadir oxygen saturation of 74%. Thirteen patients (38%) became symptomatic with chest pain, shortness of breath, and lightheadedness, but there were no severe complications or medical emergencies during the flights. The presence of pulmonary hypertension should increase the clinician's suspicion of hypoxemia in-flight and prompt HAST testing.[56]

Finally, the BTS guidelines recommend providing oxygen to PH patients in NYHA functional classes III and IV. Air travel is contraindicated for patients in NYHA functional class IV who also have risk factors for poor outcomes (e.g., decompensated right heart failure, recurrent syncope due to pulmonary hypertension). Because functional class correlates poorly with in-flight symptoms or in-fight medical events in travelers with PH, some authors have proposed assessing right ventricular dysfunction by performing an echocardiogram during the HAST in susceptible patients.[52]

SICKLE CELL DISEASE AND TRAIT

Patients with sickle cell disease are at risk for vaso-occlusive crises, commonly manifested as acute pain syndromes (e.g., acute chest syndrome [see Chapter 127], dactylitis), splenic infarction (usually early in life), acute ischemic stroke, priapism, and sequelae (e.g., pulmonary hypertension, hyposthenuria). Because air travel poses a risk of sickling prompted by hypoxemia, patients with sickle cell disease are at risk for such events during altitude exposure and air travel.

While patients with sickle cell trait and related hemoglobinopathies (e.g., HbSC, HbS, β- thalassemia) are characteristically less clinically affected, the hypoxic stress of altitude exposure and air travel can similarly precipitate vaso-occlusive events in these individuals, most commonly reported as splenic infarction, though instances of pulmonary infarction have been described as well.[57–60] A 2005 series summarized 47 cases of splenic infarction in patients with sickle cell trait at high altitude.[57] Compared to those with sickle cell disease, those with sickle cell trait have a distinctive in-flight risk for splenic infarction. Those with HbSS characteristically have infarcted spleens early in life, thereby averting further risk of acute splenic syndrome.[60] In contrast, those with sickle trait may only experience splenic infarction in the context of a hypoxic insult such as travel to high altitude or air travel. Indeed, many reports document workup for a previously unsuspected hemoglobinopathy prompted by in flight acute abdominal pain, diagnosed as splenic infarction.

Although sickle cell disease and sickle trait are not discussed in the otherwise comprehensive BTS guidelines on managing patients with stable respiratory disease who are planning air travel, preflight assessment should include eliciting a family history of hemoglobinopathy and diagnostic suspicion in appropriate ethnic groups. The clinician must be aware that the prevalence of sickle trait in the United States is 7–10% among African Americans and 0.046% in other persons.[60] For patients known or found to have sickle cell disease or trait, altitude exposure should be avoided if possible but, if required, such patients should likely receive supplemental oxygen in flight and be counseled to avoid dehydration and exertion at altitude.

RESTRICTIVE LUNG DISEASE DUE TO CHEST WALL DEFORMITY, NEUROMUSCULAR DISEASE, OR INTERSTITIAL LUNG DISEASE

Patients with restrictive ventilatory impairment are particularly prone to desaturation in flight, and physicians should have a low clinical threshold for performing HAST in such individuals. Christensen et al.[61] and Bandyopadhay et al.[62] showed that patients with interstitial lung disease and kyphoscoliosis with adequate oxygenation at sea level (i.e., oxygen saturation >95%), frequently desaturated during HAST. Like oxygen saturation, other clinical parameters (e.g., dyspnea score, lung function variables, and arterial blood gases at rest) failed to predict desaturation with HAST. Not surprisingly, patients with interstitial lung disease tend to desaturate more profoundly with light activity at altitude.[63] Though actual published experience with patients with restrictive chest disease who have flown is scant, reported experience suggests that such patients generally tolerate air travel well. For example, one small study of six patients with pulmonary fibrosis traveling for lung transplant evaluation showed no adverse in-flight events.[63,64]

CYSTIC FIBROSIS

Because improved care of patients with *cystic fibrosis* (CF [see Chapter 68]) has greatly enhanced life expectancy, such patients are traveling more frequently. Although patients with CF have been reported to desaturate frequently below the 50 mm Hg (6.6 kPa) threshold during hypobaric hypoxia,[65–68] symptoms during air travel or with exposure to simulated cabin altitudes are uncommon.[66,67] Furthermore, in contrast to what is observed in COPD patients, sea-level pulse oximetry or arterial Po_2 correlate poorly with either simulated or actual in-flight hypoxemia in CF.[66,67] The discordance between sea-level oxygenation and in-flight oxygenation has led some[67,68] to advocate using other parameters (e.g., FEV_1, looking for a threshold value less than 50% predicted; or cardiopulmonary exercise testing) or to perform HAST during light exercise in preflight assessment of patients with CF.

TRANSMISSION OF RESPIRATORY INFECTIONS DURING AIR TRAVEL

Features of the cabin environment alter the risk of transmitting airborne infection. On the one hand, cabin air is both filtered and recirculated with approximately 20 to 30 complete air exchanges within the cabin hourly. Furthermore, high-efficiency particulate air filters on commercial airplanes can effectively remove droplet nuclei carrying bacteria, fungi, and viral particles. Also, the side-to-side and top-to-bottom air circulation in the cabin prevents front-to-back airflow, thereby limiting dissemination of airborne particles between the rows.[69] On the other hand, seating within airliners places passengers in close proximity, thereby increasing the risk of transmitting respiratory infection through contact, large droplet transmission, or fomites.[69] As possible evidence of transmission during air travel, Coker et al. noted that among 468 patients with lung disease who flew, the prevalence of patients seeking medical treatment rose from 9% before the flight to 19% within 4 weeks of returning[19]; 65% of these patients received antibiotic treatment for lower respiratory tract infections.

Evidence that infection can be transmitted during air travel comes from the experience with tuberculosis. Available reports show that there were skin test conversions among fellow passengers traveling with an infected individual.[69–74] The overall risk of tuberculosis transmission has been estimated to be 0.1–1.3% among travelers on long-haul (>8 hours) flights.[75] World Health Organization and BTS guidelines both recommend against air travel by patients who have "infectious tuberculosis."[76] Patients who have completed 2 weeks of antituberculous therapy and who are not suspected to have drug-resistant tuberculosis are permitted to travel. On the other hand, those with multidrug-resistant tuberculosis or extremely or totally resistant tuberculosis are advised not to fly until two consecutive sputa are culture negative. Physicians should report to the local public health authority when they become aware of a patient with potentially infectious tuberculosis who intends to travel or has traveled within the previous 3 months. Airline companies are also instructed to deny boarding to persons known to have infectious or potentially infectious tuberculosis.

Incidents of viral transmission during air flight also underscore the risk of infection transmission during air travel. Instances of transmitting influenza,[77–79] coronavirus associated with the severe acute respiratory syndrome, and measles have been documented.[80,81] Sitting within two rows of an index passenger for more than 8 hours has been associated with an elevated risk of infection.[69] However, in one instance, patients who were sitting as far as seven rows from the index passenger contracted the severe acute respiratory syndrome.[80] Several reports now implicate aircraft transmission of COVID-19,[81a,81b] although, in one report,[81c] the virus was not transmitted to any of the 25 travelers sitting within two rows of a COVID-19–infected traveler or to the cabin crew. Prudence dictates that air travel by COVID-19–positive individuals should be avoided.

Measles transmission during commercial air travel has also been reported.[82,83] Due to the resurgence of measles and several severe cases associated with travel, the CDC recommends the MMR vaccine to travelers who have not been vaccinated or who have never had measles.[84]

RISK OF VENOUS THROMBOEMBOLISM DURING AIR TRAVEL

Air travel increases the risk for *venous thromboembolism* (VTE), presumably related to stasis from immobility and or hypercoagulability associated with air travel. Estimates from three major airports in Europe[85–88] suggest that the overall prevalence of VTE associated with air travel is 0.2 to 0.4 per 1 million travelers, though these rates may underestimate the actual prevalence because they do not account for connecting passengers or admission to hospitals other than the hospital from which the report originated and they lacked a systematic method for ascertaining VTE.

The main pathophysiologic factor predisposing to VTE during air travel is thought to be immobility. In this context, flights of distances greater than 5000 km have been associated with a much higher prevalence of VTE compared to shorter flights (1.5 cases per million vs. 0.01 cases/million).[85] A meta-analysis of VTE during travel[88] suggests that the risk of VTE increases by 26% for every additional 2 hours of air travel. The odds ratio for VTE in this study was 2.2 (confidence interval, 1.4 to 3.2). Furthermore, patients who are seated in non-aisle seats appear to be more prone to VTE.[89,90] Though attribution is unclear, VTE during air travel has been dubbed "economy class syndrome" due to the cramped nature of the coach class, which may further limit mobility compared to seating in other classes.[89]

Preflight assessment of risk for VTE should include consideration of other risk factors for VTE. In one series,[87] 87% of patients whose VTE was associated with air travel had other risk factors for VTE. On the basis of this risk, the BTS[20] recommends that travelers who are at moderately increased risk of VTE (e.g., family history of VTE, past history of provoked VTE, thrombophilia, body mass index greater than 30 kg/m^2, height greater than 1.90 m or less than 1.16 m, significant medical illness within the previous 6 weeks, cardiac disease, immobility, pregnancy or estrogen therapy, and postpartum patients within 2 weeks of delivery) should wear below-knee elastic compression stockings during flight. For travelers who are at higher risk of VTE (i.e., past history of unprovoked VTE, major surgery or trauma within 6 weeks, or active malignancy), the BTS recommends a preflight prophylactic dose of low-molecular-weight heparin with consideration of full therapeutic anticoagulation on an individual basis. After an episode of VTE, the BTS recommends deferring travel for 4 weeks or until complete clinical and symptomatic resolution of proximal deep vein thrombosis.

PRACTICAL ASPECTS OF ASSESSING THE PATIENT WITH PULMONARY SYMPTOMS IN FLIGHT

Most (≈70%)[91] in-flight medical complaints are managed by the cabin crew without the request for or intervention by an onboard medical professional. However, requests for assistance have been estimated at a frequency of 1 per 14,000 passengers.[91] When a request for assistance for an onboard medical professional is expressed, some practical information regarding available equipment and medications as well as the implications of serving as a Good Samaritan[92] is useful.

By FAA mandate, every commercial airliner must carry at least one first-aid kit (and sometimes multiple kits depending on the aircraft passenger capacity) as well as an automated external defibrillator.[93] The minimal contents of the onboard medical kit are dictated by FAA directives and are presented in Table 106.6. In our experience, passengers on the plane will have a variety of medications in their onboard luggage, so that if a need arises for a medication not available in the medical kit, asking the cabin crew to announce the need for a specific medication may be productive.

When deciding to respond to the cabin crew's request for medical help, it is useful to understand the culture and implications of stepping forward as "the doctor on the plane" when such requests come. While there is no clear legal requirement to step forward, there is a moral and professional obligation to serve a patient in need. By U.S. law, Good Samaritan provisions protect passengers who offer medical assistance in flight from liability

Table 106.6 Federal Aviation Administration Required Contents of an Onboard Medical Kit

Content	Number
Sphygmomanometer	1
Stethoscope	1
Airways, oropharyngeal (3 sizes): 1 pediatric, 1 small adult, 1 large adult or equivalent	3
Self-inflating manual resuscitation device with 3 masks (1 pediatric, 1 small adult, large adult or equivalent)	1 with 3 masks
CPR mask (3 sizes), 1 pediatric, 1 small adult, 1 large adult, or equivalent	3
Intravenous administration set:	
Tubing with 2 Y-connectors	1
Alcohol sponges	2
Adhesive tape, 1-inch standard roll adhesive	1
Tape scissors	1 pair
Tourniquet	1
Saline solution, 500 mL	1
Protective nonpermeable gloves or equivalent	1 pair
Needles (2–18, 2–20, 2–22 gauge, or sizes necessary to administer required medications)	6
Syringes (1–5 mL, 2–10 mL, or sizes necessary to administer required medications)	4
Analgesic, nonnarcotic, tablets, 325 mg	4
Antihistamine tablets, 25 mg	4
Antihistamine injectable, 50 mg (single-dose ampule or equivalent)	2
Atropine, 0.5 mg, 5 mL (single-dose ampule or equivalent)	2
Aspirin tablets, 325 mg	4
Bronchodilator, inhaled (metered-dose inhaler or equivalent)	1
Dextrose, 50%/50 mL injectable (single-dose ampule or equivalent)	1
Epinephrine 1:1000, 1 mL, injectable, (single-dose ampule or equivalent)	2
Epinephrine 1:10,000, 2 mL, injectable (single-dose ampule or equivalent)	2
Lidocaine, 5 mL, 20 mg/mL, injectable (single-dose ampule or equivalent)	2
Nitroglycerin tablets, 0.4 mg	10
Basic instructions for use of the drugs in the kit	

CPR, cardiopulmonary resuscitation.

as long as no gross negligence or willful misconduct was conducted. Gross negligence is defined as deviating from the care "ordinarily to be expected from a person undertaking his particular role and professing to have his particular skills."[91] The standard is usually met when other physicians attest that they would have acted similarly, with the caveat that there is clear understanding that care provided in the limited medical environment of an airplane cabin is very different than that provided in a medical facility. Overall, experience suggests that it is extremely rare for a passenger to take action against a Good Samaritan.[91]

One of the issues embedded in serving as a health professional in response to a request from the cabin crew is whether the patient's condition requires diversion of the plane to an earlier landing. Airlines generally have on-ground support with algorithms that help the captain determine the need for diversion. While the captain of the plane bears ultimate responsibility for the decision to divert, the input of a physician attending to the patient in flight may be sought.

SUMMARY

Assessing prospective air travelers with lung disease requires careful consideration of the effect of the special environmental conditions at cabin altitude on respiratory disease. Most of the available experience and hence current recommendations are based on travelers with COPD, particularly in the assessment of in-flight oxygen requirements. Thus, there is a need for studies that clarify the steps in assessing patients with other lung diseases who intend to travel by air. Awareness of the specific risks associated with conditions like pneumothorax, VTE, and pulmonary hypertension, among others, is critical for determining fitness to fly and for optimal preflight assessment.

Fortunately, recognizing that available experience with in-flight medical emergencies is biased somewhat by a "healthy traveler" effect, the frequency of in-flight medical events, diversions of aircraft, and in-flight mortality is very low in the context of the expansion of air travel and the increasing availability of air travel for individuals with pulmonary disease. As the science of preflight assessment improves, clinicians must continue to exercise careful expertise in balancing the appetite for travel with awareness of travel-related risks, with the goal of optimizing patients' ability to travel safely.

Key Points

- Consideration of special environmental conditions in the aircraft cabin, particularly hypobaric hypoxia, is key to the preflight evaluation of patients with lung disease.
- In particular, a preflight clinical assessment should be performed for all patients with history of respiratory symptoms during previous air travel, severe COPD, bullous lung disease, asthma, cystic fibrosis, severe restrictive lung disease, comorbidities that could worsen with hypoxemia, history of pneumothorax or venous thromboembolism, and preexisting need for oxygen.
- A high-altitude simulation test combined with a 6-minute walk test can identify patients with COPD who will need in-flight oxygen and provide guidance for other respiratory conditions.
- Patients with diffuse cystic lung disease with chest pain or dyspnea should seek evaluation in order to exclude a pneumothorax before traveling by air.
- The presence of pulmonary hypertension should increase the clinician's suspicion of hypoxemia in flight and prompt performance of a high-altitude simulation test.
- Preflight assessment of risk for *venous thromboembolism* (VTE) should include consideration of other risk factors for VTE. Patients with acute VTE should defer air travel for at least 4 weeks or until complete clinical resolution. Patients with risk factors and previous VTE history should be considered for prophylactic measures, including compression stockings and, for those with highest risk, prophylactic or full anticoagulation.
- Patients with active tuberculosis should not travel by air. In patients with established or suspected coronavirus infection (e.g., severe acute respiratory syndrome, COVID-19), air travel should be avoided.

Key Readings

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107 DIVING MEDICINE

MICHAEL S. LIPNICK, MD • KAREN B. VAN HOESEN, MD

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INTRODUCTION

Diving and work in compressed air have provided an occupational exposure to hazardous environments for nearly 400 years. In the 1600s, diving bells were first reported in use for marine salvage. These inverted metal containers provided a pocket of trapped air to transport divers to depth and also served as a reservoir of compressed air in between excursions from the bell while at depth. In 1670, Sir Robert Boyle first described decompression disease in animal studies and, in the 1800s, surface-supplied diving gear emerged to provide new degrees of freedom for divers and also new risks. *Decompression sickness* (DCS) in humans was first reported in the mid-1800s, in coal miners and caisson workers who worked in underground cavities pressurized to keep out water.[1] The term "the bends" originated from the distinctive forward-bent posture caused by joint symptoms from DCS and was first used to describe construction workers for the Eads and Brooklyn Bridges in 1870.[2] Around the turn of the 20th century, seminal work by Paul Bert, J.S. Haldane, and E.W. Moir helped lay the groundwork for modern dive medicine.

Since the advent of the *self-contained underwater breathing apparatus* (scuba), diving has become a recreation for millions of individuals around the world. Any physician may encounter a recreational, scientific, or occupational diver for an illness related to diving or for medical clearance for diving. Occasionally, a physician may be confronted with an acute medical emergency related to diving, such as DCS, arterial gas embolism, or drowning. This chapter reviews fundamental diving physiology and disorders and provides the basis for initiating treatment, seeking consultation, or furthering education in this evolving area of environmental medicine.

ADAPTATION TO DIVING

Many air-breathing animals have developed remarkable adaptations for diving and survival underwater. Several aquatic species are among the most hypoxia-tolerant animals on the planet. Diving Weddell seals (*Leptonychotes weddellii*) have reached arterial partial pressures of oxygen (P_{O_2}) of 18 mm Hg during 27-minute dives and may reach much lower partial pressures during dives known to last nearly 45 minutes.[3] Some diving mammals (Cuvier's beaked whales [*Ziphius cavirostris*]) reach depths of nearly 3000 m on dives lasting more than 2 hours.[4] Many diving mammals have evolved to possess many specialized adaptations, including larger spleens, high mass-specific blood volumes (>200 mL/kg in sperm whales as compared with 70 mL/kg in human adults), enhanced myoglobin structure and distribution, anatomic adaptations of the middle ear and sinuses, and specialized intrathoracic anatomy.[5,6] Contrary to popular belief, increasing total lung capacity is not a uniform adaptation in diving mammals. In fact, some of the deepest-diving whales have markedly small lung volumes relative to body mass. Certain diving mammals (e.g., seals) even exhale before diving. Collectively, these adaptations and adaptive behaviors aim to increase oxygen delivery to the vital organs, minimize potentially fatal consequences of absorbing compressed oxygen or nitrogen at extreme depths, and avoid painful compression or rupture of air-filled structures.[7]

All diving mammals, including humans, have developed a characteristic physiologic response to diving. Triggered by apnea and cold-water facial immersion, this dive response includes bradycardia (which decreases oxygen consumption), peripheral vasoconstriction (which shunts blood to vital organs), and splenic contraction (which increases

circulating red blood cell volume). The Japanese Ama pearl divers and Bajau ("sea nomads") of Southeast Asia are two of the human populations most closely studied for their diving adaptations.[8] The Bajau, who spend up to 60% of their working day breath-holding at depths of more than 70 m, have genetic adaptations that increase spleen size and modify their human diving reflex.[9,10] Studies of competitive free divers have demonstrated increased total lung capacity, splenic volume, hypercarbia tolerance, and hemoglobin concentration.[11]

EQUIPMENT AND TECHNIQUES

BREATH-HOLD DIVING

Humans breath-hold dive (i.e., dive on a breath-hold without a source of compressed gas) for many reasons, including recreation, hunting, and competition. The record for the deepest competitive breath-hold dive without fins is 125 m, and the longest static apnea (breath-holding in a pool) is 11 minutes 35 seconds. Many breath-hold divers use no equipment or little more than a face mask and weight belt. In some competitive breath-hold diving categories, divers may use weighted sleds, specialized fins, and inflatable ballasts to assist with more rapid descent and ascent at depths of more than 200 m. Although hypocapnia decreases respiratory drive and increases breath-hold duration, extreme voluntary hyperventilation is ill advised and can lead to loss of consciousness or death during breath-hold diving, in part because of decreased cerebral blood flow.

OPEN-CIRCUIT SCUBA

The most commonly used breathing equipment in diving is the open-circuit scuba. This equipment (Fig. 107.1) consists of a metal cylinder containing compressed air connected to a pressure regulator that lowers pressure from the tank to ambient pressure. This device delivers ambient-pressure air only when inhalation is initiated and allows flow that matches the minute ventilation of the diver. Expired air is released directly into the surrounding water. A typical scuba cylinder can supply approximately 2100 L of air at the surface (1 *atmospheres absolute* [ATA]). This volume is reduced in direct proportion to ambient pressure. For example, at a depth of 66 *feet of seawater* (fsw) or 3 ATA pressure, the effective volume of air is decreased to 700 L. With a minute ventilation of 20 L/min, this air supply would last 105 minutes at the surface but only 35 minutes at 66 fsw. Open-circuit scuba is usually limited to depths less than 200 feet because of limited air supply, nitrogen narcosis, and oxygen toxicity, as discussed in subsequent sections.

REBREATHER DIVING

There are several types of rebreather devices, including the oxygen rebreather, semiclosed-circuit rebreather, and closed-circuit rebreather. The closed-circuit rebreather apparatus uses a carbon dioxide absorbent to remove exhaled carbon dioxide and replenishes the circuit with oxygen (Fig. 107.1 and eFig. 107.1). Inert gas is conserved

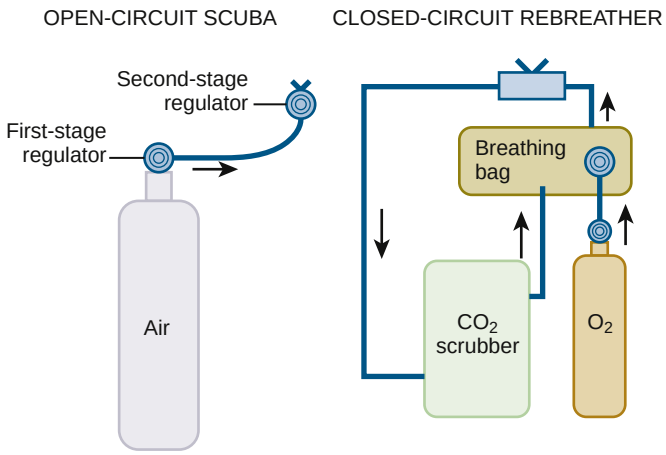

Figure 107.1 Two types of self-contained diving systems. The open-circuit scuba is the system commonly used for recreational diving. Air is exhaled into the surrounding water. Rebreather systems allow exhaled breathing gas to be recycled through a *carbon dioxide* (CO_2) scrubber, mixed with additional breathing gas, and returned to the diver through a breathing bag. Breathing gas is replenished through a demand valve. This system can be used with 100% *oxygen* (O_2) or oxygen-enriched air mixtures. Other forms of rebreather systems contain separate oxygen and inert gas supplies, and mixing is controlled with a small computer to maintain a constant oxygen partial pressure.

by recycling the exhaled gas through the carbon dioxide absorbent and then adding oxygen before the gas is rebreathed. Little gas is released into the surrounding water, exhaled heat and humidity are conserved, oxygen can be carried in volumes adequate for several hours of exposure, and gas consumption is independent of depth. Although use of rebreather diving in the past was confined to commercial and military divers, these systems are now becoming popular among technical divers and even some recreational divers. Dive incidents related to the use of closed-circuit rebreathers are often related to failures in equipment setup or maintenance, incomplete carbon dioxide scrubbing, and higher-risk dive profiles (i.e., dives lasting many hours at extreme depths) among many other factors.[12]

SURFACE-SUPPLIED EQUIPMENT

Commercial diving often uses surface-supplied gas equipment. The diver breathes compressed air or other gas mixtures pumped from the surface to a helmet or mouthpiece regulator. Diving helmets may be attached at the collar to a diving suit so that air can flow from the helmet into the suit to maintain an air layer for thermal protection. Modern systems contain a demand mask built into the helmet.

Surface-supplied equipment is also encountered in recreational diving although, contrary to popular belief, it has the same risks as scuba diving with tanks. Improvised surface-supplied setups (i.e., hookah diving support systems) are often used by fishermen in low- and middle-income countries. These setups can expose divers to unsafe gas pressures or hazardous gases (e.g., compressed carbon monoxide from an air compressor intake placed near the

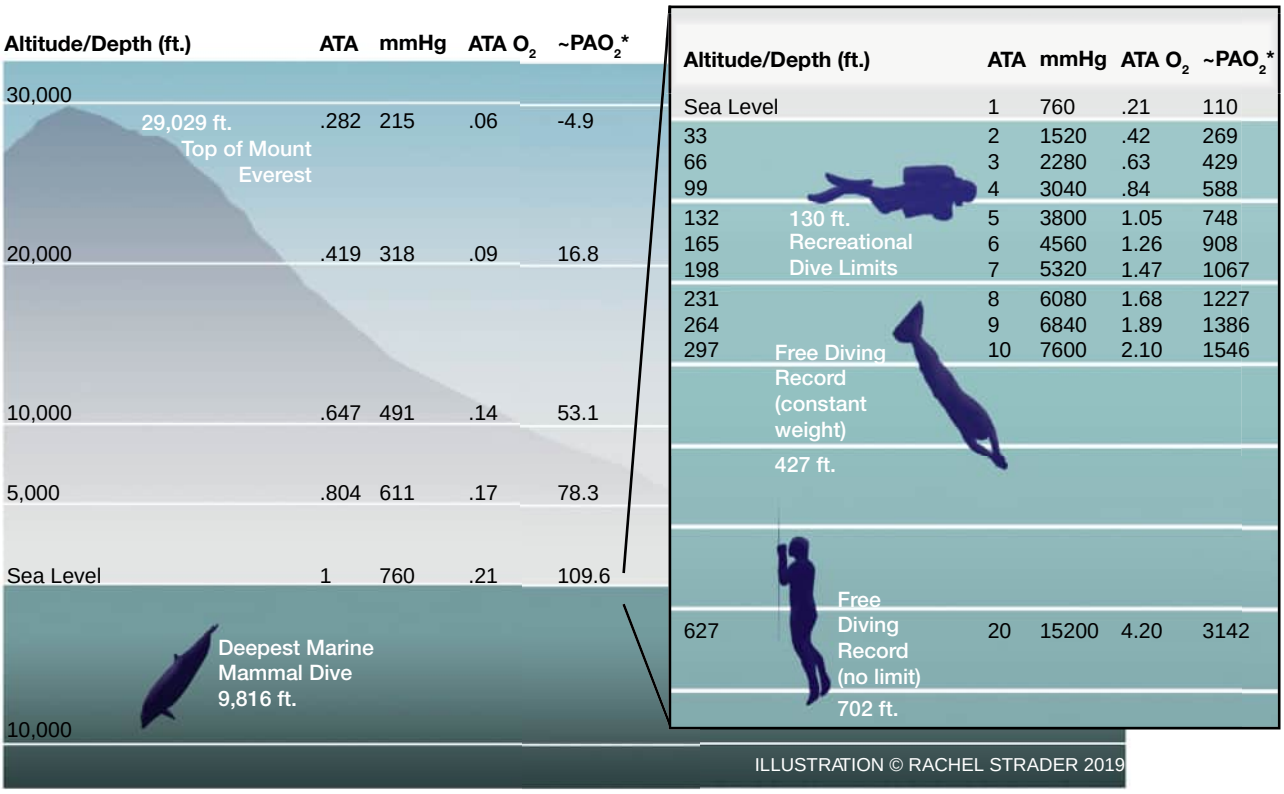

Figure 107.2 Pressure equivalents for high altitude and for depth. Relatively small changes in depth cause large changes in pressure, whereas extremely large changes in altitude are required for significant pressure changes. For example, descending from sea level to 33 *feet of seawater* (fsw) doubles the pressure, whereas one must ascend to nearly 16,000 feet to halve atmospheric pressure. *Hypothetical *alveolar partial pressure of oxygen* (P_{AO_2}) if breathing 21% inspired fraction of oxygen, assuming an *arterial partial pressure of carbon dioxide* (P_{aCO_2}) of 40 mm Hg and an ambient temperature of 15°C. Of note, at high altitude, climbers demonstrate profound hyperventilation to less than 10 mm Hg arterial P_{CO_2}, thus resulting in significantly higher alveolar P_{O_2} values than the hypothetical values shown if arterial P_{CO_2} remained at 40 mm Hg. ATA, atmospheres absolute. (Copyright Rachel Strader, 2019.)

engine exhaust).[13] Divers who use these setups in resource-constrained settings frequently experience decompression illness as a result of long dive durations and erratic depth changes.

SATURATION DIVING

The term *saturation* refers to a steady state when the diver remains at depth and is no longer increasing absorption of inert gas. Saturation divers delay surfacing and thus delay their decompression. In other words, divers who have reached saturation can remain at depth for a prolonged period of days or weeks without affecting the amount of time they must eventually spend decompressing (i.e., slowly ascending to release inert gas burden) at the end of the dive. To facilitate this, divers reach a working depth and then remain at that depth for the duration of the work period by entering a living habitat. In between working excursions, the living habitat may remain at depth or be transported to the surface; in either scenario, the habitat remains compressed at the working depth pressure. This type of diving was originally developed in the 1960s to facilitate dam repairs, although at present it is most commonly used in the open-water oil industry. These divers routinely spend 2 weeks "at depth," although saturation periods of up to 1 month have been reported. Once saturation is reached, the decompression time (which may last days or weeks) is the same for any duration of dive.

DISORDERS RELATED TO DIVING: NOMENCLATURE

Golding and coworkers[14] described disorders related to supersaturation of inert gases in tissues with subsequent bubble formation as *decompression sickness*. DCS is categorized as type I and type II: (1) type I, a nonsystemic (peripheral) form that involves only the skin, bones, and joints and (2) type II, a systemic form of DCS that involves the central nervous system, the lungs, the inner ear, and the circulation.

Arterial gas embolism (AGE) and pulmonary barotrauma are additional diving-related disorders with pathophysiology distinct from DCS. Francis and Smith[15] suggested the term *decompression illness* to describe DCS and AGE collectively because these disorders can be clinically difficult to separate and require similar therapy.[15] In fact, numerous dive-related disorders are attributable to the effects of dissolved gases or barotrauma.

PRESSURE EFFECTS AND BOYLE'S LAW

RELATION OF GAS VOLUME TO DEPTH

The terms *atmosphere* (ATM) and *atmosphere absolute* (ATA) both refer to pressure; ATM, however, can be used as a relative term (33 fsw depth is equivalent to 1 ATM of water), whereas ATA is always used for absolute pressure (33 fsw depth is equivalent to 2 ATA, or 1 ATM at the surface with an additional 1 ATM from the 33 fsw). *Atmosphere absolute* is the term used in this chapter and is always used for equations, such as Boyle's law. Boyle's law states that if the temperature of a fixed mass of an ideal gas is kept constant, then volume and pressure are inversely related. Consequently, when the pressure is doubled, the volume is reduced to one-half of the original volume. Because the gas volume is proportional to the absolute pressure, the volume change from the surface (1 ATA) to 33 fsw (2 ATA) is greater than the change from 33 (2 ATA) to 66 fsw (3 ATA).

Underwater exposure results in increasing pressure directly proportional to depth. Of note, relatively small changes in depth cause large changes in pressure, whereas extremely large changes in altitude are required for significant pressure changes. For example, descending from sea level to 33 fsw doubles the pressure, whereas one must ascend to nearly 16,000 feet to halve atmospheric pressure (see Fig. 107.2).

The relationship between pressure and depth holds true for all exposures to pressure, including hyperbaric chambers, pressurized tunnels, and caissons used for underwater construction. As depth increases, the diver breathes gas of increased density. Increased depth and pressure also lead to decreases in gas volume and increases in the amount of gas dissolved in body tissues. When human breath-hold divers descend to approximately 99 fsw, the lungs compress to a point at which the divers become negatively buoyant and actually sink.

BAROTRAUMA

Barotrauma is the most common medical problem in scuba diving and refers to tissue damage resulting from pressure imbalances in the body. Barotrauma may happen both during descent (pulmonary barotrauma, ear barotrauma, sinus barotrauma, and mask squeeze) and during ascent (pulmonary barotrauma, and AGE, alternobaric vertigo, reverse squeeze, gastrointestinal barotrauma).

Barotrauma of Descent

Pulmonary Barotrauma in Breath-Hold Divers. Lung barotrauma or lung squeeze is a rare consequence of breath-hold diving. This complication is not found in scuba divers and others breathing with an open glottis. When a breath-hold diver descends to such a depth that total lung volume is reduced to less than residual volume, transpulmonic pressure can exceed intra-alveolar pressure, thus leading to transudation of fluid and pulmonary edema, as well as rupture of pulmonary capillaries with bleeding. A diver with a total lung volume of 6000 mL and a residual volume of 1200 mL could theoretically dive to a maximum depth of 132 fsw (5 ATA) before developing lung squeeze. However, breath-hold divers have dived much deeper, probably because of central pooling of blood that would reduce the residual volume. Lung barotrauma can also take place at shallow depths and may be associated with inadequate training.[16,17]

Sinus Barotrauma. When a sinus orifice is occluded, pressure within the sinus becomes negative with respect to ambient pressure, and mucosal blood vessels become engorged and eventually rupture. Pain over the affected sinus during descent and epistaxis on ascent are usual symptoms. Headache following a dive may indicate sphenoid sinus barotrauma. Treatment includes topical and oral decongestants and maneuvers to drain the affected sinus. Persistence of blood in the sinus may result in bacterial sinusitis. This complication can be prevented by avoiding diving when the nasopharynx is congested and by using decongestants. If a maxillary sinus orifice is occluded, the maxillary branch of the trigeminal nerve may be compressed during ascent and result in infraorbital paresthesias that usually resolve in 2 to 3 hours.[22]

Less Common Forms of Barotrauma. Facial barotrauma ("mask squeeze") happens in the area of distribution of the diving mask. Facial edema, ecchymoses, and conjunctival hemorrhages can be noted after diving. The disorder is self-limiting, and no treatment is needed. Retro-orbital hematoma with diplopia or visual loss is a rare complication of face mask barotrauma.[23,24] A diver with suspected orbital hemorrhage must be referred for emergency imaging and ophthalmologic consultation.

Tooth barotrauma leading to severe toothache results when air pockets under fillings or areas of decay become compressed on descent. Careful dental work prevents this disorder.[25]

Barotrauma of Ascent

Pulmonary Barotrauma and Arterial Gas Embolism. The gas that a diver breathes is pressurized to the ambient pressure so that pressure gradients from the breathing supply to the airways are not altered as the diver descends. Behnke[26] and Polak and Adams[27] described lung barotrauma in ascending divers that resulted from inadequate exhalation during ascent and overexpansion of the lungs. Later studies provided further insight into mechanisms and prevention of pulmonary barotrauma.[28] Breath-holding during ascent from a depth as shallow as 4 fsw can result in fatal pulmonary barotrauma.[29] Patients with pulmonary blebs, cysts, or air trapping caused by obstructive disease can experience rupture on ascent that leads to pneumothorax.

PATHOPHYSIOLOGY. Under experimental conditions, transpulmonary pressures (i.e., the difference between intratracheal and intrapleural pressures) of 95 to 110 cm H_2O are sufficient to disrupt the pulmonary parenchyma and force gas into the interstitium.[28] Extra-alveolar gas can migrate through perivascular sheaths to cause mediastinal emphysema and pneumomediastinum. Less frequently, air can be vented through the visceral pleura and thereby cause a pneumothorax.[28] Gas can also dissect into the retroperitoneum and into the subcutaneous tissues of the neck. Extra-alveolar gas can pass into ruptured blood vessels, travel to the left side of the heart, and enter the arterial circulation as gaseous emboli, commonly referred to as an AGE. The

Middle Ear Barotrauma. Middle ear barotrauma is the most common diving-related disorder.[18] The middle ear undergoes barotrauma when the eustachian tube is blocked during descent, and the middle ear space cannot equilibrate with increasing ambient pressure. The tympanic membrane is displaced inward and may rupture. The middle ear may fill with blood from engorged mucous membranes. Infection and hearing loss are complications. Symptoms during descent include pain in the affected ear that increases with depth. Relief of pain without proper equalization of the middle ear pressure usually indicates that the tympanic membrane has ruptured. Cold water entering the middle ear when the tympanic membrane ruptures may cause vertigo because of unilateral vestibular stimulation. Late complications include bacterial otitis media, serous otitis media, and chronic tympanic membrane perforation.[18] In rare cases of middle ear barotrauma, the facial nerve is injured by the increased pressure, and temporary facial paralysis results.[19] A modified Valsalva maneuver is commonly used to equilibrate middle ear pressure. Because middle ear barotrauma causes edema and hemorrhage in the middle ear, equalization is usually impossible to achieve until healing is complete. The presence of middle ear barotrauma usually prohibits diving until it is resolved.

Inner Ear Barotrauma. Inner ear barotrauma may develop on descent in divers who perform a forceful Valsalva maneuver to equalize middle ear pressure. When the eustachian tube is blocked, middle ear pressure becomes progressively more negative relative to ambient pressure.[18,20] When a Valsalva maneuver is then performed, intrathoracic pressure, central venous pressure, spinal fluid pressure, and inner ear pressure rise to a level greater than ambient pressure, thereby increasing the gradient between the inner ear perilymph and the middle ear. Membranes separating the inner and middle ear (e.g., round and oval windows) can rupture, and perilymph can then leak from the inner to the middle ear.

Symptoms include vertigo, nausea, vomiting, tinnitus, and loss of hearing on the affected side. Severity may vary, and some divers report hearing loss, tinnitus, or vertigo only after diving.

Treatment varies from conservative therapy to surgical repair of ruptured membranes. Vertigo and nausea can be treated with benzodiazepine medications. Tinnitus and reduced hearing may become chronic, particularly without treatment. Divers who exhibit clinical evidence of inner ear barotrauma with intact round and oval windows may have a pressure injury to the organ of Corti and the vestibular system.[21]

dissemination of gas bubbles throughout the arterial circulation can injure numerous organs, including skeletal muscle, which may be manifest by a rise in serum creatine kinase level.[30]

Pulmonary barotrauma usually results from a rapid or uncontrolled ascent to the surface, typically caused by running out of air, panic, or sudden development of uncontrolled positive buoyancy. Occult lung disease may contribute to unexplained barotrauma and AGE.[31] Epidemiologic studies have not demonstrated a significant relationship between asthma and an increased risk for pulmonary barotrauma.[32]

Clinical Manifestations of Arterial Gas Embolism. The brain is commonly involved with AGE events. Within minutes of surfacing, the diver can experience loss of consciousness, hemiplegia, stupor, confusion, seizures, vertigo, visual disturbances, sensory changes, or headache. Circulatory collapse can result from filling of the heart and great vessels with air; these individuals may be unresponsive to cardiopulmonary resuscitation and advanced life support measures.[33] Most individuals with AGE fully recover if they are promptly recompressed.[34] Because AGE can lead to loss of consciousness on surfacing, a diver may aspirate water and drown. Chest radiographs may show a pattern of diffuse pulmonary edema (Fig. 107.3).[35] A report of 31 patients with cerebral air emboli from diving included the following findings: 25% demonstrated pneumomediastinum, 10% had subcutaneous emphysema, 6% had pneumocardium, 3% had pneumoperitoneum, and 3% had pneumothorax. Laboratory evaluation may show an elevated hematocrit level reflecting plasma extravasation from endothelial injury or an elevated creatine kinase from injury to skeletal muscle.[30,36]

Mediastinal emphysema is generally associated with mild substernal pain that may be exacerbated by inspiration, coughing, or swallowing. Unless massive, this condition is not usually associated with circulatory compromise.

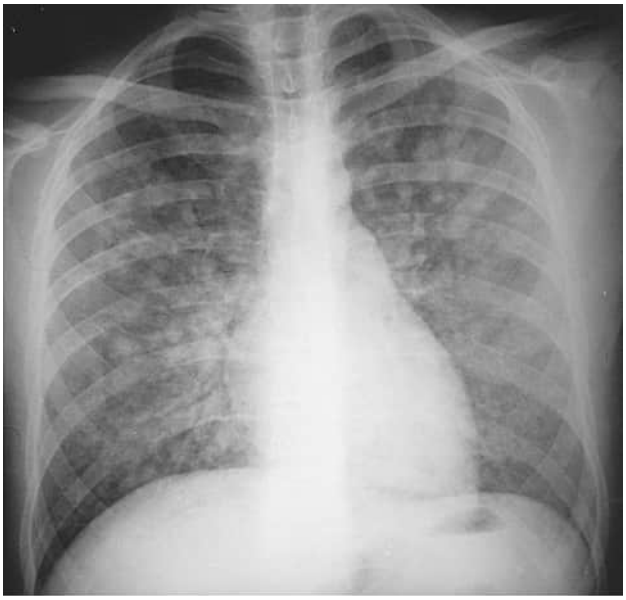

Figure 107.3 Chest radiograph from a diver who survived drowning. The diffuse pulmonary edema pattern is suggestive of water aspiration.

On physical examination, a crunching sound synchronous with the cardiac cycle may be auscultated (the Hamman sign). The chest radiograph confirms the diagnosis, and no treatment is usually necessary.

Subcutaneous emphysema may cause swelling and crepitus in the base of the neck and supraclavicular fossa, sore throat, hoarseness, and dysphagia. Radiographs may be helpful in detecting subtle cases, but *computed tomography* (CT) scans are more sensitive and can be useful to confirm the diagnosis of barotrauma in doubtful cases. Treatment of AGE requires recompression in a hyperbaric chamber (see later).

Alternobaric Vertigo. Vertigo may develop on ascent when the reduction of middle ear pressure is not uniform in both ears. The pressure imbalance causes differential stimulation of the labyrinths and results in what is called *alternobaric* vertigo. Although usually only transient, the sensation of vertigo rarely may persist for 1 to 2 hours after diving and gradually disappears without therapy. Symptoms are similar to labyrinthitis and can include nausea, vomiting, and generalized malaise. Some divers may be particularly susceptible to alternobaric vertigo if they have had previous injury or infection of the labyrinths. In susceptible individuals, use of moderate doses of antihistamines or decongestants may prevent symptoms. The disorder must be differentiated from vestibular DCS (see "Decompression Sickness"). The differential diagnosis of alternobaric vertigo may also include motion sickness, benign positional paroxysmal vertigo, and inner or middle ear barotrauma, among other potential conditions.

Reverse Squeeze. Inability to release increasing pressure from the middle ear during ascent can result in high-pressure translocation or rupture of the tympanic membrane, also known as reverse squeeze. This may result if the eustachian tubes are blocked by mucus or from incomplete equalization during descent. Reverse squeeze may be manifest by pain, sensation of ear fullness, or vertigo on ascent.

Gastrointestinal Barotrauma. Gastrointestinal barotrauma results when air enters the stomach during diving because of faulty breathing apparatus or air swallowing. On ascent, the expanding air distends the stomach or intestine. Gastric distention can occlude the esophageal-gastric junction or cause stomach rupture and pneumoperitoneum.[37] Divers with previous gastric surgery may be prone to gastric air trapping.[38]

DISSOLVED INERT GAS EFFECTS AND HENRY'S LAW

INERT GAS KINETICS

Gases dissolve in tissues, fats, and water according to Henry's law: $Q = c \times P$, where a solubility coefficient (c), and the partial pressure of the gas (P), determine the quantity (Q) of dissolved inert gas. Increased ambient pressure elevates the dissolved gas concentration in the tissues. The partial pressure of the gas and the solubility of the gas in the specific tissue (Table 107.1) determine dissolved gas content. Although Henry's law determines the amount of gas in the tissue, there is a finite time required for equilibrium to be achieved. Factors that affect the rate of entry

include blood flow and the rate of diffusion of gases into the tissue. During a dive, tissue gas concentration follows an asymptotic curve. When ambient pressure is reduced on ascent, similar kinetics control the washout of inert gas from tissues. Different body compartments have different gas exchange characteristics.[39] The lungs, blood, and brain equilibrate quickly relative to tissues that have high capacity for inert gas uptake or have relatively poor perfusion (e.g., ligaments, cartilage, and fat).

Because most diving is of short duration (i.e., minutes to hours) and shallow (i.e., in depths less than 200 feet), only a few tissue compartments reach equilibrium according to Henry's law. Divers can return to the surface from these short-duration dives by following a schedule of ascent based on depth and time.[39] When diving exposure is long enough, all tissues reach equilibrium at the new ambient pressure and are fully saturated with inert gas. Divers can spend prolonged periods (weeks) under pressure, with all tissues saturated at the increased pressure, without harm (see "Saturation Diving").[40]

INERT GAS SUPERSATURATION IN TISSUES

When the diver ascends after breathing pressurized gas, tissues become supersaturated with gas. When the degree of supersaturation becomes excessive, dissolved gas leaves solution and form free gas. Studies suggest that blood microparticles may act as a nidus for bubble formation in blood.[41]

DECOMPRESSION SICKNESS

On decompression, dissolved gases can change phase to the gaseous form.[42] DCS is the disorder caused by damage to organs and tissues as a result of free gas production.

Bert[43] first described the pathophysiology of DCS. Subsequent investigators in the early 20th century concluded from autopsies on divers and caisson workers that DCS is caused by free gas in blood and tissues.[44] Based on the volume and location of free gas on autopsy, they were able to explain the variety and severity of the symptoms. Paralysis resulted from free gas in the spinal cord, cerebral dysfunction was thought to result from free gas in the brain, and dyspnea was associated with free gas in the pulmonary circulation. Muscle and joint pain may be the result of free gas in ligaments, fascia, periosteum, marrow, or nerve sheaths.

Hallenbeck and colleagues,[45] as well as subsequent studies,[46,47] described a multitude of effects of free gas in blood and tissues, including platelet activation, intravascular coagulation, plasma leakage from the intravascular space, activation of the inflammatory cascade, hemoconcentration, and hypovolemia. More recent studies have outlined the role of cellular and biochemical changes involving inflammation, oxidative stress, and vascular endothelial cell activation in the pathogenesis of DCS.[41,48,49] The inflammatory response increases fluid leakage into the interstitial tissues of the systemic and pulmonary vascular beds.[50] Venous gas emboli are commonly present before overt symptoms of DCS appear (Fig. 107.4 and Video 107.1).[51,52]

Risk Factors

The use of ultrasonography for intravascular bubble detection has provided insight into the presence of bubbles following diving.[53] Many divers demonstrate venous gas emboli but no manifestations of DCS (see Fig. 107.4). The concept of a threshold or dose-response effect has been postulated, wherein a certain volume of free gas is needed to produce the clinical disorder, and divers with lesser amounts are asymptomatic.[54] Venous bubbles in asymptomatic divers and aviators are associated with increased risk for developing DCS after diving or altitude exposure.[55,56]

Symptoms can be prevented by keeping the degree of supersaturation lower than a certain level. The body can be considered as a set of tissue compartments with different rates of gas uptake and elimination.[57] Although these tissues do not represent discrete anatomic structures, they provide a convenient means for understanding the kinetics of inert gas exchange. In most decompression schedules, stops during ascent are selected to avoid excess

Table 107.1 Characteristics of Inert Gases*

Gas	Molecular Weight	Lipid Solubility†	Water Solubility	Narcotic Potential‡
Helium	4	0.015	0.009	0.23
Neon	20	0.019	0.009	0.28
Hydrogen	2	0.036	0.018	0.55
Nitrogen	28	0.067	0.013	1.00
Argon	40	0.140	0.026	2.32

*Solubility of the various gases in lipid is related to their narcotic potential. Helium is the least, and argon the most, narcotic gas in the list.
†Expressed as gas volume/solute volume at 1 bar.
‡Values relative to nitrogen.
Modified from Bennett PB: Inert gas narcosis and HPNS. In: Bove AA, ed. *Bove and Davis' Diving Medicine*. 4th ed. Philadelphia: Saunders; 2004:225–240.

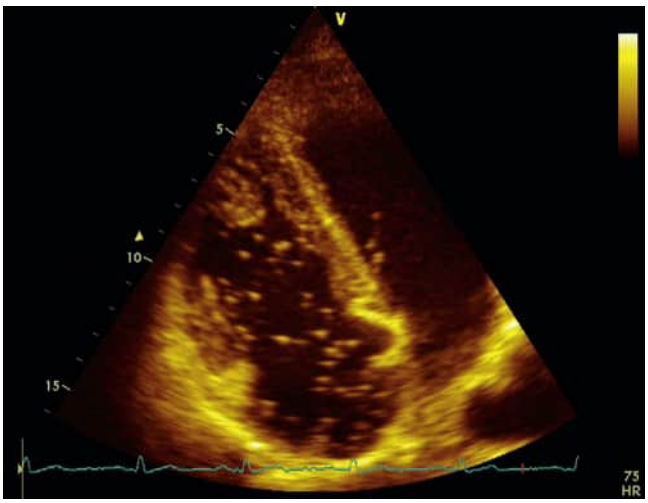

Figure 107.4 Gas bubbles after diving with compressed gases. Gas bubbles are commonly seen in the right side of the heart (*left*) after diving with compressed gases. Although the number of bubbles correlates with risk of decompression sickness, the presence of bubbles does not always imply decompression sickness and clinical symptoms (see also Video 107.1). (From Germonpré P, Papadopoulou V, Hemelryck W, et al. The use of portable 2D echocardiography and 'frame-based' bubble counting as a tool to evaluate diving decompression stress. *Diving Hyperb Med.* 2014;44:5–13.)

supersaturation in tissues with specific gas-exchange rates (Fig. 107.5). Decompression procedures are well defined for air and other mixtures of nitrogen and oxygen; helium and oxygen; nitrogen, helium, and oxygen (trimix); hydrogen and oxygen; and a few rare earth gases such as argon and neon.

There are several additional known risk factors for developing DCS, including exercise and temperature during decompression, decreased physical conditioning, lack of expertise, patent foramen ovale, older age, and subsequent exposure to high altitude (i.e., low pressure). Breath-hold divers can develop DCS from frequent repetitive dives.[58] Carturan and colleagues[59] found correlations among bubble formation, increased age, and decreased physical condition in sport divers. Klingmann and coworkers[60] reported an increased incidence of DCS in novice divers compared with more experienced divers. Blatteau and associates[61] reported that age and depth of dive exposure increased DCS risk. The presence of a *patent foramen ovale* (PFO) may be associated with a twofold to fourfold increase in the risk for DCS and is discussed further in the subsequent section on fitness to dive.[62] Risk for DCS in divers with PFOs may be mitigated by implementing conservative dive strategies.[63]

Exposure to altitudes higher than 18,000 feet (0.5 ATA) may increase the risk of DCS because of supersaturation of inert gases dissolved at atmospheric pressure.[64] Divers can develop free gas in tissues when going to higher altitude after diving even though they follow established protocols for ascent from depth to the surface. It is common for sport divers to fly in commercial aircraft (about 8000 feet equivalent altitude) shortly after diving, although special consideration is warranted and minimum preflight post-dive waits are recommended. Diving while at high altitude (e.g., in high-altitude lakes) can be more complex because of lower atmospheric pressure and the increased relative difference between atmospheric and underwater pressures.

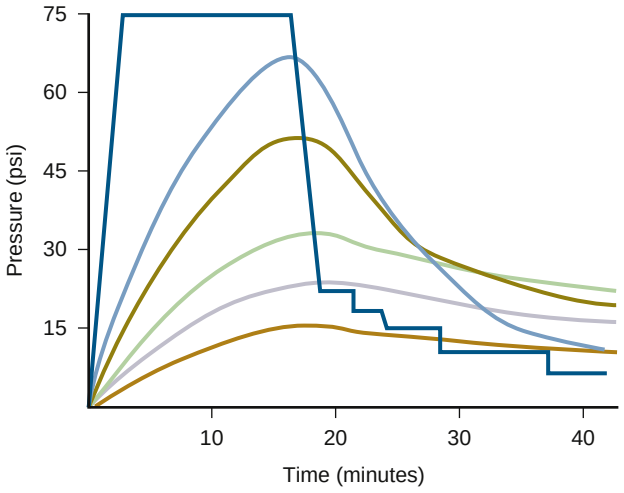

Figure 107.5 Theoretical nitrogen gas concentrations. Theoretical nitrogen gas concentrations are expressed in units of pressure for an exposure of 75 psi (5.1 ATA) following the depth-time profile indicated by the straight line. Curves are shown for five theoretical tissue compartments with different rates of gas exchange. Gas concentrations increase to different levels in the different tissue compartments during exposure to pressure. When pressure is reduced, gas concentrations in the different tissue compartments fall at different rates. Stops during return to baseline allow tissue concentration to fall to a safe level of supersaturation before reducing pressure further. (Data from Boycott AE, Damant GCC, Haldane J. The prevention of compressed air illness. *J Hyg [Lond].* 1908;8:342–443.)

Clinical Manifestations

The incidence of DCS in sport divers is estimated to be between 2 and 4 per 10,000 dives. In commercial divers, the incidence of DCS has been reported to be between 1 and 10 per 10,000 dives, although it can be as high as 35.5 per 10,000 dives.[65–70] Diving fishermen in low- and middle-income countries may have among the highest incidence of DCS, although data are limited.[72] Musculoskeletal DCS (type I) is the most common form of DCS in all divers.

DCS can mimic a variety of other disorders (Table 107.2). Free gas entering the venous system causes varying degrees of pulmonary vascular obstruction. A classic syndrome ("chokes") manifested by chest pain, dyspnea, and cough is described.[73] A common manifestation of DCS in divers is spinal cord dysfunction, usually at levels below the diaphragm.[74] Symptoms include paresthesias, muscle weakness, paralysis of the lower extremities, bowel or bladder incontinence, urinary retention, and sexual impotence.[75] A sudden ascent from deep depth ("blowup") can cause a massive DCS syndrome with both cerebral and spinal neurologic symptoms, unconsciousness, hypovolemic shock, pulmonary edema, and a high mortality rate.

The musculoskeletal form of DCS is manifested by pain in the extremities and joints.[76,77] Symptoms of local joint pain are often confused with pain from injuries, and the diagnosis of DCS may be missed. Exposure to high ambient pressures may cause aseptic necrosis of the bone, commonly seen in the juxta-articular femur and humerus. This condition, known as dysbaric osteonecrosis, is found in divers who have experienced musculoskeletal DCS in the distant past or who have experienced deep, prolonged exposures in caisson work, as well as in diving instructors and workers in commercial diving operations.[77,78] An erythematous or purpuric skin rash (cutis marmorata) may also be a manifestation of DCS. A systematic method for diagnosing DCS has been described by Latham and coworkers.[24]

Rare but important symptoms of serious (type II) DCS are sudden acute sensorineural hearing loss and vestibular dysfunction. DCS of this type usually follows deep,

Table 107.2 Frequency of Symptoms in 100 Cases of Decompression Sickness

Symptom	All DCS Symptoms (%)
Bone or joint pain	54
Spinal or neurologic	22
Respiratory	21
Fatigue or malaise	13
Spinal or back pain	11
Headache	11
Skin itch	4

DCS, decompression sickness.
Modified from U.S. Department of the Navy. *U.S. Navy Diving Manual*, vol 5, rev 6: *Diving Medicine and Recompression Chamber Operations* (NAVSEA 0910-LP-106-0957). Washington, DC: U.S. Department of the Navy; 2011.

prolonged diving exposures and, if untreated, can result in permanent deafness.[79] Inner ear DCS may be seen within 2 hours of surfacing and may include vertigo and hearing loss.[80] The mechanism is poorly understood but may involve formation of bubbles in the inner ear or embolism of systemic bubbles. Divers with inner ear DCS have been reported to have a higher prevalence of PFO, which increases the risk for right-to-left shunts of air bubbles and thus of decompression events. Such an association suggests that inner ear DCS may also result from air emboli.[81–83] The proper therapy for inner ear DCS is hyperbaric recompression.

Diagnostic Testing

Chest radiography can be used to diagnose pneumothorax, pneumomediastinum associated with pulmonary overpressure accidents, and the pulmonary abnormalities associated with aspiration or capillary leakage. Chest or abdominal CT can be used to diagnose pneumothorax, pneumomediastinum, or pneumoperitoneum. In cases of pulmonary barotrauma, a chest radiograph must be obtained prior to recompression to rule out a pneumothorax. If present, a chest tube will need to be inserted to prevent a tension pneumothorax from developing during a reduction in chamber pressure. Neurologic and psychological testing may be useful in determining response to treatment when brain injury is present. Electronystagmography and audiography may be useful in distinguishing inner ear DCS from inner ear barotrauma. Inner ear DCS requires recompression, whereas inner ear barotrauma is managed with bed rest, avoidance of straining, and possibly surgical intervention. The circumstances causing the two syndromes are distinct and are helpful in the differential diagnosis; the major difference is that inner ear barotrauma is caused during descent, whereas inner ear DCS is caused when surfacing. Central nervous system injury can be diagnosed by magnetic resonance imaging and correlated with clinical findings.[84,85] Magnetic resonance images of the brain in divers with no history of decompression-related disorders have also been found to be abnormal in some studies.[73]

Treatment

The clinical manifestations of DCS and AGE often overlap. The definitive treatment of DCS and AGE should ideally always be a return to pressure by recompression in a hyperbaric chamber and administration of oxygen at increased ambient pressure.[86,87] Timely fluid resuscitation, nonsteroidal anti-inflammatory drugs, and antiplatelet agents may also be part of the initial treatment.[88] Once stabilized with pressure and oxygen, the patient must be decompressed slowly to permit the inert gas to be carried away from tissues by the circulatory system and then to be exhaled by the lungs. With early treatment, DCS and AGE generally have an excellent prognosis for recovery. When treatment is delayed or when the injury is severe, there may be permanent injury to the brain or spinal cord.

Hyperbaric Therapy

Treatment of DCS and AGE should be instituted with recompression as soon as possible after the injury.[89] A history and physical evaluation, including a neurologic examination and cognitive assessment, should be obtained before treatment when possible. Therapy is provided by a trained medical team using either a monoplace (single-person) or multiplace (multiperson) hyperbaric chamber. A multiplace chamber allows medical personnel (also known as tenders) to be present in the chamber to administer additional therapies and tend to the patient. It is possible to place intubated patients in hyperbaric chambers. The usual practice is to follow the standard protocols for pressure treatment outlined in the *U.S. Navy Diving Manual,* which involves a pressure exposure equivalent to 60 fsw by using intermittent oxygen therapy (eFig. 107.2).[90] Oxygen breaks are used to limit potential for central nervous system oxygen toxicity. Most practitioners use a hyperbaric treatment protocol lasting approximately 5 hours for treatment of types I and II DCS. This treatment protocol reaches a simulated depth of 60 fsw (~3 ATA). Recompression therapy for cutis marmorata resulting from DCS has been recommended by some investigators, but most cases resolve spontaneously. Itching and erythema of the skin may also be noted following hyperbaric chamber exposures, but these skin findings alone do not require recompression therapy.

When a diver ascends from extreme depths with significant missed decompression, the practitioner may choose to use recompression tables that pressurize the diver to a "depth of relief," to use alternate gas mixtures (i.e., helium and oxygen), or to hold the diver for more than 24 hours at a single depth to stabilize the medical status (saturation treatment).[86] For surface-supplied air and scuba divers, the principal treatment gases are oxygen and air. For treatment depths greater than 60 fsw, enriched nitrogen-oxygen (nitrox) or helium-oxygen (heliox) may also be used to minimize unwanted effects of excess nitrogen exposure.

Repeated hyperbaric oxygen treatments can be given, although end points for repetitive therapy are not well defined. Treatments can be administered until complete resolution of symptoms, until no further change of symptoms is found or for a fixed number of exposures (e.g., five). Controlled trials to determine efficacy of repetitive treatments are not available. Treatment of AGE follows similar protocols. Recompression to 60 fsw and oxygen therapy are usually successful.[91] Recompression to 165 fsw depth equivalent (6 ATA) may be recommended if symptoms persist after recompression to 60 fsw.[90]

In selected cases of DCS when no hyperbaric chamber is readily accessible, the controversial practice of in-water recompression is sometimes used by specially trained teams. During in-water recompression, the diver descends to depths that are usually shallower than standard treatment tables and effectively begins decompression treatment immediately without delay encountered while transporting to a decompression chamber.[92] However, during in-water recompression, the diver is unable to receive supportive care and is subject to additional environmental risks. Central nervous system oxygen toxicity during in-water recompression can result in drowning.

Prehospital Care: Oxygen and Fluids. Early administration of 100% oxygen (10 L/min by non-rebreather face mask) on the surface and during transport is beneficial for treating both DCS and AGE.[93] Oxygen enhances the rate of absorption and resolution of inert gas bubbles and treats

hypoxemia if present. Intravenous fluid administration is also recommended as part of initial treatment. As discussed earlier, both DCS and AGE manifest with hemoconcentration caused by plasma leakage as a result of endothelial injury from gas bubbles. Measurement of hematocrit and urine output is useful to guide fluid replacement therapy. Central nervous system injury may be exacerbated by hyperglycemia, and glucose-containing intravenous solutions should be administered cautiously.

Several adjunctive medications have been proposed for the treatment of DCS and AGE, including heparin, aspirin, nonsteroidal anti-inflammatory drugs, corticosteroids, and lidocaine. However, experimental and clinical data do not support the use of these therapies. In the case of spinal cord DCS causing paralysis, subcutaneous low-molecular-weight heparin should be initiated to prevent thromboembolic disease.[94,95]

Arrangements for transfer to the nearest hyperbaric chamber must be initiated as soon as possible. The *Divers Alert Network* (DAN), a not-for-profit diving safety medical organization, offers medical assistance to the recreational, public safety, and scientific diving communities all over the world. DAN has a diving medicine physician available 24 hours a day, 7 days a week, who can help with the diagnosis and immediate care of an injured diver. DAN can provide the location of the nearest hyperbaric treatment facility and assist with arrangement of transport and treatment for all diving injuries. In the United States, the DAN hotline number is 919-684-9111.

INERT GAS NARCOSIS

Inert gas narcosis (e.g., "nitrogen narcosis"), another diving disorder related to dissolved inert gas, takes place after breathing air at depths greater than 100 fsw.[96] Symptoms include loss of fine motor control and high-order mental skills, inappropriate response to emotional stress, hostility, and unconsciousness. Symptoms increase with increasing depth greater than 100 fsw. At 300 to 400 fsw, unconsciousness may result from the anesthetic effect of nitrogen at this pressure. Fatigue, heavy work, and hypothermia can augment the narcosis effect of nitrogen, as can concurrent use of sedating medications (e.g., certain decongestants). Symptoms disappear immediately on ascending to a shallow depth. Often there is amnesia for the events.[96] Narcosis potential varies among the inert gases (see Table 107.1). Of note, the narcosis effect of nitrogen on human performance has been demonstrated even at sea level. If the nitrogen component of room air at sea level is replaced by helium, human performance measurably improves.[97] Stated differently, we are all partially sedated.

OTHER PHYSIOLOGIC AND PATHOPHYSIOLOGIC CONSIDERATIONS FOR DIVING

OXYGEN TOXICITY

Pulmonary oxygen toxicity is rare in diving but may be of some concern in prolonged hyperbaric oxygen treatments. This toxicity results from free radical–induced inflammation and cell death, manifest initially with symptoms of mild substernal pressure or pleuritic chest pain (i.e., tracheobronchitis), and it may be present after as little as 12 to 16 hours at 1 ATA, 8 to 14 hours at 1.5 ATA, or 3 to 6 hours at 2 ATA.[98,99] Pulmonary oxygen toxicity progresses with characteristic exudative and proliferative phases, similar to acute respiratory distress syndrome.

Oxygen toxicity in divers primarily affects the central nervous system.[100] Acute toxicity to the brain can develop when oxygen partial pressure exceeds 1.4 ATA (see Fig. 107.2). Higher partial pressures may be tolerated for brief periods especially while at rest. This is the case during hyperbaric therapy, which routinely reaches 2 to 3 ATA. A diver affected by central nervous system oxygen toxicity may experience auditory or visual hallucinations and commonly has a grand mal seizure. When a diver is underwater, a seizure can lead to drowning. For example, a 21% oxygen mixture will expose a diver to 1.4 ATA of oxygen at 187 fsw, and a 32% oxygen mixture ("enriched air nitrox") will expose a diver to 1.4 ATA of oxygen at 111 fsw. Divers have been known to develop seizures when using these breathing gases at greater depths. Hyperthyroidism, carbon dioxide retention, and exertion are among many factors that may increase the risk of oxygen toxicity.[101–103]

To avoid oxygen toxicity, recreational dive limits are set to avoid exposures to more than 1.4 ATA of oxygen (see Fig. 107.2). Commercial, scientific, or other specialized divers who exceed these limits must decrease the inspired oxygen concentration with increasing depth to keep the Po_2 lower than 1.4 ATA. For example, some scientific scuba divers routinely reach depths approaching 200 m and breathe trimix (helium, oxygen, and nitrogen). By lowering the oxygen concentration to approximately 7%, even at depths up to 200 m (20 ATA), the Po_2 remains less than 1.4 ATA.

THERMAL EXPOSURE

Most diving takes place in water colder than skin temperature, and the diver loses heat throughout the dive. Hypothermia happens rapidly in the absence of protective garments even in relatively warm water (e.g., 22–23°C). Cold stress evokes thermogenic responses, reflected by a rise in oxygen consumption to generate additional body heat and minimize core temperature change. Cold-water diving also leads to peripheral vasoconstriction; the magnitude of the vasoconstriction depends on the body core temperature, which, in turn, is affected by the amount of thermal protection and the water temperature. Heat loss is inhibited in divers doing moderate work in water warmer than 30°C and, in this situation, hyperthermia can develop.

Exertion at depth increases tissue temperature and increases gas solubility. During surfacing and decompression, the relative lack of exertion coupled with cold-water exposure causes decreased perfusion in the skin and extremities, as well as decreased gas solubility. The increased solubility at increased temperature followed by a decreased solubility at cooler temperatures can contribute to development of type I DCS; the nitrogen absorbed during a time of increased temperatures comes out of solution when the

HIGH-PRESSURE NERVOUS SYNDROME

Helium is used in diving as an alternative inert gas to replace nitrogen and avoid its narcosis effects at depth. However, at depths of more than 600 fsw (18 ATA), dissolved helium can also cause problems. At these depths, helium can cause a reversible state of excitation (i.e., high-pressure nervous syndrome) characterized by tremor, dizziness, and nausea, among other symptoms.[98]

temperature drops and is poorly eliminated in areas of low perfusion such as skin.

WATER IMMERSION

Intrathoracic blood volume increases with water immersion.[105] With the head above water, increased hydrostatic pressure during immersion decreases blood pooling in the peripheral veins, increases transdiaphragmatic pressure, and increases venous return.[100,106] The magnitude of the increase in intrathoracic blood volume during immersion with the head above water has been estimated to be 700 mL and may be augmented by colder water temperatures. In healthy divers, the central blood shifts result in increased cardiac output and an increase in venous return.[106] The increase in intrathoracic blood volume can cause diuresis resulting from release of natriuretic hormones and suppression of antidiuretic hormone. In patients with cardiac valvular disease, diastolic dysfunction, or systolic dysfunction, increased preload from immersion can result in volume overload. Water immersion has additional pulmonary physiologic considerations, including increased gas density and imposition of a restrictive deficit.

IMMERSION PULMONARY EDEMA

Diving can result in a condition known as immersion pulmonary edema. Immersion pulmonary edema has been reported in scuba divers at depth and surface swimmers undergoing heavy exertion, particularly military recruits and triathlon swimmers. Although the exact pathophysiology is uncertain, it is thought that increased pulmonary blood flow and vascular pressure can cause stress failure of the capillaries. A similar mechanism has been reported in race horses who develop extremely high pulmonary vascular pressures leading to stress failure at the capillary level.[107]

Immersion causes an increase in preload from central pooling of blood combined with increased sympathetic output leading to vasoconstriction and cold-induced vasoconstriction, all contributing to increased pulmonary vascular resistance, pulmonary capillary wedge pressure, systemic vascular resistance in the setting of increased venous return, and increased cardiac output. Symptoms include dyspnea, cough, tachypnea, frothy sputum, hemoptysis, and hypoxemia. In rare circumstances, immersion pulmonary edema can be fatal. Chest radiography typically shows evidence of pulmonary edema (i.e., Kerley B lines, cephalization of flow, air space consolidation) with a normal heart size. Conservative treatment is recommended because the symptoms usually resolve within 12 hours. Oxygen, β-adrenergic inhalers, and diuretics can be given, but the majority of patients will improve spontaneously.[108,109] Older patients with possible underlying cardiovascular disease should be evaluated for acute coronary syndrome.

Takotsubo cardiomyopathy has been reported in scuba divers who presented with pulmonary edema and transient myocardial systolic dysfunction. Gempp and colleagues[110] reported reversible myocardial dysfunction in 28% of 54 divers admitted for acute immersion pulmonary edema that was associated with age greater than 50 years, hypertension, and release of natriuretic peptides.[110–112]

MEDICAL CLEARANCE TO DIVE

GENERAL FITNESS FOR DIVING

Diving is a safe sport; however, certain physical conditions can lead to increased risk for injury while diving. Medical standards have been developed for the various diving communities (eTable 107.1). Recreational divers follow medical standards outlined in the Recreational SCUBA Training Council Medical Statement (http://wrstc.com/standards-downloads/). Medical standards for scientific divers fall under the auspices of the American Academy of Underwater Sciences (http://aaus.org/diving_standards). Commercial diving medical standards are governed by the Association of Diving Contractors International, Inc (http://adc-int.org).

Based on epidemiologic data of dive accidents and fatalities from DAN, many diving fatalities are associated with underlying cardiovascular disease. Disorders that limit cardiovascular or pulmonary function during exercise, physical deconditioning, metabolic disorders that limit exercise capacity, and certain physical disabilities can compromise diving safety (eTable 107.2). Contraindications to diving include (1) any condition that interferes with equalization of any air spaces within the body; (2) any condition that could lead to unconsciousness underwater; (3) any condition that impairs tissue diffusion of inert gas and increases the risk for DCS; (4) poor exercise tolerance; and (5) inability to tolerate the physiologic effects of diving (e.g., changes in preload, airway resistance, pulmonary arterial pressure, systemic vascular resistance, and myocardial metabolic demand).

PULMONARY DISORDERS

Primary Spontaneous Pneumothorax (see Chapter 110)

Primary spontaneous pneumothorax arises without trauma or an iatrogenic event and in patients with no apparent underlying lung disease. A history of primary spontaneous pneumothorax is widely considered a contraindication to diving because of the possibility that, with overinflation, lung defects may be susceptible to pulmonary barotrauma and AGE. Although risk declines over time or with pleurodesis, and has been associated with certain clinical and imaging findings, inadequate data exist to recommend a return to diving for most patients with a history of primary spontaneous pneumothorax.[113] A history of iatrogenic or traumatic pneumothorax is not a contraindication to diving. For individuals with a history of significant lung injury or surgery, in whom there is concern for air trapping, a high-resolution chest CT scan with inspiratory and expiratory views can confirm or rule out air trapping.

Asthma and COPD

Asthma has been a concern in diving because of possible bronchoconstriction, air trapping, and pulmonary overinflation during ascent. However, an increased risk for

ENERGY NEEDS

A scuba diver swimming underwater at a speed of 1.0 knot (about 100 feet/min or 1.15 miles/hr or 1.85 km/mile) consumes approximately 25 mL of oxygen/kg/min (eFig. 107.3).[90,104] A diver with a maximum oxygen consumption of 40 mL/kg/min would tolerate swimming at 1.3 knots for a few minutes but would become extremely tachypneic to compensate for lactate production. For this diver, a sustainable swimming speed, at 50% of maximum capacity, would be about 0.9 knots or 90 feet/min, whereas a diver with a maximum oxygen consumption of 25 mL/kg/min would be able to sustain a swimming speed of only approximately 0.55 knots or 55 feet/min. Safety considerations suggest that the sport diver should be able to tolerate a sustained workload of about 20 mL/kg/min (50% of maximum).[90,104] Poorly conditioned divers can experience severe dyspnea under even mildly stressful conditions that exceed their anaerobic threshold.

eTable 107.1 Criteria for Medical Clearance to Dive for Recreational, Scientific, and Commercial Diving

	Recreational Diving	Scientific Diving	Commercial Diving
Source	World Recreational Scuba Training Council (RSTC)	American Academy of Underwater Sciences (AAUS)	Association of Diving Contractors International (ADCI)
Provider	Evaluation performed by a physician	Evaluation performed by or under the direction of a licensed physician, preferably one trained in diving or undersea medicine	Evaluation performed by licensed physicians qualified to perform commercial diver medical examinations
Testing	■ Cardiac risk assessment if >40 yr old ■ Formalized stress testing encouraged if there is any doubt regarding physical performance capability ■ Further testing as indicated by history and examination	■ Urinalysis (all examinations) ■ Chest radiograph (first examination after age 40 yr) ■ ECG (all examinations after age 40 yr) ■ CAD risk assessment (history, blood pressure, hemoglobin A1c or fasting glucose, lipid profile) (all examinations after age 40 yr) ■ Exercise testing if indicated by history and CAD risk assessment	■ Urinalysis (annually) ■ CBC (annually) ■ CMP (optional) ■ Pregnancy test ■ Sickle cell test (optional) ■ TB screening (optional) ■ ECG stress testing if >10% Framingham risk score ■ PFTs (FEV_1, FVC, $FEF_{25\%–75\%}$ annually) ■ ECG (annually after age 35 yr) ■ Lipids (annually after age 35 yr) ■ Audiogram (annually) ■ Bone and joint radiographs (initial examination) ■ Chest radiograph (PA and lateral) (every 3 years) ■ Drug screen recommended ■ Visual acuity and field of vision testing
History and physical examination*	History and physical with RSTC Medical Statement Form, which includes structured questionnaire and guidelines for history and physical examination	■ History and physical with Diving Medical History, Evaluation and Examination forms, which include a structured questionnaire and guidelines for history and physical examination ■ <40 yr old: medical evaluation every 5 yr ■ 40–60 yr old: medical evaluation every 3 yr ■ >60 yr old: medical evaluation every 2 yr	■ History and examination forms provided ■ Request past medical records if available for chest radiograph, long bone radiograph, MRI, spine radiograph, PFTs, audiogram, ECG, stress testing ■ Annual examinations required

*Clearance to return to dive must be obtained for previously cleared divers who have subsequently experienced major injury or illness, conditions requiring chronic medication, or conditions that may be contraindications to diving.

CAD, coronary artery disease; CBC, complete blood count; CMP, comprehensive metabolic panel; ECG, electrocardiogram; $FEF_{25\%–75\%}$, mean forced expiratory flow between 25% and 75% of the forced vital capacity; FEV_1, forced expiratory volume in 1 second; FVC, forced vital capacity; MRI, magnetic resonance imaging; PA, posteroanterior; PFT, pulmonary function test; TB, tuberculosis.

eTable 107.2 Considerations for Medical Clearance for Recreational Diving

System	Severe Risk Conditions*	Relative Risk Conditions*	Temporary Risk Conditions*
Neurologic	■ Seizures (other than childhood febrile) ■ History of transient ischemic attack or cerebrovascular accident ■ History of serious decompression sickness with residual deficits (central nervous system or inner ear)	■ Complicated migraines ■ Head injury with sequelae ■ Herniated disc ■ Peripheral neuropathy ■ Multiple sclerosis ■ Spinal cord injury ■ Intracranial tumor or aneurysm	■ History of cerebral arterial gas embolism without residual pulmonary air trapping and low probability of recurrence (e.g., provoking event)
Cardiovascular	■ Intracardiac right-to-left shunt ■ Hypertrophic cardiomyopathy ■ Valvular stenosis ■ Heart failure ■ Impaired exercise tolerance resulting from cardiac disease	■ History of coronary artery bypass grafting ■ Coronary artery disease ■ History of myocardial infarction ■ Hypertension ■ History of dysrhythmias requiring ongoing treatment ■ Valvular regurgitation	■ Condition requiring a pacemaker (pacemaker must be certified by manufacturer to withstand increased pressure at depth)
Pulmonary	■ History of spontaneous pneumothorax ■ Intrapulmonary right-to-left shunt ■ Impaired exercise tolerance resulting from pulmonary disease	■ Asthma ■ COPD ■ Exercise-induced bronchospasm ■ Solid, cystic, or cavitary pulmonary lesions ■ Pneumothorax resulting from surgery, trauma, or overinflation injury ■ Obesity ■ History of immersion pulmonary edema ■ Interstitial lung disease	—
Gastrointestinal	■ Gastric outlet obstruction or gastroparesis causing recurrent vomiting ■ Recurrent or chronic small bowel obstruction ■ Severe gastroesophageal reflux ■ Achalasia ■ Paraesophageal hernia	■ Inflammatory bowel disease ■ Functional bowel disorders	■ Peptic ulcer disease with severe reflux ■ Unrepaired abdominal hernias
Metabolic and endocrine	■ Pregnancy	■ Diabetes mellitus	—
Otolaryngologic	■ Open tympanic membrane ■ Tube myringotomy ■ Middle or inner ear surgery ■ Tracheostomy ■ History of vestibular decompression sickness	■ Recurrent otitis externa, otitis media or sinusitis ■ Obstruction of external auditory canal ■ History of tympanic membrane perforation or round window rupture ■ History of tympanoplasty, mastoidectomy, neck radiation, or mid-face fracture ■ History of eustachian tube dysfunction ■ Significant hearing loss	■ Acute upper respiratory infection ■ Acute sinusitis ■ Acute otitis media ■ Recent or unhealed oral surgery
Orthopedic	—	■ Amputation ■ Scoliosis with impact on respiratory or exercise performance ■ Aseptic osteonecrosis	■ Back pain
Hematologic	—	■ Polycythemia vera ■ Hematologic malignancies ■ Coagulopathy ■ Sickle cell disease	—
Behavioral health	■ Inappropriate motivation to dive ■ Claustrophobia ■ Active psychosis ■ Untreated panic disorder	■ Use of psychotropic medications ■ History of psychotic episodes	—

*Severe risk conditions are generally considered contraindications to diving and imply a substantially elevated risk of decompression sickness, pulmonary or otic barotrauma, or altered consciousness with subsequent drowning. Relative risk conditions may be relative contraindications and imply a moderate increase in risk that requires individual consideration for fitness to dive. Temporary risk conditions are temporary or responsive to treatment, although they may be contraindications to diving and require careful consideration.

Data from the Recreational Scuba Training Council (RSTC) Medical Statement; wrstc.com/standards-downloads/ and Van Hoesen KB, Lang MA. Diving medicine. In: Auerbach PS, ed. *Auerbach's Wilderness Medicine*. 7th ed. Philadelphia: Elsevier; 2017.

pulmonary barotrauma has not been supported by accident data.[114] Although scuba diving can decrease peak expiratory flow rates, individuals with well-controlled asthma, known triggers that do not include cold or exercise, and normal pulmonary function test results with a reduction of less than 20% in peak midexpiratory flow with exercise can be cleared for diving.[115] The use of provocative inhalational challenges (e.g., hypertonic saline, cold dehumidified air, or methacholine) has been variably implemented, with no data to guide use. A current asthma exacerbation is a contraindication to diving. A more detailed discussion of issues related to asthma and diving has been published.[116]

Because patients with COPD by definition are unlikely to meet the functional or pulmonary function criteria discussed earlier, these patients generally should not be cleared for diving.

Bullous Lung Disease

Patients with COPD or risk factors for COPD have the additional potential for bullae. Individuals with known pulmonary cysts, blebs, or significant obstructive lung disease are not allowed to dive because of the potential for air trapping and subsequent pulmonary barotrauma.

CARDIAC DISORDERS

Coronary Artery Disease

Patients with coronary disease may experience angina pectoris, myocardial infarction, or sudden death while diving. The highest incidence of diving-related death from cardiovascular disease in divers is in the age range from 50 to 70 years.[117] In recreational divers, cardiac events are associated with approximately one-fourth of diving fatalities.[118] In the DAN Annual Diving Reports on Fatalities, Injuries, and Incidents, the data suggested that acute cardiac events are a leading cause of disabling injury.[119] More than one-half of the recreational diving fatalities were in divers older than 50 years, and heart disease, high blood pressure, and obesity were among the most common preexisting health conditions.[120] Diving candidates should be screened for cardiovascular risk factors (smoking history, hypertension, obesity) and undergo lipid profile, electrocardiogram, and exercise stress testing as indicated.

Atrial Septal Defect

Diving candidates with atrial septal defects that allow right-to-left intracardiac shunting are at risk for paradoxical embolism of gas bubbles that form in the venous circulation during decompression.[87,121] Patients with a right-to-left shunt and arterial hypoxemia will normally have severely limited exercise capacity and should not dive. Because of the lack of right-to-left shunting, a ventricular septal defect does not necessarily produce a risk for paradoxical embolization of bubbles. A detailed discussion of this topic can be found elsewhere.[122]

Patent Foramen Ovale

PFO is an active area of discussion in the diving medical community because of the potential for right-to-left shunting of bubbles. Community-based autopsy and transesophageal studies have revealed the prevalence of PFO at approximately 25%.[123,124] In a prospective community-based study of 588 randomly selected subjects, transesophageal echocardiography revealed PFO in 148 subjects (26%); of these, 84 had shunting at rest (57%), and 136 had shunting after Valsalva maneuver or cough (92%).[124] In a contrast echocardiographic study of 76 healthy volunteers, PFO was present in 14 (18%), and 4 (5%) subjects had shunting at rest.[125] In 30 divers with a history of DCS, Moon and colleagues[121] reported a higher prevalence of PFO (37%). Eighteen patients in this cohort had a history of serious DCS, and 11 (61%) of this subgroup had shunting through a PFO. Several studies suggest that presence of a PFO can increase the risk of serious DCS.[62,126–130]

However, the high prevalence of PFO in the population and the very low incidence of DCS suggest that a PFO likely plays only a minor role in the pathophysiology of DCS. DAN and the Undersea and Hyperbaric Medical Society held a consensus guideline workshop on PFO and diving.[131] Routine echocardiographic screening for a PFO is not indicated, and there is no routine need to close a PFO as a prophylactic measure.[129,132] Consideration should be given to testing for a PFO in a diver when there is a history of repeated episodes of neurologic, vestibulocochlear, or cutaneous DCS.

If a diver is known to have a PFO, closure of the PFO is controversial. Current data suggest that closure of a PFO does reduce the risk of neurologic DCS. Henzel and colleagues[133] followed 11 professional divers with PFOs who reported a total of 62 episodes of DCS before closure of their PFOs. All divers returned to unrestricted diving and made more than 3000 dives collectively; no episodes of decompression illness were reported after the intervention, and no diver reported complications from the procedure. Similarly, in a 2019 study by Anderson and colleagues,[63] 42 individuals underwent closure of their PFO or atrial septal defect and reported a significant decrease in DCS incidence rate compared with 23 individuals who continued diving without closure of the defect. Eight subjects reported an adverse event associated with defect closure.[63]

Dysrhythmias

Reflex bradycardia from diving has been described by several investigators and may be related to the mammalian diving reflex.[134,135] The autonomic adjustments to apneic diving in marine mammals appear to be an oxygen-conserving reflex, but this effect does not appear to be significant in humans. Drowning has been associated with the familial-inherited long QT syndrome in swimmers, and the same risk is likely to apply to divers. Individuals with benign dysrhythmias that do not interfere with exercise tolerance or with well-controlled atrial fibrillation can be cleared for diving.[136]

NEUROLOGIC DISORDERS

Seizure disorders are a contraindication to diving because a diver sustaining a seizure underwater is at risk for drowning and may compromise the safety of others who attempt a rescue. A diving candidate with a history of a seizure disorder should be seizure-free without antiseizure medications for 5 years and have a normal electroencephalogram before being considered for diving.[137] Many factors encountered in diving may lower the seizure threshold (e.g., exercise,

hypercapnia, hyperventilation, stress), whereas an elevated Po_2 theoretically may increase the risk of seizures in an individual with epilepsy.[138] History of unexplained syncope is also a contraindication to diving.

DIABETES

Insulin-dependent diabetes mellitus had traditionally been a contraindication for diving because of the risk of hypoglycemia, leading to unconsciousness and death underwater from drowning. However, guidelines developed through the YMCA and American Diabetes Association now exist for such patients to dive safely. Special training allows for safe diving for insulin-dependent sport divers.[83,139] Consensus guidelines for diving with diabetes are published by DAN and the Undersea and Hyperbaric Medical Society.[140]

DROWNING

For a detailed discussion of drowning, see ExpertConsult.com.

Key Points

- Middle ear barotrauma is the most prevalent diving injury, whereas pulmonary barotrauma, although uncommon, is the most severe form of barotrauma injury because of the risk of accompanying cerebral arterial gas embolism.
- Decompression sickness results when inert gas dissolved in the body at increased pressure forms free gas in blood and tissues on decompression.
- Clinical manifestations of acute decompression sickness include disorders of the brain and spinal cord, musculoskeletal pain, chest pain, dyspnea, and skin rash seen up to 24 hours following an exposure to increased pressure.
- Treatment of decompression sickness and arterial gas embolism should be instituted with recompression in a hyperbaric chamber as soon as possible after the injury. Assistance can be sought at all hours by calling the Divers Alert Network (919-684-9111).
- Assessment of fitness for diving includes consideration of the type of diving (recreational, scientific, commercial, or military) and of the number of comorbidities that can be aggravated by the diving environment. A history of primary spontaneous pneumothorax or the presence of an atrial septal defect is considered a contraindication to diving, although patent foramen ovale is not necessarily a contraindication. Obstructive pulmonary diseases require special consideration.
- Although drowning without aspiration is theoretically possible, most drownings are associated with aspiration of water into the lungs and accompanying hypoxemia.
- Goals of therapy for a drowning victim include reversing hypoxemia with positive-pressure ventilation and oxygen, treating metabolic acidosis, and managing accompanying cardiac arrhythmias.

Key Readings

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Complete reference list available at ExpertConsult.com.

DROWNING

Drowning is reported by medical examiners as the leading cause of death in the approximately 50 to 60 scuba fatalities in the United States each year; however, sudden cardiac death or AGE may be the precipitating factor or even the cause of death in many of these accidents.[119,141,142] Drowning (from all causes, not just diving) causes nearly 400,000 deaths per year and is the third leading cause of unintentional injury or death.[143]

Historically, the terms *drowning* and *near drowning* have been used to describe victims who either died or survived, respectively. The World Health Organization now defines drowning as "the process of experiencing respiratory impairment due submersion or immersion in liquid" with possible outcomes of death, morbidity, or no morbidity. It is simpler and preferable to use the term *drowning* for all individuals who experience submersion incidents.[141]

Among drowning victims from all circumstances, (i.e., not only diving), a significant proportion may survive with organ dysfunction, including persistent hypoxemic respiratory failure and neurologic injury. Intentional hyperventilation before breath-hold diving is associated with drowning episodes. Hyperventilation reduces the arterial partial pressure of carbon dioxide (P_{CO_2}), so the breath-hold breakpoint is prolonged sufficiently for hypoxemia to develop before the individual is forced to breathe. The hypoxemia in turn causes the individual to lose consciousness and then drown.[144] This is the hypothesized pathophysiology for what has been termed "shallow water blackout." Atrial and ventricular arrhythmias are known to happen during prolonged breath-holding experiments, but whether these arrhythmias play an important role in drowning incidents needs further study.[145.]

Hypothermia leading to drowning has been reported frequently; however, in diving fatalities this is unusual because of the almost universal use of thermal protection by divers. Hypothermia reduces a person's ability to function until the point of unconsciousness or helplessness is reached.[146] At that time, for someone at the surface, the head falls into the water, and drowning results. Maximum breath-hold times can drop dramatically in cold water, thus further compromising the ability to survive in rough water when intermittently submerged. In rare circumstances, hypothermia can have a protective effect on the drowning victim (see later). Hypothermia is only one of many conditions that can precipitate drowning by causing unconsciousness. As previously discussed, loss of consciousness caused by contamination of the diver's air supply with carbon monoxide and oxygen-induced seizures have been implicated as the cause of drowning in many diving-related incidents.

PATHOPHYSIOLOGY

Investigators have reported that 2–15% of drowning victims may not aspirate fluid during immersion.[147,148] It has been hypothesized that reflex laryngospasm that persists until reflex ventilatory activity ceases may account for this finding. However, review of early "dry" animal studies does not support the dry drowning hypothesis for fatal cases.[149] It is much more likely that these cases actually represent arrhythmic deaths, and the true number of drowning victims without aspiration is extremely low.

Unlike victims without aspiration, those who aspirate remain hypoxemic, even after being removed from the fluid medium and after ventilation is reestablished. As a result, the prolonged period of hypoxemia may cause secondary damage to other organ systems.[150,151]

There are many potential mechanisms contributing to oxygenation and ventilation defects after aspiration during drowning, including direct alveolar membrane injury by the aspirated fluid, altered ventilation-perfusion matching, increased airway resistance, washout of surfactant, volume overload, aspiration of particulate (e.g., vomit, mud, sand, algae), neurogenic pulmonary edema, and organization of proteinaceous exudate or secondary infection during recovery.[152,153]

Historically, the literature has emphasized a distinction between freshwater and saltwater aspiration, although more recently it is less clear that this difference has significant clinical relevance.[154] Aspiration of hyperosmolar fluid (i.e., saltwater) can cause transudation of fluid into alveoli, increased lung weight, increased serum osmolality, and hypovolemia.[155,156] Although this pathophysiology has been demonstrated in numerous animal studies and in exceptional circumstances in humans (e.g., aspiration of markedly hypertonic solution in the Dead Sea), it is uncommonly observed in drowning victims, especially those who survive.[151,156–158] Aspiration of fresh water can have the opposite effect, leading to intravascular volume overload and hypotonic serum. This requires aspiration of more than 11 mL/kg and is usually rapidly redistributed.[159–161] Human drowning victims rarely aspirate large enough volumes of water to produce life-threatening changes in intravascular volume or electrolytes.[158]

Aspiration of water (fresh water or seawater) during drowning causes washout of surfactant and often leads to noncardiogenic pulmonary edema as well as acute respiratory distress syndrome.[150] These abnormalities can persist until the lung damage resolves or until surfactant is regenerated.

In victims who swallow large amounts of fluid during the drowning episode, further impairment in ventilatory function can result from gastric distention. Profound acidemia may be present in response to concurrent hypercarbic respiratory failure and lactic acidosis caused by struggling during the drowning episode. Finally, if hypoxemia and decreased cardiac output persist long enough, there can be anoxic brain injury and cardiac arrest.[162,163]

Because cardiac arrest from downing is secondary to hypoxemia, it may be delayed by a significant amount of time. If the water is cold enough, if the surface area/mass ratio of the victim is large enough, and if the victim swallows enough water, then core temperature may decrease significantly. At low core temperatures. oxygen demand may be low enough that victims can occasionally survive even prolonged submersion.[164]

Postmortem evaluations of humans and animals after death by drowning reveal hyperexpansion of the lungs that can resemble acute emphysema. This finding may be attributable to rupture of alveoli secondary to marked changes in airway pressure during extreme ventilatory efforts in

the setting of a closed glottis or airway obstruction from water.[165,166]

CLINICAL PRESENTATION

The clinical presentation of drowning victims is highly variable. The patient who is unconscious and reported to be without vital signs at the site of the accident may be hemodynamically stable and neurologically intact in the emergency department, whereas the victim initially thought to be hemodynamically stable at the scene may deteriorate significantly before arrival at the hospital.

Cardiovascular System

Given the hypoxia associated with drowning, victims typically experience sinus tachycardia from the initial struggle, followed by bradycardia, pulseless electrical activity, and then asystole. Ventricular fibrillation is rare in near drowning victims.[167] Victims of significant drowning may suffer cardiac arrest and respond to on-scene resuscitative measures. Whether this represents premature cardiopulmonary resuscitation or a response to therapy is not certain. However, it is also not uncommon for a victim to be brought to the emergency department still requiring cardiopulmonary resuscitation. If the patient "responds" to cardiopulmonary resuscitation at the scene of the rescue with a stable rhythm or if the patient never has a cardiac arrest, supraventricular tachycardias are commonly seen. If the patient presents with a viable rhythm, it will most likely be supraventricular tachycardia secondary to hypoxemia and acidosis.[168] Patients with underlying cardiac disease may have primary cardiac arrest that may mimic a drowning episode.[142] The spectrum and frequency of cardiac channel defects such as prolonged QT syndrome in swimming-triggered arrhythmia events may be greater than previously suspected.[168,169] Pathologic diagnoses may be further complicated by terminal aspiration secondary to agonal breathing after cardiac arrest, and thus postmortem analyses that depend on the presence of aspiration may be misleading.[170,171]

Pulmonary System

Patients with water aspiration may present with few or no respiratory complaints or with severe pulmonary edema caused by direct lung injury.[172] Patients who have aspirated any significant quantity of water will likely have a widened alveolar-arterial P_{O_2} difference and anything from mild to severe hypoxemia. Arterial P_{CO_2} can be low or elevated depending on alveolar ventilation (eTable 107.3).

eTable 107.3 Average Blood Gas Measurements in Hospitalized Drowning Victims Breathing Room Air on Admission

	pH	$Paco_2$ (mm Hg)	Pao_2 (mm Hg)	Base Excess (mEq)
Fresh water	7.26	38	66	−9
Seawater	7.37	36	56	−5
All	7.30	37	62	−7

$Paco_2$, arterial partial pressure of carbon dioxide.
Modified from Modell JH, Davis JH, Giammona ST, et al. Blood gas and electrolyte changes in human near-drowning victims. *JAMA*. 1968;203:337–343.

Initial chest radiographs are often normal but can show patchy opacities, which are most common in the periphery or in the medial basal regions, or frank (noncardiac) pulmonary edema (see Fig. 107.3).[173] The clinical course cannot be predicted with certainty by the radiographic picture of lung injury. Victims with obvious respiratory symptoms may show minimal radiographic abnormalities, and those with minimal clinical signs may have markedly abnormal radiographic images.

Central Nervous System

The neurologic status of patients can also be quite variable. The central nervous system is extremely sensitive to hypoxemia and is the organ system most susceptible to the detrimental effects of drowning. Severe permanent neurologic injury is the most devastating long-term consequence for the victim of a drowning episode. Although a normal head CT scan on admission is of limited prognostic value, an initial abnormal CT scan that shows evidence of edema, focal infarct, or loss of gray and white matter differentiation is predictive of a poor outcome. The most important predictor of outcome is duration of submersion; in general, submersion times longer than 30 minutes suggest a poor prognosis. However, there are cases of good neurologic outcome despite prolonged submersions, especially in children younger than 6 years who drown in water temperatures less than 6°C (43°F), and with the use of advanced therapies such as extracorporeal membrane oxygenation.[174]

TREATMENT

Because cardiac arrest caused by drowning results from hypoxemia and acidosis, it is critically important to restore circulation, establish a patent airway, and provide oxygen rapidly. With a suspected drowning victim, the rescuer should provide cardiopulmonary resuscitation with rescue breathing in accordance with basic life support guidelines.[175–179] Establishing an airway and providing oxygen are priorities in the initial resuscitation. Rescue breathing may even be initiated during extraction from the water. Use of a subdiaphragmatic thrust (Heimlich maneuver) is no longer recommended because most water expelled by this technique originates from the stomach rather than the lungs and increases the risk of aspiration.[180,181] Endotracheal intubation is the preferred method for establishing an airway. This approach must account for the possibility of a concomitant unstable neck injury if there is associated trauma, as well as the risk for aspiration of gastric contents.[182] However, without a focal neurologic deficit or significant mechanism of cervical spine injury (e.g., diving into shallow water), the risk for an unstable cervical spine injury is low, and spinal immobilization should not take priority over resuscitation.[183]

A nasogastric tube should be inserted to decompress the stomach, and core body temperature readings should be obtained to diagnose and manage potential hypothermia. In the presence of a significantly lowered body temperature, rewarming measures should be instituted, although the rate of rewarming and temperature goals for drowning victims after cardiac arrest remain areas of active research. Although mild therapeutic hypothermia has been shown to decrease cerebral oxygen use and improve neurologic

outcomes in patients with return of spontaneous circulation after witnessed ventricular fibrillation arrest, there are no prospective studies comparing therapeutic hypothermia with normothermia after return of spontaneous circulation in drowning victims. There are several case reports of complete neurologic recovery after therapeutic hypothermia in drowning victims. Return of spontaneous circulation and hemodynamic stability take precedent over the decision to induce hypothermia.[174,184,185]

Occasionally, drowning patients will have marked hemodynamic instability, and resuscitation must be managed accordingly while accounting for the likelihood of concurrent pulmonary edema and acute respiratory distress syndrome. Positive end-expiratory pressure is extremely effective in reversing abnormal ventilation-perfusion matching leading to hypoxemia. Usually, pulmonary injury from drowning improves significantly over a period of 48 to 72 hours, and ventilatory support in most circumstances is relatively brief, unless infection develops. Consequently, if tolerated, noninvasive positive airway pressure ventilation strategies or a high-flow nasal cannula may be reasonable for short-term support. Oxygenation, ventilation, hemodynamics, and glycemic control should be managed in accordance with current critical care guidelines, including those for management of cerebral edema and post–cardiac arrest critical care, if applicable.

The use of antibiotics in drowning victims should be reserved for those who demonstrate signs of infection. Because most pulmonary infections in the near drowning victim appear to be hospital acquired, prophylactic antibiotics may serve only to select for more resistant organisms. If pneumonia is present, antibiotic therapy should be guided by microbiologic data, antibiograms, and standard protocols. If the victim aspirates heavily contaminated water with a known or suspected organism (as in the case of aspiration in a hot tub), the use of prophylactic antibiotics may be appropriate. Although bronchoscopy for the routine management of the drowning victim is not warranted, consideration of this procedure should be made when unexpected difficulties with mechanical ventilation arise, to evaluate for rare complications of drowning such as the aspiration of sand or gravel.[186]

Routine use of corticosteroids to treat the lung injury associated with drowning is unwarranted. Experimental evidence strongly suggests that steroids do not improve the short-term or long-term outcome.[187] Artificial and animal-derived surfactants, extracorporeal membrane oxygenation, cardiopulmonary bypass, and hypothermia have also been used to treat the pulmonary injury associated with drowning.[188–191] Any victim with more than minimal respiratory symptoms, an abnormal chest radiograph, or abnormal arterial blood gas measurements should be observed because pulmonary damage may not be clinically manifest for several hours after the incident.[192] Nearly all patients who will demonstrate significant problems of gas exchange will do so by 4 to 8 hours after the incident; therefore, consideration for discharge from the emergency department may be appropriate in people who can be observed in this fashion.[193] In a pediatric study, normal oxygen saturation and lack of field intervention after pediatric drowning were independent predictors of safe discharge from the emergency department.[194]

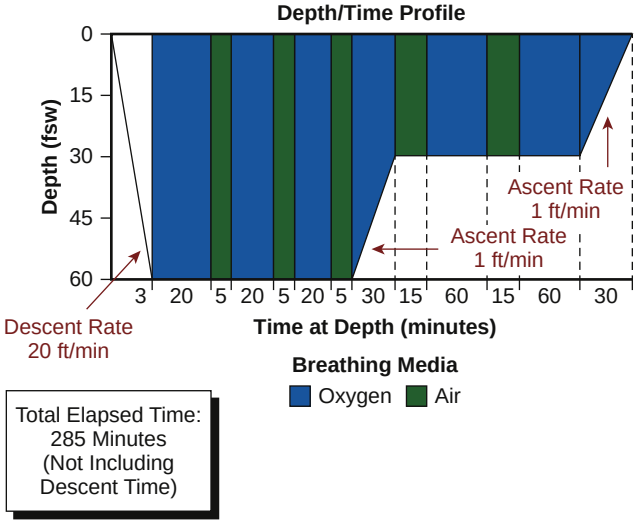
PROGNOSIS

The prognosis of the drowning victim depends mainly on the duration of immersion, the length of the anoxic period, and the degree of damage secondary to the anoxic episode. Restoration of normal neurologic function, although unusual, has been described even after prolonged drowning-induced cardiac arrest.[195] An apparent (i.e., undocumented) cardiac arrest does not in itself suggest a poor outcome; however, cardiac arrest that persists through the period of initial first aid and transport to the hospital is a poor prognostic sign. The presence of spontaneous respirations on presentation to the emergency department following cardiac arrest in the field is a good prognostic sign.[196] The duration of immersion correlates with the degree of damage secondary to the anoxic episode and therefore with the outcome. No prognostic test has shown to provide a reliable basis for treatment decisions, and predictions concerning outcome cannot be made in the presence of severe hypothermia, as discussed earlier. Multiple reports have described survivors of cold-water drownings after more than 20 minutes of submersion.[197,198] Notably, certain cold-water aquatic species such as the crucian carp can survive weeks or even months of anoxia (with concurrent hypothermia) and may hold the answers for many ongoing research efforts to improve human capacity to survive hypoxic and ischemic insults.[199]

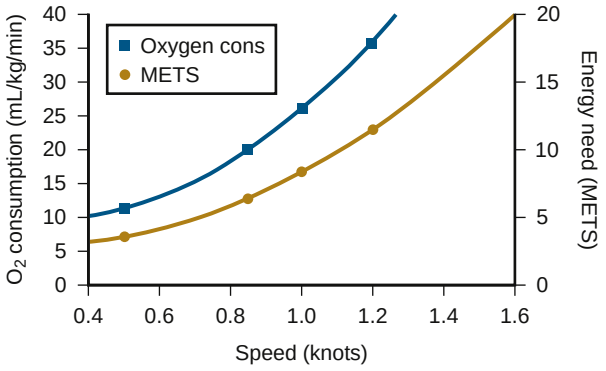
eFIGURE IMAGE GALLERY



eFigure 107.1 Closed-circuit rebreather apparatus. Scientific diver using a closed-circuit rebreather apparatus at 125 m with counter-lungs (a part of the loop that changes in volume to accommodate the diver's tidal volume) and multiple compressed gas tanks, including helium and 7% fraction of inspired oxygen mix. (Courtesy Luiz Rocha; copyright 2018 California Academy of Sciences.)



eFigure 107.2 U.S. Navy Diving Manual Decompression Treatment Table. This diagram illustrates the standard of care for hyperbaric chamber treatment for most cases of decompression illness. Patients are compressed to the pressure equivalent of a depth of 60 fsw with alternating periods of 100% and 21% oxygen provided. The periods of 100% oxygen facilitate nitrogen elimination, whereas the periods of 21% oxygen "air breaks" help minimize potential oxygen toxicity. (From U.S. Department of the Navy. *U.S. Navy Diving Manual, vol 5, rev 7: Diving Medicine and Recompression Chamber Operations.* Publication no. SS521-AG-PRO-010; 0910-LP-115-1921. Washington, DC: U.S. Department of the Navy; 2016.)



eFigure 107.3 Oxygen consumption and metabolic equivalents (METS) shown for underwater swimming. The speed is shown in knots; 1 knot is 1 nautical mile per hour; 1 knot = 100 feet per minute = 1.15 miles per hour = 1.85 kilometers per hour. (Data from U.S. Department of the Navy. *U.S. Navy Diving Manual, vol 1, rev 3: Air Diving.* Publication no. NAVSEA 0994-LP-001–9110. Washington, DC: U.S. Department of the Navy; 1996.)

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SECTION **M**

DISORDERS OF THE PLEURA

108 *PLEURAL EFFUSION*

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INTRODUCTION

The pleural space is bounded by two membranes: the visceral pleura covering the lung and the parietal pleura covering the chest wall and diaphragm. Into this space, normal liquid and protein enter from the systemic circulation and are removed by the parietal pleural lymphatics. Pleural pressure is subatmospheric and ensures inflation of the lung. Because the mesothelial boundaries are leaky, excess liquid can move across into this lower pressure, high capacitance space and accumulate as a pleural effusion. Thus, pleural effusions are common and of highly diverse etiologies. These effusions can form based on disease of the pleural membranes themselves or of thoracic or abdominal organs. Depending on the protein and *lactate dehydrogenase* (LDH) concentrations of the liquid, these effusions can be categorized as exudates or transudates.

Other chapters cover the anatomy of the pleural membranes (see Chapter 1), the physiology of the pleural space (see Chapter 14), and the pleural diseases related to pleural infections (see Chapters 109) and pleural malignancy (Chapter 114). In addition, pneumothorax, chylothorax, pleural fibrosis, and hemothorax are covered individually in Chapters 110 to 113, respectively. This chapter covers effusions in general, with attention to transudates and exudative effusions caused by nonmalignant and noninfectious causes.

APPROACH TO PATIENTS WITH PLEURAL EFFUSION

Three common symptoms are associated with pleural effusion: dyspnea, cough, and chest pain. Dyspnea appears to be caused by mechanical effects, either due to the expansion of the chest wall and muscles of breathing and/or due to the inversion of the diaphragm.[1–4] Dyspnea due to an effusion can be quickly relieved by removal of the fluid, indicating

the return of improved mechanics. One consequence of this is that even a patient with a trapped lung that cannot reinflate can have improvement of dyspnea if removal of the fluid restores the chest wall and diaphragm to a more normal position. In a recent prospective trial, 73% of patients experienced an improvement in dyspnea with thoracentesis (median volume, 1.7 L); the improvement was greatest in those with baseline abnormal diaphragm movement. Of interest, the improvement in dyspnea was seen in those with or without trapped lung.[5] Cough is another symptom of large effusions and may be due to the distortion of the lung with volume loss. Pleuritic chest pain can be seen due to inflammation, infection, or malignant involvement of the pleura. Pain fibers are most likely those of the parietal pleura, but there are also pain fibers now recognized in the visceral pleura and in adhesions.[6]

Physical findings of a pleural effusion include dullness to percussion, decreased breath sounds, egophony at the upper level of the effusion, and decreased tactile fremitus. With large effusions, signs can include asymmetrical chest expansion or even bulging of the intercostal spaces. A systematic review concluded that the most useful physical findings were dullness to percussion and decreased tactile fremitus[7] (see Chapter 18).

The possibility of a pleural effusion should be considered in any patient with an abnormal chest radiograph. Increased opacity on chest radiography is frequently attributed to a parenchymal abnormality when it actually represents pleural fluid. Free pleural fluid gravitates to the most dependent part of the thoracic cavity, which, in an upright patient, is the posterior costophrenic sulcus. Therefore, if the posterior costophrenic angle is blunted or if the posterior part of the diaphragm is not visible on the lateral chest radiograph, an ultrasonic examination of the pleural space can be obtained to ascertain whether free pleural fluid is present (see Videos 23.10 and 23.11). If the effusion is small and difficult to obtain by thoracentesis, the pleural effusion is not likely to be clinically significant. If the effusion is larger and accessible by thoracentesis, an effort should be made to determine its cause. Various studies have shown that ultrasonic determination of the separation of the visceral from the parietal pleura correlates with pleural effusion volume. In one study, sonographic measurements were more accurate than lateral decubitus radiographic measurements for pleural fluid volume.[7a] In another study, the maximal distance separating the visceral and parietal pleura determined on a transverse section could be related roughly to the volume of pleural fluid removed by multiplying the distance (in mm) by 20. By this method, a maximal distance of 20 mm would allow the pleural volume to be estimated as 400 mL. In this study, a maximal distance less than 10 mm was considered too small to allow thoracentesis.[7b]

DIFFERENTIAL DIAGNOSIS OF PLEURAL EFFUSION

Many different diseases may have an accompanying pleural effusion (Table 108.1). The vigor with which various diagnoses are pursued should depend on the likelihood that the person has that particular disease. In several studies of pleural fluid etiology, *congestive heart failure* (CHF) and cirrhosis are responsible for almost all transudative pleural effusions.[8,9] Pneumonia, malignant pleural disease, *pulmonary embolism* (PE), and gastrointestinal disease account for at least 90% of all exudative pleural effusions (eTable 108.1).[9] Pleural effusions often have more than one cause; in one study, as many as 30% of patients could be shown to have more than one cause, with CHF as the most common contributing cause.[10] As proposed in Chapter 14, one disease may

Table 108.1 Differential Diagnoses of Pleural Effusions

TRANSUDATIVE PLEURAL EFFUSIONS

Congestive heart failure
Hepatic hydrothorax
Nephrotic syndrome
Peritoneal dialysis
Myxedema
Pericardial disease
Central venous occlusion
Pulmonary veno-occlusive disease

VERY LOW PROTEIN TRANSUDATES

Urinothorax
Subarachnoid-pleural fistula
Iatrogenic

EXUDATIVE PLEURAL EFFUSIONS

Neoplastic diseases (see Chapter 114)
- Metastatic disease
- Mesothelioma
- Primary effusion lymphoma
- Pyothorax-associated lymphoma

Infectious diseases (see Chapter 109)
- Pyogenic bacterial infections
- Tuberculosis
- Actinomycosis and nocardiosis
- Fungal infections
- Viral infections
- Parasitic infections

Pulmonary embolism

Abdominal diseases
- Esophageal perforation
- Pancreatic disease
- Intra-abdominal abscesses
- Postabdominal surgery
- Liver transplantation
- Bilious pleural effusion

Inflammatory diseases
- Rheumatoid pleuritis
- Lupus pleuritis
- Immunoglobulin G4–related disease
- Sarcoidosis
- Asbestos-related disease
- Uremia
- Post–cardiac injury syndrome
- Post–coronary artery bypass surgery
- Drug-induced pleural disease (see Chapter 99)
- Eosinophilic granulomatosis with polyangiitis
- Granulomatosis with polyangiitis
- Sjögren syndrome
- Acute eosinophilic pneumonia

Miscellaneous
- Lung transplantation
- Meigs syndrome
- Endometriosis
- Ovarian hyperstimulation syndrome
- Trapped lung (see Chapter 112)
- Yellow nail syndrome
- Misplaced catheters

Hemothorax (see Chapter 113)
Chylothorax (see Chapter 111)

eTable 108.1 Approximate Annual Incidence of Various Types of Pleural Effusions in the United States

Type of Effusion	Incidence
Congestive heart failure	500,000
Pneumonia (bacterial)	300,000
Malignant disease	200,000
■ Lung	60,000
■ Breast	50,000
■ Lymphoma	40,000
■ Other	50,000
Pulmonary embolization	150,000
Viral disease	100,000
Post–coronary artery bypass surgery	60,000
Cirrhosis with ascites	50,000
Gastrointestinal disease	25,000
Collagen vascular disease	6000
Tuberculosis	2500
Asbestos exposure	2000
Mesothelioma	1500

Modified from Light RW. *Pleural Diseases*. 6th ed. Philadelphia: Lippincott Williams & Wilkins; 2013.

cooperate with another to produce an effusion, especially if one disease enhances fluid entry into the pleural space and the other compromises pleural fluid exit via lymphatics.

SEPARATION OF EXUDATES FROM TRANSUDATES

A diagnostic thoracentesis should be performed on nearly every patient with free pleural fluid that measures more than 10 mm on the lateral decubitus film, ultrasound, or chest CT scan (eFig. 108.1). If the patient has obvious CHF, consideration can be given to postponing the thoracentesis until the heart failure is treated. However, if the patient is febrile or has pleuritic chest pain or if the effusions are not of comparable size on both sides, CHF is an unlikely explanation for the effusion, and a thoracentesis should be performed without delay.

Thoracentesis is a safe procedure when performed by an experienced operator.[11] It may be even safer when performed with ultrasound guidance.[12] Because of the small-bore needle required, it can be safely performed in patients with coagulopathies and thrombocytopenia,[13] and in patients on positive mechanical ventilation.[14,15] Questions have arisen about safety of thoracentesis in patients on the potent antiplatelet agent clopidogrel; cases of hemorrhage are few,[16] and there are several reports of the safety of thoracentesis in patients on clopidogrel.[17–19] The Society of Interventional Radiology currently recommends withholding clopidogrel for 5 days before thoracentesis when possible.[20] Nonetheless, there are risks to withholding anticoagulants or reversing their effects, and no large studies or published guidelines have provided guidance.[21] Thus, the risks should be balanced and, if thoracentesis is needed, it should be performed by experienced clinicians using ultrasound guidance.

Descriptions of the technique emphasize proper positioning of the patient, identification of the area of decreased tactile fremitus, and use of ultrasound, as recommended by the British Thoracic Society 2010 guidelines.[12] Adequate local anesthesia means anesthetizing the parietal pleura and the skin. The needle should run over the top of the rib to avoid the neurovascular bundle that travels in each intercostal space. Of note, this bundle travels in the middle of the intercostal space for approximately 5 to 6 inches (13 cm) from the spine before taking its safer position beneath the upper rib (eFig. 108.2).[14] Thus, one should avoid thoracentesis medial to the midclavicular line. Doppler ultrasound is increasingly used to identify the intercostal arteries and possible collateral arteries.[22] Drainage of the pleural fluid by manual pumping using one-way valve tubing may be safer than by vacuum drainage, with less pain and fewer complications.[23]

Complications from thoracentesis include pneumothorax and hemothorax. Estimates of each complication from prospective studies are low (2–6% for pneumothorax; 1% for hemothorax), with only half of the pneumothoraces requiring chest thoracostomy.[24] In a more recent prospective cohort study of 9320 procedures over 12 years with the routine use of ultrasound, complications were even lower: 0.6% for pneumothorax, 0.2% for bleeding, and 0.01% for reexpansion pulmonary edema.[11] Pneumothorax is often associated with procedural events, such as aspiration of air, multiple needle passes, and development of new symptoms. The risk for pneumothorax appears to be higher in patients with prior radiotherapy to the chest, multiple prior thoracenteses, or the use of vacuum bottles. In an uncomplicated thoracentesis that is well tolerated by the patient, there appears to be no value for routine chest radiography postprocedure.[24,25] Ultrasound detection of lung sliding in the uppermost part of the chest (where air would collect) can also be performed to exclude pneumothorax. Even when performed, routine post-thoracentesis radiographs rarely show new findings.[24]

The first question that should be answered with the diagnostic thoracentesis is whether the patient has a transudative or an exudative pleural effusion (Fig. 108.1). The identification of transudates or exudates is made by analysis of the levels of protein and LDH in pleural fluid and serum. Exudative pleural effusions meet at least one of the following criteria, whereas transudative pleural effusions meet none[26]: (1) pleural fluid protein/serum protein ratio greater than 0.50, (2) pleural fluid LDH/serum LDH ratio greater than 0.60, and (3) pleural fluid LDH greater than two-thirds of the upper normal limit for serum. If none of these criteria is met, the patient has a transudative pleural effusion, and the pleural surfaces can be ignored while the CHF, cirrhosis, or nephrosis is treated. In the rare cases where malignancy has been associated with a transudate, extrapleural effects of the tumor or other causes such as concurrent CHF are the most likely cause, as evidenced by the rarity of a positive cytology in those effusions.[27,28]

The above criteria may misidentify a transudative effusion as an exudative effusion in as many as 25% of cases.[29] If a patient appears to have a transudative effusion clinically, additional tests can be assessed to verify its transudative etiology. If the difference between the protein concentration of serum and pleural fluid exceeds 3.1 g/dL or if the difference between the albumin concentration of serum and pleural exceeds 1.2 g/dL, the patient in all probability has a transudative effusion.[29,30] If pleural concentrations of *N-terminal pro–brain natriuretic peptide* (NT-proBNP) are elevated (>1500 pg/mL), the patient likely has a transudate from a cardiac cause.[31,32]

Most studies dichotomize pleural effusions into transudates or exudates based on a single cutoff point. However, it is more realistic to consider biologic variation on a continuum, in which very high or very low values are almost always indicative of exudates and transudates, respectively, whereas values near the cutoff levels can be associated with either transudates or exudates and can be considered *indeterminate*. Indeterminate values may indicate that more than one process is acting, as mentioned above,[10,33,34] or that the underlying process has been evolving, such as after diuresis of patients with transudates due to CHF (see later).

When dealing with a patient who has a high likelihood of having a transudative pleural effusion, the most cost-effective use of the laboratory is to order only protein and LDH levels on the pleural fluid and obtain other laboratory tests only if the fluid turns out to be an exudate.[35] If one suspects initially that the patient has an exudate or if the fluid turns out to be an exudate, additional specimens can be sent.

DIFFERENTIATING EXUDATIVE PLEURAL EFFUSIONS

Once it has been determined that the patient has an exudative pleural effusion, one should attempt to determine which of the diseases listed in Table 108.1 is responsible for the effusion, remembering that pneumonia, malignancy,

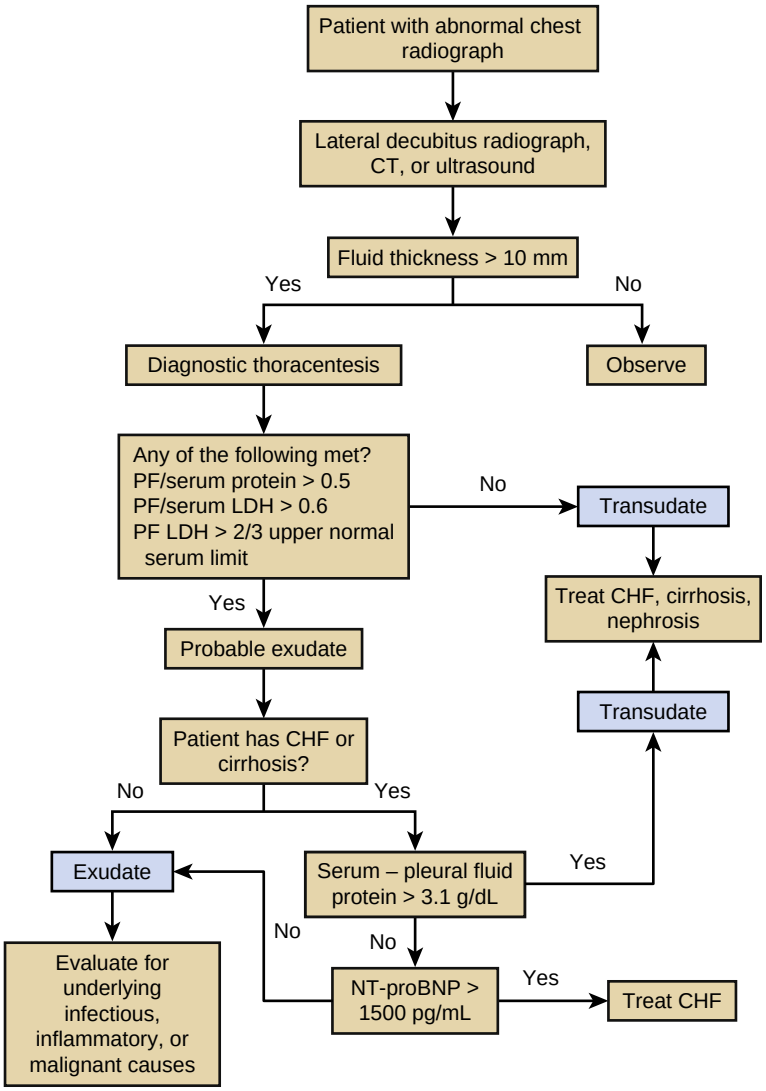

Figure 108.1 Algorithm for distinguishing transudative from exudative pleural effusions. With the results of the initial thoracentesis, one can usually determine whether the effusion is an exudate or a transudate. If a transudate, the treatment can be directed to the likely causes—*congestive heart failure* (CHF), liver disease, or kidney disease. If the protein and *lactate dehydrogenase* (LDH) results are borderline exudative and there is also CHF or cirrhosis present, there is a possibility that the effusion is still transudative. To determine this, one can use two additional tests: If the difference between the serum and pleural fluid protein concentrations is greater than 3.1 g/dL, one can assume that the effusion is transudative. If not, one can test the pleural or serum *N-terminal pro–brain natriuretic peptide* (NT-proBNP); if greater than 1500 pg/mL, one can conclude that CHF is at least one of the causes of the effusion. Once the effusion is determined to be exudative, one can focus on further evaluation of the underlying inflammatory, infectious, or malignant cause. CT, computed tomography; PF, pleural fluid.

and PE account for the great majority of all exudative pleural effusions. In all patients with undiagnosed exudative pleural effusions, the appearance of the fluid should be noted, and the pleural fluid protein and LDH levels (if not already obtained), glucose level, differential cell count, and microbiologic and cytologic studies should be obtained.[36] In selected patients, other tests on the pleural fluid, such as amylase, *antinuclear antibody* (ANA), rheumatoid factor, *adenosine deaminase* (ADA), lipid analysis, and so forth, may be of value. It is certainly not cost-effective, however, to obtain all these tests routinely on patients with undiagnosed exudative pleural effusions.

Appearance of Pleural Fluid

The gross appearance of the pleural fluid should always be described and its odor noted. If the pleural fluid smells putrid, the patient has a bacterial infection (probably anaerobic) of the pleural space. If the fluid smells like urine, the patient probably has a urinothorax. If the pleural fluid is bloody, a pleural fluid hematocrit or erythrocyte count should be obtained. To estimate the hematocrit, the erythrocyte count can be divided by 100,000.[37] For example, a pleural fluid erythrocyte count of 2,000,000/μL divided by 100,000 would give a estimated hematocrit of 20%. If the pleural fluid hematocrit is greater than 50% that of the peripheral blood, the patient has a hemothorax and the physician should strongly consider inserting chest tubes (see Chapter 113). If the pleural fluid hematocrit is less than 1%, the blood in the pleural fluid has no clinical significance. If the pleural fluid hematocrit is between 1% and 50%, the patient most likely has malignant pleural disease, a pulmonary embolus, or a traumatically induced pleural effusion.[38]

If the pleural fluid is turbid, milky, or bloody, the fluid should be centrifuged and the supernatant examined. If the pleural fluid is turbid when originally obtained and the turbidity clears with centrifugation, the turbidity is due to cells or debris in the pleural fluid; if the turbidity persists after centrifugation, the patient probably has a chylothorax or a pseudochylothorax. (eFig. 108.3A and Video 108.1) These two entities can be differentiated by the patient's history, examination of the sediment for cholesterol crystals (see eFig. 108.3B), and lipid analysis of the supernatant. With chylothorax, the disease process is acute, the pleural surfaces are not thickened, there are no cholesterol crystals present, and the pleural fluid triglyceride level is usually

greater than 110 mg/dL (1.24 mmol/L). With pseudochylothorax, the disease process is usually chronic, the pleural surfaces are usually thickened, there may be cholesterol crystals, and the pleural fluid triglyceride level is usually not elevated. (For further discussion of chylothorax and pseudochylothorax, see Chapter 111).

Pleural Fluid Protein

The pleural fluid protein level tends to be elevated to a comparable degree with all exudative pleural effusions and is therefore not generally useful in the differential diagnosis of an exudative pleural effusion. However, if the protein level is greater than 5.0 g/dL, the likelihood of a diagnosis of tuberculous pleurisy is increased. If the pleural fluid protein level is very low (<0.5 g/dL), the patient probably has a urinothorax, a leak of cerebrospinal fluid into the pleural space, or an effusion secondary to the misplacement of a central intravascular line.

Pleural Fluid Lactate Dehydrogenase

Whereas both pleural liquid protein and LDH arise from filtration from serum and thus serve as indicators of vascular permeability, LDH, as an intracellular enzyme, also indicates the level of inflammation and cell turnover within the pleural space. Nonetheless, the pleural fluid LDH level is increased to a comparable degree in patients with all categories of exudative pleural effusions and therefore is of no utility in the differential diagnosis of exudative pleural effusion.[26] Likewise, the pleural fluid LDH isoenzymes are of limited use in the differential diagnosis of exudative pleural effusions. However, pleural fluid LDH concentration should be measured every time a diagnostic thoracentesis is performed because the level of LDH in the pleural fluid reflects the degree of inflammation in the pleural space. If the pleural fluid LDH concentration increases with serial thoracentesis, the degree of inflammation in the pleural space is worsening, and the physician should be more aggressive in pursuing the diagnosis. Alternatively, if the pleural fluid LDH level decreases with serial thoracentesis, the pleural disease is resolving, and observation of the patient is indicated.[37] When an effusion meets exudative criteria on the basis of LDH but not protein, the effusion is usually malignant or parapneumonic.[26]

Pleural Fluid Glucose

A low glucose concentration probably indicates the coexistence of two abnormalities: a thickened, infiltrated pleura leading to an impaired diffusion of glucose into the pleural space plus increased metabolic activity leading to increased glucose utilization within the pleural space. The glucose level should be measured in all undiagnosed exudative pleural effusions because the demonstration of a reduced pleural fluid glucose level (<60 mg/dL, 3.33 mmol/L) narrows the diagnostic possibilities to seven: parapneumonic effusion, malignant effusion, tuberculous effusion, rheumatoid effusion, hemothorax, paragonimiasis, or *eosinophilic granulomatosis with polyangiitis* (EGPA).[37] If a patient with a parapneumonic effusion has a pleural fluid glucose level less than 40 mg/dL (2.22 mmol/L), tube thoracostomy should be considered. Many patients with rheumatoid pleural effusions have a pleural fluid glucose level less than 30 mg/dL (1.66 mmol/L).[39] In contrast, most patients with pleural effusion secondary to *systemic lupus erythematosus* (SLE) will have a pleural fluid glucose level greater than 80 mg/dL (4.44 mmol/L).[40] Patients with malignant pleural disease and a low pleural fluid glucose level usually have a positive pleural fluid cytology, maybe as a sign of more extensive pleural involvement. However, despite reports that low glucose or pH correlated with mortality or with failure of pleurodesis,[41,42] later studies have failed to confirm these findings.[43,44]

Pleural Fluid White Cell Count and Differential

Pleural liquid submitted for white cell count and differential should be sent in a tube with an anticoagulant to prevent the cells from clumping.[45] In the normal pleural space, the cell count has been reported to be 1700 cells/μL.[46] In effusions, the total cell count has limited diagnostic value. A pleural fluid white blood cell count of 1000/μL roughly separates transudative from exudative pleural effusion, whereas a pleural fluid white blood cell count greater than 10,000/μL is most common with empyemas and parapneumonic effusions but can also be seen with pancreatitis, PE, and collagen vascular diseases and, occasionally, with malignancy and tuberculosis.[38]

The differential cell count on the pleural fluid is much more useful than the total white cell count itself. The normal pleural space contains predominantly macrophages (75%), followed by lymphocytes (23%).[46] A change in differential from this normal distribution provides a clue to the underlying disease process. For the pleural fluid differential cell count, the cells should be partitioned into the following categories: polymorphonuclear leukocytes, eosinophils, small lymphocytes, mesothelial cells, and other mononuclear cells. Pleural effusions due to an acute disease process, such as pneumonia, pulmonary embolization, pancreatitis, intra-abdominal abscess, or early tuberculosis, contain predominantly polymorphonuclear leukocytes. Pleural effusions due to a chronic disease process contain predominantly mononuclear cells.

Pleural fluid eosinophilia (10% or more eosinophils by differential count) is most commonly due to a reaction to air or blood in the pleural space. On occasion, no pleural fluid eosinophils are found in the initial thoracentesis, but many eosinophils are seen in a subsequent thoracentesis, most likely due to entry of air or blood caused by the initial thoracentesis.[47] The eosinophilia appears to be due to production of *interleukin* (IL)-5 by CD4 T cells within the pleural space[48] and has been associated with a type 2 innate immune response.[49] At times, the pleural fluid eosinophilia associated with a hemothorax can be associated with eosinophilia in the peripheral blood.[50] The bloody pleural effusion complicating PE frequently contains many eosinophils.[51] With pneumothorax, pleural eosinophilia appears within 3 days of the pneumothorax and reaches a peak after 6 days.[52] With traumatic hemothorax, pleural fluid eosinophilia may not appear until the second week.

After excluding air or blood as the underlying cause, the etiologies of 392 cases of eosinophilic pleural effusions have been reported as follows: 40% idiopathic, 17% malignancy, 13% parapneumonic, 6% tuberculosis, 4% PE, 8% transudates, and 13% other.[53] A later review found that, of 135 patients with eosinophilic pleural effusion, the most common cause was malignancy (35%), followed by infections (19%).[54] A more recent review of 687 cases of eosinophilic pleural effusions identified malignancy as the most common cause (26%), followed by idiopathic (25%)

and parapneumonic effusions (13%).[55] Although malignancy appears to be common in eosinophilic effusions, it is not associated with a high eosinophil percentage.[54,55] If the etiology of the eosinophilia is not evident, several unusual diagnoses should be considered. Benign asbestos pleural effusions are frequently eosinophilic. In one series, 15 of 29 patients (52%) with benign asbestos pleural effusions had pleural fluid eosinophilia.[47] Patients with pleural effusions secondary to drug reactions typically have pleural fluid eosinophilia.[37] The pleural fluid of patients with pleural paragonimiasis is typically eosinophilic with low glucose, low pH, and high LDH level.[56] EGPA is the only other disease that produces this constellation of pleural fluid findings.[57]

Mesothelial cells line the pleural cavities. It is unusual to find mesothelial cells in effusions due to tuberculosis. However, the absence of mesothelial cells is also common with other conditions in which the pleura becomes coated with fibrin, such as a complicated parapneumonic effusion.

Lymphocytic pleural effusions by definition contain greater than 50% small lymphocytes. Most lymphocytic pleural effusions are due to malignancy or tuberculosis. In two series, 90 of 96 exudative pleural effusions (94%) with greater than 50% small lymphocytes were due to tuberculosis or malignant disease.[38,58] Because these two diseases can be diagnosed with needle biopsy of the pleura, the presence of pleural fluid lymphocytosis should alert the physician to consider needle biopsy of the pleura for diagnosis. In general, separation of pleural lymphocytes into T and B lymphocytes has not been useful diagnostically because most lymphocytic effusions contain a predominance of T cells (CD4) whether the diagnosis is malignancy or tuberculosis.[59] Such partitioning can be useful diagnostically, however, when a diagnosis of chronic lymphocytic leukemia or lymphoma is suspected. With these diseases, the pleural lymphocytes are usually of B-cell origin.[60] Lymphocytic effusions can also raise the possibility of chylothorax, sarcoidosis, rheumatoid pleuritis, post–coronary artery bypass graft surgery, and *immunoglobulin* (Ig) G4-related disease.

Pleural Fluid Cytology

A pleural fluid specimen from every patient with an undiagnosed exudative pleural effusion should be sent for cytologic studies. The first pleural fluid cytologic study is positive for malignant cells in up to 60% of malignant effusions.[38] If three separate specimens are submitted, up to 90% with pleural malignancy have positive cytopathology. The percentage of cases in which cytologic study of the pleural fluid establishes the diagnosis of a malignant pleural effusion ranges from 40–87%.[38,61,62] The frequency of positive pleural fluid cytologic tests is dependent on the tumor type. For example, fewer than 25% of patients with Hodgkin disease have positive cytology,[63] whereas most patients with adenocarcinomas have positive cytology.[62] The percentage of positive diagnoses is higher if both cell blocks and smears are prepared by standard protocols and examined by an experienced cytologist.[64] Each additional sample may increase diagnostic yield in part by providing a higher percentage of fresher cells. During thoracoscopy, pleural lavage has been found to increase the diagnostic yield, perhaps by harvesting more fresh cells for analysis.[65] The percentage of positive diagnoses is obviously dependent on the skill of the cytologist. Flow cytometry has been useful in the diagnosis of hematologic metastatic disease in the pleura and may have a role in nonhematologic malignant disease, where discovery of epithelial antigens not present on mesothelial cells can increase the confidence in a diagnosis of malignancy.[66]

Immunohistochemical stains of malignant cells are used to confirm a diagnosis and to specify tumor type, with many new markers available and being used in panels for optimal diagnostic efficacy; cell blocks can also be immunostained for programmed death ligand-1, although the cutoff values for initiating immunotherapy are not yet known.[64,67–69] Immunohistochemical detection of loss of BRCA1-associated protein 1 can now improve the sensitivity for diagnosis of mesothelioma.[70] Cytology can provide enough DNA to assess mutational analysis for *epidermal growth factor receptor* (EGFR)-activating mutations when extremely sensitive techniques including next-generation sequencing are used.[71–74] Cellular material, often from cell blocks but also from cell-free supernatant, may be used as a source of DNA or RNA.[74] In fact, "liquid biopsies" from pleural and other fluids closer to the metastatic site may be more sensitive than blood[75] and are an alternative to tissue biopsies, with a low risk of false negatives.[76]

Other Diagnostic Tests for Malignancy

Cytology may be nondiagnostic either because of a problem of specificity (e.g., the malignant cells cannot be differentiated from reactive mesothelial cells and "atypical" benign cells) or because of a problem of sensitivity (e.g., the malignant cells are rare). Several assays are being evaluated for their ability to increase the specificity of cytology for diagnosis of malignancy.[77] Fluorescent in situ hybridization with chromosome-specific probes can confirm abnormal numbers of specific chromosomes (aneuploidy), thereby confirming that abnormal cells are indeed malignant.[78] Fluorescent in situ hybridization now has value for detecting loss of p16 (CDKN2A) as evidence of pleural mesothelioma.[70] Early findings of malignancy, including DNA methylation, can be detected by methylation-specific *polymerase chain reaction* (PCR),[79] and gene expression patterns can help distinguish mesothelioma and adenocarcinoma.[80] EGFR mutations can predict response to EGFR tyrosine kinase inhibitors. On the other hand, biomarkers have generally been disappointing due to nonspecificity. However, pleural fluid mesothelin measurements hold promise for the diagnosis of mesothelioma; mesothelin measured in the pleural fluid is more accurate than serum mesothelin for the diagnosis of mesothelioma, and a low value in the pleural fluid can be useful in excluding the diagnosis.[81,82] At this time, routine use of mesothelin is not advised[82] (see Chapter 114).

Culture and Bacteriologic Stains

Pleural fluid from patients with undiagnosed exudative pleural effusions should be cultured for bacteria (both aerobically and anaerobically), mycobacteria, and fungi. A Gram stain should also be obtained. In the case of a probable complicated parapneumonic effusion with an initial negative Gram stain, the sediment of the pleural fluid should be stained because the bacteria will be precipitated in the sediment along with

the white blood cells and the debris. The yield of bacterial culture can be increased by using blood culture bottle cultures in addition to standard cultures; in 62 patients with pleural infection, the added inoculation of a set of aerobic and anaerobic blood culture bottles increased the identification of pathogens from 38–59%.[83]

One potentially useful adjunct is molecular detection of bacterial antigens or DNA. Such molecular tests can be rapid and accurate. Antigen-based assays have shown promise in diagnosing empyema caused by *Streptococcus pneumoniae*[84,85] and *Streptococcus pyogenes*.[86] Amplification and sequencing of bacterial 16S ribosomal RNA have identified bacteria in pleural empyema, showing, in one study, that the bacteriology of pleural infections differed from that of pneumonia[87] and, in another study, that a subgroup of empyemas had a bacteriology similar to that of brain abscesses, pointing to hematologic seeding from the oral cavity.[88] It is likely that use of species-specific PCR will become a more standard molecular test for a panel of organisms; it improves detection when compared to 16S PCR and has the potential to make specific diagnoses, although false-positive results are a potential limitation.[89]

OTHER DIAGNOSTIC TESTS FOR PLEURAL FLUID

N-Terminal Pro–Brain Natriuretic Hormone

Natriuretic peptides have proven useful in identifying CHF as the primary or contributing cause of pleural effusions. In one meta-analysis of 12 studies, a pleural fluid NT-proBNP level of greater than 1500 pg/mL was 94% sensitive and 91% specific for CHF-related effusions.[90] NT-proBNP has been shown to be superior to BNP for the purpose of identifying CHF as the underlying cause of the effusion.[31] It is useful to consider that NT-proBNP levels in the pleural fluid are very similar to those in the serum, and thus either can be used for this purpose.[91] NT-proBNP levels are not elevated in the other major transudative effusion, hepatic hydrothorax,[92] nor are they elevated in effusions due to coronary artery bypass graft surgery or PE.[93]

Pleural Fluid pH

The pleural fluid pH can be reduced to less than 7.20 with 10 different conditions: (1) complicated parapneumonic effusion, (2) esophageal rupture, (3) rheumatoid pleuritis, (4) tuberculous pleuritis, (5) malignant pleural disease, (6) hemothorax, (7) systemic acidosis, (8) paragonimiasis, (9) lupus pleuritis, or (10) urinothorax.[37] The decreased pleural fluid pH appears to result from lactic acid and carbon dioxide accumulation in the pleural fluid.[94] The pleural fluid pH is most useful in determining whether chest tubes should be inserted in patients with parapneumonic effusions.[95] A fall in the pleural fluid pH appears to be a sensitive indicator that the patient has a highly inflammatory parapneumonic pleural effusion that will require drainage.

The measurement of pleural fluid pH should be considered only in patients with parapneumonic effusions. In general, pleural fluids with a low pH also have a low glucose[94]; thus, pleural fluid glucose can be used as an alternative to the pH measurement. Although they have been found to have a nonlinear relationship and one cannot predict the other, they reach their diagnostic cutoffs similarly and thus either has been shown to be a valid test.[96] When the pleural fluid pH is used as a diagnostic test, it must be measured with the same care as arterial pH. The fluid should be collected anaerobically in a heparinized syringe and placed on ice. If the sample is left open to air, a spuriously high pH value can be obtained because of the rapid loss of carbon dioxide. The pH must be measured with a blood gas machine; a pH meter or indicator paper is not accurate.[97] Pleural fluid pH, but not glucose, may be significantly altered by residual air or lidocaine in the syringe.[98] In a 2012 study, 40% of pulmonologists did not appreciate that blood gas analysis was the only accurate method to measure pleural fluid pH, and nearly 40% of pulmonologists incorrectly believed their laboratory was using blood gas analysis.[99] The pleural fluid glucose is a preferable test when the accuracy of pH measurements cannot be ensured.

Pleural Fluid Amylase or Lipase

The pleural fluid amylase is elevated in patients with pleural effusions secondary to esophageal perforation, pancreatic disease, or malignant disease. However, because such a small percentage of effusions are due to esophageal perforation or pancreatic disease, the routine measurement of pleural fluid amylase is not indicated.[100] In the case of esophageal rupture, the origin of the amylase is the salivary glands.[101] In animal models of esophageal rupture, the pleural fluid amylase concentration is elevated within 2 hours of esophageal rupture.[102] In effusions due to pancreaticopleural fistulas, the amylase concentration is extremely high (>4000 U/mL), reflecting the concentrations in pancreatic secretions.[103] In approximately 10% of malignant effusions, the pleural fluid amylase level is mildly elevated. The site of the primary tumor in such patients is usually not the pancreas.[104] Malignancy can be differentiated from pancreatic disease with amylase isoenzymes because the amylase with malignant effusions is primarily of the salivary type.[105] Because lipase originates only from the pancreas, finding a high concentration of lipase in the pleural effusion should help identify the source as the pancreas.

Tests for Collagen Vascular Diseases

About 5% of patients with rheumatoid arthritis[106] and 50% of patients with SLE[107] have a pleural effusion sometime during the course of their disease. At times the effusions may be the first manifestation of the disease; therefore, these diagnostic possibilities should be considered in patients with undiagnosed exudative pleural effusion.

Measurement of the ANA titer is the best screening test for lupus pleuritis, although it is now evident that a positive pleural fluid ANA is not specific for the diagnosis. Although all patients with lupus pleuritis have a positive pleural liquid ANA (>1:40), the finding of a positive ANA has been found in 10–27% of all other effusions.[108,109] Neither the titer of ANA, ratio of pleural to plasma ANA, nor the pattern of staining has been found to increase the specificity for SLE.[110] A positive pleural fluid ANA in patients without SLE may be associated with malignancy, including mesothelioma.[110,111] In patients with SLE and a pleural effusion of uncertain etiology, a lack of ANA (e.g., double-stranded DNA, extractable nuclear antigens) in the pleural fluid argues against the diagnosis of lupus pleuritis.[112]

When a rheumatoid pleural effusion is suspected, the clinical picture usually establishes the diagnosis. If any question exists, the level of rheumatoid factor in the pleural fluid should be measured. Only patients with rheumatoid pleuritis have a

pleural fluid rheumatoid factor titer of 1:320 or greater and equal to or greater than the serum titer.[113]

Adenosine Deaminase

Adenosine deaminase (ADA), a product of activated lymphocytes, catalyzes the conversion of adenosine to inosine and is important for normal immune function. The pleural fluid ADA levels are elevated in almost all patients with tuberculous pleuritis but not generally with other conditions, even when associated with lymphocytic effusions.[114] Despite earlier concerns about false-negative values in human immunodeficiency virus–positive patients, ADA remains a sensitive marker for tuberculous pleurisy in patients with human immunodeficiency virus.[115] ADA levels can be elevated in other conditions and also in neutrophilic effusions; in one study, ADA greater than the cutoff (35 U/L) was seen up to 40% of parapneumonic effusions and in half of effusions due to lymphoma.[116] ADA has also been described as elevated in IgG4-related pleural effusions.[117] Because it is a highly sensitive test, the ADA can be a useful test to exclude the diagnosis of tuberculosis when the ADA level is low (<40 U/L).[118] A falsely low ADA, however, may be found in elderly or critically ill patients, for whom a low ADA should not exclude a diagnosis of tuberculosis.[119]

Other pleural fluid tests for *Mycobacterium tuberculosis* are discussed at ExpertConsult.com and in Chapter 109.

PLEURAL MANOMETRY

Measuring the pleural pressure at the time of a thoracentesis adds information on the pleural elastance, the change in pressure resulting from the removal of a certain volume. The normal elastance is considered to be less than 14 cm H_2O/L; in other words, with the removal of 100 mL, the pleural pressure should fall less than 1.4 cm H_2O. Much interest has centered on whether use of pleural manometry would help avoid complications of thoracentesis; currently, routine manometry has not been shown to be of value in avoiding chest pain[132] or *reexpansion pulmonary edema* (RPE), although the incidence of RPE is low enough that such a study would require larger numbers of patients. Probably the best use of pleural manometry now is to diagnose trapped lung,[133] which can be difficult to diagnose based on imaging alone, although there are also reports that the pressures do not always correlate with radiologic evidence of incomplete expansion.[134] At this time, pending ongoing studies, there is no established role for routine pleural manometry.

USEFUL RADIOGRAPHIC TESTS IN PATIENTS WITH SUSPECTED PLEURAL DISEASE

The possibility of a pleural effusion should be considered whenever a patient with an abnormal chest radiograph is evaluated. Two main factors influence the distribution of free fluid in the pleural space. First, the fluid collects in the most dependent part of the thoracic cavity because the lung is less dense than the pleural fluid. Second, because of their elastic recoil, the lobes of the lung maintain their traditional shape at all stages of collapse.

When the patient is upright, the fluid first accumulates between the inferior surface of the lower lobe and the diaphragm. If there is less than 75 mL of fluid, it may occupy only this position without overflowing into the costophrenic sinuses. When more fluid accumulates, it spills over into the posterior costophrenic angle and obliterates the posterior part of the diaphragm on the lateral projection. The possibility of a pleural effusion should be suspected whenever the posterior part of one or both hemidiaphragms is obscured or one hemidiaphragm appears elevated (see eFig. 20.14). The presence of a clinically significant amount of free pleural fluid can be excluded if both posterior costophrenic angles are clear. Pleural effusions on radiography can be missed in the setting of lower lobe consolidation and, in the setting of pneumonia, consideration should be given to seeking the presence of effusions with additional imaging.[135]

When there are larger amounts of pleural fluid, the lateral costophrenic angle on the frontal radiograph becomes blunted. Collins and associates[136] demonstrated that at least 175 mL of pleural fluid had to be injected into the pleural space of cadavers before the lateral costophrenic angle was blunted. In some of their cases, more than 500 mL of pleural fluid could be present without blunting the lateral costophrenic angle. As more fluid accumulates, the entire outline of the diaphragm on the affected side is lost, and the fluid extends upward around the anterior, lateral, and posterior thoracic walls, producing opacification of the lung base and the typical meniscus shape of the fluid. The changes just discussed are suggestive rather than diagnostic of the presence of pleural fluid. Lateral decubitus radiographs (see eFig. 108.1 and eFigs. 20.12 and 20.14) or more commonly ultrasonic examination (see Fig. 23.5) should be obtained in most instances when free pleural fluid is suspected.

Pleural fluid may become encapsulated by adhesions anywhere between the parietal and the visceral pleurae or in the interlobar fissures. Pleural fluid loculates most frequently in association with conditions that cause intense pleural inflammation, such as with a complicated parapneumonic effusion or tuberculous pleuritis. When the loculation is situated between the lung and the chest wall, there is a characteristic radiographic picture. The loculation is D-shaped, with the base of the D against the chest wall and the smooth convexity protruding inward toward the lung (see Figs. 20.37 and 109.4). The absence of air bronchograms helps differentiate a loculated pleural effusion from a parenchymal opacity. A definite diagnosis of loculated pleural effusion is best established by ultrasonography or *computed tomography* (CT).

Ultrasound

Ultrasound is used to identify and locate pleural fluid. In the presence of pleural fluid, the proximal echoes from the skin, intercostal muscles, and parietal pleura are separated from the distal echoes arising from the visceral pleura and the lung by a central echo-free space (see Fig. 23.5). The advantages of ultrasound over CT are the ease and speed with which the examination can be performed, the lack of ionizing radiation, the relatively low cost, and the ability to provide continuous guidance for thoracentesis or pleural biopsy[137] (see Chapter 23).

Interferon Gamma

Interferon gamma, a T-cell lymphokine, plays a critical role in the effective clinical response to *M. tuberculosis*. Pleural fluid interferon gamma appears to be almost as useful as ADA; because ADA is less expensive and has more evidence to support its cutoff values, ADA is preferred. Compared to ADA and interferon gamma, the interferon gamma release assays of pleural fluid, however, have not been shown to be of use in the diagnosis or exclusion of active pleural tuberculosis; these tests are not currently recommended for pleural fluid.[120–123]

Molecular Techniques for Diagnosis of *Mycobacteria tuberculosis*

Four molecular techniques are now available: PCR to detect specific mycobaterial DNA sequences in clinical specimens (pleural liquid or biopsy), nucleic acid probes to identify the organism in culture, restriction fragment length polymorphism to compare strains in epidemiologic studies, and gene-based susceptibility studies to screen for known genes associated with drug resistance.[124]

In theory, PCR tests such as Xpert MTB/RIF (Cepheid) have a great potential for providing a rapid, highly sensitive, and specific diagnosis of mycobacterial infection. In practice, PCR amplification of clinical samples has been limited by a low sensitivity,[125,126] which may be due to degradation of the target DNA by sample processing or by inhibitors of amplification in clinical fluids. Because of the low sensitivity (30% in a recent systematic review), the PCR test is of no value in excluding the diagnosis.[126] Nonetheless, PCR amplification assays show a high specificity and thus, when positive, can help make the diagnosis and detect rifampicin resistance.[127–129] Xpert MTB/RIF has been shown to have a higher sensitivity when used to test pleural biopsy material than pleural fluid.[130,131]

The appropriate site for a thoracentesis can be identified using ultrasound.[14] If a patient has a moderate or large effusion, the thoracentesis may be performed without ultrasound, but large studies have shown a lower incidence of pneumothorax when ultrasound is used.[138] Ultrasound should definitely be used if the effusion is small or if the patient has increased risks due to anticoagulation or comorbidity. When ultrasound is used to identify the site for thoracentesis, it is important to perform the thoracentesis at the time of the ultrasonic examination. If the skin is marked and the patient returned to his or her room, thoracentesis may be unsuccessful because the relationship between the skin and the pleural fluid may have changed. In addition, when the thoracentesis is performed at the time of the ultrasonic examination, the immediate feedback is valuable in improving the skill of the ultrasonographer. An additional advantage may be the use of color Doppler to identify the course of the intercostal artery before thoracentesis.[22] In the 2010 British Thoracic Society guidelines, ultrasound guidance is strongly recommended for all thoracenteses.[12]

Computed Tomography

Chest CT is currently the best way to visualize the entire pleural space.[137] Chest CT has its greatest utility in distinguishing parenchymal and pleural abnormalities.[139] With current protocols involving the rapid injection of intravenous contrast medium, the unaerated perfused lung parenchyma will enhance, whereas the pleural fluid will not.[140] The use of CT to discriminate transudates from exudates by their attenuation (Hounsfield units) has not been found to be clinically useful due to a great deal of overlap.[141] A CT with contrast enhancement has been recommended in the workup of a unilateral effusion if the diagnosis is still unclear after history, physical examination, chest radiograph, and thoracentesis that excludes a transudate.[142]

Chest CT is quite useful in distinguishing a parenchymal lung abscess located near the chest wall from an empyema with an air-fluid level. The most distinctive features are the margins of the abnormality. With empyema, the cavity walls are of uniform thickness both internally and externally, and the adjacent lung is usually compressed. The angle of contact with the chest wall may be obtuse. In addition, most empyemas have a lenticular shape (see Fig. 109.5) and demonstrate the "split pleura" sign (Fig. 108.2A).[143] With lung abscess, the walls of the cavity are not of uniform thickness, and the adjacent lung is not compressed (see Figs. 50.2 and 50.3). The angle of contact with the chest wall may be acute (see Fig. 108.2B).

In diffuse pleural disease, chest CT is useful in distinguishing malignant from benign causes. Features associated with malignancy include circumferential pleural thickening, pleural nodules (see Fig. 114.1), parietal thickening greater than 1 cm, and mediastinal pleural involvement (Video 108.2).[144] The distinction of metastatic disease from mesothelioma can be difficult, although hilar adenopathy is more common with metastatic disease.[137]

CT pulmonary angiography (CTPA) has become the first-line imaging test for the evaluation of PE[145,146] (see Chapters 20 and 81). The evaluation of a patient with a pleural effusion for PE can begin with a Doppler ultrasound of the lower extremities. If the ultrasound identifies thrombus, the patient can then be treated for thromboembolic disease. If it is negative, the patient may still have a PE. In the past, the standard approach was to proceed to lung ventilation-perfusion scanning. However, this has largely been replaced by CTPA. CTPA is highly sensitive and specific for pulmonary emboli in the proximal, segmental pulmonary arteries.[145] In contrast to ventilation-perfusion lung scanning, CTPA is generally more available, is less affected by the presence of a pleural effusion, and can establish alternate diagnoses as well[146] (see

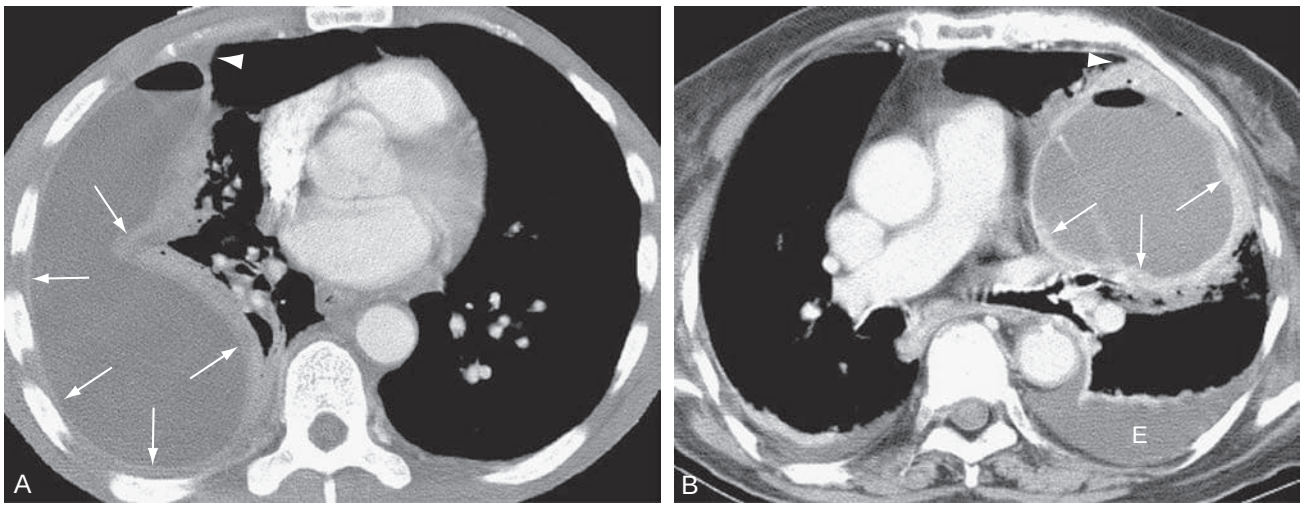

Figure 108.2 Typical *computed tomography* (CT) features of a pleural empyema versus a lung abscess. (A) Axial CT through the lower thorax in a patient with fever and pleuritic chest pain shows features typical of empyema, including the formation of obtuse angles between the lesion and chest wall (*arrowhead*), a lenticular shape, a smooth internal surface (*arrows*), and mass effect on surrounding structures (note slight leftward shift of the heart and great vessels). Note enhancement of the parietal and visceral pleura, representing the split-pleura sign (*arrows*) and the presence of an air-fluid level, indicating the presence of a bronchopleural fistula. (B) Axial CT through the midthorax in a patient with fever and cough productive of foul-smelling sputum shows features typical of a pulmonary abscess, including the formation of acute angles between the lesion and the chest wall (*arrowhead*), a round shape, a thick, irregular internal surface (*arrows*), and relatively little mass effect on surrounding structures, despite the large size of the lesion. The lack of mass effect results because pulmonary abscesses tend to destroy adjacent lung more than they displace it. An effusion (*E*), found to be an empyema, is also present. (Courtesy Michael B. Gotway, MD.)

Chapter 81). In addition, CTPA can be used to assess severity; measurements of right ventricle to left ventricle diameter greater than 1 are associated with a fivefold risk of death from PE and should increase concern for such a patient, although treatment guidelines do not currently incorporate these findings into clinical decision making.[147]

Magnetic Resonance Imaging

At the present time, *magnetic resonance imaging* (MRI) is less satisfactory than ultrasound or CT for the evaluation of pleural effusions.[148] It is possible that with improved MR technology, the characteristics of pleural fluid can be determined noninvasively. At the present time, respiratory and cardiac motion is the major limitation in evaluating specific intensity patterns of fluid collections of various compositions. MRI may have current value in delineating malignancy in the pleural space and may be better than chest CT for determining chest wall or diaphragmatic invasion.

Positron Emission Tomography and Computed Tomography

Positron emission tomography (PET) visualizes tissues that are metabolically active by their concentration of ^{18}F-fluorodeoxyglucose. Because most malignant cells have a higher metabolic rate than nonmalignant cells, PET can help differentiate malignant from benign lesions, help stage patients with malignancy, and help identify recurrence.[137] PET/CT integrates the metabolic information of PET with the detailed anatomic information of CT. Compared with CT or PET alone, PET/CT can allow detection of additional lesions, localize them more accurately, characterize them as highly likely to be malignant, and discriminate malignant from surrounding normal tissue[149] (see Chapter 114).

INVASIVE TESTS IN PATIENTS WITH UNDIAGNOSED EXUDATIVE PLEURAL EFFUSIONS

In the patient with an undiagnosed exudative pleural effusion, several invasive tests might be considered, including closed- or image-guided needle biopsy of the pleura, bronchoscopy, thoracoscopy or video-assisted thoracic surgery, and open biopsy of the pleura.

Nonspecific Findings on Invasive Testing

Nonspecific findings are common after invasive testing. After closed-needle biopsy, Poe and coworkers[150] reported that, of 207 patients with adequate biopsies, as many as 143 (68%) had nonspecific or normal results. In follow-up of these 143 patients at 12 to 72 months, 29 patients were diagnosed with malignant pleural disease and one patient was diagnosed with tuberculous pleuritis. In all 29 cases in which malignancy was eventually diagnosed, the diagnosis of malignant neoplasm was suggested by clinical criteria, such as weight loss, constitutional symptoms, or a history of previous cancer. These authors concluded that most patients with undiagnosed exudative pleural effusions in whom the clinical picture does not suggest malignancy are best managed by observation. In those with symptoms suggestive of malignancy, image-guided pleural biopsy or thoracoscopy are probably the procedures of choice.

Even thoracotomy often fails to provide a diagnosis in patients with pleural effusions. Over the 11-year period from 1962 to 1972, 51 patients with pleural effusion at the Mayo Clinic had no diagnosis after an open pleural biopsy.[151] In 31 of these patients (61%), there was no recurrence of the pleural effusion, and no cause ever became apparent. However, 13 of the patients were eventually proved to have malignancy: 6 had lymphoma and 4 had malignant mesothelioma. Thus, observation of patients with undiagnosed pleural effusions is often warranted unless there is compelling reason to pursue the diagnosis of malignancy. Since the time of this study, there have been many improvements in diagnostic tests that may increase the diagnostic yield of invasive procedures and the treatment options available.

If one looks to more recent data of outcomes after thoracoscopy and *video-assisted thoracic surgery* (VATS), the conclusions are similar. Two retrospective studies by Davies and colleagues[152] and McDonald and colleagues[153] yielded almost identical results. After thoracoscopy or VATS, 31% of patients in both studies (99/319 combined) had nonspecific findings. When these patients with nonspecific findings were followed for approximately 2 years, 11% in both studies (11/99 combined) were found to have malignancy. One can conclude that, in many patients with undiagnosed exudative pleural effusions, the problem will resolve. Thus, three factors should influence the vigor with which one pursues the diagnosis with invasive tests. (1) The symptoms and the clinical course of the patient: if the symptoms of the patient are minimal or if the symptoms are improving with time, a less aggressive approach is indicated. (2) The trend of the pleural fluid LDH level with time: if the pleural fluid LDH increases with serial thoracenteses, a more aggressive approach is indicated. (3) The attitude of the patient: if the patient is anxious about the cause of the pleural effusion, an aggressive approach should be taken. Furthermore, when an undiagnosed exudate resolves without treatment, two diagnoses should still be considered and excluded: PE and tuberculosis.

Needle Biopsy of the Pleura

Small specimens of the parietal pleura can be obtained with needle biopsy, also called blind or closed-needle biopsy. The needles most commonly used for this procedure are the Cope needle and the Abrams needle.[37] Because needle biopsy of the pleura is useful mainly to establish the diagnosis of malignant or tuberculous pleural effusions, this procedure should be considered when one of these diagnoses is suspected.

In malignant pleural disease, the needle biopsy of the pleura will be positive in 40–60% of patients.[154–156] Overall, the yield from pleural fluid cytology tends to be higher, probably because it samples cells dislodged from the entire pleura, whereas the needle biopsy can only sample from a localized area. In two series of malignant pleural effusions (n = 347), the cytology was positive in 58–69%, whereas the pleural biopsy was positive in 43–48%; the pleural biopsy added some diagnoses of malignancy in a few cases where the cytology was negative.[154,156] A prudent approach to the patient with a suspected malignant pleural effusion is to obtain a pleural biopsy only if the cytology obtained at the time of the initial diagnostic thoracentesis is nondiagnostic.

If the CT shows pleural thickening or nodularity, an image-guided pleural biopsy is an excellent option.[157,158]

Needle biopsy of the pleura has greater utility for the diagnosis of tuberculous pleuritis than of malignancy.[159] The initial biopsy is positive for granulomas in 50–80% of patients with tuberculous pleuritis.[160] Combining histology plus culture, the sensitivity of closed pleural biopsy for tuberculosis can be as high as 92%.[161] The demonstration of granulomas on the pleural biopsy is virtually diagnostic of tuberculous pleuritis; caseous necrosis or acid-fast bacilli need not be demonstrated. On rare occasions, fungal diseases, sarcoidosis, or rheumatoid pleuritis can produce granulomatous pleuritis. When tuberculous pleuritis is suspected, some of the pleural biopsy specimens should be cultured for mycobacteria.

The greatest value of needle biopsy for a patient with tuberculosis is in obtaining material for culture of *M. tuberculosis* for the determination of drug susceptibility. Often, the presentation of a patient with a recent purified protein derivative conversion and an exudative pleural effusion with lymphocytosis is classic and unlikely to be due to any diagnosis other than tuberculous pleurisy. The diagnosis can be further supported by measurements, where available, of pleural fluid ADA. In a patient with a recent skin test conversion, a lymphocytic exudate and an elevated pleural fluid ADA, treatment for tuberculosis can be offered with confidence without needle biopsy confirmation. However, when the patient may have been exposed to drug-resistant organisms, needle biopsy will increase the likelihood of obtaining organisms for culture and is recommended. Sputum induction can also be useful for culturing the organism, even when the patient is suspected to have only pleural involvement and the chest radiograph shows no pulmonary involvement; in this setting, sputum induction has been shown to have a yield similar to culture of the pleural biopsy (52% vs. 62%).[162] Medical thoracoscopy has a higher yield than closed-needle biopsy for obtaining pleural material for culture. When different approaches were compared in the same 51 patients, thoracoscopy obtained a positive culture of *M. tuberculosis* in 76%, whereas the Abrams needle obtained a culture in 48%.[163] If the need for obtaining positive cultures is high, the more invasive diagnostic tests, including medical thoracoscopy, may be preferred.

The two major complications of needle biopsy of the pleura are pneumothorax and bleeding. Pneumothoraces require a chest tube in only about 1% of pleural biopsies.[150,154,161] Many pneumothoraces likely develop because of leakage of air through the biopsy needle and do not necessarily indicate puncture of the lung. A hemothorax can result from inadvertent biopsy of an intercostal artery or vein. Although an older series reported two deaths from hemothorax in 227 biopsy procedures,[150] more recent series have not reported significant hemothorax.[161] The pleural biopsy needle can also be mistakenly inserted into the liver, spleen, or kidney, which can lead to hemorrhage in these organs. However, in general, bleeding complications are rare.

Image-Guided Pleural Biopsy

In patients with pleural abnormalities consistent with malignancy, CT-guided cutting-needle biopsies may supplant closed pleural biopsy for diagnosis, where image-guided technology is available.[164] In a randomized study of 50 patients with suspected malignant pleural effusions with negative cytology, those randomized to image-guided biopsy were more likely to be diagnosed (87% sensitivity) than those randomized to closed pleural biopsy (47%).[157] In situations where the effusion is small or where there is loculation or pleural thickening without an effusion, CT image-guided pleural biopsy is an excellent choice. Ultrasound guidance may also be used for closed pleural biopsy or transthoracic needle aspiration.[158] PET/CT may increase the yield further by improving interpretation and selection of biopsy targets (see earlier).

Bronchoscopy

Another procedure that should be considered in the patient with an undiagnosed pleural effusion is bronchoscopy. If the patient has an associated parenchymal lesion or hemoptysis, fiberoptic bronchoscopy will provide a diagnosis in nearly 75%.[165] On the other hand, if the patient has neither a parenchymal abnormality nor hemoptysis, a diagnosis for the pleural effusion is established less than 10% of the time.[166] At the present time, chest CT should be performed in all patients with undiagnosed exudative pleural effusions. Bronchoscopy should then be performed only if the CT scan demonstrates parenchymal abnormalities or if the patient has hemoptysis. At the time of bronchoscopy, special attention is paid to portions of the lung in which the parenchymal abnormalities were demonstrated.

Thoracoscopy or Video-Assisted Thoracic Surgery

Thoracoscopy may be useful diagnostically in patients in whom the origin of a pleural effusion remains unclear after routine fluid analysis and needle biopsy of the pleura. (See Chapter 29.) In many cases, especially for the evaluation of malignancy, thoracoscopy may supplant needle biopsy because of a greater diagnostic yield and the added ability to provide a pleurodesis. Thoracoscopy can be performed by pulmonologists using local anesthesia and conscious sedation for direct visualization of the pleural surfaces, tissue sampling, and pleurodesis; VATS, performed by thoracic surgeons, uses general anesthesia and single-lung ventilation by double-lumen intubation and allows greater access to the pleura and lung for surgical procedures.

Which patients with undiagnosed pleural effusions should undergo thoracoscopy? A diagnosis can be established in more than 90% of patients with malignancy, including those with mesothelioma.[167] Moreover, talc can be insufflated at the time of the procedure, which will control the effusion in the majority of patients. Nonetheless, thoracoscopy is not universally available, and there are risks of the procedure, a need for postprocedure chest tube(s), and a procedure cost that should be considered. Thoracoscopy is therefore recommended for the patient with a pleural effusion that remains undiagnosed after thoracentesis and needle biopsy of the pleura, and in whom the diagnosis of malignancy is strongly suspected and in whom one wishes to establish this diagnosis.

TRANSUDATIVE PLEURAL EFFUSIONS

Transudative pleural effusions accompany many common clinical disorders. It is noteworthy that the primary

abnormality in most cases of transudative pleural effusions originates in organs other than the pleura or lungs, especially the heart, liver, and kidneys. This association emphasizes the fact that although patients may visit their physicians for respiratory complaints, these symptoms may be caused by extrapulmonary disorders.

CONGESTIVE HEART FAILURE

CHF is probably the most common cause of pleural effusion.[37] The incidence of pleural effusion in patients with CHF is high. In one series of 60 patients with an exacerbation of stable CHF, chest CT scans demonstrated that 50 patients (83%) had a right-sided pleural effusion and 46 patients (77%) had a left-sided effusion. Approximately one-third of the effusions had a volume that exceeded 700 mL.[168] In a retrospective series of more than 3000 patients with acute heart failure, effusions were noted in 46%, of which most were bilateral.[169]

Pathophysiology (See Chapter 14)

The pleural fluid that accumulates with CHF is related to the clearance of pulmonary interstitial fluid across a leaky mesothelium into the pleural space.[170] In studies in which sheep lungs were isolated in situ, volume loading led to an increased transudation across the lung into the pleural space.[171] The pleural fluid had the same protein concentration as that of the lung lymph and the interstitial edema liquid in the lung. The volume of pleural fluid constituted about 25% of all edema formed in the lung.[171] In the clinical situation, patients with CHF are much more likely to have a pleural effusion if there is radiologically apparent pulmonary edema.[172]

Clinical Manifestations

Patients with pleural effusion resulting from CHF usually have symptoms and signs of heart failure, such as dyspnea on exertion, orthopnea, nocturia, peripheral edema, distended neck veins, crackles, and a cardiac gallop. The chest radiograph almost always reveals cardiomegaly in addition to the pleural effusion.

The pleural effusions seen with CHF tend to be bilateral, with larger effusions on the right (Fig. 108.3A). On CT imaging, interstitial and alveolar edema can often be detected by the presence of thickened septae and patchy opacities (Video 108.3, see Fig. 108.3B–C). Thickened septa represent interstitial edema, as seen in edematous lungs frozen to demonstrate the location of edema; the interstitial edema is continuous with the interlobular septa and the subpleural space, from which the edema has been shown to move across the visceral pleura to the pleural space (see Fig. 108.3D).[171]

CHF, either alone or as a contributing factor, is associated with bilateral and unilateral effusions. In an autopsy study of 250 patients with CHF and pleural effusion, 88% of the patients had bilateral pleural effusions, with the mean volume of pleural fluid in the right pleural space (1084 mL) slightly greater than the mean volume of fluid in the left pleural space (913 mL).[173] Of the 35 patients with CHF who had unilateral pleural effusions, 46% also had either PE or pneumonia.[173] Weiss and Spodick[174] reported that 73% of 51 patients with CHF had bilateral effusions, 19% had unilateral right-sided effusions and 9% had unilateral left-sided effusions. In a study of 100 patients with bilateral pleural effusions, the causes were often multiple; in fact, most of the effusions were exudative and, of these, CHF was the second most common cause.[33] In a study of unilateral effusions, of 130 prospectively studied patients, 30% had multiple causes, of which CHF was the most common contributing cause.[10]

The reason that effusions are generally larger on the right side may lie in the fact that they originate from the larger lung on the right side.[175] In volume-overloaded sheep, the rate of liquid leakage from the right lung was higher than from the left, likely due to the larger volume and surface area of the right lung.[171] In another study in awake sheep, there was no difference in the rate of absorption of effusions from the right and left pleural spaces,[176] suggesting that differences in formation are the cause of the difference in size.[175,176]

Although CHF is by far the most common cause of bilateral pleural effusions, an alternative explanation should be sought if there is no cardiomegaly. In one early series of 78 patients with bilateral effusions but a normal-sized heart, only 4% of the effusions were caused by CHF.[177]

Diagnosis and Management

The diagnosis is usually suggested by the clinical picture of CHF. A diagnostic thoracentesis should be performed if the pleural effusion is unilateral, if bilateral effusions are not comparable in size, if the patient is febrile, if the patient has pleuritic chest pain, or if the patient does not have cardiomegaly.[37] Otherwise, one can treat the CHF and observe; if the effusions do not resolve in a few days, a diagnostic thoracentesis should be performed.

The pleural fluid from a patient with CHF is usually a transudate.[26] However, if the patient has been on diuretics, the pleural fluid protein and LDH ratios may be increased sufficiently that the pleural fluid meets exudative criteria. A similar phenomenon has been described in the ascites literature.[178] The LDH ratio can also increase if intrapleural LDH increases due to injury from repeated taps and if serum LDH falls when diuresis reduces liver congestion.[178] In general, if the effusion protein and LDH values meet Light's criteria for an exudate, it is only by a small amount.[179] The transudative origin of the pleural fluids can be established in such patients if the serum minus the pleural fluid protein concentration is greater than 3.1 g/dL or the serum minus the pleural fluid albumin concentration is greater than 1.2 g/dL,[30] or by measurement of the pleural fluid NT-proBNP hormone.

Measurement of pleural fluid NT-proBNP is useful in this setting and may be more accurate, although more expensive, than the serum-to-pleural protein gradients for correctly classifying effusions from CHF.[31] Pleural fluid NT-proBNP is superior to BNP.[31] In a systematic review and meta-analysis of 10 studies, pleural fluid NT-proBNP was shown to be very useful for the diagnosis of pleural effusions due to CHF; the studies used different threshold values, but in this review the authors proposed a threshold for diagnosis of 1500 pg/mL (the average level was greater than 6000 pg/mL).[180]

Patients with CHF and pleural effusion should be treated with afterload reduction, diuretics, and inotropes, as needed. When the heart failure is successfully managed,

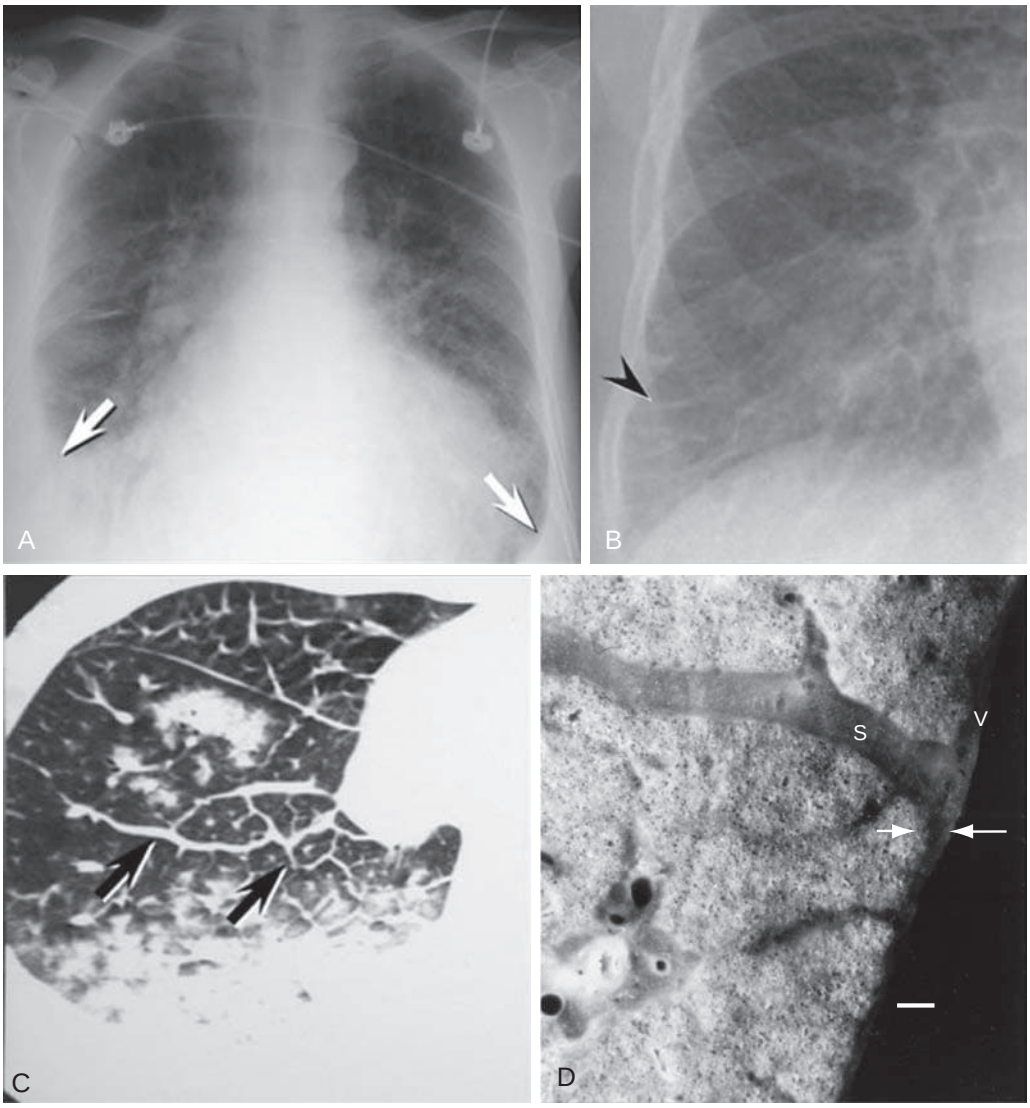

Figure 108.3 Pulmonary effusion from congestive heart failure. (A) Frontal chest radiograph in a patient with pulmonary edema shows cardiomegaly, bilateral pleural effusions (*arrows*), and central interstitial thickening. Note that the right effusion is slightly larger than the left effusion. (B) Detail frontal chest radiograph in a patient with increased pressure edema shows marked peripheral interlobular septal thickening (Kerley's B lines, *arrowhead*). (C) Chest computed tomography in a patient with pulmonary edema shows interstitial edema with smooth interlobular septal thickening (*arrows*). Bilateral pleural effusions are also present. (D) Frozen sheep lung after volume loading showing edema as a continuous band (*between arrows*) from the interlobular septa (S) to beneath the visceral pleura (V), which it can cross to enter the pleural space. Horizontal bar = 1 mm. (A–B, Courtesy Michael B. Gotway, MD. C, From Broaddus VC, Wiener-Kronish JP, Staub NC. Clearance of lung edema into the pleural space of volume-loaded anesthetized sheep. *J Appl Physiol.* 1990;68[6]:2627.)

the pleural effusion usually resolves. If the patient is markedly dyspneic when first evaluated, a therapeutic thoracentesis to relieve the dyspnea should be considered. Rarely, despite intensive therapy of the CHF, a patient has persistent large effusions; if such patients are dyspneic and if their dyspnea is relieved by a therapeutic thoracentesis, consideration can be given to controlling recurrent effusions with a pleurodesis using a sclerosing agent, such as talc, or the insertion of an indwelling pleural catheter.

HEPATIC HYDROTHORAX (See Chapter 126)

The incidence of pleural effusions with cirrhosis is approximately 6%.[181,182] The incidence appears to be much higher if ascites is present; however, in some patients with hepatic hydrothorax, no ascites can be detected, presumably because all ascitic fluid moves to the pleural space because of prevailing pressure gradients and low-resistance diaphragmatic defects (Fig. 108.4).[175,183]

Pathophysiology

The predominant mechanism leading to a pleural effusion in a patient with cirrhosis and ascites appears to be the movement of the ascitic fluid from the peritoneal cavity through defects in the diaphragm into the pleural space.[184] The decreased plasma oncotic pressure is only a secondary factor.

The diaphragmatic defects have been demonstrated in many ways. Lieberman and coworkers[181] introduced 500 to 1000 mL of air into the peritoneal cavity of five patients with cirrhosis, ascites, and pleural effusions and found that a pneumothorax developed in all patients within 48 hours. In addition, they were able to demonstrate air bubbles coming

through an otherwise undetectable diaphragmatic defect at thoracoscopy in one of their patients. In two of their patients, diaphragmatic defects were demonstrated at postmortem examination.[181] By thoracoscopy, different types of defects have been documented, such as blebs or fenestrations[185] (eFig. 108.4). Normally, there are no direct lymphatic connections between the peritoneal and the pleural spaces. Thus, the connections between the spaces are either preexisting developmental defects or are defects caused by trauma or stretching.

Clinical Manifestations

The clinical situation in patients with pleural effusions from cirrhosis is usually dominated by the cirrhosis. At times, however, the presence of a large pleural effusion may produce severe dyspnea. The pleural effusion associated with cirrhosis and ascites is frequently large and can occupy the entire hemithorax. The large effusions form because the diaphragmatic defect permits fluid to flow from the peritoneal cavity into the pleural cavity until the pleural pressure approaches the peritoneal pressure. The pleural effusions are usually right sided (80%) but occasionally are left sided (17%) or bilateral (3%).[184] Effusions can develop suddenly, presumably when the diaphragm becomes increasingly thinned and a rent develops (Fig. 108.4).

Diagnosis and Treatment

The diagnosis of hepatic hydrothorax is usually easily established from the clinical picture. If doubt exists, the diagnosis can be confirmed by scanning the chest after technitium-99m sulfur colloid is injected into the peritoneal cavity.[186] Both a paracentesis and a thoracentesis can be performed to confirm that the ascites and the pleural fluid are both transudates. Xiol and associates[187] performed thoracentesis on 60 patients with pleural effusion in the setting of cirrhosis and ascites. The pleural fluid analysis yielded a diagnosis other than hepatic hydrothorax in 18 (30%), including 9 spontaneous bacterial pleuritis, 2 tuberculosis, 2 adenocarcinomas, 2 parapneumonic effusions, and 3 undiagnosed exudates. The protein in the pleural fluid is usually higher than that in the ascitic fluid but is still less than 3.0 g/dL,

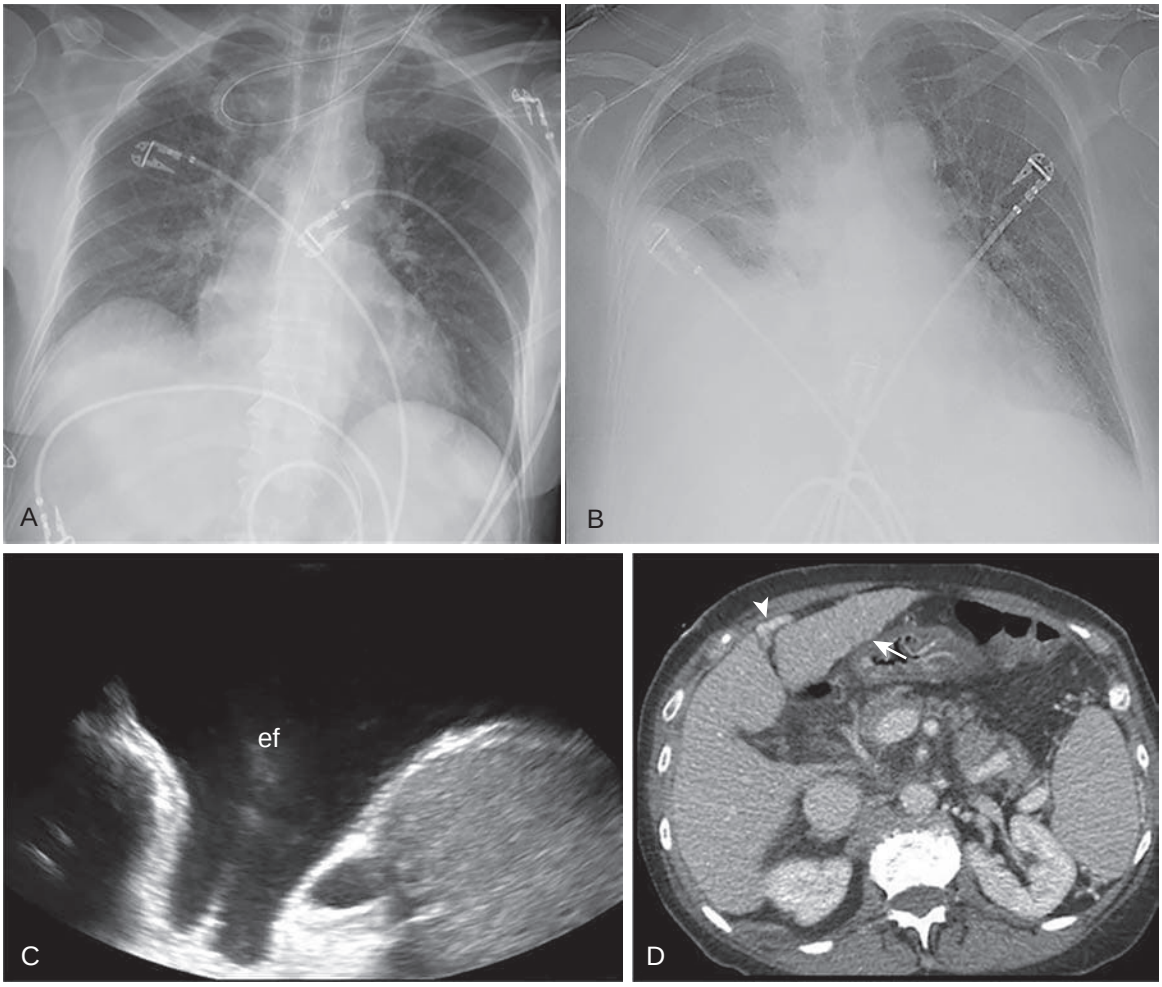

Figure 108.4 Rapid development of hepatic hydrothorax. (A) Frontal chest radiograph shows an elevated right diaphragm but no other significant findings. (B) Frontal chest radiograph performed about 30 hours after A shows a new large right pleural effusion, shown to be a transudate. (C) Thoracic ultrasound performed for thoracentesis shows a large right pleural effusion (*ef*). (D) Axial enhanced computed tomography of the abdomen shows a nodular liver contour (*arrow*) consistent with cirrhosis. A recanalized periumbilical ligament (*arrowhead*) is consistent with portal hypertension. No ascites is present in the upper abdomen, suggesting that it has all moved into the pleural space. (Courtesy Michael B. Gotway, MD.)

and the LDH is low.[181] If the polymorphonuclear cell count is greater than 500 cells/μL, the diagnosis of spontaneous bacterial pleuritis in conjunction with spontaneous bacterial peritonitis should be considered.[188]

The initial management of the pleural effusion associated with cirrhosis and ascites should be directed toward treatment of the ascites. Chest tube insertion should be avoided because the ascitic fluid will also drain through the chest tube, which can lead to massive protein depletion and even fatal cardiovascular collapse.[183] Instead, the patient should be given a low-salt diet and treated with diuretics, usually furosemide and spironolactone.

If diet and diuretics cannot control the effusion, the treatment of choice is liver transplantation.[183,189] Patients with hepatic hydrothorax have been found to do well posttransplant, at least as well as matched cirrhotic patients without hepatic hydrothorax[189]; however, although hepatic hydrothorax increases the mortality risk for patients with cirrhosis, this condition does not yet merit higher priority for transplant.[190] The next best approach is probably implantation of a *transjugular intrahepatic portal systemic shunt* (TIPS). Kinasewitz and Keddissi[183] summarized the literature on 115 patients who received TIPS for refractory hepatic hydrothorax and reported that the procedure controlled the hydrothorax in 80%, but 12% of the patients developed encephalopathy. In a study of TIPS with a long follow-up, 73 patients underwent TIPS with 59% complete response at 1 month and a 21% partial response; however, hepatic encephalopathy developed in 15%, and 30-day mortality was 19%. Survival was associated with the pre-TIPS *Model for End-stage Liver Disease* (MELD) score: with a MELD score less than 15, median survival was 875 days; with a MELD score greater than 15, it was 180 days.[191] Pleurodesis has been described in a few patients, but is complicated by rapid fluid movement into the pleural space.[192] If neither TIPS nor liver transplantation is feasible, the best alternative treatments are probably videothoracoscopy with closure of the diaphragmatic defects and pleurodesis[193,194] or placement of an indwelling pleural catheter.[195] An indwelling pleural catheter has been used as a bridge to liver transplant and as a palliative treatment; approximately 30% can experience a spontaneous pleurodesis, making this an attractive option.[192] Surprisingly, complications due to volume or electrolyte depletion have not been a problem, but infectious complications have been reported at 10–18%.[195,196]

Spontaneous Bacterial Pleuritis

Spontaneous bacterial pleuritis is, by definition, infection of a preexisting hepatic hydrothorax in which a parapneumonic infection has been excluded. Originally termed spontaneous bacterial *empyema*, we prefer the term *pleuritis* to emphasize its similarity to spontaneous bacterial peritonitis and to indicate that its treatment does not require tube thoracostomy. The diagnosis of spontaneous bacterial pleuritis is made if the pleural fluid culture is positive, the pleural fluid neutrophil count is greater than 250 cells/μL, and a pneumonic process has been excluded; the diagnosis of *culture-negative* spontaneous bacterial pleuritis is made if the pleural fluid cultures are negative and the pleural fluid neutrophil count is greater than 500 cells/μL.[188] They appear to be transudative. In one series in Spain, 16 of 120 patients (13%) admitted with a diagnosis of hepatic hydrothorax had spontaneous bacterial pleuritis; 10 of 24 episodes (43%) of spontaneous bacterial pleuritis were not associated with bacterial peritonitis.[188] Appropriate treatment of spontaneous bacterial pleuritis requires systemic antibiotics, but tube thoracostomy does not appear to be necessary. It remains to be seen whether spontaneous bacterial pleuritis is common in the United States.

NEPHROTIC SYNDROME

There is a high incidence of pleural effusion in patients with nephrotic syndrome. In one early study of 52 patients, 21% had pleural effusions.[197] The mechanism responsible for the transudative pleural effusion associated with nephrotic syndrome is probably the combination of decreased plasma osmotic pressure and increased hydrostatic pressure due to salt retention and hypervolemia. The pleural effusions in patients with nephrotic syndrome are usually bilateral and are frequently infrapulmonary in location.[197]

A diagnostic thoracentesis should be performed in all patients with nephrotic syndrome and a pleural effusion to prove that the pleural fluid is a transudate. Nonetheless, the possibility of PE should always be considered. In one series of 36 patients with nephrotic syndrome, 22% had pulmonary emboli.[198] If the pleural fluid is an exudate, a CTPA should be obtained.

The treatment of the pleural effusion associated with nephrotic syndrome should be aimed at increasing the level of protein in the serum by decreasing the protein loss in urine. If this is unsuccessful and patients are symptomatic from the pleural effusion, pleurodesis with a sclerosing agent or placement of an indwelling pleural catheter can be considered.

PERITONEAL DIALYSIS

Peritoneal dialysis is occasionally complicated by the development of an acute hydrothorax. In a review of 3195 patients receiving continuous ambulatory peritoneal dialysis in Japan, 1.6% developed a pleural effusion as a result of the movement of the dialysate from the peritoneal cavity into the pleural cavity.[199] The effusion developed within 30 days of initiation of the dialysis in 50% of the patients, but 18% had been receiving dialysis for more than 1 year before the effusion developed.[199] The effusions are right sided in about 90%.[199,200]

The pleural fluid in these patients is characterized by a glucose level intermediate between that of the dialysate and the serum, a protein level less than 10 g/L (1.0 g/dL), and a low LDH level. The LDH level is higher and the glucose level is lower in the pleural fluid than in the ascitic fluid.[200] Although the communication closes spontaneously in some patients, a surgical approach is usually required if continuous ambulatory peritoneal dialysis is to be continued. The treatment of choice is probably thoracoscopy with closure of the diaphragmatic defects, followed by pleurodesis. Alternative treatments are pleurodesis alone or thoracotomy with repair of the diaphragmatic defects.

MYXEDEMA

A pleural effusion sometimes arises as a complication of myxedema. Patients with myxedema and pleural effusion often have a concomitant pericardial effusion. In one early series of 25 patients with pericardial effusions secondary to myxedema, 13 of the patients (52%) had concomitant pleural effusion.[201] The isolated pleural effusion seen in conjunction with myxedema is generally borderline between a transudate and an exudate. Although the mechanism of formation of the effusion is unknown, a decrease in lymphatic function due to low thyroid levels or to deposition of mucopolysaccharides may contribute.[28,202] Thyroid replacement is the obvious treatment for pleural effusions associated with myxedema.

PERICARDIAL DISEASE

Pleural effusion is commonly seen in patients with pericardial disease (Video 108.4). Few of these effusions have been characterized but can be transudative or exudative. In one series of 35 patients with constrictive pericarditis, 60% of the patients had radiologically demonstrable pleural effusions.[203] Weiss and Spodick[204] reviewed 124 patients with pericardial disease and found that 35 (28%) had a pleural effusion. Of the group of 35 patients, 21 had only a left-sided pleural effusion (eFig. 108.5), 2 had only a right-sided pleural effusion, and the remaining 12 were bilateral. However, in another series of 21 patients with constrictive pericarditis and pleural effusion, the pleural effusion was right sided only in 9 (43%) and was bilateral in the remaining 12 (57%).[203]

The mechanism responsible for the pleural effusion associated with pericardial disease is not clear. In some cases, the pleura and the pericardium may be affected by the same systemic disease and develop effusions in concert; such conditions could include drug reactions, collagen vascular diseases, or IgG4-related disease. In constrictive pericarditis, one explanation for the effusions is that the pulmonary and systemic capillary pressures are elevated secondary to the pericardial disease, resulting in a transudative pleural effusion. However, one would expect these effusions to be bilateral. In inflammatory pericardial disease, however, the pleural effusion tends to be left sided (see eFig. 108.5) and, although the characteristics of the fluid have not been well described, it is probable that the effusion forms from extension of the pericardial inflammation to the adjacent pleura[204] or possibly from direct movement of the fluid across the pericardium into the pleural space.

CENTRAL VENOUS OBSTRUCTION

Central venous obstruction can cause large, persistent transudative effusions most likely due to increases in systemic venous pressure, leading to increased formation of liquid and to decreases in lymphatic clearance. Venous obstruction as a cause of persistent transudative effusions should be considered in situations with prior central venous instrumentation and have been reported from occlusions of the hemiazygous vein, brachiocephalic vein, and superior vena cava (eFig. 108.6). Relief of the obstruction can lead to resolution of the effusion.[205] Most cases have been reported in patients on hemodialysis, with an ipsilateral arteriovenous fistula, brachiocephalic stenosis or thrombosis, ipsilateral arm swelling, and a left-sided transudate.[206]

VERY LOW PROTEIN TRANSUDATES

Urinothorax

Obstruction of the urinary tract resulting in a retroperitoneal urine collection (urinoma) can lead to a pleural effusion.[207] The mechanism by which the urine accumulates in the pleural space is unknown, but it is thought that a retroperitoneal urine collection forms and then drains along pressure gradients into the pleural space. The fluid actually represents urine, and the pleural fluid smells like urine. Patients with urinothoraces have pleural fluid creatinine levels higher than those in serum, but about 10% of other effusions also meet this criterion.[207] When the urinary tract obstruction is relieved, the pleural effusion rapidly disappears. Although most are transudates, some with very low protein concentrations; in one systematic review of 88 patients, as many as 44% were exudates, usually because of the LDH value. The elevated LDH likely represented the effects of trauma, the most common cause of the urinary tract disruption in that review.[208]

Subarachnoid-Pleural Fistula

A subarachnoid pleural fistula allows accumulation of cerebrospinal fluid in the pleural space. The pleural fluid looks like cerebrospinal fluid with a very low protein and LDH level, although several have been reported to be exudates, perhaps because they arose postoperatively. Subarachnoid pleural fistula can follow ventriculopleural shunting or penetrating injuries, fractures, or surgery of the thoracic spine.[37] If there is doubt about the diagnosis, measurement of the pleural fluid β_2-transferrin or beta-trace protein is useful because only cerebrospinal fluid contains these proteins.[209,210] Patients often complain of headache or other neurologic symptoms. MRI has been used to identify the leak, although the leak may be missed if intermittent. There are several reports in which noninvasive positive pressure was used to slow and on occasion allow healing,[211] but, if such noninvasive measures fail to control the leak, surgical repair will be needed.

Iatrogenic

Transudative pleural effusions can result from misplaced catheters delivering intravenous fluids either directly into the pleural space or into the mediastinum, with leak or rupture into the pleural space. When the mediastinum is infiltrated, effusions can be bilateral.[212] Depending on the constituents of the infused material, the pleural fluid may have high fat content or high glucose concentrations; many are transudative.[213] These are probably underreported, and recognition depends on a high index of suspicion in any patients with indwelling lines or catheters. Once recognized, the offending catheter should be removed immediately (see "Pleural Effusions Due to Misplaced Catheters" later).

OTHER CAUSES OF TRANSUDATIVE PLEURAL EFFUSIONS

Pulmonary veno-occlusive disease frequently has small pleural effusions.[214] The characteristics of the pleural fluid have not been described, but it is probably a transudate because the effusions are likely related to the increased interstitial fluid. Patients with right heart failure secondary to pulmonary hypertension frequently have small bilateral pleural effusions.[215]

PE has been reported to be associated with a transudative pleural effusion. However, in a study of the pleural fluid findings in patients with PE, all 60 pleural fluids were exudates.[51] Pleural amyloidosis is associated with transudative effusions, probably due to a combination of heart failure and pleural infiltration with amyloid.[216] Cytokines such as *vascular endothelial growth factor* (VEGF) may play a role because, in a recent series, three out of four patients with persistent pleural effusions due to primary systemic amyloid improved with treatment with an antibody against VEGF, bevacizumab.[217]

Malignancy has been thought to cause transudates. If so, it is likely that the malignancy is extrathoracic, affecting the draining lymphatics, and exhibiting a negative pleural cytology.[218] It is also possible that there is another cause of the effusion, such as CHF (see also Chapter 14).

EXUDATIVE PLEURAL EFFUSIONS

Exudative pleural effusions are common clinical problems. These effusions may develop as a result of inflammation, injury, or malignancy, which can involve the pleural surfaces, the adjacent lung, or more distant tissues, such as mediastinal or abdominal organs. Further discussion of effusions due to infections can be found in Chapter 109; special types of effusions (chylothorax and hemothorax) are discussed in Chapters 111 and 113, respectively, and effusions secondary to pleural malignancy are presented in Chapter 114.

PULMONARY EMBOLISM

The diagnosis most commonly overlooked in the differential diagnosis of a patient with an undiagnosed pleural effusion is PE. It has been estimated that, due to the high incidence of PE and associated pleural effusion, one should expect to see more cases of pleural effusion secondary to PE than to bronchogenic carcinoma. Nevertheless, in most large series, PE accounts for less than 5% of pleural effusions. The diagnosis and treatment of PE are discussed in Chapters 81 and 82.

Clinical Manifestations

Patients with PE can be divided into three categories, depending on their presenting symptoms: (1) pleuritic pain or hemoptysis, (2) isolated dyspnea, and (3) circulatory collapse. In the *Prospective Investigation of Pulmonary Embolism Diagnosis* (PIOPED) study, 56% of the patients with pleuritic pain or hemoptysis had pleural effusion, and 26% of those with isolated dyspnea had pleural effusion, but none of the patients with circulatory collapse had pleural effusion.[219]

Approximately 50% of patients with paraembolic effusions have parenchymal opacities seen on chest radiographs[220] (Fig. 108.5). The opacities are usually in the lower lobes, are pleural based, and are convex toward the

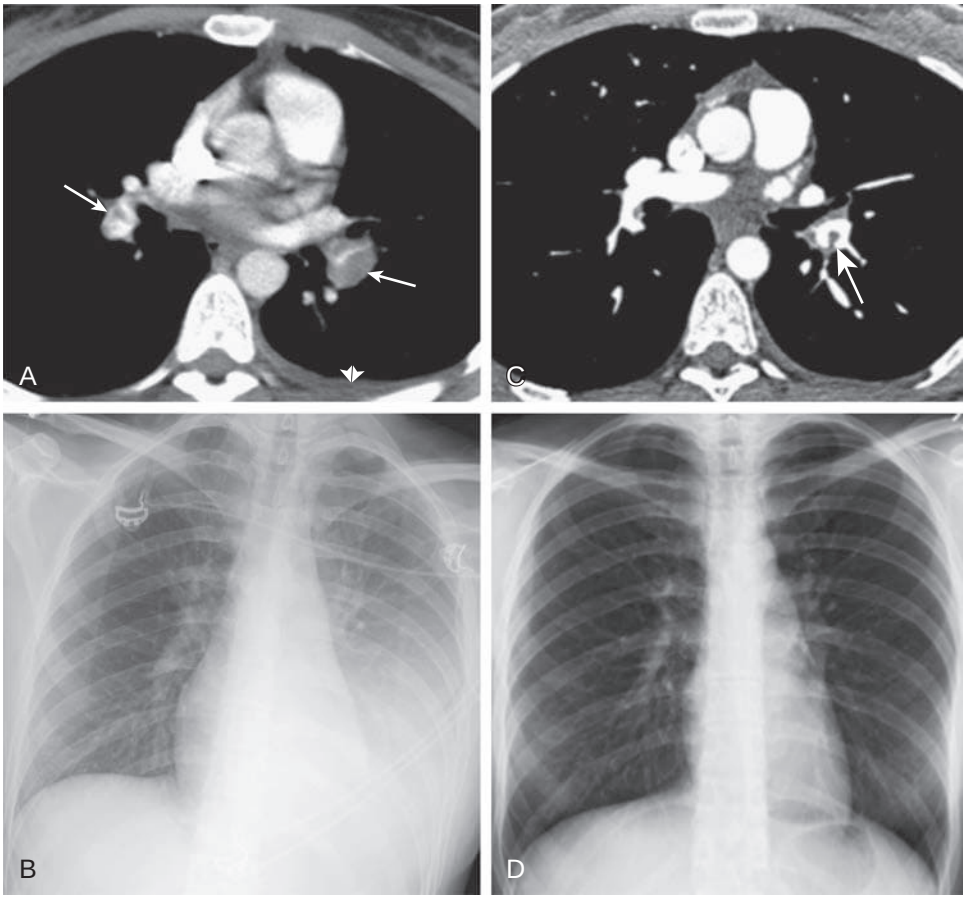

Figure 108.5 Pleural effusion related to acute pulmonary embolism. (A) Axial *computed tomography* (CT) pulmonary angiography shows bilateral acute pulmonary emboli (*arrows*); a trace left pleural effusion (*double arrowheads*) is present. (B) Frontal chest radiography performed 5 days after the CT pulmonary angiogram (A) shows left basal consolidation with a large left pleural effusion. (C) Axial CT pulmonary angiography performed more than 1 month after presentation, during treatment, shows near-complete resolution of the bilateral pulmonary emboli (*arrow*). (D) Frontal chest radiography performed more than 1 month after presentation shows complete resolution of the left basal consolidation and pleural effusion. (See also Videos 108.5A and 108.5B.) (Courtesy Michael B. Gotway, MD.)

hilum. Paraembolic effusions are usually small; in one series, 48 of 56 patients (86%) had only blunting of the costophrenic angle, and no patient had an effusion that occupied more than one-third of a hemithorax.[219] The pleural effusions may be unilateral or bilateral. In one study of 63 patients with PE and pleural effusion, the effusions were bilateral in 16 (25%).[221] Of interest, in more recent studies using CTPA in patients suspected of having PE, patients found to have PE were no more likely to have pleural effusions than those without PE (50% vs. 58%,[222] 57% vs. 56%,[223] 55% vs. 53%,[224] respectively). However, in other studies using CTPA, those found to have PE were more likely to have pleural effusions than those without PE (48% vs. 34%[225], 20% vs. 9%,[226] respectively); nonetheless, effusions tended to be small and very few large enough to warrant thoracentesis. Of interest, in those with PE, pleural effusions have been found to be almost twice as common in those with pulmonary infarct (47% [29/62]) than without (24% [74/305]).[227] Patients suspected of having PE likely have other underlying conditions that predispose them to pleural effusions, such as CHF or pneumonia.

Pleural fluid analysis is of limited value in establishing the diagnosis of paraembolic effusion because there is nothing characteristic about the fluid. The pleural fluid is almost always an exudate.[51] The pleural fluid red blood cell count exceeds 100,000/μL in less than 20% and is less than 10,000/μL in at least 30%. The pleural fluid white blood cell count can vary from less than 100 to greater than 50,000/μL. The differential white blood cell count may reveal predominantly polymorphonuclear leukocytes or mononuclear cells; eosinophils may be present.

Diagnosis

The diagnosis of PE is discussed in Chapter 81. The possibility of PE should be considered in every patient with a pleural effusion, even if the patient has obvious CHF. In an early autopsy series of 290 patients with CHF and pleural effusion, 60 (21%) had PE.[173] When a paraembolic effusion is strongly suspected, the patient should be started on heparin treatment while the diagnostic evaluation for PE proceeds.[228] In the patient with an undiagnosed pleural effusion for whom PE is suspected, CTPA appears to be the preferred test compared to ventilation-perfusion scanning because it also provides information about the lung parenchyma, the mediastinum, and the pleural surfaces, which may provide clues to the etiology of the pleural effusion (Videos 108.5A and 108.5B) and may highlight incidental findings that may need urgent evaluation.[229]

Treatment

The treatment of the patient with a paraembolic effusion is the same as for any patient with PE (see Chapter 82). The presence of bloody pleural fluid is not a contraindication to the administration of anticoagulation or, if indicated, thrombolytic therapy.[220] Paraembolic effusions usually reach their maximum size within the first 3 days.[230] If the effusion increases in size after this time, the patient probably has recurrent emboli, a pleural infection, or a hemothorax, and a diagnostic thoracentesis should be performed. Hemothorax has been associated with pulmonary infarction, where the bleeding may be seen 1 to 2 weeks later.[231] If the pleural fluid hematocrit value is greater than 50% of the peripheral hematocrit, a hemothorax is present. In this instance, anticoagulation should be discontinued, and tube thoracostomy should be performed.

ABDOMINAL DISEASES

Many abdominal diseases can cause pulmonary signs and symptoms. This section describes the most important of these disorders that cause pleural effusion (see Chapter 126).

Esophageal Perforation

The diagnosis of esophageal rupture should always be considered in the differential diagnosis of exudative pleural effusions because, if this condition is not rapidly treated, the mortality increases, with current estimates ranging from 30–60%. Approximately 60% of patients with esophageal perforation have a pleural effusion, whereas about 25% have a pneumothorax.[232] The pleural effusion is usually left sided (Fig. 108.6), but it may be right sided[233] or bilateral.

The esophagus most commonly perforates as a complication of esophagoscopy and is more likely when there is an attempt to remove a foreign body or to dilate an esophageal stricture.[234] Overall, the incidence of esophageal perforation with esophagoscopic examination is 0.15–0.70%.[232] The insertion of a Blakemore-Sengstaken tube for esophageal varices can be complicated by esophageal rupture. Frequently, the diagnosis is missed in these patients because of the severity of their illness and the multiple coexisting problems.[232] Esophageal perforation may also result from transesophageal echocardiography, foreign bodies, esophageal carcinoma, gastric intubation, chest trauma, chest surgery, or vomiting (Boerhaave syndrome). In a review of 120 consecutive patients with esophageal perforation from all causes, the incidence of pleural effusion was 52% and pneumothorax was 11%.[235]

Clinical Manifestations. The symptoms associated with esophageal perforation result from the acute mediastinitis produced by contamination of the mediastinum by the oropharyngeal contents. Most of the morbidity from esophageal perforation is caused by infection of the mediastinum and the pleural space by the oropharyngeal bacterial flora.[102]

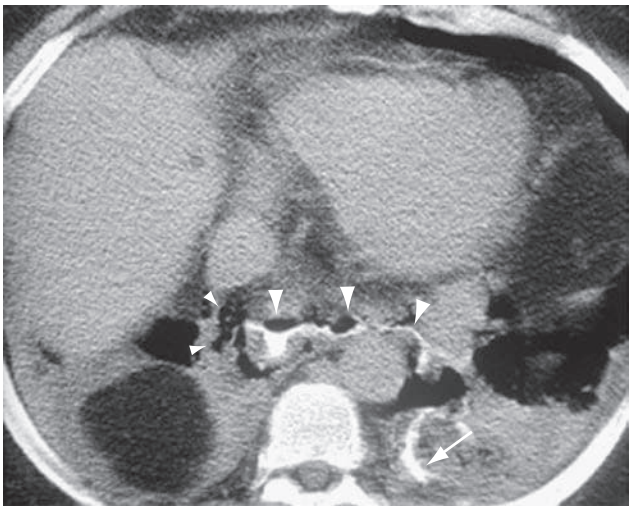

Figure 108.6 Effusion due to esophageal perforation. Axial computed tomography through the lower thorax in a patient with chest pain shows pneumomediastinum (*small arrowheads*) and leakage of water-soluble oral contrast from the ruptured esophagus (*large arrowheads*) through the mediastinum into the left pleural space (*arrow*). (Courtesy Michael B. Gotway, MD.)

A patient with an esophageal perforation is usually acutely ill. With a spontaneous rupture, there is frequently a sensation of tearing or bursting in the lower part of the chest or the epigastrium. The chest pain is characteristically excruciating and is often unrelieved by opiates. Greater than 50% of patients have small amounts of hematemesis. The presence of subcutaneous emphysema in the suprasternal notch is suggestive of the diagnosis. However, less than 10% of patients have subcutaneous emphysema within the first 4 hours of rupture.[236] When the esophagus is perforated during esophagoscopy, the endoscopist generally does not realize it; however, the patients usually develop persistent chest or epigastric pain within a few hours after the procedure.

Diagnosis. The diagnosis of esophageal rupture should be considered in all acutely ill patients with an exudative pleural effusion. The best screening test for esophageal rupture appears to be the level of amylase in the pleural fluid.[236] The pleural fluid amylase level is elevated owing to the amylase in saliva entering the pleural space.[101] The pleural fluid pH is usually decreased below 7.00 in patients with pleural effusion secondary to esophageal perforation due to the intense inflammatory response resulting from the mediastinitis and not the regurgitation of gastric juice into the pleural space. The demonstration of squamous epithelial cells or particularly of food particles in the pleural fluid is highly suggestive of the diagnosis. Other findings suggestive of esophageal rupture are a chest tube output greater than 500 mL/24 hr or polymicrobial flora in the pleural fluid. The diagnosis is established when esophageal perforation is confirmed by contrast studies of the esophagus (see Fig. 108.6).

Treatment. The treatment of the esophageal rupture may range from nonoperative stenting to primary repair to esophagectomy depending on the underlying disease of the esophagus and the size of the rupture.[235] Mediastinitis from esophageal perforation and other causes is discussed in detail in Chapter 116.

Pancreatic Disease

Three different types of nonmalignant pancreatic disease can have an accompanying pleural effusion: acute pancreatitis, chronic pancreatitis with pseudocyst, and pancreatic ascites.

Acute Pancreatitis. In two prospective reports a decade apart, exactly 50% of the nearly 200 patients admitted with acute pancreatitis had a pleural effusion on chest CT scan.[237,238] In both reports, patients with acute pancreatitis and a pleural effusion had more severe disease and a higher mortality rate than did those without effusions.[237,238] The exudative pleural effusion accompanying acute pancreatitis results from the diaphragmatic inflammation and transdiaphragmatic transfer of the exudative fluid arising from acute pancreatic inflammation. Even though small, pleural effusions may be a marker of significant inflammation.

The clinical picture is usually dominated by abdominal symptoms, including pain, nausea, and vomiting. However, at times, respiratory symptoms consisting of pleuritic chest pain and dyspnea may dominate the clinical picture. In addition to the small to moderate-sized pleural effusion, the chest radiograph may reveal an elevated diaphragm and basilar opacities. Demonstration of an elevated pleural fluid amylase level is highly suggestive of the diagnosis, but the diagnosis of esophageal rupture must be excluded. The pleural fluid is an exudate with predominantly polymorphonuclear leukocytes and a normal glucose level. It usually resolves as the pancreatic inflammation recedes.[239]

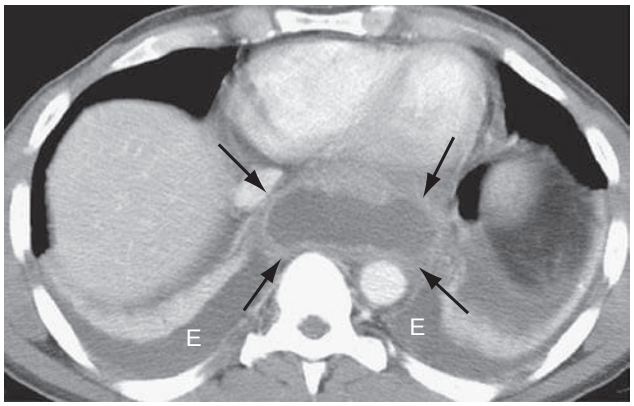

Figure 108.7 Effusion due to pancreatic pseudocyst. Axial computed tomography image through the lower thorax in a patient with chronic pancreatitis shows bilateral pleural effusions (*E*) and a cystic mass in the middle mediastinum (*arrows*) representing a pseudocyst. (Courtesy Michael B. Gotway, MD.)

Chronic Pancreatic Pleural Effusion. Patients with chronic pancreatic disease often have a large chronic pleural effusion. When the pancreatic ductal system is disrupted, a pseudocyst may form in the pancreas. A sinus tract can then extend from the pseudocyst through the aortic or esophageal hiatus into the mediastinum. Once the sinus tract reaches the mediastinum, the process may be contained to form a mediastinal pseudocyst, or it may rupture into one or both pleural spaces, resulting in a large chronic pleural effusion[103] (Fig. 108.7).

The clinical picture of patients with chronic pancreatic disease and pleural effusion is usually dominated by chest symptoms, such as dyspnea, cough, and chest pain. Most patients do not have abdominal symptoms because the pancreaticopleural fistula decompresses the pseudocyst. The pleural effusion is usually massive and recurs rapidly after thoracentesis.[103] The effusion is usually left sided but may be right sided or bilateral.

The key to the diagnosis is a markedly elevated pleural fluid amylase level, generally greater than 1000 U/L, whereas the serum level of amylase may be only mildly elevated. Patients with chronic pancreatic pleural disease are generally easily differentiated from those with malignant pleural effusion, who also may have an elevated pleural fluid amylase level, because the amylase level is much higher with the pseudocyst. In rare cases in which the differentiation is not obvious, the diagnosis can be made by measuring amylase isoenzymes, because the amylase associated with malignancy is of the salivary, not the pancreatic, type.[105] Both ultrasound and CT are useful in establishing the diagnosis of pancreatic pseudocyst. Endoscopic retrograde cholangiopancreatography usually documents the fistulous tract or other pancreatic pathology.

Interruption of the fistula and repair of pancreatic drainage will control the pleural effusion (see Chapter 126). Conservative therapy to suppress pancreatic secretion (nasogastric suction, no oral intake, somatostatin) may

be tried for minor leaks; however, if it fails, a more direct approach, usually by endoscopic means to drain internally or stent the pancreatic duct, is warranted.[240] Decortication of the pleura may be necessary for some patients to remove the thick pleural peel created by the intense inflammation caused by the presence of pancreatic enzymes.

Pancreatic Ascites. Some patients with pancreatic disease develop ascites characterized by high amylase and protein levels. If these patients should happen to have or develop a defect in their diaphragm, they develop a large pleural effusion as a result of the flow of fluid from the peritoneal cavity to the pleural cavity. The treatment for pancreatic ascites aims to stop the pancreatic leak, first with conservative measures (nothing by mouth, total parenteral nutrition, perhaps octreotide) and, if these measures fail, by endoscopic stenting.[240]

Intra-abdominal Abscesses

Pleural effusions are frequently seen with intra-abdominal abscesses. The possibility of an intra-abdominal abscess should be considered strongly in any patient with an undiagnosed exudative pleural effusion containing predominantly polymorphonuclear leukocytes, particularly when there are no pulmonary parenchymal abnormalities. The mechanism responsible for the development of the exudative pleural effusion is probably diaphragmatic irritation.

Subphrenic abscess is the intra-abdominal abscess most commonly associated with a pleural effusion; pleural effusions develop in approximately 80% of patients with subphrenic abscess.[241] The approximate incidence of effusions with other intra-abdominal abscesses is 40% in pancreatic abscesses, 30% in splenic abscess, and 20% in intrahepatic abscesses. With pancreatic abscess, the pleural fluid may have a high amylase level.

Clinical Manifestations. Subphrenic abscess most commonly develops as a postoperative complication 1 to 3 weeks after intra-abdominal surgery.[241] Splenectomy and gastrectomy are particularly likely to be complicated by left subphrenic abscess. There is no antecedent abdominal surgery in approximately 10% of patients with subphrenic abscess.[241] The abscess may result from perforation of the stomach, duodenum, appendix, colon, or a diverticulum, or from diverticulitis, cholecystitis, pancreatitis, or trauma. Most patients have fever, leukocytosis, and abdominal pain, but frequently there are no localizing signs or symptoms.

Most patients with pyogenic intrahepatic abscesses have fever and anorexia. Abdominal pain is common, but frequently it is not localized to the right upper quadrant. On physical examination, an enlarged, tender liver can be demonstrated. Laboratory tests reveal leukocytosis, anemia, elevated alkaline phosphatase levels, and hyperbilirubinemia.[242]

Pancreatic abscess usually follows an episode of acute pancreatitis. This diagnosis should be suspected if the patient does not respond to the initial therapy or if fever, abdominal pain, and leukocytosis develop within 3 weeks of the episode of acute pancreatitis. Splenic abscess is uncommon, usually seen in patients with systemic infection. Bacterial endocarditis is the most common underlying infection.

The pleural fluid that accumulates in patients with intra-abdominal abscesses is an exudate with predominantly polymorphonuclear leukocytes. The pleural fluid white blood cell count may exceed 50,000/μL, but the pleural fluid pH and glucose concentration usually remain greater than 7.20 and 60 mg/dL (3.33 mmol/L), respectively. Only rarely does the pleural fluid become infected.

Diagnosis and Treatment. The diagnosis of intra-abdominal abscess is best established with an abdominal CT scan (eFig. 108.7 and Video 108.6),[243] which should be obtained in every patient with an undiagnosed exudative pleural effusion characterized by predominantly polymorphonuclear leukocytes if there are no parenchymal abnormalities. The appropriate treatment for a patient with an intra-abdominal abscess and a pleural effusion is drainage of the abscess combined with parenteral antibiotics.

Post-abdominal Surgery

Approximately 50% of patients undergoing abdominal surgery develop a pleural effusion in the first few days after surgery.[244,245] The incidence of postoperative pleural effusion is greater in patients undergoing upper abdominal surgery, in patients with postoperative atelectasis, and in patients with free abdominal fluid at surgery.[244,245] Ultrasonography appears to be better at detecting pleural effusion than chest radiography in this setting, particularly with the difficulty in obtaining a true upright film.[246] The accumulation of pleural fluid within the first 72 hours after abdominal surgery is probably related to either diaphragmatic irritation or transdiaphragmatic movement of intra-abdominal fluid. A postoperative patient with a significant amount of pleural fluid, particularly when associated with fever, should have a diagnostic thoracentesis to rule out pleural infection as a cause of the effusion. In addition, the possibility of PE should be considered. If the effusion develops more than 72 hours after surgery, it is probably not related to the surgical procedure itself, and alternative explanations must be sought, such as PE, intra-abdominal abscess, and hypervolemia.

Liver Transplantation

Most patients who undergo an orthotopic liver transplantation develop a pleural effusion after surgery. In one study, 68% of 300 patients undergoing liver transplantation developed a pleural effusion, and the effusion occupied more than 25% of the hemithorax in 21 patients (7%).[247] Of the 206 patients with effusions, the effusion was unilateral right sided in 153 (74%) and bilateral in 53 (26%); none were unilateral on the left. The effusions are large enough to require therapeutic thoracentesis or tube thoracostomy in approximately 10%.[247] The natural history of these effusions is that they increase in size over the first 3 postoperative days and then gradually resolve over several weeks to several months. The pathogenesis of these effusions is probably related to injury or irritation of the right hemidiaphragm caused by the extensive right upper quadrant dissection. Those with pleural effusions requiring drainage have been found to have worse preoperative MELD scores and a worse outcome than those that without.[248]

Bilious Pleural Effusion

Bilious pleural effusions are due to a fistula from the biliary tree to the pleural space.[249] The fistula may be secondary to trauma, suppurative complications of biliary tract infections,

right-sided percutaneous transhepatic biliary drainage, or surgery, particularly when biliary obstruction is present. Percutaneous transhepatic biliary drainage can traverse the costophrenic sulcus, thereby connecting the bile duct to the pleural space.[250] The diagnosis should be suspected in any patient with an obstructed biliary tract or recent biliary interventions. The pleural fluid usually appears bilious or even black[251] but, at times, the diagnosis may depend on the demonstration that the ratio of pleural fluid to serum bilirubin is greater than 1.0. A pleural fluid glycocholic acid, a component of bile acids, can also identify the source.[252] Appropriate treatment consists of reestablishment of biliary drainage.

INFLAMMATORY DISEASES

Rheumatoid Pleuritis

The pleura is occasionally involved in the course of rheumatoid arthritis. Approximately 5% of patients with rheumatoid arthritis have a pleural effusion, and approximately 20% experience pleuritic chest pain.[106,253] Rheumatoid pleurisy has a striking male predominance, despite the higher prevalence of rheumatoid disease in women; greater than 10% of men, but less than 2% of women, with rheumatoid disease have a pleural effusion.[106,253]

Clinical Manifestations. Almost all patients with rheumatoid pleural effusions are older than 35 years. Approximately 80% are men, and approximately 80% have subcutaneous nodules. The pleural effusion usually develops only after the arthritis has been present for several years[106] but, on rare occasions, a patient may present with a pleural effusion.

Patients with rheumatoid pleuritis may be asymptomatic or symptomatic with pleuritic chest pain, fever, or both,[106,113] and some patients experience dyspnea secondary to the presence of pleural fluid. In most patients, the chest radiograph reveals a small- or moderate-sized pleural effusion. In approximately 25% of patients, the effusion is bilateral.[106] Over time, the effusion may alternate from one side to the other or may come and go on the same side. Other intrathoracic manifestations of rheumatoid disease are present in up to one-third of patients.[106]

Diagnosis. The diagnosis is suggested by the clinical picture of rheumatoid arthritis in the presence of a pleural effusion. The pleural fluid with rheumatoid pleuritis is distinctive, characterized by a glucose level less than 30 mg/dL (1.67 mmol/L), a high LDH level (>2 times the upper limit of normal), a low pH (<7.20), and a high rheumatoid factor titer (>1:320 and equal to or greater than the serum titer).[113] On occasion, the pleural fluid glucose is not low when the patient is first seen, but serial pleural fluid glucose determinations reveal progressively lower pleural fluid glucose levels. Another interesting characteristic of rheumatoid pleural effusions is their tendency to contain cholesterol crystals or high levels of cholesterol,[254] diagnostic of a pseudochylothorax, even without pleural thickening.[255] A unique cytologic appearance of elongated macrophages, called comet-tail cells, is also considered specific for the diagnosis[256] (eFig. 108.8).

With the characteristic pleural fluid findings, the primary alternative diagnosis to exclude is complicated parapneumonic effusion. The incidence of complicated parapneumonic effusion is high in patients with rheumatoid pleuritis,[257] so this differentiation is important. It is particularly important to examine the Gram stain of the pleural fluid and to culture the fluid both aerobically and anaerobically.

Prognosis and Treatment. The natural history of rheumatoid pleuritis varies. Most patients experience a spontaneous resolution within 3 months, but the effusion is persistent in an occasional patient, and massive pleural thickening sometimes develops. Rheumatoid pleural effusion may respond to systemic steroids or anti–tumor necrosis factor therapy; the results after intrapleural corticosteroids have been mixed.[37,258] There are case reports of response to newer anti-immune therapy (e.g., atabacept, tocilizumab).[259,260] Decortication can be considered in dyspneic patients with thickened pleura. This procedure is particularly difficult in patients with rheumatoid pleuritis because it is not easy to develop a plane of dissection between the lung and the fibrous peel.

Lupus Pleuritis

Approximately 40% of patients with SLE or drug-induced lupus have a pleural effusion during the course of their disease.[107]

Clinical Manifestations. Most patients with lupus pleuritis have arthritis or arthralgias before the development of a pleural effusion. Almost all patients with lupus pleuritis have pleuritic chest pain, and most are also febrile. Lupus pleuritis frequently develops in association with an exacerbation of the underlying disease. The pleural effusions secondary to lupus are usually small and are bilateral in about 50% of patients.[261]

Many medications have been incriminated for producing drug-induced lupus erythematosus (see Chapter 99).[37] Hydralazine, procainamide, isoniazid, phenytoin, and chlorpromazine are the ones most commonly associated with drug-induced lupus, but more than 70 other drugs possibly induce lupus. For the latest information on possible drug reactions, including lupus reactions, an excellent online source is www.pneumotox.com. The presenting signs, symptoms, and radiographic abnormalities are similar, whether the pleuritis is due to spontaneous or to drug-induced lupus. The symptoms associated with drug-induced lupus characteristically abate within days of discontinuing the offending drug.

Diagnosis. The possibility of lupus pleuritis should be considered in any patient with an exudative pleural effusion of unknown cause. The pleural fluid can contain a predominance of either polymorphonuclear or mononuclear cells, depending on the timing of the thoracentesis in relation to the development of the symptoms.[40] Elevated ANA titers in the pleural fluid (>1:160) are a sensitive test for effusions caused by lupus[108,112,262,263] but are not specific because elevated ANA can also be found in other conditions, particularly malignancy. The diagnosis of lupus pleuritis is based primarily on the clinical picture and the serologic findings for lupus. However, a low pleural ANA in a patient with SLE would argue for another cause for the effusion.[112]

Treatment. The pleuritis with systemic lupus responds to corticosteroid administration. It is recommended that patients with lupus pleuritis be treated with oral prednisone, with rapid tapering once the symptoms are controlled. At times, the effusion is large, is symptomatic, and does not respond to corticosteroid therapy. In such a situation, consideration should be given to chemical pleurodesis. Of

course, if the patient has drug-induced lupus, the offending drug should be withdrawn.

Immunoglobulin G4–Related Pleuritis

First reported in Japan in 2001,[264] IgG4-related disease is a systemic condition that can involve the lung and the pleura. It manifests as a fibroinflammatory disorder with IgG4-positive plasma cell infiltration into tissues. Pleural masses, pleuritis, and pleural effusion can be part of the disease or present by themselves, although pleural effusion appears in less than 5% of patients with this condition.[265] Despite its rarity, the reason to consider it is that IgG4-related pleural effusion presents as a lymphocytic exudate, often with a positive ADA, and thus can be mistaken for a tuberculous effusion.[117] In one retrospective study of idiopathic pleural effusions in Japan, IgG4 staining was positive in 34%, suggesting that, at least in Japan, this entity may account for one-third of otherwise undiagnosed effusions. The diagnosis requires a pleural biopsy showing plasma cell infiltration and staining positively for IgG4. Serum and pleural fluid levels of IgG4 may or may not be elevated.[266] Criteria for the diagnosis of respiratory disease have been published.[267] The condition responds to corticosteroids.[266] Its incidence and prevalence outside of Japan is unknown.

Sarcoidosis

The prevalence of pleural effusion with sarcoidosis (see Chapter 93) is about 1%.[268,269] Patients with pleural effusion due to sarcoid usually have extensive parenchymal sarcoidosis and frequently extrathoracic sarcoidosis[268] (Fig. 108.8). The symptoms of pleural involvement with sarcoidosis vary; many patients have no symptoms, although an equal number have pleuritic chest pain or dyspnea.

The pleural effusions with sarcoidosis are usually small and are bilateral in approximately one-third of cases. The pleural fluid is almost always an exudate, and its cell differential is characterized by predominantly small lymphocytes.[268,269] In the patient with known sarcoidosis, one can attribute the presence of the pleural effusion to sarcoid only when other causes of exudative lymphocyte-predominant pleural effusions, such as tuberculosis, are excluded.[270] The pleural effusion secondary to sarcoidosis may resolve spontaneously, or may require corticosteroid therapy for its resolution.

Asbestos-Related Disease

An otherwise unexplained pleural effusion may result years after exposure to asbestos, which may have been brief or intermittent, and in the immediate or distant past. Epler and coworkers[271] reviewed the medical histories of 1135 asbestos workers whom they had followed for several years and found that 35 (3%) of the workers had pleural effusions for which there was no other ready explanation. In general, the heavier the asbestos exposure, the more likely the patient is to develop a pleural effusion. The pleural effusion sometimes develops within 5 years of the initial exposure but, in one large series, the mean latency was 30 years.[272]

The pathogenesis of the pleural effusion arising after asbestos exposure is unknown.[273] Asbestos fibers, both long and short, move from the lung to the pleural space and lodge in the parietal pleura, where they appear to be concentrated in specific locations that correlate with lymphatic drainage.[274] Here their presence leads to a continuous low-grade inflammation. Now, with the ability to test different lengths of man-made nanotubes, it has been shown that the length of the fiber is important, presumably because the longer fibers are preferentially retained in the pleural space.[275] This chronic inflammation can either decrease the lymphatic clearance of the pleural space or increase the permeability of the capillaries in the parietal pleura, either of which could lead to the development of an exudative pleural effusion. An immune mechanism has been invoked to explain the fluctuations in the degree of pleuritis with time.[272]

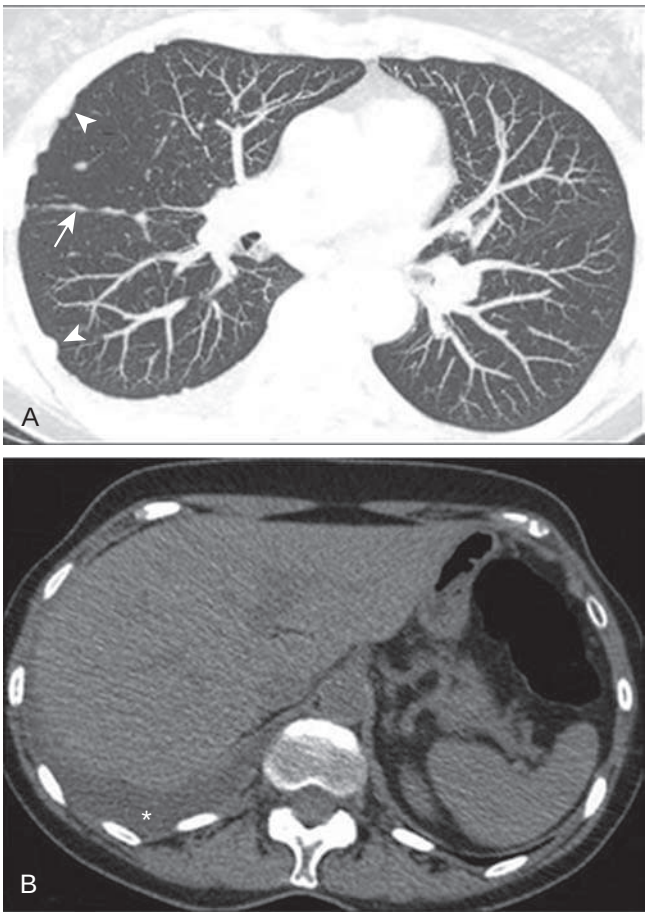

Figure 108.8 Sarcoidosis with pleural effusion. (A) Axial unenhanced maximum intensity projected computed tomography shows subpleural nodules along the costal (*arrowheads*) and fissural (*arrow*) pleural surfaces, consistent with the perilymphatic distribution of nodules in sarcoidosis. (B) Axial computed tomography through the lung bases displayed in soft tissue windows shows a small right pleural effusion (*asterisk*); biopsy of the pleura showed noncaseating granulomas. (Courtesy Michael B. Gotway, MD.)

Clinical Manifestations. Patients with pleural effusion secondary to asbestos exposure have surprisingly few symptoms. In the series of Epler and coworkers,[271] 66% had no symptoms. The chest radiograph usually reveals a small- to moderate-sized effusion, which is bilateral in about 10%. The pleural fluid is an exudate, and the pleural fluid differential can reveal either predominantly polymorphonuclear leukocytes or mononuclear cells. Of interest, pleural fluid eosinophilia was present in 15 (52%) of the 29 patients with asbestos pleural effusions for whom pleural fluid differentials were reported.[47]

Diagnosis. The diagnosis of benign asbestos effusion is one of exclusion. It requires the following criteria: history of direct or indirect exposure to asbestos; exclusion of other causes, notably infection, PE, and malignancy; and follow-up of at least 2 years to verify that the effusion is benign.[272] Biopsies via CT guidance or by medical thoracoscopy are useful to exclude mesothelioma and other potentially treatable conditions.[276]

Prognosis. The natural history of the patient with an asbestos pleural effusion is one of chronicity, with frequent recurrences and sometimes the development of extensive fibrosis of the parietal pleura.[271] On average, the pleural effusion persists for 3 months but eventually clears and leaves no residual pleural disease. Massive pleural fibrosis can develop in about 20% of patients, with ipsilateral blunting of the costophrenic angle in another 20%.[271] Rounded atelectasis also develops in about 10% of patients. There is no known treatment for asbestos pleural effusion. Further information about asbestos-induced lung disease is provided in Chapter 101.

Uremia

Uremia may be complicated by a fibrinous pleuritis and pleural effusion.[37] The pathogenesis of the pleural effusion associated with uremia is unclear. It is probably somewhat analogous to that for uremic pericarditis because more than half of the patients with uremic pleuritis also have uremic pericarditis (eFig. 108.9). The incidence of pleural effusions with uremia is approximately 3%, and there does not seem to be a close relationship between the degree of uremia and the presence of an effusion.[277] When patients are on chronic hemodialysis, the incidence of pleural effusion is high; with CT scanning, the incidence of pleural effusion in patients on chronic hemodialysis has been shown to be approximately 50%.[278] The etiologies of 100 effusions seen in hospitalized patients with uremia on hemodialysis in one study were as follows: heart failure, 46; uremia, 16; parapneumonic, 15; atelectasis, 11; and miscellaneous, 12.[279] In another study of 76 patients with effusions on hemodialysis, uremia was considered the cause in 24%, with parapneumonic effusion (24%) and CHF (20%) also common.[280]

The pleural effusion seen with uremia may occupy greater than 50% of the hemithorax and is bilateral in about 20% of patients.[277] Greater than 50% of patients are symptomatic from the pleural disease, with fever (50%), chest pain (30%), cough (35%), and dyspnea (20%) being the most common symptoms. The pleural fluid is an exudate that is frequently serosanguineous or bloody. The differential white blood cell count reveals predominantly lymphocytes.[277] Pleural biopsy specimens invariably reveal chronic fibrinous pleuritis.

The diagnosis of uremic pleuritis is one of exclusion in the patient with chronic renal failure. After beginning dialysis, the effusion gradually disappears within 4 to 6 weeks in about 75% of patients. In the remaining patients, the effusion persists, progresses, or recurs. An occasional patient develops marked pleural thickening that may require decortication[281] (see Chapter 112).

Post–Cardiac Injury Syndrome

Post–cardiac injury syndrome (PCIS), also known as postpericardiectomy or post–myocardial infarction (Dressler) syndrome, is characterized by combinations of pericarditis, pleuritis, and pneumonitis that develop after injury to the myocardium or pericardium.[282,283] In one report, noncomplicated PCIS was defined as the presence of temperature greater than 100.5°F, patient irritability, pericardial friction rub, and a small pericardial effusion with or without pleural effusion after cardiac trauma; a complicated PCIS was defined as a noncomplicated PCIS plus the need for hospital readmission with or without the need for pericardiocentesis or thoracentesis.[284] Imazio and colleagues[285] have recently defined PCIS as the presence of at least two of the following: fever without alternative explanation, pleuritic chest pain, pericardial friction rub, new or worsening pleural effusion, and new or worsening pericardial effusion. PCIS has been described after myocardial infarction (eFig. 108.10), cardiac surgery, blunt chest trauma, percutaneous left ventricle puncture, implantation of a pacemaker, and catheter ablation of arrhythmias.[282,286] The incidence of PCIS is approximately 1% after myocardial infarction and is somewhat higher after cardiac surgery.[37] The exact pathogenesis of this syndrome is unknown, but it appears to have an immunologic basis.

Clinical Manifestations. The syndrome typically develops about 3 weeks after the injury, but it can happen any time between 3 days and 1 year. The two cardinal symptoms are fever and chest pain. The chest pain often precedes the onset of fever and can vary from an agonizing crush to a dull ache. At times, it may have a pleuritic component. Most patients have a pericardial friction rub. Pulmonary opacities are present in about 50% of patients, and laboratory evaluation reveals leukocytosis with an elevated erythrocyte sedimentation rate.

A pleural effusion arises in about two-thirds of patients with PCIS.[282] The pleural effusions are bilateral and small in most patients. The pleural fluid is an exudate that is frequently serosanguineous or bloody. The pleural fluid differential may reveal either predominantly polymorphonuclear leukocytes or mononuclear cells, depending on the acuteness of the process.[282]

Diagnosis. The diagnosis of PCIS should be considered in any patient who develops a pleural effusion after injury to the heart. The diagnosis of the syndrome is established by the clinical picture and by excluding CHF, PE, and pneumonia.

Treatment. PCIS usually responds to treatment with antiinflammatory agents, such as aspirin, colchicine or indomethacin. Corticosteroids may be necessary in more severe cases.

Post–Coronary Artery Bypass Surgery

Although it is less commonly performed due to less invasive options, *coronary artery bypass graft* (CABG) surgery is the most commonly performed cardiac surgery in the world, with 200,000 cases in the United States each year.[287] Because approximately 10% of patients who undergo CABG surgery will develop a pleural effusion occupying greater than 25% of their hemithorax in the subsequent month,[288] CABG surgery is one of the more common causes of pleural effusions in the United States. The prevalence of small pleural effusions is high after CABG surgery. In one study, the prevalence of pleural effusions in 47 patients as detected by ultrasound was 89% at 7 days, 77% at 14 days, and 57% at 30 days.[289] In a study of 349 patients post-CABG, the

prevalence of pleural effusion on chest radiograph 30 days postoperatively was 62%; 40 of the 349 patients (11%) had an effusion occupying greater than 25% of the hemithorax.[288] The pleural effusions after CABG surgery tend to be left sided or bilateral, and if bilateral, the effusion is usually larger on the left.[288] They are a frequent cause for readmission to hospital.[290]

The primary symptom of a patient with a large pleural effusion post-CABG is dyspnea.[288] The presence of either chest pain or fever should alert the physician to an alternative diagnosis. When all patients with large pleural effusions after CABG surgery are considered, the effusions can be divided into those that are bloody and those that are serous. The bloody effusions are caused by bleeding into the pleural space; they reach their maximal size within 30 days of surgery, are frequently associated with pleural fluid or peripheral eosinophilia or both, have a high pleural fluid LDH level, and respond to one or two therapeutic thoracenteses.[291] In contrast, the cause of the serous pleural effusions is unknown. They tend to reach their maximal size more than 30 days after surgery, have greater than 50% small lymphocytes, and have a relatively low pleural fluid LDH level.[291] Most of these late effusions can also be managed with one or two therapeutic thoracenteses,[288] but some are refractory. It is unknown whether anti-inflammatory agents or diuretics are beneficial in the treatment of these effusions. A placebo-controlled, double-blind, randomized study of 360 patients undergoing cardiac surgery compared the effectiveness of colchicine with placebo in preventing postoperative effusions.[292] These investigators reported that the patients who received colchicine had a significantly lower incidence of pleural effusion (12.2% vs. 26.5%) and a significantly lower incidence of pericardial effusion (12.8% vs. 22.8%).

Drug-Induced Pleural Disease

Lupus-like syndromes arise in conjunction with the administration of many different medications, as discussed earlier in this chapter and in Chapter 99. Although many drugs have been associated with pleural disease,[296] several drugs are particularly well known to induce pleural disease, including nitrofurantoin, dantrolene, methysergide, and ergot drugs. Less common drugs include procarbizine and amiodarone. Newer drugs, such as IL-2 and dasatinib (a broad inhibitor of tyrosine kinases) cause pleural effusions.[297] In general, one should consider a drug etiology for every patient with an undiagnosed exudative pleural effusion. Referring to pneumotox.com can be helpful, especially for newer drugs without published reports. At the time of this writing, 100 drugs are listed on pneumotox.com as causing pleural effusions.

A discussion of some of these drugs is available at ExpertConsult.com.

Other Inflammatory Diseases

Pleural effusions occasionally develop in the course of EGPA (see eFig. 96.5), granulomatosis with polyangiitis, and Sjögren syndrome, which are described in detail in other chapters. Pleural effusions are found in most patients with acute eosinophilic pneumonia (see eFig. 96.4). The pleural disease seen with these diseases constitutes a relatively minor portion of the clinical picture.

MISCELLANEOUS

Lung Transplantation

With lung transplantation, the lymphatics that normally drain the lung are severed. In accordance, the fluid that normally exits the lung via these lymphatics may then exit into the pleural space. The presence of chest tubes in the first few days after lung transplantation prevents the accumulation of pleural fluid. Pleural complications such as hemothorax, empyema, and persistent air leak contribute substantially to the postoperative morbidity and mortality. The incidence of pleural effusions at 3 months posttransplantation is about 30–60%.[306,307] The incidence of effusion at 12 months is less than 10%.[307] The effusions are characteristically a lymphocyte-predominant exudate with a benign course.[306] However, patients who develop complications after lung transplantation are likely to develop pleural effusions. In one study, pleural effusions were seen with 74% of 19 episodes of acute rejection, 88% of 8 instances of chronic rejection, 55% of 11 episodes of infection, and 75% of 4 instances of lymphoproliferative disease.[308] Late effusions may also form due to constrictive pericarditis.[309] (More details about lung transplantation are provided in Chapter 140.)

Meigs Syndrome

Meigs and Cass[310] originally described a syndrome characterized by ascites and pleural effusion in association with solid benign ovarian tumors. Subsequently, it has become apparent that a similar syndrome can be seen with benign cystic ovarian tumors, with benign tumors of the uterus (fibromyomas), and with low-grade ovarian malignant tumors without evidence of metastases.[37] The ascites appears to result from the secretion of large amounts of fluid by the tumors. VEGF may play an important role in the pathogenesis of the ascites and pleural fluid because VEGF levels are high in both the ascites and pleural fluid.[311] It is thought that the pleural effusion results from the ascitic fluid passing through defects in the diaphragm into the pleural space, usually on the right side.

Patients with Meigs syndrome usually have a chronic illness characterized by weight loss, pleural effusion, ascites, and a pelvic mass. It is important to realize that not all patients with this constellation of symptoms have a disseminated malignancy. Approximately 70% of the effusions are right sided, and 20% are bilateral. The pleural fluid is usually an exudate with a relatively low white blood cell count (<1000/μL) and occasionally is bloody.[312] The level of cancer antigen-125 in the pleural fluid may be elevated and should not be taken as an indication of malignancy.[311]

The diagnosis of Meigs syndrome should be considered in all women who have a pelvic mass, ascites, and a pleural effusion. If the cytology of the pleural fluid is negative in such patients, a diagnostic laparoscopy or an exploratory laparotomy should be performed to determine whether there are peritoneal metastases. The diagnosis is confirmed when the ascites and the pleural fluid resolve after the primary neoplasm is removed and do not recur. The pleural fluid disappears from the chest within the first 2 weeks after surgery.

Nitrofurantoin. Pleuropulmonary reactions occasionally result from the administration of nitrofurantoin. Such reactions can have an acute or a chronic presentation.[298] The acute presentation is seen within 1 month of initiation of therapy and is manifested by dyspnea, nonproductive cough, and fever. About 20% of patients have an opacity and an effusion, and about 3% have only an effusion. Most patients have both peripheral eosinophilia (>350/μL) and lymphopenia (<1000/μL).[299] The chronic syndrome is seen when the patient has been taking nitrofurantoin for 2 months to 5 years and is much less common than the acute syndrome. Pleural effusion develops in less than 10% of patients, and no patient with the chronic syndrome has had a pleural effusion without an opacity.[298]

The diagnosis of nitrofurantoin pleuropulmonary reaction should be suspected in all patients with a pleural effusion who are taking nitrofurantoin. If the drug is discontinued, the patient usually improves clinically within 1 to 4 days, and the chest radiograph becomes normal within a week with the acute syndrome, whereas the time course is much longer for the chronic syndrome.[298]

Dantrolene. Dantrolene sodium is a long-acting skeletal muscle relaxant with a chemical structure similar to that of nitrofurantoin. Its administration can lead to the development of pleural or pericardial disease.[300] The pleural effusion is unilateral and develops 2 months to 12 years after the initial administration of dantrolene. Patients may be febrile and may have pleuritic chest pain. The pleural fluid is an eosinophilic exudate with a normal glucose level.[300] When dantrolene is discontinued, the patient improves symptomatically within days, but it may take several months for the pleural effusion to resolve completely.

Methysergide. The administration of methysergide can lead to a pleuropulmonary disease similar to that seen with nitrofurantoin.[301] Symptoms consisting of chest pain, dyspnea, and fever develop 1 month to 3 years after methysergide therapy is initiated. The chest radiograph commonly shows bilateral loculated pleural effusions and pleural thickening.[301] When methysergide is discontinued, the symptoms of the patients improve. However, in one series of 13 patients, severe pleural fibrosis persisted in two patients who had continued to take the drug for the longest period (18 and 36 months, respectively) after the onset of the pleurisy.[301]

Ergot Alkaloids. The administration of ergot alkaloid drugs, such as bromocriptine, ergotamine, dihydroergotamine, nicergoline, pergolide, and dopergine, in the long-term treatment of Parkinson disease can lead to pleuropulmonary changes.[296] As of 1988, a total of 23 patients had been reported. All the patients were men, and the drug had been taken for 6 months to 4 years before symptoms developed. From 2–5% of patients receiving long-term ergot alkaloid therapy develop pleuropulmonary disease. The incidence of pleural disease is higher if the patient has previous exposure to asbestos.[302] The chest radiograph reveals unilateral or bilateral pleural thickening or effusion in most patients. Analysis of the pleural fluid reveals an exudate with predominantly lymphocytes and frequently eosinophilia.[303] The natural history of pleuropulmonary disease during ergot alkaloid therapy is unclear. The disease progresses only in some of the patients who continue taking the drug.[303]

Procarbazine. There have been two detailed case reports of pleuropulmonary reactions consisting of chills, cough, dyspnea, and bilateral pulmonary opacities with pleural effusion after treatment with procarbazine.[37] In both cases, symptoms developed within hours after procarbazine therapy; in both instances, rechallenge with procarbazine again produced the opacities and pleural effusions. With discontinuation of the drug, the symptoms and radiographic changes resolved within several days.

Amiodarone. Amiodarone is an antiarrhythmic that may produce severe pulmonary toxicity. Pleural effusions are seen as a manifestation of amiodarone toxicity, but they are uncommon. Most cases have concomitant parenchymal involvement, but cases have been reported in which there is none.[296] The pleural fluid is an exudate and may have predominantly lymphocytes, macrophages, or polymorphonuclear leukocytes.[296]

Interleukin-2. Recombinant IL-2 is sometimes used in the treatment of malignancies, especially melanoma or renal cell carcinoma. One of the primary side effects of IL-2 administration is the development of pulmonary opacities and pleural effusion that are probably related to a generalized capillary leak syndrome.[37] The incidence of pleural effusion after IL-2 administration is approximately 50%.[296] The characteristics of the pleural fluid have not been described. After the IL-2 therapy is stopped, the effusions tend to disappear. However, in one study 17% of patients still had a pleural effusion 4 weeks after cessation of therapy.[304]

Dasatinib. Dasatinib, an inhibitor of multiple tyrosine kinase inhibitors, is used primarily for treating adults with chronic myeloid leukemia with resistance to prior therapy. Use of dasatinib is associated with a high incidence of pleural effusion.[297] Quintas-Cardama and associates[305] reported that the effusion developed in 35% of 135 patients receiving the drug and about half the effusions occupied more than 25% of the hemithorax. The effusions were bilateral in 80% of the patients. The effusions were mostly exudates. The effusions resolved when dasatinib was discontinued or when steroids were administered. The effusions are less common when dasatinib is administered once rather than twice per day.

Endometriosis

An occasional patient with severe endometriosis presents with massive ascites. In one review, 10 of 27 patients (37%) also had a pleural effusion.[313] The effusions are usually right sided but may be bilateral. The pleural fluid is a bloody or a chocolate-colored exudate. The serum carcinoembryonic antigen level may be elevated, suggesting ovarian carcinoma. Hormonal therapy, including gonadotropin-releasing hormone agonists, may be attempted, but frequently it is ineffective, and many patients require total abdominal hysterectomy plus bilateral salpingo-oophorectomy.[313]

Ovarian Hyperstimulation Syndrome

This syndrome is a serious complication of ovulation induction. The dramatic clinical picture is characterized by massive ovarian enlargement with multiple cysts, hemoconcentration, and the third-space accumulation of fluid.[311] The full-blown syndrome may be complicated by renal failure, hypovolemic shock, thromboembolic episodes, acute respiratory distress syndrome, and death. Although the pathophysiology of this syndrome is incompletely understood, it is likely that the increased capillary permeability is due to the upregulation of VEGF expression in the ovarian granulosa cells by the exogenous human chorionic gonadotropin.[311]

Patients with the syndrome present within 2 to 3 weeks of receiving the human chorionic gonadotropin. Patients typically present with abdominal pain and distention, nonproductive cough, and dyspnea caused by the ascites, pleural effusion, or both. The pleural effusion is usually right sided, and the pleural fluid is most often exudative with predominantly neutrophils and a relatively low LDH level.[314] The treatment of severe cases requires restoration of intravascular volume, correction of electrolyte abnormalities, and venous thromboembolism prophylaxis.[311]

Trapped Lung (See Chapter 112)

Effusions that are remarkably stable over time, that recur after thoracentesis, and that are resistant to diagnosis may be due to an underlying trapped lung (Fig. 108.9). After an earlier episode of inflammation, a fibrous peel may form over the visceral pleura and can prevent the underlying lung from expanding fully, thereby "trapping" the underlying lung. The resulting negative pleural pressure leads to the development of a chronic pleural effusion.[315,316]

Patients with a chronic pleural effusion secondary to trapped lung are often asymptomatic but may have symptoms of dyspnea. Symptoms of acute pleural inflammation, such as pleuritic chest pain and fever, are distinctly uncommon, but the patient often gives a history of such events in the past. One characteristic of the pleural effusion secondary to trapped lung is that the amount of fluid is quite constant from one study to another. With trapped lung, the pleural fluid is often a borderline exudate; the ratio of pleural fluid to serum protein is about 0.5, and the ratio of pleural fluid LDH to serum LDH is about 0.6.

The diagnosis of pleural effusion secondary to trapped lung should be suspected in any patient with a stable, chronic pleural effusion, particularly if the patient has a history of uremia, thoracic radiation, pancreatitis, collagen-vascular disease or prior thoracic surgery.[316,317] The thickened visceral pleura can be demonstrated if 200 to 400 mL of air is injected into the pleural space at the time of a thoracentesis. At some institutions, pleural manometry is used routinely during a therapeutic thoracentesis; if the pleural pressure falls rapidly (greater than 14 to 15 cm H_2O/L pleural fluid removed), air is allowed to enter the pleural space to return the pleural pressure to a more normal range (−5 cm H_2O) so that an air-contrast chest CT scan can be obtained to evaluate the visceral pleura.[316]

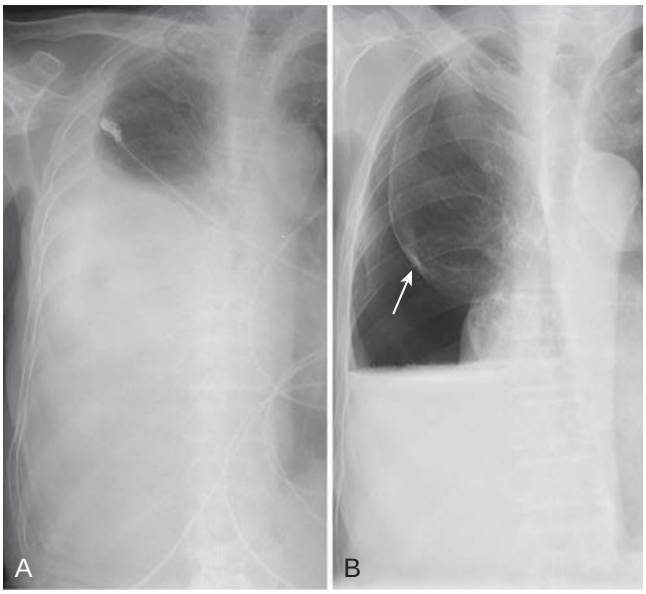

Figure 108.9 Effusion with trapped lung. (A) Frontal chest radiograph shows a large right pleural effusion. (B) On a subsequent radiograph, the effusion has been partially drained, revealing the underlying lung with some visceral pleural thickening (*arrow*). The lung failed to reexpand despite negative intrapleural pressures. The intrapleural air likely entered the pleural space from the atmosphere along the drainage track. (Courtesy Michael B. Gotway, MD.)

For symptomatic patients, decortication can be considered but is considered major surgery and may not benefit the patient, especially if the underlying lung is also diseased. If the patient is asymptomatic or minimally symptomatic, the patient can be observed if the clinical picture, pleural fluid findings, and pleural pressure measurements are all compatible with the diagnosis of trapped lung.

Yellow Nail Syndrome

This syndrome consists of the triad of deformed yellow nails, lymphedema, and pleural effusions.[318] The three entities may manifest at widely disparate times and therefore are not all present in every patient at the same time. The basic abnormality responsible for this syndrome appears to be hypoplasia of the lymphatic vessels[319,320] or a decrease in function of lymphatics.[321] The onset of the condition is after puberty (mean age of onset was 53 in one study[322] and 61 in another[323]). The condition may be acquired[322] and may resolve without treatment.[322]

Typically, the nails are pale yellow to greenish in color and are excessively curved from side to side (eFig. 108.11). They are also thickened and may show transverse ridging or onycholysis (separation of nail from bed). The pleural effusions are bilateral in about 50% of cases and can be massive; chylothoraces are also described.[318] Once a pleural effusion has developed with this syndrome, it tends to persist and to recur rapidly after thoracentesis.[319] The pleural fluid is usually an exudate with predominantly lymphocytes.[319] The

pleural fluid LDH tends to be relatively low relative to the pleural fluid protein level.[37]

The diagnosis is usually established by the presence of the triad of pleural effusion, lymphedema, and yellow nails. The diagnosis may be difficult to establish if the pleural effusion is the first manifestation of the syndrome. There is no specific treatment for the syndrome but, if the effusion is large and is producing symptoms, the effusion can be treated with pleurodesis.[37] Some reports suggest that treatment of associated bronchiectasis or rhinosinusitis can ameliorate the syndrome.[324,325]

Misplaced Catheters

Both internal jugular and subclavian vein catheterization can be complicated by misplacement of the catheter tip into the mediastinum or pleural space that results in a large unilateral (eFig. 108.12) or bilateral pleural effusion. The pleural fluid may have the characteristics of the intravenous fluid, or it may be bloody from laceration of the blood vessels.[213] If the patient is receiving lipids through a central line, the fluid may look chylous.[326] The diagnosis of a misplaced central venous catheter should be considered in all patients with such lines who rapidly develop pleural effusions, and the patients should be evaluated by diagnostic thoracentesis.

In the past several years, the development of soft, flexible, small-bore polyurethane feeding tubes has made nasogastric and nasoenteric feeding more practical and comfortable for patients. However, misplacement of these tubes can lead to serious pleural complications. Pneumothorax is the most common complication, but infusion of the enteral formula into the pleural space or the development of an empyema, or both, are also common.[327] These small flexible tubes are inserted with a stylet in place that enables easier advancement of the device. However, with the stylet in place, the tubing becomes stiff enough that it can perforate structures relatively easily. The risk is much greater if the patient has an endotracheal tube in place or is obtunded.[327] To prevent these complications, these tubes should be inserted only by experienced persons, and the tube should be immediately removed if the patient starts coughing. The tube should not be advanced if resistance is felt and, before feeding is initiated, the position of the tip of the tube should be confirmed radiographically.[328] If enteral solutions enter the pleural space, tube thoracostomy should be performed to remove the solution. In addition, the patient should be carefully observed for the development of an empyema.[327]

Key Points

- Transudates usually result from systemic changes in hydrostatic and/or osmotic pressures that lead to collection of a relatively low protein and *lactate dehydrogenase* (LDH) fluid (pleural/serum protein ratio < 0.5 *and* pleural/serum LDH < 0.6 *and* LDH less than two-thirds the upper limit of normal (Light's criteria).
- Transudates with a very low protein concentration (<0.5 g/dL) come from entry of cerebrospinal fluid, urine, peritoneal dialysis fluid, or intravenous fluids into the pleural space.
- Exudates result from pleural or extrapleural injury or inflammation due to a multitude of inflammatory, infectious, or malignant diseases, leading to an effusion with a relatively high protein and/or LDH concentration.
- Most transudates arise from *congestive heart failure* (CHF). When the cause is unclear or when the protein and LDH ratios are not clearly transudative, as can happen after diuresis, the pleural fluid *N-terminal pro–brain natriuretic peptide* (NT-proBNP) is a sensitive and specific marker for a cardiac etiology.
- Most exudates arise from either pneumonia, malignancy, or pulmonary embolism.
- Many effusions have multiple etiologies, often with CHF included. Pleural fluid NT-proBNP (>1500 pg/mL) can help identify an underlying contribution from CHF.
- Pleural fluid chemistries may be indeterminate, meaning not clearly transudative or exudative, a situation that may point to more than one etiology or to changes to a pleural effusion caused by diuresis.
- Pleural fluid glucose is as useful as pH but is an easier and a more reliable test.
- Pleural fluid and pleural cytology now have the potential for clinically useful molecular testing: detection of lung cancer treatment targets (epidermal growth factor receptor–activating mutations, programmed death ligand-1), metagenomics for bacterial and viral infection, and molecular testing for tuberculosis. The clinical role for these tests is evolving.
- No diagnosis is ever established for approximately 30% of all exudative pleural effusions, even after thoracoscopic biopsies, and many resolve spontaneously, leaving no residua. The degree to which a diagnosis is pursued by invasive procedures will depend on (1) the symptoms and the clinical course of the patient, (2) the trend of the pleural fluid LDH level with time, and (3) the eagerness of the patient for a diagnosis. Follow-up of such patients is warranted because 10–15% of these patients can later develop cancer.

Key Readings

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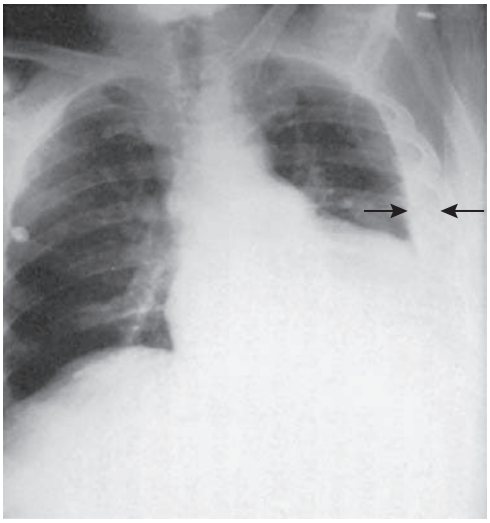
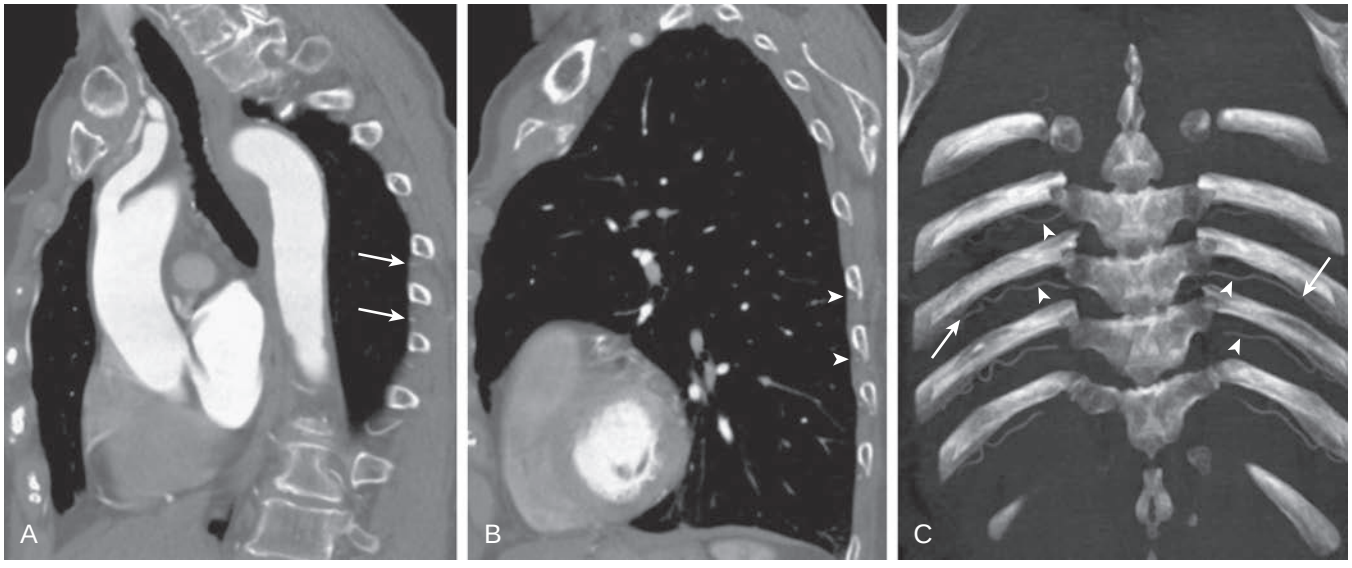
Complete reference list available at ExpertConsult.com.

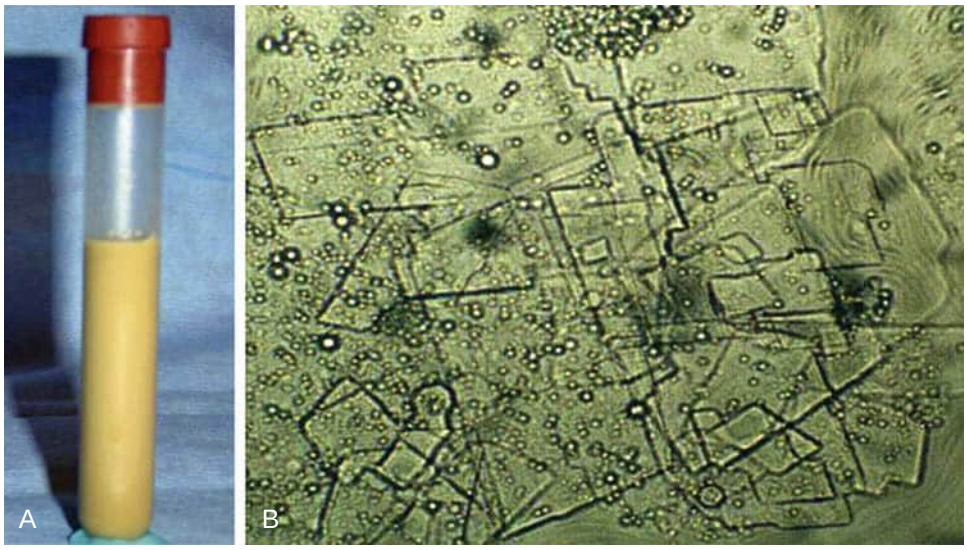
eFIGURE IMAGE GALLERY



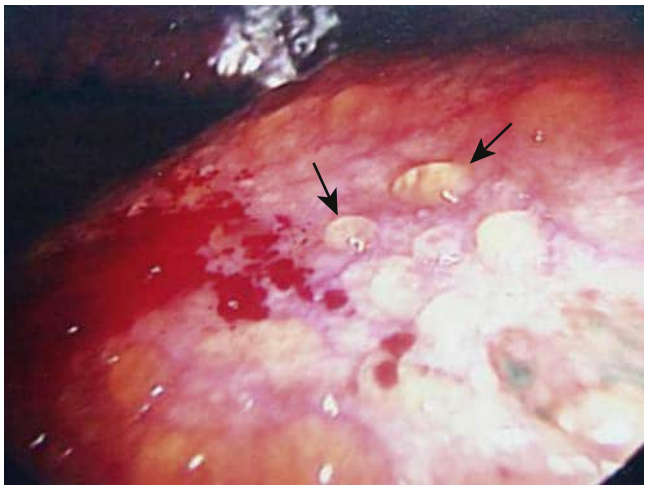
eFigure 108.1 Left lateral decubitus chest radiograph demonstrating the presence of free pleural fluid. The amount of pleural fluid can be semiquantified by measuring the distance between the two *arrows*.



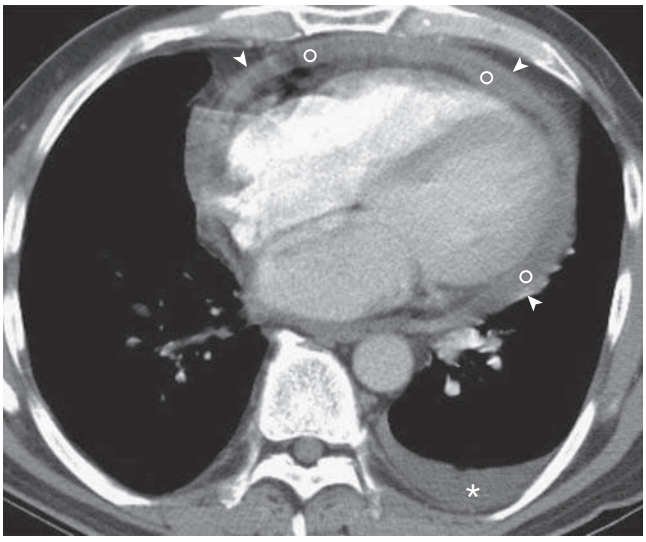
eFigure 108.2 Intercostal arterial anatomy at enhanced thoracic *computed tomography* (CT). Sagittal enhanced chest CT centrally (A) and more peripherally (B) shows the presence of the intercostal arteries positioned in the middle of the intercostal space (*arrows,* A) compared with the position along the inferior margin of the rib more laterally (*arrowheads,* B). (C) Coronal maximum intensity projected enhanced CT image shows the courses of the intercostal arteries, positioned in the middle of the intercostal space medially (*arrowheads*) and along the inferior margin of the rib more laterally (*arrows*). (Courtesy Michael B. Gotway, MD.)



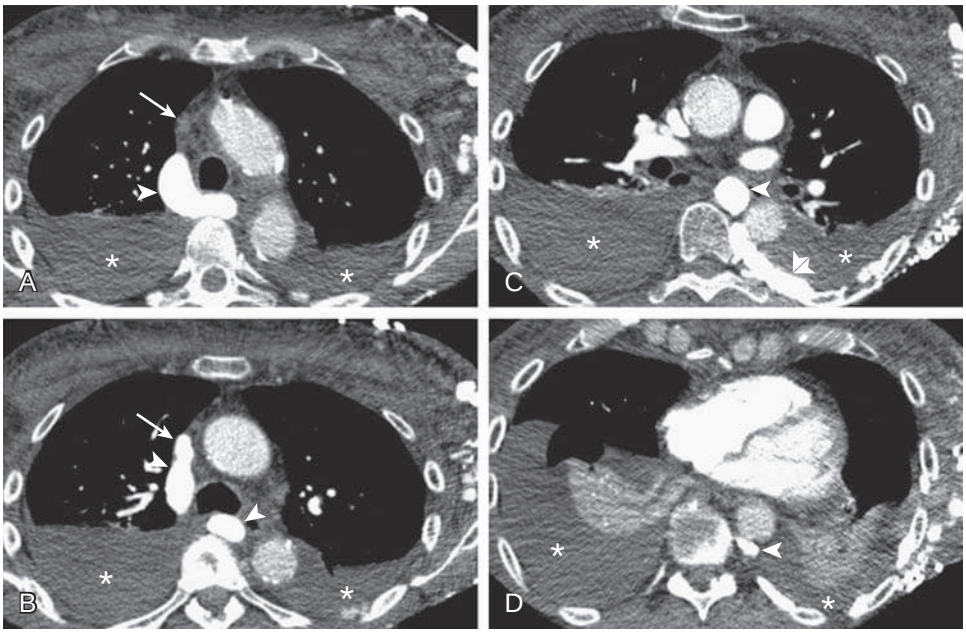
eFigure 108.3 Pleural fluid from a patient with pseudochylothorax. (A) The milky appearance of the pleural fluid persisted after the centrifugation. (B) The presence of cholesterol crystals in microscopic examination of the pleural fluid established the diagnosis. (From Kalomenidis I, Lee YCG. Chylothorax, pseudochylothorax, LAM, and yellow nail syndrome. In: Laurent GJ, Shapiro SD, eds. *Encyclopedia of Respiratory Medicine.* Waltham, MA: Academic Press; 2006:392.)



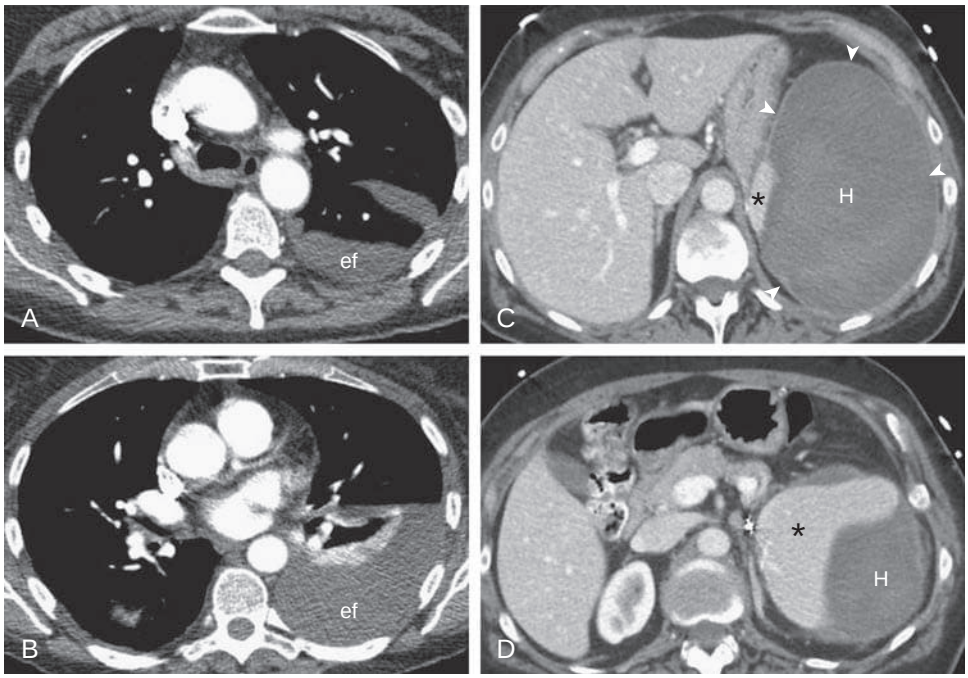
eFigure 108.4 Porous diaphragm in a patient with hepatic hydrothorax. After aspiration of the pleural fluid, the diaphragm can be seen to be leaking fluid across the surface in many locations as evidence of increased porosity (*arrows*). (From Huang PM, Chang YL, Yan CY, Lee YC. The morphology of diaphragmatic defects in hepatic hydrothorax: thoracoscopic finding. *J Thorac Cardiovasc Surg.* 2005;130:141–145.)



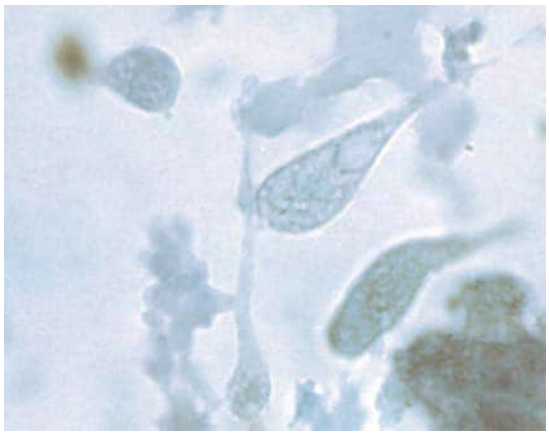
eFigure 108.5 Acute pericarditis with left pleural effusion. Axial enhanced chest computed tomography shows a small pericardial effusion (*open circles*) with smooth thickening of the pericardium (*arrowheads*). A small left pleural effusion (*asterisk*) is present. (Courtesy Michael B. Gotway, MD.)



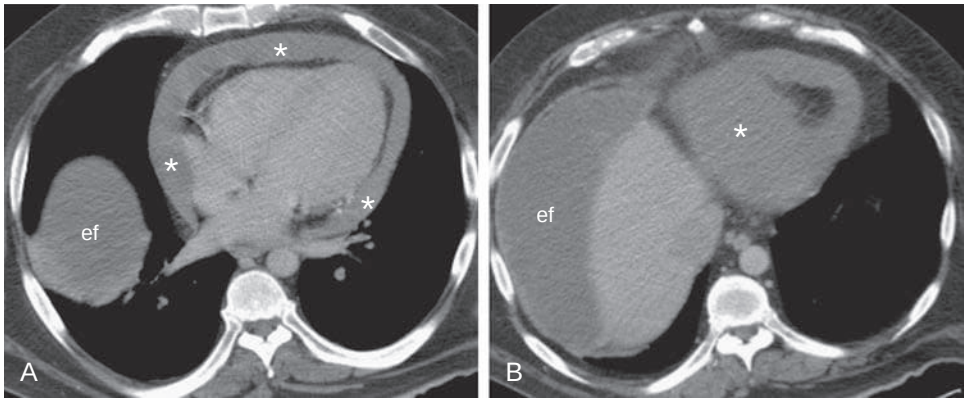
eFigure 108.6 Pleural effusions associated with superior vena caval obstruction. (A–D), Axial enhanced chest computed tomography in a patient with superior vena caval stenosis after central venous catheter placement shows lack of enhancement of the narrowed superior vena cava (*arrow,* A). The superior vena caval stenosis is supraazygos in location, which results in intense enhancement of the azygos vein (*arrowheads*) due to retrograde flow through this vessel into the infraazygos portion of the superior vena cava (*arrow,* B]. Marked enlargement and intense enhancement of left intercostal veins (*double arrowheads,* C), is present. Bilateral pleural effusions (*asterisks*) are present. Extensive edema of the subcutaneous fat bilaterally is visible as well, and intensely enhancing left chest wall collateral veins are also visible. (Courtesy Michael B. Gotway, MD.)



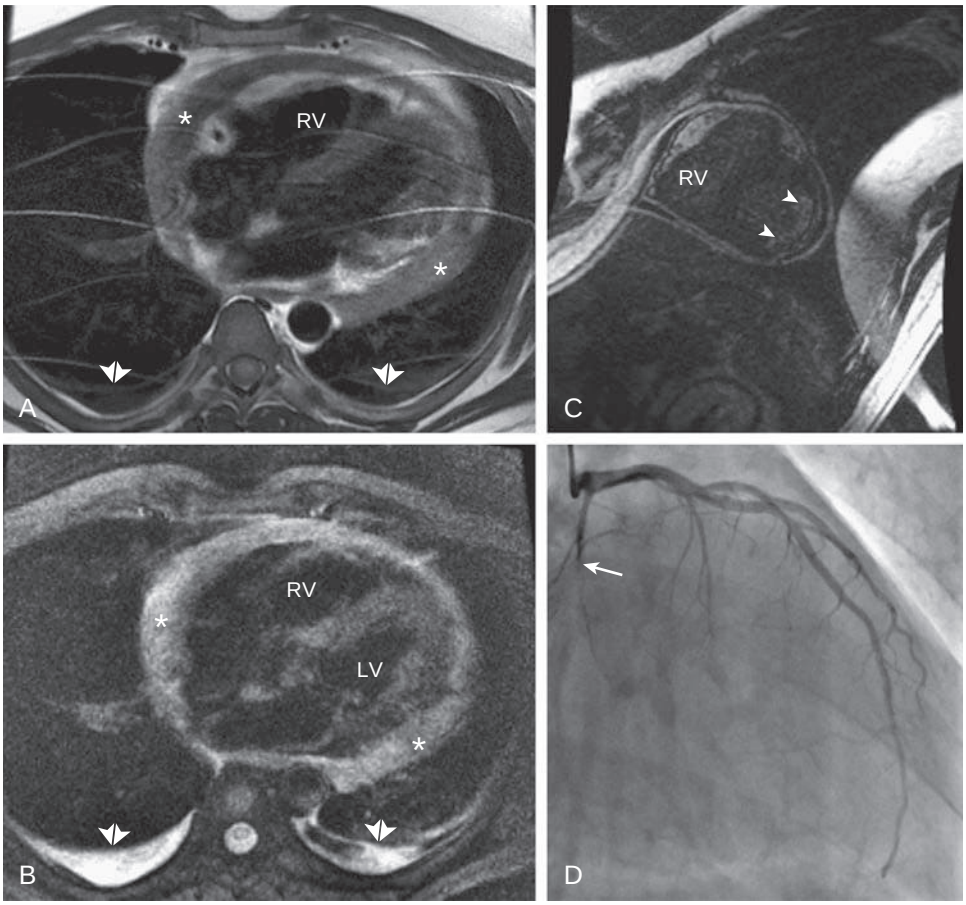
eFigure 108.7 Pleural effusion resulting from intra-abdominal pathology. (A–B) Axial enhanced chest computed tomography shows a moderately large left pleural effusion (*ef*). (C–D) Enhanced abdominal computed tomography shows a large hypoattenuating structure reflecting a subcapsular splenic infected hematoma (*H, arrowheads*). Note that the abnormality compresses and deforms the spleen (*asterisk*). (Courtesy Michael B. Gotway, MD.)



eFigure 108.8 Comet-shaped cell in *rheumatoid arthritis* (RA). Cytologic examination of the pleural fluid of a 33-year-old woman with RA and a right pleural effusion. Papanicolaou stain showed elongated macrophages, with oval nuclei and tadpole-like tails. When seen, this feature, along with a granular amorphous background, has been described as characteristic of RA. (From Brucato A, Tombini V, Guffanti C. Clinical image: comet cells in rheumatoid arthritis. *Arthritis Rheumatol.* 2006;54:243.)



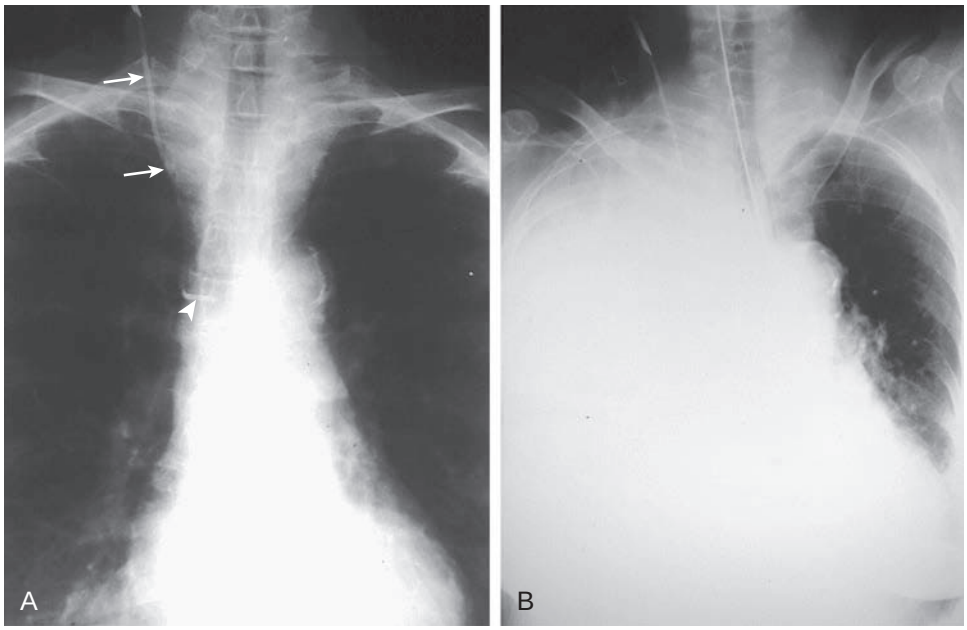
eFigure 108.9 Uremic pleural and pericardial effusions. (A–B) Axial unenhanced chest computed tomography in a patient in renal failure shows a moderate-sized pericardial effusion (*asterisks*) and a loculated right pleural effusion (*ef*). (Courtesy Michael B. Gotway, MD.)



eFigure 108.10 Post–cardiac injury syndrome: pleural and pericardial effusions resulting from recent myocardial infarction. The myocardial infarction was unrecognized, and the patient presented to magnetic resonance imaging with a 3-week complaint of chest pain. Axial double (A) and triple (B) inversion recovery sequences show a moderate pericardial effusion (*asterisks*). Small bilateral pleural effusions (*double arrowheads*) are present. (C) Short-axis segmented, T1-weighted inversion recovery late gadolinium enhancement sequence shows subendocardial enhancement (*arrowheads*) involving the basal and midcavity left ventricular muscle, consistent with myocardial infarction. (D) Catheter coronary angiogram shows occlusion of the left circumflex coronary artery (*arrow*). LV, left ventricle; RV, right ventricle. (Courtesy Michael B. Gotway, MD.)



eFigure 108.11 Nails in a patient with yellow nail syndrome. Nails can be yellow or pale green, are thickened, smooth, and excessively curved from side to side. Nail growth is slow, and the nail may separate from the nail bed (onycholysis). The abnormal nails and the formation of pleural effusions are thought to result from a deficit in lymphatic drainage. (From Habif TP. *Clinical Dermatology: A Color Guide to Diagnosis and Therapy.* 5th ed. Philadelphia: Mosby; 2010.)



eFigure 108.12 Massive pleural effusion due to central venous catheter misplacement. (A) Frontal chest radiograph shortly after right internal jugular venous catheter placement shows the line projected over the expected course of the right internal jugular vein (*arrows*), although the catheter tip takes an unusual medial course inferiorly (*arrowhead*). (B) Frontal chest radiograph performed shortly after the initiation of total parenteral nutrition delivered through the right neck catheter shows development of a massive right pleural effusion, proven to be the result of instillation of total parenteral nutrition fluid into the right pleural space due to the misplacement of the central venous catheter. (Courtesy Michael B. Gotway, MD.)

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109 PLEURAL INFECTIONS

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INTRODUCTION

Of the approximately 1 million patients hospitalized with pneumonia each year in the United States, approximately 60,000 will develop frank empyema.[1] A further 25,000 are estimated to develop pleural infection for other reasons, including trauma and iatrogenic instrumentation.[2,3] The annual estimated hospital cost for treating these cases is in excess of $500 million.[2,3] The morbidity and mortality rates in patients with pneumonia and associated pleural effusions are higher than for those in patients with pneumonia alone, and one study suggested that the increased relative risk for mortality was 3.4 times higher.[4] The incidence of pleural infection has increased globally over the past decades, but despite continued advances in the management of this condition, morbidity and mortality have essentially remained static over the past decade.[5–8]

Bacterial pleural empyema is responsible for the majority of pleural infections, with tuberculous pleuritis common in countries with a high prevalence of tuberculosis.[9,10] Rarer bacterial pathogens, such as *Nocardia* and *Actinomyces,* can also affect the pleural space. Fungal lung infections can be complicated by spread of pathogens to the pleura, with serious consequences. Viruses are likely to be responsible for a significant proportion of undiagnosed pleural effusions, both in association with primary atypical pneumonias and in the absence of parenchymal opacification on chest radiographs. Finally, certain parasitic infections can involve the pleura.

BACTERIAL PLEURAL EMPYEMA

HISTORICAL PERSPECTIVE

Infection of the pleural space is an ancient disease, with the earliest recorded description more than 5000 years ago[11] and the first consistent description of its manifestations and treatment credited to the father of modern medicine, Hippocrates. Open thoracic drainage was the standard treatment for pleural infection before 1918; however, there was a 70% mortality rate associated with this treatment. Following an outbreak of hemolytic streptococcal infections in American military camps in the winter of 1917 to 1918, the U.S. Army Empyema Commission was formed to address the problem. The commission noted that dogs with empyema died more often if they were treated with early open drainage rather than with delayed intervention, and the commission recommended using the closed-tube drainage techniques described by Hewitt and Bülau.[12,13] The commission's summary recommendations were as follows: adequate pus drainage with a closed tube, avoidance of early open drainage, obliteration of the pleural space, and proper nutritional support. A landmark paper by Graham[14] charted the successes seen during this time, with short-term mortality plummeting to 4%. These treatment principles, described almost 100 years ago, remain essentially unchanged to this day. The discovery of penicillin in the 1940s was a major advance that led to a further reduction in mortality. Surgical techniques beyond open drainage were developed in the late 19th century, with thoracoplasty described by Estlander[15] and Schede[16] and with decortication described by Fowler.[17] More recently, however, the introduction of *video-assisted thoracic surgery* (VATS) has meant that increasing numbers of patients undergo this less invasive surgical procedure as the operation of choice for their pleural infection.

INCIDENCE

There have been some reports from the United States, Canada, Europe, and Asia, all showing a dramatic increase in the incidence of pleural infection over the past 2 decades.

This seems to be the case for both children and adults and, although most data are derived from populations in the developed world, this pattern has been replicated around the globe.[4–8,14–16,18–20] The incidence of pleural infection began to rise in the middle to late 1990s. This rather surprising increase was captured by Grijalva and colleagues,[7] who examined the trends in parapneumonic empyema in the United States over a 13-year period and demonstrated a doubling in the rates of empyema hospitalizations between 1996 and 2008, from 3.04 to 5.98 per 100,000. Similar results were demonstrated by a Canadian study, which also confirmed a significant disparity in empyema incidence between persons 65 years of age and older (17 to 20 per 100,000) and those 19 years of age or younger (2 to 4 per 100,000).[5] The finding of a higher incidence in older age groups has been replicated in more recent studies from Finland and Taiwan.[21,22]

Mortality rates from empyema also seem to be on the rise. A study looking at the population of Utah showed a sixfold rise in mortality from the period of 1950 to 1975 to the period of 2000 to 2005.[23] In a large series, inpatients were found to have a mortality up to 18% in the short term,[24] with patients in intensive care experiencing mortality as high as 41%.[25] In a large multicenter trial from the United Kingdom, patients (with an average age of 59 years) were shown to have a mortality rate from 8–20% 1 year after treatment for empyema.[26]

The explanation for the increase in empyema incidence and mortality is not clear. Following the licensing of the heptavalent *pneumococcal conjugate vaccine* (PCV7) for children and infants in 2000, there was concern that nonvaccine serotypes could replace vaccine serotypes in the nasopharynx.[8,27] Because PCV7 did not include the two pneumococcal serotypes commonly responsible for empyema (serotypes 1 and 19A),[27–29] the increase in pleural infection and invasive pneumococcal disease may be explained by this replacement phenomenon. Indeed, genetic sequence typing of pediatric empyema cases in Utah suggested that replacement with serotype 1 pneumococcus was a contributing factor in the increase in incidence following PCV7 introduction.[30]

However, vaccine effects are unlikely to be entirely responsible for the rising incidence of pleural infection, not least because subsequent pneumococcal vaccines (the 13-valent conjugate vaccine and the 23-strain polysaccharide vaccine) included serotypes 1 and 19A. Alternative explanations include aging populations,[31] emergence of new influenza strains causing pandemics,[32] and increasing antimicrobial resistance.[7] Increased detection resulting from wider availability of imaging techniques such as *computed tomography* (CT) may have also contributed.[7,33]

EPIDEMIOLOGY

Pleural infection is seen in patients of all ages but in a bimodal distribution, with a peak in childhood and a second rise in older adults. Men are affected twice as often as women,[34] as illustrated in Fig. 109.1, which shows the age and sex distribution of adult patients in the *Multicenter Intrapleural Sepsis Trial* (MIST) 1 study, the largest cohort in the literature to date.[35] Pleural infection is also more common in persons with diabetes, alcohol dependency or drug addiction, and rheumatoid arthritis.[34,35] Poor dentition and aspiration are also risk factors.[24]

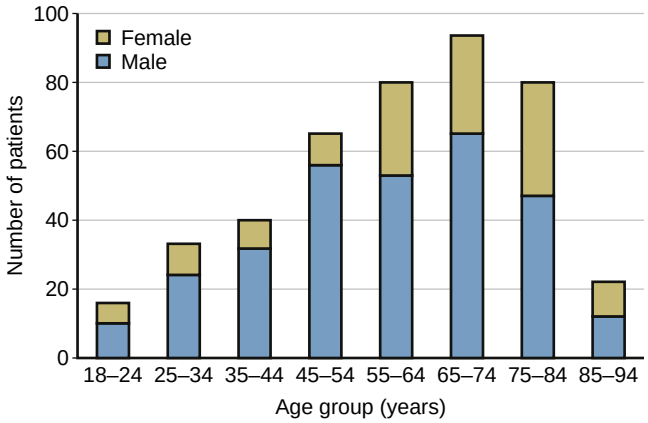

Fig. 109.1 Age and sex distribution of pleural infection in adults in a large UK cohort. The disease is more common in men, and the peak incidence in adults is in the 65- to 74-year age range. (Data from Maskell NA, Davies CW, Nunn AJ, et al. U.K. controlled trial of intrapleural streptokinase for pleural infection. *N Engl J Med.* 2005;352:865–874.)

The underlying etiology of pleural infection is varied, although most cases originate in the community.[36] Often this is a consequence of community-acquired pneumonia; however, many cases show no evidence of consolidation on CT imaging.[37] These cases are thought to have been acquired through hematogenous bacterial spread or by translocation of colonizing bacteria from the oropharynx, with the latter phenomenon being particularly relevant in the intensive care setting.[38,39] In the next largest group of patients, the infection develops in the hospital, often as the result of prolonged hospital admissions for other reasons, or complications following surgery or invasive procedures. For example, pleural infections and other pleural complications are common after lung transplantation.[40] Other potential causes include direct (transdiaphragmatic) spread of abdominal sepsis, blunt or penetrating chest trauma, esophageal perforation, or rupture of a peripheral lung abscess into the pleural space.[35,41,42]

PATHOGENESIS

The evolution of a pleural infection can be divided into three stages, which may overlap. The first, *exudative* stage is characterized by the rapid outpouring of sterile pleural fluid into the pleural space. Some of this fluid likely comes from the interstitial spaces of the lung and some from the parietal pleura due to increased permeability (see Chapter 14). The pleural fluid has a low white blood cell count and *lactate dehydrogenase* (LDH) level, together with a normal glucose level and pH.[43,44] At this stage, chest tube drainage is rarely required, and antibiotics alone should suffice.

The second, *fibropurulent* stage evolves if bacteria invade the sterile exudative effusion. During this stage, there is an accumulation of leukocytes, bacteria, and cell debris together with increased pleural fluid output. Fibrin is deposited over the visceral and parietal pleura, and there is a tendency for loculations to form within the pleural fluid, which may prevent or limit effective drainage via a chest tube. The pleural fluid pH and glucose level are lower, and the LDH level rises, often dramatically.

The final *organization* stage is characterized by thickening of the pleural surfaces to form a membrane called the "pleural peel." This may reduce lung functionality considerably, although it should resolve with time if the infection is controlled. The pleural fluid is often thick, consisting of pus and cellular debris.

In contrast to these three stages of parapneumonic empyema, primary empyema can arise from direct inoculation of the pleural space with bacteria, which can translocate from the oropharynx or via hematogenous spread. In these circumstances, bacteria invade the pleural space as the initial insult, leading directly to the fibropurulent stage.

CLINICAL PRESENTATION

The classic presentation of pleural infection is difficult to separate from that of pneumonia, whereby patients have dyspnea, cough, fever, malaise, and perhaps pleuritic chest pain, often over a prolonged period.[45] In fact, a significant number of patients with pneumonia will go on to develop a parapneumonic effusion without a change in symptoms to offer clues to its existence.

Parapneumonic effusions are often categorized as uncomplicated or complicated. An *uncomplicated* parapneumonic effusion is defined as an effusion with a glucose level higher than 40 mg/dL, pH greater than 7.2, and negative Gram stain and culture results without loculation on ultrasonography. A *complicated* parapneumonic effusion has a glucose level lower than 40 mg/dL or pH less than 7.2 or is loculated on ultrasonography (eFig. 109.1).[46,47] Although there is no symptomatic discriminator between patients with complicated effusions and patients with uncomplicated effusions, a high index of suspicion should be maintained for those patients whose conditions fail to improve within a few days of initiating antibiotic therapy[48] or who exhibit persistent fever or signs of sepsis. Further investigations should be undertaken swiftly in these patients because they may require urgent drainage.[49] With long-lasting infection, the course of patients with pleural infection can mimic that of a malignant process, with significant weight loss, sweats, and loss of appetite.

PLEURAL FLUID SAMPLING

Investigation and management of pleural infection are summarized in Fig. 109.2. Abnormal signs, symptoms, or blood test results in the context of a suggestive radiograph should lead to confirmation of the presence of an effusion and early sampling of the fluid. However, in a small retrospective series, Skouras and colleagues[50] suggested that parapneumonic effusions less than 2 cm in thickness on chest CT scan can be treated with antibiotics without sampling because these effusions are unlikely to become complicated or require intervention. Such patients would still require close monitoring and appropriate antibiotic therapy.

Confirmation of the presence of pleural fluid and identification of a safe and suitable site for aspiration require thoracic ultrasound guidance. Ultrasonography also provides useful information on the size and complexity of the fluid that can guide the need for further intervention.

BIOCHEMISTRY

In cases where overt pus is revealed on initial aspiration, no further biochemical analysis is necessary, and chest tube placement is required. Microbiologic analysis is still important, however.

Pleural fluid pH may be the best indicator of the need for chest tube insertion. Many studies have demonstrated better patient outcomes when drainage is instituted based on the early biochemical changes related to infection. In a meta-analysis by Heffner and coworkers,[51] the receiver operating characteristic for the diagnostic accuracy of pleural fluid pH showed that if the pH was less than 7.2, a chest tube was likely to be necessary. As a result, current guidelines regard a pH of 7.2 as diagnostic of complexity, thus making this the definitive cutoff below which drainage should take place.[52] A pH analysis (or glucose analysis) therefore should be performed in all cases where pleural infection is included in the differential diagnosis. The pH should be measured using a blood gas machine because pH strips and pH meters are not sufficiently accurate.[53] Some institutions rely on the glucose concentration instead and find it equally useful as pH and less prone to error.

Fluid pH values may be appreciably altered by minor variations in sampling and processing techniques, with significant subsequent effects on management strategy. In a study of pleural fluid pH, Rahman and associates[54] reproduced several common scenarios that could arise during testing. Small amounts of residual heparin or local anesthetic agent in a sample syringe could dramatically lower pH; residual air in the syringe could increase pH (if 1 mL of air was in the syringe with 2 mL of fluid, the pH rose by an average of 0.08).[54] These errors represented a clinically significant change in more than two-thirds of patients. These and other studies emphasize that the pH must be measured in a blood gas analyzer and the sample must be handled anaerobically, as one would handle an arterial blood sample; with exposure to the air, the loss of carbon dioxide will cause the pH to rise rapidly.[55,56] Thus, if clinical decisions depend on an accurate pH measurement, pleural fluid should be withdrawn anaerobically into a heparinized syringe and taken on ice immediately to the blood gas machine for measurement of the pH at 37°C.

As mentioned earlier, when pH measurements are not easily obtainable, a glucose level can be useful.[51] Samples should be collected in a blood glucose tube and sent to the laboratory, with a value of less than 2.2 mmol/L (40 mg/dL) indicating the need for chest tube drainage.[51,54] It should be noted that pH and glucose level can also be low in malignant pleural effusions, rheumatoid pleural effusions, and pleural effusions secondary to esophageal rupture. Therefore, their value for guiding chest tube drainage should be restricted to the setting of parapneumonic effusions.

LDH measurements tend to be high in all cases of complicated parapneumonic effusions and empyema. LDH tends to rise rapidly as the pleural infection progresses through the fibropurulent and organizing stages of the disease. When a patient is being treated with antibiotics alone, a rising LDH level on repeated thoracentesis may indicate that an effusion is not responding and chest tube drainage should be considered.

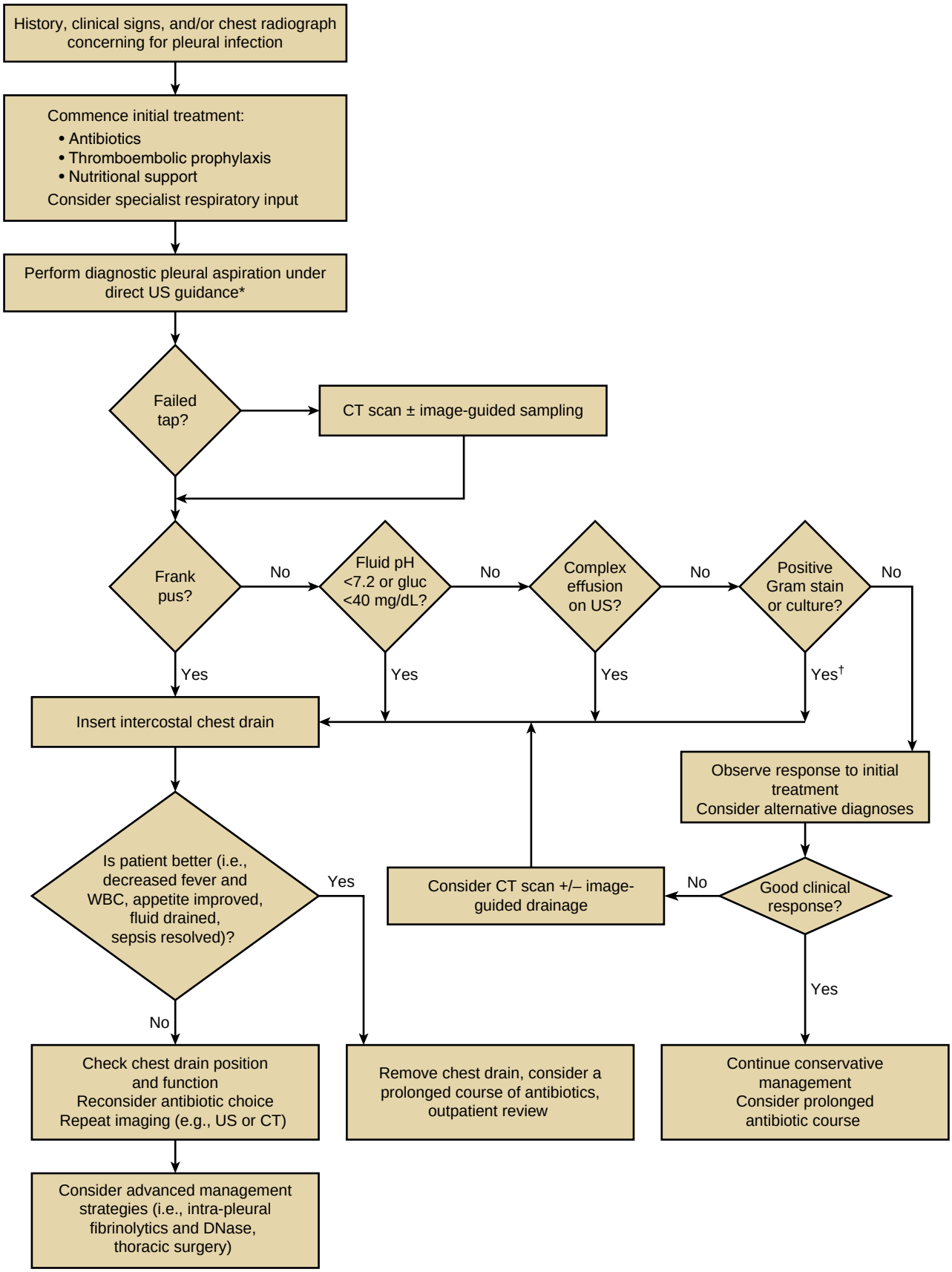

Fig. 109.2 Algorithm demonstrating the investigation and management of suspected pleural infection. *Ideally this should be performed before administration of antibiotics; however, treatment should not be delayed if aspiration cannot be performed immediately. †A positive pleural culture or Gram stain result usually means that a chest drain is required; however, the patient's clinical course should be considered when making this decision. CT, computed tomography; US, ultrasound; WBC, white blood cells.

MICROBIOLOGY

The bacteriologic features of culture-positive pleural fluid have changed since the introduction of antibiotics. In the pre-antibiotic era, the most common pathogens were *Streptococcus pneumoniae* and *Streptococcus haemolyticus*.[57] After this period, between 1955 and 1965, *Staphylococcus aureus* was the most common causative organism. Over time, there have been further shifts in the frequency and type of causative organisms, predominantly attributable to the introduction and evolution of antibiotics. There also appear to be global and regional differences in the frequencies and range of the causative organisms.

To increase the detection of causative organisms, standard culture methods can be combined with nucleic acid amplification, an approach that yielded a 74% overall identification rate in one UK-based pleural infection study.[58] Cloning techniques were also applied to a small number of cases (3%), limited by cost. Nucleic acid amplification identified an organism in 38% of the culture-negative samples, with the same organism found by both culture and nucleic acid amplification (or cloning) in 35% of cases. More recently, a study from Sweden found that DNA sequencing using 16S rDNA identified a causative bacterium in 94 of 152 (62%) patients with pleural infection, compared with 26 of 152 (17%) on standard microbiologic culture.[59] In patients with complex pleural effusions, detection rates were even higher, at 69 of 74 (93%) compared with 23 of 74 (31%) positive cultures. In both cohorts, which consisted of predominantly community-acquired pleural infections, the *Streptococcus anginosus* group (formerly *Streptococcus milleri* group) was the most frequently identified bacterial species.[58,59] These and other gram-positive aerobes were implicated in up to 65% of cases, thus confirming inherent differences in empyema etiology compared with pneumonia. Other organisms included staphylococci (11%), gram-negative aerobes such as *Escherichia coli* (9%), and anaerobes (20%). Polymicrobial samples were identified in 20% of cases, but this may be an underestimate of the true incidence, as suggested by the cloning results and the possibility that anaerobes, which have been identified in up to three-fourths of cases of community-acquired pleural infection in other series, may have been underrepresented here.[60]

Hospital-acquired pleural infections made up just 15% of the UK cohort but were markedly different from the community-acquired pleural infections. Most (58%) cases were attributed to gram-negative organisms or staphylococci, with more than 70% of the latter attributed to methicillin-resistant *S. aureus*.[58] This finding is likely to reflect the period over which the data were collected because infection control measures and antibiotic stewardship have reduced the incidence of methicillin-resistant *S. aureus* infections over subsequent years.[61] A systematic review and meta-analysis of 75 pleural infection studies published between 2000 and 2017 revealed methicillin resistance in 33% of community-acquired *S. aureus* infections (6% of all community-acquired infections) and in 58% of hospital-acquired *S. aureus* infections (22% of all hospital-acquired infections).[36] The bacteriology of hospital-acquired pleural infection is clearly very different from that of community-acquired pleural infections and therefore requires different empirical antibiotics.

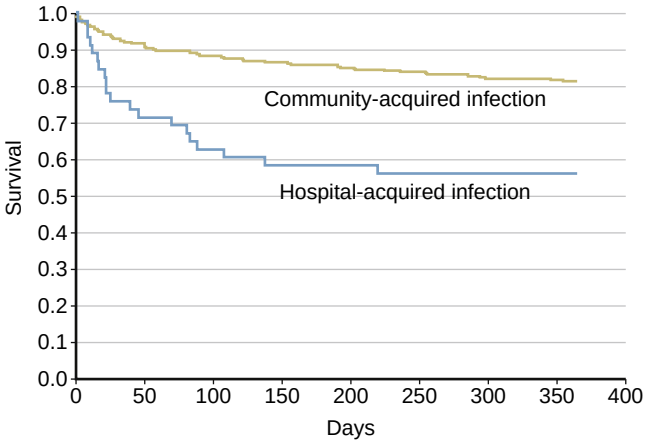

Fig. 109.3 Kaplan-Meier survival curves of patients with community-acquired and hospital-acquired pleural empyema. In the Multicenter Intrapleural Sepsis Trial cohort, there was a significantly higher mortality rate in patients with hospital-acquired pleural infection ($n = 46$) compared with patients with community-acquired infection ($n = 394$). (From Maskell NA, Batt S, Hedley EL, et al. The bacteriology of pleural infection by genetic and standard methods and its mortality significance. *Am J Respir Crit Care Med.* 2006;174:817–823.)

The use of blood culture bottles for culturing pleural fluid can increase yield. Menzies and colleagues[62] provided the first comparative, prospective evidence of increased microbiologic diagnostic yield in pleural infection by using the BACTEC blood culture bottle system (Becton Dickinson). Addition of blood culture bottle–inoculated pleural fluid to standard pleural fluid culture increased microbiologic diagnostic yield by 21% and, in a small proportion of cases (4%) where results of standard culture were positive, use of blood culture bottles suggested the presence of additional organisms that would alter antibiotic management. These findings are supported by the lack of false-positive culture results from noninfected control samples. In addition, results of standard cultures were positive in 29% of cases where blood culture bottle culture results were negative, a finding suggesting potential organism preference for certain growth media. As a result of this study, international guidelines recommended the use of blood culture bottles alongside standard culture techniques in the diagnosis of pleural infection.[52]

ANTIBIOTIC SELECTION AND DURATION

The initial empirical antibiotic selection at presentation should be based on whether the pleural infection is community acquired or hospital acquired. Hospital-acquired pleural infection has a different range of causative organisms and a considerably higher mortality (Fig. 109.3).

Because anaerobic bacteria are commonly seen in pleural infection and often fail to grow in culture, they should be covered empirically in all cases of presumed pleural infection. Liaison with local infectious disease specialists or microbiologists is invaluable in deciding the best combination of antibiotics to use because resistance patterns vary significantly from one geographic region to the next.

There are no robust studies looking at the optimal duration of antibiotics for pleural infection. In our experience, if

a patient is ill enough to require hospitalization, then intravenous antibiotics are usually indicated. Conversion to oral antibiotics should be based on clinical and biochemical parameters, specifically the presence of ongoing fevers and the C-reactive protein value. Radiologic appearance is less useful because it often lags behind clinical improvement, although thoracic ultrasound can be used to assess the volume of residual fluid in the chest and its appearance. An extended course of oral antibiotics, often up to 4 weeks in total, may be required if clinical parameters suggest residual fluid or ongoing infection.

There are no randomized controlled data supporting the use of intrapleural antibiotics. Because most intravenous antibiotics penetrate the pleural space in suitable concentrations, there is currently no role for intrapleural antibiotic use in pleural infection. However, intravenous aminoglycosides do not penetrate the pleural space well and should be avoided.



Fig. 109.4 Pleural empyema seen on a frontal chest radiograph. The D-shaped opacity, suggesting an extraparenchymal process, is commonly seen in cases of pleural infection.

NUTRITION

Patients with pleural infection, particularly those with empyema who have had a delayed presentation, experience the protracted catabolic consequences of chronic infection. A low albumin level has been shown consistently to be a marker of poor outcome.[63–65] Addressing the patient's nutritional status at presentation is often overlooked and should be an early priority alongside tube drainage and the prescribing of suitable antibiotics. Early nutritional assessment should be mandatory.

EARLY RISK STRATIFICATION

Although complex interactions are likely to exist between genetic and environmental factors that contribute to the development of pleural infection, these have not yet been determined.[66] There are, however, certain risk factors, particularly long-term alcohol excess and intravenous drug use, which likely increase the risk as a result of aspiration of gastric contents. In addition, Chalmers and colleagues[64] described four other independent risk factors associated with pleural infection: serum albumin level lower than 30 g/L, serum C-reactive protein greater than 100 mg/L, platelet count higher than 400×10^9/L, and serum sodium level lower than 130 mmol/L. Interestingly, patients with COPD appear to be at lower risk for developing pleural infection, perhaps because of a background level of generalized inflammation causing an attenuated response to a pleural bacterial challenge.[67]

A reliable and sensitive clinical prediction model of poor outcome in pleural infection would enable clinicians to triage patients according to risk and to select the most aggressive and expensive therapies for patients who may otherwise have the poorest outcomes. Chalmers and colleagues[64] proposed a risk scoring system based on the six factors outlined earlier; however, this score has not been independently validated. In contrast, Rahman and colleagues[65] used data from the UK MIST1 trial to develop an outcome score in patients with confirmed pleural infection and then validated the tool using a second cohort from the MIST2 trial. They found that five presenting factors (serum urea level, age, fluid purulence, likely origin of infection, and serum albumin level) could predict the eventual outcome, with patients divided into low-, medium-, or high-risk groups. At 3 months, patients in the lowest-risk group had mortality rates of less than 5%, whereas patients in the highest-risk group had mortality rates higher than 30%, with an odds ratio of 14.1 (95% confidence intervals, 3.5 to 56.8) for death. They named the score RAPID, a mnemonic for renal function, age, purulence, infection type, and dietary status.

The RAPID score was further validated in a prospective cohort of 551 patients enrolled in the Pleural Infection Longitudinal Outcome Study.[68] At 3 months, a low-risk RAPID score was associated with lower mortality than a high-risk score (2% vs. 30%). Further work is now required to determine whether targeting interventional therapies to high-risk groups can reduce mortality.

INVESTIGATIVE TECHNIQUES FOR PLEURAL INFECTION

Radiologic tests such as chest radiography, CT, and ultrasonography are vital in the initial diagnosis and management of pleural infection. Bronchoscopy is useful in selected cases, particularly for those patients with suspected airway obstruction.

Radiology

The presence of fever, pleuritic pain, and pleural effusion should always alert the physician to the possibility of pleural infection. Pleural fluid loculation can result in a D-shaped homogeneous peripheral opacity (Fig. 109.4 and eFig. 109.2A) on chest radiography. Posterior collections and posterior tracking of fluid in patients imaged in the supine position may result in generalized haziness of the hemithorax on the chest radiograph.

Thoracic ultrasonography (see eFig. 109.1) is advisable in all cases of suspected pleural infection because it can provide important information about the size and nature of the collection, as well as allowing accurate chest tube placement into the most appropriate site. Use of ultrasonography has also been shown to reduce iatrogenic injury.[69]

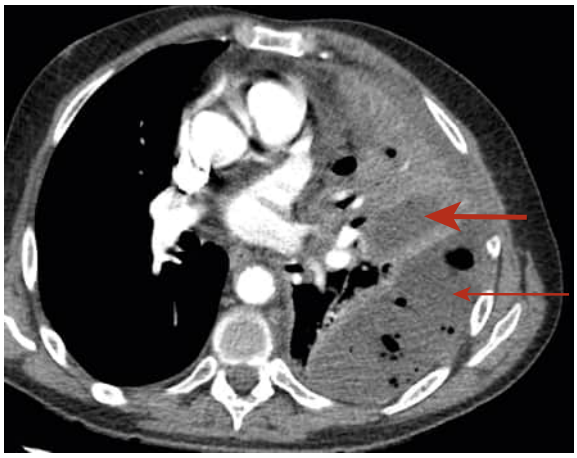

Fig. 109.5 Contrast-enhanced chest computed tomography showing both pleural empyema and a lung abscess. With contrast-enhanced computed tomography, pleural lesions can be discriminated from parenchymal lesions. The *thin arrow* shows empyema, and the *thick arrow* indicates a lung abscess. Note the lenticular shape of the empyema in contrast to the rounded shape of the abscess. The pleural collection does not have a visible "wall," whereas the abscess wall is thick and irregular. Within the empyema are multiple separate locules of gas, suggesting that the pleural collection is septated. Also see Table 109.1 for features that differentiate between empyema and lung abscess.

Table 109.1 Key Differences Between the Radiographic Appearance of Pleural Infection and Lung Abscesses

Empyema	Lung Abscess
Lenticular shape	Rounded
Surrounding lung often compressed	Boundary between lung and fluid indistinct, with necrosis of lung
Margins of collection creating obtuse angles with chest wall	Contact with chest wall made at acute angle
Thick smooth wall	Thick irregular wall
No vessels close by	Vessels seen passing through or near collection

Ultrasonography is also more accurate than CT imaging in detecting loculations and septations and can detect the presence of small quantities of pleural fluid not visible on chest radiography.[70]

Chest CT, particularly contrast-enhanced chest CT (eFigs. 109.2B–E and 109.3), is not necessary in all patients with pleural infection and should be reserved for those patients with persistent collections despite attempted chest tube drainage, those who may have a suspected obstructing lesion within the airway, and those in whom surgery is being considered. Chest CT provides detailed information about fluid loculation (Video 109.1), identifies chest tube position, and differentiates between empyema and lung abscesses when there is diagnostic uncertainty (Fig. 109.5, Fig. 108.2, and Table 109.1) (see also Chapter 50).

Magnetic resonance imaging is usually reserved for those patients who are unable to undergo CT imaging or for persons at high risk from irradiation. It is very good at visualizing septations and loculations within the pleural fluid (Fig. 109.6).

Bronchoscopy

Practitioners should be aware that a proximal airway obstructing lesion may be the cause of empyema. Although uncommon (<4% in one large series), this diagnosis should be considered in patients with a suggestive plain chest radiograph, for example, if the mediastinum is shifted *toward* the side of the effusion, or in patients failing to respond to simple first-line management. Bronchoscopy and chest CT are the investigations of choice if a bronchial obstruction is suspected. Aside from this situation, there is no role for routine bronchoscopy in patients with pleural infection.

When empyema is discovered distal to an obstructed bronchus, the underlying cause is usually either malignancy or aspirated foreign body, with malignancy the more common diagnosis. If a tumor is seen at bronchoscopy, histologic features should be confirmed and relief of the obstruction should be attempted using radiation therapy, laser resection, or stent insertion. Foreign objects are simply removed, often leading to reinflation of the distal lung and resolution of symptoms. In either setting, prolonged oral antibiotics may be required to prevent ongoing sepsis.

Chest Tube Drainage

Chest tube drainage is usually indicated in patients with loculated effusions, frank pus on aspiration, culture-positive pleural fluid or identification of organisms on Gram stains, or biochemical parameters suggestive of infection (pleural fluid pH < 7.2 or pleural fluid glucose < 2.2 mmol/L [40 mg/dL]). However, for some patients, particularly those with a small effusion or pneumococcal infection, conservative management with antibiotics alone can result in effusion resolution.[52,71] Observational data have suggested that repeat therapeutic thoracentesis may be an acceptable and effective alternative to chest drainage in some patients, with an associated reduction in inpatient hospital stay.[72,73]

Over the past decade, there has been a shift away from large-bore catheters to small-bore chest tubes inserted by the Seldinger technique. This change in practice is not so much the result of large, well-conducted, randomized controlled trials but more likely is due to the relative ease of the technique and the benefits of the smaller drains, which cause the patient less pain during insertion and while in place.[74] In the MIST trial, data were collected on the size of chest tubes placed in 405 patients. No difference between small- and large-bore tubes was found in the frequency with which patients either died or required thoracic surgery. However, patients with larger chest tubes reported significantly more pain both at the time of insertion and while the drain remained in place.[75] In another study of 103 patients with pleural infection, the small-bore chest tubes provided definitive treatment in 78% of cases,[76] similar to the success rates of two other series in which large-bore chest tubes were used.[77,78] In this study, radiologists guided tube placement, and this almost certainly helped the result.

The optimal drainage approach for an individual patient should be chosen at the time of treatment, based on clinical and patient-related factors. However, for most patients, initial placement of a small-bore (12-French) chest tube under ultrasonographic guidance in the largest locule in a dependent part of the pleural effusion is appropriate. Subsequent management with regular saline flushes may help ensure

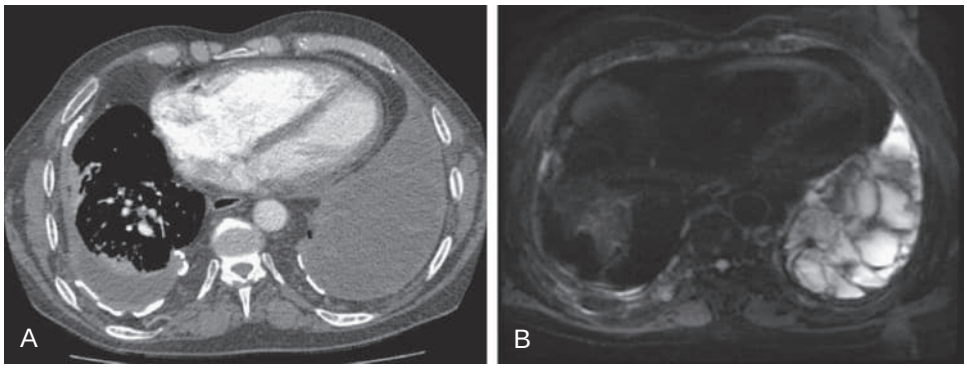

Fig. 109.6 Imaging of pleural empyema. (A) Contrast-enhanced chest computed tomography revealing a complex, large left pleural fluid collection secondary to pleural infection. (B) T2-weighted magnetic resonance imaging in the same patient that shows the presence of multiple septations and loculations.

that the drain does not become occluded. Guidelines recommend the instillation of 30 mL saline every 6 hours via a three-way stopcock.[52] If this fails to drain the effusion effectively, a large-bore drain may be necessary. It is more common for tubes to be replaced not because of obstruction but because they have become dislodged or have fallen out as a result of failure to secure the chest tube correctly.

FIBRINOLYTIC THERAPY

The use of fibrinolytic agents to disrupt fibrinous pleural septations was first described in 1949, by Tillett and Sherry,[79] who used partially purified streptococcal fibrinolysin that contained both streptokinase and streptodornase (a DNase) to drain infected postoperative hemothoraces. This approach was associated with immunologic side effects and did not become routine practice.

In a series of 24 patients, in 1997, Davies and coworkers[80] began to allay fears regarding intrapleural thrombolysis, which was found to be safe and also led to improvements in clinical outcomes. Other studies tended to focus more on the use of urokinase in loculated effusions, with benefits demonstrated of a reduction in treatment failure (as judged by surgical referral or death), reduced length of hospital stay, and better surgical outcomes.[81–83] However, these studies were often small trials or case series, which limited their ability to be generalized.

Thus, a large randomized study was designed to test the role of streptokinase in empyema. The 2005 MIST1 trial recruited 454 UK patients with pleural infection to receive either intrapleural streptokinase or placebo.[35] Entry criteria reflected real-world practice, with a strong reliance on local physician diagnosis, antibiotic choice, chest tube use, and surgical referral. The trial showed no significant benefit from the use of streptokinase in either surgical referral or death. There was also no improvement in the length of stay or in any signal in any subgroup analysis. The choice of single-agent streptokinase as the primary lytic may have contributed to these negative results because data from the subsequent MIST2 trial demonstrated that a combination of a fibrinolytic agent and a DNase was effective, whereas monotherapy with either agent was not.[26] In addition, streptokinase has several limitations compared with newer fibrinolytic agents, including antigenicity and the need for an additional step in its activation pathway.[84,85] However, a Cochrane review concluded that intrapleural fibrinolytic agents conferred benefit both in reduced treatment failure and reduced need for surgical intervention in pleural infection, but not reduced mortality.[86] Based on the Cochrane review, the 2010 British Thoracic Society guidelines advised that intrapleural fibrinolytic agents should not be used routinely, but may be considered in selected cases.[52]

Following the disappointing results with single-agent streptokinase, MIST2 was designed to test the *combination* of a fibrinolytic agent with a DNase. The combination approach was based on experimental in vitro and in vivo data that showed better lysis when a fibrinolytic agent was given together with DNase, a finding suggesting that the digestion of the long strands of DNA derived from degenerating cells facilitated fibrinolysis.[87,88] In this blinded, 2 × 2 factorial trial, 210 patients with pleural infection were randomly assigned to receive 1 of 4 study treatments for 3 days: intrapleural *tissue plasminogen activator* (tPA) and DNase, tPA and placebo, DNase and placebo, or double placebo.[26] The primary outcome was the change in pleural opacity, measured as the percentage of the hemithorax occupied by effusion on chest radiography on day 7 as compared with day 1. The mean change in pleural opacity was significantly greater in the tPA-DNase group than in the double-placebo group (−29.5% vs. −17.2%); the change observed with tPA alone and with DNase alone (−17.2% and −14.7%, respectively) was no different from that observed with placebo. In addition, the frequency of surgical referral at 3 months was lower in the tPA-DNase group than in the double-placebo group (4% vs. 16%). Finally, combined tPA-DNase therapy was associated with a reduction in the hospital stay as compared with double placebo (difference, −6.7 days), whereas the hospital stay with either agent alone was not significantly different from that with placebo. The study investigators concluded that intrapleural tPA-DNase therapy improved fluid drainage in patients with pleural infection and reduced the frequency of surgical referral and the duration of the hospital stay. Treatment with DNase alone or tPA alone was ineffective; indeed, by itself, DNase appeared harmful, with a threefold increase in surgical referrals.

The combination of a fibrinolytic agent with DNase was not associated with an excess of adverse events. Indeed, real-life data from centers across Europe and North America have confirmed that intrapleural tPA with DNase has an acceptable safety profile. In a report of 107 patients from 8 centers, the use of tPA with DNase showed benefit in patients who did not respond to antibiotics and chest tube drainage, with bleeding seen in just 2 patients (1.8%), both of whom had additional risk factors for bleeding, including preexisting coagulopathies.[89] Neither case resulted in fatality. In 3 further reports of a total of 209 patients in 4 centers,

the use of intrapleural tPA with DNase was associated with an overall 2.9% bleeding incidence.[90–92] All studies noted an increase in analgesia requirement following fibrinolytic administration. The cost of fibrinolytic agents, particularly tPA may be prohibitive in some health care settings.

Given that the dose of tPA with DNase used in the MIST trials (10 mg tPA and 5 mg DNAse) was chosen empirically, it may be possible to reduce the dose, thus lowering costs with no reduction in efficacy. Popowicz and colleagues[93] used 5 mg of tPA with 5 mg of DNase in 61 patients with pleural infection, with a 93% success rate (defined as survival to discharge and no need for surgery). Effective pleural drainage with 1 mg of tPA and 5 mg DNase has been reported in a single case, with studies underway investigating the efficacy of 2.5 mg tPA.[94] Pleural irrigation, in which saline is administered via the chest tube, may be an inexpensive yet effective alternative to fibrinolytic agents in patients with a persisting effusion after initial management. In their randomized trial of 35 patients, Hooper and colleagues[95] allowed 250 mL of normal saline to flow into the pleural space via gravity, three times a day for nine doses. Patients allocated to saline irrigation had a greater reduction in the volume of residual pleural collection on CT at day 3 compared with patients receiving standard care (which included small volume flushes of up to 20 mL of saline four times a day). Fewer patients in the irrigation group required surgery, with no serious adverse events noted in either arm of the study. Interestingly, the outcomes following pleural irrigation were comparable to those seen in patients who received tPA and DNase in the MIST2 trial, with a 32% reduction in radiologic opacification (compared with 29% in MIST2) and an odds ratio for referral to surgery of 0.14 (vs 0.17 in MIST2).[26]

MONITORING RESPONSE TO MEDICAL MANAGEMENT

Identifying patients who are not responding to medical management can be challenging. Radiologic appearances often lag behind clinical improvement and therefore, in our opinion, are not good indicators of the need for further intervention. The best markers of response to medical management include a falling C-reactive protein (halving in value and ideally falling to less than 100 mg/L) or a falling white blood cell count, the settling of a spiking temperature, and clinical signs associated with resolution of sepsis, such as improving energy levels and return of appetite. If these markers are all improving, then further interventions with additional chest tubes or surgery rarely become necessary. In sum, in assessing response to medical management, the most important factor is the patient's clinical condition, not the imaging.

When patients appear to have avoided surgery by the narrowest of margins, prolonged oral antibiotics (for 4 to 6 weeks) and close follow-up as outpatients with monitoring of the chest radiograph and C-reactive protein is advised.

SURGICAL OPTIONS

Patients are usually referred for surgical intervention if initial medical treatment fails or if they present late with highly organized empyemas that demonstrate significant pleural thickening and loculation. Practice varies, and some centers have a low threshold for early surgery.[96] The point at which medical management is deemed to have "failed" is necessarily ill defined, but one important indicator would be signs of ongoing sepsis despite attempted chest tube drainage and adequate antibiotic therapy. Another potential consideration is the risk for long-term respiratory embarrassment from the fibrin and loculated fluid, although observational evidence suggests that the pleural abnormalities usually resolve over time without acute surgical intervention.[97,98]

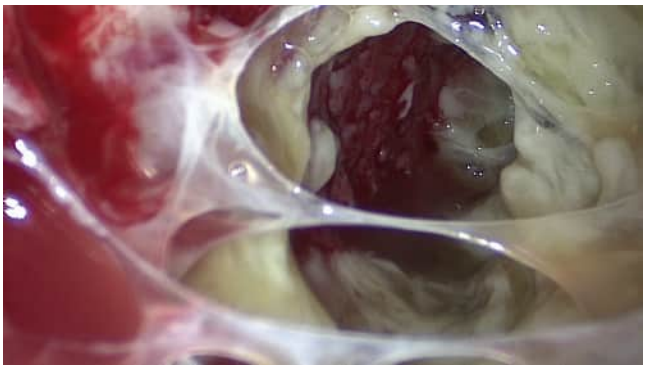

Fig. 109.7 Empyema during video-assisted thoracic surgery. Empyema in a 26-year-old woman at the time of video-assisted thoracic surgery shows thick pus within the pleural cavity, with inflammation and bleeding visible on the parietal pleural to the *left* of the picture. Septations are visible running between the visceral and parietal pleura.

It is currently unclear whether surgical intervention is better than medical management of pleural infection. A Cochrane review summarized the evidence and concluded that there was no difference in mortality between the two approaches, although surgery may be associated with shorter length of stay.[99] However, most studies were performed in pediatric populations, with only two small trials involving adults. Of these trials, one compared VATS with tube drainage and fibrinolytic agents,[100] and the other compared VATS with simple drainage without fibrinolytic agents.[101] To date, no randomized trial has directly compared all three approaches (simple drainage, tPA with DNase, VATS) to determine which is the most appropriate front-line treatment. The MIST3 trial is currently underway in the United Kingdom, aiming to assess the feasibility of such a trial, with a full-scale study potentially to follow.

Modern surgical options are varied and may be tailored to the individual. VATS typically requires general anesthesia and single-lung ventilation but can be performed using local anesthesia in patients deemed to be too high risk for general anesthesia (Fig. 109.7 and Video 109.2). Although originally used for thorough pleural débridement, VATS is now increasingly used to perform decortication in patients with particularly advanced or chronic empyema.[102,103] Studies show similar resolution rates following VATS compared with open surgery, with the added benefits of a minimally invasive approach resulting in reduced postoperative pain and other complications.[102,104] Overall success rates for VATS, based on resolution of sepsis and clinical stability, exceed 85%, with mortality rates of less than 1.5%.[105]

Open thoracotomy was formerly a mainstay of treatment for empyema, but its role has diminished as VATS has

superseded it as the standard of care.[102] It is now used when less invasive approaches have failed, with open thoracotomy more likely to be necessary in patients with a delayed presentation, a longer duration of illness, or resistant gram-negative infection.[106,107] A study from 2009 described a mortality of approximately 3.5% for this operation.[108]

Decortication via thoracotomy allows complete mobilization of the lung and is therefore particularly useful in cases of trapped lung.[109] However, in patients in the acute stages of pleural infection, decortication should be considered only for the control of infection. Decortication should not be performed just to remove thickened pleura because such thickening usually resolves spontaneously over the subsequent 4 to 6 months.[97,98]

For patients who have recurrent or particularly complex empyema, small prosthetic devices may be inserted between the ribs to maintain a drainage route. The more permanent way to achieve this effect is to perform an open-window drainage. This involves the resection of two or three ribs to create a direct opening to the thoracic cavity, which affords the opportunity to pack the pleural space.[110] The advantage of this open flap (Eloesser flap) (eFig. 109.4) is that it creates a skin-lined fistula that provides drainage without tubes. Should methods such as these fail, thoracomyoplasty may become necessary, whereby a large muscle is used to pack the thoracic cavity. This is usually reserved for patients with bronchopleural fistulas, trapped lung, or postoperative empyema.[109]

A more conservative approach, which may be applied in highly selected patients who have high risks for surgery, is the insertion of an indwelling pleural catheter together with long-term oral antibiotic therapy.[111,112] In our experience, this approach can occasionally be extremely useful and certainly warrants further research.

PLEURAL TUBERCULOSIS

In many parts of the world, the most common cause of an exudative pleural effusion is *tuberculosis* (TB). However, in the United States, tuberculous pleuritis is relatively uncommon, with only 7549 cases reported in the 10 years from 1993 to 2003; these pleural TB cases represent only 3.6% of the total number of cases of TB seen over this period.[113] In some African countries, the incidence of pleural involvement in TB appears to be much higher because pleural TB represents more than 30% of the total number of TB cases.[114] This high incidence may be a result of coinfection with *human immunodeficiency virus* (HIV) because TB effusions are much more prevalent in areas of high HIV prevalence.[115,116]

PATHOGENESIS

A tuberculous pleural effusion can either be a sequel to a primary infection acquired 3 to 6 months previously or can represent reactivation TB. A molecular epidemiologic study confirmed that tuberculous pleurisy is usually an early manifestation of TB infection.[117]

Pleural TB may manifest as tuberculous pleuritis or TB empyema. Historically it was thought that tuberculous pleuritis was caused by a delayed hypersensitivity reaction to mycobacterial antigens, whereas TB empyema was a result of fulminant TB infection of the pleural space. This theory was based on animal studies, in which the intrapleural injection of tuberculin protein in sensitized guinea pigs resulted in the rapid appearance of an exudative pleural effusion.[118] When the animals were given antilymphocyte serum, the development of the effusion was suppressed.[119] The observation that pleural fluid culture results are negative in approximately 80% of patients with tuberculous pleuritis supported the contention that delayed hypersensitivity played a role in the development of tuberculous pleural effusions in humans.

However, improvements in microbiologic techniques and culture media have refuted this theory. One study showed that combining liquid culture of pleural fluid and pleural biopsy tissue resulted in identification of bacilli in more than 60% of patients.[120] This finding suggests that tuberculous pleuritis actually reflects paucibacillary infection of the pleural space, with subsequent immunologic reaction.[115] The initial, neutrophil-predominant acute inflammatory response evolves into a chronic lymphocyte-driven immune reaction, with associated granuloma formation and containment of viable mycobacteria. The study demonstrated that the percentage of lymphocytes in pleural fluid was inversely correlated with the likelihood of obtaining positive culture results.[120] This finding suggests that with sufficient lymphocyte activity, it is possible to suppress all active bacilli and sterilize the pleural space, thus explaining why tuberculous pleuritis resolves spontaneously in some patients.[121]

By this theory, tuberculous pleuritis and TB empyema are different stages on an immunologic spectrum, rather than two distinct disorders. In TB empyema, a high mycobacterial load leads to an exaggerated and sustained acute inflammatory response, with neutrophil leukocytosis and pus formation. This gives rise to a culture-positive, purulent pleural effusion unlikely to resolve without clinical intervention.

CLINICAL MANIFESTATIONS

Tuberculous pleuritis manifests as an acute illness in about two-thirds of cases and as a chronic illness in the remaining one-third. The acute illness, marked by cough and chest pain in approximately 75% of patients, often mimics the presentation of bacterial pneumonia with a parapneumonic effusion (Fig. 109.8A). The chronic form is characterized by low-grade fever, weakness, and weight loss.

Effusions secondary to tuberculous pleuritis can manifest in a similar fashion as malignant effusions, being almost always unilateral, and usually small to moderate in size, although they may be large to the point of occupying the entire hemithorax.[115] Up to 86% of patients will have coexisting parenchymal disease (see Fig 109.8). In such patients the pleural effusion is almost always on the side of the parenchymal opacity and usually indicates active parenchymal disease. It is likely that, even in cases with no radiographic evidence of parenchymal involvement, the effusion is associated with a subpleural focus of infection. Evidence to support this contention is provided by a study in which the microbiologic yield of *Mycobacterium tuberculosis* from induced sputum was as high in patients with no radiographic evidence of parenchymal involvement (55%) as in patients with



Fig. 109.8 Tuberculous effusion and pneumonia resembling bacterial parapneumonic effusion and bacterial pneumonia. (A) Frontal chest radiograph shows left apical consolidation and a hazy left base with a well-delineated fluid collection visible in left costophrenic area. The patient also has a metabolic bone disorder creating abnormal appearances of the humeral heads. The findings are nonspecific, but the upper zone distribution of the infective change raises the possibility of mycobacterial infection. Drug-sensitive *Mycobacterium tuberculosis* was cultured from both the pleural effusion and bronchoalveolar lavage of the left upper lobe. The patient improved after 6 months of treatment for tuberculosis. (B) Chest computed tomography in the same patient shows an encapsulated effusion posteriorly in the left hemithorax, with fluid tracking along the fissure. Tree-in-bud changes are visible anteriorly in the left lung, thus indicating pulmonary infection. (C) Mediastinal windows show lenticular, smooth pleural thickening, with division of the parietal and visceral pleural clearly visible (*arrows*), representing the "split-pleura" sign.

parenchymal disease (45%).[122] Occasionally, dense parenchymal consolidation can rupture into the pleural space and cause TB empyema, often with concomitant pneumothorax (eFig 109.5). The risk of bronchopleural fistula is high in these patients. Rarely, TB empyema may decompress percutaneously, giving rise to empyema necessitans.

In patients with HIV infection, tuberculous pleuritis is more likely to manifest with systemic features of illness (i.e., significant weight loss and high fevers). In addition, in HIV-positive patients, concomitant parenchymal opacities and culture-positive pleural fluid are more common than in HIV-negative patients.[115,116] In addition, the cellular and cytokine profile of TB effusions in HIV-positive patients differs from that of HIV-negative patients, as a reflection either of the underlying immunocompromise or of a different pathogenic pathway.[116] Despite this, delayed hypersensitivity remains implicated in the development of TB effusions in HIV infection because the prevalence of tuberculous pleurisy is higher in patients with CD4 counts greater than 200 cells/μL than in patients with lower CD4 counts.[123]

PLEURAL FLUID

The pleural fluid from patients with tuberculous pleuritis is an exudate that usually contains predominantly small lymphocytes. This is not universally seen; in a series from 2012, 17% of confirmed cases were found to have less than 50% lymphocytes in pleural fluid,[120] and in approximately 11% of cases, the fluid has a polymorphonuclear leukocyte predominance, a pattern more likely in the earlier stages of the disease.[124] The pleural fluid glucose level is usually similar to that of serum, but it can also be reduced. A pleural fluid protein level higher than 5.0 g/dL is suggestive of tuberculous pleuritis, perhaps because of the intense inflammation and leakiness of the pleural capillaries.

DIAGNOSIS

The possibility of tuberculous pleuritis should be considered in every patient with an undiagnosed exudative pleural effusion, even though TB causes only a small percentage of such effusions in the United States.[113] For the past 40 years, the most common way to establish the diagnosis of tuberculous pleuritis has been with biopsy of the pleura, and this remains the gold standard test. However, more recently, pleural fluid tests have been developed that may be useful in establishing or excluding the diagnosis of tuberculous pleuritis. The pleural fluid tests found to have the most utility, especially in combination, are (1) the level of adenosine deaminase, (2) polymerase chain reaction for mycobacterial DNA, and (3) interferon-γ levels.[125,126] The last test requires direct measurement of the levels of interferon-γ with an enzyme-linked immunosorbent assay because interferon-γ release assays on pleural fluid are insufficiently sensitive to be of diagnostic benefit in tuberculous pleuritis.[126,127] The performance of these tests varies depending on the prevalence of TB, with higher specificity than sensitivity. Consequently, interpreting results in combination can enhance the diagnostic accuracy.

All patients with an undiagnosed exudative pleural effusion should undergo mycobacterial culture of their pleural fluid. An induced sputum sample should also be sent for smear and culture because results will be positive in approximately 50% of patients, even when there is no evident pulmonary involvement.[122] A *microscopic observation drug susceptibility* (MODS) assay, in which the TB is grown in liquid culture with drugs included to provide drug susceptibility information, can be applied to sputum or pleural fluid and has diagnostic accuracy similar to that of standard solid media culture, but it is less expensive and faster, and it provides information on drug resistance patterns.[128] The MODS assay is of particular benefit in resource-poor settings, where its use is approved by the World Health Organization.

If the culture of fluid or sputum becomes positive, standard treatment for TB should be initiated. If the culture result is negative, the decision to start antituberculous therapy should be based on the presence of other supportive test results, the overall index of suspicion for TB infection, and the balance of risk and benefit of starting treatment. In areas with a high incidence of resistant TB, the importance of obtaining an organism and testing drug susceptibility is

higher; thus, it may be appropriate to obtain pleural tissue for cultures. Thoracoscopic biopsies remain the ideal way of obtaining tissue but, if this resource is not available, then traditional blind pleural biopsy remains an important diagnostic modality,[129] especially when used in combination with adenosine deaminase and differential cell count.[130] Blind pleural biopsy with an Abrams needle may be preferable to other forms of blind biopsy when combined with ultrasonographic guidance.[131] If the patient does not respond to therapy, then further investigations for alternative causes are warranted.

TREATMENT

Patients with tuberculous pleuritis should be treated with antituberculous medications using the same treatment regimens as for patients with pulmonary TB. With treatment, patients generally become afebrile within about 2 weeks, and the pleural effusion resolves within 6 weeks. On occasion, the pleural effusion worsens after antituberculous therapy is initiated, or a pleural effusion develops while patients are being treated for parenchymal TB.[132,133] In these situations, the possibility of a wrong diagnosis must be considered, but paradoxical worsening can be seen with the correct diagnosis and appropriate antituberculous medications.[132,133] Mild degrees of residual pleural fibrosis are present a year after therapy is begun in approximately 50% of patients. Some investigators have used fibrinolytic agents in tuberculous effusions, with resulting improved drainage of fluid and less residual pleural thickening in the long term.[134,135] However, the clinical consequence of residual pleural thickening following tuberculous pleuritis is unknown; therefore, the utility of fibrinolytic agents in this scenario is not certain.

Systemic corticosteroids may reduce the time to resolution of TB effusions and reduce the degree of residual pleural fibrosis, although the evidence supporting these observations is of low quality.[136] Adverse events are more frequent in persons treated with corticosteroids, and there is some anxiety that, in HIV-infected patients, Kaposi sarcoma is more likely following prednisolone treatment, although this suggestion is based on observations in just four patients.[136,137] If corticosteroid treatment is contemplated, it should be initiated after antituberculous therapy has been commenced.

ACTINOMYCOSIS

More than 50% of patients with thoracic actinomycosis have pleural involvement.[138] In a series of 15 patients, 6 had pleural effusions and an additional 6 had marked pleural thickening.[139] The characteristic chest radiographic finding is a localized lung lesion extending to the chest wall with pleural thickening or effusion. The pleural fluid with actinomycosis may be either frank pus with predominantly polymorphonuclear leukocytes or serous fluid with predominantly lymphocytes.

The diagnosis of actinomycosis should be considered when a chronic infiltrative pulmonary lesion extends to adjacent lobes through intralobar fissures. The presence of chest wall abscesses or draining sinus tracts suggests the diagnosis, as do bone changes consisting of periosteal proliferation or bone destruction (see eFig. 46.42). The definitive diagnosis is established with the demonstration of *Actinomyces israelii* by anaerobic cultures. Patients with pleural actinomycosis should be treated with high doses of penicillin or another suitable antimicrobial agent for prolonged periods. The management of the pleural effusion is similar to that for patients with any other bacterial pneumonia.

NOCARDIOSIS

Patients with pleural effusion secondary to nocardiosis almost always have an associated parenchymal opacity (eFig. 109.6). The pleural fluid can range from serous fluid to frank pus, and pleural fluid culture results may or may not be positive. Because most patients who develop nocardiosis are immunosuppressed,[140] this diagnosis should be considered in the immunosuppressed patient with a parenchymal opacity and a pleural effusion. The diagnosis is usually established with aerobic cultures, although polymerase chain reaction has been successfully used for diagnosis in some cases.[141] Cultures should be observed for at least 2 weeks because *Nocardia asteroides* is a slow-growing organism. Patients with pleural nocardiosis should be treated with sulfonamides or suitable alternative antimicrobial agents, and the pleural effusion should be managed as any pleural effusion that complicates pneumonia.

FUNGAL INFECTIONS

Fungal infections of the lungs are discussed in Chapter 56. This section considers the pleural complications of aspergillosis, blastomycosis, coccidioidomycosis, cryptococcosis, and histoplasmosis. In addition, *Pneumocystis jirovecii* has been included.

ASPERGILLOSIS

The pleural space occasionally becomes infected with *Aspergillus,* usually *Aspergillus fumigatus*.[142] Pleural aspergillosis usually arises in one of two settings: in patients who were treated in the past with artificial pneumothorax therapy for TB and, less commonly, in patients following lobectomy or pneumonectomy, in which case a bronchopleural fistula is almost always present. Pleural aspergillosis has been described in a healthy individual.[143]

The diagnosis of pleural aspergillosis should be suspected in any patient with a history of artificial pneumothorax therapy for TB who has signs and symptoms of a chronic infection, such as weight loss, malaise, low-grade fever, and chronic cough. The chest radiograph reveals increasing degrees of pleural thickening and usually an air-fluid level in the pleural space, thus indicating the presence of a bronchopleural fistula.[142] In some patients, fungal balls may be evident in either the lungs or the pleural space. The diagnosis is confirmed by the demonstration of *Aspergillus* on fungal cultures of the pleural fluid. Patients with pleural aspergillosis almost always have positive precipitin blood test results for antibodies against *Aspergillus*.

The optimal treatment for pleural aspergillosis is likely to be a combination of surgical removal of the involved pleura and resection of the involved lobe or the entire ipsilateral lung and concomitant medical therapy, which may take

the form of systemic therapy or intrapleural antifungal treatment.[144] Lung resection is usually necessary because the infection tends to invade and destroy the underlying lung. Surgery, if appropriate, should be performed as early as possible to avoid progressive destruction of the lung. Some patients with pleural aspergillosis are too debilitated to undergo a major surgical procedure. Such patients can undergo open drainage (Eloesser flap) with daily insertion of gauze impregnated with amphotericin B.[145]

Systemic medical treatment is usually given both before and after surgery. A potential regimen is an initial 2- to 4-week period of therapy with amphotericin B, followed by longer-term administration of a more modern agent such as an azole. Treatment should continue for at least 6 months, although some patients may require much longer periods of treatment.[144] Topical pleural antifungal treatment may be used as an adjunct to systemic therapy.[144–146]

BLASTOMYCOSIS

Infection with *Blastomyces dermatitidis* produces a pleural effusion in approximately 10% of patients, and an additional 40% or more have pleural thickening.[147] Patients with pleural blastomycosis have signs and symptoms similar to those seen in tuberculous pleuritis. The pleural fluid is usually an exudate with predominantly small lymphocytes, although polymorphonuclear leukocytes may predominate. Because pleural biopsy results may reveal noncaseating granulomas, one should consider the diagnosis of blastomycosis in patients with a clinical picture compatible with tuberculous pleuritis and granulomas on pleural biopsy. The diagnosis is established by demonstrating the organism in secretions, pleural fluid, or histologic sections. Patients with pleural blastomycosis should be treated with itraconazole or amphotericin B.

COCCIDIOIDOMYCOSIS

Two types of pleural disease are seen in association with coccidioidomycosis. The first is associated with a primary benign infection and may or may not have concomitant parenchymal involvement. The second develops when a coccidioidal cavity ruptures to produce a hydropneumothorax.

Primary Coccidioidomycosis

The incidence of pleural effusion in hospitalized patients with primary coccidioidomycosis is approximately 15%.[148] Most patients are febrile and have pleuritic chest pain. The pleural effusion is almost always unilateral and can occupy more than 50% of the hemithorax.[148] There is a coexisting parenchymal opacity in approximately 50% of patients. The pleural fluid is an exudate containing predominantly small lymphocytes and frequently eosinophils.[148] At times the pleural fluid can be pus. Pleural fluid culture results are positive for *Coccidioides immitis* in only approximately 20%, with poor results also from polymerase chain reaction.[149] Culture results of pleural biopsy specimens, however, are almost always positive. Most patients with primary coccidioidomycosis and pleural effusion require no systemic therapy. Because the complement fixation titers are usually high in patients with coccidioidal pleural effusion, a high titer alone should not be used as an indication for treatment. Only patients with prolonged or severe symptoms, evidence of dissemination, or at high risk for dissemination should be considered for first-line treatment with an azole.

Rupture of Coccidioidal Cavity

Hydropneumothoraces develop in 1–5% of patients with chronic cavitary coccidioidomycosis (see Fig. 56.6). The rupture of the cavity into the pleural space is usually heralded by the development of an acute illness with systemic signs of toxicity. These patients should undergo tube thoracostomy immediately to drain the air and fluid from the pleural space. Most patients require thoracotomy with partial or total lobectomy, and most require some degree of decortication.

CRYPTOCOCCOSIS

Pleural involvement in patients with cryptococcosis appears to result from extension of a primary subpleural cryptococcal nodule into the pleural space. Approximately 50% of patients with pleural cryptococcosis have disseminated disease, and most have an accompanying parenchymal abnormality. Most patients who have a cryptococcal pleural effusion are immunosuppressed, and many of the patients have *acquired immunodeficiency syndrome* (AIDS).[150] The pleural fluid is an exudate, usually with a predominance of small lymphocytes. Pleural cryptococcosis is treated with systemic antifungal therapy, with corticosteroids required in severe disease or disease in immunocompromised hosts.[151] Cryptococcal antigen titers can help confirm the diagnosis and evaluate response to treatment.[152]

HISTOPLASMOSIS

Pleural effusion is rare in patients with histoplasmosis. In a review of 259 patients with pulmonary histoplasmosis, only 1 patient had a pleural effusion.[153] Patients with pleural effusions secondary to histoplasmosis may have a subacute illness characterized by low-grade fever and pleuritic chest pain. The chest radiograph usually reveals an opacity or a subpleural nodule in addition to the pleural effusion.[154] The pleural fluid is usually a lymphocytic-predominant exudate, and the pleural biopsy may reveal noncaseating granulomas. No systemic treatment is generally necessary for a pleural effusion secondary to histoplasmosis because the effusion normally resolves spontaneously over several weeks. Systemic therapy should be administered if the effusion persists more than 3 to 4 weeks or if the patient is immunosuppressed.

PNEUMOCYSTIS JIROVECII

Pleural effusions are rare in patients with *Pneumocystis jirovecii* pneumonia, but they have been reported. There is, however, no evidence to support the routine testing of pleural fluid for *P. jirovecii,* except in severely immunocompromised patients.[155] When pleural effusions are present, they appear to be extensions of the pulmonary process, and concurrent pneumothoraces are common. The pleural fluid is an exudate with a relatively low protein level but an LDH level higher than the upper normal limit for serum. At times, organisms can be visualized in the pleural fluid.

VIRAL INFECTIONS

Viral infections are believed to account for a sizable percentage of undiagnosed exudative pleural effusions. However, the diagnosis is rarely established because it usually depends on the isolation of the virus or the demonstration of a significant increase in antibody titers to the virus. Molecular sequencing has been applied to pleural fluid, thereby identifying respiratory viruses in 20.7% (12 of 58) of children with a parapneumonic effusion or empyema.[156] However, these tests are not routinely performed on patients with undiagnosed pleural effusions.

PRIMARY ATYPICAL PNEUMONIA

The incidence of pleural effusions in patients with so-called primary atypical pneumonia (usually caused by *Mycoplasma* or viruses) is as high as 20%.[157] The effusions associated with atypical pneumonia are usually small, exudative, and contain predominantly neutrophils. If there is sufficient fluid, as described earlier, thoracentesis should be performed to exclude a complicated parapneumonic effusion.

OTHER VIRUSES

Viral infection is probably responsible for a much higher percentage of pleural effusions without parenchymal opacities than is generally recognized. In one epidemic, 559 soldiers in Turkey had an acute febrile illness characterized by pleuritic chest pain and a mononuclear cell–predominant pleural effusion without parenchymal opacities. No pathogens were demonstrated, and it was assumed that this self-limited disease was caused by a virus, although serologic studies were not performed.[158]

Almost all patients with the hantavirus pulmonary syndrome have a pleural effusion. Initially the fluid is a transudate, probably resulting from cardiac dysfunction, but subsequently the fluid becomes exudative.[159] Almost all patients with severe cases of dengue hemorrhagic fever have pleural effusions. Pleural effusions have also been reported to result from infection with hepatitis virus, Epstein-Barr virus (the agent of infectious mononucleosis), respiratory syncytial virus, influenza viruses, measles after the administration of inactivated virus vaccine, cytomegalovirus, herpes simplex virus, and Lassa fever virus. Pleural effusions can be seen after infection with Ebola virus, usually secondary to vascular leakage.[160]

ACQUIRED IMMUNODEFICIENCY SYNDROME

Pleural effusions are seen in patients with AIDS but are less common than are parenchymal opacities. In a series of 1225 consecutive hospital admissions of patients with AIDS in Jacksonville, FL, the incidence of pleural effusion was 15%.[112] The distribution of the diseases responsible for pleural effusions in patients with AIDS varies widely. In series from industrialized countries that included predominantly intravenous drug users, the most common cause is parapneumonic effusions; in series with predominantly homosexual patients, the most common cause is Kaposi sarcoma; in series from Africa, the most common cause is TB. Other causes of pleural effusions in patients with AIDS include primary effusion lymphoma (see eFig. 123.36), *P. jirovecii* infection, opportunistic infections, renal failure, and congestive heart failure.

In pulmonary Kaposi sarcoma, the incidence of pleural effusion is approximately 50% (eFig. 109.7). Most patients with a pleural effusion secondary to Kaposi sarcoma have bilateral parenchymal opacities (see eFig. 109.7B). The diagnosis of pleural involvement is difficult and often depends on the demonstration of pulmonary Kaposi sarcoma by bronchoscopic examination, high-resolution CT, or thoracoscopy. The pleural fluid is an exudate that is usually serosanguineous or hemorrhagic. Pleural fluid cytologic examination results are invariably negative with pleural Kaposi sarcoma; pleural biopsy results are also usually negative because the parietal pleura is generally not involved.

Patients with AIDS with an exudative pleural effusion should have a diagnostic thoracentesis that includes bacterial, mycobacterial, and fungal cultures and measurement of the pleural fluid adenosine deaminase level. If this does not establish a diagnosis, consideration should be given to performing thoracoscopy, at which time pleurodesis may be considered in symptomatic patients. A patient with AIDS and parapneumonic effusions should be managed as any patient with a parapneumonic effusion would be managed, while recognizing that the incidence of complicated parapneumonic effusion is higher in patients with AIDS.[113]

PARASITIC DISEASES

Parasitic infections of the lungs are discussed in Chapter 58. Those parasitic infections that may also involve the pleura—amebiasis, echinococcosis, and paragonimiasis—are also considered in this section.

AMEBIASIS

Approximately 20% of patients with amebic liver abscess will develop pleuropulmonary complications.[161] Pleural effusions arise by two different mechanisms. First, an amebic liver abscess may irritate the diaphragm and produce a sympathetic pleural effusion in a manner analogous to that caused by a pyogenic liver abscess. Second, a pleural effusion develops when an amebic liver abscess ruptures into the pleural space through the diaphragm (see eFig. 46.61).[162]

The sympathetic effusion in amebic liver abscess is the more common of the two presentations. The pleural fluid has not been well characterized. The diagnosis can be established by positive gel diffusion, indirect hemagglutination, or enzyme-linked immunosorbent assay tests, the results of which are positive in more than 98% of patients with extraintestinal invasive amebiasis.[162] Patients with amebic abscess and a sympathetic pleural effusion should be treated with antiamebic drugs.

The transdiaphragmatic rupture of an amebic liver abscess is usually heralded by an abrupt exacerbation of pain in the right upper quadrant and may be accompanied by a tearing sensation.[161] Shortly thereafter, progressive respiratory distress, sepsis, and occasionally shock develop. The pleural effusion is frequently massive, with opacification of the entire hemithorax and shift of the mediastinum to the contralateral

side.[161] The diagnosis of amebic abscess with transdiaphragmatic rupture is suggested by the discovery of "anchovy paste"– or "chocolate sauce"–like pleural fluid on diagnostic thoracentesis. Patients with transdiaphragmatic rupture should undergo urgent tube thoracostomy. These patients should be treated with the same antiamebic drugs (e.g., metronidazole) recommended for patients with amebic sympathetic effusions. Although the pus in amebic empyema is sterile,[163] microbiologic cultures of the pleural fluid should be obtained because bacterial infection of the pleural space complicates the process in about one-third of patients. If bacterial infection is present, appropriate antibiotic therapy should be initiated.

ECHINOCOCCOSIS

Pleural involvement with hydatid disease can develop in one of three situations: (1) a pulmonary hydatid cyst may rupture into the pleural space, (2) a hepatic hydatid cyst or rarely a splenic cyst may rupture through the diaphragm into the pleural space, or (3) a hydatid cyst may slowly enlarge into the pleural space.[164] When a cyst ruptures into the pleural space, either empyema or pneumothorax can result.[164] In a series of 474 patients with pulmonary hydatid disease, 6% had pleural thickening or effusion.[165]

When a hydatid cyst ruptures into the pleural space, the patient develops acute symptoms, with sudden tearing chest pain, dyspnea, and shock from the antigenic challenge to the body. The cyst can also rupture into the tracheobronchial tree, thus producing a bronchopleural fistula with hydropneumothorax that may become secondarily infected.[164]

The diagnosis of pleural echinococcosis is established either by the demonstration of echinococcal scolices with hooklets in the pleural fluid or in the pleural biopsy specimen or by a combination of serologic testing and radiology. Lobulated cystic lesions in the pleural space may be seen on CT or magnetic resonance imaging.[163] Eosinophils are frequently present in the pleural fluid unless it is secondarily infected. Patients with pleural echinococcosis should be immediately subjected to thoracotomy to remove the parasite, to excise the original cyst, and to close the bronchopleural fistula.[164] Patients with hydatid cysts should be treated with antiprotozoal therapy if all the cysts cannot be removed or if a cyst has ruptured. An alternative nonsurgical approach is PAIR therapy (puncture of the cyst, aspiration, injection of 95% ethanol or hypertonic saline for a period of time, and reaspiration), although this can cause allergic reactions.[163]

PARAGONIMIASIS

Pleural disease is common in patients with paragonimiasis. In a series of 71 patients, 43 (61%) had pleural disease, including 20 with unilateral pleural effusions, 6 with bilateral pleural effusions, 6 each with unilateral and bilateral hydropneumothorax, and 5 with pleural thickening.[166] Paragonimiasis can be found in natives of the United States who have never left the country.

Patients with pleural paragonimiasis present with a chronic illness. There is a concomitant parenchymal opacity in approximately 50% of patients. The pleural fluid in paragonimiasis is characteristic: exudative with a glucose level less than 10 mg/dL (0.56 mmol/L), an LDH level more than three times the upper limit of normal for serum, a pH lower than 7.10, and a high percentage of eosinophils on cell differential.[167] In addition, cholesterol crystals[120] or chyle[121] may be present. Pleural paragonimiasis is one of only two conditions in which the pleural fluid is characterized by a low pH, a low glucose level, and many eosinophils; the other is eosinophilic granulomatosis with polyangiitis. Usually, there are no ova in the pleural fluid.

The diagnosis of pleural paragonimiasis is strongly suggested by the unique pleural fluid findings, although in some cases lung biopsy may become necessary. The diagnosis is established definitively by demonstrating the typical operculated eggs in sputum, stool, or pleural fluid. A complement fixation titer greater than 1:8 for *Paragonimus westermani* is strongly suggestive of the diagnosis.[167]

Key Points

- The incidence of pleural infection and the mortality associated with it are increasing globally in both adults and children, for unclear reasons.
- Standard bacterial culture results are positive in only approximately 60% of pleural infection cases. Blood culture bottles can be combined with standard cultures to increase the yield.
- The organisms causing pleural infection often differ from those causing pulmonary infection.
- Community-acquired pleural infection is caused by a different range of organisms from hospital-acquired pleural infection and should be treated with different empirical antibiotics at presentation.
- The cornerstones of pleural infection management remain intravenous antibiotics, adequate drainage of the pleural collection, and adequate nutrition.
- A parapneumonic effusion with a pH of less than 7.20, a glucose level lower than 40 mg/dL, or a significantly loculated pleural collection generally requires chest tube drainage.
- Surgical techniques such as video-assisted thoracic surgery have become widely available and can be offered to most patients if less invasive approaches are unsuccessful.
- Intrapleural tissue plasminogen activator in combination with DNase has been shown to improve the chest radiographic evidence of empyema and to decrease hospital length of stay. The role of fibrinolytic therapy needs to be evaluated further before its routine use can be recommended.

Key Readings

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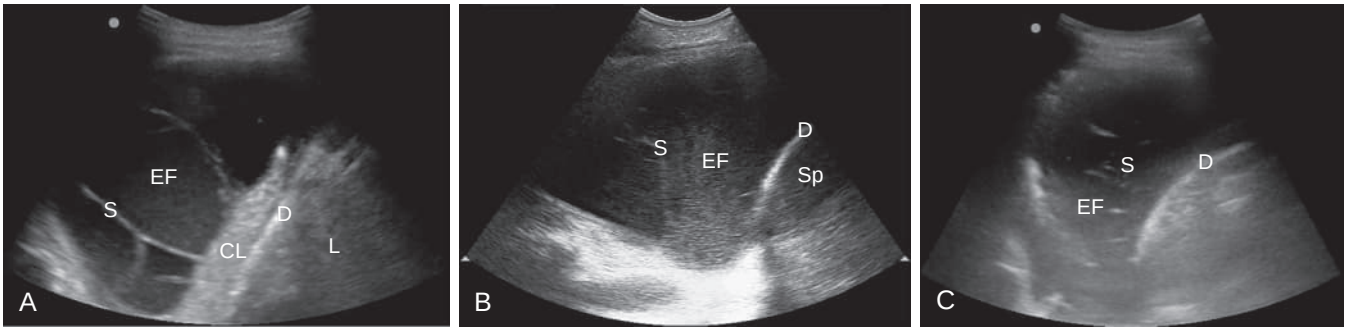
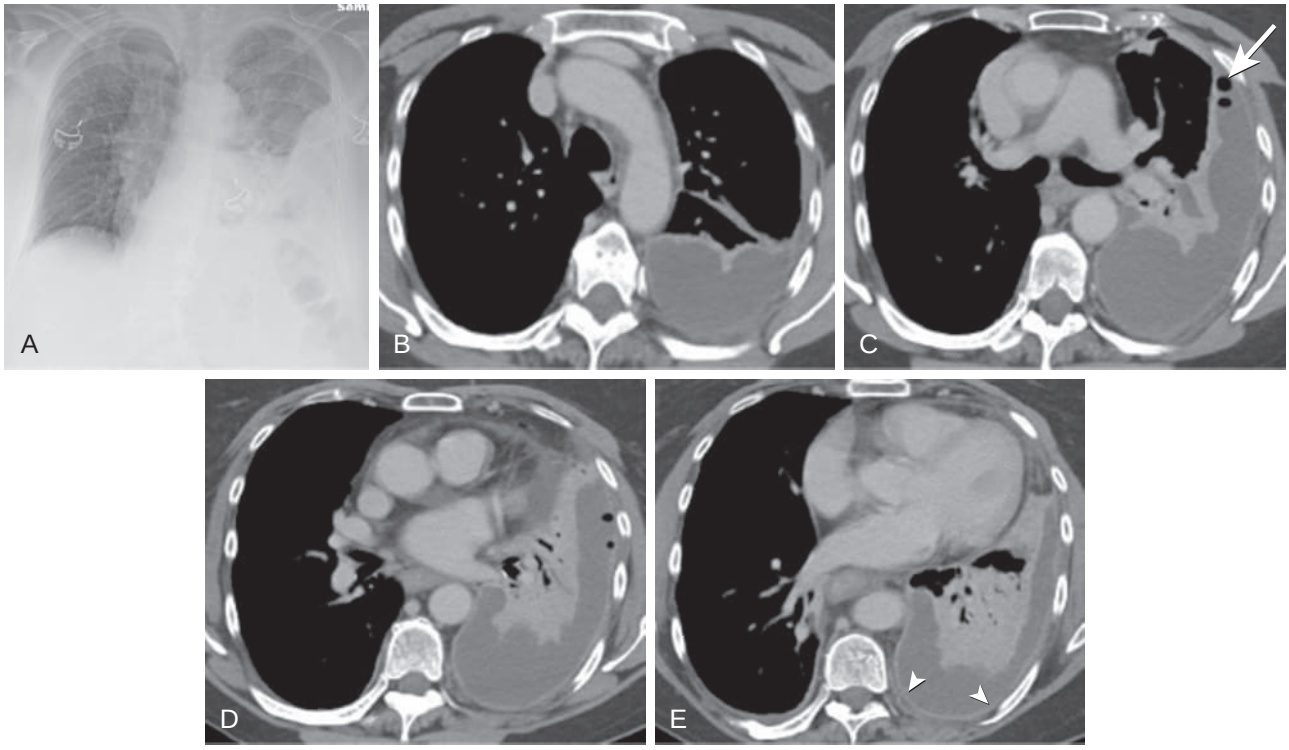
Complete reference list available at ExpertConsult.com.

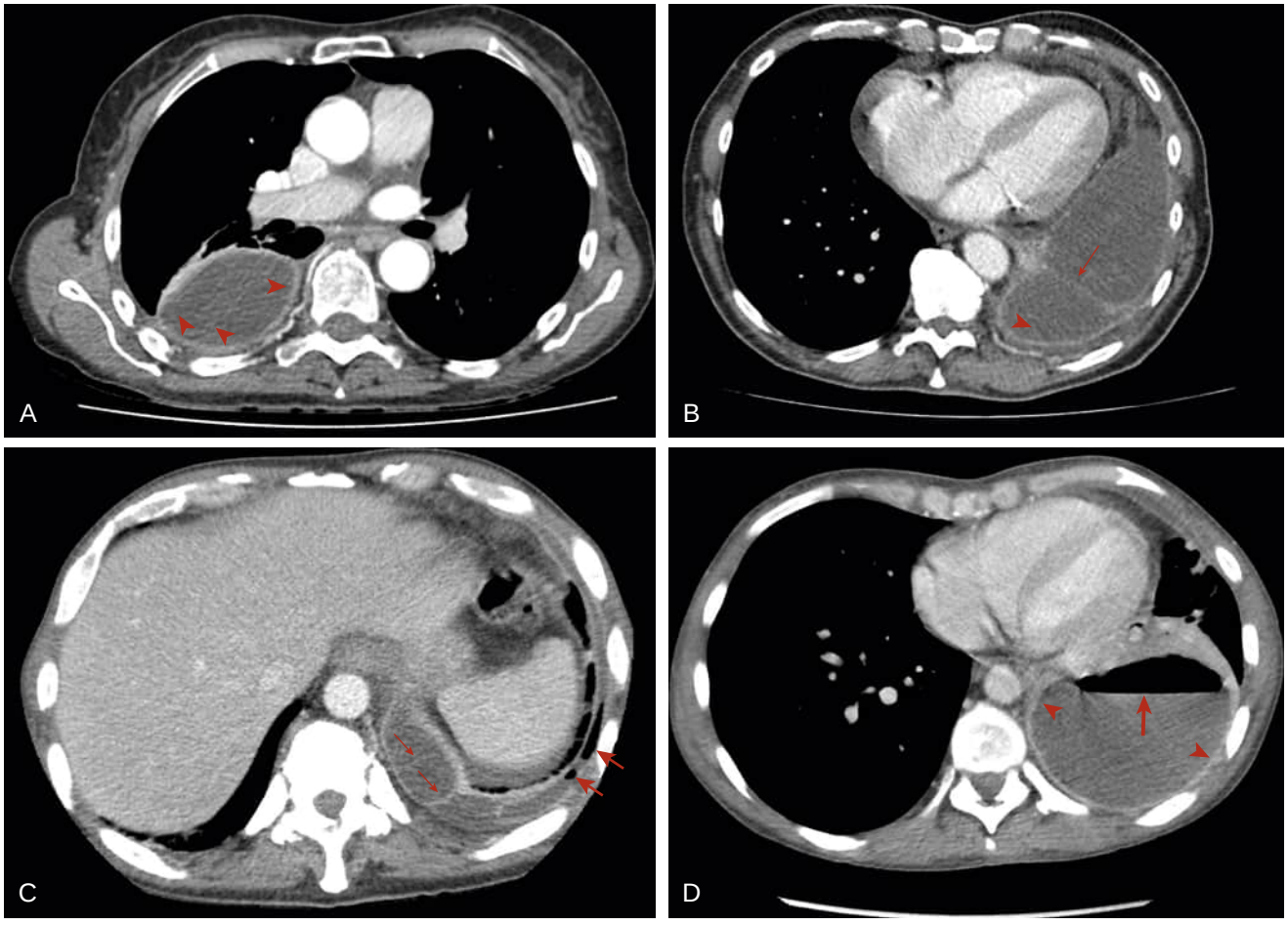
eFIGURE IMAGE GALLERY



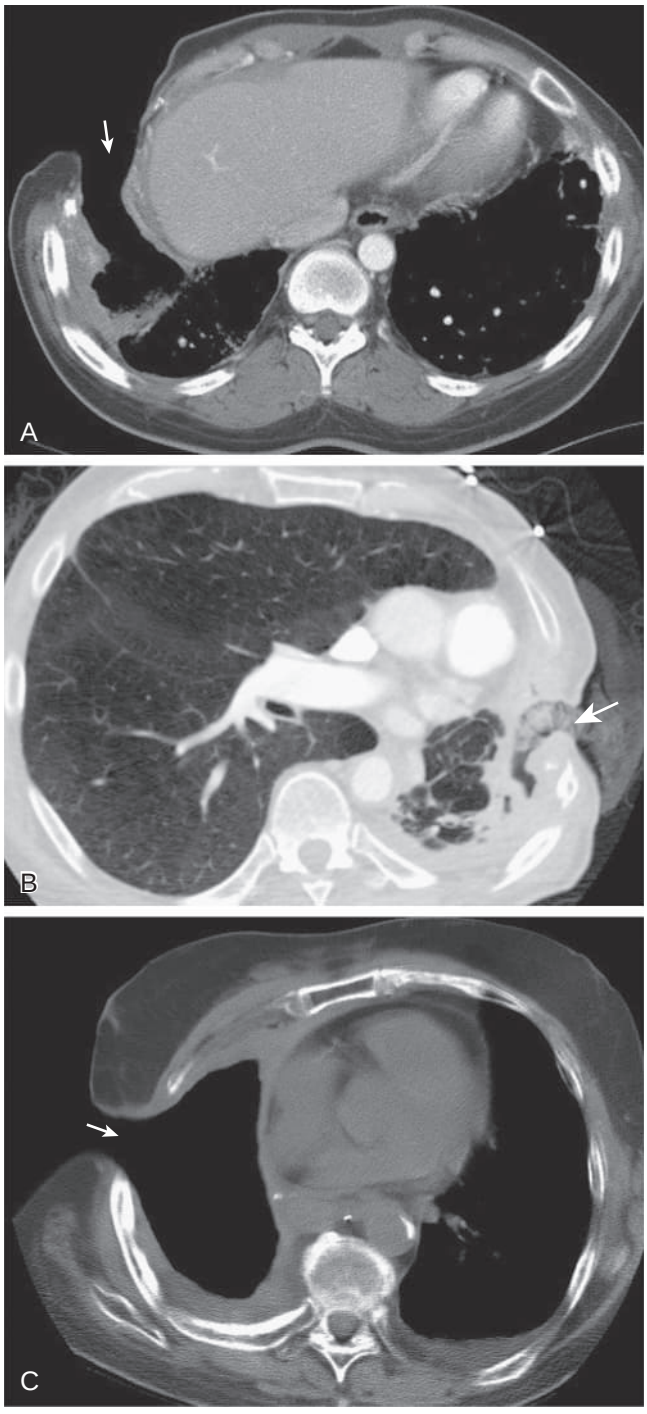
eFigure 109.1 Thoracic ultrasound imaging of pleural infection. (A) A moderately sized effusion is shown, lying cranial to a flattened diaphragm (D) and underlying liver (L). Collapsed and consolidated lung (CL) is seen above the diaphragm. Several septations (S) running through the fluid create multiple loculations. The fluid itself appears echogenic (EF). (B) Large echogenic effusion (EF), with a few thin septations (S) running through it. The diaphragm (D) and spleen (Sp) are imaged caudal to the fluid. (C) *Echogenic fluid* (EF) with multiple *septations* (S) running through it sits above the *diaphragm* (D).



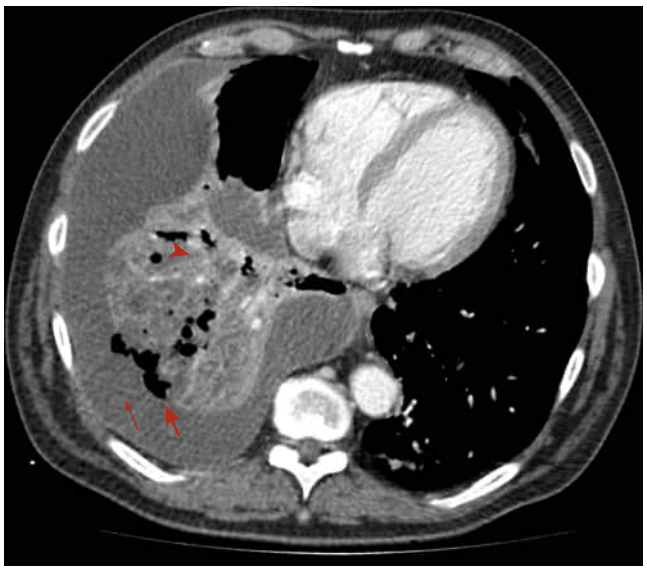
eFigure 109.2 Empyema: chest radiographic and thoracic computed tomography appearance. (A) Frontal chest radiograph shows a left-sided large, homogeneous opacity, without air bronchograms, occupying the left thorax. (B–E) Axial enhanced thoracic computed tomography shows multiloculated left pleural fluid associated with areas of nondependent gas (C, *arrow*) and smooth pleural thickening (E, *arrowheads*). Polymerase chain reaction analysis of material obtained at thoracoscopic débridement showed *Streptococcus anginosus* group bacteria as the causative agent. (Courtesy Michael B. Gotway, MD.)



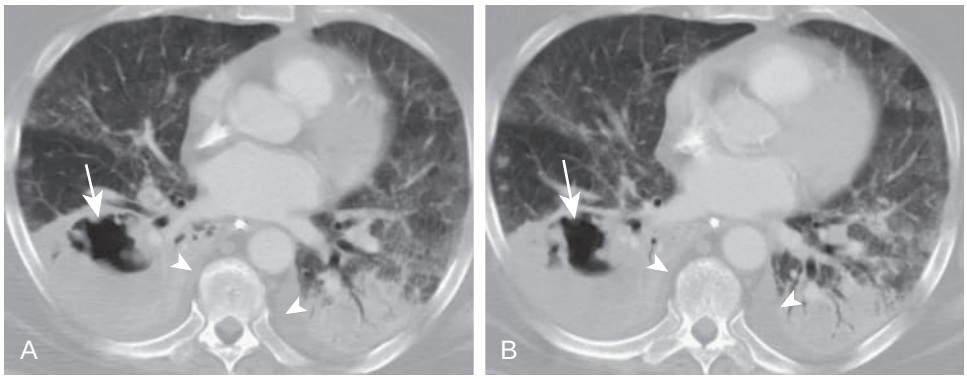
eFigure 109.3 Empyema: contrast chest computed tomography appearance. (A–D) Contrast-enhanced chest computed tomography in four different patients with empyema shows loculated pleural fluid collections with foci of smooth pleural thickening (*arrowheads*). In parts B and C, the collection is loculated, with fine septations (C, *thin arrows*) separating the fluid into pockets. (C–D) Two of the cases show gas-fluid levels (*thick arrows*), both appearing before intervention, a finding suggesting bronchopleural fistula.



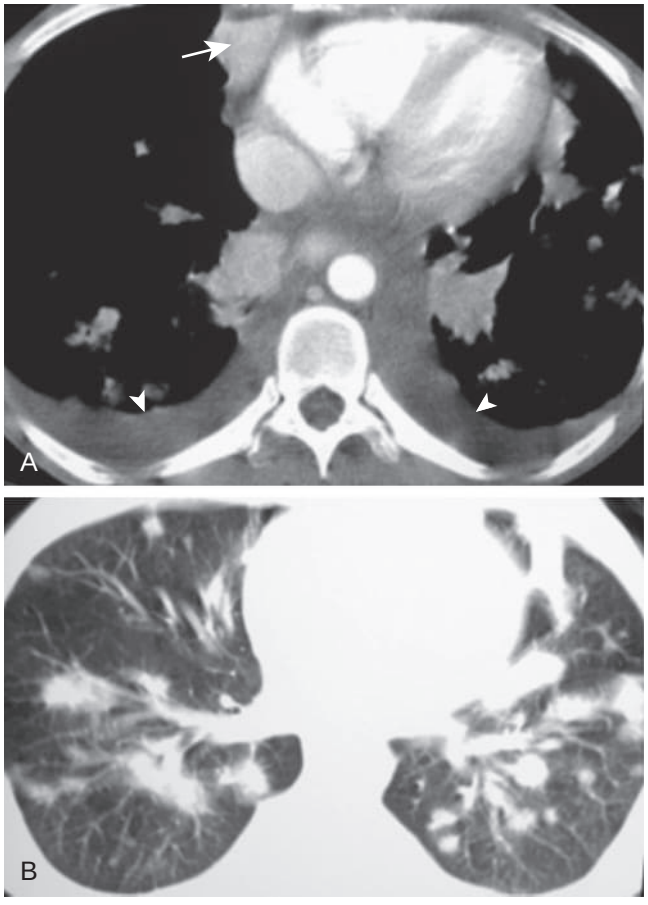
eFigure 109.4 Eloesser flap: chest computed tomography appearance. Axial (A) and (B) contrast and (C) noncontrast chest computed tomography images in three patients who underwent the Eloesser flap procedure, (A) one for chronic empyema, (B) one for treatment of bronchopleural fistula, and (C) the other as part of surgery for mesothelioma. All three images show a clear connection between the thorax and exterior (*arrows*). (C) The patient with mesothelioma shows concentric pleural thickening. (Courtesy Michael B. Gotway, MD.)



eFigure 109.5 Necrotizing pulmonary tuberculosis with associated pleural effusion. On axial chest computed tomography, free gas is visible within the lung (*arrowhead*). This finding represents parenchymal necrosis, with gas seen tracking into the pleural cavity (*thick arrow*), thus demonstrating a bronchopleural fistula. A single septation is seen within the fluid (*thin arrow*).



eFigure 109.6 *Nocardia asteroides* pulmonary infection with pleural effusion. (A–B) Axial enhanced chest computed tomography displayed in lung windows shows bilateral lower lobe consolidation, cavitary on the right (*arrows*). Trace bilateral, nonspecific pleural effusions (*arrowheads*) are present. (Courtesy Michael B. Gotway, MD.)



eFigure 109.7 Pleural effusions in Kaposi sarcoma. (A–B) Axial contrast chest computed tomography displayed in (A) soft tissue and (B) lung windows shows small, symmetrical, bilateral pleural effusions (*arrowheads*). Enhancing right cardiophrenic angle lymphadenopathy (*arrow*) is present. The typical appearance of bilateral, patchy, poorly defined peribronchial nodular opacities is readily appreciated on the lung window images (B). (Courtesy Michael B. Gotway, MD.)

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INTRODUCTION

Pneumothorax, or air in the pleural space, is a common clinical problem. A pneumothorax as a result of injury to the chest wall is termed traumatic. If pneumothorax results from an invasive medical procedure (e.g., pacemaker or central venous line insertion), it is referred to as iatrogenic. The term *spontaneous pneumothorax* is reserved for cases arising without preceding trauma or injury. These are typically further subdivided into *primary spontaneous pneumothorax* (PSP), developing in patients with apparently "normal" lungs, and *secondary spontaneous pneumothorax* (SSP), developing in patients with known lung disease. The *British Thoracic Society* (BTS) guidelines suggest that pneumothorax in patients who are older than 50 years or with significant smoking history should be labeled SSP, because there is a high likelihood of pathologic lung changes, even in the presence of a normal *chest radiograph* (CXR).[1]

SPONTANEOUS PNEUMOTHORAX

EPIDEMIOLOGY

The best epidemiologic data for pneumothorax come from large national datasets, of which there have been two recent publications. The largest, covering 50 years of hospital admissions in England, included over 170,000 admissions. This study showed an increase in the incidence of pneumothorax from 1968 to 2016,[2] although the reason for this increase is unknown. In 2016, there were 14.1 pneumothorax admissions per 100,000 people aged 15 years or older. The rate was higher for men (20.8) than for women (7.6 per 100,000),[2] and the study confirmed the classic bimodal age distribution, with a first peak at age 15 to 34 years and an increasing incidence beyond 60 years in both men and women, which had been shown in smaller studies.[3–5] The second large epidemiologic study from France showed similar incidence rates, but the classic bimodal distribution was not seen.[6] The English study for the first time described the admission rates by PSP and SSP on a large scale: 60.8% of patients in 2016 had chronic lung disease and were classified as having SSP.[2]

ETIOLOGY

Historically, patients with spontaneous pneumothorax are subcategorized into PSP and SSP because the outcome and clinical course are very different; consequently, management strategy differs significantly. The mortality and morbidity from patients admitted with SSP is higher than PSP.[5] However, the traditional view that PSP presents in the absence of lung disease is being challenged, and it is likely that these patients do not have completely "normal" lungs.[7,8] This section focuses on the two spontaneous entities, PSP and SSP. Other etiologies such as traumatic, iatrogenic, and catamenial are covered separately.

PRIMARY SPONTANEOUS PNEUMOTHORAX

Ectomorphic Body Shape

The classic body shape for the patients with PSP is "tall and thin." Indeed, PSP is more common in taller patients with low body mass index and in smokers.[9–11] A large-scale study of 5604 cases of pneumothorax in Japan found a significantly lower weight/height ratio in patients with pneumothorax compared to healthy individuals.[10] The risk of recurrence (i.e., another episode of pneumothorax) in PSP patients was higher in taller patients, but only in men. Interestingly, height (in women) and a lower body mass index (in either sex) were not associated with increased risk of recurrence.[9]

Abnormal Lung Parenchyma and Smoking

Although PSP may present in patients without overtly recognized lung pathology, there is evidence that patients with PSP have macroscopic and microscopic structural abnormalities characterized by microscopic evidence of distal airways inflammation, "pleural porosity," and emphysema-like changes. Such emphysema-like changes include subpleural blebs and bullae, commonly seen in

patients with PSP on surgical inspection and on *computed tomography* (CT) scans,[12–18] but also in healthy volunteers (both smokers and nonsmokers).[12,19] Therefore, one cannot assume that these abnormalities are the sole cause of pneumothorax because they are not present in all patients with PSP and may be present in healthy individuals without PSP.

Smoking is a well-known risk factor for pneumothorax.[20,49] Although the exact mechanism is unclear, it has been postulated that small airways inflammation associated with smoking results in weakening of the visceral pleura, or dilation of the distal airways, resulting in increased airway pressure. However, it should be noted that not all smokers get pneumothorax, and there is likely an underlying susceptibility to cigarette smoke that results in the pneumothorax phenotype. Interestingly, risk of recurrence is not consistently increased in smokers compared to nonsmokers.[9,20–22] It is not yet known whether pneumothorax and lung changes are associated with the use of marijuana or e-cigarettes.

Blebs and Bullae. The anatomic lesion known as a bleb was first described in 1947 by Miller, as distinct from a bulla (or bullous emphysema).[23] A bleb is defined as an outpouching (or vesicle) of the visceral pleura caused by air in the interstitium, forming between the lamina elastica interna and externa of the visceral pleura, typically less than 1 cm in diameter (Figs. 110.1 and 110.2). In contrast, a bulla is an airspace measuring greater than 1 cm, which is sharply demarcated by a thin wall (≤1 mm in thickness). In 1967, Reid further subdivided bullae into three types: type I, a small amount of hyperinflated lung tissue that is narrow (pedunculated) and contains no lung parenchyma; type II, a relatively smaller amount of hyperinflated lung tissue that is broad (sessile); and type III, a large amount of hyperinflated lung tissue extending to the pulmonary hilum, with ill-defined margins and minimal parenchyma in each bulla.[24] These areas of disrupted mesothelial cells at the visceral pleura, replaced by an inflammatory fibroelastic layer, along with observed small pores, may contribute to a more general "pleural porosity."

Microscopic Abnormalities. Microscopic abnormalities have been identified in the lungs of PSP patients. In an early pathologic study of 20 young patients with PSP, resected lung parenchyma showed features of chronic distal airway inflammation with lymphocyte and macrophage infiltration alongside fibrotic changes.[25] In another study of 79 patients with PSP, *respiratory bronchiolitis* (RB) was identified on surgical biopsy in 88.6%.[26] Unfortunately, all the patients in this study were smokers, a known cause of RB. Thus, whether RB was a causal step in the development of pneumothorax or simply a marker of smoking status remains unclear. A subsequent study of 126 surgical cases found that RB was present in only 50% of patients.[27] In the same patients, light microscopic assessment demonstrated thickening and fibroelastosis of the pleura. Reid type I bullae were found to have microscopic changes in keeping with that originally described by Miller with respect to blebs, with formation of small air-containing spaces between lamina elastic interna and externa that contains no lung parenchyma (see Fig. 110.1).[24,27] Whether these

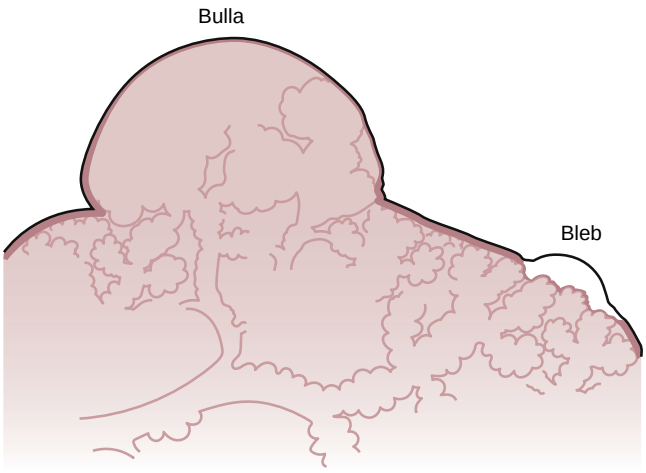

Figure 110.1 Blebs and bullae. The anatomy of emphysematous lung lesions is shown, representing a bleb and a bulla. (From Lyra R de M. Etiology of primary spontaneous pneumothorax. *J Bras Pneumol*. 2016;42[3]:222-226.)



Figure 110.2 Thoracoscopic view of a bleb on the visceral pleural surface. A bleb tends to be small (<1 cm in diameter) and forms within the visceral pleura. (Courtesy M. Noppen, Brussels University Hospital.)

microscopic changes lead to rupture of air into the pleural space and PSP is speculative, the abnormalities found in this study support the hypothesis that the underlying lung in PSP patients is not normal.

Historically, it has been postulated that rupture of blebs or bullae creates direct communication between the alveolar air and the pleural space, thus creating a pneumothorax. This view was contested by the observation that the presence of visible air leaks at thoracoscopy or thoracotomy is highly variable,[28] with many blebs or bullae remaining intact and, in some cases, with no macroscopic lesions at all. The concept of pleural porosity as a possible driver of PSP, rather than bulla or bleb rupture, was elegantly demonstrated in a study by Noppen et al.[19] (see Video 29.11). Twelve patients with PSP were compared to 17 control subjects at thoracoscopy using fluorescein-enhanced autofluorescence. Control subjects were undergoing sympathectomy (for hyperhidrosis) and therefore did not have any lung disease or history of pneumothorax. In both groups, there were areas of parenchymal abnormality, seen as areas of subpleural fluorescence or visible fluorescence leak when inspected under ultraviolet light, at regions of the lung that otherwise appeared normal with inspection under white light. However, high-grade lesions were seen only in PSP patients. Two patients with emphysema-like changes

demonstrated air leak, but the leakage was not directly at the site of the macroscopic blebs or bullae.[19] Thus, areas of porosity appeared to be more closely associated with air leakage than did the blebs and bullae.

Abnormal Elastosis. Areas of porosity may be a consequence of airway inflammation. One theory is that there is an imbalance in the protease-antiprotease systems. *Matrix metalloproteinases* (MMPs) are a group of zinc- and calcium-dependent endopeptidases that can damage basement membrane.[29] MMP-2 and MMP-9, two interstitial collagenases, have been postulated to be pathogenic in other lung diseases,[30] including asthma and COPD.[31] Two Taiwanese groups have examined surgical resection specimens from patients undergoing surgery for PSP and demonstrated overexpression of MMPs.[29,32] In the first study, immunohistochemistry showed overexpression of MMP-2, MMP-7, and MMP-9 in the tissue of PSP patients compared to controls.[29] In the second study, high MMP-2 and MMP-9 expression was found in patients undergoing surgery for recurrence prevention, and higher levels were found in patients presenting with a recurrent pneumothorax compared to those with a first episode.[32] Although these studies present intriguing data on elevated MMP levels in PSP, further prospective studies are required to confirm these findings and determine their clinical applicability in terms of risk stratification of patients or potential treatment options.

Familial Causes

Most episodes of PSP arise sporadically. However, an estimated 10% of patients have a significant family history.[33,34] A number of important inherited conditions predispose to pneumothorax, including Marfan syndrome,[35] *Birt-Hogg-Dubé* (BHD) syndrome,[36] alpha$_1$-antitrypsin deficiency,[37] and homocystinuria.[38] Marfan syndrome is caused by mutations in the *fibrillin 1 (FBN1)* gene; the major manifestations include increased height, disproportionately long limbs and digits, subluxation of the lens of the eye, and dilation of the aortic root.[35] Apical blebs and spontaneous pneumothorax have been described as minor diagnostic criteria for Marfan syndrome.[35] Whether mutations in *FBN1* predispose individuals to PSP in the absence of Marfan syndrome is not clear. Mutations in *FBN1* are not the cause of all autosomal dominant familial spontaneous pneumothorax; an analysis of two pedigrees of patients with a strong family history of spontaneous pneumothorax did not find associated mutations in *FBN1*.[39] It is presumed that the fibrillin mutation causes a weakness in the fibroelastic layer in the visceral pleura, but this has not been proven. BHD syndrome is an autosomal dominant inherited disease caused by mutations in the *folliculin (FLCN)* gene. BHD is characterized by benign skin tumors, diverse types of renal cancer, pulmonary cysts, and spontaneous pneumothorax.[36,40] It is likely that, as our understanding of pathogenesis increases, more genes with a role in pneumothorax will be discovered.

Although familial patterns of inheritance of spontaneous pneumothorax, particularly with autosomal dominance, are uncommon, a strong family history of pneumothorax should prompt further investigation. In this situation, the pneumothorax event may be a precursor to an unrecognized connective tissue disorder (Marfan or Ehlers-Danlos syndrome), skin disease (BHD), or metabolic disorder (homocystinuria) with the need for potential lifelong surveillance for other severe associations (e.g., renal cancer or aortic rupture).

It seems likely that minor mutations in *FBN1* or *FLCN* could predispose to the development of PSP without causing the full clinical spectrum of Marfan or BHD syndrome. This is an area that requires large-scale prospective studies with the collection of genetic and clinical data. Such data, if successful in identifying causative genetic mutation(s), could potentially determine an individual's risk of recurrence.[41,42] Clinicians should be vigilant for PSP being the first manifestation of a systemic disease and should have a low threshold for referral for genetic counseling.[41,42] At present, routine CT scan of the chest and pulmonary function testing are not standard after uncomplicated treatment of a first episode of PSP. However, some clinicians opt for a low-dose CT scan in female patients or males with a strong family history to exclude important familial diagnoses (above) or underlying lung disease such as *lymphangioleiomyomatosis* (LAM).

SECONDARY SPONTANEOUS PNEUMOTHORAX

A host of airway and lung diseases can be complicated by SSP. In the United Kingdom, the most common of these is COPD.[43] The most common cause worldwide remains pulmonary tuberculosis. Other common causes include cystic fibrosis, lung cancer, necrotizing pneumonias, and human immunodeficiency virus–related *Pneumocystis jirovecii* lung infection. However, there are few large-scale epidemiologic studies quantifying the risk of pneumothorax in these chronic diseases. Two rare infiltrative lung diseases are commonly associated with SSP: pulmonary Langerhans cell histiocytosis and LAM, with or without other features of tuberous sclerosis[44] (eFig. 110.1). Indeed, spontaneous pneumothorax in younger women (30 to 40 years old) may be the first manifestation of LAM.[44] Recurrent pneumothorax in women of childbearing age should prompt consideration of catamenial pneumothorax due to thoracic endometriosis.[45,46] The causes of SSP are summarized in Table 110.1.

TENSION PNEUMOTHORAX

Tension pneumothorax is a medical emergency. Tension develops when the leak in the visceral pleura functions as a one-way valve allowing air into the thorax but not allowing escape, thus progressively increasing intrapleural pressure. The increased pressure causes chest discomfort, reduces venous return, and eventually results in hypotension and hemodynamic compromise due to compression of the right ventricle and subsequent reduction in left ventricular end-diastolic filling pressure. These patients require urgent decompression with a cannula placed anteriorly in the second intercostal space in the midclavicular line. The unilaterality of the patient's complaints and signs on examination should be sufficient to identify the pneumothorax; in this setting, treatment should not be delayed for radiologic confirmation.[1] Tension is relatively rare in PSP and usually develops in the context of trauma or in ventilated patients in intensive care units,[48] but it should be noted that the true incidence is unclear.

Table 110.1 Disorders Associated With Spontaneous Pneumothorax

Common	COPD, pulmonary tuberculosis
Uncommon	Cystic fibrosis, lung cancer, *Pneumocystis jirovecii* infection
Rare	**Interstitial lung diseases**: idiopathic pulmonary fibrosis, sarcoidosis, pulmonary Langerhans cell histiocytosis, lymphangioleiomyomatosis **Connective tissue diseases**: rheumatoid arthritis, scleroderma, ankylosing spondylitis, Marfan syndrome **Familial conditions:** Birt-Hogg-Dubé syndrome, Ehlers-Danlos syndrome, homocystinuria, catamenial pneumothorax

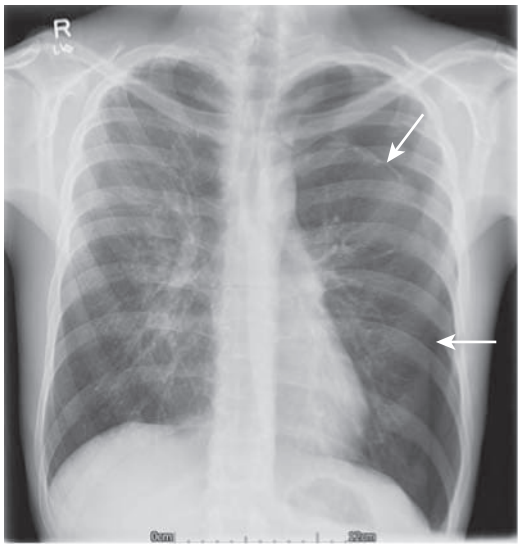

Figure 110.3 Chest radiograph showing left-sided pneumothorax without mediastinal shift. The visceral pleura is clearly visible (*arrows*) with an absence of lung markings distally.

DIAGNOSIS AND MANAGEMENT

Symptoms

Patients usually present with chest pain and/or breathlessness. The cause of chest pain is not clear but may be due to acute inflammation of the parietal pleura[47] or to tearing of small adhesions as the visceral pleura moves away from the parietal surface. Tearing of adhesions would be likely to cause some bleeding (hemopneumothorax), but significant intrapleural bleeding is a rare complication of pneumothorax; on the other hand, the CXR in many patients with pneumothorax demonstrates a basal air-fluid level if this is carefully looked for, perhaps suggesting a small pleural bleed. The physiologic cause of breathlessness is not clear—this may be due to expansion of the chest wall and depression of the diaphragm or an alteration in respiratory mechanics and perception. Such changes have been postulated to contribute to breathlessness in patients with emphysema and in those with pleural effusion.

Clinical Examination

On examination, there is usually ipsilateral increased chest wall size, decreased chest wall expansion with breathing, a hyperresonant percussion note (tympany), and diminished breath sounds. However, signs can be subtle in patients with small pneumothoraces or when the patient has underlying emphysema or cystic lung disease. Deviation of the trachea to the contralateral side on examination, if present, with hemodynamic compromise along with tympany and enlargement of the hemithorax on the affected side would signify tension pneumothorax and the urgent need to intervene (see later). Arterial blood gas measurements are not usually clinically indicated; in a large and acute pneumothorax, these may demonstrate hypoxemia and an increase in the alveolar-arterial oxygen tension difference. However, in most pneumothoraces where the underlying lung is not diseased, very little disturbance to oxygen saturations is seen, possibly because of matched perfusion-ventilation defects as a result of lung collapse (see Chapter 44).

Imaging

In patients with suspected non–tension pneumothoraces, a CXR should be used to confirm the diagnosis: the visceral pleura is clearly visible as a line with an absence of lung markings distally (Fig. 110.3). Often the distinction of the visceral pleural line and other lines, such as skinfolds, can be challenging (Fig. 110.4). A pleural line should have air on both sides, have no lung markings distal to it, and be continuous along the length of the pneumothorax.

In most cases, a standard erect frontal CXR is sufficient to confirm the diagnosis of pneumothorax. Small pneumothoraces can be difficult to ascertain and may be missed on a frontal CXR. In cases where there is a high clinical index of suspicion, lateral CXRs are sometimes useful and can detect pneumothorax in up to an additional 14% of cases.[49] In a supine patient, the intrapleural air of a pneumothorax will move and lie in the anterior region of the pleural space, where it will have a different appearance on CXR. As an example, in a supine patient, a pneumothorax can produce the deep sulcus sign, in which the air collects between the diaphragm and chest wall (Fig. 110.5).

However, with ready access to CT scanning, many physicians opt for a chest CT to avoid any doubt. This is particularly important in situations in which missing a small pneumothorax may have detrimental consequences, such as in patients with extensive lung disease or in those on positive-pressure ventilation.[50] Another indication for CT scan is to differentiate pneumothorax from severe bullous lung disease because an erroneous diagnosis and subsequent chest tube insertion could lead to puncture of the lung, with risk of ongoing leak and bronchopleural fistula (Fig. 110.6).

Midline Shift. Midline shift refers to deviation of the mediastinal structures away from the side of the pneumothorax. Certainly, a tension pneumothorax will show a midline shift (unless the mediastinum is fixed in place). However, midline shift can also be seen in patients without hemodynamic compromise and thus does not equate to tension pneumothorax. If the mediastinum is not fixed in place, the mediastinum can shift in response to a difference in pressure between the two hemithoraces without one side having positive intrapleural pressure indicative of tension physiology.

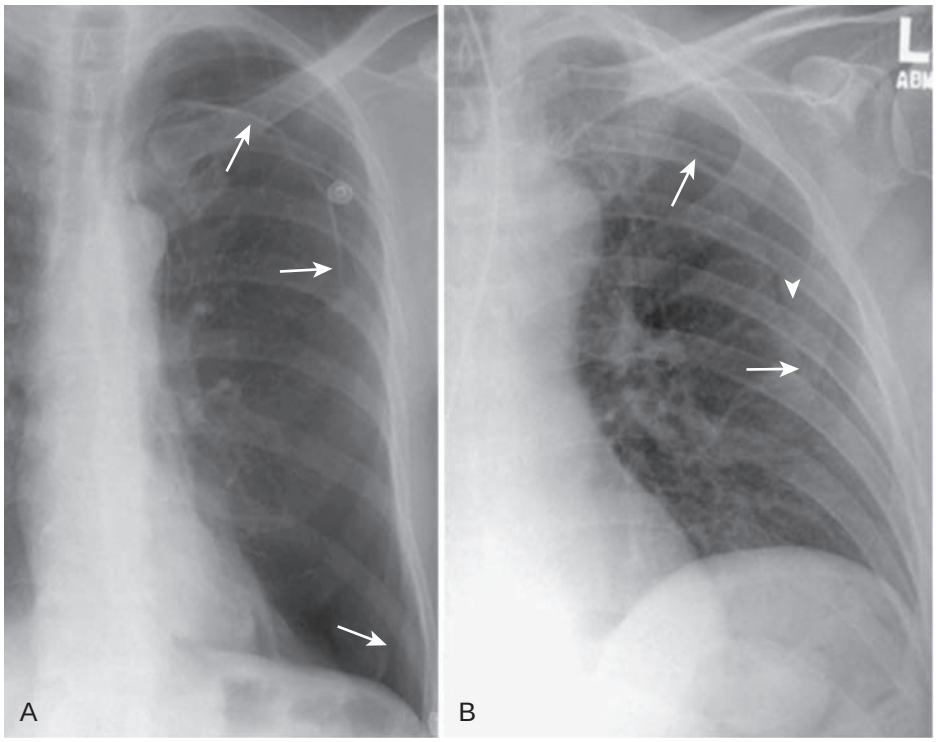

Figure 110.4 Distinguishing a pneumothorax from a skinfold. (A) Chest radiograph of a pneumothorax. The pleural line has lucency on either side, representing air in the pleural space on one side of the line and air in the lung on the other. The line is sharply demarcated and can be traced along its course (*lower arrow*). No blood vessels can be seen beyond the superior (*upper arrow*) and lateral (*middle arrow*) extent of the line. (B) Chest radiograph of a skinfold (*arrows*) that could be mistaken for a pneumothorax. The border is more of an edge, with lucency on only one side. The edge is poorly defined and cannot be followed continuously (*lower arrow*). Blood vessels can be traced beyond the border of the fold (*arrowhead*).

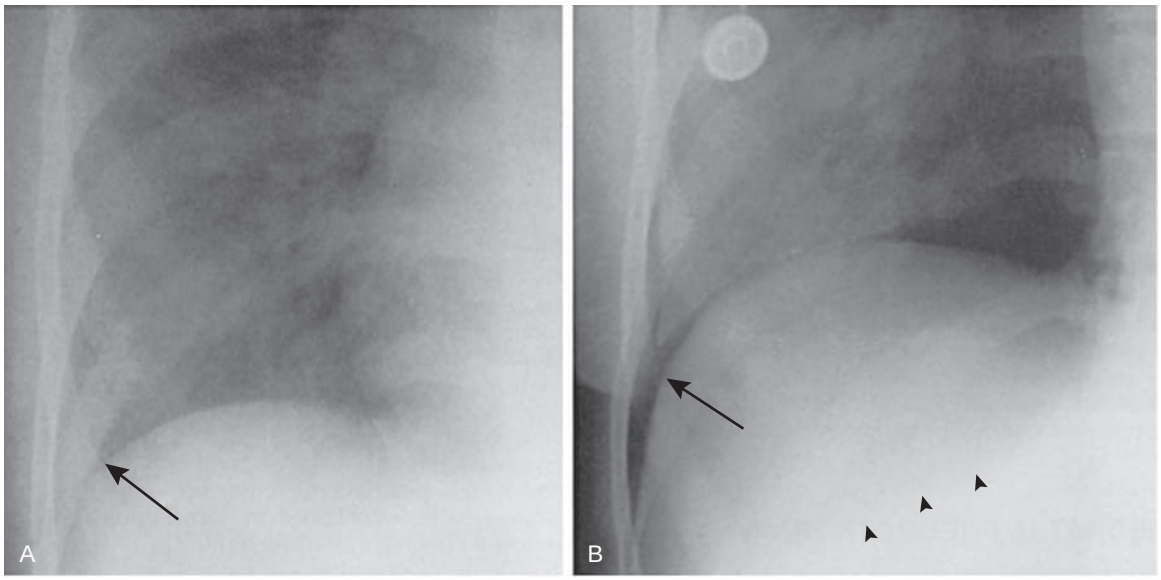

Figure 110.5 Deep sulcus sign of pneumothorax in a supine patient. Detailed views of the right costophrenic angle from successive supine chest radiographs taken before (A) and after (B) the development of a pneumothorax. Both images show diffuse infiltration in the right lower lung field. Note change in costophrenic angles (*arrows*) caused by air in the pleural space between the diaphragm and chest wall: the deep sulcus sign. Air in the anterior pleural space can also be recognized by an air-tissue interface (*arrowheads*).

Use of Ultrasound in Pneumothorax. There is increasing interest in the use of thoracic ultrasound to diagnose pneumothorax (see Chapter 23). The majority of the studies are prospective case series comparing imaging modalities in diagnosing pneumothorax in the context of trauma, iatrogenic (e.g., post–image-guided biopsy), or critical care. The absence of normal-appearing lung on thoracic ultrasound (i.e., the absence of the normal findings of lung sliding and of B lines) can be used to diagnose pneumothorax with very high sensitivity and specificity. There are now *randomized controlled trials* (RCTs) assessing clinical impact or outcome and four

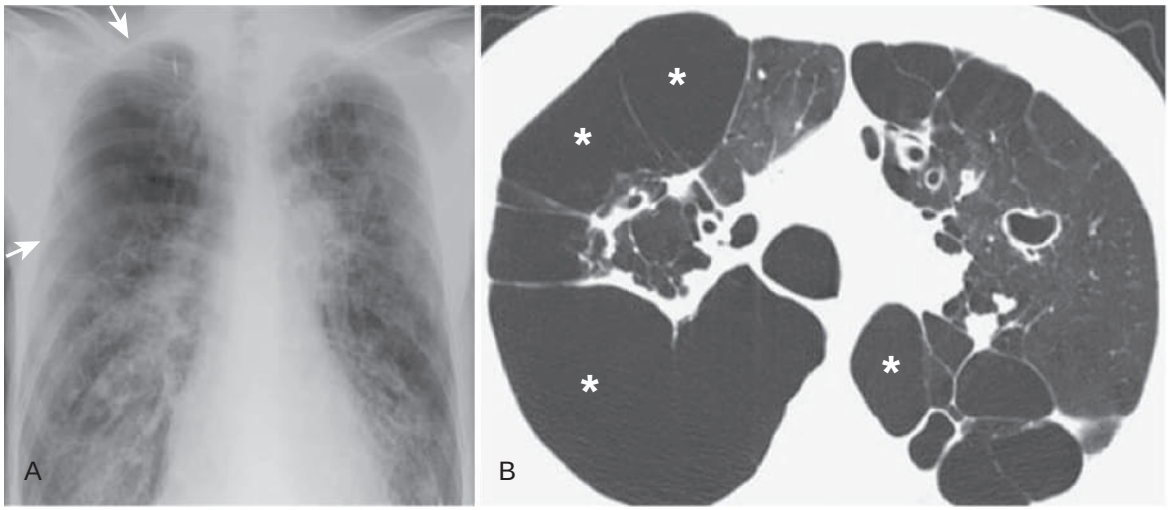

Figure 110.6 Bullae resembling pneumothorax. (A) Frontal chest radiograph of a patient with cystic fibrosis and extensive bullous disease of the right apex that was initially mistaken for a pneumothorax. Note lucent area (*arrows*) within the right upper lung field. (B) Computed tomography scan confirms the presence of bullae (*asterisks*) and excludes pneumothorax.

meta-analyses of these data comparing the accuracy of thoracic ultrasound for pneumothorax compared to CXR.[51–54] Pooled sensitivity for ultrasound was 78–90% with a specificity of greater than 98%. CXR performed more poorly with a pooled sensitivity of 39–52% but a similar specificity. However, the vast majority of these patients were trauma patients lying in a supine position in the emergency department, which naturally reduces the sensitivity of CXR.

It is important to note that there are also false-positives for ultrasound in diagnosing pneumothorax, particularly in patients with underlying lung diseases. This is particularly evident in patients with COPD who may have bullae close to the pleural surface, which can also show an absence of the lung sliding sign and thereby give an appearance similar to pneumothorax.[55]

Thoracic ultrasound can potentially be used to identify pneumothorax post–lung biopsy[56–58] or to determine when pneumothoraces have resolved after chest tube drainage.[59] However, further studies are required before this becomes standard practice. We use thoracic ultrasound in the diagnosis of pneumothorax post–lung biopsy and during pleural procedures but not as a primary diagnostic strategy in most cases, in which a combination of CXR and CT is optimal.

Decisions on Intervention

The first treatment decision is whether intervention is required or not. Clinically stable patients with a small PSP on CXR can be managed conservatively (i.e., observation alone) with close CXR follow-up to ensure resolution. However, there is considerable controversy about the optimal treatment of a minimally symptomatic PSP patient with a large pneumothorax on CXR, and management therefore varies.

Size of Pneumothorax. The size of a pneumothorax is difficult to infer from the two-dimensional CXR image. There are a number of methods of estimating pneumothorax size. One is the Light index, calculated using the ratio of the cube of lung diameter to hemithorax diameter.[37] Using this formula, a pneumothorax with a 2 cm depth at the level of the hilum on CXR has an approximate volume of 50% of the hemithorax. Another method suggested by Rhea et al. uses the average of the interpleural distances measured at the apex, midpoint of the upper half of the lung, and midpoint of the lower half of the lung on an erect CXR.[60] However, international guidelines do not agree on size measurement criteria.[1,7,61] In clinical practice, the most commonly used methods are the two adopted by the BTS and the American College of Chest Physicians, which rely on depth of pneumothorax from the chest wall, possibly because these are relatively simple and therefore applicable in clinical daily practice.

The BTS definition of a large pneumothorax is greater than 2 cm of air between the lung margin and the chest wall measured at the level of the hilum on CXR.[1] The American College of Chest Physicians consensus statement proposes that a large pneumothorax has 3 cm or greater of air measured from the apex to the inner chest wall at the thoracic cupola.[61] The Belgian Society of Pneumology proposed that a large pneumothorax has a visible lung visceral pleural line along the whole length of the lateral chest wall[62] (also referred to by some authors as complete dehiscence). However, it is clear that there is little consensus and potentially limited use in size calculation. A study of 49 cases of pneumothorax compared the classification of pneumothorax size across these three guidelines and found agreement in only 47%[63] of cases. In addition, it is acknowledged that size of the pneumothorax on CXR does not correlate to symptoms. The BTS guidelines include the caveat that "in some patients with a large pneumothorax but minimal symptoms, conservative management may be appropriate."[1] Therefore, the decision to treat or not is largely based upon clinical judgment rather than size; patients with a small pneumothorax but severe symptoms may require intervention, whereas stable patients with a pneumothorax classified as large may be initially managed conservatively with observation only.

In a recently reported randomized trial in moderate to large PSP, conservative management (i.e., no intervention) was compared to standard care (i.e., aspiration and/or chest tube insertion). The conservative group did quite well, and the majority of patients in both arms had resolution of their pneumothorax by 8 weeks.[64] These data add evidence

to the BTS guidance that patients with minimal symptoms can be safely managed conservatively.

In contrast to PSP, in which observation or short-term treatment is encouraged as the first treatment, current guidelines recommend that all patients with SSP should be admitted to the hospital for at least 24 hours and receive supplemental oxygen. Most SSP will require a chest tube.[1] This cautious approach is recommended in SSP because the underlying lung disease is thought to increase the risk of complications (such as respiratory failure) or prolonged ongoing air leak; indeed, there are data suggesting that spontaneous resolution of pneumothorax is far less common in SSP versus PSP.[65,66]

Initial Management Options

Once the decision is made to intervene, the next choice is whether to attempt *needle aspiration* (NA) or to insert a small-bore chest tube. BTS guidelines recommend NA (using a 16- to 18-gauge cannula) of up to 2.5 L of air as initial treatment. If NA is unsuccessful in expanding the lung, chest tube insertion is required.[1] These recommendations are based upon RCTs showing "equivalence" of NA and chest drainage in terms of initial success rates, varying between 59% and 80%.[67–70] However, there were significant differences in the definition of "initial success," and trial design between the studies (eTable 110.1), and none of the studies was designed as a true noninferiority comparison.

In 2007, the first Cochrane review of this topic[71] included only one RCT. This study by Noppen et al. included 60 patients with a first episode of PSP randomized to either NA or chest tube. Initial success rates were not significantly different between the groups: 59.3% after NA and 63.6% after chest tube.[69]

In 2017, Carson-Chahhoud et al. updated the Cochrane review,[72] this time with six RCTs,[67–70] including Parlak,[73] who also recruited patients with traumatic (as well as spontaneous) pneumothoraces. The Cochrane review concluded that immediate success rates were higher in the chest tube group than the NA group.[72] However, there was heterogeneity in the definitions of immediate success. Recurrence rates were no different between the groups. Hospital stay was shorter in the NA group with fewer complications compared to the chest tube group.[72]

Since that review, two more RCTs have been published: Ramouz et al. enrolled patients with PSP and again found similar immediate success rates with NA and chest tube and shorter hospital stay in the NA group.[74] Thelle et al. recruited both PSP and SSP patients and reported NA to be more effective than chest tube drainage for initial treatment success (68.8% vs. 31.8%), although 37.5% of patients required a second aspiration.[75] This was the first study to include significant numbers of patients with SSP and to report the results separately; there was a higher success rate for NA in both PSP and SSP patients. The authors suggest the guidelines should be changed to treat SSP in the same way as PSP (i.e., with NA as initial treatment).[75] However, it should be noted that the chest tube group had a lower success rate (31.8%) than in previous studies; thus, first-line treatment of SSP with NA requires further validation before it can be widely recommended.

Supplemental Oxygen

In patients who are not undergoing intervention to drain the pneumothorax, supplemental oxygen can be prescribed. Evidence from a small study in 1971 suggests that use of 100% oxygen in patients with spontaneous pneumothorax can increase the rate of absorption fourfold compared to air (on the basis of mean reduction in pneumothorax size of 4.8 and 18 cm^2/day, respectively).[76] The rationale is that by reducing the partial pressure of nitrogen in the inspired gas, and thus in pleural capillaries, the rate of nitrogen absorption from the pneumothorax is increased, thereby increasing the rate of resolution of the pneumothorax.

Reexpansion Pulmonary Edema

Unilateral pulmonary edema (*reexpansion pulmonary edema* [RPE]) may develop in certain patients whose lung has been rapidly reinflated after a period of collapse secondary to a pneumothorax or a pleural effusion. This is likely due to mechanical stress on the lung leading to increased permeability of the pulmonary vasculature during rapid reexpansion. The incidence of RPE is likely to be low: retrospective series suggest that the incidence may be as low as 0%[77] or 1%[78] in patients treated for pneumothorax. More recent series report a high incidence of RPE (16%, 27/173), but this was largely asymptomatic because only five patients (3%) required treatment.[79]

Typically, patients with RPE will report cough or chest tightness. In extreme cases, patients can be hypoxemic and hypotensive. Treatment is supportive with supplemental oxygen and diuretics.

Ambulatory Care

With the increasing pressures on health care systems, ambulatory management has been proposed for patients with a number of medical conditions. Given that patients with PSP tend to have little comorbidity, this patient group might represent an ideal cohort for outpatient management to reduce both inconvenience and risk for patients and the economic costs of an inpatient hospital stay. This is not a new concept; a number of studies have demonstrated the feasibility of outpatient management for PSP using a chest tube attached to a one-way (also called a flutter or Heimlich) valve, but this treatment has not been widely adopted. As far back as 1976, a case series of 226 patients with PSP managed by observation or flutter valve concluded that outpatient management was "safe, efficient, and economical."[80] The first randomized trial of 30 PSP patients compared "thoracic vent" to standard chest tube. This study showed no significant difference in complications or reexpansion rates, but 70% of the "vent" patients were managed as outpatients and required fewer analgesics, with patients in the control group (standard chest drain) hospitalized for a median of 8 days.[66] Since then, a number of observational or retrospective studies also describe high rates of success with outpatient management of PSP with one-way valves.[81–85] These data were summarized in a 2013 systematic review[86] in which an overall success rate was reported as 85.8% and successful outpatient management reported in 77.9% with "few complications." However, the evidence was of poor quality with a high risk of bias.[86] As a result, a large multicenter RCT was designed to answer the question of efficacy and safety of ambulatory management.[87] In this trial, ambulatory management (using an ambulatory device containing a one-way valve) was compared to standard care (aspiration with or without chest tube, per BTS

eTable 110.1 Randomized Controlled Trials of Needle Aspiration vs. Chest Tube: Initial Success Rates

Study	Year	*N*	Needle Aspiration Success Rate (%)	Chest Tube Initial Success Rate (%)
Harvey[67]	1994	73	80	100
Andrivet[68]	1995	61	67	93
Noppen[69]	2002	60	59	64
Ayed[70]	2006	137	62	68
Ho*[136]	2011	48	48	72†
Parlak‡[73]	2012	56	68	81
Thelle§[75]	2017	77	74	38
Ramouz[74]	2018	70	54	69

*Percentage discharged home after initial management.
†Chest tube with Heimlich valve.
‡Includes traumatic (22/56).
§Primary spontaneous pneumothorax data only.

guidelines). Ambulatory management significantly reduced hospital stay compared with standard care (median, 0 days [interquartile range, 3 days] vs. 4 days [interquartile range, 8 days]; $P < 0.0001$). Patients who underwent ambulatory treatment had fewer pleural procedures, but serious adverse events were higher due to hospital readmission.[87]

Suction. Suction refers to the application of negative pressure to the intrapleural space via the chest tube. Use of suction is not recommended by the current guidelines.[1] There have been two small RCTs, neither of which showed a significant difference in success rates when comparing suction to standard underwater seal management.[88,89] However, suction is advocated by some physicians in cases of nonresolution of pneumothorax (particularly if the lung has not reinflated). Suction aims to remove air from the pleural space at a rate faster than it can accumulate in the chest, hence, speeding resolution of the pneumothorax; however, it should be noted that this does not treat the underlying visceral pleural defect. However, some authorities state that full lung expansion allows earlier healing of the pneumothorax due to apposition of the visceral and parietal pleura. This hypothesis has not been proven, and recent data argue the opposite.[64] In a recent RCT, those managed conservatively (e.g., without drainage of air) had a lower recurrence of pneumothorax over the next year than those receiving standard management (e.g., with aspiration and/or chest tube drainage),[64] suggesting that slow reexpansion may improve healing.

Although the guidelines do not explicitly recommend suction, they state that a "high volume" (up to 15–20 L/min) "low pressure" suction could be used.[1] The application of suction is not without risk; rapid reinflation of the lung may precipitate RPE and, perhaps more worryingly, the increased airflow through the visceral leak could increase the size of the hole in the visceral pleura. Therefore, the use of suction needs to be considered carefully.

Failure of Medical Management

In most patients with pneumothorax, the visceral pleural injury and therefore the air leak will resolve spontaneously, with drainage intended to prevent symptoms and complications such as tension. Failure of medical management for patients with pneumothorax describes the clinical situation in which the lung has not reinflated with chest drainage and/or there is a prolonged air leak.

A number of treatment options are possible in this situation. However, it is important to understand the rationale behind each treatment before it is used in an unstructured manner.

Prolonged Air Leak. *Prolonged air leak* (PAL) is typically defined as an ongoing leak despite 5 to 7 days of chest tube drainage. There are data to suggest that most PSP patients with PAL will eventually resolve given time. Chee et al. found that 100% of patients with PSP with PAL for greater than 7 days had resolved by 14 days.[65] Therefore, any decision to define failure must be considered as a balance between allowing time for the leak in the visceral pleura to heal (with spontaneous cessation of PAL) and the inconvenience and expense of having a chest tube in place while in the hospital for an extended period.

Current BTS guidelines suggest that drainage should be attempted for at least 3 days, and a thoracic surgical opinion should be sought "early" at 3 to 5 days.[1] Presumably, this recommendation was intended to allow the necessary arrangement for surgical intervention as, in theory, PAL is not confirmed until at least day 5.[1] However, these timings are somewhat arbitrary and not evidence based.

Chest Tube Size. In the presence of a large air leak, some physicians and surgeons may advocate replacing a small-bore tube with a large-bore tube to allow a greater total flow rate of air or using high-volume, low-pressure suction attached to the chest tube. The larger chest tube allows a greater flow rate because turbulent flow is proportional to the fifth power of the radius of the tube, as described by the Fanning equation: $v = \pi^2 r^5 P/fl$ (where v is flow, r is radius, P is pressure, l is length, and f is a friction factor).[89a] The goal is to remove air faster than air is entering, thereby reinflating the lung. This approach would seem rational if there is clear evidence of insufficient drainage of air (e.g., subcutaneous emphysema, increasing pneumothorax size, major bubbling through the water seal, or worsening clinical condition). However, there is no good trial evidence to support the use of larger drains or suction in stable patients with PAL.

Thoracic Surgery. Definitive treatment for failed medical treatment or recurrence prevention is thoracic surgery. It is important to distinguish the two purposes of surgery in this situation. The first is to repair the leaking lung, allowing full lung expansion and removal of the chest drain, which is required only in cases of PAL. The second is recurrence prevention, which is largely an elective operation; if air leak repair is to be performed at surgery, it makes sense to conduct recurrence prevention surgery at the same time.

Surgery is performed by *video-assisted thoracoscopic surgery* (VATS), which has superseded open thoracotomy in most countries as the approach of choice. During surgery, the operator aims to identify and seal any areas of air leakage, resect any visible blebs or bullae on the visceral pleura, and perform a pleurodesis procedure. Pleurodesis is required alongside bleb/bullectomy to achieve lower recurrence rates.[28,90,91] Pleurodesis can be achieved by pleural abrasion, pleurectomy, or chemical pleurodesis (typically by insufflation of talc, called "poudrage"). A study of VATS for PSP recurrence prevention (or for PAL) showed a lower rate of recurrence with talc poudrage (1.8%) compared with subtotal pleurectomy (9.2%) regardless of whether ligation or stapling of bullae was performed.[92] The low recurrence was confirmed in two large case series of VATS with talc poudrage after bleb/bullectomy, which reported recurrence rates of only 1.7%[93] and 1.9%.[94]

Where the option exists, patients with PAL could undergo medical thoracoscopy performed under conscious sedation (rather than under general anesthesia, as in VATS) with talc poudrage. Although this is being performed in Europe, it is not current practice in the United Kingdom or United States. An RCT comparing medical thoracoscopy with talc poudrage to standard chest tube alone showed a reassuringly low recurrence rate of 5% compared to 34% for chest tube drainage.[95] It should be noted that deep conscious sedation or general anesthesia

is required to perform talc poudrage pleurodesis at thoracoscopy in patients with pneumothorax because this procedure can be painful.[96]

Recurrence Prevention After First Pneumothorax. In cases in which a recurrent pneumothorax is likely and would be accompanied by serious clinical consequences, efforts to prevent recurrence are indicated. This can be approached with a surgical, usually VATS, or medical thoracoscopy or with a medical, usually talc, pleurodesis. Also, various additional procedures have been used to stop ongoing air leaks to allow pleurodesis or discharge.

Surgical Pleurodesis. At present, recurrence prevention surgery after a first episode of spontaneous pneumothorax is recommended only in certain circumstances and usually when the patient's occupation would increase risk in the event of a recurrence (e.g., airline pilot or commercial diver). Otherwise, the indications for surgery are recurrence (either ipsilateral or contralateral), synchronous bilateral pneumothorax, or PAL.[1] However, there are advocates of surgical intervention after a first episode of PSP. There have now been two RCTs comparing early VATS to conservative management after a first PSP. The first study randomized 41 patients to either VATS within 24 hours of admission to the hospital or to "conservative" treatment with chest tube drainage.[97] They found no recurrence (0%) in the VATS group but 40.9% in the conservative group. It should be noted that the recurrence rate in the conservative group is significantly higher than expected from other studies in the literature,[2,6] and that this study was small and therefore underpowered. A larger RCT by Olesen et al.[98] of 373 PSP patients showed a significantly lower recurrence rate in those treated with VATS (13%) compared to conservative treatment (34%). The 13% recurrence in the VATS group was unexpectedly high but may be due to the use of abrasion rather than talc as the method of pleurodesis.

The main issue regarding recurrence prevention after the first event is determining which patients would benefit. Around 28–30% of patients will have a recurrence after simple chest tube drainage,[2,6] but 70% will not. It therefore follows that operating on all patients results in approximately 70% having an unnecessary operation. Although VATS or medical thoracoscopy is generally considered a safe procedure, there are still risks of significant morbidity or mortality, especially persistent chest pain.[99] If patients at higher risk could be identified, a more personalized approach could potentially shift the balance of risks and benefits towards early surgery or thoracoscopy.

Risk stratification based on high-resolution CT scan findings was proposed by Ouanes-Besbes et al.[100] Unfortunately, stratification by bullae size or "dystrophic score" has not convincingly identified patients at higher risk of recurrence. As such, the case for early surgery or thoracoscopy for PSP recurrence prevention has yet to be made. The combination of clinical and radiographic findings may provide better information for patients and clinicians on potential risks and benefits of early intervention, although validated data are currently lacking.

Patients Unfit for Surgery. By definition, patients with SSP have demonstrable lung disease. Patients with long-standing lung disease such as COPD and interstitial fibrosis are particularly susceptible to PAL and recurrence. Unfortunately, the respiratory disease renders such patients unfit for surgery due to the high risk of general anesthesia. These patients present a significant management challenge for physicians and may have multiple episodes of pneumothorax with prolonged hospital stays due to the presence of bronchopleural fistulas.[101] Heimlich valves attached to chest tubes offer the option of discharge from the hospital and outpatient follow-up, but this may only be feasible in the most stable patients. Alternatively, a pleurodesis procedure could be performed via the chest tube, via chemical pleurodesis or the instillation of autologous blood (blood patch pleurodesis) in an attempt to reduce or stop the ongoing air leak.

Medical Pleurodesis. Pleurodesis is the application of chemical or mechanical injury to the pleura, inducing inflammation and subsequent adhesion of the pleural layers, to prevent reaccumulation of fluid or air. Medical pleurodesis is the instillation of a chemical irritant to the pleural space. This is commonly performed to prevent the reaccumulation of pleural fluid (usually in the context of malignancy)[102] (see Chapter 114). A number of pleurodesis agents can be used for recurrence prevention in spontaneous pneumothorax, including talc, tetracycline, minocycline, and autologous blood.[103] Graded talc (talc with the smallest particles removed) is the most commonly used and successful agent for pleurodesis.[1,7,8] In the treatment of malignant pleural effusion, the success rates of talc for pleurodesis are high (around 70–80%).[102,104] It should be noted that for pleurodesis of any form to work, there needs to be apposition of the visceral and parietal pleura; therefore pleurodesis has no role in the presence of a pneumothorax with complete separation of the visceral and parietal layers. The minimal amount of apposition required to achieve success with pleurodesis is debated.

In an RCT by Chen et al,[105] pleurodesis was attempted for patients presenting with a first episode of PSP. Minocycline was instilled via chest tube in the intervention arm, compared with standard tube drainage only, and reduced the rate of recurrence at 1 year to 29.2% compared to 49.1% in the control group. However, the recurrence rate in the control arm was much higher than previously reported,[7] and this strategy results in treating a significant number of patients who may never have a recurrence.

A systematic review has compared efficacy of chemical pleurodesis agents in spontaneous pneumothorax via either medical or surgical approaches.[103] In the medical approach (i.e., without surgery on the lung), talc poudrage during medical thoracoscopy had the lowest recurrence rate at 2.5–10%. The recurrence rates following instillation through the chest tube were 13–33% for tetracycline and 34% for talc (as a slurry).[95] On this basis, medical pleurodesis is most commonly conducted using talc and, while recurrence rates are lowest using VATS or medical thoracoscopy, slurry via chest tube remains an option, especially for those not fit enough for surgery.

Blood Patch Pleurodesis. Blood patch pleurodesis involves the instillation of 1 to 2 mL/kg of autologous venous blood into the pleural space via chest tube. Although this is technically not pleurodesis, it can successfully resolve PAL in some cases.[106] It is presumed that the fibrin and clotting factors within the blood aid the repair of the visceral leak

and help resolve the pneumothorax. Case series support the use of this technique using 2 to 4 mL/kg of blood, but definitive data are lacking.

Endobronchial Valves. Another possible treatment option is the use of endobronchial valves, which are increasingly used in COPD treatment to achieve lung volume reduction. These valves, inserted at bronchoscopy, occlude the relevant lung segment corresponding to the site of the air leak, thereby closing the bronchopleural fistula.[107] While there are case reports and small case series suggesting successful treatment, high-quality evidence on their efficacy is lacking, but they remain a useful option in difficult-to-treat patients. Once the leak is controlled and the lung reinflates, a medical pleurodesis can be attempted to reduce recurrence risk.

Total Pleural Covering. The visceral pleura can be covered with an absorbable cellulose mesh via VATS in an attempt to reinforce the visceral pleura and reduce recurrence without creating a pleurodesis. This novel approach has been attempted in selected patients with a high risk of recurrence (e.g., innumerable cysts that preclude resection) and reasons to avoid pleurodesis. Pleurodesis in patients with LAM increases bleeding complications at the time of future lung transplantation and, although pleurodesis is not a contraindication for lung transplantation, alternatives to pleurodesis are desirable. Total pleural covering has been used in both BHD[108] and LAM,[109] where it appears to be a promising approach to reduce recurrence. An ATS treatment guideline advocates further study of this option.[110]

Follow-up. Patients should be counseled about risk of recurrence and recommendations regarding air travel and scuba diving. Patients should be advised to return to the emergency department if they experience similar chest pain or breathlessness.[1] During follow-up, the possibility of underlying lung disease should be considered and investigated.

Lifestyle advice on smoking cessation should be reinforced because continued smoking increases the risk of recurrence.[4,94] Advice on air travel is mandatory (see Chapter 106). An undrained pneumothorax will increase in size as a result of the decreased ambient pressure in the aircraft cabin and potentially cause respiratory compromise; thus, an untreated pneumothorax is an absolute contraindication to air travel. Current guidance recommends waiting for 7 days after full resolution of pneumothorax on CXR before it is considered safe to fly.[111] Patients who have had definitive surgical management with pleurodesis for pneumothorax can fly once they have fully recovered from surgery, but they should be aware that their recurrence risk is still around 1–2%. In patients with SSP who are not fit for surgery, patients should seek safer modes of transportation (road or rail) instead of flying.[111]

Scuba diving (using compressed gas) should be avoided lifelong after pneumothorax unless recurrence prevention surgery with pleurodesis has been conducted[112] (see Chapter 107). There is no evidence to link recurrence with physical exertion, but general advice is that patients can return to work and normal physical activities once symptoms have resolved. Pragmatically, patients should refrain from high-impact physical sports in the short term.

TRAUMATIC PNEUMOTHORAX

The incidence of pneumothorax after blunt trauma depends on the severity of trauma. Data on incidence of pneumothorax are limited but, in some series, the incidence exceeds 35%.[113]

A traumatic pneumothorax can result from either penetrating or nonpenetrating chest trauma (see Figs. 104.4, 104.7, and 104.8 and eFigs. 104.10 and 116.5). In penetrating chest trauma, air can enter the pleural space from the outside via a wound in the chest wall, or from the lung via a break in the visceral pleura. With nonpenetrating trauma, a pneumothorax may develop if the visceral pleura is lacerated secondary to a rib fracture or dislocation. However, in the majority of patients with pneumothorax secondary to nonpenetrating trauma, there are no associated rib fractures. In this circumstance, pneumothorax may result from the sudden chest compression abruptly increasing the alveolar pressure, thereby causing alveolar rupture. Air then enters the interstitial space and dissects toward either the visceral pleura or the mediastinum. A pneumothorax develops when either the visceral or the mediastinal pleura ruptures.

DIAGNOSIS

The diagnosis of pneumothorax is commonly made by CXR or CT. However, patients with significant trauma will commonly be lying in a supine position and may be immobilized. As mentioned earlier, pneumothorax on CXR in the supine position can be easily missed. CT scans, increasingly used in major trauma, will identify many more pneumothoraces, even small ones. A pneumothorax detectable on CT, but not on CXR, is called an occult pneumothorax and accounts for about 40% of traumatic pneumothoraces[114] (see Fig. 104.7).

TREATMENT

There is some controversy about whether treatment is required for traumatic pneumothorax. Most clinicians initiate treatment with chest tube for a large pneumothorax. However, whether to intervene in patients with occult or small pneumothoraces is not clear. In one series of 803 patients, 300 with pneumothoraces less than 1.5 cm were initially managed without chest tubes, and only 33 (10%) subsequently required chest tube insertion.[115] The remaining 504 patients were treated with chest tubes, but 66% had the chest tube removed within 24 hours because the lung reexpanded and air leak ceased.[115] As discussed earlier in regard to PSP and SSP, if the leak persists for more than a few days, consideration should be given to performing thoracoscopic surgery to identify and repair the site of the air leak.[116]

IATROGENIC PNEUMOTHORAX

On the basis of two large series, iatrogenic pneumothoraces are probably more common than PSPs and SSPs combined.[117,118] A leading cause of iatrogenic pneumothorax is transthoracic needle aspiration. Historically, the incidence

of iatrogenic pneumothorax postaspiration was as high as 25%, although this has reduced since the introduction of ultrasound for all pleural procedures.[119] Another leading cause of iatrogenic pneumothorax is CT-guided transthoracic lung biopsy. This procedure is more likely to result in a pneumothorax if the patient has COPD, if the lesion is deep within the lung, or if larger needles are used. In a meta-analysis, the pneumothorax rate was 25.3% for core lung biopsy and 18.8% for fine-needle aspiration.[120]

Other common causes of iatrogenic pneumothorax (with approximate incidences) are subclavian vessel puncture (e.g., during cardiac pacemaker insertion; 22%), pleural biopsy (8%), mechanical ventilation (7%), and transbronchial lung biopsy (6%).[1] Iatrogenic pneumothorax also frequently complicates cardiopulmonary resuscitation. Radiofrequency ablation is increasingly used to treat lung tumors but carries a high incidence of pneumothorax (≈30%).[121,122] A series of 137 radiofrequency ablation procedures found 27 symptomatic pneumothoraces requiring chest tube drainage.[123] In another series, the risk for pneumothorax was associated with the number of tumors ablated, electrode positions, and the electrode trajectory through aerated lung.[122]

DIAGNOSIS

The diagnosis should be suspected in any patient who becomes more dyspneic or whose condition deteriorates after an intervention procedure. Importantly, the pneumothorax can present late and therefore may not be evident for 24 hours or longer after the procedure.[124] The diagnosis needs confirmation by ultrasound or radiographic imaging. In patients with extensive pulmonary opacities, there may be little evidence of lung collapse; the air in the pleural space may instead be indicated by the deep sulcus sign (Figs. 110.5 and 104.8).

Iatrogenic pneumothorax should be suspected in any patient treated by mechanical ventilation whose clinical condition suddenly deteriorates. A sensitive indicator of the development of a pneumothorax in such patients is increased peak and plateau pressures if the patient is on a volume-cycled ventilator or a decreased tidal volume if the patient is on a pressure-cycled ventilator.

TREATMENT

The treatment of iatrogenic pneumothorax differs from that of spontaneous pneumothorax in that preventing recurrence is not an issue. If the patient has minimal or no symptoms and the pneumothorax is small, the patient can be observed. However, in cases of symptomatic patients or larger pneumothoraces, practice varies significantly.[125] Simple needle aspiration can be attempted, but many patients require chest tube insertion. More recently, two studies have postulated an "early discharge strategy" in which patients with significant pneumothoraces are managed as outpatients with small-bore chest tubes attached to Heimlich valves.[126,127]

The management of patients with an iatrogenic pneumothorax secondary to positive-pressure mechanical ventilation should include urgent tube thoracostomy to reduce the risk of tension pneumothorax. If the patient continues to receive mechanical ventilation, the chest tube should be left in place for at least 48 hours after the air leak stops. Two studies have demonstrated that high-frequency ventilation does not consistently improve gas exchange or decrease air leak through the fistula.[128,129]

CATAMENIAL PNEUMOTHORAX

A catamenial pneumothorax is a pneumothorax that develops in conjunction with menstruation. It is probably underdiagnosed and underreported.[130] With catamenial pneumothorax, respiratory symptoms usually develop within 24 to 48 hours of the onset of menstruation.[131] Most pneumothoraces are right-sided, but left-sided and bilateral pneumothoraces have been reported. Catamenial pneumothoraces tend to be recurrent; patients typically have five pneumothoraces before the diagnosis is recognized.[131]

Case series report an incidence of catamenial pneumothorax in 3–6%[45] of pneumothoraces in young women, but the rate may be as high as 30–40%[46] in patients requiring surgery for recurrence or ongoing air leak.

PATHOGENESIS

The pathogenesis of catamenial pneumothorax is unclear. When the syndrome was initially described,[132] it was hypothesized that air gained access to the peritoneal cavity during menstruation and then entered the pleural cavity through a diaphragmatic defect. In a subsequent review of 28 patients who had undergone thoracoscopy, endometriosis (primarily diaphragmatic) was present in 18 and diaphragmatic perforations or nodules were present in 21.[133] It has been suggested that diaphragmatic endometriosis tissue undergoes cyclical necrosis, leading to a diaphragmatic defect.[134] These authors concluded that diaphragmatic abnormalities play a fundamental role in the pathogenesis of catamenial pneumothorax.[133,134] Alternatively, endometriosis of the visceral pleura could lead to alveolar pleural air leaks during menstruation.

TREATMENT

Any woman who has a spontaneous pneumothorax within the first 48 hours of her menstrual period should be suspected of having a catamenial pneumothorax. The treatment of catamenial pneumothorax is aimed at treating endometriosis, known or suspected, by suppressing the ectopic endometrium. This can be attempted by suppression of ovulation with oral contraceptives or by suppression of gonadotropins with danazol or gonadotropin-releasing hormone to produce a medical oophorectomy. Alternative treatments include thoracoscopy with stapling of blebs, closure of diaphragmatic defects, and parietal abrasion or pleurectomy, or pleurodesis.[130] One study reported significantly reduced recurrence by combining surgical treatment with hormonal therapy over a 4-year follow-up period.[135]

Key Points

- Patients with pneumothorax present with chest pain, perhaps due to inflammation of the pleura or pleural tethering, and dyspnea, potentially caused by expansion of the chest wall.
- Mediastinal shift on imaging indicates a difference in pleural pressures on the right and left sides without necessarily indicating tension. Tension pneumothorax signifies positive intrapleural pressure that completely collapses the lung, reduces venous return causing hemodynamic compromise, and requires emergency decompression.
- Pneumothorax in a young woman should raise the possibility of catamenial pneumothorax or lymphangioleiomyomatosis.
- In *primary spontaneous pneumothorax* (PSP) a conservative approach with no drainage may also be an option for patients with mild or moderate symptoms who can be followed as outpatients. Those with severe symptoms should be managed initially by needle aspiration followed by chest tube insertion in those who do not respond to treatment.
- Secondary spontaneous pneumothorax should be treated initially with chest tube drainage; consideration should then be directed to prevent recurrence, usually with talc pleurodesis.
- Patients with PSP are now recognized to have abnormal underlying lung, with inflammation and emphysema-like changes (blebs, bullae, and pleural porosity) that represent areas of abnormal tissue beneath the visceral pleura.
- PSP may be the first manifestation of a systemic disease (e.g., Birt-Hogg-Dubé syndrome or Marfan syndrome) that may require further investigation for associated abnormalities.
- All patients require advice on flying, scuba diving, and smoking cessation.

Key Readings

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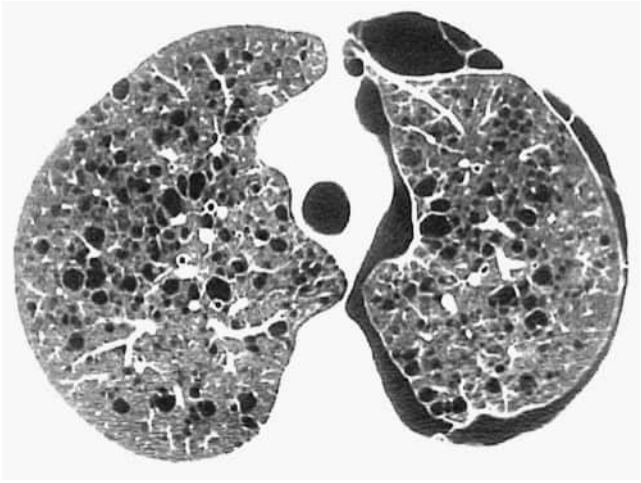
Complete reference list available at ExpertConsult.com.



eFIGURE IMAGE GALLERY



eFigure 110.1 Chest computed tomography scan of a patient with lymphangioleiomyomatosis. Note the numerous thin-walled cysts, rounded and relatively uniform in shape, and a pneumothorax on the left. (Courtesy Dr. Lisete Teixeira, University of Sao Paulo, Brazil.)

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111 CHYLOTHORAX

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INTRODUCTION

Chylothorax, first described by Bartolet in 1633,[1] is defined as the presence of chyle in the pleural space. Chylothorax is uncommon, with an incidence rate less than 2.5% in a single-center retrospective study containing 876 consecutive thoracenteses.[2] Chylous effusions are often underrecognized or misdiagnosed as empyema, causing a delay in management. Finding the underlying cause is important. A multidisciplinary therapeutic approach is often necessary to control its recurrence.

OVERVIEW OF THE LYMPHATIC SYSTEM AND DRAINAGE OF THE THORACIC DUCT

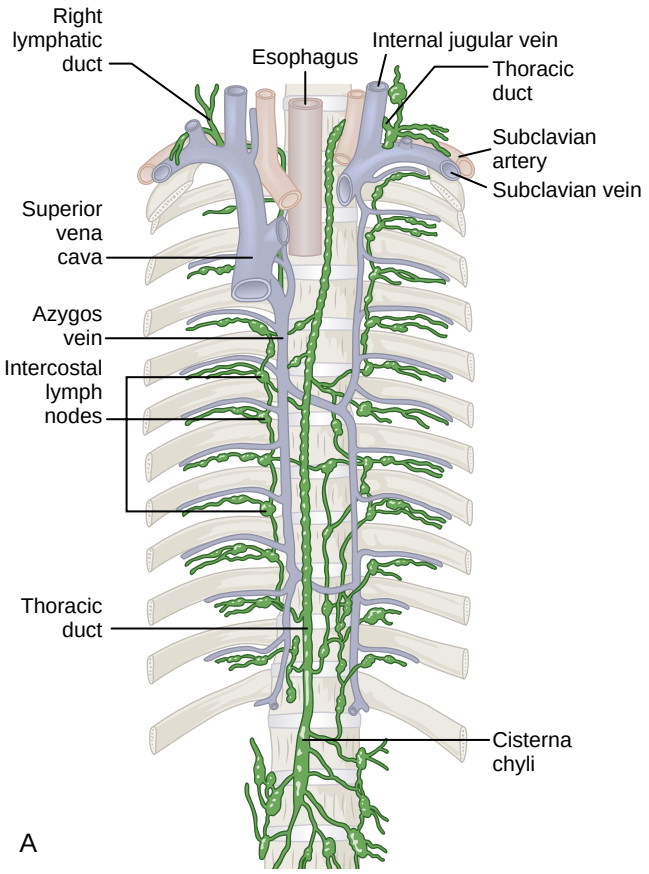
ANATOMY

The thoracic duct originates at the cisterna chyli, a dilated sac at the anterior aspect of the bodies of the first and second lumbar vertebrae receiving the chyle from the intestines, and passes through the aortic hiatus of the diaphragm on the anterior surface of the vertebral body between the aorta and the azygos vein into the posterior mediastinum. The thoracic duct then ascends extrapleurally along the right side of the anterior surface of the vertebral column. At the level between the bodies of the fourth to sixth thoracic vertebrae, the duct crosses to the left side of the vertebral column and continues cranially to enter the superior mediastinum along the left border of the esophagus. Here it passes behind the aortic arch and then runs posterior to the initial segment of the left subclavian artery (Fig. 111.1A–B). The thoracic duct may ascend as multiple channels[3–5] or as a plexiform structure[3,5–7] instead of as a single duct. Once the thoracic duct passes the thoracic inlet, it arches above the clavicle and descends anterior to the first part of the left subclavian artery. The thoracic duct may terminate into the venous system either as a single channel or as multiple channels[5,7–10]; in a small proportion of cases, the thoracic duct may terminate on the right side (6%).[7] From a systematic review summarizing studies in the past century, the thoracic duct most commonly enters the venous system at the internal jugular vein (46%), contrary to the traditional belief, then at the junction of the internal jugular and subclavian veins, the jugulovenous angle (32%), and lastly at the subclavian vein (18%).[7] The duct itself has several valves at the lymphovenous junction that prevent the reflux of blood into the duct.[7,11] The above classical description of the thoracic duct pathway is only present in about 50–65% of the population,[3,12] and various anatomic variations exist.[7]

COMPONENTS OF CHYLE

Chyle, the fluid drained in the thoracic duct, consists of lymph and emulsified fats from the intestine. Most dietary lipids are transported via the lymphatics,[13] and 75% of the body's lymph is drained by the thoracic duct.[7] Chylomicrons are formed in the intestine and are then transported to the cisterna chyli and thoracic duct. On the other hand, the majority of absorbed *medium-chain triglycerides* (MCTs) are systemically absorbed and transported in the portal vein to the liver,[14] and less than 1% is transported via the thoracic duct.[15]

Chyle is alkaline in nature[16–18] and conventionally said to be bacteriostatic,[19] though this has not been formally assessed. Chyle is also not believed to be an irritant and is



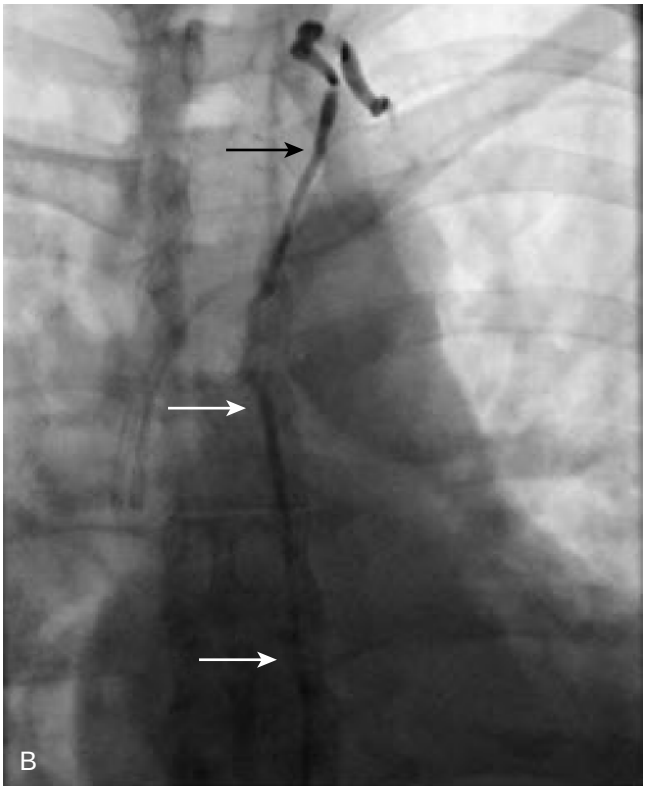


Figure 111.1 Normal anatomy of the thoracic duct. (A) The thoracic and right lymphatic ducts. (B) Normal thoracic duct (*arrows*) in a patient undergoing lymphangiography, who developed chylous effusion postesophagectomy. No leak was detected on imaging. The chylothorax resolved after lipiodol lymphangiography, octreotide treatment, and implementation of a fat-free diet. (A, Modified from Strandring S, ed. *Gray's Anatomy*. 40th ed. London: Elsevier; 2008.)

unlikely to induce pleural thickening. It contains abundant immunoglobulins, white blood cells (mostly T lymphocytes),[17,20] protein (20 to 40 g/dL),[17,18,21] and electrolytes (similar in content to serum).[17,18]

FLOW OF CHYLE

The thoracic duct normally conveys 1500 to 2500 mL of chyle daily[16,17,22]; ingestion of fat can increase its flow by as much as tenfold for several hours.[16,23] Ingestion of water (but not protein or carbohydrate),[24,25] physical activity, and increases in interstitial fluid pressure can also increase the lymph flow.[17] In contrast, the flow rate can drop to 14 mL/hour if the patient is immobile, starved, receiving continuous nasogastric suction, or when the pressure of the lymphovenous system is raised.[17] Numerous substances, such as octreotide and somatostatin, can slow the flow of collecting lymphatics and the thoracic duct.[25,26]

ETIOLOGY AND CLINICAL MANIFESTATIONS OF CHYLOTHORAX

ETIOLOGY OF CHYLOTHORAX

Chylothorax can form whenever there is disruption of the integrity of the lymphatic wall along the thoracic duct and its tributaries (Table 111.1).

Chylothorax can result from traumatic and nontraumatic causes; their relative frequencies vary among series. In a summary of five separate series from the 1960s and 1980s totaling 143 patients, more than half of chylothoraces were caused by tumors, especially lymphoma, followed by trauma.[1,27–31] In a single tertiary institute series of 203 patients containing adult and pediatric patients, trauma/surgery were the most common (50%) causes compared to nontraumatic causes (44%).[32] No recent large reports exist on the contemporary epidemiology of chylothorax.

Traumatic Chylothorax

Traumatic chylothorax is now more likely to be caused by iatrogenic injury (especially postoperative) than by physical injury.[32,33] The anatomic variation and the multiple collateral channels make the thoracic duct vulnerable to injury from surgical procedures involving the esophagus,[34,35] cardiovascular system,[36,37] lungs,[38–40] spinal cord,[41–44] neck,[45] and upper abdomen.[46] Esophagectomy in adults and congenital heart surgery in the pediatric group are commonly associated with postoperative chylothorax,[32,47] with an incidence of 0.2–4.0%[34,35,48,49] and 0.9–6.6%,[36,50–57] respectively. Squamous cell carcinoma, low body mass index, preoperative chemoradiotherapy, and high intraoperative fluid balance are risk factors for postesophagectomy chylothorax.[58] Chylothorax can also present after pulmonary resection, with an incidence rate of 1.4–4.0%,[39,40,59] and bilateral chylothoraces may develop following bilateral neck dissection.[60] Chylothorax may also develop following surgical repair of congenital diaphragmatic hernia in neonates (incidence

Table 111.1 Common Causes of Chylothorax

Type	Cause	Examples
Traumatic	Iatrogenic	Surgical procedures along the thoracic duct (e.g., esophagectomy, lung resection, CHD repair, neck or thyroid surgery, spinal surgery) Vascular intervention (e.g., SVC or SCV cannulation, pacemaker implantation) Thoracic irradiation
	Non-iatrogenic	Penetrating injury Blunt injury Spine fracture or hyperextension, rib fracture
Nontraumatic	Malignancy	Lymphatic obstruction or infiltration (e.g., lymphoma, metastatic lymphadenopathy, lung cancer) SVC obstruction
	Increased venous pressure	CHF, cardiomyopathy, restrictive pericarditis, SVC or SCV thrombosis
	Lymphatic obstruction	Retrosternal goiter, TB, sarcoidosis, fibrosing mediastinitis, post-thoracic irradiation
	Lymphatic disorders	LAM; Gorham, Down, Noonan, and yellow nail syndromes
	Transdiaphragmatic movement of fluid	Chylous ascites

CHD, congenital heart disease; CHF, congestive heart failure; LAM, lymphangioleiomyomatosis; SCV, subclavian vein; SVC, superior vena cava; TB, tuberculosis.
Data from Skouras V, Kalomenidis I. Chylothorax: diagnostic approach. *Curr Opin Pulm Med*. 2010;16(4):387–393.

4.6%), especially if patch repair or extracorporeal membrane oxygenation is employed.[61,62] Surgical procedures that involve the posterior mediastinum (e.g., esophageal surgery) and mobilization of the left subclavian artery are particularly prone to postoperative chylothorax. Thrombosis of the *superior vena cava* (SVC) or subclavian vein after catheterization[63–69] may lead to chylothorax due to increased venous pressure and obstruction of chyle flow. Direct injury to the thoracic duct by needle puncture may also cause chylothorax.

Although penetrating injury may precipitate chylothorax[70] by direct thoracic duct injury,[71] blunt chest injury,[70,72,73] especially when associated with hyperextension, dislocation or fractures of the spine, or posterior ribs,[32,74–77] can also sever the thoracic duct. Vigorous coughing,[78] vomiting,[79] excessive stretching while yawning[80] (especially after a fatty meal[81]), and childbirth[82] have been associated with the development of chylothorax.

Nontraumatic Chylothorax

Malignancy is the most common nontraumatic cause of chylothorax.[32,83] Lymphoma and metastatic carcinomas can result in lymphadenopathy or metastatic deposits in the mediastinal region obstructing or infiltrating the thoracic duct with a resultant chyle leak.[84–87] SVC obstruction due to malignancy can also lead to chylothorax.[88]

Benign causes of chylothorax can include various congenital and acquired disorders. *Lymphangioleiomyomatosis* (LAM); lymphatic dysplasia syndromes,[89,90] including yellow nail[91] and Gorham syndromes[92–94]; Down syndrome; Noonan syndrome[89,95–100]; and syndromes due to other chromosomal aberrations[99,101] are associated with lymphatic maldevelopment and chylothoraces. Other acquired benign diseases can impede chyle flow by physical obstruction via lymphadenopathy (e.g., tuberculosis[102] and sarcoidosis[103]) or development of a retrosternal goiter.[104] Although uncommon, conditions that raise venous pressure into which the thoracic duct drains (e.g., mediastinal radiotherapy,[32,105,106] amyloidosis with restrictive cardiomyopathy,[107,108] and heart failure)[32,109,110] can potentially cause chylothoraces. Chylothorax can present in patients with liver cirrhosis due to various mechanisms.[111–114] Numerous other rare causes not covered account for the remaining small percentage of all chylothoraces.[16] In about 5–10% of cases, no identifiable cause can be found.[32]

Specific syndromes and conditions related to chylothorax are discussed at ExpertConsult.com.

CLINICAL MANIFESTATIONS

Chylothorax may present in a patient with symptoms related to a pleural effusion or incidentally during the workup of another disease (especially lymphoma).[33] Breathlessness is the most common symptom with large effusions. Chest pain and fever are uncommon, presumably because of the nonirritative nature of chyle.[16] The classic milky appearance of the pleural fluid (often described as looking like a vanilla or strawberry milkshake) should alert the clinician to the possibility of chylothorax; however, not all chylothoraces are milky in appearance. It is important to remember that a clear effusion can also be a chylothorax.

The laterality of effusion depends on the etiology and site of chyle leak. Defects of the thoracic duct between T4 and T6 levels may produce bilateral chylothorax, whereas lesions below and above this point may lead to right and left chylothoraces, respectively.[84] The rapidity of clinical decompensation depends on the rate of fluid leakage and duration of chyle loss.[33,84] Symptoms may be noted within 1 or 2 days after major thoracic duct damage but may be delayed by 2 to 7 days in case of minor injury.[84] Chyloma, a collection of chyle generally formed in the mediastinum, may produce symptoms due to pressure on vital structures before it ruptures into the pleural space as a chylothorax.[33,77,149–154] For persistent pleural effusions of undetermined cause, chylothorax should be considered in the differential diagnosis.[29]

Specific Syndromes/Conditions Related to Chylothorax

Lymphangioleiomyomatosis. LAM is a multisystem disease of women characterized by proliferation of abnormal smooth muscle–like LAM cells leading to cystic lung destruction and extrapulmonary disease (e.g., renal angiomyolipomas).[115,116] The obstruction of lymphatic vessels and lymph nodes in the mediastinum by infiltration of LAM cells is believed to be the reason for chyle leak.[117,118] The incidence of chylothorax in LAM ranges from 0–48%, with a rate of 21% in the largest registry containing 230 patients.[118–121] Chylothorax is considered one of the characteristic clinical features of LAM in the latest practice guideline[122] and may occasionally be the initial presentation.[119,121] From observations, chylothorax arises more commonly in sporadic LAM than in tuberous sclerosis complex–associated types of LAM.[119,123] Dyspnea and cough are common symptoms.[124] Most chylothoraces are unilateral (76%) and right sided (63.2%).[124] The size of the chylothorax does not correlate with the extent of lung involvement,[125] but most are large enough to require intervention.[118] Typical clusters of HMB45-positive LAM cells can also be found in the chylous pleural fluid.[126–130] (See Chapter 97.)

Hepatic Cirrhosis. Chylothorax and chyloascites can present in patients with liver cirrhosis. High portal venous pressure can increase thoracic duct lymph flow and pressure,[111] eventually leading to rupture of dilated serosal lymphatic vessels and the creation of chylothoraces.[112] Flow of chylous ascites across defects in the hemidiaphragm into the pleural cavity can give rise to chylothorax, which is usually right-sided.[113,114] In a retrospective cohort involving 1038 cirrhotic patients, 49 (4.7%) and 3 (0.3%) patients had hepatic hydrothorax and chylothorax, respectively.[111] Although uncommon, coexisting chylothorax should be considered in cirrhotic patients with recurrent pleural effusion.

Fetal and Neonatal Chylothorax. Fetal chylothorax, sometimes termed primary fetal pleural effusion or congenital chylothorax, is rare with an incidence of 0.005–0.03% of newborns.[131–134] Although rare, chylothorax is the most common cause of neonatal pleural effusion.[135–137] It is usually idiopathic[47] but can be associated with nonimmune hydrops fetalis (3.2–66.7%),[133,138] congenital malformations,[132,139] lymphatic disorders, congenital syndromes, and genetic mutations.[140–145]

Fetal chylothorax usually presents as bilateral pleural effusions on prenatal ultrasound screening and as respiratory distress after delivery.[132–134] Chylothorax can cause respiratory depression within the first week, particularly in the first 24 hours after birth.[146,147] The presence of lymphocytic (>80%) effusion in neonates without alternative cause found is highly suggestive of chylothorax.[95,148]

Prolonged drainage of chyle, especially in postoperative chylothorax, may lead to multiple complications, including hypolipidemia,[155] hypovolemia,[132,156] electrolyte imbalance,[156,157] metabolic acidosis,[1,44] depletion of trace elements,[158] venous thrombosis,[159–161] and immunodeficiency from ongoing loss of T and B cell lymphocytes.[50,84,131,163–167] Drugs (digoxin,[168] cyclosporin A,[169,170] and possibly amiodarone[171,172]) normally carried in the chyle may leak into the pleural space, causing subtherapeutic plasma levels. The incidence and clinical significance of most of these complications have not been extensively studied in a prospective way.[162]

DIAGNOSIS

Chylothorax should be suspected for any pleural effusion in a compatible clinical context or for any drainage of milky fluid.

FLUID APPEARANCE

The milky fluid appearance should not be expected in all chylothoraces; in fact, this classic appearance presents in only 44% of cases[148,173] (Fig. 111.2A). The turbidity depends on the ingested fat contents, and chyle leak may not look milky if the patient is fasting.[174] A chylothorax may have a serous appearance when caused by diseases that cause transudative effusions.[2,173,175,176] A bloody appearance may point towards trauma or LAM as the underlying cause.[150,173,124,125] A change to a milky appearance after the resumption of diet from a fasting state (or consumption of high-fat diet)[75,177] or a bluish-green discoloration after ingestion of a fatty meal mixed with methylene blue may establish the diagnosis of chylothorax. However, the latter method may not be helpful in posttraumatic chylothorax because discoloration of pleural fluid can also be observed in patients with esophageal perforation.[84]

BIOCHEMICAL ANALYSIS

Confirmation of the presence of chylomicrons in pleural fluid by lipoprotein electrophoresis is the gold standard test to define chylothorax.[33] However, lipoprotein electrophoresis is not widely available,[84,178] and Sudan III staining to detect the presence of oil is not sufficiently specific.[33,73,84] Instead, pleural fluid *triglyceride* (TG) levels greater than 110 mg/dL (>1.24 mmol/L) are virtually diagnostic of chylothorax, while pleural fluid TG levels less than 50 mg/dL (<0.56 mmol/L) can rule out chylothorax in 95% of cases.[29] High TG levels may be misleading in two circumstances. In patients with hypertriglyceridemia, high TG values in pleural fluid may not indicate chylothorax; in these patients, using fluid/serum TG ratio greater than 1 as another diagnostic test for chylothorax may avoid this false-positive pitfall.[114,179] High TG level can also be seen in pseudochylothorax; thus, a simultaneous cholesterol measurement is also suggested.[180] Low TG levels in chylothorax may be found during fasting, a malnourished state, or the presence of a second pathology contributing to the effusion.[33,114,148,173] In situations in which chylothorax is suspected but the TG level is low or in the borderline range (50 to 110 mg/dL), one can measure chylomicrons[29,33,173,178] or monitor for a change in the fluid color and recheck the fluid TG level after administration of a high-fat enteral meal.[148,162]

The chylous fluid is usually exudative based on the protein criterion of Light's criteria,[2,181] but the lactate dehydrogenase level is often low. An elevated lactate dehydrogenase level in chylothorax should raise concerns of coexisting inflammatory or lymphomatous conditions driving pleural fluid production.[2,114,173] Some (14%) chylothoraces are transudative[173] and are usually due to concurrent conditions known to produce transudates,[114] especially cirrhosis and nephrotic syndrome.[107] Chylothorax is typically lymphocytic if the effusion is due simply to leakage from the thoracic duct.[2] Alternative, or concurrent, causes should be considered if the fluid is neutrophilic. Pleural biopsy or thoracoscopy is usually not indicated in the workup of patients with a chylothorax because the pathology primarily involves the thoracic duct, not the pleura.

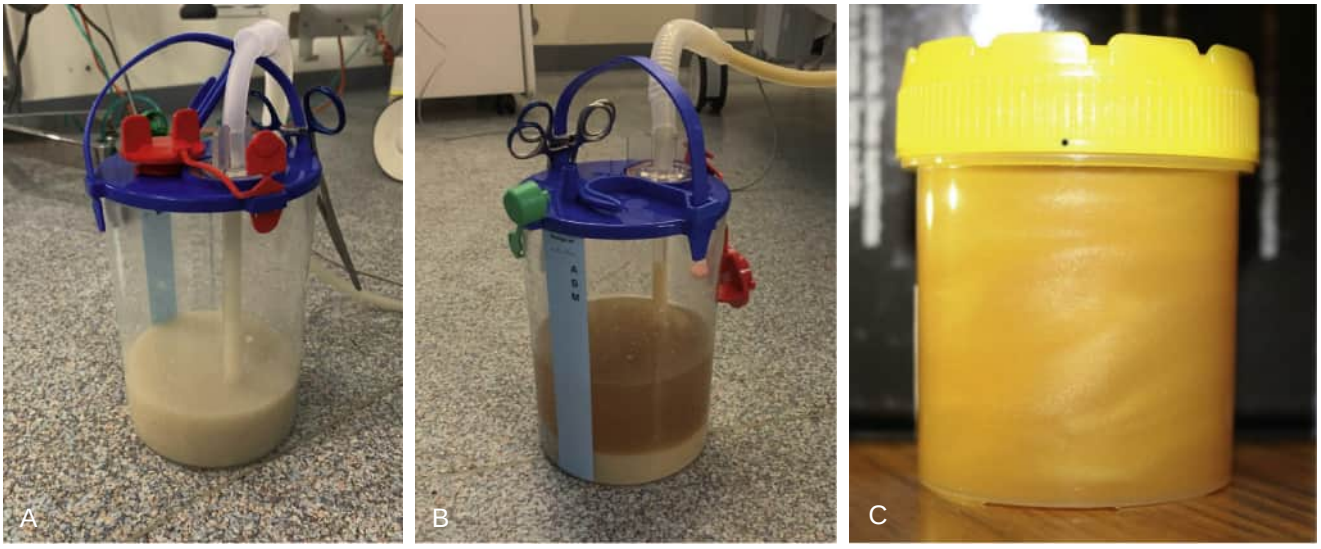


Figure 111.2 Milky-appearing pleural fluid collections. (A) Chylothorax. This pleural fluid was drained from a patient with chylothorax due to lymphoma, showing a homogeneously milky appearance. If this fluid were allowed to sit overnight, there would be no evident change in appearance. (B) Empyema. Pleural fluid drained from a patient with empyema allowed to sit overnight, showing a relatively clear supernatant with a sedimented bottom layer of cells and debris. (C) Pseudochylothorax. Pleural fluid collected after drainage of a pseudochylothorax, showing an opaque appearance with a satin-like sheen.

Two other causes of turbid pleural fluid, empyema and pseudochylothorax, must be considered and differentiated from chylothorax. In empyema, the milky appearance is caused by suspended leukocytes and debris, which will sediment upon centrifugation, leaving a clearer supernatant (Fig. 111.2B). In chyle and pseudochyle, the milky appearances are caused by TG or cholesterol (or lecithin-globulin complexes), respectively, and the supernatant will remain cloudy after centrifugation. Rarely, leakage of *total parenteral nutrition* (TPN) from a central line into the pleural space can present as a milky pleural effusion that also will not clear on centrifugation.[182–184]

IMAGING

Ultrasound is sensitive for the detection of pleural fluid but cannot identify effusions as chylous.[185] Cross-sectional imaging, including *computed tomography* (CT) and magnetic resonance imaging, may sometimes indicate the cause of chylothorax.[33,175] CT can sometimes show low-density collections consistent with the presence of fat (Video 111.1). Magnetic resonance imaging can help identify the thoracic duct,[186] and chyle often appears with high signal on T2-weighted imaging.[194]

To identify the site of chyle leak, lymphatic imaging such as lymphangiography or ^{99}Tc lymphoscintigraphy can be used.[187–190] In conventional lymphangiography, particulate substances are injected into the web spaces of the foot to opacify draining lymphatics, which can then be injected with oil-based contrast (Lipiodol). Direct inguinal lymph node injection is a more efficient technique that involves ultrasound-guided Lipiodol injection into the sinus of an inguinal node (eFig. 111.1). Following either injection technique, serial fluoroscopic imaging is performed to track the contrast to the cisterna chyli and thoracic duct. When opacified, the thoracic duct can be accessed with a needle, then threaded with a wire and microcatheter. Contrast is injected into the microcatheter within the thoracic duct, revealing the site of the chyle leak.[189] Noncontrast CT following lymphangiography may identify the site of chyle leak in up to 75% of cases.[190] Lymphangiography may have additional therapeutic value as described later.[182] Lymphoscintigraphy requires an intradermal injection of a radioactive tracer, Tc-99m-labeled albumin, followed by imaging with a gamma camera.[187,188] Focal abnormal uptake of radiotracer can reveal the site of the leak. Combination with targeted single-photon emission CT can help define the specific anatomic site.[191,192]

Novel magnetic resonance techniques also provide potential noninvasive investigation.[188] High-resolution T2-weighted imaging can delineate the thoracic duct due to its high contrast.[193] Dynamic contrast magnetic resonance lymphangiography is a new technique that involves bilateral ultrasound-guided punctures of the inguinal nodes and intranodal injection of gadolinium-based contrast.[188] Dynamic imaging and high-resolution magnetic resonance angiography sequences obtained in this manner can provide detailed anatomy of the lymphatics and the lymph flow within and, in some cases, identify the site of chyle leak.[188,194]

TREATMENT

GENERAL APPROACHES

The management of chylothorax may vary among patients and is partly governed by the etiology, availability of therapeutic options, physicians' preference, overall condition of the patient, anatomy of the thoracic duct, and other clinical factors such as the rate of chyle leak. The lack of high-quality evidence explains the lack of formal structured treatment recommendations.[16,162] A combination of treatment modalities is often used[174] (Table 111.2).

DRAIN THE PLEURAL FLUID

The level of breathlessness varies and in part relates to the size of the chylothorax. With large chylothoraces, pleural fluid drainage for symptom relief is often necessary. Every attempt should be made to avoid prolonged continuous drainage, which can result in chyle loss and resulting malnutrition and immunosuppression.

In refractory cases, a pleuroperitoneal shunt can relieve symptoms, minimize chyle loss,[195] and reduce the need for TPN.[196] The presence of ascites is a relative contraindication for pleuroperitoneal shunt placement.[197] Drain patency should be checked regularly because the shunt is easily clotted due to the high quantity of fibrinogen in the chyle.[150]

Indwelling pleural catheters (IPCs) in refractory chylothoraces have been reported in several retrospective series.[198–200] Although there have been concerns of chronic nutritional loss through the intermittent drainage via the IPC, there is no evidence to support this suspicion.[201] Instead, the use of IPCs may negate the need and risks of repeated pleural interventions.[200] Caution must still be exercised, and IPC should only be considered in selected cases given the paucity of prospective and randomized clinical data.

REDUCE THE FLOW OF CHYLE AND CLOSE THE DEFECT

Reducing or stopping chyle flow in the thoracic duct can promote healing of the defect.

Table 111.2 Management of a Chylothorax

Drain the pleural fluid to improve respiratory symptoms ▪ Thoracentesis and tube thoracostomy (short term only) ▪ Pleuroperitoneal shunt ▪ Indwelling pleural catheter
Reduce the flow of chyle and close the defect ▪ Dietary management: fasting ± TPN, low-fat or fat-free diet with MCT supplementation ▪ Drugs: octreotide, somatostatin, etilefrine, midodrine ▪ Minimally invasive treatments: lymphangiography, TD embolization, TD disruption ▪ Surgery: TD ligation
Replace chyle components and nutrients
Treat the underlying disease
Obliterate the pleural space: pleurodesis

MCT, medium-chain triglyceride; TD, thoracic duct; TPN, total parenteral nutrition.

Dietary Management

There is no high-quality evidence or formal guidelines on the optimum method of dietary management.[174,203] Enteral nutrition with high-fat content can increase lymph flow and should be avoided. A low-fat or fat-free (<5 kcal per serving with MCT supplementation) diet may be tried to reduce the flow of chyle[16,17,174,204,205] (eFig. 111.2).

For patients with short-term self-limiting causes of chyle leak (e.g., postsurgery or trauma), a short period of fasting with TPN may significantly minimize chyle flow and enhance healing. When TPN was given to patients with postoperative chylothorax (including patients after esophagectomy) who were only allowed to take clear oral fluid, 67% of thoracic lymph leaks resolved.[206]

The latest systematic review analyzing 31 retrospective case series found that 72% of chylothoraces successfully resolved without surgical intervention. TPN has a slightly lower success rate compared with the low-fat/fat-free diet, but no statistically significant difference in the rate of resolution of chyle leak.[174] If effective, the low-fat/fat-free diet should be continued for at least four weeks after control of chylothorax before returning the patient to a normal diet.[51]

Drugs

Somatostatin and its analogue octreotide can slow chyle flow.[207] The mechanism is unclear, but a reduction of gastrointestinal motility, blood flow, and secretion[208–215] may contribute.[207,212,216] The drugs are commonly used as an adjunct to dietary management in congenital and postoperative chylothorax, but the evidence is largely limited to pediatric reports.[207,216–218] Both agents are considered safe with few side effects (e.g. flushing, nausea, diarrhea).[207,208,216,219,220] Octreotide is usually the treatment of choice because of its longer half-life, greater potency, and ability to be delivered subcutaneously (or intravenously).[207] However, there is no practice recommendation for either agent at the moment.[221] Variable dosage and titration regimens have been reported,[207,216,218,221–225] and 5 to 6 days of treatment may be required to observe an effect.[216,226]

Etilefrine (a sympathomimetic agent)[17,227–231] and midodrine (an α-1 adrenoreceptor agonist)[232] can induce vasoconstriction of the lymphatic system and reduce chyle flow, especially in refractory postoperative and idiopathic chylothoraces.[233–235] Midodrine is more readily available and may be a better option than etilefrine. However, the efficacy of these agents needs further verification.

Conservative measures (e.g., dietary management and pharmaceutical interventions) should be attempted but have a variable (20–80%) success rate in slowing down chyle flow in traumatic chylothorax. A high rate of chyle leak (e.g., output >500 to 1000 mL/day) predicts failure of these interventions.[17,49,217,236,237]

Minimally Invasive Treatments: Lymphangiography, Embolization, and Disruption

There are multiple minimally invasive treatments for high-output chylothorax, including lymphangiography, thoracic duct embolization, and thoracic duct disruption.[33,189,238–244] These have much lower rates of morbidity and mortality than surgery.[189]

Lymphangiography with direct injection of Lipiodol into the inguinal lymph node has been shown to be useful not only in imaging, but also in treating high-output chylothorax.[189,238,239] The therapeutic effect may be due to a sclerosing or other direct action of the Lipiodol. A meta-analysis from Kim et al. demonstrated a clinical success rate of 56.6% (despite a high technical success rate of 94.2%).[242] Although the clinical efficacy is relatively low, watchful waiting after lymphangiography can be considered before proceeding to more invasive treatments, especially if the chylothorax has a low output (<500 mL/day).[242,245]

Thoracic duct embolization (TDE) is an image-guided procedure designed to occlude the thoracic duct. After the cisterna chyli is opacified with Lipiodol, it is percutaneously accessed with a wire, and a microcatheter is inserted over the wire to the thoracic duct. Contrast is injected through the microcatheter to demonstrate the chyle leak. Embolic agents include coils, alcohol, glue (histoacryl), or a combination of these (Fig. 111.3).[190,244] In patients with a hypoplastic or absent cisterna chyli, the thoracic duct can be accessed either through a transabdominal approach similar to a cisterna chyli puncture or a retrograde catheterization following a puncture of the left subclavian vein.[189] The technical success of TDE, reported at 63.1%, is limited by the difficulty in cannulating the cisterna chyli or thoracic duct.[242] However, if technically possible, TDE has a high success rate of 79.4%.[242]

Thoracic duct disruption is considered when the thoracic duct cannot be catheterized. The thoracic duct is disrupted by numerous passes of a needle through it or the cisterna chyli within the upper abdomen, limiting the flow of lymphatics up to the site of the leak.[243] The explanation for the effect of the needle disruption is unknown but is speculated to involve healing after the needle injury. The clinical success rate of thoracic duct disruption is 60.8%.[242]

The overall complication rate for interventional procedures is low at around 0–2%.[191] There is no reported associated mortality. Rare complications include infection, pulmonary artery embolization with Lipiodol, and chylous ascites.[189,244]

Surgery: Thoracic Duct Ligation

Thoracic duct ligation (TDL) is a surgical approach that should be the last resort to stop the chyle leak if TDE or thoracic duct disruption is unavailable or fails. It can lower the mortality[35,246,247] and complication rates[148] in traumatic chylothorax. Although the benefit of TDL may be maximized if it can be done early, conservative treatments should be initiated first before proceeding to surgery.[84,156,162,247,248] Indications for early surgical referral have been proposed[249] but have not been prospectively validated.[16] In a systemic review, patients with greater peak 24-hour drainage rates were more likely to undergo surgical intervention.[174] The decision to proceed to TDL must balance considerations of nutritional status, disease prognosis, and expected success rate of conservative treatment.[16,250]

Accurate localization of the thoracic duct and its leakage site is essential to avoid extensive dissection and exacerbation of chyle leak during TDL.[33] Preoperatively, radiologic localization should be performed.[251–253] Intraoperatively, localization can be enhanced by enteral

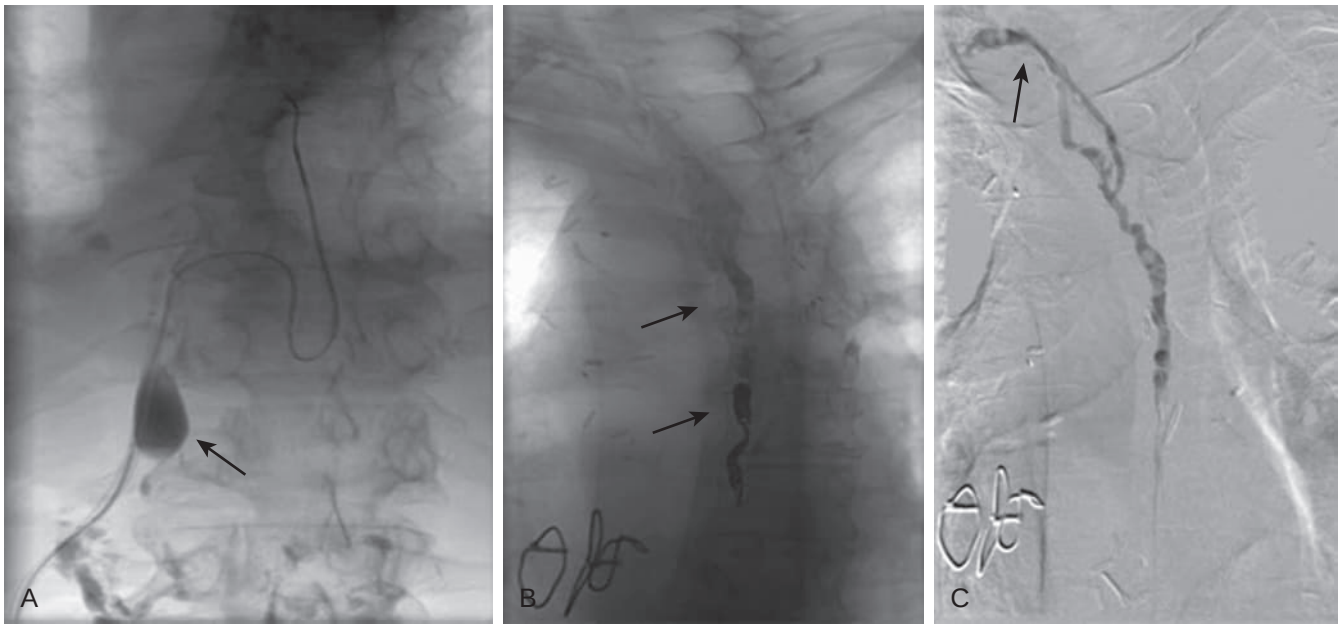


Figure 111.3 Thoracic duct embolization. (A) A microcatheter has been placed directly into the cisterna chyli (*arrow*) by a percutaneous route. (B) Coils and glue (*arrows*) are placed in the *thoracic duct* (TD) to occlude the TD inferior to the site of the leak. (C) TD leak in the thoracic inlet with pooling and extravasation of contrast (*arrow*). The terminal TD entering the subclavian vein is not seen above the leak.

feeding of approximately 50 to 60 mL of cream to stimulate the flow of chyle.[33,75,254] The duct is ligated above and below the site of the leak. If the duct cannot be identified,[84,255,256] mass ligation of all tissue between aorta, spine, esophagus, and pericardium above the diaphragmatic hiatus can be performed.[84] It halts the flow from any unidentified accessory ducts and offers a 90% success rate in resolving a chylothorax.[150,257–259] Lymph flow may be temporarily obstructed proximal to the ligated site until new collateral channels are formed that carry the chyle around the ligated site of the leak, which may require 2 to 3 weeks.[156,260]

REPLACE CHYLE COMPONENTS AND NUTRIENTS

Complications may arise after prolonged drainage of chylothorax and loss of chyle components.[17] No high-quality evidence exists to recommend replacement of other chyle components (including immunoglobulins, anticoagulation factors, and albumin).[162,261,262] Supplementation with MCTs is necessary to replace the essential fatty acids when adopting the no-fat diet. Octanoic acid may be the preferable MCT substrate.[15] However, long-term use of pure MCTs may result in linoleic acid deficiency, reduction in vitamin E status, and adverse gastrointestinal symptoms.[14,263] Input from an experienced dietitian is desirable.[15,264] The reinfusion of chyle back into the systemic circulation is not supported by evidence, has risks of anaphylaxis,[265] and is technically difficult.[266,267]

TREAT THE UNDERLYING DISEASE

Successful control of the underlying etiology of the chylothorax is the ideal management for chylous effusions. The likelihood of success depends on individual disease.[268–272]

Mediastinal Lymphadenopathy (Especially Lymphoma) and Obstructive Mediastinal Structures

Removal of obstructive lesions along the thoracic duct may help to restore the chyle flow. Chylothorax can resolve after oncologic treatment for malignant mediastinal or SVC lesions,[87,88,268,271] excision of retrosternal goiter,[104] corticosteroids for sarcoidosis,[273] or anticoagulation and thrombolysis for SVC thrombosis.[68,274,275]

Lymphangioleiomyomatosis

The mammalian target of rapamycin inhibitors, sirolimus and everolimus, are now standard therapies for LAM.[117,124,125,276–278] A systematic review found that sirolimus is effective in all LAM patients with chylothorax, with complete and partial resolution in 87% and 13% of patients, respectively,[124] although the resolution may take a few months.[276,279] Treatment can significantly reduce the need for therapeutic pleural drainage.[276]

Pleurodesis is the second most commonly used treatment option for LAM-related chylothorax, with a favorable outcome in 56.8%.[124] Lung transplantation in LAM is not contraindicated after pleurodesis, though the complication rate (especially for bleeding) is higher. Hence the decision to perform pleurodesis should be undertaken together with a transplant surgeon.[281]

Hepatic Cirrhosis

Correction of portal hypertension in cirrhosis may decrease thoracic duct flow[282–284] and reduce chyle leak. Both surgical portosystemic shunt[285,286] and transjugular intrahepatic portosystemic shunt[287–290] can decrease the portosystemic pressure gradient, reduce hepatic and gastrointestinal lymph flow, and promote healing of the thoracic duct. Pleurodesis is

often unsuccessful in chylothorax due to the rapid fluid reaccumulation, especially in cirrhosis-related cases.[291]

OBLITERATE THE PLEURAL SPACE

The pleural space can be obliterated through a pleurodesis procedure to prevent accumulation of chylothorax. It is useful when conservative treatment fails and TDL is not feasible.[292] The success rate of thoracoscopic talc pleurodesis was reported to be 100% in patients with lymphoma-related chylothorax who were refractory to chemotherapy and radiotherapy.[293] Different pleurodesis agents have been studied, with talc more commonly used in adults,[294,295] fibrin glue in postoperative patients,[256,296–298] and OK-432 in the fetal/pediatric group.[299–303] Surgical techniques may also be considered in cases of complicated chylothorax and may include pleural decortication with pleurodesis.[84,255]

A brief discussion of the prevention of chylothorax during thoracic and neck surgery and on long-term outcomes is available at ExpertConsult.com.

PSEUDOCHYLOTHORAX

Pseudochylothorax, also known as cholesterol pleurisy or chyliform effusion, is defined as the presence of cholesterol crystals in the pleural space. *Tuberculosis* (TB) (including those cases treated with artificial pneumothorax) and *rheumatoid arthritis* (RA) underlie most cases of pseudochylothoraces.[319,320] Other reported associations include paragonimiasis,[321,322] echinococcosis,[323] hydatidosis,[324] malignancy,[320] and coronary artery bypass surgery.[325] Previous successful treatment for TB does not preclude the development of pseudochylothorax.[320]

PATHOPHYSIOLOGY

Although pseudochylothorax was first reported over a century ago, its precise pathogenesis remains unknown. A majority of patients have a gradual onset of their effusion over several years. The pleura is thickened and sometimes calcified.[85,326,327] A minority of patients (≈20%) have a recent onset effusion without pleural thickening.[319,328,329] It is often hypothesized that the cholesterol crystals are formed due to the degeneration of cellular lipid membranes in long-standing pleural fluid and become trapped in the poorly vascularized and fibrotic pleural space.[85] However, this belief has been challenged in patients without pleural thickening.[319,329]

CLINICAL MANIFESTATION

Pseudochylothorax may develop in patients with long-standing pleural effusions. Pleural thickening is a prominent feature in TB-related, but not in RA-related, pseudochylothorax.[319] Breathlessness is common but may not be noticed in up to one-third of patients, presumably because of its gradual onset.[326,330]

The pleural fluid from a pseudochylothorax is milky (sometimes turbid, cloudy, or with a "motor-oil" appearance) with a satin-like sheen due to the high levels of cholesterol or lecithin-globulin complexes[16] and cholesterol crystals[326] (Fig. 111.2C). Complications are uncommon but may include infection (reactivation of TB, fungal), fistula formation (bronchopleural, pleurocutaneous), poor lung function, and poor quality of life.[85]

DIAGNOSIS

Thoracentesis is needed to establish the diagnosis. The demonstration of cholesterol crystals with a typical rhomboid appearance in the pleural fluid is considered confirmatory, although its absence does not exclude pseudochylothorax. Alternatively, a high fluid cholesterol level greater than 200 mg/dL may serve as a cutoff to diagnose pseudochylothorax, but it may miss 25% of cases.[319] Instead, a cholesterol/TG ratio greater than 1 has a higher sensitivity of up to 97.4% and helps to differentiate from chylothorax.[319] The cholesterol level usually decreases after serial aspiration of the pleural fluid[326]; therefore it should be tested on the first pleural fluid sample. Pleural fluid TG levels can be elevated in pseudochylothorax, which mimics chylothorax. Adding 1 to 2 mL of ethyl ether will clear the milky appearance seen in pseudochylothorax, which can differentiate this condition from chylothorax.[331] The fluid TP and lactate dehydrogenase levels are usually elevated, with a predominance of lymphocytes.[319] However, the fluid cell count may not be reliable due to interference with the counting by the presence of cholesterol crystals.[332] Pleural thickening may be observed on imaging or thoracoscopy,[85] though this is not a universal observation.[319,329]

In patients with a secured diagnosis of pseudochylothorax, it is crucial to look for underlying TB and RA if these conditions are not already established. The yield of TB culture from pleural fluid and biopsy may be low.[85,319,320] The pleural fluid adenosine deaminase level can be misleading in pseudochylothorax and should not be used to guide diagnosis or therapy.[320,328,333] Fibrosis and chronic inflammatory changes are common findings in biopsy samples, which only give limited additional evidence, especially in those with intensely thickened pleura.[319,334] Pseudochylothorax may precede the clinical manifestation of arthralgia symptoms in patients with RA.[335]

TREATMENT

There is no high-quality evidence on treatment of pseudochylothorax. The underlying disease should be treated, and TB should always be considered. Anti-TB therapy is recommended for patients with a positive stain or culture for TB and those with enlarging effusions of suspected tuberculous origin. Pleural fluid drainage should only be considered if the effusion is large enough to cause respiratory symptoms or if there is evidence of infective complications, because recurrence is frequent and there is the risk of fistula formation.[320,326] The lung is often nonexpandable (trapped) from grossly thickened pleura.[330] Surgical decortication has been attempted in selected cases,[320,334,336] with an overall success rate of 86.7% according to a systematic review[280] (see also Chapter 112).

Acknowledgment

We thank Charles Handley, MD, for his assistance in chylothorax imaging and thoracic duct embolization.

PREVENTION OF CHYLOTHORAX DURING SURGERY

Efforts should be taken to prevent thoracic duct injury during thoracic and neck surgery. However, this can be technically challenging due to the unpredictable route of the thoracic duct, extensive tributaries, and difficult identification.[304,305] Preoperative manipulation to highlight the thoracic duct (as described in the section on TDL) can be considered during surgery.[17,84,148,306]

Whether the thoracic duct should be ligated prophylactically during esophagectomy to prevent postoperative chylothorax is a matter of debate.[35,307–310] Compared with preservation of the thoracic duct, prophylactic TDL lowered the incidence of chylothorax (0.3% vs. 2.1% in a randomized trial)[308] without a significant difference in postoperative complications.[311] However, a subsequent retrospective analysis revealed that prophylactic TDL had shorter median survival times and did not reduce the incidence of chylothorax.[310] The access of the surgical site for esophagectomy may play a role, although there is no strong evidence favoring a transhiatal[35] or transthoracic approach.[34] Administration of low-fat tube feeding following esophagectomy was associated with a lower incidence of chylothorax.[312]

PROGNOSIS

The long-term outcome depends on the etiology, rate of chyle leak, and treatment used. Patients with malignant chylothoraces secondary to solid malignancy had a shorter life expectancy than those caused by lymphoma.[271] Postesophagectomy chylothorax has a worse prognosis than other postoperative chylothoraces, with more respiratory complications, longer hospital stay, higher reintervention rate, lower response rate to TPN, and higher mortality (0–50%).[35,48,49,154,206,307,313–315] Chylothorax complicating congenital heart surgery was associated with significantly longer ventilator dependence,[161] higher incidence of central venous thrombosis,[161] longer ICU stay,[53] longer hospital stay,[53] and more early postoperative complications.[53] Its mortality rate ranges from 0–23%,[36,50–53,55,161,219,316–318] but it is not consistently increased when compared with those without chylothorax.[53,161]

Key Points

- Due to the long route of the thoracic duct and its extensive tributaries, leakage of chyle and resultant chylothoraces can result from any disruption (especially trauma, iatrogenic causes, and malignancy) of the lymphatic wall along the duct and its tributaries.
- Breathlessness is the most common presenting symptom. Prolonged drainage of chylothorax can result in nutritional deficiency, electrolyte disturbance, and lymphocyte depletion.
- The appearances of pleural fluid from chylothorax and pseudochylothorax are similar. Chylothorax is defined as the presence of chyle in the pleural space, which can be confirmed by a high triglyceride level or presence of chylomicrons in the pleural fluid. Pseudochylothorax is defined as the presence of cholesterol crystals in the pleural space.
- A computed tomographic scan of the thorax may identify the underlying etiology, and lymphangiography or lymphangioscintigraphy may help locate the site of chyle leak.
- The flow of chyle through the thoracic duct can be slowed or stopped by different treatments, including dietary, pharmacologic, embolization or disruption of the thoracic duct, or surgical ligation. However, the lack of high-quality evidence precludes formal structured treatment recommendations. A combination of treatment modalities is commonly needed, and the choice is often based on the etiology, availability of therapeutic options, and other patient factors.
- The mammalian target of rapamycin inhibitors sirolimus or everolimus are effective in treating lymphangioleiomyomatosis-related chylothorax, while thoracic duct embolization is an emerging modality for chylothorax with known leakage sites along the thoracic duct.
- Pseudochylothorax is most often associated with tuberculosis and rheumatoid arthritis.

Key Readings

Agrawal V, Doelken P, Sahn SA. Pleural fluid analysis in chylous pleural effusion. *Chest*. 2008;133(6):1436–1441.

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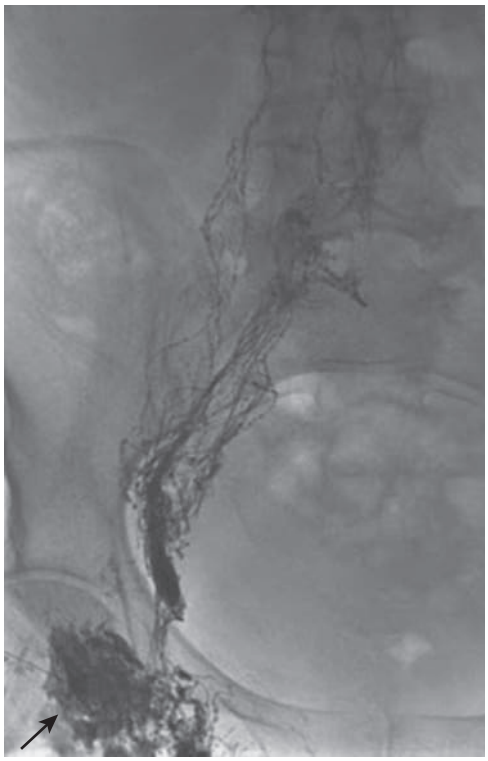
Complete reference list available at ExpertConsult.com.

eFIGURE IMAGE GALLERY



eFigure 111.1 Direct Lipiodol injection of right inguinal lymph node (*arrow*). This technique enables ready visualization of the draining lymphatics and thoracic duct.



eFigure 111.2 Chylothorax pleural fluid before and after low-fat diet. (A) Milky appearance of a chylothorax, with a triglyceride level of >700 mg/dL and cholesterol <70 mg/dL. (B) Clear appearance of pleural fluid obtained after a low-fat diet along with a reduced triglyceride level in the fluid. (From Scholz GA, Sirbu H, Anders K, et al. Persisting right-sided chylothorax in a patient with chronic lymphocytic leukemia: a case report. *J Med Case Rep.* 2011;5:492.)

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112 PLEURAL FIBROSIS AND UNEXPANDABLE LUNG

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INTRODUCTION

Any insult or injury to the pleural membranes can result in inflammation (pleuritis) and subsequent fibrosis. In some cases the extent or location of this fibrosis may be deemed pathologic, with a range of clinical sequelae possible. Pleuritis may be caused by benign or malignant processes within the pleural cavity and variably causes symptoms and/or pleural effusion.

The anatomic location of the pleural fibrosis has important clinical and potentially medicolegal implications. For example, localized parietal pleural fibrosis, in the form of asbestos-related pleural plaques, is not thought to cause sufficient physiologic impairment to result in respiratory symptoms but may alert the patient to significant asbestos exposure.[1] However, if a fibrotic, thickened "rind" develops in the visceral pleural membrane, this can result in reactive infolding of the underlying lung (known as folded lung, rounded atelectasis, or Blesovsky syndrome) and a restrictive defect, which may lead to symptoms of breathlessness.

The mechanisms by which the pleural membrane becomes fibrotic are not well understood, although imbalances of fibrin turnover are likely to be crucial.[2] Release of tissue factor during an acute insult stimulates the conversion of fibrinogen to fibrin and thereby matrix formation. The imbalance between the profibrotic pathways (matrix formation and *tissue factor pathway inhibitor* [TFPI] production), and the fibrinolysis pathways is the likely driver of pleural fibrosis. Several cytokines have been implicated in these processes, including vascular endothelial growth factor, transforming growth factor-β, and basic fibroblast growth factor.[3]

Inconsistent use of the terminology relating to pleural fibrosis and its clinical sequelae can lead to confusion. *Unexpandable lung* or *nonexpandable lung* refers to an irreducible pleural space, caused by either a restrictive visceral pleural rind, which impairs expansion of the underlying lung, endobronchial obstruction, or prolonged atelectasis.[4] *Trapped lung* and *lung entrapment* are both causes of unexpandable lung but are intended to describe different pathophysiologic processes. Trapped lung refers to fixed, established fibrosis encasing and restricting the lung, whereas lung entrapment refers to the restriction seen with active pleural inflammation or malignancy that may be reversible. It has been proposed that these two entities may be differentiated using pleural manometry during a therapeutic pleural aspiration, although this has not been confirmed.[4] The importance of this distinction is in ensuring that the cause of any potentially reversible, ongoing inflammation in the context of lung entrapment is promptly treated. Finally, the term *fibrothorax* refers to fibrotic fusion of the visceral and parietal pleural layers resulting in complete obliteration of the pleural cavity. This is usually the result of prolonged or extreme inflammation and can cause volume loss of the hemithorax, a restrictive pulmonary defect and, depending on its extent, refractory dyspnea. A summary of terminology is provided in Table 112.1.

We would suggest that these three terms are simply different potential disease courses of the inflammation and scarring within the pleural cavity after an insult or injury. It is not understood, for example, why some patients will get an unexpandable lung and why others develop a fused pleural cavity (fibrothorax). One can speculate that the different outcome may relate to whether a pleural effusion was part of the initial insult.

DIAGNOSIS OF PLEURAL FIBROSIS AND OF UNEXPANDABLE LUNG

Pleural fibrosis is usually initially identified radiologically. Chest radiography may reveal features, such as calcified pleural plaques or costophrenic angle blunting and, in more pronounced disease, peripheral thickening or loss of hemithorax volume (Fig. 112.1). Thoracic ultrasound may be used to identify pleural thickening, with this made easier if there is an adjacent pleural effusion to provide greater visual contrast. Cross-sectional modalities, however, are normally used to diagnose and monitor pleural fibrosis

Table 112.1 Nomenclature Associated With Pleural Fibrosis and Unexpandable Lung

	Definition
Pleuritis	Inflammation of the pleural membrane(s); often associated with the typically sharp pain of pleurisy
Pleural fibrosis	The deposition of fibrotic material within the pleural membranes, likely as a result of previous inflammation
Unexpandable lung/ nonexpandable lung	The lack of apposition of visceral and parietal pleura at the end of a therapeutic pleural drainage procedure
Trapped lung	Unexpandable lung due to a fibrous, visceral pleural peel as a result of a resolved inflammatory insult
Lung entrapment	Unexpandable lung due to an active pleural process (e.g., malignancy or inflammation)
Fibrothorax	Fibrosis and fusion of the visceral and parietal pleura

Modified from Huggins JT, Maldonado F, Chopra A, et al. Unexpandable lung from pleural disease. *Respirology*. 2018;23:160–167.

because they are usually able to provide an estimate of overall disease burden and can allow precise measurements where necessary, facilitating more effective monitoring. *Computed tomography* (CT) imaging, preferably with contrast enhancement timed for pleural enhancement, is most commonly used. Aside from the research setting or rarer specific circumstances, such as in some cases of suspected malignancy, there is a limited role for magnetic resonance imaging and *positron emission tomography* (PET) in the diagnosis of pleural fibrosis. Pleural biopsy may be obtained by image guidance or by thoracoscopy and may be useful when there is an increased index of suspicion for underlying malignancy or active infection.

Establishing a diagnosis of pleural fibrosis is aided by identifying an underlying cause. Finding a likely cause for pleural fibrosis may be relatively straightforward, depending upon the clinical presentation and knowledge of the patient's background. However, if there is ongoing diagnostic uncertainty, a thorough, systematic approach is advised (Table 112.2). If a cause for fibrosis does not become apparent, there should be careful follow-up to ensure progression does not take place, particularly for those with previous asbestos exposure who are at risk of malignant

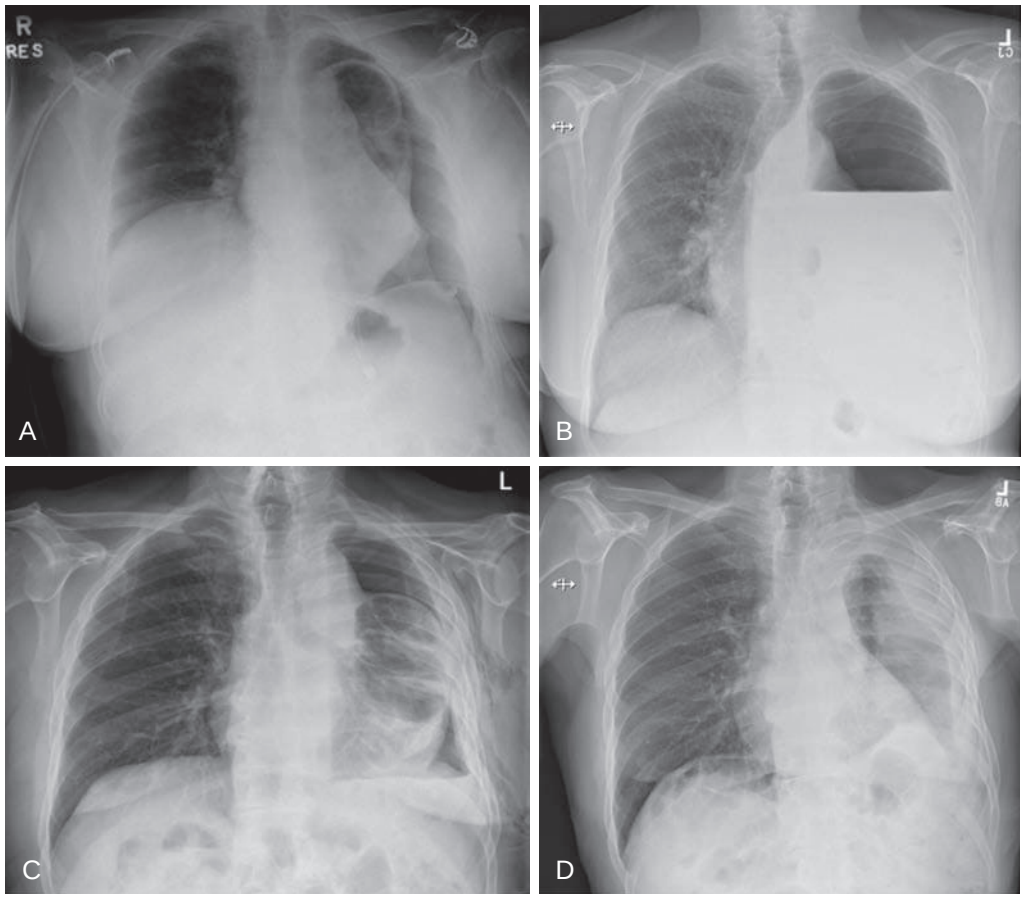

Fig. 112.1 Chest radiographic appearance of unexpanded lung following intervention. (A) Frontal chest radiography in a patient with malignant pleural mesothelioma after thoracoscopy shows left-sided pneumothorax despite the presence of a thoracostomy tube, consistent with unexpanded lung. Note presence of visceral pleural thickening. (B) Frontal chest radiography 1 week after thoracoscopy shows a large left hydropneumothorax. (C) Frontal chest radiography in a patient with chronic left pleural space infection shows an unexpanded left lung associated with left-sided hydropneumothorax with visceral pleural thickening. (D) Three months after (C), substantial left-sided pleural thickening associated with left thoracic volume loss is noted, although the sepsis had resolved and the patient had only minimal breathlessness.

Table 112.2 The Approach to Diagnosis of Pleural Thickening

History and physical examination	Previous chest trauma Previous or current infective symptoms Risk assessment for TB: previous history, TB contact, travel history Rheumatic symptoms Weight loss, systemic symptoms Full asbestos exposure history Previous pneumothoraces: may be seen in PPFE History of previous pleurodesis Drug history: specifically bromocriptine, cabergoline, pergolide, and methysergide; β-blockers; and tyrosine kinase inhibitors (imatinib and dasatinib)
Pleural fluid analysis (if fluid present)	Review biochemistry, cytology, cultures, TB culture Consider special tests: ADA: increased in TB pleuritis and IgG4 Flow cytometry: if effusion lymphoma considered. Evaluate symptomatic benefit from therapeutic pleural aspiration: to help inform future effusion management strategy Consider post-aspiration CXR or pleural manometry to look for unexpandable lung
Imaging	Ultrasound: may help evaluate effusion and define chest wall invasion in suspected malignancy CT: interval CT follow-up may be required in undiagnosed cases for at least 2 years, particularly if previous asbestos exposure PET: if suspected malignancy; may be helpful in suspected IgG4-related disease MRI: may be useful in certain cases (e.g., to identify if chest wall invasion in suspected malignant pleural thickening)
Pleural biopsy	Obtain biopsy and consider special stains for amyloid, IgG4 Evaluate for specific disease patterns: PPFE, IgG4-related disease Send for standard culture and TB culture
Additional tests	Full autoimmune profile: including ANA, complement, anti-CCP antibodies, rheumatoid factor, ANCA Ferritin: elevated in adult-onset Still disease Myeloma screen: if considering amyloid Serum IgG4 levels

ADA, adenosine deaminase; ANA, antinuclear antibodies; ANCA, antineutrophil cytoplasmic antibody; CCP, cyclic citrullinated peptide; CT, computed tomography; CXR, chest radiograph; IgG4, immunoglobulin G4; MRI, magnetic resonance imaging; PET, positron emission tomography; PPFE, pleuroparenchymal fibroelastosis; TB, tuberculosis.

mesothelioma, which may have nonspecific CT and fluid cytology features in the early stages.[5]

In patients with a symptomatic pleural effusion, identification of unexpandable lung may help with the selection of the most appropriate treatment strategy for that individual. Specifically, the lack of pleural apposition caused by substantial unexpandable lung will result in talc pleurodesis being ineffective and, therefore, if long-term control of an effusion is needed, an indwelling pleural catheter may be a better treatment option for these patients. In certain patients, pleural intervention may not be necessary, particularly in those with unexpandable lung resulting from a confirmed pathology and in those without symptoms of breathlessness. However, we would almost always advocate an initial trial of therapeutic thoracentesis for patients with suspected unexpandable lung, to ensure that fluid removal confers symptomatic benefits before a more definitive intervention is considered.

During a thoracentesis, patients with unexpandable lung may experience symptoms of pain, cough, or central chest tightness, and the operator may notice increased resistance to drainage. In this circumstance, discomfort may improve if air is introduced into the pleural cavity, either by the operator through active entrainment of air back through the aspiration device (a therapeutic pneumothorax)[6] or after the formation of a pneumothorax ex vacuo, which may arise due to high transpulmonary pressures, either causing a small parenchymal-pleural fistula or pulling air alongside the catheter into the pleural space.[4] Postdrainage chest radiography in the context of unexpandable lung may thus reveal a pneumothorax or hydropneumothorax, with no specific treatment for this required. Indeed, the risk of additional pain or injury to the lung may be increased by attempting to inflate the lung further.

Noninvasive detection of unexpandable lung may also be possible using thoracic ultrasound. In a small study of patients with large pleural effusions, motion-mode (M-mode) ultrasound was used to image the atelectatic lung. With the requisite knowledge and skill, the operator could recognize that movement of the collapsed lung in response to the cardiac impulse was significantly reduced in those with unexpandable lung compared to those without, typified by reductions in total lung movement and the degree of measured deformation.[8]

The presence of unexpandable lung can also be established using pleural manometry during thoracentesis. This is a well-described technique that allows measurement of pleural pressure during thoracentesis, using either a water manometer (sometimes damped to reduce the effect of respiratory motion) or a digital equivalent within the drainage circuit.[7] Although continuous measurement has been described experimentally,[8] the acquisition of readings usually requires the interruption of drainage every 100 to 200 mL, which contributes to the practical challenge of implementing pleural manometry for the majority of centers. Newer electronic devices, with measurement components

integrated into the thoracentesis catheter and linked to a real-time graphic display, are currently being tested and may make manometry more accessible in the future.[9]

Measured pleural pressure values can be used to calculate pleural elastance (the change in pleural pressure divided by volume removed), which is usually displayed in the form of elastance curves (Fig. 112.2). These are then grossly characterized as monophasic or biphasic and described further by the steepness of the elastance curve(s). The presence of unexpandable lung is inferred by a steeper curve (higher elastance values) because resistance to lung expansion is manifested in rapidly decreasing pleural pressure as volumes are withdrawn. Monophasic curves are seen when the whole lung expands (or fails to expand) to drainage in a relatively uniform fashion, whereas biphasic curves may be seen when isolated regions or lobes of the lung have varying degrees of restriction.[4,10]

Despite pleural pressure measurement being technically feasible and able to identify unexpandable lung, its role in routine management remains uncertain.[11] A multicenter, randomized controlled trial involving 128 patients allocated participants with pleural effusions to undergo either thoracentesis guided by symptoms alone or thoracentesis guided by symptoms in addition to predetermined pleural manometry criteria.[12] The study showed no difference in chest discomfort between treatment groups, confirming retrospective data that also contradicted the previously held belief that knowledge of real-time pleural pressures could reduce the likelihood of complications during or after thoracentesis.[13–15] In those with malignant pleural effusion, early pleural manometry and favorable elastance values have been correlated with pleurodesis success, although only in relatively small studies.[16] Despite these data, clinical management pathways for malignant pleural effusion that incorporate early detection of unexpandable lung are not the norm due to the practical limitations mentioned earlier. However, ongoing randomized trials may change this, with investigators exploring whether first-line indwelling pleural catheter treatment for those with suspected unexpandable lung on initial thoracentesis is worthwhile.[9,17]

GENERAL MANAGEMENT PRINCIPLES

The management of pleural fibrosis and resultant unexpandable lung depends on the underlying cause; specific etiologies are discussed in more detail later (Table 112.3). If there is an ongoing inflammatory process within the pleural cavity, such as infection or an active rheumatologic condition, targeting this with disease-specific measures may help prevent progression of pleural fibrosis. Recognition, removal, and future avoidance of drugs that may contribute to pleural fibrosis are also important.

Thereafter, managing symptomatic effusions with repeated pleural drainage may be indicated, and indwelling pleural catheters may have a role in some patients, especially those with malignant infiltration of the pleural membranes. Continued drainage is only indicated if the effusion is determined to be causing or contributing to the patient's symptoms. As mentioned, often the effusion merely collects in the pleural space when the lung cannot reinflate to fill

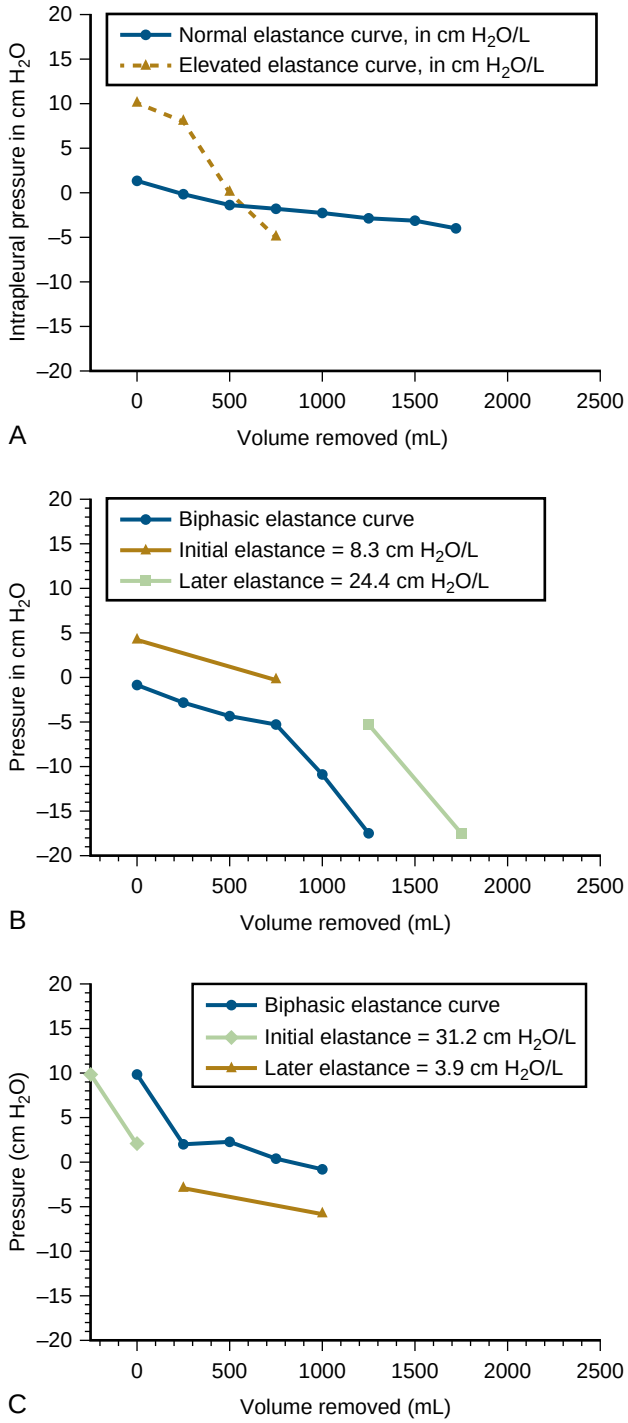

Fig. 112.2 Pressure/volume curves in patients receiving pleural manometry. (A) Monophasic pressure/volume curves of uniform slope. These curves are from two different patients, one with normal elastance and the other with abnormal elastance. (B) Biphasic pressure/volume curve with a distinct inflection point after 1000 mL of volume removed. Note the two distinct portions of the curve, with lines drawn to demonstrate the different slopes. Patients with biphasic curves usually have a normal elastance followed by a high elastance. (C) Biphasic pressure/volume curve with a distinct inflection point after 250 mL removed. Note the initial steep portion of the curve, followed by a more flat curve, with normal elastance. Curves with an initial steep portion followed by a more shallow section can sometimes be seen in patients with large hydrothoraces. The initial steep portion is likely due to lung stiffness from the hydrothorax that is relieved with drainage. (From Heidecker J, Huggins JT, Sahn SA, Doelken P. Pathophysiology of pneumothorax following ultrasound-guided thoracentesis. *Chest.* 2006;130:1173–1184.)

Table 112.3 Causes of Pleural Thickening

Cause	Specific Conditions	Specific Investigations	Management Considerations
Asbestos related	Pleural plaques	Consider CT to exclude other asbestos-related diseases	
	Diffuse pleural thickening		Follow-up for up to 2 yr to ensure no evolving features to suggest mesothelioma
	Mesothelioma	Pleural biopsy	For current therapy of mesothelioma, see Chapter 114
Rheumatologic	Rheumatoid arthritis SLE Sjögren Systemic sclerosis Dermatomyositis Granulomatosis with polyangiitis Ankylosing spondylitis Periodic fever syndromes Adult-onset Still disease	Autoimmune screen (ANA, ANCA, rheumatoid factor, complement, anti-CCP antibodies)	Proactively manage underlying condition to minimize risk of unexpandable lung (e.g., with suitable immunosuppression)
	IgG4-related disease	Serum IgG4 levels Biopsy pleural thickening Consider PET	
Malignancy	Primary (mesothelioma) or secondary	Pleural fluid/biopsy to confirm diagnosis	If coexisting effusion, perform therapeutic pleural aspiration to assess symptom benefit and evaluate for unexpandable lung
Infection	Bacterial pleural infection	Pleural fluid aspiration Consider pleural biopsy to increase microbiologic yield	Get control of sepsis through effusion drainage, antibiotics, and surgery/fibrinolytics if required Residual pleural thickening will usually resolve within 6 mo
	Tuberculosis	Pleural biopsy Pleural fluid TB culture ADA	Treat TB according to usual protocols Steroids unlikely to be beneficial
Iatrogenic	Drug causes	Bromocriptine Cabergoline Pergolide Methysergide β-Blockers Tyrosine kinase inhibitors (imatinib and dasatinib)	Stop causative agent
	Previous pleurodesis Post-CABG effusion After thoracic radiotherapy		No specific treatment required
Traumatic	After hemothorax		
Miscellaneous	Amyloid PPFE	Congo red stain of pleural tissue	
	Uremia		May require initiation or alteration of renal replacement therapy

ADA, adenosine deaminase; ANA, antinuclear antibodies; ANCA, antineutrophil cytoplasmic antibody; CABG, coronary artery bypass graft; CCP, cyclic citrullinated peptide; CT, computed tomography; IgG4, immunoglobulin G4; PET, positron emission tomography; PPFE, pleuroparenchymal fibroelastosis; SLE, systemic lupus erythematosus; TB, tuberculosis.

the space; in this setting, no drainage is needed. In all patients with unexpandable lung, the use of repeated drainage techniques must be considered carefully. Whereas some patients will gain symptomatic benefit from each drainage, and may even have their lung fully or partially reexpand over time, others will experience significant or limiting pain or cough on each occasion and, in such cases, it may be more suitable to manage dyspnea pharmacologically or conservatively. However, drainage may be the optimal approach. In a recent study of 145 patients with symptomatic pleural effusions, relief of dyspnea after drainage was documented in 73%; importantly, symptomatic improvement did not depend on whether or not the lung reexpanded.[17a] Thus, one must not neglect the potential benefit of drainage even when the lung cannot expand.

Surgical decortication is also a recognized treatment option but is very rarely required. The role for surgery depends on the underlying disease process. In general, there is a dearth of evidence regarding best practice in all disease areas relating to pleural fibrosis and unexpandable lung, and future studies looking at long-term function and symptom outcomes are warranted.

CAUSES OF PLEURAL FIBROSIS

A broad range of benign and malignant conditions can result in pleural fibrosis (see Table 112.3).

ASBESTOS-RELATED PLEURAL FIBROSIS

Occupational asbestos exposure is known to cause pleural thickening. Pleural plaques are well demarcated, raised, nontapering areas of parietal pleural fibrosis or calcification. However, due to their discrete position on the parietal pleura, they do not impair respiratory motion or function and usually are asymptomatic, unless they conglomerate and are extensive. In a recent study evaluating the lung function of miners, who were exposed to asbestos-contaminated vermiculite, the presence of pleural plaques did not significantly accelerate the decline in lung function.[18]

Diffuse pleural thickening (DPT) is another potential consequence of previous asbestos exposure and develops in 4–5% of asbestos-exposed individuals.[19] About 40% of cases are preceded by an episode of benign asbestos pleural effusion.[20] Likely as a result of significant mechanical impairment of lung expansion by thickening of the visceral pleura, DPT is associated with a restrictive defect and usually symptoms of breathlessness. On imaging, an adjacent area of folded lung (also called rounded atelectasis) may be seen (see eFig. 101.13). Recent observational data suggest that forced vital capacity is substantially reduced if the costophrenic angle is obliterated by DPT compared to control subjects or those without costophrenic angle involvement, but the most marked lung restriction is seen in those with bilateral DPT.[21] DPT must be carefully monitored to ensure that an underlying diagnosis of mesothelioma is not missed. DPT is usually slowly progressive. Surgical intervention is not usually beneficial, and management is supportive.

RHEUMATOLOGIC DISEASES

A number of inflammatory conditions cause pleuritis and, if pleural inflammation is persistent, may lead to pleural fibrosis. If pleuritis from rheumatologic disease is suspected, it is worthwhile looking for evidence of a serositis elsewhere (e.g., pericardial disease or a contralateral effusion). Often the initial inflammatory insult is associated with pain, a pleural effusion, and diffuse smooth pleural thickening and, over time, if the pleural inflammation persists, a fibrotic pleural peel can develop, preventing underlying lung expansion.

Pleural involvement is a well-established complication in rheumatoid arthritis; the extent of resultant pleural fibrosis can range from small, fibrous plaques to extensive fibrosis. Proactively targeting the underlying inflammatory condition with systemic steroids or other immunosuppressive agents and managing an associated symptomatic effusion is the mainstay of management. The aim of treatment is to reverse the inflammatory element and prevent the development of pleural fibrosis. Fibrothorax has also been reported in systemic lupus erythematosus.[22] Other collagen diseases, such as Sjögren, systemic sclerosis, dermatomyositis, granulomatosis with polyangiitis, ankylosing spondylitis, periodic fever syndromes, and adult-onset Still disease can also result in inflammatory pleural effusions that, if left untreated, can lead to pleural thickening.[23]

MALIGNANCY (See Chapter 114)

Malignant infiltration of the pleura can result in thickened, restrictive pleural fibrosis. The pleura can either be affected by a primary malignancy (mesothelioma) (see Figs. 114.3 and 114.5) or metastasis from elsewhere. This is often associated with a malignant pleural effusion, although many patients with malignant involvement of the pleura have isolated pleural thickening with no pleural effusion. If there is sufficient visceral pleural involvement, unexpandable lung may become evident after drainage. Unexpandable lung can be quite common in mesothelioma, affecting 33% of patients in one observational cohort.[24]

In the context of a malignant pleural effusion, if the lung fully reexpands and visceral and parietal pleural apposition is obtained, and the patient has symptomatic benefit from the removal of the effusion, attempting a pleurodesis is a reasonable approach. With pleurodesis, one attempts to obliterate the pleural cavity and prevent future pleural fluid reaccumulation. However, if the lung is not able to expand, pleurodesis is not indicated. Although guidelines would suggest pleurodesis can be attempted with as little as 50% pleural apposition,[25] placement of an indwelling pleural catheter, followed by repeated drainage for symptomatic benefit, is likely to be a more effective solution in this setting. As mentioned, although an isolated IPC drainage may not lead to full lung reinflation, the restoration of diaphragmatic motion and return of the chest wall to a more normal position can result in symptomatic relief for patients, albeit not universally.[26] In the presence of unexpandable lung, IPC drainage often needs to be undertaken cautiously and stopped if pain or significant cough arises. At present, there does not appear to be a role for decortication in malignant lung entrapment, although a feasibility study evaluating the role of pleurectomy decortication compared to IPCs in mesothelioma is ongoing.[27]

UREMIA

Pleural thickening and inflammatory changes were first described in the context of chronic renal disease as far back as the early 1800s.[28] Later, as uremic pneumonitis became increasingly recognized as a distinct entity, so did associated pleuritis, with the latter identified in up to 20% of cases of a 107-patient series of those with pneumonitis.[29] Literature and evidence regarding uremic pleuritis specifically, however, remains relatively sparse; in a report from 1970, uremia was recognized as the primary cause of pleural exudate in less than 1% of cases.[30] In those small series, which describe the causes of exudates specifically in patients with renal disease, approximately one-quarter are attributed to uremia.[31,32] The precise mechanism for uremic pleuritis is unclear but is assumed to result from accumulated toxins that would otherwise be excreted by normal kidneys. Despite this, pleuritis has been described in patients who are otherwise well managed on hemodialysis.[33] Overall, effusions are found in only 10% of kidney failure patients, and their presence is often attributed to other coexisting etiologies, for example, congestive cardiac

failure, nephrotic syndrome, or infection, particularly in the immunocompromised.[34]

Treatment strategies for uremic pleuritis vary. Management of symptomatic effusions is important, and successful use of empirical corticosteroids has been described.[35] Some authors consider the presence of uremic pleuritis, much like pericarditis, to be an indication for initiating dialysis[36] or for increasing the frequency or intensity of dialysis; however, pleuritis is not mentioned at all in certain high-profile guidelines.[37] As with other chronic pleural inflammatory conditions, the development of a restrictive fibrous peel has been described after uremia.[38] For those few patients in whom there is sufficient restriction, and in whom an operation is appropriate, surgical decortication has been reported to be effective,[33,39] although it is rarely performed.

TUBERCULOSIS

TB pleuritis, due to a delayed (type IV) hypersensitivity reaction within the pleural cavity, is thought to be triggered by release of TB antigens into the pleural space from rupture of an area of subpleural pulmonary disease. Fulminant empyema due to TB pleural infection is much rarer. After TB pleuritis, a subgroup of patients may be left with residual pleural thickening and adhesions, which have the potential to impair respiratory function. In a Spanish study of 81 patients treated for TB pleuritis, 10% had spirometric evidence of a restrictive ventilatory defect after a median follow-up for 23 months.[40] Pleural thickening may be more common after TB empyema (see Fig. 20.35).

Some data suggest that early pleural fluid drainage to empty the pleural cavity as completely as possible may minimize symptoms of breathlessness and limitation in lung function at 12 months.[41] A Cochrane review has evaluated the role of oral corticosteroids in TB pleuritis and found that their use may improve chest radiographic appearances of residual pleural changes. However, there appeared to be no difference in terms of long-term respiratory impairment, and steroids were found to be associated with a higher incidence of adverse events.[42]

IMMUNOGLOBULIN G4–RELATED DISEASE

This systemic, fibroinflammatory condition was described only relatively recently.[43] Given the paucity of clinical data on IgG4-related disease–associated pleural thickening, which is limited to a handful of case reports in the literature, the natural history, prognosis, and functional outcomes are not yet well established.

The condition is characterized by tissue infiltration with lymphoplasmacytic IgG4-positive plasma cells, storiform (e.g., whorled, cartwheel pattern) fibrosis, and obliterative phlebitis (Fig. 112.3). It can affect almost any organ system, and pulmonary involvement can manifest as hilar or mediastinal lymphadenopathy, lung nodules, airways disease, interstitial lung disease, or pleural involvement.[44] In the pleura, IgG4-related disease most commonly causes a pleural effusion, although isolated pleural thickening has been reported.[45,46]

The diagnosis requires a biopsy demonstrating the characteristic features, although a recent study suggests that high levels of IgG4-positive cells in a pleural fluid cell block may help support the diagnosis.[45] Serum IgG4 and pleural fluid adenosine deaminase levels may also be elevated, although these are neither sensitive nor specific.[44,47] Because patients appear to be at an increased risk of cancer, a clinical suspicion of IgG4-related pleural disease should prompt further imaging to exclude other disease sites and exclude occult malignancy.[44] IgG4-related disease is often avid on PET imaging, although there are reports of IgG4-related pleural disease without abnormal PET scans.[48] Typically, the condition is responsive to oral steroid treatment although, in resistant or relapsing cases, other immunosuppressive agents, such as rituximab, may be needed.[48]

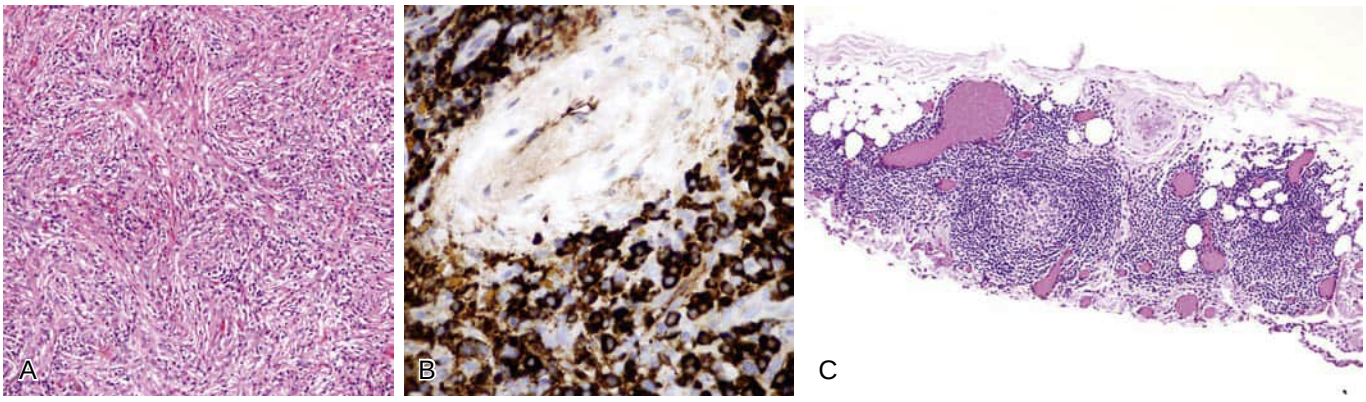

Fig. 112.3 Pathologic findings of *immunoglobulin* (Ig)G4-related disease. (A) IgG4-related disease fibrosis with a storiform or loose-swirling pattern. This image is of the disease affecting the lung in a 52-year-old man. (B) IgG immunohistochemical staining for IgG4 shows numerous plasma cells with a strong cytoplasmic positivity in IgG4+ sclerosing lung disease. There should be >50 IgG4+ plasma cells per 10 high-power field, with an IgG4/IgG ratio of >40%. (C) In IgG4-related pleural disease, the pleura is surfaced by a dense lymphoplasmacytic infiltrate that includes germinal centers. The other characteristics of IgG4-related disease are not evident in this case. However, the clinical features were strongly suggestive of IgG4-related disease as was the IgG4 immunostain. (A, From Lindberg MR. *Diagnostic Pathology: Soft Tissue Tumors*, ed 3. Philadelphia: Elsevier; 2019. B, From Suster S, Moran CA. *Diagnostic Pathology: Thoracic,* ed 2. Philadelphia: Elsevier; 2017. C, From Deshpande V, Khosroshahi A. Diagnostic guidelines for IgG4-related disease with a focus on histopathological criteria. *Diagn Histopathol.* 2013;19:119–127.)

AMYLOID

Pleural amyloid is a rare phenomenon, found in just 1–2% of patients with systemic amyloid, and may manifest as masslike pleural thickening mimicking malignancy.[49] Pleural biopsies are diagnostic but may require specific staining using Congo red to identify the amyloid proteins.

MEDICATIONS AND IATROGENIC CAUSES

A variety of drugs have been implicated in the formation of pleural fibrosis, including amiodarone, ergot alkaloids (such as bromocriptine, cabergoline, pergolide, and methysergide), β-blockers, and tyrosine kinase inhibitors (imatinib and dasatinib).[50,51] Once pleural fibrosis is identified, it is important these drugs be stopped and avoided in the future. Primarily in the malignant setting, agents such as talc, doxycycline, or iodopovidone are often introduced into the pleural space, with the express intention of creating pleural inflammation and a lasting pleural fibrosis. Previous pleurodesis may become apparent as calcification on CT or localized avidity on PET[52] but is not known to result in functional or spirometric impairment.

Previous radiation therapy to the thoracic cavity can result in pleural thickening. In one study, pleural thickening was evident on CT in 70% (19 of 27) of patients 12 months after chemoradiotherapy for stage II non–small cell lung cancer.[53]

PLEUROPARENCHYMAL FIBROELASTOSIS (See Chapter 90)

Pleuroparenchymal fibroelastosis (PPFE) is a rare, upper zone–predominant fibrotic lung condition associated with visceral pleural thickening (Fig. 112.4 and Figs. 90.12 and 90.13). Some patients may present with recurrent pneumothoraces. PPFE has specific histopathologic features of collagenous visceral pleural fibrosis, subpleural elastosis, and intra-alveolar collagenous fibrosis. It may be idiopathic, drug induced (e.g., bleomycin and cyclophosphamide),[54,55] or associated with other conditions, including stem-cell or lung transplantation or connective tissue diseases. The rate of progression can vary, with some experiencing an indolent course and others having more rapidly progressive and often fatal disease. Steroids or immunosuppression are rarely effective in slowing disease progression, and occasionally lung transplant is required.[56]

PLEURAL INFECTION

Infection in the pleural space creates the ideal acute inflammatory environment for the development of pleural thickening. In rare cases, this can lead to the development of a restrictive pleural rind.[57] Most often, the pleural thickening post-empyema resolves[61] and, even if it persists, it may not have a significant impact on pulmonary function.[66]

The mainstays of pleural infection treatment are antibiotics and drainage. In those patients who have already developed septation or loculation, intrapleural therapy is increasingly common, particularly in those who are not surgical candidates. This typically takes the form of combination fibrinolytic and deoxyribonuclease, with single-agent treatment proven to be either ineffective in comparison to placebo or potentially harmful[59,60] (see Chapter 109). In the majority of cases, however, it appears that any pleural thickening associated with pleural infection resolves over 3 to 6 months with basic antibiotic and drainage therapy.[61,66]

When sepsis due to pleural infection is not responding to medical therapy, thoracic surgery remains an option. There are also numerous reports of surgery being used specifically to manage chronic or established (stage III) disease in both adults and children.[62–64] The nature of the procedure chosen is often reliant upon the stage at presentation, with débridement of the pleural space typically sufficient in early disease but decortication, which may require a thoracotomy approach, preferred by some when a thick pleural peel has become established because it is believed to improve lung function and chest expansion.[65] In one retrospective study of patients after VATS, the degree of visceral pleural thickening was associated with the duration of postoperative chest tube drainage and hospitalization time.[67] In another retrospective study comparing VATS and thoracotomy, those undergoing VATS débridement had the shortest postoperative length of hospital stay (6 days vs. 15 days in the open decortication group). On long-term follow-up, 42% of patients included in the study reported residual symptoms, and 46% were found to have some degree of respiratory impairment.[57] Regardless of approach, surgical intervention for late-stage

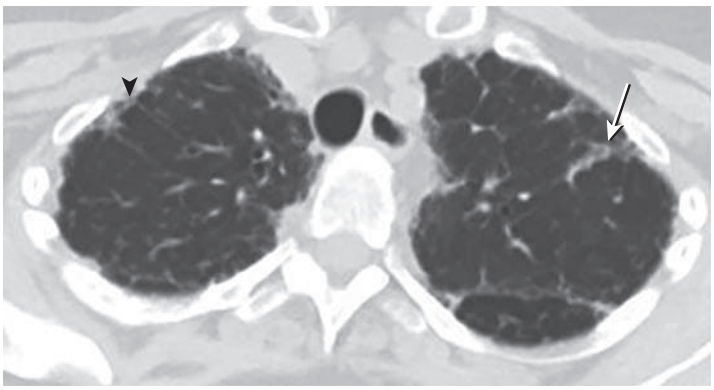

Fig. 112.4 Pleuroparenchymal fibroelastosis. Axial high-resolution chest computed tomography image shows patchy areas of subpleural linear and reticular (*arrowheads*) abnormalities, some of which are bandlike, extending from the pleural surface centrally (*arrow*). (Courtesy Michael B. Gotway, MD.)

pleural infection carries a significant risk of early mortality and morbidity, with these reported as up to 3% and 25%, respectively.[57,68]

Despite reports of favorable surgical results, there has been no comparison of surgical and nonsurgical outcomes. Given that pleural thickening after empyema generally resolves spontaneously[61,66] surgery should only be considered in those rare individuals who have symptomatic pleural thickening that persists or progresses at least 6 months after the empyema.

POST–CORONARY ARTERY BYPASS GRAFT SURGERY

Pleural effusions have been described in as many as 89% of patients post–*coronary artery bypass graft* (CABG).[69] Whereas many of these are seen early in the postoperative period as a direct result of surgical trauma, a small proportion (0.4%–9.7%)[70–75] develop into chronic exudates, often despite repeated thoracentesis or tube drainage, and are described as "late" or "persistent" if present for more than 2 to 6 months.[76] A further subgroup may go on to develop unexpandable lung, although it is not clear why this happens or what the risk factors are.[69] No clear association between the operative approach for the CABG and the development of a late effusion has been found.[72,74]

A small case series described histologic appearances of post-CABG effusions requiring thoracic surgical intervention and found that the development of established fibrosis was time dependent and was preceded by initially raised and then diminishing levels of B cell lymphocyte–predominant inflammation over periods of many months, although the trigger and role for the lymphocytes remained unclear. Collagen deposition over the longer term was not wholly attributable to fibroblast activity; the authors speculated that mesothelial cells may also have a role in the formation of pleural rind in this context.[69]

Data regarding the optimal approach for those with established post-CABG pleural fibrosis are limited, with most data drawn from retrospective, single-center, and noncomparative studies that do not differentiate between those with true unexpandable lung and chronic but simple inflammatory changes. Nonetheless, the use of VATS or thoracotomy to facilitate decortication for those found to have fibrous pleural peel is well described and, according to a systematic review of 10 studies (none of them randomized), appears to be safe and efficacious. The authors of this study suggest, although acknowledging the lack of quality data, that early surgical intervention in preference to thoracentesis or drainage may be the best approach to established post-CABG effusions.[77]

HEMOTHORAX (See Chapter 113)

Hemothorax can arise spontaneously or as a result of thoracic trauma, rib fracture, or surgery. Small and uncomplicated cases may resolve with conservative management, but drainage is frequently required for more substantial or infected collections (or hemopneumothoraces) to relieve symptoms and prevent complications. Long-term pleural sequelae from hemothorax may include the development of unexpandable lung and pulmonary restriction.[2] This is rare, however, being described in less than 1% of cases of hemothorax,[78] meaning data specific to the treatment and long-term outcomes of patients with visceral fibrosis originating from hemothorax are scarce.

Reports from a number of settings seem to support the use of early surgical intervention, usually VATS débridement, for the management of complex retained hemothoraces with a view to preventing unexpandable lung.[79,80] There are also limited data reporting the successful use of intrapleural urokinase in patients with residual hemothorax post–lung surgery.[81] In the posttraumatic population, however, a retrospective comparative series of streptokinase versus VATS débridement found that those treated by surgical débridement appeared to have more complete radiographic improvement and a shorter postoperative stay.[82]

Key Points

- Pleural inflammation, thickening, and fibrosis can be caused by a wide range of conditions.
- The diagnosis of pleural fibrosis is heavily reliant on identifying potential cause(s) from the history and on cross-sectional imaging.
- Most cases of pleural thickening will resolve spontaneously or in response to treatment of the underlying cause.
- Visceral pleural fibrosis can cause unexpandable lung.
- Unexpandable lung may be challenging to manage; however, if patients have symptomatic improvement from effusion drainage, they may be benefit from repeated pleural drainage or an indwelling pleural catheter. In the presence of unexpandable lung, drainage may offer symptomatic improvement by improving chest wall or diaphragmatic mechanics.
- Pleural thickening after empyema usually resolves within months after successful treatment of the empyema. Therefore, surgical decortication of post-empyema pleural thickening is rarely necessary and should be considered only if symptomatic pleural thickening persists for more than 6 months post-empyema.

Key Readings

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113 HEMOTHORAX

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INTRODUCTION

Hemothorax is defined as the accumulation of blood within the pleural space; it is recognized when the hematocrit of the pleural fluid is greater than 50% of the hematocrit of the patient's peripheral blood. Due to the significant color change of pleural fluid with very small amounts of blood, it is imperative to confirm the diagnosis by fluid analysis. The etiology of hemothorax is varied but can be broadly classified as traumatic, nontraumatic, and iatrogenic.

DIAGNOSIS

The detection of hemothorax is largely based on a high degree of suspicion, physical examination, and thoracic imaging. A hemothorax should be suspected in any patient with chest trauma, whether penetrating or blunt, a recent invasive thoracic procedure, or an undiagnosed pleural effusion in a hypotensive patient. Examination of the patient with hemothorax may reveal signs consistent with any pleural effusion, such as asymmetric chest expansion, diminished breath sounds, and dullness to percussion. The sensitivity of the exam findings increases with the size of the effusion.

The chest radiograph is often the initial imaging modality of choice to identify a pleural effusion when hemothorax is suspected. Lateral decubitus, anteroposterior, and upright lateral views may accurately display the presence of pleural fluid. Supine films may fail to display a large volume of pleural fluid, where it can appear only as a slight and uniform haziness. A carefully performed lateral decubitus chest radiograph is the most sensitive plain radiograph and can reportedly detect as little as 10 mL.[1] After trauma, a pneumothorax can accompany a hemothorax. In a series of patients enrolled with blunt trauma, 2.4% (207/8661) had hemothorax, and 1.3% had both hemothorax and pneumothorax.[2] In a separate series of patients with hemothorax after penetrating trauma, 83% (307/373) had pneumothorax.[3]

The sensitivity of the more commonly performed anteroposterior upright chest radiograph is significantly less than that of other views and typically requires blunting of the costophrenic angle with approximately 200 mL of fluid in the chest.[4] Other findings include blunting of the cardiophrenic angle and mediastinal shift away from the effusion. The hemidiaphragm is generally obscured with a pleural effusion of 500 to 650 mL.[4] Lateral films can identify a smaller amount of fluid because the costophrenic angles are deepest posteriorly.

Blackmore and colleagues devised a prediction model for visual estimation of pleural fluid volume in 1996[5]; this model was verified and updated by Mammarappallil et al. in 2015.[4] Frontal and lateral radiographic images were given a score of 1 to 3 based on the presence of a meniscus below the hemidiaphragm, at the hemidiaphragm, and above the hemidiaphragm, respectively (eFig. 113.1). These levels were validated by *computed tomography* (CT) imaging; on a frontal chest radiograph, a score of 1 indicated a mean volume of approximately 100 mL, a score of 2 indicated approximately 250 mL, and a score of 3 indicated approximately 650 mL or more.

Ultrasound is increasingly used due to its portability, diagnostic speed, and reliability in patients who are immobile or difficult to transport. The sensitivity of ultrasound in the diagnosis of pleural effusion is reported to be 67–100% with a specificity of 99% or higher.[6] The ability to predict the volume of pleural fluid may be achieved with a greater than 80% accuracy when correlated to aspirated volume using a simple calculation from measurements obtained during ultrasound imaging.[7] In a systemic review and meta-analysis of 19 studies, ultrasound was found to be accurate for the diagnosis of pleural effusion assumed to be hemothorax and for pneumothorax in trauma patients seen in the emergency department.[8] Ultrasound may have particular value in monitoring the size of a known hemothorax, aiding in deciding whether to continue to observe or to intervene.[9]

CT is a highly sensitive diagnostic modality and offers the benefit of identifying additional injuries or relevant diagnostic findings for the patient. CT is considered the gold standard for identifying hemothorax size as well as related injuries to the thorax or vessels. It is important to note that hemothorax may present in a delayed fashion in up to 20% of patients with thoracic injury, most commonly in patients with blunt trauma and in those with one or more rib fractures; thus repeat imaging of patients with thoracic injury is advised within 24 to 36 hours (Fig. 113.1).[10–13]

CT attenuation values have been used in an attempt to distinguish hemothorax from nonhemorrhagic pleural effusion. In images obtained *without* intravenous contrast, Hounsfield units 15.9 or greater (or the ratio of Hounsfield

units in pleural fluid to aortic blood of 0.56 or greater) predicted the presence of hemothorax with significant accuracy.[14] The presence of a "hematocrit effect" (i.e., the linear separation of cellular and liquid components of blood creating a plasma-blood interface) suggests the presence of unclotted blood products, indicating either coagulopathy or active hemorrhage within the pleural space (Fig. 113.2 and eFig. 113.2).[15]

Identification of a small to moderate pleural effusion concerning for hemothorax requires thoracentesis and pleural fluid analysis. A pleural fluid hematocrit greater than 50% of the peripheral blood is diagnostic for hemothorax. Alternatively, if a pleural hematocrit is not available, the pleural fluid hematocrit can be roughly estimated by dividing the pleural fluid red blood cell count by 100,000. (For example, a pleural fluid red blood cell count of 2 million/μL would be equivalent roughly to a hematocrit of 20%.[16])

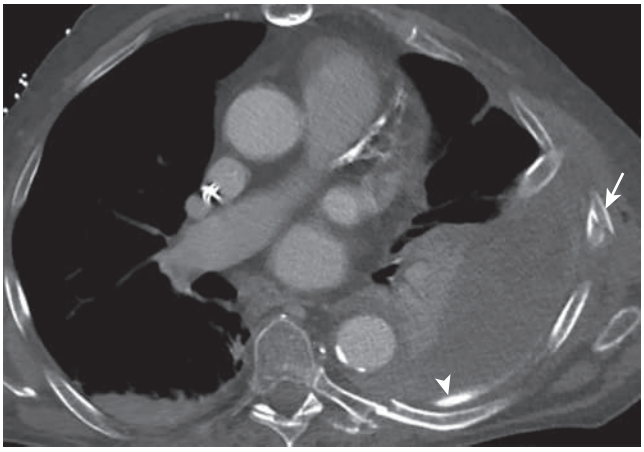

Figure 113.1 Delayed hemothorax following thoracic trauma. Ten days after a fall, an 86-year-old man on anticoagulation developed acute hypotension with a drop in his hemoglobin. Computed tomography scan showed a large left hemothorax, acute rib fractures (*arrow*), as well as active contrast extravasation (*arrowhead*) consistent with active hemorrhage. The patient was emergently referred for transcatheter intercostal artery embolization with selective intercostal artery angiography confirming intercostal artery injury with active hemorrhage. (Courtesy Michael B. Gotway, MD.)

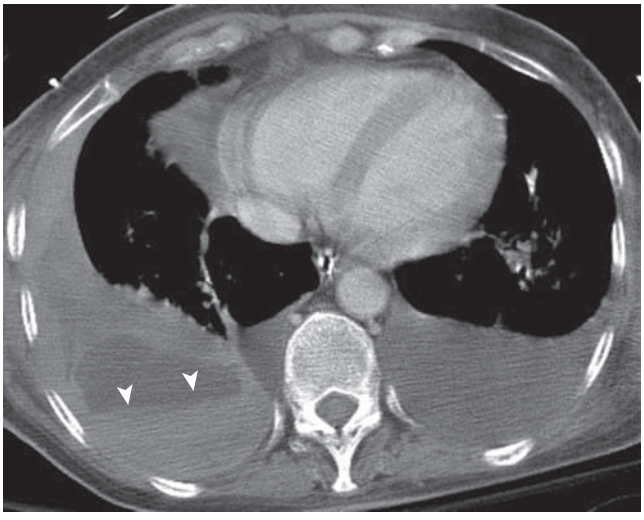

Figure 113.2 Hematocrit effect seen in hemothorax. Axial enhanced chest computed tomography in a patient with hemothorax showing the "hematocrit effect." Note the presence of a fluid-fluid level (*arrowheads*). (Courtesy Michael B. Gotway, MD.)

ETIOLOGY

The etiology of hemothorax may be largely categorized into three types: traumatic, nontraumatic, and iatrogenic.

TRAUMATIC HEMOTHORAX

Trauma is the most common cause of hemothorax, with nearly 300,000 cases in the United States each year.[17] Blunt force injury to the intercostal vessels, lung, diaphragm, great vessels, or mediastinal structures may be caused by motor vehicle collisions or falls. Penetrating injury, such as a gunshot or stab wound, often leads to clinically significant hemothorax. Rib fractures may be associated with hemothorax in patients with thoracic trauma. Lin et al. identified a positive correlation between the incidence of hemothorax and number of rib fractures; patients with more than five rib fractures were found to have a 48% or greater likelihood of concomitant hemothorax.[18] Hemothorax may lead to significant hemodynamic instability due to hypovolemia and thus should be considered in all patients with thoracic trauma, particularly if they are unstable.

NONTRAUMATIC HEMOTHORAX

Spontaneous pneumothorax is the most common cause of nontraumatic or spontaneous hemothorax. Hemothorax develops in 2–7% of spontaneous pneumothorax cases, most commonly from torn adhesions between the visceral and parietal pleura when the lung collapses, or from rupture of a vascularized bullae.[19]

A second etiology of nontraumatic hemothorax is vascular pathology leading to vascular rupture. Hemothorax, usually on the left side, can complicate descending aortic rupture resulting from aortic dissection of the aorta.[20] The aorta can also rarely rupture without trauma, aneurysm, or dissection. Rupture of pulmonary arteriovenous malformation, often associated with hereditary hemorrhagic telangiectasia, is another known cause of hemothorax due to vascular pathology.[21-23]

Neoplasms such as schwannoma, soft tissue tumors, and pleural metastases are rare causes of hemothorax. Resection of hemorrhagic schwannoma has resulted in a favorable outcome in documented cases.[24,25] Conversely, hemothorax can arise with neurofibromatosis type 1 and pleural metastasis and is associated with high mortality.[24-27]

Intrathoracic ectopic endometrial implants may lead to hemothorax in young women and has been documented in 14% of women with thoracic endometriosis syndrome.[28,29] Hemothorax in the setting of endometriosis, although rare, is often right sided and reflects a large pleural endometrial burden.[30,31]

IATROGENIC HEMOTHORAX

Iatrogenic causes of hemothorax have been documented following thoracic surgical procedures, thoracentesis, pleural biopsies, lung biopsies, vascular catheterization, anticoagulation, and cardiopulmonary resuscitation (Fig. 113.3; see also eFig. 21.5).

The incidence of hemothorax following thoracentesis is typically low, with a reported overall risk of 0.01%.[32] The addition of ultrasound guidance allows for identification of

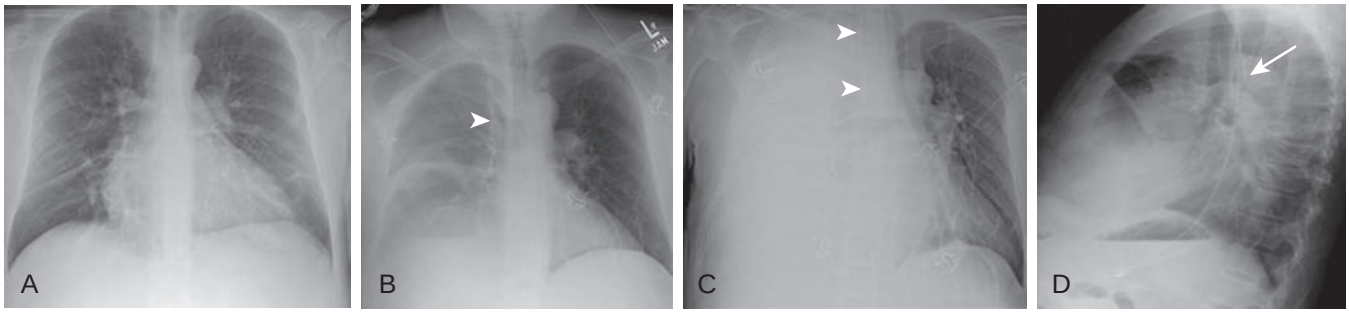

Figure 113.3 Hemothorax following central venous catheter insertion. (A) Frontal chest radiograph obtained several hours prior to right internal jugular central venous catheter insertion. (B) Frontal chest radiograph obtained immediately following right internal jugular central venous catheter insertion later the same day, 14 hours after A, shows new right pleural effusion. The catheter (*arrowhead*) projects over the expected location of the superior vena cava. Frontal (C) and lateral (D) chest radiography performed 6 hours after B shows complete opacification of the entire right hemithorax with contralateral mediastinal shift, consistent with a large pleural effusion. The lateral chest radiograph (D) shows that the catheter (*arrow*) has an abnormal posterior course, clearly posterior to the trachea, and incompatible with superior vena cava placement.

the superior border of the rib and avoidance of the inferior rib border where the intercostal vessels are located and at risk for disruption. A vascular ultrasound probe with color flow may allow for improved identification and avoidance of vascular thoracic structures.[33]

Although there are no randomized trials reviewing bleeding complications associated with thoracentesis and coagulopathy, current data suggest that there is no association between laboratory values of coagulopathy, administration of anticoagulative therapy, and risk of bleeding complication. Historically, correction of *international normalized ratio* (INR) greater than 2.0 and platelets for counts less than 50,000/μL were encouraged prior to thoracentesis due to presumed increased bleeding risk. Ault et al., in a prospective study over 12 years of thoracenteses, found no significant correlation between postprocedural bleeding and INR, partial thromboplastin time, and platelet count values.[34] Hibbert et al. completed a prospective cohort analysis of patients with INR greater than 1.6 and/or platelet values of less than 50,000 μL. The patients were placed into two groups, those whose coagulopathy was corrected prior to thoracentesis and those whose procedures were completed without correction. Hibbert et al. identified a total of two hemothoraces requiring evacuation out of 303 thoracenteses performed. Both hemothoraces were in the group of patients receiving correction of coagulopathy.[35] A third study reviewing thoracentesis or the placement of small-bore chest tubes in patients on clopidogrel reported 1 of 25 (4%) patients with hemothorax whereas no patients in the non-clopidogrel group had the same complication.[36] Clinical judgment and procedural experience is used to determine the need for corrective blood products or coagulopathy reversal agents. In elective procedures and extreme coagulopathy such as platelet counts 20,000/μL or less, INR 5 or greater, or use of multiple antithrombic medications, consideration of reversal agents is recommended. Conversely, in patients where the risk of holding or correcting anticoagulation is high, such as in the setting of recent deep vein thrombosis/pulmonary embolism, stroke, or cardiac intervention, one may consider proceeding without administration of reversal agents. In these higher-risk settings, the use of ultrasound guidance and an experienced operator are required.

The incidence of hemopneumothorax following central venous catheter placement is reported as 1.3–1.5% with no significant difference in the subclavian versus internal jugular approach.[37] Currently, ultrasound guidance is the standard of care for placement of a central venous catheter. Inadvertent puncture of the subclavian artery and development of hemothorax are significantly reduced using ultrasound guidance.[38]

MANAGEMENT

The first line of treatment for hemothorax is pleural drainage. Most commonly, this is performed with tube thoracostomy. The *Eastern Association for the Surgery of Trauma* (EAST) practice management guidelines recommend drainage of all hemothoraces irrespective of presumed volume.[17] However, risks associated with tube thoracostomy placement are documented at 22% and include empyema, pneumonia, residual hemothorax, and chest tube malposition with need for a second chest tube.[39,40] Due to these risks, there have been challenges to these guidelines to determine the minimal volume requiring pleural drainage. Updated EAST guidelines from 2020 have suggested that clinical judgement and the effect on pulmonary function may be considered in the decision to drain small hemothoraces.[40a]

The classic model of expectant management was described by Stein et al., who determined the "Stein line," or height at which a meniscus is visible on upright chest radiograph and likely represents an effusion volume of 200 to 300 mL. Stein determined that those patients with pleural fluid volumes below 300 mL could be managed without pleural drainage.[41] This view was further supported in 2018 by Demetri et al. in a retrospective review of 340 patients with traumatic hemothorax. A hemothorax greater than 300 mL, concurrent pneumothorax, and advanced patient age were predictors for failed observation, requiring placement of a tube thoracostomy or intervention after 24 or more hours of observation.[42] Several additional studies suggest that successful expectant management may be achieved in patients with 300 mL or less with close observation and repeat imaging.[9,43-45] To date, there is no universally accepted approach to patients with hemothorax. In patients who are expectantly managed, it is recommended that trends in hematocrit, changes in the physical exam, and review of subsequent axial or upright anteroposterior imaging over 24 hours direct the decision to proceed with more invasive procedures.

In patients for whom tube thoracostomy is indicated, historically, a large-bore (32-French or greater) tube was recommended. More recent studies suggest that smaller-bore percutaneous thoracostomy tubes result in equivalent pleural drainage and complication rates. In a prospective study by Bauman et al., patients requiring chest drainage were reviewed and evaluated for volume of drainage, complications, and failure rate. The study determined that the use of 14-French pigtail catheters were not inferior to larger bore (32- to 40-French) chest tubes.[46] Several additional studies in trauma patients with hemothorax have returned similar findings.[47-49] Kulvatunyou et al. compared patients with large-bore chest tubes and patients with 14-French catheters placed both emergently at day 0 and delayed up to 10 days with a mean placement date of 2.3 days. The patients with 14-French catheters were found to have equivalent drainage.[50] Traditional thoracic surgical dogma is that a chest tube should be placed at the base of the lung for optimal drainage of a hemothorax. In a 2015 study in the *Journal of Trauma*, the authors determined whether the positioning of a "directed" chest tube led to improved drainage of acute hemothorax. Tube location was confirmed by CT imaging. The findings in the 291 patients reviewed suggest that, in patients with acute hemothorax, inserting a tube in any location, preferably in the "triangle of safety," as shown in Figure 113.4, with the application of suction should provide equivalent drainage of hemothorax.[51]

In patients with significant comorbidity or those deemed poor surgical candidates, transcatheter arterial embolization of the intercostal artery may be considered in patients with intercostal artery hemorrhage identified on imaging or due to high suspicion. Following embolization, 90% of patients require surgical intervention ranging from chest tube placement to video-assisted thoracic surgery/thoracotomy for evacuation of hemorrhage.[52] Patients with severe anemia or chronic liver failure, or those requiring embolization of two or more arteries, are at increased risk of technical failure and rebleeding.[52] Although embolization is often safe and reliable, complications can be serious; spinal cord ischemia resulting from inadvertent displacement of embolic material into the artery supplying the spinal cord (the artery of Adamkiewicz or the anterior segmental medullary artery) and hemoptysis due to collateral vessel rupture have been documented.[53]



Figure 113.4 Triangle of safety. The triangle of safety is bordered by the pectoralis major muscle anteriorly, the latissimus dorsi muscle posteriorly, and the fourth to fifth intercostal space distally.

The need for surgical intervention in patients with hemothorax is based largely on experience acquired during the Vietnam War.[54] Expert opinion has led to the recommendation for surgical intervention in patients with acute blood loss of 1500 mL or more upon chest tube placement or 500 mL of retained hemothorax on chest radiograph following tube thoracostomy.[54] This scrutiny also led to the suggestion that patients with persistent drainage of 250 mL or more over 3 to 4 hours undergo surgical intervention. Karmy-Jones et al. corroborated this observation in a retrospective multicenter review. The risk for death was 3.2 times greater if chest tube drainage exceeded 1500 mL prior to thoracotomy than with chest tube drainage of 500 mL or less.[55]

Retained hemothorax, seen in up to 35% of patients managed with tube thoracostomy, may progress to empyema (see below).[56] Although surgery is the most common strategy for those with retained hemothorax, observation alone has been reported to be successful in selected patients such as those with fluid collections estimated as less than 300 mL on CT, the elderly, those without rib fractures, and those whose chest tubes were initially placed for management of pneumothorax.[43,56] Due to the increasing use of lytic therapy for the management of empyema, this therapy has been proposed as an alternative to surgery for patients with retained hemothorax.[57] A meta-analysis published in 2019 suggests that up to 87% of patients with retained hemothorax avoided surgical intervention with the use of lytic therapy. Additionally, less than 7% of patients who were given tissue plasminogen activator experienced a bleeding complication.[58] Despite these positive findings, current literature recommends the use of lytic therapy only in patients who cannot tolerate surgery due to their inability to tolerate single-lung ventilation or to the presence of comorbidities precluding surgery as a safe option.[17] This view has been supported by the 2020 EAST practice guidelines.[40a]

As a general rule, in the majority of patients with recent hemothorax, the hemothorax can be evacuated effectively with minimally invasive surgical approaches. Patients who present with hemodynamic instability or with more mature or chronic hemothoraces are more likely to require a thoracotomy.[17]

COMPLICATIONS OF HEMOTHORAX

Documented complications in patients with hemothorax include empyema and pneumonia. Fibrothorax, although often considered a complication, has not been confirmed to be a complication of hemothorax.

Empyema, as previously mentioned, can be a complication of retained hemothorax. A prospective observational multicenter study of 328 patients with retained hemothorax found an incidence of empyema of 26%.[56] Empyema was associated with higher volumes of hemothorax retention (>300 mL) and was more common in patients who required bilateral chest tube placement following traumatic injury. In this cohort of posttraumatic patients, independent risk factors for the development of empyema included longer duration of tube thoracostomy, longer intensive care unit length of stay, rib fractures, presence of pulmonary contusion, and need for exploratory laparotomy.[56] However, in another study of trauma patients with hemothorax, the incidence of empyema was lower (4.9%), with a similar incidence in those with retained hemothorax and

those with completely drained hemothorax. The authors suggest that incidence of empyema in their study was not related to retained hemothorax, but to other factors such as shock, pleural contamination, pneumonia, and duration of chest tube drainage.[59] In another study of 102 patients with hemothorax, 9% developed empyema; however, the incidence of empyema was higher in those with retained hemothorax (33%) than in those without (2%).[60] These studies suggest that all patients with hemothorax require close observation to ensure that the development of empyema is quickly identified and managed.

Pneumonia has been documented in 20% of patients with retained hemothorax in trauma patients. Development of pneumonia following hemothorax is associated with age greater than 55 years, blunt trauma, and the presence of pneumothorax requiring tube thoracostomy placement. Additionally, the development of pneumonia was found to be associated with patients who were not dosed with empiric antibiotics at the time of chest tube insertion.[61] Conversely, a 2004 prospective multicenter study comparing cefazolin dosed for 24 hours and cefazolin dosed for the duration of tube placement versus placebo failed to identify a significant decrease in the incidence of empyema or pneumonia.[61a] Currently, there is no official recommendation for or against the use of antibiotics to reduce the incidence of empyema or pneumonia in chest tube placement.[62] Further studies are currently reviewing the use of antibiotics in the setting of chest tube placement.

Fibrothorax or "trapped" lung has historically been a concern for delayed management of retained hemothorax; however, the association between retained uncomplicated hemothorax and development of fibrothorax has not been established. Findings suggest that retained hemothorax is not an independent risk factor for development of clinically relevant fibrothorax. Rather, fibrothorax is more likely due to the presence of poor or delayed empyema management.[60,63] Aggressive identification and management of empyema with appropriate drainage versus decortication if required is recommended (see Chapter 112).

SURGICAL INTERVENTION

Either video-assisted thoracoscopic surgery or open thoracotomy is an appropriate surgical approach to hemothorax. Video-assisted thoracoscopic surgery should only be considered in hemodynamically stable patients. In hemodynamically unstable patients, thoracotomy is preferred. The operation is performed in lateral decubitus position in both video-assisted thoracoscopic surgery and thoracotomy. If a thoracotomy is required, typically a posterolateral approach is used, and the chest is approached through the fourth or fifth interspace. The surgeon may choose to alter the interspace or even the type of incision, depending upon where the preponderance of clot burden appears to be on the preoperative chest CT or the presence of additional injuries. Video-assisted thoracoscopic surgery is usually performed with three ports—an anterior, utility, and camera port—but has been used with one port.[64] Regardless of the approach, the operation is accomplished using suction and generous irrigation with sterile water or saline to remove free blood and loose clot. Mechanical removal is typically required for more mature clot, and a decortication with sharp dissection may be required for empyema or fibrothorax. The pleural space is inspected for a bleeding source that, if identified, may be controlled with a variety of techniques, including electrocautery, suture ligation, mechanical stapling, lung resection, and/or application of hemostatic agents. The goals of the operation are to remove all the blood from the chest, control any identified bleeding source, and achieve maximal lung reexpansion; for optimal postoperative care, the goals of surgery are to provide adequate chest tube drainage to maintain lung expansion and to identify/evacuate any subsequent bleeding. The typical number of chest tubes placed ranges from one to three depending upon the operative findings, the procedure performed, and the surgeon's judgment/experience.

Key Points

- Hemothorax is an accumulation of blood within the pleural space.
- Hematocrit of the pleural fluid is greater than 50% of the hematocrit of the patient's peripheral blood in hemothorax.
- Hemothorax can be traumatic (blunt or penetrating), nontraumatic, or iatrogenic.
- Computed tomography scan is the gold standard in the detection of hemothorax. Ultrasonography and chest radiography may also diagnose and monitor hemothorax.
- The first line of treatment for hemothorax is pleural drainage.
- Small-bore (14-French) tube thoracostomy is not inferior to large-bore (32- to 40-French) drainage catheters.
- Expectant management may be achieved in patients with a small hemothorax, of 300 mL or less, with close observation and repeat imaging.
- Arterial embolization can be considered in patients with active intercostal artery bleeding who are considered poor candidates for surgery.
- Surgical intervention may be required when there is (1) acute blood loss of 1500 mL, (2) retained hemothorax of 500 mL or greater on chest radiograph following tube thoracostomy, or (3) persistent drainage of 250 mL or more over 3 to 4 hours.

Key Readings

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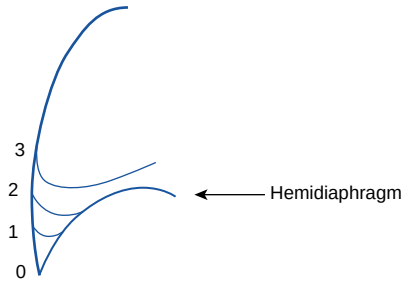
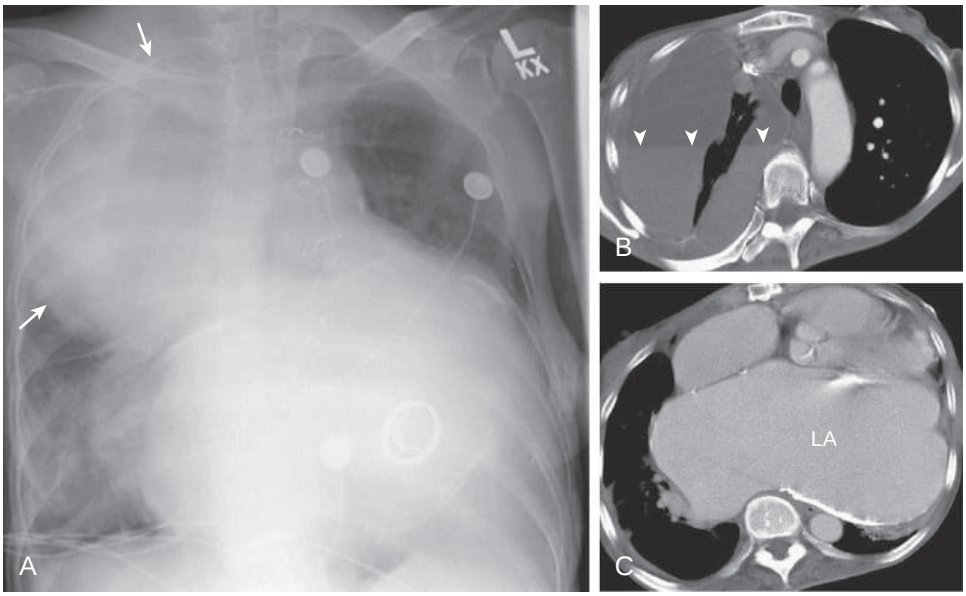
Complete reference list available at ExpertConsult.com.

eFIGURE IMAGE GALLERY



	Normal	Blunting below Hemidiaphragm	Blunting at Hemidiaphragm	Obscuring of Hemidiaphragm
Score	0	1	2	3
Mean Volume		100 mL	250 mL	650 mL

eFigure 113.1 Prediction model for visual estimation of pleural fluid on the frontal upright chest radiograph. A score of 0 corresponds to a normal image. A score of 1 indicates a blunted costophrenic angle and the presence of a meniscus below the hemidiaphragm. A score of 2 indicates a blunted costophrenic angle and meniscus identified at the level of the hemidiaphragm. A score of 3 indicates that the hemidiaphragm is completely obscured. The scores 1, 2, and 3 are given a volume of up to 100 mL, 250 mL, and 650 mL, respectively.



eFigure 113.2 Iatrogenic hemothorax following thoracentesis showing the "hematocrit effect." (A) Frontal chest radiography in a patient with rheumatic heart disease treated with anticoagulation shows a large, homogeneous opacity in the superior right thorax (*arrows*) that developed following thoracentesis for right pleural effusion. Note prosthetic mitral valve. (B–C) Axial enhanced thoracic computed tomography shows a hematocrit level (i.e., blood-fluid level [*arrowheads*]; the dependent high attenuation is due to the heavier blood elements settling dependently). Note enlarged left atrium (LA) with wall calcification. (Courtesy Michael B. Gotway, MD.)

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114 PLEURAL MALIGNANCY

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INTRODUCTION

Malignant pleural effusion (MPE) is the second most common cause of exudative pleural effusion, after infection.[1] In most cases, MPE represents spread of metastatic cancer, and the treatment goal is palliation, not cure. Survival is generally poor, with a median of 4 months, although significant individual variations exist.[2] In the United States, there are approximately 126,000 hospital admissions for MPE annually, with a mean length of stay of 6.3 days.[3] Thirty-day readmission rates are almost 40%,[4] which is significantly higher than for acute myocardial infarction and congestive heart failure. Hospitalization costs for MPE amounted to $1.37 billion in the United States alone in 2014.[3]

Malignant mesothelioma is the most common primary pleural cancer and affects approximately 15,000 persons per year worldwide. Its global incidence is growing, especially in developing regions.[1] Mesothelioma is universally fatal with a median survival of 12 months.[5] Less common tumors such as solitary fibrous tumor of the pleura, primary effusion lymphoma, and pyothorax-associated lymphoma are also discussed.

METASTATIC PLEURAL DISEASE

TYPES OF TUMOR

Most primary cancers can spread to the pleura, the most common being lung, breast, gastrointestinal, and genitourinary cancers, as well as lymphomas (Table 114.1). Pleural effusion is the most common presentation of pleural malignancies. Most cases are exudative.[6] Transudative malignant effusions are now a recognized phenomenon as a result of concurrent causes of transudative fluid formation (especially cardiac failure in the elderly). In occasional cases of MPE, the primary tumor is never identified, although this is becoming less common with advances in diagnostic pathology.[7]

The patterns of metastatic spread are different between primary and secondary malignant pleural cancers. Malignant mesotheliomas generally originate on the parietal pleura and spread to the visceral pleura, whereas metastases from lung or other cancers usually involve the visceral pleura before spreading to the parietal pleura.[6,8] Most MPEs from bronchogenic carcinoma arise from the ipsilateral side of the primary tumor.[8]

CLINICAL FEATURES

Breathlessness, and sometimes cough, are the most common symptoms of an MPE (see also Chapter 108). These symptoms are nonspecific and often multifactorial. Removal of the fluid may be the only means to determine if, and how much of, the breathlessness and cough are attributable to the MPE. In a series of 150 patients undergoing pleural fluid drainage (median, 1.6 L), 27% did not find relief of breathlessness after fluid evacuation.[9] Clinicians should search for other pleural (tumor encasement of the lung), pulmonary (e.g., pulmonary emboli, pneumonia, tumor obstruction of airways), or systemic (e.g., anemia) causes for the symptoms.[10]

Chest pain can often be described as a dull ache and may indicate involvement of the chest wall and/or parietal pleura. Systemic symptoms associated with cancer (e.g., weight loss and malaise) should not be overlooked.

MALIGNANT PLEURAL EFFUSIONS

Malignant pleural disease can exist without pleural effusion (Video 114.1). In autopsy studies of patients with malignancy, pleural malignancy was found *without* an effusion in 40%[8] to 45%[6] of cases. Malignant cells can reach the

pleural space without effusion and lavage of the pleural space before resection of lung cancer in those without effusion can have positive cytologic results in as many as 5.3% in a study of 1200 patients undergoing surgery.[11] Positive cytologic results on pleural lavage indicate poorer prognosis and may be incorporated into future modifications of lung cancer staging systems. The development of an MPE may depend on the ability of the tumor cells themselves to secrete bioactive mediators or their ability to initiate inflammatory, angiogenic, or fibrinolytic processes in the normal tissues.[12]

Lung cancer is the most common cause of MPEs[13] (see Table 114.1) and, together with breast cancer, accounts for more than half of all MPEs. Of the histologic types of bronchogenic cancers, adenocarcinomas are most frequently associated with MPEs, but effusions may be seen with all types.[14] In patients who had surgical resection of lung cancer, presence of visceral pleural invasion beyond the elastic layer is now a recognized adverse prognostic factor.[15,16] Standardized grading for visceral pleural invasion (from PL0 to PL3) has been incorporated into the International Association for the Study of Lung Cancer tumor-node-metastasis staging scheme.[17,18]

Breast cancer is the second most common cause of MPEs.[13,19] Effusion often develops within a few years of the initial diagnosis but can present much later, even after 20 years. The effusion is usually ipsilateral to the site of the original tumor (50%) but can also be contralateral (40%) or bilateral (10%).[20]

Lymphoma is the third most common cause in most series[13] but is possibly the most common cause in young adults.[19] Pleural effusions are common in both non-Hodgkin (eFigs. 114.1 and 114.2A) and Hodgkin lymphoma.[21] In patients with non-Hodgkin lymphoma, approximately 16% will develop malignant effusions, and most will have the effusion at the time of initial diagnosis in association with evidence of disease elsewhere.[22] Chylothorax is common with non-Hodgkin lymphoma; in one analysis of 88 patients with chylothorax, 12.5% were due to lymphoma, all non-Hodgkin lymphoma.[23] In Hodgkin lymphoma, effusions may be caused by hilar or mediastinal lymph node involvement as well as pleural involvement.[21] In one study of 110 patients presenting with Hodgkin lymphoma, effusions were present in 26 (24%); these were equally unilateral or bilateral. The presence of effusion was more common in those with higher-stage cancer, extranodal involvement, and bulky mediastinal disease.[24]

Malignancies produce pleural fluid accumulation often both by increasing the entry of fluid into the pleural cavity and decreasing its exit (Table 114.2) (see Chapter 14). Pleural fluid formation can be increased by several mechanisms: (1) increased permeability of the pleural vessels by direct invasion of tumor cells, inflammatory and vasoactive cytokines (e.g., *vascular endothelial growth factor* [VEGF]), or injury (e.g., radiation induced); (2) increased permeability of *pulmonary* vessels by infection, pulmonary embolism, or pulmonary infarct, with movement of liquid from lung to pleural space; (3) increased hydrostatic forces due

Table 114.1 Primary Tumors Responsible for Malignant Pleural Effusion

Primary Tumor Site	Total (%)
Lung	37.5
Breast	16.8
Lymphoma	11.5
Gastrointestinal	6.9
Genitourinary	9.4
Other*	7.3
Unknown	10.7

A compilation of data from five different reports with a total of 2040 patients.
*Includes ovarian carcinoma, sarcomas, uterine and cervical carcinomas, and other carcinomas.
From Antunes G, Neville E, Duffy J, Ali N. BTS guidelines for the management of malignant pleural effusions. *Thorax*. 2003;58:ii29–ii38.

Table 114.2 Physiologic Mechanisms (Neoplastic and Paraneoplastic*) by Which Malignancy May Cause Pleural Effusions

Means of Increasing Liquid	Mechanism	Site/Source	Examples
Increased entry	Increased vascular permeability	Pleural vessels	Invasion by tumor Cytokines (e.g., VEGF) Injury (e.g., radiation)
		Pulmonary vessels	Infection (e.g., postobstructive pneumonitis) Cytokines/injury
	Increased vascular hydrostatic gradient	Pleural vessels	Decreased pleural pressure (e.g., atelectasis) Increased venous pressure (e.g., SVC syndrome) Decreased plasma osmotic pressure (e.g., hypoproteinemia)
	Nonvascular entry	Thoracic duct	Chylothorax
Decreased exit	Increased resistance to lymphatic flow	Pleural lymphatics Lymph nodes	Infiltration of parietal pleura Infiltration of mediastinal lymph nodes
	Increased gradient opposing lymphatic flow		Decreased pleural pressure (e.g., atelectasis) Increased venous pressure (e.g., SVC syndrome)

Both an increase in entry and a decrease in exit are likely required to produce a stable pleural effusion.
*Refers to mechanisms taking place outside the pleural space.
SVC, superior vena cava; VEGF, vascular endothelial growth factor.
Modified from Broaddus VC. Physiology: fluid and solute exchange in normal physiological states. In Light R, Lee Y, eds. *Textbook of Pleural Diseases*. 2nd ed. London: Hodder Arnold; 2008:43–48.

to venous obstruction or hypoproteinemia; and (4) entry of other sources of fluid (e.g., chyle) from a disrupted thoracic duct. Exit of fluid from the pleural space can decrease by mechanisms that reduce lymphatic drainage: (1) infiltration of parietal pleural lymphatics or mediastinal lymph nodes, (2) lowered pleural pressure due to atelectasis from bronchial obstruction, or (3) elevated central venous pressure, as from superior vena cava syndrome. Often multiple factors combine to form a pleural effusion in association with malignancy.[25]

Pleural malignancy may come to light when the advent of another nonmalignant condition, such as heart failure or pneumonia, precipitates the appearance of a symptomatic pleural effusion. In these cases, malignancy may contribute to, but not be the sole cause of, the effusion.[25] The combination of different processes may explain how malignancy can be associated with transudative effusions, for example, if malignancy interferes with lymphatic clearance and a separate transudative process increases entry of fluid into the pleural space.[26] In the same way, malignancy may lead to bilateral effusions; in a prospective study of bilateral effusions, malignancy was found to be a common contributing cause along with other processes.[27]

Understanding the mechanisms of effusion formation could lead to new therapeutic approaches, especially to counteract the vascular hyperpermeability. In several animal studies, bioactive molecules involved in angiogenesis and permeability, such as VEGF and monocyte chemotactic protein-1,[28–30] have been identified that may play key roles in accumulation of effusions in malignancy.[12] However, there remains no convincing evidence of clinical benefits of therapy targeted to VEGF (e.g., bevacizumab or cediranib) to control MPE to date.[31,32]

PLEURAL FLUID ANALYSIS

The majority of MPEs are exudates. The higher protein and lactate dehydrogenase values are caused by increased vascular permeability and inflammatory changes. Interestingly, at least 5% of MPEs are transudates.[33] The primary etiology of fluid formation, in most of these cases, is a transudative cause (e.g., congestive heart failure, superior vena cava syndrome, volume overload) in which malignancy has a secondary, contributing role.[33]

The fluid usually is lymphocyte predominant. Although eosinophils may be present, they are not helpful in diagnosis. In a study of 460 effusions, 20% of the eosinophilic effusions were found to be malignant, as were 20% of noneosinophilic effusions.[34] Eosinophilia is most likely a result of prior entry of air or blood into the pleural space. Malignant disease is the most common cause of bloody effusions.[35] However, about half of malignant effusions are not bloody in appearance (pleural fluid red blood cell counts < 10,000 cells/μL).[35]

MPEs are often metabolically active with low pleural fluid pH and glucose concentrations.[36] Some studies have reported a shorter survival with MPEs of a low pleural pH or glucose,[37,38] presumably a reflection of larger pleural tumor burden as well as a lower likelihood of pleurodesis success; however, these associations were not shown in other studies.[37–41] Neither pleural fluid pH nor the glucose level should therefore be relied on for selecting patients for pleurodesis.

Pleural fluid amylase concentration is elevated in 10% of MPEs.[42] However, the origin of the amylase is from a salivary rather than a pancreatic source.[43] In one series of consecutive effusions, a very high amylase concentration in MPE (>600 IU/L) was a poor prognostic factor.[42] Hyaluronan is known to be present in higher concentrations in mesothelioma pleural effusions[44,45] but is not considered to have sufficient diagnostic accuracy as a standalone test. Its supplementary role to fluid cytology[46] and other biomarkers such as mesothelin[44,45] is a subject of research.

RADIOGRAPHIC EVALUATION

The size of MPEs varies from small to complete "whiteout" of the hemithorax. In one retrospective series of 766 patients, malignancy was found as the cause of 55% of large (opacifying two-thirds of the hemithorax) and massive (opacifying the entire hemothorax; see eFigs. 114.1A and 114.2A) effusions[47]; the other causes were pleural empyema and tuberculous effusions. Interestingly, cytologic examination was no more likely to be positive in these large/massive effusions than in smaller ones (63% yield from large effusions, 53% from small).[47]

If the effusion is large, the mediastinum is expected to shift contralaterally in an uncomplicated situation (see eFig. 114.2A). If the mediastinum stays midline, one can suspect either significant ipsilateral lung collapse offsetting pressure from the presence of the effusion, or a fixed mediastinum that cannot shift in response to a pressure differential. If the mediastinum is shifted toward the side of the effusion, the pressure is most likely lower on the side of the effusion than on the other side (Video 114.2); in that case, a central bronchial obstruction or significant lung infiltration by tumor (see eFig. 114.2B) should be suspected, and the lung is unlikely to expand fully with fluid drainage.

Pleural ultrasound is useful to detect the presence of pleural fluid, guide thoracentesis, and allow assessment of the parietal and diaphragmatic pleura (see Video 23.16) and can help direct biopsy. Findings of pleural thickening greater than 1 cm, pleural nodularity, and diaphragmatic thickening greater than 7 mm are highly suggestive of malignant disease.[48]

Computed tomography (CT) is part of routine workup of MPE. Features that have been found to be helpful in distinguishing malignant from benign pleural disease are circumferential pleural thickening, nodular pleural thickening, parietal pleural thickening greater than 1 cm, and mediastinal pleural involvement[49] (Fig. 114.1 and eFig. 114.3). The specificities of these findings were 100%, 94%, 94%, and 88%, respectively, and the sensitivities were 41%, 51%, 36%, and 56%, respectively. In a CT study of 211 consecutive patients with effusions, the most specific findings for malignancy were pleural nodules and nodular thickening.[50] Pleural thickening alone was not as specific and could be seen in many benign conditions. When present, pleural nodules were highly specific, but they were evident only in 17% of MPEs. Half of the patients with malignant effusions had no pleural abnormalities detected on CT, possibly due to the relative lack of difference in attenuation between the pleural thickening, nodules, and adjacent pleural fluid. Interestingly, the presence of air in the pleural cavity—because of nonexpandable lung or genuine

air leak—can outline fine pleural abnormalities (especially nodules) on CT.[51]

CT may also reveal the site of the primary cancer (e.g., pulmonary or breast lesions) and/or other metastatic sites. These features would favor a malignant cause for the effusion (Video 114.3).[50] Even minimal pleural effusions may represent malignant involvement; in patients with lung cancer, a minimal (<10 mm thick) effusion on CT has been shown to be a poor prognostic factor; these minimal effusions were thought to indicate early malignant involvement of the pleural space or of the mediastinal lymph nodes.[52] When performing a CT for the workup of a pleural effusion, a pleural phase enhancement contrast scan may help to uncover subtle pleural abnormalities.[53]

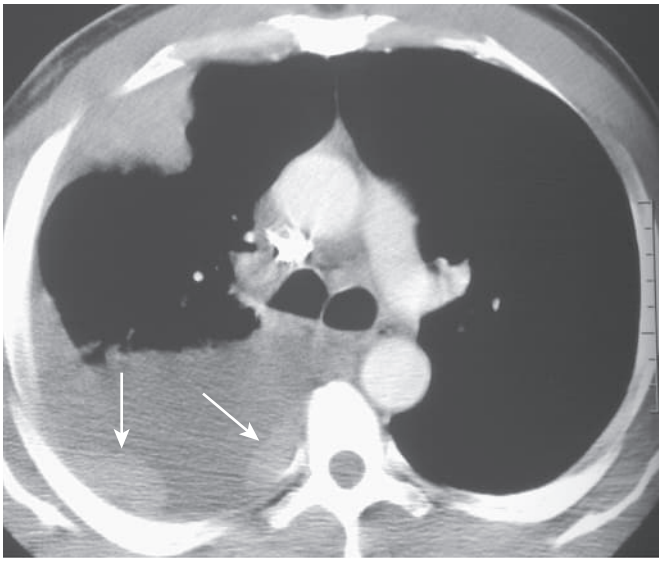

Figure 114.1 Metastatic adenocarcinoma. Axial contrast-enhanced chest computed tomography shows right pleural effusion associated with enhancing nodular masses (*arrows*) emanating from the parietal pleura, later shown to be metastatic adenocarcinoma. (Courtesy Michael B. Gotway, MD.)

Magnetic resonance imaging is not advocated for routine evaluation of MPEs. However, its excellent soft tissue contrast may be useful for a detailed evaluation of tumor invasion, especially of the chest wall and pleura as well as in the apices of the hemithoraces.[54]

Positron emission tomography (PET) with *^{18}F-fluorodeoxyglucose* (^{18}FDG), used appropriately, can add valuable information to the workup of potential MPEs in several ways. In cases of significant pleural thickening, absence of ^{18}FDG uptake favors a benign etiology and may help to avoid pleural biopsies. ^{18}FDG-avidity can be due to malignancy but can also represent active pleural inflammation of a benign nature. For example, ^{18}FDG-avidity can persist (probably indefinitely) after talc pleurodesis[55] (Fig. 114.2). In patients with diffuse pleural thickening (or abnormalities) suitable for image-guided pleural biopsy, a preceding PET scan may help in the selection of biopsy sites. PET may also reveal extrapleural sites (e.g., regional lymphadenopathy) more accessible than the pleura for a biopsy to provide a diagnosis. PET with novel tracers other than ^{18}FDG may offer information other than inflammation (e.g., cell proliferation with ^{18}F-thymidine) and is an area of active research.[56,57]

DIAGNOSIS

Cytologic examination is reportedly diagnostic in approximately 60% of patients,[58] but the diagnostic yield varies with the type of tumor, extent of tumor involvement of the pleura, and the expertise of the cytologist. Cytologic results are more likely to be positive in adenocarcinoma than in squamous cell lung cancer, for example, perhaps because adenocarcinoma is more often located peripherally and has a greater tendency to invade the pleural space.[35] Interestingly, cytologic yield does not vary greatly with the size of the effusion, as mentioned.[47] Generally speaking, repeating thoracentesis does not increase the yield of cytology for malignancy unless the first sample was inadequately processed or was very small in volume.

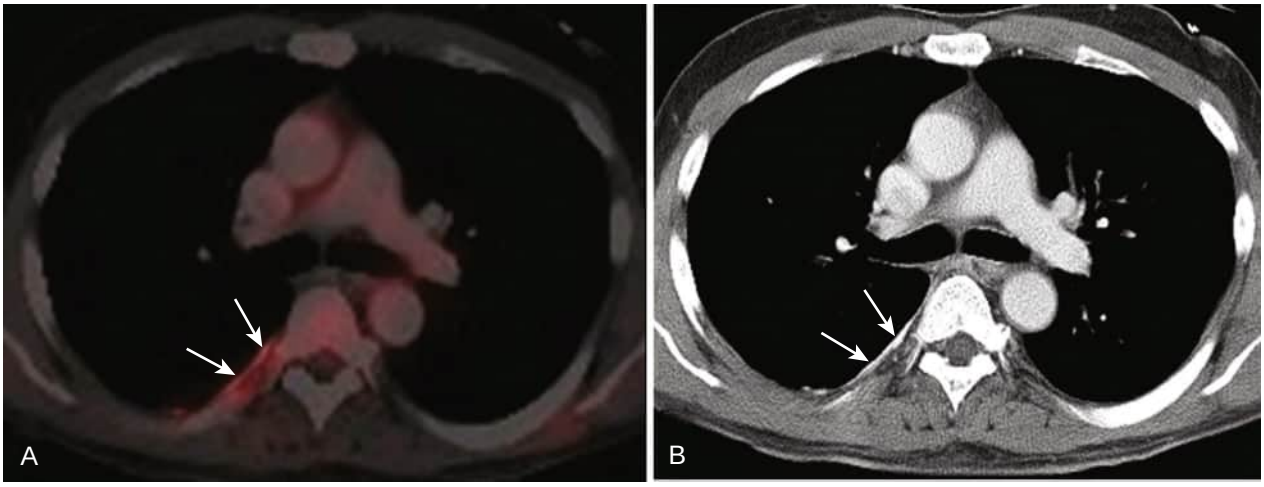

Figure 114.2 Increased *positron emission tomography* (PET) activity at site of talc pleurodesis. (A) A PET/*computed tomography* (CT) scan obtained in a patient with a prior talc pleurodesis for recurrent pneumothorax shows increased pleural uptake (*arrows*). (B) The axial chest CT image confirms that the area of increased PET uptake corresponds to an area of high attenuation (*arrows*) characteristic of talc deposits. (Courtesy Michael B. Gotway, MD.)

Immunohistochemical staining of cell blocks can be quite useful for diagnosis. Certain markers, such as thyroid transcription factor 1, have a high specificity for a primary lung tumor, whereas GATA3 may be useful for breast cancer.[59]

Molecular studies can be carried out using cytologic specimens, including sequencing for mutations of epidermal growth factor receptor[60]; with highly sensitive sequencing (e.g., next-generation sequencing),[61] such markers may be detected even when cytologic examination reveals a low percentage or even no malignant cells.[62] Pleural fluid supernatant and cells can both be tested to increase the yield.[63,64]

Biopsy may be necessary when cytologic examination is negative or indeterminate. In the past, closed (or "blind") pleural biopsy was performed as a next step in cases where cytologic results were negative. However, the patchy involvement of the parietal pleura by malignancy appears to make closed pleural biopsy a hit-or-miss technique and, not surprisingly, image-directed biopsies have been shown to be more accurate. In one randomized study comparing CT-guided biopsy with closed pleural biopsy using an Abrams needle, CT-guided biopsy was significantly more sensitive (87% vs. 47%) with a better negative predictive value (80% vs. 44%).[65] Thoracoscopy is a well-tolerated procedure that permits excellent visualization of the entire pleural surface (see Chapter 29). Directed biopsies of suspicious areas lead to a correct identification of metastatic pleural disease in nearly 100% of cases.[66] This technique has additional advantages, including the ability to provide large biopsy specimens for immunohistochemical and genetic analysis for molecular markers (e.g., epidermal growth factor receptor), if needed, to provide information about the gross appearance of tumor, to provide information for staging, to lyse adhesions, and to drain the pleural space for talc pleurodesis. It is worth remembering that an initial approach to the diagnosis of metastatic disease may be by fine-needle aspirates of abnormal lymph nodes in the supraclavicular or cervical regions or in the mediastinum, which can obviate the need for more invasive procedures.

Biomarkers in pleural fluid have the potential to assist the cytologic diagnosis. Unfortunately, biomarkers have had indeterminate sensitivity and specificity, leading to overlap between malignant and nonmalignant conditions. One approach has been to combine tumor markers to improve diagnostic yield, although malignancy can also be predicted by using clinical characteristics (time of symptoms >1 month, absence of fever, serosanguineous fluid, and chest CT findings of malignancy).[67] For mesothelioma, detecting the molecule mesothelin, a product of mesothelial cells, may have diagnostic utility in certain circumstances (see "Mesothelioma" section later).[68–70] However, pleural fluid mesothelin levels are elevated in some patients with malignant effusions other than mesothelioma, whereas the mesothelin level is not elevated in benign effusions (provided the patient has no renal impairment). A high mesothelin level is therefore strongly suggestive of the presence of pleural malignancy and requires further workup.[70]

Two new diagnostic markers have significantly improved the diagnosis of mesothelioma from cytologic and histologic specimens and have been included in diagnostic guidelines.[71] Loss of *BRCA-1 associated protein* (BAP)-1 by immunostaining and homozygous loss of the cyclin-dependent kinase inhibitor 2A gene by fluorescent in situ hybridization in cells of mesothelial lineage are now recognized as diagnostic of mesothelioma.[72] (See "Mesothelioma" section later for details.)

The future of diagnosis may include genetic analysis, either for features of malignancy (DNA methylation, mutations, microsatellite, telomerase, aneuploidy) or in the genetic expression fingerprint (microarray) characteristic of tumors.[73,74] High-throughput sequencing technology enables rapid sequencing of either the whole genome or the small percentage of the genome coding for expressed genes (i.e., the exome). Cell-free DNA, captured either in pleural fluid supernatant or blood, has shown significant promise in helping diagnose certain cancers and in capturing driver mutations in lung cancer patients.[75]

THERAPY AND PALLIATION

The therapeutic and palliative approach to MPEs is guided by many factors (Table 114.3). First, the clinician should determine whether the effusion is causing either dyspnea or cough, symptoms that can be due to the volume of the effusion and its effect on lung and cardiac function. Often that may be evident from the parallel worsening of symptoms and progressive increase of effusion on imaging. In patients with multiple causes of breathlessness (such as severe cardiac dysfunction, extensive parenchymal lung disease, or significant pulmonary emboli), it is useful to establish the extent of symptom relief of fluid removal (e.g., by therapeutic thoracentesis) before embarking on any invasive "definitive" procedures for long-term fluid control. In the PLEASE (Pleural Effusion And Symptom Evaluation) study,[9] 27% of the 145 patients who underwent fluid drainage (median, 1.6 L) did not have significant improvement

Table 114.3 Options for Control of Symptomatic Malignant Effusions

Option	Patient Eligibility and Considerations
Chemotherapy, targeted therapy	Responsive tumor
Therapeutic thoracentesis	Slowly recurring effusion Used for patients with very short life expectancy
Pleurodesis	
Via chest tube	Lung able to reinflate
Via thoracoscopy	Can free up lung tacked down by adhesions, obtain biopsies Thoracoscopy must be available
Indwelling pleural catheter	Can be used as first line and coupled with talc pleurodesis if suitable Good outpatient situation Good for trapped lung
Pleuroperitoneal shunt	Patient able to operate pump Good for trapped lung Good for chylothorax (provided there is no concurrent ascites)
Pleurectomy	
Via thoracoscopy	When other less-invasive options have failed
Via thoracotomy	Good patient status and life expectancy

in breathlessness. In these patients, effort should focus on treating other reversible causes of breathlessness and, if that fails, management should be directed towards symptom control measures (e.g., oxygen supplementation, opiates, use of fans) rather than further pleural fluid drainage procedures.

In patients with a symptomatic MPE, several approaches of varying invasiveness are available to help control the effusion. Because most patients with MPE have limited life expectancy, the overall goal is to provide the greatest symptom relief using options that are least invasive and require the fewest days in hospital. Management issues have also been addressed in clinical guidelines from the American Thoracic Society/Society of Thoracic Surgeons/Society of Thoracic Radiology and a statement from the European Respiratory Society/European Association of Cardiothoracic Surgeons.[76,77]

If the underlying malignancy may respond significantly to systemic therapy (e.g., lymphoma, lung cancer with targetable mutations), it would be reasonable to use simple pleural fluid drainage to provide temporary relief to allow time for initiation of systemic treatment. However, these therapies often eventually fail over time, and the fluid recurs. At that point, more definitive control of the MPE is recommended. Radiation therapy is not useful for MPE management because tumor involvement of the underlying pleura is generally extensive. Irradiation of the entire parietal, pleural, and diaphragmatic pleura is not practical.

Repeated thoracentesis may be used for the occasional patient whose fluid reaccumulates slowly or who has a short life expectancy. Most MPEs recur rapidly and, to avoid frequent drainages, "definitive" treatment is preferred. This refers to approaches with an intent to provide long-term control of fluid-related symptoms without requiring repeated invasive drainage procedures. In broad terms, definitive treatment for MPEs at present generally refers to pleurodesis or placement of an *indwelling pleural catheter* (IPC), or both.

Pleurodesis involves iatrogenic obliteration of the pleural cavity to prevent fluid accumulation. It requires induction of pleural fibrosis that results in symphysis of the parietal and visceral pleural surfaces, usually either by mechanical means (e.g., pleural abrasion or pleurectomy) or via intrapleural administration of a sclerosant. Pleurodesis is only feasible if the underlying lung expands sufficiently and comes in contact with the parietal pleura. No data exist on how much of the lung needs to be expanded to provide a meaningful pleurodesis. Nonexpandable (trapped) lung most commonly results from malignant visceral pleural involvement prohibiting full expansion (see also Chapter 112). Occasionally central airway obstruction can cause nonexpandable lung. In the former case, surgical decortication (resection of the visceral pleural peel) can theoretically be attempted to "free" the trapped lung. Limited quality data exist, however, to support decortication for malignancy, which is known to carry risks of injuring the lung and creating (often prolonged) air leak.[78] In a randomized trial for mesothelioma, 6% of patients who received pleurectomy/decortication experienced prolonged (>10 days) air leak postoperatively.[78]

Pleural manometry has been recommended as a means of predicting nonexpandable (trapped) lung to guide choice of management for patients with MPE. However, recent studies have failed to confirm a clinical role of pleural manometry. First, manometry did not accurately predict nonexpandable lung when compared with postdrainage chest radiographs in 70 MPE patients.[79] In another study, manometry also failed to predict subsequent nonexpandable lung in patients undergoing IPC insertion.[80] Furthermore, in a two-center randomized study, monitoring pleural pressures with manometry also had no benefits in preventing cough and breathlessness during thoracentesis.[81] At present, there is no justification to perform manometry routinely during pleural procedures.[82]

Talc is the most effective pleurodesing agent in animal studies and in clinical head-on comparison studies with other agents, including tetracycline and bleomycin.[83,84] Nonetheless, there is significant variability in the practice of pleurodesis, as shown in a survey of pulmonologists in five countries.[85] Other agents include tetracycline derivatives (e.g., doxycycline and minocycline), bleomycin, iodopovidone, silver nitrate, OK-432, and *Staphylococcus* endotoxin C.[84] Agents such as nitrogen mustard and *Corynebacterium parvum* are seldom used.

Talc can be delivered to the pleural space by instillation as a slurry through a chest tube or by insufflation as a powder (poudrage) during thoracoscopy. Talc slurry has been compared with talc poudrage (via surgical thoracoscopy) in three randomized trials[86–88] and in a fourth trial against talc poudrage during medical thoracoscopy (pleuroscopy).[89] No advantage was found with thoracoscopic talc poudrage in any of these studies, which is perhaps not surprising. One of the proposed advantages of poudrage is the ability to distribute talc powder more evenly over the pleural surfaces. However, talc most likely works by inducing an acute pleural inflammatory response rather than by serving as a "glue." Hence, direct spread of talc over the entire pleural membrane appears not to be essential.

Talc slurry can be given via small or large chest tubes, with or without rotation of the patient. A multicenter randomized trial[90] showed a slightly lower pleurodesis failure rate at 3 months using larger (24 French vs. 16 French) chest tubes (24% vs. 30%, respectively), but the former was associated with more pain at most of the time points captured. Small studies have found no benefit from rotation of patients as determined by instillation of radiolabeled talc and by outcome.[91]

Success rates of talc pleurodesis vary significantly in the reported literature. However, recent large multicenter trials have consistently shown a success rate of around 70%.[86,89,90,92] It should be noted that failure of pleurodesis appears to increase over time, although long survivors were few in the studies.[86]

Talc pleurodesis can be painful and, in a small percentage of patients, can lead to pulmonary edema and acute respiratory failure.[1] Evidence suggests that the smaller talc particles (<10 μm) can exit the pleural space and distribute systemically; in a randomized study, pleurodesis with graded talc (with most particles <10 μm removed) was associated with fewer complications than a mixed talc that included small particles.[93]

IPC has been accepted by the latest MPE guidelines as an effective alternative to talc pleurodesis and can also lead to a symphysis and removal of catheters in many patients. The

catheter is inserted under local anesthesia, and the patient or caregiver drains the effusion at home. Several randomized trials have found that IPCs provide symptom relief as effectively as talc slurry pleurodesis[92,94] and improve patients' quality of life.[95]

An added benefit of this outpatient approach is a reduction in hospitalization time, a particularly attractive feature for patients with advanced cancer. The Australasian Malignant Pleural Effusion-1 randomized trial found that MPE patients treated with IPC spent an average of 3.6 fewer days in the hospital in their remaining life compared with those who received talc slurry pleurodesis.[92] The Therapeutic Intervention for Malignant Effusion-2 randomized controlled trial compared IPC against talc slurry pleurodesis in 106 patients with MPEs.[94] Patients spent significantly fewer days in the initial hospital stay because insertion of an IPC generally is a same-day procedure. A similar benefit was found in a randomized trial of IPC versus doxycycline pleurodesis.[96]

Both the Australasian Malignant Pleural Effusion-1 and Therapeutic Intervention for Malignant Effusion-2 studies found that use of IPC significantly reduced the need for further pleural drainage procedures. More patients in the talc group underwent further pleural procedures (22% vs. 6%).[94] However, in both studies, the IPC group experienced more adverse events over time. IPC-related pleural (and superficial) infections and symptomatic loculations are complications seen in 4–12%[97] and approximately 10%[98] of patients, respectively. IPC-related pleural infection is a concern for clinicians, but studies have consistently demonstrated very low morbidity (≈0.3%)[97] from the infections, which can be treated with systemic antibiotics and intrapleural fibrinolytic/deoxyribonuclease therapy. Interestingly, pleurodesis commonly develops postinfection and often allows catheter removal. Symptomatic loculations respond well to intrapleural fibrinolytic treatment.[98] Other less common IPC-related complications have been described elsewhere.[99]

An exciting development is the combined use of IPC and talc slurry pleurodesis. In a randomized trial of talc slurry (vs. placebo) instillation via IPC in 154 patients with MPE, Bhatnagar et al.[100] showed that outpatient administration of talc via IPC was feasible (with only one case of significant catheter blockage) and significantly promoted the likelihood of successful pleurodesis and catheter removal. Combining the benefits of IPC and talc offers the best of both worlds to patients. Similar approaches combining IPC and talc therapy are being evaluated in the OPTIMUM and Australasian Malignant Pleural Effusion-3 trials compared to conventional chest tube talc pleurodesis or video-assisted thoracic surgery pleurodesis, respectively.

At present, IPC is the guideline-recommended option for patients with nonexpandable lung (estimated to be one-third of all MPE patients) and for those who failed talc or video-assisted thoracic surgery pleurodesis. Using IPC as the first approach negates the need for determining before the procedure if the patient's lung will expand; if the underlying lung expands, talc slurry via IPC would be appropriate; if not, IPC for long-term ambulatory drainage is appropriate.

It is important to recognize that all the above options have limitations and, in the setting of patient palliation, patient preference must be taken into consideration in guiding treatment choice.[94]

Pleuroperitoneal shunting is another alternative for palliation when the lung cannot reexpand or pleurodesis is unsuccessful, but it is no longer commonly used, especially with the easy availability of IPCs.

Pleurectomy via thoracotomy can achieve a pleural symphysis. However, with the advent of effective alternatives such as pleurodesis and IPCs, pleurectomy cannot be recommended.

PROGNOSIS

The overall prognosis is poor for most patients with MPEs. When used to predict survival for any individual patient, pleural fluid pH or glucose level is not sufficiently robust.[2] Performance status remains one of the strongest predictors. In a prospective trial of 85 consecutive patients with MPEs referred for thoracoscopic pleurodesis, those with a Karnofsky score above 70 had a median survival of 13.2 months, whereas those with a score below 30 had a median survival of 1.1 months.[40]

The first validated prognostic score in MPE was derived in 2014 from a study of data from 789 MPE patients from the United Kingdom, the Netherlands, and Australia in which 14 variables were analyzed (Table 114.4). The LENT

Table 114.4 The LENT Score to Predict Survival in Patients with MPE

	Variable	Score
L	**LDH level in pleural fluid (IU/L)**	
	<1500	0
	>1500	1
E	**ECOG performance score**	
	0	0
	1	1
	2	2
	3–4	3
N	**Neutrophil/lymphocyte ratio**	
	<9	0
	>9	1
T	**Tumor type**	
	Lowest-risk tumor types:	0
	Mesothelioma	
	Hematologic malignancy	
	Moderate risk tumor types:	1
	Breast cancer	
	Gynecological cancer	
	Renal cell carcinoma	
	Highest risk tumor types:	2
	Lung cancer	
	Other tumor types	
Risk Categories		**Total Score**
Low		0–1
Moderate		2–4
High		5–7

Using this score, survival can be estimated. In this study, those with an MPE and a low risk score had a median survival of 319 days, whereas those with a high-risk score had a median survival of 44 days.[101]

ECOG, Eastern Cooperative Oncology Group; LDH, lactate dehydrogenase; MPE, malignant pleural effusion.

From Clive AO, Kahan BC, Hooper CE, et al. Predicting survival in malignant pleural effusion: development and validation of the LENT prognostic score. *Thorax*. 2014;69(12):1098–1104.

(lactate dehydrogenase, *Eastern Cooperative Oncology Group* [ECOG] performance status, blood neutrophil/lymphocyte ratio, and tumor type) scoring system classifies patients as low-, moderate- and high-risk groups and predicts survival with significantly better accuracy than ECOG performance status alone.[101] Based on data from 203 patients in one cohort, the low-risk group lived a median duration of 319 days (interquartile range, 228–549 days; $n = 43$), the moderate-risk lived 130 days (47–467 days; $n = 129$), and the high-risk group lived 44 days (22–77 days; $n = 31$), respectively. In the high-risk group, only 65% (20 of 31) of patients survived 1 month from diagnosis, and just 3% (1 of 31) survived 6 months.

In the tumor-node-metastasis classification of lung cancer, pleural malignancy (malignant effusions or pleural nodular malignancy) is considered along with contralateral lung nodules as intrathoracic metastatic disease (M1a). Intrathoracic metastatic disease (M1a) is classified separately from extrathoracic metastatic disease (M1b) because of a somewhat better prognosis.[102]

MESOTHELIOMA

INCIDENCE AND ETIOLOGY

Malignant mesothelioma is a universally fatal malignancy originating from serosal surfaces lined by mesothelial cells. Mesothelioma typically affects the pleural cavity (in more than 90% cases), although primary disease of the peritoneum, pericardium, and tunica vaginalis can also happen.

The majority of mesotheliomas develop as a result of prior asbestos exposure. Asbestos is a heat-resistant, fibrous silicate mineral that was heavily used for insulation in industry as well as domestic constructions, especially in Europe and Australia, where use of asbestos has since been banned. However, asbestos is still actively mined in countries such as Russia, China, Brazil, and Kazakhstan. Global consumption of asbestos continues to increase because of its low cost and excellent fire retardant/insulation properties.

Asbestos can be divided into the amphibole and serpentine groups. Amphibole asbestos—the most common ones being crocidolite (blue asbestos) and amosite (brown asbestos)—are long, thin, sharp fibers that are difficult to degrade once inhaled. In experimental animals, they are up to 100 times more likely to induce mesothelioma than the more frequently used serpentine group, which mainly consists of chrysotile (white asbestos).

Patients with mesothelioma can be classified by their source of asbestos exposure.[103] The first wave consisted of workers directly involved in handling raw asbestos material during its mining, milling, and transportation. The second wave describes those exposed in their work with asbestos-containing materials. Because asbestos has been included in many manufactured goods, exposed workers include building and construction workers and tradespersons such as plumbers, boilermakers, electrical installers, shipbuilders, and dockyard workers. The third wave, or those exposed in their environment, affects a much wider part of society because people are environmentally exposed in their workplaces and homes, especially when asbestos products used in buildings have aged and loose fibers are released into the atmosphere. Householders renovating their asbestos-containing houses are typical subjects in this group.

Erionite, a nonasbestos crystalline fibrous form of the mineral zeolite, shares physical similarities with asbestos fibers. Erionite is a recognized cause of mesothelioma in regions where it is present in the environment, such as Cappadocia in central Turkey. Carbon nanotubes[104,105] are even finer than crocidolite fibers and share their resistance to degradation. In animal experiments, they can cause significant mesothelial changes mimicking the early stages of mesothelioma development.

Inhalation of these fibers induces a cascade of biological events that can contribute to the pathogenesis of mesothelioma: direct mesothelial damage, generation of toxic oxygen radicals, disorganization of cell-signaling pathways, and dormancy of tumor suppressor genes including *BAP1*, cyclin-dependent kinase inhibitor 2A, (or p16), and neurofibromin 2.[106,107]

Thorium dioxide, a radiocontrast agent used between the 1930s and 1950s, had been associated with mesothelioma. Exposure to simian virus 40 (e.g., via contaminated polio vaccines in the 1950s) and contact with human-made vitreous fibers (rock/slag wool and fiberglass) have been postulated, but largely dismissed,[108–113] as potential causes of mesothelioma. Cigarette smoking has no role in the development of mesothelioma.

Although asbestos exposure causes most mesotheliomas, only a small fraction of asbestos-exposed subjects develops the disease. Genetic predisposition may play a role. Patients with germline *BAP1* mutation are predisposed to a range of uncommon cancers (*BAP1* tumor predisposition syndrome),[114] including mesothelioma, uveal and cutaneous melanoma, and renal cancers. Germline mutations in *BAP1* are present in an estimated 1–2% of Europeans[115]; hence, work is ongoing to search for other complex genetic-environmental interactions. Clinicians should consider genetic testing for *BAP1* in mesothelioma patients presenting with a family history of the disease or multiple malignancies (particularly of the skin, eyes, and kidneys) and in those who are young and/or without significant asbestos exposure. It should be noted that not all carriers of germline *BAP1* mutations will develop tumors.[116]

DEMOGRAPHICS

The incidence of mesothelioma is highest in the United Kingdom, Australia, and the Netherlands, reflecting previous asbestos mining and/or its heavy use. The incidence of mesothelioma in the United States has remained stable[117] at around 2500 cases per year.[118] Similarly, the incidence in Australia has been stable but has not decreased[106] as initially predicted. The World Health Organization has raised significant concerns about rapidly rising incidences of mesothelioma in developing countries where use of asbestos is poorly regulated.

The risk of mesothelioma increases with time after first exposure to asbestos. Owing to reduction of occupational asbestos use since the 1960s, mathematical models predict a reduction in the incidence of mesothelioma in the people younger than 74 years, but a rise in those older

than 75 years[119] (who were already exposed), in part due to longer life expectancy in the general population. This was observed recently by Kerger et al.[117] and Soeberg et al.[120] using data from the United States and Australia, respectively. These older patients are likely to have more comorbidities, which will influence individuals' diagnostic and treatment options.

CLINICAL FEATURES

Mesothelioma often presents 20 to 40 years following the first asbestos exposure; hence, the average age of diagnosis is in the mid-70s.[121] Men and women are equally vulnerable; however, more than 80% of patients are male, reflecting demographics of workers in at-risk occupations.

Most patients present with a pleural effusion, and some with pleural thickening or mass. Breathlessness (especially on exertion), cough, chest pain, and constitutional symptoms (fever, fatigue, weight loss, and night sweats)[122] are common. Contraction of the ipsilateral hemithorax or palpable tumor extension into the chest wall can be seen in patients presenting at an advanced stage. Laboratory findings are nonspecific. Anemia, thrombocytosis, and raised inflammatory markers have been associated with poorer prognosis.

Soluble mesothelin-related protein, or mesothelin, is a Food and Drug Administration–approved biomarker for mesothelioma.[68] This glycoprotein is expressed on the surface of mesothelial cells and overexpressed in mesothelioma (and some other cancers, especially ovarian). Mesothelin can be measured in pleural fluid and/or serum.[70] Because it is renally excreted, mesothelin can be elevated with renal impairment, leading to falsely positive results. An elevated mesothelin level strongly suggests malignant pleural disease, especially mesothelioma. A negative mesothelin test does not exclude mesothelioma. Mesothelin has a potential role in monitoring for disease progression and/or treatment response.[123]

Other biomarkers, including serum osteopontin and fibulin-3, do not improve diagnostic accuracy sufficiently to warrant their clinical use.[124]

SUBTYPES

Histologic subtypes of mesothelioma have clear prognostic significance. Mesothelioma can be of epithelioid (approximately 60% of cases) or sarcomatoid (20%), including desmoplastic, subtypes. The remaining 20% are mixed (biphasic)[125] if they consist of at least 10% of both subtypes. Studies of surgically excised lung showed that the more areas of pleura sampled, the more likely a mixed subtype will be found.[126,127] Studies have consistently shown that epithelioid mesothelioma has the best prognosis, sarcomatoid the worst, with biphasic mesotheliomas in between.[128,129]

DIAGNOSIS

Securing a diagnosis of mesothelioma relies on a multifaceted approach. Recent guidelines emphasized the importance of multidisciplinary discussion involving pulmonologists, radiologists, pathologists, palliative care physicians, clinical nurse specialists, and administration staff.[130–132]

RADIOGRAPHIC EVALUATION

Pleural effusion, with the associated imaging features, is the most common presentation. CT features of mesothelioma are akin to those of malignant pleural disease, as described previously. No distinguishing features reliably differentiate mesothelioma from other pleural malignancies or between epithelioid and sarcomatoid subtypes of mesothelioma.[133] Asbestos-related pathologies such as pleural plaques may be seen (eFig. 114.4; Video 114.4), but their absence does not exclude mesothelioma.

As mesothelioma progresses, tumor can encase the lung and contract the hemithorax, causing ipsilateral mediastinal shift (Fig. 114.3). Pleural nodularity and chest wall invasion often develop (eFigs. 114.5 and 114.6; Video 114.5). Lymphatic involvement may be seen on CT (eFig. 114.7). Contralateral pleural, pericardial, or transdiaphragmatic spread can be seen late.

Needle tract metastases are common with mesothelioma. Studies have shown that the larger the pleural puncture sites (e.g., thoracotomy or thoracoscopy), the higher the risks of tract metastases.[134] Hence, clinicians should always try to minimize the number of procedures in patients with mesothelioma and, when appropriate, choose the least invasive interventions.

The revised, modified Response Evaluation Criteria in Solid Tumors[135] is commonly used in research to monitor treatment response using CT scans but is not useful in routine clinical management.

Magnetic resonance imaging does not offer routine diagnostic advantage but, in selected cases, can help define tumor invasion into the chest wall, mediastinum, and diaphragm[136–139] (Fig. 114.4, eFig. 114.8).

The role of ^{18}FDG-PET in mesothelioma has not been fully defined.[140] Mesothelioma is generally FDG avid provided that the pleural abnormality is of sufficient thickness (Fig. 114.5; eFigs. 114.5 and 114.9; see also Fig. 25.6). PET avidity, however, cannot differentiate malignant

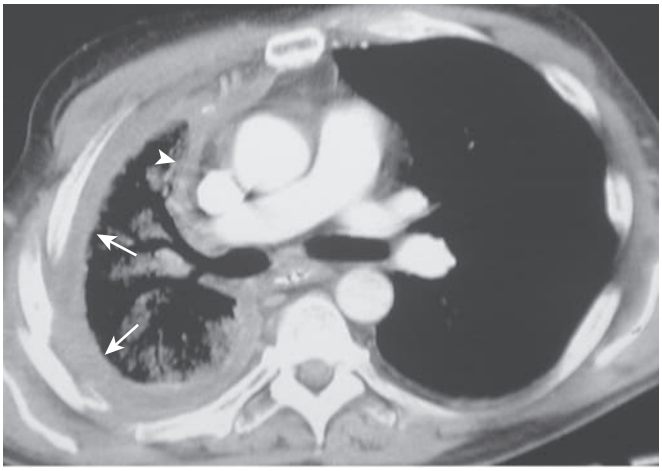

Figure 114.3 Mesothelioma. Axial chest computed tomography scan shows diffuse right pleural thickening (*arrows*) associated with marked volume loss in the right thorax. Note the presence of mediastinal pleural involvement (*arrowhead*). (Courtesy Michael B. Gotway, MD.)

from inflammatory pleuritis or separate mesothelioma from metastatic pleural diseases. PET can guide percutaneous pleural biopsy, especially in patients with concurrent benign pleural thickening. Total glycolytic volume can help in monitoring disease response and may have prognostic value.[141]

PATHOLOGIC FEATURES

Because most mesothelioma patients present with a pleural effusion or pleural thickening/mass, the same diagnostic approaches as described for MPE apply. The pathologic diagnosis of mesothelioma critically depends on the experience of the pathologist. Referral to specialist pathologists for expert or further opinion, especially in cases of high suspicion, can potentially save unnecessary invasive procedures.

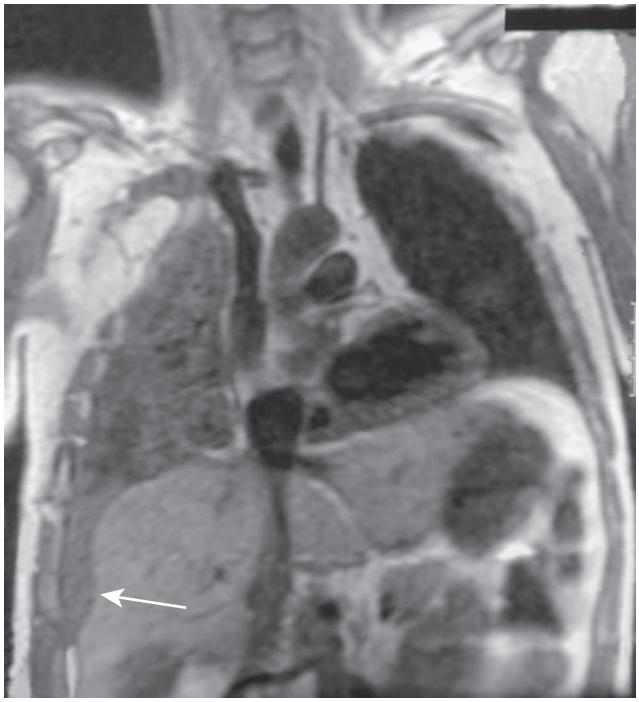

Figure 114.4 Mesothelioma. Magnetic resonance imaging of the same patient as in Fig. 114.3 with malignant mesothelioma showing invasion across the diaphragm by tumor (*arrow*). (Courtesy Michael B. Gotway, MD.)

The diagnosis is challenging because mesothelioma cells may be morphologically similar to metastatic carcinomas. In most cases, they can be distinguished by immunohistochemical panels; confirmation of mesothelial lineage of malignant cells will define mesothelioma.

Another challenging aspect is separating normal or reactive mesothelial cells from malignant mesothelioma cells. This explains the low diagnostic yield of pleural fluid cytology in many centers and the conventional need for tissue biopsies to establish invasion of the abnormal cells (of mesothelial lineage) into deeper structures as evidence of malignancy. In specialist centers, however, cytologic diagnosis of mesothelioma can be achieved with high accuracy. A large single-center study with such expertise found that definitive cytologic diagnosis was made in 377 out of 517 cases of mesothelioma, resulting in an "absolute" sensitivity of 73%, compared with subsequent histologic or postmortem confirmation, and with no false-positive diagnoses of malignancy. Latest guidelines from the International Academy of Cytology, the Papanicolaou Society of Cytopathology,[71,125,142] and the International Mesothelioma Interest Group all advocate diagnosis of epithelioid-containing mesothelioma on cytopathologic grounds. Recent advances in molecular markers have made this more feasible for nonspecialist pathologists. Demonstration of loss of *BAP1* expression by immunohistochemical panels (present in more than 60% of mesothelioma cases) and/or confirmation by fluorescent in situ hybridization of homozygous deletion of the cyclin-dependent kinase inhibitor 2A (*p16INK4a*) gene in abnormal cells of mesothelial lineage confirms mesothelioma. Detection of these mutations in combination may identify up to 85% of mesothelioma cases.[72,143] It is anticipated

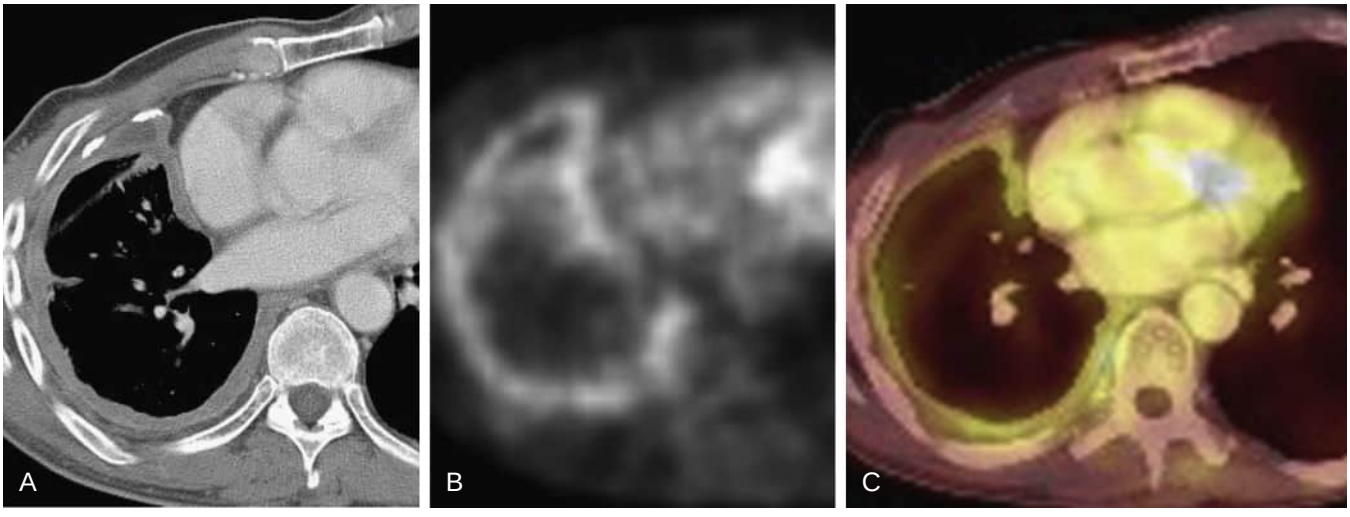

Figure 114.5 Malignant pleural mesothelioma: *positron emission tomography* (PET)/*computed tomography* (CT) appearance. (A) Axial enhanced chest CT shows extensive, nearly circumferential right pleural thickening associated with volume loss affecting the right thorax. (B) PET and (C) fused PET/CT images show extensive metabolic activity within the tumor, correlating with the location of the pleural thickening seen at CT. (Courtesy Michael B. Gotway, MD.)

that the need for tissue biopsy to confirm mesothelioma will decrease over time.

STAGING

Most of the staging systems are based on suitability for surgery. There are no clear benefits of performing additional procedures purely for the purpose of staging because it generally does not influence management. The inaugural staging system was proposed in the 1970s.[144] The tumor-node-metastasis–based system was originally introduced by the International Mesothelioma Interest Group. International Association for the Study of Lung Cancer and International Mesothelioma Interest Group committees introduced the currently adopted eighth iteration of the tumor-node-metastasis–based system.[145,146]

PROGNOSIS

Reported median survival rates of mesothelioma range between 9 and 18 months from the time of diagnosis, and fewer than 5% of patients survive more than 5 years.[117] Rare cases of long-term survivors have been reported.

Individual survival varies significantly and is difficult to predict. Performance status and histologic subtype[147,148] (sarcomatoid being worse) are the most consistent prognosticators. In the Surveillance, Epidemiology, and End Results database, median survival of patients who underwent surgery (i.e., fitter patients) with sarcomatoid mesothelioma was 4 months compared to 19 and 12 months with epithelioid or biphasic disease, respectively ($P = 0.01$).[149]

Other poor prognostic predictors include advanced age, male gender, serologic markers of systemic inflammation, including anemia, thrombocytosis, leukocytosis, elevated C-reactive protein or lactate dehydrogenase levels, and an increased neutrophil/lymphocyte ratio.[150–152]

Imaging modalities may also carry prognostic implication with increased disease burden, advanced stage, and increased total glycolytic volume on ^{18}FDG-PET/CT imaging, portending a poor outcome.[150,153]

Various scoring systems have been suggested, yet no reliable, universally applicable tool is useful for routine clinical practice.[147,154–156] Brims et al. derived, from classification and regression tree modeling, a scoring system that incorporates most of the known factors (e.g., histologic subtype, performance status, hemoglobin and albumin levels, and weight loss) to stratify patients into categories of different median survival[128] (Fig. 114.6). In this scoring system, the strongest predictive variable was weight loss. Group 1 had the best outcome (median survival, 34.0 months), and group 4 had the worst (median survival, 7.4 months).

APPROACH TO THERAPY

There is no cure for mesothelioma; symptom palliation, maintenance of quality of life, minimization of invasive procedures, and hospitalization are important. Significant controversies exist, and various guidelines advocate differing management approaches. It is advisable that clinicians adhere to best available evidence in determining therapy. Unproven treatment should be tested in clinical trial settings.

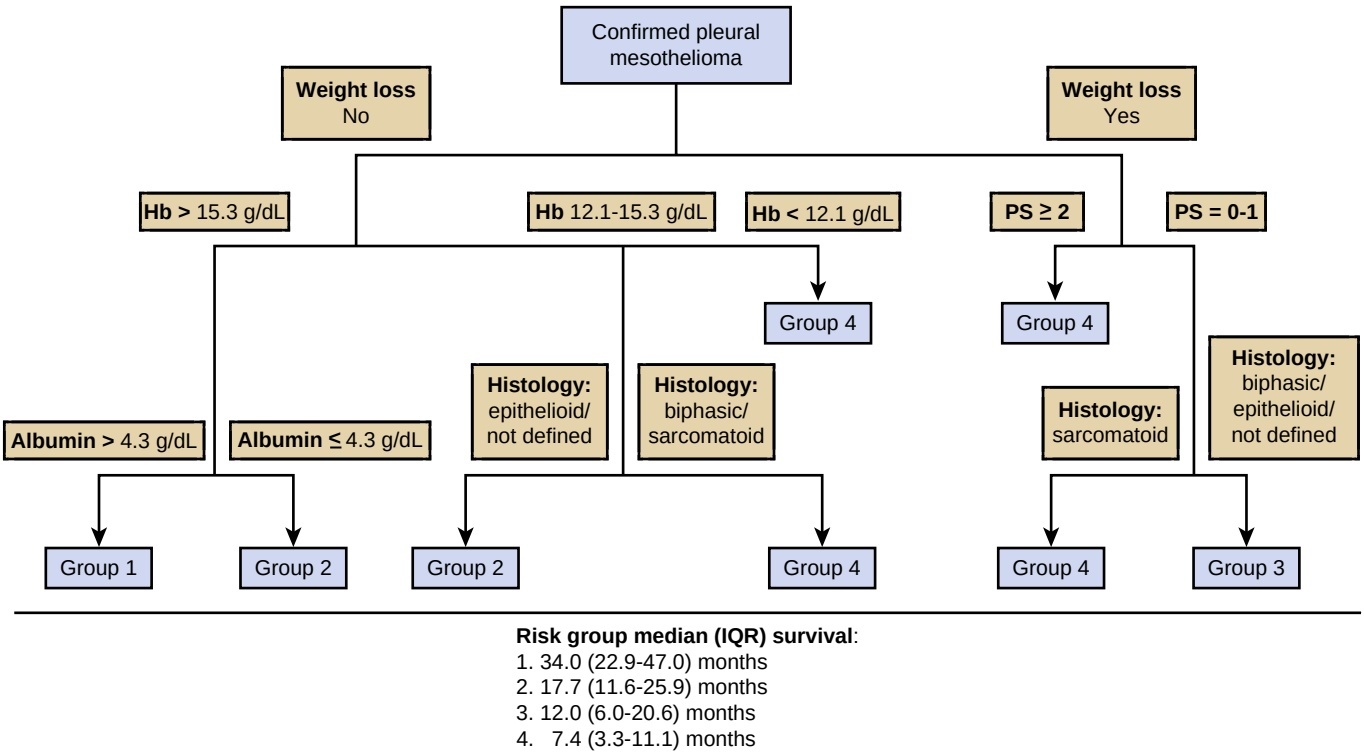

Figure 114.6 A predictive model of survival in mesothelioma patients based on simple, commonly obtained parameters. In this model, the strongest predictive variable was weight loss, defined as any weight loss deemed significant by the caring physician. Median survivals range from 34.0 months to 7.4 months. Hb, hemoglobin; IQR, interquartile range; PS, Eastern Collaborative Oncology Group performance status. (From Brims FJ, Meniawy TM, Duffus I, et al. A novel clinical prediction model for prognosis in malignant pleural mesothelioma using decision tree analysis. *J Thorac Oncol*. 2016;11[4]:573–582.)

Surgical Therapy

There is no proven role for radical surgical resection of mesothelioma, although it is still practiced in many centers. Mesotheliomas are usually multifocal tumors that spread along the pleural surfaces and invade the deeper tissues, making complete surgical eradication impossible. In postmortem series, distant tumor metastases (often silent clinically) are common[157] and may explain why local surgical clearance of mesothelioma failed to affect survival, and distant "relapse" is common even after *extrapleural pneumonectomy* (EPP).[158]

EPP is one of the most aggressive thoracic surgeries in its attempt to provide complete resection of pleural mesothelioma. It removes the lung with its visceral pleura, the hemidiaphragm, pericardium, and parietal pleura. This aggressive procedure has very high postoperative mortality (at least 5%) and major morbidity (25%). The Mesothelioma and Radical Surgery trial[159] randomized 50 mesothelioma patients to EPP or no surgery. EPP was harmful and *shortened* median survival by 5 months (14.4 vs. 19.5 months), with a hazard ratio of 2.75 compared with no surgery, even after adjusting for histology, staging, age, and sex. EPP should no longer be recommended to patients.

Extended pleurectomy/decortication aims to debulk the tumor by removing the same structures as EPP but sparing the lung. The Meso-VATs trial[78] randomized 175 mesothelioma patients to debulking parietal pleurectomy performed under video-assisted thoracic surgery or to only talc pleurodesis. Surgery conferred no survival benefit at 12 months (52% vs. 57% of talc group) but was associated with more complications, especially prolonged air leak.

Neither the most (EPP) nor the least (video-assisted thoracic parietal pleurectomy) aggressive form of surgical resection confers survival benefits in mesothelioma. The more aggressive the procedure, the more complications and the more detrimental it is to clinical outcomes.[160]

Combining surgery with other treatments (e.g., radiotherapy and/or chemotherapy, hyperthermic treatment, photodynamic therapy) has not been subjected to prospective randomized trials.

Chemotherapy

Only three randomized trials on treatments for mesothelioma have shown survival benefits (albeit small). Combination of cisplatin and multitargeted antifolate drugs have been shown in two randomized trials (one using pemetrexed[161] and one raltitrexed[162]) to improve median survival (12.1 months with pemetrexed/cisplatin vs. 9.3 months with cisplatin alone). Addition of folic acid and vitamin B_{12} reduces toxicity.

The Mesothelioma Avastin Cisplatin Pemetrexed Study (n = 448) evaluated platinum/pemetrexed therapy[163,164] with or without bevacizumab, a monoclonal antibody inhibitor of VEGF. Addition of bevacizumab improved median overall survival from 16.1 to 18.8 months but induced more adverse effects.

No second-line therapies have shown benefits in randomized trials. Various targeted therapies, such as antiangiogenic tyrosine kinase inhibitors directed against receptors of VEGF or platelet-derived growth factor, have demonstrated no convincing advantage over routine clinical care.[165–170]

Immunotherapy

Immunotherapy for mesothelioma is an area of intense research with many ongoing clinical trials[171] examining various *immune checkpoint inhibitors* (ICIs) singly or in combination with other ICIs or with chemotherapy. Promising results in pilot nonrandomized studies are accumulating. However, the first published randomized trial (DETERMINE study)[172] found no survival benefits in those treated with tremelimumab, a cytotoxic T lymphocyte–associated antigen-4 monoclonal antibody (n = 382), and those who received placebo (n = 189). Interest has since shifted to the use of anti–programmed death ligand 1 therapy, in patients with and without programmed death ligand 1 expression. Again, promising data in small, nonrandomized or noncontrolled studies (e.g., INITIATE[173] and MAPS2[174] trial) have attracted strong interest but, until phase III studies are available, the benefit of immunotherapy will remain contentious. Clinicians should encourage interested patients to enroll in clinical trials.

Alternative immunotherapy agents (e.g., antimesothelin strategies, dendritic cell-harvested immunotherapy, and vaccine against Wilms tumor 1) are under investigation. Gene (immunogene) therapy is another approach under investigation.[175]

Radiation Therapy

Although mesothelioma is radiosensitive, therapeutic doses of radiation for mesothelioma result in significant pneumotoxicity and damage to adjacent organs. Use of radiotherapy as neoadjuvant or adjuvant treatment in conjunction with surgery has not yet been shown to be beneficial. Intensity-modulated conformal radiotherapy is being studied,[176] but definitive evidence supporting its use is still lacking. However, radiation for symptom palliation, such as for chest wall metastases for pain control, remains useful.

The role of prophylactic radiotherapy at pleural puncture sites to prevent tract metastasis has been refuted by two multicenter randomized trials.[177,178] Both found a small and statistically nonsignificant reduction of incidence of tract metastasis: 3.2% versus 5.3% from Bayman et al. (n = 375)[177,178] and 9% versus 16% by the SMART study group (n = 203).[177,178] Prophylactic radiotherapy should not be routinely applied. Irradiation of symptomatic IPC tract metastases is safe and does not require prior catheter removal.[179]

Palliative Therapy

As an incurable malignancy, the key goals of care for mesothelioma are symptom palliation, improvement in quality of life, and minimization of hospitalization. A multidisciplinary approach incorporating physical aspects as well as nutritional, psychological, and social needs is advisable. Early referral to a palliative care service, however, has not shown benefits in a randomized trial,[180] implying that these care needs can be adequately delivered by pulmonologists/oncologists in most cases.

Management strategies for MPE associated with mesothelioma generally follow those outlined earlier in this chapter.[181] In an unselected review of 390 mesothelioma patients, 42.3% underwent pleurodesis, surgically (n = 78) or by bedside instillation of sclerosants (n = 87). As in other MPE studies, surgical pleurodesis showed no advantages

over bedside pleurodesis in efficacy (32% vs. 31% failures requiring further drainage; $P = 0.98$). No clinical, biochemical, or radiographic parameters tested adequately predict pleurodesis outcome.

Pain is common and generally can be controlled with analgesia, especially opioids. Radiotherapy to pain site (if localized) should be considered early. With severe diffuse pain refractory to conventional measures, nerve blocks or percutaneous or intrathecal drug delivery may be required. Cervical cordotomy has been evaluated in small studies as effective but requires procedural expertise.[182]

Mesothelioma patients often have unique psychosocial needs.[183,184] Anger and frustration towards being exposed to an avoidable occupational source is common. Patients with occupational asbestos exposure should be referred for possible compensation.[184a] It should also be noted that compensation claims can be protracted and induce stress. Old literature describing mesothelioma patients dying from drowning due to a growing effusion, suffocation, and untreatable pain often create additional anxiety for patients and caregivers.

SCREENING AND CHEMOPREVENTION

At present, no uniformly agreed upon screening test for mesothelioma exists, and its role, given the poor overall prognosis and lack of curative treatment, remains debatable. Previous studies of high-risk populations have assessed use of low-dose CT imaging, serum, and exhaled biomarkers (i.e., mesothelin, osteopontin, and volatile organic compounds); none demonstrated sufficient sensitivity as a screening tool for early-stage disease.[68,185–189]

Chemoprevention efforts in asbestos-exposed populations have not shown efficacy.[190]

SOLITARY FIBROUS TUMOR OF THE PLEURA

Solitary fibrous tumors are mesenchymal tumors that can arise not only in the pleura but throughout the body, including the mediastinum.[191] The term *solitary fibrous tumor of the pleura* (SFTP) is now used in preference to earlier terms such as *benign mesothelioma* or *localized mesothelioma* for several reasons: to distinguish it clearly from malignant mesothelioma, to acknowledge that it may contain malignancy within it, to appreciate there is no relationship with asbestos contact, and also to recognize that its cellular origin is more likely from pluripotential fibroblasts than from mesothelial cells.[192,193] These tumors are rarer than mesotheliomas, accounting for 8% of all benign pathologic processes of the chest and 10% of all pleural neoplasms.[194]

CLINICAL FEATURES

More than half of patients are asymptomatic, and the tumor is found incidentally on radiographic examination.[195] If symptoms do arise, chest pain, breathlessness, and cough are most common, usually related to the local mass effect of the tumor.[192,196] Paraneoplastic syndromes can develop. Hypertrophic pulmonary osteoarthropathy has been described in 14%[196] to 19%[192] of patients and usually resolves a few months following tumor resection.[192] Hypoglycemia, from tumor release of insulin-like growth factor-2 (Doege-Potter syndrome), has been described in 4%[192] and 14%[196] of patients[197] and resolves after surgical resection. Corticosteroids, which act to suppress insulin-like growth factor-2 production, have been successful in controlling the hypoglycemia.[198]

RADIOLOGIC FEATURES

Chest radiography usually reveals a solitary, clearly defined, circumscribed lesion (eFig. 114.10; see also eFigs. 80.7 to 80.9 and 80.11), which rarely occupies the entire hemithorax (see eFig. 80.10). Smaller masses result in an obtuse angle with the chest wall, whereas larger or lobulated lesions form an acute angle; rarely they appear to arise intra-parenchymally due to the latter characteristic[199] (see eFig. 80.7). Pleural effusion is rare, but calcification may be seen regardless of the tumor's neoplastic potential.

CT or magnetic resonance imaging scans characteristically reveal a smooth, well-defined, rounded mass with no invasion of adjacent structures (Fig. 114.7). Heterogeneous areas of enhancement pathologically correlating with areas of cystic necrosis and hemorrhage may be seen in larger tumors (see eFigs. 80.8 and 80.10). Magnetic resonance imaging demonstrates a low signal on T1- and T2-weighted images and may better define mediastinal and diaphragmatic involvement (see eFigs 80.8C–D).[200]

PET may be helpful to differentiate benign solitary fibrous tumor of the pleura from malignant disease (see eFig. 80.11C).[201]

PATHOLOGIC FEATURES

Macroscopically, most solitary fibrous tumors arise from the visceral pleura.[196] They appear as a smooth, rounded or lobulated, firm mass surrounded by a translucent vascular membrane. Malignant tumors are often larger (e.g., >10 cm in diameter). On cut section, the tumor has a fibrous, gray, whorled appearance with occasional calcification, hemorrhage, and/or central necrosis.

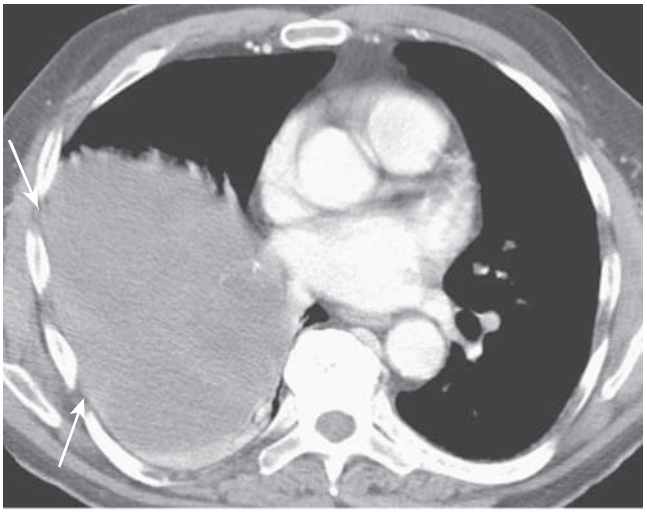

Figure 114.7 Solitary fibrous tumor of the pleura. Axial computed tomography image shows a large, somewhat heterogeneous mass in the right lower chest with extensive chest wall contact (*arrows*). (Courtesy Michael B. Gotway, MD.)

Histologically bland, elongated spindle cells are arranged haphazardly in a storiform or patternless pattern, interspersed with varying amounts of fibrohyaline tissue. Malignant transformation often exhibits increased cellularity, increased mitotic activity, nuclear pleomorphism, and prominent areas of necrosis or hemorrhage. On immunohistochemical staining, SFTPs can be distinguished from sarcomatoid mesothelioma by positive staining for STAT6[202]; nuclear staining is present in more than 98% of SFTPs but is negative in mesothelioma.[202,203] Additionally, SFTPs are generally negative for cytokeratin staining, although focal expression may be present.[125,204] Sarcomatoid mesotheliomas are generally positive, at least focally, for the broad-spectrum antikeratin 1 and 3 and pancytokeratins.[71,125,205]

Solitary fibrous tumors can be distinguished from several other uncommon tumors (e.g., synovial sarcoma and histiocytoma) by their staining for vimentin,[206] a marker of mesenchymal cells, CD34 (a hematopoietic progenitor cell antigen), and Bcl-2 protein; these tumors typically are negative for thyroid transcription factor-1 and keratin.[196,207]

STAGING

Staging of SFTP depends on the tumor size and origin together with its histologic malignant potential. Designation of stage allows prognostication and estimation of the risk of recurrence[208] (eTable 114.1).

Surgery is advised in most cases, allowing both a diagnostic excision biopsy and definitive treatment. Complete resection is curative in approximately 90% of cases. It is often performed via thoracotomy or video-assisted thoracic surgery, with a tumor margin of more than 1 cm recommended. Tumor recurrence may present more than a decade following initial resection; therefore, surveillance is advised. The risk of recurrence is much greater in patients with stage III or IV disease, which shows malignant histology and either sessile or metastatic morphology.[208,209] Occasionally malignant changes are documented in the recurrent tumor despite a benign primary lesion (see eFig. 80.13).[192,210]

The prognosis of benign solitary fibrous tumors is generally good, with near 100% 5-year survival rates. Patients with malignant transformation, however, have poorer outlook, with 0% 5-year survival reported for stage IV disease.

Treatment of recurrent tumors is resection. Approaches targeting VEGF and angiogenesis pathways are being evaluated.[191,210a]

PRIMARY PLEURAL LYMPHOMA

Two distinct forms of primary lymphoma affect the pleura: primary effusion lymphoma and pyothorax-associated lymphoma.

Primary effusion lymphoma is a type of high-grade B-cell lymphoma that develops along serosal surfaces (i.e., the pleura, peritoneum, or pericardium). Human herpesvirus-8/Kaposi sarcoma herpes virus infection is always present, and its identification is required for the diagnosis of primary effusion lymphoma[211]; approximately 50% of patients display Epstein-Barr virus coinfection.[212] The majority of body cavity–based primary effusion lymphomas arise in patients with *human immunodeficiency virus* (HIV), although it has been described in HIV-negative patients, usually elderly persons of Eastern European/Mediterranean descent, in an epidemiologic pattern similar to that of HIV-negative, classic Kaposi sarcoma.

Primary effusion lymphoma mirrors mesothelioma radiologically, and histologic differentiation is essential (Fig 114.8). Pleural fluid is exudative and lymphocyte dominant. Cytologically, the lymphocytes typically stain negatively for B and T cell antigens,[213] yet flow cytometry can reveal clonality sufficient to secure the diagnosis. Occasionally, pleural biopsy is required. Identification of human herpesvirus-8 can be performed by extracting DNA from involved tissues followed by Southern blot analysis, by in situ hybridization of slides from paraffin-embedded samples, and by in situ reverse transcriptase polymerase chain reaction of cytologic smears or cell blocks.[214]

Prognosis is poor, with survival reported between 6 and 9 months.[213] Treatment with chemotherapy and, if HIV positive, antiretroviral agents may help with management of the pleural effusion.[215]

Pyothorax-associated lymphoma is a human herpesvirus-8–negative high-grade non-Hodgkin B cell lymphoma strongly associated with Epstein-Barr virus[216] (in up to 70% of tumors in the largest series).[217] Typically, pyothorax-associated lymphoma develops in patients who had a pyothorax as a complication of artificial pneumothorax used for the treatment of pleuropulmonary tuberculosis, often more than 2 decades before.[218] It is more commonly reported in Japan than in the Western world, where few cases are described.[219] Chest radiograph or CT scan images reveal a localized pleural mass in an area of chronic pleural abnormality; intense FDG avidity is seen on PET/CT.[220,221]

There are no large series evaluating specific treatments for this disease. Various treatments have been studied, including surgical excision, chemotherapy, or radiotherapy,[217,222] with limited success. Overall prognosis is poor with a 5-year survival of 22%.[217]

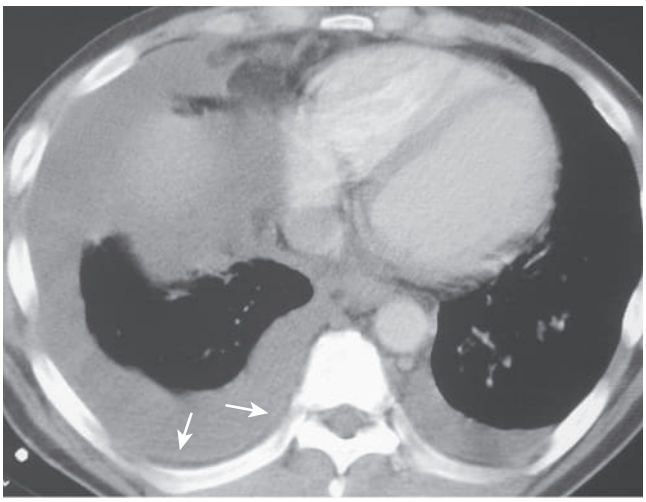

Figure 114.8 Primary effusion lymphoma. On axial computed tomography, the malignancy is manifest in bilateral effusions. *Arrows* indicate a minimally thickened parietal pleura, without nodularity. (Courtesy Michael B. Gotway, MD.)

eTable 114.1 Staging of Solitary Fibrous Tumor of the Pleura

Stage	Histology	Morphology
0	Benign	Pedunculated
I	Benign	Sessile or inverted*
II	Malignant	Pedunculated
III	Malignant	Sessile or inverted
IV	Malignant	Metastatic, synchronous

*Inverted tumors can grow inside the lung parenchyma without actual invasion, as seen in <3% of cases.

Modified from de Perrot M, Fischer S, Brundler MA, et al. Solitary fibrous tumors of the pleura. *Ann Thorac Surg*. 2002;74(1):285-293.

IMMUNE CHECKPOINT INHIBITOR–RELATED PLEURAL EFFUSION

The rapidly growing use of ICIs, such as pembrolizumab, nivolumab, and atezolizumab, has led to the recognition of many new immune-related adverse events,[223] including development of pleural effusion that requires differentiation from pleural spread of the primary cancer. Pleural fluid of ICI pleuritis is typically a cytologically negative lymphocyte-rich exudate. If patients are symptomatic, the ICI should be withheld and pleural drainage undertaken. Corticosteroids can be considered in appropriate cases.

Key Points

- Malignant effusions are most commonly due to lung cancer, followed by breast cancer and lymphoma. The incidence of mesothelioma varies among countries.
- Malignant effusions, especially those from adenocarcinomas, can often be diagnosed by cytologic examination of the pleural fluid. If cytologic results are negative, biopsy of the pleural tissue using image-guidance modalities or thoracoscopy should be considered to help establish a diagnosis. Cell-free DNA from pleural fluid supernatant or blood can help detect driver mutations in malignant pleural effusion from lung cancer patients with epidermal growth factor receptor mutations.
- In the eighth edition of tumor-node-metastasis staging for lung cancer, pleural malignancy with or without effusion is now classified as a metastatic lesion (M1a, intrathoracic metastasis).
- In most patients with a symptomatic malignant pleural effusion, palliation of symptoms is the key management goal. Therapeutic thoracentesis, talc pleurodesis, and indwelling pleural catheter drainage are established options. The choice depends on the life expectancy of the patient and whether the lung can reexpand.
- Indwelling pleural catheters are now accepted as an alternative to talc pleurodesis for first-line definitive management of malignant pleural effusions. The catheter has been shown in randomized trials to improve symptoms and quality of life while reducing days spent in the hospital. It can be combined with talc slurry to increase the likelihood of pleurodesis and catheter removal.
- Malignant pleural mesothelioma should be considered in any patient with an exudative effusion, especially if there is a history of exposure to asbestos, chest pain, and a rind-like nodular thickening of the pleura.
- Recent randomized studies have changed management practice for mesothelioma. Chemotherapy with cisplatin, pemetrexed, and bevacizumab can improve survival. All randomized trials to date have found no benefits of surgical resection for malignant pleural mesothelioma. Routine use of prophylactic radiotherapy is not recommended.
- Solitary fibrous tumors of the pleura are mesenchymal tumors that can involve the visceral pleura. Most are benign and can be successfully resected.
- Primary effusion lymphoma and pyothorax-associated lymphoma arise in the pleural cavity, often presenting *without* and *with* a mass, respectively. Primary effusion lymphoma is associated with systemic immunosuppression from human immunodeficiency virus and is caused by human herpesvirus-8; pyothorax-associated lymphoma is associated with long-standing pleural inflammation and is associated with Epstein-Barr virus.

Key Readings

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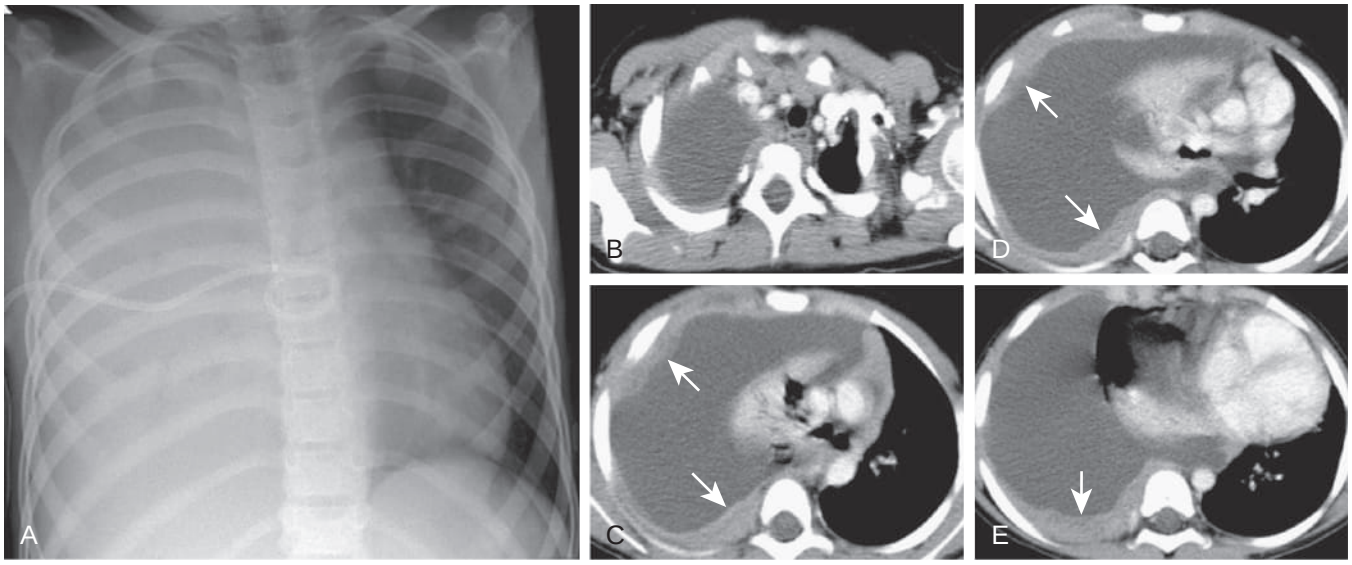
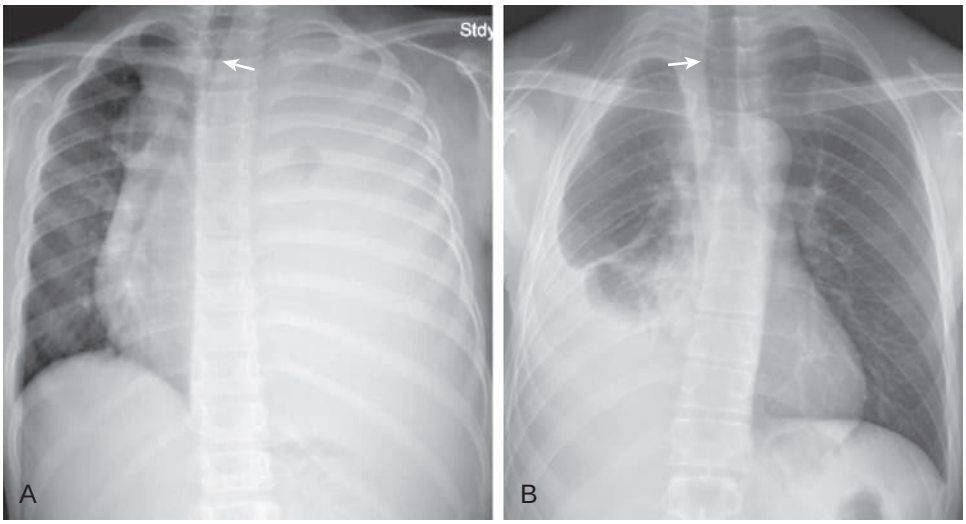
Complete reference list available at ExpertConsult.com.

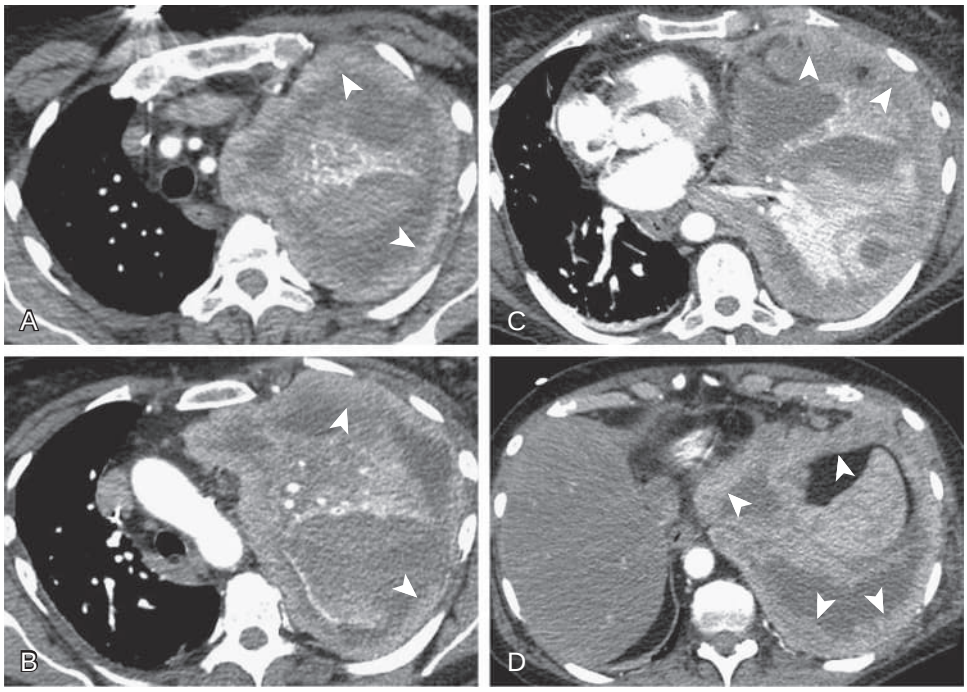
eFIGURE IMAGE GALLERY



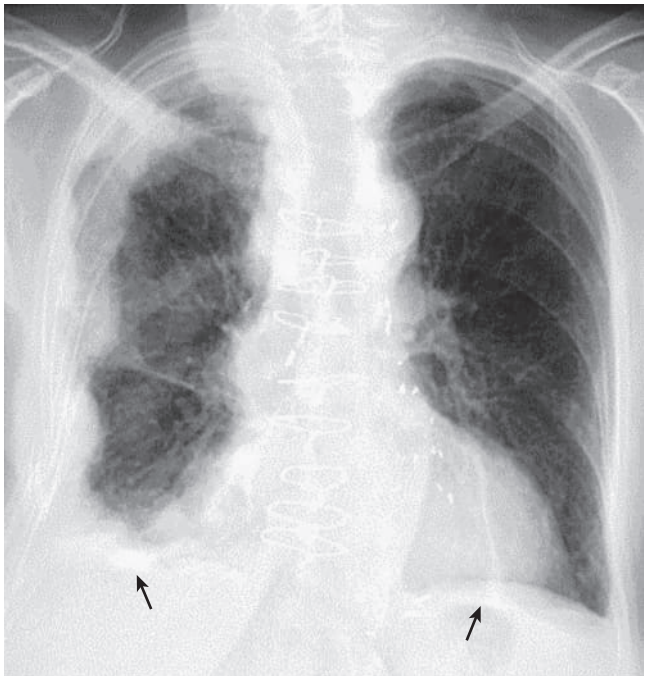
eFigure 114.1 Pleural effusion due to non-Hodgkin lymphoma. (A) Frontal chest radiograph shows complete opacification of the right hemithorax due to a massive right pleural effusion. (B–E) Axial enhanced chest computed tomography shows a large right pleural effusion associated with prominent multifocal pleural thickening (*arrows*). (Courtesy Michael B. Gotway, MD.)



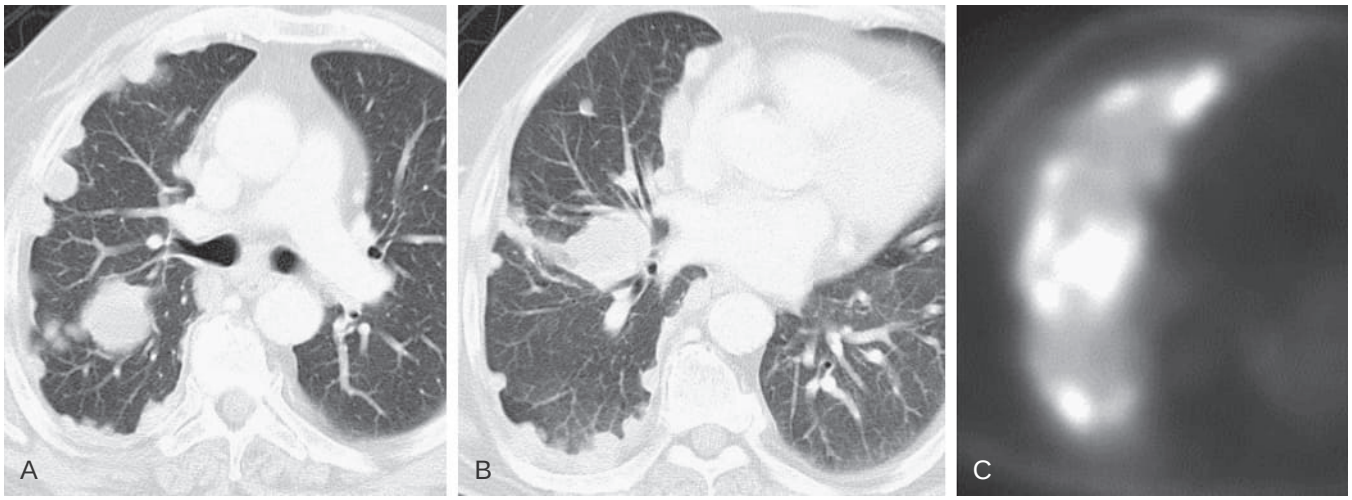
eFigure 114.2 Pleural effusion effect on mediastinal position. (A) Frontal chest radiograph in a patient with a large left effusion due to non-Hodgkin lymphoma shows *contralateral* shift of the cardiomediastinal structures; note rightward displacement of trachea (*arrow*). (B) Frontal chest radiograph in a patient with a moderate right pleural effusion shows slight *ipsilateral* shift of the cardiomediastinal structures; note slight rightward displacement of trachea (*arrow*). The right pleural effusion in this patient was due to metastatic mucinous adenocarcinoma with extensive infiltration of lung. (Courtesy Michael B. Gotway, MD.)



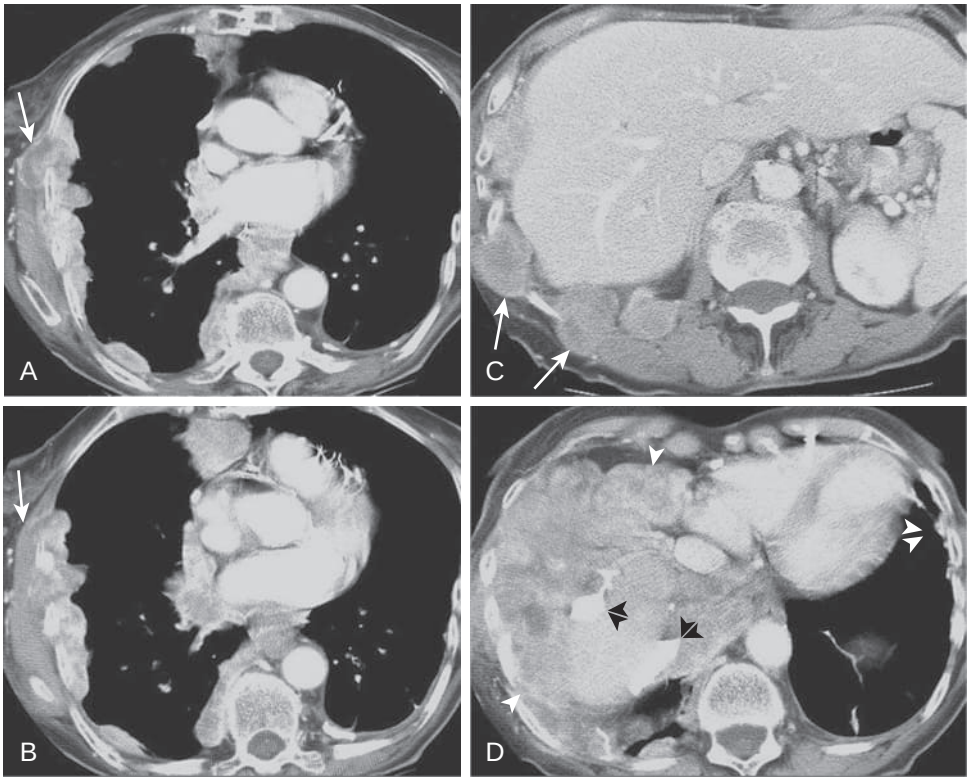
eFigure 114.3 Chest computed tomography appearance of malignant pleural disease. (A–D) Axial enhanced chest computed tomography shows extensive, nodular, circumferential pleural thickening (*arrowheads*) due to metastatic bronchogenic malignancy. (Courtesy Michael B. Gotway, MD.)



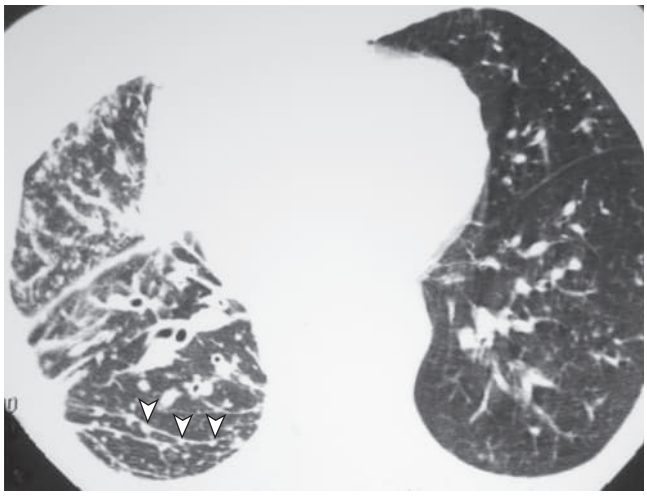
eFigure 114.4 Malignant pleural mesothelioma complicating asbestos-related pleural disease. Frontal chest radiograph shows extensive nodular pleural thickening affecting the right pleura associated with mild volume loss affecting the right lung. Calcified diaphragmatic pleural plaques (*arrows*), reflecting asbestos-related pleural disease, are present. (See chest computed tomography for this patient in eFig. 114.6.) (Courtesy Michael B. Gotway, MD.)



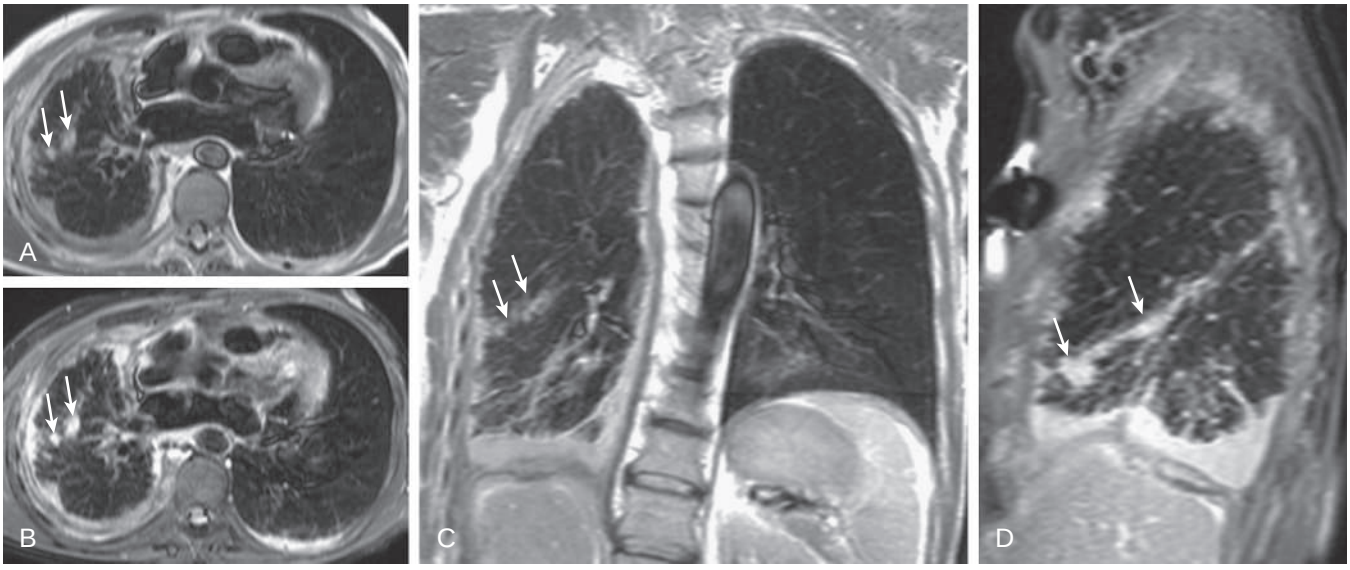
eFigure 114.5 Malignant pleural mesothelioma: pleural nodules. (A–B) Axial chest computed tomography displayed in lung windows shows large nodules nearly circumferentially involving the right pleura. (C) Axial positron emission tomography image shows extensive metabolic activity within the nodules. (Courtesy Michael B. Gotway, MD.)



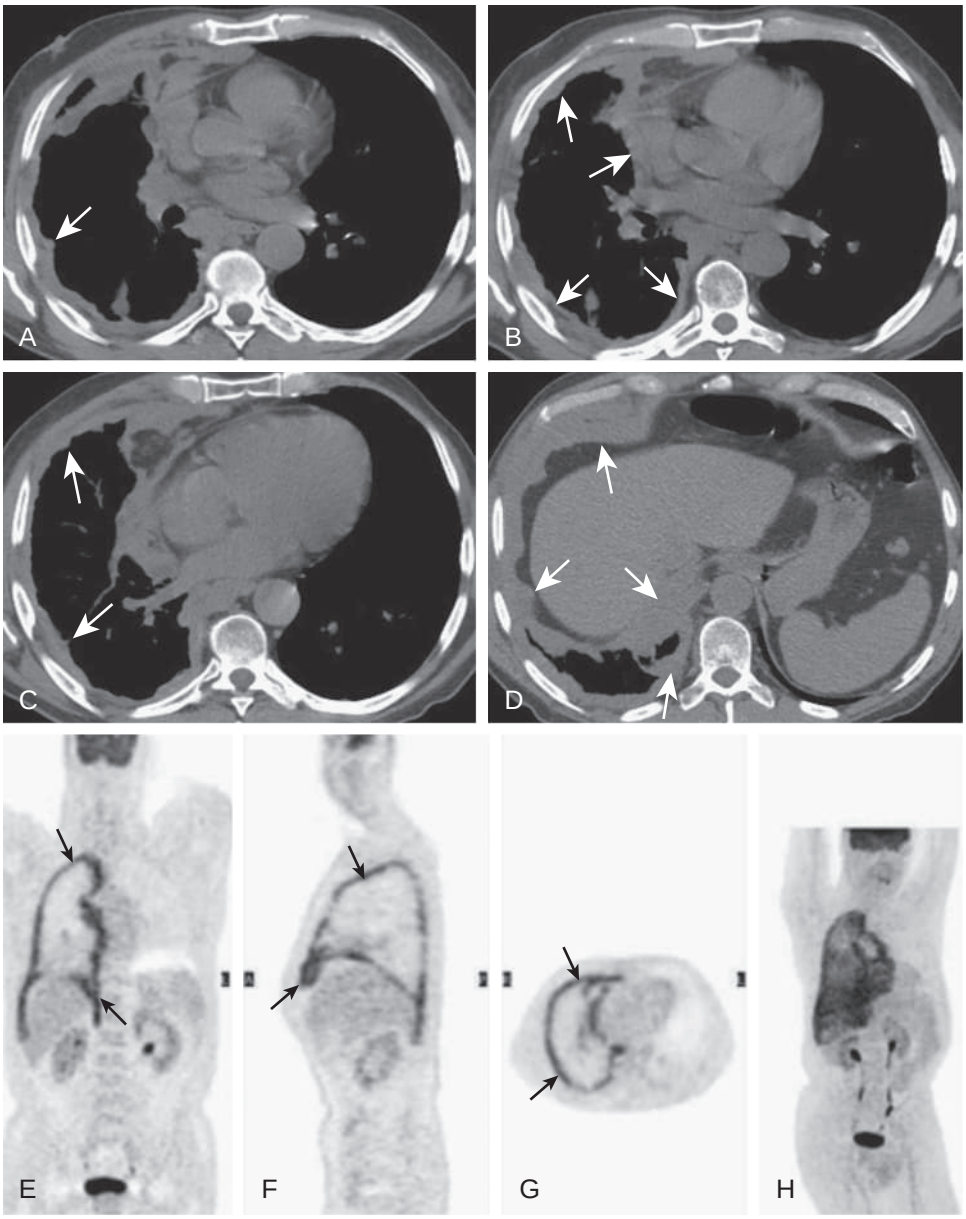
eFigure 114.6 Malignant pleural mesothelioma: chest wall and diaphragm invasion. (A–D) Axial enhanced chest computed tomography shows extensive, nodular right pleural thickening with extension of the pleural disease into the adjacent chest wall (*arrows*). Extensive nodular soft tissue thickening involving the basal pleura and right hemidiaphragm (*arrowheads*) is present, and partially calcified pleural plaques (*double arrowheads*), representing asbestos-related pleural disease, are seen bilaterally. (Courtesy Michael B. Gotway, MD.)



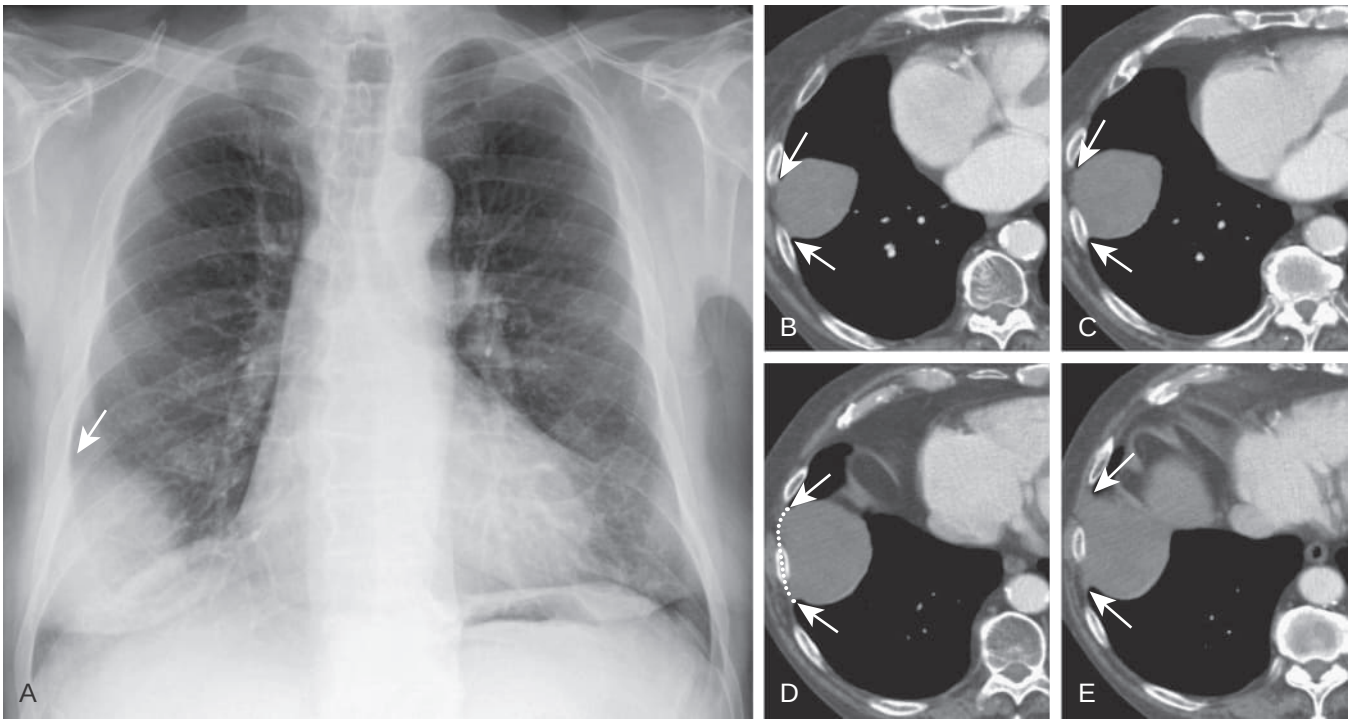
eFigure 114.7 Malignant pleural mesothelioma: lymphatic metastases. Axial chest computed tomography displayed in lung windows shows volume loss affecting the right thorax associated with extensive interstitial thickening. Clear nodular interlobular septal thickening (*arrowheads*) is present. (Courtesy Michael B. Gotway, MD.)



eFigure 114.8 Malignant pleural mesothelioma: magnetic resonance imaging appearance. (A–B) Axial T1-weighted imaging before (A) and following (B) intravenous contrast administration shows enhancing circumferential right pleural thickening with clear nodularity involving the right major fissure (*arrows*). Coronal unenhanced (C) and sagittal fat saturation enhanced (D) T1-weighted images show extensive pleural thickening and enhancement with a nodular appearance involving the right major fissure (*arrows*). (Courtesy Michael B. Gotway, MD.)



eFigure 114.9 Malignant pleural mesothelioma: chest computed tomography and *positron emission tomography* (PET)/computed tomography appearance. (A–D) Axial unenhanced chest computed tomography shows extensive, circumferential, nodular pleural thickening (*arrows*) associated with mild right thoracic volume loss. (E–H) Coronal (E and H), sagittal (F), and axial (G) PET images show intense metabolic activity circumferentially involving the right pleura (*arrows*), correlating with the chest computed tomography findings. (Courtesy Michael B. Gotway, MD.)



eFigure 114.10 Solitary fibrous tumor of the pleura creating acute angles with the chest wall. (A) Frontal chest radiograph shows a focal, circumscribed right peripheral chest mass creating an acute angle (*arrow*) at its cranial point of contact with the chest wall. (B–E) Axial enhanced chest computed tomography shows a circumscribed, homogeneous mass abutting the right inferior chest wall, creating acute angles (*arrows*) with the chest wall, raising the possibility of a location within the subpleural lung rather than the chest wall. The long length of contact of the lesion with the chest wall (*dotted lines*, D) favors a chest wall origin. Tissue sampling showed fibrous tumor of the pleura. (Courtesy Michael B. Gotway, MD.)

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SECTION **N**

DISORDERS OF THE MEDIASTINUM

115 *MEDIASTINAL TUMORS AND CYSTS*

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INTRODUCTION

The mediastinum is the region in the chest between the pleural cavities that contains the heart and other thoracic viscera. The mediastinum should be considered a unique body region due to the diversity and importance of the structures it contains and the multiplicity of disease processes that can affect it. Mass lesions that arise in the mediastinum represent a heterogenous group of benign and malignant processes that defy easy categorization. The nonspecific clinical manifestations of most of these disorders and the relative inaccessibility for tissue sampling result in considerable challenges to the clinician evaluating mediastinal disease. This chapter describes the normal anatomy and contents of the mediastinum, the clinical manifestations produced by mediastinal disease, and the means available for diagnostic investigation. It then reviews the features of specific mediastinal lesions by compartment and outlines an overall clinical approach to the evaluation of mediastinal disease. Discussion of pathology is focused on lesions that arise primarily in the mediastinum; lung cancer is discussed briefly as it pertains to findings in the mediastinum and is covered more fully in other chapters (see Chapter 76). Mediastinal inflammatory and infectious conditions that cause lymphadenopathy and mass-like lesions are also discussed in Chapter 116.

NORMAL ANATOMY OF THE MEDIASTINUM

The anatomy of the mediastinum has been traditionally divided into anterior, middle, and posterior compartments.[1] This three-compartment model is consistent with embryonic development of the region and with the characteristic distribution of individual clinical disorders. The three-compartment model was developed using margins of a lateral radiograph, but the International Thymic Malignancy Interest Group more recently advocated utilizing a similar three-compartment division scheme based on axial *computed tomography* (CT) images: defining prevascular (anterior), visceral (middle), and paravertebral (posterior) compartments.[3] The compartments correspond to the traditional radiographic definition,[2] with added precision with respect to boundary structures.[3] The anatomic relationships of the mediastinal viscera and tissue planes are best appreciated in the axial and sagittal planes on tomographic images (Fig. 115.1).[3] All the mediastinal compartments are defined superiorly by the thoracic inlet and inferiorly by the diaphragm.

The anterior or prevascular compartment consists of everything anterior to the pericardium; its boundaries are

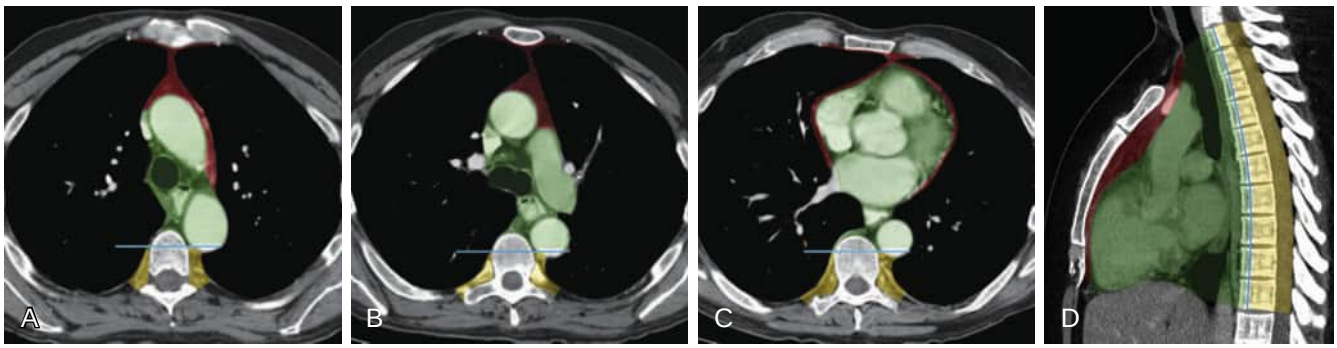

Figure 115.1 Mediastinal compartments by contrast-enhanced chest computed tomography. Red denotes the anterior/prevascular compartment; green, middle/visceral compartment; yellow, posterior/paravertebral component. (A) Axial image slightly below the aortic arch. (B) Axial image at the level of the left pulmonary artery. (C) Axial image at the level of the left atrium. (D) Sagittal image denoting the components. (From Carter BW, Tomiyama N, Bhora FY, et al. A modern definition of mediastinal compartments. *J Thorac Oncol.* 2014;9[9]:S97–S101.)

the sternum, the first rib, and an imaginary curved line following the anterior heart border and brachiocephalic vessels from the thoracic inlet to the diaphragm. Within the anterior compartment lie the thymus gland, any substernal extensions of the thyroid and parathyroid glands, and lymphatic tissue.

The middle or visceral compartment extends from the anterior aspect of the pericardium to a posterior margin on CT developed by creating a vertical line connecting a point on each thoracic vertebral body at 1 cm posterior to its anterior margin. It contains the heart, the pericardium, the aortic arch and its major branches, the innominate veins and *superior vena cava* (SVC), the pulmonary arteries and hila, the trachea, and several groups of lymph nodes. The esophagus, descending aorta, azygos and hemiazygos veins, paravertebral lymph nodes, and thoracic duct are now considered within this compartment. In addition, the phrenic and upper vagus nerves course through the middle mediastinal compartment.

The posterior or paravertebral compartment occupies the space posterior to the boundaries of the middle compartment defined above, with posterolateral boundaries created by a vertical line at the posterior margin of the chest wall at the lateral margin of the transverse processes of the thoracic spine.[3] The lower portions of the vagus nerve and sympathetic chains lie within the posterior mediastinum.

CLINICAL PRESENTATIONS OF MEDIASTINAL DISEASE

There are three broad reasons mediastinal disease comes to the attention of clinicians: (1) the mediastinum is being assessed in the setting of lung cancer or other metastatic malignancies (particularly tumors originating in the head and neck, the esophagus, the genitourinary tract, the breasts, and the skin); (2) an asymptomatic mass in the mediastinum is detected incidentally; or (3) there are systemic symptoms that point to the mediastinum as a site of disease. The majority of mediastinal masses are discovered incidentally—at least half of all mediastinal masses are asymptomatic and detected by chest radiography performed for unrelated reasons. About 80% of such asymptomatic masses are benign, whereas more than half of those that produce symptoms are malignant.[4–6]

Symptoms in patients with mediastinal mass lesions are nonspecific and are usually caused by compression or invasion of adjacent intrathoracic structures.[4,5] Chest pain, from traction on mediastinal tissues, tissue invasion, or bone erosion, is common. Cough may be due to extrinsic compression of the trachea or bronchi, erosion into the airway, and sometimes postobstructive pneumonia. Hemoptysis, hoarseness, or stridor also may be part of the clinical presentation. Invasion or inflammation of the pleural surface may produce a pleural effusion and cause pain and dyspnea. Compression or direct invasion of the esophagus may lead to dysphagia or odynophagia. Rarely, anterior mediastinal tumors can cause pericarditis or pericardial tamponade, and masses in the middle mediastinum can produce right ventricular outflow obstruction and right heart failure.

The SVC is especially vulnerable to extrinsic compression and obstruction because it is thin-walled and has low intravascular pressure; thus any encroachment, such as tumors in the middle mediastinum, can result in the SVC syndrome.[7] This is characterized by dilation of collateral veins in the upper portion of the thorax and neck, edema and plethora of the face, neck, and upper torso. Neurologic symptoms such as headache, disturbance of consciousness, and visual distortion may be present. Numerous benign causes of SVC syndrome are described,[8] but bronchogenic carcinoma (Video 115.1 and eFig. 115.1) and lymphoma (Video 115.2 and eFig. 115.2) are now the most common etiologies.[9,10] The compression or invasion of nerves may result in hoarseness from involvement of the recurrent laryngeal nerve, Horner syndrome from involvement of sympathetic ganglia, dyspnea from involvement of the phrenic nerve causing diaphragmatic paralysis, tachycardia from involvement of the vagus nerve, and clinical manifestations of spinal cord compression. In addition, primary mediastinal tumors are associated with a wide array of distinctive systemic syndromes, which provide clues to the etiology of the tumor.[4,5,11–13] For example, thymomas are classically associated with myasthenia gravis (Video 115.3 and eFig. 115.4).

Table 115.1 Characteristic Chest Computed Tomography Findings in Mediastinal Disease

Feature	Likely Etiology
Bulky mass on initial presentation	Anterior: lymphoma, germ cell tumor, thymic neoplasm, metastatic disease Posterior: neurogenic tumor
Fat density	Mediastinal lipomatosis or lipoma, liposarcoma, thymolipoma, teratoma
Calcification in mass	In rim of mass: cystic thymoma or thyroid adenoma, aneurysm (including saphenous vein bypass grafts), silicosis ("eggshell" calcification), teratoma In center of mass: goiter, teratoma, thymic neoplasm, treated lymphoma, sarcoidosis, mediastinal granuloma
Teeth or bone	Teratoma
Phleboliths	Hemangioma
Air-fluid level in mass	Esophageal disease, abscess, diaphragmatic hernia, developmental cyst, cystic teratoma (rare)
Mass with associated parenchymal opacity	Granulomatous inflammation/infection Metastatic bronchogenic carcinoma Lymphoma with direct extension into lung Esophageal abnormality with aspiration pneumonitis Bronchial compression by primary mediastinal mass
Mass with associated pleural effusion	Metastatic disease with pleural involvement Granulomatous inflammation of lymph nodes Thymic neoplasms (with "drop" metastases)
Superior vena cava obstruction	Recent onset: Bronchogenic carcinoma, lymphoma, catheter-associated thrombosis, extrinsic compression Long-standing: fibrosing mediastinitis
Erosion or destruction of bone	Metastatic disease, discitis/osteomyelitis, arterial aneurysm, tumors of peripheral nerves or sympathetic ganglia, meningocele
Spine or rib deformity	Enteric cyst, neurofibromatosis
Intensely enhancing lesions	Thyroid disorders, vascular abnormalities, metastases (renal cell carcinoma, thyroid carcinoma, melanoma, cholangiocarcinoma), Kaposi sarcoma, paraganglioma, angiofollicular lymphoid hyperplasia (Castleman disease), hemangioma

IMAGING THE MEDIASTINUM

The mediastinum is relatively inaccessible for examination or exploration; thus imaging studies play an important role in the initial evaluation of mediastinal disease. These include conventional radiographic studies, CT, *magnetic resonance imaging* (MRI), transthoracic and endoscopic ultrasonography, *positron emission tomography* (PET), and other radionuclide studies.

CONVENTIONAL RADIOGRAPHIC TECHNIQUES

Most mediastinal abnormalities are first detected by standard posteroanterior and lateral chest radiographs, and certain mass lesions have characteristic findings (Table 115.1). These findings give clues to the possible origin of a mediastinal mass, but further imaging evaluation is usually required. Although largely supplanted by CT, other studies may be useful in specific circumstances. For example, barium esophagram can demonstrate extrinsic compression, esophageal diverticulum, tumor invasion, or fistula formation.[4] Angiography can identify vascular compression or invasion, can define the vascular supply of tumors, and can sample blood for hormonal localization of certain tumors. Myelography may help delineate intraspinal extension of posterior mediastinal tumors and differentiate neurogenic neoplasms from meningoceles.

COMPUTED TOMOGRAPHY

CT imaging is the mainstay of radiographic evaluation of the mediastinum because this modality can firmly determine the anatomic location, morphology, and tissue density of a mass. The axial plane of CT is well suited for assessment of mediastinal structures, most of which are oriented perpendicularly to this plane. Administration of intravenous contrast helps delineate vascular structures as they relate to a mass and to other mediastinal structures. Easily identified CT patterns include the high density of calcified tissue and contrast-enhanced blood vessels, and the characteristic low density of fat (Fig. 115.2).[14] Normal anatomic variations and fluid-filled cysts can be confidently distinguished from bulky solid masses, which may be irregularly bordered and possess necrotic areas. Additionally, the site of origin of mediastinal masses can often be identified.[15] Characteristic CT findings in a variety of mediastinal disorders have been described (see Table 115.1). For example, the specificity of the CT appearance of teratomas (Video 115.4, eFigs. 115.9 and 115.10), thymolipomas (Video 115.5 and eFig. 115.11), and omental fat herniation (Video 115.6 and eFig. 115.12) is nearly 100%, but the overall accuracy of CT for predicting the diagnosis of all mediastinal masses is less than 50%.[14]

Lymph nodes are readily identifiable on CT scan and can be categorized by size and morphology. Mediastinal lymph nodes greater than 1 cm in diameter in the short axis are considered to be abnormally enlarged and are suspicious

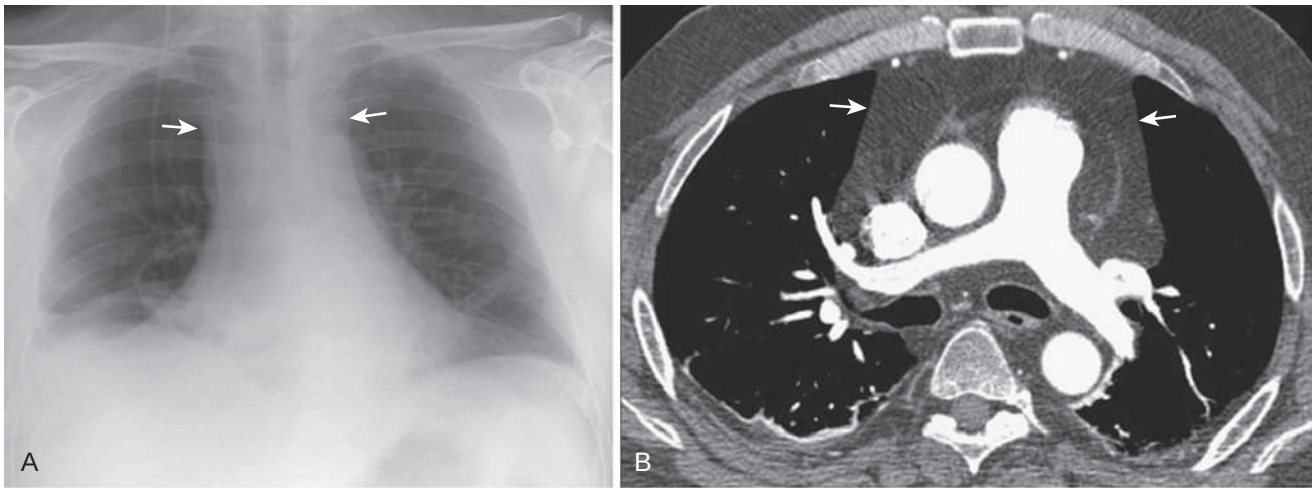

Figure 115.2 Mediastinal lipomatosis. Chest radiograph (A) showing diffuse mediastinal widening *(arrows)* and chest computed tomography scan (B) showing extensive fat deposition *(arrows)* in the anterior mediastinum in a patient with mediastinal lipomatosis.

for malignancy in the proper clinical context. Mediastinal lymph nodes greater than 2 cm in diameter are virtually always abnormal; however, CT cannot reliably distinguish between benign and malignant disease.[16] Nonetheless, CT remains the initial imaging procedure of choice for the evaluation of the mediastinum in patients with a suspected primary mediastinal mass[11–13] or with suspected lung cancer.[17] CT can precisely defines the mediastinal anatomy and guides subsequent invasive diagnostic and staging procedures or can confirm a clinical suspicion of extensive mediastinal involvement or visceral organ invasion that precludes curative resection.

MAGNETIC RESONANCE IMAGING

Although CT is often the initial modality used in diagnosing mediastinal abnormalities, MRI exhibits superior soft tissue resolution. This is advantageous in assessing the precise localization of tumors, extension and tissue boundaries, and relationship with other anatomic structures.[18–22] The respiratory and cardiac variation that has typically been a significant limitation can be overcome through pneumatic belt compression of the chest, breath-hold sequences, or continuous image acquisition synchronized with diaphragmatic movement.[18] Blood vessels are identifiable without the need for contrast enhancement (Fig. 115.3) (Video 115.7A–B); thus MRI can provide an alternative to patients who cannot be given iodinated contrast material required by CT. Ionizing radiation exposure is also eliminated.[23] Although much less frequently used than CT in evaluating mediastinal lesions, MRI is used most frequently for the evaluation of cystic and indeterminate mediastinal masses. MRI has utility in evaluating neurogenic tumors, and it may also be useful in evaluating thymoma and distinguishing it from congenital cyst or thymic carcinoma.[24] MRI can be helpful for defining anatomy before surgical resection of superior sulcus tumors or those invading the mediastinum, chest wall, or diaphragm (eFig. 115.15 and Video 115.8).[17,25]

There have been efforts to use MRI to distinguish benign from malignant masses. In a study of 53 mediastinal lesions, diffusion-weighted MRI distinguished between malignant and benign mediastinal lesions based on apparent diffusion coefficient levels with a sensitivity of 95% and specificity of 87%,[20] with evidence of lower apparent diffusion coefficient values indicating a slower diffusion of water molecules in the malignant lesions. The use of MRI to establish malignancy or benignity requires further study. However, lesions that have features of benignity can sometimes be followed with serial imaging.[26]

ULTRASONOGRAPHY

Ultrasonography can confirm the cystic nature of mediastinal masses, but it cannot readily distinguish between benign and malignant cystic lesions. Both transthoracic and endoscopic ultrasound probes are useful in the evaluation of mediastinal disease in the context of guiding endoscopic biopsy procedures, discussed later.[27]

NUCLEAR IMAGING

Nuclear imaging studies rely on the localization of markers based on specific metabolic or immunologic properties of the target tissue to provide a functional image of a lesion. The spatial resolution of radionuclide scans is relatively poor, but the overall diagnostic accuracy may be high if a sufficiently specific probe is available. Nuclear studies offer the potential to identify a primary malignancy and identify distant metastases with a single scan of the entire body.

PET is a widely used nuclear imaging technique that relies on high-energy photon-emitting probes, such as ^{18}*F-fluorodeoxyglucose* (FDG), which are chemically trapped within metabolically active neoplastic cells. The result is a high signal-to-background ratio and excellent spatial resolution for a functional image of a tumor. Use of combined and coregistered PET and CT images has allowed for more accurate anatomic localization of the lesions in question.[16,28]

PET is useful in the evaluation of mediastinal involvement of thoracic malignancies, and its role in lung cancer staging is discussed in Chapter 25. Although PET is indicated for staging lung cancer, granulomatous, inflammatory, infectious conditions or brown fat can also lead to

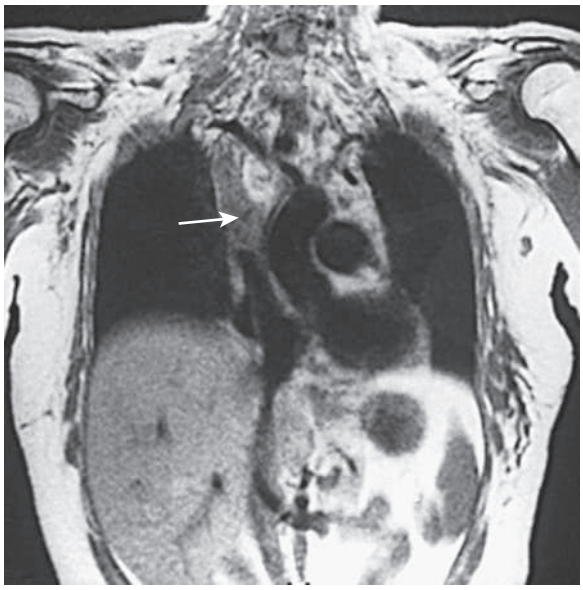

Figure 115.3 Magnetic resonance imaging of superior vena cava syndrome. A 52-year-old woman with multiple myeloma experienced symptoms of superior vena cava obstruction following placement of an indwelling central venous catheter in preparation for bone marrow transplantation. Vertically oriented structures are clearly discernible, and black flow void is present within the heart and great vessels. The superior vena cava is completely obstructed by thrombus *(arrow)*.

elevated FDG uptake in mediastinal lymph nodes; thus tissue confirmation is usually required.[29]

The utility of PET for the evaluation of primary mediastinal lesions is not as well established as it is for lymph node metastases. FDG-PET may differentiate between thymoma and thymic carcinoma,[30] but has low sensitivity in differentiating between nonaggressive and aggressive subtypes of thymoma,[24] and is not used routinely for staging of thymoma. However, PET is considered standard of care in the pretreatment workup and follow-up of mediastinal lymphoma (see "Lymphoma" later). FDG-PET also plays a role in detecting residual postchemotherapy malignant germ cell tumors, specifically seminomas, of the mediastinum. There is little role for PET in evaluating neurogenic tumors.[31]

Several other imaging techniques are utilized for specific conditions. Radioiodine scanning is used for the detection of ectopic thyroid tissue and a positive result is pathognomonic for that condition[4]; I-meta-iodobenzylguanidine scintigraphy is used for detection of neuroblastic tumors and may be used with MRI to improve the prediction for unfavorable histology.[32] ^{99m}Technetium sestamibi scanning is used for primary hyperparathyroidism.[33]

TECHNIQUES FOR OBTAINING MEDIASTINAL TISSUE

In many cases of a mediastinal mass with a confident presumptive clinical diagnosis, a patient may proceed with definitive surgical resection, precluding the need for a diagnostic biopsy (see "General Approach to a Mediastinal Mass" later). When pathologic confirmation is required to make decisions about medical treatment, as in the case of lymphoma or metastatic adenopathy, tissue biopsy can be obtained by image-guided and surgical approaches.

IMAGE-GUIDED BIOPSY

Endobronchial and Endoscopic Ultrasound-Guided Aspiration

Endobronchial ultrasound-guided transbronchial needle aspiration (EBUS-TBNA) of mediastinal tumors adjacent to the airways is a less invasive option than surgical tissue sampling and is commonly used in the setting of lung cancer staging (see Chapter 27). TBNA with a 19- or 22-gauge needle is performed under real-time ultrasonographic guidance via a curvilinear probe on the end of a bronchoscope (Videos 115.9A–B). The ability to visualize the area of interest as well as adjacent vascular structures has vastly improved diagnostic yields over blind bronchoscopic TBNA.[34–39] Upper and lower paratracheal, subcarinal, and hilar lymph nodes are readily accessible by EBUS-TBNA, as is any mediastinal or hilar lesion immediately adjacent to a large airway. EBUS-TBNA has the advantage over mediastinoscopy in accessing the posterior subcarinal lymph nodes as well as hilar nodes or masses, in addition to being an ambulatory procedure with lower associated health care costs.[40]

Beyond its role in lung cancer, EBUS-TBNA is useful in the evaluation of isolated mediastinal adenopathy due to other conditions. The diagnostic yield of EBUS-TBNA for the diagnosis of sarcoidosis manifesting as mediastinal and hilar adenopathy is superior to blind TBNA, with a sensitivity of 83% and specificity of 100%.[41] In a prospective trial of 77 patients with isolated mediastinal adenopathy, a specific diagnosis of sarcoidosis, tuberculosis, lymphoma, or other malignancy was made in 87%, thus obviating the need for a more invasive surgical mediastinoscopy.[42] EBUS-TBNA can be useful in providing a definitive diagnosis of primary or recurrent lymphoma; however, its role in the initial diagnosis of mediastinal lymphoproliferative disorders is likely inferior to surgical biopsy because the amount of tissue provided may not be adequate for histologic subtyping, which is of particular importance in identifying Hodgkin lymphoma.[42–44]

Endoscopic ultrasound (EUS)–guided sampling is similar and relies on the placement of biopsy needles through the working channel of a gastroscope.[45] It is particularly useful for assessing the posterior subcarinal nodes in selected cases and can be used alone or in conjunction with EBUS-TBNA in lung cancer staging.

Transthoracic Needle Aspiration and Biopsy

Transthoracic needle aspiration and biopsy of mediastinal masses, usually in the anterior compartment, can be performed percutaneously using ultrasound or, more often, CT guidance[46] (Fig. 115.4; see also Chapter 21). Transthoracic needle aspiration of the mediastinum has acceptable morbidity and yields comparable to those from percutaneous biopsy of pulmonary lesions. As with TBNA, serious bleeding is seldom encountered,[41] and accurate diagnosis of a wide variety of lesions has been reported.

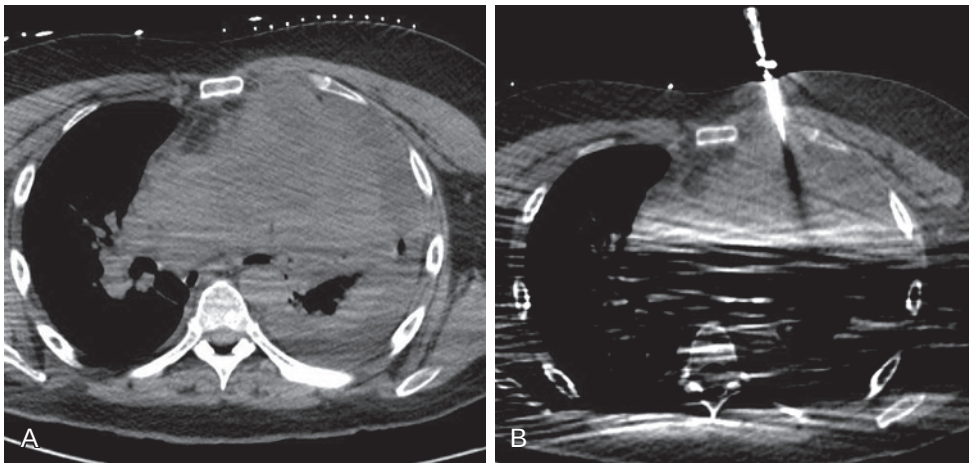

Figure 115.4 Bulky anterior mediastinal mass with CT-guided needle aspiration. (A) A 45-year-old man presenting with hoarseness was found to have a 12 × 10 × 11 cm anterior mediastinal mass. On this noncontrast computed tomography (CT) image, there is central necrosis and mass effect with concurrent left pleural effusion. (B) CT-guided needle aspiration of the mass. The needle is lateral to the sternum. The final diagnosis was primary mediastinal B cell lymphoma.

SURGICAL BIOPSY

Mediastinoscopy

Cervical mediastinoscopy provides direct access to the paratracheal and subcarinal lymph nodes, whereas an *anterior mediastinotomy* (Chamberlain procedure) provides access to the lymph nodes in the aortopulmonary window. Although more invasive than a percutaneous or endobronchial approach, mediastinoscopy has the advantage of providing the entire lymph node for histologic examination, rather than the cellular aspirates or small tissue fragments produced by needle biopsy techniques. Mediastinoscopy is most frequently used in the staging of bronchogenic carcinoma,[47] but has utility in evaluating mediastinal adenopathy or mass lesions of other etiologies. Either frozen section or imprint cytology methods can provide rapid, accurate results and facilitate immediate decisions about the feasibility of curative resection.[48,49]

From the perspective of the surgeon performing a mediastinoscopy, mediastinal anatomy is considered according to whether structures lie anterior, posterior, or immediately to the right or left of the trachea.[50] Mediastinoscopy is feasible for tumors adjacent to the airways, but is not a good option for anterior mediastinal or posterior mediastinal masses. Mediastinoscopy is performed using general anesthesia and is typically an outpatient procedure.[51] Mediastinoscopy is safe and well tolerated. Complications are rare, and include pneumothorax, hemorrhage, recurrent laryngeal nerve or phrenic nerve paralysis, injury to the trachea, esophageal perforation, thoracic duct laceration, air embolism, and mediastinitis.

Video-Assisted Thoracoscopic Surgery

Biopsies of mediastinal lymph nodes or mediastinal masses can also be performed by *video-assisted thoracoscopic surgery* (VATS). VATS provides access to any intrathoracic structure and hence, unlike mediastinoscopy, allows sampling from any tissue in the anterior, middle, or posterior mediastinum. VATS can also be a tool for the evaluation of pleural and lung abnormalities in the management of mediastinal diseases. Mediastinal lymph nodes can be sampled to aid in the staging of malignancies such as esophageal carcinoma and for the diagnosis and resection of primary mediastinal tumors and cysts.[52–54] VATS requires general anesthesia, the ability to tolerate single-lung ventilation, chest tube placement at the conclusion of the procedure, and typically a limited inpatient stay.

MEDIASTINAL MASS

CLASSIFICATION

Mediastinal masses are considered primary, that is, arising solely from structures within the mediastinum, or secondary, usually as metastatic disease from intrathoracic or extrathoracic malignancy. In the most practical classification of primary mediastinal masses, lesions characteristically found in the anterior, middle, or posterior compartments are grouped together (Table 115.2). Nonetheless, it is important to recognize that masses will not necessarily respect anatomic borders and may have extended from another area in the mediastinum.

In a series of 400 consecutive patients with a primary mediastinal lesion,[55] 25% had a primary benign cystic lesion and 42% had a malignant lesion. The anterior compartment was the most common compartment for a lesion, which was more likely to be malignant, followed by the posterior and then middle compartments. Only one-third of lesions are malignant, and the likelihood of malignancy depends on the location, age of the patient, and presence or absence of symptoms.[56,57]

INCIDENCE

The true incidence of primary mediastinal masses is difficult to ascertain. In a study of more than 9000 patients in a lung cancer CT screening trial, the prevalence of an incidentally detected mediastinal mass was 0.77%; among 11,000 follow-up scans, only one additional incident mediastinal mass was detected.[58] Historically, thymomas and developmental cysts were the most common masses found in adults,

Table 115.2 Disorders Presenting as a Mass in the Mediastinum

Anterior/Prevascular Mediastinum	Middle/Visceral Mediastinum	Posterior/Paravertebral Mediastinum
Thymic neoplasms	Lymphadenopathy	Neurogenic tumors
Germ cell tumors	Reactive and granulomatous inflammation	Meningocele
Teratoma	Metastasis	Diaphragmatic hernia (Bochdalek)
Seminoma	Angiofollicular lymphoid hyperplasia (Castleman disease)	Extramedullary hematopoiesis
Nonseminomatous germ cell tumors	Lymphoma	Lymphadenopathy
Embryonal cell carcinoma	Developmental cysts	Lesions arising from posterior spine
Choriocarcinoma	Pericardial cyst	Metastases
Lymphoma	Foregut duplication cysts	Discitis/osteomyelitis
Hodgkin lymphoma	Bronchogenic cyst	Thoracic duct cyst
Non-Hodgkin lymphoma	Enteric cyst	
Thyroid neoplasms/goiter	Others	
Parathyroid neoplasms	Vascular enlargements (i.e., descending aortic aneurysm)	
Mesenchymal tumors	Diaphragmatic hernia (hiatal)	
Lipoma	Esophageal lesions	
Fibroma	Carcinoma	
Lymphangioma	Diverticula	
Hemangioma	Varices	
Mesothelioma		
Sarcoma		
Diaphragmatic hernia (Morgagni)		
NUT midline carcinoma		
Lymphadenopathy		
Vascular lesions		

NUT, nuclear protein in testis.

followed by neurogenic tumors and lymphoma, based on the collection by Silverman and Sabiston of nearly 2400 cases.[4] More recent series suggest a similar pattern,[6,59] although Cohen and associates have observed both a rising incidence of mediastinal masses in general and an increasing proportion of lymphoma and malignant neurogenic tumors over the course of their 45-year survey.[6] Neurogenic tumors, thymomas, and developmental cysts account for about 60% of all mediastinal masses. Lymphomas and germ cell tumors such as teratoma and seminoma account for about 25%, and a large number of other lesions, both benign and malignant, constitute the remaining 15%.[6]

SPECIFIC MEDIASTINAL TUMORS AND CYSTS

LESIONS OF THE ANTERIOR MEDIASTINUM

Thymic Neoplasms

Thymoma is the most common neoplasm arising in the anterior mediastinum.[4,5,15,60] It remains a rare tumor, with an overall incidence of 0.13 per 100,000 person-years in the United States.[61] The peak incidence of thymoma is between the ages of 40 and 60 years and is higher in Asians and African Americans, with equal gender predilection.

Although most thymomas are not biologically aggressive, about one-third of thymomas have already invaded their capsules when discovered. Certain histologic subtypes, as outlined in the World Health Organization classification, are biologically more aggressive.[62] Advanced disease involves extension into local structures, transdiaphragmatic extension into the abdomen, or pericardial involvement, but lymphogenous and hematogenous metastases are rare.[57] Clinical staging historically relied upon the Masaoka or the Masaoka-Koga systems, which are based on the degree of tumor invasion into adjacent structures.[57] The International Thymic Malignancy Interest Group and the International Association for the Study of Lung Cancer have established a tumor-node-metastasis–based classification system based on a multinational cohort of more than 10,000 cases of thymic malignancy, with the T-status largely reflective of invasion. This clinical staging system is poised to become the gold standard.[63]

The majority of patients with thymoma are asymptomatic, although one-third of patients will present with nonspecific chest pain, cough, or dyspnea due to local tumor effects.[64] From 40–70% have at least laboratory evidence of one or more of the two dozen systemic "parathymic" syndromes that have been recognized.[4] Thymomas are associated with numerous systemic syndromes, most of which appear to be autoimmune in origin.[4,5,12] The most familiar of these is myasthenia gravis, reported in 10–50% of patients with thymoma,[4] and thought to be due to autoantibodies to the postsynaptic acetylcholine receptor.[65,66] Other associated syndromes include pure red blood cell aplasia, myocarditis, and hypogammaglobulinemia. Patients with thymoma also have an increased incidence of collagen vascular disease, Whipple disease, and malignancy elsewhere in the body.

On chest radiography, thymomas appear as an ovoid, smooth or lobulated unilateral mass near the junction of the heart and great vessels (Fig. 115.5).[67] Compared

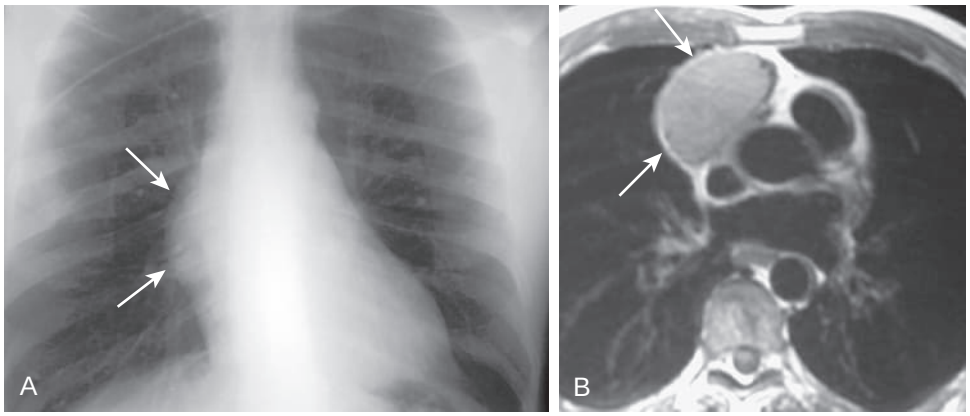

Figure 115.5 Thymoma. (A) Frontal chest radiograph shows a smoothly marginated mass along the right side of the mediastinum *(arrows)*. (B) Axial magnetic resonance T1-weighted image through the base of the heart shows that the mass *(arrows)* is slightly hyperintense compared with the skeletal muscle and resides within the anterior mediastinum. Note the smooth, well-defined margins of the mass, consistent with an encapsulated thymoma. (Courtesy Michael B. Gotway, MD.)

with thymic hyperplasia, which is typically symmetrical, thymoma usually distorts the gland's normal shape asymmetrically and extends to one side.[68] On CT scan, most thymomas present as a solid 5- to 10-cm anterior mediastinal mass outlined by fat; up to one-third of thymomas contain cystic, necrotic, or hemorrhagic areas that enhance heterogeneously. Contrast CT is necessary for the staging of thymoma, specifically for discerning vascular involvement. MRI can help distinguish benign cysts from a cystic thymoma or thymic carcinoma. Due to their relatively indolent nature, most thymomas have low FDG uptake, which limits the utility of PET imaging to discriminate a benign from a malignant thymic mass.[24,57]

The mainstay of therapy for thymomas is surgical resection, which provides the best chance for an optimal prognosis.[57] For advanced stage disease, adjuvant radiotherapy is typically provided, and preoperative or adjuvant chemotherapy is considered on an individual basis.[5,60,69–71]

Patients whose tumors are fully encapsulated with no evidence of invasion can expect postoperative survival equal to that of the general population. Invasive tumors have a poorer prognosis, with 50–77% 5-year and 30–55% 10-year survival.[72] Thymoma recurs after resection in nearly one-third of patients.[72] The largest retrospective survey of thymic tumors from the European Society of Thoracic Surgeons database showed that higher Masaoka stage (with evidence of invasion), incomplete resection, and nonthymoma histology (e.g., thymic carcinomas and neuroendocrine thymic tumors) were factors in recurrence and worse survival.[73]

Thymic carcinoma is an aggressive epithelial malignancy that invades locally and frequently metastasizes.[74,75] This rare cancer develops predominantly in middle-aged men, who present with symptoms of cough, dyspnea, and chest pain as well as nonspecific systemic symptoms.[57] On imaging, thymic carcinomas are heterogenous masses with areas of necrosis and calcifications. They are highly FDG-avid on PET scan.[24,30] The prognosis, which depends on the histologic grade and the anatomic stage, is generally poor. Surgical resection is the treatment of choice, if possible, though recurrence is common. Chemotherapy and radiation therapy are advocated for unresectable disease, and are often used as adjuvant therapy for resectable disease.[73]

Carcinoid tumors occasionally arise in the thymus.[76,77] They may cause Cushing syndrome and be associated with multiple endocrine adenomatosis. Locally invasive carcinoids may be difficult to resect completely, but characteristically have an indolent clinical course.[4] Interestingly, the thymus is also a common site for mediastinal Hodgkin lymphoma, and normal thymic tissue may enlarge following chemotherapy for lymphoma (a process termed *thymic rebound*) (eFig. 115.25), mimicking recurrence of the primary disease.[78] Other thymic mass lesions include benign conditions such as thymic hyperplasia (eFig. 115.26), thymic cysts, and thymolipoma (Video 115.5 and eFig. 115.11).[79]

Germ Cell Tumors

Approximately 10–12% of primary mediastinal masses are derived from multipotent germ cells that migrated abnormally during early embryonic development.[4,5,80,81] These extragonadal *germ cell tumors* (GCT) are classified into three groups: teratoma, seminoma, and nonseminomatous GCT.[81]

Benign teratomas, the most common GCT, are by definition comprised of tissues foreign to the area in which they arise. Ectodermal derivatives predominate, but structures originating in all three primary germ cell layers may be found. *Dermoid cyst* refers to a lesion that contains only the epidermis and its derivatives. Teratomas arise most often in young adults but have been reported in all age groups; men and women are affected with equal frequency. Most patients with teratomas have symptoms caused by the tumor.[4,82] Usual symptoms are pain, cough, and dyspnea. Rarely, teratomas can rupture into the bronchial tree, pleural space, or pericardium.[83] If the tumor erodes into a bronchus, the patient may have hemoptysis or even expectorate differentiated tissue such as hair (trichoptysis) or sebaceous material.[82] On chest radiographs, teratomas

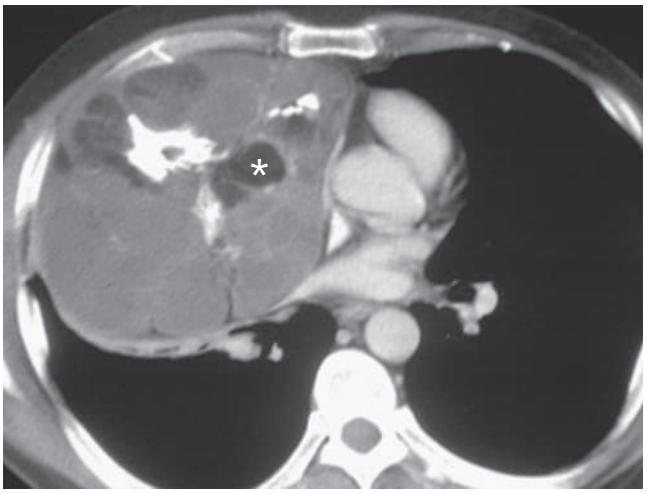

Figure 115.6 Teratoma. Axial computed tomography image through the base of the heart shows a large right-sided anterior mediastinal mass with heterogeneous attenuation. Elements of calcium, soft tissue, and fat *(asterisk)* are present. The presence of fat within an anterior mediastinal mass is most consistent with teratoma. (Courtesy Michael B. Gotway, MD.)

appear smooth, rounded, and circumscribed if they are cystic. Solid lesions can appear lobulated and asymmetric. On CT scans (Video 115.4 and eFig. 115.10), soft tissue, fat, and calcification (and occasionally fully formed teeth and bone) can be identified, rendering this one of few mediastinal tumors that can be diagnosed confidently before surgery[14] (Fig. 115.6). All teratomas should be resected due to malignant potential and effects of impingement on adjacent vital structures. In malignant teratoma, adjuvant combination chemotherapy may result in improved survival.[84]

Malignant primary mediastinal GCT include seminomas and nonseminomatous GCT and affect men in the third and fourth decades of life. These lesions nearly always cause symptoms[5] and appear as a large anterior mediastinal mass on chest imaging (Video 115.10 and eFig. 115.29). Most patients seek medical attention because of chest pain, dyspnea, cough, hoarseness, or dysphagia.

Seminomas are aggressive malignant tumors that extend locally and metastasize distantly, usually to skeletal structures. They may secrete human chorionic gonadotropin, but not alpha-fetoprotein. Factors associated with a poor prognosis include age greater than 35 years; SVC obstruction; supraclavicular, cervical, or hilar adenopathy; and fever.[85,86] Seminomas are extremely radiosensitive and may respond dramatically to chemotherapy, even in cases with dissemination.[81,87] With aggressive cisplatin-based regimens, long-term survival for all mediastinal seminomas is approximately 80%.[81,88]

Nonseminomas include embryonal cell carcinoma and choriocarcinoma.[4,5,85] These malignancies carry a poorer prognosis relative to seminomas and cancers arising from the gonads or other extragonadal sites.[81,89,90] Embryonal cell carcinoma is also called endodermal sinus or yolk sac tumor (Video 115.11 and eFig. 115.30). These highly aggressive tumors often secrete human chorionic gonadotropin and alpha-fetoprotein. In contrast to gonadal GCT, mediastinal GCT have been associated with Klinefelter syndrome[91] and hematologic malignancy.[92] Most patients present with disseminated disease.[5] Cisplatin-based treatment regimens have markedly improved the outcome, with more than 50% of patients achieving long-term survival.[81,92] Long-term survival may also be possible in those who undergo a complete surgical resection following chemotherapy.[93] High-dose chemotherapy followed by autologous hematopoietic cell transplantation is now standard therapy for relapsed metastatic disease.[94–96]

Lymphoma

Lymphoma is distinguished from other mediastinal lesions in that management is primarily medical, not surgical. In most series, lymphomas represent between 10% and 20% of mediastinal masses in both adults and children[4–6,59] and are the most common anterior and middle mediastinal masses in children.[97] The categorization of lymphoid malignancies now encompasses nearly 90 distinct entities based on molecular, histologic, and clinical features.[98] For practical purposes, lymphomas may be classified as *non-Hodgkin lymphoma* (NHL) or *Hodgkin lymphoma* (HL). NHL arises most commonly in older adults, whereas HL has a bimodal distribution, arising in adolescents and young adults as well as in those older than 50. Given that lymphoma can involve any organ of the body, there is a broad range of symptoms. Classically, lymphomas present with painless adenopathy (which can include mediastinal adenopathy) accompanied by constitutional symptoms such as fever, weight loss, and fatigue.

The lymphomas that arise specifically in the mediastinum present similarly but have distinct histologic features. Both *primary mediastinal B cell lymphoma* (PMBCL), a rare subset of NHL, and classic nodular sclerosing HL arise from thymic B cell precursors.[99] A B cell lymphoma that exhibits histologic features of both PMBCL and HL is considered a *mediastinal gray zone lymphoma*.[100] These entities affect adolescents and young adults and are more common in females.[101] These lymphomas present as a bulky anterior mediastinal mass involving the thymus (see Fig. 115.4), sometimes with hemorrhage or necrosis on chest CT. Presenting symptoms include dyspnea, cough, and dysphagia due to compression of the trachea; compression of the great vessels may result in pleural and pericardial effusions. For PMBCL, extrathoracic disease, such as supraclavicular adenopathy or lung metastases, is rare on initial presentation but is often a feature of relapsed or refractory disease. SVC syndrome is a common presentation of PMBCL, but less so for HL (Video 115.2 and eFig. 115.2), which can involve the hilar nodes and lung parenchyma.[102] HL is characterized by the Hodgkin/Reed Sternberg cell in a nodular growth pattern with a specific immunophenotype of $CD30^+$, $CD45^-$, and $CD15^+$ in 85% of cases. PMBCL is histologically characterized by an infiltrate of large cells in a diffuse pattern with an immunophenotype of a mature B lymphocyte expressing CD20 but not CD15.

The prognosis of lymphoma in general has improved strikingly in the past two decades with improvements in disease staging, chemoradiotherapy regimens, and a greater understanding of the underlying biology allowing for targeted therapies. HL is curable in approximately 75% of patients, although late toxicities of conventional treatment contribute significantly to late mortality. Despite similarities, it is important to distinguish HL from PMBCL or other

NHL in order to guide therapy; thus tissue biopsy is indicated. The current standard of treatment for early-stage, bulky mediastinal HL is combined modality therapy, consisting of ABVD (doxorubicin, bleomycin, vinblastine, and dacarbazine) and radiation. Optimal therapy for nonbulky mediastinal HL is controversial; clinical trials suggest no difference in overall survival but an increase in risk for disease progression with chemotherapy alone.[103,104] The benefits of radiation therapy must be balanced with the risk for serious late complications, including pulmonary fibrosis, cardiovascular disease, and secondary malignancies such as breast and lung cancer.[100]

As with other B cell lymphomas, the standard regimen for PMBCL includes R-CHOP (rituximab, cyclophosphamide, doxorubicin, vincristine, prednisone)–based regimens, followed by radiation. In spite of high response rates, this standard approach including radiation confers serious long-term toxicities. More recently the regimen of DA-EPOCH-R (dose-adjusted etoposide, prednisone, vincristine, cyclophosphamide, doxorubicin, rituximab) has gained traction as standard front-line therapy, given high event-free survival rates of greater than 85–93% without the need for up-front radiation.[105–107] PET scan, which is often used to restage aggressive lymphomas, appears to have a high negative predictive value and may be useful in determining when to omit radiotherapy after primary chemotherapy.[108,109]

For advanced-stage refractory or relapsed disease (HL, PMBCL, as well as other subtypes of NHL), hematopoietic cell transplantation remains an option. Given that HL and PMBCL tumors have up-regulated immune checkpoint pathways that evade antitumor immune surveillance, the novel immune checkpoint inhibitors, including pembrolizumab, a programmed death-1 blocking antibody, appear to have utility as salvage treatment.[110-112] Genetically modified chimeric antigen receptor T cells targeting CD19 receptors on B cell malignancies is promising cellular-based immunotherapy for refractory B cell lymphomas, including PMBCL.[113]

Thyroid Lesions

In surgical series, ectopic thyroid glands account for fewer than 10% of mediastinal masses but, in clinical practice, they probably represent a higher proportion (see Chapter 128). Thyroid tissue within the mediastinum is of two distinct origins: from the thyroid or from embryonal tissue. Most commonly, a cervical goiter extends substernally into the anterior mediastinum,[114] whereas primary intrathoracic goiter, presumably originating from an embryonic nest of heterotopic thyroid tissue, is rare. Most such goiters are in the anterior mediastinum, but they may arise in the middle or posterior mediastinum as well.[4,5] Intrathoracic goiter presents predominantly in middle-aged or older women. Although it is usually asymptomatic, goiter may cause hoarseness, cough, or swelling of the face and arms. Intrathoracic thyroid tissue is easily recognized by radioactive iodine scanning,[115] as long as the scan is completed before intravenous iodinated contrast injection, which may block iodine uptake for weeks. It may be suspected on the basis of high radiodensity on CT scans, particularly after iodinated contrast injection.[116,117] Treatment is surgical resection.

Parathyroid Lesions

Mediastinal parathyroid tissue accounts for up to 10% of cases of hyperparathyroidism, and the mediastinum is the most common site for ectopic parathyroid adenomas in surgically resistant hyperparathyroidism.[118] Half of ectopic parathyroid adenomas lie in the anterior mediastinum, usually near the thymus (eFig. 115.5). Parathyroid cysts may enlarge sufficiently to appear as a mass on the chest radiograph and to produce symptoms but, in many cases, ectopic tissue may be difficult to locate.[119] Evaluation of the lesion is typically conducted using CT angiography, ultrasound, MRI, and the sensitive 99m-technetium sestamibi scanning.[120] Selective arteriography and venous sampling for parathyroid hormone levels have largely been supplanted by sestamibi radionuclide scanning.[120,121] Parathyroid adenomas are cured by complete resection, and VATS is increasingly utilized.[52] Parathyroid carcinoma may be functional, resulting in varying degrees of hyperparathyroidism, but it is also locally invasive and may metastasize.[122] Cure is possible with aggressive surgical management.[123]

Mesenchymal Tumors

Included in this group of unusual mediastinal masses are lipomas, fibromas, mesotheliomas, and lymphangiomas (see Table 115.2).[4] They arise from connective tissue, fat, smooth muscle, striated muscle, blood vessels, or lymphatic channels and can be found in any region of the mediastinum. Histologically and clinically, they are not substantially different from their counterparts elsewhere in the body. The presence of symptoms usually indicates that the lesion is malignant.[4,15]

Lipoma is the most common mesenchymal tumor of the mediastinum and is most often located in the anterior mediastinum. It may be encapsulated or unencapsulated, appearing as a smooth and rounded lesion with well-defined margins. The characteristic low density of lipomas on CT images (Fig. 115.7) permits a confident diagnosis unless there is associated heterogeneity, invasion of surrounding tissues, or poor demarcation of the mass's perimeter, in which case malignancy (liposarcoma or lipoblastoma) or teratoma must be excluded.[15] Considerably more common than lipoma is mediastinal lipomatosis, or generalized overabundance of histologically normal unencapsulated fat (see Fig. 115.2).[124] Mediastinal lipomatosis appears on the conventional radiograph as a smooth widening or bulging of normal mediastinal contours, and its low homogeneous CT density confirms the diagnosis.[15]

Sarcomas involving the mediastinum are rare but, if present, are likely to be due to nerve sheath sarcoma, spindle cell sarcoma, leiomyosarcoma, or liposarcoma.[125] Prior radiation therapy appears to be a predisposing factor in some cases.[126] Primary mediastinal sarcoma is a rare entity that affects adults; it can present with distant metastases[127] and tends to have an aggressive course.

NUT Carcinoma

Numerous rare neoplasms of the mediastinum have been described in larger case series of mediastinal tumors as well as in isolated case reports.[5,128] In the 1990s, cases of young patients with a highly aggressive squamous cell carcinoma presenting in the mediastinum and other midline

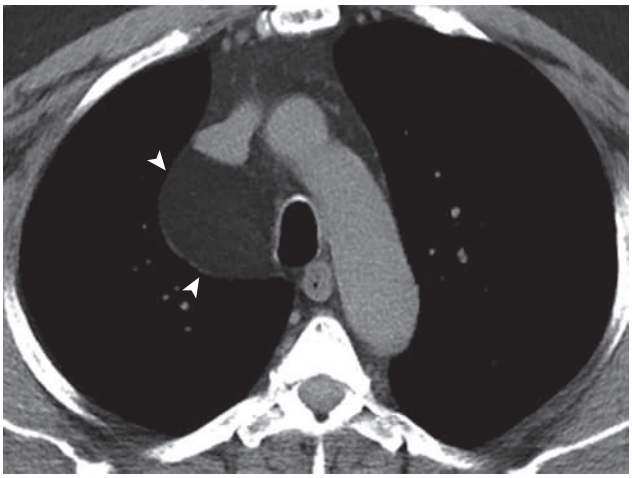

Figure 115.7 *Computed tomography* (CT) of mediastinal lipoma. Axial enhanced chest CT shows a circumscribed, rounded, right paratracheal fat density lesion *(arrows)* typical of lipoma. Note that there is no internal soft tissue or complexity and that the attenuation of the lesion exactly matches that of subcutaneous fat. (Courtesy Michael B. Gotway, MD)

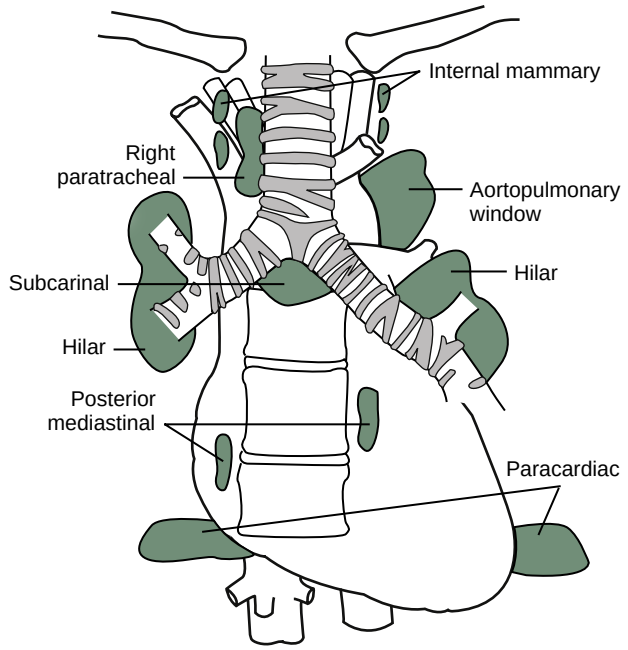

Figure 115.8 Simplified schematic diagram depicting mediastinal lymph node groups. (Modified from McLoud TC, Meyer JE. Mediastinal metastases. *Radiol Clin North Am.* 1982;20:453–468.)

structures were reported; these tumors were found to have t(15;19) translocations, resulting in a *BRD4-NUT* (nuclear protein in testis) fusion oncogene.[129,121] Since these original descriptions, NUT carcinomas have been described outside the thorax. They can present as large masses with local mass effects and distant metastases. Cure is rare.

LESIONS OF THE MIDDLE MEDIASTINUM

Enlargement of Lymph Nodes

Numerous classifications exist for the mediastinal lymph nodes, and this is often most relevant in tumor-node-metastasis staging for non–small cell lung cancer.[130] Figure 115.8 presents a simplified grouping of the main mediastinal nodes that corresponds to findings on chest radiography and CT scans.[131] Most authors consider 1-cm diameter at the short axis to be the upper limit of normal.[16]

Evaluating the mediastinum in the context of staging lung cancer is discussed elsewhere in the textbook (see Chapters 27 and 76). Mediastinal lymph node enlargement is most often due to lymphoma,[132] metastatic cancer,[131] granulomatous inflammation, such as that caused by sarcoidosis, or infection. Infection should be considered when the adenopathy is associated with a pulmonary opacity. Tuberculosis is a notable cause of mediastinal adenopathy that can mimic sarcoidosis or malignancy and should be suspected in a host with known tuberculosis risk factors.[133] Fungal infections that cause granulomas, particularly histoplasmosis, may present with mediastinal and hilar adenopathy in the absence of a pulmonary opacity.[134]

Numerous less-common causes of mediastinal adenopathy are described, including angiofollicular lymphoid hyperplasia (Castleman disease). Mediastinal adenopathy is common in HIV-infected patients and is usually caused by infection, although adenopathy may also be caused by lymphoma, Kaposi sarcoma, and other noninfectious processes.[135]

Ongoing inflammation from prior exposure to histoplasma or tuberculous components can lead to aggregation of caseous lymph nodes into a mass-like lesion called *mediastinal granuloma* (see Fig. 116.6). These can exhibit characteristic calcifications and can drain via fistulization into other organs such as the esophagus (Fig. 116.7). They can compress adjacent tissues but do not invade them. Mediastinal granuloma is not treated with antibiotics but can be drained via VATS if symptomatic. For a full discussion of this entity and related entities such as fibrosing mediastinitis and mediastinal adenitis, see Chapter 116.

Developmental Cysts

Developmental cysts of various sorts comprise 10–20% of all mediastinal masses.[4,136] Most can be identified as bronchogenic, enteric, or pericardial.[4] Bronchogenic and enteric cysts are often referred to as *foregut duplication cysts* because of their origin from aberrant portions of the ventral and dorsal foregut, respectively.

Bronchogenic cysts are found near large airways, often just posterior to the carina (Fig. 115.9), although they may be attached to the esophagus or even lie inside the pericardial space.[4] The cyst wall often contains cartilage and respiratory epithelium. Most are discovered incidentally and cause no symptoms. However, bronchogenic cysts may communicate with the tracheobronchial tree and become infected[137]; enlarge sufficiently to cause local effects including airway obstruction,[138] pulmonary artery compression,[139] or hemodynamic collapse[140]; or rupture.[141]

Enteric cysts are similar in location and appearance to bronchogenic cysts but have digestive tract epithelium. They are relatively uncommon in adults but are the most common cysts found in infants and children, in whom they may be associated with spinal extension and malformations

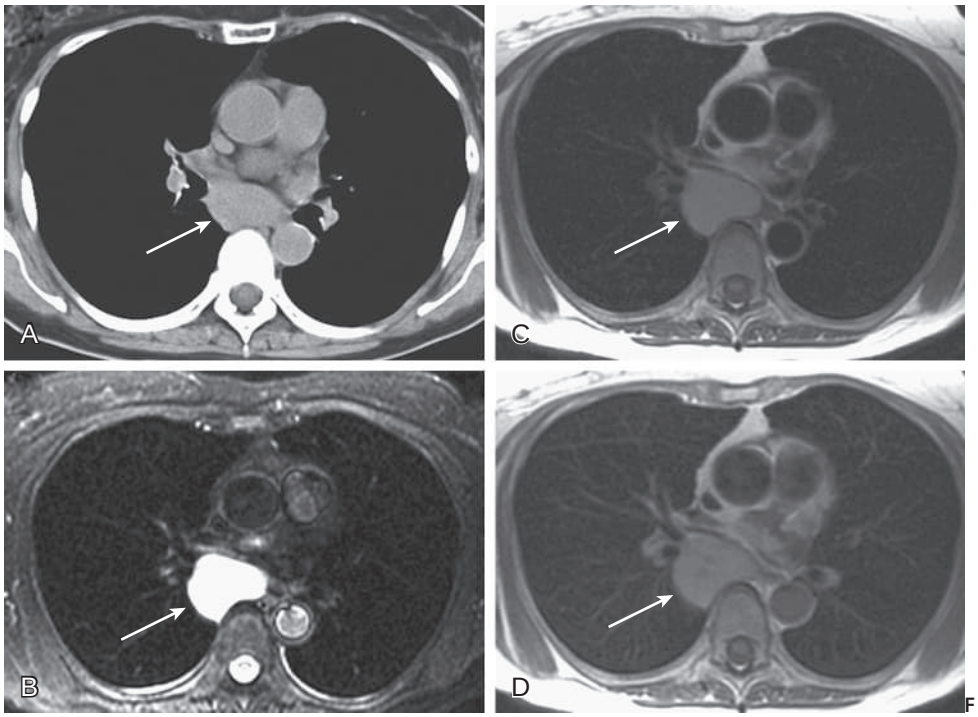

Figure 115.9 Bronchogenic cyst. Axial unenhanced chest computed tomography (A) shows a mildly hyperattenuating structure *(arrow)* in the subcarinal space. Axial triple inversion-recovery magnetic resonance imaging (B) and axial unenhanced double inversion-recovery (DIR) image (C) show the same lesion *(arrows).* Note the very high signal on the fluid-sensitive triple inversion-recovery image (B), consistent with fluid, and the mildly increased signal on the unenhanced DIR image (C), consistent with proteinaceous or hemorrhagic fluid; the latter mechanism also accounts for the hyperattenuating appearance on computed tomography. Enhanced DIR magnetic resonance imaging (D) shows no enhancement of the lesion *(arrow)* following intravenous gadolinium administration, typical of a foregut duplication cyst. (Courtesy Michael B. Gotway, MD.)

of the vertebral column (called *neurenteric cysts*). Enteric cysts can occasionally be multiple and associated with duplications of other portions of the gastrointestinal tract.

Pericardial cysts account for about one-third of cystic masses in adults but are much less common in children. They lie against the pericardium, diaphragm, or anterior chest wall in the right cardiophrenic angle. Rarely, pericardial cysts may communicate with the pericardial space. Although typically harmless, pericardial cysts may enlarge enough to cause right ventricular outflow obstruction,[142] or they may rupture and hemorrhage to cause pericardial tamponade[143] or sudden cardiac death.[144]

These developmental cysts are usually identified by CT (see Fig. 115.9A) or ultrasonography, and the diagnosis may be confirmed by aspiration cytology. MRI is valuable for confirming the cystic nature of these lesions (see Fig. 115.9B–D). Pericardial cysts can be monitored with serial imaging and need not be resected unless they cause symptoms. Bronchogenic cysts can also be followed conservatively if asymptomatic[145]; however, most authorities favor resection for purposes of diagnosis and to reduce the potential for complications.[137,141] Alternatives to thoracotomy include therapeutic aspiration[146,147] and thoracoscopic or mediastinoscopic excision.[53,148,149]

LESIONS OF THE POSTERIOR MEDIASTINUM

Neurogenic Tumors

The vast majority of tumors in the posterior mediastinum represent neoplasms arising from neural tissues,[4,5] historically accounting for about 20% of adult cases and twice that proportion in children. Neurogenic tumors appear radiographically as a unilateral paravertebral mass.[4,150,151] Clinical manifestations include chest pain from nerve or bone erosion, dyspnea secondary to tracheal compression, and neurologic deficits resulting from spinal cord compression by intraspinal tumor extension. In addition, many neurogenic tumors are hormonally active. MRI is usually indicated when there is suspicion for a neurogenic lesion. Although most neurogenic tumors are benign, surgical resection is indicated to alleviate local symptoms from mass effects of the tumor. Neurogenic tumors are classified by site of origin: nerves and their sheaths, sympathetic ganglia, or paraganglionic tissue (Table 115.3).

Arising from nerves and their sheaths, neurofibromas are the most common tumor of this group. They are incompletely encapsulated and may grow quite large, producing symptoms by compression of nerves or other structures. Mediastinal neurofibroma may be one manifestation of neurofibromatosis. As with these tumors found elsewhere in the body, neurofibromas may eventually transform into malignant neurosarcoma in 10–15% of patients.[5]

Arising from the neural sheath itself, schwannoma (neurilemoma) (Videos 115.12A–B and eFig. 115.43) is most often seen in the third to fifth decades of life. Schwannoma usually causes no symptoms and appears as a well-circumscribed, homogeneous density on chest radiography (Fig. 115.10A).[4,5] Schwannomas are always completely encapsulated and do not invade surrounding tissues, although they may extend into intervertebral foramina (Fig.

115.10B–C). Malignant tumors of nerve sheath origin are also known as malignant neurofibroma, malignant schwannoma, or neurogenic fibrosarcoma. These tumors behave aggressively, with both local invasion and distant metastasis. Half arise in patients with neurofibromatosis.[13] Treatment requires wide excision and usually adjuvant radiation.[13]

Arising from sympathetic ganglia, tumors generally affect children and display a spectrum of neoplastic behavior. Ganglioneuromas are benign and cause symptoms merely by mass effect. Ganglioneuroblastomas are malignant, have intermediate behavior, and can invade locally but are less likely to metastasize.[5] Neuroblastoma rapidly displaces and invades adjacent structures and may be widely metastatic at the time of presentation.[152,153] These tumors often elaborate endocrine peptides and catecholamines that cause diarrhea, fever, anorexia, and weight loss.[4] The propensity to produce catecholamines is used to advantage by promoting tumor uptake of the catecholamine precursor ^{123}I- or ^{131}I-meta-iodobenzylguanidine scintigraphy for purposes of diagnosis, identification of distant tumor metastases, and treatment.[154,155] Treatment of neuroblastoma involves using escalating multimodality therapy strategies based on the risk for disease progression.[156]

Arising from paraganglionic or chemoreceptor tissue, neoplasms include pheochromocytomas, which are found rarely in the mediastinum and are indistinguishable clinically and histologically from their counterparts in the abdomen, and paragangliomas (chemodectomas).

Table 115.3 Neurogenic Tumors of the Mediastinum

NEOPLASMS ARISING FROM PERIPHERAL NERVES
Neurofibroma
Schwannoma (neurilemoma)
Neurosarcoma
NEOPLASMS ARISING FROM SYMPATHETIC GANGLIA
Ganglioneuroma
Ganglioneuroblastoma
Neuroblastoma
NEOPLASMS ARISING FROM PARAGANGLIONIC TISSUE
Paraganglioma (pheochromocytoma-like)
Paraganglioma (chemodectoma)

Paragangliomas may secrete catecholamines just as do pheochromocytomas and thus may also be detected and perhaps treated with I-meta-iodobenzylguanidine.[157] They appear benign under the microscope and seldom metastasize but spread locally in an aggressive fashion and thus have high morbidity and mortality rates.[4]

MISCELLANEOUS MEDIASTINAL MASSES

Benign Lesions

Pancreatic pseudocysts may extend into the mediastinum, usually through the aortic or esophageal hiatus,[5,158,159] and have been reported in all three mediastinal compartments. Hydatid cysts also arise rarely in the mediastinum.[5] The posterior mediastinum is occasionally the site of a thoracic duct cyst.[4,59] Also, extramedullary hematopoiesis (Video 115.13 and eFigs. 115.44 and 115.45) in patients with chronic hemolytic anemia or myelofibrosis may appear as a mediastinal mass, often in a posterior location. Meningoceles, outgrowths of the spinal meninges that protrude along the course of a spinal nerve, can produce posterior mediastinal masses.

Vascular Masses and Enlargements

Although not technically masses, a variety of vascular lesions must be considered in the differential diagnosis of a mediastinal mass seen on the chest radiograph.[5,60] These include poststenotic aortic dilation, aneurysms (Video 115.14 and eFig. 115.46) or tortuosity of the aorta and great vessels, aortic coarctation, innominate vein and SVC aneurysm, persistent left vena cava, azygos (Video 115.15 and eFig. 115.48) and hemiazygos vein enlargement, anomalous pulmonary venous return, pulmonary venous varix, and varices associated with portal hypertension (eFig. 115.49).[160,161] Idiopathic dilation of the pulmonary trunk and pulmonary arterial hypertension of any cause may appear as a mediastinal mass, and traumatic aortic transection or more subtle vascular injuries may result in mediastinal hematoma.

Angiography has been the traditional means of diagnosing mediastinal masses of vascular origin, but now CT imaging with intravenous contrast provides a more convenient diagnosis.[162,163] MRI may permit definitive diagnosis without radiation or contrast exposure.

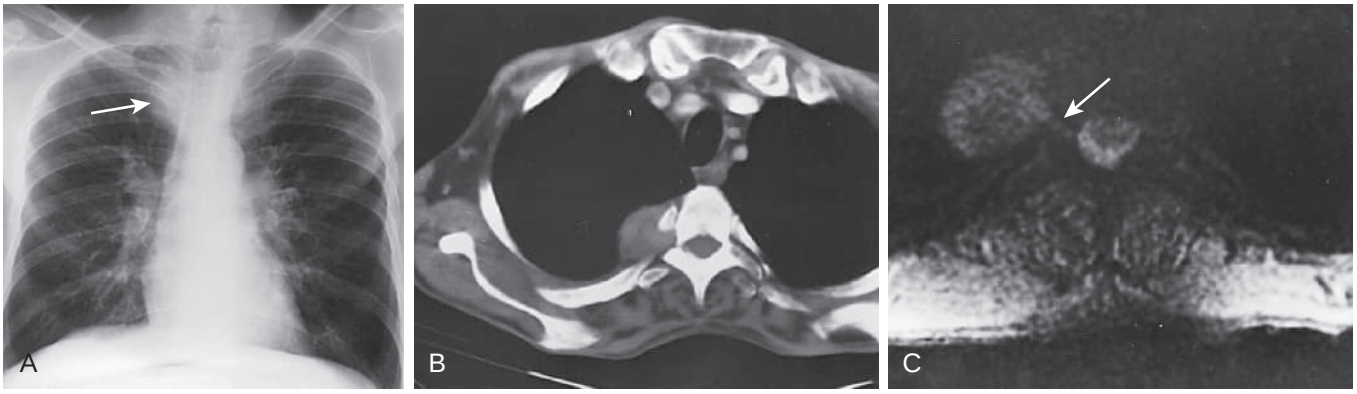

Figure 115.10 Series of imaging studies of a 64-year-old asymptomatic man with a surgically proved schwannoma (neurilemoma). (A) Frontal chest radiograph showing an incidental finding of a discrete mass behind the right clavicular head *(arrow)*. (B) Axial chest computed tomography showing homogeneous, well-circumscribed appearance and posterior location adjacent to the vertebral column. (C) Magnetic resonance image showing extension of the tumor into the intervertebral foramen *(arrow)*.

Diaphragmatic Hernia

Omental fat (Video 115.16 and eFig. 115.50; also Video 115.6 and eFig. 115.12) or other abdominal contents may protrude through the diaphragm via several potential routes, producing mediastinal mass lesions in any compartment.[15] A hernia through the foramen of Morgagni (eFig. 115.50) produces a cardiophrenic angle mass, usually on the right side in the anterior mediastinum. Bochdalek hernia (eFig. 115.51), in the posterior mediastinum, generally appears on the left side, presumably because the liver prevents herniation on the right. Herniation of fat around the esophagus is believed to precede hiatal hernia formation; either may appear as a mediastinal mass on chest radiography. Fine linear opacities are often demonstrable in diaphragmatic fat herniations on CT imaging. These are thought to represent omental vessels within the hernia, and they may help differentiate a hernia from a lipoma.[15]

GENERAL APPROACH TO A MEDIASTINAL MASS

INITIAL EVALUATION

With the advent of advanced imaging techniques such as CT, MRI, and nuclear imaging, the evaluation of a mediastinal mass is best made in a multidisciplinary setting involving the pulmonologist or internist, a radiologist, and a thoracic surgeon. The differential diagnosis of a mediastinal mass depends significantly on patient demographics, the presence of clinical symptoms, as well as the anatomic location, size, and morphology. For a mediastinal mass found incidentally, the primary concern for a clinician is to determine whether it is benign or malignant and, if benign, whether it has the potential to cause local symptoms. At a minimum, a chest CT scan with contrast should be obtained to evaluate any mediastinal mass detected by conventional radiography. This narrows the differential diagnosis and suggests further imaging or a diagnostic and/or therapeutic procedure. A stable appearance, in comparison to older films, can obviate the need for further investigation in selected patients. A few benign lesions in the mediastinum can be diagnosed with confidence based on clinical information and CT scan appearance; these include vascular lesions, extramedullary hematopoiesis, pericardial and developmental cysts, and mediastinal lipomatosis. Suspected mediastinal thyroid tissue can be confirmed by radioactive iodine scans.

SURGICAL MANAGEMENT

In most cases the optimal diagnostic and therapeutic maneuver is surgical resection of the mass.[164] The decision to perform a biopsy versus resection is thus based on the presumptive diagnosis based on the imaging characteristics. A suggested approach for evaluation is shown in Figure 115.11.

In the anterior mediastinum, well-encapsulated lesions are resected, whereas biopsy will be performed in those situations where there is a high degree of suspicion for lymphoma. Biopsy is also preferred for locally invasive or frankly unresectable anterior mediastinal lesions. Cervical mediastinoscopy is less useful for anterior mediastinal masses because the anterior mediastinal mass is not

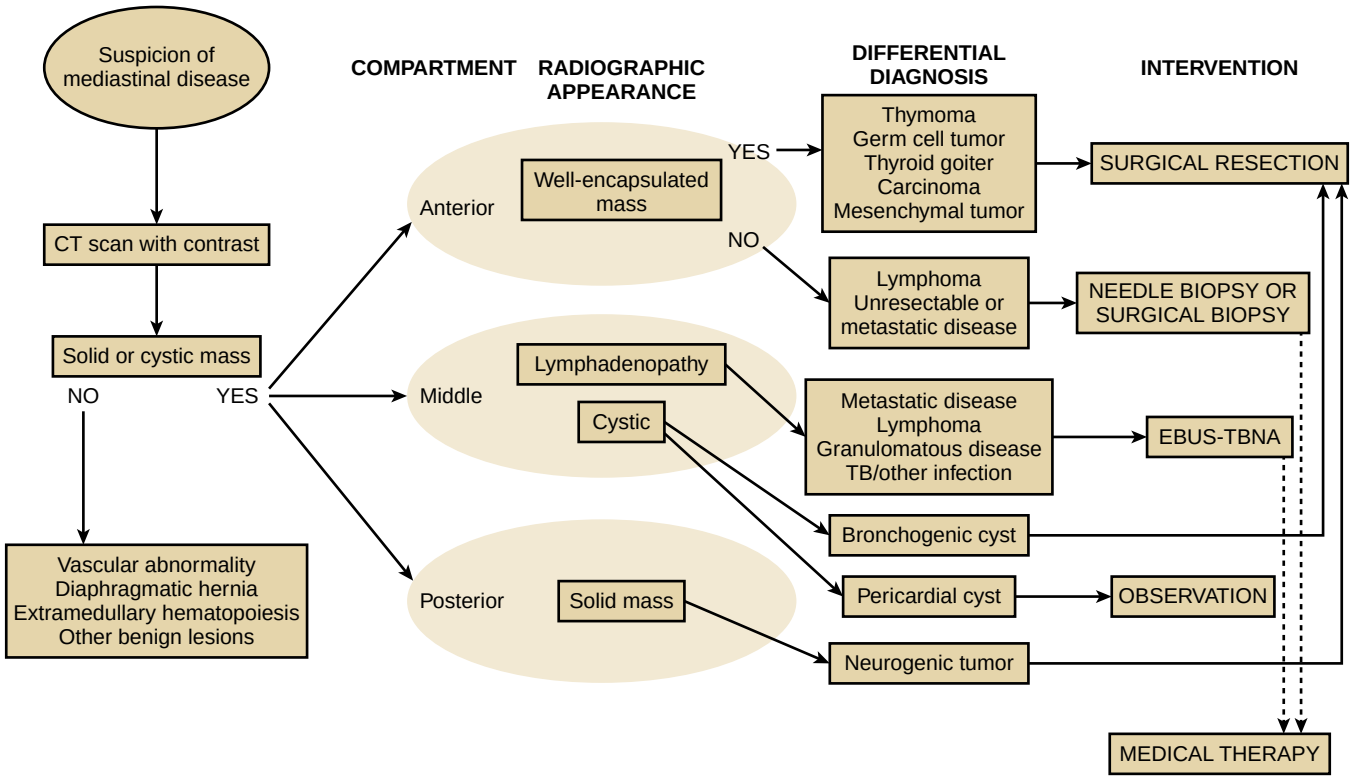

Figure 115.11 Suggested algorithm for the diagnostic approach to mediastinal masses. CT, computed tomography; EBUS-TBNA, endobronchial ultrasound-guided transbronchial needle aspiration; TB, tuberculosis.

near the pretracheal plane used by the mediastinoscope. Interventions by VATS are generally reserved for those lesions amenable to resection. Definitive resection of anterior mediastinal masses can be performed by VATS, median sternotomy, or a transcervical approach (e.g., Cooper thymectomy). A robotic VATS approach offers the advantage of increased instrument maneuverability and visualization and has gained in popularity in recent years for resection of anterior mediastinal masses.[165–167]

In the middle mediastinum, the majority of masses in adults are malignant, the most common being lymphoma or metastatic disease. Hence, for lesions in the middle mediastinum, biopsy is the typical initial approach. Biopsy can be performed by either CT-guided needle techniques, EBUS or EUS-TBNA, or by mediastinoscopy or VATS. Given the proven sensitivity and negative predictive value of EBUS–TBNA, this is the preferred sampling option. When benign-appearing cystic lesions are found by diagnostic imaging, the lesions are removed by either VATS or open thoracotomy.

In the posterior mediastinum, most lesions are resected either with a VATS or thoracotomy approach. A thoracotomy is preferred if there is any suggestion of malignancy (to ensure free resection margins), size greater than 5 cm, or presence of inflammation or infection that can obscure dissection planes. Surgical experience plays a large part in determining the technique utilized for intervention.

Key Points

- The mediastinum, which contains thoracic viscera in the center of the chest, can be divided into three main compartments based on anatomic boundaries seen on axial images of chest computed tomography.
- The majority of all mediastinal masses are benign. However, when symptomatic, a mediastinal mass is more likely to be malignant.
- The most common masses in the anterior or prevascular compartment include thymomas, thyroid tumors, germ cell tumors, and lymphoma.
- The most common masses in the middle or visceral compartment include lymphadenopathy and benign developmental cysts. Isolated mediastinal adenopathy may represent sarcoidosis, tuberculosis, lymphoma, lung cancer, inflammatory lymphadenopathy, or metastatic disease from an extrathoracic malignancy.
- The posterior or paravertebral compartment includes mainly neurogenic tumors.
- Computed tomographic imaging is typically used for initial diagnostic evaluation; however, magnetic resonance and nuclear imaging tests improve the specificity of diagnosis in certain cases.
- Most mediastinal tumors and cysts should be surgically removed due to the potential for malignancy and for local compressive and invasive effects on adjacent vital structures.

Acknowledgments

We acknowledge the contributions of David J. Pierson, MD, who wrote this chapter for the first and second editions and coauthored the third edition, and David R. Park, MD, who coauthored the third through sixth editions.

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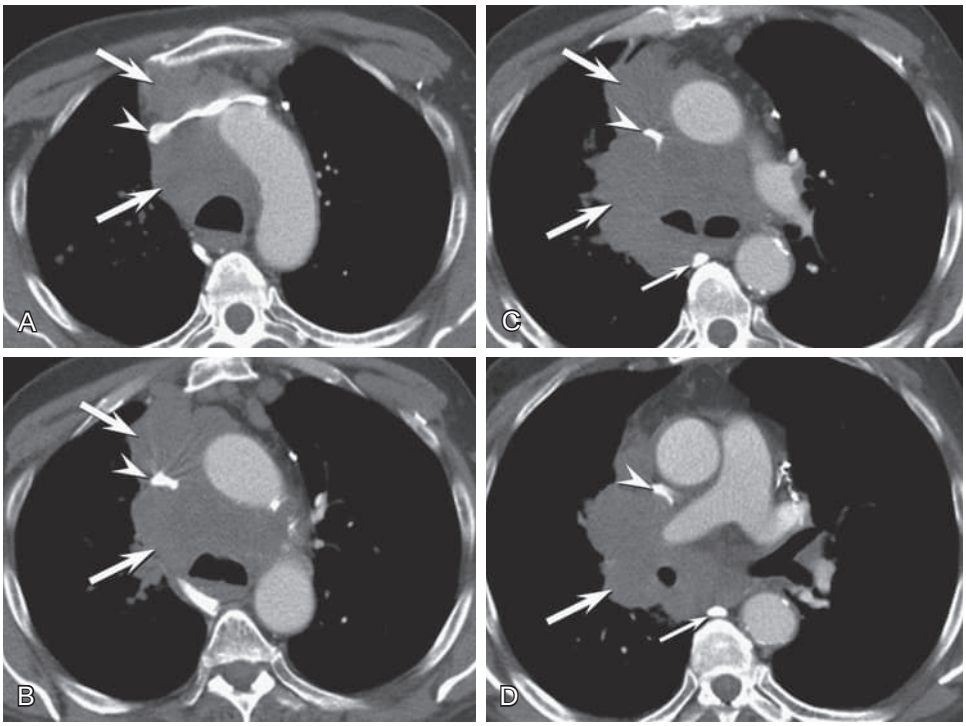
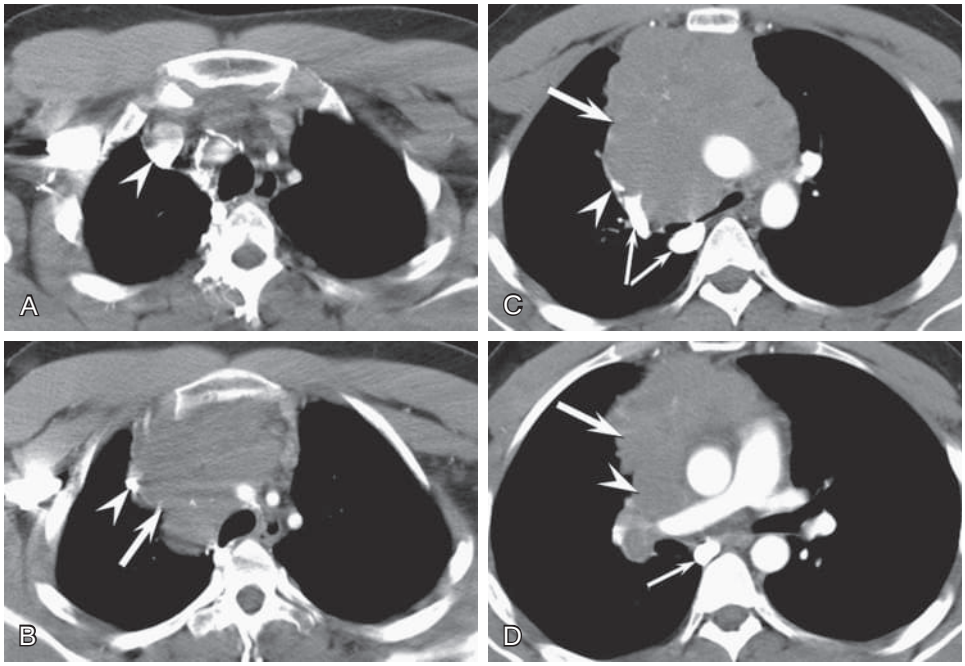
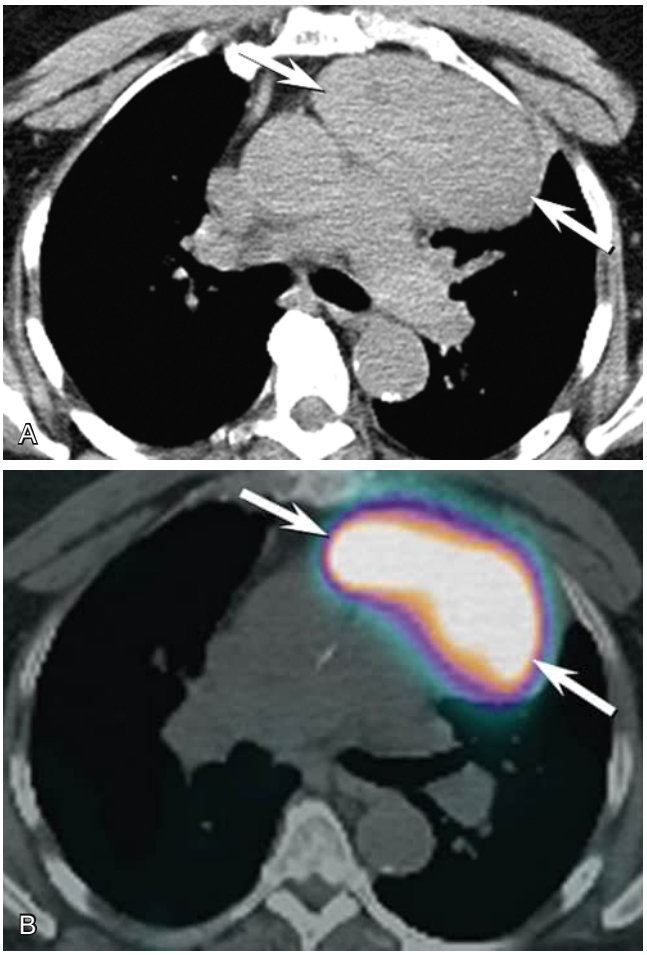
Additional figures and videos, along with the complete reference list, are available at ExpertConsult.com.



eFigure 115.1 Superior vena cava syndrome due to bronchogenic carcinoma. Axial contrast-enhanced chest computed tomography in a patient with bronchogenic carcinoma and superior vena cava syndrome shows a confluent mediastinal mass *(arrows)* occupying the anterior and middle mediastinum, compressing the superior vena cava *(arrowheads),* resulting in collateral circulation through the azygos vein *(small arrow)*. See Video 115.1 for the full study. (Courtesy Michael B. Gotway, MD.)



eFigure 115.2 Superior vena cava syndrome due to lymphoma. Axial contrast-enhanced chest computed tomography in a patient with lymphoma and superior vena cava syndrome shows a confluent mediastinal mass (*arrows*, B–C) occupying the anterior and middle mediastinum, compressing the SVC (*arrowheads*, C–D), resulting in collateral circulation through the azygos vein *(small arrows)*. The caudal superior vena cava is occluded (*arrowhead* in D). The *arrowheads* in A and B show the enhanced right brachiocephalic vein, distended in A, and compressed and laterally displaced adjacent to the mediastinal mass in B. See Video 115.2 for the full study. (Courtesy Michael B. Gotway, MD.)



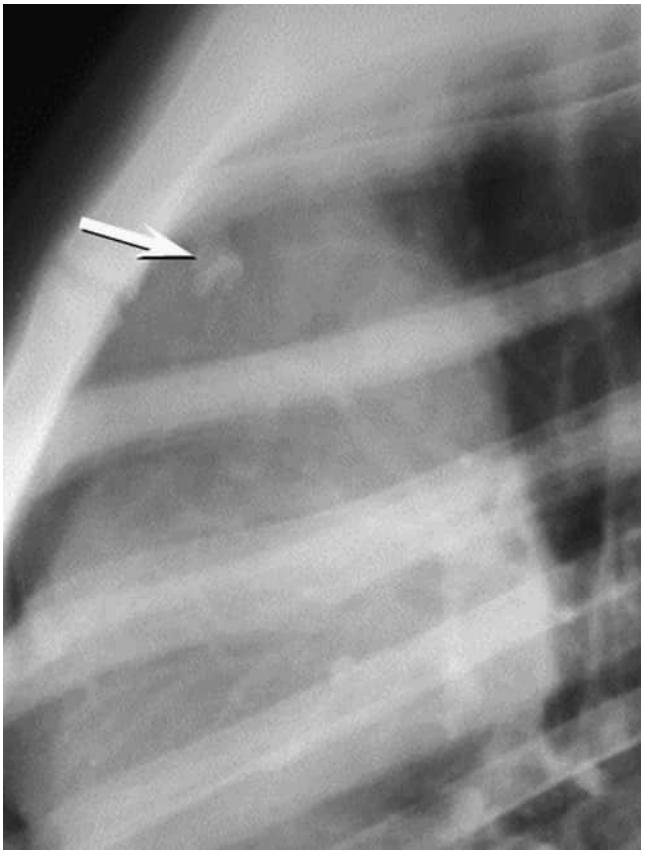
eFigure 115.3 Anterior mediastinal mass due to thymic carcinoma. Axial unenhanced chest computed tomography (A) and fused ^{18}F-fluorodeoxyglucose positron emission tomography image (B) in a patient with Cushing syndrome shows an anterior mediastinal mass *(arrows)* in a patient with thymic neuroendocrine malignancy (e.g., thymic carcinoma). (Courtesy Michael B. Gotway, MD.)



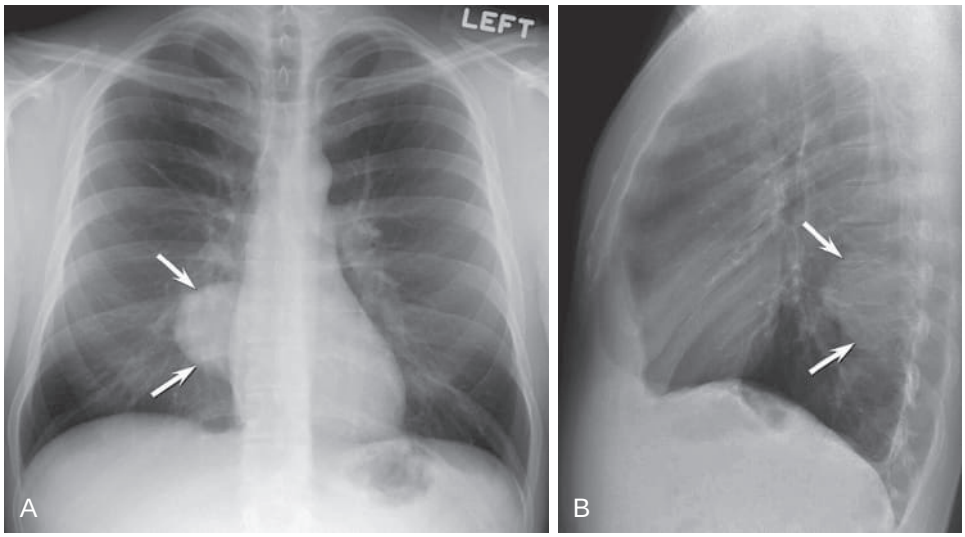
eFigure 115.4 Anterior mediastinal mass due to thymoma. Axial enhanced chest computed tomography in a patient with myasthenia gravis shows an anterior mediastinal mass *(arrow)* representing thymoma. See Video 115.3 for the full study. (Courtesy Michael B. Gotway, MD.)



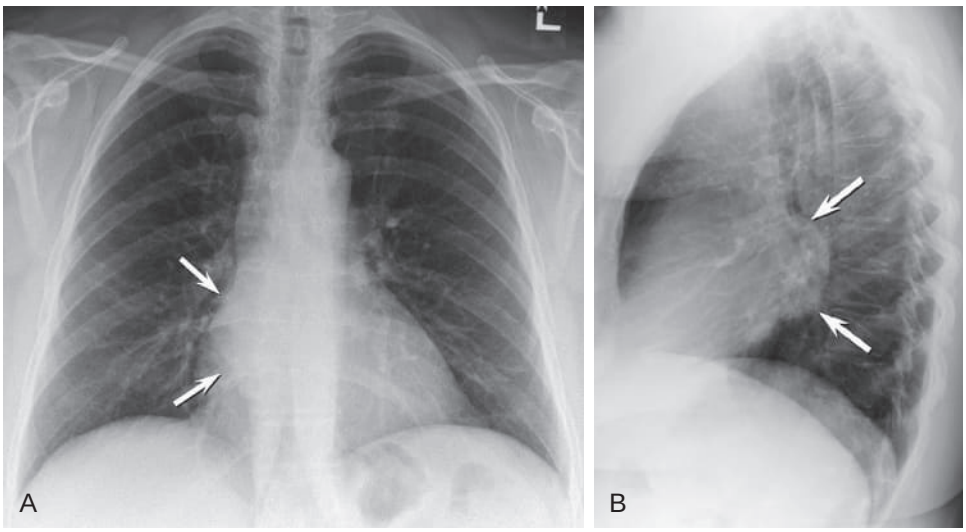
eFigure 115.5 Anterior mediastinal mass due to ectopic parathyroid adenoma. Axial enhanced chest computed tomography in a patient with recurrent hyperparathyroidism following previous parathyroidectomy shows an intensely enhancing anterior mediastinal mass *(arrows)* representing an ectopic parathyroid adenoma. (Courtesy Michael B. Gotway, MD.)



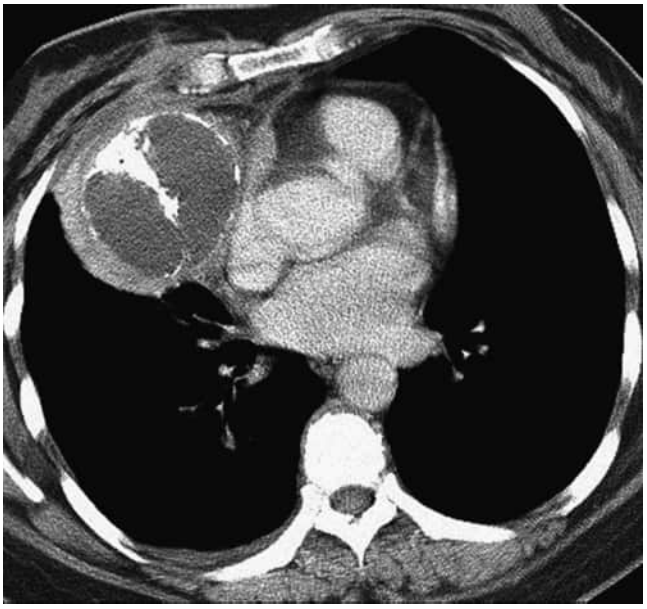
eFigure 115.6 Anterior mediastinal mass due to teratoma. Detail lateral chest radiograph in a patient with teratoma shows a tooth *(arrow)* in the anterior mediastinum. (Courtesy Michael B. Gotway, MD.)



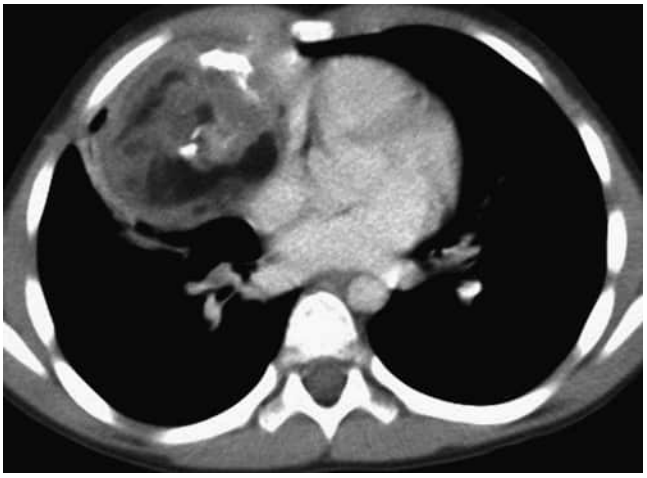
eFigure 115.7 Posterior mediastinal mass due to a neurogenic neoplasm. Frontal (A) and lateral (B) chest radiographs show a circumscribed right-sided mass *(arrows)*. On the frontal projection (A), note the interface between the mass with the mediastinum—the lesion has significant contact with the mediastinum, evidenced by the lack of visualization of the medial border of the lesion. The appearance is consistent with a posterior mediastinal lesion. The lateral radiograph (B) shows the lesion *(arrows)* projected over the spine, also indicative of a posterior mediastinal location. (Courtesy Michael B. Gotway, MD.)



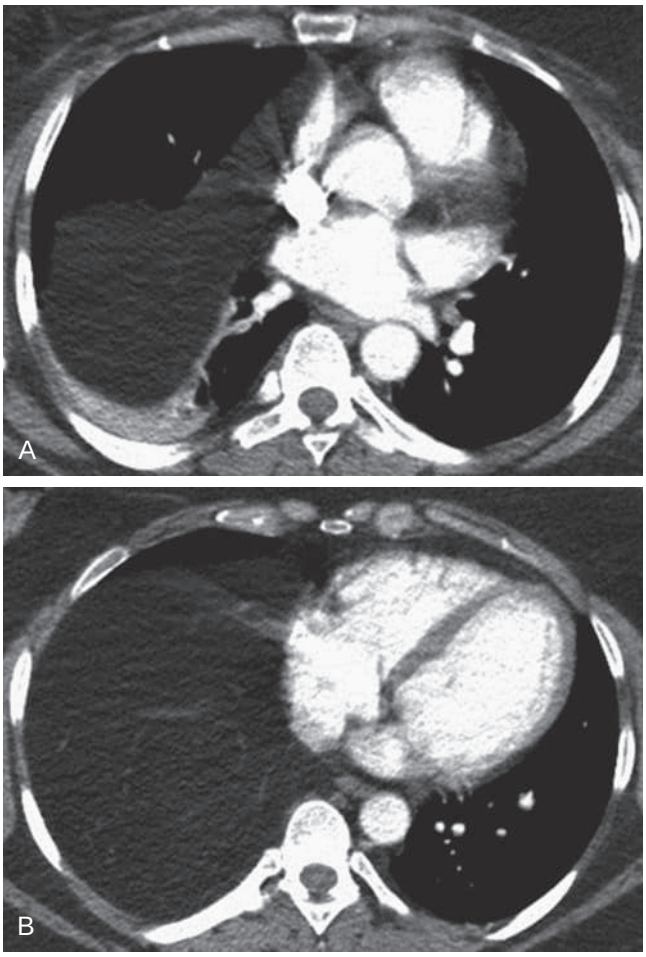
eFigure 115.8 Middle mediastinal mass due to a bronchogenic cyst. Frontal (A) and lateral (B) chest radiographs show a circumscribed right-sided mediastinal mass *(arrows)*. The lateral projection (B) shows the mass is related to the subcarinal space—the most common location for mediastinal bronchogenic cysts. (Courtesy Michael B. Gotway, MD.)



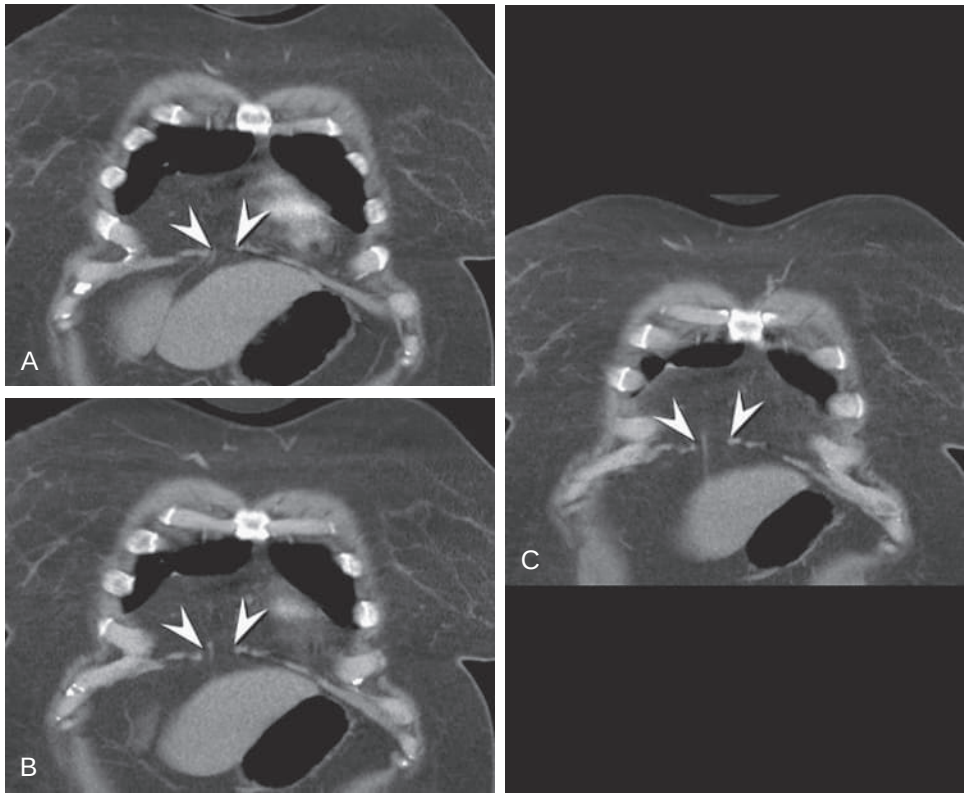
eFigure 115.9 Anterior mediastinal mass due to teratoma. Axial enhanced chest computed tomography in a patient with an anterior mediastinal teratoma shows the excellent visualization of calcium within the lesion. (Courtesy Michael B. Gotway, MD.)



eFigure 115.10 Anterior mediastinal mass due to teratoma. Axial enhanced chest computed tomography in a patient with an anterior mediastinal teratoma shows the excellent visualization of low-attenuation fat and hyperattenuating calcium within the lesion. See Video 115.4 for the full study. (Courtesy Michael B. Gotway, MD.)



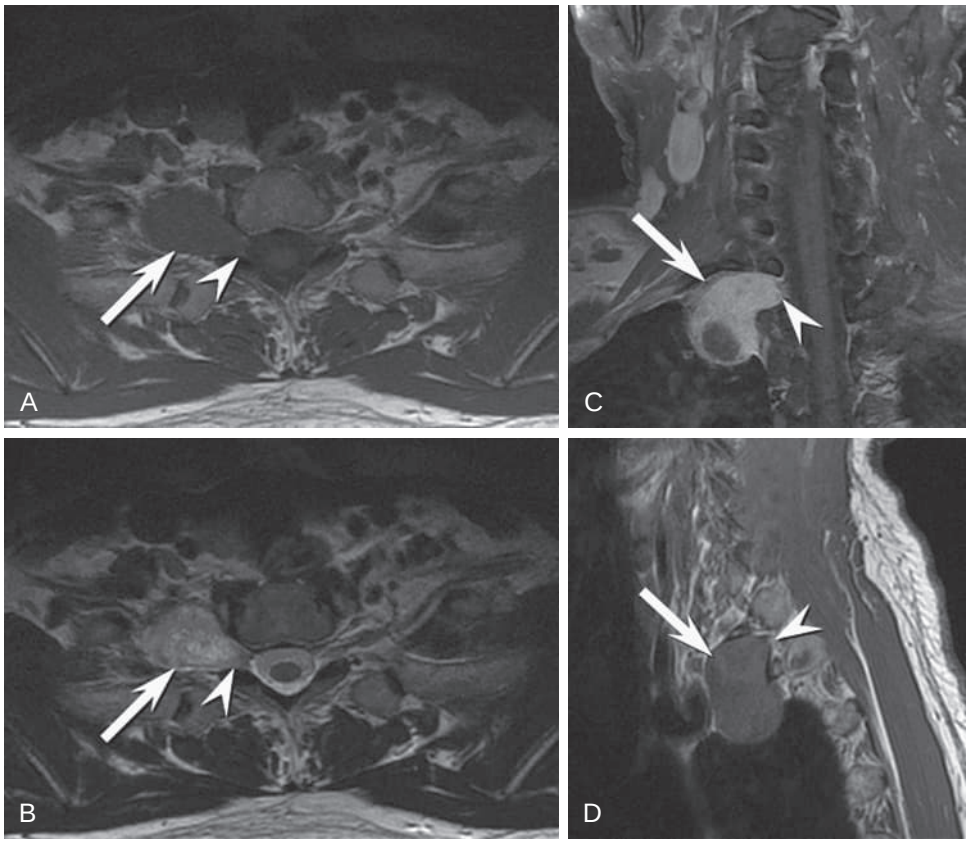
eFigure 115.11 Thymolipoma. Axial enhanced chest computed tomography through the mid (A) and lower (B) thorax shows a fatty mass occupying the right mediastinum. See Video 115.5 for the full study. (Courtesy Michael B. Gotway, MD.)



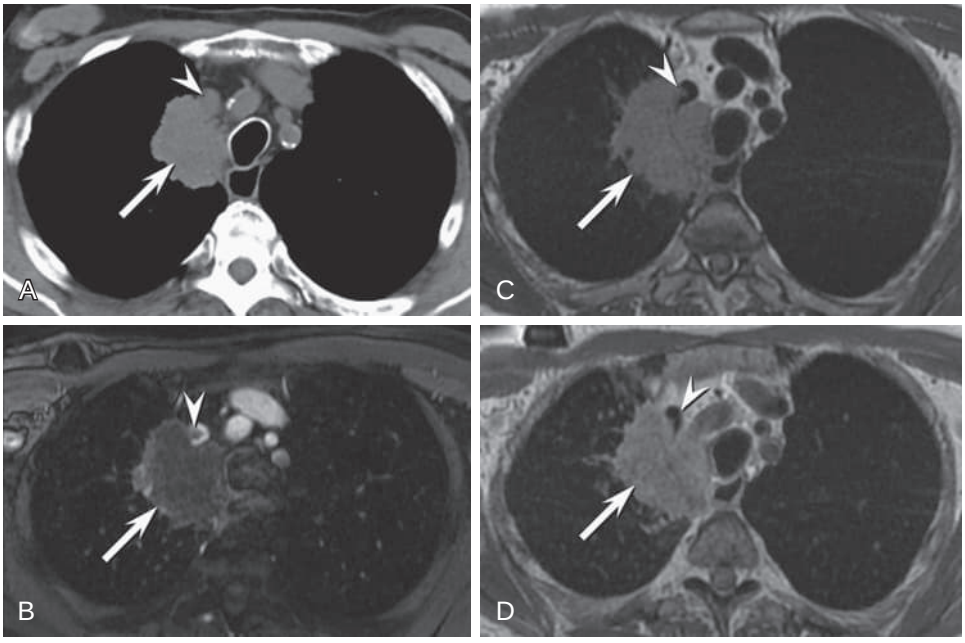
eFigure 115.12 Omental fat hernia due to foramen of Morgagni hernia. Coronal enhanced chest computed tomography through the anterior thorax shows a fatty mass occupying the right mediastinum, arising from the abdomen and extending through a diaphragmatic defect *(arrowheads)* into the thorax. A vessel accompanying the fat herniation is clearly visible in C. See Video 115.6 full the full study. (Courtesy Michael B. Gotway, MD.)



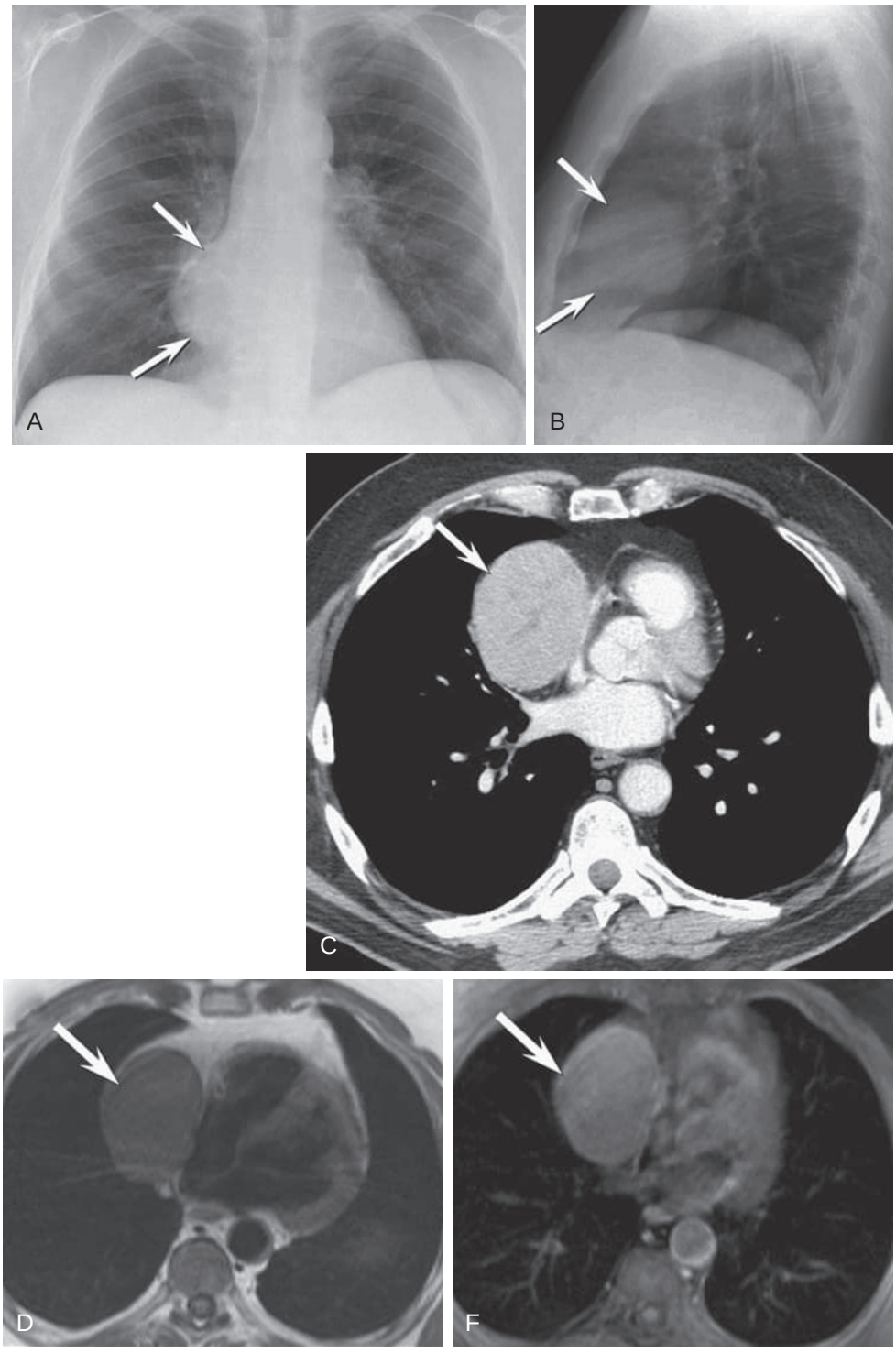
eFigure 115.13 Anterior mediastinal mass due to lymphadenopathy caused by breast cancer. Axial enhanced chest computed tomography in a patient with breast cancer shows left internal mammary lymphadenopathy. (Courtesy Michael B. Gotway, MD.)



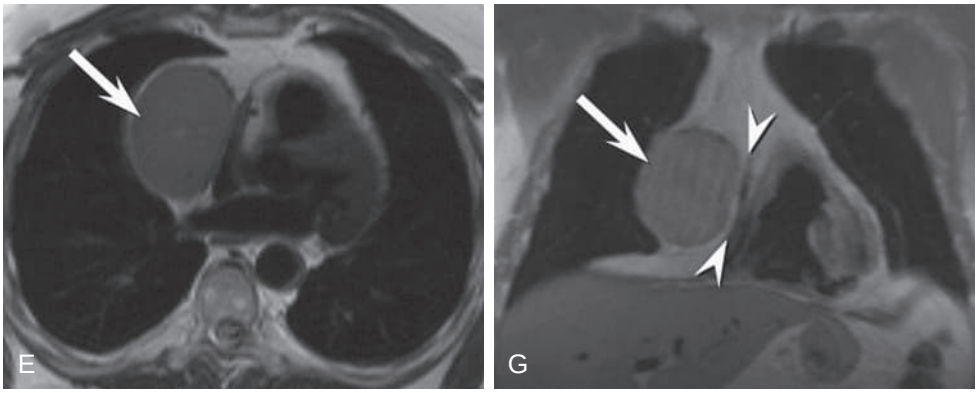
eFigure 115.14 Neurogenic tumor on magnetic resonance imaging. Axial thoracic T1-weighted (A), T2-weighted (B), coronal enhanced T1-weighted (C), and sagittal unenhanced T1-weighted (D) magnetic resonance images show a neurogenic tumor *(arrows)*. Note the tumor extension from the neural foramen *(arrowheads)*. The lesion shows increased signal on T2-weighted images (B) and intense contrast enhancement (C). (Courtesy Michael B. Gotway, MD.)



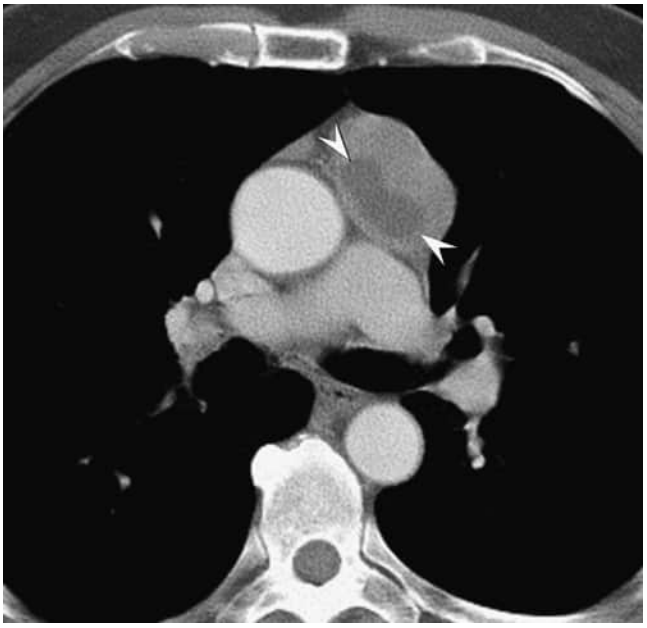
eFigure 115.15 Utility of magnetic resonance imaging for determining mediastinal involvement in bronchogenic malignancy. (A) Axial unenhanced chest computed tomography shows a medial right upper lobe bronchogenic malignancy (*arrow*) with extensive contact with the mediastinum, especially the right brachiocephalic vein (*arrowhead*). (B) Axial thoracic steady-state free precession, unenhanced (C) and enhanced (D) T1-weighted magnetic resonance imaging shows extension of the neoplasm (*arrows*, B–D) into the mediastinal fat with invasion of the right brachiocephalic vein, evidenced by the small intravascular nodule (*arrowheads*, B–D). See Video 115.8 for the full study of part B. (Courtesy Michael B. Gotway, MD.)



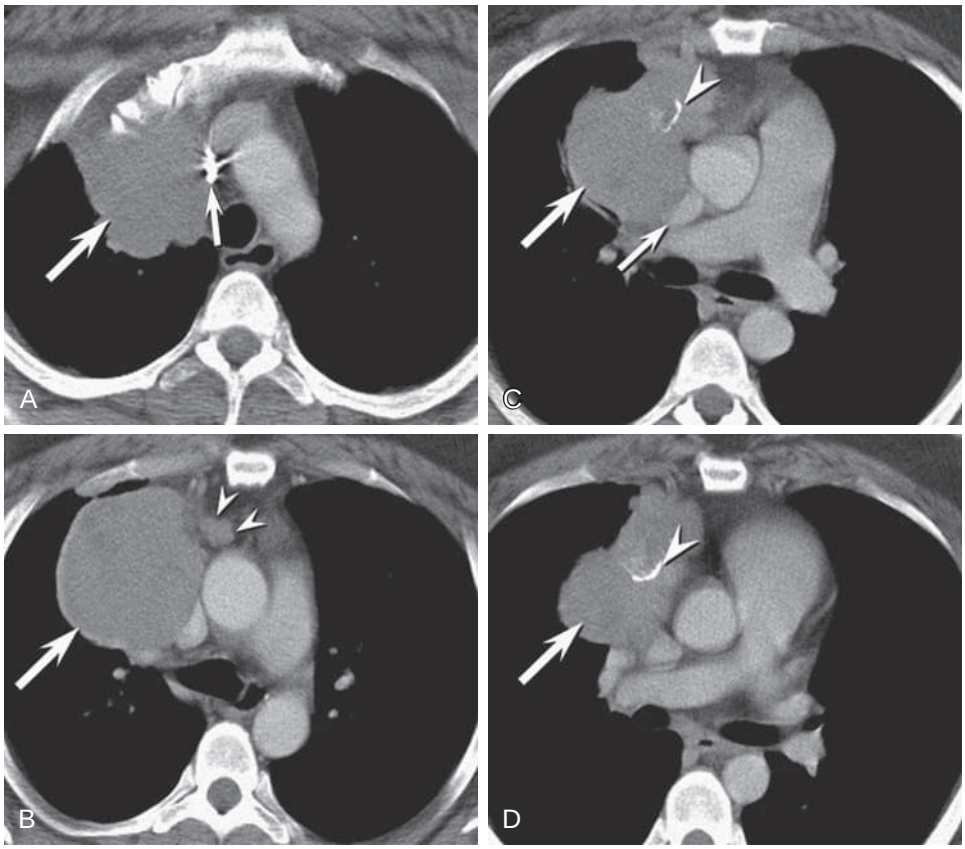
eFigure 115.16 Typical appearance of thymoma at thoracic imaging. Frontal (A) and lateral (B) chest radiographs show a smoothly circumscribed mediastinal mass (*arrows*) at the level of the junction of the heart and great vessels. The obscuration of the right heart border on the frontal projection (A) and the presence of the mass overlying the heart on the lateral projection (B) indicates that the mass is adjacent to the heart. (C) Axial enhanced chest computed tomography shows the smoothly circumscribed, enhancing mediastinal mass (*arrow*). Axial T1-weighted (D), T2-weighted (E), enhanced, fat saturation T1-weighted (F), and coronal T1-weighted (G) images show the mediastinal lesion (*arrows*) to advantage. In particular, the indolent nature of the mass, evidenced by the maintained fat plane between the mass and pericardium (*arrowheads*, G) is well shown. The lesion shows intermediate-to-slightly-decreased signal on T2-weighted imaging (E), consistent with the cellular nature of the neoplasm. (Courtesy Michael B. Gotway, MD.)



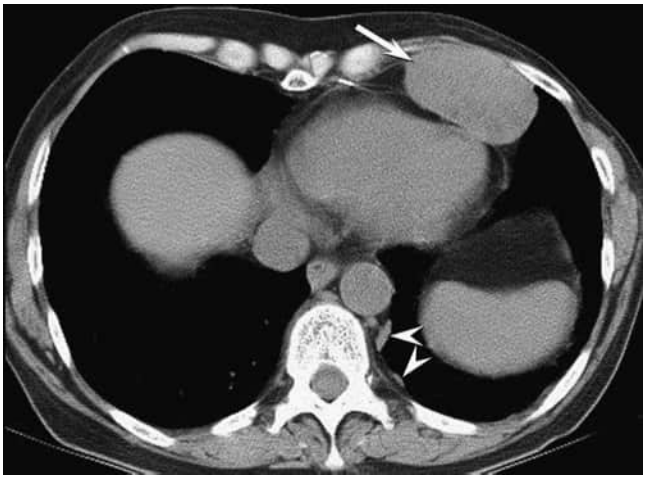
eFigure 115.16, cont'd



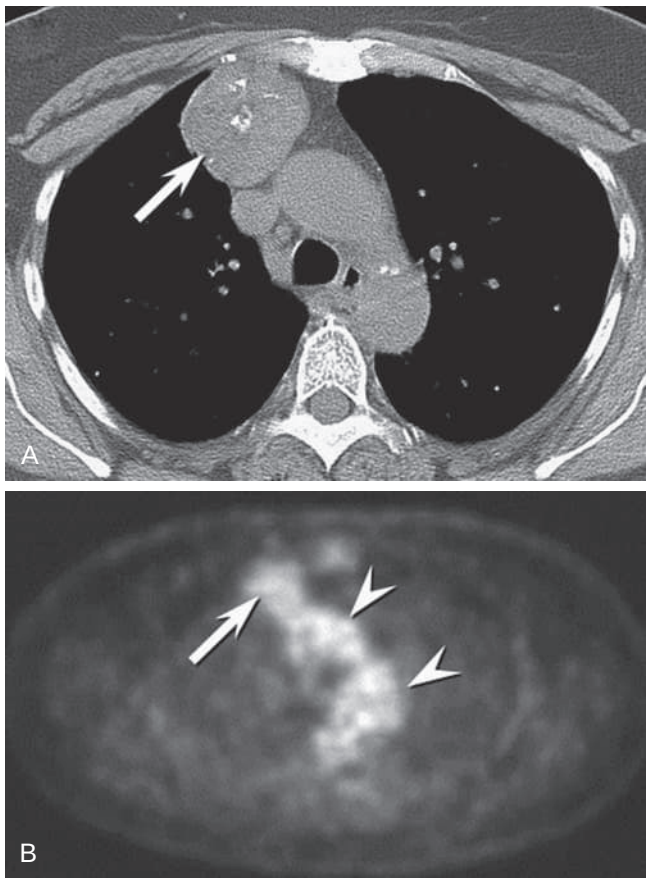
eFigure 115.17 Cystic degeneration within a thymoma. Axial enhanced chest computed tomography shows an enhancing anterior mediastinal mass containing internal low attenuation (*arrowheads*) consistent with cystic change or necrosis. (Courtesy Michael B. Gotway, MD.)



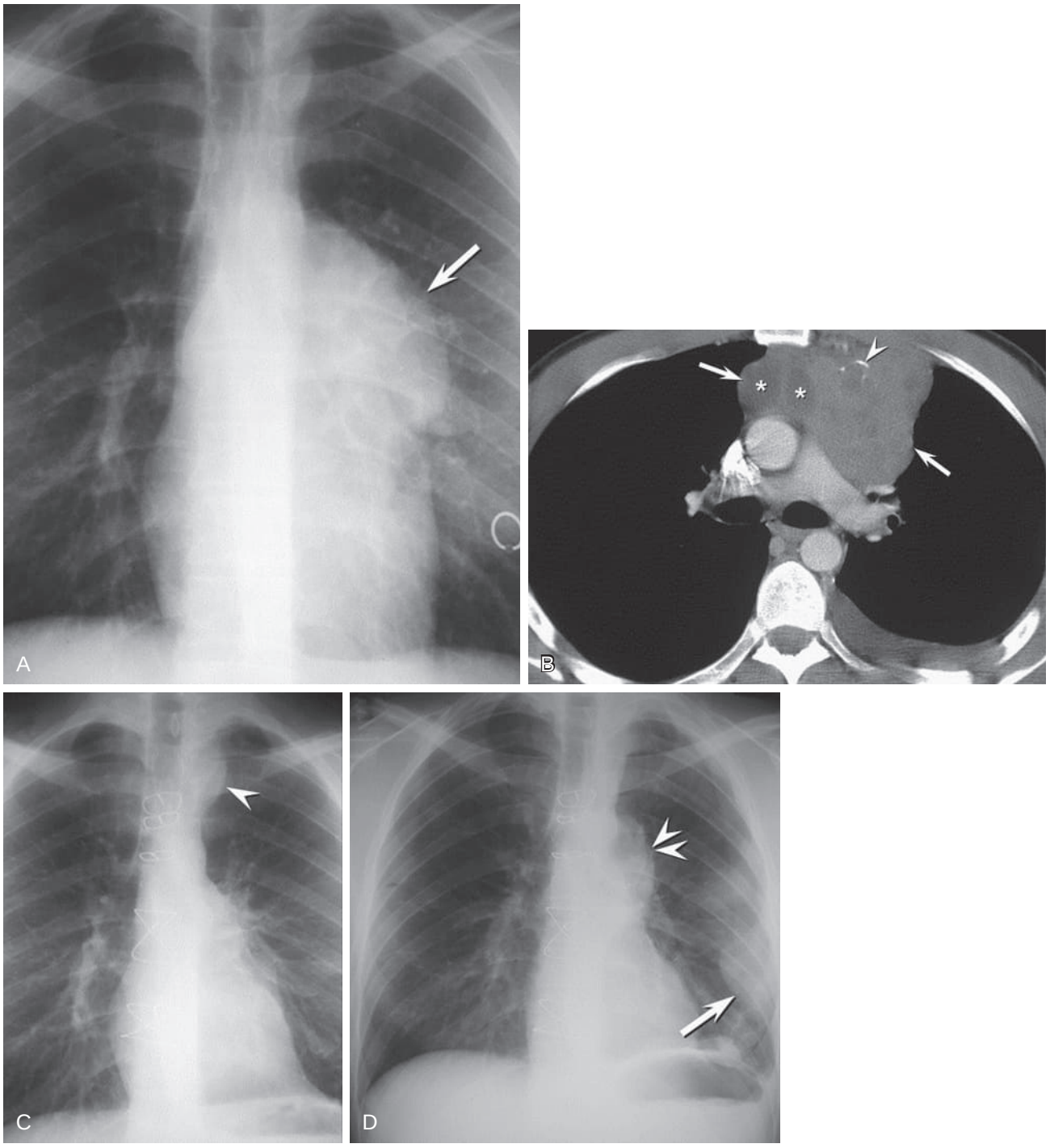
eFigure 115.18 Utility of chest computed tomography for thymic neoplasm staging. (A–D) Axial enhanced chest computed tomography shows a lobulated mass (*large arrows*, A–D) with foci of calcification (*arrowheads*, C–D). The computed tomography scan shows features consistent with an aggressive neoplasm, including lobulation, mediastinal fat infiltration, regional lymphadenopathy (*double arrowhead*, B), and marked vascular compression (*small arrows,* A and C). Compare the appearance of this aggressive neoplasm with the more indolent lesion shown in e-Fig. 115.16. (Courtesy Michael B. Gotway, MD.)



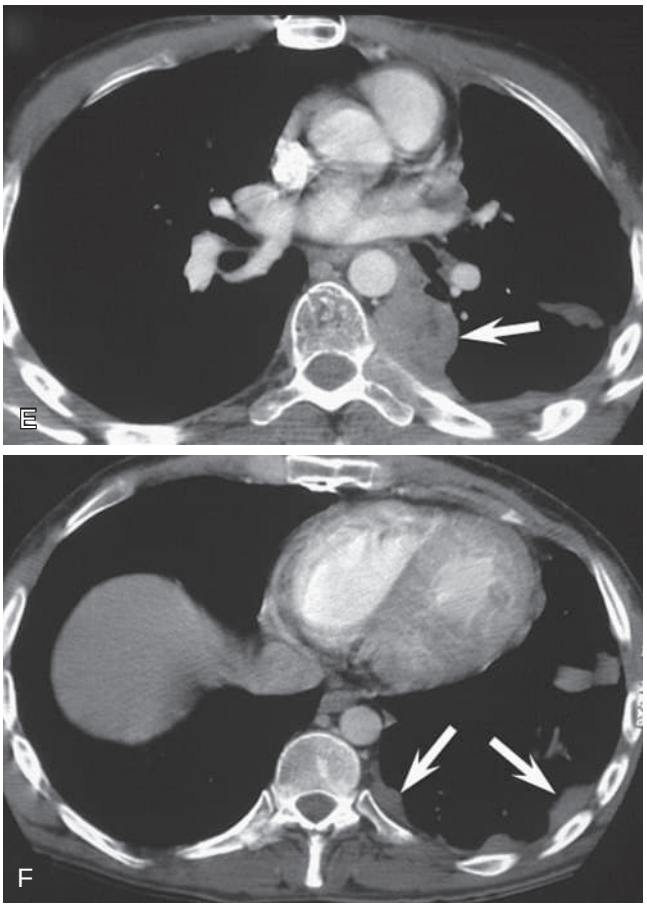
eFigure 115.19 Utility of chest computed tomography for thymic neoplasm staging. Axial chest computed tomography shows a circumscribed anterior mediastinal mass (*arrow*) in contact with the pericardium. While the circumscribed nature of the lesion initially suggests a relatively indolent neoplasm, potentially amenable to surgical resection, chest computed tomography also shows pleural nodules (*arrowheads*) in the left lower medial thorax, representing intrathoracic metastatic disease. (Courtesy Michael B. Gotway, MD.)



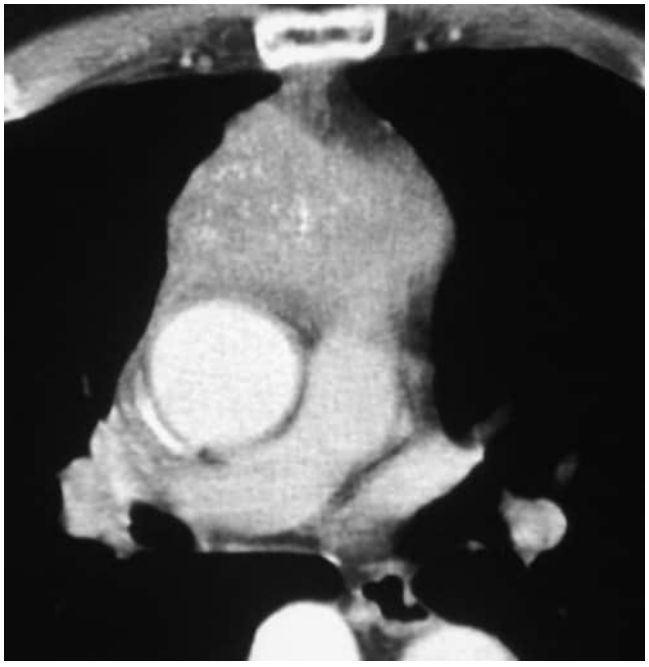
eFigure 115.20 Limited utility of ^{18}F-fluorodeoxyglucose positron emission tomography (FDG-PET) for thymic neoplasm evaluation. (A) Axial unenhanced chest computed tomography shows an anterior mediastinal mass (*arrow*) consistent with a thymic neoplasm; note calcification within the lesion. (B) ^{18}FDG-PET image shows modest glucose utilization within the tumor (*arrow*), but the degree of tracer uptake does not exceed that of mediastinal blood pool (*arrowheads*). In general, tracer activity must exceed that seen within mediastinal blood pool to indicate a malignant process. (Courtesy Michael B. Gotway, MD.)



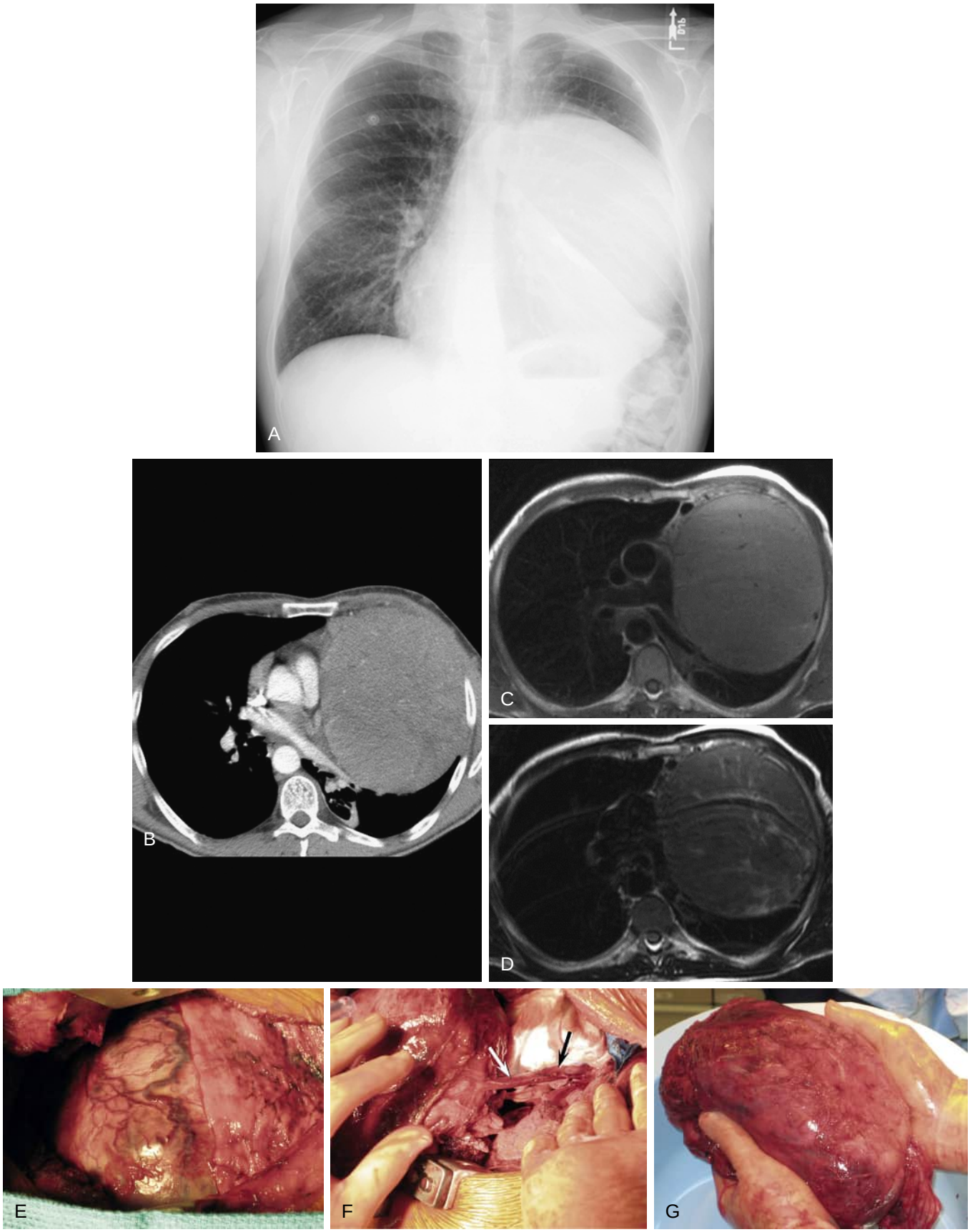
eFigure 115.21 Thymic neoplasm recurrence. Frontal chest radiograph (A) and enhanced chest computed tomography (B) at presentation show a left-sided mediastinal mass (*arrows*) subsequently shown to represent thymic neoplasia; note the lobulation, cystic change (*asterisks*), vascular compression and displacement, and calcification (*arrowhead*) on computed tomography scan (B), all suggestive of an aggressive neoplasm. (C) Frontal chest radiograph performed months following resection of the thymic neoplasm shows a new lesion abutting the posterior mediastinal surface of the left superior thorax (C, *arrowhead*), consistent with tumor recurrence. (D) Frontal chest radiograph several months following C shows an enlarging mediastinal mass (*double arrowheads*) and enlarging pleural metastatic deposits (*arrow*, D). (E and F) Enhanced chest computed tomography confirms pleural metastatic disease (*arrows*). (Courtesy Michael B. Gotway, MD.)



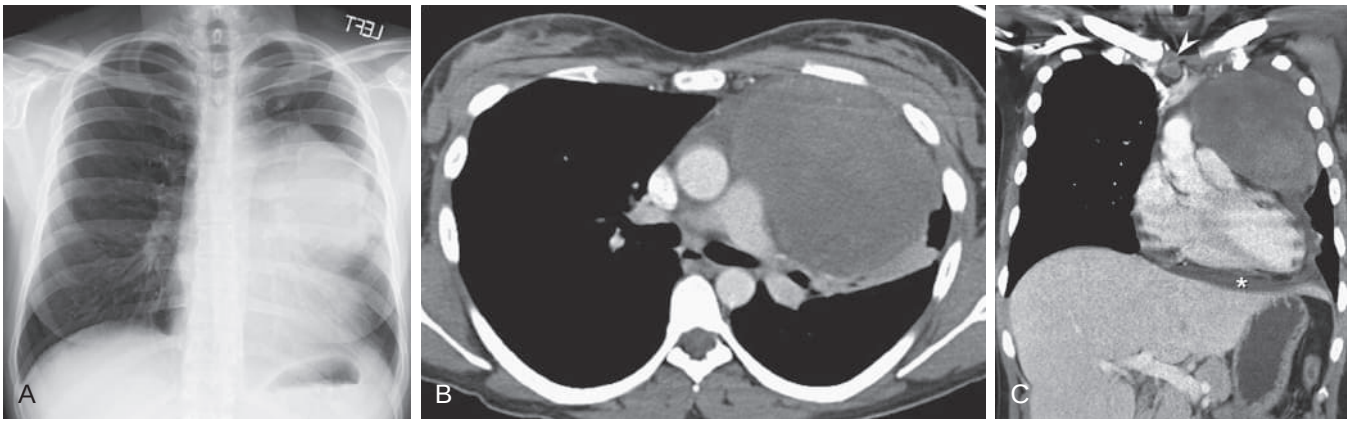
eFigure 115.21, cont'd



eFigure 115.22 Chest computed tomography scan of thymic carcinoma. Focused axial enhanced chest computed tomography shows a lobulated anterior mediastinal mass with foci of stippled calcification and extensive contact between the mass and vessels, in particular with obliteration of the fat plane between the mass and main pulmonary artery. (Courtesy Michael B. Gotway, MD.)



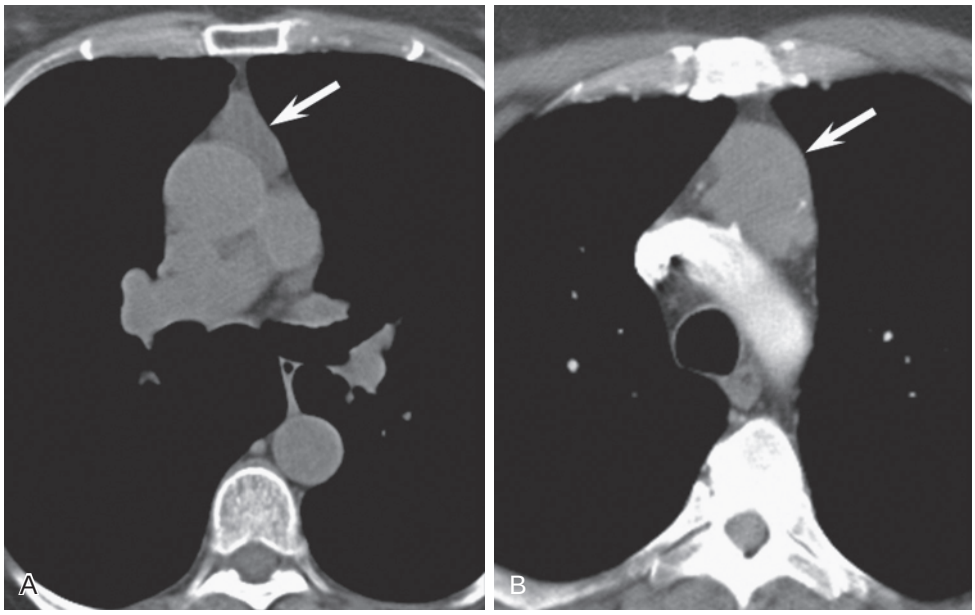
eFigure 115.23 Neuroendocrine thymic malignancy ("thymic carcinoid tumor"). (A) Frontal chest radiograph shows a smoothly circumscribed left-sided anterior mediastinal mass. (B) Axial enhanced chest computed tomography scan shows a solid, homogeneously enhancing left-sided anterior mediastinal mass with contralateral mediastinal shift, but no other overtly aggressive features. Axial double inversion recovery T1-weighted (C) and T2-weighted (D) magnetic resonance images also show the lesion and its mass effect, but no locally invasive behavior. The T2-weighted (D) image shows intermediate signal within the lesion, indicative of a relatively cellular neoplasm. The small black dot anterior and medial to the mass represents a flow void within an enlarged mediastinal vein. (E–F) Intraoperative view of the lesion during resection shows the large vein on the surface of the neoplasm; this vascular pedicle (*arrows*, F) was identified at surgery and ligated. (G) Photograph of the resected specimen. (A–D, Courtesy Michael B. Gotway, MD; E–G, Courtesy Andrew H. Goldstein, MD.)



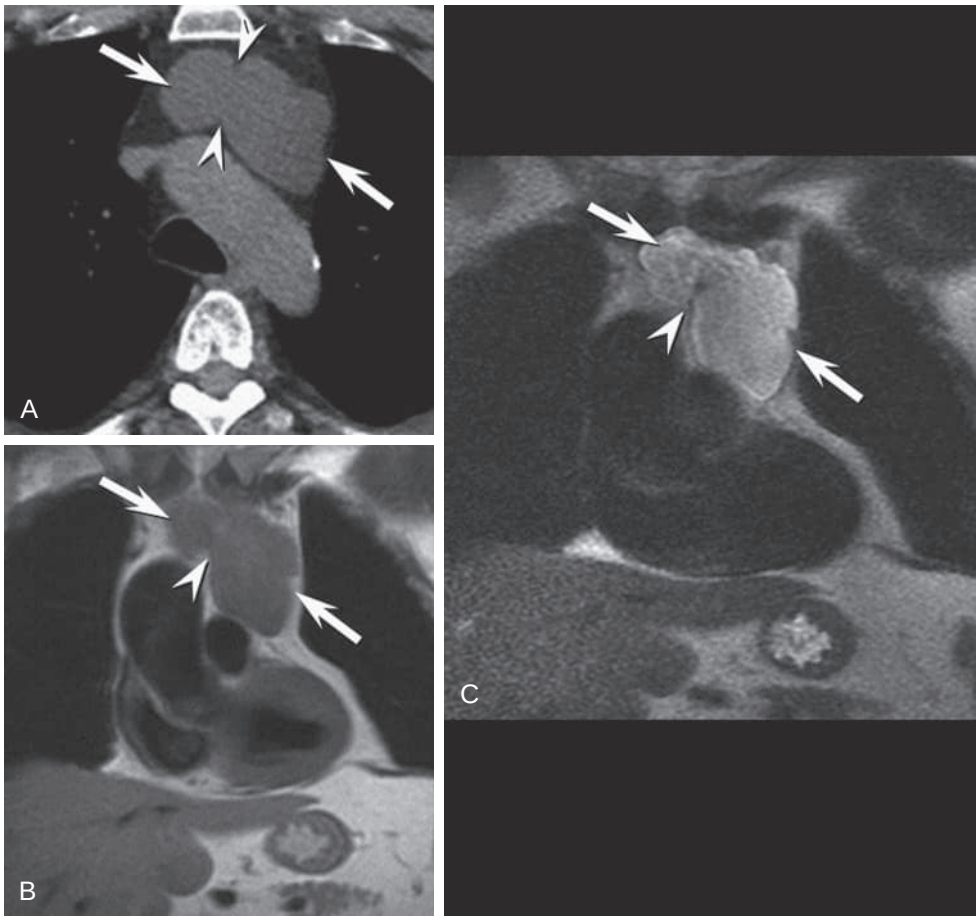
eFigure 115.24 Hodgkin lymphoma involving the thymus. (A) Frontal chest radiograph shows a large left-sided anterior mediastinal mass. Axial (B) and coronal enhanced (C) chest computed tomography scans show a minimally lobulated slightly inhomogeneous left-sided anterior mediastinal mass. The appearance is similar to thymic neoplasia. The pericardial effusion (*asterisk*) and regional necrotic lymph node enlargement (*arrowhead*) are indicative of an aggressive process. (Courtesy Michael B. Gotway, MD.)



eFigure 115.25 Thymic "rebound" hyperplasia. (A) Enhanced chest computed tomography in a young patient with breast malignancy at time of diagnosis shows minimal soft tissue mixed with fat (*arrows*), consistent with normal residual thymus. (B) Axial unenhanced chest computed tomography shows marked increase in the soft tissue within the anterior mediastinum (*arrows*) several months following chemotherapy, consistent with "thymic rebound." The appearance can be difficult to distinguish from neoplasia. (C) Enhanced chest CT 1 year after B shows return to a more normal appearance of the thymus (*arrows*). (Courtesy Michael B. Gotway, MD.)



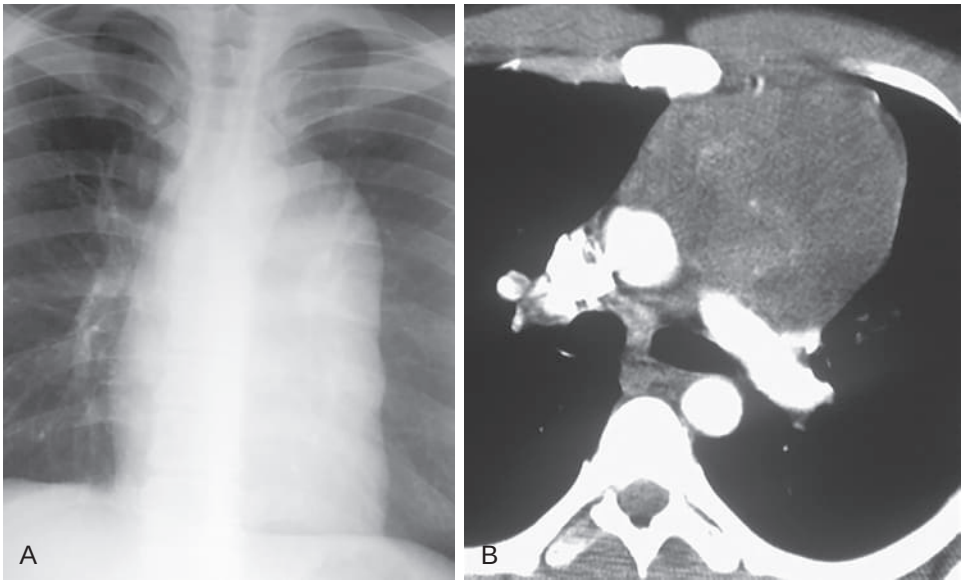
eFigure 115.26 Thymic hyperplasia versus thymoma. (A) Unenhanced chest computed tomography in a patient with thymic hyperplasia shows a homogeneous low attenuation, smoothly circumscribed anterior mediastinal lesion (*arrow*) consistent with thymic hyperplasia; note the morphology of this lesion still resembles normal thymus. This appearance contrasts with (B), the lobulated, irregular appearance of thymoma (*arrow*). (Courtesy Michael B. Gotway, MD.)



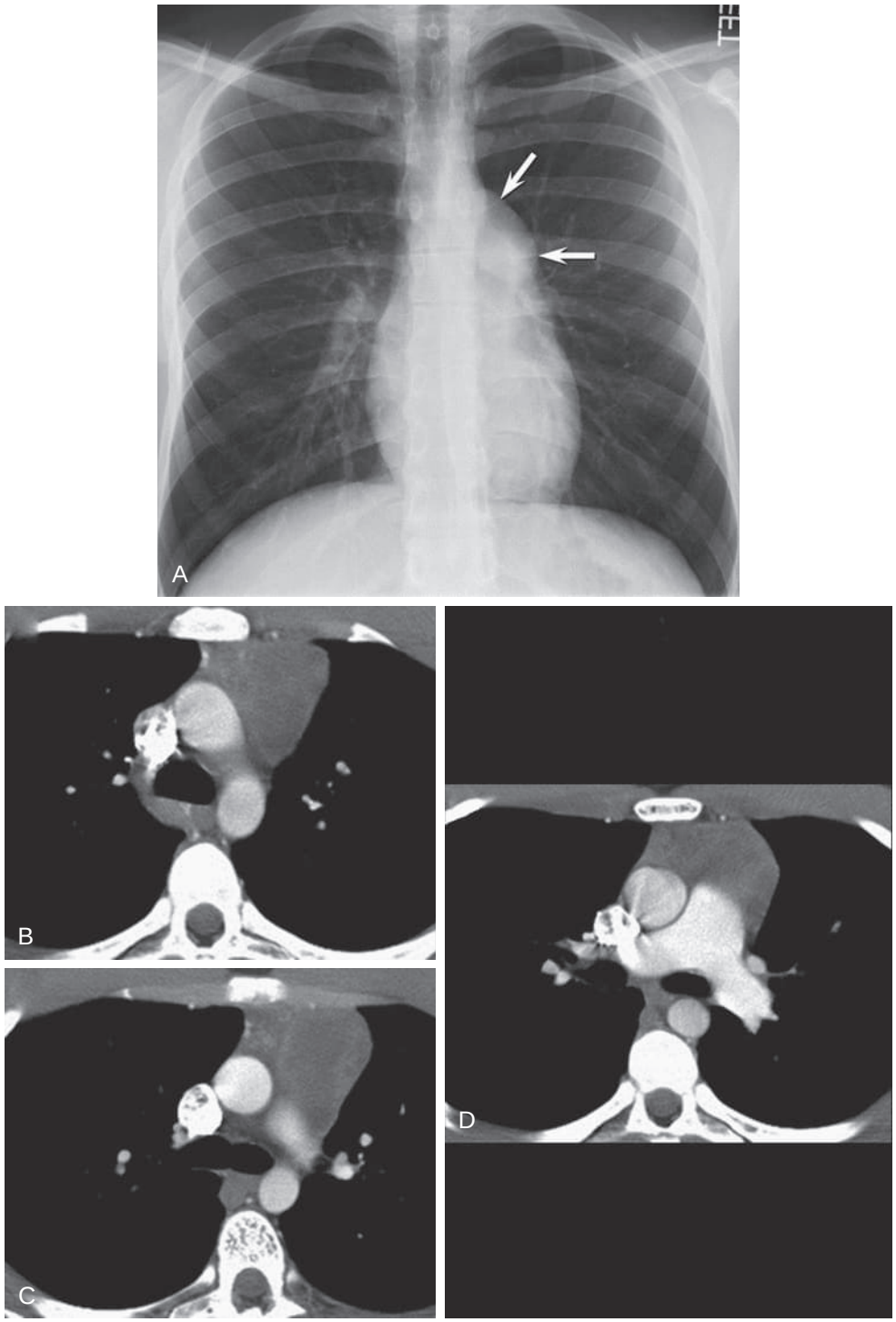
eFigure 115.27 Thymic cyst. (A) Axial unenhanced chest computed tomography shows a homogeneously (water density) low-attenuation anterior mediastinal lesion (*arrows*). Note the cleft in the lesion (*arrowheads*); this morphology is reminiscent of the normal bilobed thymus. Coronal double inversion recovery unenhanced T1-weighted (B) and fast spin-echo T2-weighted magnetic resonance (C) images show low and high signal, respectively, within the lesion (*arrows*), consistent with fluid. This lesion has remained stable for a number of years. Both images show the cleft within the lesion (*arrowheads*). (Courtesy Michael B. Gotway, MD.)



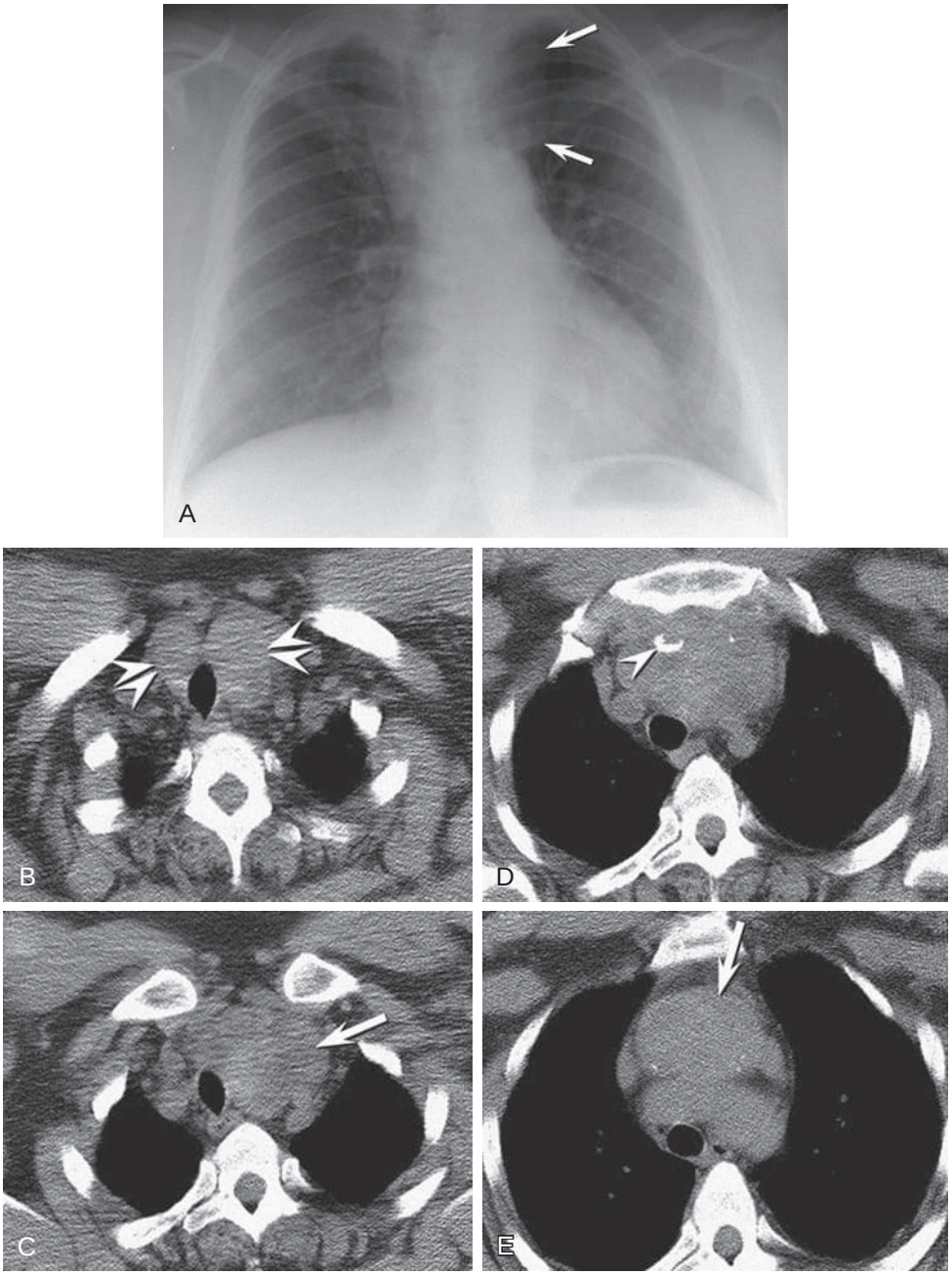
eFigure 115.28 Teratoma. Frontal chest radiograph shows a large right-sided mediastinal mass, representing teratoma. (Courtesy Michael B. Gotway, MD.)



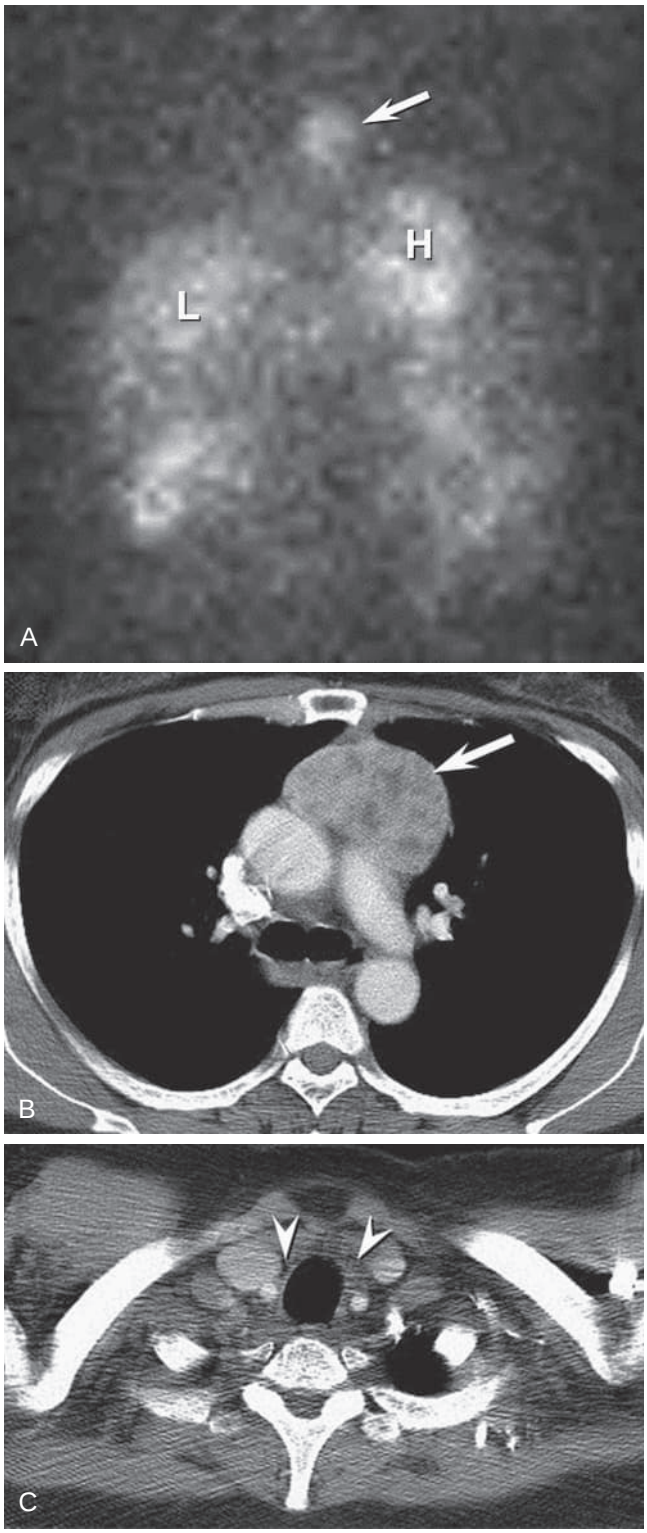
eFigure 115.29 Seminoma. (A) Frontal chest radiograph shows a large left-sided mediastinal mass obscuring the left cardiac border. (B) Axial enhanced chest computed tomography shows a mildly inhomogeneous mass obliterating the fat plane with the ascending aorta and let pulmonary artery. (Courtesy Michael B. Gotway, MD.)



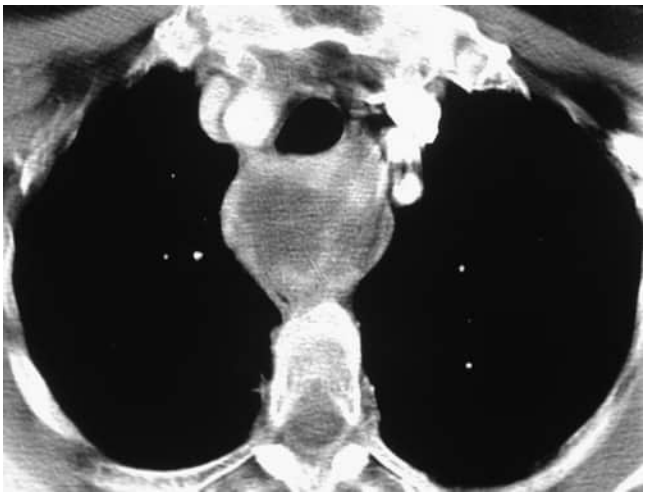
eFigure 115.30 Embryonal cell carcinoma. (A) Frontal chest radiograph shows a circumscribed left-sided anterior mediastinal mass (*arrows*). (B–D) Axial enhanced chest computed tomography shows a heterogeneous anterior mediastinal mass that obliterates fat planes with the adjacent vessels. Internal low attenuation within the tumor, as seen in the example, is more commonly encountered as nonseminomatous mediastinal germ cell neoplasms than seminomas. See Video 115.11 for the full study. (Courtesy Michael B. Gotway, MD.)



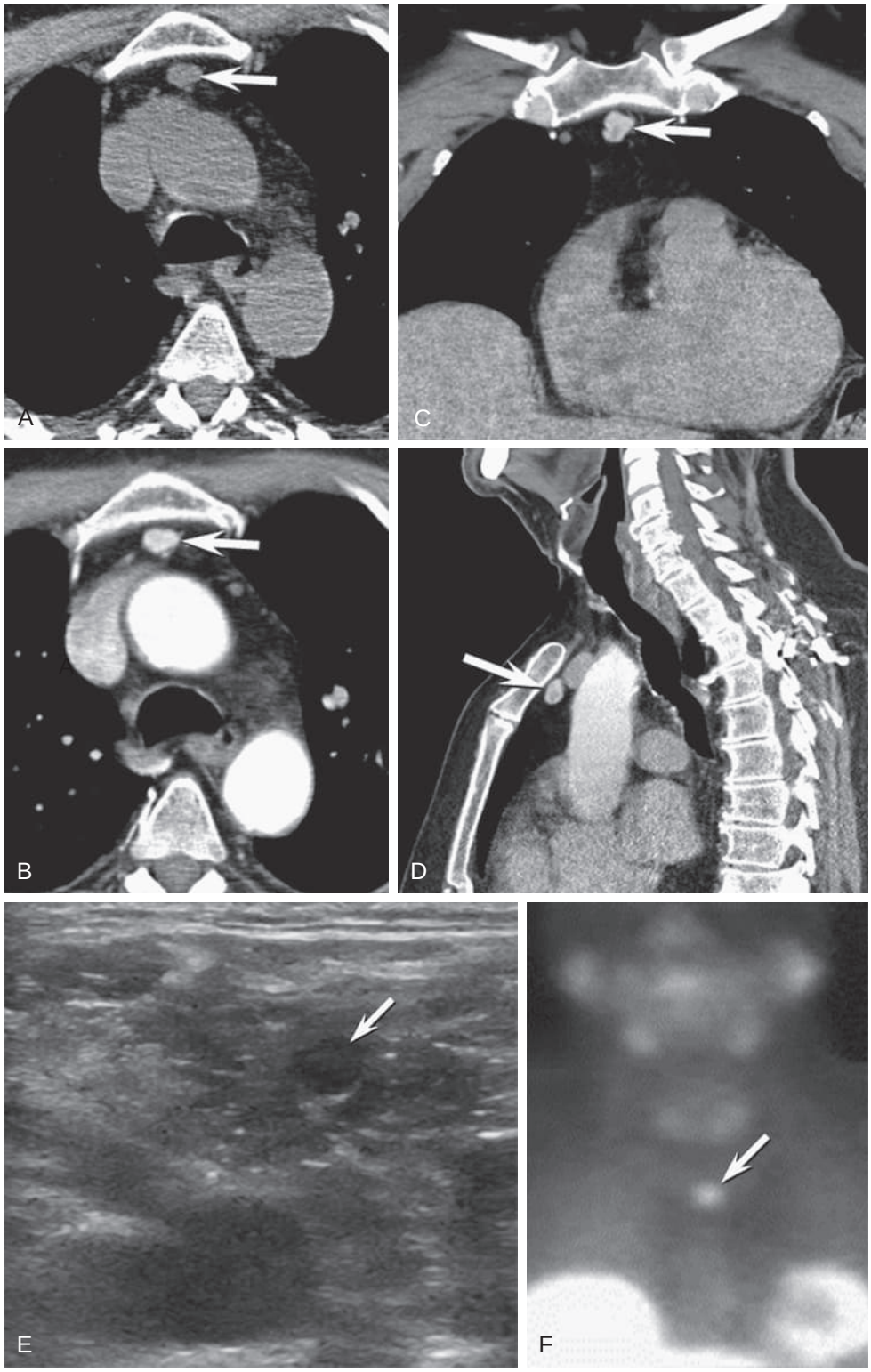
eFigure 115.31 Anterior mediastinal extension of a thyroid goiter. (A) Frontal chest radiograph shows widening of the superior mediastinum with rightward shift of the trachea resulting from a mediastinal mass (*arrows*). The superior mediastinal widening extends into the base of the neck. (B–E) Axial unenhanced chest computed tomography shows enlargement of the cervical thyroid gland (*double arrowheads,* B). The anterior superior mediastinal mass (*arrows*, C and E) extends from the base of the neck, originating from, and in contact with, the cervical thyroid gland. The mass contains calcification (*single arrowhead,* D), a common finding in thyroid goiters. Continuity of a mediastinal lesion with the cervical thyroid gland is key for confidently establishing a mediastinal mass as thyroidal in origin. (Courtesy Michael B. Gotway, MD.)



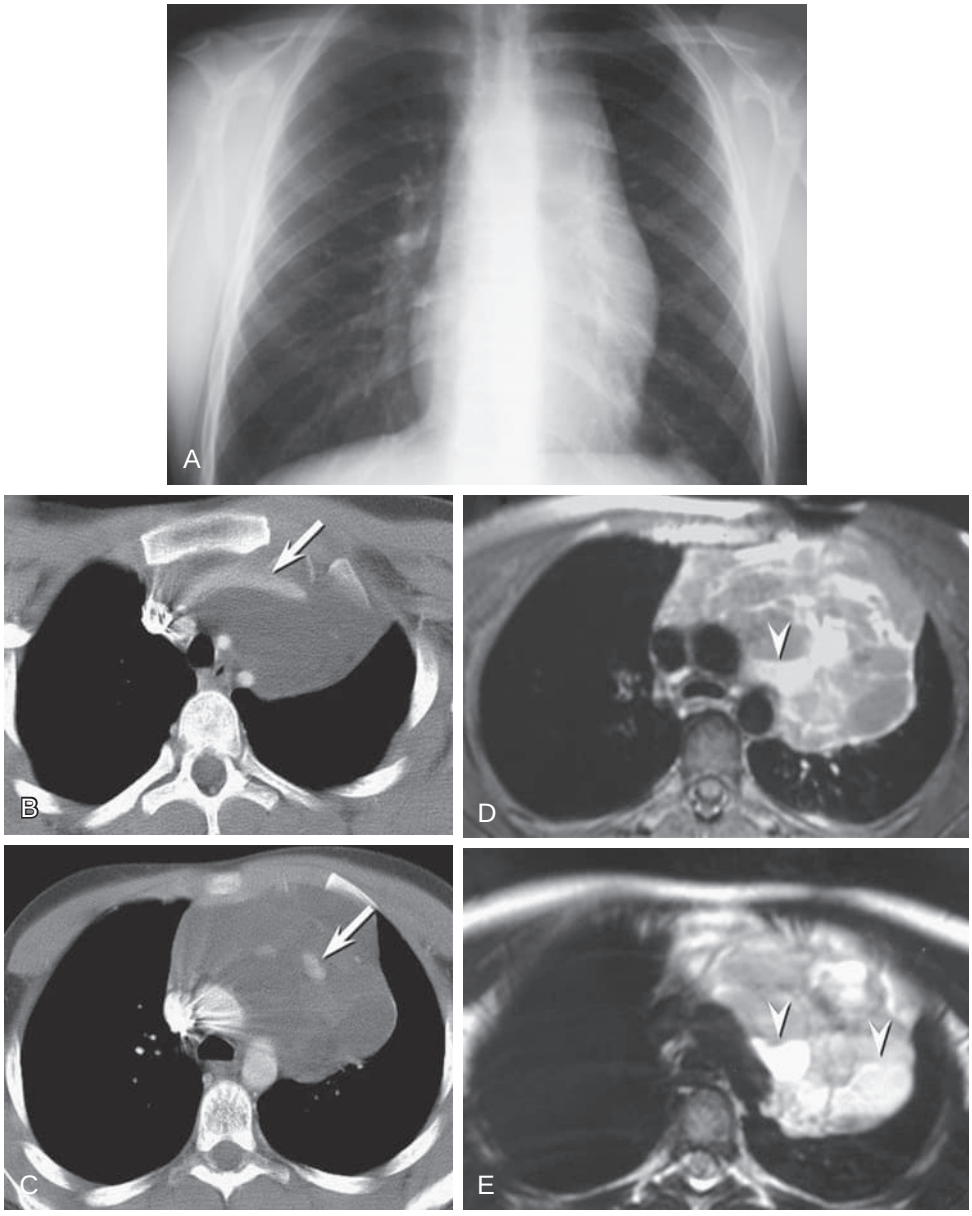
eFigure 115.32 Ectopic mediastinal thyroid tissue. (A) Planar frontal 99m-technetium sestamibi scintigraphy shows faint tracer uptake within the mediastinum (*arrow*), separate from the heart (H) and liver (L). Axial enhanced chest computed tomography shows a heterogeneously enhancing anterior mediastinal mass (*arrow*). (C) Axial computed tomography image through the cervicothoracic junction shows absence of a normal thyroid gland (*arrowheads*, C). (Courtesy Michael B. Gotway, MD.)



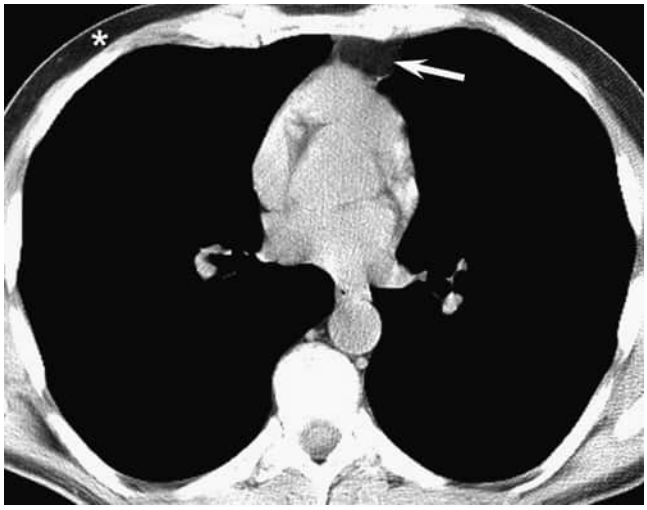
eFigure 115.33 Middle mediastinal extension of a thyroid goiter. Axial enhanced chest computed tomography shows a peripherally hyperenhancing mass with central necrosis posterior to the trachea. This lesion was in contact with thyroid tissue at the base of the neck, establishing it as mediastinal goiter extension. (Courtesy Michael B. Gotway, MD.)



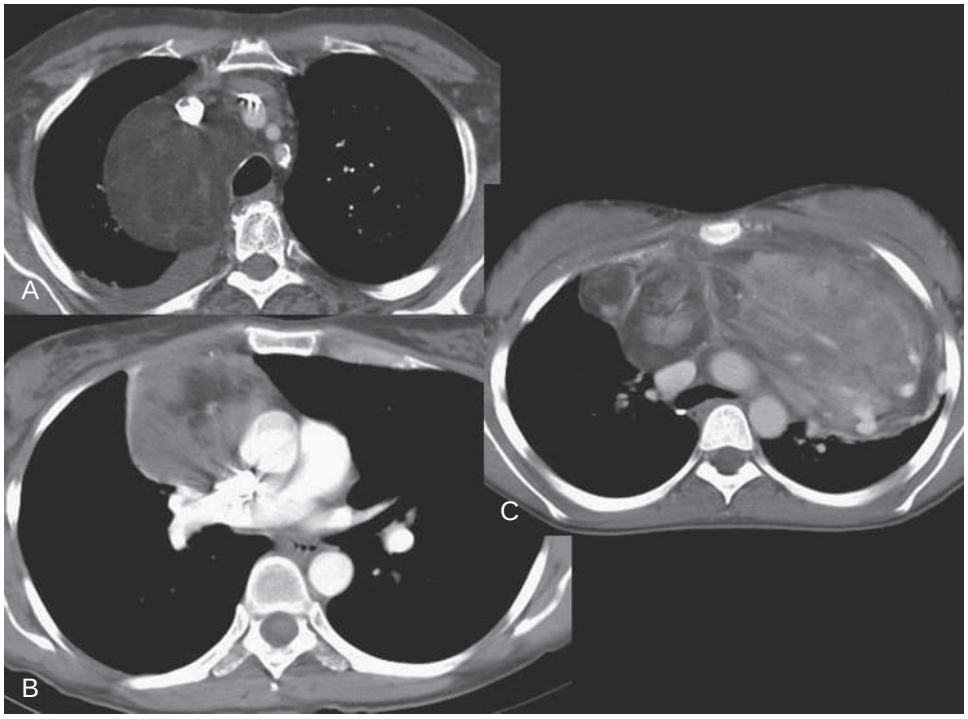
eFigure 115.34 Ectopic anterior mediastinal parathyroid adenoma. Axial unenhanced (A) and axial (B), coronal (C), and sagittal (D) enhanced chest computed tomography shows an intensely enhancing lesion (*arrow*) in the anterior mediastinum. (E) Transverse sonography performed at the level of the suprasternal notch shows a hypoechoic nodule (*arrow*) corresponding to the computed tomography abnormality. (F) Planar frontal 99m-technetium sestamibi scintigraphy shows avid tracer accumulation within the anterior mediastinal lesion (*arrow*), confirming ectopic parathyroid adenoma. (Courtesy Michael B. Gotway, MD.)



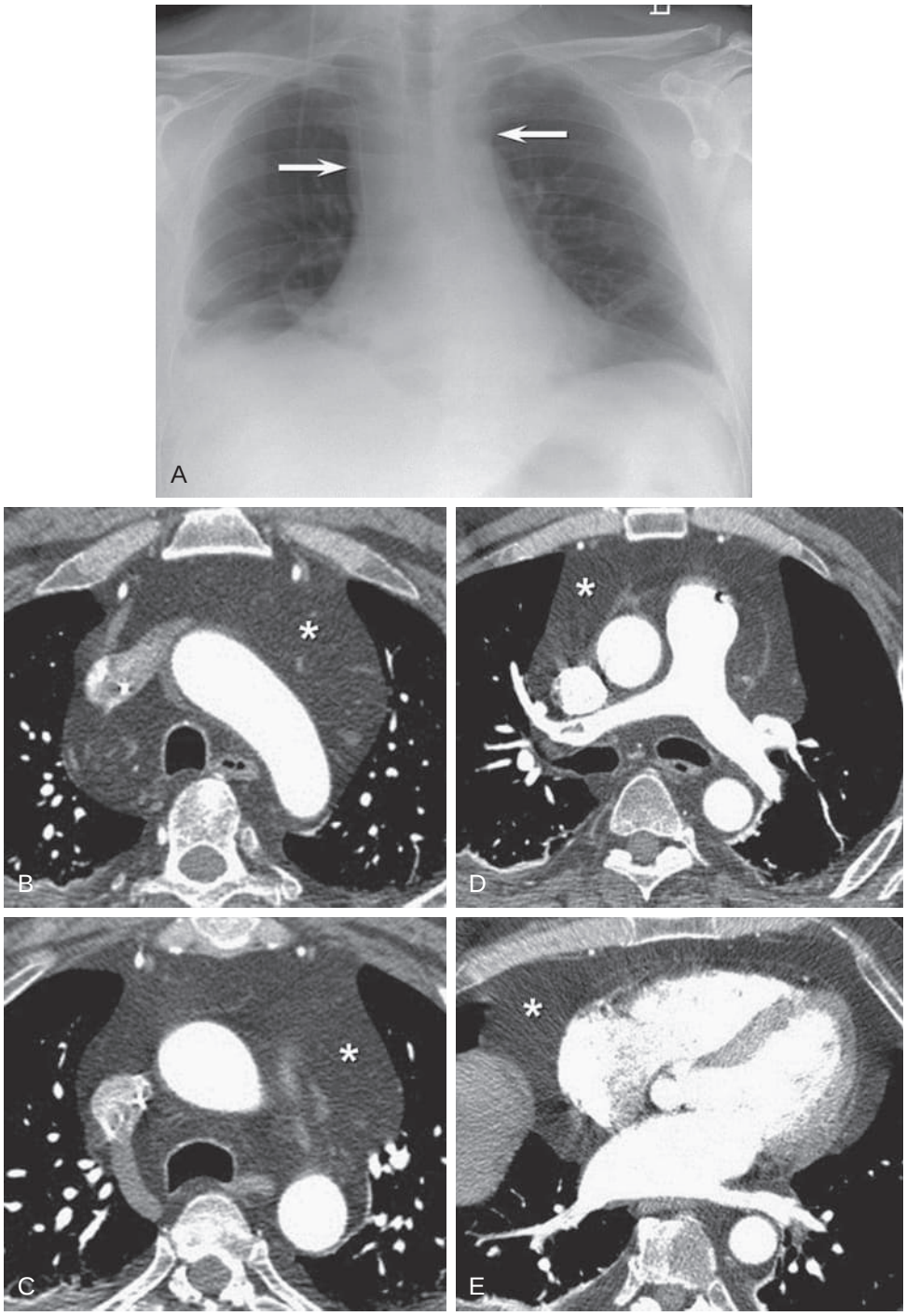
eFigure 115.35 Mediastinal lymphangioma. Frontal chest radiograph in a 13-year-old boy shows a circumscribed left mediastinal mass without mediastinal shift. (B and C) Axial enhanced chest computed tomography shows an anterior and superior low-attenuation mediastinal lesion surrounding, but not compressing, the left brachiocephalic vein (*arrows*); this behavior indicates that the lesion is relatively "soft." Axial fat saturation T1-weighted (D) and T2-weighted (E) magnetic resonance images show a mass with heterogeneous signal intensity containing multiple fluid-fluid levels (*arrowheads*). The dependent signal within the areas of fluid-fluid level formation is bright on both T1- and T2-weighted images, consistent with blood. (Courtesy Michael B. Gotway, MD.)



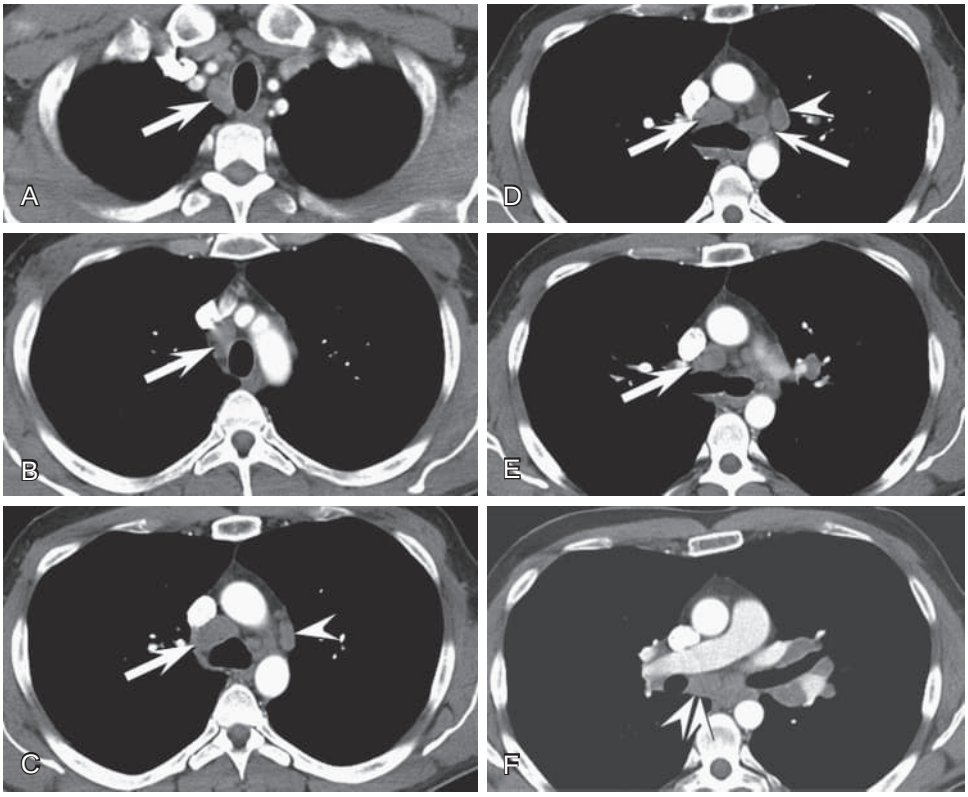
eFigure 115.36 Anterior mediastinal lipoma. Axial enhanced chest computed tomography shows an encapsulated fat-containing lesion (*arrow*) consistent with a small lipoma. (Courtesy Michael B. Gotway, MD.)



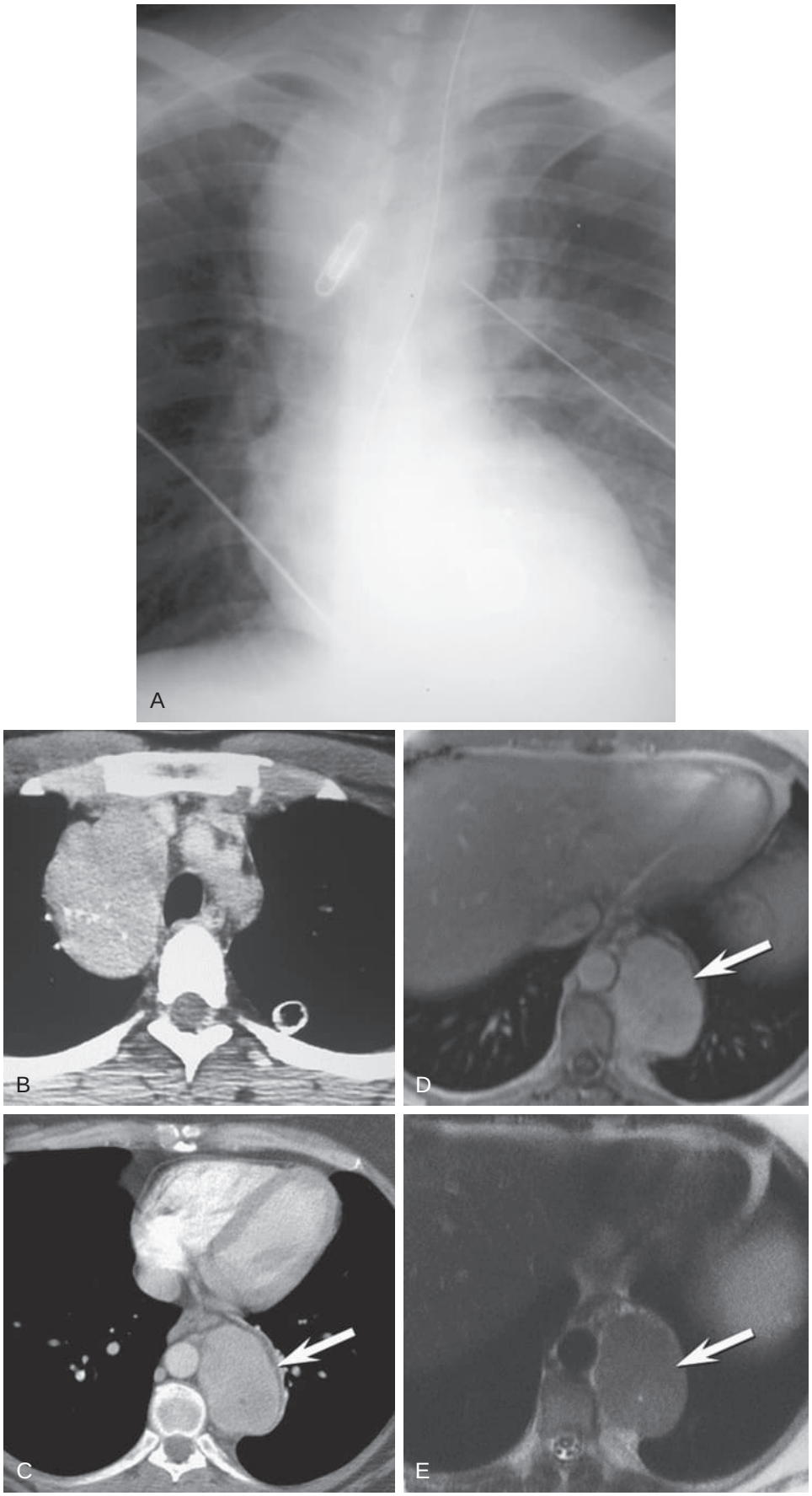
eFigure 115.37 Mediastinal liposarcoma. (A) Axial chest computed tomography shows a predominantly fatty attenuating mass, representing well-differentiated liposarcoma. (B) Axial chest computed tomography shows a mediastinal mass again containing fat, but with considerably more soft tissue than the well-differentiated lesion in A, representing moderately differentiated mediastinal liposarcoma. (C) Axial chest computed tomography shows a large inhomogeneous mass containing fat, but also with soft tissue components and extensive vascularity, representing poorly differentiated mediastinal liposarcoma. (Courtesy Michael B. Gotway, MD.)



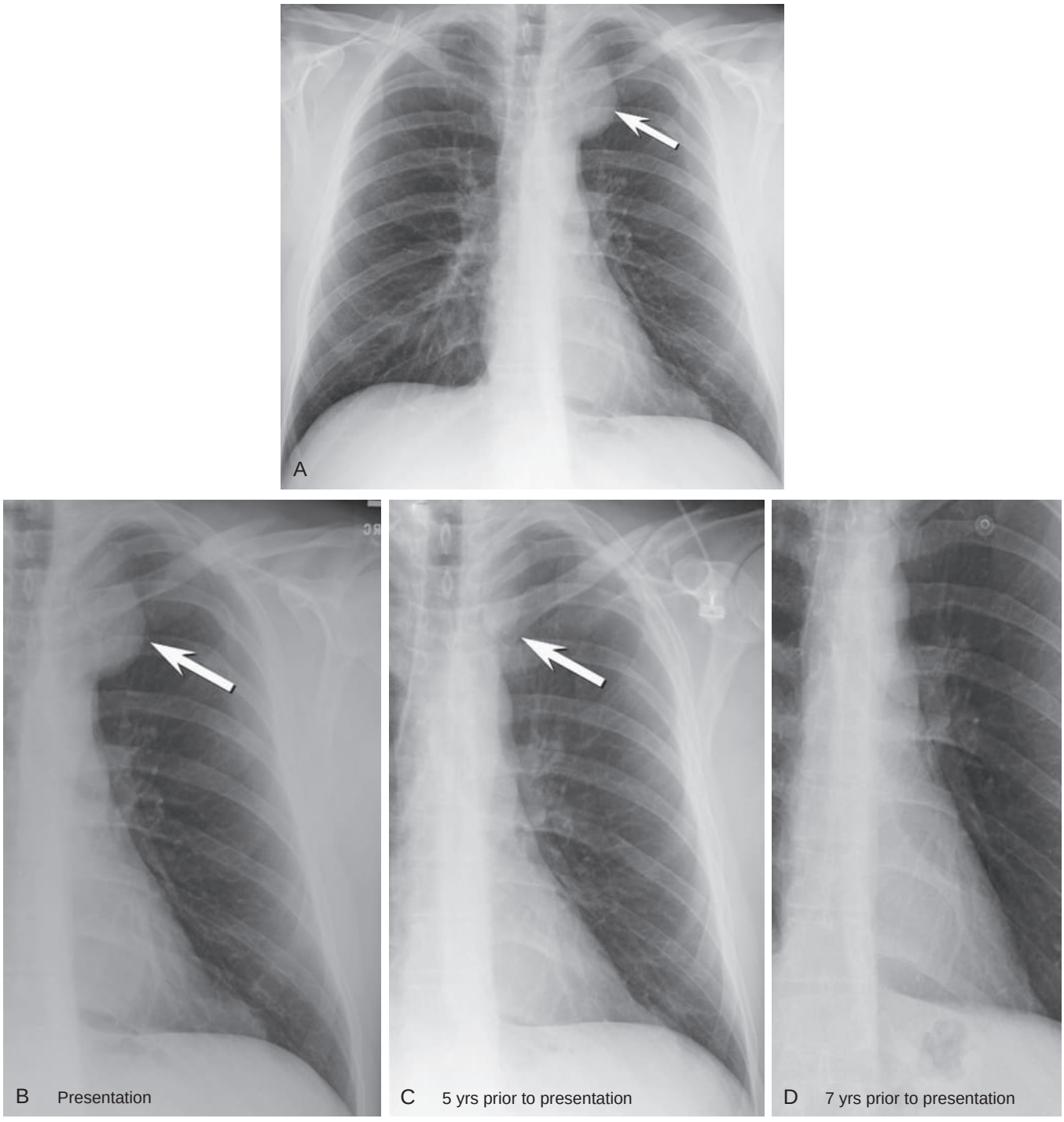
eFigure 115.38 Mediastinal lipomatosis. (A) Frontal chest radiograph shows widening of the superior mediastinum (*arrows*), but the contours of the mediastinum are not lobulated, nor is the mediastinum abnormally dense. (B–E) Axial enhanced chest computed tomography shows abundant, unencapsulated mediastinal fat (*asterisk*) on both sides of midline, without significant nodularity. (Courtesy Michael B. Gotway, MD.)



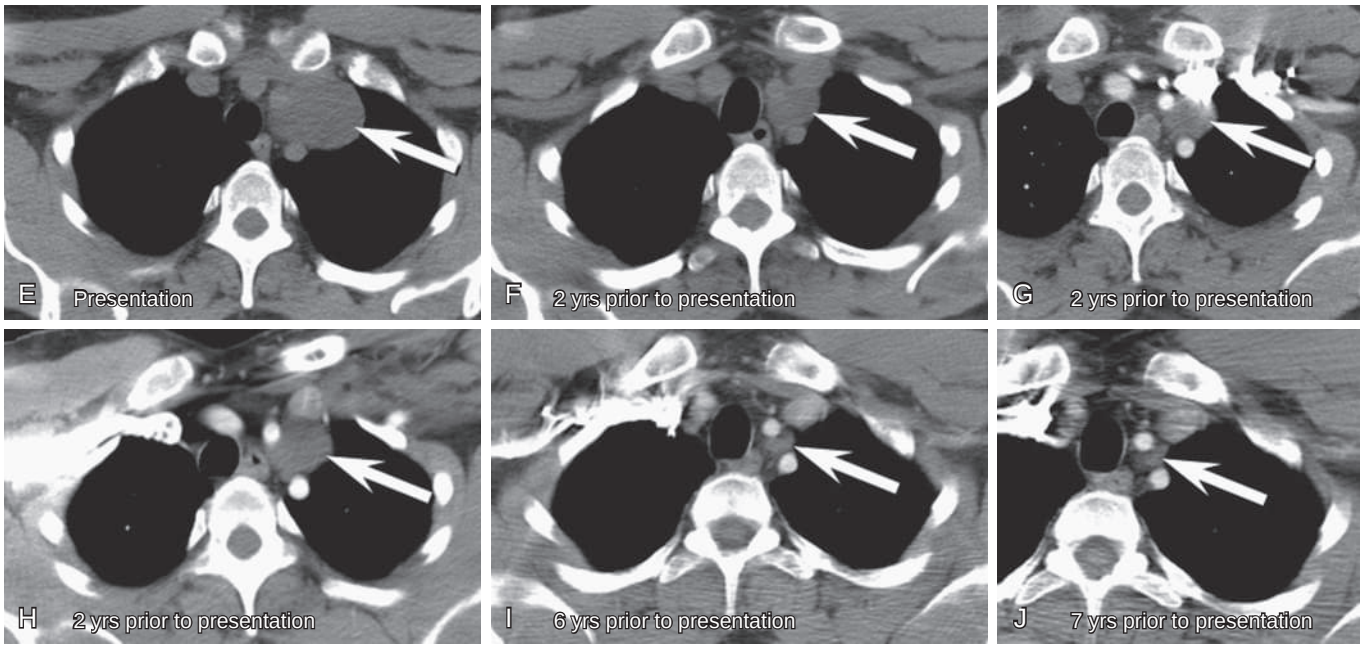
eFigure 115.39 Mediastinal lymphadenopathy in a patient with sarcoidosis. (A–F) Axial enhanced chest computed tomography shows mildly enlarged lymph nodes in multiple mediastinal stations: (A) highest right paratracheal nodes (station 1R, *arrow*); (B) upper right paratracheal nodes (station 2R, *arrow*); (C–E) lower right paratracheal nodes (station 4R, *arrows*); (D) lower left paratracheal nodes (station 4L, *thin arrow*, D) and aortopulmonary window nodes (station 5, *arrowhead*, D); (F) subcarinal nodes (station 7, *double arrowheads*, F). (Courtesy Michael B. Gotway, MD.)



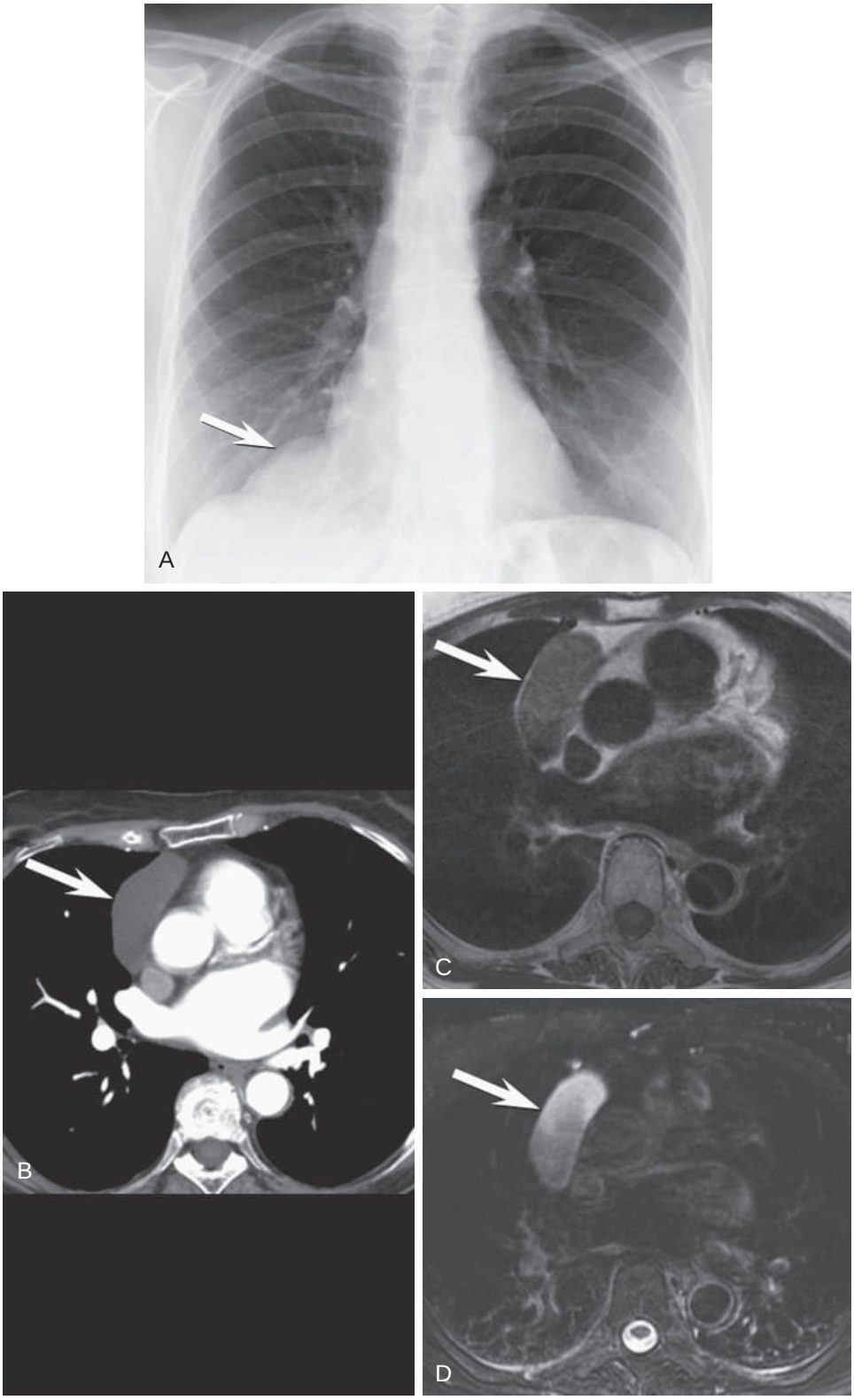
eFigure 115.40 Angiofollicular lymphoid hyperplasia (Castleman disease). (A) Frontal chest radiograph shows a right paratracheal mass in a patient with an anterior chest wall stab wound, with penetrating entry site on the skin marked by a paper clip. (B) Axial enhanced chest computed tomography shows an enhancing right paratracheal mass with small foci of calcification, shown to reflect angiofollicular lymphoid hyperplasia at surgical resection. (C) Axial enhanced chest computed tomography (C), T1-weighted (D) and T2-weighted (E) magnetic resonance images in a different patient show a posterior mediastinal mass (*arrows*) shown to reflect angiofollicular lymphoid hyperplasia at surgical resection. (Courtesy Michael B. Gotway, MD.)



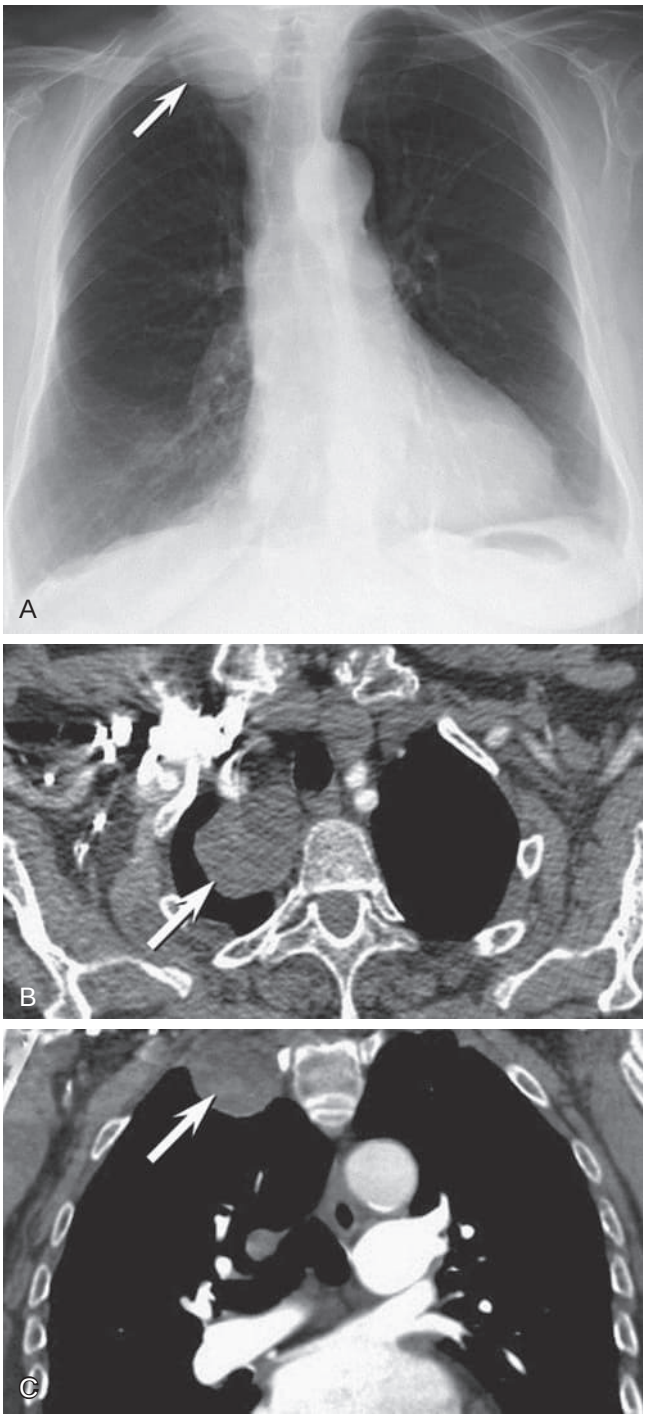
eFigure 115.41 Growth of a bronchogenic cyst over time. (A) Frontal chest radiograph shows a smoothly circumscribed lesion (*arrow*) in the left superior mediastinum. (B–D) Retrospective review of serial chest radiographs obtained over the previous 7 years shows slow enlargement of the lesion (*arrows*). (E–J) Axial chest computed tomography shows serial enlargement of the lesion (*arrows*) over a 7-year period. (Courtesy Michael B. Gotway, MD.)



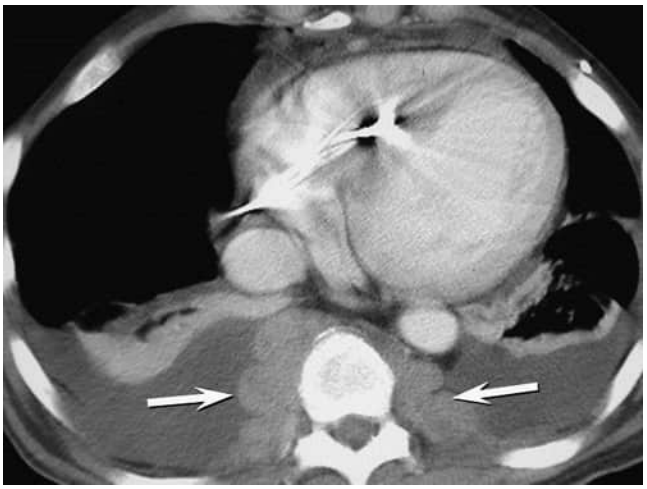
eFigure 115.41, cont'd



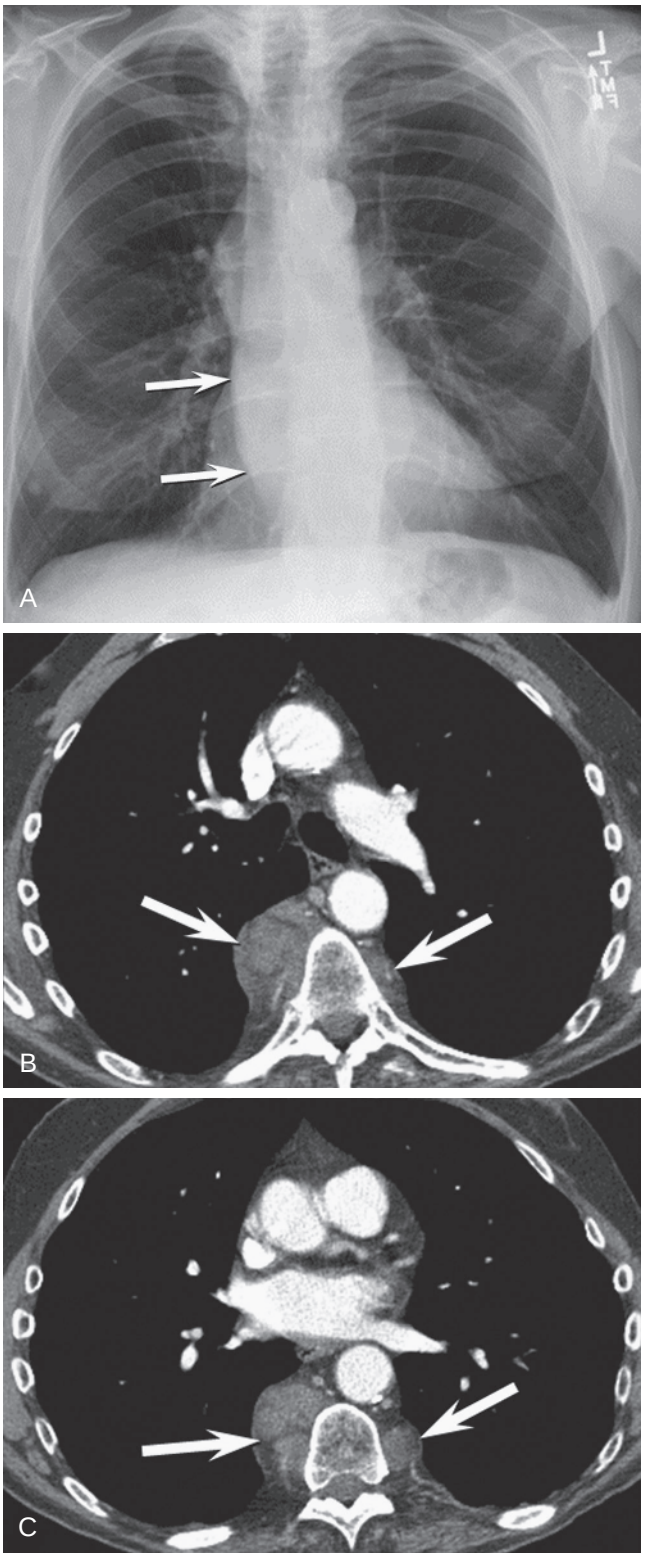
eFigure 115.42 Pericardial cyst. (A) Frontal chest radiograph shows a smoothly circumscribed right cardiophrenic angle mass (*arrow*). (B) Axial enhanced chest computed tomography shows a homogeneous water density mass (*arrow*) abutting the right pericardium. Axial double inversion recovery T1-weighted (C) and axial triple inversion recovery (D) magnetic resonance images show fluid signal within the mass (*arrows*). Triple inversion recovery sequences (D) suppress fat signal, with water signal appearing bright (note the high signal of the cerebrospinal fluid posteriorly). The slight "shading" of the signal intensity posteriorly within the pericardial cyst may reflect debris or hemorrhage. (Courtesy Michael B. Gotway, MD.)



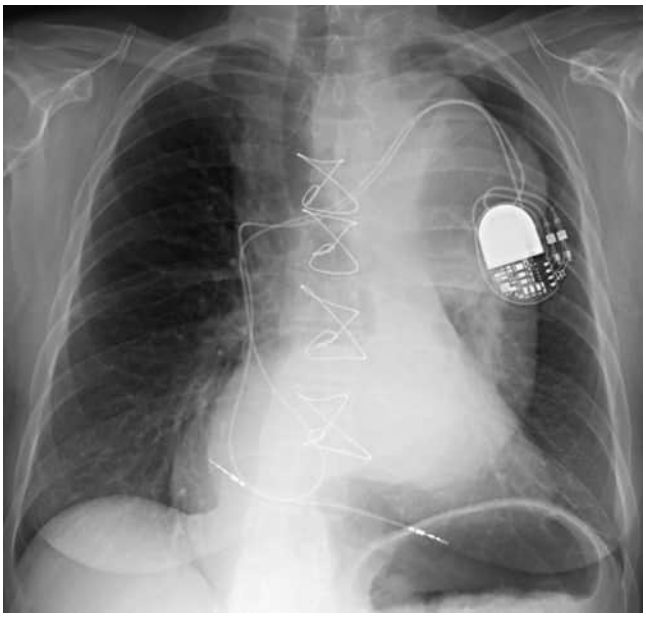
eFigure 115.43 Schwannoma. (A) Frontal chest radiograph shows a smoothly circumscribed lesion (*arrow*) at the right thoracic apex. The extensive contact with the chest wall and lack of visualization of the superior border of the lesion (often referred to as the *incomplete border sign*) are consistent with a non–lung parenchymal origin. Axial (B) and coronal (C) enhanced chest computed tomography shows a homogeneous low-attenuation lesion (*arrows*) in contact with the right superior mediastinum and chest wall. The lesion was shown to reflect schwannoma. See Video 115.12 for the full studies. (Courtesy Michael B. Gotway, MD.)



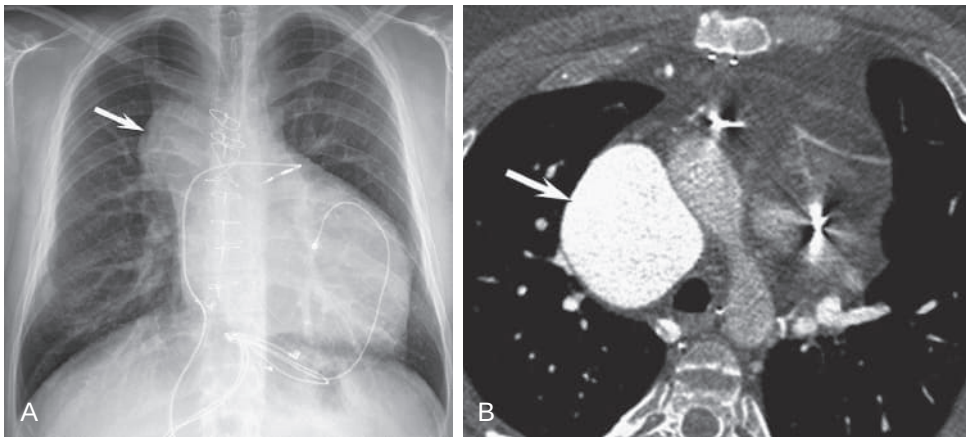
eFigure 115.44 Extramedullary hematopoiesis. Enhanced chest computed tomography in a patient with thalassemia shows enhancing paravertebral soft tissue *(arrows)*, representing extramedullary hematopoiesis. (Courtesy Michael B. Gotway, MD.)



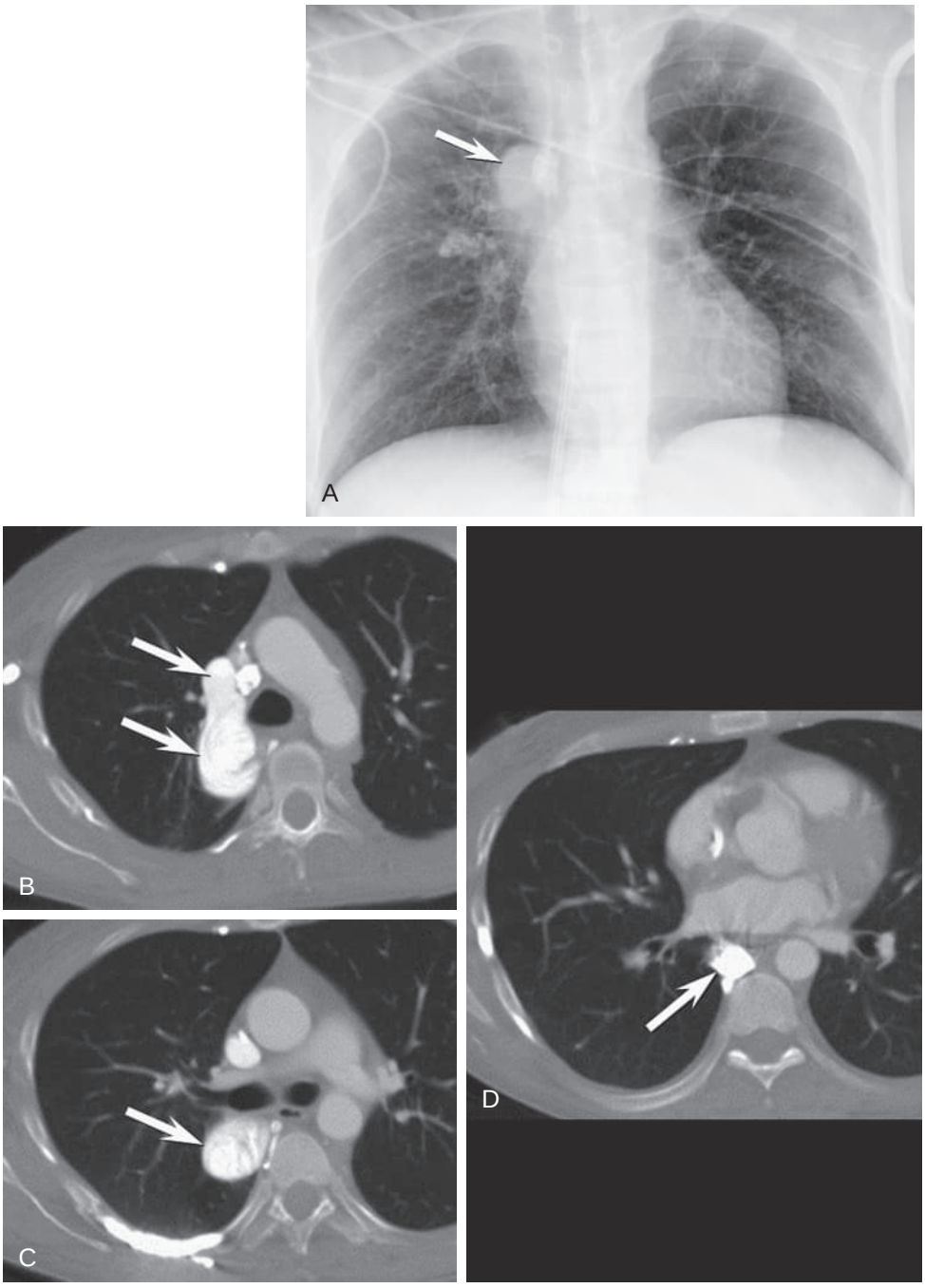
eFigure 115.45 Extramedullary hematopoiesis containing fat. (A) Frontal chest radiograph in a patient with anemia shows an abnormal right-sided posterior mediastinal contour (*arrows*); a similar abnormal contour can be appreciated in the left retrocardiac region. The posterior mediastinal location is suggested by the relatively long contour abnormality without obscuration of the right heart border or lateral displacement of the right hilum. (B and C) Axial enhanced chest computed tomography shows bilateral posterior mediastinal masses (*arrows*) mixed with some areas of low attenuation, the latter consistent with fat. See Video 115.13 for the full study. (Courtesy Michael B. Gotway, MD.)



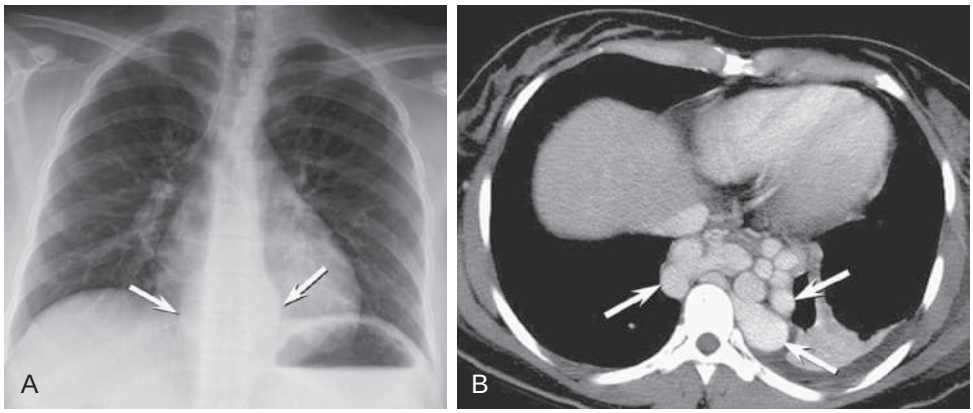
eFigure 115.46 Mediastinal mass caused by aortic aneurysm. Frontal chest radiograph shows a huge left-sided mediastinal mass without visualization of a normal thoracic aorta. See Video 115.14 for an enhanced chest computed tomography showing a huge aneurysm of the descending thoracic aorta with mural thrombus. (Courtesy Michael B. Gotway, MD.)



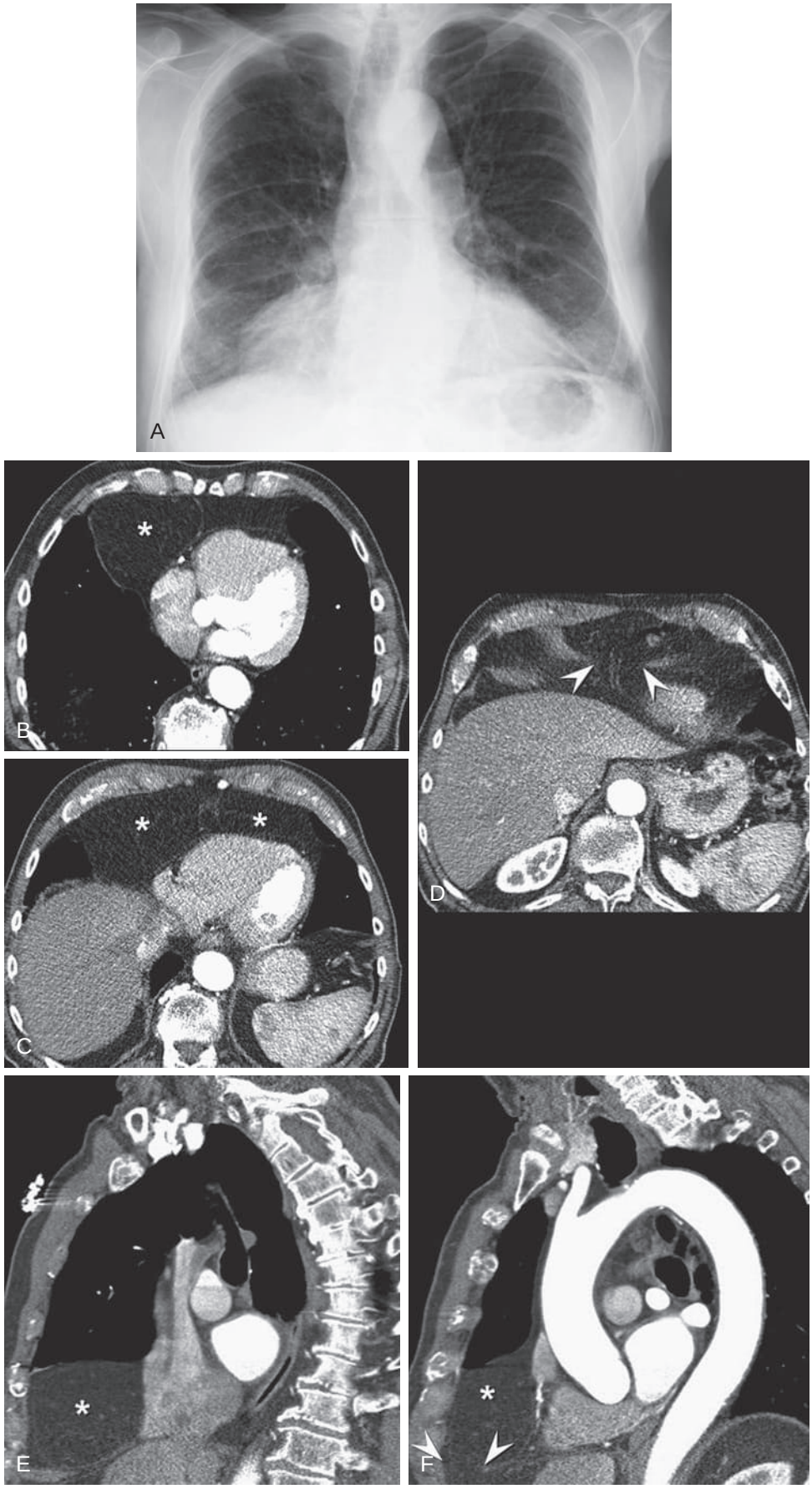
eFigure 115.47 Mediastinal mass caused by superior vena cava aneurysm. (A) Frontal chest radiograph shows a right-sided mediastinal mass (*arrow*). Patient had undergone Glenn shunt (superior vena cava-to-pulmonary artery) for double outlet right ventricle. (B) Axial enhanced chest computed tomography shows a 6-cm aneurysm of the superior vena cava (*arrow*). (Courtesy Michael B. Gotway, MD.)



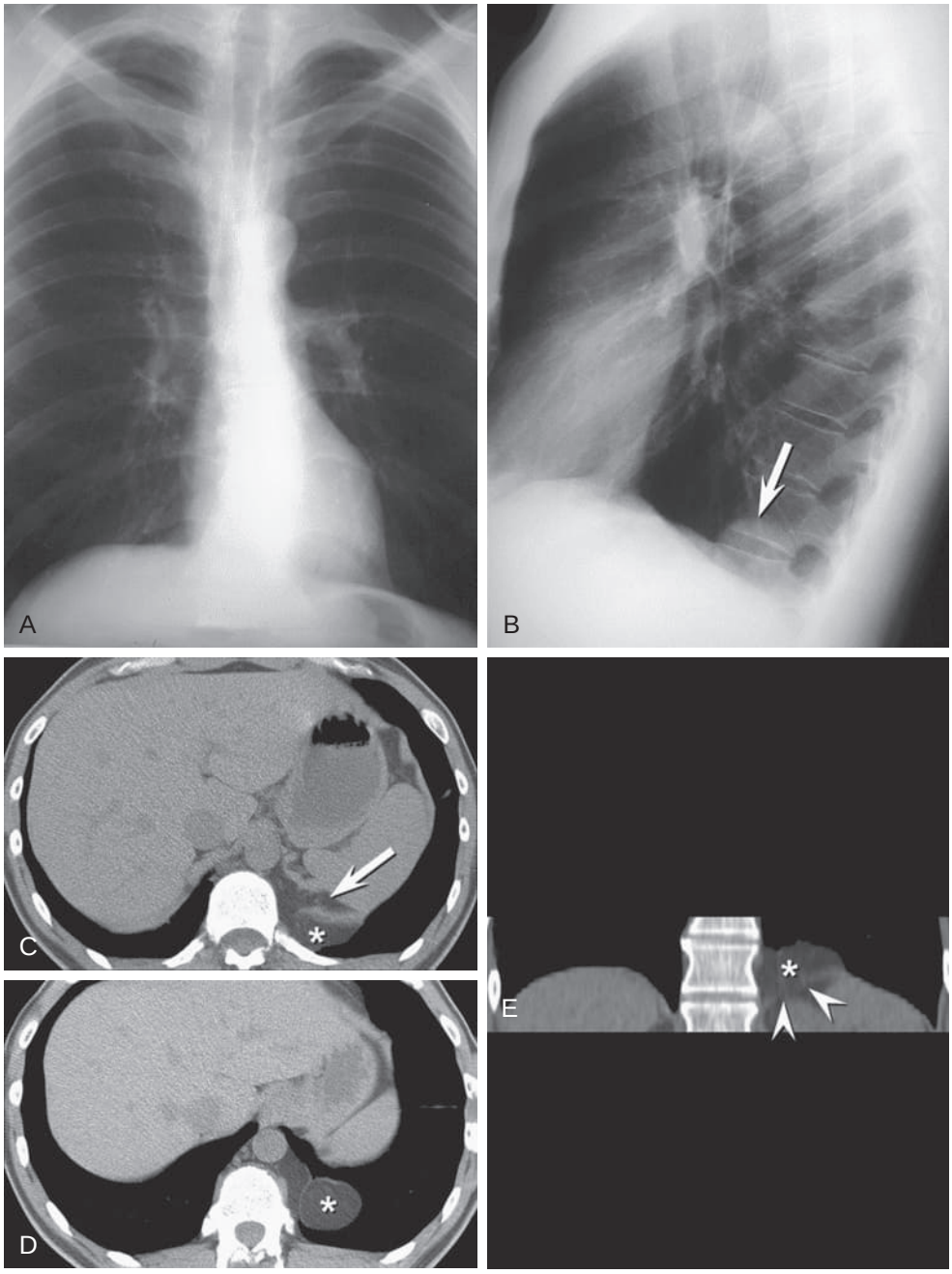
eFigure 115.48 Mediastinal mass caused by enlargement of the azygos vein. (A) Frontal chest radiograph shows a mass (*arrow*) in the right tracheobronchial angle; this is the normal position of the anterior portion of the azygos vein. (B–D) Axial enhanced chest computed tomography shows dense contrast enhancement of the enlarged azygos vein (*arrows*). See Video 115.15 for the full study. (Courtesy Michael B. Gotway, MD.)



eFigure 115.49 Mediastinal mass caused by esophageal varices. (A) Frontal chest radiograph shows bilateral paraspinous line displacement (*arrows*) consistent with a posterior mediastinal mass. (B) Axial enhanced chest computed tomography shows that the posterior mediastinal mass is caused by periesophageal varices (*arrows*). (Courtesy Michael B. Gotway, MD.)



eFigure 115.50 Foramen of Morgagni hernia. (A) Frontal chest radiograph shows a smoothly circumscribed right cardiophrenic angle mass. Axial (B–D) and sagittal (E and F) enhanced chest computed tomography scans show that the right cardiophrenic angle mass (*asterisk*) contains fat and originates within the abdomen, herniating into the thorax through an anteromedial diaphragmatic defect (*arrowheads*, D and F). Note that vessels, seen as thin linear hyperattenuating streaks, can be seen accompanying the fat herniation (D). See Video 115.16 for the full axial study. (Courtesy Michael B. Gotway, MD.)



eFigure 115.51 Foramen of Bochdalek hernia. Frontal (A) and lateral (B) chest radiographs show a smoothly circumscribed contour abnormality along the posterior left diaphragm (*arrow*, B). The finding is difficult to appreciate on the frontal chest radiograph (A) but is readily seen on the lateral projection (*arrow*, B). Axial (C and D) and coronal (E) unenhanced chest computed tomography shows that the lesion (*asterisk*) consists entirely of fat, originating from the abdomen and extending into the posteromedial thorax through a diaphragmatic defect (*arrow*, C, and *arrowheads*, E). (Courtesy Michael B. Gotway, MD.)

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116 MEDIASTINITIS AND FIBROSING MEDIASTINITIS

ROBERT J. LENTZ, MD • JAMES E. LOYD, MD

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INTRODUCTION

Mediastinitis refers to an inflammatory insult to the mediastinum of any origin. Inflammation confined within a mediastinal organ or structure but not involving the interstitium of the mediastinum is not considered mediastinitis (e.g., esophagitis, myocarditis, or granulomatous inflammation within lymph nodes secondary to sarcoidosis or contained infection). Acute mediastinitis usually has an infectious component. Several mechanisms underlie the majority of cases, including perforation of a nonsterile hollow viscus or extension of infection from an adjacent site (e.g., neck, abdomen, sternotomy incision). There are also two notable chronic inflammatory and/or fibrotic mediastinal processes, fibrosing mediastinitis and mediastinal granuloma, that may compromise one or more of the vital structures contained within.

ACUTE MEDIASTINITIS

Acute mediastinitis is a serious illness with high rates of morbidity and mortality and usually implies bacterial infection within the mediastinal space. Despite its sometimes dramatic presentation, prompt clinical detection is often challenging and requires a sufficiently high index of suspicion in the evaluation of an acutely ill patient. Diagnostic efforts focus on confirming mediastinitis, identifying the mechanism by which mediastinitis has developed, and elucidating the mediastinal structures involved. Management nearly always includes antibiotics and mechanical débridement via operation or, in selected cases, percutaneous drainage. Endoscopic interventions are emerging as useful adjuncts in specific situations.

The incidence of acute mediastinitis is difficult to determine given the wide range of insults that may result in mediastinitis often reported in distinct literatures and typically in case series format. For example, in Iceland over a 28-year period, esophageal perforation was reported to have an incidence of 3.1 per million per year, with 52% of these cases resulting from iatrogenic injury, 24% spontaneous, and 17% related to foreign body ingestion.[1] Descending necrotizing mediastinitis is widely considered a rare but grave diagnosis without a well-described incidence but with a mortality ranging from 10–15% to 50%.[2–4] Post-sternotomy mediastinitis or deep sternal wound infection has been reported to have an incidence of 1–2%, with an associated mortality of 20–30%.[5,6]

Clinical presentation, useful diagnostic studies, and etiologic mechanisms underlying acute mediastinitis are reviewed here, followed by a discussion of management considerations (Table 116.1).

ANATOMIC CONSIDERATIONS

The mediastinum is the space in the central chest that is situated between distinct left and right pleural cavities and is additionally bound by the sternum anteriorly, the vertebral column posteriorly, the thoracic inlet superiorly, and the diaphragm inferiorly. This space is home to a diverse cast of structures, including the heart, great vessels, esophagus, trachea and proximal mainstem bronchi, thymus, thoracic duct, an extensive network of lymph nodes and connecting lymphatic channels, the sympathetic trunk, and phrenic, vagus, and left recurrent laryngeal nerves, all enveloped by mediastinal fat and loose connective tissue.

Pertinent to potential causes of infectious contamination of the normally sterile mediastinum, it is noteworthy that two nonsterile hollow viscera, the esophagus and trachea with proximal mainstem bronchi, transit the mediastinum. The mediastinum is also contiguous via shared fascial planes with the deep spaces of the neck and the retroperitoneum.

A delineation of the mediastinum into anterior, middle, and posterior compartments is commonly encountered. Because these divisions are not anatomic (or universally agreed on), their consideration is of limited utility in the diagnosis and management of acute mediastinitis, and they are not reviewed here. They may have more value with respect to the diagnosis of mass lesions within the mediastinum (see Chapter 115).

CLINICAL PRESENTATION

The prototypical presentation of acute mediastinitis, and historically the most common cause, is Boerhaave syndrome. A classic case includes overeating and/or overdrinking followed by vomiting forceful enough to cause spontaneous rupture of the esophagus, thus resulting in spillage of gastric contents, oral or enteric flora, and air into the mediastinum.[7–9] This results in immediate and unrelenting retrosternal chest pain, worse on inspiration and with cough, followed rapidly by signs and symptoms of a robust systemic inflammatory response, including fever, chills or rigors, tachycardia and tachypnea, and ultimately shock. Pain radiating to the epigastrium, neck, or interscapular region may also be present, implying involvement of the inferior, superior, and posterior aspects of the mediastinum, respectively. Pneumomediastinum (Fig. 116.1, eFig. 116.1), unilateral or bilateral pneumothorax or hydropneumothorax (progressing rapidly to empyema), and subcutaneous emphysema or palpable neck or chest wall crepitus are frequently present. The Hamman sign, a systolic crunching sound at the cardiac apex caused by cardiac motion within an air-filled mediastinum, is occasionally reported.[10] Mackler's triad of chest pain, vomiting, and subcutaneous emphysema is identified in a minority of patients.[11–13]

Although acute mediastinitis of any origin tends to share aspects of this classic description, not all patients will present in such a dramatic and stereotypical fashion. The presentation varies depending on the mechanism and location of the insult, the magnitude of the infectious and/or noninfectious inflammatory inoculum, and the underlying immune status of the patient. For example, the rapid clinical deterioration often seen in classic Boerhaave syndrome results from substantial polymicrobial contamination by swallowed oral flora in addition to reflux of acidic gastric contents through the esophageal defect, which typically develops near the gastroesophageal junction. Such a fulminant course may not be observed in the setting of an iatrogenic injury during esophageal dilation in a patient with an empty stomach, early institution of antibiotics in response to rapid recognition of a possible complication, and possibly endoscopic intervention.

In cases of direct extension of infection from a compartment in communication with the mediastinum, the initial symptoms of the primary infection may dominate the

Table 116.1 Acute Mediastinitis: Causes and Clinical Settings

PERFORATION OF A THORACIC VISCUS
Forceful vomiting (Boerhaave syndrome)
Direct penetrating trauma to esophagus or trachea
Foreign body ingestion or aspiration
Iatrogenic complication of instrumentation: endoscopy, bronchoscopy, intubation or airway management, transesophageal echocardiography, central venous catheter placement
Erosion of carcinoma or necrotizing infection
DIRECT EXTENSION FROM OUTSIDE MEDIASTINUM
Descending necrotizing mediastinitis from pharyngeal, odontogenic origin
Pancreatitis
Pneumonia or empyema
Osteomyelitis of rib, vertebrae, or paraspinous abscess
MEDIASTINITIS AFTER CARDIOTHORACIC SURGERY
SPONTANEOUS MEDIASTINITIS
Hematogenous seeding, usually by *Streptococcus*
Hemorrhagic mediastinitis of inhalational anthrax

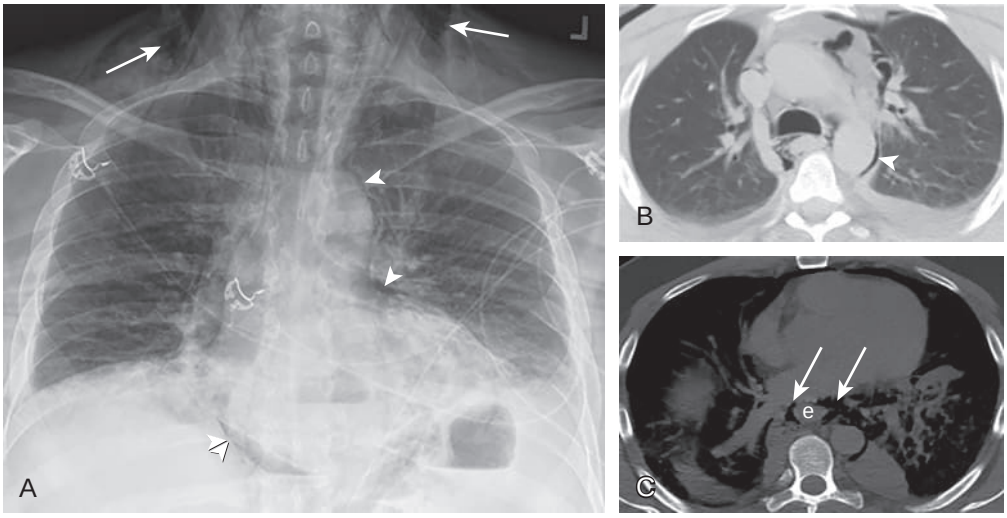

Figure 116.1 Esophageal perforation. (A) Frontal chest radiograph shows pneumomediastinum outlining the aortic arch and left mediastinum (*single arrowheads*) as well as along the diaphragm (*double arrowheads*), and bilateral subcutaneous emphysema (*arrows*). (B–C) Axial unenhanced computed tomography displayed in lung (B) and soft tissue (C) windows shows pneumomediastinum along the aortic arch (*arrowhead,* B) and concentrated more distally around the esophagus (*arrows,* C). e, esophagus. (Courtesy Michael B. Gotway, MD.)

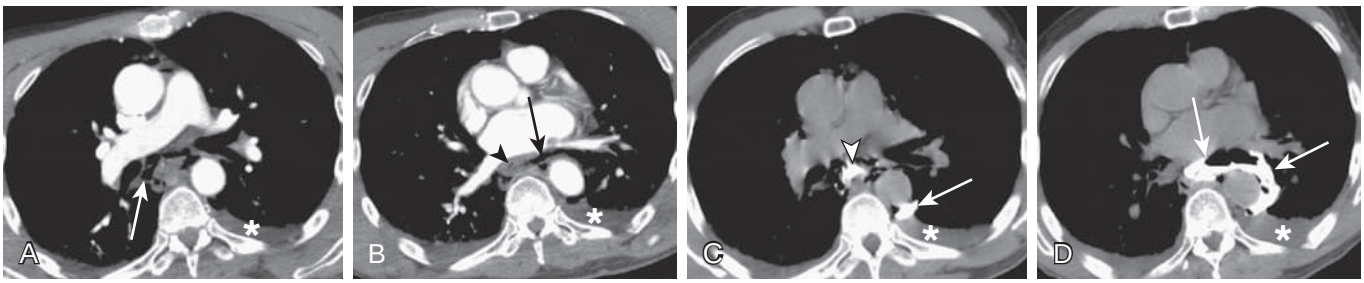

Figure 116.2 Esophageal rupture (Boerhaave syndrome). Axial chest computed tomography initially performed following intravenous contrast administration, before oral contrast administration (A–B), and after administration of oral contrast (C–D) shows pneumomediastinum (*arrows* in A and B) in close proximity to the esophagus (*arrowhead* in B). Left pleural effusion *(asterisks)* is evident. Following administration of oral contrast medium, contrast material can be seen to distend the esophagus (*arrowhead* in C), subsequently opacifying the areas of pneumomediastinum (*arrows* in C–D) and extending toward the left pleural space, thus confirming an esophageal source of the perforation. (Courtesy Michael B. Gotway, MD.)

clinical picture, with early recognition of comorbid mediastinitis reliant on a high index of suspicion combined with recall of pertinent anatomic relationships. Poststernotomy mediastinitis typically manifests with signs and symptoms of systemic infection with signs of local wound infection.

EVALUATION AND USEFUL STUDIES

Evaluation for acute mediastinitis should be tailored to the clinical scenario, with close attention to structures suspected to be involved based on history, including any recent invasive interventions. Chest radiography, contrast esophagram, *computed tomography* (CT) scan of the chest, and pleural fluid analysis frequently assist in the diagnosis. Chest radiography often demonstrates a widened mediastinum. If a hollow viscus has been perforated or there is extensive gas formation from the infection, pneumomediastinum, pneumothorax, and/or hydropneumothorax may be seen. Naclerio's "V" sign, formed by air in the lower left mediastinum that permits V-shaped silhouetting of the descending aorta and left hemidiaphragm, is identified in a minority of patients[14,15] (eFig. 116.1G). In two series including 142 patients, chest radiographs were 90% sensitive for esophageal perforation, with pneumomediastinum and left hydropneumothorax most commonly present.[12,16–18] After an iatrogenic injury, radiologic signs of esophageal perforation were discernable in some patients after 1 hour and were present in 75% after 12 hours.[12,16,18,19]

If esophageal injury is suspected, or no other cause of acute mediastinitis is apparent, contrast esophagography should be pursued. Contrast extravasation into the mediastinum and/or pleural space(s) confirms the diagnosis of esophageal perforation or rupture. Water-soluble agents such as Gastrografin (diatrizoate meglumine and diatrizoate sodium solution) are suggested by many investigators instead of barium sulfate out of concern that the barium could induce further inflammation if extravasated.[20] However, barium, with higher density and better mucosal adherence, is more sensitive, with a false-negative rate for detection of esophageal perforation of 10% versus 20% for Gastrografin.[12,18,21] Thus, despite some concerns about the risks of using barium, some investigators prefer barium esophagram as the initial test when a confident diagnosis of esophageal perforation would lead to lifesaving surgery.[12]

Chest CT is the most sensitive single study for mediastinitis of any origin and offers the first radiographic indication of mediastinitis in up to one-third of cases.[22] In esophageal perforation, extraluminal air is detected in up to 92% of cases. Other suggestive findings include esophageal wall thickening, periesophageal fluid collection or abscess, extravasated contrast material from prior examinations, frank pneumomediastinum, and pleural abnormalities[12,22–24] (Fig. 116.2, eFig. 116.2). However, the perforation site is definitively identified in as few as 15% of cases in some series, demonstrating the continued need for contrast esophagram.[12,22]

In descending necrotizing fasciitis, CT of the chest and neck is nearly 98% sensitive, with common findings including fluid collections with or without gas bubbles in the mediastinum, soft tissue thickening, loss of fat planes, and pericardial and pleural effusion.[2] In post-sternotomy mediastinitis, CT may reveal fluid collections or air along with edema (eFig. 116.3). In a series of 50 patients, CT noting such abnormalities was 100% sensitive for mediastinitis within 2 weeks of surgery but only 33% specific because some postoperative air and fluid collection is expected. After postoperative day 14, such findings were 100% sensitive and specific for mediastinitis.[25]

Pleural fluid analysis may provide valuable information in the context of an acutely ill patient with pleural effusion or hydropneumothorax secondary to undiagnosed esophageal perforation. A high level of amylase or pH less than 6.0 is suggestive of the diagnosis.[26] Food particles may also be recovered. In resource-poor settings, esophageal rupture has been established by asking the patient to drink a colored liquid and then observing passage of the liquid out of a previously placed chest tube.

MEDIASTINITIS RESULTING FROM VISCERAL PERFORATION

Two hollow nonsterile viscera transit the mediastinum: the esophagus and the trachea (continuing into proximal mainstem bronchi). Perforation or rupture of either structure, whether from disease, procedural complication, or trauma, can result in mediastinal contamination and subsequent mediastinitis.

Spontaneous Esophageal Rupture (Boerhaave Syndrome)

Hermann Boerhaave's exuberantly verbose 1724 index description of the death of 51-year-old Baron John van Wassenaer, Great Admiral of the Dutch Navy, remains a classic anecdote in medical history.[15,27,28] The Baron, experiencing indigestion following a large meal of duck, experienced sudden severe chest pain while retching after taking bitter *Carduus* (thistle root extract) to induce emesis for relief. Prescribed treatments, in addition to bloodletting and an enema, included a large volume of orally administered liquid consisting of olive and almond oil, Danzig spruce beer, oats in water, wine, and a variety of herbal tinctures and teas, each exacerbating his pain. Finally, additional emetogenic agents yielded little emesis but rapid unconsciousness and death in the 18th hour of illness. Suspecting a gastric malady, Boerhaave marveled, "What reason could there be for an empty stomach into which so much liquid had gone?" Bilateral hydropneumothoraces were discovered, and "on both sides the [fluid] color was of Danzig beer thinned with Carduus and dark red and there was distinct odor of duck flesh." A left-sided esophageal defect was discovered near the diaphragm and was correctly identified as the source of his dramatic illness.

The pathophysiology of spontaneous esophageal rupture, also referred to as effort-associated or postemetic rupture, relates to increased intraesophageal pressure during intense vomiting or, less commonly, other maneuvers (weightlifting, forceful cough or sneeze, straining, childbirth, seizure, external blast injury), such that a bubble of esophageal mucosa dissects through longitudinal esophageal muscle fibers and ruptures.[7–9,29] This most commonly happens along the left posterolateral wall of the distal esophagus, accounting for 90% of cases, although the esophagus may also rupture at its mid-thoracic and cervical walls.[7,30,31] The distal left posterolateral wall weak point is at the margin of two sets of muscle fibers and is the reliable location of rupture in experiments involving human cadaveric esophagi, in which the pressure required to cause rupture was noted to be 270 to 340 mm Hg.[30] Defects average 2 to 6 cm in length but may be up to 10 cm.[7,8]

A high index of suspicion for spontaneous esophageal rupture is required to ensure prompt recognition and rapid initiation of treatment, including surgical planning. When an acutely ill patient reports the abrupt onset of typical symptoms associated with forceful emesis, suspicion for this diagnosis tends to be appropriately high. However, altered or intoxicated critically ill patients may be incapable of providing classic historical clues and therefore may present with less differentiated chest and/or abdominal pain, with differential considerations including acute coronary syndrome, aortic dissection, perforated gastric or duodenal ulcer, and pancreatitis (see Chapter 38).

In the largest series to date, including 989 cases, the mean age was 52 years and 82% of patients were men. The most common comorbidities were alcohol abuse and peptic ulcer disease, at 40% each.[8] Historically, mortality exceeded 50%, although more contemporary series report a mortality of 10% or less with urgent management within 24 hours of onset.[8,12,32–34]

Other causes of noniatrogenic esophageal perforation include malignancy-related perforation and acute esophageal necrosis. With approximately 40 case reports since the 1960s, acute esophageal necrosis is an uncommon, likely ischemic syndrome manifesting as a black, necrotic esophagus at endoscopy; this condition is associated with vascular disease, diabetes, and malnutrition and has a poor prognosis in part related to the development of mediastinitis.[35]

Iatrogenic Injuries

Iatrogenic injury of the esophagus or trachea now accounts for the majority of cases of mediastinitis caused by visceral perforation.[1,12,18,34,36] Of various procedures conducted within these structures, therapeutic esophageal maneuvers, such as dilation or endoscopic mucosal resection, are associated with the highest incidence of perforation, at 2–6%.[36] Of the various causes, malignant lesions and benign strictures caused by caustic ingestion are at greater risk for perforation.[37–39]

Mediastinitis following diagnostic endoscopy is rare but represents an important cause given the frequency with which these procedures are performed. Esophageal perforation complicates less than 0.03% of upper endoscopies.[40] In contrast, tracheal perforation during diagnostic flexible bronchoscopy, in the absence of significant disease or intervention, has not been reported, a finding related to the greater tensile strength of the large cartilaginous airways. Airway perforation may, however, complicate therapeutic bronchoscopy. In a retrospective study of 775 rigid bronchoscopies performed over a 7-year period, there was one case (0.13%) of pneumothorax, attributed to airway laceration from laser and mechanical débridement of an endobronchial tumor, and no cases of mediastinitis.[41] It is common practice to administer antibiotics if therapeutic bronchoscopy exposes tracheal cartilaginous rings, although there are few data to guide this practice.

The esophagus and large airways are intentionally perforated during two common, analogous procedures: transesophageal endoscopic ultrasound-guided fine-needle aspiration and endobronchial ultrasound-guided transbronchial needle aspiration. During these procedures, 19- to 25-gauge needles are directed through the esophagus and airway, respectively, into lesions of interest (typically, enlarged lymph nodes) within the mediastinum under ultrasound guidance. Despite making repeated small perforations and moving needles from a nonsterile lumen through the mediastinal interstitium en route to the biopsy targets, mediastinitis develops only rarely, at a rate of 0.09% for endobronchial ultrasound-guided

transbronchial needle aspiration.[42] Sampling cystic structures, highly necrotic nodes, or mediastinal granulomas (reviewed in detail later in this chapter) may increase the risk for subsequent mediastinitis, likely related to an introduction of bacteria into the interior of a lesion with poor immune surveillance.[43–46]

Another cause of tracheal or esophageal injury is iatrogenic injury during airway management. Tracheal injuries during intubation or percutaneous tracheostomy tend to involve the muscular posterior membrane of the trachea, which lacks cartilaginous support, resulting in longitudinal tracheal defects.[47] Treatment ranges from conservative management with antibiotics alone, particularly when ongoing mechanical ventilation is not required, to airway stenting or surgical repair.[48] Esophageal perforation has been described when airway adjuncts that engage the esophagus, such as the esophageal obturator airway, are used.

Other rare iatrogenic causes of esophageal perforation include transesophageal echocardiography, reported at a rate of 0.01% in a study of more than 7200 cardiac surgical patients, and central venous catheter migration into the mediastinum[49,50] (eFig. 116.4, Video 116.1).

Other Visceral Insults

Other mechanical or chemical trauma to the esophagus or trachea may result in perforation and mediastinitis (eFig. 116.5, Video 116.2). Penetrating and blunt trauma to the chest results in airway disruption with an incidence of 0.5–2% for both mechanisms of injury.[51] Penetrating cervical injury is more likely to result in tracheal injury than is thoracic trauma, with an incidence of up to 8%.[51] Esophageal injury accompanies airway injury in approximately 30% of penetrating cervical trauma cases and 10% of cases of penetrating chest trauma.[51] Injurious ingestions are another cause of esophageal injury. One series described six prison inmates who swallowed hypodermic needles fashioned into the shape of stars to win temporary reprieves from incarceration, all of whom required surgical intervention.[52] Intentional and accidental ingestions of corrosive agents, including alkaline ingestions such as lye or alkaline batteries, acidic compounds, or paraquat (an herbicide that causes tissue injury via oxidative stress) are well-described causes of esophageal injury.[38]

MEDIASTINITIS SECONDARY TO EXTENSION FROM OUTSIDE THE MEDIASTINUM

Although its lateral aspects are enclosed by the mediastinal portion of the parietal pleura on either side, the mediastinum is contiguous superiorly with deep spaces of the neck and inferiorly with the abdomen. The same fascial plane investing the trachea, esophagus, and carotid sheaths extends through the thoracic inlet with these structures, then through the diaphragm with the descent of the esophagus, aorta, and inferior vena cava into the retroperitoneum, thus comprising the visceral space. Additional deep spaces in the neck are contiguous with the mediastinum, including the prevertebral, retrovisceral (divided into the "retropharyngeal" and "danger" spaces by the alar fascia), and pretracheal spaces[3,53] (Fig. 116.3).

Descending Necrotizing Mediastinitis

Acute mediastinitis caused by direct extension of an oropharyngeal or cervical infection is most commonly referred to as descending necrotizing mediastinitis, so named because the infection descends via one of the deep spaces in the neck into the mediastinum and is classically polymicrobial, including gas-producing organisms that effect rapid tissue necrosis.[4] This life-threatening complication of periodontal, peritonsillar, odontogenic, or pharyngeal infection is rare, with approximately 400 cases reported between 1960 and 2008.[2] The preantibiotic mortality rate of 50% has steadily declined but remains significant at 10–15% in more contemporary series.[2,4,54,55] Pharyngeal infections have overtaken odontogenic infections as the most common source.[2] Extension into the posterior mediastinum via the "danger space" subdivision of the retrovisceral space appears most common, up to 70% in some series, where infection may also access both pleural spaces, the pericardium, and the abdomen.[2,4,54–56] Gravity and negative intrathoracic pressure rapidly propagate infection into the mediastinum once pathogens violate fascial planes to gain access to a deep space in the neck. Infection descending into one mediastinal compartment often does not remain confined there, given the necrotizing nature of this infection.[2]

Clinical manifestations of descending necrotizing mediastinitis may be masked by symptoms of the cervical or oropharyngeal infection, thereby causing a delay in diagnosis. In one series, one-third of patients had already been hospitalized at another institution before the diagnosis was established.[2] Dyspnea, chest discomfort, and signs of worsening sepsis should prompt further investigation for mediastinitis. Involvement of the pericardium may lead to tamponade. Patients with descending necrotizing mediastinitis may have widening of the retrovisceral space, with or without associated air-fluid levels. CT scans of the neck and chest are usually definitive[2,4] (Fig. 116.4).

Ascending and Other Uncommon Causes of Mediastinitis From Direct Extension

Rarely, mediastinitis may result from intra-abdominal processes. Pancreatic disease is a rare but well-known cause of pleural disease, typically by way of pancreaticopleural fistulas extending through the esophageal or aortic hiatus connecting pancreatic pseudocyst to the left pleural space. Acute or recurrent pancreatitis can lead, by similar mechanism, to enzymatic mediastinitis, a rare example of a noninfectious cause of acute mediastinitis.[57,58] Ascending mediastinitis has also been associated with emphysematous pyelonephritis.[59] Benign gastric or esophageal ulcers have rarely been reported to rupture into the mediastinum or sometimes into the pericardium, with subsequent mediastinitis or pneumopyopericardium.[60,61] Tuberculous osteomyelitis involving the vertebrae (Pott disease) or ribs has rarely been reported to contaminate the mediastinum by direct extension.

MEDIASTINITIS FOLLOWING CARDIAC SURGERY

Mediastinitis after cardiac surgery is another significant manifestation of iatrogenic acute mediastinitis in the modern era. Most cases result from direct extension via an infected median sternotomy incision. Mediastinal infection

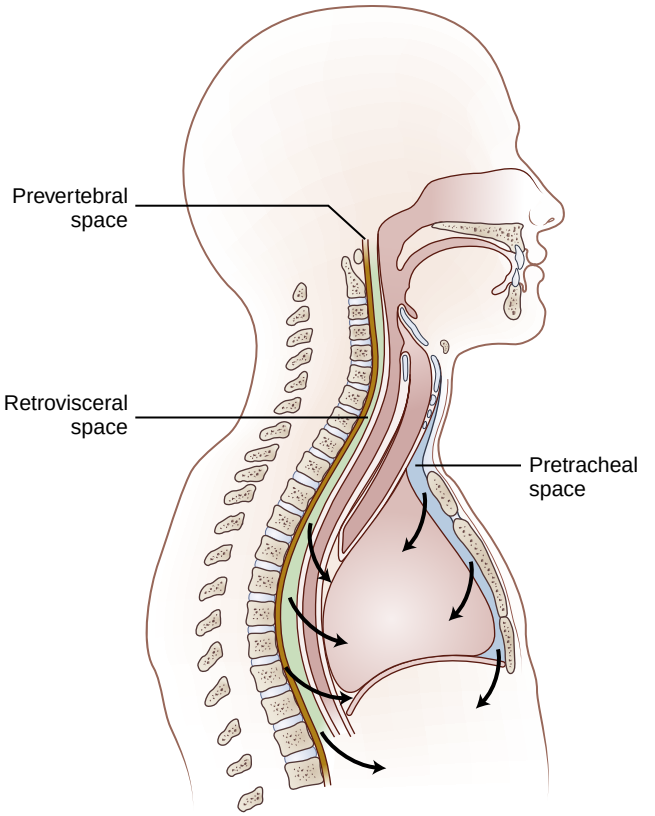

Figure 116.3 Deep spaces of the neck and their communication with the mediastinum. The retrovisceral space is commonly divided into the danger space (extending to the diaphragm) and the retropharyngeal space (terminating at T1), which are separated by loose alar fascia. (Modified from Freeman RK, Vallières E, Verrier ED, et al. Descending necrotizing mediastinitis: an analysis of the effects of serial surgical debridement on patient mortality. *J Thorac Cardiovasc Surg.* 2000;119:260–267.)

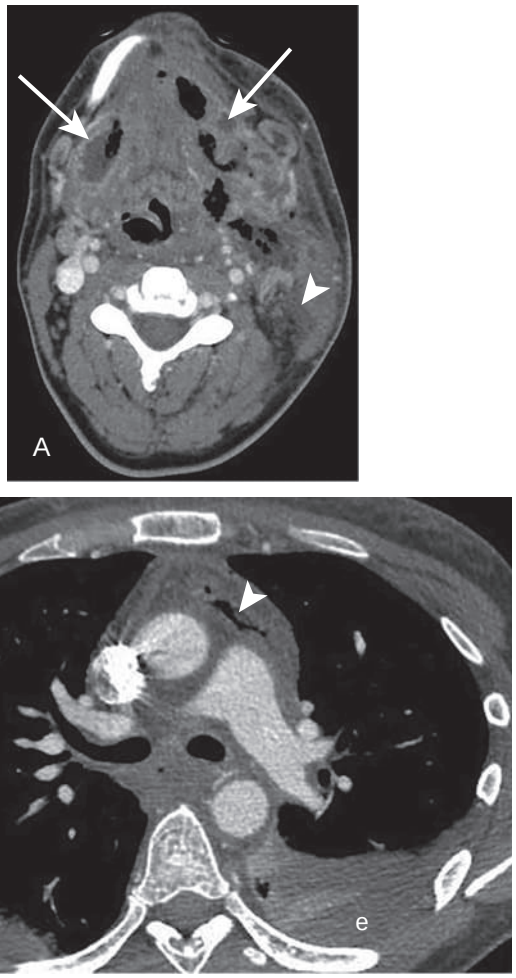

Figure 116.4 Descending necrotizing mediastinitis. (A) Axial enhanced neck computed tomography shows bilateral abscesses near the submandibular spaces (*arrows*) with soft tissue gas and fat stranding (*arrowhead*) in the left posterior triangle. (B) At the level of the main pulmonary artery, pneumomediastinum (*arrowhead*) is evident. Soft tissue infiltration is present throughout the anterior mediastinum and left-greater-than-right pleural effusions (e) are present.

following cardiac surgery is uncommon, with an estimated incidence of approximately 1% in most contemporary series.[5,62] Given the frequency with which cardiac surgery is performed and the widespread use of median sternotomy, post-sternotomy mediastinitis has become a substantial clinical problem, with a mortality rate of 20–30%.[5,6]

Risk factors associated with the development of mediastinitis after cardiac surgery in several large series consisting of more than 40,000 patients included diabetes mellitus, obesity, use of internal mammary arteries (higher risk if bilateral), prolonged operation, postoperative intensive care unit stay exceeding 5 days or ventilation exceeding 48 hours, need for reexploration, and assist device implantation.[5,6,63–66] Other comorbidities, such as COPD, advanced age, and renal failure, have been reported in some studies. Diabetic patients undergoing coronary artery bypass grafting in which both internal mammary arteries are used appear to be at especially high risk for post-sternotomy mediastinitis and have a higher mortality than nondiabetic patients experiencing the same complication.[5] Guidelines developed to reduce the risk of postoperative deep sternal wound infections include the use of topical nasal mupirocin to curb *Staphylococcus* carriage, a preoperative chlorhexidine bath or shower, strict perioperative glycemic control, appropriate perioperative antibiotic use and application of topical antibiotics to the cut edges of the sternum, avoidance of bone wax, and careful attention to techniques to maintain sternal stability in patients at higher risk for sternal malunion (including patients with obesity or COPD).[67] Several series report nearly total elimination of post-sternotomy mediastinitis after institution of some of these suggested best practices.[68,69] The use of a skeletonized rather than pedicled internal mammary graft harvest technique has also been suggested to reduce the risk.[70] The reason for this difference may be that skeletonized grafts, in which the artery is dissected away from associated lymphatic and venous drainage, preserve more collateral circulation to the sternum than do pedicled grafts.

Cardiac surgery–related mediastinitis tends to be less acutely devastating than in the settings described previously. The clinical course consists of fever and systemic signs, followed by bacteremia and local signs of wound infection.[71] The diagnosis is usually made at the time of reexploration of the sternotomy wound and rests on a high clinical suspicion in the appropriate setting. CT is particularly helpful in identifying and discerning soft tissue swelling, fluid

collections, and sternal erosion or dehiscence[72] (see eFig. 116.3). Patients with fever, positive blood culture results, and wound abnormalities in the post-sternotomy period should be evaluated surgically to confirm the presence of mediastinitis, and any necessary débridement should be performed.

"SPONTANEOUS" OR "PRIMARY" MEDIASTINITIS

Acute mediastinitis in the absence of visceral perforation, descending or ascending infection, recent cardiac surgery, trauma, or another obvious direct-extension mechanism is extremely rare but has been reported. Such cases fall into two categories: spontaneous mediastinitis typically involving *Streptococcus* species and inhalational anthrax.

Spontaneous Mediastinitis

Acute mediastinitis has been reported in the absence of the typical predisposing and etiologic factors reviewed earlier in this chapter. Known in the literature predominantly by case reports, such cases have been labeled "spontaneous mediastinitis" or "primary mediastinitis." Some cases coincide with known foci of infection, such as pneumonia, empyema, or bacteremia,[73–76] whereas others have been reported in isolation of any known infectious source.[77,78] The mechanism of mediastinal infection is presumed to be bacteremia or extension directly or via lymphatic transit in patients with comorbid pneumonia and/or empyema.

Hemorrhagic Mediastinitis Secondary to Inhalational Anthrax

Anthrax, caused by *Bacillus anthracis* infection, is primarily a disease of livestock and is historically most prevalent in the Middle East, although it remains endemic in the soil with sporadic but worldwide distribution.[79] More recently, anthrax has emerged as an important disease of bioterrorism. Clinical syndromes are classified by the primary site of infection: cutaneous, gastrointestinal, injectional, or inhalational.

Inhalational anthrax, or *woolsorter's disease*, is contracted by inhaling *B. anthracis* spores, which are highly resistant to environmental degradation.[79] Spores inhaled into distal conducting airways and alveoli are ingested by pulmonary macrophages and are transported to hilar and mediastinal lymph nodes. Here, *B. anthracis,* which resists killing because of its capsule, produces large amounts of two toxins, lethal factor and edema factor, leading to local edema, necrosis, and hemorrhage characteristic of hemorrhagic mediastinitis, followed by pathogen and toxin leakage into the systemic circulation, with resulting septic shock and death.[79,80]

Sporadic inhalational anthrax is rare. Before bioterrorism-related incidents in 2001, the last fatal domestic case, attributed to yarn imported from Pakistan, was in 1976.[81] Modern clinical knowledge of inhalational anthrax has been derived from several outbreaks. An accidental release of weapons-grade anthrax in Sverdlovsk, Russia, in 1979 resulted in at least 42 deaths.[82,83] In 2001, intentional dispersion of *B. anthracis* spores via the U.S. Postal Service resulted in 11 cases each of cutaneous and inhalational anthrax, with five deaths in the latter group.[84,85] Incubation time is typically 4 to 6 days, followed by onset of a biphasic illness with an initial prodromal flu-like phase lasting 2 to 4 days characterized by fever, malaise, myalgias, and nonproductive cough. This is followed by a fulminant phase of acute mediastinitis, respiratory distress, chest pain, and septic shock culminating in death within days.[80,84–86] Antibiotics in the prodromal phase may be lifesaving, but treatment initiated in the fulminant phase is unlikely to change the clinical course.[86]

Chest radiographs and chest CT scans typically show mediastinal widening and pleural effusions.[87] The triad of hemoconcentration, widened mediastinum, and altered mental status is characteristic.[88] The diagnosis is established by demonstration of gram-positive, boxcar-shaped bacilli in tissue or body fluid specimens or in the blood buffy coat. Direct fluorescent antibody testing, polymerase chain reaction, and serologic tests are available for confirmation. Prompt antibiotic administration at the first suspicion of anthrax is the cornerstone of treatment. Historically, inhalational anthrax is a devastating disease even with appropriate treatment: 12 of 13 well-documented sporadic cases in the United States had fatal outcomes.[81] In the 2001 bioterrorism outbreak, prompt diagnosis and initiation of antibiotic therapy in addition to aggressive drainage of mediastinal and pleural collections resulted in survival of 6 of 11 patients.

MANAGEMENT OF ACUTE MEDIASTINITIS

Acute mediastinitis management nearly universally focuses on two interventions: prompt initiation of appropriate antimicrobial coverage and timely mechanical débridement. Additionally, patients with suspected esophageal perforation should immediately cease oral intake and be started on gastric acid suppression.

Microbiology and Antimicrobial Selection

The microbiology of mediastinitis varies according to the mechanism of infection. In mediastinitis complicating esophageal perforation or descending necrotizing mediastinitis, the predominant microorganisms are oral and upper aerodigestive tract flora. An estimated 40–60% of such infections are polymicrobial, most often a mix of anaerobic and aerobic bacteria.[2,89] Most nonmixed infections are anaerobic, with aerobic infections accounting for approximately 20% of cases.[2,89] Commonly isolated anaerobes include *Bacteroides*, *Peptostreptococcus*, *Fusobacterium*, *Propionibacterium*, and *Prevotella* sp. *Streptococcus* sp dominate among aerobic isolates in most series, with *Staphylococcus*, *Haemophilus*, *Klebsiella*, and *Pseudomonas* sp isolated with less frequency.[2,89] Accordingly, broad antibiotic coverage, including agents active against gram-negative, gram-positive, and anaerobic organisms, is prudent in such cases.

Post-sternotomy mediastinitis is most often caused by skin flora. *Staphylococcus epidermidis* and *Staphylococcus aureus* are the most frequent isolates in most series.[65,90–93] Polymicrobial infections are present in a significant proportion of cases (6–20%). More contemporary series also report that significant numbers of infections are caused by gastrointestinal pathogens, with *Enterobacteriaceae*

accounting for 25% of deep sternal wound infections in one series.[92] Methicillin-resistant *S. aureus* remains an uncommon cause, accounting for approximately 0.5–2% of cases.[92,94]

Fungal mediastinitis related to any etiologic mechanism is rare but can be devastating. *Candida* species are uncommonly recovered from mediastinal cultures following esophageal violation or cardiac surgery, with mortality rates reported in excess of 70%.[95] *Aspergillus* mediastinitis has also been reported in the context of recent cardiac surgery or descending necrotizing mediastinitis, and it has a high fatality rate.[96,97] Other angioinvasive fungi are reported as infrequent causes of fungal mediastinitis, such as mediastinal mucormycosis, with mortality exceeding 85%.[98] Tuberculous and nontuberculous mycobacteria are other uncommon causes of post-sternotomy mediastinitis, with tuberculosis accounting for 95% of mycobacterial sternal wound infections in a study involving cases from 23 countries but dominated by cases from India.[99]

When hemorrhagic mediastinitis of inhalational anthrax is suspected, ciprofloxacin or doxycycline with a second agent, either clindamycin or penicillin, is recommended.[88] Anthrax is resistant to third- and fourth-generation cephalosporins. Most patients in the bioterrorism outbreak were treated with multiple agents including a fluoroquinolone.[84] For postexposure prophylaxis, ciprofloxacin or doxycycline orally along with immunization with antitoxin antibodies is recommended.[88,100]

Mechanical Débridement: Operative, Percutaneous, and Endoscopic Interventions

Débridement and/or percutaneous drainage of infected or inflamed mediastinal tissues is typically necessary in acute mediastinitis, although the approach and urgency of débridement may vary widely, reflective of the wide variation in causes of mediastinitis.

Mediastinitis with frank uncontrolled sepsis requires urgent surgical intervention. Such is typically the case in classic Boerhaave syndrome and descending necrotizing mediastinitis. In esophageal rupture, mortality has been reported to increase from 10–15% to 40–60%, because of the onset of multiorgan dysfunction, when intervention (or presentation) is delayed more than 24 hours.[12,32–34] The surgical approach varies according to the location of the esophageal defect and other affected mediastinal or pleural structures.[12] Rarely, nonoperative management in the setting of a significant esophageal defect may be considered. Several investigators have reported successful medical management when sepsis is absent several days after the injury, a wide-mouthed defect is well encapsulated within the mediastinum and contents can freely drain back into the esophagus, and the pleural spaces are uninvolved, among other criteria.[101–103] In descending necrotizing mediastinitis, delay in diagnosis, delay in operative intervention, and lack of thoracotomy to permit comprehensive mediastinal exploration and débridement, in addition to transcervical drainage, have been associated with worse outcomes. With prompt intervention, including thoracic exploration, mortality rates of 10–15% have been reported, with one meta-analysis suggesting a mortality of 47% with the transcervical approach alone.[2–4,54]

Similarly, post-sternotomy mediastinitis requires early surgical exploration with débridement and drainage, in addition to appropriate antimicrobial therapy.[5,66,71,90,96] The clinical course of severe mediastinitis secondary to visceral perforation, descending infection, or post-sternotomy status often includes reoperation and prolonged hospitalization.

Because most mediastinitis cases from perforated viscus in the modern era relate to endoscopic injuries or surgical anastomotic complications that often have a more indolent course and/or more focal mediastinal involvement, percutaneous and endoscopic interventions have emerged as options in selected cases. Percutaneous intervention can be used to drain focal abscesses or fluid collections related to perforation if more widespread mediastinal contamination is absent (eFig. 116.6). In one series describing 51 patients, 3 patients died before intervention, 31 underwent standard thoracotomy and repair that led to 11 deaths, and 17 highly selected patients with contained mediastinal contamination by imaging and endoscopic inspection were managed successfully with targeted drainage and antibiotic therapy.[13] Endoscopic therapies include clips, stents, tissue adhesives, endoscopic stitching, and vacuum therapy. Reports of these treatments often suggest success rates higher than 80% in selected patients, although these reports are generally case series and so are limited in methodologic vigor.[18,36,104,105]

FIBROSING MEDIASTINITIS AND MEDIASTINAL GRANULOMA

There are two notable syndromes of chronic mediastinal inflammation and/or fibrosis: *fibrosing mediastinitis* (FM) and *mediastinal granuloma* (MG). A third subacute inflammatory syndrome, mediastinal adenitis, is also reviewed, given a degree of clinical overlap with early MG.

FM describes a progressive fibrotic mass typically emanating from a mediastinal lymph node station that causes fusion of adjacent tissue planes and invasive incorporation into and stenosis or obliteration of nearby structures, including pulmonary arteries, veins, airways, *superior vena cava* (SVC), or esophagus[106] (Fig. 116.5). MG refers to a thinly encapsulated collection of semiliquid granulomatous debris typically comprising coalesced necrotic mediastinal lymph nodes, which often become partially or entirely calcified with time[106,107] (Fig. 116.6). Mediastinal adenitis refers to robust enlargement of an involved hilar or mediastinal lymph node related to acute or subacute granulomatous pulmonary infection[106] (eFig. 116.7).

All three syndromes are most commonly attributed to aberrantly robust and persistent immune responses to *Histoplasma*, an environmental fungus with wide distribution worldwide and the most common endemic mycosis in the Americas.[106] A syndrome similar to post-*Histoplasma* FM has been described in association with IgG4-related disease, granulomatosis with polyangiitis, and rare histiocytic disorders. MG and mediastinal adenitis can also result from other granulomatous infections, namely from tuberculosis in endemic areas.

Distinguishing these syndromes from one another and, in the case of FM, determining whether the syndrome is a

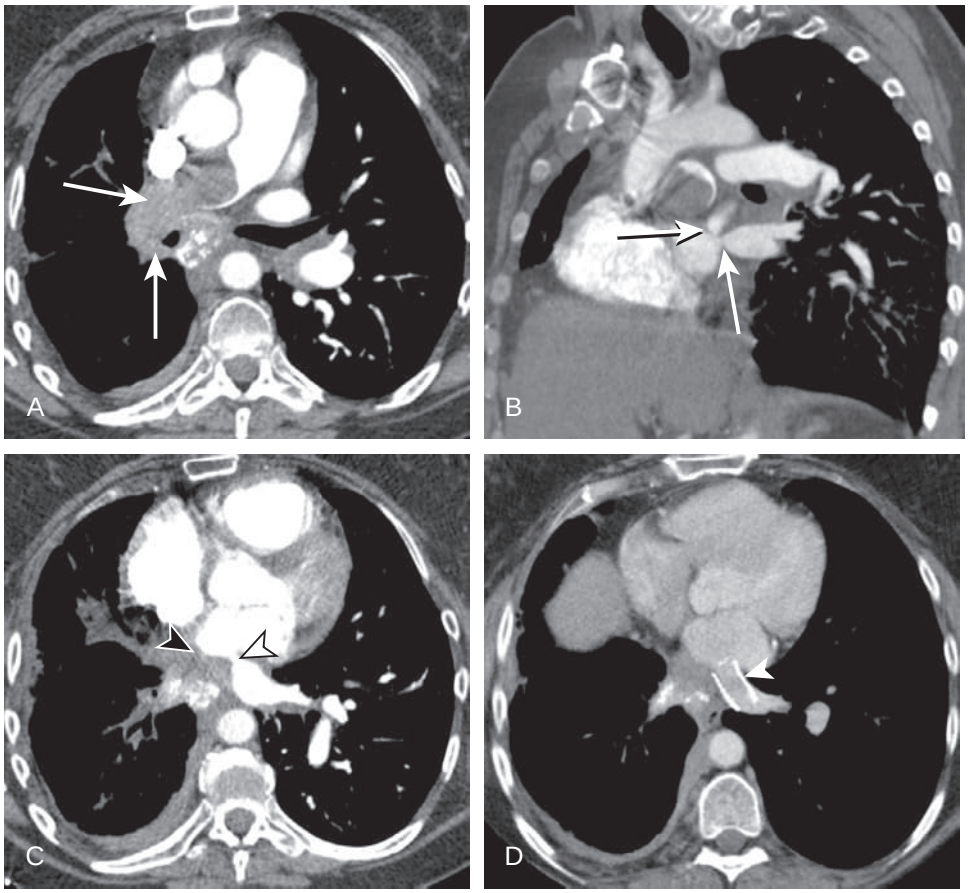

Figure 116.5 Fibrosing mediastinitis in a 44-year-old woman. (A) The right main pulmonary artery is completely obstructed shortly after its origin by a fibrotic mass *(arrows)*. A subcarinal mass with speckled calcification and right-sided large airway stenosis are also present. (B) In this oblique reconstruction, the left upper and lower pulmonary veins are constricted to 2 mm at their origins *(arrows)*. (C–D) Left inferior pulmonary vein before and after vascular stenting *(white arrowheads)*. Completely obstructed right inferior pulmonary vein *(black arrowhead)* is also visible. (Courtesy James Loyd, MD.)

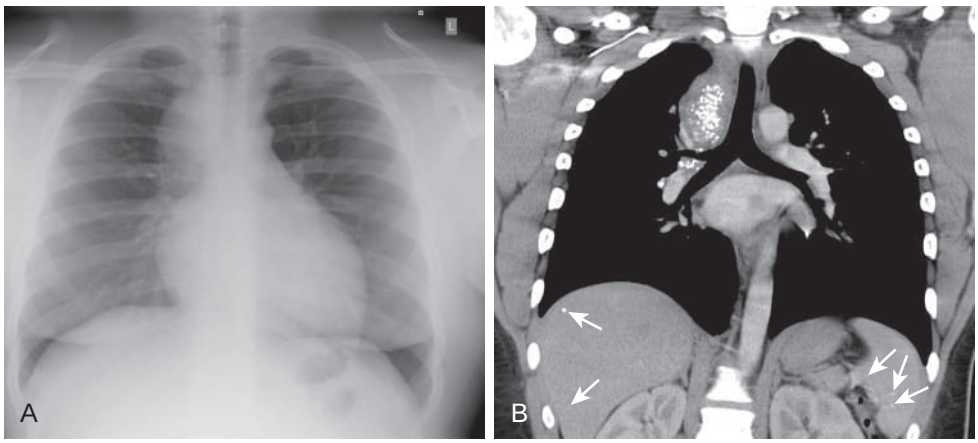

Figure 116.6 Mediastinal granuloma in a 15-year-old boy. (A) Chest radiograph showing a right paratracheal abnormality. (B) Coronal computed tomography showing mediastinal granuloma with pathognomonic highly speckled internal calcification. Note also characteristic punctate calcifications in the liver and spleen *(arrows)*. (Courtesy James Loyd, MD.)

post-*Histoplasma* condition or has another cause, is imperative prognostically and therapeutically because there is wide variation in appropriate treatments and prognosis among these entities[108–110] (Table 116.2). Chapter 115 discusses mediastinal tumors and cysts, which may also occasionally be challenging to distinguish on presentation.

FIBROSING MEDIASTINITIS

Most of the population of several millions in the middle of the United States has been infected with *Histoplasma capsulatum*, usually with no recognized symptoms. The most severe late complication of *Histoplasma* exposure or infection is *post-Histoplasma fibrosing mediastinitis* (PHFM). Twenty percent of all PHFM patients have involvement of both lungs, a condition that carries a very high mortality.[111,112] If mediastinal structures are involved bilaterally, the disease is almost uniformly fatal.[113] The prevalence of PHFM has not been described; however, as an indication of its prevalence, in a single institution in Tennessee an average of 10 new PHFM patients have been evaluated annually for several decades.[112,114]

No other infection triggers a syndrome like PHFM. Even before modern imaging, observant clinicians noted 4 decades ago, "it is difficult to prove that all cases of MG and FM are due to histoplasmosis when the cultures and

Table 116.2 Key Distinguishing Features of Fibrosing Mediastinitis and Mediastinal Granuloma

Fibrosing Mediastinitis	Mediastinal Granuloma
Solid fibrotic mass	Large, heterogeneous mass composed of thinly encapsulated semiliquid debris
Usually contains calcification, from punctate to highly calcified	No calcification in early MG; late MG with pathognomonic speckled, subcapsular, or uniform calcification
Invasive stenosis or obstruction of vasculature or airways	No stenosis or stenosis by extrinsic compression
Age >10 yr, usually 20–40 yr	Age >2 yr, incidental finding at any age
Unilateral loss of lung function in 80%; lethal in 20% with bilateral disease	Mostly asymptomatic; rarely fistulizes and drains to nearby structures; mortality very rare
Surgery high risk; vascular stenting may increase survival in bilateral disease	Resection is indicated for symptomatic disease
Most commonly post-*Histoplasma*; rare idiopathic noncalcified form associated with IgG4-RD, GPA, histiocytic disorders that may respond to medical therapy	Most commonly post-*Histoplasma*; can be precipitated by other granulomatous infections (e.g., tuberculosis)

GPA, granulomatosis with polyangiitis; *IgG4-RD,* immunoglobulin G4–related disease; *MG,* mediastinal granuloma.

silver stains are so often negative; however, we have not seen FM with tuberculosis or sarcoidosis."[115] The report bearing those words was the final in a series describing 124 patients with PHFM or MG during 25 years at a single institution. The investigators provided remarkable insight, but their hypothesis that FM is caused by rupture of fibrocaseous material from mediastinal lymph nodes has been shown to be incorrect.[112] The premise that MG was the basis for PHFM led to an era of frequent resection of MGs to prevent FM, a practice that, unfortunately, still has some advocates.[116] PHFM and MG are distinctly different clinical syndromes, with distinct natural history, which are clearly distinguishable in most cases and have different therapies.[112]

Although the basis for PHFM remains unknown, it is hypothesized that rare individuals carry a predisposition to respond excessively to *Histoplasma* cell wall remnants in mediastinal lymph nodes, thus provoking dense scar formation that invades deep within vital mediastinal structures.[108] PHFM is associated with human leukocyte antigen DQB1*04:02. In 58 PHFM patients who were studied using genome-wide association, loci were identified that provide possible clues to the location of a profibrotic genetic variant.[117,118]

Clinical Features

PHFM typically affects young adults in the second through fourth decades of life. Symptoms are often acute but belie a slow, silent progression of fibrosis to a threshold that leads to first symptoms when flow is critically reduced in vessels or airways. Hemoptysis, chest pain, and dyspnea are common.[112] Most PHFM patients (80%) ultimately experience loss of function of one lung; among those patients, most (80%) lose function of the right lung, typically by occlusion of the proximal right pulmonary artery.[112] Unilateral loss of lung function from PHFM has a generally favorable prognosis, except when serious hemoptysis caused by systemic collateral arteries arises, which may be life-threatening.[106] In contrast, bilateral involvement with PHFM has very high mortality, although this may be improved by vascular stenting.[111,113,114]

Diagnosis

The features necessary to confirm a clinical diagnosis of PHFM include (1) invasive obstruction of pulmonary arteries or veins, SVC, or airways, in nearly any combination, resulting from a (2) mediastinal mass usually containing calcification (from punctate to highly calcified), in the (3) absence of emboli, cancer, radiation, or another cause.[112]

When all features of PHFM are present, a confident diagnosis may be made without the need for tissue sampling, especially when results of *Histoplasma* serologic tests (by complement fixation and/or immunodiffusion) are positive, as seen in about one-half the patients.[106] CT imaging is typically diagnostic in the appropriate clinical setting. In the past, diagnostic thoracotomy was often conducted, at significant risk.[112] An operative finding of fibrotic tissue within the mediastinum does not, by itself, indicate FM because focal mediastinal scarring has many potentially causes.

Only a few PHFM patients report a history of acute *Histoplasma* infection, a finding that is not surprising because most of the population in the middle of the United States is routinely infected without identifiable symptoms.[109] The burden of organisms in FM is typically very low, and organisms are not viable in culture, so antigen testing results are negative, and surgical biopsy rarely identifies organisms.

Treatment

PHFM patients with obstruction of vessels of both lungs are at greatest risk and may benefit the most from cardiac catheterization at expert centers to attempt intravascular stenting of pulmonary arteries, veins, or both.[114] Pulmonary veins are commonly involved but may be easily overlooked because they are sites not commonly affected by other diseases. SVC occlusion may have surprisingly few symptoms when adequate collateral flow has developed, which speaks to the indolent nature of this disease. When SVC syndrome does develop, stenting may provide significant symptom relief.[119]

Presumably, fibrosis in PHFM progresses in the period before clinical presentation because clinically important disease progression is uncommon after diagnosis. Disease progression is sometimes observed at sites that were formerly affected but typically has little clinical impact; for instance, subsequent occlusion of a pulmonary vein has no significant physiologic impact when the ipsilateral pulmonary artery is already occluded. Although progression of the disease to involve new sites is uncommon, some centers pursue annual CT angiography to screen for new involvement of structures in the contralateral unaffected lung.

Antifungal and other medical therapies including steroids have no apparent impact on the development or

progression of PHFM. Treatment with rituximab has been associated with decreased activity on positron emission tomography scan in three patients.[120] Convincing evidence that rituximab has a clinical impact on the course or outcome of PHFM, however, has not been reported to date.

Hemoptysis may be severe and even life-threatening, related to systemic bronchial arterial collateral formation in the setting of pulmonary artery compromise or to pulmonary venous hypertension in the setting of venous obstruction. The former can usually be controlled by bronchial artery embolization, whereas the latter, typically caused by disruption of fragile engorged submucosal veins that result from impaired venous drainage, can be temporized by ablative bronchoscopic interventions, although these procedures also risk precipitation of more airway hemorrhage.

Surgery with a therapeutic intent in PHFM is rarely beneficial and is very high risk because the tissues are hypervascular and normal tissue planes are fused, thus making blunt dissection impossible. This can be a particular problem in uncommon situations in which it is difficult to distinguish PHFM from MG because surgery is the only clearly effective treatment for symptomatic MG.

Idiopathic Fibrosing Mediastinitis and Fibrosing Mediastinitis From Other Causes

In the United States, PHFM comprises more than 95% of FM cases. *Idiopathic fibrosing mediastinitis* (IFM) is clinically distinct and important to distinguish because some patients with IFM respond to medical therapy, unlike in PHFM.[110] IFM is typically more diffuse and bulkier, less invasive, and not calcified, and it affects extrathoracic sites such as the retroperitoneum in one-half of patients. When imaging suggests IFM, then IgG4-related disease, granulomatosis with polyangiitis, Erdheim-Chester disease, and other rare conditions should be sought. Unlike PHFM, IFM may regress spontaneously or with medical therapy. The distinction of IFM from PHFM is not well delineated in the literature. In at least one series describing IFM, a CT image was included showing a large, heavily calcified subcarinal node, the classic clinical signature of PHFM, but that was not identified as such by the pathologist investigators.[121] The absence of identifiable organisms in pathology samples does not exclude *Histoplasma* as the original trigger.

MEDIASTINAL GRANULOMA

MG is the gross pathologic term for a conglomerate mass of caseous lymph nodes. A resected MG may not contain any microscopic granulomas or organisms on staining or culture, and it may be hilar in location rather than mediastinal. MGs may be quite large (5 to 10 cm) and single or multiple, and they typically contain semiliquid contents with the consistency of toothpaste or putty inside a thin, 2-mm capsule.[115] MGs comprise as many as 10% of resected mediastinal masses in some series.[115] Mycobacteria are known to cause MG, and these organisms should be sought in the appropriate demographic circumstances. The pathogenesis of MG, akin to that of FM, appears to result from an excessive host response rather than from active proliferation of organisms because antifungal treatment has no demonstrable impact on the course, and the organism fails to grow in culture. Whereas PHFM is presumed to develop late (years) after infection, MG may be seen either late (with calcification) or early, within months of infection, in which case no calcifications are yet present and it may be difficult to distinguish from mediastinal adenitis.

Clinical Features

MG can manifest at any age, even in children as young as 2 years, sometimes with calcifications even at that age. Historical *Histoplasma* skin testing in the 1950s showed positive results in one-half the children by the age of 1 year in some regions.[122] In contrast, FM is very rare at ages younger than 10 years. MGs may extrinsically compress vessels or airways, especially in young children, but because MGs are not invasive they can generally be dissected away from mediastinal structures.

Diagnosis

MGs are most often located in the right paratracheal region, where they are apparent on plain radiography (see Fig. 116.6), but they also commonly manifest in the subcarinal region, which may be hidden on a chest radiograph. CT has much greater sensitivity and specificity than plain radiography, so studies performed before the widespread use of CT in the chest (before ~1980) have serious limitations. Heterogeneity of the density is the most characteristic feature, and late MGs also exhibit pathognomonic speckled, subcapsular, or uniform calcification (eFig. 116.8; see also Fig. 116.6). Serologic titers for *Histoplasma* are positive in one-half of patients, and antigen testing results are usually negative.

MGs, for unclear reasons, occasionally become reinflamed and may attach, fistulize, and drain their contents into an adjacent structure such as the esophagus, bronchus, lung parenchyma, pleural space, subcutaneous space in the neck or, rarely, the pericardial space.[123] Specific imaging findings to indicate that an MG has drained may include a decrease in size, new air density within the MG, or a decrease in the number of individual calcifications within an MG (Fig. 116.7). Spontaneous marked decrease in size is occasionally observed and sometimes is erroneously attributed to successful antifungal treatment, although silent fistulization to the esophagus is the more likely explanation, especially if the calcification burden has decreased, which should never happen with antifungal therapy (Fig. 116.7, eFig. 116.9). When MG drains to an airway, to the soft tissue of the neck, or along the tract of a mediastinoscopy scar, recognizable clinical signs of the drainage are obvious. Sometimes there is recurrent drainage, typically to the same site. New chest pain seems to be a harbinger of fistulization and drainage in patients with late MG.

Despite their often pathognomonic appearance, MGs may not be recognized as such. When a radiologist incorrectly characterizes MG as FM, appropriate surgery may not be pursued because of the widely recognized surgical risk of FM. Conversely, when a radiographically classic MG is construed to be an indeterminate lesion, unnecessary tissue sampling may result in infectious complications (see the earlier discussion of acute mediastinitis secondary to visceral perforation).[46] In patients with early MG, when calcifications have not yet developed, suspicion of lymphoma and lack of awareness of MG and the possible therapeutic role for surgery can lead to a suboptimal operation in which only a diagnostic procedure is attempted.

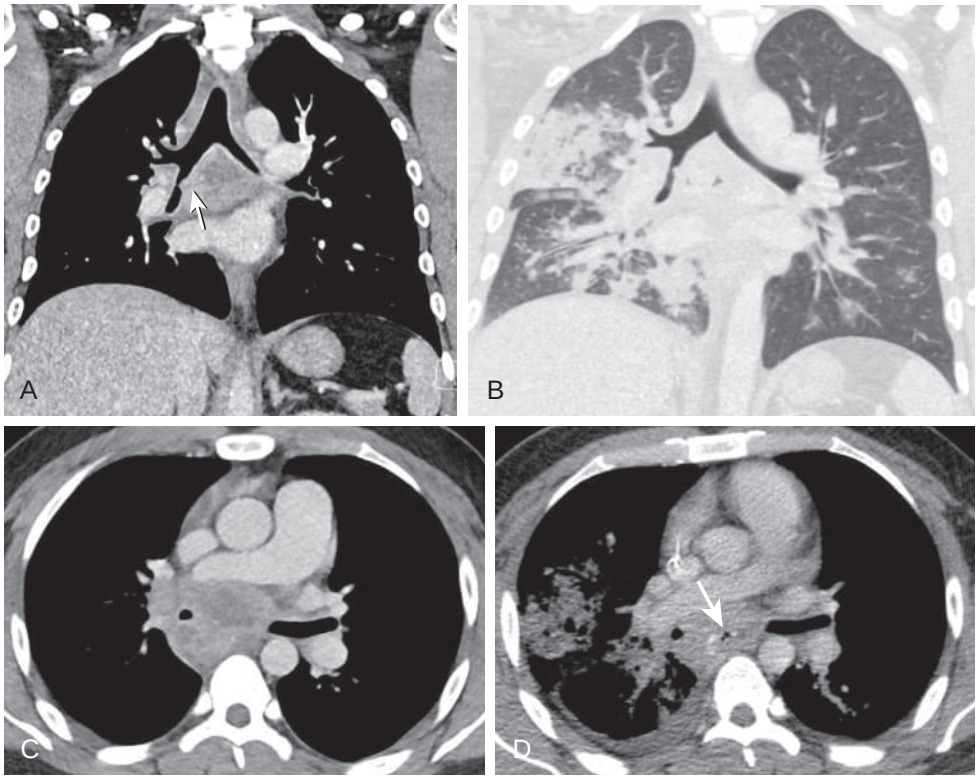

Figure 116.7 Mediastinal granuloma in a 23-year-old man with spontaneous fistulization to esophagus, bacterial superinfection, and then fistulization to bronchus intermedius. (A and C) Large, heterogeneous subcarinal mediastinal granuloma with punctate calcifications and nodular protrusion into the bronchus intermedius (*arrow* in A). (B and D) Following fistula formation at the site of nodular bronchus intermedius protrusion, the subcarinal mediastinal granuloma has decompressed part of its contents into the right-sided airways, thus causing multifocal consolidations. Residual mediastinal granuloma is smaller and has fewer calcifications, and foci of air (*arrow* in D) are now present within it. (Courtesy Robert J. Lentz, MD.)

Treatment

Surgical drainage is the most effective therapy, and it is appropriate when MGs are symptomatic because they can usually be resected at low risk, sometimes by a thoracoscopic approach. Resection should remove the free wall and semiliquid contents; components adherent to vital mediastinal structures may be left in place without apparent consequence. If MG contents are spilled, such as to the pleural space, they do not appear to be inflammatory.

Treatment of MG with antifungal agents is often recommended because it is generally safe, but evidence of efficacy is minimal. In general, MGs are avascular, so it seems unlikely that antifungal agents reach therapeutic concentrations in their interior, but no data exist.

MG drainage to central airways, into prior surgical sites such as a tract left by the mediastinoscope, or into the soft tissues of the neck is usually apparent and often bothersome but generally not dangerous. When MGs drain into the esophagus, they sometimes develop retrograde superinfection with enteric bacteria and require broad-spectrum antibiotics and possibly resection[124] (see Fig. 116.7). MGs may also become infected from bacteria inoculated during endobronchial ultrasound-guided transbronchial needle aspiration sampling, where immune surveillance and antibiotic therapy do not appear to be sufficient to handle the introduced bacteria[46] (see eFig. 116.8). Rarely, MGs may drain into the pericardium and cause pericardial tamponade or fistulize to multiple sites including esophagus and pericardium[123] (see eFig. 116.9). These life-threatening scenarios are very rare and are amenable to surgical correction, so mortality from MG is extremely rare, a finding contrasting with the very high lethality of bilateral PHFM involvement.

MEDIASTINAL ADENITIS

Histoplasma is unique in many respects, including its propensity to cause inflammatory mediastinal adenopathy. Because the late syndromes FM and MG involve the same lymph node sites, they seem likely to be related to prior adenitis, although serial imaging from the early stage through late complications is hardly ever available.

It is not known why some individuals are predisposed to develop symptomatic mediastinal adenitis. The burden of inhaled spores does not seem to be the explanation because massive inhalation can cause dozens of nodules affecting both lungs, but with no higher rate of mediastinal adenitis. Similarly, there is essentially no understanding why some individuals develop FM and other individuals develop MG, whereas most persons who are exposed to *Histoplasma* develop only small calcifications distributed throughout mediastinum, hilum, and lung parenchyma, faithfully reported as incidental "old granulomatous disease" on subsequent imaging studies.

Clinical Features

Severe central chest pain, typically worse during inspiration, which accompanies fever in a young adult, along with imaging showing enlarged mediastinal lymph nodes without calcification, is a typical presentation. There are no data on whether symptomatic mediastinal adenitis is required to produce late complications after *Histoplasma* infection.

Diagnosis

Clinical features in the appropriate radiographic setting are highly suggestive, so that with a characteristic presentation, experienced physicians recognize the syndrome and then confirm it with serologic titers, which are positive in 80% of patients[109,125] (see eFig. 116.7).

Other organisms, including mycobacteria, certainly cause mediastinal or hilar adenopathy and should be sought in appropriate clinical settings; however, patients with these disorders do not present with severe inspiratory pain. Deposition of calcification eventually develops in most affected nodes but it may require years, so an early MG that has not yet developed calcification may be difficult to distinguish from adenitis. CT imaging demonstrating coalescence of nodes and heterogeneous density of contents would argue for transition to early MG.

Treatment

The symptoms of mediastinal adenitis remit spontaneously after a few weeks. However, the enlargement of affected nodes often persists because MGs with characteristic calcifications are evident after several years.

Oral antifungal agents are commonly recommended, and they seem prudent to use to avoid dissemination when corticosteroids are given for symptomatic relief. There remains, however, no evidence that antifungal treatment alters the incidence of late complications (i.e., development of FM or MG).

ACKNOWLEDGMENTS

We thank Erin A. Gillaspie, MD, for her critical review and support of this work.

Key Points

- Acute mediastinitis, a severe clinical syndrome with high morbidity and mortality, most commonly results from spontaneous or iatrogenic perforation of the esophagus, descending necrotizing infection of pharyngeal or odontogenic origin, or deep poststernotomy wound infection.
- All forms of acute mediastinitis are life-threatening and require prompt diagnosis, imaging, mechanical débridement most commonly in the form of surgical intervention, and antimicrobial treatment.
- Fibrosing mediastinitis and mediastinal granuloma are late sequelae of *Histoplasma* infection (rarely, other causes) resulting from an aberrant immunologic response rather than the result of progressive infection.
- Fibrosing mediastinitis describes dense invasive scarring that integrates into adjacent vasculature or airways in violation of normal tissue planes, thus resulting in stenosis or obliteration of these structures. Bilateral lung involvement, present in 20%, is highly lethal. Vascular stenting may improve survival.
- Mediastinal granuloma is a coalesced group of caseous lymph nodes with semiliquid contents contained within a thin capsule and characterized by heterogeneous density on computed tomography and, in most cases, an eventual pathognomonic calcification pattern. Although usually asymptomatic, they may fistulize and drain to airways, esophagus, or other sites. Symptomatic mediastinal granuloma can be managed by resection.

Key Readings

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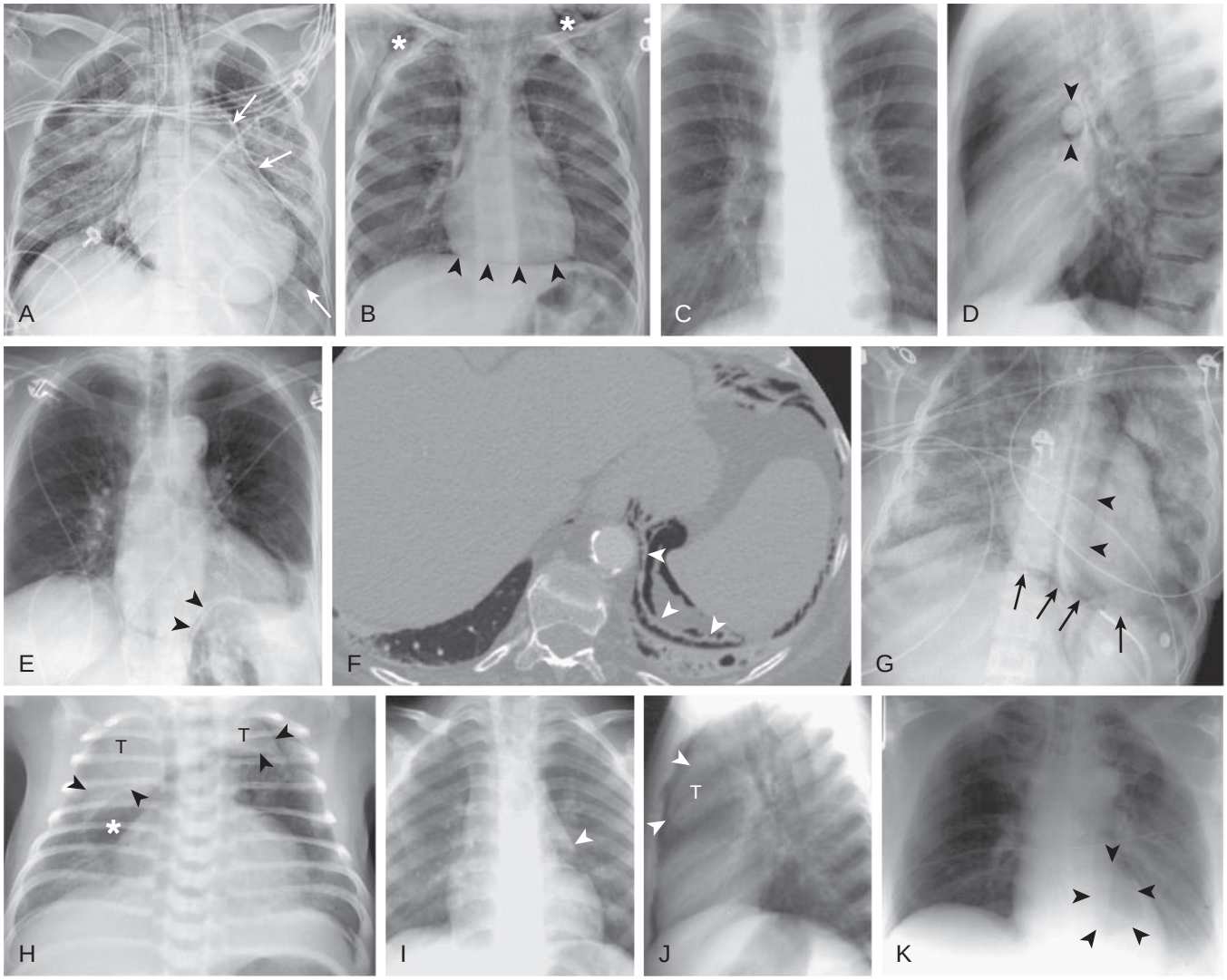
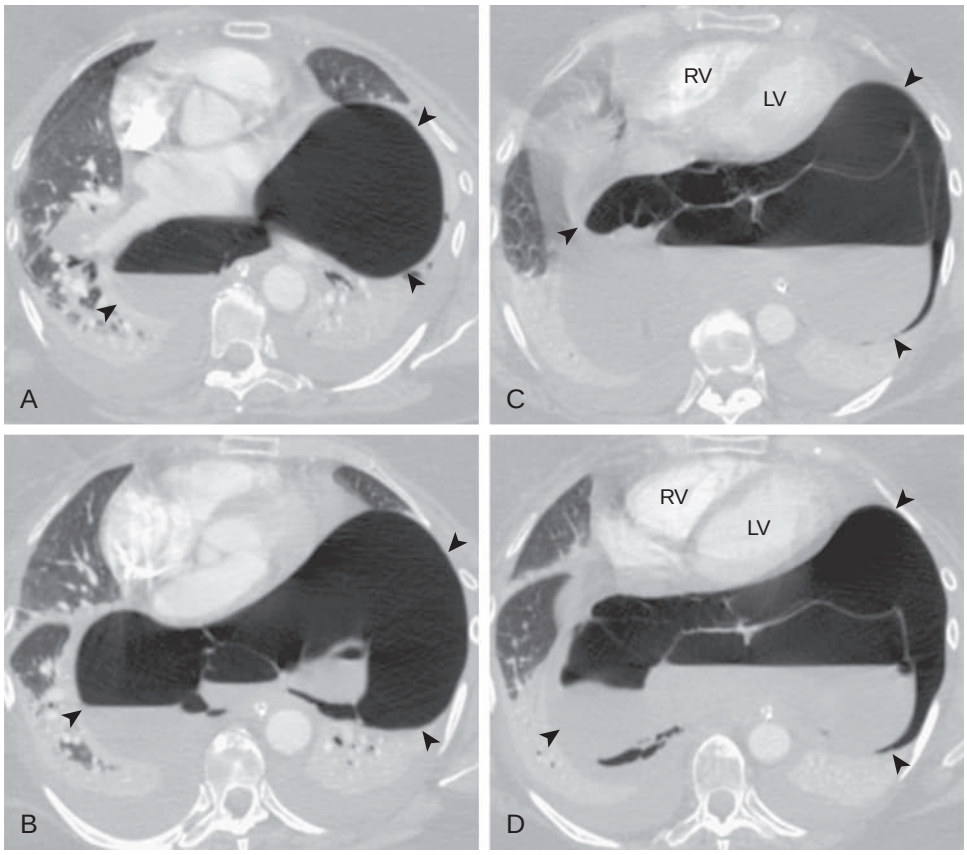
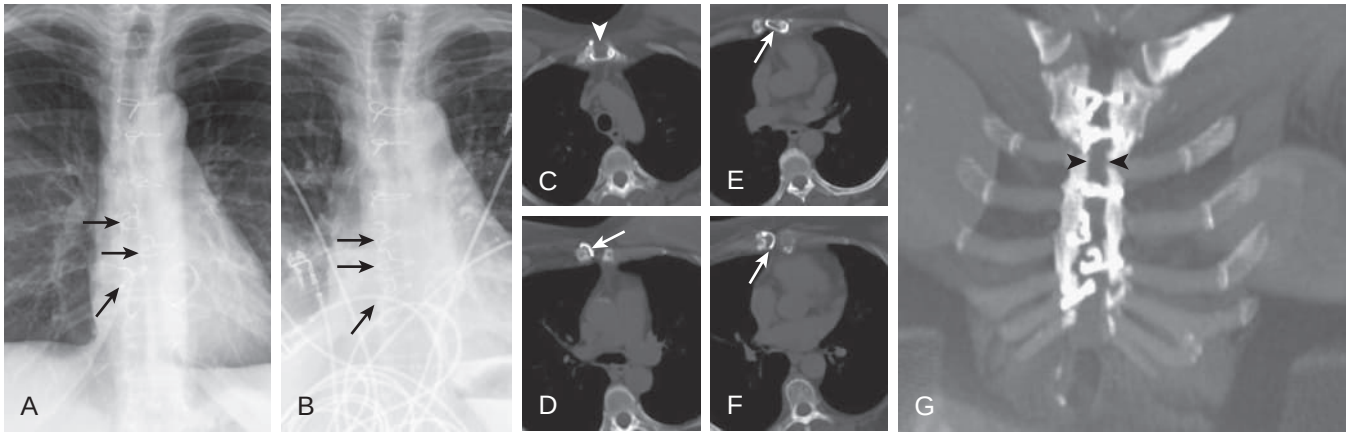
eFIGURE IMAGE GALLERY



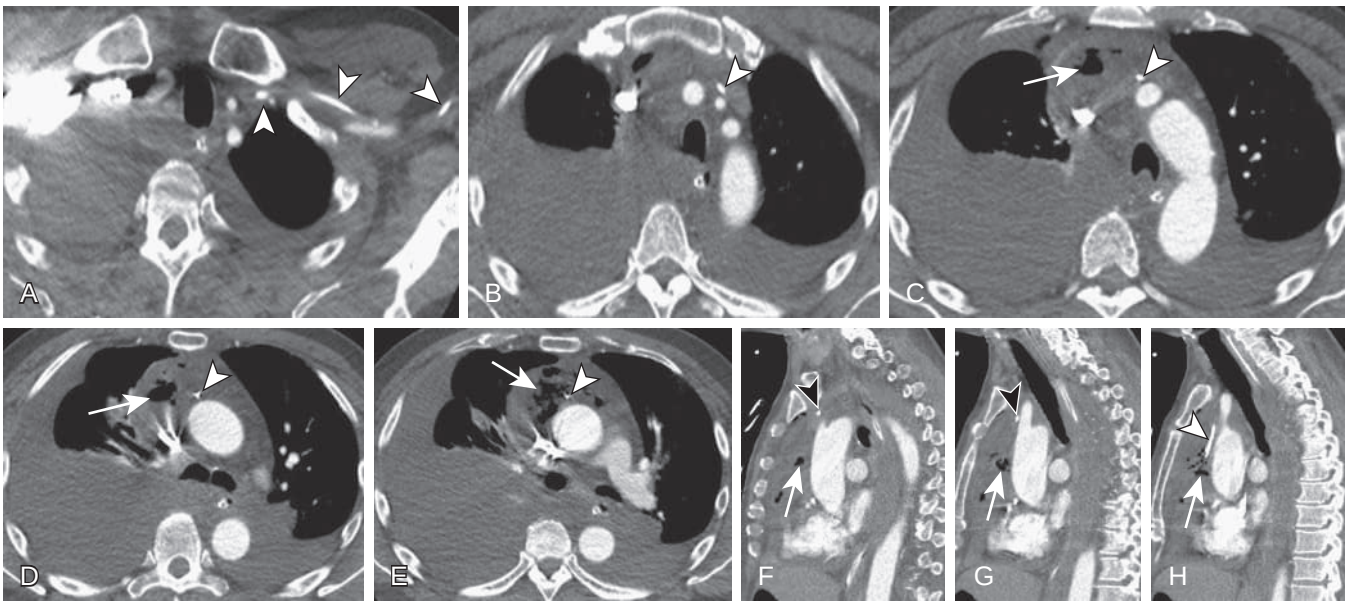
eFigure 116.1 Chest radiographic findings of pneumomediastinum. (A) Frontal chest radiograph shows abnormal lucency interposed between the left cardiac border and left mediastinal pleura *(arrows)* secondary to the presence of mediastinal gas. Gas outlines the superior mediastinum and extends into the neck as well. (B) The "continuous diaphragm" sign. Frontal chest radiograph shows a linear gas lucency between the heart and diaphragm *(arrowheads),* thus rendering the diaphragm visible where it is normally obscured because of contact with the inferior pericardium and heart. (C–D) Chest radiographic findings of pneumomediastinum: "ring-around-the-artery" sign. (C) Frontal chest radiograph shows few features that allow the confident diagnosis of pneumomediastinum. (D) Lateral chest radiograph shows gas surrounding and sharply outlining the extrapericardial segment of the right pulmonary artery *(arrowheads).* (E–F) Chest radiographic findings of pneumomediastinum: the "extrapleural air" sign. (E) Frontal chest radiograph shows gas lucency separating the diaphragm from the combined parietal and visceral pleural layers *(arrowheads).* (F) Axial chest computed tomography displayed in lung windows shows gas, representing pneumomediastinum outlining both sides of the medial left hemidiaphragm *(arrowheads).* (G) Chest radiographic findings of pneumomediastinum: Naclerio's "V" sign. Frontal chest radiograph shows lucency extending along the descending thoracic aorta *(arrowheads)* and extending laterally between the parietal pleura and medial left hemidiaphragm, intersecting gas lucency along the latter *(arrows).* Other chest radiographic features of pneumomediastinum, such as sharp outlining of the aortic arch and left mediastinum, are evident. (H) Chest radiographic findings of pneumomediastinum: note that the gas lucency "elevates" the thymus (*asterisk*), causing the "thymic spinnaker-sail" sign. Frontal chest radiograph in an infant shows abnormal mediastinal lucency that forms an interface *(arrowheads)* with superior mediastinal tissue, representing the thymus *(T);* note that the gas lucency "elevates" the thymus. (I–J) Frontal and lateral chest radiographs in an older child show gas lucency along the left mediastinum *(arrowhead)* on (I) the frontal projection, and sharply outlining *(arrowheads)* the thymus *(T)* on the lateral projection (J). (K) Chest radiographic findings of pneumomediastinum: gas in the pulmonary ligament. Frontal chest radiograph shows triangular gas lucency in the retrocardiac area *(arrowheads),* the apex of which points superiorly. This finding resolved on repeat chest radiography 1 week later. (Courtesy Michael B. Gotway, MD.)



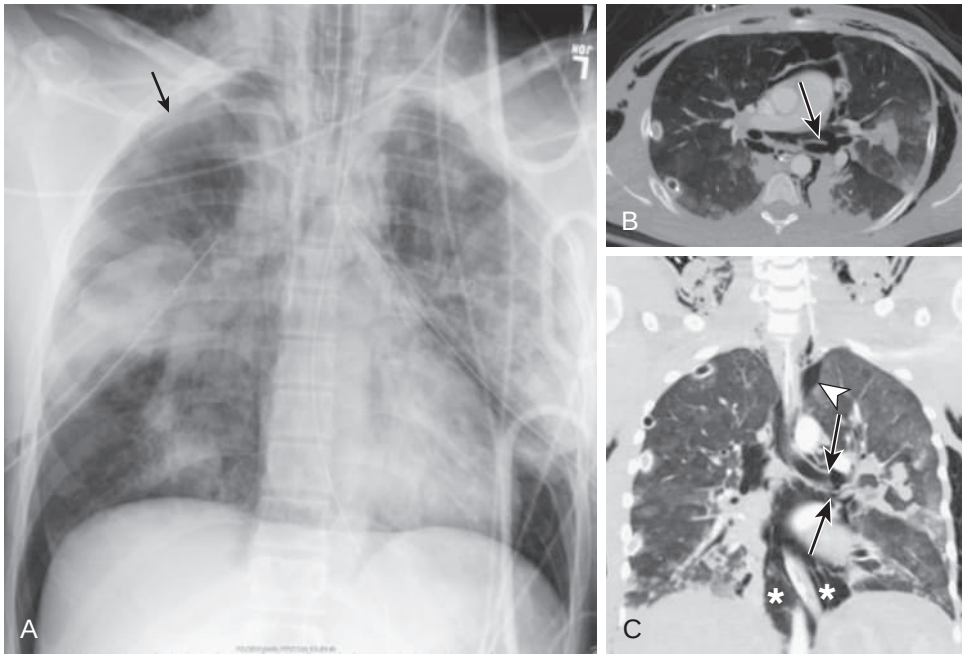
eFigure 116.2 Tension pneumomediastinum. (A–D) Axial chest computed tomography images displayed in lung windows show a large gas collection with numerous internal loculations in the middle mediastinum *(arrowheads)* resulting from esophageal perforation. The gas collection exerts significant mass effect on the heart, compressing and distorting the ventricles. Mediastinitis from the esophageal rupture was present, and the mediastinal gas and fluid were decompressed through placement of several thoracostomy tubes followed by repair of the esophageal laceration. LV, left ventricle; RV, right ventricle. (Courtesy Michael B. Gotway, MD.)



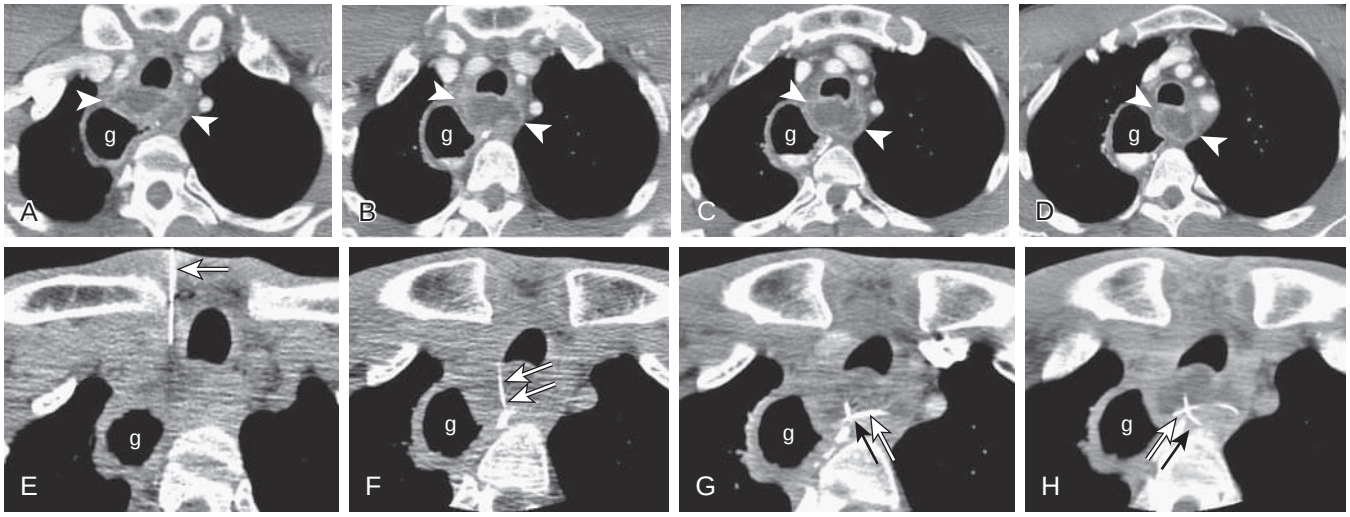
eFigure 116.3 Sternal dehiscence: imaging findings. (A) Frontal chest radiograph obtained at presentation in a patient complaining of increasing chest pain and tenderness several months after a sternotomy. (B) Frontal chest radiograph obtained shortly after the sternotomy, prior to symptoms, is shown for comparison. Note migration of sternal wires *(arrows)* on part A, the presentation image, compared with part B. (C–F) Axial unenhanced chest computed tomography shows that the sternal wires have "pulled through" the sternum (*arrows* in D–F), resulting in marked widening of the space between the two sternal halves (*arrowhead* in C). (G) Coronal unenhanced chest computed tomography shows sternal widening *(arrowheads)*. (Courtesy Michael B. Gotway, MD.)



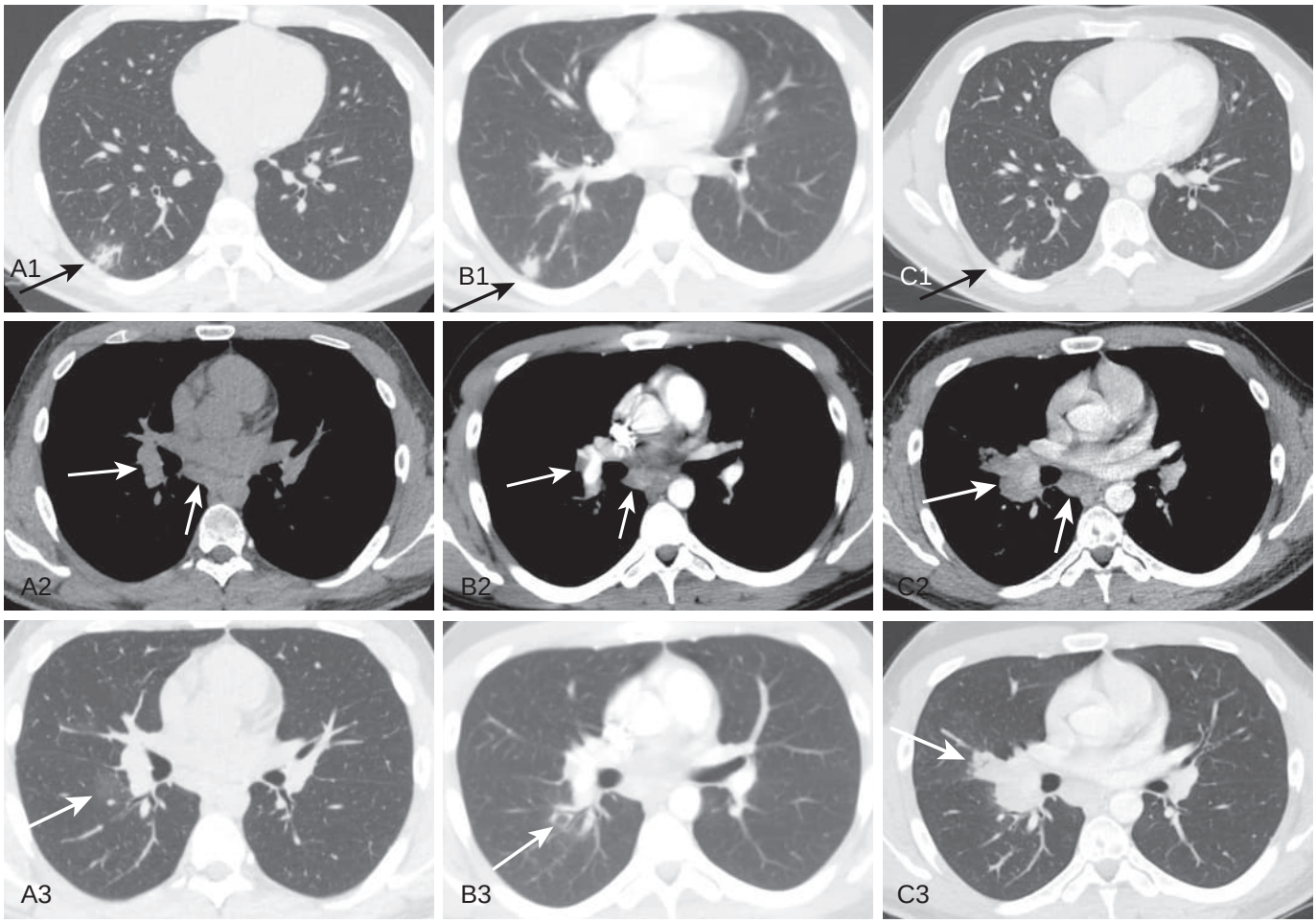
eFigure 116.4 Venous perforation of a peripherally inserted venous catheter with entry into the mediastinum. (A–E) Axial (see Video 116.1) and (F–H) sagittal enhanced chest computed tomography show a left upper extremity peripherally inserted venous catheter *(arrowheads)* coursing through the left subclavian and brachiocephalic veins (*arrowheads* in A–C), but then coursing caudally into the anterior mediastinum (*arrowheads* in D–H). A mediastinal gas collection *(arrows)* represents a developing abscess. (Courtesy Michael B. Gotway, MD.)



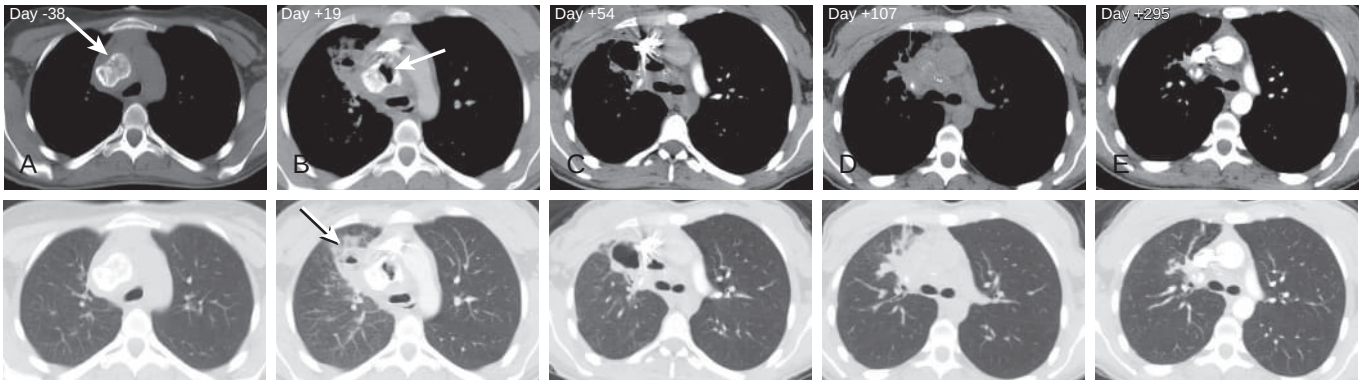
eFigure 116.5 Left mainstem bronchial fracture following motor vehicle collision. (A) Frontal chest radiograph shows subcutaneous emphysema with pneumomediastinum with a right apical pneumothorax *(arrow)* and a deep sulcus sign, also on the right. A left pneumothorax has been addressed with a left thoracostomy tube, although clinically a persistent air leak from this tube was present. (B–C) Axial (see Video 104.3) and coronal (see Video 116.2) chest computed tomography displayed in lung windows shows subcutaneous emphysema with pneumomediastinum *(asterisks)* with a complete fracture of the left mainstem bronchus *(arrows).* A residual left apical pneumothorax (*arrowhead* in C) remains. (Courtesy Michael B. Gotway, MD.)



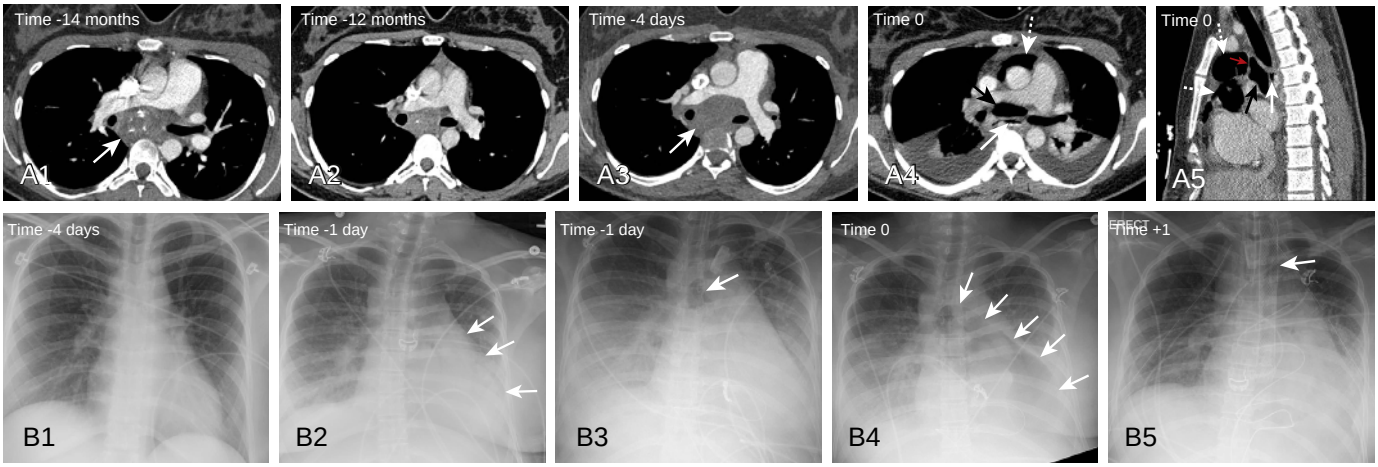
eFigure 116.6 Percutaneous drainage of mediastinal abscess: computed tomography findings. (A–D) Axial contrast-enhanced chest computed tomography displayed in soft tissue windows shows an enhancing fluid collection *(arrowheads)* in the mediastinum, representing an abscess that was seen after attempted dilation of a stricture following esophageal resection and gastric pull-through. (E–H) Computed tomography images of the percutaneous drainage of the mediastinal abscess. Axial chest computed tomography obtained during percutaneous drainage of the mediastinal abscess shows placement of a coaxial needle (*arrow* in E) into the anterior margin of the abscess through a paratracheal approach. (F–H) Subsequent images show a wire *(double arrows)* coiling in the abscess, over which a small drainage catheter was placed. g, intrathoracic stomach following gastric pull-through. (Courtesy Michael B. Gotway, MD.)



eFigure 116.7 Evolving *Histoplasma*-associated mediastinal adenitis over 6 months. (A) Initial computed tomography scan. (B) Scan at 3 months. (C) Scan at 6 months. *Row 1* demonstrates slow organization and enlargement of a peripheral right lower lobe nodule, representing the site of initial *Histoplasma* infection. *Row 2* demonstrates enlarging right hilar and subcarinal adenopathy (*arrows*). *Row 3,* at the same level as *row 2,* demonstrates evolving perihilar parenchymal inflammation associated with the adenopathy, starting with subtle ground-glass opacity (*arrow* in A3), more prominent ground-glass opacity (*arrow* in B3), and then worsening consolidative changes (*arrow* in C3). This young European patient, studying in the southeastern United States, experienced a 2-week febrile illness with cough 1 month before the first computed tomography scan. *Histoplasma* antibody titers to mycelial and yeast antigens both exceeded 1:128 and immunodiffusion detected precipitans to both H and M *Histoplasma* protein antigens. The imaging changed despite treatment with itraconazole and corticosteroids. (Courtesy Robert J. Lentz, MD.)



eFigure 116.8 Superinfection of a mediastinal granuloma by endobronchial ultrasound-guided transbronchial needle aspiration, with fistulization to right upper lobe. (A–B) Image columns are dated with respect to when endobronchial ultrasound-guided transbronchial needle aspiration of a mediastinal granuloma exhibiting pathognomonic calcification pattern (*arrow* in A) was performed. On day +19, air can be seen within the mediastinal granuloma as well as loss of some of its calcified contents (*arrow* in B; soft tissue windows). There is new cavitary lesion, as well as consolidation within the right upper lobe (*arrow* in B; lung windows). (C–E) Slow resolution subsequent to mediastinal débridement and washout on day +20. Operative cultures grew viridans streptococci. (Courtesy Robert J. Lentz, MD.)



eFigure 116.9 Mediastinal granuloma in a 24-year-old woman with spontaneous fistulization to esophagus and pericardium resulting in pneumopericardium with tamponade. (A) Computed tomography. (B) Radiography. Dates with respect to the date of A4. (A1) Diagnosed with subcarinal mediastinal granuloma *(arrow)* 14 months earlier. (A2) Two months later, mediastinal granuloma was noted to be smaller, attributed to itraconazole treatment, but a significant decrease in the number of internal calcifications indicates that the mediastinal granuloma must have fistulized and drained (almost certainly to the esophagus, given it was clinically silent). A year later she presented with several months of pleuritic chest pain. (B1) Chest radiograph was unremarkable, but (A3) computed tomography noted an increase in mediastinal granuloma size *(arrow)*. On hospital day 3, she had abrupt onset of tachycardia, hypotension, and hypoxemia, with (B2) chest radiograph revealing a significant increase in size of the cardiac silhouette *(arrows)*. (B3) Echocardiogram revealed pericardial debris with tamponade, for which a pericardial window was performed with clinical improvement, although new air was noted in the subcarinal space postoperatively *(arrow)*. (B4) The next day, she experienced another abrupt clinical decompensation and was found to have pneumopericardium *(arrows)*. (A4) and (A5) Air now occupied the decompressed subcarinal mediastinal granuloma cavity *(white arrows)*, with new precarinal air collection *(black arrows)* connecting to pneumopericardium *(dashed arrows)* at the *red arrow* (in A5). (B5) Urgent operation with pericardial and mediastinal exploration was performed, with intraoperative esophagoscopy notable for a 1-cm fistula to the mediastinal granuloma, for which an esophageal stent was placed *(arrow)*. She has since recovered with no recurrence of mediastinal granuloma, which was unroofed and débrided. (Courtesy James Loyd, MD.)

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SECTION O

DISORDERS OF SLEEP AND CONTROL OF BREATHING

117 CONTROL OF BREATHING AND UPPER AIRWAYS DURING SLEEP

RICHARD L. HORNER, PHD, FCAHS • ATUL MALHOTRA, MD

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INTRODUCTION

Some of the key brain circuits that generate the states of wakefulness, *non–rapid eye movement* (non-REM) sleep and *rapid eye movement* (REM) sleep, are summarized in this section. Knowledge of these mechanisms leads to understanding the principle of the "sleep switch."[1,2] This principle is used to explain how the common, serious, and at times life-threatening problems associated with sleep and drug-induced brain sedation and respiratory depression can work through common brain pathways.

GENERATION OF WAKEFULNESS AND SLEEP

Wakefulness

Figure 117.1A illustrates some of the main neuronal clusters involved in the regulation of brain activity in wakefulness and sleep. Serotonin, noradrenaline, histamine, dopamine, orexin (also called hypocretin), acetylcholine, and glutamate-containing cell groups collectively contribute to the brain activation of wakefulness. Such brain activation manifests as relatively low-voltage and fast-wave activity in the *electroencephalogram* (EEG) and resting motor tone in the electromyogram recorded from postural muscles.

Some of the neuronal clusters that contribute to the brain activation of wakefulness include dorsal and caudal raphe neurons located in the pons and medulla respectively (serotonin containing), the locus coeruleus (noradrenaline containing), the tuberomammillary nucleus (histamine containing), the ventral periaqueductal gray (dopamine containing), the perifornical region of the lateral hypothalamus (orexin/hypocretin containing), the pedunculopontine and laterodorsal tegmental nuclei in the pons as well as regions of the basal forebrain (acetylcholine containing), and several of the aforementioned cell clusters plus distributed neurons in the pons and midbrain, including the parabrachial nucleus (glutamate containing).

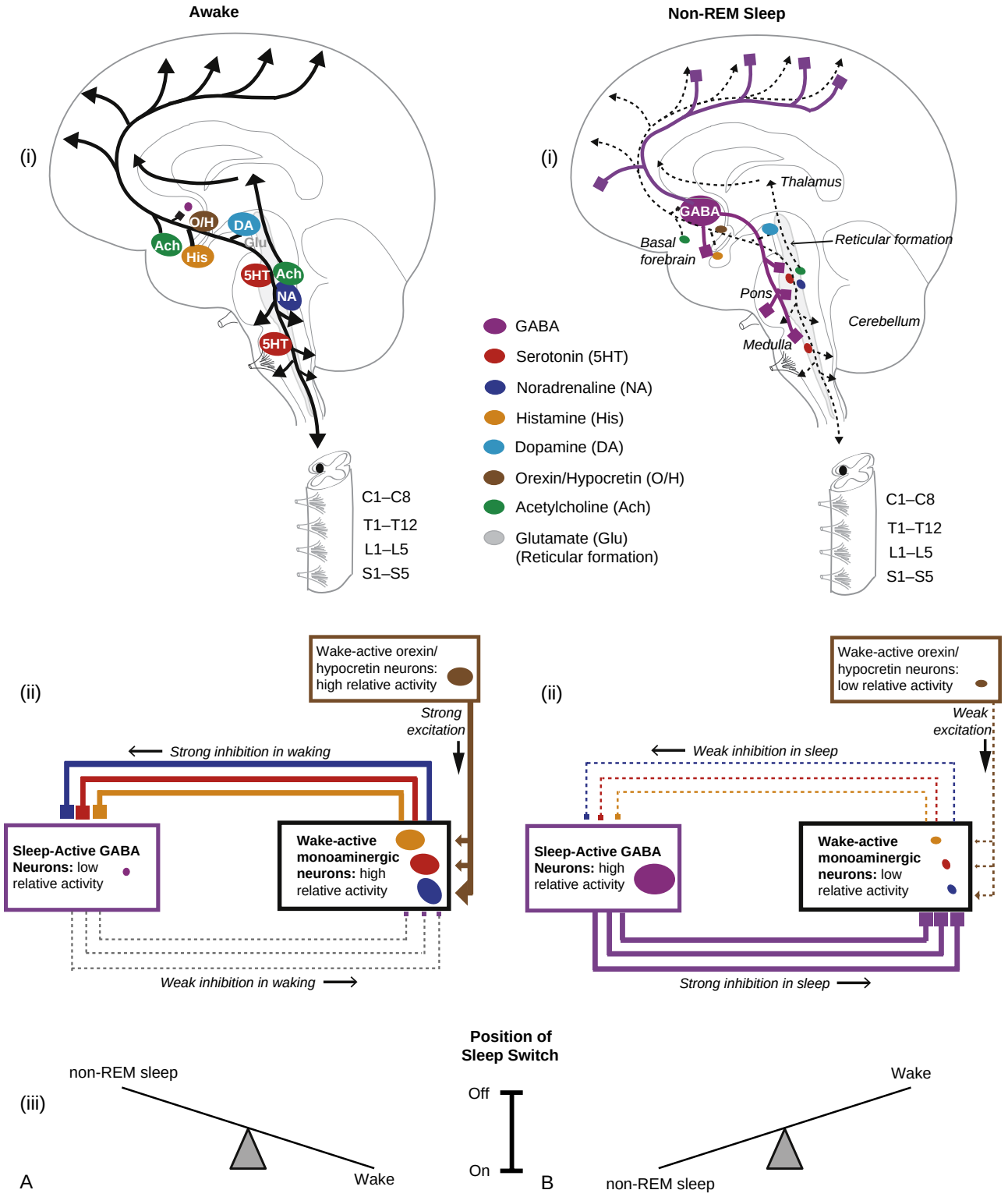

Figure 117.1 Schema showing the main neuronal groups and their organizational interactions for generating the brain states of wakefulness (A, left panels) and *non–rapid eye movement* (non-REM) sleep (B, right panels). Shown are the major neuronal clusters (*i*) whose ascending projections are responsible for producing the electrocortical arousal of wakefulness and whose descending projections influence brainstem autonomic networks and spinal motor activity. Non-REM sleep is generated when these wakefulness-generating systems are inhibited by clusters of neuronal groups containing the inhibitory neurotransmitter *gamma-aminobutyric acid* (GABA). The organizational structure for the maintenance of wakefulness and non-REM sleep, and the switch between the two states, are also shown (*ii* and *iii*). Mutual inhibitory interactions between wakefulness and sleep-promoting neuronal groups lead to the "switch" being stable in either position, thus producing consolidated periods of sleep at night and wakefulness during the day. The propensity to transition to a consolidated period of sleep at night (and later a consolidated period of wakefulness in the morning) is linked to the circadian-mediated decrease (and then the later increase) in body temperature; the decrease in body temperature activates the GABA sleep-promoting neuronal systems, whereas the increase deactivates them. The non-REM sleep-active GABA neuronal groups include those in the ventrolateral preoptic region of the thalamus as well as those in the basal forebrain and anterior hypothalamus. The relative position and sizes of neuronal groups are shown for visual clarity and are not meant to represent their strict anatomic positions. Relatively high levels of neuronal activity are represented by large symbols and solid lines, whereas relatively low levels of neuronal activity are represented by small symbols and dashed lines. Inhibitory neuronal projections from cell groups are indicated by *squares,* and excitatory projections by *arrowheads.* (Modified from Horner RL. Emerging principles and neural substrates underlying tonic sleep-state-dependent influences on respiratory motor activity. *Philos Trans R Soc Lond B Biol Sci.* 2009;364:2553–2564; Horner RL. Central neural control of respiratory neurons and motoneurons during sleep. In: Kryger MH, Roth T, Dement WC, eds. *Principles and Practice of Sleep Medicine,* ed 5. St Louis: Elsevier; 2011:237–249; Horner RL. Respiratory physiology. In: Kushida C, ed. *Encyclopedia of Sleep*, vol. 1. Waltham, MA: Academic Press; 2013:517–524; and Saper CB, Scammell TE, Lu J. Hypothalamic regulation of sleep and circadian rhythms. *Nature.* 2005;437:1257–1263. Copyright Richard L. Horner, PhD, University of Toronto.)

Non-REM Sleep

Non-REM sleep is often thought of as the "restorative" non-dreaming phase of sleep. It is promoted and sustained by a system of neurons that inhibit the brain arousal systems of wakefulness (Fig. 117.1B). The chief cell groups that comprise this non-REM sleep-active inhibitory system include neurons in the ventrolateral preoptic area and anterior region of the hypothalamus, and regions of the basal forebrain. The cell groups that comprise this non-REM sleep-active inhibitory system synthesize and secrete the inhibitory amino acid *gamma-aminobutyric acid* (GABA) and the neuropeptide galanin. GABA is one of the chief inhibitory neurotransmitters in the brain. The direct GABA-mediated inhibition of the brain arousal systems, in combination with activation of cortically projecting inhibitory GABA neurons, is responsible for the relatively higher-voltage and slower-wave EEG activity that typifies non-REM sleep.

REM Sleep

REM sleep is associated with the dreaming phase of sleep and is accompanied by paralysis (atonia) of the skeletal musculature, an effect that can also impact breathing (particularly accessory muscle function). There are two major circuits involved in REM sleep generation (Fig. 117.2). The activation of these circuits produces the defining signs of REM sleep: (1) low-voltage and fast-wave EEG activity and (2) suppression of postural motor tone. Important for the changes in EEG activity is reactivation of the cholinergic cell groups in the pons and basal forebrain that were relatively inactivated during non-REM sleep. The spinal motor activity in REM sleep is suppressed through recruitment of descending neural circuits that involve glycine (principally) and GABA. However, the upper airway muscle activity in REM sleep is suppressed through processes

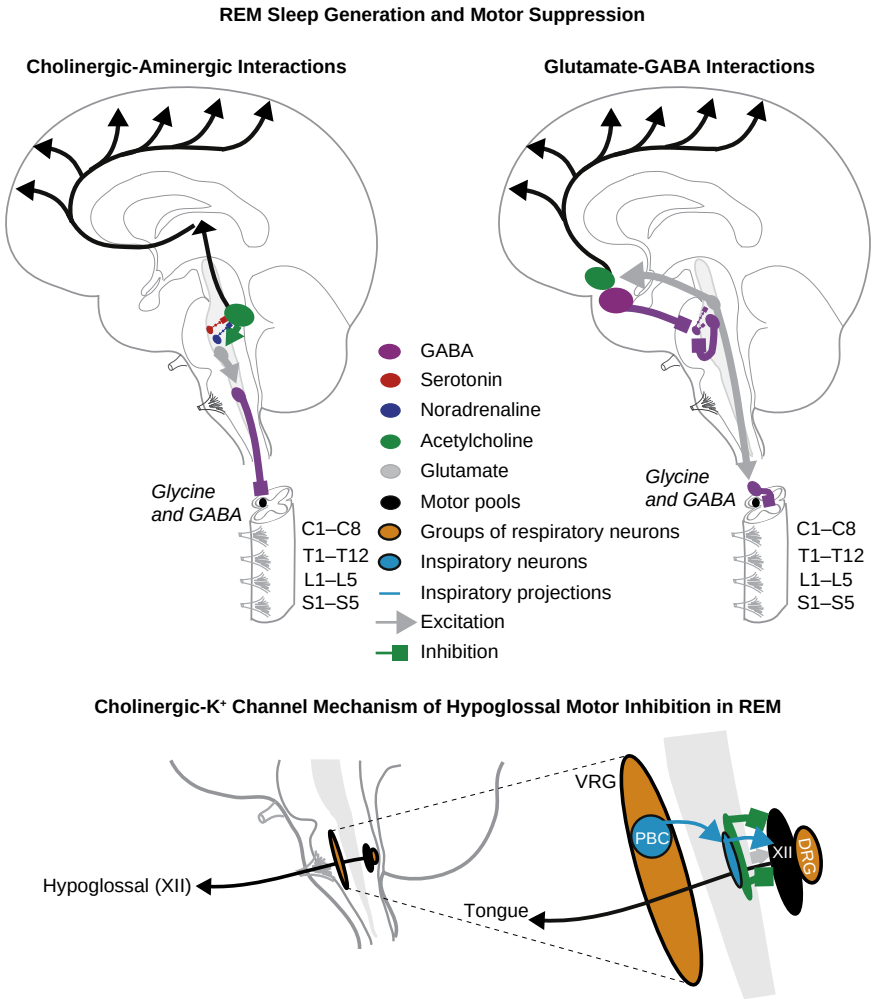

Figure 117.2 Schema showing the main neuronal groups and their organizational interactions for generating the brain state of REM sleep. There are currently two explanations of *rapid eye movement* (REM) sleep generation: one involving interactions of cholinergic and aminergic cell clusters (*top left*) and the other involving interactions of glutamatergic and *gamma-aminobutyric acid* (GABA)-ergic cell clusters (*top right*). Although the finer details are discussed in the text, the main point is that each can explain the cardinal features of REM sleep: ascending cortical activation and descending spinal motor inhibition. The inhibition of spinal motor activity in REM sleep is mediated by descending projections to the medial and ventral horn of the spinal cord and increased release of the inhibitory amino acids glycine (predominantly) and GABA onto spinal motoneurons. The mechanism of upper airway motor suppression in REM sleep appears different. For the hypoglossal motor pool, for example, which innervates the musculature of the tongue via cranial nerve XII, a cholinergic mechanism mediates the strong motor inhibition of REM sleep. This inhibition counteracts the inspiratory drive to this motor pool that originates from the ventral respiratory group (VRG) via the pre-Bötzinger complex (PBC) and pre-motoneurons in the brainstem (the latter two indicated as inspiratory neurons and shown in *blue*). The dorsal respiratory group (DRG) is also shown for completeness. The hypoglossal motor pool also receives tonic state-dependent drive from the brainstem (shown in *gray*). Inhibitory neuronal projections are indicated by *squares* and excitatory projections by *arrowheads*. (Copyright Richard L. Horner, PhD, University of Toronto.)

of (1) *disfacilitation* (i.e., withdrawal of excitatory inputs), mediated principally by reduced noradrenaline and serotonin excitation at the hypoglossal motor pool, and (2) *inhibition*, mediated by a muscarinic receptor mechanism linked to G-protein–coupled potassium channels.[3]

THE "SLEEP SWITCH"

As discussed, there are *mutually opposing* interactions between the wakefulness-promoting neuronal systems and the non-REM sleep-promoting neuronal systems. This organization leads to wakefulness being associated with both a relatively high level of activity in the wake-promoting neuronal arousal systems combined with a relatively low level of activity in the opposing sleep-promoting GABA system (see Fig. 117.1A, panel ii). In contrast, non-REM sleep is associated with both a relatively high level of activity in the sleep-promoting GABA system combined with a relatively low level of activity in the opposing wake-promoting neuronal arousal systems (see Fig. 117.1B, panel ii).

The mutually opposing interactions between the wake-promoting and sleep-promoting neuronal systems produce a situation in which the brain is in a stable state when either one of the respective neuronal systems dominates. This arrangement constitutes the "sleep switch" in which the position of the "switch" is stable in either state because, when one side is active, the alternate state is simultaneously inhibited. In non-REM sleep, for example, the activation of GABA neurons reinforces their own activation via inhibition of the wake-active neuronal systems at the same time.

EFFECTS OF COMMON NEURODEPRESSIVE DRUGS ON BRAIN AROUSAL STATE

The balance of brain neurochemicals involved in the opposing wakefulness and sleep-promoting systems, however, is not only changed across natural states of wakefulness and sleep; the balance is also changed in predictable ways by the ingestion of commonly used neurodepressive drugs. Such drugs include benzodiazepines, imidazopyridines (non-benzodiazepine sedative hypnotics), barbiturates, ethanol, and some general anesthetics that are either inhalational (e.g., isoflurane) or injectable (e.g., propofol or etomidate). All these listed agents interact with binding sites on GABA receptors that enhance neuronal inhibition.[4] There are several sites within the endogenous sleep-wake circuitry where such neurodepressive GABAergic drugs act to depress the brain arousal state and promote sedation and/or loss of consciousness.[4] Such agents therefore effectively tip the balance within the endogenous sleep-wake circuitry "toward" sedation and "away" from brain arousal.

The principle of the sleep switch helps us understand that the depression of brain arousability in both natural sleep and with neurodepressive drugs is the product of two mechanisms. The first is the augmentation of inhibitory GABAergic influences, and the second is the concomitant depression of arousal-related stimulatory influences. There is a dual effect because these inhibitory and excitatory mechanisms cannot operate independently because of their inherent interconnectedness. This principle has further implications for understanding sleep and drug-induced respiratory depression.

APPLICATION TO SLEEP AND DRUG-INDUCED RESPIRATORY DEPRESSION

During both natural sleep and in the presence of many commonly used sedative and anesthetic drugs, there is both augmentation of the GABAergic inhibitory system and corresponding reductions in excitatory influences from the brain arousal systems (as outlined earlier). The net result is a tipping of the balance in the sleep switch toward low brain arousability plus alteration of drives to the respiratory network. These state-dependent drives affect the musculature particularly of the upper airways, thus predisposing to obstructive sleep apnea and hypopnea in susceptible individuals.[5] In essence, the brain functions as a "gain setting" device for breathing by altering brain neurochemistry of the key elements of respiratory control: the respiratory neurons, the motoneurons, and the sites involved in the reflex modulation of breathing.

Opioid drugs can also produce profound sedation, an effect clinically important in their contribution to both respiratory depression and the failure to arouse. Opioids such as fentanyl contribute to respiratory depression via direct inhibitory effects on the major components of the respiratory network, including respiratory neurons, motoneurons, chemosensors, and reflexes, as well as depress the aforementioned brain arousal systems. Research is ongoing to address the mechanisms behind these adverse physiologic responses.

BREATHING AND ITS CONTROL

The complexity of the brainstem respiratory network can be distilled into three essential elements:

1. *Respiratory neurons* that generate respiratory rhythm and drive the expression of rhythmic activity in other components of the respiratory network.
2. *Respiratory motor pools* that innervate and activate the primary and secondary muscles of breathing. The primary respiratory muscles are so designated because they generate airflow (e.g., the diaphragm). In contrast, the secondary (accessory) muscles of breathing do not generate airflow but either importantly modulate its passage (e.g., pharyngeal muscles that maintain a patent upper airway) or otherwise support the act of breathing (e.g., the intercostal muscles that contribute to the maintenance of lung volume).
3. *Chemosensors* that detect alterations in blood gases and elicit a physiologic response. In the case of hypoventilation during sleep, for example, the appropriate physiologic response includes both an attempted chemoreceptor-mediated increase in ventilation and arousal from sleep. The importance of arousal from sleep is critical to survival in some situations when the ventilatory response is futile by itself (e.g., to shake off a suffocating blanket in the case of a sleeping infant to prevent asphyxia and sudden infant death syndrome).

RESPIRATORY NEURONS

Organization

Figure 117.3 illustrates the main components of the respiratory network generating respiratory rhythm and motor activation. The *ventral respiratory group* (VRG) contains

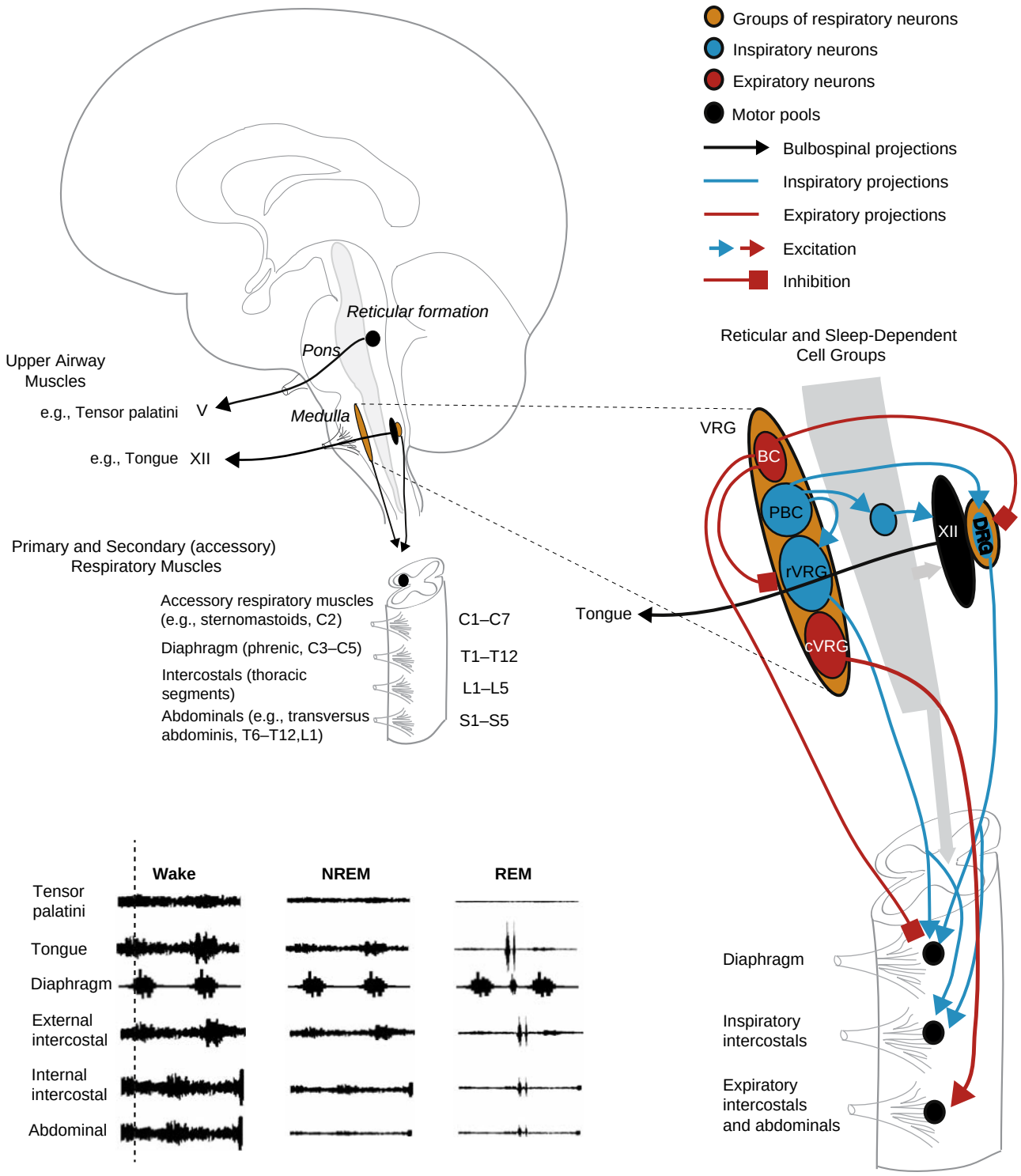

Figure 117.3 Schema showing some of the main neuronal groups and their organizational interactions for the generation of efferent motor output to different respiratory muscles. On the upper left are shown the main neuronal groups and selected motor pools innervating the muscles of the upper airway and the primary and secondary (accessory) muscles of the respiratory pump. On the right, at higher magnification, are shown the main clusters of neurons comprising the *ventral and dorsal respiratory groups* (VRG and DRG, respectively), and their projections to other neurons comprising the respiratory network. The innervation of the hypoglossal motor pool by state-dependent neurons of the reticular formation is also shown. See text for further details on the relevance of this latter point. The electromyographic activities of various respiratory-related muscles are also shown: palatal, tongue, diaphragm, and the accessory, intercostal, and abdominal respiratory muscles. Note that the level of respiratory-related and tonic activities varies for different muscles, with some muscles such as the tensor palatini expressing mainly tonic activity and others, such as the tongue and intercostals, expressing both tonic and respiratory activity. This relative balance of tonic and respiratory-related activity can change across sleep-wake states, with tonic activity being typically suppressed in sleep. The onset of muscle activity with respect to the diaphragm is shown by the *dashed line*. The rootlets of cranial nerves V (trigeminal) and XII (hypoglossal) and the *cervical* (C), *thoracic* (T), *lumbar* (L) and *sacral* (S) segments of the spinal cord are included. BC, Bötzinger complex; NREM, non–rapid eye movement; PBC, pre-Bötzinger complex; REM, rapid eye movement; rVRG, rostral VRG; cVRG, caudal VRG. (Modified from Horner RL. Emerging principles and neural substrates underlying tonic sleep-state-dependent influences on respiratory motor activity. *Philos Trans R Soc Lond B Biol Sci.* 2009:364;2553–2564; Horner RL. Central neural control of respiratory neurons and motoneurons during sleep. In: Kryger MH, Roth T, Dement WC, eds. *Principles and Practice of Sleep Medicine*, ed 5. St Louis: Elsevier; 2011:237–249; Horner RL. Respiratory physiology. In: Kushida C, ed. *Encyclopedia of Sleep*, vol. 1. Waltham, MA: Academic Press; 2013:517–524. Copyright Richard L. Horner, PhD, University of Toronto.)

Bötzinger complex (expiratory) neurons, pre-Bötzinger complex (inspiratory) neurons, rostral VRG (predominantly inspiratory) neurons, and caudal VRG (predominantly expiratory) neurons. The *dorsal respiratory group* (DRG) contains mainly inspiratory neurons. The DRG and its associated regions of the nucleus tractus solitarius are also the projection sites for afferents important to the reflex control of breathing: the carotid and aortic chemoreceptors and baroreceptors and lung vagal afferents.

The brainstem also includes motoneurons of the hypoglossal and trigeminal motor nuclei that innervate muscles important to the maintenance of upper airway patency.[5] Regions of the nucleus ambiguous also contain motoneurons that innervate the muscles of the larynx and pharynx via the vagus, glossopharyngeal, and accessory nerves. Respiratory neurons in the pons also modulate the activity of medullary respiratory neurons.

Respiratory Rhythm and Motor Activation

Some respiratory neurons are identified as propriobulbar, that is, neurons that project to, and influence the activity of, other medullary respiratory neurons but do not themselves project to motoneurons.[5] Others are identified as bulbospinal respiratory pre-motoneurons, that is, neurons that project to spinal motoneurons, which in turn innervate the respective respiratory pump and abdominal muscles of breathing.

Inspiration. The pre-Bötzinger complex is often emphasized given its role in respiratory rhythm generation. The pre-Bötzinger complex is a propriobulbar respiratory neuronal group that plays a key role in generating the fundamental respiratory rhythm in mammals.[6] Pre-Bötzinger complex neurons drive activation of bulbospinal neurons of the DRG and VRG during inspiration, which then activate spinal inspiratory phrenic and intercostal motoneurons. Inactivation of pre-Bötzinger complex neurons in animal models leads to ataxic breathing and central apneas, especially in sleep.[7,8] The pre-Bötzinger complex is also a critical site mediating respiratory rate depression by opioids.[9]

Expiration. In expiration, the expiratory neurons of the Bötzinger complex inhibit inspiratory pre-motoneurons and motoneurons. Caudal VRG neurons also increase excitability of spinal expiratory motoneurons in expiration, although this excitation does not necessarily manifest as demonstrable expiratory muscle activation at rest.

Respiratory Rhythm Generation and Central Apnea

The automatic and nonconscious rhythm of breathing is ultimately generated by the intrinsic membrane properties and connections of the individual neurons that comprise the respiratory network. Essential to expression of this rhythmicity, however, is provision of a sufficient level of underlying tonic excitation. Key sources of tonic excitation are from the aforementioned wakefulness-dependent neural systems as well as the peripheral and central chemoreceptors (eFig. 117.1).

An important physiologic principle that emerges from identification of the necessity and sufficiency of tonic excitation for respiratory rhythm generation is that removal of such tonic excitation can abolish respiratory rhythm. Sleep or neurodepressive drugs (such as GABAergic sedative hypnotics and/or opioid drugs), or reduced chemoreceptor inputs, can each lead to cessation of respiratory rhythm and development of central sleep apnea.

RESPIRATORY MOTOR POOLS AND MUSCLE ACTIVITY

Respiratory Muscles Vary in the Degree of Their Relationship to Breathing

Different respiratory muscles express varying degrees of respiratory-related activity and/or tonic (i.e., nonrhythmic, continuous or background) activation. The diaphragm, for example, is almost exclusively respiratory related, whereas the palatal, tongue, intercostal, and abdominal muscles express both respiratory and tonic activities to varying degrees. The physiologic basis for this variation is that the respiratory neurons that ultimately drive the respective respiratory muscles themselves vary in the strength of their relationship to breathing.[10] Some respiratory neurons, for example, are almost exclusively driven by respiratory rhythm-generating neurons and are weakly influenced by other inputs. In contrast, some respiratory neurons are weakly influenced by respiratory rhythm-generating neurons but more strongly influenced by tonic nonrespiratory inputs.[10] Such tonic nonrespiratory inputs can arise from sleep state–dependent cell groups.

Effects of Sleep

The identification of respiratory neurons and motoneurons that vary in the strength of their relationship to breathing assumes greater significance because of a key physiologic principle.[10] This principle states that respiratory neurons that are most strongly driven by respiratory rhythm-generating neurons are least affected by the transition from wakefulness to non-REM sleep, whereas respiratory neurons that are more strongly influenced by tonic nonrespiratory inputs are most affected by the change from wakefulness to sleep. In the latter case, activity within certain respiratory muscles can cease or be markedly depressed during sleep, especially those showing prominent tonic muscle activity in wakefulness, such as the muscles of the upper airway and chest wall. The key physiologic and clinical implications of this effect explain the susceptibility to obstructive sleep apnea; the major suppression of upper airway muscle activity in sleep is because those muscles are most strongly influenced by tonic nonrespiratory inputs that are decreased in sleep.

CHEMOSENSORS AND CHEMOREFLEXES

Location and State Dependence of Responses

Arterial oxygen and *carbon dioxide* (CO_2) levels are regulated by peripheral chemoreceptors located at the bifurcation of the common carotid arteries and central chemoreceptors located in the brain. More specifically, the central chemoreceptors are located close to the ventral surface of the medulla in the caudal region of the retrotrapezoid nucleus (eFig. 117.1).[11] Cells in this region of the retrotrapezoid nucleus are intrinsically sensitive to changes in CO_2/H^+. These CO_2/H^+-sensitive neurons have dendrites that extend to the ventral medullary surface by which they sense the pH of the surrounding cerebrospinal fluid. They also have

axons that project to the rostral region of the VRG by which they drive respiratory network activity.

In addition to the retrotrapezoid nucleus, some wakefulness-active/sleep-inactive cell groups, such as serotonergic and noradrenergic neurons, are also responsive to alterations in CO_2/H^+ levels. For any given inspired CO_2, the activity and responsivity (i.e., slope of response) of such neurons are reduced in sleep compared to wakefulness. As discussed later, this change in cell activity in response to hypercapnia from wakefulness to sleep parallels the change in overall ventilatory response.

INTEGRATIVE PHYSIOLOGIC MECHANISMS UNDERPINNING RESPIRATORY DYSFUNCTION AND INSTABILITY DURING SLEEP

BREATHING IS DEPENDENT ON FEEDBACK REGULATION IN SLEEP

Principle

A prevailing level of tonic excitation into the respiratory network is essential to drive respiratory rhythm and muscle activation (see "Respiratory Rhythm Generation and Central Apnea"). The brain arousal systems of wakefulness provide a major source of such excitation to modulate breathing volitionally and/or nonvolitionally, together termed *behavioral influences* or the *wakefulness stimulus* to breathing[12] (Fig. 117.4). Overall, the term behavioral influences encompasses wakefulness-dependent mechanisms that influence breathing whether one is aware of them or not, or whether they are conscious acts or not (e.g., conscious hyperventilation or unconscious continuous excitation of the respiratory system provided simply by the presence of wakefulness). Such behavioral influences on respiratory network activity are reduced or withdrawn when moving from wakefulness to non-REM sleep. As a result, the respiratory system becomes dependent on feedback regulation in non-REM sleep to sustain sufficient activity.

Tonic activity of the peripheral and central chemoreceptors is normally sufficient to sustain effective breathing in non-REM sleep. Without that tonic activity (e.g., caused by any reduction or defect in feedback chemoreceptor control for any reason), there will be respiratory disturbance in non-REM sleep because the stimulatory effects of wakefulness on the respiratory system are withdrawn. Interestingly, compared to the situation in non-REM sleep, in REM sleep the heightened state of brain arousal can restore sufficient nonspecific behavioral drives to the respiratory network to restore breathing.

Application

Hypocapnia is a potential cause of central apnea. Interestingly, hypocapnia by itself is not sufficient to elicit central apneas in wakefulness or in REM sleep because of the concomitant presence of the behavioral influences on breathing. However, in non-REM sleep, hypocapnia can elicit central apneas because the stimulatory effects of brain arousal (i.e., behavioral influences) to the respiratory network are absent. This critical combination of factors—hypocapnia and absence of behavioral influences to breathing in non-REM sleep—removes two of the crucial sources of tonic drives to the brainstem network that normally generate and sustain breathing. Hypocapnia may be present at the onset of sleep as a result of hyperventilation during wakefulness caused, for example, by heightened chemoreceptor drive (e.g., resulting from congestive heart failure) or by exaggerated behavioral influences on breathing (e.g., caused by anxiety). Hypocapnia at sleep onset can also result from the transient hyperventilation caused by sleep disturbance and brief arousal from prior sleep: the hyperventilation predisposing to unstable breathing by depleting the carbon dioxide reserve (defined later in the section "Loop Gain and Its Importance"). Whenever there is hypocapnia at sleep onset, central apneas may become clinically important in non-REM sleep.

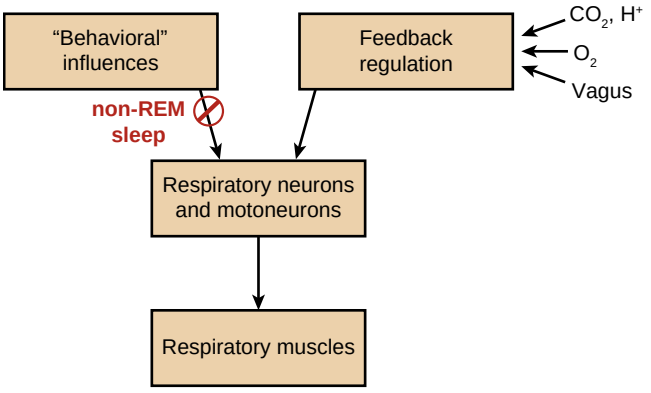

Figure 117.4 Conceptual model showing how behavioral influences and feedback regulation control the efferent output from respiratory neurons and motoneurons. Feedback regulation includes control by CO_2/H^+, O_2 levels, and responses to mechanical and ventilatory events in the airways and lung via the vagus nerves. Notably, the behavioral influences are significantly reduced or withdrawn in *non–rapid eye movement* (non-REM) sleep. The physiologic principle that arises from this effect is that breathing is essentially dependent on metabolic (CO_2 and O_2) control in non-REM sleep. The consequence is that any defect in metabolic control, for any reason, will cause severe respiratory disturbance in sleep but not necessarily in wakefulness. Behavioral influences include both volitional and nonvolitional (but wakefulness-dependent) mechanisms that influence breathing. (Copyright Richard L. Horner, PhD, University of Toronto.)

As a second example of the importance of tonic stimulation, patients with *congenital central hypoventilation syndrome* (CCHS) have a defect in chemoreception and exhibit major disturbances of ventilation in non-REM sleep but ventilate normally during wakefulness and during REM sleep. In more than 99% of CCHS patients, mutations have been found in the *PHOX2B* gene, a gene expressed by neurons involved in peripheral and central chemoreception.[13] That *PHOX2B* is expressed in chemoreceptor neurons and not in respiratory neurons is thought to explain the ability of these patients to breathe during wakefulness[14] (i.e., the state of wakefulness itself provides sufficient excitatory drive to the respiratory system to mask the major defect in chemoreceptor activity caused by the *PHOX2B* mutation). The ability of the CCHS patients to breathe normally in REM sleep further reinforces the principle that the relatively high levels of brain activation inherent to REM sleep can provide sufficient restoration of the behavioral drives to the respiratory network to reinstitute breathing.

As a final example that highlights the powerful effect of wakefulness as an independent driver of respiratory activity, it is noted that deep non-REM sleep and anesthesia are the most vulnerable states for respiratory rate depression by opioids.[9] In this situation, breathing can be sustained by wakefulness even when opioids are present at the pre-Bötzinger complex, a key site for respiratory rhythm generation in mammals, as well as other components of the respiratory network that together generate rhythmic breathing and lung ventilation. However, loss of this important wakefulness stimulus to breathing can lead to hazardous respiratory depression in non-REM sleep and anesthesia. This example further emphasizes the principle that wakefulness per se can provide sufficient excitatory drive to the respiratory system to mask (at least partially) otherwise important defects in respiratory control—in this case, defects induced by drugs. The clinical relevance of this principle is that sedating agents and opioid drugs can be deemed well tolerated in the initially alert patient but, when the stimulating effects of wakefulness are withdrawn during sleep, the patient may sustain major respiratory depression (i.e., "crash"). Such a scenario is particularly dangerous when patients with sleep-related breathing problems use opioids for pain management, especially if taken in combination with benzodiazepines and/or alcohol at home.

LOOP GAIN AND ITS IMPORTANCE

Principle

Loop gain is an engineering term that describes the overall gain, or sensitivity, of a feedback control system. A high gain system is one prone to instability, whereas a low gain system is intrinsically stable. The major factors contributing to overall loop gain are plant gain and controller gain (Fig. 117.5). *Plant gain* largely reflects the effectiveness of breathing to eliminate carbon dioxide, that is, how much a given change in ventilation itself affects arterial carbon dioxide. *Controller gain* largely reflects chemoresponsiveness, that is, how much a given change in arterial carbon dioxide itself affects ventilation. The equilibrium point for resting breathing (sometimes called the set point) is defined as the intersection of the ventilatory response to arterial P_{CO_2} and the change in arterial P_{CO_2} that results from a change in ventilation.

Overall, a high loop gain promotes ventilatory instability because it predisposes to a situation whereby a perturbation in ventilation can trigger cessation of breathing because the larger drop of the arterial P_{CO_2} due to a robust ventilatory response makes it more likely to reach the apnea threshold. Loop gain is defined and quantified as the magnitude of the ventilatory response to a given disturbance in breathing divided by the magnitude of the causal disturbance in ventilation itself. In practical terms, for example, this can be measured by how much a level of reduced ventilation (e.g., caused by an apnea or hypopnea) elicits a subsequent level of hyperpnea (i.e., response divided by disturbance).

If loop gain is less than 1, then the system corrects itself (i.e., breathing normalizes) but, if loop gain is 1 or greater, then the system remains unstable. In the latter case, a large ventilatory response to a particular perturbation in breathing can itself become a subsequent disturbance and therefore precipitate persistent instability. Overall, an increase in plant and/or controller gains can destabilize breathing because it increases the risk of lowering arterial P_{CO_2} below the chemical apnea threshold.[15]

Application

There are several situations in which altered plant and/or controller gains can predispose to sleep-disordered breathing. An increased plant gain can be seen, for example, when there is low functional residual capacity, or low dead space. Of note, the baseline level of arterial P_{CO_2} has an important effect on plant gain (e.g., a high arterial P_{CO_2} has a higher plant gain because the efficiency of carbon dioxide excretion is impacted accordingly). In each setting of high plant gain, a given increase in ventilation will more effectively lower arterial P_{CO_2} toward the apnea threshold. The increase in plant gain leads to a corresponding increased tendency to unstable breathing by virtue of the effectively reduced carbon dioxide reserve.[15] Interventions such as *continuous positive airway pressure* (CPAP) or positive end-expiratory pressure can help stabilize breathing in this context by increasing both functional residual capacity and dead space, thereby effectively reducing plant gain. Acetazolamide, a carbonic anhydrase inhibitor, can stabilize breathing in part via a lowering of P_{CO_2} with a concomitant fall in plant gain. Subtler distinctions between steady state and dynamic plant gains have been discussed elsewhere.[16] Patients with alveolar hypoventilation secondary to central nervous system disturbances or neuromuscular weakness are also predisposed to unstable breathing in sleep via increased plant gain.[15] This predisposition is also explained by virtue of their lowered carbon dioxide reserve, despite having an elevated resting arterial P_{CO_2}, due to a shift to the right in their equilibrium position for resting breathing[15] (see Fig. 117.5).

In contrast, an increased controller gain can be seen in patients with heart failure who also experience unstable breathing during sleep. In these patients, the increased chemoresponsiveness associated with heart failure–induced sympathetic nervous system activation leads to increased controller gain and lowered carbon dioxide reserve and thus predisposes to instability.

AROUSAL FROM SLEEP: A CONSEQUENCE AND CAUSE OF RESPIRATORY DISTURBANCE

Principle

The ventilatory responses to hypoxia and hypercapnia are fundamental to the homeostatic regulation of arterial blood gases. These ventilatory responses are reduced in non-REM sleep compared to wakefulness and are further reduced in REM sleep[17] (Fig. 117.6). The threshold level of hypercapnia to provoke arousal from sleep is similar, on average, between non-REM and REM sleep in humans, whereas the level of asphyxial hypoxia (e.g., hypoxia of the type experienced in obstructive sleep apnea) often elicits arousal at lower arterial oxygen saturations in REM sleep than in non-REM sleep[17] (see Fig. 117.6). Isocapnic hypoxia, however, is generally a weak stimulus to elicit arousal from sleep and the threshold is similar, on average, between non-REM and REM sleep.[17]

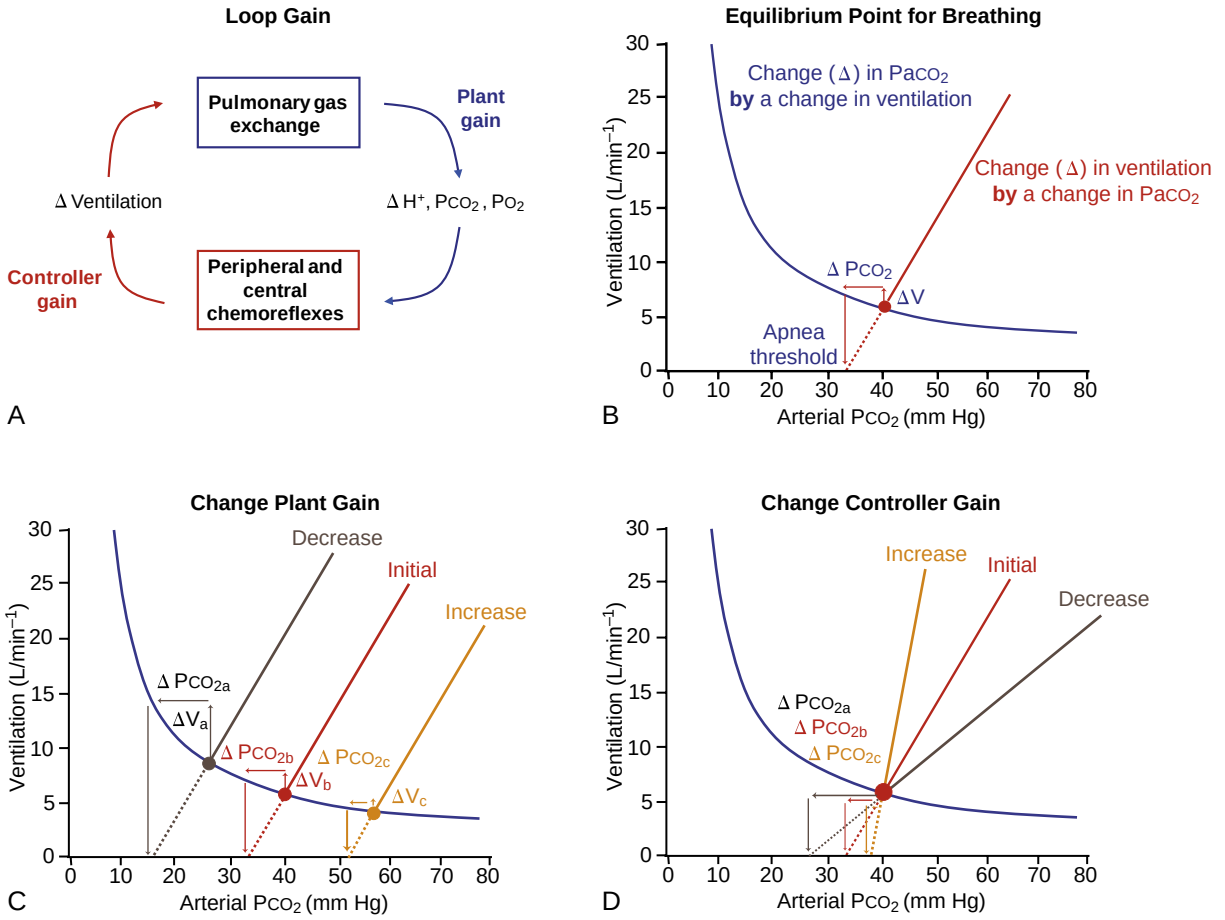

Figure 117.5 Schema illustrating how loop gain (comprised of plant and controller gains) determines the equilibrium point for breathing and influences breathing stability/instability. (A) Pulmonary gas exchange changes ventilatory variables, which themselves influence breathing. *Plant gain* largely reflects the effectiveness of ventilation to eliminate CO_2 (e.g., with a low functional residual capacity, low dead space, or low metabolic rate). *Controller gain* is largely a result of chemoresponsiveness (e.g., increased in heart failure). (B) The equilibrium point for stable breathing is illustrated by the *red circle*. This equilibrium point for resting breathing sits at the intersection of the ventilatory response to increased arterial P_{CO_2} (*red line*) and the change in arterial P_{CO_2} that results from a change in ventilation (the metabolic hyperbola; *blue line*). Reductions in arterial P_{CO_2} reduce ventilation according to the ventilatory response (*dashed red line*), until apnea develops (the apnea threshold). The magnitude of the increase in ventilation that will lower arterial CO_2 to the apnea threshold is termed the CO_2 reserve. (C–D) The predisposition to unstable breathing based upon the equilibrium position for resting breathing and the apnea threshold. Decreases in plant or controller gains produce a situation in which a larger increase in ventilatory disturbance is necessary to deplete the CO_2 reserve before apnea (*brown line*). In contrast, increases in plant or controller gains produce a situation in which a smaller increase in ventilatory disturbance is necessary to deplete the CO_2 reserve before apnea (*orange line*). The physiologic principle that arises from this effect is that the predisposition to ventilatory instability and disordered breathing in sleep is significantly determined by the plant and controller gains. For example, patients with alveolar hypoventilation secondary to central nervous system disturbance or neuromuscular weakness are predisposed to periodic breathing in sleep despite having an elevated resting arterial CO_2 (*yellow circle* in C). Likewise, patients with heart failure who have sympathetic nervous system–mediated increases in chemoreflex responsiveness are also predisposed to periodic breathing in sleep (*yellow line* in D). (Modified from Phillipson EA, Bowes G. Control of breathing during sleep. In: Cherniack NS, Widdicombe JG, eds. *Handbook of Physiology, section 3, The Respiratory System, Vol II, Control of Breathing, part 2*. Bethesda, MD: American Physiological Society; 1986:649–689; Dempsey JA, Veasey SC, Morgan BJ, O'Donnell CP. Pathophysiology of sleep apnea. *Physiol Rev* 2010;90:47–112. Copyright Richard L. Horner, PhD, University of Toronto.)

The normal decrease in ventilation from wakefulness to sleep usually results in trivial changes in arterial oxygen saturation because the starting alveolar P_{O_2} is on the flat portion of the oxyhemoglobin dissociation curve. However, the arterial oxygen saturation can decrease more from wakefulness to sleep if an individual is *initially* hypoxemic and therefore initially positioned on the steep portion of the dissociation curve (see Fig. 117.6). This situation can happen with an individual at altitude, with lung disease, or with depressed ventilation and/or impairments in breathing for any reason. The physiologic principle that arises from these relationships is that any situation that lowers alveolar P_{O_2} in wakefulness for any reason (e.g., altitude, lung disease, etc.) predisposes to worsening hypoxemia in sleep, especially during REM sleep.

Application

Interactions between the ventilatory responses to hypercapnia and hypoxia, and arousal from sleep, can provoke unstable breathing and central apneas. Figure 117.7 outlines these interactions using the ventilatory responses to hypercapnia as the example (see legend for additional details specific to this figure). As a general rule, however, the same predisposition to unstable breathing via arousal from sleep also applies to the ventilatory responses to hypoxia or to combined hypercapnia and hypoxia (i.e., asphyxia as seen in sleep-disordered breathing). The physiologic principle that arises from these interactions is that any separation of equilibrium points for stable breathing in wakefulness and non-REM sleep for any reason can lead to unstable

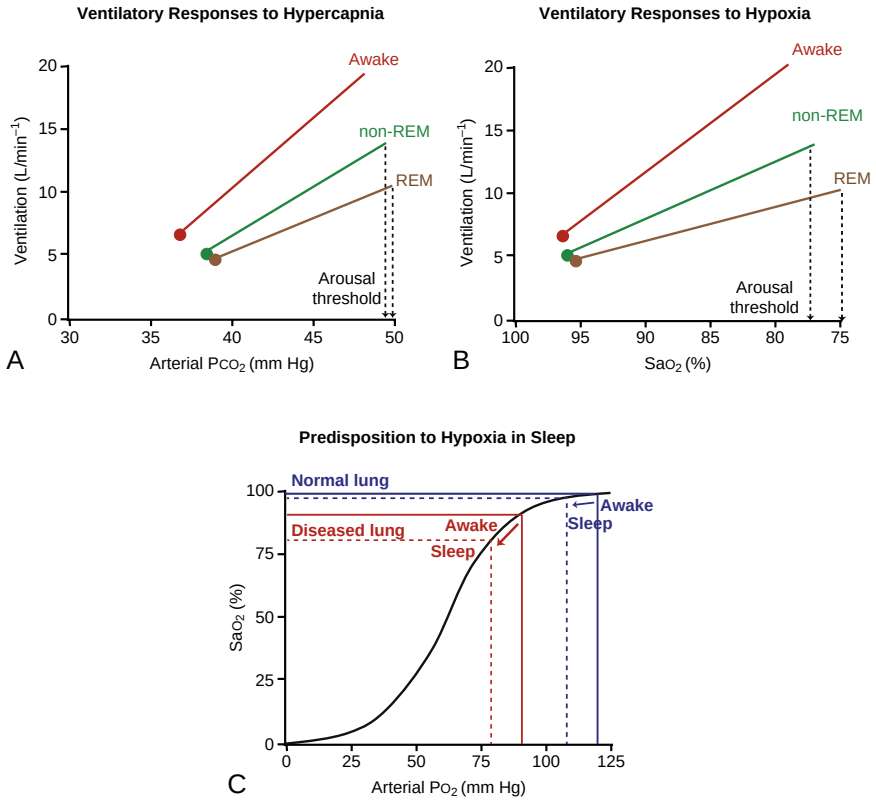

Figure 117.6 Ventilatory and arousal responses to hypercapnia (A) and hypoxia (B). Note the following points: (1) the decrease in basal ventilation from wakefulness (*red circle*) to *non–rapid eye movement* (non-REM; *green circle*) and REM (*brown circle*) sleep, (2) ventilation is greater in wakefulness at any given elevated arterial CO_2 or lowered arterial oxygen saturation (Sa_{O_2}) compared to non-REM sleep and REM sleep, and (3) the slope (gain) of the ventilatory responses to hypercapnia and hypoxia is also greater in wakefulness than in non-REM sleep and is most depressed in REM sleep. Also shown are the thresholds for hypercapnia (A) and asphyxial hypoxia (B) to elicit arousal from sleep (see text for additional details). (C) Also shown is the relationship between the starting (waking) arterial partial pressure of O_2 and the magnitude of the decrease in Sa_{O_2} from wakefulness to sleep. Normal decreases in ventilation from wakefulness to sleep lead to normal decreases in Pa_{O_2} but only modest or trivial decrease in Sa_{O_2} in sleep; this is because the starting Pa_{O_2} is on the flat portion of the oxyhemoglobin dissociation curve (*blue lines* in C). Such a situation, for example, would be typically experienced by individuals living at sea level or with healthy lungs and/or with normal ventilation and lung perfusion. The same magnitude of decrease in ventilation and Pa_{O_2} from wakefulness to sleep, however, can lead to a large decrease in Sa_{O_2} if an individual is initially hypoxic and therefore initially positioned on the steep portion of the dissociation curve (starting Sa_{O_2} of ≈90%). (Modified from Douglas NJ. Respiratory physiology: understanding the control of ventilation. In: Kryger MH, Roth T, Dement WC, eds. *Principles and Practice of Sleep Medicine,* ed 5. St Louis: Elsevier; 2011:250–258; Thompson SR, Ackermann U, Horner RL. Sleep as a teaching tool for integrating respiratory physiology and motor control. *Adv Physiol Educ.* 2001;25:101–116; Horner RL. Pathophysiology of obstructive sleep apnea. *J Cardiopulm Rehabil Prev*. 2008;28:289–298; Horner RL. Respiratory physiology. In: Kushida C, ed. *Encyclopedia of Sleep*, vol. 1. Waltham, MA: Academic Press; 2013:517–524. Copyright Richard L. Horner, PhD, University of Toronto.)

breathing and central apneas at sleep onset, especially when sleep onset follows a perturbation to breathing such as arousal from sleep (see Fig. 117.7). Such a separation could be seen in one or more clinically relevant scenarios. For example, the equilibrium point for waking ventilation could shift to the left (i.e., expressed as decreased waking arterial PCO_2 and increased ventilation) in situations of acute or chronic hyperventilation caused by anxiety, congestive heart failure, sympathetic nervous system overactivity, or other causes. Likewise, the equilibrium point for sleeping ventilation could shift to the right (i.e., expressed as increased sleeping arterial P_{CO_2} and lowered ventilation) with drug-induced respiratory depression due to the neurodepressive effects on respiratory network activity and chemoresponses. In either case, the arousal from sleep per se acts as the initial perturbation to elicit the unstable breathing and central apnea.

Another important clinical implication of the above physiology is that there is an expected reduction in arterial P_{O_2} in patients with parenchymal lung disease at sleep onset. Even patients without hypoxemia during wakefulness may experience clinically significant hypoxemia during sleep, leading some clinicians to screen for desaturation in such patients. Data would indicate that sleep-induced hypoxemia is a more sensitive metric for clinically significant hypoxemia than is exercise-induced hypoxemia, leading some to advocate for sleep testing, for example, in patients with COPD who do not meet criteria for supplemental oxygen based on baseline measurements during wakefulness. However, interventional data are currently lacking to support the use of supplemental oxygen to treat nocturnal hypoxemia. Nonetheless, several studies have suggested a major role for noninvasive ventilation for hypercapnic COPD patients (covered in Chapters 45, 119, and 122).

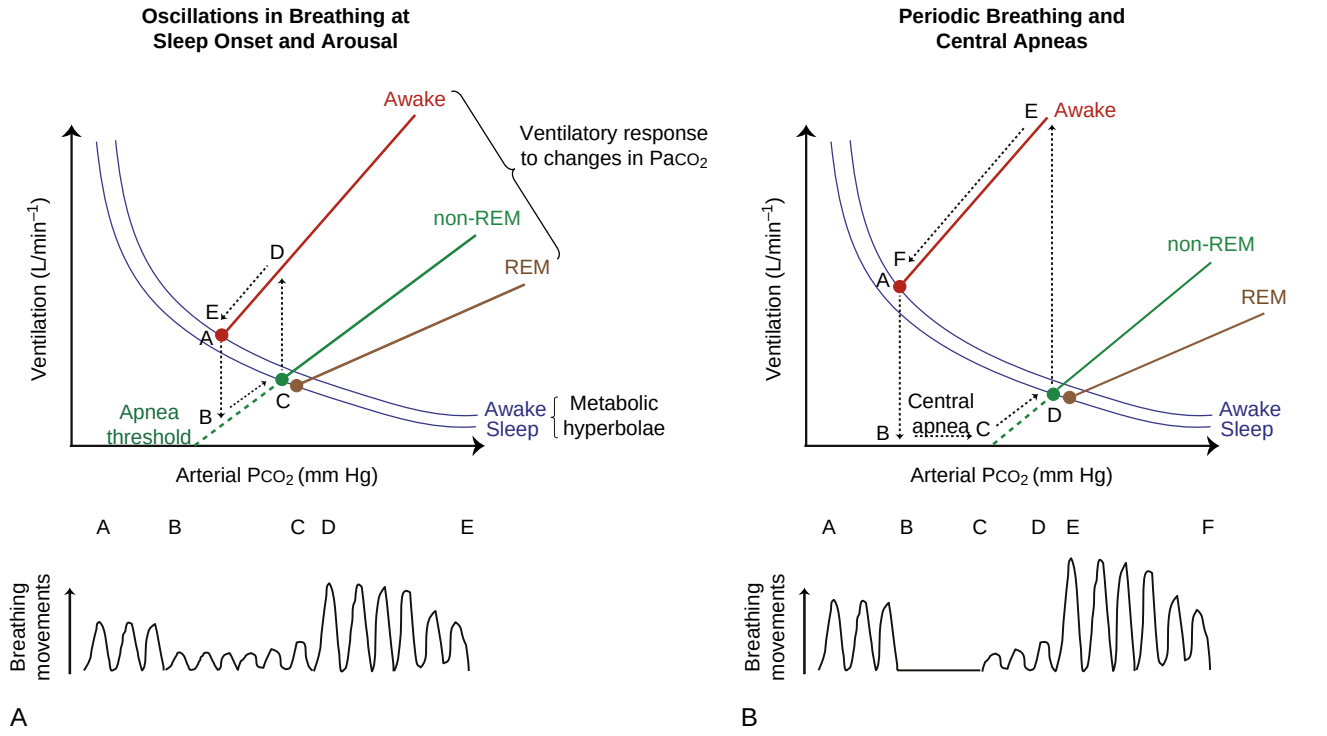

Figure 117.7 How interactions between the ventilatory responses to hypercapnia and transitions between sleep and wakefulness can provoke unstable breathing and central apneas. The equilibrium point for stable breathing in wakefulness is illustrated by point A (*red circle,* A). This equilibrium point intersects the ventilatory response to increased arterial P_{CO_2} (*red line*) and the change in arterial P_{CO_2} that results from a change in ventilation (metabolic hyperbola; *blue line*). The ventilatory response to increased arterial P_{CO_2} in *non–rapid eye movement* (REM) and REM sleep are also shown (*green line* and *brown line,* respectively). Also shown is how a decrease in arterial P_{CO_2} in non-REM sleep can result in reduced ventilation and eventually apnea (*dashed green line*). At sleep onset, the arterial P_{CO_2} that was previously present in wakefulness (*point A*) produces lesser ventilation in sleep according to the extrapolation of the ventilatory response to CO_2 in sleep (*dashed green line, point B*). This decrease in ventilation is out of proportion to metabolic rate so ventilation progressively increases toward the new sleeping equilibrium position (point C, *green circle*). If there is arousal from sleep, then the arterial P_{CO_2} that represents the equilibrium point for breathing in sleep (*green circle*) now represents a hypercapnic stimulus according to the ventilatory response to CO_2 in wakefulness, so that ventilation increases dramatically (points C to D). The elevated level of ventilation at point D is out of proportion to the prevailing metabolic rate so ventilation progressively decreases toward the waking equilibrium position (points D to E, *red circle*). The cycle of waxing and waning of ventilation with the waxing and waning of wakefulness and sleep will continue until sleep is established. The physiologic principle that arises from this effect is that any separation of equilibrium points in wakefulness and non-REM sleep (*red circle* and *green circle*), for any reason can lead to periodic breathing and central apneas at sleep onset. Such periodicity and central apnea is shown in B. (Copyright Richard L. Horner, PhD, University of Toronto.)

UPPER AIRWAY MOTOR TONE AND COMPENSATORY REFLEX RESPONSES ARE PARTICULARLY SENSITIVE TO DEPRESSION IN SLEEP

Principle

The key source of respiratory drive to the hypoglossal motor pool is brainstem sleep-sensitive neurons, whereas the source of drive to spinal respiratory neurons is bulbospinal respiratory neurons. As a consequence of this and other organizational features, hypoglossal motoneurons are not inhibited in expiration, unlike spinal inspiratory motoneurons. Thus, the activity of the genioglossus muscle in expiration is simply a manifestation of the prevailing tonic inputs. It is important to reiterate that the brainstem contains cell groups with sleep state–dependent activity. This organizational feature imparts an important modulation of excitability of the hypoglossal motor pool across natural sleep-wake states as well as a particular susceptibility to the suppressant effects of neurodepressive drugs.

Although change in brainstem neural activity in sleep exerts major effects on the excitability of the upper airway motor pools, it also influences the spinal motor pools via the reticulospinal tract. Notably, this sleep-wake state–dependent influence on the phrenic motor pool is significantly reduced compared to the upper airway motor pools because of the reduced density/impact of those reticulospinal connections. The key physiologic and clinical implications of this organizational feature are that the upper airway muscles are more susceptible to changes in activity across the sleep-wake states and with neurodepressive drugs than is the diaphragm. This notion explains the principle that activity of the diaphragm is relatively preserved across sleep-wake states compared to other respiratory muscles, especially those that serve dual respiratory and nonrespiratory or postural functions such as the muscles of the tongue and chest wall.

Application

Several implications arise from the differential effects of sleep on the respiratory and tonic components of respiratory muscle activity, particularly for the upper airway muscles. For example, the tonic activity of the tongue and palatal musculature contributes to both baseline airway size and stiffness, and the decreased activity in sleep is linked to airway narrowing and the pathogenesis of obstructive

sleep apnea. Suppression of chest wall muscle activity in sleep is thought to increase the compliance of the chest wall (i.e., lower elastic recoil) and contribute to a decreased functional residual capacity; these effects can contribute to hypoventilation, especially in infants because of the already highly compliant chest wall.

OVERARCHING PRINCIPLE: VARIOUS TRAJECTORIES CAN LEAD TO A SLEEP-DISORDERED PHENOTYPE

As outlined in the previous sections, different individuals can experience respiratory dysfunction in sleep for varying reasons; that is, different combinations of factors contribute to both pathogenesis and severity in varying degrees. Given that the involvement of these factors in the pathogenesis of respiratory dysfunction in sleep can also vary within and between subjects— including across the night, between sleep states, at different ages and body weights, and with prescription and nonprescription drugs—there is no single critical mechanism for pathogenesis and no single critical target for therapy for all types of sleep-disordered breathing. The clinical challenge is to devise simple and effective ways to identify the physiologic phenotype of each patient and target the relevant mechanisms operating in each individual. In short, various trajectories can lead to a sleep-disordered phenotype, and the specific mechanisms mediating the trajectories should be identified for each individual to achieve the goal of personalizing therapy.

CLINICALLY RELEVANT CONCEPTS IN RESPIRATORY CONTROL

OBESITY

The high and increasing global prevalence of obesity has led to an increasing appreciation of its important effects on respiratory function. Whereas the obesity-related syndromes of obstructive sleep apnea and obesity hypoventilation are fairly well defined, obesity also impacts other conditions such as asthma and COPD.

Principle

The respiratory effects of obesity can be broadly classified into mechanical influences on the upper airway and chest wall, neurohumoral effects of various adipocytokines, and the possible effects on central respiratory drive as described by the arterial P_{CO_2} set point. By its mechanical effects, obesity has an impact on the upper airway via fat accumulation around the airspace (in the tongue and soft tissues) that increases the propensity for airway collapse.[18] The transmural pressure across the pharyngeal airway is an important variable determining its patency; fat deposition leads to a more negative (less positive) transmural pressure, favoring its collapse. Abdominal fat deposition can further worsen pharyngeal patency by causing small end-expiratory lung volumes that increase upper airway collapsibility through reduced caudal traction forces. Lowered lung volumes also increase the plant gain (i.e., efficiency of carbon dioxide excretion) and thereby increase the tendency to unstable breathing in response to a given perturbation. By its generation of proinflammatory cytokines, obesity has also been implicated in airway inflammation, perhaps contributing to the development of asthma in obese people. Mouse models have suggested an important role for leptin in the control of breathing because ob/ob leptin-deficient mice hypoventilate, and leptin repletion restores their ventilation. However, the impact of leptin on ventilation in humans with obesity is less clear.[19] Finally, by altering arterial P_{CO_2} equilibrium points (or set points, as defined earlier), obesity may affect central respiratory drive. A subset of morbidly obese individuals has elevated arterial P_{CO_2} equilibrium points, likely as a result of cumulative carbon dioxide retention during sleep. It is thought that the elimination of carbon dioxide following arousal is insufficient to eliminate the carbon dioxide that has accumulated during antecedent sleep; the result is a gradual elevation of arterial P_{CO_2} during sleep that eventually persists into wakefulness. However, the underlying genetic and/or neurobiologic mechanisms of obesity hypoventilation syndrome remain to be established (see also Chapter 45).

Application

Obesity is the major reversible risk factor for obstructive sleep apnea. Substantial data show the importance of weight loss in reducing apneas and arterial oxygen desaturations. However, several points about this relationship between obesity and obstructive sleep apnea deserve further emphasis. First, weight loss is difficult to achieve through diet and exercise, and thus bariatric surgery has been receiving an increasingly prominent role in the management of obstructive sleep apnea. Second, even with substantial weight loss, the magnitude of improvement in obstructive sleep apnea severity is often quite modest. For example, in one study, weight loss of 10.7 ± 0.7 kg led to a reduction in the apnea-hypopnea index of only 9.7 ± 2.0 events per hour of sleep.[20] Thus, considerable weight loss may be required to resolve apnea for many patients. Third, several studies have shown that, following either medical or surgical weight loss, obstructive sleep apnea can redevelop over time even without regain of weight. Presumably redistribution of fat and aging both contribute to the recurrence of sleep apnea in these patients. Fourth, some data as well as clinical experience suggest that treatment of sleep apnea is often associated with weight gain.[21] The mechanisms underlying this observation have been debated but are likely related to the fact that treatment of obstructive sleep apnea reduces energy expenditure during sleep and restores social behaviors associated with calorie intake, such as dining out. Regardless of the underlying mechanism, diet and exercise instructions should be provided to the majority of obstructive sleep apnea patients regardless of the treatment approach.

HEART FAILURE

Accumulating literature has suggested a bidirectional relationship between sleep disturbance and heart disease[22] (see also Chapters 119, 120, and 121). Sleep deprivation and sleep apnea have both been associated with an increased incidence of cardiovascular disease. In addition, patients with cardiovascular disease have a very high prevalence of

sleep-disordered breathing. For example, roughly two-thirds of patients with impaired left ventricular systolic function have either obstructive or central sleep apnea. Obstructive apnea and central apnea exist on a spectrum; they often manifest in the same patient and may have similar underlying mechanisms. Although some physiologic literature exists regarding the mechanisms underlying unstable breathing in congestive heart failure, the underlying neurobiology and clinical relevance are less well defined.

Principle

Multiple mechanisms underlie disordered breathing in patients with heart disease. First, chemoreceptor activity is high in patients with congestive heart failure and central sleep apnea compared to that of matched heart failure patients without central apnea.[23] Thus, controller gain, a major component of overall loop gain, is likely high in congestive heart failure patients with central sleep apnea. In patients with pulmonary edema, hypoxemia is commonly present, which may further increase ventilatory drive. Second, because baseline arterial P_{CO_2} is often low in patients with congestive heart failure, these patients are closer to their apnea threshold than are patients with more stable breathing patterns.[24] Third, elevated left atrial pressure can increase ventilatory drive (via reflex mechanisms) and the propensity for apnea by reducing the carbon dioxide reserve.[25] Fourth, accumulation of extravascular lung water has the effect of lowering end-expiratory lung volume (by increasing elastic lung recoil) as well as stimulating juxta-capillary receptors to drive ventilation. Edema formation around the upper airway may also be important in the predisposition to upper airway closure seen in congestive heart failure.[26] Thus, both obstructive and central sleep apnea can develop in these patients due to unstable ventilatory control as well as impaired pharyngeal mechanics.

Application

The treatment of sleep-disordered breathing in congestive heart failure is focused on therapy for the underlying heart failure. In addition, other therapies such as oxygen (which lowers controller gain) and acetazolamide (which lowers circulating CO_2 tension and thus lowers plant gain) can help stabilize breathing,[27] particularly for patients with elevated loop gain. CPAP therapy can benefit some patients, although disordered breathing can frequently persist despite adherence to treatment.[28] In theory, positive airway pressure should be beneficial for these patients because it can reduce cardiac preload and afterload as well as decrease plant gain by increasing functional residual capacity and dead space. Multicenter trials assessing the impact of positive-pressure therapy on clinical outcomes are still ongoing. The data thus far are suggestive, but not definitive, that treatment of obstructive or central sleep apnea is beneficial for patients with congestive heart failure.

AGING

Aging is a major risk factor for both obstructive and central sleep apnea. Other than for children, who have risk of obstructive sleep apnea if they have adenotonsillar hypertrophy, obstructive sleep apnea increases in prevalence with increasing age. Menopause is a risk factor in women.[29] Central sleep apnea also increases in prevalence with increasing age. However, the mechanisms underlying these observations are unclear.

Principle

Aging influences many of the physiologic traits underlying sleep apnea. Aging has been associated with impairment in many reflexes, including those relevant to the upper airway such as the negative pressure reflex that increases pharyngeal dilator muscle activity in response to subatmospheric airway collapsing pressures.[30] Such reflex impairments plus loss of tensile tissue strength over time both likely contribute to the observed increase in collapsibility of the pharyngeal airway during sleep in older as compared to younger individuals. Because fat also tends to deposit preferentially around the upper airway with aging, the parapharyngeal fat pads are increased in size in older versus younger individuals, independent of overall body weight. Aging is also known to reduce lung elastic recoil, although the impact of this finding on pharyngeal mechanics remains unclear. Regarding control of breathing, several studies have shown no major impact of aging on overall loop gain,[31] although ongoing research is further examining this issue.

Application

Given that the mechanisms underlying sleep apnea in older individuals may be different from those in younger individuals, there may be clinical implications to these findings. For example, an individualized approach to therapy may target an impaired negative pressure reflex in an older individual by pharmacologic manipulation of the sensory or central neural components, whereas other approaches may be more fruitful in younger obstructive sleep apnea patients. In addition, because the mechanisms underlying apnea may differ in older individuals, the adverse consequences may well be different in older versus younger obstructive sleep apnea patients. For example, esophageal pressures become less negative in elderly obstructive sleep apnea patients compared to younger patients,[32] presumably due to aging-related differences in either the arousal threshold or ventilatory drive. Because esophageal pressure is a surrogate for the pressure outside the heart, it would be predicted that transmural cardiac pressures (and hence cardiac wall stress/afterload) would be lower in elderly as compared to younger obstructive sleep apnea patients for a given respiratory event. Such pathophysiologic findings may help explain the fewer consequences to obstructive sleep apnea in the elderly as compared to younger patients.[33] Indeed, sleep apnea in the elderly may have a different underlying pathophysiology than in younger individuals and both the causes and consequences may vary with age.

OTHER CLINICAL CONDITIONS

Most respiratory disorders show deterioration in gas exchange during sleep. Although the neurobiologic basis underlying the observed abnormalities is less well understood, several principles can be discussed further regarding hypoventilation syndromes, neuromuscular disease, and parenchymal lung disease.

Principles

At least three factors are likely essential to the deterioration of gas exchange frequently observed during sleep in patients with respiratory disorders. First, the behavioral influences or the wakefulness stimulus to breathing is withdrawn upon transition from wakefulness to non-REM sleep. Accordingly, with the onset of sleep the drive for ventilation is reduced almost immediately. As a result, arterial P_{CO_2} levels tend to rise in sleep, and hypoventilation tends to get worse in patients with chronic respiratory acidosis. During REM sleep, however, the behavioral influences may be restored to some extent compared to non-REM sleep, leading to improvement in gas exchange in some patients. Second, as discussed earlier, the upper airway narrows during non-REM sleep so that controller gain as defined by chemoresponsiveness is reduced. This reduction of controller gain leads to lower change in minute ventilation for any given increase in arterial P_{CO_2}. Third, during REM sleep, there is atonia of the accessory muscles of respiration so that patients reliant on these muscles become more dependent on diaphragmatic activity to achieve ventilation. For some patients, REM sleep thus leads to marked hypercapnia and hypoxemia due to a concomitant fall in chemosensitivity compared to non-REM sleep. End-expiratory lung volume also decreases in various stages of sleep, likely as a function of decreased motor output to the muscles of the chest wall, leading to a reduced functional residual capacity and increased propensity for oxygen desaturation and unstable breathing by increases in plant gain.

Application

The aforementioned conditions lead to deterioration of gas exchange in patients with most respiratory conditions, including those with alveolar hypoventilation, neuromuscular disease, and parenchymal lung disease.

Hypoventilation. Patients with baseline hypercapnia often experience worsening hypercapnia during non-REM sleep. The effect of REM sleep is quite variable, however, because some patients, such as those with CCHS, actually show improvement in gas exchange during REM sleep. On the other hand, some hypoventilation patients, such as those with obesity hypoventilation, may experience further worsening of gas exchange during REM sleep compared to non-REM sleep. In general, bilevel ventilation is effective at maintaining gas exchange during non-REM and REM sleep in hypoventilation patients, although CPAP alone has been effective in obesity hypoventilation syndrome. Various respiratory stimulants have also been considered but, in general, the results have been disappointing.

For patients using chronic opioids, central sleep apnea and hypoventilation are common, although mechanisms are not well studied. In theory, the elevated baseline arterial P_{CO_2} seen with opioids can lead to breathing instability via an increased plant gain. Sleep-disordered breathing (both obstructive sleep apnea and central sleep apnea) is common in patients using chronic opioids, affecting up to 50% of patients in some series. Sleep disturbance has been associated with worsening pain, which leads some patients to seek increased analgesia. Some authors have shown a dose dependence to opioid-induced central apnea, so that a reduction in dose should be a first-line measure. Other treatment options have been considered, including adaptive/auto-servoventilation, but rigorous outcome data are lacking.

Neuromuscular Disease. Patients with neuromuscular disease also experience deterioration of gas exchange during non-REM sleep with further worsening during REM sleep (see also Chapter 130). The loss of the wakefulness stimulus, compromise of upper airway motor tone, atonia of the accessory respiratory muscles during REM sleep, and fall in functional residual capacity may all contribute to respiratory compromise in these patients. Treatment of these patients involves addressing the underlying cause (if possible) and using bilevel noninvasive ventilation as part of supportive care.

Parenchymal Lung Disease. In patients with parenchymal lung disease, such as emphysema or pulmonary fibrosis, similar mechanisms can underlie the worsening gas exchange experienced during non-REM and REM sleep. Treatment is again supportive; it should also address the underlying lung disease to the extent possible. A subset of patients also exists with the so-called overlap syndrome, which consists of the combination of COPD with obstructive sleep apnea. These patients are known to have excess cardiovascular mortality, although no clinical trials to date have addressed the optimal treatment of such overlap patients (see Chapters 119 and 122).

INDIVIDUALIZED THERAPY TARGETING UNDERLYING MECHANISMS

The current treatment of choice for obstructive sleep apnea is nasal CPAP. This treatment option has excellent efficacy and is generally well tolerated, but results can be somewhat variable in clinical practice. Alternative therapies exist, but these also have limited effectiveness and can be expensive and cumbersome for the patient. As a result, many investigators have advocated for further mechanistic-based research to define new therapeutic approaches based on the individual predisposition to sleep-disordered breathing. The recent appreciation for the multifactorial nature of obstructive sleep apnea[34] has opened the way to treatment for this disorder based on underlying endotypes or mechanisms; for example, there may be anatomic abnormalities at the level of the soft palate (the velopharynx) or behind the tongue (the retroglossal airspace). Clinical studies show that the upper airway almost always collapses at the level of the velopharynx in patients with obstructive sleep apnea, but in about half of these patients the obstruction also extends caudally to the retroglossal airspace.[35] In REM sleep, the lower level of the obstruction can extend to even more caudal levels compared to non-REM sleep, most likely due to the greater suppression of pharyngeal muscle activity in REM sleep. For individuals with a primary problem of velopharyngeal compromise, palatal surgery such as uvulopalatopharyngoplasty would be predicted to have reasonable efficacy, but less so for individuals with retroglossal airway collapse.

For those individuals with obstructive sleep apnea driven primarily by increased loop gain, interventions that effectively lower loop gain, such as inhaled oxygen or oral acetazolamide, would be predicted to improve respiratory abnormalities. However, the conceptual and clinical utility of loop gain is in the experimental research and validation stages and requires sophisticated interventional and analytic tools, which has limited more widespread application at this time. Some individuals may have a primary problem of upper airway muscle tone in sleep and/or reflex compensatory responses; such individuals may respond to pharmacologic approaches to increase hypoglossal output[36] or potentially to efforts to stimulate the hypoglossal nerve.[37] Although some recent studies have suggested drug combinations that may have utility,[38] we would advocate for larger well-designed studies showing improvements in clinical outcomes before making clinical recommendations. Individuals who have multiple predisposing factors contributing to obstructive sleep apnea may benefit from combinations of therapies to resolve the underlying abnormalities. The potential for an individualized approach to obstructive sleep apnea therapy based on underlying mechanisms has received recent attention using the concept of personalized medicine. This concept can be applied to the spectrum of respiratory abnormalities during sleep.

Key Points

- Obstructive sleep apnea is common; combinations of upper airway anatomic abnormalities, instabilities in ventilatory control, and variations in upper airway dilator muscle control all contribute to the predisposition to upper airway obstruction within an individual.
- *Rapid eye movement* (REM) sleep is associated with generalized skeletal muscle atonia that also affects the tone in the upper airway dilators such as the genioglossus. Mechanisms of genioglossus muscle atonia are thought to include withdrawal of excitatory inputs from wakefulness-dependent cell groups and active inhibition.
- Non-REM sleep plus sedative and anesthetic-induced neurodepressive brain states are associated with reduced hypoglossal motor output and tongue muscle activity that contribute to upper airway obstruction, particularly in individuals who are anatomically predisposed.
- Opioid narcotics contribute to central apnea and respiratory depression by activating opioid receptors and thereby suppressing the output from the pre-Bötzinger complex, a key site for respiratory rhythm generation in mammals, as well as from other components of the respiratory network that together generate rhythmic breathing and lung ventilation. Opioid narcotics can also contribute to severe respiratory depression in sleep by blunting the tonic excitatory stimulation of arousal-related inputs to the respiratory network, dampening the compensatory ventilatory responses to asphyxia, and causing sedation and failure to arouse.
- The normal decrease in ventilation from wakefulness to sleep usually results in trivial decreases in arterial oxygen saturation because the starting alveolar P_{O_2} is on the flat portion of the oxyhemoglobin dissociation curve. However, any situation that lowers alveolar P_{O_2} in wakefulness (e.g., altitude, lung disease) predisposes to hypoxemia in sleep, especially in REM sleep, if the awake alveolar P_{O_2} is on or close to the steep portion of the oxyhemoglobin dissociation curve.
- Obesity contributes to obstructive sleep apnea primarily through anatomic effects on the upper airway and the chest wall, although influences of adipocytokines on ventilatory control may also be important.
- Loop gain is a term used to describe the predisposition to instability in a feedback control system. Elevated loop gain defines a system prone to instability (i.e., one that can develop periodic behavior after even minor perturbations). Conditions such as congestive heart failure may be associated with increased loop gain as manifested by unstable breathing patterns.
- Aging is associated with impaired protective upper airway reflexes and anatomic changes that may make the pharyngeal airway vulnerable to collapse.

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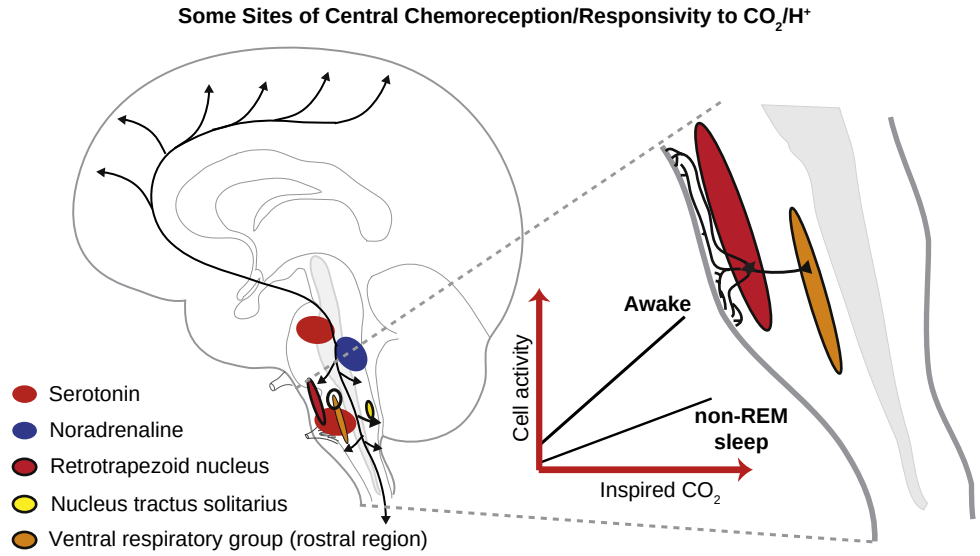

eFigure 117.1 There are multiple sites of chemoreception/responsivity to changes in CO_2/H^+ in the brain. Some of these sites are intimately associated with regulation of brain arousal in sleep and wakefulness (e.g., serotonin and noradrenaline containing cell clusters; see Figure 117.1). Other sites are intimately associated with respiratory neuronal activity and reflex responses (e.g., nucleus tractus solitarius and ventral respiratory group; see Figure 117.3). A key site intrinsically sensitive to alterations in CO_2/H^+ is the retrotrapezoid nucleus located near the ventral surface of the medulla. This region of the brain is magnified in the panel at *right*. Branching dendrites from retrotrapezoid neurons "taste" the cerebrospinal fluid at the medullary surface and are activated by increased CO_2 (lowered H^+). Activity related to CO_2/H^+ influences several brain regions, including the ventral respiratory group, thus driving breathing. The *inset* shows the response of a brainstem serotonergic neuron to increases in inspired CO_2. There are several features of note: (1) baseline activity (i.e., at zero inspired CO_2) is higher in wakefulness than in sleep; (2) the neuronal activity at any given inspired CO_2 is greater in wakefulness than in sleep; and (3) the slope (gain) of response is also greater in wakefulness than in sleep. Together, these three features parallel with the changes in the overall respiratory responses to CO_2 as measured by changes in ventilation (compare with Figure 117.6). (Copyright Richard L. Horner, PhD, University of Toronto.)

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118 CONSEQUENCES OF SLEEP DISRUPTION

VIDYA KRISHNAN, MD, MHS • SANJAY R. PATEL, MD, MS

INTRODUCTION
EFFECTS OF SLEEP DISRUPTION ON ACUTE AND CHRONIC DISEASE
Neurocognitive Changes
Psychiatric Disorders
Pain Perception
Cardiovascular Disease
Immune Function
Endocrine and Metabolic Dysfunction
Cancer Risk
SPECIAL PATIENT POPULATIONS
Maternal-Fetal Health
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Primary Sleep Disorders
Comorbid Illnesses
KEY POINTS

INTRODUCTION

Sleep is an integral part of health and well-being. It is an active process that is highly regulated and evolutionarily conserved. Sleep is required for preservation of energy, restoration, reparation, and rejuvenation of normal physiologic function, including immunity, muscle growth, tissue repair, protein synthesis, and clearance of brain metabolites such as adenosine. Sleep facilitates brain neural plasticity, the process by which the central nervous system alters itself both structurally and functionally in response to experiences, which is important for consolidating memories and learning.

Healthy sleep is characterized by optimal regularity of sleep over many days, satisfaction with sleep quality, daytime alertness (i.e., restorative capacity), proper timing (i.e., aligned with one's circadian rhythm), high efficiency (i.e., a low number of awakenings and time spent awake after falling asleep), and sufficient duration.[1] Sleep disruption can therefore be defined as any process that threatens healthy sleep. Many of the causes of sleep disruption are behavioral or environmental and can include staying up late to watch television or engage on social media, loud noises or lights that interfere with the ability to sleep (common in inpatients), and caregiving requirements for spouses, children, or others who have care needs through the night. Primary sleep disorders are another important cause of sleep disruption that impacts sleep across multiple domains. For example, *obstructive sleep apnea* (OSA) fragments sleep; it decreases continuity, reduces quality, and impairs daytime alertness. Shift work (i.e., work outside the standard 9 AM to 5 PM business day) adversely impacts all sleep health domains. Finally, comorbid illnesses can impair sleep either directly (e.g., nocturnal asthma causing frequent awakenings or depression causing early morning awakenings) or indirectly (e.g., nighttime β-agonist use causing insomnia or diuretic use causing frequent awakenings).

Sleep-wake patterns are regulated for the most part by two strong drivers—circadian rhythms and homeostatic pressures.[2] Circadian output from the suprachiasmatic nucleus in the hypothalamus tends to maintain a regular daily timing for sleep and wakefulness as well as a wide range of other physiologic processes. While the intrinsic circadian period in humans is about 24.3 hours, regular light exposure, a major modulator of the circadian rhythm, maintains circadian rhythms on a 24-hour period in normal humans. In addition, homeostatic forces regulate sleep so that the drive to sleep increases as time since the last period of sleep increases. These two forces interact to support a regular daily sleep pattern over time. Sleep itself can be further divided into two separate states, *rapid eye movement* (REM) and *non-REM* (NREM) sleep, different from each other and from wakefulness in their unique *electroencephalogram* (EEG) patterns and physiologic characteristics. REM sleep is characterized by an EEG pattern similar to wakefulness (mixed frequency, low amplitude), but with skeletal muscle atonia (except for the extraocular muscles and diaphragm). NREM sleep, in contrast, is characterized by a slowing of EEG frequency as compared to wakefulness (stage N1), synchronized EEG signals (sleep spindles, K complexes in stage N2), and slower delta frequency EEG activity (stages N3, slow-wave sleep, delta sleep). Both REM and NREM sleep have their own circadian and homeostatic regulation interacting to produce the typical sleep architecture of normal sleep, which displays a pattern of four to five cycles of sleep approximately 90 minutes in duration. Each of these *ultradian* (less than 24 hours) cycles consists of NREM sleep (in progressively deeper stages) followed by a period of REM sleep, with each progressive ultradian cycle exhibiting longer periods of REM sleep and less slow-wave sleep (Fig. 118.1). Sleep disruption that interferes with normal sleep architecture can reduce amounts of REM and/or slow-wave sleep, resulting in physiologic perturbations.

Sleep health can be assessed across at least six dimensions (regularity, satisfaction, daytime alertness, timing, efficiency, and duration). The pattern of deficits can be helpful in identifying the underlying etiology. A combination of interview and standardized questionnaires from the patient, as well as objective testing, can be used to assess each of these dimensions (Table 118.1). This information

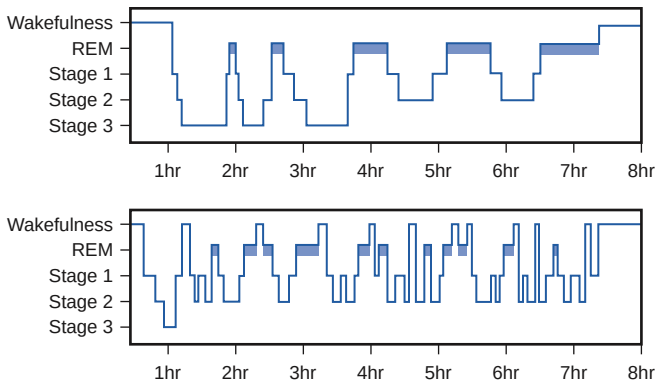

Figure 118.1 Hypnograms of normal sleep architecture and severe sleep fragmentation. Hypnograms and sleep stages of a healthy individual (*top*) are distinct from those of a patient with obstructive sleep apnea (*bottom*). The patient with obstructive sleep apnea has severe fragmentation with disrupted sleep architecture characterized by loss of stage 3 sleep, significantly reduced rapid eye movement (REM) sleep, and frequent awakenings.

can then narrow the differential diagnosis. For example, reduced sleep satisfaction and alertness associated with adequate duration are suggestive of reduced sleep efficiency from a sleep fragmentation disorder such as OSA. Reduced alertness in the setting of normal sleep efficiency and normal to increased duration indicate a primary hypersomnia disorder such as narcolepsy.

Table 118.1 Examples of Subjective and Objective Measurements of Sleep Health Dimensions

	Subjective	Objective
Regularity	Sleep log or diary	Actigraphy
Satisfaction	Insomnia Severity Index PROMIS Sleep Disturbance	(none)
Daytime alertness	Epworth Sleepiness Scale Stanford Sleepiness Scale PROMIS Sleep-Related Daytime Impairment	Multiple Sleep Latency Test Psychomotor Vigilance Test Oxford Sleep Resistance Test
Timing	Sleep log or diary Morningness/eveningness Questionnaire	Actigraphy Dim light melatonin onset Core body temperature monitoring
Efficiency	Sleep history Sleep log or diary	Actigraphy Polysomnography
Duration	Sleep history Sleep log or diary	Actigraphy Polysomnography

PROMIS, patient-reported outcomes measurement information system. Modified from AG, Buysse DJ. *Treating Sleep Problems: A Transdiagnostic Approach*. New York: Guilford Press; 2017.

EFFECTS OF SLEEP DISRUPTION ON ACUTE AND CHRONIC DISEASE

The effects of sleep disruption on acute illness have been examined through observational studies and short-term intervention trials, often with experimentally induced sleep disruption. The evidence for long-term effects of chronic sleep disruption is primarily derived from observational longitudinal cohort studies. Sleep disruption results in various pathophysiologic disturbances, causing short- and long-term consequences (Fig. 118.2). Increased recognition of the impact of sleep disruption on safety and health has led to greater efforts to develop robust, randomized long-term evidence to evaluate the effectiveness of sleep-focused interventions to improve health.

NEUROCOGNITIVE CHANGES

Acute Effects

The fact that even a single night of sleep disruption can cause significant disturbance in memory, concentration, and attentiveness should not come as a surprise to anyone who has experienced a sleepless night. The cognitive dysfunction associated with sleep restriction for 28 hours has been shown to be roughly equivalent to that associated with consuming alcohol up to a blood alcohol concentration of 0.10%, which is considered legally impaired if driving.[3] Neurocognitive testing in patients with acute total or partial sleep deprivation reveals global cognitive impairment, but certain cognitive domains, including executive function, sustained attention, and long-term memory, are particularly susceptible.[4] Persons with sleep deprivation are therefore prone to cognitive limitations such as decreased insight, inability to integrate emotion and cognition to guide moral judgments, decreased flexibility in thinking, a propensity for perseveration, difficulty with understanding the temporal order of information, and difficulty assimilating and integrating new information.[5–7]

Imaging studies have been employed to identify the regions of the brain responsible for the neurocognitive impairments seen with sleep disruption. The prefrontal cortex, thalamus, and posterior parietal cortices appear to be regions of the brain responsible for attention and higher-order cognition.[8] With sleep deprivation, there are global decreases in activity in these cortical and subcortical structures,[9–10] which may explain the findings of reduced attention and working memory with sleep disruption.

Impaired neurocognition is likely a major factor in the increased incidence of work-related injuries and death in persons with sleep disorders. Extremely sleepy workers are 70% more likely to be involved in accidents than non-sleepy workers.[11] In a large 20-year Swedish prospective cohort study, sleep disruption in the previous 2 weeks was associated with nearly double the risk of fatal occupational accidents.[12] Sleep disruption has been implicated, at least in part, in some of the most devastating human and environmental health accidents around the world, including the nuclear reactor meltdowns at Three Mile Island and Chernobyl; the chemical plant leak in Bhopal, India; the grounding of the Exxon Valdez oil tanker; and the space shuttle Challenger explosion.[13] The Agency for Healthcare Research and Quality has identified both fatigue and sleep deprivation of health care providers as threats to patient safety, primarily as a result of errors in medical decision making and clinician burnout.[14]

Chronic Implications

Chronic sleep disruption is implicated as both a cause and an effect of cognitive impairment, and the body of supporting

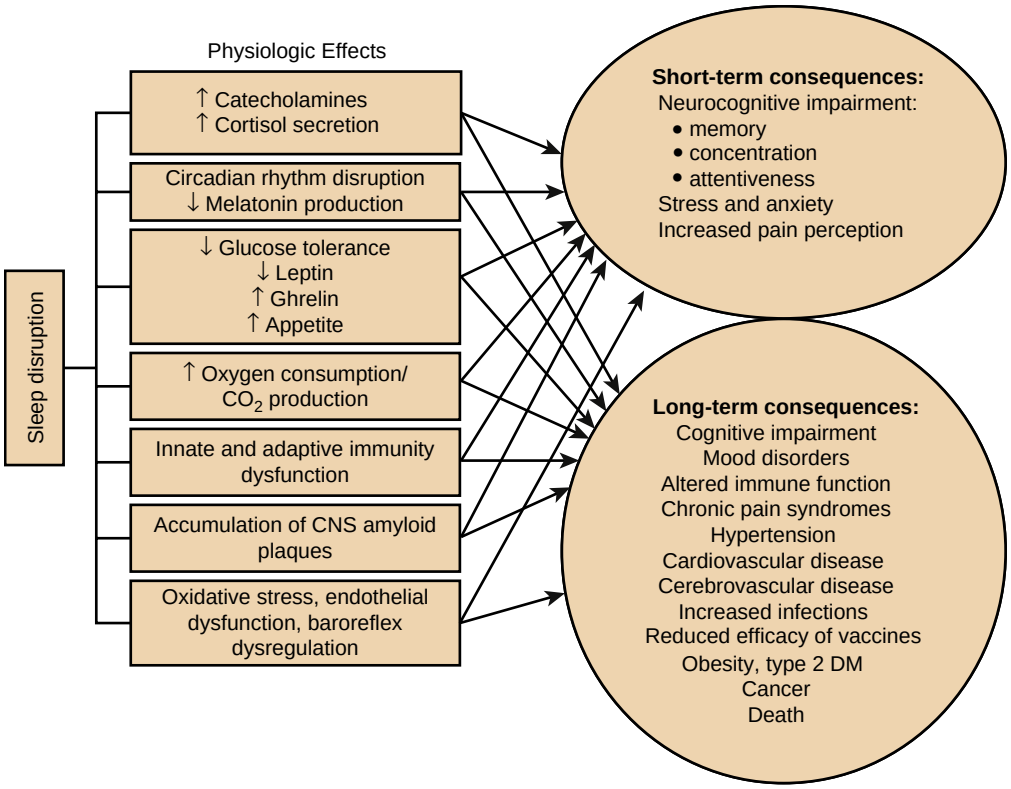

Figure 118.2 Physiologic effects and consequences of sleep disruption. Sleep disruption leads to multiple physiologic changes. These changes lead to short-term and long-term consequences for health. CNS, central nervous system, DM, diabetes mellitus.

evidence is growing. Sleep disruption is common in patients with preclinical Alzheimer disease, mild cognitive impairment, Parkinson disease, and Lewy body dementia, as manifested by disordered sleep architecture, excessive daytime sleepiness, and daytime napping.[15–18] Alterations in physiologic circadian rhythms, reduced melatonin secretion, degeneration of retinal ganglion cells, and dysregulation of circadian clock gene expression have been demonstrated in Alzheimer disease patients.[19] The clinical significance of this is less straightforward given that polymorphisms in these clock genes have not yet been associated with sleep-wake disturbances.[20] Chronotherapy, particularly bright light therapy, targeted to treat circadian rhythm disturbances in patients with Alzheimer disease, has been shown to improve the duration and continuity of nighttime sleep, reduce sundowning agitation, and improve cognition.[21] Characteristic pathophysiologic changes of amyloid-β deposition and neurofibrillary tangles in the *central nervous system* (CNS) often affect the hypothalamus, where hypocretin-1, a sleep-wake regulating polypeptide, is synthesized.[22,23] The prevalence of OSA is more than 40% in patients with Alzheimer disease and other dementias, further contributing to sleep fragmentation in these patients.[15,24]

Sleep disruption may contribute to the development and progression of cognitive decline through numerous mechanisms. One of the proposed teleologic functions of sleep is to provide time for clearance of metabolites and compounds from the CNS. Mouse models have been used to demonstrate that amyloid-β is cleared most efficiently during sleep through the glymphatic system of the CNS; with chronic sleep deprivation, accumulation of amyloid plaques is accelerated.[25] Consistent findings are found in human studies, with self-reported sleep deprivation or poor sleep quality associated with increased amyloid-β deposition in the CNS.[26] The intermittent hypoxia and sleep fragmentation characteristic of OSA may also cause neurodegeneration through inflammation and cell signaling impairment, but these mechanisms require further investigation. Nevertheless, the rate of progression in cerebrospinal fluid amyloid-β levels over 2 years correlates with OSA severity.[27]

PSYCHIATRIC DISORDERS

Sleep is an integral part of mental health. Indeed, sleep disruption is included as part of the diagnostic criteria for many psychiatric diseases.[28] Sleep disturbances are a risk factor for onset and exacerbation of psychiatric disorders, particularly depression, bipolar disorder, posttraumatic stress disorder, and alcoholism, emphasizing the need to address sleep disorders in parallel with treatment of the psychiatric condition. Conversely, many psychiatric diseases can impair sleep. In addition, common pharmacologic therapies for psychiatric disorders, including benzodiazepines, antidepressants, and antipsychotics, have adverse effects on sleep, including both sedation and insomnia that can limit the effectiveness of these medications.

Acute sleep deprivation can exacerbate psychiatric disease and has been demonstrated to increase anxiety levels.[29] This increase in anxiety along with emotional dysregulation and disrupted circadian rhythms caused by a lack of sleep may explain why acute sleep deprivation can serve as a trigger for acute mania in patients with bipolar disorder as well as a trigger for suicidal behavior.[30,31]

Major depressive disorder is the most extensively studied mood disorder with regards to sleep. Self-reported poor

sleep quality is present in 90% of individuals in a depressive episode, with two-thirds reporting insomnia and about 15% reporting hypersomnia.[32,33] Polysomnographic characteristics of sleep in patients during a depressive episode include longer sleep latency, increased *wake (or wakefulness) after sleep onset* (i.e., the periods of wakefulness after sleep onset), and more early morning arousals—all resulting in poorer sleep efficiency. Changes in sleep architecture are common in mood disorders. REM sleep abnormalities are the most consistent finding in depression, including reduced REM latency, prolonged duration of the first episode of REM, increased REM density (frequency of eye movements during REM), and reduced time in NREM slow-wave sleep.[34] Many classes of antidepressant medications are linked to suppression of REM sleep.[35] Patients with bipolar disease demonstrate similar polysomnographic findings of frequent arousals, reduced slow-wave sleep, shortened REM latency, and increased REM density.[36] Changes in sleep architecture in patients with major depressive disorder and bipolar disease may persist even after an acute episode, and persistence of these sleep abnormalities predicts an increased risk of relapse.[37–40]

There is strong evidence that poor sleep predisposes to, exacerbates, and perpetuates mood disorders. One meta-analysis found that patients with insomnia symptoms are 2.6 times more likely to develop new-onset depression as compared to those without insomnia symptoms.[41] A population-based cohort study that included polysomnography data showed that frequent complaints of difficulty falling asleep accompanied by abnormalities in sleep latency, continuity, and duration all predicted development of incident depression.[42] Reduced sleep efficiency predicted worsening of manic symptoms over 19 months in a longitudinal cohort study of patients with either depression or bipolar disorder.[43] Treatments targeting sleep disruption are associated with improved outcomes in patients with mood disorders. In patients with comorbid major depressive disorder and insomnia, randomized trials have shown insomnia therapy combined with antidepressant therapy improves depressive symptoms more than antidepressant therapy alone.[44] Circadian phase also plays an important role in mood disorders; individuals with delayed sleep phase are at higher risk for depressed mood, and morning light therapy, which advances sleep phase, can improve mood. In fact, morning bright light therapy is the first-line treatment for seasonal affective disorder.

Sleep disruption is a hallmark of posttraumatic stress disorder and may include nightmares, insomnia, dream enactment, and sleep apnea. Flashbacks of trauma are experienced as nightmares that disrupt normal sleep and may incite and perpetuate fear of sleeping. A constant state of excessive hyperarousal frequently leads to an inability to fall asleep or return to sleep during middle-of-the-night awakenings. Daytime hypersomnia may or may not be present, depending on the degree of the underlying state of hyperarousal. Nightmares and insomnia are often refractory to medications (antidepressants and α-antagonists), but sleep-focused behavioral interventions, including image rehearsal therapy and cognitive behavioral therapy for insomnia, have proven successful in improving both sleep symptoms and overall posttraumatic stress disorder severity.[45] Treatment of comorbid OSA may also improve sleep symptoms and posttraumatic stress disorder severity.[46]

Alcohol is a common drug used to self-medicate in an attempt to treat insomnia, and alcohol use is considered a marker of severity of insomnia. As a soporific, alcohol promotes sleep at the beginning of the night by inducing drowsiness, but it disrupts sleep later in the night by lowering the arousal threshold as blood alcohol levels fall, increasing the likelihood of early morning awakenings.[47] It also worsens snoring and sleep apnea, further disrupting sleep through arousals related to disordered breathing events. Patients with alcohol-induced sleep disruption may escalate their alcohol consumption in an attempt to treat the early morning awakenings, contributing to a vicious cycle of abuse. Consumption of alcohol may delay circadian rhythms and further increase the risk of alcohol use disorder.[48] Insomnia is a strong predictor of relapse in patients with alcohol use disorder,[49] highlighting the importance of treating comorbid insomnia in this population.

PAIN PERCEPTION

Chronic pain is a highly prevalent condition, with 20.4% of U.S. adults reporting chronic pain and 8% of U.S. adults reporting pain severe enough to interfere with their ability to engage effectively in employment, self-care, social interactions, and recreational activities.[50] Chronic pain is associated with substantial health care costs, reduced quality of life, and indirect societal costs such as job absence, reliance on opioid pain medications, and reduced work productivity. There is a bidirectional relationship between pain and sleep quality. Pain can be a significant reason for interruption of sleep. Conversely, disturbed sleep can result in increased pain perception, particularly hyperalgesia. Possible hypotheses for pain amplification due to sleep disruption include (1) exacerbation of the underlying painful condition due to sleep disruption (e.g., worsening headache related to insufficient sleep syndrome), (2) increased sensitivity of peripheral nociceptors, (3) heightened sensitivity for pain signals in the CNS, and (4) reduced inhibitory mechanisms of pain perception in the CNS.[51–53]

Acute Effects

The effects of short-term sleep disruption on pain perception have been studied in experimentally altered sleep conditions, primarily with complete and partial acute sleep deprivation. Just 1 or 2 nights of total sleep deprivation results in increased pain perception in response to exposure to both cold and heat, as well as in both superficial and deep tissues, when compared to habitual sleep (i.e., average nightly sleep duration).[54–56] Studies examining stage-selective sleep deprivation (targeted deprivation of just slow-wave sleep or REM sleep) have resulted in mixed and inconclusive results about whether sleep stages are important in perception of pain and, if so, which ones.[52]

Chronic Implications

Chronic sleep disruption in conditions such as untreated sleep-disordered breathing, insomnia, sleep insufficiency, and shift work may also affect pain thresholds. While acute sleep disruption affects immediate sensitivity to pain, chronic sleep disorders interfere with the ability to habituate to chronic pain.[57] Persons without pain at baseline are also at greater risk of developing pain disorders with chronic

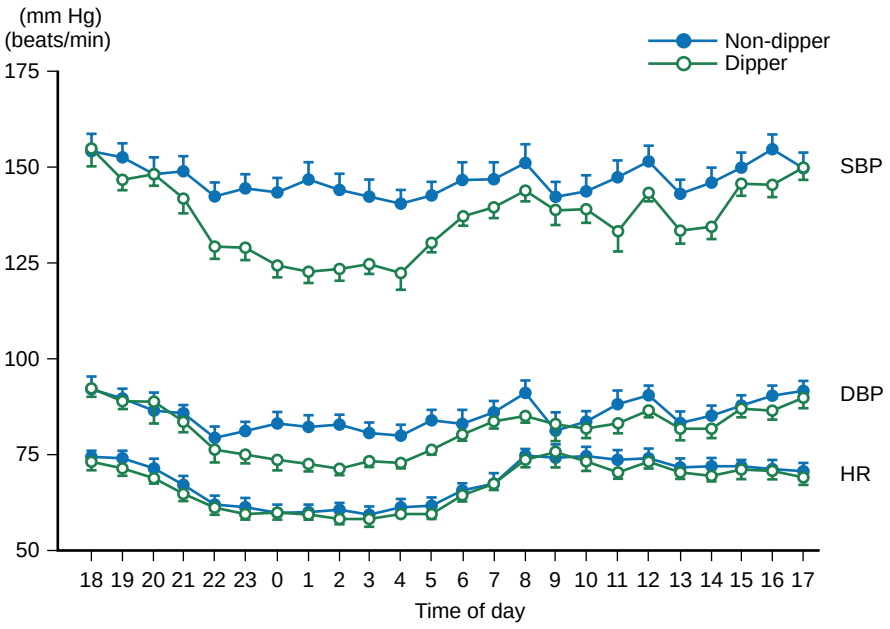

Figure 118.3 Demonstration of dipper and non-dipper patterns of blood pressure during sleep. Diurnal changes in blood pressure in dipper and non-dipper essential hypertensive subjects. The changes in *systolic blood pressure* (SBP) and *diastolic blood pressure* (DBP) were significantly different between the two groups. The changes in *heart rate* (HR) were not different between dipper and non-dipper hypertensive subjects. (From Kohara K, Nishida W, Maguchi M, Hiwada K. Autonomic nervous function in non-dipper essential hypertensive subjects. Evaluation by power spectral analysis of heart rate variability. *Hypertension*. 1995;26[5]:808-814.)

sleep disruption. In a 2-year longitudinal study, nurses who were free of pain at baseline were more likely to develop lower back pain if they were shift workers, and the effects were amplified in shift workers who were overweight/obese.[58]

OSA has been implicated in altering pain processing through both sleep fragmentation and recurrent nocturnal hypoxemia, although the differential effects of these two mechanisms on chronic pain are unclear. Some evidence suggests that chronic sleep fragmentation results in hyperalgesia, although other studies do not support this association.[59,60] Interestingly, intermittent hypoxemia may actually reduce opioid requirements for pain control by increasing expression of opioid receptors.[61] Extension of sleep duration over a 4-day period in patients with objective evidence of mild hypersomnia reduced pain sensitivity and improved daytime somnolence, suggesting a potential therapeutic sleep intervention.[62] Patients with chronic pain and chronic sleep insufficiency randomized to no sleep intervention had more postoperative pain and more postoperative narcotic pain medication requirements after hip or knee surgery than those who were randomized to extension of their sleep by 1 hour/night for a week prior to surgery.[63]

CARDIOVASCULAR DISEASE

The complex association between sleep and cardiovascular health has been a topic of interest for researchers for decades. Elevated blood pressure is the most common cardiovascular condition associated with disrupted sleep and likely contributes to other cardiovascular morbidities. Both sleep fragmentation, with recurrent sympathetic activation from sleep arousals, as well as sleep deprivation, increase nocturnal blood pressure and dampen the normal "nocturnal dipping" pattern of blood pressure seen with healthy sleep (Fig. 118.3).[64,65] Non-dipping is also associated with untreated OSA. Any disruption to sleep, whether from sleep-disordered breathing, sleep-related movement disorders, or primary insomnias, may lead to persistent elevation of blood pressure at night. This persistent elevation of blood pressure in non-dippers is thought to contribute to cardiovascular sequelae and is independent of perceived sleep quality. For example, insufficient sleep duration and poor sleep consolidation have been identified as independent predictors of incident hypertension.[66,67] Shift workers with night work have interference with the nocturnal dipping in blood pressure, resulting in elevated blood pressure the following shift, and increased risk for chronic hypertension and cardiovascular disease.[68] Potential mediators of cardiovascular pathology due to sleep disruption include oxidative stress, inflammation, endothelial dysfunction, and baroreflex dysregulation.[69,70] Sympathetic nervous system activity is likely to be increased as well, although this is not a consistent finding in clinical studies.[71–73]

There is growing evidence identifying sleep disruption as a predictor of subsequent cardiovascular disease. Self-reported short sleep duration has been associated with incident coronary artery disease and increased coronary artery calcification.[74,75] In subjects with established coronary artery disease, objectively measured short sleep duration (less than 6 hours) and long sleep duration (greater than 8 hours) are both associated with increased atherosclerotic burden even after controlling for multiple known cardiovascular risk factors.[76] Short sleep duration is also associated with atrial fibrillation, with each hour of sleep reduction associated with 1.09- and 1.17-fold increase in risk of incident and prevalent atrial fibrillation, respectively.[77] Observational studies have demonstrated an association of insomnia with coronary artery disease as well as with congestive heart failure.[78] The conditioned hyperarousal state, which predisposes a person to chronic insomnia, is characterized by increased sympathetic nervous system activity and hypothalamic-pituitary-adrenal axis stimulation, which may be causally related to coronary artery disease risk.[78,79]

Sleep disruption is also associated with increased incidence of cerebrovascular disease. Self-reported sleep duration appears to be strongly associated with stroke risk, with an overall hazard ratio for stroke in short sleep duration of 1.15 (95% confidence interval, 1.07 to 1.24) and hazard ratio for stroke in long sleep duration of 1.45 (95% confidence interval, 1.30 to 1.62).[80] Insomnia is also a predictor of stroke risk. Those who reported insomnia symptoms had a 54% higher risk of stroke over a 4-year follow-up period compared to an age- and gender-matched control group.[81]

Multiple epidemiologic studies have demonstrated a U-shaped curve of the association of self-reported habitual sleep duration and mortality; both subjective short sleep duration and long sleep duration are associated with higher mortality.[74,82–84] Interestingly, however, studies that quantify sleep duration with objective measures (e.g., actigraphy [i.e., activity monitoring] or polysomnography) have not consistently found an association between longer sleep and mortality, suggesting this paradoxical association with self-reported long sleep may not be due to prolonged sleep per se. Instead, the excess mortality associated with habitual self-reported long sleep may be due to coexisting OSA, poor sleep efficiency, or other sleep disorders, which may cause the perception of long sleep duration.[85]

IMMUNE FUNCTION

Sleep plays an integral role in the normal function of the immune system. Both circadian and homeostatic drives have important effects on immune function, with sleep regulating both innate and adaptive immunity. Circadian rhythms, independent of nocturnal sleep, are responsible for regulation of both innate and adaptive immune cells, with maximum circulating cell counts in the evening followed by reductions through the night. This regularity is driven by various systems, primarily changes in both the hypothalamic-pituitary-adrenal axis and the sympathetic nervous system.[86] Sleep-dependent changes happen in both innate and adaptive immunity. Natural killer cellular activity, an innate immune response, increases with sleep. Similarly, production of adaptive cytokines, including *interleukin* (IL)-2, interferon-γ, and IL-12, and a reduction of IL-10, an anti-inflammatory cytokine, are observed with nocturnal sleep.[86]

Disturbances of sleep thus can impact both the innate and adaptive immune systems. These conclusions are drawn from numerous supportive studies resulting in impaired response to infectious challenges as well as cellular and gene markers of inflammation. For example, with a single night of sleep deprivation, natural killer cell function and activity are reduced. Increased wake (or wakefulness) after sleep onset is associated with reduced natural killer cell mobilization after a stressor, and impaired recovery to baseline natural killer cellular function even after 30 minutes.[87] Similarly, circulating inflammatory markers, such as tumor necrosis factor and vascular endothelial activation markers, are elevated after a single night of total sleep deprivation, whereas other inflammatory markers, including IL-6 and C-reactive protein, show elevations after more prolonged periods (4 to 7 nights) of sleep restriction.[86,88] In contrast, adaptive immunity is suppressed after a single night of sleep deprivation, including reduced T cell production of IL-2, reduced helper T cell 1:2 ratios, and reduced monocyte production of IL-12.[86,89] Elevated levels of corticosteroids associated with sympathetic nervous system activation and sleep disruption result in hyperglycemia and increased susceptibility to infection, and also suppress function and numbers of both B and T cell lymphocytes.[90]

One clinical consequence of chronic poor sleep, therefore, is an increased susceptibility to infection. Extremes of sleep duration, both habitual short (5 hours or less) and long sleep (9 hours or greater) duration, as well as perceived poor sleep quality, are risk factors for community-acquired pneumonia.[91] Short sleep duration and sleep fragmentation, but not long sleep duration, have been linked to an elevated risk of development of the common cold after intranasal inoculation with rhinovirus in healthy patients.[92]

Sleep deprivation also blunts the immune response to vaccinations. In healthy mice, sleep deprivation blocks the expected immune response to an influenza vaccine.[93] In humans, the hepatitis B secondary antibody response (6 months after a series of three immunizations) was lower in persons with shorter sleep duration, independent of the response to initial therapy.[94] Influenza vaccination–induced H1N1 antibody titers were also reduced after a single night of sleep deprivation but, with healthy sleep, antibody levels recovered by day 10 postimmunization.[95] These findings suggest that poor sleep during infections may compromise inherent immune responses to combat infections.

ENDOCRINE AND METABOLIC DYSFUNCTION

Healthy sleep is vital for normal metabolism, endocrine function, and glucose tolerance. Disrupted sleep predisposes an individual to diabetes and obesity by altered glucose metabolism and dysregulation of appetite control via neuroendocrine pathways. Pituitary hormone secretion is also deranged as a result of sleep disruption.

Acute Effects

Altered glucose metabolism is observed even with short periods of partial sleep deprivation. In one study of 11 healthy men, 6 days of partial sleep deprivation (4 hours sleep/night) was associated with impaired glucose tolerance and reduced beta cell responsiveness when compared to 6 days with full nights (up to 12 hours in bed/night) of sleep.[96] Interestingly, selective suppression of slow-wave sleep for 3 consecutive nights, without reducing total sleep time, also resulted in decreased insulin sensitivity, reduced glucose tolerance, and increased risk of type 2 diabetes mellitus.[97] This highlights the importance of slow-wave sleep in glucose metabolism and potentially explains the increased risk of glucose intolerance with increased age, because there is also a reduction in slow-wave sleep with age.

Regulation of appetite control is also affected by acute sleep disruption. Leptin and ghrelin work in opposing manners to affect metabolism, energy expenditure, appetite, and wakefulness. Leptin is secreted by adipocytes and acts on the hypothalamus to suppress food intake. Ghrelin, which stimulates appetite and hunger via the hypothalamus, is released by gastric parietal cells tonically; release is inhibited by gastric stretch following a meal.[98] Although some studies have shown a reduction in leptin and elevation of

ghrelin levels with short-term partial sleep deprivation, not all studies have replicated these findings.[99,100]

Pituitary hormones and their targets are linked to sleep and can have abnormal secretion profiles with sleep disruption. With healthy sleep, cortisol secretion is suppressed, while *growth hormone* (GH), thyroid-stimulating hormone, and prolactin all increase during sleep. Estrogen levels have been shown to be suppressed by melatonin.[101] With a night of total sleep deprivation, the rate of decline of cortisol levels in the evening is attenuated, and cortisol levels remain elevated at night. Conversely, GH and thyroid-stimulating hormone levels are reduced with total sleep deprivation. In habitually healthy sleepers, with a single night of total sleep deprivation followed by subsequent daytime recovery sleep, cortisol, GH, and thyroid-stimulating hormone levels trend back to normal.[102,103]

Chronic Implications

Chronic sleep disruption can lead to increased risk of type 2 diabetes mellitus and obesity. Sleep disruption, as seen with OSA, is associated with an increased odds of developing diabetes (odds ratio, 1.4 to 2.2).[104–106] Another study found a dose-response association between OSA severity and glycemic control in diabetic patients, with higher hemoglobin A1c levels in patients with more severe OSA.[107] Many population-based longitudinal studies have shown a robust association of chronic sleep deprivation with weight gain and obesity risk.[108–110] However, clinical trials have not yet robustly demonstrated that OSA treatment or interventions to increase sleep duration can reduce metabolic risk.

Over time, there appears to be longitudinal adaptation of GH secretion in the setting of chronic sleep deprivation, with the suppression of GH secretion with acute sleep deprivation gradually evolving into two small pulses of GH secretion (one before and one after sleep).[100] Chronic partial sleep deprivation is also associated with reduced leptin and ghrelin levels, independent of weight.[108,111]

CANCER RISK

There is a growing body of literature to support the association of sleep disruption and cancer incidence, particularly with solid tumors. The potential mechanisms linking sleep disruption and oncologic risk are mostly speculative, including (1) dysregulation of normal metabolism of hormones (such as estrogen), (2) systemic inflammation and immune dysfunction, and (3) potential DNA damage and oxidative stress.[112] The strongest evidence is in the link between circadian rhythm disorders and risk of breast cancer. There is consistent evidence that incident breast cancer risk is inversely associated with elevated melatonin metabolite levels (6-sulfatoxymelatonin, aMT6), and that night-shift workers have reduced aMT6 levels compared to day-shift workers.[113,114] The majority of the population-based cohort data regarding circadian rhythm disruption and breast cancer supports an overall increased incidence of breast cancer (increase ranging from 5–48%).[112] In fact, melatonin has been studied as a promising oncostatic agent in breast cancer due to its ability to inhibit breast cancer cell growth.[101] Whereas many of the studies were carried out on nurse cohorts, particularly on nurses involved in active shift work, the definition of circadian rhythm disturbance has included any lifetime exposure to night-shift work and nocturnal light exposure. So, despite a wide range of exposures with potentially opposing circadian directional shifts, the association of breast cancer risk with circadian rhythm disorders remains robust. Beyond the association with breast cancer, night-shift work has been associated with an increased risk of prostate and colorectal cancer. Based on the total body of literature to date, a working group of the International Agency for Research on Cancer concluded night-shift work is probably carcinogenic in humans.[115]

OSA has also been postulated to be a novel cancer risk factor. Using mouse models, both intermittent hypoxemia and sleep fragmentation have been found to promote tumor growth and metastasis.[116,117] Epidemiologic studies have suggested patients with OSA are at greater risk for cancer.[118] Some, but not all, studies suggest OSA may be a risk factor for lung cancer in particular.[119,120] Altered sleep habits have also been postulated to increase lung cancer risk. A meta-analysis of 32 prospective cohort studies found both short and long sleep durations were associated with elevated lung cancer risk.[121] These findings are limited by inadequate characterization and accounting for known lung cancer risk factors, particularly tobacco exposure.

SPECIAL PATIENT POPULATIONS

MATERNAL-FETAL HEALTH

The impact of sleep disruption on maternal and fetal health is an area of growing interest. Pregnancy is a condition involving normal maternal physiologic changes of increased estrogen and progesterone levels, increased minute ventilation, and increased abdominal girth. Healthy sleep during pregnancy may be compromised by a number of sources, including (1) physical symptoms, such as nausea, discomfort, and pain; (2) exacerbation of chronic medical conditions, such as asthma or pulmonary hypertension[122]; (3) care of other family members, particularly young children; and (4) development of new sleep disorders during pregnancy, such as restless legs syndrome or OSA. There is a growing body of knowledge that sleep disruption may interfere with both the mother's health and fetal development.

A review of the consequence of sleep disruption on maternal-fetal health can be found at ExpertConsult.com.

CRITICALLY ILL PATIENTS

The acute effects of poor sleep are well illustrated, and perhaps magnified, in critically ill patients (see also Chapter 119). Disrupted sleep can suppress immune function, resulting in more frequent and more severe infections. Cardiovascular consequences of sleep disruption (including OSA) include elevated blood pressure, arrhythmias, and worsened pulmonary hypertension, all of which can aggravate a patient's underlying critical illness. Insufficient sleep can lower the seizure threshold, increasing the likelihood of seizures in patients who are predisposed. Short-term neurocognitive impairment is associated with poor sleep and includes slowed response times and reduced situational awareness. This, in turn, can significantly impair patient recovery by leading to development of delirium,

Maternal Health

During pregnancy, sleep duration, timing, and continuity in the first two trimesters have been shown to be associated with increased maternal health complications. Studies of self-reported short sleep duration in the first and second trimesters of pregnancy reveal an association between sleep duration and risk of gestational diabetes mellitus with a relative risk ratio of 5.6 among women reporting 4 hours or less per night versus 9 hours per night as well as mean third-trimester blood pressure.[123,124] In a prospective cohort study of nulliparous pregnant women, both short sleep duration and delayed sleep timing, objectively measured by actigraphy, were associated with increased risk of gestational diabetes mellitus but not hypertensive disorders.[125]

Sleep-disordered breathing is more frequent in pregnant women compared to prepregnant women due to weight gain, hormonal changes to ventilatory control, and hyperemia to the upper airway resulting in upper airway narrowing. Maternal sleep-disordered breathing, as determined by clinical symptoms and studied objectively by polysomnography, is associated with gestational diabetes mellitus, gestational hypertension, and preeclampsia.[126]

Maternal sleep disruption is also associated with pain perception and mood disorders. Sleep duration in the third trimester may impact the perception of pain during labor and the duration of labor. Women with less than 6 hours of sleep in the third trimester as measured by actigraphy are more likely to have longer labor durations and 4.5 times more likely to have a cesarean section compared to those obtaining at least 7 hours of sleep.[127] Sleep insufficiency is associated with higher levels of proinflammatory cytokines, and the proinflammatory state during pregnancy is associated with postpartum depression risk.[128] Insomnia during pregnancy is common, with 40–60% of pregnant women reporting significant distress due to difficulty with sleep initiation or maintenance, and is related to postpartum depression. Cognitive behavioral therapy for insomnia during pregnancy results in improvement in insomnia severity, faster remission of insomnia, and a small but significant reduction in postnatal depression symptoms.[129]

Fetal Development

Fetal health is dependent on maternal health and behaviors. The findings of a meta-analysis on the topic of maternal sleep and fetal outcomes indicate that OSA, short sleep duration, and poor sleep quality during pregnancy may be associated with preterm birth and stillbirth but do not predict fetal growth or birth weight.[130] Differences in definitions of fetal outcomes severely limited the findings of the meta-analysis. Further research is clearly needed to understand the potential impact of poor maternal sleep during pregnancy on fetal outcomes.

interference with patient cooperation during spontaneous breathing trials for extubation, and inability to participate in physical rehabilitation.

A more in-depth review of the consequence of sleep disruption in critically ill patients can be found at ExpertConsult.com.

TREATMENT OF SLEEP DISRUPTION

Treatment of sleep disruption entails behavioral interventions that promote sleep health, evaluation and treatment of primary sleep disorders, and evaluation and optimization of treatment of comorbid illnesses from a sleep-centered framework. This includes addressing iatrogenic causes of sleep disruption, most commonly medications prescribed for comorbid illnesses.

SLEEP HYGIENE

Sleep hygiene is the term used to describe the adoption of behaviors that promote sleep health across dimensions. A healthy sleep-wake pattern is established in part by increasing knowledge and awareness of the multiple dimensions necessary for restorative sleep. In addition, utilizing and enhancing the underlying biologic drivers of sleep, namely the homeostatic and circadian forces that promote sleep, are key components to sleep hygiene.

A necessary foundation for healthy sleep is having a quiet, dark, comfortable, and safe place to sleep and having sufficient time allocated for sleep at the same time every night. The time allocated for sleep should ideally match the individual's underlying circadian tendency. This is of particular relevance in institutionalized populations who are not allowed to determine their own sleep environment. This includes hospitalized patients, for whom bright lights, noise, frequent disruption for vital sign checks, and early morning awakenings for phlebotomy or imaging commonly produce massive disruptions in sleep.

Activities that promote wakefulness or that combat daytime sleepiness may impede nighttime sleep onset. Daytime naps, a common compensatory mechanism for poor sleep, will reduce the homeostatic pressure for sleep the next night and, in general, should be avoided. Caffeine consumption in the morning or in the afternoon is common to promote wakefulness but should be avoided at least 6 hours prior to sleep time. Coffee, tea, and soda are the most common caffeine-containing beverages, but even "decaffeinated" versions of these beverages and cocoa-containing foods and beverages contain enough caffeine to impede nighttime sleep. Exercise is an energizing activity that promotes wakefulness and has numerous health benefits, but because it increases adrenergic activation and can delay sleep onset, exercise should be avoided in the 2 to 3 hours prior to bedtime.

Circadian rhythms are reinforced by maintaining a regular 24-hour schedule. This includes keeping a regular bedtime and wake-up time, thereby allowing for optimal duration of time in bed sleeping, both during work or school days and during weekends, vacations, or less-structured days. Exposure to light during the daytime and a dark environment at night are the strongest factors signaling the physiologic secretion of melatonin in the evening, facilitating sleep initiation. Whereas light is the strongest *zeitgeber* ("time-giver," synchronizer), other external cues fortify the circadian rhythm, including regular meal times, physical activity, social interactions, and environment. Thus keeping a regular schedule in all of these daytime activities can improve sleep. A bedtime routine, such as quiet reading time or writing in a journal, can also become a zeitgeber and facilitate nighttime sleep. These behaviors also allow the individual to disconnect from the physical and emotional stresses of the day, facilitating sleep onset. A warm shower or bath prior to bedtime will augment the natural cooling of the core body temperature in the evening, a circadian cue to initiate sleep.

Some activities co-opted during times of stress are maladaptive behaviors. Alcohol consumption should be avoided for at least 4 hours before bedtime due to its effects on lowering the arousal threshold as blood alcohol levels fall, increasing the likelihood of early morning awakenings and delaying circadian rhythms. Nicotine is a stimulant drug that will delay sleep onset and should be avoided altogether, but especially 2 hours prior to bedtime. Large meals eaten close to bedtime may interfere with sleep onset by causing discomfort and requiring ongoing digestion.

Electronics, including televisions, laptops, tablets, and smartphones, can contribute to nighttime light exposure and mental stimulation, hindering the process of sleep initiation. As a result, these should ideally be kept out of the sleep environment. The use of social media in particular near bedtime can be a problem. The algorithms underlying these applications are designed to increase use by activating the cortex and thereby can prevent sleep.

PRIMARY SLEEP DISORDERS

General treatment approaches to common sleep disorders are given in Table 118.2. Sleep-disordered breathing can contribute to sleep fragmentation, poor sleep quality, and impaired daytime functioning. Treatment options, as described in Chapter 122, include weight loss, lateral positioning, and avoidance of alcohol as well as more aggressive measures such as positive airway pressure and oral appliance therapy. Restless legs syndrome can cause sleep-onset insomnia and reduced sleep duration. Treatment options include iron supplementation (in the setting of iron deficiency), behavioral interventions, discontinuation of medications that may exacerbate the condition, and pharmacologic therapies. Jet lag disorder and shift-work disorder can be anticipated by scheduled travel or work hours and may be treated with a combination of behavioral interventions, melatonin, and light therapy, although pharmacologic sleep aids or stimulants may be indicated.[157]

Insomnia impairs sleep quality and daytime alertness and can also reduce sleep duration and regularity. *Cognitive behavioral therapy for insomnia* (CBT-I) has been demonstrated in randomized trials to treat insomnia effectively and is recommended as first-line therapy instead of pharmacologic approaches due to minimal side effects.[158] The most effective components of CBT-I are stimulus control, preventing anxiety and frustration in bed by avoiding clockwatching, getting out of bed if one cannot sleep, and

The *intensive care unit* (ICU) setting has historically not been an environment conducive for healthy sleep. Noise pollution from equipment, hospital staff, and other patients, as well as interruptions of sleep for periodic nursing assessments and provider examinations, impede healthy sleep. Furthermore, the timing of blood draws and diagnostic tests in the early morning hours to facilitate morning rounds curtails sleep and can disrupt circadian rhythms. Environmental light at night also compromises sleep onset and maintenance, and lack of sunlight exposure during daytime may contribute to shifts in circadian rhythms. Medications frequently used in the ICU setting, such as sedatives, analgesics, β-adrenergic receptor antagonists, vasopressors, and antiepileptic medications, interfere with normal sleep patterns. Ventilator dys-synchrony may also cause sleep disruption among patients requiring mechanical ventilation.[131] Air leaks from noninvasive ventilators may disrupt sleep by impairing respiratory sufficiency or by stimulating orofacial sensory mechanoreceptors.[132] Circadian rhythms in hospitalized patients are frequently misaligned. Lack of sunlight exposure as well as critical illness (particularly sepsis) alter melatonin secretion. Additionally, secondary circadian cues, such as intermittent meals (versus continuous feeding) and social interactions (daytime versus all day/night) are absent in critically ill patients and further misalign the circadian rhythm of critically ill patients. Other patient factors, including pain, anxiety, critical illness, and preexisting comorbid conditions, are additional factors that limit healthy sleep in the ICU.

ICU survivors report poor subjective sleep and inadequate sleep duration as major sources of stress and anxiety during hospitalization.[133] Studies with objective sleep characterization by polysomnography show that, instead of the normal sleep pattern with a major sleep period (7 to 8 hours) at nighttime, critically ill patients experience markedly fragmented sleep, with sleep bouts averaging 15 ± 9 minutes throughout the 24-hour period, including half of sleep bouts during the daytime. REM sleep and NREM stage 3 restorative deep sleep are often completely absent in critically ill patients.[134–136]

The causal relationship between lack of sleep among ICU patients and ICU-associated delirium is suspected but not firmly established. Many observational studies establish an association between both the reduction of total sleep and REM sleep and the presence of delirium.[137–139] There is significant overlap in the symptoms of sleep disruption and delirium, including inattention, fluctuating mental status, and cognitive dysfunction. Delirium and insufficient wakefulness are implicated in the prolonged duration of intubation. Successful extubation is more likely in patients with higher levels of wakefulness and when there is correlation between the two cerebral hemispheres with respect to depth of sleep.[140] (The depth of sleep is not routinely compared between the sides of the brain, and the pathophysiologic implications of this finding are not known.) Pharmacologic interventions intended to improve sleep, such as nocturnal dexmedetomidine, have shown promising results in preventing delirium, but larger clinical trials with better assessment of sleep are needed.[141,142] Delirium has been associated with longer ICU length of stays, increased costs, increased mortality, and increased risk for the development of dementia.[143–145]

Sleep inadequacy may also contribute to poor respiratory mechanics, resulting in prolonged intubation time. In a study of healthy men who were sleep deprived for 30 hours, muscle endurance, as measured by pressure-time index, and maximum voluntary ventilation were both significantly reduced.[146] Studies evaluating the effect of sleep deprivation on ventilatory response to hypercapnia have shown mixed results.[147–149] Atelectasis and low lung volumes can predispose patients to upper airway collapsibility. Sleep disruption can further compromise upper airway patency, causing OSA physiology and possible respiratory compromise.[150]

Of interest are the strategies to improve sleep in critically ill patients. While most ICU providers acknowledge the importance of sleep for patient recovery, only a minority of ICUs in the United States report protocols for sleep-promoting interventions.[151] Interventions to improve sleep quality in ICU patients should include optimization of the environment (minimizing noise and light during sleep time), judicious use of medications that alter sleep quality (including minimizing sedation), and promotion of wakefulness and physical activity during the day. Among patients requiring ventilator support, preventing ventilator asynchrony has been recognized to improve sleep. The use of proportional assist ventilation instead of traditional pressure support ventilation can improve sleep quality (reduced sleep arousals, increased REM and slow-wave sleep).[152] The benefit of proportional assist over pressure support modes of ventilation was not seen, however, when studied in patients with ventilator synchrony.[153] In patients with tracheostomy undergoing a protracted ventilation liberation, sleep duration and sleep efficiency (though not sleep quality) seem to be improved when patients are on ventilator support at night.[154]

Insufficient, disrupted, and mistimed sleep may contribute to depression, long-term cognitive dysfunction, and possibly impaired exercise tolerance among ICU survivors.[155] Sleep disturbances that begin during hospitalization often persist after hospitalization and are reported in 10–61% more than 6 months after hospital discharge.[156] Some centers have implemented ICU survivor outpatient clinics to manage the chronic sequelae of ICU hospitalization, including sleep disruption.

Table 118.2 Most Common Sleep Disorders and Initial Management Approaches

Sleep Disorder	First-Line Therapy	Second-Line and Adjunctive Therapy
Insufficient sleep syndrome	Sleep hygiene	
Insomnia	In person CBT-I	BBT-I Internet-based CBT-I Pharmacotherapy
Obstructive sleep apnea	PAP, oral appliance	Weight loss and exercise Avoidance of aggravating medications Avoiding supine sleep Alcohol avoidance Upper airway surgery
Restless legs syndrome	Iron replacement Avoidance of aggravating medications Pharmacotherapy	Behavioral approaches
Delayed sleep phase disorder	Behavioral modification Timed morning light therapy	Timed evening melatonin Pharmacotherapy
REM behavior disorder	Avoidance of aggravating medications Pharmacotherapy	Safe sleep environment to prevent injury
Narcolepsy	Pharmacotherapy	Sleep hygiene

BBT-I, brief behavioral therapy for insomnia; CBT-I, cognitive behavioral therapy for insomnia; PAP, positive airway pressure; REM, rapid eye movement.

sleep restriction, whereby time allowed for sleep is temporarily reduced to increase sleep efficiency and quality and then slowly increased back to a targeted goal duration. Additional components include promoting good sleep habits, relaxation, and cognitive therapy aimed at addressing misconceptions about sleep, resetting expectations about sleep, and reducing assumptions that the worst will happen if sleep goals are not achieved. Because the lack of clinicians trained in CBT-I has prevented widespread implementation of this treatment, simpler strategies have been developed that can be more readily incorporated into clinical practice. These include brief behavioral therapy that can be administered by nonexpert clinicians in one or two sessions and internet-based CBT-I. Randomized trials have demonstrated the utility of both of these options.[159,160]

COMORBID ILLNESSES

Many diseases are exacerbated at night due to circadian, behavioral, or positional factors. These include asthma, gastroesophageal reflux disease, heart failure, neuromuscular disorders affecting respiration, and chronic pain syndromes. Asthma has a circadian pattern, with increased airway responsiveness at nighttime. Nocturnal wheezing is identified as a marker of poor asthma control and a cause of nocturnal awakening. Control of nocturnal asthma symptoms can improve sleep quality and aid in control of daytime asthma symptoms.[161] Nocturnal gastroesophageal reflux disease is worsened by certain foods, such as spicy or highly acidic foods, and by large meals close to bedtime. Nocturnal reflux symptoms result in poor sleep quality and sleep fragmentation due to discomfort and have been implicated as a possible risk factor for OSA.[162] Classic heart failure symptoms, including orthopnea and dyspnea, are a result of the supine positioning during sleep and the redistribution of circulating blood volume from the periphery into the pulmonary circulation. This pulmonary vascular congestion predisposes to increased pulmonary edema, nocturnal dyspnea, and central sleep apnea (as described in Chapter 121) and, if not adequately controlled at night, will disrupt sleep, resulting in reduced pain threshold and result in a vicious cycle perpetuating chronic pain syndromes.

Many medications, particularly psychiatric, neurologic, cardiovascular, and pulmonary medications, have side effects that can include sedation and/or insomnia. Other medications, such as diuretics, can fragment sleep if taken at night. Opiate medications may be prescribed to control pain but may also worsen sleep disorders such as OSA. It is important therefore to ask patients about the timing of all medications and ensure timing is aligned with optimization of healthy sleep.

Acknowledgments

We thank Dr. Maria Antonelli, Dr. J. Daryl Thornton, and Dr. Edward Warren for their editorial comments.

Key Points

- Healthy sleep has the following dimensions: (1) optimal regularity of sleep over many days, (2) satisfaction with sleep quality, (3) daytime alertness (i.e., restorative capacity), (4) proper timing (i.e., aligned with one's circadian rhythm), (5) high efficiency (i.e., a low number of awakenings and time spent awake after falling asleep), and (6) sufficient duration.
- Sleep disruption has pervasive health consequences, including neurocognitive, psychiatric, cardiovascular, immunologic, metabolic, and oncologic derangements.
- Health consequences can disrupt the sensitive system required to initiate and maintain sleep, resulting in a potentially vicious feedback loop.
- Critically ill patients who experience sleep disruption during illness may be at higher risk for higher acuity illness, delirium, longer lengths of stay, and repercussions after discharge from the hospital.
- An emphasis on healthy sleep and correction of conditions that cause sleep disruption may play a pivotal role in promotion of overall health.

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119 SLEEP-DISORDERED BREATHING: A GENERAL APPROACH

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KEY POINTS

INTRODUCTION

Sleep medicine is a field focused on the evaluation of disorders affecting nocturnal breathing, movements, behaviors, sleep-wake cycles, and the daytime consequences of disrupted sleep. It encompasses a broad range of disorders in which nocturnal ventilation, oxygenation, patency of the upper airway, and sleep-wake centers are highly relevant to caring for pulmonary patients in both inpatient and outpatient settings. Sleep disorders are germane to a multitude of different medical and surgical specialties, including those for which pulmonary consultants are commonly called to lend expertise in guiding care. An adequate fund of knowledge in sleep medicine is even more relevant to subspecialties within pulmonary medicine, such as asthma, COPD, interstitial lung disease, the intensive care unit, and chronic respiratory failure secondary to chest wall disorders and neuromuscular disease. This chapter presents an approach to thinking about sleep disorders, unifying concepts within Section O and Chapter 45, and reviews common clinical scenarios during which the impact of sleep should be considered. In-depth reviews of *obstructive sleep apnea* (OSA), central sleep apnea, hypoventilation, sleep disruption, and control of breathing are covered in other chapters.

THINKING LIKE A SLEEP PULMONOLOGIST

THE GOLDEN 8 HOURS

Sleep accounts on average for 30% of our adult lives. In an ideal undisturbed state, sleep restores physical and mental wellness and is critical to consolidation of learning and executive function.[1–5] When sleep disorders are present, the opposite is true, exposing affected individuals to pathologic states of intermittent or sustained hypoxemia, hypercapnia, inflammation, oxidative stress, cardiopulmonary mechanical stress, and/or sleep deprivation (see Figs. 118.2 and 120.5). Sleep affords a golden 8 hours during which we have a physiologic reset to promote healthy metabolic and cognitive function.

Although sleep medicine encompasses more than *sleep-disordered breathing* (SDB), mastering an understanding of respiratory physiology during sleep increases the aptitude of the astute pulmonary clinician to expand the differential diagnosis of clinical presentations, recommend and tailor personalized therapies, and educate other learners on the basis of sound physiologic principles. Indeed, a primary goal of this chapter is to increase awareness of the impact of SDB on common comorbidities frequently encountered by the pulmonary consultant or intensivist.

VENTILATION, OXYGENATION, AND MECHANICS DURING SLEEP

Considering the time spent asleep each night, consequences of SDB, such as hypoxemia and hypercapnia, are likely to be more clinically significant than initially recognized, especially in patients with underlying pulmonary disease. Frequently only the awake, upright oxygen saturation of medically stable pulmonary patients measured during outpatient visits is factored into assessments, differential diagnoses, and medical decision making. However, many factors affecting nocturnal oxygenation and ventilation must be considered when evaluating a patient with suspected SDB or an associated comorbidity (eTable 119.1). Recognizing all forms of SDB, including OSA, hypoventilation syndromes,

eTable 119.1 Factors Influencing Sleep-Disordered Breathing

ALTERATIONS IN VENTILATORY CONTROL

- Change in chemoreceptor set point for $Paco_2$
- Change in central ventilatory drive
  - Sedative hypnotics
  - Centrally acting non-sleep medications (i.e., opioids, benzodiazepines)
- REM-related reduction in ventilation

MECHANICAL CHANGES

- Reduced FRC
- Collapsibility of the upper airway
- Chest wall restriction
- Rostral fluid redistribution

UNDERLYING OBSTRUCTIVE VENTILATORY DEFECTS

- Increased dead space, reduced alveolar ventilation
- Hyperinflation and flattening of the diaphragm
- Circadian influence on bronchoconstriction
- Reduced oxygenation and ventilation during REM

UNDERLYING RESTRICTIVE VENTILATORY DEFECTS

- Neuromuscular disease (neuromuscular junction, myopathy, innervation)
- Skeletal abnormalities (pectus excavatum, kyphoscoliosis)
- Parenchymal disease (interstitial lung disease)
- Reduced oxygenation during REM and NREM

PULMONARY VASCULAR DISEASE

OBESITY-RELATED CHANGES

- Reduced FRC, ERV, small airway closure, expiratory flow limitation
- Ventilation-perfusion inequality
- Neurohormonal changes
- Excessive carbon dioxide production
- Obstructive sleep apnea
- Increased work of breathing
- Reduced central respiratory drive
- Obesity hypoventilation syndrome

ERV, expiratory reserve volume; FRC, functional residual capacity; NREM, non-rapid eye movement; $Paco_2$, arterial partial pressure of carbon dioxide; REM, rapid eye movement.

and hypoxemia, enables an understanding of downstream consequences such as *pulmonary hypertension* (PH), arrhythmias, and cognitive impairment.

Patients whose oxygen saturation is near the steep part of the oxyhemoglobin dissociation curve may maintain oxygenation while awake and upright but frequently desaturate once in a recumbent position and even further once asleep. Patients desaturate because of (1) increased ventilation-perfusion mismatch with increased perfusion to areas of decreased ventilation, (2) elimination of behavioral input into ventilation at sleep onset, (3) decreased chemosensitivity to both oxygen and carbon dioxide leading to mild hypoventilation,[6,7] (4) an upward shift in the ventilatory set point for *arterial partial pressure of carbon dioxide* (P_{CO_2}) by 2 to 3 mm Hg,[8] and (5) alterations in respiratory mechanics, including reduced functional residual capacity and restricted chest wall expansion (limited expansion in the posterior and downward dimensions when supine).[9–11] The effects of respiratory mechanics are more pronounced in individuals with central obesity and in those with underlying parenchymal disease (see also Chapters 10 and 11). OSA, especially when severe, may exacerbate hypoxemia and hypercapnia through repetitive occlusion of the upper airway leading to cyclic desaturation without recovery to normoxia or baseline between apneas. It is important to keep in mind that not all SDB is OSA and that patients can experience hypoventilation or hypoxemia in the absence of OSA.

IDENTIFYING PULMONARY PATIENTS AT RISK FOR COMORBID SLEEP DISORDERS

All patients with evidence of daytime hypoxemia or hypercapnia should be screened for SDB, particularly if nocturnal symptoms and daytime dysfunction (i.e., excessive daytime sleepiness) are present (Table 119.1). The association between OSA and pulmonary diseases such as COPD, asthma, interstitial lung disease, and even cystic fibrosis is increasingly recognized[12] (see the sections on COPD and asthma later and Chapter 120). Although OSA is not implicated in the pathogenesis of these pulmonary diseases, whether treatment of comorbid OSA leads to improved morbidity and mortality is an active area of research. Routine screening for OSA in asymptomatic adults without risk factors is not indicated.[13]

TAKING A RELEVANT SLEEP HISTORY

As with any specialty evaluation, there are unique aspects to taking a sleep history and performing a targeted physical examination. The purpose of the history is to elucidate the reason the patient perceives he or she has been referred to a sleep specialist, solicit symptoms that support or refute differential diagnoses, determine the most appropriate diagnostic workup, and gauge interest and ability to comply with recommended treatments. Not every referral for OSA will result in a diagnosis of OSA. In many cases, more than one sleep disorder is present, or the symptoms are nonspecific and attributable to another diagnosis, such as insomnia, circadian rhythm disorders, or movement disorders. It is of utmost importance to maintain the perspective that patients are often referred for symptoms, even when the referral asks to "rule out sleep apnea," and that not every sleep disorder seen by a pulmonologist will be sleep apnea. That said, OSA is highly prevalent, and treatment of OSA may very well resolve the initial complaint of nonrefreshing sleep, poor sleep quality, or nocturia. Patients are also referred to sleep specialists to evaluate for the presence of OSA suspected of complicating another comorbidity (i.e., before cardioversion for atrial fibrillation), even if the patient lacks perceived sleep disruption or sleep-related symptoms. In the absence of symptoms, negotiating a care plan that involves nightly adherence to a treatment for an asymptomatic disease becomes challenging. Motivational interviewing and identifying goals of care may be helpful in these cases. Table 119.2 summarizes the key components of a sleep history and targeted physical examination to generate a differential diagnosis for sleep complaints and to determine next steps in the evaluation process. Pulmonary consultants should consider the impact of SDB and sleep disruption on every patient, understand when screening questionnaires are indicated and when full sleep histories should be taken, and know the indications for sleep testing (Fig. 119.1) so they may reach the most accurate diagnoses and provide the most comprehensive recommendations possible.

Table 119.1 Signs, Symptoms, and Comorbidities Suggestive of Sleep-Disordered Breathing

SIGNS
Chronic compensated respiratory acidosis
Arterial P_{CO_2} >45 mm Hg
Serum bicarbonate >27 mEq/L
Resting awake, upright Sp_{O_2} <94%
DAYTIME SYMPTOMS
Excessive daytime sleepiness
Nonrefreshing sleep quality
Morning headaches
Morning confusion or fogginess
Impaired cognitive function
Difficulty with memory or concentration
NOCTURNAL SYMPTOMS
Snoring or witnessed apneas
Nocturnal wheezing, dyspnea, cough
Nocturia
Concern about breathing from bed partner
Excessive movements noted by bed partner
Orthopnea
Repetitive awakenings for unclear reasons
COMORBIDITIES
Obesity
Arrhythmia
Ischemic heart disease
Stroke
Gastroesophageal reflux disease
Interstitial lung disease
COPD
Asthma
Neuromuscular disease

P_{CO_2}, partial pressure of carbon dioxide; Sp_{O_2}, oxygen saturation as measured by pulse oximetry.

QUESTIONNAIRES

Several validated questionnaires are currently used to screen for SDB (STOP [*snoring, tiredness, observed apnea, high blood pressure*],[14] STOP-Bang [*STOP plus body mass index, age, neck*

Table 119.2 Components of a Sleep History and Physical Examination

Sleep history	■ Symptoms ■ Duration ■ Exacerbating and alleviating factors ■ Known triggers for sleep disruption or behaviors (i.e., nightmares, alcohol, choking or gasping) ■ Use of sleeping medications ■ Circadian preference (natural time to go to sleep and wake up) ■ Restless leg symptoms ■ Bed partner perspective/input ■ Witnesses apneas, snoring ■ Abnormal behaviors (dream enactment, vocalizations)
Sleep schedule	■ Time of lights out ■ Sleep latency ■ Number and cause of awakenings ■ Latency to return to sleep ■ Time of final morning awakening
Morning symptoms	■ Sleep quality ■ Perceived sleep duration ■ Morning headaches, dry mouth, sore throat
Social history	■ Shift work ■ Caffeine consumption: quantity and time of day of last caffeinated beverage ■ Alcohol use: quantity, time of consumption, whether alcohol is used to induce sleep ■ Nicotine use: quantity and timing ■ Exercise: duration and timing (i.e., within 3 hr of target bedtime)
Family history	■ Known sleep disorders (OSA, insomnia) ■ Neuromuscular disease (when relevant)
Sleep-specific physical examination	■ Obesity ■ Body habitus (pear vs. apple) ■ Neck circumference ■ Mallampati classification ■ Tonsillar hypertrophy ■ Palatal shape (i.e., high arch) ■ Nasal septal deviation, turbinate hypertrophy, polyps ■ Nasal valve collapse ■ Patency of nasal airflow ■ Presence and health of dentition ■ Occlusion (i.e., retrognathia) ■ Scalloping of tongue (due to imprint of teeth on edges of enlarged tongue)

OSA, obstructive sleep apnea.

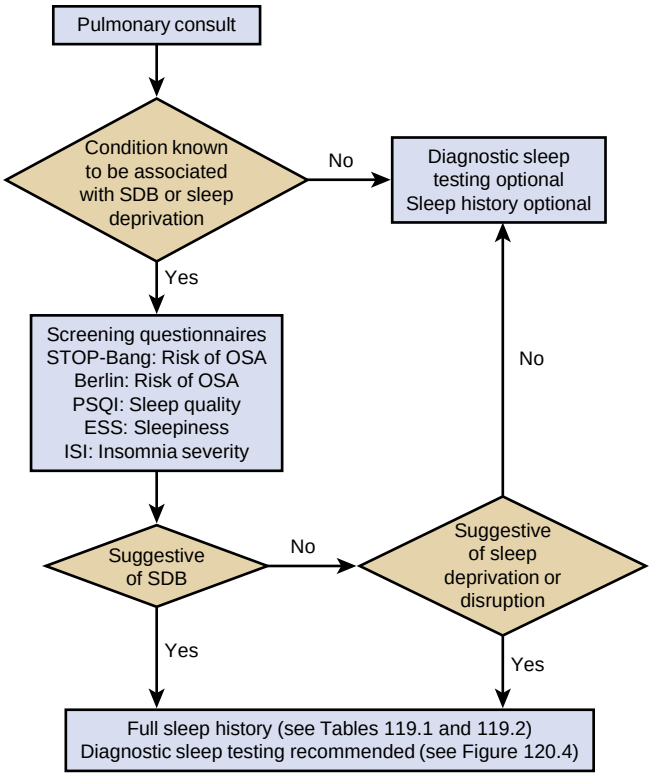


Figure 119.1 Approach to identifying sleep disorders in patients seen by the consulting pulmonologist. Familiarity with comorbidities associated with *sleep-disordered breathing* (SDB) or sleep disruption is essential to identifying patients at risk of nocturnal hypoxemia, hypercapnia, and *obstructive sleep apnea* (OSA). Once identified, patients can be screened using validated questionnaires to determine whether referral to a sleep specialist is warranted and whether further diagnostic testing is indicated. ESS, Epworth Sleepiness Scale; ISI, Insomnia Severity Index; PSQI, Pittsburgh Sleep Quality Index; STOP-Bang, snoring, tiredness, observed apnea, high blood pressure, body mass index, age, neck circumference, and male sex.

circumference, and male gender],[14] Berlin Questionnaire[15,16]), evaluate sleep quality and daytime symptoms (Pittsburgh Sleep Quality Index,[17] Functional Outcomes of Sleep Questionnaire,[18] Epworth Sleepiness Scale[19]), and identify other primary sleep disorders such as restless leg syndrome, insomnia, circadian rhythm abnormalities, and parasomnias. Sensitivity and specificity of each questionnaire in detecting sleep disorders depend on the population. The STOP-Bang[20] questionnaire, based on three reported symptoms (snoring, feeling tired, having witnessed apneas) and five physical characteristics (hypertension, obesity, age, enlarged neck circumference, and male gender) is one of the most widely used screening questionnaires for OSA in both medical and surgical populations. The addition of pulse oximetry,[21] serum bicarbonate levels,[22] and body shape[23] (apple vs. pear) to the STOP-Bang questionnaire has been evaluated for improved prediction models of patients at risk of OSA.

There is a paucity of literature validating traditional sleep screening questionnaires in patients with pulmonary disease. Most studies have evaluated the Berlin Questionnaire, Epworth Sleepiness Scale, Sleep Apnea Clinical Questionnaire, and STOP-Bang Questionnaire only in patients with COPD.[24–27] Few investigators have sought to validate sleep questionnaires in patients with interstitial lung disease, cystic fibrosis, or other pulmonary disorders. Growing interest in the overlap of SDB and COPD has led to the development of newer questionnaires such as the Manchester Respiratory-Related Sleep Symptom Questionnaire,[28] focused on the assessment of sleep symptoms and on patient-reported outcome measures in patients with COPD.

DIAGNOSTIC SLEEP TESTING

Sleep testing using *home sleep apnea testing* (HSAT) or in-laboratory *polysomnography* (PSG) evaluates for OSA, nocturnal hypoventilation, and nocturnal hypoxemia. All three should remain in the initial differential diagnosis of SDB given that treatment may include *continuous positive airway pressure* (CPAP), *bilevel positive airway pressure therapy* (BPAP), supplemental oxygen, or a combination thereof. Currently, sleep testing is required to establish a

diagnosis of OSA but is not necessary to fulfill requirements for qualifying patients for home oxygen therapy, which is based on nocturnal pulse oximetry or arterial blood gas. A sleep study demonstrating a minimum apnea-hypopnea index of at least five events per hour is needed to diagnose OSA and qualify the patient for treatment.[29,30] Patients with hypoventilation syndromes or hypoxemia must meet specific objective criteria demonstrating hypoxemia, hypercapnia, or a combination of both to qualify for noninvasive ventilation or home oxygen therapy.[31,32] In-laboratory sleep studies can demonstrate hypoventilation through the use of transcutaneous or end-tidal carbon dioxide monitoring, assist with determining optimal pressures for noninvasive ventilation, and enable education about and acclimation to positive airway pressure therapy by the sleep technologist during the study.

Overnight oximetry may identify patients who would benefit from further sleep testing, but it rarely suffices as a diagnostic tool on its own because it uses only a single-channel measurement and is thus considered insufficient to establish a diagnosis of OSA. Oximetry is, however, a useful tool in the assessment of efficacy of treatment; it is frequently used to ensure normalization of oxygen saturation during CPAP, noninvasive ventilation, or supplemental oxygen therapy. Severely reduced oxygen indices on overnight oximetry should prompt consideration of sleep apnea, hypoventilation, nocturnal hypoxemia, or a combination thereof.

HSAT and PSG are both validated methods of establishing a diagnosis of sleep apnea (see also Chapter 120 and Fig. 120.4). PSG has long been considered the gold standard and requires a patient to spend the night in a sleep laboratory. PSG entails monitoring of sleep (electroencephalography), respiratory effort (respiratory inductance plethysmography), nasal-oral airflow (pressure transducer recording), oxygen saturation (pulse oximetry), movements of the eyes (electrooculography) and the masseter and tibialis muscles (electromyelography), heart rate and rhythm (electrocardiography), snoring (microphone recording), and position (actigraphy). HSAT uses far fewer channels and is generally performed in a patient's home or inpatient setting, unattended by a technologist. HSAT devices may measure peripheral arterial tonometry and cardiorespiratory parameters (pulse oximetry, respiratory effort, nasal or nasal-oral airflow, and heart rate), as well as position, snoring, limb movements, and, in some cases, sleep (electroencephalogram). Determining which method of diagnostic sleep testing should be performed is based on current clinical guidelines,[29] patients' characteristics (i.e., cognitive function), availability of testing, payer coverage, and patient and provider preference.

NAVIGATING DEVICES AND TECHNOLOGIES

There is an increasing number of wearable, in-bed, and noncontact devices available that monitor sleeping patterns and physiologic parameters, including movement (by accelerometry), snoring, heart rate variability, skin temperature, and skin conductance (measurement of electrical conductance based on moisture of the skin, a marker of sympathetic nervous system activity). These devices often connect to cloud-based storage, enabling incorporation into digital health platforms. These data, along with data from traditional medical devices (diagnostic and therapeutic) and the electronic health record (health outcomes and measures), provide an enriched source of data through which we will learn more about population health, predictive analytics (i.e., identifying those at risk for SDB), and behavioral interventions to improve compliance with prescribed therapies. Wearable devices that track sleep are not yet accepted in lieu of PSG or HSAT, but there is widespread agreement that these devices do increase consumer and patient awareness of sleep and may support care plans involving biofeedback and self-management.[33,34] A discussion on devices used to treat SDB can be found in Chapter 122.

COMMON CLINICAL SCENARIOS TO CONSIDER SLEEP-DISORDERED BREATHING

There are some clinical conditions in both the inpatient and outpatient settings where sleep is highly relevant. Thinking about how the nocturnal sleeping period affects these conditions is important and will lead to a greater understanding about the role of sleep-related hypoxemia, hypoventilation, and apnea in the incidence or progression of the underlying disease, as well as how pulmonary diseases can affect sleep quality. Identifying sleep disorders in these conditions provides the opportunity to implement interventions and potentially mitigate poor outcomes.

ARRHYTHMIAS

Epidemiologic evidence supports an independent link between OSA and arrhythmias.[35–38] Both atrial and ventricular arrhythmias are strongly associated with OSA, particularly atrial fibrillation,[39,40] ventricular arrhythmias,[41] and sudden cardiac death.[42,43] Most of the studies focus on treatment of sleep apnea and its impact on the risk of recurrence of atrial fibrillation.[44–48] There is an overall paucity of studies investigating the impact of treatment of sleep apnea on non–atrial fibrillation arrhythmias.[49]

Prevalence of Arrhythmias in Obstructive Sleep Apnea

The prevalence of arrhythmias in individuals with OSA has been reported in the Sleep Heart Health Study,[50] the first population-based cohort study, consisting of 6441 participants (age ≥40 years) and designed to investigate the link between OSA and cardiovascular disease, including arrhythmias. In the 4 to 7 years following baseline enrollment, 3295 participants underwent repeat overnight PSG. Age-, race- or ethnicity-, and body mass index–matched samples with severe OSA (n = 228; respiratory disturbance index of 30 or more events per hour of sleep) and without OSA (n = 338; respiratory disturbance index <5 per hour of sleep) were obtained. All ventricular and supraventricular arrhythmias were more frequent during PSG in participants with OSA compared with participants without OSA (Fig. 119.2). Notably, atrial fibrillation was four times more common in participants with OSA than in those without OSA (4.8% vs. 0.9%; $P = .003$).[35] After adjusting for

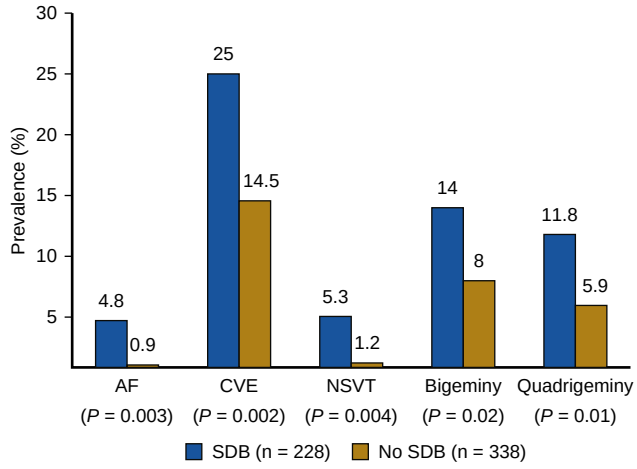


Figure 119.2 Arrhythmia prevalence in the Sleep Heart Health Study. Arrhythmia prevalence (%) according to *sleep-disordered breathing* (SDB) status. AF, atrial fibrillation; CVE, complex ventricular ectopy; NSVT, nonsustained ventricular tachycardia. (From Mehra R, Benjamin EJ, Shahar E, et al. Association of nocturnal arrhythmias with sleep-disordered breathing: the Sleep Heart Health Study. *Am J Respir Crit Care Med.* 2006;173:910-916.)

confounding variables, OSA was found to be independently associated with atrial fibrillation (*odds ratio* [OR], 4.0; *95% confidence interval* [CI], 1.0 to 15.7), complex ventricular ectopy (OR, 1.7; CI, 1.1 to 2.7), and nonsustained ventricular tachycardia (OR, 3.4; CI, 1.0 to 11.2). Conduction delay arrhythmias were also common among participants with sleep apnea. Findings from this cross-sectional study demonstrate a robust association between OSA and cardiac arrhythmias.[35] However, because OSA was not associated with new-onset atrial fibrillation (OR, 0.97; CI, 0.91 to 1.03), data from this study cannot be used to counsel patients on the risk of developing atrial fibrillation as a consequence of untreated OSA.[51] Other studies since then have demonstrated a strong association between OSA and new-onset atrial fibrillation,[52] but this is likely the result of referral and selection bias (i.e., enrollment from cardiology clinics or based on referrals to a sleep specialist).[51,52] Of note, in the Sleep Heart Health Study, central sleep apnea was independently associated with new-onset atrial fibrillation (OR, 3.0; CI, 1.4 to 6.4), discussed later.

Fatal cardiac arrhythmias have also been linked with OSA. The association between OSA and sudden cardiac death was prospectively investigated in 10,701 adults referred for overnight PSG at the Mayo Clinic Sleep Disorders Center between 1987 and 2003.[43] During an average follow-up period of 5.3 years (up to 15 years), 142 patients had sudden cardiac death (either resuscitated or fatal). In multivariate analysis, sudden cardiac death was predicted by an apnea-hypopnea index greater than 20 (*hazard ratio* [HR], 1.6; CI, 1.1 to 2.2), mean nocturnal oxygen saturation less than 93% (HR, 2.9; CI, 2.0 to 4.3), and lowest nocturnal oxygen saturation less than 78% (HR, 2.6; CI, 1.9 to 3.7).[43] On the basis of these data, the European Society of Cardiology[53] recommended that the aforementioned parameters of SDB be considered as important risk factors for sudden cardiac death; however, definitive evidence on the link between OSA and sudden cardiac death in individuals free of underlying cardiovascular disease is lacking. Similarly, no study to date has examined the impact of treating sleep apnea on reducing the risk of sudden cardiac death.[54]

Contributing Mechanisms

The potential mechanisms that link OSA to arrhythmias include (1) intermittent hypoxemia and hypercapnia, (2) elevations in sympathetic tone, (3) autonomic dysfunction, (4) increased transmural pressure on the atrial and ventricular walls as a consequence of wide variation in intrathoracic pressure during airway occlusion, (5) reduction of the atrial effective refractory period due to enhanced vagal tone, (6) surges in blood pressure resulting in increased cardiac oxygen demand and afterload, (7) QT prolongation that can trigger ventricular arrhythmias, and (8) elevated vagal tone contributing to bradyarrhythmias (see also Chapter 120).[55,56]

Impact of Obstructive Sleep Apnea Treatment on Arrhythmia

Whether treatment of OSA reduces the frequency of cardiac arrhythmias is not clear because of a lack of *randomized controlled trials* (RCTs). However, numerous observational studies suggest that treatment of OSA with CPAP reduces the risk for atrial fibrillation recurrence. A meta-analysis[47] of seven prospective cohort studies assessed the overall impact of CPAP on atrial fibrillation recurrence risk (n = 1087), and CPAP was associated with a marked reduction in atrial fibrillation recurrence (relative risk, 0.58; CI, 0.51 to 0.67). The benefit of CPAP was noted both in patients who were medically managed for their atrial fibrillation and in patients who underwent catheter ablation with pulmonary vein isolation. Therefore, in nonrandomized controlled studies, CPAP therapy is significantly associated with a reduced risk of atrial fibrillation recurrence regardless of the treatment pathway for atrial fibrillation.

In the largest RCT (n = 2717) evaluating cardiovascular end points[57] in patients with OSA who were treated with CPAP compared with patients without CPAP, new-onset atrial fibrillation was similar between the groups. Atrial fibrillation was not a prespecified end point in this study, and therefore the study may have been underpowered. Thus, more studies are needed to clarify whether sleep apnea treatment reduces the risk of new-onset and recurrent atrial fibrillation.

CPAP appears to reduce the risk of nocturnal arrhythmias in observational studies but, similar to atrial fibrillation, data from larger RCTs are lacking. In a prospective study of 23 patients with OSA and implanted loop recorders to monitor heart rhythm, 6 months of CPAP therapy abolished nocturnal ventricular bradycardia or asystole.[58] In a similar RCT of patients with heart failure and OSA,[59] patients using CPAP had a 58% reduction in premature ventricular beats compared with patients without CPAP. However, once again, RCTs are lacking to determine whether ventricular arrhythmias are reduced with sleep apnea treatment.

In summary, observational data suggest a strong and independent link between OSA and cardiac arrhythmias, particularly atrial fibrillation and fatal ventricular arrhythmias. However, for risk of recurrent or new-onset atrial fibrillation or sudden cardiac death, definitive data from RCTs are limited and not suggestive of benefit.

STROKE

Epidemiology of Obstructive Sleep Apnea and Central Sleep Apnea in Stroke

Both OSA and central sleep apnea are prevalent in patients who have had a stroke. A systematic review[60] of nearly 30 studies of 2342 patients with stroke or transient ischemic event reported an overall prevalence of any sleep apnea of 72% (apnea hypopnea index >5 events per hour); central sleep apnea predominance was observed in only 7% of the patients. Whereas central events typically resolved 3 months after stroke or transient ischemic attack, obstructive events persisted.[61] In addition to being commonly found in patients with stroke, OSA is also recognized as an independent risk factor for stroke. A meta-analysis of 10 observational cohort studies demonstrated that OSA increases the risk of stroke by more than twofold (eFig. 119.1).[62] This association also holds true in population-based cohorts,[63] a finding suggesting that referral bias is less likely to play a major role in this association.

Contributing Mechanisms

Multiple mechanisms have been implicated in the increased risk of stroke associated with OSA, including heightened sympathetic activity[64] with a resultant catecholamine surge[65] and development of hypertension,[66] which is a strong risk factor for stroke. Furthermore, intermittent hypoxemia results in vascular dysfunction and atherosclerosis[67,68] through oxidative stress, vascular inflammation, and immune activation. Furthermore, OSA may be an independent risk factor for stroke through its enhanced risk of atrial fibrillation,[39] a known risk factor for stroke (Fig. 119.3).

Impact of Continuous Positive Airway Pressure on Stroke Risk

Two of the largest RCTs to date, the *Randomized Intervention With CPAP in Coronary Artery Disease and Sleep Apnea* (RICCADSA)[69] and *Sleep Apnea Cardiovascular Endpoints* (SAVE)[57] trials, failed to show that treatment of OSA with CPAP reduces the risk of recurrent or new-onset cardiovascular events, including stroke. RICCADSA[69] determined the effects of CPAP on a composite of cerebrovascular and myocardial infarction outcomes in non-sleepy patients with a history of coronary artery disease. In the intention-to-treat analysis, OSA treatment did not significantly reduce the risk for recurrent major cardiovascular disease, including stroke. Similarly, SAVE[57] found no overall improvement in the risk of incident stroke or myocardial infarction in patients with OSA who were randomized to receive CPAP or no CPAP treatment. However, a prespecified propensity score–matched analysis in SAVE revealed that CPAP was beneficial in preventing recurrent stroke, but not myocardial infarction. eFigure 119.2 shows intention-to-treat and adherence analysis results summarized from the three major RCTs[57,69,70] designed to assess the impact of CPAP on cardiovascular outcomes. This figure is adapted[71] to demonstrate the impact of sleep apnea treatment on stroke in individuals compliant with CPAP for 4 or more hours a day.

Most recently, a systematic review and meta-analysis[72] (10 clinical trials; N = 7266) concluded that the use of CPAP compared with no treatment or sham treatment was not associated with a reduced risk of cardiovascular events (including stroke) or death in patients with OSA. An accompanying editorial[73] pointed out that the estimated risk reduction with CPAP for cardiovascular events, although not statistically significant, was sizeable (23%). The editorial attributed the lack of statistical significance of CPAP's impact on cardiovascular events to (1) poor adherence (mean CPAP use slightly more than 3 hours per night), (2) use of therapies known to reduce the background rate of cardiovascular disease events (e.g., statins), and (3) lack of better risk stratification of patients with OSA to predict those who would most benefit from CPAP.

In summary, definitive recommendations to treat OSA to reduce recurrent stroke risk cannot be made on the basis of existing evidence, although, of all cardiovascular outcomes, stroke risk reduction with sleep apnea treatment is the most promising according to available data. Further studies are

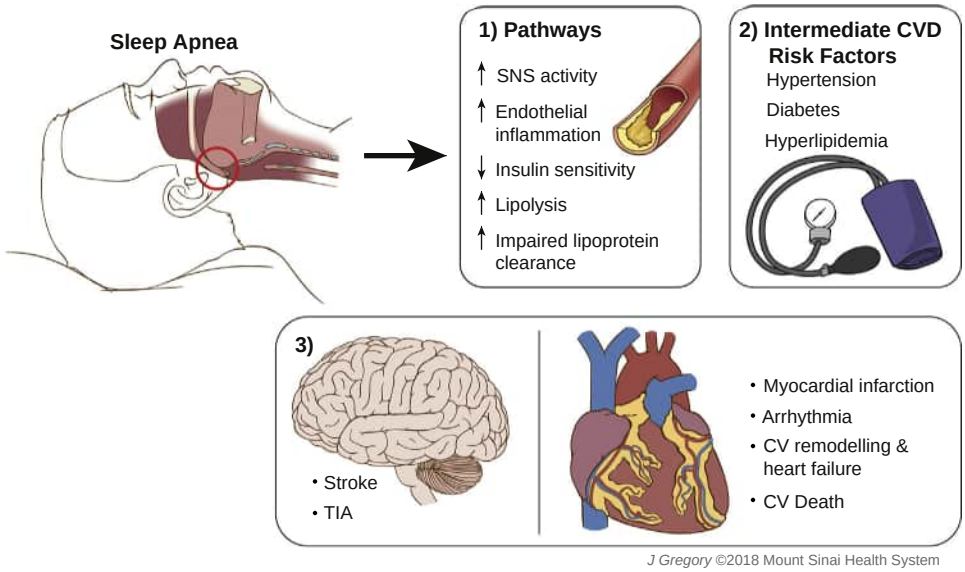


Figure 119.3 Mechanisms contributing to cerebrovascular and cardiovascular outcomes. *Obstructive sleep apnea* (OSA) is associated with several mechanistic pathways that influence the development of disease states such as hypertension, diabetes and hyperlipidemia, known to be risk factors for cerebrovascular and *cardiovascular disease* (CVD). The end result is an overall increased risk of stroke, transient ischemic attack (TIA), myocardial infarction, arrhythmia, cardiac remodeling, heart failure, and *cardiovascular* (CV) death. SNS, sympathetic nervous system. (Illustration by Jill Gregory. Copyright 2018 Mount Sinai Health System.)

needed to clarify the impact of OSA treatment on primary and secondary stroke risk reduction.

Impact of Continuous Positive Airway Pressure on Neurologic Outcomes After Stroke

Limited evidence suggests that treatment of sleep apnea may improve functional neurologic recovery after stroke. Most of the evidence comes from small clinical trials and prospective cohort studies.[74,75] A systematic review and meta-analysis[74] of 10 RCTs assessed the impact of CPAP on neurologic recovery in stroke patients with sleep apnea. Findings from this meta-analysis demonstrated improvement in neurofunctional scales (i.e., National Institutes of Health Stroke Scale and Canadian Neurological Scale) with CPAP, although there was significant variability across trials. Although CPAP appears to improve short-term functional recovery after stroke, it is not as clear whether CPAP alters long-term outcomes. Larger homogenous studies are needed to ascertain whether CPAP improves long-term outcomes, including mortality, after stroke.

PULMONARY HYPERTENSION

The prevalence of PH in patients with OSA without concomitant lung disease or left ventricular dysfunction is approximately 30%. When PH is present, it is often mild.[76] However, the independent link between OSA and PH in not clear. Similarly, treatment of sleep apnea with CPAP has been shown to reduce pulmonary arterial systolic pressures.[77,78] However, evidence demonstrating survival benefit with CPAP therapy in patients with sleep apnea and PH is lacking.

INPATIENT AND INTENSIVE CARE UNIT PATIENTS

Sleep serves a fundamental role for normal cognition, cardiovascular function, immune function, metabolism, and recovery from illness. Acutely ill hospitalized patients particularly benefit from sleep's restorative effects, but they are among the most at-risk populations for frequent nocturnal interruptions and poor sleep quality.[79] Whereas the literature on the sleep architecture of inpatients is scant because of the difficulty of measuring sleep in the hospital setting, available studies demonstrate consistent reductions in slow-wave and rapid eye movement sleep and marked increases in wakefulness after sleep onset, findings consistent with sleep fragmentation and nonrestorative sleep.[80] In certain groups of patients, such as those with critical illness, sleep is so abnormal that standard sleep staging may not even be possible.[81] Lack of the normal diurnal variation of melatonin suggests loss of normal circadian patterns and may in part explain why sleep in hospitalized patients is scattered throughout the 24-hour day.[80,82] These disruptions may be amplified in older patients who, at baseline, already have alterations in sleep architecture, such as reduced slow-wave sleep, decreased sleep efficiency, and altered circadian rhythms.[79] Whereas sleep surveys completed by patients generally corroborate these findings of poor sleep quality, provider-derived assessments overestimate both sleep time and sleep quality.[81] In fact, poor sleep quality is consistently reported by patients as one of the most disturbing experiences during their hospitalization.

There are many reasons for disrupted sleep in hospitalized patients. Poor sleep quality may be related to the acute illness necessitating hospitalization, an underlying preexisting medical condition or sleep disorder, or a combination thereof. External factors, including high noise levels, elevated nighttime ambient light levels, disruptive roommates, and patient care interactions such as wound care and phlebotomy, all contribute to sleep disruption.[82] Both the introduction and the withdrawal of medications can also affect sleep quality.

The physiologic effects of sleep deprivation are well known (see also Chapter 118). Sleep deprivation in healthy patients modulates immune function, disrupts neuroendocrine control systems (i.e., hippocampal-pituitary-adrenal axis), increases insulin resistance, decreases respiratory muscle strength, increases risks of falls, and increases the likelihood of poor cardiovascular outcomes. How these factors affect hospitalized patients is less well known because of the challenge of studying such populations and controlling for confounders. A growing literature suggests that acute sleep loss in hospitalized patients is associated with a variety of poor patient outcomes.[79] Importantly, sleep disruption persists for many patients long after their hospitalization.

Guidelines advise a multifaceted approach to address modifiable disrupters of sleep in the inpatient setting.[83] Such interventions include earplugs, eye masks, music therapy, relaxation techniques, bright light exposure during daytime hours, and scheduling nursing workflow to decrease nighttime interruptions. Such interventions appear to improve sleep quality and seem to be of low risk, although barriers such as mixed buy-in from staff and patients exist.[82] Pharmacologic interventions are frequently prescribed for hospitalized patients.[84] In general, hypnotic agents should not be used in inpatients because many of these drugs are associated with delirium, have significant side effects, interact with other medications, and contribute to polypharmacy. If a pharmacologic sleep aid is deemed to be absolutely necessary, it should be tailored to the individual patient profile. Melatonin has generated increased interest given its tolerability and low risk of side effects. In small, randomized trials, melatonin appears to improve sleep quality and duration.[85,86]

OSA is often considered an outpatient problem, and an inpatient diagnostic workup may be deferred for a variety of reasons, including decompensated cardiopulmonary disease and lack of availability of and reimbursement for testing. Inpatient testing is not recommended by current guidelines despite evidence that it is feasible and reliable in a variety of patient populations.[29,87] Home CPAP is also frequently discontinued in hospitalized patients,[88] thus representing lost opportunities to engage patients in teachable moments about *positive airway pressure* (PAP) therapy and to identify and address barriers to adherence. A diagnosis of OSA carries important implications for admitted patients because they are at increased risk of having complications and poor outcomes compared with patients without OSA, both during hospitalization and following discharge.[82] For example, in patients with heart failure with reduced ejection fraction, initiating CPAP before hospital discharge reduces readmission rates, improves ejection fraction, and

increases transplant-free survival.[89,90] Similarly, early initiation of CPAP in acute poststroke patients improves neurologic recovery.[91] Benefit from early initiation of CPAP or BPAP during or immediately following hospitalization has also been shown in patients admitted with acute exacerbations of COPD, decompensated obesity hypoventilation syndrome, and pneumonia.[92]

PERIOPERATIVE EVALUATION

Given its high prevalence in the general population,[93,94] it is not surprising that OSA is a common comorbidity in patients undergoing surgical procedures. This prevalence appears to be increasing in concert with rising rates of obesity[95] and with greater awareness of the need to screen surgical candidates in the preoperative period. Nonetheless, most patients remain undiagnosed before surgery.[96] In certain at-risk populations, such as those undergoing bariatric surgery, the rate of OSA may be as high as 90%.[97] OSA is associated with an increased incidence of respiratory complications, postoperative cardiac events, impaired wound healing, a longer hospital stay, and possibly mortality.[98,99] Screening for OSA in patients undergoing surgery is now routinely recommended.[100]

In addition to general pulmonary considerations, the consulting pulmonologist should include an assessment of OSA risk as part of the evaluation. Identifying patients at risk for or with known OSA frequently affects surgical and anesthetic approaches, as well as plans for postoperative monitoring to mitigate the increased risk of complications. Questionnaires have been developed that provide a simple, practical, and reliable method for identification and triage of patients at high risk for OSA. The most validated and widely used questionnaire in surgical patients is the STOP-Bang tool[101] (eFig. 119.3). A score of 0 to 2 (out of a possible 8) suggests that the patient is at low risk for OSA, whereas a score of 3 or more has a high sensitivity for moderate to severe OSA. Higher values on the STOP-Bang tool directly correlate with an increased probability of severe OSA.[102] Other screening tests of comparable accuracy in the surgical population include the perioperative sleep apnea prediction score, Berlin questionnaire, and American Society of Anesthesiologists checklist.[103] Other routine tests are not usually indicated but may be available. These tests include the serum bicarbonate level, which, if higher than 28 mmol/L, may increase the specificity of the STOP-Bang questionnaire[22] and identify patients at risk for obesity hypoventilation syndrome. The presence of suspected OSA may also prompt further workup for other associated conditions, such as PH.[103]

Identification of an increased risk for OSA in the preoperative setting raises a dilemma for the treatment team in deciding whether to cancel or delay surgery to pursue further evaluation and treatment. Formal testing may not be possible because of time and resource constraints. Conversely, proceeding without treatment may place the patient at an increased risk of complications. Suspected or known OSA should be incorporated into decision making regarding scheduling of surgery on an ambulatory basis, with particular attention paid to higher-risk procedures involving the upper airway or those requiring high doses of analgesic agents. Routine admission of patients with OSA to the intensive care unit is not necessary.[97] Patients and providers should be informed that the effects of surgery and postoperative analgesia on sleep architecture and SDB may persist for several days after surgery, or longer if narcotics are used.[104]

There is considerable uncertainty regarding the appropriate way to manage such patients, and decision making should include the patient, surgeon, and anesthesiologist. Although most patients will not experience any major perioperative complications related to OSA, complications can be catastrophic. Thus, efforts to optimize cardiopulmonary status, including treatment of OSA, are recommended. This includes using regional anesthesia when feasible, anticipating a difficult airway, and achieving high levels of consciousness in patients before extubation. Postoperative strategies include use of the upright, semiupright, or lateral positioning; minimization of respiratory depressants in the postoperative period; use of opioid-sparing analgesia; and close monitoring of oxygenation and ventilation.[105]

For patients with a known diagnosis of OSA, a preoperative workup should include a review of the patient's sleep studies, adherence to current therapy, and residual symptoms.[103] Patients whose OSA is well controlled with home PAP therapy should continue with treatment in the perioperative period. Continuation of PAP therapy has been shown to reduce unplanned intensive care unit transfers, hospital length of stay, cardiovascular complications, and pulmonary complications.[99,106] Unfortunately, fewer than two-thirds of patients using home CPAP therapy continue to receive it in the postoperative setting.[107,108] The pressure required to maintain a patent upper airway may be higher in the postoperative setting in response to fluid shifts, the effects of medications, or swelling from upper airway manipulation during anesthesia or surgery itself.[109] Empirical preoperative PAP in patients with suspected OSA is feasible, especially with auto-adjusting CPAP devices that automatically adjust pressures to maintain an unobstructed airway.[108] Despite studies demonstrating improvements in certain outcomes, empirical preoperative PAP is not routinely recommended in guidelines,[103] except for the particularly high-risk patient. Nonetheless, there should be a low threshold to start PAP therapy if there is hypoxemia, obstruction of the upper airway (i.e., witnessed apneas), or hypoventilation in the patient at risk for OSA. Use of CPAP can be continued after most operations, including bariatric surgery, without increasing the risk of anastomotic leak.[110] Patients undergoing transsphenoidal surgery or who have other anterior skull base defects are at risk for developing pneumocephalus with the application of PAP; in these patients, PAP should be avoided in the immediate postoperative period.[111]

CHRONIC OBSTRUCTIVE PULMONARY DISEASE

Respiratory abnormalities of COPD can disrupt sleep. The degree of sleep disruption correlates with the severity of airway obstruction (forced expiratory volume in 1 second).[112] In addition, sleep disturbances can affect COPD and may comprise an independent risk factor for exacerbations and mortality.[113] The physiologic changes of sleep well tolerated by healthy individuals are a significant challenge for the COPD patient with impaired pulmonary mechanics and baseline gas-exchange abnormalities. Pulmonologists, however, must not assume that poor sleep and nocturnal

hypoxemia are normal for their patients with COPD, and failure to identify the coexistence of SDB may place the patient at future risk.

The coexistence of COPD and OSA is often described as the overlap syndrome,[114] although the term has also been applied to patients with OSA and PH and to patients with OSA and asthma. It is prudent therefore to specify the specific overlap syndrome being discussed. Since it was first described in the 1980s, the *OSA-COPD overlap syndrome* has received the most attention in the literature. Nonetheless, it is not yet established whether OSA is more common in patients with COPD than in the general population and vice versa, and this uncertainty may result in part from the heterogeneity of COPD phenotypes as well as from varying definitions of OSA. The "pink-puffer," for example, with relatively preserved gas exchange, lower body mass index, and lung hyperinflation, may well be protected against OSA, whereas the "blue bloater," with a higher body mass index, lower respiratory drive, and peripheral fluid retention, could be at higher risk. Other pathophysiologic mechanisms that link OSA and COPD include increased upper airway inflammation and skeletal myopathy in patients with COPD, thus leading to greater collapsibility of the upper airway, and the potential for OSA to exacerbate lower airway inflammation in patients with COPD. Furthermore, medications used for COPD may be beneficial (e.g., theophylline) or harmful (e.g., inhaled corticosteroids) for patients with OSA.[114] On the basis of conservative estimates of 10% prevalence for each, at least 1% of the population may have an OSA-COPD overlap syndrome.[115,116] Patients with more severe obstruction appear to be at higher risk for OSA.[117]

Patients with OSA-COPD overlap syndrome may present with clinical features of either or both, depending on the severity of each. They are at high risk for hypercapnia, hypoxemia, and PH and thus may manifest signs and symptoms of those conditions at an earlier stage than expected given the degree of airway obstruction.[114] As in the general population, the diagnosis of OSA requires a sleep study. Patients with COPD not requiring supplemental oxygen may be candidates for HSAT. Use of in-laboratory PSG with carbon dioxide monitoring is preferred when moderate to severe obstructive lung disease, hypercapnia, or significant hypoxemia is anticipated. Monitoring of carbon dioxide levels may be particularly helpful for PAP titration studies to determine efficacy of ventilatory support because PAP parameters are adjusted throughout the night. Regardless of the modality used, conventional SDB metrics that help define severity (i.e., apnea hypopnea index) may not be as applicable in patients with COPD as in patients without COPD.[118] Nocturnal oximetry has limited utility as a diagnostic tool for OSA in patients with COPD because it cannot differentiate the relative contribution of each to the nocturnal hypoxemia observed.[119] Unless the baseline awake saturation is less than 88%, PSG is usually performed without supplemental oxygen. This allows for characterization of hypopneas, which may otherwise be missed.[118] Because of sleep-associated hypoventilation and reductions of functional residual capacity resulting in ventilation-perfusion mismatching, patients with COPD often experience significant hypoxemia, even when daytime saturations are normal.[120] Different patterns of oxygen desaturation are recognized in patients with OSA, COPD, and OSA-COPD overlap syndrome. Patients with OSA and normal underlying lung function have a normal baseline oxygen saturation with cyclical intermittent episodes of desaturation from a non-hypoxemic baseline saturation and often return to normal between apneic or hypopneic events. Patients with COPD, particularly those with advanced disease, have a lower baseline oxygen saturation with intermittent desaturation that can be sustained and profound during rapid eye movement sleep because of loss of accessory muscle use for breathing (atonia) characteristic of rapid eye movement sleep. Patients with OSA-COPD overlap demonstrate a combination of the two profiles, with intermittent desaturation from baseline hypoxemia and severe desaturation during rapid eye movement sleep (Fig. 119.4).[114] Patients with OSA-COPD overlap have more severe nocturnal hypoxemia parameters than patients with either OSA or COPD alone.[112,114,121] Additional PSG features specific to COPD include expiratory flow limitation and air trapping.[118]

A systematic review (n = 29,341) estimated the prevalence of OSA-COPD overlap syndrome to be 1–3.6% in the general population, 7.6–55.7% in patients with OSA, and 2.9–65.9% in patients with COPD.[121] OSA-COPD overlap syndrome is associated with several deleterious outcomes, including worse quality of life, increased health care use and cost, and increased cardiovascular morbidity compared with patients with COPD alone.[121] Patients with OSA-COPD overlap syndrome can have daytime hypercapnia with relatively preserved lung function if their ability to hyperventilate between apneic events is diminished, thus resulting in retention of carbon dioxide and progressive desensitization of the respiratory system to hypercapnia.[122] Hypoxemia is also more common, and the combination of hypoxemia and hypercapnia contributes to the increased incidence of PH in patients with OSA-COPD overlap.[123,124]

COPD and OSA are independently associated with an increased risk of cardiovascular disease, and this risk is amplified in patients with OSA-COPD overlap syndrome. Measures of inflammation (e.g., inflammatory molecules, oxidative stress, endothelial dysfunction) are elevated in both OSA and COPD.[114] In addition to PH, atrial fibrillation appears to be more common in patients with OSA-COPD overlap[125] than in either condition alone. In the overlap syndrome, nonrandomized trials suggest that all-cause cardiovascular mortality is increased,[126] with one study finding a synergistic effect only in women.[126]

Patients with COPD and nocturnal hypoxemia (without OSA) benefit from standard long-acting β-agonist and anticholinergic inhaled therapy, which independently increases nocturnal oxygen saturation compared with placebo[127,128] (see also Chapter 64). Other measures to optimize the underlying condition, such as smoking cessation and pulmonary rehabilitation, can be expected to improve breathing during sleep. Controversy exists regarding the clinical importance of "fixing" gas-exchange abnormalities that arise during rapid eye movement sleep in patients with COPD, but the profound derangements occasionally seen provide a rationale for therapy.[118] Supplemental oxygen may be indicated if significant nocturnal oxygen desaturations persists despite optimal pharmacotherapy. Oxygen should be carefully titrated to bring the saturation into the region of 90–92%.[112] Supplemental oxygen does not appear to be associated with significant additional risk of hypercapnia, but there is also limited evidence of improved survival, an issue that is being investigated in a large clinical trial.[129,130]

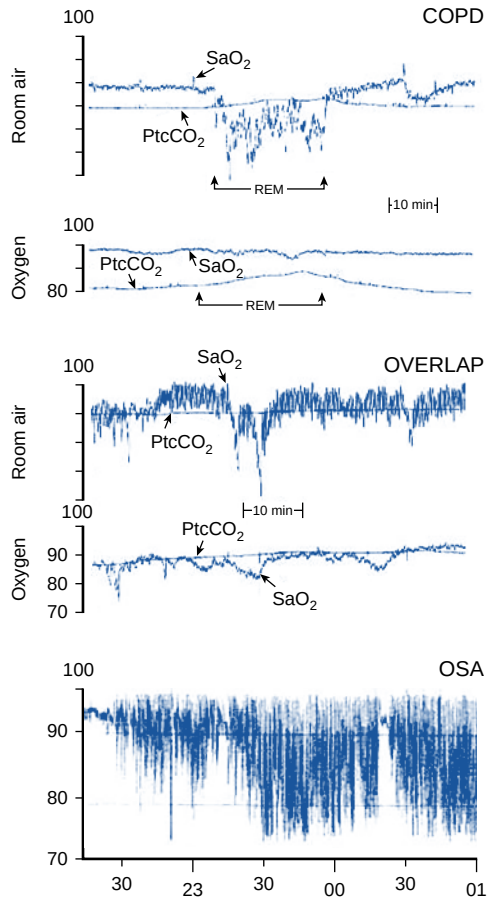
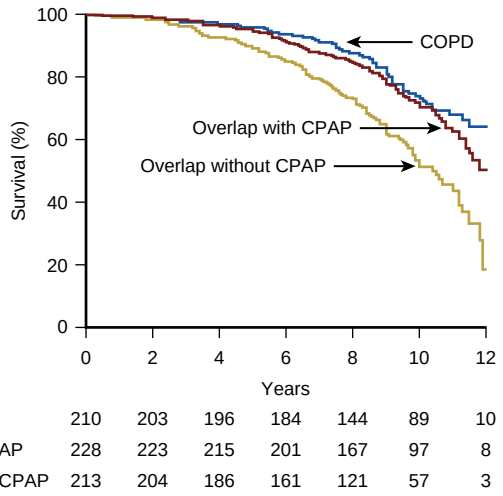


Figure 119.4 Different patterns of oxygen desaturation during sleep. Patients with COPD, overlap syndrome, and *obstructive sleep apnea* (OSA). Patients with moderate to severe COPD alone (*top*) desaturate during *rapid eye movement sleep* (REM) from associated REM atonia of respiratory accessory muscles, showing sustained, rather than cyclical, desaturation. Patients with overlap syndrome (*middle*) have lower baseline arterial oxygen saturation (Sa_{O_2}) and oxygen saturation as measured by pulse oximetry (Sp_{O_2}) while asleep and have greater cyclic variation in saturation correlating with OSA. The differences between arterial oxygen saturation and transcutaneous carbon dioxide levels are demonstrated in overlap patients on room air versus with supplemental oxygen. Although less desaturation is observed during use of supplemental oxygen, a greater increase in transcutaneous carbon dioxide tension (Ptc_{O_2}) levels is observed. Patients with OSA alone (*bottom*) demonstrate intermittent cyclical desaturation to varying degrees. (From McNicholas WT. Chronic obstructive pulmonary disease and obstructive sleep apnoea: the overlap syndrome. *J Thorac Dis.* 2016;8:236–242.)



No. at risk							
COPD	210	203	196	184	144	89	10
Overlap with CPAP	228	223	215	201	167	97	8
Overlap without CPAP	213	204	186	161	121	57	3

Figure 119.5 Outcomes in patients with COPD and overlap syndrome with and without *continuous positive airway pressure* (CPAP). Kaplan-Meier survival curves for outcomes among chronic obstructive pulmonary disease patients without obstructive sleep apnea (OSA) (COPD group), patients with overlap syndrome treated with CPAP since enrollment (overlap with continuous PAP group), and patients with COPD and coexisting OSA not treated (overlap without CPAP group). The difference in survival among patients with COPD only and those with overlap with CPAP are statistically significant from the patients with COPD and overlap without CPAP ($P < 0.001$). A similar significant difference was also seen in exacerbations (not shown). (From Marin JM, Soriano JB, Carrizo SJ, Boldova A, Celli BR. Outcomes in patients with chronic obstructive pulmonary disease and obstructive sleep apnea: the overlap syndrome. *Am J Respir Crit Care Med.* 2010;182:325–331.)

In patients who have OSA-COPD overlap, PAP is the optimal therapy. Two large observational cohorts demonstrated significant mortality benefit with the use of CPAP in OSA-COPD overlap syndrome after adjusting for confounders (Fig. 119.5).[131,132] Patients with severe COPD or gas-exchange abnormalities should be titrated in the laboratory setting by the most skilled sleep technician available. BPAP or noninvasive ventilation is indicated when there is significant hypoventilation and COPD-related hypercapnic respiratory insufficiency. There are several mechanisms by which BPAP could benefit patients with OSA-COPD overlap, including resting chronically fatigued respiratory muscles, reversing atelectasis, resetting the chemoreceptor drive to breathe, and improving gas-exchange variables. A large meta-analysis and systematic review[133]of the role of home noninvasive ventilation in 51,085 patients using either BPAP or home mechanical ventilation showed a lower risk of mortality in those patients who used BPAP versus no device (22.3% vs. 28.6%; CI, −10.3% to −0.8%; OR, 0.66; $P = 0.003$), fewer all-cause hospital admissions (39.7% vs. 75%; CI, −49.4% to −21.1%; OR, 0.22; $P < 0.001$), and less need for intubation (5.3% vs. 14.7%; CI, −14.8 to −1.3%; OR, 0.34; $P = 0.02$). A similar reduction in all-cause hospital readmissions but not mortality was observed with home mechanical ventilation.[133] Supplemental oxygen in addition to CPAP or BPAP may at times be necessary if gas exchange parameters do not resolve with PAP alone.[134] Given the frequent sleep symptoms in patients with OSA-COPD overlap syndrome and COPD, the question of hypnotic agents frequently arises. Benzodiazepines should be avoided given their adverse effects on ventilation. The nonbenzodiazepine hypnotic agents, such as zolpidem, appear safer but should also be avoided if possible.[135] Newer agents such as melatonin receptor agonists or receptor antagonists to orexin (a neuropeptide involved in wakefulness) may improve sleep parameters without affecting respiratory parameters.[112,136] Cognitive behavioral therapy is the preferred therapy for insomnia in patients with COPD and has been shown to be effective.[137,138]

ASTHMA

Sleep disturbances in asthmatic patients are common.[139] Poorly controlled asthma leads to disrupted sleep and impaired cognitive performance, which has been shown to be reversible with effective daytime asthma treatment.[140,141] Nocturnal asthma symptoms are markers of poor asthma control and are frequently assessed in asthma

questionnaires. In addition to poor asthma control, other reasons for impaired sleep include coexisting rhinosinusitis, gastroesophageal reflux disease, anxiety, and depression, all of which are more common in asthmatic patients.[139,142] Not surprisingly, daytime sleepiness is also common.[143]

The prevalence and incidence of OSA are increased in asthmatic patients compared with the general population[144-146] (see Chapter 61). OSA has become an increasingly recognized comorbid condition in asthma, and both OSA and asthma are associated with obesity. Obese asthmatic patients are at risk for OSA and represent an asthma phenotype particularly difficult to control.[147] The presence of OSA in asthmatic patients appears to be associated with worse outcomes.[143,148,149] Severe exacerbations are more common and directly correlate with the apnea-hypopnea index.[150] The mechanisms of OSA contribution to these poor outcomes are being investigated. Sleep fragmentation, intermittent airway occlusion, and hypoxemia induced by OSA may lead to increased oxidative stress and inflammation, resulting in bronchoconstriction, increased airway resistance, and poorer asthma control.[151] Upper airway closure may trigger vagally mediated bronchoconstriction.[152,153] Asthma may also contribute to OSA. Asthmatic patients have greater reductions in lung volumes during sleep compared with persons without asthma, and this change may lead to a more collapsible upper airway. Asthma-associated systemic inflammation may impair the strength of respiratory muscles, including the upper airway dilators. Systemic corticosteroids used to treat acute exacerbations of asthma can lead to weight gain and cause myopathy of the pharyngeal dilator muscles, which may increase the risk of OSA.[145]

The nocturnal symptoms of OSA and asthma may be difficult to distinguish by history alone. PSG or HSAT should be considered when SDB is suspected or when nocturnal symptoms persist despite otherwise seemingly good asthma control. In asthmatic patients with significant OSA, CPAP remains the standard of therapy to improve daytime symptoms and nocturnal sleep. CPAP improves asthma quality of life measures, reduces the frequency of exacerbations, and reduces the use of bronchodilators, although the effect on objective lung function is equivocal.[149,154] In addition to maintaining upper airway patency, CPAP improves reflux symptoms, another trigger for nocturnal symptoms in asthmatic patients. CPAP is not a recommended treatment for asthmatic patients without OSA. The effects of second-line treatments for OSA, such as mandibular repositioning devices, have not been studied. The effects of asthma medications on OSA outcomes have also not been studied. At this time, there are no guidelines to manage the patient with both asthma and OSA, and the patient should be treated optimally according to standard asthma and OSA guidelines. Larger trials are urgently needed given the high prevalence of these two conditions and evidence suggesting that CPAP may increase bronchial hyperresponsiveness in patients without asthma and degrade sleep architecture in asthmatic patients without OSA.[146]

Key Points

- Patients with arterial P_{O_2} near the steep portion of the oxyhemoglobin dissociation curve may maintain oxygenation while upright and awake but frequently desaturate when recumbent and asleep.
- Not all sleep-disordered breathing is sleep apnea, and the absence of sleep apnea does not exclude the presence of hypoventilation or hypoxemia.
- Obstructive sleep apnea has a strong and independent association with cardiac arrhythmias, particularly with atrial fibrillation and fatal ventricular arrhythmias. Further randomized controlled trials evaluating the impact of positive airway pressure therapy on new-onset or recurrent arrhythmias are needed.
- Treatment of obstructive sleep apnea following acute stroke improves neurologic recovery, although the role of CPAP in improving long-term outcomes after stroke has not been shown.
- Screening for obstructive sleep apnea in patients undergoing surgery is now routinely recommended.
- In patients with COPD and hypercapnia, use of home bilevel positive airway pressure reduces all-cause hospital admission and intubation and improves survival.
- Patients with asthma who have nocturnal symptoms should be screened for obstructive sleep apnea. Treatment with positive airway pressure improves symptoms attributable to obstructive sleep apnea, improves asthma symptoms and quality of life, and reduces exacerbations.

Key Readings

Chung F, Memtsoudis SG, Ramachandran SK, et al. Society of Anesthesia and Sleep Medicine guidelines on preoperative screening and assessment of adult patients with obstructive sleep apnea. *Anesth Analg*. 2016;123(2):452–473.

Dong R, Dong Z, Liu H, Shi F, Du J. Prevalence, risk factors, outcomes, and treatment of obstructive sleep apnea in patients with cerebrovascular disease: a systematic review. *J Stroke Cerebrovasc Dis*. 2018;27(6):1471–1480.

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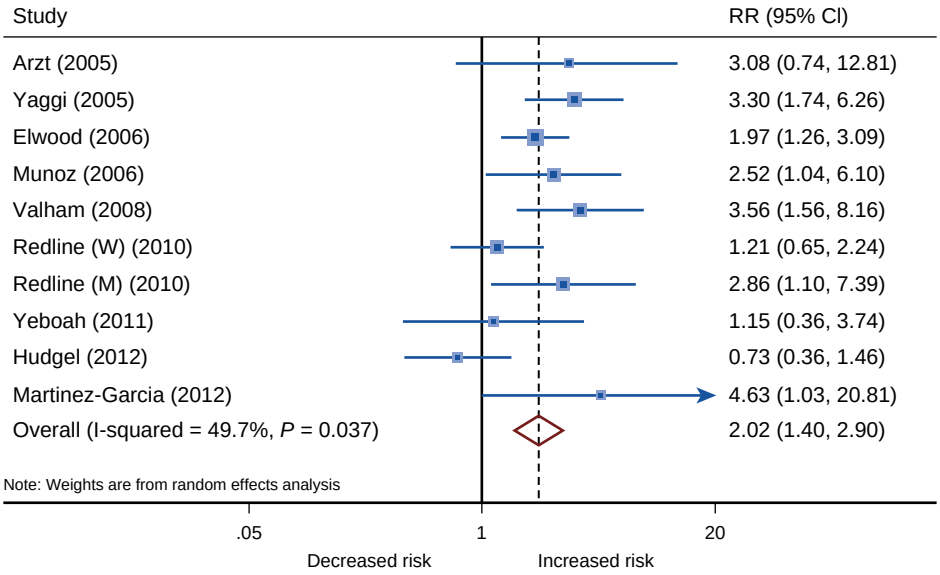
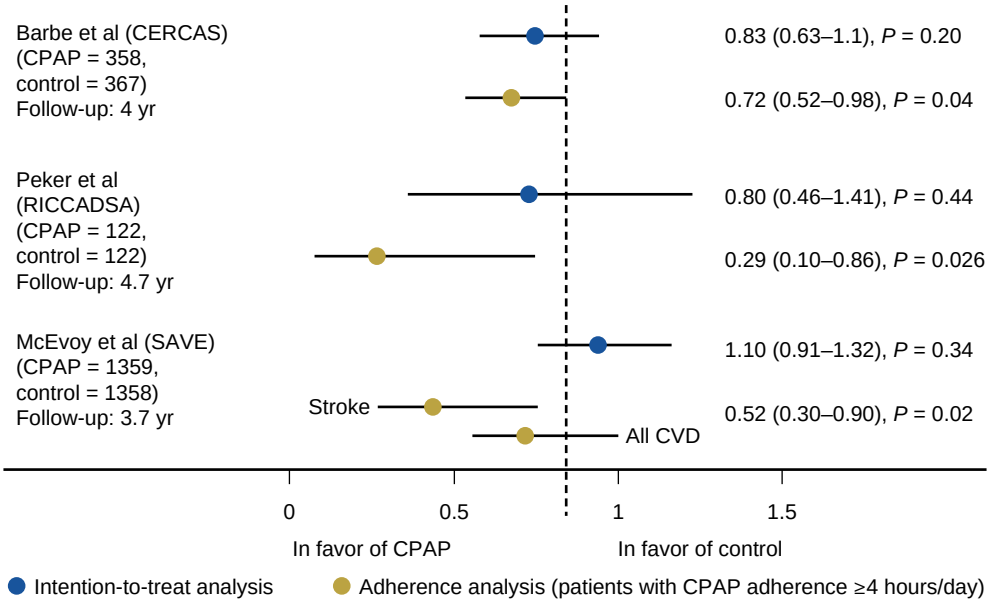
Complete reference list available at ExpertConsult.com.

eFIGURE IMAGE GALLERY



eFigure 119.1 Meta-analysis of the relationship between obstructive sleep apnea and risk of stroke. Random effects meta-analysis of the relationship between obstructive sleep apnea and stroke risk. CI, confidence interval; M, men; RR, relative risk; W, women. (From Dong JY, Zhang YH, Qin LQ. Obstructive sleep apnea and cardiovascular risk: meta-analysis of prospective cohort studies. *Atherosclerosis.* 2013;229:489–495.)



eFigure 119.2 Effect of *continuous positive airway pressure* (CPAP) treatment on cardiovascular risk. Incidence risk for the primary composite end points in three randomized controlled trials in the CPAP group vs. the control group (hazard ratio or incidence density ratio, 95% confidence interval) in the intention-to-treat analysis (*blue dots*) and in the adherence analysis (patients with CPAP adherence ≥4 hr/day; *yellow dots*). In the McEvoy study, the significant cardiovascular improvement in patients who used CPAP for 4 hr/day or longer was achieved only in the risk of a cerebrovascular event, but not in the primary composite outcome. CVD, cardiovascular disease; RICCADSA, Randomized Intervention With CPAP in Coronary Artery Disease and Sleep Apnea; SAVE, Sleep Apnea Cardiovascular Endpoints. (Modified from Javaheri S, Barbe F, Campos-Rodriguez F, et al. Sleep apnea: types, mechanisms, and clinical cardiovascular consequences. *J Am Coll Cardiol.* 2017;27[6]:1471–1480.)

SNORING? Do you **snore loudly** (louder than talking or loud enough to be heard through closed doors)?	Yes	No
TIRED? Do you often feel **tired, fatigued, or sleepy** during the daytime?	Yes	No
OBSERVED? Has anyone **observed** you **stop breathing** during your sleep?	Yes	No
PRESSURE? Do you have or are you being treated for **high blood pressure?**	Yes	No
BODY MASS INDEX more than 35 kg/m^2?	Yes	No
AGE older than 50 years?	Yes	No
NECK circumference? Neck circumference greater than 40 cm?	Yes	No
Gender=male?	Yes	No

eFigure 119.3 The STOP-Bang questionnaire. Low risk for obstructive sleep apnea = yes to 0 to 2 questions. High risk for obstructive sleep apnea = yes to 3 or more questions. STOP-Bang, snoring, tiredness, observed apnea, high blood pressure, body mass index, age, neck circumference, and male gender. (From Chung F, Yegneswaran B, Liao P, et al. STOP questionnaire: a tool to screen patients for obstructive sleep apnea. Anesthesiology 2008;108:812–21.)

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120 OBSTRUCTIVE SLEEP APNEA

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KEY POINTS

INTRODUCTION AND DEFINITIONS

Sleep-disordered breathing (SDB) is characterized by discrete episodes of absent (apnea) or reduced (hypopnea) breathing, and/or by sustained reductions in breathing during sleep (hypoventilation) compared with wakefulness. The most common form of SDB results from closure of the upper airway during sleep and is called *obstructive sleep apnea* (OSA). SDB is diagnosed by *polysomnography* (PSG), which is a comprehensive multichannel sleep study, or by limited-channel home sleep apnea testing devices (see "Diagnosis" section later). In obstructive apneas, there are sustained respiratory efforts during the event, often identified using thoracic and abdominal respiratory inductance plethysmography bands, which demonstrate paradoxical thoracoabdominal motion (Fig. 120.1). In contrast, during central apneas, there is transient loss of respiratory drive output from the central respiratory controller, with absence of respiratory effort during the event. Mixed apneas are events that begin as central apneas but become obstructive.

In adults, an *apnea* is defined as a cessation of breathing longer than 10 seconds.[1,2] *Hypopneas* are associated with a reduction in airflow rather than complete cessation of airflow. These events are associated with a fall in oxygen saturation or a brief arousal from sleep (microarousal). Whereas the definition of apneas is well standardized, various criteria have been used to identify hypopneas based on the extent of flow reduction, oxygen desaturation, and microarousals.[1–3] Currently, the *American Academy of Sleep Medicine* (AASM) recognizes two alternative definitions of hypopnea[1,2] (Table 120.1). Another type of event is termed a *respiratory effort–related arousal* (RERA). These are episodes of mild upper airway narrowing during sleep, typically identified as flattening of the airflow signal from the nasal pressure cannula, with a reduction in flow amplitude not large enough to be scored as hypopnea,[4] terminating with a microarousal[1,2] (Fig. 120.2). The scoring criteria for respiratory events recommended by the AASM are shown in Table 120.1.

The standard metric for OSA severity is the *apnea-hypopnea index* (AHI), which is calculated as the number of apneas and hypopneas during sleep divided by total sleep time, represented in events per hour. OSA severity is graded as follows: normal (no OSA): AHI less than 5; mild sleep apnea: AHI 5 or greater but less than 15; moderate sleep apnea: AHI 15 or greater but less than 30; and severe sleep apnea: AHI of 30 or greater. Current AASM criteria for PSG analysis also define the *respiratory disturbance index* as the number of apneas, hypopneas, and RERAs per hour of sleep.[2]

Several factors can influence the AHI value derived from polysomnographic recordings.[1,5–8] For example, the technology used to assess airflow has evolved from reliance on oronasal thermistors to include the addition of the nasal pressure signal, which is more sensitive for obstruction and detection of mild reductions in airflow.[5] Prevalence estimates for OSA derived from studies that used thermistor technology only[9,10] are lower than from recent studies that also recorded nasal pressure.[11,12] Differences in hypopnea definitions (extent of flow reduction with associated O_2 desaturation and/or microarousal) can also lead to sizeable differences[6] in assessments of OSA severity and prevalence, as demonstrated by recent studies evaluating the differences between previous and current AASM-recommended scoring criteria.[7,8,13–15] Thus, it is

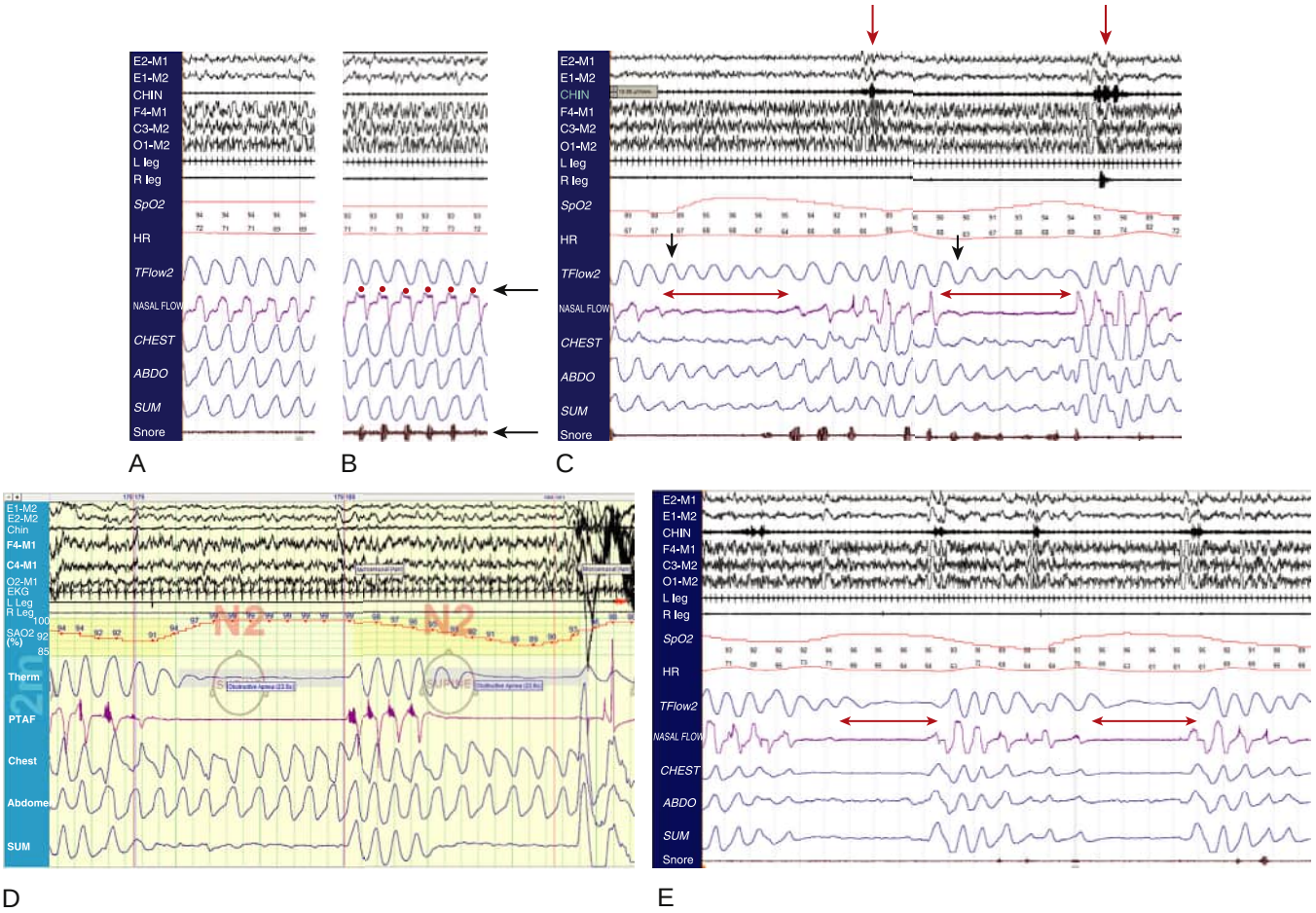


Figure 120.1 Polysomnographic tracings. Tracings illustrate stable breathing (A), simple snoring (B), obstructive hypopneas (*red arrows*, C), obstructive apneas (*blue markers*, D), and central apneas (*red arrows*, E). Note in panel B that the snores are shown as a microphone signal (snore) along with an inspiratory flattening on the nasal pressure flow signal *(red dots)*. Note in panel C that there is evidence of persistent airflow during events on the thermistor (Tflow2) signal while the nasal pressure signal shows no flow. The event is therefore scored as a hypopnea because flow must be absent on both signals to score an apnea (as in D and E). The events in panels C and D are considered obstructive because there is persistent effort during the event with paradoxical inward motion of the ribcage on the thoracic effort channel (Chest). In panel D, the events are apneas because of absent flow on both the thermistor (Therm) and nasal pressure (PTAF) channels. In addition, the paradoxical movement of the chest and abdomen result in no signal on the sum of these two channels (SUM) because the upper airway is completely obstructed and airflow is completely absent. The apneas in panel E are considered central because the absence of airflow is accompanied by an absence of effort (Chest, Abdomen).

essential in interpreting clinical reports of polysomnographic studies, or published research data, that the criteria for scoring respiratory events be stated clearly and considered when interpreting the findings.

Not all patients with OSA have symptoms related to respiratory disturbance. The term *sleep apnea syndrome* refers to the concurrence of OSA with symptoms, classically excessive daytime sleepiness.[16] The latter is often identified by the Epworth Sleepiness Scale,[17] in which the respondent indicates the likelihood of dozing (scale from 0 to 3) in eight common circumstances (Table 120.2). A score of 11 or greater is commonly accepted as indicating excessive sleepiness.[17] Currently, the *International Classification of Sleep Disorders* (third edition) identifies a diagnosis of adult OSA as an AHI of 5 or greater with symptoms, or an AHI of 15 or greater regardless of symptoms[16] (eTable 120.1).

Sleep-associated hypoventilation is defined as a sustained reduction in breathing associated with an increase in arterial P_{CO_2}. The *International Classification of Sleep Disorders* (third edition) threshold values are an arterial P_{CO_2} greater than 55 mm Hg for more than 10 minutes of recording or a value of greater than 50 mm Hg, which is more than 10 mm Hg above waking values, for more than 10 minutes of the PSG recording. Sleep-associated hypoxemia is identified when CO_2 monitoring is not recorded or CO_2 values for hypoventilation are not achieved, but there is a sustained reduction in arterial S_{O_2} less than 88% for more than 5 minutes of the night.[16] Various conditions are associated with hypoventilation during sleep. One of the most common is seen in obese individuals, which can progress to chronic hypercapnic respiratory failure and *obesity hypoventilation syndrome* (OHS). OHS is diagnosed in obese individuals (body mass index >30 kg/m^2) with SDB and elevated daytime arterial P_{CO_2} (>45 mm Hg) without other identifiable causes.[16] Elevated serum bicarbonate levels can point to the diagnosis, but measurement of CO_2 levels may be needed for the diagnosis. OHS is associated with OSA in 90% of cases and with severe OSA in 70%. In those with OSA, the risk for OHS increases with higher body mass index and lower lung function.[18] Patients often present with excessive daytime sleepiness and may be hypoxemic with signs of pulmonary hypertension and right heart failure (e.g., lower extremity edema); in up to 40% of cases, they may present with acute hypercapnic respiratory failure[19,20] (see Chapter 45).

eTable 120.1 Definition of Adult Obstructive Sleep Apnea

OSA is present when A and B or C are present:

A. AT LEAST ONE APPLIES:

- The patient reports daytime sleepiness, unrefreshing sleep, fatigue, or insomnia
- The patient wakens with breath holding, gasping, or choking
- The bed partner reports habitual snoring, breathing interruptions, or both during the patient's sleep
- The patient has been diagnosed with hypertension, mood disorder, cognitive dysfunction, coronary artery disease, congestive heart failure, stroke, atrial fibrillation, or type 2 diabetes

and

B. SLEEP RECORDING* SHOWS:

- Five or more predominantly obstructive respiratory events (obstructive or mixed apneas, hypopneas, or RERAs) per hour

or

C. SLEEP RECORDING* SHOWS:

- Fifteen or more predominantly obstructive respiratory events (obstructive or mixed apneas, hypopneas, or RERAs) per hour

*Sleep recording may be either laboratory *polysomnography* (PSG), or out-of-laboratory portable testing which typically does not record signals to allow sleep staging. Respiratory event numbers are expressed per hour of sleep for PSG and per hour of recording for portable monitors. Portable monitors tend to underestimate event indices as compared with PSG because patients typically are not asleep for an entire recording period. Hypopneas associated with arousals and RERAs cannot be scored from portable monitors without sleep staging capability because arousals cannot be identified.

OSA, obstructive sleep apnea; RERA, respiratory effort–related arousal.

Modified from American Academy of Sleep Medicine. *International Classification of Sleep Disorders* 3rd ed. Darien, IL: American Academy of Sleep Medicine; 2014.

Table 120.1 Definitions of Respiratory Events for Diagnostic Polysomnography

APNEA

- An event lasting ≥10 sec characterized by ≥90% reduction from pre-event baseline in oronasal thermistor airflow. An apnea is scored as:
  - Obstructive, if there is continued or increasing respiratory effort throughout the event
  - Central, if effort is absent throughout the entire event
  - Mixed, if effort is initially absent, then resumes in the latter part of the event
- There is no minimum desaturation or microarousal requirement for scoring of an apnea.

HYPOPNEA

- An event lasting ≥10 sec characterized by a ≥30% reduction from pre-event baseline in peak nasal pressure inspiratory airflow which is associated with:
  - Definition 1A: either a ≥3% reduction in arterial So_2 pre-event baseline or a microarousal
  - Definition 1B: a ≥4% reduction in arterial So_2 from pre-event baseline value
- The hypopnea is scored as *obstructive* if during the event there is any snoring, inspiratory airflow limitation, or paradoxical thoracoabdominal motion not present during pre-event breathing.
- The hypopnea is scored as *central* if none of the events described earlier is present.

RERA

- A sequence of breaths lasting ≥10 sec that does not meet criteria for apnea or hypopnea, which is characterized by increasing respiratory effort or inspiratory flattening of the nasal pressure flow signal leading to a microarousal.

HYPOVENTILATION

- An increase in arterial Pco_2 to >55 mm Hg for ≥10 min or an increase in arterial Pco_2 ≥10 mm Hg above awake supine values to >50 mm Hg for ≥10 min

RERA, respiratory effort–related arousal.
Modified from Berry RB, Abreu AR, Bibbs ML, et al. *The AASM Manual for the Scoring of Sleep and Associated Events*. Version 2.6 ed. Darien, IL: American Academy of Sleep Medicine; 2020; and American Academy of Sleep Medicine. *International Classification of Sleep Disorders* 3rd ed. Darien, IL: American Academy of Sleep Medicine; 2014.

PATHOGENESIS

The pathogenesis of OSA involves a complex interaction of factors including altered upper airway anatomy, tissue characteristics, neuromuscular function, sleep-related decrements in upper airway dilator muscle activity, attenuated protective reflexes, and altered ventilatory and arousal responses to chemical and other respiratory stimuli (Fig. 120.3). Different factors may predominate in different individuals, yielding different OSA phenotypes. Because the upper airway in OSA closes only during sleep, sleep-dependent

Table 120.2 Epworth Sleepiness Scale

Situation	Chance of Dozing (Score 0–3)
Sitting and reading	
Watching television	
Sitting inactive in a public place (such as a theater or meeting)	
Riding as a passenger in a car for an hour without a break	
Lying down in the afternoon when circumstances permit	
Sitting and talking to someone	
Sitting quietly after a lunch without alcohol	
In a car, while stopped for a few minutes in traffic	
	Total score (normal <11)

Instructions to patient: "What is the chance that you would doze off or fall asleep (not just "feel tired") in each of the following situations? Rate the chance for each situation. If you are never or rarely in the situation, please give your best guess for that situation."
Chance of dozing: 0, never; 1, slight chance; 2, moderate chance; 3, high chance. The individual scores are summed.

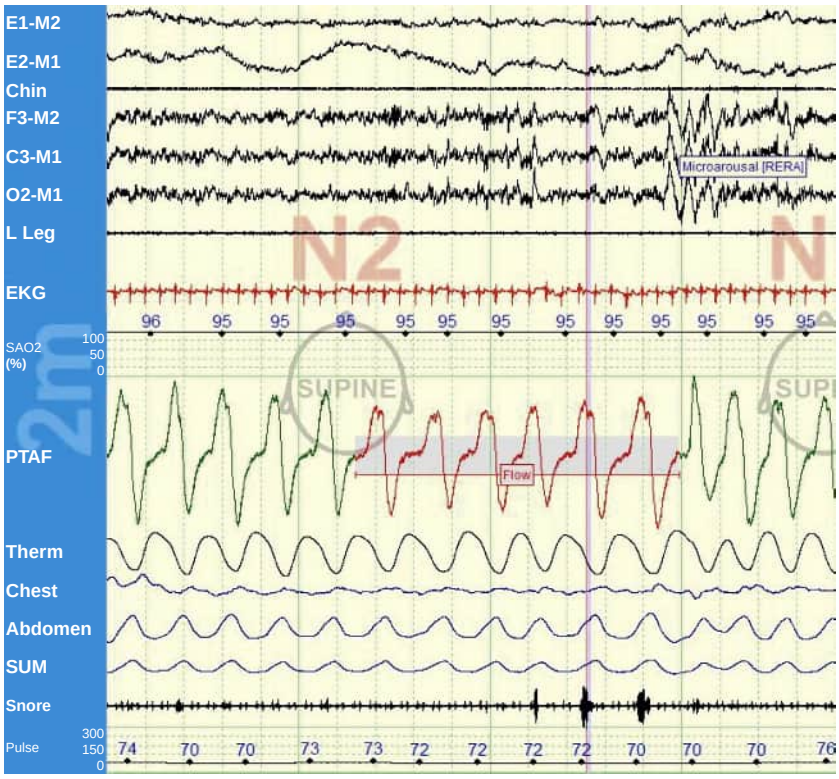


Figure 120.2 Polysomnographic tracing illustrating a respiratory effort-related arousal. The red-highlighted breaths on the nasal pressure flow signal (PTAF) show inspiratory flattening (flow limitation) reflective of upper airway narrowing. Flow is not reduced sufficiently to meet hypopnea criteria and there is no change in arterial So_2, but the electroencephalographic channels above demonstrate microarousal (label) at the termination of the respiratory effort–related arousal (RERA) event.

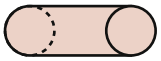
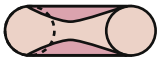
Factors affecting upper airway patency	Patency	Collapse
		
Anatomic configuration (bony structure, soft tissue, fat)	Normal	Reduced dimensions
Lung volume	Normal lung volume: traction on upper airway	Lower lung volume: less traction
Lining fluid surface tension	Normal	Increased
Intraluminal pressure	Less negative	More negative
Extraluminal tissue pressure	Less positive	More positive
Airway collapsibility (P_{crit})	Lower	Higher
Sleep-related decrements in muscle activity	Normal, mild compared with wakefulness	Marked compared with heightened compensatory levels during wakefulness
Chemosensitivity	Normal	Blunted or heightened
Negative pressure reflexes	Mild sleep-related decrement	Blunted (latency, amplitude)
Chronic dilator muscle activation	Adaptation	Injury, dysfunction
Denervation (sensory, motor)	Absent	Present: neural and muscular dysfunction
Edema: inflammation; nocturnal fluid shift	Absent	Present: altered airway caliber and tissue characteristics

Figure 120.3 Schema illustrating factors that favor upper airway collapse during sleep in obstructive sleep apnea. (Modified from Kimoff R. The upper airway. In: Hamid QS, Martin JG, eds. *The Physiologic Basis of Respiratory Disease*. Hamilton, Canada: BC Dekker; 2005.)

changes in output to upper airway dilator muscles must be fundamental. The airway collapses when dilator muscle activity and compensatory reflexes are no longer sufficient to maintain patency of the compromised airway. The key elements of sleep-related influences on respiratory motor output and current approaches to pathophysiologic endotyping of OSA are discussed in detail in Chapter 117. This section focuses on structural and functional changes in the upper airway predisposing to airway closure.[21–23]

UPPER AIRWAY DIMENSIONS

A variety of imaging methods have shown that upper airway dimensions are reduced in OSA.[24] Airway size may be compromised by alterations in bony structures such as a small retrognathic mandible,[25] or by increased volume of soft tissues (tongue, lateral walls).[26] In addition to a reduction in the cross-sectional dimensions, airway length may also be increased, with increased length predisposing to collapse.[27,28] Upper airway caliber is also influenced by the effect of lung volume on tracheal traction, so that reductions in lung volume (e.g., in recumbency) lead to less tracheal traction and reduced upper airway patency.[29,30]

UPPER AIRWAY COLLAPSIBILITY

Due to a lack of rigid supporting structures, much of the human upper airway is a collapsible tube. Pressure-flow relationships in the airway have been modeled using the Starling resistor model, in which collapsibility is expressed as the *critical closing pressure* (P_{crit}). P_{crit} is measured during sleep by decreasing the intraluminal pressure (e.g., lowering *continuous positive airway pressure* [CPAP] level in an OSA patient or applying negative pressure in a normal subject) and assessing flow reductions. A more negative P_{crit} denotes a less collapsible airway. Studies have shown a continuum of upper airway collapsibility in subjects with normal breathing ($P_{crit} < -10$ cm H_2O), nonapneic snoring (P_{crit} range, -10 to -5 cm H_2O), obstructive hypopnea (P_{crit} range, -5 to 0 cm H_2O), and obstructive apnea ($P_{crit} > 0$ cm H_2O).[31–33] These values are for passive P_{crit}, which reflects the passive mechanical properties of the airway. Techniques are also available to measure active P_{crit}, which reflects active neuromuscular compensation for reduced intraluminal pressure, which is significantly impaired in some OSA patients.[23,33,34]

NEUROMUSCULAR FACTORS

In addition to the attenuation of protective reflexes during sleep discussed in Chapter 117, several factors may contribute to impaired neuromuscular upper airway function in OSA.[35–38] Loading of the upper airway dilators leads to myoadaptive changes (fiber type shifts) so that, whereas contractility appears preserved in most patients, the muscles are more fatigable.[38,39] In some patients with severe OSA, muscles may be injured, leading to reduced contractility, as described in the English bulldog model of OSA.[40] Changes in mechanical coupling due to connective tissue alterations[41] and fat deposition may also alter the efficacy of muscle activation. There is also evidence for upper airway neuropathy in OSA, with both sensory/afferent impairment[38,42,43] and efferent neuropathy in the form of muscle denervation,[37,44] both of which could impair neuromuscular compensatory responses.[21]

UPPER AIRWAY INFLAMMATION

There is increased inflammation in upper airway tissues in OSA, which may contribute to the pathogenesis of OSA.[41,45] Tissue trauma from snoring and apneas, oxidative stress, acid-pepsin reflux, smoking, and alcohol could all lead to inflammation. Increased inflammation, in turn, may produce edema and airway narrowing, lead to changes in soft tissue composition (e.g., increased collagen deposition) and mechanics, impair muscle contractility,

and contribute to upper airway afferent and efferent neuropathy.[21,41] Few studies to date have assessed the effects of anti-inflammatory therapy on OSA, though inhaled nasal steroids have been shown to improve mild OSA.[46]

FLUID SHIFT

There is growing evidence that spontaneous shifts in fluid volume from the legs to the neck during recumbency or sleep play a role in the pathophysiology of OSA.[47,48] In OSA, the extent of spontaneous overnight fluid shift correlates with AHI,[47,49] and interventions to reduce fluid shift may improve OSA severity in some patient subgroups.[48,50,51] Compression stockings to prevent daytime fluid accumulation reduced nocturnal fluid shift and AHI,[52,53] as did increased physical activity in sedentary patients.[48] Diuresis may improve AHI, particularly in hypertensive patients,[48,51] and increased dialysis/ultrafiltration improves fluid shift and sleep apnea severity in patients with end-stage renal disease.[48,50]

PREDISPOSING FACTORS

OBESITY

There are strong links between obesity and OSA.[54,55] Approximately 58% of moderate to severe OSA patients are obese.[54] Obesity may reduce upper airway caliber due to adipose tissue deposition as well as through a lung volume–dependent effect.[30] A change in weight is also associated with changes in AHI. In the Wisconsin cohort over 8 years of follow-up, a 10% increase in body weight was associated with a 32% increase in AHI and a sixfold increase in risk of developing an AHI of 15 or greater. A 10% weight loss was associated with a 26% reduction in AHI.[56] Weight-related changes in AHI are more marked in men than in women.[54,55] Despite the strong links between OSA and obesity, many obese individuals do not have OSA, and up to one-third of OSA patients are not obese.

UPPER AIRWAY ANATOMIC ABNORMALITIES

Abnormalities that may predispose to OSA include marked craniofacial disproportion, as is seen in Pierre-Robin syndrome,[57] benign tonsillar hypertrophy, macroglossia, and acromegaly.[58] Nasal obstruction may contribute to OSA[59] by increasing negative inspiratory driving pressure to maintain airflow, which may contribute to dynamic oropharyngeal collapse. However, surgical correction of mechanical nasal obstruction alone typically has minimal effects on OSA severity.[60,61] Several case series have reported a high incidence of OSA in patients with head and neck cancers,[62–64] related either to anatomic narrowing by tumor mass or surgical- or radiation-induced airway changes.[63,64]

GRAVITY/BODY POSITION

The frequency of OSA events is often higher in the supine position compared with the lateral decubitus position due to the effects of gravity on upper airway size and shape. Positional OSA is commonly defined as a supine AHI at least twice as high as that in the lateral position.[65–67] The duration of obstructive events and extent of associated oxygen desaturation may also worsen in the supine position.[68] Prevalence estimates vary depending on PSG recording and scoring techniques[66,69] and the patient population under study. Positional OSA was identified in 49.5% of mild (AHI 5 to 15), 19.4% of moderate (AHI 15 to 30), and 6.5% of severe (AHI ≥30) OSA patients in one study.[70] In the recent HypnoLAUS population study, positional OSA was present in 42% of women and 31% of men with AHI of 5 or greater and in 52% of women and 41% of men with AHI of 15 or greater.[69]

GENETIC FACTORS

Studies in diverse populations have demonstrated a familial propensity for OSA. The relative risk for OSA in a first-degree relative of an affected patient is approximately 2.0.[71–73] Obesity is a major OSA risk factor, which also has a genetic basis; it is estimated that approximately 40% of the genetic variance in AHI is shared with pathways that mediate obesity.[74,75] The remainder of heritability likely resides in genes controlling craniofacial structure, ventilatory control, sleep-wake patterns, and inflammation.[73,76–78] Candidate gene, genome-wide linkage, and genome-wide association studies have revealed gene loci and/or polymorphisms associated with OSA risk, severity, and complications, with findings in some cases differing between sex and ethnicities. Work is ongoing to translate these findings into clinical predictive and therapeutic strategies.[73,76–78]

ENDOCRINE DISTURBANCES

OSA has been reported in 25–35% of patients with untreated hypothyroidism.[79–81] Predisposition to OSA may be due to increased mucopolysaccharide and protein deposition in upper airway tissues. Altered central respiratory control or neuropathic changes in upper airway muscles may also play a role. Thyroid replacement therapy improves OSA in many patients, though there may be residual sleep-disordered breathing requiring continued standard treatment.[79,80] A clinical history suggesting hypothyroidism should be sought during evaluation of OSA patients, but routine biochemical screening of all potential OSA patients is not warranted.[82]

Sleep-disordered breathing is found in approximately 70% of patients with acromegaly.[81,83,84] While OSA predominates, central sleep apnea may also be observed. Upper airway dimensions are reduced due to both soft tissue (glycosaminoglycan and collagen deposition, edema) and bony changes.[58] Upper airway myopathy may also play a role. Correction of the endocrine disturbances in acromegaly results in variable improvements in OSA; continued treatment with CPAP is often required.[80]

OSA is found in up to 70% of women with polycystic ovarian syndrome.[85,86] Potential mechanisms include hormonal changes (relative androgen excess) and increased central adiposity. Polycystic ovarian syndrome is associated with a high rate of metabolic dysfunction. OSA may worsen metabolic function, and OSA treatment may improve metabolic parameters in these patients.[86,87]

SMOKING

Cigarette smoking has been linked to snoring and OSA in some epidemiologic studies,[88,89] with one analysis showing a significant positive dose-response relationship between cigarette smoking and OSA severity.[90] Possible mechanisms include worsening of upper airway inflammation

and sleep-disruptive effects of nicotine producing respiratory instability.

ALCOHOL, DRUGS

Alcohol is known to worsen snoring and OSA. This may be due to direct effects on upper airway motor activity or to a deepening of sleep and impairment of arousal responses.[91,92] Other drugs with similar effects include muscle relaxants, sedative-hypnotics, and opioids, although the latter may also produce central and/or complex sleep apnea. Drug effects on upper airway function remain an active area of study.[92–94]

EPIDEMIOLOGY

PREVALENCE

The original Wisconsin Sleep Cohort study in 1993 reported the prevalence of OSA syndrome (AHI ≥5 with daytime sleepiness) as 4% in men and 2% in women,[95] and the prevalence of AHI 15 or greater regardless of symptoms as 9% in men and 4% in women. Since this estimate, obesity has increased markedly in the United States and elsewhere,[96] and the Wisconsin Cohort investigators updated their estimates of OSA prevalence in 2013,[97] with OSA syndrome (AHI ≥5 with Epworth Sleepiness score ≥11) now estimated at 14% in men and 5% in women. Prevalence estimates from other studies vary based on differences in recruitment, ethnicity, airflow recording technology, definitions of hypopnea, and symptoms included for OSA syndrome.[98,99] However, these studies all confirm a high prevalence of OSA in the general population. Recently, Benjafield et al.[12] reported that 936 million individuals have mild to severe OSA (AHI ≥5) while 425 million have moderate to severe OSA (AHI ≥15) worldwide.

SEX DIFFERENCES

OSA is two to three times more prevalent among men than women. Several factors account for this, including differences in body fat distribution, upper airway anatomy (cross-sectional area, length) and collapsibility, ventilatory control, and other genetic factors. OSA is approximately three times more prevalent among postmenopausal than premenopausal women, pointing to a role for sex hormones.[100,101] Hormone replacement therapy may have a protective effect,[102,103] but appears to have little impact on OSA once present.[104] The clinical presentation of OSA may also differ, with complaints of insomnia, fatigue, and depressive symptoms being more common in women than men, while heavy snoring and nocturnal choking may be less prominent.[101,105,106]

ETHNICITY

Overall OSA prevalence is similar among African Americans and whites,[107] although it is comparatively higher among African Americans younger than 25 years[108] or older than 65 years.[109] Symptoms of OSA[110,111] and PSG-based prevalence are slightly higher among Hispanics than whites, with some ancestries more prominently affected than others.[77,112,113] OSA prevalence among Asians is comparable to that in whites, despite a lower prevalence of obesity among Asians.[77,113,114] While obesity remains an important risk factor, craniofacial structure may play a more prominent role in OSA pathogenesis among Asians.[113,114] Studies on ethnicity may be confounded by socioeconomic factors. Low socioeconomic status is linked to OSA risk among children.[115,116] Living in poor neighborhoods is associated with shorter sleep time and increased sleep disruption; air quality may also be worse, which could worsen OSA through increased airway inflammation.[117] CPAP compliance is reportedly lower in African Americans, which may be related to socioeconomic status[118] and shorter sleep duration.[119]

AGING

The prevalence of OSA increases with age. The updated Wisconsin Sleep cohort prevalence of OSA (AHI ≥5, Epworth Sleepiness score ≥11) among men was 12% for ages 30 to 49 years versus 18% for ages 50 to 70 years, and among women was 3% for ages 30 to 49 years and 8% for ages 50 to 70 years.[97] Studies in individuals older than 65 years have reported a high incidence of OSA (50–60%).[120–122] OSA is often underrecognized in elderly patients but may be associated with daytime sleepiness, neurocognitive dysfunction, depressive symptoms, falls, and adverse cardiovascular outcomes.[121,123–125] Recent *randomized controlled trials* (RCTs) in patients older than 65 years have shown improvements with CPAP in sleepiness and neurocognitive outcomes. Findings varied between studies, but improvements were greater in patients with more severe OSA and better CPAP compliance.[125–128]

PREGNANCY

OSA may develop or worsen over the course of pregnancy, with an estimated 17–45% of women affected by their third trimester.[129,130] A recent large cohort study of over 2500 nulliparous women (NuMom2b) found an OSA prevalence of 3.6% and 8.3% in early and mid-pregnancy, respectively, based on less sensitive level 3 sleep recordings (e.g., similar to home-based tests; see later).[131] Standard clinical prediction indices are not highly accurate, whereas incorporation of anthropometric factors (age, body mass index, chronic hypertension) improves accuracy.[132,133] Observational studies demonstrate links between maternal OSA and gestational hypertension/preeclampsia and gestational diabetes and, in some studies, low infant birth weight.[130,134] Two large registry studies also showed links to serious outcomes, including maternal cardiomyopathy, congestive heart failure requiring intensive care admission, and maternal death.[135,136] Data on the effects of CPAP or other OSA treatments during pregnancy are currently limited, though small, short-term studies suggest benefits in lowering blood pressure[130] and, in one study, in achieving better glycemic control.[130] Clinically, CPAP treatment during pregnancy can be challenging but may provide symptomatic benefit. However, large-scale trials are still required to evaluate the impact on maternal and fetal pregnancy outcomes.

CLINICAL EVALUATION

CLINICAL PRESENTATION

The patient with OSA classically presents with a history of heavy habitual snoring and *excessive daytime sleepiness*

(EDS). However, OSA is a heterogenous condition and may present with a variety of manifestations, and some patients with even moderate to severe OSA have few if any symptoms. Different symptom clusters have been identified in OSA that may include predominantly nocturnal symptoms with insomnia and disturbed sleep, predominantly EDS, or few if any symptoms.[137,138] OSA symptoms typically develop over many years in association with aging, weight gain, or onset of menopause, and may be underappreciated by the patient. Conversely, EDS may be the manifestation of a number of conditions other than OSA. A comprehensive sleep history should be obtained in evaluating patients, to assess not only features of OSA but also the impact of sleep habits and other potential sleep disorders on clinical symptoms.

ELEMENTS OF A COMPLETE SLEEP HISTORY

The chief complaint and the patient's main concerns should be elicited. The spouse or bed partner's observations can be invaluable with respect both to the manifestations during sleep and any impact on daytime functioning. It is also important to obtain the occupational history because of the potential risks related to EDS or impaired attention (e.g., commercial truck driver), and impact on daily functioning. Shift work is also associated with impaired sleep quality and EDS.[139]

The history should include medications taken. Benzodiazepines and other sedative-hypnotics, antidepressants, antipsychotics, lithium, anticonvulsants, opioids, stimulants, β-blockers and other cardiovascular medications, antihistamines, and other classes of drugs can affect sleep architecture, risk of OSA, or daytime functioning.[92] Similarly, other substance use should be elicited (nicotine, caffeine, alcohol, cannabis, illicit substances), including recent discontinuation, which could account for possible withdrawal symptoms.

A family history of sleep-disordered breathing can be helpful for diagnosis, whereas other conditions may affect treatment decisions (e.g., early cardiovascular disease).

OSA patients may manifest a number of nocturnal symptoms (Table 120.3). Loud, disruptive snoring is often present, which may lead the spouse to sleep in a separate room.

Table 120.3 Symptoms of Obstructive Sleep Apnea

NOCTURNAL
Heavy, habitual snoring
Apneas witnessed by bed partner
Nocturnal choking
Nocturia
Restless sleep
Sweating
Erectile dysfunction
Gastroesophageal reflux
Unrefreshing sleep
Headache upon awakening
Insomnia
Violent/jerking movements
DAYTIME
Excessive daytime sleepiness
Difficulty concentrating
Memory loss/cognitive changes
Irritability, personality change
Depressive symptoms
Fatigue
Lightheadedness

Snoring is not a specific symptom for OSA and has a high prevalence in the general population. An important finding is a report by the bed partner of witnessed apneas. Whereas the frequency or duration of events reported may not be accurate, a description of episodes during which breathing stops, followed by loud gasping or snoring, is highly suggestive of OSA. Patients themselves are often unaware of apneic episodes, and it is surprisingly uncommon for patients to report nocturnal choking or shortness of breath upon awakening. The differential diagnosis for nocturnal choking includes paroxysmal nocturnal dyspnea related to heart failure and Cheyne-Stokes respiration, nocturnal asthma, laryngospasm (idiopathic or due to acid-pepsin reflux), orthopnea due to diaphragm dysfunction, or insular seizures.[140] Other nocturnal symptoms of OSA include restless sleep, diaphoresis, and palpitations. Patients may report dry mouth upon awakening, a feeling of awakening unrefreshed, or morning headache.

The cardinal daytime symptom of OSA is EDS,[141] defined as a propensity to fall asleep in unwanted situations during normal waking hours. Patients should be asked whether they have experienced drowsiness while driving or have fallen asleep at the wheel because OSA increases the risk for crashes or near-crashes.[142,143] Patients may also describe symptoms of fatigue or lack of energy.[144] Other symptoms of OSA include cognitive impairment such as difficulty with concentration or memory loss, mood disturbances such as irritability or depression, and impaired quality of life. OSA may also be associated with nocturia, enuresis (in severe cases), reduced libido, and impotence.[145]

Although EDS is a common symptom of OSA, it is important to consider other potential causes of sleepiness (eTable 120.2). Many medical conditions may be associated with sleep disruption, resulting in excessive sleepiness and/or predisposing to OSA. A complete medical history and review of systems should assess for weight gain, menopause, endocrine disorders (hypothyroidism, acromegaly, Cushing disease), respiratory and cardiac history (e.g., with nocturnal cough or dyspnea), allergic rhinitis, nasal or oropharyngeal trauma or surgery, gastroesophageal reflux disease, neuropathic or chronic pain, and genetic syndromes. Psychiatric disorders such as depression may present with excessive sleepiness or insomnia. Anxiety, panic disorder, and posttraumatic stress disorder may affect sleep. Neurologic disorders, including head trauma, prior stroke, and neurodegenerative diseases, can impact EDS, sleep architecture, and sleep-disordered breathing.

The sleep history should include the habitual sleep schedule, including any daytime naps, and details of the patient's usual bedtime, time to fall asleep, number and duration of nocturnal awakenings, usual waking time, and whether wakening is spontaneous or requires one or more alarms. The regularity and timing of work and sleep schedules should also be ascertained. Short sleep duration during the week, with recovery sleep time on weekends, is often a sign of insufficient sleep. When habitually present for 3 months or more, this is termed *insufficient sleep syndrome*.[16] Patients should be questioned about light exposure and use of electronic devices before bedtime and in bed, given the impact of blue light on sleep and circadian rhythms.[146,147]

Symptoms of other sleep disorders should be elicited. The most common of these are narcolepsy, idiopathic

hypersomnolence, restless legs syndrome, and various *rapid eye movement* (REM) and non-REM *parasomnias* (i.e., complex movements, behaviors, or experiences during sleep).[16]

Additional descriptions of disorders of hypersomnolence, movement disorders, circadian sleep-wake disorders, and parasomnias are provided at ExpertConsult.com.

MEASUREMENT OF SLEEPINESS

The most commonly used questionnaire to quantify daytime sleepiness is the Epworth Sleepiness Scale described earlier (see Table 120.2).[17] Values of 11 or greater indicate excessive sleepiness. The Stanford Sleepiness Scale[178] asks subjects to rate their degree of sleepiness at a single moment in time. This scale has been used more commonly in research, and normative values have not been established, limiting its clinical applicability. Objective measurements can be made in the sleep laboratory during a series of scheduled daytime nap sessions to measure either physiologic sleepiness (Multiple Sleep Latency Test) or the ability to remain awake (Maintenance of Wakefulness Test).[179,180] The Oxford Sleep Resistance Test (OSLER Test), a more accessible behavioral test that does not require PSG recording, has been found to approximate findings on Maintenance of Wakefulness Test.[181,182]

DIAGNOSIS

QUESTIONNAIRES/PREDICTION EQUATIONS

Clinical prediction models that incorporate symptoms and anthropomorphic measurements (e.g., body mass index, neck circumference) have been developed to grade OSA risk.[183–187] These models tend to be relatively sensitive (76–96%) but not very specific (13–54%) when compared with PSG.[188] Several questionnaires such as the Berlin Sleep,[189] STOP-Bang,[190] and more recently the NoSAS[191] and GOAL questionnaires[192] have been developed, with slightly improved specificity. However, whereas questionnaires or prediction models are useful for screening or estimating pretest probability, objective sleep recording is required to establish a diagnosis of OSA and determine its severity.[193]

LABORATORY POLYSOMNOGRAPHY

The gold standard test for OSA has long been considered to be in-laboratory, technologist-attended complete overnight PSG, referred to as level 1 sleep testing. Standards for the performance and analysis of full PSG have been established by the AASM.[194] Level 1 recordings include monitoring of electroencephalography, electro-oculography, chin electromyography, electrocardiography, oronasal airflow and snoring, pulse oximetry, thoracic and abdominal movement, body position, and tibialis anterior electromyography for scoring periodic leg movements (see Fig. 120.1). Transcutaneous CO_2 is monitored in some laboratories to detect sleep-related hypoventilation. Infrared video monitoring is also used to record complex behaviors and movements to diagnose parasomnias. Sleep-wake state is scored using electroencephalography, electro-oculography, and electrocardiography signals. Respiratory events are scored based on airflow, thoracoabdominal motion, and oximetry signals using the criteria described in Table 120.1. PSG records may be autoscored or manually scored by trained technologists according to standard criteria[194] and summary data on sleep, respiratory, and other associated events generated in tabular and graphic summary format (eFig. 120.1).

UNATTENDED SLEEP STUDIES

Although complete in-laboratory PSG is the gold standard for OSA diagnosis, there is limited access to this resource in many locations.[195,196] There are now "out-of-center" or home sleep apnea testing options available, which are adequate for diagnosis of OSA in many instances. In addition to level 1 sleep testing (in-laboratory PSG), three other levels of sleep testing are defined by the AASM based on number of channels recorded. Level 2 testing involves a full PSG performed in an unattended, nonlaboratory setting; this has been used in population-based studies[10] and has clinical utility when full PSG recording is desirable but the patient cannot come to the sleep laboratory (e.g., intensive care unit or disabled patients). Level 3 home sleep apnea testing devices acquire respiratory airflow (nasal pressure and/or oronasal thermistor), respiratory effort, oximetry, and often snoring and body position (eFig. 120.2). Level 3 devices are increasingly being used for the diagnosis and management of OSA. Level 4 devices record oximetry and sometimes one other signal such as airflow, thus yielding less information than level 3 monitors. Recent guidelines recommend use of portable monitoring for evaluation of moderate- to high-pretest probability patients[193] (Fig. 120.4). A positive test in such patients will rule in a diagnosis of OSA, whereas a negative test does not exclude more subtle forms of disease, and full PSG should then be performed. Current guidelines do not recommend the use of portable monitoring for OSA diagnosis in the presence of major medical comorbidities or for diagnosis of sleep hypoventilation or central sleep apnea. However, for moderate to severe OSA patients, recent data show that the use of portable monitors in ambulatory-based clinical management algorithms results in similar treatment adherence and clinical outcomes as conventional level 1–based approaches[196–198] (see "Disease Management Strategies" section).

IN-HOSPITAL DIAGNOSIS

Patients with OSA and OHS have increased hospitalization rates and adverse outcomes.[199–201] In hospitalized patients, SDB is highly prevalent but underdiagnosed. In patients presenting with acute cardiac disease, OSA not previously diagnosed has been found in up to 78%.[202–204] Among patients hospitalized on internal medicine wards with a body mass index of 35 kg/m^2 or greater, 31% met criteria for OHS.[201]

Hospitalization presents an opportunity to detect and treat SDB because treatment appears to improve outcomes during current[201,202] and future hospitalizations[205] and reduces rehospitalization rates.[202] Access to level 1 PSG is limited for hospitalized patients. Protocols using level 3 testing and *auto-positive airway pressure* (APAP) titration can facilitate diagnosis and rapid treatment initiation. Level 3 studies in

eTable 120.2 Differential Diagnosis of Excessive Daytime Sleepiness

Insufficient sleep (behaviorally induced)
Circadian rhythm disorders
Delayed sleep-wake phase syndrome ▪ Advanced sleep-wake phase syndrome ▪ Irregular sleep-wake rhythm disorder ▪ Non–24-h sleep-wake rhythm disorder ▪ Shift work disorder
Sleep-related breathing disorders ▪ Obstructive sleep apnea ▪ Central sleep apnea ▪ Sleep-related hypoventilation
Hypersomnia of central origin ▪ Narcolepsy type 1 ▪ Narcolepsy type 2 ▪ Idiopathic hypersomnia ▪ Periodic hypersomnia (e.g., Kleine-Levin syndrome)
Insufficient sleep syndrome
Sleep-related movement disorders ▪ Restless legs syndrome ▪ Periodic limb movement disorder
Parasomnias ▪ REM sleep behavior disorder ▪ Sleepwalking ▪ Confusional arousals
Sleep-related eating disorder
Sleepiness due to medical disorders, medication, and other conditions

REM, rapid eye movement.

DIFFERENTIAL DIAGNOSIS

HYPERSOMNIAS OF CENTRAL ORIGIN

The most common disorder is narcolepsy, which typically presents in the second or third decade of life and is characterized by a tetrad of symptoms including daytime sleepiness, cataplexy, hypnagogic or hypnopompic hallucinations (hallucinations that take place in the transition between wakefulness and sleep), and sleep paralysis.[148,149] Narcolepsy is a disorder of REM sleep with an "unpackaging" of REM phenomena so that aspects of REM sleep become apparent during wakefulness. Cataplexy is the sudden loss of muscle tone, as takes place in REM sleep, which is precipitated by emotion (laughter, anger, surprise) during wakefulness. It starts in facial muscles and can be partial and limited to the face or total and diffuse, leading to collapse, mimicking syncope, though there is no true loss of consciousness. Cataplexy is associated with objective transient areflexia. Cataplexy is highly specific to narcolepsy and is a virtually pathognomonic symptom, although narcolepsy can be seen without cataplexy (narcolepsy type 2).[16] Hypnagogic or hypnopompic hallucinations are vivid dreams typically with a strong visual component that are experienced either at sleep onset or when awakening from sleep. Individuals with sleep paralysis wake up from sleep unable to move because they are emerging from REM sleep and the REM-associated atonia has not been switched off.[148,149] Although particularly common in narcolepsy, sleep paralysis may also be experienced by otherwise healthy individuals. The diagnosis of narcolepsy is confirmed with cerebrospinal fluid hypocretin-1 deficiency or a Multiple Sleep Latency Test showing reduced mean sleep latency and sleep-onset REM periods in at least two naps, in the absence of other causative factors.

Excessive sleepiness in narcolepsy is commonly treated with stimulant medication.[150,151] Modafinil is the drug of choice due to a better side-effect profile and lesser potential for abuse than for other stimulants. When modafinil is ineffective, alternative stimulants are methylphenidate or amphetamine preparations.[150] The stimulant solriamfetol[152] and the histamine H_3 receptor agonist pitolisant[153] are novel treatment options for EDS in narcolepsy. Residual EDS in OSA may also be treated with modafinil, solriamfetol, or pitolisant, when other contributing factors have been carefully excluded.[154] Improvements in EDS with stimulant therapy in narcolepsy can be associated with improvement in other symptoms such as cataplexy and sleep paralysis, though specific medication may be required. Cataplexy is commonly treated with antidepressants (tricyclic, selective serotonin-noradrenalin reuptake, and monoamine oxidase inhibitor classes).[150,151] The central nervous system depressant sodium oxybate (Xyrem) is approved for treatment of cataplexy and may also improve nocturnal sleep quality and excessive daytime sleepiness. Its use is limited by cost and potential side effects such as headache, mood swings, nausea, enuresis, sleepwalking, and others, including potential need to retitrate CPAP in those with OSA, which raises concerns about respiratory depression.[155–157] Pitolisant also appears to reduce cataplexy but it is not currently approved for this indication.[158]

Periodic Hypersomnia

Kleine-Levin syndrome is a rare cause of EDS, which usually presents in adolescence and is characterized by intermittent episodes of intense hypersomnia with normal intervening sleep and alertness.[16,151] Episodes of extreme hypersomnia may last for days and patients may sleep for up to 20 hours each day. Episodes are associated with behavioral abnormalities, including binge eating and hypersexuality. Treatment is usually supportive during the episodes, with a limited role for stimulants; lithium may be effective in some cases.[151]

Idiopathic Hypersomnia

This disorder is a diagnosis of exclusion and is characterized by persistent marked excessive sleepiness despite documented adequate sleep duration and hygiene, frequent daytime napping that is typically unrefreshing, unlike in narcolepsy,[159] subjectively uninterrupted nocturnal sleep, and normal nocturnal PSG recording, without symptoms of another sleep disorder or medical cause for hypersomnolence.[16] Although most patients have prolonged nocturnal sleep, some may not. The current *International Classification of Sleep Disorders* does not distinguish between these two variants.[16] Pathophysiology is not well understood, but patients have a high prevalence of autonomic symptoms (e.g., vasomotor, secretomotor, orthostatic intolerance).[160] Management is similar to narcolepsy, although symptoms may be more difficult to control.[150,151]

MOVEMENT DISORDERS DURING SLEEP

Movement disorders during sleep may cause sleep disruption and EDS. The most common is the *restless legs syndrome* (RLS),[16] which is characterized by an urge to move the legs, usually accompanied by uncomfortable or unpleasant sensations in the legs that (1) get worse with periods

of physical inactivity or rest, (2) are partially or totally relieved by movement such as walking or stretching, and (3) are worse or are felt only in the evening or night. The timing of symptom onset is such that the patient has difficulty falling asleep until the uncomfortable sensations ease and the urge to move subsides, which may take 2 to 3 hours after bedtime. Several factors can precipitate or exacerbate RLS, the most common of which is iron deficiency. Serum iron and ferritin levels should be checked in all RLS patients. Caffeine, stimulants, and other medications may exacerbate RLS. RLS is common in renal dialysis and congestive heart failure patients and in patients with neuropathic disorders and may emerge or worsen during pregnancy.[161] Familial RLS has been described, and genetic studies have identified several loci linked to RLS, though to date these have not led to major insights into etiology, prevention, or treatment.[162]

Treatment of RLS[163,164] first involves avoidance of precipitating factors and correction of potential precipitating factors. Oral iron replacement is recommended when serum ferritin levels are 75 μg/L or less. Intravenous preparations can be used if oral replacement fails, but some formulations are associated with anaphylactic reactions.[164,165] Pharmacologic treatment of RLS includes dopamine agonists such as pramipexole , ropinirole, or the rotigotine patch.[163,164] They can be used intermittently for occasional symptoms or regularly for persistent symptoms but are associated with impulse control disorders such as pathologic gambling and the augmentation phenomenon (worsening of symptoms, including earlier onset, increased intensity, or spread of symptoms to the arms). For patients with chronic persistent symptoms, α2δ ligands can be used, including gabapentin, enacarbil, and pregabalin.[163,164,166] They may be preferred in those with a predominant painful component and those with insomnia. There is, however, a concern about potential respiratory depression, especially when combined with other central nervous system depressant medication, in those with respiratory conditions, and in the elderly.[167] In those with resistant symptoms, oxycodone, alone or in combination with naloxone, has been found to be efficacious and safe.[164]

CIRCADIAN RHYTHM DISORDERS

This set of clinical disorders is characterized by disturbances of the internal "biological clock"[168] so that sleep is usually normal but takes place at abnormal times.[169] The most common disturbance is delayed sleep-wake phase disorder.[16,169] Affected individuals may present with complaints of difficulty initiating sleep and inability to awaken on time in the mornings. The natural bedtime preference of someone with delayed sleep-wake phase disorder is during the early morning hours (commonly 2 AM or later), and rise time preference is late morning or mid-day. Because sleep is otherwise normal, patients with delayed sleep-wake phase disorder report few daytime symptoms so long as they are able to follow their natural sleep schedule. However, when work or school imposes a conflicting schedule, sleep time is restricted, and daytime sleepiness ensues. Management of delayed sleep-wake phase disorder includes interventions to shift the biological clock, such as administration of melatonin in the evening and exposure to bright light in the morning.[169–171] While changes in sleep schedule can be achieved, the effects may not be dramatic, and patients tend to revert easily to a delayed schedule if circadian measures are not rigorously maintained. Some patients choose occupations or work schedules that are compatible with their delayed phase.

Other circadian disorders include *advanced sleep-wake phase disorder*, in which sleep begins in the early evening and terminates in the early morning.[16] When social or work schedules conflict with this schedule, treatment with bright light exposure in the early evenings can be instituted to delay sleep onset.[170,171] *Jet lag disorder* results from circadian misalignment due to travel across time zones with subsequent sleep disruption and daytime symptoms.[172] Management includes sleep scheduling, appropriately timed light therapy, and possible use of melatonin.[169,170] *Shift work disorder* is characterized by more than 1 month of excessive sleepiness during scheduled work time, and insomnia during scheduled sleep times in the context of nonconventional and/or rotating work schedules.[16] Management includes optimizing the sleep environment and sleep schedule, preshift napping, bright light exposure during night shifts, and avoidance of bright light during the return trip home in the morning. Evidence supports the use of melatonin and judicious use of hypnotics to promote sleep, and modafinil and caffeine to promote wakefulness during work.[170]

PARASOMNIAS

Parasomnias are complex movements, behaviors, or experiences happening during sleep, and can be divided into REM and non–REM-related parasomnias. Non–REM-related parasomnias are disorders of arousal and include confusional arousals, sleepwalking, sleep terrors, sleep-related eating disorder, and sexsomnia.[16] Typically, patients will have recurrent episodes of abnormal behaviors with incomplete awakening and limited memory of the events. The most common REM parasomnias are *REM sleep behavior disorder* (RBD) and nightmare disorder. RBD manifests as movements or vocalizations related to dream content. Behaviors can be violent, endangering both the patient and bed partner. RBD results from loss of normal REM atonia, which normally prevents dream enactment, and can be confirmed on PSG. RBD is associated with certain antidepressant medications and with α-synucleinopathies (e.g., Parkinson disease).[173] Nightmare disorder is characterized by recurrent highly unpleasant dreams that result in significant distress. Nightmare disorder should be differentiated from other causes of nightmares, such as nightmares secondary to posttraumatic stress disorder. Stereotyped behaviors or dystonic posturing suggest nocturnal seizures.[174]

Management of parasomnia starts with optimizing lifestyle and sleep hygiene and avoiding triggers such as sleep deprivation. Causative medications (e.g., some antidepressants) or substances (e.g., alcohol) should be discontinued if possible. Safety measures should be taken to avoid injury to the patient or their bed partner. Patients should be evaluated and treated for OSA, which can exacerbate parasomnias, presumably by increasing propensity for arousal. Clonazepam has been used with reasonable efficacy in the management of non-REM parasomnias[175] as well as RBD. Due to safety concerns with long-term use of clonazepam, especially in older individuals, melatonin is now the preferred treatment for RBD.[176] Second-line options include ramelteon, a melatonin receptor agonist.[177]

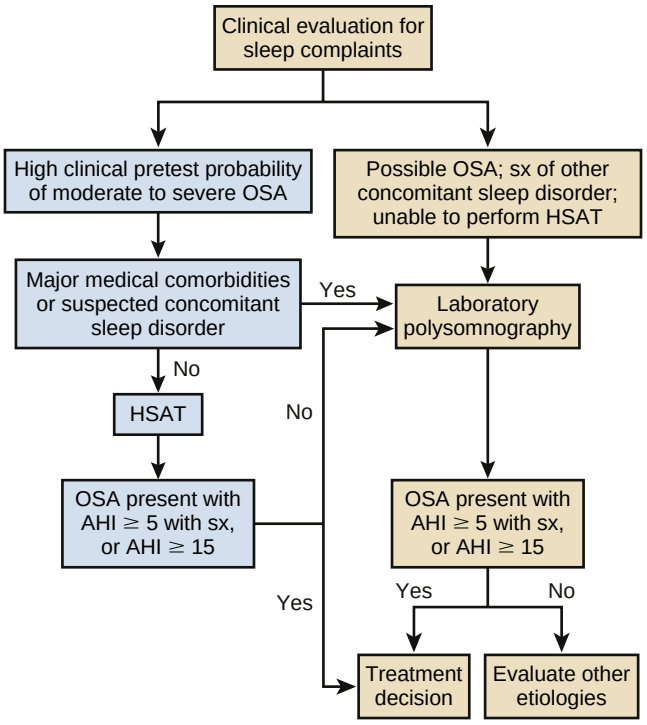


Figure 120.4 Schema illustrating an approach to the diagnosis of *obstructive sleep apnea* (OSA). An ambulatory pathway for patients with symptomatic moderate to severe OSA without other major comorbidities is shown in blue. Patients with a lower pretest probability of OSA or who are suspected of having another sleep disorder are recommended for evaluation in the laboratory-based pathway in orange. AHI, apnea-hypopnea index; HSAT, home sleep apnea testing; sx, symptoms.

hospitalized patients have acceptable technical success rates in patients with comorbidities[202,206] and satisfactory accuracy.[203,207,208] Results can be used to optimize management and initiate in-hospital positive airway pressure therapy as appropriate.[202,206] However, physiologic changes after the hospitalization may change the diagnosis.[209] Medical management should be optimized and the patient reevaluated, particularly when central sleep apnea is detected.[202,206]

OSA is found in 10–20% of surgical patients and up to 70% of those presenting for bariatric surgery.[19] OSA predisposes to perioperative complications,[210,211] including cardiovascular events.[212] OHS is associated with particularly high complication rates.[213] Life-threatening perioperative events are rare,[210] but potentially catastrophic and preventable. Hence, screening for SDB may allow appropriate precautions, interventions, and monitoring to reduce complications. Questionnaires (e.g., STOP-Bang) have been used as a screening method in this context and can predict increased complication rates, but specificity is low (i.e., high false-positive rates).[211] Serum bicarbonate measurement in addition to STOP-Bang may help identify patients with OHS at highest risk.[214] Overnight pulse oximetry is a relatively simple screening test and, when used for preoperative detection of OSA, was found to reduce perioperative hypoxemia but not complication rates, length of stay, intensive care unit transfers, or mortality.[215] The feasibility of full sleep testing preoperatively has not been well studied.[210] Hence, it is generally accepted that OSA and particularly OHS may increase perioperative risk and that screening should be performed prior to surgery. However, evidence is currently insufficient to guide screening and optimization of OSA and OHS in this context, notably regarding which patients are at greatest risk of complications and which interventions are effective[210] (see also Chapter 122).

PATHOPHYSIOLOGY OF CONSEQUENCES

NEUROCOGNITIVE SEQUELAE

A majority of apnea and hypopnea events terminate with an arousal (see Fig. 120.1). Thus, recurrent respiratory events and their associated arousals lead to sleep fragmentation and marked disruption of sleep continuity. Furthermore, OSA is also typically associated with a reduction in the duration of deeper, more "restorative" sleep, including Stage N3 (slow wave) and REM sleep, which contribute to excessive daytime sleepiness and other neurocognitive sequelae of OSA. Application of CPAP to treat OSA aims to restore sleep continuity and may be associated acutely with a rebound increase in N3 and REM sleep, which patients perceive as improved sleep quality.[216]

Although respiratory-related sleep fragmentation alone without oxygen desaturation can produce EDS, in studies of moderate to severe OSA, sleepiness and other neurocognitive sequelae correlate more closely with OSA-associated hypoxemia than with measures of sleep disruption.[22,141,217] Studies in mice that were exposed to intermittent hypoxia mimicking OSA showed that severe hypoxia can produce excessive sleepiness, which persists up to 6 months following return to normoxia.[218] Neuronal injury in these mice was identified in specific wake-promoting areas (monoaminergic neurons in the locus coeruleus, periaqueductal gray), with evidence that injury is mediated by nicotinamide adenine dinucleotide phosphate hydrogen oxidase–dependent oxidative mechanisms.[218,219] Intermittent hypoxia in mice also induces deficits in learning and memory, with the hippocampus being a particular site of neuronal injury.[220] Neuroimaging studies in OSA patients have demonstrated changes in the hippocampal region and in other areas subserving cognitive functions known to be impaired in OSA.[221,222] It is therefore likely the hypoxia-reoxygenation associated with human OSA may produce sleepiness and other neurocognitive changes through similar pathways to those identified in experimental animals. Intermittent hypoxia in mice has also been shown to induce arousals and significant changes in sleep architecture.[223] When animals were asleep, the 30-second intermittent hypoxia exposure produced an arousal response 100% of the time, concomitant with the nadir of hypoxia. REM sleep was nearly eliminated in these mice after intermittent hypoxia exposure when compared to nonhypoxic sleep fragmentation. Thus, these findings suggest that intermittent hypoxia exposure may have greater negative impacts on sleep architecture compared to nonhypoxic arousals. Debate continues concerning the relative roles of sleep fragmentation and hypoxic-mediated injury in producing OSA-related neurocognitive deficits.[224,225]

Excessive sleepiness in OSA patients may also be influenced by factors other than those directly related to OSA

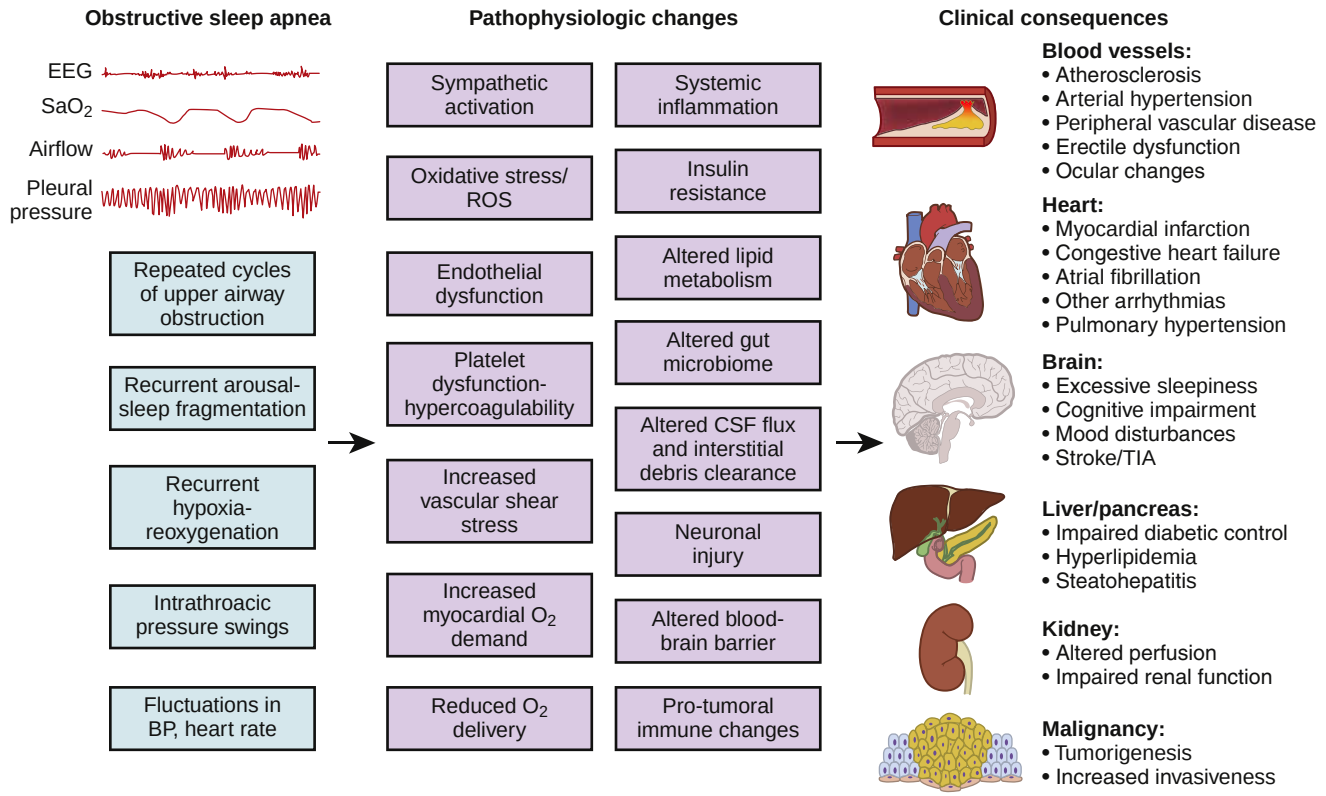


Figure 120.5 Schema depicting the pathophysiologic changes resulting from obstructive sleep apnea, which in turn lead to a diversity of clinical sequelae. See text for detailed discussion. BP, blood pressure; CSF, cerebrospinal fluid; EEG, electroencephalogram; ROS, reactive oxygen species; TIA, transient ischemic attack.

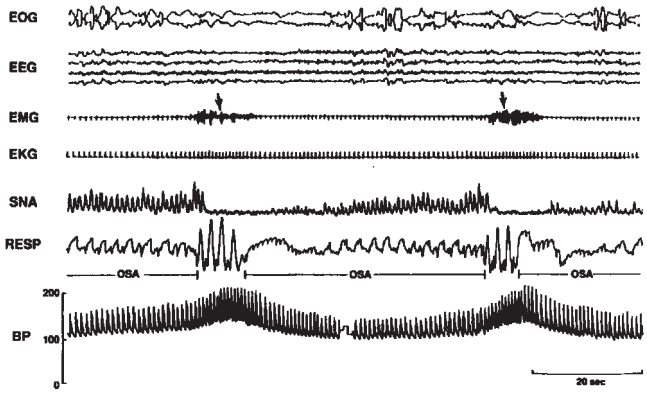


Figure 120.6 Sympathetic nerve activity during obstructive apneas. Tracing demonstrating increased sympathetic nerve activity (SNA) during obstructive apneas together with associated changes in blood pressure and heart rate. BP, blood pressure; EEG, electroencephalogram; EKG, electrocardiogram; EMG, electromyogram; EOG, electrooculogram; OSA, obstructive sleep apnea; RESP, respiration. (From Somers VK, Dyken ME, Clary MP, Abboud FM. Sympathetic neural mechanisms in obstructive sleep apnea. *J Clin Invest*. 1995;96[4]:1897–1904.)

itself. For example, sleep schedule, obesity per se, and depression may all contribute to symptoms of sleepiness in OSA patients.[226,227]

CARDIOMETABOLIC SEQUELAE

The intermittent hypoxia, negative intrathoracic pressure swings, and microarousals from obstructive apneas and hypopneas trigger a cascade of acute hemodynamic, autonomic, biochemical, inflammatory, and metabolic effects that can produce both acute and long-term changes in cardiovascular function[228–230] (Fig. 120.5). Autonomic tone is altered during apneas, with acute sympathetic-mediated increases in blood pressure and heart rate observed at airway reopening[231] (Fig. 120.6). In OSA, the persistent increase in sympathetic drive during sleep abolishes the physiologic blood pressure dipping that is important for cardiovascular health.[232,233] The increased sympathetic neural activity during apneas may persist into wakefulness, long after the immediate effects of apneas and hypopneas have subsided, contributing to sustained hypertension.[231] This ultimately leads to increased vascular resistance and vascular remodeling, contributing to the observed increase in blood pressure.[234] Blood vessel shear stress is also increased due to hypertension and hemodynamic surges. The negative intrathoracic pressures generated during obstructed inspiratory efforts increase left ventricular transmural pressure and, therefore, afterload, a stimulus for ventricular hypertrophy and an excessive load for a compromised ventricle.[229] OSA-associated hypoxia-reoxygenation has analogous biologic effects to ischemia-reperfusion, leading to generation of reactive oxygen species.[235] This oxidative stress activates nuclear transcription factors, including hypoxia inducible factor-1α and nuclear factor-κB, which activate a diverse number of proinflammatory pathways.[235,236] Inflammatory mediators, in turn, may lead to endothelial cell dysfunction,[237] promote atherogenesis,[238] and have antifibrinolytic/prothrombotic effects that could contribute to acute vascular events. These effects, in concert with increased sympathetic activity and increased insulin resistance, likely further contribute to the elevated cardiovascular risk associated with OSA.[239,240]

Both human and animal studies have demonstrated that intermittent hypoxia[241–246] and sleep fragmentation[239,247,248] are associated with abnormal glucose homeostasis, including increased insulin resistance and elevated glucose levels. A CPAP withdrawal study with recurrence of OSA was associated with dynamic increases in nocturnal glucose levels, cortisol, and free fatty acids, in parallel with respiratory obstructive events.[249] Over time, these disturbances may lead to the development of type 2 diabetes. Animal studies also indicate that intermittent hypoxia can adversely affect lipid metabolism, further contributing to the pro-atherogenic effects of OSA.[238] There is growing evidence, on the basis of these pathophysiologic mechanisms, that OSA has important clinical effects on cardiometabolic morbidity and mortality.

There are emerging studies suggesting that intermittent hypoxia resulting from OSA may protect the myocardium during ischemic periods by reducing infarct size, a concept referred to as ischemic preconditioning.[230,250–252] Two clinical studies showed lower troponin-I[253] and troponin-T levels[254] as markers of myocardial infarct size in patients with OSA and acute myocardial infarction. OSA has been shown to increase coronary collateral vessel development, and therefore an alternative source of blood flow in patients with total coronary occlusion.[255] In the setting of myocardial infarction, there are increased numbers of endothelial progenitor cells with heightened proliferative and angiogenic properties, indicating compensatory angiogenesis in patients with OSA compared to patients without OSA.[256] Thus, while intermittent hypoxia is known to be associated with adverse cardiovascular sequelae, recent literature also suggests that intermittent hypoxia may evoke a variety of adaptive cardioprotective pathways. Further research is therefore required to understand the mechanisms determining the balance of adaptive versus maladaptive effects of intermittent hypoxia.

There is tremendous heterogeneity between OSA patients in their risk for developing adverse neurocognitive and cardiometabolic sequelae. While genetic and environmental factors play an important role, alterations in the gut microbiome have also been shown to account for some of this phenotypic variation. Growing literature has identified the importance of the gut microbiome composition in obesity and metabolic disease.[257,258] In children with OSA, insulin resistance was associated with gut endotoxemia.[259] Sleep fragmentation in mice induced significant changes in the gut microbiome and metabolomic profile.[259] Similarly, alterations in gut microbiota have also been observed after intermittent hypoxia,[260,261] and some of these were irreversible after a period of normoxic recovery.[261] One animal study demonstrated that alterations in gut microbiota may have a causal role in contributing to hypertension in patients with OSA.[262] Future studies are needed to understand whether manipulation of gut flora plays a role in the management of hypertension in patients with OSA.

CONSEQUENCES/COMPLICATIONS OF OSA

NEUROBEHAVIORAL COMPLICATIONS OF OSA

Excessive Sleepiness and Motor Vehicle Operation

EDS is the most common symptom of OSA. It can have profound adverse effects on quality of life, social relationships, and professional safety and performance. Patients with untreated OSA and daytime sleepiness are at significantly increased risk for motor vehicle crashes. Meta-analyses[142,263] have identified a two- to threefold increase in risk of vehicular crashes among patients with untreated OSA (e.g., *odds ratio* [OR], 2.4; 95% *confidence interval* (CI), 1.2 to 4.9).[142] CPAP therapy was found to reduce the number of near-accidents and accidents in OSA patients in parallel with reduced subjective EDS.[264] Meta-analyses found that treatment with positive airway pressure for severe OSA decreased the risk ratio for motor vehicle crashes to 0.3 (95% CI, 0.2 to 0.4),[265,266] translating into a reduction of 65–78% in crash rates with OSA treatment.

There are important public safety and medicolegal implications of OSA for the practicing physician. Practice guidelines on OSA, sleepiness, and crash risk have recently been published.[143,267] Whereas the prediction of crash risk in individual OSA patients is imprecise, it is important to identify high-risk patients who have symptoms of excessive sleepiness while driving and have a history of a previous crash or near-miss due to sleepiness.[268] Such individuals should be warned of the dangers of driving prior to treatment, undergo diagnostic sleep testing within 1 month, and be promptly initiated on CPAP treatment following a positive diagnostic test.[143] Clinicians should also familiarize themselves thoroughly with legal requirements in their jurisdiction for reporting of OSA and the consequent driving restrictions.

One area of particular concern is the increased rate of motor vehicle crashes among commercial drivers.[267,269,270] Several studies have shown a high prevalence of OSA among commercial drivers.[271–273] OSA was found to increase accident rates specifically among commercial drivers who are nonadherent to CPAP therapy.[274] Screening for OSA is recommended as part of the general medical evaluation for commercial drivers.[269] However, such screening relies heavily on self-reporting of sleepiness and OSA symptoms by drivers, who are known to under-report due to concerns about work restrictions.[273] Drivers may be more likely to report symptoms if they can do so anonymously online.[275] However, an employer-mandated program of OSA screening and treatment can successfully reduce accidents and be cost-effective.[276] Several entities have proposed recommendations concerning OSA screening of commercial vehicle operators including rail workers, assessment of fitness for duty, and evaluation for return to work following OSA treatment.[267]

Fatigue

Rather than sleepiness, some patients with OSA will complain of fatigue, lack of energy, or tiredness.[144] This is more often found in women. Fatigue may be associated with greater dysfunction than EDS.[277,278] Hence, lack of EDS should not discount OSA as a possible underlying problem. Moreover, these symptoms have been found to improve with adherence to CPAP therapy.[279]

Mood Disturbances: Depression, Anxiety

Depressive symptoms are common in OSA patients and are more prevalent in women.[280] Although epidemiologic studies indicate that the presence of untreated OSA is a risk factor for developing depression,[281] the interaction between depression and OSA remains poorly understood.[280,282] Depression

may also worsen symptoms of sleepiness and fatigue in OSA.[227] A meta-analysis has found that OSA treatment with either CPAP or a mandibular advancement device resulted in improved depressive symptoms.[283] The prevalence of OSA among patients with clinical depression is not known,[280] but symptoms of OSA should be sought in all patients with depression, given the potential beneficial effects of OSA treatment. Conversely, depression may be a cause for residual sleepiness in treated OSA patients. Anxiety, which has not to date been extensively studied, also appears to interact with OSA. Treating OSA can help anxiety symptoms.[284]

Quality of Life

OSA can have a substantial negative impact on patients' overall quality of life. Disease-specific indices have been developed to assess the impact of OSA on quality of life, including the Functional Outcomes of Sleep Questionnaire,[285] Calgary Sleep Apnea Quality of Life Index,[286] and the Quebec Sleep Questionnaire.[287] Studies using these measures indicate that OSA-related impairment can be substantial and that OSA treatment can significantly improve quality of life,[288,289] particularly in women[290] and the elderly.[204]

Cognitive Impairment

OSA is associated with cognitive impairment.[222] OSA produces impairments in attention and vigilance, visuospatial construction abilities, verbal episodic and visuospatial memory, and subdomains of executive function.[291–293] Treatment of OSA can improve global cognitive function, attention/vigilance, verbal and visual memory, and executive function.[291,293] However, results have been inconsistent.[266] The multicenter trial, APPLES (Apnea Positive Pressure Long-term Efficacy Study), assessed domains of cognitive function in OSA after 2 and 6 months of effective versus sham CPAP treatment[294] and did not demonstrate sustained improvements in cognition. However, baseline function was high in study participants. It has become clear that individuals have different propensities for the cognitive effects of OSA, related to genetic factors, premorbid cognitive functioning, and comorbidities.[295] Patients with OSA and comorbid insomnia may have more marked cognitive impairment.[296] The elderly appear to be particularly vulnerable. CPAP treatment of OSA in the elderly may improve function in several cognitive domains over a period of a few months, particularly in severe OSA.[126,204,297]

OSA has also been associated with falls and gait disturbances,[298] which are affected by cognitive function.[299] EDS is associated with fall risk in older women.[300] Preliminary data suggest gait can improve with CPAP therapy,[279,301] though it remains unknown if risk of falls can be reduced by treating OSA in older individuals.

Neurodegenerative Disease and Dementia

OSA in the elderly is thought to be different from that in middle-aged individuals with respect to presentation, evolution, and outcomes.[128] Though older individuals are less prone to adverse OSA-related cardiovascular outcomes and mortality compared with middle-aged individuals,[302,303] OSA in the elderly has been associated with an increased risk of neurodegenerative processes. First, there is an association between OSA and Alzheimer disease.[304] Additionally, several, but not all,[305] prospective studies and a meta-analysis have found that older individuals with OSA, cognitively intact at baseline, are at increased risk for future cognitive impairment or dementia.[306,307] Large database studies have also found that those with OSA have an increased risk of Parkinson disease.[308,309] Moreover, OSA is associated with reduced cognitive function in Parkinson disease.[310,311] A number of mechanisms resulting from intermittent hypoxia and sleep fragmentation (see "Pathophysiology of Consequences" section and Chapters 117 and 118) have been implicated in the relationship between OSA and neurodegeneration, including changes in synaptic plasticity, small and large vessel disease, neuroinflammation, changes in brain structure and network function, as well as abnormal clearance of metabolic debris from the brain.[312,313] Blood and CSF biomarkers hold promise for future studies on this topic.[314] In summary, although OSA appears to increase the risk of neurocognitive decline, some individuals are likely more prone than others, although the characteristics conferring this susceptibility are currently unknown.

CPAP therapy has been shown to reduce the risk of developing mild cognitive impairment in older individuals in a cohort study.[307] Unfortunately, adherence to CPAP therapy in the elderly is reported to decline with age,[315] and may be even more challenging in individuals with cognitive or physical impairment. This may explain the lack of positive findings in some trials.[127] Nevertheless, CPAP has been successfully used in selected patients with Alzheimer[316] and Parkinson disease.[317,318] In Alzheimer disease, CPAP was found to improve sleep architecture and reduce daytime sleepiness with short-term use.[319] Sustained use appeared to benefit sleep and mood, and reduce cognitive decline.[320] In Parkinson disease, CPAP reduced sleepiness.[317] In a 12-month observational study, CPAP improved nonmotor symptoms of Parkinson disease, including sleep quality and anxiety, as well as cognition.[318] However, others did not demonstrate cognitive improvement with CPAP.[311] Observational data suggest that CPAP may also help stabilize gait and motor function in Parkinson disease over 12 months,[321] though this also requires further study. Hence, while CPAP therapy may be a challenge for those with neurodegenerative disorders, a trial of treatment is likely warranted given the potential benefits.

CARDIOMETABOLIC COMPLICATIONS

Hypertension

The evidence linking OSA to cardiovascular complications is strongest for hypertension. Experimental studies have shown that repeated airway obstruction during sleep in dogs induces hypertension during wakefulness[322] and that intermittent hypoxia produces hypertension in rodents.[323] Cross-sectional studies demonstrate an independent association of OSA with hypertension after controlling for confounders.[324,325] Several studies have reported a high prevalence of OSA (50–60%) in patients with refractory hypertension, with OSA representing the most common cause of secondary hypertension in these patients.[326] Data from the Wisconsin Sleep Cohort showed dose-response relationships over 4 to 8 years of follow-up between OSA severity and odds of developing incident hypertension[327] and nondipping in nocturnal systolic blood pressure,[328] although findings from other longitudinal cohort studies have been discrepant.[329,330]

The strong weight of evidence from RCTs is that positive airway pressure treatment improves hypertension. Several meta-analyses have been published.[266,331–335] In the most recent,[335] positive airway pressure was associated with reductions of systolic and diastolic blood pressure compared to control (mean: −2.5 mm Hg systolic, −2.5 mm Hg diastolic). Although the observed reductions in blood pressure with CPAP are relatively small, they have significant implications for primary cardiovascular prevention at the population level.[336] The observed reductions may have been diminished by inclusion of normotensive/treated participants[337] and/or milder OSA. Indeed, patients younger than 60 years with uncontrolled baseline pressure and more severe OSA/oxygen desaturation have been found to have the greatest reductions in blood pressure on CPAP[334,335,338] (e.g., −7.1 mm Hg systolic and −4.3 mm Hg diastolic for uncontrolled hypertensives in one analysis).[338] There is also a significant positive correlation between the duration of CPAP use and decrease in blood pressure.[339–342]

Despite reduced efficacy of treatment, mandibular advancement devices have shown similar reductions in blood pressure compared to CPAP, possibly due to greater adherence.[343] Patients who use CPAP and also lose weight may experience greater reductions in blood pressure compared to CPAP or weight loss alone.[344]

Arrhythmias

OSA is associated with cardiac arrhythmias.[345,346] Bradyarrhythmias, including sinus pauses and atrioventricular block, are more common in severe OSA than in the general population. Although some data suggest that CPAP may improve bradyarrhythmias, RCT data are lacking.[345] Studies linking OSA to ventricular arrhythmias have produced conflicting results.[345] In one recent prospective cohort study, 3 months of CPAP was associated with a decrease in extrasystoles, atrial fibrillation, and nonsustained ventricular tachycardia.[347] There is growing evidence showing strong associations between OSA and atrial fibrillation.[345,346,348] Atrial fibrillation is more common in individuals with severe OSA than in those without OSA.[345,349] Untreated OSA is associated with a higher rate of recurrent atrial fibrillation after either cardioversion[350–352] or catheter ablation.[352,353] Among patients with atrial fibrillation, Holter monitoring showed reduced atrial and ventricular ectopy after 3 months of CPAP.[354] In a meta-analysis of seven prospective cohort studies including over 1000 patients, CPAP was associated with a significant reduction in recurrence of atrial fibrillation (RR, 0.6; 95% CI, 0.5 to 0.7).[355] In another meta-analysis, CPAP-treated patients had a lower risk (25%) of recurrent atrial fibrillation after catheter ablation compared to non-CPAP-treated (42%) groups.[356] CPAP also reduced the left atrial diameter and increased the left ventricular ejection fraction.[356] Although one randomized trial did not find any significant reduction with CPAP in recurrence of atrial fibrillation after electrical cardioversion in OSA,[357] this study was limited by small sample size (25 participants) and limited evaluation of atrial fibrillation.[358] Whereas larger RCTs are needed to confirm an effect of OSA treatment on control of atrial fibrillation, evaluation for OSA and, if present, institution of treatment should be considered in patients with atrial fibrillation (see also Chapter 119).

Myocardial Infarction

OSA is associated with ischemic heart disease. In the Sleep Heart Health study, there was a modest association of OSA with coronary heart disease (adjusted OR, 1.3; 95% CI, 1.0 to 1.6).[359] In a meta-analysis of four cohort studies, OSA was significantly associated with an increased risk of ischemic heart disease in men (OR, 1.9; 95% CI, 1.1 to 3.5),[360] whereas no significant association was observed in the one study of women.[303] However, OSA is prevalent among patients who have had an acute myocardial infarction[361] and, when present, OSA is associated with worse cardiovascular outcomes.[362–364] Patients with OSA also have a greater propensity to have myocardial infarction and sudden cardiac death between midnight and 6 AM,[365,366] indicating a diurnal variation in myocardial infarction in patients with OSA. Given that REM sleep is associated with increased myocardial demand and sympathetic activity, it follows that REM sleep–specific severe OSA (REM AHI >30, non-REM AHI <5) has been reported to be associated with worse cardiovascular outcomes in patients with prevalent cardiovascular disease when compared to individuals with no OSA.[367] In observational studies on OSA patients, compliance with OSA treatment has been associated with significantly reduced cardiovascular morbidity and mortality compared to refusal of treatment.[199,266,368,369] However, refusal of CPAP may be a marker of poor health behavior, which could also adversely affect outcomes.

More recently, prospective RCTs have been conducted to assess the effects of OSA treatment on cardiovascular outcomes.[266,370] The MOSAIC trial evaluated the effects of CPAP compared to control on reduction of a surrogate cardiovascular risk score in OSA and found that calculated risk was not significantly reduced.[371] However, CPAP significantly improved endothelial function in a subgroup of MOSAIC subjects,[372] and a 2-year follow-up of a subset of patients showed a small but significant reduction in overall vascular events with CPAP.[373] A Spanish collaborative group trial showed no significant difference over 7 years in incident cardiovascular events and hypertension in CPAP-treated compared to control groups.[339] However, there was a significant reduction in events for patients compliant with CPAP for at least 4 hours a night (incidence density ratio = 0.7 [95% CI, 0.5 to 0.9] compared with control). In the Sleep Apnea Cardiovascular Endpoints trial, 2717 patients with a history of coronary artery disease or cerebrovascular disease received either CPAP or usual care with a mean follow-up of 3.7 years.[374] CPAP did not show a reduction in a composite end point including death from a cardiovascular cause, myocardial infarction, stroke, hospitalization due to unstable angina, heart failure, or transient ischemic attack.[374] However, a major limitation to the study was the poor CPAP adherence at only 3.3 hours per night, which may have been an inadequate dose to prevent cardiovascular events.[375] A propensity-matched analysis showed a trend to benefit on the primary outcome in CPAP-adherent (>4 hours/night) participants.[374] The RICCADSA trial addressed whether CPAP reduced recurrent cardiovascular events in revascularized patients with coronary artery disease who were not sleepy but had OSA.[376] Although the study was negative, a subgroup analysis found significant risk reduction in patients who used CPAP more than 4 hours per night.[376] A meta-analysis of the latter three trials and a secondary prevention study in patients with OSA

and stroke[377] concluded that CPAP use was not associated with a reduced risk of major adverse cardiac events overall over 4 years, except in patients who used CPAP for more than 4 hours per night.[378] However, the recent ISAAC trial, which assessed patients who were admitted to hospital with acute coronary syndrome who were nonsleepy, did not show improvements in the composite cardiovascular end point with CPAP[379] even in CPAP-compliant subgroups. Potential reasons for the marked discrepancies between observational studies showing strong benefit of CPAP treatment[266] and these RCTs include, in addition to low CPAP compliance, the exclusion of very sleepy and severely hypoxemic patients, even though such patients are the most likely to be compliant in clinical practice.[370] In addition, as discussed earlier, OSA may provide a protective effect through ischemic preconditioning in some patients while leading to deleterious effects in others.[230,253,254] Further RCTs are needed to evaluate the effects of CPAP treatment with optimized compliance on cardiovascular outcomes in well-defined groups of both sleepy and nonsleepy patients with severe OSA.

Cerebrovascular Events

Cross-sectional and longitudinal epidemiologic studies show that OSA is associated with stroke,[380–382] with a recent meta-analysis showing a twofold increased risk of incident stroke.[383] Thus, OSA predisposes to stroke, though stroke may also, in turn, produce or worsen sleep-disordered breathing. However, studies suggest that in many cases OSA preceded the stroke.[384,385] Overall, OSA is highly prevalent among those with stroke and transient ischemic attacks, with a recent meta-analysis reporting a prevalence of 63% (95% CI, 58–68%) for AHI greater than 10 (data from 24 studies).[385] The presence of OSA after stroke appears to confer a worse prognosis for recurrent stroke and poststroke mortality.[386] Treatment of OSA with CPAP in stroke patients may be challenging and, whereas several studies suggested that OSA treatment may improve poststroke functional outcomes, the impact of treatment on stroke recurrence and mortality remain inconclusive.[386,387] In the Sleep Apnea Cardiovascular Endpoints trial discussed earlier, no difference in stroke incidence was noted between the CPAP and usual care group.[374] However, in the propensity-matched analysis including CPAP-adherent patients, there was a reduced cerebrovascular event rate with CPAP (hazard ratio, 0.5; 95% CI, 0.3 to 0.9; $P = 0.02$). A large trial of CPAP for stroke prevention (The Sleep for Stroke Management and Recovery Trial, NCT03812653) is currently underway[388] (see also Chapter 119).

Congestive Heart Failure

OSA was found to be associated with *congestive heart failure* (CHF) in the Sleep Heart Health study (OR of 2.4 for the highest category of OSA severity) in the initial cross-sectional analysis[359] and with development of new heart failure in longitudinal follow-up.[303] OSA has been identified in 11–53% of patients with stable chronic CHF (with central sleep apnea–Cheyne-Stokes respiration also being present in 11–35%, yielding an overall apnea prevalence of approximately 50% in CHF patients).[229,389] OSA may worsen left ventricular function. Experimentally induced severe OSA in a dog model produced changes in left ventricular dimensions and reduced systolic function after 8 weeks.[390] As of 2017, the American College of Cardiology/American Heart Association recommends screening for OSA in patients with New York Heart Association class II to IV heart failure.[391] However, RCTs are required to demonstrate long-term improvement in both cardiac function and outcomes with OSA treatment in patients with CHF. The ongoing ADVENT-HF trial (NCT01128816) will evaluate the impact of adaptive servoventilation on CHF patients with OSA.

Pulmonary Hypertension

The reported prevalence of pulmonary hypertension in OSA varies considerably between studies, ranging from 15–75%,[392–394] although pooled data from several studies yielded a 10% prevalence (mean pulmonary artery pressure > 25 mm Hg at cardiac catheterization).[389] Most OSA patients without major comorbidities have normal pulmonary artery pressures; pulmonary hypertension, when present, is mild.[389,394] More severe pulmonary hypertension, in some instances leading to right ventricular dysfunction and right heart failure, may develop in patients with underlying lung function abnormalities (COPD, obesity restriction, neuromuscular disease), many of whom will present with daytime hypoxemia and hypercapnia.[389,392,394–397] Early studies in patients with severe OSA showed that pulmonary artery pressure can improve substantially following tracheostomy but may not normalize.[398,399] Limited studies evaluating the effects of CPAP on pulmonary hypertension indicate that both pulmonary pressures and indices of right ventricular function may improve with CPAP therapy.[389,392,394,400,401] However, in the recent Pickwick study, improvements in pulmonary artery pressure and interventricular septal thickness were seen after 2 months treatment in OHS patients treated with bilevel positive airway pressure but not CPAP.[402] Long-term effects have not yet been evaluated.

Renal Perfusion/Dysfunction

Both OSA and central sleep apnea are prevalent in patients with chronic kidney disease[403,404] and are associated with a greater risk of cardiovascular disease and mortality.[405,406] OSA has been shown to worsen kidney function via mechanisms that include OSA-induced elevations in sympathetic activity and blood pressure.[407,408] Some studies suggest that chronic kidney disease itself may worsen OSA through mechanisms of hypervolemia and uremia-induced myopathy.[409] Early observations found that nocturnal hemodialysis in patients with chronic renal failure improved OSA.[410] In addition, treatment of OSA with CPAP has been shown to improve renal hemodynamics.[411,412] In the only RCT that has examined kidney function, the Sleep Apnea Cardiovascular Endpoints trial found no difference in the rate of decline in kidney function in the CPAP versus control group.[374] Further RCTs that are adequately powered to evaluate kidney function are needed to determine if CPAP can slow the progression of chronic kidney disease.

Metabolic Disturbances: Insulin Resistance, Dyslipidemia

In addition to compelling evidence that OSA alters metabolic function, OSA is strongly associated with glucose dysregulation, including prediabetes and type 2 diabetes.[413]

The prevalence of OSA among patients with type 2 diabetes is estimated to be approximately 60–85%,[413] and prospective cohort studies have shown that OSA is associated with incident type 2 diabetes.[414,415] However, questions remain about the relationship between OSA and metabolic dysfunction after RCTs with CPAP have shown mixed results.[416–423] Chronicity of the underlying metabolic disturbance (i.e., prediabetes versus type 2 diabetes),[424] varying use of antidiabetic medications, degree of obesity, presence/absence of excessive daytime sleepiness,[425] adherence to CPAP therapy,[420,423] and inconsistency in the metabolic outcome being measured (i.e., fasting glucose, hemoglobin A1c, 24-hour glucose, insulin sensitivity) may all contribute to the heterogeneity in RCT results.[413,420] Whereas it is still not clear whether CPAP improves glycemic outcomes, there should be a high level of clinical suspicion for OSA in patients with type 2 diabetes, and treatment of OSA in such patients may have a host of beneficial effects beyond improvement in glucose control.

A growing body of literature also supports an association between OSA and abnormal lipid metabolism. Intermittent hypoxia leads to hyperlipidemia and up-regulation of genes involved in lipid synthesis.[426,427] Decreases in triglycerides and high-density lipoprotein in association with OSA have been demonstrated in a number of clinical studies,[428–430] while others have shown no association between OSA and lipid profiles.[431,432] A meta-analysis that included over 18,000 patients demonstrated that OSA was associated with elevated triglycerides and total cholesterol concentrations and lower high-density lipoprotein.[433] However, in a meta-analysis of six RCTs examining the impact of CPAP on lipid profiles, reductions in total cholesterol were observed, without any changes in triglyceride, low-density, or high-density lipoprotein profiles.[434] Given the few RCTs done to date, with limitations of small sample sizes and variable adherence rates to CPAP, further studies are required to evaluate the relationship between OSA and dyslipidemia.

Hepatic Sequelae/Steatohepatitis

Emerging studies have shown that OSA is associated with nonalcoholic fatty liver disease,[435] even in nonobese individuals and children. Nonalcoholic fatty liver disease is part of the group of conditions called metabolic syndrome, and glucose metabolism and lipid abnormalities are key contributors in its development. Early animal models of intermittent hypoxia showed that genes of lipid biosynthesis in the liver were up-regulated after exposure to chronic intermittent hypoxia.[426] CPAP trials examining liver fibrosis as an outcome of treatment have been negative to date.[436,437]

Mortality

In keeping with the links between OSA and cardiometabolic dysfunction, OSA has been associated with increased mortality in large prospective cohort studies. The signal is strongest for severe OSA when compared with non-OSA cohort participants. Most of the increased mortality is cardiovascular and is seen largely in individuals with severe OSA, with an increase in mortality risk of 1.5- to 5-fold over follow-up periods of 8 to 20 years, compared with non-OSA cohort participants.[302,438–440] More recent data from 9 years of follow-up of Sleep Heart Health participants showed an increased mortality risk of 1.4 among patients with severe REM-isolated OSA.[367]

OTHER COMPLICATIONS

There is increasing evidence that OSA may interact with other medical conditions in addition to those discussed earlier.

A discussion of links between OSA and ocular disease (nonarteritic ischemic optic neuropathy, glaucoma, floppy eyelid syndrome, and other conditions), erectile dysfunction, and cancer incidence and mortality is provided at ExpertConsult.com.

DISEASE MANAGEMENT STRATEGIES

This chapter focuses on clinical and diagnostic aspects of OSA; OSA treatment is covered in Chapter 122. Clinical practice requires an integrated approach to OSA diagnosis and management to improve clinical outcomes. Given the high prevalence of OSA and the high costs and limited access in many countries to laboratory PSG,[195] alternative strategies to conventional PSG-based diagnosis and titration in highly specialized centers[476] are needed for management of OSA.[198,477,478] An initial study by Mulgrew et al.[479] demonstrated that ambulatory-based diagnosis of severe OSA (see Fig. 120.4) followed by titration using *automatic positive airway pressure* (APAP) and then treatment with fixed CPAP yielded equivalent clinical outcomes at 3 months compared with a conventional in-laboratory diagnostic and manual titration approach. A series of subsequent publications supported these findings, with later studies also including more moderate OSA.[197,480–483]

All of these studies, however, were conducted in specialty sleep centers and involved traditional interactions between patients and specialized sleep physicians. More recently, several groups have evaluated either specialist nurse–led or family physician/community nurse–led ambulatory management of moderate to severe OSA and compared outcomes with traditional PSG- and specialist physician–based management.[196,198] Improvements in sleepiness and other symptoms and CPAP compliance were in general similar for either the nurse-led[198,484] or family physician–led[198,485] strategies compared with specialist- and laboratory-based strategies. Telemedicine approaches may be complementary and provide improved access to care.[486] However, these studies have largely focused on symptomatic OSA patients with few comorbidities. Future studies will need to identify optimal approaches for matching patient needs with care providers, integrating broadly accessible community-based management with specialty center–based management for complex patients.

Recommendations for treatment of OHS have been provided by the American Thoracic Society.[19] For stable ambulatory OHS patients with severe OSA, CPAP therapy has been shown to be as effective as noninvasive bilevel ventilation for first-line treatment in terms of resolution of hypercapnia, need for oxygen supplementation, improvement in sleepiness and quality of life, and days in hospital.[19,487] However, those who are hospitalized for acute hypercapnic respiratory failure, those without significant OSA, as well as those who do not respond to CPAP should be managed with noninvasive ventilation[19] (see also Chapter 122).

OSA and Ocular Disease

OSA has been linked to a number of ocular conditions, including nonarteritic ischemic optic neuropathy, glaucoma, central retinal vein occlusion, central serous retinopathy, and floppy eyelid syndrome.[441,442] The hemodynamic sequelae, intermittent hypoxia, and sympathetic activation associated with OSA (see "Pathophysiology of Consequences") have been proposed to underlie the putative effects of OSA on ocular health. However, it remains unclear whether there is a direct causal effect of OSA in relation to these conditions. Nonarteritic ischemic optic neuropathy is the most common optic neuropathy in the population, typically presenting with sudden unilateral visual loss and for which there is no known treatment. Prospective studies have reported the presence of OSA in 55–89% of affected patients.[441,442] In one recent study, OSA patients who were adherent to CPAP treatment had a reduced risk of progression to involvement of the second eye.[443] However, larger, randomized trials are required to more clearly evaluate the role of OSA in this condition.

Numerous studies have evaluated potential links between OSA and glaucoma, which is the second leading cause of blindness worldwide.[441,442] OSA has been hypothesized to contribute to the optic nerve head damage and visual field impairment that characterize glaucoma either through ischemia-reperfusion and oxidative stress injury or by changes in intraocular and ocular perfusion pressure profiles.[441,442] Several meta-analyses have shown an increased risk of 1.4- to 2.5-fold for OSA among patients with open-angle or normal-pressure glaucoma. However, many of the studies included did not adjust for potential confounding effects of comorbidities known to increase glaucoma risk.[441,442] Three more recent large cohort studies with better characterization of participants did not demonstrate a significant association between OSA and glaucoma.[441] However, one 5-year prospective study of 1012 OSA patients showed a 1.7-fold increase in risk for development of incident glaucoma compared with controls.[444] The effect of CPAP treatment on the progression of glaucoma has not been well studied.[441] OSA may be associated with a reduction in the normal nocturnal increase in intraocular pressure and may be associated with increased diurnal intraocular pressure, though findings vary.[441] CPAP treatment can restore a normal nocturnal pattern,[445] but there are conflicting reports with respect to diurnal intraocular pressure.[441,442] Thus, the relationship between OSA and glaucoma is not yet firmly established, and there is no basis for recommending routine screening for OSA in patients diagnosed with glaucoma. The effect of OSA treatment with CPAP on outcomes in glaucoma patients requires further study; patients with glaucoma initiated on CPAP should have regular ophthalmologic follow-up.

Floppy eyelid syndrome (FES) is characterized by increased eyelid laxity, ptosis, tendency to easy lid eversion, and associated conjunctivitis and other corneal changes.[442,446,447] FES may be unilateral favoring the sleeping side or bilateral in 40%.[446] OSA has consistently been reported to be highly prevalent (85–90%) among patients with FES[446,447] and has been hypothesized to contribute to the pathogenesis of FES. Histopathologic studies of tarsal tissue demonstrate decreased elastic fiber content and increased matrix metalloproteinase 7 and 9 expression.[442,446] Matrix metalloproteinases are up-regulated in response to intermittent hypoxemia, and increased circulating matrix metalloproteinase 9 has been identified in both animal models and human OSA.[448] Furthermore, case reports and nonrandomized case series have reported improvement in FES manifestations following CPAP and, in one study surgical, treatment of OSA.[446,447] Whereas CPAP may also be associated with increased ocular symptoms in some FES patients, OSA treatment is currently recommended as a mainstay approach in FES management prior to considering ophthalmic surgical intervention.[446,447]

Erectile Dysfunction

OSA may be associated with erectile dysfunction,[449,450] which has been linked to nitric oxide and nicotinamide adenine dinucleotide phosphate hydrogen–related pathways in animal models[451,452] and endothelial dysfunction in humans[4,49] CPAP treatment of OSA has been shown to improve erectile function and sexual satisfaction,[453–455] and may provide additive benefits to exercise, lifestyle modification,[456] and pharmacotherapy.[453–455,457]

OSA and Cancer

There is growing evidence for a link between OSA and cancer incidence and mortality.[458–460] The Wisconsin Cohort investigators reported an increase in cancer-associated mortality with increasing OSA severity, with an adjusted OR of 4.8 for severe OSA (AHI >30) and an even stronger effect in relation to severity of OSA-related hypoxemia.[461] A Spanish cohort study also reported increased cancer-associated mortality associated with increasing severity of OSA-related hypoxemia, particularly in patients younger than 65 years.[462] However, a more recent study in 5.6 million members of a U.S. nationwide employee health database did not identify an increase in OSA-related cancer mortality.[463] The differences in findings may be related to the patient populations studied, methods used for OSA diagnosis, or other factors; further studies are required in this area.

Studies evaluating incident risk for specific cancers in relation to OSA have shown varying results. A meta-analysis of five studies evaluating the risk of incident cancer in 34,402 patients with OSA found a significant risk ratio of 1.4 for any incident cancer in OSA compared with controls, even after adjustment for traditional cancer risk factors.[460] The nationwide health database study cited earlier showed significant increases in adjusted risk for kidney and pancreas cancer and melanoma but not other cancers in OSA patients.[463] Another study including over 34,848 OSA patients showed significant increased risk for incidence of any cancer and for kidney, breast, and uterine cancers and melanoma compared to patients without OSA.[464] Results for breast[463–466] and lung[464,467–469] cancer have been conflicting between studies. The heterogeneity in findings likely reflects methodologic differences with respect to the patient populations studied, diagnostic strategies for both cancer and OSA, as well as variable accounting for confounders. Nonetheless, links between OSA and melanoma appear quite robust across studies, with evidence for increased incidence of melanoma as well as increased aggressivity of tumor markers and clinical behavior in relation to OSA.[470,471]

Mechanistic studies have identified several pathways by which OSA may promote tumorigenesis and cancer progression.[458,459,472,473] Intermittent hypoxia promotes tumor growth, invasiveness, and metastasis in experimental animals,[472] which, as illustrated in Figure 120.5, is related to oxidative stress, free radical generation, and inflammatory changes promoting DNA damage and tumorigenesis, and activation of hypoxia-inducible factor-1α and other transcription factors with diverse cellular effects, including production of angiogenic factors[474] and proangiogenic exosomes,[475] which promote tumor vascularization and growth.[458,473] Altered function of tumor-associated macrophages to a pro-tumoral phenotype has been shown in response to both intermittent hypoxia and sleep fragmentation.[458,473] Further discussion on the mechanisms by which sleep fragmentation impacts cancer biology is provided in Chapter 118. Further research is required to determine whether the association exists and, if so, whether treatment of OSA will improve cancer outcomes in specific cancer subtypes.

Key Points

- *Obstructive sleep apnea* (OSA) is a frequent health problem in the general population, estimated to affect 14% of men and 5% of women, with the risk increasing further in women after menopause.
- Pathogenic factors contributing to OSA may differ between individuals, and include reduced airway dimensions, sleep-associated decrements in upper airway muscle activity and protective reflexes, changes in upper airway tissue characteristics and neuromuscular function, nocturnal fluid shift, altered microbiome and altered chemosensitivity, and arousal responsiveness.
- Diagnosis of OSA syndrome rests on both clinical history and a diagnostic sleep recording objectively documenting the presence of obstructive events during sleep.
- Simplified, portable sleep recordings perform well for the diagnosis of moderate to severe OSA in patients without major comorbidities, improving access to diagnosis.
- OSA is associated with daytime sleepiness and increased motor vehicle accidents and may adversely affect cognitive function, mood, and quality of life.
- High-level evidence indicates that treatment of OSA improves daytime sleepiness and quality of life. Evidence also indicates that OSA treatment reduces motor vehicle accidents and may be associated with improved mood and cognitive function.
- OSA is linked to multiple other morbidities including hypertension, arrhythmias, vascular ischemic events, congestive heart failure, pulmonary hypertension, renal dysfunction, metabolic dysfunction (insulin resistance and dyslipidemia), steatohepatitis, cancer incidence and progression, and increased mortality.
- OSA patients compliant with CPAP therapy experience significant improvements in cardiovascular and metabolic outcomes, as shown in observational studies. Randomized controlled trials have thus far yielded less-compelling results. This may, in part, be related to limited CPAP adherence in these trials and the exclusion of severely somnolent and hypoxemic patients.
- Obesity-hypoventilation syndrome develops in a minority of OSA patients, presenting with awake hypercapnia, often with daytime sleepiness, pulmonary hypertension, right heart failure, and may present with acute hypercapnic respiratory failure. Full polysomnography with CO_2 monitoring is the recommended diagnostic test.
- For stable patients with obesity-hypoventilation syndrome and severe OSA, CPAP therapy is shown to be as effective as noninvasive bilevel ventilation in improving clinical outcomes; however, bilevel ventilation is required for management of acute respiratory failure.

Key Readings

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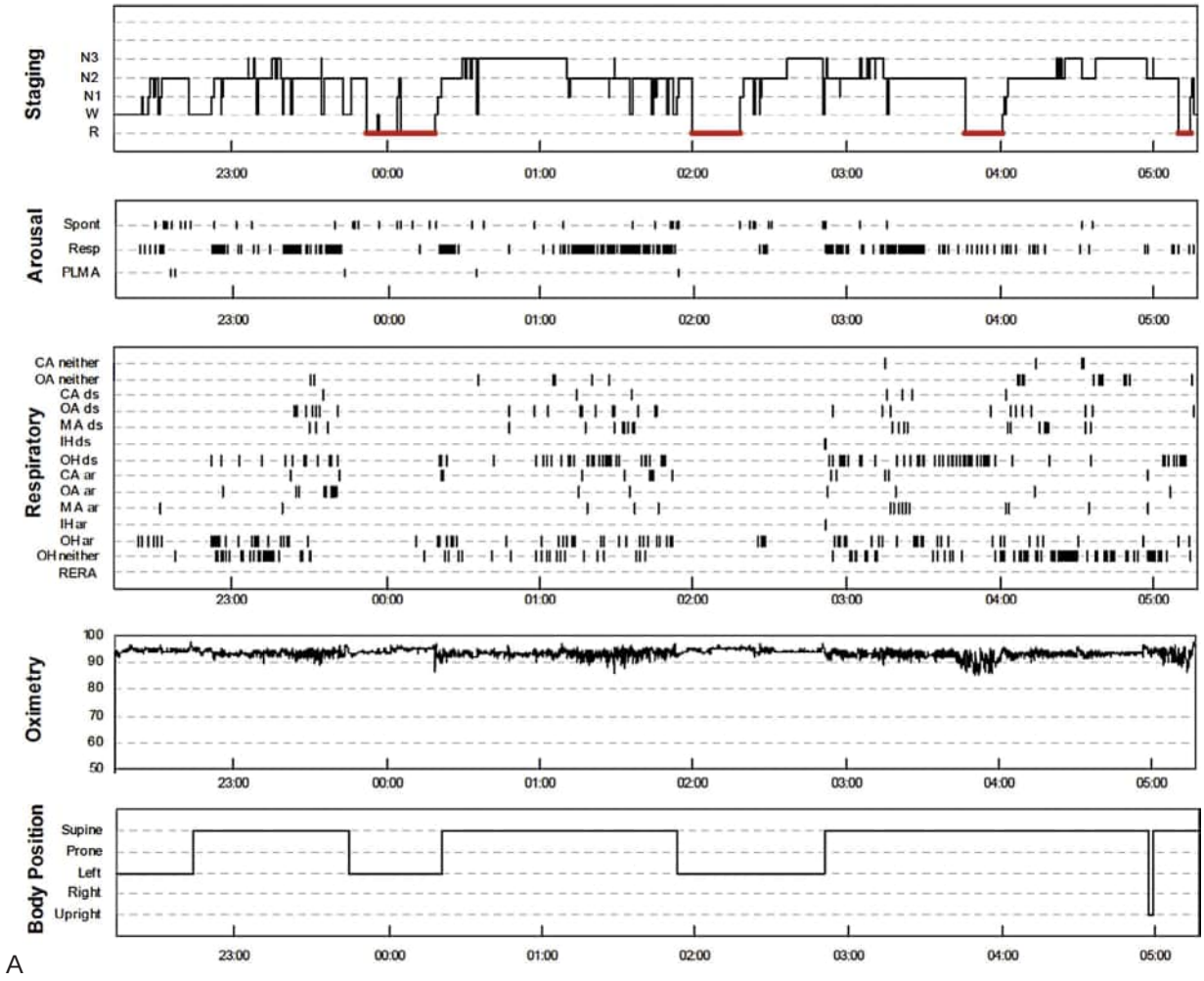
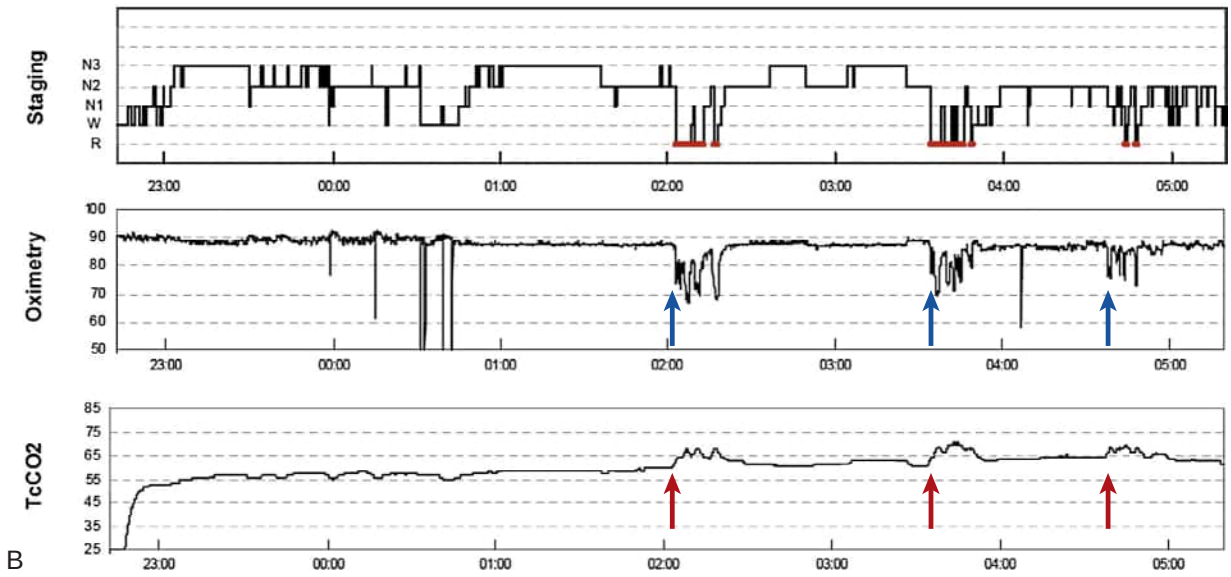
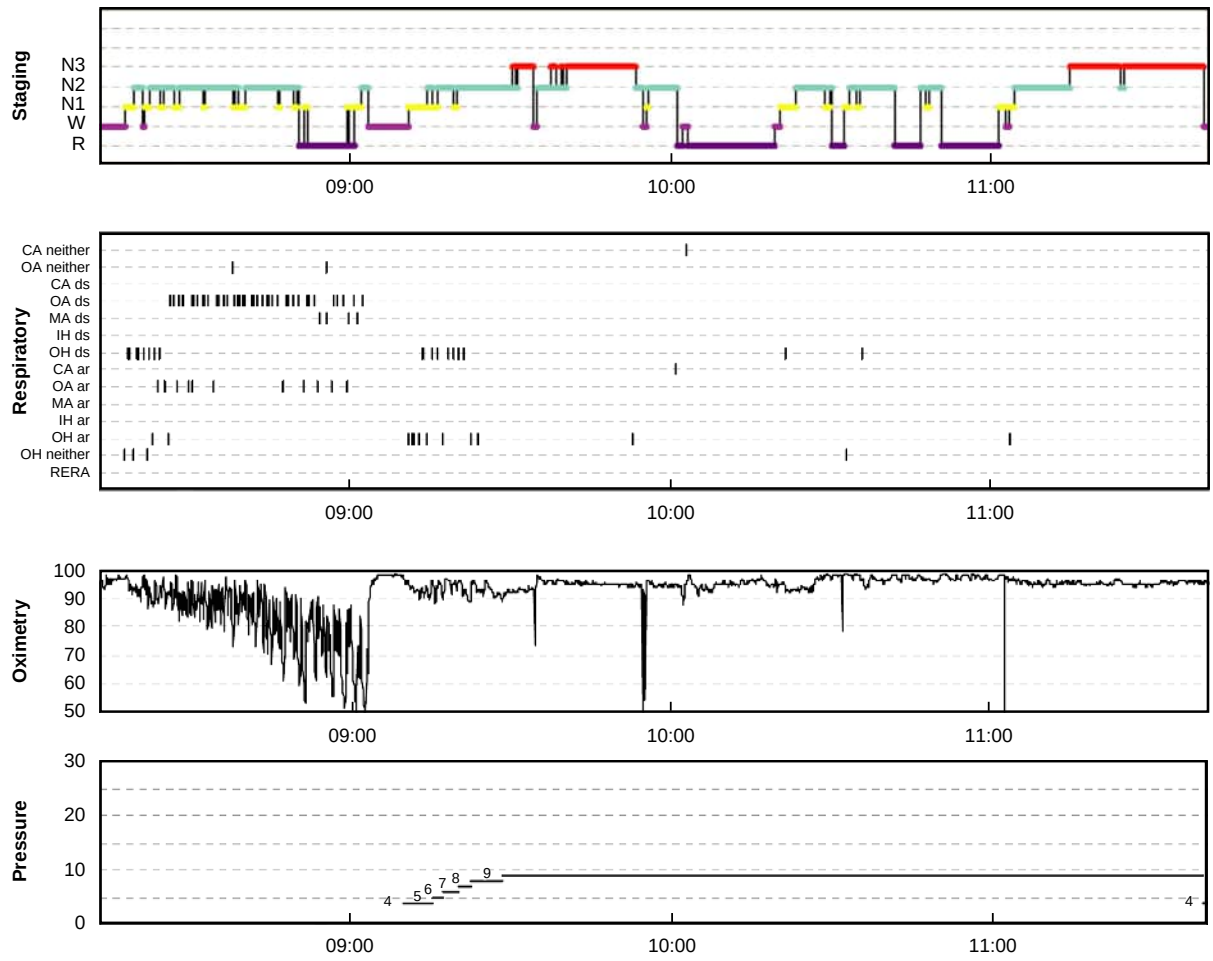


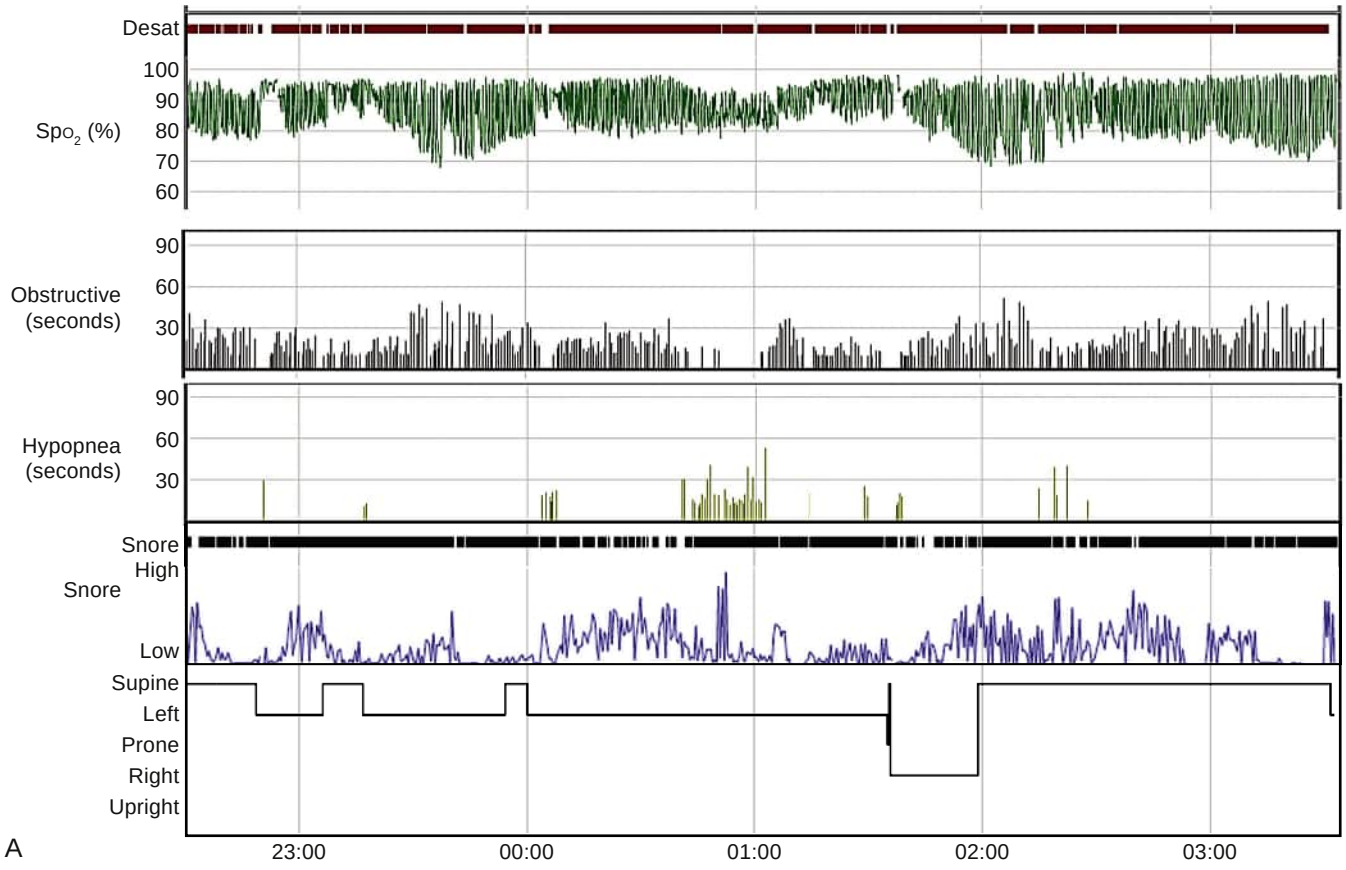


eFigure 120.1 Composite hypnograms generated by sleep analysis software after manual scoring of sleep-wake stages and respiratory events. (A) A typical report from a patient with *obstructive sleep apnea* (OSA). In this patient, apneas and hypopneas happen predominantly when the patient is sleeping supine; O_2 desaturation is more marked for events in supine *rapid eye movement* (REM) sleep (stage *R*; *red lines*) than in stages N (non-REM), which is often the case. (B) Sleep-associated hypoventilation, with a progressive rise in transcutaneous CO_2 ($TcCO_2$) over the night from an initial value of 54 mm Hg to a peak of 72 mm Hg, without apneas or hypopneas. There is worsening of hypoventilation during periods of stage R (REM) sleep when there are larger increases in CO_2 *(red arrows)* and falls in arterial So_2 *(blue arrows)*.

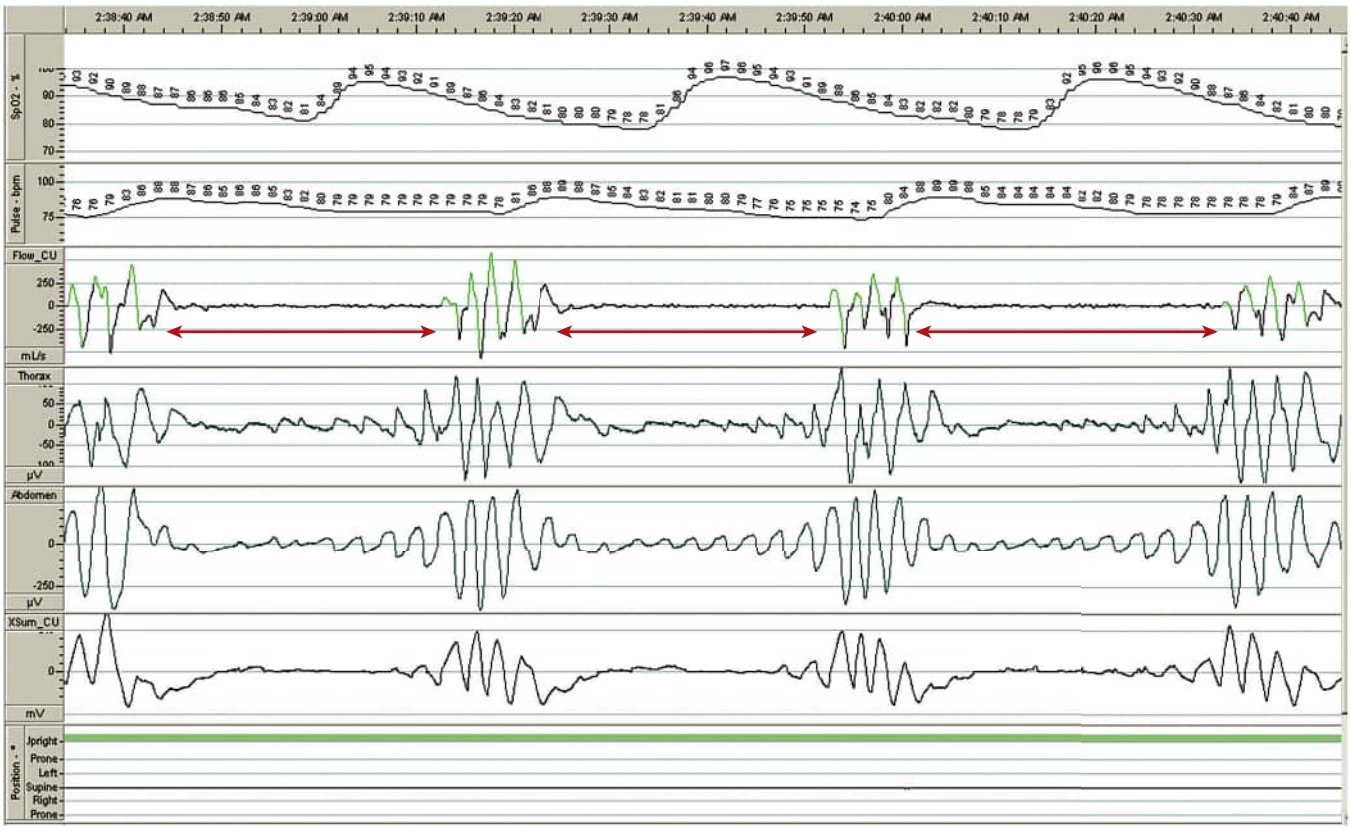


C

eFigure 120.1 cont'd (C) A composite hypnogram for a split diagnostic and therapeutic polysomnogram. This study was performed during the daytime in a patient with marked hypersomnolence. The initial diagnostic segment of the recording demonstrates severe OSA (apnea-hypopnea index of 98). Continuous positive airway pressure (Pressure) was applied beginning at approximately 9:10 AM and increased from 4 to 9 cm H_2O, resulting in resolution of apneas and hypopneas, normalization of arterial So_2, and prolonged periods of rebound stage N3 (non-REM) and R (REM) sleep. A, apnea; Ar, arousal; C, central; DS, desaturation ≥4%; H, hypopnea; M, mixed; neither, neither Ar or DS; O, obstructive.



A



B

eFigure 120.2 Home study of severe obstructive sleep apnea. Full night summary data (A) and 2-minute, 16-second data tracings (B, apneas shown with *red arrows*) from a portable level 3 sleep recording performed in a patient's home, demonstrating severe obstructive sleep apnea.

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121 CENTRAL SLEEP APNEA

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INTRODUCTION

A central apnea during sleep results from a transient abolition of central respiratory drive to the respiratory muscles, leading to cessation of airflow, most often due to a fall in *arterial partial pressure of carbon dioxide* ($Paco_2$) below the threshold required to stimulate breathing. By convention, *apnea* in adults is defined as an absence or reduction of airflow to less than 90% of the baseline level for at least 10 seconds. In contrast to obstructive apneas, during which central drive and respiratory efforts continue throughout the apnea, causing deformation of the chest wall, during central apnea, there is no respiratory effort and therefore no movement of the chest wall. *Hypopneas* can also be central; in this case, airflow and tidal volume decrease by 30–90% compared to normal breathing for at least 10 seconds in association with oxygen desaturation and/or an arousal from sleep, but without evidence of airflow limitation due to upper airway obstruction. However, distinguishing central from obstructive hypopneas can be difficult depending on the type of instrumentation used to detect them.

A *central sleep apnea* (CSA) disorder is defined as recurrent central apneas and hypopneas during sleep. However, a clear threshold above which a CSA disorder can be said to exist has not been well defined owing to its relative rarity and its heterogeneous pathophysiology, clinical symptoms, and complications. Nevertheless, the following criteria have been proposed to define a CSA disorder: an *apnea-hypopnea index* (AHI) of 5 to 15 as mild, of 15 to 30 as moderate, and greater than 30 as severe, of which the majority of events are central. Similarly, criteria for a *CSA syndrome* have not been clearly defined but include the presence of a CSA disorder accompanied by symptoms, which may include habitual snoring, restless sleep, nocturnal awakenings, morning headaches, insomnia, or excessive daytime sleepiness (Table 121.1).[1,2]

DIAGNOSIS OF CENTRAL SLEEP APNEA

Full overnight polysomnography or home sleep apnea testing with instrumentation capable of detecting respiratory effort and airflow limitation is required for the diagnosis of CSA.[3,4] Respiratory effort is best determined noninvasively by respiratory inductance plethysmography.[5–8] Techniques such as piezo-electric crystal bands, oronasal thermistors, and nasal pressure are not reliable in detecting the presence or absence of respiratory effort and therefore of distinguishing central from obstructive events.[9–11] Although distinguishing central from obstructive apneas is not difficult with appropriate instrumentation, differentiation of central from obstructive hypopneas can be challenging due to the presence of some respiratory effort in both cases (eFigs. 121.1 to 121.3). Most laboratories do not differentiate between central and obstructive hypopneas, which is a problem because, in patients with *obstructive sleep apnea* (OSA) or CSA, most respiratory events are hypopneas. Thus, in many cases the classification of the type of sleep apnea disorder is made based on apneas, which constitute a minority of respiratory events. Central hypopneas are characterized by attenuated in-phase thoracoabdominal motion due to reduced respiratory drive without airflow limitation due to upper airway obstruction.[3] In some cases, more sensitive techniques may be required to detect the presence of respiratory effort or airflow limitation, such as measurement of intrapleural pressure by an esophageal catheter or diaphragm electromyographic activity.[8,12] The use of oxygen desaturation criteria for hypopneas is controversial because it has been shown that central events in patients with heart failure are accompanied by less oxygen desaturation than obstructive events of similar duration,[13] and it is unclear to what extent oxygen desaturation contributes to morbidity or mortality.[14]

CLASSIFICATION AND APPROACH TO CENTRAL SLEEP APNEA

Central sleep apnea is not a single disease entity but rather includes several heterogeneous disorders as outlined in Table 121.2. Common to all forms of CSA is a transient reduction in $Paco_2$ below the level required to stimulate breathing during sleep; that is, the apnea threshold as illustrated in Figure 121.1. Two distinct underlying

Table 121.1 Clinical Characteristics and Symptoms of Patients With Central Sleep Apnea

Characteristic	Hypercapnic	Nonhypercapnic
Sex distribution	Equal	Predominantly male
History of respiratory failure	Frequent	Not reported
Peripheral edema and right heart dysfunction	Frequent	Not reported
Polycythemia	Frequent	Not reported
Muscle weakness	Frequent	Not reported
Morning headaches	Common	Uncommon
Snoring	Common	Frequent
Nasal obstruction	Uncommon	Common
Hypertension	Uncommon	Common
Nocturnal choking	Uncommon	Common
Nocturnal awakenings and insomnia	Uncommon	Common
Daytime sleepiness	Frequent	Frequent
Restless sleep	Common	Common

From Bradley TD, Phillipson EA. Central sleep apnea. *Clin Chest Med.* 1992;13:493–505.

Table 121.2 Classification of Central Sleep Apnea

Hypercapnic (P_{CO_2} > 45)	Nonhypercapnic ($P_{CO_2} \leq 45$)
DECREASED RESPIRATORY DRIVE OR LIMITED MECHANICAL RESPONSE	**NORMAL OR INCREASED RESPIRATORY DRIVE**
Secondary ■ Developmental or degenerative diseases ■ Brainstem tumors ■ Cerebrovascular disease ■ Neuromuscular diseases Primary ■ Central alveolar hypoventilation syndrome	Secondary ■ Congestive heart failure (Cheyne-Stokes respiration) ■ Cerebrovascular disease ■ Atrial fibrillation ■ Renal failure ■ Acromegaly ■ High altitude ■ Opioid use ■ Complex sleep apnea Primary ■ Idiopathic CSA

CSA, central sleep apnea; P_{CO_2}, partial pressure of carbon dioxide.

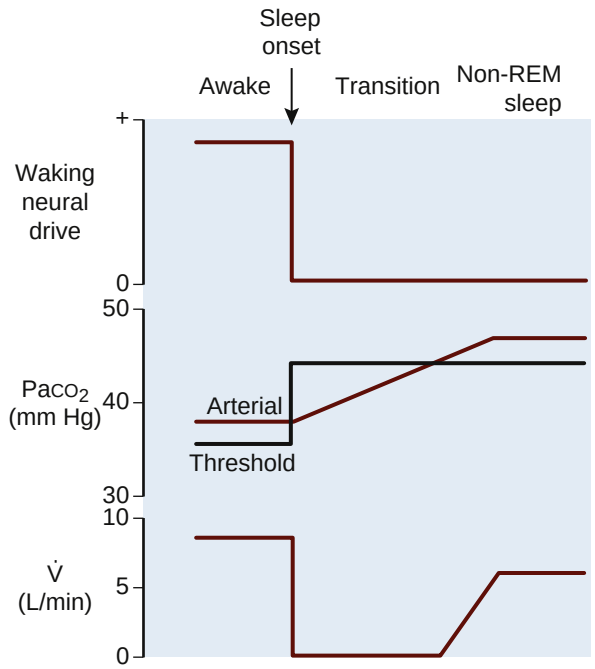

Figure 121.1 Schematic diagram showing a proposed mechanism underlying central sleep apnea at sleep onset. With the loss of the waking neural drive to breathing at sleep onset, there is an increase in the arterial partial pressure of carbon dioxide (P_{aCO_2}) threshold required to maintain respiratory rhythm. As a result, the P_{aCO_2} present during wakefulness may be below the threshold P_{aCO_2} for rhythm generation in sleep. Hence ventilation ($\dot{V}$) falls to zero and apnea ensues until P_{aCO_2} rises above the threshold level for rhythm generation in sleep, whereupon rhythmic breathing resumes. REM, rapid eye movement. (From Bradley TD, Phillipson EA. Central sleep apnea. *Clin Chest Med.* 1992;13:493–505.)

mechanisms can account for cessation of central respiratory output during sleep, causing either hypercapnic or nonhypercapnic CSA. An approach to evaluating a patient with CSA is outlined in Figure 121.2.

In *hypercapnic CSA*, there are outright defects in the respiratory control system or in the respiratory neuromuscular apparatus. Such defects generally result in suppressed respiratory drive and a chronic alveolar hypoventilation syndrome, manifested by some degree of daytime hypercapnia. However, the full impact of such defects becomes most apparent during sleep, when nonchemical waking neural drive to breathing is abolished and the stimulatory influence of behavioral, cortical, and reticular inputs to the brainstem respiratory neurons are reduced so that breathing becomes critically dependent on the defective metabolic respiratory control system, resulting in more pronounced hypercapnia during sleep than wakefulness.[15,16] This happens in conjunction with a markedly elevated P_{aCO_2} apneic threshold. Figure 121.3 illustrates a typical central apnea in a patient with hypercapnic CSA: as respiratory drive diminishes during sleep, there is a gradual reduction in tidal volume until cessation of breathing.

In contrast, in *nonhypercapnic CSA*, there are transient fluctuations or instabilities in an otherwise intact respiratory control system. These instabilities typically manifest during drowsiness and light *non–rapid eye movement* (NREM) sleep and, because there is no suppression of respiratory drive, P_{aCO_2} levels during wakefulness or sleep are normal or low. This type of CSA is typically triggered by a sudden increase in ventilation that causes P_{aCO_2} to fall below the apnea threshold, often due to an arousal from sleep, as illustrated in Figure 121.4A. This type of CSA is characteristically associated with periodic breathing, during which there are regularly recurring alternations in tidal volume between central apneas, hypopneas, and hyperpneas. Several theoretical and experimental models have been developed to account for such transient fluctuations in central respiratory drive. Common to all these models is a P_{aCO_2} level during sleep that falls transiently close to (hypopnea) or below (apnea) the critical threshold value required for maintenance of regular respiratory rhythm.

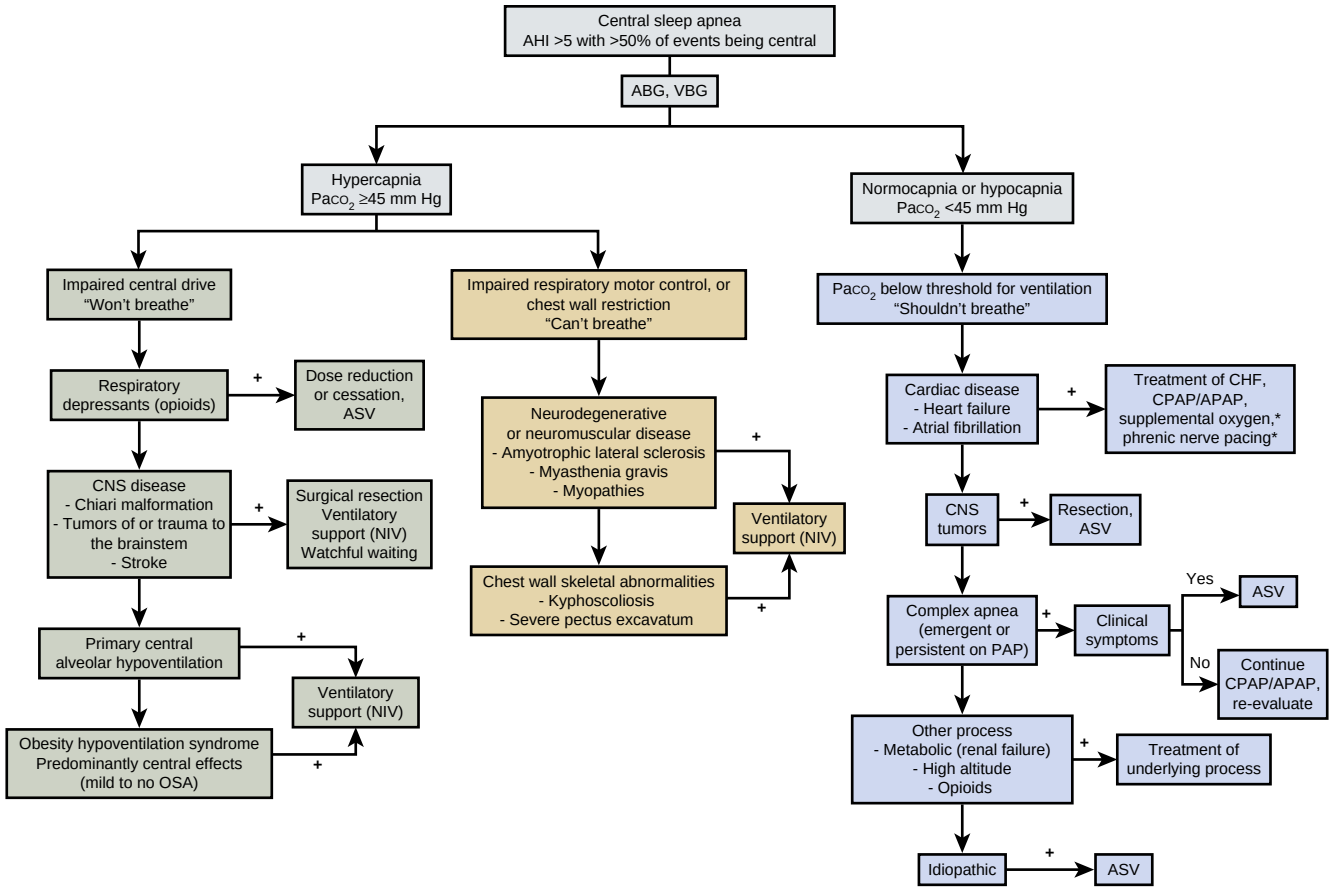

Figure 121.2 Algorithm demonstrating a diagnostic approach to central sleep apnea. *These treatments are under investigation. +, yes; –, no; ABG, arterial blood gas; APAP, auto-adjusting positive airway pressure, ASV, adaptive servoventilation; AHI, apnea–hypopnea index; CNS, central nervous system; CPAP, continuous positive airway pressure; OSA, obstructive sleep apnea; $Paco_2$, arterial partial pressure of carbon dioxide; PAP, positive airway pressure; VBG, venous blood gas.

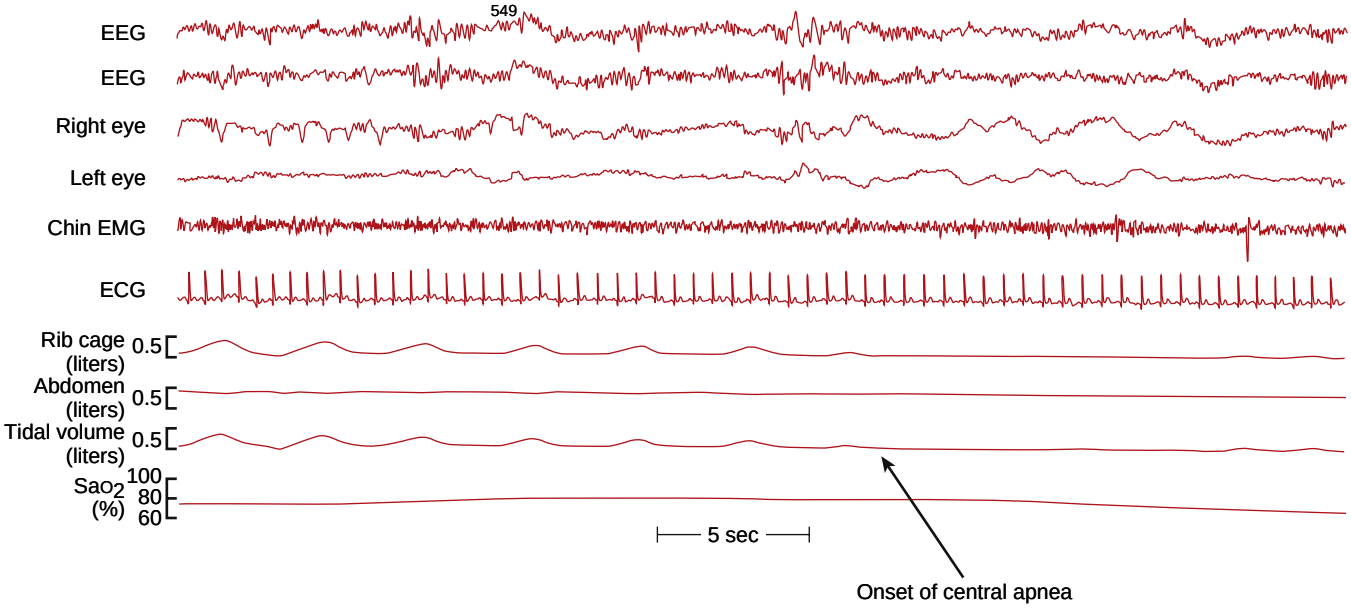

Figure 121.3 Hypercapnic central sleep apnea. Polysomnographic recording of a central apnea is from a patient with hypercapnic central sleep apnea due to primary central alveolar hypoventilation syndrome. Note the typical gradual reduction in tidal volume just before the onset of the central apnea and severe degree of hypoxemia with arterial oxygen saturation (Sao_2) below 80% throughout the recording. ECG, electrocardiogram; EEG, electroencephalogram; EMG, electromyogram.

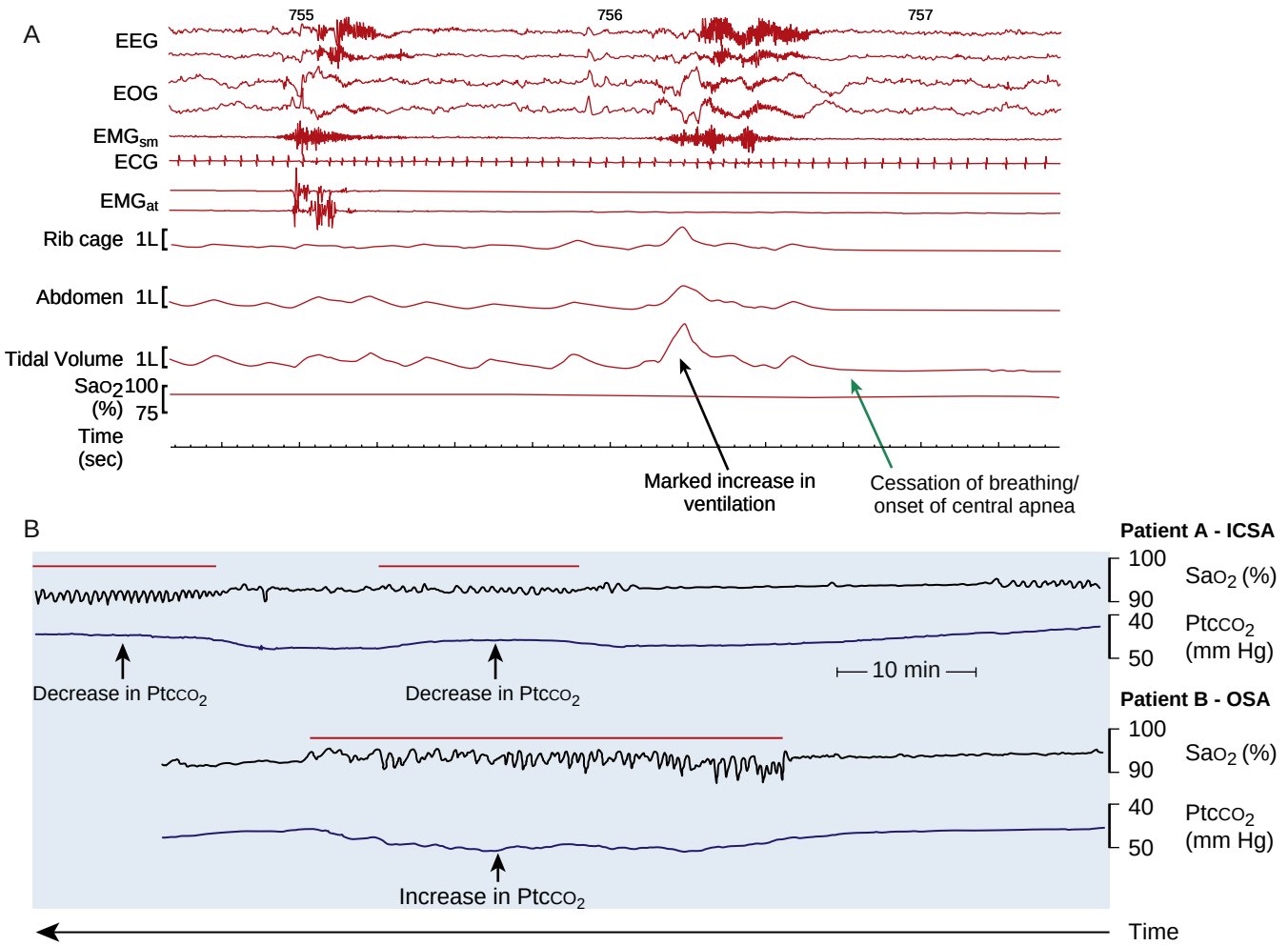

Figure 121.4 Nonhypercapnic central sleep apnea and comparison to obstructive sleep apnea. (A) Polysomnographic recording from a patient with nonhypercapnic central sleep apnea due to idiopathic central sleep apnea (ICSA). Note that, in contrast to the central apnea shown in Fig. 121.3, central apnea in this case follows an abrupt increase in ventilation triggered by an arousal, after which there is an abrupt decrease in ventilation to zero. In addition, note that in contrast to the recording shown in Fig. 121.3, arterial oxygen saturation (Sao_2) is within normal limits. (B) Note compressed records of nocturnal Sao_2 and transcutaneous $Paco_2$ ($Ptcco_2$) in a patient with ICSA (patient A), and in a patient with obstructive sleep apnea (patient B). Record reads from right to left. Note that in patient A the segments containing recurrent apneas (indicated by oscillations in Sao_2) are preceded by a small decrease in $Ptcco_2$. In contrast, in patient B the segment containing recurrent apneas is accompanied by a small increase in $Ptcco_2$. The *solid lines* indicate the apneic periods. Note also that in the $Ptcco_2$ scales an upward deflection of the signal indicates a fall in $Ptcco_2$, and vice versa. ECG, electrocardiogram; EEG, electroencephalogram; EMG_{at}, anterior tibialis electromyogram; EMG_{sm}, submental electromyogram; EOG, electrooculogram; $Paco_2$, arterial partial pressure of carbon dioxide. (A, From Xie A, Wong B, Phillipson EA, Slutsky AS, Bradley TD. Interaction of hyperventilation and arousal in the pathogenesis of idiopathic central sleep apnea. *Am J Respir Crit Care Med.* 1994;150:489–495. B, From Bradley TD, Phillipson EA. Central sleep apnea. *Clin Chest Med.* 1992;13:493–505.)

Such transient discrepancies in $Paco_2$ levels arise in several conditions, the most common of which is the transition from wakefulness to sleep. Because of the waking neural drive to breathe, ventilation is higher and $Paco_2$ levels are lower during wakefulness than during sleep.[16] Withdrawal of this drive at the transition from wakefulness to sleep results in a $Paco_2$ level that, although appropriate for wakefulness, is below the value appropriate for sleep (see Fig. 121.1). If this $Paco_2$ level of wakefulness is below the threshold value to stimulate ventilation during sleep, an outright apnea will ensue at sleep onset until $Paco_2$ rises to the critical threshold value when ventilation will resume. If sleep becomes firmly established at this point, regular breathing resumes without further apneas or hypopneas. However, in some individuals prone to periodic breathing, the transition from wakefulness to sleep is characterized by repeated fluctuations in central nervous system state between "awake" and "asleep." With each momentary arousal from sleep toward wakefulness, the $Paco_2$ levels that were present during sleep represent a hypercapnic stimulus during wakefulness, and ventilation therefore increases in accordance with the awake response to CO_2, resulting in an hyperpneic phase during which there is ventilatory overshoot causing $Paco_2$ to fall below the apnea threshold upon the transition to sleep. In this scheme, the magnitude of fluctuation in ventilation with changes in central nervous system state depends on the difference between the awake and sleeping values of $Paco_2$ and the steepness of the ventilatory response to CO_2 during wakefulness.[17] Any factor that magnifies these variables enhances the tendency to periodic breathing and CSA.

HYPERCAPNIC CENTRAL SLEEP APNEA

The automatic process of breathing originates from the central respiratory rhythm generator located in the pons and medulla. This central generator provides most of the input to spinal motoneurons responsible for activation of respiratory muscles. Hypercapnic CSA results from processes that damage the cerebral cortex, brainstem, spinal cord, muscles, or motor nerves. CSA arising in association with hypercapnia almost always presents as chronic respiratory failure with hypercapnia during wakefulness and sleep due mainly to a reduction in central respiratory drive. At the transition from wakefulness to sleep, the already reduced central drive is further reduced, causing a gradual reduction in ventilation until there is complete cessation of respiratory drive that leads to transient central apneas (see Fig. 121.3). Coincident with this reduction in ventilation, $Paco_2$ rises and Sao_2 falls. Apneas and hypopneas are more frequent during *rapid eye movement* (REM) sleep than *non-REM* (NREM) sleep owing to a further reduction in ventilator drive and partial paralysis of the respiratory muscles in REM sleep.[18]

Patients with hypercapnic CSA characteristically present with a clinical picture dominated by symptoms and sequelae of chronic respiratory failure with hypercapnia and hypoxemia that can include cyanosis, polycythemia, peripheral edema, and right heart dysfunction.[2] They may present at variable time points after the onset of the underlying disease. Symptoms suggestive of CSA may include snoring, restless sleep, morning headaches, excessive daytime sleepiness, and fatigue. However, some patients with hypercapnic CSA may not have symptoms suggestive of a sleep apnea syndrome.[2]

SECONDARY FORMS OF HYPERCAPNIC CENTRAL SLEEP APNEA

The brainstem includes the medulla, midbrain, and pons. Although the central respiratory controller is located predominantly in the medulla, it has projections to other areas of the brainstem. Diseases affecting the brainstem, such as Chiari malformations, tumors, cerebrovascular disease, and neurodegenerative diseases, may induce hypoventilation and CSA via a number of mechanisms, such as (1) physical compression of the brainstem resulting in damage to the respiratory center and reticular activating system, (2) stretching of the lower cranial nerves and damage to the peripheral chemoreceptors that carry inputs from the carotid bodies to the medulla, (3) depletion of medullary chemosensitive respiratory neurons,[19] or (4) degeneration of the central rhythm generator located in the dorsolateral pons.

Developmental and Degenerative Diseases

Chiari malformations are congenital abnormalities of the craniocervical junction with downward displacement of the cerebellar structures often in association with syringomyelia, myelomeningocele, hydrocephalus, and aqueductal stenosis. Other bony anatomic abnormalities associated with these Chiari malformations include platybasia, basilar invagination, Klippel-Feil anomaly (failure of segmentation of two of the seven cervical vertebrae), and scoliosis. Chiari malformations are classified into three types: type I, II, and III. These anatomic abnormalities can lead to degeneration of brainstem respiratory neurons with resulting hypoventilation and, in some cases, CSA.

In children with type I Chiari malformation, prospective studies show a prevalence of CSA of 9–15%, with an increased risk of CSA in those with hydrocephalus.[20,21] In adults with type I Chiari malformation, prospective studies report high rates of sleep-related breathing disorders (59–75%),[22] but the reported prevalence of CSA has varied widely from 1–59%.[23,24,25] In a small cross-sectional study of patients with Chiari malformation type II and associated myelomeningocele, the prevalence of CSA was higher at 63%.[26]

Congenital central hypoventilation syndrome (CCHS) is a rare genetic disease with an incidence of approximately 1 in 200,000 live births, caused by a mutation of the *PHOX2B* gene.[27–29] Most cases present in the neonatal period or early childhood with acute or chronic respiratory failure as a result of a loss of respiratory drive. However, it may present de novo in adults after a severe respiratory infection with combined CSA and OSA.[30–32] A diagnosis is considered only in those in whom metabolic, neurologic, pulmonary, and medication-induced disorders have been excluded. When CCHS is suspected, the *PHOX2B* gene screening test is recommended for purposes of genetic counseling.[33,34]

Neurodegenerative diseases of the brainstem, including multiple system atrophy, Leigh syndrome (or subacute necrotizing encephalomyelopathy), and Parkinson disease, can be accompanied by CSA.[35–37] Prevalence rates vary depending on the severity of the disease. In those with multiple system atrophy, CSA is reported to range from 9–20%.[38–40] In patients with multiple sclerosis, a demyelinating disease that can affect the brainstem and spinal cord, CSA may develop in those with medullary lesions affecting the respiratory neurons.[41,42] The prevalence of CSA in such patients is, however, unknown.

Brainstem Tumors

There have been fewer than a dozen documented cases of CSA associated with brainstem tumors, suggesting that tumors are a rare cause of hypoventilation with CSA.[43–49] Tumors such as gliomas, meningioma, astrocytoma, or neurofibromas have been implicated. The tumor type is probably less important than its location, which usually involves the medulla or pons. A retrospective study involving a series of children with brainstem tumors referred for assessment to a sleep clinic over an 8-year period found a prevalence of CSA of 14% (2 of 14).[45]

Cerebrovascular Disease

CSA can develop after stroke. The stroke location associated with hypercapnic CSA is usually the nucleus tractus solitarius region of the medulla responsible for neural output to the diaphragm.[50–53] Prevalence is probably low because there are only a small number of cases reported in the literature. Of interest, in Fabry disease, which is an X-linked recessive multisystem disease characterized

by vasculopathic changes and ischemia, CSA was reported in 22% of those with white matter lesions in the brainstem.[54,55]

Neuromuscular Diseases

Muscular dystrophies, myotonic dystrophy, and other types of inherited and acquired myopathies may result in hypoventilation and hypercapnic CSA. These diseases impair function of the inspiratory muscles, including the diaphragm, leading to alveolar hypoventilation. At the transition from wakefulness to sleep, the associated reduction in ventilatory response to CO_2 and hypoxemia, combined with the loss of respiratory muscle tone, can lead to apneas without respiratory effort (i.e., CSA).[56,18] Although some central output to the respiratory muscles may be present, and therefore, strictly speaking, events may not be central, the muscles are unable to respond; the reduced or absent muscle force generation leads to hypopneas and apneas, respectively, that have the appearance of central events. From the clinical viewpoint, it is reasonable to classify these as hypercapnic CSA because their treatment is similar to that for CSA arising from an absence of central drive.

Many of these disorders present in childhood. Although phenotypically variable, they are characterized by progressive muscular weakness and the development of hypoventilation over time. In addition to the high prevalence of hypoventilation, a significant proportion (20–60%) in adults and children develop CSA.[57–60] Nonhypercapnic Cheyne-Stokes respiration with CSA may also be seen in myotonic dystrophy or Duchenne muscular dystrophy when there is associated cardiomyopathy and heart failure.[61,62]

Diseases of the motor neurons include amyotrophic lateral sclerosis, spinal muscular atrophy, and postpolio syndrome. Due to varying degrees of degeneration of the respiratory motor neurons, hypoventilation and CSA can ensue. Recent studies in amyotrophic lateral sclerosis have reported either no CSA or a very low prevalence of 5%.[63,64] The prevalence of CSA is reported to be approximately 18% in amyotrophic lateral sclerosis[65] and approximately 5% in postpolio syndrome.[66] In one small study involving patients with traumatic spinal cord injury affecting the cervical spinal cord and resulting in tetraplegia, a high prevalence of CSA (60%) was reported.[67,68] Exaggerated sleep-related hypoventilation as a result of altered medullary motor output is thought to be the responsible mechanisms for the CSA.[69,70]

Myasthenia gravis is a disease of the postsynaptic neuromuscular junction. The reported prevalence of CSA in myasthenia gravis is highly variable (0–35%) and is probably dependent on disease severity.[58,71,72]

PRIMARY HYPERCAPNIC CENTRAL SLEEP APNEA

Central Alveolar Hypoventilation Syndrome

This is a rare syndrome that presents as chronic hypercapnic respiratory failure with normal respiratory mechanics, chest wall configuration, and muscle strength in the absence of any of the above secondary causes. The primary abnormality giving rise to hypoventilation is reduced sensitivity of the central and peripheral chemoreceptors.[73] In some cases, this may be due to CCHS.[74] Only a few cases of CSA have been described in association with primary central alveolar hypoventilation syndrome.[18,75] This diagnosis is made only after the exclusion of other causes of CSA and hypoventilation syndromes, including CCHS.

TREATMENT

The initial approach to treatment of hypercapnic CSA is to determine the underlying cause. In some cases, treatment of the underlying etiology will alleviate the CSA. For example, in those with tumors compressing the pons or medulla, resection may abolish CSA.[76] Surgical treatment of Chiari II malformations is dependent on the severity of the malformation and, despite posterior fossa decompression for the Chiari II malformation, CSA will often persist.[26] No specific intervention is usually required for patients with acute stroke and CSA because CSA may resolve with improvement of the stroke. However, if respiratory failure and CSA persist, specific therapy for these conditions may be indicated, as described later. For those with neuromuscular disease, pharmacologic therapies available for some inherited myopathies or myasthenia gravis may also alleviate CSA by improving muscle strength.[77]

In most patients, the management of CSA is the same as for chronic alveolar hypoventilation syndromes. However, few studies have specifically addressed the treatment of hypercapnic CSA. The main aim of treatment is to augment ventilation and thereby improve gas exchange and abolish CSA.

It is important that patients be cautioned against the use of sedative medications that can induce acute respiratory failure and aggravate CSA. In patients with CSA in association with central alveolar hypoventilation, a trial of the respiratory stimulant medroxyprogesterone can be given but is successful in only a minority of patients.[78] Supplemental nocturnal oxygen may alleviate hypoxia and CSA and may even lower $Paco_2$ if hypoxia caused central nervous system depression.[73,75] However, there is a potential for supplemental oxygen to abolish hypoxic respiratory drive and worsen CSA. Therefore, a trial of supplemental oxygen should be accompanied by careful monitoring of $Paco_2$, end-tidal CO_2 or transcutaneous CO_2, and either Po_2 or *arterial oxygen saturation* (Sao_2).

Where pharmacologic therapies are unavailable or are ineffective, noninvasive ventilation is often indicated, either via *bilevel positive airway pressure* (BPAP) support ventilation or volume-cycled ventilation.[79] The aim of noninvasive ventilation is to reduce $Paco_2$ below 45 mm Hg while awake and below 50 mm Hg while asleep and maintaining Sao_2 at or above 90%. This is best achieved by performing polysomnography during a trial of noninvasive ventilation in which transcutaneous $Paco_2$ or fraction of end-tidal CO_2 and Sao_2 are monitored. It is sometimes possible to maintain normal gas exchange during sleep and wakefulness by noninvasive ventilation only during sleep. If the underlying disease progresses despite the above measures, tracheotomy and invasive mechanical ventilation may be required. Unfortunately, there are no randomized trials or long-term observational studies that have determined the effects of noninvasive and invasive mechanical ventilation on morbidity, mortality, and quality of life in patients with hypercapnic CSA.

NONHYPERCAPNIC CENTRAL SLEEP APNEA

Nonhypercapnic CSA differs from that of hypercapnic CSA in that symptoms are mainly related to the sleep disturbance similar to that observed in OSA, but with insomnia being a more prominent feature. There are many causes of this type of CSA, and Table 121.1 is based mainly on symptoms related to idiopathic CSA. Nevertheless, symptoms related to secondary forms of nonhypercapnic CSA are, in general, similar.

SECONDARY FORMS OF NONHYPERCAPNIC CENTRAL SLEEP APNEA

Central Sleep Apnea in Association With Heart Failure: Cheyne-Stokes Respiration

Central sleep apnea in heart failure is manifest by a *Cheyne-Stokes respiration* (CSR) pattern. CSR can, however, happen during sleep and wakefulness. Because this chapter focuses on central apnea during sleep, CSR with central apneas during sleep is referred to as CSR-CSA. CSR-CSA is distinguished from other forms of CSA and periodic breathing by its characteristic crescendo-decrescendo pattern of tidal volume in which hyperpneas are markedly prolonged compared to those in patients without heart failure owing to reduced cardiac output and prolonged lung-to-chemoreceptor circulation time (Fig. 121.5). Therefore, a finding of CSR-CSA on a polysomnogram is highly suggestive of low cardiac output; it is seen most often in patients with reduced ejection fractions (i.e., *heart failure with reduced ejection fraction* [HFrEF]) and rarely affects the non–heart failure population.[80] Mechanisms that mediate CSR-CSA remain incompletely understood. However, as in all other forms of nonhypercapnic CSA, central to the process is respiratory control instability resulting from the dependence of the sleep state on metabolic control of ventilation, especially $Paco_2$.[2] A proposed pathophysiologic scheme for CSR-CSA is illustrated in Figure 121.6.

In heart failure, a key factor destabilizing the respiratory control system and predisposing to CSR-CSA is the presence of chronic hyperventilation that lowers $Paco_2$ during wakefulness and sleep and maintains it close to the apnea threshold (see also Chapter 117). Because $Paco_2$ is closer to the apnea threshold than normal, small perturbations, such as arousals from sleep that augment ventilation, may be enough to drive $Paco_2$ below the apnea threshold and trigger central apneas. The main factor contributing to this instability and hyperventilation is increased loop gain. Loop gain is an engineering term first used when a mathematical model was developed to explain factors involved in the instability within the respiratory control system in patients with CSR-CSA.[81] Simply put, *loop gain* is the ratio of ventilatory output to a given stimulus. Ventilation becomes unstable when loop gain is elevated so that the ventilatory output for a given stimulus is higher than normal. Thus, if central sensitivity to CO_2 is augmented, any given increase in $Paco_2$ will cause a greater-than-normal increase in ventilation that can then drive $Paco_2$ close to, or below, the apnea threshold. Several factors interact to increase the tendency to respiratory instability and hyperventilation. These include:

1. Increased peripheral and central chemoresponsiveness.[82,83]
2. Elevated pulmonary capillary wedge pressure that causes pulmonary congestion and activation of the pulmonary juxtacapillary irritant receptors that augment central drive and ventilation.[84]
3. Impaired cerebral vascular reactivity and blood flow responses to changes in the $Paco_2$, leading to instability of breathing.[85–87] Whereas this has been proposed as a mechanism for ventilator instability, it requires a differential effect of $Paco_2$ on the cerebral arterial and venous vessels that has not been fully demonstrated or explained. In consequence, this potential mechanism remains controversial and not fully established.
4. Sleep state instability in which arousals from sleep during the hyperpneic phase of CSR-CSA cause a transient awakening with an associated engagement of the wakefulness drive to breathe, increased chemosensitivity, and a lower $Paco_2$ apnea threshold.[88,89] Unlike OSA, where arousals take place at apnea termination and contribute to airway opening and resumption of airflow, arousals after central apnea generally take place several seconds after resumption of airflow but before the peak of hyperventilation.[90,91] Thus, they appear not to have the same protective role as they do in OSA. Although recurrent arousals during the ventilatory phase have been shown to trigger and propagate CSR-CSA,[88,92] the absence of arousals in 27% of central events suggests that they are not a critical factor.[91]
5. The response of the lungs (as assessed by the change in $Paco_2$ or arterial partial pressure of oxygen (Pao_2) per unit change in ventilation, that is, *plant gain*) is a predictor of CSR-CSA during nighttime and daytime. Plant gain is higher in those with heart failure and CSR-CSA compared to those without CSR-CSA.[83]

CSR-CSA typically arises during NREM sleep and resolves or becomes less prominent in REM sleep.[2,88] There are several reasons for this. First, breathing is predominantly under metabolic control during NREM sleep and is therefore highly dependent on $Paco_2$. Thus, reductions in $Paco_2$ below the apnea threshold will invariably give rise to central apneas. However, breathing is largely independent of metabolic control during REM sleep so that breathing is not nearly as dependent on $Paco_2$ as in NREM sleep. Second, ventilatory responses to CO_2 and hypoxemia are brisker in NREM than in REM sleep, so the potential to hyperventilate is greater in the former state than in the latter. Third, arousal thresholds for $Paco_2$ and Pao_2 are significantly lower in NREM than in REM sleep. Thus, people are more arousable and therefore more prone to respiratory control system instability in NREM than in REM sleep. Fourth, the respiratory muscles, save for the diaphragm, are essentially paralyzed in REM but not in NREM sleep. Thus, for any given chemical (e.g., $Paco_2$) or nonchemical (e.g., arousal) stimulus, the augmentation in ventilation will be greater in NREM than in REM sleep, making hyperventilation more likely in the former state.

Regarding the role of low cardiac output and prolonged circulation time in the pathogenesis of CSR-CSA, it appears that these are not crucial to the pathogenesis of the central

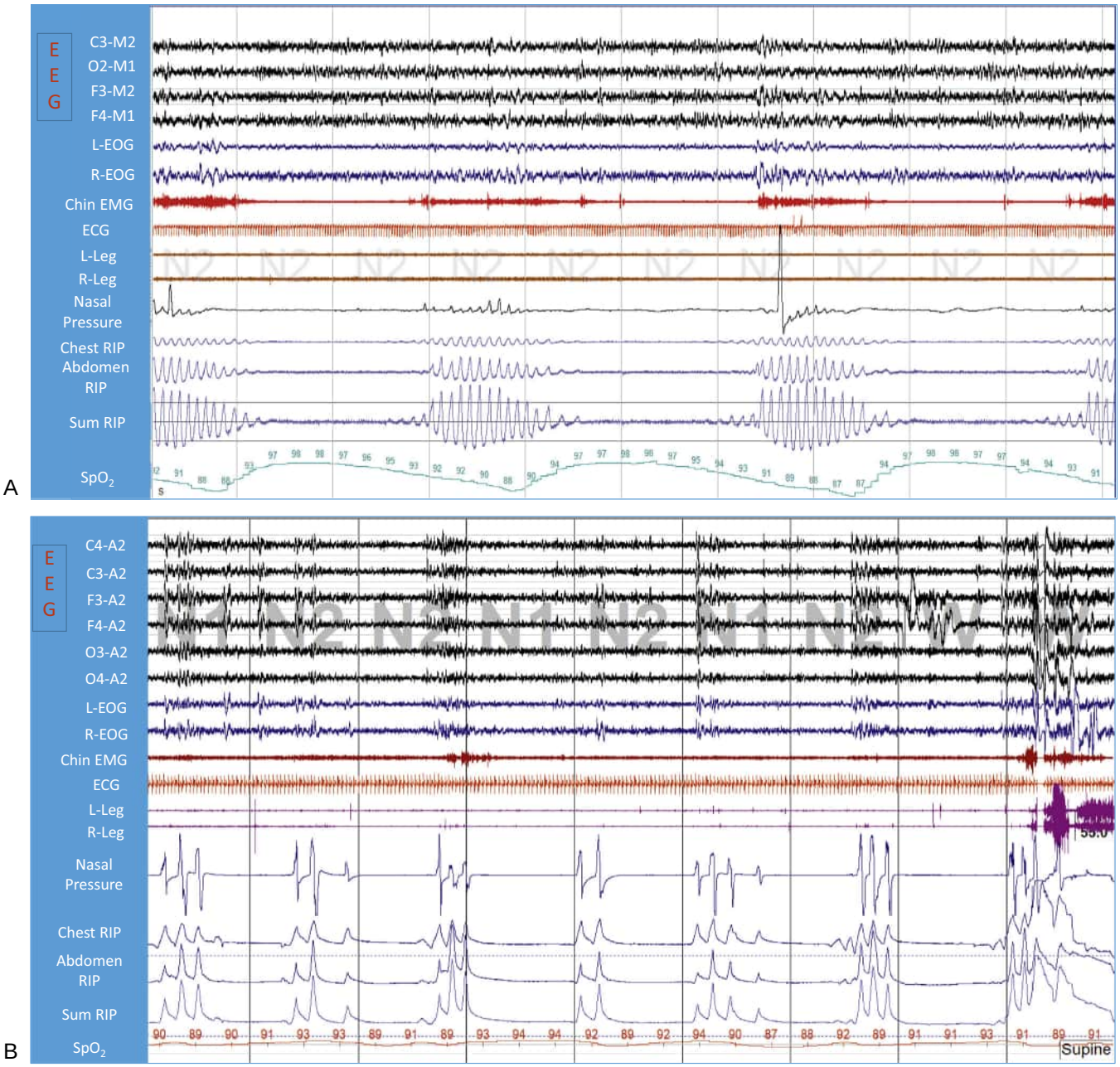

Figure 121.5 Central sleep apnea polysomnographic recordings. (A) Polysomnographic recording of Cheyne-Stokes respiration with central sleep apnea pattern (CSR-CSA) during stage N2 sleep. There is an absence of rib cage (chest RIP) and abdominal (abdominal RIP) motion as illustrated by the chest, abdominal, and SUM Respitrace recordings. There is no airflow as illustrated by the nasal pressure transducer recording. Note the typical long apnea-hyperpnea cycle duration (i.e., 90–100 seconds) with prolonged crescendo-decrescendo pattern of hyperpnea. Apneas are accompanied by cyclical mild oxygen desaturations. This is a 5-minute recording. (B) Polysomnographic recording of central apneas during stage N1/N2 sleep from a patient with opioid-induced central sleep apnea. There is no airflow as illustrated by the nasal pressure transducer recording and an absence of rib cage (chest RIP) and abdominal (abdominal RIP) motion. Note the typical short apnea-hyperpnea cycle duration (i.e., 30–35 seconds) with cyclical mild oxygen desaturations that contrasts with the long cycle duration in CSR-CSA. ECG, electrocardiogram; EEG, electroencephalogram; EMG, electromyogram; EOG, electrooculogram; RIP, respiratory inductance plethysmography; Spo_2, pulse oxygen saturation.

apneas because there is evidence that cardiac output in heart failure patients with CSR-CSA does not differ significantly from that in heart failure patients without CSR-CSA.[93] Moreover, experimentally induced prolongation of lung-to–carotid body circulation time in dogs only precipitated periodic breathing in a minority of experiments and then only when circulation times approached 1 minute or longer, a time far exceeding that observed in human heart failure.[94] However, these factors play a role in sculpting the crescendo-decrescendo pattern of hyperpnea[83] because the rate of rise of tidal volume and the duration of the hyperpnea are directly proportional to lung-to-chemoreceptor circulation time and indirectly proportional to cardiac output.[95] In consequence, in patients with heart failure, cardiac output is lower, and lung-to-chemoreceptor circulation time, hyperpnea, and periodic breathing cycle duration of CSR-CSA are longer than they are in CSA in patients without heart failure.[95] Figure 121.5A also shows the latency from

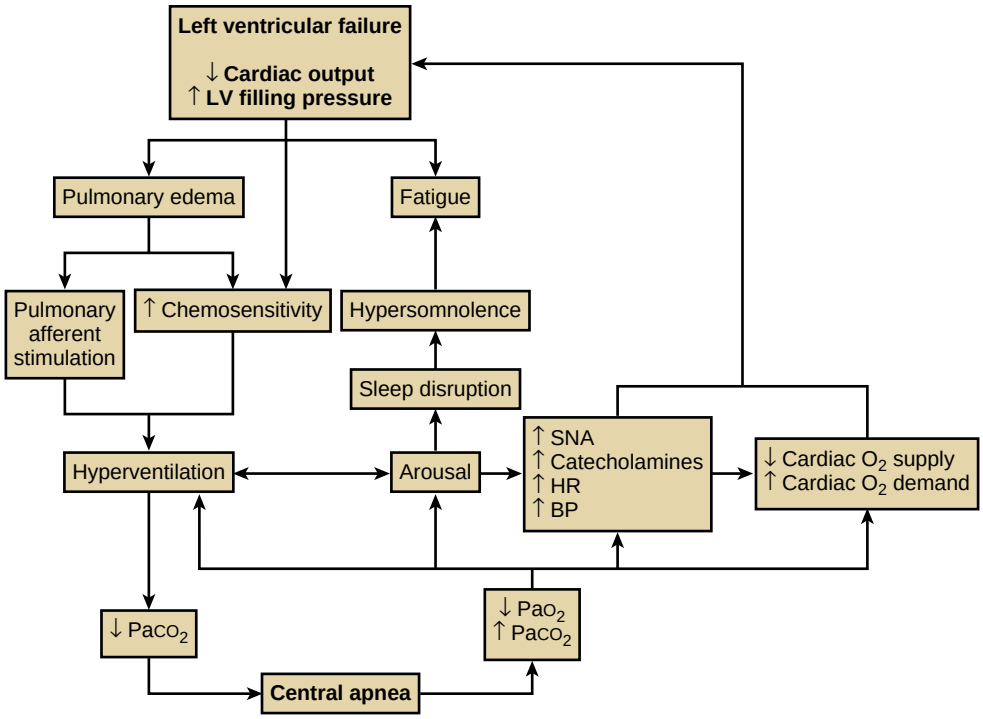

Figure 121.6 Pathophysiologic scheme of Cheyne-Stokes respiration with central sleep apnea. Left ventricular failure leads to reduced cardiac output and increased filling pressure that cause pulmonary edema and stimulation of pulmonary vagal irritant receptors that then, together with increased chemosensitivity, provoke hyperventilation and hypocapnia. A fall in $Paco_2$ below the apnea threshold triggers central apnea, during which Po_2 falls and $Paco_2$ rises, eventually leading to resumption of ventilation and arousals that provoke further hyperventilation and central apneas. The combination of hypoxia and arousals from sleep augment sympathetic nervous system activity that provokes rises in heart rate and blood pressure and, in turn, increases cardiac oxygen demand in face of reduced supply. The combination of oxygen demand/supply mismatch and sympathetic overactivation could lead to worsening left ventricle failure. In addition, sleep fragmentation due to recurrent arousals could contribute to fatigue and, in a minority, hypersomnolence. BP, blood pressure; HR, heart rate; LV, left ventricular; $Paco_2$, arterial partial pressure of carbon dioxide; Pao_2, arterial partial pressure of oxygen; SNA, sympathetic nervous system activity. (From Leung RS, Bradley TD. Sleep apnea and cardiovascular disease. *Am J Respir Crit Care Med.* 2001;164:2147–2165.)

the termination of a central apnea to arousal in the patient with CSR-CSA (panel A), but an arousal is seen immediately upon central apnea termination in the patient with opioid-induced CSA (panel B).

Heart failure is a prevalent condition affecting approximately 1.5% of the general population.[96] Among patients with symptomatic heart failure, earlier studies involving only men reported a prevalence of CSR-CSA of approximately 40%.[97] However, more recent epidemiologic studies involving both men and women have shown a substantially lower prevalence of CSR-CSA in those with optimally treated heart failure of 15–26%,[98–101] probably because CSR-CSA is very uncommon in women.[102] CSR-CSA also appears to be common in patients with asymptomatic left ventricular systolic dysfunction.[103] Risk factors for CSR-CSA include older age (>60 years); male sex; atrial fibrillation; awake hypocapnia ($Paco_2 \leq 38$ mm Hg); diuretic use; more severe heart failure, defined by lower *left ventricular ejection fraction* (LVEF); higher New York Heart Association functional class; higher brain natriuretic peptide level; and higher pulmonary capillary wedge pressure[84] and left ventricular end-diastolic volume.[97–99,101,104]

OSA and CSA can coexist in patients with heart failure. In a significant minority of patients, a shift between these two types of sleep apnea may happen overnight or over longer periods.[93,105–107] Predominantly obstructive events may shift to central events in association with reductions in the $Paco_2$ and prolongation of circulation time and the hyperpnea phase.[106,107] This suggests deterioration in cardiac output and elevation in left ventricular filling pressure as a result of the adverse hemodynamic effects of OSA.[108,109] Conversely, the shift from CSA to OSA is associated with improvements in LVEF and shortening of circulation time.[105] These observations suggest a pathophysiologic interaction between heart failure and sleep apnea, indicating that sleep apnea can influence cardiac function, whereas heart function can influence sleep apnea type. Thus, in some heart failure patients, OSA and CSA may be part of a spectrum of sleep-related breathing disorders that can shift according to underlying cardiovascular function.

One factor that may contribute to the pathogenesis of OSA and CSR-CSA, and to shifts in predominant apnea type over time in patients with heart failure, is fluid retention in the legs during the day and its overnight rostral redistribution during the night (eFig. 121.4). Strong relationships between the amount of fluid displaced from the legs due to gravity overnight and the AHI have been described in patients with heart failure and either OSA or CSA.[110] In the case of OSA, the fluid shift was accompanied by an overnight increase in neck circumference that correlated strongly with the AHI. These observations suggest that fluid accumulation in the neck was contributing to severity of OSA, likely by increasing peripharyngeal tissue pressure[111] and thereby increasing its collapsibility.[112] In the case of CSA, the fluid shift correlated inversely with nocturnal $Paco_2$, suggesting

that some of the fluid was redistributed into the lungs, where it stimulated pulmonary irritant receptors, causing hyperventilation and reductions in the $Paco_2$ close to or below the apneic threshold.[110,113] In addition, the magnitude of the fluid shift from the legs was greater in those with CSA than in those with OSA. Thus, it is possible that varying degrees of rostral fluid shift could lead to changes in predominant apnea type over time. The degree of nocturnal rostral fluid shift is related directly to time spent sitting in the day and inversely to physical fitness. Thus, fluid accumulation in the legs during the daytime results largely from the heart failure state itself, as well as inactivity with passive gravitational collection of fluid in the legs that also moves rostrally due to gravity when lying down at night.

Clinical Features of Cheyne-Stokes Respiration–Central Sleep Apnea. Although symptoms of heart failure, including orthopnea, paroxysmal nocturnal dyspnea, witnessed apnea, fatigue, and insomnia are common in those with CSR-CSA,[114] no specific constellation of symptoms has been identified in association with CSR-CSA. For example, patients with CSR-CSA do not usually have snoring or excessive daytime sleepiness.[98,115,116] Nor is there clear evidence that CSR-CSA has an adverse impact on quality of life.[116]

It is still a matter of debate whether CSR-CSA is merely a manifestation of elevated left ventricular filling pressures and poor cardiac function, or whether it has an adverse effect on cardiac function and prognosis independently of other risk factors. The balance of the evidence suggests that CSR-CSA has an adverse effect on prognosis. Most, but not all, single-center observational studies have reported a twofold to threefold increased risk of death or cardiac transplantation in association with CSR-CSA.[99,117–123] Caution is recommended in interpreting these studies because patient populations were generally small, and definitions and quantification of CSR-CSA were inconsistent. Because several of these studies were reported before widespread treatment of heart failure with β-blockers, implantable cardiac defibrillators, and cardiac resynchronization therapy, their findings may no longer be applicable to the present environment.[120–123]

One factor that might contribute to poor prognosis in CSR-CSA is elevated sympathetic nervous system activity, which is known to have a deleterious effect on the prognosis of patients with heart failure.[124] There is evidence that CSR-CSA increases sympathetic nervous activity during sleep and wakefulness,[125] probably via intermittent apnea-related hypoxia and arousals from sleep.[126–128] High sympathetic nervous activity induces activation of the aldosterone-renin pathway and reduces myocardial contractility over time due to abnormalities in calcium handling with precipitation of cardiac arrhythmias.[103] This combination of autonomic dysfunction and propensity to arrhythmogenesis and sudden death are the presumed mechanisms by which CSR-CSA contributes to increased mortality in heart failure.[98,129,130] This is supported by evidence of a 50% higher rate of appropriate implantable-defibrillator discharges in those with CSR-CSA compared to those without sleep-disordered breathing.[131]

On the other hand, there is evidence that CSR-CSA does not cause adverse hemodynamic effects in patients with heart failure. A recent study demonstrated that, in contrast to obstructive apneas during which stroke volume and cardiac output decrease, during central apneas, stroke volume and cardiac output actually increase slightly but fall slightly during hyperpnea.[108] Phenotyping of CSR-CSA–related features has suggested patterns that may aid in stratification of those most at risk of adverse outcomes. These include (1) measurement of the cycle length, lung-to-periphery circulation time, and time to peak flow, whereby a longer CSR cycle length, circulation time, and time to peak flow are associated with adverse outcomes in heart failure[132] and (2) identification of the pattern of the hyperpnea phase. Two separate patterns of hyperpnea during CSA-CSR have been identified: a positive pattern, in which the end-expiratory lung volume is at or above the functional residual capacity and a negative pattern in which the end-expiratory lung volume falls below the functional residual capacity (Fig. 121.7).[133] The negative CSR-CSA pattern is associated with poorer cardiac function. End-expiratory lung volume can only fall below functional residual capacity through activation of the expiratory muscles that would generate a greater degree of positive intrathoracic pressure than would be the case if end-expiratory lung volume was at or above functional residual capacity. Such pressure could have a compressing effect on the heart with augmentation of stroke volume similar to external chest compressions during cardiopulmonary resuscitation.[133] The observation that, in comparison to the positive, the negative CSR-CSA pattern is associated with smaller relative reductions in stroke volume and reduced myocardial workload during hyperpnea is supportive of this possibility. This raises the possibility that CSR-CSA with the negative hyperpnea pattern could be a form of autoresuscitation that acts as a compensatory mechanism to maintain stroke volume in those with severe heart failure.[134] Thus, under certain circumstances, CSR-CSA may provide some compensatory effect for low cardiac output and may not be entirely detrimental to cardiovascular function.[135]

Treatment of Cheyne-Stokes Respiration. Because few symptoms have been attributed to CSR-CSA, symptomatic targets for therapy are difficult to identify. However, because CSR-CSA is associated with increased risk of morbidity and mortality, a logical goal in treating CSR-CSA would be to reduce morbidity or mortality. Nevertheless, no treatments have been shown to affect these outcomes in randomized trials. Thus, because there are no clear-cut indications for treating CSR-CSA, a decision to treat CSR-CSA rests on clinical judgment, and the following possibilities can be considered with the proviso that therapies that reduce the severity of CSR-CSA may not lead to improvements in patient symptoms, quality of life, or long-term outcomes. All interventions in current use for CSR-CSA require further study to assess their long-term effectiveness and safety.

Treatment of Heart Failure. Because CSR-CSA arises as a consequence of heart failure, it would be reasonable to optimize pharmacologic and device treatments for the underlying heart failure to manage CSR-CSA. A few nonrandomized observational studies suggest that angiotensin-converting enzyme inhibitors,[136] β-blockers,[137] and cardiac

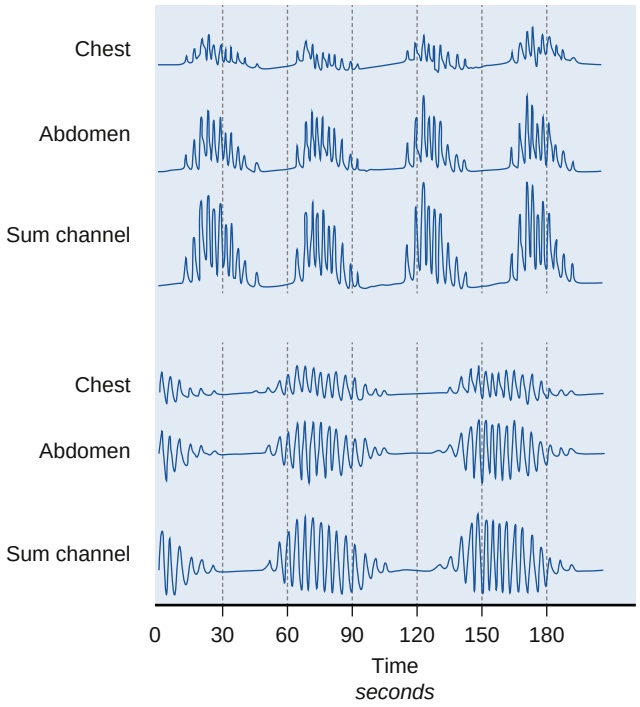

Figure 121.7 Different patterns of hyperpnea during Cheyne-Stokes respiration. Raw data tracing of chest, abdomen, and sum channels of the respiratory inductance plethysmograph demonstrating two patterns of hyperpnea during Cheyne-Stokes respiration with central sleep apnea. The upper tracings show a positive pattern in which end-expiratory lung volume remains at or above functional residual capacity, and the lower tracings show a negative pattern in which end-expiratory lung volume falls below functional residual capacity. (From Perger E, Inami T, Lyons OD, et al. Distinct patterns of hyperpnea during Cheyne-Stokes respiration: implication for cardiac function in patients with heart failure. *J Clin Sleep Med.* 2017;13:1235–1241.)

resynchronization therapy[138] may reduce severity of CSR-CSA in chronic heart failure. However, these findings have not been confirmed in randomized trials, and one large epidemiologic study showed no reduction in frequency or severity of CSR-CSA with institution of β-blockers.[98] In one study, atrial overdrive pacing led to a reduction in the AHI in patients with bradyarrhythmias and CSA but without heart failure.[139] However, these findings have not been reproduced. In another small study, it was reported that cardiac transplantation for end-stage heart failure reduced severity of CSR-CSA.[140] Although consideration can be given to the implementation of one or more of the above approaches for therapy of CSR-CSA, none of them is specifically indicated for therapy of CSR-CSA, and their use should be reserved to treat the underlying heart failure as required.

Positive Airway Pressure

Continuous Positive Airway Pressure. The effects of *Continuous positive airway pressure* (CPAP) have been studied extensively in patients with heart failure and CSR-CSA. Its acute application in patients with heart failure increases intrathoracic pressure, thereby reducing right and left ventricular volumes (i.e., preload), left ventricular transmural pressure (i.e., afterload), and the work of breathing by unloading the inspiratory muscles.[125,141] It also augments stroke volume and cardiac output in those with elevated left ventricular filling pressures but has the opposite effect in those with normal or reduced left ventricular filling pressures.[142]

Several small randomized trials in heart failure patients with CSR-CSA lasting 1 to 3 months have demonstrated that CPAP reduces the AHI by 50–60%.[125,143] The means by which it reduces the AHI is not well understood but may include (1) raising lung volume, thereby increasing the lung O_2 reservoir, which can stabilize breathing by dampening fluctuations in Pa_{O_2}, and (2) reducing lung water, thereby reducing pulmonary irritant receptor stimulation, reducing ventilation, and allowing Pa_{CO_2} to rise above the apnea threshold.[125] Other small randomized trials in heart failure patients with CSR-CSA also demonstrated that CPAP increases LVEF, reduces mitral regurgitation, and decreases sympathetic nervous system activity.[125,144]

The largest randomized trial involving CPAP was the *Canadian Positive Airway Pressure for Patients with Central Sleep Apnea and Heart Failure* (CANPAP), which involved 258 patients over a mean and maximum follow-up of 24 and 64 months, respectively.[145] CPAP reduced the AHI by approximately 55%, improved LVEF and 6-minute walking distance, and reduced sympathetic nervous system activity. However, it had no effect on the primary outcome, which was heart-transplant–free survival. Therefore, it cannot be recommended for routine use as therapy for CSR-CSA. However, in a post hoc analysis of the trial, it was observed that, among patients in whom CPAP reduced the AHI to less than 15, heart-transplant–free survival was significantly better than in the control group and in the CPAP subgroup in which the AHI remained above 15.[146] These results suggest that a trial of CPAP may be given to heart failure patients with CSR-CSA and, if their AHI is reduced to below 15, CPAP can be continued because of its potential to reduce morbidity and mortality. However, if the AHI remains above 15, discontinuation of CPAP could be considered because of the potential for harm.[146]

Adaptive Servoventilation. *Adaptive servoventilation* (ASV) is a form of positive airway pressure specifically designed to alleviate CSA with or without CSR. For CSR-CSA, ASV is analogous to a cardiac pacemaker: When it detects a central apnea, it provides intermittent pressure support ventilation on top of expiratory positive airway pressure; when it detects that the patient is breathing spontaneously, the inspiratory assist is turned off. In heart failure patients with CSR-CSA, it causes a greater fall in the AHI than CPAP, BPAP, and supplemental O_2.[147–149]

The *minute-ventilation–targeted ASV* (ASVmv) device, whose algorithm targets minute ventilation to alleviate CSA, has been assessed in the multicenter international randomized controlled *Treatment of Sleep-Disordered Breathing with Predominant Central Sleep Apnea by Adaptive Servo Ventilation in Patients with Heart Failure* (SERVE-HF) trial.[102] It enrolled 1325 patients with heart failure and reduced ejection fraction of 45% or less (HFrEF) on optimal heart failure therapy and with an AHI of 15 or more events per hour. For those who were randomized to usual care or usual care plus ASVmv, ASVmv reduced the AHI from 31.2 at baseline to 6.6, indicating reasonably good control of CSA. However, over the median 31 months of follow-up, adherence to ASVmv was only 3.7 hours per night, and the dropout rate from ASVmv was high (29%), whereas 16% of patients in the control group crossed over

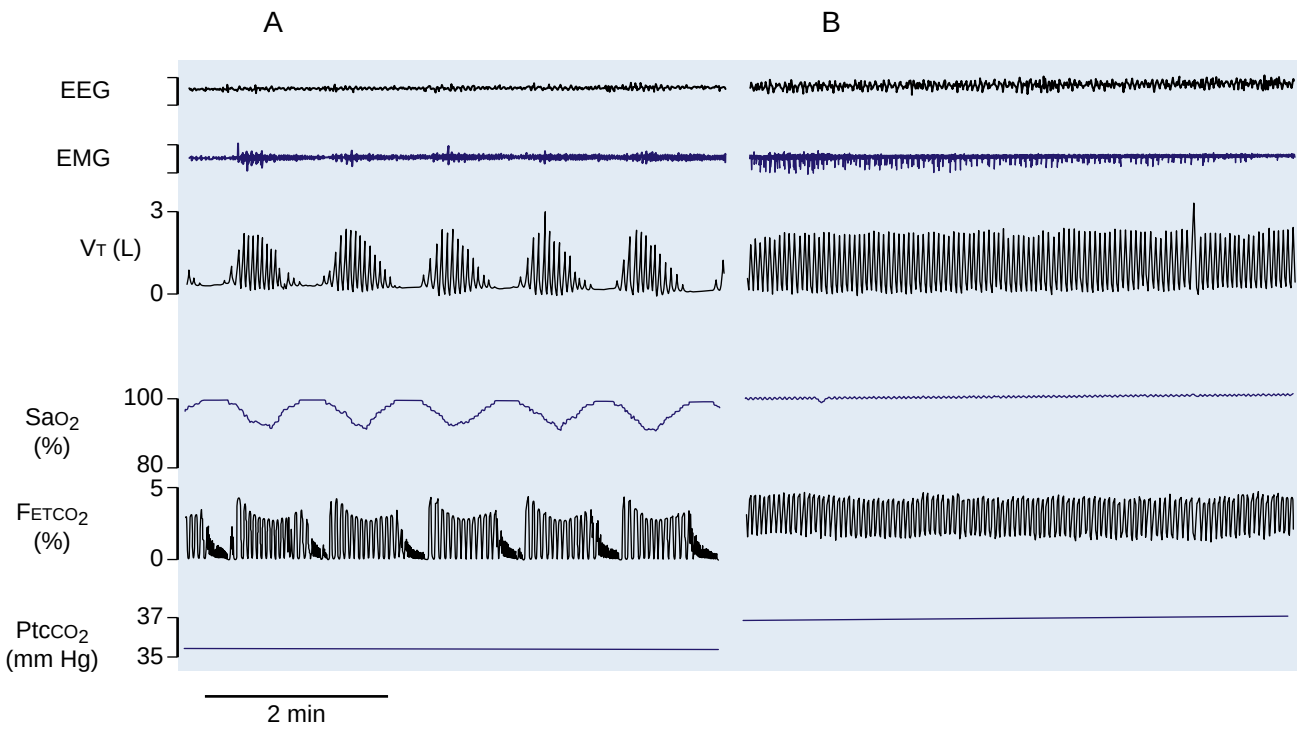

Figure 121.8 Inhaled carbon dioxide abolishes Cheyne-Stokes respiration. Polysomnographic recordings are shown from a patient with recurrent central apneas associated with Cheyne-Stokes respiration during stage 2 sleep while breathing air (A) and 1% carbon dioxide in air (B). Note abolition of both central apneas on the tidal volume (VT) trace and of recurrent decreases in arterial oxygen saturation (Sao_2) during carbon dioxide inhalation, in association with an increase in transcutaneous $Paco_2$ ($Ptcco_2$) of 1.6 mm Hg. EEG, electroencephalogram; EMG, submental electromyogram; FETCO, end-tidal carbon dioxide concentration. (From Lorenzi-Filho G, Rankin F, Bies I, et al. Effects of inhaled carbon dioxide and oxygen on Cheyne-Stokes respiration in patients with heart failure. *Am J Respir Crit Care Med.* 1999159:1490–1498.)

to some form of positive airway pressure therapy. The intention-to-treat analysis revealed no difference between the two groups in the composite primary outcome of all-cause mortality, cardiac transplantation, implantation of a ventricular assist device, resuscitation after sudden cardiac death, lifesaving shock, or unplanned hospitalizations for worsening heart failure (hazard ratio for the ASVmv group of 1.1; 95% confidence interval [CI], 1.0 to 1.3; $P = 0.10$). However, more concerning were the 28% and 34% increased all-cause and cardiovascular death rates in the ASVmv group (hazard ratio of 1.3; 95% CI, 1.1 to 1.6; $P = 0.01$; and hazard ratio of 1.3; 95% CI, 1.1 to 1.7; $P = 0.006$, respectively).

The cause of the excessive death rate in the ASVmv group was sudden cardiac death. The greatest risk for death in the ASVmv group was observed in those with a lower LVEF of 30% or less and those with a higher proportion of CSR related to their CSA. However, the cause of this increased rate of sudden death has not been identified.[150] Possibilities include that CSA is compensatory in heart failure and its reversal is harmful,[135] that positive intrathoracic pressure generated by ASVmv may have compromised cardiac output due to reduced preload, or that inspiratory pressure support generated by ASVmv may have induced hyperventilation, hypocapnia, alkalosis, and hypokalemia with an increased propensity for arrhythmias, particularly in those taking diuretics. Because of relatively poor adherence to the study protocol, a subsequent on-treatment analysis was performed and confirmed that use of ASVmv was associated with a higher cardiovascular death rate.[151] These trial results indicate that ASVmv is contraindicated to treat CSA in patients with HFrEF.

In a subsequent ancillary study of SERVE-HF involving a subset of 312 patients, several secondary physiologic outcomes were examined. These included echocardiographic measures of LVEF, LV diastolic function and dimensions, right ventricular dimensions, and biomarkers, including N-terminal pro–brain natriuretic peptide, troponins T and I, C-reactive protein, tumor necrosis factor-α, and creatinine. ASVmv had no significant effect on any of these secondary outcome variables compared to the control group.[102]

A second randomized trial of usual care versus usual care plus ASVmv, the *Cardiovascular Outcomes with ASV Therapy in Heart Failure* (CAT-HF) trial, was performed in patients hospitalized with acute decompensated heart failure on optimal therapy and sleep-disordered breathing with an AHI of 15 or greater.[152] It included patients with heart failure and either reduced or preserved ejection fraction and did not distinguish between CSA and OSA. The primary end point was the global rank composite of death, cardiovascular hospitalizations, and 6-minute walking distance. However, this study was halted prematurely after publication of the SERVE-HF trial results because the same ASVmv device was being tested, and there was overlap in the study populations. At that time, only 126 patients had been enrolled and, during the 6-month follow-up period, adherence to ASVmv was relatively poor at 2.7 hours per night. There was no difference in the primary end point between

the control and ASVmv groups. In accordance, these data do not support the use of ASVmv to treat CSA in patients with acute decompensated heart failure with either reduced or preserved ejection fraction.

Supplemental Oxygen. Supplemental oxygen reduces central apnea–related dips in Pa_{O_2}, thereby reducing peripheral chemoreceptor stimulation. Reduced chemoreceptor responsiveness decreases loop gain and lessens the chance of ventilatory overshoot and dips in Pa_{CO_2} below the apnea threshold.[153] Where Pa_{CO_2} has been measured during supplemental oxygen administration, Pa_{CO_2} was reported to increase when the AHI was markedly reduced[154] but did not change when the AHI only decreased marginally,[155] indicating that one of the mechanisms through which oxygen attenuates CSR-CSA is via dampening ventilation and raising Pa_{CO_2} above the apnea threshold.

Small randomized trials, from one night to 1 month in duration, have demonstrated that nocturnal oxygen reduces the AHI by approximately 50% in heart failure patients with CSR-CSA.[154,156–158] However, the effects of oxygen on physiologic and clinical outcomes have been inconsistent. Staniforth and colleagues[157] found that supplemental oxygen for 1 month reduced overnight urinary norepinephrine excretion but had no effect on daytime plasma norepinephrine, brain natriuretic peptide, neurocognitive function, sleepiness, or quality of life. In another randomized trial, Andreas and colleagues[156] reported that administration of nocturnal oxygen for 7 days to 22 heart failure patients improved peak oxygen consumption and ventilatory efficiency but had no effect on quality of life. Arzt and colleagues[159] allocated 10 consecutive patients to nocturnal oxygen and the next 16 consecutive patients to CPAP at 8 to 10 cm H_2O for 3 months. Both CPAP and oxygen reduced the AHI by 67%, but only CPAP improved ventilatory efficiency and LVEF. Neither intervention had any effect on peak exercise oxygen consumption. The Home Oxygen Trial[160] randomized 51 patients to receive or not to receive supplemental oxygen over 1 year. Those who received oxygen had a significant reduction in severity of CSR-CSA and a significant improvement in quality of life as measured by the specific activity scale compared to the control group. However, there was no difference in cardiac event rates between the groups.

Although oxygen attenuates CSR-CSA in patients with heart failure and can reduce nocturnal sympathetic activity, there is no consistent evidence that it improves cardiovascular function or clinical outcomes in such patients.[161] Moreover, administration of supplemental oxygen to patients with heart failure could cause hyperoxia and, by doing so, induce oxidative stress that can exert adverse hemodynamic effects, such as raising vascular resistance, blood pressure and left ventricular filling pressure, and lowering cardiac output.[162–164] Therefore, there is insufficient evidence to support the use of oxygen to treat CSR-CSA in patients with heart failure. In consequence, larger long-term trials are required to determine whether oxygen improves clinical outcomes in patients with heart failure and CSR-CSA.

Respiratory Stimulants. Acetazolamide is a carbonic anhydrase inhibitor that causes a metabolic acidosis that induces a constant stimulus to breathe, thereby raising ventilation and lowering the Pa_{CO_2} apneic threshold.[165] Two small 6-day randomized trials demonstrated modest (from 38–50%) reductions in the AHI in heart failure patients with CSR-CSA in association with reductions in daytime sleepiness and fatigue.[166,167] However, there are concerns regarding acetazolamide related to the promotion of transient elevations in sympathetic nervous activity from the metabolic acidosis, hyperventilation contributing to increased fatiguability, and hypokalemia that could predispose to cardiac arrhythmias.[168] Theophylline is an adenosine antagonist that stimulates central respiratory drive and augments cardiac contractility. In a 5-day randomized trial involving 15 patients with heart failure and CSR-CSA, theophylline reduced the AHI but did not improve LVEF.[169–171] However, although once used widely for therapy of acute heart failure, theophylline is no longer used for this purpose because it increases the risk of cardiac arrhythmias and sudden death.[172,173] In consequence, neither of these agents can be recommended for therapy of CSR-CSA because their long-term safety and efficacy remain to be demonstrated.

Carbon Dioxide. Increasing Pa_{CO_2} above the apnea threshold either by inhalation of CO_2 or the addition of dead space abolishes CSR-CSA instantaneously in patients with heart failure, as illustrated in Fig. 121.8.[174] However, there is no evidence that raising Pa_{CO_2} through these means provides any clinical benefits. Moreover, because CO_2 increases sympathetic nervous activity and disrupts sleep[175] and, because no long-term studies have demonstrated its safety or clinical efficacy, it cannot be recommended for therapy of CSR-CSA.

Transvenous Phrenic Nerve Pacing. Modulation of ventilation by unilateral transvenous phrenic nerve stimulation via the superior vena cava is under investigation as a treatment for CSR-CSA on the premise that activation of the diaphragm during central apneas will improve cardiac function. A 3-year open-label, multicenter, randomized controlled trial was designed to explore the therapeutic efficacy and safety profile over a 24-month period of overnight intermittent phrenic nerve stimulation. Efficacy was defined as a 50% or greater reduction in the AHI, which was achieved in 93% of the treatment group at 24 months.[176] The actual change in AHI was from 47 per hour at baseline to approximately 16 per hour at 24 months, indicating that a significant proportion of subjects had residual CSA. Ten percent of subjects sustained serious adverse events related to the phrenic stimulator, which included mainly complications from the implantation procedure. All these events resolved readily, and therefore the device was deemed to have an acceptable safety profile. Further studies will be necessary to evaluate whether such an intervention improves clinically important outcomes.

Central Sleep Apnea Associated With Cerebrovascular Disease

Nonhypercapnic CSA has been observed in patients with cerebrovascular accident, where its prevalence is approximately 10–15%.[177,178] Its pathogenesis and clinical features have not been well described. However, several studies have found no relationship between the vascular territory or type of stroke and the presence of CSA.[177–179] In some patients, CSA appears in a CSR-CSA pattern. In

such cases, CSR-CSA is associated with left ventricular systolic dysfunction[180] or left atrial enlargement, bilateral hemispheric involvement, or greater neurologic disability.[179] These observations strongly suggest that CSR-CSA in patients with stroke is related to either underlying occult cardiac dysfunction or preexisting cerebrovascular disease. A therapeutic approach to CSA in patients with stroke has not been studied in any depth, although a small observational study demonstrated short-term efficacy of ASV in alleviating CSA.[181] Thus, the implications of finding CSR-CSA in patients after stroke is that one should investigate for evidence of left ventricular systolic dysfunction to evaluate candidacy for ASV. However, there is currently insufficient evidence to recommend a therapeutic approach to CSR-CSA or to CSA of any kind in patients after a stroke.

Central Sleep Apnea Associated With Atrial Fibrillation

Among patients with heart failure, atrial fibrillation is associated with increased odds of having CSR-CSA.[98] Among patients with CSA but without heart failure, cerebrovascular disease, or renal disease, atrial fibrillation was observed in 27%.[182] Both CSR-CSA and CSA are predictors of incident atrial fibrillation risk in older men (>65 years) without heart failure.[183] The reason for the strong association between CSA and atrial fibrillation was not identified. However, the most likely possibility is that atrial fibrillation predisposes to CSA by mechanisms similar to those that predispose patients with heart failure to CSR-CSA: atrial fibrillation lowers cardiac output and raises pulmonary venous pressure that could trigger hyperventilation and hypocapnia through stimulation of pulmonary vagal irritant receptors.

Central Sleep Apnea Associated With Renal Failure

CSA has also been described in those with end-stage renal disease.[184,185] Prevalence rates are difficult to estimate because many of the studies are small. In earlier studies, the prevalence of CSA was reported to be 7–75%.[184–187] In a more recent study of 89 patients with stage 4 or 5 chronic kidney disease and 75 with end-stage renal disease on hemodialysis, CSA was uncommon, and the median central apnea index was 0 to 0.7 per hour.[188] However, the combination of obstructive, central, and mixed events is frequently reported in hemodialyzed patients with end-stage renal disease.[186,187,189] Predictors for CSA include atrial fibrillation, an increased cardiothoracic ratio on a chest radiograph, and low $Paco_2$, all of which suggest mechanisms for CSA in renal disease similar to those in heart failure and atrial fibrillation, including fluid overload.[185]

With respect to fluid overload, in end-stage renal failure, greater total-body extracellular fluid and neck, thorax, and leg fluid volumes were demonstrated in those with sleep apnea compared to those without.[190] Nonrandomized studies showed that one night of CPAP alleviated CSA in 6 patients with end-stage renal disease[187] and that conversion from conventional thrice-weekly hemodialysis to more intense 7 days per week of nocturnal hemodialysis in 14 patients with a mixture of obstructive and central respiratory events reduced all types of events in association with an increase in $Paco_2$.[186] In addition, among 15 patients with end-stage renal failure on thrice-weekly hemodialysis, fluid removal by ultrafiltration on a nondialysis day attenuated OSA and CSA with a 36% overall reduction in AHI. The improvement was not associated with any changes in blood urea concentration or venous $Paco_2$, indicating that this effect was due to fluid removal per se and not to a change in degree of uremia. Furthermore, the reduction in the AHI correlated with reductions in total-body extracellular fluid and neck and thorax fluid.[191] This suggests that greater fluid removal during nocturnal hemodialysis compared with conventional hemodialysis contributed to alleviation of OSA and CSA through reductions in overnight fluid shifts into the neck, in the case of OSA, and into the lungs, in the case of CSA.[110,186,192]

Central Sleep Apnea Associated With Acromegaly

Acromegaly is associated with OSA and CSA. The prevalence of CSA in small studies has ranged from 5–20% of patients with acromegaly.[193–195] In one small study, the $Paco_2$ was either low or normal and was associated with increased ventilator responsiveness to CO_2 and hypoxia, as well as to higher growth hormone and insulin-like growth factor-1 levels compared to patients with OSA or no sleep apnea. Slopes of the hypercapnic ventilator responses were related to growth hormone and insulin-like growth factor-1 levels, suggesting that these substances have effects on breathing control. Moreover, the severity of CSA was directly related to the level of insulin-like growth factor-1and to CO_2 responsiveness.[195] Thus, the pathogenesis of CSA in acromegaly appears similar to other forms of nonhypercapnic CSA.

Clinical features of CSA in acromegaly have not been well characterized but appear to be similar to symptoms of OSA, including loud snoring and excessive daytime sleepiness.[195] In small nonrandomized studies involving patients with acromegaly and sleep apnea, medical treatment of acromegaly by hormonal control was associated with reductions in the AHI that involved central and obstructive events.[193,196] Similarly, in another nonrandomized study involving six patients with acromegaly and a mixture of OSA and CSA, treatment of acromegaly by transsphenoidal adenomectomy alleviated OSA and CSA, but effects on symptoms of sleep apnea were not assessed.[197] These results suggest a causative role of acromegaly for CSA and OSA.

Central Sleep Apnea Associated With High Altitude (See Chapter 105)

At high altitude, hypobaric hypoxia provokes hyperventilation that causes $Paco_2$ to fall recurrently below the apnea threshold during sleep.[198] Although high-altitude CSA is observed in natives of high and low altitudes, not everyone is susceptible.[199] Alterations in cerebral blood flow and cerebrovascular reactivity to $Paco_2$ are likely to be important pathophysiologic mechanisms in high-altitude CSA.[200,201] Men are more likely to develop CSA at high altitude than women for unknown reasons, just as they are more prone to other forms of nonhypercapnic CSA.[202]

In lowlanders, there is a progressive increase in the frequency of central events and a reduction in the periodic breathing cycle length with increasing altitude from 2400 to 7546 m.[203–205] The progressive reduction in cycle length

is probably due to increasing cardiac output and therefore reduced lung-to-chemoreceptor circulation time. Over time, as individuals acclimatize to high altitude, CSA attenuates.[206,207] This is due mainly to metabolic compensation for respiratory alkalosis; over 2 to 3 days, bicarbonate moves out of the cerebrospinal fluid and is excreted by the kidneys in association with renal retention of H^+ ions, acidifying the arterial blood and cerebrospinal fluid, causing pH to move toward normal. As a consequence, the difference between $Paco_2$ and the apnea threshold increases, causing periodic breathing to dampen over time.[165] Complaints related to CSA at high altitude include poor quality sleep, nocturnal dyspnea, morning headaches, and impaired cognition.[208–211]

Return to low altitude quickly reverses high-altitude CSA. Specific therapies for high-altitude CSA include supplemental oxygen that causes $Paco_2$ to rise above the apnea threshold with immediate reversal of CSA and subjective improvement in sleep quality.[210] Respiratory stimulants can alleviate high-altitude CSA. For example, a randomized trial involving 30 subjects with high-altitude CSA demonstrated virtual elimination of CSA by either acetazolamide or theophylline. However, 60% of subjects on acetazolamide reported paresthesias and altered taste, and 70% of subjects receiving theophylline complained of palpitations.[212] In a randomized trial involving 33 subjects at high altitude, the sedative medication temazepam caused a modest reduction in severity of CSA.[213] Although no data on mechanism of action were provided, the proposed mechanism of action of this sedative is that, by reducing the frequency of arousals from sleep, it prevents abrupt hyperventilation and consequent fall in $Paco_2$ below the apnea threshold.

A comparative study of ASVmv versus supplemental oxygen or no treatment was performed in 18 nonacclimatized subjects with high-altitude CSA at 3800 m. Oxygen eliminated CSA, whereas the effect of ASVmv on CSA did not differ from no treatment.[214] The likely reason for this is that ASVmv requires several seconds to adjust and implement pressure support, which works well in CSR-CSA, where the cycle length is long, but not as well in high-altitude CSA, where the cycle length is shorter. In a recent randomized double-blind sham controlled cross-over study in 19 subjects with high-altitude CSA, a portable expiratory resistance mask containing a small amount of dead space designed to elevate the $Paco_2$ achieved a 49% reduction in the AHI.[215] At present, although firm recommendations cannot be given regarding the pharmacologic treatment of high-altitude CSA, it seems most logical to use supplemental oxygen and/or acetazolamide because they are routinely used at high altitude to correct hypoxemia and to prevent acute mountain sickness and high-altitude pulmonary edema, respectively.

Central Sleep Apnea Associated With Opioid Use

Both OSA and CSA have been described in patients using opioids.[216–218] Unfortunately, little is known about the pathophysiology of opioid-induced CSA. There are at least two physiologic effects of opioids that could predispose to CSA. First, opioids activate endogenous opioid receptors in areas of the brain that inhibit inspiratory drive and cause respiratory depression, particularly in the pre-Botzinger complex of the medulla.[219] Exaggeration of such inspiratory depression at the onset of sleep could therefore cause central apneas and hypopneas. If so, then one would expect it to happen in the presence of hypercapnia. However, when arterial blood gas analyses have been performed in awake subjects with methadone-related CSA, $Paco_2$ has generally been within normal limits and bore no relationship to the presence or severity of CSA.[217,220–222] In consequence, opiate-induced CSA appears not to be associated with hypercapnia and respiratory depression per se but, rather, appears to fall into the nonhypercapnic category.

Second, opioids also cause arterial and venous dilation in the pulmonary and systemic circulation via stimulation of histamine receptors.[223,224] This venous dilating effect causes peripheral venous pooling and, in patients with acute cardiogenic pulmonary edema, this reduces left ventricular filling pressure and pulmonary congestion.[225] It is therefore possible that chronic opioid use could cause chronic venous pooling in the capacitance vessels of the splanchnic circulation and legs. If so, there may be substantial rostral fluid shift upon lying down at night that could accumulate in the lungs and stimulate vagal irritant receptors that would provoke hyperventilation and a fall in $Paco_2$ toward the apnea threshold similar to that described in patients with heart failure and CSA.[110,226] However, such a mechanism remains speculative.

The severity of CSA in those on narcotics may vary from night to night depending on the dosage: The higher the dose is, the higher the AHI.[217,227,228] The prevalence of CSA among opioid users remains uncertain because of a lack of prospective studies. In retrospective studies of opioid users referred to sleep clinics, the prevalence of isolated CSA ranged from 14–30%.[217,227,229,230]

Central nervous system symptoms of opioids include dizziness, nausea, neurocognitive impairment, and hypersomnolence.[231] The extent to which these symptoms are due to opioid use or to CSA is difficult to determine. Chronic opioid use can increase the risk of sudden death, possibly due to cardiac arrhythmias, but there is no evidence to date that this is related to CSA or other sleep-related breathing disorders.[232]

In patients with opioid-induced CSA, opioid withdrawal resolves or reduces the severity of CSA and daytime hypersomnolence.[233,234] However, opioid withdrawal is often not feasible because of addiction or chronic pain. CPAP, BPAP, and ASV have been tested for therapy of opioid-induced CSA. A systematic review has shown CPAP to be largely ineffective and BPAP with or without supplemental oxygen to be effective in 62% of patients.[235] ASV has been evaluated in two small prospective studies. In the first study, ASV was assessed over a single night and was highly effective (AHI 50.3 ± 22.2 to 2.5 ± 3.5 events/hr).[236] In the second study, performed over a 3-month period, ASV was also effective in reducing the median AHI from 32.5 to 5.8 events per hour, although the longer-term adherence was poor at 49%.[237] Because of the paucity of data on effectiveness of various interventions, randomized trials are needed to determine the impact of treatments on opioid-induced CSA and related symptoms.

Complex Sleep Apnea

Complex sleep apnea was originally described as the emergence of CSA in patients with OSA during or after

initiation of CPAP therapy (i.e., CPAP-emergent CSA). Subsequently, the emergence of CSA in patients with OSA has also been described after maxillomandibular advancement surgery,[238,239] application of mandibular advancement devices,[240] tracheostomy,[241] and nasal surgery[242] (i.e., *treatment-emergent CSA*). There is, however, controversy as to the definition of complex sleep apnea and whether it is a distinct entity. The term complex sleep apnea has also been used to describe persistence of only central events after treatment of a combination of CSA, mixed, and OSA (i.e., *treatment-persistent CSA*). Therefore, a clear definition of complex sleep apnea has yet to emerge.[243,244] For the purposes of this chapter, the term complex sleep apnea includes treatment-emergent and treatment-persistent CSA.

The main postulated mechanism of CSA emergence upon initiation of CPAP and the other therapies mentioned above in patients with OSA is that relief of upper airway obstruction in someone with a high central respiratory drive facilitates augmented ventilation that reduces $Paco_2$ below the apneic threshold.[243,245]

During CPAP titration in patients with OSA with and without heart failure, the prevalence of treatment-emergent CSA ranges from 5–20%.[245–250] After 2 to 3 months of acclimatization to CPAP, treatment-emergent CSA dissipates in greater than 50% of subjects without heart failure.[246,248] A gradual reduction in treatment-emergent CSA has also been described over 6 months posttracheostomy.[251]

In unselected sleep cohorts, risk factors identified for the development of treatment-emergent CSA were poorer sleep efficiency, hypertension, coronary artery disease, heart failure, opioid use, and more severe OSA.[246,248,252] In the heart failure population, predictors for development of treatment-emergent CSA included older age, lower $Paco_2$, poorer New York Heart Association class, less diuretic therapy, and increased ventilatory responsiveness to CO_2.[250] However, up to one-third of those with treatment-emergent CSA do not have any of these risk factors.[253]

In most patients, no specific treatment is necessary for treatment-emergent CSA because these events may dissipate over 2 to 3 months with ongoing CPAP use. Furthermore, even in those with persistent treatment-emergent CSA, daytime sleepiness is usually alleviated.[246] For those in whom complex CSA persists despite CPAP or other therapies, there is no available information on long-term consequences.

Treatments for persistent treatment-emergent CSA include BPAP, ASV, oxygen, and addition of dead space. In most studies, decisions to treat complex CSA were not based on patient symptoms. Studies with BPAP are conflicting, with one study demonstrating an improvement[254] and two studies demonstrating no improvement in CSA.[255,256] A retrospective study evaluating the addition of 50 to 200 mL of dead space via a nonvented mask to a standard CPAP unit reported abolition of CSA.[257] In retrospective studies, ASV was reported to abolish treatment-emergent CSA in 79–100% of patients on titration studies.[258–260] In small prospective randomized trials, treatment of treatment-emergent CSA was abolished by ASV in 97–100% of patients after between 6 and 12 weeks.[250,252,261]

PRIMARY NONHYPERCAPNIC CENTRAL SLEEP APNEA

Idiopathic Central Sleep Apnea

Idiopathic CSA (ICSA) is a form of CSA in which there are central apneas and hypopneas without evidence of cardiovascular diseases or other lesions that might explain their presence. Two large epidemiologic studies reported a prevalence of CSA of 0.4% in men[262] but essentially 0% in women.[263] Because these populations were considered healthy, one can assume that most cases of CSA identified were ICSA. In accordance, ICSA appears to be rare.

Patients with ICSA hyperventilate with low $Paco_2$ during wakefulness and sleep. The tendency to hyperventilate is related to increased responsiveness of the peripheral and central chemoreceptors that increase loop gain and lead to respiratory instability.[89,264,265] Episodes of central apneas and hypopneas during sleep are typically precipitated by an abrupt increase in ventilation usually triggered by an arousal, after which $Paco_2$ drops below the apnea threshold. Their dependence on hypocapnia is illustrated by the observation that increasing the $Paco_2$ either by inhalation of a small concentration of CO_2 or by addition of dead space immediately abolishes this breathing disorder.[266] As in CSR-CSA, central events happen predominantly during NREM sleep with a reduction in frequency or complete cessation of events during REM sleep. Compared to heart failure patients with CSR-CSA, the durations of the hyperpnea and periodic breathing cycle are much shorter due to shorter lung-to-chemoreceptor circulation time and higher stroke volume and cardiac output (see Fig. 121.4).[95]

In some respects, the clinical presentation of ICSA resembles that of OSA. Patients are usually middle-aged or older men who are overweight and report snoring, restless sleep, and possibly excessive daytime sleepiness but more often complain of insomnia. There are no studies on the natural history of this disorder, so its overall clinical significance is difficult to assess. Treatments assessed include the respiratory stimulant acetazolamide,[212,267] which provides a constant stimulus to breathe and therefore reduces fluctuations in ventilation. Studies evaluating acetazolamide have been nonrandomized and produced inconsistent results without careful evaluation of clinical outcomes. Therefore, acetazolamide cannot be recommended as chronic treatment for this disorder at this time.

Because increased arousals and sleep instability can precipitate CSA, sedative medications have been tested to reduce arousability and thereby alleviate ICSA. In a nonrandomized, open-label, 9-week trial of the nonbenzodiazepine gamma-aminobutyric acid receptor agonist zolpidem,[268] the AHI fell by 55% in association with a reduction in arousal frequency and subjective daytime sleepiness. In a one-night randomized trial, the benzodiazepine hypnotic triazolam[269] was also reported to reduce the AHI modestly in association with a reduction in arousal frequency. Because these studies included only small numbers of subjects, much larger randomized studies will be required before more evidence-based treatment recommendations can be made. There are no published studies evaluating the effects of positive airway pressure devices in ICSA.

Key Points

- *Central sleep apnea* (CSA) is characterized by a reduction (hypopnea) or cessation (apnea) of airflow in the face of reduced or absent respiratory effort, respectively. Hypopneas and apneas are caused by reductions in *arterial partial pressure of carbon* dioxide ($Paco_2$) close to (hypopnea) or below (apnea) the apnea threshold during sleep, either because the $Paco_2$ falls or the apnea threshold rises.
- CSA is a heterogeneous disorder, and classification is based on the presence or absence of hypercapnia. There are two major types, hypercapnic and nonhypercapnic.
- Hypercapnic CSA is associated with hypercapnia arising from impaired central respiratory drive or neuromuscular weakness affecting the respiratory muscles, which is exacerbated during the transition from wakefulness to sleep by the withdrawal of the waking drive to breathe and is most prominent in *rapid eye movement* (REM) sleep.
- Nonhypercapnic CSA is associated with normocapnia or hypocapnia that is often associated with augmented central respiratory drive that predisposes to alternating periods of hyperventilation that drive $Paco_2$ recurrently down toward or below the apnea threshold. It is most prominent in non-REM sleep.
- Cheyne-Stokes respiration with CSA, a form of nonhypercapnic CSA most commonly associated with heart failure, is characterized by a waxing and waning pattern of respiration during hyperpnea typically seen during non-REM sleep and is associated with increased mortality risk.
- Complex sleep apnea is a form of CSA that *arises* after treatment of obstructive sleep apnea by continuous positive airway pressure or other interventions (i.e., treatment-emergent CSA) or *persists* after treatment of a combination of central, mixed, and obstructive sleep apnea (i.e., treatment-persistent CSA).
- Treatment of CSA varies depending on the underlying etiology. First-line therapy should target the underlying disorder (e.g., reduce opioid medication or initiate appropriate pharmacotherapies for heart failure). If CSA persists and is associated with symptoms, noninvasive bilevel positive airway pressure should be considered in hypercapnic CSA. In those with nonhypercapnic CSA, positive airway pressure therapies, including adaptive servoventilation, may be effective.

Key Readings

Aurora RN, Chowdhuri S, Ramar K, et al. The treatment of central sleep apnea syndromes in adults: practice parameters with an evidence-based literature review and meta-analyses. *Sleep*. 2012;35(1):17–40.

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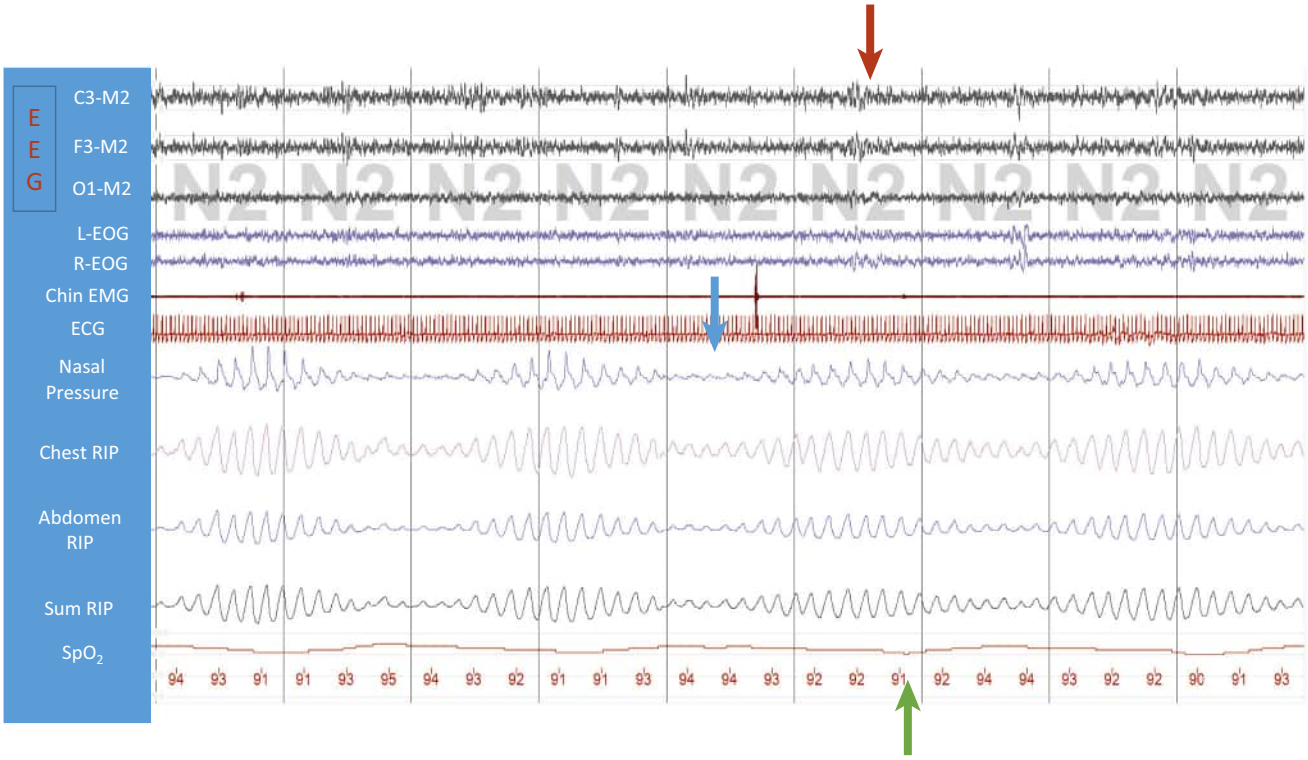
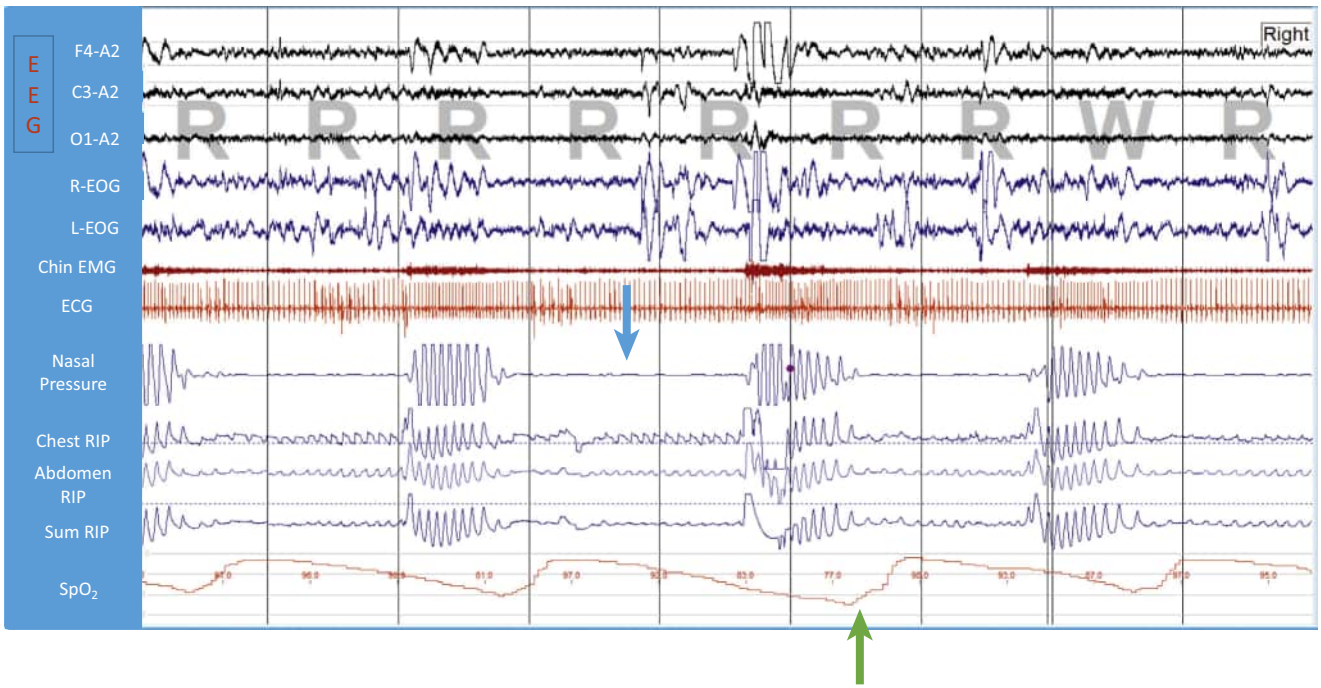
Complete reference list available at ExpertConsult.com.

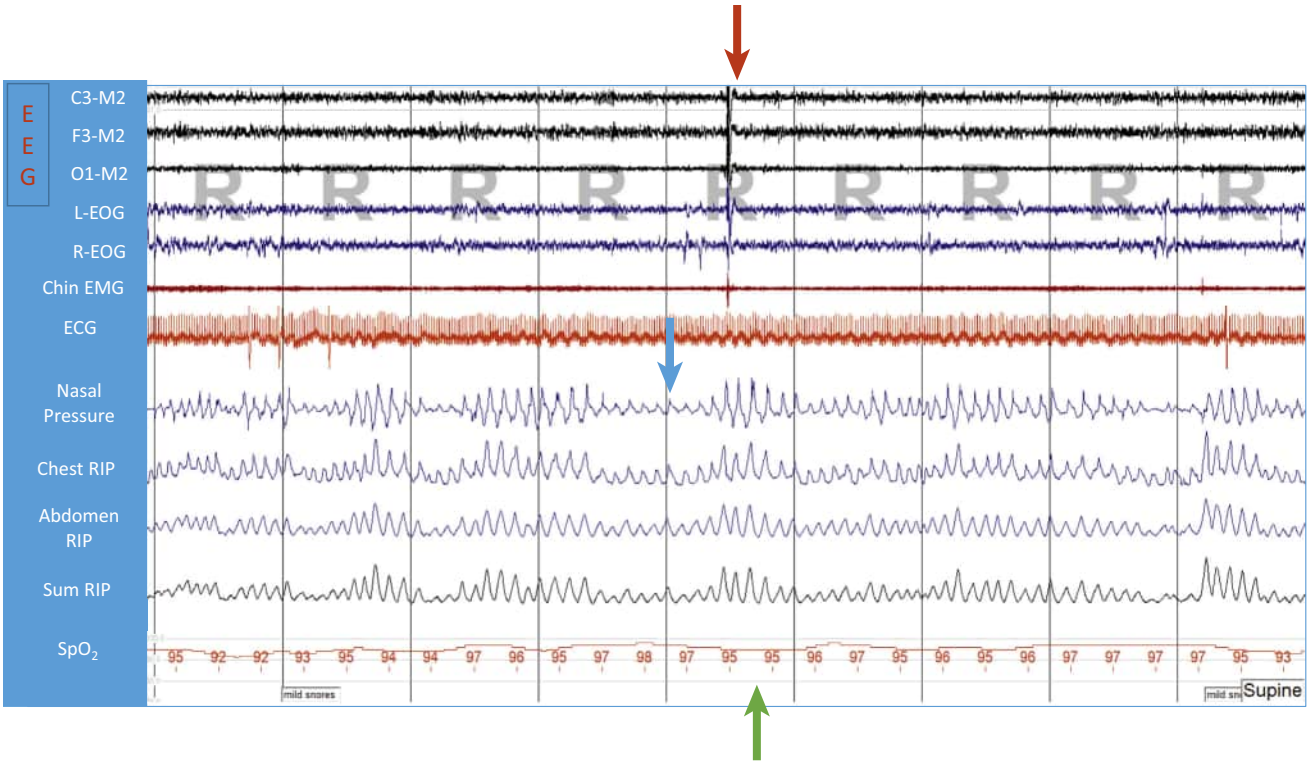
eFIGURE IMAGE GALLERY



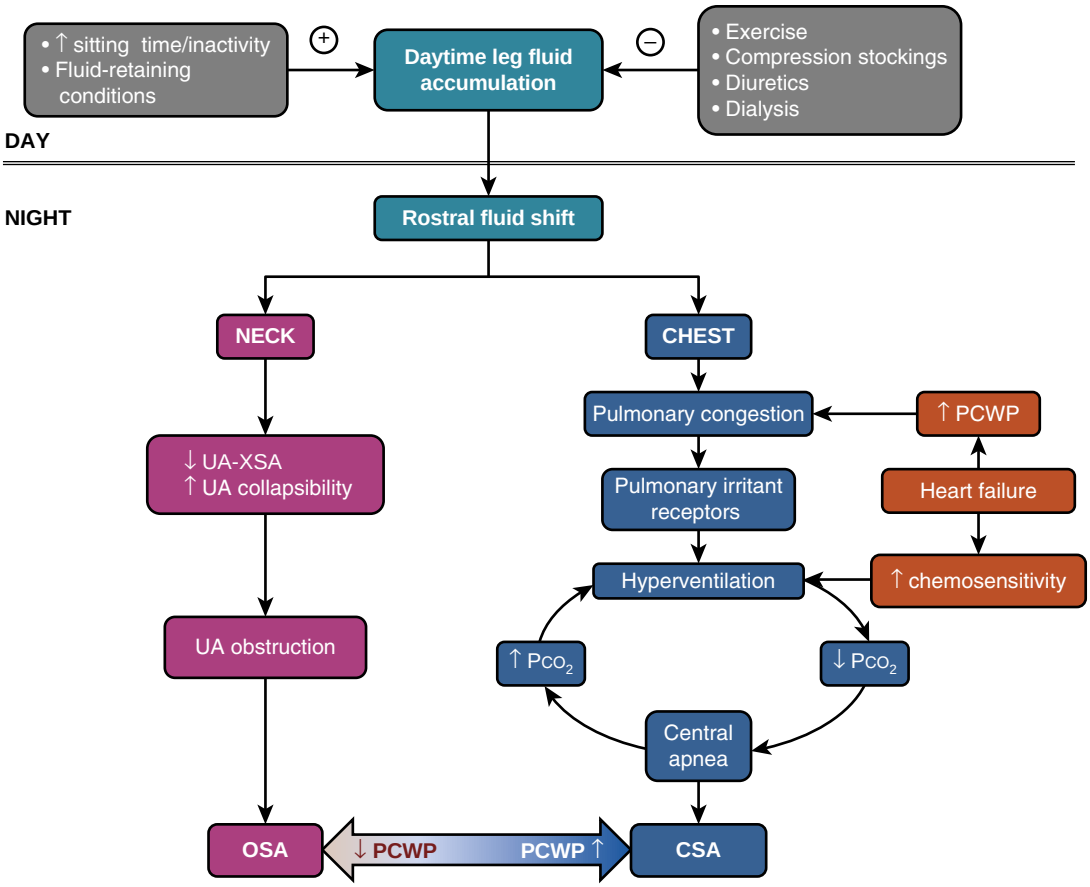
eFigure 121.1 Polysomnographic 5-minute recording of central hypopneas during stage N2 sleep in a Cheyne-Stokes respiration–central sleep apnea pattern. There are peak signal excursion drops of 30% or greater of pre-event baseline as illustrated by the nasal pressure, and there are in-phase motions of the rib cage and abdomen and reduced airflow (*blue arrow*). There is a 3% oxygen desaturation (*green arrow*) and an associated arousal on the electroencephalogram (*red arrow*). ECG, electrocardiogram; EEG, electroencephalogram; EMG, electromyogram; EOG, electrooculogram; RIP, respiratory inductance plethysmography; Spo_2, pulse oxygen saturation.



eFigure 121.2 Polysomnographic 5-minute recording of obstructive apneas during rapid eye movement sleep. There is an absence of airflow as illustrated by the nasal pressure transducer recording (*blue arrow*). There is paradoxical rib cage and abdominal motion. There is associated severe oxygen desaturation with the events (*green arrow*). ECG, electrocardiogram; EEG, electroencephalogram; EMG, electromyogram; EOG, electrooculogram; RIP, respiratory inductance plethysmography; Spo_2, pulse oxygen saturation.



eFigure 121.3 Polysomnographic 5-minute recording of obstructive hypopneas during rapid eye movement sleep. There are peak signal excursion drops of greater than or equal to 30% of pre-event baseline as illustrated by nasal pressure (*blue arrow*). There is paradoxical rib cage and abdominal motion. There is associated oxygen desaturation (*green arrow*) and arousal on the EEG (*red arrow*). ECG, electrocardiogram; EEG, electroencephalogram; EMG, electromyogram; EOG, electrooculogram; RIP, respiratory inductance plethysmography; Spo_2, pulse oxygen saturation.



eFigure 121.4 The role of overnight rostral fluid shift in the pathogenesis of obstructive and central sleep apnea (OSA and CSA). Overnight fluid shift from the legs to the neck can affect upper airway mechanics and lead to OSA, whereas fluid shift to the lungs can provoke hyperventilation, hypocapnia, and CSA. In addition, the type of apnea can shift from one type to another according to fluid status. Pco_2, partial pressure of carbon dioxide; PCWP, pulmonary capillary wedge pressure; UA, upper airway; UA-XSA, upper airway cross-sectional area. (From White LH, Bradley TD, Logan AG. Pathogenesis of obstructive sleep apnoea in hypertensive patients: role of fluid retention and nocturnal rostral fluid shift. *J Human Hypertens.* 2015;29:342–350.)

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122 SLEEP-DISORDERED BREATHING: TREATMENT

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INTRODUCTION

Sleep-disordered breathing comprises several entities: *obstructive sleep apnea* (OSA), *central sleep apnea* (CSA), CSA Cheyne-Stokes breathing, and sleep-related hypoventilation, each with specific pathophysiology and therefore specific treatment. OSA treatment is evolving in such a way that identification of endophenotypes of critical closing pressure, loop gain, arousal threshold, and muscle recruitment can be used to develop targeted, personalized therapeutic approaches. The chapter is mainly focused on the options for treatment of OSA.

CSA is characterized by temporary failure of breathing rhythm generation (from levels of arterial *partial pressure of carbon dioxide* [P_{CO_2}] falling to less than the apneic threshold) or lack of respiratory effort during cessation of air flow. CSA treatment is targeted by reducing the delta gap and stabilizing a high loop gain system. CSA, including treatment, is covered in depth in Chapter 121. Finally, sleep-related hypoventilation comprises a group of disorders resulting in hypercapnia and hypoxemia during sleep resulting from alveolar hypoventilation, neuromuscular disease, and/or primary pulmonary disease, with therapies aimed at addressing sleep-related hypercapnia and hypoxemia (see also Chapter 45).

An understanding of the physiologic basis of sleep breathing disorders is only one aspect of a more global understanding of which therapy is best suited for a given individual; patient preference, motivations to engage in treatment, social determinants of health (i.e., spousal support, stable housing, occupation requiring frequent travel), and history of compliance are also important considerations in selecting the most effective therapy.

OBSTRUCTIVE SLEEP APNEA

The most common sleep disorder the pulmonologist will be asked to evaluate in the outpatient setting is suspected OSA. Objective sleep testing should be obtained before initiation of any therapy for OSA to facilitate decision making about the most appropriate treatment option for an individual, which may include alternatives to *positive airway pressure* (PAP).[1] Discussions with patients with a new diagnosis of sleep apnea should include education about pathophysiology relevant to their comorbidities (i.e., sympathetic activation and the association with hypertension), symptoms (i.e., nocturia or daytime sleepiness), consequences of not engaging in treatment (i.e., risk of major adverse cardiac events), and treatment options available. For providers, a primary goal is to identify the therapeutic option the patient is most likely to engage with long term, to facilitate a shared decision-making process with patients when multiple therapies are appropriate, and to educate patients on the importance of behavioral changes in their success with chronic disease management.

Machine learning is gaining traction in the realm of predictive analytics for sleep medicine. The ability to identify patients who are most likely to adhere to any given therapy and those least likely to comply (i.e., refill a medication or apply a *continuous positive airway pressure* [CPAP] mask nightly) is critically important; one will require lesser resource intensity to achieve adherence with treatment, and the other will require greater engagement or should be considered for definitive treatment (i.e., maxillomandibular advancement). Data sources for deep learning models include electronic health records (e.g., comorbidities, medication refill records, demographics, health care use rates), nonmedical wearable devices (e.g., activity trackers or other applications with patient-generated data), sleep testing databases to identify patterns of upper airway obstruction and sleep disruption, genetic databases, and therapeutic databases (i.e., PAP manufacturers).

Selection of an initial therapy to treat OSA should be viewed as nonbinding. When one approach fails, others are often possible. Combination therapy is not uncommon (e.g., simultaneous use of a PAP device and an oral appliance), and most therapy options are not mutually

exclusive (e.g., surgical treatment does not preclude the use of PAP). Multiple therapies may be acceptable first-line treatments, and this approach should be tailored to the individual patient as much as possible. One such approach to thinking about therapeutic options is outlined in Figure 122.1.

NONSURGICAL OPTIONS

Numerous nonsurgical therapies are available for consideration in the treatment of OSA (Fig. 122.2), although treatment should be personalized as much as possible. Not all treatment options are appropriate for all patients with OSA. Factors to consider in the selection of treatments include severity of sleep apnea, patient preference (with emphasis on long-term adherence), urgency of the intervention (CPAP is immediate vs. 3 months to complete oral appliance evaluation, fabrication, and adjustments), presence and condition of dentition, patency of nasal air flow, comorbidities (e.g., reduced ejection fraction heart failure), medications (i.e., opioids or other medications that suppress ventilatory drive), and likelihood of engaging in chronic disease management (i.e., will they be able to make behavioral modifications to adhere to prescribed nightly treatment). Understanding the physiologic basis of the patient's sleep-disordered breathing will guide treatment decisions.

Weight Loss

Weight loss interventions through dietary approaches and/or exercise are strongly recommended to be included in the treatment approach of OSA by the American

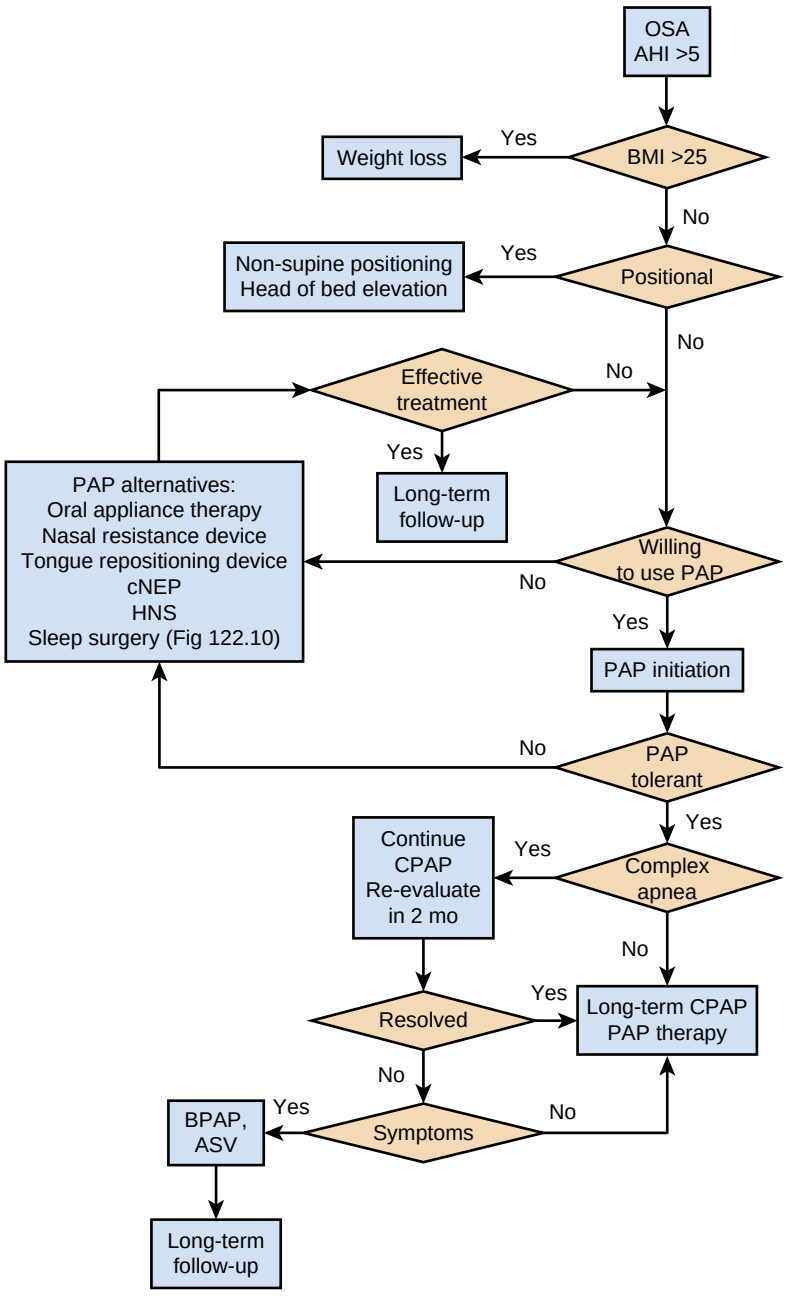

Figure 122.1 Algorithm for selecting appropriate therapies for the treatment of sleep-disordered breathing. An approach to understanding appropriate treatment options for *obstructive sleep apnea* (OSA). Weight loss is always recommended for patients who are overweight or obese. For those with sleep apnea only when supine, positional therapy may be sufficient as a stand-alone intervention. Both weight loss and positional therapy can be recommended in combination with any other treatment for obstructive sleep apnea. *Positive airway pressure* (PAP) remains the most common treatment, and the decision to proceed with PAP versus an alternative is based on a patient's preference. Evaluation of residual events following initiation of therapy facilitates identifying treatment-emergent central events (complex apnea). When these events persist and are associated with symptoms, the PAP mode can be changed to target resolution of these events. When PAP is not accepted or tolerated, treatment alternatives are considered. Some alternatives may be used in combination with any other therapies (i.e., *continuous positive airway pressure* [CPAP] and oral appliance, nasal resistance device and positional therapy). AHI, apnea-hypopnea index; ASV, adaptive servoventilation; BMI, body mass index; BPAP, bilevel positive airway pressure; cNEP, continuous negative external pressure; HNS, hypoglossal nerve stimulation.

Academy of Sleep Medicine,[2] particularly because the *body mass index* (BMI) of patients with OSA in sleep clinics is typically 30 to 40 kg/m^2.[3] At least nine randomized clinical trials support the utility of comprehensive lifestyle intervention compared with no intervention in patients with moderate to severe OSA for overweight and obese persons leading to improvement in the *apnea-hypopnea index* (AHI) and sleepiness symptoms. As such, a program including a reduced-calorie diet, exercise or increased physical activity, and behavioral counseling is strongly endorsed by existing guidelines.[4] Upper airway imaging data suggest that intensive lifestyle intervention or bariatric surgery–related weight loss may exert benefit on OSA pathophysiology by reducing volumes of upper airway soft tissue, including tongue fat.[5,6] Even modest weight loss of 10% observed in epidemiologic studies has been shown to reduce the AHI by 26%.[7] Dose-response relationships are present, so that the effect on AHI reduction is even more pronounced with more substantial weight loss.[8,9] Changes in AHI secondary to weight loss are accentuated in men compared with women.[10,11] Although the etiology of sex-specific differences in weight loss in OSA severity is unclear, a higher proportion of central adiposity in men, including visceral adiposity or hormonal influences on upper airway tone, is a plausible explanation. All lifestyle interventions (diet, exercise, and the combination) reduce the severity of OSA as defined by the AHI by similar magnitudes.[12] Anti-obesity pharmacologic therapy modestly improves OSA symptoms and severity, but benefits should be balanced with risks of these medications.[13] Gastric banding and lifestyle modification provide similar benefit of improving OSA severity and sleep symptoms. However, OSA-specific trials have not been performed to assess the impact of bariatric procedures resulting in greater weight loss, such as gastric bypass and sleeve gastrectomy, on OSA severity, although these surgical procedures may improve glycemic control and quality of life.[13]

Positional Therapy

Positional OSA (POSA) is characterized by breathing events happening exclusively or the majority of time when in the supine posture. Three classification systems are used for POSA: Cartwright, Bignold, and *Amsterdam Positional OSA Classification* (APOC). The Cartwright definition stipulates that POSA requires a 50% or more AHI difference between supine and nonsupine positions.[14] The Bignold criteria require "an overall AHI ≥15, supine AHI at least twice the nonsupine AHI; ≥20 min of sleep in supine and non-supine postures and non-supine AHI <15."[15] The APOC criteria focus on likelihood of benefit from positional therapy by defining three classes of POSA severity dependent on the relationship between the best and worst sleep position (on the basis of the AHI). All APOC classifications require at least 10% of sleep time in the best and worst sleep positions.[16] Patients classified as APOC I have an AHI lower than 5 in their best sleep position. APOC II allows for an AHI of 5 or more in the best sleep position, which should be in a lower AHI severity category than the overall AHI. APOC III is defined by an overall AHI higher than 40 and a 25% decrease from the overall AHI in the best sleep position.[16]

Population-based epidemiologic studies suggest a prevalence of POSA of 75% in middle-aged and older adults with OSA, and exclusively (sleep apnea present in *only* the supine position) in slightly more than one-third of patients with OSA, findings highlighting the importance of this entity.[17] Although POSA can be treated with PAP or oral appliances, positional therapy is effective and an excellent first-line treatment. Adherence to positional therapy has historically been unmeasurable and presumed to be low because of the challenge of remaining nonsupine during

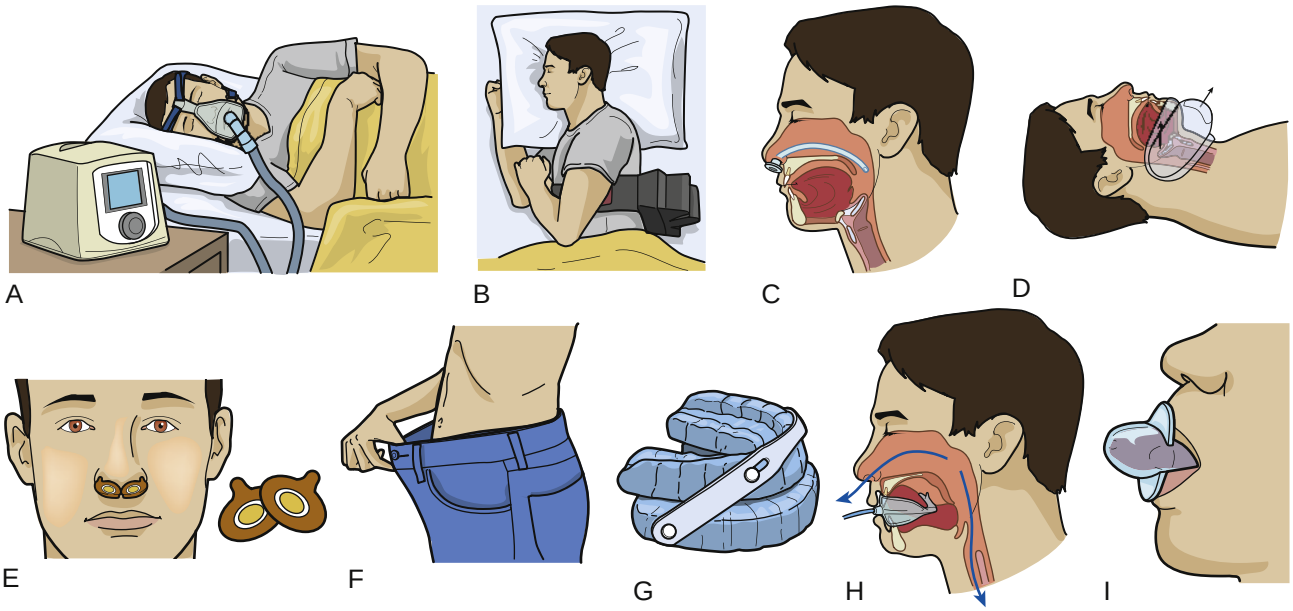

Figure 122.2 Noninvasive methods for treating obstructive sleep apnea. (A) Positive airway pressure, (B) positional devices, (C) nasal bypass, (D) continuous negative external pressure therapy, (E) nasal resistance device, (F) weight loss, (G) mandibular advancement device, (H) oral pressure therapy, and (I) tongue-retaining device.

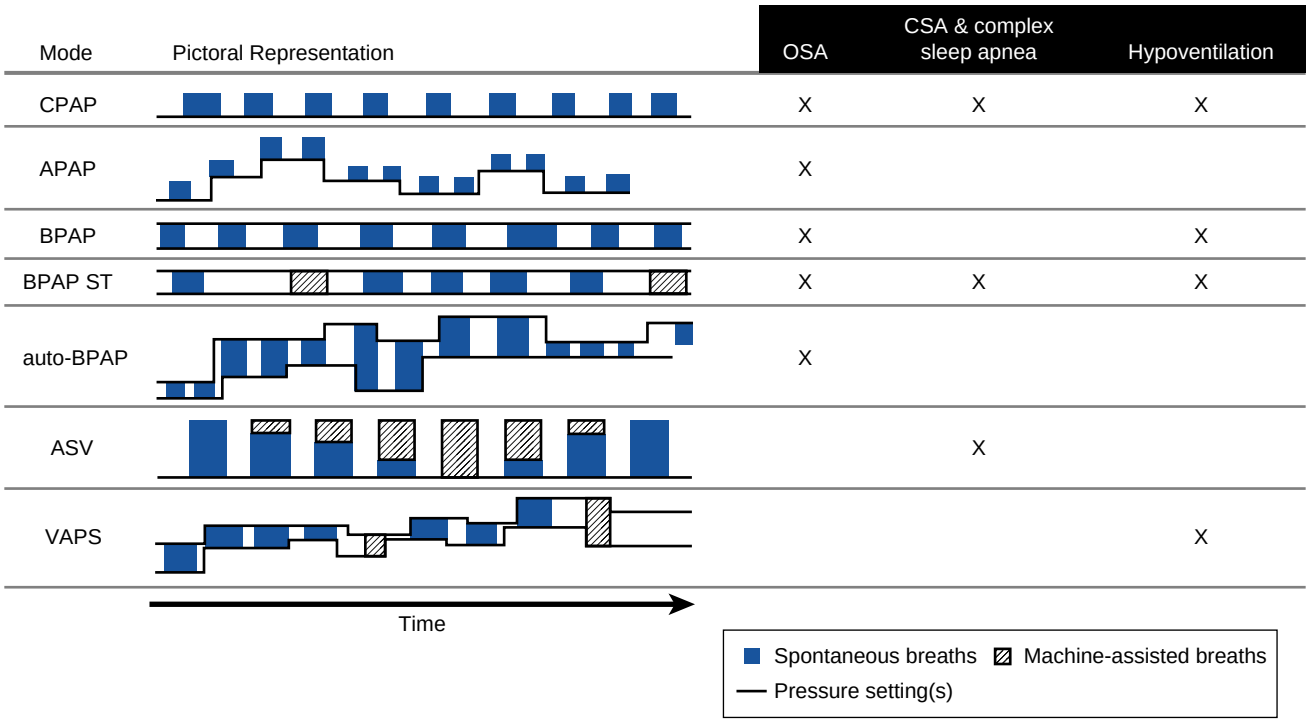

Figure 122.3 Positive airway pressure modes. Representation of different modes of positive airway pressure from simple to more complex, with the x-axis representing time and y-axis pressure. *Blue rectangles* represent patient-initiated breaths, and *black hatched rectangles* represent machine-initiated or assisted breaths. Which modes are appropriate for the three broad categories of sleep-disordered breathing are noted by an X. Continuous positive airway pressure is appropriate for obesity hypoventilation syndrome when moderate to severe obstructive sleep apnea is also present. Pressures are not drawn to scale. APAP, autotitrating positive airway pressure; Auto-BPAP, autotitrating bilevel positive airway pressure; ASV, adaptive servoventilation; BPAP, bilevel positive airway pressure; ST, spontaneous timed; VAPS, volume-assured pressure support. (From Cleveland Clinic Center for Medical Art & Photography © 2020. All rights reserved.)

the unconscious state of sleep; adherence is improved with more recent innovations to create low-profile, comfortable devices that alert users to undesirable positioning.[18] Newer-generation approaches involve attaching a small device to the neck or chest that delivers a subtle vibrating stimulus to serve as negative reinforcement for supine positioning. These devices are associated with high short-term adherence compared with 10% self-reported adherence with the traditional approach of tennis balls sewn into the back of a shirt or use of bulky attachments that prevent rolling onto the back.[18] In addition to nonsupine sleeping, even modest (7.5-degree) head-of-bed elevation is another positional therapy that may result in mild improvements in the AHI irrespective of lateral, prone, or supine position.[19] Head-of-bed elevation may also alleviate gastroesophageal reflux disease symptoms and thereby improve sleep architecture.

Positive Airway Pressure

CPAP serves as a pneumatic splint for the upper airway throughout the respiratory cycle, thus preventing collapse of the soft tissues in the upper airway and improving sleep architecture.[20] Proprietary algorithms have been developed by PAP manufacturers to adjust pressures dynamically according to continuous feedback from these devices. Autoadjusting devices such as *automatic PAP* (APAP) and *auto-bilevel PAP* (auto-BPAP) devices sense changes in flow and resistance in the circuit and, when flow is absent, send test air or sound pulses to determine whether lack of flow is the result of an obstructive or nonobstructive event. Detection of respiratory events guides these autoadjusting devices to increase or decrease the pressure being delivered (Fig. 122.3). The Centers for Medicare & Medicaid Services allow coverage of PAP therapy on the basis of an AHI or respiratory disturbance index of 15 or greater regardless of symptoms or comorbidities, or an AHI (or respiratory disturbance index) of 5 or higher if accompanied by other symptoms or complications, including history of stroke.[21]

Once a decision is made to initiate PAP therapy, a mode must be selected. PAP devices can be started following in-laboratory titration or by recommending empirical settings on an autoadjusting device such as APAP (Table 122.1). CPAP or APAP is generally recommended as initial therapy for OSA when treatment needs to be instituted immediately and when sleep apnea is severe.[1] Remote monitoring of PAP usage and efficacy can be performed through telehealth because most PAP devices are now equipped with modems to transmit data about usage (e.g., when the devices are turned on and how long they are used) and treatment outcomes (e.g., residual apneas and mean pressures required to achieve this) (Fig. 122.4). Use of remote monitoring is considered standard of care and facilitates delivery of sleep care through telephone and video chat visits (telemedicine).[1] There are entire care pathways engaging patients solely through telehealth, even for initiation of PAP, including mask fittings. Regardless of whether care is delivered in person or by telehealth, longitudinal follow-up by sleep medicine providers should be provided to ensure ongoing adherence to and tolerance of OSA therapy.[1]

Table 122.1 Settings Available for Each Mode of Positive Airway Pressure Devices (in cm H_2O)*

Mode	EPAP	$EPAP_{min}$	$EPAP_{max}$	IPAP	PS_{min}	PS_{max}	P_{max}	RR	VT (mL)
CPAP	4–20								
APAP		4	20						
BPAP-S	4–25			4–25					
BPAP-ST	4–25 or 30 (manufacturer dependent)			4–25				1–30/auto	
Auto-BPAP		4–25	25		0–8	PS_{min}+8	25		
ASV	4–25				0–3	0–21	25	4–30/auto	
VAPS	4–25				0–20	0–20	25	1–30/auto	200–1500 mL (6–8 mL PBW)

*Settings are informed by in-laboratory titration, empirically (i.e., APAP initiation), or by device download (i.e., Fig. 122.4). Pressures <5 cm H_2O are generally ineffective for obstructive sleep apnea. Higher pressure requirements correlate with higher apnea-hypopnea index and body mass index, particularly when weight is distributed centrally. The EPAP setting targets elimination of apneas, and IPAP targets resolution of hypopneas. All pressures can be adjusted based on review of efficacy data from the device. When ventilation is the goal, an IPAP-EPAP difference of at least 4 cm H_2O should be targeted. CPAP = EPAP = PEEP; PS = IPAP − EPAP; $P_{max} = EPAP_{max} + PS_{max} = IPAP_{max}$; VT based on patient-predicted body weight and disorder.

APAP, autotitrating positive airway pressure; ASV, adaptive servoventilation; auto-BPAP, autotitrating bilevel positive airway pressure; BPAP, bilevel positive airway pressure; CPAP, continuous positive airway pressure; EPAP, expiratory positive airway pressure; IPAP, inspiratory positive airway pressure; P_{max}, maximum pressure; PBW, predicted body weight; PS, pressure support; RR, respiratory rate; S, spontaneous; ST; spontaneous timed; VAPS, volume-assured pressure support; VT, tidal volume.

Continuous Positive Airway Pressure. CPAP, the most commonly used modality for OSA treatment, provides the same fixed pressure on both inspiration and expiration and has no set respiratory rate (see Fig. 122.3).[1] This expiratory PAP is analogous to positive end-expiratory pressure during mechanical ventilation, although pressure is transmitted largely to the upper airway. CPAP devices can be programmed with any pressure between 4 and 20 cm H_2O (see Table 122.1). Randomized clinical trials of CPAP therapy in OSA have shown consistent modest reduction in high blood pressure, improvement in sleepiness, and improvement in quality of life.[22–25] Some CPAP and APAP devices have an expiratory pressure relief setting triggered at the end of the inspiratory cycle that allows brief lowering of the pressure during exhalation. This setting is a comfort feature and is commonly used in patients who report difficulty exhaling against a constant pressure (pressure intolerance), but it has not been shown to improve adherence in patients without this symptom.[1]

Automatic Positive Airway Pressure. APAP is a mode very similar to CPAP in that only one pressure is delivered both for inspiration and expiration; however, this pressure can change throughout the night according to an algorithm sensing obstructive respiratory events (see Fig. 122.4). APAP settings require a range of pressures (e.g., 5 to 12 cm H_2O); if there is no range set (e.g., 5 to 5 cm H_2O), then the machine becomes equivalent to CPAP because it provides a single pressure on inspiration and expiration without adjustment throughout the period of use (see Table 122.1 and Fig. 122.3). APAP can either be used for an initial time-limited home titration, which guides selection of a fixed CPAP pressure,[26] or as long-term therapy. APAP can be initiated in patients with OSA without significant comorbidities, but it has not been systematically studied in other subgroups, particularly patients with chronic cardiac or respiratory failure.[26] For example, patients with heart failure who begin APAP should be closely monitored because standard APAP algorithms may perpetuate central and mixed events in this predisposed group, thereby posing a theoretical risk.[26,27]

APAP and CPAP adherence and patient preference are similar in adults. APAP may also be a reasonable alternative for patients experiencing aerophagia with CPAP because, with APAP, the pressure is continually adjusted throughout the night and often leads to a lower mean pressure on any given night than with CPAP, which is generally fixed at the highest pressure most effective at eliminating apneas during rapid eye movement or supine sleep.[28] That said, emerging data suggest that APAP may result in sleep disruption, somewhat offsetting the advantage conferred by CPAP therapy on outcomes such as improved blood pressure and renal function.[29–34] More data are needed to elucidate these APAP-specific influences more clearly. APAP is used only for OSA, not CSA, because the algorithms respond primarily to upper airway respiratory events. Inappropriate increases in pressure from APAP may result in periodic breathing or *treatment-emergent CSA* (i.e., emergence of central respiratory events as a result of PAP therapy, also referred to as complex sleep apnea).[35] However, treatment-emergent CSA can be seen with both CPAP and APAP modes. Often, treatment-emergent CSA is transient, resolving within 90 days (55%).[36] Treatment-emergent CSA can be persistent in 25% of patients and can be effectively treated with BPAP or adaptive servoventilation if clinically indicated.[36]

Bilevel Positive Airway Pressure. BPAP delivers two set pressures: a higher inspiratory pressure and a lower expiratory pressure (see Fig. 122.3). *Spontaneous mode BPAP* (BPAP-S) provides only patient-initiated breaths



Figure 122.4 A one-night positive airway pressure download. *Top box (purple):* The pressure curve throughout the night. *Middle box (blue):* Detected respiratory events, including periodic breathing (PB), clear airways (central) apneas (CA), obstructive apneas (OA), hypopneas (H), flow limitation (FL), vibratory snore (VS), and respiratory event-related arousals (RE). *Bottom box (yellow):* Information on unintentional leak throughout the night. Summary statistics are provided at right in each box. This download shows a high leak associated with increased respiratory events; the patient-mask interface should be assessed and adjusted as needed to improve device performance. AHI, apnea-hypopnea index; CPAP, continuous positive airway pressure; LPM, liters per minute; max, maximum; min, minimum.

compared with a BPAP-*spontaneous and timed* (ST) BPAP mode, which involves a device-delivered breath if a patient-initiated breath is not sensed in a prespecified time period (Table 122.2). For patients reporting pressure intolerance or aerophagia without benefit from expiratory relief on APAP, BPAP is a reasonable alternative, given the lower expiratory pressure level delivered. BPAP devices also offer the flexibility to increase inspiratory pressure to greater than 20 cm H_2O when higher pressure is needed.

Auto-BPAP is a mode where the *expiratory PAP* (EPAP) and pressure support, which jointly determine the *inspiratory PAP*, can each vary within a limited range. The set values are the EPAP range, pressure support range, and inspiratory PAP maximum (see Fig. 122.3 and Table 122.1). The range of pressure support varies by the device manufacturer, with most using a flow trigger to determine inspiratory PAP. Auto-BPAP is appropriate for treating OSA but not CSA.

Adherence to Therapy

PAP therapy is typically quite effective in reversing OSA pathophysiology; however, when adherence is suboptimal, symptom-related and health benefits are not realized.[37–40] Increasing age, early PAP adherence, self-reported daytime somnolence, treatment-emergent CSA, and psychological traits have most consistently been identified as both positive and negative predictors of long-term PAP adherence.[36,40] Psychological associations with low PAP adherence include depression, hypochondriac personality, avoidant coping strategies, and low self-efficacy (belief in one's ability to execute behaviors to attain treatment goals).[41] Numerous factors can compromise tolerance of or willingness to use PAP (Table 122.3). Key strategies to optimize adherence

Table 122.2 Modes of Ventilation

Modes of Ventilation	Interpretation
Spontaneous (S)	1. Breaths are patient triggered, pressure limited, and flow cycled. 2. Breaths are triggered by patient effort. Breathing frequency is determined by the patient. The effort needed to start a breath is either determined by software or set by the clinician. Devices of different manufacturers trigger differently. 3. Breaths arc flow cycled from inhalation to exhalation. This can be determined by the software or the clinician. Devices of different manufacturers cycle differently.
Pressure control (PC)	1. Breaths are patient or time triggered, pressure limited, and time cycled. 2. Breaths are triggered by the patient or by the ventilator if the patient becomes apneic. 3. Breaths are cycled by the set inspiratory time.
Spontaneous timed (ST)	Combination of above: 1. Breaths are triggered by the ventilator when the patient's breathing rate falls below the backup rate. 2. Breaths are pressure supported if triggered by the patient or pressure controlled if triggered by the ventilator.

From Sahni AS, Wolfe L. Respiratory care in neuromuscular diseases. *Respir Care*. 2018;63(5):601–608.

include disease education, discussion of treatment goals, establishing a patient support network (including peer-to-peer support), and early and consistent follow-up.[42] Motivational interviewing, cognitive-behavioral therapy–based interventions and, in the PAP NAP study, an abbreviated sleep study to facilitate PAP desensitization and acclimatization, have proven to be beneficial in optimizing PAP adherence.[43,44]

Negative External Pressure Therapy

Continuous negative external pressure (cNEP) therapy is still in trial phases for home use in the United States. The basis of cNEP is similar to the concept of iron lung ventilation, in which negative extrathoracic pressure rather than PAP is applied to facilitate ventilation. Patients with OSA have higher critical closing pressures (a measurement of upper airway collapsibility) than patients without OSA. In patients with OSA, the critical closing pressure is close to atmospheric pressure, whereas the pressure in patients without OSA is markedly negative.[45] cNEP involves applying negative external pressure to the neck, thereby decreasing the critical closing pressure toward normal. As negative pressure is created within a soft silicone collar, which is fitted across the anterior neck surface connected to a vacuum pump, the soft tissue structures comprising the pharyngeal airway are pulled anteriorly, mitigating airway collapsibility. The cNEP device reduces obstructive apneas in patients undergoing mild to moderate sedation and has been approved for use in procedural settings (i.e., same-day surgery, colonoscopy) to maintain upper airway patency in patients

Table 122.3 Troubleshooting Common Issues for Positive Airway Pressure Treatment That May Affect Adherence

Issue	Possible Solutions
Hesitancy about trying therapy or difficulty maintaining therapy	■ Education ■ Motivational interviewing ■ Early and consistent follow-up ■ Peer support group ■ PAP buddies (pairing an experienced and adherent peer coach with new PAP user) ■ PAP nap (short supervised nap in a sleep laboratory to address barriers and provide reassurance)
Nasal congestion	■ Increasing humidification ■ Checking for mask leak ■ Checking for mouth breathing ■ Nasal steroids ■ Oral antihistamines ■ Nasal saline rinse ■ Otolaryngology referral
Air leaks	■ Assessment of mask fit ■ Change of mask for improved cushion seal ■ Change of mask for hose location (e.g., to the top of head for frequent turners) ■ Chinstrap if mouth breathing with nasal or nasal pillow mask ■ Adjustment of hose placement to reduce traction on mask ■ Shaving of facial hair
Claustrophobia	■ Desensitization ■ Low-profile mask ■ Helmet mask
Aerophagia	■ Elevation of head of bed ■ Expiratory pressure relief ■ Transition from CPAP to APAP ■ Transition from CPAP/APAP to BPAP ■ Increase in ramp time and decrease in ramp pressure ■ Treatment of underlying GERD ■ Consideration of metoclopramide to increase lower esophageal sphincter tone
Pressure too low: suffocation	■ Increase in CPAP pressure ■ Increase in IPAP on BPAP ■ Increase in minimum pressure for APAP or EPAP for BPAP, ASV, or VAPS
Pressure too high	■ Enabling of ramp feature to lower pressures temporarily for up to 45 min or to match the patient's sleep latency ■ Decrease in maximum APAP pressure to 2 cm H_2O above 90th or 95th percentile pressure use on PAP download ■ Switch from CPAP to APAP ■ Expiratory pressure relief ■ Transition from CPAP/APAP to BPAP ■ In BPAP modes, decrease in EPAP and, if needed to treat resulting residual hypopneas, increase in pressure support

APAP, autotitrating positive airway pressure; ASV, adaptive servo-ventilation; BPAP, bilevel positive airway pressure; CPAP, continuous positive airway pressure; EPAP, expiratory positive airway pressure; GERD, gastroesophageal reflux disease; IPAP, inspiratory positive airway pressure; PAP, positive airway pressure; PAP nap, abbreviated sleep study to facilitate positive airway pressure desensitization and acclimatization; VAPS, volume-assured pressure support.

with OSA.[46] cNEP therapy has been found to be effective with few side effects and appears to be safe and effective for short-term OSA treatment.[47] However, larger trials are needed to document efficacy and adherence to this therapy before large-scale adoption.

Nasal Therapies

The nasal end-expiratory PAP devices create a back-pressure in the oropharynx by using the patient's own breathing to create increased resistance during expiration (see Fig. 122.2). The oropharyngeal back-pressure created during expiration prevents collapse of the upper airway and increases functional residual capacity, thereby treating OSA. This is the same mechanism as PAP; however, these are either disposable or multiple-use devices that do not require any electricity, tubing, or water instillation. Instead, a device attaches to and occludes the nares. Therefore, this option is advantageous to patients who do not have access to electricity (e.g., while camping) or are intolerant of PAP therapy secondary to claustrophobia. Nasal end-expiratory PAP reduces the AHI and oxygen desaturation index by 40–50% and improves the lowest oxygen desaturation.[48]

Therapies targeting improved air flow through nasal passages, including nasal corticosteroids, montelukast, and internal or external dilators, can improve snoring but have not been shown to be effective in controlling moderate to severe sleep apnea in adults.[49–51] Internal dilators are effective in the treatment of nasal valve collapse, which improves nasal air flow, but effectiveness in treatment of mild sleep apnea remains unclear.[52] For patients with OSA and nasal congestion, nasal steroids and similar therapies are recommended before starting PAP to decrease the PAP pressure needed to control respiratory events and to improve adherence.[53,54]

Oral Appliances

Mandibular Advancement Device. *Mandibular advancement devices* (MADs) are oral appliances that have shown benefit for some indications (see Fig. 122.2). Although PAP remains the mainstay of therapy for OSA, according to the most recent American Academy of Sleep Medicine and American Academy of Dental Sleep Medicine clinical guidelines,[55] MADs are recommended for use in primary snoring and as a first-line alternative to CPAP for mild to moderate OSA.[56,57] MADs can also be an adjunct to PAP therapy to decrease the pressure needed for effective therapy.[56,57] Custom oral appliances are tightly fitted on both upper and lower dental arches and are connected through a variety of mechanisms (i.e., hooks, rubber or plastic bands, or they are fixed in place), and lower and advance the jaw in a protruded state, thereby increasing both the posterior pharyngeal space and the critical closing pressure.[58] Candidates should have at least eight supporting teeth per arch, healthy periodontal tissue, a protrusion range of more than 5 mm, mandibular bone loss of less than 50%, and evenly distributed occlusal tooth contact.[55] Compared with PAP devices, MADs are considered more comfortable by many patients, are more portable, and require less maintenance. Short-term side effects include excessive salivation or dryness, tooth pain, gum soreness, gingival irritation, and myofascial pain. Custom, titratable devices made by qualified dentists with expertise in MAD therapy are preferred over other commercially available boil-and-bite devices.[56] MAD adherence is often greater than for CPAP, albeit with attenuated improvement in AHI and hypoxemia indices and comparable improvement in degree of subjective sleepiness symptoms.[59] There is also evidence that a MAD improves 24-hour ambulatory blood pressure measures and markers of inflammation.[57]

Tongue-Repositioning Devices. Several devices reposition the tongue to prevent it from occluding the upper airway (see Fig. 122.2). Devices may be applied directly to the tongue itself (anterior displacement), or they may use negative intraoral pressure through active continuous suction to draw oropharyngeal soft tissue, particularly the tongue, anteriorly and superiorly toward the hard palate.[60] Reported success rates varied widely from 23–71% on the basis of the definition of successful treatment; however, when the definition of success was a decrease of AHI of at least 50% *and* a reduction of AHI to less than 10, success rates were 25–37%.[61]

Nocturnal Supplemental Oxygen

Nocturnal supplemental oxygen (NSO) in OSA can address obstructive respiratory event–related hypoxemia; however, except for a small proportion of patients with high loop gain and modest airway collapsibility, NSO does not directly address the obstructive airway events of OSA.[62] Practically, because associated hypoxemia is inherent in scoring of hypopnea events, NSO can mask identification of hypopnea events, thereby leading to underestimation of the true degree of OSA. Sympathetic nervous system activation, large swings in intrathoracic pressure, and sleep fragmentation are consequences of upper airway collapse that will persist in most patients with isolated supplemental oxygen administration.[63] NSO has minimal impact on sleep architecture and neurobehavioral OSA consequences.[64–66] Although intermittent hypoxemia increases blood pressure in experimental animal models, NSO has not been shown to reduce blood pressure profiles in clinical trials. This finding suggests that other nonhypoxemic mechanisms such as microarousals and/or sleep fragmentation likely contribute to blood pressure elevation in OSA.[24,67] However, a more recent clinical trial using higher-flow NSO rates (5 L/min vs. 2 to 3 L/min used in previously published studies) did show an effect on blood pressure.[68] This crossover trial consisted of participants with moderate to severe OSA. Participants were taken off their CPAP therapy (CPAP withdrawal) and randomized to either NSO or room air for 14 nights. Participants had a 14-night washout period on their usual CPAP settings followed by 14 nights of the other trial condition (room air or NSO). The investigators found that NSO prevented morning blood pressure elevation seen in the control (room air) condition as well as reversal of hypoxemia but without improvement in sleepiness between the groups.[68] NSO in this trial abolished the morning rise in blood pressure after CPAP withdrawal.[68] Although these data suggest a potential favorable role for NSO in OSA on blood pressure, additional well-conducted trials are needed to verify these findings. Of note, NSO is also used as an adjunct to

PAP therapy when sleep-related hypoxemia persists after obstructive respiratory events are eliminated by PAP, as is often seen in patients with underlying cardiopulmonary disease who are on the steep portion of the oxyhemoglobin dissociation curve. However, hypoventilation as a cause of hypoxemia in these patients should be ruled out before initiation of NSO.

Pharmacologic Therapy

Tidal volume and respiratory rate are attenuated during sleep compared with wakefulness. In patients with a low arousal threshold, sleep is disrupted more easily. These disruptions may trigger changes in ventilation, thus leading to vacillations between high and low minute ventilation. This predisposes to cyclic respiratory events such as periodic breathing as well as postarousal central apneas. Medications promoting sleep and sedation can both increase the arousal threshold and reduce ventilatory instability by altering loop gain (see also Chapter 117).

When used in reference to ventilation, *loop gain* describes the stability of the respiratory system and is characterized as being high or low. Physiologically, loop gain reflects the degree of compensation in ventilation triggered by a given disturbance (i.e., an arousal). High loop gain promotes unstable breathing by triggering an overcompensation in ventilatory response to a given stimulus. This hyperventilation may, in turn, become the perpetuating stimulus for further disordered breathing events. Several small studies have shown that short-term (1 night) administration of medications such as acetazolamide attenuate loop gain and improve the AHI.[69–71]

Although there are no approved drug therapies to reduce apnea severity, a crossover trial of atomoxetine (a selective norepinephrine reuptake inhibitor) and oxybutynin (an antimuscarinic agent) decreased AHI by 63% (mean, 28.5 to 7.5).[72] Atomoxetine alone improved Epworth sleepiness scores and global quality of life measures, but it did not produce a significant change in AHI.[73] However, larger trials over a longer follow-up period are lacking.

Psychostimulant pharmacologic therapy in patients with OSA and residual hypersomnia despite optimal PAP adherence and sufficient sleep with no other identifiable somnogenic contributing factors (i.e., another organic sleep disorders such as periodic limb movement disorder) consists of Food and Drug Administration schedule IV drugs (i.e., with a low potential for abuse or dependence). Residual hypersomnia after adequate OSA treatment is reported in 10–60% of patients,[74,75] and it is putatively attributable to long-term intermittent hypoxemic exposure and sleep fragmentation, leading to injury of the wake-promoting neurons.[76,77] Improvement in overall functioning with the use of modafinil, a psychoactive drug that increases wakefulness by unknown mechanisms, was 61–68%, respectively, compared with 38% in the placebo arm.[78] Armodafinil, the r-enantiomer of modafinil, is also effective for improving sleepiness, fatigue, and overall clinical condition.[79] Solriamfetol, a selective dopamine and norepinephrine reuptake inhibitor, improves sleepiness measured both objectively and subjectively.[80] Other stimulants can also be used, including methylphenidate, amphetamine salts, and dexamphetamine. However, there is little published evidence on the safety and efficacy of these medications for this purpose.

SURGICAL OPTIONS: ANATOMIC TARGETS (See Chapter 70)

How to Think About Upper Airway Surgery for Obstructive Sleep Apnea

Upper airway surgery has become an important option in the care of patients with OSA. Sleep surgery is part of a continuum of care for OSA that involves medical, pharmacologic, and behavioral therapy. The main purpose of upper airway surgery for OSA is not necessarily to achieve "cure" based on the AHI alone. The chronic nature of OSA means that ongoing management will always be required. However, an effective reduction in AHI from surgery allows patients more options for treatment.

Upper airway surgery for OSA may not alter arousal threshold, loop gain, or muscle tone. It can, however, significantly change the critical closing pressure.[81] This is the same mechanism of action as PAP or MADs. The aim of surgery for OSA is restoration of function rather than mere reconstruction of anatomy.[82]

Sleep surgery has historically been viewed as having a phased approach.[83] Phase 1 involves soft tissue surgery such as tonsillectomy, uvulopalatal flap, septoplasty and turbinate reduction, uvulopalatopharyngoplasty, hyoid suspension, or genioglossus advancement, or a combination of these (expanded descriptions later).[83,84] Phase 2 operations include skeletal surgery such as maxillomandibular advancement.

Nasal Procedures

Every effort is made to establish nasal breathing, instead of mouth breathing, for all patients. Assessment should involve endoscopic examination to identify all possible anatomic and functional causes of nasal obstruction.[85] Whereas there is only modest correlation between the severity of disease and grading of airway collapse during Mueller's maneuver, the negative pressure maneuver is a quick method to assess upper airway collapsibility.[86] A mandibular protrusion maneuver can be performed at the same time to visualize the degree of lateral pharyngeal wall dilation and tongue base advancement. Of note, dynamic airway assessment has been augmented with examination under *drug-induced sedation (sleep) endoscopy* (DISE)[87,88] (Video 122.1).

In the office, nasal examination is not limited to the nose. Long-term nasal obstruction leads to facial changes, most often in the appearance of a long midface, open bite, and retruded mandible. Intraoral examination tends to show narrow, high-arch maxilla with the appearance of a relatively large tongue and redundant soft palatal tissue. This is the classic adenoid facies associated with chronic mouth breathing.[89–91]

The internal nasal valve, the most restrictive location of nasal air flow, is a key area for intervention. The internal nasal valve includes the septum, the inferior turbinates, the upper lateral cartilage, and the nasal floor. Patients can undergo procedures to address each of the indicated areas. Whereas operations addressing the septum (septoplasty), nasal valve collapse (valve reconstruction or stabilization

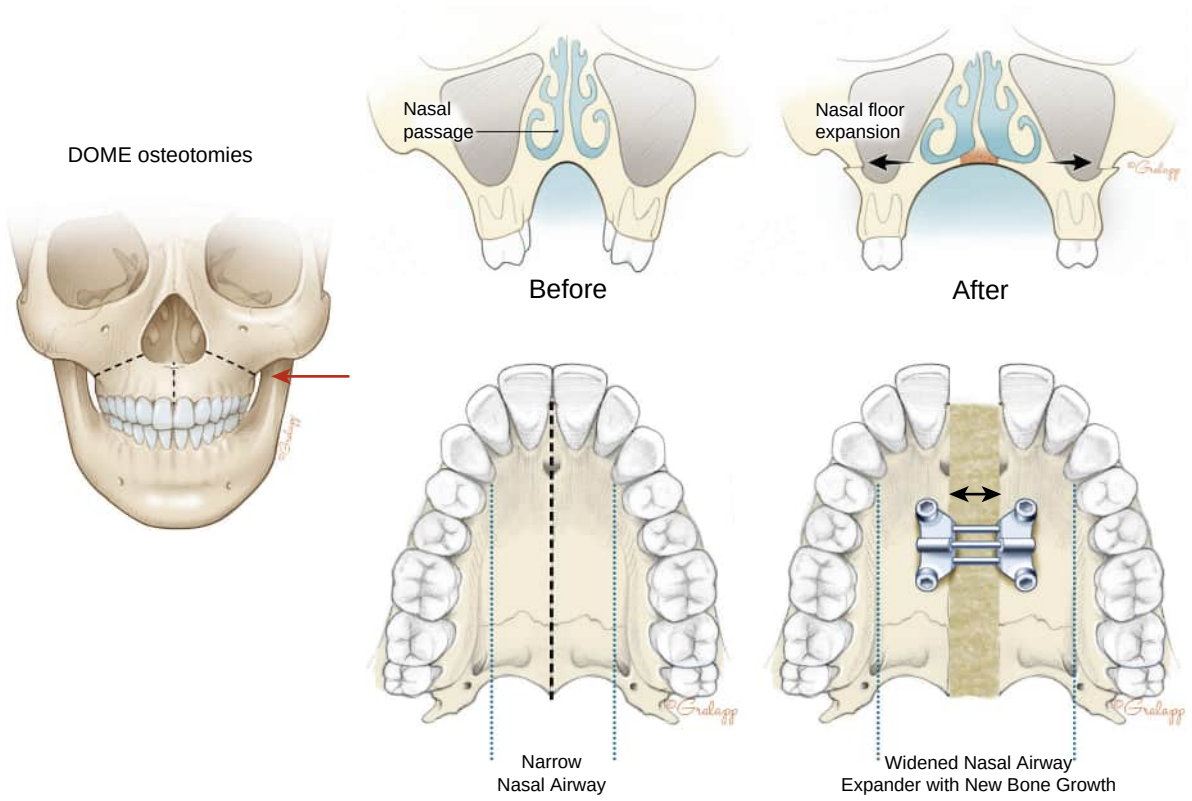

Figure 122.5 Expansion of the nasal floor and palatal roof with *distraction osteogenesis with maxillary expansion* (DOME). Conceptually similar to pediatric rapid maxillary expansion, DOME effectively addresses the same anatomic phenotype in adults. The procedure involves osteotomy only at the Lefort 1 level (*red arrow*), followed by splitting of the midpalatal suture. The goal of DOME is to transform a narrow, arch-shaped palate into a wider, dome-shaped palate, thereby creating greater intraoral and nasal airway volumes. The nasal floor at the internal nasal valve can expand 8 to 10 mm within 1 to 2 months. Orthodontic treatment is required to restore occlusion. (Copyright 2017 Chris Gralapp. Courtesy Christine Gralapp, CMI/chrisgralapp.com.)

procedures), and inferior turbinate reduction (submucosal procedures using various modalities) are well known, expansion of the nasal floor for adults is described more recently. This is particularly helpful with a phenotype of patients with OSA who present with a narrow and high-arch maxilla.[91] They tend to struggle with both nasal obstruction and lack of intraoral volume for the tongue during sleep. For this subgroup, intranasal surgery may not be adequate, and *distraction osteogenesis with maxillary expansion* (DOME) has shown promising results.[92–95] Minimally invasive osteotomies can be made at the Lefort I level through an intranasal incision. A miniscrew-secured expander is placed at the roof of the maxilla. The patient turns the expander fairly rapidly at a rate of 0.025 mm a day, which generally results in 8 to 10 mm of widened nasal floor at the internal nasal valve in a month. Orthodontic treatment restores the occlusion. Conceptually similar to pediatric rapid maxillary expansion, DOME effectively addresses the same anatomic phenotype in adults.[95–99] (Fig. 122.5).

Soft Palate Procedures

Uvulopalatopharyngoplasty remains the most commonly performed sleep surgical procedure worldwide.[100] Most surgeons specialized in OSA have stopped performing earlier methods of uvulopalatopharyngoplasty, which tend to be ablative by including resection of the uvula. This is particularly true in procedures such as the laser-assisted uvulopalatopharyngoplasty, which worsened AHI in 44% of patients, according to meta-analysis.[101] Isolated soft palate surgery has the highest success rate in Friedman stage I patients who have enlarged tonsils but an otherwise uncrowded, unobstructed airway.[102] In clinical practice, various forms of uvulopalatopharyngoplasty are often performed as part of multilevel surgery to maximize surgical success.[83,103,104] In the classic phased protocol described earlier, a uvulopalatal flap is performed as part of multilevel surgery with genioglossus advancement during phase 1. The uvulopalatal flap was designed as a reversible soft palate procedure in the event of velopharyngeal (soft palate) insufficiency, which can lead to alterations in speech and nasal sounds.[84] Most forms of contemporary uvulopalatopharyngoplasty focus on palatal muscle expansion and stabilization with targeted vectors during suturing.[105–108] Another indication for isolated uvulopalatopharyngoplasty is part of a phased approach toward *hypoglossal nerve stimulation* (HNS). Because complete concentric collapse of the soft palate (velum) seen during DISE is an exclusion criterion for HNS, palatopharyngoplasty can reverse this collapse pattern and thereby increases candidacy for HNS[109] (Fig. 122.6).

Tongue Muscle Strengthening: Genioglossus Advancement

Genioglossus advancement is usually performed in conjunction with other procedures (uvulopalatopharyngoplasty,

maxillomandibular advancement).[110] The genioglossus muscle, one of the most powerful dilators of the upper airway, is attached to the genial tubercles (bony protuberances on the inside of the anterior mandible). By advancing the genial tubercles, contractility of the genioglossus muscle increases through muscle fiber remodeling, thus allowing greater tongue advancement during sleep.[111] With the wide availability of computed tomography, virtual surgical planning and cutting guides allow the contemporary genioglossus advancement to be considerably more precise.[112] Genioglossus advancement can often be performed in conjunction with genioplasty (chin advancement) to improve overall facial balance in retrognathic patients.[113] This combination also exerts strengthening effects on the suprahyoid muscles (Fig. 122.7).

Tongue Volume Reduction: Lingual Tonsillectomy

Reduction of the posterior tongue volume and lingual tonsillectomy can be accomplished by the use of laser, robotic assistance or coblation (i.e., controlled ablation, involving radiofrequency at a low temperature).[114–116] The removal of tissue in this area can be supplemented by an anterior anchorage of the epiglottis to the base of the tongue for treating epiglottis collapse. With high-quality optics for improved visualization and instrumentation, robotics have been adapted and introduced to target the posterior tongue.[116,117] Although transoral robotic surgery offers unparalleled visualization, the use of multiarmed robots originally designed for the abdominal cavity can be cumbersome for the upper airway. Results for the use of transoral robotic surgery as part of a multilevel surgical approach for OSA are promising for selected patients. However, the cost and morbidity may be greater than with other techniques, thereby offsetting its advantages in visualization and precision.[118] The advent of a single-port robot system designed for single-cavity operative sites is promising.[119] Augmented reality–assisted transoral robotic surgery using a single-port robot will reduce morbidity such as bleeding and increase precision in distinguishing fat from muscle.[120]

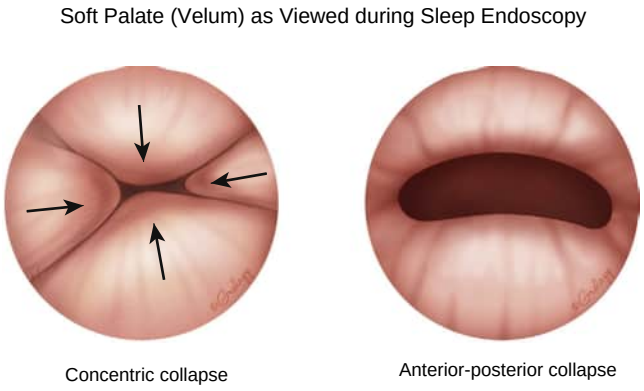

Figure 122.6 Change of concentric collapse at velum with palatopharyngoplasty. *Left*, Concentric collapse at the velum has been shown not to benefit from *hypoglossal nerve stimulation* (HNS) and is thus a contraindication. *Right*, Palatopharyngoplasty can be performed to alter this pattern so that now, with anterior-posterior collapse, patients become eligible for HNS. (Copyright 2017 Chris Gralapp. Courtesy Christine Gralapp, CMI/chrisgralapp.com.)

Hypoglossal Nerve Stimulation

HNS, a surgical treatment for OSA, targets reduced upper airway dilator muscle activity during sleep without altering the anatomy (Fig. 122.8). It generates a unilateral respiration-synchronized stimulation of the medial hypoglossal nerve branches and C1 nerve, leading to tongue stiffening and protrusion during sleep through the genioglossus and geniohyoid muscles (lowering critical closing pressure). The hypoglossal nerve (cranial nerve XII) innervates both the tongue protrusor (genioglossus) and retrusor (styloglossus and hyoglossus) muscles through its medial and lateral divisions. Selective stimulation of the protrusor muscles leads to anterior movement of the tongue and causes an increased air flow and reduced pharyngeal collapse during sleep.[121] Selective stimulation of the deep and horizontally oriented genioglossus fibers results in curling and stiffening of the tongue, thus further increasing patency of the upper airway[122] (Video 122.2).

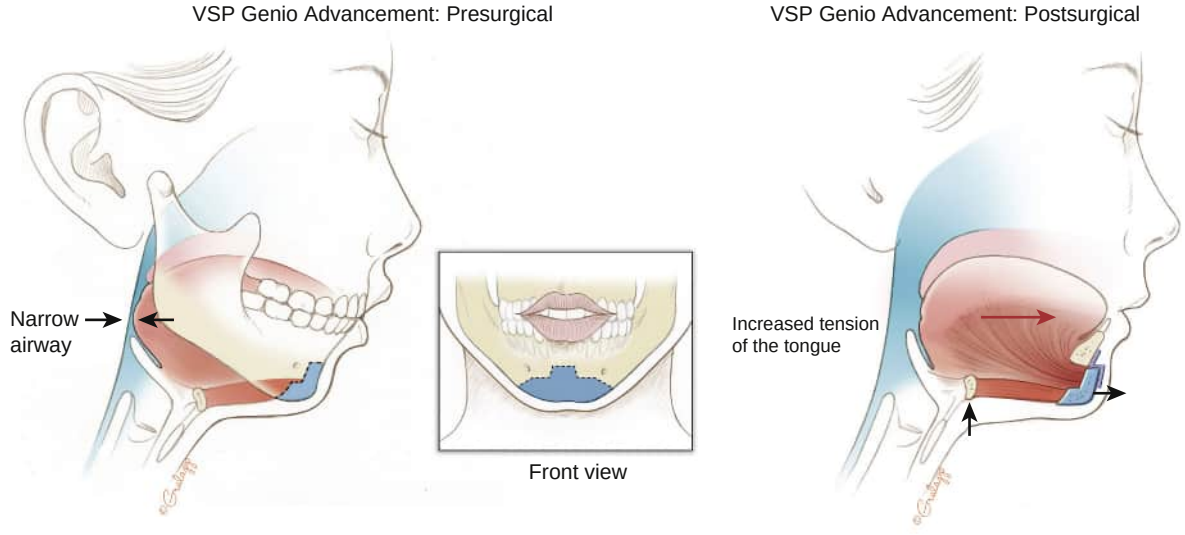

Figure 122.7 Contemporary genioglossus advancement and genioplasty (Genio). Virtual surgical planning (VSP) and cutting guides allow genioglossus advancement with or without genioplasty to be considerably more precise. The airway is widened by the anterior advancement of the genioglossus and the chin. (Copyright 2017 Chris Gralapp. Courtesy Christine Gralapp, CMI/chrisgralapp.com.)

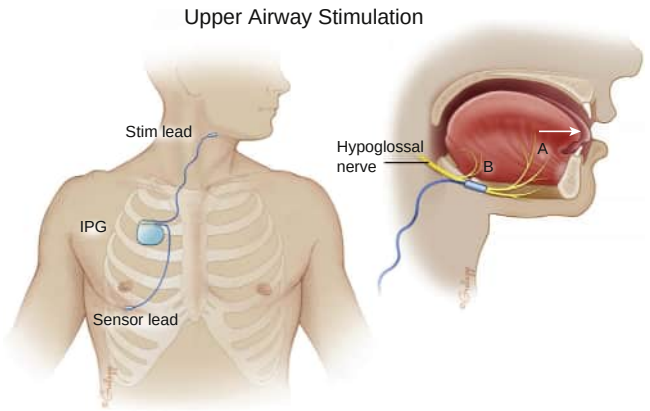

Figure 122.8 Hypoglossal nerve stimulation. The hypoglossal nerve (cranial nerve XII) innervates the tongue protrusor (genioglossus) and retrusor (styloglossus and hyoglossus) muscles through its medial and lateral divisions, respectively. Selective stimulation of the protrusor muscles leads to anterior movement of the tongue and results in increased air flow and reduced pharyngeal collapse during sleep. The stimulation lead is placed around the medial branches (protrusor, *B*), whereas the lateral branches (retrusor, *A*) are excluded. The sensing lead is placed between the internal and external intercostal muscles for timing the stimulation with breathing. The implantable pulse generator (IPG) receives input from the sensing lead and signals the stimulation lead to activate the hypoglossal nerve at the end of expiration. (Copyright 2017 Chris Gralapp. Courtesy Christine Gralapp, CMI/chrisgralapp.com.)

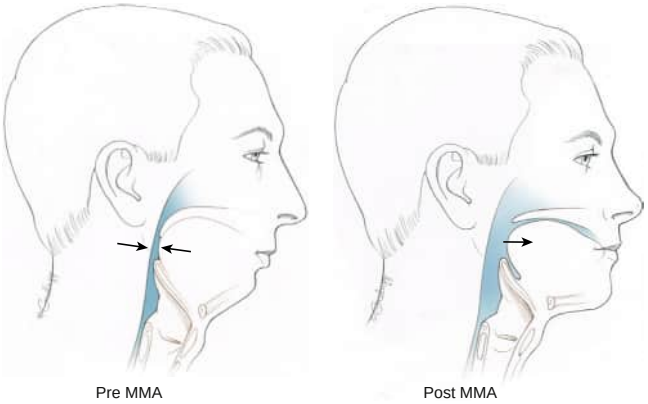

Figure 122.9 *Maxillomandibular advancement* (MMA). MMA involves osteotomies of the maxilla and mandible, followed by their advancement, which frequently incorporates counterclockwise rotation. This rotation allows the jaw complex to move forward and upward while maintaining facial balance. It remains one of the most effective surgical interventions for patients with obstructive sleep apnea. (Copyright 2017 Chris Gralapp. Courtesy Christine Gralapp, CMI/chrisgralapp.com.)

The Food and Drug Administration approved this therapy in 2014. The existing HNS system consists of a sensing lead, pressure sensor, implantable pulse generator, stimulation lead, and cuff electrode. The Stimulation Treatment for Apnea Reduction (STAR) trial, a multicenter prospective trial, enrolled patients with moderate to severe OSA (AHI ≥20); these investigators reported a reduction of AHI of 68%, from 29.3 to 9, and an oxygen desaturation index reduction of 70% from 25.4 to 7.4.[123] Clinical indication–based inclusion criteria consist of age older than 22 years, AHI of 20 to 65 with less than 25% central apneas, inability to use CPAP, and lack of complete concentric collapse of the velum on DISE. HNS is most effective in patients with a BMI less than 32 kg/m^2; however, a BMI of 32 to 35 kg/m^2 is acceptable. Predictors of effectiveness include increasing age, lower BMI, and female sex.[124] Approximately 2 months after implantation, patients undergo titration of HNS where voltage is adjusted to alleviate residual obstructive apneas and hypopneas. The therapy is turned on by the patient nightly by using a remote control. HNS is well-tolerated by patients,[123] and it improves subjective sleep quality, quality of life, and daytime sleepiness.[86] Evaluation of outcomes at 5 years in 71 patients showed that HNS is effective in achieving an AHI less than 5 in 44% and, by less stringent definitions, effective at reducing both the AHI by at least 50% and the residual AHI to less than 20 in 75% of patients.[125]

Maxillomandibular Advancement

Maxillomandibular advancement (MMA) was pioneered by Riley and Powell at Stanford Hospital in the late 1980s and addresses total upper airway collapse. It remains one of the most effective surgical interventions for patients with OSA and has compared favorably to CPAP in a variety of studies.[83,111,126–131] MMA involves osteotomies of the maxilla and mandible, followed by their advancement that is frequently accompanied with counterclockwise rotation[132,133] (Fig. 122.9). The rotation is intended to maximize advancement of the jaw complex without negative impact on overall facial balance. The net effect includes greater volume for intraoral soft tissue structures and, more importantly, stability of the upper airway dilator muscles[134–137] (Video 122.3). In general, indications for MMA are (1) moderate to severe OSA with or without a history of phase 1 surgery, (2) OSA of any severity if there is a comorbid dentofacial deformity, and (3) concentric and lateral pharyngeal wall collapse seen with DISE.[133,137–139] Age and severity of disease have not been shown to affect the technical aspects of MMA in a high-volume center.[140]

In a meta-analysis evaluating the treatment efficacy of MMA in 22 studies involving 627 patients who underwent MMA, the mean AHI decreased from 63.9 to 9.5. The investigators defined surgical success with the following criteria: a minimum of 50% reduction with a final AHI less than 20.[141] The surgical success rate was 86.0%, and the cure rate (AHI <5) was 43.2%. The predictive factors for surgical success were younger age, lower BMI, and greater degree of maxillary advancement.[142] The major and minor complication rates were 1.0% and 3.1%, respectively. This meta-analsysis was updated with 45 studies and 528 patients reporting success and cure rates of 85.5% and 38%, respectively.[143] In 40 patients who underwent MMA with average follow-up of 4.2 years (range, 1 to 12 years), 36 (90%) patients maintained a significant reduction in respiratory disturbance index (71.2 to 7.6) and improvement in daytime sleepiness.[142] In another study with mean follow-up of 12.5 years, surgical success rate remained 100% in patients who were both younger than 45 years and had a BMI less than 25.[144]

Beyond the AHI, MMA has shown normalization of sleep architecture as shown by an increase in rapid eye movement sleep and a decrease in wakefulness after sleep onset when compared with age-matched healthy controls. It has also shown improvements in multiple health-related and functional outcomes.[145]

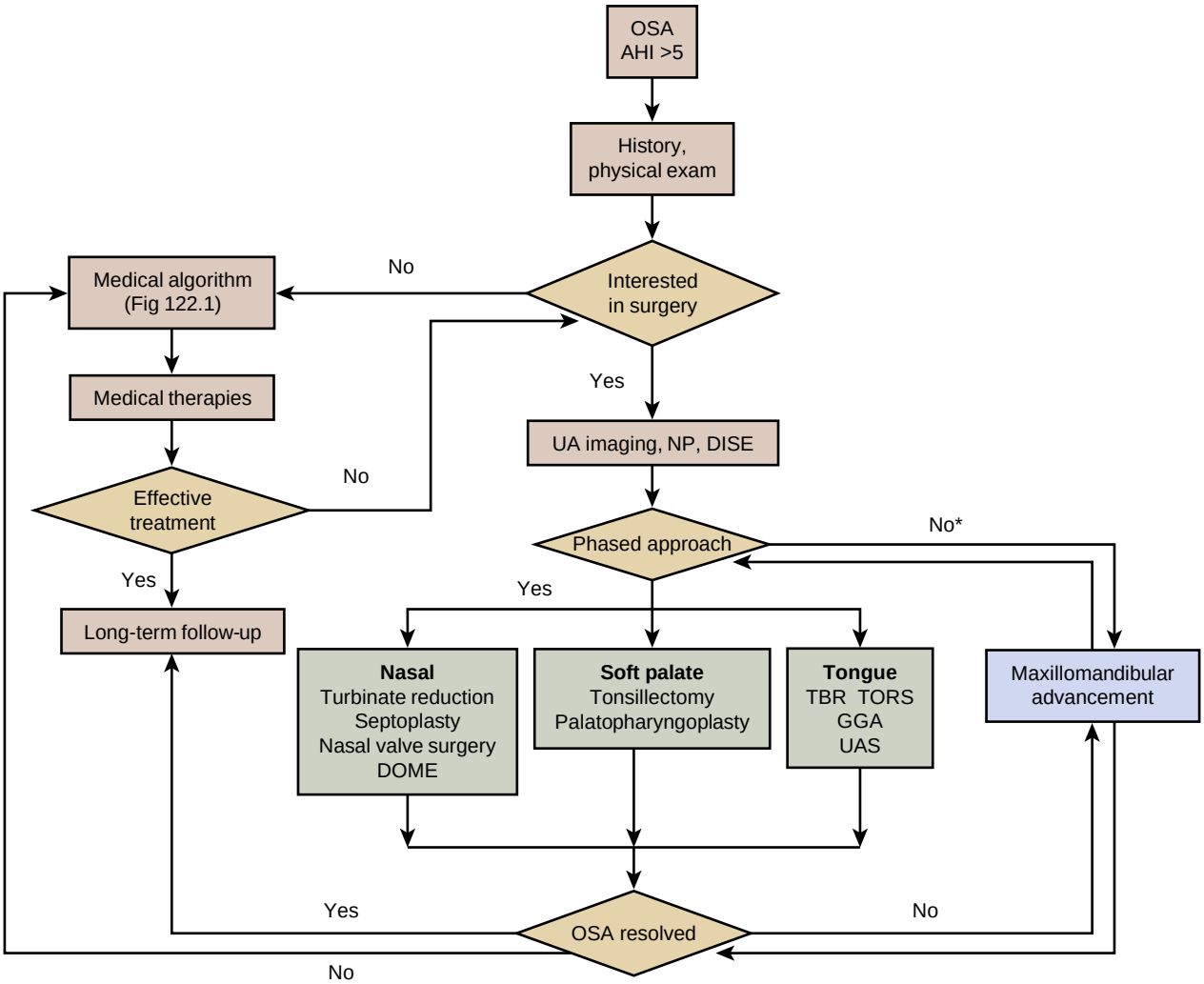

Figure 122.10 Updated sleep surgery algorithm. The updated algorithm places sleep surgery within the continuum of care and readily incorporates multimodal therapy. It improves precision in three key areas: (1) patient selection, (2) identification of unaddressed anatomic phenotypes, and (3) surgical techniques. Patients can flow between medical and surgical management strategies depending on the treatment preference of the patient as well as candidacy for interventions. For example, patients considered for surgical intervention may proceed to soft tissue surgery (e.g., nose, soft palate, or tongue) or directly to skeletal-based surgery with maxillomandibular advancement, depending on the degree of obstructive sleep apnea (OSA) severity, dentofacial deformity, and pattern of pharyngeal wall collapse on drug-induced sleep endoscopy (DISE). A classic phased approach includes soft tissue surgery first and then skeletal-based surgery. However, a phased approach may not be the best initial choice on the basis of the foregoing factors, and a phased approach does not have to be followed sequentially. If one approach does not resolve the obstructive sleep apnea, other surgical interventions may still be considered (i.e., maxillomandibular advancement may follow a uvulopalatopharyngoplasty, and vice versa). *Patients with a preexisting dentofacial deformity (e.g., maxillary and/or mandibular hypoplasia) and complete concentric and lateral pharyngeal wall collapse seen during DISE may be candidates for maxillomandibular advancement surgery first, rather than a phased approach. AHI, apnea-hypopnea index; DOME, distraction osteogenesis maxillary expansion; GGA, genioglossus and genioplasty advancement; LPW, lateral pharyngeal wall; NP, nasopharyngoscopy; TBR, tongue base reduction; TORS, transoral robotic surgery; UA, upper airway; UAS, upper airway stimulation.

APPLYING THESE CONCEPTS: AN ALGORITHM INCORPORATING SURGICAL AND NONSURGICAL TREATMENTS

An early Stanford protocol used for 3 decades suggested beginning with a multilevel phase 1 approach (tonsillectomy, uvulopalatal flap and genioglossus advancement), followed by phase 2 MMA in nonresponders.[130] This combined approach compares favorably with PAP therapy, especially with the inclusion of MMA.[128] The drawback to this approach is its unidirectional nature. It assumes that OSA does not recur if a cure, defined as AHI less than 5 events per hour, is achieved at one point. It also does not take into account patient preferences of these elective procedures and does not incorporate treatment such as PAP and MADs.

This phased approach has been replaced by an updated algorithm reflecting a more multidisciplinary and multimodal strategy for managing OSA[137–139] (Fig. 122.10). This updated algorithm places sleep surgery within a continuum of care, where medical management can precede or follow surgical interventions. It is characterized by improved precision in anatomic phenotyping, thereby facilitating the selection of the most appropriate patients for procedures such as DOME, HNS, and MMA.[123,135,136] It also adds greater precision to the way older procedures, such as genioglossus advancement and MMA, are performed.[94,112]

The algorithm begins with a thorough history, physical examination, review of sleep testing results, nasopharyngoscopy, and DISE. The indication for DISE is based on specific patient characteristics and needs. An initial decision is made regarding optimization of PAP, weight management, or oral appliance therapy. Nasal operations targeting resolution of nasal obstruction can be effective in improving adherence to PAP and may be considered an adjunct to PAP management. Weight is a key element determining successful outcomes with nearly all therapies other than PAP. The efficacy of upper airway surgery for OSA decreases as BMI increases. Thus, medical weight loss and bariatric surgical evaluation and treatment should precede upper airway surgery in selected candidates.

Nasopharyngoscopy and DISE results guide candidacy for both soft tissue and skeletal surgical procedures. DISE is currently required to rule out complete concentric collapse of the upper palate (velum) before considering HNS, because concentric collapse and lateral pharyngeal wall collapse seen on DISE are associated with a low success rate of soft tissue surgery.[146,147] MMA is reliable in reversing these collapse patterns.[135,136] MMA can also be a first-line consideration for patients with any degree of OSA with concurrent dentofacial deformity. Comorbidities (medical and psychiatric), likelihood of compliance with a therapy requiring daily initiation (HNS, CPAP, MAD), and patient preference are also considered when determining candidacy for these procedures.

The updated surgical algorithm adds precision in three areas: (1) patient selection, (2) identification of previously unaddressed anatomic phenotypes, and (3) surgical techniques.[137–139] Conceptually, whereas focus had been on individual surgical success, this algorithm provides a roadmap to overall treatment success. Because surgery is elective for patients with OSA, an effective algorithm accommodates the patient's personal preferences. Patients may elect to start with phase 1 procedures or with MMA and still remain candidates for other treatment regardless of their order. The key is to have surgeons experienced in sleep therapies and capable of performing the entire spectrum of procedures and counseling patients appropriately on chosen treatment paths.

Whereas this updated algorithm attempts to help guide the surgical care of patients with OSA, the most pressing need is its integration with physiologic phenotyping.[148] The combination of cutting-edge sleep surgery with advances in modulation of arousal threshold, loop gain, and muscle tone will truly redefine precision in OSA care.

Treatments for CSA, including CPAP, BPAP, supplemental oxygen, compression stockings and diuretic agents, and phrenic nerve stimulation, can be found at ExpertConsult.com and in Chapter 121.

SLEEP-RELATED HYPOVENTILATION SYNDROMES

Sleep-related hypoventilation syndromes primarily consist of those related to *obesity hypoventilation syndrome* (OHS), advanced obstructive lung disease, and restrictive lung disease caused by neuromuscular disease or intrinsic parenchymal or pulmonary vascular disease. These disorders often require *noninvasive ventilation* (NIV) with settings guided by the acuity and severity of disease and the patient's unique needs (see Figs. 122.1 and 122.3) (see also Chapter 136).

Not all hypoventilation syndromes require NIV. Some hypoventilation syndromes such as OSA-OHS respond well to alleviation of upper airway obstruction. Selection of a given mode of PAP (CPAP, APAP, BPAP-S, BPAP-ST, BPAP-PC, and VAPS add-on) requires an understanding of the underlying physiology of the respiratory disorders involved. Use of NIV in patients with neuromuscular disease and hypercapnic COPD reduces morbidity and mortality, as does use of CPAP in OSA-OHS and overlap syndrome.

OBESITY HYPOVENTILATION SYNDROME

OHS is defined by obesity (BMI >30 kg/m^2), daytime hypercapnia (arterial P_{CO_2} >45 mm Hg), and sleep-disordered breathing following exclusion of other causes of chronic alveolar hypoventilation (see also Chapters 45 and 120). For patients with a low to moderate probability of OHS, a rapid and sensitive screening test is serum bicarbonate.[162] A serum bicarbonate level lower than 27 dramatically decreases the probability of OHS.[162] However, arterial P_{CO_2} rather than serum bicarbonate is recommended in patients with OSA and a high pretest probability of OHS.[162] OHS is accompanied by OSA in 90% and by severe OSA in 70% of patients.[162] CPAP is effective at eliminating both OSA and OHS in 80% of patients, in whom upper airway obstruction rather than reduced drive to breathe is the primary cause.[163,164] Thus, CPAP is recommended as initial therapy for patients with severe OSA and OHS (eFig. 122.1). If sleep-related hypoventilation and hypoxemia persist despite effectively addressing upper airway obstruction with CPAP, then the BPAP-S mode can be tried. Although randomized clinical trials have been small, existing data suggest that CPAP and BPAP-S result in similar improvements in quality of life and adherence. BPAP-S has also been shown to improve sleep quality in the absence of severe nocturnal hypoxemia.[165] Resolution of hypoventilation with several weeks of treatment is evident in normalization of serum bicarbonate or arterial P_{CO_2} (see Chapter 136).

In some patients, BPAP-S therapy is not effective as a result of reduced respiratory drive. These patients can be identified by their low minute ventilation. Minute ventilation would be considered inadequate if there is either no change or worsening in carbon dioxide by surrogate monitoring during therapy. In these cases, bilevel modes with backup rates such as BPAP-ST or average volume-assured pressure support may be considered, the latter at 8 to 10 mL/kg ideal body weight with adjustments guided by carbon dioxide monitoring.[166] Selection of settings on BPAP-ST should include strategies to increase inhalation time favoring larger tidal volumes and improved gas exchange, such as increasing rise time, prolonging inspiratory time, or lowering cycle sensitivity.[166] The backup respiratory rate is usually set approximately two breaths below the patient's spontaneous frequency or auto-rate. End-expiratory PAP settings alleviate the obstructive component of sleep-disordered breathing, as well as oppose reduced respiratory system compliance from abdominal compression; the higher the AHI, and the greater the chest

CENTRAL SLEEP APNEA

Treatment of CSA with PAP devices, supplemental oxygen, compression stockings, and phrenic nerve stimulation is briefly covered in this chapter and discussed in depth in Chapter 121. Pharmacologic therapies are discussed exclusively in Chapter 121.

Continuous Positive Airway Pressure

Although CPAP mainly functions to maintain upper airway patency, it also confers advantages of reducing left ventricular afterload, improving ventilation-perfusion mismatch, and slightly increasing arterial P_{CO_2} which may help to stabilize ventilation in a high loop gain system.[149] The Canadian Continuous Positive Airway Pressure trial showed that whereas intermediate measures, including left ventricular ejection fraction and urinary catecholamines improved, no survival benefit was conferred by CPAP in CSA in patients with systolic heart failure.[150]

Bilevel Positive Airway Pressure With Backup Rate

Although BPAP with backup rate (BPAP-ST) has the potential to address both obstructive and central aspects of sleep-disordered breathing, few studies have reported the effectiveness of this therapeutic approach.[151] Treatment-emergent CSA is defined by the emergence of central respiratory events during PAP therapy, and it affects up to 20% of patients with OSA.[152,153] Indeed, patients with predominantly obstructive events on baseline sleep testing may have unmasking of central events during early exposure to PAP therapy. General recommendations are to treat with a trial of CPAP therapy while recognizing that central events will commonly resolve over the first 3 months of therapy.[152,153] If close follow-up reveals persistence of CSA on CPAP, the use of a BPAP (adaptive servoventilation or ST) mode is a reasonable next step. The addition of a backup rate may reduce transient cycling between hyperventilation and hypoventilation that causes or perpetuates central events.

Adaptive Servoventilation

Adaptive servoventilation adjusts breath-by-breath levels of inspiratory pressure support to counterbalance either overshooting or undershooting of ventilation; that is, it increases pressure support during apneas and hypopneas and reduces support during hyperventilation by analyzing the breathing pattern in a moving average and applying pressure support according to predefined parameters (see Fig. 122.3). Adaptive servoventilation devices can be programmed with either fixed or variable expiratory pressure to address obstructive respiratory events (similar in concept to CPAP and APAP). Adaptive servoventilation devices also have a nonadjustable (preprogrammed by the manufacturer) or adjustable backup rate to address central apneas. The use of adaptive servoventilation in treatment-emergent CSA, idiopathic CSA, and CSA associated with heart failure, opioids, and high altitude is covered in Chapter 121.

Supplemental Oxygen

NSO resulting in mild hyperoxia may reduce excessive chemoreceptor sensitivity, thereby reducing AHI. Randomized controlled trials with small sample sizes demonstrated improvement of CSA in patients with heart failure with use of NSO therapy by reduction of hypoxic ventilatory drive and reduced sympathetic activation, as well as improvement in quality of life measures.[154] However, multicenter clinical trial data suggested improvement in physical activity and quality of life measures with NSO therapy in non–CSA-predominant sleep-disordered breathing.[155] The definitive role of supplemental oxygen as an effective isolated treatment option needs further study. This is further discussed in Chapter 121.

Compression Stockings

Venous compression stockings have shown benefit in reducing fluid accumulation in the lower extremities that reduces redistribution of the edema to the neck during sleep, thereby addressing one mechanism contributing to the pathogenesis of both OSA and CSA. A direct relationship between the amount of fluid displaced from the legs and the AHI has been described in patients with heart failure and either OSA or CSA.[156] Fluid shifts correlated inversely with nocturnal arterial P_{CO_2}, a finding suggesting that some of the fluid was redistributed into the lungs, thus stimulating pulmonary irritant receptors and leading to hyperventilation and reductions in the arterial P_{CO_2} close to or below the apneic threshold.[156,157] In the case of OSA, this fluid shift decreases patency of the upper airway through accumulation of fluid in the neck and increased peripharyngeal soft tissue edema,[158] thereby increasing its collapsibility.[159] It is possible that varying degrees of rostral fluid shift could lead to changes in predominant apnea type over time. In fact, the magnitude of fluid shifts from the legs is greater in patients with CSA than in patients with OSA. Therefore, addressing both pulmonary edema and rostral neck edema beneficially affects both CSA and OSA sleep-disordered breathing.[160] Intensification of diuretic therapy also represents another strategy in the management of lower extremity edema.

Phrenic Nerve Stimulation

Transvenous phrenic nerve stimulation has emerged as an effective treatment for CSA (eFig. 122.2). One lead is implanted in the brachiocephalic or left pericardiophrenic vein to stimulate the phrenic nerve, and a second lead senses breathing for respiratory gating. The stimulation lead is attached to a pulse generator responsible for delivering low-energy stimulation to the phrenic nerve to alleviate central apneas. Initial outcomes show a 50% reduction in AHI and more than 90% reduction in the central apnea index. A subsequent multicenter randomized clinical trial confirmed these findings of a significant reduction in the severity of CSA of more than 50% at 6 months, as well as improvement in oxygenation and quality of life measures.[161]

wall restriction is, the higher the end-expiratory PAP will need to be set. Additionally, higher pressure support is often needed to ensure that adequate target tidal volumes are achieved. In general, compared with BPAP, volume-assured pressure support improves hypercapnia, hypoxemia, and sleep quality.[167,168] In unstable OHS (i.e., acute respiratory failure), NIV should be used during hospitalization and on discharge. NIV with empirical settings should be provided to the patient with expeditious follow-up (less than 3 months) for in-laboratory polysomnography, ideally with transcutaneous carbon dioxide surrogate monitoring, because end-tidal carbon dioxide values cannot be accurately obtained during PAP therapy as a result of washout. End-tidal capnography does not provide accurate data in the presence of obstructive lung disease, in cases where there is no end-expiratory plateau, there is an increase in dead space, or during use of either NIV or supplemental oxygen.[169–171] Adequacy of therapy can be assessed by monitoring for carbon dioxide normalization with serum bicarbonate or arterial P_{CO_2}.

NEUROMUSCULAR DISEASE

The goals of treatment for neuromuscular weakness are to reduce the load on the respiratory system, reduce physiologic dead space, and increase minute ventilation. For patients with neuromuscular disease and OSA with no evidence of hypoventilation, CPAP and close monitoring can be considered. Early initiation of NIV in amyotrophic lateral sclerosis is feasible and has been shown to improve quality of life, slow lung function decline, and improve survival.[172] Weighing the risks and benefits of NIV is crucial because patients with significant bulbar symptoms and sialorrhea may have poorer adherence and increased risk of aspiration. That said, early NIV has been shown to improve quality of life and survival in patients with bulbar symptoms, when tolerated. Another challenge is triggering NIV breaths in patients with diaphragmatic weakness. Indicators of diaphragm function include maximum inspiratory pressure, arterial P_{CO_2}, forced vital capacity in the upright and/or supine position, and overnight oximetry. Thus, initiation of NIV is based on impairment in any of these parameters, including forced vital capacity less than 50% of predicted, maximal inspiratory pressure 60 cm H_2O or lower, awake arterial P_{CO_2} greater than 45 mm Hg, or nocturnal desaturation of up to 88% for at least 5 minutes.[173] Symptoms, objective evidence of sleep-related hypoventilation, and the rate of disease progression should all be considered in the timing of ventilatory support.[166] Initiation of NIV for neuromuscular disease, including selection of initial device settings, is outlined in eFigure 122.3 and is based on the degree of impairment of respiratory function, as well as the presence of bulbar disease. NIV can be provided through either home mechanical ventilators, which include internal batteries but are larger and heavier, or BPAP respiratory assist devices, which are more portable but must be connected to an electrical outlet or an external power pack. Monitoring of NIV in patients can be done remotely through telehealth. BPAP devices allow data from the patient to be viewed and settings to be changed remotely. Home mechanical ventilators can send data from the patient to the provider for review but do not allow remote adjustments to settings, which must be done in person.

COPD

Mild hypoventilation at sleep onset is a normal phenomenon of non–rapid eye movement sleep. Rapid eye movement sleep is characterized by paralysis of accessory muscles of respiration, resulting in cyclic reductions in minute ventilation, hypercapnia, and hypoxemia in patients with advanced COPD. Patients perched on the cusp of the steep portion of the oxyhemoglobin dissociation curve who have awake, upright daytime measurements of oxygen saturation as measured by pulse oximetry lower than 94–95% should be considered for overnight oximetry or sleep testing to evaluate for sleep apnea, sleep-related hypoventilation, or sleep-related hypoxemia.

COPD and OSA frequently exist in the same patient, with up to 66% of patients with COPD also having a diagnosis of OSA.[163] Comorbid COPD and OSA, also known as overlap syndrome, is associated with an increased risk of hospitalization and death[174] from COPD exacerbations compared with patients who have COPD only. This increased risk is likely the result, in part, to greater nocturnal and daytime hypoxemia, as well as increased risk of pulmonary hypertension caused by chronic lung disease (see also Chapter 85). Currently, polysomnography rather than home sleep apnea testing is recommended to diagnose OSA, although the level of evidence for this recommendation is weak.[175]

Treatment goals are defined by the results of sleep testing, and they may include alleviation of OSA alone, treatment of isolated hypoventilation and/or hypoxemia, or a combination thereof. Given hypercapnia is a contributing factor of mortality, it follows that a reduction in arterial P_{CO_2} may improve overall prognosis. In patients with overlap syndrome, CPAP has shown improved survival and reduction of first-time hospitalization for COPD exacerbation.[164] When NIV is deemed a more appropriate therapy than CPAP (i.e., as a result of pressure intolerance or persistent hypercapnia), it can be initiated following in-laboratory polysomnography for stable outpatients or empirically on the basis of predischarge inpatient settings when criteria for NIV or home mechanical ventilation are met. Both inpatient observation and in-laboratory studies allow continuous monitoring of oxygen saturation and, where available, monitoring of transcutaneous, end-tidal carbon dioxide, or arterial blood gases.

Various strategies have been used in the treatment of hypoventilation caused by overlap syndrome or COPD. Initial studies using low-intensity BPAP (small delta between inspiratory and expiratory pressure settings) did not show a substantial difference in hospitalizations, exacerbations, quality of life, or even awake arterial P_{CO_2}.[176] Conversely, high-intensity BPAP in patients with severe stable hypercapnic COPD reduces hospitalization readmission and death.[177,178] Current European Respiratory Society guidelines support using NIV in chronic stable COPD with hypercapnia and after acute COPD exacerbation requiring NIV.[179] In further support of this, a meta-analysis of patients with chronic hypercapnic COPD concluded

that home ventilation with BPAP versus no device at all reduced all-cause mortality, all-cause hospitalizations, and intubation.[180]

Key Points

- Numerous options are available for treatment of sleep-disordered breathing. Patients' characteristics and preferences are key to initiating therapy that will be effective long term.
- Positive airway pressure is the primary therapy for obstructive sleep apnea, some forms of central sleep apnea, and hypoventilation syndromes. Understanding the physiologic basis of obstructive sleep apnea, central sleep apnea, and hypoventilation syndromes facilitates an understanding of how to select the most appropriate positive airway pressure mode for an individual patient or disease process.
- Oral appliances should be considered first-line therapy for mild to moderate obstructive sleep apnea, and they may be used in combination with positive airway pressure therapy to reduce the pressure required to achieve a therapeutic apnea-hypopnea index.
- Surgical interventions aim to restore function by promoting stability of the upper airway against collapse. Soft tissue and skeletal procedures can be used as primary therapies or to improve tolerance or response to treatments such as positive airway pressure and oral appliances.
- Drug-induced sedation (sleep) endoscopy has allowed more precise surgical decision making, particularly with the selection of responders to hypoglossal nerve stimulation and maxillomandibular advancement.
- Hypoglossal nerve stimulation and phrenic nerve stimulation are novel implantable neurostimulation therapies for obstructive sleep apnea and central sleep apnea, respectively.
- Continuous positive airway pressure or bilevel positive airway pressure use in obesity hypoventilation syndrome is determined by stability and severity of hypoventilation. Continuous positive airway pressure is effective in 80% of patients with combined obstructive sleep apnea and obesity hypoventilation syndrome.
- Noninvasive ventilation improves morbidity and mortality and should be instituted early in hypoventilation caused by progressive neuromuscular disease, such as amyotrophic lateral sclerosis.

Key Readings

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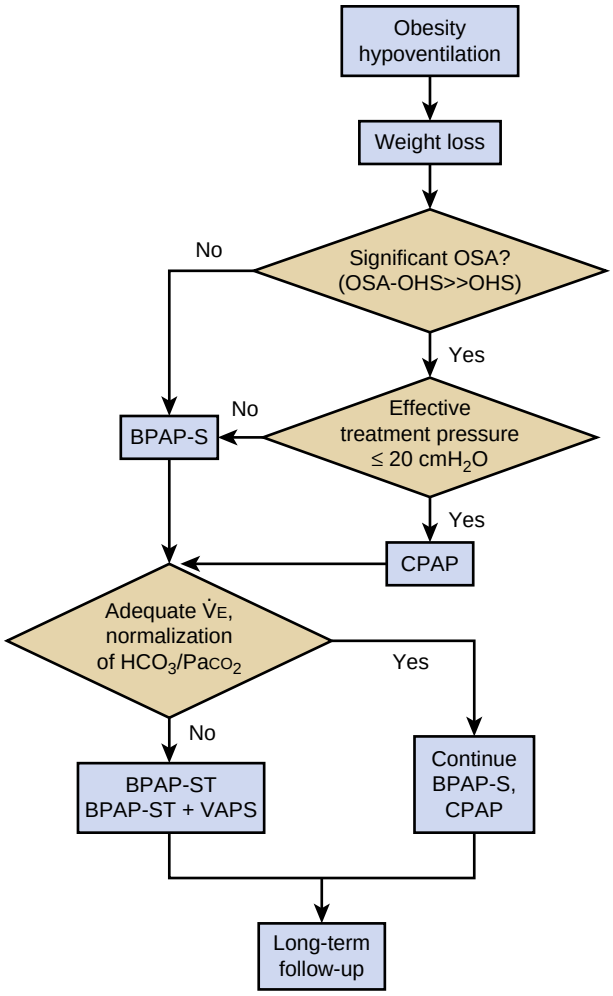
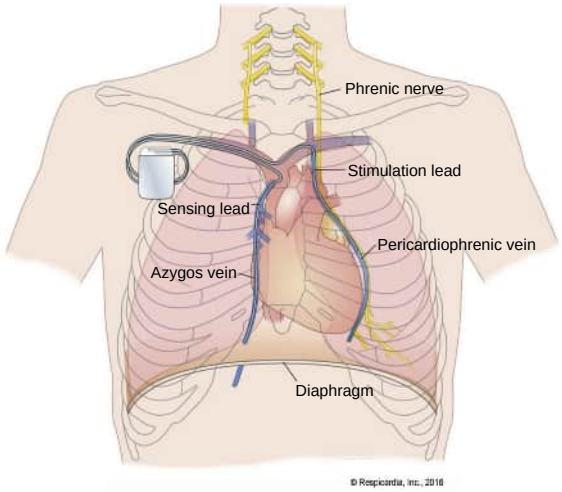
Complete reference list available at ExpertConsult.com.

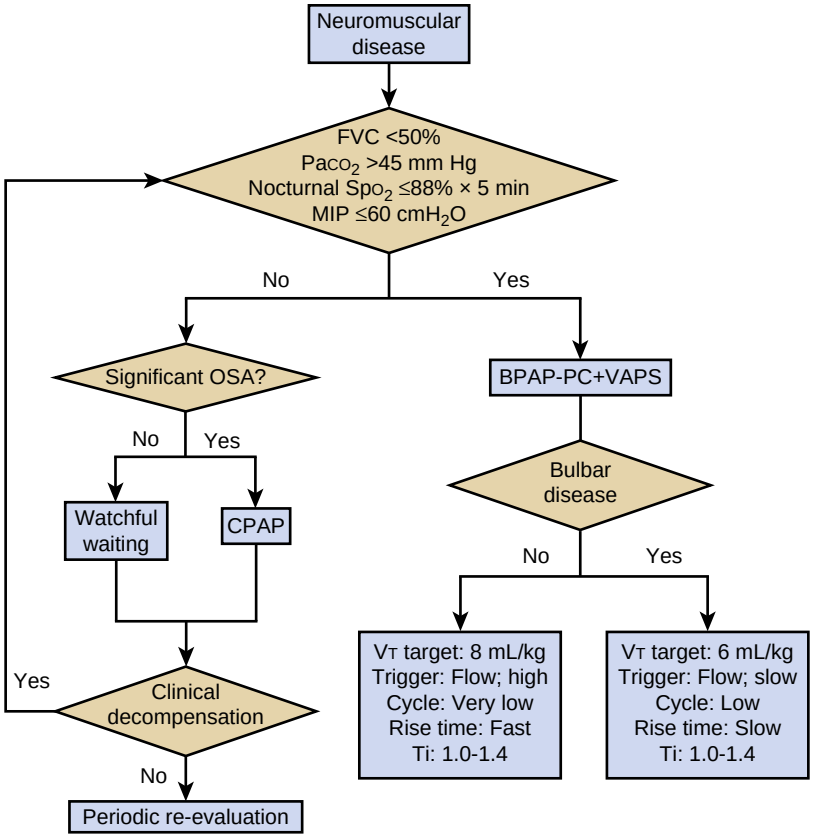
eFIGURE IMAGE GALLERY



eFigure 122.1 ***Obesity hypoventilation syndrome*** **(OHS) outpatient treatment algorithm.** Management of OHS in medically stable outpatients begins with weight loss but usually requires treatment with positive airway pressure therapy. When there is a significant degree of *obstructive sleep apnea* (OSA), *continuous positive airway pressure* (CPAP) is effective in alleviating upper airway obstruction, thereby facilitating improved ventilation. When there is mild or no OSA, initiation of bilevel therapy is indicated. Patients requiring pressures higher than 20 cm H_2O will also require bilevel treatment because all CPAP devices have a maximum possible pressure of 20 cm H_2O. If adequate ventilation is not achieved, adding a backup rate or volume-assured pressure support (VAPS) add-on is indicated. If sufficient weight loss is achieved, de-escalation of bilevel therapy to CPAP may be possible. BPAP, bilevel positive airway pressure; HCO_3, bicarbonate; $Paco_2$, arterial partial pressure of carbon dioxide; S, spontaneous; ST, spontaneous timed.



eFigure 122.2 Neurostimulation in central sleep apnea treatment. Phrenic nerve stimulation consists of a generator, implanted stimulating lead (located within the pericardiophrenic vein), and sensing lead (located within the azygos vein). The sensing lead detects respiratory effort. The device can be programmed to deliver timed pulses at a fixed rate (asynchronous mode), or it can be set to deliver a pulse only when the sensing lead detects a prolonged pause in breathing (synchronous mode). (Remed ē system. Courtesy Respicardia, Inc., Minnetonka, MN.)



eFigure 122.3 Neuromuscular disease treatment algorithm. Management of patients with neuromuscular disease is based on markers of ability to ventilate effectively. When the underlying disease is advanced and ineffective ventilation is evident, noninvasive ventilation should be instituted. Early in the underlying disease course when ventilation is preserved, patients may be offered continuous positive airway pressure (CPAP) or alternative treatments if obstructive sleep apnea (OSA) is diagnosed. If no sleep-disordered breathing is present, watchful waiting is acceptable. Initial settings for patients with and without bulbar disease are suggested, although therapy should be tailored at an individual level. BPAP-PC, bilevel positive airway pressure-pressure control; FVC, forced vital capacity; MIP, maximal inspiratory capacity; $Paco_2$, arterial partial pressure of carbon dioxide; Spo_2, oxygen saturation as measured by pulse oximetry; VAPS, volume-assured pressure support; V_T, tidal volume.

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SECTION P

RESPIRATORY MANIFESTATIONS OF EXTRAPULMONARY DISORDERS

123 PULMONARY COMPLICATIONS OF HIV INFECTION

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INTRODUCTION

Since the recognition of the first cases of *acquired immunodeficiency syndrome* (AIDS) in 1981, our understanding of *human immunodeficiency virus* (HIV) and its myriad infectious and noninfectious complications has markedly increased. The prognosis for persons infected with HIV has undergone dramatic change for those with access to effective combination *antiretroviral therapy* (ART) and medications for treatment and prevention of HIV-associated infectious complications. These advances have resulted in a dramatic decline in the incidence of new AIDS cases and the number of AIDS-associated deaths where this care is widely and consistently available.[1]

The lungs remain one of the chief target organs of HIV morbidity and mortality. The spectrum of pulmonary manifestations is broad and includes infectious and noninfectious complications (Table 123.1).[2] These complications include diseases that are AIDS defining (e.g., *Pneumocystis* pneumonia) or HIV associated (e.g., bacterial pneumonia), disorders that are not identified classically as HIV associated but appear to be more common in those with HIV infection (e.g., lung cancer, *pulmonary arterial hypertension* [PAH], and COPD), and conditions whose association with HIV is inconclusive or purely coincidental (e.g., sarcoidosis).

EPIDEMIOLOGY

Global estimates indicate that 38 million people were living with HIV in 2019.[3] Overall, approximately 0.7% of adults age 18 to 49 years are infected with HIV worldwide

Table 123.1 Spectrum of Pulmonary Complications

INFECTIONS
Bacteria*
Streptococcus pneumoniae
Haemophilus species
Staphylococcus aureus
Pseudomonas aeruginosa
Other bacteria
Mycobacteria
Mycobacterium tuberculosis†
Mycobacterium avium complex‡
Mycobacterium kansasii‡
Other mycobacteria‡
Fungi
Pneumocystis jirovecii (formerly *P. carinii*)§
Cryptococcus neoformans‡
Histoplasma capsulatum‡
Coccidioides immitis‡
Aspergillus species (most often *A. fumigatus*)
Blastomyces dermatitidis
Talaromyces marneffei (formerly *Penicillium marneffei*)
Other fungi
Viruses
Cytomegalovirus§
Other viruses
Parasites
Toxoplasma gondii¶
Other parasites
MALIGNANCIES
Kaposi sarcoma§
Non-Hodgkin lymphoma§
Bronchogenic carcinoma
INTERSTITIAL PNEUMONITIDES
Lymphocytic interstitial pneumonitis‖
Nonspecific interstitial pneumonitis
OTHER
COPD
Asthma
Pulmonary arterial hypertension
Sarcoidosis
Immune reconstitution inflammatory syndrome

*AIDS-defining diagnosis in adults and adolescents (>13 years) if recurrent (≥2 episodes in 12 months). Not applicable as AIDS-defining diagnosis in children.
†AIDS-defining diagnosis in adults and adolescents. AIDS-defining diagnosis in children if extrapulmonary or disseminated.
‡AIDS-defining diagnosis if extrapulmonary or disseminated.
§AIDS-defining diagnosis.
¶AIDS-defining diagnosis if central nervous system is involved.
‖AIDS-defining diagnosis in children. Not applicable as AIDS-defining diagnosis in adults or adolescents.
Modified from Murray JF, Mills J. Pulmonary infectious complications of human immunodeficiency virus infection. *Am Rev Respir Dis.* 1990;141:1356–1372, 1582–1598.

in 2019. Eastern and sub-Saharan Africa have 54% of the global population living with HIV. After Eastern and sub-Saharan Africa, the regions with the highest burden are Asia and the Pacific, and Western and central Africa. The estimated prevalence of diagnosed HIV infection in the United States was 374.6 per 100,000 population in 2018.

New HIV infections have declined over the past 2 decades, from 3.4 million in 1996 to 1.7 million in 2019.[3] AIDS-related mortality has also declined by 39% since 2010.[3] Because survival has improved for HIV-infected patients since the introduction of ART, more people are living with HIV in the United States than ever before.[5] Furthermore, in the recent era, HIV-infected adults in clinical care in the United States are more likely to be prescribed ART, to have a suppressed HIV viral load, and to have a higher median $CD4^+$ T cell count.[6]

The gender and racial/ethnic demographics of HIV-infected populations vary worldwide. In sub-Saharan Africa, women account for the majority of people estimated to be living with HIV.[3] In the United States, women comprise approximately 24% of adult AIDS cases.[4] Although early in the epidemic HIV was predominantly seen among non-Hispanic white *men who have sex with men* (MSM), HIV increased disproportionately in minorities, especially Blacks and Hispanic/Latin Americans, and recently for Native Hawaiians/other Pacific Islanders.[4,7,8]

IMMUNOLOGIC ABNORMALITIES

Without ART, HIV causes a gradual and inexorable loss of host immunity characterized as a syndrome of immune dysregulation, dysfunction, and deficiency involving multiple components of the immune system. HIV is tropic for $CD4^+$ lymphocytes and monocytes.[9] After initial infection, HIV leads to massive depletion of $CD4^+$ effector-memory lymphocytes from mucosal-associated lymphoid tissue.[10] During the chronic phase of untreated HIV infection, there is generalized immune activation and ultimately a progressive decline in the naive and memory T cell pool that results in systemic $CD4^+$ lymphocyte depletion.[10,11] As well as being decreased in number, T cells are also dysfunctional and mount abnormal responses to antigens. HIV infection is also associated with B cell dysfunction, with polyclonal activation, hypergammaglobulinemia, and defective specific antibody responses. This combination of immune dysfunction, dysregulation, and depletion of $CD4^+$ lymphocytes results in increased risk of infections and other complications if HIV infection is untreated.

Among *people living with HIV* (PLWH) treated with ART,[10] chronic inflammation and immune activation decrease, although they can persist, particularly in those who began ART at lower $CD4^+$ cell counts or those whose treatment is interrupted.[12,13] Premature mortality and comorbidities, including pulmonary, cardiovascular, neurologic, renal, and liver disease, have been associated with residual inflammation and immunodeficiency despite ART.[14,15]

HIV infection alters several lines of host defense in the lung and respiratory tract that contribute to an increased risk for pulmonary infections.[16] Among other defenses, HIV alters mucociliary function and soluble defense molecules in respiratory secretions. Within the lung, innate and adaptive immune responses to pathogens may be impaired. For example, alveolar macrophages from HIV-infected individuals have deficiencies in pathogen recognition, including abnormalities in toll-like receptor 4 signaling.[17,18] *Bronchoalveolar lavage* (BAL) $CD4^+$ T cells from HIV-infected individuals display impaired responses

to respiratory pathogens, including influenza virus and *Mycobacterium tuberculosis*.[19] HIV can also result in chronic stimulation and activation of inflammatory cells within the alveolar space.[20] Studies in animal models suggest that certain HIV proteins disrupt the barrier function of the alveolar epithelium.[21]

Persistently increased inflammation and immune activation related to HIV have been linked to chronic lung complications. Within the alveolar space, HIV infection is associated with changes in the cellular profile[16]; however, the mucosal depletion of $CD4^+$ T cells that takes place in the gastrointestinal tract is not observed in the lung. Instead, BAL fluid from HIV-infected individuals has more $CD4^+$ T cells than does the terminal ileum.[22] Lung cells that can be infected with HIV include alveolar macrophages, T cells, and fibroblasts.[16] Alveolar macrophages and T cells may be reservoirs of HIV in the lung.[23] The clinical significance of the lung as a compartment for HIV-infected cells is incompletely understood.[24]

DIAGNOSTIC APPROACH

The evaluation of an HIV-infected patient with pulmonary disease is aimed at making a specific diagnosis. Although each pulmonary disease has characteristic clinical and radiographic features, these features often overlap. On occasion, the presenting features are atypical, or more than one pulmonary disease is present. Without appropriate therapy, patients with pneumonia can progress rapidly to respiratory failure and death. The therapies used to treat HIV-associated pulmonary diseases have substantial toxicities and interactions with other medications.

The evaluation should begin with the history and physical examination.[25] Laboratory testing should be performed and a chest radiograph obtained in patients with suspected pulmonary disease. Frequently, the results of this evaluation suggest a specific differential diagnosis and management plan. On occasion, additional studies such as *pulmonary function testing* (PFTs) or chest *computed tomography* (CT) are needed to narrow the differential diagnosis and to refine the management plan.

$CD4^+$ LYMPHOCYTE COUNT

The blood $CD4^+$ lymphocyte count is an indicator of an HIV-infected patient's risk for development of opportunistic infections or neoplasms. Many HIV-associated pulmonary diseases present at or below a characteristic $CD4^+$ lymphocyte count and are seldom seen at higher counts.[26] Exceptions are diseases that can present in persons without HIV infection, such as bacterial pneumonia, *tuberculosis* (TB), and *non-Hodgkin lymphoma* (NHL). In HIV-infected persons, these diseases can present at any $CD4^+$ lymphocyte count, although their incidence increases and their characteristic presentation changes as the $CD4^+$ lymphocyte count declines.

The risk of opportunistic infections is best reflected by the current $CD4^+$ T-lymphocyte count.[27] At $CD4^+$ T cell counts less than 200/μL, bacterial pneumonia is often accompanied by bacteremia, and *M. tuberculosis* disease is often extrapulmonary or disseminated. Moreover, below this $CD4^+$ lymphocyte count, *Pneumocystis* and *Cryptococcus* pneumonia become important considerations, whereas neither typically presents in a patient with a count significantly higher than 200 cells/μL. At $CD4^+$ T cell counts less than 50 to 100 cells/μL, endemic fungi, certain viruses (*cytomegalovirus* [CMV]), protozoa (*Toxoplasma gondii*), *nontuberculous mycobacteria* (NTM; *Mycobacterium avium* complex [MAC]), and pulmonary involvement from *Kaposi sarcoma* (KS) become important considerations. Many of these diseases present with extrapulmonary or disseminated manifestations that may dominate the clinical presentation.

FIBEROPTIC BRONCHOSCOPY

Bronchoscopy should be considered for any HIV-infected patient with pulmonary disease whose severity warrants a prompt and accurate diagnosis, for patients with suspected pulmonary KS, for patients with suspected NHL (if other diagnostic procedures are more hazardous or less likely to provide the diagnosis), for patients whose diagnosis remains unknown despite less invasive diagnostic studies (e.g., induced sputum), and for patients whose empirical therapy is failing.

The decision to perform BAL with or without *transbronchial biopsy* (TBB) depends on the suspected diagnosis and on the sensitivities of these procedures for that diagnosis. At the beginning of the AIDS epidemic, both BAL and TBB were usually performed during the initial bronchoscopy. Currently, BAL alone is generally performed when *Pneumocystis* pneumonia (PCP) is suspected.[28] The sensitivity of BAL fluid examination for *Pneumocystis* is 97% or higher; therefore, a negative BAL fluid examination for *Pneumocystis* rules out the diagnosis of PCP in all but the rarest cases.[28]

In contrast, TBB improves the sensitivity of bronchoscopy for diagnosing other pathogens, including TB and endemic fungal pneumonias. Furthermore, tissue confirmation from TBB or another biopsy specimen is required for a definitive diagnosis of invasive aspergillosis, CMV pneumonia, and NHL. Therefore, when the clinical and radiographic features suggest one of these diseases, both BAL and TBB are warranted during the initial bronchoscopy.

INFECTIOUS COMPLICATIONS

In this section the major pulmonary infectious complications of HIV disease are reviewed according to category of infectious microorganism (see Table 123.1).

BACTERIA

Recurrent bacterial pneumonia, defined as two or more episodes within 12 months, is an AIDS-defining illness.[29,30] During the ART era (1996 to the present), the incidence of community-acquired bacterial pneumonia among HIV-infected persons has declined.[31–35] The shift to earlier initiation of ART over time has further contributed to a decrease in bacterial pneumonia. For example, initiation of ART early in individuals with $CD4^+$ cell counts greater than 500 cells/μL resulted in a lower incidence of bacterial infection, including pneumonia, compared to individuals who

had ART initiated when the CD4+ cell count fell below 350 cells/μL or when AIDS complications developed.[36]

However, despite a decrease in incidence since the introduction of ART, bacterial pneumonia remains more common in PLWH compared to uninfected persons, and is a leading cause of morbidity even for persons on ART and with CD4+ cell counts in the normal range.[37–39] In the United States and Western Europe, bacterial pneumonia is now the most common HIV-associated pneumonia in populations on ART.[40] Several factors may account for the persistence of bacterial pneumonia despite effective ART. For one, cigarette smoking is prevalent in HIV-infected populations, and is associated with increased rates of pneumonia in HIV-infected patients at all CD4+ lymphocyte cell counts,[30,38,41,43] whereas smoking cessation decreases the risk for pneumonia.[44] Injection drug use also remains a risk factor for bacterial pneumonia in the ART era. As patients are aging, conditions such as COPD, heart disease, and cancer also contribute increased risk for bacterial pneumonia.[45]

Several bacterial species cause pneumonia in HIV-infected patients. Similar to community-acquired bacterial pneumonia in non–HIV-infected populations, *Streptococcus pneumoniae* and *Haemophilus* species are the most frequently identified pathogens in people with HIV infection and account for approximately 50–60% of cases combined,[30,46] and they remain the most commonly isolated bacteria in the ART era.[47,48] *Staphylococcus aureus* can be isolated as a cause of community-acquired pneumonia in patients both with and without a history of injection drug use,[47,49,50] and *Pseudomonas aeruginosa* is a cause of community-acquired bacterial pneumonia in HIV-infected persons with advanced AIDS (eFig. 123.1). Other bacteria that are occasional causes of community-acquired bacterial pneumonia in HIV-infected persons include *Legionella* species, *Rhodococcus equi,* and *Nocardia* species; these are discussed in detail later.

Of hospital-acquired pneumonias, the two most common bacterial causes in HIV-infected persons are *S. aureus* and *P. aeruginosa.* Both of these organisms are more likely to be isolated in patients with lower CD4+ lymphocyte counts.[46,51] Staphylococcal pneumonia is frequently complicated by bacteremia, methicillin resistance, and high mortality.[51] *S. pneumoniae* and *Klebsiella pneumoniae* are also relatively frequent causes of pneumonia in HIV-infected hospitalized patients.[51]

Clinical Features. In HIV-infected persons, the clinical and radiographic features of bacterial pneumonia are similar to those in immunocompetent persons, with a few important exceptions.[52] Of note, HIV-infected individuals have a substantially increased risk for bacteremia and invasive disease due to *S. pneumoniae*. The rate of pneumococcal bacteremia in HIV-infected patients has been estimated to be up to 100 times greater than that in age-matched non–HIV-infected persons.[53] Findings that confer greater risk for bacteremic pneumococcal pneumonia include alcohol abuse, cigarette smoking, recent hospitalization, and presence of comorbid illnesses.[54] The risk of invasive pneumococcal disease is decreased in those on ART and in those who have received pneumococcal vaccine.[55] However, although the incidence of invasive pneumococcal disease has decreased in the current era, the clinical presentation can be severe and may be complicated by respiratory failure.[56] Providers should consider HIV testing for individuals with unknown serostatus presenting with invasive pneumococcal disease.[55]

CD4+ Lymphocyte Count. Bacterial pneumonia can develop throughout the course of HIV infection and at any CD4+ T cell count. As the CD4+ T cell count declines, the incidence of bacterial pneumonia and the frequency of bacteremia increase. Most cases of *P. aeruginosa* pneumonia are seen in HIV-infected patients with a CD4+ T cell count less than 100 cells/μL and usually less than 50 cells/μL.[57,58]

Imaging. As illustrated in Figure 123.1, the majority of bacterial pneumonias due to *S. pneumoniae* in HIV-infected patients present with segmental, lobar, or multilobar consolidation on chest radiograph.[59] Radiographic findings of pneumococcal pneumonia do not appear to be different among patients on ART than in those not on ART.[60] Although less common, focal or diffuse alveolar patterns and interstitial opacities in association with *S. pneumoniae* or *Haemophilus influenzae* are also seen.[61,62] Pneumonia due to *P. aeruginosa* may present with focal consolidation, similar to pneumococcal or *Haemophilus* pneumonias, although a substantial proportion of radiographs demonstrate cavitary opacities.[57,63]

Diagnosis. The diagnostic approach to bacterial pneumonia is the same for HIV-infected as for non–HIV-infected persons.[27,64] Blood cultures should be obtained, particularly in those with low CD4+ cell counts, given the increased risk for bacteremia in this group.[65] Thoracentesis should be considered for patients with pleural effusion, especially if the effusion is large or if there is concern for empyema.



Figure 123.1 Pneumococcal pneumonia. Frontal chest radiograph in a 50-year-old HIV-infected man with positive urinary pneumococcal antigen shows homogeneous opacity with air bronchograms, extending to the pleural surface, representing a lobar pneumonia pattern, typical of pneumococcal pneumonia. (Courtesy Stephen Aston, MBChB; Malawi-Liverpool–Wellcome Trust Clinical Research Programme.)

Efforts to culture the causative bacteria to enable drug susceptibility testing are especially important in communities where drug-resistant bacteria are prevalent.

Pneumococcal urinary antigen testing offers the potential for early, specific diagnosis. In a study of 70 adults with pneumococcal pneumonia, 47 of whom were HIV infected, pneumococcal urinary antigen testing had a sensitivity of 81%, specificity of 98%, positive predictive value of 98%, and negative predictive value of 82%.[66] The test performed equally well in HIV-infected and non–HIV-infected persons.

Serum procalcitonin and C-reactive protein levels may assist in the differentiation of bacterial community-acquired pneumonia and pulmonary TB in HIV-infected patients; procalcitonin and C-reactive protein levels were higher in patients with bacterial pneumonia than in patients with pulmonary TB, although overlap exists between these causes of pneumonia, particularly in regions endemic for tuberculosis.[67,68] Because procalcitonin increases in response to bacterial and not viral infections, levels are sometimes used as a biomarker of bacterial pneumonia.[69] Elevated procalcitonin levels can predict increased mortality in HIV-infected patients with lower respiratory tract infections due either to TB or to bacterial causes.[70]

Treatment. The treatment of patients with community-acquired pneumonia is similar for HIV-infected and non–HIV-infected persons (see Chapter 46).[27,64] The choice of antimicrobial agent should be based on the results of a sputum Gram stain, the presence of comorbid conditions (e.g., COPD, congestive heart failure, alcohol use), the clinical and radiographic presentation, and the severity of the pneumonia. As in non–HIV-infected persons, treatment should be initiated promptly. Initial empirical therapy should include coverage against frequently identified organisms (e.g., *S. pneumoniae* and *Haemophilus* species). Local prevailing drug resistance patterns must be considered when the antibiotic is selected. Empirical monotherapy with a macrolide is not advised in HIV-infected patients, particularly when they are already on macrolide prophylaxis for MAC because of increasing pneumococcal resistance to macrolides.[27] Patients on *trimethoprim-sulfamethoxazole* (TMP-SMX) prophylaxis may be more likely to have penicillin- and TMP-SMX–resistant *S. pneumoniae.*[71] For patients with $CD4^+$ T cell counts less than 100 cells/μL, especially if associated with recent hospitalization, neutropenia, or broad-spectrum antimicrobial use, coverage of *P. aeruginosa* should be included. Evaluation for opportunistic infections should also be considered in patients who have $CD4^+$ T cell counts less than 200/μL.

Prevention. Pneumococcal vaccine should be given to HIV-infected patients. For adult (age 19 years and older) immunocompromised patients, including those with HIV who have not been previously immunized, current recommendations from the Advisory Committee on Immunization Practices are for the 13-valent pneumococcal conjugate vaccine to be given first, followed by the 23-valent pneumococcal polysaccharide vaccine 8 weeks or more later.[72] For those who have already received the 23-valent pneumococcal polysaccharide vaccine, the 13-valent pneumococcal conjugate vaccine should be given at least 1 year later. A repeat dose of the 23-valent pneumococcal polysaccharide vaccine should be given 5 years after the first, with another dose given after age 65 years. These recommendations may be revised based on ongoing clinical trials; refer to the Advisory Committee on Immunization Practices and *Centers for Disease Control and Prevention* (CDC), *National Institutes of Health* (NIH), and the *HIV Medicine Association of the Infectious Diseases Society of America* (HIVMA/IDSA) guidelines for additional details.[27,72] Because influenza is a major risk factor for bacterial pneumonia, prevention also includes yearly administration of inactivated or recombinant influenza vaccine in all HIV-infected individuals.

OTHER BACTERIA

Legionella pneumonia is an infrequent cause of bacterial pneumonia in HIV-infected patients and can be community or hospital acquired.[73] Cases have been reported in persons with severe immunosuppression and in individuals with well-controlled HIV on ART.[74] The chest radiograph typically reveals alveolar opacities; bilateral involvement is common. Extrapulmonary manifestations can also be seen, especially of the gastrointestinal tract and central nervous system. In one series, respiratory failure developed in 12 of 15 hospitalized, HIV-infected subjects (80%) with *Legionella* pneumonia and 3 died.[74] Although *Legionella pneumophila* is the most common species identified, other *Legionella* species have been reported. Rapid diagnosis of *Legionella* pneumonia can be obtained with urinary antigen testing. However, cultures and/or serology should still be considered as part of the diagnostic evaluation because the urinary antigen primarily detects *L. pneumophila* serogroup 1 and can have a lower sensitivity in cases of mild disease.[75] Its performance has not been prospectively evaluated in HIV-infected patients.

R. equi pulmonary disease has been reported in HIV-infected persons. A review of more than 100 reported cases of *R. equi* infection found that approximately two-thirds were in HIV-infected persons, with pulmonary disease present in the majority.[76] HIV-infected persons were more likely to have *R. equi* bacteremia or extrapulmonary manifestations, or both, than persons without HIV infection. Most cases present when the $CD4^+$ T cell count is less than 200 cells/μL and usually less than 100 cells/μL.[76] In one multicenter series of 67 HIV-infected patients with *R. equi* infection, the mean $CD4^+$ T cell count was 35 cells/μL (range, 1–183 cells/μL).[77] The chest radiograph can reveal cavitary lesions that may mimic TB or nocardiosis, or focal consolidation that may mimic bacterial pneumonia.[78] Sputum, blood, bronchoscopy, and pleural fluid specimens can establish the diagnosis of *R. equi* pneumonia.[77] The optimum treatment regimen and duration are not well defined.[76] Combination antimicrobial therapy is generally recommended, and treatment for a minimum of 2 months (and frequently 6 months) is often required. Because relapses are common, chronic suppressive therapy is probably indicated.

Nocardia asteroides is the most common species identified in several reports of *Nocardia* infection in HIV-infected patients, and the lung is the most commonly affected site. Most cases present when the $CD4^+$ T cell count is less than 200 cells/μL. In one series of 30 HIV-infected patients with nocardiosis, the mean $CD4^+$ T cell count was 109 cells/μL

(median, 92 cells/μL; range, 12–266 cells/μL).[79] The presenting symptoms often mimicked TB. Imaging (eFig. 123.2) usually reveals cavitary lesions or lobar or multilobar opacities, especially in the upper lung zones, although reticulonodular opacities, solitary masses, and pleural effusions are also seen.[80] Sputum or bronchoscopy can establish the diagnosis of pulmonary nocardiosis. A modified *acid-fast bacilli* (AFB) stain may provide an early presumptive diagnosis in the proper clinical setting. Long-term TMP-SMX is the treatment of choice.

MYCOBACTERIA

Early in the AIDS epidemic, mycobacteria were recognized as major sources of HIV-associated morbidity and mortality. Initially, disseminated MAC was noted to develop in HIV-infected patients. Subsequently, the strong association between HIV and *M. tuberculosis* and NTM, such as *Mycobacterium kansasii,* became clearer. Other NTM are also occasionally identified as causes of pneumonia in HIV-infected persons.

Mycobacterium tuberculosis

TB is the most prevalent opportunistic infection complicating HIV worldwide. Unlike most HIV-associated infections, *M. tuberculosis* is transmissible from person to person, including to those without HIV infection. In fact, clusters of transmission of TB that include at least one HIV-infected person are larger, last longer, and have a shorter time period between successive cases than clusters composed of solely non-HIV persons.[81]

The AIDS epidemic contributed to marked increases of TB throughout the world, especially in low-income countries, where it is often the first manifestation of HIV and the leading cause of mortality. The *World Health Organization* (WHO) estimated that there were 862,000 cases of TB in persons with HIV in 2018, with the vast majority of these cases in sub-Saharan Africa.[82] There are also approximately 11 million HIV-infected individuals with latent TB. More than 208,000 HIV-infected persons died of TB in 2019, making it the leading cause of death in HIV-infected populations worldwide.[82]

The AIDS epidemic has also affected TB in the United States. Before 1985, the incidence of TB in the United States regularly declined by 5–6% per year. From 1985–92, the AIDS epidemic led to dramatic increases in TB cases. Since 1992, TB cases have continued to decline, and in 2019, 8920 new TB[83] cases were reported, the lowest number since TB reporting began in 1953.[84] The proportion of TB cases with known HIV infection has also decreased from 15% in 2003 to 4.9% in 2019.[83,84]

It remains unclear whether HIV-infected persons are more likely to acquire infection after exposure to *M. tuberculosis* than non–HIV-infected persons, but it is clear that HIV infection increases the risk for development of primary TB disease, as well as progressing from *latent tuberculosis infection* (LTBI) to active tuberculous disease. Instead of a 5% lifetime risk of disease, the risk for TB among HIV-infected persons with LTBI in the pre-ART era has been estimated to be as high as 10–16% per year.[27] Even with effective ART, the risk of TB disease among HIV-infected persons exceeds that of non–HIV-infected persons.

Multidrug-resistant tuberculosis (MDR-TB), defined as resistance to at least isoniazid and rifampin (also known as rifampicin in many countries), poses a particularly grim prospect for the HIV-infected person. The risk of drug-resistant TB has been reported to be greater among HIV-infected patients than among others, and drug-resistant TB appears to be associated with decreased survival, particularly in those with lower $CD4^+$ T cell counts or in individuals not receiving ART.[85–87] Factors that lead to acquired drug resistance include an inadequate initial treatment regimen, patient nonadherence with the prescribed regimen, and the addition of a single drug to a failing regimen. MDR-TB can also develop as a result of exogenous reinfection from a multidrug-resistant source.[88]

Extensively drug-resistant tuberculosis (XDR-TB), defined as resistance to at least isoniazid and rifampin, plus resistance to any fluoroquinolone and at least one second-line injectable drug, was first reported in 2006.[89] It has been documented in all regions of the world and in HIV-infected persons.[90–92]

Clinical Features. Worldwide, TB is the most common initial manifestation of HIV infection.[93] Thus any person diagnosed with TB should also undergo testing for HIV. The clinical and radiographic features of TB in both HIV-infected and non–HIV-infected persons vary and are fully discussed in Chapter 53. HIV infection is independently associated with an increased risk for extrapulmonary TB.[94] HIV infection is also associated with a lower frequency of cavitary TB, especially in patients with fewer than 200 $CD4^+$ T lymphocytes/μL at the time of TB diagnosis.[95]

$CD4^+$ Lymphocyte Count. TB may develop throughout the course of HIV infection, regardless of the $CD4^+$ lymphocyte count, but the incidence of TB increases as the count decreases. The clinical expression of TB in HIV-infected persons is determined by the degree of immunodeficiency, as indicated by the $CD4^+$ lymphocyte count (see eTable 123.1). Persons with early HIV disease without profound depletion of $CD4^+$ T cells typically present with a picture suggestive of reactivation TB, with disease usually limited to the lungs. In contrast, persons with more advanced HIV disease typically present with findings resembling primary pulmonary TB, often with disseminated or extrapulmonary TB. Any extrapulmonary site may be involved; common sites include lymph nodes (usually cervical, supraclavicular, and axillary), bone marrow, genitourinary tract, central nervous system, and liver.[96]

Imaging. The prevalence of specific chest radiograph features of TB also depends on the degree of immunodeficiency. Early in the course of HIV infection, TB mirrors that encountered in immunocompetent persons: upper lung zone opacities, often with cavitation, on chest radiograph. However, with profound depletion of $CD4^+$ T cells, TB often presents with middle and lower lung zone opacities (Fig. 123.2, eFig. 123.3); with diffuse opacities, including a miliary pattern (eFig. 123.4); or with a normal chest radiograph. As the $CD4^+$ lymphocyte count declines, cavitation becomes less common[95] and intrathoracic adenopathy (Fig. 123.3, eFig. 123.5) becomes more common. ART also affects the chest radiographic appearance in HIV-infected patients with TB;

eTable 123.1 Manifestations of HIV-Associated Tuberculosis Related to Extent of Immunodeficiency

Feature	HIV With Minimal Depletion of $CD4^+$ T Cells (≥350/μL)	HIV With Marked Depletion of $CD4^+$ T Cells (<200–350/μL)
Extrapulmonary	10–15%	>50%
Radiographic distribution	Upper zones	Lower and middle zones
Radiographic findings		
Cavitation	Common	Uncommon
Adenopathy	Uncommon	Common
Miliary	Uncommon	Common
Pleural effusion	Uncommon	Rare

Modified from Murray JF. Cursed duet: HIV infection and tuberculosis. *Respiration.* 1990;57:210–220; with data from Geng E, Kreiswirth B, Burzynski J, Schluger NW. Clinical and radiographic correlates of primary and reactivation tuberculosis: a molecular epidemiology study. *JAMA.* 2005;293(22):2740–2745.

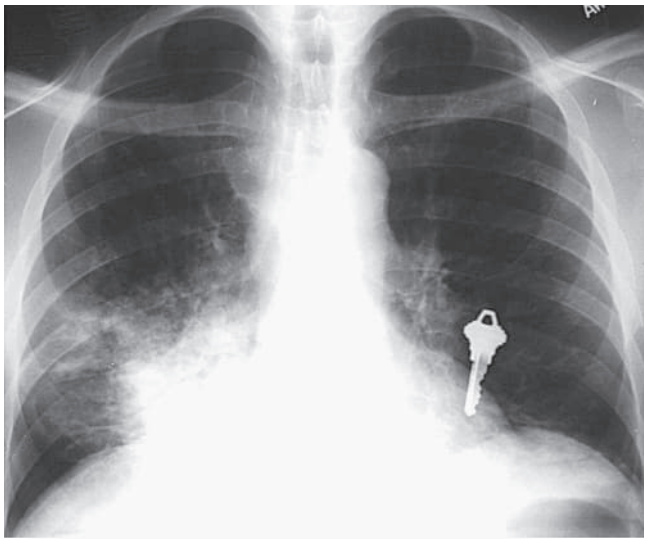

Figure 123.2 Tuberculosis in patient with HIV and a low CD4⁺ count. Frontal chest radiograph of an HIV-infected patient showing focal right lung consolidation with air bronchograms. Culture of sputum revealed *Mycobacterium tuberculosis* that was rifampin resistant. Knowledge of the patient's CD4⁺ lymphocyte count (<50 cells/μL) and understanding that tuberculosis can present with middle to lower lung zone consolidation during "late" HIV infection were instrumental in making the diagnosis of tuberculosis. The key was in the patient's pocket. (Courtesy L. Huang.)



Figure 123.3 Tuberculosis in patient with HIV and a low CD4⁺ count. Frontal chest radiograph of an HIV-infected patient showing mediastinal adenopathy. Culture of biopsy material revealed *Mycobacterium tuberculosis.* Among HIV-infected persons, the proportion of cases that present with intrathoracic adenopathy on chest radiograph increases as the CD4⁺ lymphocyte count decreases. (From Murray JF, Mills J. Pulmonary complications of HIV infection. *Am Rev Respir Dis.* 1990;141:1356–1372, 1582–1598.)

in one study of 209 patients, 82% of patients receiving ART presented with a radiographic pattern of TB resembling that in immunocompetent persons, compared with 44% of patients not receiving ART ($P < 0.001$).[97]

Diagnosis. The diagnostic approach to TB is the same for HIV-infected as for non–HIV-infected persons, especially isolation and identification of *M. tuberculosis* by culture or by nucleic acid amplification (see Chapter 53). Three sputum specimens should be examined for AFB and cultured for mycobacteria.[27] Current recommendations support the use of nucleic acid amplification testing of at least one sputum specimen because these tests can confirm the presence of TB and detect drug resistance in smear-positive patients and because nucleic acid amplification testing is more sensitive than AFB smear, allowing more rapid diagnosis of TB in smear-negative, culture-positive samples.[27,98–100] The WHO recommends the use of Xpert MTB/Rif (Cepheid) nuclear amplification test as an initial test for HIV-associated TB and in MDR-TB.[101] A new Xpert MTB/Rif test has been developed (MTB/Rif Ultra), and it improves upon the sensitivity of the prior version, especially in smear-negative cases.[27] In patients with a nonproductive cough or scant secretions, sputum induction should be performed. Virtually any specimen can be studied for mycobacteria, including sputum, pleural fluid, urine, cerebrospinal fluid, and BAL fluid; transbronchial needle aspiration, fine-needle, and bone marrow aspirates; and all biopsy and tissue specimens. Blood cultures are specific and should be obtained, especially from those persons with a CD4⁺ lymphocyte count less than 200 cells/μL.

All cultures positive for *M. tuberculosis* should be submitted for susceptibility testing because the results are essential in identifying cases of drug resistance and in tailoring definitive treatment. More rapid identification of drug-resistance may be possible with genotypic testing to identify drug-resistance mutations in places where these tests are available.[27,98,99,102]

Treatment. The treatment of patients with TB is similar for HIV-infected and non–HIV-infected persons (see Chapter 54).[27] Because TB is transmissible, persons with suspected TB should be rapidly evaluated and started on appropriate antituberculous treatment to reduce the risk of transmission. The detection of AFB on smear, a positive molecular test or culture for TB, regardless of the source, is an indication for empirical antituberculosis treatment until final identification is obtained. HIV-infected persons with suspected TB should be started on four antituberculous drugs: isoniazid, rifampin, pyrazinamide, and ethambutol along with pyridoxine.[27,103] Directly observed therapy is recommended,[27] and daily rather than intermittent TB therapy is recommended.[104] If resistance to rifampin is suspected or confirmed, moxifloxacin or levofloxacin and an aminoglycoside or capreomycin should be included in the initial regimen and a TB expert consulted.[27] When results of species identification and susceptibility testing become available, treatment can be tailored as needed. In the United States the response to TB therapy and the time to convert sputum cultures from positive to negative appear to be similar in HIV-infected and non–HIV-infected patients.[103] In sub-Saharan Africa, however, the likelihood of death, especially during the first 2 months of therapy, and the likelihood of relapse after apparently successful treatment is considerably higher in HIV-infected than in non–HIV-infected patients.[105]

HIV-infected patients with TB are more likely to experience toxicity from antituberculous drugs than are non–HIV-infected persons.[106] HIV-infected patients are frequently receiving additional medications, and it is often difficult to distinguish an adverse drug effect to antituberculous drugs from those of other medications. As a result,

the first-line antituberculous drugs (especially isoniazid and rifampin) should only be discontinued permanently if there is strong evidence that these specific medications were the cause of toxicity.[103]

Despite challenges in ART use during TB therapy, ART given concurrently with TB treatment rather than sequentially has been associated with decreased mortality, greater AIDS-free survival, and more rapid conversion of sputum smears and culture in randomized studies.[27,107–111] Thus all HIV-infected individuals with pulmonary TB should receive ART.[27] If the patient is naive to ART, it is recommended that ART be initiated within 2 weeks of TB treatment initiation in individuals with $CD4^+$ cell counts less than 50 cells/μL and within 8 weeks in all others.[27] Note: In patients with TB meningitis (with or without pulmonary TB) and low $CD4^+$ counts, early ART may pose a risk for severe adverse effects, and an HIV-TB expert should be consulted to assist in this decision.[27] Individuals receiving ART should continue its use during TB therapy, but ART may need to be modified to minimize drug-drug interactions.

Clinicians need to be aware of several challenges of ART use during TB treatment. HIV-infected patients with TB who begin therapy for both *M. tuberculosis* and HIV infection may develop *immune reconstitution inflammatory syndrome* (IRIS), a paradoxical reaction presenting as exacerbation of clinical and radiographic features, which is more common with ART started early during antituberculosis therapy and among those with disseminated TB.[108–112] Furthermore, simultaneous treatment of HIV and *M. tuberculosis* poses additional challenges in terms of drug interactions. HIV *protease inhibitors* (PIs) and certain *non-nucleoside reverse transcriptase inhibitors* (NNRTIs) have significant interactions with the rifamycins, especially rifampin, principally related to the induction or inhibition (or both) of the hepatic *cytochrome P-450* (CYP) enzyme system.[103] Decreased drug levels are associated with development of drug resistance by both HIV and *M. tuberculosis,* whereas increased drug levels are correlated with toxicity. In persons receiving PIs, rifabutin is preferred over rifampin because it is a less potent CYP 3A4 inducer. Coadministration of rifampicin with *integrase strand transfer inhibitors* (INSTIs) is associated with a reduction in their trough levels. However, doubling the dose of INSTIs such as raltegravir was associated with optimal antiviral levels (bictegravir and elvitegravir should not be used with rifamycin-based therapies). Results from clinical trials on rifampicin and dolutegravir in active TB are expected soon (ClinicalTrials.gov Identifier: NCT02178592).[113] Information on the interactions between specific antiretroviral drugs and different rifamycins is regularly updated and can be found on such websites as the CDC website http://www.cdc.gov/tb and the U.S. Department of Health and Human Services AIDSinfo website https://aidsinfo.nih.gov/. Clinicians caring for HIV-infected patients with TB should consult experts for aid in management before initiating TB or HIV therapy.

Prevention of Exposure. In health care facilities, all persons with HIV infection and signs or symptoms compatible with TB should be placed in respiratory isolation until three sputum smears or molecular tests are negative. Prevention of transmission of drug-resistant TB is particularly important.

Prevention of Disease. HIV-infected persons are at high risk for progressing from LTBI to active TB. Therefore HIV-infected persons should be tested for LTBI by either a *tuberculin skin test* (TST) or *interferon-γ* (IFN-γ) release assay when HIV infection is first identified.[27,114] HIV-infected persons who are at risk for exposure to *M. tuberculosis* (either ongoing or repeated) should be tested for LTBI annually with TST.[27] In addition, persons who initially had a negative test but subsequently experienced an increase in their $CD4^+$ lymphocyte count to greater than or equal to 200 cells/μL due to ART should be retested for LTBI.[27] Any individual with a positive test for LTBI should be screened for symptoms and chest radiographic findings suggestive of active TB, and LTBI treatment should be given only to those without evidence of active TB.[27]

Several studies document that the risk of LTBI reactivation is virtually eliminated if an HIV-infected person who has been infected with a drug-susceptible organism takes adequate LTBI treatment.[27,114–116] HIV-infected persons with a positive TST (defined as 5-mm induration or greater), a positive IFN-γ release assay, or with a history of either of these and who have not received prior treatment for either LTBI or active TB should receive LTBI treatment. HIV-infected individuals who are close contacts of anyone with active TB should also receive treatment.[27] The standard treatment is isoniazid (300 mg daily) plus pyridoxine for 9 months.[27] Alternative treatments include isoniazid (plus pyridoxine) plus rifapentine (both weight-based dosing) once weekly for 12 weeks or rifampin daily for 4 months. Expert consultation should be sought for patients receiving ART or for individuals exposed to drug-resistant TB. Routine use of preventive therapy in anergic or purified protein derivative–negative HIV-infected persons is not generally recommended.[27,114]

Mycobacterium avium Complex

As discussed in Chapter 55, MAC consists of several related *Mycobacterium* species, including *M. avium* and *M. intracellulare.* With the use of ART, however, the incidence of disseminated MAC has declined since 1996.[1,117,118] MAC is ubiquitous in the environment, with species found in water and soil. Acquisition of infection in PLWH is chiefly through the gastrointestinal tract and occasionally through the lungs.[119] Person-to-person transmission is believed to be uncommon. Although numerous subspecies can cause pulmonary disease, cases of disseminated MAC are most frequently caused by *M. avium*, which suggests that there are important differences in exposure to or virulence of these particular strains.

Clinical Features. Isolated pulmonary disease from MAC is rare in the context of AIDS.[120] The most common clinical presentation is disseminated MAC disease, characterized by a febrile wasting syndrome consisting of fever, night sweats, fatigue, anorexia, and weight loss; other manifestations include abdominal pain and chronic diarrhea, hepatosplenomegaly, lymphadenopathy, progressive anemia, and, rarely, extrabiliary obstructive jaundice.[121] Laboratory abnormalities include anemia, which is often severe, and an elevated alkaline phosphatase level.

$CD4^+$ Lymphocyte Count. More than 95% of cases of disseminated MAC are seen in HIV-infected patients whose

$CD4^+$ lymphocyte count is 50 cells/μL or less.[121] Other risk factors for disseminated MAC include a plasma HIV viral level greater than 1000 copies/mL, history of previous opportunistic infection, and previous MAC colonization of the respiratory or gastrointestinal tract.[27]

Imaging. The chest radiograph is typically normal, even when the organism is cultured from respiratory tract secretions.[119] Focal pneumonia has been reported (eFig. 123.6) but is extremely rare,[120] as is presentation with solitary or multiple pulmonary nodules (eFig. 123.7). More frequently seen, but still uncommon, are endobronchial lesions without pneumonia.[122] These endobronchial lesions appear to be submucosal "pearls" (eFig. 123.8) with many AFB on biopsy. Lymphadenopathy, with or without necrosis, is a common imaging manifestation of thoracic MAC infection in HIV-infected patients (eFig. 123.9). Many of the cases of isolated pulmonary MAC were reported in patients who received ART, thus raising the possibility that this particular manifestation is an example of immune reconstitution. Clinicians should be aware of this possibility when starting patients on ART because IRIS may be seen either in patients with diagnosed disease or in those with subclinical infection.

Diagnosis. In HIV-infected patients with MAC, the organism can be cultured from numerous sites, with blood, bone marrow, liver, or lymph nodes representing the most productive sources.[121] Cultures should be performed on both solid and liquid culture media to increase sensitivity. The sensitivity of blood cultures for disseminated MAC has ranged from 86–98% of cases in which disseminated disease was confirmed by autopsy. The diagnosis of disseminated MAC can also be established by cultures from any normally sterile body site. Often, MAC is cultured from respiratory specimens such as sputum or BAL fluid, but, depending on the clinical situation, this finding may not indicate either pulmonary or disseminated disease.[119,123] If patients have abnormal chest radiographs with positive sputum cultures, the diagnostic criteria for immunocompetent hosts recommended by the *American Thoracic Society* (ATS) and IDSA, listed in Table 55.3, should be applied.[123] Species identification can be performed with a variety of techniques, including line probe assays, 16S ribosomal RNA gene sequencing, single- and multigene sequencing, and matrix-assisted laser desorption ionization–time of flight mass spectrometry, depending on laboratory capabilities.[124] The pathologic findings of MAC infection are characteristic but not definitive; AFB are remarkably abundant and are often packed within foamy macrophages or histiocytes; granulomas are usually absent or poorly formed.

Treatment. As emphasized in Chapter 54, the key to any regimen is the use of at least two drugs, including a macrolide: clarithromycin (500 mg twice daily) is preferred, but azithromycin (500–600 mg daily) can be substituted if needed.[27] One of these should be combined with ethambutol (15 mg/kg/day). Sensitivity testing of isolates to clarithromycin or azithromycin should be performed. Use of a third or fourth agent, such as rifabutin (300 mg daily), an aminoglycoside (i.e., amikacin 10–15 mg/kg intravenously daily), or a fluoroquinolone (i.e., levofloxacin 500 mg daily or moxifloxacin 400 mg/day), can be considered in patients with advanced immunodeficiency, high mycobacterial burden, or the inability to take ART.[27] As with TB, the use of rifabutin must be carefully scrutinized with concurrent administration of an NNRTI or a PI.

Prevention of Exposure. Although MAC can be found in environmental sources such as food and water, there are no specific recommendations regarding exposure avoidance as a prevention strategy.[27] Similarly, although the presence of MAC in a stool or respiratory specimen is predictive of disseminated disease, routine screening is not recommended.

Prevention of Disease. The CDC, NIH, and HIVMA/IDSA guidelines recommend that MAC primary prophylaxis be administered to HIV-infected patients with a $CD4^+$ lymphocyte count less than 50 cells/μL, no clinical evidence of disseminated MAC, and who have no options for a fully suppressive ART regimen.[27] Primary prophylaxis is not recommended for PLWH who are immediately initiated on ART.[27] Preferred MAC prophylaxis regimens include azithromycin (1200 mg weekly or 600 mg twice weekly) or clarithromycin (500 mg twice daily). Rifabutin is an alternative regimen if patients are intolerant of azithromycin or clarithromycin.[27] If rifabutin is to be used, TB must first be excluded because its use for MAC has been associated with rifampin monoresistance in *M. tuberculosis*. Individuals with a history of disseminated MAC should receive secondary prophylaxis/chronic maintenance therapy with a MAC treatment regimen cited earlier. In the setting of ART with increases in the $CD4^+$ lymphocyte count to greater than 100 cells/μL for at least 6 months—and after a minimum of 12 months of a macrolide-based MAC treatment regimen—most patients can discontinue therapy without relapse.[27] Initiation of secondary prophylaxis should be considered for PLWH if a fully suppressive ART regimen is not possible and the patient has $CD4^+$ counts consistently less than 100 cells/μL.

Mycobacterium kansasii

As described in Chapter 55, *M. kansasii* has a geographic distribution, predominantly in the southern and central United States.[123] Clusters of disease have also been reported in Europe, Asia, and Africa. Before the AIDS epidemic, infection and disease due to *M. kansasii* were uncommon. Thereafter, a dramatic increase in the incidence associated with HIV infection was observed, even in areas where *M. kansasii* was not thought to be endemic. Although rates of opportunistic infection from MAC and *M. kansasii* have generally declined in PLWH in the combination ART era, an increasing proportion of pulmonary mycobacterial disease due to NTM, including from *M. kansasii,* has been reported around the world.[125,126] Although *M. kansasii* pulmonary disease can be clinically indistinguishable from TB,[127] person-to-person transmission has not been documented, and infection is thought to arise from environmental sources, with tap water being most commonly implicated.

$CD4^+$ Lymphocyte Count. Similar to TB in HIV-infected persons, *M. kansasii* pneumonia can develop at any $CD4^+$ lymphocyte count. Most HIV-infected patients with *M. kansasii,* however, have evidence of severe immunodeficiency

with $CD4^+$ lymphocyte counts typically less than 100 cells/μL.[127–129] In the ART era, Canueto-Quintero and colleagues[127] reported a mean $CD4^+$ lymphocyte count of 20 cells/μL among 25 HIV-infected patients with *M. kansasii.* Witzig and coworkers[129] found that 32 of 49 HIV-infected patients (65%) with *M. kansasii* had isolated pulmonary disease (mean $CD4^+$ lymphocyte count, 75 cells/μL), whereas the remainder had disseminated disease (mean $CD4^+$ lymphocyte count, 28 cells/μL).

Imaging. The chest radiographic findings of *M. kansasii* vary. The most common radiographic findings resemble TB and include alveolar opacities, diffuse opacities, and cavities (see Fig. 55.6; eFig. 123.10); masses, intrathoracic adenopathy, and pleural effusions have also been reported. In a series of 83 HIV-infected patients with *M. kansasii,* the most frequent findings were consolidation (66%) and nodules (42%); abnormalities were most often located in the midlung and lower lung zones (89%), and in 10%, radiographs were normal.[130]

Diagnosis. The diagnosis of *M. kansasii* rests on its isolation and subsequent identification by culture. Pulmonary disease can be diagnosed by all of the techniques used for the diagnosis of TB. Unlike TB, however, in which identification of *M. tuberculosis* is diagnostic of disease, the identification of *M. kansasii* can occasionally represent colonization rather than disease.[131] The ATS/IDSA guidelines have defined criteria for diagnosis of NTM pulmonary disease that includes *M. kansasii* (see Table 55.3).[123] Nucleic acid probe testing, high-pressure liquid chromatography, and biochemical tests can be used for species identification.

Treatment. Treatment options for *M. kansasii* pulmonary disease include azithromycin (250–500 mg daily) or clarithromycin (1000 mg daily), with rifampin (600 mg daily) plus ethambutol (15 mg.kg daily). An alternative regimen for treatment of *M. kansasii* pulmonary disease consists of isoniazid (300 mg daily), rifampin (600 mg daily), and ethambutol (15 mg/kg daily).[123] Isolates should be tested for sensitivity to rifampin. If rifampin resistance is present, testing for susceptibility to other potential agents should be performed. Patients should also receive pyridoxine (50 mg daily) during treatment. Treatment options require consideration of drug-drug interactions and adjustment of regimens, such as avoidance of rifampin and substitution with rifabutin in those on PI or NNRTIs. Pyrazinamide is not useful because all *M. kansasii* isolates are resistant. Patients should receive treatment for a minimum of 12 months after their cultures become negative.

Prevention. There are no recommended prevention strategies for *M. kansasii*.

Other Mycobacteria

MAC and *M. kansasii* account for the great majority of NTM infections complicating HIV. Other mycobacteria, however, have occasionally been identified.[121,132] Increased frequency of exposure or specific defects in host defenses might account for the predominance of MAC and *M. kansasii* over other NTM in AIDS patients; differences in the virulence of the various mycobacterial species are also likely to play an important role.

FUNGI

Several fungi cause pulmonary disease in HIV-infected persons.[133] *Pneumocystis jirovecii,* formerly called *Pneumocystis carinii,* remains a common cause of HIV-associated pneumonia. *Cryptococcus neoformans,* the most common cause of meningitis in HIV-infected persons, often presents with an associated pneumonia. The endemic fungi *Histoplasma capsulatum, Coccidioides immitis, Penicillium marneffei,* and, to a lesser extent, *Blastomyces dermatitidis* are among the chief causes of HIV-associated disease seen in their particular geographic regions, and all have important pulmonary presentations. Finally, invasive aspergillosis is often a devastating pulmonary disease seen in HIV-infected persons with severe immunodeficiency. Further information about fungal pulmonary diseases is provided in Chapters 56 and 57.

Pneumocystis jirovecii

PCP remains the most common AIDS-defining opportunistic infection in the United States, even though its overall incidence has declined.[1] Early in the AIDS epidemic, PCP accounted for nearly two-thirds of AIDS-defining diagnoses, and PCP developed in an additional 15–20% of patients at some time during their HIV disease. Two factors—the use of ART and *Pneumocystis* prophylaxis—dramatically reduced the number of cases. Nevertheless, PCP remains a risk, chiefly among persons who are unaware of their HIV infection, those who fail to seek medical care, and those who fail to adhere to or respond to ART or *Pneumocystis* prophylaxis.[134–136]

History and Epidemiology. *Pneumocystis* was initially recognized as a human pathogen in the 1940s and 1950s. Despite more than a century of experience, several gaps in our understanding of this omnipresent organism remain.[137–140] One major obstacle that has impeded further advances has been the inability to culture *Pneumocystis* in vitro. Although mammals are the only known hosts of *Pneumocystis* and a number of mammals are susceptible to infection, *Pneumocystis* strains are species specific.[141] Although *Pneumocystis* can be transmitted between mammals of the same species, animal studies that have attempted to transmit *Pneumocystis* from one species to another have been unsuccessful.[141] In recognition of the host-species specificity of *Pneumocystis,* the *Pneumocystis* that causes *Pneumocystis* pneumonia in humans is now referred to as *P. jirovecii,* in honor of Otto Jirovec, the parasitologist credited with first identifying *Pneumocystis* as the cause of pulmonary disease in humans.[142,143]

The ecologic niche for *P. jirovecii* and its mode of transmission is unknown.[139,144,145] The inability to maintain human *Pneumocystis* in culture suggests that *P. jirovecii* may be unable to grow outside of its human host.[146,147] Given its species specificity, it is doubtful that other mammals are the reservoir for *P. jirovecii.* This host-species specificity also implies coevolution of humans and *P. jirovecii* that, in turn, implies long-term carriage of *P. jirovecii* in its human host. Infection with *P. jirovecii* is almost ubiquitous. Up to 85–100% of the U.S. population have antibodies to *P. jirovecii* by the age of 3 years.[148,149] In the setting of severe immunodeficiency, PCP can affect significant proportions of people. These studies and others suggest that activation of latent infection is a cause of *P. jirovecii* disease among

immunocompromised hosts. Outbreaks of newly acquired infection after de novo exposure to persons with PCP have also been documented, which suggests person-to-person transmission of *P. jirovecii* and the rapid development of disease. Results of studies that have used molecular tools to detect *Pneumocystis* are consistent with transmission of *P. jirovecii* from patients with PCP to their household and hospital contacts,[150,151] probably via inhalation of a *Pneumocystis*-containing aerosol.[152,153]

Risk Factors. Risk factors for PCP among HIV-infected adults include a $CD4^+$ lymphocyte count less than 200 cells/μL, a history of PCP, and oropharyngeal candidiasis.[154,155]

$CD4^+$ Lymphocyte Count. Approximately 95% of adolescent and adult cases of PCP are seen in HIV-infected patients whose most recent $CD4^+$ lymphocyte count is less than 200 cells/μL or $CD4^+$ percentage is less than 14%.[155]

Clinical Features. HIV-infected adults, unlike other immunocompromised persons, usually have a prolonged prodromal illness associated with PCP, often several weeks in duration.[156,157] This duration of symptoms can often be used to distinguish PCP from pyogenic pneumonia, which typically presents with 3 to 5 days of symptoms. Classically, PCP presents with fever, nonproductive cough, and dyspnea on exertion. High temperature, rigors, purulent sputum, and pleuritic chest pain are uncommon and can be used to distinguish PCP from pyogenic pneumonia.

Physical examination of the chest may be normal. When abnormal, the most frequent findings on lung auscultation are inspiratory crackles, which have been reported to be associated with a greater disease severity and an increased mortality.[157] Oxygen desaturation with exertion is a sensitive but nonspecific indicator of PCP.

Numerous studies have shown that the serum *lactate dehydrogenase* (LDH) level is increased in patients with PCP; however, an elevated serum LDH level does not establish the diagnosis of PCP, nor does a normal serum LDH value rule out the diagnosis. β-D-glucan, has been reported to be a potential diagnostic tool for PCP.[158,159] Immunoassays are another new diagnostic approach that could be used as a point-of-care test, especially in resource-limited settings.[160]

Imaging. Classically, PCP presents with bilateral, symmetrical reticular opacities (eFig. 123.11) or as granular opacities (eFig. 123.12A)[161]; these opacities typically begin in the perihilar region and extend outward as the disease severity increases. The ground-glass opacity appearance is particularly associated with the chest CT manifestations of this disorder (eFig. 123.12B). On occasion, the opacities are unilateral or asymmetrical (eFig. 123.13); a lobar or focal radiographic pattern is uncommon. Thin-walled cysts, or pneumatoceles, are seen in 10–20% of cases (Fig. 123.4).[162] Pneumatoceles may be single (eFig. 123.14A) or multiple (eFig. 123.14B–D), and small or large, and predispose patients to pneumothorax (eFig. 123.15), which is another radiographic presentation of PCP. Usually pneumatoceles resolve (see eFig. 123.14B–D), but occasionally they persist despite successful therapy.

Nearly any radiographic finding, including focal, lobar, or segmental consolidation (eFigs. 123.16 to 123.18), nodules (eFig. 123.19) with or without cavitation, and a miliary pattern, can be seen occasionally.[162] Intrathoracic adenopathy and pleural effusions are rarely due to PCP. These radiographic findings should prompt a search for an alternate or at least a coexisting process, such as bacterial pneumonia, TB, fungal pneumonia, or pulmonary.

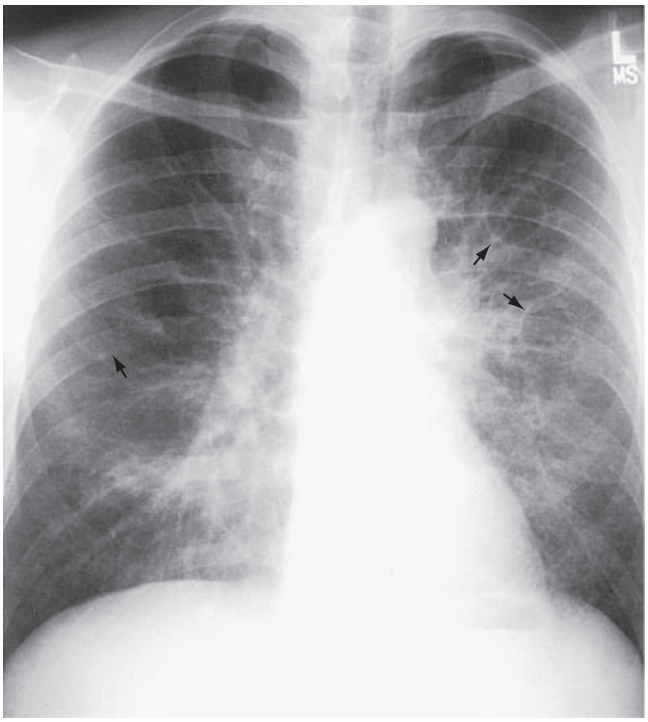

Figure 123.4 *Pneumocystis* pneumonia. Frontal chest radiograph of an HIV-infected patient with *Pneumocystis* pneumonia showing bilateral, predominantly perihilar, granular opacities, and three pneumatoceles (*arrows*). Pneumatoceles may be single or multiple in number, small or large in size, and may predispose patients to pneumothorax. (Courtesy L. Huang.)

KS PCP may also present with a normal chest radiograph. In several studies, a normal radiograph was present in 0–39% of patients with PCP.[161–165] In persons with a high clinical suspicion for PCP but a normal chest radiograph, high-resolution chest CT can be useful.[164]

Diagnosis. The diagnosis of PCP depends on microscopic visualization of *P. jirovecii* cysts or trophic forms (or both) on stained respiratory specimens. Often, the procedures to obtain these respiratory specimens (e.g., bronchoscopy) are lacking in the areas of the world with the greatest burden of HIV/AIDS.[165]

The standard methods for detection of *P. jirovecii* have been with cyst wall stains, such as methenamine silver and toluidine blue-O or with Giemsa and Diff-Quik, which stain both the cystic and trophic forms; monoclonal antibodies to *P. jirovecii* are also used.[166] *Polymerase chain reaction* (PCR)-based techniques have also been used and have been reported to be more sensitive but also less specific than these other methods.[166,167]

Sputum induction is an appropriate initial diagnostic procedure for PCP, but the sensitivity of induced sputum testing is less than 100%, and thus a negative result should be followed by bronchoscopy with BAL performed in the most

affected lobe visualized on chest radiograph.[28] For patients with diffuse radiographic disease, BAL in the right middle lobe is usually performed. For patients with an upper lung zone predominance on radiograph, lavage in both an upper lobe and the right middle lobe should be considered.

Treatment. The treatment of choice for patients with mild, moderate, and severe PCP remains TMP-SMX administered for 21 days.[27] The usual dose of TMP is 15 mg/kg/day (range, 15–20 mg/kg/day), and that of SMX is 75 mg/kg/day (range, 75–100 mg/kg/day), divided into three or four daily doses (eTable 123.2). Dosing may be intravenous (recommended for patients with moderate or severe PCP) or oral, and patients started on intravenous TMP-SMX can switch to oral formulations after clinical improvement. Adverse effects from TMP-SMX are frequent in HIV-infected patients and include rash, fever, gastrointestinal complaints (i.e., nausea, vomiting), elevated aminotransferases, hyperkalemia, and bone marrow suppression, especially anemia and neutropenia; these often develop during the second week of therapy. In a proportion of HIV-infected patients, the side effects of TMP-SMX are treatment limiting. Rare adverse reactions include Stevens-Johnson syndrome, toxic epidermal necrolysis, and a clinical syndrome resembling septic shock. Studies are conflicting regarding the presence of potential TMP-SMX drug resistance in *Pneumocystis,*[168,169] but patients who develop PCP despite receiving TMP-SMX prophylaxis can usually be treated with TMP-SMX.

For patients with allergy to or intolerance of TMP-SMX, alternative treatment regimens (see eTable 123.2) include intravenous pentamidine, clindamycin plus primaquine, TMP plus dapsone, and atovaquone.[27] Several reports demonstrate efficacy of echinocandans for PCP.[170,171] As in TB, HIV-infected patients with PCP who begin therapy for *Pneumocystis* and initiate ART may develop paradoxical reactions, usually a temporary exacerbation of clinical and radiographic features but occasionally respiratory failure due to immune reconstitution.[172,173] The diagnosis of IRIS is one of exclusion. Patients with paradoxical reactions only rarely require discontinuation of antiretroviral therapies, and symptomatic therapy is recommended.

Corticosteroid Therapy. Corticosteroids should be given to adults or adolescents with documented or suspected PCP if they have an arterial Po_2 level less than 70 mm Hg or an alveolar-arterial Po_2 difference greater than 35 mm Hg. Corticosteroids, either oral prednisone or intravenous methylprednisolone, should be started at the same time that anti-*Pneumocystis* treatment is begun, regardless of whether the diagnosis has been confirmed.

Early in the AIDS epidemic, acute respiratory failure secondary to PCP, if severe enough to warrant mechanical ventilation, had a mortality rate of 86% or greater.[175] Although the mortality associated with acute respiratory failure secondary to PCP remains significant (≈30–50%),[176,177] HIV-infected patients with PCP and respiratory failure requiring mechanical ventilation should be managed with lung-protective strategies as for patients with acute respiratory distress syndrome.[178] At least one retrospective study[176] suggests that ART may be beneficial in these cases, although prospective randomized clinical trials in the intensive care unit involving mechanically ventilated patients are lacking.[179,180]

Prevention of Exposure. The natural reservoir for human *Pneumocystis* remains unknown.[181] Environmental and human reservoirs have been suggested.[144,182] Whether PCP results from reactivation of latent infection or also from a recent infection is debated; reports of clusters of PCP among different immunocompromised populations support the theory that PCP can result from a recent exposure and person-to-person transmission. In accordance, some authorities have argued that HIV-infected and other immunocompromised persons at risk for PCP should avoid close contact with any individuals who have PCP. However, the current CDC, NIH, and HIVMA/IDSA guidelines state "there are insufficient data to support isolation as standard practice to prevent PCP."[27]

Prevention of Disease. HIV-infected adults or adolescents (including those on ART) who have a $CD4^+$ lymphocyte count less than 200 cells/μL or a $CD4^+$ percentage less than 14% should receive primary *Pneumocystis* prophylaxis, and persons with prior PCP should receive secondary prophylaxis (eTable 123.3).[27] Once started, HIV-infected adults and adolescents should remain on PCP prophylaxis, unless their $CD4^+$ lymphocyte counts increase from less than 200 cells/μL to greater than 200 cells/μL for at least 3 months as a result of ART.[27] Discontinuation of PCP prophylaxis can be considered in those with a $CD4^+$ lymphocyte count between 100 and 200 cells/μL if the HIV RNA level remains below the limits of detection for at least 3 to 6 months as a result of ART.[27]

TMP-SMX, dapsone, atovaquone suspension, and aerosolized pentamidine are the standard options for PCP prophylaxis.[27] TMP-SMX is the first-line choice for primary and secondary prophylaxis against *Pneumocystis.* For those patients intolerant of TMP-SMX, dapsone and atovaquone are both oral drugs that can be used. Many authorities would add pyrimethamine (plus leucovorin) to these drugs for patients with a history of PCP, a $CD4^+$ lymphocyte count less than 100 cells/μL, or both. For patients who are *T. gondii* immunoglobulin G antibody positive, pyrimethamine should be added. Monthly aerosolized pentamidine remains an effective and well-tolerated prophylaxis option; however, caution must be exercised when using this drug for secondary prophylaxis or in patients with a $CD4^+$ lymphocyte count less than 100 cells/μL because prophylaxis breakthrough may be more frequent in this population.

Cryptococcus Species

Cryptococcosis is caused by *C. neoformans or Cryptococcus gattii,* encapsulated fungi that can infect either healthy or immunocompromised people; these fungi are characterized by a polysaccharide capsule that can be detected using India ink or mucicarmine staining.[183] *Cryptococcus* is transmitted by aerosol. *C. neoformans* is global in distribution and is most commonly isolated from bird excrement, decaying fruit, and soil. Most cryptococcal disease in HIV-infected persons is due to *C. neoformans*. *C. gattii* has been isolated from Australia, South America, the Pacific Northwest of the United States, and southwestern Canada, where outbreaks of disease have been reported; sporadic cases have

eTable 123.2 Treatment Regimens for *Pneumocystis* Pneumonia*

Treatment Regimen	Dose(s), Frequency	Toxicities
MILD PCP† (Pao_2 > 70 mm Hg *AND* ALVEOLAR-ARTERIAL Po_2 DIFFERENCE < 35 mm Hg)		
TMP-SMX	15–20 mg/kg (TMP component) daily (q6–8 hr)	Fever, dermatologic, gastrointestinal, hematologic
TMP *plus* dapsone	15–20 mg/kg daily (q6–8 hr) 100 mg once daily	Dermatologic, gastrointestinal, hematologic
Clindamycin *plus* primaquine	1800 mg daily (q6–8 hr) 30 mg (base) once daily	Dermatologic, gastrointestinal, hematologic
Atovaquone	750 mg three times daily	Dermatologic, gastrointestinal
MODERATE-SEVERE PCP‡ (Pao_2 ≤ 70 mm Hg *OR* ALVEOLAR-ARTERIAL Po_2 DIFFERENCE ≥ 35 mm Hg)		
TMP-SMX	15–20 mg/kg (TMP component) daily (q6–8 hr)	Fever, dermatologic, gastrointestinal, hematologic
Pentamidine	3–4 mg/kg IV once daily	Renal, pancreatic
Clindamycin *plus* primaquine	1800–2400 mg (q6–8 hr) 30 mg (base) once daily	Dermatologic, gastrointestinal, hematologic

*Recommended duration of therapy = 21 days.
†Oral route is preferred for patients with mild PCP who are treated as outpatients.
‡IV route is preferred, at least until clinical improvement, for patients with moderate to severe PCP. Adjunctive corticosteroids (prednisone 40 mg PO twice daily for 5 days, then 40 mg PO once daily for 5 days, then 20 mg PO once daily for 11 days or potency-equivalent Solu-Medrol IV) should also be administered.
IV, intravenous; Pao_2, arterial partial pressure of oxygen; PCP, *Pneumocystis* pneumonia; PO, orally; TMP-SMX, trimethoprim-sulfamethoxazole.

eTable 123.3 Prevention of *Pneumocystis* Pneumonia

Prevention Regimens	Alternative Dosing	Comments
Trimethoprim-sulfamethoxazole 1 double-strength tablet daily	One single-strength tablet daily or 1 double-strength tablet 3 times weekly	Also effective prophylaxis against *Toxoplasma gondii* and many bacterial pathogens
Dapsone 100 mg daily		Combine with pyrimethamine and leucovorin in persons who are *T. gondii* immunoglobulin G antibody positive Consider combining with pyrimethamine and leucovorin when used for secondary prophylaxis
Atovaquone suspension 1500 mg daily or 750 mg twice daily		Improved bioavailability compared to tablets
Aerosolized pentamidine 300 mg monthly via RespirGard II nebulizer		May be associated with increased risk of extrapulmonary disease

been reported in the southeastern United States. *C. gattii* is more likely to infect immunocompetent hosts, although it also causes disease in HIV-infected individuals.

Clinical Features. Although the portal of entry is the lung, cryptococcal pulmonary infection is often asymptomatic or minimally symptomatic, and the most commonly encountered manifestation of cryptococcal disease is meningitis.[184–186] Less than 5% of patients with cryptococcal disease present with isolated pneumonia.[185,187] However, autopsy studies suggest that pulmonary disease is underdiagnosed, particularly in settings where diagnostic facilities are limited.[188] When present, the most frequent respiratory complaints are cough and dyspnea.[185,186] Pleuritic chest pain and productive cough have also been reported,[190] perhaps distinguishing pulmonary cryptococcosis from PCP. Although rarer, cases of acute respiratory failure have been reported.[188]

CD4⁺ Lymphocyte Count. In most cases, cryptococcosis infects patients with a $CD4^+$ lymphocyte count less than 200 and typically less than 100 cells/μL. A study of 1644 patients reported a median $CD4^+$ count of 24 cells/μL with a range of 0 to 480 cells/μL.[184] A study from Uganda from the ART era reported a median $CD4^+$ count of 23 cells/μL.[191]

Imaging. Cryptococcal pneumonia most commonly presents with diffuse bilateral interstitial opacities.[190,192] In one study,[193] interstitial opacities were most frequently reported in 60 of 92 radiographs (65%) (eFig. 123.20), followed by hilar adenopathy (27%) (eFig. 123.21), pleural effusion (14%), focal consolidation (13%) (eFig. 123.22), nodular opacities (11%) (eFig. 123.23), and cavitation (11%) (Fig. 123.5). Rarely, radiographic findings include a miliary pattern (eFig. 123.24),[194] solitary pulmonary nodules,[195] pulmonary masses,[196] isolated pleural effusion,[197] and pneumothorax.[198] Cryptococcal pneumonia may also present with a normal chest radiograph.[193]

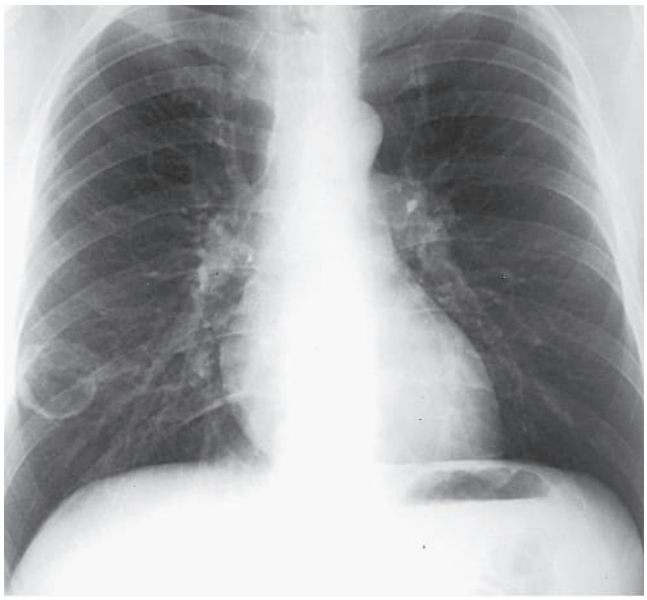

Figure 123.5 Cryptococcal infection. Frontal chest radiograph of an HIV-infected patient showing a solitary cavitary lesion in the right lower lung field. Culture of bronchoalveolar lavage fluid revealed *Cryptococcus neoformans*. In HIV-infected patients, cryptococcal disease can present with a wide range of chest radiographic findings, including a normal chest radiograph. (From Stansell JD: Fungal disease in HIV-infected persons: cryptococcosis, histoplasmosis, and coccidioidomycosis. *J Thorac Imaging.* 1991;6:28–35.)

Diagnosis. The diagnosis of cryptococcal infection begins with the *cryptococcal antigen* (CRAG) test, which can be performed on serum, cerebrospinal fluid, urine, BAL fluid,[199] or pleural fluid. The serum CRAG test is sensitive and specific for cryptococcemia. A negative serum CRAG virtually rules out a diagnosis of cryptococcal meningitis but can be seen rarely in some cases of isolated pulmonary cryptococcosis. A positive serum CRAG test should prompt an evaluation for disseminated disease, especially meningitis, but false-positive results can be seen in the presence of rheumatoid factor or infection with the fungus *Trichosporon asahii* (formerly *T. beigelii*), or with bacteria from the *Stomatococcus* or *Capnocytophaga* genera. However, a positive CRAG can sometimes be found in individuals without clinical evidence of disease and can portend a worse outcome; screening of individuals with low $CD4^+$ cell counts and preemptive treatment are advocated.[27,200–202] Blood fungal cultures are specific and should be obtained as part of the diagnostic evaluation. New cutaneous lesions may be signs of dissemination and should prompt consideration for biopsy.

Pulmonary cryptococcosis is usually diagnosed by culture of sputum or BAL fluid and occasionally of pleural fluid. Specimens from TBB and pleural biopsy can also be diagnostic. Batungwanayo and coworkers[190] found that BAL diagnosed 27 of 33 cases (sensitivity, 82%) of cryptococcal pneumonia compared with TBB, which diagnosed 10 of 21 cases (sensitivity, 48%). In some cases, cultures are negative, but a BAL or pleural fluid CRAG test can establish the diagnosis.[193] Because the treatment is identical, the diagnosis of pneumonia may be inferred in the presence of disseminated cryptococcal disease (e.g., meningitis) and a compatible radiographic presentation. However, other opportunistic infections such as PCP may be present concurrently and can demonstrate identical radiographic findings.

Treatment. There are no randomized controlled trials for HIV-infected patients presenting with isolated cryptococcal pneumonia or with concurrent cryptococcal pneumonia and meningitis.[203] Some experts would treat isolated mild cryptococcal pneumonia with fluconazole alone (400 mg daily for 12 months) in combination with effective ART; however, patients with clinically significant cryptococcal pneumonia should be considered at high risk for early deterioration and treated similarly to those with disseminated disease during the induction phase of therapy using the lipid formulation of amphotericin B (3–4 mg/kg/day) in combination with flucytosine for at least 2 weeks.[27,204] Treatment should be continued until the patient is clinically improved, at which point the patient can be switched to fluconazole (400 mg daily) to complete at least an 8-week course of consolidation therapy. The patient should then be maintained on fluconazole (200 mg daily) to complete at least 12 months of maintenance azole therapy. IRIS may develop in patients with cryptococcosis who begin dual therapy for *C. neoformans* and HIV infection and has been associated with increased mortality. Therefore, a delay in

initiation of ART for at least the initial 2 weeks of induction therapy and potentially through the entire consolidation therapy phase is recommended.[27,205] Patients who had cryptococcal meningitis may present with aseptic meningitis and have elevated intracranial pressure. In addition, patients with cryptococcal pneumonia and nodules on chest radiograph may develop cavitation of their nodules or new intrathoracic adenopathy.[205]

Prevention. There are no specific recommendations regarding exposure avoidance, but screening for *C. neoformans* with serum CRAG testing among HIV-infected individuals with $CD4^+$ lymphocyte counts less than 100 cells/μL in high-burden countries and preemptive treatment with fluconazole significantly reduces mortality due to cryptococcal meningitis.[200,204,206] Some experts advocate screening of asymptomatic HIV-infected individuals in the United States with $CD4^+$ cell counts less than 100 cells/μL.[27] Primary prophylaxis is not recommended in the United States.[27]

Histoplasma capsulatum

Histoplasmosis is caused by the dimorphic, soil-dwelling fungus *H. capsulatum.* The fungus is found on all continents except Antarctica, but it is most common in North America and the Caribbean basin.[207] The heaviest concentration is found in the Mississippi, Ohio, and St. Lawrence River valleys. In these areas the fungus exists in environments related to the enrichment of the soil with bird or bat excrement, which helps promote sporulation. In the soil the fungus exists in a mycelial form producing asexual spores, the characteristic tuberculate macroconidia, and microconidia. Microconidia are easily aerosolized when disturbed and inhalation leads to primary pulmonary infection that is usually clinically silent.

Once deposited in the alveoli, *H. capsulatum* transforms into its yeast (or parasitic) form, and an area of pneumonitis develops. During this period before cell-mediated immunity develops, the organism spreads to regional lymph nodes and to reticuloendothelial organs. Two to 3 weeks after exposure, a flulike syndrome with fever, chills, myalgias, a nonproductive cough, and chest pain develops in about 40% of immunocompetent individuals. As covered in Chapter 56, 99% of these cases spontaneously resolve with the development of specific cell-mediated immunity. In contrast, progressive disseminated histoplasmosis develops in HIV-infected and other persons deficient in cell-mediated immunity. Although most cases of HIV-associated histoplasmosis appear to result from de novo exposure, the disease can reactivate. These cases account for the histoplasmosis seen in nonendemic areas, such as San Francisco or New York.[208]

Clinical Features. Although the portal of entry is the lung, in HIV-infected persons, histoplasmosis most often presents as a febrile wasting illness with disseminated infection. In a large series of 72 HIV-infected patients with disseminated histoplasmosis, 69 patients (96%) presented with fever and weight loss; in approximately 10% of cases, the presentation was dramatic with a sepsis-like syndrome associated with hypotension, respiratory failure, liver and renal failure, and coagulopathy.[209] Prognosis in these patients is poor. Respiratory complaints at presentation, chiefly cough and dyspnea, are found in patients who are likely to have abnormal chest radiographs.[209,210]

$CD4^+$ Lymphocyte Count. Most cases of disseminated histoplasmosis are seen in patients with $CD4^+$ lymphocyte counts less than 100 cells/μL and often less than 50 cells/μL. Isolated respiratory disease is more likely in patients with $CD4^+$ cell counts greater than 300 cells/μL.[27] Frequent laboratory findings include anemia, leukopenia, thrombocytopenia, and liver function test elevations. Serum LDH and serum ferritin elevations, often pronounced, have also been reported.[27,207]

Imaging. Disseminated histoplasmosis presents with a normal chest radiograph in 35–55% of cases.[192,209,211] The most frequent abnormalities are diffuse, coarse reticular or reticulonodular opacities as shown in Fig. 123.6. On occasion, alveolar opacities are present[192]; focal opacities are less common and seen in 7–11% of cases.[210] Hilar and mediastinal adenopathy and calcified granulomata are each found in less than 5% of patients.[209]

Diagnosis. The workup of histoplasmosis begins with the *Histoplasma* antigen test, which is a sensitive method for rapid diagnosis of disease.[27] The antigen test can be performed on urine, serum, cerebrospinal fluid, or BAL fluid. In AIDS patients with disseminated histoplasmosis, the antigen was detected in the urine of 100% and in the serum of 92% of patients.[212] In isolated, chronic pulmonary disease,



Figure 123.6 Disseminated fungal infection. Frontal chest radiographic close-up of the left midlung of an HIV-infected patient showing a medium to coarse reticulonodular pattern characteristic of disseminated fungal disease. (From Stansell JD: Fungal disease in HIV-infected persons: cryptococcosis, histoplasmosis, and coccidioidomycosis. *J Thorac Imaging.* 1991;6:28–35.)

serum or urine antigen testing is less sensitive.[27] In patients with pulmonary involvement, antigen testing of BAL fluid combined with cytopathology evaluation can complement serum or urine testing and increase the sensitivity for diagnosis of disease.[27,213] With successful therapy, antigen values fall and, during relapses, antigen values rise; thus changes in antigen values can be useful for assessing response to therapy and for evaluating possible relapse.[214] A persistently positive *Histoplasma* antigen test indicates continued disease and warrants continued therapy. False-positive *Histoplasma* antigen test results have been seen in patients with other disseminated fungal diseases (blastomycosis, coccidioidomycosis, paracoccidioidomycosis, and penicilliosis, and rarely with aspergillosis); such results have not been described in patients with cryptococcosis or candidiasis. *Histoplasma* can also be cultured from involved sites, although growth may require several weeks. Blood fungal cultures are specific and should be obtained as part of the diagnostic evaluation. Wheat and colleagues[209] reported that fungal blood cultures were positive in 65 of their 72 cases (90%). On occasion, the peripheral blood smear reveals intracellular yeast. Other potential diagnostic sources include bone marrow, lymph node, and skin. Serologic tests are generally less helpful in those with disseminated disease but may be useful in patients who are less severely immunocompromised with isolated pulmonary disease.[27]

Treatment. A lipid formulation of amphotericin B (3 mg/kg daily) is the treatment of choice for HIV-infected patients with moderate to severe disseminated histoplasmosis, whereas itraconazole is an alternative for patients with mild disease.[27] In those who cannot tolerate itraconazole, oral posaconazole or voriconazole may be effective; fluconazole is less effective than itraconazole, and echinocandins do not have activity against *Histoplasma*.[27] Treatment with amphotericin B should be continued for at least 2 weeks or until the patient is clinically improved, at which point the patient can be switched to itraconazole to complete at least a 12-month course. Patients with isolated pulmonary disease and $CD4^+$ cell counts greater than 300 cells/μL should be treated similarly as for non–HIV-infected patients (see Chapter 56).

Coccidioides immitis

Coccidioidomycosis is caused by the dimorphic, soil-dwelling fungi *C. immitis* and *C. posadasii.* As described in Chapter 56, the chief manifestation of coccidioidomycosis is as a mild flulike, often undiagnosed illness, from which most previously healthy people spontaneously recover. Chronic pulmonary disease manifests in roughly 5% of infected persons and disseminated disease in even fewer. Manifestations of coccidioidomycosis in HIV-infected persons include focal or diffuse pneumonia, cutaneous disease, meningitis, liver or lymph node involvement, or disseminated disease that can be fatal.

The fungus is endemic to the semiarid regions of North America, notably the southwestern United States (central California, southern Arizona, southern New Mexico, and western Texas) and also northern Mexico.[215] California's southern San Joaquin Valley and southern Arizona are hyperendemic areas.[215] *Coccidioides* is also found in South America, especially central Argentina. In soil the fungus exists in a mycelial form with characteristic arthrospores. When the soil is disrupted, arthrospores, whose size is optimal for deposition in the distal airways and alveoli after inhalation, become airborne. After deposition in the lungs, the arthrospores transform into spherules that may develop several hundred endospores. Rupture of the spherules allows widespread dissemination of the endospores, which then form additional spherules, replicating the cycle. Although most cases of HIV-associated coccidioidomycosis appear to result from de novo inhalation, disease may also reactivate.

Clinical Features. The clinical presentation is often nonspecific; fever and chills (68%), night sweats (36%), and weight loss (50%) are all common.[216] Although the portal of entry is the lung, coccidioidomycosis can present with disseminated disease and meningitis. Other frequently involved sites include the skin, lymph nodes, liver, and skeletal system. In one study, 42% of HIV-infected patients with coccidioidomycosis presented with disseminated disease; overall, 25% of the patients in this series died.[217] Focal pneumonia can present similarly to bacterial pneumonia, and diffuse pulmonary involvement can be difficult to distinguish from PCP.

$CD4^+$ Lymphocyte Count. The risk of symptomatic disease is highest if $CD4^+$ counts are less than 250 cells/μL.[27] Most cases of disseminated coccidioidomycosis are seen in patients with a $CD4^+$ lymphocyte count less than 100 cells/μL and often less than 50 cells/μL.[216,217] Focal pneumonia is more common when the $CD4^+$ cell count is greater than 250 cells/μL.[27] Cerebrospinal fluid examination is warranted in all patients with suspected disseminated coccidioidomycosis.

Imaging. In a series of 91 HIV-infected patients with coccidioidomycosis, diffuse reticulonodular opacities (see Fig. 56.5) were seen in 65%; focal opacities were less common in 14% of cases and consisted of focal opacities, single or multiple nodules, and cavities.[216] A miliary pattern may be seen (eFig. 123.25). Pleural effusion and hilar adenopathy as well as normal chest radiographs have all been reported.

Diagnosis. Serologic tests are useful in the evaluation of suspected coccidioidomycosis. Several studies have found an 80–90% sensitivity of complement fixation and tube precipitin tests.[218] Sensitivity of enzyme-linked immunoassays may be higher but may be less specific. False-negative titers usually arise in the most severely immunodeficient patients with diffuse pulmonary disease; in those with positive tests, the titer appeared to reflect the disease activity and proved useful for monitoring response to therapy.[219] A urinary and serum antigen test specific to *Coccidioides* has been developed and is useful for diagnosis of severe cases of coccidioidomycosis; however, other endemic fungi, including *Histoplasma* or *Blastomyces*, can cross-react.[220,221]

A definitive diagnosis can be established by isolation and identification of the fungus by culture or identification of pathognomonic giant spherules in cytologic or histologic preparations. In cases of suspected coccidioidomycosis, it is critical to alert the microbiology laboratory so that proper

precautions can be implemented to prevent laboratory transmission. Direct examination and culture of sputum, BAL fluid, or TBB can establish the diagnosis of pulmonary coccidioidomycosis in HIV-infected patients. Singh and associates[216] found that sputum culture in 13 of 19 cases (68%) and cytology in 8 of 11 cases (73%) had a high yield. BAL fluid culture diagnosed 29 of 42 cases (69%), and BAL fluid cytology diagnosed 32 of 48 cases (67%); in addition, TBB culture diagnosed 8 of 10 cases (80%), and biopsy histology diagnosed all 14 cases (100%).

Treatment. Either amphotericin B or a lipid formulation of amphotericin B is the treatment of choice for HIV-infected patients with severe (i.e., diffuse) pulmonary or disseminated coccidioidomycosis.[27] Treatment with amphotericin B should be continued until the patient is clinically improved, at which point the patient can be switched to fluconazole or itraconazole. Monitoring complement-fixing antibody titers every 12 weeks can be useful to assess response to therapy.[27] In patients with clinically mild infection, such as focal pneumonia, fluconazole or itraconazole may be used throughout.[27] Although clinical experience is limited, voriconazole or posaconazole may be considered in refractory coccidioidomycosis.[222] In patients with severe, diffuse disease, lifelong suppressive therapy with fluconazole or itraconazole should be continued after initial treatment is complete, particularly in those with meningeal involvement because the risk of relapse is high.[27] In patients who have had focal coccidioidal pneumonia and who have had a sustained response to ART with $CD4^+$ lymphocyte counts greater than 250 cells/μL, therapy may be discontinued after 12 months, but periodic surveillance with chest radiograph and *Coccidioides* serology is recommended.[27]

Aspergillus Species

Aspergillus species are found worldwide, and exposure is universal. Nevertheless, disease is infrequent unless phagocyte number or function is reduced.[223] *A. fumigatus* is the most common disease-causing species and accounts for approximately 90% of cases of invasive aspergillosis. Although invasive aspergillosis is a well-documented complication of various immunodeficiency disorders, particularly in patients with hematologic malignancy or organ transplantation, it is an uncommon problem in patients with HIV disease. Risk factors for the development of aspergillosis other than HIV-induced immunodeficiency included use of corticosteroids, neutropenia, marijuana use, and broad-spectrum antimicrobial drugs.[224] In the ART era and also with the introduction of voriconazole, the incidence of invasive aspergillosis has further declined.[225] Holding and coworkers[226] reported an aspergillosis incidence of 3.5 cases per 1000 person-years among HIV-infected individuals enrolled in the CDC-led Adult and Adolescent Spectrum of HIV Disease Study.

Clinical Features. The entire spectrum of *Aspergillus*-related lung disease (see Chapter 57) has been observed in HIV-infected persons, from colonization of the respiratory tract or a preexisting cavity, to tracheobronchitis or obstructing bronchial aspergillosis, to invasive aspergillosis, by far the most severe manifestation.[224,227–229] Most patients with invasive aspergillosis have a $CD4^+$ lymphocyte count less than 100 cells/μL. Risk factors for the disease are decreased phagocyte number and function, as determined by neutropenia and/or monocytopenia and use of corticosteroids or broad-spectrum antibiotics. However, in a study from France, fewer than half of the cases of invasive aspergillosis in HIV-infected patients met criteria for risk factors established for the European Organisation for Research and Treatment of Cancer/National Institute of Allergy and Infectious Diseases Mycoses Study Group.[225] Patients with aspergillosis typically present with fever, cough, dyspnea, and occasionally with pleuritic chest pain. Hemoptysis is another presenting feature. The imaging findings are variable and include unilateral or bilateral opacities, cavitary lesions (eFigs. 123.26 and 123.27), nodular (eFig. 123.27) and pleural-based opacities, and pleural effusions.[230]

Diagnosis. The definitive diagnosis of aspergillosis requires demonstration of tissue invasion and isolation of the organism by culture. Neither sputum nor BAL is sufficient. Microscopy alone cannot distinguish *Aspergillus* species from *Fusarium* or *Pseudallescheria* species. The results of TBB are usually negative, but specimens from sputum, BAL fluid, or percutaneous aspirates are often positive on culture. The absence of histologic proof of tissue invasion is always somewhat disquieting, especially in attempting to distinguish invasive disease from possible colonization of damaged airways. Repeated isolation of the fungus in large numbers with a compatible clinical setting makes the diagnosis more tenable.

Galactomannan antigen testing on serum or BAL specimens is useful in the diagnosis of invasive pulmonary aspergillosis in other immunocompromised patients (see also Chapters 19 and 57),[231] although its performance has not been prospectively evaluated in HIV-infected patients with suspected aspergillosis. Several other fungi, including *Histoplasma* and *Blastomyces,* can cross-react.[232]

Treatment. Compared with the fungi previously discussed, there is less experience treating aspergillosis in HIV-infected patients.[223] Voriconazole is the first-line recommended therapy.[27] Alternative agents include amphotericin, caspofungin, and posaconazole. Interactions with ART drugs must be considered because the antifungal azoles inhibit specific cytochrome P-450 enzymes. Even with the prompt institution of therapy, the prognosis is poor, largely because aspergillosis is nearly always a late complication of advanced HIV disease. However, survival has improved to 70% in the ART era with use of voriconazole therapy.

Blastomyces dermatitidis

Blastomycosis is caused by the endemic, dimorphic fungus *Blastomyces dermatitidis.* Blastomycosis is coendemic with histoplasmosis throughout much of the central United States (see Chapter 56), but it is less common than histoplasmosis, and reports of HIV-associated blastomycosis are infrequent.[233,234]

Clinical Features. The largest case series reported 15 cases of HIV-associated blastomycosis; all but one patient had a $CD4^+$ lymphocyte count less than 200 cells/μL.[233] That series noted two distinct patterns of disease: One group of patients had disease clinically limited to the respiratory

system, whereas the other group had disseminated blastomycosis involving multiple organ systems, including the lungs. Eleven of 15 patients (73%) had abnormal chest radiographs, with diffuse interstitial or miliary disease (55%) as the most common radiographic finding. Definitive diagnosis requires the growth of *B. dermatitidis,* although visualization of the characteristic budding yeast form is strongly suggestive and therefore warrants antifungal therapy while awaiting the results of culture.

Treatment. Intravenous amphotericin B is the treatment of choice for HIV-infected patients with severe disease.[233,234] Treatment with amphotericin B should be continued until there is clinical improvement; patients can then be switched to oral itraconazole maintenance therapy for at least 12 months, with itraconazole continued indefinitely for AIDS patients without immune reconstitution.[235] With prompt institution of therapy, most patients with disease limited to the lungs respond well; in contrast, patients with disseminated disease do poorly (40% mortality in 30 days).[233]

Talaromyces marneffei

Talaromycosis is a disease caused by *T. marneffei,* a dimorphic, soil-dwelling fungus formerly known as *Penicillium marneffei.* It is endemic in southeastern Asian countries, and in northern Thailand, it is the third most common opportunistic infection (after TB and cryptococcosis) in HIV-infected patients with AIDS, accounting for 15–20% of all AIDS-related illnesses.[236,237] Infection can also be encountered in other regions of the world in travelers or immigrants from endemic regions. Disease is related to soil exposure, especially during the rainy season (May–October), and infection is likely acquired via inhalation. Although less frequent, reactivation of latent infection has been observed.

Clinical Features. Most cases of talaromycosis are seen in patients with a $CD4^+$ lymphocyte count less than 100 cells/μL. The clinical presentation is similar to that of TB, cryptococcosis, or histoplasmosis. The most common symptoms include fever, weight loss, cough, and generalized papular skin lesions, usually with central umbilication.[238] Symptoms are often present for weeks. In addition to the cutaneous findings, physical examination often reveals peripheral lymphadenopathy and hepatomegaly. Respiratory symptoms include cough and shortness of breath. Skin lesions of papules with central necrosis can involve the face, trunk, and extremities and are a late manifestation of infection. Anemia is a prominent laboratory finding.

Diagnosis. *T. marneffei* is most commonly a disseminated disease in HIV-infected patients, and the diagnosis is usually made by isolation of the organism from blood or bone marrow aspirate cultures. Other involved sites include the skin, lymph nodes, and lungs. Microscopy of tissue samples can detect yeast-laden macrophages. Of note, galactomannan assays typically used for *Aspergillus* can cross-react and yield a positive result with *Talaromycosis.*

Treatment. Amphotericin B, followed by itraconazole, is the standard treatment for *P. marneffei.*[27] Mild forms of disease can be treated initially with itraconazole. The duration of amphotericin B treatment is 2 weeks, followed by an additional 10 weeks of itraconazole. Voriconazole and posaconazole are alternative treatments.[27]

VIRUSES

Many viruses are known to cause pulmonary disease in immunocompromised persons. Of viral infections, CMV is regarded as a potentially important agent of pulmonary disease in HIV-infected persons.

Cytomegalovirus

CMV, a double-stranded DNA virus in the Herpesviridae family, is described in Chapter 46. The risk of exposure to CMV increases with age, and evidence of CMV infection is extremely common in healthy persons. In HIV-infected patients, CMV disease is believed to result chiefly from reactivation of latent infection; however, disease has been documented from de novo infection in recipients of solid organs, bone marrow, and blood, which raises the possibility that new infection or superinfection from exogenous sources may also arise in HIV-infected persons. Although clearly the source of significant pathologic conditions in the retina, gastrointestinal tract, and nervous system, the role of CMV in producing pulmonary disease in HIV-infected persons is debated. Many consider this ubiquitous virus a "passenger" rather than a pathogen in most instances. However, there are also clear instances in which documented pulmonary disease results from CMV.

Clinical Features. Retinitis and gastrointestinal disease are the two most common forms of HIV-associated CMV disease. CMV is a frequent isolate from the BAL fluid of patients with advanced immunosuppression who undergo evaluation for opportunistic infections, notably *Pneumocystis.* Because CMV is shed in respiratory secretions, its mere presence in BAL fluid cannot be construed as diagnostic of CMV pulmonary disease. When dual pulmonary infection is discovered, treatment directed against the coexisting disease and not against CMV usually results in clinical resolution[239]; however, sometimes CMV causes pulmonary disease, and the challenge for clinicians is to recognize these instances.[240,241]

The most common symptoms of CMV pneumonia are cough, dyspnea, and fever. In a case series,[241] these symptoms were seen in 94%, 94%, and 89%, respectively, of the 18 patients reported. Respiratory symptoms were present for up to 2 weeks in 50% and between 2 and 4 weeks in an additional 44%. Most cases of CMV disease are seen in patients with a $CD4^+$ lymphocyte count less than 50 cells/μL.[241]

Imaging. The imaging findings of CMV pneumonia vary and include reticular or ground-glass, alveolar, and nodular opacities (eFig. 123.28).[241] Pleural effusions may be seen as well.

Diagnosis. When CMV pulmonary disease is suspected in conjunction with other end-organ disease (e.g., retinitis), CMV therapy must be initiated immediately. CMV is usually a disseminated disease and commonly involves multiple organ systems. Treatment of CMV disease in one end-organ treats all affected organs, although the length of therapy

can differ by organ system. The therapeutic dilemma is much greater when only the lungs appear to be afflicted. The only precise criterion for diagnosis of CMV pulmonary disease is the demonstration of widespread specific cytopathic changes in the lungs on biopsy. Culture of BAL fluid[242] or PCR detection of CMV are not sufficient by themselves to make the diagnosis of CMV pneumonitis. Patients suspected of having CMV pneumonitis should undergo retinal examination by an ophthalmologist, even if there are no ocular complaints.

Treatment. Data for treatment of CMV pneumonia in HIV-infected patients are limited. Intravenous ganciclovir or foscarnet is recommended for severe pneumonitis.[27] Although oral valganciclovir has been suggested for less severe pneumonitis, there are no data regarding its use in this setting.[27] With these drugs, an initial course of induction therapy should be continued until there is clinical improvement; the length of induction therapy for CMV pneumonia, however, is undetermined. A 21-day course for isolated CMV pneumonitis has been recommended. After resolution of acute disease and initiation of effective ART, chronic maintenance is not regularly recommended.

Other Herpesviruses

Symptomatic pulmonary viral infection from herpesviruses other than CMV is uncommon in HIV-infected persons. Herpes simplex virus, although frequently cultured from BAL fluid, is usually a contaminant from upper airway carriage. Lower respiratory tract involvement is rare in HIV-infected persons (0.2–4% of autopsy cases) compared to other immunosuppressed hosts. Herpes simplex virus pulmonary disease causes a focal pneumonia or a diffuse interstitial pneumonitis.[243] The focal pneumonias appear to result from contiguous spread of herpes simplex virus to the lung parenchyma and are often associated with necrotizing tracheobronchitis, whereas the diffuse interstitial pneumonias appear to be a manifestation of hematogenous herpes simplex virus dissemination. Varicella-zoster virus is a rare cause of pneumonia in HIV-infected adult patients.[244] Epstein-Barr virus DNA has been identified in lung biopsy specimens of infants and children with lymphocytic interstitial pneumonitis, but the precise role of the virus in this disease is uncertain.[245]

Influenza

Influenza-related mortality has been reported to be increased in adults with AIDS compared to the general population in studies using data from the United States and from sub-Saharan Africa.[246,247] Influenza generally presents similarly and has a comparable clinical course in HIV-infected as in non–HIV-infected adults. Prompt initiation of antiviral therapy directed against influenza in HIV-infected patients with suspected or confirmed disease is recommended. All HIV-infected persons should receive the inactivated or recombinant influenza vaccine annually.[27]

Coronavirus Disease 2019

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) is the etiologic agent that causes *coronavirus disease 2019* (COVID-19). Emerging from Wuhan, China, in late 2019, COVID-19 has become a global pandemic. HIV-infected persons are at risk of infection similar to HIV-uninfected persons. Emerging data thus far do not show a differential risk of infection with SARS-CoV-2 or severity of disease among PLWH.[248] Because HIV antiviral therapies are being investigated as possible treatments for COVID-19, further studies on the impact of HIV treatment regimens and possible benefits of modifying ART in PLWH to mitigate risk of infection are warranted. Exposure to different classes of ART regimens may be associated with differential risk and severity of COVID-19.[249]

PARASITES

Of the classic unicellular and multicellular parasites that afflict otherwise healthy humans (see Chapter 58), several also cause pulmonary disease in HIV-infected hosts. Of these, *T. gondii* is the most frequent.

Toxoplasma gondii

Toxoplasmosis is a zoonosis caused by the intracellular protozoan *T. gondii,* with domestic cats as its definitive host, but with an infectious reservoir that encompasses all animals. Infection is transmitted to humans when raw or undercooked meat containing *T. gondii* is eaten. Domestic cat feces in litter boxes are an additional source of potential *T. gondii* infection. Infection can be transmitted vertically from mother to fetus. In HIV-infected patients, the majority of cases of toxoplasmosis result from reactivation of chronic, latent infection. Thus, the keys to preventing toxoplasmosis are prevention of exposure for those not yet infected and prophylaxis for those already seropositive. The seroprevalence of *Toxoplasma* varies. In the United States the seroprevalence is 10–50%, whereas in Western Europe the seroprevalence may be as high as 90%.

Clinical Features. Central nervous system complications of *T. gondii* are well recognized in HIV disease and include encephalitis and focal brain abscess. Pulmonary involvement is uncommon but is seen in patients with central nervous system or disseminated disease, can present as isolated pneumonia, and can rarely be associated with acute respiratory distress syndrome.[250–252] Toxoplasmosis presents at the lower range of $CD4^+$ lymphocyte counts, typically less than 50 cells/μL.[251]

Imaging. The chest radiograph usually reveals bilateral opacities, either in a fine reticulonodular pattern indistinguishable from PCP or in a coarse nodular pattern similar to that seen with TB or fungal pneumonias.[253] Pleural effusions can be seen, and a variety of other radiographic findings have also been described.[254]

Diagnosis. The diagnosis of pulmonary toxoplasmosis is usually established by bronchoscopy and study of BAL fluid.[254] *T. gondii* can be detected via Giemsa staining, PCR amplification, and culture.

Treatment. The treatment for pulmonary toxoplasmosis is identical to that for central nervous system toxoplasmosis. First-line treatment is sulfadiazine plus pyrimethamine with leucovorin to lessen the likelihood of hematologic toxicities associated with pyrimethamine.[27] The preferred

alternative regimen is clindamycin plus pyrimethamine with leucovorin.[27]

Other Parasites

In general, pulmonary helminth infections are uncommon in HIV-infected persons.[255,256] Both pulmonary cryptosporidiosis and pulmonary microsporidiosis in HIV-infected patients with concurrent intestinal disease have been reported and may result from aspiration or hematogenous spread.[257] The most common respiratory symptoms are cough, dyspnea, and pleuritic chest pain.[257] The diagnosis of *Strongyloides stercoralis* pulmonary disease (eFig. 123.29) can be made by either sputum study or bronchoscopy.[258,259] *Strongyloides* hyperinfection syndrome has also been reported in HIV-infected patients[260] but is uncommon, even in countries where the parasite is endemic.[261]

NONINFECTIOUS DISORDERS

As more people with HIV/AIDS are living longer on effective ART, noninfectious complications and comorbid illnesses have increased in frequency.[262] HIV-infected patients appear to have an increased risk for a number of noninfectious pulmonary diseases, including COPD, lung cancer, and PAH.[263] Increasing age and a high prevalence of cigarette smoking combined with an independent risk from HIV infection itself may all contribute, particularly to the increases in COPD and lung cancer.[264,265]

MALIGNANCIES

HIV-associated malignancies, particularly KS and NHL, may involve the thorax, including the lung parenchyma, airways, pleura, or hilar or mediastinal lymph nodes. Intrathoracic disease from either neoplasm is usually a manifestation of disease already recognized elsewhere, but occasionally both KS and NHL may present with isolated pulmonary disease.[266]

Kaposi Sarcoma

The most common AIDS-defining, HIV-associated malignancy is KS, although its incidence has decreased dramatically with ART.[267–269] KS is an angioproliferative tumor associated with *human herpesvirus 8* (HHV8; also termed the KS-associated herpesvirus).[270–272] KS most commonly presents with mucocutaneous involvement. The lymph nodes, gastrointestinal tract, and lungs can also be involved. Approximately 90–95% of cases of KS in HIV-infected individuals in the United States are seen in MSM.[273]

Clinical Features. Pulmonary KS is detected clinically in approximately one-third of patients with known KS, with the proportion detected at autopsy approaching 50–75%. Most but not all patients with pulmonary KS have concomitant mucocutaneous disease. Huang and coworkers[274] found that 85% of 168 consecutive patients diagnosed with pulmonary KS by bronchoscopy had evidence of mucocutaneous involvement at the time of bronchoscopy. The 15% without mucocutaneous involvement had pulmonary disease that ranged from isolated tracheal lesions to diffuse endobronchial involvement. A significant proportion (about one-third) of patients with pulmonary KS also have a concurrent opportunistic infection.[274] These observations underscore the need to evaluate each patient with KS who presents with respiratory symptoms, not only for pulmonary KS but also for opportunistic infection. Patients with pulmonary KS who develop opportunistic infection may also experience a rapid progression of their KS that mimics an infectious process.

Pulmonary KS presents at the lower range of $CD4^+$ lymphocyte counts, typically less than 100 cells/μL.[274] Additional immunologic risk factors for KS in the ART era include CD4/CD8 ratio of 0.5 or less or a $CD8^+$ T cell count greater than 1000/μL, regardless of the $CD4^+$ T cell count.[275]

Imaging. Pulmonary KS characteristically presents with bilateral opacities in a central or perihilar distribution, as shown in Figure 123.7 and eFigure 123.30A. Typical chest radiograph findings include peribronchial cuffing and "tram track" opacities (in about 90%); linear opacities, nodules or nodular opacities of varying size (80%); and pleural effusions (50%).[276] Chest CT findings in patients with pulmonary KS (see eFig. 123.30B–D) include flame-shaped areas of peribronchovascular ground-glass opacity and nodularity, often with interlobular septal thickening and pleural effusion, and less commonly, lymphadenopathy. Atypical imaging manifestations of KS are occasionally encountered (eFig. 123.31). Although radiographic findings strongly suggest the diagnosis of pulmonary KS in HIV-infected MSM, no findings are diagnostic for KS. Therefore, patients with suspected pulmonary KS should have their diagnosis confirmed.

Diagnosis. The diagnosis of pulmonary KS is usually established by bronchoscopy. The observation of characteristic endobronchial, red or violaceous, flat or slightly raised lesions is sufficient to diagnose pulmonary involvement

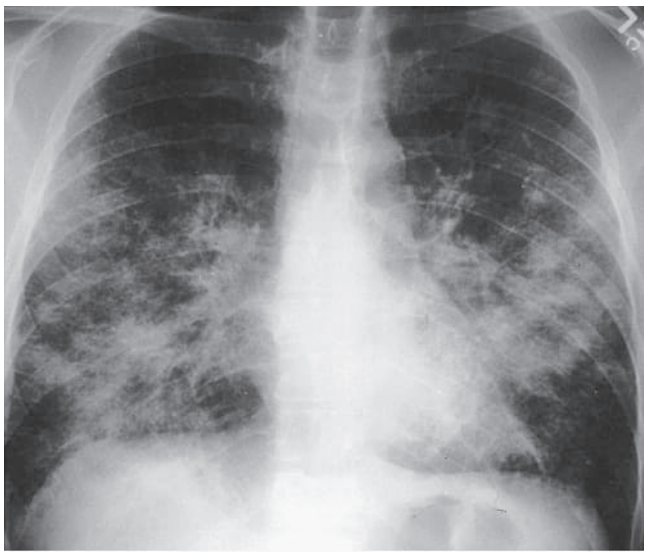

Figure 123.7 Kaposi sarcoma. Frontal chest radiograph of an HIV-infected patient with pulmonary Kaposi sarcoma diagnosed by bronchoscopy showing the characteristic bilateral, perihilar distribution of abnormalities consisting of nodules and nodular opacities. (Courtesy L. Huang.)

(Fig. 123.8). The presence of these mucosal lesions does not preclude a concurrent infection, nor does their absence in the observable airway preclude more distal disease or parenchymal, pleural, or nodal involvement. TBB is typically not required, although it can establish a diagnosis in patients in whom there is a strong clinical and radiographic suspicion for pulmonary KS but who have no visible endobronchial lesions. HHV8 may be detected in BAL. Pleural effusions, if present, are exudative. Cytologic evaluation of pleural fluid and thoracoscopic biopsy of the pleura in patients with KS are not typically useful for diagnosis.[277]

KS is negative on gallium scans. In contrast, opportunistic infections and NHL are gallium avid. Among HIV-associated pulmonary diseases, this unique feature of KS has created a clinical niche for the use of gallium scans. Patients with cutaneous KS who develop new respiratory complaints should undergo a thorough evaluation to rule out a concomitant opportunistic infection or other process.

Treatment. Tumors can regress in size and number in response to ART, and therefore combination ART is recommended for all patients with KS.[278] Treatment of more advanced disease also includes intralesional or systemic chemotherapy. Mortality in patients with KS may be related to an increased rate of other malignancies, particularly lymphomas.[279] Of malignancies, KS is the most likely to be associated with IRIS in patients who initiate ART.



Figure 123.8 Kaposi sarcoma. Characteristic Kaposi sarcoma lesions in the trachea of an HIV-seropositive patient seen via bronchoscopy. (Courtesy L. Huang.)

Non-Hodgkin Lymphoma

Almost all HIV-associated NHLs are of B cell origin. Most are classified as small, noncleaved Burkitt, diffuse large cell with centroblastic features, or diffuse large cell with immunoblastic features.[280] The majority are associated with Epstein-Barr virus infection. Many HIV-infected patients have an advanced stage of disease at the time of presentation. As with KS, the incidence of NHL has declined dramatically in the era of ART and is projected to continue to decrease through 2030.[269,281]

Clinical Features. Most HIV-infected patients with NHL present with disseminated disease and extranodal involvement.[282] Frequent extranodal sites include the liver, spleen, bone marrow, meninges, gastrointestinal tract, and pericardium. Intrathoracic involvement is seen in a smaller proportion. The reported incidence of intrathoracic disease ranges up to 31% of patients at the time of clinical diagnosis and is usually higher at the time of autopsy. On occasion, the lung is the only site involved.

NHL can present at a wide range of $CD4^+$ lymphocyte counts, although typically patients are more severely immunocompromised. Prolonged HIV viremia and recent immunosuppression are risk factors for NHL, with risk increasing as the $CD4^+$ count declines to less than 500 cells/μL and particularly when less than 50 to 100 cells/μL.[283]

Imaging. The most common chest radiograph findings include single (Fig. 123.9; eFig. 123.32) or multiple parenchymal nodules (eFig. 123.33), nodular opacities or masses (eFig. 123.34), lobar opacities, and diffuse interstitial opacities (eFig. 123.35).[284] More rarely, cases of endobronchial lesions have been reported.[285] Pleural effusions are the most common radiographic abnormality, seen in 40–70% of cases, and are often bilateral.[284] Bilateral hilar and mediastinal adenopathy can be found in up to 60% of patients. Isolated intrathoracic adenopathy without identifiable extrathoracic nodal involvement is a rare presentation for HIV-associated NHL.

Diagnosis. The diagnosis of NHL requires demonstration of malignant lymphocytes on cytology or biopsy specimens.

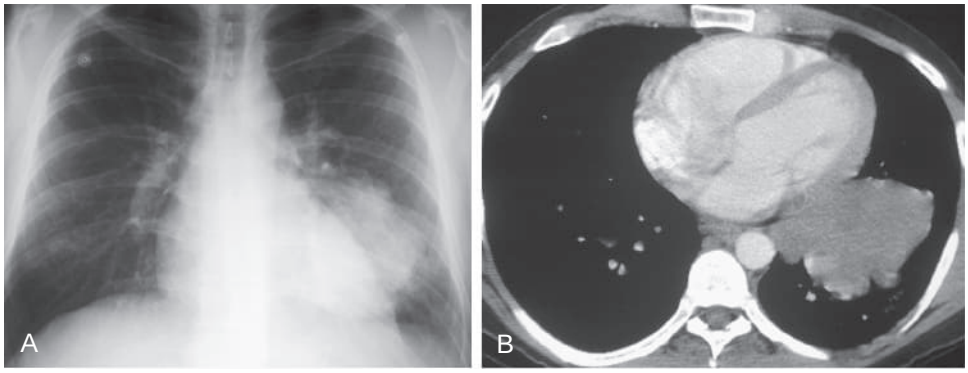

Figure 123.9 Non-Hodgkin lymphoma. (A) Frontal chest radiograph from a patient with AIDS with non-Hodgkin lymphoma showing a large left lower lobe mass. (B) Axial computed tomography shows a mass in the left lower lobe without an air bronchogram, suggestive of a neoplasm. (Courtesy Michael B. Gotway, MD.)

Most often the diagnosis is made by needle aspiration or biopsy of an extrathoracic site. Persons who present with isolated intrathoracic involvement should undergo bronchoscopy with biopsies (e.g., transbronchial and/or endobronchial ultrasound guided), if abnormal lesions and nodes are within reach through the bronchoscope,[284] whereas fluoroscopic or CT-guided fine-needle aspiration should be considered for more distal lesions. Other options include mediastinoscopy and open-lung biopsy. For patients with pleural effusions, pleural fluid cytology, biopsy, or both are often diagnostic.[284] Pleural fluid is exudative, lymphocytic predominant, and often has very high levels of LDH.[284] The yield of pleural cytology is significantly higher in HIV-associated pulmonary lymphoma than in non–HIV-infected cases.[286]

Treatment. Pulmonary involvement in NHL is treated as part of systemic disease. Median survival from AIDS-related NHL has greatly improved as a result of combining ART with chemotherapy.[287] Chemotherapy is frequently complicated by the development of opportunistic infections, particularly PCP, and by the presence of decreased bone marrow reserve. Therefore, *Pneumocystis* prophylaxis should be considered in all cases, particularly in patients treated with steroids, who are lymphopenic, and/or in whom the $CD4^+$ lymphocyte count remains less than 200 cells/μL.

Primary Effusion Lymphoma

Classic primary effusion lymphoma is a distinct subtype of NHL that presents with isolated effusions in body cavities, including the pleura (eFig. 123.36), pericardium, and peritoneum in the absence of a discrete nodal or extranodal mass.[288] A rare disease, these tumors are found nearly exclusively in HIV-infected MSM. HIV infection is usually advanced, with $CD4^+$ lymphocyte counts less than 200 cells/μL.[288] HIV-infected patients with primary pleural effusion lymphoma typically present with symptoms related to the space-occupying nature of the effusion (i.e., dyspnea). Diagnosis is established by pleural fluid histology and identification of HHV8, which can be found in all cases.[289] Primary effusion lymphomas usually lack classic B cell and T cell markers.[278] Treatment options include ART and systemic chemotherapy. Antiviral therapy, immunomodulatory agents, or proteasome inhibitors have also been tried. Prognosis is poor, with median survival of approximately 6 months.

Multicentric Castleman Disease

Multicentric Castleman disease (MCD) is a rare lymphoproliferative disorder of the plasma cell type.[290] It is characterized histologically as angiofollicular lymph node hyperplasia.[277] MCD may be associated with KS in HIV-infected and in non–HIV-infected patients. Most HIV-infected patients with MCD are also infected with HHV8. MCD can be seen in patients with controlled or uncontrolled HIV. Common presenting symptoms and signs of systemic MCD can mimic lymphoma and include fever, weakness, generalized lymphadenopathy (eFig. 123.37), anemia, hypergammaglobulinemia, and hemophagocytic syndrome in life-threatening forms of MCD.[277] Presenting symptoms and signs include cough, dyspnea, and crackles on lung examination. Chest radiographic findings include reticular and/or nodular interstitial patterns, with mediastinal lymphadenopathy and, less commonly, bilateral pleural effusions.[277,291] Bronchovascular nodularity, consolidation, and mediastinal lymphadenopathy have been described on chest CT.[292]

The diagnosis of MCD is typically based on pathologic evaluation of an involved lymph node or extranodal mass that confirms MCD and excludes other diseases such as TB or lymphoma. Involved cells are B cells with plasma-cell differentiation. HHV8-infected cells can be detected by immunohistochemistry, and HHV8 may be detected by PCR in BAL fluid. Prognosis is generally poor, and disease can recur. Treatment options are based on expert opinion and include initiation of ART, if the patient is not already on it, rituximab, and potentially systemic chemotherapy depending on the extent of involvement. Antiviral therapy may be considered, although efficacy data are limited. Cases of IRIS, some of them fatal, have been reported in patients with MCD initiated on ART.

Non–Small Cell Lung Cancer

The incidence of non–small cell lung cancer, but not small cell lung cancer, is greater among HIV-infected persons than among non–HIV-infected persons.[266] Whether this increased incidence is due to HIV infection or to other potential confounders, such as increased smoking among HIV-infected populations, has been controversial. However, several cohort studies have demonstrated an increased risk associated with HIV that remains significant even after adjusting for smoking.[293–295] Whereas AIDS-defining cancers such as KS and NHL have decreased, non–AIDS-defining cancers in HIV-infected patients have increased, primarily among HIV-infected persons age 50 years and older and are projected to remain elevated.[269,281,296] In HIV-infected persons, lung cancer is now the most common infection-unrelated, non–AIDS-defining cancer and is a leading cause of mortality.[269,296–301]

Clinical Features. HIV-infected patients develop lung cancer at slightly younger ages than do non–HIV-infected patients, after controlling for demographic differences (50 vs. 54 years in one study).[302] Most HIV-infected patients in whom lung cancer develops are cigarette smokers. The characteristic presentation and radiographic finding of bronchogenic carcinoma are similar in HIV-infected and non–HIV-infected patients (eFig. 123.38). Although all pathologic types are seen, adenocarcinoma has been the most frequent pathologic type reported, similar to that seen in non–HIV-infected patients; squamous cell carcinoma is the second most frequently observed pathologic type.[294,295] Stage of lung cancer at presentation is similar by HIV status, with nearly 70% of all patients diagnosed at stage III/IV in the absence of screening.[295,303]

Although lung cancer can develop at any $CD4^+$ lymphocyte count, immunodeficiency is postulated as a mechanism for the enhanced risk for lung cancer associated with HIV.[298,304,305] A low $CD4^+$ cell count is associated with a greater risk for lung cancer in some studies but is not a consistent marker of risk in all studies. Immune dysregulation, reflected by a lower CD4/CD8 ratio over time preceding cancer diagnosis, has also been associated with an increased risk for lung cancer.[306] There is no clear relationship between HIV viral load and use of ART with lung cancer risk.[293]

Prior lung disease and pulmonary infections, particularly bacterial pneumonia and TB, increase the risk for

subsequent lung cancer.[307] In some studies, previous pneumonia explains the excess risk of lung cancer observed in those with HIV, particularly in those with well-controlled HIV disease.[308] Whether pneumonia reflects immune deficiency in the lung that also predisposes to lung cancer, or whether pneumonia triggers mechanisms that spur carcinogenesis or decrease immune surveillance is unclear.

Diagnosis and Treatment. Diagnosis and treatment of lung cancer in an HIV-infected patient is similar to that in a non–HIV-infected individual. Ongoing areas of controversy include the role of newer immune therapies and checkpoint inhibitors in HIV-infected patients, although initial data suggest potential benefits and acceptable side-effect profiles.[309] Median survival in HIV-infected patients with lung cancer is similar to age-matched non–HIV-infected lung cancer patients.[303]

Lung cancer screening with annual low-dose CT appears to have a similar beneficial effect on mortality in HIV-infected smokers who have well-controlled HIV as in older, non–HIV-infected heavy smokers in the National Lung Cancer Screening Trial.[310–312] Adapting the Cancer Intervention and Surveillance Modeling Network lung cancer policy screening model to HIV-infected persons demonstrated similar benefits and harms when screening individuals meeting the same criteria as people without HIV, namely, current or formers smokers age 55 to 74 years with 30 pack-years of smoking and who quit within the past 15 years, if they are adherent to ART and have well-controlled HIV disease. Smoking cessation should also be prioritized to decrease the risk of lung cancer in people living with HIV.

PULMONARY ARTERIAL HYPERTENSION

Studies have reported an increased frequency of PAH in the HIV-infected population, with a prevalence of approximately 0.5%,[313] and HIV-associated PAH is classified in the WHO Group 1 PAH category, rather than pulmonary hypertension due to cardiopulmonary conditions such as left heart disease (Group 2) or chronic lung disease (Group 3) (see Chapter 84). A systematic review and meta-analysis reported a prevalence in HIV-infected adults of 0.5% based on right heart catheterization and a higher prevalence of 8.5% based on cardiac echocardiography. The pathology of HIV-associated PAH is indistinguishable from that of idiopathic PAH, and therefore similar pathogenetic mechanisms may be involved. In addition, HIV viral proteins,[315] chronic inflammation due to underlying HIV, and use of illicit drugs (e.g., cocaine, methamphetamine)[316] in HIV-infected persons likely contribute. Animal studies indicate that HIV-associated PAH is associated with skewing of monocytes and alveolar macrophages toward a proinflammatory, profibrotic phenotype and a diminished capacity to down-regulate chronic inflammation.[317] In these same animal models, the use of statins has reduced inflammation and prevented the development of PAH.[318]

HIV-infected persons may also have pulmonary hypertension due to other causes (e.g., underlying cardiac or pulmonary disease) that are also increased in prevalence in HIV populations, and thus this diagnosis must be considered when evaluating persons with HIV and cardiopulmonary complaints.[319]

Clinical Features. In a review of 131 cases of PAH in HIV-infected patients,[320] the presenting symptoms and radiographic, pulmonary function, electrocardiographic, echocardiographic, and pathologic findings were similar to those in non–HIV-related idiopathic PAH (see Chapter 84).

Diagnosis. As with idiopathic PAH, the diagnosis of HIV-associated PAH requires confirmation of elevated pulmonary arterial pressures and the exclusion of secondary causes. Higher levels of endothelin-1 are associated with HIV-associated PAH assessed by both cardiac echocardiogram and right heart catheterization.[321]

Treatment. The optimal treatment of HIV-associated PAH is unclear.[322] In general, patients should receive antiretroviral therapy because this will reduce HIV RNA levels and HIV-related immune activation and inflammation. Cessation of illicit drug use is also paramount. Similar to patients with idiopathic PAH, patients with HIV-associated PAH and WHO functional class II, III, or IV should be referred to a specialist for PAH-specific therapy. In general, the choice of therapy is similar to that in persons without HIV.[323] In persons with HIV who are on an ART regimen that contains a pharmacologic boosting agent (i.e., ritonavir or cobicistat), certain endothelin receptor antagonists and phosphodiesterase inhibitors may require dose adjustments.

OBSTRUCTIVE LUNG DISEASE

A variety of PFT abnormalities are seen in people living with HIV infection. Spirometry is frequently abnormal, and *diffusing capacity for carbon monoxide* (D_{LCO}) is reduced.[324–329] Although pulmonary function abnormalities are more common in smokers, impairment in D_{LCO} has been reported in HIV-infected individuals without a history of smoking,[330] and HIV has been found to be an independent risk factor for decreased D_{LCO}.[331,332] Spirometry results are variable, with some studies reporting similar findings in populations with and without HIV infection,[331] an increased risk of airflow obstruction in those with HIV,[334] or a concurrently decreased *forced expiratory volume in 1 second* (FEV_1) and *forced vital capacity* (FVC) in those with HIV.[335,336] Nonetheless, the prevalence of abnormal spirometry is high in persons with HIV infection, with 37% of patients in the national Lung HIV Study having abnormal spirometry (27% obstructed and 10% restricted pattern).[337]

Risk factors for decline in lung function over time include uncontrolled HIV disease, pulmonary infections, and current smoking.[324,340] Although earlier data were conflicting based on observational studies suggesting increased airway obstruction in HIV-infected individuals receiving ART,[330,342] a randomized controlled trial of timing of ART initiation found no association between ART and lung function decline.[341] Impairment in FEV_1 and D_{LCO} in HIV-infected individuals is associated with decreased health status, an increased burden of respiratory symptoms, and higher mortality.[343,344]

COPD

COPD is common in HIV-infected populations, diagnosed in approximately 15–20%. HIV appears to increase risk for

COPD, independent of smoking and pulmonary infections related to HIV.[334,345–348] Although not all studies have found a significant difference in the prevalence of COPD among those with and without HIV,[335,336] a systematic review and meta-analysis of 30 studies found that the prevalence of COPD was significantly higher in PLWH than in non-HIV control subjects, even after adjusting for cigarette smoking.[349]

Emphysema is a common subphenotype of COPD in PLWH.[346,350,351] HIV is also associated with a greater risk of chronic respiratory symptoms consistent with chronic bronchitis, another major subphenotype of COPD.[352] Emphysema in HIV-infected patients has been found to be more severe and diffuse when compared to uninfected patients in some studies,[350] although HIV was not associated with an increased risk of radiographic emphysema in other studies.[353] As in investigations comparing PFTs, differences in HIV-infected and control populations, nadir $CD4^+$ and timing of ART initiation, and varying prevalence of exposure to risk factors, including cigarette smoking, may account for the varying results in these studies.

Inflammation and immune dysfunction related to HIV are associated with greater risk of COPD, suggesting a role for HIV in disease pathogenesis. The prevalence of COPD is higher in individuals with HIV who have lower $CD4^+$ cell counts and higher HIV viral load.[324,333,335,338] Severity of immunocompromise before start of ART, reflected by a nadir $CD4^+$ cell count less than 200 cells/μL, and ongoing immune dysfunction, reflected by a low CD4/CD8 ratio (<0.4), are also associated with radiographic emphysema in those with HIV.[350,355] Chronic inflammation and immune activation, which can persist despite ART in individuals with well-controlled HIV, have also been associated with COPD in HIV. Levels of inflammatory markers, such as C-reactive protein and interleukin-6, are higher in HIV-infected individuals with airflow obstruction and low D_{LCO}.[356,357] In addition, markers of immune activation, such as soluble CD14, the lipopolysaccharide coreceptor, are higher in HIV-infected individuals with emphysema,[350] and soluble CD163 is increased in HIV-infected persons with a low FEV_1/FVC ratio and low D_{LCO}.[358]

Data are limited on the impact of HIV on the clinical course of COPD. Rates of COPD exacerbation may be higher in those with HIV.[359,360] COPD is a significant risk factor for increased frailty, decreased physical function, and increased mortality in HIV-infected persons.[361,362]

Asthma

HIV-infected individuals may have asthma that precedes their HIV infection or that develops after the onset of HIV. HIV-infected patients are more likely than non–HIV-infected patients to have bronchial hyperresponsiveness to methacholine.[328] In one clinic-based study, a history of asthma was reported in 21% and current asthma in 17% of 136 patients attending a primary care clinic for HIV infection.[363] Another study found that physician-diagnosed asthma was present in 21% of participants, and bronchodilator responsiveness was present in 9%.[364] The prevalence of asthma may be increasing in adolescents with HIV, as one study of 1201 HIV-positive youth found that asthma incidence increased significantly from 2008–14 compared to the period 2004–07.[365] $CD4^+$ lymphocyte counts greater than 200 cells/μL are associated with current asthma in those with HIV infection,[363] and one report has linked use of asthma medication to ART use in HIV-infected children, suggesting that immune responses are important, but this association has not been replicated in all cohorts.[364,366] Other factors such as female sex and obesity have also been found to be associated with asthma in HIV-infected individuals.[364]

Treatment of COPD and Asthma

In general, treatment of asthma and COPD should be similar to that for the non–HIV-infected population (see Chapters 62 and 64) because data are limited on whether and how to tailor therapy for obstructive lung disease for people living with HIV. Attention to drug-drug interactions between antiretrovirals and respiratory medications is required. PIs, particularly ritonavir, can increase systemic levels of inhaled or intranasal fluticasone and other inhaled corticosteroids leading to Cushing syndrome or adrenal suppression.[367] Beclomethasone has the least interaction and is the preferred inhaled corticosteroid when used in combination with strong CYP3A4 inducers, including boosted regimens (cobicistat, ritonavir) and most PIs. Use of inhaled corticosteroids for COPD in individuals with HIV also requires careful monitoring for oral candidiasis and bacterial pneumonia.[368] In terms of long-acting β-agonists, no clinically significant interactions have been reported between olodaterol and formoterol with antiretroviral medications. However, salmeterol can interact with different antiretrovirals to cause QTc prolongation. Long- or short-acting muscarinic antagonists (ipratropium or tiotropium) do not have known clinically significant drug-drug interactions with antiretrovirals and represent first-line bronchodilator therapy for COPD.

INTERSTITIAL PNEUMONITIDES

Although opportunistic infection and neoplasia dominate the clinical spectrum of HIV-associated pulmonary diseases, a small number of patients present with signs and symptoms attributable to one of the interstitial pneumonitides, *lymphocytic interstitial pneumonitis* (LIP) or *nonspecific interstitial pneumonitis* (NSIP).[369]

Lymphocytic Interstitial Pneumonitis

Clinical Features. The most striking feature of HIV-associated LIP is the effect of age on its incidence. Early in the AIDS epidemic, one-third to one-half of AIDS-defining diagnoses in HIV-infected children in high-income, industrialized countries were due to LIP. In contrast, LIP is rare in adults[370] and adolescents[371] but has now been described in all settings, including low- and middle-income settings.[372]

The chest radiograph presentation of LIP is nonspecific (Fig. 123.10) and is characterized by bilateral reticulonodular interstitial opacities with a middle to lower lung zone predominance.[373] Hilar or mediastinal adenopathy is occasionally seen. Chest CT scans may reveal small (2- to 4-mm) nodules, often in a peribronchovascular distribution (eFig. 123.39), or diffuse areas of ground-glass opacity.[374]

Diagnosis and Treatment. The definitive diagnosis of LIP requires histologic confirmation by biopsy. There are so



Figure 123.10 Lymphocytic interstitial pneumonitis. Frontal chest radiograph of an HIV-infected patient showing diffuse reticulonodular infiltration. Biopsy specimen revealed lymphocytic interstitial pneumonitis.

few studies of LIP among HIV-infected adults that neither definitive therapy nor benefit of therapy has been determined. Cases of LIP that responded to ART alone have been reported.[370,375]

Nonspecific Interstitial Pneumonitis

NSIP is a pulmonary disorder characterized histologically by infiltration of mononuclear cells, predominantly lymphocytes and plasma cells, into the peribronchiolar and perivascular interstitium (see Chapter 90). NSIP has been reported with various frequencies in HIV-infected patients. Because it is a histologic diagnosis, its incidence depends on the frequency with which biopsy is performed during the diagnostic evaluation.

Clinical Features. The clinical features of NSIP are indistinguishable from those of PCP; however, NSIP may present at $CD4^+$ lymphocyte counts greater than 200 cells/μL, whereas PCP rarely (≤5%) does. For example, in a series of 67 HIV-infected patients with NSIP, the mean $CD4^+$ lymphocyte count in the patients with NSIP was 492 cells/μL compared with 57 cells/μL for the matched control subjects with PCP.[376] The chest radiographic presentation of NSIP is usually a nonspecific diffuse interstitial pattern, which is also indistinguishable from that of PCP; however, one study reported that 16 of 36 (44%) patients with HIV-related NSIP had normal radiographs.[377]

Diagnosis and Treatment. The diagnosis of NSIP requires both histologic confirmation and the exclusion of other etiologies. The natural history of HIV-associated NSIP is poorly understood, but it usually resolves or stabilizes without therapy.[376] Observation is all that is required, but if the patient becomes severely ill, repeat bronchoscopy and biopsy are indicated to look for a different, usually infectious, disorder.

SARCOIDOSIS

Although sarcoidosis would seem an unlikely disorder among patients with HIV, a number of cases of sarcoidosis or sarcoid-like disease have been reported in this population. Many of these case reports have correlated the use of ART with the development of sarcoidosis.[378,379] Whether sarcoidosis in HIV represents a manifestation of IRIS is debated. Approximately 75% of HIV-infected patients with sarcoidosis have $CD4^+$ lymphocyte counts greater than 200 cells/μL.[378]

Both the clinical and imaging findings (eFig. 123.40) of sarcoidosis in HIV-infected patients mirror findings of sarcoidosis in non–HIV-infected patients.[378,379] As described in Chapter 93, granulomatous inflammation of the lungs and other involved organs is characteristic. Stains and cultures of tissue should be obtained and, to diagnose sarcoid, must be negative for microorganisms (e.g., mycobacteria, fungi). Lymphocytic alveolitis with a high percentage of $CD4^+$ lymphocytes may be encountered.[380] Management should follow guidelines as outlined for non–HIV-infected persons with sarcoidosis.

IMMUNE RECONSTITUTION INFLAMMATORY SYNDROME

IRIS describes a paradoxical worsening of clinical status related to recovery of the immune system after a period of immunosuppression. The syndrome typically develops after the initiation of ART in HIV-infected patients. IRIS manifests as an exuberant host inflammatory response to previously recognized (paradoxical IRIS) or subclinical infections (unmasking IRIS). IRIS may also result from an inflammatory or immune response to cancer or self-antigens, as cases of IRIS have been reported to present with worsening tumor or autoimmune disease.[381]

Clinical Features. Numerous disease processes have been associated with IRIS. These include many infections, sarcoidosis, autoimmune conditions, and tumors.[382,383] Among infectious triggers, mycobacterial infections, particularly *M. tuberculosis* (eFig. 123.41) and MAC, are most frequently encountered. Fungal infections, including PCP and *Cryptococcus,* and viral infections, such as CMV, can also be exacerbated by IRIS. The majority of cases of IRIS are seen within the first 1 to 3 months after the initiation of ART, although cases may present several months after the initiation of ART.[383]

Diagnosis and Treatment. The diagnosis of IRIS requires compatible clinical features and exclusion of alternative causes for worsening clinical status. IRIS is frequently associated with starting ART in close proximity to treatment for an acute opportunistic infection.[384,385] IRIS is more likely when ART is initiated in individuals with a very low $CD4^+$ cell count, generally less than 100 cells/μL, although IRIS can develop in response to TB at higher $CD4^+$ cell counts. IRIS is also more likely when there is a rapid virologic and immunologic response to ART.

Despite the risk of IRIS, studies support starting ART concurrently or very soon after starting treatment of opportunistic infection because this strategy results in improved survival.[109–111,386] Recommendations regarding the exact timing of ART initiation depend on the patient's $CD4^+$ cell

count, type of infection or complication, and organ system involved.

In resource-limited countries, TB is among the most common opportunistic infections in HIV-infected patients. Prednisone decreased risk of TB-associated IRIS in high-risk individuals in the PredART Clinical Trial. HIV-infected patients with $CD4^+$ cell counts less than 100 cells/μL who are within 30 days of initiation of TB treatment had a significantly decreased risk of TB-associated IRIS when given prophylactic prednisone for 4 weeks (40 mg daily for 14 days, followed by 20 mg daily for 14 days) without evidence of increased risk for other severe infections or cancers.[387] Sequelae of TB-associated IRIS may include worsening of lung function,[388] although declines in FEV_1 and FVC after ART initiation were less apparent in individuals in the PredART study.[389] These findings raise the possibility that TB-associated IRIS may contribute to the overall high prevalence of abnormal spirometry in HIV-infected patients after TB.

In patients who develop IRIS, ART should generally be continued, although careful review on a case-by-case basis is required and expert consultation is recommended.[27] Nonsteroidal anti-inflammatory agents can be used to decrease inflammation. Steroids may be indicated if the excessive inflammatory response can be particularly harmful, for example, in TB meningitis or with other life-threatening lesions, such as those involving the central nervous system or those causing airway compromise. Optimal steroid dosing is uncertain. However, in one trial of patients with moderately severe paradoxical TB-IRIS, outcomes were improved in patients treated with prednisone at 1.5 mg/kg per day for 2 weeks, followed by 0.75 mg/kg per day for the next 2 weeks.[390]

Key Points

- Without effective combination *antiretroviral therapy* (ART), *human immunodeficiency virus* (HIV) infection results in immune dysregulation, dysfunction, and deficiency, with a progressive decline in $CD4^+$ T lymphocytes. HIV infection also causes alteration in several lines of host defense in the lungs and respiratory tract. As a result, HIV-infected persons are at increased risk for a wide spectrum of opportunistic infections.
- The peripheral $CD4^+$ lymphocyte count influences the risk for pulmonary complications in HIV-infected persons; as the $CD4^+$ count decreases, the risk of opportunistic infections and HIV-associated malignancies increases.
- Worldwide, tuberculosis is the most common infectious lung complication and a major cause of HIV-associated morbidity and mortality.
- Bacterial pneumonia and *Pneumocystis* pneumonia are also common infectious lung complications associated with HIV.
- Noninfectious conditions encountered with increased frequency in patients with HIV include chronic obstructive pulmonary diseases, lung cancer, and pulmonary arterial hypertension.
- *Immune reconstitution inflammatory syndrome* (IRIS) can develop after the initiation of ART in HIV-infected patients. IRIS results from the reconstitution of the immune system leading to exuberant host inflammatory responses to previously recognized (paradoxical IRIS) or subclinical infections (unmasking IRIS).
- The differential diagnosis for pulmonary diseases in HIV-infected patients is broad, and the clinical features and radiographic findings of many diseases may overlap significantly. Definitive diagnosis is highly recommended in patients with HIV. When feasible, early bronchoscopy with bronchoalveolar lavage for opportunistic pathogens should be performed in patients with pneumonia who do not have an established microbiologic diagnosis.
- Treatment of noninfectious lung diseases in HIV-infected patients generally follow guidelines for uninfected persons. When initiating therapy for lung diseases, careful attention to drug-drug interactions with antiretrovirals is indicated.

Key Readings

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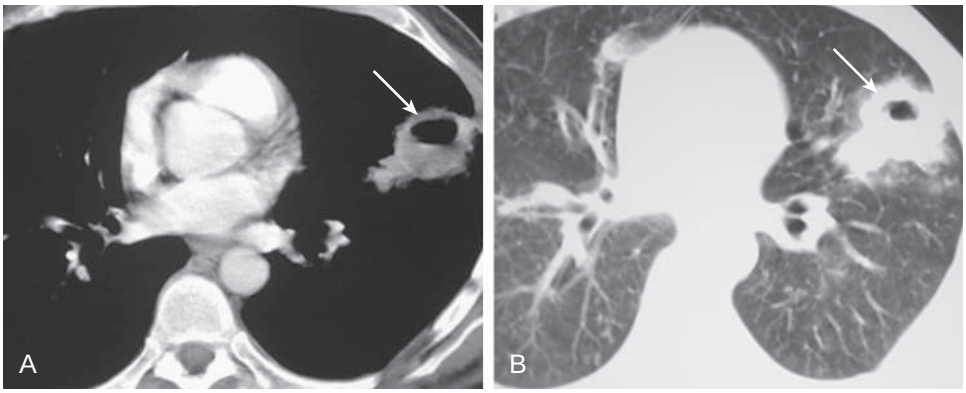
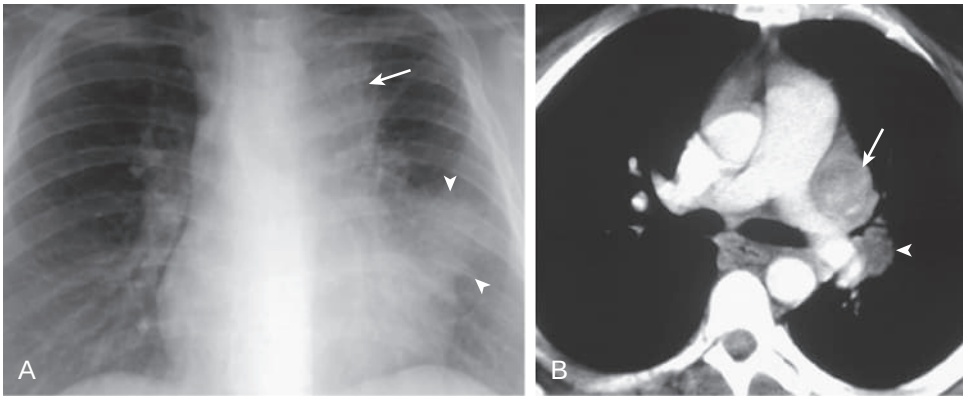
Complete reference list available at ExpertConsult.com.

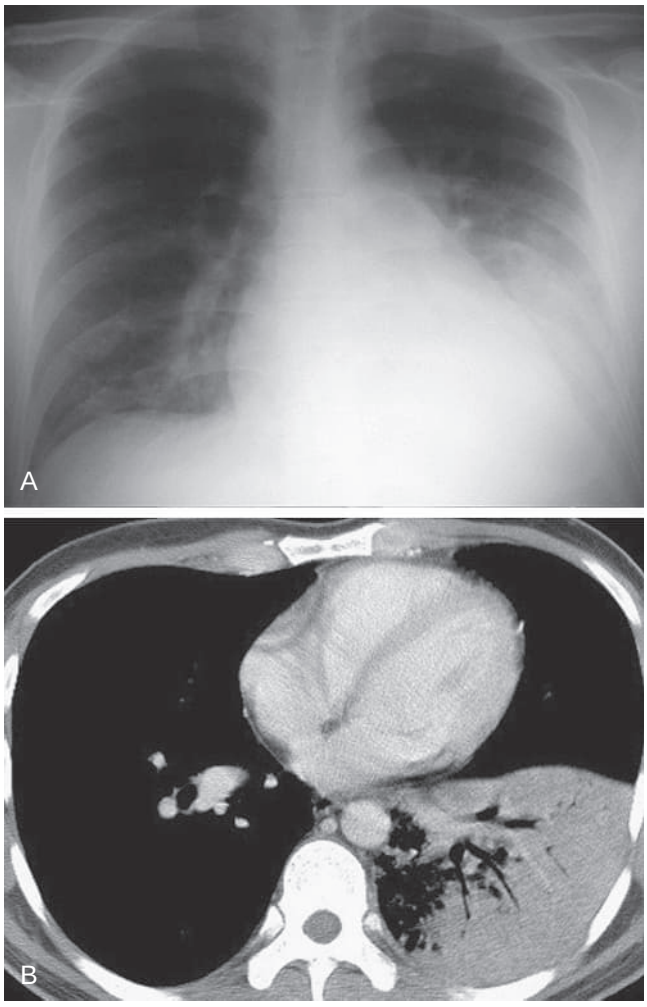
eFIGURE IMAGE GALLERY



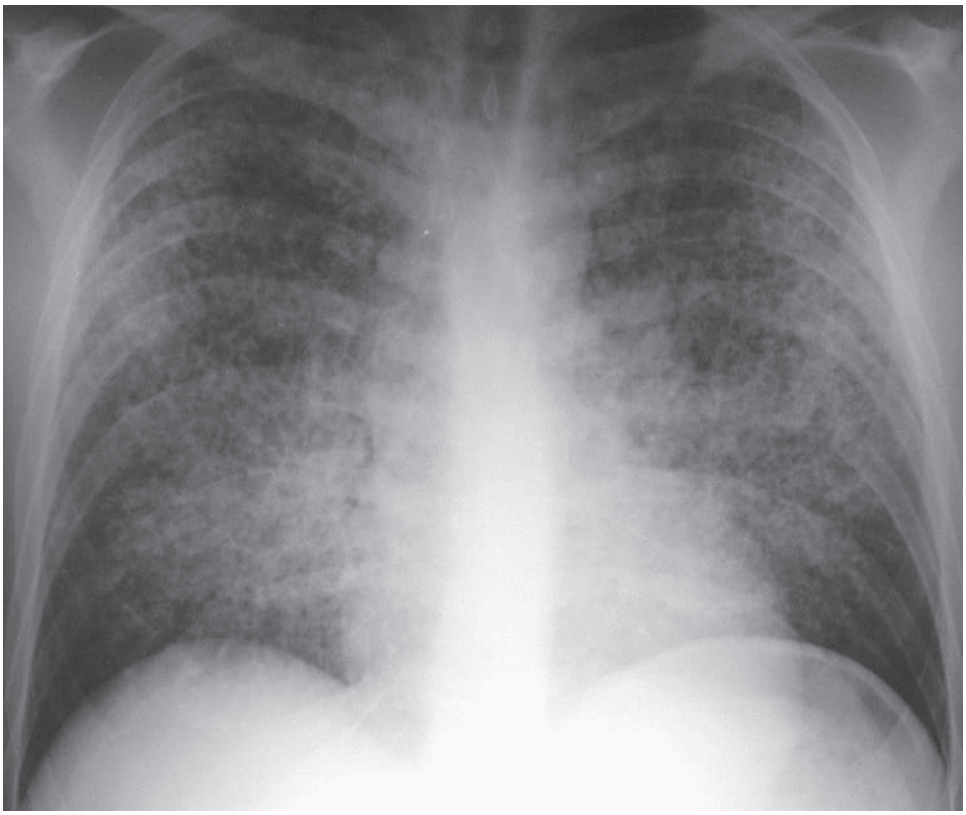
eFigure 123.1 *Pseudomonas aeruginosa* pulmonary abscess. Axial chest computed tomography scans in soft tissue (A) and lung windows (B) show a thick-walled lingular cavity (*arrows*) with surrounding consolidation. *P. aeruginosa* was recovered from blood and sputum. The imaging appearance is nonspecific and could be seen with other causes of pulmonary abscess and malignancy (note similarity with primary lung malignancy shown in eFig. 123.38). (Courtesy Michael B. Gotway, MD.)



eFigure 123.2 *Nocardia asteroides* thoracic infection. (A) Frontal chest radiograph in an HIV-infected patient with a low $CD4^+$ count shows left superior mediastinal widening (*arrow*) consistent with mediastinal lymphadenopathy. A lingular masslike opacity (*arrowheads*) is present. (B) Axial chest computed tomography displayed in soft tissue windows shows subaortic (*arrow*) left peribronchial (*arrowhead*) lymphadenopathy. (Courtesy Michael B. Gotway, MD.)



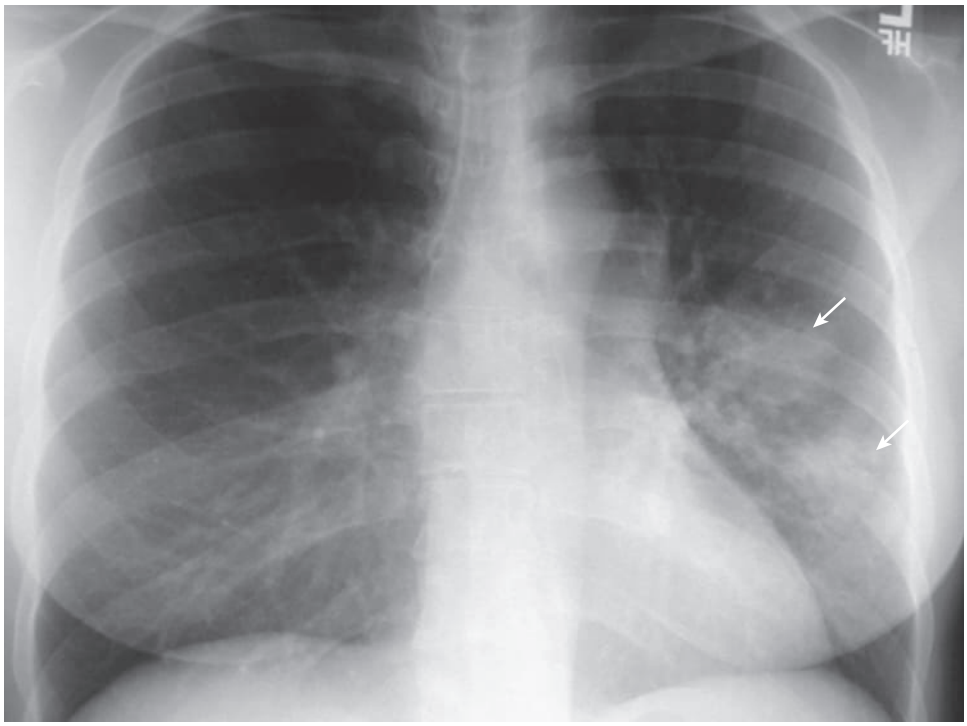
eFigure 123.3 Primary *Mycobacterium tuberculosis* infection in an HIV-infected patient. (A) Frontal chest radiograph in an HIV-infected patient with a low $CD4^+$ count shows dense opacification of the left lower lobe. (B) Axial chest computed tomography displayed in soft tissue windows shows left lower lobe consolidation. The imaging appearance is entirely consistent with a lobar pneumonia pattern, often seen with pneumococcal or *Klebsiella* pneumonias. Sputum grew *M. tuberculosis,* and the patient responded to antituberculous therapy. (Courtesy Michael B. Gotway, MD.)



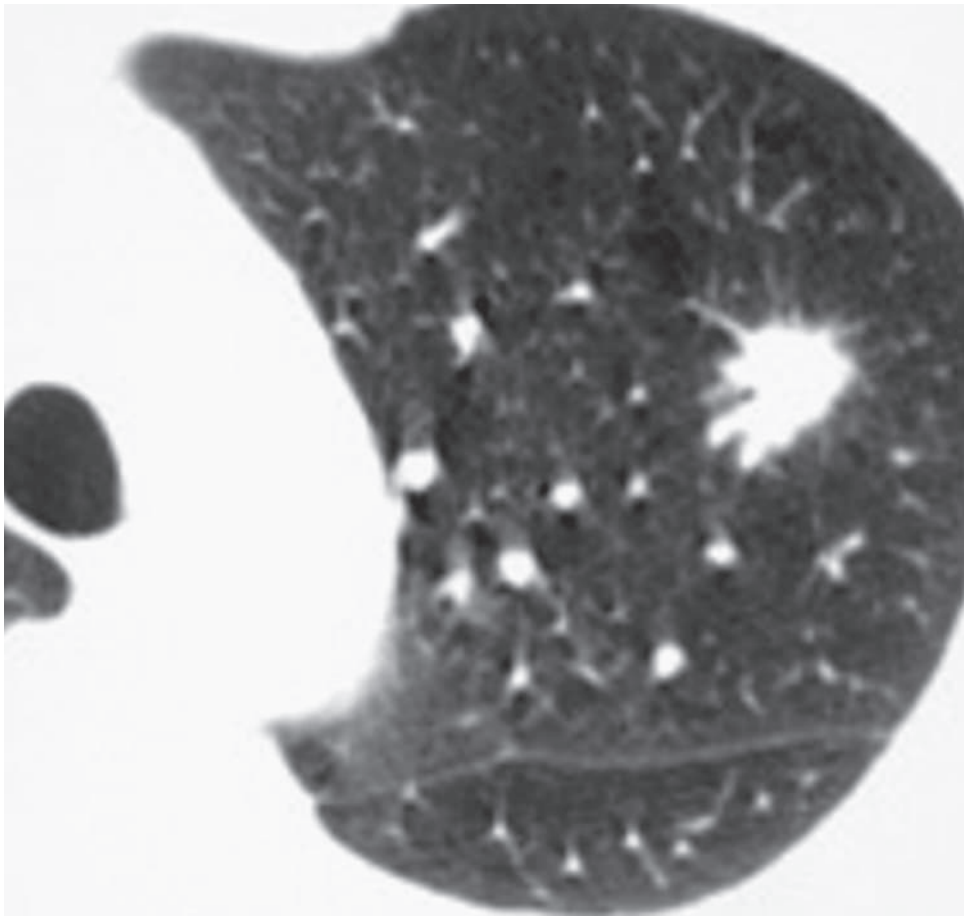
eFigure 123.4 *Mycobacterium tuberculosis* miliary pulmonary infection. Frontal chest radiograph in an HIV-infected patient with a low $CD4^+$ count shows numerous, bilateral, randomly disseminated, small pulmonary nodules. (Courtesy Michael B. Gotway, MD.)



eFigure 123.5 *Mycobacterium tuberculosis* lymphadenitis. Frontal chest radiograph shows right hilar (*arrow*) and right paratracheal (*arrowheads*) lymphadenopathy in an HIV-infected patient with a low $CD4^+$ count. (Courtesy Michael B. Gotway, MD.)



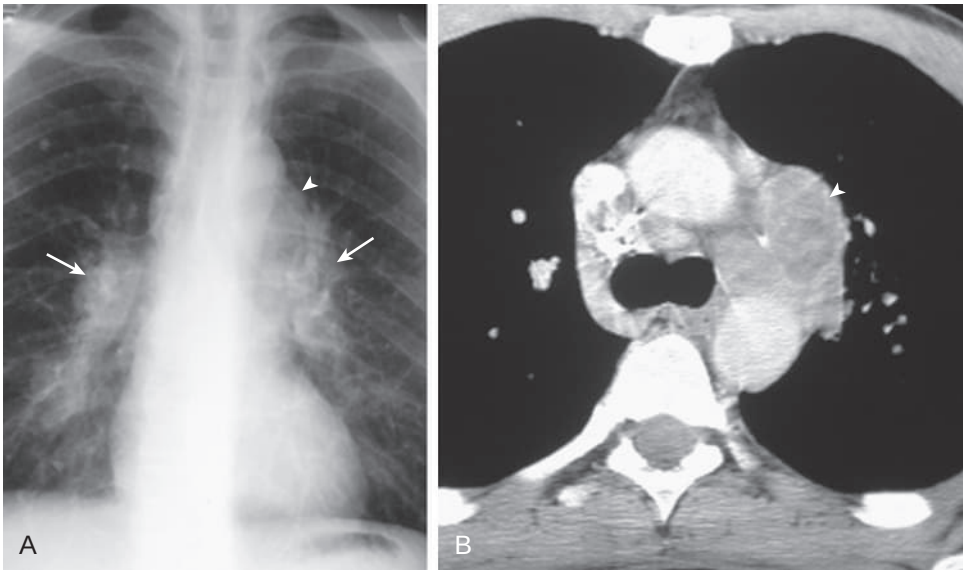
eFigure 123.6 *Mycobacterium avium* complex focal pulmonary infection. Frontal chest radiograph in an HIV-infected patient with a $CD4^+$ count less than 50 cells/μL shows focal nodular left perihilar opacities (*arrows*) representing *M. avium* complex infection. (Courtesy Michael B. Gotway, MD.)



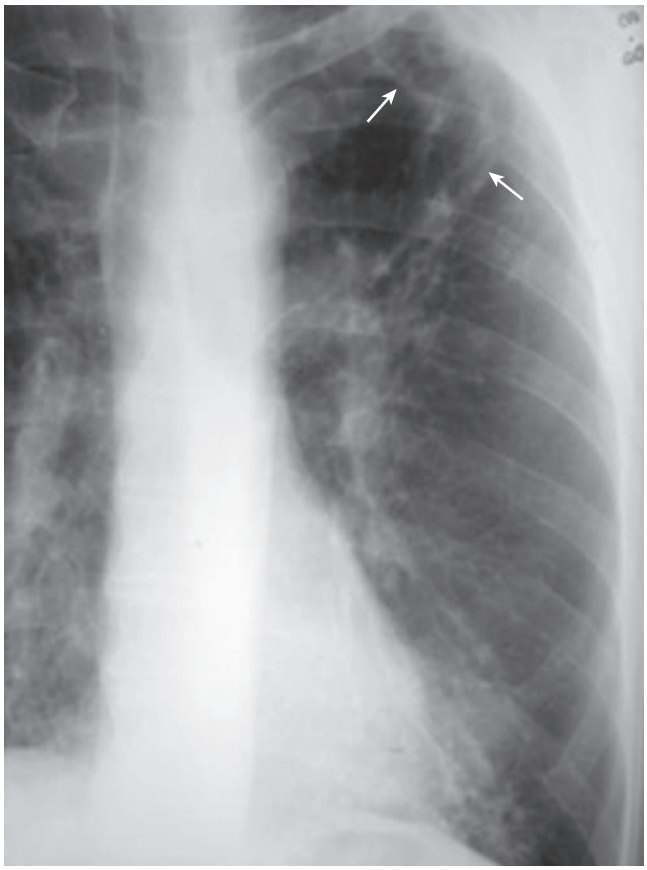
eFigure 123.7 *Mycobacterium avium* complex presenting as a pulmonary nodule. Chest computed tomography displayed in lung windows performed in an HIV-infected patient with a $CD4^+$ count less than 50 cells/μL shows a spiculated left upper lobe nodule suspicious for primary pulmonary malignancy. Transthoracic percutaneous needle biopsy proved *M. avium* complex infection. (Courtesy Michael B. Gotway, MD.)



eFigure 123.8 *Mycobacterium avium* complex endobronchial infection in an HIV-infected patient with a low CD4⁺ count. Bronchoscopic image shows small white nodular areas (*arrows*). Biopsy recovered *M. avium* complex organisms. (Courtesy Michael B. Gotway, MD. Case courtesy Syed A.J. Zaidi, MBBS, FCCP, Pulmonary–Critical Care section, Maricopa Medical Center, Phoenix, AZ.)



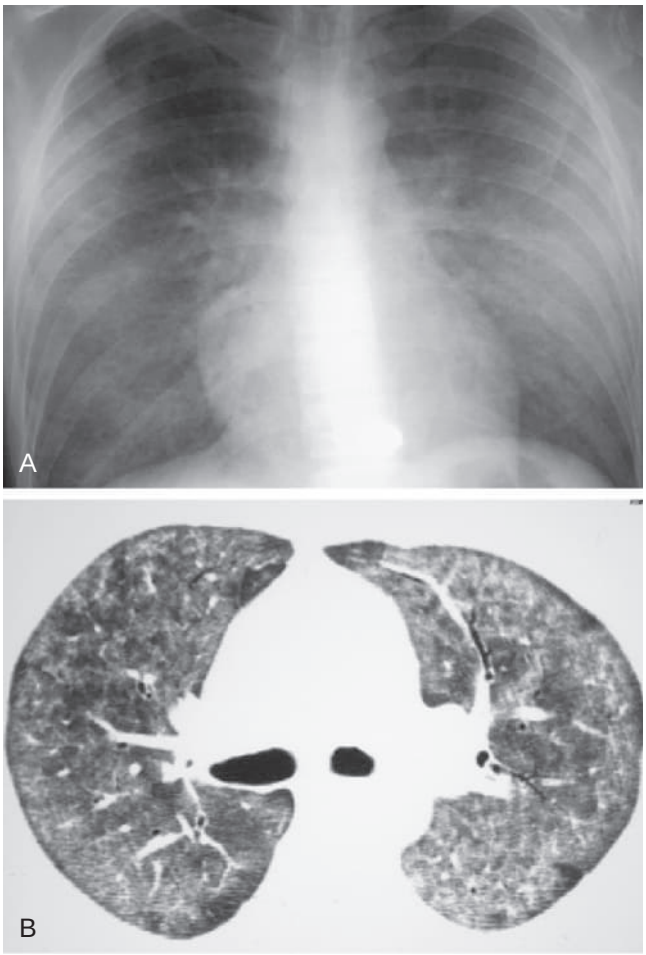
eFigure 123.9 *Mycobacterium avium* complex lymphadenitis. (A) Frontal chest radiograph in an HIV-infected patient with a CD4⁺ count less than 50 cells/μL shows bilateral hilar (*arrows*) and left mediastinal *(arrowhead)* lymphadenopathy. (B) Axial enhanced chest computed tomography confirms presence of enlarged aortopulmonary lymph nodes (*arrowhead*) as well as left tracheobronchial lymphadenopathy. Note the presence of low attenuation areas, consistent with necrosis. (Courtesy Michael B. Gotway, MD.)



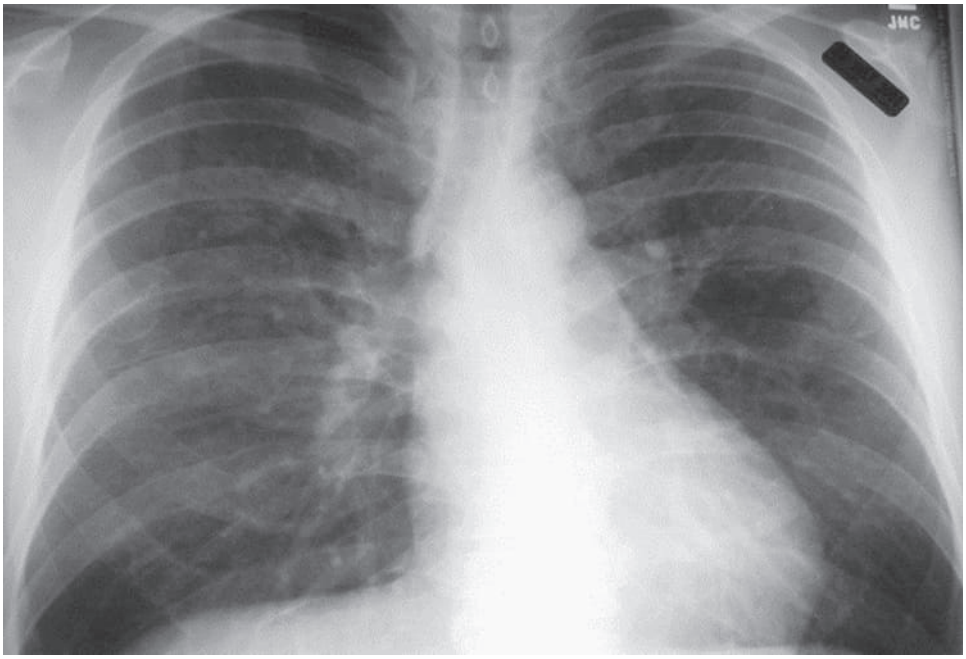
eFigure 123.10 *Mycobacterium kansasii* pulmonary infection. Frontal chest radiograph performed in an HIV-infected patient with a $CD4^+$ count less than 50 cells/μL shows linear bronchovascular thickening in the left upper lobe associated with left apical thin-walled cavities (*arrows*). (Courtesy Michael B. Gotway, MD.)



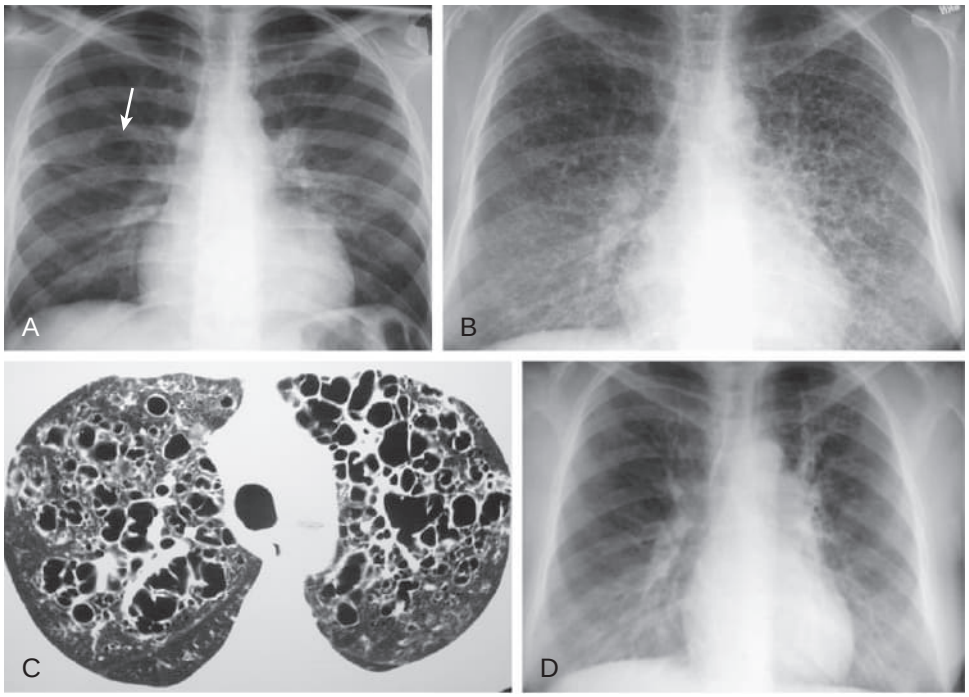
eFigure 123.11 Typical imaging appearance of *Pneumocystis jirovecii* pneumonia. Frontal chest radiograph in an HIV-infected patient with a $CD4^+$ count less than 200 cells/μL shows bilateral, symmetric perihilar indistinctness. Sputum induction recovered *P. jirovecii.* (Courtesy Michael B. Gotway, MD.)



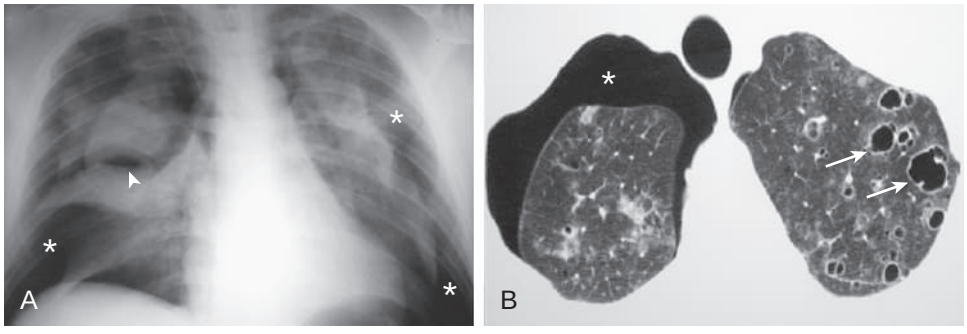
eFigure 123.12 Typical imaging appearance of *Pneumocystis jirovecii* pneumonia. (A) Frontal chest radiograph in an HIV-infected patient with a $CD4^+$ count less than 200 cells/μL shows bilateral, interstitial thickening with increased attenuation consistent with a granular or ground-glass appearance (increased pulmonary attenuation without obscuration of the underlying vascular and bronchial margins). Sputum induction recovered *P. jirovecii.* (B) Axial chest computed tomography displayed in lung windows shows the typical appearance of multifocal, bilateral ground-glass opacity in HIV-infected patients with *P. jirovecii* pneumonia. (Courtesy Michael B. Gotway, MD.)



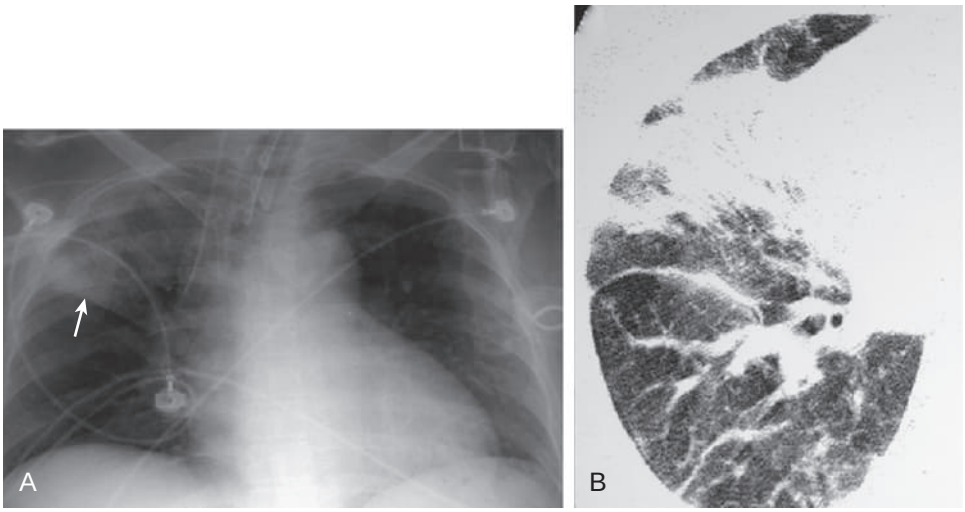
eFigure 123.13 Atypical imaging appearance of *Pneumocystis jirovecii* pneumonia. Frontal chest radiograph in an HIV-infected patient with a $CD4^+$ count less than 200 cells/μL shows faint predominantly right perihilar bronchovascular indistinctness; minimal left perihilar indistinctness is present. Asymmetry or frankly unilateral pulmonary findings are an atypical imaging manifestation of *P. jirovecii* pneumonia. Nevertheless, in an HIV-infected patient with a $CD4^+$ count less than 200 cells/μL such an imaging appearance is suspicious for *P. jirovecii* pneumonia. (Courtesy Michael B. Gotway, MD.)



eFigure 123.14 Imaging appearance of *Pneumocystis jirovecii* pneumonia: pneumatocele formation. (A) Frontal chest radiograph in an HIV-infected patient with a $CD4^+$ count less than 200 cells/μL shows bilateral mild bronchovascular thickening and indistinctness, consistent with *P. jirovecii* pneumonia. A thin-walled right perihilar cyst (*arrow*) is present, consistent with a pneumatocele. (B) Frontal chest radiograph in an HIV-infected patient with a $CD4^+$ count less than 200 cells/μL shows innumerable bilateral linear, reticular, and cystic foci. (C) Axial chest computed tomography displayed in lung windows shows numerous, bilateral thin-walled cysts with a few areas of ground-glass opacity also visible. The appearance is somewhat reminiscent of Langerhans cell histiocytosis. (D) Follow-up chest radiograph obtained several months after part A shows resolution of the cysts. (Courtesy Michael B. Gotway, MD.)



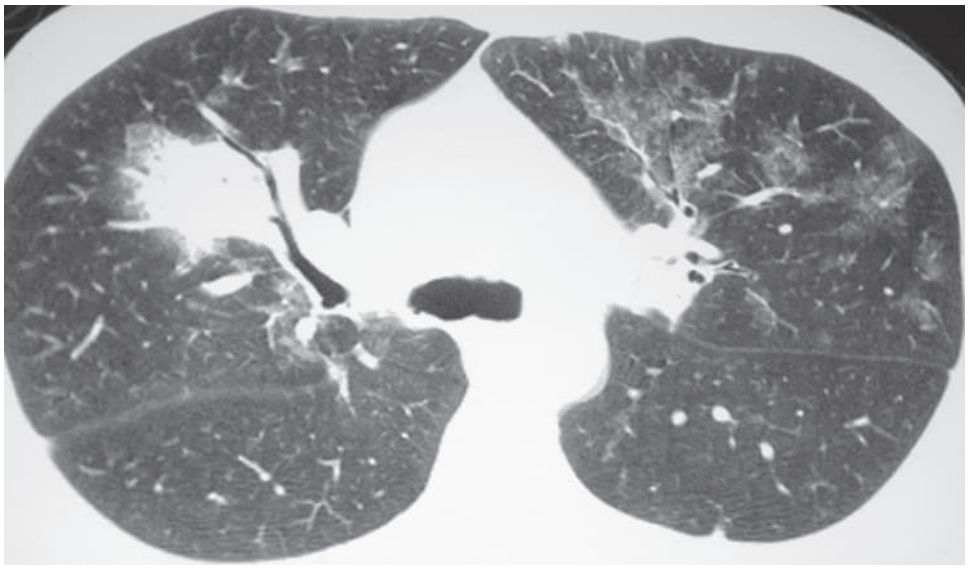
eFigure 123.15 Imaging appearance of *Pneumocystis jirovecii* pneumonia: pneumothorax due to pneumatocele formation. (A) Frontal chest radiograph in an HIV-infected patient with a $CD4^+$ count less than 200 cells/μL shows bilateral pneumothoraces (*asterisk*) on the right side tracking into the fissural surfaces (*arrowhead*). (B) Axial chest computed tomography displayed in lung windows in a different patient shows patchy bilateral ground-glass opacity, consistent with *P. jirovecii* pneumonia, complicated by thin-walled cysts (*arrows*), representing pneumatoceles. A right-sided pneumothorax (*asterisk*) is present. (Courtesy Michael B. Gotway, MD.)



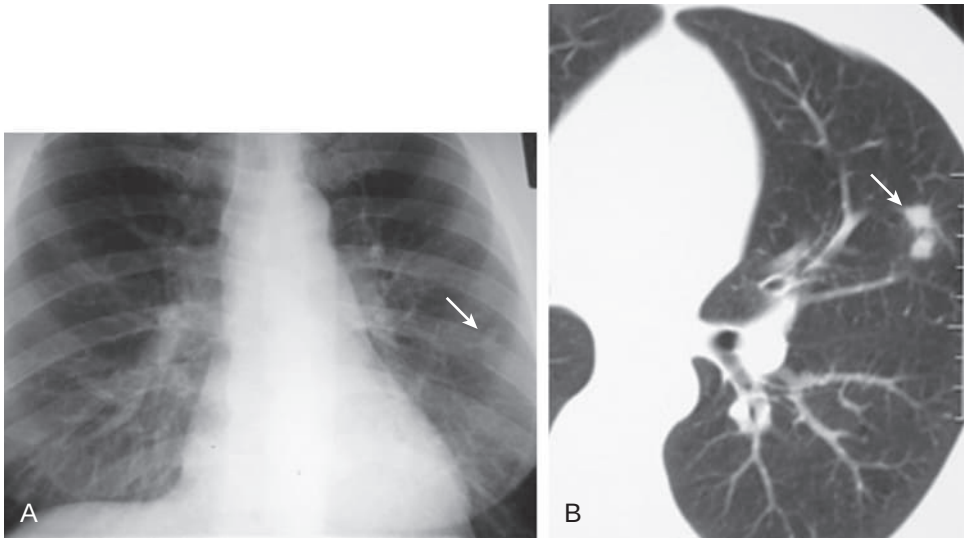
eFigure 123.16 Atypical imaging appearance of *Pneumocystis jirovecii* pneumonia: focal consolidation. (A) Frontal chest radiograph in an HIV-infected patient with a $CD4^+$ count less than 200 cells/μL shows focal right upper lobe opacity (*arrow*), demarcated by the right horizontal fissure. (B) Focused axial chest computed tomography displayed in lung windows in a separate patient shows air space consolidation in the right middle lobe. Sputum induction recovered *P. jirovecii* in both patients. (Courtesy Michael B. Gotway, MD.)



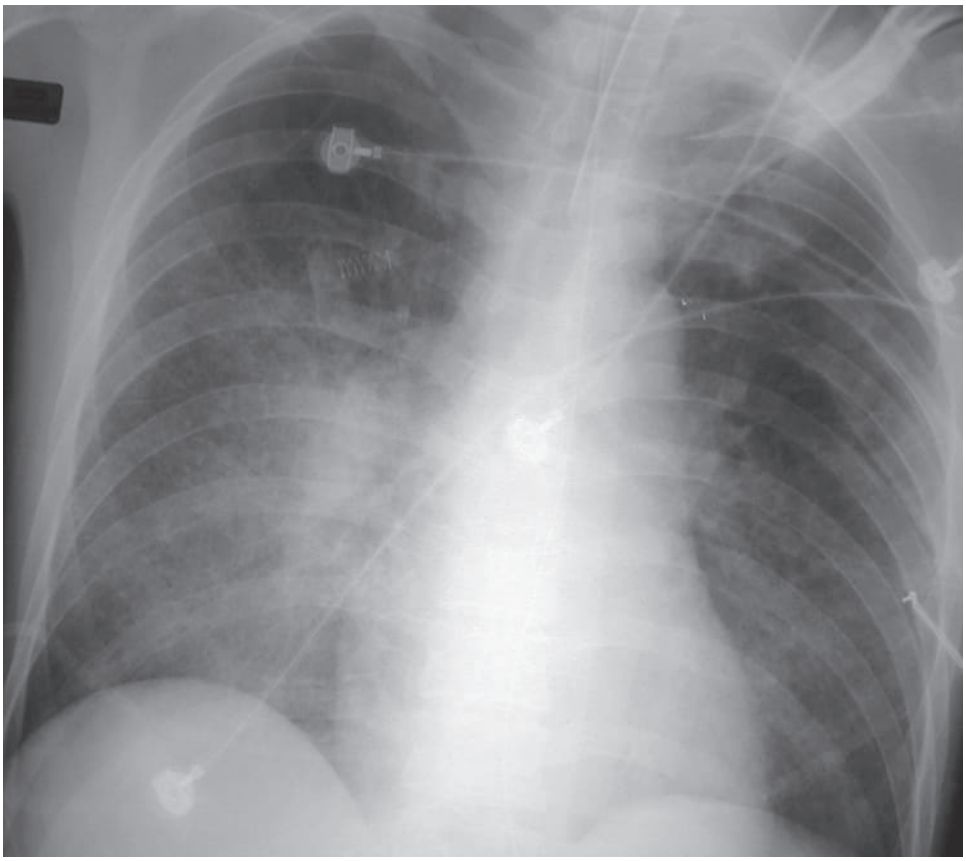
eFigure 123.17 Frontal chest radiograph in an HIV-infected patient with a $CD4^+$ count less than 200 cells/μL shows patchy bilateral opacities consistent with *Pneumocystis jirovecii* pneumonia. The more focal left midlung opacity (*arrow*) raises the possibility of a second, superimposed process, but no other organisms could be recovered and the pulmonary abnormalities resolved with treatment of *P. jirovecii.* (Courtesy Michael B. Gotway, MD.)



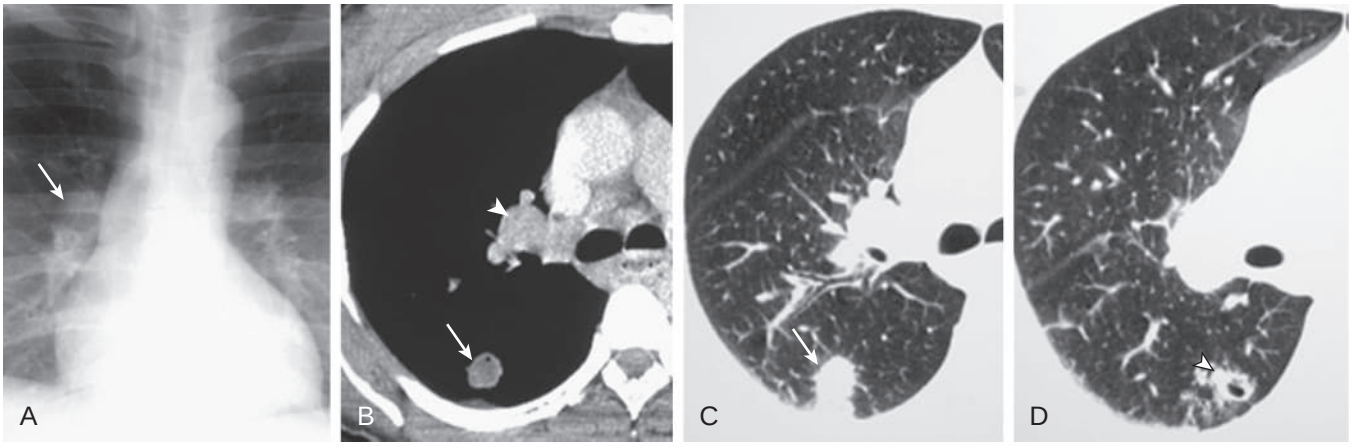
eFigure 123.18 Atypical imaging appearance of *Pneumocystis jirovecii* pneumonia: focal lung opacity. Axial chest computed tomography displayed in lung windows performed in an HIV-infected patient with a $CD4^+$ count less than 200 cells/μL shows air-space consolidation in the right upper lobe. Patchy left upper lobe ground-glass opacity is also present, consistent with *P. jirovecii* pneumonia. The patient underwent transthoracic percutaneous lung biopsy of the focal opacity to exclude the possibility of a second process superimposed on *P. jirovecii* pneumonia; this biopsy showed only *P. jirovecii* organisms. (Courtesy Michael B. Gotway, MD.)



eFigure 123.19 Atypical imaging appearance of *Pneumocystis jirovecii* pneumonia: focal nodules. (A) Frontal chest radiograph in an HIV-infected patient with a $CD4^+$ count less than 200 cells/μL shows faint left midlung nodular opacity (*arrow*). (B) Axial chest computed tomography displayed in lung windows shows two focal lingular nodules (*arrow*). Transthoracic percutaneous lung biopsy showed only *P. jirovecii* organisms. (Courtesy Michael B. Gotway, MD.)



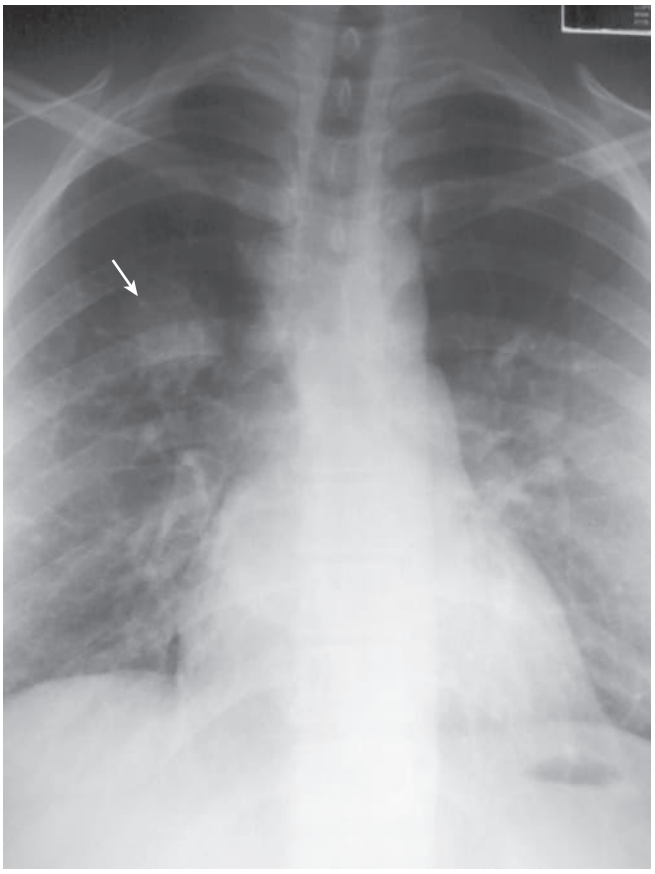
eFigure 123.20 Cryptococcal pulmonary infection: interstitial appearance. Frontal chest radiograph in an HIV-infected patient with a low $CD4^+$ count shows bilateral, right-greater-than-left, perihilar ground-glass attenuation and linear, interstitial thickening, suspicious for *Pneumocystis jirovecii* pneumonia; however, the opacities were proven to be the result of cryptococcal pulmonary infection. (Courtesy Michael B. Gotway, MD.)



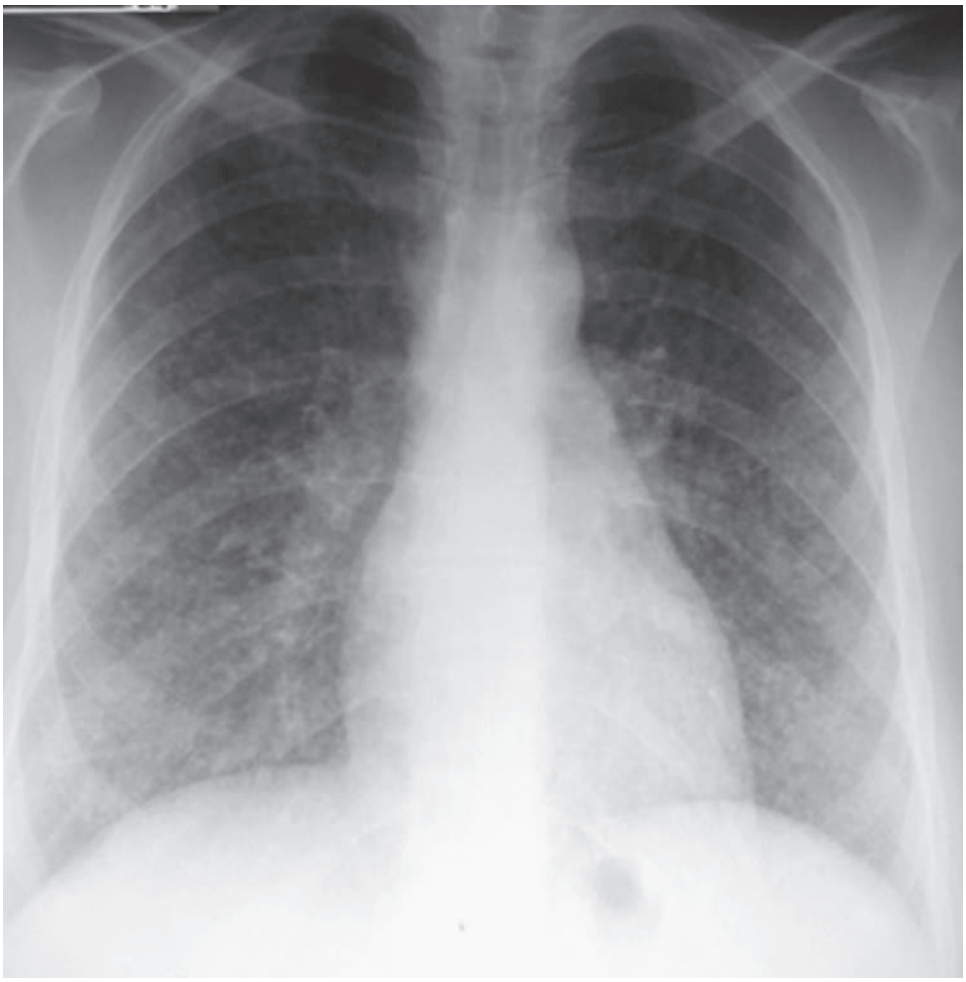
eFigure 123.21 Cryptococcal pulmonary infection: thoracic lymphadenopathy and nodules. (A) Frontal chest radiograph in an HIV-infected patient with a low $CD4^+$ count shows right hilar lymph node enlargement (*arrow*). (B–D) Axial chest computed tomography displaced in soft tissue (B) and lung windows (C–D) confirms right peribronchial lymph node enlargement (*arrowhead*, B) and shows a nodule in the right lower lobe (*arrows,* B–C); note the tiny focus of cavitation evident within the nodular anteriorly in part B). A separate cavitary nodule (*arrowhead*, D), with surrounding satellite opacities, is seen slightly more inferiorly in the superior segment of the right lower lobe. (Courtesy Michael B. Gotway, MD.)



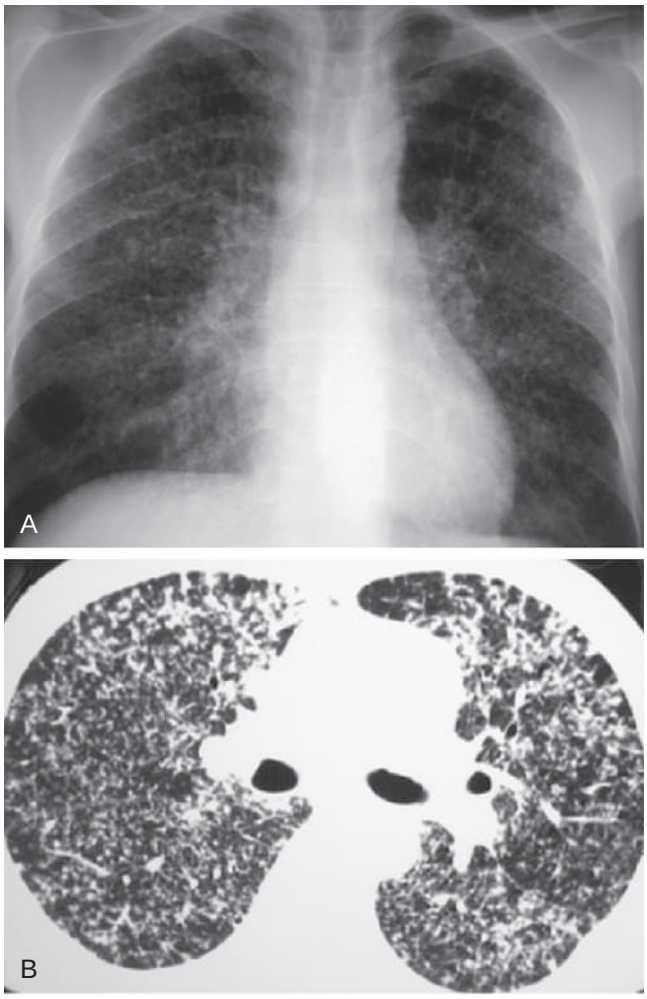
eFigure 123.22 Cryptococcal pulmonary infection: focal pulmonary opacity. Frontal chest radiograph in an HIV-infected patient with a low $CD4^+$ count shows focal right lower lobe consolidation superimposed on more diffuse interstitial thickening throughout the right lung. (Courtesy Michael B. Gotway, MD.)



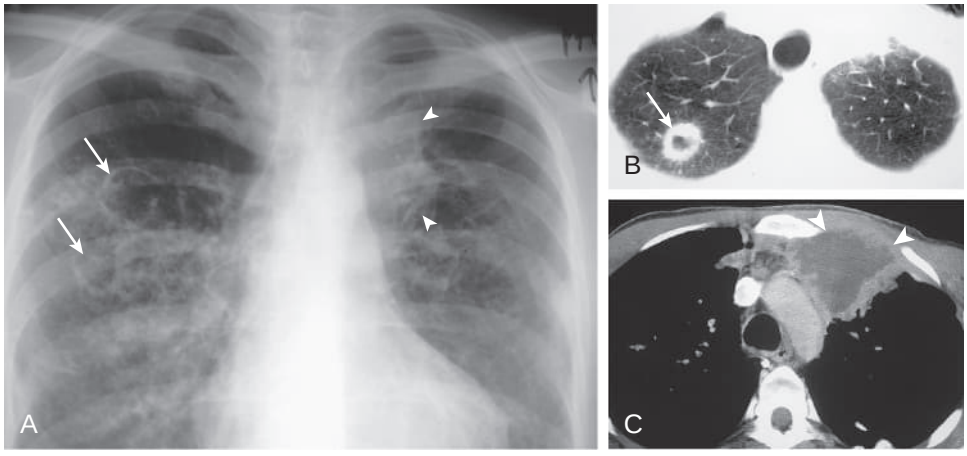
eFigure 123.23 Cryptococcal pulmonary infection: pulmonary nodule. Frontal chest radiograph in an HIV-infected patient with a low $CD4^+$ count shows a right suprahilar pulmonary nodule (*arrow*). Transthoracic percutaneous lung biopsy demonstrated cryptococcal infection. (Courtesy Michael B. Gotway, MD.)



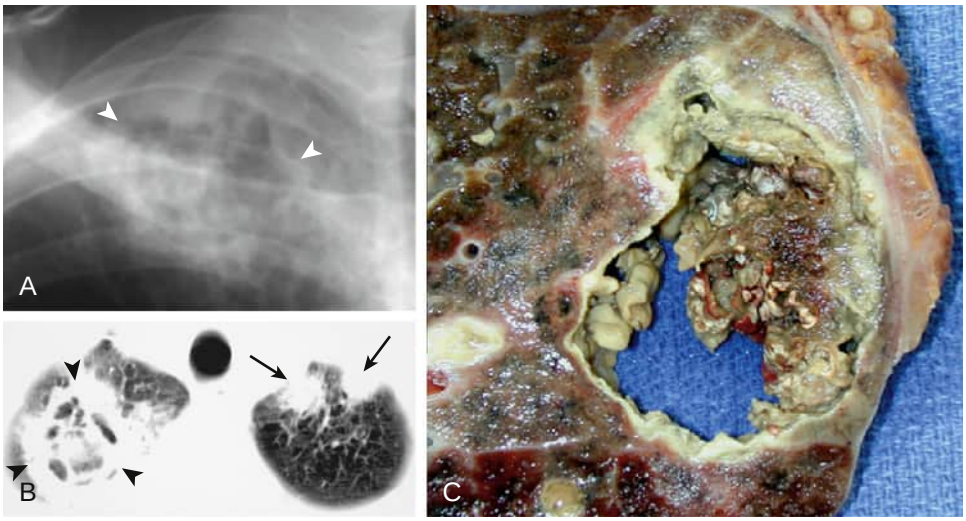
eFigure 123.24 Cryptococcal pulmonary infection: miliary infection. Frontal chest radiograph performed in an HIV-infected patient with a low $CD4^+$ count shows numerous symmetrical bilateral small pulmonary nodules. (Courtesy Michael B. Gotway, MD.)



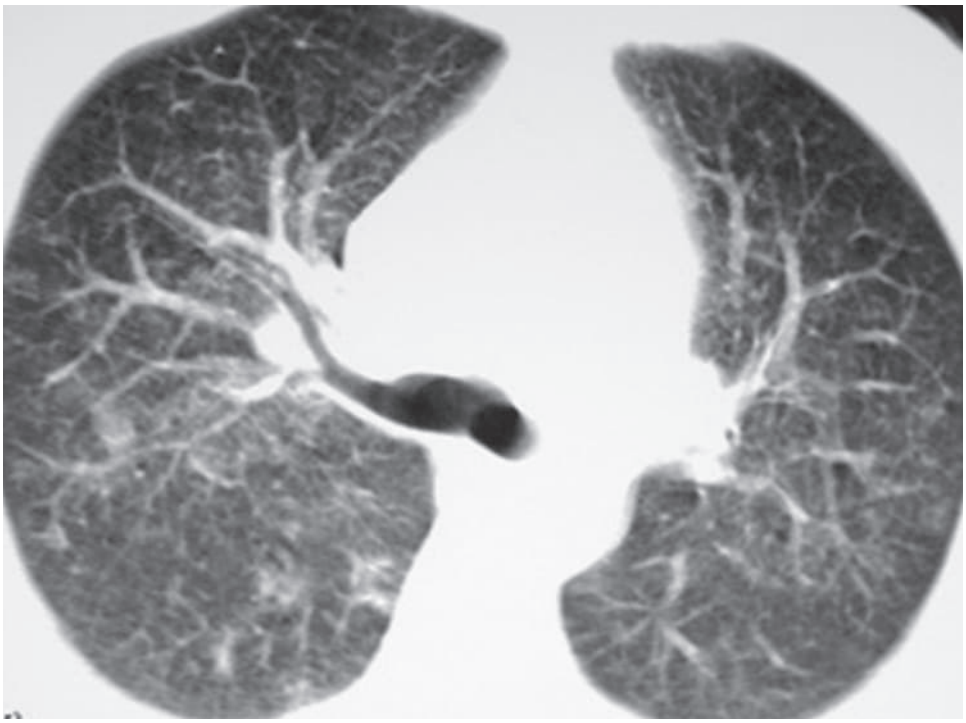
eFigure 123.25 *Coccidioides immitis* pulmonary infection: miliary infection. (A) Frontal chest radiograph in an HIV-infected patient with a low $CD4^+$ count shows numerous symmetrical bilateral small pulmonary nodules. (B) Axial chest computed tomography shows numerous bilateral pulmonary nodules, consistent with a random small nodular, or miliary, pattern. Bronchoscopy with transbronchial biopsy proved *C. immitis* infection. (Courtesy Michael B. Gotway, MD.)



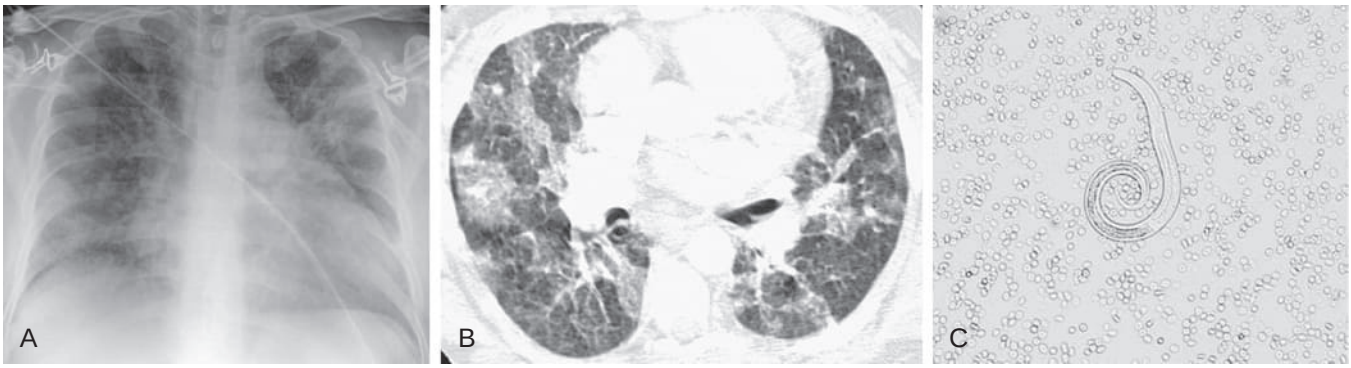
eFigure 123.26 *Aspergillus* pulmonary infection. (A) Frontal chest radiograph in an HIV-infected patient with a low $CD4^+$ count shows right upper lobe cystic lesions (*arrows*) with surrounding small nodules and left superior mediastinal soft tissue (*arrowheads*). Axial chest computed tomography displayed in lung windows (B) and soft tissue windows (C) shows a right apical cavity (*arrow*, B) and a necrotic mass in the left superior mediastinum (*arrowheads*, C) invading the chest wall anteriorly. Transthoracic percutaneous lung biopsy of the left-sided mass recovered *Aspergillus fumigatus*. (Courtesy Michael B. Gotway, MD.)



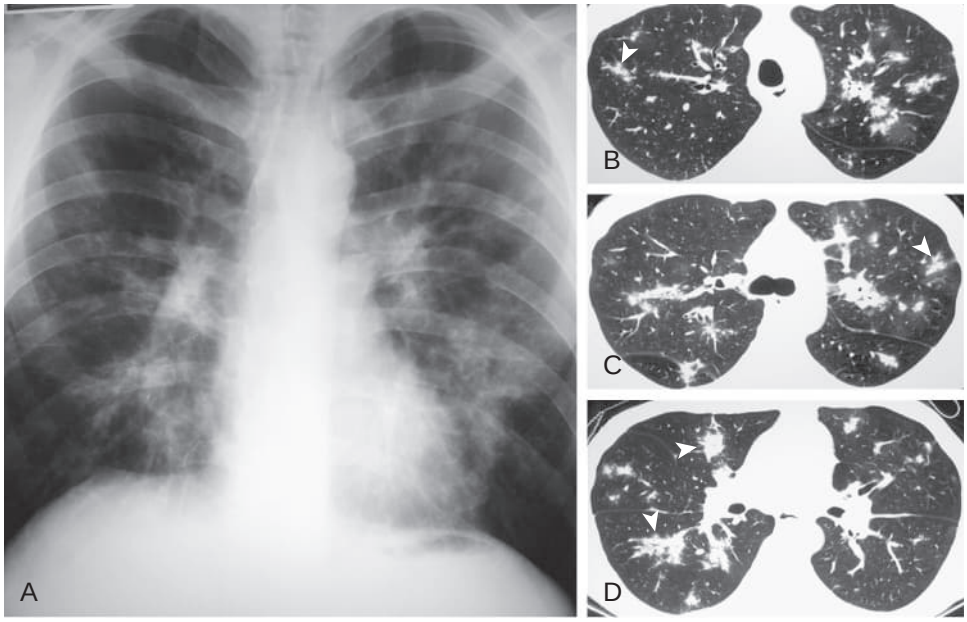
eFigure 123.27 *Aspergillus* pulmonary infection. (A) Focused frontal chest radiograph in an HIV-infected patient with a low CD4+ count shows an irregular cavity (*arrowheads*) in the right apex. (B) Axial chest computed tomography displayed in lung windows shows a complex cavity with internal opacity (*arrowheads*) and right apical lung nodules (*arrows*). (C) Postmortem right lung specimen shows a necrotic right apical cavity with complex internal material, correlating with the computed tomography findings. Numerous areas of arterial and venous invasion with thrombosis and infarction were identified, and *Aspergillus fumigatus* was recovered from the material within the cavity. (Modified from Gotway MB, Dawn SK, Caoili EM, et al. The radiologic spectrum of pulmonary *Aspergillus* infections. *J Comput Assist Tomogr.* 2002;26:159–173.)



eFigure 123.28 Cytomegalovirus infection. Axial chest computed tomography in an HIV-infected patient with a low CD4+ count shows patchy, variably sized pulmonary nodular opacities. The imaging features are very nonspecific. (Courtesy Michael B. Gotway, MD.)



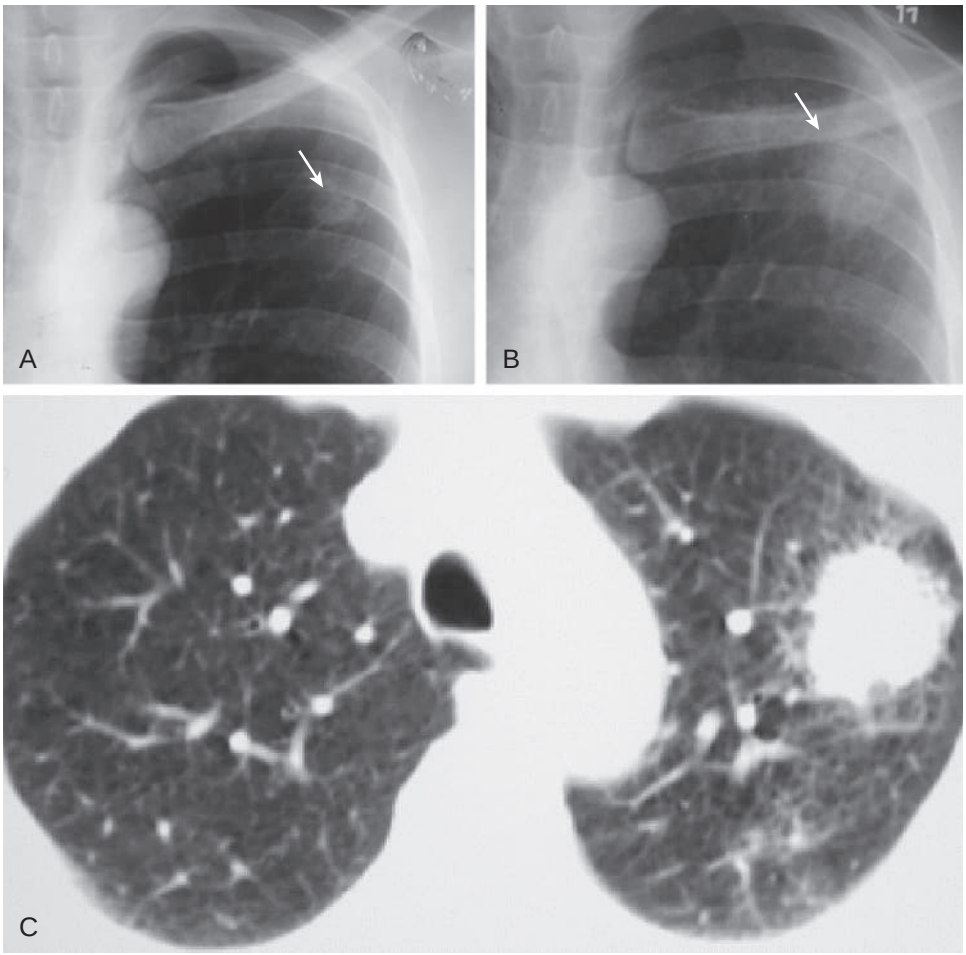
eFigure 123.29 *Strongyloides stercoralis* pulmonary infection. (A) Frontal chest radiograph in an HIV-infected patient with a low CD4⁺ count shows nonspecific bilateral areas of linear opacity and interstitial thickening, predominating in the perihilar regions. (B) Axial chest computed tomography displayed in lung windows shows patchy, multifocal, bilateral areas of ground-glass opacity associated with mild linear and reticular opacities. (C) Surgical lung biopsy recovered *S. stercoralis* organisms. (A–B, Courtesy Michael B. Gotway, MD.)



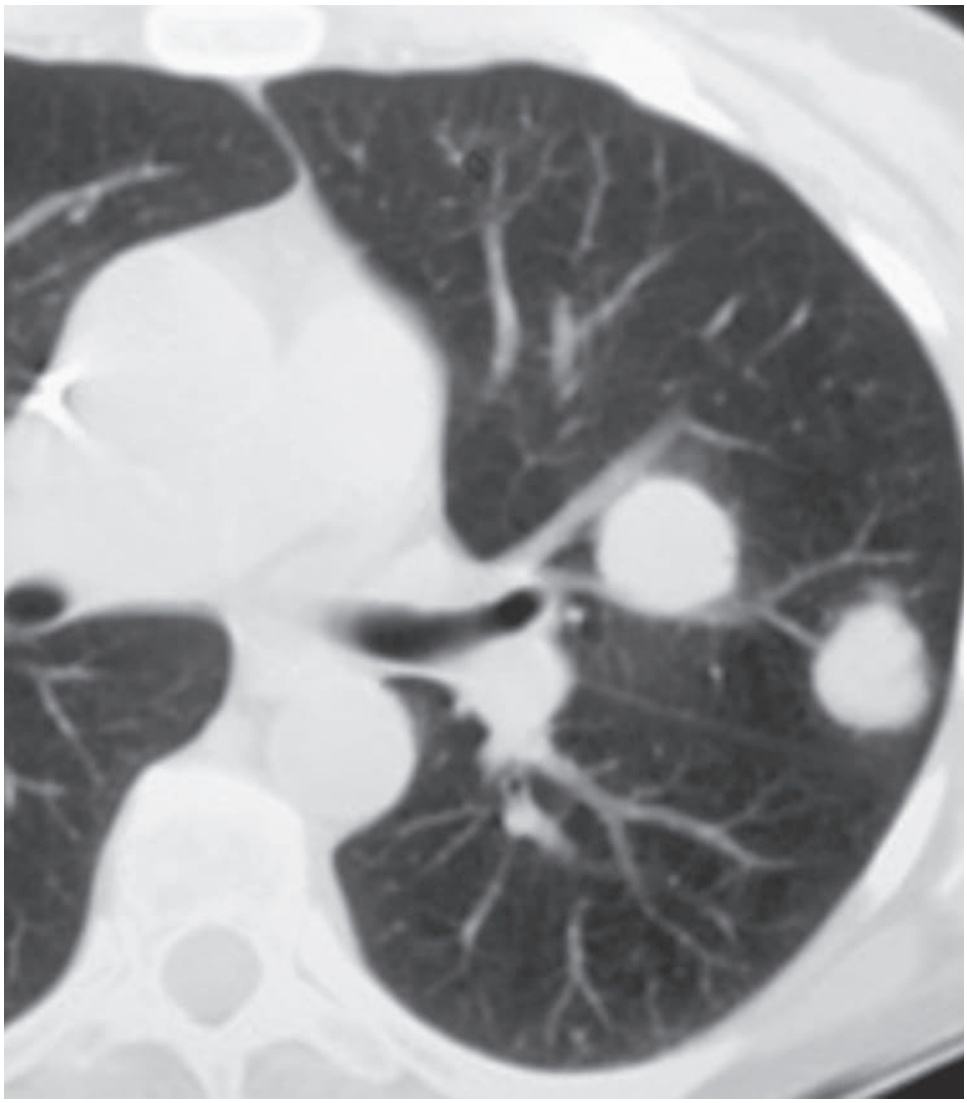
eFigure 123.30 Pulmonary Kaposi sarcoma: typical imaging appearance. (A) Frontal chest radiograph in an HIV-infected patient with a low CD4⁺ count shows multifocal, bilateral, perihilar bronchovascular thickening and nodularity. (B–D) Axial chest computed tomography displayed in lung windows shows patchy multifocal peribronchovascular nodular thickening (*arrowheads*). Note the presence of some patchy peribronchovascular ground-glass opacity (left upper lobe in B–C). (Courtesy Michael B. Gotway, MD.)



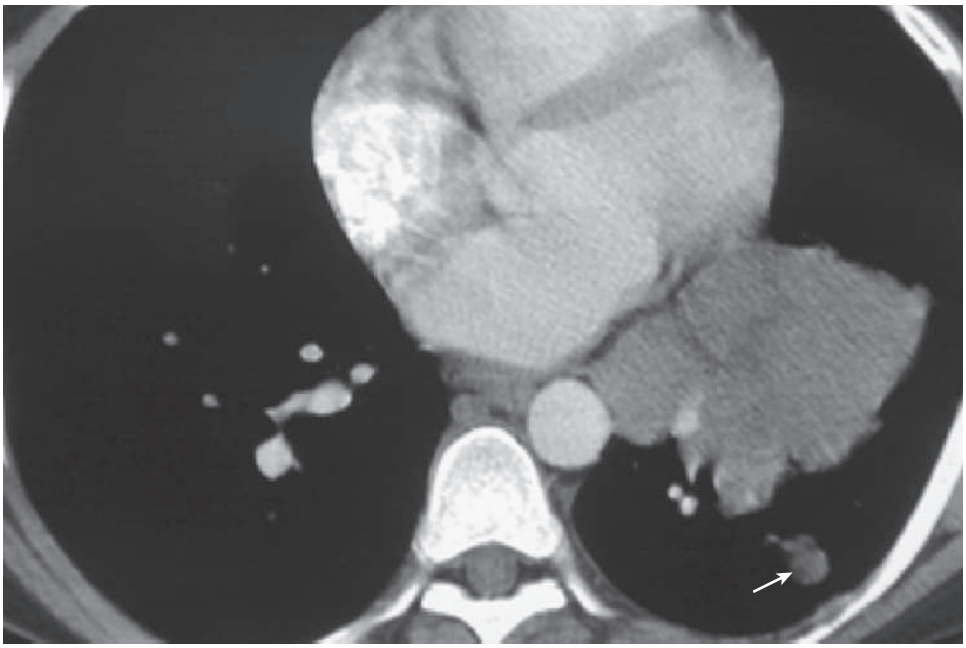
eFigure 123.31 Pulmonary Kaposi sarcoma: atypical imaging appearance. (A) Frontal chest radiograph in an HIV-infected woman with cardiomyopathy and a low CD4⁺ count shows cardiomegaly and a faint peripheral left lung nodular opacity (*arrow*). (B) Frontal chest radiograph 8 months after part A shows growth in the peripheral left lung opacity (*arrow*). (C) Axial chest computed tomography displayed in lung windows performed at the time of part B shows a subpleural, superior segment left lower lobe nonspecific nodule (*arrowhead*); this nodule was not calcified. Percutaneous transthoracic fine-needle aspiration and core lung biopsy was performed but was nondiagnostic. Surgical lung biopsy subsequently proved to be Kaposi sarcoma. (Courtesy Michael B. Gotway, MD.)



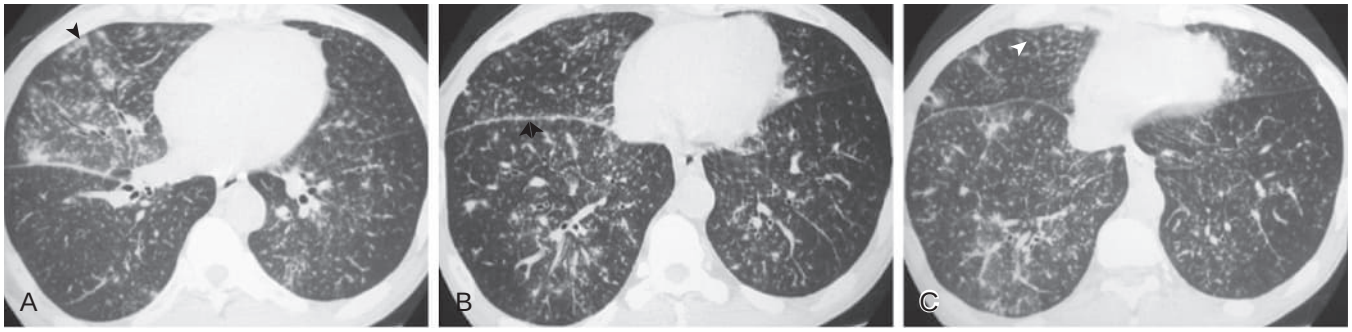
eFigure 123.32 Non-Hodgkin lymphoma in HIV infection: solitary nodule/mass. (A) Frontal chest radiograph in an HIV-infected patient with a low $CD4^+$ count shows an ill-defined left upper lobe nodule (*arrow*). (B) Frontal chest radiograph obtained 3 months after part A and after presumptive antimicrobial therapy shows that the left upper lobe lesion (*arrow*) has grown into a mass. (C) Axial chest computed tomography displayed in lung windows shows a poorly defined peripheral left upper lobe mass. Percutaneous transthoracic fine-needle aspiration and core lung biopsy showed non-Hodgkin lymphoma. (Courtesy Michael B. Gotway, MD.)



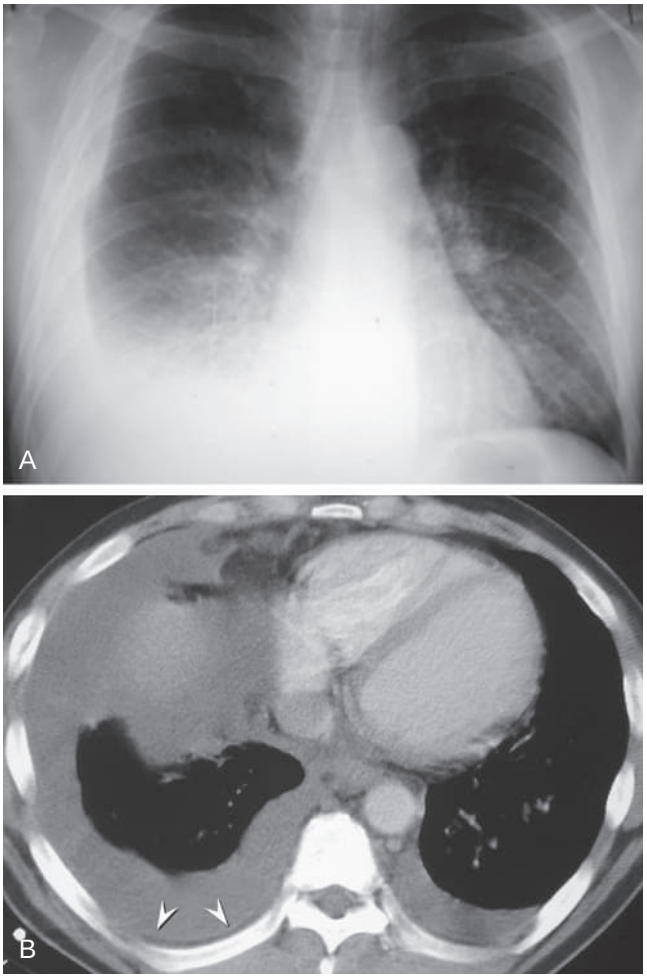
eFigure 123.33 Non-Hodgkin lymphoma in HIV infection: multiple nodules. Axial chest computed tomography performed in an HIV-infected patient with a low $CD4^+$ count displayed in lung windows shows two circumscribed, minimally lobulated left upper lobe nodules proven by percutaneous transthoracic fine-needle aspiration and core lung biopsy to be due to non-Hodgkin lymphoma. (Courtesy Michael B. Gotway, MD.)



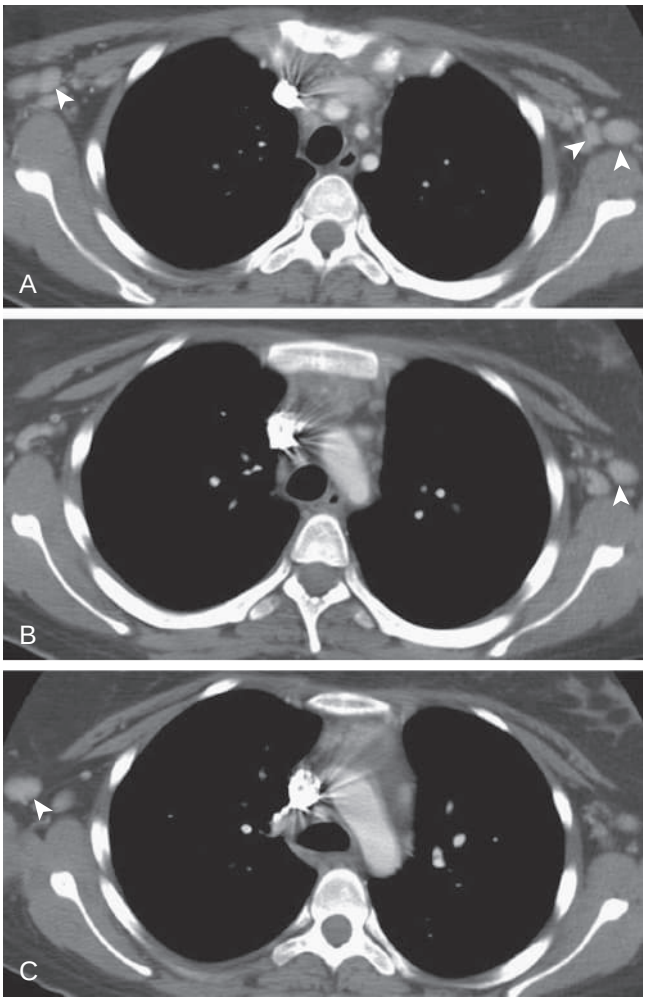
eFigure 123.34 Non-Hodgkin lymphoma in HIV infection: pulmonary mass. Axial chest computed tomography performed in an HIV-infected patient with a low $CD4^+$ count displayed in soft tissue windows shows a left lower lobe soft tissue mass proven by percutaneous transthoracic fine-needle aspiration and core lung biopsy to be due to non-Hodgkin lymphoma. An additional tumor nodule (*arrow*) is also present. (Courtesy Michael B. Gotway, MD.)



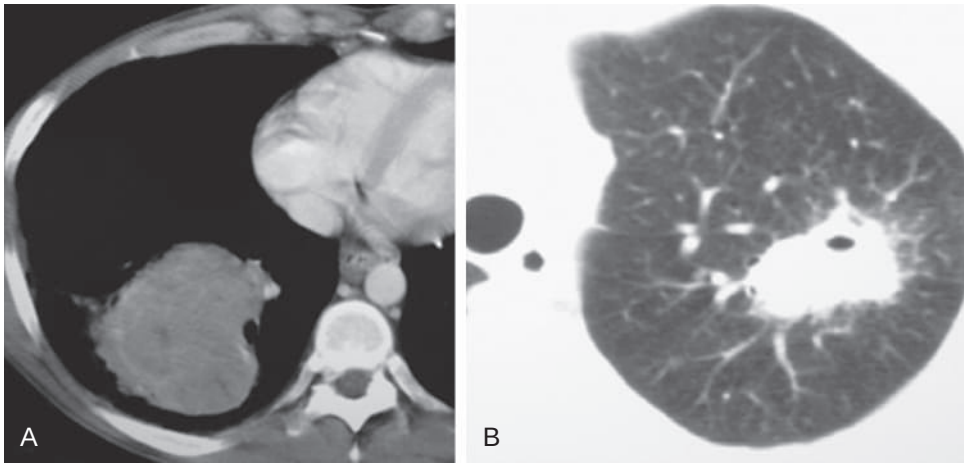
eFigure 123.35 Non-Hodgkin lymphoma in HIV infection: small nodules in a perilymphatic distribution. (A–C) Axial chest computed tomography performed in an HIV-infected patient with a low $CD4^+$ count displayed in lung windows shows innumerable small, well-defined nodules distributed along the fissures (*double arrowheads,* B), in the centrilobular region (*arrowhead,* A), and along mildly thickened interlobular septae (*arrowhead,* C). These nodules are located in the regions of pulmonary lymphatics; this small nodular pattern is referred to as a perilymphatic nodule distribution at high-resolution computed tomography. Bronchoscopy with transbronchial biopsy showed that these nodules were due to non-Hodgkin lymphoma. (Courtesy Michael B. Gotway, MD.)



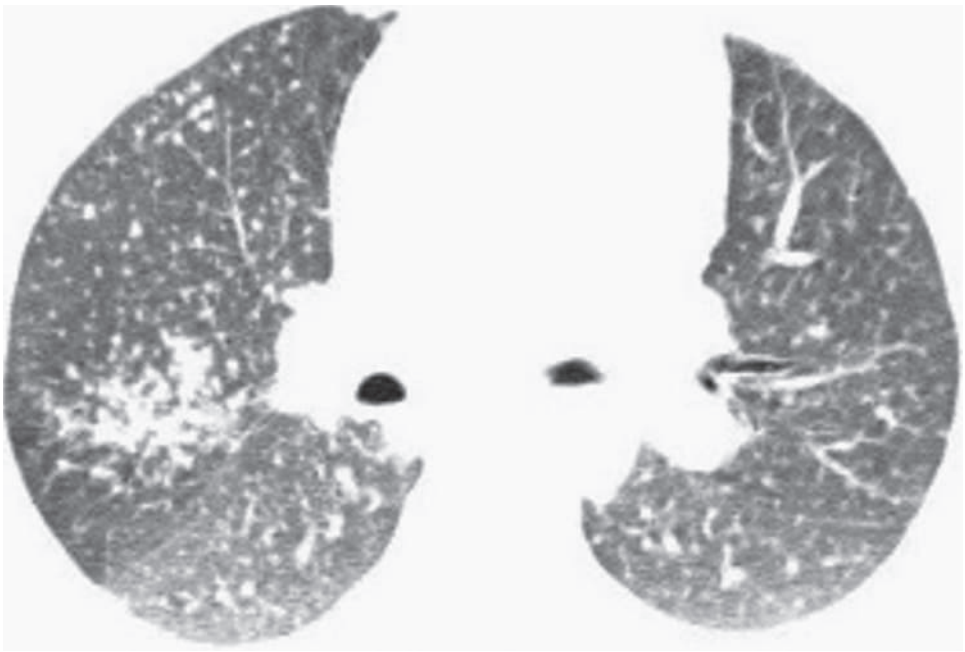
eFigure 123.36 Primary effusion lymphoma in HIV infection. (A) Frontal chest radiograph in an HIV-infected patient with a low $CD4^+$ count shows a right pleural effusion and moderate, right-greater-than-left linear interstitial thickening. (B) Axial enhanced chest computed tomography displayed in soft tissue windows shows bilateral pleural effusions; trace pleural thickening (*arrowheads*) may be present on the right. Thoracentesis showed the presence of lymphoma. (Courtesy Michael B. Gotway, MD.)



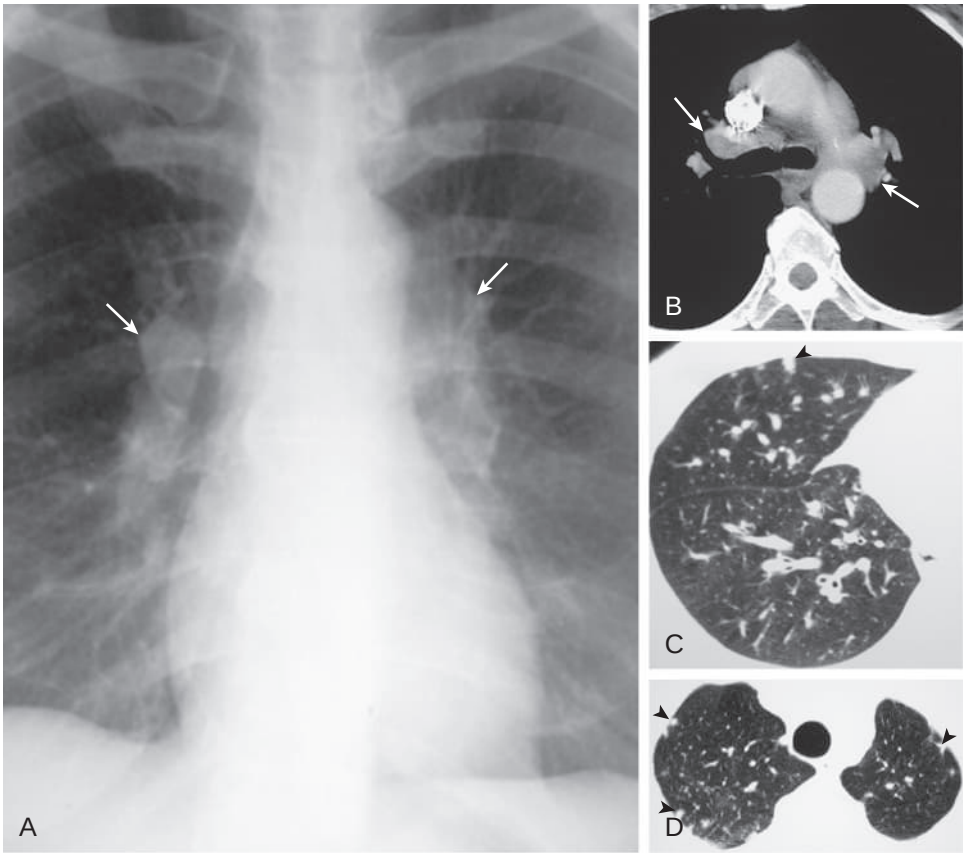
eFigure 123.37 Multicentric Castleman disease in HIV infection. (A–C) Axial enhanced chest computed tomography displayed in soft tissue windows performed in an HIV-infected patient with a low $CD4^+$ count shows bilateral, mildly enhancing axillary lymphadenopathy (*arrowheads*), proven to reflect Castleman disease on excision. (Courtesy Michael B. Gotway, MD.)



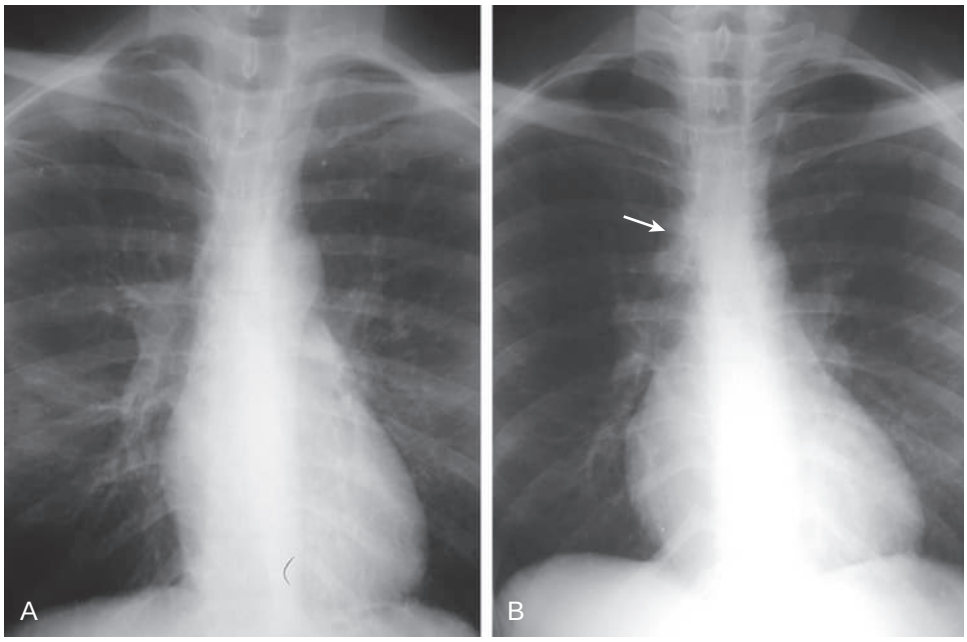
eFigure 123.38 Bronchogenic carcinoma in two patients with HIV infection. (A) Axial enhanced chest computed tomography shown in soft tissue and (B) lung windows shows bronchogenic carcinomas in two patients with HIV infection. The right lower lobe mass (A) represented large cell malignancy; the cavitary left upper lobe lesion (B) represented squamous cell carcinoma. (Courtesy Michael B. Gotway, MD.)



eFigure 123.39 Lymphocytic interstitial pneumonia in HIV infection. Axial chest computed tomography displayed in lung windows in a child with HIV infection shows multiple circumscribed small nodules proven on transbronchial biopsy to represent lymphocytic interstitial pneumonia. (Courtesy Michael B. Gotway, MD.)



eFigure 123.40 Sarcoidosis in HIV infection. (A) Frontal chest radiograph in an HIV-infected patient with a $CD4^+$ count greater than 200 cells/μL shows bilateral symmetrical hilar lymphadenopathy (*arrows*). (B) Axial enhanced chest computed tomography displayed in soft tissue windows shows bilateral lymph node enlargement (*arrows*). (C–D) Chest computed tomography displayed in lung windows shows the upper lobe predominant perilymphatic nodules (*arrowheads*) typical of sarcoidosis. (Courtesy Michael B. Gotway, MD.)



eFigure 123.41 Immune reconstitution inflammatory syndrome. (A) Frontal chest radiograph appears normal in an HIV-infected patient with a low $CD4^+$ count, in whom *Mycobacterium tuberculosis* was recently diagnosed. (B) Frontal chest radiograph performed 2 months after institution of combination antiretroviral therapy shows development of right paratracheal lymphadenopathy (*arrow*). (Courtesy Michael B. Gotway, MD.)

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124 PULMONARY COMPLICATIONS OF PRIMARY IMMUNODEFICIENCIES

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INTRODUCTION

Primary immune deficiency disorders (PIDDs) are genetic defects of the immune system that predispose individuals to infection, malignancy, and autoimmunity.[1,2] Most PIDDs are inherited but, in some disorders, such as *common variable immunodeficiency* (CVID), a family history may be absent. Furthermore, in some diseases, somatic mutations, not germline mutations, are the cause.[3]

The frequency of clinically important PIDDs is approximately 30 to 50 per 100,000 individuals.[4] Although PIDDs may manifest and be diagnosed in children, some PIDDs, such as CVID, commonly manifest in young adulthood, and approximately 20% of patients with CVID are diagnosed at 50 years of age or older. Therefore, older age should not be used to exclude the diagnosis of a PIDD, and most persons affected with PIDD are adults, not children.[5] Of the patients in the United States who are receiving *intravenous immune globulin* (IVIG), 23% are 30 to 44 years old, and 34% are 45 to 65 years old.[5] The increasing age of patients with PIDD is the result, in part, of improvements in recognition, diagnosis and treatment, and longer survival.[4]

A diagnostic evaluation for PIDD is often overlooked in the evaluation of patients with pulmonary infections. Early diagnosis and treatment of PIDD can reduce the morbidity and mortality associated with recurrent infections. For example, early *hematopoietic stem cell transplantation* (HSCT) (<3.5 months of age) results in dramatically improved outcomes in infants with *severe combined immunodeficiency* (SCID).[6,7] Treatment with high-dose IVIG or *subcutaneous immunoglobulin* (SCIG) can prevent many of the infectious sequelae in patients with primary antibody deficiency states.[8] Many routine childhood vaccines use attenuated, live organisms, and the use of such vaccines may lead to disseminated infections in patients with antibody or cellular immunodeficiencies and is therefore contraindicated.[9] Although early detection can improve outcomes, long delays in the diagnosis of PIDD are common.[10]

Respiratory tract infections are common in all types of PIDDs, and guidelines are available to aid in the evaluation of PIDDs in patients with pulmonary infections (Table 124.1, Fig. 124.1). Evaluation of the immune system is warranted in patients with two or more radiographically documented cases of pneumonia, a single infection of the lung with an opportunistic or unusual pathogen, or complicated pneumonia. A patient with a first pneumonia, but with a history of intractable sinus disease or recurrent gastrointestinal infection or with other disorders with increased frequency in patients with primary PIDD (e.g., autoimmunity, intractable eczema, unusual facies), should also be evaluated for a PIDD. Poor response to antibiotic therapy may also suggest an underlying PIDD.

The history and clinical presentation of patients with primary immunodeficiencies suggest the type of immunologic defect present (Table 124.2). Patients with antibody deficiencies, such as *X-linked agammaglobulinemia* (XLA), usually present after 6 months of age when maternal antibodies are no longer present. Recurrent and severe upper and lower

respiratory tract infections are the usual mode of presentation. In contrast, diseases associated with cellular immunodeficiencies usually begin in infancy or early childhood. Infections include disseminated and severe viral infections, as well as those caused by opportunistic or unusual pathogens such as nontuberculous mycobacteria, *Pneumocystis*, *Candida*, or other fungi. Diarrhea and malabsorption are common, and growth is delayed. Complement deficiencies may manifest in a manner similar to antibody deficiencies or with recurrent *Neisseria* sp infections. In contrast to patients with cellular immunodeficiencies, growth is usually not delayed in patients with complement or antibody deficiencies. Phagocyte defects such as chronic granulomatous disease (from *nicotinamide adenine dinucleotide phosphate* [NADPH] oxidase deficiency) may manifest with severe infection with catalase-positive organisms (*Staphylococcus, Pseudomonas, Klebsiella,* or *Serratia*).

A common misconception is that opportunistic pathogens cause most infections in patients with primary immunodeficiencies; actually, many infections in immunodeficient patients are with pathogens common in the community. In patients with PIDD, however, these infections may be of unusual severity and respond poorly to therapy. For example, recurrent infections with *Streptococcus pneumoniae* are frequent in patients with antibody deficiencies, complement deficiencies, *toll-like receptor* (TLR) signaling deficiencies (e.g., MyD88, *IL-1 receptor–associated kinase* [IRAK]-4), and mutations in *nuclear factor-κB essential modulator* (NEMO).[11] Although this chapter deals exclusively with PIDDs, it is essential to evaluate

Table 124.1 General Criteria That Warrant an Immunologic Evaluation

Chronic infections
Recurrent infections
Opportunistic or unusual pathogens
Unusual sites of infections
Incomplete clearing of infection
Poor response to antimicrobial therapy
Associated conditions (unusual facies, tetany, failure to thrive, intractable sinus infections, intractable diarrhea, thrush, intractable eczema, autoimmunity)

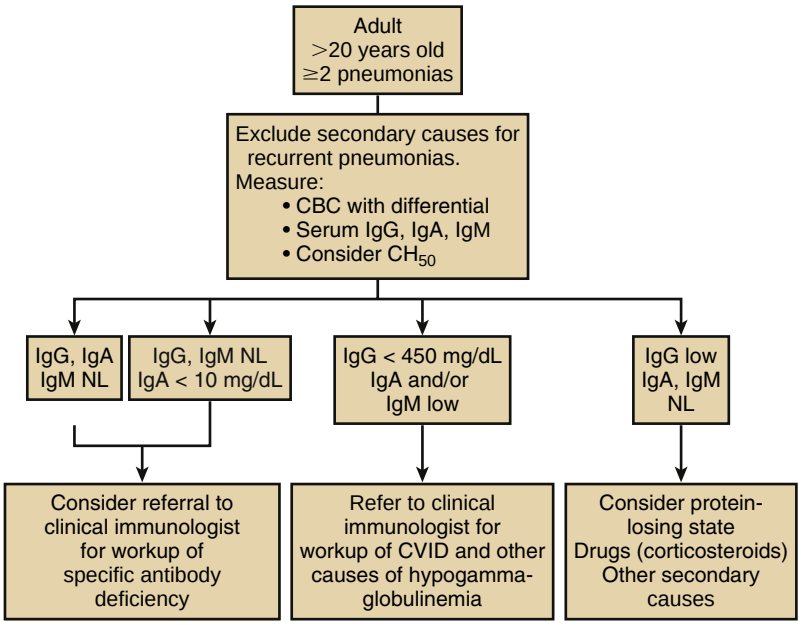

Fig. 124.1 Algorithm to screen adult patients with recurrent pneumonias for primary immunodeficiency. In an adult, with *common variable immunodeficiency* (CVID) as the most common diagnosis, a screening approach is shown. It would be unusual for an adult to present with a phagocytic defect or combined immunodeficiency; thus, antibody levels, *complete blood count* (CBC), and complement are appropriate for initial screening. An absent CH_{50} is consistent with complement deficiency and should result in referral to the clinical immunologist, whereas a low CH_{50} is consistent with complement consumption. Ig, immunoglobulin; NL, normal.

Table 124.2 Examples of Infections in Specific Primary Immunodeficiencies

Type Of Immunodeficiency	Example	Mode of Presentation
Antibody (humoral)	XLA, CVID	Upper and lower respiratory tract infections (encapsulated and atypical bacteria), giardiasis
Cellular (for clearance of intracellular organisms)	IFN-γ/IL-12/IL-23 axis	Atypical mycobacterial, *Salmonella,* and *Pseudomonas* infections, opportunistic infections
Combined (B cell and T cell)	SCID (multiple causes)	Opportunistic infections, upper and lower respiratory tract infections, thrush, intractable diarrhea, failure to thrive
Phagocyte	CGD	Recurrent abscesses (*Staphylococcus aureus, Burkholderia cepacia),* fungal infections (*Aspergillus* sp)
Complement	C5-C9	Recurrent *Neisseria meningitidis* infections

CGD, chronic granulomatous disease; CVID, common variable immunodeficiency; IFN, interferon; IL, interleukin; SCID, severe combined immunodeficiency; XLA, X-linked agammaglobulinemia.

Table 124.3 Screening Tests for Immune Function

Immune Function	Quantitative Assays	Functional Assays
Antibody immunity	Flow cytometry: $CD19^+$ or $CD20^+$ B cells	IgG, IgA, IgM, IgE levels* Specific antibody response to immunization*
Cellular immunity	CBC with differential* Flow cytometry for: $CD3^+CD4^+$ T cells $CD3^+CD8^+$ T cells $CD16^+CD56^+$ NK cells FISH for 22q11 and 10p11 deletion	Cutaneous delayed hypersensitivity T cell mitogen responses
Phagocyte	CBC with differential* Flow cytometry for: LFA-1 (CD18/CD11a) CD15	Oxidase function (DHR,* NBT) Enzyme assays (MPO, G6PD) Chemotaxis assays
Complement	C3, C4 Specific complement components Complement split products (C3a, C4a)	CH_{50} (classical pathway)* AH_{50} (alternative pathway)*

*Preferred initial screening tests.
CBC, complete blood count; DHR, dihydrorhodamine; FISH, fluorescence in situ hybridization; G6PD, glucose-6-phosphate dehydrogenase; Ig, immunoglobulin; LFA-1, lymphocyte function antigen 1; MPO, myeloperoxidase; NBT, nitroblue tetrazolium; NK, natural killer.

patients with recurrent or severe pulmonary infections for secondary immunodeficiencies or other medical conditions that compromise immunity (e.g., human immunodeficiency virus infection, lymphoproliferative disorders and malignancy, malnutrition, immunosuppressive drugs, protein-losing states, kidney failure, liver failure, heart failure, sickle cell disease, chronic liver disease, diabetes mellitus).

DIAGNOSTIC WORKUP

Readily available and inexpensive screening tests should be used in the initial evaluation of a patient with possible immunodeficiency (Table 124.3).[12,13] Abnormalities found in these screening tests indicate the need for additional studies in collaboration with a clinical immunologist. Genetic testing using either gene panels or whole-exome sequencing is increasingly used to make a definitive diagnosis; as the cost of DNA sequencing decreases, genetic testing may become the preferred strategy to diagnose PIDDs. The goal in the evaluation of immunodeficient patients is to define the causal genetic abnormality so that optimal treatment and prophylaxis can be provided.

ANTIBODY DEFICIENCIES

The quantitative measurement of immunoglobulin G (IgG), IgA, and IgM is the single best test to screen for primary antibody deficiencies, whereas low IgE levels are useful in evaluating patients with possible CVID.[14] Serum IgE levels are undetectable in more than 80% and are lower than the normal range in 90% of patients with CVID. In contrast, elevated IgE can raise the suspicion of an undiagnosed or undertreated atopic disease. Undiagnosed or inadequately treated asthma is a frequent cause for referral to clinical immunologists for recurrent respiratory tract infection.

The pattern of the levels of IgG, IgA, and IgM may provide insight into the etiology of antibody deficiency. For example, in steroid-induced hypogammaglobulinemia, IgG levels are usually moderately depressed (usually >400 mg/dL), and the magnitude of reduction reflects the dosage and duration of corticosteroid treatment,[15] whereas IgA and IgM levels tend to be preserved. In CVID, IgG levels are usually more profoundly depressed (<400 mg/dL); IgA levels are reduced (<10 mg/dL) in 90% of patients, and IgM levels are reduced (<25 mg/dL) in approximately 80% of patients.[14,16,17] Patients with CVID have a profound defect in their ability to make antigen-specific antibodies following immunization.[18]

The enumeration of B cells by flow cytometry using monoclonal antibodies directed against the CD19 or CD20 surface antigens may also provide clues to the type of B cell immunodeficiency. In X-linked and *autosomal recessive* (AR) agammaglobulinemia, B cells are usually severely reduced in number, whereas B cells are severely reduced or absent in only 10–15% of patients with CVID. It is important to obtain a careful medication history because agents such as rituximab, a chimeric monoclonal antibody directed against CD20, can lead to profound decreases in B cell numbers for months after treatment.

In assessing response to immunization, it is important to immunize with both a protein and polysaccharide antigen and to assess the response 4 to 6 weeks after immunization. The immunologic requirements to make antibodies (e.g., T cell help, cytokine requirements) in response to immunization with a protein or polysaccharide antigen differ. Some patients with normal quantitative immunoglobulins or selective IgA deficiency exhibit a selective inability to make antibody to polysaccharides, but not to protein antigens.[19] This immunologic defect (specific antibody deficiency) results in recurrent sinopulmonary infections and, in selected instances, may require replacement immunoglobulin therapy.

Protein antigens commonly used to assess specific antibody responses include tetanus and diphtheria toxoids. The *Haemophilus influenzae* type B (Hib) vaccine and the conjugated pneumococcal vaccines (Prevnar) use conjugates of the capsular polysaccharide (polyribose phosphate) to a protein carrier. Quantitation of antibodies to these vaccines measures competence of the immune system to make specific antibodies to a protein, not purely to polysaccharide antigens. Many adults have not been immunized to Hib, thus making the Hib vaccine particularly useful in the evaluation of this group of patients.

Polysaccharide antigens used to test antibody responses are available in two unconjugated vaccines: the pneumococcal polysaccharide (Pneumovax) and *Salmonella typhi* Vi polysaccharide vaccines. When using the pneumococcal vaccine, the measurement of antibody responses to several (12 or more) capsular antigens is indicated. There is considerable controversy about what constitutes a normal response to the pneumococcal vaccine, and a clinical immunologist should make the interpretation of specific

antibody responses.[20,21] Furthermore, there is substantial variability in the measurement of antibody responses to specific pneumococcal antigens among commercial laboratories. Therefore, prepneumococcal and postpneumococcal polysaccharide antibody titers should be obtained from the same laboratory.[22] When using the *S. typhi* vaccine, the interpretation of antibody response is a bit more clear. This is because, in contrast to the pneumococcal vaccine, most persons in the United States and other industrialized countries have not been immunized with the *S. typhi* Vi vaccine. Therefore, the specific antibody response is to a neoantigen, which makes interpretation of the results more straightforward. Furthermore, antibodies directed against the Vi polysaccharide are not present in commercially available immunoglobulin preparations in the United States, thereby allowing for the assessment of antibody response even during treatment with IVIG or SCIG.[23] Importantly, children younger than 2 years frequently do not make antibody responses to polysaccharide antigens. Thus, the use of polysaccharide vaccines to diagnose antibody-deficient states in this age group is not indicated.

CELLULAR IMMUNODEFICIENCY

Many patients with impaired cellular immunity have either reduced T cell numbers or abnormal T cell function, or both (see Table 124.3). T cell numbers are easily determined by flow cytometry. The CD3 antigen measures the total number of T cells, whereas CD4 and CD8 antigens are present on the T helper and T cytotoxic subsets, respectively. The pattern of abnormalities in the number of cells in specific lymphocyte subpopulations (T cells, *natural killer* [NK] cells, B cells) is helpful in guiding identification of the molecular abnormality in SCID (Table 124.4). In all forms of SCID and many other combined immunodeficiencies, the numbers of naive T cells are low. Therefore, the measurement of the numbers of naive ($CD3^+CD45RA^+$) and memory ($CD3^+CD45RO^+$) T cells is also essential in the global assessment of patients with possible PIDDs. T cell function can be assessed by testing cutaneous *delayed-type hypersensitivity* (DTH). In the DTH test, a small amount of an antigen is injected into the dermis, and a positive reaction is indicated by induration (>2 mm) 48 to 72 hours later at the site of the injection. Antigens such as tetanus toxoid, *Candida,* and *Trichophyton* may be used because most individuals will have had a prior immune response to these antigens. However, DTH responses are frequently absent in normal infants, so in vitro assays of T cell function are indicated in this group of patients instead. In many cases, T cell proliferation studies in response to mitogens such as phytohemagglutinin have replaced DTH responses because they are not substantially affected by age, are highly reproducible, and are easily obtained.

Table 124.4 Common Etiologies of Severe Combined Immunodeficiencies

Form of SCID	Prevalence	Absent Cell Type	Inheritance
Common γ chain IL-2 receptor deficiency	19%	T/NK	X-linked
IL-7R	12%	T	AR
ADA deficiency	10%	T/B/NK	AR
RAG1/RAG2	17%*	T/B	AR
JAK3	6%	T/NK	AR

*Total prevalence of patients with mutations in either the *RAG1* or *RAG2* gene.
ADA, adenosine deaminase; AR, autosomal recessive; IL, interleukin; JAK, Janus activating kinase; NK, natural killer; SCID, severe combined immunodeficiency.

PHAGOCYTE DEFICIENCIES

The initial screening test for phagocytic defects includes a complete blood count, with quantitation of leukocyte number and morphology (see Table 124.3). Functional studies of phagocytes include the *dihydrorhodamine* (DHR) or nitroblue tetrazolium tests, which measure the generation of superoxide free radicals; defects in these tests are seen in *chronic granulomatous disease* (CGD).[24]Advantages of the DHR test include its ease, rapidity, and reproducibility, along with the capacity to detect CGD carrier states; it is the preferred test and has largely replaced the nitroblue tetrazolium test. In the DHR test, phagocytes are loaded with the fluorescent dye DHR and are activated with phorbol myristate acetate. Activated phagocytes then produce superoxide free radicals that reduce DHR, thus leading to a change in fluorescence quantitated by flow cytometry. Other functional assays for phagocytes include enzyme assays for myeloperoxidase and glucose-6-phosphate dehydrogenase, chemotaxis assays, phagocytic tests, and bactericidal assays. Abnormalities in the adhesion molecules CD18 and CD15 that result in leukocyte adhesion deficiency 1 and leukocyte adhesion deficiency 2, respectively, can be detected by flow cytometry.

COMPLEMENT DEFICIENCIES

The screening tests for complement deficiency states associated with increased infections are the CH_{50} and AH_{50}, which measure the integrity of the classical and alternative pathways of complement activation, respectively (see Table 124.3).[25] The CH_{50} measures the volume (or dilution) of serum required to lyse 50% of the antibody-coated erythrocytes; AH_{50} is a similar measure testing the alternative pathway but without antibody opsonization. Abnormalities in CH_{50} or AH_{50} could result from inappropriate activation and consumption of complement or from deficiencies in individual components of complement. Often these possibilities can be distinguished by the measurement of two or more individual components (e.g., C3 and C4) of the classical or alternative complement pathway and the measurement of complement split products. Complement *consumption* is indicated by low levels of more than one component of complement, which may vary over time, and by the elevation of complement split products (C3a and/or C4a). The CH_{50} level in this instance is typically low, but not absent. In contrast, in complement *deficiency* states the CH_{50} level is zero with fixed, depressed levels of an individual member of the complement pathway without elevated levels of complement split products.

ANATOMIC DEFECTS

Other structural defects should be considered in a patient with recurrent sinopulmonary infections, particularly in a patient with a relatively normal immune workup. In patients with certain syndromes, such as DiGeorge syndrome or CHARGE syndrome (coloboma, heart defects, atresia choanae, growth retardation, genital abnormalities, and ear abnormalities), or in patients with neurologic impairment, recurrent aspiration pneumonias can mimic a primary immunodeficiency. In these cases, the pneumonias are typically dependent and basilar. Investigation of these patients may include a swallow study and pH probe analysis to detect gastroesophageal reflux. In addition, primary ciliary dyskinesia can be mistaken for a primary immune defect and should be considered in any patients with recalcitrant sinusitis, bronchiectasis, and recurrent pneumonias.[26] Ciliary biopsy with electron microscopy, genetic studies, and nasal and exhaled nitric oxide may suggest a ciliary defect, and treatment is similar to that in patients with cystic fibrosis.[26] Finally, any disease that affects the normal barrier function of the skin (e.g., eczema) or mucosal surfaces can lead to recurrent infections.

GENETIC TESTING

Over the past 10 years, advances in genetic sequencing technologies have allowed the description of a large number of PIDDs. There are currently more than 350 genetic defects that may affect the immune system and, with increased use of next-generation sequencing, unusual and surprising presentations of known PIDDs are being detected.[27] It is now easier, less expensive, and faster to screen for several hundred PIDDs with a single sequencing panel than to try to predict which PIDD is present in a patient with recurrent infections.[28] These panels, however, should be interpreted by an immunologist familiar with these diseases and with interpretation of genetic data. Benign variants of these genes are common, and their detection may lead to misdiagnosis and unnecessary laboratory evaluation and unnecessary intervention.

ANTIBODY DEFICIENCIES

One of the hallmarks of antibody, or humoral, immune deficiencies is recurrent respiratory tract infections, including sinusitis, bronchitis, bronchiectasis, and pneumonias.[29] Infections with encapsulated bacteria, such as *S. pneumoniae* and *H. influenzae,* are most common; infections with viruses, especially enteroviruses, also contribute. Chronic gastrointestinal infections, such as giardiasis, also accompany antibody deficiencies. Noninfectious pulmonary complications, such as granulomatous and interstitial lung disease or autoimmune cytopenias, may also be clues to an immunodeficiency.

X-LINKED AGAMMAGLOBULINEMIA

XLA (Bruton's agammaglobulinemia) is a primary antibody deficiency with an estimated frequency of 1 in 190,000 male births.[30,31] Mutations in the gene for Bruton's tyrosine kinase (*BTK*) are responsible for this immunodeficiency.[32] BTK is required for B cell receptor signaling through phosphorylation of phospholipase Cγ2 and other targets, and BTK is essential for the survival and differentiation of immature B cells. Nearly all patients with XLA have a marked deficiency in B cells (<2% of lymphocytes) and profound hypogammaglobulinemia. BTK is also expressed on myeloid cells and platelets but not on NK cells or T cells, and as many as 25% of patients with undiagnosed XLA and infection have concomitant neutropenia, which may contribute to the severity of infection.[33] T cell function is normal in XLA. XLA accounts for approximately 85% of inherited forms of agammaglobulinemia, with AR forms of agammaglobulinemia caused by mutations in *IGHM, IGLL1, CD79, BLNK, PIK3R1,* or *TCF3* accounting for the remainder.[32]

Small or absent tonsils and lymph nodes are the only characteristic physical findings in XLA. Most patients with XLA have recurrent upper (otitis media, sinusitis) and lower respiratory tract infections, with more than 50% of patients having recurrent infections by 1 year of age and nearly all patients symptomatic by the age of 5 years. The most common pathogens causing pneumonia are encapsulated bacteria (*S. pneumoniae* and *H. influenzae*).[30] Respiratory tract infections with atypical bacteria such as *Mycoplasma pneumoniae* or *Ureaplasma urealyticum* are also frequent. Gastrointestinal tract infections develop in nearly one-fourth of patients and are most commonly caused by *Giardia lamblia,* although bacteria (*Salmonella* sp, *Shigella* sp, *Campylobacter fetus, Helicobacter pylori*) and viruses (*Rotavirus,* enteroviruses) are other common causes. Disseminated infections that include encephalitis resulting from infection with enteroviruses, in particular echovirus, were formerly major causes of mortality in patients with XLA, although these infections are less frequent with use of high-dose immunoglobulin replacement therapy.[30]

The pulmonary complications of XLA or AR agammaglobulinemia, including bronchiectasis and right heart failure, are major causes of morbidity and mortality.[30] Complete pulmonary function tests and a *high-resolution computed tomography* (HRCT) scan of the chest are indicated in the initial evaluation of these patients. High-dose IVIG decreases pulmonary infections, but it may not prevent progression of bronchiectasis. Bronchiectasis, if detected, should be treated with daily pulmonary hygiene (e.g., inhaled β-agonists, hypertonic saline, chest physiotherapy) and aggressive antimicrobial therapy for intercurrent pulmonary infections. The efficacy of rotating antibiotics or long-term antimicrobial therapy in patients with bronchiectasis and immunodeficiency is unknown (see also Chapter 69).

IVIG and SCIG are the most commonly used forms of antibody replacement for treatment of XLA and CVID. Compared with IVIG, SCIG has fewer infusion-related and late-onset adverse reactions.[34] High doses of immunoglobulin (400 to 600 mg/kg per month) are superior in preventing infections compared with "conventional" doses of IVIG (100 to 150 mg/kg), and the optimal dose should be based on prevention of infection rather than level of IgG.[35,36] Intercurrent sinopulmonary infections should be aggressively treated with appropriate antimicrobial therapy to include coverage of common encapsulated bacteria and atypical bacterial pathogens (*Mycoplasma* sp, *Ureaplasma*).[37]

A pitfall in managing patients with antibody deficiencies (e.g., XLA, CVID) is that serologic assays in the diagnosis of infections can yield false-positive or false-negative results. With the exception of IgA and IgG subclass deficiency, patients with antibody deficiency typically do not make specific antibodies in response to exogenous antigens. Therefore, antibody studies to detect specific pathogens are unreliable. Diagnostic studies that detect microbial antigens or nucleic acids (polymerase chain reaction assays) and/or microbiologic cultures must be used in place of serologic assays.

COMMON VARIABLE IMMUNODEFICIENCY

CVID, also known as acquired hypogammaglobulinemia, is a primary immunodeficiency affecting approximately 1 in 20,000 to 50,000 live births.[38] CVID is a clinical syndrome representing a group of disorders that exhibit the common phenotype of abnormal antibody production and defective vaccine responses. Although variable, the mean onset of symptoms in patients with CVID is in the third decade of life. The diagnosis can be delayed up to 10 years after the onset of symptoms.[16,17,39,40] Unlike in XLA, T cell abnormalities are common in patients with CVID and contribute to the more protean clinical manifestations of this disease.[16,17] The diagnosis of CVID should be considered in any person older than 2 years with recurrent respiratory tract infections (e.g., two or more confirmed pneumonia cases).

The etiology of CVID is largely unknown, but multiple genetic mechanisms have been implicated. Heterozygous variants in *TACI* are found in approximately 5–10% of patients, and these variants increase the risk of developing CVID, whereas biallelic mutations always lead to CVID.[41–46] Other monogenic disorders that lead to CVID include mutations in *ICOS,* TNFRSF13C *(BAFF-R), CTLA4, LRBA, XIAP, SH2D1A,* and many others.[47] The presentation of these disorders can vary greatly, but they usually exhibit defective immunoglobulin levels and responses to vaccines. For example, genetic variants *CTLA4* and *LRBA* manifest with immune dysregulation and autoimmunity, whereas variants in *XIAP* and *SH2D1A* manifest with Epstein-Barr virus–driven lymphoproliferation, but all can have laboratory findings consistent with CVID.[48–50] Broad genetic screening (whole-exome sequencing or extensive genetic panels) should be considered in patients with CVID with an early onset and/or severe phenotype because monogenic defects will be found in more than 25% of such patients.

The definitive diagnosis of CVID requires demonstration of a low serum level of IgG (usually <450 mg/dL), low serum IgA and/or IgM, impaired capacity to make specific antibodies in response to immunization or infection, and the exclusion of other primary or secondary antibody deficiencies.[51] B cell subset analysis by flow cytometry is valuable in predicting risk to develop certain complications of CVID. Low numbers of switched memory B cells ($CD27^+$, IgM^-, IgD^-) in the peripheral blood are frequently found in patients with lymphoproliferation, splenomegaly, and systemic granulomatous disease involving the lungs and other organs.[17,52–54] T cell abnormalities are found in approximately 40% of patients and include anergy, T cell lymphopenia, and poor in vitro proliferative responses to mitogens and antigens.

Nearly all patients present with recurrent respiratory tract infections, including bronchitis, sinusitis, otitis media, and pneumonia. Common pathogens include encapsulated (*H. influenzae, S. pneumoniae*) or atypical (*Mycoplasma* sp) bacteria.[16,37,55] Pulmonary infections can also be caused by gram-negative rods, especially in patients with long-standing CVID or impaired cellular immunity. Opportunistic organisms cause fewer than 10% of infections in patients with CVID.[56] Apart from respiratory tract infections, bone and joint infections caused by these organisms have also been reported. Gastrointestinal tract infections with pathogens similar to those found in XLA (*Campylobacter jejuni, Salmonella* sp, *G. lamblia*) are also common.[16,57] More recently, norovirus has been implicated in the enteropathy associated with CVID.[58] The prevalence of hepatitis is increased in CVID and hepatitis is found in approximately 12% of patients. The prognosis of hepatitis C is poor, and the disease may be rapidly progressive in patients with CVID.

The mortality of CVID related to common infectious pathogens has declined with the increased use of high-dose immunoglobulin replacement.[8] Noninfectious complications of CVID, including chronic lung disease, malignancy, liver disease, and gastrointestinal tract disease, have now become risk factors for early mortality.[17] Although patients with CVID are unable to make antibodies to foreign antigens, they exhibit an increased propensity to make autoantibodies. Consequently, the prevalence of autoimmune disorders, in particular idiopathic thrombocytopenic purpura and autoimmune hemolytic anemia, is increased.[16,17]

Patients with CVID are at high risk for developing malignancy. In particular, the prevalence of non-Hodgkin lymphomas and gastric carcinoma is increased in CVID, and these cancers are major causes of morbidity and mortality.[59–61]

The pulmonary disorders associated with CVID are also major causes of mortality.[29,52,54,62–64] It is essential to screen patients with CVID with HRCT of the chest to define pulmonary disease because chest radiographs and pulmonary function tests are not sensitive to diagnose *interstitial lung disease* (ILD) or airways disease in patients with CVID. For example, HRCT of the chest detected ILD in 31% and bronchiectasis in 64% of patients with CVID, whereas pulmonary function tests and routine chest radiographs detected ILD or bronchiectasis in only 6% of patients.[65] Bronchiectasis is the most common pulmonary disorder in CVID, and it develops in more than 30% of patients. It is not clear whether early diagnosis along with globulin replacement therapy can prevent the development of bronchiectasis in patients with CVID.[40] Bronchiectasis in patients with CVID is managed with standard approaches including mobilization of pulmonary secretions through the use of medications such as hypertonic saline or β_2-agonists combined with chest physiotherapy and the long-term administration of macrolides.[66–68] Cryptogenic organizing pneumonia has also been described and appears to respond to corticosteroid therapy.[69,70]

Diffuse ILD, including granulomatous lung disease, lymphocytic interstitial pneumonia, follicular bronchiolitis, and bronchiolitis obliterans with organizing pneumonia (cryptogenic organizing pneumonia), develops in approximately 10–25% of patients with CVID; these disorders are refractory to IVIG therapy.[52,54,62–64,71]

The term *granulomatous-lymphocytic interstitial lung disease* (GLILD) is used to characterize the pulmonary disorder specific to CVID and monogenic CVID-like disorders. In comparison with sarcoidosis, GLILD exhibits a lack of spontaneous remission; a poor response to corticosteroid therapy; panhypogammaglobulinemia with low numbers of switched memory B cells; a high prevalence of autoimmune disease, in particular immune thrombocytopenia; a history of recurrent infections; and large areas of organizing pneumonia on biopsy.[72,73] Patients with GLILD and CVID frequently have hepatosplenomegaly with diffuse adenopathy, and they are at increased risk for developing non-Hodgkin lymphoma.[52,54,72] GLILD represents a multisystemic lymphoproliferative and granulomatous disease because granulomas are not limited to the lung but may be found in virtually any organ, including bone marrow, liver, spleen, and lymph nodes. In GLILD, HRCT demonstrates multiple abnormalities, including mediastinal adenopathy, ground-glass abnormalities, areas of consolidation, and small and large nodules. The parenchymal abnormalities in GLILD are typically in the lower lung zones (Fig. 124.2), a finding that contrasts with sarcoidosis, which is predominantly a micronodular, upper lung zone disease.[72,74]

The etiology of GLILD is unknown. However, increasing numbers of monogenic defects have been found in patients with CVID and GLILD, including mutations in *TACI*, *LRBA*, *CTLA4*, and *XIAP* and hypomorphic variants in *RAG1*.[29] Untreated GLILD can cause progressive pulmonary fibrosis (Fig. 124.3).[74]

In the diagnostic evaluation of patients with suspected GLILD or other forms of ILD, it is essential to obtain sufficient tissue to exclude the diagnosis of lymphoma and other parenchymal diseases. Video-assisted thoracoscopic surgery is currently the most definitive method to obtain the diagnosis. Cryobiopsy performed by bronchoscopy is a promising diagnostic modality, although definitive studies comparing the diagnostic sensitivity and specificity between thoracoscopic surgery and bronchoscopic cryobiopsy in the evaluation of ILD are lacking.

Corticosteroids are the most commonly used immunosuppressive agents in patients with GLILD.[75] However, disease relapse on discontinuation or weaning of corticosteroids is common, and it is unclear whether corticosteroids alter disease progression. A retrospective study of 39 patients with CVID and GLILD over 12 years showed that rituximab and antimetabolite therapy (azathioprine or mycophenolate mofetil) substantially improved the HRCT scores of the chest in over 90% of patients.[75a] Several measures of lung function also improved. Relapse-free survival was 57% at 5.4 years or longer. Damaging mutations in genes that predispose to the development of CVID (*TNFRSF13B*) or cause a CVID-like PID (*CTLA4, KMT2D, BIRC4*) were present in 21% of patients. The efficacy of rituximab and antimetabolite therapy was similar in patients with or without damaging mutations. Immunosuppression was tolerated well, and infections were uncommon (Fig. 124.4).[76] This approach has also been used successfully for pediatric patients.[77] Other treatments have included monotherapy with rituximab,[78] low-dose cyclosporine, tacrolimus,[79] and infliximab.[80]

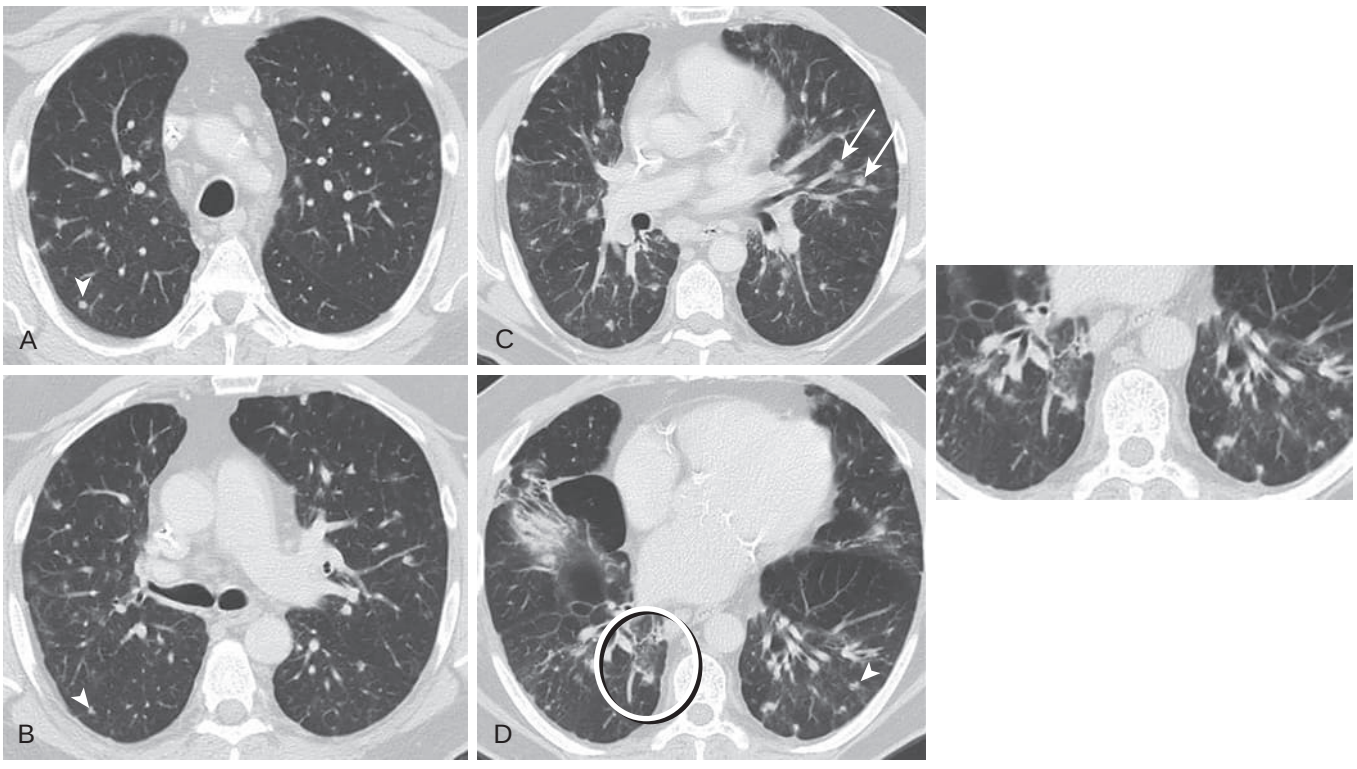

Fig. 124.2 Axial chest computed tomography showing typical features of granulomatous-lymphocytic interstitial lung disease. (A–D) Granulomatous-lymphocytic interstitial lung disease is characterized by the presence of larger nodules (*arrows*) and smaller nodules (*arrowheads*) and areas of ground-glass opacity (*circle*), with a somewhat lower lobe predominance. Nonspecific mediastinal lymph node enlargement is visible (in A and B). (Courtesy Michael B. Gotway, MD.)

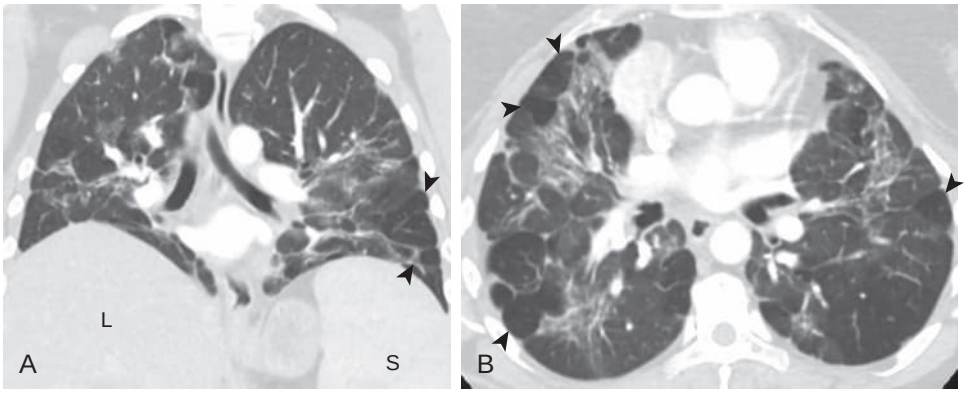

Fig. 124.3 Computed tomography in granulomatous-lymphocytic interstitial lung disease. (A) Coronal and (B) axial chest computed tomography in a patient with long-standing untreated granulomatous-lymphocytic interstitial lung disease. Imaging shows severe pulmonary fibrosis, manifesting as band-like linear opacities associated with architectural distortion and lobular low-attenuation areas of irregular air space enlargement (*arrowheads*). Hepatosplenomegaly is evident. L, liver; S, spleen. (Courtesy Michael B. Gotway, MD.)

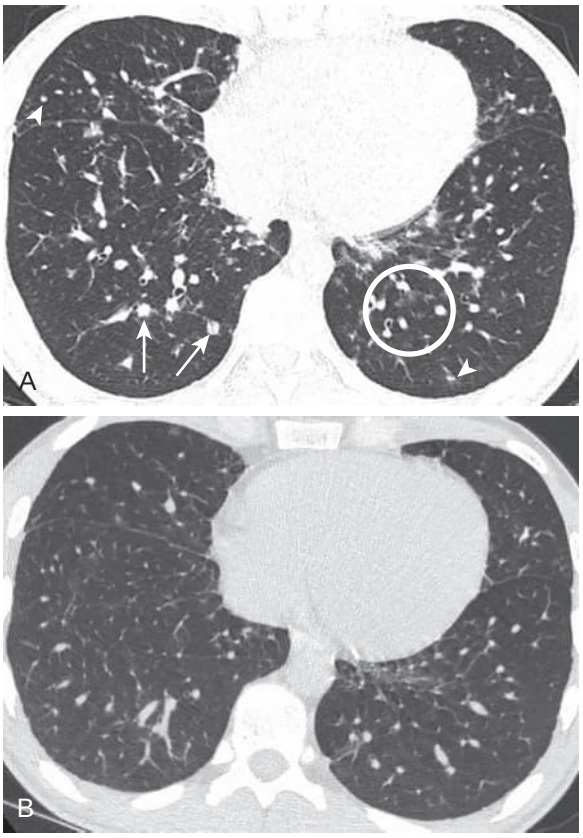

Fig. 124.4 Axial high-resolution of the chest of a patient with granulomatous-lymphocytic interstitial lung disease before and after treatment. (A) Computed tomography shows small nodules (*arrowheads*) and relatively larger nodules (*arrows*) and foci of ground-glass opacity (*circle*). (B) Following treatment with rituximab and azathioprine, there is marked improvement of the lung parenchymal findings. (Courtesy Michael B. Gotway, MD.)

The combination of hypogammaglobulinemia and thymoma is distinct from CVID and is known as Good syndrome.[81–83] Various immune abnormalities have been described in Good syndrome; the most common are hypogammaglobulinemia, absent or low numbers of B cells, and low numbers of $CD4^+$ T cells. Apart from thymoma and pulmonary infections, diffuse panbronchiolitis has also been described.[84] Importantly, thymoma is often not apparent on routine chest radiograph, a finding that reinforces the need to perform an HRCT scan of the chest on all patients with CVID or CVID-like disorders. Resection of the thymoma is recommended, although this does not resolve the immunodeficiency or autoimmunity.[81]

IMMUNOGLOBULIN A DEFICIENCY

The frequency of IgA deficiency varies among different ethnic groups, but the overall incidence may be as high as 1 in 400 live births.[85,86] The etiology of IgA deficiency remains obscure. Rarely, IgA deficiency may evolve into CVID, and familial cases of both IgA deficiency and CVID arise, suggesting a common genetic basis.[87] Medications, such as anticonvulsant agents, can cause IgA deficiency or hypogammaglobulinemia, and immunoglobulins may normalize with discontinuation of the drug.

There is considerable controversy about whether IgA deficiency alone predisposes to infection.[86,88] Most patients with IgA deficiency do not have increased frequency of infections, and the disorder is often discovered during an evaluation for problems unrelated to infection. However, some patients with IgA deficiency have recurrent infections, predominantly respiratory tract infections.[88] Certain of these patients may have a concomitant IgG subclass deficiency and/or deficiencies in mannose-binding lectin, and these abnormalities may contribute to their susceptibility to infection.[89] Unlike patients with more severe forms of antibody deficiency, such as CVID or XLA, antibody replacement is not warranted with isolated IgA deficiency. Indeed, patients with very low IgA levels are predisposed to adverse reactions to administration of IVIG because of the presence of anti-IgA antibodies in their circulation.[90] In patients with IgA deficiency and concomitant IgG subclass deficiency who have recurrent and persistent respiratory tract infections, determination of the antibody response following vaccination should be used to ascertain whether antibody replacement is warranted.[91]

Infectious complications associated with IgA deficiency include recurrent upper (otitis media, sinusitis) and lower respiratory tract infections, as well as gastrointestinal infections such as giardiasis.[88] The prevalence of atopic diseases (asthma, allergic rhinitis, eczema) and autoimmune diseases (systemic lupus erythematosus, celiac disease, rheumatoid arthritis) is increased in patients with IgA deficiency.[90]

SPECIFIC ANTIBODY DEFICIENCY

Specific antibody deficiency is a primary antibody deficiency disorder characterized by normal levels of IgG, IgA, and IgM but an inability to make specific antibodies, most commonly in response to purified polysaccharide antigens such as in Pneumovax.[19,92,93] Patients with specific antibody deficiency present with recurrent sinopulmonary infections, similar to other forms of hypogammaglobulinemia.

The diagnosis is made by demonstrating abnormal specific antibody responses following immunization with polysaccharide vaccines, most commonly the unconjugated pneumococcal vaccine. Cellular immunity is normal in this disorder. The initial treatment of specific antibody deficiency is similar to that of IgA deficiency; however, antibody replacement may be indicated in patients who have recalcitrant sinopulmonary infections and in whom more conservative treatment fails.

IMMUNOGLOBULIN G SUBCLASS DEFICIENCY

IgG subclass deficiency is defined by normal total serum IgG levels with a low level of one or more IgG subclasses. There are four isotypes of IgG in humans: IgG1, IgG2, IgG3, and IgG4. The predominant subclass is IgG1, accounting for more than 60% of the total IgG. In some patients evaluated for recurrent sinopulmonary infections, low levels of one of the IgG subclasses are found. However, the significance of IgG subclass abnormality is unclear[94,95] because IgG subclass deficiencies, including genetic deletions of IgG subclass loci, have been found in healthy individuals.[96] Because the clinical significance of isolated IgG subclass deficiencies is unclear, the measurement of IgG subclasses is not warranted in the initial evaluation of patients with recurrent sinopulmonary infections. In patients whose isolated IgG subclass deficiency is associated with recurrent infections, antibody replacement should be considered if the antibody response to vaccination is defective.

HYPER–IMMUNOGLOBULIN M SYNDROME (B CELL INTRINSIC)

Hyper-IgM syndrome (HIGM) is a descriptive term that reflects abnormalities in serum quantitative immunoglobulin levels (high serum IgM level with low serum IgA and IgG levels), which is found in several otherwise dissimilar types of immunodeficiencies (Table 124.5).[97] Despite the name, high levels of IgM are an inconsistent feature of HIGM.[30,98] Grouping these distinct immunodeficiencies together, some of which are intrinsic B cell abnormalities and others of which are complex combined cellular and humoral immunodeficiencies, can lead to diagnostic confusion. Nevertheless, the classification remains widely used. Although we group HIGM under "predominantly antibody deficiencies," only mutations in *activation-induced cytidine deaminase (AICD)* or *uracil nucleotide glycosylase (UNG)*, which are selectively expressed in B cells, result in a pure antibody deficiency. The other forms of HIGM, which are more severe, are complex cellular and humoral immunodeficiencies (CD40 deficiency, CD40-L deficiency, NEMO), and are discussed in the combined immunodeficiency section of this chapter.

Mutations in *AICD* or *UNG*

Mutations in *AICD*[99] or *UNG*[100] are causes of AR forms of HIGM. AICD and UNG are essential for class switch recombination,[101] hence, mutations result in high serum levels of IgM, with low serum levels of IgG and IgA. Patients with mutations in either *AICD* or *UNG* have a similar clinical phenotype with impaired humoral immunity and intact cellular immunity,[102] resulting in recurrent upper and lower respiratory tract infections and gastrointestinal tract infections. Lymphadenopathy is frequent, and autoimmunity (autoimmune hemolytic anemia and idiopathic thrombocytopenic purpura) develops in approximately 20% of patients.

Table 124.5 Etiologies of Hyper-IgM Syndrome

Mutation	Inheritance	Clinical Phenotype
CD40L	X-linked	Abnormal cellular immunity, neutropenia in 50%, early onset, recurrent sinopulmonary infections, *Pneumocystis jirovecii* pneumonia, chronic diarrhea from *Cryptosporidium* infection, diarrhea, inflammatory bowel disease, autoimmunity
CD40	Autosomal recessive	Similar to CD40-L mutation
NEMO (IKK-γ) or *IKBA (IκBα)*	X-linked (NEMO) Autosomal dominant (IKBA)	Impaired cellular immunity, variable serum levels of IgM or IgA, ectodermal dysplasia (most), recurrent pyogenic infections, viral infections, mycobacterial infections
AICD or *UNG*	Autosomal recessive	Impaired humoral immunity, normal cellular immunity, later age of onset than other types of hyper-IgM syndrome, increased autoimmunity and lymphadenopathy
Unknown	Variable	Similar to *AICD/UNG* mutations

AICD, activation-induced cytidine deaminase; Ig, immunoglobulin; IKBA, IκBα; IKK, IκB kinase; NEMO, nuclear factor-κB essential modulator; UNG, uracyl nucleotide glycosylase.

DEFICIENCY IN BOTH CELLULAR IMMUNITY AND ANTIBODY PRODUCTION (COMBINED IMMUNODEFICIENCIES)

Combined immunodeficiencies are so named because they have features of antibody deficiencies and defects in cell-mediated immunity. These patients present with respiratory and gastrointestinal tract infections similar to patients with antibody deficiencies, but they also present with opportunistic infections (e.g., viruses, *Pneumocystis*, mycobacterial disease). These patients tend to be chronically ill, may have growth problems, and can have manifestations of autoimmunity.

HYPER–IMMUNOGLOBULIN M SYNDROME (COMBINED)

X-Linked Hyper-IgM Syndrome

The *X-linked form of hyper-IgM syndrome* (XHIGM), which accounts for approximately two-thirds of cases of all forms of HIGM, results from a mutation in the CD40 ligand (CD40-L) gene.[102,103] Mutations within the CD40 gene are a rare cause of AR HIGM, which has a clinical phenotype similar to that of XHIGM.[104] CD40-L is expressed on activation of CD4 T cells and interacts with CD40, which is expressed on the surface of B cells. The interaction of CD40 on B cells with CD40-L on activated T cells in conjunction with specific cytokines (e.g., *interleukin*

[IL]-4, IL-21) is required for immunoglobulin class switching. Consequently, mutations in CD40-L (or CD40) result in a failure to class switch, thereby leading to defective production of IgG, IgA, and IgE and to increased levels of IgM. CD40 is also expressed on monocytes and dendritic cells, and the lack of CD40-L T cell interaction with CD40 on monocytes and dendritic cells leads to decreased production of IL-12 with a decreased generation of *type 1 T helper* (Th1) cells and impaired cellular immunity.[105,106] In patients with XHIGM, serum levels of IgG are consistently low, and serum levels of IgA are reduced in the majority of patients. Serum levels of IgM are high in approximately 50% of patients.[103] Antibody responses to immunization show a weak IgM response, without development of IgG- or IgA-specific responses and the absence of immunologic memory. The numbers of switched memory B cells ($CD27^+$, IgD^-, IgM^-) are extremely low.[107] Neutropenia is found in approximately 50% of patients and may require treatment with *granulocyte colony-stimulating factor* (G-CSF). Intrinsic neutrophil defects, including impairment of the respiratory burst and decreased microbicidal activity, are also common in XHIGM.[107]

Patients with XHIGM have recurrent infections beginning early in life. More than one-half of patients with XHIGM are diagnosed by the age of 1 year and nearly all by 4 years of age. Pneumonia, frequently caused by infection with *Pneumocystis jirovecii,* is common, seen in as many as 80% of patients. Sinusitis, otitis media, and other respiratory tract infections are also common. Intractable diarrhea, sometimes caused by infection with *Cryptosporidium*, develops in nearly one-third of patients. Infection of the central nervous system (encephalitis, meningitis), frequently from infection with echovirus, is a major cause of morbidity and mortality. Pulmonary alveolar proteinosis has been described in XHIGM,[108] likely the result of abnormalities in alveolar macrophage function. Treatment of XHIGM includes antibody replacement, prophylaxis against *P jirovecii*, and treatment with G-CSF for neutropenia. HSCT is increasingly the treatment of choice for XHIGM, although it remains unclear whether transplantation improves mortality.[109]

Mutations of NF-κB Essential Modifier

Hypomorphic mutations within the *NF-κB essential modulator* (*NEMO*) gene, an X-linked gene, cause an immunodeficiency characterized by recurrent pyogenic infections, increased susceptibility to mycobacterial infections, and variable B cell and T cell abnormalities.[110,111] NEMO, also known as IKK-γ, is part of the *IκB kinase* (IKK) complex. IKK is responsible for phosphorylating the inhibitor of NF-κB (IκBα), thereby releasing NF-κB and allowing for its nuclear translocation. The protean immunologic and clinical manifestations of mutations in *NEMO* reflect the importance of NF-κB in multiple biologic processes. Approximately 80% of patients with mutations in *NEMO* have ectodermal dysplasia (abnormal teeth, decreased numbers of sweat glands, fine hair, frontal bossing). The ectodermal dysplasia in these patients is caused by the inability of the ectodysplasin A receptor to induce activation of NF-κB. The susceptibility to mycobacterial infection is likely the result of an inability of CD40 ligation to activate the NF-κB pathway, thus leading to deficient IL-12 production by monocytes and dendritic cells and deficient interferon (IFN)-γ production by T cells and NK cells.[112]

Results of common immunologic screening tests of immune function may be normal in up to 40% of patients with NEMO deficiency. Hypogammaglobulinemia or decreased specific responses to vaccination are found in approximately 60% of patients, and a high serum level of IgM is found in only 15% of patients. NK cell function has been reported to be abnormal in all patients with mutations in *NEMO,* and NK cell function determination may be a helpful adjunctive screening test for this disorder.[111,113]

Patients with *NEMO* mutations have severe infections usually beginning early in life. Common sites of infection include the lung, sinuses, middle ear, skin, and deep tissues (abscesses), bloodstream, gastrointestinal tract, and central nervous system. Pyogenic infections are frequently caused by *Staphylococcus aureus, S. pneumoniae,* and *H. influenzae,* and they are observed in nearly 90% of patients. Mycobacterial infections (pneumonia, cellulitis, lymphadenitis, osteomyelitis) are seen in more than 40% of patients and are usually caused by *Mycobacterium avium-intracellulare.* Severe viral infections (encephalitis, gastroenteritis, viremia) develop in approximately 20% of patients. Herpesviruses (herpes simplex virus, cytomegalovirus) and adenoviruses are the most frequent viral pathogens. Opportunistic infections with *P. jirovecii* or fungi develop in 10% of patients. Autoimmune disease—in particular inflammatory colitis—manifests in approximately 20% of patients and can lead to intractable diarrhea. Treatment of patients with *NEMO* mutations includes immunoglobulin replacement and antimicrobial prophylaxis (*Pneumocystis,* mycobacteria). HSCT is increasingly performed in these patients but may not improve the inflammatory bowel disease.[114]

Combined Hyper-IgM Syndrome Caused by Other Mutations

Mutations in genes whose products act in the CD40-L to CD40 and related pathways also cause HIGM with combined cellular and antibody deficiencies. These include mutations in CD40, *phosphatidylinositol 3-kinase catalytic delta* (PIK3CD), *phosphatidylinositol 3-kinase regulatory subunit 1 alpha* (PIK3R1), *inducible T cell co-stimulator* (ICOS), and certain DNA repair proteins.[115] These forms of HIGM are rare and have clinical manifestations comparable in severity to those of XHIGM.

SEVERE COMBINED IMMUNODEFICIENCY

SCID is a syndrome that encompasses a variety of molecular defects that result in absent or severely impaired T cell and B cell number and function.[116,117] One commonly used method to classify SCID is based on whether the molecular defects decrease the numbers of T, B, and/or NK cells (see Table 124.4). The molecular defects that lead to SCID include mutations that cause abnormalities in cytokine signaling (e.g., the common γ chain of the IL-2 receptor; Janus activating kinase 3 [JAK3], or IL-7 receptor) and T cell receptor signaling (e.g., CD45, ZAP-70, CD3ζ, CD3ε, CD3δ), defective T cell and B cell receptor gene recombination (e.g., *RAG1, RAG2*), defective nucleotide salvage pathway (*adenosine deaminase* [ADA] deficiency), and defects in the expression of major histocompatibility complex class I or class II molecules. X-linked SCID, caused by the mutation in the *common γ chain of the IL-2 receptor* ($IL2R\gamma_c$), is the most common form of SCID. $IL2R\gamma_c$ is used by the receptors for IL-2, IL-4,

IL-7, IL-9, IL-15, and IL-21. Consequently, the immunodeficiency resulting from mutation of the IL2Rγ_c is caused by the combined effects of loss of function of these cytokine receptors. Atypical forms of SCID may also result from mutations of genes associated with classical SCID that are *hypomorphic*, meaning that the mutation leads to a protein with reduced function. One such example is Omenn syndrome, which has clinical manifestations including severe skin disease (erythroderma, granuloma, desquamation), hepatosplenomegaly, lymphadenopathy, and high IgE levels.[118]

The clinical presentation of SCID is characterized by severe infections, most commonly of the respiratory and gastrointestinal tract, in early infancy. Infections are caused by common and opportunistic pathogens, and disseminated infections are frequent. Pneumonitis caused by cytomegalovirus, adenovirus, respiratory syncytial virus, or *Pneumocystis* can be the presenting sign and should be investigated in infants, particularly if they have other manifestations of the syndrome, including oral thrush, persistent diarrhea, and impaired growth. Engraftment of maternal T cells in an infant with SCID can lead to graft-versus-host disease. The prompt treatment of infection, administration of IVIG, and prophylaxis against *P. jirovecii* are indicated until HSCT can be performed. In the event blood transfusions are needed, only irradiated, cytomegalovirus-negative blood should be used. Live, attenuated vaccines should not be given to infants with known or suspected SCID.

Early diagnosis and treatment by HSCT (<3.5 months of age) of SCID lead to a markedly improved prognosis.[6] Population-based screening of newborns for SCID was implemented in Wisconsin in 2008, and now all states screen newborns for SCID because it is included in the Uniform Panel of newborn screening tests recommended by the U.S. government.[119,120]

In the absence of newborn screening, such as with immigrants or other populations that may be resistant to newborn screening, the lack of a thymic shadow on chest radiograph and severe lymphopenia (<2500/μm) in an infant with recurrent infections should prompt further studies to evaluate the diagnosis of SCID. The diagnosis of SCID is confirmed by enumerating lymphocytes and subsets of naive T cells, B cells, and NK cells by flow cytometry and abnormal proliferation of T cells to mitogens.

HSCT is the preferred treatment for SCID, except for SCID caused by ADA deficiency, where ADA enzyme replacement is also efficacious. Gene therapy for X-linked SCID and SCID caused by ADA deficiency has resulted in immune reconstitution, and gene therapy for ADA-induced SCID is now approved by the European Medicines Agency.[107,121–123] The retroviral vectors used in earlier studies of gene therapy resulted in insertional mutagenesis with activation of the proto-oncogene *LMO-2* leading to γδ T cell leukemia in some patients. Current trials of gene therapy for SCID use self-inactivating lentiviral vectors, which appear safer in trials to date.[124]

COMBINED IMMUNODEFICIENCIES OR SYNDROMIC IMMUNODEFICIENCIES

Certain immunodeficiencies involve genes whose products have functions beyond the immune system, including in development. Many of these immunodeficiencies are associated with characteristic anatomic anomalies and dysfunction in other organ systems.

DIGEORGE SYNDROME

DiGeorge syndrome (DGS), also known as 22q11.2 deletion syndrome or velocardiofacial syndrome, is one of the most common primary immunodeficiencies, found in approximately 1 in 3000 live births. Most patients with DGS have hemizygous deletion of varying degrees in chromosome 22q11.2, with rare cases caused by deletion of 10p13. The molecular basis for many of the clinical manifestations of DGS appears to be deletions or mutations in *TBX1*, a T-box transcription factor important in embryonic development.[125] Other genes are thought to contribute to the phenotype in DGS because patients with identical deletions of 22q11.2 may have markedly different clinical phenotypes. Patients with DGS exhibit characteristic facies, including hypertelorism (wide spacing of the eyes), saddle nose, shortened philtrum, and low-set ears.[126] Other common features of DGS include hypoplasia of the thymus and parathyroid glands, cardiac abnormalities, velopharyngeal insufficiency, speech delay, developmental delay, and behavioral and psychiatric problems. The velopharyngeal insufficiency may contribute to the risk of aspiration pneumonia. Nearly 90% of infants diagnosed with DGS have cardiac abnormalities, and screening for DGS should be considered in an infant with any form of congenital heart disease, especially for those forms associated with DGS, such as interrupted aortic arch, truncus arteriosus, tetralogy of Fallot, and anomalous aortic arch, with or without a ventral septal defect.[126]

The immunodeficiency associated with DGS is highly variable and correlates with the degree of thymic hypoplasia.[126] Patients with *complete* DGS, comprising less than 0.5% of DGS patients, have a profound deficiency of T cells, similar to patients with SCID, and require thymic transplantation.[127] In contrast, most patients with DGS are referred to as having *partial* DGS. Patients with partial DGS may have moderately diminished numbers of T cells, and T cell defects in these patients are usually mild, with relatively normal in vitro and in vivo assessment of T cell function. Intact thymic function is essential for deletion of autoreactive T cells and the production of T regulatory cells. Consequently, patients with DGS have an increased prevalence of autoimmune disorders, including juvenile arthritis, autoimmune hemolytic anemia, and immune thrombocytopenia.[128] Studies of humoral function have yielded conflicting results, and abnormalities in humoral immunity requiring immunoglobulin replacement therapy are infrequent in DGS.[129]

Most patients with DGS tolerate live virus vaccines without complications, but an assessment of humoral and cellular immune function should be performed before administration of these vaccines. Infectious complications of partial DGS usually include recurrent sinopulmonary infections and otitis media. Structural and functional abnormalities of the palate may contribute to recurrent sinus disease and aspiration pneumonia in these patients. Opportunistic infections other than oral and esophageal thrush are infrequent in partial DGS. Patients with complete DGS are highly susceptible to infection with opportunistic pathogens, thus reflecting the much more severe

cellular immunodeficiency. In these patients, attenuated, live virus vaccines should be avoided, and irradiated blood products should be used to avoid graft-versus-host disease until thymic transplantation can be accomplished.

WISKOTT-ALDRICH SYNDROME

Wiskott-Aldrich syndrome (WAS) is an X-linked disorder characterized by recurrent infections, eczematous skin disease, and thrombocytopenia caused by a mutation in the *WAS protein (WASp)* gene.[130,131] The function of WASp is complex, but through its interaction with a variety of adaptor molecules and kinases, WASp is involved in the integration of cytoplasmic signaling with the reorganization of the actin cytoskeleton. WASp is critical in the formation of immunologic synapses (i.e., the molecular interface between lymphocytes and target cells or antigen-presenting cells), cellular motility, cellular trafficking, and protection against autoimmunity.[130,131] Mutations in the WASp gene cause four distinct diseases: (1) classic WAS, (2) X-linked thrombocytopenia, (3) intermittent thrombocytopenia, and (4) congenital X-linked neutropenia without other features of WAS.

The laboratory evaluation of patients with WAS usually demonstrates increased levels of serum IgE and IgA with a low level of IgM and a normal level of IgG. Despite normal serum IgG levels, antibody responses following immunization to polysaccharide antigens are consistently impaired.[131] T cell and NK cell function is frequently abnormal, resulting in a partial combined immunodeficiency.[132] Decreased platelet counts, platelet function, and platelet size are hallmarks of the disorder and lead to the marked bleeding diathesis.

The clinical expression of WAS includes prolonged bleeding episodes beginning in infancy, recurrent pyogenic infections, autoimmunity, eczematous dermatitis, and an increased prevalence of Epstein-Barr virus–related lymphomas. Upper and lower respiratory infections caused by encapsulated organisms (*S. pneumoniae* and *H. influenzae*) are common and reflect the inability of patients with WAS to make specific antibodies to polysaccharide antigens. Pulmonary infections with opportunistic pathogens (*P jirovecii,* herpesviruses) are also common. Infection and hemorrhage are frequent causes of death. The treatment of WAS includes aggressive treatment of intercurrent infections and immunoglobulin replacement.[130,131] Thrombocytopenia usually responds to splenectomy. HSCT is the treatment of choice for WAS, with long-term survival rates higher than 70%.[130,131] Gene therapy using a lentiviral vector to introduce a normal WAS gene into hematopoietic stem cells has been used in patients lacking a suitable stem cell donor, with satisfactory short term outcomes.[133,134] Interim analysis of an ongoing study examining this approach has revealed that it is safe and corrects the hematologic and immunologic abnormalities.[135]

ATAXIA-TELANGIECTASIA

Ataxia-telangiectasia (AT) is an AR disorder caused by a mutation in the *AT* gene, which is involved in the repair of DNA breaks.[136,137] The clinical manifestations of AT include neurologic dysfunction (cerebellar ataxia, oculomotor apraxia, delayed motor development), telangiectasias, and immunodeficiency. Elevated levels of carcinoembryonic antigen and alpha-fetoprotein are present in nearly all patients with AT. The mutation in the AT gene leads to an increased radiosensitivity and the increased incidence of malignancies such as lymphomas and epithelial tumors. Serum immunoglobulins are usually normal in AT, but selective IgA deficiency and impaired responses to polysaccharide antigens are common. Patients with AT develop recurrent sinopulmonary infections either because of the immunodeficiency or as a result of a swallowing dysfunction, usually in infancy or early childhood. Lung involvement can reflect recurrent infections and bronchiectasis, recurrent aspiration related to worsening neurologic status, or ILD, which develops in approximately 20% of patients with AT.[136–138] The optimal treatment of the ILD in AT is not known, although corticosteroids have been used with some success.[138] Even though there is no definitive treatment of AT, antibody replacement has been used in patients to prevent the infectious complications.

HYPER–IMMUNOGLOBULIN E SYNDROME

Hyper-IgE syndrome (HIES), also known as Job's syndrome, is a syndrome characterized by recurrent skin and lung infections, severe eczema, and elevated levels of serum IgE. There are two forms of HIES. The more common *autosomal dominant* (AD) form of HIES is caused by mutations in the transcription factor *signal transducer and activator of transcription-3* (STAT-3) and has extraimmunologic features (connective tissue disorders, skeletal abnormalities) not present in the AR forms that result from variants in *PGM3* or *DOCK8*.[139–142] Biallelic mutations in the transcription factor *ZN341*, which regulates STAT-3 transcription, also results in a phenotype similar to the AD form of HIES.[143]

The most common AR form of HIES is caused by mutations or large deletions in the gene coding for the *dedicator of cytokinesis 8* (DOCK8), a protein involved in intracellular signaling.[144,145] DOCK8 deficiency is characterized by cutaneous viral infections (human papillomavirus, molluscum contagiosum), and neurologic complications, but it lacks the characteristic facies present in the AD form of HIES.[145,146] Biallelic mutations in *PGM3*, which is involved in glycosylation of proteins, causes an immune deficiency with severe atopy and neurologic abnormalities.

The clinical features of HIES appear in early infancy and include moderate to severe eczema, eosinophilic pustular folliculitis, skin abscesses, mucocutaneous candidiasis, and recurrent cases of pneumonia with pneumatoceles.[140,147] Pneumatoceles are thought to be a consequence of disordered healing following primary infection of the lung. Common primary pathogens in HIES syndrome include *S. aureus, S. pneumoniae, H. influenzae,* and *Candida albicans*. Secondary infection of the pneumatoceles with *Aspergillus* sp or *Pseudomonas aeruginosa* may lead to invasion of the pulmonary vasculature leading to pulmonary hemorrhage or central nervous system infection, which are major causes of death.[147,148] The signs and symptoms of serious infection are frequently absent in patients with HIES. Abscesses may develop without signs of external inflammation (cold abscess), or pneumonia may be present with limited clinical symptoms. Bronchopulmonary fistula leading to empyema

may form following pulmonary surgery performed to manage the complications of HIES.[149]

Patients with AD HIES have a characteristic facies (coarse facial features with a protuberant mandible and forehead, hypertelorism, and a broad, fleshy nasal tip), retained primary teeth, severe osteopenia with fractures following minimal trauma, scoliosis, and hyperextensible joints.[150] In addition, patients with HIES have a proclivity to develop aneurysms, particularly of the coronary arteries.[151]

The diagnosis of HIES cannot be made by routine assays of immunologic function. Typical abnormalities in the laboratory evaluation of patients with HIES include an elevated IgE (>2000 IU/mL) and eosinophilia. These laboratory abnormalities are not pathognomic of HIES and may be present in patients with severe atopic dermatitis. Elevated levels of serum IgE may wane with age, and a normal IgE level does not exclude the diagnosis of HIES.

An understanding of the molecular pathogenesis of HIES was significantly advanced with the discovery that mutations in the *STAT3* gene are the cause of this disorder. [139] The *STAT3* gene codes for a transcription factor essential for the biologic activities of numerous cytokines, including IL-6 and IL-10.[152] The absence of the anti-inflammatory effects of IL-10 likely contributes to the dysregulated inflammatory response seen in HIES patients.[153] IL-6 is required for the genesis of $CD4^+$ Th17 cells in humans, and Th17 cells are therefore deficient in HIES.[154] Th17 cells are important in the defense against extracellular bacteria and fungi.[155]

The treatment of HIES focuses on the prevention and prompt treatment of infection. Antimicrobial prophylaxis is often given to prevent infection with *S aureus*. The role of antifungal prophylaxis is unknown. Optimal skin care, including the use of bleach baths, topical corticosteroids, and hydrating measures for eczema, is essential. Antibody replacement, antimicrobial prophylaxis, and IFN-γ may benefit some patients.[156,157] HSCT of the STAT-3 form of HIES improves the immunodeficiency but does not necessarily improve the extraimmunologic features, including preexisting pneumatoceles.[158] HSCT for the AR-HIES caused by DOCK8 deficiency results in a marked improvement of the immunodeficiency and is now considered the treatment of choice.[146,159]

PHAGOCYTE DISORDERS

There are several clinical indications for evaluation for phagocyte abnormalities, including neutropenia or the lack of neutrophilia with significant infection, infections with unusual or opportunistic pathogens (e.g., fungi such as *Aspergillus;* bacteria such as *Serratia marcescens, Burkholderia cepacia,* or *Nocardia*), unusual sites of infection (e.g., recurrent osteomyelitis, abscesses in the brain, lung, or liver), systemic bacterial infections, recurrent skin infections, upper or lower respiratory tract infections, and cold abscesses.[160] Apart from infection, patients with phagocyte defects may have ongoing chronic inflammatory responses in the skin (e.g., eczematoid dermatitis) or mucous membranes (e.g., periodontitis, aphthous stomatitis) and disordered inflammatory responses leading to delayed or abnormal wound healing.

DEVELOPMENTAL DEFECTS IN NEUTROPHILS

Cyclic neutropenia is an AD disorder caused by mutations in the gene for *neutrophil elastase-2 (ELA2)*. It is thought that mutations of *ELA2* induce premature apoptosis of neutrophil precursors by induction of the unfolded protein response.[161,162] In cyclic neutropenia, there is a regular, 21-day fluctuation of neutrophils and other blood components (platelets, monocytes, reticulocytes). During periods of neutropenia, patients are predisposed to bacterial infection with pyogenic bacteria and opportunistic pathogens. The diagnosis of cyclic neutropenia should be suspected when neutropenia coincides with recurrent infections.

Congenital agranulocytosis (Kostmann syndrome) typically appears in early infancy with life-threatening infections such as cellulitis, meningitis, perirectal abscesses, pneumonia, or sepsis. Patients with congenital agranulocytosis have severe neutropenia with an absolute neutrophil count of less than 200 cells/mm^3. The clinical manifestations of congenital agranulocytosis are more severe than those of cyclic neutropenia. Most cases of congenital agranulocytosis are AR, resulting from mutations in the gene for *HAX1*, a mitochondrial protein thought to protect myeloid cells against apoptosis.[163] Other causes of congenital neutropenia include mutations in *WASp, GFI*, and *G6PC3*.[27,163] Administration of G-CSF is indicated in cyclic neutropenia and congenital agranulocytosis because it is effective in increasing neutrophil counts and reducing infection in the majority of patients with these disorders. In patients with severe neutropenia unresponsive to G-CSF, HSCT should be performed.[164]

LEUKOCYTE ADHESION DEFICIENCY

The influx of leukocytes, including neutrophils, to sites of infection involves production and release of neutrophils from the bone marrow, activation of neutrophils by chemotactic factors with subsequent adhesion of neutrophils to the endothelium, and transmigration of neutrophils through the endothelium of postcapillary venules. The first step in the egress of neutrophils from the circulation to sites of infection is mediated by the rolling (loose) adhesion of neutrophils to endothelium, mediated predominantly by CD15s (sialyl $Lewis_x$) on the neutrophil and its counter-ligands (E-selectin, P-selectin) on the endothelium. The following step in adhesion, which is of higher affinity, is mediated predominantly by the interaction of the integrin *leukocyte function–associated antigen* (LFA-1; CD11a/CD18) on the leukocyte with its counter-ligand intracellular adhesion molecule-1 on the endothelium. Integrins are composed of two subunits (α, β) which are non-covalently associated. The common β chain (CD18) associates with CD11a (LFA-1), CD11b (Mac-1 or CR3), CD11c (gp150/95), and CD11d, which are expressed on a variety of leukocytes. Therefore, mutations in CD18 reduce the cell surface expression of CD11a/CD18, CD11b/CD18, and CD11c/CD18, resulting in defects in the endothelial adhesion of all leukocytes. Defects in CD18 and CD15s lead *to leukocyte adhesion deficiency type I* (LAD-I) and *LAD*

type II (LAD-II), respectively.[165,166] LAD type III, a rare AR disorder, is caused by a mutation in the gene encoding kindlin-3, a member of a protein family that may regulate integrin function.[167,168]

LAD-I is divided into two broad categories based on whether the deficiency of LFA-1 is severe (<0.5% of normal levels) or moderate (5–10% of normal levels).[169] Patients with a complete deficiency in LFA-1 expression present in the neonatal period with delayed separation of the umbilical cord, infection of the umbilical cord (omphalitis), and severe infections of the skin, gingiva, gastrointestinal, and upper and lower respiratory tracts. Moderate deficiencies of LFA-1 result in a milder phenotype, with delayed diagnosis. Patients with LAD-I exhibit neutrophilia, even in the absence of systemic infection, because of the inability of leukocytes to adhere to the endothelium. The definitive diagnosis of LAD-I deficiency is made by the demonstration of low levels of LFA-1 on neutrophils by flow cytometry. The treatment of LAD-I includes the aggressive use of antimicrobials in the treatment of infection. HSCT is the only definitive treatment for patients with severe deficiencies of LFA-1.[170]

LAD-II is an extremely rare disorder characterized by developmental delay, mental retardation, and recurrent infection similar to LAD-I. A mutation in the guanosine diphosphate–fucosyl transporter leads to the absence of CD15s on leukocytes and expression of the Bombay blood phenotype.[171]Oral fucose administration can induce the expression of CD15s, leading to improvement of the central nervous system abnormalities and decreased infection,[172] although this has not been successful in all patients with LAD II. LAD III is characterized by a profound bleeding tendency, recurrent bacterial and fungal infections, and failure to form pus despite marked leukocytosis.[166–168]

CHRONIC GRANULOMATOUS DISEASE

CGD is a rare (1 in 200,000) immunodeficiency caused by mutation in one of the four subunits of the *phagocyte NADPH oxidase* (PHOX; NOX2) system.[173] The function of NADPH oxidase is to transfer an electron to molecular oxygen (O_2), leading to the formation of superoxide.[174,175] Approximately two-thirds of cases of CGD are X-linked as a result of mutations in the g91phox subunit of NADPH oxidase.[176,177] Mutations of the other subunits of NADPH oxidase (p22, p47, p67) are AR and account for the remainder of cases.[173]

The clinical manifestations of CGD usually begin early in life (mean age of onset, 4.4 years) but they may not manifest until adulthood.[173,176] CGD is characterized by recurrent infections with catalase-positive organisms (*Aspergillus* sp, *S. aureus, B. cepacia,* and others). Tuberculosis is common in CGD patients where tuberculosis is endemic, and vaccination with live, attenuated bacille Calmette-Guérin can cause local and disseminated infection.[178] Residual NADPH oxidase function, which is more common in AR forms of CGD, leads to a milder phenotype, delayed onset of disease, and longer survival.[179,180] Pneumonia and skin infections are the most common infections, but osteomyelitis, liver abscesses, lymphadenitis, and anorectal infections are also frequent.[173] Aerosolized exposure to organic dust can lead to fulminant fungal pneumonia termed "mulch pneumonitis" and may be the presenting manifestation of CGD, especially the AR forms.[181,182] Prolonged antimicrobial or antifungal therapy, often in conjunction with systemic corticosteroids, is necessary to treat many of the infectious complications of CGD.[176,183,184] The most common chest computed tomography abnormalities include areas of consolidation and nodular opacities, both associated with either infection or granulomatous inflammation.[173,185,186] Invasive aspergillosis is the most common primary cause of death. Autoimmune diseases appear to be increased in CGD, and most patients develop inflammatory colitis. Carriers of X-linked CGD are at increased risk for discoid lupus, photosensitivity, and inflammatory bowel disease.[187] Carriers with skewed X-inactivation that results in less than 10% of neutrophils with a normal respiratory burst may have a clinical phenotype similar to X-linked CGD.[188] The diagnosis of CGD is readily made by the DHR test for phagocyte NADPH oxidase function.

Apart from infectious complications, disordered inflammation and wound healing are hallmark manifestations of the disease.[183,189] Inflammatory granuloma formation may lead to urinary or gastrointestinal tract obstruction, which is treated by systemic corticosteroids. Noninfectious, granulomatous ILD also can be seen.[190] Exuberant granulation tissue leads to disordered wound healing, including wound dehiscence following surgical procedures. The molecular basis for the disordered inflammatory response characteristic of CGD is complex. Comparison of global gene expression of normal and X-linked CGD neutrophils indicate that CGD neutrophils constitutively overproduce proinflammatory mediators and exhibit defective apoptosis resulting from the overproduction of the antiapoptotic protein Bcl-xl.[191] Additionally, on apoptosis, CGD neutrophils do not properly externalize phosphatidylserine, the ligand that enables macrophages to recognize and clear apoptotic cells.[192] Consequently, there is a delay in the removal of apoptotic CGD neutrophils by macrophages.[193] The deficiency in uptake of apoptotic cells may also lead to decreased production of anti-inflammatory mediators such as transforming growth factor-β, thereby contributing to the overproduction of inflammatory cytokines.[183] Thus, the increased production of proinflammatory mediators, reduced apoptosis, and delayed clearance of apoptotic neutrophils all likely lead to the disordered inflammatory response in CGD.

Therapy of CGD includes aggressive treatment of infection, including early surgical incision and drainage.[194] Prophylactic administration of trimethoprim-sulfamethoxazole markedly reduces infection, especially infections caused by *S. aureus.*[195] Prophylactic itraconazole reduces serious fungal infections.[196] Interferon-γ reduces infections and decreases mortality in both X-linked and AR CGD, although the utility of IFN therapy has been questioned.[197,198] HSCT is the preferred treatment for CGD when an appropriate donor is available.[199] Gene therapy using γ-retroviruses in patients with X-CGD resulted in only a short-lived improvement in immunity, likely because of a lack of a

selective advantage of stem cells harboring the transduced gene, and it was complicated by retroviral insertional mutagenesis leading to myelodysplasia. Further refinements in gene therapy for CGD are needed to make this a viable therapeutic option.[200]

GATA-2 DEFICIENCY

An AD inherited deficiency in GATA-2 underlies a unique combined immunodeficiency.[201–207] This rare disorder is also known as "dendritic cell, monocyte, B and NK cell deficiency," familial myelodysplasia/leukemia with lymphedema, or MonoMac (monocytopenia with *Mycobacterium avium* complex).

As the many names illustrate, the clinical manifestations, which usually appear in adolescence or adulthood, are diverse. The immunologic features include a loss of dendritic cells, monocytes, NK cells, and B cells. Patients may develop pulmonary alveolar proteinosis not associated with anti–granulocyte-macrophage-CSF antibodies (see Chapter 98). Opportunistic infections with nontuberculous mycobacteria, usually *M. avium* complex, are common. Infection with human papillomaviruses leads to warts, increased carcinomas in situ, and cervical carcinoma. The bone marrow typically shows cytogenic abnormalities, fibrosis, megakaryocyte dysplasia, and cytopenias, and leukemia may develop. The monocytopenia may precede the clinical manifestations by years. HSCT is the only known cure for the disorder.[208]

MENDELIAN SUSCEPTIBILITY TO MYCOBACTERIAL DISEASE

Th1 cells are defined by their capacity to produce high levels of cytokines (IL-2, IFN-γ, tumor necrosis factor-α) essential in the generation of a robust cellular immune response. Interferon-γ, which is also produced by NK cells, interacts with a heterodimeric receptor, *IFN-γ receptor 1* (IFN-γR1), the ligand-binding subunit, and *IFN-γ receptor 2* (IFN-γR2), which is required for downstream signaling. On ligand binding by IFN-γR1/R2, the *Janus kinases 1 and 2* (JAK1 and JAK2) are activated, which phosphorylate the STAT-1 protein in the cytoplasm, thus leading to homodimerization of STAT-1, translocation to the nucleus, and transcriptional activation of STAT-1–dependent genes. One important biologic function of IFN-γ is to induce the production of IL-12 p70 by dendritic cells and macrophages, a positive feedback loop to induce more production of IFN-γ by NK cells and T cells. IL-12 p70 is composed of two disulfide-linked subunits, p35 and p40, the latter of which also associates with the p19 subunit to form IL-23. The *IL-12 receptor* (IL-12R) is composed of two subunits, IL-12Rβ1 and IL-12Rβ2. IL-12Rβ1 also serves as part of the heterodimeric IL-23 receptor (IL-12Rβ1 and IL-23R). Thus, the IFN-γ/IL-12/IL-23 axis is intrinsically linked by the biologic functions of IFN-γ and IL-12, the shared cytokine subunit of IL-12 and IL-23 (p40), and the common cytokine receptor subunit of IL-12R and IL-23R (IL-12Rβ1).

Table 124.6 Etiologies of Mendelian Susceptibility to Mycobacterial Disease*

Gene	Inheritance	Defect	Patients With MSMD	Treatment
IFNγR1	AR/AD	C/P	39%	AR-C: HSCT AD-P: IFN-γ
IFNγR2	AR	C/P	4%	AR-C: HSCT AR-P: IFN-γ
STAT1	AD	P	5%	Varies depending on location of mutation
IL12B	AR	C	9%	IFN-γ
IL12Rβ1	AR	C	40%	IFN-γ
NEMO (IKK-γ)	X-linked	P	3%	HSCT

*Rare cases of MSMD caused by mutations in *ISG15* (AR) or *IRF8* (AD/AR) have been found.

AD, autosomal dominant; AR, autosomal recessive; C, complete deficiency; HSCT, hematopoietic stem cell transplantation; IFN, interferon; MSMD, mendelian susceptibility to mycobacterial disease; P, partial deficiency.

Mutations of the genes including *IFN-γR1* or *IFN-γR2*, *STAT-1*, *IL-12B*, *IL-12Rβ1*, and *NEMO* (see earlier discussion) define a group of primary immunodeficiencies known as *mendelian susceptibility to mycobacterial disease* (MSMD) (Table 124.6).[27,209] Given the marked heterogeneity in inheritance, the functional consequences of mutations in these 6 genes (complete or partial) leads to 13 distinct genetic disorders associated with MSMD. Patients with mutations in one of these six genes are susceptible to infection with *Mycobacteria* and/or *Salmonella*, but they are usually resistant to infections with most other pathogens.[210,211] This narrow susceptibility to infection in humans is somewhat surprising given the importance of Th1 responses in combating infection with a wide variety of pathogens in studies using mice.

AR complete IFN-γR1 deficiency is characterized by infection with environmental mycobacteria, including rapid growers such as *Mycobacterium fortuitum*, and *Salmonella*, at an early age (<3 years). Without treatment with HSCT, the disorder is fatal. AD partial IFN-γR1 deficiency has a much less severe phenotype, with a mean age of onset at 13 years of age. These patients are susceptible to infection with environmental mycobacteria and may develop disseminated disease following vaccination with bacille Calmette-Guérin. Additionally, patients with partial IFN-γR1 deficiency are predisposed to mycobacterial osteomyelitis, a complication that should trigger an evaluation for this disorder. AR complete IFN-γR2 deficiency and AR partial IFN-γR2 deficiency are rare, and the described phenotype to date is similar to AR complete IFN-γR1 deficiency and AD partial IFN-γR1 deficiency, respectively. The phenotype of patients with a STAT-1 mutation varies depending on the site of the mutation in the gene.

AR complete mutations of IL-12B result in a markedly increased susceptibility to infection with *Salmonella* in addition to mycobacterial disease. Similarly, AR complete IL-12Rβ1 deficiency, which is the most common

cause of MSMD, also results in an increased susceptibility to infection with mycobacteria and *Salmonella.* Patients with deficiency in IL-12B and IL-12Rβ1 are also susceptible to mucocutaneous candidiasis.[212,213] The clinical phenotype of AR complete IL-12Rβ1 deficiency is milder than complete defects in IFN-γR1 or IFN-γR2 and only a few patients succumb to disease. Interferon-γ is useful in the treatment of patients with either IL-12B or IL-12Rβ1 deficiency.

DISORDERS IN INNATE IMMUNITY

As described in depth in Chapter 15, innate immunity provides early responses to infectious challenges, before the generation of antibody or T cell responses. Although polymorphisms in innate immune receptors have been associated with increased susceptibility to certain common infections, defects in genes encoding adaptor molecules that coordinate signaling from multiple innate receptors are associated with more severe immunodeficiencies. Similarly, defects in humoral mediators of innate immunity, such as complement proteins, can be associated with recurrent and severe infections.

MYD88 AND IRAK-4 DEFICIENCIES

Toll-like receptors (TLRs) are a family of pattern recognition receptors activated following microbial infection, resulting in activation of innate immune responses. TLRs recognize conserved motifs derived from a variety of pathogenic microorganisms, including bacteria, fungi, and viruses. Upon ligand binding, all members of the TLR family, with the exception of TLR3, use MyD88 as a key adaptor molecule to recruit IRAKs leading to signaling resulting in the activation of the transcription factors NF-κB and activator protein-1. Mutations in either MyD88 or IRAK-4 result in phenotypically similar primary immunodeficiencies characterized by noninvasive and invasive infections (meningitis, septicemia, liver abscess) predominantly with *S. pneumoniae* (40% of patients) or *S. aureus* (26% of patients) and *P. aeruginosa* (18%).[214–217] No severe infections with viruses, fungi, or parasites have been observed, a surprising finding based on the broad immunodeficiency found in mice with targeted deletion of MyD88. The onset of invasive infections is early in life, with most before the age of 2 years but, for unknown reasons, the condition improves with age. Nearly all deaths in patients with IRAK-4 deficiency take place by 8 years of age. Patients with MyD88 or IRAK-4 deficiency are frequently unable to generate a normal inflammatory response (e.g., fever, increased C-reactive protein and white blood cells), and this contributes to the severity of the infections. Results of standard screening tests of immune function are often normal. Peripheral blood mononuclear cells exhibit decreased inflammatory cytokine production in response to IL-1 and to all TLR agonists except agonists of TLR3. The proper management of patients with MyD88 or IRAK-4 mutations remains to be determined, but prophylactic antibiotics and antibody replacement are considered essential.

COMPLEMENT DEFICIENCIES

Complement has many important functions that include the modulation of inflammatory responses (e.g., vasodilation, leukocytosis, and chemotaxis), clearance of immune complexes, modulation of the immune response (e.g., enhanced production of antibodies), and microbial elimination (e.g., opsonization, neutralization, and microbicidal activity). Complement may also be important in the efficient removal of apoptotic cells, thereby resulting in the presentation of self-antigens and the induction of autoimmunity. Deficiencies in components of the complement system are usually manifest by an increased propensity to infection or autoimmunity. There are several indications for the evaluation of the complement system, such as a strong family history of autoimmune diseases, recurrent infections caused by encapsulated bacteria, a family history of meningococcal disease, infection caused by unusual types of meningococcus (Y, W-135), age older than 9 years at the time of meningococcal disease, and recurrent angioedema.

Defects in the early components of complement (C1q, C1s, C2, C4) typically lead to autoimmune disease, primarily systemic lupus erythematosus.[218] Redundancies in the complement pathway, including the alternative and mannose-binding lectin pathways, may explain why only a minority of patients with early complement deficiencies will develop serious bacterial infections. Encapsulated bacteria (*S. pneumoniae, H. influenzae*) are the most common pathogens in persons with recurrent infection resulting from deficiency in early complement components.[25] C2 deficiency is the most common early component deficiency, seen in 1 in 10,000 to 1 in 28,000 live births.

The classical, alternative, and mannose-binding lectin pathways all converge at C3. For this reason, deficiencies in C3 result in more severe infections than deficiencies in other components of complement. Patients with C3 deficiency have an increased prevalence of autoimmune disease and present in a manner similar to patients with antibody deficiency.

Deficiencies in the late components of the complement pathway (C5 to C9) are predisposed to infection with *Neisseria meningitidis and Neisseria gonorrhoeae.* For unclear reasons, meningococcus serogroups W-135 and Y account for the majority of meningococcal infections in these patients. The prevalence of autoimmune disease is also increased, but to a much lesser extent than with deficiencies in the early components of the complement cascade. Patients with late-component deficiencies usually have the onset of infection at an older age, and many are asymptomatic well into adolescence.[25] Deficiencies in components of the alternative pathway (factor D, properdin) are extremely rare and present with recurrent bacterial infections, including infections with *Neisseria* sp. Properdin deficiency is an X-linked disorder, in contrast to the other complement deficiencies.

Therapy for complement deficiencies is primarily supportive. Individuals should be vaccinated against common bacterial pathogens associated with complement deficiency (e.g., *S. pneumoniae, H. influenzae, N. meningitidis*). Prophylactic antibiotics may be used in selected situations.

Key Points

- Patients with recurrent upper airway infections, intractable sinusitis, or more than one radiographically documented case of pneumonia should be evaluated for primary immune deficiency disorders. Abnormal screening tests for primary immune deficiency disorders should lead to referral to a clinical immunologist for a specific diagnosis.
- Although infection with opportunistic pathogens should always lead to a search for primary or secondary immunodeficiencies, infections in patients with primary immune deficiency disorders are often caused by common pathogens.
- Primary immune deficiency disorders frequently are not diagnosed in a timely manner, thus leading to increased morbidity and mortality. Treatment can include replacement antibody for humoral immunodeficiencies or, in those with a severe phenotype, hematopoietic stem cell transplantation.
- Primary immune deficiency disorders can be caused by deficiencies in antibody production, cellular immunity, complement, or phagocyte function. In an adult, common variable immunodeficiency is the most common diagnosis, and phagocytic defects and combined immunodeficiencies are rare.
- Although immunodeficiency in adults is more commonly secondary than primary, primary immune deficiency disorders are seen in adults. In fact, there are more adults with primary immune deficiencies than children.
- Diffuse interstitial lung disease develops in 10–25% of patients with common variable immunodeficiency and has been termed granulomatous-lymphocytic interstitial lung disease.
- In patients with profound antibody deficiencies, diagnosis of microbial infection cannot rely on serologic (antibody) responses but must instead use culture or detection of microbial antigens or nucleic acids.

Key Readings

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125 PULMONARY COMPLICATIONS OF STEM CELL AND SOLID ORGAN TRANSPLANTATION

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INTRODUCTION

Over the past 50 years, hematologic cell and solid organ transplantation have transformed the outlook for millions of individuals who experience life-threatening hematologic disorders and end-stage organ failure. Long-term outcomes for transplant recipients have improved with advances in the transplantation procedures as well as in supportive care.[1-4] However, transplant recipients are vulnerable to a variety of pulmonary complications that are diagnostically and therapeutically challenging for the chest physician. In addition to acute lung injury and infections complicating the early posttransplant period, providers must also contend with previously unanticipated chronic lung problems that arise in long-term transplant survivors. This chapter reviews infectious and noninfectious complications common to both *hematopoietic cell transplantation* (HCT) (also known as stem cell transplantation) and *solid organ transplantation* (SOT), followed by noninfectious complications specific to HCT and SOT. After HCT, the majority of the noninfectious complications happen in allogeneic transplants; concerns in autologous HCT are discussed where relevant. Given the emergence of lung transplantation as a distinct field within pulmonary medicine, the discussion regarding noninfectious complications in SOT focuses primarily on heart, kidney, and liver transplantation. The unique noninfectious complications of lung transplantation are covered in greater detail in Chapter 140.

HCT is a curative form of cellular therapy for a number of malignant and nonmalignant hematologic or immune disorders that replaces diseased or nonfunctioning bone marrow with healthy stem cells. To allow cellular engraftment into the patient's bone marrow, patients must undergo a conditioning regimen of cytotoxic chemotherapy with or without total body irradiation. *Myeloablative* conditioning regimens eliminate the recipient immune system in order to reduce the risk of malignancy relapse but carry increased risk of subsequent organ toxicity. *Nonmyeloablative* or reduced-intensity conditioning regimens are increasingly used to reduce organ toxicities for older recipients. The patient's marrow is then rescued by an infusion of healthy stem cells. *Allogeneic* HCT utilizes cells harvested from bone marrow or peripheral blood from related or unrelated individuals; umbilical cord blood is an alternative donor source that may be used if an appropriate matched donor is not found. *Autologous* HCT uses stem cells harvested from the patient's own blood. The use of allogeneic versus autologous cells depends on the disease indication; acute leukemias are generally treated with allogeneic HCT, while some lymphomas and multiple myeloma are preferentially treated with autologous HCT. Autoimmune diseases, such as systemic sclerosis[5] and multiple sclerosis,[6] are primarily treated with autologous transplants. Engraftment following stem cell infusion generally takes 2 to 3 weeks. In allogeneic HCT, donor T cells may attack recipient tissues, a condition called *graft-versus-host disease* (GVHD), requiring intensified immunosuppression; GVHD does not happen in autologous HCT. GVHD is a life-threatening disease that can involve nearly every organ system but preferentially affects the skin, lungs, mucous membranes, gastrointestinal tract (including the liver), and eyes. If an allogeneic HCT recipient has successfully engrafted without evidence of GVHD, long-term immunosuppression may not be required. This contrasts with SOT recipients, who have

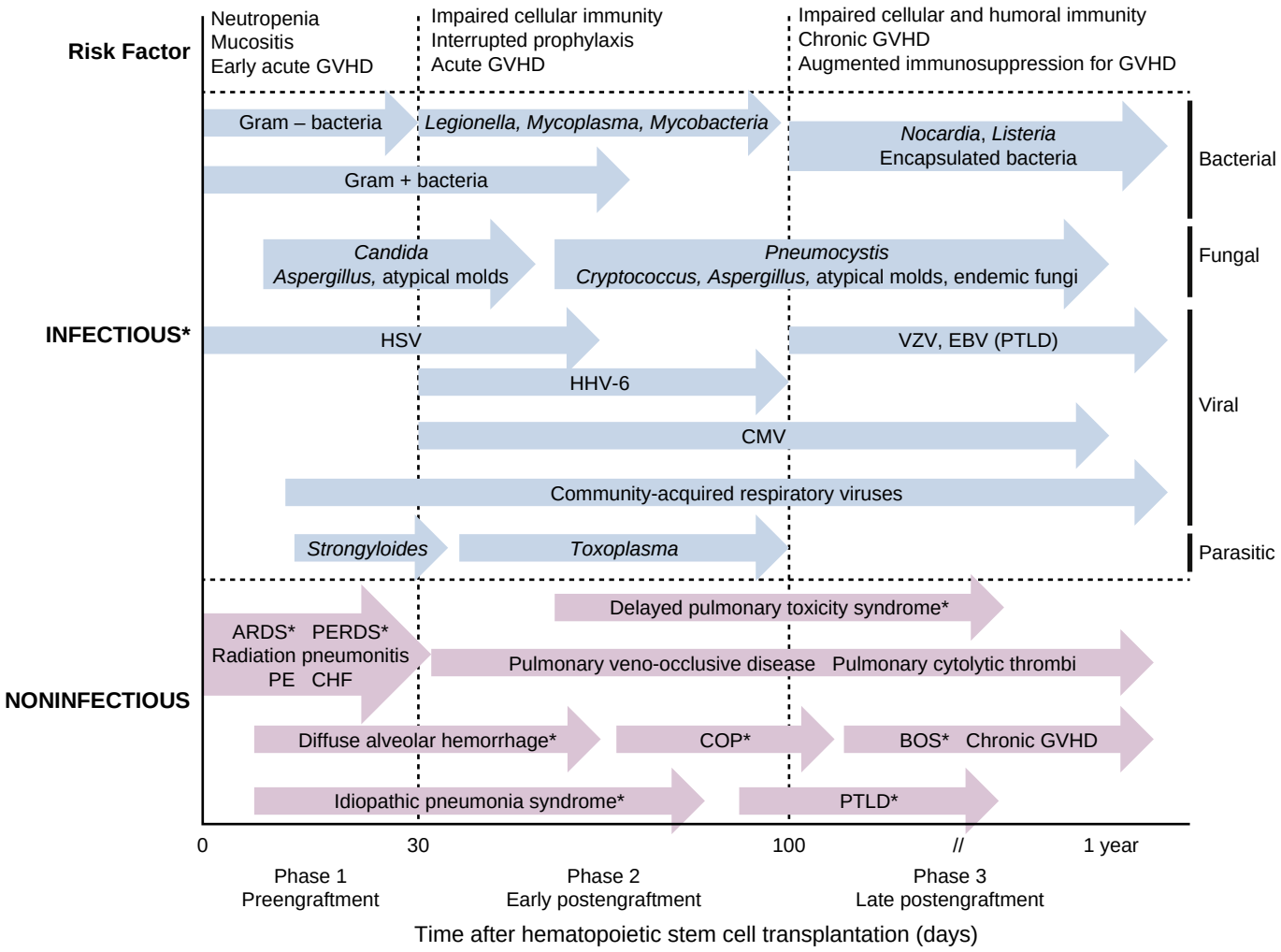

Figure 125.1 Hematopoetic cell transplantation: timeline of infectious and noninfectious pulmonary complications. Complications develop in a temporal relationship to the transplant conditioning regimen and immune status of the transplant recipient. In the immediate preengraftment phase (<1 month) prior to engraftment, patients experience profound neutropenia as well as immediate effects of the procedure. The early postengraftment phase (1–3 months) is a period of impaired cellular immunity as well as extrinsic immunosuppression for treatment of acute *graft-versus-host disease* (GVHD); this remains a vulnerable period for lung infections and acute lung injury. During the late postengraftment phase (>3 months), community-acquired infections and opportunistic infections in the setting of chronic GVHD treatment as well as chronic forms of noninfectious lung disease emerge. *Consider diagnostic bronchoscopy to (1) establish or exclude an infectious etiology and/or (2) diagnose a noninfectious process. ARDS, acute respiratory distress syndrome; BOS, bronchiolitis obliterans syndrome; CHF, congestive heart failure; CMV, cytomegalovirus; COP, bronchiolitis obliterans organizing pneumonia/cryptogenic organizing pneumonia; EBV, Epstein-Barr virus; HHV-6, human herpes virus-6; PE, pulmonary embolism; HSV, herpes simplex virus; PERDS, peri-engraftment respiratory distress syndrome; PTLD, posttransplant lymphoproliferative disorder; VZV, varicella-zoster virus. (Modified from Soubani AO. Respiratory infections following hematopoietic stem cell transplantation. In: Agusti C, Torres A, eds. *Pulmonary Infection in the Immunocompromised Patient: Strategies for Management.* West Sussex, UK: Wiley-Blackwell; 2009:213-256, and Afessa B, Peters SG. Chronic non-infectious pulmonary complications in hematopoietic stem cell transplantation. In: Agusti C, Torres A, eds. *Pulmonary Infection in the Immunocompromised Patient: Strategies for Management.* West Sussex, UK: Wiley-Blackwell; 2009:257-284, and from Harris B, Lowy FD, Stover DE, Arcasoy SM. Diagnostic bronchoscopy in solid-organ and hematopoietic stem cell transplantation. *Ann Am Thorac Soc.* 2013;10[1]:3949.)

functioning immune systems but require intense immunosuppression early after transplant and ongoing degrees of immunosuppression lifelong to prevent graft rejection. The level of immunosuppression in SOT varies; small intestine, lung, heart, and multiorgan transplant recipients, who are at higher risk for organ rejection, often receive a higher intensity of immunosuppressive therapy.

Transplant recipients are subject to specific infectious and noninfectious complications in relation to the stage of immunocompromise and graft biology. The risk of these complications can be conceptualized as immediate (<1 month), early (1 to 3 months), and late (>3 months) periods roughly corresponding to the degree of intrinsic immunocompromise and augmented immunosuppression (Figs. 125.1 and 125.2). Infections are common in the immediate and early periods and continue to contribute to morbidity and mortality in the late period. Noninfectious complications arise immediately posttransplant as a consequence of the grafting procedure as well as of the allograft itself; these complications can lead to lifelong immunologic consequences for the recipient. For example, recipients of HCT are often pancytopenic from their underlying hematologic malignancy or disease, cytotoxic chemotherapy or immune modulation, and radiation or ablative chemotherapy required prior to graft infusion. After engraftment, cellular and humoral immune reconstitution may not be

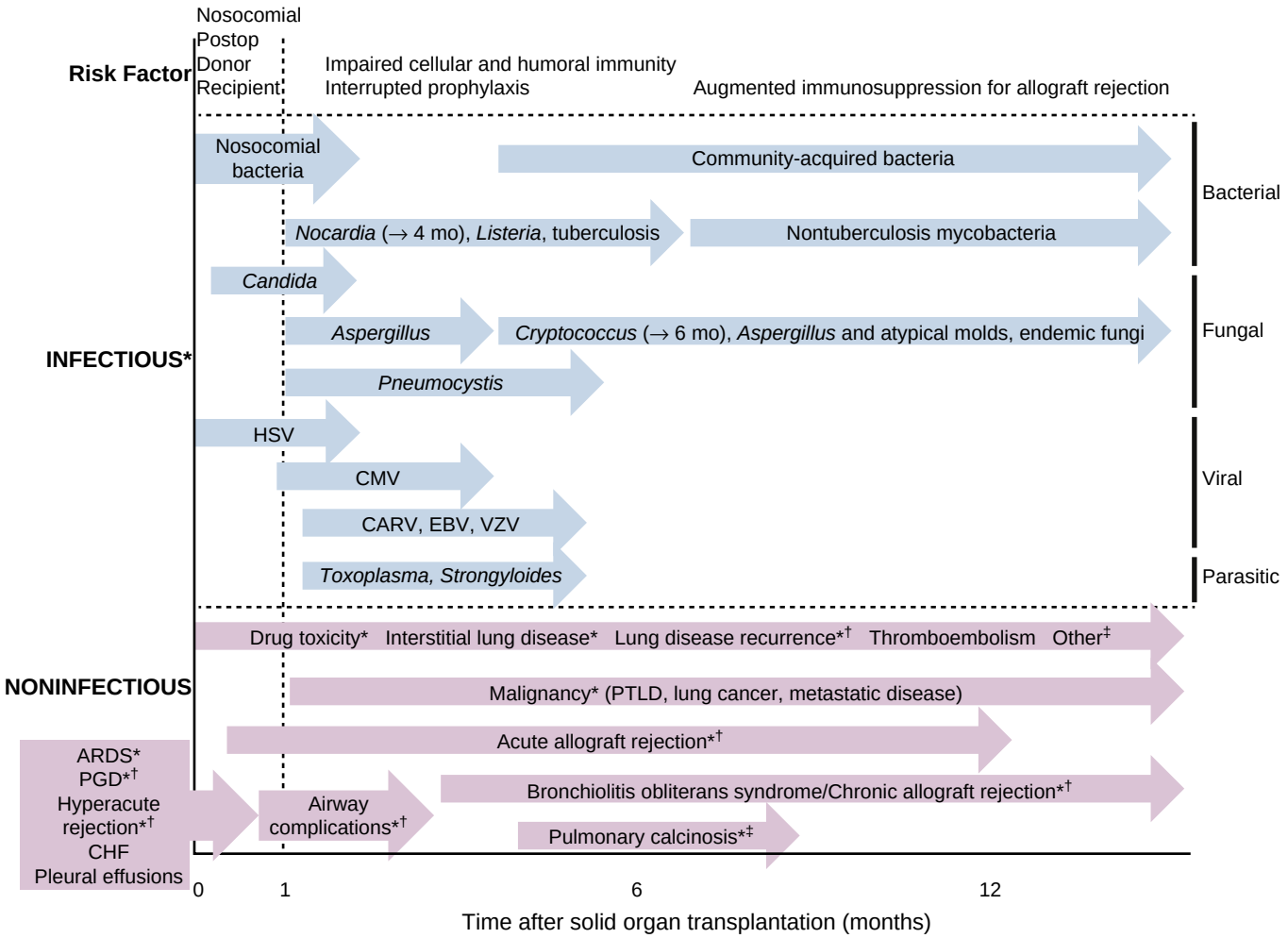

Figure 125.2 Solid organ transplantation: timeline of infectious and noninfectious pulmonary complications. The immediate postoperative period for a solid organ transplant recipient is complicated by nosocomial infections as well as surgical complications leading to acute respiratory failure. In the months after transplant, pharmacologic immunosuppression to prevent graft rejection leads to opportunistic infections. Later posttransplant, community-acquired infections predominate and noninfectious complications include malignancy, drug toxicity, and thromboembolism. Of note, bronchiolitis obliterans syndrome is a common late complication of lung transplantation (see Chapter 140). *Consider diagnostic bronchoscopy to (1) establish or rule out an infectious etiology; (2) diagnose a noninfectious etiology, such as acute allograft rejection, malignancy, or interstitial lung disease; or (3) inspect bronchial anastomoses and other airway abnormalities. †Lung transplant recipients only. ‡Diagnostic bronchoscopy is warranted for pulmonary metastatic calcinosis for atypical presentations on imaging in renal transplant recipients. ARDS, acute respiratory distress syndrome; CARV, community-acquired respiratory viruses; CHF, congestive heart failure; CMV, cytomegalovirus; EBV, Epstein-Barr virus; HSV, herpes simplex virus; PGD, primary graft dysfunction; PTLD, post-transplant lymphoproliferative disorder; VZV, varicella-zoster virus. (Modified from Harris B, Lowy FD, Stover DE, Arcasoy SM. Diagnostic bronchoscopy in solid-organ and hematopoietic stem cell transplantation. *Ann Am Thorac Soc*. 2013;10(1):39-49 and based on data from Fishman JA: Infection in solid-organ transplant recipients. *N Engl J Med*. 2007;357:2601-2614.)

complete for months to years. Prevention and treatment of GVHD during the early (acute GVHD) and late (chronic GVHD) periods require prolonged immunosuppression for some individuals.[7] In the immediate posttransplant period, SOT recipients undergo intense immunosuppression with glucocorticoids and agents directed towards T lymphocytes to prevent immediate graft rejection as well as postoperative stresses that can lead to acute respiratory failure. After this period, lifelong immunosuppression is required for solid organ graft survival. Organ dysfunction, antibiotic effects on the microbiome, drug-related adverse effects, alterations in nutritional intake, and posttransplant depression are just some of the factors that may contribute to prolonged immunosuppression in transplant recipients.

INFECTIOUS COMPLICATIONS

The lung is a leading site of infection for transplant recipients. With newer and more efficacious anti-infective agents and improved prophylactic strategies, the impact of pulmonary infections has shifted from early in the course of transplant to later during posttransplant survival. Successful strategies for preventing and treating opportunistic fungal and viral infections have also led to the emergence of resistant pathogens.[8-10] Radiographic and clinical presentations of various infectious pneumonias are often indistinguishable from one another (Fig. 125.3) and from noninfectious lung disease.[7] Coinfection with more than one pathogen is also common. Because of these concerns as well as the

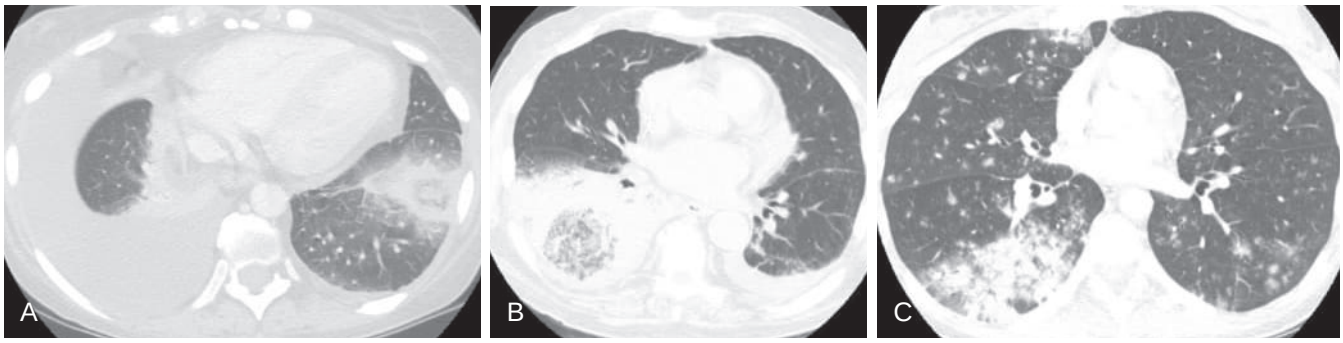

Figure 125.3 Pulmonary infections in allogeneic hematopoietic cell transplant recipients. Infectious pneumonia is caused by a broad spectrum of pathogens that can present similarly on chest imaging. Thus, bronchoscopy is important for determining the underlying pathogen. These examples represent chest computed tomography images from hematopoietic cell transplant recipients who underwent bronchoscopy to diagnose the lung opacities. The pathogens identified were methicillin-sensitive *Staphylococcus aureus* (A), *Rhizomucor oryzae* (B), and human metapneumovirus (C). Note the reverse halo, or "bird's nest" sign in B, which is suggestive of mucormycosis.

potential adverse effects of empiric therapy, a specific diagnosis should be pursued whenever possible. Bronchoscopy with analysis of the *bronchoalveolar lavage* (BAL) fluid remains the diagnostic procedure of choice for the evaluation of enigmatic pulmonary consolidations or opacities in both HCT and SOT.[11] Diagnostic yield is highest when bronchoscopy is performed prior to empiric antimicrobials and within 24 hours of presentation.[12,13] Because many of these infections are rare, a comprehensive review is beyond the scope of this chapter, which focuses on the most clinically relevant entities.

BACTERIAL PNEUMONIA

After HCT, the precise incidence of bacterial pneumonia is difficult to ascertain due to the frequent use of empiric broad-spectrum antibiotics in the early posttransplant period. Nevertheless, bacterial pneumonia has been reported in 7–11% of allogeneic and 5–15% of autologous HCT recipients.[14-16] The most common bacterial pathogens include *Escherichia coli, Pseudomonas aeruginosa, Klebsiella pneumoniae, Staphylococcus aureus,* and *Streptococcus pneumoniae*.[16,17] In addition to early neutropenia, important risk factors for early pneumonia after HCT include mucositis from total body irradiation, alterations in the gut microbiome, acid suppression, and prolonged immunosuppression.[18,19] Iron affects innate and cellular immunity by several mechanisms, including inhibition of macrophage and lymphocyte function.[20,21] Iron overload, which is common in HCT recipients who receive frequent blood transfusions pre- and posttransplant, has been associated with increased risk of infectious pneumonia (primarily bacterial and fungal) in these patients.[22,23]

In SOT, bacterial pneumonia is an important source of early posttransplant morbidity and mortality and is often the source of sepsis. In liver transplant patients, the incidence of bacterial pneumonia is 8–23%, mostly presenting in the early postoperative period as ventilator-associated or health care–associated pneumonia[24-27]; risk factors for early-onset pneumonia (<1 month) include increased severity of end-stage liver disease (quantitated as the model for end-stage liver disease score) pretransplant, prolonged intubation, and restrictive pattern on preoperative pulmonary function testing.[24-26] In heart transplant patients, the incidence of early postoperative pneumonia is as high as 34%; risk factors include preoperative intubation and perioperative blood transfusion and the use of extracorporeal membrane oxygenation.[28] In renal transplant patients, bacterial pneumonia is second only to urinary tract infections as an infectious cause of morbidity and mortality, with pneumonia requiring hospitalization in 12% of patients in a cohort of 1467 patients; risk factors for mortality include elevated C-reactive protein, nosocomial multidrug-resistant organisms, and the need for renal replacement therapy.[29]

Most early posttransplant bacterial pneumonias in SOT are health care facility–acquired species and are therefore more likely to be multidrug-resistant pathogens. The most frequently documented bacterial pathogens are gram-negative bacteria, including *P. aeruginosa* (eFig. 125.1), *K. pneumonia, E. coli, Acinetobacter* sp., and *Stenotrophomonas maltophilia* as well as gram-positive bacterial, including methicillin-resistant *S. aureus.*[25,27,30] Beyond the early transplant period, as immunosuppression is modified, SOT recipients experience pneumonia with community-acquired organisms such as *S. pneumoniae, Haemophilus influenzae,* and *Moraxella catarhallis*.[31] A causative agent is often never identified and patients are treated empirically.[32]

Transplant patients are also at increased risk for infections from less commonly encountered nosocomial and opportunistic bacteria. Intrinsically antibiotic-resistant pathogens such as *Burkholderia* sp. and *S. maltophilia* are more common in transplant recipients due in part to selection pressure from antibiotic therapy.[33-35] In addition, *Nocardia* sp. are often seen in transplant patients, particularly those treated with high-dose glucocorticoids, often presenting as nodules that mimic fungal pneumonia.[35,36] *Legionella* sp. pneumonias can be devastating infections in transplant patients, with reports of nearly 30% mortality.[36] *Legionella* infections, including those with non-pneumophila species and non-serotype 1 *Legionella pneumophila*, should be considered, particularly in patients with community-acquired pneumonia or among clusters of inpatient pneumonias.[37]

MYCOBACTERIAL INFECTIONS

In HCT, active *tuberculosis* (TB) is rare, in part due to a low rate of *latent tuberculosis infection* (LTBI) in this population, the use of fluoroquinolone prophylaxis, and possibly the up-regulation of T helper type 1 immune activation during transplant conditioning, which may protect against active TB infection.[38,39] In a study from the University of Minnesota, estimates of the prevalence of active TB following HCT ranged from 0.23–0.79%[40] but can be expected to vary substantially between countries. In a contemporary series of 2531 autologous and allogeneic HCT recipients in a low endemicity region, there were no cases of active TB after a minimum of 3 years of follow-up, which included 63 patients identified with LTBI, of which 46% never received treatment for LTBI.[39] Rates of TB in HCT have been reported to be higher in regions where the prevalence of TB in the population is higher.[41] Experts disagree on the value of routine versus targeted LTBI testing among HCT recipients, but treatment is recommended to patients who have documented LTBI (see also Chapter 42).

In SOT, the incidence of active TB ranges from 1.2–12%, depending on the prevalence of TB in the corresponding population.[42] The highest incidence is in kidney transplant recipients, but lung transplant recipients are also at high risk.[43] Donor-derived mycobacterial infections have been reported.[44] All potential SOT recipients should be tested for LTBI with a tuberculin skin test and/or an interferon-gamma release assay.[45] Neither the tuberculin skin test nor interferon-gamma release assay can distinguish between latent and active disease and may yield false-negative results in immunocompromised patients, although interferon-gamma release assay may be better than tuberculin skin test, particularly in patients with liver or kidney disease.[43] Additional screening with chest radiography should be considered in patients with negative or indeterminate tuberculin skin test/interferon-gamma release assay in high-risk epidemiologic areas. Therapy for LTBI is recommended prior to transplant.[43]

LTBI can be treated with rifampin-based regimens[46] or with isoniazid-based regimens (see Table 42.4).[47] Therapy for active TB should follow standard guidelines and include isoniazid, rifampin, pyrazinamide, and ethambutol.[42,48] The use of rifampin can be a problem due to the increased risk of hepatotoxicity and the induction of cytochrome P450 isoenzymes, which can reduce serum concentrations of several immunosuppressants and azole antifungals, potentially leading to allograft rejection and infection. During rifampin treatment, doses of the immunosuppressants cyclosporine, tacrolimus, and sirolimus must be increased and signs of rejection closely monitored.[43] Rifampin is used most frequently due to its potent antituberculous activity, but rifabutin may be preferable because it is a less potent inducer of cytochrome P450.

In HCT, *nontuberculous mycobacterial* (NTM) pulmonary infections are uncommon, particularly in the early posttransplant period,[49,50] but NTMs are increasingly recognized as a late infectious problem. This likely reflects advances in diagnostic testing, increased long-term survival, and the changing epidemiology of NTM at large.[51] In a cohort of 1047 allogeneic HCT recipients, NTMs were identified in 2.7%, a markedly higher rate than in the general population. The vast majority of cases (93%) presented with lung disease at a median time after HCT of 343 days. NTM was associated with severe chronic GVHD and *cytomegalovirus* (CMV) viremia.[51] NTMs can also be seen in the early posttransplant period as central catheter-associated and skin infections.[49] In SOT, pulmonary NTM is primarily a concern for thoracic SOT, although disseminated NTM in renal transplant patients can contribute to allograft loss and mortality.[52] Lung transplant recipients in particular are at risk for infections at the anastomotic site with *Mycobacterium abscessus*, an organism notoriously difficult to treat.[53] NTM infections contribute to increased mortality in SOT[54] (see also Chapter 55).

FUNGAL INFECTIONS (See Chapter 57)

Aspergillus sp., primarily *A. fumigatus*, are responsible for the vast majority of fungal pneumonias, or *invasive aspergillosis* (IA). Other major *invasive fungal infections* (IFIs) that involve the sinopulmonary tract include *Mucorales* sp. (most frequently *Rhizopus, Mucor,* and *Rhizomucor* sp.), dimorphic molds, and rare infections due to *Fusarium* sp., *Lomentospora prolificans*, *Scedosporium apiospermum,* dematiaceous molds, and multiple other species.[55] In most transplant populations, patients present with primary pulmonary disease, but sinus involvement is common.[56] For lung transplant recipients, tracheobronchitis due to IA may lead to dehiscence of the bronchial anastomoses.[57,58] In addition to respiratory tract disease, IFIs can present with other manifestations, including skin nodules or gastrointestinal tract and/or central nervous system disease. It is important to note that most epidemiologic studies follow the current consensus definitions of IFI from the European Organization for Research and Treatment of Cancer and the Mycoses Study Group Education and Research Consortium and include only probable or proven IA, and thus may underrepresent the true incidence due to the difficulties of establishing the diagnosis before empiric therapy is initiated.[59]

Epidemiology and Clinical Characteristics

In the past 2 decades, improved diagnostic testing, changes in transplant practice, and novel antifungal agents have significantly reduced the burden of IFIs in the immunocompromised population.[60] Risk for fungal infections is dependent on the underlying disease, donor source, conditioning regimen, and use of glucocorticoids. The incidence of IFI ranges from 4–23% after allogeneic HCT and from 1–4% after autologous HCT.[55,61-64] Novel therapies used in conjunction with glucocorticoids for treatment of GVHD, such as ibrutinib, may further increase risk.[65,66] Additionally, risk of developing some IFIs may also be dependent on environmental variables such as temperature and rainfall. Due to improvements in antifungal therapy, mortality due to IA has improved, but IFI from non-*Aspergillus* mold species such as those caused by *Mucorales* and *Fusarium* remain highly lethal in these populations.[67-69]

In SOT, IFIs are most commonly seen in lung transplantation, followed by liver, heart, and kidney transplantation.[70–72] The 1-year cumulative incidence of IA in a multicenter surveillance cohort for lung, heart, liver, and kidney transplants was 2.4%, 0.8%, 0.3%, and 0.1%, respectively. While IA was relatively uncommon, the

mortality rate was high, ranging from 20% for lung transplants to 67% for heart and kidney transplants.[70,73] A recent study showed that the cumulative incidence of IFI in SOT is rising, particularly in lung transplantation, as the burden of disease is shifting to long-term survivors.[73] Other fungal infections, such as cryptococcosis, and endemic molds (e.g., coccidioidomycosis, histoplasmosis), which are more common in SOT recipients, are described in more detail in Chapter 56).

In HCT, the main risk factors for IFI, including IA, are prolonged neutropenia, allogeneic grafts, myeloablative conditioning, and acute GVHD.[55] Prior use of voriconazole, iron overload,[23,74] and high environmental temperatures (particularly summer season), are additional risk factors associated with mucormycosis.[69,75,76] Lung transplant recipients are often colonized with *Aspergillus* pretransplant and thus are at particular risk for lower respiratory tract disease.[58] In SOT, risk factors for IA include environmental exposures (e.g., gardening, construction), state of immunosuppression, and the need for retransplantation.[57] There is increasing evidence that CMV infection is a significant risk factor for IFI, including aspergillosis and *Pneumocystis jirovecii* pneumonia, which has been hypothesized to be due to ganciclovir-induced neutropenia as well as to virally induced cellular immune alterations.[77] More recent publications have also linked the development of IA to influenza, but data in transplant populations remain mixed.[78-82]

Symptoms of IA vary widely but often include high fever, dry cough, chest pain, dyspnea, and hemoptysis. Fever may be absent in SOT, and HCT recipients can present with only fever or be found to have asymptomatic pulmonary nodules. Tracheobronchitis may present early with wheezing and/or stridor or late with frank hemoptysis.

Diagnostic Testing

The radiographic presentation of pulmonary IA differs between HCT and SOT owing to the type of immune risk.[57] In HCT, solitary or multiple nodules and large dense consolidations are typically seen, whereas, in SOT, peribronchial consolidation, ground-glass opacities, and tree-in-bud nodules are more common[83] (eFig. 125.2). In HCT recipients early posttransplant who have yet to engraft, the "halo sign" is a classic finding of a nodule with surrounding ground-glass changes (eFig. 125.3). Fungal nodules may increase both in size and number despite appropriate therapy during neutrophil recovery posttransplant, as immune cells home to sites of infection and cause an apparent increase in inflammation.[84] Cavitation may also present during treatment (eFigs. 125.4 and 125.5). A reverse halo sign, or "bird's nest" consolidation, is suggestive of mucormycosis (see Fig. 125.3).[85]

Because clinical and radiographic presentations may be similar for bacterial infections and noninfectious etiologies (see Fig. 125.3), a microbiologic diagnosis by bronchoscopy in conjunction with serologic testing should be attempted whenever possible.[7,86] The serum galactomannan assay is useful for the diagnosis of IA in HCT but is less sensitive for SOT recipients.[87] Serum galactomannan level is also predictive of outcomes in HCT.[88] Galactomannan detected in BAL fluid is a more sensitive assay for IA; proven disease requires histologic evidence of invasion and culture evidence of mold from a sterile sample.[59] Serum β-D-glucan has been used as an alternative serum marker for IFI; however, it is not sensitive for some dimorphic molds and for mucormycosis.[89] Emerging molecular diagnostics, such as *polymerase chain reaction* (PCR) for molds from blood or BAL fluid, are used increasingly for diagnosis and are included in recently updated guidelines for management of IFI.[59,90,91]

Treatment

The availability of third-generation mold-active and orally available triazoles—voriconazole, posaconazole, and isavuconazole—has greatly improved the treatment and prevention of IA.[7,60] Infectious Disease Society of America Guidelines recommend voriconazole or isavuconazole as first-line therapy for IA; posaconazole is likely an option for IA but has only been assessed in salvage trials and prevention trials.[86] Patients who either cannot tolerate azole therapy, develop breakthrough infection on triazole prophylaxis, or who have clinical and radiologic findings suspicious for mucormycosis should be treated with liposomal or lipid-complex amphotericin B. Compared to earlier treatment, delaying treatment for mucormycosis with amphotericin B for 6 or more days after diagnosis is associated with a twofold increase in mortality.[92] Isavuconazole has also been approved for mucormycosis therapy.[93] Regardless of antifungal therapy, surgical intervention is crucial for all patients diagnosed with pulmonary mucormycosis, and all should be evaluated by cardiothoracic surgery for possible surgical resection. Following surgical intervention and prolonged amphotericin B therapy, most patients can be considered for step-down therapy with either posaconazole or isavuconazole. Treatment teams should be aware of increasing reports of azole-resistant *Aspergillus* sp. and emergence of non-*Aspergillus* pathogens.[94-96]

Prophylaxis against molds is recommended in high-risk groups, including allogeneic HCT recipients with high-grade GVHD. In low-risk patients, fluconazole can be used as primary prophylaxis but, for high-risk patients, the preferred agent is posaconazole; voriconazole is used at some centers.[97] The use of triazole prophylactic agents including fluconazole may be a reason for the rarity of early posttransplant endemic fungal infections (e.g., histoplasmosis, cryptococcosis). In lung transplant recipients, universal or preemptive prophylaxis is given with inhaled liposomal amphotericin during the early posttransplant period.[57,98] In spite of prophylactic strategies, IFIs remain a significant problem.

Pneumocystis jirovecii Pneumonia

In the setting of appropriate prophylaxis (with trimethoprim-sulfamethoxazole or dapsone, atovaquone, and pentamidine for those with sulfa allergies), *Pneumocystis jirovecii pneumonia* (PJP) is rare in HCT recipients, seen in only 0.63% and 0.28% of allogeneic and autologous HCT recipients, respectively, as demonstrated by a large registry study.[99] However, the mortality of PJP in HCT remains high, with a hazard of mortality nearly seven times higher than matched controls. In HCT, risk factors for PJP include lymphopenia, mismatched grafts, and GVHD (which is usually treated with systemic glucocorticoids).[99] In SOT, in the absence of prophylaxis, PJP developed in 5–15%, with the risk of infection greatest in the first 6 months posttransplant. Prophylaxis with low-dose trimethoprim-

sulfamethoxazole is used for a year, then discontinued, except in lung transplant patients, in whom it is continued indefinitely.[100] In non-lung SOT, PJP is rare when prophylaxis is given in the 6- to 12-month period after transplantation but rises significantly in the first year without standard prophylaxis. Risk factors include advanced age, antecedent CMV infection, and lymphopenia.[101-103] Diagnosis of PJP includes direct immunofluorescent staining of respiratory samples; PCR of respiratory samples for PJP and serum β-D-glucan assays are increasingly being used for diagnosis.[104,105] First-line therapy for PJP is intravenous trimethoprim-sulfamethoxazole, but other options, such as clindamycin/primaquine, are available for those who cannot tolerate sulfa drugs. The use of adjunctive steroids in transplant recipients may be considered, particularly in severe cases.[106]

VIRAL INFECTIONS

Herpesviruses

In HCT, preemptive treatment with ganciclovir and foscarnet has dramatically reduced the incidence of CMV disease, particularly of CMV pneumonia, which historically affected patients within the early posttransplant period.[107,108] However, the incidence of CMV pneumonia in the modern era is very low, seen in less than 1% of patients.[109-111] Late CMV reactivation has emerged as a consequence of preemptive and prophylactic strategies. HCT recipients who are CMV seropositive are at highest risk for CMV pneumonia, particularly patients who receive transplants from CMV seronegative donors or cord blood transplants.[112] This is similar for SOT, and risk is highest among lung transplant recipients.[113,114] Prophylaxis with ganciclovir and valganciclovir has significantly reduced risk in SOT recipients.[115] The application of letermovir, a novel agent targeting the DNA terminase complex, for prophylaxis has been shown to decrease the risk of CMV viral reactivation in high-risk patients.[109]

Clinically, patients with CMV pneumonia most often present with shortness of breath, hypoxemia, cough, and fever.[116] Radiographically, CMV pneumonia may present similarly to noninfectious complications, with diffuse ground-glass changes, a nonspecific lung injury pattern, or with diffuse or focal nodules and/or consolidations (eFigs. 125.6 to 125.9). Diagnosis of CMV pneumonia requires detection of CMV by viral culture, shell vial or PCR from the lower respiratory tract, or less frequently through biopsy samples demonstrating CMV-specific staining[117]; specific viral load cutoffs for CMV pneumonia among HCT recipients have been developed.[118] Treatment with CMV-active agents has significantly decreased mortality among these high-risk patients, although CMV pneumonia remains a life-threatening complication in transplant patients.[119] Drug resistance, while uncommon, can complicate therapy among transplant recipients with CMV pneumonitis.[9,120]

Herpes simplex virus and varicella zoster virus are rare causes of viral pneumonitis,[121-123] especially with acyclovir or valacyclovir prophylaxis.[124] Emerging literature suggests that *human herpesvirus-6* (HHV-6), when detected in the lower respiratory tract, is associated with increased mortality[125] and possibly acute noninfectious lung injury (see below).[126]

Community-Acquired Respiratory Viruses

Community-acquired respiratory viruses (CARVs), such as influenza A/B, respiratory syncytial virus, parainfluenza viruses, adenoviruses, metapneumovirus, rhinoviruses, and human coronaviruses are increasingly recognized as important sources of morbidity and mortality in immunocompromised transplant populations, particularly when upper respiratory tract disease progresses to lower respiratory tract disease and acute respiratory failure. Novel CARVs such as enterovirus-D68[127] and severe acute respiratory virus coronavirus 2 (SARS-CoV-2, agent of coronavirus disease 19 [COVID-19])[128] are unexpected pathogens that have also emerged over the past few years. CARVs are also associated with the development of late-onset noninfectious lung complications (see below). Adenovirus is unique because most adenovirus pneumonias in transplant recipients are not related to recent acquisition, but reactivation from latent disease.[129,130] Transplant patients with CARVs usually present with upper respiratory infection symptoms of rhinorrhea, sore throat, cough and fever, and less commonly with hypoxemia and acute respiratory failure. Typical symptoms in the general population may be absent in transplant recipients.[131,132] In a multicenter study of transplant recipients with influenza, only two-thirds presented with fever, one-third with a sore throat, and fewer than one-half with myalgias.[132] As a result, clinicians must have a low index of suspicion for testing patients. This may be most important pre-HCT because patients with symptomatic respiratory viruses should have their transplant delayed if at all possible due to associated increased risk of posttransplant mortality.[133]

On chest imaging, viral pneumonia due to CARVs presents with diffuse or patchy bilateral ground-glass opacities, tree-in-bud opacities or consolidations (eFig. 125.10). Diagnosis has increasingly shifted to multiplex PCR panels, which allow for early and rapid identification[134]; these assays can also be used on BAL samples to identify lower respiratory tract infection. A bronchoscopic diagnosis for viral etiologies remains important, even when noninvasive evaluation of CARVs has been performed, because what is detected in the upper respiratory tract (e.g., nares, pharynx) does not always reflect findings from lower respiratory tract samples.[135] In addition, transplant patients may be more likely to have multiple viruses or other co-pathogens found on assessment of the lower respiratory tract by BAL.

CARVs, such as human rhinovirus, that are not considered common causes of viral pneumonia in immunocompetent hosts, can lead to life-threatening complications in transplant patients.[136] Progression from upper respiratory infection to lower respiratory tract infection is highly dependent on timing posttransplant and the level of immunosuppression. Lung transplant and allogeneic HCT patients are at highest risk for development of lower respiratory tract infection.[137] There are few options for treatment of CARVs, although neuraminidase inhibitors (e.g., oseltamivir) are known to be effective for influenza, and ribavirin is approved for treatment of respiratory syncytial virus. Treatment of influenza should be initiated less than 48 hours after symptom onset because this has been associated with improved outcomes in transplant patients.[138] Resistance is a concern in transplant patients who are at high risk for development of oseltamivir-resistant influenza strains during the course of therapy.[139] Patients with increasing viral loads, or those who progress despite antiviral therapy, should be evaluated for drug resistance.[140] Use of ribavirin

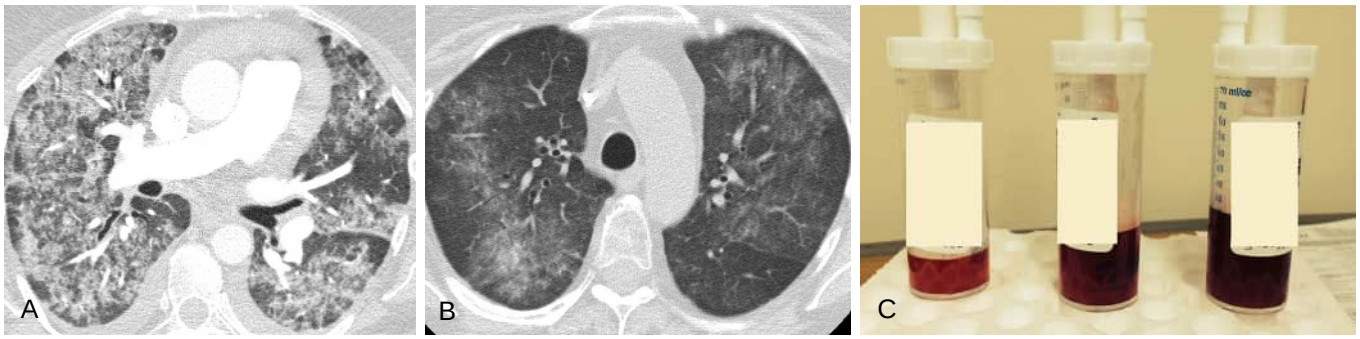

Figure 125.4 Diffuse alveolar hemorrhage after allogeneic hematopoietic cell transplantation. A 61-year-old woman with acute myelogenous leukemia received an allogeneic transplant with nonmyeloablative conditioning and total body irradiation. At day +21 after hematopoietic cell transplantation, she experienced acute shortness of breath and hemoptysis requiring mechanical ventilation; chest computed tomography showed severe diffuse pulmonary opacities (A), which were diagnosed as diffuse alveolar hemorrhage. She was treated with corticosteroids and aminocaproic acid (an antifibrinolytic) and recovered. (B) At day +120, follow-up chest computed tomography showed diffuse hazy ground-glass opacities greatest in the upper lobes. (C) Bronchoscopy revealed increasing blood return in the lavage consistent with recurrence of diffuse alveolar hemorrhage.

remains a point of debate in the transplant community due to the costs of inhaled ribavirin[141] and to the limited data supporting oral ribavirin use in these patients,[142] however, some centers use these treatments in patients with respiratory syncytial virus[143]; data supporting their use against other respiratory viruses is limited.[144]

Notably, early reports regarding the novel coronavirus SARS-CoV-2 describe a variety of presentations and clinical courses for COVID-19 in SOT recipients, including respiratory failure and critical illness.[145-148] Larger cohorts and case control studies from the early period of the global pandemic suggest that the short-term mortality rates for hospitalized patients and risk factors for death are similar to that of the general population.[148a–c] In the largest U.S. cohort to date, the level of immunosuppression was not associated with mortality.[148a] Patients with active hematologic malignancies, poor functional status, and neutropenia appear to be at higher risk for severe disease and death.[149] Among HCT recipients, data from a large transplant center in New York demonstrated that over 20% developed severe disease (defined as requiring ICU level care or goals of care changed to comfort care rather than escalation to ICU), and 70% of those with severe disease died. Optimal treatment options are under investigation. In randomized clinical trials, the novel antiviral agent remdesivir has been shown to decrease length of stay in hospitalized individuals,[150,151] and dexamethasone was shown to decrease mortality when given to critically ill patients.[151a–c] Patients with hematologic malignancies, including those undergoing transplantation, may have prolonged shedding for weeks to months following primary infection either as noted on repeat PCR testing or in some cases by culturable SARS-CoV-2.

NONINFECTOUS COMPLICATIONS OF HEMATOPOIETIC CELL TRANSPLANTATION

EARLY-ONSET COMPLICATIONS

Idiopathic Pneumonia Syndrome

Idiopathic pneumonia syndrome (IPS) is broadly defined as widespread acute alveolar injury in HCT recipients in the absence of lower respiratory tract infection, cardiac or renal dysfunction, or iatrogenic volume overload. IPS encompasses a spectrum of acute lung injuries, including *diffuse alveolar hemorrhage* (DAH), peri-engraftment syndrome, and acute fibrinous and organizing pneumonia. The classification of these entities is based on the presumed site of primary tissue injury (i.e., pulmonary parenchymal, vascular endothelial, or airway epithelial).[152] There is no pathognomic pathology because the pathology depends upon the site of injury. Diffuse alveolar injury is a common feature for the earlier, more acute forms, whereas fibrosis and alveolar granulation characterize the latter presentations (i.e., organizing pneumonia).

The clinical presentation of IPS is characterized by acute to subacute dyspnea and progressive hypoxemia associated with bilateral pulmonary opacities or ground-glass opacities on chest imaging (Fig. 125.4A–B and eFig. 125.11). This may be indistinguishable from an infectious pneumonia; hence, bronchoscopy is often necessary to exclude infectious etiologies. Indeed, anti-infective prophylaxis early posttransplant has led to reduced incidence of bacterial and CMV pneumonia.[1,60] Of the IPS subtypes, DAH is perhaps the most dramatic in presentation and associated with the highest mortality. The diagnosis is based on progressively bloodier return of BAL fluid (see Fig. 125.4C; see also Chapter 94).

The advent of less-toxic conditioning regimens prior to allografting has reduced the clinical burden of IPS.[153] A contemporary single-center analysis suggested that the incidence of IPS is approximately 3%, and risk factors include the use of total body irradiation, African ancestry, and severe pulmonary impairment prior to transplant. Mortality is high, particularly for DAH, ranging from 60–80%, and nearly 100% for those that are mechanically ventilated with concurrent renal and liver dysfunction.[153,154] Improved supportive care in the intensive care unit may be reducing early mortality, but the 1-year mortality remains high at 70%, in contrast to 30% for HCT recipients without IPS.[155]

The pathogenesis of IPS likely involves a toxic insult from the HCT conditioning regimen or an occult pulmonary infection that triggers subsequent aberrant graft-mediated immune cell injury.[156] Preclinical murine models replicating the conditions of human transplantation have

demonstrated that a cascade of donor-derived cytokines and chemokines drive the noninfectious inflammatory lung injury, which involves a cellular alveolar infiltrate and alveolar epithelial and endothelial cell injury.[157] Experimentally, it has been shown that donor-derived, not host-derived, tumor necrosis factor-α mediates the lung injury through increased major histocompatibility complex expression, neutrophil infiltration, and cell-mediated cytotoxicity.[158,159] While there is a role for alloreactive donor T cells in mediating the lung attack, direct evidence of IPS as a manifestation of acute GVHD has not been definitely established.

Although considered noninfectious, IPS may be triggered by occult infections. In light of advances in diagnostic methods such as multiplex PCR, it has been recently recognized that many cases classified as IPS had occult infections at the time of presentation. In a retrospective series of 69 patients with IPS, approximately half had pathogens detected in the BAL fluid when these newer diagnostic methods were used. The most frequent pathogens were HHV-6, human rhinovirus, CMV, and *Aspergillus* sp.[160] HHV-6, like CMV, is a human beta-herpesvirus that latently infects 95% of healthy adults and frequently reactivates during critical illness.[161] Detection of reactivated HHVs, including HHV-6, in the early posttransplant period has been associated with the subsequent development of IPS, an observation that has been experimentally replicated in murine models.[126] Moreover, the presence of HHV-6 in the BAL of patients with acute respiratory failure after HCT is associated with increased mortality.[125]

The management of IPS and DAH relies primarily on systemic corticosteroids with the addition of tumor necrosis factor-α blockade.[162,163] However, the mainstay of care for those with respiratory failure remains supportive care with lung protective mechanical ventilation.

Delayed pulmonary toxicity syndrome, characterized by acute lung injury and subsequent fibrosis after engraftment, develops in the context of autologous transplant recipients who have received bischloroethylnitrosourea (carmustine) as part of their conditioning regimen (eFig. 125.12). This was initially described in the early 1990s, and contemporary incidence is quite low. Delayed pulmonary toxicity syndrome is generally responsive to treatment with corticosteroids.[164]

Engraftment syndrome encompasses what is known to critical care physicians as peri-engraftment respiratory distress syndrome, characterized by systemic and inflammatory capillary leak in the setting of neutrophil recovery. Engraftment syndrome is best described in autologous HCT[165] and is also observed in allogeneic HCT, and is potentially associated with the onset of acute GVHD.[166,167] In children with autologous HCT, pulmonary opacities are seen in 25% or more of patients with engraftment syndrome; however, in adult recipients of myeloablative and nonmyeloablative conditioning for allogeneic transplants, the presence of pulmonary opacities with engraftment syndrome is nearly universal.[168,169] Peri-engraftment respiratory distress syndrome accounted for 2.5% of the pulmonary complications in a series of more than 1200 autologous HCT recipients at the Mayo Clinic.[15] Clinically, engraftment syndrome is characterized by fever, skin rash, and noncardiogenic pulmonary edema appearing early after transplant during neutrophil recovery. Acute respiratory failure can develop, and the pulmonary opacities are characterized by neutrophilic inflammation. Short-term prognosis is generally good with the administration of intravenous corticosteroids; however, recent studies suggest that engraftment syndrome is a marker for poor long-term survival in allogeneic HCT recipients.[167,168]

Pulmonary Alveolar Proteinosis

In the context of HCT and hematologic malignancies, pulmonary alveolar proteinosis is thought to be due to qualitative and quantitative macrophage dysfunction rather than the presence of autoantibodies against granulocyte macrophage–colony stimulating factor, a critical regulator of surfactant homeostasis, as in primary pulmonary alveolar proteinosis. Although rare, pulmonary alveolar proteinosis has been reported following autologous HCT, cord blood transplantation, and in association with respiratory viral infections.[170] Chest *computed tomography* (CT) shows diffuse or patchy ground-glass opacities that may be indistinguishable from viral pneumonia or IPS. Milky, opaque BAL fluid revealing foamy alveolar macrophages that stain positive with periodic acid–Schiff is diagnostic in the appropriate clinical setting. Treatment is directed at the underlying condition (i.e., treatment of the malignancy or infection) in addition to supportive care, including whole lung lavage (see also Chapter 98).

Pulmonary Vascular Disease

In addition to venous thromboembolic disease, rare thrombotic vascular complications can cause acute respiratory failure after HCT. Pulmonary veno-occlusive disease presents 3 to 4 months after transplant with insidious onset of fatigue and exertional dyspnea. The pathologic lesion is diffuse intimal proliferation and fibrosis of pulmonary venules.[171] Chest CT reveals ground-glass opacities, septal thickening, and mediastinal adenopathy.[172] The presence of pulmonary hypertension with normal pulmonary artery occlusion pressures should elevate suspicion of pulmonary veno-occlusive disease. Treatment with high-dose corticosteroids has been reported to be beneficial,[173] but the majority of patients succumb to progressive heart failure.[174] Pulmonary veno-occlusive disease is a clinically underrecognized cause of late morbidity, as suggested by the presence of pulmonary veno-occlusive disease in 34% of cases in an autopsy series of HCT recipients who had survived at least 1 year.[175] *Pulmonary cytolytic thrombus* is a complication specific to HCT presenting primarily in children with an onset 1 to 12 months posttransplant. Pulmonary cytolytic thrombus presents with fever, cough, respiratory distress, and chest CT findings of small peripheral nodules and diffuse opacities.[176,177] The diagnosis is made by lung biopsy, which shows vascular occlusion with entrapped leukocytes and endothelial disruption in distal pulmonary vessels adjacent to areas of infarct.[178] *Transplant-associated thrombotic microangiopathy* after HCT is caused by small-vessel endothelial injury with systemic and multiorgan manifestations. Whereas the kidneys are most commonly affected, pulmonary arteriolar involvement can lead to severe and acute pulmonary hypertension, right heart failure, and death.[179,180] It has been reported to complicate DAH after HCT.[181]

LATE-ONSET COMPLICATIONS

Given the increasing survival of HCT recipients, particularly those with allogeneic HCT, late pulmonary complications are of growing concern for survivors and their providers. The burden of late pulmonary complications is second only to infectious complications, reflected in the hospitalizations and causes of death in long-term survivors of allogeneic HCT for cancer compared with cancer patients not treated with HCT.[182] A prospective study of 200 consecutive allogeneic HCT recipients demonstrated an incidence of late-onset noninfectious pulmonary complications of 20%, confirming prior estimates from retrospective series.[183]

Bronchiolitis Obliterans Syndrome

Bronchiolitis obliterans syndrome (BOS) is the most common and well-described late noninfectious pulmonary complication, seen in 3–10% of all allogeneic transplant recipients, and 14% in those with chronic GVHD.[183-185] BOS is the clinical correlate of obliterative bronchiolitis, an end-stage pathologic entity characterized by fibrous obliteration of terminal bronchioles also seen in the context of lung transplantation, connective tissue disorders, and toxic environmental exposures.[186]

In allogeneic HCT recipients, BOS is considered a manifestation of chronic GVHD, a systemic condition in which alloreactive donor immune cells attack host tissues and promote tissue fibrosis. It is postulated that small airway epithelial injury induces alloreactive T cell–mediated inflammation and subsequent aberrant repair response leading to fibrosis.[187,188] In murine models of chronic GVHD, follicular helper T cells, donor B cell antibody production and germinal center B cells are required for the development of BOS lesions and physiologic airflow obstruction.[189] Clinical series of lung biopsies in patients who meet BOS spirometric criteria show a spectrum of pathologies, including a lymphocytic bronchiolitis, suggesting that some cases are potentially reversible with early intervention.[190]

Many factors, including conditioning regimen, donor source, and history of pneumonitis, have been implicated in the development of BOS, but only chronic GVHD has been consistently associated. There is mounting evidence that community-acquired respiratory viral infections play a role in the development of BOS.[191-194] Early subclinical lung dysfunction has been associated with BOS,[183,195] consistent with observations in lung transplantation,[196] and suggests that lung injury early posttransplant may predispose the airways to subsequent alloimmune attack.[195] However, identifying patients at risk remains a clinical challenge because respiratory viral infections and early spirometric changes are nonspecific events in many patients after allogeneic HCT.

BOS is characterized by new-onset irreversible airflow obstruction. Patients present with subacute exertional dyspnea or a cough unresponsive to antibiotics before airflow obstruction is identified by pulmonary function testing. An asymptomatic decline on routine *pulmonary infection tests* (PFTs) may alert the clinician to the diagnosis. High-resolution chest CT with inspiratory and expiratory images may show mosaic attenuation indicative of air trapping (eFig. 125.13). BOS has been described as early as 50 days and as late as 10 years posttransplant; most cases present within the first 2 years after HCT.[184,185,197,198] By the time symptoms develop, the *forced expiratory volume in 1 second* (FEV_1) is often less than 50% predicted, highlighting the importance of routine spirometric monitoring in this population.[199] Rapidly progressive airflow obstruction less than 1 year posttransplant carries a poor prognosis.[198] Contemporary series show a 2-year survival of 70–75%, which is an improvement compared with initial reports,[199,200] possibly due to increased recognition and better supportive care. The main causes of death are primary respiratory failure or lung infections.[185,199,201]

Due to the morbidity of lung biopsy in HCT recipients, the diagnosis of BOS relies on spirometric and clinical criteria. The National Institutes of Health Chronic GVHD Consensus Guidelines provide a uniform definition for BOS based primarily on spirometric criteria of FEV_1 decline and airflow obstruction and supporting evidence of small airways disease[202] (eTable 125.1). Whereas this definition provides consistency for the purposes of clinical trials, it does not reflect the full clinical spectrum of BOS. A phenotype of reduced FEV_1 with a preserved FEV_1/forced vital capacity ratio, which is well described in COPD, has also been described in BOS after HCT.[203] Moreover, early identification of disease remains a challenge with the Consensus Guidelines definition, which uses a cutoff of FEV_1 less than 75% predicted. A decline of more than 5% per year in percent predicted FEV_1 more accurately identified patients who experienced fixed airflow obstruction after HCT and was associated with increased mortality not attributable to hematologic relapse.[204]

The goal of therapy for BOS after HCT is to prevent further lung function decline, although if BOS is diagnosed and treated early, it may be possible to improve lung function. The use of an inhaled corticosteroid with a long-acting β-agonist (budesonide/formoterol) is associated with short-term improvement in FEV_1 in patients with newly diagnosed BOS.[205] The combination therapy of fluticasone, azithromycin, and montelukast, with or without prednisone, is well tolerated and associated with FEV_1 stability for most individuals.[197,206] However, the use of azithromycin in this context has been called into question in light of data associating azithromycin with hematologic relapse when given early after allogeneic HCT,[207] and an increased risk for secondary neoplasms.[201] The benefit of azithromycin has not been definitively demonstrated for BOS after HCT.[208] Secondary treatments for progressive BOS include extracorporeal photopheresis and other established immunosuppressive medications for steroid-refractory chronic GVHD.[209] Supportive care measures, including supplemental oxygen, pulmonary rehabilitation, airway clearance, and antimuscarinic bronchodilators, may help improve quality of life. Lung transplantation has been successfully performed in patients with end-stage BOS without evidence of malignancy or other end-organ complications from their allogeneic HCT.[210,211]

Restrictive Lung Dysfunction and Interstitial Lung Disease

Late-onset restrictive pulmonary dysfunction after allogeneic HCT may be due to *interstitial lung disease* (ILD),[212] as a manifestation of BOS,[213] or to truncal sclerosis from extrapulmonary chronic GVHD.[202] In some instances, the

eTable 125.1 Summary of 2014 National Institutes of Health Clinical Criteria for the Diagnosis and Staging of Chronic GVHD: Bronchiolitis Obliterans Syndrome

1. FEV_1/vital capacity <0.7 or the lower limit of normal.
2. FEV_1 <75% of predicted with ≥10% decline over <2 years and does not correct to >75% with bronchodilator.
3. Absence of infection in the respiratory tract, documented with investigations directed by clinical symptoms.
4. One of the two supporting features of BOS: (A) evidence of air trapping by expiratory CT or small airway thickening or bronchiectasis by high-resolution chest CT, or (B) evidence of air trapping by elevated residual volume or residual volume/total lung capacity ratio.
   - Only 1–3 need to be met if there is chronic GVHD in another organ.
   - Lung biopsy is required to establish chronic GVHD if BOS is the only manifestation of chronic GVHD for the purposes of enrollment on clinical trials.

BOS, bronchiolitis obliterans syndrome; CT, computed tomography; FEV_1, forced expiratory volume in 1 second; GVHD, graft-versus-host disease.

Modified from Jagasia MH, Greinix HT, Arora M, et al. National Institutes of Health Consensus Development Project on Criteria for Clinical Trials in Chronic Graft-versus-Host Disease: I. The 2014 Diagnosis and Staging Working Group report. *Biol Blood Marrow Transplant*. 2015;21:389-401, e381.

etiology for restriction is never determined. In a prospective longitudinal study of 198 allogeneic HCT recipients, restrictive lung disease not identified as ILD was responsible for 5% of the cases of late-onset lung disease.[183] Restriction, due to ILD or other causes, may develop concurrently with obliterative bronchiolitis.[214] Retrospective studies show that restrictive lung dysfunction in long-term survivors may develop in as many as 12% of adults[215]; restrictive lung dysfunction has been documented in 19–25% of children surviving at least 5 years.[216,217] Forms of ILD after HCT are diverse: histologic patterns include organizing pneumonia, nonspecific interstitial pneumonia, and lymphoid interstitial pneumonia.[212] The presence of GVHD is a common theme.[183,188,218,219] These diverse etiologies may in fact represent direct or indirect manifestations of GVHD in the respiratory system, similar to the concept of restrictive allograft syndrome in lung transplantation as a manifestation of chronic lung allograft dysfunction.[220] Restrictive lung disease may also result from late toxicity from prior chest irradiation or total body irradiation,[183,216] which is a known risk factor for acute lung injury syndromes.[155]

Organizing Pneumonia

Organizing pneumonia (OP) after HCT is considered a manifestation within the spectrum of acute lung injury in the IPS family. Because it tends to present later after transplant (after day +100), it is considered here as a late-onset ILD after HCT. The histology, as in cryptogenic OP in the general population, is characterized by a histology of patchy plugs of granulation tissue occupying distal terminal airways, alveolar ducts, and alveolar sacs; widened alveolar septa and mononuclear cell infiltration; as well as the accumulation of foamy macrophages within alveoli.[219] OP after HCT is associated with the presence of acute or chronic GVHD.[214,219,221,222] Other risk factors include donor HLA disparity, female donor-to-male recipient transplant, peripheral blood stem cell source from a related donor, and radiation as part of a myeloablative conditioning regimen.[222]

As in other settings, OP after HCT presents with cough, progressive dyspnea over days to weeks, sometimes fever, and associated hypoxemia. In a case series of 49 patients, the median time to diagnosis was 108 days after HCT, after a median symptom duration of 13 days.[219] OP misdiagnosed as infectious pneumonia or simply unrecognized may progress to acute respiratory failure. The radiographic hallmark of OP after HCT on chest CT is patchy ground-glass, linear or peribronchial opacities, often in an upper lobe distribution.[223] Given that surgical lung biopsy is uncommon, the diagnosis of OP is often made presumptively after exclusion of infectious etiologies with BAL. However, biopsy series suggest that radiographic abnormalities consistent with OP may represent a spectrum of interstitial pathologies.[212]

Treatment consists of corticosteroids. For moderate disease, it is reasonable to initiate 0.75 mg/kg/day of prednisone until there is symptomatic or radiographic improvement before initiating a slow taper over at least 4 to 6 months.[224] Anecdotally, chronic macrolide therapy has been given as an adjunctive anti-inflammatory treatment to those with refractory disease or an intolerance to prednisone.[225] Azathioprine or other immunosuppressive agents may be used in refractory disease. Overall, prognosis for OP after HCT is good because the majority of cases respond to corticosteroids. Relapse is common, particularly when the steroid taper is accelerated, which may often be necessary given the significant side effects of long-term corticosteroids.[221,226]



Figure 125.5 Chest computed tomography of patient with pleuropulmonary fibroelastosis. Apical fibrosis with traction bronchiectasis, pleural thickening, and reduced lung volumes is apparent. This patient subsequently received a lung transplant 29 years after his allogeneic bone marrow transplant. (From Bergeron A, Cheng GS. Bronchiolitis obliterans and other late pulmonary complications after allogeneic hematopoietic stem cell transplantation. *Clin Chest Med*. 2017;38:607-621 and courtesy Anne Bergeron, MD, PhD.)

Pleuropulmonary Fibroelastosis

Pleuropulmonary fibroelastosis (PPFE) is a rare entity characterized by pleural and subpleural parenchymal thickening due to elastotic fibrosis and the presence of intra-alveolar fibrosis with minimal cellular inflammation.[227] In the setting of HCT, BOS lesions are often seen along with subpleural pathology, suggesting alloimmune involvement.[214] CT findings are characterized by dense fibrosis in an apical distribution, traction bronchiectasis, pleural thickening, and volume loss (Fig. 125.5); these abnormalities may progress to include the lower lung zones.[228] In some retrospective series, PPFE identified by chest imaging is primarily responsible for restrictive lung impairment.[213] It is likely underrecognized as a complication of HCT because it can be seen late, after patients have returned to community care. In a series of 15 patients, the diagnosis of PPFE developed nearly 9 years after HCT.[229] PPFE may be the result of a cumulative series of lung insults, including total body irradiation, infectious pneumonias, and chronic GVHD.[229] Prognosis is poor because most cases progress to chronic respiratory failure. Pneumomediastinum and pneumothorax often complicate PPFE.[230,231] Lung transplantation is the only definitive therapy.[188]

NONINFECTIOUS COMPLICATIONS IN SOLID ORGAN TRANSPLANTATION

POSTOPERATIVE RESPIRATORY FAILURE

While infectious pneumonia predominates as an early complication in SOT, noninfectious complications related to the surgical procedure also impact early outcomes. Postoperative respiratory failure is a particular concern for liver transplant

recipients, who have a high rate of prolonged postoperative intubation and reintubation when mechanically ventilated for longer than 24 hours.[232] The poor medical condition of patients with end-stage liver disease, impaired respiratory muscle function from upper abdominal surgery, and volume overload leading to pulmonary edema contribute to the high incidence of acute respiratory failure.[233] Acute respiratory distress syndrome complicates 2–4% of liver transplants. Transfusion-related acute lung injury is a notable cause for respiratory failure in liver transplantation in light of the large amount of blood products that must be transfused in a patient with coagulopathy from end-stage liver disease. In addition, those with pretransplant hepatopulmonary syndrome may require prolonged postoperative ventilatory or oxygen support because the hepatopulmonary syndrome does not correct immediately after transplant,[234,235] and the mortality rate for those with severe hypoxemia is as high as 45%.[236] Patients with portopulmonary hypertension are also at increased risk for poor perioperative outcomes; many cases are not eligible for transplantation unless vasodilator therapy can bring mean pulmonary artery pressures to 35 mm because major perioperative changes in hemodynamics can result in acute right heart failure.[237]

PLEURAL EFFUSIONS

In liver transplantation, postoperative pleural effusions are the most common posttransplant pulmonary complication, ranging in incidence from 32–96%.[30] The majority are mild, right sided, and self-limited. Thoracentesis is reserved for persistent large pleural effusions or when there is a concern for infection.[30] Early postoperative pleural effusions after heart transplantation are also common.[238] In one series, the incidence of pleural effusion was 85% by 1 year posttransplant. The majority of effusions were bilateral, small, and self-limited.[234]

DIAPHRAGMATIC DYSFUNCTION

Diaphragmatic dysfunction may develop due to injury to the phrenic nerve resulting from hypothermic or mechanical damage during surgery. The incidence of diaphragmatic dysfunction after heart or heart-lung allograft surgery has been reported to be 12–43%.[239-241] This is also common after liver transplantation, attributed to right phrenic nerve crush injury at the time of suprahepatic vena cava clamping.[242]

METASTATIC PULMONARY CALCIFICATION

Metastatic pulmonary calcification (or pulmonary calcinosis) is a well-known complication of chronic renal failure characterized by deposition of calcium salts in the alveolar epithelial basement membrane. This has been reported as a rare complication in renal transplant recipients without apparent abnormalities of calcium or phosphate.[243] The lesions present as nodular opacities 2 to 12 mm in diameter that may be unilateral or diffuse with an upper lobe distribution (eFig. 125.14). Patients are often asymptomatic, but may develop dyspnea, and show a restrictive pattern as well as abnormal diffusing capacity on pulmonary function testing.[244] Progression to respiratory failure has been reported.[243]

DRUG-INDUCED PNEUMONITIS

Many agents used to maintain allograft function have been implicated in lung disease after transplantation, particularly immunosuppressive medications common to both HCT and SOT. The most common agent implicated in drug-induced pneumonitis for transplant recipients is sirolimus, an inhibitor of the *mammalian target of rapamycin* (mTOR) regulator of cell metabolism. Toxicity from sirolimus is most common in kidney transplant recipients, in which the incidence is 11%.[245,246] This agent is used alone or together with other agents to prevent graft rejection in renal transplant.[247] (The calcineurin inhibitor cyclosporine has also been associated with capillary leak and acute respiratory distress syndrome.[248-251]) Tacrolimus has been associated with cryptogenic OP.[252] Sirolimus-induced pneumonitis is commonly found in renal transplant patients, with the onset usually within 6 months, although it can develop as late as 1 year after initiation of the drug.[253] Patients present with cough, fatigue, fever, dyspnea and, on occasion, hemoptysis. Hypoxemia and crackles are present in half the cases, and chest CT findings usually include patchy bilateral peripheral consolidations and or reticular and ground-glass opacities.[245] BAL can exclude infection; lavage fluid reveals a lymphocytic or eosinophilic alveolitis. Histologic patterns of injury include OP with lymphocytic interstitial pneumonitis, pulmonary hemorrhage, diffuse alveolar damage and, rarely, pulmonary alveolar proteinosis.[245,246,253,254] The pulmonary toxicity from mTOR inhibitors is considered a class effect because the related drug, everolimus, has been reported to cause pneumonitis in 4.3% of cardiac transplant recipients.[247] As with any drug-induced lung injury, the mainstay of treatment is discontinuation of the drug, with or without a short course of corticosteroids at 1 mg/kg/day.[245] However, the need for continued immunosuppression to prevent graft rejection in SOT recipients requires that the offending agent be replaced with another appropriate agent.

MALIGNANCY AFTER TRANSPLANTATION

Transplant recipients are at high risk for developing malignancies, owing to prolonged immunosuppression, increasing age of the transplant population, and the longer survival after successful allografting.[182,255,256] In HCT, malignant neoplasms in long-term survivors contribute to excess mortality, particularly in individuals who underwent transplantation as children.[257-260] In SOT, lung transplant recipients have the highest cumulative incidence of malignancies, followed by heart, kidney, and liver recipients.[256] Mortality after SOT due to cancer is higher than that of the general population.[261] Posttransplant malignancies affecting the lung include lymphoma, bronchogenic carcinoma, and Kaposi sarcoma.[259,260,262]

Posttransplant lymphoproliferative disorder (PTLD) is a heterogenous group of disorders characterized by abnormal clonal proliferation of lymphoid cells developing in association with immunosuppression for maintenance of the allograft. Hodgkin lymphoma and diffuse large B cell lymphomas that develop in the posttransplant period may be classified as PTLD. Oncogenic viral activation with *Epstein-Barr virus* (EBV) is a key factor in 50–80% of cases,[263] and

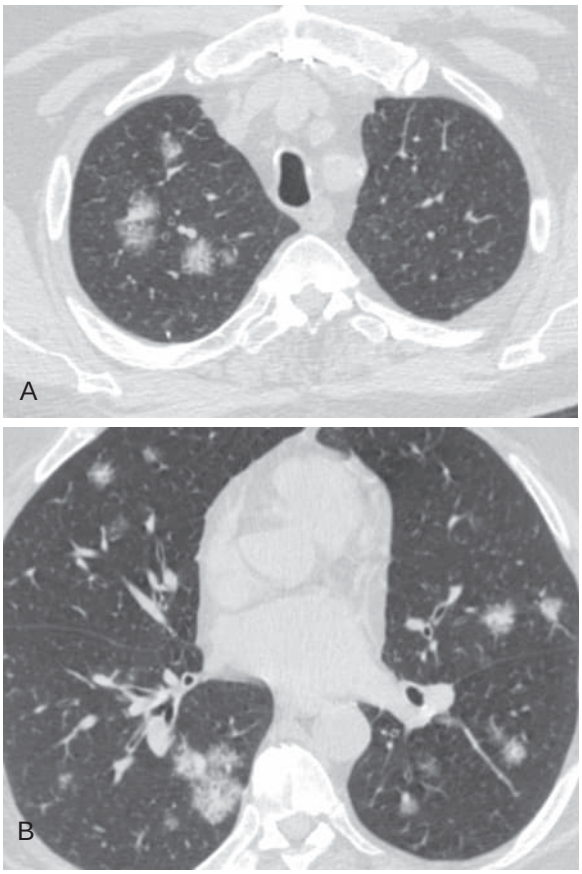

Figure 125.6 Posttransplant lymphoproliferative disorder after solid organ transplantation. A 60-year-old man presented with progressive nodular opacities 9 years after a heart transplant while on tacrolimus and mycophenylate mofetil. Numerous bilateral irregular ground-glass nodular opacities progressed in size over 2 months. (A–B) Different cuts of the same chest computed tomography scan. Infectious workup including bronchosocopy with bronchoalveolar lavage was negative. Lung biopsy revealed a diffuse large B cell lymphoma that was Epstein-Barr virus positive by in situ hybridization, consistent with posttransplant lymphoproliferative disorder. (Courtesy Cynthia Fisher, MD.)

the risk for PTLD is greatest for patients who are EBV seronegative receiving an allograft from an EBV-seropositive donor. PTLD can also arise that is negative for EBV by RNA detection on histology. For allogeneic HCT, most cases of PTLD happen within the first year while, in SOT, the cumulative incidence continues to increase.[264] The median time to presentation of EBV-negative PTLD is 109 months after renal transplantation.[265] In allogeneic HCT, the incidence of PTLD is highest in recipients of cord blood allografts (1.6%) and lowest in match-related donor grafts (0.40%).[266] The cumulative incidence of PTLD is 2.1% at 10 years in kidney transplant recipients[267] and is higher for heart, liver, and lung transplant recipients.[263,268]

PTLD arises in multiple organs, including the lymph nodes (eFig. 125.15), central nervous system, liver, gastrointestinal tract, and the lung.[263] In the lung, PTLD presents as multiple pulmonary nodules that must be distinguished from opportunistic infection or other noninfectious complications (Fig. 125.6, eFig. 125.16). Treatment strategies include reduction of immunosuppression, which carries a risk of allograft rejection. Anti–B cell therapies such as rituximab and standard chemotherapy regimens for lymphoma are used. Overall prognosis is currently poor.[264,266]

ACKNOWLEDGMENT

We acknowledge David K. Madtes, who first authored this chapter in the previous edition.

Key Points

- Pulmonary complications are common and significantly impact the clinical course for hematopoietic cell transplant and solid organ transplant recipients.
- Infectious lung complications present in relation to the immune status of the transplant recipients and prophylactic strategies.
- Infectious etiologies must be distinguished from noninfectious etiologies, often with the use of bronchoscopy, for accurate diagnosis and treatment.
- Early lung injury syndromes in hematopoietic cell recipients are rare but still have high mortality.
- Most late-onset noninfectious pulmonary complications in recipients of hematopoietic cell transplant, including bronchiolitis obliterans syndrome, are related to chronic graft-versus-host disease.
- Noninfectious pulmonary complications in solid organ transplant recipients often relate to early postoperative complications.

Key Readings

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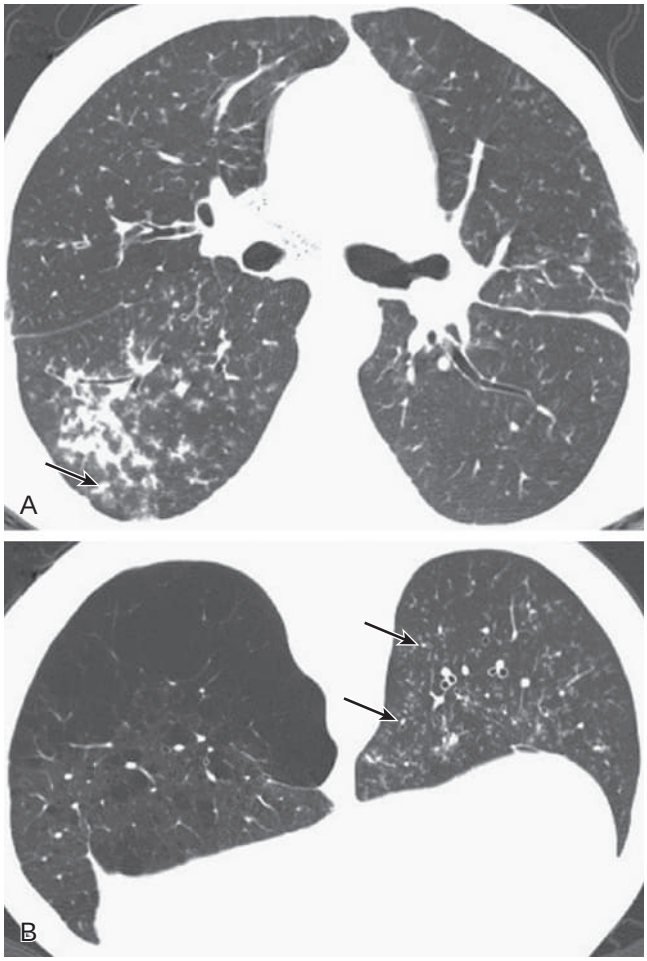
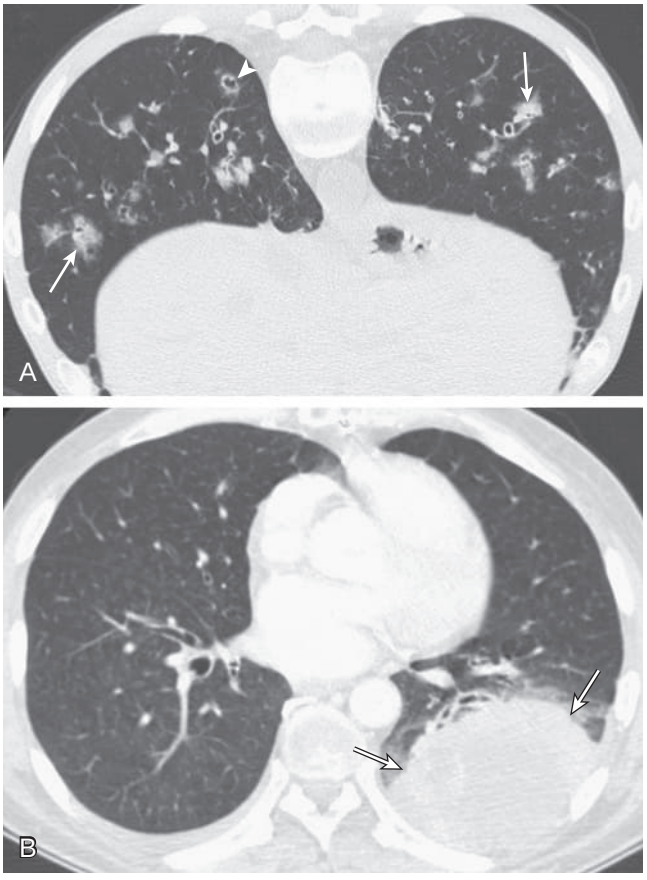
Complete reference list available at ExpertConsult.com.

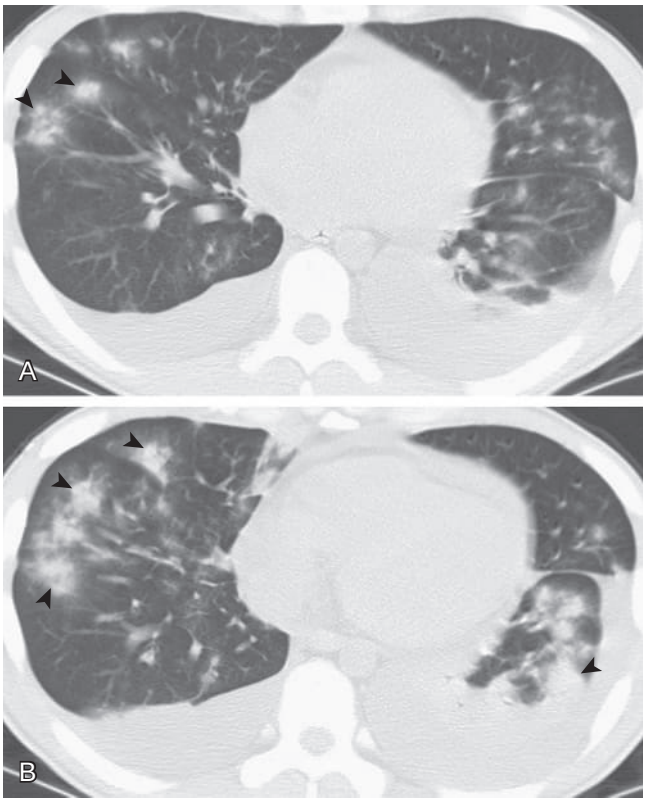
eFIGURE IMAGE GALLERY



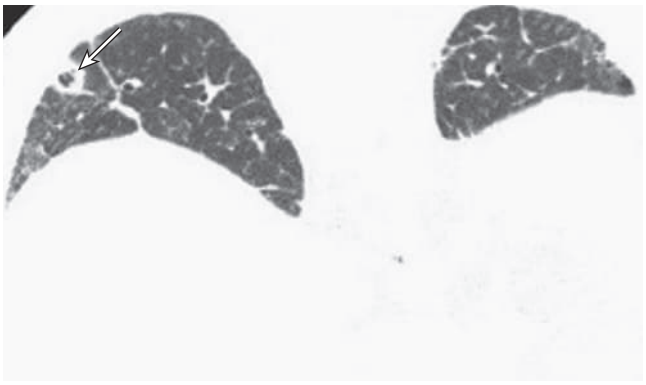
eFigure 125.1 *Pseudomonas* bacterial pneumonia in lung transplant recipients. Axial (A) and prone (B) chest computed tomography through the lower lungs in two lung transplant recipients shows consolidation and small nodules (*arrows*), the latter consistent with infectious bronchiolitis. (Courtesy Michael B. Gotway, MD.)



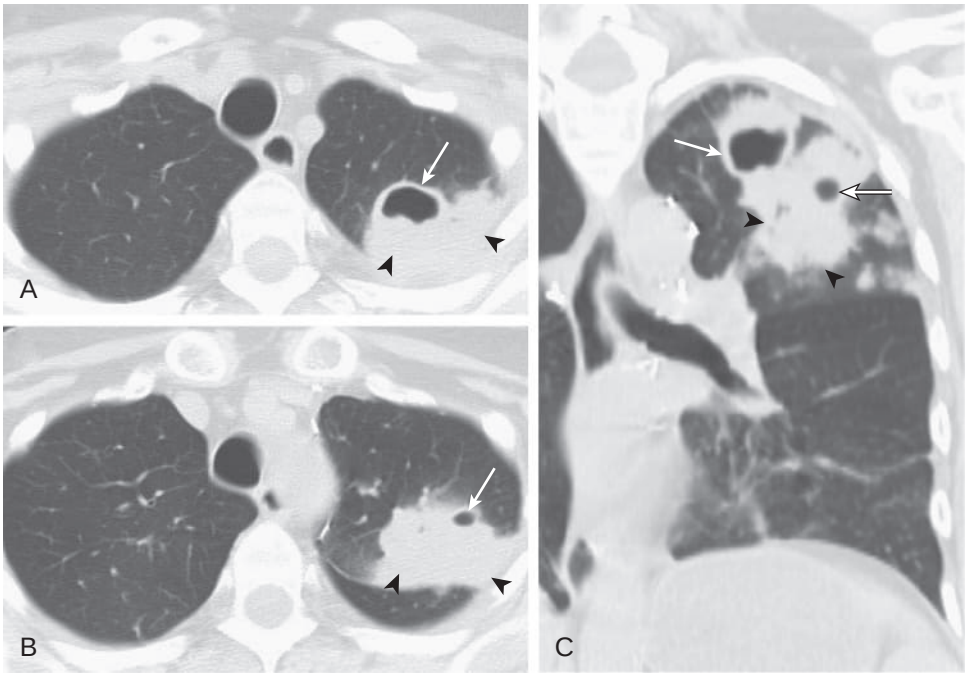
eFigure 125.2 *Aspergillus fumigatus* infection in a lung transplant recipient: variable chest computed tomography appearances. Prone (A) and axial (B) chest computed tomography in two separate lung transplant recipients shows extensive peribronchial ground-glass opacity and consolidation (*arrows,* A) and a small cavitary nodule (*arrowhead*, A) in one patient and a large mass (*arrows,* B) in another patient, both shown to represent *Aspergillus* infection. (Courtesy Michael B. Gotway, MD.)



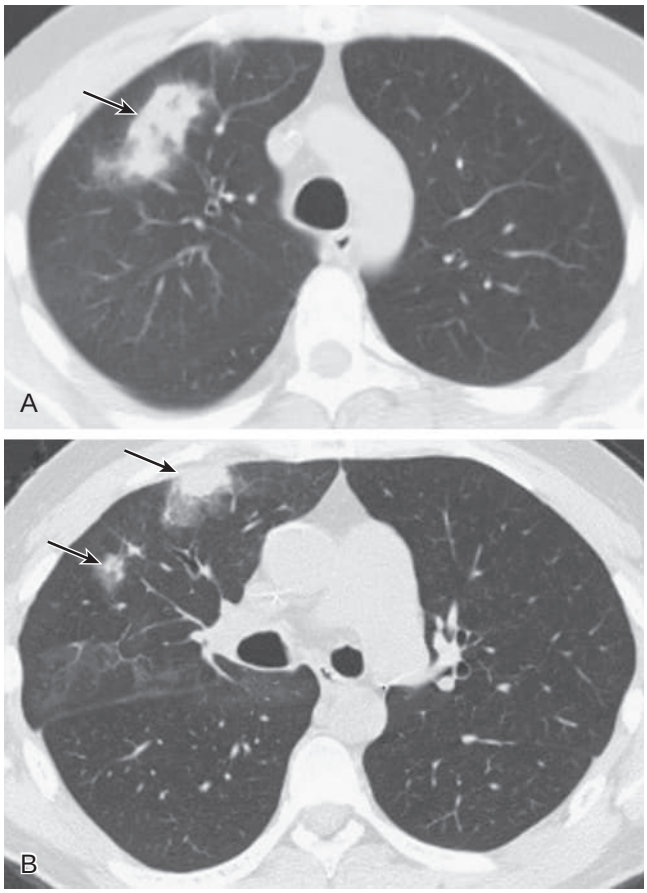
eFigure 125.3 Invasive *Aspergillus fumigatus* infection in a stem cell transplant recipient. (A–B) Axial chest computed tomography through the lower lungs shows basal consolidation and pleural effusions with poorly defined nodules with surrounding ground-glass opacity halos (*arrowheads*); the latter finding is consistent with the ground-glass "halo" sign, typical of angioinvasive aspergillosis when encountered in severely immunocompromised patients. (Courtesy Michael B. Gotway, MD.)



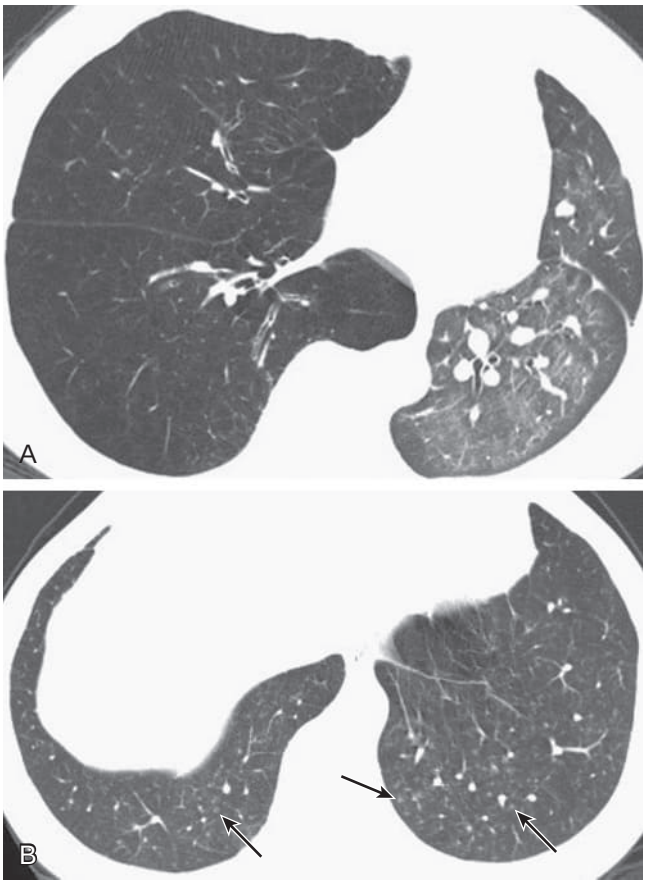
eFigure 125.4 *Aspergillus fumigatus* infection in a lung transplant recipient. Prone chest computed tomography shows a subpleural right lower lobe cavitary nodule (*arrow*) proven to represent *Aspergillus* infection. (Courtesy Michael B. Gotway, MD.)



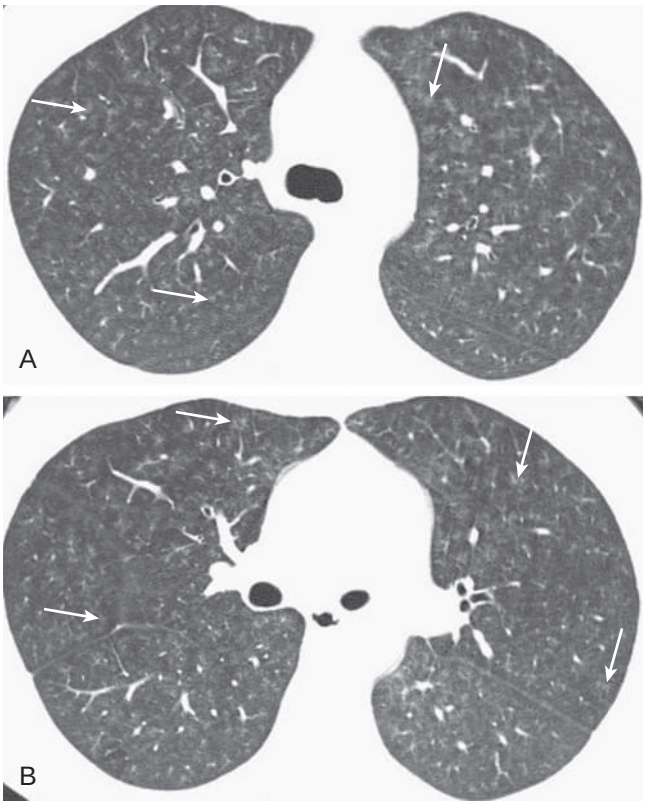
eFigure 125.5 Non-*Aspergillus* mold infection in a lung transplant recipient: mucormycosis. Axial (A–B) and coronal chest (C) computed tomography shows a left upper lobe subpleural mass (*arrowheads*) with areas of cavitation (*arrows*) consistent with invasive fungal infection, proven to represent mucormycosis. (Courtesy Michael B. Gotway, MD.)



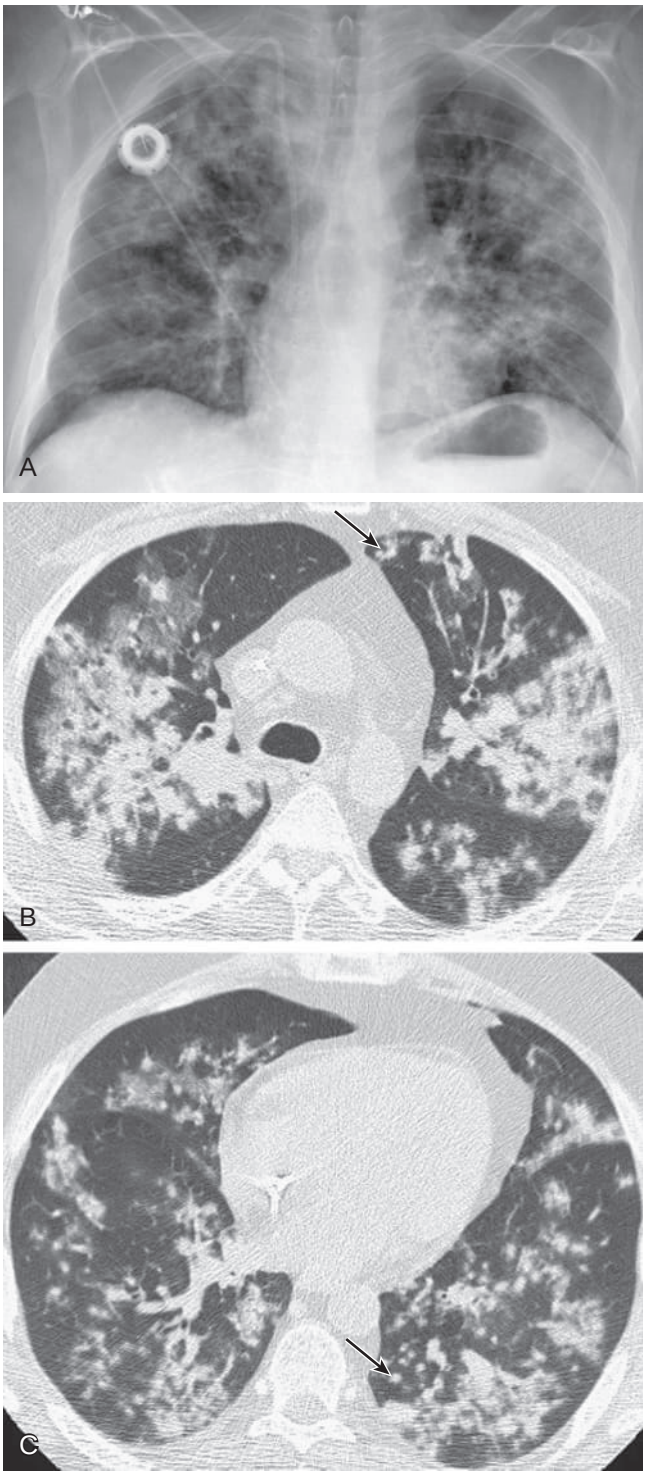
eFigure 125.6 Cytomegalovirus infection in a lung transplant recipient. (A–B) Axial chest computed tomography through the upper (A) and mid (B) lungs shows nodular opacities (*arrows*) with peripheral ground-glass opacity halos, suggesting the possibility of invasive fungal infection. Tissue sampling, however, established the presence of cytomegalovirus infection. (Courtesy Michael B. Gotway, MD.)



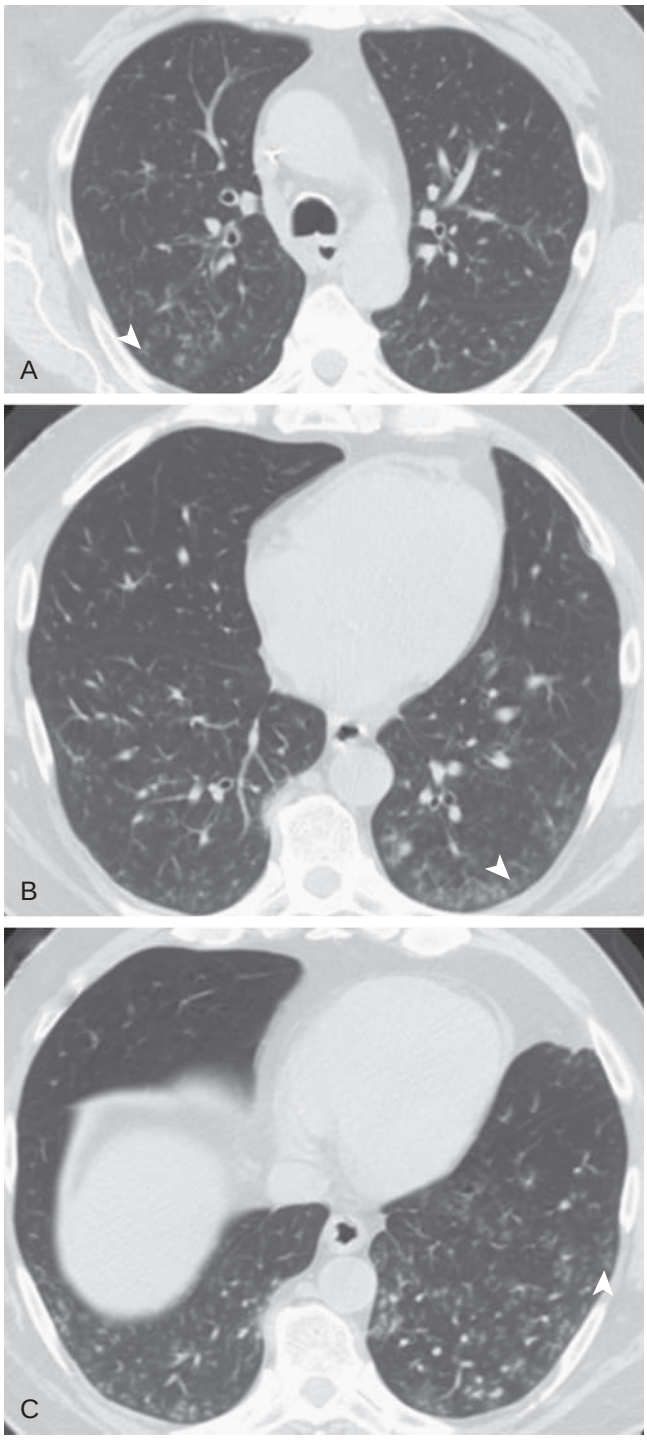
eFigure 125.7 Cytomegalovirus infection in a lung transplant recipient: variable chest computed tomography appearances. (A–B) Axial chest computed tomography through the lower lungs in two lung transplant recipients shows patchy left lower lobe ground-glass opacity in one patient with proven cytomegalovirus infection (A) and small nodules (*arrows*), also proven to represent cytomegalovirus infection, in a different patient (B). (Courtesy Michael B. Gotway, MD.)



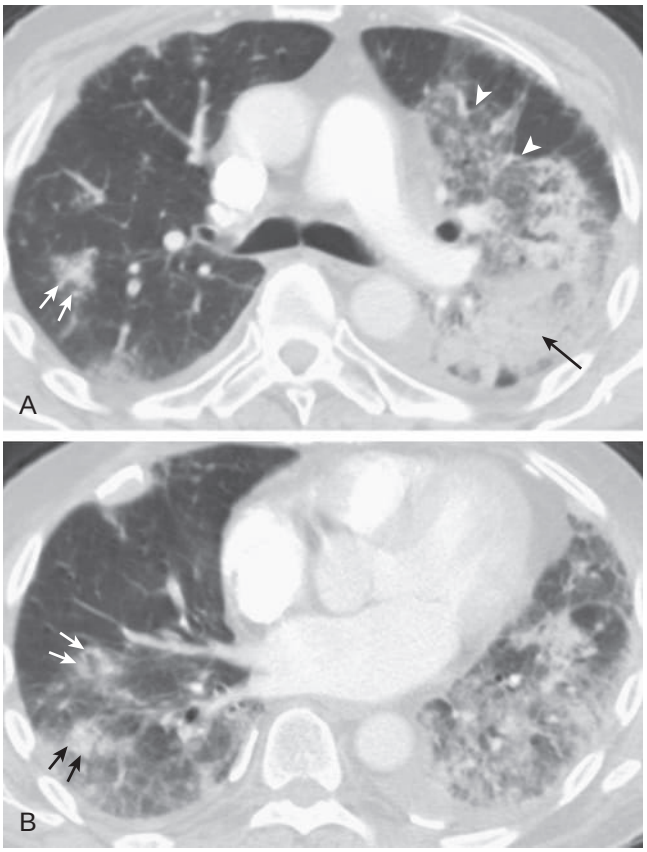
eFigure 125.8 Cytomegalovirus infection in a renal transplant recipient. Axial chest computed tomography through the upper (A) and mid (B) lungs shows diffuse, bilateral, poorly defined centrilobular nodules (*arrows*) shown to represent cytomegalovirus infection. The appearance resembles hypersensitivity pneumonitis. (Courtesy Michael B. Gotway, MD.)



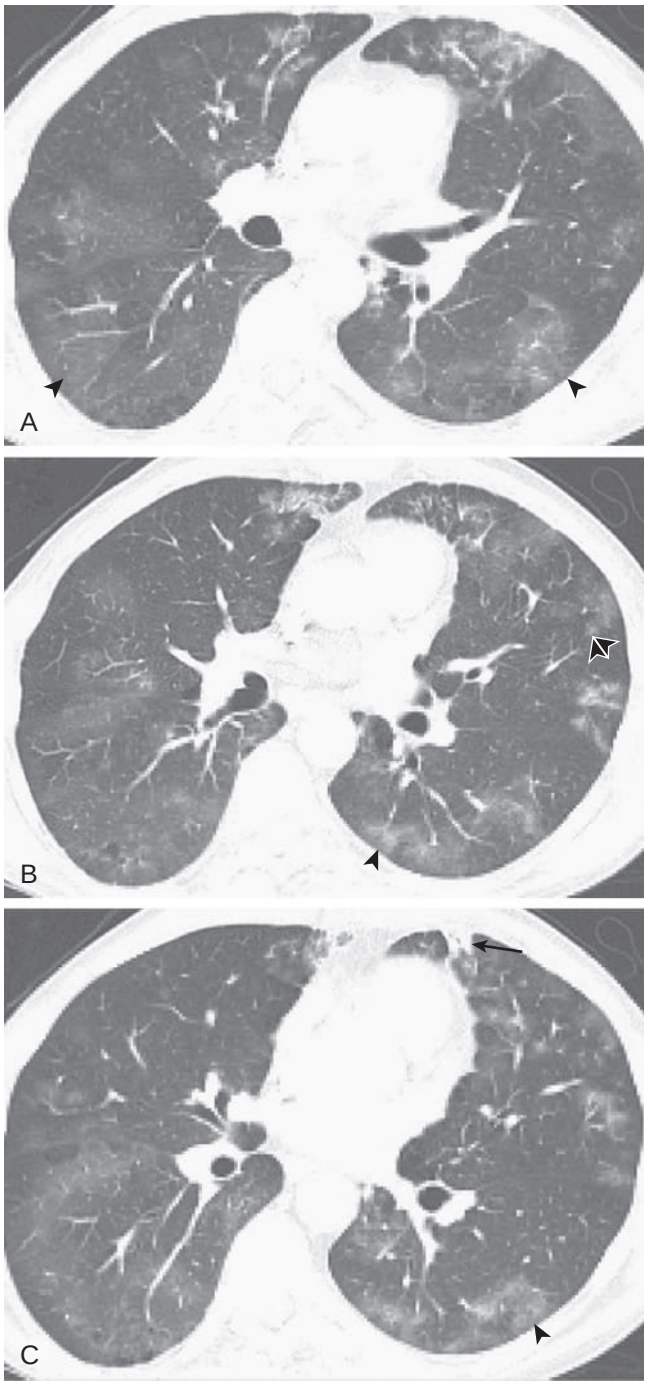
eFigure 125.9 Cytomegalovirus infection in a stem cell transplant recipient. Frontal chest radiograph (A) shows extensive, bilateral poorly defined nodular consolidation without pleural effusion. Axial chest computed tomography through the mid (B) and lower (C) lungs shows extensive ground-glass opacity and consolidation with small, solid, centrilobular nodules (*arrows*). (Courtesy Michael B. Gotway, MD.)



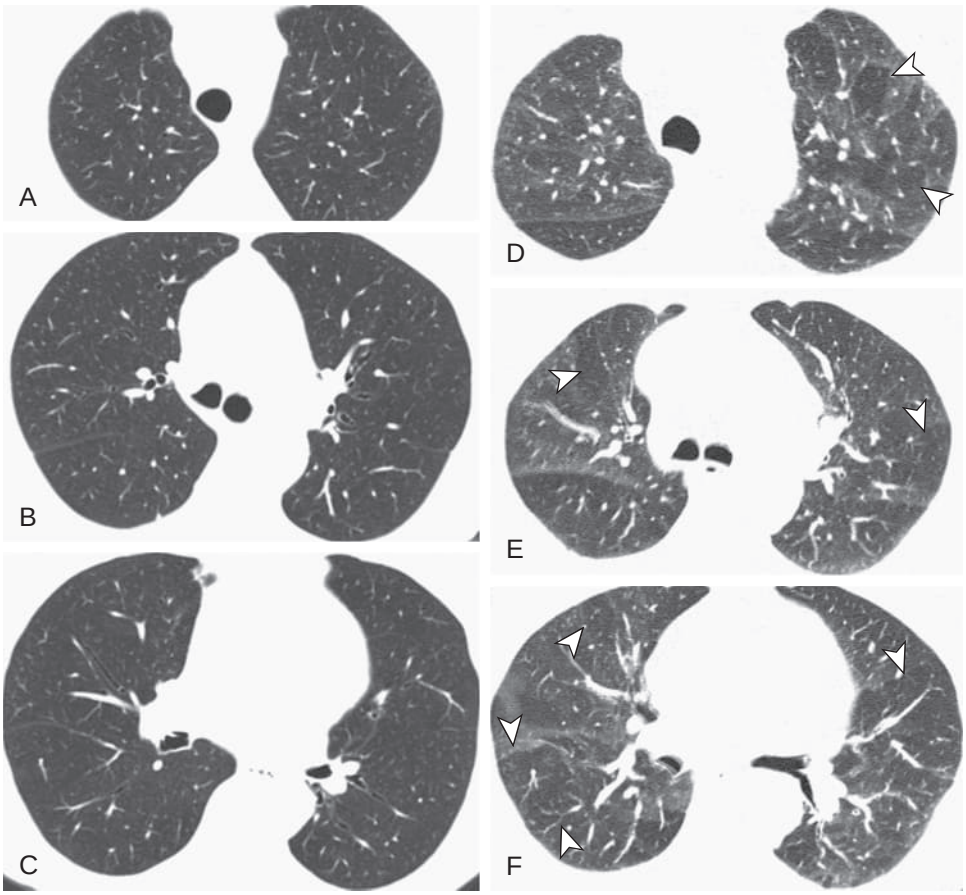
eFigure 125.10 Metapneumovirus infection in a stem cell transplant recipient. Axial chest computed tomography through the upper (A) and lower (B–C) lungs shows small nodules with branching configurations (*arrowheads*) consistent with tree-in-bud opacities and infectious bronchiolitis. (Courtesy Michael B. Gotway, MD.)



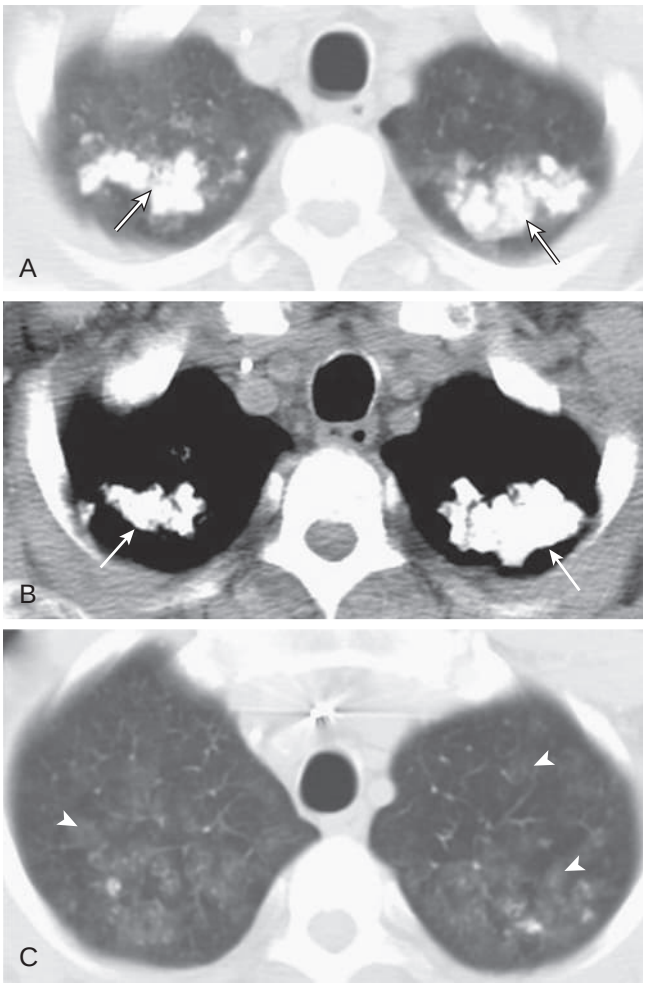
eFigure 125.11 Idiopathic pneumonia syndrome following stem cell transplantation. (A–B) Axial chest computed tomography in a patient who underwent allogenic stem cell transplant 40 days earlier and then developed a cough shows extensive multifocal consolidation (*arrow,* A), nodular on the right side (*double arrows*), as well as patchy ground-glass opacity associated with reticular abnormalities (*arrowheads,* A). Imaging findings are nonspecific and could reflect infection or hemorrhage, among other noninfectious pulmonary complications following stem cell transplant. Evaluation excluded diffuse alveolar hemorrhage and infection as causes of the opacities. (Courtesy Michael B. Gotway, MD.)



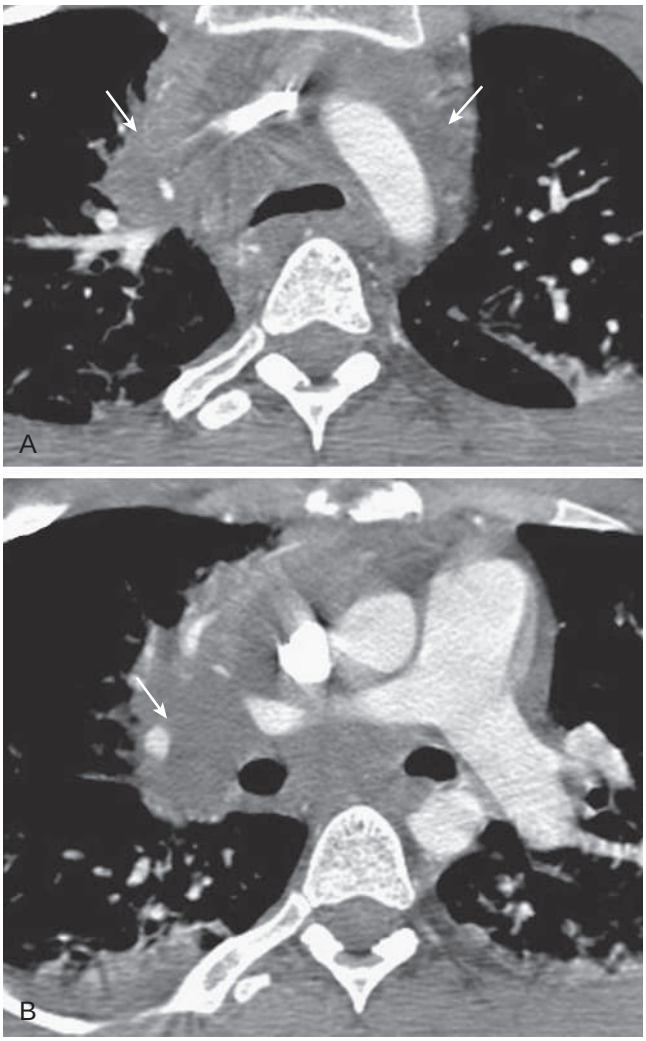
eFigure 125.12 Delayed pulmonary toxicity syndrome following stem cell transplantation. (A–C) Axial chest computed tomography through the mid and lower lungs in a patient treated with bischloroethylnitrosourea who underwent stem cell transplant 70 days earlier and then developed nonproductive cough and shortness of breath shows multifocal ground-glass opacity (*arrowheads*), small nodular opacities (*double arrowheads,* B), and areas of consolidation (*arrow,* C). Imaging findings are nonspecific and could reflect infection or hemorrhage, among other noninfectious pulmonary complications following stem cell transplant. Evaluation excluded diffuse alveolar hemorrhage and infection causes of the opacities. (Courtesy Michael B. Gotway, MD.)



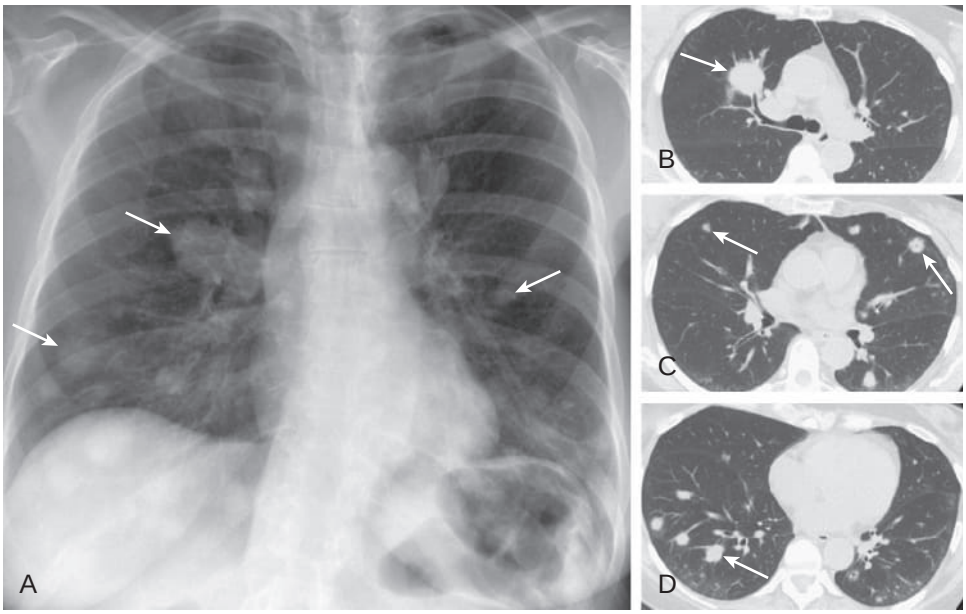
eFigure 125.13 Bronchiolitis obliterans in an allogenic stem cell transplant recipient with graft-versus-host disease. (A–C) Axial chest computed tomography at inspiration through the upper (A), mid (B), and lower (C) lungs shows no significant abnormalities. (D–F) Postexpiratory axial chest computed tomography shows development of inhomogeneous lung opacity, with areas of decreased attenuation (*arrowheads*) representing multifocal air trapping, typical of bronchiolitis obliterans. (Courtesy Michael B. Gotway, MD.)



eFigure 125.14 Metastatic calcification in a renal transplant patient. (A–C) Axial chest computed tomography in lung (A) and soft tissue (B) windows shows nodular, calcified opacities (*arrows*) in the apices bilaterally. Axial chest computed tomography performed through the upper lobes (C), slightly inferior to A and B, shows ground-glass centrilobular nodules (*arrowheads*), typical of pulmonary metastatic calcinosis. (Courtesy Michael B. Gotway, MD.)



eFigure 125.15 Posttransplant lymphoproliferative disease in an allogeneic stem cell recipient. (A–B) Axial enhanced chest computed tomography through the upper (A) and mid (B) lungs shows extensive mediastinal and hilar lymphadenopathy (*arrows*), proven to represent posttransplant lymphoproliferative disorder. (Courtesy Michael B. Gotway, MD.)



eFigure 125.16 Posttransplant lymphoproliferative disease in a renal transplant recipient. (A) Frontal chest radiograph shows multiple, bilateral pulmonary nodules (*arrows*). (B–D) Axial chest computed tomography performed through the upper (B), mid (C), and lower (D) lungs, displayed in lung windows, shows multiple nodules (*arrows*), many associated with bronchi. Tissue sampling established the diagnosis of posttransplant lymphoproliferative disorder. (Courtesy Michael B. Gotway, MD.)

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126 PULMONARY COMPLICATIONS OF ABDOMINAL DISEASES

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INTRODUCTION

This chapter is devoted to the pulmonary complications of abdominal diseases, including diseases of the retroperitoneal organs, the kidneys. The objective in each section is the same: to update the most relevant clinical, pathophysiologic, and therapeutic aspects of the principal abdominal diseases to assist the clinician in diagnosing and managing their sometimes complex and challenging pulmonary complications.

GASTROESOPHAGEAL AND GASTROINTESTINAL DISORDERS

GASTROESOPHAGEAL REFLUX DISEASE

Gastroesophageal reflux disease (GERD) is defined as "a condition which develops when the reflux of stomach contents causes troublesome symptoms and/or complications."[1] It affects up to 28% of the population in the United States.[2] In addition to the classic symptoms of heartburn and acid regurgitation, extraesophageal manifestations of GERD include chronic cough, asthma, and chronic laryngitis. Furthermore, associations between GERD and idiopathic pulmonary fibrosis, as well as post–lung transplant outcomes have been identified.

Pathophysiology

Two general mechanisms have been proposed to explain the pathophysiology of respiratory manifestations of GERD.[3] The "reflux" theory proposes that direct contact of gastric contents with the bronchial and laryngeal tissue is responsible for causing symptoms. Supporting this mechanism, Jack et al. measured tracheal and esophageal pH levels in asthmatics with GERD and found that episodes of reflux followed by a decline in intratracheal pH were associated with a marked reduction in peak expiratory flow rate.[4]

The "reflex" theory, in contrast, proposes that reflux into the distal esophagus stimulates the vagus nerve resulting in cough or bronchoconstriction. The esophagus and tracheobronchial tree are both derived from the embryologic foregut and thus share common innervation allowing for this "esophagobronchial" reflex. This reflex mechanism can be reproduced with the infusion of hydrochloric acid into the esophagus of some[5] but not all[6] patients with asthma.

The relationship between GERD and respiratory disorders is further complicated by the fact that physiologic alterations associated with asthma, cough, and their treatments may themselves promote GERD. Bronchoconstriction may result in a drop in pleural pressures and subsequent increase in the transdiaphragmatic pressure gradient, thus facilitating reflux.[7] Obstructive sleep apnea may act by the same mechanism to increase nocturnal reflux.[8] In addition, hyperinflation and air trapping may result in impaired diaphragmatic function, which is believed to impair the antireflux barrier.[9,10] Finally, bronchodilator therapies, such as theophylline and β-agonists, may further contribute by decreasing lower esophageal sphincter tone.[11,12]

Asthma

Estimates of the prevalence of GERD among asthmatics range from 30–80%, depending on the population studied and the diagnostic testing used.[13–15] In part due to the high prevalence of both diseases, establishing a causal

relationship between GERD and asthma symptoms and identifying patients likely to respond to antireflux therapy remains challenging. In a recent meta-analysis of randomized controlled trials of acid suppressive therapy in adults with asthma, *proton-pump inhibitor* (PPI) therapy was associated with a statistically significant, but unlikely to be clinically significant, improvement in morning peak flow compared to placebo (mean difference 8.7 L/min, 95% CI 2.4–15.0).[16] Subgroup analysis suggested a trend towards greater improvement in morning peak flow in studies that specifically enrolled patients with GERD (mean difference 16.9 L/min, 95% CI 0.9–33.0). PPI therapy was not associated with improvement in secondary outcomes such as *forced expiratory volume in 1 second* (FEV_1) or Asthma Quality of Life Questionnaire Score. Overall, current evidence does not support the use of empiric PPI therapy in patients with asthma without symptoms of GERD. In patients with typical esophageal symptoms such as heartburn, acid regurgitation, or nocturnal asthma symptoms, treatment for GERD with lifestyle modifications and PPI therapy is recommended and should be managed per society guidelines.[17] The role of surgery in patients with GERD-associated asthma remains uncertain. While data from observational studies suggest that surgery may improve asthma control, there is little evidence that it improves pulmonary function.[18]

Chronic Cough

In patients referred to specialty cough clinics, GERD is identified as a contributing factor in up to 41% of cases.[19,20] The relationship between GERD and chronic cough is supported by evidence that instillation of acid into the distal esophagus in patients with chronic cough increases both the frequency of cough and cough reflex sensitivity to inhaled capsaicin.[21,22] As with asthma, the benefit of antireflux therapy is unclear. Overall, evidence does not support the use of empiric acid-suppressive therapy in patients with nonspecific chronic cough without symptoms of reflux.[23] In patients with chronic cough and symptoms of reflux, patients with evidence of pathologic acid exposure (i.e., abnormal pH monitoring) may experience therapeutic benefit with acid-suppressive therapy.[19] Furthermore, combining acid-suppressive therapy with lifestyle modifications and/or weight loss may be more effective than acid-suppressive therapy alone.[24]

Other Lung Diseases

Although GERD and microaspiration have been proposed as risk factors for the development and progression of *idiopathic pulmonary fibrosis* (IPF), causal data supporting pathogenesis are lacking.[25] In a recent meta-analysis of 18 case-control studies, Bédard Méthot et al. concluded that, once smoking is accounted for, there is no association between GERD and IPF.[26] Along these lines, two meta-analyses and a pooled analysis of three large clinical trials of pirfenidone in IPF did not show a consistent improvement in IPF outcomes with antireflux therapy.[27–29] Nevertheless, consensus guidelines conditionally recommend the use of antireflux therapy in patients with IPF despite the paucity of data supporting this practice.[30]

Enthusiasm related to the use of antireflux therapies in patients with IPF and other causes of end-stage lung disease is in part derived from retrospective studies of patients referred for lung transplant.[31] In lung transplant recipients, pretransplant GERD has been associated with early allograft dysfunction and decreased early posttransplant survival.[32] Surgical treatment of GERD has also been shown to reduce the incidence of posttransplant bronchiolitis obliterans syndrome and delay its onset and progression.[33–35] Although data are limited, GERD may be particularly important in the subset of patients with scleroderma-associated interstitial lung disease given the high prevalence of concomitant gastroesophageal manifestations in this disorder.[31]

Diagnosis and Treatment

If the clinical history is typical of GERD and a trial of PPI therapy is successful, no further diagnostic workup may be required. For many patients, however, confirming a diagnosis of GERD may be necessary. Unfortunately, neither the presence of symptoms, nor the response to an empiric trial of antireflux therapy is sensitive or specific enough to diagnose GERD as a cause of respiratory symptoms.[3] The measurement of esophageal acid exposure with ambulatory pH monitoring remains the gold standard for diagnosing GERD. Traditionally, this was achieved with a catheter placed transnasally and worn for 24 hours.[36] More recently, the introduction of a catheter-free wireless pH monitoring device (pH Bravo) attached to the esophageal mucosa during upper endoscopy has gained enthusiasm because it is better tolerated and allows for longer periods of monitoring (typically 2 to 4 days).[37] Multichannel intraluminal impedance (i.e., the electrical impedance of liquid boluses between electrodes on a probe) may also be measured together with catheter-based pH assessment to allow for the detection of nonacidic reflux.[38] The utility of other imaging and endoscopic studies is limited. While upper endoscopy may reveal evidence of tissue damage such as esophagitis or Barrett's esophagus, such abnormalities are uncommon.[39] In contrast, abnormalities on fiberoptic laryngoscopy may be seen in over 80% of normal subjects, thereby limiting its utility for diagnosing GERD.[40] While lipid-laden macrophages found in bronchoalveolar lavage fluid may support the diagnosis, routine measurement is not recommended.[41]

The optimal management of patients with respiratory symptoms thought to be exacerbated by GERD remains unclear. In patients with symptomatic GERD, weight loss and elevation of the head of the bed have been shown to decrease esophageal acid exposure and improve symptoms.[42] Other lifestyle modifications, such as dietary restrictions, are not clearly effective. The majority of studies evaluating the efficacy of acid-suppressive therapy in patients with respiratory symptoms have investigated the use of twice-daily PPI.[24] This is generally the recommended practice for patients for whom the decision has been made to institute acid-suppressive therapy. The benefit of antireflux surgery in patients with respiratory disorders also remains unclear, with limited data supporting its use in patients being considered for lung transplantion.[33–35]

INFLAMMATORY BOWEL DISEASE

Extraintestinal complications of *inflammatory bowel disease* (IBD) are common and have been described in virtually all organ systems. Respiratory manifestations of IBD were first

recognized in the 1970s by Kraft et al., who described six adult patients with IBD who developed unexplained chronic bronchitis with or without bronchiectasis.[43] Although the true prevalence is unknown, respiratory system involvement is increasingly appreciated. While the pathogenesis is not completely understood, it is hypothesized that the association between IBD and pulmonary disease may be related to the shared embryonic origin of the respiratory and colonic epithelium from the primitive foregut.[44] Unlike most extraintestinal manifestations of IBD, which are more common in Crohn disease, pulmonary complications are more commonly seen in ulcerative colitis.[45] While respiratory symptoms typically develop after the diagnosis of IBD has been made, they occasionally precede the diagnosis of IBD, and their severity does not necessarily correlate with bowel disease activity.

Pulmonary Function Disturbances

A spectrum of pulmonary function test abnormalities has been reported in asymptomatic patients with IBD.[46] The most consistent finding is a mild reduction in *diffusing capacity for carbon monoxide* (DL_{CO}).[47–52] While most asymptomatic patients will have normal spirometry, some studies show a small absolute reduction in FEV_1 in IBD patients compared to controls.[52] Others have reported a small but significant increase in residual volume/total lung capacity ratio[48] and evidence of bronchial hyperresponsiveness.[53,54] These findings are concordant with evidence that many asymptomatic IBD patients will have subtle abnormalities on high-resolution *computed tomography* (CT) scans including hyperinflation, air trapping, and bronchiectasis.[48,55]

Intrinsic Pulmonary Complications

A wide array of intrinsic (noniatrogenic) respiratory manifestations of IBD have been identified, ranging from asymptomatic pulmonary function abnormalities to progressive interstitial lung disease (Table 126.1). Most symptomatic intrinsic pulmonary complications of IBD involve inflammation of the airways—anywhere from the larynx to the bronchioles—and may take the form of epiglottitis, tracheal stenosis, bronchiectasis, chronic bronchitis, or bronchiolitis. Large airway disease, particularly bronchiectasis, is the most common.[46,56,57] Patients classically present with cough and increased sputum production. Bronchoscopic examination may show mucosal inflammation and distortion of the airway lumen. Biopsy specimens may reveal mucosal ulceration, thickening of the basement membrane, and infiltration by neutrophils and plasma cells.[57,58] Bronchoalveolar lavage frequently shows a lymphocytosis.[59,60] Rarely, the inflammatory process in the trachea or subglottic space can result in significant upper airway obstruction requiring interventional bronchoscopic or surgical airway management.[46,61]

In addition to airway pathology, there is growing evidence that patients with IBD are also more likely to have other immune-mediated respiratory disorders such as asthma and allergies. A large cohort study of 8072 patients with IBD from the University of Manitoba registry demonstrated an increased likelihood of asthma in patients with IBD compared to matched controls.[62] Smaller studies have shown similar findings for allergic disease.[63] Furthermore, patients with IBD and concomitant asthma or allergies may suffer higher symptom burden and have a more severe disease course.[64,65]

Table 126.1 Noniatrogenic Respiratory Involvement in Inflammatory Bowel Disease

AIRWAY DISEASE
Epiglottic-subglottic stenosis
Tracheobronchitis
Chronic bronchitis
Chronic bronchial suppuration
Bronchiectasis
Bronchiolitis
Bronchiolitis obliterans
Diffuse panbronchiolitis
PARENCHYMAL LUNG DISEASE
Cryptogenic organizing pneumonia
Sarcoidosis
Eosinophilic pneumonia
Interstitial lung disease
Pulmonary fibrosis
Nodules
Chronic pneumonia (esophagobronchial or colobronchial fistula)
SEROSITIS
Pleural effusion
Pleuropericarditis
PULMONARY VASCULAR DISEASES
Pulmonary vasculitis
Pulmonary embolism
Chronic thromboembolic pulmonary hypertension

While less common than airway pathology, parenchymal lung disease is also associated with IBD. The majority of such cases are seen in patients with ulcerative colitis.[46] A wide spectrum of interstitial lung disease pathology has been described including cryptogenic organizing pneumonia, nonspecific interstitial pneumonia, and eosinophilic pneumonia (see Table 126.1). Of these, cryptogenic organizing pneumonia is the most common.[46] Necrobiotic pulmonary nodules may also be seen and must be differentiated from malignancy and infection.[66,67] Finally, associations between IBD and both sarcoidosis and $alpha_1$-antitrypsin deficiency have also been suggested.[46,58,68]

Lastly, growing evidence suggests that patients with IBD have an approximately threefold risk of *venous thromboembolism* (VTE) including both deep vein thrombosis and pulmonary embolism.[69,70] The risk of VTE is higher in individuals experiencing a flare of their IBD, particularly in those requiring hospitalization.[71] This risk is further increased in patients requiring systemic corticosteroids.[72] For this reason, consensus guidelines support the use of anticoagulant VTE prophylaxis in hospitalized patients with IBD who are not experiencing active bleeding.[73]

Iatrogenic Pulmonary Complications

In patients with IBD presenting with respiratory symptoms, iatrogenic complications are far more likely than

noniatrogenic causes and must be excluded. Many agents used to treat IBD are associated with direct pulmonary toxicity. The 5-aminosalicylic acid compounds mesalamine and sulfasalazine are associated with eosinophilic pneumonia, eosinophilic pleural effusions, and interstitial pneumonitis.[74] Methotrexate is well known to cause adverse effects in the lungs including potentially lethal pneumonitis. The anti–*tumor necrosis factor* (anti-TNF) biologic agents such as infliximab, adalimumab, and certolizumab have rarely been associated with acute lung injury as well as with sarcoidosis-like granulomatous disease.[75–78] If recognized early, such pulmonary toxicity often improves with removal of the offending agent and in some cases treatment with systemic corticosteroids (see Chapter 99).

In addition to drug-induced pulmonary toxicity, most agents used to treat moderate to severe IBD result in immunosuppression. Systemic corticosteroids, methotrexate, 6-mercaptopurine, azathioprine, and the anti-TNF agents are all associated with increased risk for opportunistic infections including *Pneumocystis jirovecii*, *Mycobacterium tuberculosis*, and endemic fungal infections.[74] A strong index of suspicion for opportunistic infection should be maintained for any patient with IBD on immunosuppressive agents presenting with pulmonary symptoms and abnormal chest imaging.

HEPATIC DISEASES

Pulmonary complications of advanced liver disease are common and contribute substantially to morbidity and mortality. The most concerning, hepatopulmonary syndrome and portopulmonary hypertension, affect the pulmonary vasculature. In addition, a handful of systemic diseases can affect both the lungs and the liver, and these are discussed below.

PLEURAL EFFUSION

Hepatic hydrothorax is a potentially debilitating complication of advanced liver disease that affects approximately 5–10% of patients with cirrhosis (see Chapter 108).[79,80] Such effusions develop in the absence of coexisting cardiopulmonary disease and are attributed to small diaphragmatic defects that allow ascitic fluid to pass from the abdomen into the pleural space.[81,82] Unless complicated by infection, nearly all effusions are transudative.[83] The majority (85%) are unilateral right-sided effusions, although left-sided and bilateral effusions can be seen.[80] While most patients also have ascites, hepatic hydrothorax may exist in the absence of detectable ascites, presumably because the rate of ascites production is low enough that all the ascites moves into the chest as it is produced.[84] In contrast to ascites, which may result in only mild symptoms despite large amounts of fluid accumulation, most patients with hepatic hydrothorax will be symptomatic with dyspnea and/or cough.[85]

The clinical management of hepatic hydrothorax is challenging. While some patients experience resolution of the effusion with sodium restriction and diuretic therapy, many will have refractory effusions requiring additional treatment.[80] Repeated thoracentesis often results in only transient symptom palliation with cumulative risk of complications inherent to repeated procedures.[86] Conventional thoracostomy tube drainage is not recommended given an unacceptably high risk of complications including substantial protein and electrolyte loss, infection, and renal failure.[87,88] *Transjugular intrahepatic portosystemic shunting* (TIPS) reduces portal hypertension and, in turn, reduces the volume of both ascites and pleural fluid. Initial response rates to TIPS may be as high as 70–80%, but long-term complications including shunt occlusion, worsening liver function, and hepatic encephalopathy limit its applicability.[80,89] In patients with refractory effusions who are not candidates for TIPS, video-assisted thoracoscopic surgery to repair diaphragmatic defects and/or induce pleurodesis may be considered.[90] One interesting approach is the use of indwelling pleural catheters, which at this point can best be considered as a bridge to liver transplantation or for palliation.[91,92]

PULMONARY FUNCTION DISTURBANCES

A wide variety of gas exchange abnormalities can be seen in patients with advanced liver disease. The most common finding on pulmonary function testing is a reduced D_{LCO}.[93] Obstructive physiology is relatively uncommon and, when present, is associated with a smoking history.[93–95] The coexistence of massive ascites can result in restrictive physiology as well as a reduction in D_{LCO}, which both may improve with therapeutic paracentesis or diuresis.[96] On arterial blood gas analysis, there is a tendency towards hyperventilation and hypocapnia (reduced arterial *partial pressure of carbon dioxide* [P_{CO_2}]). Several mechanisms for this respiratory alkalosis have been proposed. First, hyperammonemia and hepatic encephalopathy may induce hyperventilation.[97] Second, increased circulating levels of estradiol and progesterone may directly stimulate ventilation via activation of receptors in the central nervous system.[98] Third, ascites, hepatic hydrothorax, hepatopulmonary syndrome, and portopulmonary hypertension may all result in dyspnea with compensatory hyperventilation.[99] Although overt hypoxemia is uncommon, patients with cirrhosis will also often have lower alveolar *partial pressure of oxygen* (P_{O_2}) and a higher *alveolar-arterial* P_{O_2} *difference* [(A–a)P_{O_2}] compared to matched controls.[100]

HEPATOPULMONARY SYNDROME

Definition and Diagnosis

Hepatopulmonary syndrome (HPS) is a pulmonary vascular complication of liver disease characterized by pulmonary precapillary and capillary vasodilation and abnormal gas exchange. According to the European Respiratory Society Task Force on pulmonary-hepatic vascular disorders and the International Liver Transplantation Society, HPS is defined by the clinical triad of (1) *intrapulmonary vasodilation* (IPVD), (2) abnormal arterial oxygenation (defined as an (A–a)P_{O_2} ≥15 mm Hg or >20 mm Hg if age >64 years) in the absence of an alternative cause of hypoxemia, and (3) advanced liver disease.[101–104]

Pathologic features of HPS include pronounced dilation of precapillary and capillary peripheral branches of

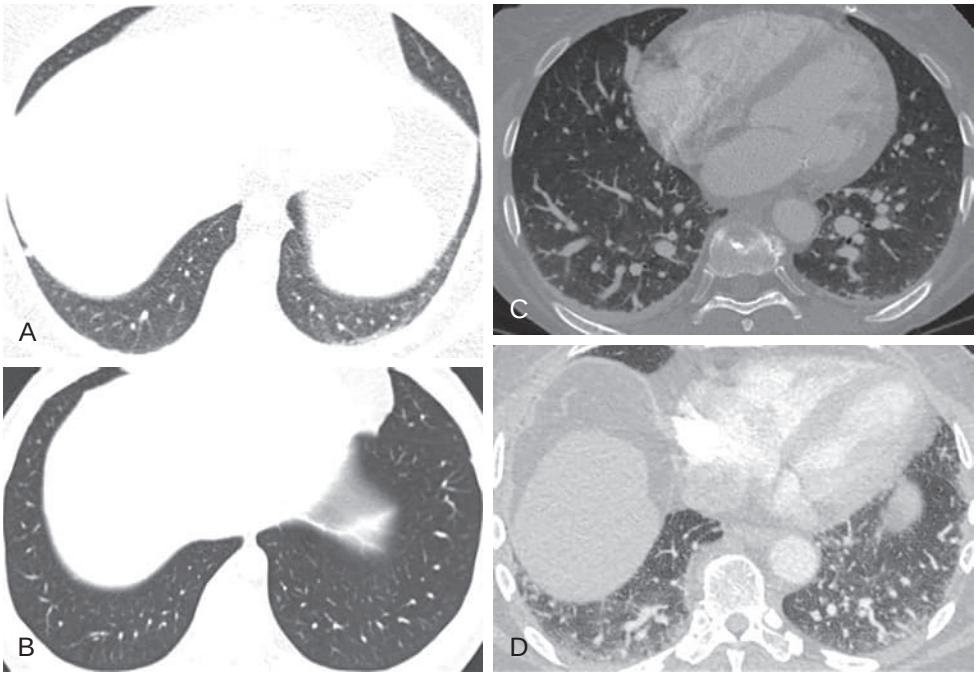

Figure 126.1 The normal appearance of peripheral pulmonary arteries in the lung bases versus the dilated peripheral pulmonary arteries in hepatopulmonary syndrome. (A–B) Unenhanced chest *computed tomography* (CT) displayed in lung windows shows the normal appearance of peripheral pulmonary arteries in the lung bases. (C–D) Enhanced CT through the lung bases in two patients with hepatopulmonary syndrome show dilated peripheral pulmonary arteries. (Courtesy Michael B. Gotway, MD.)

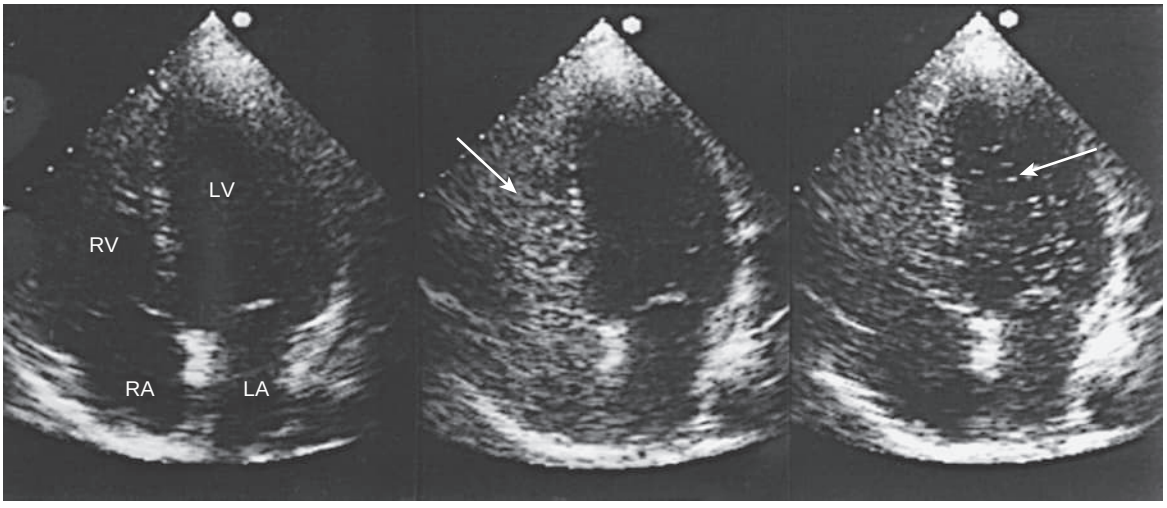

Figure 126.2 Contrast-enhanced echocardiograms in a patient with hepatopulmonary syndrome. *Left,* Normal four-chamber view. *Center*, Injected microbubbles appear in the RV (*arrow*). *Right*, Within 5 beats, microbubbles appear in the LV (*arrow*). The demonstration of microbubbles in the left cardiac chambers is highly suggestive of the presence of intrapulmonary vascular dilations, or, alternatively, of anatomic arteriovenous malformations. LA, Left atrium; LV, left ventricle; RA, right atrium; RV, right ventricle.

the pulmonary vessels, a finding that can be appreciated at chest CT (Fig. 126.1), but the etiology of which remains unclear (see "Pathogenesis" section later). Pulmonary capillaries can be dilated up to 100 μm in diameter (normal capillary diameter 8–15 μm) (eFigs. 126.1 and 126.2). In clinical practice, IPVD is detected with either *contrast-enhanced transthoracic echocardiography* (CE-TTE) or technetium-labeled macroaggregated albumin lung perfusion scanning. CE-TTE is considered the gold standard and is more sensitive than lung perfusion scanning for detection of IPVD.[101] With CE-TTE, agitated saline microbubbles are injected into a peripheral vein. Normally, the microbubbles are trapped in the small capillaries of the pulmonary circulation. In the setting of IPVD, however, microbubbles pass through the enlarged pulmonary capillaries and are subsequently visualized in the left heart, typically within 3 to 6 beats after opacification of the right-sided chambers (Fig. 126.2) (Video 88.1).[103] CE-TTE can also distinguish intrapulmonary from intracardiac shunting, in which microbubbles appear in the left heart almost immediately (within 1 to 2 beats) after opacification of the right-sided heart chambers. With lung perfusion scanning, demonstration of technetium-99m-macroaggregated albumin activity over extrapulmonary organs (e.g., liver, spleen, kidneys, and brain) also indicates the presence of right-to-left shunting. Although macroaggregated albumin lung perfusion scanning cannot differentiate intracardiac from intrapulmonary shunting, it can quantify shunt severity by estimating the percentage uptake of macroaggregated albumin in the brain (normal <6%) and can be helpful to determine

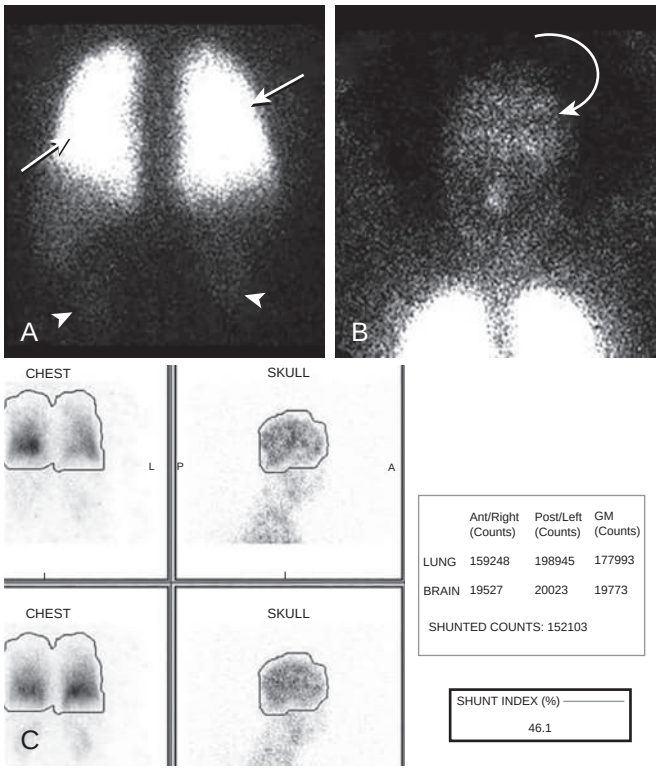

Figure 126.3 Hepatopulmonary syndrome with systemic shunt: ventilation-perfusion scintigraphy. (A) Technetium-99m–labeled albumin macro-aggregates show homogeneous tracer distribution within the lungs (*arrows*) but activity is present within the kidneys (*arrowheads*) and brain (B, *curved arrow*). The brain activity is used to calculate systemic shunting. (C) The calculated shunt index was 46.1% (*box*). (Courtesy Michael B. Gotway, MD.)

the primary cause for hypoxemia in a patient with HPS and concomitant lung disease (Fig. 126.3).[103,105]

The (A–a)Po_2, rather than the arterial Po_2, is used to define HPS because it is more sensitive for detection of abnormal arterial oxygenation. This is particularly true in patients with advanced liver disease who typically hyperventilate, resulting in a decrease in alveolar Pco_2 and an elevation in arterial Po_2 without a change in the (A–a)Po_2.[102] Pulse oximetry is insensitive for detecting HPS, so arterial blood gas testing is needed.[106] HPS severity is classified as mild, moderate, severe, or very severe, depending on the degree of hypoxemia (Table 126.2). Abnormal gas exchange in HPS can be attributed to three distinct mechanisms: *ventilation-perfusion* (V/Q) *mismatch*, *intrapulmonary shunting*, and *diffusion limitation*. *V/Q mismatch* is the predominant mechanism of hypoxemia in most patients and arises in HPS when there is increased perfusion relative to ventilation. Along these lines, most patients with HPS increase their arterial Po_2 in response to increases in inspired oxygen, as expected with V/Q mismatch. In some patients, *intrapulmonary shunting* via dilated intrapulmonary vessels and pulmonary and pleural-based arteriovenous malformations can develop, resulting in worse hypoxemia and a blunted response to supplemental oxygen.[103,107] A *diffusion limitation* has been postulated to be due to a "diffusion-perfusion defect" for oxygen in dilated pulmonary capillaries (Fig. 126.4). The hypothesis is that pulmonary vascular dilation

Table 126.2 Grading of Severity of Hepatopulmonary Syndrome*

Stage	Alveolar-Arterial Po_2 Difference	Arterial Partial Pressure of Oxygen
Mild	≥15 mm Hg or >20 mm Hg if age >64 yr	≥80 mm Hg
Moderate		<80 to ≥60 mm Hg
Severe		<60 to ≥50 mm Hg
Very severe		<50 mm Hg

*All with positive contrast-enhanced echocardiography, breathing room air at rest and at sea level.

causes inadequate diffusion of oxygen to the center of the enlarged capillary. Moreover, the coexistence of a hyperkinetic state, as is often seen in cirrhosis, results in a shorter transit time of red blood cells, which exaggerates this diffusion limitation.[108] Hypoxemia in HPS can thus be attributed to a number of factors. (See also Chapter 44.)

Epidemiology

HPS affects 5–32% of patients with advanced liver disease.[101,103] IPVD, as diagnosed by an abnormal CE-TTE, is present in 20–50% of patients with chronic liver disease,[109,110] but only half of patients with IPVD also have abnormal gas exchange and thus meet diagnostic criteria for HPS. Patients with a positive CE-TTE without coexisting gas-exchange disturbances are considered to have a *forme fruste* of HPS whose natural history is not yet known. Compared to patients with a normal CE-TTE, these patients have worse liver disease severity and an increased prevalence of autoimmune liver disease, but do not seem to have any evidence of clinical or functional impairment.[110–112] Although HPS most commonly develops in the setting of cirrhosis and portal hypertension, it can also develop in acute or chronic hepatitis and acute liver failure. There is no association between the presence or severity of HPS and age, sex, or the etiology or severity of the underlying liver disease.[109,113]

Pathogenesis

The precise mechanism underlying HPS pathogenesis remains uncertain despite numerous investigations. Whether the mechanism of IPVD and hypoxemia is related to insufficient production or metabolism of one or more circulating vasoactive substances by the injured liver or to altered clearance of putative vasodilator molecules produced by endothelial cells[114] remains unknown.

Nitric oxide (NO), a ubiquitous vasodilator considered to be a "fine-tuner" of vascular tone, is presumed to be a pivotal signaling molecule of importance in the pathobiology of HPS.[103,115] Both a constitutive isoform of *NO synthase* (NOS), expressed in endothelial cells (eNOS, or type III NOS),[116] and the *inducible NOS* (iNOS, or type II NOS), expressed in target tissues such as bronchial epithelial cells after exposure to proinflammatory cytokines,[117] have been implicated in experimental models of HPS. Increased levels of exhaled NO have also been observed in patients with HPS.[118] Interventions designed to reduce NO production, however, have not been effective in treating HPS to date.[119–121]

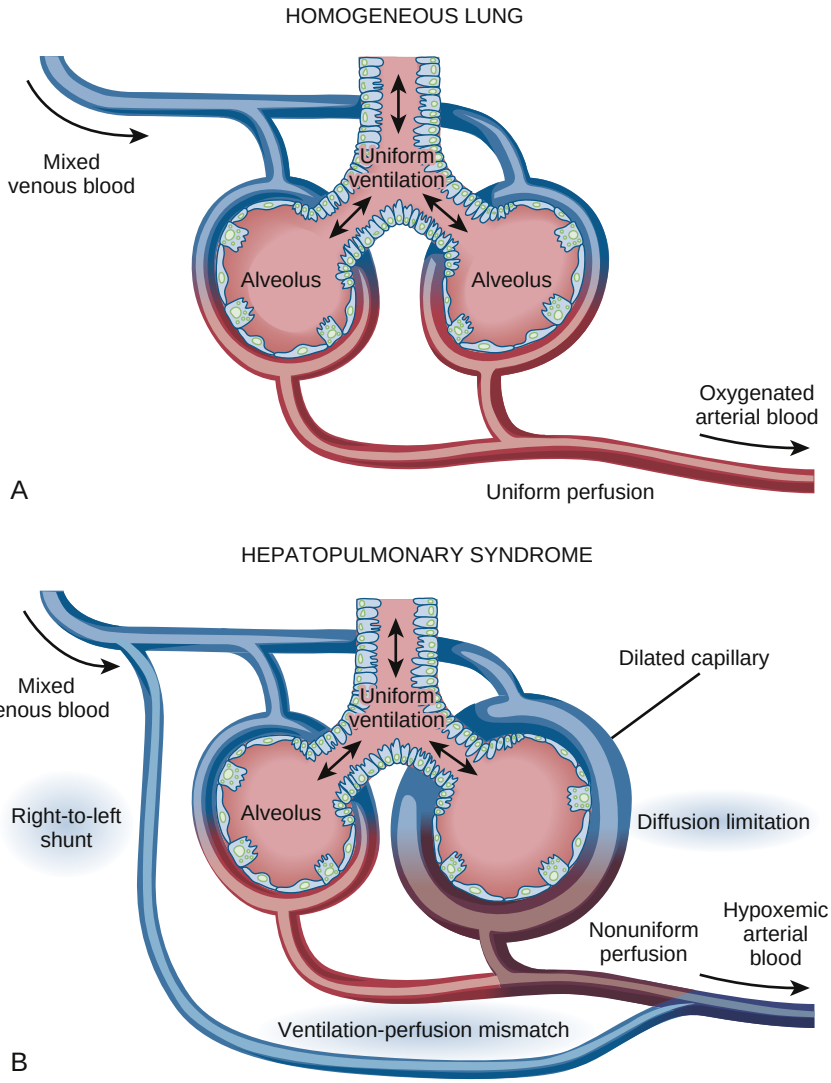

Figure 126.4 Mechanisms of arterial hypoxemia in hepatopulmonary syndrome in a two-compartment gas exchange model. (A) In the homogeneous lung of a healthy individual, with uniform alveolar ventilation and pulmonary blood flow, the capillary ranges between 8 and 15 μm in diameter and oxygen diffuses properly into the capillary while ventilation-perfusion is well balanced. (B) In hepatopulmonary syndrome, where many capillaries are dilated and blood flow is nonuniform, alveolar ventilation-to-pulmonary perfusion mismatch emerges as the predominant mechanism at any clinical stage, either with or without the presence of intrapulmonary shunt and coexistent with oxygen diffusion limitation into the center of the dilated capillaries in the most advanced stages.

Experimental studies in HPS have suggested that endothelin-1, TNF-α, monocytes, placental-derived growth factor, and increased angiogenesis play important roles in HPS disease pathogenesis.[103,122–124] Polymorphisms in genes related to the regulation of angiogenesis are associated with an increased risk of HPS, highlighting the importance of angiogenesis in disease pathogenesis.[125] Carboxyhemoglobin, a known vasodilator and breakdown product of hemoglobin, has also been found to be elevated and to correlate with abnormal blood gas parameters in HPS, suggesting a possible contributory role.[126]

Clinical Manifestations

Clinical manifestations of HPS include dyspnea, platypnea (increased dyspnea in the upright position), hypoxemia, orthodeoxia (i.e., arterial hypoxemia that worsens by at least 5% or 4 mm Hg when the patient is upright vs. recumbent), cyanosis, clubbing, and spider angiomata. Additional nonspecific features of HPS include a decreased D_{LCO} on pulmonary function testing and peripheral pulmonary vasodilation on chest CT scan.[103] Although pulmonary function tests and chest imaging are not diagnostic of HPS, they are useful tests to evaluate for concomitant lung disease, which can be present in approximately one-third of patients with HPS.[127]

Treatment

The only successful treatment for HPS is liver transplantation. Despite recent advances in knowledge regarding the pathophysiology of HPS, there are no approved medical therapies, so treatment is predominantly supportive, with the use of supplemental oxygen. Small studies have evaluated several agents that work through different mechanisms, such as methylene blue (inhibits the effect of nitric oxide on guanylate cyclase),[119,128,129] N(G)-nitro-L-arginine methyl ester (reduces nitric oxide production),[121,130] somatostatin,[131] cyclooxygenase inhibitors,[132,133] almitrine (pulmonary vasoconstrictor),[134,135] propranolol (ameliorates portal hypertension),[136,137] antibiotics (selective gut decontamination),[138,139] pentoxifylline (TNF-α inhibitor),[140] and sorafenib, a tyrosine kinase inhibitor used as a blocker of angiogenesis,[141] all with disappointing results. Garlic was associated with improved oxygenation in patients with HPS in two small studies, but these results have not been replicated in larger multicenter studies.[142,143]

Since liver transplantation remains the only known effective treatment for HPS, all patients with HPS should undergo an expedited liver transplant evaluation.[144] Patients with severe or very severe HPS (arterial P_{O_2} <60 mm Hg) are eligible to receive a *Model for End-stage Liver Disease* (MELD) exception, which awards increased waitlist priority points to expedite transplantation.[145] Youth, a good arterial P_{O_2} response to 100% oxygen, and less pretransplant hypoxemia are all factors associated with a favorable response to liver transplantation.[146] Collectively, these elements may indicate a more reactive pulmonary vasculature and less profound intrapulmonary shunting. As might be expected, the worse the hypoxemia before transplantation, the longer it takes to resolve after surgery.[147]

Prognosis

Compared to liver transplantation candidates without HPS, transplant candidates with HPS have a twofold increased pretransplant risk of death.[148] In the absence of liver transplantation, patients with HPS have a median survival of 41 months following diagnosis and an average decline in arterial P_{O_2} of approximately 5 mm Hg per year.[103] Liver transplantation is associated with improved outcomes in HPS[149] and thus should be considered in all patients with HPS.[101] Posttransplant outcomes in patients with HPS are excellent and similar to non-HPS patients, but more severe pretransplant hypoxemia (arterial P_{O_2} ≤44 mm Hg) has been associated with worse posttransplant survival.[150] Recurrence of HPS is rare and is typically related to recurrence of the underlying liver disease.[151]

PORTOPULMONARY HYPERTENSION

Definition and Diagnosis

Pulmonary arterial hypertension (PAH) associated with portal hypertension—known as *portopulmonary hypertension* (POPH)—is another mysterious pulmonary vascular disorder that develops in the setting of chronic liver disease and portal hypertension.[102,104,146] Because both the diagnosis and the outcome of POPH, particularly in relation to the effect of liver transplantation, are substantially different from those of HPS, it is important to highlight the distinctions between these two disorders (Table 126.3). According to the Sixth World Symposium on Pulmonary Hypertension, POPH belongs to Group 1 PAH and is defined by an elevated mean pulmonary arterial pressure greater than 20 mm Hg at rest, a mean pulmonary artery wedge pressure of 15 mm Hg or less, and an elevated pulmonary vascular resistance of 240 dynes•sec•cm^{-5} or greater (normal is <130 dynes•sec•cm^{-5}).[101,102,152] The presence of POPH impacts liver transplant eligibility and perioperative risk stratification, so guidelines recommend routine transthoracic echocardiography for screening in patients being considered for liver transplantation.[144] Characteristic echocardiographic findings of PAH (elevated right ventricular systolic pressure and/or right ventricular dilation or dysfunction) in the setting of portal hypertension suggest, but are not definitive for, POPH. Right heart catheterization is needed to confirm the diagnosis.

Epidemiology

POPH is found in approximately 5–6% of patients evaluated for liver transplantation.[153] Reported prevalence rates vary depending on the cohort studied and the hemodynamic definition used to define POPH. In classic retrospective postmortem studies, the prevalence of histopathologic evidence of PAH in patients with liver cirrhosis ranged from 0.25–0.73%.[154] According to these and subsequent observations, POPH has been classified as a category of PAH with hemodynamic criteria consistent with the standard classification and definition of PAH, as discussed in Chapter 84.[104,155] Independent clinical risk factors associated with an increased risk of POPH include female sex and autoimmune hepatitis, whereas hepatitis C is associated with a decreased risk. In parallel to HPS, the incidence and severity of POPH is not associated with the severity of the underlying liver disease.[153]

Pathogenesis

The pathogenesis of POPH is not known. Chemla and colleagues[156] postulated that the portosystemic shunting of vasoactive agents such as thromboxanes, serotonin,

Table 126.3 Comparison of Clinical Features of Hepatopulmonary Syndrome and Portopulmonary Hypertension

	Hepatopulmonary Syndrome	Portopulmonary Hypertension
Symptoms	Dyspnea, platypnea, fatigue	Dyspnea, fatigue, lower extremity edema, abdominal distension
Physical exam findings	Clubbing, cyanosis, spider angiomata, orthodeoxia	Jugular venous distension, prominent pulmonic component of the second heart sound, tricuspid regurgitation murmur, ascites, lower extremity edema
Prevalence	5–32%	5–6%
Gas exchange	Elevated alveolar-arterial P_{O_2} difference with mild to severe hypoxemia	Normal or mild hypoxemia
Contrast-enhanced transthoracic echocardiogram	Intrapulmonary vasodilation (late appearance of microbubbles in the left-sided chambers)	Elevated right ventricular systolic pressure and/or right ventricular dilation or dysfunction
Pathology	Precapillary and capillary vasodilation	Plexiform lesions, intimal thickening, smooth muscle proliferation and in situ thrombosis
Medical treatment	Supportive	Pulmonary arterial hypertension–targeted therapy
Effect of liver transplantation	Resolution of hypoxemia	Variable outcomes

bradykinin, and neuropeptide Y, which are normally metabolized by the healthy liver, may result in pulmonary arterial vasoconstriction. This hypothesis is supported by an increased prevalence of spontaneous portosystemic shunts in patients with POPH.[157] Recent case-control studies in patients with POPH have identified higher levels of macrophage migration inhibitory factor, a proinflammatory cytokine involved in the regulation of innate immunity, reduced levels of bone morphogenetic protein 9, an endothelial quiescence factor, and higher estradiol levels suggesting that inflammation, endothelial dysfunction, and sex hormones may play important roles in disease pathogenesis.[158–160] From a histopathologic viewpoint, the vascular lesions in POPH are indistinguishable from those identified in idiopathic PAH (see Chapter 84), namely intimal thickening, smooth muscle proliferation, plexogenic pulmonary arteriopathy, and in situ thrombosis,[161] all of which—plus vasoconstriction—contribute to the increased pulmonary vascular resistance.[162]

Clinical Manifestations

The most common symptom of POPH is shortness of breath, particularly with exertion; patients may also experience fatigue, decreased activity tolerance, chest pain, syncope, and signs and symptoms of right heart failure (lower extremity edema, abdominal distension) which can often be difficult to differentiate from decompensated cirrhosis.[163] Radiographically, both an enlarged cardiac silhouette and a pulmonary artery prominence are noted in approximately one-half to two-thirds of patients with POPH.[153,163] Generally, spirometry and lung volumes are normal or nearly normal, whereas $D_{L_{CO}}$, arterial P_{O_2}, and the $(A–a)P_{O_2}$ may be abnormal, although less so than in HPS.[153] Transthoracic echocardiography typically demonstrates an elevated right ventricular systolic pressure with or without right ventricular dilation and/or dysfunction and can be used as a screening test with reasonable sensitivity and specificity.[164] Right heart catheterization is required for diagnosis and demonstrates an elevated mean pulmonary arterial pressure and pulmonary vascular resistance. Cardiac output may be normal or elevated but can decline as right heart failure develops. Compared to patients with idiopathic and heritable PAH, patients with POPH have more favorable hemodynamics with a lower mean pulmonary arterial pressure, right atrial pressure, and pulmonary vascular resistance and a higher cardiac index at the time of diagnosis.[162]

Treatment

Treatment for POPH is similar to idiopathic PAH, although there are few prospective data to guide management, given that patients with POPH have been excluded from many clinical trials of PAH-targeted therapy. In small, uncontrolled, and predominantly single-center studies, PAH therapy in patients with POPH has been associated with improvements in exercise capacity and pulmonary hemodynamics.[165] Although there are no randomized controlled trials specific to POPH to guide therapeutic choices, currently available agents to treat PAH and POPH include epoprostenol, treprostinil, selexipag, iloprost, sildenafil, tadalafil, riociguat, bosentan, ambrisentan, and macitentan. The approach to treatment of PAH is discussed further in Chapter 84 and is typically similar for POPH, although treatment goals in POPH may be affected by liver transplant eligibility and urgency. In contrast to idiopathic PAH, calcium channel blockers should be avoided in patients with POPH because they can worsen splanchnic vasodilation.[101] Patients with POPH may also require diuretics for management of edema and right heart failure, if present. β-Blockers, which are often used for prophylaxis in patients with esophageal varices, can worsen cardiac output and exercise capacity in patients with POPH and should be avoided if feasible.[101]

Liver transplantation can be safe in selected patients with POPH with preserved right ventricular function and appropriate hemodynamic responses to PAH therapy. Similar to HPS, patients with POPH are eligible for a MELD exception to expedite liver transplantation. In contrast to HPS, however, POPH is not considered an indication for liver transplantation because posttransplant outcomes are variable; approximately half of patients with POPH remain on PAH therapy posttransplant.[166] Prospective studies are clearly needed to provide guidance regarding the role of medical therapy and liver transplantation in the management of POPH.

Prognosis

In the absence of PAH therapy or liver transplantation, survival in patients with POPH is extremely poor, with 5-year survival rates of 14%, as shown in a 2008 study.[167] Even in the modern PAH treatment era, 5-year survival in a multicenter U.S. registry was only 40%, and survival for patients with POPH was significantly worse than for those with idiopathic PAH despite better hemodynamics.[168] The presence of cirrhosis, worse liver disease severity, higher pulmonary vascular resistance, and lower cardiac index have been associated with worse survival in patients with POPH.[161,169] POPH is associated with increased perioperative risk, so screening for POPH is recommended in all candidates for liver transplantation.[144] Perioperative cardiopulmonary mortality risk can be stratified by mean pulmonary arterial pressure, and liver transplantation should be avoided in patients with a mean pulmonary arterial pressure greater than 45 to 50 mm Hg due to a high risk of death.[101,170] In selected patients with POPH who undergo liver transplantation, 1-year posttransplant survival rates are 77–85% and the risk of death is highest within the first 6 months posttransplant.[166,171]

PRIMARY BILIARY CIRRHOSIS

Primary biliary cirrhosis (PBC) is a progressive, autoimmune cholestatic liver disease characterized by diffuse inflammation and destruction of the intrahepatic bile ducts.[172] The disease primarily affects middle-aged women and serologically is characterized by the presence of antimitochondrial antibodies in up to 95% of patients. It is often associated with other autoimmune diseases including Sjogren syndrome, systemic lupus erythematosus, and scleroderma. In addition to the pulmonary manifestations common to all forms of advanced liver disease, an association between PBC and interstitial lung disease is well established. The most common pathologic finding is lymphocytic interstitial pneumonitis. Fibrosing alveolitis, interstitial fibrosis, nonnecrotizing

granulomas, and organizing pneumonia have also been described.[173] The presence of concomitant Sjogren syndrome is strongly associated with the development of interstitial lung disease.[174] As with other liver diseases, pulmonary function tests in patients with PBC frequently show a reduction in D_{LCO}, even in asymptomatic individuals.[175] Bronchoalveolar lavage may show an increased proportion of lymphocytes with $CD4^+/CD8^+$ ratios similar to those seen in sarcoidosis.[176] Other rare associations between PBC and obstructive lung disease, chest wall deformities, pulmonary hypertension, sarcoidosis, and pulmonary hemorrhage also have been described.[177]

CHRONIC HEPATITIS C

Chronic hepatitis C is characterized by chronic diffuse hepatic parenchymal inflammation and hepatic cell necrosis. Patients with untreated infection have a significant potential to progress to cirrhosis as well as to hepatocellular carcinoma.[177] Although some authors have suggested an association between chronic hepatitis C and pulmonary fibrosis, this association is controversial and remains unproven.[178,179] It has also been suggested that patients with chronic hepatitis C virus infection and coexistent COPD may experience an accelerated annual decline in FEV_1.[180]

SCLEROSING CHOLANGITIS

Sclerosing cholangitis is a chronic progressive liver disease that results in chronic inflammation of both the intrahepatic and extrahepatic bile ducts. Approximately 70% of patients with sclerosing cholangitis will have concomitant inflammatory bowel disease.[181] As with isolated inflammatory bowel disease, sclerosing cholangitis has been linked with inflammatory upper airway diseases such as bronchiectasis.[182]

ALPHA$_1$-ANTITRYPSIN DEFICIENCY

Alpha$_1$-antitrypsin deficiency is a hereditary disorder nearly always associated with the homozygous PiZZ phenotype (see Chapter 63). Infants with alpha$_1$-antitrypsin deficiency often present with hepatomegaly and evidence of cholestasis. Most children with alpha$_1$-antitrypsin–induced liver disease recover, but cirrhosis develops in about 15%, presumably from toxic effects of the mutant antitrypsin protein retained in the endoplasmic reticulum of hepatocytes.[183] Emphysema is the most common pulmonary complication and is unrelated to the presence of liver disease. This emphysema develops in adults and is characterized by panacinar emphysema, especially in the lower lung zones, and bronchial abnormalities, including bronchiectasis (Fig. 64.5 and Video 64.2).[177]

PANCREATIC DISEASES

ACUTE PANCREATITIS

Acute pancreatitis is an inflammatory disorder of the pancreas most commonly caused by gallstones or alcohol abuse. Most episodes of acute pancreatitis are mild and resolve with supportive care, but approximately 20% of cases are severe and complicated by multisystem organ dysfunction with an associated mortality of 15–25%.[184] Pulmonary complications are common and contribute substantially to morbidity and mortality. They range from mild hypoxemia to the *acute respiratory distress syndrome* (ARDS). Overall, intrathoracic complications are implicated as a contributing factor in more than 50% of deaths from acute pancreatitis.[185]

Early Respiratory Insufficiency and Imaging Abnormalities

In the early stages of acute pancreatitis, mild respiratory alkalosis and hypoxemia are common, even in patients with normal chest radiographs.[186,187] The mechanisms of hypoxemia in the setting of a normal chest radiograph remain poorly understood. Murphy et al. showed that in a small cohort of patients who developed hypoxemia, the primary cause was V/Q mismatch resulting in right-to-left intrapulmonary shunting.[188] These authors suggested that hypoxemia, even in the absence of radiologic abnormalities, may be related to changes in pulmonary vascular permeability, similar to but milder than those described in ARDS.[188] Early respiratory insufficiency is a risk factor for progressive pulmonary complications and poor outcomes independent of pancreatitis severity.[189] Therefore, asymptomatic patients with early mild respiratory insufficiency should be watched closely for signs of worsening respiratory impairment.

The majority of patients with acute pancreatitis will develop chest radiographic abnormalities during their disease course, the most common findings being pleural effusions, atelectasis, and pulmonary edema. Pleural effusions are seen in over 50% of patients.[190] The effusions typically are small, and the majority (68%) are left sided.[191] Most are exudative and, in some cases, pleural fluid amylase levels will be high.[184] The presence of pleural fluid is a marker of disease severity and is correlated with increased risk of respiratory failure and mortality.[190] Most pleural effusions associated with acute pancreatitis are self-limited and resolve without therapeutic drainage after the pancreatic inflammation subsides.

Nonspecific basilar atelectasis and consolidation are also common findings in acute pancreatitis. Pain, splinting, and increased vascular permeability are likely contributing factors. Experimental models of pancreatitis-associated lung injury also support the hypothesis that atelectasis in dependent lung regions may in part be secondary to impaired surfactant production and activation.[192] Furthermore, proinflammatory cytokines secreted in acute pancreatitis cause a decrease in diaphragmatic muscle strength and endurance, contributing to atelectasis.[193]

Acute Respiratory Distress Syndrome

The most feared pulmonary complication of acute pancreatitis is ARDS (see also Chapter 134), which develops in approximately 15–20% of patients and is responsible for up to 60% of deaths[194–196] (Fig. 126.6). It typically manifests between 2 and 7 days following the onset of pancreatitis. In patients with ARDS who survive, quality of life is frequently impaired.[197] Autopsy studies show that pathologic changes

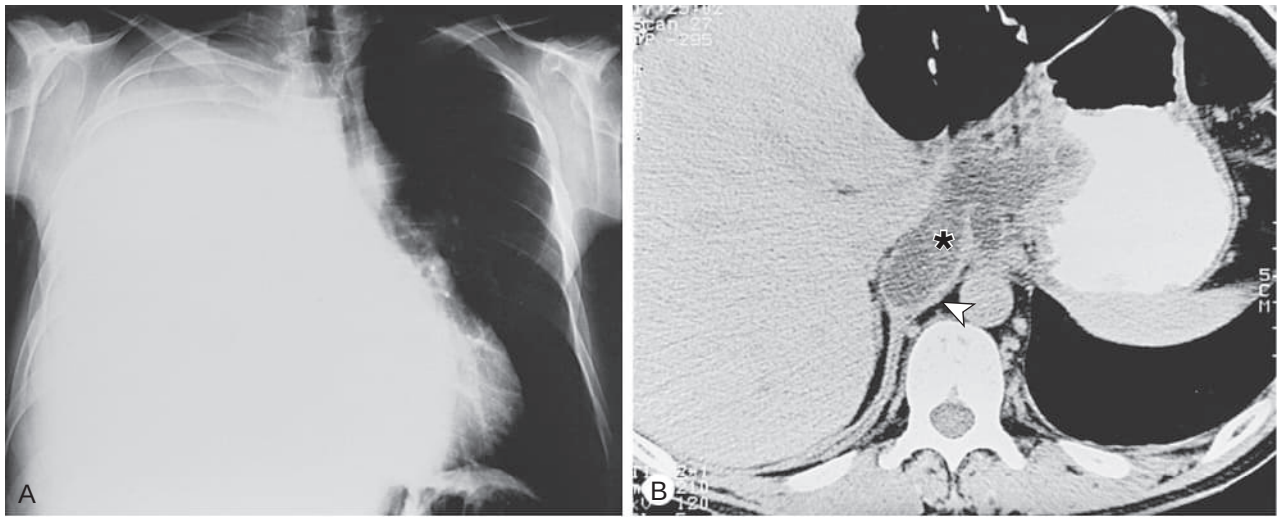

Figure 126.5 A massive pleural effusion associated with a pancreatic pseudocyst. (A) Chest radiograph demonstrates a massive pleural effusion in the right hemithorax. (B) Computed tomography scan of the upper abdomen performed after pleural drainage shows the cranial extension of the pseudocyst (*asterisk*) through the right crural insertion (*arrowhead*) and the esophageal hiatus. (Courtesy Dr. S. Navarro, Hospital Clinic, Universitat de Barcelona, Spain.)

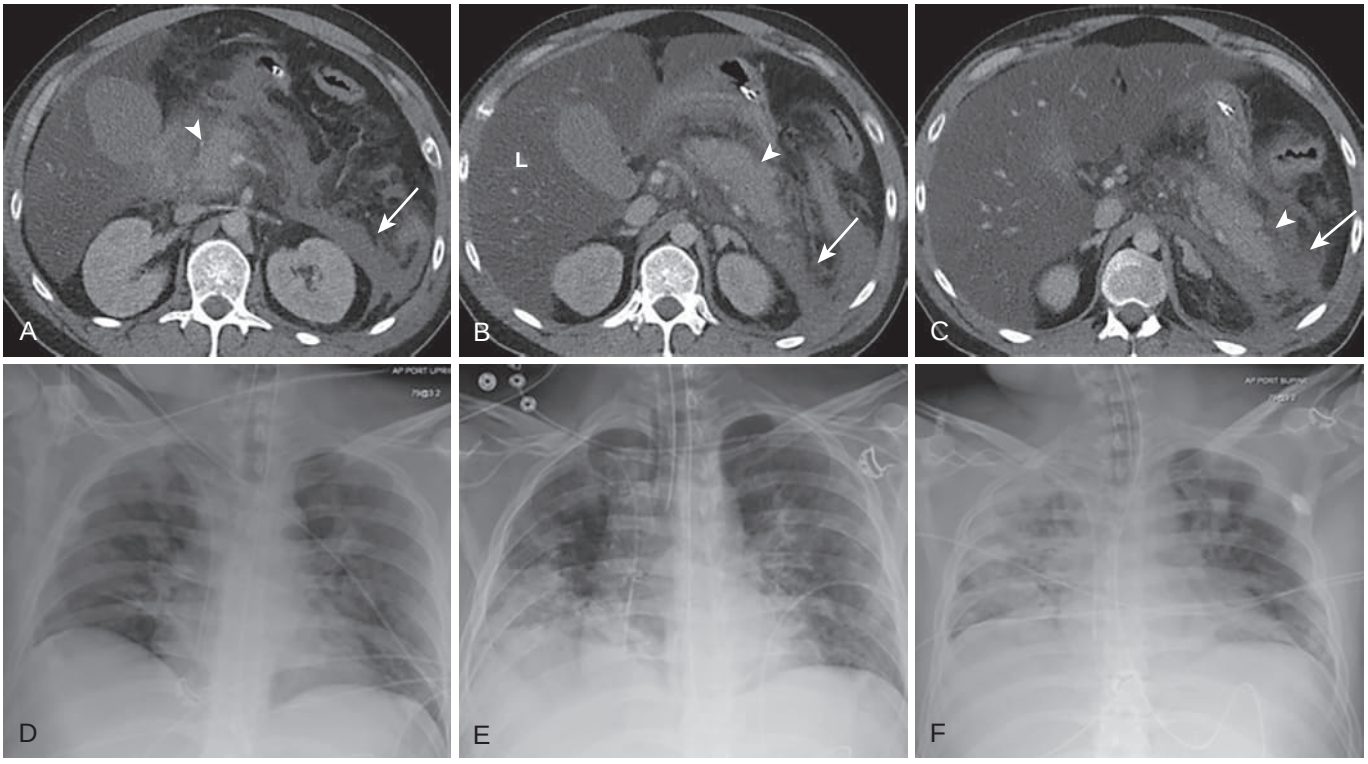

Figure 126.6 Acute respiratory distress syndrome in a patient with pancreatitis. (A–C) Axial enhanced abdominal computed tomography shows extensive inflammation surrounding the pancreas head (A, *arrowhead*), body (B, *arrowhead*), and tail (C, *arrowhead*). Fluid is present in the left anterior pararenal space (*arrows*). The liver (L) shows diffusely decreased attenuation consistent with fatty infiltration, consistent with alcohol use, the precipitating cause of the patient's pancreatitis. (D–F) Frontal chest radiographs performed at the patient's presentation, several days prior to the abdominal computed tomography (D), 6 days after presentation (E), and 14 days after presentation (F) show progressive, multilobar, right-greater-than-left opacities in a patient intubated for respiratory failure, consistent with acute respiratory distress syndrome (Courtesy Michael B. Gotway, MD.)

in the lungs are identical to those seen in ARDS caused by other conditions.[198]

Injury to the lung may result from a direct toxic effect of pancreatic enzymes, from secondary release of inflammatory mediators, or from both. Several pancreatic enzymes have the potential to induce lung injury. Animal studies suggest that elastase and lipase, which are released systemically during pancreatitis, may increase lung vascular permeability and induce lung injury.[199] Phospholipase A_2 induces the enzymatic degradation of surfactant, thereby promoting alveolar collapse and increased vascular permeability.[184,191] There is a strong correlation between serum phospholipase A_2 levels and respiratory insufficiency.[200] In addition to the direct effect of pancreatic by-products,

sequestration of activated neutrophils within the alveolar and interstitial spaces is believed to play an important role in inducing lung injury. Proinflammatory cytokines released during pancreatic injury include TNF-α and IL-8, which augment neutrophil recruitment and activation in the lungs.[191] Finally, there is evidence that reactive oxygen species, adhesion molecules, platelet-activating factor, and many other cytokines may also contribute to increased vascular permeability and induce lung injury.[191,201]

Treatment of pancreatitis-associated ARDS is supportive and does not differ from that for other forms of ARDS (see Chapter 134). Key measures include cardiovascular support and lung-protective ventilation. Although aggressive fluid resuscitation remains a pillar in the management of acute pancreatitis, overzealous resuscitation may increase the rate of both pulmonary and nonpulmonary complications.[202,203] Two small studies from the mid-1990s suggest that octreotide, a potent inhibitor of exocrine pancreatic secretion, may decrease both mortality rates and the incidence of ARDS among patients with severe acute pancreatitis.[204,205] This potential therapy warrants investigation in larger randomized controlled trials.

DELAYED COMPLICATIONS OF ACUTE PANCREATITIS

Patients who survive the initial acute inflammatory response associated with acute pancreatitis remain at risk for late pulmonary complications. Like all hospitalized patients, patients with acute pancreatitis can develop hospital-acquired infections and venous thromboembolism.[206] Most pancreatitis-associated pleural effusions will resolve within 2 weeks without intervention but, in rare cases, an effusion will persist. The presence of a persistent large pleural effusion should raise concern for development of a pancreaticopleural fistula resulting from the formation of a direct communication between the pancreas and the pleural space (see Fig. 126.5). In this setting, the pleural fluid will have very high amylase levels and may be massive in size and recur rapidly after drainage.[190] Although some patients will respond to chest tube drainage and administration of somatostatin analogues to reduce pancreatic secretions, management may require endoscopic retrograde cholangiopancreatography with stenting and, in rare cases, surgery.[207] Other rare delayed complications include mediastinal pseudocyst formation and acute mediastinitis.[206]

AUTOIMMUNE PANCREATITIS

Autoimmune pancreatitis or sclerosing pancreatitis is a rare form of chronic pancreatitis. Two forms of autoimmune pancreatitis are recognized. Type 1 autoimmune pancreatitis, also referred to as *immunoglobulin G4* (IgG4)-related pancreatitis, is characterized by a dense lymphoplasmacytic infiltrate rich in IgG4-positive plasma cells, a swirling appearance of fibroblasts called a "storiform" fibrosis and, in some cases, elevated serum IgG4 concentrations.[208] Patients with type 1 autoimmune pancreatitis frequently have disease affecting other organs including the lungs. Pulmonary involvement typically presents as interstitial pneumonia or parenchymal inflammatory pseudotumor. Lung biopsy specimens will show a similar lymphoplasmacytic infiltrate with increased IgG4-positive plasma cells.[209] Lung involvement typically improves along with administration of glucocorticoids.[210] Type 2 autoimmune pancreatitis, also referred to as idiopathic duct-centric pancreatitis, does not involve an IgG4-positive cellular infiltrate and typically only affects the pancreas.[211]

KIDNEY DISEASES

Dyspnea is commonly reported by patients with both acute and chronic kidney diseases. In patients with acute kidney injury, respiratory symptoms are often attributed to pulmonary edema or represent a manifestation of the underlying disease process, as is the case with the pulmonary renal syndromes (see Chapter 87). In patients with *chronic kidney disease* (CKD) and *end-stage renal disease* (ESRD), the pathophysiology of dyspnea is often more complex and these etiologies are discussed further in this section.

PULMONARY EDEMA

In patients with ESRD, interstitial pulmonary edema is highly prevalent, even in asymptomatic patients, and correlates strongly with measures of physical functioning.[212,213] In general, physical exam findings such as crackles on lung exam and lower extremity edema correspond poorly with the degree of interstitial edema. There is growing evidence that thoracic ultrasonography may be a more sensitive tool to identify pulmonary edema in this population.[214,215]

In patients with CKD, the etiology of the pulmonary edema is often multifactorial and may be attributed to a combination of increased pulmonary hydrostatic pressure secondary to fluid overload or congestive heart failure, reduced pulmonary capillary oncotic pressure due to hypoalbuminemia, and increased permeability of the alveolar-capillary membrane in the setting of uremia.[216] The relative importance of each of these pathophysiologic mechanisms is heavily debated.

Heart failure plays an important role in the development of pulmonary edema associated with CKD. Cardiac disorders are common in ESRD, and a variety of factors, including hypertension, diabetes mellitus, anemia, surgical arteriovenous fistulas, and ischemic heart disease, may adversely affect cardiac function.[217] In addition, patients with CKD may develop a specific "uremic cardiomyopathy," the existence of which is supported by evidence that left ventricular dysfunction may be partially reversible with dialysis or renal transplantation.[218,219]

Evidence that interstitial pulmonary edema in patients undergoing regular hemodialysis is at least partially independent of prescribed ultrafiltration rate, intradialytic weight, and pulmonary capillary wedge pressure suggests that factors in addition to heart failure and fluid overload are also likely involved.[220] Early autopsy studies showing the presence of protein-rich edema fluid, hyaline membranes, and alveolar hemorrhage in the lungs lend support to the relative importance of increased vascular permeability in the development of pulmonary edema.[221,222] The demonstration of increased protein content in edema fluid sampled directly by endotracheal aspiration reinforces this hypothesis.[223]

Regardless of the etiology, interstitial pulmonary edema remains a major source of morbidity and mortality in patients with CKD.[212,224] For many patients on dialysis, achieving the optimal balance of fluid removal with ultrafiltration while avoiding hypovolemia during dialysis can be challenging.[225] In addition, acute alveolar pulmonary edema and fluid overload are common causes of hospital and ICU admission in patients with ESRD. While many episodes will resolve with emergent dialysis, hospitalization for fluid overload is associated with high costs and poor long-term survival.[225–227]

PULMONARY HYPERTENSION

Pulmonary hypertension is highly prevalent in patients with CKD and ESRD, affecting 30–50% of patients.[228] There is significant overlap between CKD and comorbid conditions traditionally associated with pulmonary hypertension. Not surprisingly given the high incidence of comorbid cardiac disease, *World Health Organization* (WHO) group 2 pulmonary hypertension is overwhelmingly the most common form seen in this patient population. Nevertheless, other etiologies of pulmonary hypertension are also seen and, in some patients with CKD, the etiology of pulmonary hypertension may be multifactorial. Conditions such as HIV, scleroderma, and cirrhosis are associated with both WHO group 1 pulmonary hypertension and CKD. COPD and obstructive sleep apnea are highly prevalent in patients with CKD, which increases the likelihood of WHO group 3 pulmonary hypertension. Patients with CKD are also at increased risk for venous thromboembolic disease and pulmonary embolism following arteriovenous access thrombectomy, which are associated with WHO group 4 pulmonary hypertension. Finally, a significant number of patients with CKD will have "unexplained" WHO group 5 pulmonary hypertension.[228] Regardless of the etiology, there is evidence that a longer time on hemodialysis increases the risk for development of pulmonary hypertension and is predictive of increased mortality in patients on dialysis and also in those who undergo kidney transplantation.[229–231]

Echocardiography can be misleading both in diagnosing and clarifying the etiology of pulmonary hypertension in patients with CKD. In the PEPPER study of patients with stage 4 and 5 CKD with unexplained dyspnea and normal echocardiograms, 77% of patients on hemodialysis had evidence of pulmonary hypertension on right heart catheterization.[232] Of those with pulmonary hypertension, over 80% of patients had an elevated pulmonary capillary wedge pressure (postcapillary disease). This highlights the importance of right heart catheterization in the diagnosis and management of pulmonary hypertension in CKD patients.

Treatment of pulmonary hypertension in CKD is dependent on the etiology. Supplemental oxygen is recommended for all patients who are hypoxemic with a goal to maintain saturations with exercise greater than 90%. In general, targeted PAH therapies are reserved for patients with WHO group 1 pulmonary hypertension, whereas treatment for patients with disease secondary to other conditions is geared towards treatment of the underlying process. Studies of individual PAH-targeted agents are limited in patients with CKD, and more research is needed. Diuresis and/or dialysis for left-sided heart disease would be warranted; however, right heart catheterization in the euvolemic state is necessary to characterize the hemodynamic changes present.[228]

PLEURAL DISEASE

Pleural effusion is a frequent complication of CKD, particularly for patients requiring dialysis. In unselected hospitalized patients on dialysis, the prevalence is around 20%.[233,234] In symptomatic dialysis patients, the prevalence of pleural fluid on CT scan may be as high as 50%.[235] Although hypervolemia is the most common etiology, effusions secondary to uremic pleuritis, pneumonia, and atelectasis are also common.[234] Effusions are bilateral in 60% of cases and, of these, the majority of effusions are transudative. The presence of bilateral transudative effusions is strongly associated with heart failure or hypervolemia as the underlying etiology.[233–235]

In patients with unilateral effusions, non–heart failure etiologies should be strongly considered. Compared to patients with heart failure or hypervolemia, those with other etiologies are more likely to report chest pain in addition to dyspnea.[233] Unilateral effusions are frequently exudative and are most commonly parapneumonic or secondary to atelectasis.[233]

Uremic pleurisy is a fibrinous pleuritis that may result in pleural effusions, chronic pleural inflammation, and fibrosis in patients with CKD. Close to 60% of patients who die of chronic renal insufficiency will have some degree of fibrinous pleuritis identified at autopsy.[233,236] The etiology is unclear. Uremic effusions may be unilateral or bilateral and tend to be exudative, lymphocyte predominant, and frequently serosanguinous.[237] Pleuritic chest discomfort and pleural friction rub on auscultation may be present.[237,238] In rare cases the pleural fibrosis may be severe enough to cause restrictive physiology requiring surgical decortication[239] (see Chapter 112).

In addition to the pleural diseases common to all dialysis patients, patients on peritoneal dialysis can develop an acute large pleural effusion related to preexisting or acquired pleuroperitoneal communications; this complication has been estimated to present in 1–2% of patients on peritoneal dialysis.[240] The majority (90%) of these effusions are right-sided and, when sampled, are transudative and often have an overtly elevated pleural fluid glucose compared to serum.[241] There is no consensus regarding the optimal management of such patients. Options include discontinuing peritoneal dialysis and initiating hemodialysis and video-assisted thoracic surgery for pleurodesis and/or attempted repair of diaphragmatic defects.[242]

PULMONARY CALCIFICATION

Metastatic pulmonary calcification is a common consequence of CKD seen in 60–80% of dialysis patients at autopsy.[243,244] It is characterized by diffuse calcium deposits in the pulmonary parenchyma and visceral organs. In the lungs, the calcium deposition tends to be in the alveolar epithelial basement membranes.[244] The pathogenesis is complex and several factors may play a role, including (1) the effect of chronic metabolic acidosis, which results in the efflux of calcium from bones; (2) the effect of secondary hyperparathyroidism, which results in increased bone reabsorption and intestinal calcium absorption; and (3) the effect of low glomerular filtration rate, which results in hyperphosphatemia and elevation of the calcium-phosphorus product.[243,245]

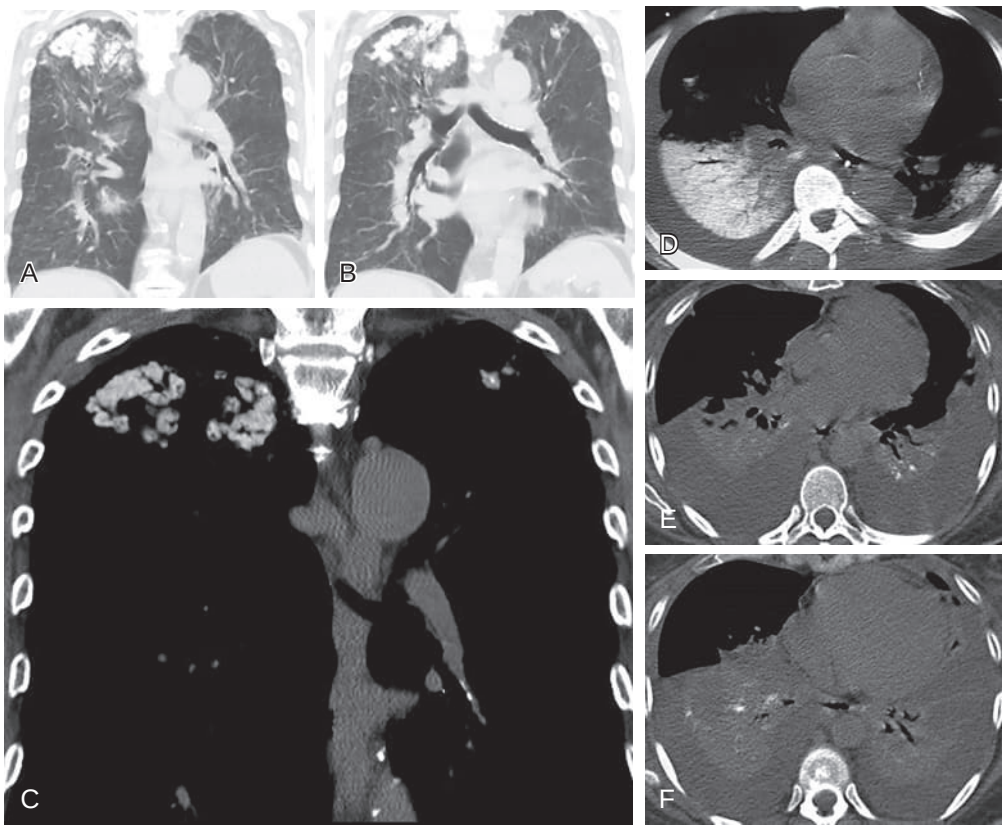

Figure 126.7 Metastatic calcinosis in patients with end-stage renal disease. (A–B) Coronal *computed tomography* (CT) scan displayed in lung windows shows confluent centrilobular hyperattenuating nodules in the apices. The calcification of these opacities is more evident with CT displayed in soft tissue windows (C). (D) In another patient, axial CT displayed in soft tissue shows more confluent lower lobe parenchymal calcification. (E–F) In a third patient, axial CT displayed in soft tissue windows shows spotty, more nodular-appearing lower lobe calcification. (Courtesy Michael B. Gotway, MD.)

While highly prevalent, metastatic pulmonary calcification is frequently undetectable by ordinary chest radiograph and most patients are asymptomatic.[243] High-resolution CT scan is more sensitive for detecting small amounts of calcification. Findings may include multiple diffuse calcified pulmonary nodules, diffuse or patchy ground-glass opacities, or high-density parenchymal consolidations (Fig. 126.7 and eFig. 126.3). Changes are often most pronounced in the upper lung zones, thought to be due to the lower carbon dioxide and higher pH in the upper zones. In contrast to infectious processes, these opacities are relatively stable over time, which may aid in the diagnosis. Pulmonary function tests are typically normal but may reveal a restrictive ventilatory defect and/or a reduction in DL_{CO}.[245] When necessary, the diagnosis can be confirmed by pulmonary uptake with technetium-99m-diphosphonate scanning.[246]

In general, treatment options are unsatisfactory. Patients with asymptomatic, nonprogressive disease do not require treatment. For symptomatic patients with progressive disease, treatment options include maintaining adequate dialysis, lowering the calcium-phosphorus product with phosphate binders, and treating hyperparathyroidism, when present.[243] Renal transplantation may either improve or worsen the condition.[243]

SLEEP DISORDERS

The high prevalence of sleep disorders in patients with CKD and, in particular ESRD, is well recognized. (Sleep disorders in the general population and their treatment are described in Chapters 119 and 122). Compared to the general population, patients with ESRD have higher rates of most common sleep disorders, including insomnia, excessive daytime sleepiness, restless leg syndrome, and sleep apnea.[247] Not only is sleep disturbance one of the most commonly reported symptoms in patients with ESRD, but it is also strongly associated with both decreased health-related quality of life and mortality.[248,249]

Insomnia is reported by up to 40–70% of patients with ESRD.[250,251] Patients may complain of difficulty initiating and maintaining sleep as well as early morning wakening. On polysomnography, patients will often exhibit poor sleep architecture including fragmented sleep, reduced total sleep time, and reduced sleep efficiency.[247] The cause of this high rate of insomnia is likely multifactorial. Patients on dialysis frequently lack the normal circadian rhythm in melatonin secretion, which may lead to disturbances in the sleep-wake cycle.[252] Coexisting medical conditions including psychiatric illnesses and chronic pain are other influences.[248] Finally, a high incidence of other sleep disorders including restless leg syndrome and sleep apnea, as well as poor sleep hygiene and the use of medications that inhibit sleep may also contribute.[247]

Sleep apnea is also significantly more common in patients with ESRD compared to the general population, reported in more than 50% of patients.[253] In the Sleep Heart Health Study, patients on hemodialysis had a fourfold increase in sleep apnea and had more episodes of severe hypoxemia compared to matched controls, even after adjusting for comorbid conditions.[254] While *obstructive sleep apnea* (OSA) is the most common form of sleep apnea seen in patients with ESRD, central sleep apnea is also described and may be underreported.

Various mechanisms have been proposed to explain the high prevalence of OSA in patients with ESRD. One possibility is that the accumulation of uremic toxins may exacerbate OSA in patients with ESRD. This theory is supported by evidence that conversion from conventional daytime hemodialysis to nocturnal hemodialysis reduces the severity of sleep apnea.[255] Another hypothesis is that fluid overload increases the susceptibility to upper airway collapse during sleep.[256] Studies in healthy subjects have shown shifting fluid to the upper body by applying high pressure to the lower body leads to both increased pharyngeal resistance and increased upper airway collapsibility.[257,258] Such data support the hypothesis that chronic fluid overload and subsequent fluid displacement during recumbency predisposes patients with ESRD to OSA.

As in the general population, continuous positive airway pressure is considered the first-line therapy for OSA in patients with ESRD.[259] Other treatments such as dental appliances and surgery have not been extensively studied in this population. There are anecdotal reports of improvement in OSA after renal transplantation, but this is not universal.[260,261]

HEMODIALYSIS-INDUCED HYPOXEMIA

Hypoxemia during hemodialysis is a well-recognized phenomenon. In general, oxygen saturation tends to drop at the start of dialysis, reaching a nadir after 30 to 60 minutes and improving to predialysis levels or higher at the end of treatment.[262] A recent large prospective cohort study of chronic hemodialysis patients identified that, even with modern dialysis techniques, the prevalence of prolonged interdialytic hypoxemia (arterial So_2 < 90% for at least one-third of the treatment time) was 10%.[263] Intradialytic hypoxemia was associated with adverse clinical outcomes, including all-cause hospitalization and mortality.

The mechanisms responsible for intradialytic hypoxemia are likely multifactorial. Initially, it was recognized that the severity of the hypoxemia varied depending on the type of dialysis membrane used as well as the dialysate composition.[264,265] For instance, intradialytic hypoxemia is more frequent with the use of acetate buffer than with bicarbonate buffer.[265] Cardiopulmonary comorbidities likely also contribute. As previously discussed, patients with ESRD have high rates of congestive heart failure, volume overload, pulmonary hypertension, pulmonary calcification, and obstructive sleep apnea, which may all contribute to hypoxemia. In addition, there is increasing evidence that COPD is a frequent and likely underdiagnosed comorbidity in patients with ESRD.[266] The importance of such cardiopulmonary comorbidities is supported by the study by Meyring-Wosten et al. in which patients with congestive heart failure or COPD were significantly more likely than other patients to experience prolonged intradialytic hypoxemia.[263]

Given the wide array of potential etiologies of intradialytic hypoxemia, the optimal management remains unknown. Not surprisingly, small studies have suggested that use of supplemental oxygen improves hypoxemia; however, whether this improves clinical outcomes remains unknown.[267]

Key Points

- Gastroesophageal reflux disease is highly prevalent. Extraesophageal manifestations include asthma and chronic cough. The benefit of acid-suppressive therapy in patients with gastroesophageal reflux–associated respiratory symptoms remains unclear.
- Inflammatory bowel diseases have been associated with a variety of chronic pulmonary diseases. These include diseases of the airways such as asthma, chronic bronchitis, and bronchiectasis and, less commonly, disorders of the lung parenchyma, such as interstitial fibrosis and cryptogenic organizing pneumonia.
- Patients with end-stage liver disease can develop characteristic pulmonary complications including hepatic hydrothorax, hepatopulmonary syndrome, and portopulmonary hypertension. Hepatopulmonary syndrome is characterized by intrapulmonary vasodilation and abnormal gas exchange and resolves following liver transplantation. Portopulmonary hypertension, in contrast, is characterized by pulmonary arterial hypertension and right heart failure, is treated with pulmonary arterial hypertension–targeted therapy, and has variable posttransplant outcomes.
- Episodes of severe acute pancreatitis are associated with a high frequency of pulmonary complications, including hypoxemia, pleural effusions, and acute respiratory distress syndrome. Pulmonary complications are a major cause of excess morbidity and mortality.
- Patients with chronic kidney disease are at risk for multiple pulmonary complications including pulmonary edema, pleural effusions, and sleep apnea. Some respiratory symptoms may be alleviated by dialysis and/or renal transplantation.

Key Readings

Black H, Mendoza M, Murin S. Thoracic manifestations of inflammatory bowel disease. *Chest*. 2007;131(2):524–532.
Browne GW, Pitchumoni CS. Pathophysiology of pulmonary complications of acute pancreatitis. *World J Gastroenterol*. 2006;12(44):7087–7096.
Hom C, Vaezi MF. Extraesophageal manifestations of gastroesophageal reflux disease. *Gastroenterol Clin North Am*. 2013;42(1):71–91.
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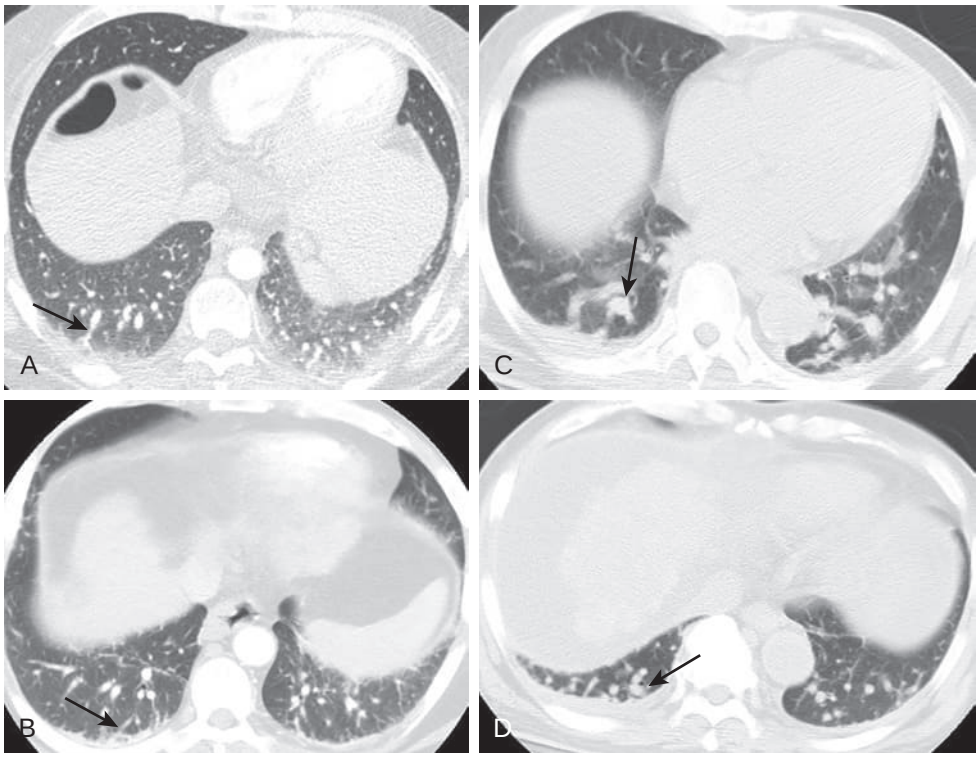
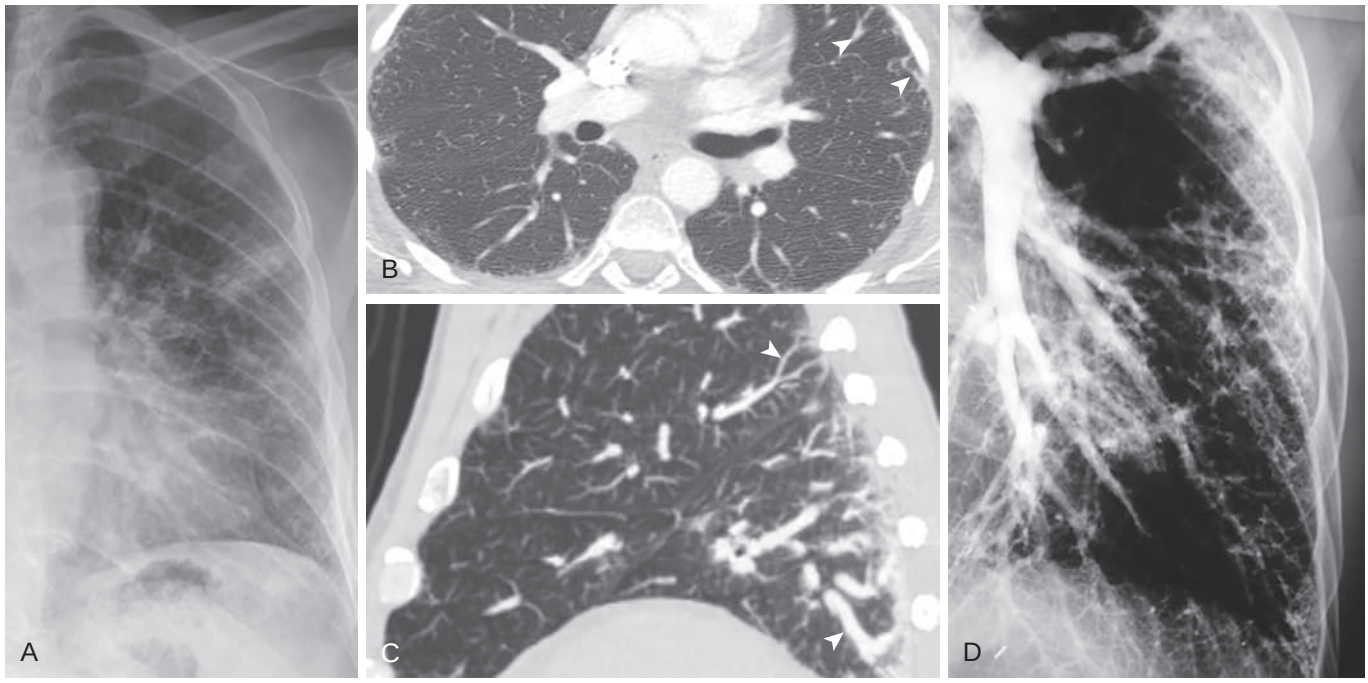
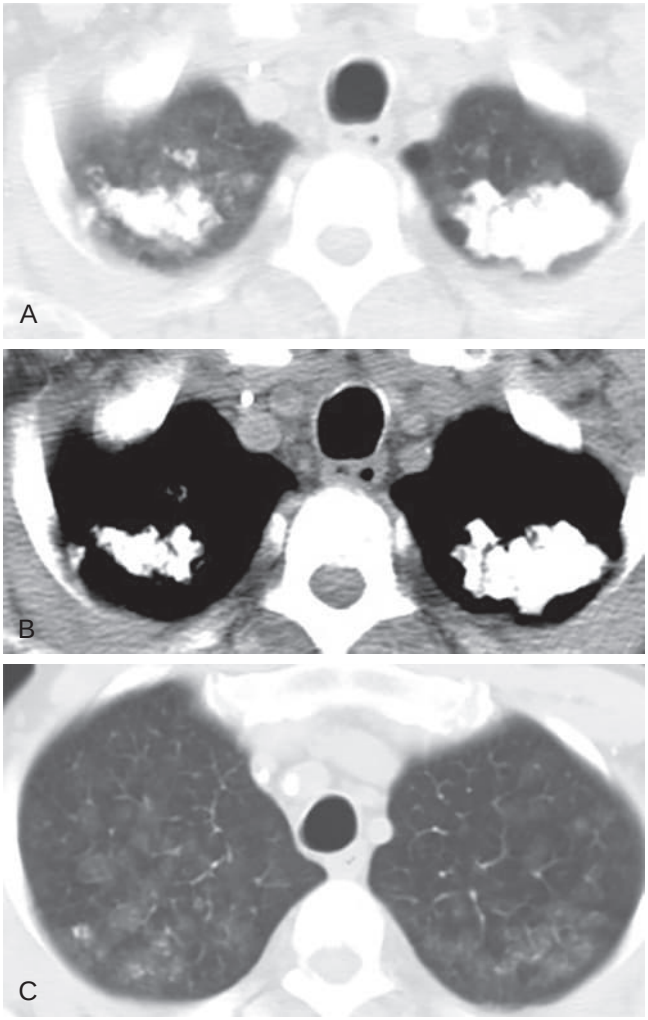
Complete reference list available at ExpertConsult.com.



eFigure 126.1 ***Computed tomography*** **(CT) changes in hepatopulmonary syndrome.** (A–B) Axial enhanced chest CT images through the extreme lung bases displayed in lung windows show relatively "mild" dilation of the peripheral pulmonary arteries (*arrows*). (C–D) Axial enhanced chest CT images through the extreme lung bases displayed in lung windows show comparatively more pronounced dilation of the peripheral pulmonary arteries (*arrows*). (Courtesy Michael B. Gotway, MD.)



eFigure 126.2 Dilated peripheral pulmonary arteries in hepatopulmonary syndrome. (A) Chest radiograph focused on the left lung in a patient with hepatopulmonary syndrome shows peripheral reticulation. Axial (B) and sagittal (C) computed tomography shows that the peripheral reticular appearance is due to dilation of the peripheral pulmonary arteries (*arrowheads*). (D) Catheter pulmonary angiography confirms the peripheral reticular appearance in chest radiography is due to dilated peripheral pulmonary arteries. (Courtesy Michael B. Gotway, MD.)



eFigure 126.3 Metastatic calcinosis in patients with end-stage renal disease. (A) Axial *computed tomography* (CT) scan displayed in lung windows shows confluent dense calcification in the apices. The calcification of these opacities is more evident with CT displayed in soft tissue windows (B). (C) Axial CT slightly caudal to (A) shows that the apical opacities have a hazy centrilobular nodular appearance, which is commonly encountered in end-stage renal disease patients with metastatic calcinosis. (Courtesy Michael B. Gotway, MD.)

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127 PULMONARY COMPLICATIONS OF HEMATOLOGIC DISEASES

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INTRODUCTION

Hematologic diseases and their specific therapies can adversely affect several aspects of cardiopulmonary function by reducing the oxygen-carrying capacity of the blood, by impairing pulmonary vascular function and pulmonary immune defenses, and by damaging the pulmonary parenchyma directly. This chapter reviews the clinical manifestations, epidemiology, pathophysiology, and treatment of pulmonary complications of disorders of the hematologic system.

RED BLOOD CELL DISORDERS

ANEMIA

Anemia is defined as a reduction in the number of circulating *red blood cells* (RBCs). By decreasing the oxygen-carrying capacity of the blood, anemia can impair cardiopulmonary function. However, because multiple compensatory mechanisms exist to adjust to a reduced oxygen-carrying capacity of blood, the signs and symptoms induced by anemia depend on its degree, the rate at which it evolves, the oxygen demands of the patient, and the presence of chronic cardiopulmonary disease. For instance, in resting adults subjected to acute isovolemic anemia, oxygen delivery can be maintained at hemoglobin concentrations as low as 5 g/dL,[1] a finding also seen in individuals with chronic severe anemia.[2] As such, anemia, even when severe, rarely causes heart failure or pulmonary edema and, when it does, it is likely that heart failure from chronically high cardiac output is superimposed on some other coexisting cardiac abnormality. From the hemodynamic standpoint, as the hemoglobin level decreases (particularly with hemoglobin values < 7 g/dL), cardiac output increases, filling pressures tend to decrease, and systemic and pulmonary vascular resistances decrease. These changes are readily reversible after RBC transfusions.[2,3] Finally, when anemia is severe, in the absence of coexisting cardiopulmonary disease, gas exchange is usually well maintained.

Pulmonary hypertension (PH) is an increasingly recognized complication of chronic hereditary and acquired hemolytic anemias. Remarkably, virtually every cause of hemolytic anemia has been associated with PH (Table 127.1). The PH associated with hemolytic disorders is considered in the group 5 classification of PH, characterized by unclear/multifactorial mechanisms (see Chapter 83).[4,5] In contrast, there have been no reports of PH associated with nonhemolytic anemias, such as the anemia of chronic disease or iron deficiency anemia. This suggests that the hemolytic component of anemia is necessary for the development of PH, which is discussed in detail in the section on hemoglobinopathies.

POLYCYTHEMIA

Polycythemia is characterized by an abnormally high hematocrit (>48% and >52% in women and men, respectively), hemoglobin concentration (>16.5 or >18.5 g/dL in women and men, respectively), or RBC count. These measurements are dependent on the plasma volume and the RBC mass; thus, before classifying a patient as having true polycythemia, one must exclude a decrease in plasma volume as the etiology for these abnormalities. A state of chronically reduced plasma volume with elevated hemoglobin or hematocrit has been called Gaisböck disease,[6] spurious polycythemia, stress erythrocytosis, apparent polycythemia, and pseudopolycythemia and has been associated with use of diuretics, alcohol, obesity, hypertension, and renal disease. On the other hand, patients with true elevations in RBC mass have absolute polycythemia and are categorized as primary or secondary forms. Primary polycythemia is caused by an acquired or inherited mutation, such as in the *JAK2* gene,[7] leading to an abnormality within RBC progenitor cells; it includes polycythemia vera and rare familial variants (e.g., activating mutations of the erythropoietin receptor or Chuvash polycythemia). Secondary polycythemia is caused by a circulating factor stimulating erythropoiesis, usually related to the production of erythropoietin

Table 127.1 Hemolytic Disorders Associated With Pulmonary Hypertension

HEMOGLOBINOPATHIES
Sickle cell disease
Thalassemia intermedia and major
Hb-Mainz unstable hemoglobin hemolytic anemia
RED CELL MEMBRANOPATHIES
Hereditary spherocytosis
Hereditary stomatocytosis
Paroxysmal nocturnal hemoglobinuria
Alloimmune hemolytic anemia
RED CELL ENZYMOPATHIES
Pyruvate kinase deficiency
Glucose-6-phosphate dehydrogenase deficiency
MICROANGIOPATHIC HEMOLYTIC ANEMIA
Thrombotic thrombocytopenic purpura
Hemolytic uremic syndrome
Hemolysis from mechanical heart valves
Left ventricular assist devices and cardiopulmonary bypass procedures
MALARIA

as a physiologic response to chronic hypoxia (e.g., chronic hypoxic lung disorders and disorders affecting hemoglobin oxygen affinity), but can also result from erythropoietin-secreting tumors.

Most of the symptoms of polycythemia are related to an increase in blood viscosity, which leads to impairment in systemic and pulmonary blood flow (see eFig. 85.1). Thromboembolic events have been described in approximately 30% of patients with polycythemia vera and account for 31% of their deaths.[8] Pulmonary nodular lesions secondary to thrombosis, stasis, or infarction have been described in these patients.[9] Late-stage polycythemia vera, which is characterized by myelofibrosis, may cause pulmonary and pleural masses that are related to extramedullary hematopoiesis.[10]

PH has been reported in patients with polycythemia and other myeloproliferative disorders.[9,11–14] In several case reviews, PH was common and often considered a direct cause of death.[11,13,15] The pathogenesis of PH in these disorders is not well established but can involve chronic thromboembolic disease or hypercoagulability and hyperviscosity leading to in situ thrombosis, as well as hemoglobin-dependent scavenging of endothelium-derived *nitric oxide* (NO)[16–20] and upregulation of *hypoxia inducible factor-1α* (HIF-1α)–mediated pathways, such as endothelin-1.[13]

In patients with polycythemia vera, the mainstay of therapy is phlebotomy and myelosuppression with *hydroxyurea*, to keep the hematocrit below 42% in women and 45% in men, and antithrombotic therapy with aspirin or anagrelide.[21,22] Hydroxyurea acts by inhibiting ribonucleotide reductase, the enzyme involved in transforming ribonucleosides into deoxyribonucleosides, thus inhibiting DNA synthesis and causing cell death. In case series, treatment of polycythemia vera has been shown to improve PH.[11] In patients with chronic hypoxic disorders, such as COPD and interstitial lung disease, long-term oxygen therapy should reduce the number of patients who become severely polycythemic. In patients with COPD and severe polycythemia, phlebotomy—to achieve a hematocrit of about 50%—is associated with both a decrease in *mean pulmonary artery pressure* (mPAP) and in *pulmonary vascular resistance* (PVR), as well as an improvement in exercise performance.[23] However, the use of phlebotomy should be reserved as adjunctive therapy in symptomatic patients with marked polycythemia who remain significantly polycythemic despite appropriate long-term oxygen therapy.

HEMOGLOBINOPATHIES

SICKLE CELL DISEASE

Sickle cell anemia, the most common and most severe form of *sickle cell disease* (SCD), is seen in individuals who are homozygous for a single nucleotide substitution in the β globin gene. This results in the synthesis of *hemoglobin S* (Hb S), a structural variant that, when deoxygenated, is much less soluble than normal hemoglobin (Hb A).[24,25] Deoxygenated Hb S polymerizes and aggregates inside sickled erythrocytes as they traverse the microcirculation. Rigid, dense, and sickled cells can become entrapped in the microcirculation, a process that is enhanced by their increased propensity to adhere to endothelium. Mechanistic studies in transgenic mice expressing exclusively human Hb S suggest that microvascular occlusion results in ischemia and reperfusion injury, which promotes inflammatory, thrombotic, and oxidant stress.[26–29] In patients with SCD, vaso-occlusion leads to the frequent episodes of bone pain and acute chest syndrome that complicate SCD. Furthermore, the membrane of erythrocytes containing intracellular Hb S polymer is constantly exposed to mechanical and oxidant injury as the erythrocytes traverse the microcirculation. Ultimately, cumulative membrane damage shortens red cell life span so that SCD is characterized by a chronic hemolytic anemia. Intravascular hemolysis releases cell-free hemoglobin into the plasma, which scavenges NO, a critically important gaseous signaling molecule that mediates vasodilation. Hemolysis also releases RBC arginase into the plasma, which catabolizes arginine, the substrate for NO synthesis.[17,30,31] Intravascular hemolysis thus produces a state of endothelial dysfunction, vascular proliferation, and pro-oxidant and proinflammatory stress.[32–38] After hemolysis, hemoglobin can oxidize and release heme, which has been shown to activate the *toll-like receptor 4* (TLR4) and inflammasome signaling to amplify inflammation.[39–41] In the lung microvasculature, cell-free hemoglobin and heme, and inflammatory stimuli such as lipopolysaccharide, can stimulate P-selectin–dependent platelet-neutrophil aggregates that entrap erythrocytes and further drive lung inflammation.[39]

It is estimated that about 250,000 children worldwide are born with homozygous sickle cell anemia every year.[42] Approximately 0.15% of African Americans are homozygous, and 8% have the sickle cell trait. Despite significant improvements in the life expectancy of patients with SCD, estimates of the median age at death range from 48 to 58.5 years for women and 42 to 53 years for men.[43,44]

Acute and chronic pulmonary complications of SCD are common but are often underappreciated by health care providers. Acute complications include asthma and the *acute chest syndrome* (ACS), whereas chronic complications

include pulmonary fibrosis and PH. Pulmonary complications account for a large proportion of deaths among adults with SCD.[43,45,46] According to the Cooperative Study of Sickle Cell Disease, a prospective multicenter study of 3764 patients, more than 20% of adults presumably had fatal pulmonary complications of SCD.[43] Among the 299 patients enrolled in the long-term follow-up study of patients who participated in the *Multicenter Study of Hydroxyurea in Sickle Cell Anemia* (MSH), pulmonary disease was the most common cause of mortality, accounting for 28% of all deaths.[47]

Acute Chest Syndrome

ACS represents a lung injury syndrome in patients with SCD analogous to that of the *acute respiratory distress syndrome* (ARDS). In a patient with SCD, ACS is clinically defined by the development of a new pulmonary opacity involving at least one complete lung segment, consistent with alveolar consolidation, not atelectasis, and accompanied by chest pain, fever, tachypnea, wheezing, or cough.[48]

Epidemiology. ACS is the second most common cause of hospitalization in patients with SCD and is the leading cause of both admission to an intensive care unit and premature death.[43,46] More recently, however, increased awareness, the chronic use of hydroxyurea, and the early and aggressive use of transfusion therapy appear to have decreased ACS-related morbidity and mortality, as evidenced by a lower rate of ACS in a multicenter trial of inhaled NO for vaso-occlusive crises.[49]

ACS can develop in any of the sickle hemoglobinopathies but is more common in individuals with homozygous SCD (Hb SS). In the Cooperative Study of Sickle Cell Disease, there was a 29% incidence of ACS in 3751 subjects over a 2-year period, representing an attack rate of 12.8 episodes per 100 patient-years for Hb SS disease.[43] The incidence was higher in children than in adults (24.5 events vs. 8.8 events per 100 patient-years). Up to half of ACS episodes develop in association with vaso-occlusive pain crisis, and many patients will have a painful event within 2 weeks of the diagnosis.[50,51] Because up to 20% of patients admitted with acute vaso-occlusive pain crisis will develop ACS in the first 3 days of hospitalization, physicians must be vigilant for this common and potentially lethal complication.

Steady-state laboratory parameters associated with an increased risk for the development of ACS include an elevated *white blood cell* (WBC) count, a higher hemoglobin level, and a lower fetal hemoglobin level.[50,51] In children, a number of studies now suggest that asthma is a risk factor for the development of ACS.[52–54] Other clinical events associated with increased risk for the development of ACS include major surgical procedures, acute rib infarcts, avascular necrosis of the hips, pregnancy, use of narcotics, acute anemic events, and previous pulmonary events.[50,51]

During acute hospitalization for vaso-occlusive crisis, the development of ACS is often preceded by an abrupt drop in hemoglobin levels (mean decrease of 0.8 g/dL from steady-state values) and increases in markers of hemolysis, such as *lactate dehydrogenase* (LDH). ACS may also be preceded by a drop in the platelet count (see later). Many clinicians monitor trends in hemoglobin and platelet counts and pay careful attention to patients with drops in steady-state values.

Pathophysiology. Three major mechanisms appear to be involved in the pathogenesis of ACS: infection, bone marrow fat embolization, and direct red cell intravascular sequestration causing lung injury and infarction (Fig. 127.1).

The most common etiology of ACS in both children and adults is infection by a community-acquired pathogen (eFig. 127.1), followed by an excessive inflammatory lung injury response. It is increasingly clear that patients with SCD are predisposed to develop severe lung injury triggered by relatively minor infections. Greater than 80% of adults with SCD report a history of having been admitted to the hospital for "pneumonia," which could be due to infectious pneumonia or to the infiltrates of ACS itself.[32] The National Acute Chest Syndrome Study Group analyzed 670 episodes of ACS in 538 patients with SCD to determine the cause, outcome, and response to therapy; respiratory samples obtained from sputum and bronchoalveolar lavage were analyzed for viral and bacterial infections.[48] Among the infectious agents identified most frequently were atypical bacteria, viruses, *Staphylococcus,* and *Streptococcus.* Community-acquired encapsulated bacteria were rarely isolated, despite the fact that patients with Hb SS disease usually have abnormal splenic function. Cases of severe ACS related to outbreaks of seasonal influenza have also been described.[55,56]

Fat embolization syndrome is the second most common cause of ACS and is more common in adults. It arises as a complication of vaso-occlusive pain crisis involving multiple bones, which results in bone marrow edema, infarction, and necrosis. As a result, bone marrow contents are released into the systemic circulation and trapped in the pulmonary circulation, producing acute PH, severe lung inflammation, and hypoxemia (Fig. 127.2 and eFig. 127.2).[57] Bone marrow fat released into the bloodstream is also converted by secretory phospholipase A_2 to free fatty acids, which can produce direct inflammatory lung injury.[58]

Vaso-occlusion is associated with the development of ACS in some patients, with a small percentage developing wedge-shaped pulmonary infarction (eFig. 127.3), sometimes followed by central cavitation.[59] In situ thrombosis is presumed to play a role, as suggested by a study showing segmental thromboemboli without any evidence of peripheral venous thrombosis.[60] In addition, a possible thrombotic thrombocytopenic purpura–like mechanism may exist in a subset of patients with ACS as suggested by studies demonstrating that free hemoglobin might inhibit activity of ADAMTS13, a protease whose deficiency underlies most cases of thrombotic thrombocytopenic purpura.[61–63]

Activation of Inflammatory Pathways in Patients With Sickle Cell Disease

See ExpertConsult.com for a discussion.

Clinical Features and Evaluation. The clinical features at presentation are age dependent, which likely reflects the different etiologies of ACS in different age groups, with children having a higher proportion of infectious etiologies and adults more likely to have fat embolization. Overall, 80% of patients present with fever, 62% with cough, and approximately 40% have chest pain, tachypnea, dyspnea, and abdominal, arm, leg, rib, or sternal pain.[48] Most adult patients present with severe extremity or chest pain and 24 to 72 hours later

Why do SCD patients develop severe acute lung injury, often after infection with more benign community-acquired infections, such as respiratory syncytial virus, parvovirus, rhinovirus, cytomegalovirus, Epstein-Barr virus, and herpes simplex virus? Recent data suggest that inflammatory stimuli activate innate sterile inflammatory pathways through TLR4 and the inflammasome, together with P-selectin–dependent adhesion of activated platelets and neutrophils, which form aggregates in the pulmonary microvasculature and entrap Hb S–containing erythrocytes and further stimulate release of interleukin-1β.[39,41] Of interest, in sickle cell mice, small doses of hemoglobin, heme, or lipopolysaccharide can trigger this inflammatory cascade, suggesting an overexuberant inflammatory response underlies the severe lung injury response that is so common in SCD patients. It is likely that the innate immune system is chronically activated by hemolysis and the stimulation of hemoglobin and heme in plasma, setting up the patient for a second "hit," often a community-acquired upper respiratory infection (eFig. 127.4). Clearly, a potential role for hemolysis-derived plasma-free hemoglobin and free heme as novel mechanisms in ACS is emerging. Ghosh and colleagues[64] administered lysed RBCs into the circulation of sickle cell mice, which resulted in increased pulmonary vascular permeability without affecting permeability in other organs; moreover, studies from the same group have demonstrated that *intravenous* (IV) administration of hemin to sickle cell mice induces severe and lethal acute lung injury.[65] In vitro studies also suggest that hemin induces pulmonary endothelial cell barrier dysfunction via necroptotic cell death in a TLR4-dependent manner.[66] In addition, higher plasma-free heme levels were associated with increased odds of ACS in children with SCD,[67] and genetic variants in inducible heme-oxygenase-1, the rate-limiting enzyme in heme catabolism, which causes increased hemeoxygenase-1 activity, have been associated with lower rates of ACS.[68] These data suggest that plasma-free hemoglobin and/or heme specifically may contribute directly to lung injury.

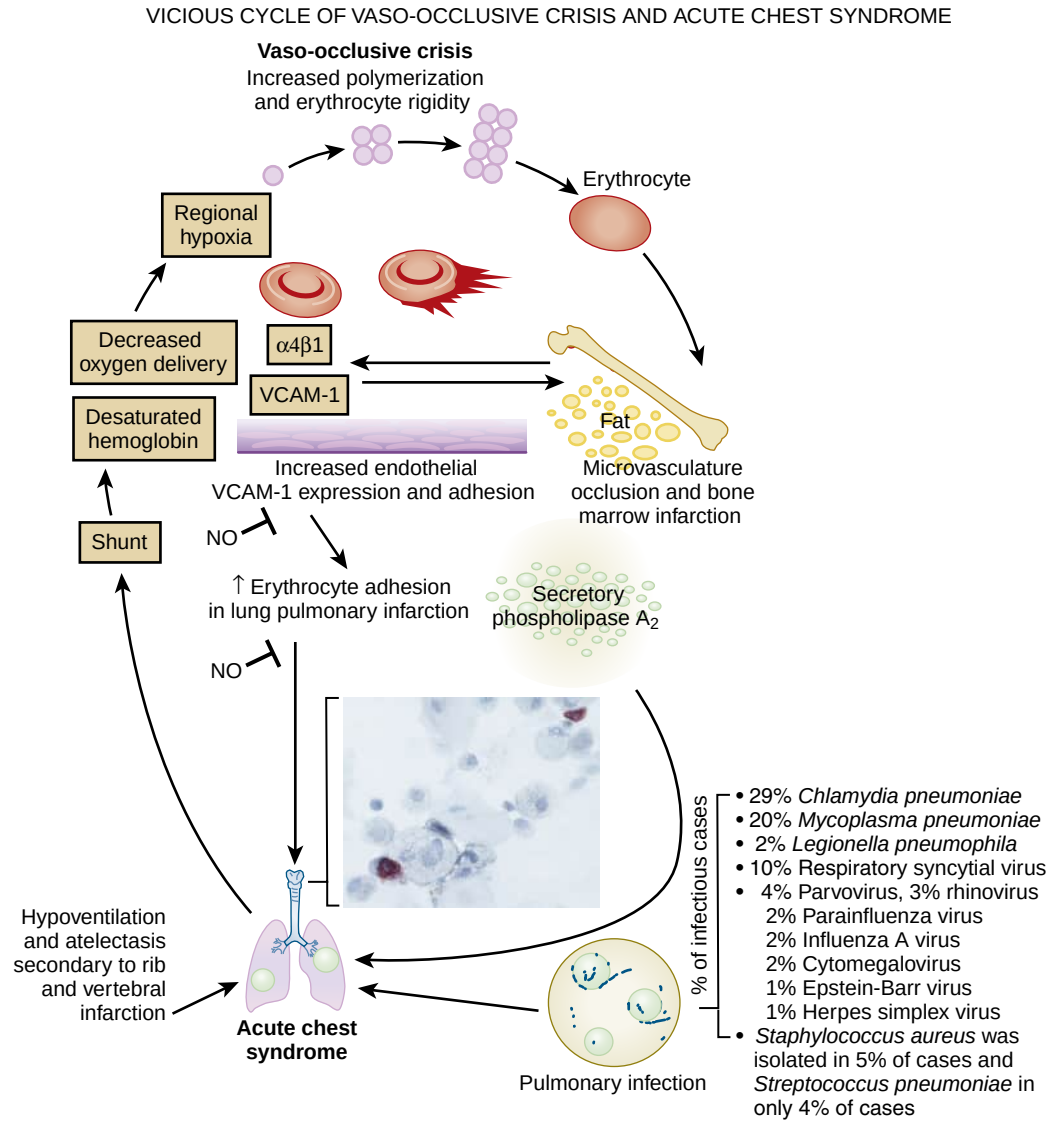

Figure 127.1 Pathogenesis of the acute chest syndrome. Three major triggers are associated with the development of acute chest syndrome: infection, bone marrow fat embolization, and direct red cell intravascular sequestration causing lung injury and infarction. Lung injury results in ventilation-perfusion mismatch/shunt and hypoxemia, which leads to increased hemoglobin S polymerization and erythrocyte vaso-occlusion. This worsens bone marrow infarction and pulmonary vaso-occlusion to promote a vicious cycle. Fat embolization can be diagnosed by oil red O staining of pulmonary alveolar macrophages, revealing the characteristic red lipid inclusions (see inset). NO can inhibit steps in the pathologic process, but NO is scavenged by free hemoglobin released by hemolysis. α4β1, an integrin dimer; NO, nitric oxide; VCAM-1, vascular cell adhesion molecule-1.

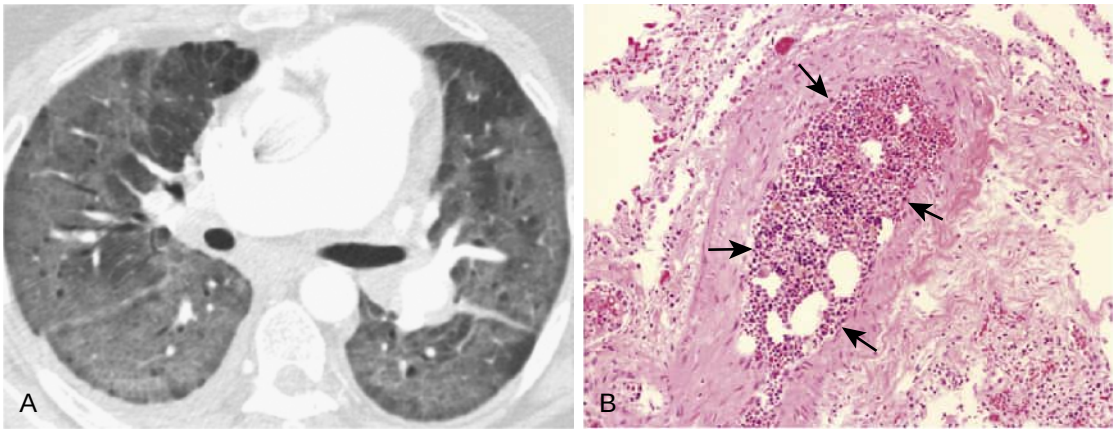

Figure 127.2 Fat embolization in acute chest syndrome. (A) Axial chest computed tomography scan of a patient with acute chest syndrome and fat embolization shows multifocal ground-glass opacity (same patient as in eFig. 127.2). (B) Postmortem examination specimen of a patient who died suddenly during an episode of vaso-occlusive crisis and acute chest syndrome demonstrating bone marrow elements *(arrows)* lodged in the small pulmonary artery. (Hematoxylin and eosin stain, magnification ×20.)

develop ACS. Reactive airway disease is observed in 13% of cases of ACS and is much more common in children. Adults are more likely to develop rapidly progressive ACS, defined as ACS progressing to respiratory failure less than 24 hours from onset of respiratory symptoms.[69]

ACS is associated with signs of systemic inflammation, with mean peak temperatures of 38.9°C and mean WBC counts of 23,000 cells/μL[40,48] Although high steady-state hemoglobin level is a risk factor for developing ACS, the acute presentation is often associated with a drop in hemoglobin and increases in hemolysis markers. A platelet count less than 200,000/μL appears to be a marker of ACS severity, associated with increased risk of neurologic complications and mechanical ventilation.[49] Secretory phospholipase A_2 levels are elevated early in the course of ACS, even before the development of radiographic changes, and have been used to predict the onset of the syndrome.[70]

Because the clinical manifestations can be indistinguishable from the other causes of ACS, the diagnosis of pulmonary fat embolization syndrome relies on the identification of oil red O–positive lipid accumulations within alveolar macrophages (see Fig. 127.1). In a 30-center clinical trial, the National Acute Chest Syndrome Study Group identified fat embolization syndrome in 16% of ACS cases in adults and children on the basis of positive lipid accumulations in alveolar macrophages.[48] Bronchoscopy has been used to help confirm the diagnosis of pulmonary fat embolization syndrome. Induced sputum may be a noninvasive alternative; in one study the yield from induced sputum sampling of alveolar macrophages was found to be similar to that from bronchoalveolar lavage.[71]

Some patients with ACS develop *systemic* fat embolization. Systemic fat embolization should be suspected in patients presenting with acute multiple organ failure, including acute hypoxic respiratory failure, right heart failure, renal and hepatic dysfunction, alterations in mental status, seizures, thrombocytopenia, and coagulopathy.[72,73] In patients with ACS, those with lipid-laden macrophages in induced sputum have significantly more extrathoracic pain, more neurologic symptoms, a lower platelet count, and higher transaminase levels than do those without lipid-laden macrophages.[71] This suggests that the fat embolization syndrome is both a major cause of ACS and has a more severe course with systemic complications.

The mean length of hospitalization for ACS is 10.5 days compared with 3 to 4 days for uncomplicated vaso-occlusive pain crisis. Thirteen percent of all patients with ACS require mechanical ventilation, and the overall mortality is 3% for all patients and 9% for adults. Risk factors for mechanical ventilation and poor outcome include a platelet count less than 200,000/μL (likely indicative of the fat embolization syndrome), a larger number of lobes involved on chest radiograph, and a self-reported or medical record history of cardiac disease. The latter complication is now thought to represent occult PH and right heart failure. In fact, in a study of 84 consecutive hospitalized patients with ACS, 13% of patients manifested right heart failure, a subgroup that had the highest risk for mechanical ventilation and death.[74] Thus, PH and right heart dysfunction likely represent a major comorbidity during ACS, and right heart failure should be considered in patients presenting with shock or severe hypoxemia.

Table 127.2 Treatment of the Acute Chest Syndrome

Oxygen therapy to maintain arterial hemoglobin oxygen saturation > 92%
Pain control and incentive spirometry to reduce chest wall splinting and pulmonary atelectasis
Close clinical observation ■ Monitor P_{O_2}/F_{IO_2} ratio ■ Particular attention to worsening respiratory function
Asthma therapy if indicated
Empirical antibiotics ■ Cover typical and atypical respiratory pathogens ■ Consider regional and seasonal risk of methicillin-resistant *Staphylococcus aureus* ■ Anticipate influenza A or B infections and treat/prevent accordingly
Transfusion therapy ■ Main indication for transfusion therapy in ACS is worsening respiratory function ■ Simple transfusion is as effective as erythrocytapheresis in the usual patient ■ Patients with high initial hemoglobin concentrations (≥9 g/dL) or patients with more severe disease should receive erythrocytapheresis ■ Transfused blood should be matched to Rh, C, E, and Kell antigens, and transfusion records documenting history of prior alloantibodies should be obtained

ACS, acute chest syndrome; F_{IO_2}, fractional concentration of oxygen in inspired gas; P_{O_2}, partial pressure of oxygen.

Treatment. In the outpatient setting, patients with a history of ACS should be treated with hydroxyurea because this therapy has been shown to reduce the risk of developing ACS by approximately 50%.[75,76] Although the precise mechanisms for this effect are largely unknown, the primary action appears to be that hydroxyurea induces the expression of fetal hemoglobin, thereby inhibiting RBC sickling. A chronic transfusion regimen is also effective in reducing the incidence of ACS.[77] Because the triggers and risk factors for ACS are well known, clinical surveillance plus aggressive and early therapy are likely to improve prognosis. This could be accomplished by close monitoring of patients during a vaso-occlusive crisis, during a febrile illness, and in the postoperative state.

If ACS develops, a range of treatment strategies is recommended, as outlined in Table 127.2. Oxygen therapy should be given routinely to maintain oxygen saturation above 92%. Aggressive pain management and incentive spirometry can minimize chest wall splinting, with consequent relief of atelectasis and hypoxemia. The use of incentive spirometry has been shown to decrease the incidence of new pulmonary opacities in patients admitted with vaso-occlusive pain affecting the chest wall.[59]

Given the high prevalence of infectious etiologies for ACS, we recommend the use of empirical antimicrobial therapy in all patients. Considering the high prevalence of atypical bacteria and encapsulated organisms, empirical coverage should include agents such as macrolides or fluoroquinolones, which are effective against these organisms. It is also important to consider alternative organisms, such as methicillin-resistant *Staphylococcus aureus* or influenza viruses, especially in patients not responding to therapy or during the annual influenza season.

Blood transfusion remains the mainstay of ACS therapy, although its value has not yet been demonstrated in randomized trials. Acute red cell transfusion increases arterial *partial pressure of oxygen* (Po_2) and hemoglobin oxygen saturation and may rapidly resolve the pulmonary event.[48,78] Because transfusion can also increase blood viscosity and the consequent risk of vaso-occlusion, it is recommended that the hemoglobin level not rise above 11 g/dL. The National Acute Chest Syndrome Study Group found no significant differences in outcomes between patients treated with simple transfusion or with *erythrocytapheresis* (i.e., RBC exchange), suggesting that simple transfusion is preferred as initial therapy.[48] For patients with high initial hemoglobin concentrations (>9 g/dL) or with more severe disease, however, erythrocytapheresis is recommended but, because most patients have a low hemoglobin at presentation, the transfusion of 2 to 4 units of packed red cells over 24 to 48 hours can usually be performed without complication. To decrease the risk of delayed hemolytic transfusion reactions related to alloimmunization against minor RBC antigens, all transfused blood should be matched to Rh, C, E, and Kell antigens.

Some initially promising treatments, including corticosteroids, inhaled NO, and *noninvasive ventilation* (NIV), have not been shown to have a role in ACS. Although treatment with corticosteroids has been shown to reduce the severity of pain and length of hospitalization, this therapy is complicated by a high rate of rebound pain and hospitalization.[79,80] One study evaluating a slow corticosteroid taper to limit rebound pain and readmission was terminated early because of slow accrual.[81] Inhaled NO does not appear to have any effect on the duration of pain crisis, narcotic use, pain scores, development of ACS, rate of ACS treatment failure, or need for transfusion.[49,82] In one small single-center randomized trial, NIV improved respiratory rate and gas exchange but did not reduce the number of patients remaining hypoxemic at day 3 and was associated with greater patient discomfort. In addition, NIV did not change transfusion rates, pain scores, narcotic dose, or hospital length of stay but instead prolonged length of stay in the step-down unit.[83] Reports of use of extracorporeal membrane oxygenation are still limited, and mortality is high.[84]

Pulmonary Hypertension

PH has emerged as a major threat to the well-being and longevity of patients with SCD. SCD could represent one of the most common causes of PH because, of the 30 million individuals worldwide with SCD,[85] approximately 10% of adults evaluated in screening studies have an mPAP greater than 25 mm Hg.

Epidemiology. Studies have shown that PH is common in patients with SCD, with prevalence as high as 30% when diagnosed by Doppler echocardiography, demonstrating a *tricuspid regurgitant jet velocity* (TRV) at least 2 standard deviations above the normal mean value (≥2.5 m/sec).[32,73,86–88] However, the prevalence seems to be much lower, at approximately 10%, when diagnosed by the gold standard diagnostic test, right heart catheterization.[89–91] Risk factors for developing PH include increased age, history of renal or cardiovascular complications, increased systemic systolic blood pressure, elevations in LDH (marker of hemolysis), elevated alkaline phosphatase, low transferrin levels, and a history of priapism in men.[30,32,92–94] Of interest, the number of vaso-occlusive episodes, markers of inflammation, fetal hemoglobin levels, or platelet counts are not risks for development of PH.[32,89,90,92,95] Although a high mPAP could result from the high cardiac output state associated with chronic anemia, this does not seem to be a major contributor to elevated mPAP because there has been no report of PH associated with nonhemolytic anemia. See Chapter 83 for details about echocardiography and diagnosis of PH.

See ExpertConsult.com for further details about the epidemiology of PH in SCD.

Mortality. An elevated mPAP increases the risk of death for patients with SCD. Several studies have demonstrated that mortality in patients with SCD significantly rises with both increasing TRV and increasing NT-proBNP level.[32,87,88,102] Similarly, multiple studies have also shown that the presence of PH documented by right heart catheterization is a major risk factor for death. Among patients with PH on right heart catheterization compared to no PH, mortality has ranged from 23% to as high as 50%, and each 10-mm Hg increase in mPAP associated with a 1.7-fold increase in the mortality.[89,91,95,103] In one study conducted by the NIH, specific hemodynamic variables were independently and significantly related to mortality, including mPAP, diastolic mPAP, systolic mPAP, *pulmonary capillary wedge pressure* (PCWP), transpulmonary gradient, and PVR.[95] These data suggest that mortality in adults with SCD and PH is proportional to the physiologic severity of pulmonary vascular disease.

Pathogenesis

See ExpertConsult.com for a detailed description of the development of PH in patient with SCD.

Clinical Features and Evaluation. The diagnostic evaluation of patients with SCD suspected of having PH should follow the same guidelines established for other causes of PH.[135,136] Given the high prevalence of PH in this population and the associated high mortality, an expert panel from the American Thoracic Society recommends that all adults with SCD undergo universal noninvasive screening with Doppler echocardiography or with assessment of steady-state plasma NT-proBNP levels.[137] In patients with SCD, as described earlier, the echocardiographic estimation of pulmonary artery systolic pressures (where pulmonary artery systolic pressure = 4 × TRV^2 + estimate of the right atrial pressure) correlates reasonably well with measured pulmonary systolic pressures by right heart catheterization.[32,138] See Chapter 83 for details about use of echocardiography and diagnosis of PH.

Although no prospective data on prevalence and risk of PH are available for children, we currently recommend that children with hypoxemia, high hemolytic rates (hemoglobin values < 7 g/dL with high LDH values), and/or recurrent ACS be screened. It is important that such screening be performed in the steady state because pulmonary pressures rise during vaso-occlusive painful crisis.[139]

A variety of studies, both retrospective and prospective, have identified a high prevalence of PH in patients with SCD. Retrospective studies have reported that 20–30% of patients with SCD have an elevated pulmonary artery systolic pressure estimated noninvasively by Doppler echocardiography by a TRV that is 2 standard deviations above the normal mean value (≥2.5 m/sec).[73,86] Autopsy studies suggest that up to 75% of sickle cell patients have histologic evidence of PH at the time of death (eFig. 127.5).[96]

These data are corroborated by three prospective studies.[32,87,88] In the *National Institutes of Health* (NIH) PH echocardiographic screening study, 23% of patients with SCD had borderline to mild elevations in pulmonary artery systolic pressures (defined by a TRV > 2.5–2.9 m/sec, which corresponds to a pulmonary artery systolic pressure of 30–39 mm Hg), and 9% had moderately to severely elevated pressures (defined by a TRV > 3.0 m/sec, which corresponds to a pulmonary artery systolic pressure of approximately 40–45 mm Hg).[32] Similar rates were found in echocardiographic screening studies performed at two other centers.[87,88]

Measurement of *N-terminal pro–brain natriuretic peptide* (NT-proBNP), a prohormone released by the right and left ventricular myocardium under pressure stress, in stored plasma samples has shown a high prevalence of abnormal values that may correlate with PH. Of those enrolled in the MSH in 1996, 30% of individuals had elevated levels, suggesting the possible presence of PH.[92] Similarly, among patients enrolled in the Cooperative Study of Sickle Cell Disease from 1978–88, 27.6% of adults had elevated levels of NT-proBNP.[97] In both studies, elevated NT-proBNP was independently associated with a higher risk of death.

PH has been shown to increase over time and with increasing age. Two centers independently reported the follow-up of adult sickle patients who on initial echocardiographic screening had normal TRVs. After 2 to 3 years of follow-up, 13–15% of these patients developed high TRVs, suggesting an increasing incidence of PH of about 4–7% per year.[93,98] Increasing age is associated with an increased risk of elevated TRV. For example, in the NIH PH echocardiographic screening study, patients with an elevated TRV were significantly older than patients without (38 ± 19 years for patients with TRV > 3.0 m/sec and 39 ± 12 years for patients with TRV 2.5–2.9 m/sec, compared with 34 ± 10 years for patients with TRV < 2.5 m/sec; $P = 0.02$).[32] An increasing number of studies suggests that PH is developing in children with SCD; however, few children have TRV values greater than 3.0 m/sec, and the implications in terms of functional capacity and associated mortality have not been determined.[94,99,100]

Epidemiologic risk factors associated with PH include a history of renal or cardiovascular complications, increased systemic systolic blood pressure, elevations in the marker of hemolysis (LDH), elevated alkaline phosphatase, and low transferrin levels.[32,92,101] In men a history of priapism was also an independent factor associated with PH.[32] These risk factors have also been observed in recently published studies using right heart catheterization to define PH.[89,90,95] Of interest, the development of PH was not associated with the number of vaso-occlusive episodes, markers of inflammation, fetal hemoglobin levels, or platelet counts.[32,89,90,92,95] Although a high mPAP could also result from the high cardiac output state associated with chronic anemia, this hyperdynamic state does not seem to be a major contributor to significant elevations in mPAP because there has been no report of PH associated with nonhemolytic anemia. In summary, PH represents a component of the systemic vasculopathy of SCD characterized by systemic hypertension, renal failure, and priapism.

Finally, three studies have provided insights into the prevalence of PH in SCD, using the gold standard diagnostic test for the disease, right heart catheterization demonstrating an mPAP of 25 mm Hg or greater. In the NIH screening study (2001–10, median follow-up of 4.4 years),[89] 86 of 533 subjects underwent right heart catheterization and, of these, 56 (10.5%) were diagnosed with PH. Similarly, in a screening study of 80 patients from Brazil, 32 (40%) had an elevated TRV and, of those who underwent right heart catheterization, eight (10% of the total population) had PH.[90] In a third large screening study of 398 patients with SCD in France using right heart catheterization,[91] 6% were shown to have PH. Of note, the French study excluded approximately 10% of patients, those with "severe" renal, liver, or lung disease, with severity defined as a creatinine clearance of less than 30 mL/min; an abnormal prothrombin time (international normalized ratio > 1.7); and chronic restrictive lung disease defined by a total lung capacity of less than 70% predicted. It is not clear why these patients would be excluded from a prevalence study of SCD-related PH, especially considering the fact that all of these complications develop as a direct consequence of SCD, and all three represent significant published risk factors for developing PH in SCD.

Epidemiologic studies suggest that the central risk factor for the development of PH in patients with SCD is the severity of hemolytic anemia (eFig. 127.6).[32,87,88,104] The association between the development of PH and the intensity of hemolytic anemia has been observed in three prospective screening studies of adult patients with SCD,[32,87,88] in an expanding number of pediatric studies,[94,99,100,105,106] and in studies using right heart catheterization to define PH.[89,90,95] This suggests that hemolysis is related mechanistically to PH. That relationship is plausible and biologically significant because free hemoglobin inactivates the intrinsic vasodilator NO.[17,31] Hemolysis also releases arginase, which depletes L-arginine, the substrate for NO synthesis.[30] These combined mechanisms result in a state of decreased NO bioavailability and "resistance" to NO-dependent vasodilation.[17]

Hemolysis and decreased NO bioavailability also induce platelet activation,[107] thrombin generation, and tissue factor activation.[108] There is also a correlation between the rate of hemolysis and the levels of procoagulant factors in blood in patients with SCD.[109–111] Hemolysis is also associated with the formation of RBC microvesicles expressing phosphatidylserine, which activates tissue factor.[111,112] These factors all contribute to an increased risk of thrombosis. In addition, sickle cell patients with functional asplenia and thalassemia patients with surgical splenectomy have increased levels of cell-free hemoglobin and red cell microvesicles, providing a potential mechanism for the hypercoagulability associated with both diseases.[111] Finally, the accumulation of redox-active heme and iron from lysed RBCs further contributes to the generation of

reactive oxygen species that can exacerbate ischemia-reperfusion injury, thrombosis, and vascular proliferative responses.[113] In fact, microthrombotic and/or thromboembolic lesions are common findings at postmortem examination in patients with SCD.[114,115] Acute or organizing thrombi in the pulmonary arteries, predominantly distal, were commonly seen in a series of 11 SCD patients with the diagnosis of PH,[116] and an association was found between the postmortem diagnoses of PH and thromboembolism in another autopsy series.[117] Functional or surgical asplenia could also contribute to the development of PH in patients with SCD. Splenectomy has been reported to be a risk factor for the development of PH (especially chronic thromboembolic PH),[118] particularly in patients with hemolytic disorders.[119–121] Loss of splenic function may trigger platelet activation, promoting pulmonary microthrombosis, and red cell adhesion to the endothelium.[122] The spleen also plays a critical function in the removal of senescent and damaged erythrocytes.[123,124] After splenectomy, moreover, the rate of intravascular hemolysis increases.[111]

Another downstream effect of hemolytic anemia includes increased endothelin-1–mediated vasoconstrictive and proliferative responses. In patients with SCD, both at steady state and during vaso-occlusive pain crises, plasma endothelin-1 levels are increased.[125] In vitro sickled erythrocytes increase endothelin-1 production by cultured human endothelial cells. All told, hemolysis acts via multiple mechanisms to block NO-induced vasodilation, activate procoagulant activity, injure endothelial cells, and exacerbate vasoconstriction and proliferation.

Chronic hypoxia and normoxic activation of HIF-related pathways are involved in the etiology of various forms of PH. SCD is also characterized by normoxic activation of hypoxic responses. In a recent study, Zhang and colleagues[126] compared clinical characteristics and *peripheral blood mononuclear cell* (PBMC) genomic profiles of subjects with SCD to those of subjects with Chuvash polycythemia, a monogenic disorder where homozygosity for von Hippel-Lindau syndrome R200W leads to posttranslational stabilization of the alpha subunits of HIF at normoxia, and increased levels of HIF-1 and HIF-2, leading to altered transcription of a number of genes and elevated systolic mPAP.[127–129] The study suggested that greater than 50% of PBMC gene expression variation in hemoglobin SS patients may be related to the hypoxic response because there was strong correlation between the gene expression profiles of the two patient populations.[126] Further, an expression quantitative trait locus in *MAPK8*, a hypoxia down-regulated gene (rs10857560) that has a prominent role in promoting apoptosis,[130] was associated with right heart catheterization–documented precapillary PH in patients with SCD. Finally, in another study, elevated levels of placental growth factor, which activates HIF-1α in normoxia and have been shown to be elevated and associated with elevated systolic mPAP in SCD. [131]

Genetic modifiers could also play a role in susceptibility to PH in SCD. Single nucleotide polymorphisms for genes in the transforming growth factor-β superfamily, including activin A receptor, type II–like 1 *(ACVRL1)*, bone morphogenetic protein receptor 2 *(BMPR2)*, and bone morphogenetic protein 6 *(BMP6)*; the β_1-adrenergic receptor *(ADRB1)*[132]; and thrombospondin-1 *(THBS1)*[133] have been associated with an elevated pulmonary artery systolic pressure in patients with SCD. Desai and colleagues[134] investigated the potential role of PBMC-derived gene signatures as biomarkers for PH in SCD.[134] The study found 631 transcripts and 12 micro-RNAs correlating with right ventricular systolic pressure (RVSP). Biologic-pathway analysis of these 631 genes revealed that pathways that have been associated with pulmonary vascular remodeling, such as Wnt signaling, calcium signaling, vascular smooth muscle contraction, and cancer pathways, were significantly overrepresented in subjects with elevated RVSP. Support vector machine analysis identified a 10-gene signature, including *GALNT13* (encoding polypeptide *N*-acetylgalactosaminyltransferase 13, a glycosyltransferase enzyme responsible for the synthesis of *O*-glycan), which distinguished patients with and without increased RVSP with 100% accuracy. This finding was then validated in a separate cohort of patients with PH documented by right heart catheterization, with an overall accuracy of 90%. A genetic association study comparing patients with an elevated RVSP and those with a normal RVSP revealed five significant single nucleotide polymorphisms within *GALNT13* associated with an elevated RVSP.

Historically, PH in patients with SCD was thought to derive from the repetitive episodes of pulmonary vaso-occlusive crisis and ACS. However, this association has not been supported by epidemiologic studies in which the number of episodes of vaso-occlusive crisis and ACS have not been shown to be associated with PH.[32,92]

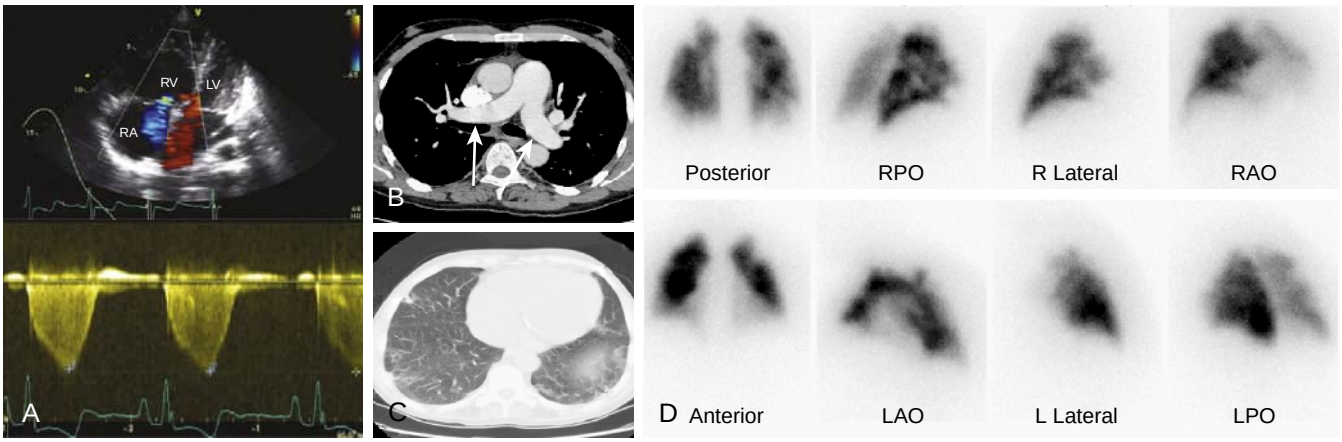

Figure 127.3 Imaging features of sickle cell disease and pulmonary hypertension. (A) *Top,* Echocardiographic apical four-chamber view of the heart, illustrating severe right ventricular (RV) and right atrial (RA) dilation and moderate tricuspid regurgitation (*blue* Doppler). *Bottom,* Doppler tracing from a patient with severe pulmonary hypertension reveals a jet velocity of greater than 4 m/sec. (B) Axial chest computed tomography scan showing enlargement of pulmonary arteries *(arrows)* in severe pulmonary hypertension. (C) Chest computed tomography showing mild pulmonary fibrosis typical of patients with sickle cell disease and pulmonary hypertension. (D) Perfusion scan demonstrating patchy areas of abnormal perfusion. Ventilation scans were normal (not shown). LAO, left anterior oblique; LPO, left posterior oblique; LV, left ventricle; RAO, right anterior oblique; RPO, right posterior oblique.

The diagnosis of PH in patients with SCD can be challenging (Fig. 127.3; Videos 127.1 and 127.2). Exertional dyspnea, the most typical presentation of PH, is also a cardinal symptom of chronic anemia, and therefore a high index of suspicion for PH is necessary. Other conditions that commonly present in patients with SCD, such as left ventricular dysfunction, pulmonary fibrosis, and liver cirrhosis, could also present in a similar fashion and result in PH. Patients with PH tend to be older and have higher systolic arterial blood pressure, lower hemoglobin levels, higher indices of hemolysis (such as high bilirubin or LDH values), lower hemoglobin oxygen saturation, greater degree of renal and liver dysfunction, and a higher number of lifetime RBC transfusions.[32] As such, the diagnostic evaluation of these patients should include an aggressive search for other conditions that might contribute to PH, such as iron overload, chronic liver disease, human immunodeficiency virus, nocturnal hypoxemia, and thromboembolism.

A diagnostic right heart catheterization is essential to confirm the diagnosis and exclude diastolic dysfunction (see later).[109] The 6-minute walk test is a useful surrogate for functional capacity in this patient population even considering the high prevalence of confounding factors such as the presence of avascular necrosis of the hip. Specifically, the *6-minute walk distance* (6MWD) inversely correlates with the severity of PH[113] and survival[95] and is improved by PH-specific therapy.[125]

The Doppler echocardiogram is an important tool for population screening and estimation of mPAP, but it cannot be used to diagnose or define PH in an individual patient. For a given patient, a diagnosis of PH is based on the measurement of the mPAP via a right heart catheterization. In a single individual, finding a TRV greater than or equal to 2.5 m/sec has low specificity for a diagnosis of PH,[91] with only 25% of those patients having the diagnosis of PH. Combining a TRV greater than or equal to 2.5 m/sec, a high NT-proBNP level (>164.5 pg/mL), and a low 6MWD of less than 333 m gives a positive predictive value for PH of 62%, with a false-negative rate of 7%.

Abnormal pulmonary function can be found in most patients with SCD. The pulmonary function abnormalities are characterized by mild restrictive lung disease (mean total lung capacity values of about 79% of predicted), abnormal diffusing capacity, and radiographic signs of mild pulmonary fibrosis,[46,140–144] and the severity of these defects seems to be slightly greater in those patients with PH.[145] However, in these patients, the degree of pulmonary function abnormalities is rarely severe enough to be a major contributor to the etiology of PH.

A ventilation-perfusion scan is an indispensable component of the evaluation because chronic thromboembolic PH, if amenable to pulmonary endarterectomy, is a potential curable cause of PH reported in patients with chronic hemolytic disorders. In the majority of cases, scintigraphic evidence of thromboembolic disease is uncommon, and the most common abnormality is patchy areas of abnormal perfusion, similar to findings described in other forms of PH.[145,146] Chronic thromboembolic PH is present in approximately 5% of sickle cell patients with severe PH[145] (Fig. 127.4). As such, patients should undergo imaging studies and, if suggestive of chronic thromboembolic PH, should undergo more invasive studies (i.e., angiography) to exclude this potentially surgically treatable condition.

NT-proBNP levels can be used as a PH biomarker for diagnosis and risk stratification in patients with SCD.[92] In a contemporaneous cohort, NT-proBNP levels were higher in patients with SCD-associated PH than without PH and correlated directly with the severity of PH and the degree of functional impairment. An NT-proBNP level of 160 pg/mL or greater had a 78% positive predictive value for finding an elevated TRV. In this and in other studies, an elevated NT-proBNP was an independent predictor of mortality.[97]

In contrast to patients with traditional forms of PH (e.g., idiopathic pulmonary arterial hypertension [PAH] or scleroderma-associated PAH) who may be symptomatic with mPAP in the range of 50 to 60 mm Hg, patients with SCD may be symptomatic with a mild to moderate degree of elevation in mPAP, in the range of 30 to 40 mm Hg. These patients may also have coexistent mild elevation in

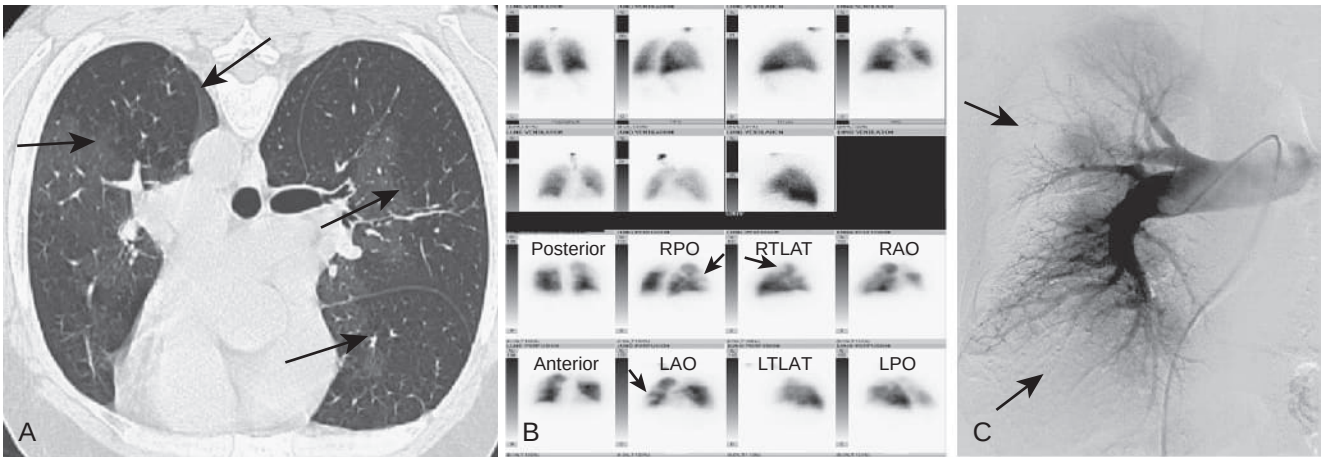

Figure 127.4 Chronic thromboembolic pulmonary hypertension in a patient with sickle cell disease. (A) High-resolution computed tomography scan demonstrating mosaic pattern of attenuation. Multiple hyperlucent regions represent areas with decreased perfusion *(arrows)*. (B) Ventilation-perfusion scan demonstrating multiple unmatched perfusion defects *(arrows)*. Ventilation scans, top seven images; perfusion scans, bottom eight images. (C) Digital subtraction pulmonary angiogram that shows diffuse peripheral areas of hypoperfusion, which represent multiple peripheral small filling defects *(arrows)*. LAO, left anterior oblique; LPO, left posterior oblique; LTLAT, left lateral; RAO, right anterior oblique; RPO, right posterior oblique; RTLAT, right lateral.

PCWP, suggesting left heart failure (Table 127.3). Right heart catheterization data from multiple studies[21,23–26] show that the hemodynamic etiology of the PH in patients with SCD is multifactorial: precapillary PH (defined by a mPAP ≥25 mm Hg and a PCWP ≤15 mm Hg) is present in 50% of catheterized patients, whereas pulmonary venous hypertension secondary to left ventricular diastolic dysfunction disease (defined by a mPAP ≥25 mm Hg and a PCWP >15 mm Hg) is present in 50%.

Furthermore, using echocardiography in a cohort of 141 patients with SCD, Sachdev and associates[147] found that 47% of patients had PH, diastolic dysfunction, or both. PH and diastolic dysfunction were associated with a relative risk of death of 5.1 and 4.8, respectively, whereas the relative risk of death when both were present was 12.0.[147] These data suggest that both PH and diastolic dysfunction independently carry mortality risk.

Regardless of the hemodynamic etiology, SCD patients with chronic anemia, who maintain a high compensatory resting cardiac output to ensure adequate oxygen delivery, normally have a reduced PVR and appear to be poorly tolerant of even small increases in PVR. When compared with age-, gender-, and hemoglobin-matched patients with SCD without PH, individuals with PH exhibited a lower 6MWD, lower peak oxygen consumption on cardiopulmonary exercise testing, and higher ventilatory equivalent for carbon dioxide at anaerobic threshold on cardiopulmonary exercise testing.[113] Patients with SCD and PH appear to have worse functional capacity than is reported for patients with PH from other etiologies.[148] In addition, in patients with SCD, PVR sharply rises with exercise, suggesting that pulmonary vascular disease contributes to functional limitation in these patients.[139] Taken together, these data suggest that, in SCD patients with chronic anemia, mild to moderate PH has a severe adverse impact on functional and aerobic exercise capacity.

Table 127.3 Hemodynamic Profiles in Patients With Sickle Cell Disease

	Without PH	With PH
mPAP (mm Hg)	19 ± 0.7	36 ± 1
RAP (mm Hg)	6 ± 0.4	10 ± 1
PCWP (mm Hg)	11 ± 0.5	17 ± 1
CO (L/min)	10 ± 0.5	9 ± 0.3
PVR (dynes • s • cm^{-5})	59 ± 6	197 ± 14

CO, cardiac output; mPAP, mean pulmonary artery pressure; PH, pulmonary hypertension; PCWP, pulmonary wedge pressure; RAP, right atrial pressure; PVR, pulmonary vascular resistance.
Data from references 145, 264, and 265, except PVR, which comes from references 145 and 265.

Treatment. Data on the specific management of patients with SCD and PH are limited, although an increasing number of informative open-label intervention studies have been published. Most of the recommendations are based on expert opinion or extrapolated from data derived from observational intervention studies in patients with SCD or from other forms of PH and lack data from randomized controlled trials.[136,137] The general approach should include maximization of SCD-specific therapy (i.e., treatment of primary hemoglobinopathy), treatment of hypoxemia with chronic oxygen therapy, and treatment of associated conditions, such as iron overload, chronic liver disease, human immunodeficiency virus infection, nocturnal hypoxemia, and thromboembolic disorders. For patients with SCD with PH (mPAP ≥ 25 mm Hg and PCWP < 15 mm Hg with a relatively high PVR, > 160 dynes • s • cm^{-5}), targeted therapy with pulmonary vasodilator/antiremodeling agents can be considered. See Fig. 127.5 for an algorithm proposed by the American Thoracic Society for the diagnosis, risk stratification, and management of PH in SCD.[137]

Because chronic intravascular hemolysis is a central mechanism in the development of PH, it is likely that optimizing SCD therapy would be beneficial through amelioration of the principal mechanism involved in the pathogenesis of PH. Hydroxyurea has been shown to decrease the incidence of pain episodes and ACS, reduce the need for transfusions, and lower overall mortality.[47,75] It is possible that some of

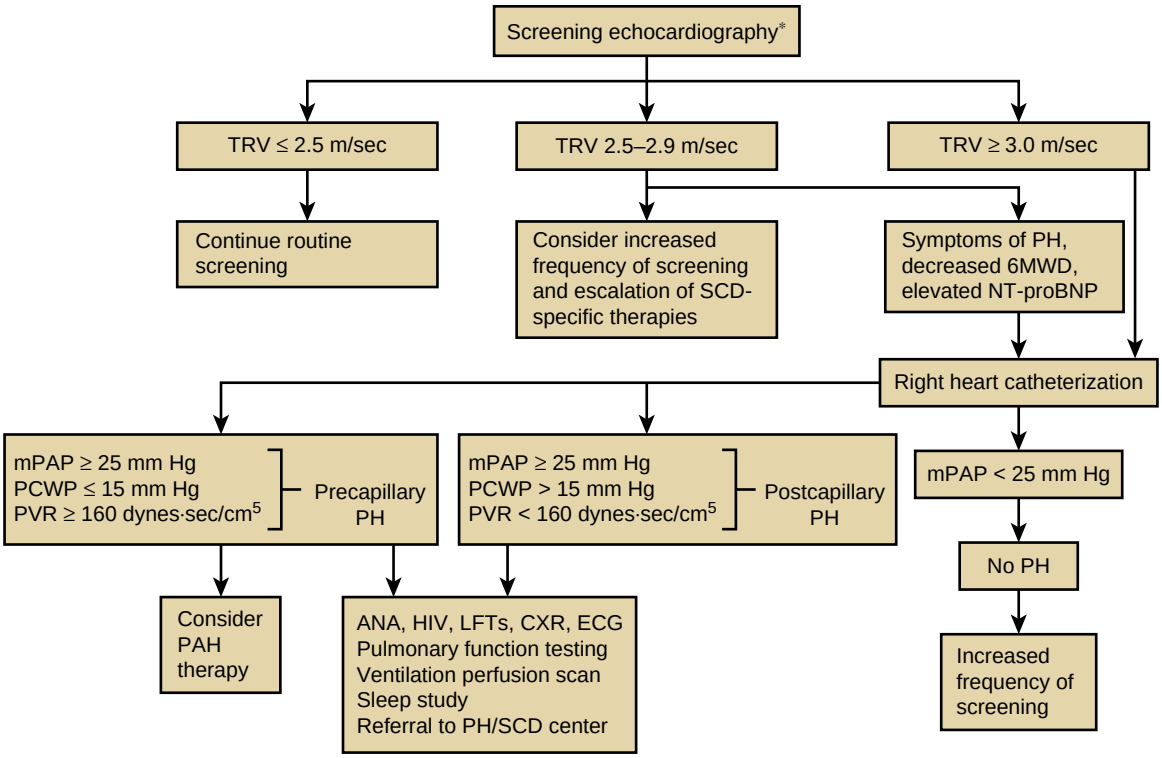

Figure 127.5 Proposed algorithm for evaluation of pulmonary hypertension related to sickle cell disease. Echocardiography should be performed while patients are clinically stable. Patients with an mPAP between 20 and 25 mm Hg need further study because they may be at increased mortality risk. *The use of the term *screening* refers to mortality risk assessment. ANA, antinuclear antibody; CXR, chest radiograph; ECG, electrocardiogram; HIV, human immunodeficiency virus; LFTs, liver function tests; mPAP mean pulmonary artery pressure; 6MWD, 6-minute walk distance; NT-proBNP, N-terminal pro–brain natriuretic peptide; PCWP, pulmonary capillary wedge pressure; PH, pulmonary hypertension; PVR, pulmonary vascular resistance; SCD, sickle cell disease; TRV, tricuspid regurgitant jet velocity. (From Klings ES, Machado RF, Barst RJ, et al; American Thoracic Society Ad Hoc Committee on Pulmonary Hypertension of Sickle Cell Disease. An official American Thoracic Society clinical practice guideline: diagnosis, risk stratification, and management of pulmonary hypertension of sickle cell disease. *Am J Respir Crit Care Med.* 2014;189[6]):727–740.)

the decreases in pulmonary and cardiovascular deaths seen in hydroxyurea-treated patients could be related to an improvement in PH. For patients with creatinine levels less than 1 mg/dL, hydroxyurea is started at a dose of 15 mg/kg/day and titrated up to a maximum of 35 mg/kg/day. Detailed treatment guidelines have been published.[76,149] Patients with renal dysfunction tend not to tolerate the myelosuppressant effects of hydroxyurea and, in those cases, we recommend adding erythropoietin to the regimen. Long-term transfusion therapy lowers the risk of most complications of the disease, including the risks of pulmonary events and central nervous system vasculopathy,[150–152] and might improve cardiopulmonary function and prevent the progression of PH. For example, in a small series of 13 patients with SCD and precapillary PH, chronic exchange transfusion therapy improved functional capacity (improved 6MWD and New York Heart Association functional class) and decreased PVR.[153] A large multicenter randomized trial of erythrocytapheresis on top of standard of care is currently sponsored by NHLBI, with randomization starting in 2020 (SCD CARRE trial). Haploidentical peripheral blood stem-cell transplantation and lung transplantation have also been shown to normalize pulmonary pressures and to improve short-term outcome measures in these patients.[154,155]

The potential benefits of warfarin therapy observed in patients with idiopathic PAH (group 1, see Chapter 84) have to be weighed against the risk of hemorrhagic stroke in adults with SCD or hemorrhage in chronically anemic individuals. We believe that the relatively low risk of hemorrhagic stroke (0.21 events per 100 patient-years[156]), compared with the high risk of death in patients with severe PH, supports anticoagulation in patients without a specific contraindication who have hemodynamic evidence of PH or chronic thromboembolic PH.

There are limited data on the specific treatment of PH in SCD, and the choice of agents (prostacyclin analogues, phosphodiesterase inhibitors, or endothelin receptor antagonists) is largely empirical and based on the safety profile of the drugs and physician preference. In general, randomized multicenter placebo-controlled studies evaluating the role of PH therapy in patients with SCD have not yet provided clear guidance.[157,158]

Prostacyclin-based therapy has been shown to reduce pulmonary pressures and increase 6MWD and functional class in patients with SCD and PH.[159,160] This study demonstrated dose-response relationships between subcutaneous, inhaled, and IV prostacyclin analogues and improvements in estimated pulmonary pressures and 6MWD. However, there are specific treatment concerns regarding the use of these drugs in patients with hemolytic diseases. For example, the use of prostanoids can produce systemic vasodilation and increases in cardiac output, raising the concern for the potential development of high-output heart failure in anemic patients. In addition, the risk of chronic IV-line–related complications, such as thrombosis and sepsis, is likely higher in patients with SCD.

Sildenafil and other phosphodiesterase inhibitors function by inhibiting the metabolism of cyclic guanosine monophosphate, the second messenger that mediates the effects of NO. In a series of seven patients with either thalassemia or sickle-thalassemia and severe PH, treatment with sildenafil from 4 weeks to 48 months resulted in an improvement in TRV, New York Heart Association functional class, and 6MWD.[161] In another case series of 12 patients with SCD treated with sildenafil for a mean of 6 months, mean pulmonary artery systolic pressure decreased by 9 mm Hg, 6MWD improved, and mean NT-proBNP decreased.[162] The main concern related to the use of sildenafil is the potential for the development of priapism in men with SCD.

Endothelin antagonists have limited evidence to support their use for PH. Minniti and colleagues[163] reported on the use of bosentan and ambrisentan in a cohort of 14 patients with SCD and PH documented by right heart catheterization. Endothelin antagonist therapy either as monotherapy or in combination with sildenafil was well tolerated and resulted in a modest improvement in 6MWD. The main toxicity of endothelin-1 receptor antagonists is hepatocellular injury, which could limit their applicability in patients with SCD at risk for liver dysfunction (e.g., iron overload, hepatitis C). Another class effect of these agents is a dose-related decrease in hemoglobin levels, usually by approximately 1 g/dL.[148]

Chronic Lung Disease

Sickle cell chronic lung disease has been used as a broad term to encompass pulmonary fibrosis resulting from recurrent ACS and PH.[46] Current understanding of sickle cell chronic lung disease suggests that pulmonary fibrosis is quite mild and that PH is a more important cause of chronic pulmonary disease. For this reason, we believe that this older terminology should be replaced with a more specific diagnostic classification.

In patients with SCD, repetitive episodes of acute injury to the lung related to ACS can result in parenchymal damage and typically mild restrictive lung disease (eFig. 127.7). In a study of 310 patients with homozygous SCD, pulmonary function was abnormal in 90% of adult patients; the most common abnormalities included mild restrictive physiology and decreased diffusing capacity.[164] These abnormalities worsen with age and are associated with increases in mPAP.[145,164]

In patients with SCD, airway hyperactivity is much more common in children than in adults.[165] Data are conflicting on whether children with SCD have a much higher prevalence of asthma and airway hyperactivity, when compared with ethnically and aged-matched control subjects.[53,166] Studies also suggest that wheezing and obstructive lung disease may arise independently of asthma and are markers of disease severity or a high-output state.[167,168] Compared to children with SCD who do not have asthma, children with SCD and asthma appear to have a higher incidence of ACS, cerebral vascular accidents, and need for blood transfusions, arguing for aggressive diagnosis and treatment of asthma in this population.[53,54,169] Similarly, adults with SCD who have asthma or recurrent episodes of wheezing have increased SCD-related morbidity, such as more episodes of pain, higher likelihood of development of recurrent ACS,[170] decreased lung function, and increased risk of death compared to adults with SCD without asthma symptoms.[171–176]

Sleep-disordered breathing has been reported in children and adults with SCD. In children, sleep-related upper airway obstruction and hypoxemia are the most common disturbances. In an uncontrolled study, adenotonsillectomy led to symptomatic improvement and amelioration of oxygen desaturation.[177,178] Evidence suggest that nocturnal hypoxemia contributes to the development of neurologic events and vaso-occlusive crisis via mechanisms that could involve upregulation of several inflammatory endothelial cell adhesion molecules.[179–181]

THALASSEMIA

Thalassemia refers to a spectrum of diseases characterized by reduced or absent production of one or more α or β globin chains. β-Thalassemia results from impaired production of β globin chains, which leads to a relative excess of α globin chains.[182] These excess α globin chains are unstable, incapable of forming soluble tetramers on their own, and precipitate within the cell, leading to ineffective erythropoiesis and hemolytic anemia.[182] Thalassemia major, or homozygous β-thalassemia, is a severe disorder due to the inheritance of two β-thalassemia alleles. Starting during the first year of life, patients develop severe and lifelong transfusion-dependent anemia, hepatosplenomegaly, and skeletal deformities due to bone marrow expansion; they are also prone to infection and skeletal fractures.

β-Thalassemia minor, also called β-thalassemia trait, arises in heterozygotes who have inherited a single gene leading to reduced β globin chain production. Such patients are asymptomatic, may be only mildly anemic, and are usually discovered when a blood count has been obtained for other reasons. β-Thalassemia intermedia is seen in patients with disease of intermediate severity, such as those who are compound heterozygotes of two thalassemic variants. Such patients may have the skeletal abnormalities and hepatosplenomegaly seen in thalassemia major. However, their hemoglobin concentrations usually range from 5 to 10 g/dL, and they usually require transfusions only when they have an intercurrent event, such as an infection, that impairs erythropoiesis. Their clinical symptoms may not be apparent until well after the first year of life. Another related condition is due to hemoglobin E, the most common hemoglobin variant in the world, which has a point mutation in the β-globin gene. In the heterozygous or homozygous states, patients with hemoglobin E are mostly asymptomatic or have a mild microcytic anemia. When hemoglobin E is present along with β-thalassemia, the condition is called hemoglobin E–thalassemia; about half of these patients are phenotypically similar to patients with thalassemia major and require regular transfusion therapy, with the other half having courses similar to patients with thalassemia intermedia.

Several cardiopulmonary abnormalities arise in patients with β-thalassemia, including restrictive and obstructive defects, hyperinflation, abnormal diffusing capacity, and decreases in aerobic exercise capacity.[183–185] However, in the majority of cases, these pulmonary function abnormalities are not associated with clinical symptoms. Several clinical complications are related to complications of therapy, such as transfusion-related iron overload, infection, thrombosis, possible acute deterioration in pulmonary function associated with the use of the iron chelator deferoxamine,

and PH related to splenectomy. In patients who are poorly transfused, extramedullary erythropoiesis can rarely cause pulmonary parenchymal masses, mediastinal masses (see eFigs. 115.44 and 115.45), and pleural effusions.

Similar to what is seen with SCD, PH is a common complication of thalassemia. Approximately 40–50% of patients with thalassemia intermedia[186] and 10–75% of patients with thalassemia major have echocardiographic evidence of PH.[187–189] In a multicenter cross-sectional study of β-thalassemia patients, those with a TRV of 3.2 m/sec or more (3.6% of the study group) underwent right heart catheterization. The prevalence of PH on right heart catheterization was 2.1% (4.8% in patients with thalassemia intermedia and 1.1% in patients with thalassemia major).[190]

PH in patients with thalassemia appears to be amenable to therapy. In spite of its potential complications, chronic transfusion therapy in severe thalassemia has changed the clinical course of the disease and is likely to have a favorable impact in individuals with PH. This idea is supported by a report that, in well-transfused, iron-chelated patients with thalassemia major, PH was completely prevented.[191] A favorable response to sildenafil has been reported in patients with thalassemia major and intermedia.[161,192] In a recent open-label study of 10 patients with β-thalassemia and a TRV greater than 2.5 m/sec, sildenafil decreased the TRV and improved left ventricular end-systolic/diastolic volume but did not improve 6MWD.[193] There are also case reports of favorable response to bosentan[194] and epoprostenol[195] in patients with right heart catheterization–confirmed precapillary PH. However, there are no studies evaluating either the specific hemodynamic derangements associated with PH or the impact of PH on survival in this patient population.

OTHER HEMOGLOBIN DISORDERS

Hemoglobin gene mutations can result in functional abnormalities in the globin chains that alter gas ligand affinity and oxygen uptake and delivery. Remarkably, there are more than 120 human hemoglobin gene mutations that have been associated with abnormal hemoglobin oxygen affinity.[196] Patients with moderately high-affinity hemoglobins usually present with erythrocytosis and are typically asymptomatic, but patients with variants associated with high oxygen affinity can present with cyanosis or symptoms related to increased RBC mass (polycythemia). In addition, whereas patients with low oxygen affinity hemoglobin variants are usually asymptomatic, some can present with cyanosis. The initial step in the workup of patients suspected of having a hemoglobinopathy affecting oxygen affinity is to evaluate the red cell oxygen equilibrium curve, whereby both the oxygen saturation of hemoglobin and P_{O_2} are directly measured to obtain a p50, the P_{O_2} at which hemoglobin is 50% saturated. This initial step should obviate the need for unnecessary and potentially invasive diagnostic procedures.

Methemoglobin is a nonfunctional state of hemoglobin in which the irons of heme are oxidized to the ferric (Fe^{3+}) state and are unable to bind oxygen. In addition, the oxygen affinity of any accompanying ferrous (Fe^{2+}) hemes in the hemoglobin tetramer is increased so that the oxygen dissociation curve is "left shifted," and oxygen delivery to the tissues is impaired.[153] Three mechanisms are associated with the development of methemoglobinemia: a genetic mutation resulting in abnormal hemoglobin (hemoglobin M), a congenital deficiency of methemoglobin reductase enzyme (cytochrome b_5 or cytochrome b_5 reductase deficiency), and a drug/toxin-induced oxidation of hemoglobin. Drugs that can induce methemoglobinemia include nitrates, nitrites, sulfonamides, dapsone, and several others. Most individuals with congenital methemoglobinemia are asymptomatic, and their primary complaint is "cyanosis" presenting as a slate-blue color of the skin and mucous membranes.

Cyanosis is clinically apparent when the absolute concentration of methemoglobin exceeds 1.5 g/dL, equivalent to approximately 10% methemoglobin.[197] In cases associated with drugs and toxins, the severity of the methemoglobinemia depends on the dose of the agent and the individual's susceptibility. At methemoglobin levels greater than 35%, patients can complain of headaches, weakness, and dyspnea; levels greater than 80% are typically incompatible with life.[196] Symptomatic patients should be treated with methylene blue (given IV at a dose of 1–2 mg/kg), which acts as a cofactor for the enzyme *reduced nicotinamide adenine dinucleotide phosphate* (NADPH)-methemoglobin reductase. Electrons are transferred from NADPH to methylene blue, which leads to a reduction of the heme iron.[198] Methylene blue should not be administered to individuals with glucose-6-phosphate dehydrogenase deficiency because it may precipitate hemolysis.[199]

Carbon monoxide (CO) binds to hemoglobin to form *carboxyhemoglobin* (COHb). CO has a much greater affinity for hemoglobin than does oxygen. The binding of CO to heme creates an allosteric change that diminishes the ability of hemoglobin to release oxygen to peripheral tissues, resulting in impaired oxygen transport and utilization. As such, CO poisoning is a major cause of morbidity and mortality. The clinical effects of CO poisoning are nonspecific and easily confused with other illnesses, such as viral illness, benign headache, and various cardiovascular and neurologic syndromes.[200] As the severity of exposure increases, patients develop more pronounced symptoms, with oxygen-dependent organs (the brain and the heart) showing the earliest signs of injury. Oxygen therapy improves tissue hypoxia and accelerates elimination of CO. Hyperbaric oxygen therapy should be considered in patients with severe CO poisoning (e.g., COHb > 25%, evidence of tissue ischemia, and loss of consciousness) and may reduce the incidence of the late neurocognitive deficits associated with severe CO intoxication.[201,202]

Cyanide binds the Fe^{3+} ion of cytochrome oxidase a3, inhibiting this final enzyme in the mitochondrial cytochrome complex and thereby preventing oxygen use by tissues. A small amount of cyanide can also bind to the Fe^{2+} iron ion of hemoglobin to form cyanhemoglobin, which is unable to transport oxygen and thus further exacerbates tissue hypoxia.[203]

WHITE BLOOD CELL DISORDERS

LEUKEMIAS

Although the majority of clinical pulmonary manifestations in patients with leukemia are not directly related to the disease, autopsy studies show that thoracic involvement is common in all types. Overall, the most common finding is

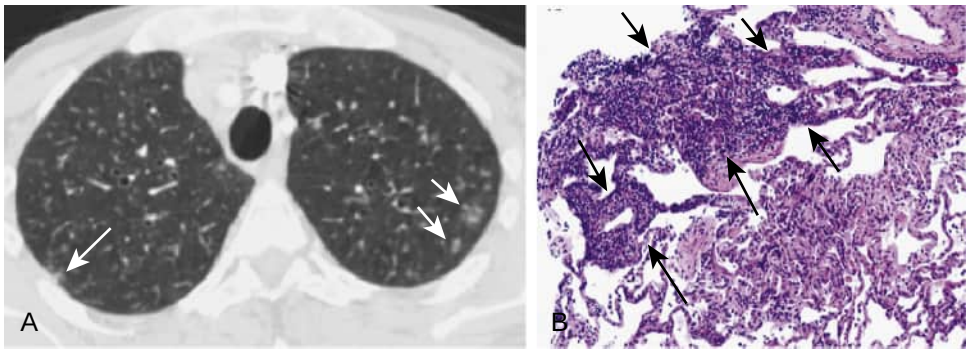

Figure 127.6 Leukemic infiltrates in a patient with chronic lymphocytic leukemia. (A) Diffuse nodular opacities *(arrows)*. (B) Transbronchial biopsy specimen demonstrating diffuse infiltration of lung interstitium by leukemic cells (especially *between arrows*). (Hematoxylin and eosin stain, ×20 magnification.)

mediastinal and lymph node involvement, but pleural and pulmonary infiltration is found in 20–65% of those who die with leukemia in autopsy series.[204–206]

The mediastinum is the most commonly affected intrathoracic site. This often manifests as a focal mass (eFig. 127.8) or as generalized mediastinal involvement. Hilar adenopathy is seen in 15–25% of patients.[207,208] Pleural effusion, usually unilateral, can present in up to 25% of cases and is seen more frequently in myeloid leukemias.[209] In the majority of cases, the effusion is related to lymphatic obstruction, congestive heart failure, or infections, with only approximately 5% of cases caused by leukemic infiltration.[209]

Leukemic pulmonary infiltrates are clinically significant in approximately 10% of patients (Fig. 127.6).[204] The usual radiographic pattern of involvement is a bilateral reticular pattern with septal lines resembling interstitial edema or lymphangitic carcinomatosis (eFig. 127.9). Interlobular smooth or nodular septal thickening is the most common high-resolution CT finding, followed by thickening of bronchovascular bundles. Other manifestations include peribronchovascular or random nodules, which can coalesce into masslike consolidation, focal areas of air space disease, and ground-glass opacities.[209–212] The diagnosis of leukemic infiltrates is one of exclusion because most of the pulmonary parenchymal abnormalities in these patients are associated with processes other than the hematologic disease, such as infections, hemorrhage, or pulmonary edema.

Pulmonary leukostasis or hyperleukocytosis is characterized by the distention of small pulmonary vessels by leukemic blast cells. It is most commonly seen in patients with acute leukemias and WBC counts greater than 100,000 cells/μL, with a predominance of blast cells.[213] Clinical and radiographic findings include dyspnea and hypoxemia associated with a bilateral reticular pattern with septal lines or air space consolidation.[213,214] Symptomatic leukostasis is a medical emergency, and efforts should be made to lower the WBC count rapidly. In most patients, rapid cytoreduction can be achieved by chemotherapy, but leukapheresis should be considered in severe cases or in patients who cannot receive chemotherapy immediately. Finally, patients can present with presumed acute spurious hypoxemia caused by an ex vivo decrease in arterial Po_2 mediated by the enhanced metabolism of the malignant cells; this process has been referred to as "leukocyte larceny." Pulse oximetry provides a more accurate assessment of arterial oxygen saturation in such circumstances.

Leukemic cell lysis lung disease arises in patients with high leukocyte counts undergoing chemotherapy and is part of the spectrum of tumor lysis syndrome. Severe hypoxia and diffuse bilateral opacities develop within 48 hours after the initiation of chemotherapy, resembling the clinical and pathologic presentation of ARDS.[215] In patients at intermediate or high risk for the development of tumor lysis syndrome, preventive measures are recommended, such as aggressive IV hydration, urine alkalinization in selected patients, and the use of agents to decrease uric acid levels, such as allopurinol and rasburicase.[216] These therapeutic strategies also apply to patients with established tumor lysis syndrome.

PLASMA CELL DISORDERS

Thoracic involvement in multiple myeloma is common, seen in 46% of patients, with the majority of cases related to neoplastic infiltration of the skeleton.[217] Pleural effusion caused by malignant infiltration has been reported and, for unclear reasons, the effusion appears to involve the left lung more frequently.[218] Pulmonary parenchymal or airway involvement is also rare, taking the form of single or multiple masses, diffuse parenchymal opacities, or endobronchial lesions.[217] Pulmonary amyloidosis can also result from systemic amyloid deposition, which can be a complication of different forms of plasma cell disorders (eFig. 127.10).[219]

Plasmacytoma is a circumscribed proliferation of plasma cells not associated with a plasma cell disorder. The vast majority of plasmacytomas involving the respiratory tract arise in the pharynx, followed by the trachea and, much less commonly, the lower airways and the pulmonary parenchyma.[220,221] Pulmonary parenchymal plasmocytomas present as a nodule or mass that is indistinguishable from bronchogenic carcinoma and may rarely present as a mass in the chest wall (eFigs. 127.11 and 127.12) or in the mediastinum (eFig. 127.13).

THROMBOSIS AND DISORDERS OF COAGULATION

INHERITED THROMBOPHILIA

Inherited thrombophilia encompasses the various mutations associated with venous thromboembolism (see Chapters 81 and 82 for further details). The most frequent causes of an inherited thrombophilia are the factor V Leiden mutation and a prothrombin gene (G20210A) mutation, which together account for 50–60% of cases. Mutations in

Table 127.4 Inherited Thrombophilic Disorders

Disorder	Prevalence in Healthy Individuals (%)	Frequency in Patients With VTE (%)	Relative Risk of First Episode of DVT	Relative Risk of Recurrence of VTE
Factor V Leiden (heterozygous)	0.05–4.8	18.8	7	1.4
Factor V Leiden (homozygous)	0.02	1.5	80	N/A
Prothrombin G20210A allele	0.06–2.7	7.1	2.8	1.7
Protein C deficiency	0.2–0.4	3.7	6.5	1.8
Protein S deficiency	0.16–0.21	2.3	5.0	1.0
Antithrombin III deficiency	0.02	1.9	20	2.6
Hyperhomocysteinemia	5–7	10	3.0	0.9

DVT, deep venous thrombosis; N/A, not available; VTE, venous thromboembolism.
Modified from Whitlatch NL, Ortel TL. Thrombophilias: when should we test and how does it help? *Semin Respir Crit Care Med*. 2008;29:25–39; and Dalen JE. Should patients with venous thromboembolism be screened for thrombophilia? *Am J Med*. 2008;121:458–463.

the genes coding for protein S, protein C, and antithrombin account for most of the remaining cases, although dysfibrinogenemias are rare causes of hypercoagulability (Table 127.4).[222,223] Patients with these disorders usually present with recurrent thromboembolism at a young age, typically younger than 50 years.

Several of these disorders are associated with an increased risk of initial and recurrent thromboembolism (see Table 127.4). There is, however, controversy about whether screening of individuals with venous thromboembolism for these inherited defects is warranted. Expert opinion suggests that evaluation for inherited thrombophilic disorders should be pursued in individuals with idiopathic thrombosis who are younger than 50 years, with a history of recurrent thrombosis, or with thrombosis in an unusual site; in those with a first-degree relative with thrombosis at a young age; or in women with thrombotic events during pregnancy or while taking oral contraceptives.[224,225] These recommendations must be contrasted with the results of epidemiologic studies, suggesting that a thrombophilic workup after a first thrombotic event is unlikely to confer clinical benefit.[226–228] The presence of a thrombophilic disorder does not impact the acute management of a thromboembolic event but could have an impact on the duration of chronic anticoagulant therapy.[229] Patients with antithrombin, protein C, or protein S deficiency should be considered for lifelong anticoagulation. Patients with heterozygous factor V Leiden or prothrombin gene mutations generally do not need lifelong anticoagulation but will likely benefit from extended anticoagulant therapy to reduce the risk of recurrence, as shown in other patients with idiopathic thromboembolism.[230,231] Patients with more than one allelic abnormality should also be considered for lifelong anticoagulation.

COAGULOPATHIES AND PLATELET DISORDERS

Spontaneous pulmonary hemorrhage does not appear to be a common complication of disorders of coagulation, such as the hemophilias, von Willebrand disease, or thrombocytopenia. The risk of bleeding appears to increase in individuals with preexisting pulmonary lesions or after physical or procedural trauma to the respiratory system. However, episodes of pulmonary hemorrhage, hemomediastinum, and tracheal and pleural hematomas have been described in patients with hemophilias.[232] Radiographic abnormalities, such as scarring, fibrosis, pleural thickening, abnormalities in pulmonary vessels, and hyperinflation and cases of PH, have also been described in patients with hemophilia.[196]

COMPLICATIONS OF TRANSFUSION

TRANSFUSION-ASSOCIATED ACUTE LUNG INJURY

Transfusion-related acute lung injury (TRALI) is an acute lung injury syndrome resulting from the transfusion of blood products containing plasma, most commonly whole blood, fresh frozen plasma, platelets, and packed RBCs. TRALI is currently the leading cause of transfusion-related morbidity and mortality.[233] Recently, the TRALI Delphi panel proposed a new consensus TRALI definition.[234] TRALI type I includes patients without risk factors for ARDS who meet the following criteria: acute onset of hypoxemia (arterial P_{O_2}/*fractional concentration of oxygen in inspired gas* [F_{IO_2}] ≤ 300 or oxygen saturation on room air < 90%), bilateral pulmonary opacities on imaging, no evidence of left atrial hypertension (LAH, or if LAH is present, it is not judged to be the main contributor to hypoxemia), and within 6 hours of infusion of a blood product. TRALI type II includes patients who have risk factors for ARDS but who have not been diagnosed with ARDS or who have existing mild ARDS (arterial P_{O_2}/F_{IO_2} of 200–300) but whose respiratory status deteriorates and is judged to be due to transfusion based on findings described in TRALI type I, and stable respiratory status in the 12 hours before transfusion.

Epidemiology

The incidence of TRALI is not well established but appears to be one episode for every 5000 blood component transfusions.[235] This likely underestimates the true incidence of the disease. Studies using systematic methods to identify

TRALI cases suggest that the incidence may be 5 to 50 times higher than previously thought.[236–239] A TRALI study group determined the incidence of TRALI by prospective, active surveillance in a case-control design in two academic medical centers.[240] The annual TRALI incidence decreased from 2.6 per 10,000 units transfused in 2006 to 0.8 per 10,000 units transfused in 2009, most likely related to TRALI mitigation strategies implemented in these centers.

TRALI has been reported in all age groups and with equal incidence in men and women. A single-center study suggested that patients with hematologic malignancies or cardiovascular disease requiring cardiopulmonary bypass operations are at a higher risk of developing this complication.[236] Administration of fresh frozen plasma, prolonged storage of blood products, and acute underlying conditions, such as recent surgery, massive transfusion, cytokine therapy, sepsis, and thrombocytopenia have also been implicated as risk factors for TRALI.[236,238,241–245] Multiparous women are the donors most commonly associated with cases of TRALI, which probably reflects the role of the antibodies formed due to exposure to fetal leukocyte antigens during pregnancy (see next section, "Pathogenesis").[235,246,247]

In the TRALI study group report, recipient factors associated with increased risk of TRALI included chronic alcohol abuse, shock, higher serum interleukin-8 levels, liver surgery, current smoking, higher peak airway pressure on mechanical ventilation, and positive fluid balance. Features of transfused blood products associated with increased risk of TRALI in the recipient were receipt of plasma or whole blood from female donors, high levels of human leukocyte antigen class II antibody, and anti–human neutrophil antigen–positive granulocytes. Little or no risk was associated with older RBC units, noncognate or weak cognate class II antibody, or class I antibody.[240]

Pathogenesis

Two leading hypotheses have been put forth to explain the mechanisms underlying the pathogenesis of TRALI. One theory proposes that transfused leukocyte antigens interact with antibodies to cause granulocyte activation and lung injury. An alternative "two-hit" hypothesis proposes that active substances accumulate as the blood product is stored and are transferred to a susceptible host, priming granulocytes that secondarily produce lung injury in the setting of systemic inflammation from another insult, such as sepsis.

The antileukocyte antibody hypothesis has support from several lines of evidence. Antileukocyte antibodies are found in donors or recipients after clinical episodes of TRALI, and infusion of antileukocyte antibodies in animals causes a similar form of lung injury.[248,249] In three case reports, TRALI was produced in healthy volunteers by infusions of plasma containing strong leukocyte antibodies.[250] Antibodies against human leukocyte antigen class I and II antigens are also found in patients with TRALI.[251]

The other two-hit hypothesis is also supported by several studies. The age of transfused blood has been reported as a risk factor for multiorgan failure in trauma patients.[252] The presence of bioactive lipids implicated in the pathogenesis of lung injury, such as lysophosphatidyl choline, is higher in blood products given to patients who develop TRALI.[238,244] CD40 ligand, which induces injury to activated microvascular endothelial cells, accumulates in stored blood products, and significantly higher levels have been found in blood products given to patients who develop TRALI.[253]

Clinical Features and Evaluation

Patients typically present with the sudden onset of respiratory distress 1 to 2 hours after the transfusion of blood products. Clinical signs include fever, tachypnea, tachycardia, and occasionally hypotension.[242] The patients may cough pink frothy secretions with a high albumin content indicative of increased permeability (noncardiogenic) pulmonary edema. Chest radiography classically reveals bilateral alveolar opacities with a normal cardiac silhouette and without pleural effusion. The finding of granulocyte, leukoagglutinating, or lymphotoxic antibodies in the serum from either the donor or recipient supports the diagnosis of TRALI, but these abnormalities are not found in all patients. The main differential diagnosis in these patients is transfusion-associated circulatory overload, and the differentiation of these two conditions can be difficult. The measurement of brain natriuretic peptide levels has been described as a helpful tool to differentiate these two entities.[254]

Approximately 70% of patients require mechanical ventilation at the time of presentation.[251] The illness tends to resolve within the first 48 hours, and with few exceptions, chest radiographs typically return to normal in 4 days. The estimated mortality associated with TRALI is 5%.[251]

Treatment

Because patients usually improve spontaneously, the management of TRALI is supportive. In patients requiring mechanical ventilation, the approach should be the same as recommended for patients with ARDS (see Chapter 134). There is no convincing evidence to support the use of corticosteroids in patients with TRALI. Individuals developing TRALI should not receive further blood products from the implicated donor but do not appear to be at increased risk for recurrent episodes with products from other donors.[255] Finally, in the TRALI study group case-control study, the incidence of TRALI decreased after the reduction of transfusion of plasma from female donors.[240]

Transfusion-Associated Circulatory Overload

Transfusion-associated circulatory overload (TACO) is likely the most common transfusion reaction affecting the respiratory system. It is characterized by pulmonary edema that develops due to volume excess or circulatory overload, primarily in patients who receive large volumes of transfusions over a short period of time, or in patients with underlying cardiac or renal disease. TACO can be typically differentiated from TRALI based on a combination of clinical, laboratory, and imaging characteristics, and response to diuretic therapy. These components have been incorporated in a recently revised international surveillance case definition.[256]

Given the variability in clinical definitions, the incidence of TACO is reported to range from 1–12%.[257] Patient-related risk factors for TACO include increasing age, female sex, white race, small body weight and stature, and a history of cardiac, renal, or lung disease.[257–261] Transfusion-related risk factors include number of units transfused,

faster infusion rate, and possibly plasma transfusion.[257,260] Approximately 70% of patients with TACO require mechanical ventilation.[260,261] TACO is associated with increased hospital length of stay, in-hospital mortality, and 1-year mortality.[260,262,263]

Several preventive strategies, including strict adherence to restrictive transfusion strategies, identification and close monitoring of at-risk patients, infusion of blood products at a low rate, and possibly preemptive diuretics in at-risk patients, would likely be effective in reducing the incidence of TACO.[257] The acute management of TACO is mostly supportive and includes discontinuation of the infusion of blood products if possible, oxygen therapy, ventilatory support, and most important, administration of diuretics.

Key Points

- Primary polycythemia is caused by either an acquired or inherited genetic abnormality; secondary polycythemia is mainly related to excess erythropoietin production from chronic hypoxia. Pulmonary complications include an increased risk of thromboembolism, pulmonary parenchymal disease, and *pulmonary hypertension* (PH).
- The acute chest syndrome and PH are leading causes of recurrent disability and premature death in *sickle cell disease* (SCD). Acute chest syndrome is thought to result from infection, bone marrow fat embolization, and/or direct red cell intravascular sequestration causing lung injury and infarction. PH is thought to result from hemolysis that alters nitric oxide activity and endothelial function.
- American Thoracic Society guidelines recommend yearly screening of adults with SCD for PH using Doppler-echocardiographic assessment of the tricuspid regurgitant jet velocity and plasma levels of *N-terminal pro–brain natriuretic peptide* (NT-proBNP). A tricuspid regurgitant jet velocity value of 2.5 m/sec or greater, especially with a plasma NT-proBNP level of 160 ng/pL or greater, suggests a high risk of PH and death and warrants intensification of SCD-specific care and evaluation for PH by sickle cell disease and PH specialists. Patients with PH are at high risk of having groups 1, 2, and 4 forms of PH and should be evaluated for hypoxemia, pulmonary arterial hypertension, right heart failure, and chronic thromboembolic PH, and managed accordingly.
- Thalassemia major is a severe heritable lifelong, multisystem disease owing to the presence of two β-thalassemia alleles; by contrast, thalassemia minor patients inherit just a single gene and may be asymptomatic with only mild anemia. PH is the most common pulmonary complication of this disorder.
- Leukemias and plasma cell disorders involve the pulmonary parenchyma uncommonly, although mediastinal involvement, lymphadenopathy, and pleural infiltration are common at autopsy.
- There is controversy about whether screening of individuals with venous thromboembolism for the presence of inherited thrombophilic defects is warranted; criteria for diagnosis have been suggested, but epidemiologic studies show little clinical benefit. Optimal chronic management of patients with inherited thrombophilia is not well established.
- Transfusion-related acute lung injury and transfusion-related circulatory overload are common causes of transfusion-related morbidity and mortality. Several risk factors have been identified, and multiple causes may play a role. The overall incidence appears to be diminishing, and clinical management remains supportive.

Key Readings

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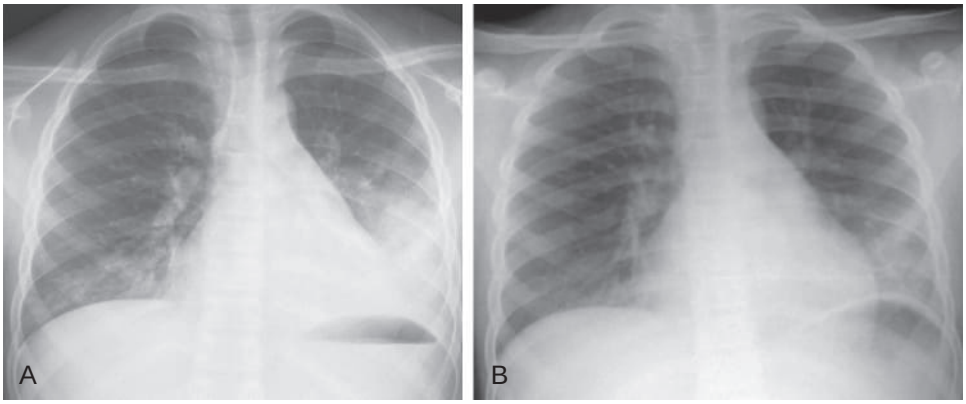
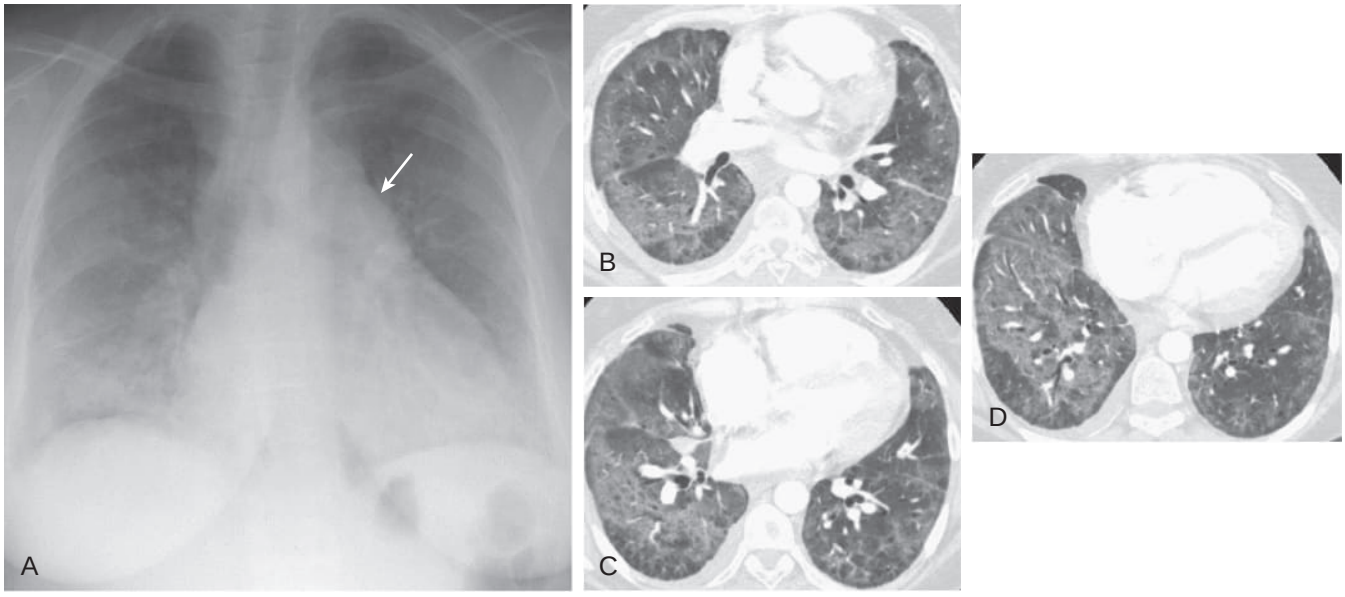
Complete reference list available at ExpertConsult.com.

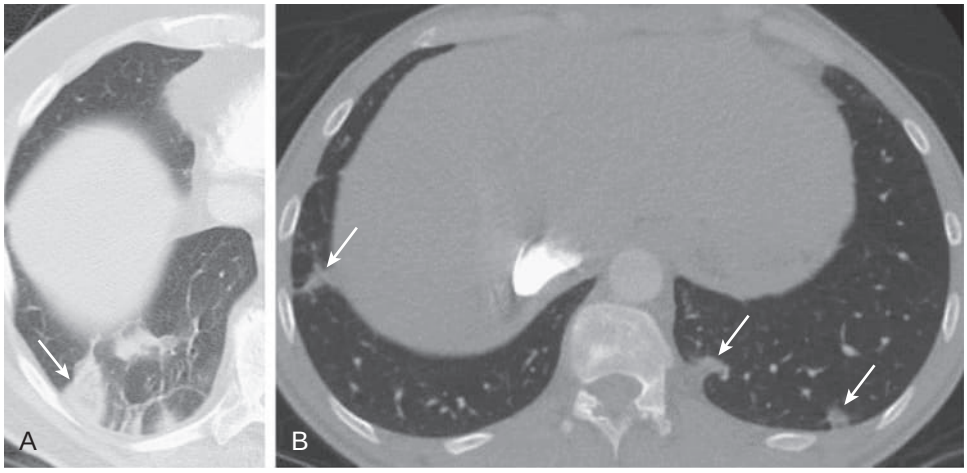
eFIGURE IMAGE GALLERY



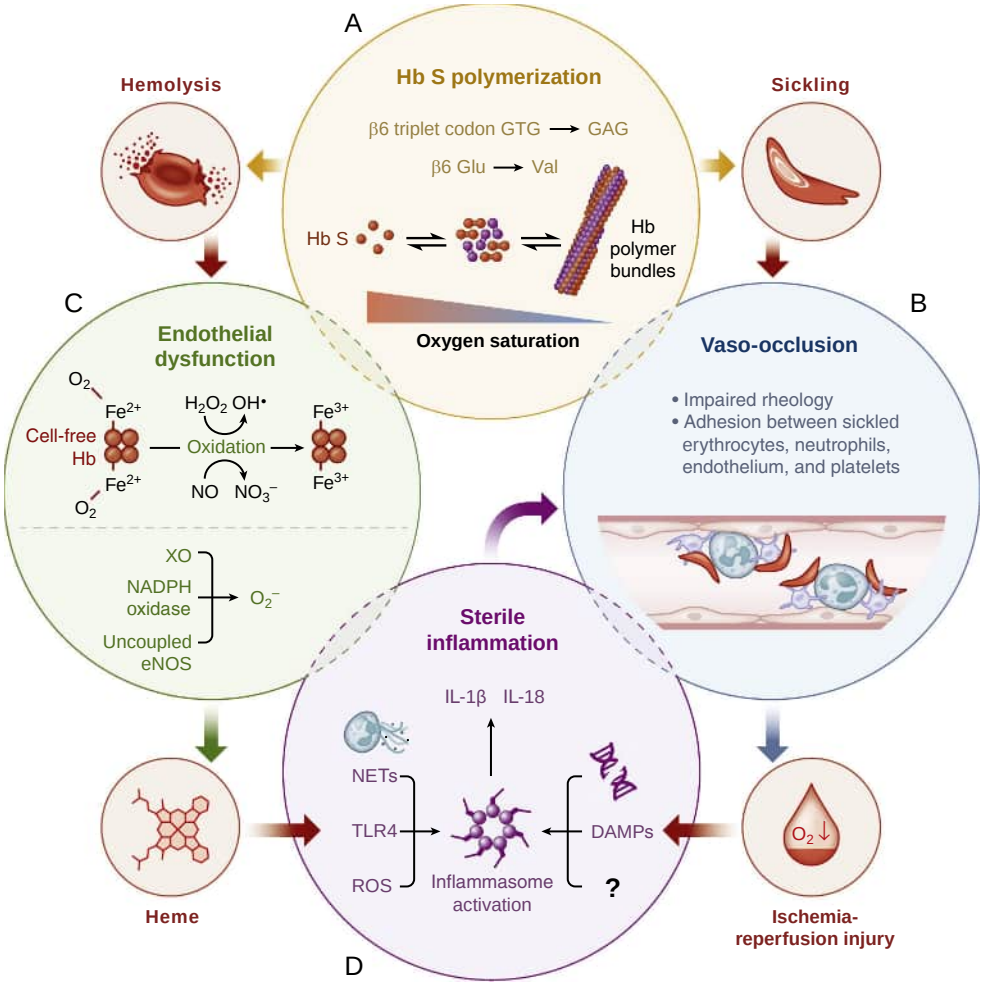
eFigure 127.1 Acute chest syndrome in sickle cell disease: pneumonia. (A) Frontal chest radiograph shows left-greater-than-right lower lobe consolidation, consistent with pneumonia. (B) Frontal chest radiograph 5 days later after antibiotic therapy shows improvement in the lower lobe opacities. (Courtesy Michael B. Gotway, MD.)



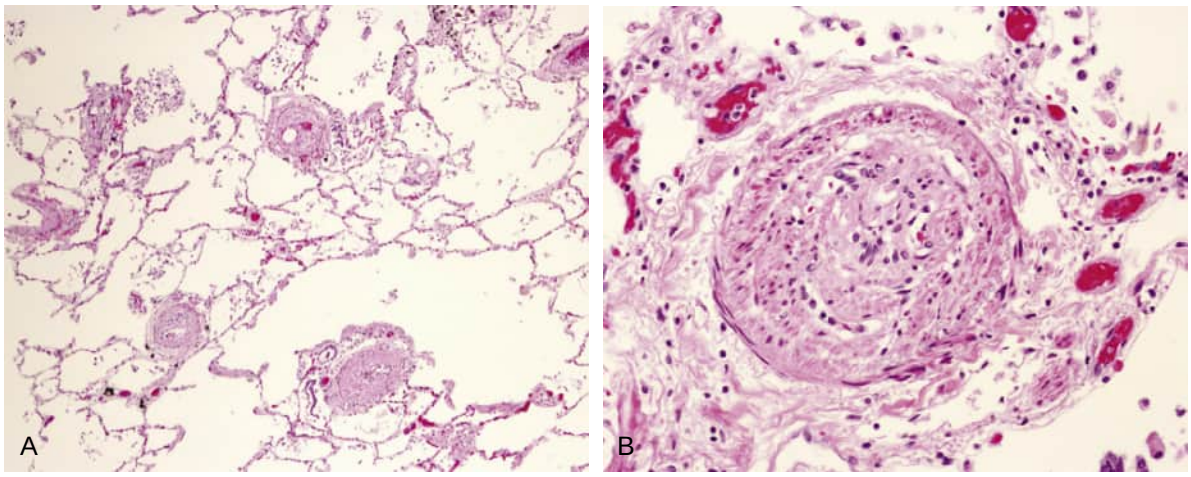
eFigure 127.2 Acute chest syndrome in sickle cell disease: fat embolization. (A) Frontal chest radiograph in a patient with acute chest pain accompanied by hypoxemia and thrombocytopenia shows bilateral right-greater-than-left increased opacity associated with cardiomegaly and pulmonary arterial enlargement *(arrow).* (B–D) Axial chest computed tomography displayed in lung windows shows bilateral, essentially diffuse ground-glass opacity associated with mild reticular elements. Bronchoscopy revealed intra-alveolar macrophages containing fat. (Courtesy Michael B. Gotway, MD.)



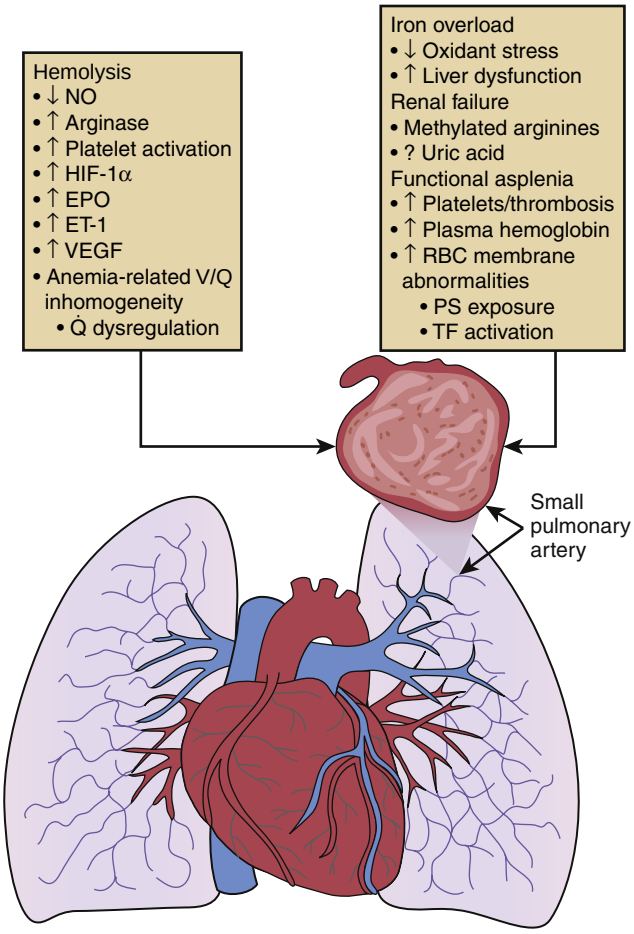
eFigure 127.3 Acute chest syndrome in sickle cell disease: pulmonary infarction. (A) Axial chest computed tomography through the lower lobes shows triangular-shaped, subpleural opacity *(arrow)* with the apex of the triangle facing toward the pulmonary hilum. The internal opacity is ground-glass attenuation, surrounded by consolidation. The appearance is typical of acute pulmonary infarction. (B) Axial chest computed tomography through the lower lobes shows irregular, somewhat nodular subpleural opacities *(arrows)* bilaterally, consistent with pulmonary infarction from previous thromboembolic episodes. (Courtesy Michael B. Gotway, MD.)



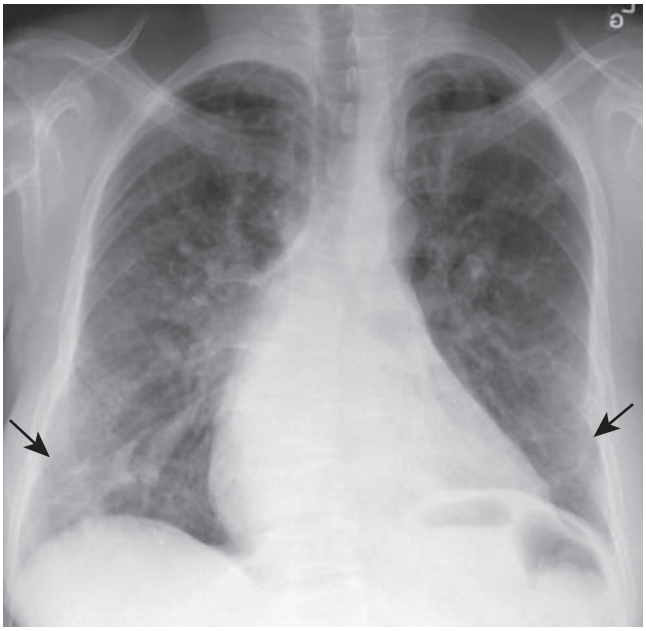
eFigure 127.4 Molecular pathophysiology of sickle cell disease. (A) A single nucleotide polymorphism in the β-globin gene leads to substitution of valine for glutamic acid at the sixth position in the β-globin chain. After deoxygenation, the mutated hemoglobin S (Hb S) molecules polymerize to form bundles. The polymer bundles result in erythrocyte sickling *(clockwise),* which in turn results in impaired rheology of the blood and aggregation of sickle erythrocytes with neutrophils, platelets, and endothelial cells to promote stasis of blood flow, referred to as vaso-occlusion (B). Vaso-occlusion promotes ischemia-reperfusion (I-R) injury *(clockwise).* (A) Hemoglobin (Hb) polymer bundles also promote hemolysis or lysis of erythrocytes *(counterclockwise),* which releases cell-free Hb into the blood circulation (C). Oxygenated Hb (ferrous iron [Fe^{2+}]) promotes endothelial dysfunction by depleting endothelial nitric oxide (NO) reserves to form nitrate (NO_3^-) and methemoglobin (ferric iron [Fe^{3+}]). Alternatively, Hb can also react with hydrogen peroxide (H_2O_2) through the Fenton reaction to form hydroxyl free radical (OH•) and methemoglobin (Fe^{3+}). Also, reduced nicotinamide adenine dinucleotide phosphate, xanthine oxidase (XO), and uncoupled endothelial NO synthase (eNOS) generate oxygen free radicals to promote endothelial dysfunction. Methemoglobin (Fe^{3+}) degrades to release cell-free heme *(counterclockwise),* which is a major erythrocyte damage-associated molecular pattern (DAMP). (D) Reactive oxygen species (ROS) generation, toll-like receptor 4 (TLR4) activation, neutrophil extracellular trap (NET) generation, release of tissue or cell–derived DAMPs, DNA, and other unknown factors (?) triggered by cell-free heme or I-R injury can contribute to sterile inflammation by activating the inflammasome pathway in vascular and inflammatory cells to release interleukin (IL)-1β. Finally, sterile inflammation further promotes vaso-occlusion through a feedback loop by promoting adhesiveness of neutrophils, platelets, and endothelial cells. GAG, guanine-adenine-guanine; Glu, glutamic acid; GTG, guanine-thymine-guanine; Val, valine. (From Sundd P, Gladwin MT, Novelli EM. Pathophysiology of sickle cell disease. *Annu Rev Pathol.* 2019;14:263–292.)



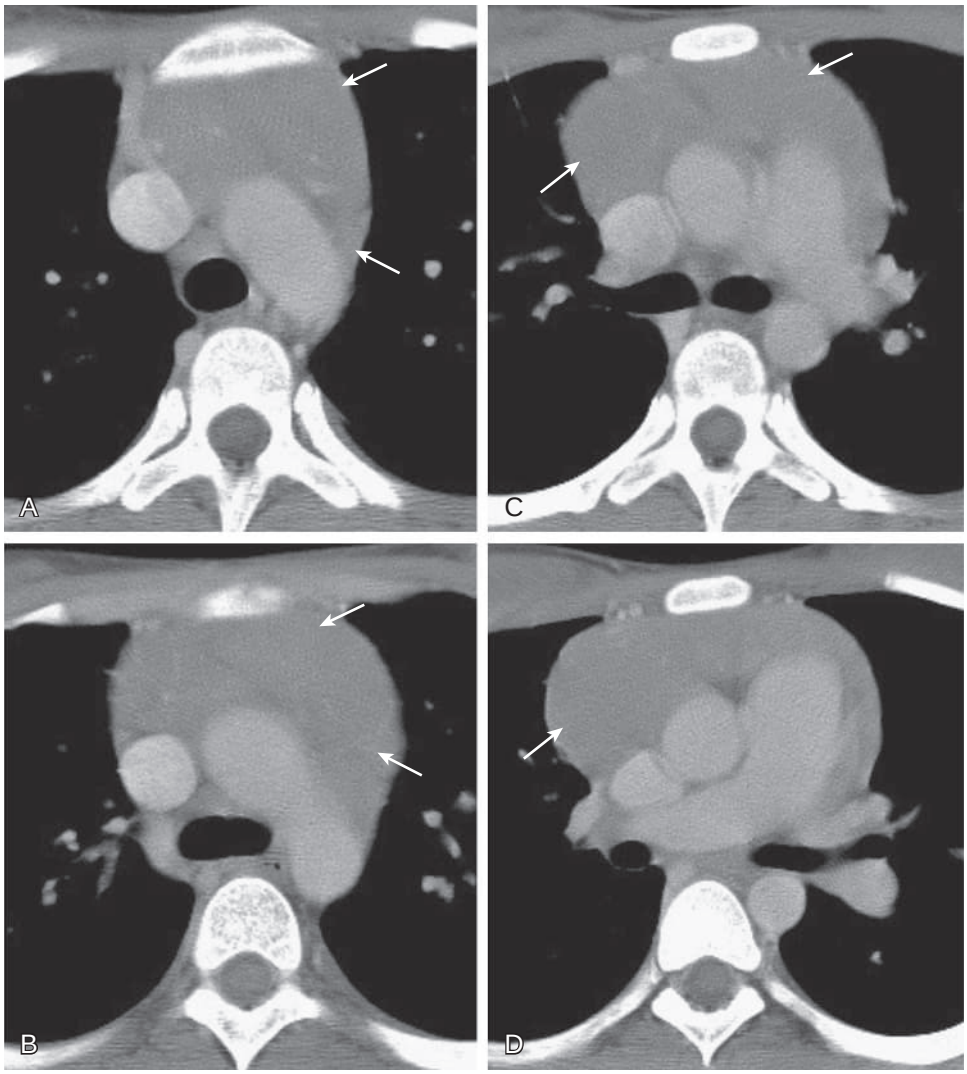
eFigure 127.5 Pulmonary arteriopathy in sickle cell–related pulmonary hypertension. (A) Low-power photomicrograph demonstrating pulmonary arterial smooth muscle hypertrophy (hematoxylin and eosin stain, magnification ×10). (B) Higher-power photomicrograph of one of the arteries showing a plexogenic lesion with medial thickening, laminar intimal hyperplasia, recanalization, and fibrosis (hematoxylin and eosin stain, magnification ×40).



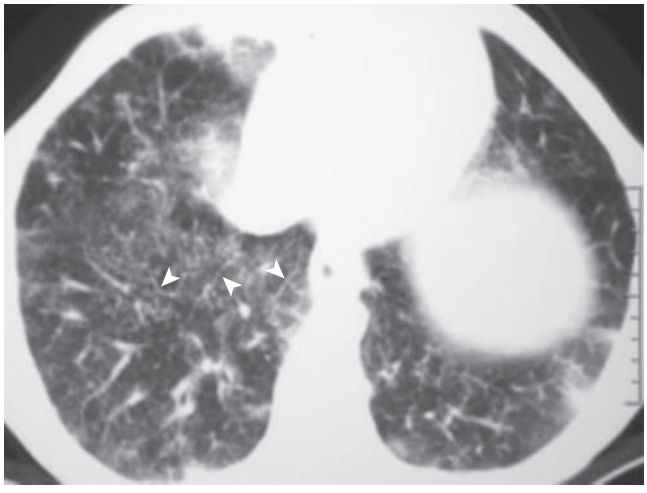
eFigure 127.6 Multifactorial pathogenesis of pulmonary hypertension in sickle cell disease, focusing on changes at a small pulmonary artery. Pulmonary hypertension is thought to arise from multifactorial effects of hemolysis and from the anemia, leading to increased cardiac output and multiorgan damage from iron overload, renal failure, and asplenia. EPO, erythropoietin; ET-1, endothelin-1; HIF-1α, hypoxia inducible factor-1α; NO, nitric oxide; PS, phosphatidylserine; Q̇, cardiac output; RBC, red blood cell; TF, tissue factor; VEGF, vascular endothelial growth factor; V/Q, ventilation-perfusion.



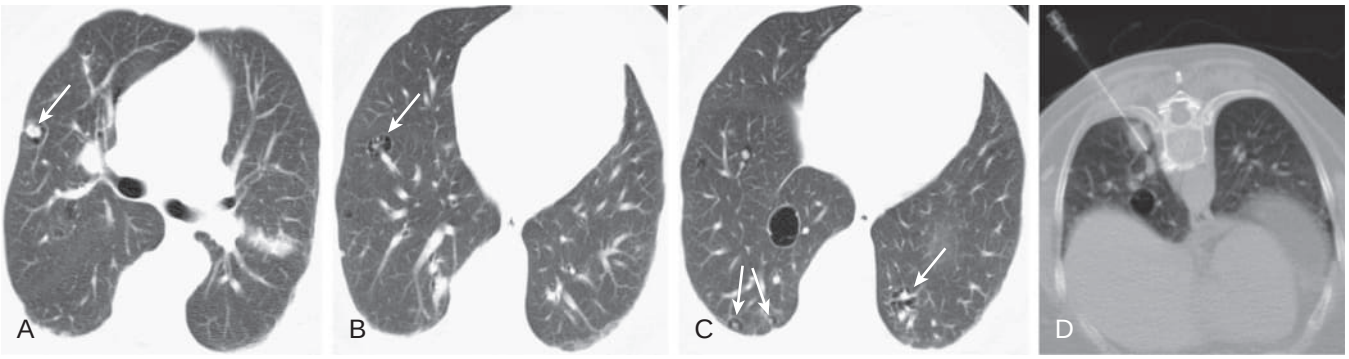
eFigure 127.7 Pulmonary fibrosis complicating multiple episodes of acute chest syndrome. Bibasilar (right greater than left) reticular opacities *(arrows)* are seen in the chest radiograph.



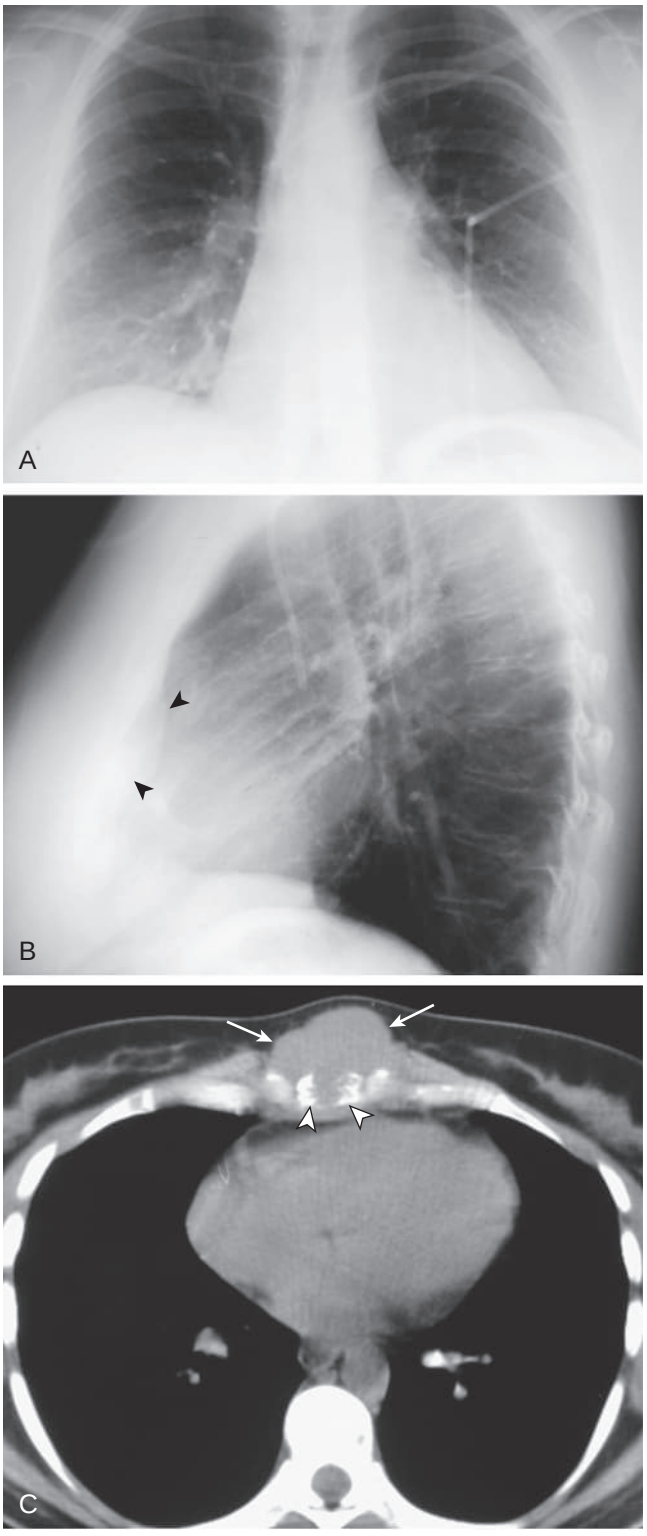
eFigure 127.8 Thoracic leukemia: mediastinal mass. (A–D) Axial enhanced chest computed tomography shows a soft tissue mass *(arrows)* in the anterior mediastinum proven to represent leukemic infiltration. (Courtesy Michael B. Gotway, MD.)



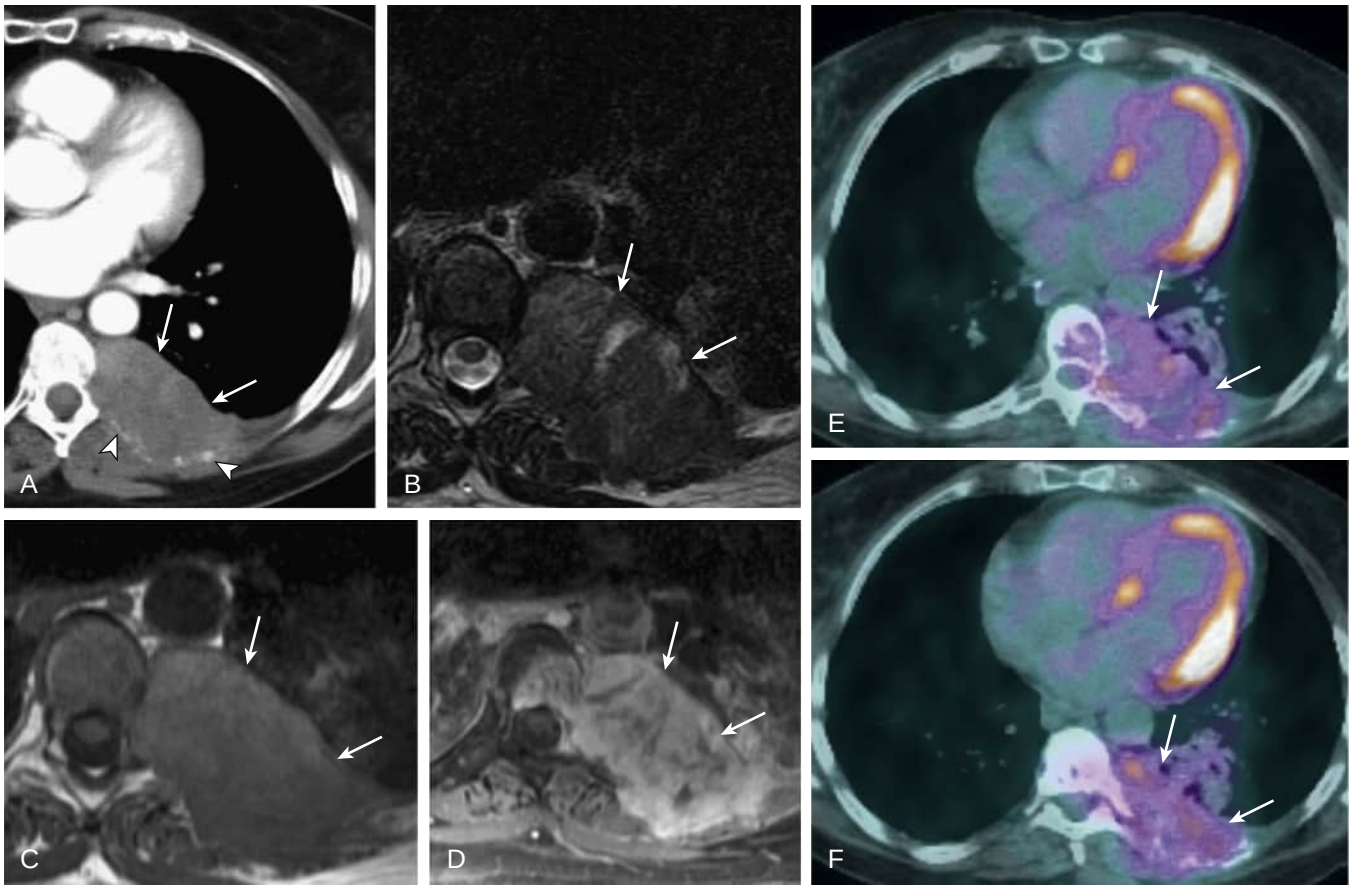
eFigure 127.9 Thoracic leukemia: pulmonary parenchymal infiltration. Axial chest computed tomography shows small nodules in the lung bases bilaterally associated with interlobular septal thickening *(arrowheads);* biopsy revealed pulmonary leukemic infiltration. (Courtesy Michael B. Gotway, MD.)



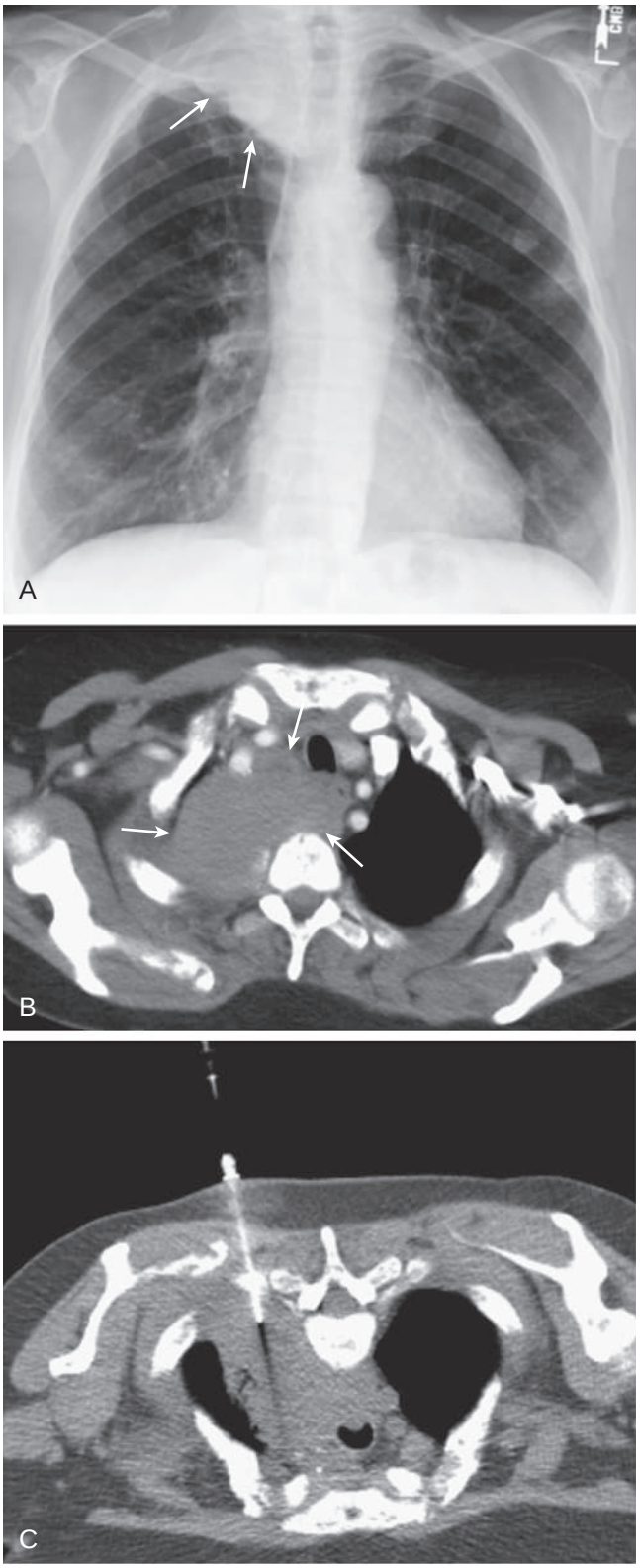
eFigure 127.10 Amyloidosis. (A–C) Axial chest computed tomography shows multiple pulmonary nodules associated with cystic change *(arrows),* proven on biopsy (D) to represent pulmonary amyloidosis. (Courtesy Michael B. Gotway, MD.)



eFigure 127.11 Thoracic plasmacytoma: chest wall origin. (A) Frontal and (B) lateral chest radiographs show a substernal contour deformity *(arrowheads).* (C) Axial unenhanced chest computed tomography shows sternal destruction *(arrowheads)* associated with a soft tissue mass *(arrows).* (Courtesy Michael B. Gotway, MD.)



eFigure 127.12 Thoracic plasmacytoma: chest wall origin. (A) Enhanced chest computed tomography. (B) T2-weighted, (C) unenhanced, and (D) enhanced fat saturation T1-weighted magnetic resonance imaging shows a mass *(arrows)* arising from the posterior medial chest wall, proven to represent plasmacytoma. Note the extensive rib destruction seen with computed tomography (*arrowheads,* A) and profound enhancement best seen at enhanced magnetic resonance (D). (E–F) ^{18}F-fluorodeoxyglucose positron emission tomography shows intense metabolic activity within the lesion *(arrows).* (Courtesy Michael B. Gotway, MD.)



eFigure 127.13 Thoracic plasmacytoma: mediastinal origin. (A) Frontal chest radiograph shows a superior thoracic mass *(arrows)*. (B) Axial chest computed tomography shows the mass *(arrows)*. The extensive contact with mediastinal structures (posterior wall of the trachea, esophagus, and great vessels) indicates a mediastinal origin for the lesion. (C) Percutaneous transthoracic biopsy-proved plasmacytoma. (Courtesy Michael B. Gotway, MD.)

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128 PULMONARY COMPLICATIONS OF ENDOCRINE DISEASES

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INTRODUCTION

The endocrine system consists of various glands and their hormones that circulate and mechanistically interact with all physiologic systems. This chapter provides an overview of how the major endocrine disorders affect the respiratory system; these disorders include diabetes mellitus, hypothyroidism and hyperthyroidism, growth hormone deficiency and excess, calcium dysregulation, including hyperparathyroidism, adrenal gland disorders, and hypophysitis from immune checkpoint inhibitors. An understanding of these endocrinopathies will assist the pulmonologist in the prevention, recognition, and management of the associated respiratory complications.

DIABETES

The global prevalence of diabetes mellitus continues to increase (422 million, or 8.5% of the adult population).[1] Type 1 and type 2 diabetes mellitus afflict 30.3 million Americans (9.4% of the population). Approximately 1.5 million new cases are diagnosed each year in the United States, and prediabetes afflicts 84.1 million American adults.[2] Type 1 diabetes results from autoimmune destruction of pancreatic beta cells in genetically susceptible patients and may be triggered by environmental factors. *Type 2 diabetes mellitus* (T2DM) results from insulin resistance associated with genetic predisposition, obesity, leptin resistance, diet, smoking, and a host of inflammatory mediators causing beta cell loss or dysfunction. The pathophysiologic hallmark of chronic hyperglycemia, nonenzymatic protein glycosylation, leads to accumulation of advanced glycation end products and heightened binding to and activation of their receptors,[3] lipo-oxidative stress, especially when associated with obesity, a chronic low-grade proinflammatory state, deranged connective tissue metabolism, generalized irreversible collagen cross-linking in tissue,[4,5] autonomic neuropathy, and macroangiopathy and microangiopathy,[6–8] which resemble the phenotype of accelerated aging.

These generalized pathophysiologic features affect the respiratory system, making diabetic patients vulnerable to pulmonary dysfunction. Lungs from diabetic subjects show qualitative abnormalities, including collagen and elastin accumulation and retarded connective tissue breakdown.[9] Parenchymal congestion, histiocytosis, prominent alveolar septal interstitium, smooth muscle hypertrophy, hyperplasia of alveolar type 2 epithelium, thickened basement membrane, fibrosis, and septal obliteration have been noted at autopsy in the lungs of diabetic subjects.[10] Given that the lung is the largest microvascular organ in the body and the only organ receiving the entire right ventricular cardiac output, it is not surprising that microvascular complications of diabetes adversely affect nearly all aspects of respiratory structure and function (Table 128.1). The major abnormalities are discussed below and in eFigure 128.1.

VENTILATORY IMPAIRMENT

Diabetes may impair ventilatory responses to hypoxia, hypercapnia, or exercise due to autonomic neuropathy,[11] abnormal cholinergic bronchomotor tone, and/or thoracopulmonary restriction. Tidal volume may increase excessively upon exertion resembling changes seen after vagotomy. Maximal ventilation and ventilatory response during exercise[12] and isocapnic hypoxia[13] may be reduced. Perception of inspiratory resistive loading may be diminished,[14] while perception of dyspnea is

Table 128.1 Pulmonary Complications of Diabetes Mellitus

Pathophysiologic Processes	Clinical Consequences
Autonomic neuropathy, control of breathing	▪ Increased parasympathetic tone ▪ Increased inspiratory effort ▪ Increased perception of dyspnea ▪ Impaired response to ventilatory challenges ▪ Sleep-disordered breathing ▪ Nocturnal hypoxemia
Thoracopulmonary restriction	▪ Increased chest wall stiffness ▪ Reduced lung volumes and compliance ▪ Reduced maximal ventilation ▪ Increased work of breathing
Airway dysfunction	▪ Airway hyperresponsiveness ▪ Aggravates coexisting COPD and cystic fibrosis
Lung microangiopathy	▪ Loss of alveolar microvascular reserves ▪ Reduced D_{LCO} at a given pulmonary blood flow
Respiratory muscle dysfunction	▪ Reduced respiratory muscle strength and endurance
Impaired immune defenses	▪ Impaired cytokine response and macrophage function ▪ Susceptibility to infections—bacterial, viral, mycobacterial, fungal, mucormycosis, aspiration pneumonitis
Major comorbidities that accentuate pulmonary impairment	▪ Obesity and the metabolic syndrome, cystic fibrosis, asthma, COPD, pulmonary fibrosis

accentuated with a disproportionately greater inspiratory effort and a smaller increase in tidal volume during hypoxia challenge.[15,16] Obesity further exaggerates ventilatory abnormalities and could impede acclimatization to high altitude or ventilatory compensation in response to lung disease. T2DM is also an independent risk factor for sleep-disordered breathing and nocturnal hypoxemia by altering sleep architecture.[17]

LUNG AND CHEST WALL RESTRICTION

Otherwise healthy diabetic nonsmokers commonly exhibit mild-to-moderate ventilatory restriction at rest, including 8–20% reductions in spirometry,[18–24] lung volumes, elastic recoil, dynamic compliance,[22] and *diffusing capacity for carbon monoxide* (D_{LCO}); impairment directly correlates with glycemic control[21,25] and extrapulmonary microangiopathy (e.g., proteinuria).[26,27] Diminished lung recoil and parenchymal tethering of peripheral airways may lead to gas trapping.[28–30] Connective tissue stiffness of the chest wall and limited joint mobility[23] can exacerbate thoracopulmonary restriction, leading to elevated work of breathing and respiratory muscle oxygen requirements during exercise.[21] These increased respiratory muscle requirements eventually usurp a disproportionately large fraction of total body oxygen delivery, leaving insufficient oxygen delivery to locomotive muscles; exercise ability can then be curtailed by subjective leg fatigue (i.e., the so-called respiratory muscle "steal" phenomenon).[31]

Chronic hyperglycemia, insulin resistance, and prediabetes are independently associated with ventilatory restriction.[25,32–34] In type 1 diabetes, a low peak expiratory flow rate predicts clinical complications and mortality.[35] Poor glycemic control directly correlates with lower spirometry indices and lung volume. In T2DM, a low FEV_1 predicts mortality in some, but not all, studies.[24,32] Subclinical pulmonary dysfunction in prediabetes[36–38] independently predicts subsequent development of overt diabetes.[39–41]

LOSS OF ALVEOLAR MICROVASCULAR RESERVES

D_{LCO} reflects the rate of gas transfer across the alveolar barrier (consisting of tissue membrane, plasma, and erythrocyte membrane), the volume of pulmonary capillary blood, hemoglobin mass, and the gas binding affinity to hemoglobin. The vast alveolar-capillary surface areas and microvascular volume are underutilized at rest (i.e., apical capillaries may be perfused by plasma but not erythrocytes while epithelial surface folds reduce the *effective* gas exchange area). Upon exertion, increasing ventilation and perfusion unfold alveolar surfaces and recruit capillaries, respectively, while erythrocytes become more uniformly distributed within and among capillaries (eFig. 128.2); the recruitment of anatomic and physiologic reserves leads to an increase in D_{LCO}, an essential mechanism for maintaining a normal arterial oxygen saturation.

Chronic hyperglycemia is associated with thickened alveolar basement membrane and together with lung restriction leads to a modest reduction of D_{LCO} (10–30%) at a given pulmonary blood flow[18,20,21,42]; the reduction correlates with disease duration and extrapulmonary end-organ complications.[21,43–45] The normal sitting-to-supine postural increase in D_{LCO} may be absent,[46] an early sign of impaired microvascular recruitment. Nonsegmental pulmonary perfusion defects have been observed in diabetes correlating with a lower D_{LCO}[47]; these defects may be reversible, reflecting heterogeneous perfusion distribution. On quantitative perfusion chest *computed tomography* (CT), diabetic subjects show higher pulmonary blood flow, pulmonary blood volume, and the permeability-surface product, suggesting increased alveolar permeability.[48] Upon exercise, D_{LCO} at a given cardiac output in T2DM subjects is modestly (10–25%) below normal (see eFig. 128.2). Chronically, hyperglycemic T2DM subjects exhibit a lower D_{LCO} at a given cardiac output than T2DM subjects who maintained near-normoglycema.[26]

RESPIRATORY MUSCLE DYSFUNCTION

Respiratory muscle strength and endurance may be reduced, reflecting generalized diabetic myopathy.[49] Impairment in insulin-stimulated glucose transport activity reduces muscle glycogen synthesis, promotes intramyocellular lipid accumulation, and impedes insulin signaling.[50,51] Perfusion heterogeneity and a reduced microvascular surface area in diabetic muscle lead to diffusion impairment (low permeability-surface area product for small solutes)[52]

in parallel to the pathophysiology of diabetic diffusion impairment in the lung.

IMPAIRED IMMUNE DEFENSES

Both innate and adaptive immune factors are implicated in the pathogenesis of obesity-associated complications including insulin resistance,[53] T2DM, hyperlipidemia, hypertension, atherosclerosis, and even cancers. Obesity-induced lipo-oxidative toxicity leads to activation of immune cells (M1 macrophages and $CD4^+$ T lymphocytes), infiltration of adipose and other tissue causing low-grade inflammation,[54–56] as well as accelerated senescence of immune cells. Macrophages obtained from diabetic mice show reduced bacterial internalization and killing and altered cytokine responses.[57] Impaired immunity in diabetes predisposes to airway inflammation and hyperreactivity, pulmonary infections, and pulmonary edema.[58] T2DM is a risk factor for infections due to *M. tuberculosis*, atypical mycobacterial, and certain fungal species such as molds from the Mucorales order that cause mucormycosis.[59,60] Diabetic *cystic fibrosis* (CF) patients are more susceptible to coinfection with *S. aureus* and *P. aeruginosa* than normoglycemic CF patients; coinfection in turn worsens lung function and predisposes to pulmonary exacerbations. Glycemia-related alterations of the lung microbiome may contribute to the accelerated pulmonary decline.[61]

COMORBIDITIES

Subclinical loss of pulmonary reserves in otherwise healthy diabetic subjects is inconsequential but may become overtly debilitating under conditions of pulmonary stress (e.g., aging or high altitude exposure) and exacerbate clinical pulmonary dysfunction in the presence of comorbid conditions such as pneumonitis, emphysema, pulmonary fibrosis, acute respiratory distress syndrome, and extrapulmonary organ failure in critically ill patients. The presence of diabetes also increases risks for developing asthma, chronic obstructive pulmonary disease, pulmonary fibrosis, and pneumonia.[62]

By 35 years of age, up to 50% of CF patients develop pancreatic insufficiency with impaired insulin secretion and response to carbohydrate loading, or overt diabetes while basal insulin secretion may be preserved, leading to normal fasting glycemia, postprandial hyperglycemia,[63] and accelerated lung function decline, poor growth and nutritional status, and increased mortality.[64] Diabetes is the most common extrapulmonary complication of CF, and is primarily related to insulin insufficiency. Because patients with CF-related diabetes may remain asymptomatic for years, screening is recommended at an early age. Insulin treatment improves glycemia, nutritional status, and lung function.[65]

Diabetes is more prevalent among asthmatic youths[66] and in patients with COPD hospitalized for acute exacerbation compared to the general population[67,68]; the association is partly attributed to corticosteroid use.[69] Inhaled corticosteroid use also modestly increases the risks of diabetes onset and progression.[70,71] Recent evidence suggests additional connections between diabetes and COPD. Poor glycemic control is associated with higher mortality in patients hospitalized for acute COPD exacerbation even long after discharge.[72] In the Framingham Offspring Cohort,[25] both fasting hyperglycemia and diabetes predict pulmonary dysfunction, with a stronger relationship among ever-smokers than never-smokers, suggesting interactions between glycemia and tobacco use. Systemic inflammation is a direct measure of COPD severity; inflammatory mediators that are elevated in COPD are also elevated in diabetes.[73] Cumulative evidence suggests that pulmonary inflammation and oxidative stress in COPD predispose to development of other proinflammatory conditions, including metabolic syndrome, cardiovascular, hematologic, musculoskeletal, and malignant diseases.[74] Systemic inflammation in turn exacerbates COPD pulmonary inflammation in a reciprocal manner.[75,76] Both diabetes and cardiovascular disease are more prevalent in Global Initiative for Chronic Obstructive Lung Disease stage 3 or 4 COPD (odds ratio 1.5 and 2.4, respectively) after adjusting for confounding variables, and both comorbidities increase the risks of COPD-related hospitalization and mortality.[77] Therefore, patients with moderate to severe COPD should be screened for possible diabetes.

Limited literature suggests diabetes is a risk factor for idiopathic pulmonary fibrosis. In 65 Japanese idiopathic pulmonary fibrosis patients, the adjusted odds ratios were 5.40 for cigarette smoking and 4.06 for diabetes.[78] The association between idiopathic pulmonary fibrosis and diabetes may be related to autonomic neuropathy causing gastroesophageal reflux.[79]

ROLE OF ADIPOCYTE-DERIVED MEDIATORS

Type 2 diabetes mellitus may be associated with obesity and insulin resistance as part of the metabolic syndrome. Insulin resistance alters lung function directly or via adipocyte-derived mediators such as leptin and adiponectin. Leptin signals via its receptor to modulate energy balance, thermoregulation, bone metabolism, lung cell growth,[80] central respiratory control,[81] and proinflammatory immune responses.[82] Leptin promotes fibroproliferative acute respiratory distress syndrome via inhibition of peroxisome proliferator-activated receptor-gamma[83] and leptin resistance protects from experimental acute lung injury.[84] Serum leptin levels are variably elevated in morbid obesity,[81] associated with small lung volumes, abnormal respiratory mechanics, and sleep apnea. In nonobese normal subjects, serum leptin levels are inversely related to FEV_1,[85] suggesting that leptin plays a role in the pathogenesis of diabetic pulmonary dysfunction.

In contrast, adiponectin exhibits anti-inflammatory, antioxidative, and anti-apoptotic activities[86]; these tissue-protective effects are eliminated in experimental T2DM. In clinical T2DM, serum adiponectin levels inversely correlate with some, but not all, of the hallmarks of metabolic syndrome.[87,88] Mice lacking adiponectin spontaneously develop COPD-like phenotype with extrapulmonary inflammation, body weight loss, and osteoporosis, suggesting crosstalk between the lung and adipose tissue.[89]

PULMONARY RESPONSE TO GLYCEMIC CONTROL

Prospective interventional studies show that intense glycemic control in T2DM significantly improves spirometry;

the changes in glycosylated hemoglobin correlate inversely with spirometry.[90] In CF-related diabetes, glycemic control also improves lung function, retards pulmonary function decline, and reduces short- and long-term complications.[91,92] Diabetes medications possessing anti-inflammatory properties (e.g., metformin),[93] confer a survival benefit in T2DM[94] and, in conjunction with gliptin class medication,[95] have been reported to improve pulmonary function; improvement is positively correlated with blood antioxidants and negatively correlated with oxidative stress markers.[95]

THYROID DISORDERS

THE HYPOTHALAMIC-PITUITARY-THYROID AXIS

The hypothalamic-pituitary-thyroid axis for synthesizing the thyroid hormones thyroxine and 3,5,3′-triiodothyronine is tightly regulated. Thyroid hormone receptors are ubiquitous DNA-binding proteins that function as transcriptional factors.[96] In the nucleus, the thyroid hormone receptor complex binds to promoter regions of responsive genes to modulate gene expression. Thyroid hormones stimulate lipid metabolism, leading to fatty acid mobilization and oxidation and reductions in blood cholesterol and triglycerides. Thyroid hormones stimulate gluconeogenesis and glycogenolysis accompanied by enhanced insulin-dependent glucose entry into cells. In the cardiovascular system, thyroid hormones increase heart rate and cardiac contractility and promote vasodilation. The broad metabolic stimulation increases basal metabolic rate, thermogenesis, and oxygen consumption, which in turn increase the work of breathing. Thyroid hormones are essential for normal organ development and growth, including in the lung.

Thyroid dysfunction, both hypothyroidism and hyperthyroidism, is common, afflicting nearly 7% of the population and comprising up to 40% of endocrine practices.[97,98] Diagnosis and monitoring depend on measurements of circulating *thyroid stimulating hormone* (TSH) and free thyroid hormones. Depending on the degree of biochemical dysfunction, thyroid hormone deficiency or excess may lead to a variety of anatomic and physiologic respiratory disorders.[99–101]

HYPOTHYROIDISM

Hypothyroidism may result from failure of the hypothalamus, the pituitary gland, or the thyroid gland leading to thyroid hormone deficiency. Congenital thyroid deficiency causes cretinism, a form of severe somatic and mental retardation. Postnatal hypothyroidism is most commonly caused by autoimmunity, iodine deficiency, or thyroidectomy.[100] Hypothyroidism affects up to 3.7% of the U.S. population and up to 5.3% in European studies.[97,98,100] Hypothyroidism often presents with nonspecific symptoms such as fatigue, dyspnea on exertion, diminished exercise capacity, and even respiratory failure due to a variety of complications (Table 128.2). Although numerous studies describe hypothyroidism adversely impacting the respiratory system, most include small cohorts of patients with limited follow-up and subject to potentially biased methodology.[102]

Table 128.2 Adverse Impact of Thyroid Disorders on the Respiratory System

Hypothyroidism	Hyperthyroidism
Goiter-related airway obstruction or laryngeal dysfunction	Hyperventilation
Alveolar hypoventilation and sleep-disordered breathing	Pulmonary hypertension
Pulmonary dysfunction	Thyrotoxicosis and respiratory failure
Myopathy of respiratory muscles	Increased risk of lung cancer
Pleural effusion	

Airway Obstruction or Laryngeal Dysfunction

Anatomic complications of an enlarged thyroid gland include upper airway compression (Fig. 128.1), resulting in dyspnea, stridor, and cough,[103,104] and reduction of inspiratory flow on pulmonary function tests[105] (see Fig. 39.4A–B). Tracheal compression is slightly more common with substernal than cervical goiters and can significantly improve with goiter volume reduction.[106–108] After thyroid surgery, there can be laryngeal dysfunction due to vocal cord dysfunction following intubation or due to recurrent laryngeal nerve injury, leading to dysphonia, ineffective cough, and dyspnea.[109,110]

Pulmonary Dysfunction

In hypothyroidism, spirometry and D_{LCO} negatively correlate with serum TSH level and positively correlate with serum free thyroid hormone 4 (T4) level,[111] even when chest radiography and arterial blood gases are normal. Thyroid hormones modulate mitochondrial respiration and the production of adenosine triphosphate. Hypothyroidism impairs skeletal muscle capacity for oxidative phosphorylation and alters muscle structure and energetics,[112] leading to exercise impairment evidenced by reduced aerobic capacity, slow kinetics of oxygen uptake upon exercise, and delayed recovery after exercise. These abnormalities increase the metabolic cost of performing daily living activities and manifest as fatigue, lethargy, and dyspnea.[111]

Alveolar Hypoventilation

In patients with myxedema, a severe form of hypothyroidism, hypoxic ventilatory drive is significantly depressed despite alveolar hypoxia and markedly improved when euthyroid states are achieved.[113] Similarly, hypercapnic ventilatory response can be depressed but not improve with thyroid replacement.[113] Depressed ventilatory effort is also observed in response to hypercapnia and hypoxia in 39% of patients with hypothyroidism, particularly in women with markedly elevated serum TSH concentrations[114]; thyroid hormone replacement resulted in improvement of ventilatory response.[114] Myxedema can lead to life-threatening hypothermia, drowsiness, confusion, coma, and respiratory failure requiring mechanical ventilatory support.[115] Prompt clinical recognition and thyroid hormone replacement leads to resolution of such derangements, including the recovery of hypoxic ventilatory drive.[113] Hypothyroidism should be considered in the difficult to wean patient in the intensive care unit.[116]

Sleep-Disordered Breathing

Earlier studies reported an increased prevalence of sleep-disordered breathing in patients with hypothyroidism.[117,118]

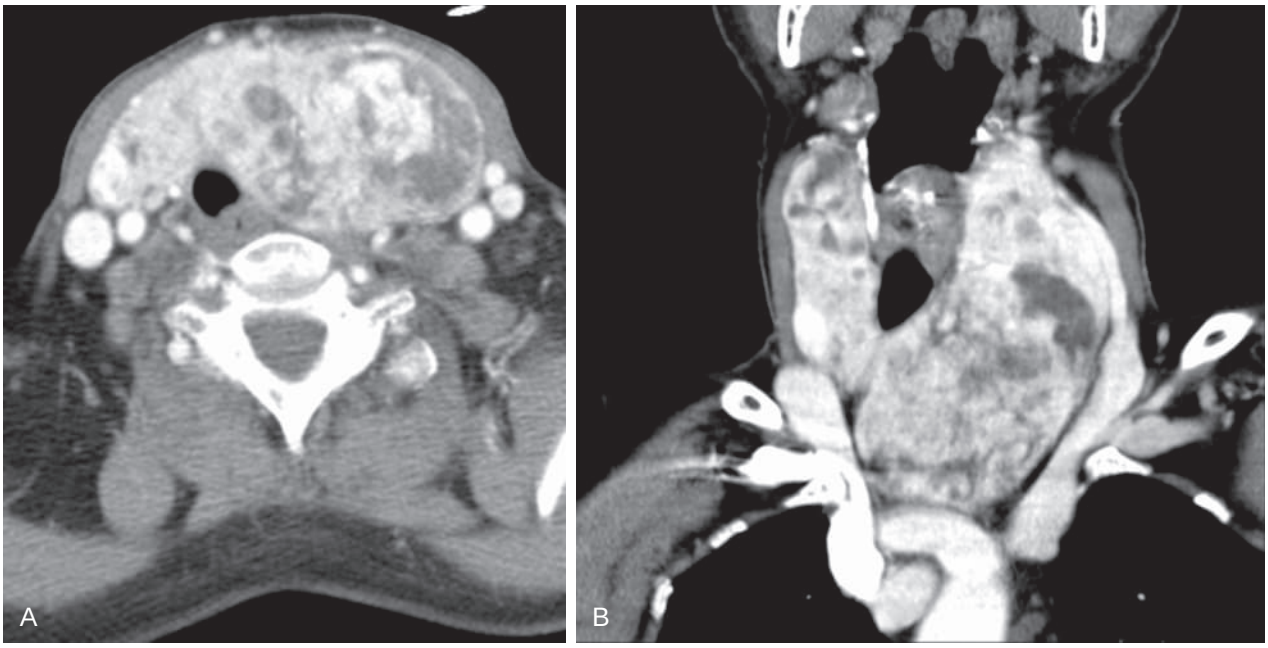

Figure 128.1 Multinodular goiter causing dyspnea. A 71-year-old woman with a large multinodular goiter experienced increasing dyspnea and required a total thyroidectomy. Note the displaced trachea. Axial (A) and coronal (B) views. (Courtesy Michael Landay, MD.)

Accumulation and soft tissue infiltration of matrix glycosaminoglycans are thought to cause macroglossia and pathologic narrowing of the pharyngeal space potentially leading to *obstructive sleep apnea* (OSA).[117,119] Thyroid replacement therapy may reduce connective tissue accumulation and, in some studies, improve or even cure sleep apnea in nonobese patients.[119–121] However, where obesity or skeletal defects are present, OSA may persist despite correction of the metabolic disorder.[117] Recent studies also suggest that thyroxine replacement in hypothyroid patients may not improve OSA without concurrent treatment with continuous positive airway pressure, suggesting persistent anatomic abnormalities.[122] A large study of thyroid function in 813 obese patients with severe OSA and daytime somnolence found a similar prevalence of hypothyroidism as in the general population, and no significant correlations between TSH, free thyroid hormones 3 or 4, and polysomnography results of breathing disorders during sleep.[123] Thus, the complex hormonal and anatomic relationship between thyroid hormone imbalance and prevalence of sleep-disordered breathing remains to be clarified. In addition to hypothyroidism, other endocrine and metabolic conditions (obesity, acromegaly, and polycystic ovary disease) may also be associated with OSA.

Respiratory Muscle Dysfunction

Thyroid hormone transcriptionally regulates the expression of myosin heavy chains, adenosine triphosphatase and other skeletal muscle proteins, and is a major determinant of muscle fiber composition and cell membrane permeability. Thyroxine deficiency impairs muscle glycogenolysis, oxidative respiration, lipid turnover,[124] repair, and myogenesis, associated with atrophy of type II (fast oxidative) fibers, compensatory hypertrophy of type I (slow oxidative) fibers, accumulation of muscle connective tissue, and decrease in muscle carnitine level.[125] These abnormalities predispose to muscle injury with elevated serum creatine kinase, myalgia, generalized muscle weakness, and, rarely, rhabdomyolysis.[125] According to the American Thyroid Association,[126] elevated serum muscle creatine kinase and/or lactic dehydrogenase persisting for at least 2 weeks justify serum TSH measurement to screen for hypothyroidism. Diaphragmatic muscle dysfunction may be a manifestation of hypothyroidism-related myopathy.[102,103] Pulmonary function tests may reveal reduced inspiratory and expiratory muscle strength in severe hypothyroidism and can lead to dyspnea and hypercapnia and contribute to respiratory failure.[103,127,128] In some studies, thyroid hormone replacement resulted in improved diaphragm and expiratory muscle strength.[127,128]

Pleural Effusion

Hypothyroidism-associated serous effusions, including ascites, pericardial effusion, and pleural effusion, are thought to develop as a result of increased capillary permeability and decreased lymphatic drainage of albumin.[129,130] Pleural effusion as a result of hypothyroidism alone is uncommon. In 128 patients with thyroid dysfunction, the majority of effusions were primarily due to other associated conditions such as pneumonia, congestive heart failure, or malignancy.[131] In these cases, although not a primary cause, the hypothyroidism may have contributed to their formation. When attributed to hypothyroidism alone, pleural effusions are small and asymptomatic due to slow fluid accumulation and may require no therapeutic intervention other than thyroid hormone replacement.[131] Management includes thoracentesis to exclude an exudative effusion caused by other conditions such as an underlying thyroid carcinoma or other malignancy,[129] thyroid hormone replacement therapy, and drainage of large effusions for symptomatic relief.

HYPERTHYROIDISM

Excess thyroxine production leads to accelerated metabolism and a spectrum of clinical disorders ranging from

asymptomatic mild elevations in thyroid hormones to nervousness, tremors, sweating, weight loss, fatigue, sleep disorders, tachycardia, arrhythmias, and life-threatening systemic thyrotoxicosis (thyroid storm).[101,132] In the respiratory system, hyperthyroidism can cause dyspnea, tachypnea, pulmonary hypertension, and extreme respiratory distress during thyroid storm. Tachypnea results from increased oxygen consumption and carbon dioxide production,[103] and hyperventilation due to heightened ventilatory responses to hypercapnia and hypoxia[133] associated with beta-adrenergic stimulation.[134] Vital capacity is reduced due to respiratory muscle asthenia, indicated by reductions in maximum inspiratory and expiratory pressures.[103]

Pulmonary Hypertension

Both hyperthyroidism and hypothyroidism may be associated with elevated pulmonary pressures[135,136] and increased morbidity and mortality from cardiovascular disease.[137] Recent data indicate a 24% prevalence of thyroid disorder in patients with *pulmonary hypertension* (PH),[136] and having an untreated thyroid disorder is a negative prognostic factor for worse survival in patients with PH.[138] Conversely, the prevalence of PH in patients with hyperthyroidism ranges from 41–65%.[135,139,140] In an echocardiographic study of patients with hyperthyroidism and normal left ventricular systolic function,[141] up to 45% had PH due to either pulmonary arterial hypertension with increased cardiac output (70%) or pulmonary venous hypertension with elevated left ventricular filling pressure (30%). Furthermore, PH in these hyperthyroid patients was largely asymptomatic and reversible following treatment with radioactive iodine and normalization of thyroid status. Proposed pathogenic mechanisms include autoimmunity, endothelial injury, and pulmonary vascular remodeling.[142]

Thyrotoxicosis

Excessive thyroid hormone activity can be asymptomatic or can lead to subclinical or life-threatening thyrotoxicosis or thyroid storm, with pulmonary hypertension, atrial fibrillation, embolism, cardiovascular collapse, and death.[132] The most common etiology of thyrotoxicosis is Graves disease, followed by toxic multinodular goiter, toxic adenoma, various forms of thyroiditis, drug-induced thyrotoxicosis from amiodarone and iodinated contrast, and rare causes such as struma ovarii, gestational trophoblastic neoplasia, exogenous thyroid hormone ingestion, activation mutations of the TSH receptor, and functional thyroid cancer metastases.[143] Multiorgan dysfunction can develop requiring intensive care unit support.[132] In its extreme form, thyroid storm has a mortality rate up to 25% and requires prompt recognition and a multidisciplinary treatment approach to reduce excess thyroid hormone while providing critical care support.[101]

Lung Cancers

In addition to mediating growth, development, and metabolism, thyroid hormone receptors also act as suppressors of tumor transformation. There is cumulative evidence that aberrant thyroid hormone receptor genes or expression are common in human cancers. Hyperthyroidism has been associated with inactivating mutations in thyroid hormone receptors that impede thyroid hormone action and increase the risk of developing prostate, breast, and lung cancers, whereas hypothyroidism is associated with a lower risk of prostate cancer and variable effects on the risk of breast cancer.[144] In the prospective, population-based Rotterdam Study, a higher free thyroxine level was associated with an increased risk of any solid cancer, including lung (1.79-fold) and breast (1.14-fold) cancers. In contrast, TSH level is not associated with cancer risk.[144]

Besides measuring thyroid hormone status, investigation of thyroid disorders commonly includes imaging by ultrasound or CT. It should be noted that, by introducing an iodine load, iodinated contrast agents can delay performance of whole-body radioiodine scans or ablation. Current water-soluble iodinated contrast agents are typically eliminated in 4 to 8 weeks, so radioiodine scanning and therapy can be performed within 1 month of contrast-enhanced CT (see also Chapter 20).

GROWTH HORMONE DISORDERS

ACROMEGALY

Primary *growth hormone* (GH) excess is a rare condition usually associated with pituitary hyperplasia or adenomas. Secondary GH excess may be due to dysregulated hypothalamic secretion of GH-releasing hormone or GH/GH-releasing hormone–secreting tumors (typically in the hypothalamus, lung, or pancreas). Excess GH stimulates *insulin-like growth factor 1* (IGF-1) production, leading to accelerated somatic growth (gigantism or acromegaly) with multiorgan manifestations.[145] Acromegaly is associated with vascular, neoplastic, and respiratory complications[146]; respiratory complications account for 25% of deaths, threefold higher than in normal subjects[147,148] (Table 128.3).

Anatomy and Respiratory Physiology

In a large cohort of acromegaly patients, pulmonary function showed larger lung volumes (forced vital capacity, total lung capacity, and residual volume) and small airway obstruction.[149] In active acromegaly (elevated GH and IGF-1 levels), CT pulmonary densitovolumetry revealed air trapping (60% of cases), airway calcification (40% of cases), and bronchiectasis (35% of cases) along with pulmonary function test findings of increased forced vital capacity, total lung capacity, and residual volume.[150] An increase in density of lung parenchyma has been attributed to GH and IGF-1 effects on smooth muscle cells and the lungs, increasing the synthesis of type I and type II collagen fibers and mucopolysaccharides.[150,151] Other proposed explanations for the increases in total lung capacity and residual volume include alveolar hyperplasia or increased number of alveoli.[152] Subclinical hypoxemia has been reported and is thought to result from ventilation-perfusion derangements.[153]

Obstructive Sleep Apnea

OSA is highly prevalent in acromegaly[117] due to skeletal and soft tissue alterations in the face, pharynx, and tongue that increase upper airway resistance and narrowing.[147,154] CT and magnetic resonance imaging reveal larger and thicker soft palates and thicker lateral pharyngeal walls in acromegaly patients with OSA, correlating

with both severity of sleep apnea and acromegaly.[155,156] Both obstructive and central sleep apnea[157] have been described,[158] and biochemical control of acromegaly improves sleep-disordered breathing.[159] Whereas OSA is prevalent in acromegaly, routine screening for acromegaly in OSA patients is not warranted due to the low prevalence of acromegaly.[160,161]

Association with Neoplasm

Excess IGF-I can increase the risk of tumor development and progression.[162] Untreated acromegaly with chronically elevated GH/IGF-1 levels has been associated with various neoplasms, including sporadic reports of lung cancer.[163] Conversely, acromegaly may be a rare paraneoplastic manifestation of GH/IGF-1-secreting pulmonary neuroendocrine tumor.[164]

Table 128.3 Pathology and Clinical Respiratory Abnormalities in Acromegaly

Pathologic Abnormalities	Clinical Conditions
UPPER AIRWAY	
Macroglossia	Obstructive sleep apnea
Soft palate and pharyngeal wall narrowing	Snoring
Mandibular protrusion	Daytime sleepiness
Vocal cord thickening	
LUNG PARENCHYMA	
Increased size of alveoli	Airflow obstruction
Increased lung volume and lung compliance	Obstructive lung disease
Cellular derangement	Ventilation-perfusion mismatch
	Mild hypoxemia
THORAX	
Kyphoscoliosis	Impaired breathing movement
Vertebral body enlargement	Rib cage stiffness
Intervertebral disc thickening	Respiratory muscle impairment
SYSTEMIC	
Chronic IGF-1 stimulation	Possible increased risk of cancers, including in the lung

IGF-1, insulin-like growth factor-1.
From Colao A, Auriemma RS, Pivonello R, Galdiero M, Lombardi G. Medical consequences of acromegaly: what are the effects of biochemical control? *Rev Endocr Metab Disord*. 2008;9(1):21-31.

Treatment

Prompt recognition and treatment of acromegaly via surgery, medication, or radiation therapy aims to control hormone excess and attenuate or reverse complications. Somatostatin analogs such as octreotide and lanreotide, or GH receptor antagonists alleviate sleep apnea in many patients (Fig. 128.2), although individual responses to therapy may vary[165] and OSA persists in 40% of patients.[117,165] Respiratory complications, represented mainly by sleep-related breathing disorders and respiratory insufficiency, are frequent at an early stage of the disease. Finally, although control of hormonal excess (surgically or medically) may improve associated respiratory conditions resulting from acromegaly, permanent irreversible anatomic changes often require persistent therapy to mitigate respiratory impairment.[166]

GROWTH HORMONE DEFICIENCY

GH deficiency has been associated with central and obstructive ventilatory defects. For example, Prader-Willi syndrome, a rare genetic disorder of loss of function in a specific region of chromosome 15, is associated with hypothalamic dysfunction and deficient GH secretion. Patients exhibit short stature, insatiable appetite, morbid obesity, hypogonadism, abnormal thermal control, sleep disturbances, and ventilatory restriction due to respiratory muscle weakness[167] and abnormal control of breathing (central hypoventilation and decreased peripheral chemoreceptor sensitivity) leading to depressed ventilatory responses to hypoxia or hypercapnia.[168] GH treatment increases ventilatory drive and activity.[169] Children with Prader-Willi syndrome exhibit abnormal sleep and arousal with increased apnea events, oxygen desaturation, increased maximum heart rate, abnormal arousal responses,[170] and daytime somnolence. In a randomized,

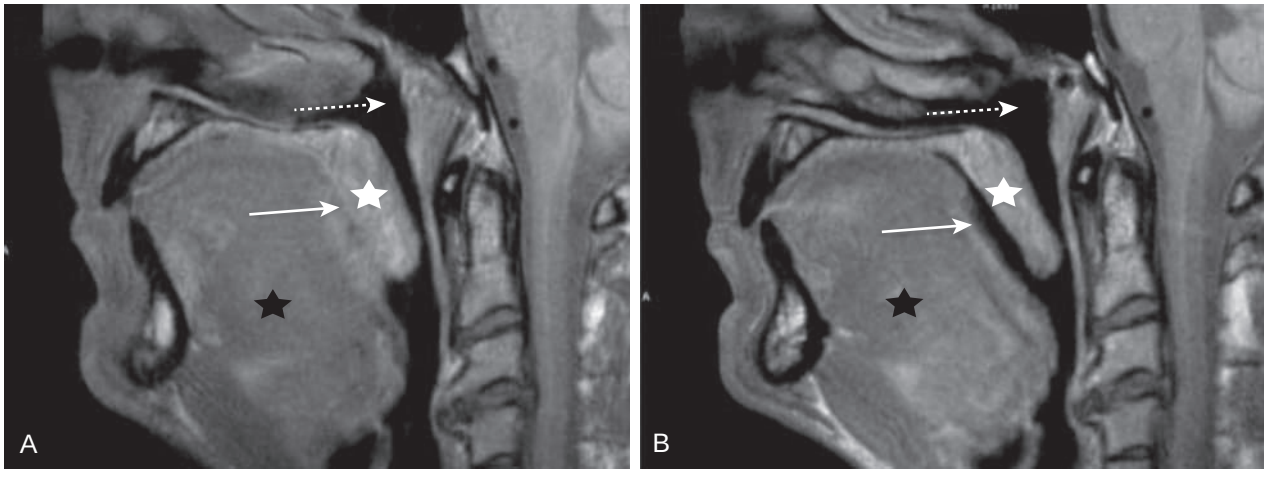

Figure 128.2 Sagittal T1-weighted magnetic resonance imaging sequences of the neck before (A) and after (B) effective treatment of acromegaly in a male patient with *obstructive sleep apnea* (OSA). The treatment of acromegaly allowed a clear decrease in thickness of the tongue (*black star*), soft palate (*white star*), and pharyngeal walls and an increase in the opening of the oropharynx space (*solid arrow*) between the tongue and soft palate and of the posterior nasopharyngeal area (*dashed arrow*), which were associated with the cure of OSA in this patient. (From Attal P, Chanson P. Endocrine aspects of obstructive sleep apnea. *J Clin Endocrinol Metab*. 2010;95[2]:483-495.)

double-blind, placebo-controlled, crossover study of GH treatment in children with Prader-Willi syndrome, peak flow rate, vital capacity, and forced expiratory flow rate improved and the number of hypopnea and apnea events and duration of apnea events tended to improve after treatment. Treatment improved linear growth velocity, resting energy expenditure, and lean body mass; optimization of body composition may have contributed to better sleep quality and pulmonary function.[171]

Pediatric snoring affects 10% of preschool-age children, while OSA affects 0.7–3.4% of all children.[172] In children with sleep-disordered breathing, depressed nocturnal GH secretion and excessive energy expenditure due to increased work of breathing during sleep are thought to contribute to growth retardation and failure to thrive.[172] Adenotonsillectomy in these children results in restored GH secretion, respiratory improvement, and catch-up weight gain.[172,173] Diminished GH secretion has also been shown in adults with primary sleep abnormalities.[174]

CALCIUM DYSREGULATION AND PULMONARY CALCIFICATION

PARATHYROID HORMONE

Parathyroid hormone (PTH) is rapidly produced by the parathyroid gland in response to a fall in serum calcium ion concentration and targets calcium-phosphorus homeostasis in bone and kidney cells. The short-acting PTH increases extracellular fluid calcium concentration by (1) stimulating osteoclast bone resorption, (2) directly promoting small intestine calcium absorption, (3) enhancing renal production of active vitamin D metabolites to up-regulate a calcium-binding protein in intestinal epithelium to facilitate calcium absorption, and (4) suppressing urinary calcium loss by simultaneously stimulating renal tubular calcium reabsorption and excretion of inorganic phosphate.[175] As serum calcium concentration increases, serum phosphate ion concentration falls; the calcium-phosphate product is maintained within normal limits, thereby preventing tissue calcium deposition.

Primary hyperparathyroidism is characterized by PTH oversecretion, commonly due to parathyroid adenoma and less commonly (≈1%) due to parathyroid carcinoma or hyperplasia in rare familial genetic abnormalities (e.g., multiple endocrine neoplasia).[176] Secondary hyperparathyroidism develops in response to low serum calcium concentration caused by chronic renal failure, intestinal malabsorption, inadequate calcium intake, or vitamin D deficiency.[176] Tertiary hyperparathyroidism develops when secondary PTH hypersecretion becomes autonomous and resistant to pharmacologic suppression and is sometimes seen after renal transplantation. Symptoms of hypercalcemia include thirst, polyuria, constipation, bone pain, fatigue, depression, and renal stones. Primary and tertiary hyperparathyroidism is usually treated by parathyroidectomy. Pharmacologic suppression of PTH involves administration of phosphate binder, vitamin D, and calcium-sensing receptor agonists.

PULMONARY CAUSES OF HYPERCALCEMIA

Hypercalcemia accompanied by appropriately suppressed PTH levels raises suspicion of metastatic cancer to the bone. Various cancers, including pulmonary carcinoma and neuroendocrine tumors, may also secrete PTH-related protein, a separate and widely expressed protein that binds to the PTH receptor and mimics PTH function. Autonomous nonrenal conversion of 25-hydroxy-vitamin D to the active metabolite 1,25-dihydroxy-vitamin D may induce hypercalciuria and hypercalcemia, typically seen in lymphoma and granulomatous lung diseases such as *M. tuberculosis*, fungal infections, and sarcoidosis.

DYSTROPHIC AND METASTATIC PULMONARY CALCIFICATION

Pulmonary calcification can result from calcium salt deposition in the lung.[177] There are two distinct types: dystrophic calcification and metastatic pulmonary calcification.[178] *Dystrophic* calcification refers to calcium deposition in previously injured, damaged lung such as previously infected or inflamed lung tissue, and takes place in the setting of *normal* serum calcium and phosphorus values. Classic examples include localized scars or granulomatous processes such as mycobacterial, fungal, viral, or parasitic disorders or other noninfectious disorders such as amyloidosis or sarcoidosis, where calcium deposits in injured or necrotic lung tissue. Histologically, calcium aggregates are seen in background fibrosis, chronic granulomatous changes, or areas with evidence of repair.[178]

Metastatic pulmonary calcification (MPC) (Fig. 128.3) refers to calcium deposition in otherwise normal lung tissue,

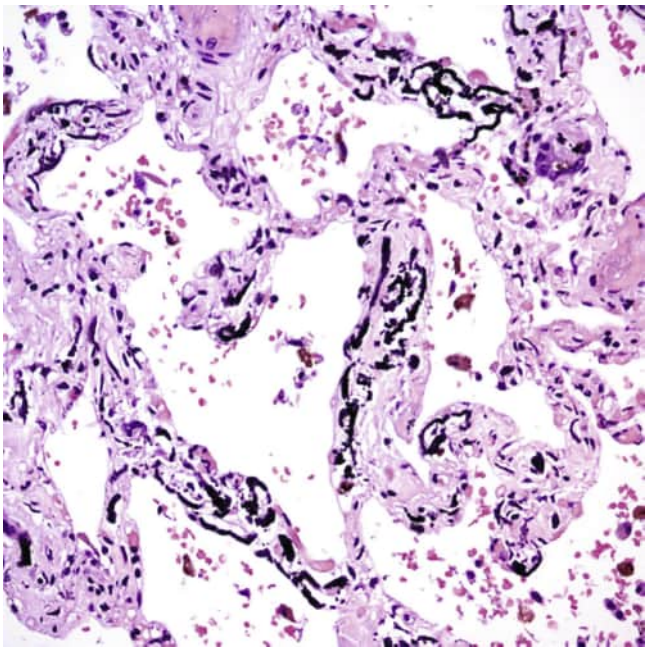

Figure 128.3 Metastatic calcification. Calcium is present as dark, basophilic fibrils within the alveolar walls and vessels in this lung. (From Zander DS, Farver CF. *Pulmonary pathology*. 2nd ed. Philadelphia: Elsevier; 2018.)

particularly in alveolar epithelial basement membrane and interstitium, and is usually the result of altered serum calcium and phosphorus metabolism. Nonmalignant causes of MPC include chronic renal failure, hyperparathyroidism, and primary bone disease.[177] Malignant causes of MPC are cancers associated with hypercalcemia such as parathyroid-related malignancies, multiple myeloma, leukemia, and small cell lung carcinoma.[177] Microscopic findings include calcium deposits within alveolar septal and vessel walls and may involve the airways in advanced cases.

Most patients with MPC are asymptomatic, reflecting the typical benign course, with up to 70% of cases diagnosed only at autopsy. Some patients may present with cough, dyspnea and, uncommonly, respiratory failure.[179,180] Clues to diagnosis include relative stability of pulmonary infiltrates in the clinical context of hypercalcemia; most patients show an elevated calcium-phosphate product above 70 mg^2/dL^2 (normal is ~40 mg^2/dL^2).[177] Depending on the burden of calcium deposition, pulmonary function tests can be normal or may reveal a restrictive pattern, decreased diffusing capacity, and hypoxemia.[179]

Radiographic Features

Chest imaging of MPC often reveals an upper lobe propensity due to a higher local ventilation-perfusion ratio there, leading to a lower arterial CO_2 tension and higher pH that encourage deposition of calcium salts.[177] However, all lung regions may be involved. Radiographic patterns include (1) multiple localized or diffuse calcified nodules, (2) diffuse or patchy areas of ground-glass opacity or consolidation, and (3) confluent high-attenuation parenchymal consolidations[179,181,182] (Fig. 128.4). Bone scintigraphy, such as with technetium-99m-methylene diphosphate, can usually diagnose MPC without the need for lung tissue biopsy[177] (Fig. 128.5).

Treatment

Pulmonary calcification may stabilize with medical strategies to reduce the serum calcium-phosphorus product.[177] In

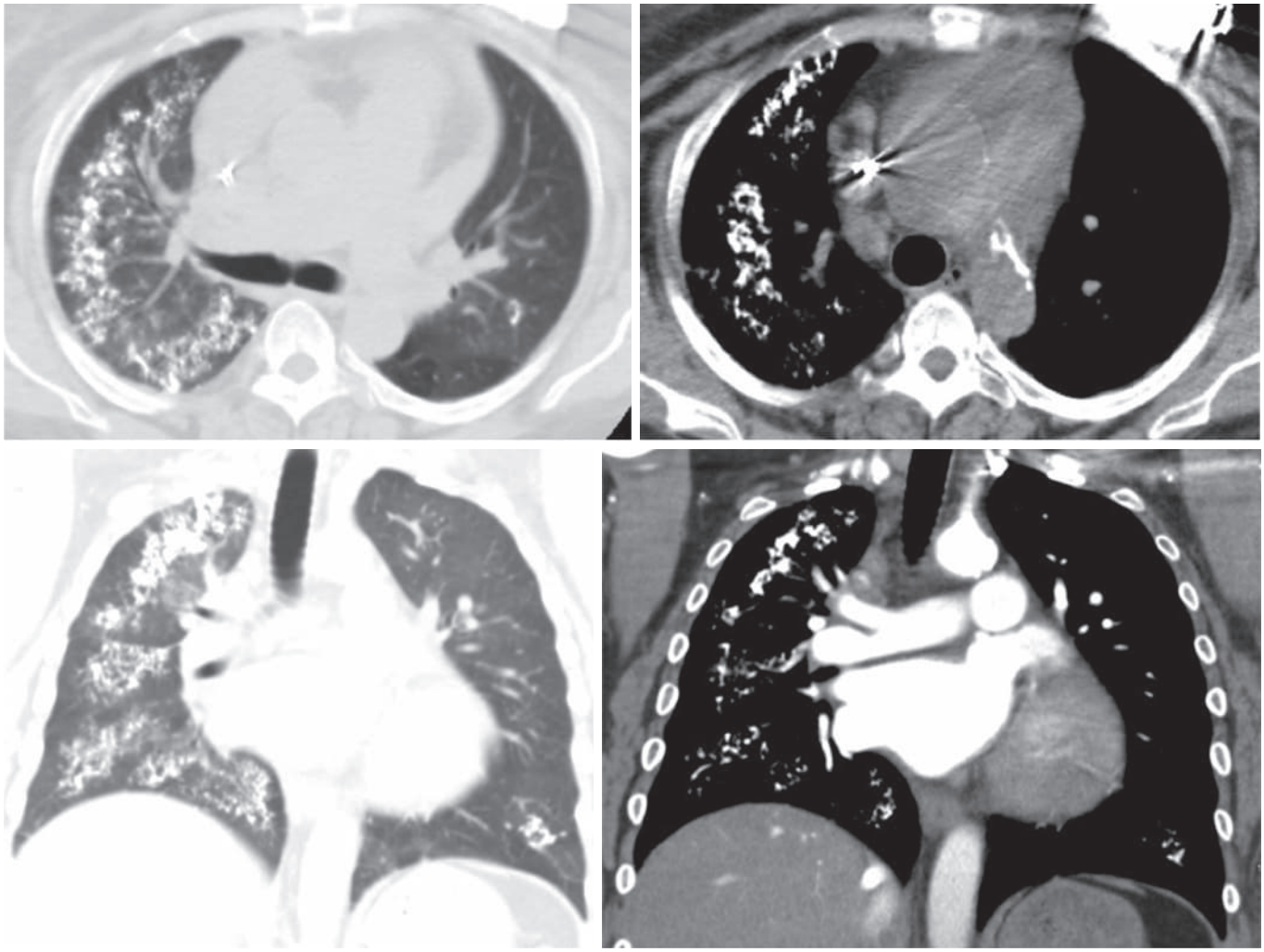

Figure 128.4 Metastatic calcification. Computed tomography in a patient with renal failure showing bilateral metastatic pulmonary calcification. There is right-sided predominance, but calcification is also seen in the left lung. There is also some apical predominance. Lung window (*left*) and soft tissue window (*right*) in axial (*top*) and coronal (*lower*) images. (Courtesy Michael Landay, MD.)

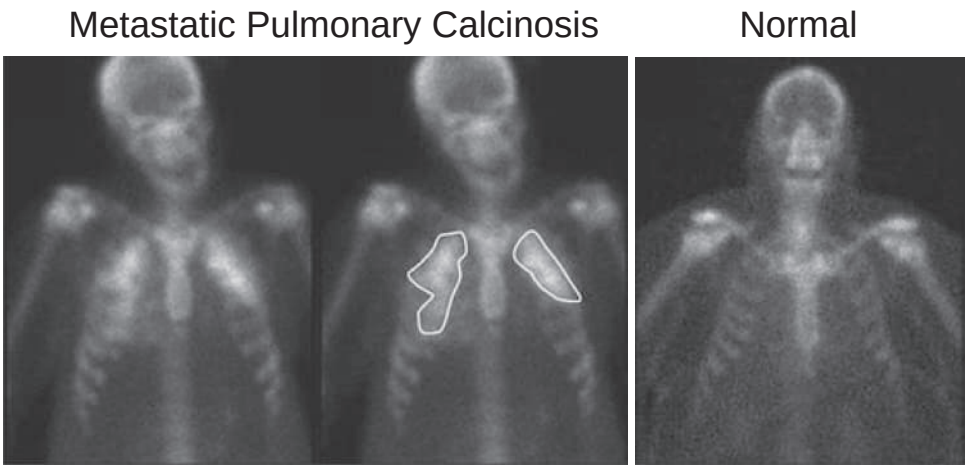

Figure 128.5 Metastatic pulmonary calcification in a patient with renal failure. *Left,* A coronal image of technetium-99m methylene diphosphonate scan shows extensive tracer uptake in both upper lungs (with and without the pulmonary uptake outlined). *Right,* A normal scan is shown for comparison. (Courtesy Michael Landay, MD, and Michael B. Gotway, MD.)

chronic renal failure, renal transplantation or dialysis may be effective but, in some cases, calcification continues to progress and may require parathyroidectomy.[183,184]

ADRENAL DISORDERS

ADRENOCORTICAL HORMONES AND LUNG DEVELOPMENT

Hypothalamic corticotropin-releasing hormone stimulates pituitary *adrenocorticotropic hormone* (ACTH) release, which in turn regulates adrenocortical production of *glucocorticosteroids* (GCs) including cortisol,[185] which mediates catabolism, blood pressure maintenance, neuronal function, stress response, and inhibitory actions on the immune system.[185] GCs mediate lung development by stimulating surfactant-associated protein production, phospholipid synthesis, cell maturation and differentiation, antioxidant enzymes, and lung fluid metabolism.[186] In neonates, serum cortisol response to ACTH stimulation increases with increasing birth weight. Antenatal dexamethasone administration during late gestation accelerates surfactant maturation and can ameliorate the development of respiratory distress syndrome in preterm infants.[187,188] Low-birthweight neonates who develop bronchopulmonary dysplasia show significantly lower ACTH-stimulated cortisol secretion than infants who recover without bronchopulmonary dysplasia, suggesting that adrenal insufficiency in low-birthweight infants may impede surfactant function and predispose to lung injury.[189] Early low-dose GC treatment improves survival of very preterm infants without bronchopulmonary dysplasia,[190] especially in the presence of added neonatal stress such as chorioamniotic.[191] In very preterm infants with severe respiratory failure supported by mechanical ventilation, GC treatment attenuates inflammatory cells and mediators and increases the alveolar desaturated phosphatidylcholine pool.[192] However, short-term benefits from GC use must be weighed against possible long-term adverse effects because high dose or repeated administration may impair somatic, brain, and lung growth and precipitate diabetes mellitus.

ADRENAL INSUFFICIENCY

Primary adrenal insufficiency resulting from disease of the adrenal cortex is accompanied by elevated corticotropin-releasing hormone and *adrenocorticotropic hormone* (ACTH) secretion. Causes include adrenalitis due to autoimmune reaction (Addison disease with antibodies against 21-hydroxylase that may be part of polyendocrinopathy syndromes)[193]; mycobacterial, fungal, and HIV-associated viral infections[194,195]; infiltrative diseases (metastatic lung cancer[196] or sarcoidosis[197]); medications (ketoconazole and etomidate[198]); and various genetic conditions.[199] *Secondary* adrenal insufficiency is caused by disorder of the anterior pituitary gland accompanied by elevated corticotropin-releasing hormone and reduced ACTH secretion. *Tertiary* adrenal insufficiency is caused by disorder of the hypothalamus accompanied by reduced corticotropin-releasing hormone and ACTH secretion. Clinical presentations include fatigue, anorexia, nausea, abdominal pain, weight loss, and orthostatic hypotension. Primary adrenal insufficiency may also present with salt craving due to mineralocorticosteroid deficit and skin hyperpigmentation due to binding of abundant circulating ACTH to the melanocortin-1 receptor in melanocytes. Chronic exogenous *glucocorticosteroid* (GC) use suppresses the hypothalamic-pituitary-adrenal axis and is the most common cause of tertiary adrenal insufficiency, which becomes manifest when the medication is rapidly tapered or abruptly discontinued.[199]

CUSHING SYNDROME

Glucocorticoid excess, or Cushing syndrome, can present with hypertension, hypokalemia, hyponatremia, and metabolic alkalosis in addition to physical exam features of buffalo hump, abdominal striae, and obesity.[200] Cushing syndrome is most commonly caused by exogenous GC use. Systemic and inhaled GC are frequently prescribed for asthma, COPD, and other pulmonary inflammatory conditions, and pulmonologists should be vigilant for this potential complication. HIV patients treated with ritonavir and inhaled corticosteroids may develop Cushing syndrome due to elevated levels of steroids from ritonavir's inhibition of the cytochrome P450 system.[201,202] In children, long-term use of oral corticosteroids results in weight gain, growth retardation, and Cushingoid

features.[203] Cushing syndrome can also arise from pituitary tumors or ectopic ACTH production by small cell lung cancer[204] and pulmonary carcinoid tumorlets.[205,206] Elevated cortisol levels predispose to pulmonary infections by various pathogens such as *Cryptococcus, Aspergillus, Nocardia, Pneumocystis*, and *Mycobacterium tuberculosis*.[207–210]

IMMUNE CHECKPOINT INHIBITORS

Immune checkpoint inhibitors block immune checkpoint proteins (CTLA-4, PD-1, and PD-L1) leading to activated T lymphocytes against various solid tumor and hematologic malignancies, including non–small cell lung cancer.[211–213] In up to 10% of patients,[212] immune checkpoint inhibitors can lead to complex immune-related endocrinopathies such as pituitary gland inflammation (i.e., hypophysitis), thyroid dysfunction, adrenal insufficiency, and, rarely, type 1 diabetes, central diabetes insipidus, and hypoparathyroidism.[211,214] Different immune checkpoint inhibitors modulate T cell response differently and exhibit distinct toxicity patterns; complications may be life-threatening if not recognized. Clinical manifestations of hypophysitis are widespread and include headache, hypotension, hypoglycemia, nausea, and multiple lab derangements including hyponatremia, low cortisol levels, low thyroid levels, and low gonadal hormonal and hypothalamic levels.[211,213] Management of immune-related endocrinopathies includes hormone level testing, supportive care, consultation with an endocrinologist, additional immunosuppression and, in some cases, withholding immune checkpoint inhibitors.[213,215]

Key Points

- The respiratory system is a target affected by multiple endocrine disorders. Conversely, primary respiratory disease may lead to endocrine abnormalities.
- Insulin resistance, diabetes mellitus, and obesity broadly impair immune defenses, ventilatory control, and respiratory structure, leading to a variety of anatomic, microvascular, mechanical, and gas-exchange abnormalities.
- Hypothyroidism can cause airway obstruction, alveolar hypoventilation, and pulmonary parenchymal and respiratory muscle abnormalities. Hyperthyroidism increases oxygen consumption, ventilation, and may lead to pulmonary hypertension and respiratory failure.
- Growth hormone deficiency retards somatic growth, whereas acromegaly predisposes to obstructive sleep apnea and malignancy, including in the lung.
- Calcium disequilibrium from parathyroid or other systemic or pulmonary diseases may lead to metastatic pulmonary calcification. Conversely, granuloma-forming pulmonary diseases such as lymphoma, fungal infections, and sarcoidosis can cause hypercalciuria and/or hypercalcemia.
- Adrenal hormone insufficiency or excess impacts fetal and postnatal lung development and may develop as a complication of exogenous glucocorticosteroid use or pulmonary malignancy.
- Immune checkpoint inhibitors used in the treatment of lung cancer can trigger complex endocrinopathies that in turn impact lung structure and function.

Key Readings

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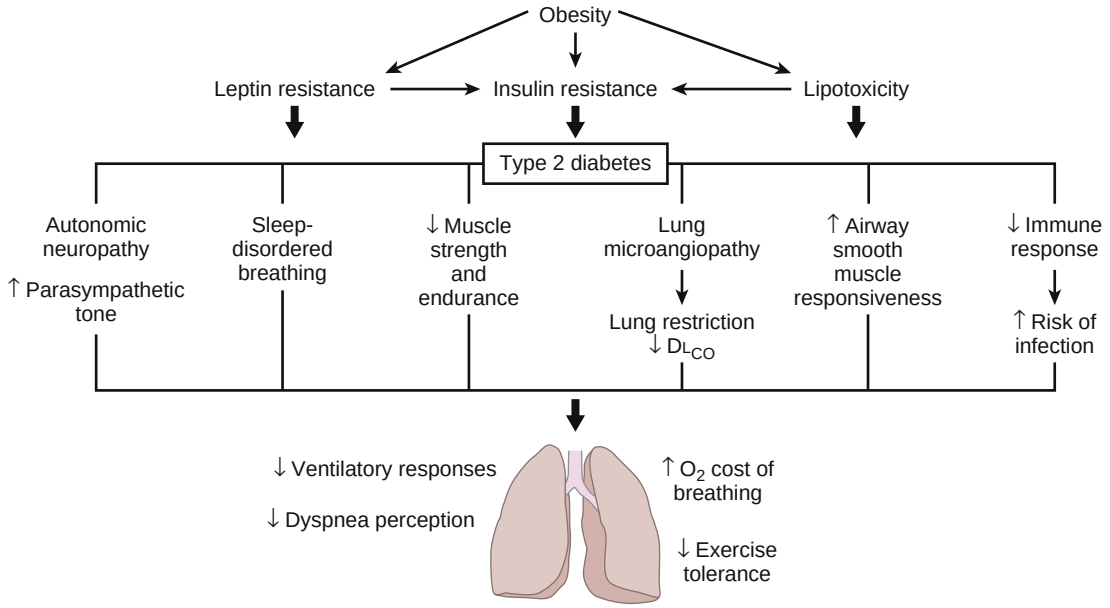
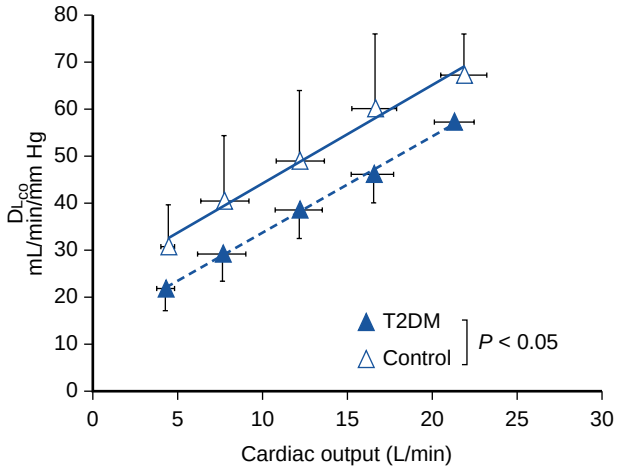
Complete reference list available at ExpertConsult.com.

eFIGURE IMAGE GALLERY



eFigure 128.1 Schema of the effects of diabetes on the lung. Multiple pathogenic mechanisms underlie respiratory dysfunction in type 2 diabetes mellitus. DL_{CO}, Lung diffusing capacity for carbon monoxide.



eFigure 128.2 Diffusing capacity reduction in type 2 diabetes mellitus. Alveolar microvascular recruitment is indicated by a linear relationship between lung diffusing capacity for carbon monoxide (DL_{CO}) and cardiac output from rest to exercise. Note how the DL_{CO} is reduced at each level of exercise in patients with *type 2 diabetes mellitus* (T2DM). Data (mean ± SD) are from 103 healthy nonsmoking subjects and 83 patients with T2DM.

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129 THE LUNGS IN OBSTETRIC AND GYNECOLOGIC DISEASES

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INTRODUCTION

Both respiratory physiology and the respiratory tract's susceptibility to disease are uniquely altered in gynecologic and obstetric conditions, including normal pregnancy. This chapter summarizes normal physiologic alterations during pregnancy and considers pathologic diseases and disorders that arise during pregnancy. Airway disorders, infectious diseases, pulmonary vascular and embolic disorders, and acute lung injury are discussed. Finally, pleural and parenchymal diseases that arise as a consequence of gynecologic conditions are addressed.

PHYSIOLOGIC ALTERATIONS DURING NORMAL PREGNANCY

Profound alterations of respiratory function and cardiovascular physiology accompany normal pregnancy in healthy women; these conditions contribute to many of the disorders of the lungs during pregnancy. The adaptive changes during the gravid period are designed to support maternal and fetal well-being during the special stresses of fetal growth and parturition, but they may exacerbate some underlying disorders and confuse interpretation of laboratory and imaging studies used to assess many other common conditions.

ALTERATIONS IN RESPIRATORY PHYSIOLOGY

Upper Airway

Upper airway, particularly nasal, mucosal edema is common in normal pregnancy. About 20% of gravid women report rhinitis symptoms, now attributed at least partially to placental growth hormone's effects on mucosal congestion.[1] The symptoms begin in the first trimester and persist throughout gestation. Many patients thought to have rhinitis of pregnancy may actually have other or coincident causes of rhinitis.[2] An important implication of nasal mucosal edema in pregnancy is that it predisposes to nosebleeds, including from nasal intubations, so an oral approach is favored if intubation is required at the time of delivery.

Chest Wall

Chest wall configuration is also altered, due to both a 50% increase in the average costal angle[3] and an increase in the circumference of the lower chest wall. Diaphragmatic position is elevated 4 to 5 cm, but excursion does not diminish.[3] Muscle strength, as measured by maximum transdiaphragmatic pressure, does not appear to be diminished from its usual mean value of about 95 cm H_2O,[4] allowing reserve for both the augmented minute ventilation of normal pregnancy and the stresses of delivery.

Lung Function

Important changes take place in lung function and lung volumes. The loss of lung volume resulting from elevation of the diaphragm is only partially offset by the increase in chest wall diameter, and therefore *functional residual capacity* (FRC) is diminished by about 18%, or 300 to 500 mL.[5] This reduction in FRC comprises an equal reduction in both the expiratory reserve volume and the residual volume.[3,5] The loss of FRC at term is made worse by recumbency, when diaphragm elevation is greatest because of the higher intra-abdominal pressure. Increased pulmonary blood volume in pregnancy may also serve to lower the FRC due to volume displacement by vascular engorgement.[6] This reduction in FRC is associated clinically with increased uptake and elimination of inhalational anesthetics and with rapid

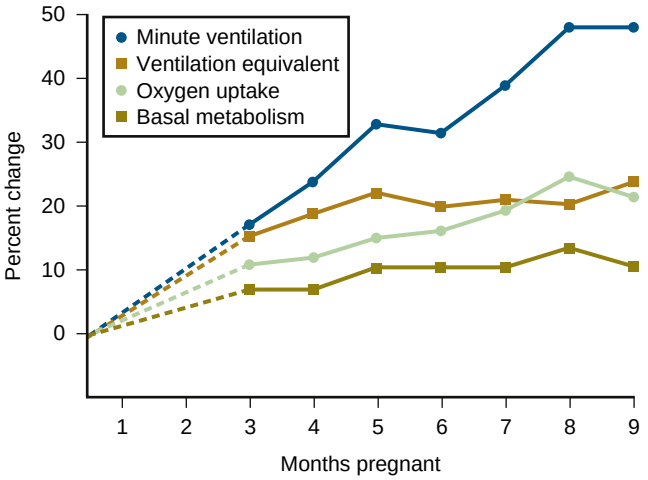

Figure 129.1 The physiology of pregnancy. The expected values for minute ventilation, the ventilatory equivalent for oxygen, oxygen uptake, and basal metabolism are shown at monthly intervals throughout pregnancy. (From Prowse CM, Gaensler EA: Respiratory and acid-base changes during pregnancy. *Anesthesiology.* 1965;26:381.)

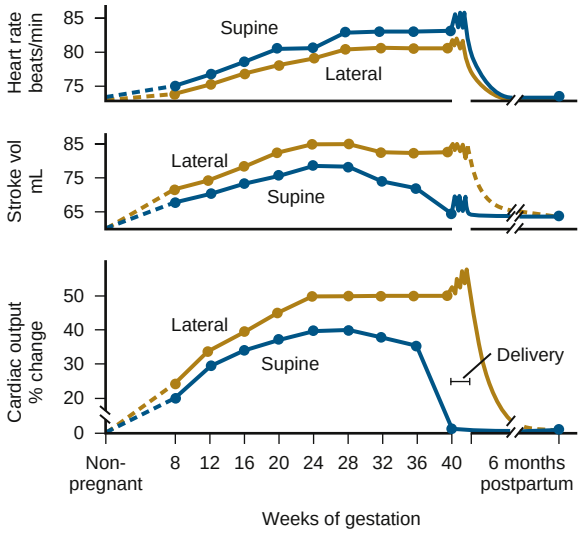

Figure 129.2 Changes in physiology in the supine position. Because the gravid uterus compromises venous return, there are characteristic changes in maternal heart rate, stroke volume, and cardiac output during pregnancy with the pregnant subject in the supine compared to the lateral position. (From Cheek TG, Gutsche BB. Maternal physiologic alterations during pregnancy. In: Shnider SM, Levinson G, editors. *Anesthesia for Obstetrics* Baltimore, MD: Williams & Wilkins; 1993.)

desaturation during hypopnea, as a result of the loss of the oxygen reservoir function of end-expiratory lung volume.[7] Endotracheal intubation at term is thus substantially more hazardous than in nongravid patients.

Airway function is largely unchanged during pregnancy.[3] Airway resistance may actually decrease slightly. Routine measurements of airflow, such as *forced expiratory volume in 1 second* (FEV_1), are thus valuable in assessing dyspnea during pregnancy.

Ventilation

The most striking changes are in respiratory drive and minute ventilation. Central drive, as assessed by the inspiratory pressure measured 100 msec after airway occlusion at the onset of inspiration ($P_{0.1}$), is increased by 13 weeks and continues to increase to week 37 of gestation, returning to normal by 24 weeks after delivery.[4] These serial changes in respiratory drive appear to correlate with changes in serum progesterone levels.[4,8] Carbon dioxide production itself increases one-third to one-half by the last trimester, related to the increased metabolic rate; however, this is more than made up for by the greatly augmented ventilation, so primary respiratory alkalosis with renal bicarbonate wasting as compensation is a normal finding.[9] Arterial blood gas measurements typically show the pH ranging from 7.40 to 7.47, with P_{CO_2} reaching as low as 28 to 32 mm Hg. P_{O_2} rises slightly as a result of the increase in alveolar ventilation.

Most of the increase in minute ventilation is due to a 30–35% increase in tidal volume. Respiratory rate is unchanged early and rises only about 10% later in pregnancy. Oxygen consumption increases 20–33% in pregnancy, owing to both maternal and fetal metabolic demands. Changes in some of these parameters are shown in Figure 129.1.

ALTERATIONS IN CARDIOVASCULAR PHYSIOLOGY

Adaptive cardiovascular changes are designed to support both maternal and fetal circulations but contribute to the risk for hydrostatic pulmonary edema; accordingly, cardiac disorders during pregnancy often present as respiratory failure. During normal pregnancy, maternal blood volume increases by about 2 L, or 40%.[10,11] Red blood cell mass increases as well, but only by 20–30%, accounting for the normal 10–12% decrease in hematocrit.[11,12] Plasma osmotic pressure also drops as intravascular volume expands, increasing the risk for pulmonary edema at lower intravascular hydrostatic pressures. During the 24 hours after parturition, osmotic pressure falls further because of blood loss and mobilization of extravascular fluid.

The enlarged intravascular volume of pregnancy is accommodated chiefly by venous capacitance vessels. Central venous pressure and pulmonary capillary occlusion (wedge) pressure are unchanged, reflecting an increase in left ventricular compliance, as evidenced by the enlarged cardiac silhouette seen on chest radiograph. The increased left ventricular end-diastolic volume results in an augmented stroke volume (ejection fraction is little changed), but systemic vascular resistance diminishes.[12,13] These changes account for the 30–45% increase in cardiac output reached by 25 to 32 weeks of gestation. After 5 weeks, heart rate increases as well,[14] but less so than stroke volume. Some of these changes, as well as the effects of supine versus lateral positioning, are depicted in Figure 129.2.

LUNG DISORDERS IN OBSTETRICS

Gravid and newly postpartum patients may develop pregnancy-specific disorders but also continue to experience common disorders that arise outside of pregnancy; the natural history or frequency of coexisting disorders is sometimes altered by the gravid state. Even for diseases not

altered by pregnancy, management requires special knowledge of the safety of therapies. Specific diseases are considered here with these principles in mind.

OBSTRUCTIVE AIRWAY DISEASE

Asthma

Asthma affects 4–8% of the general population and is the most common pulmonary disorder in pregnancy. The *National Asthma Education and Prevention Program* (NAEPP) Working Group on Asthma and Pregnancy estimated that 3.7–8.4% of pregnancies are complicated by asthma.[15] Poorly controlled maternal asthma increases the risk of preeclampsia, preterm birth, infants with low birth weight, intrauterine growth restriction, and perinatal death.[16]

Studies examining the hormonal milieu have suggested that progesterone might diminish smooth muscle contractility in the lung, as it does in the uterus and gut. Juniper and colleagues[17] performed serial measurements of bronchial reactivity to methacholine challenge in 16 women before and during pregnancy and found a decrease in airway hyperresponsiveness. Clinical and epidemiologic studies, however, have failed to provide convincing evidence of any consistent change in the natural history of asthma during pregnancy. Turner and coworkers,[18] for example, compiled the results of nine studies of asthma symptoms reported by pregnant women. Among them, 22% reported worsening, 29% reported improvement, and 49% reported no change. Other studies have reported similar figures, with about 23–42% worsening, 18–36% improving, and 40% exhibiting no change.[19,20] The differences reported in the natural history probably reflect differences in study populations, smoking history, ethnicity, or other variables.[21]

Fetal and maternal outcome for asthma and pregnancy have also been examined in a variety of studies since 1980. Adverse outcomes, including an increased incidence of preterm labor, low neonatal birth weight, increased perinatal mortality, preeclampsia, vaginal hemorrhage, chronic hypertension, and complicated labor, have been reported.[15,21] A large epidemiologic study from Sweden confirmed an association of asthma with perinatal mortality and low birth weight.[22] Nonetheless, adequate asthma therapy during pregnancy tailored to disease severity is associated with improved outcomes.[23] Therapy should be individualized according to severity of disease and frequency of symptoms, as outlined by the NAEPP and British Thoracic Society/Scottish Intercollegiate Guidelines Network.[15,24] Objective measurement of lung volumes and flow should be part of the regimen. Initial office spirometry is recommended, and home peak flow monitoring should be considered. For women who have asthma attacks during labor, which is extremely rare, fetal monitoring is considered essential by the NAEPP.

Therapy should be based on a step approach.[15] Mild intermittent asthma is best managed with inhaled short-acting β_2-agonists for symptomatic relief. Asthma that causes more than occasional symptoms should be treated daily with anti-inflammatory therapy, preferably inhaled corticosteroids. Budesonide is the best-studied and hence preferred, although substantive safety data exist for beclomethasone and fluticasone as well. Alternative therapies include cromolyn, sustained-release theophylline, or a leukotriene antagonist.[15] Frequent need for short-acting β_2-agonists should prompt institution of, or an increase in, the use of anti-inflammatory agents to treat, rather than to mask, a deteriorating clinical course. Long-acting β-agonists should only be used concurrently with long-acting inhaled corticosteroids.[21] Finally, the addition of rapidly tapered courses of oral corticosteroids should be considered for those with acute severe asthma or patients with active symptoms who are already using inhaled steroids and β-agonists. Daily or alternate-day oral steroid administration (e.g., prednisone 40 mg/day) is sometimes required.[15] Extensive practice algorithms have been made available by the NAEPP Working Group on Asthma and Pregnancy and the British Thoracic Society/Scottish Intercollegiate Guidelines Network.[15,24]

A large body of literature has examined the topic of possible teratogenicity of agents used in the pharmacotherapy of asthma in pregnancy. In general, the risks of poorly controlled asthma far outweigh the possible hazards of drug therapy. Both animal and human studies of β_2-agonists, administered either by inhalation or systemically, have indicated an acceptable safety profile for the fetus. They are also safe for use during lactation. Nonselective β-agonists, such as epinephrine, carry a risk of uterine vasoconstriction in animal models[25] and are probably best avoided. Acceptable β_2-agonists in pregnancy include metaproterenol, albuterol, pirbuterol, bitolterol, and terbutaline. Because the toxicology and pharmacology of the long-acting β-agonists salmeterol and formoterol are expected to be similar to shorter-acting β_2-agonists, these drugs have been recommended in patients with poor control on a combination of inhaled long-acting corticosteroids and short-acting β-agonists.[23,26] Limited data suggest that these drugs are safe in pregnancy.[27]

Theophylline is currently seldom used, but it passes freely to the fetus, and newborns occasionally show signs of theophylline toxicity, particularly when maternal blood levels are high. Animal studies suggest that the leukotriene inhibitors montelukast and zafirlukast are safe in pregnancy, and they can be continued in patients who have previously responded.[25,28,29] A large Danish cohort study demonstrated no increased incidence of congenital abnormalities after exposure to montelukast.[30] Zileuton has little human safety data, and animal studies have raised questions about its safety in pregnancy.[28]

Animal studies have shown an increased incidence of cleft palate with use of corticosteroids, but a very large Danish database study demonstrated no association of cleft lip/palate with first-trimester exposure to corticosteroids via either the oral, inhaled or intravenous route of administration.[31] Systemic corticosteroids have also been reported to cause intrauterine growth restriction but of a relatively modest degree. Fluorinated synthetic steroids such as betamethasone and dexamethasone cross the placenta, but nonhalogenated corticosteroids (hydrocortisone, prenisolone) are largely metabolized by the placenta and so fetal effects are not a major concern.[15] Overall, risk-benefit considerations nonetheless favor their use in persistent severe asthma with exacerbations unresponsive to other measures. A meta-analysis of the use of inhaled steroids during pregnancy demonstrated that these drugs do not increase the incidence of congenital abnormalities or

Table 129.1 Potential Fetal Risk of Drug Therapy in Pregnancy

Group	Drug	Pregnancy Risk
Inhaled β_2-agonist bronchodilators		Although data are limited, studies do not suggest an increased chance for birth defects with the use of inhaled albuterol during pregnancy.
Inhaled anticholinergic bronchodilators		Data are more limited than for inhaled β_2-agonist bronchodilators, but there is no evidence to suggest these drugs cause problems in pregnancy.
Long-acting β-agonists		Data are more limited than for short-acting bronchodilators, but there is no evidence to suggest these drugs cause problems in pregnancy.
ICSs	As a group	Studies of ICS have found no overall increased chance for birth defects. High doses of ICSs (doses similar to systemic steroid use) have not been well studied during pregnancy.
	Fluticasone and budesonide	As older, more established ICSs, these drugs have more published data to support their safety during pregnancy.
Leukotriene antagonists	Montelukast	Several large cohort studies of pregnant women exposed to montelukast have not shown an increased incidence of birth defects.
	Zafirlukast	Although data are more limited than for montelukast, an increased incidence of birth defects has not been demonstrated.
	Zileuton	Adverse fetal effects have been documented in animal studies, and there are no adequate human data to support safety in pregnancy.
Biologics	Omalizumab	No adverse fetal effects have been noted in limited early studies. For this IgG antibody, the risk of anaphylaxis must be considered and placental transfer increases as pregnancy progresses.
	Mepolizumab	No adequate data exist to assess safety, but similar concerns as an IgG antibody.
Other agents for asthma	Theophylline	Although animal studies suggest an increased risk of birth defects, this has not been demonstrated in limited human data.
	Inhaled cromolyn	No increased risk of birth defect has been demonstrated.
	Systemic steroids	Older studies suggest a small increased risk of cleft lip/palate, although this is not supported by newer data. The benefit of steroids in the management of a severe asthma attack outweighs these very small risks.
Antibiotics	β-lactams	No significant fetal risks have been identified.
	Macrolides	Several large studies have demonstrated no fetal risks from macrolide therapy. Erythromycin estolate may produce reversible hepatotoxicity in the pregnant woman.
	Quinolones	No birth defects have been demonstrated in human studies, although older animal studies did suggest some concerns.
	Tetracyclines	Tetracyclines accumulate in developing teeth and bones, and permanent discoloration of teeth can result from utero exposure.
Anticoagulants	Heparin	Heparin does not cross the placenta and is not associated with birth defects, but long-term heparin therapy during pregnancy may cause maternal osteopenia.
	LMWHs	LMWHs are not associated with adverse effects in pregnancy.
	Warfarin	Use should be avoided during the first trimester because it carries a significant risk to the fetus. Towards term, the risks of bleeding need to be considered.

In every pregnancy, the background risk for having a baby with a birth defect is 3–5%. This table describes whether exposure drugs may increase the risk for birth defects over that background risk.
ICSs, inhaled corticosteroids; Ig, immunoglobulin; LMWHs, low-molecular-weight heparins.

other adverse pregnancy outcomes.[32] A recent UK administrative database study demonstrated no adverse effects to exposure to fluticasone during pregnancy.[33] One study suggests that higher doses of inhaled corticosteroids (i.e., beclomethasone > 1000 μg/day) may be associated with a small increased risk of congenital abnormalities, although the confounding effect of increased asthma severity cannot be excluded.[34] There are limited data to confirm the safety of newer inhaled corticosteroids.[27] Table 129.1 summarizes the safety profile of commonly used asthma therapy in pregnant patients. Self-monitoring and self-management are important components of asthma care, and a telephone monitoring system using the Asthma Control Test[35] and a smartphone application[36] have been found helpful in this regard.

Labor and delivery can be especially hazardous for asthmatic patients, partly because of the drugs commonly administered. Narcotics other than fentanyl release histamine, which may worsen bronchospasm. Lumbar epidural analgesia is generally preferred but, if general anesthesia is to be used, pretreatment with atropine or glycopyrrolate assists bronchodilation. Ketamine is the preferred anesthetic, although halogenated anesthetics at low concentrations may provide bronchodilation as well.[15] Preterm labor may be safely treated with nifedipine or magnesium sulfate. Oxytocin is the optimal labor induction agent and is useful for postpartum hemorrhage, but 15-methyl prostaglandin F_{2a}, methylergonovine, and ergonovine may cause bronchospasm and should be avoided if possible.

Cystic Fibrosis

Cystic fibrosis (CF), present in about 1 in 1500 whites and 1 in 17,000 African Americans, is a common genetic disease. With improved therapy, median survival has now increased to 37 years.[37] Up to 4% of female CF patients between the ages of 17 and 37 may be pregnant at any time,[38] despite the frequent infertility of women due to delayed sexual development from nutritional deficiencies and chronic disease. Pregnancy in CF patients, as might be anticipated, has been associated with adverse fetal and maternal outcomes,[39,40] although several recent small case series have demonstrated good maternal and neonatal outcome in women with CF.[41–43] Premature delivery was more common in women with worse baseline FEV_1, and gestational diabetes was common. In a large U.S. review of 680 gravid women with CF enrolled in the U.S. Cystic Fibrosis Foundation National Patient Registry from 1985 to 1997, survival was actually better in the gravid group than in the matched 3327 control patients with CF.[44] Women with CF who became pregnant had higher predicted percentages of FEV_1 and higher weights. Pregnancy was not clearly harmful in any subgroup, after severity adjustment for age, *Pseudomonas aeruginosa* colonization, pancreatic function, and FEV_1. In another case-control study, pregnancy had little effect on patients with stable CF, although poor outcomes were seen in those with severe disease.[45] An analysis of a U.S. database documented the linear increase in CF pregnancies from 2000 to 2010, with more than 1000 deliveries from 2008 to 2010.[39] As might be anticipated, most studies suggest that risk stratifies according to severity of illness.[40,45] Declines in pulmonary function tend to mirror severity-adjusted control subjects, and clearly CF patients require substantially more care and have more visits to physicians when pregnant than when not.[41] Prepregnancy counseling, particularly for women with more severe disease, is essential in limiting excessive maternal and fetal risk. New therapies aimed at improving the function of the CF transmembrane conductance regulator are now available and provide significant clinical benefits to patients with CF (see Chapter 68). Isolated reports suggest that these may be safe during pregnancy.[46]

INFECTIOUS DISEASES

A woman's immune system changes during pregnancy to allow tolerance to paternally derived fetal antigens. This involves predominantly a down-regulation of cell-mediated immunity, balanced by an up-regulated humoral immune response. The pregnant woman is therefore at risk of more severe manifestations of certain infections, particularly viral and fungal infections, as described further in this section.

Bacterial Pneumonia

Pneumonia is a leading cause of maternal and fetal morbidity and mortality. The reported incidence varies widely, from 0.4 to 2.7 per 1000 deliveries,[47] but may not be higher than that in the general population. Some recent studies suggest an increased incidence of pneumonia in pregnant women with chronic disease and those with HIV.[47] Postpartum pneumonia may develop in the first 6 weeks after delivery and is more common after cesarean section.[48] Pneumonia accounted for 40% of pregnant women admitted to the ICU with severe sepsis in a large UK cohort study.[49]

Pregnancy increases the risk of major complications of pneumonia. In the series by Madinger and colleagues,[50] of 25 women with pneumonia from 25,000 deliveries, 40% had major complications, including five intubations, two empyemas, one pneumothorax, and one pericardial tamponade. Similarly, in the series by Briggs and associates,[51] 7 of 34 patients required mechanical ventilation, and two died. The Pneumonia Severity Index[52] used to identify severity of pneumonia for hospital admission does not appear to perform well in the obstetric population, underestimating the need for hospital admission.[53] Pneumonia (and other infections) increase the risk of preterm labor. Underlying chronic illness in the mother is a powerful predictor of adverse outcomes in both fetus and mother.

Pneumonia in pregnancy is most commonly bacterial in origin; the microbiologic spectrum mirrors community-acquired pneumonia, with *Streptococcus pneumoniae* and *Haemophilus influenzae* the most common organisms.[43,47] Other common organisms include *Mycoplasma pneumoniae* and *Chlamydia pneumoniae.* As in other community-acquired pneumonias, the causative agent is identified in only about half of the cases. Unfortunately, the diagnosis of pneumonia is frequently delayed because of reluctance to obtain a chest radiograph, due to inappropriate concerns for the effect of radiation on the fetus. A plain chest radiograph exposes the fetus to an extremely low radiation dose (<0.01 mGy) (see Chapter 20).[54] The hazard to both fetus and mother of delaying the diagnosis greatly exceeds the risk of this small radiation dose. Antibacterial therapy is similar to treatment in the nonpregnant patient, although tetracyclines and quinolones should be avoided if possible.[55] Erythromycin, clarithromycin, azithromycin, and β-lactam antibiotics are preferred because of their favorable safety profile (see Table 129.1).

Viral Pneumonia

Viral pneumonia remains a serious concern in pregnancy. In the influenza pandemic of 1918, the maternal rate of mortality from pneumonia was as high as 50%. In the epidemic of 1957, pregnant women accounted for 10% of fatalities, and about half of the women of childbearing age who died were pregnant.[56] Since then the maternal mortality rate from influenza A and B pneumonia has been relatively low but still much higher than that in the general population. Because of this, the Centers for Disease Control and Prevention recommends inactivated influenza vaccine in otherwise healthy women during any trimester of pregnancy.[57] Although influenza virus does cross the placenta, current opinion is that it is not likely to be teratogenic, despite isolated reports that link influenza with neural tube and other malformations. Amantadine has been used in pregnancy successfully, both as treatment and as prophylaxis, although there have been case reports of cardiovascular defects noted with first-trimester use, and there is considerable influenza viral resistance to the drug.

In 2009, the influenza A (H1N1) pandemic again confirmed the high risk of serious disease and appreciable mortality among pregnant women.[58,59] Surveillance by the Centers for Disease Control and Prevention in the United States identified influenza infection in 788 pregnant women, of whom 35% were admitted to the ICU and 7% died.[60] Early treatment of pregnant women and women up to 2 weeks

postpartum with oseltamivir or zanamivir appears to be beneficial.[61] Pregnant women are strongly urged to be vaccinated with the monovalent *inactivated* injectable influenza vaccine—not with the live attenuated vaccine.[62]

Varicella pneumonia, caused by a virus of the DNA herpesvirus group, has also been linked to particularly adverse outcomes during pregnancy. Haake and coworkers[63] report an increased incidence of pneumonitis in pregnant women with primary varicella infection and a 35% mortality rate in this group (over a period dating back to 1964), compared with 10% in other adults. Data are conflicting, and not all prospective studies have confirmed an increased incidence of mortality in pregnancy.[55] Treatment with acyclovir does appear to reduce mortality in gravid patients and should be used as therapy for active disease.[64] Use of varicella-zoster immune globulin should be considered within 96 hours for susceptible pregnant women who have been exposed to varicella. Administration of varicella-zoster immune globulin reduces but does not abolish risk for fetal infection or congenital varicella syndrome, and it is effective in preventing complications of varicella in the mother. Patients should be evaluated similarly to other adults, and a decision made to administer the immune globulin on the basis of immune status, type of exposure, and health status. The current licensed attenuated live vaccine against varicella is contraindicated in pregnancy.

The novel coronavirus, SARS-CoV-2, and its infection, COVID-19, is also linked to adverse outcomes during pregnancy. A pregnant woman is less likely to develop symptoms of fever and myalgia when infected.[65] Although infection is usually mild, the incidence of ICU admission and mechanical ventilation is higher than in the general population.[65–67] Risk factors for severe disease are similar to those in the nonpregnant patient and include obesity, ethnic minority status, asthma, hypertension, and age over 35 years.[65,67] Because both pregnancy and COVID are prothrombotic, the risk of thromboembolic disease is increased. The absolute risk of a poor outcome is low, but an increased mortality risk has been suggested.[65,67] Treatment is not very different than for the nonpregnant patient, although steroid dosing needs to be altered. In women at a preterm gestation, steroids are often given for fetal lung maturity and a higher dose of dexamethasone is required (e.g., dexamethasone 6 mg twice a day for 48 hours). Otherwise, a steroid that does not cross the placenta is preferably used (e.g., prednisolone). Iatrogenic preterm births are increased,[67] but the rate of spontaneous preterm labor does not appear to be increased.[65] The risk of stillbirth or neonatal death is not significantly increased, and the risk of vertical transmission and neonatal infection is very low.

Fungal Pneumonias

Fungal pneumonias are uncommon in pregnancy. Although there is no evidence that blastomycosis and histoplasmosis are more severe during pregnancy, it does appear that coccidioidomycosis is more likely to disseminate in pregnancy.[68] In the southwestern United States about 1 in 5000 pregnancies is complicated by *Coccidioides immitis* (see eFig. 56.7).[69] Dissemination is highly probable during the third trimester and is likely caused by both subtle impairment of cell-mediated immunity and a stimulatory effect of progesterone and 17-β-estradiols on fungal proliferation.[70] Amphotericin is the accepted therapy for disseminated coccidioidomycosis; azoles administered in the first trimester have been associated with branchial cleft abnormalities and should be used only after delivery.

Tuberculosis

Tuberculosis is an important cause of maternal morbidity and mortality, particularly in HIV-infected women, and in developing countries. Data from the United States have demonstrated an increasing incidence of tuberculosis in pregnant women,[71] and a study from the UK found that the incidence is significantly higher than in the nonpregnant population, particularly related to postpartum diagnoses.[72] Presentation may be atypical and disease is often extrapulmonary.[73] Diagnosis may be delayed by a reluctance to perform appropriate imaging studies. Pregnancy does not alter reactivity to tuberculin skin testing, and hence the test should be performed in the recommended groups during pregnancy. Interferon-γ-release assays are also an acceptable means of testing for tuberculous infection (see Chapters 42 and 53). Asymptomatic patients with positive skin tests should have their chest radiograph deferred until after 16 weeks of gestation. Treatment of latent infection is deferred until 2 months postpartum, except in the case of a known recent tuberculosis contact. Symptomatic patients with positive skin tests merit chest radiographs regardless of gestational stage. Isoniazid, rifampin, and ethambutol have acceptable safety profiles in pregnancy and are part of the standard treatment regimens advised by the Centers for Disease Control and Prevention and American Thoracic Society for pregnant women.[74] There is less collective experience with pyrazinamide, but this drug is recommended for use in pregnancy by the World Health Organization.[74] Worldwide data are accumulating, and pyrazinamide appears to be emerging as a drug that can be considered for treating multidrug-resistant tuberculosis and for HIV-infected women. Streptomycin, in contrast, is clearly associated with congenital deafness and is contraindicated during pregnancy.

PULMONARY EDEMA AND PULMONARY VASCULAR DISEASE

Gravid women are at special risk for pulmonary edema for a variety of reasons, including the hypervolemia and high cardiac output of pregnancy, the occasional need for tocolytic drugs that affect the vascular bed, and the unique vascular and endothelial disorders of pregnancy.

Among these effects, it is noteworthy that colloid osmotic pressure diminishes during pregnancy, although the effect on transcapillary pressure gradients is partially offset by a decrease in interstitial fluid colloid osmotic pressure (as explained in Chapter 133).[75] Etiologically, underlying cardiac disease, preexisting hypertension, use of tocolytic drugs, fluid overload, and preeclampsia are the most common causes for acute pulmonary edema in pregnancy.[75]

Increased Pressure (Cardiogenic) Pulmonary Edema

The cardiovascular adaptations to pregnancy have already been summarized. Their effects on underlying cardiac disorders are predictable. Stenotic valvular lesions are particularly poorly tolerated.[76] Of these, mitral stenosis is the

most common symptomatic valvular disease in pregnancy and frequently presents with pulmonary edema, not only during gestation but also immediately postpartum, because of the large shifts in intravascular volume associated with delivery. The gradient across a stenotic mitral valve is augmented by the increases in blood volume, cardiac output, and heart rate that take place during gestation and the puerperium. In aortic stenosis, the increase in cardiac output required for pregnancy worsens the gradient across the valve. As a compensatory mechanism, the left ventricular end-diastolic volume increases, but the low systemic vascular resistance impairs coronary artery filling during diastole and can precipitate ischemic syndromes. The reduction in systemic vascular resistance of pregnancy mitigates the consequences of mitral and aortic regurgitation and of the left-to-right intracardiac shunts of endocardial cushion defects but worsens the consequences of Eisenmenger syndrome and uncorrected tetralogy of Fallot. Depending on the cardiac disorder, perturbations induced by pregnancy can alter shunting, induce hypoxemia, or precipitate pulmonary edema.

A special problem of pregnancy is peripartum cardiomyopathy, a disorder that develops in 1 of 1300 to 15,000 deliveries, may present with congestive heart failure, and is associated with a special propensity for both pulmonary and systemic embolization toward the end of pregnancy or in the months following delivery.[77] Standard therapy for heart failure, including β-blockers, diuretics, and angiotensin-converting enzyme inhibitors (to be used only postpartum), are usually effective, but sometimes implantable defibrillators and even left ventricular assist devices, extracorporeal membrane oxygenation, and heart transplantation are required.[77,78]

Tocolysis-Associated Pulmonary Edema

The use of drugs such as β_2-sympathomimetic agents to retard premature labor is uncommon in current obstetric practice but, in the past, was associated with a 0–4% incidence of pulmonary edema.[79] A similar clinical picture has been reported during tocolysis with calcium antagonists[80] and atosiban, an inhibitor of oxytocin and vasopressin. The etiology of this disorder is controversial and likely multifactorial in nature, related to myocardial effects, vascular permeability impairment, and fluid retention. It usually presents after at least 24 hours of β-adrenergic therapy, with relatively acute onset of dyspnea and pulmonary edema seen on chest radiographs. Simple discontinuation of β-adrenergic therapy often results in rapid improvement; whether diuretics need to be given is unresolved, but furosemide is usually administered.

Pulmonary Edema Associated with Preeclampsia

About 2.9% of patients with preeclampsia or eclampsia develop pulmonary edema.[81] The spectrum of hemodynamic findings associated with pregnancy-induced hypertension and preeclampsia is wide and both hypodynamic and hyperdynamic patterns have been described (Table 129.2).[82] Systolic and diastolic function may also be impaired. The pulmonary edema commonly first presents in the postpartum period,[81] probably reflecting the effects of fluid administration at delivery. Low colloid osmotic pressure and abnormal vascular permeability are likely contributors. Hemodynamic monitoring of these patients is probably warranted if oliguria complicates the picture.

Table 129.2 Pregnancy-Induced Hypertension

	Hypodynamic	Hyperdynamic
Cardiac output	↓	↑
SVR	↑	↓
Timing	Early	Late
Fetal size	SGA	AGA
Other associations	-	Obesity

Possible hemodynamic subgroups and their clinical correlates.
AGA, appropriate for gestational age; SGA, small for gestational age; SVR, systemic vascular resistance.
Data from Ferrazzi E, Stampalija T, Monasta L, et al. Maternal hemodynamics: a method to classify hypertensive disorders of pregnancy. *Am J Obstet Gynecol*. 2018;218(1):124.e1–124.e11.

Pulmonary Embolism

Pulmonary embolism (PE; see also Chapters 81 and 82) is a leading cause of maternal mortality,[83] accounting for 15% of maternal deaths in the United States between 2003 and 2011.[83] Even though the risk for venous thromboembolism in pregnant women is about five times as great as in age-matched female nongravid controls, it is still relatively infrequent at about 0.5 to 1.2 per 1000 pregnancies.[84] The risk for thrombosis is increased in pregnancy because of an increase in coagulation factors, particularly V, VIII, X, and von Willebrand factor antigen, and also a marked fall in protein S.[85] Venous stasis, an important contributor to thrombosis, is caused by uterine compression of the inferior vena cava and the left iliac vein. Local trauma to pelvic veins at the time of delivery probably accounts for the peak incidence of thromboembolism in the postpartum period, especially after cesarean section. Specific risk factors for thromboembolism include previous thromboembolism, prolonged bed rest, a complicated or cesarean delivery, age greater than 35 years, thrombophilia, obesity, and smoking. The inherited defects include deficiencies of antithrombin, protein S, protein C, factor V Leiden, and prothrombin G20210A.[85] Antiphospholipid syndrome is an acquired thrombophilia. Previous thromboembolism or multiple risk factors warrant prophylactic heparin administration throughout pregnancy with low-molecular-weight heparins.

Clinical diagnosis of deep venous thrombosis during pregnancy and the puerperium is even more difficult than in the nonpregnant patient because of the peripheral edema associated with pregnancy, and the asymmetrical compression of the left-sided common iliac vein by the gravid uterus. The initial diagnostic test should be duplex ultrasonography (combined real-time B-mode compression ultrasonography plus Doppler venous ultrasonography). In the patient with high clinical suspicion but a negative test, a repeat examination at 5 to 7 days or magnetic resonance venography may be valuable. When venous thrombosis of the lower extremity is documented, it is usually left sided, as it was in 84 of 96 (88%) cases reported by Chan and colleagues.[86]

The diagnosis of PE in pregnant women is complicated by the overlap of some symptoms with normal findings in pregnancy (e.g., dyspnea) and the lack of validation of

many clinical prediction rules in pregnancy. Although biomarkers such as D-dimer are traditionally not considered valuable in the pregnant patient, a recent study evaluated a pregnancy-adapted YEARS algorithm incorporating three clinical criteria (clinical signs of deep vein thrombosis, hemoptysis, and PE as the most likely diagnosis) and D-dimer level.[87] This study suggested that PE could be safely ruled out by the absence of all three clinical features with a D-dimer less than 1000 ng/mL or D-dimer less than 500 ng/mL (if one to three clinical criteria are present).[87] Although these findings are supported by another study,[88] the lack of adverse events in these studies may reflect limited power to detect uncommon but important outcomes (i.e., the fact that there were very few PEs in the two studies does not necessarily mean that the proposed strategies reliably ruled out PE). The potentially catastrophic consequences of a missed diagnosis of PE means that these strategies cannot be considered safe, given that there is a certain risk of missing PE with each of these approaches. Another UK study assessing D-dimers and clinical decision rules to exclude PE in pregnancy (Diagnosis of PE in Pregnancy study) concluded that neither test could be used to exclude PE.[89,90]

Both ventilation-perfusion scanning and *computed tomography* (CT) pulmonary angiography can be performed during pregnancy in a modified fashion, and each raises issues of radiation exposure and relative accuracy. Perfusion scanning exposes the fetus to about 0.011 to 0.022 cGy (11 to 22 mrad), and simply halving the perfusion dose is standard practice in pregnancy, without greatly impairing resolution.[91] If the perfusion scan is normal, there is no need for the ventilation portion of the study. CT pulmonary angiography is associated with similarly low radiation doses to the fetus (Fig. 129.3).[91,92] However, a risk to consider is the potential carcinogenic effect of radiation exposure to the mother's breasts,[91,93] although the use of modern CT scanners has resulted in significant decreases in patient radiation exposures compared to even 10 years ago. Typical modern CT scanner radiation exposures are unlikely to result in teratogenicity, which is associated with exposure of greater than 5 to 10 cGy (5 to 10 rad). However, an increased incidence of childhood leukemia has been documented with lower fetal radiation exposure, in the range of 1 to 5 cGy (1 to 5 rad). A comparison of ventilation-perfusion scanning and pulmonary CT angiography concluded that the former method was more accurate than the latter for diagnosing PE during pregnancy.[94] Ventilation-perfusion scanning in pregnancy, due to the patient's younger age and lack of comorbidity, is associated with a low incidence of intermediate scans and high rate of normal scans.[95] Compared to its use in the nongravid woman, CT angiography may more often be technically suboptimal in the pregnant woman, due to her increased cardiac output.[96] For the same reason, CT angiography at early gestation is more likely to be technically successful than in later gestations.[97] Magnetic resonance imaging with gadolinium contrast also has promise because it can image pelvic and lower extremity veins, as well as the pulmonary arteries, and it has little contrast-associated toxicity. Its widespread use will require increased availability of ultrafast scanners and more evaluation of its accuracy.

Venous thromboembolism in pregnancy is treated with LMWH because warfarin crosses the placenta and causes nasal, ophthalmologic, and central nervous system abnormalities in the fetus. Direct oral anticoagulants should be avoided in pregnancy.[98] LMWH is preferred over unfractionated heparin in pregnancy, using a weight-adjusted dosing regimen.[99] Weight gain in pregnancy makes formulaic dosing less reliable, and some authors also advocate titrating the dose to achieve anti–factor X levels of 0.5 to 1.24 units/mL 4 hours after injection.[100] However, the lack of robust data and lack of correlation of anti–factor X levels with efficacy or complications make routine monitoring difficult to justify.[99] LMWH treatment is usually given for at least 6 weeks postpartum (for a minimum total duration of therapy of 3 months). LMWH should be held 24 hours before cesarean section or neuraxial (e.g., spinal, caudal,

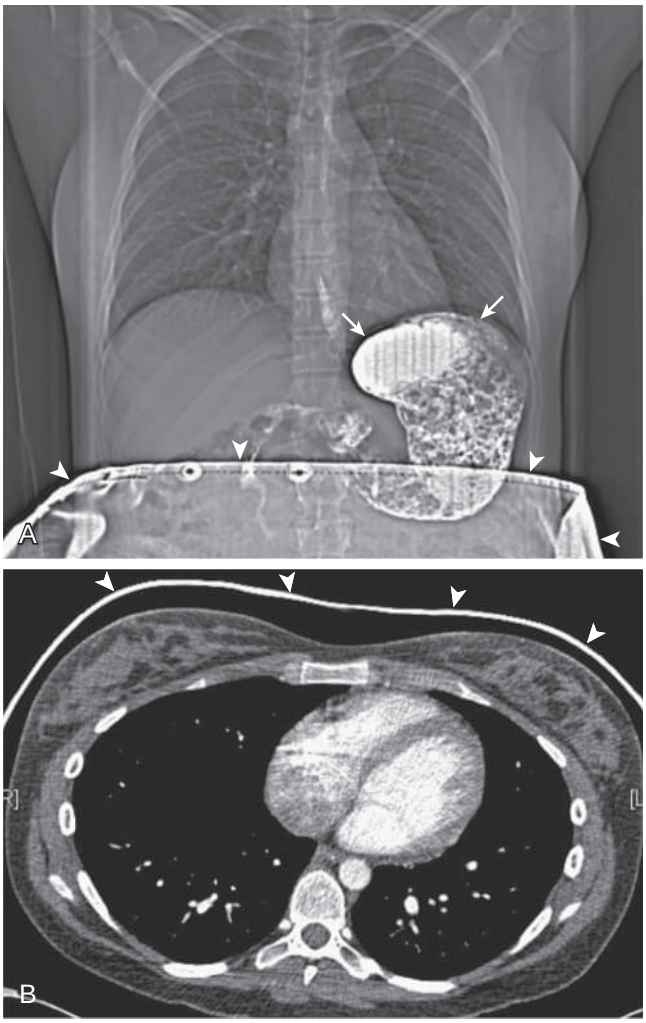

Figure 129.3 Dose-reduction methods for chest *computed tomography* (CT) in the pregnant patient. (A) Scout view before the CT acquisition shows an "internal barium shield" (*arrows*) created by having the patient swallow a dilute mixture of barium and water several minutes before CT scanning. The barium distributes within the stomach and proximal small bowel and attenuates internal maternal radiation that may otherwise expose the fetus. A lead apron (*arrowheads*) also reduces fetal radiation exposure. (B) Axial chest CT pulmonary angiogram obtained with manual reduction of both the tube current and tube voltage shows excellent vascular opacification, providing high-quality assessment for pulmonary embolism and other thoracic disorders. A maternal breast shield (*arrowheads*) has also been placed; these shields selectively filter low-energy x-ray photons that would otherwise deposit preferentially in maternal breast tissue, significantly contributing to maternal breast radiation exposure. (Courtesy Michael B. Gotway, MD.)

or epidural) anesthesia (for twice-daily dosing) or after a 50% dose the morning before delivery for daily dosing regimens.[99] In the postpartum period, warfarin can be given safely during lactation.

Thrombolytic therapy has been used successfully in life-threatening thromboembolism during pregnancy, with a complication rate similar to that in nonpregnant women.[101]

Amniotic Fluid Embolism

Small amounts of amniotic fluid may enter the circulation during uncomplicated pregnancy but rarely cause the catastrophic syndrome of amniotic fluid embolism. The reported incidence varies from 2 to 6 per 100,000 pregnancies, the variation being largely dependent on the method of case identification.[102] The onset is usually during labor and delivery or immediately after uterine manipulation, and amniotic fluid embolism should be considered in any pregnant or immediately postpartum woman with sudden cardiac arrest or cardiovascular collapse, seizures, respiratory distress or hypoxia, particularly in the context of associated coagulopathy.[103] Risk factors include older maternal age, induction of labor, high parity, cesarean section, low uterine segment laceration, and meconium staining of amniotic fluid.[101–103] Abruptio placentae is present in 50% of cases, and fetal demise in 40%.[103] The maternal mortality rate has been as high as 86%,[104] but a later report suggests a mortality rate of 11–43%.[102] Overall, amniotic fluid embolism may account for 4.9% of all maternal deaths.[83]

In a U.S. registry of cases, 78% of the patients with amniotic fluid embolism had ruptured membranes, and several had just undergone intrauterine procedures,[105] clearly implicating traumatic opening of uterine vessels in the pathogenesis. The exact quantity or constituents of amniotic fluid required to initiate the syndrome is unknown. Pathologically, fetal squamous cells are found in the maternal pulmonary circulation at autopsy (Fig. 129.4), but even in symptom-free patients, fetal cells may be aspirated from pulmonary artery catheters placed for other reasons.[106] Hemodynamically, the process is often biphasic, with pulmonary hypertension initially, followed by left ventricular failure.[107,108] These changes may be caused by leukotrienes and arachidonic acid metabolites, particularly prostaglandin F_{2a}, which appear in amniotic fluid during labor. An immunologic basis for some of the changes seems likely because women with male fetuses are more likely to acquire the disorder.[102] Clark and associates[105] seized on the similarities to anaphylaxis and suggested that the disorder be renamed *anaphylactoid syndrome of pregnancy*. A small study did not demonstrate evidence of mast cell degranulation but suggested a role for complement activation.[109] C1-esterase inhibitor activity has been shown to be depressed in patients with amniotic fluid embolism, the level correlating with severity.[110] On imaging studies, affected patients usually develop bilateral parenchymal opacities consistent with pulmonary edema associated with increased permeability lung injury (Fig. 129.5). Treatment consists of supportive

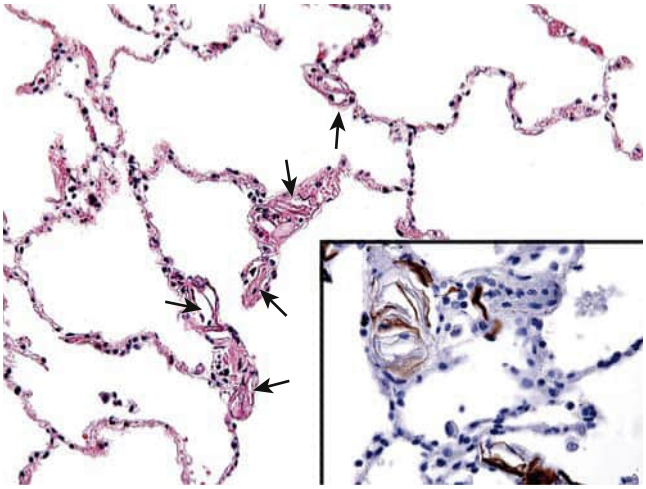

Figure 129.4 Amniotic fluid embolism. Interstitial pulmonary capillaries filled and expanded by eosinophilic fetal squamous cells (*arrows*) from a case of amniotic fluid embolism in a 39-year-old woman who succumbed within 4 hours of delivery. (H&E stain; original magnification ×200.) *Inset,* High-molecular-weight keratin stain, CK5/6 staining the intravascular fetal squamous cells (shown by brown color) (original magnification ×400). (Courtesy Dr. Gerald Berry, Stanford University.)

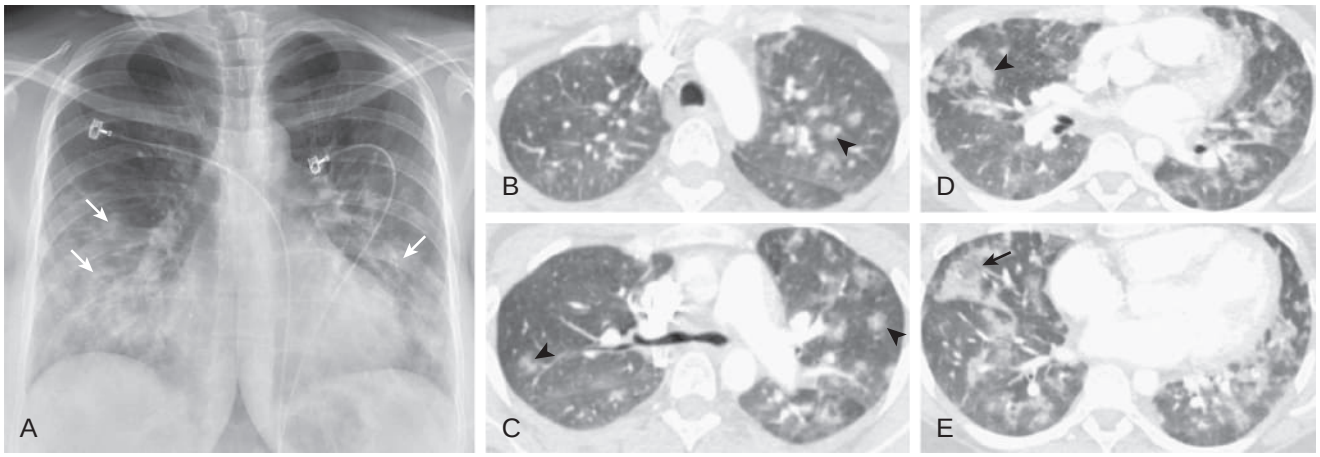

Figure 129.5 Amniotic fluid embolism. (A) Frontal chest radiograph in a patient who developed shortness of breath and cardiovascular instability during delivery shows multifocal, poorly defined opacities (*arrows*) along the bronchovascular bundles, distributed in the mid and lower lungs bilaterally. (B–E) Axial chest *computed tomography* (CT) pulmonary angiogram obtained for pulmonary embolism evaluation, displayed in lung windows, shows multifocal nodular appearing ground-glass opacities (*arrowheads*), somewhat more confluent in the right middle lobe (*arrow*). No features to suggest increased pressure edema, such as pleural effusion or interlobular septal thickening, are present, and no pulmonary embolism was detected. The CT features are consistent with an acute lung injury pattern. (Courtesy Michael B. Gotway, MD.)

care for the associated disseminated intravascular coagulation and left ventricular and respiratory failure. Isolated case reports have suggested a benefit of administration of recombinant C1-esterase inhibitor.[111] The fetus should be promptly delivered. In cases of maternal demise, emergency postmortem or periresuscitative cesarean section is warranted, as it is in other instances of cardiopulmonary resuscitation in pregnancy.[112]

Arteriovenous Malformations

Pulmonary arteriovenous malformations may expand during pregnancy because of hormonal changes, the increase in blood volume, and venous distensibility.[113] This increases the likelihood of bleeding, with life-threatening complications in about 1% of pregnant women with hereditary hemorrhagic telangiectasia.[114,115] Embolization and surgical management have been utilized successfully during pregnancy.

Air Embolism

Occasionally, venous air embolism can happen during pregnancy, presumably through the subplacental venous sinuses.[116] This disorder has been clearly documented during labor and delivery, during cesarean sections and abortions, in patients with placenta previa, and in those engaging in orogenital sex during pregnancy or the early puerperium. The patient presents with dyspnea, chest pain, and presyncope, which may progress to hemodynamic collapse. Differentiation from other similar catastrophic events may be difficult and involves exclusion of other causes. Management involves the usual resuscitative measures and administration of a high concentration of oxygen. Moving the patient into the left lateral decubitus position or Trendelenburg position will prevent air from being ejected from the right ventricle until it is absorbed.

ACUTE LUNG INJURY IN PREGNANCY

Aspiration Pneumonitis

Since Mendelson's[117] original report of 66 cases of gastric aspiration in 44,016 deliveries between 1932 and 1945 (an incidence of 0.15%), aspiration has continued to be a major cause of maternal morbidity and mortality. Increased intra-abdominal pressure due to the gravid uterus, the inhibitory effect of progesterone on the tone of the esophageal sphincter, and the assumption of the supine position for delivery all contribute. Eating during or just before labor increases the volume of emesis.[118] Aspiration of gastric contents with pH 2.5 or lower is known to cause chemical pneumonitis and increased permeability pulmonary edema. Both in Mendelson's original report and today, about two-thirds of cases of aspiration take place in the delivery suite. Emergency endotracheal intubation of patients with obstetric crises is particularly difficult,[119] and intubation in the delivery suite fails at a rate eight times that in the general surgical population.[120] To minimize the chance of acid aspiration at intubation, oral administration of histamine-2 blockers with antacids before intubation,[120] in conjunction with a formal airway assessment, is desirable. Identified risk factors in intubation include a high Mallampati class indicating poor visibility of the posterior pharynx, a short neck, protruding maxillary incisors, and a receding mandible.[121]

Acute Respiratory Distress Syndrome

ARDS is more common in pregnancy than in the general population, with an incidence of 1 in 6000 deliveries.[122] In one obstetric intensive care unit, ARDS was the leading cause of maternal death during a 6-year period.[123] The three most common nonobstetric causes are pneumonia, sepsis, and aspiration. The 2009 influenza A (H1N1) epidemic resulted in a significant increase in the incidence of ARDS in pregnancy, generating numerous publications on the epidemiologic and management issues. Australian investigators described a series of pregnant women treated with extracorporeal membrane oxygenation, with reasonable outcome.[124] Common obstetric causes of ARDS include chorioamnionitis, amniotic fluid embolism (see Fig. 129.5), and trophoblastic embolism.[125] Transfusion-related acute lung injury is an often unrecognized, potentially life-threatening complication of blood or blood product transfusion.

Ventilator management is unaltered in pregnancy and, although pregnancy was an exclusion criterion in the ARDS Network studies, the clear benefit in nonpregnant patients supports the use of low-volume ventilatory strategies in pregnant patients, with tidal volume (6 mL/kg) based on the patient's ideal weight.[125,126] Delivery does not necessarily improve the maternal respiratory condition, and should usually be reserved for situations where benefit for the fetus is also anticipated.[127] The prognosis also appears to be similar to the nonpregnant patient,[128] although ARDS outcome is dependent on the underlying etiology.

OTHER RESPIRATORY DISEASES IN PREGNANCY

Obstructive Sleep Apnea

Pregnancy may be complicated by *obstructive sleep apnea* (OSA), potentially adversely affecting both mother and fetus.[129] Although upper airway edema may potentiate obstructive events, apnea and hypopnea are uncommon in pregnancy because of the respiratory stimulatory effect of progesterone.[130] OSA usually develops in obese patients, precipitated by the airway mucosal edema and vascular congestion that accompany pregnancy. OSA is associated with preeclampsia and gestational diabetes.[130,131] Nocturnal hypoxemia may produce poor fetal growth, although snoring alone is not associated with fetal risk.[132] Pregnant women with documented OSA are at increased risk of developing preeclampsia and preterm birth, as well as other pregnancy complications[133]; in this group, treatment with continuous positive airway pressure is safe and effective.[130]

Interstitial Lung Disease

Interstitial lung disease is usually seen in patients older than those in their childbearing years.[134] When interstitial disease exists in pregnant women, the reduced diffusing capacity may cause difficulty in meeting the increased oxygen consumption requirements of pregnancy, sometimes necessitating ambulatory oxygen therapy. Associated pulmonary hypertension, regardless of its causes, carries significant risks because cardiac output increases during pregnancy. Few data exist on the management and outcome in these patients, but restrictive lung disease appears reasonably well tolerated in pregnancy.[135,136] Labor and delivery can

increase oxygen and ventilation requirements, which may be ameliorated by regional anesthesia and supported with noninvasive ventilation.

Lymphangioleiomyomatosis and systemic lupus erythematosus may worsen as a result of pregnancy.[134] Some drug therapy used for interstitial lung disease may be acceptable during pregnancy (e.g., prednisone, azathioprine), but other therapies (e.g., cyclophosphamide, rituximab, mycophenolate mofetil) are usually avoided.[134]

Pleural Disease

Pleural effusions may accompany obstetric complications such as preeclampsia and choriocarcinoma, but many women with normal pregnancies develop small, asymptomatic pleural effusions in the postpartum period.[137] These probably develop as a result of the increased blood volume and reduced colloid osmotic pressure in pregnancy, as well as from impaired lymphatic drainage due to repeated Valsalva maneuvers during labor. Moderate-size effusions or the presence of symptoms should prompt a full clinical evaluation. The Valsalva maneuvers of labor may also produce spontaneous pneumothorax and pneumomediastinum, particularly in patients with predisposing conditions such as asthma. This diagnosis should be considered in women who develop chest discomfort and dyspnea during, or immediately following, delivery.

Lung Transplantation

Improved survival after lung transplantation has resulted in women considering pregnancy in this situation, most commonly in women with lung transplantation for cystic fibrosis. The knowledge base is increasing, and registries have been established to collect data on these patients. Prepregnancy counseling is essential, and pregnancy should ideally be avoided for a minimum of 1 year and preferably 2 years posttransplant.[138] This time will allow immunosuppressive drugs to be weaned to the lowest possible doses and reduce the likelihood of requiring increased immunosuppressive therapy for early posttransplant rejection. Immunosuppression with prednisolone, azathioprine, and calcineurin inhibitors is considered acceptable during pregnancy. Pregnancy is not associated with an increased risk of rejection in stable patients, but compared with other solid organ transplants, rejection during or soon after pregnancy is more common after lung transplantation.[139] There is a high risk of spontaneous or therapeutic abortion, but the frequency of congenital malformation is not higher than in the general population. The incidence of diabetes and preeclampsia during pregnancy posttransplant is higher than in the general population.

LUNG DISORDERS IN GYNECOLOGY

CATAMENIAL PNEUMOTHORAX

Lillington and colleagues[140] introduced in 1972 the term *catamenial pneumothorax* to describe the already reported phenomenon of spontaneous pneumothorax within 24 to 72 hours after onset of menses. It appears to account for about 2.8–5.6% of spontaneous pneumothoraces in women,[141,142] most often affecting women in the third or fourth decade of life. About 30–60% of cases are attributable to thoracic endometriosis, as judged by inspection at thoracotomy (Fig. 129.6)[143]; other cases have a more obscure etiology, however, so a number of theories have been advanced. The first theory is that, during menstruation, the absence of the normal cervical mucus plug permits an open connection between ambient air and the abdominal cavity through the uterus and fallopian tubes.[142] Air can move transdiaphragmatically through right-sided diaphragmatic fenestrations into the pleural space, as it sometimes does during abdominal laparoscopy,[140] accounting for the condition's right-sided predominance.[142] A second theory is that high levels of prostaglandin F_{2a} during menstruation cause bronchospasm with attendant air trapping and pneumothorax; however, wheezing is not a common symptom of this disorder. A third theory is that pleural blebs or bullae are more susceptible to rupture during menstruation because of hormonal changes[142,143]; however, visceral pleural leaks are rarely found at surgery (see also Chapter 110 for a full discussion).

For cases of endometriosis-associated pneumothorax, a trial of gonadotropin-releasing hormones is warranted if the phenomenon is repetitive but not life-threatening. Oral contraceptives, other progestational agents, and tubal ligation have also been used with some success. For cases not clearly associated with systemic endometriosis, thoracoscopy during menstruation serves to define the etiology and can be used to achieve pleurodesis.[140]

ENDOMETRIOSIS

Endometriosis probably affects about 10% of women, shows no clear ethnic differences in prevalence, and is most commonly diagnosed at 30 to 34 years of age.[144] Although pelvic pain, dysmenorrhea, and infertility are its predominant manifestations, atypical locations, including diaphragmatic, pleural, and endobronchial sites, have been

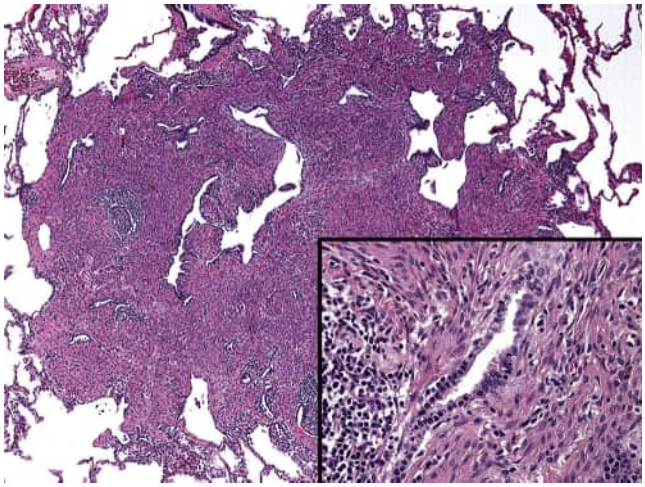

Figure 129.6 Pulmonary endometriosis. Wedge resection of right upper lobe subpleural nonencapsulated lesion in a 43-year-old woman with a history of pelvic endometriosis and recurrent pneumothoraces with menstrual cycles. (H&E stain; original magnification ×40.) *Inset,* The discrete nodule is composed of endometrial stromal cells admixed with endometrial glands. (H&E; original magnification ×200.) (Courtesy Dr. Gerald Berry, Stanford University.)

documented. As described previously, endometriosis can result in recurrent catamenial pneumothorax, which is its most common thoracic presentation (see Fig. 129.6). In one review of 110 cases with thoracic endometriosis, catamenial pneumothorax was the presenting symptom in 73% of cases, followed by hemothorax in 14% and hemoptysis in 7%.[144] Thoracic endometriosis has also been associated with right-sided pleuritic chest pain and pleural effusions. Inspection at thoracotomy or thoracoscopy typically reveals blue-brown nodules on the pleural surface, sometimes described as "gunshot" lesions.[145] The absence of known pelvic endometriosis does not exclude the diagnosis because only 20–70% of patients have associated pelvic disease. The diagnosis is suspected on clinical grounds because CT is not specific. Thoracoscopy can be diagnostic, although it may need to be performed during menses for maximum sensitivity.[146] Rarely, the endometriosis deposits are found in lung parenchyma, accounting for the catamenial hemoptysis. Most pleural and diaphragmatic disease is thought to arise from transdiaphragmatic spread from retrograde menses, even when abdominal disease is not evident. Massive ascites is sometimes related, although only 27 cases have been reported.[147] Pneumothoraces may be attributed to cyclical sloughing of tissue on key surfaces, such as the visceral pleura,[148] or to air trapping from airway involvement or compression.[149] Pulmonary parenchymal disease may be embolic in origin, as is presumed in the case of rare cases of central nervous system endometriosis.[149a] The diagnosis can be established only by biopsy showing the characteristic ectopic endometrial glands in involved sites. Medical therapy consists of progestational agents or gonadotropin-releasing hormones; surgical approaches include excision, local laser ablation, or pleurodesis.

LYMPHANGIOLEIOMYOMATOSIS

Lymphangioleiomyomatosis is a rare disorder that afflicts predominantly premenopausal women.[150] The most common presenting event is a pneumothorax, reported in 86.5% of patients in the National Heart, Lung, and Blood Institute registry.[150] It is fundamentally a low-grade neoplasm of smooth muscle cells that results in functional obstruction of vessels, lymphatics, and airways. (See Chapter 97 for a complete discussion of lymphangioleiomyomatosis.) Involvement of pulmonary vascular structures is responsible for the hemoptysis, whereas lymphatic obstruction accounts for the chylous effusions. Mediastinal and retroperitoneal lymphatic proliferation may be a feature of the disease as well. Lymphangioleiomyomatosis is also associated with renal angiomyolipomas, another hamartomatous disorder, and with tuberous sclerosis. The pathogenesis involves activation of the mTOR pathway acting synergistically with the estrogen-stimulated extracellular-signal-regulated kinase pathway.[151] Conventional therapy has included oophorectomy or progestational agents, mainly medroxyprogesterone acetate. Lung transplantation has been performed in more than 60 patients with this disorder, but it has clearly recurred in some of them. Sirolimus, an mTOR inhibitor, has been shown to improve lung function and symptoms, presumably by suppressing signaling pathways involved.[152] Data regarding the use of sirolimus in pregnancy are limited, but case reports have been published with successful outcome.[153]

GESTATIONAL TROPHOBLASTIC DISEASE

Gestational trophoblastic disease is a group of intrauterine tumors arising from nonviable fertilized tissue. These tumors may be benign (hydatidiform mole) or malignant (choriocarcinoma). The major pulmonary complication of this entity is trophoblastic embolism. In one series, however, only 2.6% of 189 patients with hydatidiform mole had an embolic event, so most episodes of respiratory distress in such patients are not caused by embolism but, rather, pulmonary edema, anemia, or another complicating event.[154] Embolization, when it happens, is most common at the time of evacuation of the mole.

OVARIAN HYPERSTIMULATION SYNDROME

The ovarian hyperstimulation syndrome can result from the use of exogenous gonadotrophins to stimulate ovulation for in vitro fertilization. This entity has been associated with complications,[155] including ovarian cysts, bilateral pleural effusions, ascites, and intravascular volume depletion. Hypovolemic shock, renal failure, and ARDS may result. PE and upper limb or superior venal caval thrombosis may result from the hypercoagulable state induced by estrogens and intravascular volume depletion. Upper limb predominance may be related to higher concentrations of estrogens drained from ascites through lymphatic ducts.[156] Women with medical comorbidities who are older than 40 years are at most risk of developing life-threatening complications.[157] The mechanism of the effusions is unclear but is likely related to increased permeability due to release of vasoactive mediators, of which vascular endothelial growth factor appears to be the most important.[158] Evidence points to mutations in the follicle-stimulating hormone receptor as etiologic in at least some cases.[159] Treatment is supportive and involves maintaining intravascular volume, thoracentesis when required for respiratory compromise from abundant pleural effusion(s), and thromboprophylaxis.

Key Points

- Normal pregnancy is associated with profound alterations in respiratory and cardiovascular physiology, which—although designed for maternal and fetal well-being—may exacerbate underlying cardiopulmonary conditions or cause new ones.
- Major physiologic perturbations found in normal pregnancies include (1) an increase in central drive to breathe, with resulting changes in P_{CO_2} (28 to 32 mm Hg) and pH (7.40 to 7.47) and (2) an increase in both maternal blood volume, of about 2 L (40%), and cardiac output, after 25 to 32 weeks of gestation, of 30–45%.
- The most common pulmonary disorder of pregnancy is asthma, but the effects of pregnancy on asthma are variable, with about 40% remaining unchanged and the rest either worsening or improving.
- The risks of poorly controlled asthma for both mother and fetus during pregnancy far outweigh the risks of drug therapy. Some standard drugs are safer than others (see Table 129.1) and should be selected whenever possible.

- Cystic fibrosis and infectious pneumonias have all been linked with adverse fetal and maternal outcomes, the risk of which depends largely on the severity of the complicating disorder. Prepregnancy counseling and avoidance of certain antimicrobial drugs (as noted in Table 129.1) are strongly recommended.
- Pulmonary edema may develop during pregnancy in women with underlying heart disease, especially valvular stenosis, cardiomyopathy, and preeclampsia. Because the causative mechanisms differ, so does specific therapy.
- Pulmonary embolism is a leading cause of maternal mortality. When indicated during pregnancy, low-molecular-weight heparins are safe for both treatment and prevention; warfarin is contraindicated. Ventilation-perfusion imaging, computed tomography pulmonary angiography, and magnetic resonance imaging can be used as needed.

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130 THE RESPIRATORY SYSTEM AND NEUROMUSCULAR DISEASES

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INTRODUCTION

Gas exchange between the atmosphere and the human body depends not only on the lungs but also in large part on the function of the "ventilatory pump," which consists of the respiratory control centers located in the brain, the bony rib cage, diaphragm, and intercostal, accessory, and abdominal muscles. A wide variety of neuromuscular disorders can result in dysfunction of the ventilatory pump that in turn can lead to respiratory failure, pneumonia, and even death. Breathing disorders are recognized as the leading cause of mortality in neuromuscular disease,[1,2] and appropriate interventions can prevent complications and prolong life in individuals with neuromuscular disease affecting the respiratory system.[3] Diseases of the chest wall are discussed in Chapter 131.

FUNCTIONAL ANATOMY OF THE RESPIRATORY SYSTEM

The ventilatory pump is designed to bring oxygen into the body to fuel energy generation and remove carbon dioxide as a waste product of cellular metabolism. The system is made up of the cortex of the brain that controls voluntary breathing; the brainstem, which is involved with automatic breathing; the spinal cord and motor neurons that transmit nerve impulses; the respiratory muscles that are the effectors of the system; and a complex system of feedback[4] receptors and nerves that regulate ventilation (Fig. 130.1). The system is remarkably flexible and can precisely maintain carbon dioxide and acid-base balance despite encountering large variations in metabolic demands that result from the activities of daily living. The following is a discussion of each of the components of this complex network.

CENTRAL NERVOUS SYSTEM

Voluntary Breathing Controllers

Voluntary breathing is controlled by signals from the cerebral cortex. Centers located within the parietal cortex send volitional signals that initiate inspiration and expiration.[4] These cortical areas project to the motor neurons in the spinal cord via the corticospinal tracts. The corticospinal tracts are separate pathways from the reticulospinal pathways that connect the central automatic breathing centers to the motor neurons.

Automatic Breathing Controllers

Automatic breathing is controlled by a complex system that includes respiratory centers in the pons and medulla, nerve tracts in the lower brainstem, the reticulospinal pathways in the spinal cord, and the feedback mechanisms that are both chemical and mechanical in nature. There are thought to be three centers that generate the rhythm and drive to breathe, one located in the pons and two in the medulla. More detailed reviews of this topic are available.[5]

Spinal Cord

The spinal cord and motor nerves conduct nerve impulses from the cortex and brainstem to the anterior horn cells of the motor neurons supplying the respiratory muscles. As noted previously, the nerve fiber tracts in the spinal cord responsible for voluntary (corticospinal tract) and automatic (reticulospinal tract) breathing are separate within the spinal cord.[6] The fibers in both of these tracts travel through the spinal cord to synapse with the lower motor neurons.

PERIPHERAL NERVOUS SYSTEM

Lower Motor Neurons

The lower motor neurons have their cell bodies in the spinal cord (anterior horn cell) and exit the spinal cord to become

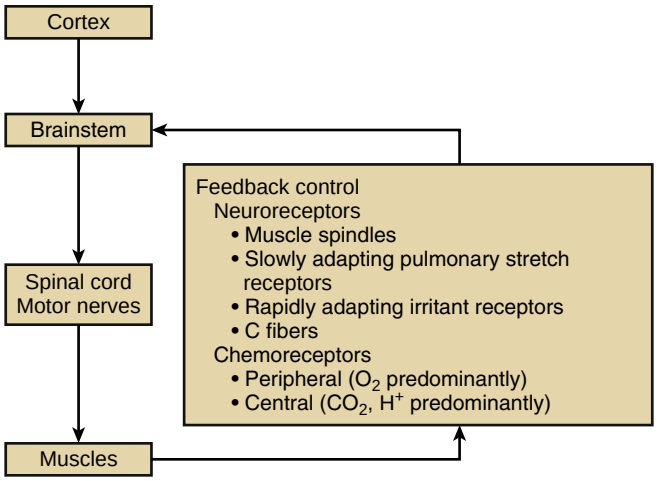

Figure 130.1 Respiratory system feedback control. Neuromechanical respiratory system flowchart indicates the neuromuscular pathways and sites of feedback control.

the spinal nerve roots and the nerves that supply the respiratory muscles. When the nerves arrive at the muscle, they divide into branches known as *twigs* that, upon reaching the muscle fiber, further divide into bulbous projections called *boutons* that apply themselves to the muscle membrane at a specialized anatomic junction called the *motor end plate.* These boutons contain acetylcholine, which is the chemical transmitter that serves to excite the muscle to contract. With nerve firing, there is release of acetylcholine at the motor end plate into the cleft between the nerve and the muscle. The acetylcholine binds to receptors on the muscle side of the motor end plate, which results in a *suprathreshold excitatory end plate potential* and depolarization of the muscle membrane muscle action potential then results in contraction of the muscle fiber.

Total Lung Capacity

Respiratory Muscles. The respiratory muscles are the mechanical effectors of the breathing system. They are often divided into three major groups: (1) the inspiratory muscles, (2) the expiratory muscles, and (3) the accessory muscles of respiration. The muscles that maintain patency of the upper airway during the respiratory cycle are sometimes also considered muscles of respiration because of their close interaction with the other respiratory muscles.

The diaphragm is the major muscle of inspiration and accounts for approximately 70% of the inhaled tidal volume in the normal individual (Fig. 130.2). Contraction of the diaphragm results in a downward piston motion of the muscle. The resultant increase in abdominal pressure pushes the lower ribs up and out along the *zone of apposition,* further expanding the thoracic cage.[7] The innervation of the diaphragm is via the phrenic nerve that originates from cervical nerve roots 3 through 5.

The intercostal muscles are thin sheets of muscular fibers that run between the ribs in the costal spaces.[8] There are two sheets of muscle fibers, the external and internal intercostals. (Fig. 130.3). The external intercostals, which are on the outside (external) of the other muscles, function to expand the rib cage during inspiration. The internal

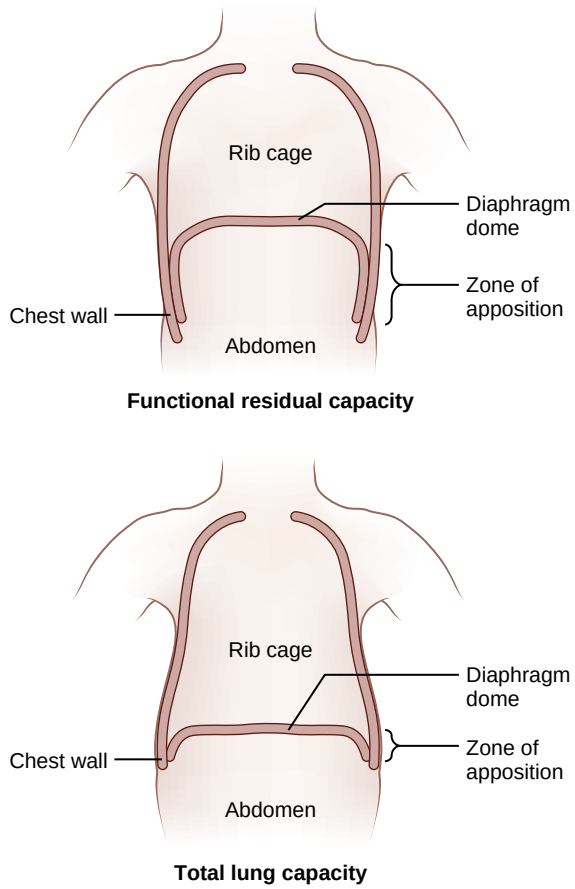

Figure 130.2 Diaphragmatic positions at rest *(top)* and at full contraction *(bottom).* At functional residual capacity *(top),* the diaphragm lies within the chest with a zone of apposition along the chest wall. At total lung capacity (*bottom),* the contracted diaphragm has displaced abdominal contents and, via the increase in abdominal pressure, has expanded the chest wall outward.

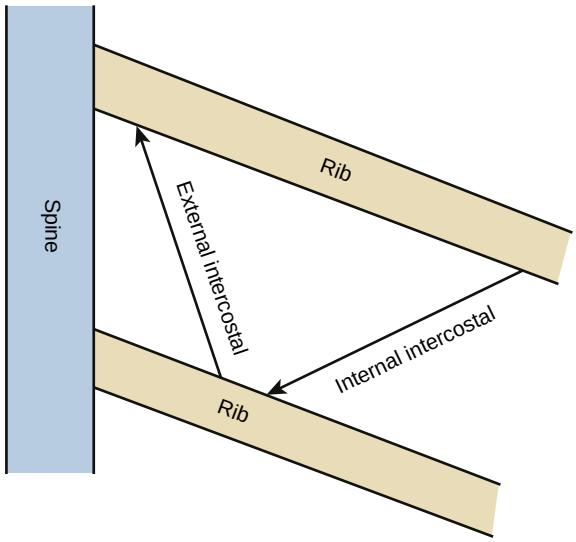

Figure 130.3 Actions of the intercostal muscles on the ribs. Contraction of the external intercostals results in an upward and outward movement of the ribs during inhalation. Contraction of the internal intercostals results in a downward and inward movement of the ribs during exhalation.

intercostals are deeper (internal) and function to decrease rib cage size during expiration. The orientation of the muscle fibers with respect to the ribs and the spinal column where the rib rotates up or down at the costovertebral joint results in the increase or decrease in the size of the rib cage; as the muscles contract, the greater torque is applied to the point more distal from costovertebral rotating joint at the spine. In the case of the external (inspiratory) intercostal muscles, the distal attachment is at the outside portion of the lower rib compared to the upper rib, so contraction tends to pull the lower rib upward and outward thereby expanding the chest. Although there is a torque on the upper rib, it is smaller so that the overall effect is to expand the chest wall. For the internal (expiratory) intercostal muscles, the distal attachment is at the inner portion of the upper rib and thus contraction of the muscle tends to pull the upper rib down and in, thereby decreasing the chest. Innervation of the intercostals is via the intercostal nerves originating from the thoracic spinal nerve roots.

The abdominal muscles (rectus abdominis, internal oblique, external oblique, and transversus abdominis) serve a number of functions in respiration that mainly assist expiration but can also function in inspiration. The internal and external obliques and the transversus abdominis result in an inward movement of the abdominal wall that displaces the diaphragm upward into the thoracic cavity and assists exhalation. The rectus abdominis as well as the internal and external obliques pull the lower rib cage caudally and thereby increase pleural pressure and exhalation. The abdominal muscles also may play a minor role in inspiration[9]; if their contraction reduces lung volume below function residual capacity, abdominal muscles can store elastic recoil energy in the chest wall that then assists expansion of the chest wall during the next inspiration. This "inspiratory assist" may be seen during exercise when expiration becomes active.

The accessory muscles of respiration (sternocleidomastoid, scalenes, trapezii, latissimus dorsi, platysma, and pectoralis major and minor muscles) can expand the rib cage and assist inspiration during situations of increased ventilatory demand such as during exercise or when other inspiratory muscles are impaired as in tetraplegia or COPD. Some of these accessory muscles function during minimal exertion and during quiet tidal breathing, even in normal persons.[10]

The muscles of the upper airway are also considered to be muscles of respiration because they maintain patency of the upper airway and allow air to flow into and out of the lungs without interruption. Some of these also participate in protection of the lower airway during swallowing, a key function in the defense of the respiratory system. The upper airway muscles include the abductors of the vocal cords, the palatal elevators, retractors of the tongue, and dilators of the nares. These muscles are innervated by cranial nerves V, VII, and IX through XII. The central control centers for these muscles are the same as those described previously for the more commonly considered ventilatory muscles.

CONTROLLER FEEDBACK

The respiratory control mechanisms depend on both neural and chemical receptors found in peripheral and central sites. The automatic respiratory centers in the brainstem respond to feedback from these receptors and adjust neural output to the ventilatory and upper airway muscles that expand the chest wall and maintain upper airway patency (see Fig. 130.1).

Neural receptors are present in the upper airway, respiratory muscles, lungs, and pulmonary vessels. Once stimulated, these receptors project signals to the central respiratory controller via the vagus nerve. The respiratory centers then adjust their output to the respiratory muscles to alter ventilation and modulate reflexes such as cough and sneeze. There are several different types of neural receptors. *Muscle spindles* and *slowly adapting pulmonary stretch receptors* predominantly respond to changes in thoracic cage and lung volume, respectively. As the chest wall and lung inflate, these receptors are stretched and dampen the output from the inspiratory centers in the medulla. These receptors are involved in the Hering-Breuer reflex in which inspiration is halted as lung volume increases.[11] They are also essential for initiating cough. *Rapidly adapting irritant receptors* respond to changes in lung volume, to chemical stimuli such as histamines and prostaglandins, and to noxious stimuli. *C fibers* in the airways and lung are stimulated by chemical stimuli in the local environment. The C fibers likely mediate the hyperventilation seen in normoxic circumstances in a number of pulmonary disorders such as asthma, pulmonary embolism, pneumonia, and pulmonary edema.

Chemical receptors or *chemoreceptors* are located both peripherally as well as in the central nervous system. The *peripheral chemoreceptors*, which include the carotid and aortic bodies, are the primary site for sensing low levels of *arterial oxygen pressure* (arterial P_{O_2}) but also respond to a lesser extent to changes in *arterial carbon dioxide pressure* (arterial P_{CO_2}) and pH. They are stimulated when the arterial P_{O_2} falls below 75 mm Hg as well as when the arterial P_{CO_2} increases and pH decreases. Whereas both receptors stimulate ventilation in hypoxia, the aortic chemoreceptors are more important in infants and the carotid receptors are more important in adults.[12] Once stimulated, the carotid bodies send impulses via cranial nerve IX to the nucleus tractus solitarius where neurotransmitters are released that increase ventilation.[13] Although the control of ventilation during exercise is not completely understood, the predominant stimulus for increased ventilation is thought to arise from the peripheral receptors. It is postulated that additional peripheral receptors exist that are yet to be identified because the hyperventilatory response of exercise cannot be fully accounted for by the carotid bodies.[14] The *central chemoreceptors* are crucial in the adjustments of ventilation to acid-base disturbances and arterial P_{CO_2}. There are four groups of chemosensitive neurons in the brainstem: the locus ceruleus, the nucleus tractus solitarius, the midline raphe, and the ventrolateral quadrant of the medulla. The central chemoreceptors are responsible for most of the response to carbon dioxide. They respond to increases in arterial P_{CO_2} by their detection of the fall in pH of the cerebrospinal fluid associated with an increase in cerebrospinal fluid arterial P_{CO_2}, which closely follows an increase in serum arterial P_{CO_2}. Of note, once the drop in pH is detected, it appears that

Table 130.1 Diseases of the Central Nervous System Associated With Respiratory Dysfunction

Cerebral Cortex	Brainstem/Basal Ganglia	Spinal Cord
Stroke	Stroke	Trauma
Neoplasm	Neoplasm	Infarction or hemorrhage
Cerebral degeneration	Poliomyelitis	Demyelinating disease
Seizures	Central alveolar hypoventilation	Disc compression
	Progressive bulbar palsy	Syringomyelia
	Multiple system atrophy	Tumor
	Anoxic encephalopathy	Epidural abscess
	Encephalitis	
	Multiple sclerosis	
	Parkinson disease	
	Chorea	
	Dyskinesias	

Table 130.2 Diseases of the Peripheral Nervous System Associated With Respiratory Dysfunction

Motor Nerves/ Anterior Horn Cell	Neuromuscular Junction	Myopathies
Acute idiopathic polyneuropathy (Guillain-Barré syndrome)	Myasthenia gravis	Muscular dystrophies
Motor neuron disease	Lambert-Eaton myasthenic syndrome	Myotonic dystrophy
Amyotrophic lateral sclerosis	Toxins	Dermatomyositis
Spinal muscular atrophy	Botulism	Polymyositis
Primary lateral sclerosis	Snake venoms	Inclusion body myositis
Critical illness neuropathy	Scorpion bites	Glycogen storage diseases
Vasculitides	Shellfish	Pompe disease
Toxins (e.g., lithium, arsenic, gold)	Crab poisoning	Forbes-Cori disease
Metabolic	Drugs	Thick filament myopathy
Diabetes	Antibiotics	Mitochondrial myopathy
Porphyria	Neuromuscular junction blockers	Nemaline body myopathy
Uremia	Anticholinesterase inhibitors	Severe hypokalemia
Diphtheria	Corticosteroids	Hypophosphatemia
	Lidocaine	
	Quinidine	
	Lithium	
	Antirheumatics	

the parasympathetic nervous system is important in the response to cerebrospinal fluid pH changes because inhibition of acetylcholine transmission can abolish the central pH response in animals.

DISEASES AFFECTING THE RESPIRATORY SYSTEM

The diseases of the neurorespiratory system can be organized most logically in the framework of functional anatomy. Diseases of the central nervous system known to affect the respiratory system are listed in Table 130.1 and those affecting the peripheral nervous system are listed in Table 130.2.

CENTRAL NERVOUS SYSTEM DISEASES

Cortical and Brainstem Disorders

Diseases of Voluntary Breathing. The pathways that connect the voluntary respiratory centers of the cortex with spinal motor neurons (corticospinal tracts) can be affected in a number of disorders. Midpontine strokes can damage the corticospinal tracts and cause what is known as the *locked-in syndrome,*[15] a syndrome with total paralysis with the exception of eye movement. Because injury to the reticulospinal tracts causes loss of volitional but not automatic breathing, the response to automatic breathing is preserved. This syndrome is most commonly due to ischemic stroke but can be due to pontine tumor, central pontine myelinolysis, high cervical demyelination, syphilitic arteritis, and head injury. Extrapyramidal disorders such as parkinsonism can also affect voluntary breathing.[16] In these disorders, patients have less ability to alter their breathing pattern voluntarily. They also may demonstrate periodic breathing or a Cheyne-Stokes respiratory pattern.

Diseases of Automatic Breathing. Automatic breathing but not voluntary breathing is classically disrupted in central alveolar hypoventilation, otherwise known as *Ondine's curse,*[17] caused by injury to the automatic respiratory centers in the brainstem. Because automatic triggering controls breathing during sleep, individuals with central alveolar hypoventilation develop central sleep apnea. Congenital central alveolar hypoventilation is a rare genetic disorder affecting infants and children, although it has now been described in adults as well.[17] Acquired central alveolar hypoventilation can result from unilateral or bilateral medullary infarction, bulbar poliomyelitis, or bilateral cervical tractotomy performed to control chronic pain. Although disorders of the neurorespiratory system generally lead to hypoventilation and the need for ventilatory support, diseases of the automatic respiratory centers in the brainstem can also lead to hyperventilation. This may be caused by diseases such as central nervous system infection or tumor[18] or by stimulation of an otherwise normal autonomic respiratory center by fever, sepsis, pain, pregnancy, medications such as progesterone or salicylates, or high altitude. A variety of irregular breathing patterns has also been associated with central nervous system disease including Cheyne-Stokes respiration and ataxic breathing.

Diseases of the Spinal Cord

Spinal Cord Injury. *Spinal cord injury* (SCI) is most commonly due to traumatic injury caused by motor vehicle accidents, falls, sports accidents, and gunshot wounds. In the United States, an estimated 250,000 individuals have suffered significant SCI; the incidence is approximately 12,000 incident cases per year with 78% of the injuries seen in males (National Spinal Cord Injury Statistical Center: http://www.spinalcord.uab.edu). Respiratory complications including atelectasis, pneumonia, and respiratory failure are the leading cause of morbidity and mortality for individuals with SCI.[19] Immediately following acute SCI, a number of physiologic changes can affect the respiratory system and predispose to respiratory complications. These aberrations include (1) cough inefficiency due to expiratory

muscle weakness, (2) ciliary dysfunction and mucous hypersecretion possibly due to impairment of the peripheral autonomic nervous system, (3) glottic dysfunction or gastric hypomotility increasing the risk of aspiration, (4) bronchial hyperreactivity due to sympathectomy, and (5) loss of consciousness at the time of the injury, increasing the risk of aspiration.[20,21]

Acute respiratory failure immediately after the injury may be due to direct disruption of respiratory muscle innervation (cervical cord injury), aspiration at the scene due to loss of consciousness, pulmonary edema, or other traumatic injuries to the chest or head. Many individuals with SCI are intubated at the scene of the accident or shortly thereafter, a valuable step that can reduce the likelihood of massive aspiration and other complications as long as care is taken to stabilize the C-spine. Further preventive measures include encouragement of deep breathing and cough, frequent changes of position, postural drainage, assisted cough (manual or mechanical), and bronchoscopy when other measures fail to clear the airways. Patients with SCI are at high risk for venous thromboembolism, with the greatest risk 3 days to 2 weeks after injury. Prophylaxis for deep venous thrombosis is highly recommended during the initial hospitalization.

The extent of respiratory muscle impairment following SCI mainly depends on the level and severity of the spinal injury because the function of respiratory muscles innervated below the level of the cord injury is lost. The innervation of the respiratory muscles is shown in Table 130.3. The overall pattern of pulmonary function abnormality is one of restriction.[22] In the first few months to a year following the initial SCI, there is a significant improvement in lung volumes and maximal inspiratory and expiratory pressures,[23] possibly due to resolution of spinal cord edema and/or strengthening of the diaphragm and accessory muscles of inspiration.

In general, the higher the SCI, the more likely that ventilatory assistance will be needed.[24] Treatment of ventilatory failure following SCI can be accomplished by invasive (tracheostomy) or noninvasive (mask or mouthpiece) methods.[25] Many individuals are ventilated through a tracheostomy tube for some time after their injury; however, transfer to noninvasive means can often be achieved even for those requiring full-time ventilatory support. The choice of invasive versus noninvasive ventilation is determined by the degree of local expertise with these forms of ventilation as well as by patient preference. For those with high cervical SCI (C1–2) and intact phrenic nerve function, diaphragm pacing with electrodes directly placed on the phrenic nerve by video-assisted thoracoscopic surgery can provide ventilatory support. Placing pacing wires directly in the diaphragmatic muscle via a laparoscopic approach is also a means of providing ventilatory support. It should be noted that those with diaphragm pacemakers implanted still need a tracheostomy in place to avoid airway obstruction during sleep owing to the absence of the normal neurologic coordination of diaphragm contraction and upper airway dilation during inspiration. Although traumatic SCI is the major cause of spinal cord pathology, other causes include vascular accidents, demyelinating diseases (multiple sclerosis, transverse myelitis), syringomyelia, tumors, and epidural abscess (see Table 130.1).

Table 130.3 Respiratory Muscles and Their Innervation

Muscle Group	Spinal Cord Level	Nerve(s)
INSPIRATORY MUSCLES		
Diaphragm	C3–5	Phrenic
Parasternal intercostals	T1–7	Intercostal
Lateral external intercostals	T1–12	Intercostal
Scalenes	C4–8	Cervical (deep branches)
Sternocleidomastoids	Above spinal cord	Spinal accessory
EXPIRATORY MUSCLES		
Lateral internal intercostals	T1–12	Intercostal
Rectus abdominis	T7–L1	Lumbar
External and internal obliques	T7–L1	Lumbar
Transversus abdominis	T7–L1	Lumbar
UPPER AIRWAY MUSCLES		
Muscles of mastication	–	CN V, VII
Laryngeal and pharyngeal	–	–
Abductors	–	CN IX–XII
Adductors	–	CN IX–XII

CN, cranial nerve.

Ventilator dependence in patients with SCI is more common with high (cervical) SCI. Because the diaphragm is the major muscle of inspiration (C3–5 spinal nerve roots), those with lesions at C3 and above invariably require ventilatory support and are at the highest risk of respiratory complications.[24] Those with injuries between C3 and C5 vary in their requirements for ventilatory support. Even if they require ventilation initially, these individuals may become independent of ventilatory support eventually. The risk for ventilator dependence in this group of patients is greatest for those with injury close to C3 or age older than 50 years.[26] Individuals with lesions below C5 almost always become independent of continuous ventilator support. In contrast to inspiratory muscle function, expiratory muscle function is impaired after all levels of cervical cord injury resulting in expiratory muscle weakness and ineffective cough. Because an effective cough depends in large part on abdominal and intercostal muscle function (spinal nerve roots T1–L1), cervical, thoracic, and even some high lumbar SCIs can impair the ability to cough and clear secretions. Therefore, measurement of cough function in these patients is very important, as is described later.

Other Respiratory Effects of Spinal Cord Injury. For unknown reasons, the frequency of sleep apnea appears to be increased by as much as fourfold in patients with SCI compared to a normal population of similar age.[20] A sleep study should be considered when symptoms of nocturnal hypoventilation such as morning headache, daytime hypersomnolence, or unexplained nocturnal awakenings are present or when daytime hypercarbia (arterial P_{CO_2} >

45 mm Hg), unexplained right heart dysfunction, or *forced vital capacity* (FVC) less than 50% predicted are present.[27] Bronchial hyperreactivity and bronchial hypersecretion are also present in some individuals following SCI, likely due to interference with normal autonomic control of the airways after injury.[28]

PERIPHERAL NERVOUS SYSTEM DISEASES

Diseases of Motor Nerves or Anterior Horn Cells and Diseases of the Neuromuscular Junction

Disorders of the motor nerves and the *neuromuscular junction* (NMJ) can arise acutely as in acute inflammatory polyneuropathy (Guillain-Barré syndrome) or botulinum toxicity or can arise more chronically as in motor neuron disease (e.g., *amyotrophic lateral sclerosis* [ALS]) or myasthenia gravis (see Table 130.2). The level of motor nerve root involvement dictates the effects of the disorder on the respiratory system.

Acute Diseases Affecting Motor Nerves

Acute Immune-Mediated Polyneuropathy. Acute immune-mediated polyneuropathy, also referred to as Guillain-Barré syndrome, is a heterogeneous group of diseases now thought to be caused by antiglycolipid antibodies.[29] Acute idiopathic demyelinating polyneuropathy is the most common form, making up about 85–90% of cases. It is an acute progressive process characterized by symmetrical, ascending muscle weakness progressing over a 2-week period and associated with loss of deep tendon reflexes. It is thought that an antecedent viral infection induces an immune response to viral epitopes that then cross-react with lipid components of the peripheral nerve.[30] The process usually starts in the lower extremities but may start primarily in the arms or the face, head, and neck (Miller-Fisher variant).[31] Acute idiopathic demyelinating polyneuropathy affects the respiratory system by causing (1) weakness of the upper airway muscles, (2) weakness of the inspiratory and expiratory muscles, and (3) secondary complications such as pneumonia or pulmonary embolism.[32] Approximately 25–50% of patients develop respiratory insufficiency severe enough to necessitate intubation and mechanical ventilation.[33] A number of variables used to predict impending respiratory failure and the need for mechanical ventilatory support have been used, including FVC, *maximal inspiratory pressure* (MIP), *maximal expiratory pressure* (MEP), and nocturnal desaturation. Generally accepted guidelines for intubation and mechanical ventilation include an FVC less than 15 mL/kg, an FVC less than 1 L, a decline in FVC to 50% or less of the normal predicted value for that individual, or an MIP of 30 cm H_2O or less.[32] FVC and MIP should be monitored frequently (multiple times per day depending on rapidity of progression). With rapidly progressive disease, the *intensive care unit* (ICU) is considered the best location for monitoring. Absolute indications for intubation include impaired consciousness, respiratory or cardiac arrest, shock, arrhythmias, blood gas alterations, or bulbar dysfunction with confirmed aspiration.[32] Noninvasive ventilation is generally not an option for these individuals because they are at a high risk for aspiration due to bulbar muscle involvement. Successful extubation may be achieved once treatment such as steroids, immune globulin, and plasmapheresis is begun and respiratory muscle strength returns.[33] Until respiratory muscle strength returns, scrupulous supportive ICU care including tracheostomy for prolonged mechanical ventilation and prophylaxis to prevent deep venous thrombosis is required to prevent complications such as ventilator-associated pneumonia, sepsis, and pulmonary embolism.

Poliomyelitis. Poliomyelitis is a viral disease affecting the anterior horn cell and motor nerve caused by a human enterovirus. Significant epidemics with frequent respiratory complications began to appear in the United States and Western Europe during the 20th century. Owing to improved sanitation and vaccine development, polio is no longer a major public health issue in the developed world. However, in the developing world, acute infections still happen.

In the developed world, the major health issue arising from polio currently is the postpolio syndrome, in which new weakness develops in survivors of the polio epidemics of the mid-20th century.[34,35] The cause of progressive neurologic deterioration in postpolio syndrome is unknown. Theories of pathogenesis suggested include (1) progressive degeneration of reinnervated motor units, (2) persistence of poliovirus in neural tissue, or (3) induction of autoimmunity with subsequent destruction of neural structures.[36] The average time to onset from the time of the initial infection is 35 years but ranges from 8 to 71 years. A high percentage of polio survivors, between 20% and 60% of individuals, complain of new muscle weakness.[36] Although the exact incidence of respiratory system involvement in the postpolio syndrome is not known, sleep-disordered breathing is common and noninvasive nocturnal ventilation can be highly effective.[37] Fortunately it appears that frank hypoventilation associated with the postpolio syndrome is unusual.[38]

Chronic Diseases Affecting Motor Nerves

Amyotrophic Lateral Sclerosis. ALS is a progressive neurodegenerative disease with no known cure. The usual clinical presentation is that of an individual with gradually progressive asymmetrical weakness associated with hyperreflexia due to upper motor nerve involvement and muscle fasciculations due to lower motor nerve involvement. Like most neurologic diseases, ALS has no direct effect on the lung; however, it significantly affects the upper airway, chest wall, and diaphragm, thereby impairing respiratory muscle function. Indeed, ALS affects all of the major muscle groups of the respiratory system, including (1) upper airway muscles leading to abnormal swallowing and inadequate cough, (2) expiratory muscles leading to inadequate cough, and (3) inspiratory muscles leading to inadequate ventilation. Therefore, all patients with ALS are at significant risk for respiratory complications. Respiratory failure, the leading cause of death in this population, has also been reported as the initial clinical presentation of ALS. Patients may complain of dyspnea, difficulty managing secretions, or inability to cough effectively. Monitoring pulmonary function in the outpatient setting is crucial. The FVC is the most commonly used measurement and has prognostic significance.[39] MIP and MEP, as well as sniff nasal inspiratory pressure, have also been used. Attention must be given to

glottic and cough function as well because aspiration and pneumonia are significant contributors to morbidity and mortality.[39] Sleep-disordered breathing is very common in ALS, and *noninvasive positive-pressure ventilation* (NPPV) has been used both at night and, as the disease progresses, during the day to improve quality and duration of life.[40–43] Patients often have difficulty managing secretions owing to swallowing dysfunction. Secretions can be reduced by using anticholinergic agents,[43] by low-dose irradiation of salivary glands,[44] or by injecting the glands with botulinum toxin.[45] As ALS progresses, NPPV ceases to be effective and a decision needs to be made concerning the appropriateness of tracheostomy and long-term invasive ventilation. Although tracheostomy can prolong survival substantially,[46] it does not alter the progression of the disease and patients ultimately become completely paretic. Due to different cultural approaches, rates of invasive ventilation vary substantially among countries.[47]

Neuromuscular Junction Diseases

Myasthenia Gravis. Myasthenia gravis is the most common disease affecting neuromuscular transmission. It is an autoimmune disease characterized by an antibody-mediated immune attack directed at acetylcholine receptors and/or receptor-associated proteins in the postsynaptic membrane of the NMJ. It causes weakness of several muscle groups, including the respiratory muscles. The respiratory muscles are particularly susceptible to fatigue during the severe, potentially life-threatening exacerbations known as *myasthenic crises*.[48] The clinical considerations during myasthenic crisis are very similar to those for acute idiopathic demyelinating polyneuropathy noted earlier, and the indications for intubation are the same.[32] Acute treatment of myasthenic crisis focuses on rapid therapies including intravenous immunoglobulin as well as plasmapheresis and corticosteroid therapy.[49,50] Assiduous attention to respiratory care provides support of the patient, allowing time for therapy of the underlying myasthenia to be effective.

Myasthenia gravis can also arise as a paraneoplastic syndrome in association with thymoma. It has been estimated that approximately 15% of all patients with thymoma will exhibit myasthenia gravis. Removal of the thymoma may result in amelioration of the myasthenia symptoms. Predictors of improvement after thymectomy have been reported to be age younger than 35 years, duration of symptoms less than 24 months, and absence of perioperative steroid use.[51]

Lambert-Eaton myasthenic syndrome (LEMS) is a myasthenic syndrome associated with small cell lung cancer; the myasthenia can affect the respiratory muscles in a fashion similar to that of myasthenia gravis. In patients with small cell lung cancer, LEMS may be present in approximately 3% of cases.[52] However, in patients with LEMS, as many as 50–60% will have a tumor, almost always a small cell lung cancer. The small cell lung cancer may be occult and should be sought for up to 5 years after the diagnosis of LEMS. LEMS is thought to be due to autoantibodies directed against presynaptic voltage-gated calcium channels,[53] thereby interfering with synaptic function. These voltage-gated calcium channels may be shared by the neuroendocrine cells of the small cell lung cancer, thus explaining the association of the two conditions. Although respiratory involvement is often a late finding, frank respiratory failure can be a manifestation of LEMS,[54] and this disorder should be considered in individuals with unexplained neuromuscular weakness. Although LEMS shares a similar pathophysiologic mechanism with myasthenia gravis, the clinical presentation is different; LEMS is characterized by (1) an increase in the compound muscle action potential with repetitive nerve stimulation, a feature not seen in myasthenia, (2) more frequent presence of proximal leg weakness, which is worse in the morning, (3) greater autonomic dysfunction, and (4) frequent association with malignancy.[55]

Botulism. Botulism is a neuroparalytic syndrome caused by a toxin produced by the gram-positive bacterium *Clostridium botulinum*, which blocks acetylcholine release at the NMJ. It can be acquired by humans in one of five ways: (1) food-borne botulism, in which there is ingestion of food contaminated with preformed toxin, (2) wound botulism, in which the bacteria growing in the wound produce toxin in vivo, (3) infant botulism, in which there is ingestion of clostridial spores allowing colonization of the host's gastrointestinal tract by the bacteria and production of the toxin in vivo, (4) adult enteric infectious botulism, which is similar to infant botulism, and (5) inhalational botulism, which follows inhalation of aerosolized toxin released in an act of bioterrorism.[56]

C. botulinum produces a number of toxins that can produce paralysis by binding to synaptotagmin I and II receptors, which then mediate toxin entry into the nerve cell cytoplasm.[57] Once intracellular, the toxin produces *irreversible* disruption in stimulation-induced acetylcholine release. The botulinum toxin is one of the most potent toxins known. Recovery from the injury requires regrowth of new synapses, a process that can take 6 months. The clinical syndrome is one of progressive paralysis with early cranial nerve involvement causing blurred vision, dysphagia, dysarthria, and facial weakness. Descending muscle weakness is the usual course, and involvement of the upper airway, diaphragm, and intercostal muscles often leads to the requirement for intubation and mechanical ventilation.[58] All patients should be monitored in the ICU and intubation should be undertaken for those who cannot protect their airway or who have an FVC of less than 30% predicted. Botulism antitoxin (intravenous botulinum immune globulin) is available for use in the United States and is given to affected infants younger than 1 year.[58] For adults in the United States, an investigational equine serum heptavalent botulism antitoxin is available through the Centers for Disease Control and Prevention.[59] For all patients, supportive care is the mainstay of therapy and, when necessary, intubation and mechanical ventilation are critical to improved survival. Prolonged hospitalization is common.

Other Neuromuscular Junction Toxins. A number of other toxins can affect the NMJ. The insecticides organophosphates and carbamates are potent inhibitors of acetylcholinesterase, leading to high levels of acetylcholine in the NMJ and resulting in parasympathetic and sympathetic overstimulation, skeletal muscle paralysis, and sometimes respiratory failure.[60] Several species of tick produce toxins that can inhibit NMJ neurotransmission (tick paralysis) by inhibiting the influx of sodium ions and preventing

presynaptic terminal axon depolarization and the release of acetylcholine at the nerve terminal.[61] Venom from a number of families of snakes produces neurotoxins that can cause paralysis, respiratory failure, and death owing to inhibition of neurotransmission.[62] Finally, a wide range of medications can cause NMJ blockade even at therapeutic doses, including D-penicillamine, aminoglycoside antibiotics, fluoroquinolone antibiotics, phenytoin and other anticonvulsants, lithium, β-blockers, glucocorticoids, and magnesium sulfate.[63,64]

Diseases of the Respiratory Muscles

A large number of disorders, both acute and chronic, can directly affect the respiratory muscles (see Table 130.2). Many causes of chronic muscle disease result in respiratory muscle dysfunction including genetic muscular dystrophies, myopathies, and myotonias as well as inflammatory myopathies and those associated with systemic diseases.

Duchenne and Becker Muscular Dystrophies. Duchenne muscular dystrophy and Becker muscular dystrophy are the most common inherited muscle diseases found in childhood, affecting 8.3 and 7.3 children per 100,000.[65] They are both progressive myopathic disorders caused by mutations of the dystrophin gene on the X chromosome (Xp21).[66] Dystrophins are glycoproteins that coat sarcolemmal, sarcomeric, and cytosolic muscle proteins. With Duchenne muscular dystrophy, dystrophin is absent whereas, in Becker dystrophy, dystrophin is reduced in quantity or quality. Both disorders are inherited as X-linked recessive traits and are characterized by progressive muscle wasting and weakness.[67] Typically, weakness of limb muscles is more severe in Duchenne than in Becker muscular dystrophy. Both diseases can involve the respiratory muscles. The diaphragm, however, may be less susceptible than limb muscle because of different gene transcription patterns.[68]

In Duchenne muscular dystrophy, weakness of proximal muscle groups usually manifests by age 2 to 3 years, while weakness of the respiratory muscles becomes evident later in childhood.[69] In Becker muscular dystrophy, weakness manifests later in childhood and individuals can remain ambulatory often into adult life. Because limb muscles are more affected than the respiratory muscles, exercise is initially limited by limb muscle weakness rather than dyspnea due to respiratory muscle weakness. However, the respiratory muscles may progressively weaken and dyspnea may appear with minimal exertion or at rest. Inspiratory muscle weakness can be assessed by measuring MIP. In children unable to perform this maneuver, maximal sniff nasal inspiratory pressures may provide a useful surrogate.[70] With severe inspiratory muscle weakness (MIP < 50% predicted), lung volumes are reduced and FVC may decline at a rate of 6–11% per year. This restrictive process is worsened by concurrent scoliosis or kyphosis, which can develop as a result of muscle dysfunction (see Chapter 131).

Glucocorticoids have been used with limited success to slow the rate of decline of lung function and delay the need for scoliosis surgery.[71–73] Idebenone, a quinone-like drug that targets mitochondrial oxidative phosphorylation, may enhance energy production at the mitochondria and mitigate the decline in respiratory function.[74] Therapies based on genetic manipulation to increase dystrophin production have evolved to include ataluren, which can act to minimize the effect of a stop codon mutation, and eteplirsen, which can help restore the proper reading frame.[75,76]

The diagnosis is often suspected by noting an elevated serum creatine kinase. However, this finding is not specific for these disorders. Analysis for deletions in the dystrophin gene and gene sequencing, if needed, will detect the majority of cases of Duchenne muscular dystrophy.[77,78] A muscle biopsy can be obtained if the diagnosis remains in doubt after genetic testing. With muscular dystrophy, there is degeneration and regeneration of muscle fibers as well as replacement of muscle by fat and connective tissue. Immunoblots for dystrophin can aid in distinguishing Duchenne from Becker muscular dystrophy. Female siblings of individuals with Duchenne or Becker muscular dystrophy should be tested to determine whether they are carriers of the disease. It is important to identify carriers not only for genetic counseling but also because they may be at higher than average risk for development of cardiomyopathy.

The combination of a restrictive pulmonary deficit and expiratory muscle weakness impairs cough and therefore predisposes these individuals to development of respiratory complications such as atelectasis and pneumonia. Methods for preventing atelectasis and infection are discussed later in this chapter.

Once- or twice-yearly measurements of FVC, MIP, and MEP provide useful markers of inspiratory muscle weakness.[79] As the inspiratory muscles weaken, the restrictive lung dysfunction worsens, with total lung capacity and FVC dropping to less than 60% predicted. At this stage, atelectasis can be reduced with lung volume recruitment maneuvers delivered by an in-exsufflation device.[80,81] Individuals with an FVC less than 30% predicted are at high risk for nocturnal hypoventilation and may complain of nonrefreshing sleep and daytime fatigue. These symptoms can present early, before muscle weakness becomes evident.[82,83] Nocturnal ventilation is usually initiated if symptoms develop related to hypoventilation, right heart failure, or elevated arterial P_{CO_2} (>45 mm Hg) either at night or during the day. In general, daytime measures of respiratory muscle strength or lung volumes are poor predictors of nocturnal hypoventilation and overnight oximetry or a sleep study should be considered in high-risk individuals. Noninvasive ventilation is a therapeutic intervention that typically can be delivered with a positive-pressure device using an interface such as a nasal mask, nasal-oral mask, or mouthpiece (discussed later). Noninvasive ventilation is likely to improve quality of life, physical activity, and hemodynamics and to normalize arterial blood gases.[84] Extension of noninvasive ventilation into waking hours may provide relief of dyspnea in more severely affected patients.[85,86] Individuals with Duchenne or Becker muscular dystrophy who require surgery may be at higher risk for respiratory complications.[87] A consensus statement has been published addressing the respiratory and other risks of anesthesia and suggesting methods for avoiding excessive morbidity and mortality.[88] Other muscular dystrophies such as limb-girdle muscular dystrophy, facioscapulohumeral dystrophy, and myotonic dystrophy can affect the respiratory muscles but do not generally cause respiratory impairment until later in the course of the disease.

Chronic Inflammatory Myopathies. *Dermatomyositis* (DM), *polymyositis* (PM), and *inclusion body myositis* (IBM) are systemic inflammatory diseases of unknown etiology that cause profound skeletal muscle weakness.[89,90] DM and PM, with a prevalence of roughly 1:100,000, affect females more than males.[91] DM, PM, and IBM have been associated with genetic abnormalities.

The myopathies have characteristic pathologic changes. Both DM and PM are characterized by muscle fiber inflammation and necrosis. With DM, the inflammatory process may be due to complement-mediated microangiopathy or related to type 1 interferons, and the locus of inflammation is the perifascicular fibers and blood vessels. With PM, the inflammatory response is cell mediated and involves the muscle fascicles themselves. With IBM, in addition to the perivascular inflammation involving the perimysium, the sheath of connective tissue surrounding groups of skeletal muscle fibers, there is also evidence of vacuoles and degenerative deposits. In IBM, tau protein and β-amyloid precursor protein may contribute to muscle injury.[92]

Inflammatory myopathies generally cause symmetrical proximal muscle weakness with insidious onset of symptoms due to slowly progressive muscle weakness. DM and PM involve proximal muscle groups, whereas IBM is typically characterized by asymmetric atrophy of distal muscles and lack of peripheral reflexes. DM can be seen in children and adults, whereas PM and IBM are generally seen only in adults, with IBM involving those older than 50 years with a male predominance. DM may be associated with a rash or underlying carcinoma.

Inflammatory myopathies can involve the diaphragm, intercostal muscles, and accessory muscles, but other peripheral muscle groups are usually more severely affected than the respiratory muscles. Thus, symptoms related to respiratory muscle weakness usually are not the presenting complaints. However, respiratory muscle weakness can develop in 5–10% of the patients with DM and PM and may be found in as many as 75% of individuals when respiratory muscle function is carefully evaluated.[93] Diaphragm dysfunction can be associated with dyspnea, nocturnal hypoventilation and, if the MIP is less than 30% of predicted, respiratory failure. Respiratory muscle weakness can also impair cough, which, in concert with esophageal dysfunction and lymphopenia, can predispose these patients to pneumonia. Aspiration due to pharyngeal muscle weakness can result in chronic interstitial changes.[94]

Individuals with DM or PM should be evaluated for the presence of restrictive pulmonary disease, which may be due to respiratory muscle weakness as well as underlying *interstitial lung disease* (ILD). ILD may develop in up to 70% of patients with DM or PM[95] and may be especially aggressive in the presence of antisynthetase antibodies.[96] ILD may be found more frequently in patients with anti-Jo antibodies.

Diagnostic workup includes measuring muscle enzymes and autoantibodies, magnetic resonance imaging, and muscle biopsy. Muscle enzymes (creatine kinase, aldolase, and lactate dehydrogenase) can be elevated in all inflammatory myopathies but more so in DM and PM than in IBM. ANA titers are significantly elevated in 80% of patients with DM and PM.[90] Serologic markers that are specific for DM and PM include autoantibodies such as anti-Jo-1 (seen in up to 50% of patients with PM); antibodies to signal recognition particle (anti-SRP antibodies); and antibodies to Mi-2, a nuclear helicase (found more frequently in DM).[97] Anti-TIF1-γ antibodies are frequently found in patients with paraneoplastic DM.[98,99] Type 1 interferon-inducible transcripts can be detected in DM and PM and may play a pathogenic role.[100] Magnetic resonance imaging provides a broad overview of muscle and is helpful in distinguishing between PM and IBM and in selecting a biopsy site. In IBM, abnormal changes can be seen throughout the muscle with inclusion body vacuoles of β-amyloid and ubiquitin, whereas, in PM, changes are noted only along fascial planes.[101] Muscle biopsy findings, described above, can be confirmatory.

Treatment of DM and PM includes the use of corticosteroids and immunosuppressive agents such as azathioprine, methotrexate, and mycophenolate mofetil. High-dose intravenous immunoglobulins can be used in patients who are refractory to corticosteroids.[102] Tumor necrosis factor-α blockers and antireceptor antibodies (rituximab, eculizumab) may be used as second-line therapy.[103,104] Aminoquinolone antimalarials have been used as steroid-sparing agents. IBM is typically more refractory to treatment.

Metabolic Myopathies

Glycogen Storage Disease. A number of enzyme deficiencies can lead to glycogen storage diseases characterized by the accumulation of glycogen in tissue, including skeletal and cardiac muscle. There are 12 types of glycogen storage diseases, seen approximately once in 40,000 live births.[105] Glycogen storage diseases are generally inherited as autosomal recessive conditions. The glycogen storage diseases most likely to affect the respiratory system are acid maltase deficiency (type II—Pompe disease) and myophosphorylase deficiency (type V—McArdle disease). These disorders usually present in childhood, but some, such as Pompe disease, have separate adult-onset forms. McArdle disease does not involve cardiac muscle and can lead to exercise intolerance without the production of lactic acid.[106] In Pompe disease, because of the deficiency of acid α-glucosidase, an enzyme that degrades glycogen to glucose, glycogen accumulates within cardiac and skeletal muscle lysosomes, resulting in myopathy. Complete enzyme deficiency results in cardiorespiratory failure and death, usually in the first year of life.[107,108] When the onset of weakness begins after age 1 year, the disease is less severe and does not involve the heart. Those with a later onset of symptoms have a better prognosis. With diaphragm involvement, there is intolerance of the supine position and the development of restrictive lung disease with reductions in MIP.[109,110] Respiratory failure can develop in most severe cases.[111] Nonpharmacologic therapies include utilization of airway clearance techniques, NPPV, inspiratory muscle training, and dietary supplements.[112] Enzyme replacement therapy with recombinant acid α-glucosidase has shown promising results, with stabilization of pulmonary function and increased survival.[113–116]

Other Metabolic Myopathies. Disorders of lipid metabolism or defects directly involving the mitochondria can result in myopathy. Disorders of lipid metabolism may be caused by an abnormal carnitine transporter protein

("primary" carnitine deficiency) or a deficiency of carnitine palmitoyltransferase (CPT1 or CPT2).[117] These disorders usually do not cause respiratory disability but involve other skeletal muscle groups (arms and legs) and may involve cardiac muscle.[118] High carbohydrate diets have had limited success in improving exercise tolerance.[119]

Mitochondrial disorders include those due to deficiencies of enzymes in the mitochondrial respiratory chain complexes and to defects of phosphorylation-respiration coupling. Disorders of mitochondrial metabolism involving complexes I, II, III, IV, and V cause multiple respiratory chain defects[120] and alter the kinetics of oxygen metabolism during exercise.[121] The main consequences of mitochondrial myopathy are muscle weakness, muscle wasting, and exercise intolerance. Dyspnea that accompanies exercise may be due to an exaggerated ventilatory response to metabolic demands.[121] Occasionally, mitochondrial myopathies cause significant respiratory muscle weakness resulting in nocturnal hypoventilation and the need for assisted ventilation.[122] Treatments that focus on bypassing the defective mitochondria include dietary supplements such as creatine, carnitine, and coenzyme Q10.[123,124]

CRITICAL ILLNESS NEUROPATHY AND MYOPATHY

Neuromuscular weakness is common and develops for a variety of reasons in mechanically ventilated patients.[125] One cause of neuromuscular weakness is critical illness neuropathy and myopathy (critical illness polyneuromyopathy), which can result in diaphragm and limb muscle weakness in up to 80% of individuals receiving mechanical ventilation.[126–129] Two major risk factors for developing critical illness polyneuromyopathy are mechanical ventilation and sepsis. Other risk factors include multiorgan failure, renal failure, hyperosmolality, systemic inflammatory response syndrome, hyperglycemia, and treatment with corticosteroids, neuromuscular blocking agents, aminoglycosides, or catecholamines.[130]

The pathology of the myopathy has been well described and includes two major patterns of disease: (1) myocyte atrophy with thick filament (myosin) destruction and (2) widespread myocyte necrosis with intracellular vacuolization and phagocytosis of muscle fibers.[131] The neuropathic changes described by electrophysiologic testing with nerve conduction studies reveal reduced motor and often sensory nerve action potentials and muscle fibrillation suggestive of denervation. Critical illness polyneuromyopathy should be distinguished from other neuromuscular diseases such as Guillain-Barré syndrome.

Pharmacologic therapy includes correcting hypophosphatemia,[132] the use of inhibitors of phosphodiesterase (PDE)3 and PDE4,[133] and the use of the calcium sensitizer levosimendan.[134]

VENTILATOR-INDUCED DIAPHRAGM DYSFUNCTION

Ventilator-induced diaphragm dysfunction is associated with atrophy of both fast and slow myofibers and begins after only 24 to 36 hours of mechanical ventilation.[135] Measurements of diaphragm thickness with ultrasound[136–140] or measurements of endotracheal pressure following stimulation of the diaphragm have been used to assess diaphragm function in ventilated patients.[128] Diaphragm pacing or using modes of mechanical ventilation that minimize patient-ventilator asynchrony are interventions that may prevent diaphragm atrophy.[136,141–143]

Unilateral Diaphragmatic Paralysis

The diaphragm is the major muscle of inspiration and is innervated by the phrenic nerve, which arises from C3 to C5 (see Fig. 130.2). Diaphragm weakness or paralysis can involve either one of the diaphragm leaflets (unilateral) or both (bilateral). Unilateral diaphragmatic paralysis is more common than bilateral diaphragmatic paralysis. The most frequent causes of unilateral paralysis include phrenic nerve injury related to cardiac or thoracic surgery, herpes zoster, cervical spinal disease, or invasive or compressive tumors (Table 130.4). With unilateral diaphragmatic paralysis, patients may be asymptomatic at rest but have dyspnea with exertion.[144] Orthopnea may be present but is not as common or severe as in bilateral paralysis. When dyspnea is present in patients with unilateral paralysis, comorbid conditions such as obesity and underlying heart or lung disease may be present. The patient also should be evaluated for other disorders that cause muscle weakness.[145] The diagnosis is often suggested by an elevated hemidiaphragm on chest radiograph and confirmed with a fluoroscopic sniff test or by diaphragm ultrasonography.[146–148] These tests are discussed in more detail in the evaluation of the patient with neuromuscular disease section later in this chapter. Diaphragm function may recover as the phrenic nerve heals. As many as half the patients who acquire acute paralysis may recover; however, it may take up to 2 to 3 years following the initial injury.[149]

Diaphragm eventration may be confused with unilateral paralysis. In eventration, a part of the diaphragm is replaced with fibroelastic tissue resulting in a localized area of diaphragm elevation, usually anteromedially. Eventration can be distinguished from unilateral paralysis by demonstrating diaphragm contraction by ultrasound or by measuring the transdiaphragmatic pressure while stimulating the phrenic nerve on the side in question.[150]

Diaphragm plication is a treatment that consists of oversewing the membranous central tendon and the muscular components of the diaphragm, thereby tightening the flaccid hemidiaphragm. Surgical plication may be indicated for unilateral paralysis when disabling symptoms are present and when there is significant elevation of the hemidiaphragm on chest radiography. By reducing the paradoxical motion of the paralyzed hemidiaphragm, surgical plication may reduce dyspnea and improve FVC, especially in the supine position.[151–153] This intervention has no role in bilateral diaphragmatic paralysis.

Bilateral Diaphragmatic Paralysis

Bilateral diaphragmatic paralysis is most often seen in the setting of a disease producing severe generalized muscle weakness. The most common causes are diffuse muscle diseases or motor neuron disease, such as ALS. However, bilateral paralysis may develop with a myriad of disorders that involve the cervical spinal cord, phrenic nerve, or

Table 130.4 Causes of Diaphragm Weakness and Paralysis.

Neuropathic Causes	Myopathic Causes
TRAUMA	**MUSCULAR DYSTROPHIES**
Cardiac surgery with cold cardioplegia	Limb-girdle
Blunt trauma	Duchenne and Becker
Spinal cord injury	**METABOLIC MYOPATHIES**
Radiation injury	Hyper- or hypothyroidism
Cervical manipulation	Acid maltase deficiency
Scalene and brachial nerve block	**RHEUMATOLOGIC**
Tumor compression	Systemic lupus erythematosus
Lung cancer	Dermatomyositis
Metastatic mediastinal tumor	Mixed connective disease
METABOLIC	**MISCELLANEOUS**
Diabetes	Amyloidosis
Vitamin deficiency (B_6,B_{12}, folate)	Malnutrition
Hypothyroidism	Idiopathic
INFLAMMATORY NEURITIS	
Idiopathic (neuralgic amyotrophy, Parsonage-Turner)	
Mononeuritis multiplex	
Vasculitis	
Paraneoplastic	
MISCELLANEOUS	
Cervical spondylosis	
Poliomyelitis	
Amyotrophic lateral sclerosis	

neuromuscular junction; examples include neuralgic amyotrophy (Parsonage-Turner syndrome) or complications following cardiac, thoracic, or neck surgery.[154]

Patients with bilateral paralysis primarily complain of dyspnea,[155] either at rest, during exercise, or during certain activities that increase abdominal pressure. These activities, such as bending, lifting, or becoming immersed in water, increase abdominal pressure and displace the paralyzed diaphragm cranially, thereby decreasing lung volume. A similar problem arises upon lying supine; thus orthopnea is a common symptom, and patients may need to use a recliner to sleep. Because sleep-disordered breathing with hypoventilation and hypoxemia is common,[156] these individuals generally respond well to NPPV.[157]

Bilateral diaphragmatic paralysis may be suspected by observing paradoxical rib cage and abdomen motion during inspiration. The gold standard diagnostic test is measuring transdiaphragmatic pressure (Fig. 130.4).[158] Alternatively, diaphragm ultrasound provides a noninvasive means of obtaining the diagnosis as discussed in the "Diaphragm Imaging" section. Once the diagnosis of bilateral diaphragmatic paralysis is confirmed, further diagnostic workup should include an evaluation for nocturnal hypoventilation and computed tomography of the chest to exclude a mediastinal mass, which may be compressing or invading the phrenic nerve. In addition, magnetic resonance imaging of the neck may be needed to evaluate the spinal cord and nerve roots.[145]

Bilateral diaphragmatic paralysis is usually not reversible unless the underlying disease is treatable. Spontaneous recovery of diaphragm function has been noted in some individuals with bilateral paralysis due to neuralgic amyotrophy (brachial plexus neuritis) with the recovery taking an average of 15 months from the onset of symptoms.[149,159] Phrenic nerve pacing requires intact phrenic nerves and has been used in patients with cervical cord injuries above C3 and in patients with congenital hypoventilation syndrome. Thus it is not applicable in most cases of diaphragmatic paralysis. Direct diaphragmatic pacing involves the implantation of electrodes in the diaphragm. Identification of the entrance points of the phrenic nerve into the diaphragm is a prerequisite for direct pacing because uniform diaphragm activation requires placing the intramuscular electrodes in these locations.[160] For unclear reasons, pacing has not been helpful in patients with ALS.[161] Interventions such as sural or intercostal nerve grafting and transfers may provide options in the future to restore diaphragm function.[160,162,163] Diaphragm dysfunction related to metabolic or hormonal imbalance (hypothyroid, hypokalemia, hypomagnesemia, hypophosphatemia, alcohol use, diabetic neuropathy) or parasitic infections may improve with treatment of the underlying disease.

APPROACH TO THE INDIVIDUAL WITH NEUROMUSCULAR DISEASE

EVALUATION

Background

Although each neuromuscular disease has a different etiology and clinical course as well as potential treatment, the respiratory effects of neuromuscular diseases can be approached in a systematic way that can be applied to any neuromuscular diagnosis. This approach uses the fact that the three major muscle groups involved in maintaining ventilation and protecting the airway and lungs are (1) the inspiratory muscles responsible predominantly for ventilation, (2) the expiratory muscles responsible predominantly for cough, and (3) the upper airway muscles responsible for cough, swallowing, and airway protection (Fig. 130.5). This section outlines a general approach for individuals with known or suspected neuromuscular disease.

Comprehensive disease-specific consensus guidelines for evaluation and management of patients with Duchenne muscular dystrophy,[164] congenital muscular dystrophies,[165] pediatric neuromuscular weakness,[166] ALS,[167–169] spinal muscular atrophy,[170] and late-onset Pompe disease[171,172] have been published. Other clinical guidelines address positive-pressure ventilation in patients with chronic respiratory failure including those with neuromuscular disease.[173–175] For patients with Duchenne muscular dystrophy, a consensus committee of the Centers for Disease Control and Prevention has recommended that clinic visits should include relevant evaluations of each of the three areas as appropriate for the stage of disease progression from ambulatory to late nonambulatory.[176]

Clinical Assessment

Individuals with respiratory muscle (particularly diaphragmatic) weakness may present with dyspnea that develops insidiously, but occasionally may be acute (e.g., as in neuralgic amyotrophy).[155,177] Dyspnea is typically exacerbated

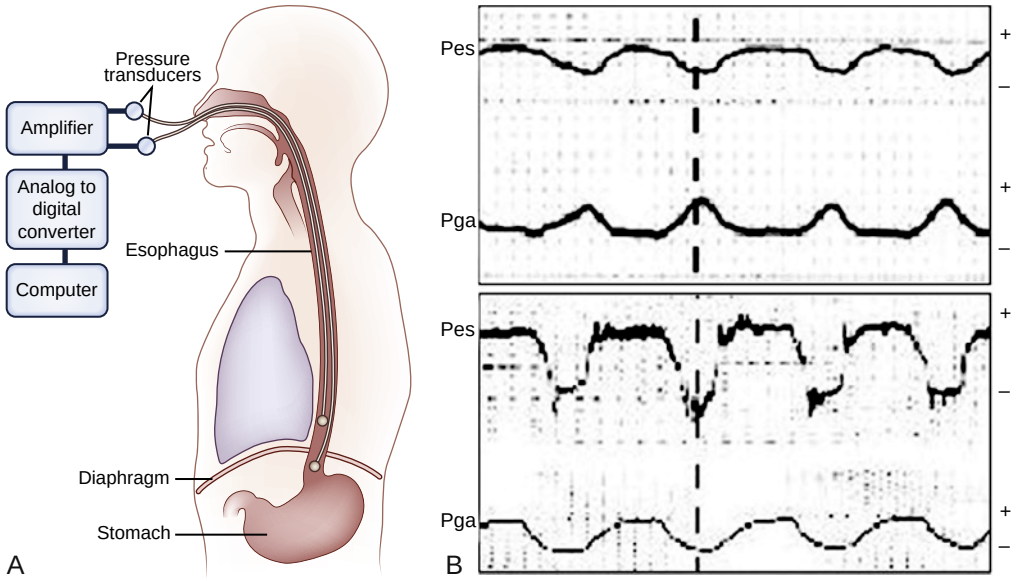

Figure 130.4 Apparatus used to measure transdiaphragmatic pressure and the pressure tracings for normal and paralyzed diaphragms. (A) Esophageal and gastric balloons placed through the nose into the esophagus and stomach, respectively, allow measurement of the pressures above and below the diaphragm simultaneously. (B) *Top*, Normal esophageal (Pes) and gastric (Pga) pressure tracings. Note Pes becomes more negative and Pga more positive during normal inspiration owing to the action of the diaphragm. *Bottom*, Diaphragmatic paralysis where Pes and Pga deflect in the same direction showing no muscular activity of the diaphragm.

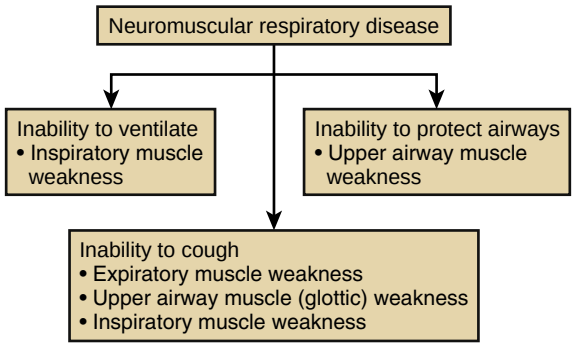

Figure 130.5 Clinical effects of weakness or dysfunction of inspiratory, expiratory, and upper airway muscles. Neuromuscular conditions lead to respiratory disease mainly via inability to ventilate, to cough, and to protect the upper airway from aspiration.

during exertion (especially if carrying heavy objects), and more specifically with recumbency, when bending forward, and when immersed in water[178] due to increased abdominal pressure and cranial displacement of the diaphragm. Frequent respiratory infections or slow recovery from respiratory infections may result from ineffective cough and secretion clearance. Sleep fragmentation, morning headache, daytime fatigue, and sleepiness may develop related to sleep-disordered breathing. A Sleep-Disordered Breathing in Neuromuscular Disease Questionnaire has been developed and validated in a small case series but has not been widely used.[179] Signs of respiratory muscle weakness may include tachypnea and paradoxical rib cage and abdomen motion during inspiration, especially when supine.

Cough Assessment. Effective cough requires a coordinated maneuver starting with adequate inspiration to high volumes, followed by glottic closure, effective expiratory muscle contraction, and rapid glottic opening.[180] Cough insufficiency may be suspected if the patient describes an inability to bring secretions to the mouth for expectoration or if there is a history of frequent respiratory infections. Cough function is best assessed by measuring *peak cough flow* (PCF) rate. This can be measured easily with an asthma peak flowmeter connected to a face mask or mouthpiece (Fig. 130.6). Normal values range from 360 to 960 L/min; a value below 160 L/min may place individuals at high risk for cough insufficiency and ventilator dependence.[181] A PCF below 270 L/min during a healthy period can drop below 160 L/min during infection. Therefore, once PCF drops below 270 L/min, cough augmentation techniques are recommended.

Bulbar Assessment. Patients with neuromuscular diseases such as ALS frequently develop bulbar muscle dysfunction due to motor neuron involvement in the brainstem. Dysfunction of the lips, tongue, and pharyngeal and laryngeal muscles can result in an increased risk of aspiration as well as difficulty generating adequate glottic closure for effective cough function. Choking is common and may even be triggered by aspiration of saliva. Swallowing may be impaired and ingesting adequate nutrition can be challenging for the patient, resulting in malnutrition or rapid weight loss.[182] Swallowing may be evaluated clinically[183] or by videofluoroscopic or fiberoptic evaluation of swallowing techniques.[184] Speech and swallowing consultation can be helpful in diagnosis and management.

Pulmonary Function Testing. Tests of pulmonary function are useful for initial assessment of and, often more important, follow-up of patients over time.[185] Spirometry classically shows a restrictive defect, but FVC may be preserved early on. A fall in FVC by more than 25% upon lying supine is more sensitive and specific than changes in upright FVC for detecting diaphragm weakness.[186] The flow-volume loop may show flow oscillations in patients with bulbar involvement.[187] Functional residual capacity, inspiratory capacity, and total lung capacity typically decline over time, while residual volume may be elevated due to expiratory muscle weakness. MIP and MEP are often both reduced but, in patients with isolated diaphragm weakness, MIP may decline while MEP is relatively preserved.[188] Tests of respiratory muscle strength may be difficult for

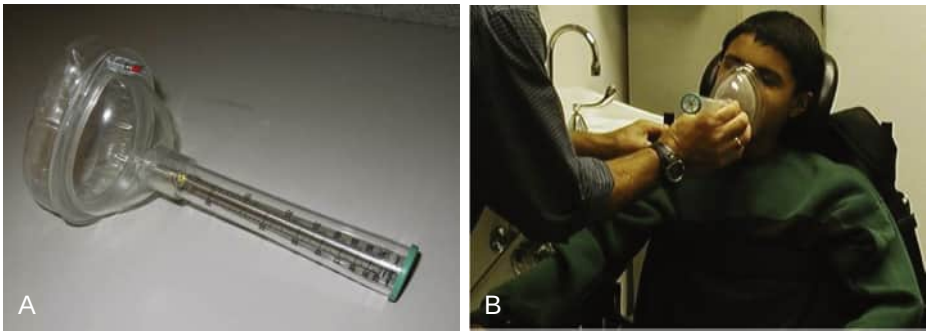

Figure 130.6 Device to measure peak cough flow and demonstration in patient with muscular dystrophy. (A) Device to measure peak cough flow consists of an asthma peak flowmeter connected to a face mask. (B) Peak cough flow device being used in a patient with muscular dystrophy.

patients with bulbar dysfunction to perform, and sniff nasal inspiratory pressure may be more reliable.[189,190] The 1999 National Association for Medical Direction of Respiratory Care National Consensus Conference, which ultimately informed the Centers for Medicare and Medicaid coverage decisions, developed guidelines for the initiation of NPPV and included MIP less than 60 cm H_2O and FVC less than 50% among the physiologic criteria to initiate NPPV in neuromuscular disease.[173]

Gas Exchange (see also Chapter 45). Carbon dioxide can be measured as arterial P_{CO_2}, the traditional measure of adequate ventilation, or as exhaled or end-tidal carbon dioxide (end-tidal P_{CO_2}), transcutaneous carbon dioxide (transcutaneous P_{CO_2}), or capillary P_{CO_2}. Arterial blood gas sampling is the most accurate means of assessing alveolar ventilation. Arterial P_{CO_2} of 45 mm Hg or greater is used to define hypoventilation for diagnostic and treatment purposes. End-tidal P_{CO_2} is an easy and accurate method of estimating arterial P_{CO_2},[191] but it may be inaccurate in patients with pulmonary disease, mouth breathing, high respiratory rates, or under specific technical conditions (e.g., moisture in tubing, use of supplemental oxygen). Transcutaneous P_{CO_2} technology is improving and may be more accurate than end-tidal P_{CO_2} in many common conditions,[192–194] including in patients with neuromuscular disease with weakness and reduced tidal volumes.[195]

Sleep Assessment. Sleep-disordered breathing in neuromuscular disease is common, precedes diurnal hypoventilation, and predicts the onset of diurnal respiratory failure.[196–198] Prevalence varies depending on the definition used.[199] The classic pattern is nocturnal hypoventilation, which is noted first in *rapid eye movement* (REM) sleep, then in both REM and non-REM sleep, and then finally in those who are awake.[200] However, some disorders may present with obstructive sleep apnea (e.g., classically a bimodal pattern in Duchenne muscular dystrophy with obstructive sleep apnea early and hypoventilation late), and with central sleep apnea in disorders associated with cardiomyopathy.[201]

Nocturnal pulse oximetry (Sp_{O_2}) monitoring, nocturnal P_{CO_2} monitoring, cardiorespiratory polygraphy, and polysomnography may be used for assessment.[198] Continuous Sp_{O_2} monitoring in the home is readily available, can detect desaturation (which is usually due to hypoventilation in neuromuscular disease),[202] and can be used to initiate NPPV because desaturation less than or equal to 88% for five minutes is one of the accepted criteria used to initiate NPPV.[173] However, nocturnal Sp_{O_2} is not as sensitive or specific for sleep-related hypoventilation as is transcutaneous P_{CO_2}.[199] Thus, transcutaneous P_{CO_2} monitoring, either alone, in combination with Sp_{O_2}, or as part of polysomnography, is a useful method for monitoring these patients during sleep. Polysomnography is the gold standard test to detect and characterize sleep-disordered breathing, can assess nocturnal oxygenation and ventilation (if continuous P_{CO_2} monitoring is used during the test), and can detect nonrespiratory sleep disorders. It is the recommended test in children with suspected sleep-disordered breathing and in adults with suspected complicated sleep-disordered breathing.[203–206] However, it is costly, labor-intensive, and not as readily available as other tests, and it may be difficult to obtain for patients with limited mobility. Current practice guidelines do not require formal sleep testing for the initiation of NPPV, although the American Academy of Sleep Medicine guidelines recommend polysomnography for titration of NPPV if possible.[207] Daytime positive airway pressure testing[208] and the use of advanced modes of NPPV with volume-assured pressure support have successfully facilitated managing NPPV without any need for formal polysomnography.[209]

Diaphragm Imaging. Chest radiography may show unilateral or bilateral diaphragm elevation suggesting diaphragmatic paralysis. This finding is moderately sensitive but nonspecific for diaphragm dysfunction[210] and diaphragm weakness must be confirmed by additional testing.[211] With unilateral diaphragmatic paralysis, fluoroscopy can be used to confirm the diagnosis by observing diaphragm motion during a sniff test. When the upright patient vigorously sniffs, there may be a cephalad or paradoxical movement of the paralyzed hemidiaphragm (see Video 20.1).[146] The paradoxical motion is due to the passive movement of a paralyzed hemidiaphragm in response to the increase in abdominal pressure (and decrease in pleural pressure) created by the contraction of the normal hemidiaphragm. However, unilateral diaphragmatic paralysis cannot be ruled out when the sniff test shows normal motion of the elevated hemidiaphragm. With bilateral diaphragmatic paralysis, there is no normal hemidiaphragm to use for comparison with an abnormal one, and chest radiography and sniff testing can yield false-negative and false-positive results in this situation.

Two-dimensional echocardiography of the diaphragm is increasingly available, with two general approaches: visualization of the dome of the diaphragm or visualization of the thickness of the diaphragm at the zone of apposition of the diaphragm to the rib cage.[147] Assessing movement of the

diaphragm dome can be diagnostic in unilateral diaphragmatic paralysis and requires less operator skill compared to the other ultrasonographic approach, but shares the same limitations as fluoroscopy.[212] Ultrasonographic imaging of the diaphragm in the zone of apposition provides an alternative means of diagnosing unilateral diaphragmatic paralysis by showing a thin diaphragm that fails to thicken with inspiration (Video 130.1).[148] It also can be diagnostic of bilateral diaphragmatic paralysis when no diaphragmatic thickening is seen on either side with inspiration.[147,148]

Specialized Testing of Diaphragm Function. The gold standard diagnostic test is measurement of *transdiaphragmatic pressure* (Pdi) using thin balloon-tipped polyethylene catheters placed in the esophagus and stomach (see Fig. 130.4A). The pressure is measured during a maximal inspiratory maneuver against an occluded airway (Pdi_{max}) or during a maximal sniff (Pdi_{sniff}) or it can be measured when the phrenic nerve is electrically or magnetically stimulated (Pdi_{twitch}). In diaphragm weakness, there is a lack of ability to generate a normal transdiaphragmatic pressure[158] (see Fig. 130.4B). Because measurement of Pdi is invasive and requires special expertise and because complementary methods of respiratory muscle strength are available, it is not used in routine clinical settings. Phrenic nerve conduction studies and diaphragmatic electromyography may be useful in distinguishing between a neuropathic or myopathic cause of diaphragmatic paralysis but can have technical limitations.[155]

MANAGEMENT

Ventilatory Support

Ventilatory support for patients with neuromuscular disease has been available for more than 60 years[213] (Table 130.5). Some of the first ventilators were known as body ventilators and included devices such as the iron lung, rocking bed, and pneumobelt.[213] With the advent of positive pressure via either invasive (tracheostomy) or noninvasive (face mask) ventilation, these body ventilators are used only rarely.

Invasive positive-pressure ventilation using an indwelling tracheostomy has been successfully employed in neuromuscular disease. Benefits of this type of ventilatory support include complete control of tidal volume and ease of access to the central airways for suctioning of secretions. The development of convenient, portable, positive-pressure generators has made this form of ventilation practical even in the home environment.[214] However, the cost of this care is significant, and the difficulty with obtaining trained caregivers reduces access to community-based living for those with a tracheostomy.[215] Invasive positive pressure should be considered in those with (1) coexisting lung disease, (2) copious secretions, (3) poor oropharyngeal muscle strength associated with ineffective clearing of secretions, (4) uncontrolled seizure disorders that can cause upper airway obstruction, (5) a preference for invasive rather than noninvasive methods, (6) orthopedic or other conditions that interfere with placement of noninvasive devices, and (7) limited access to individuals with expertise in noninvasive techniques.

Unfortunately, invasive long-term positive-pressure ventilation via a tracheostomy has been associated with several complications such as damage to the trachea from the indwelling tracheostomy tube leading to tracheal necrosis, stenosis, hemorrhage, or tracheoesophageal fistulas.[216] However, the development of low-pressure, high-volume cuffed plastic tracheostomy tubes has lowered the incidence of these complications. Tracheostomy tubes increase the risk of airway colonization with bacteria and lower respiratory tract infection. The use of a tracheostomy tube requires humidification. A number of devices and techniques have been designed to allow speech and communication while a patient has a tracheostomy and is being mechanically ventilated. These include techniques such as deflating the balloon to allow simple "leak speech," and devices such as one-way valves that allow gas to pass through the vocal cords during exhalation (Passy-Muir valve) or channels that direct compressed air through the vocal cords (Trach Talk tracheostomy tube). Unfortunately, not all individuals can use these approaches.[217]

NPPV is becoming the preferred method for treatment of patients with neuromuscular respiratory disease[218] (see also Chapter 136). NPPV was first used during the polio epidemics of the 1950s to allow patients to spend time outside the iron lung. Since the 1980s, there have been considerable refinements in the application of this technique. There are currently three ways in which NPPV may be delivered: (1) via full face mask, (2) via nasal mask, or (3) via mouthpiece with or without a lip seal (Fig. 130.7). Occasionally, more than one method may be used in the same patient; for instance, a mouthpiece may be used during the day and a nasal mask used at night.

The mouthpiece was the first interface to be used with a positive-pressure ventilator. Patients hold the mouthpiece devices between their teeth and often are able to use them while sleeping, especially when lip seal devices are added.[219] Since the late 1990s, nasal interfaces have been developed and used successfully.[220] Tidal volume is most effectively delivered when there are no leaks in the system. The use of a full face mask interface may reduce leaks but in selected patients may worsen apneas and hypopneas.[221] Pressure-cycled rather than volume-cycled devices are generally used for mask ventilation. With pressure-cycled machines, positive pressure can be delivered at two levels, a higher level during inspiration and a lower level during expiration (bi-level support). The positive-pressure

Table 130.5 Methods of Ventilation Used in Treatment of Neuromuscular Disease

NEGATIVE-PRESSURE VENTILATORS
Tank ventilator (iron lung)
Raincoat ventilator (poncho or pneumowrap)
Cuirass ventilator (chest shell)
Pneumosuit ventilator with leggings
POSITIVE-PRESSURE VENTILATORS
Invasive (tracheostomy)
Noninvasive (via full face mask, nasal mask, or mouthpiece)
VENTILATORS RESULTING IN PASSIVE MOVEMENT OF THE DIAPHRAGM
Pneumobelt
Rocking bed
PHRENIC NERVE PACING
DIAPHRAGM PACING

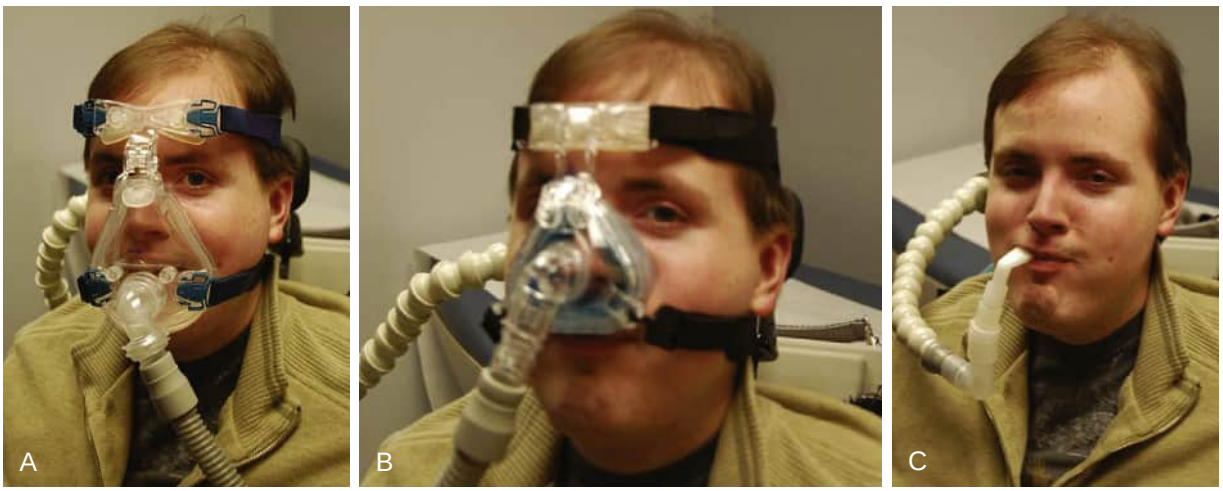

Figure 130.7 Various means of delivering noninvasive positive-pressure ventilation. (A) Full mask. (B) Nasal mask. (C) Mouthpiece.

gradient during inspiration results in delivery of a tidal volume to the patient while exhalation is passive and is terminated when the airway pressure returns to the lower expiratory level. Maintenance of a positive expiratory pressure is important for two reasons. First, the gas flow needed to maintain end-expiratory positive airway pressure flushes the ventilator tubing of exhaled carbon dioxide and prevents rebreathing.[222] Second, because the expiratory pressure is positive and greater than atmospheric, the end-expiratory lung volume is increased, which may be associated with less atelectasis and fewer areas with low ventilation-perfusion ratios or shunt than seen with low end-expiratory lung volumes.

Data Supporting Noninvasive Positive-Pressure Ventilation in Neuromuscular Disease

Nocturnal Ventilatory Support. The use of nocturnal ventilation in patients with neuromuscular disease with sleep-disordered breathing has been shown to have a number of benefits, including (1) reduced arterial P_{CO_2} and increased arterial P_{O_2} on and off the ventilator, (2) decreased symptoms of sleep-disordered breathing such as morning headache, nocturnal awakenings, vivid nightmares, and night sweats, (3) improved quality of life, and (4) reduced morbidity and most likely reduced mortality.[174]

The mechanism by which nocturnal ventilation improves daytime symptoms and arterial blood gases in patients with neuromuscular disease is not entirely clear. A number of explanations have been suggested including (1) resting of chronically fatigued respiratory muscles, (2) reversal of mechanical problems associated with neuromuscular disease, such as reduced chest wall and lung compliance, and (3) a resetting of the central respiratory control centers with an increase in chemosensitivity to arterial P_{CO_2} during the daytime, thus maintaining blood gas homeostasis.[223,224] In addition to improvement in arterial blood gases, other measures of physiologic function have been shown to improve with intermittent ventilation; for example, nocturnal ventilation can increase FVC, improve right heart function, and reduce erythrocytosis.[225] The effects of mechanical ventilation have been best studied in ALS where the use of NPPV for more than 4 hours and early initiation of NPPV has been shown to improve survival.[226,227] It is therefore generally accepted that mechanical ventilation in the home leads to improved survival in most patients.

Full-Time Ventilatory Support

For those who require full-time ventilatory support, it is possible to provide NPPV for 24 hours per day.[228–230] There have been no randomized controlled trials of continuous ventilation. In one cohort study, 24 patients with Duchenne muscular dystrophy using NPPV were compared with 22 patients who received positive-pressure ventilation by tracheostomy.[231] The individuals who used NPPV had significantly fewer hospitalizations and hospital days per year. In another retrospective study by the same group, patients with Duchenne muscular dystrophy using a protocol consisting of mouthpiece positive-pressure ventilation and breath stacking plus mechanical insufflation-exsufflation to assist cough (see "Cough Support") had significantly lower mortality (3 of 34 patients) than a group that did not have access to the protocol and either received tracheostomy or used NPPV on a near-continuous basis (27 of 31 patients).[232] In the setting of ALS, the ability to use mouthpiece ventilation improves survival by approximately 20 months as opposed to those who are unable to use the device.[233] Multiple consensus statements on the respiratory care of patients with neuromuscular disease have suggested that NPPV be considered when expertise is available for initiation of appropriate protocols.[166,173,174,176]

Cough Support

Therapeutic interventions aimed at improving cough and airway clearance are equally if not more important than ventilatory support because pneumonia is one of the leading causes of morbidity and mortality in patients with neuromuscular disease.[218,234] Normally, the cough reflex is initiated by stimulation of cough receptors in the airways that activate brainstem centers that initiate inhalation, glottic closure, and forceful contraction of expiratory muscles during which intrathoracic air is

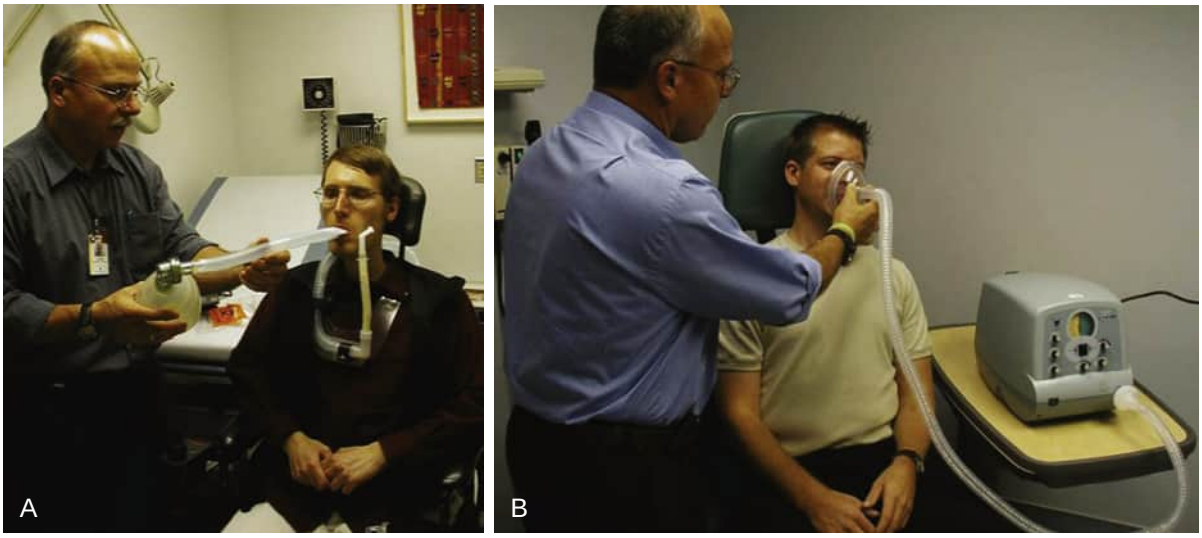

Figure 130.8 Methods to assist cough. (A) Resuscitator bag used to stack breaths to increase lung volume and thereby increase cough flow. (B) Mechanical insufflator-exsufflator being used to assist in secretion removal.

compressed under high pressures.[235] The glottis then rapidly opens, allowing an explosive release of air from the airways through the vocal cords. The high-velocity airflow shears secretions away from the airway walls and propels them out of the lung. Adequate cough is essential for airway hygiene and problems with cough sometimes lead to consideration of tracheostomy. Fortunately, there are a number of ways that an impaired cough can be augmented and pulmonary hygiene maintained without the use of a tracheostomy.

Manually assisted cough is a method of applying a rapid positive pressure to the abdomen. The increase in abdominal pressure is transmitted to the thorax and induces expiratory flow, leading to airway clearance and enhanced cough expiratory flow rates. A number of techniques are available for an attendant to apply rapid abdominal thrusts, resulting in effective clearance of secretions.[236] Increasing the volume of air in the respiratory system prior to the assisted cough increases the volume available for exhalation, optimizes the length-tension relationship of the expiratory muscles to increase potential intrathoracic pressure generation, and increases the inward elastic recoil pressure of the respiratory system, which can further increase the expiratory pressures. This maximal achievable inspired volume has been labeled the maximal insufflation capacity.[237] Inspired lung volume can be increased by patients using breath stacking or glossopharyngeal ("frog breathing") techniques[238] or by use of a resuscitator bag and mouthpiece (Fig. 130.8A). Breath stacking involves taking multiple breaths to increase lung volumes above the single breath volume and holding each successive breath in the lungs using a closed glottis. Glossopharyngeal breathing involves forcing air into the trachea using the tongue and pharyngeal muscles.[238] Increasing the lung volume to the greatest possible volume, known as lung volume recruitment, by using breath stacking or a mechanical device, may help both with improving cough function and with maintaining lung compliance and FVC in progressive neuromuscular disease.[239,240]

Mechanically assisted cough techniques are also available. A very effective secretion management device, available for more than 50 years but only recently used to any great extent, is the mechanical insufflator-exsufflator or CoughAssist (In-exsufflator) (see Fig. 130.8B). This device consists of an electric motor that can generate positive and negative pressures of up to 50 cm H_2O to insufflate and then rapidly exsufflate the lung. The pressure is applied to the patient's airway via a face mask or mouthpiece; a positive pressure of 30 to 50 cm H_2O is applied over a 1- to 3-second period followed immediately by a negative pressure of between 30 and 50 cm H_2O for a short duration. By simulating a cough, this technique moves secretions out of the airway noninvasively without violating airway integrity (Video 130.2).[241] Other noninvasive mechanical aids include devices that oscillate the chest wall or airway directly.[242] These have not been well studied in neuromuscular disease patients without tracheostomy and their role in support of secretion management of these disorders is unclear.

The decision to initiate cough assistance is determined by measurement of *peak cough flow* (PCF). Normal values for PCF range from 360 to 960 L/min. It is recommended that one or more of the previously discussed techniques should be made available to the patient when values of PCF fall below 270 L/min while the patient is well, because this correlates with a critical value of less than 160 L/min when the patient develops a respiratory tract infection.[181] This drop in cough function with respiratory illness may be due to increased muscle weakness or to the effects of the secretions themselves in reducing expiratory flow. In patients with bulbar muscle dysfunction, choking and vocal cord spasm may be triggered by aspiration of saliva. In these patients, the use of cough assist may worsen the episodes, and muscle relaxants may be more helpful.[243]

Aspiration can be a related problem for patients with neuromuscular disease (see also Chapter 43). Besides problems with cough, patients with neuromuscular disease often have problems with swallowing and airway protection.

However, treatments for swallowing muscle dysfunction are limited. The risk of aspiration and development of pneumonia in patients with ALS is due primarily to problems with upper airway function and cough. Pharyngeal and laryngeal muscle dysfunction can lead directly to aspiration of oral contents into the lungs. Other than surgical diversion of the airway,[244] no treatment directly aimed at laryngeal and glottic function is currently available. When patients develop significant dysphagia and aspiration of solids or liquids, many experts recommend placement of a percutaneous endoscopic gastrostomy tube.[245,246]

- Either nocturnal or full-time noninvasive ventilation is standard practice for patients with neuromuscular respiratory failure and likely prolongs survival.
- Cough can be aided noninvasively by manual or motorized means; cough support should be considered when the peak cough flow rate is less than 270 L/min in a patient without respiratory tract infection and definitely when the peak cough flow rate is less than 160 L/min.

Key Points

- Respiratory failure is a leading cause of morbidity and mortality in individuals with neuromuscular disease.
- Spinal cord injury to the cervical and upper thoracic spinal cord is associated with restrictive pulmonary dysfunction and respiratory muscle weakness. Diaphragm pacing is an effective means of providing long-term mechanical ventilation in patients with C1 or C2 lesions.
- Acute immune-mediated polyneuropathy (acute idiopathic demyelinating polyneuropathy or Guillain-Barré syndrome) is an ascending paralytic disease. Intubation can be life-saving and should be considered when the FVC is 15 mL/kg or less, the FVC is 1 L or less, or the maximal inspiratory pressure is 30 cm H_2O or less, or there is a lack of upper airway protection.
- Neuromuscular weakness arises commonly in individuals receiving mechanical ventilation and can result in diaphragm and limb muscle weakness.
- Unilateral diaphragmatic paralysis is most commonly due to injury to the phrenic nerve, whereas bilateral disease is most commonly due to diffuse muscle or motor neuron disease. The difference between upright and supine vital capacity can be used to screen for diaphragm dysfunction. The definitive diagnosis can be made by ultrasound measurements of diaphragm thickness or of diaphragm dome excursion.
- Respiratory assessment of the individual with neuromuscular respiratory impairment should include evaluation of muscle groups responsible for inspiration, expiration and cough, and airway protection.

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131 THE RESPIRATORY SYSTEM AND CHEST WALL DISEASES

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INTRODUCTION

Disorders of the soft tissue and bony structures of the chest wall generally cause restrictive dysfunction by limiting motion or causing disordered movement of the chest wall. Kyphoscoliosis and ankylosing spondylitis involve the spine and its articulations, pectus excavatum involves the sternum, flail chest affects the ribs, and obesity adds to the soft tissues of the rib cage and abdomen. Kyphoscoliosis has the most severe impact on respiratory function and pectus excavatum the least. Alterations in respiratory mechanics produced by these disorders are discussed in concert with the most recent developments in diagnosis and treatment. Neuromuscular diseases that affect the chest wall are reviewed in Chapter 130.

KYPHOSCOLIOSIS

DIAGNOSIS AND ETIOLOGY

Kyphoscoliosis refers to a group of disorders characterized by excessive spinal curvature in the lateral plane (scoliosis) and sagittal plane (kyphosis), as well as rotation of the spinal axis[1,2] (Fig. 131.1). Scoliosis, which is defined as a lateral spinal curvature greater than 10 degrees, is frequently associated with kyphosis and rotation of the spine around its long axis.[2] Kyphoscoliosis is a relatively common spinal abnormality, with an estimated prevalence for mild deformity of 1 in 1000 persons and for severe deformity of 1 in 10,000 persons in the United States.[1]

Kyphoscoliosis is classified as idiopathic (no known cause), paralytic or secondary (associated with neuromuscular disease), or congenital (associated with vertebral malformation present at birth)[2,3] (Table 131.1). Idiopathic kyphoscoliosis, accounting for 80% of all cases, usually manifests in late childhood or early adolescence and involves girls more often than boys, with a ratio of 4:1. Despite multiple theories linking idiopathic kyphoscoliosis to biomechanical, neuromuscular, environmental, or genetic causes, its precise etiology is largely unknown.[4] The most important sequelae of progressive kyphoscoliosis are back pain, psychosocial problems, and respiratory failure.[2]

The diagnosis of kyphoscoliosis is made by physical examination and confirmed radiographically. In severe cases, the examiner may readily notice the dorsal hump, which is caused by angulated ribs and shoulder asymmetry, and the hip tilt, which is related to spinal rotation. In mild cases with less apparent findings, it is important to inspect the spine for asymmetry and to perform the Adam forward bend test. With this test, the examiner inspects the spine for thoracic or lumbar asymmetry while the patient bends forward at the waist until the spine becomes parallel to the floor. When kyphoscoliosis is severe and complicated by right heart failure, clinical examination may reveal cyanosis, distended neck veins, peripheral edema, and hepatomegaly.[5]

Upright radiographs of the chest or spine are used to confirm the diagnosis and assess severity of the spinal deformity by measuring the Cobb angle[2] (Fig. 131.2). The greater the Cobb angle, the more severe the deformity. Angles greater than 100 degrees are usually associated with respiratory symptoms such as dyspnea on exertion, and angles greater than 120 degrees are associated with respiratory failure.[5–7]

PATHOPHYSIOLOGY

Pulmonary Function and Respiratory Mechanics

Kyphoscoliosis can produce severe restrictive impairment related to markedly decreased distensibility of the chest wall, especially with Cobb angles greater than 90

degrees[8–10] (Table 131.2). With such severe deformity, total lung capacity and *vital capacity* (VC) may be reduced to as low as 30% of predicted values.[6,9,10] In contrast, residual volume may be normal or slightly increased, resulting in an elevated ratio of residual volume to total lung capacity.[10,11] In children with severe spinal deformity, hypoplastic lung may result and contribute to reduced lung volumes.[12] Other factors contributing to the restrictive process include the number of vertebrae involved, the thoracic location of the curve, the patient's age, the presence of kyphosis, the degree of spinal rotation, and the presence of weak respiratory muscles.[13–15]

Associated abnormalities may increase the severity of restriction. For example, in the paralytic type of kyphoscoliosis, the degree of lung restriction is determined primarily by the degree of the respiratory muscle weakness rather than by the degree of the spinal curvature.[16,17] In addition, in congenital kyphoscoliosis, lung restriction may be worsened by associated rib deformities and underlying lung abnormalities.[17] For these reasons, compared with patients with idiopathic kyphoscoliosis, patients with paralytic or congenital kyphoscoliosis generally have a greater loss in VC for a given degree of spinal deformity.[17]



Figure 131.1 Chest computed tomography 3-dimensional reconstruction of the rib cage and spine in kyphoscoliosis. Kyphoscoliosis is often associated with rotation of the spine. (Modified from Chun EM, Suh SW, Modi HN, Kang EY, Hong SJ, Song HR. The change in ratio of convex and concave lung volume in adolescent idiopathic kyphoscoliosis: a 3D CT scan based cross sectional study of effect of severity of curve on convex and concave lung volumes in 99 cases. *Eur Spine J.* 2008;17:224–229.)

Table 131.1 Causes of Kyphoscoliosis

IDIOPATHIC DISORDER
■ Multigene disorder, developing by childhood or adolescence
PARALYTIC OR SECONDARY DISORDER
■ Neuromuscular (poliomyelitis, muscular dystrophy, cerebral palsy, Friedreich ataxia, Charcot-Marie-Tooth disease)
■ Disorders of connective tissue (Marfan syndrome, Ehlers-Danlos syndrome, Morquio syndrome)
■ Vertebral disease (osteoporosis, osteomalacia, vitamin D–resistant rickets, tuberculous spondylitis, spina bifida)
■ Post-thoracoplasty status
CONGENITAL DISORDER
■ Spinal or vertebral malformations at birth

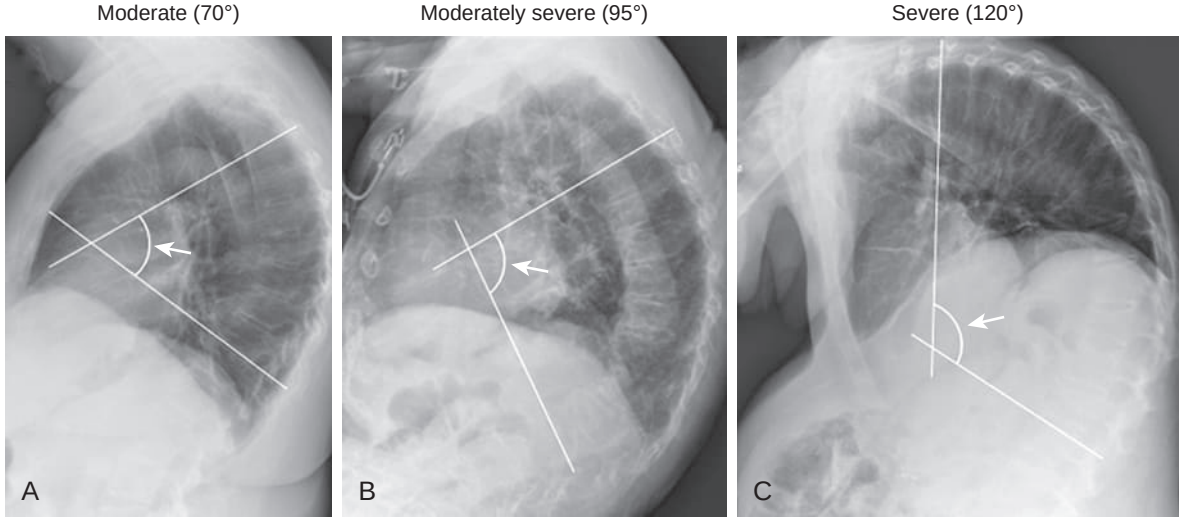

Figure 131.2 Lateral chest radiographs with different degrees of kyphoscoliosis showing calculation of the Cobb angle. Lines are drawn through the superior end plate of the vertebral body marking the cranial portion of the curve and the inferior end plate of the vertebral body marking the caudal portion of the curve. The angle of intersection between these two lines is the Cobb angle (*arrows*). Patients are shown with (A) moderate, (B) moderately severe, and (C) severe kyphoscoliosis along with their calculated Cobb angles. (Courtesy Michael B. Gotway, MD.)

Respiratory system compliance is reduced in kyphoscoliosis of any etiology, primarily because of the reduction in chest wall compliance and, to a lesser degree, a reduction in lung compliance as a result of microatelectasis.[9,18,19] Cobb angles up to 50 degrees have minimal impact on respiratory compliance, whereas angles greater than 100 degrees may reduce compliance to levels seen in the adult respiratory distress syndrome.[9,18,20] The stiff chest wall reduces the *functional residual capacity* (FRC). These factors combine to move the tidal breathing to a flatter, stiffer portion of the respiratory volume-pressure curve[8] (Fig. 131.3). This requires greater inspiratory effort for relatively small tidal breaths that increases the work and oxygen cost of breathing.[8] The increase in the oxygen cost of breathing may reach values three to five times those measured in healthy individuals[5,9,21] and thus may place patients at risk for respiratory muscle fatigue.[22]

Table 131.2 Representative Values for Pulmonary Function and Respiratory Mechanics in Chest Wall Diseases

Parameter	KS	Post-Thor	PE	AS
TLC (% pred)	45	65	90	85
VC (% pred)	30	50	90	80
RV (% pred)	95	90	100	100
FEV_1 (% pred)	40	40	95	80
FEV_1/FVC	80	60	80	75
Crs (% pred)	50	50	—	70
Ccw (% pred)	30	40	—	60
CL (% pred)	60	50	80	80
PI_{max} (cm H_2O)	40	50	90	80
MVV (L/min)	37	37	107	80

Representative values are from Bergofsky EH. Thoracic deformities. In: Roussos C, editor. *The Thorax*. New York: Dekker; 1995:1915–1949.
AS, ankylosing spondylitis; Ccw, compliance of chest wall; CL, compliance of lungs; Crs, compliance of respiratory system; FEV_1, forced expiratory volume in 1 second; FVC, forced vital capacity; KS, kyphoscoliosis; MVV, maximum voluntary ventilation; PE, pectus excavatum; PI_{max}, maximum respiratory pressure; post-thor, post-thoracoplasty; pred, predicted; RV, residual volume; TLC, total lung capacity; VC, vital capacity.

Exercise Capacity

Individuals with mild idiopathic kyphoscoliosis usually have normal exercise capacity.[23–27] If exercise is limited, it is typically the result of deconditioning rather than diminished ventilatory reserve.[23,24,28] In contrast, individuals with *moderate* idiopathic kyphoscoliosis (Cobb angles of 25 to 70 degrees), *moderately severe* kyphoscoliosis (Cobb angles of 70 to 100 degrees), or *severe* kyphoscoliosis (Cobb angles greater than 100 degrees) may have exercise limitation related to ventilatory constraints.[23,29,30] With severe deformities (Cobb angles greater than 100 degrees), cardiovascular factors may further contribute to exercise limitation.[23,29] Supplemental oxygen may improve oxygenation during exercise but usually does not affect walk distance.

Control of Breathing and Sleep-Disordered Breathing

Patients with kyphoscoliosis compensate for the increased elastic loads on the inspiratory muscles by adopting a rapid shallow breathing pattern consisting of low tidal volumes and shortened inspiratory time.[11,31] Both parameters of rapid shallow breathing, tidal volumes and inspiratory time, decrease as the Cobb angle increases.[31] However, rapid shallow breathing has the negative consequence of increasing dead space ventilation and promoting microatelectasis. Another strategy to compensate for the increased elastic load is to increase neural drive to the respiratory muscles. Indirect evidence for this compensatory strategy is the elevated mouth occlusion pressure at 100 msec seen during quiet breathing, exercise, or breathing stimulated by hypercapnia.[31,32] As the degree of kyphoscoliosis increases, the neural output to the respiratory muscles increases; that is, occlusion pressure at 100 msec correlates positively with

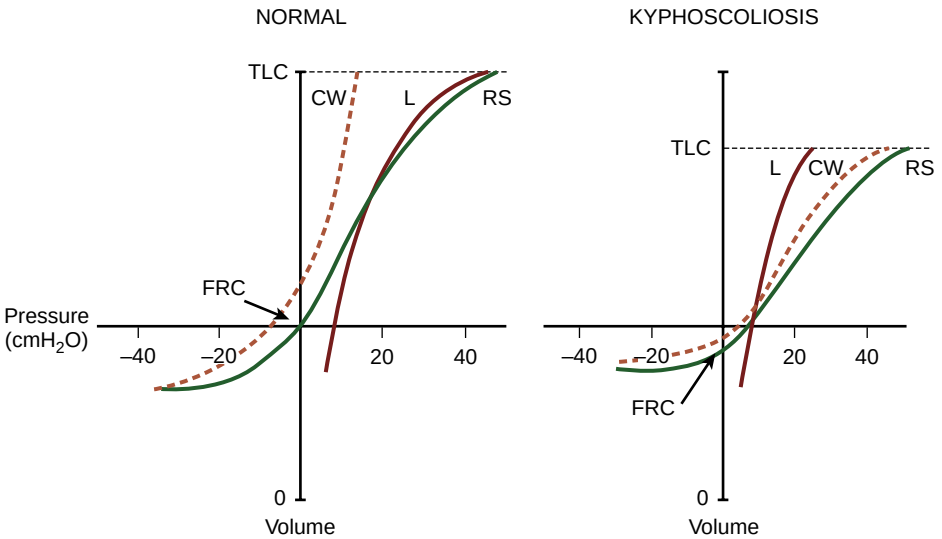

Figure 131.3 Schematic illustration of volume-pressure relationship of the *lung* (L), *chest wall* (CW), and *respiratory system* (RS) in a normal individual (left) and in kyphoscoliosis (right). Note that in kyphoscoliosis the chest wall is less compliant, leading to a reduction in *functional residual capacity* (FRC) and positioning of tidal breathing on a flatter portion of the respiratory system volume-pressure curve. TLC, total lung capacity.

the Cobb angle in these patients.[31] The increase in neural drive does not necessarily translate into increased minute ventilation because of the mechanical constraints imposed by the stiffened chest wall.

Hypoventilation is the most common breathing disorder affecting individuals with kyphoscoliosis (eFig. 131.1), and it can be particularly significant during sleep. Hypoventilation results in hypercapnia and hypoxemia and is most severe during rapid eye movement sleep when there is a reduction in neural drive to the respiratory muscles.[33,34] Of note, nocturnal hypoxemia typically predates the onset of respiratory failure, and the Cobb angle does not correlate with the magnitude of nocturnal oxyhemoglobin desaturation in these patients. Accordingly, it is important to screen for nocturnal hypoventilation with overnight oximetry even in patients with only moderate spinal deformity.[33,35,36] In addition, obstructive sleep apnea may be seen with a frequency similar to that in the general population and, if present, can further aggravate nocturnal hypoventilation.[37] (For the effects of sleep-related abnormalities on cardiorespiratory function, see "Pathogenic Aspects of Respiratory Failure in Chest Wall Diseases" later in this chapter.)

CLINICAL COURSE

Of all types of kyphoscoliosis, idiopathic kyphoscoliosis has the most benign clinical course.[2] Paralytic kyphoscoliosis may progress rapidly, largely depending on the underlying cause of neuromuscular weakness and the age of onset of the spinal deformity. An early age of onset with rapid curve progression during growth and progression after skeletal maturity increase the risk of serious respiratory complications.[38,39] Congenital kyphoscoliosis may also progress rapidly.[40]

In mild idiopathic kyphoscoliosis, the probability of developing respiratory failure with aging is similar to that in a healthy population.[2] However, the risk is higher for patients with moderate or severe deformities. Large spinal curves at presentation, skeletal immaturity, and thoracic location of the curve apex are generally considered risk factors for curve progression.[7,41] The presence of respiratory muscle weakness enhances the likelihood of developing respiratory failure.[11] In general, the spinal deformity worsens at a rate of about 1 degree of Cobb angle per year in individuals with thoracic deformities greater than 50 degrees at skeletal maturity.[41,42]

Individuals with severe idiopathic kyphoscoliosis (Cobb angles >100 degrees) should be monitored closely for respiratory complications, especially if they are middle-aged or older.[6] Initially, individuals may experience dyspnea only with exertion but, as they age and the spinal deformity progresses, dyspnea may develop even at rest.[5,6] In addition to the degree of chest wall deformity, other factors that contribute to ventilatory failure in patients with idiopathic kyphoscoliosis are inspiratory muscle weakness, sleep-disordered breathing, and airway compression caused by distortion of the lung parenchyma and twisting of airways.[5,36,43] When respiratory failure develops in a patient with kyphoscoliosis and a Cobb angle less than 100 degrees, other causes of respiratory failure should be sought, particularly treatable causes such as sleep-disordered breathing.

TREATMENT

Medical Treatment

General supportive care includes immunizations against influenza and pneumococci, smoking cessation, maintenance of a normal body weight, and physical activity to minimize deconditioning. Orthopedic braces have been used in skeletally immature individuals with idiopathic kyphoscoliosis in an effort to prevent or correct the spinal deformity. Although its efficacy is uncertain,[44,45] a brace is generally recommended for growing children with Cobb angles between 25 and 40 degrees.[2,46]

Home noninvasive mechanical ventilation is an effective treatment in individuals with severe kyphoscoliosis.[47–49] Indications for instituting noninvasive nocturnal ventilation include symptoms suggestive of nocturnal hypoventilation or signs of right heart dysfunction with either an elevated daytime arterial *partial pressure of carbon dioxide* (P_{CO_2}) or nocturnal oxygen saturation less than 88% for 5 consecutive minutes[50] (eTable 131.1). Either pressure or volume preset ventilators are effective in providing noninvasive ventilation.[51,52] Supplemental oxygen is indicated if hypoxemia persists despite correction of hypoventilation. In patients intolerant of noninvasive ventilation or unable to manage excessive bronchial secretions, tracheostomy is another option.[53]

The benefits of noninvasive ventilation are well established and include improvements in gas exchange, hemodynamic parameters, sleep architecture, number and duration of hospitalizations, quality of life, and perhaps survival[47,54–56] (eTable 131.2). Interestingly, noninvasive ventilation does not appear to improve respiratory muscle strength or endurance; instead, noninvasive ventilation may improve respiratory failure by enhancing central chemosensitivity to carbon dioxide.[57]

Surgical Treatment

In general, surgery involves fusion of the affected vertebral bodies through the posterior approach and the use of devices such as rods, wires, hooks, and pedicle screws to support the spine. This approach allows for multiplanar correction, stable fixation with less spinal fusion, and early postoperative mobilization without a cast or brace.[7] Newer techniques without spinal fusion include the use of growth-friendly rods such as expandable spinal rods, titanium rib implants, or remotely operated magnetic growth rods.[58,59] Surgery is currently recommended in individuals with skeletal immaturity and a Cobb angle greater than 45 degrees.[2] The benefits of spinal surgery on pulmonary function remain unclear.[60] Immediately following surgery, pulmonary function may be impaired as a result of rib cage trauma and changes in the chest wall caliber.[18] In the long-term, pulmonary function is more likely to improve in young children and adolescents than in adults.[6,61] In the absence of randomized controlled studies assessing the efficacy of surgery, the overall role of surgical management in restoring function and minimizing the possibility of respiratory failure is not clear.[2,7,62,63]

eTable 131.1 Indications for Instituting Long-Term Noninvasive Ventilation for Kyphoscoliosis (and Other Chest Wall Diseases)

Symptoms (e.g., fatigue, morning headaches, dyspnea) or signs of right heart dyfunction and one of the following:

- Daytime arterial P_{CO_2} ≥45 mm Hg
- Nocturnal oxygen saturation <88% for >5 consecutive minutes
- Progressive neuromuscular disease with $P_{I_{max}}$ <60 cm H_2O or FVC <50% of predicted

FVC, forced vital capacity; P_{CO_2}, partial pressure of carbon dioxide; $P_{I_{max}}$, maximal static inspiratory pressure.

Modified from Clinical indications for noninvasive positive pressure ventilation in chronic respiratory failure due to restrictive lung disease, COPD, and nocturnal hypoventilation—a consensus conference report. *Chest*. 1999;116:521–534.

eTable 131.2 Benefits of Noninvasive Nocturnal Ventilation in Chest Wall Diseases

GAS EXCHANGE
Increased arterial P_{O_2}
Decreased arterial P_{CO_2}
HEMODYNAMICS
Decreased pulmonary arterial pressure
Improved right ventricular function
MECHANICS
Reduced work of breathing
Increased maximal inspiratory pressure
SLEEP HYGIENE
Normalized sleep patterns
Fewer apneic episodes
OUTCOME
Fewer hospitalizations
Improved quality of life
Relief of dyspnea
Possible increased survival

P_{CO_2}, partial pressure of carbon dioxide; P_{O_2}, partial pressure of oxygen.



Figure 131.4 Frontal chest radiograph in a patient with a history of thoracoplasty for prior *Mycobacterium tuberculosis* infection. There is an extensive deformity of the right hemithorax consistent with prior thoracoplasty; this chest wall deformity is the likely cause of the scoliosis of the thoracic spine. L, left.

THORACOPLASTY

In the pre-antituberculous chemotherapy era, thoracoplasty was commonly used to reduce lung volume as a way to control pulmonary tuberculosis.[64] Thoracoplasty reduced lung volume by removing or fracturing ribs (Fig. 131.4), resecting the phrenic nerve, or filling the pleural space with foreign material (i.e., Lucite spheres [eFig. 131.2] oil [eFig. 131.3], and ping pong balls). Severe restrictive impairment may develop decades after the procedure, manifesting initially with dyspnea on exertion and then at rest and eventually with chronic respiratory failure.[65] The severity of the restrictive defect, which can be similar to that seen in kyphoscoliosis (see Table 131.2), may reflect a reduction in respiratory system compliance, fibrothorax, lung resection, phrenic nerve damage, scoliosis, and lung fibrosis related to prior underlying granulomatous disease.[65] Thoracoplasty is occasionally still performed to treat bronchopleural fistulas that have failed to close following decortication or persistent empyema in which decortication is not feasible or has not eradicated the infection.[64,66,67] Treatment consists of oxygen, antibiotics when appropriate, and noninvasive nocturnal mechanical ventilation.

PECTUS EXCAVATUM

DIAGNOSIS AND ETIOLOGY

Pectus excavatum is a common congenital chest wall deformity characterized by excessive depression of the sternum and its adjacent costal cartilages[68] (Fig. 131.5). It is the most common chest wall deformity, seen in approximately 0.5–2% of the population and more frequently in boys and men than in girls and women (4:1 ratio).[69] Approximately 5% of patients have a connective tissue disorder such as Marfan syndrome or Ehlers-Danlos syndrome, and 40–60% have scoliosis.[70,71] The pathogenesis of pectus excavatum is unknown.[72] A leading theory favors a developmental

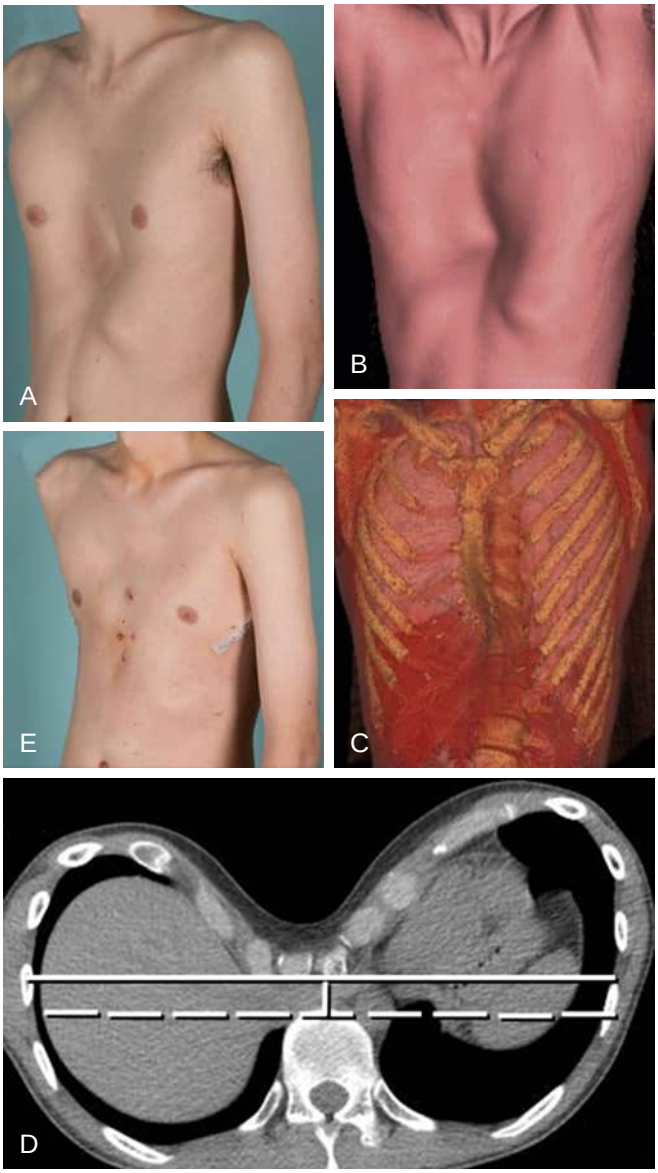

Figure 131.5 Severe pectus excavatum before and after surgery. (A) Severe pectus excavatum deformity in a 22-year-old man. (B–C) Volume-rendered computed tomography images tailored to show the cosmetic appearance of the pectus deformity (B) and to highlight the posterior sternal displacement (C). (D) Axial unenhanced chest computed tomography through the caudal sternum shows severe posterior displacement of the caudal sternum, consistent with severe pectus excavatum deformity. The pectus index, or Haller index, is calculated as the maximum transverse thoracic diameter (*solid horizontal white line*) divided by the minimum *anteroposterior* (AP) diameter (*vertical white line*). The minimum AP diameter is the distance from the posterior aspect of the pectus deformity, typically the caudal sternum or xiphoid process, to the anterior aspect of the vertebral body; the latter is typically determined by drawing a horizontal line across the anterior aspect of the vertebral body (*dashed line*), with the measurement of the minimum AP dimension intersecting this line. The calculated Haller index was 24.64; a Haller index of 3.25 or greater is considered significant. (E) The patient following surgical repair of the pectus deformity. (Courtesy D.E. Jaroszewski, MD, Consultant and Professor, Cardiothoracic Surgery, Mayo Clinic, Scottsdale, AZ.)

disorder with abnormal cartilage growth displacing the sternum inward.[72]

The magnitude of sternal deformity is best assessed by computed tomography of the chest. The transverse and anteroposterior diameters of the rib cage are measured at the level of the deepest sternal depression and are measured from the internal margins of the ribs, vertebra, and sternum. The normal ratio of the transverse to the anteroposterior diameter, also known as the Haller index, is 2.5 or less. A Haller index greater than 3.25 indicates a significant pectus deformity that may need surgical correction[73] (see Fig. 131.5).

Individuals with a significant deformity commonly have cosmetic complaints, and 30–70% of individuals may report exercise limitation or dyspnea with exertion, often out of proportion to recognized abnormalities in cardiopulmonary function.[68,74,75]

PATHOPHYSIOLOGY

Respiratory Mechanics and Exercise Capacity

Most patients with pectus excavatum have normal pulmonary function with normal mobility of the rib cage.[76] Occasionally, patients have a mild restrictive deficit, especially with concomitant scoliosis.[77,78]

Results of cardiopulmonary exercise testing are usually normal, although patients with the most severe deformities may exhibit a mild reduction in maximal work rate and oxygen consumption.[75,79,80] Although the concept is not widely accepted, right ventricular compression by the depressed sternum (Fig. 131.6 and Video 131.1) may be a mechanism contributing to exercise limitation in some individuals.[81,82]

TREATMENT

Surgical correction of pectus excavatum is usually considered for patients with a Haller index greater than 3.25 in conjunction with symptoms or evidence of cardiac or pulmonary impairment.[83,84] The modified Ravitch procedure consists of resection of costal cartilage and a sternal osteotomy, with or without fixation of the sternum by external or internal supports.[83] The Nuss procedure is currently the standard surgical practice for pectus excavatum repair in children and teenagers.[85,86] It entails placing a curved metal rod under the sternum through small incisions on each side of the rib cage. The rod is rotated under the sternum, thus forcing and holding it outward; the rod is removed after 2 to 4 years once the sternum is stabilized in its proper position.[87]

Other minimally invasive or noninvasive procedures under investigation use magnets or create a vacuum through a suction cup to pull the sternum outward and gradually correct the deformity.[88,89]

With corrective procedures, improvement of symptoms and function is difficult to predict. To date, there is no convincing evidence that correction of the deformity improves either cardiopulmonary function or exercise capacity.[75]

FLAIL CHEST

DIAGNOSIS AND ETIOLOGY

Flail chest results when double fractures of three or more contiguous ribs or combined sternal and rib fractures uncouple a segment of the rib cage from the chest wall. Consequently, the rib cage moves inward rather than outward during inspiration[90,91] (Video 131.2). Up to 25% of rib injuries result in flail chest.[92] By contrast, a "nonintegrated chest wall" refers to an unstable segment of the chest wall resulting from multiple single rib fractures to contiguous ribs that *partially* uncouples a segment of the rib cage from the chest wall.[93] Both types of rib injury may result in considerable respiratory morbidity, with 82% requiring intensive care unit admission and 59% mechanical ventilation.[92] The associated mortality can be as high as 33%.[94]

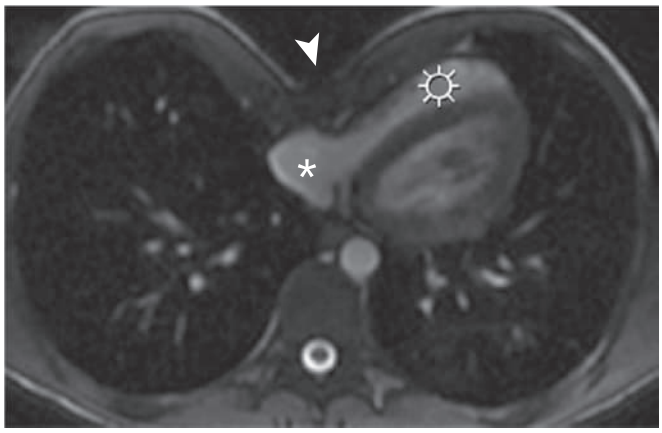

Figure 131.6 Pectus excavatum with right ventricular compression seen on magnetic resonance imaging. Steady-state free precession axial magnetic resonance images show right ventricular compression by the sternum (*arrowheads*) induced by the pectus deformity. Asterisks denote the right atrium; sunbursts denote the right ventricle. See also Video 131.1 for this patient showing cardiac motion.

The most common cause of flail chest is blunt chest trauma.[95] It is most commonly seen after automobile accidents and falls, although it may also develop after aggressive cardiopulmonary resuscitation or in patients with pathologic rib fractures.[96] Rarely, flail chest may complicate corrective rib resection or result from congenital rib abnormalities. In children, flail chest is infrequent because the chest wall is more compliant than an adult's chest wall; thus, flail chest in a child signifies a much greater degree of trauma.[97]

The diagnosis of flail chest is made by examining the rib cage and noting the characteristic paradoxical movement of a chest wall segment inward rather than outward during inspiration (Fig. 131.7 and see Video 131.2). In subtle cases, the paradoxical motion of the flail segment may be appreciated only by palpation of the chest wall, and the diagnosis of flail chest may be delayed for several days.[98] Chest radiographs can confirm the presence of multiple rib fractures; however, three-dimensional reconstruction of a chest computed tomography scan is a more sensitive technique for identifying rib fractures and the other related pulmonary injuries, such as pulmonary contusion or hemothorax.[99] In the mechanically ventilated trauma patient, the diagnosis of flail chest may not be evident until the withdrawal of sedation and resumption of spontaneous breathing.

TRAUMA AND FLAIL CHEST

The presence of flail chest following trauma signifies severe thoracic injury and is an independent risk factor for

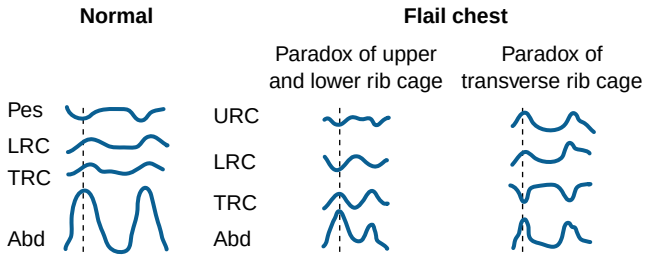

Figure 131.7 Magnetometer tracings of chest wall motion in a normal person and in two patients with flail chest. In each patient, at the point of maximal inspiration (*dashed line*), a portion of the rib cage moves paradoxically. In the patient with a paradox of the *upper rib cage* (URC) and *lower rib cage* (LRC), the upper and lower rib cage segments move inward (*downward tracing*) with outward movement of the *abdomen* (Abd) and *transverse rib cage* (TRC). In the patient with a paradox of the transverse rib cage, the transverse rib cage is the only segment moving inward with inspiration. Pes, esophageal pressure. (Modified from Tzelepis GE, McCool FD, Hoppin FG Jr. Chest wall distortion in patients with flail chest. *Am Rev Respir Dis.* 1989;140:31–37.)

respiratory failure and death.[92,100,101] In addition to flail chest, high-velocity chest injuries are associated with lung contusion, pneumothorax, hemothorax, and injuries to intrathoracic blood vessels.[92,100–102] Pain from fractured ribs can promote atelectasis, impair cough, and contribute to respiratory failure. Patients with flail chest are twice as likely to develop respiratory failure and require mechanical ventilation than patients with isolated lung contusion without flail chest.[97,101]

The presence of flail chest is a marker of increased mortality in patients with isolated chest wall trauma. Without flail chest, mortality from chest wall trauma ranges from 7–14%; with concomitant flail chest, mortality increases further.[97,101] Similarly, in patients with multiple sites of trauma, mortality is roughly 30% in those without flail chest and may be as high as 68% in those with flail chest.[97,101] The high mortality associated with flail chest is in part the result of the coexistence of other injuries such as fractures of long bones or vertebrae, head trauma, rupture of major vascular structures, or laceration of abdominal organs. Concomitant head injury and age older than 65 years are particularly poor prognostic factors in patients with traumatic flail chest.[100,103] In patients who survive the acute injury, chronic disability related to flail chest may develop. Symptoms include chest tightness, chest pain, or dyspnea on exertion. However, with operative fixation of the flail segment, even years after the injury, these symptoms can improve dramatically.[100,104]

PATHOPHYSIOLOGY

Respiratory Mechanics

Flail chest disrupts the anatomic and functional integrity of the chest wall. With flail chest, the uncoupled segment moves passively with the variations of pleural pressure. Thus, with inspiration, the decrease in pleural pressure pulls the flail segment inward; with expiration, the increase in pleural pressure pushes the flail segment outward. If the normal swings of pleural pressure are amplified by a decrease in lung compliance resulting from concomitant pulmonary contusion or atelectasis, the paradoxical motion of the flail segment becomes more pronounced.[105]

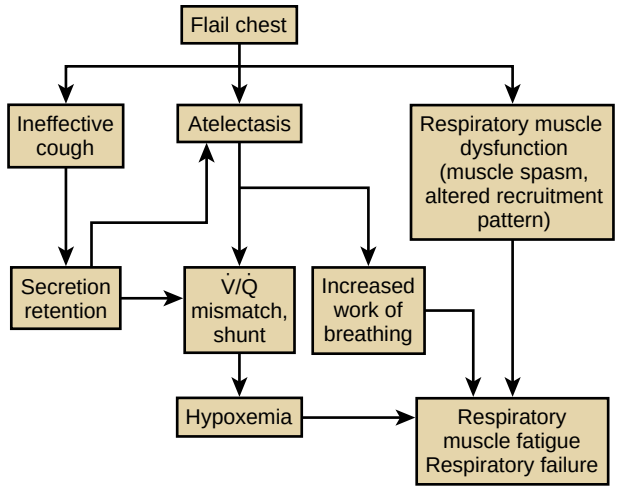

Figure 131.8 Algorithm of factors leading to respiratory failure in flail chest. Flail chest can impair cough and respiratory muscle function, which together with atelectasis and pain can lead to muscle fatigue and failure. V̇/Q̇, ventilation-perfusion.

The location of the flail segment is dependent on the site of rib fractures, with the most common location the lateral rib cage. The flail segment may move paradoxically within the rib cage itself or between the rib cage and the abdomen (see Fig. 131.7).[106] The degree of paradoxical motion also may differ at different locations. Posterior rib fractures exhibit less paradoxical motion because of splinting provided by the paraspinal muscles. Similarly, rib cage paradox may be reduced by intercostal muscle recruitment.[107,108] Different pain-induced respiratory muscle recruitment patterns may explain why some cases of flail chest remain unstable following prolonged mechanical ventilation and why lateral flail segments have a higher propensity for dislocation following surgical fixation.[109,110]

Respiratory Failure

The pathogenesis of respiratory failure in flail chest is multifactorial; hypoventilation resulting from pain, flail-induced impairment of respiratory muscle function, and concomitant lung injury all play a role. A flail segment has important physiologic consequences, even in the absence of lung contusion. First, pain impairs cough and promotes shallow tidal breathing, both of which may lead to atelectasis. Second, the flail segment impairs respiratory muscle performance by increasing the degree of muscle shortening needed for a given tidal volume and by increasing the work per breath.[106–108] Increased work of breathing, together with an inefficient use of respiratory muscles, increases the oxygen cost of breathing. When these factors are compounded by increases in elastic loads related to lung contusion or atelectasis along with hypoxemia, the respiratory muscles are predisposed to fatigue and respiratory failure or weaning difficulty ensues (Fig. 131.8).[105] Although the movement of air back and forth from the injured to the uninjured side of the chest (*pendelluft*) was once thought to be important, it is now recognized not to play a role in the pathogenesis of respiratory failure.[111]

Pulmonary Function Tests

VC and FRC are reduced immediately following the development of flail chest. VC may be reduced to 50% of

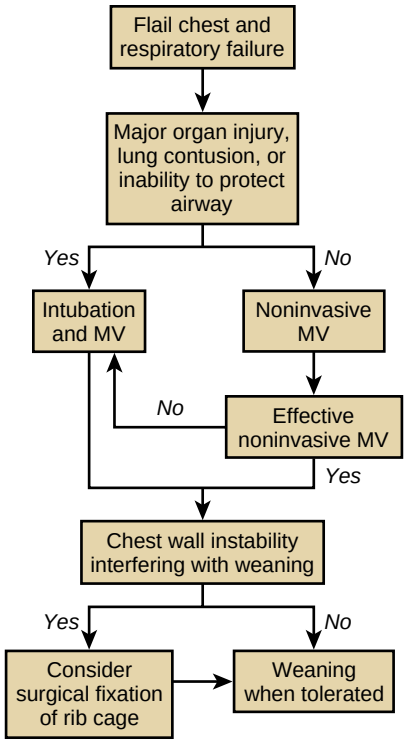

Figure 131.9 Algorithm for management of acute respiratory failure resulting from flail chest. MV, mechanical ventilation.

predicted.[98] These reductions are related to pain, disordered chest wall motion, and underlying lung contusion. In patients with flail chest without lung contusion, VC and FRC generally return to baseline values within 6 months of the acute injury.[112] In contrast, patients with flail chest complicated by lung contusion have impaired pulmonary function for up to 4 years after injury.[112] The reduced VC is likely the result of fibrosis of the contused area. Compared with conservative management, operative fixation of flail chest may be a better option to preserve pulmonary function.[110,113]

TREATMENT

General Aspects

The restoration of anatomic and functional integrity of the chest wall is key for avoiding complications related to flail chest. Surgical and nonsurgical approaches can be used to stabilize the flail segment (Fig. 131.9). Nonsurgical management is based on administration of adequate analgesia, clearing of bronchial secretions, and mechanical ventilatory assistance if needed.[114] Control of pain is crucial in averting atelectasis and achieving an effective cough. Adequate pain relief can be accomplished with oral medications, patient-controlled analgesia pumps, intercostal nerve blocks, or epidural anesthesia.[114] Adequate analgesia in combination with supplemental oxygen, effective tracheobronchial toilet, and cautious fluid replacement often results in successful treatment of flail chest and avoidance of respiratory failure. If needed, mechanical ventilation can act as a pneumatic splint to stabilize the flail segment by keeping pleural pressure positive. However, mechanical ventilation delivered through a tracheostomy or endotracheal tube solely for the purpose of providing stability to the chest wall is not recommended because of the increased morbidity and mortality associated with invasive ventilation. In contrast, positive-pressure ventilation delivered noninvasively through a nasal or face mask to patients who are spontaneously breathing and able to protect their upper airway provides an alternate means of stabilizing the flail segment.[114] Noninvasive ventilation, in conjunction with patient-controlled analgesia, improves gas exchange, allows for early patient mobilization and access for physiotherapy, and significantly reduces morbidity and mortality when compared with invasive mechanical ventilation.[115,116] If intubation and mechanical ventilation are needed, a low-impedance ventilator mode that minimizes the likelihood of generating subatmospheric pleural pressure is an optimal choice for stabilizing the flail segment and for weaning from ventilation.[106]

Surgical procedures used to stabilize a flail segment include mobilization of large chest wall flaps and insertion of devices such as medullary wires or nails, Judet struts, or titanium plates.[90,117] The few controlled studies available suggest that surgical fixation may be superior to conservative management by reducing the need for ventilatory support, reducing the length of hospital stay and days of mechanical ventilation, lowering the infection rate,[118–121] and possibly improving pulmonary function test results.[113] Although the indications are not defined, operative fixation of flail chest may be appropriate for patients who are unable to be weaned from mechanical ventilation because of chest wall instability; patients undergoing thoracotomy for concurrent injuries; or those with persistent pain, severe chest wall instability, a progressive decline in pulmonary function, or a deformity that can be repaired by fixing only one fracture per rib.[119,122,123]

ANKYLOSING SPONDYLITIS

DIAGNOSIS AND ETIOLOGY

Ankylosing spondylitis (AS) is a chronic progressive inflammatory disease involving the ligamentous structures of the spine, costovertebral, sacroiliac, and large peripheral joints.[124–126] It can be seen in 0.2–1.4% of the population and affects men more than women, whites persons more than Blacks, and up to 20% of human leukocyte antigen B27–positive persons.[127] The most common age of onset is between 15 and 25 years. Back pain, generally worse in the early morning, is a frequent symptom and may precede the diagnosis by years. Fever, malaise, and joint pain also may be present.[128,129] AS is associated with up-regulation of genes encoding the proinflammatory cytokine interleukin-17[130] and with overexpression of *tumor necrosis factor-α* (TNF-α).[131]

PATHOPHYSIOLOGY

Respiratory Mechanics

Chronic inflammation eventually leads to fibrosis and ossification of the spine (Fig. 131.10) and adjacent structures, as well as immobility of the costovertebral and sternoclavicular joints. This in concert with back pain limits rib cage mobility (Fig. 131.11).[102,126,132] Limited rib cage

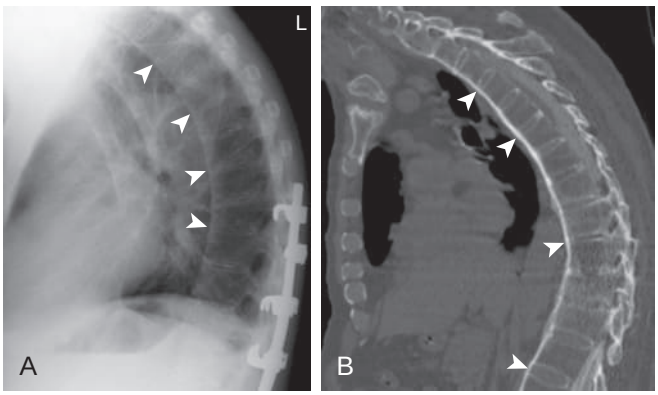

Figure 131.10 Lateral imaging of two patients with fused thoracic spine. (A) Lateral chest radiograph and (B) sagittal reformatted thoracic computed tomography myelogram from a different patient show flowing syndesmophytes (*arrowheads*) representing ossification of the outer fibers of the annulus fibrosis, bridging one vertebral body corner to another. When accompanied by longitudinal ligament ossification, fusion and kyphosis of the spine result.

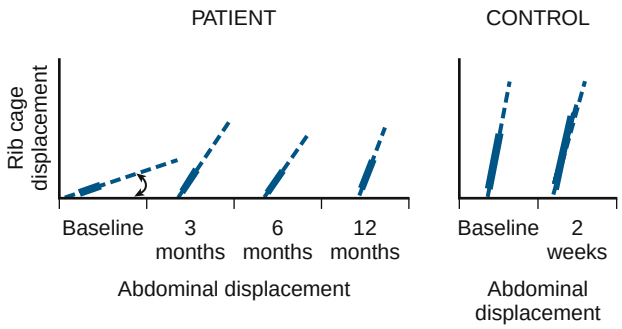

Figure 131.11 Representative plots of the rib cage and abdominal displacements during quiet breathing in a seated patient with ankylosing spondylitis, before and at various time points during therapy with anti–tumor necrosis factor-α. Note the diminished contribution of the rib cage to tidal volume at baseline and the progressive increase in the rib cage contribution to breathing with treatment, a contribution that becomes closer to the normal patterns obtained about 2 weeks apart in a healthy individual (control). (Modified from Tzelepis GE, Kalliakosta G, Tzioufas AG, et al. Thoraco-abdominal motion in ankylosing spondylitis: association with standardized clinical measures and response to therapy. *Ann Rheum Dis.* 2009;68:966–971.)

mobility, in turn, promotes lung inflation through the abdomen pathway (i.e., the lung expands along the "path of least resistance"),[133,134] resulting in a reduced contribution of rib cage expansion to breathing (from a normal contribution of 75% to tidal volume to ~50%)[135] (see Fig. 131.11). Thus, during quiet breathing, exercise, or speech, lung volume changes mostly by caudal displacement of the diaphragm and expansion of the anterior abdominal wall.[133,134,136] Consequently, transdiaphragmatic pressure increases by 2.4-fold in patients with AS at levels of ventilation at which healthy individuals increase transdiaphragmatic pressure by only 1.4-fold.[126] With advanced disease, limited rib cage mobility may lead to intercostal muscle atrophy.[126] Despite a pronounced reduction in rib cage mobility, lung compliance remains normal except in patients with fibrobullous (eFig. 131.4) or interstitial lung disease.[126,136,137]

Pulmonary and Respiratory Muscle Function

Mild restrictive lung disease may be seen in patients with AS.[138] This restriction may be caused by spinal and rib cage immobility, the presence of fibrobullous disease, or kyphosis, which may develop in up to 50% of patients with AS[139–141] and may be a consequence of osteoporosis or spinal fracture[142,143] (eFig. 131.5). Mild restriction may also be the result of back pain limiting patient performance.[144] Restriction is associated with disease activity and duration.[140]

Respiratory muscle strength may be reduced in AS, and respiratory muscle endurance may be impaired even in individuals with normal respiratory muscle strength.[126,145,146] Mild reductions in strength and endurance may be related to intercostal muscle atrophy[126] or to poor coordination or performance as a result of pain.[146,147] Patients with AS are also at risk for respiratory failure if cervical spine fractures (typically C6 or C7) cause tetraplegia.[148]

Gas Exchange and Exercise Capacity

Regional ventilation is usually normal despite the limited expansion of the rib cage.[149] A mild impairment in gas exchange may be seen (reduced diffusing capacity for carbon monoxide) in some patients, probably related to the mild reduction in lung volumes and total alveolar surface area.[139] However, when fibrobullous disease (see eFig. 131.4) is present, gas exchange may be severely compromised and arterial *partial pressure of oxygen* (Po_2) reduced.[150]

Exercise capacity may be reduced in patients with AS.[145,151] The reduction in exercise capacity may be related more to deconditioning or reduced cardiac preload than to a limitation of ventilation.[145,152] A progressive decline in exercise capacity may be significant enough to result in loss of employment.[153]

Interstitial Lung Disease

Fibrobullous upper lobe disease is present in 1–4% of patients with AS.[150] The cause of apical fibrobullous disease is unknown. Possible causes include diminished upper lobe ventilation and apical mechanical stress resulting from thoracic rigidity, as well as recurrent pulmonary infections from impaired cough. Fibrobullous disease may be unilateral or bilateral and affects male patients more than female patients. The spectrum of disease ranges from minimal upper lobe interstitial opacities to marked fibrosis, honeycombing, and cavitary lesions that may be mistaken for tuberculosis.[150] In a limited number of cases, histologic examination has revealed prominent interstitial fibrosis with hyaline and elastic degeneration of collagen and an absence of granulomas.[150] Patients are usually asymptomatic but, with severe disease, they may develop dyspnea and be at risk for spontaneous pneumothorax, aspergillosis (eFig. 131.6), or mycobacterial infection. In another 10–20% of patients with AS, nonapical interstitial lung disease develops and can be detected by high-resolution computed tomography scans of the chest.[154]

TREATMENT

Nonsteroidal anti-inflammatory drugs, together with exercise and physical therapy, are key components of

standard care.[124,155–158] Corticosteroids do not prevent progression of the disease.[159] However, the development of biologic agents represents a major advance in the treatment of AS.[160,161] The TNF-α antagonists (infliximab, etanercept, adalimumab, and golimumab) provide symptom relief, reduce spinal inflammation, and improve the quality of life in these patients.[160–162] Anti–TNF-α therapy improves rib cage mobility (see Fig. 131.11).[133] Anti–interleukin-17A monoclonal antibody has also been approved for the treatment of AS.[163] Tobacco use should be avoided. Patients should be monitored with baseline chest radiography and spirometry and should undergo repeat studies if respiratory symptoms develop. For patients treated with anti–TNF-α agents, a high index of suspicion for possible reactivation of latent tuberculosis is required.[164,165] Vertebral osteotomy may at times be performed to address spinal deformities.[166] If intubation is planned, it should be performed with caution because these patients are at increased risk for spinal cord injury given that hyperextension of a rigid cervical spine may lead to fracture and, rarely, upper airway compromise resulting from involvement with fixation of the cricoarytenoid joint. Because lung resection can be complicated by bronchopleural fistula in 50–60% of patients with fibrobullous disease,[150] this procedure is recommended only for treatment of major hemoptysis.[150]

OBESITY

DIAGNOSIS AND ETIOLOGY

The prevalence of obesity is increasing, and obesity is a recognized risk factor for many chronic diseases, including cancer and conditions affecting the lungs, heart, kidneys, and musculoskeletal system.[167] Worldwide, it is estimated that more than 600 million adults and more than 100 million children are obese, with the rate of increase of obesity in children surpassing that in adults in many countries.[167] In the United States alone, more than $300 billion in health care expenditures have been attributed to obesity, and this estimate continues to climb with time.[168] Body fat usually constitutes 15–20% of body mass in healthy men and 25–30% in healthy women. In obesity, the body fat content may increase by as much as 800% in men and 500% in women.[169] Fat-free mass also increases in obese individuals, accounting for 15–30% of the total weight gain.[170,171] Several parameters have been used to assess obesity, the most common being *body mass index* (BMI), which is calculated as the body weight in kilograms divided by the square of the height in meters (body weight/height^2). (BMI can also be calculated as the body weight in pounds multiplied by 703 and divided by the square of the height in inches.) Individuals with a BMI between 18.5 and 24.9 kg/m^2 are considered normal, persons with a BMI between 25 and 29.9 kg/m^2 are overweight, and persons with a BMI greater than 30 kg/m^2 are obese. When the BMI is greater than 40 kg/m^2, obesity is severe (morbid).[172]

When compared with persons with a normal BMI, overweight persons have a 20–40% higher risk for death, and obese persons have a 300–400% higher risk for death.[173,174] Morbidity also increases as BMI increases and is primarily related to cardiovascular and respiratory factors, with intra-abdominal fat constituting an independent risk factor for cardiovascular disease.[173,175–177]

The most frequent respiratory symptoms in obese individuals are dyspnea and exercise intolerance.[177] These symptoms may be related to abnormal pulmonary function, disordered respiratory control, and elevated levels of mediators of inflammation, such as those linking obesity to airway hyperresponsiveness[178,179] (see Chapter 61). The severity of the respiratory impairment may not correlate with the degree of obesity.

PATHOPHYSIOLOGY

Obese individuals with the same BMI may exhibit different abnormalities in respiratory function. In particular, in some obese individuals, the arterial P_{CO_2} may be normal, whereas in others with the same BMI, the P_{CO_2} may be elevated. Indeed, the level of arterial P_{CO_2} is used to distinguish obese individuals who have simple obesity (individuals who are eucapnic) from those who have the *obesity-hypoventilation syndrome* (OHS; individuals who retain carbon dioxide).[180] In addition, pulmonary function, respiratory mechanics, gas exchange, respiratory control, and exercise capacity may be significantly different in patients with simple obesity and OHS.

Pulmonary Function

In obesity, the most common abnormalities of pulmonary function are reductions in *expiratory reserve volume* (ERV) and FRC (Fig. 131.12).[181,182] For each unit increase in BMI from 20 to 30 kg/m^2, FRC and ERV decrease by approximately 3% and 5%, respectively; thereafter, for each unit increase in BMI, both FRC and ERV decrease approximately 1%.[181] Consequently, an individual with a BMI of 30 kg/m^2 can be expected to have an FRC of approximately 75% of predicted and an ERV of only 47% of predicted. The FRC is reduced by adipose tissue compressing the rib cage and abdomen, thereby reducing the outward elastic recoil of the chest wall and shifting the balance of recoil between the lung and chest wall to lower lung volumes. Because residual volume is affected to a lesser extent than FRC, ERV is preferentially reduced.[183–185] In patients with OHS, FRC and ERV may be reduced even further.[186,187]

Although total lung capacity, VC, and residual volume may be normal or only minimally reduced in individuals with simple obesity, these values may be significantly reduced (total lung capacity and VC <80% of predicted) in persons with OHS or morbid obesity (Table 131.3).[186,187] Because pulmonary function is more severely affected in OHS than in simple obesity, factors other than the BMI must be involved. The more substantial reductions in total lung capacity and VC in persons with OHS may reflect weakness of the respiratory muscles.[188] In addition, the distribution of fat may contribute to differences in lung volumes. For example, the distribution of body fat to the upper body (central fat distribution) impairs pulmonary function more than a distribution to the lower body (below the hips).[189–191] Upper body fat distribution is indicated by a waist circumference of 35 inches (89 cm) or more for women and 40 inches (102 cm) or more for men.[189–191] Diffusing capacity testing in obese patients can yield heterogeneous results; however, in general, the single-breath diffusing capacity is usually normal or increased in simple obesity (because of

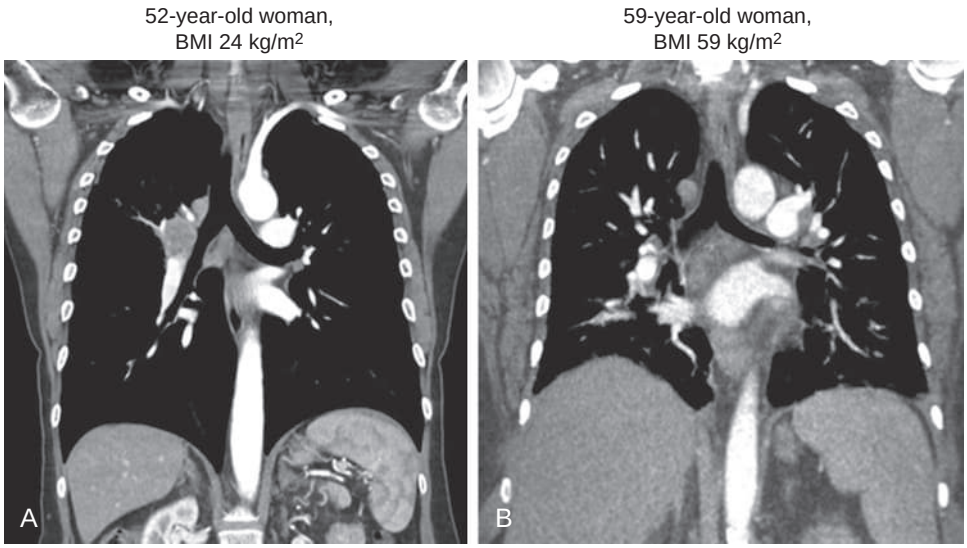

Figure 131.12 Lung volumes and obesity. Coronal computed tomography images of a nonobese person (A) and an obese individual of similar height, age and total lung capacity (B). The lung volume of the obese individual is noticeably less than that of the nonobese individual. The reason may be the added load of excess fatty tissue on the respiratory system that is most pronounced in the supine position. Typically, obesity has the greatest effect on functional residual capacity and expiratory reserve volume. BMI, body mass index.

Table 131.3 Representative Values of Respiratory Pathophysiology of Simple Obesity and Obesity Hypoventilation Syndrome

Parameter	Normal	Simple Obesity	Obesity Hypoventilation
BW (% ideal)	100	200	200
BMI (kg/m^2)	24	45	45
TLC (% pred)	100	95	80
Crs (L/cm H_2O)	0.10	0.05	0.06
Rrs (cm H_2O/L/sec)	1.2	4.0	7.8
Work of ventilation (J/L)	0.43	0.74	1.64
MVV (L/min)	160	130	90
PI_{max} (cm H_2O)	100	95	60

BMI, body mass index; BW, body weight; Crs, compliance of the respiratory system; J, joule; MVV, maximum ventilatory volume; PI_{max}, maximal static inspiratory pressure; pred, predicted; Rrs, respiratory system resistance; TLC, total lung capacity.

Modified from Rochester DF. Obesity and abdominal distention. In: Roussos C, editor. *The Thorax*. New York: Dekker; 1995:1950–1973.

increased pulmonary blood volume) and is slightly reduced in OHS. One pattern that can be seen in patients with morbid obesity–related restriction is a supranormal rate of carbon monoxide uptake from alveolar gas (also expressed as the ratio of diffusing capacity for carbon monoxide to alveolar volume), which results from a normal (or even increased) capillary blood volume passing through lungs that have incomplete alveolar expansion without compromised alveolar structure (similar to patients with other conditions limiting alveolar expansion, such as neuromuscular disease).[192,193] Results of other tests of pulmonary function, such as the ratio of forced expiratory volume in 1 second to forced VC (FEV_1/FVC ratio), maximal voluntary ventilation, and peak inspiratory flow rate, are usually normal.[186,187]

Respiratory Mechanics

Obesity reduces respiratory system compliance, primarily by lowering lung compliance (Fig. 131.13).[182,184,194–197] In simple obesity, values for respiratory system compliance are approximately 80–90% of normal and are further reduced as BMI increases or when changing from the upright to supine position.[182,194–197] In OHS, respiratory system compliance is generally less than 45% of normal.[198] The reduced compliance is likely multifactorial and depends on the degree of obesity. Studies in patients undergoing chest wall strapping (which is thought to mimic mild to moderate obesity) suggest a decreased alveolar surface compliance resulting from changes in surfactant function whereas, in more severe obesity, it is thought that the weight of adipose tissue forcing FRC and tidal breathing to low lung volumes, near residual volume, reduces lung compliance because of airway closure.[184,194,195,199] In addition, an increase in pulmonary blood volume leads to reduced lung compliance.[200] Conversely, chest wall compliance is generally normal in obesity, with a similar pressure-volume relationship as in normal individuals—only the curve is shifted to the right (see Fig. 131.13).[182,184,194] This shift is caused by excess chest wall adipose tissue and creates a threshold load by making pleural and alveolar pressure less subatmospheric or even positive at end-expiration (intrinsic positive end-expiratory pressure).[182,194] The inspiratory muscles must lower pleural pressure sufficiently to overcome intrinsic positive end-expiratory pressure before inspiratory flow ensues. The inspiratory threshold load is greater in the supine position and may account for much of the disordered chest wall mechanics in obesity.[183,194,201]

Airway resistance and total respiratory system resistance are increased in obesity primarily because of breathing at low lung volumes, where the airway diameter is lower and airway resistance is higher, with values usually twice as great as those in nonobese individuals.[197,202] However, given that airway resistance remains elevated even after normalizing for lung volume or after significant weight loss (e.g., specific airway conductance is reduced to 50–70% of normal), factors other than breathing at low lung volumes may account for some of the increase in resistance.[202–206] Increased levels of inflammation may be present in the airways of the obese patient and may promote a unique

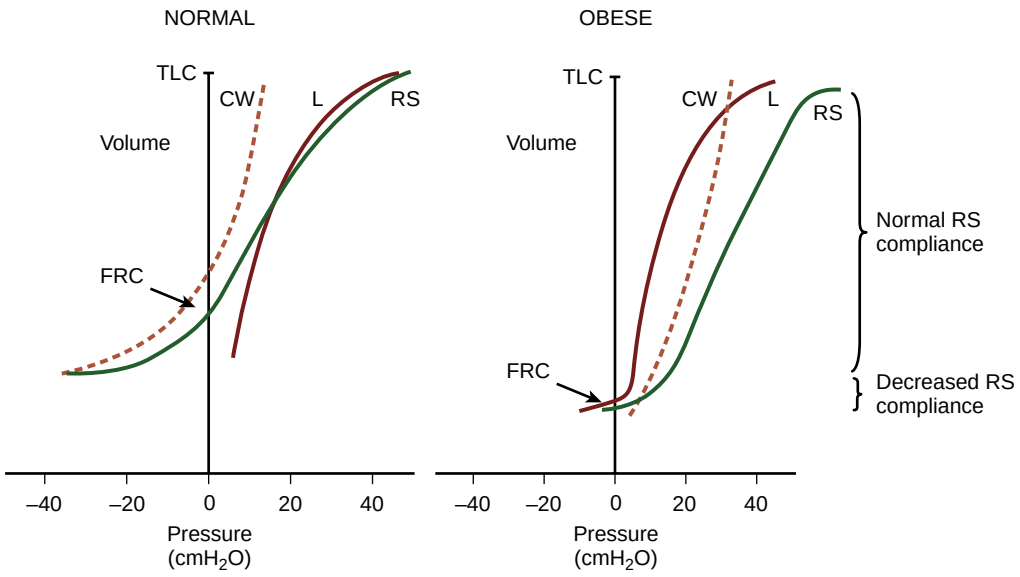

Figure 131.13 Theoretical volume-pressure curves in healthy and obese individuals. In obese persons, the *functional residual capacity* (FRC) is reset to a lower lung volume where the lung is less compliant, and tidal breathing takes place at the lower stiffer region of the respiratory system volume-pressure curve. CW, chest wall; L, lung; RS, total respiratory system; TLC, total lung capacity.

asthma phenotype, with additional airway dysfunction arising from possible proinflammatory properties of leptin (although this role remains undefined).[207–210] The normal FEV_1/FVC ratio suggests that the greatest resistance to airflow may be at the level of the small airways rather than the large airways; this view is supported by studies using impulse oscillometry.[205,211,212] The transition from the upright to the supine position may further increase airway resistance.[197] The increase in the intra-abdominal pressure when supine may further reduce FRC, thus resulting in expiratory flow limitation during tidal breathing and orthopnea in severe obesity.[182,201,213,214] The negative impact of the supine position on respiratory mechanics must be considered when evaluating obese patients for risks following general anesthesia.[215,216]

The work of breathing is increased in both simple obesity and OHS.[198,217,218] Three factors that contribute to the increase in work are increases in *elastic loads* (reductions in compliance), *threshold loads* (increases in the pressure needed to initiate inspiration), and *resistive loads* (increases in pressure needed to move air through the smaller airways).[195] The work of breathing can be up to 60% greater in simple obesity and as much as 250% higher in OHS.[198,217,218] The increased work together with a reduced efficiency of breathing increases the oxygen cost of breathing 5-fold in simple obesity and 10-fold in OHS.[192] The increased oxygen cost of breathing may place obese patients at risk for respiratory failure during states of increased ventilatory demands, such as during intercurrent illness.[218] To minimize the elastic load during inspiration and optimize the oxygen cost of breathing, obese patients adopt a rapid, shallow breathing pattern, which is more pronounced in OHS than in simple obesity.[219–222] In persons with simple obesity, the respiratory rate during quiet breathing is approximately 40% higher than in normal-weight subjects, with most of the lung volume change during tidal breathing accomplished by the rib cage rather than by abdominal displacement.[222] In OHS, however, breathing frequency is 25% higher and tidal volume 25% lower than in simple obesity.[221,223] The adverse effect of adopting a rapid, shallow breathing pattern is increased dead-space ventilation, which may contribute to carbon dioxide retention.[218,223]

Gas Exchange

In patients with simple obesity, the arterial P_{O_2} is usually normal or slightly reduced.[224] However, in patients with OHS or morbid obesity, hypoxemia is more pronounced.[186,187,224] Hypoventilation can account for hypoxemia in the setting of a normal alveolar-arterial P_{O_2} difference. Additionally, ventilation-perfusion mismatch and shunt resulting from premature airway closure can widen the alveolar-arterial P_{O_2} difference and contribute to hypoxemia.[224,225] Because of the physiologic changes described previously, hypoxemia worsens in the supine position.[182,197,225,226] The effects of these physiologic changes may be most profound in the setting of anesthesia, where the combination of these factors can lead to very rapid severe hypoxemia once the obese patient is apneic.[216,227,228] During exercise, oxygenation may improve in response to enhanced ventilation of the lung bases.[219,226] Weight loss will improve oxygenation by shifting FRC toward normal; an increase in FRC lessens the degree of airway closure during tidal breathing and improves arterial P_{O_2} roughly by 1 mm Hg for every 5 kg reduction in weight.[224] In the setting of mechanical ventilation, it has been demonstrated that appropriate adjustments in applied positive end-expiratory pressure and lung recruitment maneuvers can improve operating lung volumes, respiratory system elastance, and oxygenation.[229]

Control and Pattern of Breathing

Differences in the control of breathing may also explain why hypercapnia is found in some but not all obese individuals of similar BMI. In eucapnic obese individuals, central respiratory drive is intact. Respiratory drive—as measured by the occlusion pressure at 100 msec, ventilatory, or electromyographic responses to hypoxia or hypercapnia—is normal or even increased because of the elastic and threshold loads placed on the inspiratory muscles.[192,201,230] If the elastic and threshold loads are lessened by weight loss, the compensatory increase in ventilatory drive decreases.[231,232] In patients with OHS, however, respiratory drive is blunted, and the

occlusion pressure at 100 msec, ventilatory, or electromyographic response to hypoxia or hypercapnia is reduced.[230,233] The exact mechanism underlying the attenuated ventilatory drive in OHS is unknown. Mechanical disadvantage in OHS does not adequately explain the hypercapnia because most patients with OHS can normalize arterial P_{CO_2} through volitional hyperventilation.[234] A genetic predisposition is unlikely because ventilatory drive is intact in first-degree relatives of patients with OHS.[235] Instead, in persons with OHS, the central chemoreceptors may be "reset" because of chronic hypoxemia or hypercapnia or because of reduced leptin levels or leptin resistance. Leptin is a protein produced by adipose tissue that acts in the hypothalamus to decrease appetite, increase metabolic rate, and stimulate breathing. The development of a relative leptin deficiency or leptin resistance may contribute to diminished ventilatory responsiveness and hypercapnia in OHS.[186,236,237] Because serum leptin levels are generally increased in obesity, both in simple obesity and even more so in OHS, central resistance to leptin has been proposed.[236,237] Furthermore, these ventilatory control changes and resultant hypercapnia may be worsened by relative overproduction of carbon dioxide in patients with OHS.[238]

The increased respiratory drive in simple obesity may contribute to the sensation of dyspnea.[219,232,239] However, dyspnea is also a frequent and disabling symptom in OHS and may be related to airway disease or disordered respiratory mechanics (decreased compliance, increased airway resistance, or expiratory flow limitation).[217,219,239–242] Finally, dyspnea may result from cardiac disease, a frequent comorbid condition.

Respiratory Muscle Function

In patients with simple obesity, respiratory muscle strength is usually normal; in fact, strength may be maintained by the chronically higher elastic and threshold loads imposed on the inspiratory muscles.[197,201,242] In patients with OHS, respiratory muscle strength is usually decreased, perhaps because of deconditioning or other factors related to chronic disease.[186,242] In severely obese persons, especially those with dyspnea or OHS, diaphragm function may be impaired, especially in the supine position.[242,243] This may be related to increased intra-abdominal pressure and cranial displacement of the diaphragm.[243]

Exercise Capacity

At rest, obese persons have increased metabolic and ventilatory demands, and resting volume of oxygen inhaled per unit time can be approximately 25% higher than in nonobese subjects.[244] Given these increased demands, dyspnea scores at any submaximal work rate are higher in obese individuals.[219,245] In general, maximal work rates do not differ significantly between obese and nonobese persons, and the $\dot{V}_{O_2}$ work rate relationship is normal.[244–246] During maximal testing, a typical pattern seen in obese patients is a normal (or supranormal) peak volume of oxygen inhaled per unit time when adjusted for ideal body weight but a low peak volume of oxygen inhaled per unit time when adjusted to actual body weight (because of the increased unmeasured work being performed by an obese subject and accounting for the lower metabolic rate of adipose tissue, respectively).[246–248] In addition to the increased metabolic demands of moving relatively heavier limbs during exercise, there is evidence of a higher oxygen cost of breathing playing a small role as well.[249] The ventilatory response to exercise in obese individuals can be abnormal, and they have been shown to increase end-expiratory volume during exercise (rather than decrease it); this may serve to attenuate the expiratory flow limitation otherwise seen at lower operating lung volumes.[219] This breathing pattern may assist these persons in accommodating their higher metabolic demands and maintain relatively normal gas exchange.

TREATMENT

Weight loss is the optimal therapy but is not always attainable, and long-term weight loss maintenance is even more difficult.[250] Generally, weight loss programs emphasize diet, enhanced physical activity, and behavioral therapy as initial treatments in all obese individuals regardless of the severity of obesity. Bariatric surgery can produce not only a substantial weight loss but also long-term maintenance of weight loss.[251] It is indicated in obese individuals with a BMI of at least 40 kg/m^2 and in those with a BMI of at least 35 kg/m^2 with serious comorbidities.[250,252,253] Weight loss in obese individuals is associated with improved ERV and FRC[254,255]; however, there is no correlation between the magnitude of weight loss and the degree of improvement of lung volumes. Weight loss also may improve respiratory muscle performance,[188] resting gas exchange,[254,256] diffusing capacity (if previously morbidly obese),[224] dyspnea scores,[232,254,257] sleep apnea,[257–259] 6-minute walk test results,[254,260] airway responsiveness,[261] and respiratory drive.[232] Overall, weight reduction appears to be the most effective solution to OHS, with bariatric surgery providing the best option for managing the various comorbid conditions related to extreme obesity, such as hypertension, hyperlipidemia, cardiac dysfunction, and type 2 diabetes.[262–264]

PATHOGENIC ASPECTS OF RESPIRATORY FAILURE IN CHEST WALL DISEASES

Elastic loads imposed on the respiratory muscles are the primary causes of ventilatory failure in chest wall diseases.[105] Hypoventilation may develop acutely if the magnitude of load is excessive and there is loss of integrity of the rib cage, as in flail chest, or it may develop after a variable period of time if the load is chronic and progressive, as in kyphoscoliosis, thoracoplasty, or obesity.[105] Generally, in disorders with chronic elastic loading of the respiratory muscles, the development of respiratory failure depends on a balance between the magnitude of the elastic load and the functional status of respiratory muscles. Minimal decreases in chest wall compliance, as in pectus excavatum or in kyphoscoliosis with Cobb angles of less than 120 degrees, do not excessively overload the respiratory muscles and do not cause respiratory failure unless there is concomitant respiratory muscle weakness.[8] Similarly, when decreased distensibility of the chest wall is limited to only one of its compartments, for example, the rib cage in AS, the diaphragm adapts to accomplish lung inflation primarily through displacement of the abdomen and can thus sustain alveolar ventilation near normocapnic levels.[133,134] With excessive loads on the respiratory muscles, patients typically require a greater inspiratory

pressure to inflate the stiff chest wall with each breath.[9] In some instances, this pressure becomes a significant fraction of maximal inspiratory pressure (>50% of the maximal inspiratory pressure).[9] In this setting, the breathing pattern is altered by decreasing tidal volume and increasing respiratory frequency to decrease this greater inspiratory pressure and avoid fatigue of the respiratory muscles.[265,266] Consequently, the proportion of wasted (dead space) ventilation increases, alveolar ventilation decreases, and ultimately hypoventilation and hypercapnia ensue.[265]

Sleep-disordered breathing,[267,268] age-related decreases in chest wall compliance[269] and respiratory muscle function,[270] mechanical disadvantage of the diaphragm,[9,271,272] and underlying lung dysfunction resulting from microatelectasis[5] or, less frequently, from bronchial compression[43] by the deformed spine in severe kyphoscoliosis may significantly contribute to development of respiratory failure. The first signs of respiratory failure invariably manifest during sleep in these patients.[267,268] During wakefulness, patients with chest wall disorders typically depend on intercostal and accessory muscle activation to maintain alveolar ventilation.[11] During rapid eye movement sleep, intercostal and accessory muscle activation is inhibited and, in conjunction with a weakened diaphragm, may lead to hypoventilation.[33,34] Decreased intercostal muscle tone may further reduce FRC and in certain patients may cause chest wall instability. The supine sleep position also lowers tidal volume and worsens gas exchange because of cephalad movement of abdominal contents and displacement of the diaphragm into the thoracic cavity.[273] A mechanical disadvantage of the diaphragm can develop when the diaphragmatic muscle tension is not converted into effective pressure and when the muscle shortening is not converted into inspiratory flow; it can contribute to respiratory difficulties in patients with severe kyphoscoliosis and possibly in those with thoracoplasty and chronic flail chest.[9,271,272] This disturbance is probably related to the way the diaphragm is coupled to distorted thoracic cavity, regional differences in chest wall compliance, or rib cage muscle dysfunction. In patients with chest wall disorders, the increased work of breathing over time may lead to respiratory muscle fatigue, an altered breathing pattern with shallow and frequent breathing, and ultimately alveolar hypoventilation, development of pulmonary hypertension, right heart failure, and death.

Key Points

- Diseases that affect the chest wall, including obesity, primarily affect the respiratory system by reducing chest wall compliance. The degree to which the chest wall stiffens varies with the disease process. Individuals with kyphoscoliosis may have the greatest degree of chest wall stiffness, whereas individuals with pectus excavatum or ankylosing spondylitis may have normal chest wall compliance.
- The lung is usually an "innocent bystander" in the sense that it is usually not primarily affected by a pathologic process. When restrictive chest wall disorders limit full inflation of the lung, however, microatelectasis can lead to a reduction in lung compliance and impaired gas exchange.
- Of the chest wall disorders, flail chest is most likely to precipitate acute respiratory failure, whereas kyphoscoliosis and severe obesity are most likely to lead to chronic ventilatory failure, pulmonary hypertension, and right heart dysfunction. Coincident inspiratory muscle weakness in any of these disorders will further worsen restrictive pathophysiology and predispose persons to respiratory failure.
- Acute respiratory failure may complicate flail chest and can be treated initially with positive-pressure ventilation. In some patients with flail chest, surgical fixation of the flail segment may reduce the duration of mechanical ventilation and improve long-term pulmonary function.
- Chronic respiratory failure, which can be seen in kyphoscoliosis or with severe obesity, can be successfully managed with noninvasive nocturnal positive-pressure ventilation. This type of ventilation has markedly improved morbidity and mortality in this group of individuals.

Key Readings

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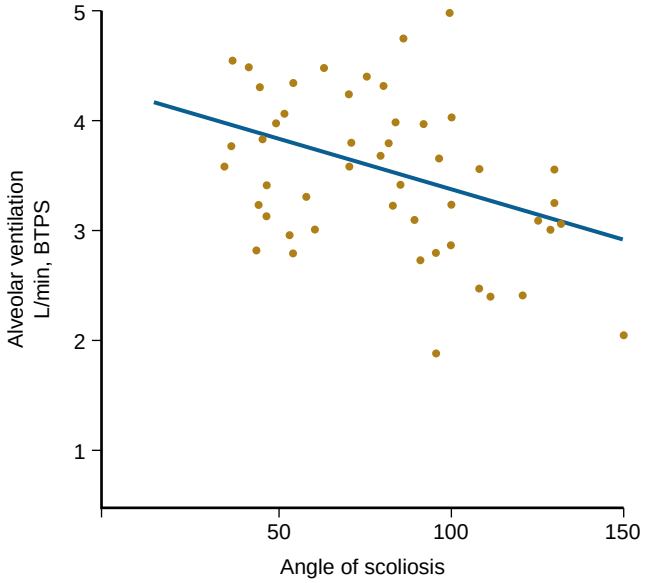
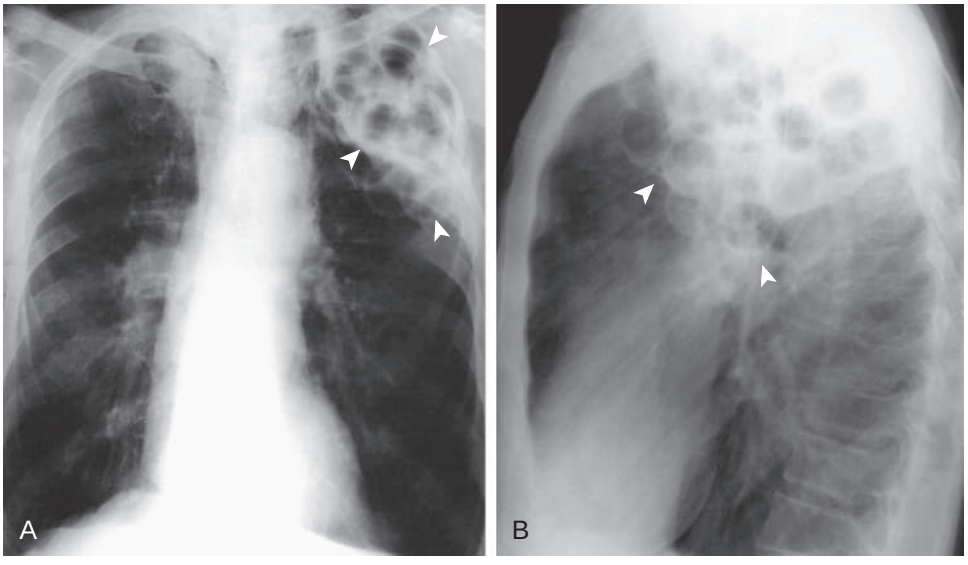
Complete reference list available at ExpertConsult.com.

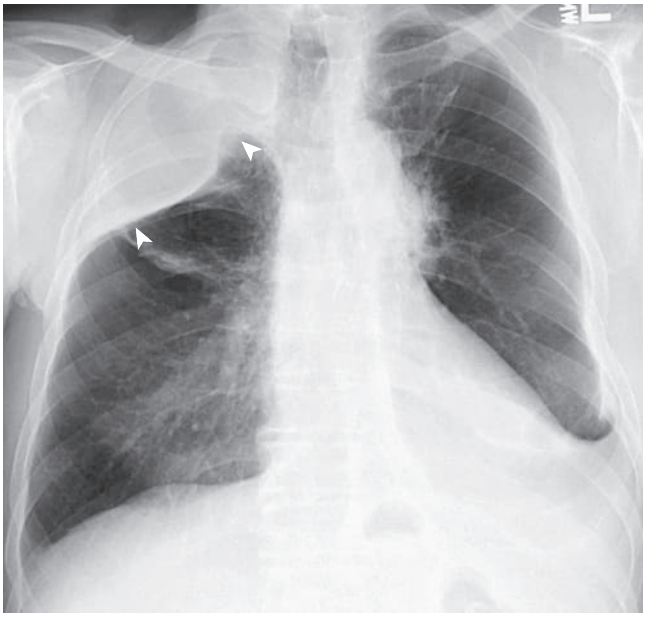
eFIGURE IMAGE GALLERY



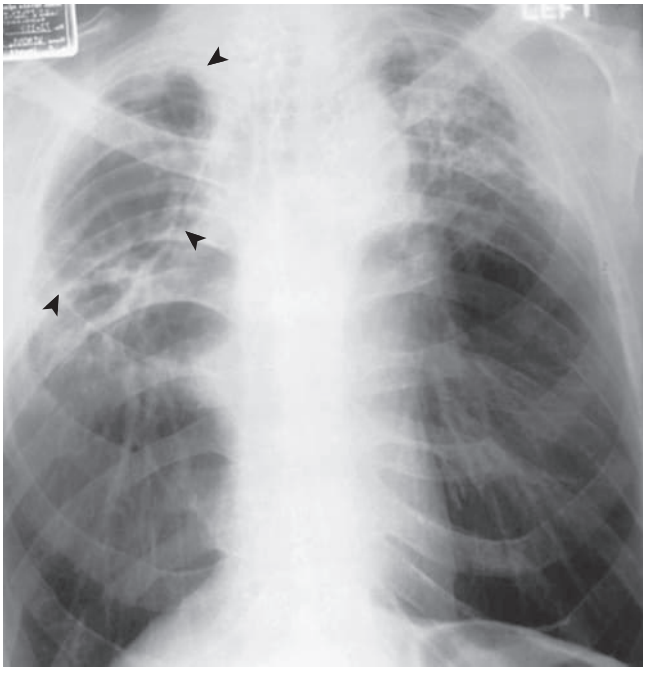
eFigure 131.1 The relationship between alveolar ventilation and angle of scoliosis in patients with idiopathic kyphoscoliosis. Note the decrease in alveolar minute ventilation below normal level (≈4.2 L/min) with the increasing angle of scoliosis. These measurements were made with the subjects awake. BTPS, body temperature, ambient pressure, saturated with water vapor. (Modified from Kafer ER. Idiopathic scoliosis. Gas exchange and the age dependence of arterial blood gases. *J Clin Invest.* 1976;58:825–833.)



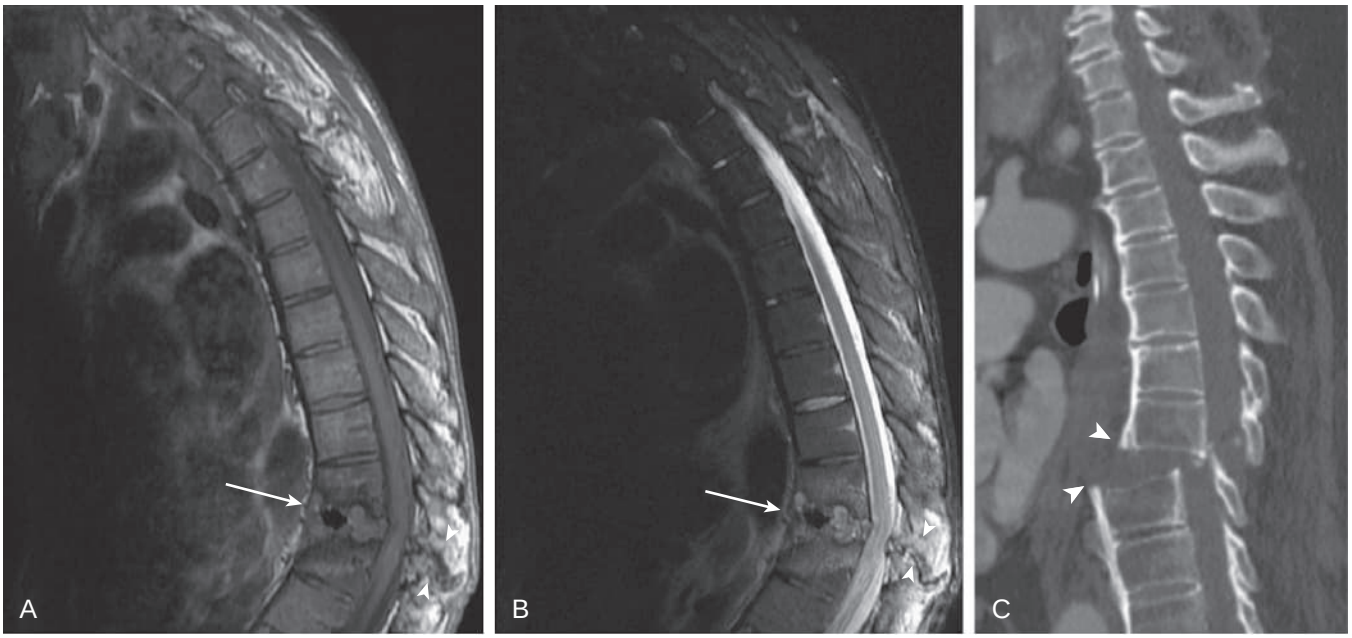
eFigure 131.2 Lucite sphere plombage seen on chest radiographs. (A) Frontal and (B) lateral chest radiographs show regular lucencies (*arrowheads*) representing Lucite sphere plombage in a patient with prior left upper lobe *Mycobacterium tuberculosis* infection.



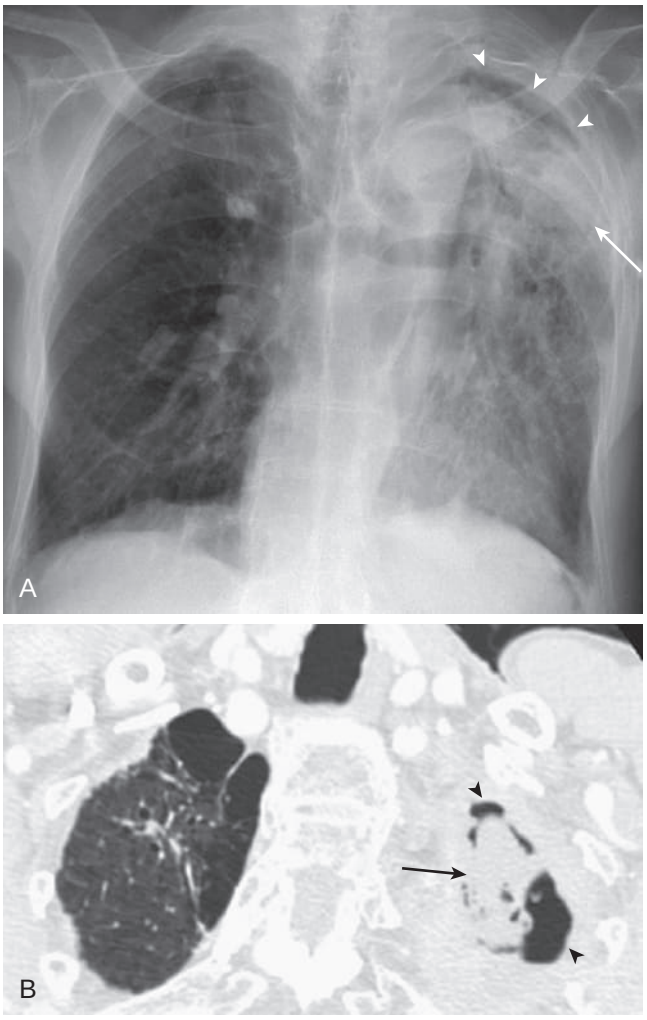
eFigure 131.3 Oleothorax seen on frontal chest radiograph. A homogeneous right upper thoracic opacity (*arrowheads*) represents extraparenchymal oil injection as a form of pulmonary collapse therapy in a patient with *Mycobacterium tuberculosis* infection.



eFigure 131.4 Ankylosing spondylitis: upper lobe fibrobullous disease on frontal chest radiograph. A thin-walled cystic structure in the right upper lobe (*arrowheads*) is associated with upper lobe fibrosis bilaterally, evidenced by bilateral hilar retraction and architectural distortion.



eFigure 131.5 Ankylosing spondylitis: fused thoracic spine complicated by fracture seen on sagittal magnetic resonance and computed tomography scans. Sagittal (A) T1-weighted and (B) T2-weighted magnetic resonance imaging shows an irregular intermediate and centrally low signal (*arrow*) extending transversely through the intervertebral disc space, associated with kyphosis centered at this level. Note that the injury extends into the posterior elements (*arrowheads*); this pattern of spinal fracture is common in ankylosing spondylitis. (B) The T2-weighted image shows increased signal in the involved vertebral bodies consistent with bone marrow edema, and it also reveals spinal cord compression. (C) Sagittal reformatted image from a thoracic computed tomography scan in a different patient shows a similar three-column fracture pattern, although more severe, complicated by distraction and displacement; note the anterior widening of the intervertebral disc space (*arrowheads*)



eFigure 131.6 Ankylosing spondylitis: fibrobullous disease complicated by mycetoma on chest radiograph and computed tomography. (A) Frontal chest radiograph in a patient with ankylosing spondylitis and upper lobe fibrobullous disease shows an irregular masslike opacity at the left lung apex (*arrow*), with lucency (*arrowheads*) along the cranial margin of the opacity. (B) Axial thoracic computed tomography displayed in lung window confirms the presence of the opacity (*arrow*) within the cavity (*arrowheads*) in the left apex, consistent with mycetoma.

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SECTION Q

MANAGEMENT OF RESPIRATORY FAILURE

132 ACUTE VENTILATORY FAILURE

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INTRODUCTION

Respiratory failure exists when the respiratory system cannot maintain gas exchange, causing dysfunction in other organs or threatening life. Such impairment primarily affects oxygenation, manifested by hypoxemia, or ventilation, manifested by hypercapnia and respiratory acidosis. This chapter deals with this latter circumstance, commonly called ventilatory failure.

Carbon dioxide (CO_2) tension in the arterial blood (arterial P_{CO_2}) is a function of *alveolar ventilation* ($\dot{V}_A$) and CO_2 production, according to the following relationship:

$$\text{arterial } P_{CO_2} = (\dot{V}_{CO_2} \times k) / \dot{V}_A \qquad \text{(Eq. 1)}$$

Total minute ventilation is the sum of both $\dot{V}_A$ and dead space ventilation, shown as minute ventilation = $\dot{V}_A$ + dead space ventilation. Either a decrease in total minute ventilation or an increase in dead space ventilation can thus decrease $\dot{V}_A$. Any decrease in $\dot{V}_A$ or increase in $\dot{V}_{CO_2}$ relative to $\dot{V}_A$ results in an increase in arterial P_{CO_2}. Because bicarbonate retention by the kidneys in response to hypercapnia is slow, a sudden increase in arterial P_{CO_2} will not be buffered quickly by bicarbonate and thus will abruptly lower arterial pH. Ventilatory failure exists whenever arterial P_{CO_2} is substantially elevated, and acute ventilatory failure is present when the change from the patient's baseline state develops rapidly enough to produce a clinically important drop in arterial pH. Because patients with severe COPD, chronic neuromuscular disease, and other disorders may already have hypercapnia at baseline, the presence of a component of acute (acute-on-chronic) ventilatory failure is determined not so much by the arterial P_{CO_2} value as by the presence of acidemia, typically to an arterial pH of less than 7.35. The presence of acute ventilatory failure cannot be determined accurately by physical examination, pulse oximetry, exhaled CO_2, or other noninvasive tests. Thus, making the diagnosis requires arterial blood gas analysis.[1]

PATHOPHYSIOLOGY

Alveolar ventilation becomes inadequate in relation to CO_2 production either because of a failure of the patient's

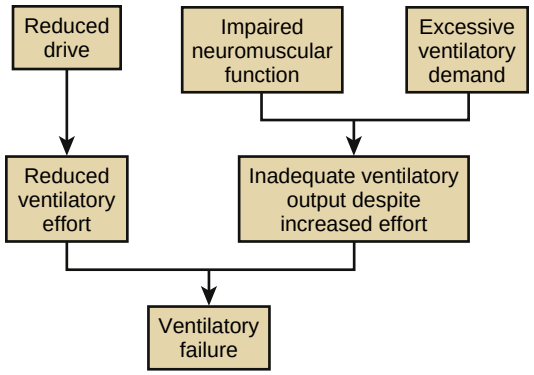

Figure 132.1 The physiologic mechanisms of acute ventilatory failure. The two major causes of acute ventilatory failure are either a reduced ventilatory effort or a reduced ventilatory output despite increased effort.

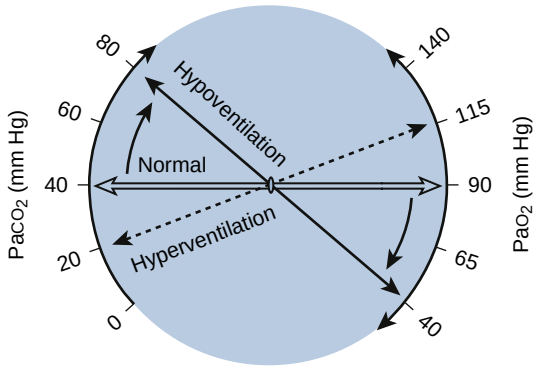

Figure 132.2 Relationship between arterial P_{O_2} and arterial P_{CO_2}. There is a reciprocal relationship between arterial oxygen pressure (arterial P_{O_2}) and arterial carbon dioxide pressure (arterial P_{CO_2}) as ventilation increases or decreases, assuming that the (A–a)P_{O_2} difference does not change and the respiratory exchange ratio is 0.8. (Modified from Pierson DJ, Kacmarek RM, eds. *Foundations of Respiratory Care*. New York: Churchill Livingstone; 1992:298.)

ventilatory capability (pump failure) or ventilatory effort (drive failure)[2,3] (Fig. 132.1). These two mechanisms are distinct in their clinical presentations. Patients with acute failure of the ventilatory pump are dyspneic and tachypneic with other signs of distress, whereas patients with failure of ventilatory drive are not short of breath and typically demonstrate bradypnea or apnea.

Although acute ventilatory failure is primarily a disorder of alveolar ventilation, hypoxemia is also usually present. Alveolar hypoventilation causes a proportional fall in *alveolar oxygen pressure* (alveolar P_{O_2}), according to the alveolar gas equation:

$$\text{alveolar } P_{O_2} = P_{I O_2} - (\text{arterial } P_{CO_2}/R) \quad \text{(Eq. 2)}$$

where arterial P_{CO_2} is assumed to be nearly the same as alveolar P_{CO_2}, P_{IO_2} is the inspired P_{O_2} (i.e., the inspired oxygen fraction multiplied by the difference of barometric pressure and 47 [water vapor pressure in mm Hg at body temperature]), and R is the respiratory exchange ratio. This relationship explains the fall in arterial P_{O_2} that accompanies alveolar hypoventilation, as shown in Figure 132.2.[2] Calculating alveolar P_{O_2} using Equation 2 permits determination of the *alveolar-arterial oxygen pressure difference* [(A−a)P_{O_2}] (commonly but imprecisely called the A–a gradient and, more precisely, the A–a oxygen tension difference). This calculation distinguishes between pure hypoventilation as an explanation for hypoxemia (in which case, (A−a)P_{O_2} is normal) and the presence of other mechanisms such as low *ventilation-perfusion* ($\dot{V}/\dot{Q}$) ratios and right-to-left shunt (in which case, (A−a)P_{O_2} is increased).

Finally, hypercapnia can be a feature of hypoxemic respiratory failure if the derangement in gas exchange is sufficiently severe. Both right-to-left shunt and low $\dot{V}/\dot{Q}$ ratios are present in *acute respiratory distress syndrome* (ARDS) and can increase dead space/tidal volume ratios,[4] thus impairing CO_2 elimination and contributing to hypercapnia.

Table 132.1 classifies the typical clinical presentations of acute ventilatory failure according to the site or type of defect and the physiologic mechanism or category of disorder responsible. Not every listed example is discussed here.

More than one mechanism may coexist in a given patient, producing a life-threatening condition even when the individual processes are only moderate in severity. For example, in decompensated obesity-hypoventilation syndrome, a patient whose underlying respiratory drive is reduced and whose obesity poses an increased elastic load on the ventilatory pump may develop acute-on-chronic ventilatory failure in the presence of a relatively modest increase in the work of breathing from an additional restrictive effect of cardiomegaly and pleural effusions.

INSUFFICIENT VENTILATORY DRIVE

CONGENITAL CAUSES

Congenital disorders associated with diminished hypoxic or hypercapnic ventilatory drive include primary alveolar hypoventilation (or Ondine's curse),[5] Prader-Willi syndrome,[6,7] hypogonadism treated with exogenous testosterone,[8] and Arnold-Chiari malformation.[9] These disorders contribute to the development of acute ventilatory failure through diminished ventilatory drive, often in combination with other contributing mechanisms (such as acute infection), and are most often seen in pediatric settings.

ACQUIRED CAUSES

Decreased ventilatory drive is a frequent contributor to the development of chronic ventilatory insufficiency but is typically not the sole mechanism for acute ventilatory failure, except for patients with drug-induced suppression.

PHARMACOLOGIC CAUSES

Depression of the drive to breathe by drugs is by far the most common circumstance of acquired acute ventilatory failure. Opioids are potent depressors of both hypoxic and hypercapnic ventilatory drive; however, most sedative, hypnotic, or anxiolytic agents cause respiratory depression if administered in sufficient quantity.[10] With the current epidemic of opiate overdoses, hospitals have seen a substantial increase in *intensive care unit* (ICU) admissions and deaths due to ventilatory failure. In one large database accrued from a consortium of 162 hospitals, ICU admissions due to opiate overdoses increased by 34% between 2009 and 2015, with a concomitant increase in ventilator use and mortality.[11] More recently, deaths due to opiate overdose have continued to rise, reaching almost 70,000 in 2018.[12] Two-thirds of these were due to synthetic opioids, and most of these were related to intravenous injection of

Table 132.1 Clinical Classification of Ventilatory Failure by Site

Site of Defect	Mechanism or Type	Clinical Examples
VENTILATORY DRIVE	Congenital	Primary alveolar ventilation (Ondine's curse)
	Acquired	Drug overdose (opioids, sedatives, alcohol); propofol; cerebrovascular accident; neoplasm; carotid body resection
	Combination	Obesity-hypoventilation syndrome; myxedema
NEURAL TRANSMISSION		
Spinal cord	Trauma	Cervical spinal cord injury
	Vascular	Vascular accident
	Tumor	Primary or metastatic
	Other	Poliomyelitis; amyotrophic lateral sclerosis
	Demyelinating	Acute idiopathic demyelinating polyneuropathy (Guillain-Barré syndrome)
Peripheral nerves	Phrenic nerve lesion	Trauma; cardiac surgery; neoplasm; idiopathic
Neuromuscular junction	Autoimmune	Myasthenia gravis
	Infectious/toxins	Botulism, tetanus, tick paralysis
	Pharmacologic	Neuromuscular blocking agents
Neuromuscular	Critical illness	ICU-acquired weakness, ventilator-induced diaphragmatic dysfunction
VENTILATORY MUSCLES	Congenital	Muscular dystrophy
	Autoimmune	Polymyositis; dermatomyositis
	Acquired	Hypophosphatemia; hypokalemia; hypomagnesemia; myxedema
THORACIC		
Vertebrae and rib cage	Decreased mobility	Kyphoscoliosis; tight casts or bandages; ankylosing spondylitis; flail chest
Soft tissues	Extrapulmonary restriction and decreased mobility	Severe obesity
Pleura	Extrapulmonary restriction	Pneumothorax; pleural effusion; pleural thickening; malignancy
AIRWAYS		
Upper	Obstruction	Epiglottitis, foreign body, tumor, vocal cord paralysis, tracheomalacia
Lower	Obstruction	COPD, acute severe asthma
PARENCHYMA	Increased dead space and very high $\dot{V}/\dot{Q}$	COPD
	Very low $\dot{V}/\dot{Q}$; shunt	Severe ARDS
PULMONARY CIRCULATION	General hypoperfusion	Hypovolemic or cardiogenic shock, CPR, pulmonary hyperinflation (intrinsic PEEP)
	Localized hypoperfusion	Pulmonary thromboembolism; venous air embolism
OTHER	Increased CO_2 production (inflammation; hypermetabolism; muscle activity)	Fever; sepsis; burns; severe trauma; shivering; tetany; seizures; malignant hyperthermia
	Exogenous CO_2 inhalation	Laboratory or industrial accident; therapeutic use; rebreathing

ARDS, acute respiratory distress syndrome; CPR, cardiopulmonary resuscitation; PEEP, positive end-expiratory pressure; $\dot{V}/\dot{Q}$, ventilation-perfusion ratio.

fentanyl synthesized illegally with a potency in reducing respiratory drive varying between 50 and 100 times that of morphine. This has led to an epidemic of opioid-related deaths that have risen rapidly during the past decade.

Propofol is another potent respiratory depressant used commonly for sedation during procedures or during mechanical ventilation that must be dosed with caution and monitored closely in patients breathing spontaneously.[13] Respiratory depression resolves as the drug is cleared from the body or is pharmacologically antagonized, as signaled by the return of spontaneous breathing efforts. Because the central nervous system effects of some agents may wax and wane due to the enterohepatic circulation, lipid storage, or other mechanisms, patients should be observed until it is clear that the respiratory drive has been reestablished before they are weaned from ventilatory support. In the case of drug overdoses and other poisoning, identifying the specific agent or agents involved and the use of any specific therapies available, such as antidotes or dialysis, is important to expedite the weaning process from ventilatory support.[10] With the current epidemic of opiate overdoses, community-based naloxone distribution and training in its administration is a public health priority aimed at early reversal of opiate-induced respiratory depression to avoid ICU admissions and deaths.[14] Patients who fail to wean from mechanical ventilation because of inadequate drive from depressant drugs breathe slowly or not at all when ventilatory support is briefly discontinued. The much more common reason for difficulty weaning after drug overdose is that other mechanisms (e.g., aspiration pneumonia or sepsis) intervene. In these circumstances, with a return of respiratory drive, patients become tachypneic and manifest signs of respiratory distress when ventilatory support is discontinued.[15]

OTHER ACQUIRED CAUSES

Myxedema[16,17] may present with hypercapnia related to acquired depression of ventilatory drive, and hypothyroidism may be a cofactor when patients present with

worsening hypercapnia. Thyroid function testing should be done routinely in patients with new or worsening hypercapnia, especially when a clear physiologic explanation is inapparent. Patients with underlying abnormalities of ventilatory drive who develop respiratory infections, congestive heart failure, or other acute illnesses are more likely to develop acute ventilatory failure compared with individuals without such defects.

Obesity hypoventilation syndrome, discussed in Chapters 121 and 136, is characterized by blunted responses to hypoxia and hypercapnia[18] and is one disorder in which patients may first present in acute ventilatory failure. Typically, such patients have a history of recent weight gain and are found to be markedly fluid overloaded, with features of right heart dysfunction. The increased work of breathing from decreased chest wall compliance, cardiomegaly, and often large pleural effusions, as well as worsening hypoxemia, all contribute to respiratory muscle fatigue and the development of severe hypercapnia and respiratory acidosis. Hypoventilation and acute ventilatory failure related to obesity are more common among hospitalized patients with severe obesity than has previously been reported.[19,20] As the prevalence of obesity increases, ventilatory failure from decompensation of the obesity-hypoventilation syndrome is likely to be encountered more frequently.[19]

Acute stroke is another setting in which disordered ventilatory drive may contribute to acute ventilatory failure, even though other processes are usually present, especially the inability to protect the airway and clear respiratory tract secretions.[21,22] The prognosis of patients with ischemic and hemorrhagic strokes who require intubation and mechanical ventilation is poor both in the short and long term, with a survival rate of 50% at 30 days and 30% after 1 year.[21,23,24] Prognosis is especially unfavorable after basilar artery occlusion due to the depressant effect on respiratory drive as well as the swallowing impairment and problems with secretion clearance seen with brainstem injury.[25]

As guidelines for the early management of patients with acute ischemic stroke continue to evolve with the development of improved pre-hospital care, in-hospital stroke teams, and advancing treatment options with intravenous and intra-arterial therapies, American Heart Association guidelines recommend mechanical ventilation for patients with acute stroke if needed.[26] This necessitates an ethical discussion with the patient and/or family to determine the patient's wishes regarding aggressive support (see Chapter 141).

PRINCIPLES OF MANAGEMENT

Because the underlying physiologic defect is inadequate ventilatory drive despite a presumably normal ventilatory pump, management focuses on restoring normal alveolar ventilation. Although *noninvasive ventilation* (NIV) is being applied in an increasing number of clinical settings to augment alveolar ventilation, its utility lies mainly in supporting ventilation in patients with normal or augmented respiratory drive and failure of the ventilatory pump, whereas endotracheal intubation is generally necessary following acute failure of respiratory drive. NIV can be quite effective in treating chronic congenital or acquired central hypoventilation in outpatients but, in the setting of acute loss of respiratory drive, invasive mechanical ventilation restores alveolar ventilation more rapidly and reliably and is more effective for airway protection and secretion clearance than is NIV.

Because of the patient's impaired ventilatory drive, a ventilator mode that provides full support with a backup rate, such as volume-targeted assist-control ventilation, should be chosen initially. In the absence of acute respiratory distress syndrome or severe airflow obstruction, ventilator settings should be chosen to aim for values of arterial pH and arterial P_{CO_2} in the normal range, and supplemental oxygen should be supplied (with *positive end-expiratory pressure* [PEEP] if necessary) to maintain normal arterial P_{O_2}. Unless there are serious coexisting pulmonary conditions, weaning should be carried out as soon as ventilatory drive is restored. Extubation is probably safe if the patient has a spontaneous cough, does not require frequent suctioning, and is judged to be able to protect the airway, even if alertness remains impaired.[27] This has been controversial, though, because extubation failure rates have been high in some studies,[28] and more sophisticated scoring systems have been proposed to determine what patients are candidates for extubation.[29]

NEURAL TRANSMISSION IMPAIRMENT (see Chapter 130)

CERVICAL SPINAL CORD INJURY

Injury to the upper cervical spinal cord may interrupt transmission of the stimulus to breathe from the respiratory centers in the brainstem to the diaphragm and other ventilatory muscles, depending on the injury level. Because the phrenic nerve roots supplying the diaphragm arise from spinal segments C3 to C5, patients with acute injury at this level or above usually require ventilatory assistance. Patients with C1–C2 spinal injury levels are permanently ventilator dependent, whereas those with C3–C4 injuries may eventually achieve at least partial ventilator independence. Lesions below C4 are usually compatible with unassisted ventilation unless there are complicating processes such as intrinsic lung disease or impaired mental status.

Adverse physiologic effects can happen within the first days or weeks after the injury, including loss of lung volumes and inability to take deep breaths (which predisposes to atelectasis), inability to cough normally (which predisposes to the development of pneumonia and complicates its management), and impaired hypoxic pulmonary vasoconstriction (which predisposes to severe and often refractory hypoxemia after atelectasis or pneumonia).[30] These effects depend on the level of injury, being more frequent with lesions above C4, and on the degree of injury, being more frequent with complete, than with incomplete, lesions.[31]

The short-term prognosis of spinal cord lesions is generally related to the level of the injury,[30] even though some retrospective studies have shown that both mortality[32,33] and ICU length of stay[30] are more strongly influenced by the development of pneumonia and other respiratory complications than by the specific cord injury level.

Although there are reports of initial management of patients with high cervical spinal cord injury (C3–C4 or higher) with NIV,[34] great expertise is required to avoid aspiration and other complications. Decisions about NIV should be made on a case-by-case basis[31]; in most centers, invasive ventilatory support is preferable, at least initially. Phrenic nerve[35–37] or diaphragm pacing,[38] permitting extubation or removal of the tracheostomy tube (decannulation), has also been reported in the later period following injury. The eventual ability to wean from ventilatory support and to undergo decannulation from tracheostomy are major determinants not only of survival but also of quality of life for patients with cervical spinal cord injury.[30,32]

MOTOR NEURON DISEASE

Amyotrophic lateral sclerosis (ALS) and other motor neuron diseases demonstrate a variable but progressive weakness of the bulbar and ventilatory muscles. This progression determines the course of ventilatory failure and pulmonary complications, which represent the most common cause of death in these patients.[39,40] Most often, ventilatory muscle weakness develops gradually after the diagnosis is already well established; therefore, repeated assessments during outpatient evaluation are useful to monitor the progression of ventilatory muscle impairment.[39–43] This permits intervention with NIV or, less often, tracheostomy before the onset of acute ventilatory failure. However, some cases present with acute ventilatory failure as the initial manifestation of the disease.[44]

Elective initiation of noninvasive ventilation has become a standard of care in motor neuron disease patients with progressive ventilatory impairment because it improves both quality of life and survival rate[42,43,45] in patients without significant bulbar involvement. NIV has been successful not only in the chronic, slowly progressive setting, but also in acute ventilatory failure complicating ALS.[46] However, bulbar weakness and a high risk of aspiration make invasive mechanical ventilation a preferred choice for ALS patients with acute ventilatory failure, at least initially. With appropriate counseling about end-of-life planning, only a small proportion of patients in the United States with ALS receive invasive mechanical ventilation, and presentation to an emergency department with acute ventilatory failure should be unusual.[47] Other cultures may take different approaches to use of tracheostomy for ALS. In a survey, 53% of Japanese caregivers favored tracheostomy compared to only 33% in the United States.[48]

INJURY OR DISEASE AFFECTING THE PHRENIC NERVE

Loss of diaphragm function leading to ventilatory failure is often due to spinal cord injury, immunologic diseases (such as Guillain-Barré syndrome or multiple sclerosis), or neuropathy (ALS, Charcot-Marie-Tooth). Unilateral paralysis of the diaphragm leading to ventilatory failure may be a result of phrenic nerve injury or disease. Its presentation ranges from an incidentally discovered radiographic abnormality without clinical impact to acute ventilatory failure requiring long-term mechanical ventilation, although the latter is quite unusual and generally due to multiple factors.[36,49] In the past, unilateral diaphragmatic palsy following phrenic nerve injury was most often caused by cold cardioplegia (phrenic frostbite) during open-heart surgery or direct injury during internal mammary artery harvesting.[50] Since routine use of insulation for the phrenic nerves during cardiac surgery, this complication is now rare, but unilateral or bilateral phrenic nerve palsies are still seen as a consequence of direct invasion by neoplasm, infectious diseases (such as herpes zoster and Lyme disease), metabolic peripheral neuropathy (diabetes or porphyria), and radiotherapy.[51] Although acute ventilatory failure as a consequence of bilateral diaphragmatic paralysis is unusual, these patients are much more symptomatic than those with unilateral paralysis and usually have severe orthopnea.

IMMUNOLOGIC NEUROPATHIES

Guillain-Barré syndrome, now known as *acute idiopathic demyelinating polyneuropathy* (AIDP), is an autoimmune polyneuropathy that accounts, together with myasthenia gravis, for the majority of admissions for ventilatory failure due to neuromuscular impairment.[52–57] Therapy with intravenous immunoglobulin and plasmapheresis improves outcomes in AIDP, although 2–10% still die, and up to 20% of individuals who survive remain seriously disabled.[58] Theoretically, death should be preventable in the vast majority of patients with this disease because mortality is primarily from potentially avoidable respiratory complications (see the discussion in Chapter 130). Although the 20/30/40 rule (FVC <20% predicted, maximum inspiratory pressure <30 cm H_2O, and maximum expiratory pressure <40 cm H_2O) is still commonly used, prediction of the need for mechanical ventilation can be challenging, especially in patients with swallowing difficulty, and close observation of these patients in an ICU is mandatory.[57,59,60]

NEUROMUSCULAR JUNCTION IMPAIRMENT

Immunologic Disease

Myasthenia gravis (MG) is less common than AIDP as a cause of acute ventilatory failure, although 15–20% of myasthenic patients experience a crisis during their lifetime. These events usually happen in patients with an established diagnosis of MG. With adequate therapy (plasmapheresis and intravenous immunoglobulin) and respiratory support through noninvasive or invasive mechanical ventilation, mortality is 5–10%.[61,62] Isolated ventilatory muscle weakness requiring mechanical ventilation has been reported as the initial manifestation of the disorder.[52]

Infectious Disease

Botulism remains an infrequent but important cause of acute ventilatory failure worldwide. In western countries, the incidence of ventilatory failure due to food-borne illness has been unusual but steady in recent decades, with about 23 cases per year in the United States.[63] The vast majority of patients with botulism manifest respiratory symptoms, and up to 75% of individuals develop clinically

significant respiratory failure due to progressive, symmetrical, descending flaccid paralysis, requiring mechanical ventilation.[64] Recovery may be prolonged, with residual ventilatory muscle weakness detectable as long as 2 years after presentation.[65] Recent reports from the Canadian Arctic associated with inadequately refrigerated seafood illustrate the importance of early recognition and treatment with botulinum antitoxin, which may speed recovery.[66]

Myopathies

Primary myopathies due to muscular dystrophies or other congenital myopathies are an uncommon cause of acute respiratory failure in most acute care hospitals but are more common in the pediatric setting. These patients usually develop ventilatory failure gradually and are begun on NIV in an outpatient setting. When they present with acute ventilatory failure, it is usually a precipitating factor, such as pneumonia or bronchitis, that causes problems with secretion retention. In such an event, they should be placed in an intensive care unit and treated with an aggressive regimen to assist with secretion clearance.[67] Endotracheal intubation may be necessary to control secretions, with weaning to NIV once the acute crisis subsides. Dermatomyositis may also cause respiratory muscle weakness severe enough to lead to acute ventilatory failure,[68,69] although not as an initial manifestation in the absence of other typical symptoms and signs of this condition. In these reported cases, ventilatory function recovered as the disease was brought under control with immunosuppressive therapy.

Pharmacologic Causes

Neuromuscular blocking drugs are sometimes administered to ventilated patients, in conjunction with sedation, to facilitate mechanical ventilation, reduce oxygen consumption, or control intracranial pressure. The clinical kinetics of these agents have been determined mainly in the context of short-term general anesthesia, and their effects on ventilatory muscle function in critically ill patients are much more variable. For example, most neuromuscular blocking drugs are cleared more slowly in the presence of hepatic or renal insufficiency. This is particularly true for pancuronium and vecuronium; the effects of these drugs can last days or even weeks in the presence of renal failure.[70] In contrast, atracurium and cisatracurium are metabolized in plasma and do not depend on renal or hepatic function for clearance; thus, they are not associated with prolonged muscle weakness as a result of delayed clearance.[71]

Train-of-four stimulation (i.e., a peripheral nerve stimulator monitoring the strength and number of impulses required for a muscular twitch) can be used to monitor the depth of neuromuscular blockade, avoiding excessive paralysis, reducing the quantity of drug used, and decreasing recovery time of neuromuscular function in critically ill patients.[72] The benefits of train-of-four monitoring may not be seen when atracurium and cisatracurium are used.[73] Furthermore, use of train-of-four testing has been controversial because it is influenced by the skill of caregivers, muscular site of monitoring, manufacturer of the device, edema, patient temperature, and other factors.[74] For this reason, the most recent Society of Critical Care Medicine guidelines suggest use of train-of-four for any of the non-depolarizing neuromuscular blockers only when combined with careful clinical assessment.[75] Minimizing the use and careful dosing of neuromuscular blocking drugs in ventilator management, a comprehensive monitoring plan, and a structured physiotherapy regimen may help reduce the incidence of prolonged paralysis.

NEUROMUSCULAR WEAKNESS ASSOCIATED WITH CRITICAL ILLNESS

Neuromuscular dysfunction associated with critical illness commonly contributes to the subsequent inability to wean such patients from mechanical ventilation.[71] Several forms of critical illness–associated neuromuscular dysfunction are recognized.

Intensive Care Unit–Acquired Weakness

Unexpected acute weakness and prolonged ventilatory failure were first reported in patients with status asthmaticus treated with corticosteroids and neuromuscular blocking drugs.[76,77] Subsequently, a similar syndrome was recognized in other groups of ICU patients, especially those with sepsis and systemic inflammation, even without corticosteroid administration or therapeutic paralysis.[71] Either muscle or nerve abnormalities can predominate, leading to a confusing array of diagnostic terms, such as critical illness myopathy, critical illness polyneuropathy, postparalytic myopathy, ICU-acquired paresis, acute quadriplegic myopathy, and the preferred term, *ICU-acquired weakness*.

The pathophysiology of ICU-acquired weakness is poorly understood but may involve elements of disuse and active muscle catabolism sparked by systemic inflammation. Electromyography reveals reduced compound muscle action potentials on motor nerve stimulation (with normal conduction velocity), increased action potential duration, and spontaneous electrical activity on muscle needle recording (e.g., fibrillation potentials, positive sharp waves).[78] Biopsy findings may include primary axonal degeneration, type II muscle fiber atrophy, thick filament (myosin) loss, and (occasionally) necrotizing myopathy.

One-quarter to nearly all patients who require more than 7 days of ICU care and the majority of patients who develop the systemic inflammatory response syndrome can be shown by neurophysiologic testing to have ICU-acquired weakness.[71] These neurophysiologic abnormalities arise early, accumulate during the course of illness, and usually affect both nerves and muscles.[79] Prospective studies have shown that about one-third of critically ill patients exhibit weakness on clinical evaluation.[71,80] The typical patient exhibits symmetrical extremity weakness in which proximal function is more impaired than distal function and the facial muscles are spared. Clinically, this disorder can produce severe neuromuscular weakness, often affects the respiratory muscles, and may prolong the need for ventilatory support.[80,81] This syndrome should be suspected in patients who are weak (Medical Research Council score <48[80]) in the context of critical illness, have the typical clinical examination, and in whom no better alternative cause for weakness can be identified. Handgrip strength may serve as a simple test

to identify ICU-acquired weakness.[82] Nerve conduction studies, electromyography, and muscle biopsy generally are not necessary to make a diagnosis, and clinical scoring systems assessing strength of multiple muscle groups can be helpful.[71] The prognosis for recovery of strength is variable, with many patients improving rapidly over days to weeks while others remain weak for many months or longer. The incidence of ICU-acquired weakness may be reduced by intensive insulin therapy,[81,83,84] although this has lost favor due to potential hypoglycemic complications. Avoiding neuromuscular blocking drugs and corticosteroids where possible and applying early mobilization[85,86] are other favored strategies to minimize ICU-acquired weakness. Because ICU-acquired weakness is so strongly associated with severity of illness, length of ICU stay, and the presence of multiple organ system dysfunction, prevention focuses on scrupulous attention to evidence-based supportive care and avoidance of iatrogenic complications.[71]

Ventilator-Induced Diaphragmatic Dysfunction

Many critically ill patients develop muscle weakness that impedes functional recovery and is associated with prolonged mechanical ventilation. Some component of this represents ICU-acquired weakness,[87] but mechanical ventilation itself (without systemic inflammation) can induce respiratory muscle weakness.[88–90] The lack of neural stimulation or associated contraction plays a role in the evolution of weakness because measures to keep muscles contracting can ameliorate weakness. The diaphragm, the muscle most responsible for sustaining the work of breathing, may be even more sensitive than other skeletal muscles to the effects of critical illness. In animal models, the diaphragm weakens and atrophies during the first 1 to 3 days of controlled mechanical ventilation thought to be related to disuse. This and excessive prolonged demands on the diaphragm are thought to induce myotrauma.[91]

Diaphragm dysfunction in these situations can be detected by ultrasound, showing diminished tidal excursions and decreased thickening corresponding to blunted contractility.[92] Using phrenic nerve stimulation, one study demonstrated weakness by measuring a reduction in maximal transdiaphragmatic pressure in a group of continuously ventilated patients in comparison with findings in normal volunteers.[93] As in studies of peripheral skeletal muscle, stimulating the diaphragm attenuates the loss of strength.[94] A transvenous bilateral phrenic nerve stimulator has been shown to preserve diaphragm function in experimentally ventilated rats and could see clinical application in the not too distant future.[95] An alternative approach proposed recently is to titrate ventilator settings so that diaphragm effort is optimized, avoiding insufficient or excessive demands,[96] and there may be a role for pharmacotherapy with theophylline, which has been shown to increase diaphragm contractility.[97]

ASSESSMENT OF NEED FOR MECHANICAL VENTILATION IN NEUROMUSCULAR WEAKNESS

Respiratory muscle weakness can be suspected when there is obvious peripheral muscle weakness, but neuromuscular abnormalities may not always be evident. Respiratory muscle weakness should also be suspected when dyspnea is out of proportion to radiographic and respiratory mechanical abnormalities. Orthopnea raises the possibility of diaphragmatic weakness or paralysis. Further, suspicion is raised when maximal inspiratory pressure is reduced or, in some instances, when ultrasound examination of the diaphragm is abnormal.

Early clinical indicators of the need for mechanical ventilation in patients with neuromuscular weakness remain controversial. In addition to subjective assessments of symptoms of dyspnea and respiratory distress, objective assessments of vital capacity and maximum inspiratory and expiratory pressures have been used to evaluate ventilatory muscle capability.

In AIDP, rapid disease progression, bulbar and bilateral facial weakness, and dysautonomia are highly correlated with the need for intubation and mechanical ventilation. Moreover, the 20/30/40 rule, mentioned above, is often invoked to assess risk for intubation.[56] However, no prospective randomized studies have assessed these variables, and predictors of the need for intubation may merely reflect the criteria in current use to determine when a patient should be intubated.

One study reported an association between electrophysiologic evidence of demyelination and the need for intubation and mechanical ventilation.[98] Another study on 44 AIDP patients who required mechanical ventilation showed greater cranial nerve involvement and immunoglobulin G anti-GQ1b antibody levels than 87 AIDP patients not requiring intubation.[99] These could also be markers of greater disease severity, thus explaining the higher intubation rates.

In MG, the criteria to predict the need for intubation are not as reliable as for AIDP, mostly due to the fluctuating nature of MG.[100] Nonetheless, serial assessments of vital capacity and the use of the same predictors as for AIDP are still recommended in MG as long as the patient is monitored closely in an ICU and caregivers are prepared for emergent intubation if necessary.[101,102]

In ALS, as previously noted, serial ventilatory muscle assessments during outpatient management are required for the timely initiation of NIV to avoid respiratory crises and the need for emergency intubation. Clinical signs of respiratory muscle weakness (such as use of accessory muscles and paradoxical or diminished excursion of the abdomen) and symptoms of diaphragm weakness (such as orthopnea) are important to assess. We recommend serial measurement of pulmonary function tests, particularly FVC, slow vital capacity, supine FVC, peak expiratory flow and peak expiratory cough flow, which have been shown to correlate with prognosis.[103,104] Sniff inspiratory pressure may also be useful as an index of diaphragm strength.[105]

In-lab sleep studies may be helpful earlier during the progression of disease if sleep apnea is suspected,[106] but these may be difficult in advanced disease due to patient unfamiliarity with the lab. Home sleep studies or nocturnal oximetry may be helpful in advanced disease to assess the efficacy of NIV. Recommendations for starting NIV in ALS patients vary widely from FVC less than 80% predicted, with the idea that deterioration in respiratory muscle function can be slowed, to less than 50% predicted in the United

States as per the threshold for Medicare reimbursement for NIV.[107,108] We believe that data are insufficient to make firm recommendations on any specific FVC threshold for NIV initiation but that, in association with pulmonary dysfunction and in keeping with its palliative role, NIV should be started when patients develop symptoms that are likely to respond to NIV. For example, dyspnea at rest or orthopnea can respond to NIV, as can symptoms attributable to poor sleep, such as daytime fatigue, hypersomnolence, or morning headaches.

Although the optimal means for monitoring respiratory muscle function remain uncertain, it is clear that initiation of NIV[109] or, if that fails, intubation and mechanical ventilation (if patients desire it), should be undertaken before the development of severe respiratory acidosis or respiratory arrest. For this reason, patients with neuromuscular disease who show signs of acute pulmonary compromise should be monitored in an ICU. Although the rate of progression may fluctuate, serial measurements of vital capacity and maximal inspiratory pressure along with repeated physical examinations focusing on bulbar function and ability to cough are advisable to avoid the need for emergent intubations (Fig. 132.3).[109]

PRINCIPLES OF VENTILATOR MANAGEMENT

Patients with acute ventilatory failure due to neuromuscular disease usually have normal underlying lung parenchyma. Although NIV is often used successfully in these patients, significant bulbar involvement is associated with a high likelihood of NIV failure and patients with these deficits should be intubated if the goal is prolongation of life. Intubated patients are usually supported with volume-targeted ventilators using tidal volumes of 6 to 8 mL/kg, rates slightly below spontaneous, and 5 to 10 cm H_2O PEEP to prevent atelectasis. These targets can also be achieved using portable pressure-limited ventilators with the pressure difference between inspiratory and expiratory pressure adjusted to achieve similar tidal volumes (pressure difference usually at least 8 to 10 cm H_2O) while avoiding respiratory alkalosis. In patients requiring continuous ventilatory assistance, settings should aim not only to maintain gas exchange but also comfort, considering that there is no convincing evidence that "exercising" respiratory muscles in neuromuscular disease speeds recovery. Some advocate a protocol using prophylactic NIV and mechanical cough assistance to facilitate extubation and avert the need for reintubation in patients with neuromuscular disease who are weaning from invasive mechanical ventilation.[67,111]

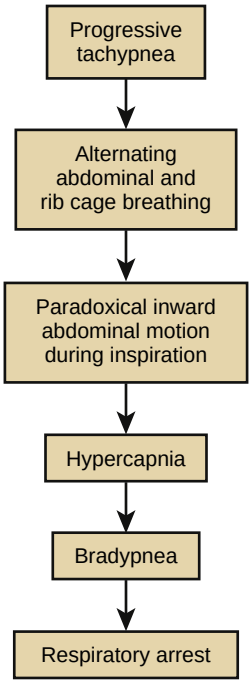

Figure 132.3 The sequence leading from ventilatory pump failure to respiratory arrest. Patients proceed through the steps at variable rates and may skip one or more stages. However, except for sudden events affecting the central nervous system or the administration of paralyzing drugs, respiratory arrest does not present abruptly without preceding physical manifestations. (Modified from Cohen CA, Zagelbaum G, Gross D, et al. Clinical manifestations of inspiratory muscle fatigue. *Am J Med.* 1982;73:308-316.)

CHEST WALL DEFECTS (see Chapter 131)

Many restrictive diseases of the lungs or chest wall progress insidiously over months or years. Critical illness in patients with restrictive disease may represent the natural history of the underlying condition but may also signal an acutely superimposed, potentially reversible crisis such as infection, pneumothorax, or thromboembolism.

CHEST WALL SKELETAL ABNORMALITIES

Thoracic restriction and ventilatory muscle dysfunction due to severe kyphoscoliosis typically lead to gradually progressive ventilatory insufficiency. Such patients can present with acute or acute-on-chronic ventilatory failure and require intensive care. Physiologic studies have shown that both lung and chest wall mechanics are impaired during acute respiratory failure in patients with kyphoscoliosis.[112] Chest trauma, especially when leading to flail chest due to rib fractures, may also cause acute hypercapnic respiratory failure. In either case, the ventilator pump fails because of inability to sustain ventilatory work due to abnormalities that compromise ventilatory function, such as increased chest wall stiffness in kyphoscoliosis and decreased ventilator efficiency due to paradoxical chest wall motion and pain in flail chest.

PLEURAL DISEASE

Primary disease of the pleura, such as asbestos-related diffuse pleural thickening or postinflammatory fibrothorax, could potentially present in a similar way as skeletal deformities, but dyspnea and hyperventilation are more common than hypoventilation with these chronic pleural diseases. Respiratory acidosis develops late in the course of these disorders, but earlier if ventilatory drive is depressed or there is concomitant lung involvement. Pleural effusion or pneumothorax can precipitate acute ventilatory failure if accumulation is rapid and large and usually in the presence

of underlying obstructive or restrictive pulmonary parenchymal disease.

PRINCIPLES OF MANAGEMENT

NIV has been shown to be beneficial in thoracic restriction due to severe kyphoscoliosis and other chest wall diseases[113] for both acute and acute-on-chronic ventilatory failure.[114–117] Some studies report that NIV reduces the need for intubation and leads to a shortened hospital stay in patients with chest trauma.[118,119]

Parenchymal Lung Disease

Idiopathic pulmonary fibrosis and other pulmonary parenchymal restrictive diseases are usually associated with hyperventilation rather than hypoventilation. However, acute ventilatory failure can arise in the late stages of these conditions, either as a manifestation of the primary disease process[120,121] or, more often, in conjunction with pneumonia, surgery, or other intercurrent illness.[122–124] Physiologic assessment has demonstrated marked increases in lung stiffness and airway resistance in patients with end-stage idiopathic pulmonary fibrosis requiring mechanical ventilation,[124] explaining the development of hypercapnia and acute ventilatory failure.

Several small case series have documented the poor prognosis of patients who present with acute respiratory failure in the setting of advanced interstitial fibrosis.[121,123,124] Outcomes appear equally poor regardless of whether ventilation is invasive or noninvasive.[125]

Principles of Ventilator Management

Due to increased lung stiffness, NIV for restrictive disease usually requires higher airway pressures than are used for COPD. Thus, avoiding gastric insufflation and air leaks around the mask can be challenging. Furthermore, considering that a superimposed condition such as a respiratory infection often precipitates the acute bout of respiratory failure, accompanied by increased work of breathing and secretion retention, invasive ventilatory support is often necessary. The best way to ventilate patients with acute respiratory failure in the setting of underlying restrictive thoracic or lung disease has not been determined by clinical trials. The potential for hemodynamic compromise, barotrauma, and ventilator-induced lung injury with the use of high pressures and the physiologic similarity to ARDS in patients with worsening pulmonary fibrosis make it reasonable to apply similar lung-protective ventilator strategies and management targets (see Chapter 135). Low tidal volumes (e.g., 6 mL/kg predicted body weight) should be applied, attempting to keep the end-inspiratory plateau pressure below 30 cm H_2O if possible. Patients with restrictive lung disease typically breathe rapidly and shallowly, so tachypnea may not be avoidable during the weaning process and should not be used as the sole reason for delaying extubation if gas exchange and other assessments are acceptable.

AIRWAY OBSTRUCTION

UPPER AIRWAY OBSTRUCTION

Upper airway obstruction is an occasional cause of acute ventilatory failure. The onset can be precipitous, as with occlusion of the glottis by an aspirated foreign body (i.e., "café coronary") or a swollen and edematous epiglottis due to acute epiglottitis.[126] The onset can also be insidious, progressing over months, as with a tracheal tumor. The severity and length of narrowing and airflow determine the airway resistance and thus the additional work of breathing imposed by the obstruction. Gradually progressive upper airway narrowing may be well tolerated, at least while breathing at rest, until a critical limit is reached, often when the airway diameter drops to the range of 5 to 6 mm.

The location and variability of the narrowing are also important in determining the clinical manifestations. Extrathoracic variable upper airway narrowing affects mainly inspiratory flow because the negative intraluminal pressure exacerbates the narrowing during inspiration. During expiration, the positive intraluminal pressure widens extrathoracic airways. Vocal cord paralysis is an excellent example of a variable extrathoracic upper airway obstruction, producing stridor and severe airway obstruction during inspiration but no significant obstruction during expiration. The opposite pertains to variable intrathoracic obstructions, with narrowing becoming less severe during inspiration because pressure gradients favor airway widening. During expiration, the airways narrow and the severity of the obstruction worsens. Tracheomalacia can cause variable intrathoracic airway obstruction. Fixed obstructions affect both inspiration and expiration regardless of their location.

Upper airway obstruction causes ventilatory failure by increasing airway resistance to the point where respiratory muscles can no longer sustain minute volume at a level adequate to maintain CO_2 homeostasis. Negative-pressure pulmonary edema caused by severe reductions in intrathoracic pressure occasionally created during upper airway obstruction can also contribute to the gas-exchange impairment.[127] Ideally, the therapeutic aim is to relieve the obstruction. This may be achieved by removal of a foreign body, laser therapy of an endotracheal tumor, placement of a stent in an area of tracheomalacia or stenosis, or tracheostomy to bypass an area of obstruction. Inhalation of heliox (to reduce airway resistance), *continuous positive airway pressure* (CPAP), or noninvasive ventilation using pressure support and PEEP can help reduce work of breathing and avoid intubation in patients who have reversible causes of their upper airway obstruction, such as postextubation stridor, or who are awaiting tracheostomy or surgical repair of an obstruction. However, these temporizing measures require close monitoring with the recognition that the patient can deteriorate abruptly.

COPD

COPD is the third leading cause of death among adults aged 65 to 84 in the United States, being the primary contributor to mortality caused by lower respiratory disease, and poses enormous costs to the U.S. health care system, mostly due to hospitalization.[128] The vast majority of hospitalizations are due to acute exacerbations of COPD, but other causes such as acute pneumonia, congestive heart failure, pulmonary embolism, and pneumothorax may contribute to the deterioration.

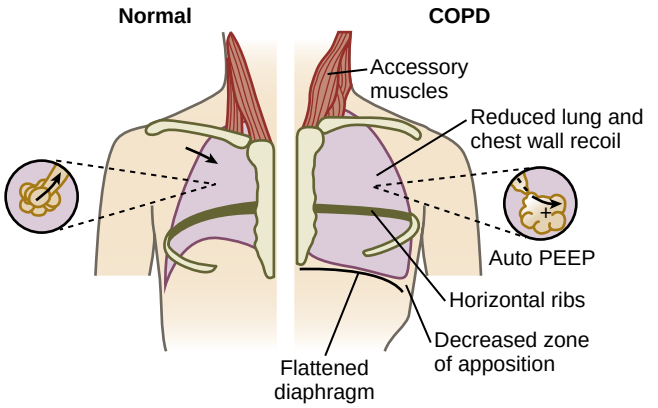

Figure 132.4 Schema depicting the chest wall configuration at functional residual capacity of a normal individual (*left*) and a patient with severe COPD (*right*). The COPD patient has a flattened diaphragm, which increases its radius of curvature and increases the tension for a given pressure. The COPD patient's ribs are horizontal, and the zone of apposition between the diaphragm and chest wall is reduced, greatly reducing the diaphragm's efficiency in expanding the chest wall. Also, *intrinsic positive end-expiratory pressure* (auto PEEP) poses an inspiratory load, adding further to the inspiratory work. Exhalation is slowed by airway collapse and the loss of elastic recoil. (Modified from Hill NS. Current concepts in mechanical ventilation for chronic obstructive pulmonary disease. *Semin Respir Crit Care Med.* 1999;20:375-395.)

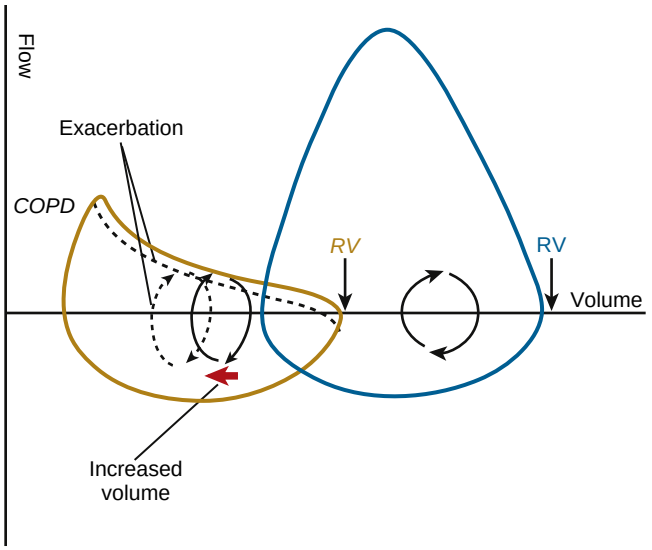

Figure 132.5 Flow-volume loops for a patient with a normal lung (*blue line*) and one with COPD (*brown line*) along with their respective tidal volume loops (*inner black loops with arrows*). Note that the expiratory flow during tidal breathing in the COPD patient reaches maximal expiratory flow. During an exacerbation (*dashed lines*), expiratory flow drops; because the flow during tidal breathing is already maximal, the only mechanism available for maintaining flow is to increase lung volume during tidal breathing (leftward shift of tidal breathing loop; *red arrow*). Although this strategy maintains expiratory flow, it increases the work of breathing and oxygen consumption, predisposing to inspiratory muscle fatigue and eventual respiratory failure. RV, residual volume. (Modified from Hill NS. Current concepts in mechanical ventilation for chronic obstructive pulmonary disease. *Semin Respir Crit Care Med.* 1999;20:375-393.)

Pathophysiology

Hyperinflation associated with severe COPD places the respiratory muscles at a mechanical disadvantage (Fig. 132.4). The loss of elastic structures is responsible for an increase in lung compliance leading to hyperinflation (with an increase in total lung capacity and functional residual capacity) and the collapse of small airways during expiration contributing to an increase of residual volume, often referred to as air trapping. The flattening of the diaphragm increases the radius of curvature, which, according to the Law of Laplace, also increases muscle tension and impedance to blood flow. In addition, ventilatory efficiency is reduced because the shortened diaphragm operates at a disadvantageous position on its length-tension curve and the horizontal orientation of the flattened diaphragm causes the lower rib cage to move paradoxically during inhalation, inward rather than outward (Hoover sign).

The hyperinflation and impairment in diaphragm function necessitate recruitment of accessory muscles to maintain ventilation at higher lung volumes, contributing to the already increased oxygen cost of breathing. Finally, the collapse of small airways predisposes to incomplete emptying and positive intrathoracic pressure at end-expiration (intrinsic or auto-PEEP). Auto-PEEP poses an inspiratory threshold load requiring inspiratory muscles to generate subatmospheric pressures from an elevated alveolar pressure in order to initiate airflow for the next breath.[129–131]

During an exacerbation of COPD, the combination of airway swelling, secretions, and bronchospasm caused by acute inflammation increases airway resistance, further worsening the expiratory flow limitation and increasing end-expiratory lung volume. As depicted in Figure 132.5, COPD patients adapt by attempting to maintain airflow by breathing at even higher lung volumes. In addition, they adopt a rapid, shallow breathing pattern further limiting the time available for expiration, aggravating intrinsic PEEP and adding further to work of breathing. The diaphragm flattens more and develops increased tension, further impeding diaphragmatic blood flow. The resulting limitation in substrate delivery to muscle is aggravated by progressive hypoxemia, caused by worsening hypoventilation and $\dot{V}/\dot{Q}$ imbalance related to secretion retention. Thus, as the demand for breathing increases, the capacity to supply breathing work diminishes. As respiratory drive increases in a futile attempt to reverse the worsening alveolar hypoventilation, muscular performance deteriorates and the diaphragm fatigues.[132] A vicious cycle ensues, leading inexorably to worsening respiratory muscle fatigue, ventilatory failure, and death unless therapeutic interventions interrupt the cycle.

Clinical Assessment

Patients with exacerbations of COPD must be carefully evaluated to identify those at risk of developing respiratory failure and to exclude other causes of respiratory failure. History and physical examination are useful. Although the Borg or visual analogue scales help gauge the level of dyspnea in clinical studies, a subjective assessment that dyspnea is worse than at baseline and of at least moderate severity suffices to identify patients who may be at risk for respiratory failure. Physical findings seen with severe exacerbations include tachypnea, accessory muscle use, abdominal paradox (inward paradoxical movement of the abdomen on inspiration demonstrating diaphragm dysfunction), Hoover sign (inspiratory inward motion of the lower lateral rib cage), cyanosis, and mental status alterations.

In addition to a sputum examination for purulence, a white blood cell count, electrocardiogram, chest radiograph, and arterial blood gas should be obtained to assess the severity of an exacerbation. The widespread use of continuous pulse oximetry and venous blood gases has decreased, but not eliminated, the need for arterial blood gases. Whereas venous pH values average 0.03 to 0.04 below arterial values, venous P_{CO_2} less closely reflects arterial P_{CO_2}, averaging 3 to 8 mm Hg above arterial[133]; nonetheless, a normal venous P_{CO_2} (in the range of 41 to 51 mm Hg) may be useful in excluding all but mild hypercapnia.[134] Arterial blood gases provide a rapid assessment of arterial P_{CO_2} and pH, information that is helpful when deciding to place patients in critical care units or to initiate mechanical ventilation and to assess response to therapy. During severe exacerbations, patients with chronic CO_2 retention develop acute-on-chronic hypercapnia, manifested by a drop in pH indicative of retained CO_2 uncompensated by bicarbonate, an important indicator of ventilatory failure that can be detected only by measurement of arterial blood gases.

Medical Therapy

Medical therapy, consisting of bronchodilators, corticosteroids, and antibiotics, should be promptly started in patients with severe exacerbations. Additional therapies, including diuretics, nitrates, or anticoagulation, should be started whenever comorbidities such as congestive heart failure or pulmonary embolism are suspected.

Oxygen should be supplemented routinely to improve hypoxemia, but it should be carefully titrated in patients with CO_2 retention to maintain a target oxygen saturation of 88–92%. Overzealous oxygen supplementation in such patients has long been known to aggravate CO_2 retention by either blunting the hypoxic ventilatory drive, increasing physiologic dead space (perhaps due to oxygen-induced bronchodilation in poorly perfused lung regions), or both.[135] Another mechanism may be the Haldane effect, in which the increased oxygen tension decreases the affinity of hemoglobin for CO_2.[136] Because hypoxemia in COPD patients is easily reversed, initial supplementation with nasal oxygen at 2 L/min is often adequate.[137] In patients with severe exacerbations, arterial blood gases should be repeated periodically (or followed with venous blood gases or noninvasive monitoring) to assess the effect of oxygen supplementation on arterial P_{CO_2}.

Noninvasive Ventilation (see Chapter 136)

Although initial medical therapy is usually effective in mild COPD exacerbations, it is often not sufficient in severe exacerbations. In severe exacerbations, tachypnea, dyspnea, and CO_2 retention may persist or worsen despite initial medical therapy. Until the mid- to late-1990s, patients in such a predicament would usually be intubated and mechanically ventilated. If they declined intubation, they were kept comfortable while medical therapy was continued, but they often died. Invasive mechanical ventilation was successful in the majority of cases, but hospital mortality rates were substantial, averaging 30% in several studies.[138] Complications of invasive mechanical ventilation were common, including upper airway trauma, pneumothorax, and nosocomial infection, all contributing to patient mortality.[139]

In 1990, Brochard and coworkers[140] demonstrated that the noninvasive delivery of pressurized air into the lungs via a face mask was effective in providing partial ventilatory assistance during COPD exacerbations. Shortly thereafter, Appendini and colleagues[141] showed that noninvasive extrinsic PEEP (to counterbalance the effects of intrinsic PEEP) combined with pressure support reduced diaphragmatic work of breathing even more effectively in COPD patients than either CPAP or pressure support alone. In this way, NIV restores the balance between supply and demand for the work of breathing, thereby serving as a "crutch" during COPD exacerbations and halting the progression of respiratory muscle fatigue while medical therapies are given time to work.

Since Brochard's study, multiple randomized controlled studies and meta-analyses have demonstrated the efficacy of NIV to treat exacerbations of COPD.[139] When compared with standard oxygen and medical therapy alone, NIV for severe exacerbations of COPD more rapidly improves dyspnea, respiratory and heart rates, arterial P_{CO_2}, and encephalopathy scores.[142–144] In addition, intubation and mortality rates drop precipitously (from roughly 75% and 30% in controls to 25% and 10%, respectively, in NIV-treated patie nts).[142,143,145] NIV also lowers complication rates and hospital lengths of stay compared with controls.[142–144] Such benefit has not been shown in milder exacerbations, when work of breathing is not substantially increased.[146,147]

Several meta-analyses[148,149] have concluded that NIV is effective in avoiding intubation (relative risk 0.42 and absolute risk reduction 28%, respectively), reducing mortality (relative risk 0.41 and absolute risk reduction 10%, respectively), and shortening hospital length of stay (by approximately 4 days). A more recent study on a large cohort of more than 25,000 patients with COPD exacerbations requiring mechanical ventilation showed reduced mortality, length of stay, and cost with NIV compared to invasive ventilation.[150] On the basis of this evidence, current guidelines,[148–155] including the most recent European Respiratory Society/American Thoracic Society guidelines from 2017,[156] have recommended that NIV be used in patients with a COPD exacerbation and acute or acute-on-chronic ventilatory failure (pH <7.35) and should be started early in the course of moderate to severe COPD exacerbations. The European Respiratory Society/American Thoracic Society guideline also recommends against NIV use in patients with mild exacerbations (with pH ≥7.35) because of the studies showing lack of efficacy in this setting.[146,147]

NIV may also be considered in patients with COPD developing acute ventilatory failure in a number of different settings. Patients with acute exacerbations of COPD complicated by pneumonia have more severe COPD exacerbations than those without pneumonia[157] but still respond favorably to NIV, with reduced intubation and mortality rates and ICU lengths of stay compared to conventional therapy in one controlled trial.[158] Patients with COPD in the postoperative and postextubation settings also benefit from NIV. In a group of patients after lung resection, one randomized controlled trial showed reduced intubation and mortality rates when NIV was compared to conventional therapy.[159] For patients in the post-extubation setting, several studies have shown improved outcomes including reduced rates of ventilatory failure, reintubation, and mortality when used

in hypercapnic patients at risk for failing extubation.[160,161] Another approach has been to facilitate extubation in COPD patients who required intubation upon presentation or who failed initial NIV.[162,163] The European Respiratory Society/American Thoracic Society guideline[156] gave a conditional recommendation for both postoperative and post-extubation applications of NIV.

Another application of NIV for patients with COPD is in those who have declined intubation.[164] This application has been controversial, with some arguing that there is little to lose because it may reverse the acute deterioration or, at least, provide relief of dyspnea and a few extra hours to finalize affairs.[165] Others have argued that this merely prolongs the dying process, consumes resources inappropriately, and may add to discomfort or counter patients' wishes about avoiding life-prolonging measures.[166] In prospective observational studies of 113[164] and 131[167] patients treated with NIV who had *do-not-intubate* (DNI) orders, survival to hospital discharge was greater than 50% for COPD and congestive heart failure patients, whereas it was lower (14–25%) for those with a diagnosis of hypoxemic respiratory failure (pneumonia) or advanced cancer. Thus, NIV can be used to treat respiratory failure for DNI patients with acutely reversible processes such as COPD exacerbations. The patient or family should be informed that NIV is being used as a form of life support that may be uncomfortable and can be removed at any time. More recent information suggests that high flow nasal cannula oxygen (see Chapter 137) may be a good choice for palliation in terminal patients with respiratory failure. In one study, 183 patients with respiratory symptoms tolerated the therapy well and 85% improved or at least remained stable.[168] Not all of these patients had COPD or ventilatory failure, though, and further study is needed to determine how well HFNC performs in the COPD subpopulation.

Table 132.2 Selection Criteria for Noninvasive Positive-Pressure Ventilation in Acute Exacerbations of COPD

ESTABLISH NEED FOR VENTILATORY ASSISTANCE

- Moderate to severe respiratory distress
- Tachypnea (e.g., RR > 24 breaths/min)
- Accessory muscle use or abdominal paradox
- pH < 7.35, arterial P_{CO_2} > 45 mm Hg *or*
- Arterial P_{O_2}/F_{IO_2} < 200

EXCLUDE PATIENTS WITH CONTRAINDICATIONS TO NONINVASIVE VENTILATION

- Cardiac or respiratory arrest
- Medically unstable (septic or cardiogenic shock, uncontrolled upper gastrointestinal bleeding, acute myocardial infarction with planned intervention, uncontrolled arrhythmias)
- Unable to protect airway
- Severe encephalopathy
- Excessive secretions
- Uncooperative or agitated
- Unable to fit mask
- Recent upper airway or upper gastrointestinal surgery

F_{IO_2}, fractional concentration of oxygen in inspired gas; NIV, noninvasive ventilation; P_{CO_2}; partial pressure of carbon dioxide; P_{O_2}, partial pressure of oxygen; RR, respiratory rate.

Modified from Liesching T, Kwok H, Hill NS. Acute applications of noninvasive positive pressure ventilation. *Chest*. 2003;124:699–713.

High Flow Nasal Cannula Oxygen

High flow nasal cannula (HFNC) consists of oxygenated gas heated and humidified to body conditions, delivered to the nares at flows up to 40 to 80 L/min depending on the manufacturer. Use of HFNC has been increasing rapidly worldwide because it is well tolerated by patients compared to standard oxygen or NIV, keeps mucous membranes moist and enhances secretion mobilization, augments ventilatory efficiency by virtue of its dead-space clearing effect, slows respiratory rate, and raises expiratory airway pressure slightly.[169] Although its greatest benefit appears to be in hypoxemic respiratory failure,[170] some studies have shown reduced work of breathing in patients with severe COPD related to reduction of dead space and respiratory rate.[171] In one controlled study based in emergency departments, patients with a variety of causes of respiratory failure were randomized to receive HFNC or NIV. There was no significant difference between groups in the major outcome variable, "treatment failure," that included both the need to cross over to the other arm of the study and intubation.[172] The lack of difference in treatment failure was seen not only in pooled patients, but also in the COPD subgroup. The authors concluded that HFNC was "noninferior" to NIV for "treatment of respiratory failure from various causes in adult patients presenting to the emergency department who do not require immediate intubation."[172] However, there was a sizable imbalance in crossovers in the study, with more HFNC patients crossing over to NIV and avoiding intubation. Thus, it is difficult to have a high level of confidence about the noninferiority of HFNC compared to NIV to treat acute ventilatory failure in COPD based on this study alone. Although HFNC offers some physiologic benefit to patients with severe COPD, pending further clinical study, NIV should still be considered the modality of first choice for patients with ventilatory failure due to COPD. In milder COPD exacerbations or in patients intolerant of NIV, HFNC may offer a noninvasive alternative, but this remains to be investigated. On the other hand, HFNC may be used as a complementary therapy in patients with acute ventilatory failure being treated with NIV. One recent study showed that HFNC is more comfortable and prevents dyspnea and increased respiratory rate when used as an alternative to standard oxygen therapy during breaks from NIV.[173]

Practical Application of Noninvasive Ventilation

A thorough discussion of the application of NIV is beyond the scope of this chapter, and the reader is referred to Chapter 136 and elsewhere for more complete descriptions.[174] The following sections focus on aspects relevant to applications in COPD patients with acute ventilatory failure.

Patient Selection. Selection of appropriate patients is key to the successful application of NIV. The selection process should take into account the patient's clinical characteristics and risk of failure on NIV (Table 132.2). Predictors of success of NIV have been identified[175–177] (Table 132.3) and include a good neurologic status (and hence more cooperativeness), ability to protect the airway, and only mild-moderate acid-base or gas-exchange derangement. Several studies have also found that improvements in pH, arterial P_{CO_2}, and level

Table 132.3 Predictors of Success for Noninvasive Positive-Pressure Ventilation in the Acute Setting

EFFECTIVE SYNCHRONY OF PATIENT WITH VENTILATOR
■ Able to cooperate and comply with NIV
■ Good neurologic status
■ Younger age
■ Minimal air leaks
■ Dentate
ABLE TO PROTECT AIRWAY
■ Low volume of secretions
■ Low aspiration risk
NOT TOO ACUTELY ILL
■ No pneumonia or ARDS
■ Lower APACHE or SAPS II score
■ Moderate arterial hypercapnia
■ Moderate acidosis
GOOD INITIAL RESPONSE (WITHIN FIRST 1 TO 2 HOURS)
■ Improvement in pH
■ Reduction in respiratory rate
■ Reduction in arterial P_{CO_2}
■ Improved level of consciousness

APACHE, Acute Physiology, Age, and Chronic Health Evaluation; ARDS, acute respiratory distress syndrome; NIV, noninvasive ventilation; P_{CO_2}, partial pressure of carbon dioxide; SAPS, Simplified Acute Physiology Score.

Data from Hess DR. The evidence for noninvasive positive-pressure ventilation in the care of patients in acute respiratory failure: a systematic review of the literature. *Respir Care*. 2004;49:810-829.

of consciousness within the first hour or two of NIV initiation are strong predictors of success.[175–177] These studies indicate that there is a "window of opportunity" when initiating NIV that opens when patients need ventilatory assistance but closes if they progress too far and become severely acidemic. Ultimately, it becomes a clinical judgment that takes into account the patient's diagnosis that led to the respiratory failure, the need for ventilator assistance, and the absence of contraindications (see Table 132.2).[178]

Mask Selection. Tolerance of the mask is key to the success of NIV. Thus, the mask must fit well and be strapped on sufficiently to control air leaks while avoiding excessive strap tension. For acute applications, the standard full-face (oronasal) mask is usually preferred because it is better tolerated and avoids the leaking of air through the mouth that can limit the efficacy of nasal masks.[179] Nasal masks may be better tolerated by some patients,[178] although air leakage through the mouth is a common problem. The helmet, available in certain European countries but not in the United States, consists of a plastic cylinder that seals over the neck and shoulders, and offers an alternative interface. It is effective for delivery of CPAP in particular. Although difficulty achieving patient-ventilator synchrony has been reported when using the helmet to deliver pressure support ventilation, increasing the PEEP level to render the helmet less compliant[180] and a newer helmet designed specifically for use with NIV[181] help with this problem. Within each mask category, many varieties of masks are available. Practitioners should have a current knowledge of available masks and their proper application in order to maximize the likelihood of NIV success.

Ventilator Selection. In the acute setting, both "critical care" and "bilevel" ventilators (pressure-limited devices designed especially for the administration of noninvasive positive-pressure ventilation) have been used with similar success rates. Earlier versions of bilevel ventilators were designed mainly for home use, lacked sophisticated alarms, and had limited oxygenation capabilities, but more recent versions offer oxygen blenders, a variety of ventilator modes, waveform display, and sophisticated alarms. In addition, many ventilators designed primarily for invasive mechanical ventilation now offer noninvasive modes programmed to improve leak compensation, silence nuisance alarms triggered by air leaks, and permit limitation of inspiratory time to enhance patient-ventilator synchrony.[182] The capabilities of these modes differ considerably between different ventilator manufacturers, however, and may require additional adjustment if there are mask leaks.[183]

NIV Initiation. Initial ventilator pressures are usually set low to enhance patient comfort and acceptance but must often be adjusted upward as tolerated to provide adequate ventilatory assistance. Typical initial settings on pressure-limited ventilators are 8 to 12 cm H_2O for inspiratory pressures and 4 to 5 cm H_2O for expiratory pressures (e.g., PEEP), with subsequent adjustments as needed to alleviate respiratory distress and hypercapnia, counterbalance intrinsic PEEP, or treat hypoxemia. Some modes offering volume-assured pressure support permit selection of a target tidal or minute volume based on the patient's ideal body weight and can facilitate the initial adjustment process.[184,185]

Some ventilators permit adjustments in airflow to enhance synchrony, such as the "rise time," which determines the time to reach the target inspiratory pressure and the adjustable inspiratory time. These may be helpful in optimizing comfort in COPD patients who tend to prefer relatively high inspiratory flows[186] (and hence short rise times, often 0.1 sec) and short inspiratory times (usually <1 second) to avoid prolongation of delivered inspiratory pressures during expiration.

Oxygenation and Humidification. Most patients with COPD exacerbations do not have severe oxygenation defects and can be managed successfully with pressure-limited bilevel ventilators designed for home care. With these ventilators, oxygen is administered at rates up to 15 L/min into ports in the mask or via a T-connector at the proximal end of the ventilator tubing, adjusted to maintain the desired level of oxygenation (usually to an arterial oxygen saturation greater than 90–92%). However, because fractional concentration of oxygen in inspired gas using this arrangement does not exceed 45–50%, ventilators with oxygen blenders designed for delivery of NIV in critical settings have replaced the earlier versions of bilevel for patients with COPD exacerbations complicated by more severe hypoxemia. Humidification should be used routinely because it may reduce the work of breathing, facilitate secretion removal, and enhance comfort and tolerance of NIV.[180,187,188]

Adaptation and Monitoring. Coaching and encouragement, especially during the first few hours, are critically

important in achieving adaptation. Judicious administration of low doses of sedatives may enhance patient acceptance. Close bedside monitoring is essential until the patient's respiratory status stabilizes. Although NIV can be administered on general medical wards, the acuteness of the patient's illness and need for close monitoring should dictate the site of administration. Acutely ill patients should be treated in an ICU or step-down unit until their condition stabilizes.[145,189] As shown in Table 132.4, patient comfort and tolerance are key initial goals, together with a reduction in work of breathing and respiratory distress and optimization of patient-ventilator synchrony. Arterial oxygen saturation is monitored continuously, and blood gases obtained as clinically indicated, at baseline and at least once during the first hour or two.

Commonly Encountered Problems and Possible Remedies. Noninvasive ventilation is safe and well tolerated in most properly selected patients. The most commonly encountered problems in COPD patients are similar to those in other patients and are related to the mask, air pressure, or airflow (see Table 132.4). Minimizing air leaks is also an important aim.

Increasing Use of NIV and HFNC for COPD

Probably lagging behind Europe by 5 to 10 years, studies in the United States using nationwide hospital databases have shown trends toward increasing use of NIV by approximately 2.5- to 4.5-fold from 2000 to 2010, especially in patients older than 85 years.[190] This increased use of NIV has been accompanied by a drop in the use of invasive mechanical ventilation and a gradual decline in mortality. The mortality rate for patients failing NIV and having to transition to invasive ventilation has crept up over the same time period, raising the concern that NIV may be used occasionally in excessively ill patients who should have been intubated initially.[191] At a single community hospital in Massachusetts, use of HFNC increased by 17.5% annually during the years 2008 through 2014 at a time when use of NIV increased 10.2% annually. The greatest increase in use was for the diagnoses of pneumonia and COPD, the latter despite the lack of evidence to substantiate benefit.[192]

Invasive Mechanical Ventilation

Indications and Patient Selection. Although invasive mechanical ventilation is being used less often for acute exacerbations, it still has an important role in supporting patients who are not eligible for or fail NIV and desire aggressive support. These and other indications for invasive mechanical ventilation are listed in Table 132.5.

Invasive mechanical ventilation in COPD must be administered with care to minimize the risk of complications. Excessive tidal volumes and rates must be avoided, and the urge to normalize arterial P_{CO_2} must be repressed in an effort to minimize intrinsic PEEP and excessive hyperinflation and alkalosis. Excessive respiratory rates reduce the respiratory cycle, shorten expiratory time, and prevent complete exhalation. This problem is aggravated by large tidal volumes. The potential adverse consequences are air trapping and intrinsic PEEP. With severe intrinsic PEEP, increased intrathoracic pressure reduces venous return and lowers cardiac output. Patients with severe intrinsic PEEP may be hypotensive with low cardiac output and elevated pulmonary artery wedge pressure (although pulmonary artery catheters are now rarely placed) due to transmission of the intrathoracic pressure. Their clinical presentation may therefore mimic that of cardiogenic shock. Temporary disconnection from the ventilator can differentiate hemodynamic compromise

Table 132.4 Monitoring Noninvasive Positive-Pressure Ventilation in COPD

ACUTE SETTING

- Patient comfort
- Mask fit and leak
- Patient-ventilator synchrony
- Sternocleidomastoid muscle activity
- Vital signs (heart and respiratory rate; systemic blood pressure)
- Continuous oximetry (until stabilized)
- Occasional blood gases (initial and after 30 to 120 minutes, then as clinically indicated)

CHRONIC SETTING

- Patient comfort
- Mask fit and leak
- Hours of use
- Problems with adaptation (e.g., nasal congestion, dryness, gastric insufflation, conjunctival irritation, inability to sleep)
- Symptoms (e.g., dyspnea, fatigue, morning headache, hypersomnolence)
- Gas exchange (daytime, nocturnal oximetry, blood gases periodically to assess arterial P_{CO_2})
- Polysomnography (if symptoms of sleep disturbance persist or nocturnal desaturation persists without clear explanation)

P_{CO_2}, Partial pressure of carbon dioxide.

Table 132.5 Indications for Invasive Mechanical Ventilation in COPD

- Severe dyspnea with the use of accessory muscles and paradoxical abdominal motion
- Severe tachypnea (e.g., respiratory rate >35 breaths/min)
- Life-threatening hypoxemia
- Severe or worsening acidosis and hypercapnia
- Respiratory arrest
- Somnolence; impaired mental status
- Cardiovascular complications (hypotension; shock; heart failure)
- Other complications (metabolic abnormalities; sepsis; pneumonia; pulmonary embolism; barotrauma; massive pleural effusion)
- Contraindication to attempt NIV
- Failure of noninvasive positive-pressure ventilation for any reason

F_{IO_2}, fractional concentration of oxygen in inspired gas; P_{CO_2}, partial pressure of carbon dioxide; P_{O_2}, partial pressure of oxygen.

From Pauwels RA, Buist AS, Calverley PM, et al. Global strategy for the diagnosis, management, and prevention of chronic obstructive pulmonary disease: NHLBI/WHO Global Initiative for Chronic Obstructive Lung Disease (GOLD) workshop summary. *Am J Respir Crit Care Med.* 2001;163:1256-1276, and with data from Davidson AC, Banham S, Elliott M, et al., BTS Standards of Care Committee Member, British Thoracic Society/Intensive Care Society Acute Hypercapnic Respiratory Failure Guideline Development Group, On behalf of the British Thoracic Society Standards of Care Committee. BTS/ICS guideline for the ventilatory management of acute hypercapnic respiratory failure in adults. *Thorax.* 2016;71(Suppl 2):ii1–35.

due to intrinsic PEEP from true cardiogenic shock because the release of intrathoracic pressure permits rapid resolution of shock due to intrinsic PEEP but not cardiogenic shock. Intrinsic PEEP may also cause patient-ventilator asynchrony if ventilator triggering is missed when patients cannot reach the triggering threshold due to the inspiratory threshold load.

Recommended Ventilator Settings. Volume-limited or pressure-limited modes can be used, but volume-limited assist-control is the most frequent choice initially and provides control over the tidal volume, which is important in avoiding dynamic hyperinflation. A small tidal volume (e.g., 5 to 7 mL/kg predicted body weight) should be used to avoid hyperinflation, overventilation, and alkalemia. The backup respiratory rate for COPD patients receiving invasive mechanical ventilation should be set between 10 and 14/min. Given an inspiratory time of 1 second, if the respiratory rate is 20/min, the expiratory time is only 2 seconds; at a respiratory rate of 15/min, expiratory time increases to 3 seconds. Thus, relatively small changes in rate have large effects on expiratory time. Another way to increase expiratory time is to shorten the inspiratory time by increasing the inspiratory flow rate. However, this strategy is not as fruitful because substantial increases in flow rate result in only minor decreases in inspiratory time. For example, if the inspiratory time is 1 second and inspiratory flow is 60 L/min, an increase in the inspiratory flow rate to 100 L/min decreases the inspiratory time to 0.6 second (if tidal volume is held constant); thus, expiratory time increases only from 2.0 to 2.4 seconds. Furthermore, rapid flow rates may increase the spontaneous respiratory rate[193] and sensation of respiratory distress; COPD patients prefer flow rates in the 60 L/min range and tend to sense faster or slower rates as less comfortable.[186]

ASTHMA

Acute ventilatory failure due to acute asthma should be unusual if patients adhere to a medical regimen including inhaled corticosteroids, monitor their peak flows, and alter their medical regimen (with the addition of oral steroids) when peak flow declines. However, patients still experience severe asthma exacerbations and studies on near-fatal asthma have identified risk factors, including poor access to health care, substance abuse, nonadherence with therapy, underuse of corticosteroids, and underestimation of the severity of attacks.[194] In addition, heavy exposures to antigens, host factors that render patients particularly sensitive to specific antigens, or lack of adherence to environmental controls may also contribute. Episodes of severe asthma exacerbations can be reduced by the use of as-needed inhalers combining corticosteroids and long-acting β-agonists[195] and biologic asthma medications, including the anti–immunoglobulin E antibody, omalizumab, first available in 2003, as well as newer agents targeting interleukin-5, including mepolizumab, reslizumab, benralizumab, and dupilumab.[196] Even though episodes of acute ventilatory failure in asthmatics appear to be dropping, such attacks remain potentially lethal, with 3500 asthma-related deaths in the United States annually.[197]

Medical Management of Acute Asthma

Patients presenting with severe asthma should be promptly treated with systemic, as well as inhaled, corticosteroids and bronchodilators. Rapidly acting β_2-agonists are administered by inhalation, although no optimal method of administration or dose has been established. Metered-dose inhalers with spacers or nebulizers may be used, usually every 20 minutes for the first hour. Some centers use continuous nebulization for severe acute asthma. Magnesium, either intravenous or inhaled, has been administered, with some evidence to suggest that it aids aggressive β_2-agonist therapy, especially in the most severely ill asthmatics.[198]

Heliox has been used since the 1930s to lower resistance to flow related to turbulence in the airways of asthma patients, just as in COPD patients. However, a Cochrane analysis concluded that there is no defined role for heliox in treating severe acute asthma.[199]

Ventilatory Management

Assessment of Ventilatory Status. In patients with acute asthma exacerbations, ventilatory failure is unusual, but signs of severe respiratory distress, such as excessive use of accessory muscles, extreme tachypnea, or abdominal paradox, warrant prompt evaluation. Considering that asthmatic patients with respiratory distress are usually hyperventilating, arterial blood gases showing normocapnia in a patient with severe respiratory distress should cause alarm because, as they fail, patients reach a "crossover" point when they can no longer sustain hyperventilation but have not become sufficiently fatigued to retain CO_2. These patients should be monitored closely and considered for noninvasive ventilation to avert the need for invasive mechanical ventilation with its attendant potential complications.

Continuous Positive Airway Pressure. CPAP alone or NIV may ameliorate respiratory distress in asthmatics by reducing the work of breathing via a direct bronchodilator effect of positive pressure,[200] enhancing the effect of inhaled albuterol and offsetting intrinsic PEEP. However, the unequal distribution of airway resistance in asthma, in contrast to the more simultaneous closure of airways in COPD, creates areas with very different expiratory time constants. In this setting, CPAP can promote overdistention of some lung regions. Thus, caution should be exercised when applying CPAP to these patients, at least at levels exceeding 5 cm H_2O, and CPAP should be reduced to 5 cm H_2O if there is no further amelioration of respiratory distress at higher levels.

Noninvasive Ventilation. The role of NIV in the management of asthma exacerbations has not been clearly defined.[201] An early cohort study observed substantial improvements in blood gases (arterial P_{CO_2} dropping from 65 to 52 mm Hg in the first 2 hours) in 17 patients treated with NIV, only two of whom required intubation.[202] More recent studies have shown more rapid improvement in airflow[203] or equivalent improvement with less β-agonist medication.[204] In a study assessing the effects of bilevel ventilation on airflow in asthmatics, bronchodilators were withheld for the first hour of therapy and the higher bilevel setting was associated with greater improvement in FEV_1 than oxygen therapy alone.[205] These results suggest that

positive airway pressure might exert a bronchodilator effect; however, neither an RCT[206] nor meta-analysis[207] were able to demonstrate clinically meaningful benefits of NIV for acute asthma. Despite the absence of data supporting its use, a 2016 cohort study[208] using data collected over 4 years from a consortium of 97 U.S. hospitals found that 556 of 13,980 patients admitted with acute asthma (4%) were treated with initial NIV compared to 5% treated with initial invasive mechanical ventilation. The NIV failure rate was 4.7%, and hospital mortality among NIV failures, those placed on initial invasive mechanical ventilation, and NIV successes, was 15.4%, 14.5%, and 2.3%, respectively. In view of the uncertainty of the evidence, the European Respiratory Society/American Thoracic Society NIV Guideline Task Force made no recommendation on the use of NIV for acute asthma.[156] They did allow that an attempt at using NIV to avoid need for intubation might be warranted in patients behaving more like COPD patients (i.e., fixed airway obstruction).

Invasive Mechanical Ventilation. Invasive mechanical ventilation in patients with acute ventilatory failure due to asthma should be used as a last resort but is necessary when patients present with coma or delirium or with hemodynamic instability. Another clear indication is failure of standard medical therapy that may include NIV. Of patients admitted to the ICU with acute severe asthma, about one-third have been reported to require invasive mechanical ventilation.[194,209] Invasive mechanical ventilation is best avoided because of the frequency and severity of potential complications but, if needed, it should be initiated before a respiratory arrest. Complications of mechanical ventilation in asthmatics include barotrauma such as pneumothorax and pneumomediastinum, reported in 6.5% of patients in one series,[210] the need for sedation and paralysis with associated risk of postparalysis myopathy, ventilator-associated pneumonia, and mortality rates in the 5–10% range.[211]

If invasive mechanical ventilation is necessary, great care must be exercised to minimize the risk of complications, using an approach similar to that used for COPD patients. Excessive respiratory rates and tidal volumes should be avoided, with the ultimate goal of keeping plateau pressures under 30 to 35 cm H_2O. Permissive hypercapnia,[212] first described in invasively ventilated asthma patients,[213] remains a sensible approach in severely obstructed patients. With permissive hypercapnia, plateau pressures are maintained in a relatively safe range (<30 cm H_2O) as the first priority while allowing the CO_2 to rise, in some reports up to more than 100 mm Hg. Using this strategy, the major risks of positive-pressure ventilation can be minimized while providing time for the medical therapy to take effect. Bicarbonate can be administered if the pH drops too low, but this is probably not necessary and may not even be effective in raising the pH, a situation also described in patients with ARDS.[214] Because of the variability of resistance between airways, some of which may be obstructed, measurement of intrinsic PEEP using the expiratory hold technique may underestimate the severity of regional hyperinflation.[215] When ventilation remains difficult, even with lung-protective ventilation and permissive hypercapnia, heliox, general anesthesia with bronchodilator anesthetics (e.g., halothane),[216] or induced hypothermia have been used in the past, but in more recent years, centers with access to it have placed patients on extracorporeal membrane gas exchangers.

Extracorporeal Gas Exchangers (see Chapter 138). Extracorporeal membrane oxygenation has been used successfully to support patients with very severe asthma attacks when mechanical ventilation fails as evidenced by case reports.[217,218] Extracorporeal membrane oxygenation can be achieved using venovenous approaches where blood is removed, pumped through a gas-exchanging membrane, and then returned to the venous system via a dual-lumen catheter. Not only is the blood oxygenated, but CO_2 is removed, and this can be used to support patients through severe asthma attacks, allowing time for the asthma to subside. Extracorporeal membrane oxygenation can also be used in a venoarterial set-up, in which blood is removed from a vein and returned to an artery providing arterial pressure, in essence providing cardiopulmonary bypass for patients with not only respiratory but also circulatory failure.[219]

Another extracorporeal form of gas exchanger focuses on CO_2 removal rather than oxygenation and is referred to as extracorporeal CO_2 removal. This also removes venous blood, pumps it through a membrane gas exchanger, and returns it to venous blood using a dual-lumen catheter, but it operates at approximately 10% of the flow rate of extracorporeal membrane oxygenation,[219] which operates at nearly full cardiac output. Therefore, extracorporeal CO_2 removal cannot be used to restore hemodynamic stability but, by removing approximately one-third of the body's CO_2 production (80 mL/min), it may reduce ventilatory needs sufficiently to avoid intubation in patients failing NIV, allow mechanical ventilation at very low airway pressures, or facilitate extubation in patients with hypercapnic respiratory failure having difficulty weaning, particularly in COPD patients.[220,221] Although not currently approved or available in the United States, extracorporeal CO_2 removal is undergoing a clinical study in the United States (VENTAVOID study) in COPD patients with hypercapnic respiratory failure to determine whether it can reduce the number of invasive mechanical ventilation days compared to standard therapy plus NIV.

VASCULAR IMPAIRMENT

An increase in physiologic dead space by disorders affecting the pulmonary vasculature reduces alveolar ventilation in relation to overall minute ventilation. Although hypercapnia might be expected in such a circumstance, it is typically prevented by a modest increase in overall ventilation. Thus, acute ventilatory failure is seldom seen in primary pulmonary vascular disease. In pulmonary thromboembolism, for example, hypercapnia is unusual. Hypercapnia following pulmonary embolism can be seen, however, in patients with a comorbid condition such as severe COPD, with blunting of ventilatory drive, or with impaired function of the ventilatory pump. Indeed, acute respiratory acidosis, with or without concomitant worsening in oxygenation, may be the initial manifestation of pulmonary thromboembolism in a patient on controlled mechanical ventilation or with a high

cervical spinal cord injury or pharmacologic paralysis who cannot increase minute ventilation.

Another rare circumstance in which acute ventilatory failure may develop as a result of a disorder of the pulmonary circulation is venous air embolism, which leads to an abrupt increase in dead space, contributing to hypercapnia and a marked discrepancy between arterial and end-tidal exhaled CO_2 levels.[222] Hypercapnia may also complicate the acute chest syndrome in patients with sickle cell disease; one series documented respiratory acidosis in 42% of patients who developed this syndrome.[223]

Key Points

- Ventilatory failure is the consequence of inadequate alveolar ventilation, generally due to poor central drive, neuromuscular disease, profound mechanical derangement of lung parenchyma or chest wall, or a combination of these factors. Presently in the United States, acute ventilatory failure due to depression of central drive is mainly a consequence of opiate use.
- Respiratory muscle weakness, regardless of the origin of the impairment (e.g., immunologic, motor neuron disease, myopathic, associated with critical illness), may either precipitate intensive care unit admission or be acquired in the intensive care unit.
- Clinical assessment, including physical examination, measurement of maximal inspiratory and expiratory pressures, breathing pattern during spontaneous breathing trials, or bedside ultrasound to visualize the diaphragm, can be helpful in identifying respiratory muscle weakness.
- COPD exacerbation is the most common cause of acute ventilatory failure seen in acute care hospitals. COPD patients may develop acute or acute-on-chronic ventilatory failure due not only to bronchitis but also to complicating comorbidities including pneumonia, congestive heart failure, pulmonary embolism, or pneumothorax.
- Noninvasive positive-pressure ventilation reduces work of breathing by applying extrinsic *positive end-expiratory pressure* (PEEP) to counterbalance intrinsic PEEP and pressure support to assist inspiration. It is especially useful in exacerbations of COPD but may also play a role in other forms of acute ventilatory failure due to COPD, such as in facilitating extubation of those who fail a trial of spontaneous breathing or in avoiding reintubation in those who fail extubation.
- Noninvasive ventilation may also be tried in other forms of acute ventilatory failure, such as those caused by acute exacerbations of asthma or in acute-on-chronic respiratory failure in patients with obesity-hypoventilation syndrome, although evidence to support these applications is not as strong as in COPD.
- Invasive mechanical ventilation can generally be accomplished using small tidal volumes of roughly 6 mL/kg predicted body weight, which limits intrinsic PEEP in COPD, reduces the risk of ventilator-induced lung injury in those with parenchymal lung disease, and minimizes the circulatory compromise that can complicate restrictive chest wall conditions.
- When initiating noninvasive ventilation, there is a window of opportunity that opens when patients need ventilatory assistance but closes if they progress too far and become severely acidemic. Improvements in pH, arterial P_{CO_2}, and level of consciousness within the first hour or two of noninvasive ventilation are strong predictors of success.
- In patients with respiratory failure due to asthma or COPD, attempts to normalize arterial P_{CO_2} generally lead to dynamic hyperinflation, thereby risking hypotension and pneumothorax; instead, permissive hypercapnia is used to limit minute ventilation and maintain airway pressures in a safe range while allowing the arterial P_{CO_2} to rise.
- Newer extracorporeal membrane gas-exchange approaches, such as extracorporeal membrane oxygenation or extracorporeal CO_2 removal, can also be used to avert intubation and support patients with severe ventilatory failure; studies are ongoing to establish the efficacy of these approaches.

Key Readings

Alshekhlee A, Miles JD, Katirji B, et al. Incidence and mortality rate of myasthenia gravis and myasthenic crisis in US hospitals. *Neurology*. 2009;72:1548–1555.

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133 PULMONARY EDEMA

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INTRODUCTION

Pulmonary edema, defined as excessive extravascular water in the lungs, is a common and serious clinical problem. Pulmonary edema can be life-threatening, but effective therapy is available to rescue patients from the consequences of disturbed lung fluid balance. Because rational and effective therapy depends on understanding basic principles of normal and abnormal liquid, solute, and protein transport in the lungs, this chapter begins with a brief overview of the major factors that govern fluid and protein filtration in healthy lungs before focusing on the pathophysiology of pulmonary edema. Next, the chapter discusses diagnosis, treatment, and resolution of pulmonary edema. Because a thorough understanding of the lung's normal fluid clearance mechanisms is helpful to categorize the subtype of pulmonary edema and decide on treatment, the reader is encouraged to review Chapters 1, 3, and 6. Chapter 134 also contains excellent information specific to *acute respiratory distress syndrome* (ARDS).

PATHOPHYSIOLOGY

Pulmonary edema results when fluid is filtered from the pulmonary circulation into the extravascular compartments of the lungs faster than it can be removed. Accumulation of fluid has serious consequences on lung function because gas exchange is impaired in fluid-filled alveoli. Lung structure relevant to the forces governing fluid and protein movement in healthy lungs and lungs with pulmonary edema has been the subject of classic and more recent reviews.[1–6] In health, there is always a net outward flux of fluid and protein crossing from the pulmonary vascular circulation into the lung interstitium. This net outflux exists because the prevailing hydrostatic driving forces normally cause filtration from the bloodstream into the interstitium and, second, because the microvascular endothelium is a modestly permeable barrier under normal circumstances. Lung lymph flow, which reflects the flow of fluid crossing the microvascular barrier or bed (the term used in this chapter to refer to sites of fluid exchange in the lungs), normally is less than 0.01% of total lung blood flow. In addition to the vast interconnecting network of capillaries embedded in the alveolar walls, fluid is exchanged across capillaries in the interstitium at alveolar wall junctions (corner vessels) and across small interstitial arteries and veins. The essential factors that govern fluid exchange in the lungs are expressed in the Starling equation for the microvascular barrier, which is elaborated in Fig. 133.1 and mathematically describes the opposing forces of a hydrostatic pressure gradient and the protein osmotic pressure gradient between capillary and interstitium.

Microvascular hydrostatic pressure is the principal force causing fluid filtration in the lungs. If blood was not flowing through the lungs, the opposing hydrostatic and osmotic forces on either side of the microvascular barrier would be equal, their sum would be zero, and there would be no filtration. However, the pumping action of the heart causes blood to flow through the lungs, generating the microvascular hydrostatic pressure that establishes the steady-state values of the other driving pressures causing filtration of fluid.[5,7] According to the Starling equation, the difference between the prevailing transmural hydrostatic pressures ($P_C - P_i$) and the protein osmotic pressures ($\pi_C - \pi_i$) provides the driving force for fluid filtration (see Fig. 133.1). The actual amount of filtrate that forms at any given driving force is determined by the integrity of the barrier to filtration, which is reflected in the *conductivity* (L_p) and *reflection* (σ) coefficients. The equation predicts the development of two fundamentally different kinds of pulmonary edema: (1) increased pressure or hydrostatic pulmonary edema—when the net result of the driving forces increases, fluid filters across the barrier at a rate that exceeds removal by lymphatic drainage and other pathways,[8] and (2) increased permeability pulmonary edema—when the normal barriers to fluid filtration are damaged, typically by some form of injury, and conductance of liquid and protein in the lungs is allowed through paracellular pathways. A third type of pulmonary edema is caused by impaired lymphatic drainage of filtered fluid, but this is a very rare cause. The lymphatic drainage of the lungs provides a vital means for removing filtered fluid and proteins from the perimicrovascular interstitial space, as discussed later.[5,7,9] When fluid accumulates in the lung interstitium from increased filtration across the lung endothelium from either hydrostatic or

$$Jv = L_pS[(P_c - P_i) - \sigma(\pi_c - \pi_i)]$$

Figure 133.1 Fluid exchange as explained by the Starling equation. The Starling equation explains the movement of fluid across a semipermeable barrier. *Jv* is the net fluid-filtration rate (volume flow) across the microvascular barrier; L_p is the hydraulic conductivity ("permeability") of the microvascular barrier to fluid filtration (a measure of how easy it is for water to cross the barrier); *S* is the surface area of the barrier; P_c is the pulmonary capillary (microvascular) hydrostatic pressure; P_i is the interstitial ("perimicrovascular") hydrostatic pressure; π_c is the capillary (microvascular) plasma protein osmotic pressure; π_i is the interstitial (perimicrovascular) fluid protein osmotic pressure; and σ is the average osmotic reflection coefficient of the barrier (a measure of how effective the barrier is in hindering the passage of solutes from one side of the barrier to the other).

Table 133.1 Safety Factors That Protect the Lungs Against Interstitial and Alveolar Edema Formation in the Presence of Increased Pressure

Opposing osmotic pressure
Compliant interstitial space
Resorption into blood vessels
Lung lymphatic system
Drainage into the mediastinum
Drainage into the pleural space
Extremely low alveolar epithelial barrier permeability (in health)
Low alveolar surface tension from surfactant
Active transport by alveolar and distal airway epithelial cells

increased permeability, the alveolar epithelial barrier functions as the principal protection against the accumulation of alveolar edema. Fluid and protein do not normally move into alveoli because the alveolar epithelial barrier has a low permeability, even to small molecules (similar to cell membrane permeability); in addition, any fluid that is filtered is continuously being pumped back into the interstitium by vectorial ion transport across alveolar epithelial cells,[2,10] drained away from the alveolar walls through the interstitium, and removed by lymphatic vessels, bronchovascular pathways, and the lung microcirculation.

The several factors that normally protect the lungs against edema have been called *safety factors* (Table 133.1). Under normal conditions, the lymphatic system pumps filtered fluid and protein out of the lungs as rapidly as they are formed, even when filtration of fluid and protein from the bloodstream into the interstitium is increased. Increases in fluid and protein filtration across the microvascular barrier also can be drained away from the alveolar walls down the prevailing pressure gradient into the loose peribronchovascular connective tissue or can be resorbed directly into blood vessels.[4] The lung lymphatics can increase their pumping capacity significantly, particularly when the microvascular wall has been injured.[5]

The safety factors are resilient in the face of significant increases in hydrostatic pressure. With higher hydrostatic pressure, the increase in filtration of water across the microvascular barrier is much larger than that of protein because the microvascular barrier has a low protein conductance.

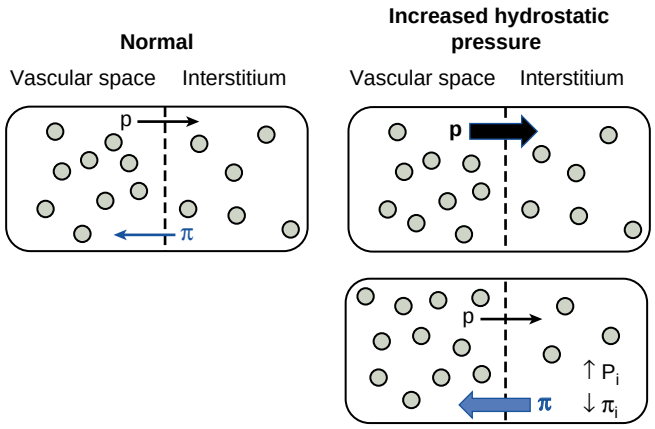

Figure 133.2 The safety factor of opposing hydrostatic and osmotic pressures across a normal microvascular barrier. In the normal state, the pressures are in relative balance, with the osmotic pressure of the proteins (π) constraining the fluid shifts from increases in hydrostatic pressure (p). With an increase in hydrostatic pressure (*large black arrow*), as more fluid moves into the interstitium, interstitial hydrostatic pressure rises and interstitial osmotic pressure falls. Both effects limit further flow from the vascular space to the interstitium (*large blue arrow*). P_i, interstitial hydrostatic pressure.

This results in dilution ("wash-down") of interstitial protein concentration and thereby an increase in the balance of the protein osmotic pressure opposing the higher hydrostatic pressure because plasma protein concentration remains high (Fig. 133.2). Furthermore, the interstitial gel also becomes hydrated, and the exclusion volume for protein decreases, either because of swelling or because its composition changes as hyaluronan is washed out from the interstitium, reducing the concentration of protein by expanding the available volume. This "sinking effect," whereby the hydrostatic gradient decreases and the protein osmotic gradient increases as microvascular hydrostatic pressure rises, is a safety factor only when the microvascular barrier is normal, as in increased pressure edema. In contrast, if the endothelial barrier is injured and its functional integrity is compromised—as in increased permeability edema—barrier conductance increases and the osmotic reflection coefficient decreases, rendering this safety factor ineffective.

The high compliance of the interstitial space also protects the lungs against edema. Increases in interstitial volume result in only small elevations of interstitial pressure until the interstitial volume is large. One study demonstrated that as much as 500 mL of edema fluid can collect in the lung interstitial space before there is alveolar flooding.[1] The accumulation of lung interstitial fluid maintains a suitably low hydrostatic driving pressure across the alveolar barrier. When interstitial pressure within the lungs rises to greater than pleural pressure, fluid flows across the highly permeable visceral pleura into the pleural space, where its effects on lung function are relatively minor. Pleural fluid is drained by lymphatics in the parietal pleura and, even when pleural liquid accumulates, does not flow back from the pleural space into the lungs[8] (see Chapter 14). Fluid that does accumulate in the alveoli is pumped out by active ion transport.[2] Several mechanisms can upregulate the rate of alveolar fluid clearance (see Chapter 3).

In summary, pulmonary edema results from increases in either driving pressures (increased pressure edema) or

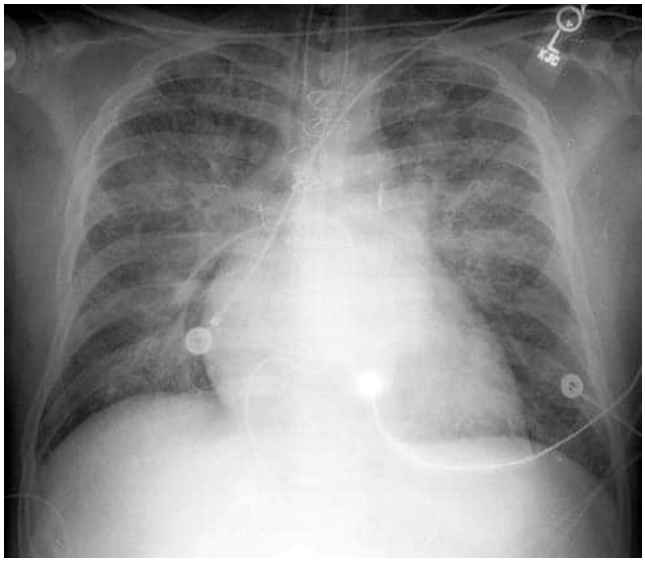

Figure 133.3 Frontal chest radiograph in a 55-year-old man with increased pressure edema due to heart failure. The heart is enlarged and bilateral perihilar linear and ground-glass opacities are present. This distribution is often referred to as a "butterfly" or "batwing" pattern and is commonly seen with chronic volume overload. (Courtesy Michael B. Gotway, MD.)

barrier conductance (increased permeability edema), or both. What distinguishes between the two types is barrier permeability, which is normal in increased pressure edema but high in increased permeability edema. Fluid flow into the lungs is driven across the barrier in both types of edema, according to the prevailing pressures and alveolar barrier permeabilities.

INCREASED PRESSURE EDEMA

Increased pressure pulmonary edema (Fig. 133.3) is caused by an increase in the net sum of driving forces for fluid filtration into the lungs. The essential feature of this edema is that the barriers to fluid and protein flow into the lungs are functionally intact. Increased pressure edema is often called cardiogenic, high-pressure, or hydrostatic pulmonary edema.

Pathophysiology

The flow of fluid and protein into the lungs increases when the sum of driving pressures is elevated. If the rate of fluid accumulation exceeds the rate at which it can be removed, increased pressure edema can result. Because the barriers limiting fluid and protein flow into the lungs are intact, the lungs are protected against edema by the prevailing (normal) safety factors. Especially important is the ability to protect against increases in the principal driving pressure, lung microvascular hydrostatic pressure. As previously explained, the reduction in plasma interstitial protein osmotic pressure in response to increased hydrostatic pressure mitigates alveolar flooding because both the hydrostatic and oncotic pressure gradients shift to favor less flow from the microvasculature to the lung interstitium. In experimental animals, slightly less than 50% of an increase in hydrostatic pressure is offset by the increase in osmotic pressure difference.[7,11] Increased pressure edema may be

Table 133.2 Effects of Vascular Congestion, Interstitial Edema, and Alveolar Flooding on Pulmonary Function and Lung Mechanics

VASCULAR CONGESTION
Increased diffusion capacity
Increased arterial P_{O_2}
Decreased compliance
Bronchoconstriction
INTERSTITIAL EDEMA
Increased closing volume
Decreased maximal expiratory flow
Increased ventilation-perfusion mismatching
Decreased arterial P_{O_2}
ALVEOLAR FLOODING
Right-to-left shunting of blood (compromising gas exchange)
Increased closing volume (air trapping)
Increased vascular resistance
Decreased lung volume (especially vital and inspiratory capacities)
Decreased compliance
Decreased diffusing capacity

P_{O_2}, partial pressure of oxygen.

gradual in onset and progression because any elevation in microvascular hydrostatic pressure is attenuated by a rise in protein osmotic pressure difference across the microvascular barrier, owing to a decline in interstitial protein osmotic pressure.

The consequences of increased pressure edema on lung mechanics and gas exchange (Table 133.2) depend on how much edema accumulates and typically proceed in a predictable manner.[12,13] At the vascular congestion stage preceding interstitial or pulmonary edema, increases in hydrostatic pressure result in enlargement of the intrapulmonary blood volume, as vessels, including capillaries, are both recruited and distended. The vascular changes cause the diffusing capacity to increase above normal, and the arterial *partial pressure of oxygen* (P_{O_2}) may rise because ventilated units are better perfused.[14] During this stage, small reversible changes in airflow resistance and dynamic compliance may also be observed, sometimes termed cardiac asthma.[15]

When interstitial edema is present, closing volume may be increased, leading to ventilation-perfusion mismatching, and maximum expiratory airflow may be decreased. These changes are likely due to a decrease in caliber of small airways caused by compression by rising volume and pressure in the peribronchovascular connective tissue spaces. This effect would have to be in airways larger than bronchioles because bronchioles and smaller airways do not have loose connective tissue sheaths,[16] and their diameter is influenced more by lung volume than transpulmonary pressure. Arterial P_{O_2} often declines due to areas of low ventilation-perfusion matching, but gas exchange is not seriously compromised until the alveoli are flooded.

With alveolar flooding, lung function declines significantly. Lung volumes are diminished.[13] Airways may close

at higher-than-normal distending pressures, resulting in trapping of larger volumes of gas in the lungs.[14] Lung compliance is reduced because lung volume decreases, and edematous lungs require more pressure to inflate. Because the flooded alveoli remain perfused, very low ventilation to perfusion lung units and right-to-left shunts are created, resulting in low arterial Po_2.[15] In addition, there is an increase in wasted ventilation (ventilation of units in which there is decreased or absent perfusion, or units with high ventilation-perfusion ratios).

Light and electron microscopic examination of human and animal lung tissue in increased pressure edema shows alveolar edema and variable red blood cell accumulation; thickened interstitial compartments, especially large peribronchovascular fluid cuffs or fluid surrounding the bronchi and vessels; and increased capillary surface area and volume.[17] Other than an increase in intercellular vesicles, there are no detectable changes in the ultrastructure of the vascular endothelium, with normal gap widths at intracellular junctions. However, when pulmonary edema is longstanding, for instance in chronic mitral stenosis, there may be remodeling that limits the development of further lung flooding. Dogs exposed to a pacing-induced chronic congestive heart failure model had thicker alveolocapillary barriers, spanning endothelium, interstitium, and epithelium.[18] Furthermore, they exhibited resistance to develop increased pressure edema—at high pulmonary vascular pressures, only half as much water and protein moved across the endothelial barrier—compared with that of control animals. Thus, remodeling may confer some protection against the development of high-pressure–induced alveolar edema and may shift up the pressure threshold at which edema forms. In addition, alveolar epithelial type 2 cells may be more numerous in chronic increased pressure edema than in normal lungs, which might signify an increased capacity to remove alveolar edema by vectorial ion transport.[2] Further, there is an increase in alveolar macrophages,[19] conceivably to clear red blood cells that accumulate in the alveoli due to chronic heart failure. However, sites of chronic severe increased pressure edema may also become organized and fibrotic and may even calcify.[20]

Mechanisms

By far the most common cause of increased pressure edema is elevated lung microvascular hydrostatic pressure. Less commonly, driving pressures into the alveolus can increase due to a reduction in perimicrovascular or alveolar hydrostatic pressure or a reduced protein osmotic pressure difference across the microvascular barrier. The possibilities are listed in Table 133.3 and reviewed individually later.

Table 133.3 Mechanisms of Increased Pressure Pulmonary Edema

INCREASED MICROVASCULAR HYDROSTATIC PRESSURE
Left ventricular dysfunction
Mechanical obstruction of left atrial outflow
Circulatory volume overload
Pulmonary venous hypertension
Overperfusion
Increased lymphatic outflow pressure
DECREASED PERIMICROVASCULAR HYDROSTATIC PRESSURE
Inspiratory airway obstruction with extremely negative intrathoracic pressure
Rapid aspiration of air or fluid from the pleural space
Increased alveolar surface tension

Increased Microvascular Hydrostatic Pressure. Congestive heart failure is the most common cause of increased pressure edema. That is why increased pressure edema is often called "cardiogenic," even though the heart is not always primarily involved. Elevated pressures in the pulmonary microvasculature are usually due to left-sided heart failure, with elevated left atrial pressures transmitted retrograde into the pulmonary circulation. Common causes are left ventricular dysfunction (e.g., caused by acute myocardial infarction, severe coronary insufficiency, tachyarrhythmias, bradyarrhythmias, cardiomyopathies, constrictive pericarditis, aortic stenosis or regurgitation, mitral regurgitation, coarctation of the aorta, rupture of chordae tendineae or intraventricular septa, systemic hypertension) or mechanical obstruction of the left atrial outflow tract (e.g., mitral stenosis, left atrial myxoma). Left atrial and pulmonary microvascular pressures can also be elevated by severe fluid volume overloading in a patient with a normal or diseased heart.

An unusual cause of increased microvascular hydrostatic pressure is pulmonary venous hypertension in the absence of left ventricular or atrial disease, which can arise if the pulmonary veins are contracted, compressed, or obstructed (e.g., because of veno-occlusive disease or fibrosing mediastinitis). Bronchial venous hypertension, in contrast, does not appear to increase fluid filtration in the lungs.[21]

Increases in fluid filtration also can be associated with increases in vascular pressure proximal to the filtration sites in the lungs. For example, pulmonary hypertension, combined with depressed left ventricular function, has been implicated in the pathogenesis of cocaine-induced pulmonary edema. Whether such increases lead to pulmonary edema depends on what happens to microvascular pressure. If high right-sided pressures are caused by increased resistance proximal to the main site of filtration in the lungs, as found in hypoxic pulmonary vasoconstriction of small arterial vessels,[22] pulmonary arterial hypertension, and pulmonary artery or valvular stenosis, pulmonary edema does not typically develop. Conversely, if the lung vascular bed is only partially constricted or obstructed, or if the vascular surface area is greatly decreased (e.g., by lung resection), higher flow in perfused vessels can lead to increased pressure edema[23] because microvascular pressures at the fluid exchange site are elevated in the overperfused lung. For example, in one study, pulmonary edema complicated approximately 15% of pneumonectomy cases and seemed to be exacerbated by administration of fresh frozen plasma,[24] likely because of increases in intravascular volume. Any increase in blood flow through the lungs increases the pulmonary microvascular pressure at the fluid exchange sites even when pulmonary venous pressure remains constant.

The mechanism of an uncommon cause of pulmonary edema, *high-altitude pulmonary edema*[25] (also discussed in

Chapter 105), may also be related, in part, to elevated pulmonary vascular pressures. As noted earlier, overperfusion of a restricted pulmonary vascular bed, even in the absence of hypoxia, causes increased pressure edema, not increased permeability edema.[23] This can explain why some cases of high-altitude pulmonary edema are correctly classified as increased pressure pulmonary edema. Evidence from climbers studied at high altitude suggests that high intravascular pressures can cause physical damage to vascular walls (so-called stress failure). In experimental animals, stress failure has been demonstrated after extreme, but sometimes transient, increases in pulmonary vascular pressures.[26] Such structural failures need not happen to many pulmonary vessels to explain an increase in permeability edema because edema would form readily and in a quantity driven by the prevailing elevated vascular pressure.[27] The suggestion has been made that high-altitude pulmonary edema results from the stress failure of overdistended, relatively thin-walled pulmonary arteries, rather than from microvascular rupture,[28] which might help explain why the prevailing vasoconstriction does not seem to offer much protection to downstream vessels, why there are no reports of gradual progression through an indolent prodrome of increased pressure edema before stress failure results, and why high-altitude pulmonary edema is first detected radiographically in the central lung fields surrounding large vessels, rather than in the lung bases and periphery. Alternative mechanisms for the increased permeability in high-altitude pulmonary edema have been proposed. However, inflammatory responses in high-altitude pulmonary edema may be a consequence rather than a cause of the edema.[29] The rapid reversibility of high-altitude pulmonary edema with descent to lower elevation, oxygen therapy, or pharmacologic reduction of pulmonary vascular pressure is more characteristic of an increased pressure pulmonary edema, not of an increased permeability pulmonary edema with coexisting inflammation.

Neurogenic pulmonary edema,[30] which can be radiographically indistinguishable from other forms of edema, also may result in part from elevated pulmonary vascular pressures. Measurements of edema fluid protein concentration relative to plasma protein concentration in 12 patients with neurogenic pulmonary edema have been reported.[31] Seven of the patients had ratios typical of increased pressure pulmonary edema. However, the other five had elevated ratios that could be consistent either with increased permeability pulmonary edema or with sampling during the later resolution phase of increased pressure pulmonary edema, at which time edema fluid protein concentration rises as fluid is reabsorbed from the alveoli at a faster rate than protein.

Decreased Perimicrovascular Hydrostatic Pressure. The sum of driving pressures favoring flow out of the vasculature would increase if perimicrovascular hydrostatic pressure was greatly diminished, thereby resulting in an increase in fluid and protein filtration at the microvascular barrier in the lungs. Pulmonary edema has been described in circumstances in which this might happen. The best clinical example may be postobstructive pulmonary edema as a consequence of upper airway obstruction or its release. Postobstructive pulmonary edema has been described after obstructions caused by laryngospasm, endotracheal tube obstruction, foreign body aspiration, epiglottitis, croup, severe acute asthma, airway compression by tumors, strangulation, or hanging. High negative intrathoracic pressures generated by inspiratory attempts against the occluded airway are transmitted to the interstitium, lowering interstitial hydrostatic pressure and promoting fluid movement into the interstitium. Mechanical effects on the cardiovascular system likely contribute to this kind of edema because high negative intrathoracic pressure increases cardiac preload, afterload, and pulmonary blood flow, all of which increase the microvascular hydrostatic pressure. In three patients with upper airway obstruction and pulmonary edema, all had low edema fluid protein concentration relative to plasma protein concentration (ratios of 0.44, 0.31, and 0.52, respectively), favoring increased pressure pulmonary edema instead of a permeability mechanism.[32,33]

Aspiration of air or fluid from the pleural space, as by thoracentesis, with consequent reexpansion of a collapsed lung, could result in a decrease in perimicrovascular hydrostatic pressure as the lung expands to fill the thorax. So-called reexpansion pulmonary edema has been reported both in experimental animals[34] and in humans[35] after lung reexpansion; however, there are conflicting reports as to the edema fluid protein concentration from human subjects[36,37] and animal models,[38] suggesting that either hydrostatic or permeability mechanisms may predominate. If high alveolar surface tension was transmitted to the interstitium, perimicrovascular hydrostatic pressure would also be lowered, thereby increasing filtration across the microvascular barrier. Such an effect has been suggested by experimental findings in dog lungs.[39] The effect of alveolar surface tension on lung fluid balance is discussed later.

Decreased Transmural Protein Osmotic Pressure Difference. Increased pressure pulmonary edema may also result from decreases in the protein osmotic pressure difference opposing the hydrostatic pressure difference across the microvascular barrier. The osmotic difference may decrease when plasma protein concentration is lowered due to cirrhosis, nephrotic syndrome, or malnutrition, or in the presence of high interstitial protein concentration. This theoretical mechanism of increased pressure edema has been the subject of study in experimental animals, with contradictory results.[40] When plasma protein osmotic pressure is low, the ability of the osmotic pressure gradient to widen in response to increased hydrostatic pressure is diminished, and edema accumulates at hydrostatic driving pressures lower than those needed to cause edema when plasma protein concentration is normal. Low protein osmotic pressure may also contribute to pulmonary edema in pregnancy and early postpartum settings.[41] Although it is uncommon to attribute pulmonary edema exclusively to the mechanism of diminished protein osmotic pressure gradient,[42] this physiologic state frequently complicates pulmonary edema due to either increased pressure or increased permeability so that patients with low plasma protein osmotic pressure develop severe edema more rapidly and may have a delayed recovery.

Alveolar Barrier Function. Although the preceding section has focused mainly on driving pressures from the microvascular (endothelial) space to the interstitium, the

same principles apply to driving pressures across the interstitial and alveolar (epithelial) barriers. Increased pressure edema can result from several conditions: if interstitial hydrostatic pressure is raised, if alveolar hydrostatic pressure falls, or if the osmotic pressure difference across the alveolar barrier is lowered. Interstitial hydrostatic pressure rises as interstitial edema accumulates in the lungs.[4,9] Increased interstitial hydrostatic pressure would raise the sum of driving pressures across the alveolar barrier and could drive edema formation across the alveolar or airway epithelium.

Experimentally, a relationship between higher alveolar surface tension and decreased interstitial hydrostatic pressure, which favors edema formation, has been observed,[43] leading to alveolar edema. Administration of a detergent aerosol in an animal model resulted in loss of surfactant activity, higher alveolar surface tension, lower static compliance, atelectasis, and pulmonary edema.[43] Supporting an increased pressure mechanism for this model of pulmonary edema, alveolar edema fluid protein concentration was low[43] and, because neither protein osmotic pressure nor pulmonary microvascular hydrostatic pressure was altered,[44] the interstitial hydrostatic pressure was likely affected. However, it is also possible that detergent administration may have directly injured the alveolar epithelium. Because increased pressure edema can impair surface activity of dog lung extracts and isolated rabbit lungs, it is possible that changes in alveolar surface tension may accelerate edema formation. However, the notion that changes in alveolar surface tension in edema lead to a self-perpetuating vicious circle of edema formation is not borne out clinically.

Near-drowning is the one clinically pertinent form of pulmonary edema caused by transmural osmotic pressure differences at the alveolar barrier.[45] Seawater is three times more osmotic (1000 mOsm) than plasma, so the volume of fluid in the air spaces after saltwater aspiration increases threefold to reach osmotic equilibrium, thus markedly increasing the alveolar edema volume beyond the aspirated seawater in the alveoli. Osmotic equilibrium is reached in minutes as water is drawn from neighboring blood vessels into the alveoli by osmotic pressure.[45] Alveolar barrier function is not significantly compromised, unless perhaps the patient aspirates gastric contents or the seawater is contaminated or rich in particulate matter, and the alveolar edema tends to be cleared rapidly if driving pressures are otherwise normal, with 50–60% of excess alveolar fluid being cleared in 4 hours. Freshwater near-drowning classically proceeds in the opposite fashion: Osmotic equilibrium is reached rapidly by flow of water out of the alveoli into the interstitium and bloodstream. Rapid water flux and hypotonicity can cause severe hemodilution, with hemolysis and fibrinolysis, and severe distortion of pulmonary ultrastructure, including damage to type 1 and type 2 cells, endothelial cell swelling, basement membrane detachment, and cell disruption. Both the alveolar epithelium and microvascular endothelium can thus be injured by the hypotonic fluid, leading to increased permeability pulmonary edema rather than an increased pressure type of pulmonary edema. In addition, aspiration of water, whether freshwater or seawater, can wash out surfactant and contribute to pulmonary edema.

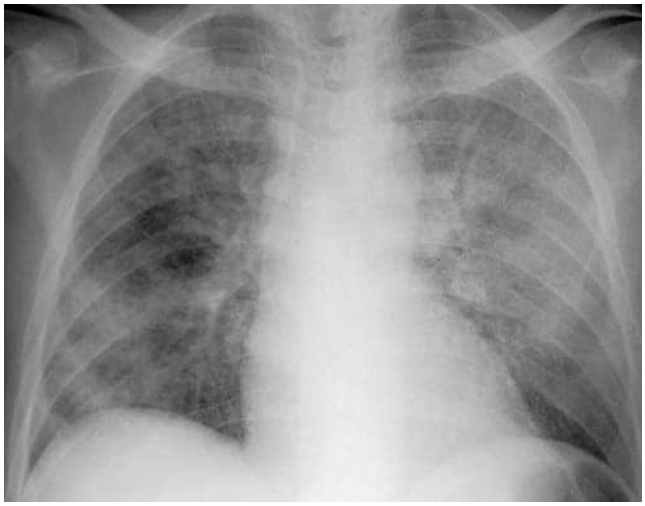

Figure 133.4 Frontal chest radiograph in a patient with increased permeability edema. Bilateral consolidation, more prominent on the left, is present. The heart is not enlarged, and no pleural effusions are present. No features typical of volume overload are evident. (Courtesy Michael B. Gotway, MD.)

INCREASED PERMEABILITY EDEMA

Increased permeability pulmonary edema (Fig. 133.4) is caused by an increase in liquid and protein conductance across the barriers in the lungs. The essential feature of this edema is impaired barrier integrity to fluid and protein flow into the lung interstitium and alveoli. Increased permeability edema is sometimes called *noncardiogenic pulmonary edema,* and the resulting clinical syndrome in humans, when clinical and radiographic criteria are met (Table 133.4), is referred to as ARDS, discussed in detail in Chapter 134.[46]

Pathophysiology

If the rate of fluid and protein accumulation from lung endothelial and epithelial barrier injury exceeds the rate at which it can be removed, increased permeability edema can result. Because the barriers limiting fluid and protein flow into the lungs do not function normally when the lungs are injured, the lungs are not protected against edema by all the safety factors listed in Table 133.1. Although the excess fluid and protein are removed by lymphatics and drained away from the alveolar walls as in increased pressure edema, much more fluid and protein are filtered at any given sum of driving pressures because the barriers to their flow are much less restrictive than normal. As a result, edema formation in injured lungs becomes extremely sensitive to driving pressures.[27] In addition to the changes in the barrier function, driving pressures are often increased when the lungs are injured because of the vasoactive effects of inflammatory mediators such as thromboxanes, which may shift the main site of resistance to postcapillary venules, thus increasing hydrostatic pressure at the microvascular fluid exchange sites,[47] or because of the effects on the heart and on the circulation. For example, elevated left atrial pressure, pulmonary venoconstriction, and an increase in cardiac output in sepsis can all increase hydrostatic pressure at microvascular fluid exchange sites.[48]

Table 133.4 Berlin Definition of ARDS[65]

Mild	Pao_2/Fio_2 > 200–300 mm Hg with PEEP ≥5 cm H_2O	Bilateral radiographic opacities consistent with pulmonary edema and not explained by effusions or atelectasis, and judged not to be explained by increased left atrial pressure	Acute onset (within 1 week of risk factor, or within 1 week of symptom onset)
Moderate	Pao_2/Fio_2 > 100–200 mm Hg with PEEP ≥5 cm H_2O		
Severe	Pao_2/Fio_2 ≤ 100 mm Hg with PEEP ≥5 cm H_2O		

ARDS, acute respiratory distress syndrome; Fio_2, fractional concentration of oxygen in inspired gas; Pao_2, partial pressure of arterial oxygen; PEEP, positive end-expiratory pressure.

Because the endothelial-epithelial barrier is more permeable than normal, protective protein osmotic pressure differences are lost so that driving pressure is unopposed by protein osmotic pressure. Thus, even at normal hydrostatic pressure, there is significant fluid and protein extravasation into interstitial and alveolar spaces. Maximal lung lymph flow increases more when the microvascular wall has been injured than when hydrostatic pressure alone is increased, but even this augmented lymphatic pumping capability is insufficient. If the epithelial barrier is injured, edema may accumulate readily in the alveoli because most of the resistance to fluid and protein flow into the alveoli resides in the epithelial barrier.[49] As mentioned earlier, because the injured barriers offer much less resistance to flow and the safety factor provided by the osmotic pressure difference is lost, increased permeability edema is often rapid in onset and progression. And, although it was historically believed that increased permeability edema was characterized by low intravascular hydrostatic pressure, and the prior ARDS consensus definition even specified that the *pulmonary artery wedge pressure* (PAWP) should be 18 mm Hg or less if measured,[50] ARDS and increased hydrostatic pressures frequently coexist. In that situation, edema may be expected to form rapidly due to elevated driving pressure unopposed by a normal barrier.

The consequences of increased permeability edema on lung mechanics and gas exchange depend on the quantity of edema and the severity of the causative lung injury.[51] As with increased pressure edema, alveolar flooding causes major effects on pulmonary mechanics. In experimental lung injury, functional residual capacity decreases as a consequence of alveolar flooding, and this loss of ventilated units accounted for virtually all the observed decrease in static lung compliance.[52] *Computed tomography* (CT) has provided new insights into structure-function relationships in ARDS[53] and demonstrated the significant heterogeneity in lung aeration even when the chest radiograph suggests diffuse edema. In classic early diffuse ARDS, edema accumulates in all lung regions with a nongravitational distribution. Increased lung weight due to edema causes collapse of more dependent lung regions through the transmission of hydrostatic forces (compression atelectasis, caused by the weight of edema).[53]

Measurements of pulmonary mechanics in mechanically ventilated patients with diffuse injury to the lung have shown a decreased static lung compliance as a consequence of loss of ventilated lung. In addition, airflow resistance is increased as a result of decreased lung volume.[51] Bronchospasm may add to the increase in airflow resistance and can be substantially reversed by bronchodilator inhalation.[54] Chest wall compliance is reduced, probably because of alterations of intrinsic mechanical properties of the chest wall by abdominal distention, chest wall edema, and pleural effusion.[51] Respiratory mechanical abnormalities and responses to *positive end-expiratory pressure* (PEEP) may differ between patients with severe ARDS originating from pulmonary disease (pneumonia with consolidation) compared to those with severe ARDS from extrapulmonary disease (associated with pulmonary edema and alveolar collapse).[55] Alternatively, it may be that the extent of radiographic consolidation—diffuse versus focal—is a major determinant of response to PEEP in ARDS,[56] regardless of the inciting injury.

Alterations to pulmonary surfactant volume and function may contribute to permeability edema pathophysiology. The injured lung may release substances that interfere with the normally low surface tension in the alveoli,[57] and activated polymorphonuclear leukocytes impair surfactant function in vitro and degrade the major surfactant apoproteins by proteolysis and oxidant-radical–mediated mechanisms.[58] Lung surfactant obtained by *bronchoalveolar lavage* (BAL) from patients at risk for diffuse injury to the lung and from those with established injury is abnormal in chemical composition and functional activity.[59] Abnormalities also may be caused by interactions between surfactant and edema proteins because plasma proteins, including fibrin, fibrinogen, and albumin, interfere with surfactant function. Intraalveolar coagulation may compound surfactant depletion. Proteinaceous edema fluid has been associated with surfactant inhibition in various experimental models.[60] The role of surfactant in the development and treatment of diffuse lung injury and the potential role for surfactant therapy are discussed in more detail later in this chapter.

Oxygenation is often severely compromised in increased permeability edema, owing both to intrapulmonary shunting of blood and to low ventilation-perfusion lung units.[61] Patients with early lung injury also have a marked increase in their pulmonary dead space fraction, indicating that many ventilated lung units are not well perfused[62]; this finding explains why minute ventilation rises to twice normal (12–16 L/min) at the onset of severely increased permeability edema. An elevated pulmonary dead space fraction also has been reported in pediatric patients with widespread lung injury,[63] the mechanism that may, in part, be explained by an increase in procoagulant and antifibrinolytic pathways in parenchymal damage.

The pathologic sequence of increased permeability edema has been well described using oxygen toxicity as one prototypical inciting cause.[64] ARDS was classically described as evolving from an exudative stage to one characterized as proliferative and then fibrotic in sequence. The earliest "exudative" changes are marked by widespread alveolar and interstitial edema and hemorrhage, along with capillary congestion and atelectasis. Hyaline membranes,

composed of precipitated plasma proteins, fibrin, and necrotic debris, are often observed, and pathologists use the term *diffuse alveolar damage* (DAD) to describe this combination of edema, hemorrhage, and/or hyaline membranes.[64] However, although DAD is often described as the morphologic hallmark of ARDS,[65] neither DAD nor hyaline membranes were universally found in the pathologic samples from patients with ARDS,[46,64] and DAD can be described in other lung diseases. More recently, a large Spanish autopsy study reported that only 45% of lungs from patients who died with ARDS exhibited DAD and, even among those with severe ARDS for at least 72 hours, the proportion with DAD was only 69%.[66] Although some have argued that ARDS in the absence of hyaline membranes may not be ARDS, a better explanation is that ARDS with hyaline membranes represents a specific subtype or level of severity.[67]

In some patients, the exudative phase is followed by a proliferative phase, which begins as early as 5 to 7 days after the onset of injury.[68] The relative contributions of the original insult, repair processes, and effects of therapies to this and subsequent phases are not well known. Furthermore, it is likely that historical mechanical ventilation strategies using larger tidal volumes (between 12 and 15 mL/kg predicted body weight)[69] were a major contributor to the pathologic progression of lung injury. In the proliferative phase, some of the edema fluid has been reabsorbed from the air spaces. Fibrin may be prominent in alveoli and interstitium, and there is infiltration with inflammatory cells and fibroblasts. The alveolar epithelium is often cuboidal, made up largely of proliferating type 2 cells. The air-blood barrier can be thickened by interstitial and epithelial enlargement. The pulmonary vascular bed may be partially or completely disrupted, and structural alterations may reduce its surface area. A final stage may follow, often about 10 to 14 days after the initial insult, in which fibrotic changes of the alveolar ducts, alveoli, and interstitium predominate; alveoli may be obliterated, alveolar walls coalesced, and functional lung units lost. Less common, the lungs show emphysema-like bullous changes.[68] Pulmonary function test results in 5-year survivors of severe increased permeability edema usually return to normal or near-normal values, but exercise limitation and physical, cognitive, and psychological impairments often persist.[70,71]

Mechanisms

The major types of clinical conditions associated with increased permeability edema are listed in Table 133.5. The most common causes are pneumonia, sepsis, gastric aspiration, and major trauma. Reperfusion injury is one of the causes of the pulmonary edema seen in transplanted lungs and appears to be predominantly an increased permeability edema.[72] In all cases, the lungs can be injured either via the airways as a *direct* injury or via the bloodstream as an *indirect* injury. The exact mechanisms by which diffuse lung injury leads to increased permeability edema have been the subject of intense investigation in humans, animal models, and cellular systems, summarized in several reviews.[73–75] Human studies have provided descriptive data about events in the air spaces before and after the onset of lung injury.

Studies using BAL in patients before and after the onset of diffuse lung injury have shown that there is a major acute inflammatory response that begins before lung injury is clinically recognized, peaks during the first 1 to 3 days of clinical involvement, and then resolves slowly over the next 7 to 14 days in patients who remain intubated.[73,76] These studies have shown the complexity of the evolving inflammatory responses, which are characterized by the accumulation of acute response cytokines and their inhibitors, oxidants, proteinases and antiproteinases, lipid mediators, growth factors, and collagen precursors involved in the repair process.[74,77–82] Extensive efforts have been made to identify single biologic markers that predict the onset or the outcome of diffuse injury to the lung, but these have met with only limited success.[47,83,84]

Table 133.5 Clinical Disorders Associated With Increased Permeability Edema

Infections, both pulmonary (pneumonia) and non-pulmonary
Sepsis
Aspiration
Trauma
Reperfusion (posttransplant)
Hemodynamic disturbances (shock)
Medications and toxins
Smoke inhalation
Drowning, especially in fresh water
Hematologic disorders
Neurologic disorders

CLINICAL ASSESSMENT

When pulmonary edema is severe, the patient is overtly hypoxemic and in respiratory distress, making the identification of edema fairly straightforward. More nuanced, however, may be the distinction between increased pressure and increased permeability edema. Although many aspects of treatment are shared between both major forms of pulmonary edema, the distinction is important as the clinician seeks to reverse the underlying cause.

SYMPTOMS AND SIGNS

The clinical manifestations of pulmonary edema vary with its severity and depend on the underlying pathophysiology and the extent to which excess edema fluid has accumulated in the lungs. Characteristic symptoms include dyspnea, cough, and tachypnea. Wheezing, when audible, may suggest a problem of airflow obstruction rather than edema.[85] Once alveoli have flooded, the diagnosis of pulmonary edema is not subtle. Patients with alveolar edema usually have severe respiratory distress with tachypnea and often productive cough of frothy and sometimes blood-tinged edema fluid. Crackles and rhonchi are heard over the lung fields, and wheezing may be present. The patient may be cyanotic if alveolar flooding has seriously compromised gas exchange.

Development of increased pressure pulmonary edema is often slow and progressive because the alveoli are protected by the normal safety factors (see Table 133.1). (However, there is a form of increased pressure edema that develops suddenly [or unexpectedly] and sometimes is called flash pulmonary edema, when protective safety factors have been surmounted.) In contrast to the typical subacute progression seen with increased pressure edema, alveolar flooding and symptoms of respiratory distress often progress rapidly from insult to respiratory failure with increased permeability edema.

Because pulmonary edema is always a sign of an underlying pathologic process, its cause must be identified so that effective therapy can be directed at the underlying problem producing abnormal transvascular fluid and protein flow into the lungs. Increased pressure edema is most often caused by cardiac failure—systolic dysfunction with impaired myocardial contractility or diastolic dysfunction with impaired relaxation—and thus is usually accompanied by a history of heart disease. Manifestations include signs and symptoms of any of the many causes of chronic and acute congestive heart failure, such as coronary insufficiency, hypertension, valvular heart disease, and severe volume expansion. Elevated jugular venous pressure, cardiac enlargement, gallop rhythms, heart murmurs, arrhythmias, an enlarged tender liver, and peripheral edema almost always suggest an underlying abnormality of cardiac function. However, pulmonary edema may be the only manifestation of silent myocardial infarction or diastolic dysfunction of the left ventricle.[86]

History and physical examination may also be helpful in differentiating between increased pressure and increased permeability pulmonary edema because most patients in the latter category usually do not have signs or symptoms of underlying cardiac disease. The cause of increased permeability edema may be suggested by a history of exposure (e.g., to toxic gases or chemicals or infectious agents, near-drowning, drug ingestion, trauma), the clinical setting (e.g., sepsis, pneumonia, emesis, seizures, pancreatitis), or the physical findings (e.g., chest trauma, long bone fractures, coma, shock). Because infections, including sepsis, are the leading causes of increased permeability edema in patients, a thorough search must be made for signs and symptoms of infection. Pulmonary and intra-abdominal sources are the most common sites of involvement, and all patients should be examined carefully, with special attention being paid to sites vulnerable to more subtle findings, including abdominal, rectal, skin, and pelvic examinations.

DIAGNOSTIC STUDIES

Laboratory and other diagnostic studies are often helpful but, by the time many of the results are confirmed to be abnormal, the diagnosis is usually obvious. Appropriate cultures for microorganisms and toxicology screens of blood and urine are useful in identifying underlying causes of increased permeability edema and to ensure appropriate antimicrobial therapy. Examination of sputum or tracheal aspirate, bronchoscopy with protected-specimen brushing or BAL, or mini-BAL are all useful in diagnosing pneumonia in ventilated patients, even those who are being treated with antimicrobial drugs.[87–90] Lung biopsy can sometimes provide a specific diagnosis in critically ill patients,[67,91] but the results may not be helpful because lung injuries caused by diverse underlying conditions have similar histologic appearances and because specific therapies may not be available. Serum and plasma testing focused by the patient's history, particularly when infection seems less likely, might include testing for pancreatitis, for carboxyhemoglobin if smoke inhalation was suspected, or for transfusion-related factors (e.g., cognate antibodies to human leukocyte antigen class I or II, or to human neutrophil antigen) if the patient recently received any blood products.[92]

CHEST IMAGING

The plain chest radiograph is the most practical test available for the detection of pulmonary edema.[93,94] Disadvantages are that chest radiographs are insensitive to small changes in lung water and are only semiquantitative.[1] An additional limitation is that chest radiographs are not consistently helpful in distinguishing increased pressure edema from increased permeability edema.[94,95] In the *Fluid and Catheter Treatment Trial* (FACTT), studying the use of central venous and pulmonary arterial catheters to target volume strategies in ARDS, the vascular pedicle width, measured as a horizontal distance from where the superior vena cava crosses the right mainstem bronchus to the left subclavian artery exiting the aortic arch,[96] had moderate correlation with PAWP but only fair sensitivity to predict whether a target PAWP had been achieved.[97] Despite these limitations, chest radiographs are noninvasive, inexpensive, easily repeatable, readily available, and free of serious side effects, apart from a small amount of radiation.

Before alveolar flooding, plain chest radiographs typically show distended vascular shadows (particularly in the upper lung fields), enlargement and loss of definition of hilar structures, development of septal lines (Kerley lines) (Fig. 133.5A and Fig. 108.3B), loss of peribronchial and perivascular definition or cuffing (see Fig. 133.5B and Video 133.1), and perihilar haze indicating the presence of interstitial pulmonary edema. Acinar shadows, often confluent and creating irregular, patchy increases in lung density that obscure vascular markings, indicate the presence of alveolar edema. Air bronchograms may be observed in severe edema. Because the radiographic signs of interstitial and alveolar edema are determined by gas and blood volumes and their distribution in the lungs in addition to the presence of edema, the recognition and quantitation of edema are not precise, and the radiographic appearance of edema is strongly influenced by the lung volume at the time the film is made. The appearance of the chest radiograph is an integral part of the Berlin definition of ARDS,[65] but the interpretation of chest radiographs is not well standardized, and significant interobserver variations have been reported.[98] One approach for scoring the chest radiograph and accounting for atelectasis correlated well with lung weight in lungs studied from brain-dead potential organ donors.[99] More recently, investigators have reported a *radiographic assessment of lung edema* (RALE) score assessing both the extent of alveolar opacity and the density of consolidation in each quadrant. This composite score exhibited strong interreviewer agreement, strong correlation with total lung weight of donor lungs, and association with arterial Pa_{O_2}/*fractional concentration*

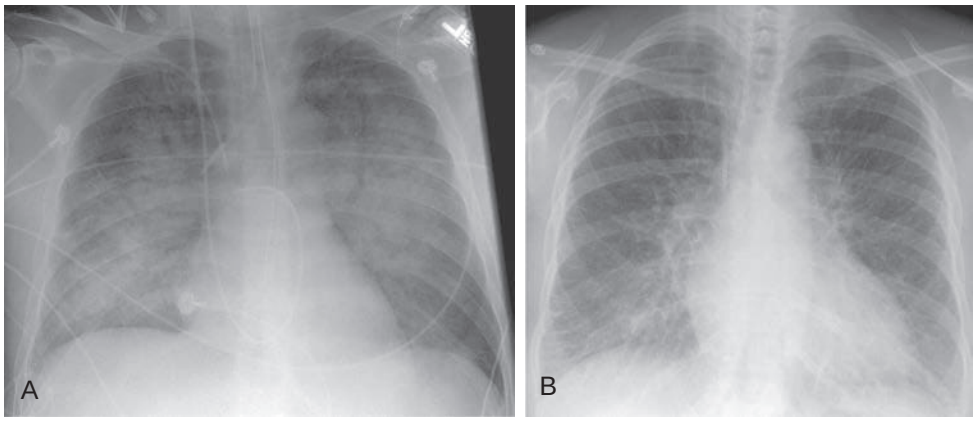

Figure 133.5 Two patients with increased pressure edema from heart failure. (A) Frontal chest radiograph in a patient with increased pressure pulmonary edema from heart failure showing alveolar edema and bilateral consolidation. Note presence of air bronchograms. (B) Frontal chest radiograph in a 56-year-old woman with increased pressure pulmonary edema from chronic heart failure showing interlobular septal thickening. Thin linear opacities are best seen in the inferolateral thorax, particularly on the right, representing thickened interlobular septae, or Kerley B lines. See the chest computed tomography scan for this patient in Video 133.1. (Courtesy Michael B. Gotway, MD.)

of oxygen in inspired gas (F_{IO_2}) ratios.[100] Although not yet widely adopted, the RALE score demonstrates the potential to apply more quantitative methods to ARDS clinical research and perhaps to clinical trials.

In addition to chest radiographs, CT of the chest may have a role in the diagnostic workup for ARDS and potentially for guiding therapy.[101] The higher resolution of CT compared to chest radiography offers more detail about the degree and density of consolidation or ground-glass opacification, which may suggest different etiologies of lung injury. CT can also display the degree of septal thickening and pleural effusion, potentially helping to discriminate increased pressure from permeability edema, and might display atelectasis, abscess, fibrosis, or pneumothorax, each of which might alter the therapeutic approach. Of importance, the use of chest CT in ARDS clinical research has fostered a better appreciation for the striking heterogeneity in aeration across different lung units[102] and has demonstrated that PEEP differentially, rather than uniformly, inflates various regions of the lung.[103] However, CT poses some challenges for critically ill patients, including the transportation of patients to the scanner and the higher radiation dose limiting frequent reassessment.[101]

Lung ultrasound, in contrast to CT, has the advantages of being portable, easy to repeat, and without radiation exposure. Thoracic ultrasonography has shown high sensitivity (97%) and specificity (95%) for pulmonary edema[104] and, when paired with cardiac ultrasound, may offer some clues to distinguish increased pressure from increased permeability edema, such as the presence of pleural effusion and impaired left ventricular function or enlarged inferior vena caval diameter.[105] Lung ultrasound has also been proposed as a mode to assess the aeration response to PEEP, although caution should be noted as there is no ultrasound corollary for lung overdistension, and thus ultrasound is not recommended as the sole method to select PEEP.[106] Lung ultrasound has been particularly useful in resource-limited areas of the world, where it can be used to identify bilateral opacities ("B" lines or consolidation without associated pleural effusion) when chest radiographs are unavailable[107,108] (see Chapters 23 and 24).

ARTERIAL BLOOD GAS STUDIES

The arterial P_{O_2}, arterial P_{CO_2}, and pH are the most informative laboratory indicators of gas exchange in patients with pulmonary edema. Arterial blood gas studies are not sensitive to early edema. Interstitial pulmonary edema does not usually affect oxygen uptake in the lungs beyond modest hypoxemia caused by ventilation-perfusion mismatching. In contrast, alveolar flooding seriously compromises gas exchange, resulting in right-to-left shunting of blood from ongoing perfusion of fluid-filled or collapsed alveoli. In two studies of groups of patients with increased permeability edema from lung injury, oxygenation appeared to depend more on the ability of the pulmonary circulation to mediate hypoxic pulmonary vasoconstriction—and thereby reduce perfusion to damaged and edematous areas of the lungs—than on the amount of edema present.[109,110]

In patients hospitalized for acute cardiogenic pulmonary edema, arterial P_{CO_2} may be low, especially in the early stages, when tachypnea results in alveolar hyperventilation. Arterial P_{CO_2} may also be within the normal range or elevated, the latter indicating alveolar hypoventilation, which can be caused by underlying lung disease, increased metabolic production of carbon dioxide (perhaps related to increased work of breathing), increased wasted ventilation (ventilation of poorly perfused alveoli), or mechanical impairment caused by weak respiratory muscles.[111] An elevated pulmonary dead space fraction in the first 24 hours after development of severe increased permeability edema identifies patients with a higher risk for death, particularly if the dead space fraction is greater than 0.60.[62]

When pulmonary edema is severe or the lungs have been injured, many patients develop metabolic acidosis as a result of tissue hypoxia, increased work of breathing, intrinsic lung lactate production, or all of these.[112] Attempts to correct acidosis with parenteral bicarbonate administration usually are not necessary; rather, the underlying cause must be identified and treated appropriately. Maintenance of a satisfactory systemic blood pressure is crucial. Respiratory acidosis caused by alveolar hypoventilation can be treated either by *noninvasive ventilation* (NIV) or by invasive mechanical ventilation with endotracheal intubation. Metabolic acidosis can be partially corrected by alleviating hypoxemia and improving cardiac function; the possibility of underlying disease amenable to surgery (e.g., intestinal ischemia or infarction, perforation of a viscus) or pancreatitis should be considered.

For further information on experimental methods to distinguish hydrostatic from permeability edema, to assess lung water and barrier function, and to consider potential biomarkers of hydrostatic pressure and permeability edema, see ExpertConsult.com.

Measurement of Pulmonary Edema Fluid Protein Concentration

When florid pulmonary edema is present, measurement of protein concentrations in both simultaneously collected edema fluid (suctioned through an endotracheal tube) and plasma provides a rapid, noninvasive method for distinguishing increased pressure edema from increased permeability edema.[113] Because the microvascular barrier is functionally intact in increased pressure edema, plasma proteins remain largely confined to the intravascular space, and edema fluid protein concentration is low relative to plasma protein concentration (the ratio of edema fluid to plasma protein concentration is generally <0.65). In contrast, in increased permeability edema, when the microvascular barrier is injured, plasma proteins cross the vascular barrier in high concentrations into the interstitial and alveolar compartments, which raises edema fluid protein concentration relative to plasma protein concentration (ratio of edema fluid to plasma protein concentration generally >0.75). Intermediate values (between 0.65 and 0.75) may indicate that both types of edema are present and suggest the relative contributions of each.

Measurement of the ratio of edema fluid to plasma protein concentrations has been shown to be a simple method for separating the two different pathophysiologic types in numerous reported series of patients with pulmonary edema.[114–117] Three studies indicated that an increasing protein concentration in serial measurements of edema fluid in increased permeability edema was a good sign, reflecting a functioning epithelial barrier and net removal of edema fluid from the alveoli.[116,117] There is new evidence that the edema fluid to plasma protein ratio has prognostic and diagnostic value.[118] Such measurements need to be correlated with the patient's clinical condition because an increasing protein concentration in edema fluid over time might also mean that increased permeability edema was complicating what had been increased pressure edema or that the lungs were injured more severely or more extensively as time passed.

Edema fluid can be collected by inserting a standard 14- to 18-gauge catheter through an endotracheal tube and advancing it into a wedged position in the distal air spaces, similar to the procedure for wedging a fiberoptic bronchoscope. Gentle suction is applied as the catheter is slowly withdrawn, and fluid is collected in a small trap. Several attempts may be needed; if no fluid can be suctioned, the clinician should try changing the patient's position. Samples grossly contaminated with airway secretions, which have a very low protein concentration (<1 g/dL), or which have a gross appearance of mucus, pus, or debris, should be discarded. The protein concentration in the edema fluid and the plasma can be measured by the clinical laboratory or estimated quickly at the bedside from the protein scale of a handheld refractometer. Standard BAL using fiberoptic bronchoscopy and mini-BAL (with a wedged suction catheter) have both been used as research and diagnostic tools that may also yield useful information about the cellular biochemical and microbial composition of the air space,[119] but lavage is not useful as a method to measure alveolar protein concentration because the instilled saline dilutes alveolar fluid by approximately 50- to 100-fold, depending on the method.[47]

MEASUREMENT OF LUNG WATER AND BARRIER FUNCTION

In theory, measurement of the quantity of water or edema fluid in the lungs could be useful in detecting early pulmonary edema and in assessing its clinical course and response to treatment; however, no optimal technique is available. Methods in use or under investigation focus on either measurement of lung density or equilibration of tracers with water in the lungs.[1,120] Interest in such measurements assumes that accurate knowledge about lung water content would be useful in diagnosis and would be beneficial in the treatment of patients with pulmonary edema. Use of a single thermal indicator for measuring extravascular lung water has shown promise based on some studies, although the actual clinical utility has not been convincingly proven.[121]

Barrier Function

The clinical distinction between increased pressure edema and increased permeability edema is difficult.[95,122] In theory the two types of edema can be separated on the basis of differences in barrier function. Detection of increased transvascular fluid flow into the lungs and measurement of barrier integrity might be more helpful than measurement of lung water content. A simple and practical method exists to evaluate barrier integrity (edema fluid protein concentration measurements, discussed earlier). By tracking the change in edema fluid protein concentration over time, it is possible to estimate alveolar fluid clearance in both animal models[117,123] and human pulmonary edema.[124,125] Furthermore, the baseline rate of alveolar fluid clearance exhibited moderate inverse correlation with baseline plasma concentrations of the *receptor for advanced glycation end products* (RAGE), a plasma marker with strong association with both development of and mortality from ARDS.[124] Although these observations lack a validated test and thresholds to use for either alveolar fluid clearance or RAGE concentrations clinically, it is nonetheless encouraging that potential quantitative measures of alveolar barrier function exist.

Acute Decompensated Heart Failure: History and Biologic Markers

Acute decompensated heart failure (ADHF) is diagnosed by history and physical examination aided by specific testing, including *amino-terminal pro–brain natriuretic peptide* (NT-proBNP). When clinical signs and symptoms strongly support a diagnosis of acute heart failure, including exertional dyspnea, fluid retention, orthopnea, and signs such as elevated jugular venous pressure, peripheral edema, and pulmonary edema, particularly in the absence of fever, the diagnosis of ADHF can be made with high probability even in the absence of additional testing.[126] For dyspneic patients with intermediate probability of ADHF, however, such as patients with abnormal electrocardiograms, patients with historical features of heart failure but without clinical signs of heart failure, or those with no prior history

of heart failure, the addition of serum natriuretic peptide testing is warranted.[126] In a prospective multicenter study of patients with acute dyspnea presenting to the emergency department, increased serum NT-proBNP (>450 pg/mL for patients younger than 50 years and >900 pg/mL for patients 50 years and older) was the strongest independent predictor for ADHF.[127] A serum NT-proBNP level less than 300 pg/mL had a negative predictive value of 99%.[127] Combining NT-proBNP testing with clinical judgment is recommended by guidelines,[128] and a clinical prediction score known as the PRIDE acute heart failure score has been validated, with a score 6 or more points demonstrating sensitivity of 96%, specificity of 84% and positive and negative predictive values of 77% and 98%, respectively, for a diagnosis of ADHF.[126]

However, although NT-proBNP performs well in an unselected population with dyspnea, the marker may have limited utility to distinguish increased pressure from increased permeability edema. In a prospective cohort study of patients with ARDS or ARDS risk factors, NT-proBNP was reported at a median value greater than 3000 pg/mL, well above the value to exclude heart failure; only one-third of ARDS subjects had normal NT-proBNP values.[129] Furthermore, although the NT-proBNP values observed in ARDS were numerically lower than those observed in the ADHF subjects from the PRIDE study, the difference between them was not statistically significant.[127,129] A few smaller studies have assessed the ability of BNP to distinguish ARDS from cardiogenic pulmonary edema, using clinician judgment as the gold standard to determine edema type, and reported limited discriminative utility.[130–132]

Biologic Markers of Lung Injury

Potential biologic markers of imminent increased permeability edema from various kinds of lung injury have been the subject of many studies and comprehensive reviews.[47,133] Naturally, considerable interest revolved around finding a simple blood, urine, or BAL test to identify patients destined to develop or who are already in the earliest stages of increased permeability edema. Such a marker could lead to an early intervention to prevent ARDS, or prognostication of outcome among patients with injured lungs. To be of clinical use, such a marker would have to be accurate, rapid, and inexpensive, as well as sensitive and specific for the detection of lung injury. An extensive search has been made for a reliable biologic marker for the detection of early or impending lung injury comparable to the decisive clinical role played by troponin measurements for diagnosing acute myocardial infarction. The long-sought silver bullet for diagnosis of increased permeability edema remains distant. Nonetheless, a growing panel of circulating and edema fluid markers have demonstrated consistent association with ARDS diagnosis, severity, or prognosis, and we will highlight a few (eTable 133.1). For more complete discussion, comprehensive reviews have been published.[74,134–136]

Most biomarkers of increased permeability edema can be characterized as playing a role in endothelial regulation, lung epithelial health, modulation of inflammation, or specific injury pathways, mirroring the current understanding of processes that contribute to lung injury.[73] Plasma angiopoietin-2, an endothelial-restricted protein that increases permeability when added to endothelial monolayers,[137] has predictive value for ARDS diagnosis in an emergency room population.[84] This marker also has prognostic significance, in that its plasma concentrations rise with ARDS severity and are higher in ARDS patients who die and, in selected populations, it seemed to be a therapeutic response indicator.[138–142] Using genetic data to perform causal inference analysis, in which observational data is used to infer biologic mechanisms, plasma angiopoietin-2 seems to be under partial genetic control and mediates a portion of ARDS risk.[143] Additional endothelial markers with consistent association with ARDS diagnosis or prognosis include soluble intercellular adhesion molecule, soluble thrombomodulin, plasminogen activator inhibitor-1, von Willebrand factor antigen, and protein C.[144–148] Plasma markers that are largely released from lung epithelium and strongly associate with ARDS diagnosis include RAGE and surfactant protein D.[149–151] Soluble RAGE in plasma is particularly interesting in that it also correlates with alveolar fluid clearance in experimental models and in humans with ARDS[124,152,153]; thus, RAGE might be a functional readout of ARDS resolution. Numerous plasma inflammatory markers also strongly associate with ARDS diagnosis among critically ill patients and associate with mortality. The best studied among these include *interleukins* (IL)-6, IL-8, and *soluble tumor necrosis factor receptor I and II* (sTNFR1, sTNFR2).

Because increased permeability edema follows a wide variety of insults that range in severity, and because many abnormalities detected in increased permeability edema are found in other severe illnesses of diverse etiology that do not involve the lungs, it seems unlikely that any single marker will be found that unequivocally identifies the risk or the presence of severe lung injury. Increased attention is being given to the sensitivity and

eTable 133.1 Selected ARDS Biomarkers With Potential Prognostic or Subphenotyping Significance[74]

IMMUNE SYSTEM MARKERS
IL-6
IL-8
IL-1, IL-1 receptor antagonist (IL-1RA), IL-18
Neutrophil extracellular traps
Soluble tumor necrosis factor receptor-1
EPITHELIAL MARKERS
Receptor for advanced glycation end products
Surfactant protein-D
Club cell 16
ENDOTHELIAL COAGULOPATHY MARKERS
Plasminogen activator inhibitor 1
Protein C
Platelet count
von Willebrand Factor
Angiopoietin-2
Soluble intercellular adhesion molecule-1
Syndecan
Endocan
PROGRAMMED CELL DEATH MARKERS
FAS/Fas ligand (FasL)

ARDS, acute respiratory distress syndrome; IL, interleukin.

specificity of combinations of markers. In support of this approach, one study found that combinations of three plasma biomarkers had a significantly improved prognostic value for predicting death compared with standard clinical predictors alone.[83] More recently, a parsimonious model using plasma markers (IL-8, IL-6, protein C, and sTNFR1) along with clinical variables (serum bicarbonate, receipt of vasoactive medications) in various combinations proved capable of reliably identifying the ARDS hyperinflammatory phenotype in multiple populations,[154,155] which could facilitate clinical trial enrichment strategies in the future.

TREATMENT

Treatment of pulmonary edema often requires vigorous life-saving measures, followed by specific therapy directed at the factors that led to accumulation of water in the extravascular spaces of the lungs. Effective therapy also requires an accurate diagnosis and an understanding of the nature of the underlying disease state and of the strategies that might prove useful in limiting further edema accumulation and in accelerating fluid removal from the lungs.[156,157]

EMERGENCY THERAPY

Patients with alveolar edema are frequently severely ill and require immediate treatment for acute respiratory failure. The basic principles of treatment of hypoxemic respiratory failure are discussed in Chapters 134 and 135. Essential requirements for patients with pulmonary edema include preservation of the airway and provision of satisfactory alveolar ventilation and arterial blood oxygenation. Maintenance of arterial blood pressure is critical. Reliable means of monitoring and sustaining oxygen saturation and blood pressure in rescue operations and ambulance travel are now widely used. Ventilatory management in patients with alveolar flooding and severe gas exchange abnormalities, regardless of cause, has generally required emergent endotracheal intubation, high inhaled oxygen concentrations, and PEEP. After stabilization, obligatory lung-protective strategies are introduced in patients with increased permeability edema (see later discussion). An alternative approach to management is being directed at noninvasive ventilatory methods (discussed later) that hasten improvement in respiratory distress and metabolic disturbances in patients with increased pressure edema, nearly always from congestive heart failure.

INCREASED PRESSURE EDEMA

In increased pressure pulmonary edema, the common goal of therapy is to reduce the movement of fluid into the lungs. Because the rate of edema formation increases exponentially with increases in pulmonary vascular pressures,[7] hydrostatic pressure control is crucial for successful therapy. Therapy must be clearly goal oriented, responsive to the underlying pathophysiology, and frequently reassessed until the patient is stable.

General Principles

The acute recognition and management of increased pressure pulmonary edema, exemplified by congestive heart failure, has been the subject of comprehensive reviews.[5,6,11,123,158,159] With increased pressure edema, the goal of therapy is to reduce the hydrostatic pressure causing edema formation in the lungs. The major objective is to achieve a net negative fluid balance without adversely affecting myocardial performance. The work of the heart must be reduced as much as possible, including by preventing pain and anxiety, which act to increase cardiac work by increasing sympathetic tone. As the heart fails, cardiac performance is reflexively preserved by progressive increases in vascular volumes that act to increase cardiac stroke volume and work (the Frank-Starling mechanism). This compensatory increase in preload of the left ventricle results in pulmonary venous hypertension and raises the driving pressure for fluid filtration out of the pulmonary microcirculation. As heart failure worsens, cardiac output falls, pulmonary and systemic venous pressures rise, systemic vascular resistance increases, and edema in the lungs and in the periphery becomes the major manifestation of compromised cardiac function.

In patients with increased pressure edema, a reduction of vascular volume and an increase in cardiac output decrease the driving pressure for edema formation. Because the normal safety factors protecting the lungs from edema are intact, the pressure needs to be lowered only toward normal. At PAWP less than 20 mm Hg, fluid filtration in the lungs usually will not cause pulmonary edema. Patients with severe cardiac failure may tolerate higher pressures—because baseline barrier permeability is lowered in the lungs and lymphatic removal capability is increased—and may even require such pressures to maintain cardiac output. Therapy is directed at reducing the work the heart must perform and at increasing the heart's efficiency for the work it must do, including, in some patients with severe increased pressure pulmonary edema, the use of positive-pressure NIV and, in the most severe cases, invasive mechanical ventilation. The resolution of alveolar edema in these patients may not simply be a function of lowering lung vascular pressures; other mechanisms to augment alveolar fluid clearance may be important.[123]

Most patients with acute pulmonary edema caused by cardiac failure have systolic dysfunction from decreased contractility, but approximately 30% of patients have diastolic dysfunction. Cardiac contraction is normal, but relaxation is impaired. Because the ventricle does not relax normally, end-diastolic pressure is increased, thereby increasing hydrostatic pressure in the lung microcirculation. Acute diastolic dysfunction producing pulmonary edema is now recognized as a common manifestation of acute myocardial ischemia or uncontrolled hypertension. Other causes include diabetes mellitus, aortic stenosis, infiltrative cardiomyopathies, endocardial fibroelastosis, hypothermia, septic shock, elevated thoracic pressures from mechanical ventilation, and pericardial effusion. Causal or aggravating conditions should be corrected (e.g., revascularization for coronary artery disease, control of systemic hypertension). The goal of therapy in acute diastolic dysfunction is to lower elevated filling pressures, by the cautious use of diuretics and afterload reduction, without significantly reducing cardiac output. These patients are prone to develop hypotension in response to diuretics and nitrates because adequate cardiac output depends on elevated filling pressures in the heart. Because systolic function is normal, positive inotropic agents do not help and can actually aggravate ischemia.

In the setting of acute increased pressure pulmonary edema, it is especially important to identify and treat correctable causes of heart failure. Acute myocardial infarction, ongoing myocardial ischemia, arrhythmias, valvular lesions, systemic hypertension, ventricular septal rupture, rheumatic or other inflammatory myocarditis, digitalis intoxication, pulmonary embolism, infection, thyrotoxicosis, or severe anemia may have caused the heart to fail and must be addressed. Cardiac patients presenting with pulmonary edema may not complain of chest pain despite significant coronary artery disease, and pulmonary edema may be the only manifestation of silent myocardial ischemia.

Ventilatory Strategies

Most patients hospitalized with increased pressure edema suffer from acute or chronic heart failure and require oxygen treatment to ensure satisfactory arterial blood oxygenation. Depending on the prevailing severity of oxygen deficiency, patients with mild abnormalities may require only supplementary oxygen administered through a nasal catheter or simple mask; those with moderate oxygen deficiency may be helped with noninvasive methods of oxygen administration. High-flow nasal cannula may be a useful means of delivering oxygen and some PEEP (see Chapter 137 and below). Finally, profound gas exchange abnormalities require endotracheal intubation with high oxygen concentrations and elevated end expiratory pressures.

Noninvasive positive-pressure ventilation, by either *continuous positive airway pressure* (CPAP) or *bilevel positive airway pressure* (BPAP) ventilation, is strongly recommended for patients with acute respiratory failure due to cardiogenic pulmonary edema, as in 2017 guidelines, with moderate certainty of evidence.[160,161]

Both CPAP and BPAP cause more rapid improvement in respiratory distress and metabolic abnormalities than standard oxygen treatment.[162] NIV is discussed more fully in Chapter 136. Here we will discuss their role briefly. CPAP is the equivalent of noninvasively applied PEEP, whereas BPAP adds inspiratory pressure support above the PEEP setting. PEEP exerts effects both on the lung, including increased functional residual capacity, recruitment of collapsed or partially flooded alveoli, and a higher mean airway pressure, typically improving oxygenation, and on the circulation, causing decreased preload, decreased afterload, and lower myocardial oxygen demand.[163] As reviewed, the net effect of PEEP on cardiac output will depend on both right ventricular and left ventricular function and ventricular interdependence so that higher PEEP may be particularly helpful in states attributed to high afterload, whereas PEEP may exacerbate states of high pulmonary vascular resistance and right ventricular septal bowing.[163] Although an early randomized trial reported no effect on short-term mortality or intubation rates comparing NIV to standard oxygen therapy,[164] systematic review and meta-analysis of an additional 24 studies encompassing more than 2600 subjects reported moderate evidence for NIV in reducing hospital mortality and reducing endotracheal intubation, without increasing acute myocardial infarction or other adverse events.[161] Patients with cardiogenic shock and pulmonary edema were traditionally excluded from randomized trials studying NIV; however, observational data from the CardShock cohort described a lower mortality for subjects in shock treated initially with NIV compared to those immediately intubated and placed on invasive mechanical ventilation.[165] The mortality difference was not observed after propensity matching that accounted for initial organ failures and severity of illness,[165] suggesting that survival was not wholly attributable to the selection of NIV. Given the preponderance of evidence, NIV is a recommended initial therapy for patients presenting with acute respiratory failure due to increased pressure edema, with close observation and timely reassessment for improvement in work of breathing, oxygenation, ventilation, and overall perfusion. If these are not rapidly improving, or certainly if they worsen, prompt intubation is indicated.

High-low nasal cannula (HFNC), an alternative means to deliver highly concentrated oxygen at high flows, and with probable, although unquantified, PEEP, has not been well studied in the cardiogenic pulmonary edema population, which was excluded from many early trials[166] (see Chapter 137). In one small, likely underpowered study, randomized assignment to HFNC versus conventional therapy in the emergency department resulted in a small decrease in respiratory rate without a reduction in the number requiring admission, NIV, or intubation, nor in observed mortality.[167] Although there are theoretical advantages to HFNC compared to NIV, particularly with regard to patient comfort and facilitating communication due to the mask interface, as yet there are incomplete data to endorse HFNC in this setting.

Invasive mechanical ventilation is used for 60–80% of patients with cardiogenic shock,[165,168] and acute cardiac dysfunction complicates 18% of ventilated patients in the United States.[169] Nonetheless, few studies have investigated the effect of ventilator strategies specifically in patients with increased pressure edema. The *National Heart, Lung, and Blood Institute* (NHLBI)'s FACTT study highlighted the coexistence of increased cardiac filling pressures with ARDS,[170] confirming that almost a third of patients have elevated PAWP or central venous pressure on study enrollment.[171] However, whereas a volume- and pressure-limited ventilator strategy has strong evidence for reducing mortality in ARDS,[172,173] data are less definitive for applying this strategy to non-ARDS respiratory failure. Observational studies in populations without ARDS suggest that higher tidal volume (>8 mL/kg *predicted body weight* [PBW]) is an independent risk factor for the development of incident ARDS[174,175] and for pulmonary complications.[176] However, a randomized trial enrolling subjects with acute respiratory failure but without ARDS and randomizing to a low (<6 mL/kg PBW) or intermediate (<10 mL/kg PBW) tidal volume strategy did not observe a difference in duration of ventilation or mortality.[177] One-fourth of study participants were ventilated as a result of cardiac arrest and 5% with cardiac failure, so subjects with increased pressure pulmonary edema seem likely to have been included. In the absence of an adequately powered trial exclusively conducted in patients with increased pressure edema, it seems reasonable to recommend that consideration be given to a ventilator strategy of lower tidal volumes (<6 mL/kg PBW), adequate PEEP to improve saturation and reduce the fraction of inspired oxygen (F_{IO_2}), and a plateau airway pressure less than 30 cm H_2O,[172] with an appreciation that tidal volumes may be liberalized as needed for patient tachypnea, acidemia, or comfort.[177]

As discussed earlier, PEEP has significant hemodynamic effects in addition to its impact on oxygenation, and increased pressure pulmonary edema may be particularly responsive to application of moderate PEEP. In selecting an initial PEEP, clinicians could use a table pairing different PEEP levels with varied F_{IO_2} settings, as has been used in ARDS clinical trials,[178] or by selecting the PEEP that seems to optimize both saturation and perfusion as gauged by blood pressure and urine output. Of note, the association between mortality and airway driving pressure, calculated as the difference between an inspiratory plateau pressure and PEEP in volume-cycled ventilator settings,[179] was not observed in a cohort of mechanically ventilated patients without ARDS.[180]

For information on right heart catheterization, see ExpertConsult.com.

Right Heart Catheterization

In 1970 Drs. H.J.C. Swan and William Ganz introduced the balloon flotation catheter for measurements of right atrial pressure, right ventricular pressure, pulmonary artery pressure, and pulmonary capillary wedge pressure, and for assessment of cardiac output and oxygen saturation values in the right heart chambers.[181] The widespread use of the *pulmonary arterial catheter* (PAC) contributed to an explosion of cardiovascular and respiratory physiologic knowledge, along with new conceptual models for the management of acute myocardial infarction, heart failure, and cardiogenic shock based on readily obtained hemodynamic data.[182] Much was learned about the cardiopulmonary physiology of sepsis and how to use a PAC to differentiate increased pressure from increased permeability edema.[50] Unfortunately, the ability to measure cardiac filling pressures did not reliably translate to improved patient outcomes, and both complications and flawed PAC interpretations were observed.[183–185] There is now general agreement that invasive hemodynamic monitoring, such as by a PAC, is not recommended for normotensive patients with acute decompensated heart failure.[128,186,187] Similarly, a systematic review from the Cochrane group concluded "that the use of a [pulmonary artery catheter] did not alter the mortality, general [intensive care unit] or hospital [length of stay], or cost for adult patients in intensive care."[188] Current guidelines for the management of heart failure maintain a class I recommendation to monitor with a PAC "in patients with respiratory distress or impaired systemic perfusion when clinical assessment is inadequate," or, with a class IIa recommendation, when persistent symptoms remain "despite empiric adjustment of standard therapies."[128] Additional indications for the PAC are commonly used, particularly to diagnose and monitor pulmonary vascular disease.[182,186]

Specific Pharmacologic Therapy

After emergency treatment has been instituted and the patient's condition stabilized, three major therapeutic options—vasodilators, diuretics, and inotropic agents—need to be considered and administered when appropriate. The goal of therapy with these agents is to lower the hydrostatic pressure at the filtration sites in the pulmonary vascular bed while maintaining adequate systemic delivery of oxygen. The choice of therapy is dictated by the patient's condition and the cause of the pulmonary edema. *The American College of Cardiology Foundation and the American Heart Association* (ACCF/AHA), in collaboration with several additional international societies, has published an extensive guideline for the management of heart failure,[128] and readers are directed to that publication's discussion of treatment for ACCF/AHA stage C and D heart failure. As follows, we consider the acute management that may be concurrent with assisting ventilation for patients with decompensated heart failure and pulmonary edema.

Vasodilators. Depending on their specific therapeutic indications, vasodilators are used for hypertension, congestive heart failure, and angina. Several medications are available, usually in combination and as part of a long-term treatment regimen. Vasodilators are useful pharmacologic agents for the treatment of acute increased pressure pulmonary edema because their effects happen rapidly, usually in minutes. Through dilation of veins, vascular capacitance is increased and blood is redistributed peripherally, thereby lowering the driving pressure for fluid filtration in the lungs. Through dilation of arteries, systemic vascular resistance (cardiac afterload) falls, increasing cardiac output and stroke volume, and the heart works more efficiently. Three classes of vasodilators may be useful in pulmonary edema: venodilators (e.g., nitrates), arteriolar dilators (e.g., phentolamine, hydralazine), and mixed dilators (e.g., nitroprusside). The most common side effects of vasodilators, such as dizziness, especially when standing, are related to low blood pressure. Tolerance to vasodilators may require revision of long-standing therapy.

Diuretics. Patients with symptoms of pulmonary edema, especially from increased vascular pressure, usually benefit from administration of diuretic agents.[128,189] These drugs may exert a modest immediate effect by increasing venous capacitance and decreasing the relative perfusion of flooded alveoli (acting as vasodilators), but their principal mechanism of action is to increase sodium and water excretion by the kidneys,[190] and they are most effective when paired with a strategy of limiting sodium intake.[191] The resultant diuresis causes a decrease in left ventricular volume and pressure and thereby a reduction in left atrial pressure and in pressure at the filtration sites in the lungs. Among the potent loop diuretics administered by slow intravenous injection, furosemide is highly effective and generally regarded as the agent of choice. Dozens of different dosage regimens of furosemide have been and are still being used to treat symptomatic patients with pulmonary edema from acute congestive heart failure. Equivalent doses of other loop diuretics (bumetanide, torsemide, or ethacrynic acid) have essentially the same effects. Decades of clinical experience have documented that intravenous administration of loop diuretics nearly always results in prompt diuresis and symptomatic relief. Nevertheless, information about safety and efficacy is lacking and optimal use of diuretics in heart failure management needs much further study and improvement.[192]

If the patient is hypotensive or in frank shock, diuretics are seldom of benefit, because poor renal perfusion limits any effects they might have on kidney function. In this circumstance, continuous venovenous ultrafiltration can reduce intravascular volume even in patients who require vasopressors for blood pressure support.[193] Similarly, if the patient has severely diseased kidneys, continuous arteriovenous hemofiltration with or without countercurrent dialysis or venovenous ultrafiltration should be considered.[194] These techniques represent considerable advances over traditional hemodialysis, which was often impossible in hemodynamically unstable patients, especially those with low cardiac output or hypotension, and peritoneal dialysis, which was both slow and poorly tolerated. Hemofiltration can be instituted, maintained, and managed successfully by well-trained intensive care unit nurses and physicians, and it is not typically complicated by hypotension because the circuits have small volumes and pressures are low. Considerable fluid (<200–300 mL/hr) can be removed when needed, with the amount being titrated to the patient's cardiovascular status.

Inotropic Agents. Patients with cardiogenic shock and other cardiac catastrophes that lower systemic blood pressure often require inotropic agents as a temporary lifesaving measure. According to ACCF/AHA guidelines,[128] patients with cardiogenic shock awaiting either resolution of the heart failure precipitant or definitive mechanical, revascularization, or transplant therapy, should receive temporary intravenous inotropic support to maintain end-organ perfusion. Adrenergic agents, including dobutamine and dopamine, as well as phosphodiesterase inhibitors, such as milrinone, are recommended.[128] In addition, short-term continuous inotropic support may be an option for symptom control in selected patients who are not eligible for mechanical cardiac support or cardiac transplantation.[128] However, long-term use of inotropes, except when explicitly used for palliative care, is potentially harmful. In addition, the ACCF/AHA guidelines recommend against use of inotropes in hospitalized patients without documented severe systolic dysfunction, low blood pressure, or significantly impaired perfusion with significantly depressed cardiac output.[128] Thus it is *not* recommended to add inotropes for a patient with depressed ejection fraction and pulmonary edema but without hypotension or impaired perfusion because such a strategy may cause harm.[195]

When increased pressure pulmonary edema accompanies impaired myocardial contractility, it has proven difficult to treat and has a poor prognosis. Options include techniques of coronary reperfusion, cardiac resynchronization therapy, durable or temporary mechanical support with ventricular assist devices, expanded use of extracorporeal membrane oxygenators for severe respiratory failure, and improvements in heart and/or lung transplantation.[128] For this reason, early consultation with heart failure experts is strongly encouraged for critically ill patients with increased pressure edema and structural heart disease.

Morphine Sulfate. Narcotics, and particularly morphine sulfate 2 to 4 mg or its equivalent, given intravenously over several minutes, has long been an emergency therapy for acute cardiogenic pulmonary edema. The reasons for using morphine include its actions as a potent vasodilator, its effect as a sedative, and its lack of myocardial contractility depression. Its vasodilating effects can substantially reduce pulmonary capillary pressure and may improve depressed cardiac output, whereas the reduced dyspnea may result in a lower afterload for the failing heart. However, observational data from several large cohorts of patients with acute pulmonary edema have detected an association between morphine and increased mortality that is incompletely explained by baseline characteristics, at least as handled by propensity score matching.[196,197] Uncertainty regarding the safety of morphine in this setting has led the European Society of Cardiology to recommend against routine use of morphine and to suggest only cautious use in patients with severe dyspnea,[198] whereas the ACCF/AHA guidelines discuss morphine only in the context of palliative care.[128] Recognizing that morphine is effective at symptom improvement and that prior reports of increased mortality are limited by their retrospective nature, there is a clinical trial planned to test the randomized administration of morphine compared to midazolam when severe dyspnea remains despite receipt of diuretics, oxygen, and vasodilator therapy for acute pulmonary edema.[199] If complications are believed to result from morphine, prompt administration of naloxone (Narcan) is recommended.

INCREASED PERMEABILITY EDEMA

As already emphasized, increased permeability pulmonary edema caused by various types of severe lung injury differs from increased pressure pulmonary edema in two crucial respects: first, the endothelial and epithelial barriers are damaged in permeability edema, whereas they are usually normal in increased pressure edema, and second, when barriers are damaged, edema develops even at low driving pressures. The goals of therapy (Table 133.6) are to treat the underlying cause of acute lung damage, to provide support while the repair phase begins, to use a lung-protective ventilator strategy that will not worsen the lung injury, and to minimize the driving pressures for fluid movement across the injured barriers into the lungs.

General Principles

Finding and treating the underlying precipitant of permeability edema is crucial. The cause of lung injury may not always be apparent and, when the cause is not obvious, it should be assumed to be infection—the most common treatable underlying cause of increased permeability edema. Although the patient is often seriously ill, diagnostic studies must be performed to identify a possible source of infection so that appropriate source control and antimicrobial therapy can be instituted. If chest radiographs provide insufficient information, ultrasonography, CT, and bronchoscopy with BAL can all be helpful. There are important mimics of ARDS to consider. These mimics might have specific, or at least conventional treatment, including atypical infections, organizing pneumonia, hypersensitivity pneumonia, eosinophilic pneumonia, or diffuse alveolar hemorrhage.[200] Chest CT may be particularly helpful for diagnosing such conditions, along with bronchoscopy and potentially transthoracic or surgical lung biopsy.[67,91] Because specific therapy for increased permeability is not usually available, unless the cause is a treatable infection or a steroid-responsive inflammation, supportive therapy is extremely important. The initial concerns are to support ventilation and circulation.

Patients with increased permeability edema may be hemodynamically unstable, and ventilatory support can be complicated by hypotension or frank shock. PEEP, which is usually required for adequate oxygenation, may compound the problem by impeding venous return to the heart and decreasing cardiac function. Furthermore, when inadequate cardiac output, due to either hypovolemia or impaired cardiac function, complicates permeability edema and results in low mixed venous saturations, the oxygen tension of arterial blood may fall dramatically, as systemic venous blood traversing "shunt" units with poor ventilation mixes with postcapillary blood from aerated units in a process termed venous admixture.[201] Improving both oxygen saturation and perfusion are often the critical, and at times highly challenging, early goals of caring for patients with permeability edema, and care involves a careful assessment of circulating volume, cardiac function, oxygen consumption, and end-organ perfusion in addition to a focus specifically on the lungs.

Aggressive hemodynamic support of critically ill patients can be detrimental if the complications of therapies become more harmful than the underlying disease itself. Strategies to increase systemic oxygen delivery (e.g., with inotropes,

Table 133.6 ARDS Management Principles

SUPPORTIVE CARE
Supplemental oxygen to ensure adequate oxygenation
Lung-protective ventilation
▪ Volume and pressure limited
▪ Ensure ventilator synchrony
▪ Prone position if Pao_2/Fio_2 < 150 despite protective ventilation
Reduce oxygen consumption if hypoxia is critical
Support adequate perfusion for other organs; focus on both cardiac output and blood pressure
FIND AND TREAT UNDERLYING CAUSE
Consider infections, mimics
MINIMIZE FURTHER EDEMA ACCUMULATION
Seek lowest pulmonary microvascular pressure that maintains adequate perfusion
Diurese/reduce vascular volume while maintaining adequate perfusion
AVOID HARM
Volume- and pressure-limited ventilation strategy
Avoid both hypotension and volume overload
Goal-directed sedation with frequent reassessment
Avoid hyperoxia
Consider early physical rehabilitation
Seek and treat neuromuscular, cognitive, and psychological impairments during recovery

ARDS, acute respiratory distress syndrome; Fio_2, fractional concentration of oxygen in inspired gas; Pao_2, partial pressure of arterial oxygen.

intravascular fluids, and blood transfusions) or to achieve supranormal values for the cardiac index or normal values for mixed venous oxygen saturation did not improve mortality when applied to critically ill patients.[202] After an initial single-center randomized trial conducted in the emergency department reported a striking mortality benefit from adding central venous saturation greater than 70% and hemoglobin greater than 10 g/dL as early perfusion goals among patients with septic shock,[203] several larger multicenter trials have failed to show benefit from this approach when applied to all septic patients.[204–206] One ARDS Network clinical trial showed that, in patients without shock, as defined by lack of need for vasopressor treatment, a strategy to restrict fluids to reduce intravascular pressures improved clinical outcomes by reducing the duration of mechanical ventilation in patients with ARDS.[207] Of note, there was no benefit observed for *pulmonary artery catheters* (PACs) over central venous catheters; PACs were associated with significantly increased complications, although not with excess mortality.[171]

A multicenter, *randomized, controlled clinical trial* (RCT) of transfusion requirements in critically ill patients with euvolemia after initial treatment compared a restrictive strategy of transfusing red blood cells if the hemoglobin concentration dropped to less than 7 g/dL to a more liberal strategy of maintaining hemoglobin concentration greater than 10 g/dL. Restricting transfusion requirements to maintain hemoglobin concentration at 7 to 9 g/dL was at least as effective and possibly superior to the strategy of giving transfusions to maintain hemoglobin concentration at 10 to 12 g/dL. Of note, few patients with acute coronary syndrome were included in this trial, making these conclusions less relevant to increased pressure pulmonary edema.[208] Transfusion thresholds for patients with acute coronary syndrome remain unclear, although a pilot trial suggested benefit of a more liberal transfusion strategy.[209]

Lung-Protective Ventilator Strategies

In experimental animals, ventilation with high tidal volumes increases vascular filtration pressures and produces stress fractures of microvascular endothelium, alveolar epithelium, and basement membrane.[210,211] The resulting injury appears to be due to the combination of large tidal excursions at high lung volumes, coupled with elevated airway pressures. This was called *volutrauma* because tidal volumes were roughly double for the same peak airway pressure when no PEEP was applied. Because the evidence from animal studies and small clinical trials provided compelling experimental rationale,[212,213] early investigations tested the potential benefit of lower tidal volumes and lower airway pressures versus standard (high) tidal volumes and elevated pressures.[214] A subsequent large National Heart, Lung, and Blood Institute ARDS Network multicenter trial was stopped prematurely after the enrollment of 861 patients with well-defined ARDS. The trial compared lower tidal volumes of 6 mL/kg and airway plateau pressures limited to 30 cm H_2O or less with a "traditional" ventilator management using initial tidal volumes of 12 mL/kg of ideal body weight and plateau pressures less than 50 cm H_2O. Mortality was lower in the group treated with lower tidal volumes than in the group treated with traditional tidal volumes—31% versus 39.8% (P = 0.007), respectively, and the number of days without ventilator use during the first 28 days after randomization was greater in this group (mean ± SD; 12 ± 11 vs. 10 ± 11, respectively; $P = 0.007$).[215]

The results of this seminal trial and several follow-up studies transformed the management and outcomes of patients with ARDS.[173] Low tidal volume ventilation strategies are also being successfully applied to critically ill patients without ARDS, albeit with varying effect on preventing lung injury or pulmonary complications.[176,177] The protocol for implementing the lung-protective ventilatory strategy is detailed in Table 134.3 and further discussed in Chapter 134.

Of interest, enacting a low tidal volume strategy in ARDS patients seems to attenuate inflammatory responses in both the lungs and bloodstream, as measured by a reduction in neutrophil and inflammatory cytokine concentrations in BAL fluid and a reduction in cytokines in circulating blood.[216] Other studies have confirmed that low tidal volume lung-protective ventilation is associated with reduction in inflammatory markers in the lung.[217] In addition, alveolar epithelial injury is probably reduced, considering the decline in surfactant protein D levels (a type II epithelial cell marker) and RAGE (a type I epithelial cell marker) in the plasma of patients treated with the lung-protective ventilator strategy.[218,219]

Although the use of PEEP has been advocated in treating ARDS since the syndrome's initial description,[46] the best method to select optimal PEEP for permeability edema remains uncertain. The pivotal ARDS Network trial comparing two tidal volume strategies used a table with a range of PEEP settings paired with different F_{IO_2} settings; as an example, a patient requiring an F_{IO_2} of 70% would be set to a PEEP of 10 to 14 cm H_2O.[172] A strong advantage of this approach includes its relative simplicity to use, so it could be enacted as a protocol for initial ventilator settings. Several randomized trials were conducted to compare a higher PEEP strategy, sometimes termed "open-lung ventilation," to this conventional PEEP strategy and, although higher PEEP groups had improved oxygenation, mortality was not different, even when the trials were combined in meta-analysis.[178,220–222] Subgroup analyses suggested that patients who were more hypoxemic might benefit from higher PEEP or that patients with improving oxygenation when randomized to higher PEEP might benefit.[222,223] Using a machine-learning algorithm known as latent class analysis and both clinical and experimental plasma markers as input variables, one group of investigators identified two subclasses of subjects with ARDS, with one being dominated by a plasma signature of high concentrations of inflammatory markers.[155] The authors detected a statistical interaction between randomized assignment to high PEEP and the subclass assignment on the observed mortality effect[155]; the effect of high PEEP was beneficial in the hyperinflammatory subphenotype group, whereas there was no benefit in the less inflamed group. Although warranting prospective validation, this work suggests that PEEP might be personalized to a patient's inflammatory state. There has been interest in the possibility that the optimal PEEP in ARDS might be selected by measuring esophageal pressure as a surrogate for pleural pressure and determining the PEEP that maintains a slightly positive transpulmonary

pressure.[224] Despite elegant rationale and a promising pilot study,[225] a randomized multicenter trial of 200 subjects comparing PEEP titrated to esophageal manometry to PEEP titrated by a PEEP-FIO_2 table did not observe any difference in mortality or days free from mechanical ventilation.[226]

Two further methods for PEEP titration bear mention. One method is to select the PEEP that minimizes the airway *driving pressure* (ΔP), which is the set inspiratory pressure on pressure-cycled ventilation or the difference between plateau pressure and PEEP on volume-cycled ventilation, while preserving oxygen saturation and blood pressure. A mediation analysis of multiple trials comparing different ventilator strategies in ARDS reported that ΔP was the variable that seemed to mediate mortality risk better than all others, including tidal volume and plateau pressure.[179] To select PEEP in this way, one practical approach would start with a conventional PEEP-FIO_2 combination and measure the plateau pressure and ΔP, then readjust the PEEP and remeasure plateau and ΔP. If ΔP is falling, PEEP continues to be titrated up and, if rising, PEEP is turned down. Another method used CT to learn if the radiographic pattern of lungs—diffuse consolidation versus focal—would predict the response to a high PEEP recruitment maneuver.[56] In patients with focal ARDS, high PEEP may overdistend the aerated lung before recruiting the consolidated regions. However, in a study of more than 400 subjects with ARDS, a strategy of personalizing the PEEP, tidal volume, and proning strategy to the diffuseness of chest radiograph did not decrease mortality.[227] Despite a lack of overall benefit from the personalization strategy, the data suggested possible harm when patients with radiographically focal ARDS received a high PEEP strategy or when diffuse ARDS received lower PEEP and larger tidal volumes.[227] In addition, this trial highlights the challenges of standardizing radiographic assessment in ARDS. In 2017, a trial was also published that demonstrates the potential danger of a high PEEP strategy, particularly when high PEEP (25–35 cm H_2O) is added while maintaining a driving pressure of 15 cm H_2O, for a maximum plateau pressure 40 to 50 cm H_2O.[228] This regimen of high PEEP recruitment had been described for refractory hypoxemia,[229] yet when patients with moderate or severe ARDS were randomized to this strategy, the mortality was 55% compared to 49% in the control group receiving conventional low tidal volume ventilation.[228] Thus, we advocate maintaining a goal plateau pressure less than 30 cm H_2O and not adopting these high PEEP recruitment strategies.[229]

Prone Position. In tandem with lung-protective ventilation, a strategy of placing the patient in the prone position for at least 16 hours a day was shown to reduce mortality and days on the ventilator for patients with moderate to severe ARDS.[230] Initial interest in prone position ventilation dates as far back as the late 1970s, when an early report described a mean PaO_2 increase of 69 mm Hg relative to supine position,[231] and an additional case series described similar efficacy[232] (see Chapter 134 and Fig. 134.7).

Physiologic studies in humans with ARDS suggested that there were two main contributors to the observed improvement in oxygenation: repositioning the heart off the posterior lungs, thereby reducing compression and airway closure, and redistributing ventilation more uniformly, thereby reducing the risk of overdistension of lung units with preserved ventilation.[233–235] Although initial RCTs of prone positioning for ARDS did not confirm a mortality benefit,[236,237] meta-analysis of six RCTs that paired prone position with a volume- and pressure-limited ventilation strategy reported a mortality benefit (relative risk of death, 0.74; 95% confidence interval, 0.59 to 0.95), whereas the benefit was attenuated in four trials that did not mandate a protective ventilation strategy.[238] In addition to this effect modification by ventilation strategy, the mortality effect of prone position seemed to differ by duration, whereby longer periods of proning (≥16 hours) demonstrated mortality benefit but shorter duration did not.[238] These data prompted a multicenter RCT of early, long-duration (≥16 hr/day) prone positioning paired with protective ventilation compared to protective ventilation alone for ARDS with PaO_2/FIO_2 ratio less than 150. More than 500 subjects were enrolled, and prone positioning resulted in a 16% reduction in unadjusted mortality and approximately 4 additional days alive and ventilator free.[230] Given this strong signal for benefit, it was surprising that, in recent trials of moderate to severe ARDS, the proportion of patients who received prone position was 3–16%[226,239] and not higher than the proportion reported in an observational survey.[240] Even in a trial enrolling subjects with very severe ARDS and PaO_2/FIO_2 ratio less than 80, prone position was instituted in only 60% before randomization.[241] Research identifying the barriers to implementing prone position and strategies to improve its use may be valuable.

Although prone position is strongly encouraged for ARDS with PaO_2/FIO_2 ratio less than 150 after application of adequate PEEP, questions remain about the application of prone position to increased pressure edema. No direct test of this therapy has been undertaken in patients with pulmonary edema from decompensated heart failure. Among adults undergoing elective surgery placed in the prone position, some anesthesia reports describe a decrease in cardiac index by up to 25%, particularly when the heart was elevated relative to limbs and head (jackknife position) and when the inferior vena cava was compressed by increased abdominal pressure.[242–244] Blood pressure was variable in these small studies, with some revealing a decrease and others no change. Patients with preexistent cardiac disease may have a more deranged hemodynamic response to prone position because one study using quantitative CT imaging showed that patients with a history of prior myocardial infarction exhibited decreased ejection fraction when prone, and patients with ischemic heart disease had more diastolic function.[244] Thus, careful attention to the patient's blood pressure, perfusion, and potentially central venous saturation (as a marker of oxygen delivery, which is proportional to cardiac output) upon assuming prone position is warranted.

Specific Pharmacologic Therapies

Several therapeutic agents, which are listed in eTable 133.2, have been studied in patients with various forms of lung injury and sepsis. None of these agents has shown a significant mortality benefit in large-scale, prospective RCTs.[245,246] In addition, some promising therapies based on pilot results in smaller ARDS populations[247] or healthy volunteers[248] have failed to show benefit in larger phase II trials, including keratinocyte growth factor[249] and mesenchymal stromal cells.[250]

Whether or not newer anti-inflammatory therapies or modified applications of some of the therapies listed in eTable 133.2 will be useful in patients with increased permeability edema from damaged lung barriers remains an important question. Although inflammatory reactions can damage tissue, it is important to remember that inflammation plays an important beneficial role in the elimination of invading microorganisms. Because inflammatory pathways are redundant, blocking any one inflammatory mediator, or even multiple mediators, may have little or no effect on the overall inflammatory response. If the mechanisms of lung injury differ after various clinical events, the application of therapy directed at one particular mechanism would not be appropriate until most or all of the underlying mechanisms have been recognized and treated successfully.



See ExpertConsult.com, as well as Chapters 134 and 138, for a discussion of evidence concerning corticosteroids, neuromuscular blocking agents, and extracorporeal membrane oxygenation.

OUTCOME

The outcome of patients with pulmonary edema depends on which of the two major pathophysiologic categories of edema formation is involved. Until recently, much less was known about the resolution of pulmonary edema than about its formation. Water, and any extravasated proteins and cellular debris, must be removed from the alveoli and the interstitial spaces to restore the lungs to their pristine, healthy condition. Edema fluid clears from the lungs via five routes: lymphatics, airways, blood vessels, pleural space, and mediastinum; in contrast, cellular debris and particulate matter must be removed from the alveoli by macrophage uptake or through the airways.

RESOLUTION OF PULMONARY EDEMA

The considerable advances in our understanding of the clearance of fluid and solute from alveoli have been the subject of several reviews.[2,10,273,274] Active sodium and chloride vectorial transport across the alveolar epithelial barrier into the interstitium drives reabsorption of edema from the air spaces (as discussed in Chapter 3). The uninjured alveolar epithelium has a remarkable ability to remove edema fluid from the air spaces rapidly. For example, serial edema fluid protein concentration measurements relative to simultaneous plasma protein concentrations in a saltwater near-drowning patient showed that 50–60% of the excess alveolar fluid in the lungs was removed over the course of just 4 hours.[45] In experimental studies in rabbits, instillation of 4 mL/kg of seawater into the lungs resulted in a 300% increase in alveolar fluid volume in less than 5 minutes, owing to the movement of mainly pure water driven by osmotic forces from the plasma into the hyperosmolar (881 ± 290 mOsm) instillate, 80% of which was cleared from the alveoli in 6 hours.[275] Equivalent volumes of iso-osmotic (292 ± 6 mOsm) saline instilled into rabbit lungs were cleared at a similar rate. In neither seawater nor saline instillation was there evidence of injury to the alveolar epithelial barrier, which is more resistant than the endothelial barrier to a wide range of injuries, including ischemia, alveolar and intravenous endotoxin and bacteria, intravenous oleic acid, acid aspiration, saltwater aspiration, hyperoxia, intratracheal bleomycin, septic and hypovolemic shock, and rewarming after severe hypothermia.

Even after mild to moderate alveolar injury, the capacity to transport salt and water is often preserved. In severe injury, however, when the barrier is disrupted, the capacity to clear edema is lost, and the vascular endothelium becomes the limiting barrier between the vascular system and the air spaces. Clinically, the capacity to remove some alveolar edema fluid, as indicated by increase in the edema fluid to plasma protein concentration ratio in the first 4 to 12 hours after the development of increased permeability edema, is a favorable prognostic finding associated with a mortality of only 20%, whereas the inability to resorb alveolar edema fluid early in the course of severe lung injuries was associated with a mortality of nearly 80%.[116,117] Thus, the functional capability of the alveolar epithelial barrier in acute increased permeability edema may be a useful prognostic index, perhaps because it serves as a marker of the severity and extent of lung injury.

Alveolar fluid clearance may also be manipulated in certain settings. Lung Na^+,K^+-ATPase activity was increased in rats recovering from experimental thiourea-induced increased permeability pulmonary edema.[276] Moreover, alveolar fluid clearance can be increased by salmeterol in uninjured ex vivo human lung,[277] and experimental studies have shown that alveolar fluid clearance can be increased pharmacologically (e.g., by catecholamines), even in the presence of increased permeability edema with alveolar flooding.[2] These observations raise the potential of therapy to hasten the resolution of alveolar edema, although an increase in alveolar clearance requires an intact alveolar epithelial barrier. In one RCT of 282 patients with ARDS, aerosolized albuterol failed to show benefit, although it is possible that an aerosolized agent did not reach the most edematous areas of lung or the alveolar barrier could not respond.[278]

Fluid cleared from alveolar spaces into the alveolar interstitium can leave the lungs by flowing into the lymphatic capillaries or by moving down the prevailing pressure gradient into the loose peribronchovascular connective tissue spaces. Large amounts of fluid in the air spaces may be partially cleared into peribronchovascular cuffs through the hypothesized "leaky" terminal-airway epithelium,[279,280] leaving alveolar fluid and solute behind to be cleared more slowly through the more impermeable alveolar epithelium.

Most of the interstitial water in pulmonary edema is in the peribronchovascular loose connective tissue spaces rather than in the alveolar walls. Because the lymphatic capillaries are arranged to drain only the alveolar wall interstitium, this route for edema removal is not available for most interstitial water. A study in goats showed that lung lymph originated mainly from alveolar wall interstitial fluid, and the contribution of the lung lymphatic system to the clearance of interstitial edema in bronchoalveolar cuffs and interlobular septa was small.[281] The maximum

eTable 133.2 Cellular and Pharmacotherapy Tested by Randomized Trials in Increased Permeability Edema[74,311–313]

Methylprednisolone, hydrocortisone (corticosteroids)
Liposomal prostaglandin E_1 and E_2
Nitric oxide
β2-Agonist (intravenous and aerolized/inhaled)
Surfactant (various preparations)
Granulocyte-macrophage colony-stimulating factor
Ketoconazole
Sivelestat (neutrophil elastase inhibitor)
Rosuvastatin, simvastatin
ω-3 Fatty acid, gamma-linolenic acid, antioxidants (enteral)
Factor VII activator inhibitor
Lisofylline
STUDIES WITH FEWER THAN 100 SUBJECTS
Keratinocyte growth factor
Activated protein C
Pentoxyfylline
N-acetylcysteine, procysteine (oxothiazolidine carboxylate)
Enalaprilat (angiotensin-converting enzyme inhibitor)
Recombinant human angiotensin-converting enzyme II
Inhaled AP301 cyclic synthetic peptide
Mesenchymal stromal cells
Mesenchymal stem cells (adipose derived)

Corticosteroids. Of all the possible pharmacologic agents used to treat critical lung injuries, corticosteroids have the longest history. Despite a seemingly compelling rationale for their use in the setting of increased permeability edema from sepsis, five separate prospective, randomized, double-blind, placebo-controlled trials of methylprednisolone therapy failed to show a reduction in ARDS mortality.[251—255] Trials differed substantially in the dose of steroids, from as low as 1 mg/kg/day to as high as 120 mg/kg/day of methylprednisolone or equivalent, and the durations ranged from 4 hours to 30 days. Two trials administered corticosteroids early in the course of ARDS, whereas three trials tested later administration, as discussed subsequently.[256] The mortality effect was deemed moderately heterogeneous between trials, although no clear factor (dose; duration; year of trial) was clearly identified to explain heterogeneity.[256] In addition, corticosteroid therapy did not prevent the development of ARDS in patients with the sepsis syndrome; neither did it hasten the reversal of ARDS, lower mortality, or improve respiratory function.[256–260] Moreover, use of corticosteroids was associated with both a greater 14-day mortality rate in patients who developed ARDS and an increased frequency of associated infections. High-dose corticosteroids also were ineffective in the sepsis syndrome and may have caused harm.[261]

Fat embolism syndrome may be one specific subtype of ARDS for which corticosteroids may have value. A prospective, randomized, double-blind, placebo-controlled trial of corticosteroid treatment in 64 patients with long bone fractures showed that high-dose methylprednisolone effectively prevented the development of the fat embolism syndrome.[262] Fat embolism is an uncommon clinical syndrome usually described in single-case reports from orthopedists; corticosteroid treatment has not been routinely used, and thus far a large-scale multicenter, randomized trial does not seem warranted.

The generally disappointing results of corticosteroid trials in patients with early or impending lung injury have not discouraged further investigations; rather, ongoing studies indicate that corticosteroids might be beneficial in subsets of patients or when given at a particular time (e.g., during the proliferative phase) or for a more sustained period.[263] Results of studies of corticosteroid therapy late in the course of ARDS (so-called rescue therapy) were encouraging, and a small (24-patient), randomized, double-blind, placebo-controlled clinical trial in patients with severe ARDS whose Lung Injury Score had failed to improve by the seventh day of respiratory failure showed improvement in lung injury and other organ dysfunction scores, as well as reduced mortality in treated patients.[253] However, an NHLBI-sponsored trial of corticosteroid therapy (methylprednisolone, 2 mg/kg) beginning on day 7 to 21 of ARDS showed no reduction in 60- or 180-day hospital mortality in patients treated with corticosteroids compared with placebo.[254] In addition, there were important neuromuscular complications in patients treated with methylprednisolone. One study suggested potential benefit with steroids in severe lung injury, although the design of the trial was suboptimal.[252] Despite the lack of consistent mortality benefit for corticosteroids, three "late steroid rescue" trials did report increased days alive and ventilator free,[256] suggesting the potential for more cost-effective care, although concerns remain about the impact of corticosteroids on neuromuscular function after ARDS. Finally, observational studies from the 2009 pandemic H1N1 influenza crisis suggested no benefit from corticosteroids, even when attempting to account for severity factors with propensity score adjustment.[264,265]

Neuromuscular Blocking Agents. When oxygen saturation is critically low, reducing oxygen consumption to the minimum is advised to reduce oxygen consumption, decrease work of breathing, and achieve ventilator synchrony. However, whether *neuromuscular blockade* (NMB) is a necessary component of a low oxygen consumption strategy has been a topic of debate. In 2010 a randomized-controlled trial showed improvement in adjusted 90-day survival and time off the ventilator in patients with ARDS and Pao_2/Fio_2 ratio less than or equal to 150 receiving early cisatracurium compared with placebo for 48 hours.[266] Because questions remained about the efficacy of NMB and its potential risks,[267,268] the NHLBI sponsored a new multicenter trial that enrolled more than 1000 subjects with moderate to severe ARDS and was completed in 2018. As in the earlier trial, randomized NMB versus placebo was administered for 48 hours along with a limited tidal volume and high PEEP ventilation strategy.[239] Patients were enrolled early after ARDS onset, and only 17% of control group subjects received NMB at any time, compared to 97% of the group randomized to NMB. At 90 days, the mortality did not differ between groups (43% in both study arms). Although subjects randomized to NMB were more deeply sedated, less physically active, and had

higher cardiovascular organ failure scores early during treatment, there were no differences in patient-reported health outcomes at 1 year.[239] Hence, although NMB can be a useful adjunct when oxygen is severely low or when ventilator synchrony is difficult to achieve, early protocolized use of NMB does not seem to improve outcomes for unselected patients with moderate to severe ARDS.

Extracorporeal Membrane Oxygenation

As further discussed in Chapter 138, *extracorporeal membrane oxygenation* (ECMO) technology has greatly evolved since the initial randomized trial described very high (90%) mortality for ARDS.[269] ECMO is now a safe and potentially efficacious alternative for severe ARDS.[241,270] The *ECMO to Rescue Lung Injury in Severe ARDS* (EOLIA) multicenter trial, published in 2018, enrolled subjects with very severe ARDS—eligibility required Pa_{O_2}/F_{IO_2} less than 50 mm Hg for 3 hours, Pa_{O_2}/F_{IO_2} less than 80 for 6 hours, or arterial blood pH less than 7.25 with Pa_{CO_2} of at least 60 mm Hg for 6 hours—and randomized them to immediate venovenous ECMO or to continued conventional lung-protective ventilation with recommended prone position and NMB. Mortality in the control group was 46% and 35% in the ECMO group, a difference that did not achieve statistical significance (relative risk, 0.76; 95% confidence interval, 0.55 to 1.04; $P = 0.09$).[241] Thus many have opined that this large and difficult trial has failed to shift opinions on whether ECMO is useful in ARDS.[271] One interpretation might be that mortality in the control group was better than predicted when using protective ventilation and prone positioning, and if a patient is improving with these interventions, perhaps the added invasiveness of ECMO is not warranted. By the same token, almost 30% of patients randomized to conventional ventilation were crossed over by their clinicians to ECMO after displaying severe persistent hypoxemia, and these patients had a very high mortality even with ECMO.[241] Would earlier ECMO have changed their outcome? That cannot be determined from the data presented. From observational and registry data, we know that when ECMO is used, outcomes tend to be better when patients are younger, immunocompetent, and on ventilators fewer than 8 days.[272] The EOLIA trial bolsters confidence in the safety of ECMO, yet selecting the patients most likely to benefit may remain a challenge.

possible contribution by lung lymphatics to the clearance of interstitial edema liquid was less than 10%.[281] In a study of in situ perfused sheep lungs with experimental low- and high-protein pulmonary edema during recovery from pulmonary edema, interstitial liquid was resorbed into the circulation in inverse proportion to its protein concentration, and only a very small fraction of interstitial edema was cleared by the lung lymphatics during recovery from either type of edema.[282,283]

So, where does the interstitial edema in the peribronchial cuffs go? Once in the peribronchial cuffs, edema may drain along pressure gradients toward the mediastinum and also toward the pleural space, where it may flow across a leaky mesothelial layer into the pleural space. Pleural effusions are fairly common, found in approximately 25–50% of patients with increased pressure pulmonary edema and in roughly 35% of patients with increased permeability edema as well.[284–286] Formation and removal of pleural effusions are discussed in detail in Chapters 14 and 108. As much as 25–30% of pulmonary edema fluid may leave the lungs through the pleural space.[8,286]

Protein is handled quite differently. Because clearance of protein from flooded alveoli is much slower (1–2% per hour) than clearance of protein-free fluid (10–20% per hour),[287,288] the protein left behind in the alveolus becomes concentrated. The increase in alveolar protein concentration does not slow fluid clearance because precipitated protein exerts no osmotic pressure, and the concentration of soluble macromolecules is too small to counteract the differences in ion concentration resulting from transepithelial transport. Removal of edema fluid from flooded alveoli may be slowed if the fluid clots, which can be seen especially when lung vascular permeability is increased. Edema fluid may clot because, after extravasation of plasma into the air spaces, the clotting system may be activated by surfactant or macrophage-derived procoagulants.

Alveolar protein clearance over the short term appears to proceed primarily by paracellular diffusion, not by transcytosis via vesicles, and is size dependent.[6] Most proteins are cleared intact rather than being degraded into smaller fragments. Over the long term, cellular mechanisms, principally phagocytosis and catabolism by macrophages, account for most protein clearance from the alveolar space.[73,289,290] Insoluble, precipitated proteins are removed in this way. Macrophages and regulatory T lymphocytes are also responsible for removing senescent and dead polymorphonuclear leukocytes and other debris. The lack of a ciliated surface area in the distal air spaces seems to indicate that the mucociliary route could account for only a minor fraction of alveolar protein clearance, although proteins might reach the mucociliary escalator along currents in the alveolar fluid layer. Even so, removal would be very slow: The half-time for mucociliary clearance of particles from the alveolar space is more than 4 weeks. Complete clearance of alveolar protein from pulmonary edema by any route is slow.[6]

Little is known about the mechanisms and signals that regulate endothelial barrier function or how increased endothelial permeability returns to normal[291]; on the other hand, the mechanisms for resolution of lung inflammation are beginning to be understood.[73]

Increased Pressure Edema

The outcome of increased pressure pulmonary edema is determined by the underlying cause and the treatment used to correct it. Because the great majority of cases of increased pressure edema are caused by heart disease, outcome is largely determined by the patient's underlying cardiac function. Although traditional reports were that patients with pulmonary edema uncomplicated by acute myocardial infarction fared reasonably well, with an annual mortality rate of less than 10%,[292] more recent data suggest hospital mortality rates exceed 26% regardless of whether *coronary artery disease* (CAD) is present,[293] perhaps signifying that hospitalization for heart failure is being reserved for patients with more severe symptoms in modern times. The presence of CAD is a risk factor for heart failure readmission after hospitalization with acute pulmonary edema, whereas revascularization and surgical procedures were associated with improved survival, perhaps indicating some degree of selection bias.[293] Typically, patients who recover from increased pressure pulmonary edema caused by chronic congestive cardiac failure require long-term outpatient management aimed at preventing recurrent episodes.

Some patients develop increased pressure pulmonary edema from noncardiac causes. Most cases are iatrogenic, being related to excessive, sometimes inadvertent, volume overload, or due to the use of drugs such as cocaine, which impair cardiac function.[294] Pulmonary edema associated with congenital or acquired heart disease is an uncommon but important problem in pregnancy, but pulmonary edema without heart disease is, perhaps, even more frequent. As discussed in Chapter 129, pregnancy complicated by pulmonary edema is occasionally caused by tocolytic treatment, fluid overload, or preeclampsia.[295]

Increased Permeability Edema

The outcome of increased permeability pulmonary edema from both ARDS and forms of milder lung injury is determined by its underlying cause and extent of lung injury, the presence of comorbidities, and the particular treatment strategy used. Trends in ARDS mortality in 2451 mechanically ventilated patients enrolled in the NHLBI ARDS Network showed "clear temporal improvement in survival," from 35% in the late 1990s to a low of 26% in 2005.[296] Although mortality in clinical trials has fallen to as low as 17%,[297] selection bias for trial populations may underestimate the true mortality burden, because observational data from global populations still report mortality of roughly 45% for severe ARDS, 32% for moderate, and 27% for mild ARDS.[65,240]

Patients with sepsis have significantly higher mortality rates than patients with other clinical disorders associated with the development of increased permeability edema.[298] Mortality is also much higher in patients with chronic liver disease or with histories of chronic alcohol abuse than in other predisposing conditions. Besides damaging the liver, chronic ethanol ingestion may reduce alveolar type 2 cell glutathione content and impair surfactant synthesis and secretion.[299] In general, mortality from ARDS increases with increasing age and ARDS severity.[65,300] Patients with self-limited causes of injury, including venous air and fat embolism, isolated lung contusion and other trauma,

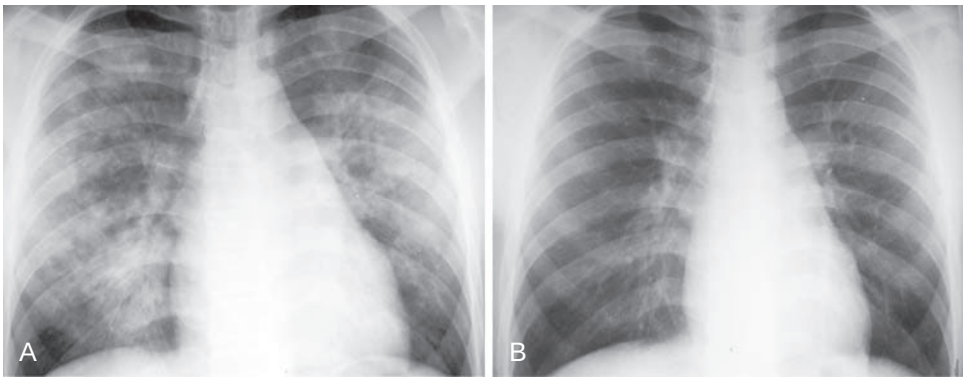

Figure 133.6 Frontal chest radiographs in a 22-year-old patient with heroin-induced increased permeability edema. The radiograph at presentation (A) shows patchy bilateral peribronchial thickening and consolidation, somewhat more prominent and nodular on the right. The vascular pedicle is narrow, with no features suggestive of volume overload. The radiograph 24 hours later (B) shows complete clearing of lung opacities. Increased permeability edema may resolve rapidly if the initiating agent of lung injury is transient and mild and the chronic phase of parenchymal lung injury (type 2 cell hyperplasia, fibrosis, connective tissue deposition, vascular remodeling) does not develop. (Courtesy Michael B. Gotway, MD.)

massive blood transfusions, postictal pulmonary edema, and heroin pulmonary edema (Fig. 133.6), have a greater chance of survival, and edema often clears rapidly. A more recently described entity, vaping-induced lung injury,[301] may also have a favorable prognosis relative to the severity of hypoxemia, although experience with this disease is in its infancy, and fatalities have been reported.

As survival from ARDS improves, the population of survivors grows, and long-term sequelae pose increasing problems. From a purely respiratory standpoint, survivors of ARDS do well on average; at 1 year post-ARDS, many have normal chest radiograph results, minimal or no complaints of dyspnea on exertion, normal lung volumes and airflow measurements, and normal resting and exercise arterial blood-gas findings, including shunt fraction.[302] Diffusing capacity seems to be the pulmonary function parameter most likely to be abnormal at 1 year[71,303] although, by 5 years, even this improves to a median of 80% of predicted (interquartile range, 70–86%).[70] At 5 years post-ARDS, while the chest radiograph is often normal, the chest CT may reveal "minor, nondependent fibrotic changes."[70]

Despite post-ARDS return of pulmonary function test results to normal or near-normal values, survivors and their partners report a significant deterioration of health-related quality of life. Disabling symptoms from muscle wasting, weakness, and fatigue were consistently noted, with reduced *6-minute walk distance* (6MWD) during the first 12 months in previously high-functioning, mostly young subjects.[71] Even 5 years after ARDS, survivors' functional ability remains impaired, with 6MWD approximately 76% of what is predicted for age.[70] The roles played by treatment of ARDS with corticosteroids and neuromuscular blocking are not clear-cut, but neither agent fully explains the deficits observed. Cognitive and emotional function was significantly impaired in those surviving ARDS at hospital discharge, 78% of whom remained symptomatic after 12 months.[71] Furthermore, psychological sequelae such as anxiety, depression, and posttraumatic stress disorder persisted in 20–40% of survivors over the ensuing 5 years.[70] The burden of ARDS on families is also substantial; caregivers commonly report symptoms consistent with depression, anxiety, and posttraumatic stress disorder themselves.[304–306]

Healing involves a fibroproliferative response in a subset of ARDS survivors, which seems to begin early in the course of increased permeability edema,[307–309] perhaps as a consequence of ventilator-induced lung injury before the era of lung-protective ventilation (Video 133.2).[310] How much of this problem is due to disease and how much to treatment is not known, but a fibroproliferative reaction portends a poor prognosis: either increased mortality or prolonged ventilation dependence. It might also be possible to accelerate reconstitution of alveolar structure in injured lungs; this hope underlies the optimism that interventions such as mesenchymal stromal cells or adult progenitor cells may improve ARDS outcome.[308,311]

Key Points

- The two main categories of pulmonary edema are (1) increased pressure edema from an increase in the hydrostatic or protein osmotic forces, or both, that act across normal endothelial and epithelial barriers restricting movement of fluid and protein in the lungs and (2) increased permeability edema from damage to those barriers.
- An evaluation of the cause of pulmonary edema should include a detailed history with a focus on risk factors for either increased pressure or increased permeability edema, a thorough physical evaluation, and laboratory and imaging data, including a chest radiograph, electrocardiogram, cardiac injury markers, microbiologic cultures, and consideration of ultrasound and echocardiography.
- Increased pressure pulmonary edema typically has one of two cardiac origins: from new-onset acute myocardial infarction or from inadequately treated and/or refractory heart failure.
- Treatment for cardiogenic (increased pressure) pulmonary edema should include support of oxygenation and ventilation, often with noninvasive ventilation, and pharmacologic measures to reduce preload and afterload. Revascularization for coronary artery disease and temporary support with ventricular assist devices may be therapeutic options.
- The diagnosis of increased permeability pulmonary edema or *acute respiratory distress syndrome* (ARDS) should include a thorough investigation for a treatable infection.

- Increased permeability pulmonary edema may be complicated by elevated pulmonary intravascular pressures; the two types of pulmonary edema can coexist in the same patient.
- Patients with increased permeability edema who require invasive ventilation should receive lung-protective ventilation with limited tidal volumes (6 mL/kg predicted body weight) and limited plateau pressures (<30 cm H_2O) with adequate positive end-expiratory pressure. When ARDS is moderate to severe (Pa_{O_2}/F_{IO_2} ratio < 150 mm Hg despite lung protective ventilation), prone positioning has been shown to reduce mortality. Extracorporeal membrane oxygenation is a safe alternative when hypoxemia is severe and persistent (Pa_{O_2}/F_{IO_2} ratio < 80 mm Hg).
- The identification of biologically distinct subgroups within ARDS populations that respond differently to different therapies offers the promise of precision therapy in the future.

Key Readings

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134 ACUTE RESPIRATORY DISTRESS SYNDROME

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DIAGNOSIS AND EPIDEMIOLOGY

DIAGNOSIS

Acute respiratory distress syndrome (ARDS) is described as noncardiogenic pulmonary edema accompanied by severe lung inflammation, hypoxemia, and decreased lung compliance leading to respiratory failure. As its name suggests, ARDS is a syndrome, reflecting a constellation of clinical and physiologic observations thought (but not confirmed) to represent a common pathology. No diagnostic gold standard exists for ARDS, and it remains unclear whether it represents a single pathophysiologic process or multiple processes with similar clinical presentations. The heterogeneity of clinical conditions associated with ARDS (discussed later), variance in outcomes by risk factor, and the existence of at least two different phenotypes suggest that ARDS is not simply a common pathologic pathway but may be a collection of pathways of injury that have not yet been separately identified. These uncertainties necessarily permeate any discussion or research into ARDS, and this chapter is no exception.

The first clinical description of ARDS appeared in a remarkable case series reported by Ashbaugh and colleagues in 1967.[1] They described 12 patients aged 11 to 48 years who presented with respiratory distress, hypoxemic respiratory failure, and patchy bilateral opacities on chest radiographs (Fig. 134.1). Most of the cases were preceded by severe trauma or viral infection and the onset of symptoms was rapid, usually within 48 to 72 hours of the insult. Many patients required positive-pressure ventilation and exhibited low respiratory system compliance, and some experienced improvement in oxygenation with the application of *positive end-expiratory pressure* (PEEP). This syndrome was initially termed the *adult* respiratory distress syndrome to distinguish it from the respiratory distress syndrome seen in infants. Subsequently, recognizing that it can also be seen in children, it was renamed the *acute* respiratory distress syndrome.

The cases described by Ashbaugh generated interest and research into ARDS. Unfortunately, the lack of diagnostic criteria and pathophysiologic understanding of the disorder made it difficult to conduct research and compare findings between studies. In 1988, a formalized and expanded definition of ARDS was proposed that consisted of three parts[2]: (1) the first part described whether the illness was acute or chronic, (2) the second part specified any associated risk factors or medical conditions (e.g., sepsis, pancreatitis, inhalational injury), and (3) the third part assigned points based on the severity of pulmonary dysfunction using the modified Lung Injury Score. This score incorporates the degree of hypoxemia, the level of PEEP, the respiratory system compliance (if available), and the degree of radiographic

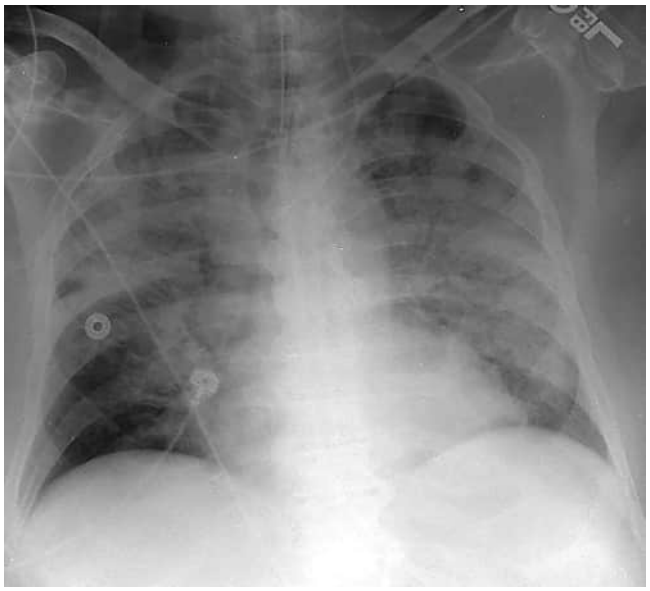

Figure 134.1 Chest radiograph of acute respiratory distress syndrome. Frontal chest radiograph in a mechanically ventilated patient shows extensive, multifocal, bilateral lung opacities, essentially involving all lobes and without features suggesting increased pressure edema, such as interlobular septal thickening or pleural effusion. (Courtesy Michael B. Gotway, MD.)

abnormality. A Lung Injury Score greater than 2.5 was considered diagnostic of ARDS. One advantage of this system was its identification of associated medical conditions, which might be pertinent to the etiology of ARDS. However, there was no attempt to exclude cardiogenic pulmonary edema because it was assumed that clinicians would do so automatically.

In 1994, investigators convened the *American and European Consensus Conference* (AECC) and published an updated definition of ARDS, which was widely adopted.[3] Aiming for simplicity, ARDS was defined as (1) a syndrome of acute onset respiratory failure with (2) bilateral opacities on chest radiography consistent with pulmonary edema, (3) pulmonary artery occlusion pressure of 18 mm Hg or less (or absence of clinical evidence of left atrial hypertension), and (4) hypoxemia as measured by the ratio of the *arterial partial pressure of oxygen* (arterial P_{O_2}) to the *fractional concentration of oxygen in inspired gas* (F_{IO_2}). Recognizing the spectrum of severity of the disease, the consensus panel recommended that arterial P_{O_2}/F_{IO_2} of 300 or less would define an entity termed *acute lung injury* (ALI) while an arterial P_{O_2}/F_{IO_2} of 200 or less would define ARDS. The simplicity of the definition led to its widespread acceptance by clinicians and its incorporation into clinical research.

One issue with the AECC definition was that the radiographic criteria (bilateral opacities consistent with pulmonary edema) were open to interpretation. This was demonstrated by one study that presented a random series of chest radiographs from intubated hypoxemic patients with arterial P_{O_2}/F_{IO_2} less than 300 to an international group of expert clinicians, many of whom conducted research in ARDS. This select group of physicians demonstrated only moderate agreement in their classification of the radiographs (kappa statistic 0.55).[4] The percentage of radiographs deemed to be consistent with ARDS by each physician ranged from a low of 36% to a high of 71%. However, in a separate study, two physicians (an intensivist and a radiologist) were able to achieve excellent agreement after consensus training.[5]

The AECC definition has also been criticized for not taking the level of PEEP into consideration. Clinicians have long appreciated that applying PEEP can improve oxygenation. This implies that the arterial P_{O_2}/F_{IO_2} will change as the level of applied PEEP changes; indeed, a patient who initially meets the AECC criteria for ARDS may no longer meet them after PEEP has been increased.[6] A study of 170 patients meeting the AECC definition for ARDS on varying ventilator settings showed that when PEEP was increased to 10 cm H_2O or greater only 70% of patients still met the ARDS criteria.[7] Moreover, by day 1 of study inclusion, only 50% of patients still met the AECC criteria for ARDS. Thus, the AECC definition, while simple to use, encompasses a heterogeneous group of patients.

In 2012, the Berlin definition of ARDS was developed to address some of these limitations (Table 134.1).[8,9] The degree of hypoxemia was stratified into mild, moderate, and severe based on the arterial P_{O_2}/F_{IO_2} ratio and a requirement for a PEEP level of 5 cm H_2O or greater was included (whether applied by endotracheal tube or, in the setting of mild disease, by noninvasive ventilation). The term ALI was eliminated. Given that the use of pulmonary artery catheters has fallen off dramatically due to lack of benefit,[10,11] the pulmonary arterial wedge pressure criteria was eliminated, and it was recommended that objective testing (e.g., echocardiography) be performed to exclude cardiogenic edema in cases for which no risk factor for ARDS could be identified. "Acute" was explicitly defined as ARDS developing within 1 week of a known risk factor.

Although considerable effort went into its design, when compared to the AECC criteria, the Berlin definition is only slightly better at predicting mortality from ARDS.[9] Moreover, interobserver variability remains high, with a recent study estimating a kappa of 0.5, corresponding to only moderate reliability; 67% of the variability was attributed to differences in interpreting chest imaging.[12]

Two additional points should be made about the diagnosis of ARDS. Whereas physicians properly think of ARDS as being distinct from cardiogenic pulmonary edema, it is important to acknowledge that many patients with ARDS will have left atrial hypertension during the course of their illness[13] and, in fact, its presence does not exclude a diagnosis of ARDS.[8] Secondly, despite the use of B-type natriuretic peptide as a diagnostic tool for acute congestive heart failure, its ability to distinguish ARDS from cardiogenic pulmonary edema is unclear.[14–16] Thus, until the discovery of a specific diagnostic marker for ARDS, cardiogenic edema is likely to remain a significant confounding factor in the diagnosis of ARDS.

Pediatric diagnostic criteria are discussed at ExpertConsult.com.

INCIDENCE

Given the multitude of definitions and the difficulty of making a confirmed diagnosis of ARDS, it is not surprising that determining the incidence of the syndrome has been

PEDIATRIC DIAGNOSTIC CRITERIA

In 2015, a set of pediatric ARDS criteria known as the *Pediatric Acute Lung Injury Consensus Conference* (PALICC) criteria were published (eTable 134.1).[17] These criteria are similar to the adult ARDS criteria with a few notable differences, such as the use of alternative indices of oxygenation (e.g., S/F ratio = pulse oximetric oxygen saturation/fraction of inspired oxygen) and the inclusion of criteria for patients on noninvasive mechanical ventilation. In keeping with the Berlin Definition, the PALICC criteria use the categories mild, moderate, and severe pediatric ARDS based on degree of hypoxemia.

When both the Berlin criteria and the PALICC criteria are applied in children, the PALICC criteria identify more pediatric patients as having pediatric ARDS; however, these patients have an overall lower mortality.[17,18]

eTable 134.1 PALICC Definition of Pediatric ARDS[17]

Criterion	Definition
Age	Exclude patients with perinatal lung disease
Timing	Within 7 days of known clinical insult
Origin of edema	Respiratory failure not fully explained by cardiac fluid or fluid overload
Chest imaging	Findings of new opacities consistent with acute pulmonary parenchymal disease
Oxygenation	1. Noninvasive mechanical ventilation with full face mask bilevel ventilation *or* CPAP ≥5 cm H_2O *and* P/F ratio ≤300 *or* S/F ratio ≤264 2. Invasive mechanical ventilation with: ■ Mild: OI 4–8 or OSI 5–7.5 ■ Moderate: OI 8–16 or OSI 7.5–12.3 ■ Severe: OI ≥16 or OSI ≥12.3

ARDS, acute respiratory distress syndrome; CPAP, continuous positive airway pressure; OI, oxygenation index = (FIO_2 × mean airway pressure (in mm Hg) × 100)/PaO_2; OSI, oxygen saturation index = (FIO_2 × mean airway pressure × 100)/O_2 saturation; PALICC, Pediatric Acute Lung Injury Consensus Conference; P/F ratio, ratio of partial pressure of oxygen (PaO_2) to fraction of inspired oxygen (FIO_2); S/F ratio, ratio of pulse oximetric oxygen saturation (SpO_2) to fraction of inspired oxygen (FIO_2).

Table 134.1 Berlin Definition of ARDS

Criterion	Definition
Timing	Within 1 week of a known precipitant or new/worsening respiratory symptoms
Chest imaging*	Bilateral opacities not fully explained by effusions, lobar/lung collapse or nodules
Origin of edema	Respiratory failure not fully explained by cardiac fluid or fluid overload If no risk factor for ARDS is present, need objective assessment (e.g., echocardiogram) to exclude hydrostatic edema
Oxygenation	
Mild	200 mm Hg < Pao_2/Fio_2 ≤300 mm Hg with PEEP or CPAP ≥5 cm H_2O
Moderate	100 mm Hg <Pao_2/Fio_2 ≤ 200 mm Hg with PEEP ≥ 5 cm H_2O
Severe	Pao_2/Fio_2 ≤100 mm Hg with PEEP ≥ 5 cm H_2O

*By chest radiography or computed tomography.

ARDS, acute respiratory distress syndrome; CPAP, continuous positive airway pressure; Fio_2, fraction of inspired oxygen; Pao_2, arterial Po_2; PEEP, positive end-expiratory pressure.

From ARDS Definition Task Force, Ranieri VM, Rubenfeld GD, Thompson BT, et al. Acute respiratory distress syndrome: the Berlin definition. *JAMA* 2012;307(23):2526-2533.

challenging. In Europe, the reported incidence of "ARDS" (AECC definition) or "moderate" to "severe" ARDS (Berlin definition) has ranged from 1.5 per 100,000[19] to 75 per 100,000 person/years[20]; however, most estimates have been in the range of 5 to 8 cases per 100,000 person/years.[21,22] In the United States, estimates have been much higher, ranging from 33.8/100,000 person/years[23] up to 75/100,000 person/years.[24] The discrepancy between United States and European figures is difficult to justify but, since most incidence studies assess only *intensive care unit* (ICU) patients, it may reflect the higher availability of ICU beds in the American context.[22]

The incidence of ALI (per the AECC definition) was estimated in a prospective study of ICU patients in Washington State to be 78.9 cases per 100,000 person/years.[25] A second study using 3 years of screening data from the original *National Heart Lung and Blood Institute ARDS Network* (ARDSNet) study calculated an incidence ranging from 22/100,000 person/years to 64/100,000 person/years depending on the assumptions used.[26] This heterogeneity may reflect differences in methodology of various studies leading to discrepancies in classification of cases and identification of the size of the population from which those cases arose. However, this variability in results may also reflect true regional variation because differences, including genetic or environmental factors and specific disease associations such as cardiopulmonary bypass or lung transplantation, may account for some of the variability.[27]

Very few comparative data exist to determine whether ARDS incidence differs between geographic regions. The *Large Observational Study to Understand the Global Impact of Severe Acute Respiratory Failure* (LUNG SAFE study) was a worldwide effort that included data from 459 ICUs in 50 countries.[28] Patients were prospectively screened over a 4-week period in the winter of 2014. The ICU incidence of ARDS (mild, moderate, and severe, per the Berlin definition) was estimated to be 10.4% of ICU admissions and 23.4% of patients receiving mechanical ventilation. There was some geographic variation, from 0.27 cases per ICU bed in Asia to 0.57 cases per ICU bed in Oceania; Europe and North America were similar at 0.46 and 0.48 cases per ICU bed, respectively.[28] The authors did not estimate population incidence because they were unable to calculate catchment areas for all of the screening hospitals. The results of the LUNG SAFE study have been criticized as overestimating the incidence of ARDS due to an unvalidated algorithm for diagnosing ARDS that was discordant with clinician assessment (only 60% of patients identified by the algorithm were diagnosed as having ARDS by the treating clinician) and the fact that 17% of patients met criteria for ARDS for less than 24 hours, which seems at odds with the natural history of the syndrome.[29] However, the mortality data revealed an average in-hospital mortality rate of 40%, which is consistent with other studies of ALI/ARDS and indicates that the acuity of the patient population was high.[28]

RISK FACTORS

Sepsis, trauma, aspiration of gastric contents, and multiple transfusions (more than 15 units in 24 hours, in one study) are associated with the highest risk of developing ARDS. The presence of more than one risk factor further increases the incidence of ARDS.[30] In early studies, up to 43% of patients with sepsis, 40% of patients receiving massive blood transfusions, and 25% of patients with multiple trauma developed ARDS.[31] A systematic review of risk factors for ARDS concluded that the strongest evidence of a causal relationship was for sepsis, trauma, multiple transfusions, aspiration of gastric contents, pulmonary contusion, pneumonia, and smoke inhalation.[32]

Premorbid conditions can also affect the likelihood of ARDS. One of the most significant predisposing factors is a history of chronic alcoholism (relative risk, 2.0; 95% confidence interval, 1.3 to 2.9). This relationship remained significant after adjustment for gender, at-risk diagnosis, and severity of illness. Patients with ARDS and a history of alcoholism also had a higher mortality rate than those without this history (odds ratio, 6.3; 95% confidence interval, 2.2 to 20.4).[33] The mechanisms of this association are unknown. More recently, active or passive exposure to cigarette smoke has been associated with the development of trauma-associated ARDS.[34]

The heterogeneity of risk factors for ARDS is remarkable. At the American-European consensus conference, investigators divided the known risk factors into those thought to cause *direct* lung injury (e.g., pneumonia), and those in which the mechanism of lung injury was thought to be *indirect* (e.g., sepsis) (Table 134.2). While conceptually attractive, this classification scheme may not reflect underlying differences in the mechanisms, severity, or outcome of lung injury.[35]

Table 134.2 Conditions Associated With Acute Respiratory Distress Syndrome by Possible Mechanisms of Injury

Direct Injury (Pulmonary)	Indirect Injury (Nonpulmonary)
Pneumonia (bacterial, viral [e.g., influenza, COVID-19])	Sepsis
Aspiration	Major trauma
Pulmonary contusion	Multiple blood transfusions
Toxic inhalation	Pancreatitis
Near-drowning	Cardiopulmonary bypass
Reperfusion injury (e.g., post–lung transplant)	Drug overdose
	Adverse effects of medication

COVID-19, coronavirus disease 2019.

ETIOLOGY AND PATHOGENESIS OF ARDS

OVERVIEW OF PATHOPHYSIOLOGY

In the past, ARDS was called *noncardiogenic pulmonary edema*, a descriptive term that reflected what was known of the pathogenesis of the disorder. Unlike congestive heart failure, in which elevated left-sided cardiac pressures cause hydrostatic pulmonary edema, in ARDS, the edema fluid that fills the alveoli is exudative. In other words, the alveolar-capillary barrier exhibits increased permeability, allowing for the leakage of protein-rich fluid into the airspaces. Alveolar filling leads to decreased respiratory system compliance as well as right-to-left shunting and profound hypoxemia. Although alveolar P_{CO_2} is generally within the normal range, dead space ventilation is significantly increased, as demonstrated by increased minute ventilation. Pulmonary hypertension is also common in ARDS, and a number of mechanisms have been proposed to account for this, including hypoxic vasoconstriction, intravascular fibrin deposition, and compression of blood vessels by positive-pressure ventilation. This section reviews the pathology of ARDS and discusses current theories of its pathogenesis.

PATHOLOGY

The pathologic features of ARDS have classically been described using three overlapping and sequential stages.[36] In the first *exudative phase* of lung injury, hyaline membranes (composed of cellular debris, proteins, and surfactant components) and protein-rich fluid fill the alveolar spaces. There is widespread epithelial disruption as well as infiltration of the interstitium and airspaces with neutrophils. These pathologic findings are termed *diffuse alveolar damage* (DAD). The exudative phase is thought to last for 5 to 7 days and is followed in some patients by the *proliferative phase*. At this point, hyaline membranes are reorganized and fibrosis appears. Obliteration of pulmonary capillaries and deposition of interstitial and alveolar collagen may also be observed, along with a decrease in the number of neutrophils and the extent of pulmonary edema. The final phase of ARDS is the *fibrotic phase*, so-called because of the appearance of pulmonary fibrosis in a subset of patients with persistent ARDS (i.e., greater than 2 weeks). Fibrosis may start sooner than previously appreciated; elevated levels of N-terminal procollagen peptide III, thought to represent collagen synthesis, can be detected in *bronchoalveolar lavage* (BAL) fluid of patients with ARDS as early as 24 hours after the onset of illness. In addition, the BAL fluid from ARDS patients has been shown to stimulate cultured fibroblasts to proliferate in vitro.[37] These and other observations have led some investigators to hypothesize that fibroproliferation may begin simultaneously with (rather than after) inflammatory lung injury.[38] (See radiologic correlates of the different ARDS phases in Fig. 134.2.)

Although DAD is considered the pathologic correlate of ARDS, multiple studies have confirmed that only about 50% of ARDS patients show evidence of DAD on autopsy or lung biopsy.[39] The patients with evidence of DAD tend to be younger, more severely ill, have poorer lung compliance, lower alveolar P_{O_2}/F_{IO_2} ratios, and require higher ventilator driving pressures. Patients with confirmed DAD also have a higher mortality and, in one study, were five times more likely to die of hypoxemic respiratory failure than patients without DAD. The pathologic findings of ARDS in patients without DAD include abnormalities such as infectious pneumonia, diffuse alveolar hemorrhage, acute eosinophilic pneumonia, and drug-associated pneumonitis.[39] Currently, there are no noninvasive techniques to identify which ARDS patients have DAD; the development of a biomarker of DAD would enable the early identification and prospective study of this high-risk subgroup of ARDS patients and would also enable the appropriate treatment of those non-DAD patients with treatable pathologies.

THE ALVEOLAR-CAPILLARY MEMBRANE

If ARDS is a disorder of increased alveolar-capillary permeability, it stands to reason that the pulmonary microvascular endothelium or the alveolar epithelium (or both) must be involved in its pathophysiology. Damage to the alveolar epithelium is thought to be a key event precipitating ARDS.[40,41] Multiple mechanisms contribute to epithelial cell death in ARDS, including cell necrosis, apoptosis, coagulation, and mechanical stretch.[41] Loss of epithelium disrupts barrier integrity, contributing to edema formation, and also prevents alveolar fluid clearance. In addition to the alveolar epithelium, the microvascular endothelium is involved; loss of pulmonary vascular endothelial barrier integrity is both necessary and sufficient for the development of ARDS.[42,43] The mechanism of alveolar-capillary membrane injury in ARDS is unknown, although epithelial and endothelial apoptosis,[44] as well as neutrophil-induced damage, are thought to play central roles (see below).

SURFACTANT

Surfactant is a complex mixture of phospholipids and proteins that reduces alveolar surface tension. Many researchers have described alterations to surfactant in patients with ARDS, including decreased amounts of surfactant-related protein and decreased amounts of the phospholipids

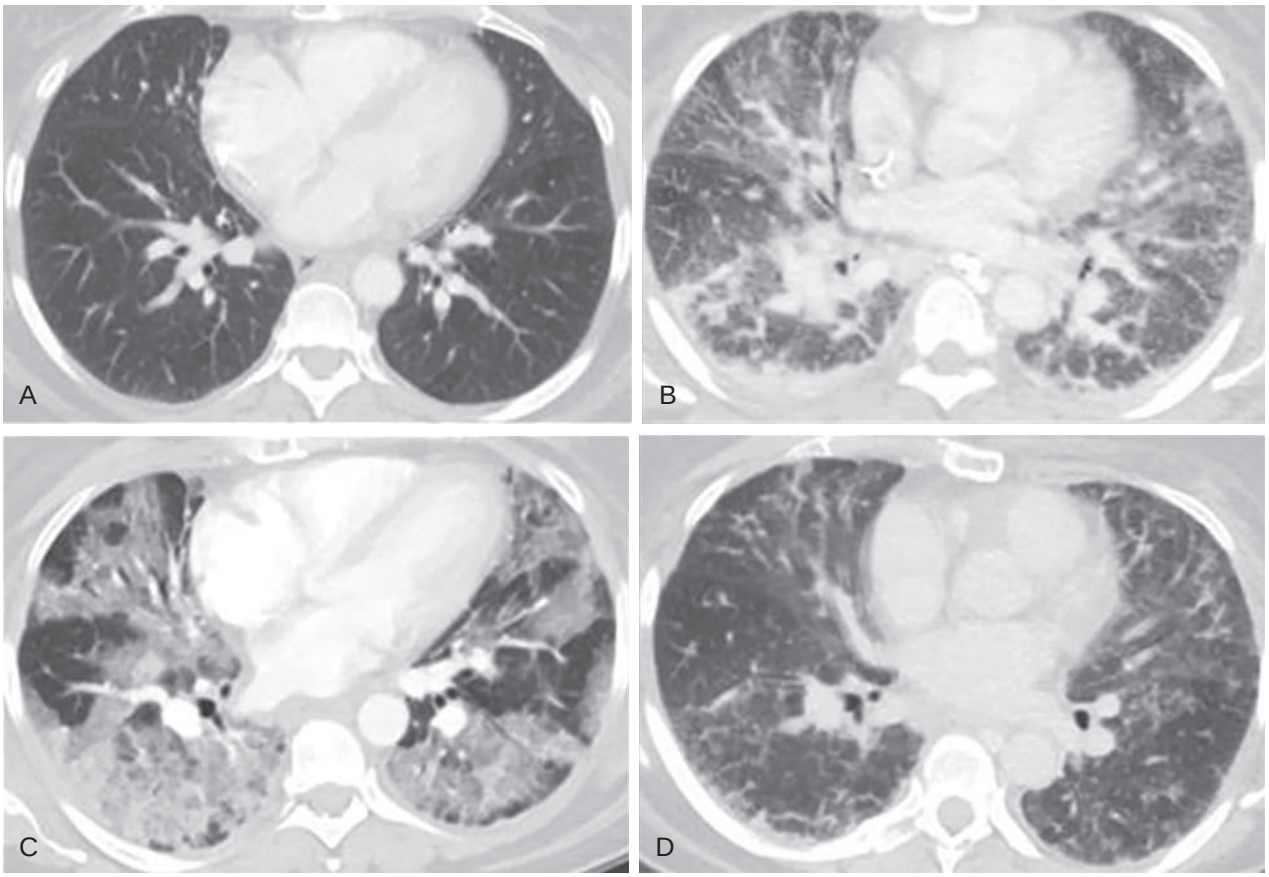

Figure 134.2 Computed tomography demonstration of the phases of the acute respiratory distress syndrome. (A) Axial enhanced chest *computed tomography* (CT) obtained approximately 1 year prior to the development of *acute respiratory distress syndrome* (ARDS) serves as a baseline. (B) Axial enhanced chest CT as the exudative phase of ARDS was developing as a complication of multifocal pneumonia shows multifocal bilateral ground-glass opacity associated with reticular opacities, but without features of increased pressure edema, such as pleural effusions. (C) Axial enhanced chest CT several weeks after the development of hypoxemic respiratory failure shows some mild architectural distortion, best seen anteriorly in the right middle lobe, with some dependent consolidation, suggesting developing organization and typical of the proliferative phase of ARDS. (D) Axial enhanced chest CT more than 1 month after the development of hypoxemic respiratory failure shows resolution of much of the ground-glass opacity, with linear and reticular abnormalities now more prominent, particularly anteriorly, consistent with the fibrotic phase of ARDS. (Courtesy Michael B. Gotway, MD.)

dipalmitoylphosphatidylcholine and phosphatidylglycerol. The proportion of large (active) to small (inactive) aggregates of surfactant is also diminished, due both to decreased production of surfactant and to increased conversion of large to small forms. Plasma proteins that leak into the alveolar space through the alveolar-capillary barrier may also interfere with surfactant function. Additionally, neutrophil elastase causes degradation of surfactant A protein in vitro,[45] consistent with degraded surfactant A being found in BAL washings from patients with ARDS.[46]

Impairment in surfactant function in ARDS theoretically predisposes alveolar units to collapse. In addition, surfactant proteins are known to have antimicrobial properties,[47,48] although whether the loss of these properties is relevant to the pathogenesis of ARDS is not known.[49] Indeed, the extent to which abnormalities of surfactant contribute to the pathogenesis of ARDS remains controversial, unlike in the *neonatal* respiratory distress syndrome in which a deficiency of surfactant underlies the pathophysiology of the disease. Four large, randomized controlled trials of exogenous surfactant supplementation in adult ARDS failed to demonstrate improvement in mortality or in the need for mechanical ventilation[45] (see "Treatment" section). Only one trial using calfactant, a natural surfactant, in pediatric patients with ARDS has shown any benefit[50]; whether this is due to the unique surfactant studied or the patient population enrolled in this trial is unknown.

NEUTROPHILS AND OTHER INFLAMMATORY MEDIATORS

Histologically, one of the hallmarks of ALI/ARDS is the accumulation of neutrophils in the microvasculature of the lung.[51] As key players in innate immunity, neutrophils can generate an impressive array of cytotoxic compounds. These include reactive oxygen species, cationic peptides (e.g., defensins), eicosanoids, and proteolytic enzymes such as leukocyte elastase. In addition, once activated, neutrophils release growth factors and cytokines, such as *tumor necrosis factor-α* (TNF-α) and *interleukin-1β* (IL-1β), that may enhance the inflammatory response. Given this destructive potential, it has long been theorized that neutrophils may be central to the pathogenesis of ARDS[52,53] (Fig. 134.3). There is an abundance of clinical and preclinical data to support this hypothesis. For example, in humans with sepsis-associated ARDS, the presence of neutrophils in

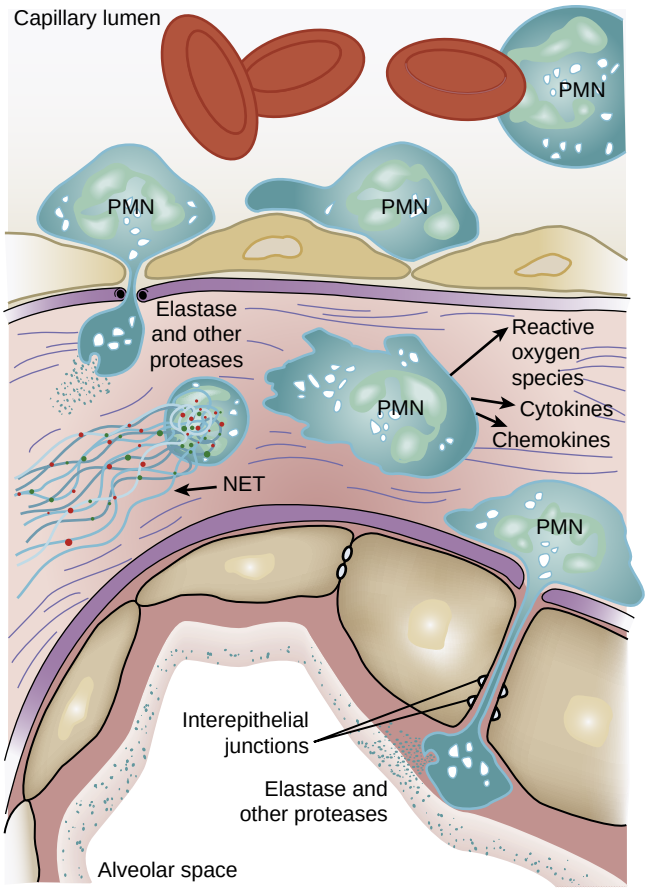

Figure 134.3 Role of neutrophils in the pathogenesis of acute lung injury. Activated *polymorphonuclear neutrophils* (PMNs) exit the bloodstream and transmigrate across the alveolar-capillary membrane, releasing cytokines, proteases, reactive oxygen species, and other compounds, as well as *neutrophil extracellular traps* (NETs). Although crucial for host defense against pathogens, compounds released by neutrophils have the capacity to damage host tissue.

BAL fluid is associated with a poor prognosis.[54] Conversely, neutrophil-depleted mice exposed to hyperoxia develop less lung injury than normal mice.[55]

One of the earliest manifestations of ARDS, even before hypoxemia, is a transient leukopenia due to sequestration of neutrophils in the lung microvasculature.[56] The diameter of the average pulmonary capillary is smaller than the diameter of the average neutrophil; therefore, they must deform to pass through the microvasculature. Activated neutrophils become "stiff" and cannot negotiate these narrow capillary segments,[57,58] leading to sequestration within the pulmonary capillaries. Inhibitors of actin polymerization can prevent this stiffening, implicating a change in the actin cytoskeleton as part of the mechanism.[59] Once sequestered in the lungs, neutrophils can migrate into the lung without the need for adhesion molecules such as L-selectin and β2-integrins.[60] Sequestered neutrophils may also induce changes in the endothelial cells that promote endothelial barrier breakdown,[61] leading to enhanced migration of neutrophils into the pulmonary interstitium.

Many studies have focused on the mechanisms of neutrophil activation. One area of interest is the interaction between neutrophils and platelets and how mutual activation may contribute to ARDS and sepsis.[62–65] Other studies have investigated components of intracellular signal transduction pathways, such as kinases (enzymes that phosphorylate substrates) and transcription factors. One such kinase is the p38 mitogen-activated protein kinase, which is activated when cells are stimulated with lipopolysaccharide.[66] Activation of mitogen-activated protein kinase stimulates TNF-α production as well as release of macrophage inflammatory protein-2, a chemotactic factor for macrophages.[67] Interestingly, inhibition of mitogen-activated protein kinase in mice, even hours after exposure to aerosolized lipopolysaccharide, attenuates neutrophil chemotaxis and migration from the lung microvasculature into alveoli.[68] Another kinase that is central to inflammation is phosphatidylinositol 3-kinase. This enzyme phosphorylates phosphatidylinositol, a lipid-derived second messenger whose phosphorylated forms have been implicated in a myriad of intracellular signaling events. Phosphatidylinositol 3-kinase-γ is preferentially activated in neutrophils exposed to the inflammatory mediators IL-8 or fMLP (a bacterial-derived peptide).[69] When compared to control mice, phosphatidylinositol 3-kinase-γ knockout mice displayed decreased neutrophil accumulation, cytokine production, and lung injury after exposure to intraperitoneal endotoxin.[70]

Neutrophils also produce proteolytic enzymes that may contribute to the pathogenesis of ARDS, particularly *neutrophil elastase* (NE) and metalloproteinases.[53] NE is a proteolytic enzyme that has the ability to degrade growth factors and cytokines and may be involved in regulating the inflammatory response. It has also been shown to degrade epithelial and endothelial cadherins, proteins that are major components of the adherens junctions holding cells together; cadherin destruction may predispose to alveolar flooding. Despite its potential to cause unwanted tissue damage, NE is likely crucial to host defense. In NE-deficient mice, administration of intraperitoneal *Klebsiella pneumoniae* causes 100% mortality within 48 hours compared to only 50% mortality in normal mice.[71] However, NE-deficient mice are paradoxically resistant to lethal doses of lipopolysaccharide. Furthermore, mice that lack both NE and another neutrophil protease (cathepsin G) are protected against alveolar damage induced by endotoxic shock.[72] These seemingly contradictory results suggest that NE, while important for a regulated inflammatory response, may nonetheless participate in inflammatory injury under certain circumstances. Unfortunately, a clinical trial of an NE inhibitor in ARDS was halted because preliminary analysis suggested lack of efficacy.[73]

Neutrophil extracellular traps (NETs) are web-like structures made of DNA, histones, and antimicrobial peptides (including myeloperoxidase, NE, cathepsin G, cathelicidin, gelatinase, and proteinase C) that are released by neutrophils and serve to trap and kill extracellular microbes.[74] One key benefit of NETs is their ability to eliminate large pathogens, such as fungal hyphae, that are too big to be phagocytosed. Some pathogens have evolved strategies to avoid NETs, including secretion of DNase enzymes that degrade the DNA structure of the NETs.[75] In sepsis, large numbers of NETs are released, which can lead to NET-associated endothelial damage as well as thrombus formation. Evidence from experimental animal models suggests NETs may play a role in the development of ARDS; in a mouse intratracheal

lipopolysaccharide model of ARDS, NET formation was identified in the lungs of experimental animals and was accompanied by severe destruction of lung structure.[76] When the animals were treated with DNase to degrade NETs, lung injury was attenuated. NET degradation also lowered IL-6 and TNF levels, suggesting that NETs promote inflammation. In a separate study, NETs were shown to be important in a mouse model of acid aspiration–induced ARDS.[77] Treatment with DNase resulted in improved lung function and survival, as did treatment with an NE inhibitor, alvestat. Finally, BAL fluid from patients with ARDS secondary to aspiration of gastric contents showed evidence of NETs, and the NET concentration correlated inversely with the degree of ARDS.[77] These studies suggest that NETs might be a target for future ARDS therapies.

Despite the evidence implicating neutrophils as a cause of lung injury, it is important to note that ARDS has been described in patients with profound neutropenia.[78,79] Indeed, it is possible that the neutrophil infiltration observed in non-neutropenic ARDS is adaptive (i.e., a physiologic response to a primary injury) rather than destructive. At present, little is known about the mechanism of neutrophil-independent ARDS, although some authors have postulated that alveolar macrophages, which are recovered in BAL fluid from these patients, might be a source of lung damage.[80,81] Understanding the mechanism of neutropenic ARDS must be a goal of future investigations.

INFLAMMATION AND COAGULATION

Inflammation and coagulation are interconnected processes, and both may play a role in the development of ARDS. The proinflammatory cytokine TNF-α, for example, causes an increase in thrombin and fibrin formation, stimulates tissue factor expression on endothelial cells, and inhibits fibrinolysis. Meanwhile, fibrin fragments are known to be chemotactic for neutrophils.[82] Activated protein C, an endogenous anticoagulant, has both direct and indirect anti-inflammatory effects. These include down-regulating IL-6 levels and attenuating neutrophil activation in sepsis.[83,84] Because abnormalities of coagulation are very common in sepsis, the most common cause of ARDS, investigators have wondered whether altered coagulation might be involved in the pathogenesis of ARDS. Animal studies have shown that anticoagulation can attenuate the severity of sepsis-induced lung injury.[85] However, human studies with activated protein C have been disappointing; a small randomized controlled trial of activated protein C in patients with ARDS was stopped prematurely due to lack of efficacy,[86] and activated protein C was subsequently pulled from the market after a large multicenter trial showed it provided no mortality benefit in patients with septic shock.[87]

Other molecular determinants of inflammation are still under investigation as therapeutic targets in ARDS. Some investigators have focused on improving the endogenous counterinflammatory response; in one study, the gene for heat shock protein 70 was ligated to an adenoviral promoter and the recombinant construct was administered into the lungs of rats with sepsis-induced ARDS. Increased heat shock protein 70 expression in the lung was associated with a significant reduction in pulmonary edema, inflammation, and even mortality.[88] Conversely, mice deficient in heat shock protein 70 showed increased mortality and lung injury.[89] The mechanisms underlying the beneficial effects of heat shock protein 70 are unclear, but may involve suppression of the proinflammatory transcription factor, nuclear factor-κB, and/or decreased lung parenchymal apoptosis.[90]

NA^+ AND WATER

Na^+ channels at the apical surface of alveolar epithelial cells mediate intracellular Na^+ uptake from the alveoli (see also Chapters 3 and 133). This creates an osmotic gradient and causes alveolar fluid to follow, thereby allowing for the clearance of pulmonary edema. Na^+/K^+ adenosine triphosphatases (ATPases) in the basolateral membrane of the epithelial cell exchange intracellular Na^+ for extracellular K^+, maintaining the intracellular sodium gradient. This process allows for the net removal of Na^+ and fluid from the alveolar space and can be accelerated (experimentally) by catecholamines.

Dysfunction of either the apical Na^+ channels or the basolateral Na^+/K^+ ATPases (or both) has been postulated to be involved in the pathogenesis of ARDS. For example, it is known that hypoxia decreases epithelial Na^+ reabsorption by impairing the expression of subunits of the epithelial Na^+ channel.[91] Hypoxia also decreases the activity of both the apical Na^+ channel[92] and the Na^+/K^+ ATPase.[93] In an animal model of hemorrhagic shock–induced lung injury, the normal up-regulation of alveolar fluid reabsorption in response to catecholamines was absent. This defect was attributed to an increase in nitric oxide in the lung, possibly due to an effect on β-adrenergic receptor signaling.[94] In a model of ventilator-induced lung injury in rats, overexpression of the Na^+/K^+ ATPase improved the clearance of lung liquid.[95] However, attempts to increase alveolar fluid clearance in a clinical setting (by using β2-adrenergic agonists) have so far been disappointing (see below).[96]

ANGIOPOIETINS

Angiopoietins are peptides involved in embryonic vascular development. Although four angiopoietins have been identified, *angiopoietin 1* (Ang1) and *angiopoietin 2* (Ang2) are the best described. Ang1 is expressed by numerous cell types, while Ang2 is expressed by endothelial cells. Both act on the Tie2 receptor tyrosine kinase that is found predominantly on endothelial cells and hematopoietic stem cells.[97] Ang1 is thought to enhance endothelial barrier integrity while Ang2 often acts as a competitive antagonist to Ang1. Several observations have generated interest in the role of these proteins in ARDS. First, elevated levels of Ang2 have been described in patients with sepsis and ARDS.[98,99] Moreover, administration of exogenous Ang2 to mice resulted in pulmonary vascular leak, an effect which could be reversed in vitro by Ang1.[100,101] Second, overexpression of Ang1 was protective against endotoxin-induced septic shock and lung injury in mice,[102] with a similar benefit observed using a synthetic agonist of the Tie2 receptor.[43,103] Third, genetic variants in Ang2 have been associated with higher plasma Ang2 levels and with increased risk of ARDS in patients of European ancestry.[99] While the mechanism of these effects remains uncertain, the data

emphasize the important role of the endothelium in the development of and recovery from ARDS and may suggest a role for Ang2 in the pathogenesis of ARDS. Agonists for Tie2 are likely to be tested in clinical trials within the next several years.

VENTILATOR-INDUCED LUNG INJURY

Although mechanical ventilation for ARDS may be lifesaving, there is abundant preclinical and clinical evidence that it can also be harmful.[104] While it was quickly recognized that excessive airway pressure could lead to barotrauma, including pneumothorax, pneumomediastinum, and subcutaneous emphysema, attention has since turned to more subtle but more common manifestations of lung injury. Mechanical ventilation can induce pulmonary edema by causing increases in both epithelial and endothelial permeability.[104] Indeed, 50 years ago, Webb and Tierney demonstrated that ventilation of rats with high peak airway pressures could lead to severe pulmonary edema[105] and, 30 years ago, investigators noted that mechanical ventilation could produce a form of increased-permeability pulmonary edema remarkably similar to ARDS.[106] Now, accumulated evidence suggests that mechanical ventilation may aggravate, if not induce, ARDS in some patients,[107] by a process called *ventilator-induced lung injury* (VILI) (see also Chapter 135).

An important mechanism of VILI is overdistension of lung units. Normal rats ventilated with high airway pressure and high tidal volumes developed increased permeability, whereas rats ventilated with the same end-inspiratory pressure but with smaller tidal volumes (achieved by strapping the chest wall to reduce the transpulmonary pressure) did not develop increased permeability.[104] Rats were also ventilated using low airway pressures with high tidal volumes (by applying negative inspiratory pressures at the chest wall). Among all these ventilatory strategies, the rats ventilated with high tidal volumes had the highest incidence of pulmonary edema, regardless of high or low airway pressures. In particular, the negative (low) pressure and high tidal volume group had the worst edema. These important observations, also confirmed in other species,[108] led to the appreciation that large tidal volumes are the most important determinant of ventilator-induced pulmonary edema. The term *volutrauma* was coined to recognize this fact.

The repetitive opening and closing of terminal lung units is also considered to be detrimental. The mechanism of this injury, termed *atelectrauma*,[109] is thought to be high shear stresses generated at the interface of collapsed and aerated tissue when a collapsed airway is reopened.[110] Theoretically, PEEP should minimize this injury by keeping the lung recruited and promoting greater lung homogeneity; however, any such advantage of PEEP would have to be balanced by the potential for greater overdistension of lung units (Fig. 134.4).

It is important to note that patients with ARDS may be especially vulnerable to VILI because of the heterogeneous nature of the parenchymal injury. Computed tomography scans of lungs from patients with ARDS show areas of normal-appearing lung interspersed with densely consolidated injured lung; as a consequence, there are marked regional differences in lung compliance.[111] A tidal volume designed to inflate an entire lung will preferentially inflate the "normal" lung, potentially leading to overdistention and volutrauma. Similarly, patients with ARDS may be more vulnerable to atelectrauma; although normal lungs can likely tolerate short periods of cyclic opening and closing of airways,[112] injured lungs, such as in ARDS, are exposed to higher shear stresses and would not be expected to fare as well.[113]

There has been a growing appreciation that VILI is not only a mechanical injury, but also reflects an underlying cellular and molecular response. The term *biotrauma* has been coined to describe the phenomenon by which mechanical ventilation causes local and systemic inflammation.[114,115] In animal studies, it has been shown that ventilation with either high tidal volumes or zero PEEP causes elevations in inflammatory cytokines in BAL fluid. Lungs ventilated with both high tidal volumes and zero PEEP showed a synergistic elevation in cytokine levels.[116] This inflammatory response to an injurious ventilation strategy has also been shown to extend beyond the lung. In an acid aspiration rat model of lung injury, a strategy of high tidal volumes and zero PEEP was associated with an increase in blood levels of various cytokines; this was not observed in animals ventilated with small tidal volumes or in those ventilated with large tidal volumes but higher PEEP levels (Video 134.1).[117]

Similar observations have been made in human patients with ARDS. In one study, patients were randomized to 36 hours of either *lung-protective* ventilation, in which the tidal volume was set to avoid over-distention and PEEP was set above the lower inflection point of the pressure-volume curve, or to a *control strategy* targeted to achieve normal arterial carbon dioxide levels and with PEEP set to achieve the greatest improvement in arterial oxygen saturation without worsening hemodynamics.[118] The first strategy aimed to avoid volutrauma and atelectrauma, whereas the second strategy aimed to optimize gas exchange. In the lung-protective group, BAL and plasma cytokine levels declined, but they rose significantly in the control group. Post hoc analyses revealed a higher number of ventilator-free days in the lung-protective group. The impact of ventilator strategy on the development of biotrauma can be remarkably quick. Within 1 hour after switching patients from a protective ventilatory strategy, Stuber and colleagues found an increase in proinflammatory cytokines in the lungs and plasma of patients with ARDS.[119]

As is discussed in the section on outcomes, patients with ARDS often die of systemic inflammatory response syndrome and multiorgan dysfunction. Thus, the observation that injurious mechanical ventilation can increase pulmonary and systemic cytokine levels is intriguing. These findings suggest that mechanical ventilation has the potential to injure the lungs and lead to a loss of compartmentalization of the pulmonary inflammatory response. Systemic dissemination of this response could be associated with the development of systemic inflammatory response syndrome and, potentially, with multisystem organ failure[120] (Fig. 134.5). One study has shown that injurious mechanical ventilation in rats not only causes elevated plasma and lung cytokine levels but also causes increased renal epithelial cell apoptosis and renal dysfunction.[121]

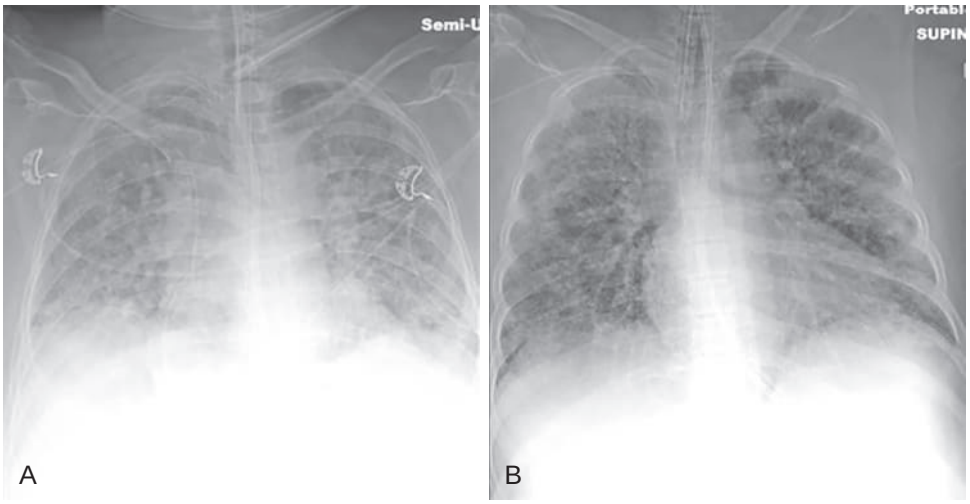

Figure 134.4 Chest radiograph showing the effects of *positive end-expiratory pressure* (PEEP). (A) Frontal chest radiograph in a patient with acute respiratory distress syndrome and a PEEP of 6 cm H_2O. (B) Frontal chest radiograph shortly after A with PEEP adjusted to 12 cm H_2O shows improved lung aeration.

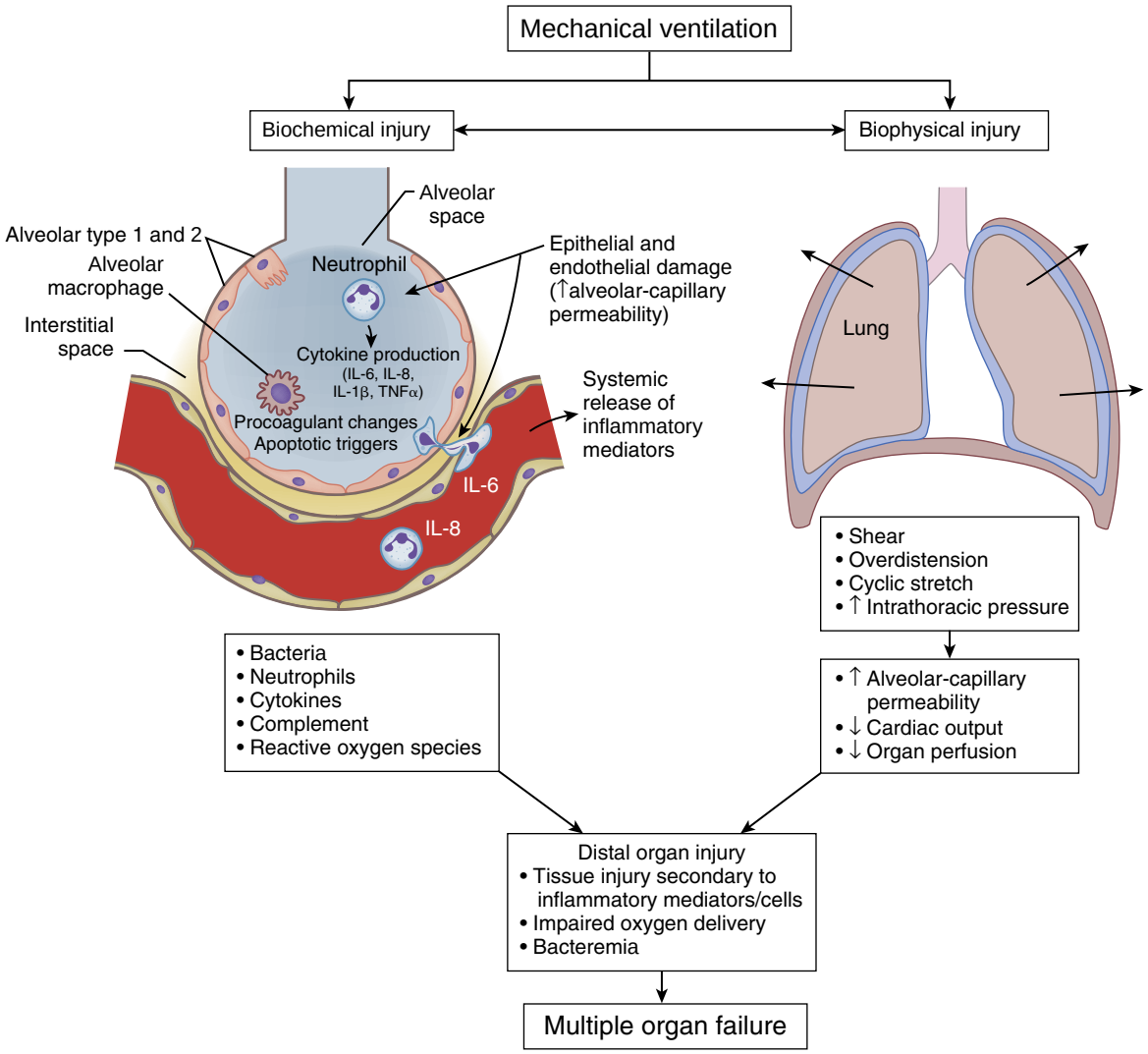

Figure 134.5 Potential mechanisms by which mechanical ventilation might cause or contribute to multiple organ failure. Both biochemical and biophysical effects of mechanical ventilation can lead to systemic inflammatory and toxic effects and, ultimately, to multiple organ failure. IL, Interleukin; TNF, tumor necrosis factor.

Finally, patients with ARDS often require a high inspired fraction of oxygen. The toxic effects of hyperoxia on the lung have been well described,[122] and the histologic appearance mirrors that of ARDS. Oxygen toxicity is thought to be mediated by both reactive oxygen and nitrogen species, which can damage tissues by a multitude of mechanisms.[123] Moreover, hyperoxia appears to worsen VILI.[124] Antioxidants have been considered as a potential therapeutic strategy for preventing and treating ARDS, although clinical trials have so far been disappointing.

GENETIC DETERMINANTS OF ACUTE LUNG INJURY

Although the heterogeneity of patients with ARDS may impede the identification of important genetic associations, genome-wide association studies in humans have suggested several candidate genes that increase the risk of ARDS. These include the *DARC* gene (Duffy antigen/receptor for chemokines) in African American patients,[125] the nuclear factor-κB gene in white patients,[126] and the *PPFIA1* (liprin alpha) gene in trauma patients.[127] Finally, genetic variants in *ANG2* were shown to be associated with plasma Ang2 levels as well as with the risk of developing ARDS in patients of European ancestry but not in patients of African ancestry.[99,128]

Another gene that has been implicated in ARDS susceptibility via genome-wide association studies is the *angiotensin converting enzyme (ACE)*. Both ACE and its homolog, *angiotensin converting enzyme-2* (ACE2), are metalloproteinases that play essential roles in the renin-angiotensin system. ACE promotes vasoconstriction by converting angiotensin I to angiotensin II, a powerful vasoconstrictor, while ACE2 counteracts the effects of ACE by degrading both angiotensin I and angiotensin II, thereby promoting vasodilation.[129] ACE and ACE2 are both expressed in the lung on alveolar epithelial type 2 cells. Although results have been somewhat mixed, a 2015 meta-analysis concluded that the absence of a 289 base pair *Alu* repeat in intron 16 of the *ACE* gene is a genetic risk factor for ARDS, particularly in white populations.[130–132] The presence of the deletion correlates with higher levels of circulating ACE in healthy human subjects.[133]

Animal studies support the hypothesis that the renin-angiotensin system plays a role in ARDS pathogenesis. Knockout of the *Ace* gene in mice improves outcomes from multiple types of experimental lung injury, while knockout of the *Ace2* gene worsens outcomes.[134] Moreover, injection of the ACE2 protein can protect mice against ARDS.[134]

Intriguingly, the *severe ARDS coronavirus* (SARS-CoV-1) was shown to bind to the ACE2 receptor.[135] In experimental models, both SARS-CoV-1 infection and overexpression of the SARS-CoV-1 spike protein, led to reduced ACE2 expression.[135] These findings suggest a mechanism whereby SARS-CoV-1 infection via the ACE2 receptor causes a reduction in ACE2 levels, thereby promoting ALI.

The novel *severe acute respiratory distress syndrome coronavirus 2* (SARS-CoV-2) also binds to the ACE2 receptor. Evidence for this interaction includes a high degree of structural homology between the SARS-CoV-1 and SARS-CoV-2 spike proteins, as well as high theoretical binding affinity of the SARS-CoV-2 spike protein for the ACE2 receptor.[136] In vitro, expression of ACE2 in human cells enabled SARS-CoV-2 infection, confirming that the virus can enter via this receptor.[137] Like SARS-CoV-1, SARS-CoV-2 causes severe lung injury in a subset of patients, which is often fatal.[138] As a result of these observations, infusion of ACE2 has been suggested as a potential therapeutic strategy in SARS-CoV-2–associated respiratory failure.[139] Whether a similar strategy would be efficacious in other forms of ARDS is an open question.

SUBPHENOTYPES OF ARDS

Latent class analysis is a statistical technique to identify unobserved groups within a dataset. In an effort to identify ARDS subsets that might be biologically different and respond differently to therapeutic interventions, latent class analysis was applied to data taken from two large clinical trials: the ARDSNet trial of high versus low tidal volume ventilation (ARMA) and the ARDSNet trial of high versus low positive-end expiratory pressures (ALVEOLI).[140] Baseline clinical data and biomarker levels for eight plasma proteins were used to define classes for the analysis. In both cohorts, a two-class model provided the optimal fit. Subphenotype 1 showed lower levels of the inflammatory markers IL-6, IL-8, soluble TNF receptor-1, and plasminogen activator inhibitor-1 along with lower heart rate, lower minute ventilation, higher blood pressure, and higher protein C levels. This was referred to as the *hypoinflammatory* phenotype.[140] Patients with phenotype 1 were less likely to be receiving vasopressors, were more likely to have trauma-associated ARDS, and were less likely to have sepsis-associated ARDS. Conversely, subphenotype 2 was described as a *hyperinflammatory* phenotype and was characterized by higher levels of inflammatory markers along with tachycardia, hypotension, higher minute ventilation, and lower levels of protein C. Subphenotype 2 was also characterized by greater vasopressor use, longer duration of mechanical ventilation, and higher mortality. The authors noted that plasma biomarker levels contributed more strongly to phenotype definitions than did clinical variables, suggesting that the phenotypes may be difficult to distinguish clinically.

When the results of the ALVEOLI trial were reanalyzed according to ARDS subphenotypes, the investigators noted differences in how the patients responded to PEEP. Patients belonging to subphenotype 1 responded favorably to low PEEP, with a 90-day mortality of 16% versus 24% for low PEEP versus high PEEP strategies.[140] Conversely, patients belonging to subphenotype 2 responded more favorably to high PEEP with a 90-day mortality of 51% versus 42%. A similar analysis was carried out using data from the Fluid and Catheter Treatment Trial of liberal versus conservative fluid management in ARDS.[141] Once again the presence of hypoinflammatory and hyperinflammatory ARDS subphenotypes was confirmed. When outcomes were reanalyzed according to subphenotypes, the investigators found a significant difference in their response to fluid strategy. Patients belonging to the hypoinflammatory subphenotype 1 responded favorably to a liberal fluid strategy (90-day mortality of 18% vs. 26%). Conversely, patients in the hyperinflammatory subphenotype 2 responded better to the conservative fluid strategy (90-day mortality rate of 50% vs. 40%).

Recently, latent class analysis was used to reanalyze the data from the HARP-2 trial, which compared simvastatin versus placebo in early ARDS.[142] The HARP-2 trial enrolled 540 adults at 40 hospitals in the United Kingdom and Ireland and did not find a difference in terms of ventilator-free days, organ-failure-free days, or 28-day mortality.[143] Latent class analysis confirmed the existence of two subphenotypes among the patients enrolled in HARP-2, a hypoinflammatory and a hyperinflammatory subphenotype. Patients belonging to the hyperinflammatory subphenotype 2 showed a positive response to simvastatin treatment, with significantly higher 28-day survival in patients receiving simvastatin compared to those receiving placebo.[142] Conversely, patients belonging to the hypoinflammatory subphenotype 1 did not show any significant response to simvastatin treatment.

Although they have yet to be prospectively tested, the concept of ARDS subphenotypes makes intuitive sense. In reanalyzing the ALVEOLI, Fluid and Catheter Treatment, and HARP-2 trials, we are left with the impression that ARDS subphenotypes are interacting differently with treatment options, resulting in confounding of study results and falsely negative clinical trials. The development of point-of-care testing strategies and prospective validation of subphenotypes and their response to therapy will be required to develop this concept into a workable clinical paradigm.

MORTALITY AND COMPLICATIONS OF ARDS

MORTALITY

The mortality rate for ARDS has fallen over the last 30 years, with a number of studies describing a decline from more than 60% to less than 40%.[144–146] The reasons for the improvement are unknown, although some have attributed it to the use of lung-protective ventilatory strategies and better supportive care in the ICU. Fewer data are available for pediatric populations; however, there does not appear to be a significant reduction in pediatric mortality rates over time. A recent meta-analysis reported a pooled hospital mortality rate of 35%,[147] similar to the mortality rate for adults, although significant disparities have been observed based on geographic location.

PREDICTORS OF POOR PROGNOSIS

Despite the importance of hypoxemia among the clinical manifestations of ARDS, the severity of hypoxemia early in ARDS does not appear to be a good predictor of death.[148] Pulmonary injury scoring systems such as the Lung Injury Score and the ARDS score have been shown to predict a prolonged (>2 weeks) requirement for intubation and ventilation,[149] while scoring systems that measure the overall severity of illness, such as the Simplified Acute Physiology Score, correlate better with survival.[150] The categories of mild, moderate, and severe ARDS, as defined by the Berlin definition, also show some correlation with duration of mechanical ventilation (5 days, 7 days, and 9 days, respectively) and mortality (27%, 32%, and 45%, respectively). However, both the Berlin and AECC definitions are poor predictors of mortality in ARDS, with *areas under the receiver operator curve* (AUROC) of only 0.58 and 0.54, respectively, representing a predictive capacity that is only slightly better than chance alone.[9]

The classic teaching is that patients with ARDS do not usually die of refractory hypoxemia, which may seem paradoxical given that hypoxemia is frequently the focus of resuscitative efforts. In fact, most patients with fatal ARDS die of sepsis and multiorgan failure.[151,152] The explanation for this apparent paradox is unknown, although it has been hypothesized that injurious mechanical ventilation may be involved (see earlier information on *biotrauma*).[120] As discussed earlier, ventilation using excessive tidal volumes has been shown to increase pulmonary and systemic cytokine levels and has been linked to renal dysfunction in an animal model.[153]

Cumulative data from multiple studies have suggested that the mortality rate from ARDS varies depending on the precipitant. The highest risk of death has consistently been reported in sepsis, whereas ARDS in the setting of major trauma has a much better prognosis.[154] In addition, it is known that chronic liver disease,[148] older age,[155] chronic alcoholism,[33] and nonpulmonary organ dysfunction[148] are all associated with higher mortality from ARDS. Other predictors of death have included a history of organ transplantation and HIV infection.[156] One study also described a higher mortality rate in African American patients relative to European-American patients and in men compared to women.[157]

As mentioned earlier, risk factors for ARDS have been classified as being direct or indirect (pulmonary or nonpulmonary) in origin. It remains unclear whether this distinction has prognostic importance. The ARDSNet investigators retrospectively analyzed data from their randomized study of low tidal volume ventilation versus traditional tidal volume ventilation. While confirming that the mortality rate for ARDS was highest in patients with sepsis and lowest in patients with trauma, there was no difference in mortality, days off mechanical ventilation, or the development of organ failure between patients with pulmonary versus nonpulmonary risk factors. In addition, there was no statistical evidence that the low tidal volume strategy was less efficacious in any particular subgroup.[154] A meta-analysis came to a similar conclusion,[35] and the recent Berlin definition of ARDS no longer includes pulmonary and nonpulmonary ARDS as distinct categories.

The development of pulmonary fibrosis is also thought to connote a worse prognosis in ARDS. In one study, 22 of 25 consecutive patients with ARDS underwent transbronchial biopsies of the most abnormal-appearing areas on the chest radiographs. The mortality rate in patients whose biopsies showed fibrosis, regardless of severity, was significantly higher than in patients whose biopsies showed no fibrosis.[158]

Lastly, there is extensive interest in the identification of biomarkers to predict mortality from ARDS.[140] Associations have been reported between elevated serum levels of the cytokines IL-6 and IL-8 and poor prognosis.[159] In patients with noninfectious ARDS, high baseline serum Ang2 levels were also shown to predict mortality whereas, in patients with infectious ARDS, mortality was

associated with increasing serum Ang2 from baseline to day 3, but not with baseline levels alone.[98] Biomarkers have also been combined with clinical predictors in an attempt to improve mortality prediction; one model combined the *Acute Physiology and Chronic Health Evaluation III* score,[160] a clinical prediction score applied at ICU admission, with five plasma biomarkers (intercellular adhesion molecule-1, von Willebrand factor, IL-8, soluble TNF receptor-1, and surfactant protein D). This model achieved moderate predictive accuracy, with an AUROC of 0.79. (An AUROC of 0.5 is no better than chance while an AUROC of 1.0 indicates perfect predictive accuracy.[161]) However, this strategy was only marginally better than Acute Physiology and Chronic Health Evaluation III score alone.

COMPLICATIONS OF ARDS

ARDS is complicated by *ventilator-associated pneumonia* (VAP) in 30–65% of cases. VAP usually presents more than 5 to 7 days after the onset of mechanical ventilation and is often preceded by colonization of the lower respiratory tract by potential pathogens.[162] The most frequent organisms include nonfermenting gram-negative rods, methicillin-resistant *Staphylococcus aureus*, and Enterobacteriaceae.[163] Although the development of VAP prolongs the duration of mechanical ventilation in ARDS, it does not appear to result in increased mortality.[162,164,165] Making a definitive diagnosis of VAP in patients with ARDS can be challenging because these patients already have radiographic opacities and not uncommonly have leukocytosis and fever. If diagnostic techniques such as BAL or protected specimen brushes are used, the yield is higher when lungs are sampled bilaterally and the patient is off antibiotics.[165,166] (See also Chapter 49.)

Another feared complication of ARDS is barotrauma (e.g., pneumothorax, pneumomediastinum, or subcutaneous emphysema; eFig. 134.1) due to the effect of positive-pressure ventilation in heterogeneous lungs with diminished compliance. Most patients with ARDS will be supine (rather than erect), so diagnosing a pneumothorax requires vigilance. The radiographic appearance of a pneumothorax can be subtle in the supine patient (e.g., air in the costophrenic angle, the deep sulcus sign), and lung ultrasound is increasingly being used to detect pneumothoraces.[167] Fortunately, data from prospective studies suggest that the incidence of barotrauma in ARDS is reasonably low (12–13%), likely due to the widespread adoption of lung-protective ventilation strategies.[168,169]

TREATMENT

SUPPORTIVE CARE

One of the first goals of therapy in ARDS is to treat the underlying cause. In particular, patients with sepsis may respond to aggressive source control, including antibiotics and, when appropriate, surgical débridement and drainage. In patients with ARDS and sepsis of unknown origin, both the lung and the abdomen should be considered and excluded as foci of infection.[151,152] Additional goals are the prevention of complications and the provision of supportive care (e.g., nutrition, ventilation) to allow the body time to heal.

HEMODYNAMIC MANAGEMENT

The optimal approach to hemodynamic management in ARDS has become less controversial since the ARDSNet study of liberal versus conservative fluid strategies.[170] Previously, it had been unclear whether clinicians should attempt to decrease pulmonary edema by diuresis at the expense of possible hypovolemia and inducing or aggravating shock, or to liberalize fluids to improve hemodynamics at the expense of increased pulmonary edema. The trial randomized 1000 patients with ARDS to one of two highly protocolized fluid strategies. Through the administration of fluids, diuretics, or vasoactive agents, the two protocols targeted either a lower intravascular pressure (conservative fluid strategy) or a higher intravascular pressure (liberal fluid strategy), as measured by a pulmonary artery or central venous catheter for 7 days. Patients randomized to the lower pressure/conservative fluid strategy had significant improvements in oxygenation and more ventilator-free and ICU-free days than the patients in the higher pressure/liberal strategy group. Importantly, patients in the conservative arm did not have a higher incidence of dialysis or shock than those in the liberal arm; in addition, mortality rates in the two arms were similar. Thus the results of this study suggest that conservative administration of fluids is safe and beneficial to patients with ARDS.

One caveat is that the ARDSNet study used a very complex algorithm for fluid administration. A simplified protocol has since been proposed but has not been validated.[171] In the meantime, we recommend that clinicians manage fluids conservatively in patients who are not in shock, taking care to avoid overdiuresis and hypovolemia. Numerous clinical trials have demonstrated that, for most patients, the information from a pulmonary artery catheter does not improve outcome.[11] For this reason, we do not recommend the routine use of these catheters in patients with ARDS.

Which fluid to use in patients with ARDS remains an open question, with only a few studies focusing on the ARDS population. On a theoretical basis, the use of albumin is appealing because it would increase intravascular oncotic pressure and predispose to less pulmonary edema. A small placebo-controlled study in ARDS demonstrated that a regimen of albumin and furosemide infusions over 5 days caused a substantial and statistically significant improvement in oxygenation accompanied by a decrease in heart rate.[172] However, most of the enrolled patients had ARDS secondary to trauma, and less than 5% had ARDS secondary to sepsis. There were no differences in important clinical outcomes (e.g., mortality), although the study was underpowered to detect these outcomes.[172] A follow-up study established that the beneficial effect on oxygenation was due to the albumin, not the furosemide,[173] and a meta-analysis concluded that there was evidence for a beneficial effect on oxygenation in ARDS but not for mortality.[174] Although a large clinical trial of ICU patients concluded that albumin was as safe as crystalloid,[175] the study did not specifically enroll patients with ARDS and only looked

at short-term outcomes. It is also important to remember that, as a blood product, the administration of albumin is associated with a very small but finite risk of transmissible diseases. Thus, pending further trials, the role of albumin in the management of patients with ARDS remains unclear. Meanwhile, the use of starch-based colloids (i.e., pentastarch) has fallen out of favor because a trial demonstrated that they increased the incidence of renal failure in patients with severe sepsis.[176] Whether pentastarch has the same detrimental effect in patients with ARDS without severe sepsis is unknown.

With respect to crystalloid fluids, data from ARDS patients is lacking and optimal treatment strategies must therefore be inferred from studies of critically ill and septic patients. Studies have shown that the use of balanced crystalloids (i.e., lactated Ringer's solution or Plasma-Lyte-A), rather than normal saline, resulted in a decreased incidence of renal failure along with a slight improvement in mortality in critically ill patients[177] and septic patients.[178] Given these data, a strategy using balanced crystalloids in place of normal saline would seem most appropriate in the treatment of ARDS, particularly when associated with sepsis.

NUTRITION

It has been hypothesized that manipulating the patient's diet can favorably affect the immune system and improve the outcome of inflammatory diseases such as sepsis and ARDS. Such dietary strategies have involved supplementing enteral feedings with one or more of arginine, glutamine, omega-3 fatty acids, and antioxidants.

Two small randomized studies examined the effect of a commercial enteral formula containing eicosapentaenoic acid (an omega-3 fatty acid found in fish oil), gamma-linolenic acid, and antioxidants, compared to a control enteral formula, in patients with ARDS and suggested potential benefit with improved oxygenation, reduced inflammatory biomarkers in BAL fluid, decreased length of ICU stay, and reduced requirement for mechanical ventilation.[179,180] The control formula in these studies, however, contained a high amount of omega-6 fatty acids, which may be proinflammatory. Subsequent randomized trials comparing enteral fish oil to saline placebo, or twice daily supplementation with eicosapentaenoic acid, gamma-linolenic acid, and antioxidants compared with an equivalent volume of a standard feeding formula, found no differences in clinical or biologic outcomes between the intervention and control arms.[181,182] Supplementation with omega-3 fatty acids is thus not recommended as a therapy for ARDS.

Many other studies of modified enteral formulas (often called *immunonutrition*) have been conducted in less well-defined populations of critically ill patients, with conflicting results. Meta-analyses on the topic have highlighted the poor quality of the evidence and have suggested that the effect of immunonutrition varies depending on the group of patients being studied.[183,184] At this point, the role of immunonutrition in the management of ARDS remains unclear.

A related issue in this area has been how much enteral nutrition should be given. A randomized controlled trial found that the rate of enteral feeding (e.g., regular feeding rate versus a low "trophic rate" delivering one-third as many calories) does not affect short- or long-term outcomes of ARDS.[185–187]

PHARMACOTHERAPY

Attempts to develop pharmacologic therapies for ARDS have been frustrating and largely unsuccessful, with no pharmacotherapies that unequivocally reduce mortality from ARDS despite a multitude of randomized controlled trials of potential agents.[188] Despite showing effectiveness in vitro or in animal studies, most potential therapies have failed to reduce mortality or other important clinical outcomes in human clinical trials. Several agents improve oxygenation but do not affect mortality from ARDS. Post hoc analyses of subgroups from many of these studies suggest benefit, but prospective data are lacking.

Corticosteroids

Because of the presumed inflammatory pathophysiology underlying ARDS, multiple trials of high- and low-dose corticosteroids have been performed in ARDS. In some, the goal was prevention of ARDS in at-risk patients (e.g., patients with septic shock), while in others, the goal was to treat established ARDS. The typical high-dose regimen was methylprednisolone 30 mg/kg every 6 hours for 1 to 2 days. None of the trials using this high-dose treatment regimen showed any benefit,[189,190] and one showed a higher incidence of infection among patients who received steroids.[191] However, all of these studies were conducted prior to the widespread adoption of lung-protective ventilation, which clearly improved outcomes from ARDS.

In the absence of data from large clinical trials, a 2016 meta-analysis used individual patient data (n = 322) from four randomized controlled trials of ARDS patients to determine the effect of low-dose glucocorticoid treatment on time to liberation from mechanical ventilation.[192] The results suggested that low-dose methylprednisolone treatment shortened the time to liberation from mechanical ventilation and increased the likelihood of liberation from mechanical ventilation by day 28. They also showed a significant decrease in hospital mortality for patients randomized before day 14 of ARDS onset (20% vs. 39%). There was no association between steroid use and nosocomial infections. A follow-up meta-analysis incorporating the results of nine randomized controlled trials came to similar conclusions.[193] Based on these findings, the investigators recommended that low-dose methylprednisolone treatment be considered in the early stages of ARDS, followed by a prolonged taper over a total of 28 days to prevent rebound inflammation.[192,193] These recommendations were incorporated into 2017 guidelines from the Society of Critical Care Medicine and the European Society of Intensive Care Medicine.[194]

A 2020 multicenter randomized clinical trial from Spain also supports the use of steroids in ARDS. In this study, 277 patients with early ARDS were randomized to receive 10 days of intravenous dexamethasone (20 mg daily for five days followed by 10 mg daily for 5 days) or placebo. Both groups received lung-protective ventilation.[195] Results showed that patients receiving dexamethasone had significantly more ventilator-free days at day 28 (12.3 days vs. 7.5 days) and significantly lower mortality at day 60 (21% vs. 36%). Nosocomial infections were not significantly

different between the groups. This study is the strongest evidence to date in favor of steroid treatment for early ARDS. Further studies will be required to determine the exact dose and duration.

The use of steroids has also been contemplated later in the course of ARDS, during the fibroproliferative phase. A randomized placebo-controlled trial of 180 patients with ARDS of at least 7 days' duration was performed by ARDSNet.[196] Patients were randomized to placebo versus a single dose of 2 mg/kg methylprednisolone followed by 0.5 mg/kg every 6 hours for 14 days, then every 12 hours for 7 days, followed by a taper. Although the patients receiving steroids showed improvements in oxygenation as well as in the number of ventilator-free and shock-free days (during the first 28 days), there was no difference in 60-day mortality. A subgroup analysis revealed that patients who began receiving steroids more than 14 days after the onset of ARDS had significantly increased 60- and 180-day mortality rate. The utility of corticosteroids late in ARDS remains controversial, pending the results of further clinical trials.

Vasodilators

Prostaglandin E1 is a vasodilator that has been studied as a potential therapy for ARDS, based largely on its putative anti-inflammatory properties. In vitro and preclinical studies in animals have suggested that prostaglandin E1 given parenterally, especially when administered in a liposomal formulation, decreased neutrophil activation. Despite promising early data,[197] a large randomized, double-blind, multicenter trial of liposomal prostaglandin E1 found that there was no improvement in survival or in ventilator dependence although there was evidence of improved oxygenation.[198]

Prostacyclin is another vasodilator that, when administered by nebulization, acts selectively on the pulmonary vasculature. Because the aerosolized solution will tend to go to the most ventilated areas of lung, this should theoretically lead to selective vasodilation of the branches of the pulmonary artery supplying these areas, resulting in improved ventilation-perfusion matching and improved oxygenation.[199] Although prostacyclin has been used as rescue therapy for refractory hypoxemia and is well tolerated,[200] there are no large randomized studies or placebo-controlled studies of its use in ARDS.[201,202]

Nitric oxide (NO) is a highly reactive gas formed endogenously from the amino acid arginine by NO synthase. It stimulates cellular guanylate cyclase, leading to increased cyclic guanosine monophosphate levels. It acts as a potent vasodilator and, when given by inhalation, causes vasodilation of the pulmonary circulation. NO is inactivated in the bloodstream by combining with hemoglobin to form methemoglobin, which is rapidly metabolized and does not accumulate to levels that are thought to be toxic (i.e., serum methemoglobin levels < 5%). As a result, NO causes the most vasodilation in the areas of the lung that are best ventilated, thereby improving ventilation-perfusion matching.[203] In addition, NO has both anti- and proinflammatory properties, although their effects in the clinical setting are unclear.[204] NO can also react with oxygen and water to form toxic metabolites, such as nitrogen dioxide and nitrous and nitric acid. At concentrations of NO below 40 ppm, this problem is not usually clinically significant.

In the largest randomized double-blind, placebo-controlled study of NO in ARDS to date, more than 170 patients were randomized to different doses of NO (from 1.25 up to 80 ppm) or placebo.[205] Although 60% of patients had an improvement in oxygenation within 4 hours of NO administration, there was no difference in survival or in liberation from mechanical ventilation.[205] In addition, the initial improvement in oxygenation was not sustained over the course of study. There were few adverse effects of NO and, for patients who were administered less than 40 ppm, methemoglobin and NO_2 levels were the same as in the placebo group. The negative results of this study confirmed the findings from other smaller unblinded trials of NO in ARDS[206,207] and were supported by the results of a systematic review.[208] In another large randomized but unblinded study of NO in ARDS, a higher proportion of patients in the NO group required renal replacement therapy than in the control group.[209] A meta-analysis of trials using NO for ARDS concluded that, while NO caused initial improvement in oxygenation, it had no impact on survival and was associated with an increased risk of renal dysfunction.[210] We suggest that NO should not be used routinely in the treatment of patients with ARDS, other than perhaps as a rescue therapy for extreme life-threatening hypoxemia. In fact, a recent individual patient meta-analysis showed no mortality benefit to inhaled NO in patients with ARDS, regardless of the degree of hypoxemia.[211]

Surfactant

As discussed in the section on pathogenesis, abnormalities of surfactant have been described in ARDS. These include an increase in inactive forms, inactivation of surfactant by proteins that have leaked into the alveolar space, damage to alveolar epithelial type 2 cells (which produce surfactant), and destruction of surfactant constituents by the inflammatory process.[49] These changes, along with the efficacy of surfactant supplementation in the neonatal respiratory distress syndrome, led to the hypothesis that surfactant supplementation might be beneficial in ARDS. Data from animal studies and small case series were promising.[212]

Enthusiasm for surfactant was greatly dampened by the results of a large multicenter, randomized, blinded, placebo-controlled trial. In this study, investigators administered an aerosolized synthetic (protein-free) surfactant or saline placebo continuously for up to 5 days to patients with new-onset (<48 hours) sepsis-induced ARDS.[213] There was no physiologic or clinical benefit from the surfactant. Despite its methodological rigor, the study has been criticized because less than 5% of the administered dose of surfactant was thought to have reached the distal lung. In addition, the lack of surfactant proteins in the synthetic surfactant may have diminished its ability to reduce surface tension.[213]

Disappointing results were also reported from a phase I–II trial of 40 patients with new-onset ARDS who were randomized to a surfactant protein C–based preparation (given up to 4 times over 24 hours) or to no drug. The surfactant was administered through a catheter placed in the endotracheal tube. The drug had no effect on oxygenation or on ventilator-free days, which were the primary outcomes of the study. The authors reported a significant decrease in IL-6 levels in BAL fluid from patients who received the surfactant preparation, although it is unclear whether this was

a prespecified end point.[214] Finally, a phase III trial of the recombinant surfactant protein C–based preparation failed to show any improvement in oxygenation, ventilator-free days, or mortality.[215]

Only one trial, using calfactant (a natural surfactant) in pediatric patients with ARDS, has shown any mortality benefit[50]; whether this is due to the unique surfactant used in this study or to differences between the patients enrolled in this trial and in the negative trials (e.g., pediatric vs. adult) is unknown. Whether surfactant will prove to be useful in well-defined subgroups of patients with ARDS remains an open question.[45]

Antioxidants and Anti-Inflammatory Agents Other Than Steroids

Oxidative stress has long been postulated to be involved in the pathogenesis of ARDS.[123] In fact, lung injury due to hyperoxia is a commonly used model to study ARDS in animals. Reactive oxygen species form as a by-product of activation of neutrophils and macrophages; in addition, the requirement of many patients with ARDS for a high inspired fraction of oxygen may predispose to oxidative stress. Decreased levels of glutathione, a major endogenous scavenger of reactive oxygen species, have been observed in the alveolar fluid of patients with ARDS. Small clinical trials with *N*-acetyl cysteine and procysteine were promising.[216] Unfortunately, despite this promising start, larger clinical trials of antioxidants in ARDS have been disappointing. A multicenter trial of the antioxidant procysteine in ARDS showed no beneficial effect of the drug and was stopped early for lack of benefit.[51]

Other agents with putative anti-inflammatory effects have been tested in ARDS. These include ketoconazole, lisofylline, and (in patients with sepsis at risk for ARDS) the nonsteroidal anti-inflammatory drug ibuprofen. In separate, well-conducted, randomized, blinded controlled trials, none of these agents demonstrated benefit in ARDS.[217–219] A randomized controlled trial evaluated the effect of recombinant platelet-activating factor acetylhydrolase in preventing ARDS in patients with severe sepsis.[220] This trial of over 100 patients showed no reduction in the development of ARDS in patients who received the drug; however, the mortality rate was lower in patients receiving an intermediate dose of the study drug.[220] Other trials of anti-inflammatory therapies have been disappointing.[188,221] A recent study of the HMG-CoA reductase simvastatin also failed to show benefit in ARDS despite positive results in preclinical models.[143] However, a post hoc analysis subdividing patients according to ARDS subphenotypes showed that patients with the hyperinflammatory subphenotype 2 may have benefited.[142] Prospective studies will be required to confirm this finding.

Catecholamines

As discussed earlier in the section on ARDS pathogenesis, alveolar fluid clearance can be augmented by catecholamines. A small trial randomized 40 patients with ARDS to intravenous salbutamol or placebo for 7 days.[222] Patients receiving salbutamol had a decrease in extravascular lung water but a higher incidence of arrhythmia. A follow-up study was performed in almost 50 ICUs in the United Kingdom and enrolled over 300 patients with ARDS. However, the trial was halted early because of an increase in mortality in the group receiving intravenous salbutamol.[96] A similar-sized trial of aerosolized albuterol (given every 4 hours for up to 10 days) for ARDS found no benefit.[223] Thus routine use of β_2-agonists cannot be recommended in ARDS.

Mesenchymal Stem Cell Therapy

Mesenchymal stem cells (MSCs) are multipotent stromal cells usually from bone marrow but which can also be isolated from adipose tissue, cord blood, placenta, and pancreas.[224] Among their many advantages, MSCs have the capacity to self-renew in vitro while maintaining their multipotency, have minimal immunogenicity secondary to low expression of major histocompatibility antigens, and have an excellent safety profile. MSCs have multiple effects in vivo that may be beneficial in ARDS: they reduce inflammation, they restore endothelial integrity, they increase alveolar fluid clearance, they recruit regulatory T cells, and they stimulate alveolar macrophages to increase bacterial clearance. Many of these effects are mediated in a paracrine fashion through secretion of soluble factors, including lipoxin A4 and keratinocyte growth factor, as well as antimicrobial peptides such as cathelicidin. MSCs also release microvesicles that transfer cellular contents, including proteins, lipids, organelles, mRNAs, and micro-RNAs, to other cells. Studies have shown that microvesicles alone (without MSCs) can improve lung injury and survival in animal models of ARDS, a phenomenon dependent on the uptake of microvesicles by monocytes and alveolar epithelial cells.[225]

MSCs have shown beneficial effects in animal models of lung injury mediated by endotoxin, pneumonia, bleomycin, injurious ventilation, and hyperoxia.[226,227] Moreover, they can be administered either intravenously or intratracheally, with equal effect. In a sheep model of pneumonia-associated ARDS, treatment with intravenous human MSCs significantly improved oxygenation and reduced extravascular lung water at 24 hours.[228] Similarly, in an ex vivo human lung model of ARDS secondary to *Escherichia coli* pneumonia, treatment with MSCs improved alveolar fluid clearance, decreased inflammation (as measured by IL-1β and IL-8 levels), and reduced bacterial load.[229]

Phase II clinical trials of MSCs in ARDS are underway. A phase I trial enrolling nine patients with moderate to severe ARDS demonstrated that MSCs could be well tolerated.[230] Recently, the first phase IIa trial of MSCs in patients with moderate to severe ARDS was reported. The patients in the treatment group (n = 40) received a single dose of intravenous MSCs while the control group (n = 20) received placebo.[231] No adverse infusion-related events were reported. There was a trend towards higher mortality in the treatment group (30% vs. 15%; $P = 0.34$), but this may have been driven by higher baseline severity of illness. The treatment group did show a significant decrease in serum levels of Ang2, while levels of IL-6, IL-8, and protein C did not change. In addition, oxygenation index ([F_{IO_2} × mean airway pressure]/alveolar P_{O_2}) improved in the treatment group during the 48 hours following MSC infusion, suggesting beneficial effects on lung function. Planning is underway for a phase IIb trial to follow up on these results.

Discrepancies Between Studies in Animals and Humans

As discussed earlier, virtually all large-scale clinical trials of pharmacotherapy for ARDS have been negative despite promising and often exciting animal studies. There are a number of reasons why results from animal studies may not have been replicated in human clinical trials. First, in animal studies, the agent being investigated is often administered at the same time or shortly after the lung is injured (e.g., cecal ligation and perforation followed by administration of the test drug within a few hours). In contrast, the onset of lung injury in humans is much more difficult to define, and potential therapies are given many hours after the initial insult. Second, most proof of principle animal studies are of short duration and do not mimic the complicated clinical course of human ARDS. Third, experimental animals represent an essentially homogeneous group; in contrast, human patients have multiple comorbidities, multiple co-interventions, and are extraordinarily heterogeneous. Fourth, animal studies involve introduction of a uniform injury whereas, even in carefully selected subgroups, the injury in patients will differ in severity and duration. This heterogeneity makes it challenging to identify agents that may be of modest clinical benefit. Finally, as discussed earlier, the current definition of ARDS is problematic, and human studies may include many patients with markedly different pathophysiology/biology.

In spite of these challenges, multiple novel therapeutic strategies for ARDS have been proposed and may reach clinical testing in the coming years (Fig. 134.6). These include intravenous and intratracheal administration of MSCs and/or their products as well as therapies that target neutrophils, enhance alveolar fluid clearance by modulating sodium channels, and protect endothelial and epithelial integrity. The success of these strategies will depend, at least in part, on the ability to identify which patients are most likely to benefit.

MECHANICAL VENTILATION IN ARDS

Mechanical ventilation is life-saving and is the standard therapy for ARDS (see also Chapter 135). Ventilatory management of ARDS has undergone dramatic changes over the last 20 years, in large part due to increased usage of computed tomography to image the lungs as well as to advances in our understanding of VILI.

PRESSURE AND VOLUME LIMITATION

Mechanical ventilation of patients under anesthesia for surgery traditionally involved large tidal volumes of 10 to 15 mL/kg, with the goal of achieving normal arterial oxygenation and arterial pH. A similar approach to ventilating patients with ARDS was followed until the beginning of the 21st century. This emphasis on achieving normal physiologic parameters in patients with ARDS was understandable at the time, because ARDS was thought to involve the lungs diffusely and homogeneously based on plain radiography.[1] Chest computed tomography, however, demonstrated that the lungs of many patients with ARDS appear heterogeneous,[232] showing patchy opacities interspersed with more normal-appearing areas of lung. The heterogeneous distribution of injury in ARDS implies that positive pressure will preferentially inflate the more compliant (or normal) areas of

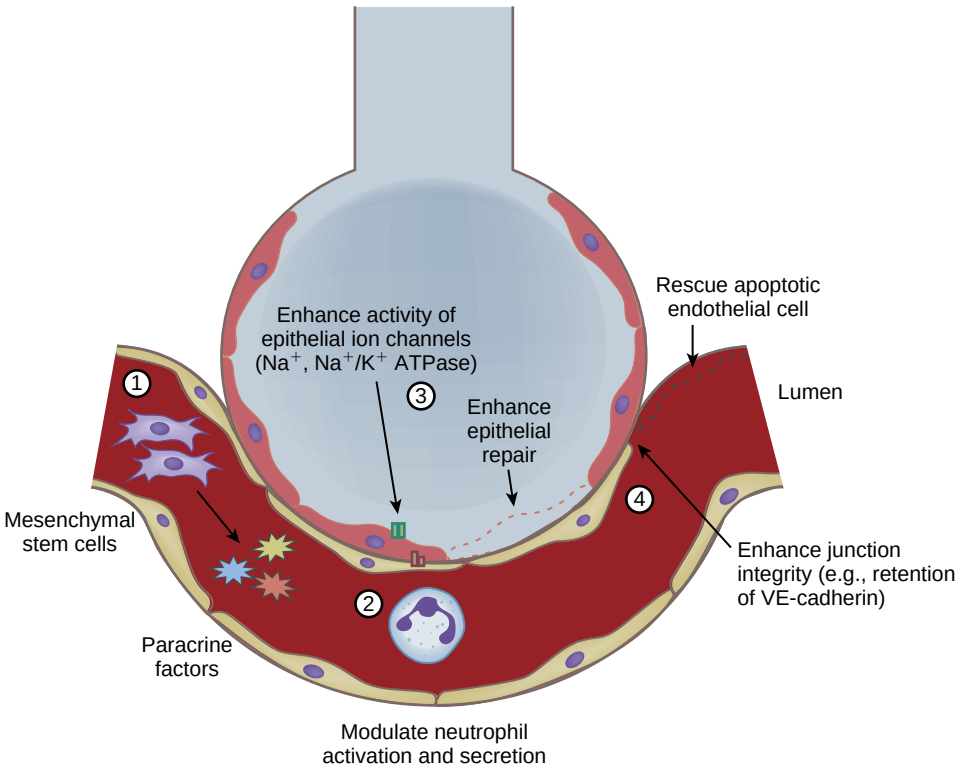

Figure 134.6 Schematic of potential novel therapeutic strategies for acute respiratory distress syndrome. *(1)* Mesenchymal stem cells can alleviate lung injury in animal models, perhaps by their paracrine effects. *(2)* Modulation of neutrophil recruitment, activation (e.g., degranulation), and apoptosis may prevent or lessen lung injury. *(3)* Alveolar fluid clearance may be enhanced by up-regulation of epithelial apical sodium channels. *(4)* The integrity of the lung endothelial barrier may be enhanced by preventing the internalization (and loss of function) of junctional proteins like vascular endothelial (VE)-cadherin and claudin-5 or by attenuating endothelial apoptosis.

lung. These regions are therefore at risk of overdistention and ventilator-associated lung injury. Mechanical ventilation with excessive tidal volumes, as discussed earlier, can cause pulmonary edema by provoking increased alveolar-capillary permeability, with remarkably similar histology to ARDS.

Despite the clear physiologic rationale and abundant experimental data to support pressure and volume limitation when ventilating patients with ARDS, it was not until the late 1990s that data from randomized clinical trials in humans began to accrue. Between 1998 and 2000, five randomized controlled trials of ventilation strategies in ARDS were published.[107,233–236] In all of these trials, patients were randomized to a strategy involving tightly regulated tidal volume or pressure limits versus a conventional ventilation strategy with higher tidal volume and pressure limits. Of the five studies, the largest was conducted by ARDSNet.[107] This landmark study randomized 861 patients to low tidal volumes (maximum 6 mL/kg of predicted body weight and plateau pressure up to 25 to 30 cm H_2O) versus traditional tidal volumes (with a plateau pressure below 50 cm H_2O). In both groups, respiratory acidosis was treated aggressively to achieve a pH of 7.3 to 7.45, and bicarbonate infusions were allowed for persistent acidosis. Preset combinations of PEEP and FIO_2 were used to target oxygen saturation of 88–95%, and sedation was used, as necessary, to reduce patient-ventilator dys-synchrony (Table 134.3).

The trial was stopped early because an interim analysis showed benefit to the small tidal volume strategy. The mortality rate was 39.8% in the traditional group compared to 31.0% in the small tidal volume group ($P = 0.007$). Patients in the small volume group were significantly more likely to be breathing without assistance on day 28; the patients in this group also had a higher number of ventilator-free days and organ failure–free days.

A key difference between the ARDSNet study and earlier studies was the use of predicted body weight to set the tidal volume instead of measured body weight. The rationale was that predicted body weight correlates better with lung size than measured body weight. The distinction is important because data from the ARDSNet study demonstrate that measured body weight was approximately 20% higher than predicted body weight. In other words, the tidal volumes used in other studies may have been higher than needed. Predicted body weight is calculated differently for men and women; the calculations for predicted body weight in kilograms are shown in the legend of Table 134.3.[107]

The ARDSNet study also adopted an aggressive approach to hypercarbia and acidemia, including the use of high respiratory rates, bicarbonate infusions, and loosening of ventilatory restrictions. As a result, hypercarbia and low pH were less marked in the treatment arm than in some other studies. This too may have contributed to lower mortality.

More recently, it has been proposed that limiting the driving pressure (plateau pressure – PEEP) may be more important than restricting tidal volume[237] in improving survival from ARDS, although this will require further study.

NEUROMUSCULAR BLOCKADE

Mechanical ventilation of patients with ARDS is often complicated by patient-ventilator dys-synchrony, which can worsen oxygenation and ventilation and exacerbate VILI.[238]

Table 134.3 Ventilation Protocol Used in the ARDSNet Study*

Parameter	Protocol
Mode of ventilation	Volume assist-control
Tidal volume	≤6 mL/kg predicted body weight†
Plateau pressure	≤30 cm H_2O
Frequency	6–35 breaths/min, titrated for pH 7.30–7.45
I:E ratio	1:1 to 1:3
Oxygenation goal	PaO_2 55–80 mm Hg, or SpO_2 88–95%
FIO_2/PEEP (cm H_2O) combinations allowed	0.3/5, 0.4/5, 0.4/8, 0.5/8, 0.5/10, 0.6/10, 0.7/10, 0.7/12, 0.7/14, 0.8/14, 0.9/14, 0.9/16, 0.9/18, 1.0/18, 1.0/20, 1.0/22, 1.0/24
Weaning	By pressure support, required when FIO_2/PEEP ≤0.4/8

*Ventilation with lower tidal volumes as compared with traditional tidal volumes for acute lung injury and the acute respiratory distress syndrome.

†When height is measured in inches, predicted body weight for men (in kg) = 50 + 2.3 (height [in] – 60), and predicted body weight for women (in kg) = 45.5 + 2.3 (height [in] – 60). When height is measured in centimeters, the equation for men is 50 + 0.91 (height – 152.4), and for women is 45.5 + 0.91 (height – 152.4).

FIO_2, fractional concentration of oxygen in inspired gas; I:E ratio, ratio of the duration of inspiration relative to expiration; PEEP, positive end-expiratory pressure; SpO_2, peripheral oxygen saturation.

From The Acute Respiratory Distress Syndrome Network. *N Engl J Med.* 2000;342(18):1301–1308.

Additionally, increased work of breathing may increase total body oxygen consumption.[239,240] To overcome these issues, clinicians often use sedative medications and, occasionally, neuromuscular blocking agents. However, neuromuscular blocking agents have unwanted side effects, including the need for heavy sedation and severe and prolonged muscle weakness.[241,242] Several recent studies have attempted to clarify the utility of neuromuscular blockade in ARDS.

In the ACURASYS trial, 300 patients with early (<48 hours), severe ARDS were randomized to a 48-hour infusion of cisatracurium with heavy sedation versus placebo with heavy sedation.[243] Both groups received lung-protective ventilation. The authors reported that, compared with placebo, cisatracurium resulted in a significant reduction in 90-day mortality (31.6% vs. 40.7%) as well as an improvement in secondary end points, including barotrauma and organ failure. There was no increase in ICU-acquired weakness. Recently, the ROSE trial enrolled 1006 patients with moderate to severe ARDS.[244] Once again, patients were randomized within 48 hours of ARDS onset. Patients in the treatment arm received 48 hours of intravenous cisatracurium with heavy sedation versus lighter sedation without routine neuromuscular blockade. A high PEEP strategy was used in both groups. The ROSE trial found no difference in the primary end point of 90-day mortality (42.5% vs. 42.8%). Moreover, there was no difference in barotrauma between the groups. A number of important differences may explain the divergent results of the ACURASYS and ROSE trials. The most important is the use of "light sedation" in the control arm of the ROSE study. Heavy sedation is associated with

poor outcomes in critically ill patients, including delayed extubation and increased mortality.[245,246] Another hypothesis is that heavy sedation without neuromuscular blockade, as used in the control group of the ACURASYS trial, may increase mortality by increasing "reverse triggering" (triggering of a diaphragmatic contraction by a ventilator-initiated breath).[247] This type of dys-synchrony is paradoxically increased in patients receiving deep sedation without paralysis and can increase VILI through breath stacking. Finally, prone positioning was more common in the treatment arm of the ACURASYS trial than in the placebo arm. Because prone positioning is associated with better outcomes in ARDS,[248] this may have helped reduce mortality in the treatment arm. In our view, neuromuscular blockade cannot be routinely recommended in patients with moderate to severe ARDS but may still benefit some patients, particularly those with ventilator dys-synchrony and/or high respiratory drive that could contribute to increased VILI.[247] Thus neuromuscular blocking agents are not currently recommended for routine use in severe ARDS.

THE ROLE OF PEEP AND RECRUITMENT MANEUVERS

As mentioned earlier, the first description of ARDS commented on the apparent utility of PEEP in improving oxygenation. From a theoretical standpoint, PEEP may be beneficial in avoiding damage from cyclic opening and closing of terminal lung units (atelectrauma; see "Etiology and Pathogenesis of ARDS" section), and allow for a reduction in tidal volume (and hence volutrauma). In addition, an improvement in oxygenation with PEEP may allow for lowering of the F_{IO_2}, thereby decreasing the risk of oxygen toxicity (see Fig. 134.4). On the other hand, if too high, PEEP can cause excessive end-inspiratory lung volume and volutrauma. PEEP can also have negative effects on cardiac output and blood pressure. The optimal level of PEEP in patients with ARDS has therefore been a source of controversy.[249–251]

In lung-protective ventilation, low tidal volumes and pressures can lead to progressive derecruitment of the lung, which can worsen hypoxemia and potentially aggravate atelectrauma. To counteract derecruitment, so-called recruitment maneuvers have been proposed. These maneuvers involve an increase in airway pressure, although the pressure to be applied and the duration have not been standardized. One example of a recruitment maneuver would be the application of 40 cm of H_2O of continuous positive airway pressure for 40 seconds. Similar to the problems with setting the PEEP, however, it is difficult to predict which patients will benefit from recruitment maneuvers and which will be harmed. Overdistention of well-perfused lung units could result in diversion of blood to poorly perfused alveoli, with consequent worsening of right-to-left shunt and hypoxemia.[252] Moreover, it might also contribute to lung injury.

A number of randomized controlled trials have addressed the issues of PEEP and recruitment maneuvers in the management of ARDS. The ARDSNet investigators randomized 549 patients with ARDS to lower or higher PEEP levels, according to preset combinations of PEEP and F_{IO_2}. The patients in the lower PEEP arm received the PEEP/F_{IO_2} levels used in the original ARDSNet trial of lung-protective ventilation (see earlier). The level of PEEP used in the higher arm varied with F_{IO_2} but was on average 5 cm H_2O higher than in the control arm. Recruitment maneuvers were initially used in the higher PEEP group but were discontinued after the first 80 patients because they were not effective.[253] After enrolling 549 of the planned 750 patients, the study was stopped because it reached a prespecified stopping rule for futility. Of note, the mortality rate in both arms was about 25%, significantly lower than had been reported in other ARDS trials.[254]

A second large trial randomized almost 1000 patients with ALI/ARDS to an *open lung* strategy versus the original ARDSNet trial ventilation protocol.[255] The open lung strategy consisted of pressure-control ventilation, recruitment maneuvers, and high PEEP (while keeping the $P_{plat} < 40$). Low tidal volumes were used in both groups. On average, on day 1 of the study, PEEP in the open lung arm was 16 cm H_2O compared to 10 cm H_2O in the control group. This trial also found no difference in mortality rates between the two groups (i.e., each at about 40%), although the open lung group had improvements in secondary end points related to hypoxemia.

A large French trial randomized 767 patients with ALI to PEEP of 5 to 9 cm H_2O versus PEEP maximized with P_{plat} less than 28 to 30.[256] On day 1 of the study, the mean PEEP in the control arm was 7 cm H_2O while the higher PEEP arm had an average of 15 cm H_2O. The study demonstrated no difference in mortality, but the higher PEEP arm had improved compliance, oxygenation, and a decreased duration of mechanical ventilation and organ failure.[256] A more recent study randomized patients with moderate to severe ARDS to a strategy of lung recruitment and PEEP adjusted to maximize respiratory system static compliance versus set PEEP levels according to the ARDSNet protocol from 2000[257]; the group that received recruitment maneuvers and titrated PEEP displayed increased 28-day all-cause mortality.

Finally, esophageal balloon monitoring (i.e., measuring the pressure in the esophagus) has been used to approximate pleural pressure, with the goal of determining the transpulmonary pressure (i.e., airway pressure minus the pleural pressure). The rationale is that the pleural pressure may be abnormally high due to comorbidities such as chest wall edema, obesity, or ascites, resulting in a low transpulmonary pressure. Under these conditions, it is possible that a higher level of PEEP could be safely applied without over-distension of the lung. However, a trial comparing this approach to preset levels of PEEP for a given F_{IO_2} showed no difference in clinically important outcomes, including death.[258]

Taken together, the data from these trials suggest that higher PEEP levels than those used in the original ARDSNet trial are safe and may improve oxygenation, but there is no evidence that they change mortality. Given the very strong animal data demonstrating the benefits of higher PEEP levels, it is somewhat of a puzzle why this is not true in the clinical context. One possibility is the yin-yang of PEEP: to the extent that PEEP recruits lung units, it may be beneficial; to the extent that it causes over-distension of lung units, it may be harmful.

The data also suggest that recruitment maneuvers in ARDS are purely supportive, with no improvement in clinically important outcomes. Many studies report a variable

and transient improvement in oxygenation after some form of recruitment,[253] which can be better maintained with a higher level of PEEP post-recruitment. It is also possible that the same degree of recruitment could be achieved by simply raising the level of PEEP.[259,260] If a recruitment maneuver is performed, the patient must be closely monitored for adverse effects on hemodynamics or oxygenation.

PERMISSIVE HYPERCAPNIA

The use of lower tidal volumes to avoid VILI often results in respiratory acidemia, an effect that has been termed *permissive hypercapnia*. The theoretical detrimental effects of hypercapnia include myocardial depression, increased pulmonary vascular resistance, and decreased renal blood flow. Perhaps the most clinically important adverse effect of hypercapnia is elevated intracranial pressure from increased cerebral blood flow. However, there are data suggesting that hypercapnia has protective effects, including attenuation of free radical–mediated lung injury and pulmonary inflammation[261,262]; other studies have reported an injurious effect on alveolar epithelial cells.[263]

Given the uncertainty about permissive hypercapnia, it is worth remembering that the original ARDSNet trial, which was the only large randomized controlled trial to show a reduction in mortality in ARDS, treated respiratory acidosis aggressively.[107] In the absence of other data, avoidance of hypercapnia where possible seems prudent.

MECHANICAL VENTILATION OF PATIENTS IN THE PRONE POSITION (PRONING)

Placing patients with ARDS in the prone position was described almost 30 years ago as a means of improving oxygenation. The mechanisms may be multiple, but the most important factor is probably the effect of proning on chest wall and lung compliance.[264] In the supine position, the anterior portions of the lungs are preferentially ventilated. Some of this is due to gravity, but the weight of the heart and the abdominal organs also contributes, as does the relatively low compliance of the posterior part of the rib cage. When a patient is placed in the prone position, the anterior chest wall is fixed (by the bed) and becomes less compliant, thus equalizing chest wall compliance anteriorly and posteriorly.[265] In addition, the volume of lung that is being compressed by the heart due to gravity is substantially decreased. The net result is more homogenous ventilation of the lung with improved V/Q matching (Fig. 134.7). Data from studies in dogs also suggest that ventilation in the prone position can attenuate the severity of VILI.[266]

A number of multicenter randomized controlled trials have examined the efficacy of proning in patients with ARDS. One study enrolled over 300 patients with ALI or ARDS and randomized them to conventional treatment using the supine position versus prone position for at least 6 hours daily for 10 days. The study found that oxygenation improved in approximately 70% of proning procedures, and that most of the improvement was evident within 1 hour. However, there was no difference in mortality between the groups. Retrospective analyses of the quartile of patients with the poorest oxygenation or highest acuity of illness showed a lower mortality at 10 days, but this difference did not persist beyond ICU discharge.[267] The study has been criticized for the short duration of the intervention and the fact that most patients spent the majority of the day supine.[268]

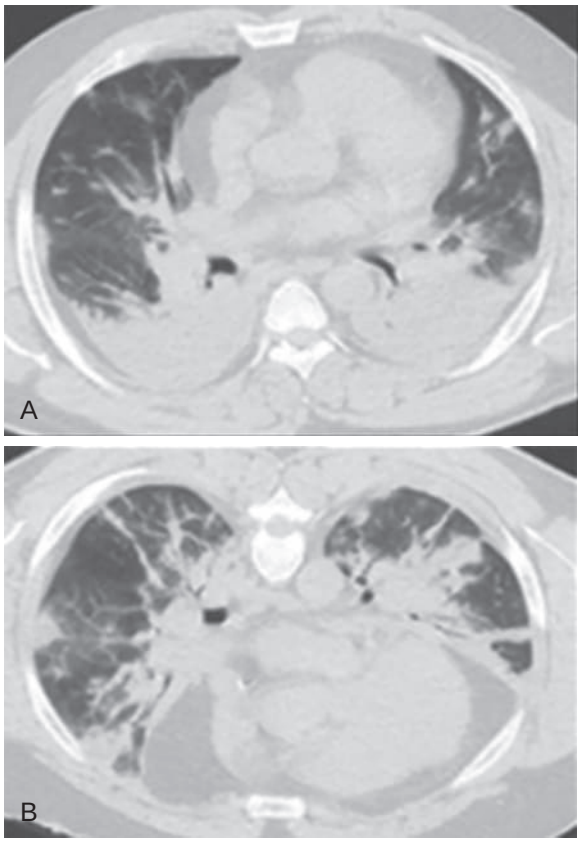

Figure 134.7 Computed tomography images of a patient with acute respiratory distress syndrome in supine and prone positions. Proning likely improves oxygenation principally by improving ventilation to the posterior portions of the lung, thereby improving ventilation/perfusion matching. Axial supine (A) and prone (B) chest computed tomography at the same positive end-expiratory pressure (5 cm H_2O) shows improved recruitment of nonaerated lung parenchyma in the prone compared to the supine position. (From Cornejo RA, Di-az JC, Tobar EA, et al. Effects of prone positioning on lung protection in patients with acute respiratory distress syndrome. *Am J Respir Crit Care Med*. 2013;188[4]:440-448.)

In 2013, the *Prone Positioning In Severe Acute ARDS* (PROSEVA) trial randomized over 400 patients with early (<36 hours) and severe ARDS (according to AECC criteria) to prolonged (>16 hours/day) proning or to standard supine positioning.[248] Patients in the proning group were placed in the prone position within the first hour after randomization and kept prone for at least 16 consecutive hours every day up to day 28. Most patients (≥80%) in both arms received neuromuscular blocking agents. Remarkably, the 28-day survival rate was 16% in the prone group and 33% in the supine group.

These results are very impressive and have led to widespread adoption of proning by intensivists. While proning was not associated with any complications in the PROSEVA trial, it is important to note that the study was conducted in centers with significant expertise in prone position ventilation, which requires much attention to detail. Lines and tubes are vulnerable to dislodgement during the process of rotating the patient, and sufficient staff must be on hand to assist with the move. Personnel should be ready for

immediate reintubation should the endotracheal tube be displaced during the maneuver. Patients who are placed in the prone position also have increased susceptibility to pressure sores on areas such as knees, anterior iliac spines, chin, and anterior shoulders, and exquisite care must be taken to ensure that no stray objects (e.g., syringes, electrocardiogram leads) are left under the patient because these will leave impressions and even scars on the body. An unstable spinal injury is an absolute contraindication to proning. In addition, in the event that CPR is required, the patient will have to be returned to the supine position emergently. Finally, the PROSEVA trial, had a number of important exclusion criteria, including elevated intracranial pressure, massive hemoptysis, recent tracheal or facial surgery, and a low (<65 mm Hg) mean arterial pressure.

VOLUME-CONTROL VERSUS PRESSURE-CONTROL VENTILATION

The volume and pressure-limited protocol used in the ARDSNet study used volume-assist control as the mode of ventilation. The Lung Open Ventilation study (described earlier) demonstrated that pressure-control ventilation could be used with equivalent outcomes.[255] Other studies that have examined this issue have also found little difference in physiologic parameters or outcome between the two modes of ventilation.[269,270]

HIGH-FREQUENCY JET VENTILATION AND HIGH-FREQUENCY OSCILLATION

In high-frequency jet ventilation, a small-gauge catheter is used to introduce gas under high pressure into the endotracheal tube. The high velocity of the gas entrains additional oxygen and humidified air from side ports in the system. This form of mechanical ventilation achieves a tidal volume of 2 to 5 ml/kg and involves frequencies of 100 to 200 breaths/min.[271] Exhalation is passive, secondary to lung and chest wall recoil. There is little evidence that high-frequency jet ventilation is superior to conventional mechanical ventilation for ARDS. A 1983 randomized trial of over 300 patients with respiratory failure compared conventional ventilation (using volume-cycled ventilation) to high-frequency jet ventilation. Although high-frequency jet ventilation was able to maintain oxygenation and ventilation with lower peak inspiratory pressures than with conventional ventilation, it did not offer any clinical benefit over conventional ventilation.[272]

In *high-frequency oscillatory* (HFO) ventilation, lung recruitment is maintained using a constant mean airway pressure, generated by an inspiratory bias flow and limitation of gas outflow from the circuit. Ventilation is achieved through rapid (e.g., 5 Hz) oscillations of a piston or diaphragm creating peak and trough pressures around the set mean airway pressure. The tidal volumes achieved through HFO are small, on the order of 1 to 5 mL/kg. In theory, HFO seems ideally suited for avoiding VILI; atelectrauma is minimized because of the relatively high mean airway pressure, which, along with small tidal volumes, limits derecruitment of the lung. Volutrauma is also minimized because the small tidal volumes limit end-inspiratory stretch.[273] Recruitment maneuvers (e.g., application of continuous positive airway pressure for approximately 30 to 40 seconds) should be applied after each time the patient is disconnected from the ventilator (e.g., open suctioning), because loss of pressure from the circuit upon disconnection will lead to portions of the lung becoming derecruited.

In an early randomized trial of HFO in adults, 148 patients with ARDS were randomized to conventional ventilation using pressure-control mode versus HFO.[274] Ventilatory parameters for both the conventional group and the HFO group were adjusted to achieve adequate oxygenation at a minimum F_{IO_2} (i.e., 88% at F_{IO_2} ≤0.60), as well as an arterial pH greater than 7.15. Because the study was begun before the publication of the ARDSNet trial on tidal volume limitation, the conventional ventilation arm targeted tidal volumes of 6 to 10 mL/kg. The trial was not powered to detect a mortality difference, and there was no significant difference in 30- or 90-day mortality or in any other outcome. In a retrospective analysis of predictors of mortality, being on conventional ventilation for more than 5 days correlated with a poor outcome.[274]

More recently, two large randomized trials of HFO compared to conventional lung-protective ventilation were published and showed no benefit in terms of survival or the duration of mechanical ventilation.[275,276] Indeed, one of the studies suggested that HFO might be harmful due to the amount of sedation required or due to its effects on hemodynamics. Because of these findings, the routine use of HFO for ARDS cannot be recommended.

LIQUID VENTILATION

Liquid ventilation relies on the oxygen and carbon dioxide–carrying capacity of organic liquids such as perfluorocarbons. These are modified hydrocarbons in which hydrogen atoms are replaced with fluorine, generating inert liquids that are nontoxic and minimally absorbed through the respiratory epithelium. The most widely studied perfluorocarbon, perflubron (perfluorooctyl bromide), can dissolve about 17 times more O_2 than saline solution and almost 4 times more carbon dioxide.[277] Total liquid ventilation is a technique in which the lungs are completely filled with liquid and an extracorporeal exchanger is used to add O_2 and remove carbon dioxide from the liquid. Partial liquid ventilation, which is much easier to use clinically, involves partially filling the lung with liquid and then using a traditional ventilator to deliver gas tidal volumes.[278]

The theoretical benefits of liquid ventilation stem from improved lung recruitment due to the lower surface tension of the perfluorocarbons and because the liquid tends to distribute to the dependent regions of the lung. Clearance of secretions (due to their displacement by the liquid) is also improved. Anti-inflammatory effects of perflubron have been described, although the clinical relevance of these effects is not well understood. To date, two randomized controlled trials of partial liquid ventilation in adults with ARDS have been published.[279,280] The first, published in 2002, randomized 90 patients with ARDS to partial liquid ventilation with perflubron or to conventional mechanical ventilation. Neither of the two ventilation strategies was protocolized, and the inclusion and exclusion criteria were modified slightly during the course of the study. No significant differences were identified in the number of

ventilator-free days (the primary outcome) or in any other prespecified outcome.[279] In 2006, a multicenter randomized trial of partial liquid ventilation with perfluorocarbon compared with conventional mechanical ventilation (tidal volume 10 mL/kg) enrolled over 300 patients with ARDS. The study found a trend towards higher mortality in the group receiving perfluorocarbon as well as a higher incidence of barotrauma, hypoxia, and hypotension.[280] Based on these data, partial liquid ventilation cannot be recommended for patients with ARDS.

SUMMARY

The modern approach to mechanical ventilation of patients with ARDS is premised on two principles: first, that the lung injury of ARDS affects the lung heterogeneously, and second, that mechanical ventilation itself can cause ALI. Until new data emerge, the lung-protective ventilation strategy adopted by the ARDSNet study[107] is the standard of care due to its beneficial effects on short-term and long-term outcomes.[281] Plateau pressure should be maintained less than 30 cm H_2O, and tidal volume should be limited to 6 mL/kg predicted body weight, when possible. The prone position should be considered in patients with a ratio of partial pressure of oxygen to fraction of inspired oxygen less than approximately 150 mm Hg in those centers that have expertise in proning patients. Given the dangers inherent to proning, it should be performed with caution and in accordance with published protocols.

The optimal level of PEEP in ARDS remains unclear, although randomized trial data indicate that using higher PEEP levels than the original ARDSNet study is safe and may improve oxygenation in patients with severe ARDS. We favor high levels of PEEP in order to prevent atelectrauma, reduce F_{IO_2}, and prevent hyperoxic lung injury in patients with severe hypoxemia (i.e., ratio of partial pressure of oxygen to fraction of inspired oxygen less than approximately 150 mm Hg), so long as the high PEEP does not depress the patient's hemodynamic status. We do not recommend the routine use of recruitment maneuvers. We use the lowest possible F_{IO_2} that maintains oxygen saturation above 90%, and empirically adopt a target F_{IO_2} of less than 0.6.

EXTRACORPOREAL MEMBRANE OXYGENATION

Extracorporeal membrane oxygenation (ECMO), also referred to as extracorporeal life support or extracorporeal lung assist, refers to the process by which the patient's blood is circulated to an external machine providing oxygenation and/or carbon dioxide removal (see also Chapter 138).[282] In theory, ECMO can be used to oxygenate patients with ARDS while minimizing mechanical ventilation, thereby avoiding VILI and oxygen toxicity and allowing the lungs time to heal. There are multiple case reports of ECMO being used in adults with ARDS, and it is routinely used in neonates with severe respiratory failure. An early randomized controlled trial of ECMO in ARDS was completed in 1979 and did not show any benefit; however, the mortality rate was approximately 90% in both the ECMO and the control arm.[283] Subsequently, a variant of ECMO dedicated to carbon dioxide removal (extracorporeal carbon dioxide removal) was developed and showed promise in a case series when compared to a historical control group.[284] This was followed by a randomized controlled trial in the 1990s comparing pressure-controlled ventilation with extracorporeal carbon dioxide removal in ARDS that failed to show any improvement in survival.[285] This study illustrates the importance of using concurrent controls when assessing a novel therapy.

One of the principal complications of ECMO is bleeding; in an early randomized trial, patients on ECMO were transfused an average of 1.7 L of blood *per day*. More recent data, however, indicate that ECMO can be safely performed in specialized centers without this high rate of transfusion. In 2009, the CESAR trial randomized patients with severe respiratory failure to be transferred to an ECMO center versus to remain at their original center for conventional mechanical ventilation.[286] The majority of patients in each arm had "pneumonia" (≈60%) or "other ARDS" (≈30%). Out of the 90 patients transferred to an ECMO center, only 68 (76%) received ECMO, while 22 (24%) were managed with ongoing conventional mechanical ventilation. In this study, referral to an ECMO center conferred a statistically significant survival benefit (relative risk of death at 6 months, 0.69; confidence interval, 0.05 to 0.97) and also significantly improved survival without disability (63% vs. 47%). However, patients in the conventional ventilation arm were cared for in multiple hospitals, did not follow a standardized ventilation protocol, and had a mortality rate of 45%. By contrast, among patients referred to the ECMO center, 76% received ECMO and a significantly higher percentage of patients received lung-protective ventilation. Thus, it is unclear whether the improvement in survival was attributable to ECMO or to better care in a specialized center. Complications associated with ECMO were relatively rare; one patient died during transfer due to a technical failure while another patient had a complication during cannulation. Major bleeding was not a significant issue. A cohort study by the same authors investigating outcomes of ECMO in patients with ARDS secondary to H1N1 influenza also suggested lower mortality with ECMO compared with matched controls.[287]

In 2018, the EOLIA trial assigned 249 patients with severe ARDS to ECMO versus conventional mechanical ventilation (with the possibility of ECMO as a rescue therapy) and showed a nonsignificant difference in mortality (35% vs. 46%, $P = 0.09$); however, there was significant crossover from the control group to ECMO (28% of patients), and the study was stopped early due to reaching a prespecified futility boundary.[288] Although the investigators believed it was unethical to prohibit rescue therapy with ECMO, the high rate of crossover may have confounded the results.[288]

There is growing interest in using extracorporeal life support as an adjunctive therapy to maximize the benefits of lung-protective ventilation. The premise is that, even at the recommended tidal volume of 6 mL/kg, there may be over-distension and VILI. In this approach, tidal volumes of less than 6 mL/kg predicted body weight are used and the resultant respiratory acidosis is managed by extracorporeal removal of carbon dioxide.[289] Because of ongoing technological improvements reducing the requirement for anticoagulation and the invasiveness of the devices, this is likely to be a fertile area of research in coming years.[290,291]

LONG-TERM OUTCOMES

Early work on ARDS outcomes has evolved from an emphasis on pulmonary physiology to generic health-related quality of life to functional and neuropsychological outcomes and their contribution to medical complexity and cost. In the context of an aging population with its multiple attendant comorbidities, ARDS may no longer be evaluated in isolation but rather assessed in the context of increasing case complexity. This is the challenge for ARDS outcomes research going forward.

PHYSICAL OUTCOMES

Despite the profound derangement in oxygenation and respiratory system compliance characteristic of ARDS, it is striking that patients who survive often have normal to near-normal pulmonary function 6 to 12 months later. Lung volumes and flows are generally normal or slightly reduced at 6 to 12 months, while diffusion capacity may remain slightly reduced.[292,293] Follow-up chest radiographs are usually normal, with a minority showing subtle abnormalities, including pleural thickening or small cysts.[293] When damage is evident, one observes linear fibrotic changes in the nondependent lung zones consistent with VILI (see Fig. 134.2D).[294] These data may reflect a fundamental survivorship bias whereby those who do survive are able to do so because their lungs do not develop extensive fibrosis as part of the reparative process.

Regardless of this impressive physiologic and radiologic recovery, patients who survive ARDS continue to have important functional limitations and a decreased health-related quality of life for at least 5 years after their illness.[295,296] This physical disability may be attributable to both ARDS and its ICU management. In one parallel cohort study, patients with ARDS reported significantly greater decrements in health-related quality of life than patients with an equivalent severity of illness due to sepsis or trauma, particularly as related to physical function and pulmonary symptoms,[297] in spite of having normal or near-normal lung function at 1 year and 5 years post ICU stay.[293,298] In other patients, a persistent reduction in physical functional capacity, as measured by a 6-minute walk test with a parallel decrement in the physical role domain of the Short-Form-36 generic quality-of-life measure, has been observed and has been attributed to persistent muscle wasting and weakness. Risk is augmented by exposure to corticosteroids, ICU-acquired comorbidities, and poor resolution of lung injury and multiple organ dysfunction.[293,299–301] This combined wasting and weakness has been termed intensive care–acquired weakness, which is a consequence of a myosin depletion myopathy and/or axonopathy arising in isolation or together.[302] Injury is partially attributed to upregulation of the ubiquitin-proteasome pathway and proteolysis that begins within hours of critical illness[303] and persists for the first week.[304] Muscle repair is heterogeneous among patients, and the recovery of contractile force and muscle mass may also be discordant at long-term follow-up.[305] Even with disability, however, patients who survive an episode of ARDS do not appear to have an increased mortality compared to other ICU survivors with similar severity of illness.[297]

PSYCHOLOGICAL OUTCOMES

Hopkins and colleagues first described neurocognitive and mood disorder outcomes in survivors of ARDS. They noted significant decrements in attention, concentration, processing speed, memory, and executive function up to 2 years after ICU discharge.[306] Schelling first described posttraumatic stress disorder in ARDS patients and its association with decrements in mental health.[307] These seminal observations have informed other investigators' evaluations of neurocognitive dysfunction. Risk factors include hypoglycemia during the ICU stay,[308] hypoxemia and fluid resuscitation,[309] duration of delirium,[310] and premorbid functional status.[311] Mood disorders including major depressive episodes and debilitating anxiety disorders are prevalent.[312]

Key Points

- *Acute respiratory distress syndrome* (ARDS) is defined by acute hypoxemia, bilateral opacities on chest imaging, and the absence of left atrial hypertension.
- The pathogenesis of ARDS is not yet known, but increased permeability of the alveolar-capillary membrane due to neutrophilic infiltration of the lungs is thought to be an important factor in many patients.
- ARDS is a syndrome, not a specific diagnosis, and clinicians must search for an underlying cause in order to institute specific therapy.
- The mortality rate for ARDS has fallen since the 1980s and is now less than 40%.
- Most deaths in patients with ARDS are from multiorgan failure rather than hypoxia.
- Mechanical ventilation is life-saving but can also induce or aggravate lung injury when inappropriately applied.
- ARDS management consists of treating the underlying cause, lung-protective ventilation with target volumes of 6 mL/kg of predicted body weight and plateau pressures below 30 cm H_2O, prone positioning in more severe patients, conservative management of fluids, and excellent supportive care.
- No pharmacologic therapies have been shown to improve survival in ARDS.
- Extracorporeal life support may improve survival in appropriately selected patients with severe ARDS.
- Survivors of ARDS often suffer from a reduced quality of life and physical, cognitive, and mental health impairments.

Key Readings

Acute Respiratory Distress Syndrome Network, et al. Ventilation with lower tidal volumes as compared with traditional tidal volumes for acute lung injury and the acute respiratory distress syndrome. *N Engl J Med*. 2000;342:1301–1308.

ARDS Definition Task Force, et al. Acute respiratory distress syndrome: the Berlin definition. *J Am Med Assoc*. 2012;307:2526–2533.

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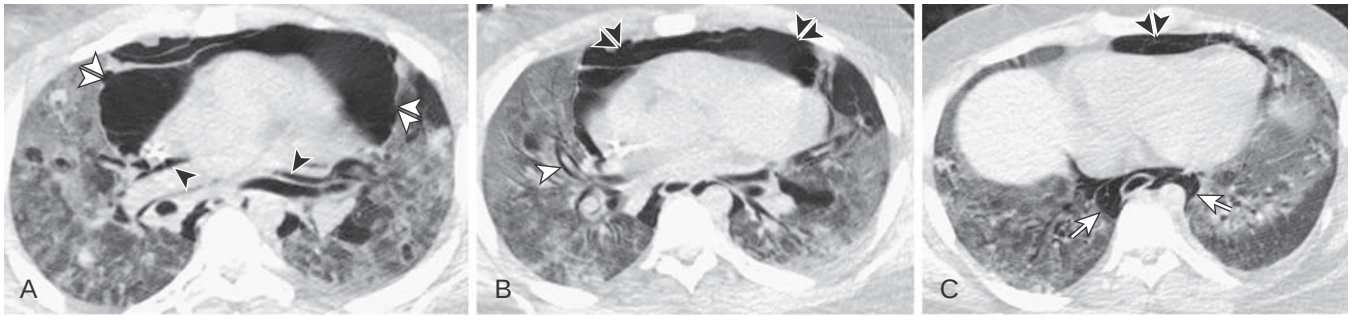
Complete reference list available at ExpertConsult.com.

eFIGURE IMAGE GALLERY



eFigure 134.1 Barotrauma during mechanical ventilation in hypoxemic respiratory failure. (A–C) Axial chest computed tomography scan in a patient with hypoxemic respiratory failure undergoing mechanical ventilation shows development of pneumomediastinum anteriorly *(double arrowheads)* and posteriorly (*arrows*, C) as well as interstitial emphysema (*single arrowheads*, A–B). (Courtesy Michael B. Gotway, MD.)

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135 MECHANICAL VENTILATION

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INTRODUCTION

Mechanical ventilation is the process of using a device such as a ventilator to support, partially or totally, the delivery of gas to the lungs. In this sense, the mechanical ventilator replaces or augments the function of the respiratory muscles. The desired effect of mechanical ventilation is to maintain adequate levels of P_{O_2} and P_{CO_2} in arterial blood while also unloading the inspiratory muscles. Although negative-pressure chambers or wraps might fulfill this definition, this chapter focuses on the use of devices that use positive airway pressures. Positive-pressure mechanical ventilation is used widely. In the United States, about 1 to 3 million patients annually are estimated to receive mechanical ventilatory support outside the operating room.[1]

POSITIVE-PRESSURE MECHANICAL VENTILATOR FUNCTION

BASIC FEATURES OF A POSITIVE-PRESSURE BREATH

Most modern ventilators utilize piston/bellows systems, turbines, or controllers of high-pressure sources to drive gas flow.[2,3] Tidal breaths are generated by this gas flow and can either be controlled entirely by the ventilator or be interactive with patient efforts. Pneumatic, electronic, or microprocessor systems provide for various breath types. In general, these can be classified by three variables: (1) the variable chosen to initiate the breath (breath trigger), (2) the variable chosen to regulate gas delivery during the breath (target variable), and (3) the variable selected to terminate the breath (cycle variable).[4,5] The *breath trigger* is generated by either a change in pressure or flow initiated by patient effort (assisted/supported breath) or by a set time (controlled breath). The *target variable* is chosen to regulate the breath delivery, generally either a set flow or a set inspiratory pressure. The *cycle variable* determines when the breath is terminated, which can either be a set volume, a set inspiratory time, or a set flow. A high-pressure cycle variable is usually also present to limit lung overdistention. Figure 135.1 uses this classification scheme to describe the five most common breath types available on the current generation of ventilators: *volume assist* (VA), *volume control* (VC), *pressure assist* (PA), *pressure control* (PC), and *pressure support* (PS).

DELIVERING VENTILATION: FLOW-TARGETED VERSUS PRESSURE-TARGETED BREATHS

There are two basic approaches to delivering positive-pressure breaths: flow targeting and pressure targeting (see Fig. 135.1).[2,4] With flow targeting (breaths 1 and 2 in Fig. 135.1), the clinician sets the inspiratory flow; *circuit pressure* (Pcir) is then the dependent variable. With pressure targeting (breaths 3 through 5 in Fig. 135.1), the clinician sets an inspiratory pressure target (with either time or flow as the cycling criterion); flow and volume are then the dependent variables (i.e., varying with the lung mechanics and patient effort). With a flow-targeted breath, changes in compliance, resistance, or patient effort will change Pcir but not flow; in contrast, with a pressure-targeted breath, similar changes in compliance, resistance, or effort will cause a change of *tidal volume* (V_T) but not Pcir (dashed lines in Fig. 135.1).

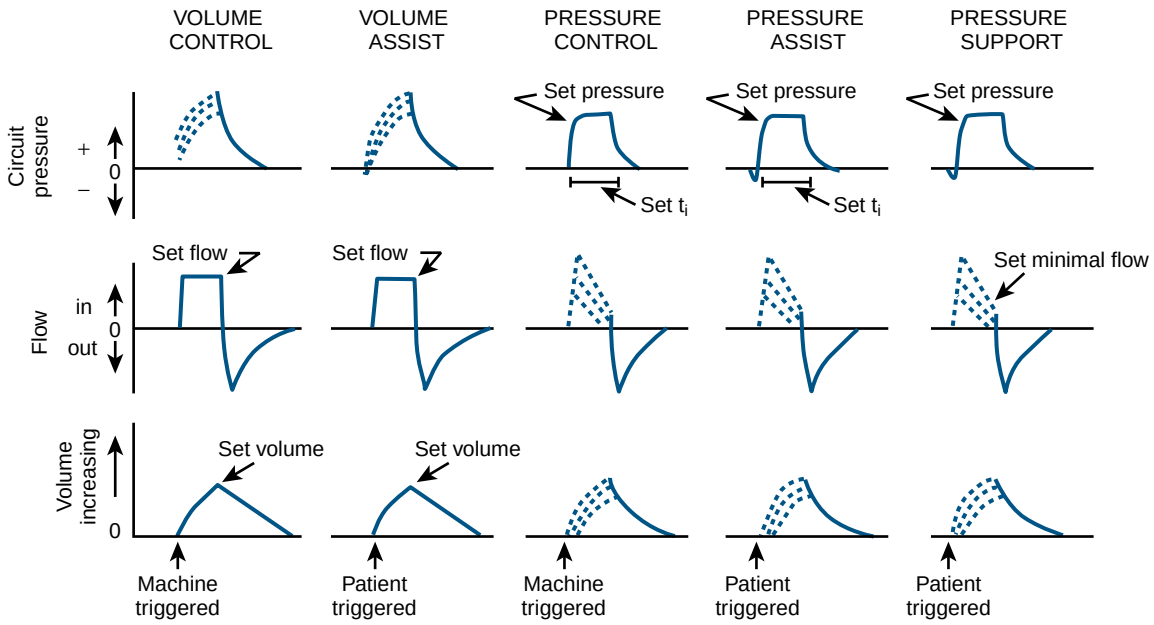

Figure 135.1 Circuit pressure, flow, and volume tracings over time depicting the five basic breaths available on most modern mechanical ventilators. Breaths are classified by the variables that determine the trigger (machine time or patient effort), target (t_i, set flow or set pressure), and cycle (set volume, set time, or set flow). The *solid lines* represent set or independent responses, and the *dashed lines* represent dependent responses. In all of these breaths, pressure is usually a "backup" cycle variable designed to terminate gas delivery if circuit pressure rises above an alarm limit.

Each strategy has advantages.[6] For flow-targeted breaths, a minimal VT is guaranteed. For pressure-targeted breaths, the rapid initial flow and subsequent adjustable flow of pressure targeting may enhance gas mixing and patient synchrony (see discussion on "Patient-Ventilator Interactions" later).

MODES OF VENTILATION

The simplest mode of mechanical ventilation is assist-control ventilation, which can provide either flow-targeted volume-cycled breaths (*volume assist-control ventilation* [VACV]) or pressure-targeted time-cycled breaths (*pressure assist-control ventilation* [PACV]). The ventilator is triggered to deliver a positive pressure breath at regular time intervals based on the set ventilation rate. If the patient's underlying respiratory rate exceeds this set rate, all breaths are patient-triggered breaths. If the patient's respiratory rate is below this guarantee, many, if not all, breaths will be time-triggered breaths (since ventilator respiratory cycle time is shorter than the respiratory cycle time of the patient's brainstem respiratory controller—the neural respiratory time).

Pressure support ventilation (PSV) is the most widely used mode of mechanical ventilation.[7] In PSV, all breaths are triggered by the patient. Once triggered, the ventilator delivers flow to meet a set inspiratory pressure. The ventilator cycles off once inspiratory flow declines to a threshold value set by the operator (usually 10–35% of peak inspiratory flow). By employing a flow threshold for cycling, PS allows patients greater control of the duration of inspiratory assistance (because inspiratory flow declines as patient effort declines) and can achieve greater synchrony with the patient's neural inspiratory time. Adjustments of the flow criteria of the PS cycle can be made to ensure appropriate synchrony of the cycle with the end of patient effort.[8] Waveforms should be carefully examined to confirm that the ventilator is not cycling prematurely (before patient effort is complete, leading to under-assistance) or late (after patient effort is complete, leading to over-assistance) (Fig. 135.2).[9] Proper breath synchrony is characterized by a comfortable patient, without evidence on the Pcir graph of continued inspiratory effort after cycling (premature cycling) or of expiratory efforts beginning during the inspiratory phase (delayed cycling).

A variety of other modes are available in clinical practice. *Synchronized intermittent mandatory ventilation* (SIMV) guarantees a set minimal number of positive-pressure breaths (delivered as VACV or PACV breaths) but, if the patient's respiratory rate exceeds this guarantee, the ventilator will allow unassisted breaths or flow-cycled PS breaths (SIMV + PS mode). SIMV has fallen out of favor based on evidence that it delays liberation from mechanical ventilation.[10]

Pressure-regulated volume control is a type of PACV mode that uses VT as a feedback control for continuously adjusting the pressure target.[11] Similarly, *volume support* (VS) uses patient-triggered, pressure-targeted, flow-cycled PS breaths where the pressure target is automatically adjusted to achieve a certain volume. Importantly, with both pressure-regulated volume control and VS breaths, an improvement in respiratory mechanics will result in a lower applied inspiratory pressure, whereas a worsening in respiratory mechanics will result in a higher applied inspiratory pressure. Similarly, increasing respiratory effort by the patient will result in a lower applied inspiratory pressure, whereas decreasing respiratory effort by the patient will result in a higher applied inspiratory pressure.

Adaptive support ventilation (ASV) is an assist-control, pressure-targeted, time-cycled mode of PACV that utilizes respiratory system mechanics to set the VT-frequency pattern.[12] The clinician sets only a desired minute ventilation and the patient's height (for estimating anatomic dead space).

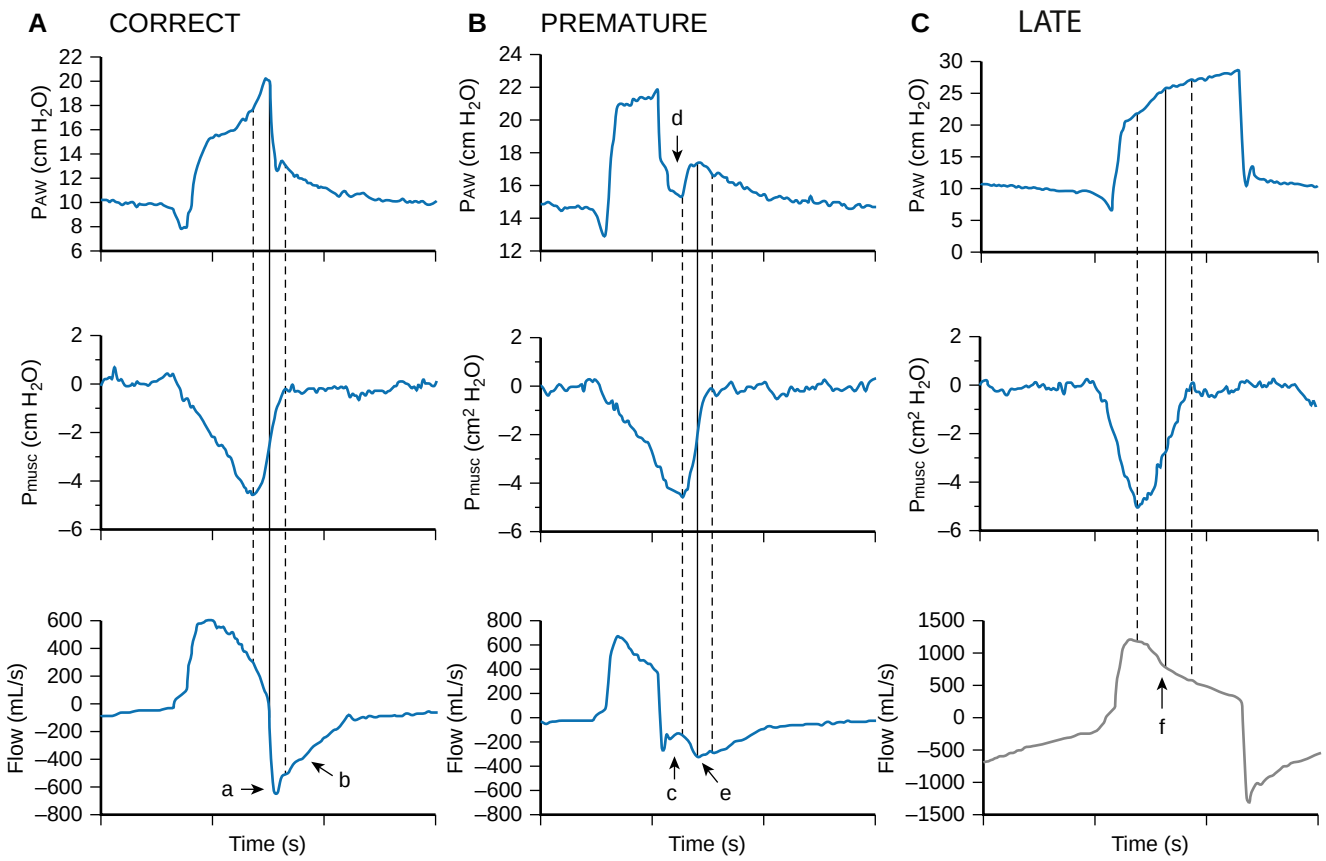

Figure 135.2 Evaluation of cycling off on pressure support ventilation by bedside waveform analysis. *Airway pressure* (PAW), *inspiratory muscle pressure* (P_{musc}), and flow are displayed where expiratory trigger sensitivity was set at 10% (A), 50% (B), and 25% (C) of cycling off. *Dashed lines* mark the beginning and end of inspiratory muscle relaxation; vertical continuous lines mark the optimal cycling off following the nadir in esophageal pressure, representing the completion of inspiratory effort. (A) During *correct* cycling off: fast decay of inspiratory flow switches directly into expiratory flow with immediate peak (*a*) followed by exponential decay (*b*). (B) During *premature* cycling off: patient inspiratory effort extended after cycling off breaks the expiratory flow, cutting off the expiratory peak (*c*) and causing a simultaneous dip in PAW (leading to under-assistance) (*d*); at the end of spontaneous inspiration, normal exponential decay of expiratory flow finally starts (*e*). (C) During *late* cycling off: sudden change from fast to slow exponential decay of inspiratory flow (*f*) marks the end of patient inspiratory effort and the beginning of a secondary phase of passive inflation (leading to over-assistance). (From Mojoli F, Iotti GA, Arnal JM, Braschi A. Is the ventilator switching from inspiration to expiration at the right time? Look at waveforms! *Intensive Care Med.* 2016;42:914–915.)

Using controlled breaths, ASV initially calculates resistance and compliance as well as the expiratory time constant (resistance × compliance). The ASV algorithm then adjusts the frequency-VT pattern to minimize ventilator work (integral of pressure over volume) and thus conceptually minimize applied forces to the lungs. The breathing pattern is also modulated by incorporating the expiratory time constant to avoid air trapping. As respiratory mechanics change, the frequency-VT pattern is automatically adjusted to maintain minimal ventilatory work. If patient efforts are triggering breaths with ASV, it behaves much like VS.

As noted above, mechanical ventilation is intended to unload the respiratory muscles; this means that greater ventilator support should be delivered when respiratory muscle effort is increased. However, none of the modes listed above delivers inspiratory pressure in proportion to patient effort. In pressure-targeted modes, the delivered ventilation is essentially independent of patient respiratory effort, while in flow-targeted modes, the delivered ventilation actually decreases when respiratory effort increases (since increased respiratory effort increases inspiratory flow). Two modes of ventilation have been introduced to address this deficiency (see discussions of "Patient-Ventilator Interactions" and "Innovations in Mechanical Ventilatory Support" later). *Proportional assist ventilation with load-adjustable gain factors* (PAV+) uses transient end-inspiratory occlusions to measure respiratory system elastance (the inverse of compliance) and resistance and estimates the pressure required to inflate the respiratory system from the equation of motion (below). The ventilator can then deliver a fixed proportion of this total inflation pressure. Accordingly, as higher patient efforts increase respiratory system inflation, delivered pressure from the ventilator also increases, reducing patient effort. *Neurally adjusted ventilatory assist* (NAVA) delivers pressure in proportion to patient effort, where patient effort is quantified from the diaphragm electrical activity signal, which is acquired from *electromyography* (EMG) electrodes affixed to an esophageal catheter; the electrodes detect electrical activation of the diaphragmatic crura, and the signal is transformed to deliver ventilator pressure in proportion to the magnitude of electrical activation. Similar to PAV+, as respiratory effort increases, ventilator pressures increase, unloading respiratory muscle effort.

OTHER ASPECTS OF VENTILATOR FUNCTION

Gas blenders mix air and O_2 to produce a *fractional concentration of oxygen in inspired gas* (FIO_2) ranging from 0.21 to

1.0. On newer systems, blenders are also available for other gases such as heliox (a mixture of helium and oxygen), nitric oxide, and anesthetic agents.

Positive end-expiratory pressure (PEEP), or positive airway pressure throughout expiration, can be generated to help maintain alveolar patency and improve *ventilation-perfusion* $\dot{V}/\dot{Q}$ matching (see "Physiologic Effects of Positive-Pressure Mechanical Ventilation" later).

With the upper airway bypassed by tracheal intubation, sufficient heat and moisture must be added to the inspired gas mixtures to avoid mucosal desiccation. *Active* humidifiers utilize external water sources and electrical power to adjust blended gas mixtures to near body conditions (tracheal temperature of >35°C, water content of >40 mg/L).[13] Heated wire circuits help facilitate this by preventing condensation and "rainout" in the ventilator tubing. *Passive* humidifiers use simple heat/moisture exchange devices in the ventilator circuit that reutilize heat and moisture trapped from expired gas. These disposable units can usually supply adequate heat and moisture (i.e., >30–33°C and water content of >28–32 mg/L) for many patients, particularly those receiving mechanical ventilation for only short periods of time.[13]

Therapeutic aerosols (e.g., bronchodilators, steroids, vasodilators, antibiotics) can be delivered through the ventilator circuitry[14] either by in-line nebulizers or by special adapters designed for metered-dose inhalers. The optimal site for aerosol delivery to maximize lung deposition appears to be in the inspiratory limb several centimeters proximal to the patient's Y-connector.[14] This location allows either nebulized medications or a metered-dose actuation to "charge" the inspiratory limb of the circuit during exhalation.

The circuit linking the ventilator to the patient usually consists of flexible tubing that often contains pressure or flow sensors, closed suctioning systems, and an exhalation valve. It is important to remember that, because this tubing has measurable compliance (2–4 mL/cm H_2O are representative values), applied inspiratory pressures may simply distend the circuitry rather than enter the patient's lungs when respiratory mechanics are severely impaired or airway opening pressure is high.[15]

PHYSIOLOGIC EFFECTS OF POSITIVE-PRESSURE MECHANICAL VENTILATION

VENTILATION AND RESPIRATORY SYSTEM MECHANICS

A firm grasp of respiratory physiology is essential to understand how mechanical ventilation is designed and how it achieves its intended goals. The pressure, flow, and volume required for ventilation depend on the mechanical characteristics of the patient's respiratory system and the efficiency of gas exchange. Knowledge of the physiology of ventilation (Chapter 10) and respiratory mechanics (Chapter 11) is essential to understand how the ventilator is applied to accomplish mechanical ventilation.

CO_2 Clearance: Alveolar Ventilation and the Equation of Motion

The primary mechanism of CO_2 clearance by conventional mechanical ventilation (similar to normal pulmonary function) is convection by bulk flow. The relationship between bulk flow obtained by the combination of patient respiratory effort and mechanical ventilation and the resulting pulmonary CO_2 clearance is given by the alveolar ventilation equation:

$$P_{aCO_2} = \frac{k}{\dot{V}_E\left(1-\frac{V_D}{V_T}\right)}\dot{V}_{CO_2}$$

where $\dot{V}_E$ is minute ventilation, $\dot{V}_{CO_2}$ is rate of CO_2 production, P_{aCO_2} is partial pressure of CO_2 in arterial blood, and V_D/V_T is dead space fraction. $\dot{V}_E$ needs to be adequate to eliminate $\dot{V}_{CO_2}$ in order to maintain a reasonable arterial P_{CO_2} (and pH).

Bulk flow (ventilation) is achieved by mechanical ventilation when pressure and flow are applied at the airway opening. These applied forces overcome respiratory system elastance (both lung and chest wall components), airway resistance, and respiratory system inertance (the resistance to a change in rate of flow) and lung tissue resistance to effect gas flow.[16,17] For simplicity, because inertance and tissue resistance are relatively small, they can be ignored yielding the simplified equation of motion:

$$P_{tot} = P_{mus} + P_{vent} = (E \times V_T) + (R \times \dot{V}) + PEEPi$$

where P_{tot} is the instantaneous total pressure required to inflate the respiratory system at any given point during the breath, given the V_T and inspiratory flow at that point; P_{vent} is the inspiratory pressure from the ventilator (peak pressure minus set end-expiratory pressure: $P_{peak} - PEEP$); P_{mus} is patient inspiratory muscle pressure generation (if present); $\dot{V}$ is the flow into the patient's lungs; R is the resistance of the circuit, artificial airway, and natural airways combined; E is the respiratory system elastance; and *PEEPi* is intrinsic PEEP. If there is PEEPi, it must be overcome by muscle and Pcir before flow and volume can be delivered; thus PEEPi will add to the inflationary pressure requirement (see later discussion).

In summary, the ventilator achieves adequate CO_2 removal by delivering sufficient pressure and flow to achieve adequate total bulk flow in and out of the lung. Increases in CO_2 production, dead space ventilation, or respiratory system resistance or elastance will increase the total pressure and flow required to achieve adequate ventilation. This pressure and flow must be applied bearing in mind not only CO_2 clearance but also the risks to the lung and their effects on respiratory muscle effort.

ALVEOLAR RECRUITMENT AND GAS EXCHANGE

Because of alveolar flooding, inflammatory exudates, and collapse, parenchymal lung injury leads to $\dot{V}/\dot{Q}$ mismatching and shunt.[18] Shunting and dead space volumes may be further exacerbated when high ventilatory pressures distend lung units that participate in ventilation, reducing blood flow to the ventilated lung. To mitigate the degree of end-expiratory lung collapse—with attendant increases in shunt and mechanical stress—the ventilator is set to maintain PEEP.

PEEP helps to recruit and maintain alveolar units open, providing several potential benefits. First, recruited alveoli improve $\dot{V}/\dot{Q}$ matching and gas exchange throughout the ventilatory cycle.[19] Second, as discussed in more detail later, alveoli that are patent throughout the ventilatory

cycle are not exposed to the risk of injury from the shear stress of repeated opening and closing.[20,21] Third, open alveoli with intact surfactant monolayers improve lung compliance.[22]

PEEP, however, can also be detrimental. Because the tidal breath is delivered on top of the baseline PEEP, end-inspiratory pressures are usually raised by the application of PEEP (although this increase may be less than the actual added PEEP because of improved compliance). This increase must be considered if the lung is at risk for regional overdistention (see "Ventilator-Induced Lung Injury" later). Moreover, since parenchymal lung injury is often quite heterogeneous, appropriate PEEP in one region may be suboptimal in another and excessive in yet another.[23–25] Optimizing PEEP is thus a balance between recruiting the recruitable alveoli in diseased regions without overdistending already recruited alveoli in healthier regions.

Another potential detrimental effect of PEEP is that it raises mean intrathoracic pressure, thereby compromising cardiac filling in susceptible patients (see "Positive-Pressure Ventilation and Cardiac Function" section later).

As described, the application of PEEP is designed to prevent derecruitment during exhalation.[19,23,26,27] Additional recruitment can sometimes be provided with the use of formal recruitment maneuvers or prolongation of inspiratory time.[28,29] Recruitment maneuvers can be performed using various methods, including sustained inflations (e.g., 30–40 cm H_2O) for up to 30 to 120 seconds, by transient elevations of the PEEP-V_T settings, and by single or multiple "sighs" that take the lung briefly to near total lung capacity.[28] Importantly, because recruitment maneuvers can have adverse hemodynamic consequences, close monitoring of the patient is mandatory during the maneuvers. Recruitment maneuvers provide initial alveolar recruitment only; maintenance of recruitment requires setting PEEP appropriately to prevent subsequent derecruitment.[28]

PEEPi and the Ventilatory Pattern

Intrinsic PEEP (PEEPi) is the positive end-expiratory alveolar pressure that arises because of inadequate expiration, caused by either inadequate expiratory time or airway collapse during expiration (or both). PEEPi increases with increased minute ventilation and decreased time for expiration (from either a decreased expiratory time fraction, or an increased respiratory system expiratory time constant).[30]

The development of PEEPi will have different effects on flow-targeted compared with pressure-targeted ventilation. In flow-targeted ventilation, the constant delivered flow and volume (and thus ΔPcir) in the setting of a rising PEEPi will increase both the peak pressure and the *plateau pressure* (Pplat). In contrast, in pressure-targeted ventilation, the set Pcir limit coupled with a rising PEEPi level will decrease ΔPcir and thus the delivered V_T (and minute ventilation). Importantly, this may help limit the buildup of PEEPi.

In the patient without respiratory effort, PEEPi can be recognized in two ways. First, when PEEPi is produced by an inadequate expiratory time, analysis of the flow graphic will show that expiratory flow has not returned to zero before the next breath is given. Second, PEEPi in alveoli with patent airways can be quantified during an expiratory hold maneuver that permits equilibration of the PEEPi with Pcir.[30]

In the patient with active respiratory effort, PEEPi can be assumed to be present if the expiratory flow has not reached zero before the next breath begins. However, the expiratory hold maneuver cannot be used to measure PEEPi in an actively breathing patient.

PATIENT-VENTILATOR INTERACTIONS

Given that the mechanical ventilator is intended to augment or replace the respiratory muscle pump, effective mechanical ventilation must interact properly with the patient's own respiratory efforts. Proper interaction entails that the ventilator delivers gas flow upon patient demand and ceases to do so when the patient's neural inspiratory cycle ends. Moreover, flow and pressure must be sufficient to unload the patient's work of breathing and relieve dyspnea. Excessive flow and pressure may impair the interaction and put the patient at risk of injury.

While some modes of ventilation are specifically designed to interact more effectively with the patient (e.g., partial-assist modes such as PSV, PAV+, and NAVA), patient respiratory effort may be present in any mode of ventilation, including assist-control modes.[31] Clinicians may incorrectly infer that changing from an assist-controlled mode to an assisted mode of ventilation will necessarily increase patient respiratory effort; in fact, patient respiratory effort may vary widely across all types of modes, whether controlled or partially assisted, and patient and ventilator may become dys-synchronous in any mode of ventilation. Consequently, both the patient's respiratory efforts as well as the ventilator's action require careful clinical assessment. Interactions take place during all three phases of breath delivery—breath triggering, flow delivery, and breath cycling—and are described in detail later in "Patient-Ventilator Dys-synchrony."

POSITIVE-PRESSURE VENTILATION AND CARDIAC FUNCTION

In addition to affecting ventilation and ventilation distribution, positive-pressure ventilation can also affect cardiovascular function.[32–34] In general, as mean intrathoracic pressure increases, right ventricular filling decreases and cardiac output/pulmonary perfusion consequently decreases. This is the rationale for using volume repletion to maintain cardiac output in the setting of high intrathoracic pressure. Of note, the effect of reduced cardiac filling on cardiac output may be partially counteracted by improvement in left ventricular function due to elevated intrathoracic pressure, which can reduce left ventricular afterload.[35] Importantly, in patients with left heart failure, the reduced cardiac filling and reduced left ventricular afterload effects of elevated intrathoracic pressure may improve cardiac function to the point that the removal of intrathoracic pressure may worsen cardiac function and thereby produce weaning failure.[36]

Intrathoracic pressures can also influence distribution of perfusion. The relationship of alveolar pressures to perfusion pressures in the three-zone West lung model helps explain this[37] (see Fig. 10.11). Specifically, the dependent lung is generally in a zone 3 (capillary distention) state. As intra-alveolar pressures rise, however, zone 2 and

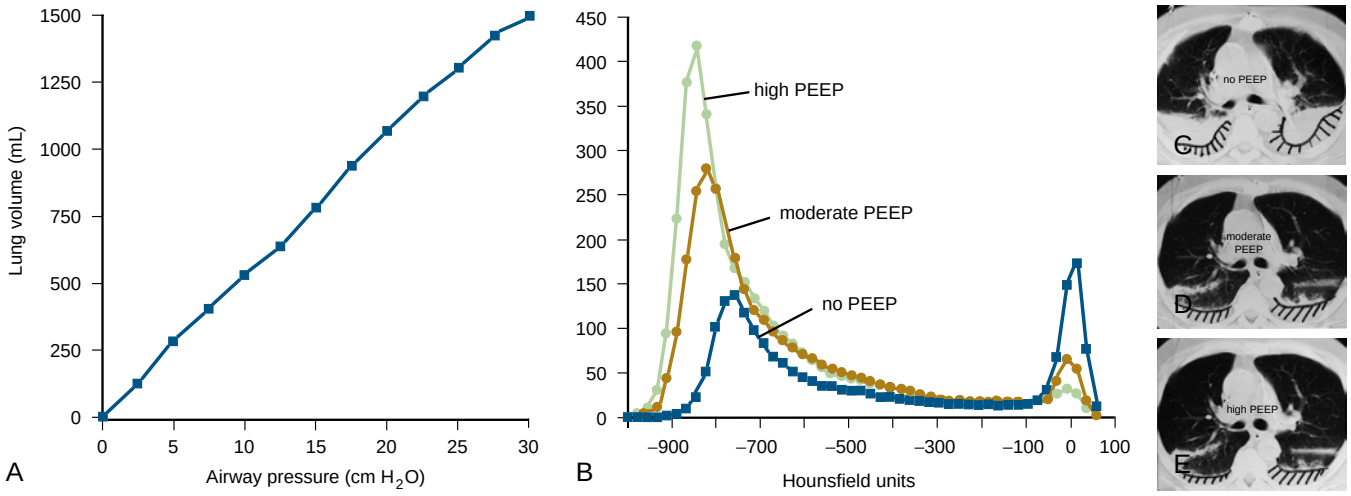

Figure 135.3 Effects of positive airway pressure in a lung with heterogeneous injury. (A) The almost linear pressure-volume relationship appears homogeneous as positive airway pressure is applied to the lungs does not reveal the underlying heterogeneity. (B) Distribution of Hounsfield units in three CT slices, at low pressure, at moderate airway pressure, and at the highest airway pressure demonstrates the underlying heterogeneity. Note that, although increasing pressure progressively reduces the number of atelectatic units (those with CT numbers near zero), these same pressures simultaneously increase the number of overdistended lung units elsewhere in the lungs (those with CT numbers less than –900 HU). (C–E) The three representative computed tomography (CT) lung slices are shown at low, moderate and maximal airway pressure. In the lung at low airway pressure (no *positive end-expiratory pressure* [PEEP]; C), note the substantial atelectasis in the dependent lung regions, which is progressively reduced as airway pressure is increased (moderate PEEP [D] and high PEEP [E]). (From Vieira SR, Puybasset L, Lu Q, et al. A scanographic assessment of pulmonary morphology in acute lung injury. *Am J Resp Crit Care Med.* 1999;159:1612–1623.)

zone 1 (capillary collapse/dead space) regions can appear, creating high $\dot{V}/\dot{Q}$ units. Indeed, increases in dead space can be a consequence of ventilatory strategies employing high ventilatory pressures, as well as with those producing PEEPi.

Positive-pressure mechanical ventilation can affect other aspects of cardiovascular function. Specifically, dyspnea, anxiety, and discomfort from inadequate ventilatory support can lead to stress-related catecholamine release with subsequent increases in myocardial oxygen demands and risk of dysrhythmias.[36] In addition, coronary blood vessel oxygen delivery can be compromised by inadequate gas exchange from the lung injury coupled with low mixed venous P_{O_2} due to high oxygen consumption demands by the inspiratory muscles.

COMPLICATIONS OF POSITIVE-PRESSURE MECHANICAL VENTILATION

VENTILATOR-INDUCED LUNG INJURY

When the mechanical stress applied to the lung is excessive, injury may result. The most obvious injury is barotrauma: alveolar rupture presenting as extra-alveolar air in the mediastinum (pneumomediastinum), pericardium (pneumopericardium), subcutaneous tissue (subcutaneous emphysema), pleural space (pneumothorax), or vasculature (air emboli).[38] The risk for extra-alveolar air increases as a function of the magnitude and duration of alveolar overdistention.

Even without producing extra-alveolar air and rupture, mechanical ventilation can induce *ventilator-induced lung injury* (VILI).[39,40] Excessive mechanical stress is translated into an inflammatory reaction within the lung (volutrauma) that can propagate via the circulation to other organs, leading to multiorgan dysfunction syndrome (biotrauma). In experimental models, acute lung injury can be produced by mechanical ventilation strategies that stretch the lungs beyond the normal maximum volume (at transpulmonary pressures of 30 to 35 cm H_2O).[41–43] A number of clinical trials clearly indicate that ventilator strategies exposing the injured human lung to transpulmonary pressures in excess of 30 to 35 cm H_2O are associated with VILI.[44–47]

Importantly, VILI is more than simply a consequence of excessive end-inspiratory stretch. Even in the setting of transpulmonary pressures less than 30 cm H_2O, excessive tidal stress and strain in the lung may contribute to VILI.[44,45] This VILI risk may be better quantified by referencing the V_T to the resting lung volume and can be termed mechanical strain.[48] In clinical practice, this stress/strain is best reflected by the *driving pressure* (Pplat – PEEP), a quantity that strongly predicts mortality in patients with *acute respiratory distress syndrome* (ARDS).[49] The frequency and velocity at which the stress is applied[50,51] may also be involved in the development of VILI. VILI may also result from shear stresses incurred when injured alveoli repetitively open and collapse during the ventilatory cycle (i.e., cyclical atelectasis or atelectrauma).[20,52,53] Additionally, vascular pressure elevations may contribute to VILI.[54,55]

The region of the lung most vulnerable to VILI is the relatively uninjured region participating in ventilation. Low-resistance/high-compliance units receive a disproportionately high regional V_T in the setting of high alveolar distending pressures. This can be appreciated using computed tomography under circumstances when pressures required for recruitment of diseased atelectatic regions simultaneously produce overdistention in already open, less-diseased regions (Fig. 135.3).[56] Regional protection of these healthier lung units is the rationale for using "lung-protective"

ventilation strategies that accept values for pH and arterial P_{CO_2} outside the usual physiologic range in exchange for lower (and safer) distending pressures (see "Applying Mechanical Ventilatory Support" later).[57]

VILI is manifest pathologically as diffuse alveolar damage.[20,41,42,58] Moreover, VILI is associated with cytokine release[58,59] and bacterial translocation,[60] which are implicated in the systemic inflammatory response with multiorgan dysfunction that results in VILI-associated mortality.

VENTILATOR-INDUCED DIAPHRAGM DYSFUNCTION

In the mid-1980s, autopsy studies in mechanically ventilated neonates found that prolonged mechanical ventilation was associated with marked diaphragm atrophy. An impressive body of experimental and clinical evidence has emerged supporting the concept that mechanical ventilation can cause diaphragm atrophy, injury, and dysfunction (*ventilator-induced diaphragm dysfunction* [VIDD]) through a variety of mechanisms (ventilator "myotrauma"). Because diaphragm dysfunction increases the risk of prolonged mechanical ventilation, VIDD raises the specter of a vicious cycle of ventilator dependence: acute respiratory failure renders patients ventilator dependent, and injurious mechanical ventilation weakens the respiratory muscles and perpetuates ventilator dependence. As with VILI, the risk of VIDD appears to depend on how mechanical ventilation is applied, suggesting that a detailed mechanistic understanding of the phenomenon may guide the development of safer, diaphragm-protective ventilation strategies that might prevent diaphragm myotrauma and accelerate liberation from mechanical ventilation.

Disuse Atrophy (Over-assistance Myotrauma)

Carefully controlled experiments in different animal models of VIDD have consistently demonstrated that (1) controlled mechanical ventilation leads to the rapid onset of diaphragm atrophy and loss of force-generating capacity in vitro, commencing within 12 hours of initiating controlled mechanical ventilation; (2) the muscle atrophy is specific to the diaphragm, and peripheral skeletal muscle is unaffected; (3) anaesthetized but spontaneously breathing control animals with only continuous positive airway pressure applied do not show any evidence of deteriorating muscle structure or function.[61–63] Taken together, these findings suggest that mechanical ventilation can be causally responsible for diaphragm atrophy.

Reduced diaphragm activity during mechanical ventilation is linked to diaphragm atrophy because of the production of reactive oxygen species,[64] possibly as a consequence of mitochondrial dysfunction.[65] This oxidative stress activates several proteolytic pathways (calcium-dependent proteolytic enzymes, ubiquitin-proteasome pathway, and autophagy).[66] The resulting imbalance between proteolysis and protein synthesis leads to progressive myofibrillar atrophy and may be responsible for myofibrillar disarray.

The development of muscular proteolysis and diaphragm weakness is attenuated when respiratory drive is intact,[67–69] and the severity of VIDD is significantly less when there are intermittent periods of spontaneous breathing during controlled ventilation.[70] Importantly, the magnitude of respiratory effort must exceed some minimum level to prevent diaphragm atrophy, because high levels of PS lead to diaphragm atrophy and muscle weakness nearly identical to the effects of controlled ventilation, whereas lower levels of PS did not result in VIDD. Thus, suppressing respiratory muscle effort injures the diaphragm irrespective of the mode of mechanical ventilation.

Clinical studies suggest that approximately 50% of patients develop at least 10% diaphragm atrophy during the first several days of mechanical ventilation.[71] These patients are at much higher risk of prolonged mechanical ventilation, reintubation, and tracheostomy.[72] Avoiding VIDD by maintaining adequate respiratory effort (the exact target is as yet uncertain) may therefore accelerate liberation from mechanical ventilation.

Load-Induced Diaphragm Injury (Under-assistance and Eccentric Myotrauma)

Excess respiratory muscle loads can cause diaphragm injury and respiratory failure. Acute inspiratory resistive loading can cause diaphragm inflammation, injury, and dysfunction when sufficiently high, although the contractile weakness is often delayed by up to 48 hours.[73] Diaphragm specimens obtained from both healthy subjects and COPD patients (who are subjected to chronically elevated resistive loads) following an inspiratory resistive loading protocol reveal sarcomere disruption, which is worse in patients with COPD.[74] The respiratory muscle load required for injury is uncertain but is surprisingly low in some studies (<20% of maximum inspiratory pressure). Loads exceeding the fatigue threshold have been documented during weaning trials in at least one study.[75]

Eccentric muscle contractions (contractile activation during muscle lengthening) are more injurious than concentric contractions (contractile activation during muscle shortening). Large eccentric contractile loads can cause significant acute diaphragm injury as demonstrated in experimental models.[76,77] The diaphragm can be eccentrically loaded during certain forms of patient-ventilatory dys-synchrony. Reverse triggering dys-synchrony, where mechanical insufflation induces neural inspiration, can result in diaphragm contractile activation while the ventilator cycles from inspiration to expiration (and lung volume precipitously falls).[78] If the ventilator cycles off into expiration prematurely (before the patient's inspiratory effort is complete), lung volume falls and the diaphragm may lengthen as it is contracting. Diaphragm contractions may also be eccentric in the context of expiratory braking, where the diaphragm is activated to prevent excessive loss of lung volume and development of atelectasis.[79] The prevalence and impact of eccentric loading on diaphragm function in the clinical setting remains to be determined.

Mechanical ventilation can prevent experimental load-induced diaphragm injury[80] and accelerates the recovery of diaphragm fatigue under high loading conditions.[81] Consequently, ventilatory support can protect the diaphragm, provided it does not excessively suppress respiratory effort or lead to patient-ventilator dys-synchrony.

OXYGEN TOXICITY

Very high inspired oxygen concentrations can cause oxidant injury in airways and lung parenchyma.[82] The data supporting this concept, however, have mostly come from

animals that often have quite different tolerances to oxygen than humans. It is thus not clear what the "safe" oxygen concentration or duration of exposure is in critically ill humans. Several observational trials suggest that even with a "safe" F_{IO_2} less than 0.4, maintaining an arterial P_{O_2} greater than 120 to 130 mm Hg may produce systemic oxygen toxicity over time.[83,84] Indeed, a single-center randomized trial of critically ill patients demonstrated that conservative oxygen therapy (targeting arterial P_{O_2} 70–100 mm Hg or oxygen saturation 94–98%) compared to a conventional strategy (targeting arterial P_{O_2} up to 150 mm Hg or oxygen saturation 97–100%) was associated with lower intensive care unit mortality rate.[85] A trial comparing even more restrictive targets (oxygen saturation 88–92% vs. ≥96%) in mechanically ventilated patients is currently underway.[86]

PATIENT-VENTILATOR INTERFACE COMPLICATIONS

The patient must be connected to the ventilator via ventilator circuitry and an artificial airway. Problems with this interface can lead to complications. The most obvious issue is disconnection from the ventilator (including artificial airway dislodgment). Other complications of the patient-ventilator interface include obstructions from secretions, circuit leaks, airway injury from inadequate heat/humidity, tracheal injury from the artificial airway, and loss of delivered V_T in a compliant circuit.

PATIENT-VENTILATOR DYS-SYNCHRONY

Patient-ventilator dys-synchrony describes the delivery of a breath from a mechanical ventilator that is not matched to patient effort. As noted earlier, this can take place during the triggering process, flow delivery, or breath cycling.

Breath Triggering Dys-synchrony

Ventilators may sense a spontaneous effort by either an airway pressure drop or an airway flow change.[87–89] Excessive or inadequate sensitivity in these triggering mechanisms gives rise to a mismatch between the patient's neural respiratory cycle times and the ventilator's respiratory cycle times, often (but not always) leading to significant patient discomfort. If ventilator triggering sensitivity is too sensitive, the ventilator may be triggered by artifactual swings in airway pressure ("auto-triggering") due to cardiogenic oscillations or water buildup in the ventilator circuit. On the other hand, insufficient sensitivity can result in significant isometric-like pressure loads on the inspiratory muscles during the triggering process. This may be worsened by excessive PEEPi from elevated airway resistance. If respiratory drive and effort are low, ventilator triggering may be ineffective, and no pressure or flow are delivered. Under these conditions, judicious use of applied PEEP can equilibrate expiratory pressure throughout the lungs and the ventilator circuit to reduce this triggering load.[90,91]

If the patient's inspiratory effort is prolonged, a second breath may be triggered as soon as the first mechanical breath is complete ("double triggering"). This results in "breath stacking," effectively doubling V_T, and putting the patient at risk of VILI. A recently described phenomenon, "reverse triggering," is produced when the machine-triggered breath elicits an inspiratory effort from the patient.[92] If the resulting effort persists beyond machine breath termination, a second breath can be triggered, and breath stacking results.

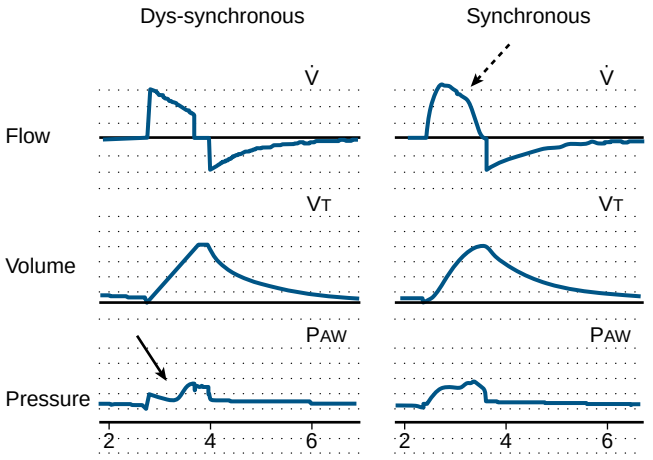

Figure 135.4 Flow and pressure pattern differences during dys-synchronous and synchronous breaths in a patient with a vigorous inspiratory effort. Depicted are flow (*upper panel*), volume (*middle panel*), and pressure (*lower panel*) for a dys-synchronous flow-targeted breath (*left*) and a more synchronous pressure-targeted breath (*right*) with matched mean flow, inspiratory time, and tidal volume (V_T). Note that, during the flow-targeted breaths (*left*), the fixed flow does not respond to the vigorous inspiratory effort, resulting in the circuit pressure being "sucked" downward (*solid arrow*). In contrast, with the pressure-targeted breath, flow adjusts and increases to meet the inspiratory effort better (*dashed arrow*). P_{AW}, airway pressure. (Modified from Yang LY, Huang YC, MacIntyre NR. Patient-ventilator synchrony during pressure-targeted versus flow-targeted small tidal volume assisted ventilation. *J Crit Care*. 2007;22:252–257.)

Flow Pattern Dys-synchrony

During an interactive breath, inspiratory muscles are contracting[93,94] and the ventilator flow delivery should be adequate to provide proper muscle unloading. This does not mean that muscle loads are eliminated. Instead, it means that a delivered flow pattern is associated with a muscle loading pattern that resembles normal, comfortable breathing[95] (synchronous flow delivery).

In general, flow synchrony is best assessed by clinical assessment and analyzing the graphic representation of Pcir over time in VACV.[95,96] Flow synchrony is manifested clinically as a relaxed patient who does not appear dyspneic. In contrast, flow dys-synchrony often manifests as tachypnea, air hunger (dyspnea), and the appearance of "flow starvation."[95] With synchronous flow delivery, the Pcir graph in ACVC should maintain either a steady baseline profile (a continuous positive airway pressure breath) or a convex upward shape (assisted/supported breath), indicating that flow is proportional to demand. Dys-synchrony (and imposed loading) is said to exist when the Pcir graph is literally "sucked downward" by effort in excess of flow delivery, often below the baseline[95,97] (Fig. 135.4). In pressure-targeted modes, flow is not controlled and therefore flow starvation is less obvious on the waveforms. However, insufficient pressure delivery can also manifest as dyspnea and distress.

Breath Cycling Dys-synchrony

Cycling dys-synchrony can arise in one of two ways. First, if the mechanical breath lasts beyond the duration of patient effort, an inadequate expiratory time may develop (along with air trapping) and/or patient expiratory efforts may be required to terminate the breath.[95] This can be a particular concern when using PS breaths in obstructive airway disease—the relatively steady inspiratory flow with PS coupled with the PS flow-cycling algorithm may significantly delay breath termination.[98] Second, if the mechanical breath terminates before the patient effort is finished, the patient may be left demanding additional flow without any being delivered. Significant imposed loading and, as noted earlier, double breath triggering may result.[95]

Clinical Implications

Determining the prevalence of patient-ventilator dys-synchrony is difficult because studies examining this question have used heterogeneous patient populations and different definitions of dys-synchrony, methods of detection, duration and timing of observation, and ventilatory modes.[95,99] Triggering dys-synchronies have been the most well studied. Depending on patient population, ventilator settings, and measurement techniques, triggering dys-synchronies have been reported in 26–82% of mechanically ventilated patients. Not surprisingly, trigger dys-synchronies were more common in patients with COPD and in those at risk for development of PEEPi.[95,99] Double triggering is the other commonly reported triggering dys-synchrony but is generally described in less than 10% of patients in these various studies.[95,99]

The incidence of other forms of dys-synchrony (flow dys-synchrony and cycle dys-synchrony) has not been as well characterized. However, a retrospective evaluation of the *National Institutes of Health ARDS Network* (ARDSNet) low V_T study reported cycling dys-synchronies associated with double triggering in 9.7% of all breaths analyzed.[100] Indeed, it is likely that patient-ventilatory dys-synchrony is ubiquitous if any patient is observed long enough during assisted/supported mechanical ventilation, especially if more sophisticated monitors (e.g., esophageal pressure or diaphragmatic EMG) are used to detect patient effort.

Although there is no doubt that many dys-synchronies are subtle and of little clinical relevance, significant dys-synchronies may be missed, thus overloading respiratory muscles and producing patient discomfort, which is a frequently cited indication for the administration of sedatives.[95,99] This may impact ventilator duration because high sedation usage is linked to longer ventilator use. Indeed, several observational studies have noted more days of mechanical ventilation and even trends toward higher mortality in patients with trigger dys-synchronies taking place more than 10% of the time.[99]

Managing Dys-synchronies

Synchronous ventilator settings first require setting the trigger to the most sensitive setting possible (without auto-triggering). If PEEPi is creating a triggering load, attempts should be made to minimize PEEPi and then judicious use of applied PEEP added to counterbalance the imposed triggering load as described later. If reverse triggering is present, reducing sedation and the need for a mandatory (controlled) breath rate should be reassessed.

Flow synchrony is often easier to achieve with variable flow pressure-targeted breaths, as noted earlier. Pressure-targeted breaths can also allow for adjustments in the rate of pressure rise (i.e., a rapid rate of rise is often desired in a patient with vigorous flow demands, whereas a much slower rate of rise is often preferable in patients with less vigorous demands[101]) and can compensate for endotracheal tube resistance (i.e., the ventilator provides the appropriate Pcir profile during both inspiration and expiration to create the desired square wave pattern in the trachea[102,103]) as a means of further enhancing synchrony. If flow-targeted breaths are desired, synchrony can be addressed with adjustments in flow magnitude and profile (sine wave, square wave, decelerating pattern). Importantly, because the patient's respiratory drive is modulated by mechanical feedback from the lungs and thorax, modes that avoid multiple different breath types (i.e., avoiding SIMV) tend to facilitate flow synchrony.[95] Finally, breath duration should be optimized for comfort and for elimination of double breaths by using adjustments in the cycle variable (volume, time, or flow).

APPLYING MECHANICAL VENTILATORY SUPPORT

MECHANICAL VENTILATORY SUPPORT INVOLVES TRADEOFFS

The goals of providing adequate support while minimizing the risk of VILI and other complications involve tradeoffs. Specifically, the need for potentially injurious levels of mechanical ventilation must be weighed against the benefits of supporting gas exchange. To this end, a rethinking of gas exchange goals has taken place over the past 2 decades so that pH levels as low as 7.15 to 7.25 and arterial P_{O_2} values as low as 55 mm Hg are now considered acceptable in order to protect the lung.[47,104,105] Ventilator settings are thus selected to provide at least this level of gas-exchange support while meeting three mechanical goals: (1) provision of enough PEEP to open the "recruitable" alveoli, (2) avoidance of a PEEP-V_T combination that unnecessarily overdistends lung regions at end-inspiration, and (3) limiting V_T to the physiologic range. These goals embody the concept of a lung-protective mechanical ventilatory strategy. Currently, these principles guide recommendations for the specific management of various forms of respiratory failure discussed below.[106–111]

CONSIDERATIONS IN CHOOSING VENTILATOR SETTINGS FOR DIFFERENT FORMS OF RESPIRATORY FAILURE

Parenchymal Lung Injury

Parenchymal lung injury means injury that involves the air spaces and the interstitium of the lung.[16,19,23,26,27] In general, parenchymal injury stiffens lungs and decreases lung volumes. It is important to realize that there are often significant regional differences in the degree of mechanical abnormalities, which should guide the ventilatory strategy. This is because delivered gas will preferentially go to the more normal regions, those with higher compliance and lower resistance, rather than to abnormal regions (Fig. 135.5). A "normal-sized" V_T may thus be distributed preferentially

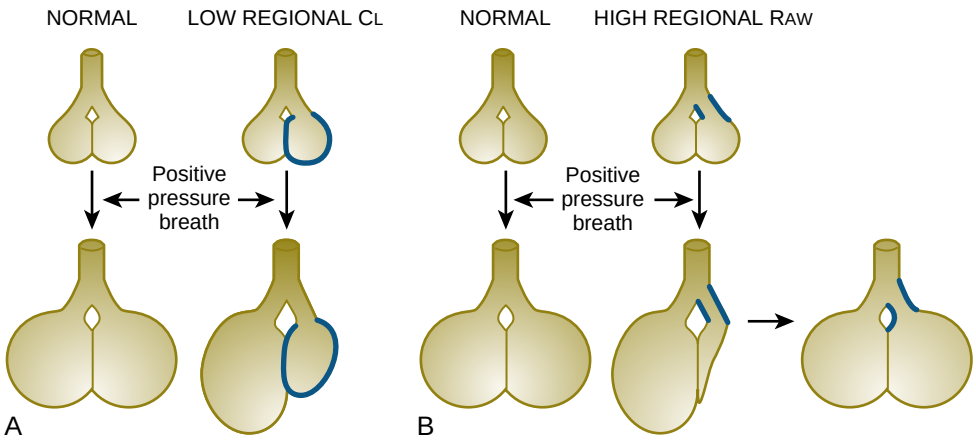

Figure 135.5 The distribution of ventilation in lung models with heterogeneous mechanical properties. Models of the lung are shown as two units with homogeneous mechanical properties (normal): (A) with abnormal compliance distribution (low regional *lung compliance* [CL]) and (B) abnormal resistance distribution (high *regional airway resistance* [RAW]). Note that in situations with heterogeneous lung mechanics, positive-pressure breaths are preferentially distributed to "healthier" regions of the lung and can produce regional overdistention—even when a normal-sized tidal volume is delivered. Note that in the obstructed example (high regional RAW), the overdistention may be transitory as gas moves from the low-resistance to the high-resistance unit over time (pendelluft). (Modified from MacIntyre NR. Mechanical ventilatory support. In Dantzker D, MacIntyre NR, Bakow E, editors. *Comprehensive Respiratory Care*. Philadelphia: WB Saunders; 1995:453.)

to the healthier regions, resulting in a regional overdistention injury. Parenchymal injury can also affect the airways, especially the bronchioles and alveolar ducts. These narrowed and collapsible small airways can also reduce regional ventilation to injured lung units, leading to regions of air trapping and possibly cyst formation during the healing phase.

Gas-exchange abnormalities in parenchymal lung injury are a consequence of alveolar consolidation, flooding, and/or collapse, producing a maldistribution of ventilation and resulting in mismatching and shunts.[18,19,23,26,27] Because $\dot{V}/\dot{Q}$ mismatching and shunt are more of an issue than dead space in parenchymal lung disease, hypoxemia tends to be more of a clinical problem than carbon dioxide elevation. (See Chapter 44.)

Frequency-VT settings for patients with parenchymal lung injury must focus on limiting end-inspiratory stretch. The benefit of reducing stretch in improving outcome has been suggested by several clinical trials[44–47,112] but has been most convincingly demonstrated by the ARDSNet Trial in which a ventilator strategy using a VT of 6 mL/kg *predicted body weight* (PBW) compared with 12 mL/kg PBW led to a 9% absolute reduction in mortality.[47] Thus initial VT settings should start at 6 mL/kg PBW.[45,113] Moreover, strong consideration should be given to reducing this setting further if end-inspiratory Pplat exceeds 30 cm H_2O.[44–47] Increases in the VT settings might be considered if there is marked patient discomfort or suboptimal gas exchange *provided that* the subsequent Pplat values do not exceed 30 cm H_2O.[44–47] Respiratory rate settings are then adjusted to control pH. Unlike the case in obstructive diseases, the potential for air trapping in parenchymal lung injury is low if the breathing frequency is less than 35 breaths/min; air trapping may not develop even at frequencies exceeding 50 breaths/min.

There is controversy as to whether *neuromuscular blockade* (NMB) and controlled mechanical ventilation should be used in the initial 24 to 48 hours of parenchymal lung injury. NMB use producing flaccid ventilatory muscles reduces total body oxygen demands and eliminates potential dys-synchronous interactions. However, ventilatory muscles inactive for as little as 24 hours are at risk for VIDD and long-term disability.[114–116] Moreover, the use of NMB usually requires substantial sedative use. A randomized trial in patients with ARDS (arterial P_{O_2}/F_{IO_2} ratios <120) showed improved mortality with NMB use for 48 hours.[117] However, a subsequent randomized trial from the Prevention and Early Treatment of Acute Lung Injury (PETAL) Network comparing 48 hours of continuous infusion of cisatracurium with deep sedation to usual care without routine NMB and lighter sedation targets demonstrated no difference in hospital mortality.[118] Importantly, patients in the intervention group were less physically active and had more adverse cardiovascular events while in the hospital than the control group. Thus, the routine use of NMB in patients with moderate/severe ARDS cannot be advocated. NMB use can be considered in selected patients to improve ventilator synchrony, particularly those at the highest risk of VILI.[119]

The inspiratory time and the *inspiratory/expiratory ratio* (I:E) in parenchymal injury is set with consideration of several issues. The usual initial I:E setting is 1:2 to 1:4, the normal and the most comfortable setting. The flow graphic should also be assessed to ensure that cycle synchrony is present and the expiratory time is adequate to avoid air trapping.

The PEEP and F_{IO_2} settings are optimized using both mechanical and gas exchange considerations. Conceptually, in setting the PEEP level in parenchymal lung injury, the goal is to provide ventilator settings between the upper and lower inflection points on the deflation limb of the pressure-volume curve (Fig. 135.6).[120] The most direct mechanical approaches use the static pressure-volume plot to set the PEEP and VT. This traditionally involves multiple VT/Pplat measurements and requires considerable clinician time along with patient sedation or even NMB. Although not widely used at present, performing a pressure-volume curve is now available as an automated feature on some newer ventilators. Another mechanical approach uses step changes

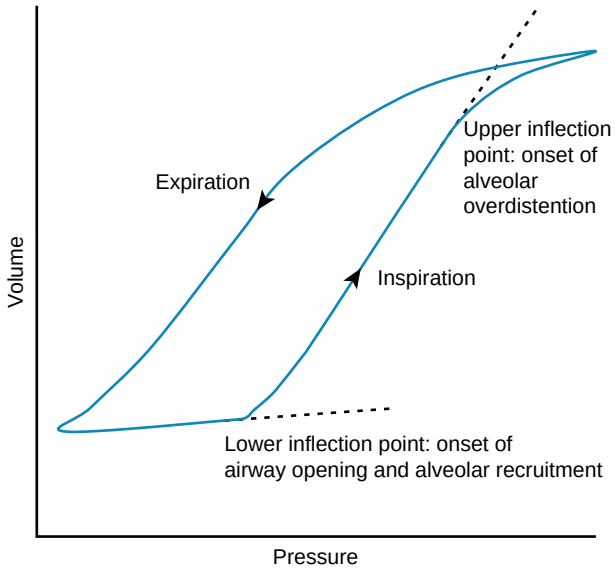

Figure 135.6 Setting ventilator pressures using the pressure-volume curve of a patient with acute lung injury. The relationship between pressure and volume (compliance) varies according to lung volume and lung volume history (i.e., incremental limb vs. decremental limb). Regions of lower compliance represent lung derecruitment (lower volume) or overdistention (upper volume). Pulmonary end-expiratory pressure is set above the lower inflection point to avoid derecruitment; maximal airway pressure is set below the upper inflection point to avoid overdistention. (Modified from Pinhu L, Whitehead T, Evans T, Griffiths M. Ventilator-associated lung injury. *Lancet*. 2003;361:332–340.)

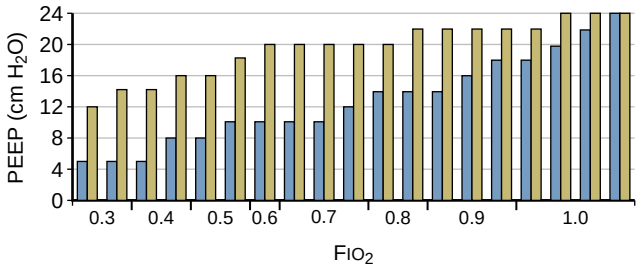

Figure 135.7 Two *positive end-expiratory pressure* (PEEP)/F_{IO_2} algorithms used in National Institutes of Health Acute Respiratory Distress Syndrome Network clinical trials. Plotted are F_{IO_2} on the horizontal axis and PEEP on the vertical axis. With both approaches, the oxygenation target (P_{aO_2} 55–80 mm Hg, S_{PO_2} 88–95%) and the maximal allowable plateau pressure (Pplat, 35 cm H_2O) are the same. Patients are moved in steps up and down the algorithm according to these targets. The two algorithms depicted either focus on higher PEEP levels ("high PEEP," *brown bars*) or lower PEEP levels ("low PEEP," *blue bars*). (Courtesy Art Wheeler, MD, and ARDS Network. Ventilation with lower tidal volumes as compared with traditional tidal volumes for acute lung injury and the acute respiratory distress syndrome. *N Engl J Med*. 2000;342:1301–1308.)

in PEEP to determine the PEEP level that gives the best compliance.[121] A simpler mechanical approach analyzes the Pcir profile during a constant-flow breath (stress index) to detect overdistention (late rising profile) or collapse/reopening injury (early rising profile).[122] With all of these approaches, a recruitment maneuver can be used to recruit the maximal number of recruitable alveoli before setting the PEEP. F_{IO_2} adjustments are then set as low as clinically acceptable.

PEEP can also be guided by gas exchange criteria, usually involving algorithms that adjust PEEP and F_{IO_2} according to certain targets. Note that constructing a PEEP/F_{IO_2} algorithm is usually an empirical exercise in balancing distending pressure, arterial O_2 saturation, and F_{IO_2} and depends on the clinician's perception of the relative "toxicities" of high thoracic pressures, high F_{IO_2}, and low arterial O_2 saturation. Although most of the reported PEEP/F_{IO_2} algorithms generally target modest levels of oxygenation (e.g., arterial P_{O_2} 55–80 mm Hg or S_{O_2} 88–95%), they tend to segregate into approaches that focus either on higher PEEP levels ("high PEEP" algorithms) or lower PEEP levels ("low PEEP" algorithms) (Fig. 135.7). Several trials have compared high versus low PEEP algorithms in conjunction with low V_T/limited Pplat strategies in patients with ARDS.[123–125] A meta-analysis of trials with mild ARDS (arterial $P_{O_2}/F_{IO_2} > 200$) compared with more severe ARDS (arterial $P_{O_2}/F_{IO_2} < 200$) demonstrated that higher PEEP strategies had a significant mortality benefit in more severe ARDS, whereas lower PEEP strategies showed a trend toward a potential benefit in mild ARDS.[126]

In patients with a rightward shift in the chest wall pressure-volume relationship and/or an increase in chest wall elastance (i.e., obesity, anasarca, abdominal compartment syndrome), the reliance on circuit airway pressures to guide ventilator settings will ignore the effect of elevated pleural pressures; for a given airway pressure, a higher pleural pressure means a lower transpulmonary pressure, which is the ultimate determinant of VILI and alveolar recruitment. Under these circumstances, it may be reasonable to allow modest increases in applied PEEP and target Pplat if usual PEEP levels are insufficient to achieve adequate arterial P_{O_2}. Alternatively, an esophageal catheter to measure esophageal pressure could be inserted to assess transpulmonary pressure directly and adjust settings accordingly.[127,128] Although a small clinical trial using esophageal pressure to guide PEEP settings suggested improved outcomes,[128] a subsequent randomized trial comparing esophageal pressure–guided PEEP titration versus a higher PEEP- F_{IO_2} table revealed no significant differences in the set PEEP nor clinical outcomes.[129] At the very least, these data suggest that esophageal manometry can be used to determine when it is safe to violate usual limits on Pplat to achieve adequate gas exchange.

Obstructive Airway Disease

Increases in airway resistance lead to respiratory failure from airflow obstruction and create two important pathophysiologic changes. First, the increased pressures required for airflow may overload inspiratory muscles, producing a "ventilatory pump failure" in which spontaneous minute ventilation becomes inadequate for gas exchange. Second, the narrowed airways create regions of lung that cannot properly empty and return to their normal "resting volume," thereby producing PEEPi.[30] These regions of overinflation create dead space and put inspiratory muscles at a substantial mechanical disadvantage that further worsens muscle function. Overinflated regions may also compress more healthy regions of the lung, impairing $\dot{V}/\dot{Q}$ matching. Regions of air trapping and PEEPi also function to increase the threshold load the patient must overcome to trigger mechanical breaths.

Frequency-V_T settings in obstructive diseases are chosen on the basis of many considerations similar to those in parenchymal lung injury. Specifically, V_T should be in the 6 to 8 mL/kg (PBW) range with Pplat targets of less than 30

cm H_2O.[44–47] In obstructive diseases, however, clinicians should also be aware that high *peak* airway pressures, even in the presence of acceptable values for Pplat, may transiently subject regions of the lung to periods of overdistention injury (see Fig. 135.5). Finally, setting the VT should also take into consideration the potential to develop PEEPi with its consequent impact on Pplat elevations and the risk of overdistention injury.

The ventilatory rate is used to control pH. Unlike the situation in parenchymal disease, however, the elevated airway resistance (and often the low recoil pressures of emphysema) greatly increases the potential for PEEPi and thus limits the range of breath rates available. Indeed, reductions in both VT and ventilatory rate to levels resulting in hypoventilation and "permissive" (or even "therapeutic"[104]) hypercapnia may be an appropriate tradeoff to limit PEEPi development and overdistention. I:E in obstructive lung disease is generally set as low as possible to minimize the development of air trapping.

The PEEP/FIO_2 settings assume a different role in obstructive lung disease than in parenchymal lung disease. Because alveolar recruitment is less of an issue and overdistention is more of an issue in obstructive lung injury than in parenchymal lung injury, the strategy in using the PEEP/FIO_2 steps in Figure 135.7 should probably be shifted more toward the use of FIO_2 for oxygenation support instead of PEEP. A specific role for PEEP in the obstructed patient arises when PEEPi serves as an added inspiratory threshold load for the patient attempting to trigger a breath. Under these conditions, judicious application of extrinsic PEEP (at levels up to 75–85% of PEEPi) can "counterbalance" PEEPi throughout the ventilator circuitry to reduce this triggering load and facilitate the triggering process.[90,91]

Finally, it is important to note that noninvasive ventilation has been demonstrated most convincingly to improve outcomes in patients with obstructive diseases.[130] In setting up noninvasive ventilation, the same principles described previously for invasive mechanical ventilation also apply (see Chapter 136).

Neuromuscular Respiratory Failure

The risk of VILI is generally less in a patient with neuromuscular failure (e.g., central nervous system injury, drug overdoses, anesthesia) because lung mechanics are often near normal and regional overdistention less likely. More "generous" VT (e.g., up to 10 mL/kg PBW) has thus been proposed as being useful to improve comfort, maintain recruitment, prevent atelectasis, and avoid hypercarbia that may adversely affect central nervous system function. However, this notion has been challenged recently by clinical trials of patients with normal lungs in the perioperative period showing reduced postoperative complications when VT is used in the 6 to 8 mL/kg (ideal body weight) range. Regardless of VT settings, maximal distending pressures should be kept as low as possible while still being compatible with the other goals noted previously.[44–47]

Mode selection in these patients is often determined by patient comfort and reliability of the respiratory drive. PEEP, even at low levels, is often beneficial at preventing derecruitment (atelectasis) when patients are supine and unable to clear secretions or sigh.

Resolving Respiratory Failure: Liberation from Mechanical Ventilation

As respiratory failure stabilizes and begins to reverse, clinical attention shifts to the process of ventilator withdrawal. Unfortunately, a number of large clinical trials have clearly demonstrated that current assessment/management strategies are not optimal, resulting in considerable delay in ventilator liberation.[130,131] Such delay leads to increased length of ICU stay, increased costs, prolonged exposure to Pcir, and increased risk of infection. Attempts to speed liberation, however, must be balanced against the risk of premature withdrawal with consequent loss of airway patency, aspiration, and inspiratory muscle fatigue. The use of a ventilator liberation protocol to identify a patient's readiness for liberation may reduce the duration of mechanical ventilation.[132] Patients should be considered candidates for liberation if (1) the lung injury is stable/resolving, (2) the gas exchange is adequate with low PEEP/FIO_2 requirements, (3) the hemodynamics are stable without pressors, and (4) the patient has the capability to initiate spontaneous breaths.[130] In these patients, a *spontaneous breathing trial* (SBT) for 30 to 120 minutes can be conducted to assess readiness for extubation. The optimal method for conducting an SBT is controversial; some guidelines recommend the use of inspiratory pressure augmentation of 5 to 8 cm H_2O[133] to counteract the imposed resistive load of the endotracheal tube, while others argue that the respiratory loading conditions postextubation are best matched by an SBT with no support (i.e., T-piece or zero airway pressure).[134] Assessments should include the ventilatory pattern, gas exchange, hemodynamics, and comfort. Patients passing this trial should be considered for ventilator liberation (i.e., extubation).

Among those patients who pass the SBT, separate assessments are required to determine if the artificial airway can be removed. These involve cough strength, suctioning frequency and, to a certain extent, the ability to follow commands.[130] Cuff leak, a bedside test that may demonstrate whether there is airway edema or compression around the endotracheal tube that could lead to postextubation airway obstruction, does not appear to be an important predictor of success, except perhaps in certain high-risk populations.[132] Extubation failures can be expected in 10–20% of all extubations. Many of these involve airway protection issues and thus indicate the need for prompt reintubation. However, in some patients, especially those with COPD, an extubation failure caused by increasing inspiratory muscle overload might be managed by noninvasive ventilation.[133,135,136]

In patients failing the SBT, a stable and comfortable level of support should be provided until the next SBT.[130] Frequent (e.g., every 2 to 12 hours) support reductions are usually not necessary because they have not been shown to speed the liberation process and only serve to consume resources and expose the patient to the risks of muscle overload. SBTs, however, should be repeated daily.[130,131] Importantly, aggressive strategies to reduce sedation can accelerate this process.[137] Indeed, some have advocated "spontaneous awakening trials" coupled to SBTs, but it is not clear if this approach is superior to carefully targeted sedation protocols.[138]

A common problem seen in patients recovering from respiratory failure but still deemed in need of an artificial airway is the presence of large VT despite low levels of ventilatory support (e.g., inspiratory pressure levels of 5 cm H_2O). Under these circumstances, a search should be made for causes of an excessive respiratory drive such as pain, metabolic acidosis, or anxiety, and these issues should be addressed. Most would argue that, in the absence of reversible causes, sedation should not be used simply to lower the VT. Regardless of the clinical scenario, whenever assisted-supported breaths are used, attention must be paid to ensuring synchronous interactions.

INNOVATIONS IN MECHANICAL VENTILATORY SUPPORT

ALTERNATIVE STRATEGIES FOR "LUNG PROTECTION"

A number of alternative strategies have been evaluated for their ability to reduce VILI.

Positive-Pressure Ventilation in the Prone Position

Mechanical ventilation of patients in the prone position offers several physiologic advantages.[139] Chief among these are two mechanisms that can improve ventilation distribution. First, the heart no longer rests on the left lower lobe, which allows better ventilation distribution to that region. Second, the sternum is restricted in its ability to move outward. This functionally stiffens the chest wall and forces a more even distribution of positive pressure.

Putting a patient in the prone position requires careful teamwork. Management of vascular lines, feeding tubes, artificial airways, ostomies, and so on need careful attention to avoid dislodging them. Avoiding pressure sores also requires careful nursing care.

There have been a number of randomized controlled trials of placing patients with ARDS in the prone position and, until recently, despite consistently better oxygenation, no consistent outcome benefit could be demonstrated.[139,140] However, the largest study to date focusing on ARDS patients with P_{O_2}/F_{IO_2} ratios less than 150 showed a significant mortality benefit to lung protective mechanical ventilation provided in the prone position for more than 16 hours/day,[142] and prone positioning has been incorporated into evidence-based guidelines.[109,111]

Airway Pressure Release Ventilation and High-Frequency Oscillatory Ventilation

Airway pressure release ventilation (APRV) (also known as biphasic ventilation, bilevel ventilation, and bilevel positive airway pressure) is a time-cycled, pressure-targeted form of ventilatory support.[141,143–146] It is actually a modification of pressure-targeted SIMV that allows spontaneous breathing (with or without PS) during any phase of the respiratory cycle.

The putative advantages of this approach are similar to others that utilize long inspiratory times. Specifically, the long inflation phase recruits more slowly filling alveoli and raises mean airway pressure without increasing applied PEEP (although PEEPi can develop with short deflation periods). The additional spontaneous efforts during inflation may enhance both recruitment and cardiac filling compared with other controlled forms of support. However, the end-inspiratory lung distention in APRV may not be less than that provided during other forms of support (and, indeed, could be substantially higher) because spontaneous VT can expand the lung beyond the volume at the APRV set pressure. In the few randomized studies that compare APRV to a true lung-protective strategy, most have not demonstrated differences in important outcomes.[144–147] A recent single-center controlled trial of 138 patients with ARDS randomized to APRV or VACV found significantly more ventilator-free days (19 vs. 2, $P < 0.001$) and shorter ICU stay (15 vs. 20, $P = 0.015$) in the APRV group.[147] However, the relatively small sample size, patients with more comorbidities randomized to the VACV group, and differences in sedation strategy between groups limit firm conclusions from this study.[148]

High-frequency oscillatory ventilation (HFOV) uses high breathing frequencies (120 to 900 breaths/min in the adult) coupled with very small VT (usually less than the anatomic dead space) to provide gas exchange in the lungs.[149] Gas transport under these seemingly unphysiologic conditions may involve such mechanisms as Taylor dispersion, coaxial flows, and augmented diffusion.[150] The putative advantages of HFOV are twofold. First, the small alveolar tidal pressure swings minimize cyclical overdistention and derecruitment. Second, a high mean airway pressure can also prevent derecruitment. Interestingly, tolerance of a higher mean pressure with HFOV may be explained by a better maintained alveolar structure with a slowly applied constant pressure as opposed to brief cyclical tidal pressures.[151]

A number of trials in the neonatal and pediatric patient population have demonstrated improved long-term lung function when HFOV is used in acute respiratory failure.[152,153] In adults, a meta-analysis of randomized trials using HFOV in adult respiratory failure suggested a benefit in patient outcomes with the use of HFOV.[154] Subsequently, however, two large randomized trials of HFOV in ARDS have called this conclusion into question. In one, mortality was identical in both the HFOV and conventional lung-protective strategy[155]; in the other, the trial was stopped early because of increased mortality in the HFOV group.[156] Both of these newer trials make it clear that HFOV should not be used routinely in adults with ARDS and, if used in patients who do not respond to any conventional lung protective strategies, should be used by clinicians experienced in the use of HFOV.[157]

AUTOMATED WEANING STRATEGIES

Over the years, a number of attempts have been made to automate the weaning process.[11] The concept behind automated weaning was that significant clinician time could be saved and ventilatory support could be automatically reduced in a timely fashion on the basis of simple ventilator measurements.

Volume support ventilation (VSV) is a strategy with the potential for automatic support reduction.[11,158] Proponents claim that this approach could "automatically" wean a patient by reducing PS as patient effort increases and respiratory system mechanics improve. Conversely, PS would

increase if patient effort diminished or respiratory system mechanics worsened. Similarly, it has also been suggested that VSV may be a useful way to maintain a more constant level of partial support in patients with fluctuating levels of effort related to drugs or neurologic conditions. All of these effects have been demonstrated in small studies focused on patients with rapidly recovering respiratory failure.[11]

Unfortunately, the simplicity of VSV may introduce problems.[11,158] For instance, if the volume set by the clinician is excessive for patient demand, a recovering patient may not attempt to take over the work of breathing for that volume and thus weaning may not progress. In addition, if the pressure level increases in an attempt to maintain an inappropriately high-set V_T in the patient with airflow obstruction, PEEPi may result. Conversely, if the volume set by the clinician is not adequate for patient demand, a patient may not receive adequate support. Under these conditions, a patient will perform excessive work to maintain a certain V_T even as the inspiratory pressure is being reduced. A transient increase in patient demand from pain or anxiety could also result in inappropriate support reduction with VSV.[158]

Adaptive support ventilation (ASV) has a sophisticated algorithm to adjust the ventilatory pattern during machine-triggered breaths, as described earlier. However, ASV performs similarly to VSV during patient-triggered breaths. Small clinical studies have demonstrated that ASV can automatically wean ventilatory support safely.[159] However, large trials have not yet compared ASV weaning to regular daily SBT strategies.

Inherent in all of these automated weaning systems is the notion that gradual support reductions (weaning) in between SBTs facilitates ventilator liberation—a notion that has little, if any, evidence supporting it in patients recovering from acute respiratory failure.[160] Two clinical scenarios, however, may be amenable to these automated approaches. The first is the patient rapidly recovering from sedatives/anesthesia where these systems can alert clinicians to the return of adequate spontaneous efforts. The second is the patient requiring prolonged mechanical ventilation who has not responded to multiple SBTs. Under these circumstances, an automated support reduction system could serve as a diagnostic tool alerting the clinician to recovery of respiratory function and the possibility of reinstating SBTs.

OPTIMIZING SYNCHRONY DURING ASSISTED MECHANICAL VENTILATION

Assisted mechanical ventilation is commonly used to improve comfort (and reduce sedation), especially during the recovery phase of respiratory failure. Alternative modes of ventilation that have conceptual appeal have been shown to perform as designed in both bench testing and small clinical studies. To date, however, large clinical trials demonstrating improvements in patient outcomes have not yet been performed.

Proportional Assist Ventilation

PAV is an approach to assisted ventilation in which the clinician sets the "gain" on patient-generated flow and volume.[161,162] PAV therefore has no set pressure, flow, or volume. Instead, the sensed patient effort is boosted according to a proportion of the measured work of breathing set by the clinician. PAV breaths are patient-initiated breaths triggered in a conventional way using Pcir or flow sensors. The PAV breath cycles when sensed flow demand has ceased. PAV+ uses transient end-inspiratory occlusions to measure respiratory system elastance and resistance, calculates work of breathing, and delivers support to a preset level of assistance.

Like pressure-targeted breaths, PAV+ flow delivery varies with patient effort; unlike pressure-targeted breaths, pressure also varies with patient effort. The conceptual benefit to PAV+ is that flow and cycle synchrony should be enhanced compared to conventional flow- or pressure-targeted breaths. Another conceptual benefit is that patient-driven V_T variability with its theoretical lung protective benefits may be enhanced.[163] Because there is no minimum pressure or flow provided, the patient is forced to breathe to receive ventilatory support. This theoretically avoids the risk of VIDD but also means that PAV+ must be used with caution in patients with low respiratory drive or respiratory muscle weakness (i.e., unable to generate inspiratory flow).

Most clinical studies with PAV have shown enhanced synchrony compared with conventional modes.[161–168] However, it is not clear how PAV+ support should be titrated in various clinical settings. One relatively new approach is to adjust the PAV support level to a target effort level; this is particularly feasible in PAV+ relative to other modes because patient effort can be directly estimated from airway pressures at a given assist level.[169] Moreover, clinical trials have not demonstrated any beneficial effects of PAV or PAV+ on important clinical outcomes (e.g., ventilator duration, sedation needs, mortality) when compared with conventional assisted/supported ventilation.[170]

Neurally Adjusted Ventilatory Assist

NAVA utilizes the diaphragmatic EMG signal to trigger, adjust flow, and cycle-assist breaths.[165,171] The conceptual benefit to NAVA is that synchrony with all three phases of breath delivery (trigger, gas delivery, and cycle) should be enhanced over conventional flow- or pressure-targeted breaths. Like PAV, another conceptual benefit is that patient-driven V_T variability with its theoretical lung protective benefits may be enhanced. Similar to PAV, there is no minimum pressure or flow provided with NAVA. Thus, NAVA must also be used with caution in patients with low respiratory drive. Moreover, there is concern about the stability of the EMG signal coming from a catheter that can move within the esophagus. Thus all patients on NAVA require careful monitoring and backup support modes.

Most clinical studies with NAVA have shown enhanced synchrony compared with conventional modes.[172–176] However, like PAV, it is unclear what the optimal EMG setting(s) should be in various clinical settings. The single randomized trial published to date found no benefit from NAVA in comparison to PSV.[177]

BEDSIDE IMAGING DURING MECHANICAL VENTILATION

Lung ultrasound is a point-of-care imaging tool that may be used to guide and monitor mechanical ventilation[178,179] (see also Chapters 23 and 24). Lung ultrasound findings

can help to identify areas of consolidation and their potential response to recruitment maneuvers, changes in PEEP, or position (e.g., proning).[180] Changes in lung aeration during a weaning trial may also help identify patients at high risk for postextubation distress.[181] Finally, lung ultrasound can help to diagnose common complications in mechanically ventilated patients, such as atelectasis, pleural effusions, and pneumothoraces.[180]

Electrical impedance tomography (EIT) is a noninvasive and radiation-free bedside imaging tool that can be used to monitor changes in lung volume, ventilation distribution, and regional respiratory mechanics during mechanical ventilation.[182] Although other imaging modalities, such as computed tomography, may have greater spatial resolution, EIT offers better temporal resolution and eliminates the need to transport the patient, making it more practical for bedside monitoring.[183] Although promising, studies using EIT have mainly focused on evaluating regional changes during PEEP titration and changes in ventilatory modes and physiologic end points. Future prospective studies are needed to investigate the utility of EIT-guided ventilatory strategies and its effects on patient important outcomes.

Key Points

- Positive-pressure breaths are characterized by three variables: the breath trigger, the flow delivery target (pressure or flow), and the cycle criteria.
- The interactions of positive-pressure breaths and respiratory system mechanics are described by the equation of motion: Pressure = (flow × resistance) + (volume/system compliance).
- In lungs with collapsed alveoli, alveolar recruitment is accomplished by transient increases in positive-pressure inflation and is maintained by positive end-expiratory pressure.
- Ventilator-induced lung injury can be caused by several mechanisms, including alveolar overdistention and repetitive alveolar collapse/reopening.
- Mechanical ventilation can also cause ventilator-induced diaphragm dysfunction through a variety of mechanisms (ventilator "myotrauma").
- Support with mechanical ventilation involves trade-offs—balancing the need for providing adequate support while minimizing the risk of ventilator-induced lung injury, ventilator-induced diaphragm dysfunction, and other complications.
- Expeditious liberation from mechanical ventilatory support requires regular sedation adjustments and assessments of spontaneous breathing capabilities.

ACKNOWLEDGMENT

We acknowledge Neil R. MacIntyre, MD, who authored earlier versions of this chapter.

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136 NONINVASIVE SUPPORT OF VENTILATION

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INTRODUCTION

Mechanical ventilation (MV), a life-saving procedure with applications in acute and chronic respiratory failure, was initially delivered through an endotracheal tube or via a tracheotomy cannula. In the early 1990s, clinicians started to demonstrate a major interest in noninvasive techniques as a way of avoiding endotracheal intubation in the acute care setting.[1–3] The indications have progressively been extended from hypercapnic *acute respiratory failure* (ARF) to a large variety of clinical situations. Currently, there are a number of specific indications for noninvasive ventilation as the standard of care for ARF, but also several situations in which there is uncertainty about the usefulness or the limits of noninvasive ventilation (Table 136.1).

For this chapter, *noninvasive ventilation* (NIV) is considered to consist of two main modes: *continuous positive airway pressure* (CPAP) and, the most frequently used mode, *bilevel positive airway pressure* (BPAP). BPAP can be delivered via several specific ventilatory modes explained below. The purposes and applications of each are discussed.

Soon after the introduction of endotracheal MV, complications of MV began to be identified,[4,5] some directly related to the intubation procedure (e.g., cardiac arrest, laryngeal or tracheal injury, hemodynamic compromise, and ventilator-induced lung injury from excessive distension), as well as others related to the bypass of the normal upper airway barrier, thus setting the stage for ventilator-associated pneumonia. Invasive MV often requires sedation, which itself is often a cause of prolonged weaning. These major safety considerations prompted efforts to develop noninvasive methods for delivering positive-pressure ventilation. Thus, in patients with ARF, the main goal of NIV is to provide ventilatory assistance without endotracheal intubation, thereby lowering the risk of adverse events associated with invasive MV. There is convincing evidence that NIV has diminished the rates of nosocomial infections[6–8] because it reduces the overall invasiveness of patient management: sedation is either avoided or administered at low levels, and the use of central venous lines, urinary catheters, and other invasive devices is reduced (Fig. 136.1).[9]

Another important factor favoring the use of NIV is the growing number of patients who are unwilling to accept endotracheal intubation or considered poor candidates for invasive MV because of a fragile underlying health status.[10,11] In these patients, NIV can offer a chance of recovery with a lower risk of complications and can be considered as a ceiling of therapy with acceptable risks. Potential benefits and risks of the technique are discussed later and summarized in Table 136.2.

PATHOPHYSIOLOGY, RATIONALE, AND EXPECTED BENEFITS

COPD EXACERBATION

Exacerbation of COPD is a common cause of admission to the hospital and ICU. The main pathophysiologic pathway is inability to maintain adequate alveolar ventilation in the presence of major abnormalities of respiratory mechanics that, along with respiratory acidosis and hypoxemia, augment the respiratory drive. Patients are unable to take sufficient tidal volumes because of high intrinsic *positive end expiratory pressure* (PEEP), high airway resistance, and a flattened diaphragm. They breathe at the limit of exhaustion, allowing the arterial *partial pressure of carbon dioxide* (P_{CO_2}) to rise. The resulting transdiaphragmatic pressure can be considerably higher than normal, increasing the risk of respiratory muscle fatigue.[3] This vicious circle can

Table 136.1 Recommendations for the Use of Noninvasive Ventilation During Acute Respiratory Failure According to Disease and Clinical Status

DISEASE				CLINICAL STATUS	
Strong Recommendation	**Intermediate Recommendation**	**Weak Recommendation**	**No Recommendation or Contraindication**	**Yes**	**No**
Exacerbations of COPD Acute cardiogenic pulmonary edema Facilitation of weaning/extubation patients with COPD Postoperative hypoxemia after major abdominal or lung surgery Acute respiratory failure in patients with obesity-hypoventilation Do-not-intubate patients	Asthma Hypoxemic respiratory failure in non-immunocompromised patients Preventive use during procedures (upper endoscopies, endotracheal intubation) Community-acquired pneumonia in patients with COPD Neuromuscular disease	Mild ARDS Community-acquired pneumonia (non-COPD) Acute respiratory failure in immunocompromised patients Trauma Extubation failure (non-COPD) Postoperative preventive esophageal or lung surgery (using low pressures)	Severe ARDS ARDS with multiple organ dysfunction End-stage interstitial pulmonary fibrosis Facial trauma Facilitation of weaning (non-COPD) Non-drained pneumothorax	Conscious and cooperative (except encephalopathy from COPD) Hypercapnic failure Hemodynamically stable No other organ failures Improvement in gas exchange, respiratory and heart rate within first 2 hr	Hemodynamic instability Loss of consciousness Abdominal distention, nausea or vomiting Non-cooperative

ARDS, acute respiratory distress syndrome; ARF, acute respiratory failure; CPE, cardiogenic pulmonary edema; ICU, intensive care unit.



Figure 136.1 Noninvasive ventilation in the intensive care unit. Photograph shows a patient treated by noninvasive ventilation using an oronasal face mask covering the nose and the mouth. A ventilator with a double circuit is used.

be modified by NIV, which allows the patient to augment tidal volumes with less effort.[3,12] As alveolar ventilation increases, arterial P_{CO_2} and pH values improve, which reduce the respiratory drive and dyspnea.

CARDIOGENIC PULMONARY EDEMA

In *cardiogenic pulmonary edema* (CPE), pulmonary congestion reduces lung compliance causing hypoxemia and increased work of breathing. In turn, intense inspiratory efforts cause large negative swings in intrathoracic pressure that not only augment venous return but also increase left ventricular afterload, impeding left ventricular ejection. Many patients with CPE improve rapidly under therapy with medications alone. A few, however, develop severe respiratory distress and/or refractory hypoxemia/hypercapnia and require ventilatory support while medication treatment continues.[13,14] PEEP applied by CPAP and other types of NIV improves lung compliance and decreases shunt and ventilation-perfusion abnormalities, resulting in improved oxygenation and reduced work of breathing and sense of dyspnea. Moreover, positive intrathoracic pressures decrease left ventricular afterload in non–preload-dependent patients[15] and reduce right and left ventricular preload.[16] The net effect on cardiac function is usually beneficial. NIV has therefore become a useful complementary approach to drug therapy in patients with CPE.[17,18]

HYPOXEMIC ACUTE RESPIRATORY FAILURE

Unlike exacerbations of COPD or CPE, hypoxemic ARF represents a heterogeneous group of diseases with different prognoses and treatments. Robust large randomized controlled trials are relatively scarce in this setting, and guidelines and recommendations are often not straightforward.[19] Specific downsides of NIV in this setting have been described over the past several years.

The hallmark of hypoxemic ARF is acute hypoxemia (arterial P_{O_2}/fractional concentration of oxygen in inspired gas [F_{IO_2}] ratio ≤300) with clinical signs of respiratory distress, hyperventilation, and hypocapnia. Hypercapnia is a serious late complication, indicating impending respiratory muscle failure. The rationale for using NIV in hypoxemic ARF is to improve hypoxemia and to alleviate the high load imposed on the respiratory muscles (prevention of latent pump failure). Notwithstanding, NIV is not a cure for the disease and, when interrupted or poorly delivered, the patient immediately returns to the pre-NIV state. In fact, a beneficial effect of NIV on gas exchange and dyspnea may even mask an underlying disease deterioration. This could lead to life-threatening respiratory failure in case of interruption. During the initial phase, patients are often able to cope with the increased respiratory workload but, by the time they become unable to

Table 136.2 Potential Benefits and Risks of Noninvasive Ventilation for Acute Respiratory Failure

Benefits	Risks
■ Respiratory muscle unloading	■ Interface intolerance
■ Improved dyspnea and gas exchange	■ Skin lesions
■ Left ventricular afterload decrease	■ Abdominal distention and regurgitation
■ Left and right ventricular preload decrease	■ Impaired cough
■ Less invasive management	■ Masking deterioration of underlying disease
■ Decreased risk of nosocomial infections	■ Patient ventilator asynchrony
■ Decreased use of sedation and vasoactive drugs associated with intubation	■ Limited ability for lung protective ventilation/risk of lung injury

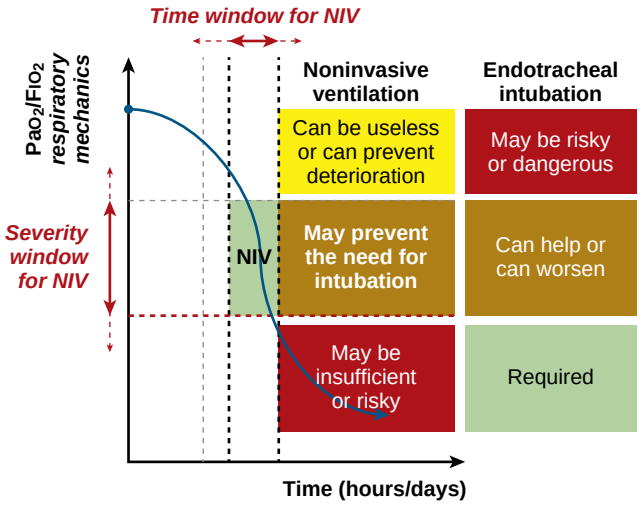

Figure 136.2 The decision windows for *noninvasive ventilation* (NIV) or endotracheal intubation. There is an optimal window of time and severity of injury in which to consider NIV. As a patient worsens over time (see curve of patient course), one must consider whether the severity is appropriate for NIV or intubation and invasive mechanical ventilation. For the right level of severity, NIV can be valuable in offering needed support and perhaps preventing the need for intubation. If the severity worsens further, NIV may be insufficient or risky, and intubation may then be required. If the condition is mild, neither NIV nor invasive mechanical ventilation would be warranted. Unfortunately, there are no strictly objective criteria that delineate the windows of severity or of time for determining exactly when NIV should be used.

meet the respiratory requirements, NIV use may be ineffective or even harmful. Therefore, there is probably a limited time and/or a severity window for delivering NIV as a preventive support beyond which its use may become risky (Fig. 136.2).[20]

Many patients with acute hypoxemia and *acute respiratory distress syndrome* (ARDS) may not be favorable candidates for NIV due to the need for delivering lung-protective ventilation. During NIV, high transpulmonary pressure swings and large tidal volumes may be generated, which could lead to the development of (unintentional) patient self-inflicted lung injury and contribute to the poor outcome observed in intubated patients who do not respond to NIV. NIV should provide a sufficient level of PEEP to improve oxygenation while ensuring an optimal pressure support to unload the respiratory muscles. These two additive pressures generate the peak airway pressure, one of the major determinants of leaks and asynchrony. Therefore, finding the right balance between the two may be challenging. Patients with poor lung compliance requiring high airway pressures may thus prove difficult to manage with NIV.

PRACTICAL AND TECHNICAL ASPECTS

MODES OF VENTILATION AND SETTINGS

Continuous Positive Airway Pressure and Bilevel Positive Airway Pressure

CPAP represents the application of a constant level of positive pressure at the airway opening during spontaneous breathing. CPAP is not always considered as a mode of ventilation support because it does not assist breathing. However, CPAP can increase functional residual capacity by opening atelectatic lung regions, which decreases intrapulmonary shunt, improves oxygenation and lung compliance, and potentially reduces the work of breathing, thus resulting in improvement in ventilation.[21] With CPAP, the presence of intrinsic PEEP can be counterbalanced with external PEEP, allowing a partial reduction of inspiratory effort. In addition, CPAP may reduce the left ventricular afterload by lowering the left ventricular transmural pressure in patients with left heart failure. In this chapter, CPAP is considered as a type of NIV.

BPAP assists the respiratory muscles by providing a pressure during inspiration, in addition to PEEP during expiration. It is most commonly delivered with *pressure support ventilation* (PSV) plus PEEP (which are often thought of as an invasive MV mode but are also feasibly and frequently delivered noninvasively). Often referred to by its proprietary name, BiPAP, BPAP is strongly recommended in cases of respiratory acidosis such as COPD exacerbations.[19] In addition to PSV plus PEEP, BPAP can also be delivered through various other ventilator modes discussed below. To avoid inducing leaks that would complicate NIV administration and impair patient-ventilator synchrony, the pressure delivered is often less than would be delivered during invasive MV; however, insufficient pressure may translate into insufficient inspiratory muscle unloading.

Asynchrony under BPAP

Success of NIV is associated with good clinical tolerance.[25,26] Intolerance can be related to patient-ventilator

asynchrony, defined as a mismatch between the patient's neural inspiratory time and the ventilator insufflation time.[25] Frequent asynchronies accounting for more than 10% of the respiratory efforts were present in 43% of patients undergoing NIV in an observational study.[27] The leading causes of asynchronies with NIV are leaks around the mask, which can be minimized by a properly selected interface and an optimal adjustment of ventilatory settings.[27] Inspiratory leaks cause prolonged inspiration (the most common asynchrony during NIV) and expiratory leaks promote auto-triggering.[28] When leaks develop during inspiration, the ventilator continues to insufflate because the delivered flow remains above the cycling criterion, resulting in a prolonged inspiration.[27] This problem was highly prevalent when using old versions of ICU ventilators. "NIV" modes are now available on ICU ventilators and on portable dedicated NIV devices. These modes include algorithms that measure and compensate for leaks.[28,29] When leaks develop during expiration, a pressure drop below the external PEEP level or a drop in expired bias flow can simulate the patient's effort and auto-trigger a breath. Auto-triggering may promote a short cycle or a flow distortion because the patient does not generate any effort and closes the glottis at the time the inspiration is auto-triggered. NIV-dedicated ventilators have specially designed algorithms that markedly limit auto-triggering.[30]

Other Modalities

In addition to PSV plus PEEP, BPAP can be delivered with various additional modes of ventilation: volume-targeted ventilation, negative pressure ventilation, and neurally adjusted ventilation, although these alternative modes are seldom used in clinical practice.

Volume-targeted ventilation delivers set flow, inspiratory time, and tidal volume with each breath; inflation pressure varies with the intensity of the patient's effort. Volume-targeted ventilation is rarely used in ARF because it may induce high peak pressures, causing discomfort and leaks, gastric distension, and skin necrosis.

Negative-pressure ventilation (i.e., iron lung) may be noninferior to invasive MV; however, it is available in only a few centers throughout the world.[3–33]

Neurally adjusted ventilation is based on the detection and quantification of the electrical activity of the diaphragm by means of an esophageal array of bipolar electrodes. The ventilator is triggered, limited, and cycled off directly by electrical activity of the diaphragm to synchronize mechanical ventilation with neural inspiration. One advantage is that neurally adjusted ventilation should not be affected by leaks. Several studies in heterogeneous groups of ICU patients demonstrated that NIV with neurally adjusted ventilation considerably reduces patient-ventilator asynchronies (mostly wasted efforts) relative to BPAP with traditional PSV plus PEEP.[34–39] Further studies will determine whether neurally adjusted ventilation improves NIV outcome.

In addition to studies of various ventilator modes for NIV delivery, there were also some early promising results on the use of helium-oxygen mixture for patients with COPD exacerbations treated with NIV. However, subsequent large trials were unable to demonstrate a significant benefit.[40–43]

VENTILATORS

Dual- or single-limb circuits can be used to deliver NIV. Mechanical ICU ventilators use a dual-limb circuit with one line for inspiration and one for expiration. Portable ventilators often use single-limb circuits and a mask with intentional leaks for CO_2 removal. Open single-tube circuits require either a vented mask with a built-in passive exhalation port or a nonvented mask with an active exhalation valve to allow for CO_2 removal. The Boussignac CPAP device is a small cylindrical plastic adaptor that fits on a modified face mask. The system uses the incoming flow of oxygen to generate a turbulent virtual pressure valve in the open expiratory side of the mask. The gas is accelerated and circumferentially enters into the open-ended cylinder, generating air entrainment and positive pressure.[44,45]

NIV can be delivered using ICU ventilators with NIV modes or ventilators specifically dedicated for NIV. ICU ventilators offer better monitoring capabilities and the ability to continue invasive MV and full ventilatory support in the event of intubation. They usually limit prolonged inspirations.[30,46] Irrespective of the type of ventilator used to deliver NIV, careful observation and frequent adjustment of the airway pressure and flow-time curves can improve patient-ventilator interaction and normalize arterial P_{CO_2} levels.[47,48]

Airway gas conditioning (i.e., the warming and humidification of inspired gas) is performed by the human airway during normal breathing. During NIV, the normal airway gas conditioning mechanisms can be insufficient when there are high-flow, high-airway pressure settings, and high inspired oxygen fractions. Inadequate humidification can cause damage to the nasal mucosa, inducing high nasal airway resistance.[49,50] ICU ventilators provide low levels of humidity compared with turbine or piston NIV ventilators due to the exclusive use of dry gas, and gas humidification is therefore needed. The humidification ability of moisture exchanger filters is reduced in the presence of leaks,[50] and their internal volume may impose an additional workload by generating CO_2 rebreathing.[51,52] Some experts have therefore suggested that heated humidifiers might be preferable to heated moisture exchangers. However, a randomized trial did not find any difference in the rate of NIV failure comparing heated moisture exchanger filters to heated humidifiers on ICU ventilators.[53]

INTERFACES

The interface is an essential component of NIV. An important distinction concerns leaky masks for single-circuit ventilators versus masks without intentional leaks for double-circuit ventilators or for a single circuit equipped with an expiratory valve. New masks are often made of two or more parts: a frame made of stiff transparent material and a cushion of soft material to seal the frame against the patient's face.[54,55] Improvements have been realized by using different cushions with new materials, by improving the fixation system, and by increasing the number of the attachment points, permitting a more uniform distribution of pressure.

Oral and nasal interfaces are mostly used for chronic NIV.[54,56] The use of nasal interfaces in ICU patients results in major leakage through the mouth that diminishes the effectiveness of NIV and promotes asynchrony and discomfort.[57–59] Oral interfaces are associated with significant leaks and asynchrony and require good patient cooperation.[60–67]

Face masks can be either oronasal or total face; both appear to have similar efficacy and patient tolerance.[68] Large masks enclosing the entire face or head (i.e., helmet) have been developed.[69,70] Large masks are comparable to standard full face masks in terms of respiratory muscle unloading, patient comfort, and arterial blood gas improvement, suggesting that the theoretical risk of rebreathing associated with the large internal volume may be small or nonexistent in clinical practice.[60,62–65,67,71]

Helmets cover the entire head and have several advantages: they allow patients to communicate, drink, and interact, are applicable regardless of the face contour, lower the risk of skin lesions, and may enhance patient tolerance. Compared with other interfaces, NIV with a helmet has been shown to reduce hospital mortality, intubation rate, and complications, mainly in patients with hypoxemic ARF.[72,73] In 2016, Patel et al. compared the traditional face mask approach with the helmet interface in patients with ARDS undergoing NIV. The single-center trial was prematurely stopped when the interim analysis found a 43% absolute reduction in intubation in favor of the helmet ($P < 0.001$).[74] Additionally, the helmet significantly reduced ventilator-free days and improved both in-hospital and 3-month mortality (56% and 34%, respectively). A concern with the helmet interface is that it may induce more rebreathing than conventional masks and may be less suitable for patients with hypercapnic respiratory failure.[75] However, changes in arterial blood gases and respiratory rate have been shown to be similar between the helmet and oronasal mask in patients with COPD and hypercapnic ARF.[76] The helmet is generally characterized by more asynchronies compared to face masks,[77,78] but a new helmet with less internal volume and better pressurization and triggering performance may improve synchrony and patient comfort.[79] However, helmets for NIV are not yet widely available.

In conclusion, although the helmet may ultimately prove to be the most beneficial NIV interface, oronasal and full face masks are often the first choice in the acute care setting. The helmet can be used as a first-line interface, when available, especially in patients who need high positive airway pressures and are intolerant to face masks. There is no ideal NIV interface for all patients in all circumstances, and several interfaces should be available at the bedside.

INDICATIONS

EXACERBATION OF COPD

In patients with COPD exacerbation, BPAP delivered via traditional PSV plus PEEP has repeatedly been shown to reduce the need for endotracheal intubation, reduce the rate of complications, shorten length of stay, and improve survival.[80–85] Early NIV can and should be used outside the ICU as an important component of first-line therapy for COPD exacerbations to prevent further deterioration.[80,85,86] In 2017, a Cochrane review of 17 randomized controlled trials involving 1264 patients with hypercapnic ARF due to COPD exacerbation confirmed that NIV decreased the mortality risk by 46%, with the number needed to treat to save an additional life of 12. It also decreased the risk of intubation by 65% and significantly decreased length of hospital stay and incidence of complications.[87] With these proven benefits, NIV is increasingly applied in COPD exacerbations with a concomitant decline in intubation, in-hospital mortality, hospital-acquired pneumonia, length of hospital stay, and cost.[88–90] Even in patients with hypercapnic encephalopathy due to COPD exacerbations, it may be worth trying to "wake them up" with NIV.[91,92]

Despite the benefits of NIV, even in experienced centers, patients who do not respond to NIV experience higher mortality than patients initially intubated and treated with invasive MV.[6,88–90,93–95] The most important determinants of NIV outcome are the process of care and careful patient selection. The most severely affected patients, such as those with a pH less than 7.30 on admission,[85] marked mental status alterations at NIV initiation, comorbidities, and a high severity score are at high risk of early NIV failure.[26,96–99] In these patients, NIV might be better applied in the ICU; indeed, many hospital centers require initiation of NIV and continued therapy for acute respiratory failure in an ICU setting. In addition, patients with respiratory arrest, apneic episodes, agitation requiring sedation, hypotension, or heart rate below 60 beats/min require urgent intubation.[19] Some patients experience late or secondary NIV failure after an initial improvement.[100] A longer time from onset of the exacerbation to NIV initiation may also reduce the likelihood of success. Every effort should be made to deliver NIV early; if NIV is begun late, when its use is known to be less effective, close monitoring is necessary.[101]

In conclusion, NIV offers many advantages over standard medical therapy and invasive MV to treat exacerbations of COPD. There is strong evidence that NIV is cost-effective, being both more efficient and cheaper compared with standard therapy alone.[102,103] The European Respiratory Society/American Thoracic Society guidelines strongly recommend a trial of BPAP for patients with ARF associated with COPD exacerbation who develop acute-on-chronic respiratory acidosis ($pH \leq 7.35$).[19]

ASTHMA

There has been a substantial increase in the use of MV (either invasive or NIV) for acute asthma over the past years, accompanied by a shift from invasive MV to NIV.[104,105] In a large retrospective series in the United States,[106] NIV was used in more than 40% of patients with acute asthma exacerbations with a failure rate (i.e., need for intubation) of 4.7%. In-hospital mortality in patients who were ventilated with NIV, ventilated with invasive MV, and experienced NIV failure was 2.3%, 14.5%, and 15.4%, respectively.[19,106] Despite its common use in asthma, the utility of NIV in asthma exacerbations has been rigorously evaluated in only a few small randomized trials with considerable heterogeneity in the protocol used, outcomes

analyzed, and results.[105,107–110] There is no evidence that NIV for the treatment of acute severe asthma reduces mortality. Therefore, no recommendation for the use of NIV in asthma exacerbation can be made, and further studies are required to shed light on this field.[19]

EXACERBATION OF OTHER CHRONIC LUNG DISEASES

All forms of acute-on-chronic ventilatory failure share several common pathophysiologic pathways. NIV seems to be an interesting option in patients with more restrictive lung disease and in cases of associated obesity, especially when respiratory system compliance is still preserved.[9,83,111–121] A large cohort study compared the efficacy of NIV in patients with COPD (n = 543) and in patients with acute respiratory failure due to obesity hypoventilation syndrome (n = 173).[122] Overall survival adjusted for confounders, length of stay, and hospital readmission were similar in both groups. In patients with COPD, obesity was associated with less late NIV failure and lower risk of hospital readmission. These results indicate that patients with obesity hypoventilation syndrome can be treated with NIV during an episode of acute exacerbation with similar efficacy as for patients with COPD.

CARDIOGENIC PULMONARY EDEMA

The first evidence of therapeutic efficacy of positive pressure use during acute CPE was shown in 1985.[123] Subsequent trials demonstrated that NIV improved arterial blood gases and respiratory rate and reduced the rate of intubation compared to standard therapy in CPE.[14,17,124,125] In 1069 patients with acute CPE randomized to receive standard medical treatment plus NIV (CPAP or BPAP) or oxygen therapy, dyspnea, heart rate, and metabolic abnormalities improved more rapidly with NIV, but the intubation and 7- and 30-day mortality rates were similar in both groups (9.8% vs. 9.5% and 16.4% vs. 15.2%, respectively).[126] However, a high crossover rate (15% of patients in the oxygen group crossed over to NIV) could have markedly diminished the ability to demonstrate benefits from NIV. A meta-analysis addressing NIV in patients with ARF due to CPE concluded that, compared with standard medical care, NIV reduced hospital mortality and decreased intubation rates with a number needed to treat for an additional beneficial outcome of 17 and 13, respectively.[127] Additionally, outcomes with CPAP were comparable to BPAP. Therefore, CPAP or BPAP should be applied early in patients with CPE and ARF, even in the pre-hospital setting.[19,128] CPAP can be recommended as a first-line treatment, but BPAP might be preferred in patients with hypercapnia associated with COPD or obesity. Notably, patients with cardiogenic shock, acute myocardial infarction, or altered level of consciousness were not included in most trials, and intubation might be the best option for them. Left ventricular ejection fraction less than 30%, B-type natriuretic peptide level of 3350 pg/mL or greater at baseline, and positive fluid balance of 400 mL or greater within 24 hours after CPE onset have been identified as risk factors for NIV failure.[129]

HYPOXEMIC RESPIRATORY FAILURE

NIV to Prevent Intubation in de Novo Respiratory Failure

De novo respiratory failure is defined as significant hypoxemia (arterial Po_2/Fio_2 < 300 mm Hg) with respiratory distress that does not develop postoperatively or post-extubation and is not associated with chronic lung diseases such as COPD or with CPE. It is the group of patients where the benefit of NIV is more questionable. Contrasting results exist between the benefits observed in short-term physiologic studies and some randomized controlled trials,[9,83,111–115,118–121,130] and the high rates of failure and risk of delaying intubation are concerning.[116,131] Meta-analyses demonstrated significant reduction in intubation rates but a less clear effect on mortality.[73,132] A large observational study in France[133] compared NIV outcomes in patients with acute exacerbation of chronic cardiac or respiratory failure to those with hypoxemic de novo respiratory failure. NIV considerably improved the outcome in the acute-on-chronic group, but not in the de novo group. In summary, identifying which subgroups of hypoxemic patients will truly benefit from NIV use with minimal risk remains unclear and is still a field for investigation. The following specific categories of patients have been studied.

NIV for Pneumonia

In patients with pneumonia, results of small randomized controlled trials are often difficult to interpret because of the concomitant presence of COPD or CPE.[83,130,134] Also, extrapolating these results to individual patients requires the same careful selection process, with exclusion of patients with contraindications. Contrary to randomized trials, observational studies of NIV in pneumonia have often shown higher rates of failure.[2,115,121,133] These results suggest that NIV should not be used when the risk of failure is high, and intubation should not be delayed when clinical signs and symptoms indicate impending NIV failure.[135] The presence of shock, loss of consciousness, respiratory arrest or respiratory pauses, NIV intolerance, or major secretions should be considered contraindications.

NIV for ARDS

ARDS is a strong predictor of NIV failure.[112,136,137] In a multicenter survey, early applications of NIV in patients with ARDS prevented intubation in no more than 50% of patients, with a 54% mortality rate among those with NIV failure.[138] On the other hand, fewer patients with mild ARDS who were treated with NIV required intubation and experienced organ failure than those receiving conventional treatment, according to a prospective, randomized controlled trial.[139] During the H1N1 pandemic, NIV was used widely with favorable results in many patients but also had a high rate of failure.[140–142] Viral transmission did not seem to be an issue, although more data are needed to address this question.[143,144] A 2016 trial that tested the performance of NIV via helmet in patients with ARDS was more encouraging. In the study by Patel et al., the rate of intubation in ARDS patients treated with helmet NIV was 18%, significantly lower than that of patients treated with NIV via face mask (62%).[74] Helmet NIV reduced 90-day

mortality by 22%, improved patient tolerance, and was related to better neuromuscular performance and functional outcomes after 1 year.[145] Notably, patients treated with helmets had higher PEEP and lower inspiratory pressure (PSV) levels than those treated with face masks, settings that may have reduced lung injury.

In general, NIV use in patients with ARDS remains debated due to several reasons. It is very difficult to target lung-protective ventilation during NIV. High respiratory drive and strong inspiratory efforts generate high transpulmonary pressures, resulting in lung stress and strain through high tidal volumes and pendelluft phenomenon (by redistribution of gas to the more abnormal and susceptible areas of lung), capillary leak, and lung edema.[146,147] An arterial Po_2/Fio_2 of 200 mm Hg or less and a tidal volume greater than 9 mL/kg of predicted body weight 1 hour following NIV have been strongly associated with need for intubation and mortality.[148,149] In the Lung Safe Study, NIV failure increased from 22.2% in mild ARDS to 42.3% and 47.1% in moderate and severe ARDS, respectively.[150] Data from Lung SAFE showed that NIV use was independently associated with increased ICU mortality (hazard ratio, 1.4; 95% confidence interval, 1.2 to 1.8) but not hospital mortality. In a propensity-matched analysis, ICU mortality was higher in NIV than in invasively ventilated patients with an arterial Po_2/Fio_2 lower than 150 mm Hg. Therefore, a recommendation against the use of NIV in ARDS patients with severe hypoxemia is reasonable. Beyond the severity of hypoxemia, factors such as high APACHE II and SOFA score, shock, increased heart rate, acidosis, altered level of consciousness, and tachypnea have been linked to NIV failure in ARDS.[149,151–154] Recently, the HACOR score, which evaluates the heart rate, acidosis, consciousness, oxygenation, and respiratory rate in hypoxemic patients, has been introduced.[154] A HACOR score of greater than 5 at 1 hour of NIV predicted NIV failure in hypoxemic patients with high accuracy (>80%) (Table 136.3).

Overall, no firm recommendations concerning the use of NIV in ARDS can be made.[19] If a trial of NIV is chosen, it should be offered at the earliest stages of ARDS, by an experienced clinical team, and in carefully selected patients (arterial Po_2/Fio_2 >200 mm Hg, no abnormal mental status, no organ failure). Patients should be closely monitored and intubation applied without hesitation in the absence of significant improvement.

NIV in Immunocompromised Patients

The prognosis of immunocompromised patients with ARF has clearly improved in the past 20 years. Invasive MV was repeatedly identified as an independent mortality predictor in this population, and the potential to reduce infectious complications and ventilator-induced lung injury was a strong rationale for NIV use in immunocompromised pat ients.[9,113,114,119,155] NIV has been shown to be beneficial in cancer patients with respiratory failure[9,113,119] and represented the first-line treatment in 49% of patients with cancer admitted to the ICU with respiratory failure, and demonstrated a 62% success rate in a large cohort.[156] Nonetheless, when ARDS was the cause of ARF in cancer patients, NIV failure was as high as 71%.[152] The application of NIV in hematologic malignancies is particularly challenging, and its failure is associated with a mortality of more than 70%. When applied in patients with hematologic malignancies, failure rates have been reported at around 50%, without significant benefit in mortality, infections, intubation rate, duration of mechanical ventilation, or ICU length of stay compared to oxygen therapy alone.[137,157–159]

NIV in ARF associated with immunosuppression has a dual effect: when it succeeds, NIV increases survival by avoiding invasive ventilation but, when it fails, mortality is higher than that compared to immediate intubation. It is therefore crucial to distinguish which patients will most likely benefit from NIV. Presence of hematologic malignancy, high SOFA score, need for vasopressors, renal replacement therapy, ARDS, severe hypoxemia, tachypnea during NIV, and delayed NIV application are predictors of NIV failure.[156,160] Therefore, NIV cannot be recommended in these patients.

Table 136.3 Calculation of HACOR Score to Predict NIV Failure

Variables	Category	Assigned Points
Heart rate (beats/min)	≤120	0
	≥121	1
Acidosis (pH)	≥7.35	0
	7.30–7.34	2
	7.25–7.29	3
	<7.25	4
Consciousness (Glasgow Coma Scale)	15	0
	13–14	2
	11–12	5
	≤10	10
Oxygenation (arterial Po_2/Fio_2)	≥201	0
	176–200	2
	151–175	3
	126–150	4
	≤100	6
Respiratory rate (breaths/min)	≤30	0
	31–35	1
	36–40	2
	41–45	3
	≥46	4

Points are assigned based on five physiologic variables according to specific categories and points above. Points are then added together for a total score ranging from 0 to 25. A score greater than 5 at 1 hour of NIV predicts failure in hypoxemic patients.

From Duan J, Han X, Bai L, Zhou L, Huang S. Assessment of heart rate, acidosis, consciousness, oxygenation, and respiratory rate to predict noninvasive ventilation failure in hypoxemic patients. *Intensive Care Med.* 2017;43(2):192–199.

PREVENTION OF POSTOPERATIVE COMPLICATIONS

Respiratory compromise complicates the course of approximately 10% of all surgical patients and almost 40% of patients undergoing an abdominal or thoracic surgery. NIV is becoming increasingly popular for the prevention or treatment of postoperative respiratory complications.[161–163]

Pathophysiology of Postoperative Respiratory Complications

After thoracic or upper abdominal surgery, the patient's pulmonary condition can worsen due to complications directly related to surgery, residual anesthesia, or pain. Major abdominal and thoracic surgeries and anesthesia may cause large reductions in functional residual capacity and transient diaphragmatic dysfunction leading to hypoxemia and/or hypercapnia. Perioperative fluid overload, high tidal volumes used during surgery, transfusion-related acute lung injury, inflammation, sepsis, and aspiration may further worsen respiratory function. Respiratory deficits are maximal in the first hours after surgery and generally recede over 1 or 2 weeks. Restoring lung volume, preventing atelectasis, improving gas exchange, and decreasing the work of breathing may be achieved through different forms of NIV, including CPAP.[161–163] The use of postoperative NIV has been advocated for both prophylactic and treatment purposes.[162,164,165]

Prophylactic NIV in the Postoperative Period

Institution of NIV early after extubation in postoperative obese patients improved oxygenation and lung function by preventing the development of atelectasis.[166–168] Early CPAP for at least 6 hours following thoracic or major abdominal surgery significantly reduced pulmonary complications and reintubation rate compared to standard care in several trials.[169–171] A 2014 multicenter trial, however, failed to demonstrate any benefit of postoperative NIV in COPD patients undergoing major lung resection.[172]

Therapeutic NIV in the Postoperative Period

NIV has been shown to improve outcomes when used as a treatment for respiratory failure after major surgery.[9,161,162,165,172–176] In a large multicenter randomized trial of 293 patients with postoperative ARF following abdominal surgery, when compared with standard oxygen therapy, NIV was associated with a decrease in the intubation rate (33% vs. 46%) and health care–associated infections (31% vs. 49%).[176] However, the ICU and hospital lengths of stay and mortality rate did not significantly differ in these studies.[165,176]

Overall, NIV (including CPAP) can be used after major surgery, either as a semi-preventive tool in hypoxemic patients or as a therapeutic tool to reduce the rate of pulmonary complications and reintubation.[19] More data are needed to assess whether this is associated with a decrease in mortality. Because the risk of surgical complications induced by positive-pressure ventilation is unclear, it is probably wise to keep airway pressures at the lowest effective level.[175]

Chest Trauma

Respiratory failure following trauma is not a classical indication for NIV, and its efficacy in systematic review analysis is, for the most part, unclear.[177,178] To date there are only three randomized trials in severe chest trauma: two compared CPAP with intubation and one compared BPAP with high-flow oxygen mask.[179–181] The results indicated no significant effect on mortality but suggested a potential benefit with regard to ICU and hospital length of stay, intubation rate, and incidence of pneumonia.

DO-NOT-INTUBATE PATIENTS

NIV is now used frequently in patients in whom intubation is not desirable.[182–188] This approach is feasible and often well tolerated, with an overall survival rate of 50–70%, depending on the patient population.[182,183] An important distinction should be made between NIV administered as the upper limit of care versus NIV as part of palliative care to relieve dyspnea at the end of life.[183,186] Regarding the first indication, NIV offers an interesting possibility to improve a substantial number of patients, and its application in do-not-intubate patients is not associated with a decline in health-related quality of life, mental health, anxiety, depression, or posttraumatic stress disorder of patients and their relatives.[189] We have only limited information on the real benefit of NIV in purely palliative care.[184,186] NIV in end-of-life patients aims to alleviate dyspnea and anxiety and to allow communication. Therefore, its use should be discouraged in patients who do not tolerate it and in those with decreased level of consciousness.

DURING THE WEANING PROCESS AND POST-EXTUBATION

Weaning

Approximately one-third of invasively ventilated patients experience difficulties in weaning, and extubation to NIV may accelerate the weaning process.[190,191] This approach was examined in several trials with contradictory results.[117,190-193] Times to extubation were usually reduced, but this was not consistently translated into a reduction in hospital and ICU stay and mortality because the total duration of ventilation was not reduced.[117,190,192,194,195] Nosocomial pneumonia and sepsis were either reduced or remained unaffected.[117,190] In the most recent multicenter trial, 364 patients who failed a spontaneous breathing trial were randomized to either early extubation to NIV or continued invasive ventilation until a successful spontaneous breathing trial.[192] The two strategies were identical in terms of liberation from MV, reintubation, tracheostomy, adverse effects, and survival. In a meta-analysis, weaning with NIV reduced mortality at hospital discharge, the incidence of VAP, the duration of invasive ventilation, and the ICU length of stay compared with standard weaning.[196] Greater benefits were seen in COPD patients, with some uncertainty about the effects of NIV weaning in the non-COPD population.

Post-extubation

In the post-extubation period, NIV can be used either to prevent the development of ARF or as a strategy to avoid reintubation when ARF develops. As a preventive measure, routine application of NIV in unselected non-high-risk patients does not reduce reintubation or mortality rates and is not supported by available data.[197] By contrast, in patients at high risk of extubation failure (i.e., >65 years, respiratory or cardiovascular comorbidities), NIV prevents post-extubation respiratory failure, reduces reintubation and, possibly, mortality.[198–203] The protective effect of NIV after extubation is greater in patients intubated due to respiratory acidosis or heart failure.[204]

NIV has been proposed as a way to minimize reintubations in the approximately 10–20% of critically ill patients who fail extubation.[205,206] However, available studies suggest that when post-extubation respiratory failure has developed, delivering NIV is often futile and, indeed, may delay reintubation and increase mortality.[199,207] In a landmark trial by Esteban et al., NIV use in patients who failed extubation significantly increased mortality, whereas a potential benefit was suggested only in patients with known COPD.[207]

In conclusion, in the post-extubation period, NIV use is justifiable only as a way to prevent ARF in selected patient populations such as patients with advanced age, underlying cardiac or respiratory disease, prolonged duration of MV, and/or hypercapnia during the weaning test. If these patients were invasively ventilated for more than 24 hours, NIV should be applied immediately after extubation, before the development of ARF.[19,208]

PREVENTIVE USE DURING PROCEDURES

Endoscopic Procedures

Endoscopic procedures of the airway, cardiac, and gastrointestinal tract are relatively invasive, often necessitate sedation, and may adversely affect gas exchange, lung mechanics, and hemodynamics. Respiratory failure is often severe, especially in patients with poor respiratory reserve.[209,210] The periprocedural NIV use can be beneficial in many ways: (1) before the procedure to preoxygenate the patient and increase the respiratory reserve, (2) during the procedure to prevent or treat alveolar derecruitment and compensate for the extra work of breathing imposed by the procedure, and (3) after the procedure to enhance patient recovery.[211] NIV is mostly studied during bronchoscopy in at-risk patients where it has been shown to improve oxygenation and lower the incidence of respiratory failure necessitating ventilator support.[61,212–216] This may translate into a reduction of procedure-related intubations, although more studies are necessary to answer this question.

Endotracheal Intubation

Severe hypoxemia during intubation of hypoxemic patients is common. Compared with bag-valve-mask, NIV preoxygenation could improve arterial P_{O_2} levels with a lower incidence of desaturations during the intubation procedure.[217] In patients already receiving NIV, discontinuation of NIV and preoxygenation with bag-mask has been associated with significantly increased adverse events.[218]

EPIDEMIOLOGY OF NONINVASIVE VENTILATION IN ACUTE CARE

Three multicenter international observational studies with up to 8000 patients, performed in 1998, 2004, and 2010,[219–221] showed that the use of NIV progressively increased from less than 5% to around 15% of all admitted ICU patients, with a consistent success rate and therefore a higher number of patients avoiding the need for intubation. A greater number of patients with COPD or heart failure were also successfully treated with NIV outside the ICU. Similar observational studies in France[26,182,222–224] showed a major increase in NIV use as first-line ventilation support for all ICU patients requiring MV. BPAP was the most used ventilatory mode (83%), followed by CPAP (8%) and assist-control ventilation (7%).[133] In the most recent French observational study,[182] NIV use continued to increase, but interestingly, with a slight but significant decrease in patients with hypoxemic ARF. Acute hypercapnic respiratory failure and acute CPE remain the most frequent indications for NIV. The type of hospital may affect the frequency of NIV use, with one study demonstrating that non-university hospitals use NIV to treat acute-on-chronic lung disease more frequently than university hospitals.[225]

HOME NONINVASIVE VENTILATION

Epidemiology

Home NIV refers to the long-term (>3 months) daily application of mechanical ventilation in the home setting through a nasal, oral, or oronasal interface.[226] Prescription of home NIV has massively increased over the past decades as a result of the increasing prevalence of obesity-hypoventilation and COPD. Major technologic improvements in ventilators and interfaces, with a progressive shift from volume-cycled to less expensive, lighter, and often more comfortable pressure-cycled ventilators, have also contributed to accelerating this approach.[226,227] The EuroVent Survey[226] studied patterns of home ventilator use in 16 European countries. The prevalence of patients receiving long-term ventilation varied widely between countries, with an overall average of 6.6 per 100,000. Although identical surveys are not available for the North American population, the prevalence is expected to be similar in the United States and Canada.[228,229] Herein we review the pathophysiology of respiratory failure in lung disease and main indications for home NIV, with special attention to the three major indications (neuromuscular diseases [NMD], obesity hypoventilation syndrome [OHS], and COPD). Monitoring of home NIV is also discussed.

Pathophysiology

Hypoventilation becomes chronic when the respiratory system becomes unable to cope with the metabolic production of CO_2 and maintain arterial P_{CO_2} within normal limits as a result of respiratory system load capacity imbalance.[230] In chest wall dysfunction and NMD, a typical vicious circle of decline begins with rapid eye movement sleep hypoventilation and bicarbonate retention. As diaphragm dysfunction progresses, non–rapid eye movement sleep hypoventilation appears and progresses to daytime hypercapnia.[231] The clinical course in COPD is most often punctuated with episodes of acute-on-chronic respiratory failure related to chest infections. Therefore, aims and targets of home NIV may not necessarily be the same for all disease categories.

Indications for Home NIV

Subjects with a condition known to cause alveolar hypoventilation should undergo regular workups to determine whether they are eligible for home NIV. Early symptoms suggestive of sleep hypoventilation should be specifically sought, such as excessive daytime sleepiness, fatigue,

morning headaches, cognitive dysfunction, depression, and dyspnea.[232] The American Academy of Sleep Medicine[233] defines hypoventilation during sleep as (1) arterial carbon dioxide (or a surrogate such as transcutaneous or end-tidal CO_2) greater than 55 mm Hg for 10 minutes or more or (2) an increase in arterial P_{CO_2} greater than 10 mm Hg from awake supine value to a value exceeding 50 mm Hg for 10 minutes or more. In addition to monitoring of early symptoms and detection of sleep hypoventilation, regular assessment of respiratory function and inspiratory muscle strength is essential for the decision to implement NIV electively for the prevention of acute respiratory failure, especially in NMD. Measuring vital capacity is highly reproducible, and decreases in vital capacity should lead to further investigations when it falls below 50% of the predicted value. Measurement of supine vital capacity is a sensitive marker of diaphragmatic dysfunction, and a fall greater than 15% when supine compared to sitting correlates well with orthopnea[234]; a decrease of greater than 20% is highly suggestive of diaphragmatic dysfunction. Inspiratory muscle strength (e.g., sniff nasal inspiratory pressure and maximal inspiratory mouth pressure) can easily be assessed with inexpensive portable devices. The former may be easier to perform in NMD, but both measurements are complementary. A negative pressure lower than −70 cm H_2O for men and −60 cm H_2O for women reasonably excludes significant inspiratory muscle weakness.[235]

Special Features in NMD

The clinical course of respiratory failure in NMD is dictated by the natural history of the underlying condition. Some conditions remain stable for decades with reported survival rates greater than 90% at 5 years, whereas others are slowly progressive or rapidly fatal. Therefore, the timing and frequency of clinical evaluation should take into account the underlying neurologic diagnosis. In NMD, an indication for home NIV is based on the reversal of early symptoms of hypoventilation and improvement of *quality of life* (QoL) in patients treated by NIV.[236] Treating subjects with an isolated nocturnal hypoventilation may be warranted. In a randomized controlled trial of NIV in NMD patients with nocturnal hypoventilation and daytime normocapnia, most patients in the control group required initiation of NIV within a few months after documentation of sleep hypoventilation.[237] Those treated by NIV had improved health-related QoL, whereas others were more likely to be admitted with acute-on-chronic ventilator failure.

Amyotrophic lateral sclerosis shares many similarities with other NMDs, but its rapid evolution requires a closer follow-up and more frequent respiratory assessment, usually every 3 months. In a randomized trial, Bourke et al. demonstrated that initiation of NIV resulted in a significant survival advantage of approximately 7 months in amyotrophic lateral sclerosis patients with mild to moderate bulbar involvement and either daytime hypercapnia or orthopnea but did not improve survival in those with severe bulbar involvement.[238]

Special Features of OHS

OHS is defined by the combination of obesity (body mass index > 30 kg/m^2), daytime hypercapnia (arterial P_{CO_2} > 45 mm Hg) during wakefulness, and sleep-disordered breathing in the absence of other causes of hypoventilation.[239] Prevalence of OHS is low in the general population, but reaches 10–20% in patients attending sleep clinics and 50% in patients hospitalized with a body mass index greater than 50 kg/m^2.[240] Pathophysiologic mechanisms include impaired respiratory mechanics with increased work of breathing, upper airway obstruction responsible for sleep-disordered breathing, and decreased respiratory drive.[241]

The choice of CPAP or BPAP for the initial management of OHS remains a complex issue. Several studies have evaluated the impact of CPAP versus BPAP therapy on short- and medium-term physiologic outcomes in patients with stable clinical condition with none showing superiority on resolution of respiratory failure.[242–244] In a 2015 large, multicenter trial, long-term patient-oriented outcomes and physiologic outcomes (hospital resource utilization, cardiovascular events, mortality, arterial blood gases, spirometry, quality of life, and side-effects) were also similar between CPAP and BPAP.[244] Taking into consideration the data from available literature as a whole, the majority of stable OHS patients with *obstructive sleep apnea* (OSA) can efficiently be treated with first-line treatment of CPAP. It is plausible that BPAP might have superior effectiveness in selected subgroups of patients. BPAP can therefore be recommended for (1) episodes of acute-on-chronic respiratory failure, (2) ineffective CPAP therapy (persistence of hypercapnia or respiratory events under CPAP, intolerance to high-pressure CPAP), and (3) when the patient has clinical characteristics strongly associated with the persistence of hypercapnia despite effective CPAP treatment (e.g., coexistence of another cause of chronic respiratory failure, very severe hypercapnia at initial presentation, low apnea-hypopnea index). Therapy with BPAP should also be assessed when the patient is in stable condition (Fig. 136.3), such as after a few months of treatment after acute hypercapnic respiratory failure,[245] or in patients with OHS who have experienced a significant weight loss.

During BPAP, expiratory positive airway pressure and inspiratory airway positive pressure can be titrated individually. Expiratory positive airway pressure is progressively increased to correct apnea and hypopnea due to obstructive physiology, and IPAP to correct hypoventilation. Use of "spontaneous" versus "spontaneous/timed" mode is under debate. In spontaneous mode, there is no backup rate, and the patient determines both the respiratory rate and the time spent in inspiratory airway positive pressure (within the set inspiratory airway positive-pressure time limits). In the spontaneous/timed mode, a backup rate is set and, if the patient does not initiate a breath within a specified time window, the NIV device will deliver a breath. The 2012 American Academy of Sleep Medicine recommendations suggest that the default setting should be "spontaneous" unless central sleep apnea is documented. However, recent clinical data have highlighted the importance of setting a backup respiratory rate when using NIV in OHS with OSA but no previously documented central sleep apnea. One study in OHS subjects on long-term NIV showed that spontaneous mode was associated with additional respiratory events, mainly central sleep apnea and mixed respiratory events, compared with spontaneous/timed mode.[246] Data from a randomized crossover trial comparing standard NIV titration to average volume-assured pressure support (AVAPS, Philips

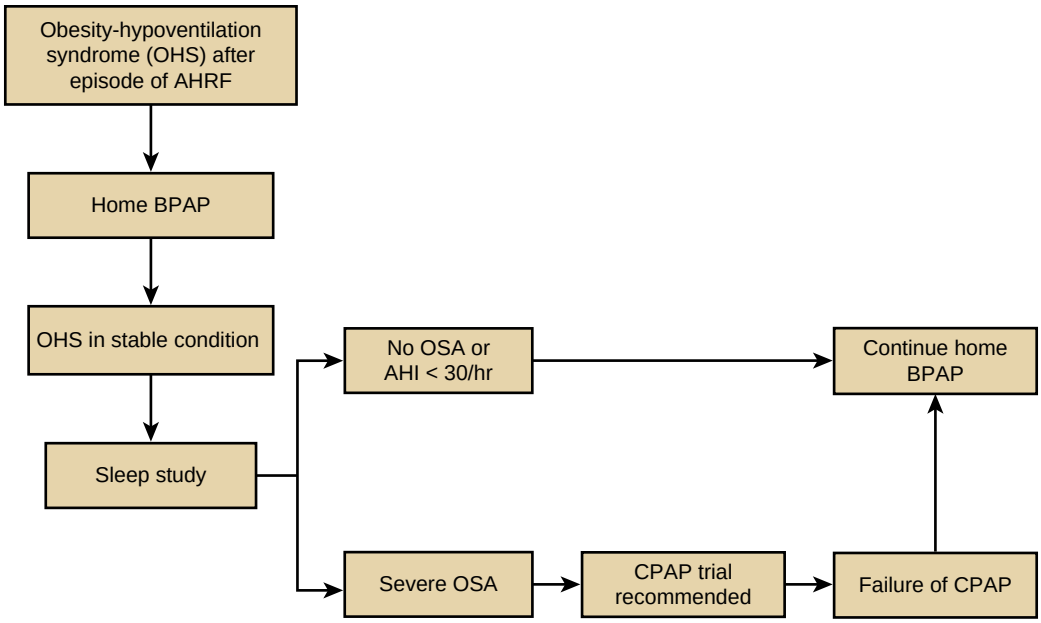

Figure 136.3 Home noninvasive ventilation in *obesity-hypoventilation syndrome* (OHS). Although *continuous positive airway pressure* (CPAP) is usually adequate for treatment of OHS, home *bilevel positive airway pressure* (BPAP) is recommended in patients with OHS after an episode of *acute hypercapnic respiratory failure* (AHRF). Ongoing need for BPAP therapy should be assessed a few months after hospital discharge and, if OSA is identified, changing to CPAP therapy may be an option. NIV, noninvasive ventilation; OSA, obstructive sleep apnea; AHI, apnea-hypopnea index.

Respironics) confirmed that controlled ventilation, defined as less than 50% of patient-triggered cycles, is associated with improved daytime arterial P_{CO_2}, better control of nocturnal hypoventilation, and improved health-related quality of life at 3 months in a post hoc subgroup analysis.[247]

Because cardio-metabolic comorbidities are important drivers of outcome in this population, cardio-metabolic and inflammatory markers should be sought for and treated. In a randomized trial with unselected OHS patients, inflammatory markers, endothelial function, and arterial stiffness were not improved after 1 month of NIV, although blood gas measures and sleep quality had improved.[248] We conclude that there is a need for a multimodal approach combining NIV therapy, lifestyle interventions, and rehabilitation programs to reduce the cardio-metabolic burden of OHS.[249,250]

Home NIV for Chronic Hypercapnic COPD

NIV is recommended for patients with ARF leading to acute or acute-on-chronic respiratory acidosis (pH ≤7.35) due to COPD exacerbation.[19] On the other hand, use of home NIV for chronic hypercapnic COPD has long been controversial. Results of early studies using a *lower level of pressure support* have been conflicting: some have yielded clear negative findings,[251] whereas others have demonstrated some improvements in dyspnea and reduced mortality after adjustment for confounders, but at the cost of a worsened QoL.[252] Most experts claim that effective delivery of pressure support to reduce arterial P_{CO_2} to a normal range or to achieve a 20% reduction in arterial P_{CO_2} is mandatory to improve QoL, readmission rates, and mortality.[253] Consequently, trials using high-intensity NIV (with higher pressure support) have been designed to address this knowledge gap. In a trial of high-intensity NIV in stable chronic hypercapnic patients, Köhnlein et al. reported a significant reduction in 12-month mortality (12% vs. 33% in the control group), as well as improvements in daytime arterial P_{CO_2}, exercise capacity, and health-related QoL.[254] Conversely, Struik et al. enrolled 201 patients surviving hypercapnic ARF after at least 48 hours without NIV. There were no significant differences between the 2 groups at 1 year in readmission rates, deaths, exacerbations, lung function, and health-related QoL.[255] In a United Kingdom trial, the authors enrolled 116 patients based on resolution of acidosis and persistent hypercapnia for at least 2 weeks but no more than 4 weeks after hospital admission for hypercapnic ARF. Time to readmission or death was significantly longer in the home NIV group compared with the oxygen alone group (4.3 months vs. 1.4 months, respectively).[256] Overall, newer studies using higher levels of NIV suggest that home NIV to treat chronic hypercapnic respiratory failure in patients with COPD may be beneficial, but a substantial degree of equipoise on this topic remains.

Evaluation and treatment of major comorbidities in COPD patients surviving the ICU may also be important to improve outcome. OSA and COPD are among the most prevalent chronic diseases and represent a major economic burden for health care systems worldwide.[257,258] Undiagnosed comorbidities, including OSA or heart failure in COPD patients surviving the ICU, are frequent[259,260] and may be associated with worse outcomes. The overlap syndrome (coexistence) of OSA and COPD is characterized by profound nocturnal hypoxemia and a higher risk of pulmonary hypertension and right heart failure. OSA and COPD share an increased burden of systemic inflammation via the activation of transcriptional factors (nuclear factor-κB and hypoxia-inducible factor-1), oxidative stress, sympathetic overactivity, and endothelial dysfunction.[261] Thus, it can be expected that cardiovascular diseases are more prevalent in patients with the overlap syndrome compared to either

OSA or COPD alone. While new OSA has been found to be highly prevalent in survivors of critical illness due to acute hypercapnic respiratory failure (the majority of whom have COPD), traditional screening questionnaires seem to perform poorly to diagnose OSA in this population compared with lung function assessment.[259] In a large prospective cohort with a median follow-up of 9.4 years, Marin et al. demonstrated that the coexistence of COPD and OSA is associated with an increased risk of death from any cause and more hospitalizations for COPD exacerbations.[262] Although there are no data from a randomized controlled study, most experts strongly encourage treatment of concomitant OSA and COPD with nocturnal NIV therapy. When OSA predominates, CPAP therapy is the most appropriate therapy. Recommendations for home NIV in COPD are summarized in Table 136.4.

Importance of Monitoring Home NIV

Patients using home NIV may develop unintentional leaks; residual respiratory events of obstructive, central, or mixed origin; patient-ventilator asynchrony; unrewarded inspiratory efforts; and periodic breathing.[263] These problems may have detrimental effects on quality of sleep and control of hypoventilation. A stepwise approach with specific goals is therefore recommended in order to adapt ventilator settings and interface accordingly (Fig. 136.4).[264]

The medical history is important, although often nonspecific and sometimes surprisingly unremarkable, despite

Table 136.4 Recommendations for Home NIV in COPD

- Use of home NIV is suggested in chronic stable hypercapnic patients (arterial P_{CO_2} > 52 mm Hg) with severe COPD.
- Use of home NIV is suggested after an acute episode of hypercapnic respiratory failure only if hypercapnia (arterial P_{CO_2} > 48 mm Hg) persists 2 to 4 weeks after the acute episode.
- When implementing NIV in COPD patients with CHRF, settings should be adjusted to decrease arterial P_{CO_2} below 48 mm Hg or reduce arterial P_{CO_2} levels by more than 20% of baseline level.
- When implementing home NIV in COPD, fixed pressure mode should be preferred to auto-titrating modes as first choice mode.

CHRF, chronic hypercapnic respiratory failure; NIV, noninvasive ventilation.

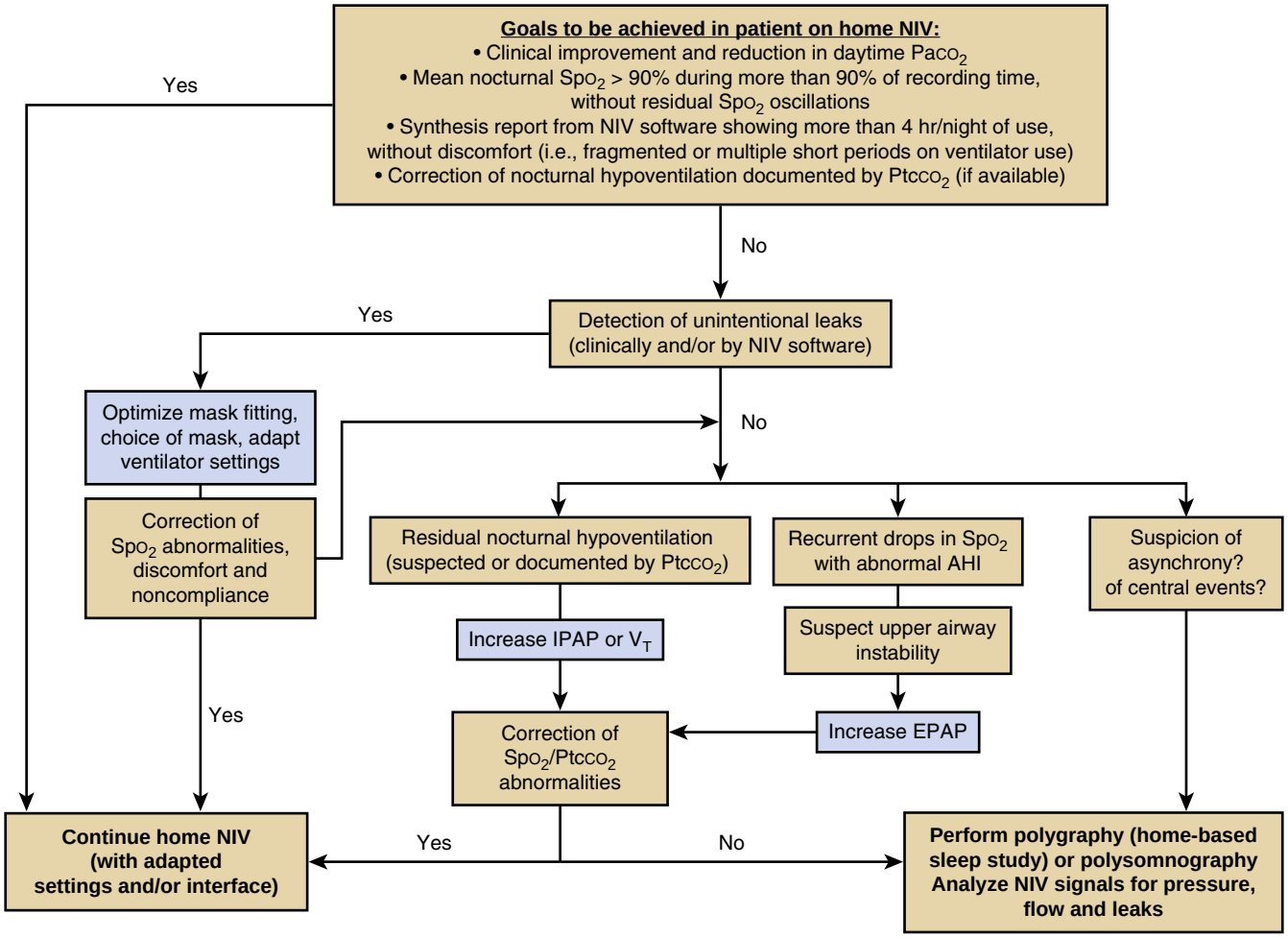

Figure 136.4 Stepwise approach to *noninvasive ventilation* (NIV) home monitoring to adapt ventilator settings and interface accordingly. At each monitoring visit for NIV, all of the goals in the box at the top of the algorithm should be reviewed. If they are met, home NIV should be continued. If any are not met, the presence of unintentional leaks should be evaluated. When leaks are present, steps on the left side of the algorithm should be taken to reduce them. If unintentional leaks are not found, lack of optimal treatment or improvement could be due to residual nocturnal hypoventilation, recurrent decreases in oxygenation with abnormal *apnea-hypopnea index* (AHI), NIV asynchrony, or central apneic events. Steps to evaluate each of those options are shown in the lower right of the algorithm. $Ptcco_2$: partial pressure of transcutaneous carbon dioxide; Spo_2, oxygen saturation detected by oximetry; IPAP, inspiratory positive airway pressure; V_T, tidal volume; EPAP, expiratory positive airway pressure. (Modified from Elliott MW, Nava S, Schönhofer B, eds. *Non-Invasive Ventilation and Weaning: Principles and Practice*. Boca Raton, FL: CRC Press, 2019.)

significant nocturnal respiratory events. Disease-specific health-related QoL questionnaires may be helpful to assess patient-oriented outcomes as a complement to physiologic monitoring of NIV. Indeed, most important domains of life affected by respiratory failure remain unexplored by physiologic monitoring. The Severe Respiratory Insufficiency Questionnaire[265] and the Maugeri Respiratory Foundation Questionnaire-28[266] are often used to assess patient-reported outcomes. However, their length and complex scoring algorithms limit their use in everyday clinical practice. Moreover, treatment-related side effects of NIV are not covered by these questionnaires. The S[3]-NIV questionnaire, an 11-item, short, self-administered tool, was designed to provide clinicians and patients with a simple and reliable tool to assess respiratory symptoms, sleep quality, and NIV-related side effects as a complement to physiologic monitoring.[267]

Pulse oximetry remains a simple tool to ensure that adequate oxygen saturation is provided and to detect short recurrent or prolonged desaturations. However, oximetry alone cannot distinguish between hypoxemia caused by ventilation-perfusion mismatch and that caused by alveolar hypoventilation. The addition of transcutaneous capnography will allow this discrimination.[268] Built-in software of home ventilators can provide informative data about compliance, pattern of NIV use, mask leaks, tidal volume, and residual apnea-hypopnea index.[268] Multichannel ventilator modules combining oxygen saturation measurement with estimation of leaks and minute ventilation have been shown to be reliable.[269] Unfortunately, the accuracy of estimated minute ventilation and leaks by the ventilator varies from one device to another,[270] and independent validation studies are still warranted for all commercially available ventilators. Finally, in OHS patients treated with NIV, a substantial agreement between automated apnea-hypopnea indexes derived from the ventilator software and manually scored apnea-hypopnea indexes using respiratory (home-based) polygraphy has been observed.[271,272]

As a rule, a stepwise approach to monitoring home NIV with simple tools is recommended as a first step. Resorting to polygraphy or polysomnography to optimize NIV settings is recommended only if targeted arterial P_{CO_2} reduction is not reached, if recurrent or prolonged alveolar oxygen saturation drops are still observed despite correction of unintentional leaks, or if NIV is poorly tolerated.[273]

Key Points

- The use of *noninvasive ventilation* (NIV) in the acute setting has increased markedly over the past decades. National and international multicenter studies have demonstrated that NIV is used in 30–52% of patients who are not intubated at the time of ICU admission.
- NIV can improve physiologic parameters, relieve dyspnea, reduce the invasiveness of patient management, and improve important clinical outcomes such as intensive care unit and hospital stay, complications, and mortality. There is convincing evidence that NIV diminishes the risk of nosocomial infections.
- The beneficial effects of NIV are best demonstrated in patients with acute exacerbation of COPD, obesity-hypoventilation syndrome, and cardiogenic pulmonary edema. In these settings, NIV is recommended as an important component of first-line therapy to prevent further deterioration. Outside of these settings, use of NIV in hypoxemic acute respiratory failure is controversial, and patients must be assessed carefully to ascertain which ones may benefit and which ones may be harmed by use of NIV because of a delay in intubation.
- NIV may be useful during the post-extubation process, as a preventive tool during the weaning process, or during various procedures such as fiberoptic bronchoscopy.
- NIV success is strongly associated with good clinical tolerance. Problems with tolerance can be related to the patient, the interface, the ventilator, and/or the ventilator settings. Mask leaks lead to discomfort and patient-ventilator asynchrony, prolonged inspiration due to inspiratory leaks, and auto-triggering due to expiratory leaks. An optimal adjustment of ventilatory settings may improve patient-ventilator synchrony, work of breathing, comfort and, potentially, the success of noninvasive ventilation.
- The interface is an essential component for NIV. In the acute care setting, the oronasal mask or full face mask is the usual first choice. On the basis of recent evidence, the helmet can be used as a first-line interface, especially in patients who need high positive airway pressures and are intolerant of face masks. There is no ideal interface for all patients, and several interfaces should be available at the bedside.
- NIV is the standard of care for home ventilation. Subjects with a condition known to cause alveolar hypoventilation should be evaluated regularly to determine whether they are eligible for home NIV.

Key Readings

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137 NONINVASIVE SUPPORT OF OXYGENATION

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INTRODUCTION

Oxygen gas was first discovered in the 1700s and was subsequently produced for inhalation at the turn of the 19th century.[1,2] By the early 20th century, oxygen was widely prescribed to patients with a variety of respiratory ailments; this oxygen therapy used nasal cannulas and tented simple face masks with rubber tubing.[1] In the modern era, oxygen has been used to treat cases of hypoxemia as well as to support patients who were thought to be at risk for hypoxemia. However, there is now clear evidence indicating the toxicity of hyperoxia; thus, oxygen supplementation should be provided only to patients with moderate to severe hypoxemia.

Hypoxia describes a state of inadequate oxygen content at the cellular level. *Hypoxemia* is a decrease in oxygen content in the blood. There can be states of cellular hypoxia in the absence of arterial hypoxemia. However, hypoxemia typically leads to tissue hypoxia. The symptoms of hypoxia can vary from mild to severe and may include serious organ dysfunction or death.

INDICATIONS FOR OXYGEN THERAPY

See ExpertConsult.com for an extended discussion; see also Chapters 10 and 44.

Current recommendations suggest oxygen supplementation in patients with hypoxemia to achieve targets such as arterial Po_2 or peripheral oxygen saturation. The British Thoracic Society guidelines for oxygen use in adults recommend a target peripheral oxygen saturation of 94–98%, corresponding to an arterial Po_2 range of 75 to 100 mm Hg.[20] However, Acute Respiratory Distress Syndrome Network trials classically target peripheral oxygen saturation ranges of 88–95% or arterial Po_2 of 55 to 80 mm Hg in acute hypoxemic respiratory failure.[21,22] In general, peripheral oxygen saturation of 90% or higher is likely sufficient for most patients requiring oxygen supplementation. The exception is in patients with obstructive lung disease at risk of hypercapnia, in whom higher oxygen targets have been associated with an increased incidence of carbon dioxide retention and death.[23,24] Thus, oxygen supplementation for patients at risk for hypercapnic respiratory failure should be titrated to a target peripheral oxygen saturation of 88–92% or an arterial Po_2 of 55 to 65 mm Hg.[20] Oxygen should be decreased once a patient recovers from an acute hypoxic illness and no longer needs supplementation.

The purpose of noninvasive oxygenation is to provide respiratory support to patients with hypoxemia who do not yet require invasive mechanical ventilation. The evidence presented in this chapter aims to guide the proper use of contemporary noninvasive oxygen therapy modalities that can suffice in many situations that would have otherwise progressed to intubation before these modalities were available.

DEVICES AND INTERFACES

Low-flow noninvasive oxygenation systems depend on a set flow rate of pure oxygen relative to the volume of ambient air inhaled during breathing to achieve a desired fractional concentration of oxygen in inspired gas. *Reservoir* systems increase the maximum effective delivery of fractional concentration of oxygen in inspired gas by increasing the fraction of pure oxygen inspired relative to ambient air. Table 137.1 contains the approximate fractional concentration of oxygen in inspired gas delivered with each device at various flow rates. *High-flow* systems aim to deliver flow rates that exceed respiratory needs to achieve accurate set delivery of fractional concentration of oxygen in inspired gas.

The goal of oxygen therapy is to avoid the negative consequences associated with tissue hypoxia. Because blood oxygen content is used as a surrogate for tissue oxygen delivery, current guidelines recommend oxygen supplementation in hypoxemic patients. Hypoxemia can be assessed by measuring the oxygen tension in an arterial blood gas test (arterial partial pressure of arterial oxygen [arterial Po_2]) or the fraction of hemoglobin saturated with oxygen either by arterial blood gas (% oxyhemoglobin, *arterial oxygen saturation*) or pulse oximetry (peripheral oxygen saturation). A normal arterial Po_2 ranges from 75 to 100 mm Hg at sea level, corresponding to concentrations of greater than 95% of oxyhemoglobin within the normal spectrum of oxygen-hemoglobin association. Hypoxemic respiratory failure is defined as an arterial Po_2 of less than 60 mm Hg. However, the arterial Po_2 can drop to as low as 30 to 40 mm Hg in a healthy person at high altitudes because of the decreasing atmospheric oxygen tension with increasing elevation.[3] Thus, values of laboratory results should be interpreted with consideration of the clinical context.

Arterial oxygen content and thereby oxygen delivery are more dependent on arterial oxygen saturation than on the absolute value of the arterial Po_2, according to the following equations:

Oxygen delivery = Cardiac output × Arterial oxygen content

Oxygen delivery = Cardiac output × [(Hemoglobin × 1.360 × % Arterial saturation) + (Arterial Po_2 × 0.0030)]

Hence, supplemental oxygen that increases saturation to acceptable levels (see later for recommended range) in a hypoxemic patient has a significant impact on oxygen delivery.

Oxygen is not without its side effects. Hyperoxia causes significant harm both at the lung tissue level and systemically, and it is associated with increased mortality in a variety of clinical settings. The mechanism of pulmonary toxicity seems to be twofold. First, high concentrations of oxygen produce free radicals that overwhelm the cellular detoxification machinery and can lead to cell injury and death. Histopathologically, hyperoxic lung injury is observed as tissue inflammation, capillary leak, cellular necrosis and apoptosis, and septal fibrosis in both animal models and human patients.[4–7] Second, oxygen washout of alveolar nitrogen can lead to *resorption atelectasis,* a process whereby the alveolar oxygen is absorbed more rapidly than replacement ventilation gas is provided and, as a result, alveoli may collapse at critically low volumes.[8,9] These detrimental effects are compounded with hyperoxia in the setting of increased alveolar pressures during positive-pressure ventilation.[10–13]

Systemically, hyperoxia produces generalized vasoconstriction, likely because of the regulatory mechanisms to reduce oxygen delivery needed to meet natural physiologic demands. In the heart, coronary vasoconstriction can lead to increased myocardial injury and decreased cardiac function.[14,15] Decreased cerebral blood flow in response to hyperoxia portends poor outcomes in patients with stroke and traumatic brain injury.[16] Hyperoxia is associated with increasing mortality in numerous clinical settings, particularly in patients with neurologic injury or after cardiac arrest.[17–19]

LOW-FLOW SYSTEMS

Nasal Cannula

Conventional nasal cannulas deliver pure source oxygen through simple nasal prongs at flow rates of 1 to 6 L/min (Fig. 137.1A). There is marginal improvement of oxygen delivery at flow rates higher than 6 L/min because of tubing resistance and increasingly turbulent air flow. Additionally, the velocity of gas felt by patients through small-bore nasal cannulas at high flow rates can be difficult to tolerate. The nasal cannula at appropriate flow rates between 1 and 6 L/min is generally well tolerated. The fractional concentration of oxygen in inspired gas delivered increases relative to the flow rate at approximately 3–4% per L/min, so that 6 L/min corresponds to a fractional concentration of oxygen in inspired gas of approximately 40–45%.[25] A caveat of this fixed low-flow delivery system is that the fractional concentration of oxygen in inspired gas fluctuates with the respiratory effort of the patient. As respiratory rate and tidal volumes increase in respiratory distress, increasing fractions of ambient air are inspired, thereby leading to lower levels of fractional concentration of oxygen in inspired gas delivered.[26,27] Additional limitations to the system include the requirement of nasal patency and unpredictable fractional concentration of oxygen in inspired gas with oral versus nasal breathing, with studies showing conflicting results. Long-term use of nasal cannulas at high flow rates can dry the nasopharyngeal mucosa, and humidification of source oxygen is advised.[20] An enhanced form of the conventional nasal cannula with three channels was initially called high-flow nasal cannula and could deliver flows up to 15 L/min, likely corresponding to an effective fractional concentration of oxygen in inspired gas of up to approximately 50–70% (Fig. 137.1B).[26,28] This nasal cannula is

Table 137.1 Estimated Effective Fractional Concentration of Oxygen in Inspired Gas of Low-Flow and Reservoir Oxygen Delivery Devices

Device	Flow (L/min)	Fio_2 (%)
Simple nasal cannula	2	28
	4	35
	6	40–45
Enhanced (Hudson) nasal cannula	10	50–60
	15	60–70
Simple face mask	5	35–40
	10	50–60
Partial rebreathing mask	10–15	50–75
Non-rebreathing mask	15	95

Fio_2, fractional concentration of oxygen in inspired gas.

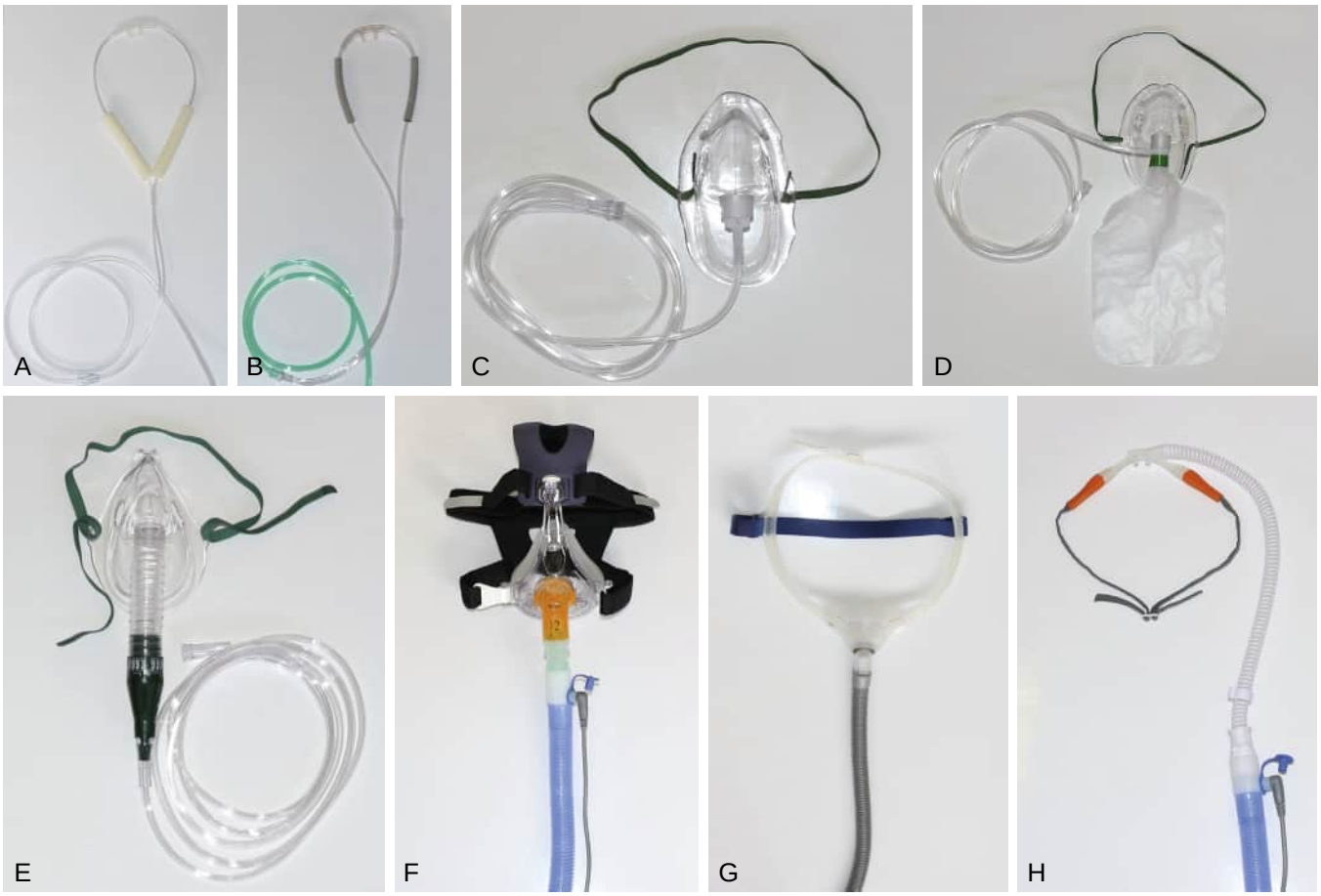

Figure 137.1 Noninvasive oxygenation interfaces. (A) Simple nasal cannula. (B) Enhanced nasal cannula capable of delivering flows up to 15 L/min. (C) Simple face mask. (D) Reservoir face mask (partial-rebreathing or non-rebreathing mask). (E) Venturi mask. (F) Full-face continuous positive airway pressure mask. (G) Nasal prong continuous positive airway pressure mask. (H) High-flow nasal cannula.

produced by Hudson RCI and is sometimes referred to as the Hudson nasal cannula. This should be not be confused with the heated *high-flow nasal cannula* (HFNC) capable of delivering flows of up to 60 L/min.

Simple Face Mask or Hudson Mask

The simple face mask provides a higher fractional concentration of oxygen in inspired gas than the traditional nasal cannula, and it is well tolerated by most patients (Fig. 137.1C). Flow rates can be adjusted from 5 to 10 L/min with a corresponding fractional concentration of oxygen in inspired gas of approximately 35–60%. However, as with nasal cannulas, the simple face mask is a fixed low-flow oxygen delivery system. As such, the effective fractional concentration of oxygen in inspired gas delivered to the patient is highly variable and depends on the patient's respiratory rate and tidal volume.[29,30] Because of a reservoir of 100 to 300 mL depending on the size of the face mask, flows of less than 5 L/min are not advisable, given the rebreathing of expired carbon dioxide, as well as increased resistance of the system during inspiration.[20,31,32] Although the simple face mask delivers higher levels of fractional concentration of oxygen in inspired gas than nasal cannulas, it has are some limitations. Patients cannot eat or drink without interruption of oxygen delivery. Additionally, long-term use can dry the oral and nasal mucosa, and humidification should be used. This mask was initially produced by Hudson RCI and is sometimes referred to as the Hudson mask.

RESERVOIR SYSTEMS

Partial-Rebreathing Mask

Partial-rebreathing masks are reservoir systems with a 600 to 1000 mL bag attached to a simple face mask. Source oxygen is delivered to the reservoir bag at a flow rate of 10 to 15 L/min but, at a minimum, at a rate to ensure inflation of the reservoir. Expired gas containing carbon dioxide and oxygen from dead-space ventilation partially fills the bag with each exhalation, and a mixture of this expired gas and fresh 100% oxygen is then rebreathed with the following inspiration. The increased fraction inhaled from the high concentration oxygen from the reservoir bag in relation to ambient air with each breath allows for higher fractional concentration of oxygen in inspired gas (50–75%, depending on the patient minute ventilation) to be delivered as compared with a simple face mask. The mask is comfortable and well tolerated by most patients, but it can be drying with long-term use and will interfere with oral intake. This mask has largely been replaced by the *non-rebreathing* (NRB) mask.

Non-rebreathing Mask

The fundamental distinction between a partial-rebreathing mask and an NRB mask is the addition of a one-way valve between the reservoir bag and face mask that prevents exhaled gases from entering the reservoir (Fig. 137.1D). To sustain inflation, the standard source oxygen flow for the NRB mask reservoir bag is 15 L/min, which can achieve an effective fractional concentration of oxygen in inspired gas of up to approximately 95%.[33,34] The NRB mask is recommended as the first-line oxygen delivery modality for patients initially presenting with severe hypoxemia (peripheral oxygen saturation < 85%).[20] As with other face masks, prolonged use can dry the mucosa. Additionally, the high fractional concentration of oxygen in inspired gas delivered can induce local pulmonary and systemic toxicity related to hyperoxia.

HIGH-FLOW SYSTEMS

Venturi Mask

The Venturi mask (Ventimask, Flexicare) is an air-entrainment mask developed by E.J. Campbell in 1967 that functions on the basis of the Venturi effect, or Bernoulli's principle (Fig. 137.1E). When a 100% source oxygen is pushed through a narrow channel, a low-pressure environment is created that entrains ambient air through apertures in close proximity to the tapered channel.[35–37] By varying the diameter of the tapered channel through which source oxygen flows and the size of the aperture through which ambient air is allowed to enter, an exceedingly accurate ratio of 100% oxygen and 21% ambient air can be delivered.[25] Current available models deliver a range of fractional concentration of oxygen in inspired gas from 24–50%. Additionally, the increased flow through the narrow source oxygen channel in combination with additional entrained air creates high total flow rates of up to 50 to 70 L/min delivered to the patients. To avoid dead-space ventilation from rebreathing expired gas in the mask, tachypneic patients may require higher than recommended source oxygen flow rates to maintain adequate flows. With sufficient flow, there is little variability of inhaled fractional concentration of oxygen in inspired gas with varying minute ventilation.[30,38,39]

A clear benefit of the Venturi mask is the fixed fractional concentration of oxygen in inspired gas delivered to the patient, a feature profoundly important in patients at high risk for complications related to excess oxygen. For quite some time, until the advent of HFNC, the Venturi mask was the only available device providing a fixed fractional concentration of oxygen in inspired gas. It is currently recommended as first-line oxygen therapy in patients at high risk for hypercarbia, such as in the case of obstructive lung diseases.[20] Although its high flows theoretically provide a small component of expiratory positive pressure, the Venturi mask is not comparable to and should not be substituted for *continuous positive airway pressure* (CPAP).[40,41]

Continuous Positive Airway Pressure

CPAP denotes a device that delivers continuous airflow at a fixed pressure throughout the respiratory cycle, typically through a full face mask (Fig. 137.1F), although nasal CPAP masks are also available (Fig. 137.1G). The full face mask covers the nose and mouth and should not be confused with the total face mask, which covers the entire face, including the eyes. Physiologically, CPAP can be provided either noninvasively through a face mask or invasively through an endotracheal tube, perhaps during a weaning trial before extubation. Although CPAP theoretically does not augment ventilation and can be thought of as purely a mechanism for the support of oxygenation by increasing the mean airway pressure, it is historically considered a mode of *noninvasive ventilation* (NIV). CPAP (and other NIV) is recommended for use in patients with respiratory failure

related to exacerbations of obstructive lung diseases and congestive heart failure.[42] Further discussion of invasive mechanical ventilation and NIV is provided elsewhere (see Chapters 135 and 136).

High-Flow Nasal Cannula

Heated HFNC delivers oxygen at rates of 40 to 60 L/min through large-bore nasal cannulas (Figs. 137.1H and 137.2). Several proprietary models are available, and all function similarly. Gas is delivered through an air-oxygen blender system to achieve a fractional concentration of oxygen in inspired gas of up to 100%. For adequate and accurate delivery of a fractional concentration of oxygen in inspired gas, the HFNC system must be set at high flow rates of 40 L/min or greater. Nasal prongs should not fully occlude the nares; instead, they should be fitted with at least a 50% gap to ensure adequate exhalation and avoid gastric distention. Humidification of gases is a standard addition to the system and is required for tolerability of the flow rates. Because maximum humidification of air, or relative humidity, is temperature dependent, HFNC units are heated to increase the humidity of delivered gases, to nearly 100% at 37°C. There are minor differences in various proprietary and locally assembled setups, but these general principles remain the same.

The most obvious benefit of HFNC is the titratable and predictable delivery of a fractional concentration of oxygen in inspired gas at high fractions. Additionally, HFNC has significant physiologic benefits in patients with hypoxemic respiratory failure. HFNC results in the application of a low level of CPAP. It has been variably estimated that each 10 L/min increase in flow generates from 0.3 to 1.0 cm H_2O CPAP.[43–46] This effect theoretically contributes to the capacity for oxygen support independent of the delivered fractional concentration of oxygen in inspired gas. As a consequence, several important physiologic benefits may accrue. In a prospective, randomized, crossover study, compared with an oxygen mask, treatment with HFNC not only caused a significant improvement in oxygenation but also decreased respiratory rate, minute ventilation, and pressure-time product, indicative of a decrease in work of breathing.[47] Tidal volume was unchanged, whereas end-expiratory lung volume increased, and the distribution of ventilation was more equitable throughout the lung. The high flow rates of HFNC also decrease physiologic dead space by reducing the fraction of rebreathed air in the upper airway, thereby providing a small fraction of ventilation support through carbon dioxide washout.[48] However, the support of ventilation is likely minimal. Thus, HFNC should not be used in place of NIV in patients needing primary ventilation support.

Another benefit of HFNC is patient comfort as compared with other high levels of oxygenation support. When compared with patients undergoing NIV, patients are generally much more tolerant of HFNC.[49] The difference is less pronounced when compared with *conventional oxygen therapy* (COT) delivery through a nasal cannula or simple face mask.[49] In a large trial comparing HFNC with COT or NIV in patients in the medical *intensive care unit* (ICU), patient comfort scores based on a visual analogue scale were best with HFNC,[50] but other studies have not shown such a significant benefit in patient comfort.[51,52]



Figure 137.2 High-flow nasal cannula in the intensive care unit. The patient is being treated with a high-flow nasal cannula for acute hypoxemic respiratory failure. This patient was successfully managed with noninvasive oxygenation for pneumonia in the setting of interstitial lung disease and mild emphysema.

INDICATIONS FOR HIGH-FLOW NASAL CANNULAS

HFNC has largely replaced many other oxygenation devices equipped to provide either high fractional concentration of oxygen in inspired gas or high airflow. Here we focus on adult patients with acute respiratory failure. In general, available evidence supports the use of HFNC in patients who have acute and acute on chronic respiratory failure with moderate to severe hypoxemia.

Indications in pediatric patients, in whom HFNC was first used, are discussed at ExpertConsult.com.

ACUTE HYPOXEMIC RESPIRATORY FAILURE

The primary indication for HFNC in adults is acute hypoxemic respiratory failure, particularly secondary to community- or hospital-acquired pneumonia. In meta-analyses of HFNC use in acute hypoxemic respiratory failure, the evidence advocates for the use of HFNC, particularly in patients with more severe hypoxemia.[63,64] Although the totality of the literature does not suggest a mortality benefit, the major benefit of HFNC is that fewer patients require escalation of therapy to intubation and mechanical ventilation, thereby reducing complications, including death, from invasive ventilation.[65]

HFNC is considered to be an aerosol-generating procedure, although the distribution of aerosolized secretions may in fact be quite modest.[66] Nevertheless, consideration should be given to its use in a negative-pressure environment in circumstances where patients with novel respiratory pathogens, such as severe acute respiratory syndrome coronavirus type 2, the agent of coronavirus disease 2019

PEDIATRIC POPULATIONS

HFNC was first used in pediatric patient populations to provide a fixed oxygen concentration through a nasal cannula while minimizing the side effects of hyperoxia in infants, such as bronchopulmonary dysplasia and retinopathy.[53] Although one study found that HFNC use in preterm neonates with respiratory distress was noninferior to nasal CPAP and NIV,[53] more recent evidence suggests that HFNC may be inferior to nasal CPAP, despite delivering a small amount of positive end-expiratory pressure and avoiding the complications associated with CPAP or NIV.[54] Given the limited evidence supporting HFNC in neonates, CPAP or NIV remains the treatment of choice for this age group.

The majority of the literature supporting the use of HFNC in the non-neonatal pediatric population is in patients with bronchiolitis, either as an initial modality for oxygen supplementation or, more importantly, as a rescue therapy when standard supplemental oxygen therapy fails. A large randomized controlled trial in infants with bronchiolitis (the PARIS study) completed through the Pediatric Research in Emergency Departments International Collaborative. compared HFNC at 2 L/kg/min with standard oxygen therapy in 1472 patients younger than 12 months.[55] Results showed that more infants randomized to standard oxygen required escalation of therapy compared with infants randomized to HFNC, although there was no increase in intubation rates, admission to the ICU, or duration of hospitalization or oxygen requirement. More notably, a majority (102 of 167; 61%) of patients in whom standard oxygen therapy failed were successfully rescued with HFNC. Similarly, a study in 202 children younger than 24 months with bronchiolitis showed higher rates of treatment failure leading to escalation of care in patients treated with standard oxygen therapy compared with HFNC, but without differences in clinical outcomes, including ICU admission and duration of therapy.[56] When compared with NIV, the superiority of HFNC is not established, particularly in children with more severe disease.[57,58]

If HFNC is used in neonates, initial flow rates should be set at 4 to 6 L/min and adjusted according to the patient's weight and clinical status.[59] In non-neonatal pediatric patients, a flow rate of 1 to 2 L/min/kg is likely sufficient.[60–62]

(COVID-19), are being treated, out of concern that aerosols generated by coughing may be augmented by HFNC use.[67]

Pneumonia

The most robust data supporting the use of HFNC are in patients admitted to medical ICUs with hypoxemic respiratory failure resulting from pneumonia. In a small open-label study comparing HFNC with Venturi mask after extubation, about one-half of the 105 randomized patients had resolving pneumonia.[68] Not surprisingly, in this population of hypoxemic individuals, the higher level of oxygen support with HFNC performed better in preventing episodes of hypoxemia, but it was also associated with fewer reintubation events. Following this, the first major clinical trial using HFNC in adults with acute respiratory failure (FLORALI) was published in 2015.[50] Frat and colleagues[50] randomized 310 patients with acute non-hypercarbic hypoxemic respiratory failure to HFNC, NIV, or an NRB mask. Most (82%) of these patients had acute hypoxemic respiratory failure resulting from pneumonia. Although the study did not reach a statistical difference in the primary outcome of need for intubation within 28 days, post hoc analysis showed a decreased rate of intubation among patients with a ratio of arterial Po_2 to fractional concentration of oxygen in inspired gas (P/F ratio) of 200 mm Hg or lower who were treated with HFNC when compared with NIV or standard oxygen through an NRB mask. Ventilator-free days, a secondary outcome, were significantly greater in the HFNC group. Additionally, even though the study was not powered to detect a mortality difference, there was a significant mortality benefit at 90 days with HFNC compared with either NIV or an NRB mask, with the majority of deaths caused by refractory shock. The mortality benefit should be interpreted with caution, however, given the aberrantly high mortality rates among all groups. These results attest to the known limitations of NIV in pneumonia,[42,69,70] and they also support a role for HFNC.

Several follow-up studies have been published, with a large proportion of study subjects having pneumonia as a cause of hypoxemic respiratory failure, although no study has specifically examined HFNC in this single diagnosis. In a large study of 604 patients, many of whom had a medical cause of respiratory failure, including pneumonia and *acute respiratory distress syndrome* (ARDS), HFNC was noninferior to NIV in post-extubation management and was associated with a shorter ICU length of stay and fewer adverse events.[71] Coudroy and colleagues[72] described the use of HFNC versus NIV in a cohort of 115 patients, one-half of whom had pneumonia, and rates of both intubation and mortality were higher in NIV. Limitations of this study include its observational design with the possibility of inherent bias as well as the immunocompromised status of the study population. In another large observational study of 1611 immunocompromised patients who mostly had pulmonary infections, HFNC was associated with lower rates of intubation and mechanical ventilation compared with NIV.[73] Most other subsequent studies were conducted in patients with acute hypoxemic respiratory failure, but often without stratification of the etiology of respiratory failure.[52,74] Taken together, current data suggest that HFNC is safe and may have benefit when compared with NIV in patients with acute hypoxemia from pneumonia. Additionally, in patients with acute hypoxemia who have absolute or relative contraindications to NIV, HFNC appears to decrease the need for invasive mechanical ventilation and perhaps mortality, and it should be used as an initial mode of oxygen therapy in patients who are not unstable enough to require immediate intubation.

Acute Respiratory Distress Syndrome

Although the diagnosis of ARDS requires a positive end-expiratory pressure of at least 5 cm H_2O delivered by either invasive or noninvasive mechanical ventilation,[75] most patients with severe hypoxemia who are treated with HFNC would otherwise meet Berlin criteria for ARDS. Furthermore, a significant portion of patients initially treated with HFNC who subsequently require NIV or mechanical ventilation remain hypoxemic (P/F ratio <300) and meet criteria for ARDS.[76]

A subgroup analysis of the FLORALI study showing benefit of HFNC in patients with a P/F ratio of 200 or lower suggests that perhaps the greatest benefit is seen in patients with more severe respiratory illness, such as in the case of early ARDS.[50] NIV may generate harmful large tidal volumes in hypoxemic respiratory failure and lead to worsened injury to the lung,[77] as suggested by the higher mortality in patients undergoing NIV in the FLORALI study and in patients with a P/F ratio lower than 150 in the LUNG-SAFE series.[78] Thus, the use of HFNC among patients with moderate to severe hypoxemic respiratory failure, especially those who appear to be progressing toward a diagnosis of ARDS, appears prudent.

Immunocompromise

Immunocompromised patients have a poor outcome in the ICU or when they receive a diagnosis of acute respiratory failure, and the requirement for intubation in this population is a predictor of increased mortality rate.[79] The initial trials using NIV in immunocompromised patients to avoid intubation and mechanical ventilation were relatively small and demonstrated a mortality benefit compared with either mechanical ventilation or COT.[80,81] Larger meta-analyses of pooled data confirmed the benefit of NIV in mortality and ICU length of stay.[82,83] However, in the most recent and largest multicenter trial of immunocompromised patients with acute respiratory failure, NIV did not perform significantly better than COT alone.[84]

Since the advent of HFNC in the adult population, NIV use has come under additional scrutiny. In a post hoc analysis of the FLORALI study, use of HFNC was associated with fewer intubations compared with either NIV or COT.[85] Furthermore, the use of NIV was an independent predictor of intubation and morality. However, in another post hoc analysis of a large randomized trial where 84% of participants had malignancies, HFNC did not perform better than NIV in subsequent need for intubation (hazard ratio, 0.42; $P = 0.2$) or 28-day mortality (hazard ratio, 0.80; $P = 0.45$).[86] A prospective cohort study also found no differences in mortality when comparing 1611 patients treated with HFNC, NIV, or standard oxygen therapy.[73] Although the study noted a statistically lower rate of intubation with HFNC, the actual clinical benefit was small.

In the single randomized trial of HFNC compared with COT in immunocompromised patients based in France

(the HIGH trial), 778 subjects were randomized to either HFNC or standard oxygen.[52] There were no statistically or clinically significant differences with respect to 28-day mortality, intubation and mechanical ventilation, and ICU or hospital length of stay. Similarly, meta-analyses of HFNC use in immunocompromised patients show mixed results.[87–90] The best guidance for clinical practice likely involves an individualized approach and a careful evaluation of the etiology of respiratory failure as opposed to a one-size-fits-all approach to immunocompromised patients.

CARDIOGENIC PULMONARY EDEMA

Although NIV clearly shows benefit in patients with cardiogenic pulmonary edema,[42] there is little evidence yet on the benefit of HFNC in patients with this disorder. To date, no randomized clinical trials have compared HFNC with NIV in hypoxemia resulting from cardiogenic pulmonary edema. Rather, many of the studies examining the utility of HFNC in patients with nonspecific hypoxemia included small proportions of patients with cardiogenic pulmonary edema.[91,92] Unfortunately, all prospective trials including patients with cardiogenic pulmonary edema patients compared HFNC with COT and did not include a comparison with NIV.[91–93] A single retrospective study comparing HFNC with NIV included patients with congestive heart failure, but this study was in immunocompromised patients, and only 8.5% of the study subjects had hypoxemia resulting from cardiogenic pulmonary edema.[72] Until further data are available, acute hypoxemic respiratory failure caused by cardiogenic pulmonary edema should be managed with NIV or intubation and mechanical ventilation, not with HFNC.

OTHER HYPOXEMIC LUNG DISEASES

With worsening hypoxemia, it is natural to escalate support through the variety of oxygenation devices available for patient care. However, in patients with acute hypoxemic respiratory failure due to interstitial lung disease, HFNC is increasingly used as an initial therapy to provide a consistent high fractional concentration of oxygen in inspired gas, a small amount of positive end-expiratory pressure to off-load respiratory effort, and the flow that comforts many patients with chronic dyspnea.[94] Of the studies evaluating HFNC in adults with acute hypoxemic respiratory failure, a small fraction of the subjects included for analysis had hypoxemia related to interstitial lung disease.[95] In small studies, patients with interstitial lung disease seem to tolerate HFNC well as an escalation therapy from COT.[96,97] Although no significant conclusions can be drawn from these studies regarding the outcome of HFNC use in interstitial lung disease, HFNC has largely replaced NIV because of improved comfort and the general lack of need for increasing ventilation in these patients who have hypoxemic respiratory failure without hypercarbia.[98,99]

As in the case of pulmonary parenchymal diseases, patients with pulmonary vascular disease with profound hypoxia and respiratory failure are often supported with HFNC, despite little data in this patient population.[91] In one small retrospective study, Li and colleagues[100] described the feasibility and efficacy of inhaled epoprostenol delivered through an HFNC in a small number of patients with pulmonary arterial hypertension or right-sided heart failure with acute worsening of hypoxia.

Other causes of acute hypoxemic respiratory failure for which HFNC has been investigated include acute pulmonary embolism. In a retrospective report, HFNC was used in 17 patients with acute pulmonary embolism with normocarbic hypoxemic respiratory failure resulting in improved clinical respiratory parameters without a need for intubation.[101] Although there are limited data on the use of HFNC in this and other specific causes of acute hypoxemic respiratory failure, it seems physiologically plausible that HFNC use would benefit most of these patients. As with all causes of acute respiratory failure and selection of noninvasive support, comorbidities and the presence of hypercarbia should be taken into account.

HYPERCARBIC HYPOXEMIC RESPIRATORY FAILURE

Although there is good evidence in support of NIV use for hypercarbic respiratory failure,[42] the rate of failure of NIV in this setting can be as high as 30–50% depending on the severity of the patient on presentation.[102] Only a few studies of HFNC in hypercarbic respiratory failure are available, and most are observational and compare HFNC with COT rather than with NIV.[103–106] There are no well-designed studies supporting the use of HFNC over NIV in hypercarbic respiratory failure, despite the theoretical benefit of carbon dioxide washout and the decrease in physiologic dead-space ventilation.[107,108] Most trials of HFNC exclude patients with hypercarbia.[50,109] Thus, HFNC should currently not be used routinely in patients with hypercarbia who require support of ventilation.

POST-EXTUBATION SUPPORT

Patients with chronic hypercarbia benefit from NIV post-extubation support in preventing reintubation.[110] HFNC has been investigated as a modality of post-extubation support for patients at either low or high risk for reintubation, with mixed results. Most extubated patients in the ICU are at low risk for respiratory failure and reintubation, but all are typically treated with supplemental oxygen.[111,112] The flow rate and oxygenation device should be selected based on the individual patient and the severity of hypoxia. When Hernández and colleagues[109] compared HFNC with COT, including a nasal cannula or an NRB mask, in 527 medical and surgical patients at lower risk for reintubation, fewer patients treated with HFNC had post-extubation respiratory failure (8.3% vs 14.4%; $P = 0.03$) and need for reintubation by 72 hours (4.9% vs 12.2%; $P = 0.004$).[109] However, in another study (the OPERA trial) of 220 non–risk-stratified, postsurgical patients randomized to either HFNC to COT by nasal cannula or face mask, no statistical differences were seen in pulmonary complications such as hypoxemia or need for reintubation.[113] These differences in trial results may stem from differences in patient populations; the study by Hernández and associates[109] included a high proportion of surgical patients, whose reintubation rate is typically lower than in medical patients. Moreover, this study

excluded patients with chronic hypercarbia, a population in whom evidence for the use of NIV is well established.

In a randomized study of 604 patients at high risk for postextubation respiratory failure, no differences were seen in the rate of reintubation or respiratory failure among those treated with HFNC when compared with NIV. However, there were significantly more adverse events, such as nasal septum and facial trauma, in patients treated with NIV (42.9% vs. 0.0%; $P < 0.001$).[71] A follow-up study excluding hypercarbic patients in a population at high risk for extubation failure was stopped early because of low recruitment and was not conclusive in evaluating the benefit of HFNC versus NIV.[74] Meta-analyses including other smaller studies of HFNC versus NIV after extubation suggest that HFNC performs better than COT, but not better than NIV, in prevention of reintubation after extubation.[114–116] These data are limited by the design and results of the included studies. Careful patient selection for an oxygenation approach after extubation is warranted given the lack of a clear benefit of HFNC in this setting.

PREOXYGENATION FOR INTUBATION

HFNC has been explored as a method of preoxygenation and of apneic oxygenation in ICU patients with acute respiratory failure before and during endotracheal intubation. Taken together, data suggest that patients with severe hypoxemia before intubation likely benefit from NIV for preoxygenation, as opposed to HFNC or COT. The evidence in support of HFNC over COT for preintubation oxygenation is mixed. In a before-after observational study of 101 patients treated either with HFNC or an NRB face mask before intubation, patients treated with HFNC had higher levels of oxygenation.[117] However, in a multicenter randomized study (PREOXYFLOW trial) of 124 patients with a P/F ratio lower than 300, there was no difference between groups treated with HFNC or face mask in oxygen saturation, adverse events related to intubation, or ventilator-free days.[118] Studies comparing HFNC with NIV have also demonstrated mixed results. In the follow-up study from the FLORALI study group (FLORALI-2), 313 patients with a P/F ratio of 300 or lower were randomized to HFNC or NIV for preoxygenation before intubation. There were no differences in outcome, other than fewer severe hypoxemic events with NIV preoxygenation in the subset of patients with a P/F ratio of 200 or lower.[119] Conversely, a smaller study (PROTRACH) of 192 patients randomized to HFNC or bag-valve-mask ventilation during rapid-sequence intubation found fewer desaturations lower than 95% (12% vs. 23%; $P = 0.045$) and peri-intubation complications (6% vs. 19%; $P = 0.007$) such as severe hypoxia, hypotension, and aspirations with HFNC.[120]

Current evidence does not support the use of HFNC for preoxygenation before intubation. At this time, HFNC for preoxygenation should only be considered for those cases of mild hypoxemia, with NIV used for more severe cases.

PERIOPERATIVE PERIOD AND DURING PROCEDURES

HFNC has been investigated in a variety of postoperative settings, particularly in patients undergoing cardiothoracic and abdominal surgical procedures. Almost all studies have failed to show clinically meaningful differences with the use of HFNC in the postoperative settings compared either with conventional oxygen by low-flow devices such as nasal cannula or face mask or with NIV. In the largest study of HFNC in surgical patients, Stéphan and colleagues[51] randomized 830 post–cardiac surgical patients who were at high risk for perioperative pulmonary complications of HFNC or bilevel positive airway pressure and found HFNC to be noninferior in prevention of respiratory failure requiring reintubation (21.0% vs. 21.9%; $P = 0.003$) and superior in causing less skin breakdown. Other studies in cardiac surgical patients show mixed results, with some suggesting less escalation of therapy with HFNC compared with nasal cannula and others showing no significant differences.[51,121,122] Similarly, no consistent decreases in intubation or pulmonary complication rates were seen with the use of HFNC compared with usual care in thoracic or abdominal surgical patients in several randomized trials.[113,123] In a meta-analysis of 14 studies of application of HFNC in postsurgical patients, pooled data suggest that HFNC significantly shortens hospital length of stay but does not reduce postoperative pulmonary complications.[124]

An intraprocedure HFNC has also been compared with NIV in high-risk patients undergoing flexible bronchoscopy, and patients in the NIV group had better oxygenation before, during, and after the procedure.[125] In summary, HFNC may be appropriate as first-line oxygen therapy for postsurgical patients, but it should not routinely be used during procedures (such as bronchoscopy).[126,127]

PATIENTS NEAR THE END OF LIFE OR NOT WISHING TO BE INTUBATED

Given the higher levels of comfort and improved general tolerability of HFNC compared with NIV, HFNC may be an appropriate choice to treat dyspnea and provide palliation for patients with severe hypoxemia who are at the end of life or do not wish to be intubated (with a do not intubate order). To date, no controlled studies in these populations have evaluated the effectiveness of HFNC. There are small cohort studies reporting improved oxygenation, fewer interruptions of oxygen therapy, and better oral intake compared with NIV in patients with hypoxemic respiratory failure and do not intubate orders.[98,128]

Key Points

- In general, a target peripheral oxygen saturation of 90% or higher (arterial partial pressure of oxygen of 60 mm Hg or higher) is likely sufficient for most patients requiring noninvasive oxygenation. In patients with obstructive lung disease at risk for hypercarbia, the target should be peripheral oxygen saturation of 88–92% (arterial partial pressure of oxygen of 55 to 65 mm Hg).
- Noninvasive oxygenation modalities include low-flow systems (conventional nasal cannula, simple face mask), reservoir systems (partial-rebreathing and non-rebreathing masks), and high-flow systems (Venturi mask, continuous positive airway pressure, and high-flow nasal cannula).

- The physiologic benefits of high-flow nasal cannula include accurate delivery of a fractional concentration of oxygen in inspired gas, an application of a small amount of end-expiratory pressure, and the theoretical but limited ventilation support through carbon dioxide washout. Since its advent, the high-flow nasal cannula has largely replaced other modalities for noninvasive oxygenation in patients with moderate to severe hypoxemic respiratory failure.
- Indications for high-flow nasal cannula include the following settings: acute hypoxemic respiratory failure resulting from pneumonia or acute respiratory distress syndrome, acute hypoxemic respiratory failure following surgery, acute on chronic hypoxemic lung diseases with escalating oxygen requirements, and end of life.
- High-flow nasal cannula *may* be considered in these settings: hypoxemic respiratory failure in immunocompromised populations, post-extubation, before intubation, and periprocedurally.
- High-flow nasal cannula should not be used in these settings: hypoxemic respiratory failure caused by cardiogenic pulmonary edema and hypercarbic hypoxemic respiratory failure.
- The major benefit of high-flow nasal cannula is that it reduces the number of patients who require intubation and mechanical ventilation.

Key Readings

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138 EXTRACORPOREAL SUPPORT OF GAS EXCHANGE

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INTRODUCTION

Extracorporeal membrane oxygenation (ECMO) is a technique of life support that diverts a fraction of the patient's blood flow through an artificial lung for gas exchange (oxygenation and CO_2 removal) and then returns it to the patient. Thanks to the improvements in technology and materials and to a deeper understanding of physiopathology, the indications, timing, and management of ECMO have changed substantially over the years. This chapter introduces the concept of ECMO and discusses its use for respiratory support in patients with acute respiratory failure.

PRINCIPLES OF EXTRACORPOREAL MEMBRANE OXYGENATION

ECMO is a generic term used to describe a number of different techniques used for prolonged cardiac and/or respiratory support. ECMO can be used for cardiac (veno-arterial bypass) or respiratory support. For respiratory support, blood can be drained either from a venous vessel (*veno-venous ECMO* [VV-ECMO]) or from an arterial vessel (arteriovenous bypass). During veno-arterial and VV-ECMO, the blood is withdrawn from the patient through a pump, whereas, during arterio-venous ECMO, the arterial pressure is the driving force. Drained *blood flow* (BF) passes through the oxygenator (*membrane lung* [ML]), where oxygen is added and CO_2 removed. Depending on the BF through the circuit, the technique may be used mainly for CO_2 removal (BF < 2 L/min) or for both CO_2 removal and oxygenation (BF up to 5 to 6 L/min). For an understanding of the different techniques available for respiratory support, it is useful to provide a brief historical perspective.

HISTORICAL PERSPECTIVE

The birth of ECMO dates to 1939 with the development of the first heart-lung machine by John Gibbon; this culminated in 1953 with the first open heart operation.[1] The first successful use of prolonged ECMO in *acute respiratory distress syndrome* (ARDS) patients was reported by Hill et al. in 1972.[2] In the following 2 years, other successful cases were reported, leading to the first multicenter randomized clinical trial of ECMO for adults with ARDS.[3] The study failed to show any survival benefit.

Contrary to its use in adults, the use of ECMO in neonatal respiratory failure showed encouraging results. After the first successful treatment in newborns reported by Bartlett et al. in 1976[4] and a few case series from different groups,[5–7] two prospective randomized controlled studies were performed.[8,9] Both studies were positive and, in a few years, ECMO became standard treatment for neonatal respiratory failure.

A landmark contribution to the use of ECMO in adults came from the pioneering work of Kolobow and Gattinoni, who addressed the reasons the National Institutes of Health ECMO trial demonstrating lack of benefit.[10] At that time, the aim of ECMO had been to provide reasonably normal blood gases.[11] For achieving normal oxygenation, a high ECMO BF rate was necessary, and the veno-arterial configuration was the standard. In 1977, recognizing that

oxygenation and carbon dioxide elimination were based on different physiologic mechanisms, Gattinoni and Kolobow realized that by removing CO_2 through the ML, ventilation of the native lung could be reduced virtually to zero.[12] They showed that nearly all the metabolic CO_2 production could be removed through an artificial lung using much lower extracorporeal BFs than those required to oxygenate the blood.[13] Based on these observations, they developed the concept of extracorporeal CO_2 removal, proposing the use of a veno-venous configuration instead of the classical veno-arterial mode and the use of low-frequency positive-pressure ventilation to rest the lung.[13] Unfortunately, the promising results of the first reports[14,15] were not confirmed by a subsequent single-center, randomized controlled trial in 40 ARDS patients.[16] In spite of this second trial finding no benefit, a few centers continued to use ECMO in adult patients; during this time, there were also important technical improvements.[17–21] In the past decade, there has been a resurgence of interest in ECMO, leading to a progressive increase in its use worldwide.

The reasons for the resurgent interest in ECMO are the following:

1. Technical developments have led to a decrease of ECMO-associated complications. Oxygenators, propelling pumps, and cannulas have all undergone substantial improvements, allowing easier, safer, and longer application of ECMO.
2. The *Extracorporeal Life Support Organization* (ELSO), founded in 1989, has gathered together most ECMO centers worldwide. ELSO maintains a registry of ECMO cases and provides annual reports on ECMO usage, survival rates, and complication rates. ELSO has also developed guidelines that represent the most important reference for ECMO users.[22]
3. The concept of *ventilator-induced lung injury* (VILI) and improvement in ARDS treatment[23] has led to the recognition that *mechanical ventilation* (MV), though necessary, can exacerbate lung damage. Ventilation with high *tidal volume* (V_T)[24–29] and high airway pressure[30–31] has been recognized as a major cause of VILI, leading to the recommendation that ARDS patients should receive "a protective ventilatory strategy." Since the concept of VILI was not recognized early in the history of ECMO, in the two aforementioned ECMO randomized trials, no attention was paid to V_T or airway pressures in either treatment group.
4. The H1N1 influenza outbreak accelerated the use of ECMO with good results. During the 2009 influenza A (H1N1) pandemic in Australia and New Zealand, 61 patients with H1N1-associated ARDS received ECMO for refractory hypoxemia, and survival was 78%.[32] Following the Australian experience, numerous case series reported survival rates ranging from 68–83%.[32–39]
5. Evidence from newer randomized trials has been viewed as positive. Two large, multicenter, randomized controlled trials published in 2009 and 2018 have compared ECMO with conventional treatment in patients with ARDS and refractory hypoxemia. The *Conventional Ventilation or ECMO for Severe Adult Respiratory Failure* (CESAR) trial[40] was conducted in the United Kingdom and published in 2009; it enrolled 180 adult ARDS patients with a Murray score of 3 or greater or uncompensated hypercapnia with a pH less than 7.20. Patients randomized to ECMO were transferred to the Leicester ECMO center, while controls remained in designated treatment centers. Survival or absence of severe disability at 6 months was 63% in the ECMO group compared with 47% of the control group. The authors concluded that referral of severely hypoxemic ARDS patients to a specialized center able to provide ECMO may increase survival. However, not all patients allocated to the ECMO group actually received ECMO, either because they died before or during transportation (5 patients) or they improved with conventional treatment after transportation to the ECMO center (17 patients). Moreover, there was no standardized protocol for MV in the control group, resulting in significantly fewer patients receiving a protective ventilatory strategy.

The second study is the ECMO to Rescue Lung Injury in Severe ARDS trial,[41] conducted more recently in France. This study included patients receiving MV for less than 7 days for refractory ARDS, defined as arterial P_{O_2}/*fractional concentration of oxygen in inspired gas* (F_{IO_2}) less than 50 mm Hg for greater than 3 hours; or alveolar P_{O_2}/F_{IO_2} less than 80 mm Hg for 6 hours; or, pH less than 7.25 with arterial P_{CO_2} 60 mm Hg or greater, despite ventilator optimization. In the first 249 patients, 60-day mortality was 35% in the ECMO group versus 46% in controls ($P = 0.09$). Because this difference did not reach statistical significance, recruitment was prematurely stopped. However, interpreting these results as "negative" is certainly too simplistic. As pointed out by Robert Bartlett in his editorial, "the 11% absolute difference in survival comparing early ECMO to conventional care with late rescue ECMO will probably be considered clinically significant by intensivists and payers for healthcare in severe ARDS."[42] Moreover, 28% of the patients in the control group required crossover to ECMO as salvage therapy, and the composite outcome of death plus crossover to ECMO was strongly in favor of ECMO treatment (relative risk, 0.62; $P < 0.001$). Finally, a post-hoc Bayesian analysis of the ECMO to Rescue Lung Injury in Severe ARDS results showed that ECMO is associated with an absolute mortality reduction of at least 2% with a 98% probability.[43]

VENO-VENOUS EXTRACORPOREAL MEMBRANE OXYGENATION

INDICATIONS

The primary indication for VV-ECMO is hypoxemic respiratory failure in patients with a high risk of mortality. According to ELSO guidelines, ECMO is indicated in patients with an arterial P_{O_2}/F_{IO_2} less than 80 mm Hg with F_{IO_2} greater than 0.90 and a Murray score of 3 to 4.[22] Several investigators have reported the association between increased mortality and more days of MV before ECMO initiation, suggesting the importance of starting ECMO early, before lung injury has become irreversible. Since 2006, several case reports have been published on the use of VV-ECMO for non-ARDS indications such as respiratory failure

due to severe trauma,[44] pulmonary embolism,[45] or severe asthma,[46] and as a bridge to lung transplant.[47]

Contraindications to ECMO include advanced age, severe disability, and incurable malignancy. Uncontrolled coagulopathy, major bleeding, and prolonged MV are considered relative contraindications, and the decision to start ECMO is discussed on a case-by-case basis.

COMPONENTS

The basic components necessary for VV-ECMO are a gas-exchange unit, a pump to propel the blood, and the cannulas and tubing for vascular access. Compared to the systems commonly adopted during cardiac surgery, ECMO systems are simpler (Fig. 138.1).

Oxygenators

Hollow-fiber oxygenators with a polymethylpentene membrane have become the standard for long-term treatment.[48–50] Compared to the original silicon membrane, hollow-fiber oxygenators have a smaller priming volume, higher gas transfer rates, and much lower resistance.[51] The use of polymethylpentene has also completely resolved the problem of plasma leakage that represented the main limitation to the use of polypropylene hollow-fiber oxygenators.[52] The gas and blood compartments are channeled, respectively, inside and outside the hollow fibers. A third compartment for heat exchange is commonly present. Each compartment has an input and an output port.

Pumps

Centrifugal pumps have almost completely replaced roller pumps for long-term applications. Modern centrifugal pumps have a hole in the center of the rotor (Mendler design)[53] and use both a magnetically suspended and a magnetically driven pump that eliminates stagnation, thrombosis, and heat production, which were common complications of earlier centrifugal pump models.

Cannulas

Vascular cannulas for ECMO have a thin wall, are commonly made of polyurethane, and are often wire-reinforced to prevent kinking or collapse. Venous cannulas have side holes close to the tip or along the last 15 to 20 cm (multistage cannulas) to facilitate drainage. Modern cannulas have heparin-coated surfaces to increase biocompatibility and reduce activation of the clotting cascade.[54] Recently, some double-lumen cannulas have become available: the most popular is the bicaval Avalon Elite.[55] With this cannula, blood is drained both from the inferior and the superior vena cava via the inflow lumen and reinfused directly into the right atrium through the return lumen aligned with the tricuspid valve.

Tubing

The tubing used for ECMO is made of polyvinylchloride, polyurethane, or silicon rubber. Appropriate connectors, with side ports for standard stopcocks, allow connection between different circuit components.

CANNULATION

The technique of choice for VV-ECMO cannulation is the percutaneous approach.[56,57] The main advantages are the reduced risk of bleeding, shorter operative time, and easier mobilization and nursing of the patient.

As a rule, the size of the cannula should not exceed two-thirds of the vessel diameter. Drainage cannulas should be big enough to ensure adequate flow with relatively

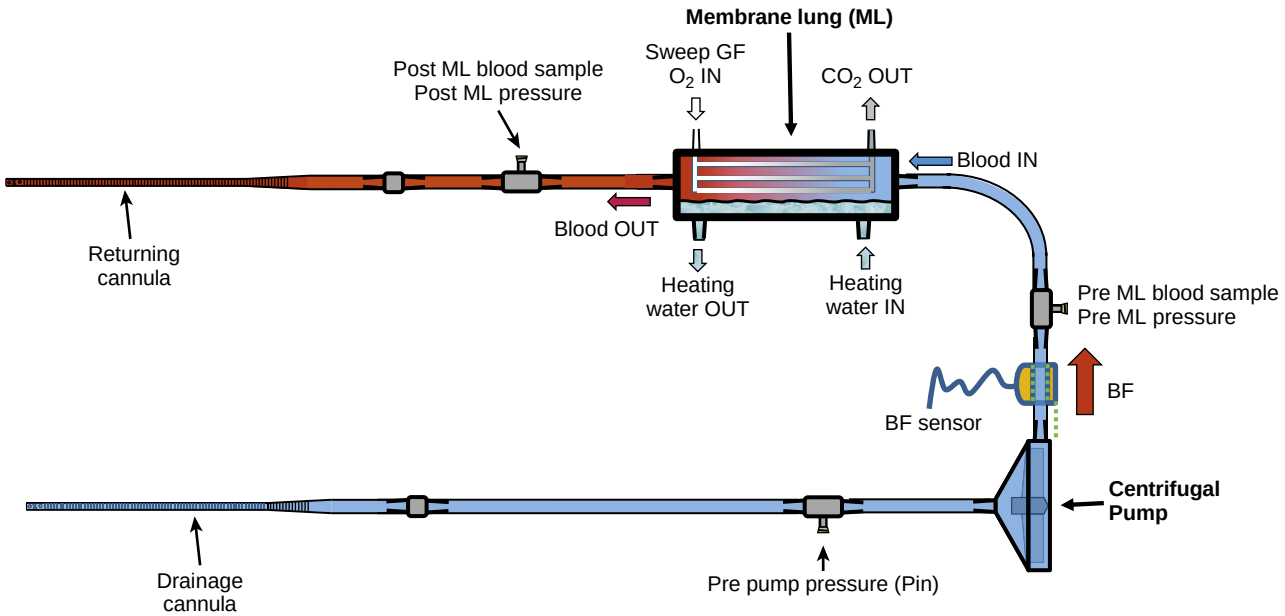

Figure 138.1 Schematic of a basic circuit for *veno-venous extracorporeal membrane oxygenation* (VV-ECMO). From the drainage to the returning cannula, a basic circuit for VV-ECMO includes a connector with stopcock for drainage pressure monitoring (pre-pump pressure or Pin); the centrifugal pump; a flow sensor for monitoring blood flow (BF); a connector with stopcock for monitoring pressure and sampling for gas analysis of the input blood (pre-membrane lung [ML] pressure); the membrane lung oxygenator (ML) (inlet and outlet port for blood, sweep gas flow (GF), and heating water are represented); and a connector with stopcock for monitoring pressure and obtaining samples for gas analysis of blood leaving the oxygenator (post-membrane [ML] lung pressure).

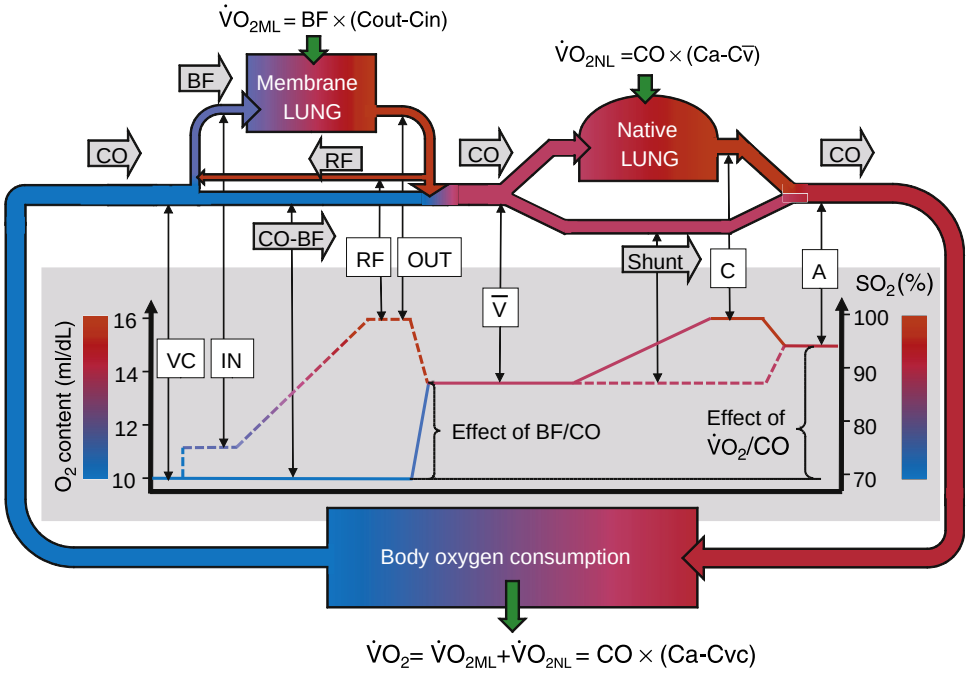

Figure 138.2 A schematic of a model of blood oxygenation during *veno-venous extracorporeal membrane oxygenation* (VV-ECMO). Blood oxygen content (mL/dL, main *y*-axis) and hemoglobin saturation (%, secondary *y*-axis) of different blood vascular districts (*left to right*: VC, vena cava; ML, membrane lung; IN, input; RF, recirculating fraction; OUT, ML output; $\bar{V}$, mixed venous; blood exiting normally functioning capillaries of the *native lung* [NL]; C; capillary; A, arterial) are represented. The oxygenation of the mixed venous blood is affected by ECMO blood flow (BF) relative to the cardiac output (CO). Arterial oxygenation is affected by the intrapulmonary shunt (Shunt). The sum of the oxygen transferred to the blood by the NL ($\dot{V}O_{2NL}$, mL/min) and the ML ($\dot{V}O_{2ML}$) equals the total patient's oxygen consumption ($\dot{V}O_2$). A more detailed description is provided in the text.

low suction pressure, and the holes and tip of the cannula should be positioned in a large, high-flow vessel.

VV-ECMO may be accomplished using three different configurations: femoral-femoral, femoral-jugular, and jugular-femoral. Factors to consider when choosing the configuration are to maximize drainage capability, allow patient mobilization, avoid complications, and minimize *recirculation* (i.e., the reentry of blood into the ML already oxygenated by the ML). The femoral-jugular access is the more frequently used; with a correctly positioned femoral cannula of 23 to 25 French, BF rates up to 6 to 7 L/min are easily obtained with minimal recirculation. The jugular-femoral approach, in which blood is drained directly from the right atrium, likely provides the best drainage, but there is a high degree of recirculation, which can effectively nullify the drainage advantage. The femoral-femoral approach offers safer access with less possibility of accidental cannula dislocation; mobilization of the patient's head is facilitated at the expense of lower limb mobilization. With this approach, however, minimization of recirculation requires careful positioning of the cannula tips, which is generally more difficult to obtain than with other approaches. To maximize the available BF, the tip of the femoral drainage cannula should be positioned in the inferior vena cava superior to the renal veins. A heparin bolus of 50 to 100 U/kg is administered immediately before insertion of the first cannula.

Double-lumen cannulas are commonly placed through the right internal jugular vein. For BF rates comparable to those commonly achieved with the traditional two-cannula configurations, insertion of cannulas up to 31 to 35 French may be necessary.

Choice of the cannulas is also based on the clinical indication. For more severely hypoxemic patients, larger cannula sizes and configurations allowing higher BFs should be selected at the start. When the patient's needs change, insertion of a second drainage cannula, an upgrade from a single to a double-cannula configuration, or a switch from VV to veno-arterial ECMO is sometimes necessary.[58]

PATIENT-MACHINE INTERACTION

The effect of VV-ECMO on arterial blood gas values is a function of the complex interplay between different factors. It is useful to discuss separately the effects on oxygenation and CO_2 removal.

EFFECT ON OXYGENATION

During VV-ECMO, the ML and the *native lung* (NL) are in series (Fig. 138.2). The physiology of VV-ECMO can be understood by following the changes in blood O_2 content from the vena cava ($Cvco_2$) to the arterial side (Cao_2). $Cvco_2$ is a function of Cao_2, *cardiac output* (CO), and the *arterial-venous O_2 difference* ($Cao_2 - Cvco_2$).

Membrane Lung

A fraction of venous return (BF/CO) is diverted through the ML. The oxygen transfer across the ML is given by $\dot{V}o_{2ML} = BF \times (Co_{2out} - Co_{2in})$, where Co_{2in} and Co_{2out} are the oxygen content of the blood respectively entering (input) and leaving (output) the ML. A fraction of output flow, the recirculation fraction, re-enters into the extracorporeal circuit, thus increasing the O_2 content of input blood and reducing the $\dot{V}o_{2ML}$. The oxygen content of the blood returning to the lung (the mixed venous blood, $C\bar{v}o_2$) is the flow-weighted average of Co_{2out} and $Cvco_2$, as follows: $C\bar{v}o_2 = [Co_{2out} \times BF + Cvco_2 \times (CO - BF)]/CO$. In practice, the effect of the ML is to increase the O_2 content of the blood returning to the lung from $Cvco_2$ to $C\bar{v}o_2$. $C\bar{v}o_2$ is then increased to the arterial concentration of oxygen by the oxygenating capacity of the patient's lung.

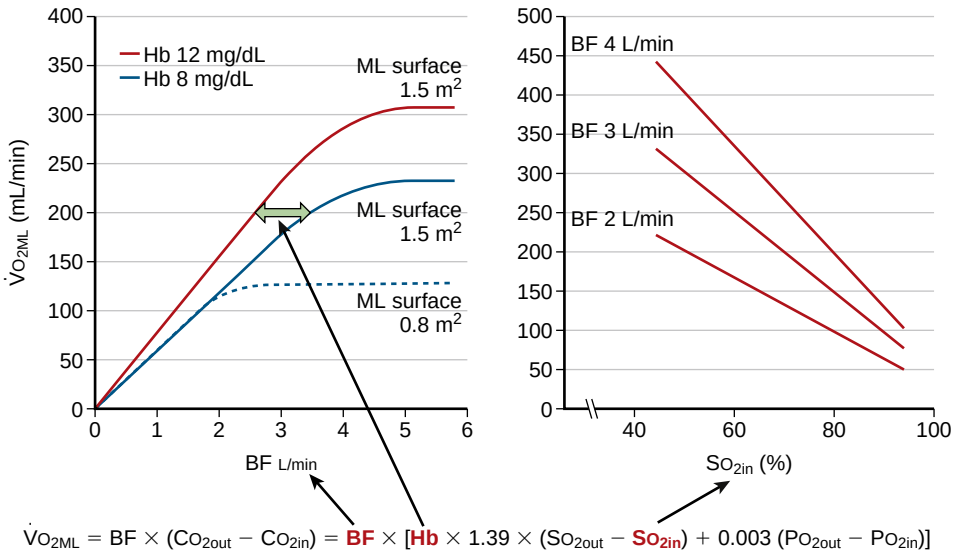

Figure 138.3 Factors determining oxygen transfer by the membrane lung. Oxygen is transferred to the blood by the membrane lung ($\dot{V}O_{2ML}$, mL/min) as a function of *extracorporeal membrane oxygenation* (ECMO) blood flow (BF, L/min, *left*) and oxygen saturation of the blood entering the *membrane lung* (ML) (So_{2in}, %, *right*). The effect of the *hemoglobin* (Hb) concentration and of the membrane lung surface area (m^2) is represented in the left panel. The formula for computation of $\dot{V}O_{2ML}$ is shown. Co_{2in}, So_{2in}, and Po_{2in} are the oxygen content (mL/dL), saturation (%), and partial pressure (mm Hg) of the blood entering the ML; Co_{2out}, So_{2out}, and Po_{2out} are the oxygen content, saturation, and partial pressure of the blood leaving the ML.

Native Lung

The oxygen transfer across the *native lung* (NL) is $\dot{V}O_{2NL} = CO \times (Cao_2 - C\bar{v}o_2)$, and the patient's total oxygen consumption is simply the sum of ML and NL oxygen transfer: $\dot{V}O_2 = \dot{V}O_{2ML} + \dot{V}O_{2NL}$.

Besides the oxygenation capability of both the ML and the NL, the main determinants of blood O_2 content are hemoglobin saturation and hemoglobin concentration. Once the hemoglobin has been saturated, the only way to increase ML O_2 transfer is by increasing the hemoglobin concentration (Fig. 138.3, left).

Under VV-ECMO, arterial oxygenation will depend on $\dot{V}O_{2ML}$, $\dot{V}O_{2NL}$, $CvcO_2$, and CO.

O_2 Transfer by the Membrane Lung. $\dot{V}O_{2ML}$ depends on three main factors (see Fig. 138.3).

1. ML. The oxygenator's oxygenation capability will depend on the membrane diffusion characteristics (thickness, material) and the membrane surface area (see Fig. 138.3, left).
2. Oxygen pressure gradient. The O_2 pressure gradient between the *gas flow* (GF) (also called the sweep gas flow) and the blood is one factor determining the transfer of oxygen. On the gas side, the O_2 partial pressure depends on the FIO_2 of the sweep gas. It is essential to understand that, similar to natural lung physiology, the transfer of O_2 through the ML is governed by ventilation-perfusion matching. And, similar to the normal lung, once a high level of partial pressure has been reached in the outlet blood, a further increase in GF will not lead to any increase in O_2 transfer. On the blood side, the higher the Co_{2in}, the lower the quantity of O_2 that can be added to the blood (see Fig. 138.3, right). An important factor that may result in a high Co_{2in} is recirculation.
3. BF. Up to a determined BF, $\dot{V}O_{2ML}$ will increase directly with the increase in flow. However, depending on the membrane surface area and the ML characteristics, there is a limit to the oxygenator flow (rated flow). Above this limit, no more O_2 can be added to the blood (see Fig. 138.3, left).

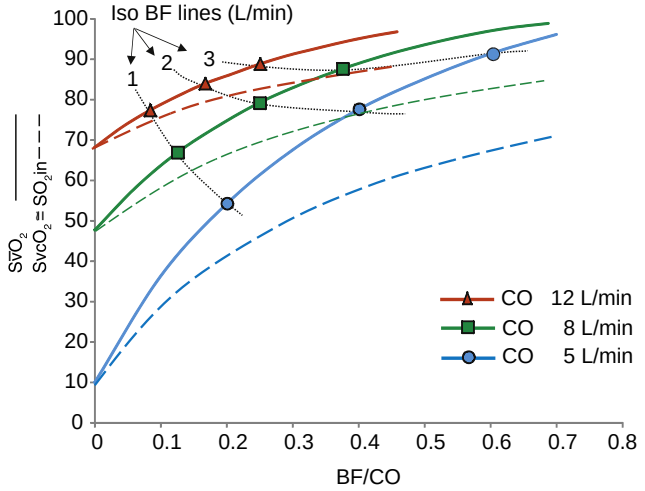

Figure 138.4 Oxygen saturation of blood entering the patient's lung ($S\bar{v}o_2$, solid lines) as a function of the blood flow (BF)/cardiac output (CO) ratio, at different CO. At constant CO and oxygen consumption, increase of BF/CO through an increase of BF results in an increase of $S\bar{v}o_2$ by two mechanisms: first, because a higher fraction of venous return is oxygenated passing through the membrane lung (ML); second, because the resulting increase in arterial O_2 saturation will lead to an increase of oxygen saturation of the blood in the vena cava ($SvcO_2$) and therefore in the input (So_{2in}) (*dashed lines*). The effect of changing BF/CO by changing CO at constant BF (iso BF lines) is also represented. Increase of CO has opposing effects on $S\bar{v}o_2$: an increasing effect resulting from the increase of $SvcO_2$ and So_{2in}, and a decreasing effect due to the lower fraction of venous return oxygenated through the ML. The former effect prevails at lower BF, while at higher BF (above 3 L/min) changes in CO have minimal effects on $S\bar{v}o_2$.

Mixed Venous Blood Oxygenation. During VV-ECMO, the main determinants of mixed venous So_2 are the oxygen saturation of the blood leaving the organs (i.e., vena cava blood saturation, $SvcO_2$) and the ratio between BF and CO (Figs. 138.2, 138.4, and 138.5). At a given BF, an increase in CO (and a decrease in BF/CO) is associated with an increase in $SvcO_2$, causing a decrease in the oxygenation contribution of the ML ($\dot{V}O_{2ML}$), thus commonly resulting in a decrease in mixed venous So_2 and ultimately a decrease in *arterial oxygenation saturation*

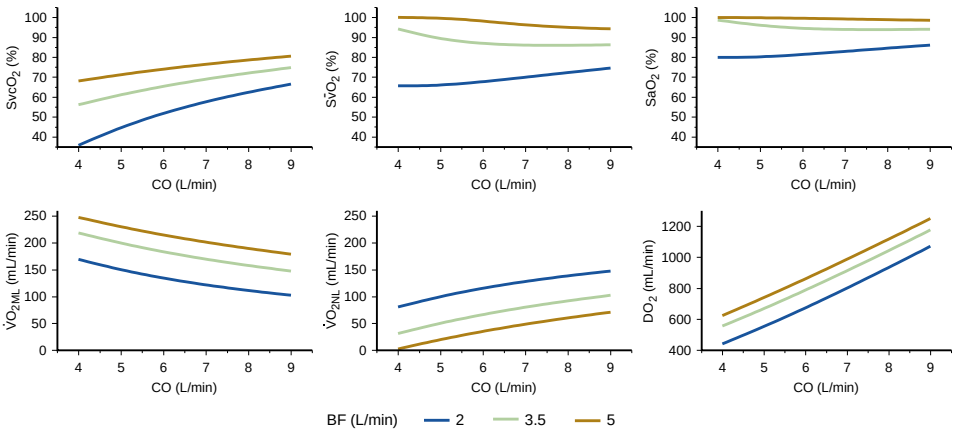

Figure 138.5 Effects of changes in cardiac output at three different *blood flows* (BFs). Oxygen saturation of the blood in the vena cava ($Svco_2$), oxygen saturation of the mixed venous blood ($S\bar{v}o_2$), oxygen saturation of arterial blood (Sao_2), oxygen transfer by the membrane lung (ML) (Vo_{2ML}), oxygen transfer by the native lung (NL) (Vo_{2NL}), and arterial oxygen delivery (Do_2) as a function of cardiac output (CO) at three different BFs in L/min.

(arterial So_2), although *oxygen delivery* ($Do_2 = Cao_2 \times CO$, the amount of oxygen delivered from the NL to the body tissues per minute) increases (see Fig. 138.5).[59] Conversely, if BF is held constant and CO is decreased (an increase in BF/CO), mixed venous So_2 and arterial So_2 will commonly increase, although $Svco_2$ and Do_2 decrease. These relationships are the basis for the manipulation of BF and CO during VV-ECMO.

Although one would hope to increase oxygenation by increasing BF/CO, there are limitations on how much the BF/CO ratio can be increased. First, a decrease in CO is associated with a parallel decrease in $Cvco_2$: below a certain threshold of BF, the expected positive effect on oxygenation of the increase in the BF/CO ratio may be offset by the decrease in $Cvco_2$ (see Fig. 138.5), resulting in a net decrease of mixed venous So_2 and arterial So_2. Second, in the presence of recirculation, either an increase in BF or a decrease in CO will increase the amount of recirculating blood, thereby blunting the expected positive effect on oxygenation. Third, an increase of BF is limited by cannula size and patient blood volume status. Fourth, oxygen delivery to peripheral organs depends on both arterial Co_2 and CO: at low oxygenation levels, a higher CO is necessary to ensure sufficient organ oxygenation.

Mixed venous blood oxygenation is also affected by the fraction of inspired oxygen of the ML (Fio_{2ML}). Increasing Fio_{2ML} increases Vo_{2ML} and thus mixed venous So_2 (eFig. 138.1).

Oxygen Uptake from the Native Lung. The NL will contribute to arterial oxygenation by adding oxygen to the mixed venous blood according to its remaining gas-exchange capacity, which depends on the severity of the lung disease (i.e., the intrapulmonary shunt fraction, $\dot{Q}s/CO$, and the *fraction of inspired oxygen of the NL* (Fio_{2NL}) (eFig. 138.2).

The main goal during VV-ECMO is to reduce and limit all the factors contributing to VILI. However, a decrease of Fio_{2NL}, *positive end-expiratory pressure* (PEEP), and/or minute ventilation may temporarily lead to worsening of gas-exchange function of the NL, increasing the reliance of patient oxygenation on the oxygenation provided by the ML. Thus, the expected level of BF and indeed the choice of ECMO equipment and cannula sizes will be strongly influenced by the oxygenation achievable by management of the NL and, most importantly, by the level of oxygenation considered clinically acceptable for delivery to the body.

EFFECT ON CO_2 REMOVAL

Removal of CO_2 during VV-ECMO is much easier to achieve than oxygenation. With any type of ML, clearance of CO_2 is always more efficient than oxygen transfer (Fig. 138.6). Whereas the amount of O_2 transfer is limited at the point at which the blood is fully saturated, there is no such limit to CO_2 removal and a substantial amount of CO_2 can be removed from venous blood. Most of the CO_2 is transported in blood in the form of bicarbonate ion. Normal venous blood carries at least 50 mL of CO_2/100 mL. This means that half a liter of venous blood contains 250 mL of CO_2, an amount equivalent to roughly the entire CO_2 production per minute by the body (approximately 250 mL/min for a 70 kg normothermic man). Thus, the entire patient CO_2 production can theoretically be removed with low BF provided that a high GF is used. At a high GF (8 to 15 L/min), the CO_2 concentration in the gas compartment remains close to 0 mm Hg, and a high CO_2 pressure gradient is maintained. The strict relationship between $\dot{V}co_{2ML}$ and GF is advantageous because it allows dissociation of CO_2 removal from oxygen transfer. In other words, the GF can be used to control CO_2 removal and BF can be used to control oxygen transfer.

This removal of a large percentage of the CO_2 production allows the clinician to decrease the minute ventilation delivered by the ventilator. If 50% of $\dot{V}co_2$ is removed by the ML, minute ventilation of the NL can roughly be halved. This is the physiologic basis for the use of ECMO to provide a more protective ventilator strategy, as discussed later.

MANAGEMENT OF THE MEMBRANE LUNG

Management of ECMO is essentially based on setting three variables:

1. BF. As we have seen, BF is the main determinant of patient oxygenation and should be set to the lowest level that provides adequate oxygenation. The required flow will be a function of the target oxygenation level and the ventilator strategy applied to the NL.
2. GF. GF is the main determinant of CO_2 removal and, consequently, it determines the minute ventilation needed from the ventilator.

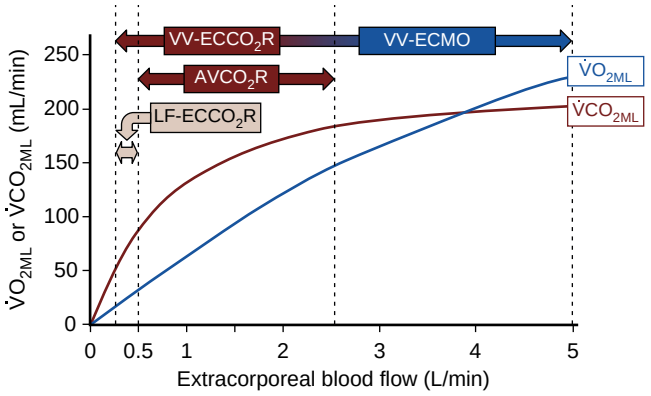

Figure 138.6 CO_2 removal and oxygen transfer as a function of *extracorporeal membrane oxygenation* (ECMO) blood flow with different available techniques. Extracorporeal carbon dioxide removal ($\dot{V}_{CO_{2ML}}$) and oxygen transfer ($\dot{V}_{O_{2ML}}$) is shown as a function of ECMO blood flow at steady state in a patient with total oxygen consumption 250 mL/min and total carbon dioxide production 200 mL/min. $AVCO_2R$, arteriovenous CO_2 removal; $LF\text{-}ECCO_2R$, low flow extracorporeal CO_2 removal; $VV\text{-}ECCO_2R$, veno-venous extracorporeal CO_2 removal; VV-ECMO, full veno-venous extracorporeal oxygenation support.

3. F_{IO_2} of the sweep gas. It is generally set to 1.0 and progressively decreased as the patient improves.

The ECMO circuit should be monitored several times daily (at least once daily by a perfusionist). Careful monitoring of the ECMO system is aimed at answering the following questions:

1. Is the oxygenator performing well? If the F_{IO_2} of sweep gas is 1, the expected P_{O_2} in the output blood should be very high (generally > 300 to 400 mm Hg). The output P_{O_2} is usually higher than 500 mm Hg at lower BFs and starts to decrease as flow approaches the rated flow for that type of oxygenator. Accounting for this effect, daily monitoring of the output P_{O_2} allows detection of any decrease in oxygenator performance, which may prompt a circuit substitution. In addition, as the oxygenator performance worsens, increasing GF rates are necessary to maintain the same arterial P_{CO_2}.
2. Is drainage from the patient effective? Efficient blood drainage is crucial. Drainage effectiveness can be assessed by monitoring the pressure proximal to the pump (Pin) (see Fig. 138.1) and the BF/revolutions per minute ratio. If drainage is insufficient, BF becomes unstable (sudden drops) and "kicking" or "swinging" of drainage lines can be noted. Pin is an essential parameter that should be monitored closely. Appropriate drainage cannula size and BF should be selected to avoid excessively negative Pin. Values of Pin above −100 mm Hg are recommended. When drainage becomes less effective, Pin and BF will decrease, and higher pump revolutions per minute must be set to maintain the same BF. The most common reason for a reduction of drainage effectiveness is a change in patient volume status and/or a decrease in venous BF proximal to the cannula tip. Volume expansion or temporary reduction of the BF is the easiest solution. It is always important to check for any change in cannula position, tube kinking, or obstruction.
3. Is there thrombosis in the circuit? The oxygenator is the main site of activation of thrombosis. Clot formation in the oxygenator may be detected by daily inspection of oxygenator surfaces, by monitoring the transmembrane pressure (difference between post (P_{postML}) and pre (P_{preML}) oxygenator pressure), and by monitoring coagulation parameters (see later).

VENTILATORY MANAGEMENT OF THE NATIVE LUNG

The main objective during VV-ECMO is to ensure adequate gas exchange while minimizing VILI.[23] As CO_2 is removed through the ML, minute ventilation can be reduced for the NL, generally by decreasing V_T (and indirectly plateau airway pressure) and/or respiratory rate. Support of oxygenation by the ML may allow a decrease in F_{IO_2} and eventually PEEP (and indirectly peak and plateau airway pressure) in the NL.

Depending on how V_T, respiratory rate, PEEP, and F_{IO_2} are set, different protective ventilatory strategies are possible. Optimal setting of the mechanical ventilator during ECMO is still a matter of debate, and strategies may vary from center to center.[60]

ELSO guidelines[22] suggest targeting ventilator management to use F_{IO_2} less than 0.4, and plateau pressure less than 25 cm H_2O while preventing lung collapse by maintaining a PEEP level of 15 cm H_2O in the first 24 hours. Notably, there are no specific recommendations about V_T setting. Peak or plateau airway pressures were the main ventilatory targets in the Conventional Ventilation or ECMO for Severe Adult Respiratory Failure[40] and the EOLIA[41] trials (see earlier).

Multicenter and single-center observational studies are the main source of information on clinical practice.[37,39–41,61–66] The largest and most recent international, multicenter, prospective cohort study on MV during ECMO is the LIFEGARDS study.[66] Data on MV settings were collected during a 1-year period in 23 medium to high case-volume ECMO centers. Within 24 hours of ECMO initiation, V_T and plateau pressure were both significantly reduced from 6.4 ± 2 to 3.7 ± 2 mL/kg predicted body weight and from 32 ± 7 to 24 ± 7 cm H_2O, respectively. On the contrary, PEEP remained unchanged or was only slightly reduced compared to pre-ECMO setting (from 12 ± 4 to 11 ± 3 cm H_2O). The results of the LIFEGARDS study largely confirmed what was reported in previous observational studies.[37,39–41,61–65]

The common trend after starting ECMO is to decrease V_T targeted to a plateau pressure below 25 to 30 cm H_2O.[29–31] Apart from isolated experienced centers that target PEEP to levels below 10 cm H_2O from the beginning,[67] most centers keep PEEP unchanged.[37,39–41,61–66] This is the dilemma between letting the lungs collapse or trying to keep them open.[68,69] Centers with greater expertise often apply different approaches in different patients or may even change the ventilatory approach in a given patient as clinical conditions change. The ventilatory strategy has a big influence on the level of BF and GF in the ML necessary to maintain adequate oxygenation. In addition, if the gas-exchange capability of the NL is poor, a higher device BF and a larger cannula size will be necessary. As soon as the lung function and the patient's clinical condition improves, the patient

may be switched from controlled to assisted MV. The current approach is to promote early mobilization. During this phase, oxygenation may not be a major problem anymore, but it is possible to manipulate GF to modulate the patient's respiratory drive and effort.

ANTICOAGULATION AND HEMATOLOGIC MONITORING

Anticoagulation during VV-ECMO is commonly achieved by continuous intravenous heparin infusion, targeted to an activated partial thromboplastin time of 45 to 60 seconds and/or to an activated clotting time of 1.5 to 2 times normal. The main advantage of activated clotting time is its prompt availability at the bedside. There has been an increasing interest in the use of thromboelastography for real-time bedside monitoring of anticoagulation. A pilot study showed that, compared to the standard of care of using activated partial thromboplastin time monitoring, use of a thromboelastography-based protocol for anticoagulation management is associated with the administration of lower heparin doses with no difference in the incidence of hemorrhagic or thrombotic complications.[70] According to ELSO guidelines, during ECMO treatment, fibrinogen and antithrombin III should be maintained within normal range.

After starting ECMO, the platelet count usually decreases. Platelet transfusions are recommended to maintain the platelet count above 50,000/μL in all patients and above 100,000/μL in the presence of active bleeding.[22]

Activation of the coagulation cascade and subsequent clot formation in the circuit are accompanied by a progressive decrease in platelet count and fibrinogen level and consumption of coagulation factors that may lead to a syndrome similar to disseminated intravascular coagulation. D-dimer levels are a reliable variable to detect circuit thrombosis. Signs of activation of the coagulation cascade along with decreased performance of the oxygenator and/or increase of transmembrane pressure should prompt replacement of ECMO circuit.

In the presence of heparin-induced thrombocytopenia, heparin infusion should be discontinued, and an alternative anticoagulant such as argatroban may be used.[71,72]

Red cell transfusion policy during ECMO is extremely variable because there is no consensus on the target hematocrit level.[73] Available guidelines recommend maintenance of hematocrit within normal limits to minimize BF requirements and maximize oxygen transfer by both the ML and the NL.

COMPLICATIONS

Bleeding complications remain the most frequent and serious complication in ECMO patients. The best sources of information on the incidence of complications are the ELSO registry reports.[74] Localized bleeding, especially from cannula insertion sites or from surgical sites, is common, seen in approximately 17% and 16% of patients, respectively. Simple compression or packing maneuvers are often sufficient to treat these complications.

Intracranial bleeding is reported in 3.9% of patients and is associated with an overall survival rate of only 17%. Pulmonary and gastrointestinal hemorrhage happens in approximately 8% and 5% of patients, respectively.

In the presence of generalized and persistent bleeding, heparin should be reduced or discontinued, and transfusion of fresh frozen plasma and platelets should be considered. To prevent bleeding, it is worthwhile to minimize procedures such as intramuscular or subcutaneous shots, thoracentesis, chest tube insertion, and substitution of nasogastric or urinary catheters.

WEANING FROM VENO-VENOUS EXTRACORPOREAL MEMBRANE OXYGENATION

Weaning from ECMO is accomplished by the progressive reduction of the ECMO contribution to oxygenation and CO_2 removal as the gas-exchange capability of the NL improves and the patient's clinical condition stabilizes (Fig. 138.7). The decision to disconnect a patient from ECMO is based on the composite assessment of several aspects of the patient's respiratory function (gas exchange function, respiratory mechanics), and hemodynamics. According to the ELSO guidelines, ECMO discontinuation can be considered when 50–80% of total gas exchange is supported by the patient's lungs.[22]

Patient readiness for weaning may easily be assessed during VV-ECMO by simply turning off the GF. At zero flow, no oxygen is added and no CO_2 is removed from the blood flowing through the ECMO circuit, and the only gas-exchange system is the patient's lung. In patients still on controlled MV, during the trial off-ECMO, respiratory rate, VT, and FIO_2 should be adjusted to values considered acceptable off-ECMO. Most commonly, ECMO is discontinued when the patient is receiving assisted spontaneous ventilation. After the GF is stopped, the patient usually has to increase respiratory effort and minute ventilation, and ventilator support should be adjusted accordingly. When the patient is considered ready, ECMO can be definitively discontinued and cannulas removed. To remove cannulas placed percutaneously, a purse-string suture, inserted around the cannulation site, is tightened immediately after decannulation and localized pressure is applied for at least 30 minutes.

LOW-FLOW CO_2 REMOVAL

Following the original concept developed by Kolobow and Gattinoni,[12,13] several devices and technical approaches have been implemented to perform extracorporeal CO_2 removal. The key is that, because these approaches use lower BFs and smaller cannulas, they are less invasive and have fewer serious side effects. The direct consequence of removing CO_2 through these devices is that it is possible to reduce the minute ventilation required through the NL, while preventing hypercapnic acidosis.

INDICATIONS

The main indications for *extracorporeal CO_2 removal* ($ECCO_2R$) are to decrease VT and RR in ARDS patients for "ultraprotective ventilation" and to decrease ventilatory needs in patients with exacerbations of COPD or severe asthma, thereby reducing dynamic hyperinflation, avoiding intubation, and facilitating weaning from MV.

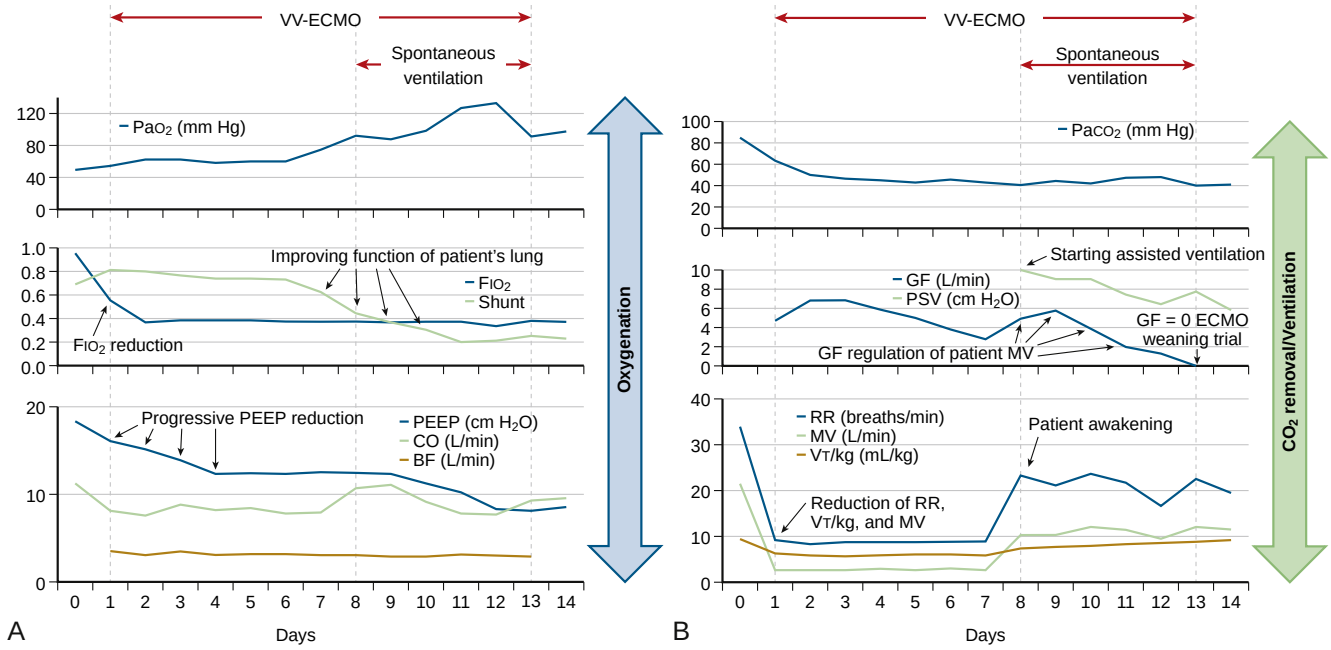

Figure 138.7 Example of ventilatory management in a patient with acute respiratory distress syndrome over 2 weeks. Oxygenation parameters (A) and ventilation parameters (B) are shown, including ventilator and *extracorporeal membrane oxygenation* (ECMO) settings, gas exchange, and hemodynamics day by day. As soon as ECMO starts, *respiratory rate* (RR), *tidal volume* (V_T/kg), and *minute ventilation* (MV) are reduced. *Positive end-expiratory pressure* (PEEP) and F_{IO_2} are reduced progressively. After the 6th day, intrapulmonary shunt (shunt) starts to decrease and Pa_{O_2} improves. On day 8, the patient is awakened. RR, V_T, and mechanical ventilation are controlled by modulating ECMO sweep *gas flow* (GF) until the patient is ready to be weaned on the day 13. Throughout the ECMO treatment, an ECMO *blood flow* (BF) of around 3 L/min is maintained while the *cardiac output* (CO) ranges between 7 and 10 L/min. PSV, pressure support ventilation.

Depending on the range of operative BFs and on the bypass configuration, the available techniques may be classified as follows:

1. *Low-flow* (LF)-$ECCO_2R$. Various devices are available that operate with very low extracorporeal BF, ranging from 250 to 500 mL/min. These systems allow removal of up to about 80 to 100 mL of CO_2/min (see Fig. 138.6). Most of these systems can be employed with small (14 to 17 French), double-lumen coaxial catheters similar to those used for continuous renal replacement. Livigni et al. were the first to describe one of these devices in 2006.[75] Since then, a number of similar devices have been described. The main limitation of these devices is the need for frequent circuit substitutions (every 24 to 48 hours). Recently, this problem has been partially solved by simplifying the circuit and using polymethylpentene oxygenators instead of the less expensive polypropylene ones. Novel systems, such as the ProLUNG, also use oxygenators with high surface areas (i.e., 1.8 m^2) to enhance CO_2 removal. A different device is the Hemolung (Alung Technologies), in which the ML and the centrifugal pump are combined and act as one unit. The rotating impeller transmits a rotational motion to the blood, thereby increasing gas-exchange efficiency.[76,77] Compared to other low-flow systems, the Hemolung shows longer duration and slightly higher CO_2 removal performance.[77]
2. *Arteriovenous CO_2 removal* ($AVCO_2R$). This arteriovenous ECMO system uses a simplified, high-technology ML (Novalung), characterized by an extremely low resistance to BF, high gas transfer efficiency, and absence of a heat exchanger. The Novalung is applied to an arteriovenous shunt obtained by connecting the femoral artery to the femoral vein using two cannulas inserted percutaneously. According to the mean systemic arterial pressure and to the size of the arterial catheter (15 or 17 French), a BF of up to 2.5 L/min can be achieved.[78,79] The main limitations of this system are the dependency on the patient's arterial blood pressure and the risk of ischemia of the leg distal to the arterial cannulation site. Close monitoring of foot temperature and pulse oximetry is recommended; if signs of ischemia are noted, prompt action is required to prevent permanent damage to the lower limb.
3. VV-$ECCO_2R$. Classical $ECCO_2R$ techniques as proposed by Gattinoni and Kolobow[12] use standard adult ECMO systems at a BF of 1.5 to 2.5 L/min. By mounting low-medium surface oxygenators such as pediatric or small adult oxygenators on small size tubes and cannulas, different ranges of flow may be achieved (from to 500 mL/min up to 2 to 2.5 L/min), allowing removal of up to 100% of the entire metabolic CO_2 production.

CO_2 REMOVAL FOR ULTRAPROTECTIVE VENTILATION IN ACUTE RESPIRATORY DISTRESS SYNDROME

The idea of ultraprotective ventilation originates from the observation that despite the use of a "protective" V_T, a substantial amount of hyperinflated lung[30] can still be present and further reduction of V_T may be beneficial. Extracorporeal CO_2 removal represents a very powerful technique to ensure protective ventilation and prevent VILI, while maintaining adequate gas exchange in patients in whom oxygenation is not a main issue. In 2006, Bein

et al. showed that use of $AVCO_2R$ allowed a reduction in ventilation to less injurious settings while oxygenation was improved.[78] $AVCO_2R$ has been employed successfully also in patients with severe influenza A. [79]

In a recent application of $AVCO_2R$, Bein et al. compared ultraprotective ventilation with VT of 3 mL/kg while on $AVCO_2R$ with a conventional protective ventilatory strategy with VT of 6 mL/kg in 79 ARDS patients. Though the study failed to show significant benefits in the 3 mL/kg group, a post hoc analysis showed a significant improvement in ventilator-free days at 60 days in the subgroup of patients with more severe hypoxemia (arterial PO_2/FIO_2 <150) at baseline.[80]

Terragni et al. were the first to use an LF-$ECCO_2R$ device in ARDS patients.[81] With this device, they were able to decrease VT from 6 to 4 mL/kg while keeping constant PCO_2 and pH levels in a group of ARDS patients. They showed a reduction of circulating inflammatory cytokines and a reduction of lung hyperinflation.

The prospective multicenter international SUPERNOVA study is the source of the most recent and largest amount of data on the use of extracorporeal CO_2 removal to enhance protective ventilation in patients with moderate ARDS.[82–84] Ninety-five patients were randomized to receive lower CO_2 extraction or higher CO_2 extraction devices (BF 300 to 500 mL/min vs. 800 to 1000 mL/min, respectively). Ultraprotective ventilation defined as VT 4 mL/kg and plateau pressure ≤25 cm H_2O or greater was achieved in 82% of patients by 24 hours from $ECCO_2R$ initiation.[82] Devices with higher CO_2 extraction capacity were able to achieve the VT target more frequently and with a lower rate of adverse events.[83] Along with higher device performance, both lower respiratory system compliance and higher alveolar dead space were associated with a greater magnitude of reduction in VT and driving pressure (ΔP, end-inspiratory plateau pressure minus positive end-expiratory pressure) from the use of $ECCO_2R$, thus suggesting that patients with these features might be most likely to benefit from $ECCO_2R$.[84]

In summary, the available literature demonstrates that the use of very low VT combined with some form of extracorporeal CO_2 removal is feasible without major side effects. However, future studies are required to demonstrate the potential survival benefits from the use of ultraprotective ventilatory strategies in ARDS patients.

CO_2 REMOVAL FOR COPD

COPD is the fourth leading cause of death in western countries and is a major cause of morbidity worldwide.[85] COPD patients experience recurrent episodes of hypercapnic respiratory failure (i.e., acute exacerbations) associated with poor prognosis and increased mortality.[86] Most patients are successfully managed with *noninvasive ventilation* (NIV), which represents the standard first-line treatment in acute exacerbations of COPD.[87] However, intubation and invasive MV are still required in 26–54% of patients.[88,89] In these patients, invasive MV is associated with a high rate of complications (e.g., ventilator-associated pneumonia, barotrauma, and failure to wean), which ultimately increases morbidity and mortality.[90–92] The main cause of NIV failure is the imbalance between the reduced capacity of the respiratory muscles to generate pressure and the respiratory load, which is increased as a result of the high ventilatory needs and expiratory flow limitation. The rationale for the use of CO_2 removal techniques is to decrease minute ventilation, and consequently airflow limitation and respiratory effort, while decreasing PCO_2 and increasing pH. $ECCO_2R$ may play a role at different stages of COPD exacerbations: to avoid intubation during the NIV phase and to reduce the duration of invasive MV and facilitate weaning.

Surprisingly, the use of $ECCO_2R$ in acute COPD patients has not been investigated until recently. The majority of the published clinical studies applied $ECCO_2R$ to prevent intubation in patients at high risk of NIV failure (pH <7.2 to 7.35, PCO_2 >45 to 95 mm Hg, or respiratory rate >27 to 40 breaths/min).[93–95] Del Sorbo et al. compared 25 patients with acute exacerbations of COPD treated with NIV and $ECCO_2R$ versus 21 historical matched controls treated only with NIV.[93] The NIV plus $ECCO_2R$ treatment showed a lower intubation rate (12% vs. 33%), and lower in-hospital mortality (8% vs. 35%); however, 52% of the treated patients showed adverse events related to the $ECCO_2R$ treatment. Kluge et al. applied an $AVCO_2R$ treatment in 21 COPD patients not responding to NIV and compared them to 21 matched controls treated with conventional invasive MV.[94] Within 24 hours of $AVCO_2R$ treatment, PCO_2 and pH significantly improved. Ninety percent of the $AVCO_2R$ patients avoided intubation, but 9 had bleeding complications. Short- and long-term survivals were similar between $AVCO_2R$ and conventional treatment. In the case-control ECLAIR study by Braune et al., VV-$ECCO_2R$ prevented intubation in 56% of the 25 treated patients.[95] Seven patients suffered from progressive hypoxemia and 9 from major bleeding. The 90-day mortality rates were 28% in both groups.

In a few cases, the use of $ECCO_2R$ to facilitate weaning from invasive MV in COPD has also been reported.[96,97] Cardenas et al. applied $ECCO_2R$ in a difficult-to-wean COPD patient: extracorporeal removal of CO_2 allowed a 30% decrease of minute ventilation with concomitant reduction in hyperinflation and improvement in gas exchange.[98] Abrams et al. successfully extubated five COPD patients within 24 hours following $ECCO_2R$ institution.[99] Garcia et al. applied VV-$ECCO_2R$ in 10 COPD patients during weaning from MV or as a bridge to lung transplant[97]; six patients were successfully weaned or underwent transplantation.

EXTRACORPOREAL MEMBRANE OXYGENATION AS BRIDGE TO TRANSPLANTATION

Lung transplantation is an important treatment option for patients with end-stage respiratory failure. The number of patients awaiting lung transplantation largely exceeds that of available organs, resulting in long waiting times. Patients developing acute exacerbation of their respiratory disease while awaiting lung transplantation have a poor prognosis, especially when invasive MV is required.[100] The mortality rate for waitlist patients with end-stage exacerbations is high.[101] In these difficult cases, bridging strategies may be necessary. The first report of ECMO as a bridging strategy dates back to 1975[102]; since then, several case series have been reported.[101–110] A recent systematic review identified 14 published studies including 441 patients from 1987 to 2013.[109] In all cases, standard veno-venous or

veno-arterial ECMO was used. The bridging time on ECMO before lung transplantation ranged from a median of 3 to 16 days. The proportion of patients successfully bridged to transplantation ranged from 50–83%, with 1-year survival rates comparable to recipients who did not receive preoperative ECMO support. In one retrospective analysis, patient outcomes were better when the patients were supported with NIV and when their bridge time until transplantation was shorter than 14 days.[110]

Clearly, proper patient selection is crucial. Absolute contraindications for ECMO bridging include the following: ineligibility for transplantation according to standard criteria, irreversible end-organ damage affecting multiple organs, sepsis and bacteremia, contraindications to systemic anticoagulation, uncontrolled metastatic disease or another terminal illness not otherwise treatable with a lung transplant, and acute intracerebral hemorrhage or stroke. Relative contraindications may vary among different centers, but usually include the following: advanced age, limitations in vascular access, obesity, frailty, and prolonged ventilatory support.[101]

Over the years, the use of ECMO to avoid tracheal intubation and MV (awake ECMO) has gained popularity, becoming the preferred first-line approach in patients awaiting lung transplantation. During ECMO support, patients are kept awake and spontaneously breathing; this helps avoid the complications associated with invasive ventilation (e.g., sedation, hemodynamic impairment, VILI, infections, diaphragmatic atrophy) but also allows active patient mobilization and facilitates respiratory physiotherapy. Moreover, the possibility of managing patients with acute respiratory failure using ECMO while avoiding intubation is also promising.

Finally, the use of low-flow extracorporeal support techniques instead of "conventional" ECMO as a bridge to lung transplantation has been described in small patient series. Fischer et al. reported on the use of $AVCO_2R$ in 12 patients with high urgency for lung transplantation experiencing severe ventilation-refractory hypercapnia and respiratory acidosis.[104] The length of extracorporeal support was 15 ± 8 days, and 10 patients were successfully bridged to lung transplantation. The only report on the use of LF-$ECCO_2R$ as a bridge to transplant is that of Ricci et al. who applied $AVCO_2R$ in 6 patients and LF-$ECCO_2R$ in another 6 patients.[107] The mean length of extracorporeal support was 13.5 ± 14.2 days with no differences between the two devices.

Key Points

- *Extracorporeal membrane oxygenation* (ECMO) refers to a technique of life support that consists of diverting part of the patient's blood to a membrane lung for gas exchange (oxygenation and CO_2 removal) and then returning it to the patient
- *Veno-venous ECMO* (VV-ECMO) is primarily indicated for hypoxemic respiratory failure in patients with a high risk of mortality or at high risk for ventilator-induced lung injury. Contraindications include advanced age, severe disability, and incurable malignancy.
- CO_2 removal is significantly more efficient than oxygenation. Depending on the *blood flow* (BF), the technique may be used mainly for CO_2 removal (BF < 2 L/min) or for both CO_2 removal and oxygenation (BF up to 5 to 6 L/min).
- ECMO BF is the main determinant of patient oxygenation. ECMO gas flow is the main determinant of CO_2 removal and, consequently, determines the minute ventilation needed from the mechanical ventilator for the native lung.
- During VV-ECMO, the native lung is ventilated in a protective way to prevent ventilator-induced lung injury. Respiratory rate, tidal volume, plateau airway pressure, and FIO_2 are generally decreased as much as possible while allowing sufficient arterial oxygenation and peripheral O_2 delivery.
- Anticoagulation during VV-ECMO is commonly achieved by continuous intravenous heparin infusion, targeted to an activated partial thromboplastin time of 45 to 60 seconds and/or to an activated clotting time of 1.5 × normal values. Bleeding remains the most frequent complication in ECMO patients. Intracranial bleeding is reported in 3.9% of patients and is associated with an overall survival rate of only 17%.
- The main indications for CO_2 removal are to permit ultraprotective ventilation of acute respiratory distress syndrome patients, to decrease the ventilatory needs of patients with exacerbations of COPD and severe asthma, to speed extubation, or to avoid intubation.

Key Readings

Abrams D, Ferguson ND, Brochard L, et al. ECMO for ARDS: from salvage to standard of care? *Lancet Respir Med*. 2019;7(2):108–110.

Acute Respiratory Distress Syndrome Network. Ventilation with lower tidal volumes as compared with traditional tidal volumes for acute lung injury and the acute respiratory distress syndrome. The acute respiratory distress syndrome network. *N Engl J Med*. 2000;342:1301–1308.

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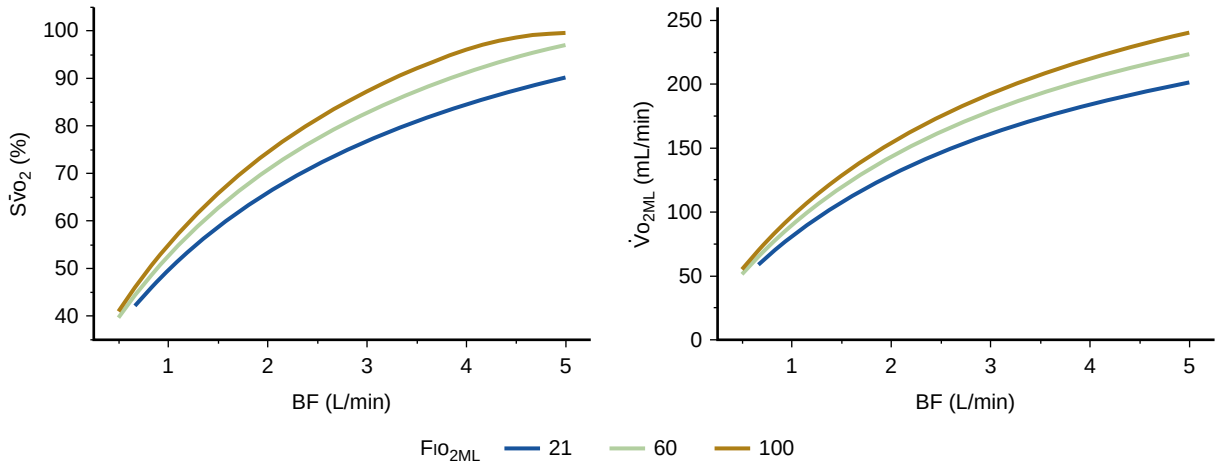
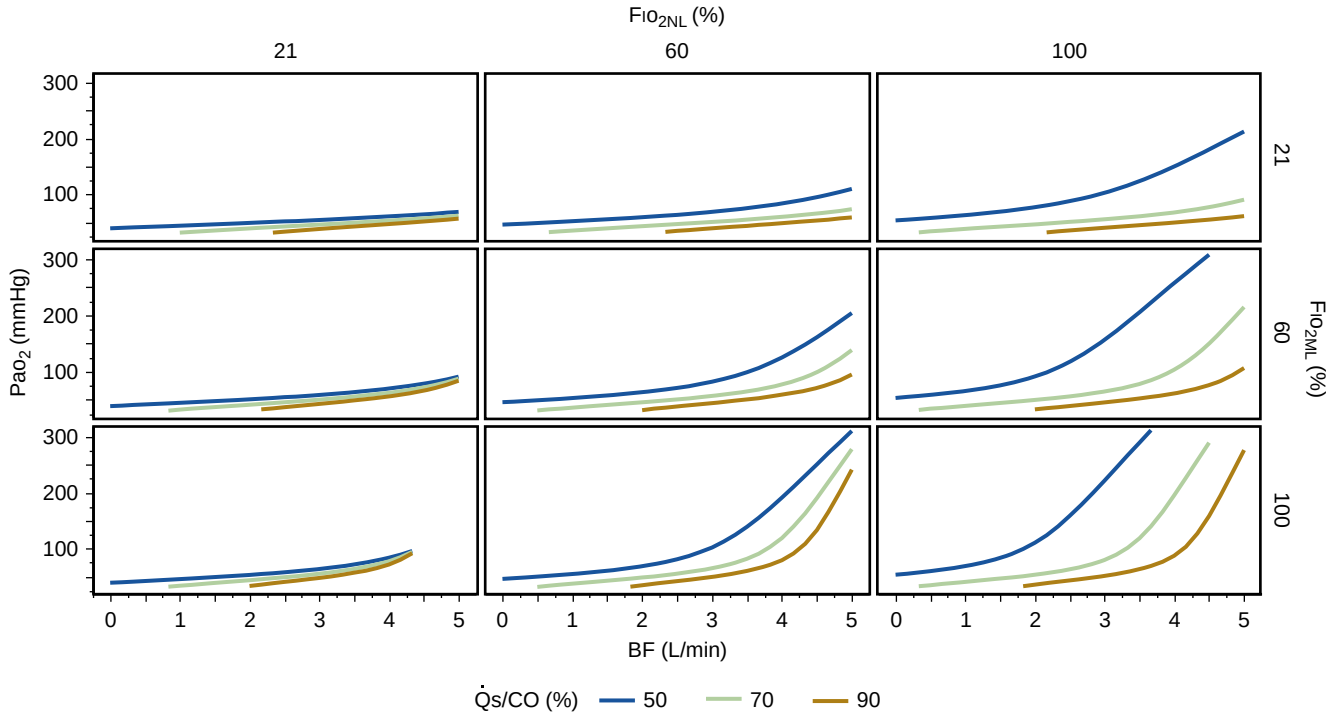
Complete reference list available at ExpertConsult.com.

eFIGURE IMAGE GALLERY



eFigure 138.1 Effects of changes in blood flow at three different FIO_2 of the gas flow. Oxygen saturation of the mixed venous blood ($S\bar{v}O_2$) and oxygen delivered by the membrane lung (ML) ($\dot{V}O_{2ML}$) as a function of blood flow (BF) at three fractions of inspired oxygen of the ML (FIO_{2ML}).



eFigure 138.2 Effect of changes in blood flow at different FIO_2 (of membrane and native lungs) and different shunt fractions. Partial pressure of oxygen in arterial blood (arterial PO_2) as a function of blood flow (BF) at three fractions of inspired oxygen of the membrane lung (FIO_{2ML}), three fractions of inspired oxygen of the natural lung (FIO_{2NL}), and three intrapulmonary shunt fractions ($\dot{Q}s/CO$).

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139 PULMONARY REHABILITATION

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INTRODUCTION AND HISTORY

Pulmonary rehabilitation (PR) is an essential component of the comprehensive and integrated care of individuals with chronic respiratory disease. This multidisciplinary, patient-centered intervention addresses distressing symptoms, exercise limitation, and reductions in health and functional status by treating the systemic manifestations of respiratory disease, including peripheral muscle dysfunction, maladaptive coping skills, inadequate self-management skills, and nutritional depletion while recognizing the complex comorbidities typically present in these patients. Positive outcomes from PR include increased exercise tolerance, reduced dyspnea and anxiety, increased self-efficacy, and improved health-related *quality of life* (QOL).[1–3] Evidence also shows that PR reduces health care use and mortality after COPD exacerbations.[3–5]

Pulmonary rehabilitation first gained widespread attention in the mid-1990s when it was shown that, despite significant airflow obstruction, patients could exercise with sufficient intensity to achieve significant improvements in skeletal muscle function and exercise capacity.[6–9] The effectiveness of PR was further supported by studies in the early 2000s showing lower health care utilization in the year following PR.[10,11] Since that time, systematic reviews and Cochrane library analyses have demonstrated unequivocal benefits of PR for people with stable COPD and following disease exacerbation.[2,3] Moreover, it is a highly cost-effective treatment.[11–13] There is substantial and growing evidence for equivalent benefits in chronic respiratory diseases other than COPD, including asthma, bronchiectasis, cystic fibrosis, lung cancer, pulmonary hypertension, and *interstitial lung disease* (ILD).[14]

DEFINITION AND RATIONALE

The most recent American Thoracic Society/European Respiratory Society statement defines PR as "a comprehensive intervention based on a thorough patient assessment followed by patient-tailored therapies that include, but are not limited to, exercise training, education, and behavior change, designed to improve the physical and psychological condition of people with chronic respiratory disease and to promote the long-term adherence to health-enhancing behaviors."[1] Notably, this intervention is designed around the needs of individual patients and their "treatable traits."[15] As such, PR addresses a complex phenotype including pulmonary pathophysiology, comorbid conditions, adaptive (or maladaptive) behaviors, available social supports, and cultural beliefs. Program organization differs across countries and health care systems; however, it is the degree of disease complexity that dictates the type of intervention and setting for the highest likelihood of success.[16]

PR provides improvements in dyspnea, exercise tolerance, and health status exceeding those of any other therapy for COPD, despite having no direct effect on pulmonary function. This apparent paradox can be explained by understanding COPD as a systemic illness with manifestations including impaired skeletal muscle structure and function, physical deconditioning, fear of dyspnea-producing activities, and inadequate pacing and coping skills, all contributing to symptoms and disability.[17–19] PR specifically targets these comorbidities. For example, exercise training leads to improved limb muscle function, with a reduced ventilatory requirement, despite no measurable change in FEV_1.[20,21] PR also addresses other comorbidities such as nutritional depletion, poor pacing techniques, maladaptive coping skills, and fear of dyspnea-producing activities, which can result in a vicious circle of deconditioning and debilitation.

Focused interventions within PR can interrupt this cycle and improve the dyspnea associated with daily activities, improve health and functional status, and reduce health care utilization.[22–24]

INDICATIONS AND CANDIDACY

People with chronic respiratory diseases who remain symptomatic and/or who experience disability despite optimized medical therapy are candidates for PR.[1,25] Patients are referred to PR by their health care provider, usually for one or more of the following reasons:

1. Severe dyspnea and/or fatigue
2. Decreased exercise tolerance or ability, and/or low physical activity levels
3. Difficulty performing *activities of daily living* (ADLs)
4. Impaired health status
5. Decreased occupational performance or ability
6. Frequent or increased medical resource utilization
7. Difficulty coping with or managing the disease
8. Recovery from COPD exacerbation (or other acute event leading to hospitalization)
9. Preparation for or recovery from lung transplantation (or other lung surgery)
10. Nutritional depletion

Given that resources for and reimbursement of PR are limited in many countries, it is important to identify individuals who are most likely to benefit from it. Whereas a majority of people with chronic respiratory disease do benefit, responses to individual components of PR vary, and patients' gains vary across different outcomes.[26] Identification of those most likely to benefit is therefore difficult and, to date, there are no clear selection criteria to determine responders versus nonresponders to PR. The structure, staffing, and resources available in individual PR programs affect the medical complexity, number, and mix of patients that can be accommodated.[19,27] Insurance coverage also often impacts patients' ability to enroll in PR. Individuals with stable chronic respiratory disease, as well as those recently hospitalized for disease exacerbation, can benefit.[1,3]

Several studies have evaluated the impact of various clinical characteristics on patients' likelihood of achieving benefits from PR. Most of this work has, to date, focused on individuals with COPD. People with a wide range of lung function impairment benefit from PR.[1,2,25,28–30] PR is effective in improving symptoms, exercise, and quality of life, even for those with very severely impaired lung function,[1] including those preparing for lung transplantation[31] and those requiring supplemental oxygen.[32] Health care professionals often refer patients to PR when disease is severe and when they cannot identify further treatment options. Although payers may pose some limitations for PR based on lung function severity, delays in referral until disease is severe are often misguided. Indeed, people with mild-severity COPD[33,34] also achieve benefits from PR. Participation in PR earlier in disease before symptoms are severe may help to promote and establish health-enhancing behaviors (including regular exercise, physical activity, and better management of exacerbations) and can help patients cope with and manage their disease, which may favorably affect disease progression and improve outcomes.

Other characteristics, including age,[35–38] smoking status,[39] and medical comorbidities,[40–44] do not reliably differentiate between those who are or are not likely to benefit from PR. Among those with COPD, the degree to which exercise capacity is limited by muscle weakness and/or fatigue as compared to ventilatory impairment may impact gains after exercise training in PR.[45–48] For example, patients with predominance of nonventilatory exercise limitations (i.e., poor aerobic fitness) are typically able to train at higher intensities, resulting in greater training effects. However, exercise capacity improves regardless of the initial mechanism of exercise limitation; therefore, PR benefits all functionally impaired COPD patients.

Exclusions from PR may include conditions that interfere with the rehabilitation process or that would place the patient at risk during exercise training. Accordingly, there are few absolute contraindications to PR. These include:

1. Unstable angina or arrhythmia
2. Unstable bone fracture
3. Communicable infectious disease
4. Unstable psychiatric condition posing harm to self or others

Relative contraindications include severe cognitive impairment, lack of motivation, severe progressive neurologic disease, severe anemia and/or severe debilitating fatigue (e.g., due to other medical illness) that would prevent participation.

COMPONENTS

The core components of PR are shown in Table 139.1.

EXERCISE TRAINING

Exercise training is the cornerstone component of PR. Several mechanisms contribute to exercise impairment associated with chronic respiratory diseases. Ventilatory limitation is important, but skeletal muscle dysfunction and cardiovascular impairments are also key contributors limiting exercise ability.[20,49,50] For example, reductions in limb muscle mass, strength, endurance, and muscle mitochondrial density; altered resting and exercise muscle energy utilization; reduced type I (slow twitch, high oxidative capacity, fatigue-resistant) muscle fibers, fiber capillarity, and oxidative enzymes; impaired balance; and other disturbances are common among people with COPD.[49,51] Skeletal muscle dysfunction is also present among individuals with ILD,[52–54] pulmonary hypertension,[55–57] cystic fibrosis,[58] and those recovering from lung transplantation.[59–61] Skeletal muscle dysfunction results from physical inactivity and deconditioning, oxidative stress, systemic inflammation, nutritional/energy imbalance, electrolyte disturbances, aging, hypoxemia, low anabolic hormone levels, systemic corticosteroid use, and other mechanisms.[1,28,49]

Importantly, deconditioning, sarcopenia, and other aspects of skeletal muscle dysfunction can be improved with

Table 139.1 Components of Pulmonary Rehabilitation

Exercise training (lower and upper extremities) ■ Aerobic training (cycling or walking-based exercise) ■ Resistance training (free weights, exercise bands, weight machines) ■ Interval training (alternating periods of high-intensity exercise and rest/lower intensity exercise) ■ Balance training ■ Other: whole-body vibration training, neuromuscular electrical stimulation, yoga/Tai Chi
Education (see Table 139.2)
Collaborative self-management skills
Disease exacerbation, medication, and oxygen management
Psychosocial support
Nutritional support and dietary counseling
Breathing training and airway clearance techniques ■ Inspiratory muscle training ■ Pursed-lip breathing ■ Chest physical therapy (percussion/postural drainage) ■ Positive expiratory pressure vibration devices ■ Pacing and energy conservation techniques
Physical activity promotion and coaching
Emphasis on long-term health-enhancing behavior change
Advance care planning
Assessment of participants' exercise and functional capacity, symptoms, QOL/health status (and other patient-centered and health-system outcomes) before and after PR program participation (see eTable 139.1) ■ Demonstrate individual patients' progress and gains made in PR ■ Demonstrate PR program effectiveness and safety ■ Monitor program costs

PR, pulmonary rehabilitation; QOL, quality of life.

exercise training.[1,28,49,62,63] Several forms of exercise training are beneficial.[1,64] The mechanisms by which exercise capacity improves following exercise training depend on the type of respiratory disease and the type and intensity of exercise training. For example, among people with COPD, exercise training–induced fiber-type switching to a more fatigue-resistant profile and increases in mitochondrial oxidative enzyme capacity and/or fiber capillarity can result in a lower lactate production for a given workload and a delay in the anaerobic threshold.[6,7] This results in lower ventilatory demand during exercise, with improvement in breathing pattern and reduction in dynamic hyperinflation.[65] This, in turn, leads to improved exercise capacity and reduced dyspnea with daily activities.

Typically in PR, a combination of aerobic and resistance training is undertaken of the upper and lower extremities.[1,64] Continuous endurance aerobic training of the legs via cycling and/or walking-based exercise (e.g., treadmill or ground-based walking) at a set target intensity is common.[2] Endurance aerobic training improves maximal exercise capacity, endurance, dyspnea, and fatigue in COPD.[1,2,66] Exercise training also improves ADL performance, reduces systemic blood pressure, improves lipid profiles, reduces depression and anxiety, and facilitates sleep. In general, exercise training at high intensity (e.g., 60–80% of maximal workload) leads to greater gains in aerobic fitness than lower-intensity exercise (<50% of maximal workload), but low-intensity exercise still confers benefits, and the optimal training intensity is not fully understood.[67] Walking-based training improves walking endurance more than cycle training,[68] although cycle-based training is associated with less oxygen desaturation.[69] One-legged exercise (single-leg cycling) can lead to greater gains in peak oxygen uptake and/or endurance compared with conventional cycling because training a smaller muscle group enables provision of a higher-intensity training load for a longer time before reaching ventilatory limitation, poses lower ventilatory demand and, in turn, can lead to overall greater increase in aerobic capacity.[70,71] Use of rollator walkers facilitates walking exercise and reduces dyspnea for people with severe dyspnea and functional limitation.[72–74] Nordic walking with walking poles also increases exercise tolerance and physical activity levels.[75]

Bronchodilator therapy (where relevant) should be optimized prior to PR to enable exercise at higher intensities and to optimize gains in exercise tolerance.[76] Supplemental oxygen therapy is typically provided for resting and/or exercise-induced hypoxemia, to improve exercise endurance,[77] maintain safety, and allow training at higher work rates. Oxygen therapy may also enable exercise training at higher intensities for nonhypoxemic patients[78]; however, this is not a universal finding.[79,80]

Interval training, wherein periods of high-intensity exercise (e.g., 20 to 30 seconds) are alternated with periods (e.g., 30 to 40 seconds) of low-intensity exercise or rest, leads to comparable gains in exercise capacity, skeletal muscle function, QOL, and reduction in dyspnea to those made during continuous endurance training in moderate-to-severe COPD.[81–83] Those with difficulty performing continuous endurance training or who have severely impaired exercise capacity and/or severe dyspnea may benefit from interval training.[84]

Resistance training, using free weights or weight machines, can improve muscle strength and/or endurance depending on the training regimen.[85,86] Combining resistance training with aerobic training in PR leads to greater gains in muscle strength and size compared to aerobic training alone.[87–89] However, the optimal resistance training regimen for maximal gains in skeletal muscle function for individuals with chronic respiratory diseases remains unknown.

Exercise training of the upper extremities has been less studied compared to lower limb training. However, because many ADLs rely on upper extremity function, optimization is an important goal. Upper limb training (both aerobic and resistive) can increase upper limb exercise capacity,[90] improve arm strength, and improve arm endurance.[90–92] The benefits of upper limb training on dyspnea and health-related QOL are less clear,[90,91] and optimal training regimens are unknown.

The exercise prescription for individual patients in PR is based on assessment of their baseline exercise capacity. Prescription of endurance training typically involves use of low-cost field tests of exercise capacity, such as the 6-minute walk test and the incremental shuttle walk test,[93] with target intensity based on target heart rate, metabolic equivalents, or maximal exercise capacity.[93,94] Formal cardiopulmonary exercise testing is undertaken in some centers[95] but requires specialized equipment

and staff, is not universally available, and adds cost. The prescription of interval-type exercise training is typically based on cardiopulmonary exercise testing measurements. Endurance training is typically two to five times per week and is ideally prescribed three to five times weekly at 60–80% of maximal work rate for 20 to 60 minutes per session.[84] Duration and workload of exercise are progressed over the course of the program as tolerated. Interval training is typically three to four times per week at 80–100% of maximal work rate for a total of 45 to 60 minutes.[96] The resistance training prescription is typically based on baseline assessment of the maximal weight the patient can lift for each exercise (the one-repetition maximum),[49] with training intensity set at a fraction of the one-repetition maximum, depending on whether the target is improved strength[85] or endurance.[96] Resistance training is recommended 2 to 3 times per week,[1] and the workload of resistance training is progressed over the course of the program as tolerated.

Several other forms of exercise training also have demonstrated efficacy for people with COPD.[64] Balance impairments, gait disturbances, and falls are common[51,97–105]; balance worsens further after an acute COPD exacerbation.[106] Although not yet routinely included in PR, balance training incorporated into PR is well tolerated[107] and improves balance and health-related QOL.[107–109] Several tests are available to assess balance.[110] The effects of balance training on fall risk are not yet known. Whole-body vibration training, wherein the patient stands or performs squat exercises on a vibration platform, also has demonstrated benefits for several parameters of exercise tolerance and health-related QOL for people with COPD.[111–115] Though not yet used widely in PR due to need for specialized equipment, its benefits are notable, and it may be particularly helpful for individuals with difficulty participating in conventional exercise training. *Neuromuscular electrical stimulation* (NMES) is another training technique that may be considered. This involves application of an electrical stimulus to elicit muscle contraction via surface electrodes placed on the skin over the muscles targeted for training. The amplitude, frequency, and stimulation pattern impact the type of training effects achieved with NMES. It is typically well tolerated, nonpainful, and safe, although it should be avoided in those with indwelling cardiac pacemakers, defibrillators, and/or with seizure disorders. NMES can improve muscle strength, muscle mass, and exercise capacity for people with severe disease who have difficulty participating in conventional exercise training due to ventilatory limitation.[116,117] A recent meta-analysis of 16 studies of NMES, including 267 patients with COPD, showed that NMES alone confers significant improvements in quadriceps force and endurance and exercise capacity.[118] NMES is also suitable for home use,[119] but as yet is not proven to provide more benefits than conventional PR.[120] Functional electrical stimulation, in which electrical stimulation is delivered concurrently with specific exercise modalities such as cycling, is a novel approach to increasing exercise training intensity.[121] Yoga and tai chi are alternative exercise strategies that incorporate breathing training and stress reduction, confer modest benefits in 6-minute walk test, dyspnea,[122–124] or QOL,[124,125] and may be appealing to some individuals. Various adjunct interventions to optimize the benefits of exercise training have been studied, including use of heliox, noninvasive ventilation, nutritional supplements, and anabolic hormone therapy. These interventions remain largely investigational to date.[1,126]

The type of exercise training included in PR depends on locally available equipment, space, staffing, and resources.[27] The choice of exercise also depends on individual patients' abilities, comorbidities (e.g., orthopedic limitations or morbid obesity) that may require or preclude performance of selected exercise, and preferences. Incorporation of at least some form of exercise that patients find enjoyable may be more likely to encourage them to undertake exercise and physical activity in the home environment both during and after completion of the PR program. Most PR programs range in duration from 8 to 12 weeks. A Cochrane review and meta-analysis of 65 randomized controlled trials including 3822 participants with COPD demonstrated that exercise training in PR (compared to usual care) led to increased maximal exercise capacity (mean difference, 6.8 watts; 95% *confidence interval* [CI], 1.9 to 11.7; n = 779; studies =16), increased 6-minute walk distance (mean difference, 43.9 meters; 95% CI, 32.6 to 55.6; n = 1879; studies = 38), reduced dyspnea, and improved quality of life (considered further in later section on outcomes of PR).[2] Longer programs may provide more sustained benefits.[127] Recommendations for continuing exercise and physical activity are commonly provided at the completion of PR. Repeat courses of PR provide a similar degree of benefit to those of initial program participation.[128]

EDUCATION

Education is another essential component of PR. In order to sustain the benefits obtained during the formal PR program, it is imperative to provide the necessary tools and strategies to patients that promote self-efficacy, which is the foundation for health behavior change and optimized disease control. Traditionally, PR programs were established for patients with COPD and common educational topics included specific disease education, inhaler technique and medication management, benefits of exercise, how to manage symptoms, and relaxation and energy conservation techniques. Because active smoking is not an exclusion criterion for program enrollment, nor has it been shown that smokers attain fewer benefits with PR, smoking cessation education and support should be included in PR for smokers. In more recent years, other topics have been added in response to patient needs and goals, such as advance care planning, importance of physical activity, and action plans for the COPD exacerbation. However, to date, no literature has clearly demonstrated which topics are essential for inclusion or how education is best delivered. A more in-depth understanding of the learning needs of patients, especially those with chronic respiratory diseases other than COPD, is warranted, and adaptation of the education component of PR is evolving.[129] Education topics included commonly in PR programs are shown in Table 139.2.

Studies that have evaluated didactic education in addition to exercise training in PR have not shown benefits beyond those seen with exercise training alone, including improvements in health-related QOL, health care

Table 139.2 Education Topics Commonly Included in Pulmonary Rehabilitation

FOR ALL

- Anatomy and physiology of respiratory disorders (e.g., COPD, ILD, PH, asthma, CF, bronchiectasis, lung cancer)
- Benefits of exercise and physical activity
- Benefits and adverse effects of respiratory medications (disease-relevant; including proper timing and technique)
- Benefits and practical aspects of supplemental oxygen therapy
- Benefits and practical aspects of noninvasive ventilation (e.g., CPAP, BPAP where relevant)
- Anxiety management, coping skills, relaxation strategies
- Recognition and management of disease exacerbations (including triggers, symptoms, and signs)
- Pacing, energy conservation, breathing techniques, body positioning to decrease work of breathing
- Nutrition
- Advance directives/end-of-life issues and care
- Partnering with health care professionals to manage disease

FOR SELECTED GROUPS

- Smoking cessation
- Airway clearance techniques and prevention of infection spread
- Exacerbation triggers
- Preparation for or recovery from lung transplantation or other surgery
- Controlled coughing/incentive spirometry
- Ambulation and deep breathing with chest tube in place (postoperatively)

BPAP, bilevel positive airway pressure; CF, cystic fibrosis; CPAP, continuous positive airway pressure; ILD, interstitial lung disease; PH, pulmonary hypertension.

utilization, symptoms, exercise capacity, functional capacity, and anxiety and depression.[2,130,131] Despite these negative findings, patients report that the education component is important and beneficial, and studies suggest that program completion and adherence to follow-up is improved in those patients receiving education alongside exercise.[130,132] It is entirely possible that the impact of educational components may not be reflected in traditional PR outcomes but may be related to recruitment, engagement, and retention in the program, and/or to long-term adherence to health-enhancing behaviors.

The exploration of patients' learning styles and needs, as well as the urgent requirement to address waning benefits over time, has transformed how PR programs convey vital information. Significant positive impacts on health care utilization and patient-centered outcomes have been demonstrated with interventions designed to improve self-management compared with usual care in chronic respiratory conditions.[133–138] As such, educational efforts are now focused on tailored self-management interventions that support patient-centered learning. As defined by international consensus, these patient-centered interactions focus on (1) identifying need, (2) increasing health beliefs and enhancing intrinsic motivation, (3) eliciting personalized goals, (4) formulating appropriate strategies to achieve those goals and, if required, (5) readjusting goals and strategies.[139] Behavior change techniques are used to elicit patient motivation, confidence, and competence. These approaches must recognize and adapt to the individual's cognitive abilities, psychological comorbidities, social context, and cultural beliefs as well as literacy level. The development of a patient-specific, collaborative self-management plan for disease exacerbations (action plan) is an important goal of PR; this includes education about the symptoms and signs associated with exacerbations to foster early recognition followed by the implementation of an action plan, which may include contacting a health care provider and/or using filled prescriptions. A 2017 Cochrane review of 22 studies involving 3854 participants with COPD showed statistically significant improvements in QOL and a lower risk for at least one respiratory-related hospital admission in patients using COPD action plans.[140] A 2019 randomized controlled trial utilizing disease exacerbation action plans in COPD patients with comorbidities showed a shorter duration for each COPD exacerbation and a lower probability of more than one respiratory-related hospitalization during the study year compared to usual care.[141] Ongoing collaboration among patient and medical team members is key to effective self-management.[142] PR provides an ideal setting for patient learning; however, due to heterogeneity of educational and study design, no firm conclusions have been made for practice recommendations.

The rise of digital technology provides additional opportunities to explore ways to extend and enhance patient learning within PR. Online tele-video sessions and other online connections, including social media, reading content on websites, use of smart device applications, and online classrooms, can support self-management learning.[143,144] In a recent Cochrane review, compared to conventional educational approaches, use of technology to support self-management led to greater improvements in health-related QOL and physical activity for 6 months but not 12 months; there was no significant difference in hospitalizations or exacerbations at any time point.[145] Several studies have explored the use of online home-based PR and reported acceptance and feasibility; however, outcome data remain sparse.[146,147] There is promise for using technology to support learning, but caution is needed because web-based resources available to people with COPD may vary significantly with respect to quality.

Finally, it is important to note that many health care professionals involved in the delivery of PR have little formal training in delivering education and facilitating learning. This is particularly relevant with techniques such as cognitive behavioral therapy, motivational interviewing, and technology-assisted learning. Increased attention must be given to educating PR professionals on educational design, adult learning theories, and implementation.

PSYCHOSOCIAL SUPPORT

Psychosocial comorbidities such as anxiety, depression, maladaptive behaviors, poor coping skills, and decreased self-efficacy contribute to the burden of advanced respiratory disease.[148] Anxiety and depression are associated with higher severity of dyspnea during activity and impairment in QOL at the start of PR and correlate with poorer outcomes after PR. In addition, psychosocial comorbidities may impact patient acceptance and/or completion of PR.[149,150] Psychosocial and behavioral interventions vary widely among PR programs but, at a minimum, often involve educational sessions or support groups focusing on areas such as coping strategies and stress management techniques. Comprehensive PR can decrease psychosocial morbidity

in patients with severe COPD, even when no specific psychological intervention is provided.[151] Techniques such as cognitive-behavioral therapy, biofeedback, family therapy, relaxation, and hypnosis may reduce not only anxiety but also dyspnea. However, the heterogeneity of available study designs does not allow for generalizations about their efficacy or routine implementation into PR.[152] Individuals with substantial psychiatric disease should be referred for appropriate professional care.

NUTRITIONAL SUPPORT

Low body mass index is present in 20–35% of patients with stable COPD.[153] It is associated with more severe lung disease, lung hyperinflation, and lower diffusing capacity. Low body mass index is also related to decreased respiratory muscle strength, handgrip strength, exercise tolerance, and health status, and increased mortality risk as compared to normal-weight individuals with COPD.[126] Given these poor outcomes, nutritional assessment and intervention is a recommended component of comprehensive PR.

Nutritional supplementation has been shown to improve outcomes in patients with COPD. In a 1998 publication, predictors of mortality were analyzed in two different cohorts of patients with COPD. In the first cohort of 400 COPD patients who had not received nutritional supplementation, body mass index was an independent predictor of increased mortality; in the second cohort of 203 COPD patients who received nutritional supplementation, weight gain in both depleted (i.e., low body weight or low *fat free mass* [FFM]) and nondepleted patients was a significant predictor of increased survival.[154] A subsequent 2012 Cochrane review of 17 studies found moderate-quality evidence that nutritional supplementation promotes significant weight gain and FFM in patients with COPD, especially for those that are malnourished. These patients also showed significant improvements in respiratory muscle strength and overall health-related QOL.[155] During PR, optimal nutritional intervention should focus on the interaction between nutritional supplementation and exercise, specifically resistance training to build FFM, and special attention should be paid to preventing weight loss in underweight patients undergoing endurance training.

The benefits of simple nutritional supplementation to underweight patients with chronic lung disease have been underwhelming, and therefore, attention has been given to multimodality interventions combining nutrition with anabolic steroids. This combined approach has shown improved body weight, FFM, exercise tolerance, symptom scores, and survival (over a 15-month study period). However, it is difficult to separate the effects of nutritional supplementation because all patients in the treatment arms also received PR.[156,157] It is unclear whether the benefits seen in clinical trials can be applied with safety and efficacy to a more generalized population.[1]

The effects of PR are similar in obese patients when compared to normal-weight individuals.[158] It is interesting to note that the degree of static hyperinflation, prevalence of low FFM and osteoporosis, and mortality are lower in obese COPD patients compared to normal-weight patients (the obesity paradox).[159] Despite these findings, it is recommended that PR programs also provide nutritional counseling and support to those patients who are significantly overweight.

INSPIRATORY MUSCLE TRAINING, BREATHING TRAINING, AND CHEST PHYSICAL THERAPY

Modalities including inspiratory muscle training, breathing training, and chest physical therapy have been part of PR over the years, but conclusive evidence supporting their routine use is, for the most part, lacking. The respiratory muscles can become weak in people with chronic lung disease due to mechanical inefficiency of the thorax. Individuals with COPD use a significantly higher proportion of their maximal inspiratory pressure as compared to healthy subjects, which correlates to higher levels of dyspnea at any given exertion level.[160] Inspiratory muscle training significantly improves maximal inspiratory pressure; however, studies have shown variable benefits in exercise capacity, dyspnea, and functional status,[161–164] and inspiratory muscle training does not have proven added benefit when combined with conventional PR.[162] At this time, inspiratory muscle training is not routinely recommended as part of PR; however, it might benefit certain subgroups of patients with markedly reduced maximal inspiratory pressure.[165]

The goal of breathing training is to reduce air trapping by controlling respiratory rate and breathing pattern. Pursed-lip breathing, performed with patients inhaling through the nose and exhaling through the mouth over 4 to 6 seconds through pursed lips in a whistling/kissing position, facilitates the recruitment of abdominal muscles during exhalation and has a favorable effect on the breathing pattern by increasing tidal volume and reducing end-expiratory lung volumes by increasing expiratory times and stenting collapsible airways with a positive end-expiratory pressure effect.[166] Successful pursed-lip breathing can result in less hypoxemia and decreased dyspnea. In some patients, pursed-lip breathing has also been shown to reduce the oxygen cost of breathing.[167]

Other breathing training techniques include breathing while bending forward and diaphragmatic breathing. The body-forward bending position with or without arm bracing has been reported to alleviate dyspnea and increase maximal inspiratory pressure in COPD patients by improving the length-tension relationship of the diaphragm and the mechanical coupling of the rib cage. Diaphragmatic breathing is performed by breathing slowly in through the nose while allowing the abdomen to move out, then exhaling while tightening the abdominal muscles and allowing them to move inward. Diaphragmatic breathing, though widely accepted as a breathing exercise to strengthen the diaphragm, has not been shown to be beneficial and, in fact, may decrease breathing efficiency and lead to more dyspnea in some COPD patients.[167]

Chest physical therapy techniques are used to facilitate secretion removal. Techniques include postural drainage, chest percussion and vibration, and directed cough. Because cough efficacy is frequently impaired in people with COPD, cystic fibrosis, and bronchiectasis, these techniques may be useful in selected patients.[168] Chest percussion must be used with caution in patients with osteoporosis. Individuals with bronchiectasis may also benefit from training with use

of vibration positive expiratory pressure devices, such as flutter or acapella devices, to facilitate airway mucus clearance. These simple handheld devices combine the principles of high-frequency oscillation and positive expiratory pressure to loosen mucus and help to expel it from the airways.

PROMOTING PHYSICAL ACTIVITY

Physical activity is associated with important health outcomes in the general population and for people with COPD, including improved cardiovascular conditioning, bone health, mental health, cognition, quality of life, and reduced obesity, diabetes, cancer risk, and mortality.[169–176] People with COPD have low activity levels compared to age-matched healthy individuals.[177,178] Activity levels decrease further during acute disease exacerbations,[179–181] with advancing disease severity,[182] over time,[183] in the presence of comorbidities,[184] and with use of supplemental oxygen.[185,186] Among those with COPD, low physical activity levels have been associated with worse lung function,[187–189] increased systemic inflammation,[190] risk of exacerbations and hospitalizations,[191–194] and mortality.[187,191,192,195] Physical activity levels are also reduced among individuals with other chronic respiratory conditions, including ILD,[196,197] asthma,[198–200] and pulmonary hypertension, [201,202] and are also linked to worse clinical outcomes.[197,203] It is hoped that interventions to increase activity levels will improve health.

Although PR consistently leads to gains in exercise capacity, the impact of PR on participants' activity levels is variable.[1,178] Although PR can lead to gains in physical activity,[204–207] it does not universally do so,[208–212] and changes in activity are variable following PR.[213] The impact of baseline exercise tolerance on gains in physical activity after PR is also variable.[214,215] Gains in exercise capacity (what the person *can* do) do not always translate into increases in physical activity (what the person *actually* does).[216] The factors that impact peoples' performance of daily activity is the subject of intensive research. Motivation, health-enhancing behaviors, social and environmental circumstances, weather and geographic area, and sociocultural norms all influence physical activity levels.[178]

Physical activity can be assessed indirectly via questionnaires[217–220] or measured directly using activity monitors worn on the waist or arm.[178] Given the importance of physical activity for clinical outcomes, efforts are underway to adapt and refine the PR intervention to foster patients' activity levels, and physical activity is increasingly included as a routine outcome measure in PR programs.[221] However, increasing physical activity is challenging because it depends on both physical ability and behavioral motivation.[222] Motivational programs using web-based activity promoting platforms,[223,224] telerehabilitation,[225] smart phone–based activity telecoaching,[226] virtual peer group behavioral interventions,[227] and simple commercially available devices (such as pedometers and wristband devices) are under investigation and have some demonstrated success. These interventions will likely be used more routinely in PR in the future.

LONG-TERM OUTCOMES AND MAINTENANCE OF BENEFITS

Although the short-term benefits of PR across multiple outcome areas are unequivocal (Table 139.3), benefits tend to decline once the program is completed unless patients continue to exercise regularly. In a landmark trial of PR, gains in exercise performance and health status obtained after 6 to 8 weeks of therapy disappeared by 18 to 24 months.[9] Several factors are likely to affect maintenance of benefits after PR, including exacerbations of underlying disease(s), burden of continuing exercise, frailty, and depression.[228,229] Understanding these barriers may help to design strategies to promote long-term adherence.

Maintenance programs largely involve exercise training but may also include continued self-management education. The ideal design of these programs is not known. A systematic review of supervised exercise programs in COPD (primarily weekly supervised exercise) found no added benefit to symptoms, exercise capacity, or health-related QOL when compared to standard care or unsupervised exercise.[230] Subsequently, a large trial showed that patients undergoing maintenance PR after an 8-week PR program had no change in their body mass index, airflow obstruction, dyspnea, and exercise tolerance index for the first 2 years of the 3-year program; the control group instead showed an increase in body mass index, airflow obstruction, dyspnea, and exercise tolerance at 2 years.[231] The PR program involved both supervised and unsupervised exercise, hospital visits, and regular phone contact.[231] A recent meta-analysis demonstrated that supervised maintenance rehabilitation reduces the risk of COPD exacerbations (risk ratio, 0.79) and respiratory-related hospital admissions (risk ratio, 0.62).[232]

Unsupervised maintenance exercise training may be a less expensive and more accessible training modality. Unfortunately, beneficial effects have only been seen following prolonged (3 to 6 months) PR programs, whereas those following programs of 8 weeks' duration did not show maintenance of exercise capacity post-program.[233,234] The addition of strategies designed to improve adherence to exercise

Table 139.3 Proven Benefits of Pulmonary Rehabilitation

IMPROVED
Exercise capacity
■ Endurance, strength, peak workload
■ Balance
■ Functional exercise ability—ADL and physical activity performance
Self-efficacy and self-management
Disease knowledge
Quality of life
Survival (when delivered after hospitalization for COPD exacerbation)
REDUCED
Dyspnea
Fatigue
Anxiety/depression
Urgent health care utilization and hospitalizations
Health care costs

ADL, activities of daily living.

has shown some promise. These additions include exercise diaries, support phone calls, follow-up assessments, pedometers, and other more complex technology.[232,235–237] Based on the available studies and the heterogeneity of interventions, it is not possible at this time to recommend one support intervention over another.

Adapting maintenance exercise programs to the needs of the individual, including alternative modes of exercise training (such as Tai Chi and water-based exercise) and complex technology (such as telerehabilitation platforms), is likely to be most successful. Incorporating the principles of PR, including exercise training, and incorporating ongoing healthy behaviors, such as physical activity, into the home setting may also lead to longer-lasting benefits. This is supported by studies of home-based programs that suggest that gains made in the home setting may be longer-lasting than those of hospital-based programs. Although regularly scheduled repeated PR sessions do not give additional prolonged benefit, "booster shots" of PR (e.g., delivered following an exacerbation) can help to return the patient to baseline functional performance.[238]

OBSTACLES TO PATIENT PARTICIPATION AND ADHERENCE

Overall uptake of PR by patients to whom it is offered remains low.[239,240] Several factors impact whether people with chronic respiratory diseases enroll in and/or complete PR. Many patients who could benefit have never been referred and are not aware of PR.[239,241–245] A recent survey of patients with chronic respiratory diseases conducted in 29 countries in Europe and the Americas illustrated that 22.4% of respondents had not been told about PR by their health care provider, 9.6% felt they did not have enough information to decide on whether to participate, and 8.9% were uncertain about the benefits it would provide.[246] Suboptimal knowledge and awareness of the process and benefits of PR among health care professionals (primary care and subspecialty providers) contributes to low patient referral rates.[239] Although training in PR for health care professionals varies across countries, formal training requirements are often minimal or lacking altogether. Among those to whom PR is offered, depression, current smoking, social isolation, transportation difficulty or travel distance, lack of perceived benefit, fear that it will be painful, poor mobility, severe dyspnea, frailty, comorbidity, and other social factors are cited barriers to PR participation.[239,246–254] Overcoming these barriers is a complex and difficult challenge. Successful approaches will likely depend on investigating and understanding the key local barriers in differing health care systems and undertaking practical solutions to foster patients' participation. This may include public awareness campaigns about PR, increased communication between health care professionals and patients about the benefits of PR, increased training for health care professionals in the discipline of PR, providing transportation and/or parking, establishment of PR programs in regions where they are currently lacking, and implementation of novel models of PR. Importantly, in many countries, PR programs are underfunded and underresourced. Limitations regarding program availability, access, insurance reimbursement, and coverage (including based on severity of disease and for repeat programs as needed) are serious obstacles to patients' participation in PR. Advocacy on the part of health care professionals, individuals with chronic respiratory diseases, and the general public is needed to improve this situation.

COMORBIDITIES

Medical comorbidities are common among individuals with chronic respiratory disease.[255–262] Multiple comorbidities typically coexist[263,264] and increase patients' morbidity and mortality risk.[18,265–268] Cardiovascular disease, peripheral vascular disease, and cognitive impairment are common among individuals referred for PR.[40,269–271] The total number or severity of comorbidities does not appear to impact PR outcomes.[40–42,44,272–274] However, individual comorbidities may impact selected outcomes for some persons.[40,42,149,150,275] PR is an important setting in which comorbidities may be newly recognized. PR providers must be aware of the spectrum of potential comorbidities, monitor patients for any concerning symptoms and signs during the program, and communicate any concerns to the referring health care professional.

Patients with complex multimorbidity may experience frequent exacerbations of symptoms, urgent care visits, hospitalizations, and/or episodes of acute-on-chronic respiratory failure. These patients have a high burden of disease-related morbidity, high health care costs, and, in many cases, an unstable condition.[19] In addition, they often face an overwhelming array of medications and testing and disease management recommendations prescribed by different providers who may not recognize the total burden for the patient. PR is an ideal setting in which to address and stabilize some of these issues (see Table 139.2). Patients with complex multimorbidity should undertake PR in a setting with a multidisciplinary health care team and a multifaceted approach that can address unique physical, functional, psychosocial, nutritional, and cognitive/behavioral needs.[16]

PROGRAM ORGANIZATION

Individuals referred to PR undergo a formal evaluation by the medical director and/or program staff to evaluate candidacy and safety for enrollment.[25] This includes a thorough medical history, physical exam, review of medical records, any testing or treatment that may be needed prior to enrollment, as well as assessment of exercise capacity, symptoms, health status, and other measures (see section on "Outcome Assessment and Measurement" later).[1] To be considered PR, programs must include, at a minimum, supervised and structured exercise training, education geared towards health-enhancing behavior change, and pre- and post-rehabilitation program outcomes measured in at least three key domains: exercise capacity, symptoms, and health status/QOL.[1,28,239,276] Assessments and outcome measures in additional areas such as physical activity, balance, anxiety/depression, health care utilization, and others are desirable but not universal.

Staffing, organization, content, and resources available in individual programs vary widely.[27,277] Staffing ranges from one or two providers to several providers in comprehensive multidisciplinary teams. PR staff typically include physiotherapists/exercise physiologists, nurses, respiratory therapists, health psychologists, and a medical director; the staff may include other disciplines such as occupational therapy, dieticians, pharmacy, social work, or others. PR program staff must demonstrate core competencies in the delivery of PR.[278–281] Staff must have familiarity with the anatomy, physiology, symptoms, comorbidities, and management of various forms of chronic respiratory disease. They should be skilled in cardiopulmonary resuscitation, and emergency resuscitative equipment should be available on site. Staff-to-patient ratios vary in different countries.[1] A program coordinator is designated in most programs. This individual develops the integrated program; organizes the program components and team members into a functioning unit; monitors the program progress, course and outcomes; and, together with the medical director, ensures that program quality metrics are met.

PR can be delivered in inpatient, outpatient, or home-based settings.[282] The severity of disease and medical comorbidities, severity of functional disability, patient preferences, available program types and locations, transportation issues, insurance coverage, and health system norms all impact the choice of PR setting. A majority of the published studies on PR have reported on outcomes of outpatient center-based or community-based programs.[1,2,66,281,283] Many outpatient programs hold sessions two to three times per week, including 1 hour of multimodality exercise training and 1 hour of education, for a total of 6 to 8 weeks, but program timing and duration vary across countries and health systems.

Inpatient PR programs are ideally suited for those with highly complex medical issues and/or needs and those who have nursing care needs or are unable to care for themselves. The criteria for admission to inpatient PR programs vary by country. In some countries such as Germany, the Netherlands, and Canada, inpatient PR centers are either the norm and/or are used widely and preferred. In contrast, in the United States, patients must have medical and/or nursing needs requiring inpatient care to qualify for inpatient PR. Typically, for inpatient programs, patients are admitted and then undertake their rehabilitation up to 5 to 6 days per week for 2 to 6 weeks.

Home-based PR often refers to programs in a nonhospital community setting or in the patient's home itself. Both of these approaches have had some demonstrated success, although largely in the context of clinical research. Presently, home-based PR is used by fewer than 5% of PR programs.[27] The structure, organization, and outcomes of home-based PR studied in the research setting are considered further under "Novel Models" later. The safety and success of home-based programs is likely dependent on the precise program structure, staffing, patient selection, and monitoring. Optimal criteria to determine which patients are most suited to undergo home-based PR are lacking to date, and insurance reimbursement and accreditation of home-based PR are not yet established or widely available. Formal accreditation of outpatient programs is available in some countries. In the United States, the American Association of Cardiovascular and Pulmonary Rehabilitation[284] accreditation requires health care professionals' participation, completion of and demonstrated knowledge in a course covering all aspects of PR, demonstration of staff competencies, formal individualized treatment plans for core components of PR (including exercise prescription), program performance measures across several outcomes, and emergency preparedness processes.[284]

OUTCOME ASSESSMENT AND MEASUREMENT

Outcome assessment for PR encompasses three areas: (1) a general audit of the effectiveness of the PR program and its components, (2) evaluation of individual patient response to the intervention, and (3) assessment of the effect of PR on society, especially with respect to its effect on health care utilization and its cost-effectiveness. Outcome assessment is also necessary to monitor patient progress, ensure patient safety, and ensure the quality of the PR program, allowing for appropriate reimbursement from payers.[1,28,285] Rehabilitation programs must demonstrate, at a minimum, outcome assessments for exercise capacity, dyspnea, and health-related QOL, key areas that have consistently shown benefit for patients. However, these outcome measures alone do not reflect the impact of PR on the complex comorbidities and systemic manifestations of chronic respiratory disease. Therefore, additional outcome areas that may be applicable in PR include anxiety, depression, disease knowledge, health literacy, self-efficacy, performance of ADLs, fatigue, adherence to medical regimens (including oxygen, smoking cessation, exacerbation rates), and health care costs. Outcome measurements commonly performed in PR can be found in the online supplement in eTable 139.1.

Dyspnea is a central and often disabling symptom in individuals with chronic respiratory disease. Dyspnea assessment should be performed both as a measurement of dyspnea during exertion and as a measurement of breathlessness over time and/or during activity using questionnaires. Exertional dyspnea is usually rated using a Borg scale or a visual analog scale. Measurement of dyspnea by questionnaire usually assesses the dyspnea associated with ADLs or the way in which exertional dyspnea limits activities. Common measurement tools include the Medical Research Council dyspnea score, Chronic Respiratory Questionnaire, Baseline Dyspnea Index/Transitional Dyspnea Index, and the University of San Diego Shortness of Breath Questionnaire.[286]

Exercise performance is a key target of the PR intervention and can be measured in the laboratory using protocols involving incremental treadmill or stationary bicycle exercise. Cardiopulmonary exercise testing comprehensively evaluates the cardiovascular, ventilatory, and musculoskeletal response to exercise and, as such, provides in-depth information on the physiologic limitations to exercise as well as on specific risks to exercise. However, field tests of exercise performance, such as the 6-minute walk test and the incremental shuttle walk test, are more commonly performed and are responsive to the PR intervention.[93,276,287–289] Both field tests are performed as per standardized protocol, and minimal clinically important

eTable 139.1 Examples of Outcome Assessment for Pulmonary Rehabilitation

Measurement	Scales/Tests
Laboratory measures of exercise performance	■ Incremental cardiopulmonary exercise testing ■ Endurance testing at constant work rate
Functional exercise capacity	■ 6-minute walk test ■ Incremental and endurance shuttle walk tests ■ Muscle strength (dynamometry) ■ Timed up-and-go testing ■ Sit-to-stand testing ■ Dowel lifting ■ Balance assessment
Exertional dyspnea	■ Borg scale or visual analogue scale during exercise testing
Dyspnea with daily activities	■ Modified Medical Research Council questionnaire ■ Baseline and transitional dyspnea indices ■ San Diego Shortness of Breath Questionnaire
Health status	■ Chronic Respiratory Disease Questionnaire ■ St. George's Respiratory Questionnaire ■ Medical Outcomes Study Short Form-36 ■ COPD Assessment Test ■ Other disease-relevant questionnaires
Functional performance	■ Pulmonary Function Status Scale ■ Pulmonary Function Status and Dyspnea Questionnaire
Physical activity	■ PROActive instrument ■ Activity monitors/accelerometers
Nutritional status/body composition	■ Body mass index ■ Body composition using bioelectrical impedance or dual-energy x-ray absorption
Psychological variables	■ Measurement of anxiety and depression (e.g., Hospital Anxiety and Depression questionnaire, Beck Depression and Anxiety Inventories)
Additional important patient-centered outcomes	■ Fatigue ■ Cognition ■ Disease exacerbations ■ Use of tobacco/vaping products ■ Patient self-efficacy, coping style, and knowledge ■ Patient satisfaction with PR program
Additional important health-system outcomes	■ Hospitalizations and urgent health care visits ■ PR program quality metrics ■ Program costs

PR, pulmonary rehabilitation.

differences have been validated for each test.[93] Additional areas of exercise assessment are increasingly undertaken in the PR setting, including muscle strength testing (using dynamometers or repetitive maximal testing), exercise ability (timed up-and-go test, sit-to-stand test), functional status,[290] ADLs,[291] and balance measurements.[107,292,293]

Clinically meaningful improvements in health-related QOL are consistently seen after PR.[2] Health status is assessed in this setting using respiratory-specific questionnaires, such as the Chronic Respiratory Disease Questionnaire or the St. George's Respiratory Questionnaire.[294,295] Effects greater than the minimal clinically important difference for each of the components of the Chronic Respiratory Disease Questionnaire (dyspnea, fatigue, emotion, mastery), and mean differences in SGRQ total score (−6.9; 95% CI, −9.3 to −4.5, $n = 1146$; studies = 19) greater than the minimal clinically important differences of 4 units, were found in the Cochrane review by McCarthy et al.[2] Some PR programs may also use a generic instrument, such as the Medical Outcomes Study Short Form-36, to complement information from the respiratory-specific questionnaires.[296]

Anxiety and depression are common in chronic respiratory disease and can influence uptake and response to PR as well as adherence to maintenance exercise and healthy behaviors. It is important to assess symptom burden on entry into PR and to measure response to this intervention. There are validated tools available, including the Hospital Anxiety and Depression Score and the Beck Depression Inventory/Beck Anxiety Inventory.[297–299]

A vitally important and rapidly growing area of interest in PR is activity promotion because physical activity levels are closely tied to important outcomes.[177] As noted previously, gains in exercise capacity made during the PR intervention do not necessarily translate into increased physical activity in daily life, and outcome measurements and interventions to promote physical activity after the PR intervention are areas of active research.[206,300]

Assessment in the areas of cognitive impairment, disease knowledge, and self-efficacy, as well as nutrition/body composition, is also possible as part of the evaluation of PR.[276,301,302] PR should be evaluated more routinely for its effect on health care utilization and its cost-effectiveness, and these outcome measures are of increasing importance to health care systems and payers. Where evaluated, PR has been shown to be one of the most cost-effective treatments with COPD, on a par with smoking cessation and bronchodilator therapy.[12,13]

It is important to note that many outcome measures performed in PR were developed in the COPD population and may not be applicable to other chronic respiratory diseases. Programs should ensure that the appropriate tools are used in these settings. In addition, routine outcome measures such as those outlined previously have not been extensively validated for individual patient assessment. Traditional one-on-one clinical assessment remains necessary for the individual patient.

NOVEL MODELS

PR remains grossly underutilized despite its recommendation by international clinical guidelines[303] (see "Policy and Access Issues" section later). Although advocacy efforts to promote traditional center-based PR are important, there is also a strong effort to develop alternative forms of program delivery. Models of home-based and community-based PR have been investigated; however, there is marked heterogeneity in the type, intensity, and frequency of both the exercise and education components. In addition, staffing and supervision vary widely. Theoretically, these alternative forms of PR might lead to improved adherence to maintenance exercise (especially for home-based programs), greater availability and accessibility to those in rural settings or with transportation issues, and cost savings.

Home-based PR has been compared with usual care without PR or with center-based programs. In both a 2010 systematic review and a 2014 meta-analysis, rehabilitation was superior to usual care with improvements in dyspnea, exercise performance, and quality of life.[304,305] Exercise training was a necessary component, but structured education was not.[304,305] The limited information also suggested noninferiority in the measured outcomes of the home-based interventions compared with center-based programs. Three equivalence trials in Canada, Australia, and England compared the effectiveness of home-based PR with center-based PR.[233,306,307] In all three trials, there was no direct supervision in the home. Completion rates favored the home-based programs, no serious adverse events were noted, and all demonstrated improvements in exercise performance and QOL over baseline. Equivalence of benefits was demonstrated in the selected outcomes tested. However, a more recent "real world" trial showed that home-based PR led to lesser improvements in exercise capacity compared with center-based PR.[308] Interactive web-based or telerehabilitation programs have shown some positive outcomes[309–312] but require further evaluation before adopting their widespread use.

Studies have also evaluated home- or community-based PR after COPD exacerbations; however, the interventions were very heterogeneous, and the results were mixed, possibly due to poor adherence in some study patients and a potentially "insufficient" dose of rehabilitation.[313–316] Video-/telerehabilitation delivered after COPD exacerbation is feasible, safe, and associated with lower hospitalization rates.[317,318] Models of PR have begun to incorporate technology-based alternatives to both supervision and delivery of educational components. These have the potential advantage of convenience to the patient and the ability to pace delivery of contents to the patient's level of mastery.[309,319,320]

Interest in delivery of PR in the home rose during the COVID-19 pandemic, wherein most PR programs necessarily suspended activities due to inability to maintain social distancing in center-based groups. Many people with chronic respiratory diseases experienced decreased functional status related to home confinement to avoid COVID-19 and to their inability to participate in PR. In addition, patients recovering from COVID-19 with muscle weakness and debility related to hospitalization and critical illness warrant rehabilitation. Although optimal strategies for rehabilitation for those recovering from COVID-19 are unknown, recommendations from an expert panel of physiotherapists have been published recently.[321] Recommendations for home-based exercise have also

been made for those on mandatory home confinement.[322] Insurance reimbursement for home-based physical therapy (including PR) during the COVID-19 pandemic has varied across countries. Unfortunately, despite general widespread increased use of telemedicine as a means of providing medical care during the pandemic, thus far in the United States, the Centers for Medicare and Medicaid Services declined to reimburse home-based PR during this period.

Studies available thus far suggest that there are no significant safety issues with PR in the home or community, but more data are needed, especially if these models include patients with advanced disease, non-COPD diagnosis, and prominent comorbidities. It is likely that these more complex patients may be better served by the resources available with center-based programs. As nontraditional models of PR are developed, additional issues must be addressed, including appropriate referrals, cost-effectiveness issues (especially if staff is required in the home),[323] and oversight as to what exactly is being delivered. This last issue is crucially important because there is a real concern about diluting a highly successful intervention and mislabeling it as PR.

PULMONARY REHABILITATION FOLLOWING COPD EXACERBATION

COPD exacerbations are associated with skeletal muscle dysfunction, decreased physical activity levels, decline in health status and lung function (which can persist for months following hospital discharge), and increased mortality.[179,323–326]

Although most research on the benefits of PR has been obtained in stable COPD, there is mounting evidence that PR is safe and beneficial following an exacerbation.[313,327] A recent Cochrane review on PR following an exacerbation reported high-quality evidence for improvements in exercise capacity and QOL, and moderate-quality evidence for decreases in health care costs.[3] Another systematic review and meta-analysis of 13 randomized controlled trials including 634 participants showed a 42% reduced risk of mortality with PR compared with usual care.[328] A recent retrospective analysis of claims data from 197,376 fee-for-service Medicare beneficiaries hospitalized for COPD in the United States in 2014 showed that participation in PR within 90 days of discharge was associated with a lower risk of death over 1 year (absolute risk difference, −6.7%; 95% CI, −7.9% to −5.6%; hazard ratio, 0.63; $P < 0.001$). Attendance at every three additional PR sessions was significantly associated with a lower risk of death (hazard ratio, 0.91; 95% CI, 0.85 to 0.98; $P = 0.01$).[329] However, uptake of PR following COPD exacerbation is low, and a better understanding of how to make post-exacerbation PR more acceptable to patients is needed.[330]

There is little available evidence evaluating PR after exacerbations in chronic respiratory diseases other than COPD. However, similar to the rationale and evidence for PR in stable non-COPD conditions, this intervention should be effective following exacerbations in other chronic respiratory diseases. In one study,[314] 15% of the study subjects had other chronic respiratory diseases, such as bronchiectasis, interstitial lung disease, and chronic asthma, with no differences in outcomes noted.

Underutilization of PR in the peri-exacerbation period is even more striking than in stable disease.[331] The optimal timing and structure of PR during the post-exacerbation period have not been well defined. This, combined with such poor uptake, raises the important issue of how to adapt a well-established successful intervention to this pivotal event in the life of an individual with chronic respiratory disease. There is an urgent need to identify barriers to participation as well as develop effective models of delivery to address this need.

PULMONARY REHABILITATION FOR DISORDERS OTHER THAN COPD

Based on the unequivocal benefits of PR in COPD, the benefits of PR for people with chronic respiratory disorders other than COPD have been investigated. The rationale for PR for non-COPD respiratory disorders is similar to that for individuals with COPD, as discussed above.[1,14] In addition to structural and functional alterations in the respiratory system, people with non-COPD respiratory disorders experience disabling symptoms, including dyspnea, fatigue, exercise impairment, anxiety, depression, and fear. They also commonly have medical comorbidities and nutritional disturbances, require complex medical regimens, may experience intermittent acute exacerbations of disease,[1,14] have difficulty coping with their disease, and may require lung transplantation. People with ILD, [332] pulmonary hypertension,[201,202] asthma,[333] cystic fibrosis,[334] non-cystic fibrosis bronchiectasis,[335] and lung cancer[336] have low physical activity levels. Skeletal muscle dysfunction has been reported for people with ILD,[53,337] pulmonary hypertension,[56] cystic fibrosis,[338,339] and those preparing for and recovering from lung transplantation.[60] Importantly, low exercise capacity is associated with worse survival for persons with ILD,[340] pulmonary hypertension,[341] and cystic fibrosis.[342] As such, PR has the potential to benefit people with these conditions. PR is recommended in disease management guidelines for idiopathic pulmonary fibrosis,[343] pulmonary hypertension,[344] and bronchiectasis.[345]

Moreover, PR is typically required prior to lung transplantation. Pretransplantation PR helps to optimize patients' conditioning and functional exercise capacity,[346] which may, in turn, improve surgical outcomes and reduce hospital length of stay.[347] It also prepares patients by providing knowledge regarding the process and potential risks versus benefits of transplantation and steps needed for recovery from it.[346]

Numerous randomized controlled trials and uncontrolled studies have confirmed benefits of PR for people with non-COPD respiratory disorders.[1,14,348] Improvements in exercise capacity, symptoms, and/or QOL have been demonstrated for individuals with ILD including idiopathic pulmonary fibrosis,[349–355] pulmonary hypertension,[356–360] cystic fibrosis and non-cystic fibrosis bronchiectasis,[58,361–364] asthma,[365–374] lung cancer,[375–379]

obesity-hypoventilation syndrome,[380] and for those recovering from lung transplantation.[381,382]

The reported magnitude of benefits varies across conditions and across different clinical outcomes, but in general, the magnitude of gain in 6-mile walk distance following PR is comparable to that seen among people with COPD.[383,384] The duration of benefits achieved in PR for non-COPD respiratory diseases also varies. For some conditions, such as ILD,[385] the duration of benefits following PR may be shorter (approximately 6 months) than the typical duration of gains (approximately 8 to 12 months) seen among those with COPD. Evidence regarding impact of disease severity on PR outcomes is limited. For people with disorders other than COPD, data regarding the impact of PR on other outcomes such as health care utilization are also, to date, largely lacking. There is little available evidence evaluating peri-exacerbation PR in chronic respiratory diseases other than COPD. However, similar to the rationale and evidence for PR in stable non-COPD conditions, this intervention should be effective following exacerbations in other chronic respiratory diseases.

The practical aspects of providing PR to individuals with non-COPD respiratory disorders have been reviewed recently.[58,348,386] Inclusion of people with varying types of respiratory disorders into PR programs that historically focused on COPD poses several logistical challenges. The exercise training regimen, education, and behavioral aspects of the program must be individualized and geared to the physiology, safety, management, and needs related to the relevant disease(s).[1,14,280,348,386] PR program staff must be trained in and familiar with the manifestations and management of the spectrum of respiratory disorders, and adequate numbers of staff members must be present so that patients are safe and their questions can be addressed. Supplemental oxygen should be available,[348,387] and specialized equipment may be needed in some circumstances (e.g., bariatric equipment for severely obese persons or telemetry for those with severe pulmonary hypertension). Education materials addressing topics relevant to a spectrum of disease states are needed.[14,386,388,389] Use of measurement tools relevant to disease outcomes is also necessary.[1,14,348,386]

Until recently, insurance coverage for PR was lacking for people with non-COPD respiratory disorders in many countries. This is changing as the evidence base supporting its use has expanded; people with non-COPD disorders are now commonly referred to and enrolled in PR programs. This will further drive the existing need for a substantive increase in access and availability of PR, which is already grossly insufficient. Further foci of research should include several key areas such as optimal candidacy, the basis of skeletal muscle dysfunction and its responsiveness to PR, optimal educational approaches and content, and outcomes such as performance of ADLs, physical activity levels, cost-effectiveness (hospitalizations, disease exacerbations), surgical outcomes, and mortality.

POLICY AND ACCESS ISSUES

Despite its well-recognized benefits and recommendation for its use in several clinical practice guidelines,[343,344,390] PR is markedly underutilized worldwide. Several factors contribute to this. Low referral rates are an important cause of PR underutilization. Currently, only 3–16% of eligible patients with COPD are referred,[391–398] and fewer than 3% receive PR after hospitalization for COPD exacerbation.[331] It is likely that referral rates are even lower for those with respiratory disorders other than COPD. Suboptimal health care professionals' knowledge and awareness of the content, process, and benefits of PR,[399–403] and suboptimal adherence to evidence-based treatment guidelines,[404] contribute to low numbers of referrals. Most health care professionals lack exposure to PR in daily practice, and detailed education regarding PR is not universally required during training, even for those specializing in respiratory disease.[239] People with chronic respiratory diseases[246] and the general public[239] also often lack knowledge about PR and, as such, they may not request referral or participate if referred.

Poor access to PR limits its delivery to and uptake by patients. In many countries, PR programs are underfunded, there are insufficient resources (space, equipment, and/or staffing) to meet patient needs,[239,405] and payers' reimbursement is insufficient for programs' sustainability.[406] Most existing PR programs accommodate fewer than 150 patients per year.[27,277] In some countries, such as the United States, there is significant geographic variability regarding access to PR; some areas, particularly rural, lack programs altogether.[407] This is also true in parts of Australia, Canada, South America, Asia, and Africa. Racial and socioeconomic disparities also affect patients' access to PR.[408]

In 2015, a joint American Thoracic Society/European Respiratory Society Task Force published an Official Policy Statement entitled *Enhancing Implementation, Use, and Delivery of Pulmonary Rehabilitation*.[239] Several recommendations and actionable items were proposed to address and improve the underutilization of PR. Progress towards implementation of these recommendations is being made gradually, but much more work in this area is needed.

Education for health care professionals,[409] provision of practical tools such as flow sheets, clinical reminders (e.g., pop-up reminders in medical records),[410] streamlining the referral process, and implementation of discharge care bundles can improve referrals to PR.[411] Increased exposure to the scientific evidence base and practical aspects of implementation and delivery of PR during the course of medical training would be desirable for health care professionals who will care for people with chronic respiratory diseases. This may require lobbying on the part of PR experts, with support of professional societies, to encourage the institutions governing health professionals' education to broaden their requirements regarding PR for trainees. Monitoring of referrals to PR as a care quality indicator would also be helpful to enhance referrals.

Public awareness campaigns, including use of social media, can increase patients' and the general public's knowledge and awareness of PR.[400,412,413] Collaborative planning between patients and their health care providers regarding treatment plans can foster patient referrals to and uptake of PR.[409,414–416] Enhanced communication between health care professionals and insurance

payers regarding the documentation of benefits and cost-effectiveness of PR, and efforts such as the US National Action Plan for COPD[417] and the United Kingdom pulmonary rehabilitation audit [283] should help foster funding and reimbursement of existing programs and support new programs in regions where they are lacking. Novel models of PR such as telerehabilitation and home-based PR are being investigated and may be suitable for some individuals, especially those who lack access to center-based programs.

For a discussion about the future of physical rehabilitation, see ExpertConsult.com.

Acknowledgements

We acknowledge the contributions of Dr. Richard L. Zuwallack and Dr. Bartolome R. Celli to this topic in the previous edition of this text.

Key Points

- *Pulmonary rehabilitation* (PR) is an essential multidisciplinary, patient-centered intervention in the management and integrated care of people with chronic respiratory disease, which should be offered routinely alongside other medical therapies.
- Important components of PR include exercise training, education, psychosocial support, nutritional therapy, and advance care planning.
- Despite lack of a direct effect on lung function, PR has been proven in randomized controlled trials to improve exercise performance, dyspnea, and quality of life. It also reduces health care utilization and improves emotional function and, when delivered following hospitalization for COPD exacerbation, improves survival.
- PR has also been shown to benefit people with COPD and several other disorders, including interstitial lung disease, asthma, pulmonary hypertension, cystic fibrosis, lung cancer, and those preparing for and recovering from lung transplantation.
- The magnitude of gains in exercise capacity, dyspnea, and quality of life expected from participation in PR are equal to or exceed those afforded by other medical therapies, such as bronchodilators for people with COPD.
- Exercise training is the cornerstone of PR: high- and/or low-intensity and/or interval aerobic training and resistance training of the upper and lower extremities are utilized.
- Promotion of physical activity in the home and community setting is an important goal of PR.
- PR is underutilized and under-resourced. This relates to suboptimal health care professionals', patients', caregivers', and payers' knowledge and awareness of its benefits; insufficient access to and payer support; insufficient number of programs and providers; and suboptimal uptake of and adherence by patients who could benefit from it.

Key Readings

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THE FUTURE OF PULMONARY REHABILITATION

The field of PR and its scientific evidence base continues to grow and expand. Major challenges exist regarding availability, funding, and resourcing for PR programs, as well as uptake of and adherence to PR. Many existing health care systems are not ideally structured to accommodate the number of patients who could benefit from PR or the complexity of patients' needs. Forward-thinking health care systems would help to build the infrastructure and resources necessary to provide services to those who could benefit, as well as routinely encourage people with chronic respiratory diseases to attend PR as a standard of care, comparable to advocacy for use of preventive vaccinations and inhaled bronchodilator therapies. Widespread incorporation of PR into routine health care processes would not only reduce the morbidity and mortality of individuals but may also substantially reduce health care costs.

Further pragmatic research is needed to demonstrate the benefits and costs of PR to payers and health care systems and to learn which patients are most suitable for which types of PR interventions/components and settings. Additional areas where further information is needed include optimal strategies for education, promoting sustained health-enhancing behavior such as physical activity following PR, PR interventions for people with disorders other than COPD, and solutions to existing barriers to uptake and adherence to PR. The biologic basis of patients' varying responsiveness to exercise training and other components of PR also merits further study. Broader training of multidisciplinary health care professionals in the discipline of PR is also needed to develop experts in the field and promote referrals of patients who could benefit.

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140 LUNG TRANSPLANTATION

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INTRODUCTION

Human lung transplantation was first attempted in 1963, but it was not until nearly 2 decades later that extended survival was achieved. Further refinements in patient selection, surgical technique, immunosuppression, and postoperative care have since facilitated the successful application of lung transplantation to a wide variety of advanced disorders of the airways, lung parenchyma, and pulmonary vasculature. The field has realized dramatic growth, with more than 64,000 procedures performed worldwide to date and approximately 4500 now performed annually.[1] Nonetheless, serious problems persist that limit the utility of this procedure. The donor pool remains insufficient to meet the demands of the many desperately ill patients awaiting transplantation. Immunosuppressive therapy is associated with a number of troubling side effects, most notably a significant risk of infection and malignancy. Despite the use of immunosuppressive agents, rejection and *chronic lung allograft dysfunction* (CLAD) develop frequently and continually threaten organ function. Though lung transplantation offers the prospect of improved functional status and quality of life, long-term survival remains an elusive goal, with only half of recipients living beyond 6 years. In order to optimize outcomes in the face of these shortcomings, judicious selection of candidates is essential and care of recipients must be rendered in a meticulous and vigilant fashion by clinicians familiar with posttransplantation management.

INDICATIONS AND CANDIDATE SELECTION

Lung transplantation is a therapeutic option for a broad spectrum of chronic debilitating pulmonary disorders of the airways, parenchyma, and vasculature. Leading indications include idiopathic pulmonary fibrosis and other idiopathic interstitial pneumonias (33% of cases), COPD (26% of cases), and *cystic fibrosis* (CF) (14% of cases).[1] Other less-common indications include emphysema caused by alpha$_1$-antitrypsin deficiency, sarcoidosis, non-CF bronchiectasis, and lymphangioleiomyomatosis. Once a common indication for transplantation, idiopathic pulmonary arterial hypertension now accounts for less than 3% of procedures, a finding reflecting major advances in the medical management of these patients. Lung transplantation in patients with lung involvement of collagen vascular disease raises concerns that extrapulmonary manifestations of the systemic disease could compromise the posttransplant course. In particular, the esophageal dysmotility and reflux that frequently characterize scleroderma could increase the risk of occult aspiration and accelerated graft loss. The demonstration that posttransplantation survival of patients with scleroderma is comparable with that of other patient populations provides reassurance that carefully selected patients can benefit from this procedure even if esophageal dysfunction is present.[2,3] Lung transplantation for locally advanced bronchioloalveolar carcinoma (now referred to as adenocarcinoma in situ) is performed only in highly selected cases because of an unacceptably high rate of cancer recurrence.[4]

Many transplant centers have abandoned an arbitrary upper age cutoff for transplant eligibility, although current selection guidelines suggest that patients older than 75 years are unlikely to be suitable candidates in most cases because of accompanying comorbidities.[5] Patients 65 years old and older represent the second largest and fastest growing cohort in the United States; they accounted for 30% of wait-list candidates in 2017.[6] However, the 5-year survival rate is considerably lower for this group compared with younger cohorts and is particularly poor for those 70 years of age and older, only 28% of whom achieve the 5-year mark.[6,7] In selecting older patients, many centers

now place an emphasis on "functional" age rather than chronologic age. This has prompted interest in using validated tools to assess frailty as part of the transplant evaluation, and emerging evidence suggests that such assessment is useful in predicting posttransplant mortality risk.[8]

Absolute contraindications to transplantation, as delineated in the most recent International Society for Heart and Lung Transplantation consensus statement, are listed in Table 140.1.[5] Several additional factors represent relative contraindications for which there is considerable variability in approach among different centers. Infection with HIV is still viewed by most centers as an absolute contraindication, but promising results with liver, kidney, and heart transplantation in HIV-positive recipients, as well as recent reports of successful lung transplantation, may soon remove this barrier.[9,10] Among candidates with CF, infection with certain species comprising the *Burkholderia cepacia* complex, in particular *Burkholderia cenocepacia* (previously known as genomovar III), is considered an absolute contraindication by many centers because of the considerable risk of posttransplantation lethal infections.[11,12] In contrast, the presence of panresistant *Pseudomonas aeruginosa* in this patient population is associated with acceptable outcomes and generally is not viewed as a contraindication.[13] Reports of recurrent *Mycobacterium abscessus* infections following transplantation have engendered reservations about listing candidates with active and poorly controlled infection preoperatively.[14,15]

The risk posed by chronic medical conditions such as diabetes mellitus, osteoporosis, gastroesophageal reflux, and coronary artery disease must be assessed individually on the basis of severity of disease, presence of end-organ damage, and ease of control with standard therapies.

Table 140.1 Absolute Contraindications to Lung Transplantation

Active or recent malignant disease
Untreatable significant extrapulmonary organ dysfunction (consider combined organ transplant procedure if feasible)
Chronic and poorly controlled infection with highly virulent and/or resistant organisms
Acute medical instability such as sepsis, myocardial infarction, or liver failure
Significant chest wall or spinal deformity expected to cause severe restriction after transplantation
Uncorrectable bleeding diathesis
Uncorrected coronary artery disease not amenable to revascularization before or at the time of transplantation
Significant obesity with a body mass index ≥35 kg/m^2
Severely limited functional status with poor rehabilitation potential
Active or recent cigarette smoking, drug abuse, or alcohol abuse
Significant psychiatric illness limiting the ability to cooperate with the medical team or adhere to the complex posttransplantation medical regimen
Repeated noncompliance with medical care
Absence of an adequate and reliable social support network

Modified from Weill D, Benden C, Corris PA, et al. A consensus document for the selection of lung transplant candidates: 2014. An update from the Pulmonary Transplantation Council of the International Society for Heart and Lung Transplantation. *J Heart Lung Transplant*. 2015;34:1–15.

Prior pleurodesis or other thoracic surgery is associated with an increased risk of intraoperative bleeding, particularly when cardiopulmonary bypass is used, but it is not a contraindication to transplantation in experienced surgical hands. Pleural thickening associated with aspergillomas similarly complicates anatomic dissection and explantation of the native lung and carries the additional risk of soiling the pleural space with fungal organisms.

Use of mechanical ventilation as a bridge to transplantation is associated with increased short-term posttransplant mortality but does not appear to affect outcomes beyond the first year.[1] Most programs are now willing to maintain some ventilator-dependent patients on the active waiting list and anticipate that the high allocation score these patients receive will expedite transplantation, but reserving the option of de-listing patients who develop intercurrent complications or progressive debility. Use of *extracorporeal membrane oxygenation* (ECMO) to bridge patients to transplantation is becoming increasingly common, with experienced centers reporting posttransplant survival rates that approximate those of nonbridged patients.[16,17] Patients undergoing ECMO who are awake, ambulatory, and liberated from conventional mechanical ventilation appear to have the best outcomes but account for a minority of patients bridged in this fashion.[18]

TIMING OF REFERRAL AND LISTING

Listing for transplantation is considered at a time when the lung disease limits basic activities of daily living and is deemed to pose a high risk of death in the short term. Disease-specific guidelines for timely referral and listing of patients, based on available predictive indices, have been published (Table 140.2).[5] The imprecise nature of these predictive indices can complicate decisions about transplant listing for all but the most severely ill patients. The patient's perception of an unacceptably poor quality of life is an important additional factor to consider but should not serve as the sole justification for listing of a patient whose disease is not deemed to be at an advanced and potentially life-threatening stage.

ALLOCATION SYSTEM

In 2005, the *Lung Allocation Score* (LAS) system was introduced in the United States, and it replaced a time-based allocation model that was perceived to bias against candidates with advanced or more rapidly progressive disease who could not tolerate prolonged waiting times.[19] The LAS system uses statistical models, incorporating more than a dozen variables, to generate predicted 1-year survival with and without transplantation for each patient.[19] Both medical urgency (1-year survival without transplantation) and "net transplant benefit" (difference between 1-year survival with and without transplantation) are factored into the calculation of the LAS. Because 1-year survival without transplantation is incorporated into both net transplant benefit and medical urgency measures, it affects the LAS more than posttransplantation survival. A raw LAS is calculated on the basis of these survival predictions and is normalized

Table 140.2 Disease-Specific Guidelines for Listing for Lung Transplantation

CHRONIC OBSTRUCTIVE PULMONARY DISEASE
■ BODE index ≥7
■ FEV_1 <15–20% predicted
■ Three or more severe exacerbations during the preceding year
■ One severe exacerbation with acute hypercapnic respiratory failure
■ Moderate to severe pulmonary hypertension
INTERSTITIAL LUNG DISEASE
■ Decline in FVC ≥10% during 6 months of follow-up
■ Decline in DL_{CO} ≥15% during 6 months of follow-up
■ Desaturation to <88% or distance <250 m on 6-min walk test or >50 m decline in 6-min walk distance over a 6-mo period
■ Pulmonary hypertension on right heart catheterization or two-dimensional echocardiography
■ Hospitalization because of respiratory decline, pneumothorax, or acute exacerbation
CYSTIC FIBROSIS
■ Chronic respiratory failure:
■ With hypoxemia alone (PaO_2 <60 mm Hg)
■ With hypercapnia ($PaCO_2$ >50 mm Hg)
■ Long-term noninvasive ventilation therapy
■ Frequent hospitalization
■ Rapid lung function decline
■ World Health Organization functional class IV (symptoms present at rest or severe with any activity)
PULMONARY VASCULAR DISEASE
■ NYHA functional class III or IV despite a trial of at least 3 months of combination therapy including prostanoids
■ Cardiac index <2 L/min/m^2
■ Mean right atrial pressure of >15 mm Hg
■ 6-min walk distance of <350 m
■ Development of significant hemoptysis, pericardial effusion, or signs of progressive right-sided heart failure (renal insufficiency, increasing bilirubin, brain natriuretic peptide, or recurrent ascites)

BODE, body mass index, airflow obstruction, dyspnea, exercise capacity; DL_{CO}, diffusing capacity for carbon monoxide; FEV_1, forced expiratory volume in 1 second; FVC, forced vital capacity; NYHA, New York Heart Association; PaO_2, partial pressure of oxygen; $PaCO_2$, partial pressure of carbon dioxide.

Modified from Weill D, Benden C, Corris PA, et al. A consensus document for the selection of lung transplant candidates: 2014-an update from the Pulmonary Transplantation Council of the International Society for Heart and Lung Transplantation. *J Heart Lung Transplant*. 2015;34:1–15.

to a scale of 0 to 100 for ease of use. As designed, the system preferentially allocates lungs to sicker patients while attempting to avoid situations in which outcomes are so poor that there would be no meaningful survival benefit. An initial LAS is assigned at the time of listing and is subsequently revised as needed to reflect changes in a patient's medical condition, thereby escalating the patient's priority as his or her condition worsens. Notably, patients succumbing to frank respiratory failure requiring mechanical ventilation and/or ECMO generally receive the highest priority under this system.

The introduction of the LAS system had a profound effect on the dynamics of lung transplantation in the United States.[20,21] Because there was no longer an incentive to place patients on the active waiting list simply to accrue time (many of these patients were ultimately deactivated from the list rather than undergoing transplantation), the number of actively listed patients fell to approximately one-half of the previous level. Median waiting time, which had ranged from 2 to 3 years under the time-based allocation system, decreased to less than 6 months, with one-quarter of patients waiting less than 35 days.[20] As a consequence of the shorter waiting times for sicker patients, there has been a significant and sustained reduction in the annual death rate of patients on the waiting list, one of the stated objectives of the LAS system.[21] Although there were initial fears that posttransplantation outcomes would suffer by preferential performance of lung transplantation in sicker patients, survival of patients with the highest LAS scores has steadily improved and currently falls only slightly below that of patients with lower scores.[6,22] A similar LAS system has since been adopted by several European countries and now accounts for allocation of approximately 60% of transplanted lungs worldwide.[23]

The LAS system does not address geographic disparities in organ allocation in the United States. Historically, allocation rules have dictated that lungs procured by a particular organ procurement organization were offered first to candidates at centers within that organization's region, even if there were candidates with higher LAS scores listed at centers in geographic proximity but beyond the existing boundaries of the local organ procurement organization. In response to a legal challenge, a new allocation policy was implemented that did away with this organ procurement organization–centered distribution rule and now initially offers lungs to transplant centers within 250 nautical miles of the donor hospital.

BRIDGING TO TRANSPLANTATION: ARTIFICIAL LUNG TECHNOLOGIES

As mentioned earlier, ECMO has been used to bridge critically ill patients to lung transplantation, although, historically, outcomes following transplantation have been suboptimal. Advances in artificial lung technology, including improved membranes, improved pumps, and even ambulatory support systems, make it increasingly possible to support selected patients successfully, thus permitting them to survive the wait for a suitable donor lung and, importantly, to achieve a successful posttransplant outcome[24–27] (see also Chapter 138).

Patients with isolated hypercapnic failure can be bridged with pumpless devices such as the interventional lung assist (iLA, Novalung), a low-resistance device with a meshwork of hollow fibers maximizing blood-gas diffusion; with this device, blood can be propelled by arterial pressure or a pump. Patients requiring oxygenation support can be supported with venovenous configured pump devices. Patients requiring circulatory support, as well as gas exchange support, can be managed with a conventional venoarterial configuration. It is important to understand the underlying physiology of the patient and to select the device configuration that provides the necessary support (Fig. 140.1). An application unique to patients with pulmonary arterial hypertension is the application of the pumpless iLA device from the pulmonary artery to the left atrium to off-load the right ventricle and provide "oxygenating septostomy" physiology. This strategy has effectively abolished wait-list mortality in a group of patients who traditionally had the highest mortality on the wait list.[25,28]

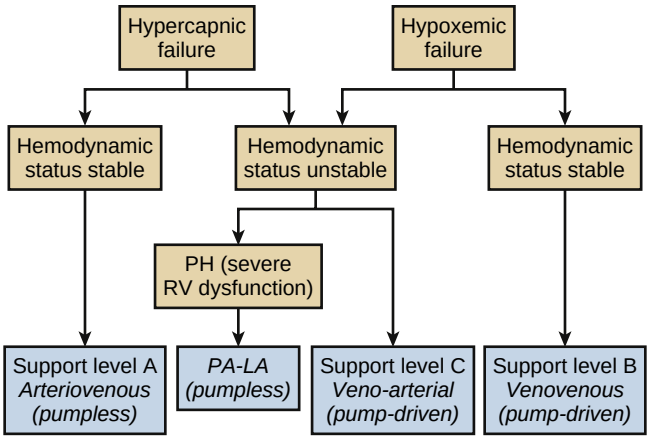

Fig. 140.1 Selection of extracorporeal lung support device and configuration. The choice of support device is largely dependent on the type of respiratory failure (hypercarbic or hypoxemic) and the hemodynamic status (stable or unstable). LA, left atrium; PA, pulmonary artery; PH, pulmonary hypertension; RV, right ventricle. (From Cypel M, Keshavjee S. Extracorporeal life support pre and post lung transplantation. In: Annich GM, Lynch WR, MacLaren G, Wilson JM, Bartlett RH, eds. *ECMO: Extracorporeal Cardiopulmonary Support in Critical Care [ELSO Red Book]*, 4th ed. Ann Arbor, MI: Extracorporeal Life Support Organization; 2011.)

Table 140.3 Standard Lung Donor Criteria

Age <55 yr
Clear chest radiograph
PaO_2 >300 mm Hg on FIO_2 1.0, PEEP 5 cm H_2O
Cigarette smoking history <20 pack-yr
Absence of significant chest trauma
No evidence of aspiration or sepsis
No prior thoracic surgery on side of harvest
Absence of organisms on sputum Gram stain
Absence of purulent secretions and gastric contents at bronchoscopy
Negative for HIV antibody, hepatitis B surface antigen, and hepatitis C antibody
No active or recent history of malignant disease (excluding localized squamous or basal cell skin cancer, localized cervical cancer, and primary brain tumors with low metastatic potential and in the absence of invasive procedures to the brain and skull)
No history of significant chronic lung disease

FIO_2, fractional concentration of oxygen in inspired gas; HIV, human immunodeficiency virus; PaO_2, arterial oxygen pressure; PEEP, positive end-expiratory pressure.

From Kotloff RM, Thabut G. Lung transplantation. *Am J Respir Crit Care Med.* 2011;184:159-71.

DONOR SELECTION AND MANAGEMENT

In addition to meeting defined criteria for declaration of brain death, deceased lung donors are selected on the basis of established guidelines (Table 140.3).[29] Lungs are particularly fragile organs in the brain-dead patient and are frequently compromised by volume overload, contusion, aspiration of gastric contents, ventilator-induced lung injury, or pneumonia, as well as by extensive prior smoking. As a result, most donors fail to meet standard criteria for lung donation, thus leading to a historical recovery rate of only 15–20% of lungs from deceased organ donors who are deemed able to donate other organs. Although it is reasonable to be conservative with recipient patient safety in mind, there is mounting evidence that these standard criteria may be too stringent, leading to unnecessary wastage of suitable lungs. In one study, 29 pairs of lungs that had been rejected for transplantation were assessed for the magnitude of extravascular water content, intactness of alveolar fluid clearance capacity, and presence of pneumonia or emphysema.[30] Twelve pairs (41%) were found to have minimal or no abnormalities and thus to be "potentially suitable" for transplantation. Additional evidence comes from published reports documenting that outcomes with use of "extended criteria" donors are similar to those achieved with use of donors meeting standard criteria.[31–35] Use of modified donor management protocols to optimize lung function through judicious fluid management, therapeutic bronchoscopy, and lung recruitment maneuvers has also been shown to enhance lung retrieval rates.[36,37] Additionally, a 2010 multicenter randomized trial demonstrated that use of a low–tidal volume, lung-protective ventilatory protocol (6 to 8 mL/kg; positive end-expiratory pressure of 8 to 10 cm H_2O) in brain-dead potential organ donors resulted in a doubling of lung harvest rates (54% vs. 27%) compared with a conventional ventilatory protocol (10 to 12 mL/kg; positive end-expiratory pressure of 3 to 5 cm H_2O).[38]

Despite increases in the number of organs successfully retrieved, the demand for organs continues to outstrip supply, thus prompting a search for alternatives to the brain-dead donor pool. One emerging source is the non–heart-beating or *donation after cardiac death* (DCD) donor who has experienced either an out-of-hospital (i.e., uncontrolled) cardiac arrest or a planned withdrawal of life support in the operating room. Currently, approximately 7% of lung transplants performed in the United States use DCD donors.[39] In contrast, DCD donors account for 23% of lung transplants in Australia, thus illustrating the extent to which this donor pool can be expanded with introduction of highly coordinated national protocols.[40] The 1-year and 5-year survival rates following DCD donor lung transplants are equivalent to those after procedures using conventional brain-dead donors.[41]

Once a donor has been identified, matching with potential recipients is based on size (either overall height or predicted total lung capacity) and ABO blood group compatibility. Recipients identified through standard pretransplant screening as having preformed circulating antibodies to foreign *human leukocyte antigen* (HLA) require virtual cross-matching to avoid donors with specific incompatible antigens.

LUNG PRESERVATION

The standard lung preservation technique is hypothermic flush preservation. The most commonly used solution is Perfadex (Vitrolife). Cold flush preservation at 4°C decreases the metabolic rate to 5% of normal and hence slows the dying process of the lung. Although this approach has been useful for clinical lung transplantation, cold static preservation has significant limitations: (1) a decision regarding lung use must be made quickly, with limited information

in the donor hospital; (2) once the organ is flushed, there is no second chance to reevaluate the organ before removal of the cross clamp at reperfusion; and (3) the focus is on slowing down the dying process, and it does not address or take advantage of opportunities to diagnose, treat, repair, or regenerate the donor lung.

Ex vivo lung perfusion has been developed to address these limitations. It is now possible to perfuse lungs ex vivo at normothermia for extended periods, thus creating a platform for more detailed assessment of lung function, more accurate diagnosis, and targeted treatment of donor lung injuries to improve the function of the lung after transplantation.[42–44] This creates the opportunity to engineer donor organs with gene therapy, cell therapy, and other advanced treatments to create "superorgans" that hopefully will one day afford the recipient long-term allograft function.[45,46]

Ex vivo lung perfusion has been shown to increase donor lung utilization of lungs that previously could not be used.[43,47] Short-term outcomes using lungs conditioned in this fashion have been highly favorable.[43,44] Ex vivo lung perfusion is now standard practice in the Toronto Lung Transplant Program,[44] and it is being increasingly applied worldwide.[48] The U.S. Food and Drug Administration has approved the XPS Lung Perfusion System (XVIVO Perfusion) for use in the United States.

AVAILABLE SURGICAL TECHNIQUES

Four surgical techniques have been developed: *single lung transplantation* (SLT), *bilateral lung transplantation* (BLT), heart-lung transplantation, and bilobar transplantation. Of these, BLT and SLT are the most commonly performed.

SINGLE LUNG TRANSPLANTATION

SLT is performed using a standard posterolateral thoracotomy, an anterior muscle sparing thoracotomy, or a partial "clamshell" incision (which gives access to the central mediastinum for easy cannulation for ECMO or cardiopulmonary bypass). Three anastomoses are performed: mid-mainstem, pulmonary artery, and left atrium (incorporating the two pulmonary veins). Compared with BLT, SLT permits more efficient use of the limited donor supply and tends to be better tolerated by elderly and frailer patients, but it provides less functional reserve in the setting of allograft dysfunction. It is an acceptable option for patients with pulmonary fibrosis and COPD. In the setting of severe pulmonary hypertension, SLT requires the new allograft to bear the burden of nearly the entire cardiac output because of high pulmonary vascular resistance in the native lung, thereby exaggerating the degree of permeability pulmonary edema that develops in the allograft. For this reason, the presence of significant pulmonary hypertension is considered a contraindication to SLT. Because of infectious concerns, SLT is also contraindicated in patients with suppurative lung disorders such as CF.

BILATERAL LUNG TRANSPLANTATION

BLT involves the performance of two sequential SLT procedures in succession in one operation. Surgical approaches include either a transverse thoracosternotomy (clamshell) incision, bilateral anterolateral thoracotomies (sparing the sternum), or a median sternotomy. In the absence of severe pulmonary hypertension, cardiopulmonary bypass can often be avoided by sustaining the patient on the contralateral lung during implantation of each allograft. BLT is the exclusive procedure for CF, other forms of bronchiectasis, and severe primary and secondary forms of pulmonary hypertension. BLT has supplanted SLT as the preferred procedure for patients with COPD and pulmonary fibrosis because of its superior functional outcomes and evidence, albeit conflicting, suggesting a survival advantage over SLT.[1,49–52] As a result of these practices, BLT now accounts for 80% of all procedures performed worldwide.[1]

HEART-LUNG TRANSPLANTATION

Historically the first procedure successfully introduced to allow replacement of diseased lungs, heart-lung transplantation is now infrequently performed because of the development of SLT and BLT procedures. Currently, fewer than 60 procedures are performed worldwide annually.[1] Indications are largely restricted to Eisenmenger syndrome with surgically uncorrectable cardiac lesions and to advanced lung disease with concurrent severe left ventricular dysfunction or extensive coronary artery disease not amenable to angioplasty or bypass surgery. In the past, the presence of profound right ventricular dysfunction in the setting of severe pulmonary hypertension was deemed to be an indication for heart-lung transplantation. However, subsequent experience with isolated lung transplantation has demonstrated the remarkable ability of the right ventricle to recover once pulmonary artery pressures have normalized. As a result, BLT is the preferred operation in patients with severe right ventricular failure.

BILATERAL LOBAR TRANSPLANTATION

Bilateral lobar transplantation—the use of two lobes to perform BLT in a smaller recipient—is an important procedure in the treatment armamentarium. This operation is most commonly performed to treat children or small-stature women who are running out of time to receive a suitably sized BLT. Various combinations of lobes can be used, or even a whole lung on one side with a lobe on the other. In experienced centers, the results of bilateral lobar transplants are expected to be similar to that of standard BLT.[53]

Living donor bilateral lobar transplantation was developed principally to serve the needs of candidates with far-advanced or deteriorating status that would not allow them to tolerate a protracted wait for a deceased donor in the pre-LAS era. The procedure involves transplantation of lower lobes from each of two living, blood group–compatible donors. To ensure that the lobes will adequately fill the hemithoraces, it is preferable to use donors who are taller than the recipient. Patients with CF are particularly well suited as a target population because, even as adults, they tend to be of small stature. Intermediate-term functional outcomes and survival among recipients are similar to those achieved with deceased donor lung transplantation.[54,55] Although no donor deaths have been reported, one report noted that 18% of donors experienced "serious" complications.[56] The

introduction of the LAS system to expedite lung transplantation in severely ill candidates ultimately obviated the need for this procedure in the United States, but it continues to be performed in Japan, where waiting times for deceased donors continue to exceed 2 years.[57]

ROUTINE POSTTRANSPLANTATION MANAGEMENT

Care of the lung transplant recipient requires close surveillance to ensure that the allograft is functioning properly, that immunosuppressive medications are properly administered and tolerated, and that complications are detected early and treated expeditiously. Most centers require patients to return frequently for office visits, blood tests, and chest radiographs during the initial 2 to 3 months following transplantation and to participate in an intensive pulmonary rehabilitation program during this time. Analogous to home glucose monitoring of the diabetic patient, lung transplant recipients chart their pulmonary function on a daily basis with a handheld microspirometer and are instructed to contact the transplant center for a sustained fall of greater than 10% in the *forced expiratory volume in 1 second* (FEV_1) or forced vital capacity.

Many transplant programs use frequent surveillance bronchoscopies and transbronchial lung biopsies within the first posttransplant year as a means of monitoring the allograft. Such an approach has been demonstrated to detect low-grade rejection in up to 30% of asymptomatic, clinically stable patients.[58] However, it has yet to be determined whether treatment of clinically silent disease has a beneficial impact on long-term graft function.

Immunosuppressive therapy is initiated immediately at the time of transplantation and is maintained lifelong. Approximately 75% of programs use *induction* therapy, a brief but potent effort to deplete and block activation of T cells. The predominant agent used for induction is the interleukin-2 receptor antagonist basiliximab because of its favorable safety profile.[1] Less commonly used in induction are the lymphocyte/thymocyte-depleting globulin preparations and the anti-CD52 monoclonal antibody alemtuzumab. The lack of consensus on the role of induction therapy reflects insufficient and conflicting data on the ability of these agents to reduce the incidence of acute rejection and CLAD in the lung transplant population. After the period of induction, *maintenance* therapy consists of a calcineurin inhibitor (tacrolimus or, less commonly, cyclosporine), purine synthesis inhibitor (mycophenolate or azathioprine), and prednisone. The mechanistic target of rapamycin inhibitor sirolimus is occasionally incorporated into the maintenance regimen. Use of this agent in place of a purine synthesis inhibitor does not reduce the incidence of acute rejection or CLAD and is associated with several bothersome side effects that commonly lead to discontinuation of the drug.[59] Its main role has been to facilitate dose reduction or discontinuation of calcineurin inhibitors in patients with renal insufficiency, with the goal of recovering or preserving renal function.[60,61] Sirolimus impairs wound healing and has been associated with life-threatening bronchial anastomotic dehiscence when it is used immediately following transplantation.[62] As a result, the drug should not be initiated until complete healing of the bronchial anastomosis has been documented.

Individuals providing care to transplant recipients must be familiar with the administration, side effects, and drug interactions of these immunosuppressive agents (eTable 140.1). Although serving as the cornerstone of therapy, calcineurin inhibitor administration is particularly challenging. When these agents are administered orally, their bioavailability is poor and unpredictable, thus necessitating frequent monitoring of blood levels to ensure appropriate dosing. These drugs are metabolized through the hepatic cytochrome P-450 system, and blood levels are influenced by the concurrent administration of other drugs that affect this enzymatic pathway. Adverse effects of these agents, as well as of the other drugs commonly used, are legion and contribute significantly to the morbidity associated with transplantation.

Management of medical comorbidities is an essential component of the care of the lung transplant recipient. Common medical issues that emerge in this population include osteoporosis, hypertension, renal insufficiency, coronary artery disease, diabetes mellitus, and hyperlipidemia.[63] Treatment of these conditions is similar to that in the general population. The incidence of many cancers is increased in immunosuppressed transplant recipients, and particular attention should be paid to screening in this patient population.

OUTCOMES

The impact of lung transplantation is assessed by conventional survival statistics as well as by functional and quality of life parameters.

SURVIVAL

Current median survival following lung transplantation is 6.5 years.[1] Disease-specific differences in survival are apparent but may be confounded by differences in severity of illness, comorbidities, and average age among these populations. In descending order, median survival is 9.5 years for CF, 7.0 years for $alpha_1$-antitrypsin deficiency, 6.3 years for idiopathic pulmonary arterial hypertension, 5.9 years for COPD, and 5.2 years for idiopathic pulmonary fibrosis and other idiopathic interstitial pneumonias.[1]

Mortality is highest during the first year, with primary graft dysfunction and infection representing the most common causes of early death. In contrast, most late deaths are attributable to the development of CLAD, the lethal effects of which result from both progressive respiratory failure and an increased susceptibility to infection.

In the absence of randomized trials, the question whether lung transplantation extends survival compared with the natural history of the underlying disease has been addressed using statistical modeling. In the case of idiopathic pulmonary fibrosis, a disease with an extremely poor short-term prognosis, studies have consistently suggested that lung transplantation does confer a survival advantage, but it is notable that none of these studies was conducted in patients with idiopathic pulmonary fibrosis who were receiving the

eTable 140.1 Commonly Used Immunosuppressive Medications

Medication (Class)	Dosing*	Adverse Effects	Drug Interactions
Cyclosporine and tacrolimus (calcineurin inhibitors)	*Cyclosporine:* dosed to achieve a whole blood trough level of 250–350 ng/mL (first year), then 200–300 ng/mL† *Tacrolimus:* dosed to achieve a whole blood trough level of 10–12 ng/mL (first year), then 6–8 ng/mL	▪ Nephrotoxicity ▪ Hypertension ▪ Neurotoxicity (tremor, seizures, white matter disease, headache) ▪ Hyperkalemia ▪ Hypomagnesemia ▪ Hyperuricemia/gout ▪ Hemolytic-uremic syndrome ▪ Gastroparesis ▪ Hyperglycemia ▪ Hirsutism (cyclosporine) ▪ Gingival hyperplasia (cyclosporine)	Increased blood levels: ▪ Macrolide antibiotics (except azithromycin) ▪ Azole antifungal agents ▪ Diltiazem, verapamil ▪ Grapefruit juice Decreased blood levels: ▪ Phenobarbitol ▪ Phenytoin ▪ Rifampin
Sirolimus (mTOR inhibitor)	Dosed to achieve a whole blood trough level of 6–12 ng/mL	▪ Thrombocytopenia ▪ Anemia ▪ Hyperlipidemia ▪ Peripheral edema ▪ Rash ▪ Impaired wound healing ▪ Interstitial pneumonitis	Same as calcineurin inhibitors
Azathioprine (purine synthesis inhibitor)	2 mg/kg/day	▪ Leukopenia ▪ Macrocytic anemia ▪ Thrombocytopenia ▪ Hepatotoxicity ▪ Pancreatitis ▪ Hypersensitivity reaction (fever, hypotension, rash)	Synergistic bone marrow suppression when administered with allopurinol
Mycophenolate mofetil (purine synthesis inhibitor)	1000–1500 mg bid	▪ Diarrhea ▪ Leukopenia ▪ Anemia	Concurrent use of cyclosporine may decrease serum concentrations of mycophenolate by limiting biliary secretion or enterohepatic recycling
Prednisone (corticosteroid)	0.5 mg/kg/day for 6–12 wk, then tapered to 0.15 mg/kg/day	▪ Hyperglycemia ▪ Hypertension ▪ Hyperlipidemia ▪ Weight gain ▪ Osteoporosis ▪ Avascular necrosis ▪ Myopathy ▪ Mood changes ▪ Insomnia ▪ Cataracts	No significant interactions
Polyclonal antilymphocyte or antithymocyte globulin	Dose depends on specific preparation used	▪ Leukopenia ▪ Thrombocytopenia ▪ Anaphylaxis ▪ Serum sickness ▪ "Cytokine release syndrome"—fever, hypotension	No significant interactions
Basiliximab (monoclonal IL-2 receptor antagonist)	20 mg IV on days 1 and 4	Hypersensitivity reactions (rare)	No significant interactions

*Dosing may vary among transplant centers.
†Measured by high-performance liquid chromatography assay.
bid, twice daily; IL-2, interleukin-2; IV, intravenously; mTOR, mechanistic target of rapamycin.

newer antifibrotic medications.[64–66] A survival advantage has been more difficult to demonstrate for COPD, which typically follows a protracted course even in the advanced stages, and available studies comparing wait-list and post-transplant survival have yielded conflicting results.[65,67] A more complex analysis of this issue, by using prognostic models of survival with and without transplantation, found that approximately 45% of patients with COPD would gain a survival benefit of at least 1 year by undergoing BLT, whereas only 22% would derive such a benefit if SLT were used.[68] Survival benefit was heavily influenced by pretransplant FEV_1 as well as several other functional and physiologic parameters. As an example, nearly 80% of patients with an FEV_1 less than 16% but only 11% of those with an FEV_1 greater than 25% were predicted to gain at least 1 year of life with BLT. Adults with CF also appear to derive a survival advantage from lung transplantation,[66] although one study found that this advantage was limited to patients with a predicted 5-year survival without transplantation of less than 50% and without *B. cepacia* and CF-related arthropathy.[69,70] In contrast, modeling studies have suggested that patients with CF who are younger than 18 years rarely achieve a survival benefit.[69,71] This contention has been challenged by several investigators who pointed out potential methodologic shortcomings of these studies.[72,73]Independent of underlying disease, the recipient's LAS at the time of transplantation appears to be a powerful predictor of survival benefit; patients with an LAS lower than 33 are unlikely to derive a survival benefit, while virtually all patients with an LAS greater than 40 are predicted to do so.[66]

PULMONARY FUNCTION

The peak effect of lung transplantation on pulmonary function parameters is usually not realized until 3 to 6 months following the procedure, at which time the adverse impact of such factors as postoperative pain, weakness, altered chest wall mechanics, and ischemia-reperfusion lung injury has dissipated. Complete normalization of pulmonary function is the anticipated result of BLT. Following SLT for COPD, the FEV_1 increases severalfold to a level of approximately 50–60% of the predicted normal value (Video 140.1). Similarly, SLT for pulmonary fibrosis results in marked but incomplete improvement in lung volumes, with persistence of a restrictive pattern.

Transplantation also leads to correction of gas exchange abnormalities. Oxygenation improves rapidly, permitting the majority of patients to be weaned from supplemental oxygen within the first week. Hypercapnia may take longer to resolve because of lingering abnormalities in the ventilatory response to carbon dioxide.[74]

EXERCISE CAPACITY

Exercise tolerance improves sufficiently to permit the majority of transplant recipients to achieve functional independence and resume an active lifestyle. Although free of limitations with usual activity, transplant recipients with normal allograft function demonstrate a characteristic reduction in peak exercise performance as assessed by cardiopulmonary exercise testing. Specifically, patients typically achieve a maximum oxygen consumption at peak exercise of only 40– 60% of predicted.[75,76] Suboptimal exercise performance persists in subjects tested as late as 1 to 2 years following transplantation. Despite the greater magnitude of improvement in pulmonary function experienced by bilateral transplant recipients, there is no significant difference in peak exercise performance between this group and patients who receive only one lung.[76,77]

Characteristically, breathing reserve, oxygen saturation, and heart rate reserve remain normal during exercise, whereas anaerobic threshold is reduced, a pattern most consistent with skeletal muscle dysfunction. Factors possibly contributing to this limitation include chronic deconditioning, steroid myopathy, and calcineurin inhibitor–induced impairment in muscle mitochondrial respiration.[75,78]

HEMODYNAMICS

When performed in patients with primary or secondary forms of pulmonary hypertension, lung transplantation results in normalization of pulmonary arterial pressure and enhanced cardiac output.[79] In response to a decrease in afterload, right ventricular geometry and performance gradually normalize in the majority of patients.[80,81] Even a severely dysfunctional right ventricle will recover; a threshold of right ventricular dysfunction below which recovery is not possible has yet to be defined.

QUALITY OF LIFE

After successful lung transplantation, quality of life measures improve markedly across most domains, driven largely by a reduced level of disability.[82,83] These improvements peak at 3 to 6 months after transplantation and remain higher than pretransplantation levels for up to 5 years. Nonetheless, several important limitations have been observed. Recipients are much more likely to demonstrate improvements in physical dimensions of quality of life than in mental dimensions because increased levels of depression and anxiety and poor perception of body image persist.[82–85] In addition, troubling side effects of immunosuppressive medications adversely affect quality of life.[85,86] Finally, the development of CLAD is associated with a significant deterioration in quality of life measures.[87]

COMPLICATIONS

The lung transplant recipient faces some complications related to the surgery itself, the consequences of immunosuppression, and the constant assault of immune and nonimmune insults on the allograft.

PRIMARY GRAFT DYSFUNCTION

Primary graft dysfunction (PGD) is a term applied to the development within 72 hours of transplantation of radiographic opacities in the allograft(s) associated with impaired oxygenation in the absence of identifiable insults such as volume overload, pneumonia, rejection, atelectasis, heart failure, or pulmonary venous outflow obstruction.[88] PGD is presumed to be a consequence of ischemia-reperfusion injury as well as suboptimal lung

preservation, surgical trauma, lymphatic disruption, and inflammatory events associated with donor brain death and mechanical ventilation. Supporting the concept of PGD as a form of acute, nonimmunologic lung injury, histologic examination of lung tissue from affected patients reveals a prevailing pattern of diffuse alveolar damage.[88] A widely used grading system classifies the severity of PGD based on the ratio of arterial oxygen pressure (arterial Po_2) to the fractional concentration of oxygen in inspired gas (Table 140.4).[89] In most cases, the process is mild and transient but, in approximately 10–20% of cases, injury is sufficiently severe to cause life-threatening hypoxemia (PGD grade 3) and a clinical course analogous to the acute respiratory distress syndrome.

Numerous risk factors for development of severe PGD have been identified.[90] Many of these are procedure-related factors: use of an elevated fractional concentration of oxygen in inspired gas during reperfusion, use of cardiopulmonary bypass, SLT, and administration of large-volume blood product transfusions. Recipient risk factors include a diagnosis of sarcoidosis, presence of pulmonary hypertension, and overweight or obese body habitus. A history of smoking has been identified as a donor-related risk factor. Although early studies suggested that prolonged graft ischemic time was a risk factor, more recent studies have not found this to be true.[90,91] An elevated level of interleukin-8 in *bronchoalveolar lavage* (BAL) fluid recovered from the donor has been associated with the development of severe PGD, a finding supporting the notion that inflammatory events preceding organ harvest may play a role.[92]

Treatment of severe PGD is supportive, relying on conventional mechanical ventilation using low–tidal volume strategies, as well as on ECMO for selected patients who otherwise cannot be stabilized.[93,94] The use of nitric oxide in patients with established graft injury has been associated with sustained reduction in pulmonary artery pressures and improvement in oxygenation.[95] However, the prophylactic administration of nitric oxide to all recipients at the time of reperfusion does not reduce the incidence of severe PGD.[96] Results of emergency retransplantation in this setting have been poor.[97,98]

With an associated mortality rate of 20–40%, severe PGD is a leading cause of early death among transplant recipients.[90,99,100] The risk of death remains excessive even beyond the first year, suggesting that PGD has lingering adverse consequences well after resolution of the acute event. Recovery among survivors is often protracted and incomplete, although attainment of normal lung function and exercise tolerance is possible.[101] There is an increased risk of CLAD following development of PGD, but data are conflicting on whether the increased risk spans all grades of PGD or is seen exclusively following the most severe grade.[102,103]

Table 140.4 Grading System for Primary Graft Dysfunction

Grade	Pao_2/Fio_2	Radiographic Evidence of Pulmonary Edema
0	Any	Absent
1	>300	Present
2	200–300	Present
3	<200	Present

Pao_2/Fio_2, ratio of arterial oxygen pressure to fractional concentration of oxygen in inspired gas.

From Snell GI, Yusen RD, Weill D, et al. Report of the ISHLT Working Group on Primary Lung Graft Dysfunction, part I: definition and grading. A 2016 Consensus Group statement of the International Society for Heart and Lung Transplantation. *J Heart Lung Transplant*. 2017;36:1097–1103.

AIRWAY COMPLICATIONS

During implantation of the allograft, the bronchial arterial circulation is not restored. As a consequence, the donor bronchus is precariously dependent on retrograde collateral blood flow through low-pressure pulmonary arterial and venous to bronchial vascular collateral vessels, placing the airway at risk for ischemic injury. Airway ischemia may result in bronchial anastomotic dehiscence, which, when extensive, can lead to mediastinitis, pneumothorax, hemorrhage, and death. The finding of peribronchial or mediastinal air collections on computed tomography scan is highly suggestive of bronchial dehiscence, but direct inspection using bronchoscopy is necessary to confirm the diagnosis and assess the extent. For mild cases, conservative management with reduction in corticosteroid dosing and chest tube placement for evacuation of an associated pneumothorax may be all that is necessary (Fig. 140.2). More extensive cases can be successfully managed with temporary placement of a bare metal airway stent across the dehiscence to provide a scaffolding on which granulation tissue can form.[104] Surgical intervention to buttress or revise the anastomosis is reserved for severe cases when bronchoscopic interventions fail or are not feasible, but surgical outcomes are disappointing. Pneumonectomy is a last resort in life-threatening situations in patients with an intact and functioning contralateral allograft.

Ischemic injury to the airway more commonly manifests as necrosis of the anastomotic cartilage and as areas of bronchial mucosal ulceration, dusky patches, and overlying pseudomembranes. These devitalized areas in turn place the patient at increased risk for superinfection of the airway with *Candida* and *Aspergillus* species; initiation of inhaled and/or systemic fungal prophylaxis is indicated until the airways have healed.

The most common airway complication currently encountered is bronchial anastomotic stenosis, with a reported frequency of 10–15% in contemporary series.[105,106] Narrowing can be caused by excessive granulation tissue, fibrotic stricture (Fig. 140.3), or bronchomalacia (the latter two mechanisms likely sequelae of prior ischemic injury). Occasionally, fibrotic strictures can extend beyond the anastomosis, thus leading to narrowing of the bronchus intermedius (eFig. 140.1) or lobar bronchi. Anastomotic narrowing typically develops within several weeks to months following transplantation. Clues to its presence include focal wheezing on the involved side, recurrent bouts of pneumonia or purulent bronchitis, and suboptimal pulmonary function studies demonstrating airflow obstruction and truncation of the flow-volume loop. Bronchoscopy

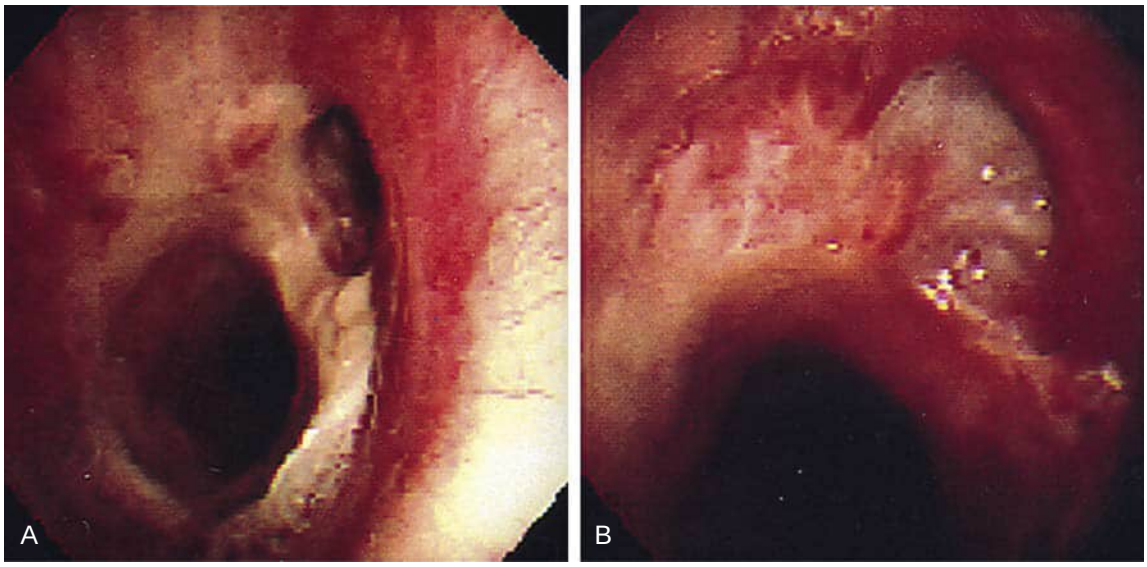

Fig. 140.2 Bronchial anastomotic dehiscence. (A) Bronchoscopic view immediately distal to the main carina demonstrates partial dehiscence of the right bronchial anastomosis at the 1 o'clock position. (B) After several weeks of expectant management, a repeat bronchoscopy demonstrates nearly complete healing of the dehiscence.

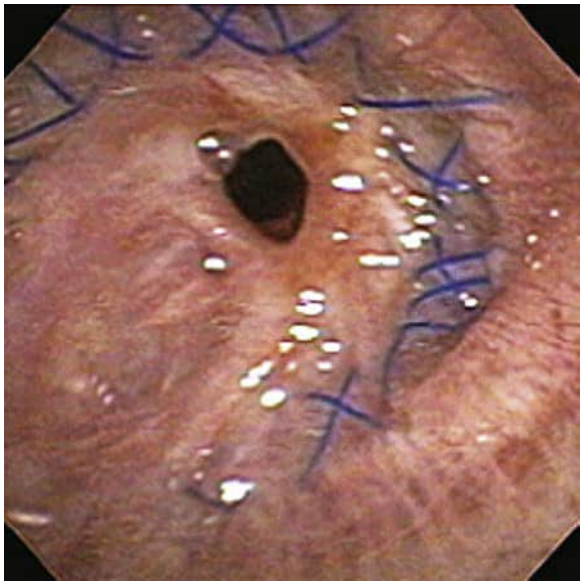

Fig. 140.3 Bronchial anastomotic stricture. Bronchoscopic view of a left mainstem bronchial anastomosis demonstrates marked narrowing of the lumen resulting from formation of a fibrous web. The true outer margin of the bronchus is outlined by the suture material.

both confirms the diagnosis and permits therapeutic interventions, including rigid bronchoscopic or balloon dilation, laser débridement, endobronchial brachytherapy, and stent placement.[107] Although these measures are often successful in the short term, recurrent stenosis is common, necessitating repeated interventions and leading to compromised functional outcomes and excess mortality.[108]

PHRENIC NERVE INJURY

Phrenic nerve injury following lung transplantation can result from intraoperative traction, use of an iced slurry to cool the allograft in the chest cavity during implantation, or transection of the nerve in the setting of extensive fibrous adhesions and difficult hilar dissection. Depending in part on whether screening is restricted to clinically suspected cases or more broadly to all recipients, the reported incidence of phrenic nerve dysfunction ranges from 3–30%.[109–112] Important albeit nonspecific clues to the presence of phrenic nerve injury include difficulty in weaning from mechanical ventilation, persistent hypercapnia, orthopnea, and radiographic evidence of persistent elevation of the diaphragm and associated basilar atelectasis. Phrenic nerve injury has been associated with increases in ventilator days, tracheostomy rates, and intensive care unit length of stay.[110] Achievement of a normal functional outcome is ultimately possible for patients with reversible injury, but recovery in some cases may be protracted or incomplete. For severely impaired patients, nocturnal noninvasive ventilatory support and diaphragmatic plication have been successful.[113,114]

NATIVE LUNG HYPERINFLATION

Acute hyperinflation of the native lung leading to respiratory and hemodynamic compromise in the immediate postoperative period has been reported in 15–30% of patients with emphysema who underwent SLT.[115,116] The combination of positive-pressure ventilation and significant allograft edema serves to magnify the compliance differential between the two lungs and may predispose to this complication. Acute hyperinflation can be rapidly addressed by use of a bronchial blocker or by initiation of independent lung ventilation, ventilating the native lung with a low respiratory rate and a long expiratory time to facilitate complete emptying.

Beyond the perioperative period, some SLT recipients with underlying emphysema demonstrate exaggerated or progressive native lung hyperinflation that more insidiously

compromises the function of the allograft. In this setting, surgical volume reduction of the native lung can result in significant functional improvement.[117]

INFECTION

Infection rates among lung transplant recipients are considerably higher than among recipients of other solid organs. The greater risk is likely related to the unique exposure of the lung allograft to microorganisms through inhalation and aspiration and to the higher level of immunosuppression maintained in these patients. A comprehensive discussion of infectious complications is beyond the scope of this chapter; only the most common pathogens are discussed.

Bacteria

Bacterial infections of the lower respiratory tract account for the majority of infectious complications and have a bimodal temporal distribution.[118,119] Bacterial pneumonia is most frequently encountered within the first month after transplantation. In addition to the immunosuppressed status of the recipient, factors that predispose to early bacterial pneumonia include the need for prolonged mechanical ventilatory support; blunted cough in response to postoperative pain, weakness, and lung denervation; disruption of lymphatics; and ischemic injury to the bronchial mucosa with resultant impairment in mucociliary clearance. Although passive transfer of occult infection with the transplanted organ is an additional concern, the presence of organisms on Gram stain of donor bronchial washings is not predictive of subsequent pneumonia in the recipient.[120] Bacterial infections, in the form of purulent bronchitis, bronchiectasis, and pneumonia, reemerge as late complications in patients who develop CLAD. Gram-negative pathogens, in particular *P. aeruginosa* (see eFig. 125.1), are most frequently isolated in association with both early and late infectious events.[118,119]

Cytomegalovirus

Cytomegalovirus (CMV) is the most common viral pathogen encountered following lung transplantation, although in the era of effective prophylaxis its incidence and impact have diminished considerably.[119] Infection can develop by transfer of virus with the allograft or transfused blood products or by reactivation of latent virus remotely acquired by the recipient. Seronegative recipients who acquire organs from seropositive donors are at greatest risk for developing infection, and these primary infections tend to be the most severe. Donor-positive–recipient-negative mismatching has also been identified as a risk factor for increased mortality at 5 years.[1,121]

In the absence of prophylaxis, CMV infection typically emerges 1 to 3 months following transplantation; antiviral prophylaxis shifts the onset to later in the course, often in the initial months after the antiviral agent is discontinued. Infection is often subclinical, evidenced only by silent viremia or shedding of virus in the respiratory tract. Clinical disease may manifest as a mononucleosis-like syndrome of fever, malaise, and leukopenia (CMV syndrome) or as organ-specific invasion of the lung, gastrointestinal tract, central nervous system, or retina. Detection of virus in peripheral blood by polymerase chain reaction techniques establishes a diagnosis of CMV infection but does not reliably predict the presence of tissue-invasive disease. Conversely, a negative peripheral blood assay result does not exclude tissue-invasive disease, particularly pneumonitis.[122] A diagnosis of CMV pneumonitis, the most common manifestation of invasive disease in the lung transplant recipient (see eFigs. 125.6 and 125.7), is unequivocally established by demonstration of characteristic viral cytopathic changes on lung biopsy or on cytologic specimens obtained by BAL, but the sensitivity of these findings is relatively low. Demonstration of CMV antigens by immunohistochemistry offers greater diagnostic sensitivity. Caution must be exercised in interpretation of a positive viral culture or polymerase chain reaction of BAL specimens because virus can be shed into the respiratory tract in the absence of tissue invasion.[122]

Standard treatment of CMV syndrome and tissue-invasive disease consists of oral valganciclovir; in severe cases, intravenous ganciclovir is preferred for initial management. Monitoring of peripheral blood viral load should be performed weekly to confirm response to therapy. Treatment should be continued until the viral load is confirmed to be below the lower limit of quantification of the assay (typically less than 200 IU/mL).[123] Some experts advocate the addition of CMV hyperimmune globulin in treatment of severe disease, but evidence supporting this practice is scant. Although treatment is effective, relapse rates of up to 40% in patients with primary infection and 24% in seropositive recipients have been reported.[124] Initiation of oral valganciclovir as secondary prophylaxis after completion of definitive treatment does not decrease the risk of relapse and is not generally recommended in consensus guidelines but is nonetheless a common practice.[123–125]

In an attempt to minimize the adverse impact of CMV infection on the posttransplantation course, emphasis has shifted to preventive strategies when either the donor or recipient is seropositive. Numerous prospective randomized trials have documented the efficacy of antiviral prophylaxis in delaying the onset and reducing the incidence and severity of CMV infection.[126] Oral valganciclovir has replaced intravenous ganciclovir as the prophylactic agent of choice because of its excellent bioavailability, ease of administration, and demonstrated efficacy.[127] Universal prophylaxis of all donor-seropositive–recipient-seronegative patients is recommended because the risk of CMV disease is high.[123] Because the risk of disease is significantly lower in seropositive recipients (independent of donor status), it has been argued that universal prophylaxis of this group leads to overtreatment, increasing costs, and unduly exposing patients to the risk of drug toxicity. In this population, preemptive strategies targeting antiviral therapy exclusively to patients demonstrating a rising viral load in peripheral blood have been advocated, but most programs still adhere to a universal prophylaxis strategy.[125,128] The duration of prophylaxis necessary to mitigate the risk of CMV was best examined in a randomized controlled trial of 136 at-risk lung transplant recipients (either donor or recipient seropositive). When patients were evaluated at month 13, there was a 4% incidence of CMV disease after a 12-month course of valganciclovir prophylaxis compared with 32% after a 3-month

course.[129] For a subset of patients followed for 4 years after completion of prophylaxis, the incidence of CMV disease remained considerably lower in the 12-month group compared with the 3-month group (12% vs. 55%).[130] Additional studies are required to determine whether 12 months is necessary or excessive and whether all at-risk subgroups require the same regimen. Consensus guidelines currently recommend a minimum of 6 to 12 months of prophylaxis for donor-positive–recipient-negative patients and 6 months for recipient-positive patients.[123]

Emergence of ganciclovir-resistant strains of CMV has been reported in 5–18% of lung transplant recipients with CMV infection.[123,131–133] Risk factors include donor-positive–recipient-negative CMV status, use of potent immunosuppressive agents such as antilymphocyte antibodies, increased number of CMV episodes, and prolonged exposure to ganciclovir.[123] High-dose ganciclovir, foscarnet, or a combination of the two is the recommended treatment regimen for ganciclovir-resistant disease.[123] Although treatment is often initially successful, the presence of ganciclovir-resistant disease is associated with decreased survival in lung transplant recipients.[131]

Aspergillus

Aspergillus species account for the majority of fungal infections following lung transplantation. Pretransplantation or posttransplantation colonization of the airways with aspergillus is most frequently cited as a risk factor for subsequent development of infection, although data remain conflicting and up to 48% of patients who develop infection have neither risk factor.[134,135]

Aspergillus infects the bronchial tree in approximately 2–5% of lung transplant recipients.[135,136] In most cases, infection is localized to the bronchial anastomosis, where devitalized cartilage and foreign suture material create a nurturing environment. Less commonly, infection may manifest as more diffuse ulcerative bronchitis with formation of pseudomembranes, typically following in the wake of a severe ischemic injury to the bronchial mucosa. Clustered within the first 3 months posttransplantation, these airway infections are often asymptomatic and detected only by surveillance bronchoscopy. Voriconazole is considered first-line therapy; nebulized amphotericin is recommended as an adjunct for airway infections.[137] Although usually responsive to treatment, airway infections have rarely progressed to invasive pneumonia or fatal erosion into the adjacent pulmonary artery.[136,138] An increased risk of subsequent bronchial stenosis or bronchomalacia has also been reported, but it is unclear whether this is a consequence of the infection or of an underlying ischemic injury to the bronchus that predisposed to infection.[139,140]

Invasive aspergillosis, a far more serious form of infection, develops in up to 7% of lung transplant recipients, most commonly within the first year.[135,136] It nearly always involves the lung but may disseminate to distant sites, particularly the brain, in a minority of patients. Symptoms are nonspecific and include fever, cough, pleuritic chest pain, and hemoptysis. Radiographically, pulmonary aspergillosis may appear as single opacity or mass (eFig. 125.2B) or nodular (see eFig. 125.2A) or cavitary opacities (Fig. 140.4 and eFig. 125.4) or as alveolar consolidation. The halo sign—a rim of ground-glass attenuation surrounding a central nodular opacity—is a suggestive but nonspecific finding on chest computed tomography scans.

Diagnosing invasive pulmonary aspergillosis can be challenging. As discussed previously, many lung transplant recipients are colonized with *Aspergillus,* thus making it difficult to interpret the significance of positive results of fungal stains and cultures derived from BAL specimens. Conversely, the sensitivity of BAL fungal stains and culture in the setting of invasive disease has been reported in the range of only 45–62% in solid organ transplant recipients.[141] Because of a similarly low sensitivity in this population, serum galactomannan (a constituent of the fungal cell wall shed during active invasion) is not recommended as a diagnostic test.[134,137] BAL galactomannan testing in this population appears to offer higher sensitivity (77–100%, with a cutoff value of 0.5) with varying specificity (40–100%) in published studies.[134] Because the prevalence of invasive disease is relatively low, however, the positive predictive value of BAL galactomannan in lung transplant recipients is as low as 24%.[142] In the context of compatible clinical and radiographic features and/or demonstration of *Aspergillus* in respiratory secretions by culture, cytology, or galactomannan assay, the clinician must exercise judgment in deciding whether to initiate an empirical trial of antifungal therapy or pursue more definitive proof by means of transthoracic needle biopsy or surgical lung biopsy.

Voriconazole is the treatment of choice for invasive aspergillosis. Addition of an echinocandin (e.g., caspofungin) is considered in cases of severe or progressive infection, although the advantage of combination therapy has not been established.

Many transplant programs use antifungal prophylaxis in an attempt to mitigate the risk of airway and invasive aspergillosis, although consensus is lacking on the best strategy and data supporting efficacy are conflicting. Voriconazole and/or inhaled amphotericin are commonly used for this purpose; the latter is typically discontinued after airway

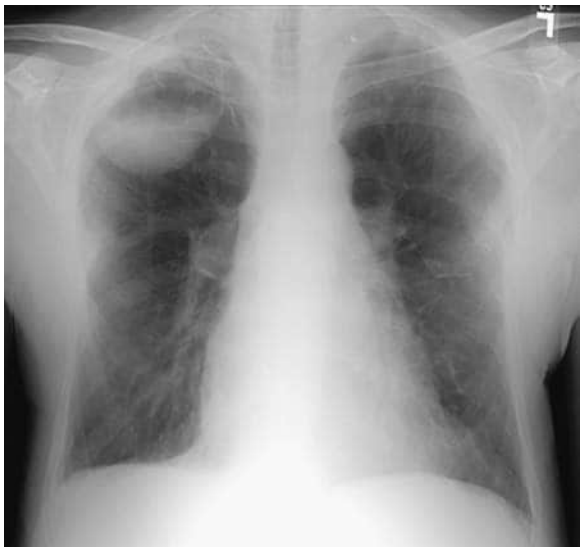

Fig. 140.4 Invasive aspergillosis. Bilateral lung transplant recipient with a large right upper lobe cavity containing an air-fluid level. Transthoracic needle biopsy demonstrated fungal elements morphologically consistent with *Aspergillus* species. The patient did not respond to antifungal therapy and required surgical resection for definitive cure.

healing has been documented. Two meta-analyses of studies involving universal antifungal prophylaxis in lung transplant recipients came to opposite conclusions on whether this resulted in reduction of posttransplantation *Aspergillus* infections.[143,144] Efficacy of an alternative strategy of targeted prophylaxis for recipients with either pretransplant or postransplant fungal colonization was demonstrated in a 2018 study from the University of Toronto group.[145]

REJECTION AND CHRONIC LUNG ALLOGRAFT DYSFUNCTION

Despite the use of potent immunosuppressive agents, allograft rejection and CLAD remain pervasive problems that constrain long-term graft and patient survival. Humoral and cellular alloimmune mechanisms have been defined to varying degrees for the more acute insults, and thus the term "rejection" is an appropriate descriptor (i.e., hyperacute rejection, acute cellular rejection, antibody-mediated rejection). However, the pathogenetic mechanisms underlying chronic forms of allograft dysfunction are less clear, and both immunologic and nonimmunologic insults have been implicated. Although still part of the transplant lexicon, the term *chronic rejection* is misleading because it oversimplifies both the mechanism and the spectrum of phenotypes that characterize long-term allograft impairment. The term CLAD has emerged as a preferred descriptor, comprising the most commonly encountered form, *bronchiolitis obliterans syndrome* (BOS), as well as the more recently described variant, *restrictive allograft syndrome* (RAS). The various forms of rejection and CLAD are described in detail in the following sections. Features of the three most commonly encountered entities—acute cellular rejection, BOS, and RAS—are summarized in Table 140.5.

Hyperacute Rejection

Hyperacute rejection is a rare but highly lethal complication mediated by preformed antibodies of recipient origin directed against HLA antigens contained in donor tissue. The pulmonary microvascular endothelium is the principal target, leading to complement-mediated and neutrophil-mediated damage and widespread deposition of platelet or fibrin thrombi.[146] Hyperacute rejection becomes clinically manifest within minutes to hours of establishing perfusion to the freshly implanted lung. The allograft appears dusky, mottled, and grossly edematous on direct inspection and densely opacified on chest radiograph. Copious amounts of pink, frothy edema fluid often are produced by the allograft and must be frequently suctioned from the endotracheal tube. Profound graft dysfunction and hemodynamic

Table 140.5 Features of Acute Cellular Rejection, Bronchiolitis Obliterans Syndrome, and Restrictive Allograft Syndrome

Feature	Acute Cellular Rejection	Bronchiolitis Obliterans Syndrome	Restrictive Allograft Syndrome
Onset after transplant	Days to months; less common beyond the first year	Beyond first year	Beyond first year
Risk factors	Uncertain	Acute rejection, lymphocytic bronchiolitis, community respiratory viruses, primary graft dysfunction, silent aspiration, CMV pneumonitis	Uncertain
Histology	Perivascular lymphocytic infiltrates	Bronchiolar submucosal inflammation and fibrosis; luminal obliteration	Intra-alveolar and subpleural fibroelastosis, diffuse alveolar damage, nonspecific interstitial pneumonia, acute fibrinoid organizing pneumonia
Signs and symptoms	Low-grade fever, dyspnea, cough, impaired oxygenation, leukocytosis	Dyspnea, chronic cough, recurrent bouts of purulent bronchitis	Dyspnea
Chest radiograph	Alveolar or interstitial opacities, pleural effusions	Clear lung fields (may show hyperinflation)	Persistent pulmonary opacities, most commonly upper lobe fibrosis and associated pleural thickening
High-resolution CT	Ground-glass or alveolar opacities, interlobular septal thickening	Tree-in-bud opacities, bronchiectasis, air trapping	Upper lobe fibrosis, pleural thickening, ground glass opacities
Pulmonary function testing	Proportional decline in FEV_1 and FVC	Disproportionate decline in FEV_1 with obstructive pattern	Decline in FEV_1 and TLC with a restrictive pattern
Yield of transbronchial biopsy	High	Low	Low
Treatment	High-dose corticosteroids	Azithromycin, retransplantation	Retransplantation; outcomes inferior to retransplant for BOS
Outcome	Favorable response to treatment	30–40% of patients demonstrate modest but often transient improvement in response to azithromycin; most patients ultimately experience progressive allograft dysfunction	Progressive allograft dysfunction

BOS, bronchiolitis obliterans syndrome; CMV, cytomegalovirus; CT, computed tomography; FEV_1, forced expiratory volume in 1 second; FVC, forced vital capacity; TLC, total lung capacity.

instability ensue. Most reported cases have resulted in death, but survival was reported in a patient managed with a combination of plasmapheresis, antithymocyte globulin, and cyclophosphamide.[147,148] Routine screening of all lung transplant candidates for preformed anti-HLA antibodies and avoidance of donors with the targeted antigens have proved to be highly effective in minimizing the risk of hyperacute rejection.

Acute Cellular Rejection

Acute cellular rejection is a T cell–mediated alloimmune process that principally targets the vascular component of the allograft and, to a lesser extent, the airways. Approximately one-quarter of transplant recipients experience an episode of acute cellular rejection requiring treatment within the first year after transplantation.[1] Beyond this initial period, the incidence of acute cellular rejection declines considerably. Risk factors for development of acute rejection remain poorly defined. Data are conflicting on whether the degree of HLA discordance between donor and recipient represents a risk factor.[58,149,150] Polymorphisms in toll-like receptor 4 that down-regulate recipient innate immune responsiveness are associated with a lower incidence of acute cellular rejection.[149]

Episodes of acute cellular rejection may be clinically silent in up to 40% of cases.[58] When present, clinical manifestations are nonspecific and include malaise, low-grade fever, dyspnea, cough, and leukocytosis. Radiographic opacities (eFig. 140.2), a decline in arterial oxygenation at rest or with exercise, and an abrupt fall of greater than 10% in spirometric values are important clues to the possible presence of rejection, but similar findings accompany bouts of infection.

Reliance on clinical and radiographic criteria alone runs the risk of misdiagnosis and needless augmentation of immunosuppression. Transbronchial lung biopsy represents the gold standard for diagnosis of acute cellular rejection, although its accuracy is less than ideal.[151] The procedure is safe, can be performed in serial fashion over time, and has a reasonable sensitivity and specificity. The histologic hallmark is the presence of perivascular lymphocytic infiltrates that, in more severe cases, spill over into the adjacent interstitium and alveolar air spaces. Lymphocytic bronchiolitis may accompany the parenchymal involvement or may be an independent feature. A histologic classification system has been adopted to grade the severity of acute cellular rejection (Table 140.6).[152]

Conventional treatment consists of a 3-day pulse of intravenous methylprednisolone at a daily dose of 5 to 15 mg/kg. In most cases, this results in rapid improvement in symptoms, pulmonary function, and radiographic abnormalities, but follow-up biopsies show histologic evidence of persistent rejection in 30% of patients with prior mild (A2) acute rejection and in 44% of patients with prior moderate (A3) acute rejection.[153] Asymptomatic and functionally stable patients with minimal (A1) rejection are often observed without treatment, but data demonstrating progression to a higher grade of acute rejection in one-quarter of cases and an increased risk of developing CLAD have challenged this approach.[154] Various modalities have been used for refractory or recurrent acute rejection, including antilymphocyte antibody preparations and extracorporeal photopheresis.

Acute Antibody-Mediated Rejection

There is emerging evidence in support of a second form of acute rejection, mediated by donor-specific anti-HLA alloantibodies most commonly to class II HLA but also to non-HLA epitopes. The clinical presentation is indistinguishable from that of acute cellular rejection, with dyspnea, hypoxemia, and diffuse radiographic opacities. The suggested diagnostic criteria for "definite" acute antibody-mediated rejection are as follows: (1) presence of circulating donor-specific anti-HLA antibodies, (2) clinical evidence of allograft dysfunction defined by functional (pulmonary function testing, oxygenation) and/or radiographic criteria, (3) compatible histopathologic features (e.g., neutrophilic capillaritis, diffuse alveolar damage), and (4) detection of C4d deposition along endothelial cell basement membrane.[155] Cases meeting all criteria except C4d deposition are considered "probable," but evidence suggests that the clinical presentation and outcomes are identical to those in patients with positive staining results.[156] Treatment focuses on rapid removal of the culprit antibody with plasmapheresis and inhibition of new antibody production with a combination of intravenous immunoglobulin and rituximab. Although most patients improve in response to this treatment, many go on to develop chronic allograft dysfunction. Prognosis appears more favorable for patients who successfully clear the circulating donor-specific anti-HLA antibodies.[156]

Bronchiolitis Obliterans Syndrome (See Chapter 72)

Bronchiolitis obliterans is the most common cause of CLAD and represents the major impediment to long-term graft and patient survival. Bronchiolitis obliterans is a fibroproliferative process characterized by submucosal inflammation and fibrosis of the bronchiolar walls that ultimately leads to complete obliteration of the airway lumen. The functional consequence of this process is progressive and largely irreversible airflow obstruction. Because the characteristic

Table 140.6 Histologic Grading System for Acute Cellular Rejection

Grade	Description
A0 (none)	Normal pulmonary parenchyma
A1 (minimal)	Scattered, infrequent perivascular mononuclear infiltrates
A2 (mild)	Frequent perivascular mononuclear infiltrates surrounding venules and arterioles; readily recognizable at low magnification
A3 (moderate)	Easily recognizable cuffing of venules and arterioles by dense perivascular mononuclear cell infiltrates, with extension of the inflammatory cell infiltrate into perivascular and peribronchiolar alveolar septa and air spaces
A4 (severe)	Diffuse perivascular, interstitial, and air space infiltrates of mononuclear cells with prominent alveolar pneumocyte damage and endothelialitis

From Stewart S, Fishbein MC, Snell GI, et al. Revision of the 1996 working formulation for the standardization of nomenclature in the diagnosis of lung rejection. *J Heart Lung Transplant*. 2007;26:1229–1242.

histologic features are difficult to demonstrate by transbronchial lung biopsy, FEV_1 has been adopted as a diagnostic surrogate for histology, and the term *bronchiolitis obliterans syndrome* (BOS) has been applied to this functionally defined disorder. BOS is defined as an otherwise unexplained and sustained fall in FEV_1 by at least 20% from posttransplant baseline. Approximately 50% of transplant recipients develop BOS by 5 years and 75% by 10 years.[157]

Acute cellular rejection and lymphocytic bronchiolitis have been consistently identified as major risk factors for development of BOS, findings supporting the view that BOS is a consequence of alloimmune injury.[158,159] Whereas the risk of BOS appears to correlate with the severity and frequency of these immunologic insults, even minimal (A1) acute rejection is associated with an increased risk.[154,160] Other possible immune-mediated risk factors include the presence of anti-HLA antibodies (particularly de novo donor-specific anti-HLA antibodies) and the development of anti–type V collagen antibodies.[161,162] Nonimmune factors may also be important in initiating or perpetuating injury, thus suggesting that BOS may represent the end result of a wide array of insults to the airway epithelium. These factors include CMV pneumonitis, community respiratory viral infections, airway colonization with *Aspergillus* or *Pseudomonas,* PGD, and gastroesophageal reflux with occult aspiration.[102,159,163–167]

Although often viewed as a late complication, BOS manifests within the first 2 years after transplantation in one-third to one-half of cases (early-onset BOS).[168,169] The decline in FEV_1 that heralds the onset of BOS may be either insidious or abrupt. Dyspnea, weight loss, cough, and recurrent bouts of purulent tracheobronchitis, with recovery of *P. aeruginosa* from sputum cultures, are characteristic clinical features. Although chest radiographs are usually unremarkable, high-resolution computed tomography commonly reveals air trapping (Fig. 140.5, eFig. 140.3, and Videos 140.2 and 140.3), tree-in-bud opacities, and/or bronchiectasis. The natural history of BOS is highly variable; patients with early or abrupt onset generally experience more rapid decline in lung function and higher mortality.[168,169] Median survival from diagnosis is 1.5 years and 2.5 years for those with early-onset and late-onset BOS, respectively.[168]

In the past, BOS was treated by augmenting immunosuppression, but this approach has not proved to be effective.[170] Use of azithromycin subsequently garnered interest based on its anti-inflammatory properties and its demonstrated benefit in treating other airway disorders. Several retrospective studies and one small prospective, randomized placebo-controlled trial documented short-term improvement in the FEV_1 in approximately 30–40% of patients with BOS who were treated with this agent.[171–174]Although still controversial, performance of surgical gastric fundoplication to control gastroesophageal reflux has been associated with improvement in lung function in some patients with BOS.[170,175] At this time, the only definitive treatment for advanced BOS is retransplantation.

The development of strategies to prevent BOS is an area of intense research, but to date there has been little substantive progress. In recognition of the established link between acute rejection and BOS, most transplant centers routinely perform surveillance lung biopsies to detect and treat clinically silent acute rejection, but the impact of this strategy on risk of BOS remains uncertain.[176] Early identification of recipients with gastroesophageal reflux and aggressive correction with fundoplication may delay or prevent onset of BOS, but this remains a controversial strategy.[177] A small, single-center, randomized placebo-controlled trial demonstrated that the prophylactic administration of azithromycin after transplantation improved BOS-free survival, but larger multicenter studies will be required to corroborate these findings.[178] Finally, some centers have used a strategy to screen for donor-specific anti-HLA antibodies and, if detected, treat with intravenous immunoglobulin and rituximab in the hope of reducing the subsequent risk of developing BOS.[179]

Restrictive Allograft Syndrome

Approximately one-third of recipients develop a form of CLAD referred to as *restricted allograft syndrome* (RAS).[180–182] In contrast to BOS, RAS is characterized by restrictive physiology and is defined by a concomitant fall in FEV_1 of more than 20% and a decrease in total lung capacity greater than 10% compared with baseline values. Another distinguishing feature is the presence of persistent radiographic opacities that most characteristically appear as predominantly upper lobe fibrotic changes, often with associated pleural thickening (Fig. 140.6). The histologic

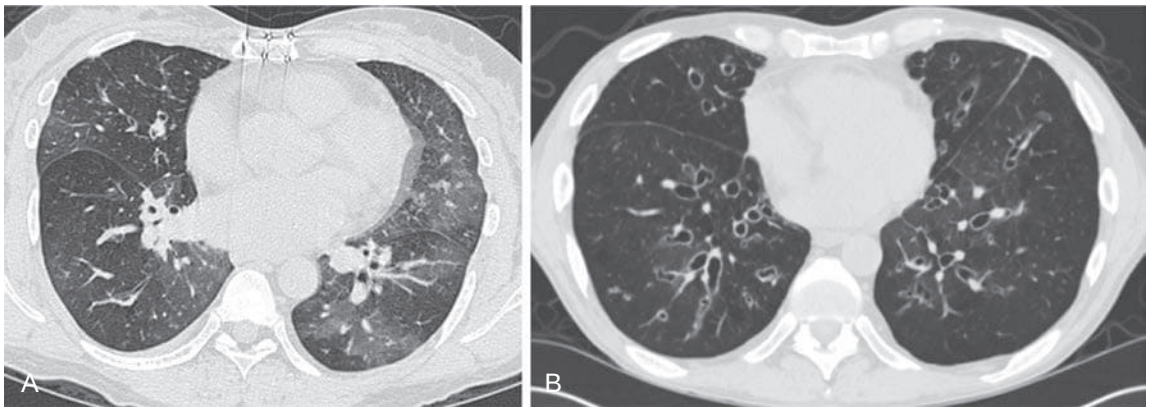

Fig. 140.5 Bronchiolitis obliterans syndrome. (A) High-resolution computed tomography image obtained during expiration demonstrates a mosaic attenuation pattern consistent with air trapping. (B) Image obtained from another patient with bronchiolitis obliterans syndrome demonstrates extensive bronchiectasis.

findings vary among published reports and include intra-alveolar and subpleural fibroelastosis, diffuse alveolar damage, nonspecific interstitial pneumonia, and acute fibrinoid organizing pneumonia. Survival is considerably worse than that associated with the more commonly encountered entity of BOS.[180]

POSTTRANSPLANTATION LYMPHOPROLIFERATIVE DISORDER

Posttransplant lymphoproliferative disorder (PTLD) describes a spectrum of abnormal proliferative responses involving B cells in the majority of cases and ranging from benign polyclonal hyperplasia to malignant lymphomas. In the majority of cases, *Epstein-Barr virus* (EBV) is the stimulus for B cell proliferation, which proceeds in an unchecked fashion because of the muted cytotoxic T cell response in the immunosuppressed host. EBV-naive recipients who acquire primary infection at the time of organ transplantation are at greatest risk of developing PTLD.[183]

The prevalence of PTLD in contemporary series is approximately 4–5% in adult lung transplant recipients.[184,185] The risk of developing PTLD is greatest within the first posttransplantation year, although up to one-half of all cases are seen beyond this point. Most early-onset cases involve the allograft and typically manifest as one or more pulmonary nodules that may be accompanied by mediastinal adenopathy (Fig. 140.7).[184,186] In contrast, beyond the first year, intra-abdominal and disseminated forms of disease predominate.

The diagnosis of PTLD is most firmly established by tissue biopsy. Care must be exercised when interpreting transbronchial lung biopsies because the aggregates of lymphocytes associated with acute cellular rejection can resemble foci of PTLD on these small tissue specimens. Diagnosis is aided by demonstration of the presence of EBV-infected cells by in situ hybridization or immunohistochemical staining. Determination of EBV-associated nuclear antigen viral load in the peripheral blood by using DNA amplification techniques has been touted as an ancillary diagnostic tool. One study of adult lung transplant recipients reported a sensitivity of 77% and specificity of 100% for a plasma EBV-associated nuclear antigen polymerase chain reaction assay.[187] However, additional studies using standardized assay techniques and threshold values for positive results are required before conclusions can be drawn about the diagnostic utility of viral load testing.

The initial therapeutic approach to PTLD involves reduction in the magnitude of immunosuppression to permit partial restoration of host cellular immunity against EBV. This may be sufficient to cause regression of tumor in mild cases, but patients with more advanced or rapidly progressive disease should be treated with rituximab (after confirmation that the tumor is CD20 positive). This agent is generally well tolerated and is associated with a complete response rate of 50–60%.[188,189] Patients with disease refractory to rituximab are treated with standard chemotherapy (cyclophosphamide, doxorubicin hydrochloride, vincristine sulfate, and prednisone regimen), although this is associated with considerable treatment-related morbidity and mortality.[188,190] There is no proven role for antiviral therapy in the setting of established PTLD.

LUNG CANCER

Lung cancers following lung transplantation arise predominantly in the native lung of SLT recipients with underlying COPD or pulmonary fibrosis, most of whom have had significant prior smoking histories.[191–195] The reported frequency of lung cancer following SLT is as high as 6.9%.[193] Data are conflicting on whether transplantation confers an increased likelihood of developing de novo lung cancer or whether the incidence is comparable with that of the general population with similar risk factors.[195] Less commonly, a previously unsuspected cancer may be incidentally detected in the explanted lung removed at the time of transplantation and may then recur in the allograft or in distant sites. Finally, there are rare reports of lung cancer of donor origin transmitted to the recipient.[196]

Lung cancer in the transplant recipient often progresses at a rapid pace, potentially leading to initial confusion with



Fig. 140.6 Restrictive allograft syndrome. Chest radiograph demonstrating upper lobe fibrosis and associated pleural thickening characteristic of restrictive allograft syndrome.

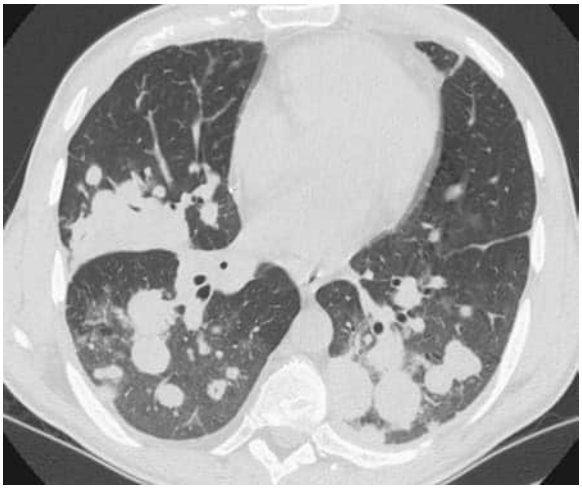

Fig. 140.7 Posttransplantation lymphoproliferative disorder. Computed tomography scan demonstrates multiple nodules and masses, proven on biopsy to represent high-grade B cell lymphoma. In situ hybridization studies revealed the presence of Epstein-Barr virus RNA.

an infectious process (eFig. 140.4).[191] This aggressive behavior may reflect loss of antitumor immune surveillance in the immunosuppressed host or may be caused by a more specific effect of calcineurin inhibitors in promoting tumor growth.[197] Overall prognosis is poor but should not preclude attempts at curative resection in the rare instances in which early-stage disease is encountered.

RECURRENCE OF PRIMARY DISEASE

Care reports and small case series describe recurrence of several primary disorders in the lung allograft.[198] Although accurate figures are not available, sarcoidosis appears to have the greatest propensity to do so. Recurrence of sarcoidosis is typically asymptomatic and marked by incidental recovery of noncaseating granulomas on transbronchial biopsy and occasionally by the presence of micronodular opacities in the upper lobes on computed tomography scan. Cases of recurrent lymphangioleiomyomatosis have also been reported. The abnormal smooth muscle cells found in the allograft are of recipient origin, a finding suggesting that the mechanism of recurrence involves migration or metastasis from an extrapulmonary site.[199] Other diseases for which recurrence has been reported include Langerhans cell histiocytosis, desquamative interstitial pneumonia, and hereditary pulmonary alveolar proteinosis. Recurrence of emphysema following transplantation for alpha$_1$-antitrypsin deficiency has been reported in the context of resumption of smoking.[200]

RETRANSPLANTATION

Outcomes following early retransplantation (within the first year) are poor.[98,201,202] This is particularly true for emergency retransplantation for primary graft dysfunction, and this practice is discouraged. In contrast, retransplantation in carefully selected patients with chronic graft failure caused by BOS results in acceptable survival rates, albeit inferior to those achieved with primary transplantation.[202,203] For unclear reasons, patients with restrictive CLAD appear to have poorer outcomes following retransplantation than do patients with BOS.[204]

The LAS system affords retransplantation candidates the same high priority as patients with idiopathic pulmonary fibrosis. This has led to shortened waiting times and to a doubling in the number of retransplantation procedures performed annually.[98]

For a discussion of the future directions in the field of lung transplantation, see ExpertConsult.com.

Key Points

- Lung transplantation is a therapeutic option for a broad spectrum of advanced disorders of the airways, lung parenchyma, and pulmonary vasculature. The most common indications are idiopathic pulmonary fibrosis, COPD, and cystic fibrosis.
- The lung allocation system now used in the United States takes into account both medical urgency (predicted 1-year survival without transplantation) and "net transplant benefit" (difference between predicted 1-year survival with versus without transplantation).
- The introduction of ex vivo lung perfusion has facilitated more precise assessment and reconditioning of marginal lungs before transplantation and successful use of organs that would previously have been discarded.
- Although there has been significant improvement in perioperative mortality, long-term outcomes have only modestly improved. Median survival following transplantation is 6.5 years.
- Common early complications include primary graft dysfunction, bronchial anastomotic dehiscence and stenosis, and bacterial pneumonia.
- Infection rates among lung transplant recipients are severalfold higher than among recipients of other solid organs, presumably because of exposure of the allograft to microorganisms by inhalation and aspiration and the higher level of immunosuppression used.
- Acute cellular rejection, characterized by perivascular lymphocytic infiltration, is commonly encountered in the first year. It usually responds to high-dose corticosteroid therapy but is a major risk factor for subsequent development of chronic lung allograft dysfunction.
- The major limitation to long-term allograft function and patient survival is chronic lung allograft dysfunction, caused in most cases by bronchiolitis obliterans syndrome and less commonly by restrictive allograft syndrome. Current therapeutic approaches to preventing and treating chronic lung allograft dysfunction are inadequate, leaving retransplantation in selected patients as the only effective means of addressing this complication.

Key Readings

Chambers DC, Cherikh WS, Goldfarb SB, et al. The International Thoracic Organ Transplant Registry of the International Society for Heart and Lung Transplantation: thirty-fifth adult lung and heart-lung transplantation report—2018. *J Heart Lung Transplant*. 2018;37:1169–1183.

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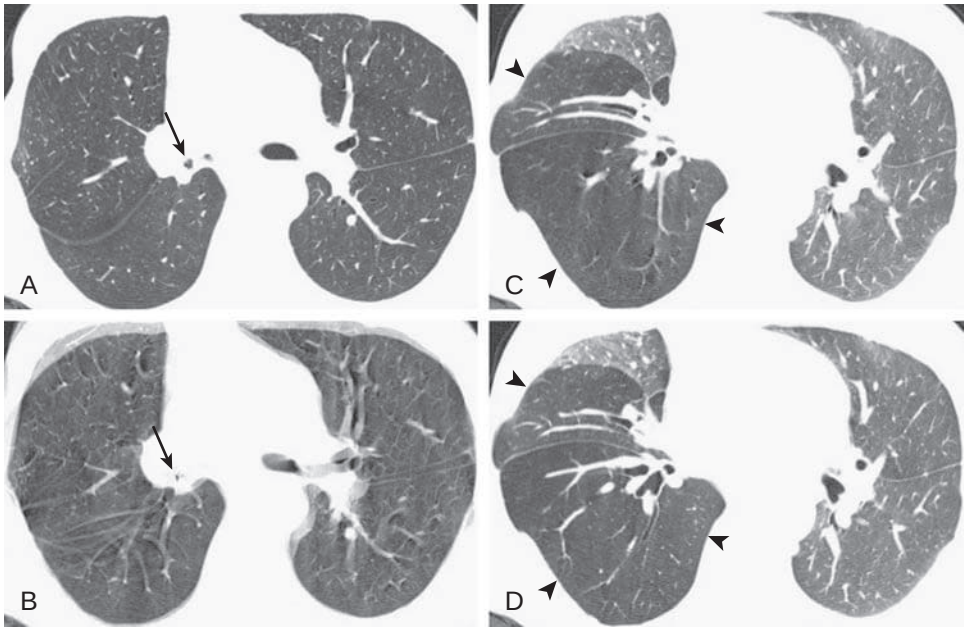
Complete reference list available at ExpertConsult.com.

FUTURE DIRECTIONS

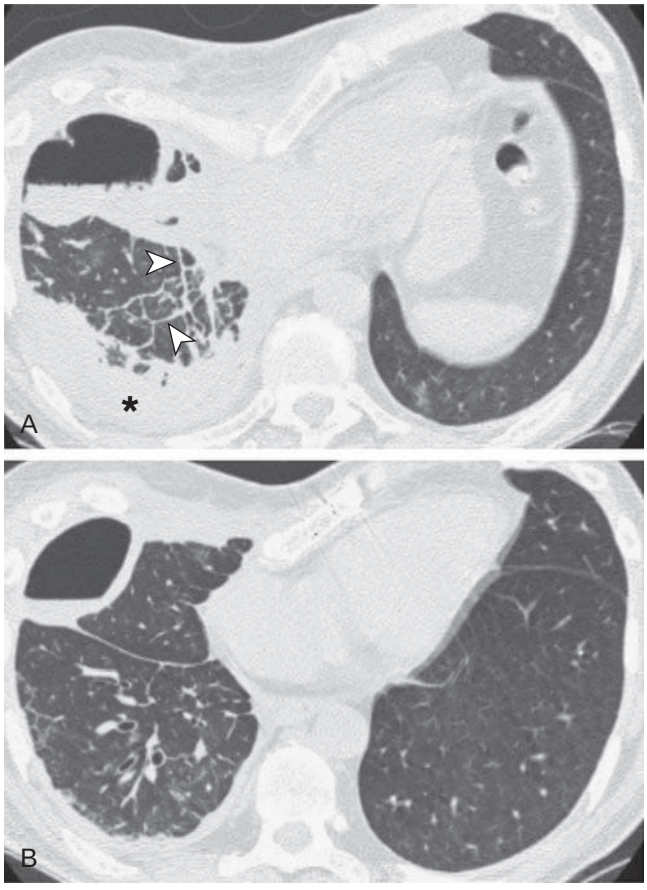
Since its introduction in 1963, lung transplantation has evolved from a heroic surgical therapy to a standard lifesaving therapeutic option for selected patients with advanced lung disease. Nonetheless, major hurdles must yet be overcome to facilitate wider applicability of lung transplantation and more enduring results. The donor organ supply must be expanded to meet demand. More effective and less toxic immunosuppressive strategies must be developed to prevent graft loss from chronic immunologic injury. An improved understanding of CLAD and its various subtypes is required to develop strategies to treat injuries of the transplanted lung in a targeted fashion.

Increased use of ex vivo lung perfusion for assessment and treatment has offered a partial solution to enhancing the number, quality, and durability of lung allografts. The ultimate solution to many of the current impediments will likely come with advances in gene therapy, stem cell therapy, and tissue engineering. Advances in immunologic manipulation of the recipient and immunologic modulation of the organs to look more like "self" will ultimately one day bring us closer to a state of immune tolerance (i.e., permanent graft acceptance in the absence of chronically administered immunosuppressive agents). It is only through these basic research initiatives that lung transplantation will truly fulfill its potential as a safe, effective, and durable treatment option.

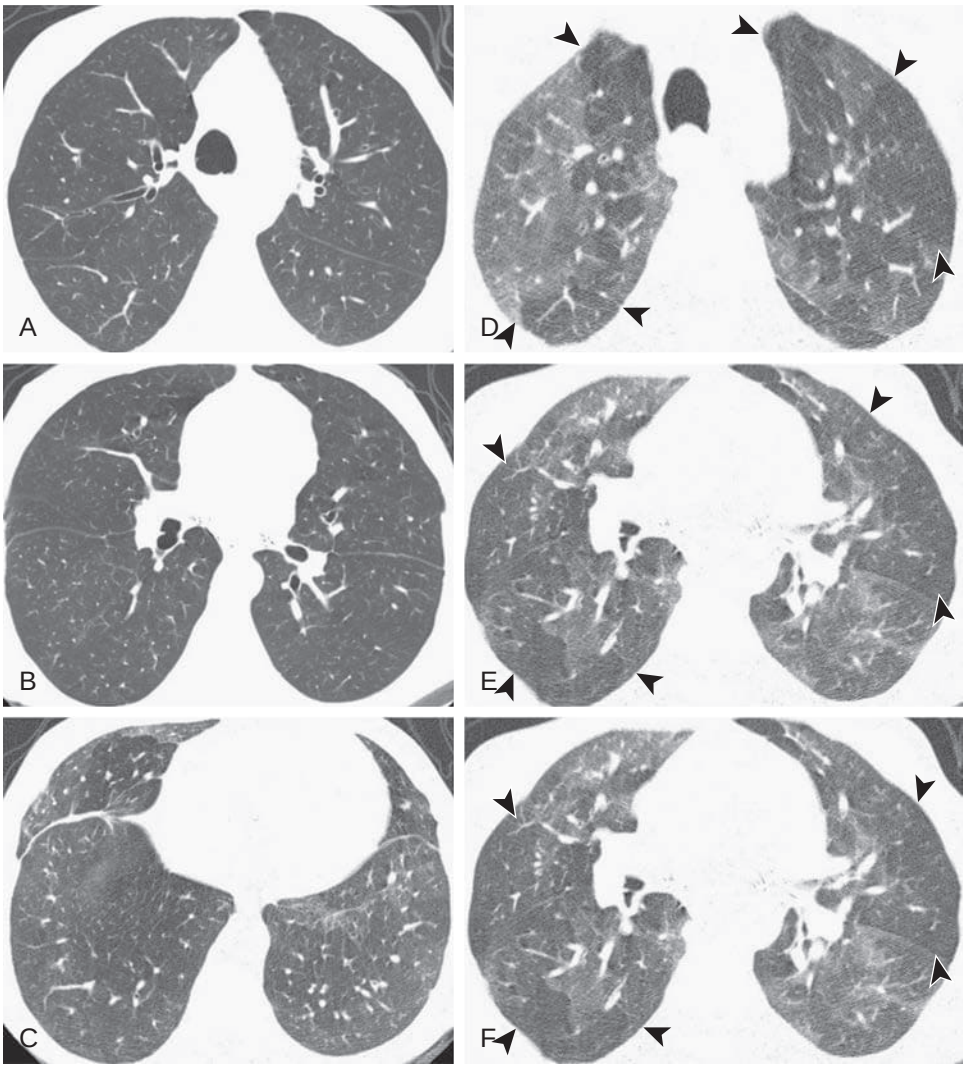
eFIGURE IMAGE GALLERY



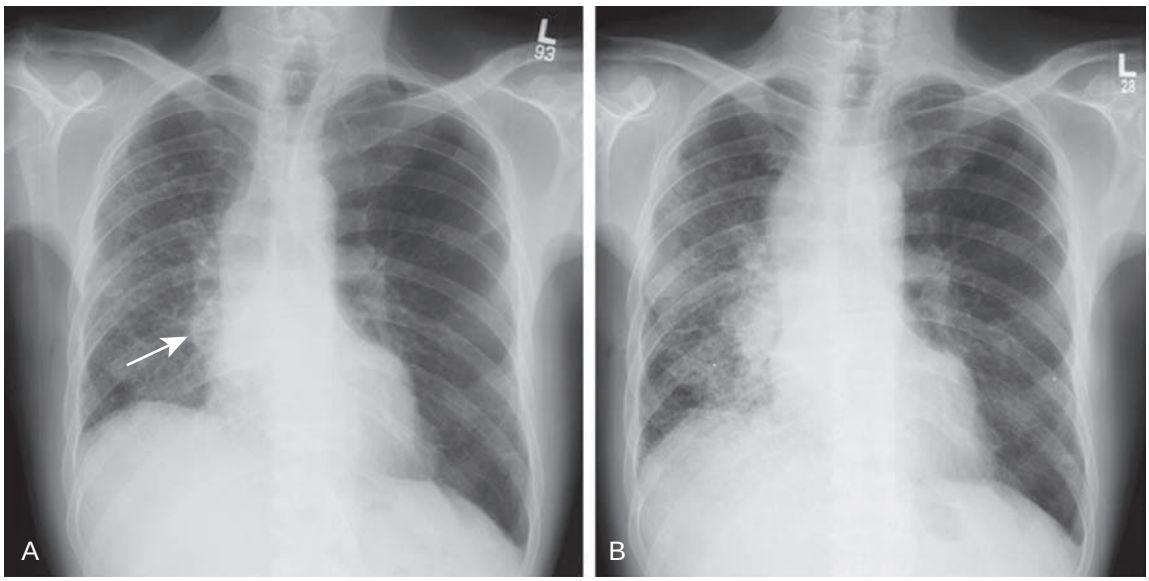
eFigure 140.1 Posttransplant ischemic anastomotic bronchostenosis. (A–D) Axial chest dynamic expiratory computed tomography (performed during a forced vital capacity maneuver) displayed in lung windows in a bilateral lung transplant recipient shows narrowing of the bronchus intermedius (*arrows*) associated with extensive hyperlucency and increased volume throughout the right lower lobe (*arrowheads*) that reflect air trapping in the lung subtended by the stenotic airway. (Courtesy Michael B. Gotway, MD.)



eFigure 140.2 Acute cellular rejection in a lung transplant recipient: high-resolution chest computed tomography findings. (A–B) Axial high-resolution computed tomography displayed in lung windows shows smooth interlobular septal thickening (*arrowheads*) in the transplanted right lung and right pleural effusion (*asterisk*) detected at the time of diagnosis of biopsy-proven acute cellular rejection; these findings are markedly reduced following augmentation of immunosuppression (B). The findings of interlobular septal thickening, volume loss, and pleural effusion are not specific for acute cellular rejection, although that diagnosis is uncommon when these high-resolution computed tomography findings are absent. (Courtesy Michael B. Gotway, MD.)



eFigure 140.3 Bronchiolitis obliterans syndrome: high-resolution computed tomography findings in a bilateral lung transplant recipient. (A–C and Video 140.2) Axial inspiratory high-resolution computed tomography shows minimal findings, with only slightly inhomogeneous lung opacity best seen in the bases (C). (D–F and Video 140.3) Axial dynamic expiratory high-resolution computed tomography (performed during a forced vital capacity maneuver) shows interval development of extensive, bilateral inhomogeneous lung opacity—the lighter regions reflect normal, collapsing lung at expiratory imaging, whereas the darker areas (*arrowheads*) represent air trapping resulting from small airway obstruction, reflecting bronchiolitis obliterans. (Courtesy Michael B. Gotway, MD.)



eFigure 140.4 Bronchogenic carcinoma arising in the native lung. The patient had undergone a left single lung transplant for idiopathic pulmonary fibrosis. (A) Chest radiograph demonstrates slight fullness in the infrahilar region of the native right lung (*arrow*). (B) Repeat chest radiograph only 2 months later demonstrates marked enlargement of the right infrahilar mass, as well as an increase in adjacent interstitial opacities. This proved to be a right lower lobe squamous cell lung cancer with associated lymphangitic spread.

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141 END-OF-LIFE CARE IN RESPIRATORY FAILURE

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INTRODUCTION

Patients with acute, chronic, and acute-on-chronic respiratory failure often have a high expected mortality and suffer from symptoms such as pain and dyspnea as their disease progresses and they approach the end of their life. These patients may receive aggressive life-extending treatments when they, their families, and their physicians believe that doing so is reasonable and consistent with the patient's treatment preferences. Alternatively, patients and their families (or surrogate decision makers) may elect to forgo life-sustaining therapies, such as mechanical ventilation, when the application of these therapies will not help the patient reach his or her goals of care. Similarly, therapies can also be withdrawn when a trial of intensive treatment fails to achieve their medical goals. When clinically appropriate, the withholding and withdrawal of life-sustaining therapy is supported by ethical and legal principles. These principles, along with the process of medical decision making and the desirable components of end-of-life care, are discussed in detail in this chapter.

PREDICTING THE OUTCOME OF RESPIRATORY FAILURE

The high prevalence of diseases that lead to respiratory failure, coupled with the morbidity and mortality they cause, has prompted clinicians and investigators alike to seek prognostic information about patients with these disorders. Prognostication is especially important when discussing end-of-life care with patients and their loved ones, but unfortunately remains imprecise.

For patients who are critically ill, there are well-known scoring systems that prognosticate mortality during the current hospital admission. Two examples of these scores are the *Acute Physiology and Chronic Health Evaluation* (APACHE) score, which has gone through four iterations,[1–4] and the *Simplified Acute Physiology Score* (SAPS), which has undergone two iterations.[5,6] Both of these scores include a host of physiologic and chronic illness variables, and perform well with areas under the receiver operating curve greater than 0.80. However, although both APACHE and SAPS are widely used in critical care research, their clinical use is less widespread.

In diseases leading to chronic respiratory failure, as in acute respiratory failure, scoring systems are also not commonly used for prognostication in a clinical context. In particular, COPD has a variable and unpredictable trajectory. Although multivariable disease severity scores, such as the *Global Initiative for Chronic Obstructive Lung Disease* (GOLD)[7] and BODE (*body mass index* [BMI], airflow obstruction, dyspnea, and exercise capacity),[8] improve mortality prediction, they do not predict mortality well in individual patients.[9–11] Two large systematic reviews from 2013[12] and 2017[11] investigated factors associated with mortality in patients with COPD. The first review included 189,772 patients hospitalized with an acute exacerbation of COPD and found that 12 factors were associated with death within 90 days (increasing age, male sex, low BMI, heart failure, chronic kidney disease, altered mental status, use of long-term oxygen therapy, lower extremity edema, GOLD stage 4, right heart failure, acidemia, and elevated plasma troponin). Another 9 factors, compared between survivors and nonsurvivors, were associated with increased death

within 2 years (increasing age, low BMI, heart failure, presence of diabetes, ischemic heart disease, malignancy, decreasing *forced expiratory volume in 1 second* (FEV_1), long-term oxygen therapy, and lower arterial Po_2 at the time of hospital admission).[12] The second systematic review aimed to identify indices and variables that predicted risk of death within 12 months in patients with COPD in the community (i.e., not after hospitalization).[11] Although some individual factors across indices predicted mortality (including FEV_1, BMI, patient-reported dyspnea, 6-minute walk distance, and history of prior severe exacerbations), this study concluded that "the quality of evidence remains low, such that no single variable or multivariable score can currently be recommended" for mortality prediction. See Chapter 63 for more information about prognosis in COPD.

As another example, *idiopathic pulmonary fibrosis* (IPF), also has an unpredictable course, with patients experiencing long periods of stability punctuated by occasional or repeated exacerbations with decompensation and even death.[13] Median survival in patients with IPF remains at 3 to 4 years after diagnosis; however, new antifibrotic therapies have been shown to delay progression of the disease. Although not yet clear, pooled data suggest that these agents may improve survival.[14,15] Many studies over the past decades have found that specific baseline and follow-up variables are associated with increased mortality in IPF, including sex, age, forced vital capacity, diffusing capacity for carbon monoxide, a decline in forced vital capacity greater than 10%, initiation of long-term oxygen, and acute exacerbation.[16–20] In addition, multivariable indices have been developed, including the Composite Physiologic Index,[21] Du Bois Prognostic Index,[17] and the GAP (Gender, Age, and Physiology) Index.[16] Similar to critical illness and COPD, these indices do not predict mortality well in individual patients, with one study finding that these scoring systems did not outperform diffusing capacity alone.[20] See Chapter 89 for more information about IPF prognosis.

Overall, prognostic scoring systems have contributed greatly to our understanding of the general outcomes of patients with respiratory failure and other conditions. Furthermore, the calibration and discriminatory power of the scoring indices may improve as more studies are performed and more patients are entered into scoring system databases. Yet, at present, the systems are imperfect in predicting outcome in an individual patient and, due to variability in disease course, these scores may never be able to predict mortality well in individuals. For the foreseeable future, therefore, the use of prognostic scoring systems should continue to be used as an aid alongside medical decision making to help in counseling patients and surrogates about the outcomes experienced by patients with similar severity of illness. However, scoring systems should not be used by themselves to decide who is destined to die despite intensive care or as the sole factor to determine whether to offer treatment or to declare a particular treatment inappropriate.

TREATMENT GOALS AT THE END OF LIFE

The limitations of prognostication are unfortunate because patients' and their families' predictions of prognosis largely determine their treatment preferences, just as physicians often base their recommendations to patients and families on their own prognostic estimates. Many patients with acute respiratory failure due to potentially reversible causes, as well as their families, generally prefer goals focused on rescue and life prolongation until death appears highly likely.[22] In contrast, patients with end-stage chronic lung diseases, such as COPD and lung cancer, often prefer care focused on maintaining comfort rather than on extending their lives.[23] These preferences appear to be related to patients' perceptions of how advanced their underlying conditions are. For example, hospitalized patients with lung cancer who thought they were going to live at least 6 months were more likely to favor life-sustaining treatment over comfort care than patients who thought they had at least a 10% chance of dying within the next 6 months.[24] Of course, the treatment goals of life prolongation and maintenance of comfort need not be mutually exclusive. Life support and symptom relief are often sought simultaneously.

The term *end-of-life care* is meant to encompass two processes. One, the withholding and withdrawal of life support, represents the tapering of life-sustaining interventions, such as pulmonary rehabilitation in the outpatient setting and mechanical ventilation in the *intensive care unit* (ICU).[25–28] The other, the administration of palliative treatment, applies to improving patient comfort by treating symptoms such as pain with analgesics, dyspnea with opiates, and anxiety with anxiolytics. Combining these two processes signifies that end-of-life care involves more than removing something—in this case, life-saving treatments—from patients. It also means giving something to patients—excellent ongoing care in the form of proper medical decision making; thoughtful communication; an appreciation of their needs and those of their families, physicians, and other caregivers; the use of an appropriate setting for death; and the management of pain, dyspnea, and other symptoms. This comprehensive and compassionate approach is what is meant by the expression "intensive caring at the end of life."[29]

WHERE AND HOW PATIENTS DIE

In less developed countries, most patients with respiratory failure who die do so at home, largely because they have limited access to hospitals and other institutional settings. In the United States and other developed nations, however, patients most often die outside the home, although the proportion of people dying at home has increased over the past 2 decades. For example, of the large cohort of hospitalized patients in the landmark 1995 *Study to Understand Prognosis and Preferences for Outcomes and Risks of Treatment* (SUPPORT), 47% died within 6 months of study enrollment, and 55% of these died during the enrollment hospitalization.[30] Of the patients who survived the enrollment hospitalization, 46% died during another hospitalization later that year, and only a minority died in a nursing home or hospice, let alone at home.[31] Similarly, in one investigation of all the deaths recorded in six states during 1999, 38% of patients died in hospitals, and 22% died after ICU admission.[32] Ten years later, a 2009 study concluded that 540,000—fully one-fifth—of all patients who die in the United States do so in ICUs each year.[33] More recently, a

subsequent study analyzed trends in U.S. deaths over 15 years and concluded that, in 2015, compared with 2000, the proportion of deaths happening in hospital decreased from 32.6–19.8%, and deaths at home increased from 30.7–40.1%.[34] However, even though more people seem to be dying at home, this same study found that use of the ICU in the last 30 days of life among decedents increased from 24.3% in 2000 to 29.0% in 2015.

Many factors account for the high prevalence of in-hospital and in-ICU deaths in the United States and, presumably, other developed countries. Among them are the availability of these facilities and the fact that, compared with other countries, fewer elderly persons still reside with their families. In addition, in the United States, patients must be determined to have less than 6 months to live to qualify for hospice care. This requirement, in light of the difficulty of predicting life expectancy, may help explain why hospice has been underutilized.[35]

When ICUs were first developed during the 1950s and 1960s in the United States and Europe, patients who died in them did so despite full support, including attempted *cardiopulmonary resuscitation* (CPR). The wishes of patients and their surrogates regarding such support rarely were solicited, and do-not-resuscitate orders were seldom written for the patients because most hospitals felt obligated to perform CPR on everyone. Indeed, a host of potentially restorative treatments were automatically provided with little concern about their effectiveness or desirability. This approach was based on the belief, then held by both health professionals and the public, that technologies should be used to preserve life whenever possible regardless of the human and economic costs.[36]

In subsequent decades, however, this technologic imperative (providers using advanced technologies to do everything possible to extend life) seems to be giving way to a more patient-centered approach in which the appropriateness of certain treatments is based on an individualized assessment of the likely burdens and benefits. In the 1980s and 1990s, it became clear that many patients do not prefer attempted restorative therapy in all instances, and courts in the United States declared that these patients have a right to refuse them.[37] The ethical, legal, and economic consensus resulting from these developments was subsequently reflected in a series of statements from professional societies[38–43] on the appropriateness of forgoing life-sustaining therapies at the end of life. As a result, although hospitalized patients once died despite attempted restorative treatment, for the past 20 to 30 years, they are more likely to die upon withholding and withdrawal of life support and the administration of palliative care, especially in the ICU.[27,28,44]

ETHICAL AND LEGAL JUSTIFICATION FOR END-OF-LIFE CARE

JUSTIFICATION FOR WITHHOLDING AND WITHDRAWING LIFE-SUSTAINING THERAPY: A HISTORY

The withholding and withdrawal of life support is justified by four ethical principles[45] (Table 141.1). The first principle is *beneficence*: the physicians' obligation to do good for patients. Relieving pain and suffering, rather than sustaining life at all costs, may be beneficent in certain situations. The second principle is *nonmaleficence*: the physicians' obligation to avoid harm. Life-sustaining interventions may be painful and unlikely to sustain life in a way judged meaningful by the patient, and forgoing such interventions may reduce harm. The third principle is *autonomy*: respect for the patients' right of self-determination. Patient autonomy is reinforced when patients are allowed to refuse unwanted life-sustaining therapies. The fourth principle is *justice*: the fair allocation of medical resources. Justice may be served if life support is withdrawn from one patient with a very poor prognosis to help another patient with a much better prognosis, such as during a mass casualty event or a pandemic.[46]

Table 141.1 Ethical (Worldwide) and Legal (United States) Principles for Withholding and Withdrawing Life-Sustaining Therapy

ETHICAL PRINCIPLES
Beneficence
Nonmaleficence
Autonomy
Justice
LEGAL PRINCIPLES: RIGHT OF INFORMED CONSENT AND REFUSAL
Exercised by patients with decision-making capacity
Exercised by family members for incapacitated patients
■ As authorized under proxy directives
■ Using a substituted-judgment standard (facilitated by instructional directives)
■ Using a best-interests standard
Exercised by a court-appointed conservator
■ Using a substituted-judgment standard (facilitated by instructional directives)
■ Using a best-interests standard
Exercised by physicians, often after ethics committee review
■ Using a substituted-judgment standard (facilitated by instructional directives) (legal justification in a few states)
■ Using a best-interests standard (no legal justification)

From Beauchamp TL, Childress JF, eds. *Principles of Biomedical Ethics*. 4th ed. Oxford, UK: Oxford University Press; 1994; and Luce JM, Alpers A. End-of-life care: what do the American courts say? *Crit Care Med*. 2001;29:N40–N45.

In the United States, the withholding and withdrawal of life-sustaining therapies is justified legally by the principles of informed consent and refusal, which have strong roots in common law.[47] The right of adults with decision-making capacity either to consent to or refuse treatment, the legal right of surrogates to act for incapacitated adult patients, and the standards of substituted judgment (through which surrogates make inferences about what treatment decisions patients *would* make if they were able to make decisions for themselves) and best interests (surrogates also may consider the patients' best interests) have been upheld in U.S. court cases for more than a century. Selected landmark cases and their rulings are summarized in Table 141.2, and their principles are now considered standard in end-of-life care.

Respect for patient autonomy was supported by the U.S. Congress with the passing of the Patient Self-Determination Act in 1990. This statute mandates that patients admitted to medical facilities be asked whether they have advance

Table 141.2 Selected United States Court Cases Establishing Right of Refusal, Right of Surrogate Decision Making, and Standards of Substituted Judgment

Principle	Case	Year	Ruling
Right of adults with capacity to consent to or refuse	*Schloendorff v. Society of New York Hospitals*[151]	1914	"Every being of adult years and sound mind has the right to determine what should be done with his own body; and a surgeon who performs an operation without his patient's consent commits an assault, for which he is liable in damages, except in cases of emergency when the patient is unconscious or when it is necessary to operate before consent can be obtained."
	Bartling v. Superior Court[76]	1984	Allowed a man with advanced COPD to have a mechanical ventilator removed against the wishes of both his physicians and the hospital.
	Bouvia v. Superior Court[77]	1986	Ordered a hospital to stop force-feeding a quadriplegic woman against her will even though she might die in the process.
Legal right of surrogates to act for incapacitated adult patients	*In re Quinlan*[78]	1976	Allowed the parents of a vegetative patient to refuse mechanical ventilation through the mechanism of surrogate decision making.
	Barber v. Superior Court[152]	1983	Allowed that not only mechanical ventilation but also nutrition and hydration—indeed, any therapy that was not clearly benefiting the patient—could be forgone.
	Cruzan v. Director, Missouri Department of Health[153]	1990	Allowed states to require "clear and convincing evidence" of patients' prior wishes before care was forgone, but did not require states to do so. Accepted the argument that the right of adult patients with decision-making capacity to refuse any and all therapies was protected under the Constitution.
Standards of substituted judgment and best interests	*In re Conroy*[154]	1983	A nephew asked that a feeding tube be withdrawn from his elderly aunt, who had not declared her wishes before becoming demented, on the grounds that forgoing nutrition and hydration was in her best interest. The court allowed the best-interests standard in this case because the burdens of continuing the patient's life outweighed the benefits and because the recurring, unavoidable pain of life with treatment was such that administering therapies such as nutrition and hydration was inhumane.
	Wendland v. Wendland[155]	2001	California Supreme Court deliberated on the issue of whether a conservator could withhold or withdraw life support from a patient who was conscious but incapable of articulating his/her current wishes. The Court ultimately ruled that life support could be discontinued only if there was clear and convincing evidence that "the patient wished to refuse life-sustaining treatment or that to withhold such treatment would have been in his best interest." The decision in this case suggests that the courts are unlikely to allow surrogates to limit treatment in patients who are neither terminally ill nor permanently unconscious unless the patients have specified what they would want done in such a situation.

directives and, if directives are not already in place, that patients be assisted in creating them.[48] Advance directives are of two types: instructional directives stating what patients want done in a given situation (e.g., living wills) and proxy directives that appoint surrogates to make decisions for them in these situations (e.g., the durable power of attorney for health care). Even though these documents can potentially extend patient autonomy beyond the point of incapacity, they are fraught with well-documented shortcomings, including (1) lack of detailed directions due to nonspecific language of the documents, (2) misalignment with patient wishes over time if the wishes change, (3) potential to be "overridden" by surrogate decision makers who face very difficult decisions when their loved ones become incapacitated, and (4) lack of access by first responders so that wishes can be appropriately communicated and followed during an emergency.[49–52] Furthermore, the paradigm of advance directives has shifted away from the mere completion of the document to the process of advance care planning, which involves conversations between patients, their surrogates, and their physicians about goals of care, which often are revisited over time as the patient's condition changes.[53] To address some of the problems associated with advance directives, many states have authorized use of a *physician/provider order for life-sustaining therapy* (POLST) form (eFig. 141.1), sometimes called a MOLST (medical) or COLST (clinician) form. These orders are enacted after conversations between patients (and their loved ones) and clinicians and generally include sections pertaining to preferences for CPR in the event of cardiac or respiratory arrest; therapies applied during events short of arrest but when life support might be needed (e.g., mechanical ventilation during a severe COPD exacerbation); and additional treatments, such as transportation to a hospital, artificial nutrition, or antibiotic therapy. Once signed, the POLST form is kept on file by the signing clinician and nearby hospitals, and a copy is placed on the patient's refrigerator in the home so

first responders can immediately understand preferences for life support. One particular advantage of a POLST form over an advance directive is that the POLST is an order from a licensed medical provider and therefore can be used by emergency personnel, whereas an advance directive may not be sufficient to avoid invasive treatment by first responders called to a home.

Legal guidelines are less clear when incapacitated patients lack family members or other surrogates, and controversy exists over how to make medical treatment decisions for these patients, who are often termed "unrepresented."[54,55] Such patients may have an advance directive, but because advance directives are not a medical order, decisions still need to be made and carried out by someone. Some states allow physicians to make decisions for such patients on the basis of wishes expressed to the physicians when the patients had decision-making capacity. However, no state explicitly allows physicians to make decisions on the basis of a best-interests standard. Be that as it may, as shown in a study from seven U.S. medical centers, some physicians do make decisions to withhold or withdraw life-sustaining therapy from incapacitated patients on the basis of best interests, usually after consultation with their colleagues or with a hospital ethics committee.[56] Other physicians ask the probate court to appoint conservators or other advocates for the patients, presumably to ensure a fair, transparent, and deliberate process of decision making for these vulnerable patients. Fortunately, a 2020 joint statement from the *American Thoracic Society* (ATS) and American Geriatrics Society specifically addresses medical decision making in unrepresented patients and provides guidance for institutions on (1) offering advance care planning to prevent a patient from becoming unrepresented; (2) implementing strategies, such as capacity assessment and exhaustive searches for surrogates, to determine if patients thought to be unrepresented may actually not be; (3) using a formal diverse interprofessional committee to manage decision making for unrepresented patients; (4) using the full gamut of available information on the patient's values and preferences to guide decisions; (5) managing decisions for unrepresented patients using a fair process; and (6) using this fair process even when state law allows less oversight.[57]

REQUESTS FOR NONBENEFICIAL TREATMENTS

A prominent ethical challenge, especially in critical care but also in pulmonary medicine, is how to respond appropriately to requests from patients and surrogates for life-prolonging interventions that the clinician believes are nonbeneficial. Some treatments are physiologically futile in that they cannot accomplish the intended physiologic goal, for example, restoration of sentient life in a patient who is found apneic and pulseless with rigor mortis. More commonly, though, these cases are not so absolute.

Literature suggests that conflicts in these cases are not uncommon, including data that 25% of physicians in European ICUs reported providing treatments that they felt were nonbeneficial, and that 20% of patients in U.S. ICUs were felt by physicians to have received nonbeneficial therapies.[58,59] In past decades the term *futility* was used to describe these conflicts, and several publications in the 1990s from investigators and professional societies attempted to provide recommendations on how to define futility and manage such disputes.[39,42,43,60] However, these guidelines were often discordant, which led to confusion, and included arguments for futility that concealed the value-laden assumptions and underlying issue of rationing inherent in these disputes.[61] There is now general consensus that, rather than revolving around true physiologic futility (where physiologic goals cannot be achieved, such as the case of the patient with rigor mortis), these conflicts commonly involve value-laden judgments about the appropriateness of particular therapies in the setting of the patient's illness.[62]

A landmark 2015 joint multisociety statement from the ATS, American Association of Critical Care Nurses, American College of Chest Physicians, European Society of Intensive Care Medicine, and *Society of Critical Care Medicine* (SCCM) specifically addressed this issue by providing clear recommendations for preventing intractable conflicts and managing requests for potentially inappropriate treatments (Fig. 141.1).[63] These recommendations include (1) implementation of preventative strategies to avoid unresolvable treatment conflicts, including early proactive communication; (2) use of the term "potentially inappropriate" rather than "futile," except in rare cases when the requested intervention is impossible to accomplish; (3) management of intractable conflicts (despite intensive communication and negotiation) by a fair conflict resolution process that includes hospital review, attempts to find an accepting provider at another institution, and external review of decisions; (4) procedural oversight when time pressures make each step of the recommendations infeasible; (5) public advocacy for policies and legislation about life-prolonging therapies.

JUSTIFICATION FOR ADMINISTERING PALLIATIVE CARE

Administering Medications for Symptom Relief During the Dying Process

The ethical and legal permissibility of providing medications for symptom management throughout the dying process has been outlined by two separate 1997 U.S. Supreme Court cases and is now the standard of care. The cases of *Washington v. Glucksberg*[64] and *Vacco v. Quill*[65] dealt with the constitutionality of laws prohibiting physician-assisted dying (see later for more information on this topic) in Washington and New York. Although the Court ruled that both states could prohibit assisted dying, the justices reasoned that this prohibition was justified because these states had no barriers preventing patients from receiving medications to relieve pain and suffering. Through this and other statements, a majority of the justices suggested that being free of pain while dying was a liberty interest protected under the Constitution.[66]

The Supreme Court distinguished assisted dying from palliative care in *Glucksberg* and *Vacco* by accepting the ethical principle of double effect. Under this rule, acts such as giving sedatives and analgesics that lead to morally good effects, such as the relief of suffering, are permissible even if they produce morally bad effects, such as the hastening of death, provided that only the good effect is intended. The morally bad effect may be foreseen

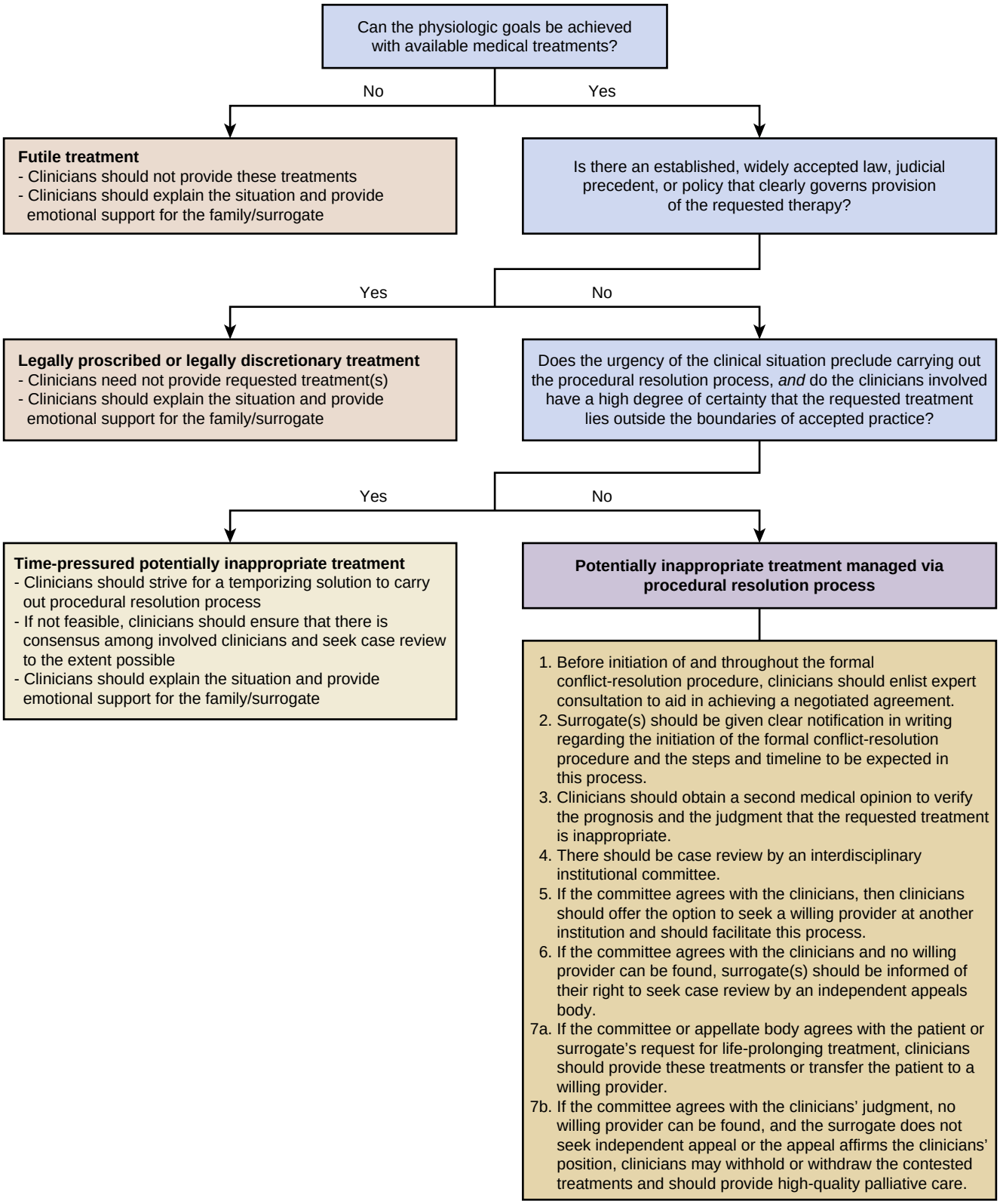

Figure 141.1 Recommended approach to managing requests for potentially inappropriate treatment. First, the clinician needs to determine if the desired physiologic goals can be achieved with available medical therapy. If yes, then the question arises whether the requested potentially inappropriate therapy is governed by a widely accepted law or precedent. The two kinds of relevant laws are (1) substantive laws that explicitly make it legal for clinicians to refuse to provide life-sustaining treatment (e.g., clinicians may refuse treatments in most U.S. states when a patient has been correctly determined to be brain dead because such patients are legally dead) and (2) procedural laws that, for example, grant clinicians authority to act as the surrogate rather than the family (e.g., in France the attending physician is the authorized decision maker for incapacitated patients). If governing laws or policies do not apply, then a series of steps to resolve the conflict over the disputed therapy (*bottom right*) should be taken. (From Bosslet GT, Pope TM, Rubenfeld GD, et al. An official ATS/AACN/ACCP/ESICM/ SCCM policy statement: responding to requests for potentially inappropriate treatments in intensive care units. *Am J Respir Crit Care Med.* 2015;191[11]:1318–1330.)

in that physicians are aware of its possibility and even its likelihood, but they may not wish it. The bad effect also may not be a means to the good effect, and the good effect must outweigh the bad one; that is, risking death is reasonable in palliating a terminally ill patient only if there are no less risky ways of relieving suffering.[67] The Supreme Court's approval of palliative care included sanctioning the practice of terminal sedation, in which patients are rendered unconscious while life-sustaining therapies, including nutrition and hydration, are withdrawn. Under *Vacco*, a state may allow terminal sedation if it is "based on informed consent and the double effect."[65]

Physician-Assisted Dying

Physician-assisted dying (PAD) refers to the practice by which heath care providers prescribe medication(s) to a patient knowing that they will be used to hasten death. PAD is currently legal in several countries including Canada, Belgium, Switzerland, the Netherlands, Luxembourg, Colombia, and Victoria, Australia. In the United States, the Supreme Court has addressed PAD in three cases. In the first two of these mentioned previously, *Washington v. Glucksberg*[64] and *Vacco v. Quill*[65] in 1997, the Court upheld the rights of states to prohibit PAD and stated that individuals do not have a constitutional right to PAD. The third case was prompted when PAD was legalized in Oregon in 1997 under that state's Death with Dignity Act. In 2006, the U.S. Supreme Court upheld a lower court decision preserving the legality of PAD in Oregon.[68]

PAD is now legal in a growing number of additional U.S. states (including Washington, Vermont, Montana, California, Colorado, Hawaii, New Jersey, and Maine) and Washington, DC. The initial Oregon statute included the following safeguards, with other states generally adopting the same principles: (1) The patient should be an adult 18 years or older; (2) the illness should be terminal with life expectancy of less than 6 months; (3) the patient should have decisional capacity; (4) the patient should undergo a mental health evaluation if impaired judgment is suspected; (5) the patient should make two oral requests with a waiting period between; (6) the patient should prepare a written request; (7) the medication should be administered by the patient; (8) the physician should provide information about other options, such as hospice and palliative care; (9) the physician should file a report with the state; and (10) there should be immunity from civil or criminal liability unless negligence or misconduct is identified. Some states also require certification by two physicians. eFigure 141.2 provides an example of the Physician Reporting Form that must be completed in Vermont.

Several publications have provided insight into how PAD is being used in the United States and throughout the world.[69–72] Few patients request lethal medications, and PAD-associated deaths represent a very small fraction of total deaths. Many patients who request PAD are also receiving hospice and/or palliative care. The most common underlying terminal illness is cancer, and patients report that their rationale for requesting PAD is concern about pain and loss of autonomy and control of bodily functions.[69-72]

MEDICAL DECISION MAKING AT THE END OF LIFE

THREE MODELS OF THE PHYSICIAN-PATIENT RELATIONSHIP

Medical decisions about value-laden choices may be made by physicians, patients, their families, or other surrogates alone or in combination. How decisions are actually made depends in large part on the preferences of patients and surrogates for their decision-making roles, which can range from independently making choices based on facts to ceding decision-making authority to clinicians.[73] There are three general models of decision-making: paternalistic, informed choice, and shared.[74]

Perhaps the oldest model is *paternalistic;* this model has also been called parental or priestly. According to it, physicians act as guardians in defining what their patients' interests are and then serving these interests as they see fit, with little or no input from the patients themselves.[75] The paternalistic model overlooks the strong social norm of respect for patient autonomy and the reality that, in pluralistic societies, it is unlikely that physicians can reliably discern what treatments best advance the interests of their diverse patients. However, some patients and surrogates prefer this model. The paternalistic model once dominated medical decision making at the end of life in the United States. In fact, the early cases such as *Bartling,*[76] *Bouvia,*[77] and *Quinlan*[78] (see Table 141.2) were brought because physicians and hospitals were unwilling to let patients or surrogates refuse therapy. It is ironic—and perhaps a cautionary tale about the limits of medical paternalism—that some physicians today demand that patients and families forgo treatment that other physicians once insisted they accept.

In the second model, *informed choice*, health care providers supply information about options to patients and their loved ones, who then independently use this information to arrive at decisions and choices about therapies.[79] Limitations of this model of decision making include that some patients and surrogates may not be able to comprehend the array of data necessary to make an informed choice, and they may feel particularly burdened by the process of making decisions in this manner.[80]

In the third model, *shared decision making* (SDM), physicians and patients/surrogates collaborate to help patients define their health-related values, discuss treatment options, and decide which alternative is best. This process is more than the mere passing of information: It is a moral deliberation, based on a mutual understanding of the medical facts and the patient's values.[81] The shared model of medical decision making is best suited for situations in which physicians, patients, and families have adequate time to deliberate, when reasonable treatment options exist, and when the best course of action may vary according to patients' values and preferences. Evidence from audio recordings of ICU family conferences suggests that the process of shared decision making about life support for incapacitated, critically ill patients is often suboptimal.[82] For example, clinicians frequently failed to explain principles of surrogate decision making, elicit patients' values and preferences, and discuss reasonable treatment options, including a purely palliative approach to care.[83–86]

There is general consensus among clinicians and policy makers that SDM should be the default approach to making treatment decisions with patients and surrogates, but confusion has surrounded its definition, use, and implementation. To provide clarification, guidance, and recommendations for SDM, the ATS and SCCM jointly published a statement in 2016 emphasizing the importance of patients and family engagement in ICUs.[73] This statement presented several recommendations about the use of SDM: (1) SDM is a collaboration between patients, surrogates, and clinicians to make health care decisions using not only the best available evidence but also the patient's values and goals; (2) SDM should be used when defining goals of care and when making major treatment decisions; (3) shared decisions should rely on three main elements: information exchange, deliberation, and making a treatment decision; (4) decision making approaches vary widely (from patient- or surrogate-directed to clinician-directed models), and providers should adapt the SDM process according to patient or surrogate preferences; and (5) providers should receive specific training in communication skills.

IMPORTANCE OF PHYSICIAN, PATIENT, AND FAMILY COMMUNICATION

Of course, American families would not need to be so involved in medical decision making in the ICU setting if physicians facilitated such decision making when the patients' diseases were less advanced and the patients could speak for themselves.[87] Yet, SUPPORT[88] and other subsequent studies[89,90] have shown that physicians and patients rarely discuss end-of-life issues in advance of the patients' deterioration, even when patients reside in nursing homes. A study of patients with severe COPD enrolled in pulmonary rehabilitation revealed that almost all had health concerns, including about being intubated, but only a minority had completed an advance directive describing their choices.[91] Furthermore, although the patients generally wanted discussions with their physicians, only 19% had such discussions, only 15% had discussed life support, and only 14% thought that their physicians understood their end-of-life wishes. In another study of advanced cancer patients, 63% of those who had an end-of-life discussion before death had that discussion as an inpatient.[90] And, in a study of patients with end-stage renal disease receiving dialysis, less than 10% reported having had an end-of-life care discussion with their nephrologist in the past year.[89]

The reasons that patients with chronic and terminal diseases do not discuss end-of-life care with their physicians have been studied since the 1990s. In the COPD pulmonary rehabilitation study noted earlier, patients who had not had discussions reported their own procrastination and their physicians not initiating the topic as the most important reasons for lack of conversations.[91] When these patients participated in an end-of-life educational intervention as part of their rehabilitation, they were more likely to pursue such discussions with their physicians and to complete durable powers of attorney for health care. In another study of patients with advanced acquired immunodeficiency syndrome, barriers to communication about end-of-life care included the patients noting that they did not "like talking about getting very sick" and "would rather concentrate on staying alive than talking about death."[92] Physicians who did not initiate discussions most often agreed that, "There is too little time during our appointments to discuss everything we should" and "I worry that discussing end-of-life with [patient name] will take away his or her hope." Many physicians in this study acknowledged that they felt uncomfortable discussing end-of-life issues, suggesting that their own discomfort was as important as the lack of time in inhibiting communication.

Limited communication between physicians and patients was also reported in SUPPORT.[88] Furthermore, SUPPORT revealed that communication was frequently inadequate between physicians and the families of critically ill patients. This finding was corroborated by a study from an ICU in France in which half the families of critically ill patients reported the same inadequacy.[93] The 2018 Royal College of Physicians report "Talking about dying: how to begin honest conversations about what lies ahead," further examined physicians discussing death and found prominent barriers in three categories: culture, confidence, and practicalities. Some physicians continue to believe that, within the culture of medicine, discussions about dying could be perceived by patients as failure. With regard to confidence, they felt that initiating these conversations was uncomfortable, that diagnostic uncertainty enhanced this discomfort, and that their training in communication skills had been inadequate. Finally, practical issues also impacted their willingness to discuss dying, and these included lack of time, cultural or religious differences, confusion over their role (for example, versus a primary care provider), and lack of privacy.[94]

Although many studies, including those discussed earlier, have demonstrated that communication about end-of-life issues is often inadequate, many other investigations have also reported that it is crucial for patient and family well-being. Families believe that timely and compassionate communication with a focus on a patient's values and goals is of key importance in patient care[95] and rate communication skills of their loved ones' clinicians as at least as important as clinical skills.[96] Improvement in family satisfaction with their relatives' care is associated with increased time spent by clinicians giving information,[97] more time by clinicians spent listening rather than speaking during conversations,[98] and specific content of these conversations, including assurances of non-abandonment and comfort, as well as support for family's decisions about end-of-life care.[99]

In a study where families were interviewed about their experiences in the ICU and about the decision-making process for withholding or withdrawing life support,[100] a high incidence of conflicts was reported, the vast majority of which were between themselves and physicians. The conflicts most often involved problems in communication or perceived unprofessional behavior, such as disregarding the primary caregiver in treatment decisions. These families identified pastoral care and prior discussion of treatment preferences as sources of psychological support. They appreciated lenient visiting hours and the availability of family conference rooms. Most of the families singled out attending physicians as the preferred source of information and reassurance.

IMPROVING COMMUNICATION AND THE QUALITY OF CARE AT THE END OF LIFE

Results from studies of various interventions to improve communication and quality of care at the end of life have been mixed, especially in those studies focusing on critical illness. Some interventions have been demonstrated to improve surrogates' satisfaction and psychological symptoms, as well as patient outcomes. These include (1) a family information leaflet that improved family understanding of how ICUs function and increased family satisfaction with ICU care[101]; (2) intensive communication achieved through proactive, frequent family meetings led by attending physicians that increased family satisfaction and decreased ICU length of stay among patients who died[102]; and (3) a brief communication intervention in French ICUs for families of patients judged certain to die that improved bereavement outcomes.[103] In a 2016 *randomized controlled trial* (RCT), communication facilitators assigned to families of critically ill patients reduced symptoms of depression among family members at 3 months, decreased ICU costs, and had no effect on ICU mortality.[104] In addition, although a 2018 cluster RCT of a multifaceted interprofessional ICU intervention, including advanced communication training for nurses, intensive support and communication for families, and implementation/quality improvement specialists to enhance incorporation of family support into clinician workflow, found no improvement in surrogates' psychological symptoms at 6 months after study enrollment, the intervention improved surrogates' perceptions of the patient-centeredness of care, and led to decreased ICU length of stay among both survivors and nonsurvivors.[105]

However, other studies have not found such improvements. Another RCT of family meetings with loved ones of chronically critically ill patients led by either palliative care specialists or intensivists did not improve the burden of anxiety or depression symptoms among surrogates.[106] Neither did another intervention consisting of a decision aid about prolonged mechanical ventilation.[107] Moreover, in an RCT comparing specific simulation-based training in communication skills for internal medicine and nurse practitioner trainees to usual education, there was no increase in the quality of communication about end-of-life care or in the quality of end-of-life care itself, and the simulation training was associated with increased symptoms of depression in patients.[108] In aggregate, the current literature suggests that purely informational interventions may not be effective at improving communication about and quality of end-of-life care, whereas interventions that incorporate longitudinal communication and emotional support may be more promising.

UNDERSTANDING WHAT PATIENTS, FAMILIES, AND CLINICIANS NEED AT THE END OF LIFE

End-of-life care could be optimized if the needs of the parties involved in the dying process were better understood.

Table 141.3 Factors Important to Patients and Family at End of Life

PHYSICAL NEEDS
Maintaining hygiene
Release from breathing difficulties
Remaining conscious and clearheaded to the end
Physical independence to the end
EMOTIONAL NEEDS
Regular update on medical condition
Opportunity to discuss fears and anxieties
Telling the absolute truth to patients
Involving patients in care policy and decisions
SPIRITUAL NEEDS
Being at one with God
Praying
Conversation with clergy about meaning of death
SOCIAL NEEDS
Capacity to help others

Modified from Natan MB, Garfinkel D, Shachar I. End-of-life needs as perceived by terminally ill older adult patients, family and staff. *Eur J Oncol Nurs*. 2010;14:299–303.

In this regard, a survey of seriously ill patients, recently bereaved families, physicians, and other caregivers revealed the needs important to all four groups, namely making decisions about treatment preferences, knowing what to expect about one's physical condition, and preparing for death.[109] Other important needs were sharing time with family and friends; being kept clean; being free of pain, anxiety, and dyspnea; and being treated as a "whole person." Patients also rated as important being mentally aware, coming to peace with God, not being a burden to their families, being able to help others, praying, having funeral arrangements planned, and gaining a sense of completion in life (Table 141.3).

The needs of families have also been assessed in several studies and were summarized in an overview[110] and emphasized in 2017 guidelines.[111] Overall, family needs include being with the dying patient, being helpful to the patient, being informed of the dying patient's changing condition, understanding what is being done to the patient and why, being assured of the patient's comfort, being comforted, having an opportunity to express emotions, being assured that the family's decisions were right, finding meaning in the patient's death, and having personal needs attended to during the dying process.

Unfortunately, the practical needs of clinicians who care for dying patients have not been well studied. Nevertheless, at a minimum, all caregivers probably need to feel comfortable during the dying process, to gain experience from it, and to feel supported by their colleagues and by their institutions. Nurses, respiratory therapists, social workers, and clergy who work alongside physicians want to know that the physicians respect them, provide them with adequate information, take their opinions into account, and engage in proper decision-making practices at the end of life.[112]

PROVIDING APPROPRIATE SETTINGS FOR DYING PATIENTS

Under the SDM model of the physician-patient relationship, physicians are obligated to help patients understand their conditions, explore their therapeutic options, and decide what is best for them. Essential to this relationship is preparing patients for death when appropriate. Such preparation should include consideration of whether the patients' interests are best served by hospital and ICU admission when death is imminent, assuming that impending death can be identified. Many patients, especially those with COPD and other chronic diseases that allow time for advance planning as death approaches, decide to die in a hospice or at home if given the opportunity.

Terminally ill patients may choose a trial of attempted restorative treatment in the hospital or undergo it because their wishes are not known. If the trial fails, such patients should be allowed to die in an environment comfortable for them and their families. A private room with enough space to accommodate visitors might be such an environment. Visiting hours should be relaxed, if necessary, to allow families and friends to spend as much time as they wish with dying patients. Some hospitals have separate palliative care units for this purpose. Others offer palliative care teams or services that consult throughout the hospital. Families of loved ones who are dying are also often offered private food and beverage carts.[112,113]

EMOTIONAL AND SPIRITUAL SUPPORT

Reviews of end-of-life care in and outside the ICU have emphasized the importance of providing emotional and spiritual support to dying patients and their families.[111,113] Physicians contribute to this support, of course, and their regular communications and presence at the bedside are deeply valued. Nurses, respiratory therapists, social workers, clergy, and other members of the health care team deliver most of the support, however. On occasion, patients or their families request that friends, caregivers, and religious persons from outside a particular institution provide consultations or participate in bedside rituals or observances. These should be allowed, if not encouraged, unless they interfere with patient care.

End-of-life care may extend after death, in that physicians, nurses, and others who have helped the patients' families when the patients were alive have much to offer thereafter. Advising on the disposition of bodies, reporting the results of autopsy studies, coordinating burials and funeral services, and attending funerals are among the professional responsibilities of caregivers greatly appreciated by families. These responsibilities can be assumed by independent bereavement follow-up services.[114] Alternatively, caregivers who have established personal relationships with families in the ICU and other settings may maintain them after the patients' death.

Physicians, nurses, and other caregivers have their own emotional and spiritual needs, as mentioned earlier, and caring for dying patients and their families exacts an appreciable toll on them. Although there is increasing attention to moral distress among clinicians, especially those working in ICUs, there have been no major breakthroughs in diagnosis, prevention, or treatment. Caregivers themselves should have opportunities to grieve. Conferences scheduled after patients die provide both an opportunity for bereavement and a mechanism for evaluating the processes of withholding and withdrawal of life support and of administering palliative care.[115,116] Such evaluation may lead to improvements in these processes for future patients.

SYMPTOM MANAGEMENT

WHY SYMPTOMS MAY BE POORLY MANAGED

Management of pain and other symptoms is a traditional role and responsibility of the medical profession. Nevertheless, patients too frequently die with pain and other distressing symptoms. Nearly 50% of SUPPORT patients or their surrogates interviewed after study enrollment reported that the patients experienced pain during hospitalization.[117] Nearly 15% reported extremely or moderately severe pain at least half the time, and many of those patients with pain were dissatisfied with its control. Uncontrolled pain was most common among patients with more dependence on others in activities of daily living and who had more comorbid conditions, more anxiety, more depression, and a poorer quality of life.[117] The prevalence of dyspnea, confusion, and mental health symptoms such as anxiety and depression is also high at the end of life.[118–120]

The poor management of pain and other symptoms in some patients is probably due in large part to the strong emphasis placed on the diagnosis and treatment of diseases rather than on the relief of symptoms. Palliative care reverses this emphasis and, when properly applied, should help increase patient comfort at the end of life. Nevertheless, the transition from restorative to palliative care is far from seamless for many patients. In this regard, it is difficult for patients and their families to know when to stop requesting treatment, just as it is for physicians and other caregivers to stop recommending life-sustaining therapies.

Pain and other symptoms may also be poorly managed because they are subjective experiences not easily assessed by objective methods. Pain and sedation scales have been developed to quantify the levels of pain and anxiety among patients who can communicate. Nevertheless, some patients cannot adequately communicate these sensations, either because they cannot find the words or because they are intubated and sedated. To detect pain in these patients, physicians and other caregivers must attend to patient grimacing and other admittedly nonspecific manifestations of pain, including tachycardia and hypertension. Although bispectral analysis of the electroencephalogram has been used to assess the level of sedation in ICU patients, the correlation of this technique with sedation scales and, most important, with the subjective experiences of patients is unclear.[121]

Another reason that symptoms are poorly managed at the end of life is that patients differ in their desire for symptom relief. Some patients value symptom relief highly and would prefer to be rendered unconscious rather than to experience pain, anxiety, or dyspnea, especially at the end of life. Others, however, would be willing to tolerate these

symptoms or have them mitigated only slightly to stay awake. Dying patients may find it difficult to titrate sedatives and analgesics to their desired level of consciousness, although they should be encouraged to do so. Physicians and caregivers may find it even more difficult to achieve the ideal level of sedation and analgesia for patients who cannot communicate or administer drugs to themselves.

Finally, symptoms may be inadequately managed because physicians and other caregivers feel uncomfortable about giving high doses of sedatives, analgesics, and other mood-altering agents. In some instances, this discomfort stems from a reluctance to cause drug addiction in dying patients, a concern irrelevant to the patients' condition. Other discomfort results from awareness that the agents may hasten death by depressing not only consciousness but also respiratory and cardiovascular function. That the U.S. Supreme Court has justified the administration of sedatives and analgesics under the principle of the double effect should help put caregivers at ease (see earlier for discussion of double effect).[67]

MANAGEMENT OF PAIN

Indirect approaches to pain control include nonpharmacologic means. For example, placing patients in a quiet environment where friends and family can visit may diminish the sense of pain, as may the proper treatment of anxiety and depression. Although respiratory depression due to drugs or underlying disease is usually undesirable in patients with COPD, the encephalopathy that results from the hypercapnia and hypoxia may be tolerated, if not favored, in terminally ill patients because it attenuates pain. Similarly, patients who forgo nutrition and hydration at the end of life may develop a euphoria that has been attributed to the release of endogenous opioids or the analgesic effects of ketosis.

Direct approaches to pain control generally center on the use of opioids, most commonly morphine. In addition to causing analgesia, morphine induces some degree of sedation, respiratory depression, constipation, urinary retention, nausea, and euphoria. It also produces vasodilation, which may cause hypotension, in part through the release of histamine. Fentanyl, a synthetic opioid approximately 100 times more potent than morphine, which has recently become a common and dangerous drug of abuse, does not release histamine and therefore causes less hypotension. Hydromorphone, a semisynthetic morphine derivative, is more sedating than morphine and produces little euphoria.[122–124]

Morphine, fentanyl, and hydromorphone can be administered orally, transcutaneously, subcutaneously, rectally, or intravenously. Opioids are usually given by the intravenous route to ICU patients, including those who are dying. These agents may be administered to inpatients and outpatients alike through the technique of patient-controlled analgesia. Long-acting oral preparations of morphine and hydromorphone are available for outpatients. Fentanyl can be administered orally in the form of a lollipop. It can also be given by the transcutaneous route (i.e., a patch), which makes this agent particularly suitable for patients who have difficulty with oral medications.

Opioids ideally should be administered in anticipation of pain and not afterwards. The optimal doses of these drugs given for pain relief are unknown and certainly vary among patients. Nevertheless, opioids generally should be started in relatively low doses, if respiratory depression and other side effects are to be avoided, and titrated upward until their analgesic effect is realized. In reports of critically ill patients undergoing the withholding and withdrawal of life support in both adult and pediatric ICUs, opioids were used in doses sufficient to achieve pain relief that caregivers considered adequate.[125,126] In dying patients, the use of opioids should not be limited by some arbitrary amount but by the balance between analgesia and any undesirable side effects.

MANAGEMENT OF ANXIETY

As in the case of pain, anxiety and its physical manifestation of agitation can be managed nonpharmacologically. If drugs are required, benzodiazepines and propofol are preferred. Benzodiazepines cause anterograde amnesia in addition to anxiolysis, and they exert a synergistic sedating effect with opioids. Benzodiazepines also cause hypotension and cardiac depression, especially when administered quickly and in high doses. Lorazepam, an intermediate-acting agent, can be given by the oral, intramuscular, or intravenous route; when given intravenously, it can be administered by bolus or by constant infusion. Midazolam, which is short-acting, is usually administered intravenously by constant infusion, although boluses may be required when therapy is initiated.[123,124,127]

Propofol is an intravenous general anesthetic agent with sedating, amnestic, and anxiolytic properties when administered in subanesthetic doses. In such doses, propofol is similar to midazolam in that it is usually given by constant infusion after bolus injection. The drugs are also comparable in the sedation they produce, although propofol has a greater propensity to cause hypotension.[123,124,127] Neither propofol nor midazolam is appropriate for the management of anxiety for outpatients and, in hospitals, their continuous use is usually restricted to the ICU.

MANAGEMENT OF DELIRIUM

Delirium may be mistaken for anxiety because it can also cause agitation. The distinction is clinically important both because the conditions are treated pharmacologically with different drugs and because the drugs used to treat anxiety can exacerbate delirium.[124] Delirious patients should be helped to obtain regular sleep, should be oriented regularly to their environment, and should avoid benzodiazepines, which cloud consciousness. Published guidelines for delirium management in critically ill patients recommend against the routine use of medications, except in patients experiencing significant distress from these symptoms.[124] Haloperidol was widely used in the past to treat delirium in critically ill patients, but it has undesirable side effects, including QT prolongation, rigidity, restlessness, and other dyskinesias. Due to these undesirable side effects, alternative agents such as risperidone, olanzapine, and quetiapine are more commonly used today but should be avoided if possible. These three medications are atypical antipsychotics, and side effects include somnolence, dizziness, movement problems, the rare neuroleptic malignant syndrome, and tardive dyskinesia. Olanzapine and quetiapine can also cause orthostatic hypotension.

MANAGEMENT OF DYSPNEA

Especially in the early stages of disease, dyspnea should be understood and managed according to its underlying pathophysiology. In patients with far-advanced lung disease, attention to pathophysiologic mechanisms is less important, and treatment is more palliative than restorative. Bronchodilators may not reduce breathlessness in such patients, corticosteroids may cause more unwanted side effects than symptom relief, and other therapies may likewise be ineffective. Patients with COPD who are dying, at home or in hospice, do not benefit from exercise training and may be too breathless to attend pulmonary rehabilitation programs; these patients should be encouraged to use wheelchairs and to rest.[128,129]

Patients with chronic respiratory failure of whatever cause should receive supplemental oxygen, which has been shown both to increase survival and to decrease breathlessness.[130,131] In the United States, Medicare reimbursement for long-term oxygen therapy is based on physiologic criteria (e.g., arterial $Po_2 < 55$ mm Hg or $Spo_2 \leq 88\%$ while breathing room air), not symptomatology. Despite this fact, many patients use oxygen primarily to relieve dyspnea, and hospice patients do not have to meet physiologic criteria to receive reimbursement. Supplemental oxygen is usually started in low doses (e.g., 1–3 L/min) and titrated to effect. The results of titration are difficult to predict inasmuch as neither the flow rate nor the route of administration of oxygen determines its impact on breathlessness.[127] Some studies have also shown that oxygen delivered to patients with advanced lung disease and refractory dyspnea does not provide any symptomatic benefit over compressed room air delivered by nasal cannula.[132,133] In addition, breathless patients are frequently relieved by exposure to fresh air in the outdoors or during automobile rides with the windows down. Those who are bedridden may benefit from using fans to blow air over their faces.[134]

For patients who have refractory dyspnea after standard medical therapy and nonpharmacologic treatments (e.g., fan, pursed-lip breathing), opioids should be considered for symptom relief.[128] Opioids may be particularly useful in patients who have pain in addition to breathlessness, such as those with lung cancer.

Benzodiazepines such as alprazolam have been shown to reduce dyspnea in some patients with COPD.[135] Yet, these agents may also cause drowsiness, discoordination, and dysphoria, and they should not be used routinely, except in selected patients whose dyspnea is refractory to other therapies.[128,134]

MANAGEMENT OF NAUSEA AND VOMITING

Nausea and vomiting may result from systemic illnesses, such as diabetes, renal failure, hypercalcemia, adrenal insufficiency, and viral infections. These symptoms may also be caused by central nervous system disorders, including cerebral metastases and other conditions that increase intracranial pressure; primary gastrointestinal diseases, such as gastric outlet obstruction; and a variety of drugs, including theophylline, phenytoin, opioids, antibiotics, and chemotherapeutic agents. Nausea and vomiting may remit with treatment of the disorder or with discontinuation of offending drugs. Because eating can increase nausea, patients may benefit by being placed on a nothing-by-mouth status or undergoing gastric decompression. Clear liquid diets may be administered to patients as tolerated. Supplemental oxygen has been shown to reduce the incidence of postoperative nausea and vomiting.[136]

Patients with nausea and vomiting who do not respond to more conservative measures may be candidates for prophylactic or therapeutic antiemetic therapy, which can be given orally, intramuscularly, intravenously, or in suppository form. Among the older antiemetics are chlorpromazine, promethazine, prochlorperazine, and other phenothiazines and muscarinic receptor antagonists, such as scopolamine, which is particularly helpful in patients with vestibular symptoms. Evidence for the use of specific agents for treating nausea and vomiting at the end of life is sparse, and there are no data suggesting that any one medication should be used preferentially.[137]

MANAGEMENT OF HUNGER AND THIRST

Evidence suggests that most patients with advanced disease who are at the end of their life do not experience hunger and thirst in the same way as healthy individuals.[138] Patients may desire food and fluids until they die; alternatively, they may choose not to eat or drink. Some patients with advanced illness also choose to stop eating and drinking as a method of hastening their own death, a practice that is ethically and legally justified.[139–141] For the few patients who are symptomatic, hunger, thirst, and dry mouth usually can be alleviated with small amounts of food and fluids or by the application of ice chips or lubrication to the lips. Similar measures can be used in other settings, including the ICU.

WITHHOLDING AND WITHDRAWAL OF LIFE-SUSTAINING THERAPY

WHAT THERAPIES ARE WITHHELD AND WITHDRAWN

Although most research on withholding and withdrawing life-sustaining therapies has taken place in ICU settings, these processes are carried out in many settings and contexts. These studies reveal that variation exists across institutions and countries in the type, number, and sequence of interventions that are withheld or withdrawn.[26,27,142–144] CPR, vasopressors, intubation/mechanical ventilation, and dialysis are generally the first interventions to be withdrawn or withheld, although notable variation across studies and patients exists, followed by other interventions, including transfusions, intravenous fluids, parenteral nutrition, antibiotics, and tube feedings. Decisions regarding withholding therapy are often reached sooner than decisions about withdrawing therapy, in part because of the psychological difficulty families (and perhaps clinicians) experience when death quickly ensues after withdrawing a life-extending treatment. In addition, whereas decisions not to intubate patients tend to be made early for patients not yet receiving mechanical ventilation, once patients are on ventilators, decisions to withdraw ventilatory support are sometimes made late, even after several other interventions are forgone.

WITHHOLDING AND WITHDRAWAL OF INTUBATION AND MECHANICAL VENTILATION

Withholding or withdrawal of intubation and mechanical ventilation is an action that commonly leads to death among patients with acute, chronic, or acute-on-chronic respiratory failure. Although patients with chronic respiratory failure often decide against these therapies if they should decompensate, some patients either request life-sustaining measures or are intubated in an emergency setting where their wishes may not be known. Similarly, patients with acute respiratory failure are frequently intubated because there is no window of opportunity to discuss goals and values and/or their conditions are assumed to be reversible. Subsequently, after days or weeks of mechanical ventilation without improvement, consideration of withdrawing intubation and mechanical ventilation often emerges. Death in the ICU most commonly results from withholding or withdrawing mechanical ventilation.[28,145]

Several published guidelines for withholding and withdrawing mechanical ventilation provide specific recommendations and procedures on how to facilitate this process.[40,41,146] After the decision for withdrawal of mechanical ventilation has been made through high-quality communication with a patient and surrogates, they should be informed about the dying process and changes in physiology that they will observe. They should also be allowed to spend time with their loved one and with clergy or other persons who provide emotional support.

Practical aspects of the withdrawal process will often need to be tailored to patient preferences. For example, a patient who wishes to remain conscious for as long as possible, even if this means enduring more suffering, would require a different approach than a patient who prefers to prioritize comfort over consciousness.[147,148] Before commencing with actual withdrawal procedures, it is important to ensure that do-not-resuscitate and do-not-intubate orders are written and that adequate analgesic and sedative medications are readily available. Interventions that do not provide comfort, such as laboratory tests, some medications, dialysis, and neuromuscular blocking agents, can then be stopped.

There are two general approaches to withdrawal of mechanical ventilation: terminal weaning and immediate extubation. High-quality evidence comparing these two approaches is lacking, so it is unknown which method is best. With terminal weaning, first described in 1983,[149] mechanical ventilation support is rapidly titrated off, usually over 10 to 20 minutes, with concomitant titration of opiates to maintain comfort. Most patients who are terminally weaned are able to breathe room air with the endotracheal tube in place. With anticipation of the need for further doses of sedatives and opiates if the airway becomes obstructed, the patient can then be extubated. With immediate extubation, ventilatory support is not gradually decreased; instead, the patient is administered preemptive opiates, often in high doses, and extubation is rapid. In one study, immediate extubation was associated with more airway obstruction and gasping, but not with increased psychological distress among surrogates; however, this study was small and observational, so it is difficult to draw inferences from it.[150] This approach requires very careful assessment of and attention to the need for anticipatory opiates because the risk for respiratory distress may be greater.

When intubation and mechanical ventilation are withdrawn, most patients with respiratory failure die of their underlying diseases. Nevertheless, some survive, and their survival should not be prevented by drugs that hasten death. At the same time, even patients who are too sick to survive should not receive drugs that interfere with observing tachypnea and other signs that may signal the need for symptom relief. For these reasons, although sedatives and analgesics may be given to relieve suffering, neuromuscular blocking agents should generally not be used in patients for whom intubation and mechanical ventilation will be withdrawn.

Key Points

- End-of-life care is a combination of palliative treatment and withholding and withdrawal of life-sustaining therapy provided to patients who are terminally ill, including those with acute, chronic, and acute-on-chronic respiratory failure.
- End-of-life care is justified by the ethical principles of beneficence, nonmaleficence, autonomy, and justice and by the legal right of informed patients to consent to or refuse any or all therapy, including that which sustains life.
- The legal right of consent or refusal may be exercised by patients themselves or by their family members and legally appointed surrogates through substituted-judgment and best-interests standards.
- End-of-life care is enhanced by a shared model of medical decision making and by intensive communication among patients, family members, and caregivers. Such care should attend to the needs of patients, families, and caregivers alike.
- When patients or their surrogates request treatments that clinicians believe are potentially inappropriate, clinicians should generally pursue a stepwise approach to dispute resolution, including intensive communication with the patient/surrogate, involvement of expert consultants (e.g., ethics consultants), review by a hospital committee, and an offer of transfer to another facility.
- Some interventions aimed at improving communication with patients and families, especially those that incorporate longitudinal communication and emotional support, seem to increase satisfaction and reduce the burden of mental health symptoms, but other interventions, especially those that are purely informational, have not shown these improvements.
- The components of end-of-life care include providing appropriate settings for dying patients; supplying emotional and spiritual support; managing such symptoms as pain, anxiety, delirium, dyspnea, nausea, vomiting, hunger and thirst; and removing unwanted therapies.
- After shared decision making with patients and surrogates, mechanical ventilation and other life-sustaining therapies can be withheld or withdrawn by following guidelines and focusing on provision of comfort measures to prevent pain and other suffering.

Key Readings

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Complete reference list available at ExpertConsult.com.



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HIPAA PERMITS DISCLOSURE OF POLST ORDERS TO HEALTH CARE PROVIDERS AS NECESSARY FOR TREATMENT
SEND FORM WITH PATIENT WHENEVER TRANSFERRED OR DISCHARGED

Medical Record # (Optional)

National POLST Form: A Portable Medical Order

Health care providers should complete this form only after a conversation with their patient or the patient's representative. The POLST decision-making process is for patients who are at risk for a life-threatening clinical event because they have a serious life-limiting medical condition, which may include advanced frailty (www.polst.org/guidance-appropriate-patients-pdf).

Patient Information. **Having a POLST form is always voluntary.**

This is a medical order, not an advance directive. For information about POLST and to understand this document, visit: www.polst.org/form

Patient First Name: _____

Middle Name/Initial: _____ Preferred name: _____

Last Name: _____ Suffix (Jr, Sr, etc): _____

DOB (mm/dd/yyyy): ____/____/_____ State where form was completed:_____

Gender: ☐ M ☐ F ☐ X Social Security Number's last 4 digits (optional): xxx-xx-___ ___ ___ ___

A. Cardiopulmonary Resuscitation Orders. Follow these orders if patient has no pulse and is not breathing.

Pick 1

☐ **YES CPR: Attempt Resuscitation, including mechanical ventilation, defibrillation and cardioversion.** (Requires choosing Full Treatments in Section B)

☐ **NO CPR: Do Not Attempt Resuscitation.** (May choose any option in Section B)

B. Initial Treatment Orders. Follow these orders if patient has a pulse and/or is breathing.

Reassess and discuss interventions with patient or patient representative regularly to ensure treatments are meeting patient's care goals. Consider a time-trial of interventions based on goals and specific outcomes.

Pick 1

☐ **Full Treatments (required if choose CPR in Section A).** Goal: Attempt to sustain life by all medically effective means. Provide appropriate medical and surgical treatments as indicated to attempt to prolong life, including intensive care.

☐ **Selective Treatments.** Goal: Attempt to restore function while avoiding intensive care and resuscitation efforts (ventilator, defibrillation and cardioversion). May use non-invasive positive airway pressure, antibiotics and IV fluids as indicated. Avoid intensive care. Transfer to hospital if treatment needs cannot be met in current location.

☐ **Comfort-focused Treatments.** Goal: Maximize comfort through symptom management; allow natural death. Use oxygen, suction and manual treatment of airway obstruction as needed for comfort. Avoid treatments listed in full or select treatments unless consistent with comfort goal. Transfer to hospital **only** if comfort cannot be achieved in current setting.

C. Additional Orders or Instructions. These orders are in addition to those above (e.g., blood products, dialysis).
[EMS protocols may limit emergency responder ability to act on orders in this section.]

D. Medically Assisted Nutrition (Offer food by mouth if desired by patient, safe and tolerated)

Pick 1

☐ Provide feeding through new or existing surgically-placed tubes ☐ No artificial means of nutrition desired

☐ Trial period for artificial nutrition but no surgically-placed tubes ☐ Not discussed or no decision made (provide standard of care)

E. SIGNATURE: Patient or Patient Representative (eSigned documents are valid)

I understand this form is voluntary. I have discussed my treatment options and goals of care with my provider. If signing as the patient's representative, the treatments are consistent with the patient's known wishes and in their best interest.

✖ (required)

The most recently completed valid POLST form supersedes all previously completed POLST forms.

If other than patient, print full name: | **Authority:**

F. SIGNATURE: Health Care Provider (eSigned documents are valid) Verbal orders are acceptable with follow up signature.

I have discussed this order with the patient or his/her representative. The orders reflect the patient's known wishes, to the best of my knowledge. [Note: Only licensed health care providers authorized by law to sign POLST form in state where completed may sign this order]

✖ (required) | **Date** (mm/dd/yyyy): Required / / | **Phone # :** ( )

Printed Full Name: | **License/Cert. #:**

Supervising physician signature: ☐ N/A | **License #:**

A copied, faxed or electronic version of this form is a legal and valid medical order. This form does not expire. 2019

1994.e1

National POLST Form – Page 2 *******ATTACH TO PAGE 1********

Patient Full Name:

Contact Information (Optional but helpful)

Patient's Emergency Contact. (Note: Listing a person here does **not** grant them authority to be a legal representative. Only an advance directive or state law can grant that authority.)

Full Name:	☐ Legal Representative ☐ Other emergency contact	Phone #: Day: ( ) Night: ( )
Primary Care Provider Name:		Phone: ( )
☐ Patient is enrolled in hospice	Name of Agency: Agency Phone: ( )	

Form Completion Information (Optional but helpful)

Reviewed patient's advance directive to confirm no conflict with POLST orders: (A POLST form does not replace an advance directive or living will)	☐ Yes; date of the document reviewed:_____ ☐ Conflict exists, notified patient (if patient lacks capacity, noted in chart) ☐ Advance directive not available ☐ No advance directive exists

Check everyone who participated in discussion: ☐ Patient with decision-making capacity ☐ Court Appointed Guardian ☐ Parent of Minor ☐ Legal Surrogate / Health Care Agent ☐ Other: _____

Professional Assisting Health Care Provider w/ Form Completion (if applicable): Full Name:	Date (mm/dd/yyyy): / /	Phone #: ( )

This individual is the patient's: ☐ Social Worker ☐ Nurse ☐ Clergy ☐ Other:

Form Information & Instructions

- **Completing a POLST form**:
  - Provider should document basis for this form in the patient's medical record notes.
  - Patient representative is determined by applicable state law and, in accordance with state law, may be able execute or void this POLST form only if the patient lacks decision-making capacity.
  - Only licensed health care providers authorized to sign POLST forms in their state or D.C. can sign this form. See www.polst.org/state-signature-requirements-pdf for who is authorized in each state and D.C.
  - Original (if available) is given to patient; provider keeps a copy in medical record.
  - Last 4 digits of SSN are optional but can help identify / match a patient to their form.
  - If a translated POLST form is used during conversation, attach the translation to the signed English form.
- **Using a POLST form:**
  - Any incomplete section of POLST creates no presumption about patient's preferences for treatment. Provide standard of care.
  - No defibrillator (including automated external defibrillators) or chest compressions should be used if "No CPR" is chosen.
  - For all options, use medication by any appropriate route, positioning, wound care and other measures to relieve pain and suffering.
- **Reviewing a POLST form:** This form does not expire but should be reviewed whenever the patient:
  (1) is transferred from one care setting or level to another;
  (2) has a substantial change in health status;
  (3) changes primary provider; or
  (4) changes his/her treatment preferences or goals of care.
- **Modifying a POLST form:** This form cannot be modified. If changes are needed, void form and complete a new POLST form.
- **Voiding a POLST form:**
  - **If a patient or patient representative (for patients lacking capacity) wants to void the form**: destroy paper form and contact patient's health care provider to void orders in patient's medical record (and POLST registry, if applicable). State law may limit patient representative authority to void.
  - **For health care providers**: destroy patient copy (if possible), note in patient record form is voided and notify registries (if applicable).
- **Additional Forms.** Can be obtained by going to www.polst.org/form
- As permitted by law, this form may be added to a secure electronic registry so health care providers can find it.

State Specific Info	For Barcodes / ID Sticker

For more information, visit www.polst.org or email info@polst.org Copied, faxed or electronic versions of this form are legal and valid. 2019

eFigure 141.1 Example of a *physician/provider/portable order for life-sustaining therapy* (POLST) form. A POLST is a medical order signed by a provider that communicates the patient's wishes in the case of a life-threatening event. This order can be placed not only in the patient's chart with the provider and local hospitals but also in the home so that first responders readily understand his or her wishes in the event of an emergency. (Courtesy National POLST Paradigm, www.polst.org.)

VERMONT

Patient Choice at End of Life — Physician Reporting Form

Mail form to:
Vermont Department of Health, Vital Records
P.O. Box 70, Burlington, VT 05402-0070

PLEASE PRINT

A	**PATIENT INFORMATION**	
	PATIENT'S NAME (LAST, FIRST, M.I.)	DATE OF BIRTH
	MEDICAL DIAGNOSIS	

B	**PHYSICIAN INFORMATION**	
	NAME (LAST, FIRST, M.I.)	TELEPHONE NUMBER (with area code)
	MAILING ADDRESS	
	CITY, STATE AND ZIP CODE	

C	**ACTION TAKEN TO COMPLY WITH LAW**	
	1. FIRST ORAL REQUEST	
	☐ The patient made an oral request for medication to be self-administered for the purpose of hastening the patient's death.	DATE
	Comments:	
	2. SECOND ORAL REQUEST (Must be made 15 days or more after the first oral request.)	
	Indicate compliance by checking the boxes. ☐ 1. Second oral request for medication to hasten death. ☐ 2. Patient informed of the right to rescind the request at any time.	DATE
	Comments:	
	3. WRITTEN REQUEST	
	☐ The patient made a written request for medication to hasten death.	DATE
	Comments:	

continued

Patient Choice At End Of Life — Physician Reporting Form

(continued)

4. PHYSICIAN DETERMINATIONS

Indicate compliance by checking the boxes. (Both the attending and consulting physicians must make these determinations.)

1. Determined that the patient:
   - ☐ a) is suffering with a terminal condition;*
   - ☐ b) is capable;**
   - ☐ c) is making an informed decision;
   - ☐ d) has made a voluntary request for medication to hasten his or her death;
   - ☐ e) is at least 18 years old and a Vermont state resident.***
2. Informed the patient in person, both verbally and in writing, of all the following:
   - ☐ a) the patient's medical diagnosis;
   - ☐ b) the patient's prognosis, including an acknowledgement that the physician's prediction of the patient's life expectancy is an estimate based on the physician's best medical judgment;
   - ☐ c) the range of treatment options appropriate for the patient and the patient's diagnosis;
   - ☐ d) if the patient was not enrolled in hospice care, all feasible end-of-life services, including palliative care, comfort care, hospice care, and pain control;
   - ☐ e) the range of possible results, including potential risks associated with taking the medication to be prescribed; and
   - ☐ f) the probable result of taking the medication to be prescribed.
3. ☐ Referred the patient to a second physician for medical confirmation.
4. ☐ Verified that the patient did not have impaired judgment based on my evaluation or as the result of a referral of the patient to a psychiatric or psychological clinician.

D MEDICATION PRESCRIBED AND INFORMATION PROVIDED TO PATIENT

To be prescribed no sooner than **48 hours after the last** of the following:

1. Patient's written request was signed;	DATE
2. The patients second oral request;	DATE
3. Offering the patient the opportunity to rescind the request.	DATE

To the best of my knowledge, all of the requirements under the Patient Choice at End of Life Act have been met.

X	PHYSICIAN'S SIGNATURE	DATE

If comments in any section exceed the space provided, please use an attached page. Supplemental comments should be identified using the appropriate alphanumeric notation (e.g., C3).

* "Terminal condition" means an incurable and irreversible disease that would, within reasonable medical judgment, result in death within six months.

** "Capable" means that a patient has the ability to make and communicate health care decisions to a physician, including communication through persons familiar with the patient's manner of communicating if those persons are available.

*** Factors demonstrating residency include, but are not limited to: 1) Possession of a Vermont driver's license; 2) Registration to vote in Vermont; 3) Evidence that a person leases/owns property in Vermont; or 4) Filing of an Vermont tax return for the most recent tax year. Only the attending physician is required to affirm Vermont residency.

This form is revised periodically. To assure that you are using the most current version, please refer to: http://healthvermont.gov

07.03.2013

eFigure 141.2 The Physician Reporting Form that must be completed in Vermont for *physician-assisted death* (PAD). In U.S. states where PAD is legal, physicians are required to file reports of each case with the state indicating that all mandatory steps in the PAD process were completed. (Courtesy Vermont Department of Health.)

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APPENDIX GLOSSARY OF TERMS AND STANDARD SYMBOLS

I. PRIMARY AND QUALIFYING SYMBOLS

GENERAL

P	Pressure (Includes also *partial* pressure of a gas in a mixture of gases or in blood.)
L	Lung
W	Chest wall
RS	Respiratory system
Pl	Pleura

VENTILATION

V	Volume of gas
$\dot{V}$	Flow of gas
I	Inspired
E	Expired
A	Alveolar
T	Tidal
ET	End-tidal
D	Dead space
STPD	*Standard Conditions: s*tandard *t*emperature (0° C), barometric *p*ressure (760 mm Hg), and *d*ry.
BTPS	*Body Conditions: bo*dy *t*emperature and ambient *p*ressure, *s*aturated with water vapor at these conditions.
ATPS	*Ambient Conditions: a*mbient *t*emperature and *p*ressure, *s*aturated with water vapor at these conditions.

GAS EXCHANGE–BLOOD FLOW

Q	Volume of blood
$\dot{Q}$	Flow of blood
F	Fractional concentration of gas
C	Concentration in blood
S	Saturation in blood
b	Blood, in general
a	Arterial blood
v	Venous blood
$\bar{v}$	Mixed venous blood
c	Capillary blood
c′	Pulmonary end-capillary blood

II. VENTILATION AND LUNG MECHANICS

STATIC LUNG VOLUMES

VC	*Vital Capacity:* The maximum volume of gas that can be exhaled after fully inflating the lungs.
FRC	*Functional Residual Capacity:* The volume of gas remaining in the lungs at the end of quiet expiration.
TLC	*Total Lung Capacity:* The volume of gas in the lungs after a maximum inspiration.
RV	*Residual Volume:* The volume of gas remaining in the lungs after a maximum exhalation.
IC	*Inspiratory Capacity:* The volume of gas that can be inhaled from resting end-expiration (FRC) to full inflation (TLC).
ERV	*Expiratory Reserve Volume:* The volume of gas that can be exhaled from resting end-expiration (FRC) to full exhalation (RV).
IRV	*Inspiratory Reserve Volume:* The volume of gas that can be inhaled from resting end-inspiration to full inflation (TLC).

DESCRIPTORS OF FORCED BREATHING MANEUVERS

FVC	*Forced Vital Capacity:* The volume of gas that can be forcibly exhaled after fully inflating the lungs.
FEV_t	*Timed Forced Expiratory Volume:* The volume of gas exhaled at a specified time after beginning the forced vital capacity maneuver. For example, FEV_1 = forced expiratory volume in 1 second.
FEV_t/FVC	*Ratio of Timed Expiratory Volume to Forced Vital Capacity:* For example, FEV_1/FVC, usually expressed as a percentage.

FEF_x *Specified Forced Expiratory Flow:* The forced expiratory flow rate during a specified portion of the forced vital capacity. For example, $FEF_{200–1200\,mL}$ = forced expiratory flow rate between 200 and 1200 mL of the forced vital capacity; $FEF_{25\%–75\%}$ = forced expiratory flow rate between 25% and 75% of the forced vital capacity.

$\dot{V}max_{x\%}$ *Specified Maximum Expiratory Flow:* The instantaneous expiratory flow rate when *x* percent of the forced vital capacity has been exhaled. For example, $\dot{V}max_{50\%}$ = maximum expiratory flow rate at 50% of the forced vital capacity.

MVV *Maximum Voluntary Ventilation:* Volume of gas exhaled while making maximum breathing efforts during a certain time interval (often 12 seconds).

VR *Ventilatory Reserve:* The difference between ventilatory capacity during maximum exercise (estimated as MVV or calculated from FEV_1) and minute ventilation at peak exercise; VR, which is also known as *breathing reserve,* represents the potential for further increase in ventilation during maximum (or peak) exercise.

$P_{I_{max}}$ *Maximum Inspiratory Pressure:* The maximum pressure generated by the respiratory muscles during an attempted inspiration.

$P_{E_{max}}$ *Maximum Expiratory Pressure:* The maximum pressure generated by the respiratory muscles during an attempted exhalation.

DESCRIPTORS OF VENTILATION

f *Respiratory Frequency:* The number of breaths during 1 minute.

V_T *Tidal Volume:* The volume of gas inspired or expired during each breath.

$\dot{V}_E$ *Expired Ventilation:* The volume of gas (BTPS), usually measured at the mouth, exhaled during 1 minute.

$\dot{V}_I$ *Inspired Ventilation:* The volume of gas (BTPS), measured or calculated, inhaled during 1 minute.

$\dot{V}_A$ *Alveolar Ventilation:* The volume of gas (BTPS), exhaled from the lungs during 1 minute, that contributed to gas exchange; calculated as expired ventilation minus dead space ventilation.

$\dot{V}_D$ *Dead Space Ventilation:* The volume of gas (BTPS), exhaled from the lungs during 1 minute, that did not contribute to gas exchange; also known as *wasted ventilation.* Calculated from the equation

$$\dot{V}_D = \dot{V}_E \frac{Pa_{CO_2} - P_{E_{CO_2}}}{Pa_{CO_2} - P_{I_{CO_2}}}$$

where Pa_{CO_2}, $P_{E_{CO_2}}$, and $P_{I_{CO_2}}$ are the partial pressures of CO_2 in arterial blood, mixed expired gas, and inspired gas, respectively.

V_D *Dead Space Volume:* The volume of the physiologic dead space; calculated as $\dot{V}_D/f$.

V_D/V_T *Ratio of Dead Space to Tidal Volume:* The proportion, usually expressed as a percentage, of each breath that does not contribute to CO_2 removal (i.e., the proportion of each breath that is wasted).

VE *Ventilatory Equivalent:* The minute ventilation required for each liter of gas exchanged, either O_2 or CO_2; used as a measure of the efficiency of the lungs as a gas exchanger. For O_2:

$$VE_{O_2} = \frac{\dot{V}_E\,(BTPS)}{\dot{V}_{O_2}\,(STPD)}$$

VOLUME-PRESSURE RELATIONSHIPS

C *Compliance:* General symbol for compliance, or the ratio of volume change of the structure per unit change in applied pressure across the structure.

C_L *Lung Compliance:* The volume change of the lung divided by the difference between alveolar pressure (Palv) and pleural pressure (Ppl), which is also known as the transpulmonary pressure (P_L).

C_W *Chest Wall Compliance:* The volume change of the chest wall divided by the difference between pleural pressure (Ppl) and body surface pressure (Pbs), which is also known as the transthoracic pressure (P_W).

Crs *Respiratory System Compliance:* The volume change of the lung and chest wall divided by the difference between alveolar pressure (Palv) and body surface pressure (Pbs), or transpulmonary pressure (P_L) plus transthoracic pressure (P_W).

Cdyn *Dynamic Compliance:* Value for compliance based on measurements made during uninterrupted breathing.

Cst	*Static Compliance:* Value for compliance based on measurements made during periods of no airflow.
C/V_L	*Specific Compliance:* Value for compliance divided by the lung volume at which it was measured, usually functional residual capacity.

FLOW-PRESSURE RELATIONSHIPS

R	*Resistance:* General symbol for frictional resistance, or the pressure difference divided by flow.
R_{AW}	*Airway Resistance:* Resistance calculated from pressure difference between airway opening (Pao) and alveoli (Palv) divided by the airflow.
R_L	*Total Pulmonary Resistance:* Resistance calculated by dividing flow-dependent transpulmonary pressure by airflow at the mouth.
G_{AW}	*Airway Conductance:* The reciprocal of R_{AW}.
G_{AW}/V_L	*Specific Conductance:* Value for airway conductance divided by the lung volume at which it was measured.

III. GAS EXCHANGE

BLOOD

Examples shown are for O_2; other gases (e.g., CO_2, N_2, CO) or other sites (e.g., $\bar{v}$, c') can be substituted when appropriate.

P_{O_2}	*Partial Pressure of O_2:* General designation (expressed in mm Hg); source usually specified (e.g., arterial P_{O_2} or Pa_{O_2}).
S_{O_2}	*Blood Saturation:* General designation (expressed as a percentage); source usually specified (e.g., arterial S_{O_2} or Sa_{O_2}).
C_{O_2}	*Oxygen Content:* General designation (expressed in mL/dL); source usually specified (e.g., arterial C_{O_2}).
$\dot{V}_{O_2}$	*Oxygen Consumption:* The volume of O_2 (STPD) utilized by the body during 1 minute; usually calculated as the amount of O_2 extracted from inspired gas.
$\dot{V}_{O_{2max}}$	*Maximum Oxygen Consumption:* The maximal volume of O_2 (STPD) that can be utilized by the body during 1 minute of maximally attainable exercise.
$\dot{V}_{CO_2}$	*Carbon Dioxide Output:* The volume of CO_2 (STPD) produced by the body during 1 minute; usually calculated as the amount of CO_2 added to exhaled gas.
RQ	*Respiratory Quotient:* The ratio of $\dot{V}_{CO_2}$ to $\dot{V}_{O_2}$ during steady-state metabolic activity.
RER	*Respiratory Exchange Ratio:* The ratio of $\dot{V}_{CO_2}$ to $\dot{V}_{O_2}$, as in RQ, but also including the influence of transient changes in body stores of respiratory gases.

GAS TO BLOOD

$(A–a)P_{O_2}$	*Alveolar-Arterial P_{O_2} Difference:* The difference in P_{O_2} between mean alveolar gas and arterial blood (expressed in mm Hg).
D_L	*Diffusing Capacity of the Lung:* Expressed as the volume of gas transferred per minute per unit of alveolar-capillary pressure difference for the gas used, which is usually specified (e.g., $D_{L_{CO}}$ or $D_{L_{O2}}$).
D_M	*Diffusing Capacity of the Alveolocapillary Membrane.*
$1/D_L$	*Total Resistance to Diffusion:* The sum of the resistance to diffusion of the test gas across the alveolocapillary membrane ($1/D_M$) and the resistance to diffusion within the red blood cells attributable to the chemical reaction between the test gas and hemoglobin ($1/\theta V_C$). These relationships are expressed by the Roughton-Forster equation: $$\frac{1}{D_L} = \frac{1}{D_M} + \frac{1}{\theta V_C}$$
D_L/V_A	*Diffusion per Unit of Alveolar Volume:* The value of D_L (STPD) divided by V_A (BTPS), both measured in the same breathing maneuver.

IV. HEMODYNAMIC DESCRIPTORS

$\dot{Q}_T$	*Cardiac Output:* The total output of the left ventricle during one minute.
$\dot{Q}_S$	*Pulmonary Shunt Flow:* The total amount of blood per minute perfusing completely nonventilated gas-exchange units; hence, blood that does not come in contact with inspired gas and does not contribute to oxygen uptake. Often called the *right-to-left shunt,* but this term also includes intracardiac shunts.

$\dot{Q}S/\dot{Q}T$ — *Pulmonary Shunt Fraction:* The total pulmonary shunt ($\dot{Q}S$), or venous admixture, expressed as a percentage of total cardiac output ($\dot{Q}T$) according to the equation:

$$\frac{\dot{Q}S}{\dot{Q}T} = \frac{Cc'O_2 - CaO_2}{Cc'O_2 - C\bar{v}O_2} \times 100$$

where $Cc'O_2$ is the O_2 content of end-capillary blood; CaO_2 is the O_2 content of arterial blood; and $C\bar{v}O_2$ is the O_2 content of mixed venous blood. While breathing 100% O_2 (and sampling systemic arterial blood, not end-capillary blood), $\dot{Q}S/\dot{Q}T$ is a measure of right-to-left shunting of blood.

PPA — *Pulmonary Artery Pressure:* The pressure—systolic, diastolic, or mean—measured in the pulmonary artery.

PLA — *Left Atrial Pressure:* The pressure, usually mean, measured in the left atrium.

Pcap — *Pulmonary Capillary Pressure:* The mean pressure in the pulmonary capillaries, sometimes abbreviated Pc, which cannot be measured directly in humans but is frequently estimated by the equation:

$$Pcap = PLA + 0.4\,(PPA - PLA)$$

PPW — *Pulmonary Wedge Pressure:* The mean pressure measured by the pulmonary artery occlusion technique, which provides an estimate of the postcapillary, or pulmonary venous, pressure.

PVR — *Pulmonary Vascular Resistance:* The resistance to blood flow through the lungs; a calculated value from the equation:

$$PVR = \frac{PPA - PLA}{\dot{Q}T}$$

in which PPW is often used to approximate PLA.

V. OTHER USEFUL TERMS

PEEP — *Positive End-Expiratory Pressure:* The condition in which the pressure in the lungs at the end of expiration is positive (i.e., higher than atmospheric). Usually applied externally by ventilator adjustments; when PEEP results from failure to exhale fully at the end of expiration, it is called *intrinsic* (PEEPi).

$P_{0.1}$ — *Mouth Occlusion Pressure:* The pressure measured in the mouth during the first 0.1 second of attempted inspiration after the airway is temporarily occluded while the subject is breathing. An estimate of the central drive to breathe.

TI/TT — *Duty Cycle:* The ratio of the duration of inspiration (TI) to the duration of inspiration and expiration (TT), a reflection of respiratory timing.

VI. USEFUL EQUATIONS

Alveolar Gas Equation — Often used to calculate mean alveolar P_{O_2} (P_{AO_2}):

$$P_{AO_2} = P_{IO_2} - \frac{P_{ACO_2}}{R}$$

where P_{IO_2} is the P_{O_2} of inspired gas; P_{ACO_2} is the alveolar P_{CO_2} (usually assumed to equal arterial P_{CO_2}); and R is the respiratory exchange ratio. Because of some assumptions, this equation is an approximation. For calculating the exact P_{AO_2}, an additional term is needed, where F_{IO_2} is the fractional concentration of O_2 in inspired gas.

$$P_{AO_2} = P_{IO_2} - \frac{P_{ACO_2}}{R} + \left[P_{ACO_2} \times F_{IO_2} \times \frac{(1-R)}{R} \right]$$

Henderson-Hasselbalch Equation — Useful for calculating any one of three variables, pH, HCO_3^-, or H_2CO_3, when two of them are known:

$$pH = pK + \log\left[\frac{[HCO_3^-]}{[H_2CO_3]}\right]$$

where pK, the dissociation constant, is 6.10 for plasma at 37° C; $[HCO_3^-]$ is the concentration of bicarbonate in plasma; and $[H_2CO_3]$ is the concentration of carbonic acid in plasma (both in mol/L). The equation can be rearranged by using P_{CO_2} (in mm Hg) and its solubility in plasma so that

$$pH = pK + \log\frac{[HCO_3^-]}{[P_{CO_2} \times 0.0301]}$$

Starling Equation — Net fluid exchange (Jv) across the microvascular barrier in the lungs:

$$Jv = LpS\,[(Pc - Pi) - \sigma d\,(\pi c - \pi i)]$$

where Lp is the hydraulic conductivity ("permeability"); S is the surface area; Pc is the microvascular hydrostatic pressure; Pi is the perimicrovascular hydrostatic pressure; σd is the osmotic reflection coefficient; πc is the microvascular colloid osmotic pressure; and πi is the perimicrovascular colloid osmotic pressure.